Recent Developments in Fluorocyclization Methodology

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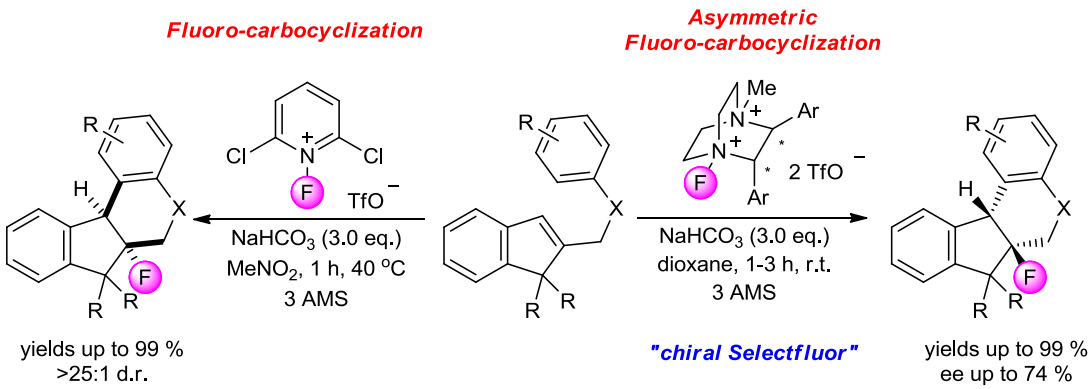
Abstract

This thesis has focussed on three main projects, all concerning electrophilic fluorination and fluorocyclization methodology. To begin with we considered the development of a novel fluoro-carbocyclization reaction, which combined the use of substrates of relatively low reactivity and rarely used carbon nucleophiles. Two major and common problems with electrophilic fluorination are the choice of a suitable reaction solvent and an appropriate fluorine source. These challenges were encountered and overcome to furnish a large library of cyclized products in excellent yields starting from indene and dihydronaphthalene class substrates. Our attempts to extend this methodology to an asymmetric variant using literature protocol for asymmetric fluorination were unsuccessful due to insufficient reactivity, which prompted us to investigate a new class of chiral reagents. Using the structural core of the widely used achiral reagent Selectfluor™, we prepared a variety of novel reagents which displayed greater fluorinating power than what is currently available in the literature. Finally, by combining the methodology for fluoro-carbocyclization with our selection of chiral reagents we were able to successfully achieve an unprecedented metal-free asymmetric fluoro-carbocyclization.



Author's Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory at the University of Oxford between Michaelmas Term 2009 and Trinity Term 2013 under the supervision of Professor Véronique Gouverneur. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

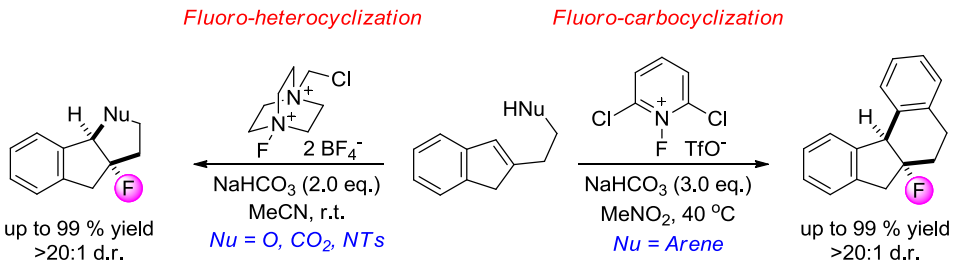
Jamie R. Wolstenhulme

August 2013

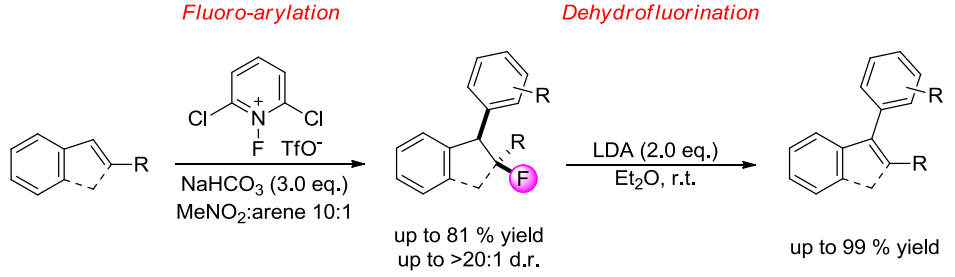
Summary

Chapter 1: A general introduction to the field of fluorocyclization is provided. Both nucleophilic and electrophilic methods are described, including the latest asymmetric examples in the literature. A foreword on electrophilic fluorinating reagents, their different types, their nature, and their reactivity, is also included.

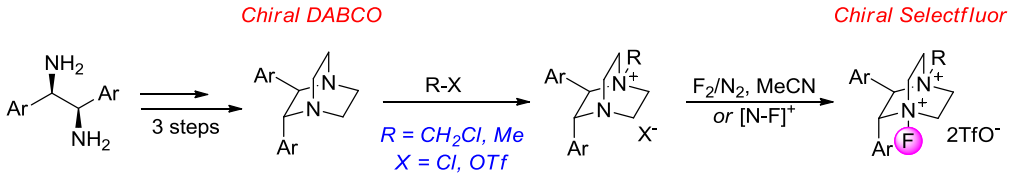
Chapter 2: Fluorocyclization methodology was successfully developed for a novel class of substrates of lower reactivity than previously reported. We first investigated a reaction featuring heteroatomic nucleophiles before moving onto more challenging carbon nucleophiles. A variety of problems caused by the constraints of electrophilic fluorination methodology were encountered and overcome.



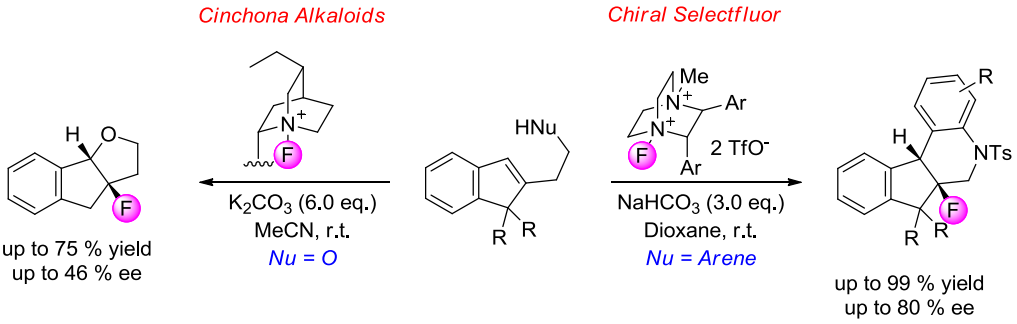
Chapter 3: A novel fluoro-arylation reaction was developed, whereby the nucleophile tether was removed. A variety of external arene nucleophiles were shown to undergo an arylation reaction in the first example of a metal-free inter-molecular C-C bond forming event triggered by C-F bond formation. The application of this reaction was illustrated by a subsequent dehydrofluorination reaction to achieve a selection of cross-coupled products.



Chapter 4: A library of novel chiral electrophilic fluorinating reagents was developed based on the structural core of Selectfluor. The synthesis involved first preparing the intermediate chiral DABCOs and then subsequent quaternization and fluorination. A method was established for *in situ* fluorination, circumventing the requirement for use of fluorine gas. Finally, we outlined procedures to measure the relative reactivity of the new reagents, as well as their purity.



Chapter 5: An asymmetric variant of the fluoro-heterocyclization methodology developed in earlier was achieved using cinchona alkaloid derived chiral reagents, the current state-of-the-art in the literature. However, substrates featuring carbon nucleophiles proved to be too unreactive for any known literature protocol. Pleasingly, by combining our fluoro-carbocyclization reaction with our novel chiral Selectfluor reagents we were able to achieve the first example of a metal-free asymmetric fluoro-carbocyclization.



Chapter 6: Experimental data is provided for the preparation of all compounds contained within the thesis. Details are also provided for optimisation studies.

Appendices (Volume II): NMR spectra for novel compounds, HPLC traces for asymmetric reactions, and x-ray crystallographic data are provided.

Acknowledgements

First and foremost I would like to thank Professor Véronique Gouverneur for giving me the opportunity to work in her laboratory and for making this thesis possible. I am greatly indebted to her for all the help and guidance she has provided me with over the past few years. In particular, I must acknowledge how I was inspired by her constant encouragement, enthusiasm, dedication, and determination to succeed.

Secondly, I would like to thank the people that have directly contributed to the work presented in this thesis. I was fortunate to supervise three Part II students during my DPhil project and am deeply grateful for their hard work. Faye Buckingham performed much of the work on asymmetric fluoro-heterocyclization, Matthew Johnson initiated the work on the fluoro-arylation methodology and Jessica Rosenqvist worked on asymmetric fluoro-carbocyclization using chiral Selectfluor. I must also thank Dr. John Ilupeju and Nathalie Wurz for highly valuable preliminary work on the development of chiral Selectfluor reagents. Finally, I would like to thank Dr. Oscar Lozano and Dr. Erika Luethi for their contribution and for all their help.

Thirdly, as well as people who have directly contributed to work presented in this thesis I would like to take the opportunity to thank a few people, past and present, for their help and very useful discussions throughout my time in the Gouverneur group. A special thank you must go to my own Part II supervisor, Dr. Romain Bejot, from whom I learned a great deal, which prepared me well for undertaking this project. Thanks also to Dr. Laurence Carroll, Dr. Matt Hopkinson, Dr. Guy Giuffredi, Dr. Keary Engle and Dr. Matt Tredwell for their help and friendship over the years. I particularly value the many helpful conversations had with Keary in either Deep Hall, the PT, or very occasionally, the lab. Finally, my thanks to Charley, Elena, George, Ida and Keary for making it such a great year group!

Fourthly, I would like to thank the CF_3 team; Miriam, Satoshi, Ida and Matt for which I was briefly part of. I would also like to thank all the people of F9, past and present, for making the lab such a great place to work; John, George, Oscar, Lorraine, Faye, Matt, Jess, Enrico, Chris as well as the good people of TJD. Finally, I will take this opportunity to acknowledge the incredible sadness felt by all upon Jeff's leaving the group. It is safe to say that none of us will ever meet another Jeff. Simply legendary.

A special mention must also go to George Pidgeon for his help with X-ray crystallographic experiments. From the moment George was asked to join the project, a piece of work that had occupied more than a decade of man-years was completed in less than a day. Even more impressive is that it was all done in the few hours before he handed in his Part II thesis. Thanks also to Guy and Dr. Lorraine Combettes for their crystallographic help.

Of course, I cannot fail to acknowledge the greatest achievement over the past four years. I am immensely proud to have captained the VG group football team for the past three seasons and to have steered the team through several successful Catalyst Cup campaigns. There can surely be no greater feeling than lifting the department's most coveted trophy in front of literally several people. Thank you to all that have played with us, trained with us, or simply supported us.

On a further (fantasy) football note, I must thank the manager of Purple Moose FC, Aidan Engle, for keeping me on my toes throughout last season and congratulate him on his maiden success. Though some may call into question his squad selection, others may describe it as creative or even just better. We'll see this year!

I have really enjoyed my time in Oxford over the past 8 years, and for that I must thank my friends and housemates. In particular I must mention the Osney Laners; Brick, Cake, Cobra

and SIMON. I would also like to thank my family for making it possible for me to come to Oxford in the first place.

It could not go without highlighting the enormous impact that the Lincoln Hall kitchen staff have had on the completion of this thesis. True culinary geniuses of their time. Whilst some might lack the inspiration required to combine Lasagne and chips, they dared to dream. A quite simply brilliant repertoire of lunches, not to be equalled across all of Oxford. Similar thanks go to Simon in Deep Hall. I'm afraid his takings never fully recovered from the loss of Guy but I have endeavoured to make up the short fall wherever possible.

My final, and biggest, acknowledgment must go to Faye who has been amazing throughout the writing of this thesis. She has tolerated me colonising the dining table and cluttering the spare bedroom. I am not sure I could have done this without your constant support and encouragement. Thank you.

Abbreviations and Acronyms

Å	Ångström (10^{-10} M)
AIBN	Azobisisobutyronitrile
Ac	Acetyl
AgRE	Silver Reference Electrode
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Bu	Butyl
CAN	Ceric Ammonium Nitrate
conc.	Concentration
Cs	*para*-Chlorobenzenesulfonyl
°C	Degrees Celsius
δ	Chemical shift
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCE	Dichloroethane
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DMAP	*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
d.r.	Diastereomeric ratio
E°	Standard electrode potential
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl

eV	Electron Volt(s)
FI	Field ionisation
g	Gram(s)
h	Hour(s)
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i	*Iso*
IR	Infrared spectroscopy
k	Rate constant
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamine
LUMO	Lowest Unoccupied Molecular Orbital
M	$moldm^{-3}$
Me	Methyl
MEM	Methoxyethoxymethyl ether
Ms	Methanesulfonyl
µL	Microlitre(s)
min	Minute(s)
mL	Millilitre(s)
mol	Moles
mp	Melting point
NFCPT	*N*-Fluoro-2,6-dichloropyridinium triflate
NFPCPT	*N*-Fluoropentachloropyridinium triflate
NFSI	*N*-Fluorobenzenesulfonimide
NMR	Nuclear Magnetic Resonance

Ns	*para*-Nitrobenzenesulfonyl
Nu	Nucleophile
PDC	Pyridinium dichromate
Pr	Propyl
PTSA	*para*-Toluenesulfonic acid
R	Alkyl
r.t.	Room temperature
SCE	Standard Calomel Electrode
TBME	*tert*-Butyl methyl ether
TCA	Trichloroacetic acid
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
V	Volt(s)

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“Fluorine leaves nobody indifferent; it inflames emotions be that affections or aversions. As a substituent, it is rarely boring, always good for a surprise, but often completely unpredictable.”

M. Schlosser, *Angew. Chem. Int. Ed.* **1998**, *110*, 1496

“If a man were to have the features of fluorine, he would be small, greedy and violent, and would therefore be either ostracised by society or governing it.”

T. Hayashi, V.A. Soloshonok, *Tetrahedron Asymmetry*, **1994**, *5 (6)*, xiii

Chapter 1:

Introduction to Fluorocyclization Reactions

1. Introduction to Fluorocyclization Reactions

1.1 Fluorine in organic molecules

Very few naturally occurring organic molecules contain fluorine, despite it being the 13th most abundant element in the earth's crust.[1] However, despite its absence in the majority of living organisms, the advantageous characteristics of fluorinated organic molecules have led to a growing interest in these compounds in pharmaceutical[2] and agricultural[3] chemistry. For example, the substitution of hydrogen by fluorine (Van der Waals radii of 1.20 Å and 1.47 Å respectively)[4] is a tactic often used in drug design, due to the documented increased resistance of the fluorinated analogue to *in vivo* metabolic transformations. Furthermore, as a consequence of the small size, the C-F bond also has a similar van der Waals radii as C=O or C-O groups[3] which, together with the strongly polarised nature of the C-F bond, can be used to alter the steric and electronic properties of molecules and change the physicochemical properties of neighbouring groups.

1.2 Fluorinating Reagents

Since very few naturally occurring fluorinated organic compounds exist, building blocks must be accessed by synthetic routes. The simplest fluorine source that could be imagined is elemental fluorine (F_2) itself, however it is typically difficult to handle as a reagent due to its incredibly reactive nature. Unlike the other halogens, where even chlorine can be handled with reasonable ease in a standard laboratory setting, fluorine cannot and requires specialized handling techniques and equipment. Whilst F_2 can certainly be used directly, with many notable examples[4] its hazardous nature restricts its use to only a few research centres, therefore limiting its applicability in general mainstream organofluorine chemistry.

Instead, fluorine is normally introduced using a fluorinating reagent, which allows for the much safer handling and tamed reactivity in the same way that bromine and especially chlorine are most usually delivered. In general, fluorinating reagents can be divided into two main classes, nucleophilic and electrophilic sources. Due to its high electronegativity (4.0 on the Pauling scale),[5] fluorine would be intuitively thought of as a nucleophilic species, however due to major advancements in the field of electrophilic fluorination over the past few decades this does not necessarily have to be the case.

1.2.1 Nucleophilic Reagents

Despite the perceived simplicity of fluoride species, the use of such reagents is not always straightforward due to problems such as solubility in organic solvents, hygroscopy, and the competing basic nature of fluoride.[6] Whilst the most atom economical source of fluorine is perhaps hydrogen fluoride, its highly toxic and corrosive properties, as well as its sometimes low reactivity resulting from relatively high bond energy can prohibit its use.[7] Over the years numerous reagents have been developed as either tamed sources (Amine•HF complexes)[8] or latent sources (DAST type reagents)[9] of hydrogen fluoride. These reagents are very important as they circumvent the need for aqueous, or worse, gaseous hydrogen fluorine. Another common class of fluoride reagents are metal fluorides, whose properties can be tuned to some extent by changing the metal cation. Generally fluoride salts are poorly soluble in common organic solvents, although the solubility can be somewhat improved by changing the cation to a larger alkali metal ion such as potassium or cesium. The major problem associated with such reagents is that they are highly hygroscopic and as such can be troublesome to handle if anhydrous conditions are required. The final common class of nucleophilic reagents are the tetraalkylammonium fluoride salts. Whilst they benefit from much better solubility than their metal counterparts, there are often problems with

competitive function as a base. Also, due to their hygroscopy their reactivity is often greatly diminished as a result of the complex hydrogen bond network formed with residual water. In fact, research into less hygroscopic tetrabutylammonium fluoride salts is the subject of ongoing work within the group.[10] A summary of the common commercially available nucleophilic reagents is described in Figure 1 below.

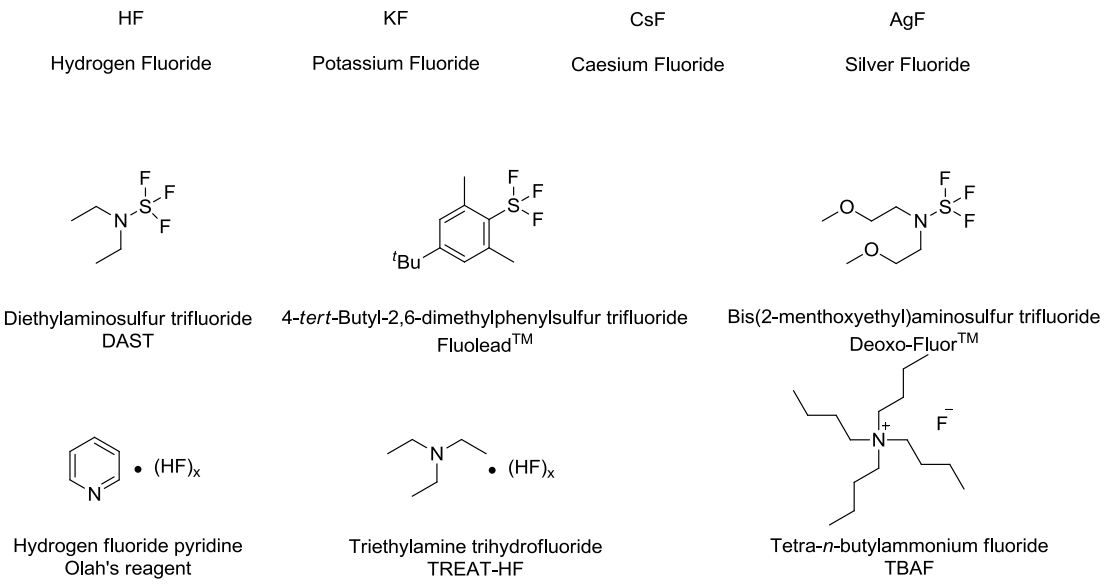


Figure 1 – Common nucleophilic fluorinating reagents

1.2.2 Electrophilic reagents

The simplest and most reactive source of electrophilic fluorine is elemental fluorine itself, F_2. The fluorine atom is small and therefore the bond in F_2 would be expected to be short and therefore strong. However, fluorine is so small that there is a large repulsion experienced between the lone pairs on the two fluorine atoms, thus weakening the bond and creating a highly reactive species. Coupled with the relatively high bond enthalpy formed with many other elements, such as hydrogen, carbon and silicon these effects allow elemental fluorine to react with almost any material, with potentially explosive consequences.[11,12] The solution

to the sometimes undesirable high reactivity is to tame the fluorine as a less reactive electrophilic reagent. Over the past 50 years countless reagents have been prepared with the goal of creating selective, easy to handle reagents. The first example, fluoroxytrifluoromethane (CF_3OF), was reported by Barton and co-workers in the late sixties.[13] Further examples followed, which included perchloryl fluoride ($FClO_3$),[14] xenon fluoride (XeF_2),[15] nitrogen oxide fluorides,[16] caesium fluorooxysulfate ($CsSO_4F$)[17] and several other hypofluorides (Figure 2).[18]

However, all these reagents suffered from being only scarcely less reactive than fluorine itself and did not improve the handling issue since many are explosive liquids and required fresh preparation using gaseous fluorine anyway. Therefore, it was not until the development of N-F type reagents that the field of electrophilic fluorine chemistry really began to develop. These reagents, which can be sub-categorised into neutral (R_2N-F) or charged ([R_3N-F^+]) classes, are far more stable and easy to handle and usually exhibit much lower reactivity than the parent fluorine gas. Since most are bench stable solids and can be generally prepared from the parent amine (R_2N-H or R_3N) using elemental fluorine many are now commercially available, which is necessary for their use to become widespread. Another great advantage of N-F type reagents is the ability to tune the reactivity by altering the electronics of the nitrogen component. A selection of commonly used reagents is outlined in Figure 2.

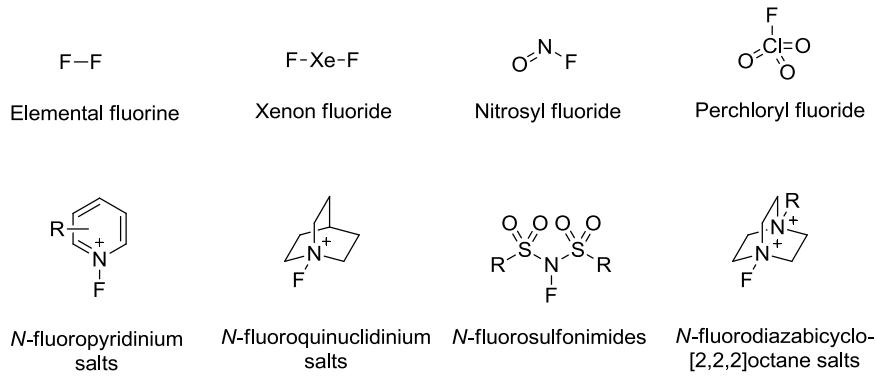


Figure 2 - Common electrophilic fluorinating reagents

N-fluoropyridinium salts were introduced by Umemoto *et al.* as an alternative to the early undesirable reagents.[19] These easily handled crystalline solids have found a pivotal role in electrophilic fluorination methods as pyridine rings offer an excellent opportunity for reagent tuning due to the huge range of commercially available pyridines. Another class of fluorinating reagents is based on the sulfonamide motif with the first example being prepared by Barnette in 1984 using dilute fluorine.[20] Other examples such as *N*-fluorobenzenesulfonamide (NFSI)[21] and *N*-fluorobis[(trifluoromethyl)sulfonyl] imide (DesMarteau's reagent)[22] followed later, which have proved to be another important class of reagents. Perhaps the most important advance in the field was made by Eric Banks and co-workers in collaboration with Air Products, with the development of the reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor or F-TEDA-BF_4).[23] Over the past two decades it has established itself as a reactive, non-hygroscopic, air stable crystalline solid. Furthermore, the reactivity can be tuned by altering the quaternizing group on the DABCO core, with the order of reactivity increasing with increasing electron withdrawing power: methyl < chloromethyl < 2,2,2-trifluoroethyl.[24]

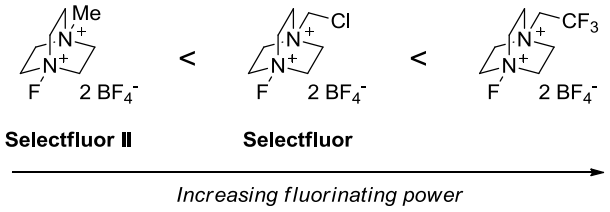


Figure 3 – Tuning the fluorinating power of Selectfluor type reagents

1.2.3 Reactivity of electrophilic fluorinating reagents

The reactivity of common electrophilic fluorinating reagents has been profiled by many different direct and indirect methods in the literature. Thus, there are many ways in which the reactivity may be assessed, each with their own merits and limitations.

1.2.3.1 Electrochemical methods

A qualitative understanding of the reactivity of such reagents is often gained by the study of the electrochemical potentials. One such study was reported by Gilicinski et al. in 1992.[25] They reasoned that whatever the precise mechanism of electrophilic fluorination, there is essentially a reduction of the fluorinating reagent. Therefore, the reactivity of the reagents with a specific nucleophile may correlate with the redox potentials, with the most oxidizing reagent having the greatest fluorinating power. They found the following data, which is presented in Table 1.

Entry	Reagent	$E_{p,\ reduction}$ in acetonitrile (V vs SCE)
1	*N*-fluoro-bis[trifluoromethylsulfonyl]imide (DesMarteau reagent)	+0.18
2	**1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor™)**	**-0.04**
3	1-Fluoro-4-methyl-1,4-diazonibicyclo[2.2.2]octane bistriflate (Selectfluor II™)	-0.09
4	*N*-fluoropyridinium pyridine heptafluorodiborate	-0.34
5	*N*-fluoroquinuclidinium triflate	-0.37
6	***N*-fluoropyridinium triflate**	**-0.47**
7	*N*-fluorocollidine triflate	-0.73
8	***N*-fluoro-benzenesulfonimide (NFSI)**	**-0.78**
9	*N*-methyl-*N*-fluoro-*p*-toluenesulfonamide	-2.10
10	*N*-propyl-*N*-fluoro-*p*-toluenesulfonamide	-2.20

Table 1 – Peak reduction potentials of selected electrophilic fluorinating reagents

The order of the peak reduction potentials indeed mirrored the order of observed chemical reactivity. For example, the DesMarteau regent (entry 1) is capable of fluorinating benzene at room temperature (50 % conversion in 18 hours) and correspondingly has the highest reduction potential of +0.18 V. Selectfluor is less reactive and fluorination of benzene is not observed. However, anisole readily fluorinates to form the corresponding *2*- and *4*-regioisomers to achieve a 72 % conversion at 40 °C in 6 hours. The corresponding Selectfluor II analogue is slightly less reactive, taking 13 hours to achieve the same level of fluorination. As can be seen from the electrochemical data, Selectfluor would be predicted to be slightly more reactive than Selectfluor II (entry 2 vs entry 3). *N*-fluoropyridinium triflate (entry 6) reacts under more forcing conditions to give a 72 % conversion at 120 °C after 18 hours. Finally, the Barnette reagents (entries 9 and 10) will only react with aromatic carbanions as predicted by their very low peak reduction potentials.

Whilst the data offers useful qualitative information about the reagents investigated, the absolute values of the reduction potentials are curious. Electrophilic fluorinating reagents are well-known to oxidise iodide to iodine to form a fluoride ion in the process, in fact this is a good way of quenching N-F reagents. For example, Selectfluor will oxidise iodide and bromide to the elements as determined by standard titration vs thiosulfate. However, the *E*° value for aqueous bromide oxidation is +0.846 V verses the standard calomel electrode and therefore it is clear that Selectfluor is a much stronger oxidizing agent than is indicated by the non-aqueous electrochemical E_p value of -0.04 V verses the standard calomel electrode.

The electrochemical reduction potentials of a variety of sulphonamide based reagents were studied by Differding.[26] The relatively small (large and negative) E_p values correlates with the experimentally determined low reactivity of the reagents mentioned. As was found previously by Gilicinski, the electron-withdrawing nature of the nitrogen substituent's was

found to influence the reduction potential of the N-F reagent, with the most destabilized sulfonamides having the greatest propensity towards reduction.

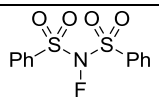
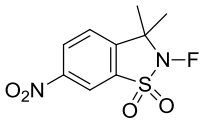
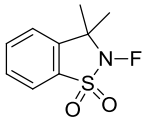
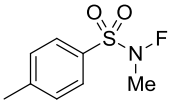
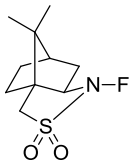
Entry	Reagent	$E_{p,\ reduction}$ in acetonitrile (V vs SCE)
1		**-0.54**
2		-0.79
3		-1.21
4		-1.44
5		-1.58

Table 2 - Peak reduction potentials of selected electrophilic fluorinating reagents

Some years later, Fainzil'berg and co-workers, performed a similar study, albeit on fewer reagents, but using a rotating disk electrode rather than the stationary electrode used in prior reports.[27] Their data fitted the same trend but this time showed Selectfluor to have a higher electrode potential than in Gilicinski's report. The value is still considerably less than for the oxidation of bromide, and this is presumably due to the non-aqueous environment. Interestingly, whilst the value of Selectfluor was shown to be greater than that predicted by Gilicinski, the value for NFSI was considerably smaller.

Entry	Reagent	$E_{p,\ reduction}$ in acetonitrile (V vs SCE)
1	**1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor™)**	**+0.33**
2	1-Fluoro-4-hydroxy-1,4-diazonibicyclo[2.2.2]octane bistetrafluoroborate (Accufluor™)	+0.32
3	***N*-fluoro-benzenesulfonimide (NFSI)**	**-1.24**

Table 3 - Peak reduction potentials of selected electrophilic fluorinating reagents

One of the most exhaustive electrochemical studies undertaken, however, was that by Dennis Evans in 1999.[28] He performed numerous cyclic voltammetry experiments to shed light on the mechanism by which electrophilic fluorinating reagents react. Cyclic voltammetry (CV) is a very powerful technique at not just determining the reduction potential of a substance but also the nature of the species in solution and even their concentrations. CV works by sweeping across a voltage (potential) range and measuring the current of the electrochemical cell. For a reversible reaction, the E° value is obtained by finding the maxima in the forward reduction step. The species present can be identified by comparing where the maxima fall and their concentrations can be calculated by the intensity of the peak. For conditions that include an electrode product that is stable on the time scale of the potential scan, the presence of a return peak in cyclic voltammetry allows us to now determine the formal potential for a redox couple, E°, by averaging the two peak potentials, according to Equation 1.

$$E^{o'} = \frac{E_{p,f} + E_{p,r}}{2}$$

Equation 1 – Calculation of $E^{o'}$ from the peak reduction/oxidation potentials

Where $E_{p,f}$ and $E_{p,r}$ represent the forward and reverse peak reduction potentials, respectively. The measured E°' value is characteristic to a redox species in the same way that a wavelength at maximum absorbance would be characteristic of a species in spectroscopic techniques. From the calculated reduction potential, the standard reduction can be calculated using the Nernst equation according to Equation 2.

$$E = E^{o'} - \frac{RT}{nF} \ln Q$$

Equation 2 – Nernst equation

In Evans' publication, he demonstrated that it was not possible to measure the reverse peak potential due to an irreversible reduction of the N-F bond. This is perhaps not too surprising since the energy price of oxidising fluoride to F^+ is enormous. Therefore, thermodynamic E° values could not be obtained. However, the work nicely showed that the more reactive fluorinating reagents had a higher reduction potential. The cyclic voltammograms obtained from three of the reagents investigated are illustrated in the figure below.

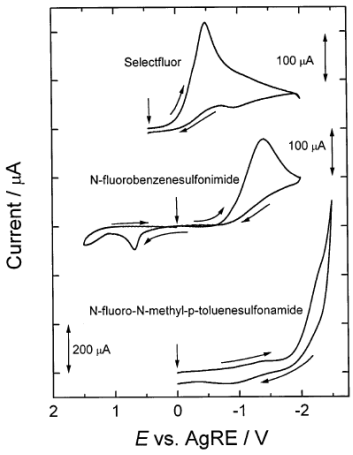


Figure 4 – Cyclic voltammograms of Selectfluor, NFSI and *N*-fluoro-*N*-methyl-*p*-toluenesulfonamide

As can be seen from Figure 4, as we go from the more reactive Selectfluor to the less reactive *N*-fluoro-*N*-methyl-*p*-toluenesulfonamide the peak reduction potential shifts to a more negative value (i.e. a worse oxidant) as we would expect. The cyclic voltammograms were recorded with scan rates ranging from 5 to 10 000 Vs^{-1} for all compounds and no intermediates were observed on the reverse scan. These results predict that the reduction occurs by dissociative electron transfer (N-F bond breaking is concerted with the electron transfer) or that the single electron transfer product (a radical or radical anion) undergoes rapid irreversible decomposition reactions (i.e. faster than the scan rate). The number of electrons transferred was found to be close to 1 for all reagents studied as outlined in Table 4.

Entry	Reagent	$E_{p,f}$/V vs AgRE	n
1	2,6-dichloro-1-fluoropyridinium tetrafluoroborate	-0.260	0.97
2	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor™)	-0.296	0.79
3	*N*-fluoropyridinium tetrafluoroborate	-0.814	1.39
4	*N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	-1.068	1.13
5	*N*-fluoro-benzenesulfonimide (NFSI)	-1.441	0.89
6	*N*-methyl-*N*-fluoro-*p*-toluenesulfonamide	< -2.2	

Table 4 – Peak potential voltages of 6 N-F reagents with the calculated n values

In conclusion, the standard reduction potentials (or peak reduction potentials where appropriate) are very useful as a guide to the reactivity of an N-F reagent. The absolute values given by voltammetry experiments are clearly not comparable to literature values taken in aqueous solution but the relative values offer a quantitative way of assigning an order of reactivity. The E° value cannot, in general, be calculated as the reverse peak reduction potential cannot be measured; a direct consequence of the reduction of F^+ being

irreversible. Therefore, an average of the peak reduction potentials (forward and reverse) cannot be calculated and so the midpoint (E°) cannot be known. The peak reduction potentials will be different to the E° value due to the overpotential (an overpotential is the difference between a half-reaction's thermodynamically determined potential and that which is experimentally observed). This overpotential is essentially the cell's efficiency and hence imperfections lead to heat loss, which causes a greater amount of potential being required than thermodynamics would predict. The consequence is that the cathode (the N-F reagent) is more negative and uses more energy than thermodynamics requires. However, the main problem with comparing a measured peak potential with literature E° values is that reduction potential measurements of N-F reagents typically have to be done in acetonitrile for solubility reasons. Standard reduction potentials are given for aqueous media, so we should not expect a direct comparison to be possible. This accounts for the apparent discrepancy on the values given for Selectfluor, where it is suggested that it is not sufficiently oxidising to oxidise bromide.

1.2.3.2 ^{19}F NMR Techniques and pKa

An alternative approach to electrochemical ordering of a series of electrophilic fluorinating reagents into their relative reactivity's is to consider the electronic environment around the N-F bond. Umemoto and co-workers considered determining the ^{19}F NMR chemical shift of a series of *N*-fluoro-pyridinium salts in an attempt to find a correlation with reactivity.[29] They reasoned that an electron poor environment, which experimentally corresponds to increased reactivity, should cause a downshift in the NMR to give a more positive chemical shift. However, another feasible way of considering the electronic environment is to look at the pKa values for the corresponding pyridines. In the same way that an electron poor pyridine would be expected to be a strong fluorinating reagent, we would also expect it to

be a strong acid/weak base. Drawing on the findings of Umemoto, an ordering of pyridinium type reagents can be established using these two complementary methods and is illustrated in the figure below.

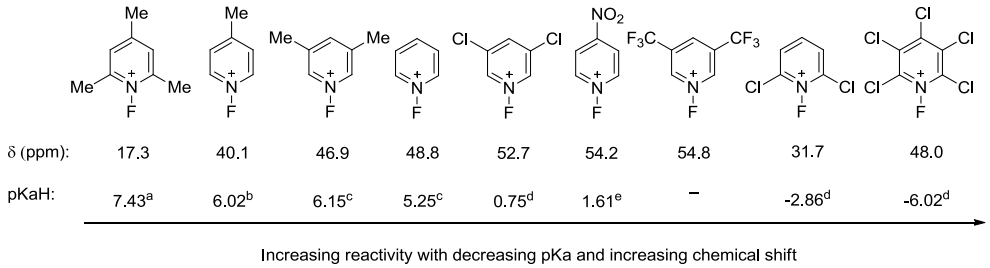
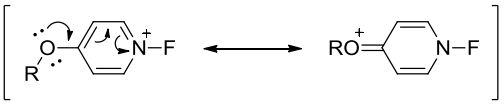


Figure 5 - Ordering of *meta*- and *para*- substituted N-fluoro-pyridinium reagents according to ^{19}F chemical shift; a) Ref 30, b) Ref 31, c) Ref 32, d) Ref 33, e) Ref 34

The first important conclusion the authors drew was that the counterion effectively made no difference to the chemical shift of the reagent and that therefore they exist in a one-coordinate form and are thus completely ionic. Secondly, there is a general trend of increasing chemical shift with increasing fluorinating power but with several apparent anomalies. The trend holds well apart from those reagents which have *ortho*-substitution. For example, the reagents derived from 2,6-dichloropyridine and pentachloropyridine display a chemical shift which would suggest a less powerful reagent than pyridine itself. Clearly, this is not the case and leads to the conclusion that for *ortho*-substituents the through space effect on the chemical shift completely suppresses the electronic effects caused by the nature of the ring. Interestingly, the report further concluded that alkyl substituents did follow the general trend in line with substitution at *meta*- and *para*-positions.

Another source of anomalous results arises from strongly electron releasing groups at the 4-position. The effect of this substitution pattern is to cause a significant upfield shift in the ^{19}F

NMR, more than would be expected by considering the observed reactivity or the pKa of the relevant pyridine. The deviation from the trend can be readily explained for these compounds by considering the difference between an *N*-protonated pyridinium species and an *N*-fluoropyridinium species. In the case of the *N*-fluoro compound, we would expect a much larger resonance contribution from the electron-releasing group at the *para* position due to the high electronegativity of fluorine on the nitrogen atom. Consequently, the nitrogen is much more stabilised than pKa values would suggest and hence the deviation from the trend.



Scheme 1 - *N*-fluoro quinonoid resonance stabilization

However, in general where the chemical shift value proves to be unreliable it is possible to use the pKa value to order the reactivity. In the series of reagents above the highly reactive chlorinated examples have an anomalous chemical shift due to the consequence of *ortho* substitution but their respective pKa values are representative of their high reactivity. Misleading information can, however, also come from the pka values, when steric effects are significant. For example, 2,6-di-*tert*-butylpyridine has a abnormally low pKa value, which is attributed to the favourable release of steric clashing upon dissociation of the acid in a dynamic protonation/deprotonation system. However, dissociation of an N-F bond does not occur in the same way and so we should expect the fluorine to experience a similar chemical shift to that of the corresponding dimethyl compound. Indeed, this was the case with the 2,6-di-*tert*-butylpyridinium reagent which was found to have a chemical shift of +23.1 ppm, compared to the +24.8 ppm shift of 2,6-lutidine. This evidence showed that pyridines

substituted with alkyl groups at the *ortho* position followed the general trend, but other substitution was not supported. In conclusion, ordering of reagents on electronic terms using the chemical shift of the fluorine and the pKa of the corresponding acid can be a very useful method for pyridinium type salts. Indeed the two properties are complementary and should be considered in combination.

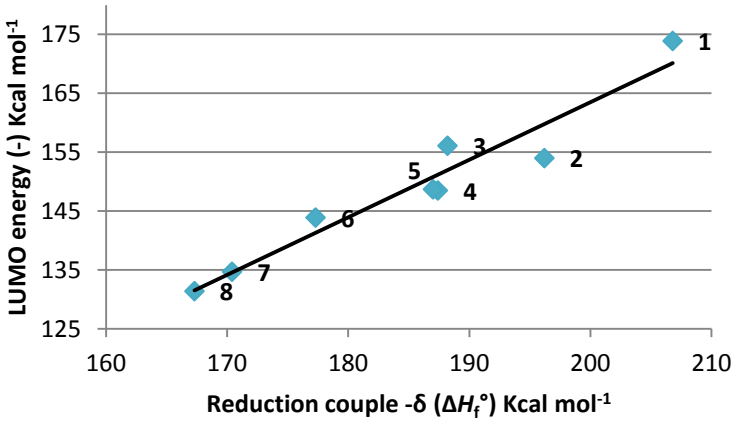
1.2.3.3 Cation LUMO Energy

In a related approach to that taken by Umemoto using chemical shift and pKa values, Sudlow and Woolf instead considered directly the molecular orbitals of the cation to assess the electronic environment of N-F bond.[35] They argued that ordering of a group of reagents according to electrochemical measurements was not a satisfactory method due to the uncertainties in their values, arising from the irreversible reduction of the "F^+" species and the overpotentials obtained on different electrode surfaces. These discrepancies indicate a possible reaction between the electrolyte and the radical formed upon reduction within the voltage scan timescale. The result is to lower the peak reduction potentials below the thermodynamic E° values, which is often worryingly ignored, being justified as consistent lowering of peak reduction potentials. Woolf also makes the point that electrochemical data pertaining to a diverse set of reagents should be treated with caution since neutral, monocationic and dicationic species will vastly affect solvation energies and will change E_p values, just as changing the solvent would. Therefore, using an electrochemical approach should generally be reserved for reagents of similar structure and should ideally be compared in the same solvent unless the E_p values are largely separated.

Using enthalpies of formation of the pyridine and the oxidised *N*-fluoro-pyridinium to obtain a reduction couple ($\delta\Delta H_f°$) and a calculated LUMO energy of the pyridinium species a correlation was drawn to link to two. Similar compounds were found to fit this trend very

precisely to produce an graphical ordering of the reagents, with low LUMO energies and more negative reduction couples corresponding to high fluorinating power. As can be seen from the chart below, the reagents fit a linear trend starting from the mildly reactive *N*-fluoro-collidine and culminating in the highly reactive *N*-fluoro-pentafluoropyridine reagent.

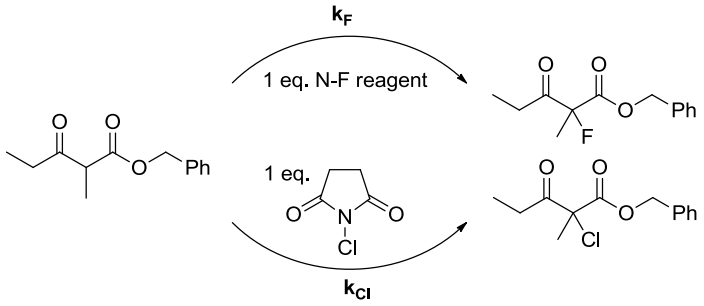
Pyridine	R_3N $\Delta H_f°$ Kcal mol^{-1}	$R_3N\text{-}F^+$ $\Delta H_f°$ Kcal mol^{-1}	Reduction couple -δ ($\Delta H_f°$) Kcal mol^{-1}	- LUMO energy of $R_3N\text{-}F^+$
1 Pentafluoropyridine	-170.5	36.3	206.8	173.9
2 Pentachloropyridine	8.7	204.9	196.2	154.0
3 2,6-difluoropyridine	-48.2	140.0	188.2	156.1
4 2,6-dichloropyridine	21.3	208.7	187.4	148.5
5 3,5-dichloropyridine	18.9	205.9	187.0	148.7
6 Pyridine	31.9	209.2	177.3	143.9
7 2,6-dimethylpyridine	19.4	189.8	170.4	134.7
8 2,4,6-collidine	11.5	178.8	167.3	131.4



1.2.3.4 Competitive halogenation

An experimental method of measuring the chemical reactivity of various N-F reagents was proposed by Togni and co-workers.[36] They used a competition reaction between

electrophilic fluorinating reagents and *N*-chlorosuccinimide to determine the relativity of a range of reagents. A β-ketoester with a chiral Lewis acid catalyst was chosen as the model reaction.



Scheme 2 - Competition reaction between N-F reagents and *N*-chlorosuccinimide

The halogenation reactions were performed in the presence of 1 equivalent *N*-chlorosuccinimide and 1 equivalent of electrophilic fluorinating reagent. After full consumption of the starting β-ketoester, the amounts of fluorinated and chlorinated product were determined by HPLC. They reasoned that the rate of the chlorination reaction (k_{Cl}) should be independent of the fluorination reaction (k_F) and so the molar ratio of the two products is a relative measure of the rate of fluorination with a specific N-F reagent, as described by the equation below.

$$k_{rel} = \frac{k_F}{k_{Cl}} = \frac{n_F}{n_{Cl}}$$

Equation 3 – Relative rate of reaction for fluorinating reagents is proportional to molar ratio of two products

Where the rate constants $k_{F/Cl}$ represents the rates of fluorination/chlorination, and the parameters $n_{F/Cl}$ are the molar amounts of fluorination/chlorination products formed. The results of the competition reactions are displayed in Table 5. In preliminary control reactions

the authors showed that the electrophilic fluorinating reagents did not react with NCS under the reaction conditions.

Fluorinating agent	Yield of fluorinated product (%)	Yield of chlorinated product (%)	k_{rel}	
Selectfluor	73	27	2.72	**Increasing reactivity**
Accufluor	65	35	1.84	
2,6-dichloro-1-fluoropyridinium tetrafluoroborate	13	87	0.15	
Synfluor	6	94	0.06	
NFSI	4	96	0.04	
N-fluoro-perfluoropiperidine	3	97	0.03	

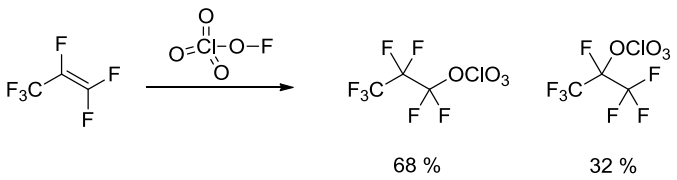
Table 5 – Results of competitive halogenations of model β-ketoester

1.2.4 Concept of electrophilic fluorine

Based on our fundamental knowledge of chemistry, we would argue that fluorine, being the most electronegative element in the periodic table, should inherently be the most negative, or at least the most δ-negative, component of any interaction between two species. Indeed, by using the term 'electrophilic fluorine' we are suggesting that the group to which fluorine is delivered must have a greater propensity to gain electrons, which intuitively would seem to be wrong. Cartwright and Woolf[37] argue that it is our fundamental understanding of electronegativity, and its misuse thereof, that it is misguided and not the reality of 'positive fluorine.' They crucially point out that electronegativity theories are derived from atomic or molecular properties of very simple molecules such as diatomic hydrogen fluoride and thus cannot be used to predict the effect of fluorine being bound to a larger, more complicated, system. For example, when fluorine can engage with back-bonding into a delocalized system it is found that these mesomeric interactions actually dominate the powerful inductive effect that fluorine has. Evidence of this counter-intuitive effect can be observed in many

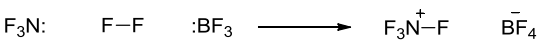
cases and is exemplified by the increase in Lewis acidity of the boron trihalides from BF_3 to BI_3. It is also interesting to note that at low temperatures and dilutions, it has been demonstrated that molecular fluorine behaves similarly to other dihalogens, with the molecular polarization necessary for electrophilic substitution of an aromatic ring being enhanced by addition of a Lewis acid to aid with the removal of a fluoride ion. The authors also draw attention to the observation of CF_3O-F undergoing fluorination reactions, even though fluorine is formally more electronegative than the trifluoromethoxy group.

In response to this report, Christie[38] criticised the support for 'positive fluorine' offered by Cartwright and Woolf. By utilizing the reaction of perfluoropropene with hypofluorous perchloric anhydride he deduced that the product outcome suggests that the O-F bond is not strongly polarized and that the observed regioselectivity is likely to be a consequence of steric factors and not electronic. The author speculated that it was the larger steric bulk of the trifluoromethyl group on the olefin that encouraged the perchlorate group to go in the terminal position. Similar results were observed upon the addition of trifluoromethyl hypofluorite to olefins. In a reasonably compelling conclusion, Christie concludes that it is only logical to expect fluorine, as the most electronegative element, to be the most electronegative group, with all other groups bearing increasing numbers of fluorine atoms asymptotically reaching the electronegativity of the fluorine atom. Put another way, he argues, the addition of fluorine to another atom of lower electronegativity cannot result in the formation of a group that has a higher electronegativity than fluorine.



Scheme 3 - Fluorination using hypofluorous perchloryl anhydride

In their retort,[39] Cartwright and Woolf highlighted that the counter-argument of Christie demonstrated exactly their point that fluorine chemists were reluctant to accept the concept of 'positive fluorine'. The authors explain that the formal positive charge on fluorine, following heterolysis of an F-F bond, can be stabilized using the formation of a tetrafluoroammonium salt. Using a relatively strong Lewis acid, to promote heterolysis and loss of fluoride, and a weak Lewis base (a strong Lewis base would simply interact with the Lewis acid) an electron deficient fluorine atom can be obtained. Indeed if half of the fluorine becomes fluoride, then by a charge-balance argument, the other half must be 'positive fluorine.'



Equation 4 - Fluorination of trifluoroamine

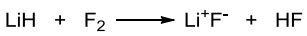
In response to the argument that fluorine, being the most electronegative element, can never show a positive polarity when combined with another group, the authors reiterated that several anomalous observations led to the conclusion that electronegativity arguments must be used with a degree of care. They also elude to the fact that the picture may not be so clear, since perchloryl fluoride can exhibit both electrophilic fluorine and electrophilic ClO_3. For example, perchloryl fluoride will substitute benzene with a ClO_3 group under Friedel-Craft conditions but 3,5-dimethoxyphenol in pyridine will fluorinate to give both 2- and 4-fluoro derivatives. Somewhat diplomatically, the authors conclude by suggesting that the differences between Christie's views and their own were possibly semantic. For example, Christie had recognized NF_4^+ as an electrophilic fluorinating reagent but not as a stabilized 'positive fluorine.' Cartwright and Woolf would identify this as a stabilized 'positive fluorine' but would still agree that "F^+" would have an enormous affinity for an electron,

exceeding that of even a proton. Thus a bare "F^+" would no more exist under ordinary conditions than would a bare proton. By convention we talk about proton sources as a source of "H^+", but we really mean stabilized 'positive hydrogen' on a Lewis base. The strength of the proton source correlates with the nucleophilicity of the stabilizing group, the lower the nucleophilicity, the greater the reactivity of the proton source (stronger acid). The same can be said of electrophilic fluorine sources, with a weak Lewis base stabilizing agent providing a highly reactive source of 'positive fluorine'.

However, in a final exchange Christie[40] further criticized the work of Cartwright and Woolf by suggesting that their interpretation of a poorly studied and complex organic reaction was speculative and deserved little merit. He instead offered an alternative model as to what 'positive fluorine' is. The model is based on the temporary formation of an induced dipole, which results from the transfer of electron density in a covalent X-F bond away from F and towards X. This forms a momentary "δ+" charge, which is the basis for the observed 'positive fluorine'. For example, in X-F when X = F (i.e. F_2) then there cannot be a permanent dipole but only an induced dipole, whereas when X is heteronuclear there can be both sorts of dipole present. The author is careful to note that this theory cannot be measured experimentally as factors such as lone valence electron pair effects would give the illusion of a different picture. Without tangible evidence for the existence of a permanent dipole, it would seem difficult to make a convincing argument for the presence of a permanent δ+ fluorine.

The principle of electronegativity states that when atoms come together to form a compound, their electronegativities are adjusted to an average intermediate value within the compound. That means that the more electronegative atoms attract a greater amount of negative charge and the less electronegative gain a positive charge to result in the formation of δ- and δ+ atoms respectively. Since fluorine is unquestionably the most electronegative of

all the elements, any X-F bond will always be polarized in the direction of a δ- fluorine atom and δ+ X species. Heavy criticism of the tetrafluoroammonium example in Cartwright and Woolf's paper was made as Christie points out that it is not the polarization of the N-F bond that leads to an electrophilic fluorination by a 'positive fluorine' but rather the consequence of coordinative saturation around nitrogen, leading to reaction through fluorine as the only option. In a disdainful riposte to the argument of the existence of "F^+" by a charge balance argument, Christie uses the example of the reaction of lithium hydride with molecular fluorine. The somewhat compelling rebuff of an over-simplistic argument detailed how an extension of this concept would require the fluorine in the HF formed in the following reaction to be positive. Clearly this could never be the case.



Equation 5 – Reaction between lithium hydride and F_2

Whilst there is clearly significant debate in the literature about what 'positive fluorine' is and how it is defined, the authors are all agreed that however the X-F bond behaves prior to the bond breaking it does, in fact, break to give the product of an electrophilic fluorination.

1.2.5 Mechanisms of electrophilic fluorination

Essentially for an electrophilic fluorination reaction using an N-F^+ reagent there are three possible mechanisms that should be considered. There is the generally pictured mechanism of electrophilic fluorination by an S_N2 type displacement of fluorine, a free radical mechanism or a single electron transfer pathway. A study of the literature revealed that

there is considerable evidence both in support and in opposition of the three mechanisms mentioned.

Desmarteau as long ago as 1983 eluded to the possibility of electrophilic fluorinating reagents following an electron transfer mechanism and not a classical electrophilic addition mechanism.[41] He argued that if the mechanism for the fluorination of olefins was indeed electrophilic addition then certain predictions or assumptions would be found to be true. For example, it would be expected that electron donating groups on the olefin would accelerate the reaction and vice versa. Also unsymmetrical olefins would be expected to exhibit some regioselectivity, with the fluorine atom adding in accordance with Markovnikov's rule. However, it was found when using trifluoromethyl hypofluorite that the reagent is extremely reactive with all olefins investigated; even $CF_3CF=CF_2$ is rapidly fluorinated at low temperature. On the other hand the analogous chlorine reagent exhibits very high reactivity towards propene and butene but requires much higher temperatures to chlorinate deactivated olefins such as $CF_3CF=CF_2$. Qualitatively, these results supported an electrophilic addition mechanism for trifluoromethyl hypochlorite but not for trifluoromethyl hypofluorite. When regioselectivity was considered it was found the chlorinating reagent, again, gave very good regioselectivity with a clear preference for the Markovnikov product. However, although some regioselectivity was observed with the hypofluorite in two cases, the products were furnished with anti-Markovnikov selectivity. This again supports the electron transfer mechanism but does also hint at there being another mechanism that is playing a role; one that allows some degree of regioselectivity. They concluded that their findings offered very little evidence for the existence of electrophilic fluorine in trifluoromethyl hypofluorite and that a free-radical mechanism offers the best explanation. It was also suggested that a different mechanism was likely to be operating in every case.

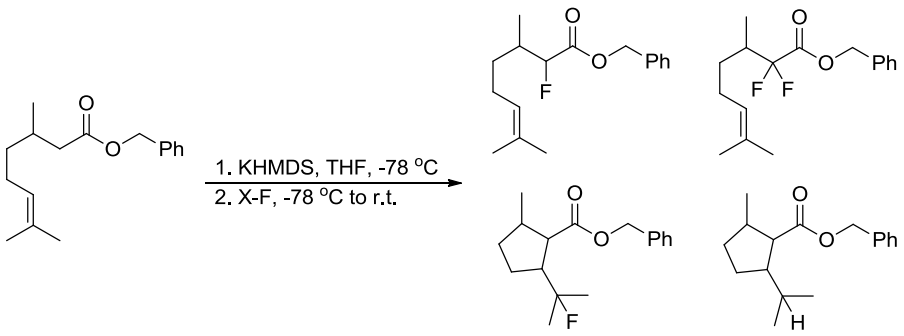
Umemoto, in 1990, provided considerable experimental evidence to support an electron transfer mechanism when studying various *N*-fluoropyridinium salts.[42] He reasoned that it is surprising that *N*-fluoropyridinium salts appear to be a source of positive fluorine when the extremely high ionisation potential of fluorine is considered along with the highly electron deficient pyridine ring. Their investigations showed that all the findings could be rationalised by a SET mechanism, involving an electron transfer from the nucleophile to the N-F^+ reagent to form a *N*-fluoropyridinium moiety and the subsequent homolytic fission of the N-F bond. Evidence for this proposal came from reactions with organometallic reagents, in the form of organolithiums and Grignard reagents. Reaction with the Grignard reagents afforded the corresponding fluorinated products, whilst reaction with the organolithiums did not. It was suggested that this could be due to the fact that Grignard reactions are known to involve a one-electron transfer mechanism.

Further support was reported in 1992 by DesMarteau and co-workers who were investigating the fluorination of a variety of olefin substrates using the DesMarteau reagent.[43] They found that the choice of solvent was very important and that polar solvents such as acetic acid were favoured because they accelerated the reaction by favouring charge separation and ion pair formation, the step that often precedes an electron transfer. Addition of an electron transfer quencher, namely *p*-dinitrobenzene, retarded the reaction and led to a poorer conversion than without the additive. Finally, 1,4-benzoquinone was added to the reaction which led to only 48 % of the desired product being recovered. It was found that benzoquinone combined with the radical anion of the reagent to give charred products. All these findings, and more, can be readily explained by an electron transfer pathway.

More recently evidence was provided by Guo in 2005 by using mass spectrometry techniques to identify reaction intermediates in fluorinations of olefins using Selectfluor.[44]

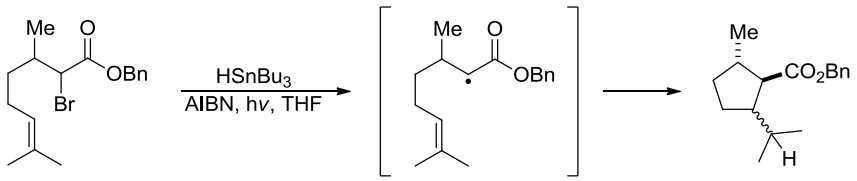
Based on the evidence that TEMPO, which is oxidised by suitable oxidants (Cl_2, Br_2 etc…) by liberation of a single electron, reacted readily with Selectfluor meant the possibility of a single electron transfer mechanism being possible seemed likely. Further support in the form of theoretical calculations and X-ray crystallographic analysis revealed that the fluorine centre had more radical than 'fluoronium' character. The authors wished to reinforce these findings by using ESI-MS to detect reaction intermediates that indicated a reaction pathway involving a radical mechanism. On the system they had chosen the results very convincingly demonstrated that the SET pathway was correct by the detection and characterization of key radical cation intermediates.

However, in a contrast to these reports, a two-part report by Differding in 1991 argued that the mechanism is, in fact, an electrophilic addition of fluorine.[45,46] In the first instance, they took a carbanion substrate that would be susceptible to cyclization, should the radical pathway be operating. However, with all fluorinating reagents tested the rearranged fluorinated cyclised product was not observed; with the proto-cyclized product only observed in small amounts (~10%) when xenon difluoride was used.



Scheme 4 – Electrophilic fluorination of a citronellic ester enolate with electrophilic fluorinating agents

In the majority of cases only the 2 products of direct fluorination were observed, resulting in either mono or di-fluorination. It was rationalised that the difluorinated product could arise from further deprotonation by excess base or by unreacted enolate. It was concluded, from this observation, that oxidation of the enolate was not occurring as otherwise the fluorinated cyclized product would have been detected. In an independent reaction, tributyltin hydride and a catalytic amount of radical initiator was added to the α-bromo-citronellate derivative and the proto-cyclized product was recovered, demonstrating that if radicals were present the cyclised product would be expected.



Scheme 5 – Cyclization of radical intermediate

This experiment ruled out the possibility of free-radicals to give the fluorinated product, whereas it suggested the proto-cyclized product does in fact arise from a free radical pathway. However, it does not rule out the possibility of a SET mechanism. It is possible the radical enolate is formed which is followed by a fast in cage recombination to give the fluorinated product. These observations simply set a lower limit to the rate at which a radical/radical-anion pair, if they indeed exist in the reaction, would have to react within the solvent cage with a fluorine radical in order to overcome diffusion and the consequential isomerisation.

In a subsequent publication[46] the same authors used rate constants to rule out the possibility of a single electron transfer mechanism. By comparing the observed rate constant

to that calculated for electron transfer they were able to show that the rate of the competing ET pathway would be too slow by many orders of magnitude to account for the reaction rate. Their data also showed that as the ratio of k_{obs}/k_{ET} approached 1, i.e. the electron transfer reaction dominated, the yield of the fluorinated product approached 0 %. Hence, when ET is the dominant pathway, the electron transfer from nucleophile to fluorinating reagent simply leads to the loss of fluorine as fluoride. They conclude that fluorination of the substrate must be occurring by an S_N2 type process.

1.3 Fluorocyclization

Fluorocyclization methodology offers a powerful technique for the construction of complex molecular framework with the tandem installation of a fluorine atom. The prevalence of cyclic structures in lead pharmaceutical drugs, together with the well-documented beneficial effects of fluorine incorporation, make new fluoro-cyclization strategies highly desirable.[2,47,48] The reactions can be mediated using a nucleophilic or electrophilic source of fluorine and proceed by either a fluorination-cyclization or a cyclization-fluorination. Currently, despite the advantages of a fluorocyclization approach, fluorinated biologically active compounds are rarely accessed by fluorocyclization techniques with just a single notable example[49] and this provides a clear need for advancement in this area of organo-fluorine chemistry.

1.3.1 Nucleophilic fluorocyclization

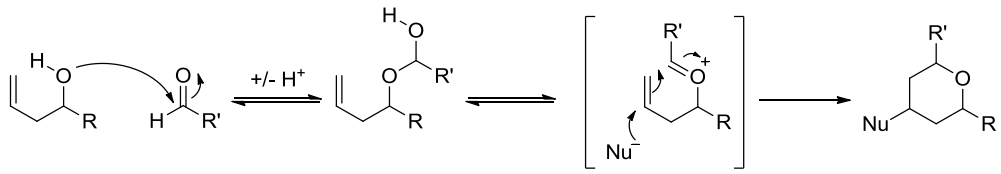
A fluorocyclization can be achieved using a plethora of techniques. Some involve pre-fluorination followed by cyclization and some involve pre-cyclization followed by fluorination. The concept of fluorocyclization has, in fact, been around for many years, with

very slow progress being made for the first decade or so. One early example of a fluoro-heterocyclization was reported by Schwertfeger and co-workers who discovered that the cyclization of 2-(2-chloroethoxy)-perfluorocarboxylic acid halides with alkali metal fluorides led to the formation of 2,3-perfluoro-1,4-dioxanes with yields of up to 84 %.[50] No further investigation into this reaction has since appeared in the literature.

Even earlier than this, Rendell and Wright published on the fluorination of trimethylamine using cobalt (III) fluoride at 100-200 °C.[51] Whilst trying to extend their search for new inhalation anaesthetics, they noticed the formation of trace amounts of various polyfluorinated imidazolidines. The high degree of fluorination observed was rationalised by a cation radical mechanism since the ionization potential of trimethylamine is relatively low. In related work, Pawelke et al. reported the reaction of perchlorodiazahexadiene with stoichiometric amounts of SbF_5 in SO_2 to furnish perfluoro-1,3-dimethylimidazolidine and its derivatives.[52] The ring closure of perfluorodiazahexadiene can be achieved using a catalytic amount of SbF_5 as the intermediate complex dissociates into the perfluorinated heterocycle, which in turn catalyzes the elimination of HF and formation of product.

1.3.1.1 Prins cyclizations

Prins cyclizations are relatively well explored in the literature as a method for fluorination-cyclization. It has been demonstrated that $BF_3{\cdot}OEt_2$, and its variants are effective Lewis acid promoters for Prins cyclizations, but that they can also provide a fluoride ion to act as the nucleophile to quench the resultant carbocation according to the general scheme below.



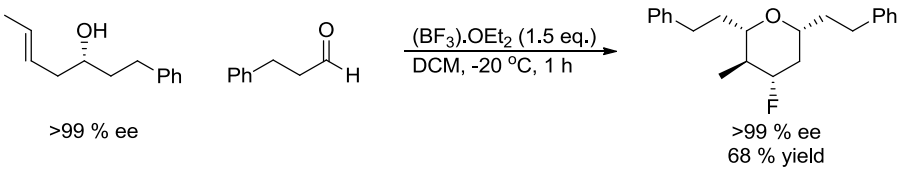
Scheme 6 - General Prins cyclization reaction to access fluorocyclized product

Over a decade ago Willis and co-workers utilized a Prins cyclization to demonstrate the fluorocyclization of a homoallylic methoxyethoxymethyl ether using borontrifluoride diethyletherate as the Lewis acid promoter.[53] They found that a fluoride ion is liberated *in situ* to quench the carbocation intermediate, which afforded a highly diastereoselective tri-substituted tetrahydropyran in a 55 % yield (Scheme 7). The authors went on to demonstrate that by varying the nature of the nucleophile and Lewis acid used, 2,4,5-trisubstituted tetrahydropyrans could be prepared with either a halide, alcohol, acetate or amide at the C-4 position.

Scheme 7 - Prins cyclization of a homoallylic methoxyethoxymethylether

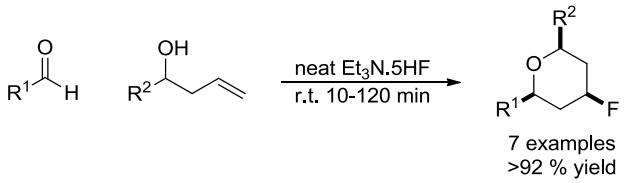
Some years later, Nakami and co-workers[54] reported the intermolecular Prins cyclization of optically active homoallylic alcohols with aldehydes using a similar borontrifluoride diethyletherate system in DCM. They found that the enantioenrichment of the starting alcohol was delivered to the product, offering a useful method for the construction of enantiopure 1,2,3,5-tetrasubstituted tetrahydropyrans when a chiral starting alcohol is

available. A small amount of 4-hydroxy product formation was found to be unavoidable, in all the reactions performed. Presence of water is inevitable as an equivalent is released in the formation of the oxocarbenium ion intermediate from the hemiacetal. This water molecule can then serve to act as the nucleophile for the Prins cyclization.



Scheme 8 - Prins cyclization of optically active homoallylic alcohols and aldehydes

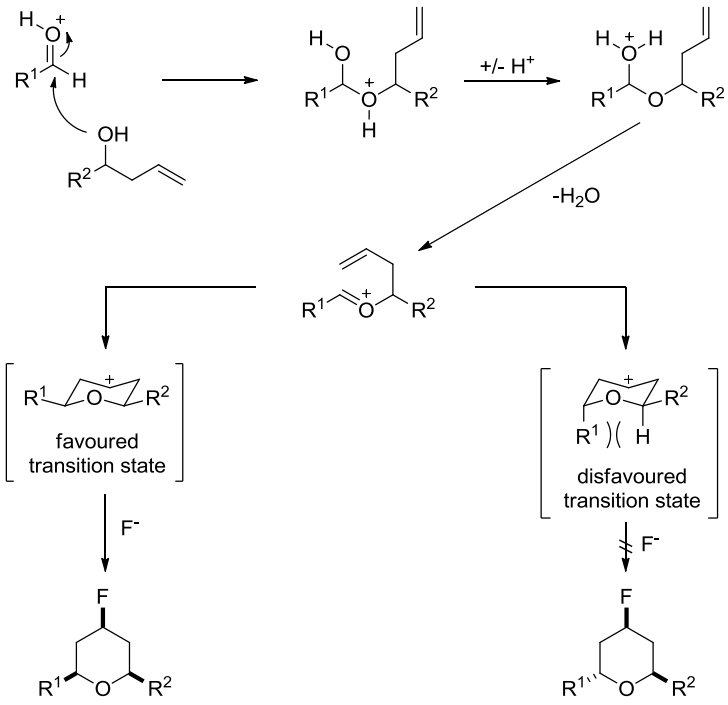
Fuchigami later published on the highly efficient Prins cyclization of homoallylic alcohols and aldehydes in the presence of fluoride to access fluorinated tetrahydropyrans in excellent yields.[55,56] Rather than use the typical borontrifluoride diethyletherate system they used an ionic liquid HF salt. They discovered that the $Et_3N{\cdot}5HF$ salts were better than the corresponding tri and tetra hydrogen fluoride salts as excess protons would protonate the contaminating H_2O and thus prohibit the nucleophilic attack of water.



Scheme 9 - Prins cyclization of homoallylic alcohols and aldehydes in the presence of HF ionic salt

The excellent diastereoselectivity of the reaction was attributed to the preferred adoption of a chair-like transition state that avoids unfavourable 1,3-diaxial interactions. It had

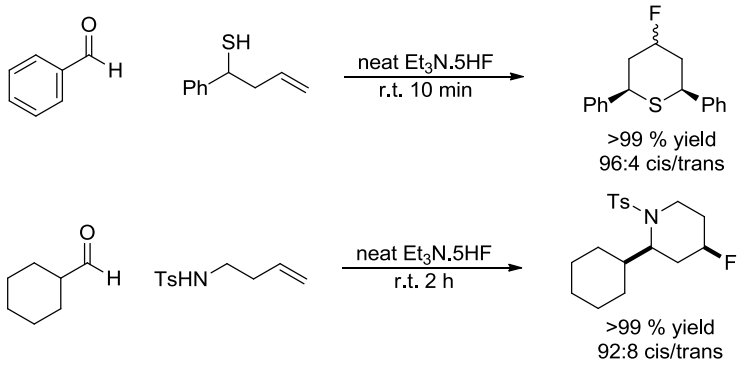
previously been shown[57] that the C^+-H bond was semi-axial in the favoured chair transition state and so attack of the fluoride nucleophile occurs exclusively from the equatorial position to avoid steric clashing upon approach (Scheme 5).



Scheme 10 - Proposed mechanism for Prins cyclization

The scope of the methodology was investigated by extending the reaction to the Prins cyclization of homoallylic thiols and homoallylic amines to make 4-fluorothiacyclohexanes and 4-fluoropiperidines, respectively. The thiols reacted smoothly to furnish the products in excellent yield with a small deteriation in diastereoselectivity. The amines, however, did not react at all due to the protonation of nitrogen by the HF salt. The problem was solved by introducing an electron withdrawing group to reduce the basicity of the amine. The reaction between homoallyl tosylamine and aliphatic aldehydes proceeded very efficiently to afford the piperidines in very good yields with excellent yields. However, the reaction with

benzaldehyde barely proceeded due to the lower reactivity of aromatic aldehydes over aliphatic aldehydes.

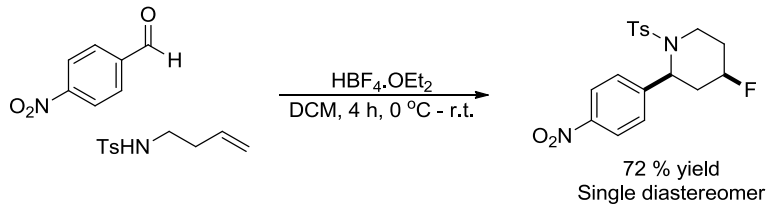


Scheme 11 – Aza-Prins cyclization of homoallyl tosylamine

A similar borontrifluroide strategy has been recently disclosed by O'Hagan and co-workers[58] for the synthesis of 4-fluoro-pyrans and -piperidines. Using microwave conditions, the reaction times were significantly decreased and, in general, the conversions of the reactions were increased. The reaction, however, suffered from a detrimental effect to the diastereoselectivity. Lowering the reaction temperature to -20 °C increased the diastereoselectivity but required longer reaction times. This is the first, and only, report of the use of the use of microwave conditions to access a fluorinated heterocycle by means of a Prins cyclization that has appeared in the literature.

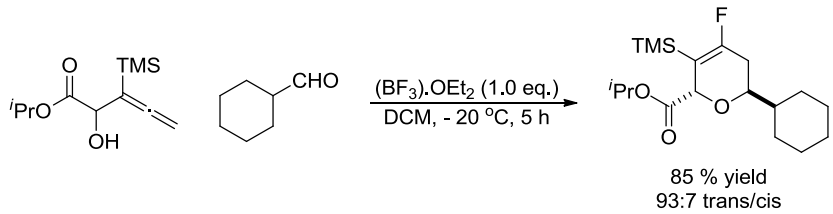
A more efficient method for the aza-Prins cyclization reaction was recently reported by Yadav et al.[59] using a slightly different fluorine source. The authors reported that $HBF_4{\cdot}OEt_2$ in DCM allowed for the smooth fluorocyclization of a range of *N*-tosyl homoallylamines and aldehydes. It should be noted that they investigated the usual sources of fluoride but found that tetrafluoroboric acid was the optimum source. Under their reaction conditions, the

product of the reaction between *p*-nitrobenzaldehyde and *N*-tosyl homoallylamine could be accessed in a 72 % chemical yield after just 4 hours as a single diastereomer.



Scheme 12 - aza-Prins cyclization of N-tosyl homoallylamines using tetrafluoroboric acid promoter

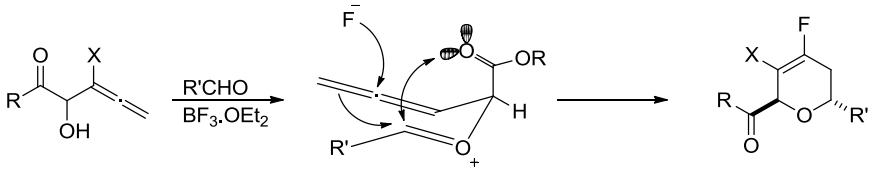
One final report on this topic was recently disclosed by Loh and co-workers in 2010 on the highly stereocontrolled synthesis of dihydropyrans.[60] All previous reports on the Prins cyclization of homoallylic alcohols have led to products with the cis- isomer being the major diastereomer. Using allenic alcohols, rather than homoallylic alcohols, and a boron trifluroide Lewis acid promoter, a range of dihydropyrans were synthesised in moderate to very good yields and in high diastereoselectivity.



Scheme 13 - Prins cyclization of trimethylsilyl allenic alcohol xx with cyclohexanecarbaldehyde

The authors proposed the high stereoselectivity can be attributed to the Prins cyclization taking place through a distorted chair transition state. The lone pairs on the ester carbonyl oxygen are involved in stabilising the oxonium ion and so the ester group preferentially

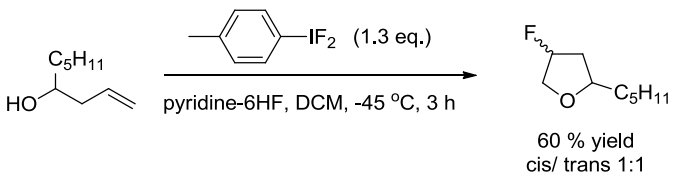
assumes an axial position. The boron trifluoride again acts as both a Lewis acid catalyst and a fluoride source.



Scheme 14 - Proposed mechanism for Prins cyclization

1.3.1.2 Hypervalent Iodine Intermediates

4-Iodotoluene difluoride is a mild oxidant and a fluorinating reagent successfully used for several important transformations such as the fluorinative ring expansion reported by Hara et al. in 2003.[61] It has also found as use as a successful reagent in fluorocyclization methodology. For example, the fluorocyclization of an unsaturated alcohol earlier reported by Hara in 2000[62] employed a hydrofluoric acid derived iodotoluene difluoride complex in a pyridine-6HF/ DCM solvent system (Scheme 14). Both the synthesis of the fluorinating reagent and the reactions themselves required extreme experimental caution and special handling. Therefore, although the reaction demonstrates the ability to fluorocyclize unactivated substrates with good yields, the conditions required are far from ideal. Furthermore, the lack of diastereoselectivity is a significant limitation.



Scheme 15 - Nucleophilic fluorocyclization using iodotoluene difluoride

Both alcohols and carboxylic acids were investigated and with different chain lengths. Both substrate classes reacted with moderate success to afford the cyclic ethers and lactones, respectively. An interesting observation was made with the homoallylic acids. Whereas the allylic acids cyclize to give the 5-membered ring and the homoallylic and 2-allylethyl alcohols cyclize to afford the 5-membered and 6-membered rings respectively, the homoallylic acids react to furnish the corresponding 5-membered ring (Table 6).

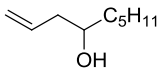
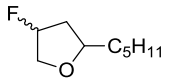
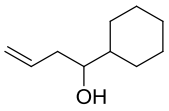
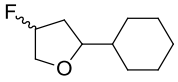
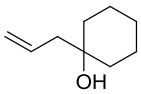
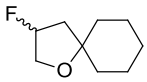
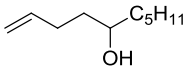
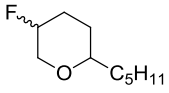
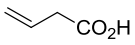
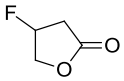
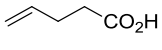
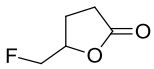
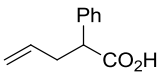
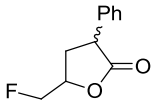
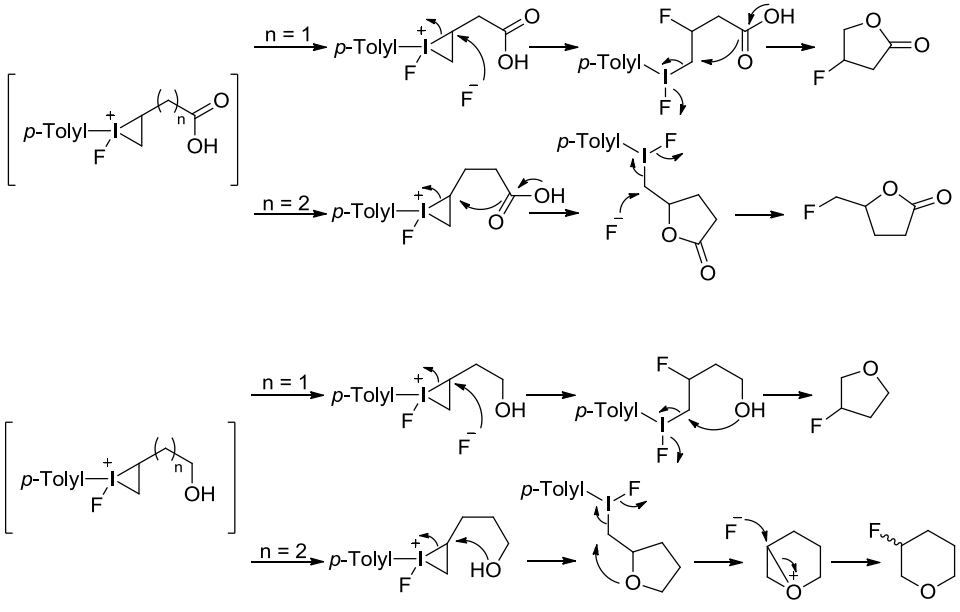
Entry	Substrate	Conditions	Product	Yield (d.r.)
1		-45 °C, 3h		60 (1:1)
2		-45 °C, 2h		55 (1:1)
3		-45 °C, 3.5h		40
4		-45 °C, 4h		50 (4:3)
5		r.t., 3 h		40
6		r.t., 3 h		40
7		r.t., 3 h		50 (2:1)

Table 6 – Substrate scope of nucleophilic fluorocyclization

The proposed mechanism featured a mechanistically-related fluorine attack for the carbon-fluorine bond forming event to that later disclosed by Hara.[61] The observation of the different reaction products suggest the feasibility of both a fluorination-cyclization and a

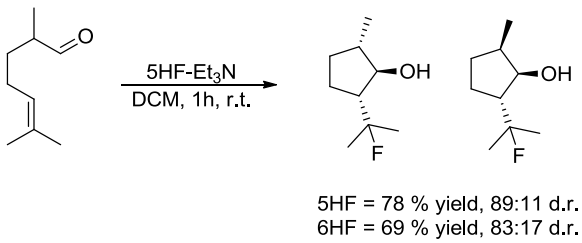
cyclization-fluorination pathway being possible. For the carboxylic acids, when n = 1, the fluorination-cyclization pathway dominates, leading to the β-fluorinated lactone. However, it seems when n = 2, the intra-molecular cyclization is a faster process than the intermolecular fluoride mediated opening of the fluoroiodonium cation, which results in the formation of the *exo* fluorinated product. For the alcohol substrates, the mechanism is very similar. When n = 1, the intermolecular fluoride mediated ring opening is the faster process, which is succeeded by an intra-molecular cyclization reaction to furnish the β-fluorinated cyclo-etherification product. When n = 2, the intra-molecular cyclization step occurs initially, but due to the higher nucleophilicity of the cyclic ether product a ring-expansion occurs faster than the fluoride displacement of the iodine species. The oxonium ion is then quenched by attack of fluoride.



Scheme 16 - Proposed mechanism for the fluorocyclization of alcohols and carboxylic acids by iodotoluene difluoride accounting for the difference in ring size for the two substrate classes

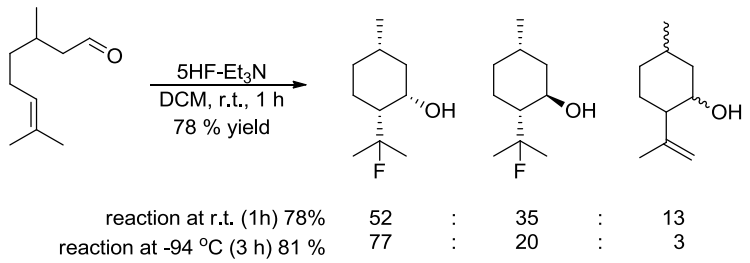
1.3.1.3 Fluorocyclization of Unsaturated Aldehydes

Another strategy for achieving a fluorocyclization is to cyclize an alkene onto a reactive aldehyde group. In 1995, Yoneda and co-workers reported the cyclizations of various unsaturated aldehydes using a nucleophilic fluorine source.[63] Amine based HF complexes were utilized to furnish carbocycles with an *exo* fluorine containing group. The authors reported that the commercially available $Et_3N{\cdot}3HF$ complex was insufficiently reactive to promote the reaction. Instead, complexes featuring up to 6HF molecules were prepared from triethylamine and anhydrous HF at -78 °C and employed successfully to a range of unsaturated aldehydes to effect a fluorocyclization. Olah's reagent (9HF-pyridine) was found to completely consume the starting material but no product could be identified. Slightly different results were obtained when using either 5 or 6HF, delivering higher yield and d.r. for the 5HF reagent. Lowering the temperature to -78 °C increased the d.r. to 93:7 but lowered the yield to 71 %.



Scheme 17 - Fluoro-carbocyclization of aldehydes

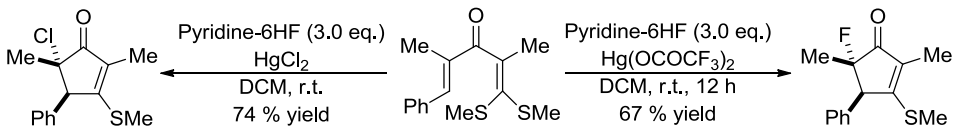
However, for a substrate designed to deliver a six-membered carbocycle a competing ene-type reaction was detected at room temperature which lead to non-fluorinated products. The formation of the ene product could be suppressed to some extent by lowering the reaction temperature, where at -94 °C the conversion to the ene product was reduced to just 3 % as described in Scheme 16.



Scheme 18 - Fluoro-carbocyclization of unsaturated aldehyde to form six-membered carbocycle

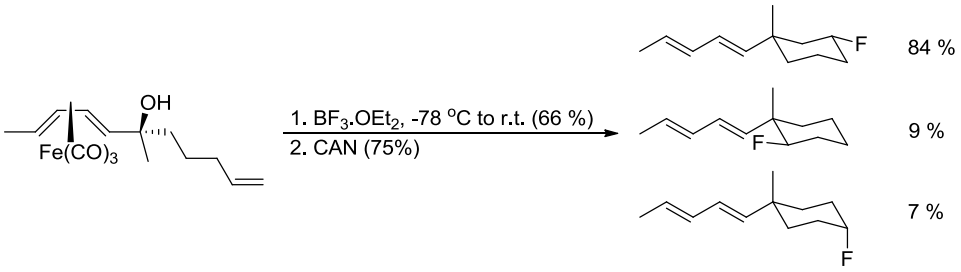
1.3.1.4 Miscellaneous Fluorocyclization Reactions

In 1999, Yoneda et al. reported a cascade Nazarov-fluorination reaction to access α-fluorinated cyclopentenones.[64] The authors proposed that the carbocation created upon cyclization could be trapped by a nucleophilic source of fluorine. However, initial attempts to isolate a fluorinated cyclopentenone were unsuccessful due to the abstraction of a proton to quench the carbocation. This problem was overcome by the addition of a methylthio-substituent. Whilst these second generation substrates underwent a cyclization, the carbocation was found to be quenched by the methylthio species liberated in the course of the reaction. To suppress the addition of this powerful nucleophile, $HgCl_2$, was added to the reaction to sequester the thiol nucleophile. This presented its own problem of competitive incorporation of chloride or fluoride, which is a consequence of the lower nucleophilicity of fluoride over the other halides. Finally, when the mercury source was changed to $Hg(OCOCF_3)_2$ the desired products could be isolated with chemical yields of up to 89 %. The scope of the substrates was found to be limited to substrates with substituted double bonds.



Scheme 19 - Nazarov fluorination-cyclization of dienones

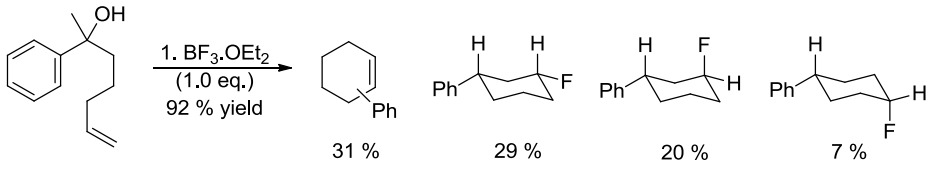
Later that year, another fluoro-carbocyclization was reported by Franck-Neumann et al.[65] Fluorinated cyclohexanes were accessed by the fluorocyclization of ω-pentenyl pentadienol tricarbonyl iron complexes in the presence of $BF_3{\cdot}OEt_2$ as a fluorine source and acid promoter, followed by decomplexation with cerium (IV) ammonium nitrate. Starting from a pentadienol, cyclization and oxidative decomplexation furnished a fluoro-cyclohexyldiene as the major isomer, along with two minor structural isomers.



Scheme 20 - Fluoro-carbocyclization of w-pentenyl pentadienol

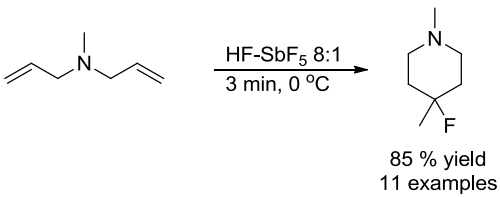
To examine the importance of the metal complexation, the cyclization was attempted without the tricarbonyl iron species. A successful cyclization-fluorination was observed, albeit with a competing elimination reaction, to afford 61 % of fluorocyclised products as a mixture of 5 structural isomers. In an attempt to increase the yield of the fluorocyclised products, the equivalents of boron trifluoride used was increased to 3, but this had a detrimental effect on the reaction, and elimination product was almost exclusively recovered. This result was rationalised by the excess Lewis acid ionising the carbon fluorine

bond that was formed and promoting the elimination of fluoride. Therefore, with the uncomplexed substrate, fluorocyclization was possible but only when the fluorinating reagent was not used in excess.



Scheme 21 - Major products isolated from the metal-free fluorocyclization of 2-phenylhept-6-en-2-ol

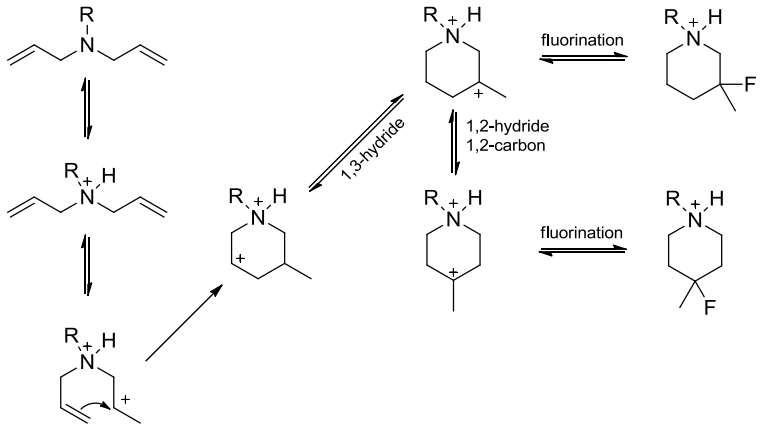
The combination of HF and antimony (V) pentafluoride to make a super acid has recently found a use in the field of fluorocyclization. The cyclization-fluorination of easily prepared 1,6-dienes to form fluorinated piperidines was reported by Thibaudeau and co-workers in a publication on the rare use of a super acid for fluorocyclization.[66] The double protonation of the molecule to form a *bis*-cation allows for the cyclation of the un-protonated double bond, which then leaves a carbocation that can be neutralised by the nucleophilic attack of fluoride. The reaction was demonstrated on a variety of *N*-protected dienes, which led, in most cases, to the formation of desired product in moderate to good yields.



Scheme 22 - Superacid mediated fluorocyclization of 1,6-dienes

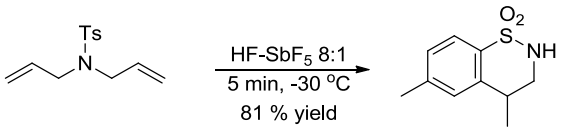
Apart from the obvious drawback of functional group tolerance, a limitation to this methodology was that the use of an aromatic group on the nitrogen atom led to the formation of a complex mixture of products. This was reasoned to be due to the competition of the alkene and arene as the nucleophile to effect the fluorocyclization. This problem was overcome by the use of electron poor aromatic groups. For example, when a benzoyl group is used, a complex mixture was observed and no yield for the desired product could be obtained but when a *para*-nitrobenzoyl group was used the yield was a more satisfactory 55 %.

An interesting observation obtained for some of the dienes investigated was the competing formation of the 3-fluoropiperidine, which was even sometimes observed as the major isomer. Since the 3-fluoropiperidine could be isolated under mild conditions, it was reasoned that it could be a potential intermediate in the reaction. Evidence for the reaction proceeding through a 3-fluoropiperidine intermediate was obtained by re-submitting the fluorinated heterocycle to the reaction conditions. The complete conversion to the 4-fluoropiperidine provided considerable evidence that the mechanistic pathway involved the formation of 3-fluoropiperidines. The mechanism proposed for the reaction is outlined in Scheme 23.



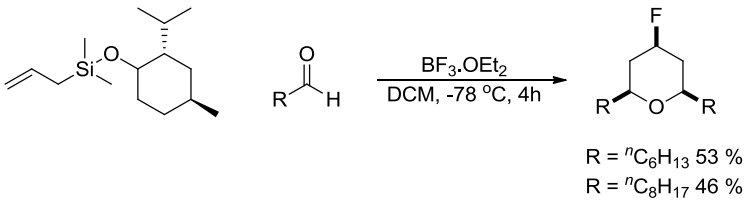
Scheme 23 - Proposed mechanism for the superacid mediated cyclization-fluorination of 1,6-dienes

Only fairly subtle modifications to the substrates were found to be possible when the substrate scope was investigated. The *p*-nitro-benzoate *N*-protecting group was chosen as the model substrate to modify. The authors found that the reaction could tolerate the double bonds being functionalised with a methyl group, however, this led to a change in mechanism and an *exo*-fluorinated pyrrolidine. The five-membered product was also obtained when an unsymmetrical diene was used. A substrate featuring a homoallylic group on one side of the nitrogen and an allyl group on the other side underwent cyclization to form a pyrrolidine but in a disappointing 28 % yield. Larger ring sizes could not be accessed by increasing the carbon units from the nitrogen to the double bond, as in this case a complex mixture was obtained. When a tosyl group was employed as the protecting group, the tolyl ring was found to preferentially cyclize onto the carbocation, rather than undergo fluoride capture. This confirmed the potential competition between double bond and aromatic ring attack. The authors commented that the mechanism of de-allylation is unclear but under investigation. Finally, attempts to extend this methodology to an oxygen variant were unsuccessful and led to complex mixtures.



Scheme 24 - Competative cyclization between aromatic ring and double bond

A final example of a boron trifluoride complex being used as a Lewis acid and fluoride source to achieve a fluorocyclization is the condensation of allylsilanes and carbonyl compounds that was reported some years ago by Chan and co-workers.[67] The authors showed that in the presence of $BF_3{\cdot}OEt_2$, the all *syn* 4-fluorinated tetrahydropyrans were obtained from the coupling of chiral allylsilanes with aldehydes in moderate yields.



Scheme 25 - Lewis acid promoted condensation of allylsilane xx with aldehydes

1.3.2 Electrophilic fluorocyclization

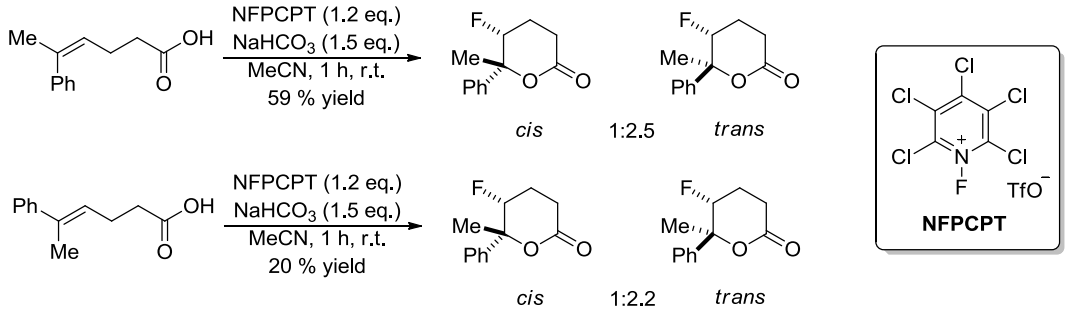
A major disadvantage to nucleophilic approaches is the lack of significant reagent tunability. Since most fluoride reagents derive from (alkali) metal fluorides or hydrogen fluoride derivatives it is generally quite difficult to control their reactivity profile. Of course, the handling of these reagents is also prohibitive to their use due to the often very high hygroscopic nature of metal fluorides and the severely corrosive properties of hydrogen fluoride reagents. These drawbacks are manifested in a notable absence of widely applicable fluorocyclization techniques which has led to the growing dominance of electrophilic techniques in recent times. The development of a wide range of electrophilic reagents with varying fluorinating power and reactivity profiles has also been instrumental in driving this area of research.

There are several generally employed strategies for electrophilic fluorocyclization reactions, which can be categorized by the nature of intermediate stabilization. Regardless of reaction mechanism, be it S_N2 type nucleophilic capture of the fluorine or a single electron transfer mechanism there will be an intermediate carbocation, which requires stabilization in order for the reaction to occur.

1.3.2.1 Benzylic and tertiary stabilised intermediates

In 1997, Taguchi and co-workers reported the fluoro-lactonization and fluoro-etherification of unsaturated alcohols and carboxylic acids mediated by *N*-fluoropentachloropyridinium triflate (NFPCPT).[68] Unfortunately, whilst moderate yields were obtained the diastereocontrol was poor, yet it was an important contribution since halo-lactonization reactions are synthetically very useful. A broad substrate scope was investigated to determine that only substrates capable of forming a benzylic or tertiary carbocation were tolerated.

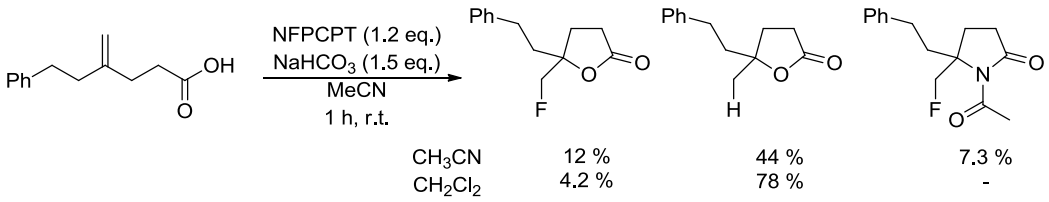
Investigation into substrates where formation of diastereomers was possible revealed that very poor stereocontrol was obtained. For example when geometrically pure substrates were subjected to the reaction conditions the results were very similar when using either the *E* or *Z* isomer. Unlike in a similar iodo-lactonization where a single diastereomer is obtained due to trans addition of the nucleophile, the authors proposed the generation of a carbocationic intermediate with subsequent nucleophilic ring closure.



Scheme 26 – Mechanistic probe into diastereocontrol

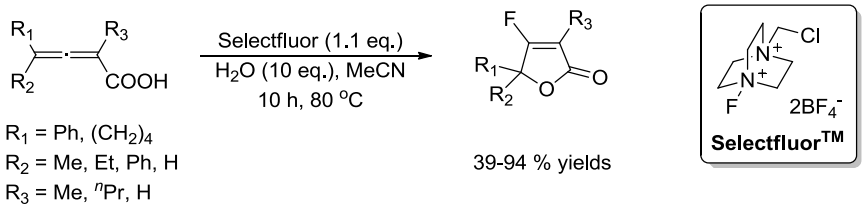
Taguchi suggested that a single electron transfer mechanism is plausible, whereby an electron is transferred between the alkene and fluorinating reagent, leading to radical fluorine capture which results in carbocation formation. When substrates were investigated

that would transit via a tertiary carbocationic intermediate, instead of a benzylic carbocationic intermediate, a competing reaction with the solvent acetonitrile took place. This observation is a testament to the subtle balance of cation stability required to achieve a fluoro-cyclization. A final important observation was that competing reactions were observed and could be suppressed by changing of the reaction conditions. When 4-methylene-6-phenylhexanoic acid was subjected to the general conditions of fluorocyclization the desired product was obtained in a disappointing 12 % yield. However, the product was accompanied by a 44 % yield of the corresponding protocyclized analogue and a 7 % yield a product derived from attack of the solvent. Changing the reaction media to DCM proved unsuccessful in increasing the reaction yield, whilst further promoting the protocyclization pathway.



Scheme 27 – Competitive reaction pathways

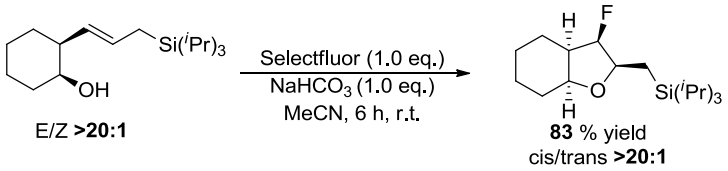
Selectfluor is generally the reagent of choice since it is easy to handle and highly bench stable and therefore methodology which makes use of it is immediately appealing. A report by Zhou and co-workers offered an elegant strategy to form fluorinated lactones using allenoic acids as substrates and Selectfluor as the fluorinating reagent.[69] As with the report by Taguchi, the substrate scope was limited to those offering benzylic and/or tertiary stabilization to an intermediate carbocation. The exact role of the water is not clear but the authors suggest that hydrogen bonding between Selectfluor and water may be important for fluorocyclization.



Scheme 28 – Fluorolactonization of 2,3-allenoic acids

1.3.2.2 *β*-silicon stabilized intermediates

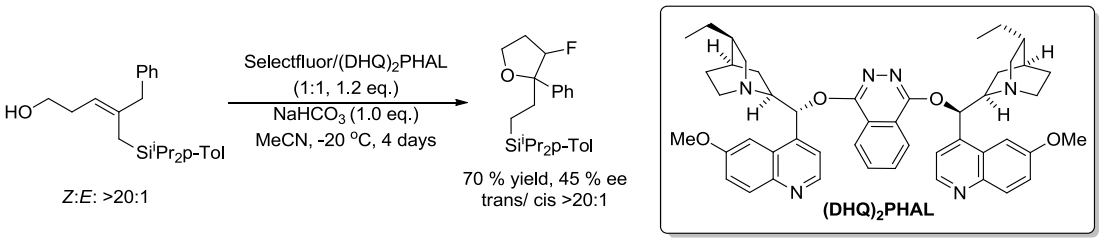
Various fluorocyclization methodology has previosuly been developed within the Gouverneur group. One of these methods involved a modification of fluorodesilylation methodology published some years previously.[70] It was found that whereas trimethylsilyl groups promoted the fluorodesilylation reaction, when a pendent nucleophile was present, silyl groups other than trimethylsilyl could be used to promote the competing fluorocyclization reaction and therefore afford a variety of fluorinated heterocycles (Scheme 29).[71] This again took advantage of the β-effect of silicon to activate the system towards electrophilic fluorination and was shown to be possible with both Selectfluor and NFSI as the fluorinating agent, with the latter requiring elevated temperatures.



Scheme 29 - Silyl promoted electrophilic fluorocyclization

An asymmetric variant of this reaction was also achieved by employing a stoichiometric amount of chiral N-F reagent, prepared *in situ* from a bis-cinchona alkaloid and Selectfluor,[71] according to the procedure developed by Takeuchi and co-workers (Scheme 30).[72] However, although activation of the system with a silyl group addresses the reactivity

problem of unactivated alkenes, it also means that the bulky silyl group must later be removed, the conditions for which are fairly harsh and not tolerant to complex functionalisation. Asymmetric fluorocyclization reactions will be covered in more detail in Chapter 5.

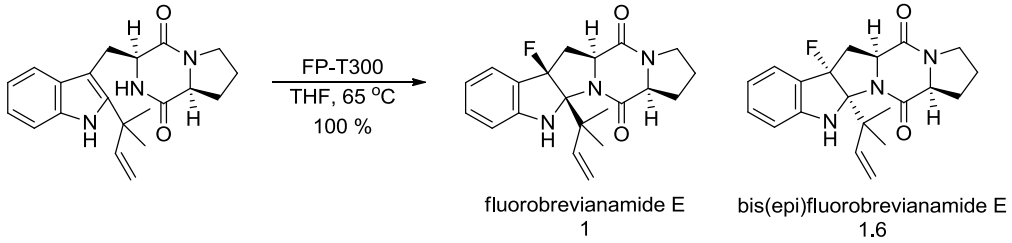


Scheme 30 - Asymmetric fluorocyclization using a stoichiometric Cinchona alkaloid/Selectfluor combination

1.3.2.3 Iminium stabilized intermediates

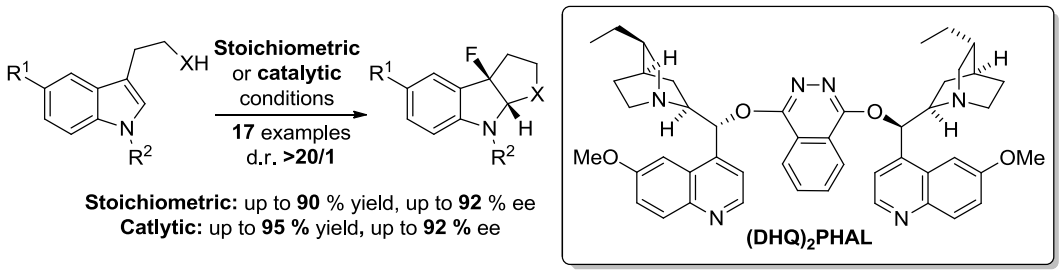
In 2001, Shibata et al. utilized a fluorination-cyclization procedure to access two biologically interesting compounds, gypsetin and brevianamide using an electrophilic fluorine source.[49] They demonstrated that an approach featuring the fluorination of an indole species at the 3-position and subsequent nucleophilic attack at the 2- position by a tethered nucleophile was an elegant method for the construction of these complex structures. Precedent for this approach was reported by the same group, which demonstrated the fluorination of indoles accompanied by the intermolecular attack of an external nucleophile.[73] Selectfluor was initially explored as a fluorinating reagent but no reaction occurred in acetonitrile, presumably due to the poor solubility of the starting material. This problem could be somewhat circumvented by using a 1:1 mixture of MeCN:THF, achieving an average yields of ~45 %. However, much better yields were required for this to be an attractive method for synthesising biologically active targets and so the authors investigated alternative fluorinating reagents. The less reactive *N*-fluorocollidine salt FP-T300 was found to be superior to Selectfluor in this instance. Fluorocyclization of the substituted indole was

optimally performed at 65 °C in THF using FP-T300, which furnished fluorobrevianamide E in a quantitative yield. Unfortunately, the fluorocyclization was not stereoselective, resulting in the formation of both possible diastereomers in roughly equal amounts.



Scheme 31 – Synthesis of fluorobrevianamide

Further fluorocyclization methodology has been disclosed in a recent publication by the Gouverneur group, in which a cinchona alkaloid/ electrophilic fluorinating agent combination was employed for the asymmetric fluorocyclization of prochiral indole systems.[74] The beneficial effect of an α-nitrogen atom was exploited in order to activate the olefin towards fluorination, resulting in a transient iminium intermediate which could be captured by an internal nucelophile. It was found that a stoichiometric amount of cinchona alkaloid could be employed, in combination with Selectfluor as the electrophilic fluorinating agent, to afford a range of fluorocyclized products in good to excellent conversions and enantioselectivites. By application of Shibata's method for asymmetric fluorination, in which a catalytic amount of cinchona alkaloid was employed in combination with NFSI and 6 equivalents of an inorganic base,[75] it was demonstrated that this fluorocyclization methodology could also be extended to a catalytic variant with only a small depletion of enantiomeric excess (Scheme 32). Importantly, this was the first example in the literature of a catalytic asymmetric fluorocyclization procedure.



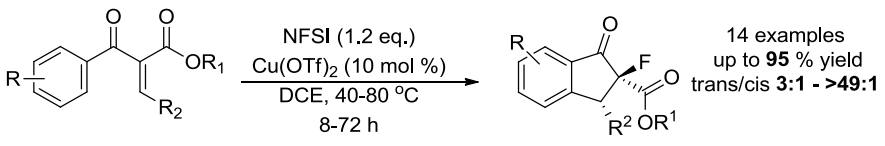
Stoichiometric: Selectfluor (1.2 eq.), $(DHQ)_2PHAL$ (1.2 eq.), $NaHCO_3$ (1.2 eq.), acetone, -78 °C
Catalytic: NFSI (1.2 eq.), $(DHQ)_2PHAL$ (20 mol%), K_2CO_3 (6.0 eq.), acetone, -78 °C

Scheme 32 - Asymmetric fluorocyclization of indole systems

Interestingly, and in contrast to literature precedent regarding asymmetric fluorination, several observations led the authors to suggest that this asymmetric fluorocyclization may not be occurring via fluorine transfer from the fluorinated alkaloid. Instead, it was noted that a mechanism involving associative complexation of the alkaloid with the substrate could not be ruled out. This reaction will be described in greater detail in Chapter 5.

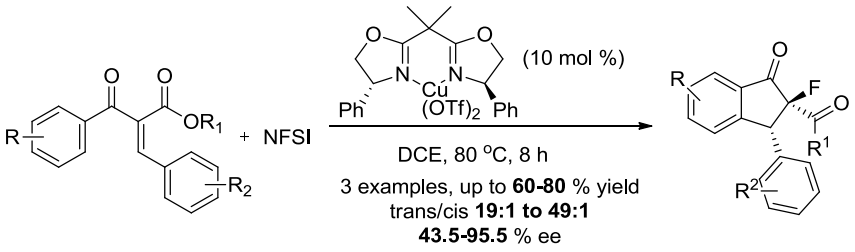
1.3.2.4 Nazarov cyclizations

An important result was disclosed by Ma and co-workers in 2007, on the synthesis of fluorinated α-indanone β-ketoester derivatives.[76] The work was essentially a catalytic variant of earlier work published by the same group.[77] Various α-alkylidene β-ketoesters were subjected to a Lewis acid mediated Nazarov cyclization, followed by fluorination of the resultant β-ketoester to afford the fluorinated products in excellent yields and diastereoselectivities (Scheme 33).



Scheme 33 - Catalytic Nazarov cyclization followed by electrophilic fluorination

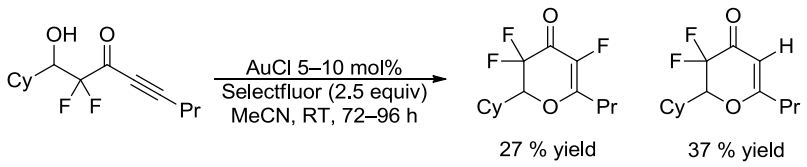
A preliminary attempt was also made to extend this work to a catalytic, enantioselective variant. There is a wealth of literature precedent regarding the asymmetric fluorination of β-ketoesters[78] and so an asymmetric variant could be achieved simply by changing the Lewis acid to one bound to a chiral ligand, in this instance the (*R*)-Ph-bis(oxazoline) ligand (Scheme 34). However, although this has the convenience of forming an enantioenriched fluorocyclized product in one-pot, this is not an asymmetric fluorocyclization, but rather a cyclization followed by an asymmetric fluorination. In fact, this same chiral catalyst has been used by both Cahard[79] and Shibata[80] for enantioselective electrophilic fluorinations.



Scheme 34 - Asymmetric catalytic Nazarov cyclization/ electrophilic fluorination

1.3.2.5 Gold mediated cyclization

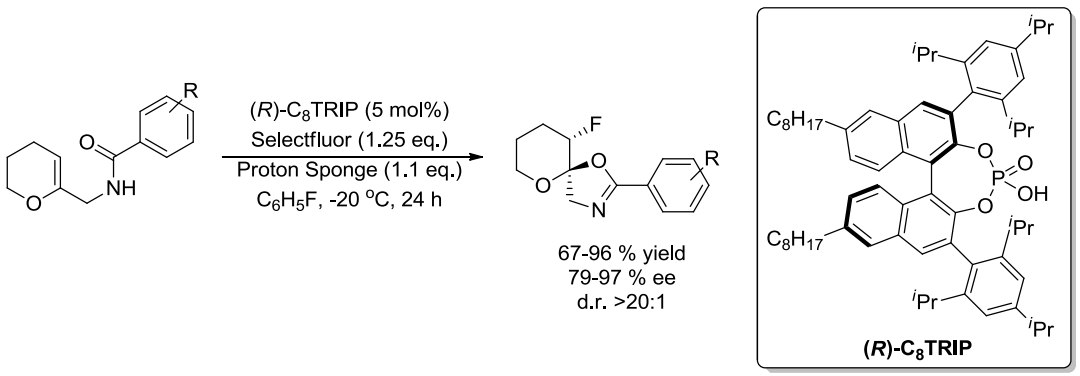
In 2008, Gouverneur and coworkers reported a Gold(I)-catalysed alkoxyfluorination of β-hydroxy-α,α-difluoroynones to give difluorinated dihydropyranones, for which there are limited synthetic routes.[81] Attractive conditions of Selectfluor in acetonitrile at room temperature in the presence of a catalytic amount of AuCl gave the desired compounds in a moderate yield along with a similar amount of the corresponding protodeaurated product (Scheme 2). This was notably the first demonstration of gold-catalysis being compatible with electrophilic fluorinating reagents. However, though a fluorocyclised product is obtained, it is not by a fluorocyclization process. Instead there is a transient vinyl gold intermediate that can undergo proto or fluorodeauration.



Scheme 35 – Gold (I) mediated alkoxyfluorination of β-hydroxy-α,α-difluoroynones

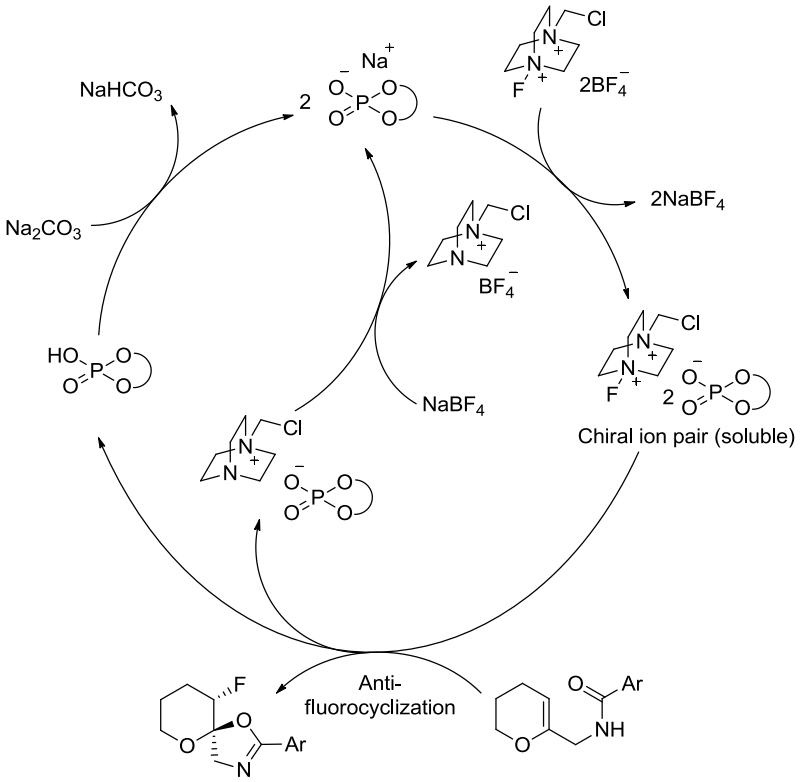
1.3.2.6 Asymmetric Phase transfer fluorocyclization

A report in 2011 by Toste *et al.* disclosed the asymmetric fluorocyclisation of dihydropyrans and dihydronaphthalenes using a pendent amide nucleophile with a chiral anion solid-liquid phase transfer catalyst derived from (*R*)-BINOL (Scheme 36).[82] This reaction offered an important addition to the asymmetric fluorocyclization toolbox since all other chiral reagent approaches have focused on chiral cations. The application of a chiral anion, thus requiring phase transfer conditions, is a very elegant way of forming an *in situ* chiral reagent as the anion may be added in a catalytic amount to commercially available Selectfluor. Catalytic methods are vital to establishing asymmetric fluorocyclizations as attractive routes towards the synthesis of cyclic compounds. The most efficient catalyst was found to be an alkyl substituted analogue of (*R*)-Trip ((*R*)-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate bearing an *n*-octyl group at the 8- position. This catalyst could be efficiently prepared from (R)-BINOL but it is important to note that commercially available (*R*)-TRIP was able to achieve fairly comparable results.



Scheme 36 - Asymmetric fluorination with anionic phase-transfer catalyst

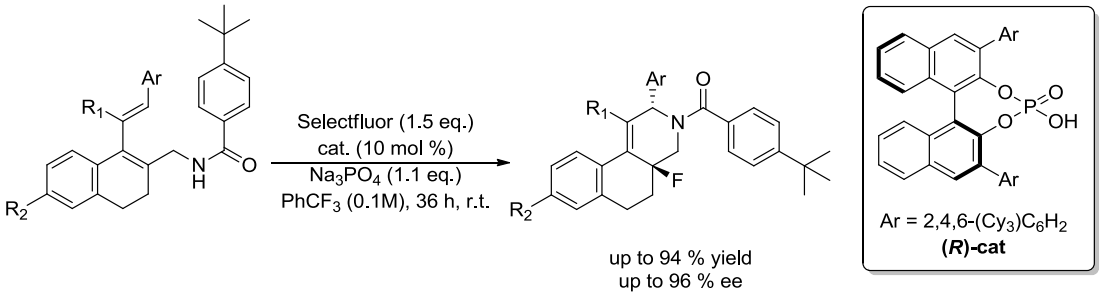
The work showed that Selectfluor could be used in a chiral phase-transfer system to successfully carry out asymmetric fluorinations. Toste proposed that the deprotonated phosphate undergoes anion exchange with the tetrafluoroborate counter ion of Selectfluor, which brings Selectfluor into solution thus allowing it to carry out the oxidative fluorination in an asymmetric manner (Scheme 37). Upon fluorination an equivalent of phosphoric acid is liberated, which following deprotonation can continue to participate in the catalytic cycle.



Scheme 37 - Proposed mechanism of anionic phase-transfer asymmetric fluorination

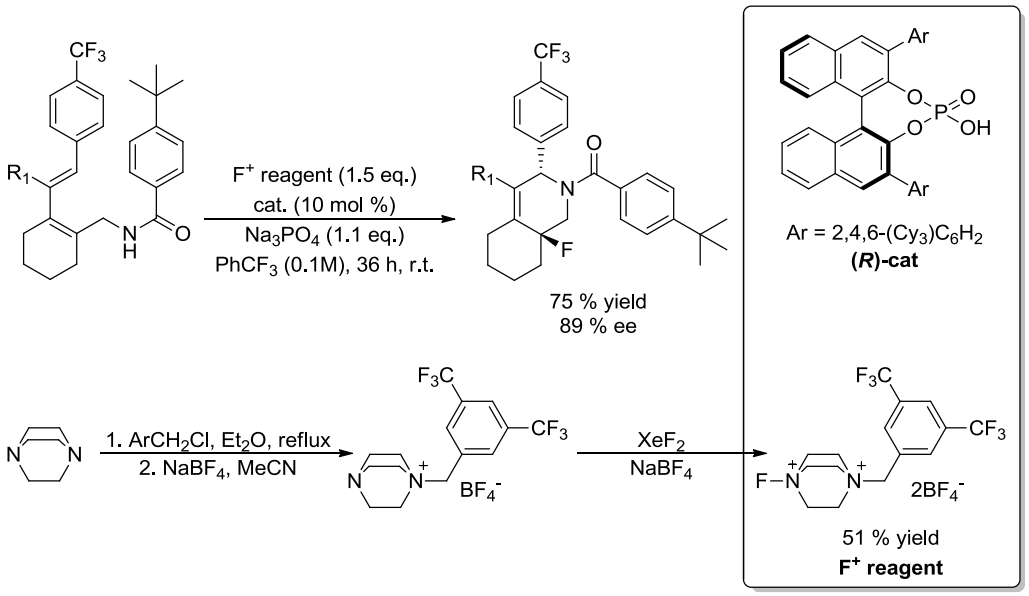
In a continuation to their work on asymmetric fluorocyclization reactions using Selectfluor as the fluorine source, Toste and co-workers have very recently reported a fluoroamination reaction utilizing a 1,4-addition to conjugated dienes.[83] Using dihydronaphthalene substrates featuring a conjugated *E* alkene at the 4 position it was found that cyclization of a pendent amide was possible, affording the products in high yields and high

enantioselectivities. The aryl group of the amide was found to be important, with others delivering the products in a reduced ee. However, the aryl group of the alkene was widely tolerated having little effect on the enantioselectivity.



Scheme 38 – Asymmetric fluoroamination of conjugated dienes

Interestingly, the authors were able to extend this reaction so that the reaction did not require a dihydronaphthalene substrate but could be done directly on a cyclohexene based system. This presented a problem as the normal system using Selectfluor as fluorine source was found to be unreactive. Their solution was therefore to modify the Selectfluor reagent in an effort to increase the reactivity. To their delight by replacing the chloromethyl group of Selectfluor they were able to achieve a very impressive 75 % yield, accompanied by an 89 % ee. Fluorination of the quaternized DABCO core was achieved using XeF_2, which has the distinct advantage of yielding Xe and NaF as the reaction by-products. It should be noted that the requirement for fine-tuning of halogenating reagents is very common and this report constitutes a rare example of where modifications of the Selectfluor motif are made to enhance reactivity or selectivity.



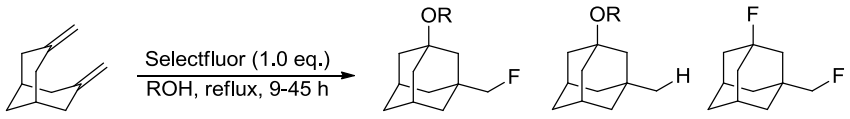
Scheme 39 – Fluorocyclization of cyclohexenes using modified Selectfluor

1.3.3 Electrophilic fluoro-carbocyclization

Terpenes and steroids, naturally occurring complex carbocyclic compounds, are important structures in counteracting/inhibiting various diseases which nature can synthesise with ease and necessary stereoselectivity. Enzymes have the ability to activate unreactive olefins and induce cascade C-C bond-forming reactions with high selectivity and therefore extensive research has been carried out in this area to try and mimic nature's biosynthetic skills by cation-π cyclisation routes.[84] However, an attractive method for constructing carbocyclic compounds is by halo-cyclisation where electrophilic halogens are used to promote cascade carbocyclisation.[85] Nature employs heme- or vanadium-based enzymes where vanadium-dependant haloperoxidases are the most common, which catalyse the oxidation of halides by hydrogen peroxide. The formation of a halonium intermediate in the process allows attack of an electron-rich internal olefin with subsequent cyclisation.[86] Organohalogen compounds are prevalent throughout the ecosystem and the planet from volcanoes, bacteria, plants and even humans. Furthermore, as some marine and bacterial compounds have antibiotic and anti-cancer properties,[87] this increases the attractiveness of this class of

compounds. Hence, the progress of halo-carbocyclisation methodologies is an important field to pursue but is currently underdeveloped. In particular, fluorine analogues are particularly important due to the well documented beneficial effects of fluorine incorporation into biologically active compounds (see Section 1.1).

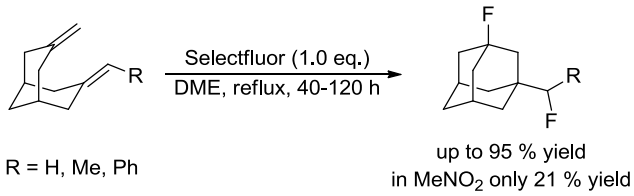
Perhaps the earliest example of a fluoro-carbocyclization involved the transannular cyclization of 3,7-*bis*methylenebicyclo[3.3.1]nonane mediated by Selectfluor.[88] The authors proposed that since bicyclononane systems could be effectively cyclized in the presence of other electrophilic halogens such as bromine or iodine, the system may also respond to electrophilic fluorine. The adamantane products were obtained as mixtures along with the corresponding proto-cyclized product. The solvent choice was proposed to be crucial to control the product distribution since the formation of by-products was suppressed when methanol was used with a 5 mol % addition of sodium acetate or a 12:1 mixture of dioxane/water. It is suggested that the reaction proceeds via an adamantyl cation, which is reported to have a similar stability to the *tert*-butyl cation, thereby facilitating nucleophilic capture by the reaction media. The authors do not comment on the origin of the difluorinated species but perhaps the tetrafluoroborate counterion of Selectfluor has some involvement to provide a fluoride equivalent.



ROH	R			
^{i}PrOH	^{i}Pr	75.6	12	12.1
MeOH (+ 5% AcONa)	Me	93	-	-
Dioxane-H_2O (12:1)	H	83	-	-

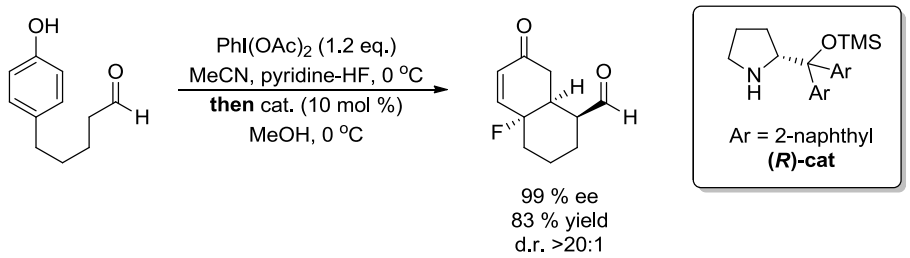
Scheme 40 – Fluoro-carbocyclization of 3,7-*bis*methylenebicyclo[3.3.1]nonane

In an extension to this early work, Serguchev and co-workers subsequently investigated a series of substituted bicycle[3.3.1]nonanes to obtain the difluorinated products.[89] They found that under the conditions of Selectfluor in refluxing DME, the difluorinated product was obtained in very high yields. However, optimisation of the reaction revealed that this reaction is also very sensitive to the solvent, since only a poor yield was obtained when nitromethane was used as the solvent. A side product detected in the reaction, which was tentatively assigned as the adduct of 1-fluoromethyladamantane with the defluorinated Selectfluor residue, covalently attached via the bridge-head nitrogen.



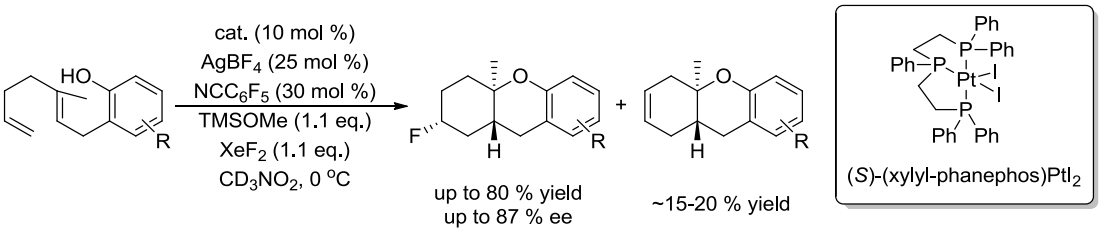
Scheme 41 – Difluorination using Selectfluor

Another example of fluoro-carbocyclization was more recently reported by Gaunt and co-workers.[90] The method is an example of a step-wise pseudo one-pot fluoination-cyclization that makes use of a phenol dearomatization process. In the first step, a hypervalent iodine source is used in conjunction with HF to achieve an oxidative fluorination which furnishes an intermediate dieneone. A chiral secondary amine is then used to desymmetrize the dieneone through a Michael addition via initial enamine formation. However, the requirement of a nucleophilic source of fluorine with an external oxidant is somewhat undesirable due to the hazards associated with HF reagents. Also, whilst the reaction is formally a fluoro-carbocyclization it is in fact a pseudo one-pot reaction since the excess HF must be quenched and the solvent exchanged prior to the addition of the chiral amine.



Scheme 42 - Nucleophilic Catalytic Enantioselective Dearomatisation

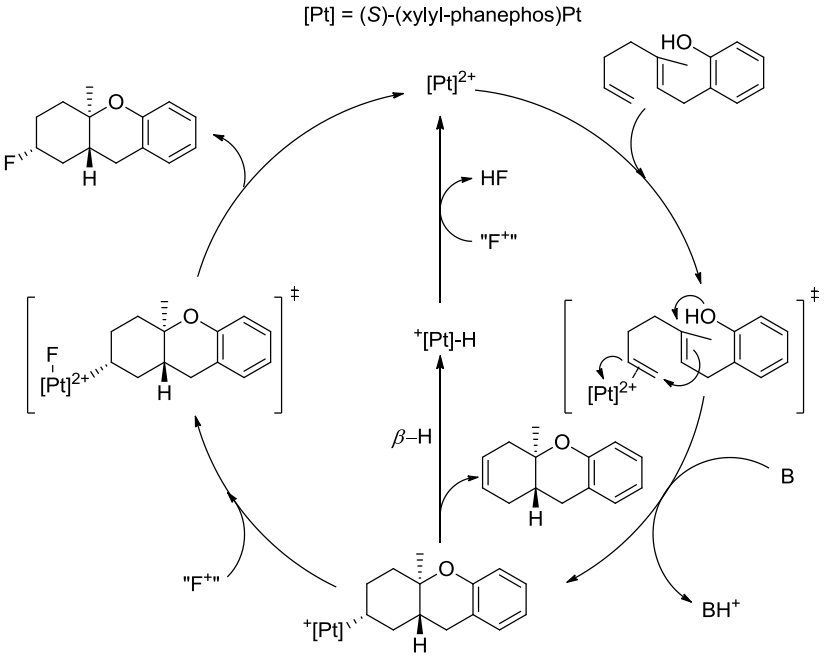
Gagne et al. recently demonstrated an example of catalytic fluorination/cyclisation using a Pt(II) catalyst.[91] The method involves the competition of the β-H elimination process with Pt-C fluorination. It was found that XeF_2 was the optimal "F^+" source competing effectively with β-H elimination. Optimal reactions was found to be (S)-(xylyl-phanephos)PtI_2, with $AgBF_4$ and NCC_6F_5 as activating agents for the Pt catalyst, TMSOMe as a HF sponge to avoid over fluorination and XeF_2. With these conditions, isolated yields of up to 69% and enantioselectivity of up to 87% was achieved (Scheme 43).



Scheme 43 - Catalytic fluorination/cyclisation using a Pt(II) catalyst

The proposed mechanism involved the initial platinum mediated cyclization of the dieneol to give the intermediate Pt(II) complex. At this stage there are two possible reaction pathways. The desired fluoro-carbocyclized product is obtained upon oxidative fluorination of Pt(II) to generate a transient Pt(IV) species which, upon stereo-retentive reductive elimination, furnishes the fluorinated product and regenerates the catalyst. Alternatively, the

intermediate platinum complex can undergo β-hydride elimination to afford the eliminated by-product, along with a Pt-hydride complex. Upon interaction with electrophilic fluorine the hydride species is oxidised to generate an equivalent of HF. In initial studies it was found that the fluorinated product was susceptible to over-fluorination of the aromatic ring, which was suggested to be a result of XeF_2 being activated by the HF produced as a by-product. Therefore, several "HF sponges" were investigated and TMSOMe was found to be the most effective.



Scheme 44 – Proposed mechanism for fluoro-carbocyclization

Various aryl groups were tolerated with electron-withdrawing para-substituents found to improve enantioselectivity. However, elimination products were always present indicating that the alternate pathway could not be removed. It is also important to note the introduction of fluorine is also done by reductive elimination and is not part of the cyclization process.

1.4 Conclusion

Over the past few decades considerable progress has been made in the field of fluorocyclization. However, in recent years the advancement has somewhat slowed, demonstrated by the relatively slow publication rate. In the early years, many publications reported the fluorocyclization of highly activated substrates, heavily biased towards the desired reaction. Alternatively, when more reasonable substrates were employed, highly reactive and generally undesirable reagents were used, which limited the appeal of fluorocyclization methodology. Asymmetric techniques are particularly scarce, but several important developments over the past few years have certainly enriched the field. The cinchona alkaloid approach of Gouverneur, the phase-transfer method of Toste and the platinum mediated strategy of Gagné have significantly broadened the scope for what is possible. There is therefore the need to develop new methodology, combining moderate substrate reactivity with attractive fluorinating reagents, preferably in an asymmetric manner.

1.5 Thesis outline

There are three areas in the field of fluorocyclization which we wished to address in this thesis, namely the substrate, the reagent and the stereoselectivity. Firstly, we wanted to investigate a substrate which was somewhat less biased towards a fluorocyclization reaction than other typical substrates in the literature. Over-functionalization of substrates to promote reactivity is sometimes undesirable later in a synthetic sequence and so development of systems which require less activation would be a valuable contribution. We were also interested to employ carbon nucleophiles to achieve a so-called fluoro-carbocyclization since this is a massively underdeveloped area in the literature. Use of a

carbon nucleophile, instead of much more nucleophilic heteroatoms would pose a much greater challenge but would facilitate the advancement of this field of research. Secondly, we were concerned to utilize reagents which were easily obtained, either from a commercial source or a short synthetic route. Any methodology benefits significantly from easily reproducible procedures and so we were determined to develop systems which would be easily replicated. Thirdly, we were excited to translate any success on a new fluorocyclization system to an asymmetric method. Given the first two remits of the thesis, we envisioned this could be a great challenge due to the requirement of relatively high reactivity of current methods in the literature.

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Chapter 2:

Fluorocyclization Reactions

2. Fluorocyclization Reactions

2.1 Introduction

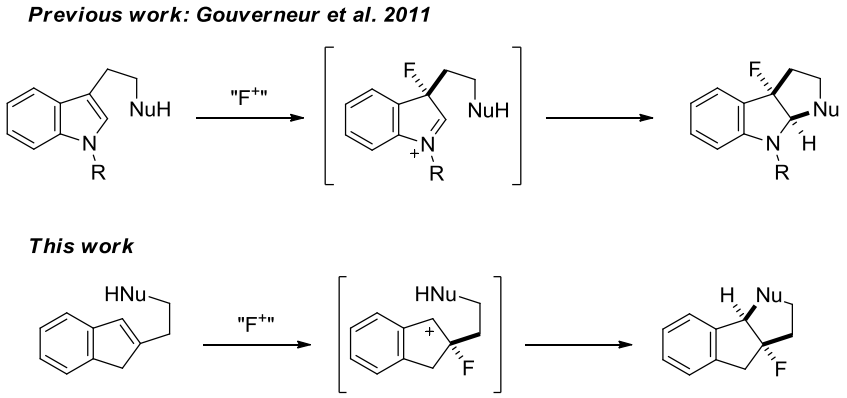
There is a clear need for the advancement of current fluorocyclization methodology to increase both scope and selectivity of reactions. As outlined in Chapter 1, whilst great progress have been made in the field of fluorocyclization over the past few decades, there is still much work to be done. Nucleophilic fluorine mediated processes still often suffer from the major shortcoming of requiring undesirable HF reagents. The choice of fluoride source is a more general problem in organofluorine chemistry than specifically for cyclization reactions and would almost certainly require major advances in reagent development before the operational simplicity of electrophilic fluorocyclization reactions could be rivalled. Therefore, with a plethora of electrophilic reagents commercially available we elected to focus on electrophilic routes towards the development of novel fluorocyclization reactions.

The remit of this thesis was primarily to extend current methodology in three important ways. Firstly, we were keen to make progress in the class of substrates which are suitable for such reactions. Typically, highly activated substrates are required, which are capable of significant intermediate carbocation stabilization. Whilst this can be easily achieved, by one of the methods outlined in Chapter 1, it is not always desirable to obtain products which feature silicon groups (β-silicon stabilization), indoles (iminium stabilization) or excessive aromatic groups (dibenzylic stabilization). Therefore, we were interested to investigate a new class of substrates which would exhibit a lower reactivity profile than those which are currently used.

Secondly, and chiefly, our objective was to investigate the use of a carbon nucleophile to achieve a fluorocyclization. To date, pendant nucleophiles used in fluorocyclization reactions

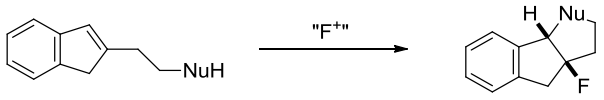
have typically focussed on hetroatoms such as nitrogen and oxygen, with amides, sulfonamides, alcohols and carboxylic acids being amongst the most common.[1] A few examples of carbon nucleophiles have been reported but they either use highly activated substrates,[2,3] a pseudo-one-pot procedure which is a fluorination followed by a cyclization,[4] or require a transition metal catalyst.[5] Our goal was therefore to develop a system which did not require unusual elaborate substrates, which could be performed using typical commercial electrophilic reagents and which did not require a transition metal catalyst. The final challenge would be to extend any such reaction to achieve an asymmetric variant. This could potentially pose a significant challenge since current asymmetric methods require considerable substrate activation.

The system that we decided to develop was based on indene and dihydronaphthalene motifs. We would therefore be relying upon benzylic stabilization of an intermediate carbocation to promote a reaction. Whilst the requirement to have an aromatic group present does not constitute a complete removal of substrate activation, it is typically far less activated than other methods reported in the literature. Moreover, styrene like systems have previously been explored but they were found to require very powerful fluorinating reagents, where we propose to optimise the reaction to utilize more standard reagents. A previously successful fluorocyclization reported by the Gouverneur group focussed on the cyclization of prochiral indoles.[6] It is this reaction which we took as a model to further develop as we envisaged the indole motif could be made considerably less reactive by using an indene motif and the pendant alcohols or amines could be replaced with a carbon nucleophile. Unlike in an indole system where a pendant nucleophile is placed on the 3-position in order to react with the intermediate iminium ion at the 2- position, in an indene system the nucleophile should be placed at the 2- position in order to react with the benzylic carbocation (Scheme 1).



Scheme 1 – Electrophilic fluorocyclization; a) indole system, b) indene system

Before we considered the possibility of using a carbon nucleophile, we wished to first investigate the use of an indene system. To validate its potential as a new class of substrate for fluorocyclization we initially experimented with a prochiral indene bearing a pendant alcohol nucleophile so that the reactivity of the nucleophile was not a concern. We proposed the following model reaction to investigate.



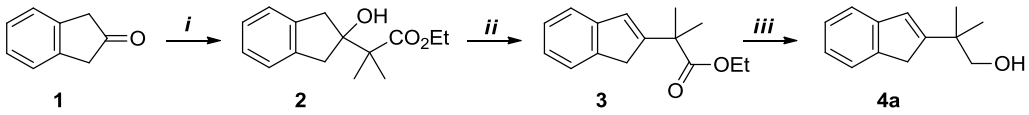
Scheme 2 – Proposed model reaction

2.2 Reaction development

Heterocyclic sub-motifs are ubiquitous in lead pharmaceutical compounds and therefore the development of methodology for the construction of fluorinated analogues would be of great interest.[1,7,8] Many existing methods to access fluorinated heterocycles rely upon the cyclisation of prefluorinated building blocks or the fluorination of a precyclised heterocycle. A more elegant approach would be to install the fluorine atom in tandem with the

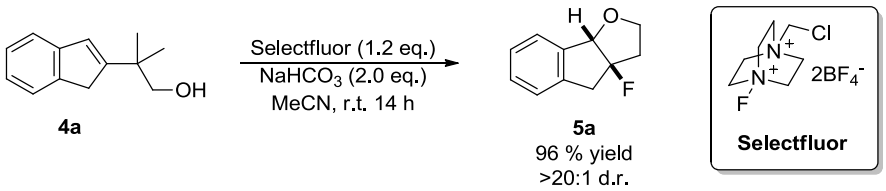
cyclisation step. Several examples of this strategy have appeared in the literature over the recent years but many involve harsh reaction conditions and poor selectivity towards the desired product.[8]

In order to validate the reactivity of the system we prepared indene **4a** which featured a pendant alcohol on the 2-position. We also included a gem-dimethyl group on the side chain, proposing that a cyclization could benefit from a Thorpe-Ingold effect.[9] The substrate was accessed by an Aldol reaction between ethyl isobutyrate and *β*-indanone (**1**) to furnish the intermediate tertiary alcohol. Dehydration to the indene was achieved by refluxing the alcohol in benzene in the presence of phosphorous pentoxide. Finally, reduction of the ester using DIBAL in ether at -78 °C afforded **4a** as a white solid (Scheme 3).



Scheme 3 – Preparation of indene **4a**; *i*) LDA, ethyl isobutyrate THF, -78 °C, 54 % yield, *ii*) P_2O_5, benzene, reflux, 1 h, 39 % yield, *iii*) DIBAL (2.7 eq.), ether, -78 °C, 1 h, 96 % yield

To achieve the fluorocyclization reaction we were keen to develop a reaction which utilized common electrophilic reagents and which was operationally very simple to carry out. We therefore elected to use Selectfluor as the fluorinating reagent as this is typically the most common reagent and normally the first to be investigated. The use of Selectfluor generally all but dictates the use of acetonitrile as the reaction solvent due to the solubility requirements of the dicationic reagent. Finally, an excess of sodium bicarbonate was employed as a mild inorganic base to remove any acid formed in the reaction, owing to the possibility of a competing proto-cyclization reaction.



Scheme 4 – Fluorocyclization of **4a** using Selectfluor

We were delighted to isolate the desired fluorocyclized product in a 96 % yield as a single detectable diastereomer. We speculated at this point that the diastereomer was that of a *syn* disposition of the fluorine and hydrogen at the ring junction due to the considerable strain associated with forming a 5,5-*trans* ring junction. What was especially pleasing was that the reaction was very clean, with the crude product following work up being of almost analytical purity. The crude ^{1}H NMR spectrum from this reaction is displayed in Figure 1.

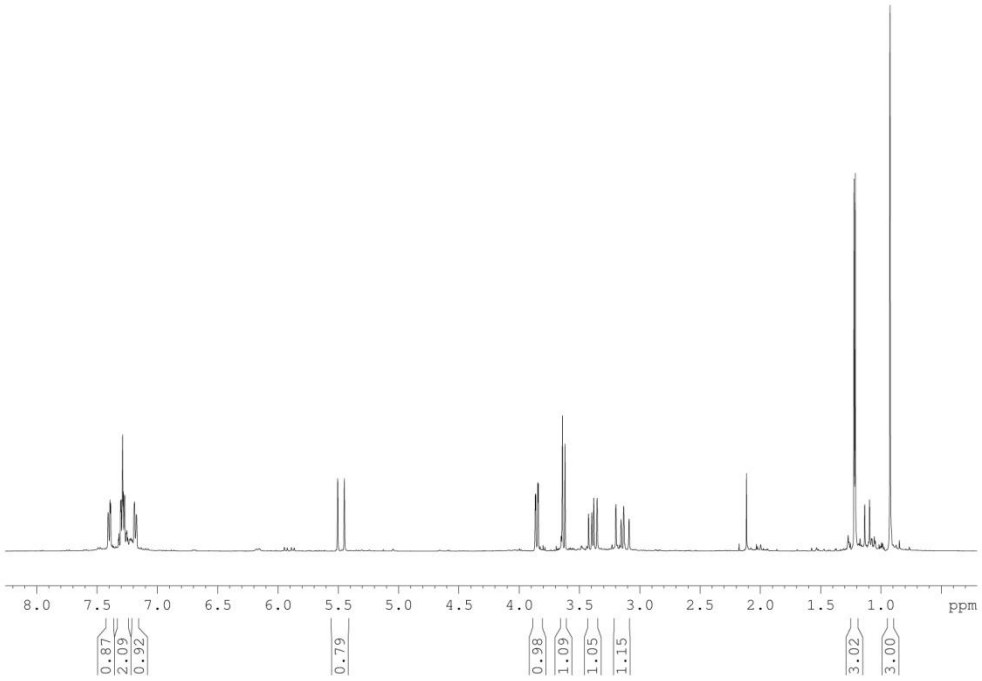
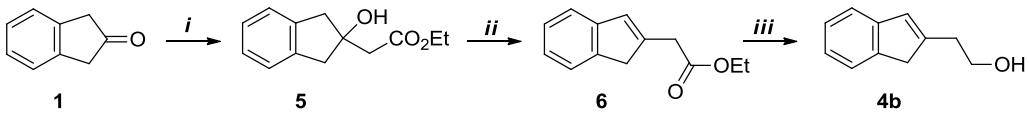


Figure 1 – Crude ^{1}H NMR spectrum of fluorocyclization reaction

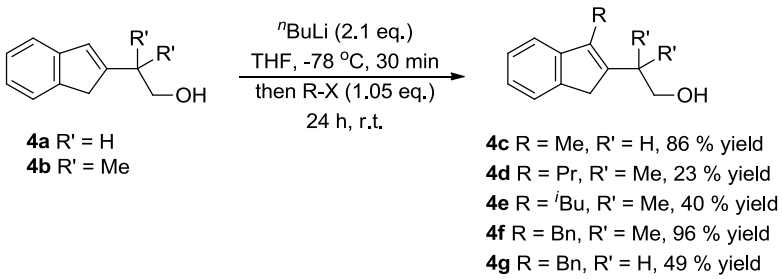
2.3 Substrate synthesis

With the reactivity of the system successfully validated, we decided to explore the substrate scope by preparing a library of indene and dihydronaphthalene substrates. We were interested if pendant carboxylic acids could be used to achieve a fluoro-lactonization and whether sulfonamide nucleophiles would be sufficiently reactive to accomplish a fluoro-amidation. We were also curious if the gem-dimethyl group was indeed necessary and began by preparing the corresponding alcohol **4b** in a similar method to that of **4a**.



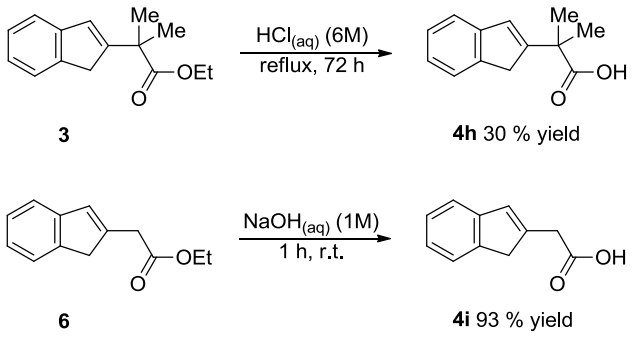
Scheme 5 – Preparation of indene **4b**; *i*) LDA, ethyl acetate THF, -78 °C, 68 % yield, *ii*) PTSA (10 mol %), benzene, reflux, 1 h, Dean-Stark, 41 % yield, *iii*) DIBAL (2.7 eq.), ether, -78 °C, 1 h, 99 % yield

To elaborate the alcohol substrates we derivatzed at the α- position by first deprotonating using ^{n}BuLi and then quenched using an appropriate alkylating reagent. It was important to use an excess of ^{n}BuLi since the first equivalent was sacrificed through deprotonation of the alcohol. Analogues of both gem-dimethyl alcohol **4a** and unfunctionalized alcohol **4b** were prepared according to Scheme 6. The amount of alkylating agent added was carefully controlled since any excess could undergo a Williamson reaction and diminish the yield of the product.



Scheme 6 – Alkylation of indenes at the alpha position

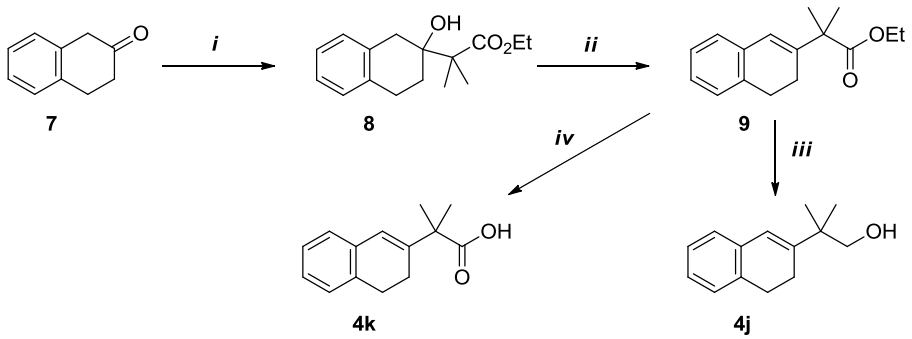
The substrates featuring pendent carboxylic acids were accessed from hydrolysis of the intermediate esters **3** and **6** instead of the reduction step. Ester **6** was found to undergo facile saponification with aqueous sodium hydroxide, however ester **3** was totally resistant to these conditions, presumably due to the neopentyl effect. We found that refluxing **3** in 6M NaOH was similarly fruitless and instead resorted to acid mediated hydrolysis. After refluxing in 6M HCl for 72 hours, a moderate yield of hydrolysed product **4h** was isolated (Scheme 7), with the remainder of the mass accounted for as unreacted starting material.



Scheme 7 – Preparation of substrates featuring pendant acid nucleophiles

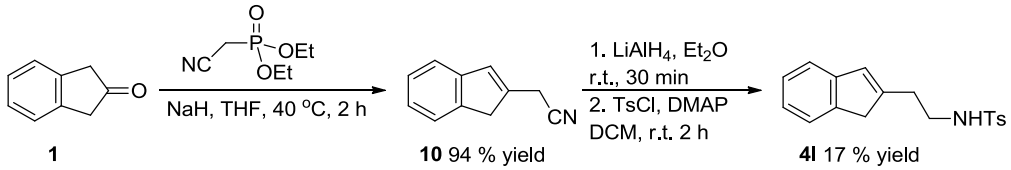
Substrates based on a dihydronaphthalene system could be synthesized in a similar way starting from *β*-tetralone. The Aldol reaction with ethyl isobutyrate furnished the intermediate alcohol in a 50 % yield, which was subsequently dehydrated in the usual way

using phosphorous pentoxide to afford dihydronaphthalene **9** in a 92 % yield. The desired alcohol **4j** was accessed by DIBAL reduction of the ethyl ester in a 85 % yield, whereas acid **4k** was saponified in a 42 % yield using refluxing aqueous sodium hydroxide.



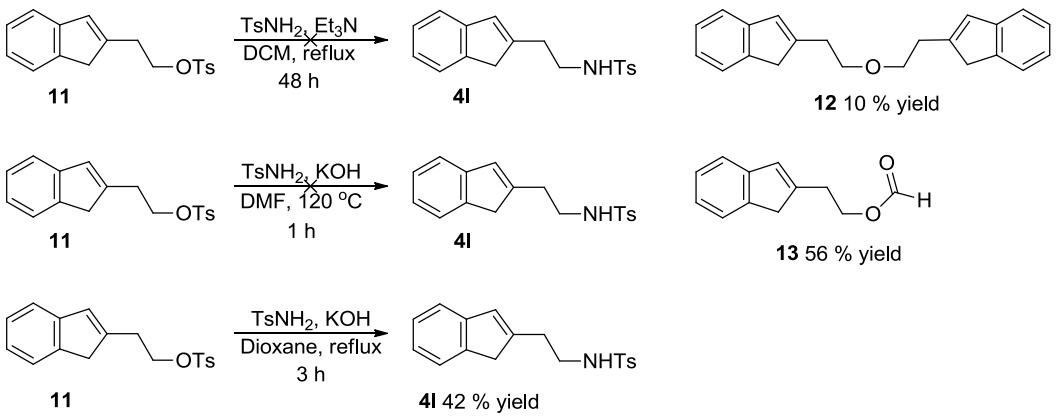
Scheme 8 – Preparation of dihydronaphthalene substrates; *i*) LDA, ethyl isobutyrate, THF, -78 °C, 50 % yield, *ii*) P_2O_5, benzene, reflux, 1 h, 92 % yield, *iii*) DIBAL (2.7 eq.), ether, -78 °C, 1 h, 85 % yield, *iv*) NaOH (1M), EtOH, reflux, 24 h, 42 % yield

Finally, we prepared a substrate featuring a pendant sulfonamide nucleophile. We would expect this nucleophile to be considerably less reactive than the alcohols or acids and might therefore offer some insight into the future difficulty of using carbon based nucleophiles. Initially we envisaged preparing a cyano compound which could be reduced to the free amine and protected with tosyl chloride (Scheme 9).



Scheme 9 – Preparation of *N*-tosyl substrate

To attempt to improve the yield of the synthesis we explored a route starting from the corresponding tosylate and attempted to simply displace the tosylate using tosyl amide. Reaction with tosyl amide in refluxing DCM in the presence of triethylamine afforded only a small amount of an ether side-product, arising from the hydrolysis of the tosylate by residual water and subsequent etherification with a second tosylate. The remaining mass was recovered starting material (Scheme 39). We propose, therefore, that tosyl amide is simply not nucleophilic enough to displace tosylate at this temperature. We therefore tried to increase its reactivity by preforming deprotonated tosylamide with potassium hydroxide in hot DMF. However, the only product that could be recovered from the reaction was that of formylation, presumably a consequence of the reaction of the intermediate alcohol with DMF. Finally, replacing the solvent with dioxane and prolonging the reaction time furnished the desired product in moderate yield.



Scheme 10 – Attempted improvement of *N*-tosyl substrate synthesis

At this point we had a library of substrates ready for fluorocyclization as illustrated in Figure 2. The overall yields for their syntheses are given but are not optimised as this was felt to be unnecessary for the project.

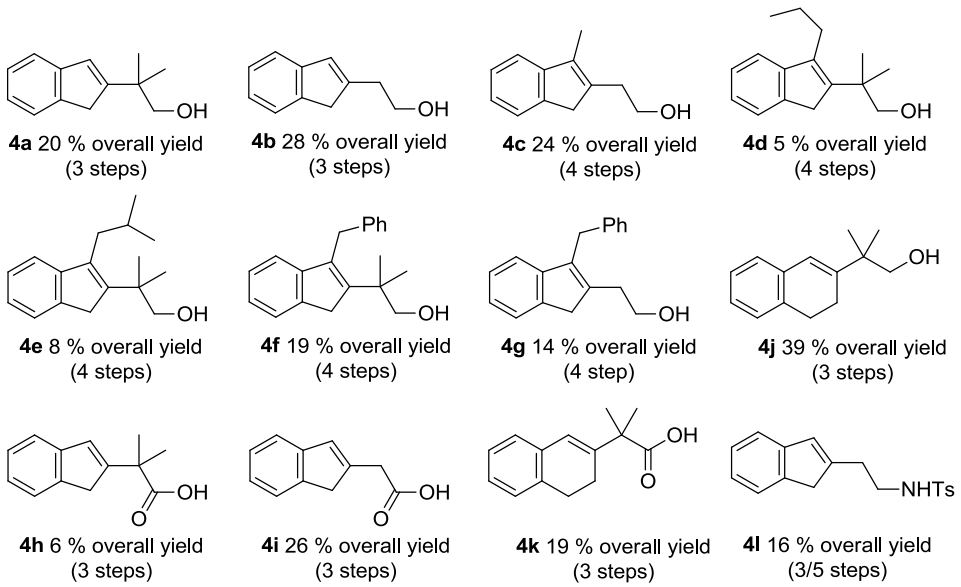
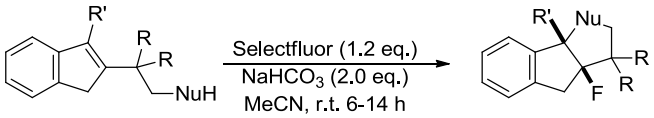


Figure 2 – Library of substrates for fluorocyclization

2.4 Substrate scope

We subjected our library of substrates to the reaction conditions initially used on **4a**. Pleasingly all the substrates reacted to afford the fluorocyclized products in moderate to excellent yields. The diastereoselectivity of the reaction was also excellent for all the substrates, consistent with the inherent strain in forming the alternative isomer. Interestingly, the reaction proceeded equally smoothly where substitution at the alpha position was present. This indicates that for this class of substrates is possible to have a tertiary benzylic stabilised intermediate carbocation.



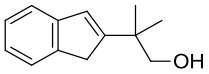
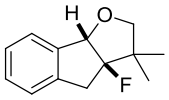
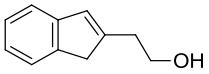
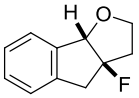
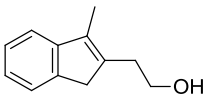
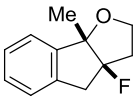
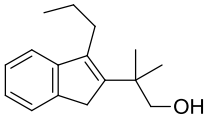
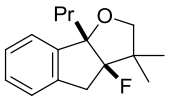
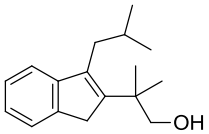
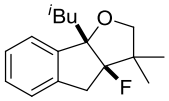
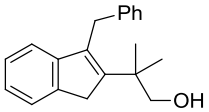
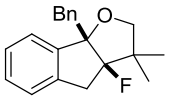
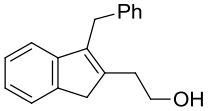
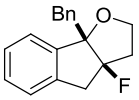
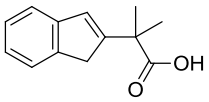
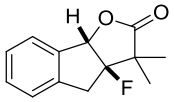
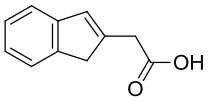
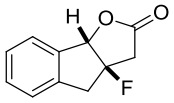
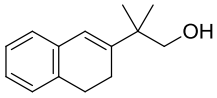
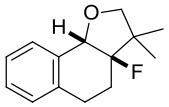
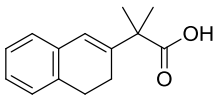
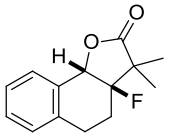
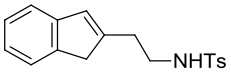
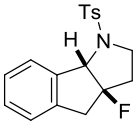
Entry	Substrate		Product		Yield (%)	d.r.
1		**4a**		**5a**	96	>25:1
2		**4b**		**5b**	58	>25:1
3		**4c**		**5c**	76	>25:1
4		**4d**		**5d**	96	>25:1
5		**4e**		**5e**	83	>25:1
6		**4f**		**5f**	73	10:1
7		**4g**		**5g**	90	>25:1
8		**4h**		**5h**	70	>20:1
9		**4i**		**5i**	42	10:1
8		**4j**		**5j**	59	10:1
11		**4k**		**5k**	58	>20:1
12		**4l**		**5l**	36	>25:1

Table 1 – Selectfluor mediated fluorocyclization of indene substrates

Conditions: Selectfluor (1.2 eq.), $NaHCO_3$ (2.0 eq.), MeCN, r.t. 6-14 h

Several of the fluorocyclized products were crystalline solids and we were able to obtain an x-ray crystallographic structure of products **5i**, **5k** and **5l**. The structures confirmed our earlier prediction of syn arrangement at the ring junction and, by analogy, we assigned the other products as being *syn*.

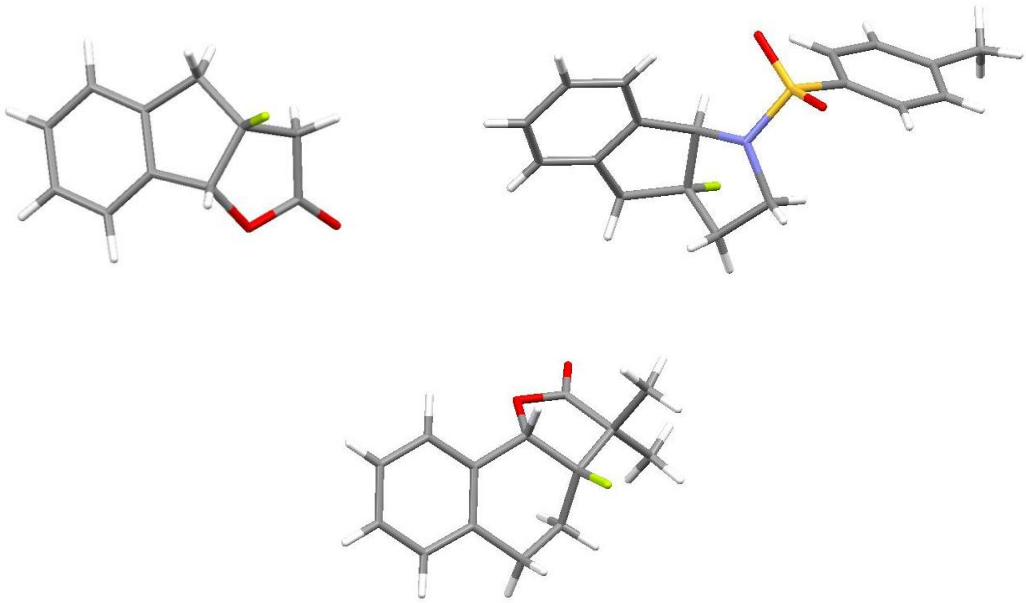
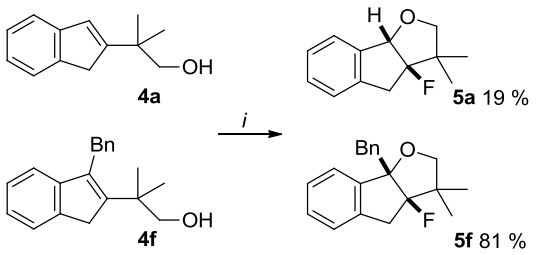


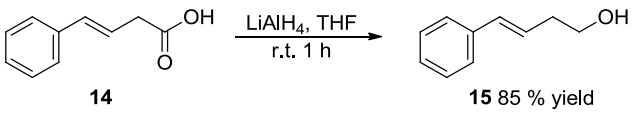
Figure 3 – X-ray crystallographic structures of **5i, 5k, 5l**

We were intrigued to elucidate the relative importance that having a tertiary stabilised benzylic carbocation had on the reaction efficiency. To probe this we conducted a competition reaction in which equimolar equivalents of 2 substrates, one tertiary and one secondary, were reacted with 1 equivalent of Selectfluor (Scheme 16). The product ratio of 81:19 in favour of the substituted indene suggests to us that tertiary stabilisation has a large effect on the reactivity of the substrates.



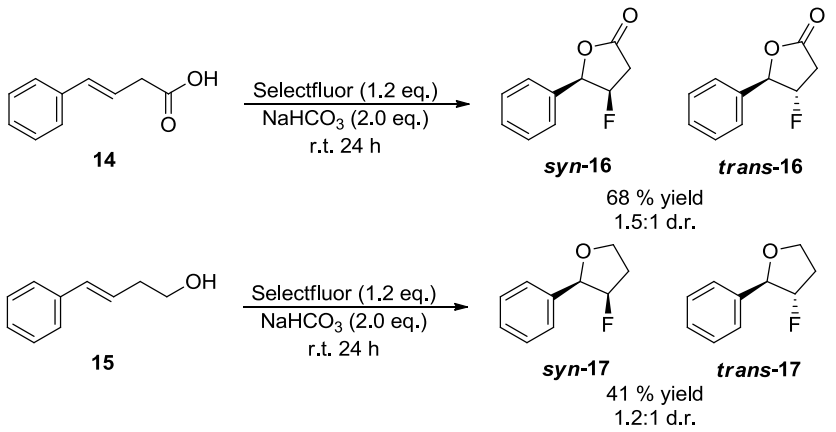
Scheme 11 - Competition reaction; *i*) Selectfluor (1.0 eq.), $NaHCO_3$ (2.0 eq.), MeCN, 14 h, r.t.

In an effort to explore the diastereoselectivity of the reaction when the system is not so biased to give a high diastereomeric ratio simply due to the rigidity of the system we explored two different substrates. *Trans*-styrylacetic acid **14** and its corresponding alcohol **15** were selected as they retained the benzylic stabilisation but not the rigidity. The alcohol was accessed by a lithium aluminium hydride reduction of the commercially available acid.



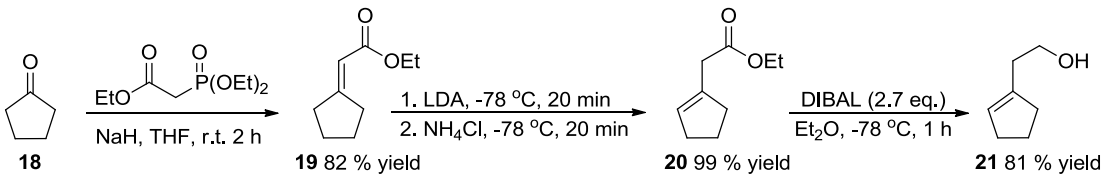
Scheme 12 – Lithium aluminium hydride reduction of *trans*-styrylacetic acid

The substrates were subjected to the same mild conditions that the indene systems were treated with to give the corresponding fluorocyclised products in moderate yields. Interestingly, whilst the starting material was purely *trans*, the reaction displayed essentially no diastereoselectivity. We found that the reactions, particularly with the carboxylic acid, gave very complex mixtures of products. Not only was there a mixture of a pair of diastereomers but the diastereomers themselves existed as two conformational isomers that are visible by NMR spectroscopy. This observation was not entirely surprising as Ma *et al.* found, with *cis*-styrylacetic acid, a complex mixture of products was observed when using similar conditions.[10]



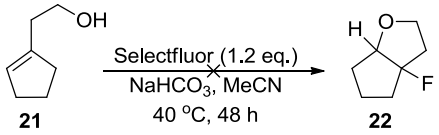
Scheme 13 – Fluorocyclization of *trans*-styrylacetic acid and *trans*-4-phenylbut-3-en-1-ol

In order to assess the limitations of this fluorocyclization methodology we wanted to investigate substrates that are even less activated. By removing the aromatic ring the stabilising effect at the benzylic position is removed and so the reactivity is greatly reduced. The substrate we initially considered was a simple alcohol that would have nothing more than secondary stabilisation of the carbocation intermediate to facilitate the fluorocyclization. Alcohol **21** was prepared from cyclopentanone by means of a Horner-Wadsworth-Emmons reaction to afford the α,β-unsaturated ester **19**. The corresponding β,γ-unsaturated ester was accessed by the deprotonation of **19** at -78 °C followed by protonation at low temperature to give the kinetic product **20** in quantitative yield. Finally DIBAL reduction of the ester furnished the desired alcohol **21** in a 66 % yield over 3 steps.



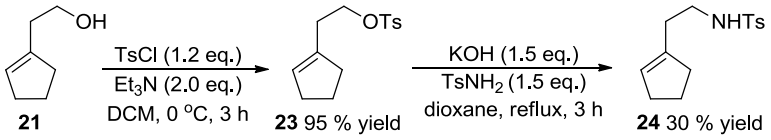
Scheme 14 – Synthesis of 2-(cyclopent-1-en-1-yl)ethanol from cyclopentanone

Alcohol **21** was subjected to similar fluorocyclization conditions with a higher reaction temperature employed due to the system being so deactivated. The reaction time was also increased to 48 hours. A characteristic peak was observed in the ^{19}F NMR spectrum of the crude reaction mixture at -191.2 ppm which could be attributed to **22**. Attempts to isolate the product, however, failed and this was speculated to be either the product being too volatile or too unstable towards purification by column chromatography.



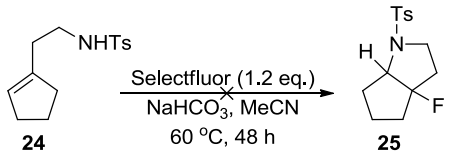
Scheme 15 – Fluorocyclization of 2-(cyclopent-1-en-1-yl)ethanol

To avoid the potential problem of volatility we opted to derivatise the substrate as the corresponding sulphonamide **24** by first tosylating **21** using standard conditions. Using a modified literature procedure of a 1:1 mixture of KOH and tosylamide in refluxing dioxane, **24** was formed in a 30 % yield starting from tosylate **23**. The remainder of the mass when the reaction was stopped was tosylate starting material. It was found to be necessary to use dioxane and not the higher boiling point DMF as, in our hands, we encountered problems of competing formylation as with the synthesis of **4l**.



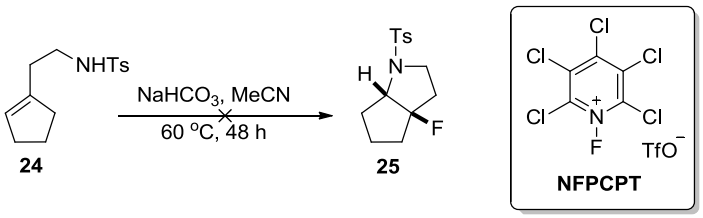
Scheme 16 – Synthesis of N-(2-(cyclopent-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide

Sulphonamide **24** was subjected to the usual fluorocyclization conditions but this time the reaction temperature was elevated to 60 °C and the reaction time kept at 48 hours. Only trace amounts of fluorinated products were observed in the crude ^{19}F NMR spectrum and none could be confidently attributed to the fluorinated heterocycle **25**.



Scheme 17 – Synthesis of N-(2-(cyclopent-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide

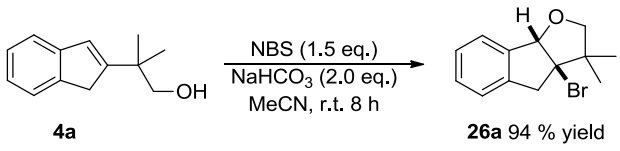
We propose that this is due to the system being too unactivated and Selectfluor being insufficiently reactive to promote the reaction. We therefore repeated the reaction using the more reactive fluorine source of *N*-Fluoropentachloropyridinium triflate. We observed an immediate strong colour change upon the addition of the fluorinating reagent, which indicates the possible contribution of an electron transfer mechanism, see Chapter 1. The product mixture showed a complex mixture of fluorinated products but no product could be detected. It was decided that the perchloropyridinium reagent was simply too reactive and led to complete decomposition. No further work was performed on substrates with this level of activation.



Scheme 18 – Attempted synthesis of *N*-(2-(cyclopent-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide

2.5 Halo-heterocyclization

We were intrigued to investigate whether this fluorocyclisation methodology could be extended to a more general halocyclization. Of course, the major difference between fluorine and the other halogens is that with fluorine the reversible formation of a halonium ion is not possible. For a fluorocyclization, the formation of the C-F bond is irreversible, therefore if fluorination can be achieved then any nucleophile more potent then external sources should successfully cyclize. In contrast, for other halogens, the formation of a C-X bond does not guarantee the accompanying cyclization since its formation is reversible. We first explored the possibility of bromocyclization using *N*-bromosuccinimide, a reagent which is as fundamental to bromine chemistry as Selectfluor is to fluorine chemistry. We reasoned that since the aforementioned fluorocyclization reaction occurred so quickly, *N*-bromosuccinimide would exhibit sufficient reactivity to promote bromocyclization. Pleasingly, by employing a small excess of the brominating reagent in the presence of sodium bicarbonate in acetonitrile, the bromocyclized product was obtained in a 94 % isolated yield after just 10 minutes of stirring at room temperature. Only a single diastereomer could be detected which is consistent with the *trans* opening of a halonium ion.



4a **26a** 94 % yield

Scheme 19 – Bromocyclization using *N*-bromosuccinimide

We assumed the single diastereomer would be the syn isomer, as was found to be the major diastereomer in the fluorocyclization reactions, but a crystal structure was obtained to

confirm the structure unambiguously. The bromocyclized product **26a** crystallized very readily by the slow evaporation of chloroform.

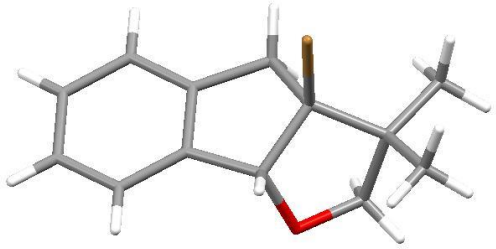
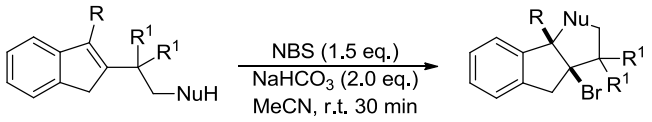
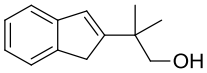
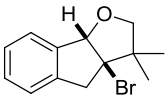
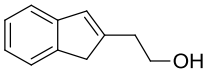
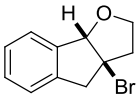


Figure 4 – X-ray crystal structure of bromocyclized product **26a**

With the bromocyclization methodology validated we next explored the substrate scope and were pleased to observe that all the substrates investigated could be bromocyclized in good to excellent yields and with complete diastereoselectivity. The products exhibited excellent stability towards work up and purification conditions, with no elimination products as a result of dehydrobromination being detected.



Entry	Substrate		Product		Yield (%)
1		**4a**		**26a**	94
2		**4b**		**26b**	75

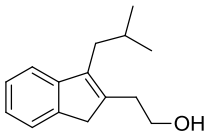
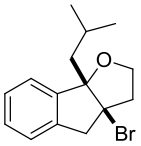
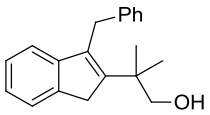
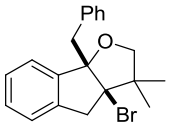
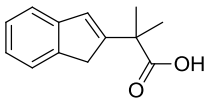
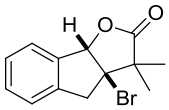
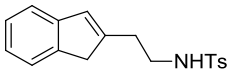
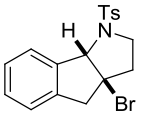
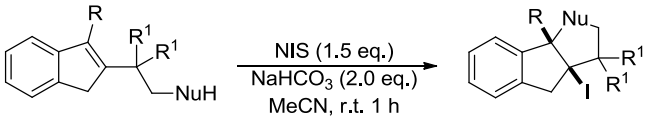
3		**4e**		**26e**	94
4		**4f**		**26f**	99
5		**4h**		**26h**	75
6		**4l**		**26l**	94

Table 2 – Bromocyclization of prochiral indene substrates

We anticipated that iodocyclization would also be possible by simply employing *N*-iodosuccinimide instead of *N*-bromosuccinimide. We were concerned that the iodocyclized products would be inherently more unstable than their brominated analogues and, in the presence of water, could lead to the alcohol derivative by hydrolysis or indene product by elimination. To minimise the decomposition of the product we changed the workup procedure and decided to instead dry load the crude reaction mixture directly onto silica gel and purify by flash chromatography. The yields were all typically good, with perfect diastereoselectivity as was observed for the other halocyclization reactions.



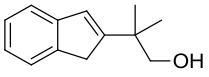
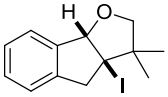
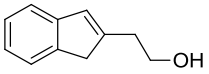
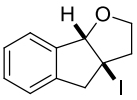
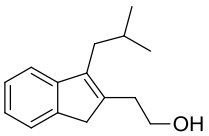
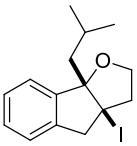
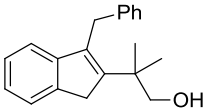
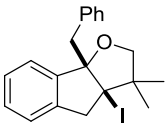
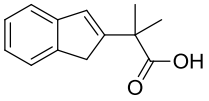
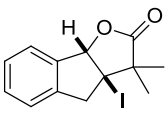
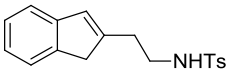
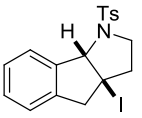
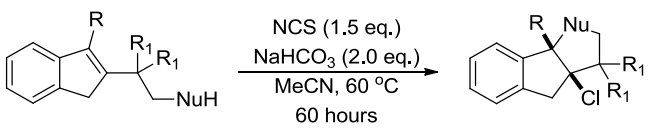
Entry	Substrate		Product		Yield (%)
1		**4a**		**27a**	93
2		**4b**		**27b**	83
3		**4e**		**27e**	71
4		**4f**		**27f**	52
5		**4h**		**27h**	86
6		**4l**		**27l**	40

Table 3 – Iodocyclization of prochiral indene substrates

The chlorine analogue of the halo-cyclization methodology proved to be a significant challenge. Attempts to perform a chlorocyclization using similar conditions failed and starting material was recovered in each case. This seemed somewhat puzzling since evidence suggests that *N*-chlorosuccinimide is of comparable reactivity to Selectfluor.[11] Since Selectfluor reacted so readily to afford the fluorocyclized products in short reaction times at room temperature, we would expect *N*-chlorosuccinimide to furnish chlorinated analogues. The failure of the chlorocyclization reaction can be attributed to a change in mechanism on going from fluorine to the other halogens in the group.

Fluorine reacts irreversibly to form a C-F bond to leave a carbocation, whereas other halogens react reversibly to form halonium ions. These halonium ions are then opened by a suitable nucleophile. We can imagine that the attack of the indene on the *N*-halosuccinimide is fast but the attack of the nucleophile is slow as the halonium ion is relatively stable. In electrophilic fluorination, the fluorination step is slow but the ensuing carbocation is very reactive so attack of a nucleophile is very fast. The irreversibility of an electrophilic fluorination is perhaps fortunate as we look towards an asymmetric version of the reaction. Once installed, the fluorine atom cannot racemise and so the enantiopurity does not diminish during the reaction. With halocyclizations, a catalytic asymmetric reaction is difficult to achieve because uncatalysed racemic reaction pathways become possible.

We proposed that the relative stability of the chloronium ion was the problem and that this could be overcome by using slightly more forcing conditions. We were pleased to observe that when elevated temperatures were employed for longer reaction times the chlorocyclized product was slowly formed. At 60 °C the reaction proceeded smoothly, albeit slowly, to afford the chlorocyclized product in a 71 % yield after 48 h. Due to the much lower reactivity of substrates towards chlorination, the nature of the substrate was very important. It was noticed that the substrates benefitting from a Thorpe-Ingold effect reacted particularly faster to furnish higher yields of products. We were delighted to observe that the substrate bearing a pendant acid group reacted equally as well to afford the corresponding chlorolactone in a 72 % yield.



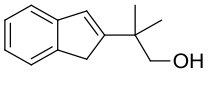
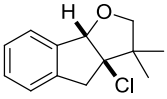
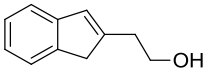
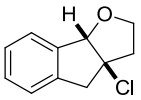
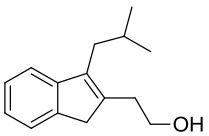
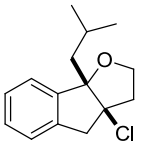
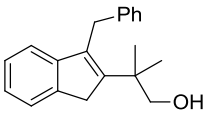
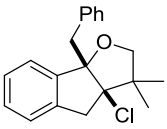
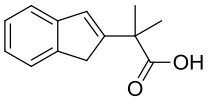
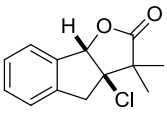
Entry	Substrate		Product		Yield (%)
1		**4a**		**28a**	71
2		**4b**		**28b**	38
3		**4e**		**28e**	99
4		**4f**		**28f**	41
5		**4h**		**28h**	72

Table 4 – Chlorocyclization of prochiral alcohols and carboxylic acids using NCS

2.6 Fluoro-carbocyclization

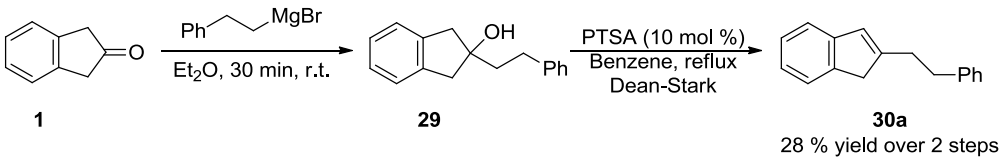
Following the success of the fluoro-heterocyclization reactions we were excited to progress to the next challenge. Having validated indenes and dihydronaphthalenes as suitable substrates for use with common fluorinating reagents we wanted to investigate the use of a carbon nucleophile. The second stage of a so-called fluoro-carbocyclization reaction would be the trapping of the resultant carbocation by a carbon nucleophile. Since this carbocation could be trapped by an external nucleophile such as water, this rules out nucleophilic solvents. Also, since acetone is very wet and difficult to obtain in a completely anhydrous form, we can rule out acetone as a solvent too. The use of acetonitrile is well known to introduce the problem of a competing fluoro-Ritter reaction. However, due to the well-

precedented superiority of acetonitrile as a solvent for electrophilic fluorinating reactions we elected to investigate this solvent in spite of the competing side-reaction. This means that the internal carbon nucleophile would need to be more reactive than the reaction medium. However, the carbon nucleophile cannot be made too reactive as then fluorination of the nucleophile will become a problem. In view of these challenges, we began by considering what nucleophiles could be suitable under the reaction conditions. Given that our olefin source would be either an indene or dihydronaphthalene, we required a carbon nucleophile which would be less reactive than this. We first considered an allyl silane as a potential candidate, which is a good nucleophile due to *β*-silicon stabilisation of the intermediate carbocation upon nucleophilic attack. However, preliminary results showed that allyl silanes were, in fact, more reactive than the indene itself, delivering corresponding fluoro-desilylation products. Due to the powerful stabilisation effect of a *β*-Si group, we imagined that removing the silicon group to leave a tertiary carbocation, and not a *β*-Si stabilised carbocation, would temper the reactivity. However, preliminary studies again revealed that the pendant nucleophile was more reactive than the indene motif. The third approach that we postulated was to use an aromatic nucleophile since arenes are typically poorly reactive with electrophilic fluorinating reagents. Therefore, we were confident that we could suppress undesired fluorination of the aromatic ring.

2.6.1 Optimization studies

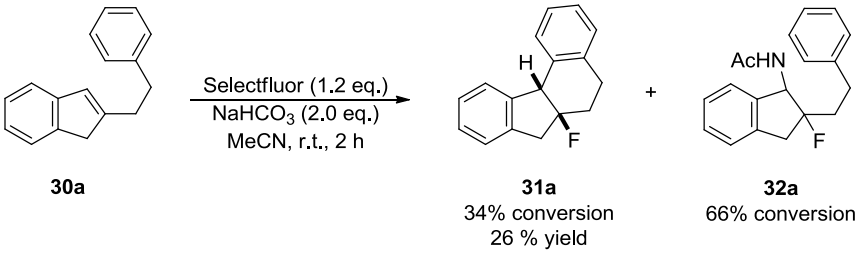
With these considerations in mind we began by considering the possible fluoro-carbocyclization of substituted indene substrates. We chose an aromatic ring as the nucleophile as it will not easily be fluorinated and can be easily modified to tune the reactivity. In the first instance we considered the formation of a six-membered carbocycle by tethering an ethylbenzene group to the 2 position of indene. The (2-phenyl)ethyl substituted

indene substrate was accessed by reaction of (2-phenyl)ethylmagnesium bromide (prepared by the reaction of magnesium and (2-bromoethyl)benzene in the usual way) on 2-indanone and subsequent dehydration of the resulting alcohol product under standard Dean-Stark conditions.



Scheme 20 – Synthesis of indene **30a**

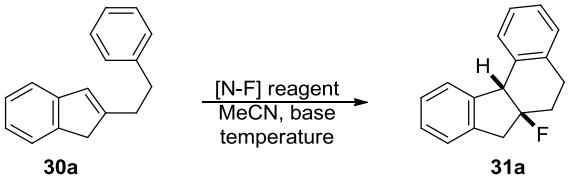
Application of Selectfluor and sodium bicarbonate in acetonitrile according to the protocol for fluoro-heterocyclization afforded an unoptimised 34 % conversion, which was then isolated in a 26 % yield. The remainder of the mass was recovered as the fluoro-Ritter product **32a**. This was an incredibly important result as it confirmed the possibility of a fluoro-carbocyclization reaction using substrates of an indene class of reactivity.



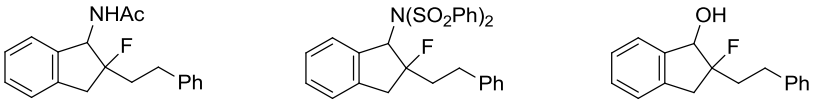
Scheme 21 – Preliminary result under fluoro-heterocyclization conditions

This lead result inspired us to further study the reaction and investigate how the problem of competing solvent capture of the intermediate carbocation could be addressed. We

undertook a full optimisation of the reaction, exploring the effect that changing the fluorine source, the solvent, temperature and base had on the reaction.



30a **31a**



32a **32b** **32c**

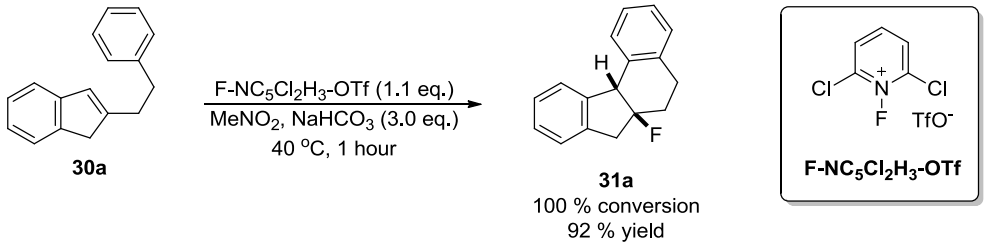
Entry[a]	N-F Source[b]	Solvent	Temp.	Ratio[c] **30a:31a:32a:32b:32c**	Yield **2a** [%][d]
1	**A**	MeCN	r.t.	0:**29**:63:0:8	26
2	**A**	MeCN	0 °C	0:**26**:69:0:5	-
3	**A**	MeCN	-40 °C	81:**3**:14:0:2	-
4[e]	**A**	MeCN	r.t.	19:**22**:49:0:10	-
5	**B**	MeCN	r.t.	56:**10**:0:33:1	-
6[f]	**A**	$MeNO_2$	r.t.	0:**93**:0:0:7	59
7[f]	**C**	$MeNO_2$	r.t.	0:**96**:0:0:4	89
8[f]	**C**	$MeNO_2$	0 °C	0:**86**:0:0:14	72
9[f]	**C**	$MeNO_2$	40 °C	0:**98**:0:0:2	92

Table 5 – Optimization of fluoro-carbocyclization; [a] General conditions: **1a** (50 mg), solvent (5 mL), $NaHCO_3$ (3.0 equiv), N–F reagent (1.1 equiv), 1 h. [b] **A** = Selectfluor, **B** = *N*-fluorobenzenesulfonimide (NFSI), **C** = *N*-fluoro-2,6-dichloropyridinium triflate. [c] Determined by ^1H NMR integration with 1-fluoro-3-nitrobenzene as an internal reference. [d] Yield of isolated product. [e] Reaction performed with 3 equiv of K_2CO_3. [f] Reaction performed in the presence of molecular sieves (3 Å).

Use of the substrate containing a 2-phenylethyl pendant nucleophile resulted in the formation of a small amount of fluoro-cyclized product (Table 5, entry 1). Complete consumption of the starting material was observed and the major side-product was the fluoro-Ritter product. Attempts to suppress the fluoro-Ritter reaction by lowering the temperature resulted in a poorer ratio of Ritter product to cyclized product (Table 2, entries

2 and 3). Examining changing the inorganic base to the more basic potassium carbonate led to a small but detrimental change in the ratio of products. The conversion was also not complete and so sodium bicarbonate was used for the rest of the optimisation reactions (Table 5, entry 4). The use of different fluorinating reagents to increase the ratio of cyclized product to Ritter-product also met with very limited success. NFSI reacted to give the corresponding fluoro-sulphonamide product and a small amount of cyclized product (entry 5).

Finally, examination of the reaction solvent proved to be very important. Use of the rather unusual solvent, nitromethane, was rewarded with considerable success (entry 6). Nitromethane appears to have the necessary properties of being polar but not excessively wet. A polar solvent is required to solubilise N-F^+ reagents and stabilise the reaction intermediates but, typically, polar solvents are both nucleophilic and contain a significant amount of residual water. Nucleophilic solvents, such as acetonitrile and methanol, lead to fluoro-Ritter and fluoro-ether products respectively. Polar, but non-nucleophilic solvents, such as acetone are typically wet and difficult to effectively dry and hence lead to fluoro-hydrin products. With full conversion of the starting material and a 59 % isolated yield, we continued to optimise the reaction further. Finally, changing the electrophilic fluorinating reagent to *N*-fluoro-2,6-dichloropyridinium triflate increased the yield to 89 % (entry 7). With the use of this new fluorinating reagent we saw a small amount of the trans diastereomer present in the ^{1}H NMR spectrum of the product. Lowering the temperature to 0 °C had a detrimental effect on the reaction yield (entry 8) but a small improvement was observed when the reaction was carried out at 40 °C (entry 9) which afforded a single diastereomer. It should be noted that the addition of freshly activated molecular sieves was critical to avoiding the formation fluoro-hydrin **32c**. The optimised reaction conditions are summarized in Scheme 22.



Scheme 22 – Optimised reaction conditions for fluoro-carbocyclization

2.6.2 Substrate synthesis

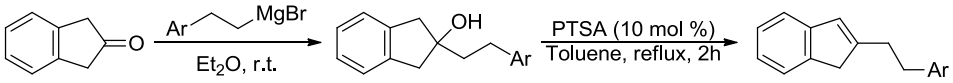
In order to conduct a broad substrate scope of this novel fluoro-carbocyclization reaction we first embarked on the synthesis of a library of representative substrates. In general, it was found that preparation of indene and dihydronaphthalene substrates was more complex than was first appreciated. The synthetic routes made use of commercially available indanones and tetralones, however surprisingly few methods were known in the literature for the preparation of pendant arenes. Several general procedures were employed and in some cases developed to furnish a library of substrates (Scheme 23).

In method 1, a Grignard reagent was first prepared from the appropriate alkyl bromide, most of which were commercially available. We found that diethyl ether was superior to THF as the solvent for the Grignard reaction and that higher temperatures were preferable to low temperature as otherwise products of Aldol condensation were detected, arising from the homocoupling of indanone. Dehydration of the intermediate alcohol could be achieved by a catalytic amount of PTSA in refluxing toluene. Interestingly, we found that Dean-Stark apparatus was not generally required, at least not on a multi-gram scale, and that the dehydration proceeded quickly without the need for dynamic removal of water.

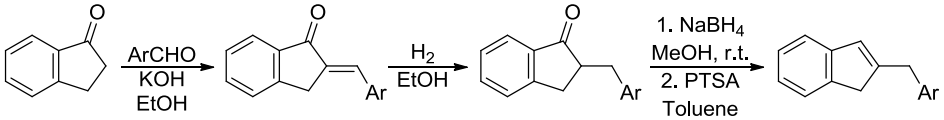
In Method 2, either α-indanone or α-tetralone can be reacted with a benzaldehyde in ethanolic potassium hydroxide to furnish the intermediate α,β-unsaturated ketone. In our hands, we found it typically favourable to reduce the alkene using standard hydrogenation

techniques prior to reduction of the carbonyl using sodium borohydride. Finally, dehydration could be achieved using the same procedure as in Method 1.

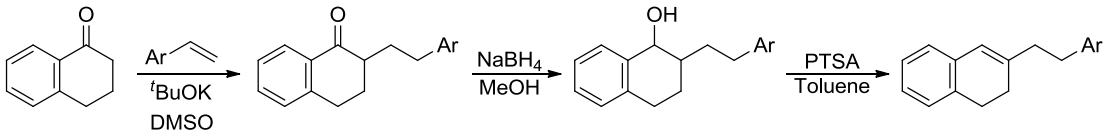
Method 1: *Grignard approach*



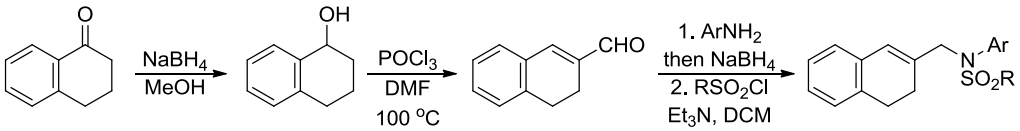
Method 2: *Aldol approach*



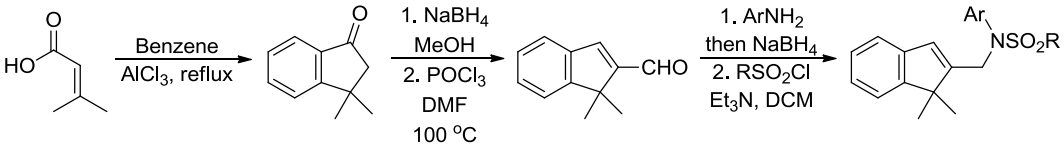
Method 3: *Styrene approach*



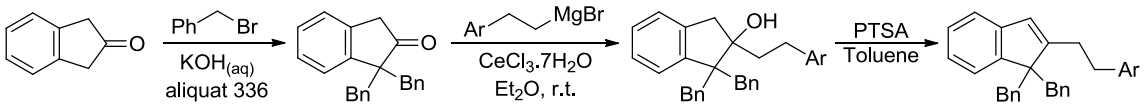
Method 4: *Reductive amination approach*



Method 5: *Friedel-Crafts acylation approach*



Method 6: *Direct alkylation*



Scheme 23 – General synthetic routes for substrate synthesis

Method 3 took advantage of a very useful reaction between α-tetralone and styrene, mediated by potassium *tert*-butoxide. The intermediate α-substituted tetralone was then reduced using sodium borohydride in the usual way and finally dehydrated. The same product can, of course, be accessed by Method 1 but the fact that α-tetralone and not β-tetralone is used as the starting material is synthetically very useful. The number of reported β-tetralones (and indanones) in the literature is far less than their α- isomer counterparts and even β-tetralone itself is rather expensive.

Method 4 offered a route to synthesize substrates featuring pendant aniline nucleophiles. In the first step α-tetralone was reduced under the usual conditions to furnish α-tetralol. After an exhaustive study of formylation reaction, only this synthetic route under Vilsmeir conditions offered any success. The reaction proceeded via the intermediate dihydronaphthalene before formylation under standard Vilsmeir conditions. Pleasingly, we found it to be unnecessary to dehydrate the tetralol prior to formylation as this occurred *in situ*. The α,β-unsaturated aldehyde was purified and isolated by column chromatography but was found to be only moderately stable towards oxidation and was therefore used reasonably quickly in the next step. Reductive amination with an appropriate aniline could be achieved in several ways, either using 2,2,2-trifluoroethanol as a solvent or under solvent free conditions. Finally, protection of the resultant secondary aniline, in order to decrease the reactivity of the aniline towards electrophilic aromatic fluorination, was performed with a variety of sulfonyl chlorides. The sulfonylation was carried out in DCM in the presence of triethylamine, however some anilines proved to be relatively unreactive and so a catalytic amount of DMAP was added to accelerate the reaction.

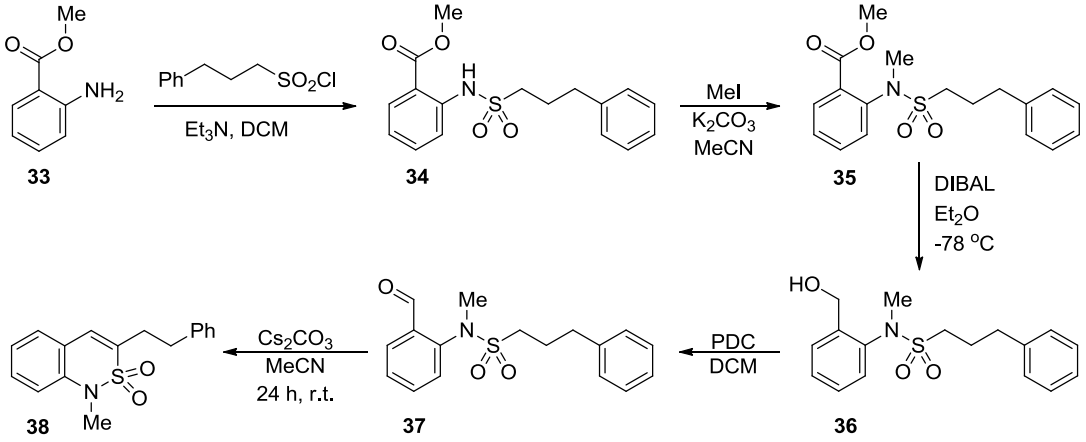
Method 5 was found to be the only successful route for indanones featuring substitution on the five-membered ring. All other methods failed to yield the desired product of 3,3-dimethyl-2,3-dihydro-1H-inden-1-one, presumably due to steric reasons. The synthetic route

involved the construction of the α-indanone, rather than the modification of a preformed indanone, using a Friedel-Crafts acylation reaction. 3-Methyl-crotonic acid was heated to reflux in benzene in the presence of a large excess of aluminium chloride to furnish the indanone in excellent yield on a multi-gram scale. The carbonyl group was next reduced using sodium borohydride and the indanol was subjected to the Vilsmeir conditions of Method 4 to afford the intermediate aldehyde. In this instance, this particular aldehyde was found to be extremely unstable, lasting only a matter of hours on the bench. It was therefore charged directly into the next step, with reductive amination being achieved under solvent free conditions. Protection was again carried out using the appropriate sulfonyl chloride with DMAP as a catalyst to promote the reaction.

Finally, a route of direct alkylation of β-indanones was investigated as attempts to synthesise indanones featuring substituents larger than methyl were unsuccessful. In Method 6, β-indanone was dialkylated with benzyl bromide in the presence of freshly powdered potassium hydroxide and a catalytic amount of aliquat 336 (*N*-methyl-*N,N*-dioctyloctan-1-ammonium chloride - a phase transfer reagent). A Grignard reaction was performed on the intermediate indanone but the addition of cerium (III) chloride was found to be necessary to achieve satisfactory yields. In the absence of the cerium additive, very low yields (<5 %) were obtained, with a large amount of Aldol type products being observed. Following the Grignard reaction dehydration was performed in the usual was to afford the 1,1-disubstituted indene.

A final substrate was prepared which featured a heteroatom in an alternative location than the pendant nucleophile. The synthesis involved the initial preparation of a non-commercial sulfonyl chloride, which was accessed from the corresponding alkyl bromide and sodium sulfite with subsequent chlorination using thionyl chloride. It was then coupled with the appropriate aniline with triethylamine added as a base and DCM as solvent. DMAP was not

added to this reaction since it was found that over-sulfonylation was possible to give the sulfonimide compound. Alkylation of the sulfonamide was achieved using iodomethane with potassium carbonate as base. Attempts to reduce the ester directly to the aldehyde were unsuccessful and so reduction to the alcohol was performed using an excess of DIBAL. The benzylic alcohol was then oxidised using PDC in DCM, so as not to over oxidise to the acid. Finally, cyclization was accomplished by stirring in acetonitrile in the presence of caesium carbonate.



Scheme 24 – Preparation of internal sulfonamide **38**

2.6.3 Substrate scope

Our first objective with these optimised reaction conditions was to explore the scope of the reaction and examine how general the methodology that we had developed was. We investigated using the cyclic indene and dihydronaphthalene substrates prepared according to Scheme 23 as their design would dictate a high level of diastereoselectivity due to ring strain considerations. We explored making smaller and larger carbocyclic rings, changing the electronics of the nucleophile and changing the stabilization of the intermediate carbocation.

We began by first exploring the size of carbocycles which could be accessed using our fluoro-carbocyclization system. We developed a selection of substrates according to method 1 of Scheme 23. Subjecting these substrates to the general conditions demonstrated that only 6-membered carbocycles could be formed (entry 1, Table 6). Presumably, the ring strain in the transition state is prohibitively high to allow cyclization to form the five-membered ring and the seven-membered ring formation is disfavoured by the high preorganisational energies required for medium ring formation. We presume that the lack of recovery of starting material is due to the sufficient reactivity of the olefin but the incompatible cyclization which leads to inter-molecular polymerization type reactions.

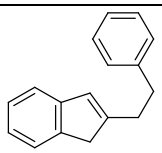
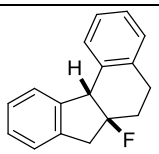
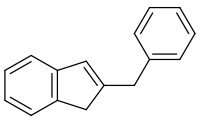
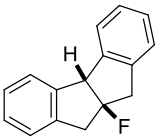
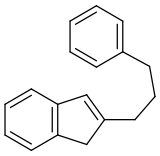
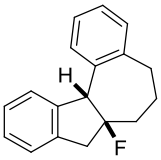
Entry	Substrate		Product		Yield	d.r. (*syn*:*anti*)
1		**30a**		**31a**	92	>25:1
2		**30b**		**31b**	0	-
3		**30c**		**31c**	0	-

Table 6 – Investigating the ring size reaction scope

We next investigated the stabilisation of the intermediate carbocation. For the heterocyclization reactions we found that α-substitution was not only tolerated but also potentially favourable and so we examined substrates which would react by an intermediate tertiary stabilised carbocation. First of all, we considered a substrate featuring a vinyl arene

with the nucleophile still at the β- position but no product was observed (entry 1, Table 7). Secondly, we probed the reactivity of two α- substituted dihydronaphthalenes that would potentially cyclize to afford a spiro-type compound. No product was observed for **30e** but **30f** delivered a trace of product. We therefore proceeded to only consider α- unsubstituted substrates.

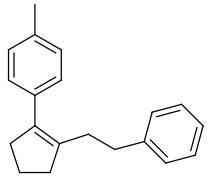
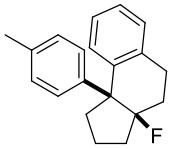
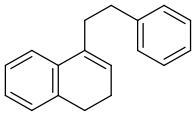
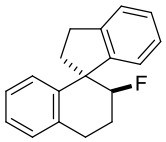
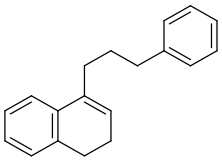
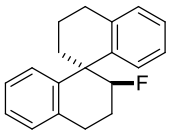
Entry	Substrate		Product		Yield	d.r. (*syn*:*anti*)
1		**30d**		**31d**	0	-
2		**30e**		**31e**	0	-
3		**30f**		**31f**	Trace	-

Table 7 – Investigating possible substitution at the α-position

Having determined the ring size and electronic factors which were compatible in our reaction, we progressed to explore the nature of the nucleophile. Substitution at the *meta*-position of the nucleophile was tolerated as demonstrated by **30g**, delivering fluoro-carbocyclized product **31g** in excellent yield. However, the regioselectivity was somewhat disappointing with a mixture of isomers caused by reaction either *ortho* or *para* to the methoxy group. Both alkyl and halogen substituents on the nucleophile at the *para* position were tolerated and demonstrated using both indene and dihydronaphthalene system.

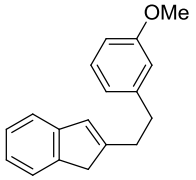
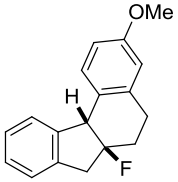
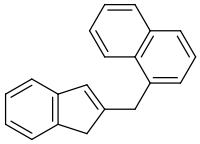
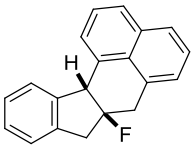
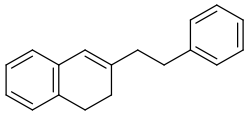
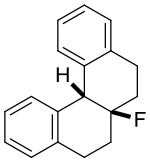
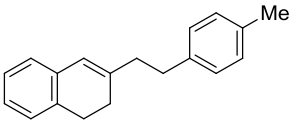
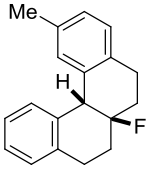
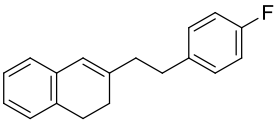
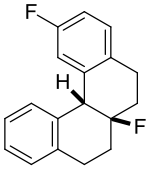
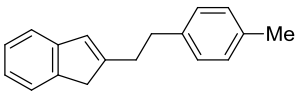
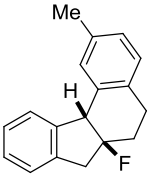
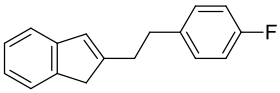
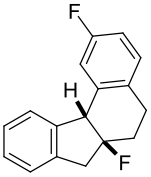
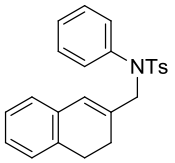
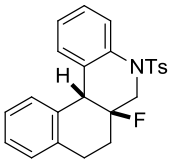
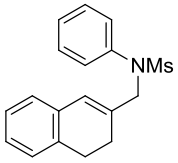
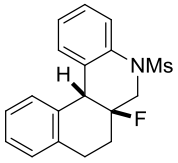
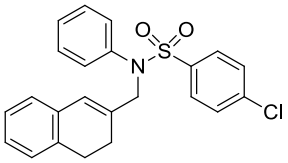
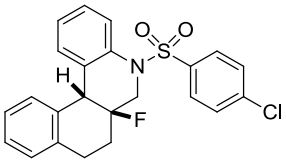
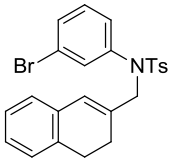
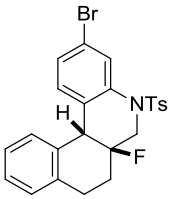
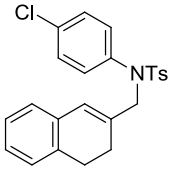
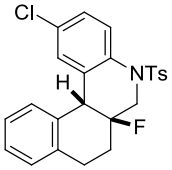
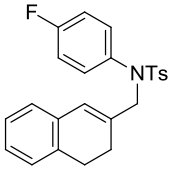
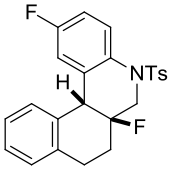
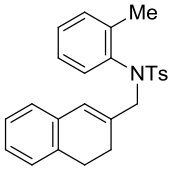
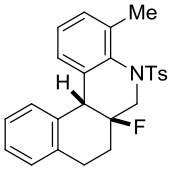
Entry	Substrate		Product		Yield	d.r. (*syn*:*anti*)
1		**30g**		**31g**	99[a]	>25:1
2		**30h**		**31h**	60	3.9:1
3		**30i**		**31i**	93	>25:1
4		**30j**		**31j**	61	>25:1
5		**30k**		**31k**	11	7:1
6		**30l**		**31l**	81	>25:1
7		**30m**		**31m**	60	>25:1

Table 8 – Reaction scope with arylethyl nucleophiles

We further demonstrated that a variety of sulfonamide protected anilines could be used as nucleophiles for the cyclization reaction. In general, the reactivity of this class of substrates was moderate, however, deactivation of anilines to this extent is a necessary requirement to avoid electrophilic fluorination of the arene. It should also be noted that the choice of

protecting group is severely limited since most common protecting groups could themselves be a competing nucleophile. For example, acylation would deliver an amide which could be highly competitive with the arene nucleophile.

Entry	Substrate		Product		Yield	d.r. (*syn*:*anti*)
1		**30n**		**31n**	52	>25:1
2		**30o**		**31o**	82	>25:1
3		**30p**		**31p**	84	>25:1
4		**30q**		**31q**	67[a]	>25:1
5		**30r**		**31r**	40	>25:1
6		**30s**		**31s**	52	>25:1
7		**30t**		**31t**	27	>25:1

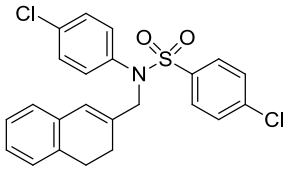
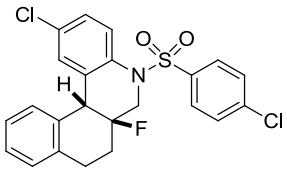
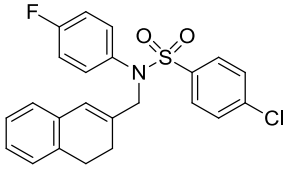
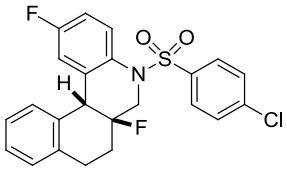
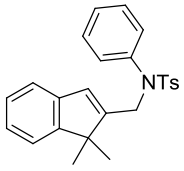
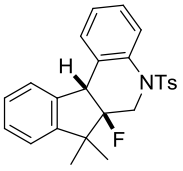
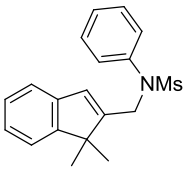
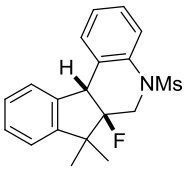
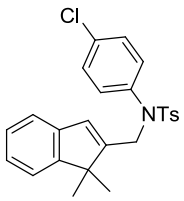
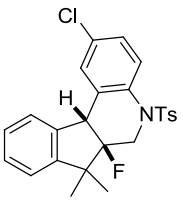
8		**30u**		**31u**	46	>25:1
9		**30v**		**31v**	35	>25:1

Table 9 – Reaction scope with aniline nucleophiles

The next class of substrates that we explored were those featuring a gem-dimethyl group on the indene core. We speculated at this early stage that substrates which displayed some functionalization of the indene ring might offer favourable facial selectivity when it came to the development of an asymmetric reaction. Pleasingly, the reaction tolerated arene nucleophiles featuring both alkyl groups and halogens and several sulfonyl protecting groups of varying electron withdrawing power delivered excellent yields. We were especially excited for the success of the nosyl (4-nitrobenzenesulfonyl) substrate due to the documented easier removal of the nosyl group with respect to the tosyl.[12]

Entry	Substrate		Product		Yield	d.r.
1		**39a**		**40a**	96	>20:1
2		**39b**		**40b**	79	>20:1
3		**39c**		**40c**	99	>20:1

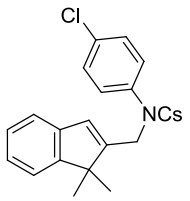
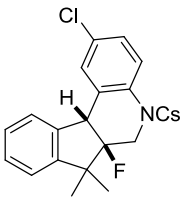
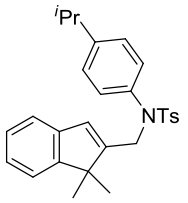
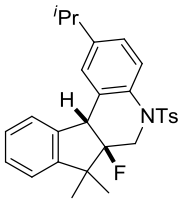
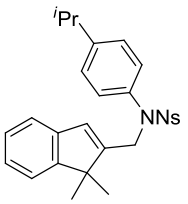
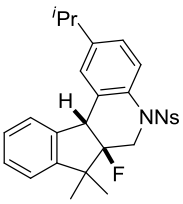
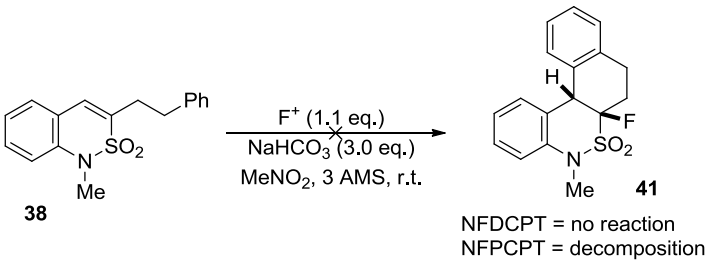
4		**39d**		**40d**	99	>20:1
5		**39e**		**40e**	99	>20:1
6		**39f**		**40f**	98	>20:1

Table 10 – Reaction scope with gem-dimethyl substrates

Unfortunately, when we subjected acyclic sulfonamide **38** to the reaction conditions no fluoro-carbocyclized product could be detected. We speculated that the conjugation of the olefin with the sulfonyl group might render the substrate far less reactive than the previous examples. However, when we repeated the reaction with the more powerful *N*-fluoro-pentachloropyridinium triflate only decomposition was observed.



Scheme 25 – Attempted fluoro-carbocyclization of **38**

Finally, we were able to obtain the x-ray crystallographic structures of fluorocyclized products **31e** and **40c**. The structure confirmed the syn relationship of the proton and fluorine atoms at the ring junction (Figure 5a and b).

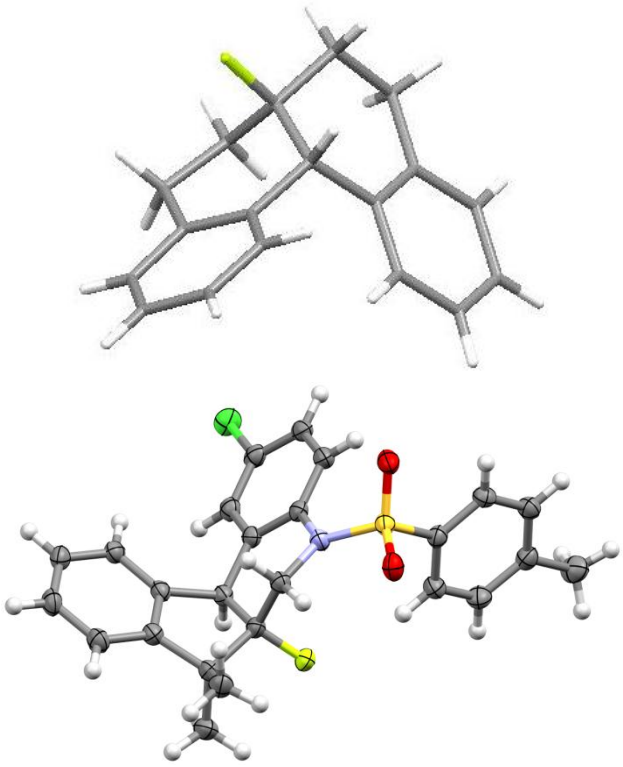
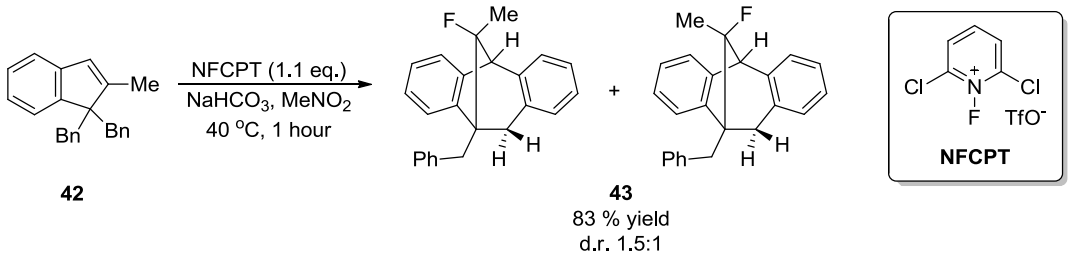


Figure 5 – X-ray crystallographic structure of fluoro-carbocyclized products; a) top: **31i**, b) bottom: **40c**

2.6.4 Desymmetrization reactions

We were curious to investigate whether a substrate bearing a gem-dibenzyl at the 1-position could undergo a carbocyclization onto the benzylic position following fluorination. In doing so, the reaction would form a fused 5,6,7-membered ring system and therefore display the enormous potential for this methodology to form highly complex fluorinated compounds from simple substrates. Since a 6-membered ring would be formed and the carbocyclization methodology has been shown to be restricted to this ring size we were confident that a reaction should be possible. To validate this hypothesis we prepared a substrate featuring a methyl group at the 2- position, instead of the usual aryl ethyl group, so that competitive cyclization would not be possible. We were delighted to observe the reaction proceeded to afford the fluoro-carbocyclized product in an 83 % yield.

Unfortunately, there was very little stereocontrol which resulted in the product being formed as a disappointing 1.5:1 mixture of diastereomers.



Scheme 34 Fluorocarbocyclisation using gem-dibenzyl substituted substrates

^{19}F-^{1}H HOESY experiments were used to determine the identity of the major and minor diastereomers due to the complicated ^{1}H NMR spectra and unusual structure of the fluorinated products (Figure 6). We found that the most crucial proton which helped us to characterise the diastereomers was H^1. Upon irradiation of the F nucleus in the major diastereomer there was no nOe detected on ^{1}H, whereas in the minor diastereomer a nOe was observed. Since in the major diastereoisomer, the fluorine is 4.099Å away from H^1 and showed no correlation in the spectra apart from with the methyl protons and H^3 and that the distance between the F and H^1 in the minor diastereoisomer is only 2.644Å we were able to confidently assign the stereochemistry.

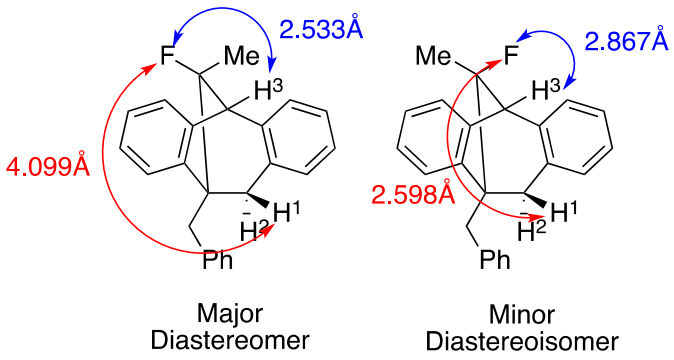
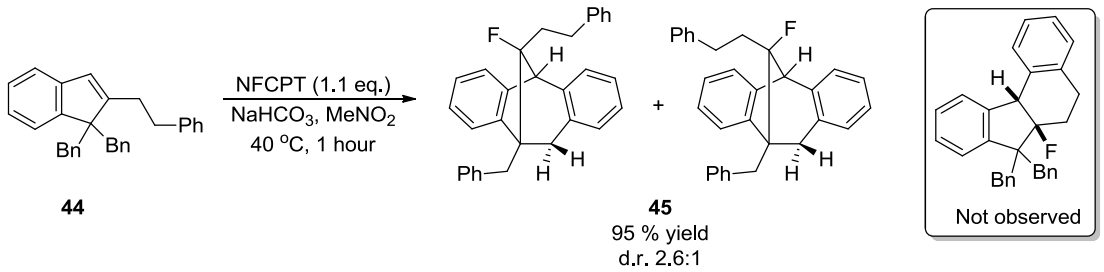


Figure 6 - ^{19}F-^{1}H HOESY for identifying the major and minor diastereoisomers

In order to determine the relative reactivity of the benzyl nucleophile, we prepared a substrate capable of undergoing a cyclization either from the 1- or 2-position and subjected it to the conditions of fluoro-carbocyclization. We were surprised to find that only the product as a result of cyclization of the benzyl group was detected (Scheme 35). An explanation to the selectivity towards the observed products could be due to the reduced rotational flexibility of the benzyl group with respect to the ethylbenzene substituent. In this instance, the diastereomers were assigned by analogy to **43** since protons H^3 (Figure 6) appeared to be extremely similar in both compounds.



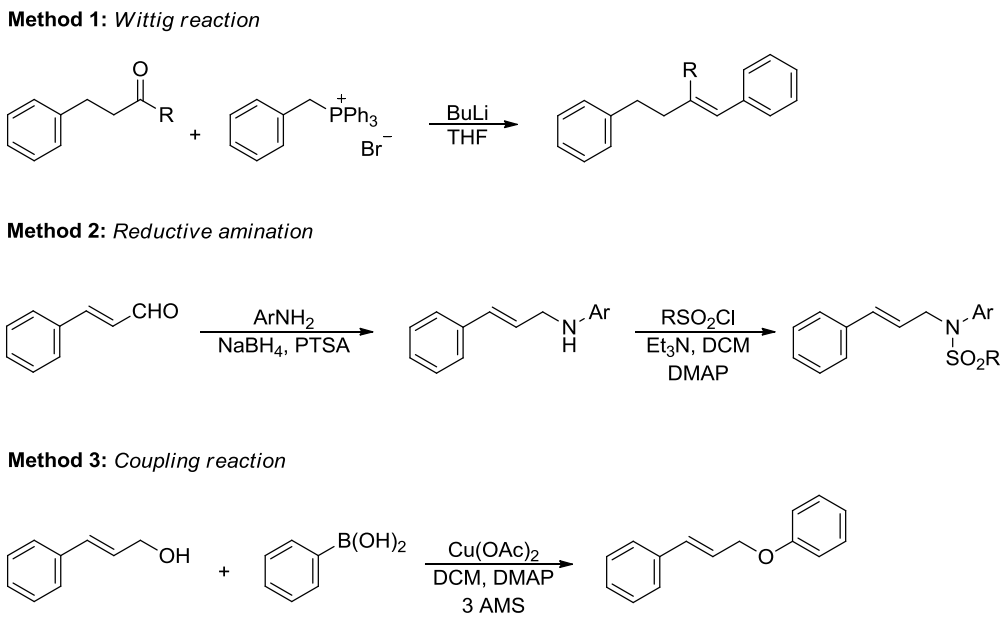
Scheme 35 Test of reactivity of benzyl nucleophile. Conditions: F-$NC_5Cl_2H_3$-TfO (1.1 eq.), $NaHCO_3$ (3.0 eq.), $MeNO_2$, 40°C, 1 hour

2.6.5 Fluoro-carbocyclization of acyclic systems

We next wanted to investigate more challenging acyclic substrates, which would not guarantee the same high level of diastereoselectivity. As well as exploring the stereoselectivity of the reaction, and factors governing it, we would more easily be able to examine the electronics of the substrates and the effect this has on the reaction.

2.6.5.1 Acyclic substrate synthesis

As with the previous library of substrates the acyclic series was prepared by a number of general procedures. Due to the ubiquitous nature of styrene like compounds in organic chemistry we were able to take advantage of the wealth of methods in the literature for their preparation.



Scheme 26 – General procedures for the synthesis of acyclic substrates

The most intuitive method for the preparation of styrene like compounds is perhaps via a Wittig process. Disconnection across the olefin allowed two possible alternative strategies. Either hydrocinnamaldehyde (or related ketone analogue) and benzyl triphenylphosphonium bromide could be used, or the synthons could be reversed and triphenyl(3-phenylpropyl)phosphonium bromide reacted with the appropriate benzaldehyde (or related ketone analogue). We found that ^{n}BuLi was a very efficient base for the reaction, except

where halogens were present on the phosphonium salt and metal-halogen exchange was a concern. In this case sodium hydride was found to be equally competent.

The synthesis of substrates featuring deactivated aniline nucleophiles was achieved by a reductive amination pathway (Method 2) as for the cyclic substrates. The solvent-free mixing of cinnamaldehyde and the appropriate aniline formed the intermediate imine, which was then directly reduced by the addition of equimolar amounts of sodium borohydride and PTSA according to the procedure by Cho and Kang.[13] Protection, or deactivation, of the aniline was achieved using various sulfonyl chloride compounds, in the presence of triethylamine and a catalytic amount of DMAP.

Finally, a very useful reaction for the synthesis of the highly activated anisole like compounds was the copper (II) mediated coupling of cinnamyl alcohol with phenylboronic acid. A stoichiometric amount of copper (II) acetate monohydrate was employed with a DMAP additive to furnish the desired compound in a single step starting from commercially available materials. By these general methods, a library of substrates was obtained which was used to probe the reactivity and selectivity of the fluoro-carbocyclization reaction.

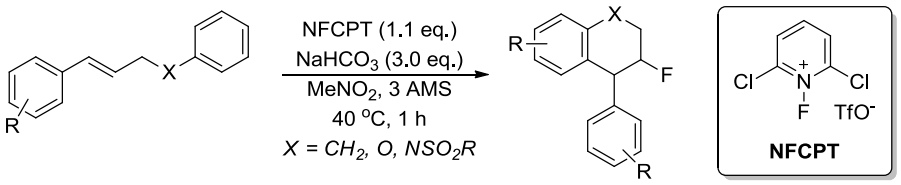
2.6.5.2 Fluoro-carbocyclization

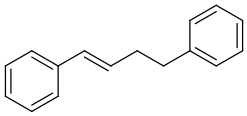
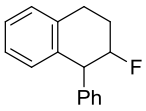
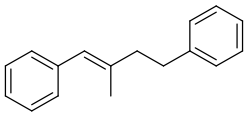
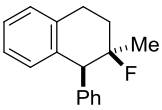
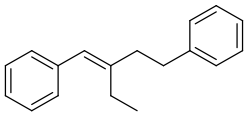
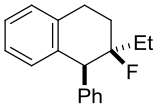
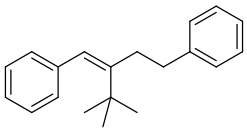
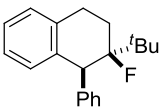
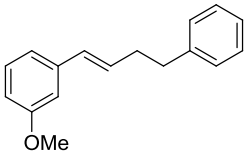
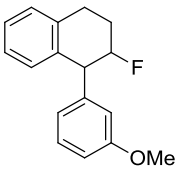
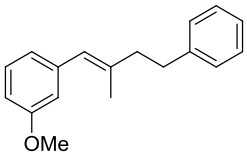
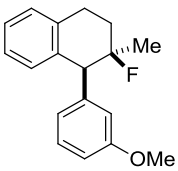
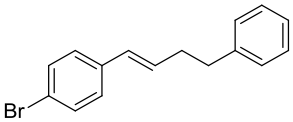
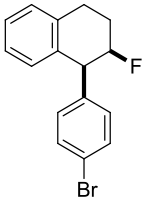
A broad range of substrates that were synthesised according to the general procedures of the previous section were subjected to the optimised conditions for fluoro-carbocyclization. Using these more easily prepared acyclic substrates we were keen to investigate the electronic and stereoselectivity aspects of the reaction. We divided the substrates into those featuring arylethyl nucleophiles and those displaying deactivated aniline nucleophiles.

The most noticeable observation was that there was no detectable correlation between the *E:Z* ratio of the starting olefin and the *syn:anti* ratio of the final product. This result was

consistent with a reaction pathway that proceeds via a carbocation which would permit free-rotation prior to the cyclization step. Hence, this would scramble any stereochemical information contained in the substrate. Indeed, the *N*-protected aniline substrates in Table 12, which were obtained exclusively in the *trans* form, reacted to give very little diastereoselectivity. The diastereoselectivity was found to be influenced by substitution at the *β*- position with good selectivity observed for the bulky *tert*-butyl substrate (entry 4). The reaction was reasonably tolerant of substitution of the styrene aromatic ring with both electron withdrawing and electron donating groups delivering excellent yields. Only the very electron poor nitro substrate **46o** was found to have insufficient reactivity, which constitutes the lower limit of permitted reactivity. Substrates based on a 2-vinyl naphthalene structure also reacted very satisfactorily to form fluorinated tetrahydronaphthalene products. Cinnamyl benzene **46p** was tested to examine whether the more flexible acyclic system would allow the formation of a cyclopentene ring. However, no identifiable products were recovered, suggesting that the transition state would involve too much strain to allow the formation of a 5-membered ring. Substitution at the allylic position was investigated using ether **3s**, however, this had no influence on the diastereoselectivity of the reaction and a very complex reaction mixture was recovered with all the possible diastereomers observed but not separated. Finally, stabilization effects of the carbocation were explored using the tertiary α-methyl (**46l**) and α-phenyl (**46m**) substrates. Both were expected to provide considerably more stabilization than is experienced in the other substrates. With the α-methyl olefin it seems the carbocation is sufficiently stable, and therefore long-lived, to allow a competing, and in this case dominating, proton abstraction of an α-proton to afford the fluorinated methylene product **47l**. When the same α-protons are not present, as in **46m**, the carbocation is stable enough to selectively react with residual water molecules and not the more entropically favoured pendent nucleophile. It is perhaps somewhat surprising

that proton abstraction from the α-CHF moiety to yield a vinylic fluoride is never observed, even though this proton would be expected to be fairly acidic.



Entry	Substrate	E:Z	Product	Yield (%)	d.r. (syn:anti)
1	 **46a**	2.3:1	 **47a**	94	1:1
2	 **46b**	1:1.8	 **47b**	59	3.0:1
3	 **46c**	1.4:1	 **47c**	50	2.7:1
4	 **46d**	>20:1	 **47d**	50[c]	12.5:1
5	 **46e**	1.9:1	 **47e**	39	1:1
6	 **46f**	1:1.6	 **47f**	86	2.3:1
7	 **46g**	1.7:1	 **47g**	72	1.3:1

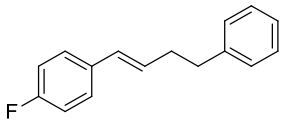
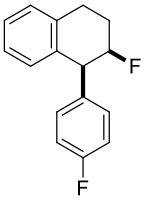
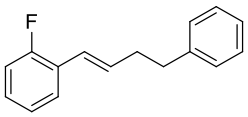
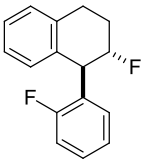
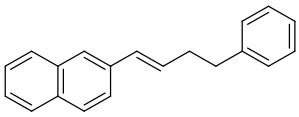
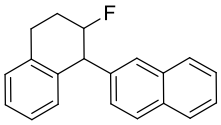
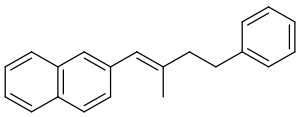
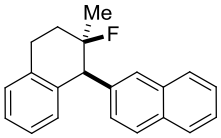
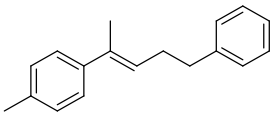
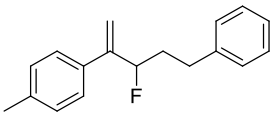
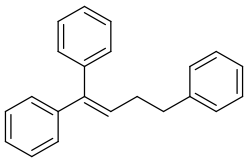
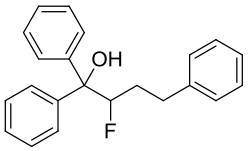
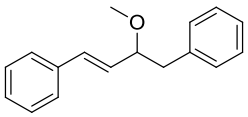
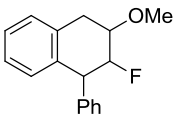
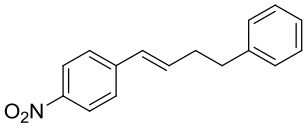
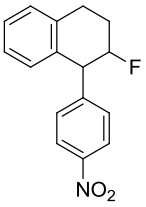
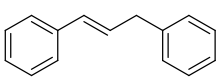
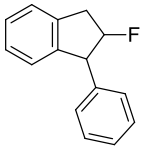
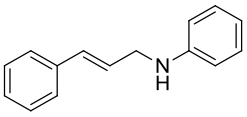
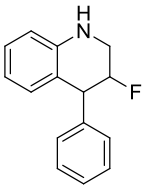
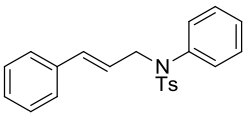
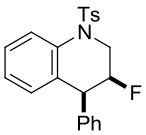
8	 **46h**	1:4.0	 **47h**	94	1.3:1
9	 **46i**	1:10.1	 **47i**	89	1:1.4
10	 **46j**	2.3:1	 **47j**	93	1:1
11	 **46k**	1:1.6	 **47k**	94	2.0:1
12	 **46l**	5.7:1	 **47l**	57	-
13	 **46m**	-	 **47m**	37	-
14	 **46n**	1:0	 **47n**	-[d]	
15	 **46o**	1:4.7	 **47o**	0[e]	-
16	 **46p**	1:0	 **47p**	0	-

Table 11 - 1.1 eq. NFDCPT, 3.0 eq. NaHCO3, MeNO2, 40 °C, 1h; [a] reaction run for 6h; [b] only syn diastereomer observed; [c] Unable to isolate from impurities; [d] non-isolated complex mixture of diastereomers; [e] no reaction

Various anilines were investigated to probe the effect of the electronics of the arene nucleophile. As anticipated, the unprotected aniline **3l** yielded no product as the nucleophile is simply too reactive towards electrophilic fluorination itself and instant blackening was observed. Since no identifiable products were recovered it is assumed that this observation is synonymous with decomposition. Deactivating the ring as the corresponding tosylamide and methane sulfonamide analogues did not considerably reduce the reactivity and permitted a clean reaction to access fluorinated heterocycles **4m** and **4n**. Protection of the aniline as the *N*-boc derivative was totally unsuccessful, with the same discolouring observed as for the unprotected aniline, eluding to a deprotection pathway under the reaction conditions. The *O*-substituted anisole afforded a small amount of product, with only the syn diastereomer recovered in poor yield following purification. It is therefore assumed that an anisole is at the very upper limit of the tolerated reactivity.

Entry	Substrate	*E:Z*	Product	Yield	d.r. (*syn*:*anti*)
1		1:0		0	-
	48a		**49a**		
2		1:0		78	2.4:1
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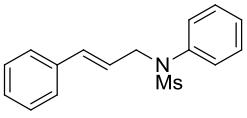
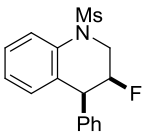
3		1:0		92	1.8:1
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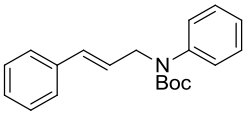
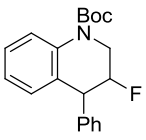
4		1:0		0	-
	48d		**49d**		

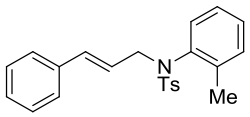
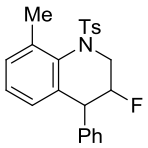
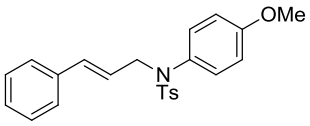
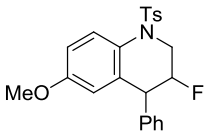
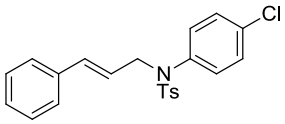
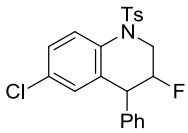
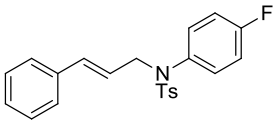
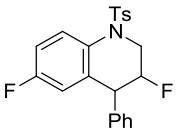
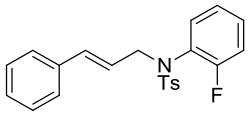
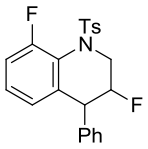
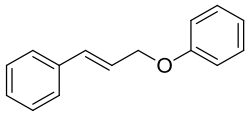
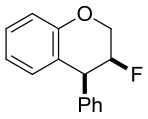
5	 **48e**	1:0	 **49e**	77	1.3:1
6	 **48f**	1:0	 **49f**	trace	-
7	 **48g**	1:0	 **49g**	95	1:5.9
8	 **48h**	1:0	 **49h**	73	<1:20
9	 **48i**	1:0	 **49i**	10	1:4.6
10	 **48j**	11.6:1	 **49j**	17	-

Table 12 – Fluoro-carbocyclization of acyclic substrates featuring aniline and anisole type nucleophiles

The investigation into the electronics of the styrene component of the substrate allowed us to summarise our findings as an order of increasing stabilisation of the intermediate carbocation (figure 6). Highly electron poor substrates, such as the 4-nitro example **46o** are simply too electron deficient to undergo a reaction and so do not react. The next class of compounds are those which are reactive enough to facilitate a reaction but so unstabilised that they react with whatever nucleophile is in their proximity. These are the substrates

which will react with the solvent, should a nucleophilic solvent be used. The next category of substrates represents the 'sweetspot' of the reaction scope where the carbocation will preferentially react with the carbon nucleophile, where the majority of the substrate library is to be found. Substrates which are more stabilized, such as those featuring an alkyl group at the α- position to make the intermediate carbocation tertiary as well as benzylic, preferentially undergo deprotonation to yield allyl fluorides, since the carbocation is sufficiently long lived. The final example is one which features dibenzylic substitution, where the carbocation is so heavily stabilised that it will wait to react with residual water, even though it is in very low concentration, as it is the "best" nucleophile in the system.

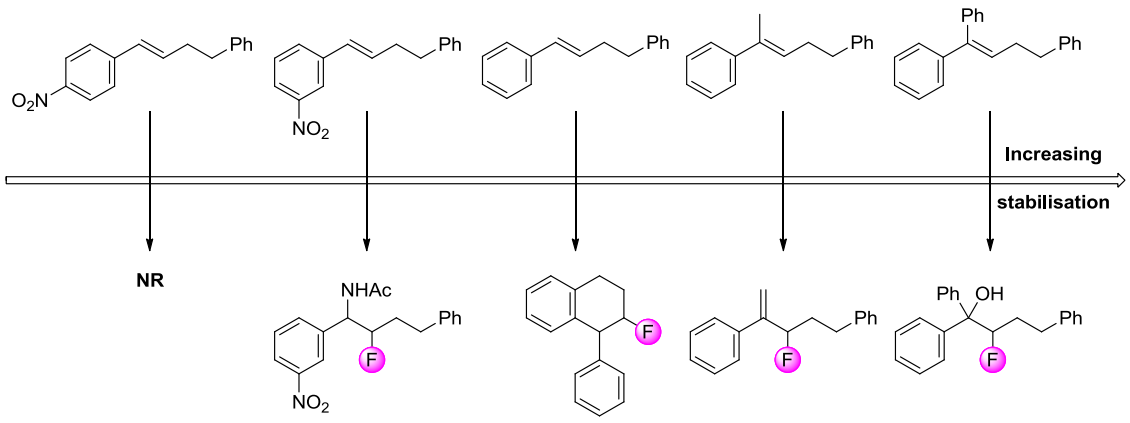


Figure 7 – Reactivity trend for substrates of increasing intermediate carbocation intermediate

2.7 Conclusion

In summary, we have shown indene and dihydronaphthalene systems to be sufficiently reactive towards electrophilic fluorocyclization reactions using commercially available fluorinating reagents, which is a significant advance on many current techniques in the literature. We initially validated this reactivity using alcohol, acid and sulfonamide internal nucleophiles, which have previously been shown to be competent nucleophiles for fluorocyclization reactions. With the sufficient reactivity profile established we next investigated the use of carbon nucleophiles, finding considerable success with aromatic groups. Aside from two early reports using highly biased systems to form fluorinated adamantane rings[2,3] this is the only other report of a metal-free fluoro-carbocyclization. Indeed, this is a huge advance in the literature since fluorocyclizations are typically limited to nucleophiles of high reactivity, thus restricting the scope of the methodology. In order to achieve this it was found that solvent choice was critical, with the most common reaction media for electrophilic fluorination, acetonitrile, proving to be unsuitable due to its nucleophilic nature. Instead we found nitromethane to be an excellent alternative, displaying similar properties of polarity, solvation and, crucially, ability to remove water. The choice of fluorinating agent was also essential, highlighting the importance of screening a wide range of fluorinating agents to find one which displays the correct reactivity profile. A comprehensive screening of substrates revealed this to be a highly effective method for the construction of six-membered carbocycles. A broad range of aromatic nucleophiles were tolerated, spanning a broad spectrum of electronic properties, from activated anisole substituents to deactivated anilines. In a final extension to this work we demonstrated the use of acyclic substrates based on substituted styrenes to achieve excellent yields, albeit with disappointing diastereoselectivity. Furthermore, it offered an excellent opportunity to explore the electronic requirements of the substrates, which had been very difficult to do for the indene and dihydronaphthalene class of substrates.

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Chapter 3:

Fluoro-Arylation Reactions

3. Fluoro-Arylation Reactions

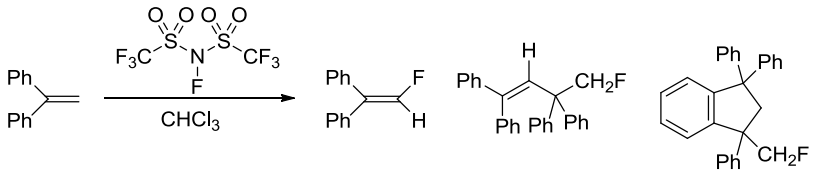
3.1 Introduction

An obvious extension to the work done on fluorocyclization methodology in Chapter 2 was to investigate the removal of the nucleophile tether, therefore developing an inter-molecular reaction. The use of an external nucleophile adds a considerable challenge to the reaction as close proximity of the nucleophile cannot be relied upon as it could be for the intra-molecular cyclization. Nevertheless, we were keen to examine if we could maintain a stereoselective reaction when the nucleophile was no longer bound to the substrate itself.

3.2 Activation of olefins by electrophilic fluorination

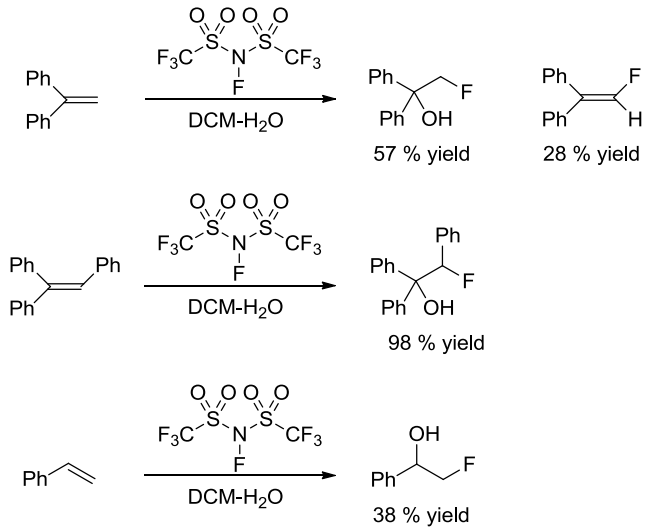
There are numerous reports for the formation of C-X bonds, triggered by the prior formation of a C-F bond. Most involve the capture of intermediate carbocations by reactive nucleophilic species such as alcohols and amines. A selection of some of the most relevant examples is presented herein.

A detailed report on the fluorination of various olefins that proceed via an α-fluoro carbocationic intermediate was provided by DesMarteau in 1992.[1] Using the DesMarteau regent, *N*-fluorobis[(trifluoromethyl)sulfonyl]imide, as a powerful source of electrophilic fluorine, different solvents were screened to investigate the effect that solvent nucleophilicity had on the reaction. In poorly nucleophilic solvents, such as chloroform, a mixture of products was observed, arising from elimination and dimerisation as displayed in Scheme 1.



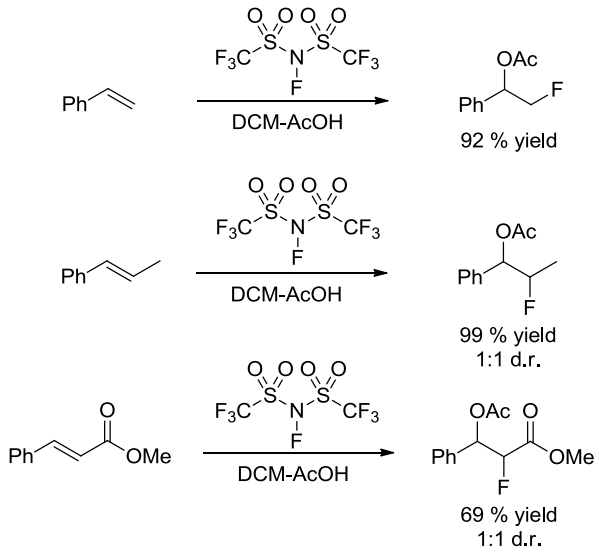
Scheme 1 – Fluorination of 1,1-diphenylethylene

When highly nucleophilic solvents such as water were used the expected fluorohydroxylated products were observed but with a significant amount of elimination product. For example, the reaction of 1,1-diphenylethylene with the DesMarteau reagent resulted in a 57 % yield of the fluorohydrin but was accompanied by 28 % of the corresponding vinyl fluoride. By changing to the more substituted 1,1,2-triphenylethylene the yield of the desired fluorohydrin was increased to 98 %. However, reducing the amount of substitution, by using styrene, resulted in a low yield of 2-fluoro-1-phenylethanol, which was attributed to the formation of undesired oligomers.



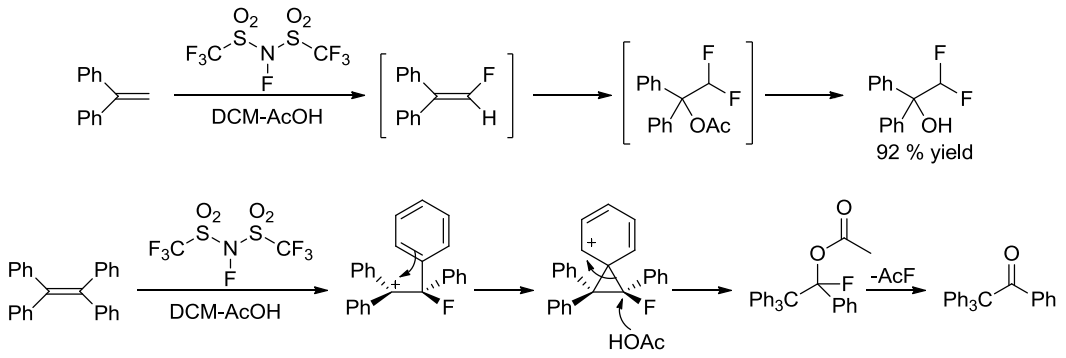
Scheme 2 – Fluorination of substituted styrenes in water/acetonitrile solvent mixture

DesMarteau also demonstrated that acetic acid was a good solvent and nucleophile for the reaction, giving rise to the corresponding β-acetoxy-α-fluoro addition products in excellent yields. The methodology was also demonstrated on a challenging α,β-unsaturated ester substrate. Fortunately, it was found that the fluorinating reagent was soluble in acetic acid and did not react even under refluxing conditions. The complete lack of stereoselectivity provided evidence for the involvement of carbocation intermediates, since stereochemically pure starting materials were used.



Scheme 3 – Mild electrophilic fluorination of substituted styrenes with acetic acid as the nucleophilic solvent

However, when more reactive substrates were investigated the desired products were not obtained. 1,1-Diphenylethylene underwent fluorination which was followed by proton abstraction to afford the intermediate vinyl fluoride. The vinyl fluoride then underwent fluoroacetoxylation followed by hydrolysis to give the difluoromethyl alcohol product. The even more reactive tetraphenylethylene underwent a fluorination followed by a rearrangement to afford a ketone product by subsequent loss of acetyl fluoride.

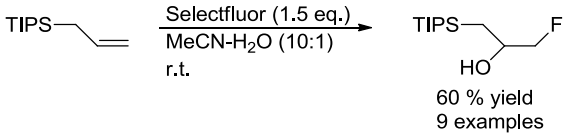


Scheme 4 – Fluorination of reactive substrates in the presence of acetic acid as nucleophile

Of particular interest was the discussion of the reaction mechanism. The authors proposed an electron transfer mechanism based on the following evidence. Firstly, a rate acceleration was detected in polar solvents, which is consistent with the electron transfer being preceded by formation of a charge transfer complex; polar solvents favour charge separation and ion pair formation. Secondly, the addition of the reagent to the alkenes led to development of an intense colour change, indicating the presence of radical intermediates. Also, when benzoquinone was added to the reaction, it combined with the radical anion of the N-F reagent and led to charred products. As a control reaction, in the absence of alkene no reaction took place between benzoquinone and the electrophilic fluorine source.

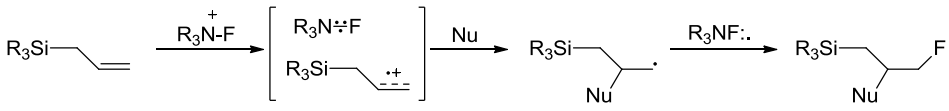
Recently, Hammond *et al.* reported the fluorohydroxylation of a variety of acyclic allyl silanes.[2] Building on work done within the Gouverneur group on fluorodesilylation,[3] and subsequently on fluorocyclization,[4] the silicon activating group was successfully used to stabilise an intermediate carbocation and promote fluorination. Silicon is well-known for its ability to stabilise β-carbocations and β-radical cations. Just as was found in the report on fluorocyclization,[4] use of bulky silicon groups minimised the competing fluorodesilylation pathway and favoured the desired fluorohydroxylation pathway. By using 10:1 acetonitrile/nucleophile mixtures as the reaction solvent the nucleophile was incorporated with complete selectivity, with no mention of the fluoro-Ritter product. The use of

acetonitrile as the main solvent was found to be important as when the reaction was run in pure ethanol no fluoro-etherification product was observed. In ethanol/acetonitrile (1:10 *v/v*) the reaction afforded 61 % of the fluoroetherification product. Finally, a variety of nucleophiles were demonstrated to be capable of trapping the intermediate carbocation. The modest yields were attributed to a small degree of fluorodesilylation.



Scheme 5 – Fluorohydroxylation of allylsilanes

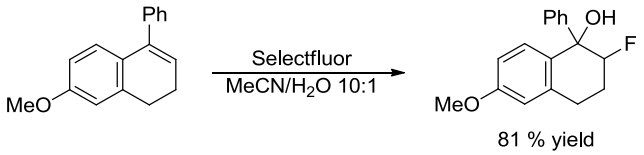
The discussion of the reaction mechanism was again very interesting. The authors proposed a two-electron process with the electrophilic fluorine being transferred in an S_N2 process. However, they acknowledged the possibility of a single electron transfer process and proposed the following SET mechanism for the reaction.



Scheme 6 – Proposed SET mechanism for fluorination of allylsilanes

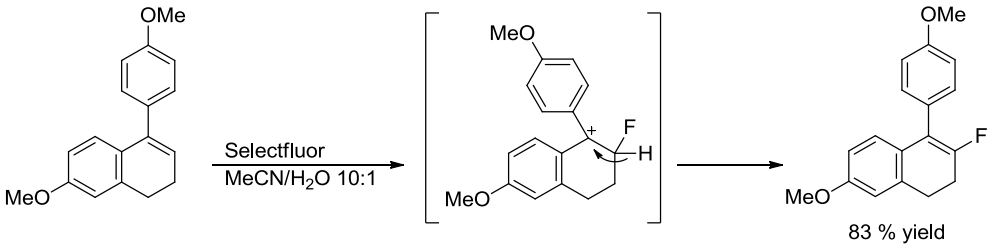
A report by Chang and co-workers in 2011 demonstrated the effect of extensive carbocation stabilisation.[5] The halogenation of various 1,1-diaryl alkenes revealed the change in major reaction product, depending on the magnitude of stabilisation employed. When using a water/acetonitrile mixture as solvent (1:10 *v/v*) the fluorohydroxylated product was

expected and this was indeed the case for all but the most electron rich systems (Scheme 7). The fluorine was incorporated into the β position, in line with the reaction proceeding through a benzylic carbocation.



Scheme 7 – Fluorohydroxylation of 1,1-diaryl systems

However, when the highly activated substrate in the scheme below was used, the corresponding vinyl fluoride was afforded in high yield. This observation was consistent with the increased stability of the carbocation which allows for intramolecular proton abstraction. This report correlates well with previous literature, as well as the findings in Chapter 2, providing a spectrum of reactivity as outlined in Figure 1.



Scheme 8 – Fluorination of very electron rich 1,1-diaryl olefins

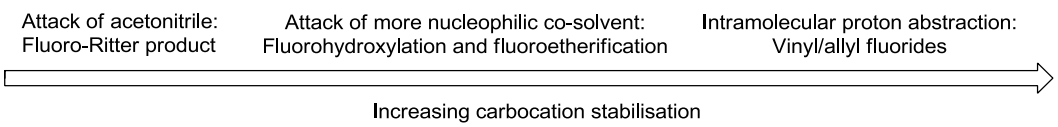
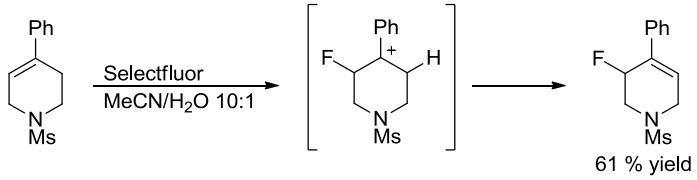


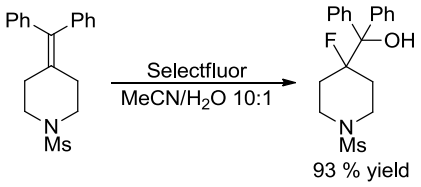
Figure 1 – Spectrum of reactivity profiles of olefins towards fluorination

An elegant synthesis of allylic fluorides starting from arene substituted piperidinyl olefins was also reported by the same authors in 2010.[6] In this case the ensuing carbocation was sufficiently stable to undergo intramolecular proton abstraction to afford allyl fluorides in reasonable yields. It was found that prolonging the reaction time or elevating the temperature was detrimental to the yield due to formation of the corresponding fluoropyridine. Interestingly, when 1,1-diaryl substituted exo-olefins were used the fluorohydroxylated product was formed exclusively. These observations indicate that stabilisation of the carbocation is significantly affected by the presence of a second stabilising group but the nature of that group is not of great importance. In Scheme 9 a single benzyl stabilising effect is sufficient to promote proton abstraction, indicating that tertiary stabilisation of the carbocation, as well as the effect of being a cyclic substrate, is more important that having further benzylic stabilisation.



Scheme 9 – Fluorination of piperidinyl olefin; Ms = methanesulfonamide

In Scheme 10 the diaryl substitution is insufficient to promote proton abstraction as would perhaps be anticipated from the group's more recent publication,[5] where di-anisolyl substitution was necessary for such an effect.



Scheme 10 – Fluorination of exo 1,1-diaryl substituted piperidinyl olefin; Ms = methanesulfonamide

In a report by Stavber and co-workers[7] the concept of the nature of the second stabilising group having little effect on the degree of increased stability was detailed. Using various substituted styrenes in the presence of Accufluor (1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]-octane) with a water (alcohol)/acetonitrile mixture as solvent, detailed kinetic studies revealed the surprisingly small effect that the nature of the second group had on the reaction rate. As can be seen from Figure 2, the effect of adding a second alpha substituent has around a three thousand fold rate acceleration on the reaction. However, there is only a 1.03 fold difference in the rate when changing between a phenyl and a methyl substituent, with the methyl group resulting in the ever so slightly faster rate. The significant rate acceleration provided by additional substituents was also detailed in an earlier report by Stavber.[8]

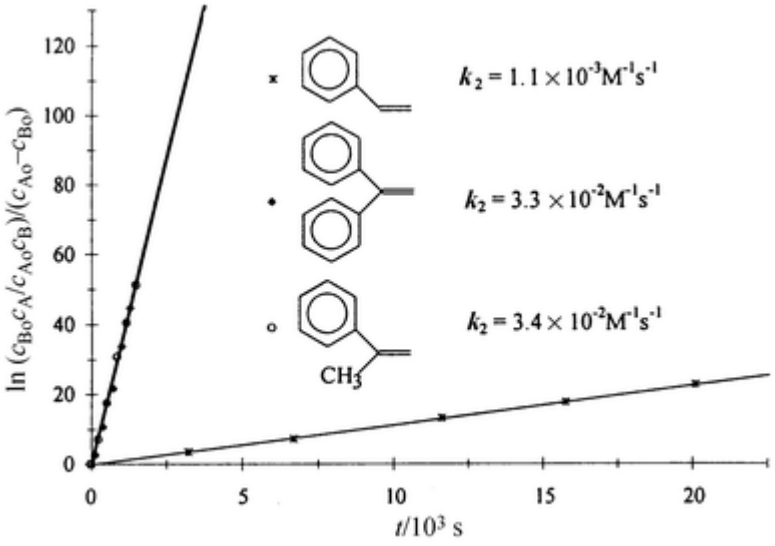
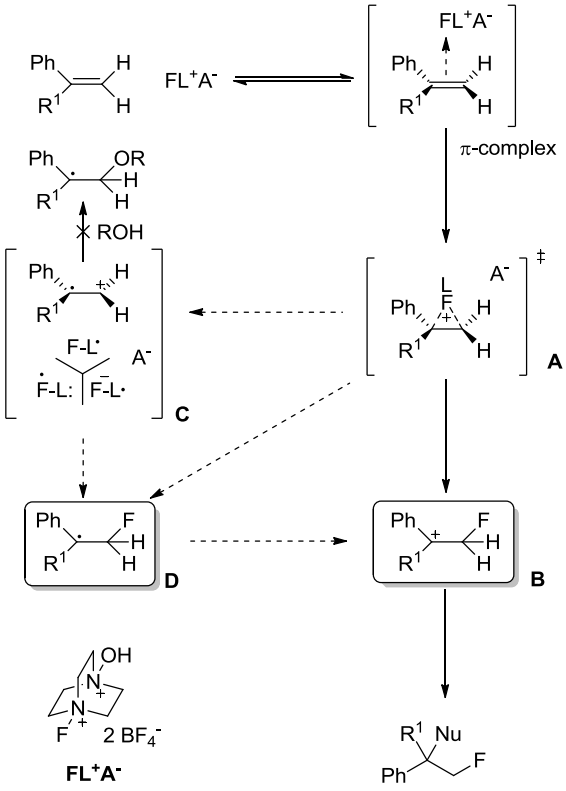


Figure 2 – Effect of olefin substitution on fluorination with Accufluor in methanol/acetonitrile

The authors found, while gathering data for Hammett correlation analysis, that the product distribution followed the trend already proposed in Figure 1. In the medium of water/acetonitrile (1:10 *v/v*) the more reactive substrates formed only vicinal fluorohydrins,

whereas the less reactive substrates formed increasing amounts of the vicinal fluoroacetamides. Their relative ratio increased from a trace amount in the case of styrene to around 50 % in the case of *m*-nitrostyrene. From their detailed studies they were able to suggest a reaction mechanism for the mild fluorination of styrenes. Since there were only small changes in the rate upon changing the solvent polarity, the authors deduced the rate determining step must have essentially non-polar character. They eluded to the formation of a π-complex between the reagent and substrate to form complex **A**. The formation of this rate-determining transition state is presumably proceeded by the formation of β-fluorocarbonium ion **B**. The most compelling argument for the involvement of a carbocation intermediate is the observed Markovnikov regioselectivity of the nucleophile. The intermediate **B** is then trapped by an external nucleophile to produce the fluorinated product.



Scheme 11 – Proposed mechanism for the mild fluorination of styrenes with Accufluor

However, the authors acknowledged that their evidence did not rule out the possibility for a single electron transfer mechanism. It is plausible that a cation-radical and anionic derivative of the fluorinating reagent could be formed to form pair **C**. This could then be transformed into the radical intermediate **D** and then very quickly into the intermediate **B**. The alternative pathway of nucleophilic attack of water or alcohol at the β- position is not possible, as determined experimentally.

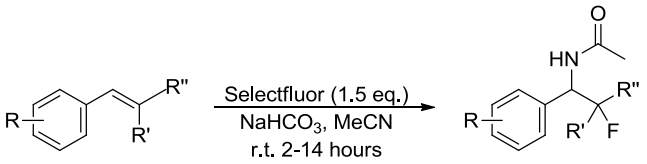
3.3 Fluoro-amidation

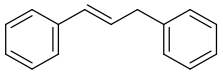
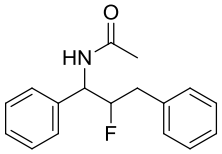
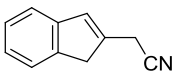
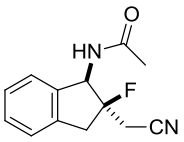
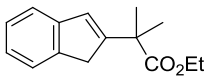
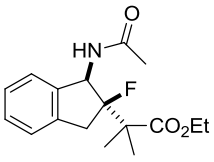
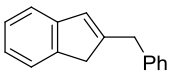
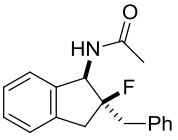
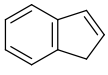
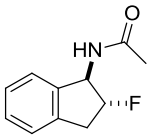
Whilst there are evidently numerous papers where olefins have been activated by an electrophilic source of fluorine, again most rely upon overly biased substrates featuring dibenzylic stabilization or are sometimes even more activated than this.

During the development of the fluoro-carbocyclization reaction described in Section 2.7 we noticed that in nucleophilic solvents such as acetonitrile, or with residual water present, a significant by-product was that of solvent capture. We reasoned that this was the result of the weakly nucleophilic internal carbon nucleophiles being comparable in reactivity to the external heteroatom nucleophiles. This reaction caught our interest since it could offer an interesting method for the activation of alkenes of moderate reactivity towards amidation and other similar transformations. We speculated that exposing a range of indene and styrene like compounds to the conditions used for fluoro-heterocyclization would result in the formation of the respective fluoro-amide product. Due to the similarity between this process and the Ritter reaction, we frequently refer to this reaction as the so-called fluoro-Ritter reaction.

A small library of substrates was subjected to the reaction conditions used for fluoro-heterocyclization with Selectfluor being employed as the fluorine source and acetonitrile

used as the solvent. Pleasingly, the styrene substrates reacted very satisfactorily to afford the fluoro-Ritter product in moderate yields. Unfortunately, fluoro-amidation of (*E*)-prop-1-ene-1,3-diyldibenzene **46p** occurred without any stereoselectivity, delivering the product as 1:1 mixture of diastereomers. Reactions of the indene substrates were very interesting, however, with excellent diastereoselectivity being observed for **52**, **53** and **55**.



Entry	Substrate	Products	Yield (%)	d.r. Anti:syn
1	 **46p**	 **50**	62	1:1
2	 **10**	 **51**	41	1:2.5
3	 **3**	 **52**	14	<1:25
4	 **30i**	 **53**	35	<1:25
5	 **54**	 **55**	33	<1:25

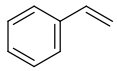
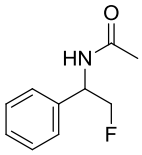
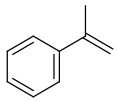
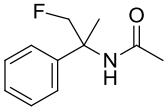
6			35	-
	56	**57**		
7			47	-
	58	**59**		

Table 1 – Fluoro-amidation of phenyl-substituted olefins

The stereochemistry was assigned by analysis of the $^{3}J_{H\text{-}F}$ coupling constant between the fluorine and the benzylic proton. Our prediction of the larger coupling constant being attributed to the syn diastereomer (i.e. with the fluorine and proton being *anti*) was confirmed by obtaining an x-ray crystallographic structure of *anti*-**51**.

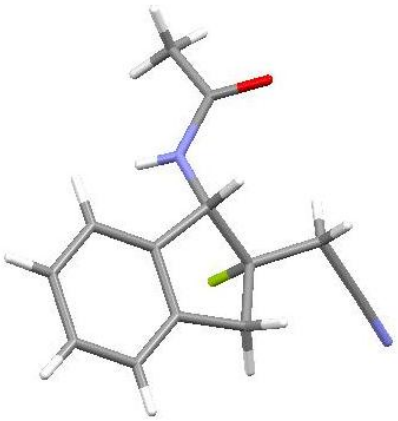
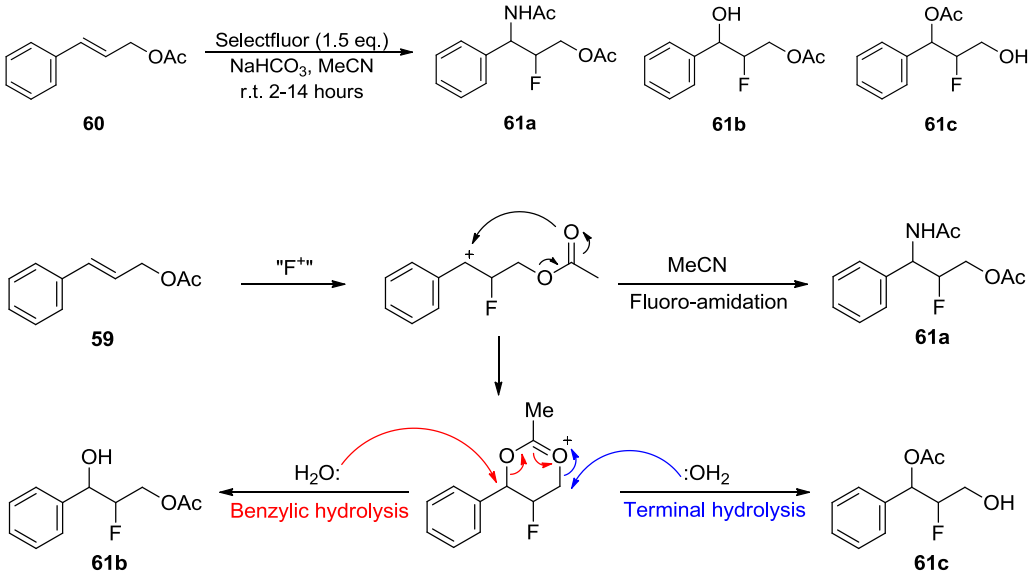


Figure 3 – X-ray crystal structure of fluoro-amide **51**

A final interesting substrate was examined which gave a complicated mixture of side-products. When cinnamyl acetate was used, a mixture of fluoro-amide product along with several different fluoro-hydrins was observed. We proposed that the two different alcohol

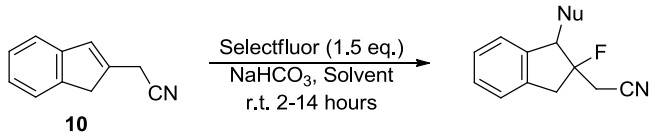
products were a result of an intermediate neighbouring group participation of the acetate, and subsequent hydrolysis with residual water. The water can open the lactone at either the benzylic position or the terminal position, to give the different regioisomers.



Scheme 12 – Proposed reaction pathways for the electrophilic fluorination of **59**

We were next interested to investigate if we could perform different transformations by conducting the reaction in different solvent systems. In the first instance, we envisaged using either water or an aqueous/organic solvent mix in order to obtain fluoro-hydrin compounds. We were confident that this should be possible using this approach, since a fluoro-hydrin by-product was one of the problems encountered in the development of the fluoro-carbocyclization reaction. Pleasingly, using the model indene **10** the corresponding fluoro-hydrin was accessed in a 36 % yield by conducting the reaction in water. When a 9:1 acetonitrile/water mixture was used the yield could be increased to 47 % with no change in diastereoselectivity. A similar result was obtained when the reaction was performed in methanol and a methanol/acetonitrile mixture where a moderate yield of the fluoro-

etherification product was obtained. However, the most interesting result was obtained when toluene was added to the acetonitrile, where a promising yield of the product arising from addition of the carbon nucleophile was achieved. What was even more intriguing was the apparent high diastereoselectivity of this reaction.



10

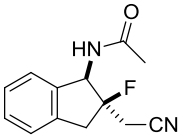
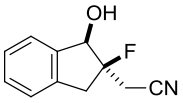
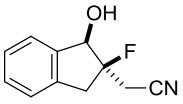
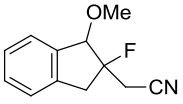
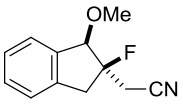
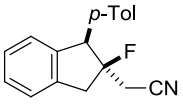
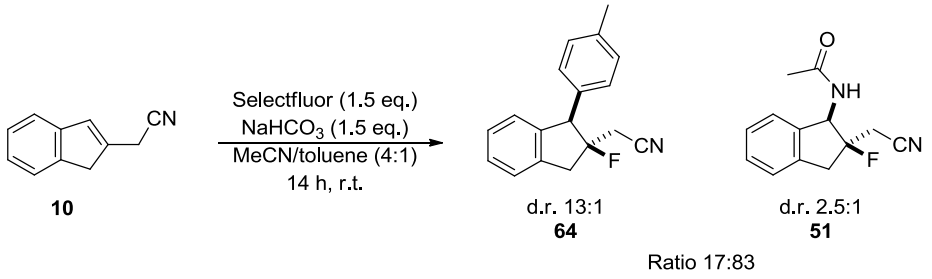
Entry	Solvent	Product	Yield (%)	d.r. anti:syn
1	MeCN	 **51**	41	1:2.5
2	H_2O	 **62**	36	1:1.5
3	MeCN/H_2O 9:1	 **62**	47	1:1.6
4	MeOH	 **63**	17	1:1
5	MeCN/MeOH 9:1	 **63**	30	1:1.4
6	MeCN/Toluene 4:1	 **64**	18	1:12.9

Table 2 – Formation of fluoroether and fluorohydrin products

3.4 Fluoro-arylation

Pleasingly, by employing a 4:1 acetonitrile: toluene mixture as the solvent for the reaction of indene **10** with Selectfluor we observed a competition between formation of the fluoro-Ritter and fluoro-arylated product (Scheme 13).



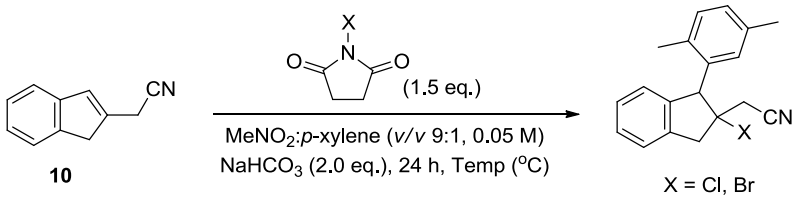
Scheme 13 - Preliminary fluoro-arylation result

Although the desired 1,1-diaryl product was obtained in a yield of just 17 %, with the remaining material being converted to the fluoro-Ritter product **51**, this preliminary result did prove that the concept of an intermolecular fluoro-arylation was possible and demonstrated a feasible route towards achieving C-C bond formation. This reaction clearly presented an opportunity for further development to investigate the range of substrates and arenes that could be used to afford a variety of fluorinated products with accompanying construction of a new C-C bond. In order to make this method viable, the most suitable oxidant as well as the optimal reaction conditions needed to be investigated.

3.4.1 The oxidant

We wished to briefly explore if other halogens could be successfully used to achieve C-C bond formation in a similar way and so we examined some common halogenating reagents.

Preliminary investigations showed that alternative halide sources did not mediate the halo-arylation successfully (Table 3) and thus an electrophilic fluorine source was established as the optimal oxidant for future work. Due to the range of fluorinating reagents available, we next wanted to determine which would potentially be most suitable for our reaction. When choosing a fluorinating reagent, there was a need to ensure that it was reactive enough to react with the olefin, but not so reactive that it also reacted with the arene which would be present in huge excess. As Selectfluor had already met this criterion, which is known only to fluorinate toluene slowly at reflux,[9] it was decided to investigate alternative $[N\text{-}F]^+$ sources that demonstrate a comparable reactivity to this.



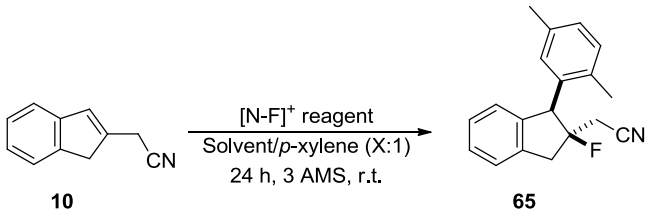
Entry	X	Temp. (°C)	Yield (%)[a]
1	Cl	r.t	NR[b]
2	Br	r.t	NR[b]
3	Br	50	NR[b]

Table 3 - Attempted halo-arylation reactions; *a) NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra, b) NR = no reaction*

3.4.2 Optimisation studies

With proof of concept established and electrophilic fluorine identified as the most appropriate stoichiometric oxidant, an optimisation study was performed to screen for the optimal reaction conditions to furnish the fluoro-arylated products. Reactions were performed on substrate **10** (prepared in Chapter 2) due to its stability and ease of handling.

P-xylene was chosen as the nucleophilic partner to prevent regioisomer formation and because it is sufficiently volatile to be removed using standard techniques. The results of the optimisation studies are shown in Table 4. Preliminary investigations revealed that performing the reaction over activated 3 Å molecular sieves was highly beneficial to the reaction as was found in Chapter 2. This is expected, as water is known to efficiently trap the intermediate in a competing reaction to form fluoro-hydrin products. Reactions were run for 24 hours before filtering through a pipette celite filter, to remove any insoluble material, and then concentrated under reduced pressure. The diastereoselectivity and yield were determined by ^{1}H and ^{19}F NMR of the crude reaction mixture using an equimolar amount of *m*-fluoro-nitrobenzene as an internal reference. A large excess of *p*-xylene was used in all reactions to favour the desired fluoro-arylated product.



10 **65**

Entry	[N-F]$^{+}$ reagent (eq.) [a]	Solvent	Ratio [b]	Additive (eq.)	Temp. (°C)	Yield (%) [c]	d.r. [f]
1	Selectfluor (1.1)	$MeNO_2$	4:1	None	r.t.	40	>20:1
2	Selectfluor (1.1)	$MeNO_2$	4:1	$NaHCO_3$ (2.0)	r.t.	42	>20:1
3	NFCPT (1.1)	$MeNO_2$	4:1	$NaHCO_3$ (2.0)	r.t.	78	>20:1
4	NFCPT (1.1)	THF	4:1	$NaHCO_3$ (2.0)	r.t.	<5 [d]	ND
5	NFCPT (1.1)	Dioxane	4:1	$NaHCO_3$ (2.0)	r.t.	9 [d]	ND
6	Selectfluor (1.1)	DMF	4:1	$NaHCO_3$ (2.0)	r.t.	<5 [d]	ND
7	NFCPT (1.1)	EtOAc	4:1	$NaHCO_3$ (2.0)	r.t.	<5 [d]	ND
8	NFCPT (1.1)	Et_2O	4:1	$NaHCO_3$ (2.0)	r.t.	<5 [d]	ND
9	NFCPT (1.1)	DCM	4:1	$NaHCO_3$ (2.0)	r.t.	52	>20:1
10	NFCPT (1.1)	DCE	4:1	$NaHCO_3$ (2.0)	r.t.	52	>20:1
11	NFCPT (1.1)	*p*-xylene	-	$NaHCO_3$ (2.0)	r.t.	<5 [d]	ND
12	Selectfluor (1.1)	MeCN	4:1	$NaHCO_3$ (2.0)	r.t.	8 [e]	ND

13	NFCPT (1.1)	$MeNO_2$	4:1	$NaHCO_3$ (2.0)	50	64	>20:1
14	NFCPT (1.1)	DCE	4:1	$NaHCO_3$ (2.0)	50	47	>20:1
15	NFCPT (1.1)	$MeNO_2$	1:1	$NaHCO_3$ (2.0)	r.t.	61	>20:1
16	NFCPT (1.1)	$MeNO_2$	2:1	$NaHCO_3$ (2.0)	r.t.	71	>20:1
17	NFCPT (1.1)	$MeNO_2$	10:1	$NaHCO_3$ (2.0)	r.t.	81	>20:1
18	NFCPT (1.1)	$MeNO_2$	20:1	$NaHCO_3$ (2.0)	r.t.	78	>20:1
19	**NFCPT (1.5)**	**$MeNO_2$**	**10:1**	**$NaHCO_3$ (2.0)**	**r.t.**	**82**	**>20:1**
20	NFCPT (1.5)	$MeNO_2$	10:1	K_2CO_3 (2.0)	r.t.	57	>20:1

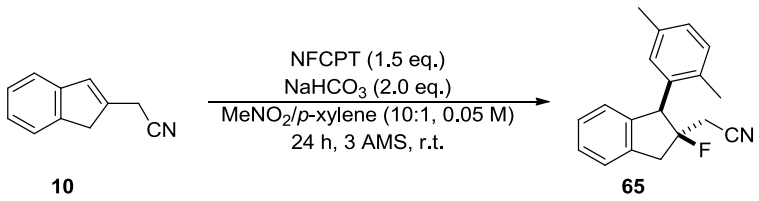
Table 4 - Optimisation of the fluorination of Indene 1; *a) NFCPT = N-Fluoro-2,6-dichloropyridinium triflate, b) Ratio of solvent to p-xylene, c) NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra, d) Significant amount of starting material observed, e) Significant amount of fluoro-Ritter and fluoro-hydrin product observed, f) Determined by ^{19}F NMR, ND = not determined.*

It was envisaged that protons liberated during the reaction could be detrimental to the yield due to competitive proto-arylation and so the role of sodium bicarbonate present in the reaction was first examined (entries 1 and 2) to determine if the addition of a base was necessary. The NMR yields were similar for both reactions but the reaction appeared to produce a cleaner crude NMR with the addition of base. Therefore, all future screening reactions were carried out with the addition of an excess of sodium bicarbonate as a precaution. The reactivity profile of the two fluorinating reagents was then probed to determine which was most effective. Both reagents were reacted in a variety of different solvents (entries 2-12) with varying yields. The limited entries for Selectfluor are a concequence of its poor solubility in many solvents. In contrast, NFCPT was investigated under a much broader range of solvents with $MeNO_2$, DCM and DCE (entries 3,9 and 10) leading to good yields. As with the fluoro-carbocyclization reaction, the highest yields for both Selectfluor and NFCPT were achieved with nitromethane as a solvent with the latter oxidant resulting in a >30 % improvement in yield over the former (entries 2 and 3). Nitromethane is presumably a successful solvent for the reaction on account that it is polar enough to stabilise the intermediate and solubilise the reagent, dry enough so as to not

form the fluoro-hydrin and most importantly because it is non-nucleophilic and thus does not compete to form side products like solvents such as acetonitrile do.

With nitromethane, DCE and DCM being the only three solvents that led to acceptable yields the effect of heating the reaction mixture was investigated. The low boiling point of DCM meant only nitromethane and DCE were heated to 50 ^{o}C (due to the potential danger of heating nitromethane it was decided that we would not heat to any higher temperatures). With both solvents, heating led to a decrease in yield (entries 13 and 14) and thus temperature was not investigated further.

The consequence of altering the ratio of arene:nitromethane was next investigated (entries 15-18). We speculated that the yield of product would be dependant on finding the optimal ratio of the two solvents; on one hand there needed to be enough nitromethane to ensure the solvent system was polar enough to stabilise the intermediate and solubilise the fluorinating agent, whereas at the other end of the spectrum, if the ratio of arene became too low, the reaction would begin to shut down. A 10:1 mixture of $MeNO_2$:arene was determined to provide the best compromise between solubility and achieving the highest product yield (entry 17). Investigations into the effect of the amount of equivalents of fluorinating reagent revealed that an increase of $[N\text{-}F]^+$ reagent to 1.5 eq. also resulted in very slightly improved yields (entry 19). We envisaged that this could be because a small proportion of the fluorinating reagent will be consumed in fluorinating the aromatic portion of the solvent and not the olefin of the indene. There is also the question of electrophilic fluorinating reagent purity, which will be addressed in Chapter 3. Finally, the slightly more basic potassium carbonate was explored as the source of base, but this proved to be inferior compared with sodium bicarbonate (entries 19 and 20). The conclusion of this extensive screening exercise led to the determination of the optimal conditions for the fluoro-arylation (Scheme 14).



10 **65**

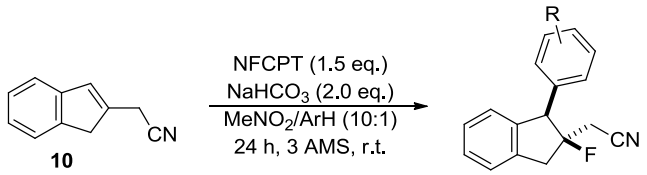
Scheme 14 - Optimal reaction conditions for electrophilic fluoro-arylation

3.4.3 Substrate scope

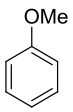
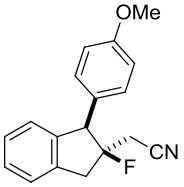
To study the scope of these optimised conditions, a series of fluoro-arylation reactions with different indene/ styrene substrates and with a variety of nucleophiles were performed. We wished to explore multiple aspects of the reaction, such as the limit in arene nucleophilicity and the regioselectivity of the arene attack.

3.4.3.1 Arene nucleophilicity

We initially investigated the cyano-indene **10** that had been used in the optimisation reactions and investigated a range of arenes with varying nucleophilicity that could successfully be used in the fluoro-arylation (Table 5).



10

Entry	ArH	Product	Yield (%)	d.r[a] (syn:anti)	*Para:ortho*[b]
1			81	10:1	5:1

66

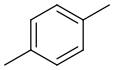
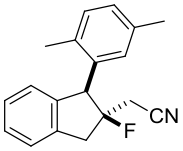
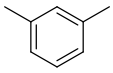
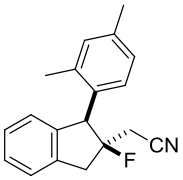
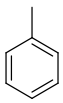
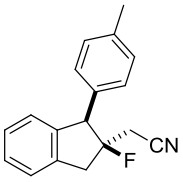
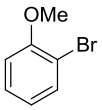
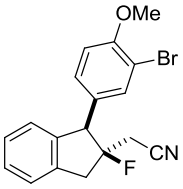
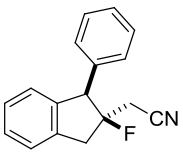
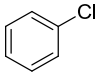
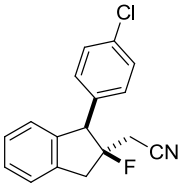
2		 **65**	77	10:1	-
3		 **67**	72	>20:1	>20:1
4		 **64**	78	11:1	>20:1
5		 **68**	42	>20:1[c]	>20:1
6		 **69**	16	>20:1	-
7		 **70**	0	-	-

Table 5 - Substrate scope investigation under optimised conditions; *a) Determined by ^{1}H NMR, b) Determined from ^{1}H NMR or ^{19}F NMR, c) 3.0 eq. of arene used*

In all reactions, no starting material was detected with any loss of yield being attributed to undetermined oligomer/ fluoro-hydrin product formation. Moving down the entries in the table saw the nucleophilicity of the arene decrease as they were substituted with successively poorer electron donating groups. This trend was found to be consistent with the

trend of decreasing isolated yield. The yield for the reaction with *p*-xylene (entry 2) was complementary with those obtained in the optimisation reactions, confirming that the compound is stable towards silica gel purification.

No reaction was observed with chlorobenzene, which is perhaps unsurprising given the low yield for the reaction with benzene. The electron withdrawing nature of the chlorine group means that the arene is simply not electron rich enough to react with the intermediate carbocation. The series of reactions enabled us to determine the scope of nucleophiles that are compatible with our system; from the very electron rich anisole at the upper limit down to benzene at the lower limit. Notably, more electron rich arenes were not investigated, as anisole is known to fluorinate readily under only slightly elevated temperatures.[9]

Considering this methodology being implemented in a synthetic sequence, it was pleasing to see the successful reaction with 2-bromo anisole (entry 5), which led to excellent regioselectivity with modest yield. The result could be of particular interest as the bromine atom on the added arene could potentially allow further functionalisation of the compound through a variety of different organo-metallic reactions. Furthermore, due to the high boiling point of 2-bromo anisole (223 ^{o}C), it would not have been possible to remove unreacted nucleophile under standard conditions as we did in all other examples. To make final purification more straightforward, we restricted the quantity of the nucleophile to 3.0 eq. and thus the moderate yield of **68** obtained (entry 5) at 42% was all the more satisfactory considering the purification implications. This finding could allow more complex arenes with low volatility to be coupled in future developments allowing the synthesis of more complex substrates.

Although most of the compounds were oils, the reaction with toluene afforded **64** as a crystalline solid. This was useful as it aided with unambiguously determining the

diastereoselectivity of our products as an x-ray crystallographic structure was obtained (Figure 4).

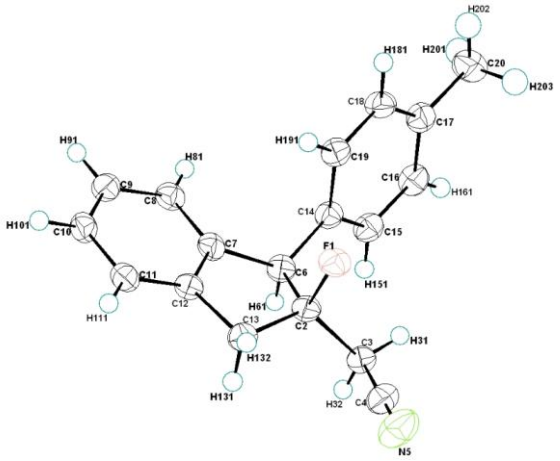


Figure 4 - Crystal structure of 2-(2-fluoro-1-(*p*-tolyl)-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (Table 5, entry 4)

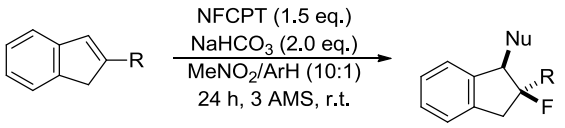
The crystal clearly shows the syn configuration of the fluorine and nucleophile in the product. It was perhaps to be expected that the syn isomer would be the preferred isomer since this would involve toluene attacking from the face bearing the fluorine atom, rather than the face bearing the more sterically encumbered acetonitrile group. In all cases, the syn isomer was the favoured product; this structural assignment was confirmed by a comparison of the coupling constants for the different products, which were all very similar (Table 6).

Product	Coupling Constant (Hz)[a]	
	Syn	***Anti***
64	26.6	22.8
65	26.5	22.7
66	26.2	-[b]
63	26.7	22.9
67	26.0	23.0
68	26.4	-[b]

Table 6 - Comparison of the syn/ anti coupling constants; *a) Determined from ^{1}H NMR, b) Not enough of the anti diastereoisomer present to enable determination of the coupling constant*

3.4.3.2 Alternative indene sources

After investigating the scope of the nucleophile, we moved on to look at the reactivity of alternative indenes under our optimised conditions (Table 7).



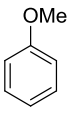
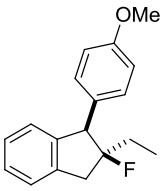
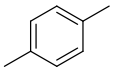
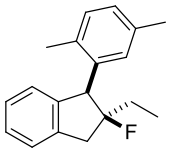
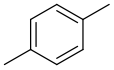
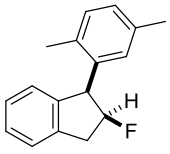
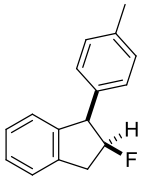
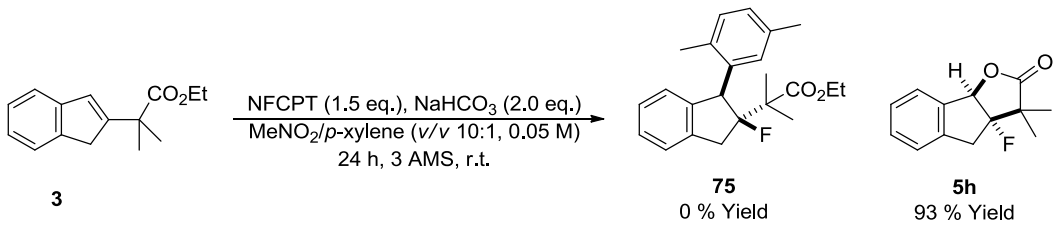
Entry	ArH	R	Product	Yield (%)	d.r[a] (syn:anti)	*Para:Ortho*[b]
1		Et	 **71**	46	>20:1	5:1
2		Et	 **72**	34	>20:1	-
3		H	 **73**	36	3.5:1	-
4		H	 **74**	40	5:1	7:1

Table 7 - Alternative indene sources applied under optimised conditions; *a) Determined from ^{1}H NMR, b) Determined from ^{1}H NMR or ^{19}F NMR*

With both categories of indene, the yields were between 30 and 40% lower when compared to the cyano-indene under the same conditions. When considering the ethyl indene (entries 1 and 2), we postulated that by changing the side chain on the indene from an electron withdrawing cyano group to a relatively electron rich ethyl group, the mechanism by which NFCPT fluorinates the olefin may change. Indeed, the mechanism of electrophilic fluorination is still in debate with different papers suggesting it could be an electrophilic reaction, a free-radical reaction or a single electron transfer process (see Chapter 1). If there is a change in the mechanism for differing substrates, this could explain the effect on the yields of the reaction. The change in mechanism is slightly supported by the fact that with the ethyl indene, a bright instantaneous colour change was observed when the NFCPT was added, suggestive of a radical intermediate.

When using indene as the substrate (entries 3 and 4) it was interesting to observe a preference for the *anti* diastereoisomer on the unsubstituted indene. Despite fluorine being slightly larger than hydrogen (Van der Waals radii of 1.47 Å and 1.20 Å, respectively)[10] it is unlikely that this difference in size is enough to explain the significant preference for the *anti* isomer. This is suggestive that the preference for the *anti* isomer is concerned with a stereoelectronic effect. In both reactions, no starting material was recovered with any loss of yield again due undetermined oligomer/ fluoro-hydrin product formation.

To determine why the cyano-indene consistently gave us better yields than the other indene compounds, we wanted to use a different indene with an electron withdrawing group to investigate whether it was the electron withdrawing properties or a different characteristic of the cyano group that was leading to the improved yields. It was therefore decided to carry out the reaction with ethyl 2-(1*H*-inden-2-yl)-2-methylpropanoate (Scheme 15), which we had available in the group.



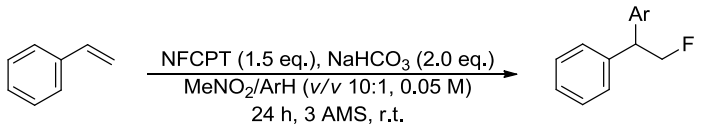
3 **75** 0 % Yield **5h** 93 % Yield

Scheme 15 - Electrophilic fluorination of ethyl 2-(1H-inden-2-yl)-2-methylpropanoate under optimised conditions

No expected product was observed with instead, excellent conversion to the fluorinated lactone **5h**. This could perhaps be rationalised by the gem dimethyl group exerting a significant Thorpe-Ingold effect on the molecule and thus promoting cyclisation.[11] This reaction is itself an interesting result as it tells us that esters are not compatible with a fluoro-carbocyclization as more general fluoro arylation reaction, since under the reaction conditions they behave as a latent source of carboxylic acid which we know to be a competent nucleophile.

3.4.3.3 Styrene based substrates

The reactions of styrene under the optimised fluorination conditions were next explored under our optimised conditions to investigate the effect of switching to an acyclic system (Table 8). Clearly it would be desirable to translate the reaction conditions to a substrate as simple as styrene to highlight the generality of the methodology.



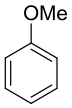
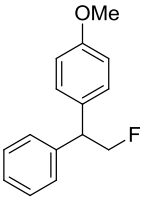
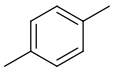
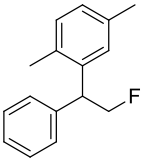
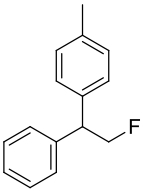
Entry	ArH	Product	Isolated Yield (%)	*Para:ortho*[a]
1		 **76**	23	>20:1
2		 **77**	47	-
3		 **78**	52	6.2:1

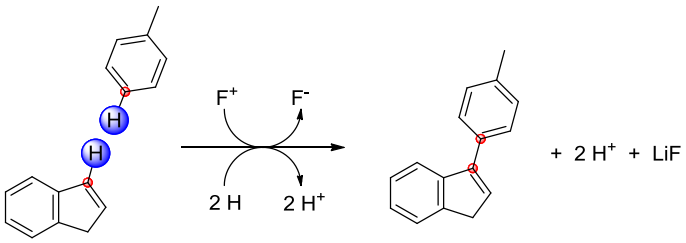
Table 8 - Application of optimised conditions to styrene; *a) Determined from ^{1}H NMR spectra*

In all reactions, as in previous examples, the loss of yield was attributed to undetermined oligomer/ fluoro-hydrin formation. Products were on the whole obtained in a reasonable yield consistent with those of the indene substrates.

3.4.4 Dehydrofluorination

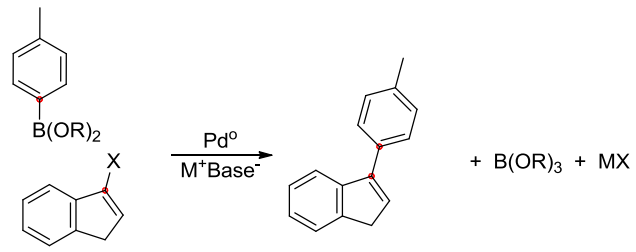
During our research in this area we were constantly vigilant of the possibility of dehydrofluorination occurring to afford a potential side-product. Whilst we never observed these products we realized that a dehydrofluorination reaction might be very interesting in its own right. Overall, the reaction would involve the coupling of indene and toluene with

the by-products of 2 protons and lithium fluoride. Overall, electrophilic F^+ would be reduced to fluoride, F^-, by the loss of 2 protons and hence the liberation of 2 electrons.



Scheme 16 – Overall outcome for coupling of indene and toluene, mediated by fluorine

If we consider how else this transformation might be carried out, the obvious conclusion would inevitably be a metal catalysed cross coupling reaction. However, this would likely involve the pre-functionalisation of the starting materials, which would mean extra steps, all being associated with a loss of yield. For example to do a Suzuki reaction, first the indene would need to be functionalised as a vinyl halide, then the toluene would need to be functionalised as the boronic acid and finally a palladium species would need to be added to couple the reagents, with formation of stoichiometric amounts of boronic acid and metal iodide. We propose that a fluoro-arylation reaction, in conjunction with dehydrofluorination, could be method is greener, in that toxic palladium waste is not generated and also that smaller amounts of by-products are generated in an overall shorter reaction sequence.



Scheme 17 – Proposed alternative Suzuki reaction

The elimination of fluoride from molecules is more difficult than the elimination of other halides such as bromide or chloride due to the high strength of the C-F bond versus the C-Cl/Br bond. This evidence is supported by a paper published by Schlosser and co-workers,[12] in which they compared the rates of dehydrofluorination from alkyl fluorides vs. dehydrochlorination/ bromination from the corresponding alkyl halides. As shown in Table 9, bromides are up to 10^5 times more reactive than the fluoride equivalents.

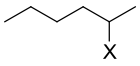
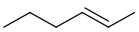
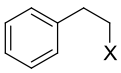
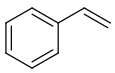
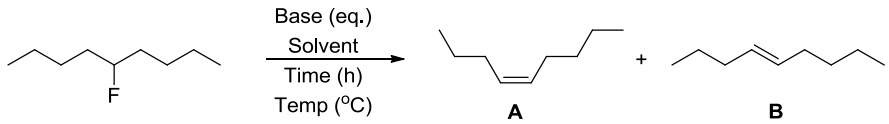
Entry	Substrate	Base	Solvent	Product	Relative rate of reaction			
					X=F	X=Cl	X=Br	X=I
1		$NaOCH_3$	Methanol		1	$2x10^3$	$1x10^5$	-
2		$NaOC_2H_5$	Ethanol		1	$7x10^1$	$4x10^3$	$3x10^4$

Table 9 - Base promoted dehalogenation of 2-hexyl and 2-phenylethyl halides: comparison of relative reaction rates

This difference in relative reaction rates is reduced when switched to a terminal alkene or a styrene. A possible reason for this is that the mechanism changes from E_2 to a more E_{1cB} like transition state, on proceeding from Cl/ Br to F.[13] This change is only possible with such substrates as they are able to stabilise the anionic character that develops in the E_{1cB} transition state due to the presence of the aromatic ring. These observations towards a more E_{1cB} route were also highlighted by Bartsch *et al.*,[14] who pointed out that as the strength of the C-X bond increases, the breaking of the C-H_β bond will become more important in the rate determining step, thus moving to a more E_{1cB} mechanism.

In the report by Schlosser,[12] different bases were investigated that could be used in the elimination of fluoride from alkylfluoride compounds (Table 10).



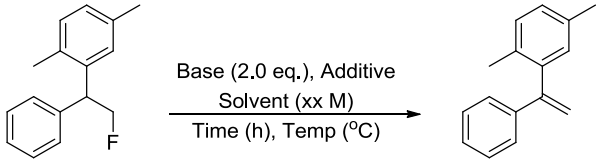
Entry	Base	Solvent	Time (h)	Temp (°C)	Yield (%)	Ratio A:B
1	$NaOCH_3$	Methanol	48	125	8	29:71
2	$KOC(CH_3)_3$	DMSO	24	50	29	19:81
3	$KOC(CH_3)_3$	Benzene	24	100	10	9:91
4	LDA	Et_2O	48	40	74	6:94
5	LDA	THF	24	25	0	-

Table 10 - Investigative studies into fluoride elimination by Matsubara

The results showed that only LDA is effective at eliminating hydrogen fluoride (entry 4) with alternative bases leading to far inferior yields. It was interesting to note the inverse relationship between solvent polarity and reactivity of LDA towards the alkyl fluoride. The reaction did not proceed at all in an LDA/ THF mix, however it was able to proceed slowly but effectively in diethyl ether at reflux. In neat hexane, elimination occurred only in trace amounts. The authors reasoned that the driving force for the departure of the fluoride leaving group was the precipitation of lithium fluoride with its enormous lattice energy. This electrophilic effect is most effective as long as the lithium is only weakly solvated, such as in relatively non-polar solvents, thus offering an explanation of the inverse polarity relationship.

3.4.4.1 Optimisation studies

An optimisation study was performed in which different bases were considered in order to find the most suitable conditions for dehydrofluorination (Table 11).



76 **78**

Entry	Base	Additive	Solvent	Temp. (°C)	Time (h)	Yield[a]
1	TBD[b]	LiOTF	DCM-d_2	r.t.	24	<5[c]
2	TBD[b]	LiOTF	DCM-d_2	40	24	<5[c]
3	TBD[b]	LiOTF	MeCN-d_3	82	24	14[c]
4	TBD[b]	LiOTF	Toluene-d_8	110	24	8[c]
5	TBD[b]	BF_3	Toluene-d_8	110	24	0
6	**LDA**	**None**	**Et_2O**	**r.t.**	**4**	**55[d]**

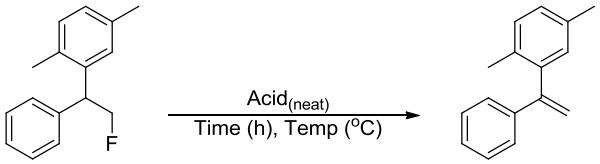
Table 11 - Optimisation of the elimination step; *a) NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra, b) TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene, c) Significant amount of starting material remaining, d) Isolated yield*

The use of an additive was considered in order to complex with the fluorine atom and aid its removal as a fluoride salt, which would act as a driving force for the reaction. Due to the high strength of the C-F[15] bond we felt a strong base would be needed and thus we first decided to use non-nucleophilic triazabicycodecene (TBD), a bicyclic guanidine base with a pk_a of 26 in THF.[16] Such bases have been used in the elimination of bromide[17] and thus we were interested to investigate whether the conditions could be translated to fluoride substrates. As discussed, the mechanism of the reaction is most likely to follow an E_{1cB} or E_2 pathway or more likely somewhere between the two and this type of reaction is normally favoured under polar aprotic conditions. We hence decided to try DCM in our initial reaction (entry 1). After 24 h, TLC suggested that primarily starting material remained this was confirmed by ^1H/ ^{19}F NMR. The reaction was repeated under reflux conditions, again showing that primarily unreacted starting material remained (entry 2).

It was decided to change to a more polar solvent with a higher boiling point, thus allowing greater heating than what could be achieved in DCM-d_2 and thus MeCN-d_3 was tested. As in

the previous cases, only a small percentage of starting material had reacted after 24 hours (entry 3). Although not a polar solvent, toluene has been used effectively in an elimination reaction in combination with DBU,[18] another guanidine base, however again only a trace reaction was detected (entry 4). The effectiveness of the additive, LiOTf, was considered and tested by substituting with BF_3, reasoning that it could abstract fluoride to form BF_4^-. However, unfortunately no improvement under these conditions was observed (entry 5). A study with the powerful base LDA resulted in a significantly increased conversion of the starting material to product, vastly improving on our yields obtained with TBD (entry 6). As found in the work by Schlosser, this base is far superior to all others at promoting the elimination.

Before settling on LDA as the most suitable method of performing the eliminations, we also wanted to investigate the possibility of using a strong Brønsted acid (Table 12). We speculated that if an acid was able to hydrogen bond to the fluorine, this could weaken the C-F bond sufficiently to move away from the E_{1cB} mechanism to a more classical E_2 elimination pathway, thus leading to the desired product.



77 **79**

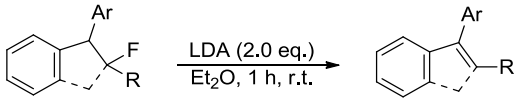
Entry	Acid	Temp. (°C)	Time (h)	Yield[a] (%)
1	Formic Acid	r.t.	8	0[b]
2	Formic Acid	100	2	0[b]
3	TFA	r.t	4	0[b]
4	TFA	72	4	0[c]

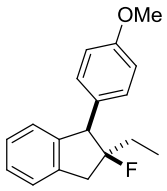
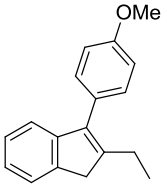
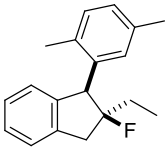
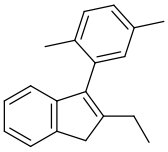
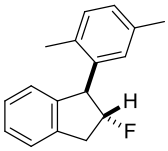
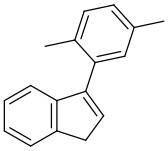
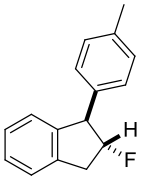
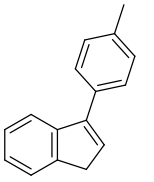
Table 12 - Optimisation of elimination under acidic conditions; *a) NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra, b) Significant amount of starting material remaining, c) Decomposition products observed*

Disappointingly, we were not able to successfully use acid to effect the elimination of hydrogen fluoride since either the starting material did not react (entries 1-3) or decomposition was observed (entry 4). Therefore, LDA was chosen as the optimal base to carry out the remaining eliminations for achieving the cross-coupled products.

3.4.4.2 Dehydrofluorination under optimised conditions

With the optimal conditions determined, we investigated the elimination reaction on the range of substrates built up from in the previous fluoro-arylation reactions (Table 13).



Entry	Substrate	Product	Temp. (°C)	Yield (%)
1	 **71**	 **80**	r.t	60
2	 **72**	 **81**	r.t	33
3	 **73**	 **82**	r.t	82
4	 **74**	 **83**	r.t	99

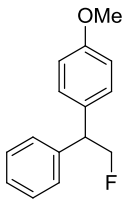
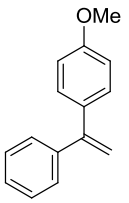
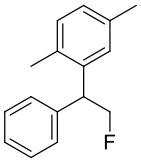
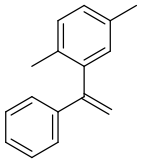
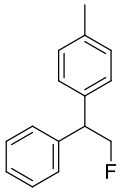
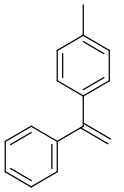
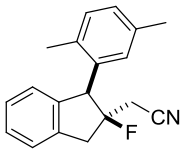
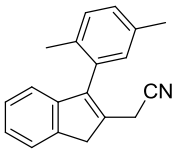
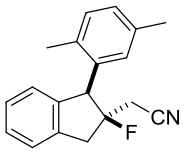
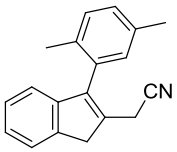
5	 **76**	 **84**	r.t	73
6	 **77**	 **79**	r.t	55
7	 **78**	 **85**	r.t	73
8	 **66**	 **86**	r.t.	0[a]
9	 **66**	 **86**	-78	0[a]

Table 13 - Elimination under optimised conditions; a) *Decomposition products formed*

In general, the use of LDA was successful in promoting the elimination of fluoride. It should be noted that although there are a number of acidic protons that could be removed in the indene systems leading to regioisomers, in all cases it was the acidic dibenzylic proton which was removed leading to the formation of the Saytzev product. However, these conditions did not lead to the desired product when applied to the fluorinated cyano indanes (entry 8). A possible explanation for this is that the protons alpha to the cyano group are acidic and so will lead to a competing deprotonation/ polymerisation reaction. We attempted to suppress

the formation of these undesired side products by cooling the mixture to -78 °C (entry 9), however this was to no avail with undetermined decomposition products forming.

3.5 Conclusion

In summary, we have successfully demonstrated that the fluoro-carbocyclization methodology developed in Chapter 2 is compatible with an inter-molecular variant. We again found choice of the fluorinating reagent was crucial to the outcome of the reaction with *N*-fluoro-2,6-dichloropyridinium triflate displaying the best fluorinating ability. We showed that the reaction is most successful with arenes of moderate electron richness and that in most cases the regioselectivity was very acceptable. The examples involving unfunctionalised styrene or indene were particularly pleasing as they illustrate the generality of the reaction, with substrate activation being preferable but by no means essential. We took the reaction one step further to explore a dehydrofluorination reaction, which accompanied by the fluoro-arylation process, allows the products of a formal C-H activation cross-coupling with fluorine being used as the oxidant. The arylation at the α- position is an interesting transformation as traditional transition-metal catalysed reactions typically arylate at the β- position or require one or both coupling partners to be activated for reaction at the α- position. Unfortunately, as yet we have not been able to perform this in a one-pot procedure but this could certainly be an exciting future line of research. A metal-free C-H activation cross-coupling would be a very interesting, and to the best of our knowledge the first reported, use of electrophilic fluorine. It should be noted that whilst the yields of the two steps are generally only moderate to good, the fact that the coupling partners do not require prior activation could be attractive in terms of reducing steps in a synthetic sequence.

References for Chapter 3

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Chapter 4:

New Chiral Fluorinating Reagents

4. New Chiral Fluorinating Reagents

4.1 Introduction

Due to the growing prevalence of fluorine in medicinal and agrochemical compounds there is a constant need to increase and improve the methods that are available for the construction of C-F bonds.[1,2] Great advances have been made over the last few decades for the introduction of fluorine on an sp^2 centre and it is therefore on aromatic rings that fluorine is most usually found in drug compounds. However, advancement of techniques for the asymmetric introduction of fluorine onto a carbon sp^3 centre would vastly increase the scope for structure modification by means of fluorine introduction. In recent years, much work has focussed on this field, which has led to powerful strategies for the enantioselective incorporation of fluorine.

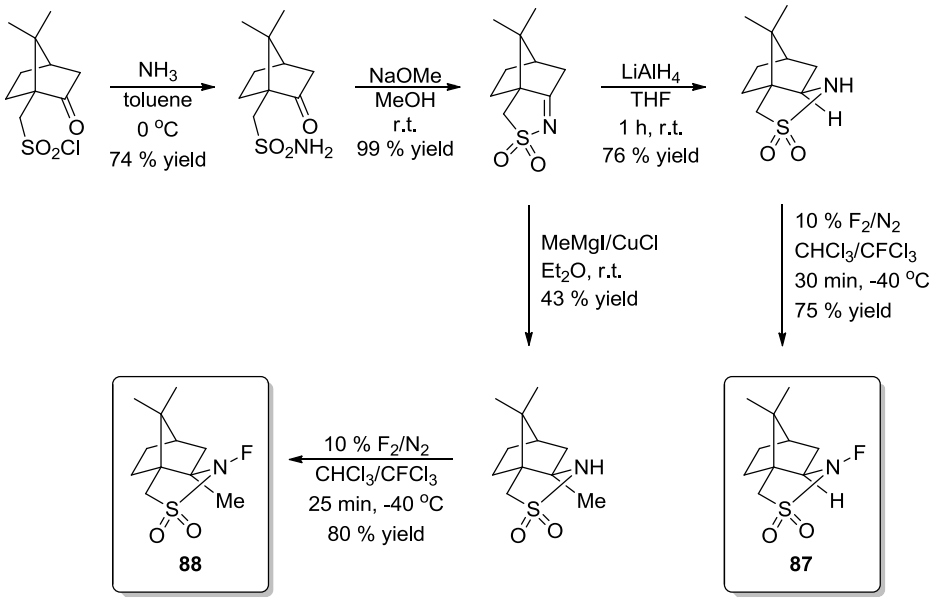
4.2 Chiral electrophilic fluorinating reagents

To achieve an asymmetric fluorination, one can imagine two distinct approaches. Either an achiral fluorine source can be used along with a chiral additive (such as a chiral Lewis acid) to allow for facial differentiation or a chiral fluorine source can be used with a prochiral substrate. Both routes have been explored extensively in the literature but this chapter will focus on the preparation and use of new chiral reagents for asymmetric electrophilic fluorination.

4.2.1 First-generation chiral reagents: Uncharged N-F reagents

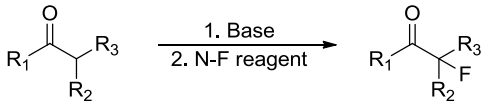
The first reported chiral N-F reagents were reported by Differding and Lang in 1988 based on fluorinated camphor-sultams.[3] The synthesis involved the treatment of camphor-10-

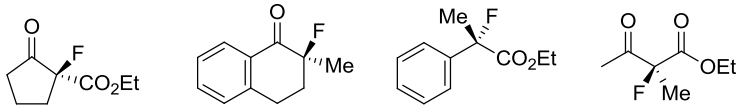
sulfonyl chloride with ammonia to form the intermediate sulfonamide, which could then be cyclized onto to the carbonyl with the addition of base. Reduction of the intermediate compound could then be performed by a hydride source or an organometalic reagent to achieve a variety of camphor-sultams. The reduction was found to occur stereoselectively on the least hindered face to afford only one isomer. Finally, direct fluorination of the sultams in a $CHCl_3/CFCl_3$ solvent system at -40 °C with 10 % F_2/N_2 furnished the *N*-fluoro-camphor-sultams according to Scheme 1.



Scheme 1 – Synthesis of first chiral fluorinating reagents

The enantioselectivity of these reagents was investigated using various metal enolates, generated by alkali metal hydrides or LDA, to access α-fluoro carbonyl compounds. The reagents were found to be highly substrate dependent, with the unsubstituted camphor-sultam **87** delivering the higher ee's. The best ee obtained was 70 %, which was very promising for a first report, thus validating the feasibility for reagent controlled asymmetric fluorination using an electrophilic fluorine source.



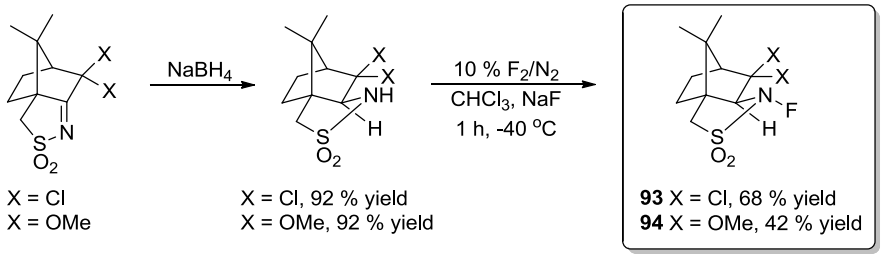


89 **90** **91** **92**

Entry	N-F Reagent	Conditions	Product	Yield (%)	ee (%)
1	**87**	NaH, Et_2O, 0 °C to r.t.	**89**	63	70
2	**88**	KH, PhMe/THF, 0 °C to r.t.	**89**	<5	<10
3	**87**	LDA, THF, -78 °C to r.t.	**90**	<5	35
4	**87**	LDA, THF, -78 °C to r.t.	**91**	27	35
5	**88**	LDA, THF, -78 °C to r.t.	**91**	34	<10
6	**87**	LiH, Et_2O, r.t.	**92**	31	<10

Table 1 – α-Fluorination of carbonyl compounds with *N*-fluorocamphorsultams

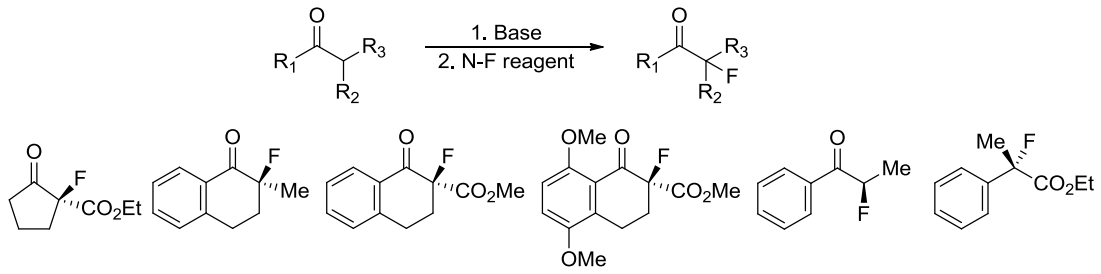
In an extension to the work done by Differding and Lang, Davis and co-workers modified the *N*-fluorocamphorsultam reagents to feature gem-dichloro or gem-dimethoxy substitution with the aim of enhancing the enantioselectivity of the reagents.[4,5] The synthesis was essentially the same as Differding's, but this time starting from the gem-disubstituted sultam. Fluorination was performed in the presence of powdered sodium fluoride using diluted fluorine in chloroform as the solvent.



Scheme 2 – Synthesis of Davis' reagent

Due to the inductively electron withdrawing nature of the gem-dichloro or gem-dimethoxy groups, the fluorinating agents are more electrophilic that Differding's and hence the

temperature could be lowered for the fluorination reaction. Unfortunately, the observed stereoselectivity was, in general, no better than the earlier report, with modest yields and ee's obtained. The lack of enantiomeric excess of propiophenone **97** was likely due to the presence of an acidic α-proton, which allows for facile racemisation under basic conditions. Unfortunately, this method suffers from the significant limitation that further structure modification is very difficult due to the sultams originating from natural products.

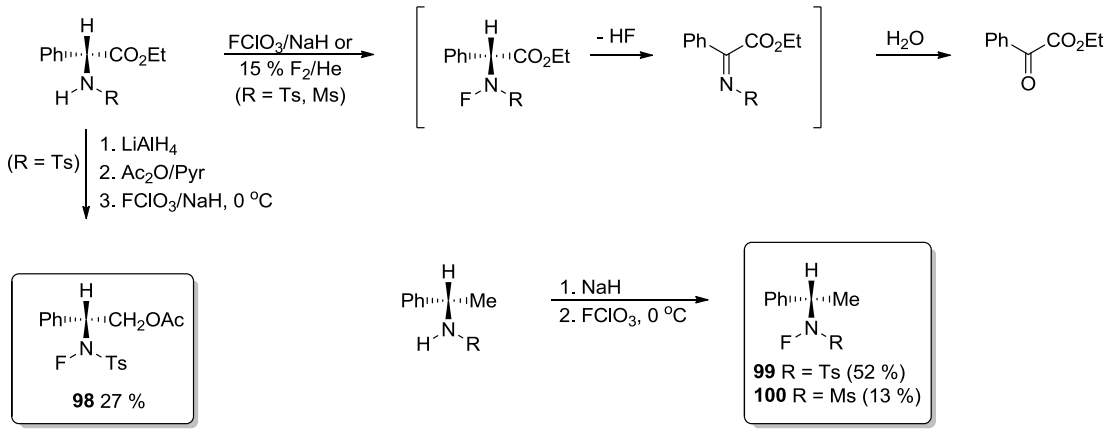


Entry	N-F Reagent	Conditions	Products	Yield (%)	ee (%)
1	**93**	NaH, Et_2O, -78 °C to r.t.	**89**	59	34
2	**94**	NaH, Et_2O, -78 °C	**89**	57	<5
3	**93**	NaHMDS, -78 °C	**90**	53	76
4	**94**	NaHMDS, -78 °C to r.t.	**90**	61	<5
5	**93**	KHMDS, THF, -78 °C	**95**	90	41
6	**93**	NaH, Et_2O, -78 °C to r.t.	**96**	95	46
7	**94**	NaHMDS, -78 °C	**97**	53	14
8	**93**	NaHMDS, -78 °C to r.t.	**91**	61	0
9	**93**	NaHMDS, -78 °C to r.t.	**91**	54	33

Table 2 – Enantioselective fluorination using Davis' reagents

A final addition to this 1st generation chiral sulfonamide class reagents was made by Takeuchi and co-workers.[6] In response to the major limitation of difficult structural modification on the sultam systems, Takeuchi proposed a series of reagents derived from amimo acids. Mild fluorination of N-tosyl and N-mesyl D-phenylglycine ethyl ester afforded ethyl benzoylformate as the only isolable product. This can be explained by facile

dehydrofluorination of the initially formed fluorinated product. Dehydrofluorination was suppressed by reducing the acidity of the alpha proton by manipulating the ester moiety to afford the acetate product **98** or the fully reduced products **99** and **100**. [N-F] compound **99** was found to be most stable, therefore optimisation of the fluorinating conditions was performed on this substrate.



Scheme 3 – Synthesis of Takeuchi reagents

Fluorination of metal enolates was performed on *in* situ formed substrates, similar to those used by Differding[3] and Davis.[4,5] The fluorinating reagents were again found to be highly substrate dependent, with the cyclic substrates delivering the higher ee's. The tetralone substituted with a benzyl group was fluorinated with slightly higher enantioselectivity than the ones substituted with a small methyl group. The low chemical yields were attributed to the lower reactivity profile of the less structurally rigid acyclic sulfonamides.

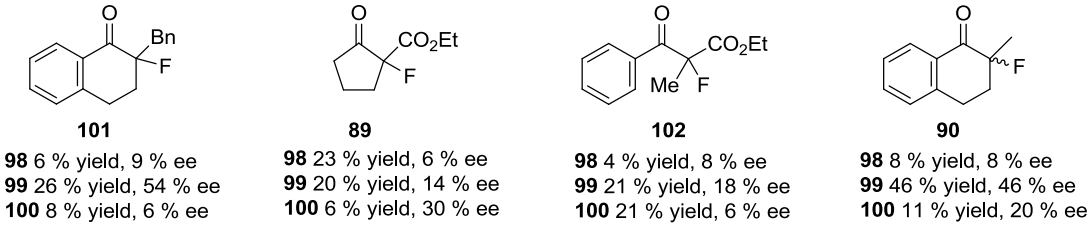
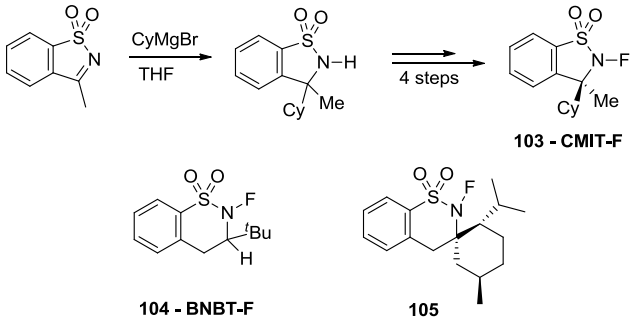


Figure 1 – Fluorination of metal enolates using Takeuchi reagents

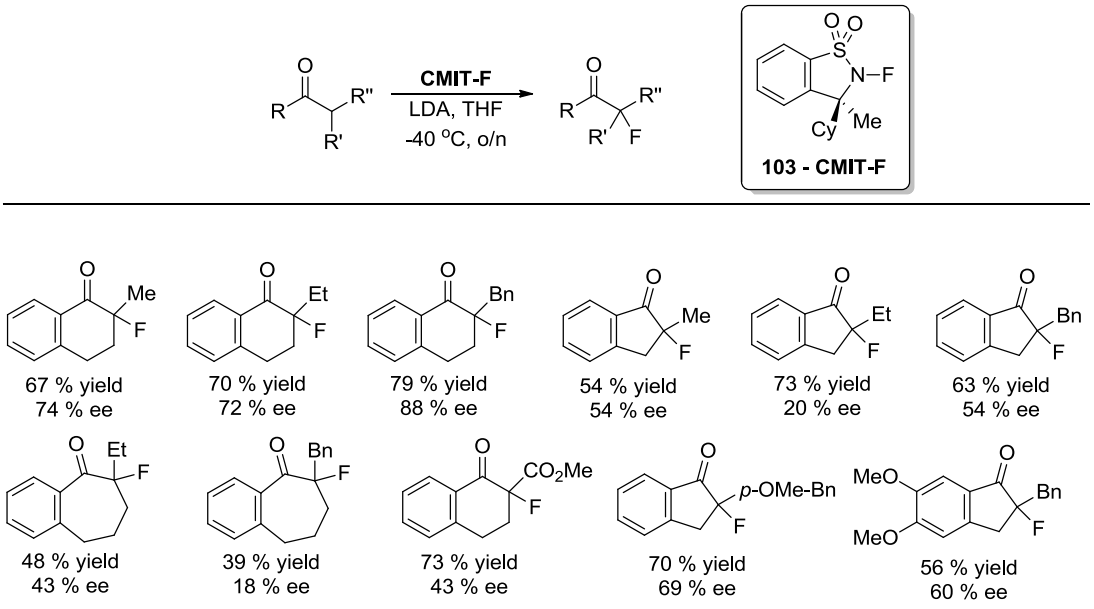
Takeuchi subsequently developed a new class of cyclic sulfonamides, which would be conformationally locked to increase their selectivity. The structure of CMIT-F was designed to produce a stable yet reactive N-F bond and also include steric factors that will favour asymmetric induction. The planarity in the system seemed likely to effect the stereochemical orientation in an ordered transition state. This is crucial as no stereochemical bias can be expected in the transfer of such a small atom. Reduction of the starting *N*-sulfonyl imine was accomplished using cyclohexylmagnesium bromide in THF. Resolution of the resulting sulfonamide was performed using menthoxyacetal chloride before removal of the resolving agent with lithium hydroxide and fluorination using 15 % F_2/He.



Scheme 4 – Synthesis of chiral cyclic *N*-fluorosulfonamides

Using the structurally rigid **CMIT-F**, the yields of asymmetric fluorination were greatly enhanced, achieving up to 79 %. The enantioselectivities were also impressive with the

benzyl substituted tetralone **101** being fluorinated in an 88 % ee (*cf* 54 % with **99**). A broad substrate scope was undertaken, which revealed five- and six- membered rings were tolerated well but seven- membered rings were obtained in a substantially lower ee.



Scheme 5 – Fluorination of indanones and tetralones using **CMIT-F**

The working model for S selectivity is shown in the transition state illustrated in Figure 2. Based on the X-ray crystallographic structure of CMIT-F the N atom is found to be highly pyramidalized, and the fluorine is almost antiperiplanar with the bulky cyclohexyl group. The chelation structure of the lithium enolate in THF is strongly indicated by the fact that addition of HMPA resulted in lowering of the enantioselectivity (14 vs 74 %).

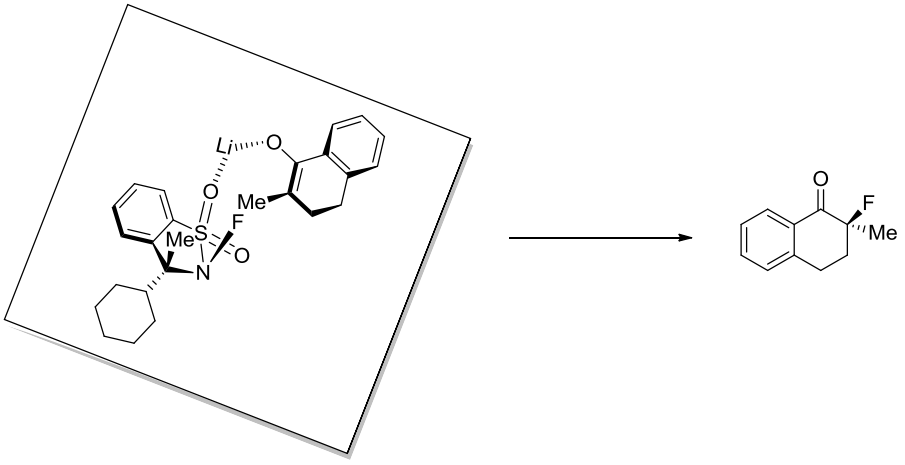


Figure 2 – Transition state model for fluorination using **CMIT-F**

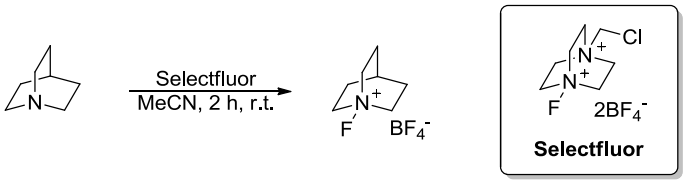
In summary, the early work on sulfonamide based reagents was very important as it demonstrated the possibilities of reagent driven asymmetric fluorination. However, the often low enantioselectivity is a serious limitation to their synthetic utility, as too is the fact that they are not commercially available and require tedious multi-step preparation. Perhaps the biggest limitation, however, is their low reactivity, which results in only very highly reactive metal enolates being suitable substrates. For a really significant advance in the field of asymmetric fluorination, it should be possible to fluorinate other, less activated substrates.

4.2.2 Second generation chiral fluorinating reagents: Charged N-F reagents

The introduction of Selectfluor by Eric Banks in the early '90s revolutionised the field of electrophilic fluorination due to its high reactivity, non-hygroscopy and easily handling.[7] The versatility of this reagent is, in no small part, due to it being a powerful fluorinating reagent, which is a consequence of its (di)cationic nature. Therefore, the second generation of chiral fluorinating reagents featured a charged $[N\text{-}F]^+$ motif, which are able to deliver fluorine to substrates of much lower reactivity. However, apart from the lack of reactivity, another major drawback of the 1st generation reagents was that they all required synthesis

from molecular fluorine, which is highly prohibitive to their use. Therefore, along with the advance in reactivity of the chiral reagents, a general method for "in house" preparation of reagents was developed.

The breakthrough in the field of asymmetric fluorination was made again by Banks and co-workers, where they described a fluorine transfer method for the fluorination of quinuclidine.[8] The concept of the transfer reaction was very simple, and relies on the reactivity difference between the "F^+ donor" and the "F^+ acceptor." In Banks' original publication he demonstrated the fluorine transfer from commercially available Selectfluor to quinuclidine in a short reaction time at room temperature in acetonitrile. The potential of this reaction is enormous, since it circumvents the need for fluorine gas, instead being replaced by a commercially available easy to handle crystalline solid.

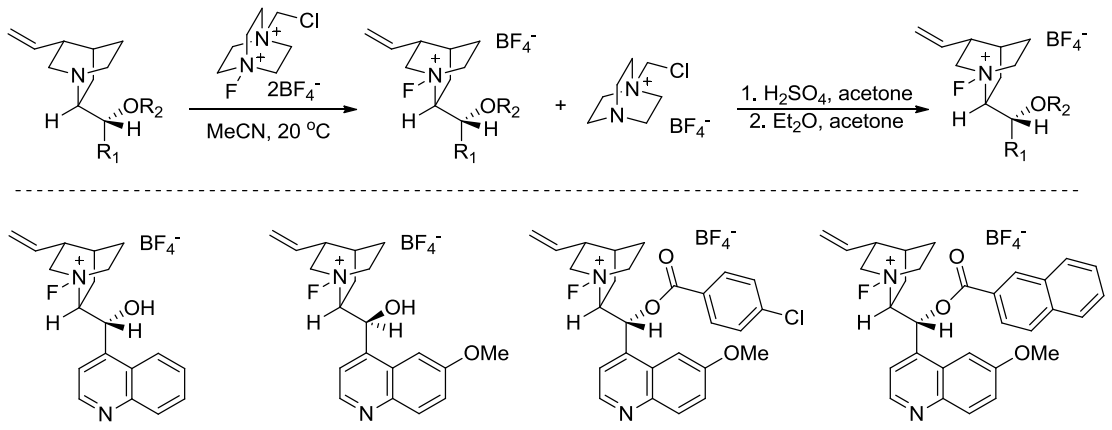


Scheme 6 – Fluorine transfer from Selectfluor to quinuclidine

Both Cahard[9] and Shibata[10] simultaneously realised the potential of this reaction by developing chiral fluorinating reagents based on cinchona alkaloids. Since their report in 2000, *N*-fluorocinchona reagents have dominated the literature for reagent driven asymmetric fluorination methods, which is due to both their excellent selectivity and commercial availability. Cinchona alkaloids are relatively inexpensive and a wide variety are available, thus when combined with Selectfluor a very attractive charged chiral fluorinating reagent can be obtained.

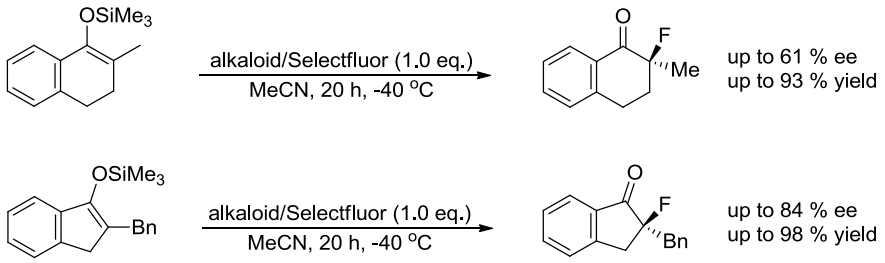
4.2.2.1 Cahard's method

Cahard utilized the fluorine transfer technique to isolate fluorinated cinchona alkaloids by mixing equimolar amounts of Cinchona alkaloids and Selectfluor in acetonitrile. The purification of the reagents, however, was not necessarily so trivial since the by-product of the fluorine transfer was de-fluorinated Selectfluor, a mono-cationic species which should have a similar solubility to the mono-cation fluorinated alkaloid. A double precipitation method was used, whereby H_2SO_4 was added to cause the precipitation of 1-chloromethyl-4-hydro-1,4-diazoniabicyclo[2.2.2]octane hydrogen sulphate, which could be removed by filtration. This was followed by the addition of diethyl ether to cause precipitation of the chiral reagent, which was again collected by filtration.



Scheme 7 – Preparation of Cahard's *N*-fluoro cinchonium salts

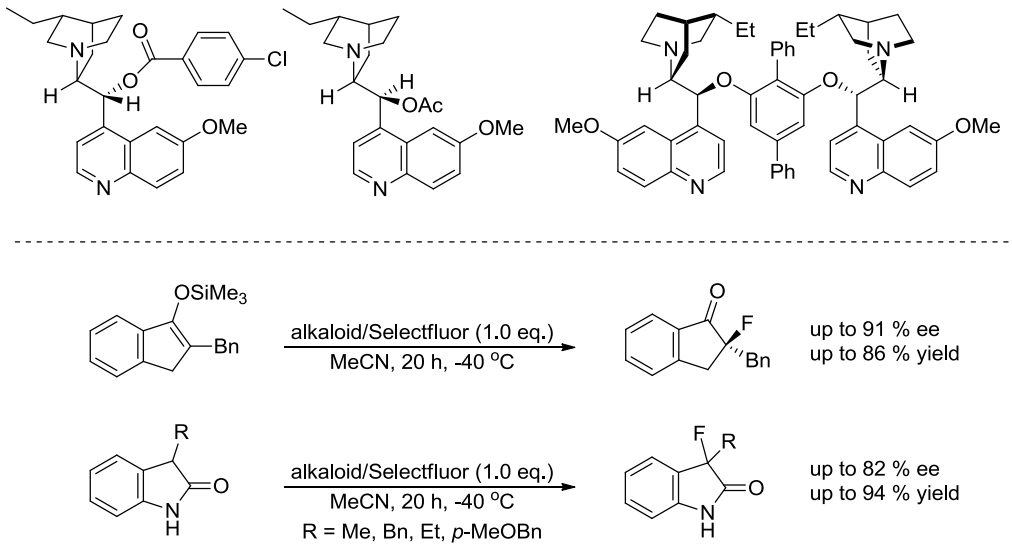
The selectivity and reactivity of these reagents was investigated using substrates such as enolates and silyl enol ethers. Pleasingly, good to excellent enantioselectivities were achieved, accompanied by excellent yields.



Scheme 8 – Fluorination of trimethylsilyl enol ether derivatives

4.2.2.2 Shibata's method

The clear limitation to Cahard's method is the requirement for isolation of the reagents. Whilst this is possible using the reported procedure, it detracts from the attractiveness of this approach. Shibata's method[10] instead proposed the generation of the fluorinated reagents *in situ* to avoid the need for isolation. Once fluorine transfer from Selectfluor is complete, typically less than an hour, the substrate is added directly to the reaction mixture. Since fluorine transfer is observed to be complete and irreversible, there is no problem of a racemic background reaction, with 1-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate acting as a passive species. A selection of alkaloids employed by Shibata is detailed below, along with the substrate classes that were investigated. As well as silyl enol ethers, other substrates included β-keto esters, β-cyano esters and oxindoles. As is commonly observed, the reagents were substrate dependant, with the substitution on the substrates being crucial to achieving the excellent enantioselectivities.

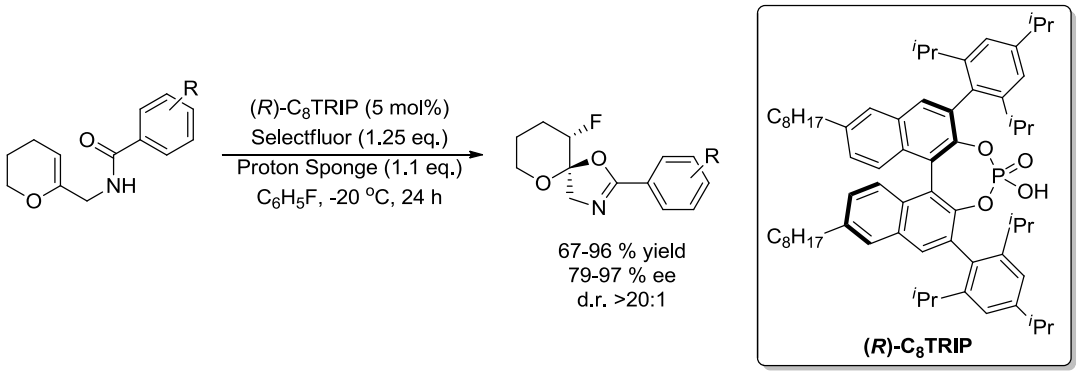


Scheme 9 – Asymmetric fluorination using *in situ* prepared reagents

4.2.2.3 Toste's method

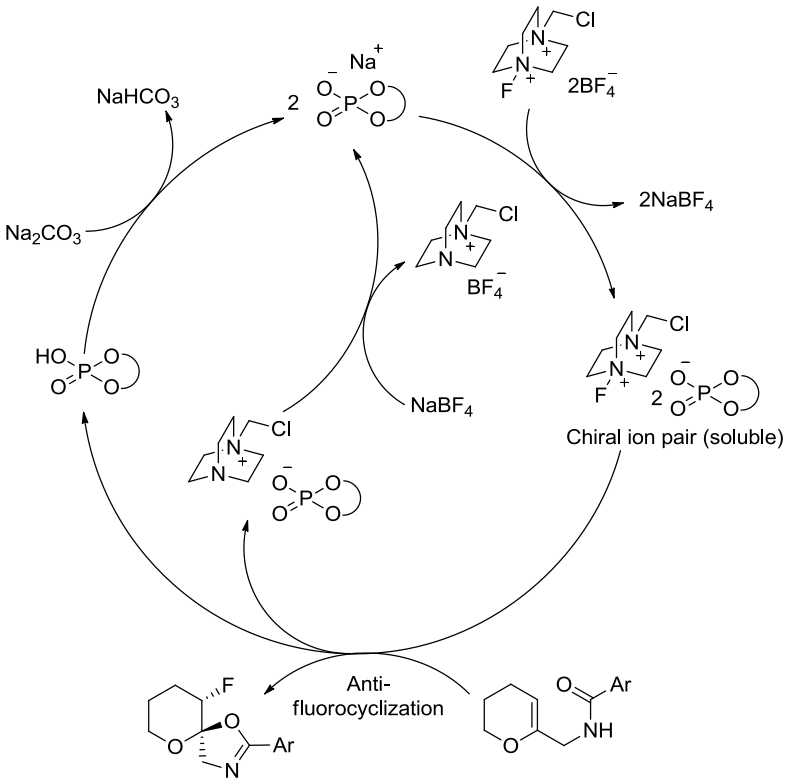
A report in 2011 by Toste et al. described the asymmetric fluorocyclisation of dihydropyrans and dihydronaphthalenes using a pendent amide nucleophile with a chiral anion solid-solution phase transfer catalyst derived from (*R*)-BINOL (Scheme 10).[11] This approach is fundamentally different to the cinchona alkaloid approach for two reasons. Firstly, instead of using Selectfluor merely as a fluorine source and transferring it to a chiral "F^+ acceptor" the Toste method modifies Selectfluor itself to achieve a chiral fluorinating reagent. The technique involves performing an *in situ* anion exchange to replace the tetrafluoroborate anions with chiral phosphate salts, which places the fluorine in a chiral environment. The reaction is also run in a non-polar solvent so that Selectfluor bis(tetrafluoroborate) is not soluble, and therefore unreactive, but Selectfluor bis(phosphate) is soluble. Secondly, because the phase-transfer approach ensures the racemic background reaction is suppressed, the chiral phosphate may be used in a catalytic amount. This offers the potential for a significant improvement over other reagent driven processes since normally a stoichiometric amount of chiral reagent is required. When the chiral reagent is either not

commercially available or prohibitively expensive, this is a considerable limitation.



Scheme 10 - Asymmetric fluorination with anionic phase-transfer catalyst

The work showed that Selectfluor could be used in a chiral phase-transfer system to successfully perform asymmetric fluorinations. The proposed mechanism in Scheme 7 above explains how deprotonated chiral phosphate anions first replace the tetrafluoroborate counterions of Selectfluor to form a new chiral Selectfluor species, which is soluble in apolar solvents. The resultant solubilised fluorinating reagent can now react with the substrate to furnish the fluorinated product in good yields with excellent enantioselectivity. Upon fluorination a chiral phosphoric acid is liberated which can then replace further tetrafluoroborate anions upon deprotonation and can hence be employed in catalytic quantities. The attraction of this phase-transfer approach is that the racemic uncatalyzed background reaction is totally suppressed as the dicationic Selectfluor will be completely insoluble.



Scheme 11 - Proposed mechanism of anionic phase-transfer asymmetric fluorination

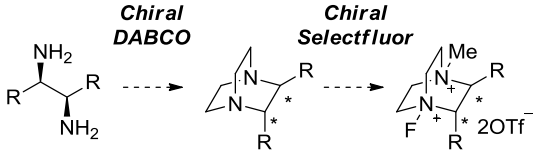
4.2.3 Summary and chapter outline

In summary many chiral fluorinating reagents have been reported based on either a first generation neutral N-F group or a second generation charged $[N\text{-}F]^+$ group. Whilst progress has been made to increase both the selectivity and the range of substrates that these reagents can support there is one significant limitation. Currently, the reagents reported thus far require fairly reactive substrates due to their relatively low reactivity. Even the charged reagents such as cinchona alkaloid based systems are low in reactivity when compared to reagents such as Selectfluor or the more powerful examples of the pyridinium class reagents. Whilst the method of Toste offers an interesting advance by retaining the reactive features of Selectfluor, the phase-transfer approach still requires a H-bond anchoring site on the substrate. This requirement limits the scope of the reaction to those substrates which incorporate a X-H bond of suitable acidity in order to associate with the

chiral phosphate. We were therefore interested to develop chiral fluorinating reagents, which exhibited a similar reactivity profile to Selectfluor but without the need for H-bond anchorage. Such a reagent would be important for the development of asymmetric fluorination reactions on substrates that are less reactive than the typical silyl enol ethers and metal enolates which are used for new reagent calibration.

4.3 Chiral Selectfluor

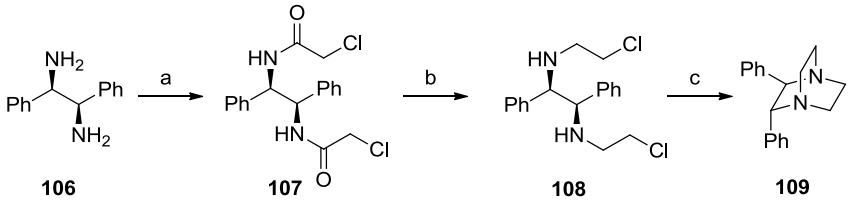
Whilst it is certainly true that a great deal of progress has been made in the field of chiral reagents, a problem that has not been extensively studied is the development of methodology that combines superior reactivity with excellent enantioselectivity. Typically, the requirement for high reactivity is circumvented by the use of reactive substrates such as allyl silanes or β-keto esters but even the chiral anion methodology, which boasts the reactivity of Selectfluor, requires a H-bond binding site on the substrate. We proposed to address this problem by focussing on the cationic component instead of the anion and hence developed a library of chiral fluorinating reagents based on the DABCO core of Selectfluor. After a detailed review of the literature, we realised that reports of the synthesis or application of chiral DABCO cores were very scarce, with only a few notable reports.[12-17] Therefore, our task was to first expand the methodology for the synthesis of chiral DABCOs and then to quaternize and fluorinate to obtain the desired chiral Selectfluor reagents (Scheme 12).



Scheme 12 - General synthetic route to chiral Selectfluor reagents

4.3.1 Synthesis of chiral DABCO

In general, there were two different structural cores that we were interested in accessing. Each structure involved a slightly different synthetic sequence and had its own merits and drawbacks due to number of synthetic steps or the availability of the starting materials. Our initial interest was in a publication by Sharpless and co-workers some twenty years ago on the synthesis of (2R,3R)-diphenyl-1,4-diazabicyclo[2.2.2]octane.[12] After re-optimisation of the original synthetic route we were able to access DABCO **109** in an overall 64 % yield (over 3 steps) according to Scheme 13.



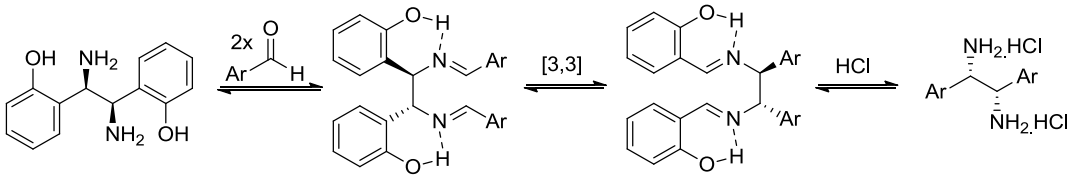
Scheme 13 - General synthetic routes to chiral DABCOs; a) chloroacetyl chloride, Et_3N, DMAP, DCM, 98 % yield; b) BH_3.THF, THF, reflux; c) DMF, reflux, 65 % yield (over 2 steps)

The first step of chloroacylation proceeded very rapidly in DCM in the presence of a catalytic amount of DMAP using an excess of chloroacetyl chloride to provide the diamide intermediate. Whilst the crude product was found to be essentially pure by NMR analysis, we found that purification by either column chromatography or recrystallization to be advantageous to the subsequent reaction steps. Reduction of the diamide was achieved with a borane-THF complex after refluxing in THF overnight. Purification of the resultant diamine was difficult due to its highly polar and non-crystalline nature but we found that destruction of the nitrogen-boron complex using dilute HCl followed by an acid/base extraction was necessary before proceeding to the cyclization step. Whilst an analytically pure sample could not generally be obtained in this way, it was necessary to remove the *n*-butanol formed from ring opening of the THF by borane under the reaction conditions. We suspected that

the butanol was responsible for detrimental effects on the yield of the cyclization, presumably due to formation of ether products upon displacement of chloride. It should be noted that a non-trivial amount of the mono-cyclized and di-cyclized product was formed under the reaction conditions and so rigorous purification is not generally suggested. The final step involved dicyclization to form the bridged DABCO core, which was achieved by refluxing in DMF for 5 hours to form a single diastereomer. Following neutralisation of the dihydrochloride salt with NaOH, DABCO **109** was purified by column chromatography to obtain an analytically pure sample. Conformation of the enantiopurity was made by comparison of the optical rotation with that in the literature.[12]

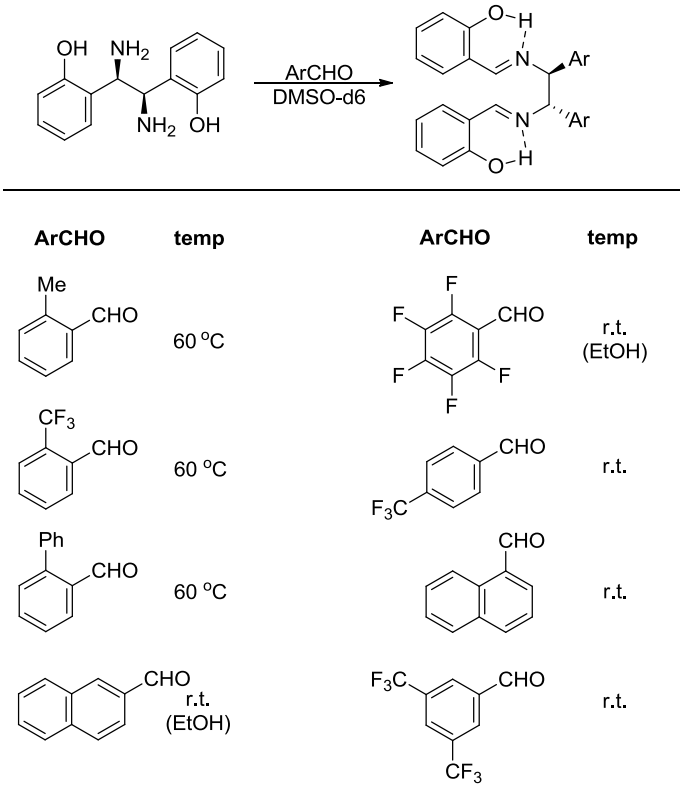
At this stage, we felt we had a robust method for the construction of enantiopure 2,3-diaryl substituted DABCO cores and so our attention turned to the synthesis of the chiral vicinal diamines which we would require for structural modification. Several feasible strategies are reported in the literature to access such structures, with probably the most classical approach involving dihydroxylation of the appropriate olefin, followed by mesylation, substitution by azide and finally reduction. Whilst, this strategy probably offers the best route to a scalable synthesis it suffers from drawbacks such as multiple steps to access the vicinal diamine and extensive optimisation may be necessary to guarantee the required enantiopurity (>99 % ee) on the dihydroxylation step. Therefore, we opted for another approach that involved starting from an enantiopure compound to generate the diamine in a single synthetic step.

According to a procedure by Chin and co-workers the chiral 'mother' diamine (1R,2R)-1,2-bis(2-hydroxyphenyl)ethylenediamine was condensed with various benzaldehydes to form the appropriate diimines.[18] These diimines then underwent a stereospecific diaza-cope rearrangement, via a chair-like transition state, to form the rearranged diimines. Upon treatment with acid, the diimines were hydrolysed to afford the 'daughter' diamines as enantiopure dihydrochloride salts (Scheme 14).



Scheme 14 – Formation of 'daughter' diamines from 'mother' diamine

In general, the diaza-Cope rearrangement was performed in DMSO and, following extraction into ether, the diimine was hydrolysed by stirring in a THF/$HCl_{(aq.)}$ mixture for several hours. However, in a few cases ethanol proved to be a superior solvent for the rearrangement step, and this was assessed by monitoring the progress of the reaction by ^{1}H NMR as described in the original paper by Chin.[18] The extent of the rearrangement, as well as the successful formation of the initial diimine, can be conveniently studied by the nature of the hydroxyl proton. As the reaction proceeds, a broad singlet in the region of 10-11 ppm (proton H-bonded to 'mother' diimine) becomes a sharp singlet in the region of 13-14 ppm (proton H-bonded to 'daughter' diimine. In all cases the reaction was performed using the minimum temperature to effect a rearrangement. Scheme 15 summarises the aldehydes we investigated, together with their preferred solvent and minimum temperature required.



Scheme 15 - General synthetic routes to chiral DABCOs

With the synthesis of the required chiral diamines completed we sought to subject them to the general synthetic route to obtain the relevant chiral DABCOs. We were pleased to discover that the route was indeed general, affording chiral DABCOs **109-115** in low to moderate yields over the four synthetic steps of diamine formation, chloroacylation, reduction and finally cyclization. The library of structures in Figure 3 obtained by this route exemplifies the first of our general strategies towards chiral DABCO synthesis.

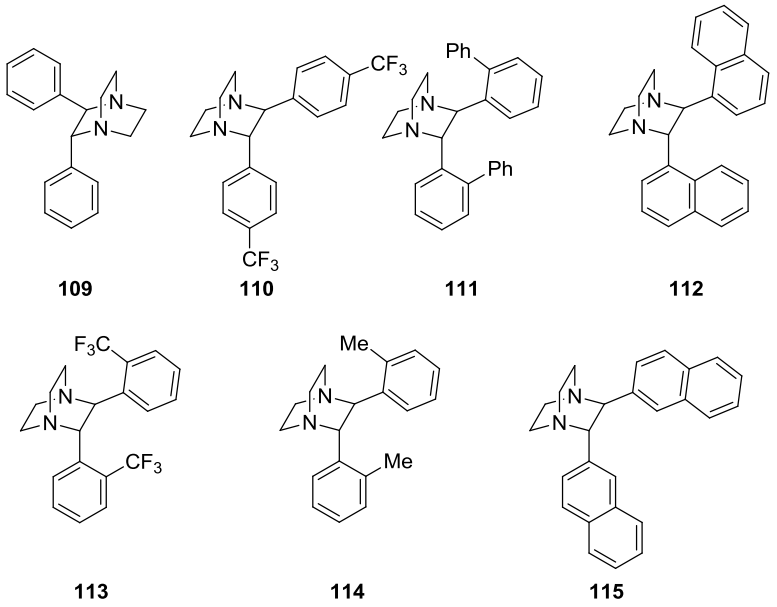
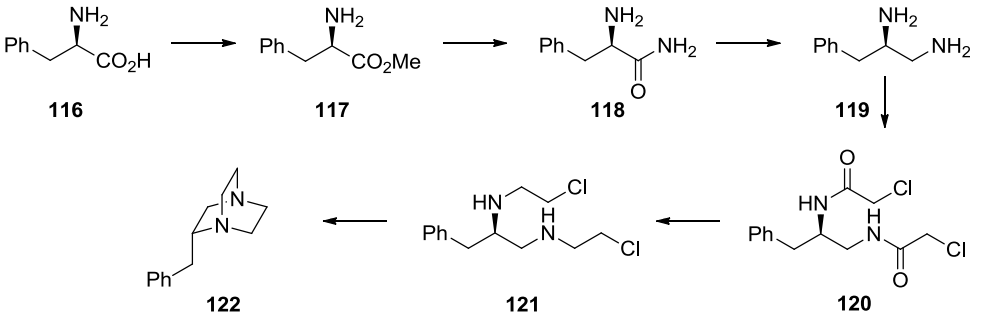


Figure 3 – Library of chiral DABCOs*

Our next interest was in the design of chiral DABCOs that featured mono-substitution to investigate whether the second aryl substituent was involved in determining the enantioselectivity of the reagent. We were again keen to start from a 'chiral pool' compound to negate the need for asymmetric synthesis or chiral resolution of the desired DABCO. For this reason, we elected to start from an amino acid, which after several chemical transformations could be modified to obtain a mono-substituted chiral vicinal diamine. The advantage of this strategy would be that our general procedure could be followed, hopefully without modification. The synthesis of benzyl substituted chiral DABCO **122** starting from phenylalanine is outlined in Scheme 16.

* DABCOs **111**, **113** and **114** were prepared with help from Dr. Oscar Lozano



Scheme 16 - Synthetic route to chiral DABCO **122**

Activation of the carboxylic acid moiety towards amidation was achieved by esterification using thionyl chloride in methanol to obtain the methyl ester hydrochloride salt. Following neutralisation, the free amino ester was treated with aqueous ammonia in toluene and stirred vigorously for 24 hours to affect the amidation. Evaporation of the reaction media afforded analytically pure amide, which was subsequently treated with $LiAlH_4$ in THF to achieve reduction to form the vicinal diamine. The crude diamine was purified by vacuum distillation before chloroacylation in the usual manner. Reduction of the diamide using borane resulted in a significant amount of the mono-cyclized intermediate, presumably due to the removal of one of the substituents over the disubstituted vicinal diamines in the first approach. Acid/base purification followed by cyclization in refluxing DMF afforded the desired mono-substituted chiral DABCO in a moderate yield over 6 steps. We further demonstrated the generality of this procedure by synthesising the mono-phenyl substituted DABCO **123** and the more elaborate DABCO **124** bearing a second stereocentre. Inclusion of an extra stereogenic centre would be of considerable interest since this structure more closely resembles that of the cinchona family of alkaloids.

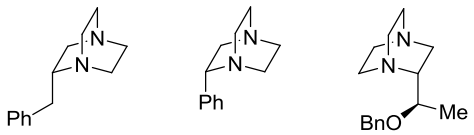


Figure 4 – Library of monosubstituted chiral DABCOs[†]

To summarize, we have developed optimised routes to access a wide variety of enantiopure substituted DABCOs. Using the two complementary strategies we are able to synthesise DABCOs featuring mono-substitution or di-substitution at the 2,3-positions. Our choice of starting material in both routes allows for facile structure modification since precursors are generally comercially available or accessible in a single synthetic step.

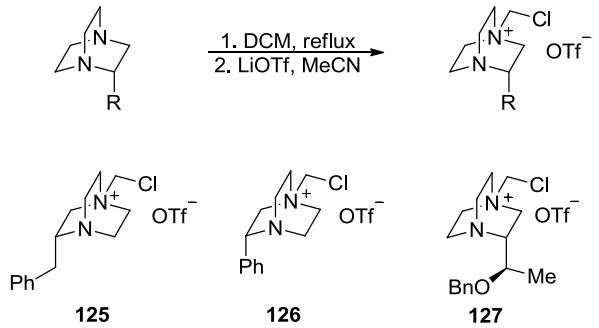
4.3.2 Quaternization of Chiral DABCOs

To form a Selectfluor-type reagent one of the nitrogen atoms on the DABCO ring must first be quaternized with an alkyl group. This is for two main reasons, the first of which concerns the stability of an *N*-fluoro-DABCO salt. Banks' original publications on the synthesis of Selectfluor-type reagents concluded that without quaternization, the resultant fluorinated DABCO cores were highly unstable except at low temperatures.[19] Consequently, they would be of no use as a synthetic reagent and so *N*-alkylation was employed to make the fluorinated salt bench stable. Advantageously, this requirement for alkylation provides a handle with which to tune the reactivity of the fluorinating reagent. Since the electronic nature of one of the nitrogen atoms in a DABCO ring has a powerful influence on the other, it is possible to modify the reactivity of the N-F^+ bond by altering the electronic nature of the quaternizing group. Use of a relatively electron releasing methyl group decreases the

[†] DABCO **124** was prepared by Dr. Erika Luethi

reactivity of the F^+ reagent, whereas use of a strongly electron withdrawing group such as the 2,2,2-trifluoroethyl group greatly increases its reactivity. The most commonly commercially available DABCO based reagent, Selectfluor, has a chloromethyl group, which imparts reactivity somewhere between the two.

To most closely resemble the reactivity profile of Selectfluor itself, we first explored methodology for the chloromethylation of chiral DABCO derivatives. Using the original conditions of Banks,[19] a chloromethyl group can be installed by either standing a solution of DABCO in dichloromethane over a few days or by refluxing for a few hours. The hence formed chloride salt then precipitates out of solution and can be collected by filtration. A convenient property of the chloromethylated DABCO core is that the quaternized nitrogen atom prohibits further alkylation of the other nitrogen atom. In the first instance, we took the mono-substituted DABCO cores that were prepared by the amino acid route and subjected them refluxing DCM to obtain the chloride salt. Since a chloride ion is incompatible with electrophilic fluorinating reagents, we needed to perform an anion exchange to replace chloride with an inert counterion. This anion exchange can be accomplished by stirring a suspension of the chloride salt in acetonitrile with a stoichiometric amount of lithium (or sodium or silver) triflate or tetrafluoroborate. The pure chloromethylated chiral mono-substituted DABCOs were afforded following filtration of the lithium chloride, removal of the solvent and recrystallization. NMR analysis confirmed only a single isomer, indicating selective chloromethylation to only one of the nitrogen atoms. Our prediction that this was the nitrogen that did not feature α-substitution was confirmed by nOe experiments, which showed no interaction between the chloromethyl protons and the proton at the site of aryl substitution. Further confirmation was from the absence of an interaction with the aromatic protons and a positive interaction with the protons that were α- to the site of substitution.



Scheme 17 – Quaternization of mono-substituted DABCOs

However, when we attempted to translate this methodology to the di-substituted DABCO cores we were surprised to observe a complete lack of reactivity. It seemed the perfect selectivity in the mono-substituted series was due to the totally inert nature of the α-substituted nitrogen. Even prolonged reaction times and elevated temperatures using a pressure tube did not lead to any detectable chloromethylation and so we changed the alkylating group to a methyl, rather than a chloromethyl group. We envisioned that this could be achieved using methyl trifluoromethane sulfonate (MeOTf), which would have the added benefit of negating the need for an anion exchange, due to the inert nature of the leaving group towards electrophilic fluorine.

The methylation was performed at low temperature to avoid dimethylation. Initially we had considered using ether as solvent, speculating that this would cause the resultant cationic product to precipitate out of solution, however we encountered solubility problems at low temperature. Instead, we chose to use DCM as this solvent displayed good solubility of the DABCO even at low temperature. Since the methylated products were found to have partial solubility in DCM, the crude reaction residue was first evaporated and then suspended in ether to effect the precipitation of the product. The resultant solid was washed with ether to remove any unreacted DABCO and then dried under vacuum. Application of this method for *N*-alkylation provided a library of methylated chiral DABCO cores which, together with

chloromethylated compounds **125-127**, would serve as the precursors to chiral Selectfluor upon fluorination.

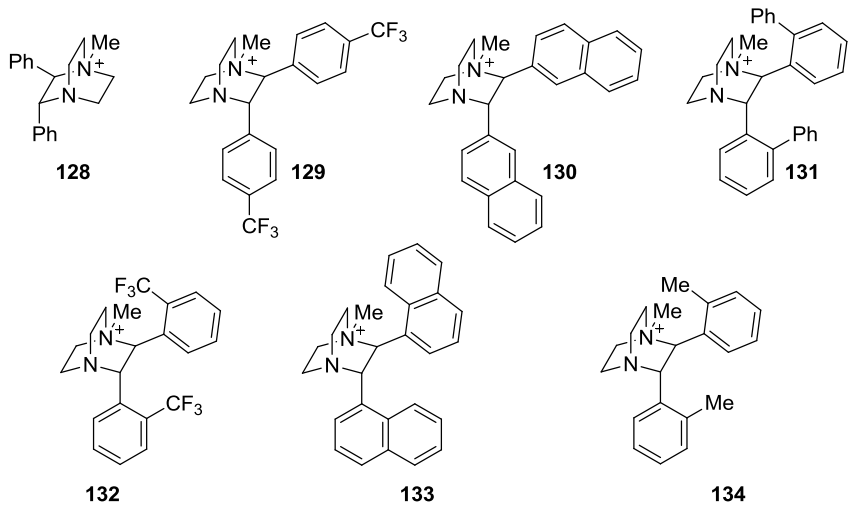


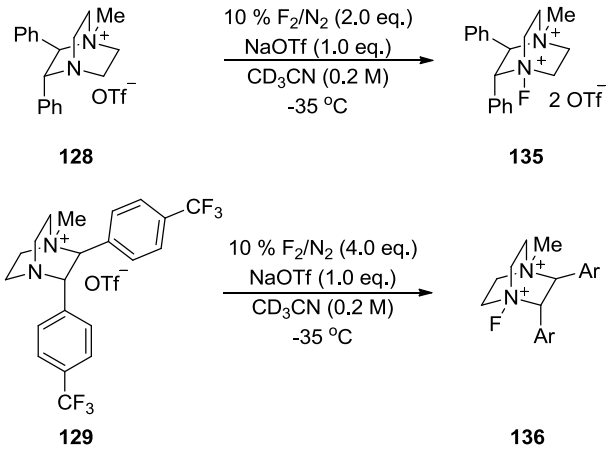
Figure 5 – Library of quaternized chiral DABCOs; triflate counterions omitted for clarity

4.3.3 Fluorination of quaternized chiral DABCOs

Fluorination of the quaternized precursors was initially performed using molecular fluorine, as it is for the commercial synthesis of Selectfluor.[‡] Unlike Selectfluor, however, the chiral DABCOs offered an extra challenge since the aromatic rings are prone to fluorination. Optimisation work was performed on the quaternized 2,3-diphenyl DABCO **128** using a diluted mixture of fluorine in nitrogen (10 % *v/v*) in acetonitrile as solvent. The temperature was kept to -35 °C, which is the minimum temperature that acetonitrile will permit due to its melting point, so as to limit unwanted fluorination of the aryl rings. Initial studies showed that concentration played an important factor and 2.0 equivalents of fluorine being found to be optimal for complete conversion. A stoichiometric amount of sodium triflate was included to act as the second counterion and to remove the equivalent of fluoride formed

[‡] *Work performed by J. Ilupeju*

upon electrophilic fluorination of the quaternized DABCO. After recrystallization from methanol/ether the novel fluorinated reagent was isolated in a 97 % yield. ^{19}F NMR showed the N-F^+ to have a chemical shift of +35.9 ppm, which is comparable to other electrophilic fluorinating reagents (cf. Selectfluor has a chemical shift of +48.1 ppm). As is often the case with fluorination using elemental fluorine, we found it necessary to optimise for each different substrate to determine the exact number of equivalents of fluorine that are necessary to achieve full conversion, without observing undesired side reactions. When this methodology was extended to the quaternized 2,3-bis(4-trifluoromethyl)phenyl DABCO **130**, it was found that 2.0 equivalents were insufficient and ultimately 4.0 equivalents were required.

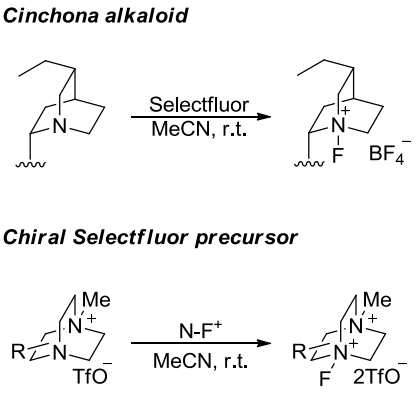


Scheme 18 – Fluorination of quaternized DABCOs using molecular fluorine

Whilst we had a good method to achieve fluorination to access the chiral reagents we were particularly interested in developing methodology that was more widely accessible. The practical implications of handling F_2 gas are highly prohibitive to its general use in organofluorine chemistry, with only specialised fluorine facilities equipped to handle it. We were therefore interested in devising a method for preparation of the chiral reagents that

did not require elemental fluorine, but rather something which did not require special handling.

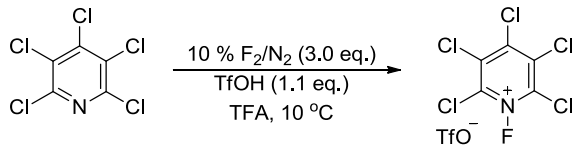
The idea that caught our attention was the method by which cinchona alkaloids are generally used for asymmetric fluorination. The attractiveness of this methodology is that a commercial alkaloid can be pre-mixed with a commercial achiral N-F reagent (such as NFSI or Selectfluor) which will undergo transfer of the fluorine from the more reactive N-F reagent to the less reactive cinchona species. The resultant chiral fluorinating reagent can be then used, without fear of a background reaction since the reactivity difference prohibits an equilibrium being formed in which there is a detectable amount of the achiral reagent. We reasoned that if we substitute the alkaloid with our quaternized chiral DABCO and substituted the achiral fluorinating reagent for something much more reactive than Selectfluor then an *in situ* formation of the chiral reagent could be achieved.



Scheme 19 – Proposed method for *in situ* fluorination of quaternized DABCO

It is crucial to use an achiral reagent that is vastly superior in reactivity to avoid incomplete fluorine transfer. We elected to use the very powerful *N*-fluoro-pentachloropyridinium triflate rather than the similarly reactive DesMarteau reagent due to commercial availability

and ease of handling. Apart from being somewhat moisture sensitive the reagent requires no special precautions for its handling and exhibits great reactivity. Whilst it is commercially available, it could be synthesised from the corresponding pentachloropyridine using elemental fluorine according to Scheme 20. Due to the very low basicity of pentachloropyridine (pKa = -6.02)[20] very forcing conditions were required to achieve fluorination. Trifluoroacetic acid was found to be the most effective solvent and triflic acid was required as an additive. Following the addition of 3.0 equivalents of fluorine, ether was added to effect trituation of the product. The electrophilic reagent was isolated in a 92 % yield and displayed a characteristic peak in the ^{19}F NMR for N-F^+ peak at +46.5 ppm, which was consistent with the literature report.



137 138

Scheme 20 – Preparation of *N*-fluoro-pentachloropyridinium triflate

We investigated the feasibility of this reaction by examining the reaction of *N*-fluoropentachloropyridinium triflate with the mono-substituted quaternized DABCO **126**. Figure 6 shows the effective transfer of fluorine from the pyridinium reagent **138** to the DABCO salt. When 0.5 eq. of the salt was used a roughly 1:1 ratio of F^+ peaks were observed in the ^{19}F NMR, thus confirming complete transfer. When a full stoichiometric equivalent was introduced complete dissapearence of the pyridinium reagent was observed, which was accompanied by formation of chiral Selectfluor **139**.

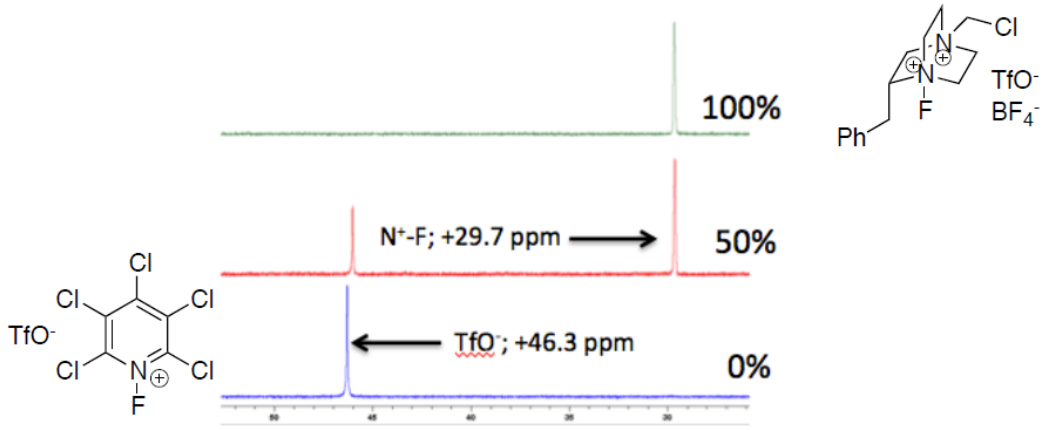
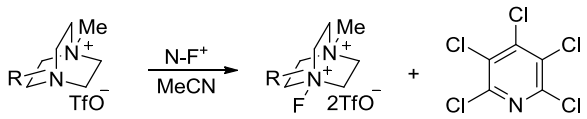


Figure 6 – Fluorine transfer to quaternized DABCO **125**

With the methodology in place, we proceeded to investigate the fluorination of our library of quaternized DABCO salts. We found that by pre-mixing the chiral Selectfluor precursors with the powerful pyridinium reagent in acetonitrile we could use the hence formed chiral fluorinating reagent without isolation. Much like in the alkaloid approach, the chiral reagent can be made *in situ* and then the substrate added without the need to isolate the intermediate fluorinating reagent. This conclusion adds great value to the methodology as it is operationally very simple to perform. Critically, we found no difference between using the isolated reagent and the *in situ* prepared reagent, meaning the extremely weak Lewis base pentachloropyridine does not have an effect on the reaction. Alternatively, if isolation of the reagent is desired then the pyridine liberated upon transfer of fluorine can be simply removed due to the vast differences in solubility between all the reaction species. Following fluorine transfer, the acetonitrile is removed and the crude residue is suspended in ether. Since the chiral Selectfluor product is cationic and the resultant pyridine is not, the latter can be removed by washing the precipitated solid with ether. Using this procedure together with direct fluorination using F_2 we were able synthesise a library of novel fluorinating reagents as illustrated in the Scheme 21.



Scheme 21 – Fluorine transfer

The library of fluorinated chiral Selectfluors obtained by fluorine transfer is illustrated in Figure 7. The majority were not isolated but characterized and used directly for *in situ* experiments.

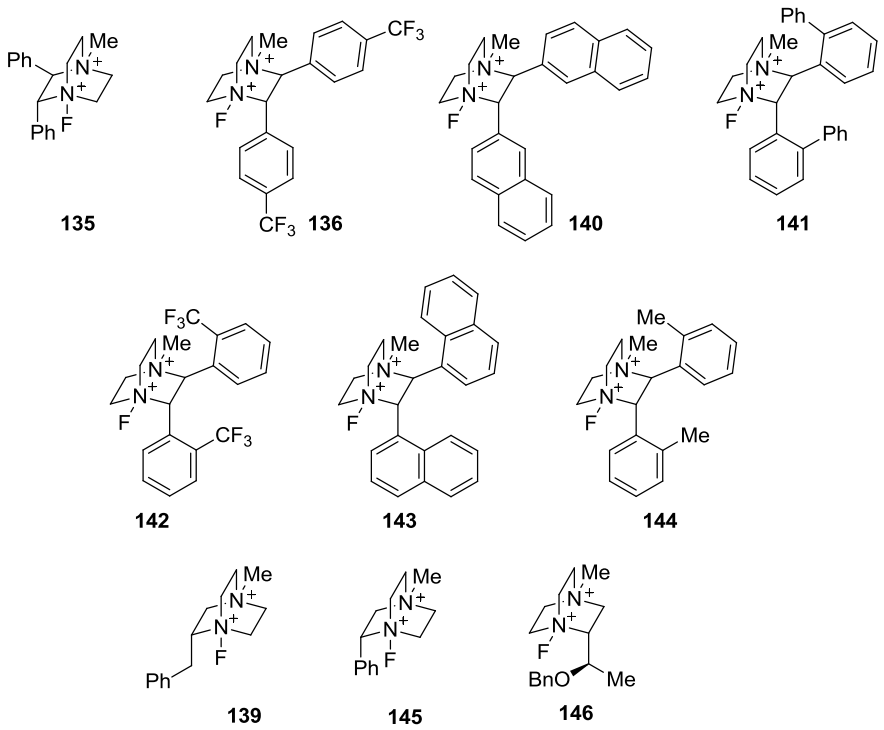
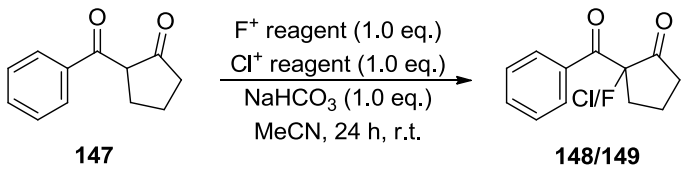


Figure 7 – Library of chiral Selectfluors

4.3.4 Reactivity of chiral Selectfluors

To investigate the reactivity of the new reagents we considered a competitative halogenation reaction to measure the relative reactivity of a series of electrophilic fluorinating reagents. This approach was inspired by a report by Togni and co-workers who investigated the relative reactivity of a series of commercial fluorinating reagents by the competative halogentaion of a β-keto ester.[21] In their work they utilized a chiral Ti Lewis acid catalyst to increase the reactivity of the substrate towards halogenation and also to measure the level of asymmetric induction. However, since we were not interested in the enantioselectivity, but merely the relative reactivity, we decided to explore a system that did not employ a chiral catalyst. Indeed, we elected to use a 1,3-diketone substrate which was highly enolizable (1:2.2 Keto:enol form in CD_3CN) and did not require any Lewis acid activation.



Scheme 22 – Competitive halogenation of 1,3-diketone **147**

Assuming that the rate of fluorination is independent of the rate of chlorination and *vice versa* the relative rates of fluorination can be determined by measuring the ratio of the fluorinated products to chlorinated products. Whilst the previous report by Togni calculated the ratio of the halogenated compounds using HPLC, we decided that it would be more convenient to use ^{1}H NMR and compare the integrals for a common proton signal in the fluorinated and chlorinated compound. As a control reaction we confirmed that both

Selectfluor and NCS independently reacted to give 100 % conversion after 24 hours. We included several commercial achiral fluorinating reagents as a reference point as well as a fluorinated cinchona alkaloid for comparison. Details on performing the competition reaction and how results are interpreted are provided in Chapter 6.

Entry	Reagent	F^+/Cl^+	k_{rel}	**X**[a]	
1	Selectfluor	74/26	2.90	**10.4**	
2	*N*-fluoro-pentachloro-pyridinium triflate	71/29	2.45	**8.8**	
3	*N*-fluoro-2,6-dichloro-pyridinium triflate	63/37	1.70	**6.1**	
4	Bis-CF_3 chiral Selectfluor **136**	59/41	1.44	**5.1**	Increasing reactivity →
5	Diphenyl chiral Selectfluor **135**	58/42	1.38	**4.9**	
6	Selectfluor II	49/51	0.96	**3.4**	
7	F-*p*ClBzDHQN-BF_4	35/65	0.54	**1.9**	
8	NFSI	22/78	0.28	**1.0**	
9	*N*-fluoro-pyridinium pyridine heptafluoro diborate	10/90	0.11	**0.4**	
10	*N*-fluoro-2,4,6-trimethylpyridinium triflate	<1/99	<0.01	**<0.1**	

F-pClBzDHQN-BF_4 = *N*-fluoro-*p*-chlorobenzoyl-dihydroquininium tetrafluoroborate; NFSI = *N*-fluorobenzenesulfonimide [a] Reactivity relative to NFSI = 1

The reactivity study of a spectrum of electrophilic fluorinating reagents revealed that Selectfluor was the most reactive, with the electron rich *N*-fluoro-2,4,6-trimethylpyridinium triflate reagent being the least reactive. Of some surprise was that *N*-fluoro-pentachloropyridinium triflate was not identified as the most reactive reagent. However, in light of the instability of this reagent in acetonitrile due to reaction with residual moisture we propose that this is due to a full stoichiometric equivalent of reagent not being available to react. In line with the findings of Togni *et al.* on their system, our results show that *N*-fluoro-2,6-dichloropyridinium triflate is somewhat less reactive than Selectfluor, although it should again be noted this pyridinium based reagent is susceptible to hydrolysis by residual

moisture but to a lesser degree than the pentachloro analogue. Pleasingly, we found that our chiral Selectfluors displayed high reactivity being much more reactive than the NFSI to which we referenced our results. Whilst both chiral Selectfluor reagents gave very similar reactivity results, the bis-CF_3 reagent was found to be slightly more reactive, which is in agreement with the electron-withdrawing properties of the trifluoromethyl group slightly enhancing the reactivity of the N-F^+ bond. The significant drop in reactivity from the unsubstituted Selectfluor reagent can be explained by the extra steric encumberment, which retards the rate of fluorination. This is good evidence that the steric, electronic and solvation properties of a reagent are all important in determining its observed reactivity. As a comparison, we studied a fluorinated cinchona alkaloid to provide evidence for the greater reactivity of our system over alkaloid based systems. We found that the fluorinated dihydro-quinine reagent was somwhat less reactive, which is in agreement with our recent publication on fluorocyclizations of less reactive substrates (Chapter 5). NFSI is also a commonly used achiral fluorinating reagent which is considered to be much less reactive than the cationic reagents as ratified by our findings. Finally, the stabilised pyridinium reagents were found to be very unreactive, with the fluorination reaction using *N*-fluoro-2,4,6-trimethylpyridinium triflate being barely detected.

The conclusions which can be drawn from this comparative study are broadly in line with other reactivity studies in the literature which mostly rely upon electrochemical methods (see Chapter 1). Several attempts to order electrophilic fluorinating reagents by direct measurement of the peak reduction potentials have been reported, however due to the nature of the experiments the absolute values can deviate significantly from report to report. It is for this reason that we decided a reactivity study based on observed reactivities and not indirect measurements was more generally helpful from an application perspective.

We envisaged, however, that an interesting qualitative interpretation of the chiral selectfluor's reactivities could been gained from analysis of the ^{19}F chemical shifts of the reagents in their respective ^{19}F NMR spectra. According to a similar report on a series of pyridinium-based reagents by Umemoto and co-workers,[22] the relative fluorinating power of a reagent should correlate with how shielded the fluorine nucleus is for a group of strucurally related reagents (Chapter 1). Logically, if a fluorine nucleus is deshielded (a more postive ^{19}F chemical shift) then it should be more reactive, and indeed this is what they found to be the case. To examine whether this method could be extended to our new reagents, we took a range of fluorinated chiral selectfluor compounds and examined their chemical shift values. All spectra were referenced to give the triflate counterion the same chemical shift for accurate comparisons.

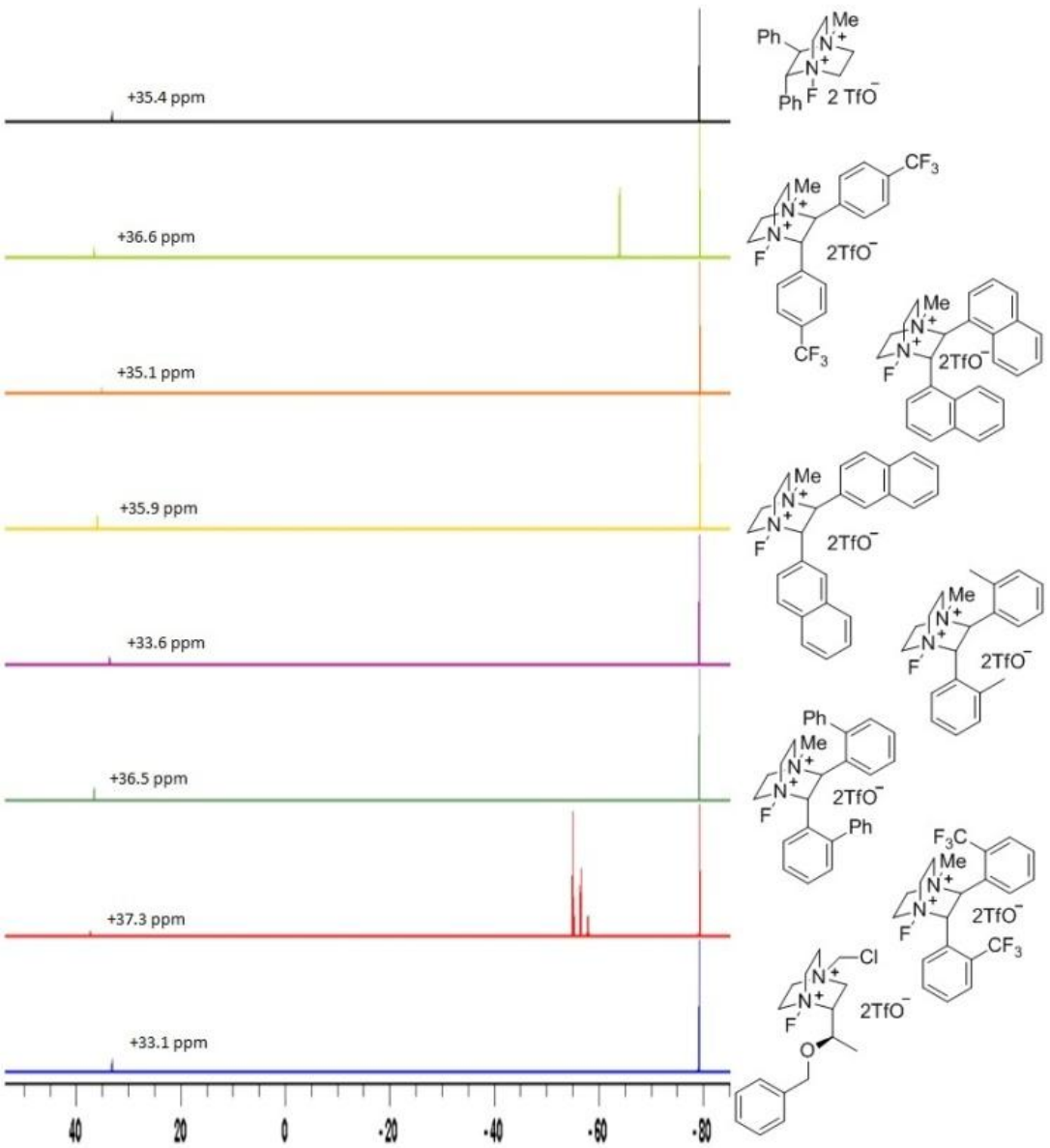


Figure 8 – ^{19}F chemical shifts of chiral selectfluors

From Figure 6, it can be observed that the most electron deficient selectfluor reagents, i.e. those with CF_3 substituted arene rings have the most deshielded (most postitive) chemical shifts and the more electron rich selectfluors, such as **144** and **146** have the least deshielded (least positive). In fact, even subtle differences are observed, with the 2-CF_3 and 4-CF_3 reagents **142** and **136** showing the ortho derivative to be the more positive, in line with it having a greater inductive effect than at the para position. This data is consistent with the

comparitative study which predicted the CF_3 substituted selectfluor to be slightly more reactive than non-substituted analogue. A note of caution, which was emphasized by Umemoto, is that only structurally very similar compounds can be analyzed in this way. For example, Selectfluor II which bears a quaternizing methyl group instead of the chloromethyl group which is used on the more common Selectfluor, has a chemical shift of +47.0 ppm when referenced to the same value for the triflate counterion. Intuitively, it should be less reactive than the chiral analogues since it does not have the extra electron withdrawing aryl substituents but its considerably higher value is likely to be due to the different in structure. The presence of a substituent at the alpha- position presumably has a great effect on the chemical environment of the fluorine nucleus. This should not be so unexpected since Umemoto found that pyridinium reagents bearing ortho substituents did not fit the general trend of those which did not feature ortho groups.

4.3.5 X-ray crystallographic analysis of chiral Selectfluor

To gain insight into the structural conformation of the reagents, at least in the solid state, we obtained an x-ray crystallographic structure of chiral Selectfluor **135**. We were interested to know if any information could be gained from the structures to help explain the stereochemical outcome of reactions involving the chiral reagents.

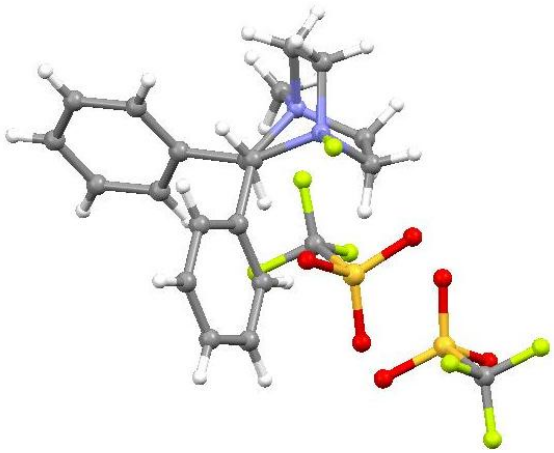


Figure 9 - X-ray crystallographic structure of Selectfluor analogue **135**

4.4 Measuring the purity of fluorinating reagents

Despite the ubiquitous use of these electrophilic reagents in organofluorine chemistry, to the best of our knowledge, there is no general method for the fast and precise determination of their fluorine content. Only one brief mention was made by Eric Banks but an operational procedure was not provided.[23] Typically, experiments are conducted assuming that the reagents are pure or have a level of purity as advertised for commercially available material. The amount of fluorinated reagent with respect to the non-fluorinated parent precursor can be determined relying on NMR spectroscopy but this method may not track other impurities that may affect reactivity. For example, triflate and tetrafluoroborate salts would not be visible by ^{1}H NMR spectroscopy and the presence of such contaminant could underestimate calculated yields for reactions using stoichiometric amounts of "F^{+}" reagents. This report discloses two complementary methods for the simple and rapid determination of the exact "F^{+}" content of various classes of electrophilic fluorinating N-F type reagents.

4.4.1 Titration Methods

By their very nature, all electrophilic fluorinating reagents are oxidants, their oxidising power varying according to their structural features. Several quantitative studies have been performed to find the precise reduction potential of electrophilic fluorinating reagents, which can be used to find an order of relative reactivity.[24-27] The basis of this method of electrochemical ordering of reagents is that the most oxidising reagent should display the greatest reactivity.

Since all N-F type reagents are oxidising to some degree it should therefore be possible to use a suitable reductant to assess the "F^+" content of a reagent by means of a titration technique. We surmised that sodium thiosulfate ($S_4O_6^{2-}/S_2O_3^{2-}$ $E°$ = +0.08 V) would be an ideal candidate for titration as this standard inexpensive laboratory reagent is a bench stable reductant which is easy to handle and prepare in bulk stock solutions. The overall reaction would therefore involve the following redox reaction (Equation 1).

$$2Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2Na^+ + 2e^-$$

$$R_3NF^+X^- + 2Na^+ + 2e^- \rightarrow R_3N + NaF + NaX$$

Overall:

$$2Na_2S_2O_3 + R_3NF^+X^- \rightarrow Na_2S_4O_6 + R_3N + NaF + NaX$$

Equation 1 – Redox reaction for titration of N-F reagents with sodium thiosulfate

An indicator is required to find the end-point of the titration. We opted for iodometric titration, a redox based titration where the appearance or disappearance of elementary iodine indicates the end point. An accurately weighed small amount of N-F reagent is added to an excess of potassium iodide, forming iodine upon oxidation, which then forms the

stable triiodide ion (I_3^-/I^- $E°$ = +0.5355 V). The triiodide ion solution is titrated against standard thiosulfate solution of known concentration to give iodide, starch being used as an indicator to accurately assess the dissapearence of iodine when in low concentration. Equation 2 confirms the favourable reduction of triiodide to iodide by thiosulfate, validating it as a sensible choice of reductant. By measuring the amount of thiosulfate required to reduce the iodine back to iodide, one can calculate the starting "F^+" concentration using Equation 2. Finally, comparing this value to the mass of N-F reagent added at the beginning, the "F^+" purity can be assigned as of a *w/w* percentage.[28]

$$S_4O_6^{2-} + 2\ e^- \rightleftharpoons 2\ S_2O_3^{2-}\ (E^o = +\ 0.08\ V)$$

$$I_3^- + 2\ e^- \rightleftharpoons 3\ I^-\ (E^o = +\ 0.5355\ V)$$

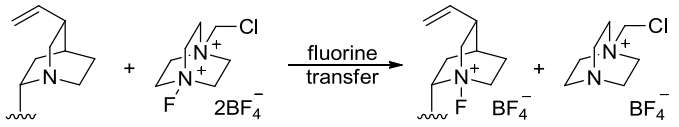
$$I_3^- + 2\ S_2O_3^{2-} \rightarrow S_4O_6^{2-} + 3\ I^-\ (E^o = +\ 0.4555\ V)$$

Equation 2 – Overall redox reaction

4.4.2 NMR Methods

An obvious and very attractive method for determining F^+ purity would be by NMR using an internal reference to obtain a so-called NMR purity. By using a stoichiometric amount of reference, the comparison between integrals of the reference and fluorinating reagent will indicate the F^+ purity. So long as small error associated with ^1H NMR integration is appreciated, this can be a very effective method for the rapid determination of the purity of a reagent. However, for some reagents it may be difficult to determine the purity in this way due to either complex NMR spectra or even the complete absence of any protons, such as in per-halogenated N-F reagents. For such reagents a different approach should be used, to allow unambiguous determination of purity.

Another property of electrophilic fluorinating reagents is their ability to transfer "F^+" to a more stabilised Lewis base in order to form a less reactive fluorinating reagent. This concept was first advanced by Banks two decades ago and has since been exploited extensively in the field of asymmetric fluorination to provide cinchona alkaloid based chiral reagents by means of a "F^+" transfer from an achiral source.[8-10] For example, Selectfluor™ transfers its fluorine essentially irreversibly to the alkaloid since the quaternised DABCO is a much weaker Lewis base than the quinuclidine core as described below.



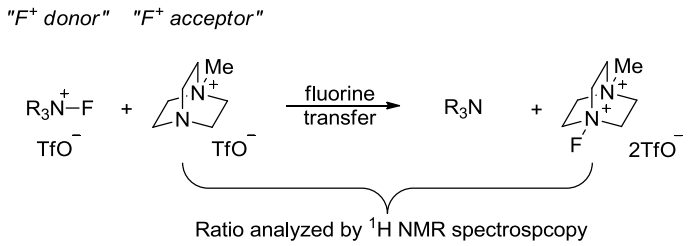
Scheme 23 – Fluorine transfer to alkaloid

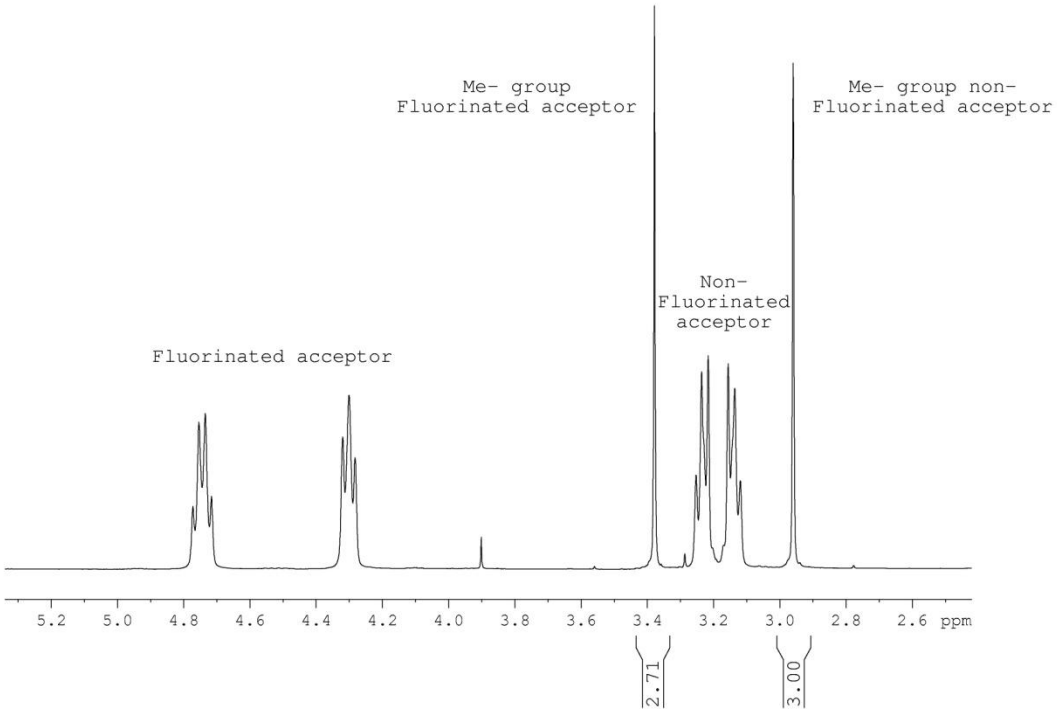
We envisioned that this technique could be utilised to assess the "F^+" content and identity by having a known quantity of "F^+" acceptor of correct reactivity. To accurately assess the identity of "F^+" present in the fluorinating reagent it is necessary to select an "F^+" acceptor which is low enough in reactivity to ensure essentially irreversible transfer but high enough in reactivity to preclude transfer from impurities of lower reactivity. Two examples are presented below.

It could be imagined that there are two potential ways that this could be achieved. Either an excess of "F^+" acceptor could be used and the purity of the "F^+" reagent assessed by measuring the ratio of the fluorinated to non-fluorinated acceptor by ^{1}H NMR or an excess of "F^+" reagent and measuring the ratio of the two N-F^+ peaks by ^{19}F NMR. It is often attractive to obtain ratios by ^{19}F NMR since {^{1}H} decoupled spectra offer uncomplicated analysis but this approach has its limitations. Firstly, it should always be appreciated that

there is an inherent error associated with ^{19}F NMR integration and so ratios calculated in this way will always carry an error of some magnitude far greater than that experienced with ^{1}H NMR. The second issue is with the stability of highly reactive "F^+" reagents in solution over time. For example, *N*-fluoropentachloropyridinium triflate was studied over a period of a few days and found to slowly decompose (mostly to the pyridone), casting doubt on this method for "F^+" purity determination.

In view of these considerations we decided to use the more accurate ^{1}H NMR strategy. As an "F^+" acceptor we chose the Selectfluor™ like methylated DABCO core, as this would be non-fluorinated in the presence of the pyridone, irreversibly fluorinated by the reagent of interest and also because its simple structure provides uncomplicated NMR spectra. An example of a typical spectrum obtained in this way using 2.0 equivalents of F^+ acceptor is outlined below.[28] The methyl protons of the two species are shifted by a large amount relative to each other due to mono- and di- quaternization. The methylene protons of the DABCO core are also shifted by a large extent upon fluorination. This ensures that extraction of the data is simple due to no overlap of the peaks.





$$F^{+}purity = \frac{2X}{X+Y} \times 100\ \% = \frac{2(2.71)}{(2.71)+(3.00)} \times 100\ \% = 95\ \%$$

Where X = integral of fluorinated compound, Y = integral of non-fluorinated compound

Figure 2 – Example of NMR titration using 2.0 eq. of F^{+} acceptor

4.4.3 Examples of electrophilic fluorinating reagent classes

To illustrate our procedure for F^{+} determination we examined the three most common classes of electrophilic fluorinating reagents. Depending on the reagent class we propose the best method for purity assessment as well as provide examples from sampling of different batches of reagents (Table 1), showing the need to purify where necessary.[28]

4.4.3.1 Selectfluor type reagents

Electrophilic fluorinating reagents based on the DABCO core, of which Selectfluor™ is the most common, are widely used in modern fluorine chemistry due to their high reactivity, ease of handling, low hygroscopy and long shelf life. Reagents such as Selectfluor™ are typically purchased as a percentage activity of "F^+" yet, whilst it would be considered standard practice to titrate other common laboratory chemicals such as alkyl lithium or Grignard reagents, this practice has yet to be considered with electrophilic fluorinating reagents. We have established a reliable protocol to quickly determine the exact "F^+" content of the reagent. Our findings indicate that the most reliable and accurate method for analysing batches of Selectfluor type reagents is by iodometric titration. However, due to the uncomplicated and well resolved nature of Selectfluor, the purity can equally be assessed by ^{1}H NMR with addition of an internal reference. We chose the structurally similar 1,4-dimethyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis-triflate compound as a suitable reference because the DABCO protons of the core should exhibit similar NMR relaxation times to that of the fluorinating reagent and thus increase accuracy of integration. It should be noted that this approach will likely suffer from more inaccuracy than a titration approach and the results thus obtained are best used in combination with those found by titration. Table 1 illustrates the results obtained from three different batches of Selectfluor. Each sample was analysed by both techniques, which were found to agree very satisfactorily with each other. Those batches which displayed an unsatisfactory F^+ purity were subjected to recrystallization and the purified reagent was confirmed to have near perfect purity.[28] The quality of the reagent can visually be seen to improve upon recrystallization as a typically clumpy amorphous solid becomes colourless needles.

4.4.3.2 NFSI type reagents

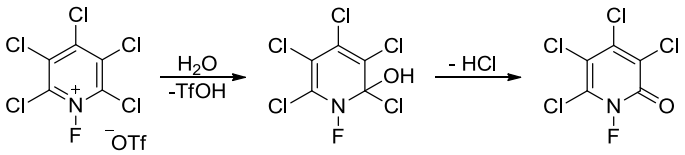
N-Fluoroarylsulfonamide based reagents, of which *N*-fluorobenzenesulfonimide (NFSI) is the most common, is another important class of electrophilic fluorinating reagents. Due to the possibility to tune the reagent's reactivity by altering the substitution of the aryl rings, this class of N-F compounds has great potential in the field of asymmetric fluorination, where the reactivity profile of the fluorinating reagent is often crucial to achieve high enantioselectivities. However, only NFSI itself is commercially available in this class and so derivatives thereof are typically prepared "in house" from the parent acid [of general structure $(ArSO_2)_2NH$)] and molecular fluorine (F_2).[29] Therefore, it is worth considering an unreacted parent acid impurity may be present, which would not only diminish the "F^+" activity but also since it is a strong acid it may cause problems with a substrate reacting with "H^+" and not "F^+".

A similar titration method to that of Selectfluor can be used to assess the exact "F^+" purity of NFSI type reagents, however in this instance, an NMR technique is not generally suitable. Typically, the purely aromatic nature of proton environments in these reagents renders "F^+" determination by an internal reference very difficult due to complex spectra. Also, due to the generally lower reactivity of this non-cationic class with respect to others, their fluorine transfer ability is weaker and so complete irreversible transfer to the "F^+" acceptor is not always observed. For this reason it is generally advised that the titration method be used instead. Should the purity transpire to be unsatisfactory the reagents may be purified by recrystallization to increase the "F^+" activity (Table 3).[28]

4.4.3.3 Pyridinium type reagents

The final common class of electrophilic fluorinating reagents is the pyridinium type, with a number of commercially available examples. Like the sulfonimide based reagents, the reactivity of the "F^+" can be effectively tuned by altering the substitution on the parent pyridine ring.

Since pyridinium reagents are made in the presence of a metal triflate/tetrafluoroborate salt (to sequester the fluoride ion formed upon fluorination with F_2) there is scope for contamination with either excess triflate/tetrafluoroborate or with unreacted pyridine.[30] Another problem is that the more reactive members of this class are often made in the presence of acid (usually TFA/TfOH) to aid fluorination. This gives rise to the possibility for highly acidic impurities, which are not so easy to differentiate from their fluorinated analogues by NMR studies. One final problem with pyridinium reagents is that they can undergo hydrolysis in the presence of water to give *N*-fluoropyridones. Indeed, *N*-fluoropentachloropyridinium triflate reacts rapidly in water to liberate HCl, TfOH and the corresponding pyridone as outlined below.



Scheme 24 – Hydrolysis of *N*-fluoropyridinium reagents

This decomposition pathway leading to an N-F compound of significantly lower reactivity renders results obtained from a titration experiment somewhat misleading since the titration merely identifies the concentration of "F^+" and not the identity of the "F^+". Whilst

running the titration (in acetonitrile) will certainly provide a concentration of "F^+" it will not reveal if the fluorinating agent is pure or whether it contains an amount of *N*-fluoropyridone. Therefore, we employed the complementary NMR method for determining both the fluorine content and its identity. A commonly used pyridinium based reagent is *N*-fluoro-2,6-dichloropyridinium triflate, which features somewhat lower reactivity than the corresponding per-chlorinated reagent but higher reactivity than Selectfluor™, as predicted by the relative oxidation potentials. Observationally, over time the pyridinium based reagent tends to become a sticky yellow oil and this is accompanied by a loss in "F^+" activity. A typical 6-month old batch was found to have an F^+ purity of 85 % and following purification the "F^+" purity was increased to 99 % (Table 1), which was accompanied by a physical change from a sticky yellow solid to a white powder.[28]

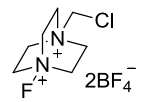
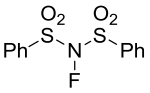
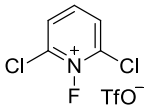
Reagent		Before Purification		Purification if required	After Purification	
	Batch 1	Titration	NMR[a]	recrystallization	Titration	NMR[a]
		94 %	90 %		97 %	94 %
	Batch 2	Titration	NMR[a]		Titration	NMR[a]
		75 %	70 %		97 %	92 %
	Batch 3	Titration	NMR[a]		Titration	NMR[a]
		98 %	95 %		-	-
	Batch 1	Titration	NMR		Titration	NMR
		99 %	-		-	-
	Batch 2	Titration	NMR		Titration	NMR
		89 %	-		98 %	-
	Batch 1	Titration	NMR[b]		Titration	NMR[b]
		-	85 %		-	99 %
	Batch 2	Titration	NMR[b]		Titration	NMR[b]
		-	92 %		-	98 %
	Batch 3	Titration	NMR[b]		Titration	NMR[b]
		-	98 %		-	-

Table 3 – Summary of purification and analysis; [a] Using 1,4-dimethyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(triflate) as an internal reference in CD_3CN; [b] Using 1-methyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate as an "F^+" acceptor

4.4.4 Summary

We have presented two complementary methods for the rapid and operationally simple determination of "F^+" purity of the most common classes of electrophilic fluorinating reagents. When hydrolysis of the reagent is not a concern, as with the Selectfluor™ and NFSI type reagents, a titration approach is favoured since this does not carry the errors associated with NMR integral comparisons. Accuracy can be improved by making a large volume of stock solution to avoid experimental errors. However, if any concerns exist over the identity of the fluorinating reagent due to hydrolysis then a NMR based titration can be performed using an easily accessed Selectfluor™ like precursor as an "F^+" acceptor. To the best of our knowledge this is the first comprehensive approach to the determination of electrophilic fluorinating reagent purity. In light of the discrepancies we observed between the "F^+" purity before and after purification, we highly recommend that determination of the reagent purity prior to performing an electrophilic fluorination reaction becomes standard protocol.

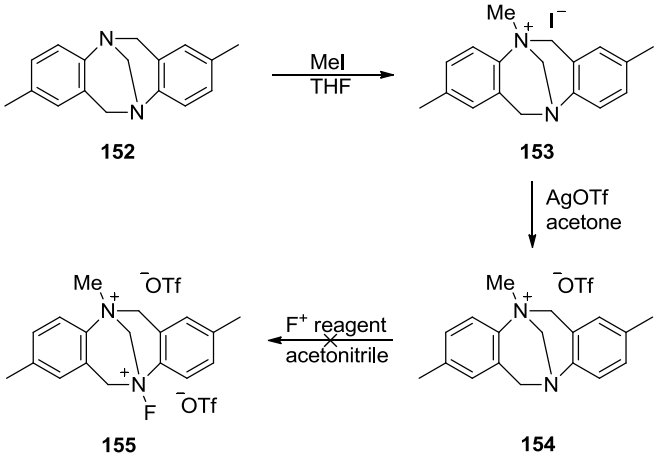
4.5 Tröger's base derived reagents

Another structural core that we considered for the basis of a new chiral fluorinating reagent was Tröger's base and derivatives thereof. Not unlike Selectfluor, the bridgehead conformationally locks the nitrogen atoms, giving rise to chirality.

4.5.1 Preparation of reagents

We began by first considering Tröger's base itself, which contains a methylene bridge. Methylation of one of the nitrogen atoms was performed using methyl iodide according to literature procedures,[31] which was followed by the necessary anion exchange with silver

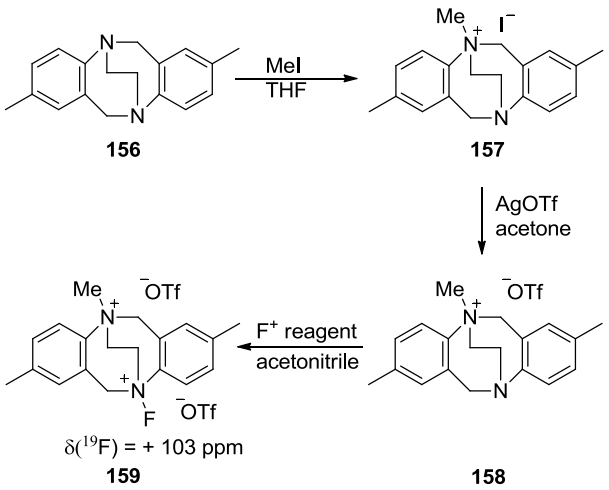
triflate. In an effort to fluorinate the remaining nitrogen atom we investigated various common fluorinating reagents in order to achieve a fluorine transfer in the same way as was used to form the chiral Selectfluor type compounds. Unfortunately, when Selectfluor and *N*-fluoro-2,6-dichloropyridinium triflate were mixed with triflate salt **154** no reaction was observed. Clean starting material was recovered, along with unreacted fluorinating reagent. When we employed *N*-fluoro-pentachloropyridinium triflate, our most powerful pyridinium reagent, some decomposition was observed but, again, no product could be detected.



Scheme 25 – Attempted synthesis of Tröger's base fluorinating reagent **150**

We therefore slightly modified the Tröger's base core by using the "2nd generation" ethano bridged structure **156**. Using the same strategy as in Scheme 25, we obtained the methylated triflate salt and subjected it to the same fluorinating reagents. With Selectfluor, mostly starting material was recovered with some evidence of minor decomposition. Encouragingly, *N*-fluoro-2,6-dichloropyridinium triflate delivered a small conversion to produce with the remainder being starting material. Finally, we were delighted to observe a significant conversion when the pentachloro reagent was used. However, given the low conversion, we speculated that such reagents would be highly reactive. In fact, the observed

F^+ peak in the ^{19}F NMR had a chemical shift of +103 ppm, which is to the best of our knowledge unprecedented for an N-F type reagent.



156 **157** **159** **158**

Scheme 26- Synthesis of (ethano)-Troger's base fluorinating reagent **159**

4.5.2 Summary

In conclusion, we have done some very preliminary work on the synthesis of a novel class of fluorinating reagent. Whilst the classical methano briddge type compounds were unsuccessful, the "2nd generation" ethano type delivered promising results. Furthermore, the extremely high chemical shifts and difficulty in fluorination that we observed is consistent with a reagent of high reactivity. It is an ideal candidate for investigation using F_2 gas, and could well offer a very useful addition to the fluorinating reagent toolbox, both as a chiral and an achiral source of fluorine.

4.6 Conclusion

In conclusion, we have developed a range of novel chiral electrophilic fluorinating reagents suitable for the enantioselective fluorination of lower reactivity substrates than were possible using previous reagents. In the first instance we focussed on the development of chiral Selectfluor compounds, which involved producing a library of intermediate novel chiral DABCO cores. Quaternization of the DABCOs using either methyl or chloromethyl presented the final challenge of fluorination. We initially optimised the reaction using dilute fluorine gas to obtain the isolated fluorinated reagents but also progressed to develop a method for *in situ* preparation. Due to the drawbacks of handling elemental fluorine we were prompted to utilise a fluorine transfer approach in a similar method to that used for cinchona alkaloids. The reactivity of the chiral Selectfluors was investigated using a quantitative competitive halogenation reaction and also a qualitative NMR comparison of the ^{19}F NMR chemical shifts of the $[N\text{-}F]^+$ groups. Finally, a general protocol was developed for the measurement of "F^+" reagent purity, given that our fluorine transfer method required accurate knowledge. As a final extension to our work on novel fluorinating reagents of superior reactivity we investigated the use of Troger base type compounds. Troger's base itself was found to be unsuitable as a fluorinating reagent but the structurally related compound with an ethano- bridge was successful. The fluorinated derivative displayed an extraordinarily high fluorine chemical shift, indicating high reactivity. Whilst the work in this area is only preliminary, a possible future line of research could be to explore structure modification of the core and the effect it has on the fluorinating power and selectivity.

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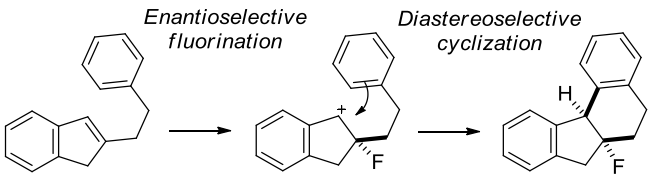
Chapter 5:

Asymmetric Fluorocyclization

5. Asymmetric Fluorocyclization

5.1 Introduction

The fluoro-carbocyclization of indenes and dihydronaphthalenes using pendent arene nucleophiles described in Chapter 2 constitutes a significant advance in the field of fluorocyclization. We were especially pleased to demonstrate this cyclization reaction on substrates that are significantly less activated towards electrophilic fluorination than traditional olefinic substrates. However, to firmly establish this methodology as a valuable route for the formation of fluorinated carbocyclic compounds we needed to develop an asymmetric variant of the reaction. We rationalised that the reaction essentially involved an enantioselective fluorination followed by a diastereoselective cyclization (Scheme 1).



Scheme 1 - Proposed reaction pathway

We therefore explored the literature for methods to achieve the electrophilic asymmetric installation of a fluorine atom. Typically, there are four general methods for such a transformation; activation of a 1,3-dicarbonyl system using a chiral Lewis acid, α-fluorination of a carbonyl compound using enamine catalysis, chiral reagents derived from enantiopure trialkylamines and the most recent chiral counterion ion approach as summarized in Figure 1.

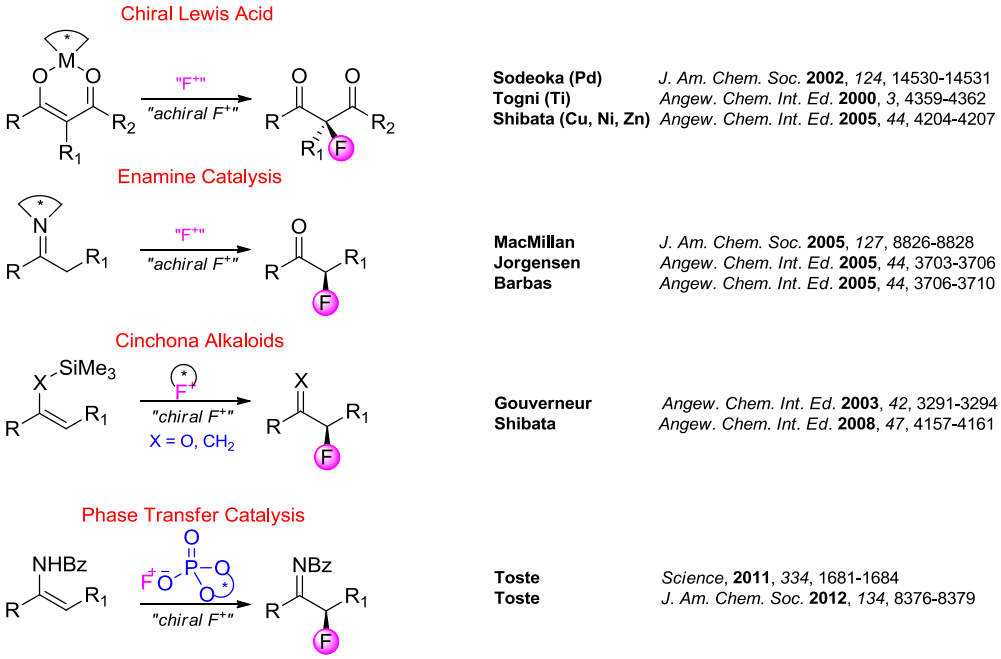
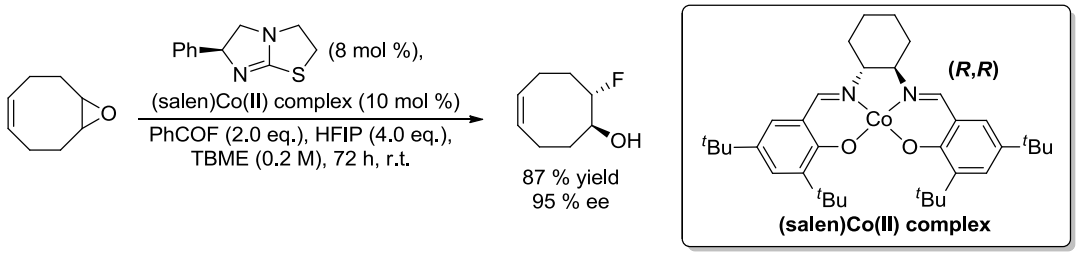


Figure 1 – General methods of asymmetric fluorination

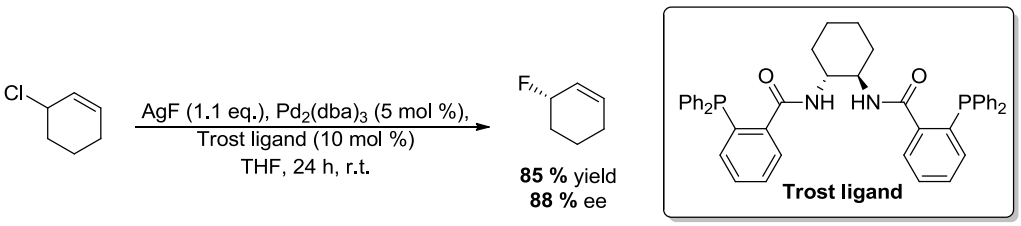
5.1.1 Chiral Lewis acid catalysis

Methods of asymmetric fluorination utilising a nucleophilic source of fluorine are somewhat rare. Work by Haufe in 2000 outlined the enantioselective ring opening of epoxides using potassium hydrogen difluoride as a nucleophilic fluorine source, in the presence of a stoichiometric amount of a chiral (salen)chromium chloride complex.[1,2] Efforts to extend this reaction to a catalytic variant were largely unsuccessful until work published by Doyle in 2010, reporting a dual catalytic process for the enantioselective ring opening of meso epoxides with fluoride.[2] A chiral (salen)cobalt complex was employed catalytically in combination with substoichiometric amounts of the chiral Lewis acid (-)-tetramisole, to deliver excellent yields and enantiomeric excesses for a range of substrates (Scheme 2).



Scheme 2 - Asymmetric catalytic ring opening of meso epoxides by Doyle et al.

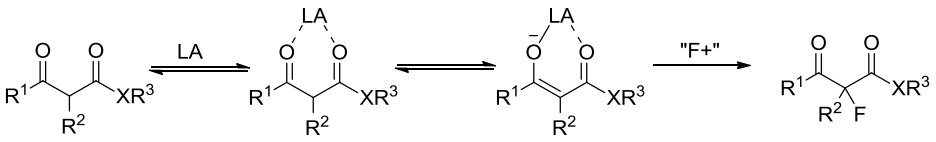
A subsequent paper, also published by Doyle, utilised the Trost ligand for the palladium mediated enantioselective fluorination of 6-membered cyclic allylic chlorides with silver fluoride (Scheme 3).[3] The authors proposed that the reaction occurred via nucleophilic attack of fluoride on an electrophilic Pd(II)-allyl intermediate. Enantioenriched cyclic allylic fluorides were obtained in high yields and enantiomeric excesses, with conditions shown to be tolerant of substrates bearing common functional groups, including ethers, amines, esters, and amides. Notably, these few transition metal catalysed reactions represent the vast majority of successful asymmetric fluorination reactions which employ a nucleophilic source of fluorine.



Scheme 3 - Palladium catalysed asymmetric fluorinatio of allylic chlorides by Doyle et al.

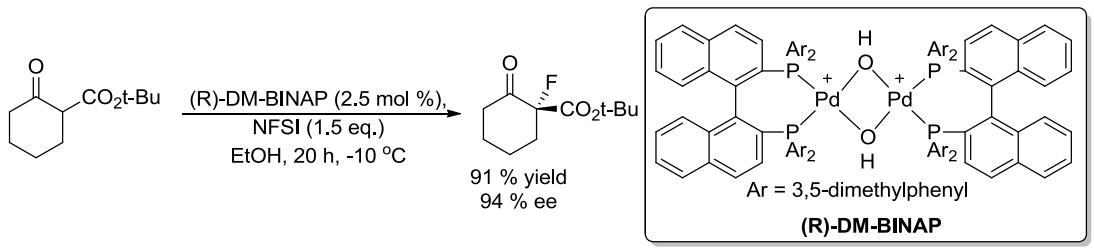
On the other hand, there is a wealth of literature describing asymmetric α-fluorinations effected by achiral electrophilic fluorine sources in combination with a chiral transition metal Lewis acid catalysts. However, this methodology is limited to very activated substrates which are capable of two-point binding, such as 1,3-dicarbonyl complexes, as bidentate co-ordination of the substrate to the metal complex is required in order to increase the acidity

of the α-proton and therefore promote metal enolate formation (Scheme 4). Enantioselectivity can be induced by use of sterically bulky chiral ligands, so that attack of the electrophile on one face is effectively blocked.



Scheme 4 - Mechanism for transition metal catalysed electrophilic a-fluorination

This approach was first reported by Togni in 2000, with the application of chiral Ti-TADDOL complexes as catalysts for the asymmetric fluorination of β-ketoesters, in combination with Selectfluor as an electrophilic fluorine source.[4] Although the enantiomeric excesses achieved were only moderate, this was an important initial demonstration of the use of chiral metal Lewis acid complexes for asymmetric fluorination. In 2002, Sodeoka disclosed the use of palladium-BINAP complexes to promote the asymmetric fluorination of β-ketoesters with excellent yields and enantioselectivity (Scheme 5).[5,6] Sodeoka was later able to successfully extend the application of chiral Pd complexes to other activated substrates such as oxindoles,[7] β-ketophosphonates,[8] lactones and lactams.[9]



Scheme 5 - Palladium mediated enantioselective fluorination of β-ketoesters

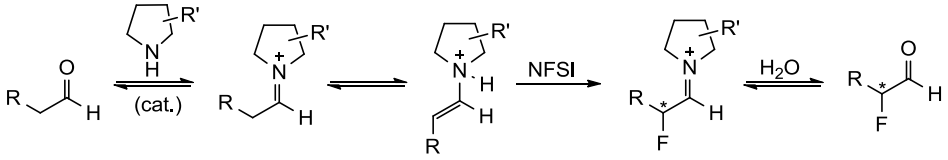
Numerous other transition metal complexes have been similarly employed for the asymmetric fluorination of two-point binding substrates, with recent publications employing nickel,[10] copper[10] and zinc[11] complexes. However, although transition metal catalysts are able to provide both excellent yields and enantiomeric excesses, substrates are restricted to those capable of two-point binding and the method is therefore severely limited in scope.

5.1.2 Organocatalytic asymmetric fluorination

Organocatalysed asymmetric fluorination is a rapidly growing area of research in modern organofluorine chemistry. The ability to introduce a fluorine atom in a highly stereoselective manner by employing an organocatalyst is an attractive alternative to traditional methods of transition metal catalysis.

5.1.2.1 Enamine catalysis

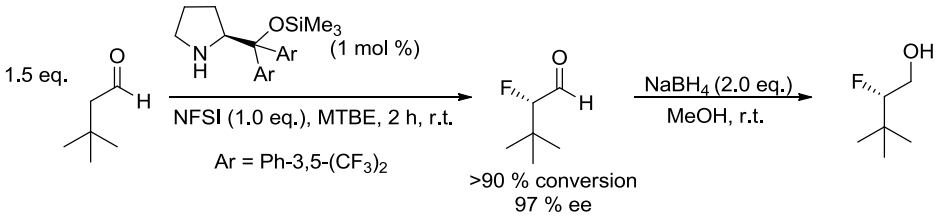
Whilst substrates capable of two-point binding are required for transition metal catalysed asymmetric fluorination reactions, the asymmetric fluorination of less activated substrates such as aldehydes and ketones can be achieved using an organocatalytic approach. In 2005, four groups independently reported the use of secondary amine catalysts to promote asymmetric electrophilic fluorination by the *in situ* formation of a reactive enamine species (Scheme 6).



Scheme 6 - Mechanism for enamine catalysed α-fluorination of aldehydes

In pioneering work, Enders investigated proline based catalysts for the α-fluorination of a range of aldehydes and ketones with Selectfluor as the electrophilic fluorinating agent, but had limited success, with enantiomeric excesses reaching only 36 %.[12]

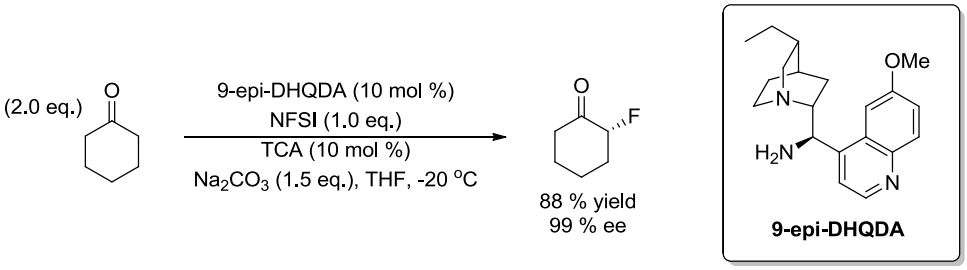
Later the same year, Jørgensen[13] and Barbas[14] published consecutive papers reporting the enantioselective α-fluorination of aldehydes and achieved much improved results by employing the less reactive NFSI as a fluorine source (Scheme 7). Jørgensen increased the enantioselectivity of the reaction by using a bulky silylated prolinol derived catalyst whilst Barbas employed stoichiometric amounts of an imidazolidine based chiral promoter. Both were able to achieve excellent yields and enantiomeric excesses and could extend this methodology to the formation of quaternary centres by use of less bulky catalysts. The low stability and significant volatility of the fluorinated aldehydes made it necessary for them to be derivatised as the corresponding fluorohydrins prior to isolation and characterisation.



Scheme 7 - Asymmetric α-fluorination by Jørgensen et al.

MacMillan also published a very similar organocatalytic method of α-fluorination of aldehydes in the same year.[15] Excellent yields and enantiomeric excesses were achieved by employing the commercially available dichloroacetate salt of the imidazolidine catalyst utilized by Barbas.[14] However, the more challenging asymmetric fluorination of ketone substrates, which condense only slowly with secondary amine catalysts, was not addressed until a further paper by MacMillan in 2011.[16] High-throughput screening of 250 primary and

secondary amines as catalysts for the α-fluorination of cyclohexanone allowed an optimum reaction protocol to be developed. It was found that use of 20 mol % of a dihydroquinidine derived catalyst, in the presence of a trichloroacetic acid co-catalyst, could be employed to afford α-fluorinated ketones with excellent yields and enantiomeric excesses (Scheme 8).



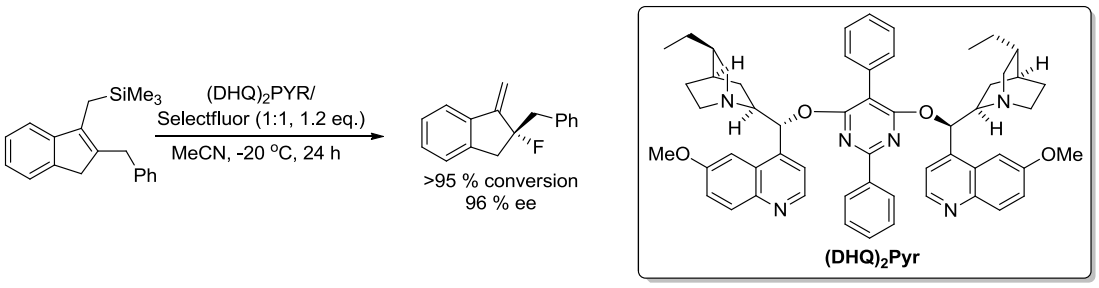
Scheme 8 - Organocatalytic α-fluorination of ketones by MacMillan et al.

5.1.2.2 Cinchona alkaloids in asymmetric fluorination

Cinchona alkaloids have featured centrally in the field of organocatalysis for many years, and over the past decade they have found a pivotal role in asymmetric fluorination.[17] Following Banks' initial findings in 1995 that *N*-fluoroquinuclidinium salts could be formed by fluorine transfer from Selectfluor to quinuclidine,[18] work was published simultaneously by Cahard[19] and Takeuchi[20] on the combination of cinchona alkaloids with Selectfluor, to afford chiral N-F reagents without the need for elemental fluorine. This preliminary work was detailed in Chapter 4.

Cinchona alkaloids are widely used for the asymmetric introduction of fluorine into an organic molecule due to their ease of use and often high level of induced enantiomeric excess. Work within the group has demonstrated the application of this method to the novel enantioselective fluorodesilylation of allyl silanes (Scheme 9).[21] This transformation took advantage of the β-effect of silicon in order to stabilise the carbocation formed in the initial

fluorination step, therefore dictating the regioselectivity of the reaction and increasing the rate.



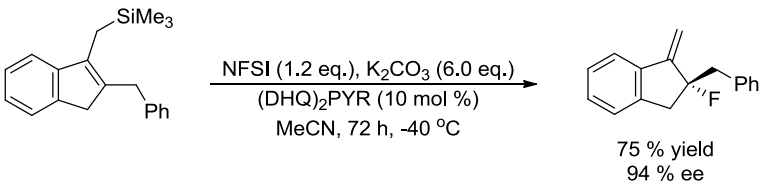
Scheme 9 - Fluorodesilylation of allyl silanes using a cinchona alkaloid/ Selectfluor combination

Shibata later attempted to develop a catalytic variant of this cinchona alkaloid mediated asymmetric fluorination reaction. In order for a high level of enantioselectivity to be achieved, the catalysed asymmetric fluorination reaction must be faster than the racemic uncatalyzed background fluorination of the substrate. Since the catalytic amount of the chiral N-F reagent present at any one time will be of similar reactivity with respect to the parent achiral fluorinating agent, this presents an obvious challenge.

In their first effort, work published by Shibata in 2006 employed silyl enol ether substrates for this catalytic reaction, but the enantioselectivity observed was negligible due to the rate of the racemic fluorination of silyl enol ethers by Selectfluor.[22] The problem was somewhat circumvented by modifying the substrates to less reactive acyl enol ethers in order to reduce the rate of the background reaction and therefore furnish the fluorinated products in good yields and with moderate enantiomeric excesses. However, it is never ideal to be required to change a substrate to match the available fluorinating agent.

The real breakthrough in reagent driven asymmetric fluorination was when a more successful reaction was published by the same group in 2008. The enantioselective

fluorination of silyl enol ethers, allyl silanes and oxindoles was achieved with good to excellent yields and enantiomeric excesses, with only catalytic amounts of cinchona alkaloid (Scheme 10).[23] The fundamental difference between the two reports was the beneficial use of the less reactive NFSI as a fluorine source as opposed to Selectfluor.



Scheme 10 - Enantioselective fluorination using NFSI with catalytic cinchona alkaloid

Notably, it was found that both conversion and enantioselectivity for the catalytic reaction were poor in the absence of potassium carbonate as a base, with optimum conditions requiring a large excess. A mechanism was therefore proposed in which after the initial fluorine transfer to the cinchona alkaloid, an anion exchange occurs to form the more reactive *N*-fluoroammonium KCO_3^- salt. It was suggested that enantioselective fluorination of the substrate then occurs from this species, regenerating the cinchona alkaloid catalyst (Figure 2).

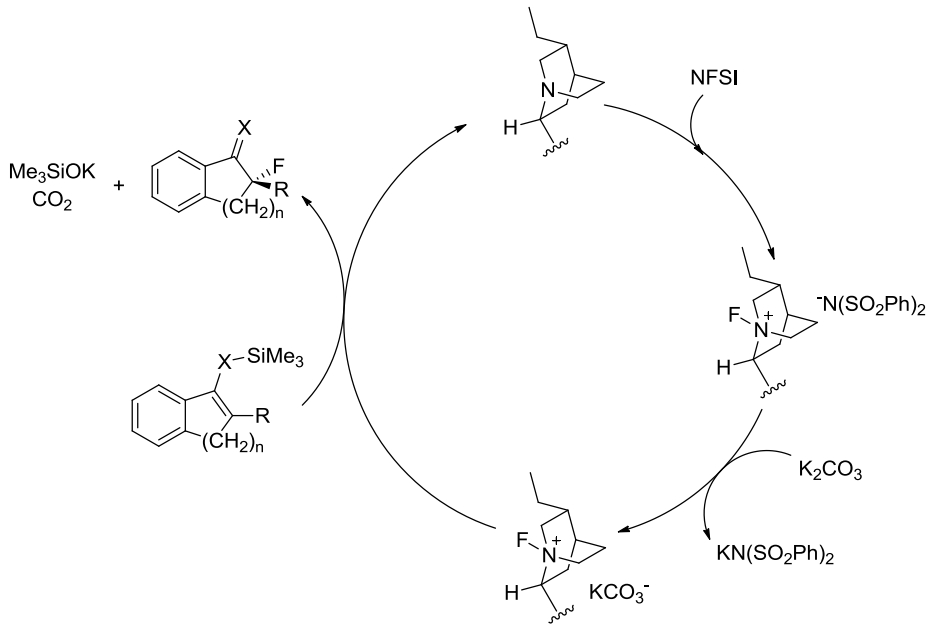
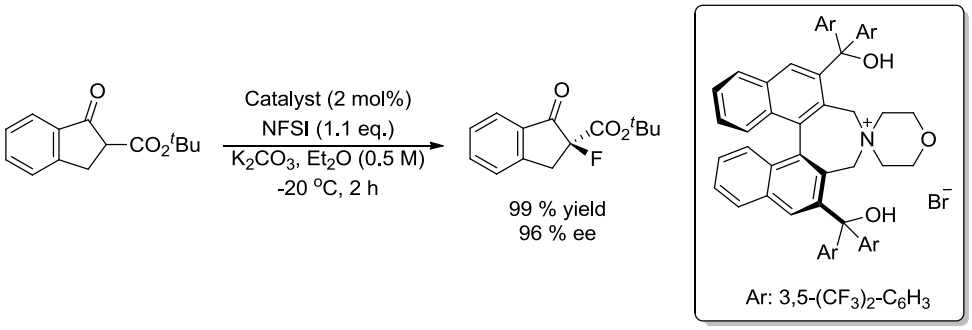


Figure 2 - Proposed mechanism for the catalytic asymmetric electrophilic fluorination

5.1.3 Asymmetric fluoro-heterocyclization using phase-transfer methodology

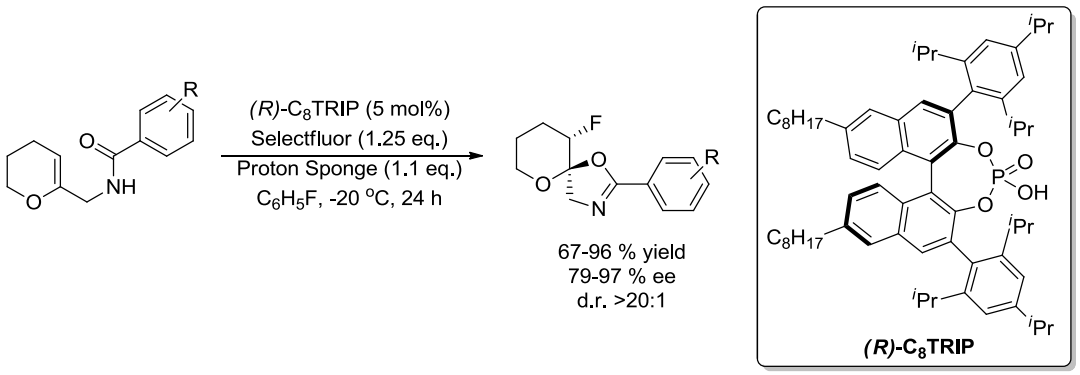
The most recent method that has been employed in the field of asymmetric fluorination is through the use of chiral phase-transfer catalysis. The term phase-transfer was first coined by Starks in 1971 to explain the role of tetraalkylammonium or phosphonium salts in certain reactions.[24] Subsequently, the first asymmetric variant was reported in 1984 by Dolling *et al.* where they utilised a cationic cinchona alkaloid derived catalyst. More recently, phase-transfer catalysts were employed by Kim in the catalytic electrophilic fluorination of *β*-ketoesters and also *α*-cyanoesters.

In 1999, Ooi *et al.* developed an entirely new type of C_2-symmetric cationic phase-transfer catalyst based on structurally rigid, chiral spiro-ammonium salts derived from commercially available (*S*)- or (*R*)-1,1'-bi-2-naphthol.[25] These catalysts have also been used in the asymmetric fluorination of *β*-keto esters (Scheme 11).



Scheme 11 - Asymmetric fluorination of *β*-keto esters with cationic phase-transfer catalyst

A second complementary type of phase-transfer catalyst to the cationic approach has recently been developed which features a chiral anion. A report in 2011 by Toste *et al.* featured the asymmetric fluorocyclisation of dihydropyrans and dihydronaphthalenes using a pendent amide nucleophile with a chiral anion solid-liquid phase transfer catalyst derived from (*R*)-BINOL (Scheme 12).[26] The mechanism for which was described in detail in Chapter 4.



Scheme 12 - Asymmetric fluorination with anionic phase-transfer catalyst

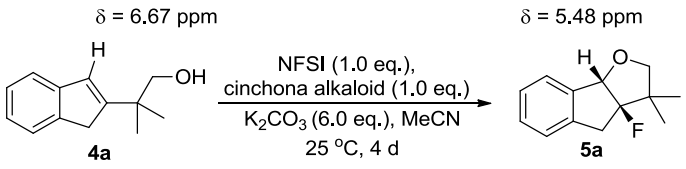
5.2 Asymmetric fluoro-heterocyclization

Following the successful fluorocyclization of indene and dihydronaphthalene substrates in Chapter 2, we were interested to investigate if a stoichiometric cinchona alkaloid/

electrophilic fluorinating reagent combination could be employed to achieve an asymmetric variant of the reaction. As with the development of the racemic carbocyclization reaction we initially investigated heteroatom nucleophiles to first explore the problem of reactivity.

5.2.1 Reaction development

Since the substrates did not feature carbonyl groups required for Lewis acid or enamine approaches we began by considering cinchona alkaloids in a chiral reagent driven method. A variety of cinchona alkaloids were screened in combination with NFSI as the electrophilic fluorine source. This neutral electrophilic fluorinating reagent was employed in preference to the more reactive Selectfluor in an attempt to reduce the rate of the racemic background reaction. Alcohol **4a** was chosen as the model substrate on which asymmetric screening reactions were carried out as preliminary experiments showed the corresponding product to be stable under the reaction, work up and purification conditions as well as in storage. In fact, it can be stirred in the presence of silica overnight, or stored in chloroform for several weeks without any decomposition. Literature precedent advises that optimum conditions for cinchona alkaloid mediated asymmetric fluorination require 6.0 equivalents of potassium carbonate. The reactions were carried out for 4 days at 25 °C, with conversions calculated by integration of the benzylic proton in the crude ^{1}H NMR, which shifts from a singlet at 6.67 ppm in the starting material to a doublet at 5.48 ppm in the fluorocyclized product (Table 1).



Entry[a]	Cinchona Alkaloid	Conversion[b] (%)	ee[c] (%)
1	Quinine	9	30
2	Quinidine	14	(-)15
3	DHQ	15	34

4	DHQD	<5	14(-)
5	Cinchonine	11	7(-)
6	Cinchonidine	14	14
7	DHCD	<5	18
8	$(DHQ)_2PHAL$	41	45
9	$(DHQD)_2PHAL$	78	25
10	$(DHQ)_2PYR$	70	0
11	$(DHQ)_2AQN$	<5	-[d]
12	BQ	45	27
13	BQ[e]	45	26
14	BQd	56	12
15	DHQB	60	38
16	DHQDB	24	21
17	None	9	0

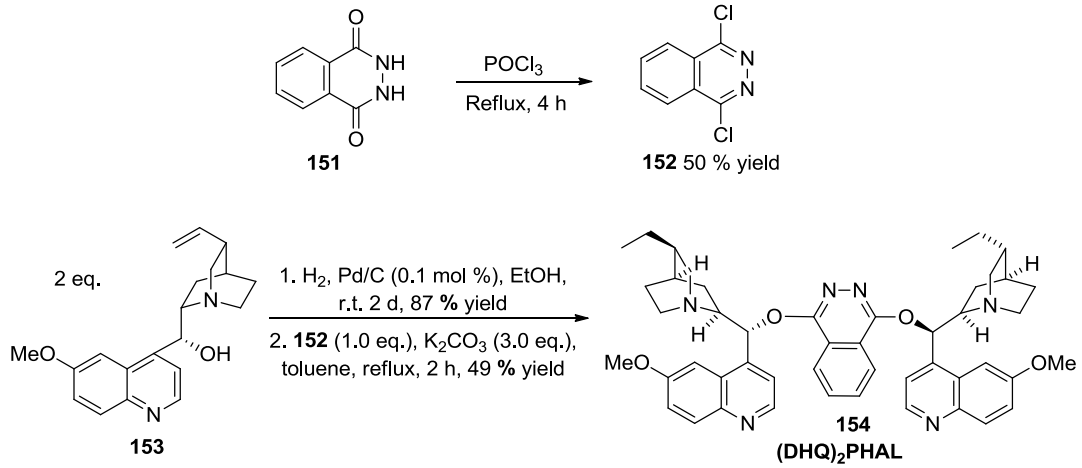
Table 1 - Cinchona alkaloid screening; [a] alcohol 4 (1.0 eq.), NFSI (1.0 eq.), cinchona alkaloid (1.0 eq.), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b] Determined by ^1H NMR; [c] Determined by stationary phase chiral HPLC; [d] ee not obtained; [e] Under atmosphere of argon

Pleasingly, we found that this cinchona alkaloid/ NFSI combination was sufficiently reactive to mediate the fluorocyclization reaction, with moderate enantiomeric excesses of up to 45 % achieved. High conversion to fluorocyclized product was possible, for example the $(DHQD)_2PHAL$ mediated reaction afforded a 78 % conversion (Table 2, entry 9), although unfortunately the enantioselectivity induced by this bis-cinchona alkaloid was poor. Both $(DHQ)_2PHAL$ and DHQB (entries 9 and 15) afforded an acceptable compromise between conversion and enantioselectivity. After three repetitions of the reactions, the result afforded by $(DHQ)_2PHAL$ was found to be more consistently reproducible and so this was the cinchona alkaloid selected for optimisation of the reaction conditions.

Conveniently, the same result was obtained when the reaction was performed under air as was obtained when precautions were taken to extrude moisture and keep the reaction

under an atmosphere of argon (Entries 12 and 13 respectively) and so all reactions were carried out under air, but using dry solvent as a precaution.

$(DHQ)_2PHAL$ is commercially available but fairly expensive due to its high molecular weight. Since we envisioned using a large amount of this bis-cinchona alkaloid for screening reactions, it was instead synthesised according to the procedure developed by Sharpless.[27] This allowed us to prepare the alkaloid on a gram scale from the easily prepared 1,4-dichlorophthalazine **152**[28] and inexpensive quinine (Scheme 13).



Scheme 13 - Synthesis of $(DHQ)_2PHAL$

We speculated that the conversion and enantiomeric excess of the reaction could be improved by optimisation of the reaction conditions. We first examined the equivalents of fluorinating agent employed (Table 2).

Entry[a]	Equivalents NFSI	Conversion[b] (%)	ee[c] (%)
1	1.0	41	45
2	2.0	>95	48

[a]alcohol **4a** (1.0 eq.), NFSI (x eq.), $(DHQ)_2PHAL$ (1.0 eq.), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^1H NMR; [c]Determined by stationary phase chiral HPLC.

Table 2 - NFSI loading screening

Remarkably, this result showed that simply doubling the equivalents of fluorinating reagent employed was sufficient to push the reaction to completion, with no drop in enantioselectivity (Table 2, entry 2). This result was somewhat surprising since the rate of racemic fluorination of the substrate could be expected to increase with a greater amount of achiral fluorinating agent present.

Having successfully optimised the reaction to achieve complete conversion, we next turned our attention to the unsatisfactory reaction time. We had previously performed all screening reactions for 4 days to ensure that maximum conversion was obtained, but anticipated that this could be improved. To our great delight, investigations eventually revealed that the same conversion and enantiomeric excess could actually be achieved within just 30 minutes (Table 3).

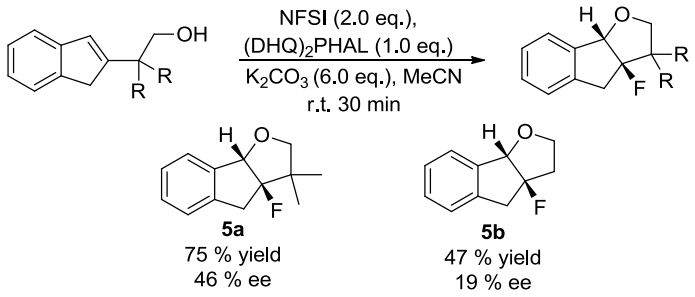
Entry[a]	Reaction time	Conversion[b] (%)	ee[c] (%)
1	30 min	>95	47
2	4 days	>95	48

Table 3 - Investigation of reaction time; [a]alcohol **4a** (1.0 eq.), NFSI (2.0 eq.), $(DHQ)_2PHAL$ (1 eq.), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C; [b]Determined by ^1H NMR; [c]Determined by stationary phase chiral HPLC

This result suggested a significant acceleration of the rate by the cinchona alkaloid, when it is considered that in the absence of alkaloid, only a 9 % conversion to product is observed

after 4 days (Table 1, entry 17). We were therefore very pleased to have optimised the reaction conditions so that not only does it reach completion, but the timescale is also appealing.

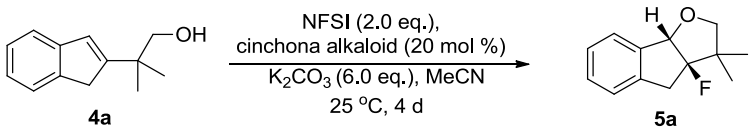
Pleasingly, we found that application of these optimised conditions to our model substrate allowed the isolation of the product in high yield with no deterioration of enantiomeric excess, therefore validating this methodology (Scheme 14). Investigation of the scope of the reaction also allowed efficient fluorocyclization of a less substituted substrate to be achieved, albeit with a much depleted ee. This result suggested the possibility that the gem-dimethyl group could be important in controlling enantioselectivity.



Scheme 14 - Isolation of asymmetric fluorocyclized products

5.2.2 Catalytic asymmetric fluorocyclization

Having successfully developed an asymmetric variant of the fluorocyclization reaction, the next challenge was to further extend this methodology to a catalytic version. Due to the well documented difficulties in performing catalytic asymmetric halocyclizations,[29] we undertook extensive optimisation studies. Model substrate **4a** was again used in order to screen a range of cinchona alkaloids, which were employed in a catalytic amount (Table 4). An excess of potassium carbonate was employed in accordance with Shibata's findings that 6.0 equivalents are optimum for asymmetric fluorination.[25]



4a **5a**

Entry[a]	Cinchona Alkaloid	Conversion[b] (%)	ee[c] (%)
1	Quinine	37	31
2	Quinidine	54	12 (-)
3	DHQ	45	42
4	DHQD	32	5(-)
5	Cinchonine	56	34 (-)
6	Cinchonidine	53	30
7	DHCD	47	43
8	$(DHQ)_2PHAL$	59	46
9	$(DHQD)_2PHAL$	59	12
10	$(DHQ)_2PYR$	54	0
11	$(DHQ)_2AQN$	36	11 (-)
12	$(DHQD)_2AQN$	32	48
13	BQ	41	12
14	BQd	65	8
15	Hydroquinine 9-phenanthryl ether	30	8
16	DHQB	40	16
17	DHQDB	31	15
18	None	32	0

Table 4 - Catalytic cinchona alkaloid screening; [a]alcohol 4 (1.0 eq.), NFSI (2.0 eq.), catalyst (20 mol %), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^1H NMR; [c]Determined by stationary phase chiral HPLC

We were very pleased to find that a catalytic variant of the asymmetric fluorocyclization was achievable, with only 20 mol % catalyst able to give enantiomeric excesses of up to 48 % (Table 4, entry 12). Conversions of up to 65 % (entry 14) demonstrated that more than one catalytic turnover was possible. However, the results obtained in these catalytic reactions were very surprising when compared to the conversions and enantiomeric excesses achieved with a stoichiometric amount of cinchona alkaloid (Table 1).

It would generally be expected that similar or increased conversions and enantiomeric excesses would be observed with an increased catalyst loading. Whilst this was found to be the case for the bis-cinchona alkaloids and the hydroxyl protected mono-alkaloids (Table 4, entries 8-17), the unprotected mono-alkaloids (Table 4, entries 1-7) showed a significant increase in conversion and some increase in enantioselectivity for the catalytic reaction. For example, when dihydrocinchonidine (DHCD) was employed in a stoichiometric amount, a conversion of <5 % was achieved with a 18 % enantiomeric excess (Table 1, entry 7). However, employing the same cinchona alkaloid in a catalytic amount resulted in a significantly higher conversion of 47 %, with 43 % enantiomeric excess (Table 4, entry 7). Even taking into account the increased amount of NFSI employed for the catalytic reactions, this observation was surprising and suggested to us that the mechanism by which the cinchona alkaloid mediates the asymmetric fluorocyclization is probably affected by whether the hydroxyl moiety of the alkaloid is capped or uncapped. We therefore embarked on an investigation of the two systems.

As was also observed for the stoichiometric reaction, $(DHQ)_2PHAL$ was the cinchona alkaloid found to give the best compromise between conversion and enantioselectivity (Table 4, entry 8). Since utilizing this alkaloid would also allow for direct comparison with the stoichiometric reaction, this was the catalyst of choice for further investigation of the substoichiometric reaction. Initially, we were interested in the variation of conversion and enantioselectivity with change of amount of alkaloid and fluorinating agent (Table 5).

Entry[a]	$(DHQ)_2PHAL$ (mol %)	1.0 eq. NFSI		2.0 eq. NFSI	
		Conversion[b] (%)	ee[c] (%)	Conversion[b] (%)	ee[c] (%)
1	10	26	63	52	36
2	20	25	49	59	46
3	30	37	56	78	48
4	50	43	56	82	46

5	80	45	46	>95	48
6	100	41	45	>95	50

Table 5 - Effect of changing loading of $(DHQ)_2PHAL$; [a]alcohol 4 (1.0 eq.), NFSI (1.0 or 2.0 eq.), $(DHQ)_2PHAL$ (x mol %), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^1H NMR; [c]Determined by stationary phase chiral HPLC.

As expected, a gradual increase in conversion was observed with increasing catalyst, until at 80 mol % catalyst the reaction tended towards the stoichiometric result (Table 5, entry 5). Interestingly though, there was no significant change in enantiomeric excess with a decreased amount of alkaloid. Notably, nor was there a major decrease in enantiomeric excess when the equivalents of fluorinating agent employed was increased from 1.0 to 2.0. As was also observed for the stoichiometric reaction, there was an appreciable increase in conversion on doubling the equivalents of fluorinating reagent, again indicating the importance of employing an excess of NFSI. Pleasingly, with 30 mol % catalyst and 2.0 equivalents of NFSI, a conversion of 78 % could be achieved, with an enantiomeric excess of 48 % (entry 3). In an effort to achieve a similarly high conversion with a lower catalyst loading of 20 mol %, we explored the effect of further increasing the equivalents of NFSI employed (Table 6).

Entry[a]	NFSI (eq.)	Conversion (%)	ee (%)
1	1.0	25	49
2	2.0	59	46
3	2.5	89	38
4	3.0	81	44
5	5.0	82	32

Table 6 - Effect of changing equivalents of NFSI; MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^1H NMR; [c]Determined by stationary phase chiral HPLC

This demonstrated that use of a large excess of NFSI allowed high conversions to be achieved with just 20 mol % of catalyst, with no depletion of enantiomeric excess. For example, 3.0 equivalents of NFSI afforded an 81 % conversion with an enantiomeric excess of 44 % (Table 6, entry 4). A catalytic version of the reaction is therefore entirely feasible, with only a slight depreciation of conversion relative to the stoichiometric reaction.

Having found optimised conditions for the catalytic asymmetric fluorocyclization with $(DHQ)_2PHAL$, we next explored how these results contrasted with those obtained using an unprotected monoalkaloid. Of the unprotected mono-alkaloid catalysts screened, the best conversion and enantiomeric excess was achieved with DHCD (Table 4, entry 7), and so this was selected as the catalyst for further mechanistic investigations for this system. In order to study the surprising discrepancy between the reactions employing a catalytic or stoichiometric amount of this alkaloid, the catalyst loading screening was repeated with this mono-alkaloid, with both 1.0 and 2.0 equivalents of NFSI (Table 7).

Entry[a]	(DHCD) (mol %)	1.0 eq. NFSI		2.0 eq. NFSI	
		Conversion[b] (%)	ee[c] (%)	Conversion[b] (%)	ee[c] (%)
1	10	17	37	46	34
2	20	17	45	47	43
3	30	16	45	47	46
4	50	14	41	33	48
5	80	<5	26	24	52
6	100	<5	18	25	46

Table 7 - Effect of changing loading of DHCD [a]alcohol 4 (1.0 eq.), NFSI (2.0 eq.), DHCD (x mol %), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^{1}H NMR; [c]Determined by stationary phase chiral HPLC

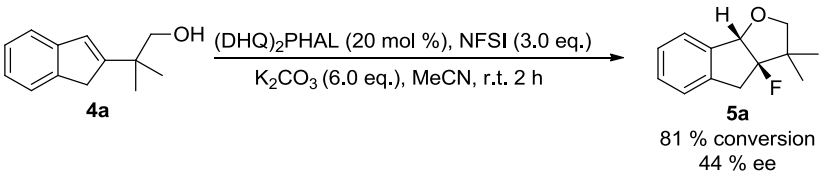
These results further demonstrated the drop in conversion, from the 46 % achieved with 10 mol % DHCD and 2.0 equivalents of NFSI, to only 25 % when the alkaloid is present in stoichiometric amounts. There was also considerable variation in enantiomeric excess with

the change of catalyst loading. Again, doubling the equivalents of fluorinating reagent had a significant effect on the conversion of the reaction. We were therefore again interested to discover if the conversion of the catalytic reaction, with 20 mol % DHCD, could be further increased by use of increased equivalents of achiral fluorinating agent (Table 8).

Entry[a]	NFSI (eq.)	Conversion[b] (%)	ee[c] (%)
1	1.0	17	45
2	1.5	30	43
3	2.0	47	43
4	2.5	52	39
5	5.0	75	32

Table 8 - NFSI loading screening; [a]alcohol 4 (1.0 eq.), NFSI (x eq.), DHCD (20 mol %), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^{1}H NMR; [c]Determined by stationary phase chiral HPLC.

These studies showed that the conversion of the catalytic reaction could be increased up to 75 % by use of 5.0 equivalents of NFSI, with only a slight depletion of enantiomeric excess (Table 8, entry 5), demonstrating that DHCD is also an effective catalyst for the catalytic asymmetric fluorocyclization of indene substrates. However, the conversion and enantioselectivity achieved using $(DHQ)_2PHAL$ were slightly superior, so that our optimum conditions for the catalytic asymmetric reaction involved employing 20 mol % of this bis-cinchona alkaloid in combination with 3.0 equivalents of NFSI (Table 6, entry 4). Despite anticipating that this would be a slow reaction, we were very pleased to find that further optimisation reactions revealed identical results could be obtained within 2 hours, providing the optimum conditions for the catalytic reaction as outlined in Scheme 15.



Scheme 15 - Optimised conditions for catalytic asymmetric fluorocyclization of indene system **4a**

At this point we were confident that we had optimised the conditions for both a stoichiometric and catalytic version of the cinchona alkaloid mediated asymmetric fluorocyclization. However, a few questions remained. Firstly, the reason for the strong dependence of the reaction conversion on the amount of NFSI employed, and the conservation of enantiomeric excess despite use of an excess of this achiral fluorinating agent. Secondly, despite showing similar reactivity when employed in a catalytic amount, $(DHQ)_2PHAL$ and DHCD displayed opposite trends with increasing catalyst loading. To gain explanations for these observations, we embarked on an investigation of the reaction mechanism.

5.2.3 Mechanistic studies

As discussed previously, in the case of fluorocyclization, the carbon-fluorine bond forming step can be assumed to be enantiodetermining, since the high strength of this bond renders the fluorination irreversible. It is therefore reasonable to consider literature precedent for asymmetric fluorination when attempting to elucidate the mechanism of the asymmetric fluorocyclization.

As demonstrated initially by Takeuchi, mixing of a cinchona alkaloid with a suitably reactive electrophilic fluorinating agent will result in the *in situ* formation of a chiral N-F reagent.[20] This approach was further developed by Shibata, who demonstrated that asymmetric

fluorination was also viable with only a catalytic amount of cinchona alkaloid.[23] It was suggested that this was possible due to a catalytic cycle, in which the sulfonamide salt initially formed by fluorine transfer to the cinchona alkaloid can undergo an anion transfer with the base, in order to furnish the more reactive carbonate salt of the *N*-fluoroammonium species. It was suggested that asymmetric fluorination of the substrate then occurs from this chiral N-F source, regenerating the catalyst. We initially anticipated that a similar mechanism of *in situ* formation of a chiral N-F reagent, followed by anion transfer, would be occurring for our fluorocyclization reaction, albeit with the cinchona alkaloid present in a stoichiometric amount and so requiring only one "catalytic" turnover.

Our first step was to validate the fluorine transfer from NFSI to $(DHQ)_2PHAL$, a transformation which can be observed by ^{19}F NMR. Equal amounts of alkaloid and NFSI were stirred in deuterated acetonitrile at room temperature. It was noted that the alkaloid was initially insoluble but was gradually solubilised after mixing with the NFSI. After 5 minutes of stirring, ^{19}F NMR indicated that complete transfer of fluorine from NFSI to the alkaloid had occurred (Figure 3).

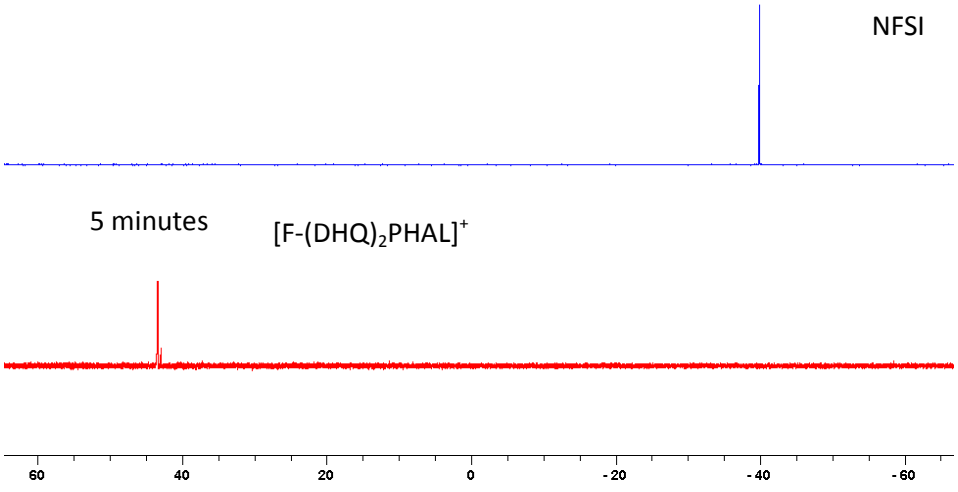
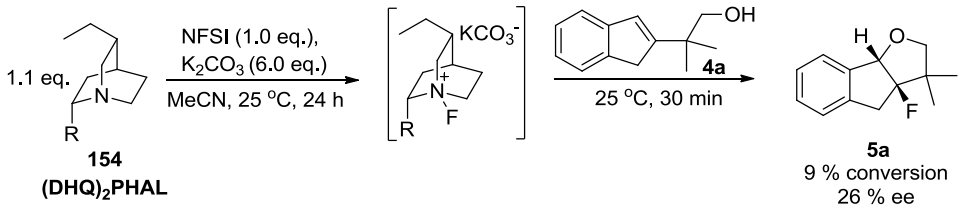


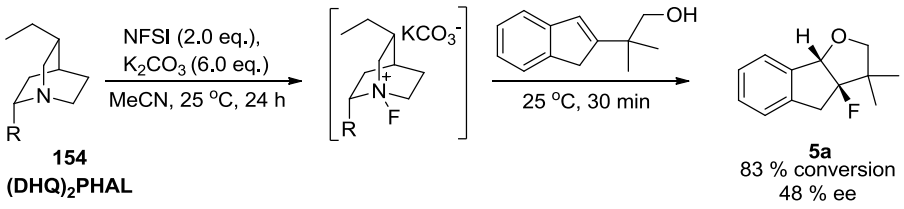
Figure 3 - NMR experiment indicating fluorination of $(DHQ)_2PHAL$

This suggested that fluorination of the alkaloid should occur rapidly under the reaction conditions. If fluorine transfer to the substrate is occurring from the *N*-fluoroammonium salt of the alkaloid, our results should be reproducible when this chiral N-F reagent is pre-formed, as opposed to being formed *in situ*. This was achieved by mixing $(DHQ)_2PHAL$, NFSI and potassium carbonate at room temperature for 24 hours prior to substrate addition (Scheme 16).



Scheme 16 - Fluorocyclization with pre-formed N-F reagent

Significantly, this reaction gave a conversion of only 9 %, in contrast to the 41 % conversion obtained when the *N*-fluoroammonium salt was not pre-formed (Table 5, entry 6). This dramatic drop in conversion was surprising since if fluorine was transferring from the fluorinated alkaloid, pre-forming the active reagent should be beneficial to the reaction. Since we had previously demonstrated the reaction conversion to be extremely sensitive to the equivalents of NFSI employed, we next performed the reaction using a stoichiometric amount of pre-formed fluorinated alkaloid as well as an extra equivalent of NFSI (Scheme 17).



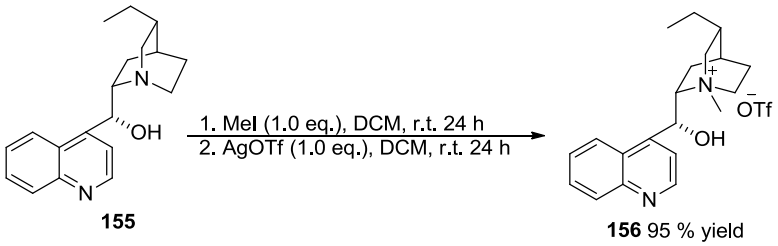
Scheme 17 – Fluorocyclization with pre-formed N-F reagent and excess NFSI

A significantly increased conversion and enantiomeric excess was observed for this reaction. In fact, the conversion obtained with excess NFSI was only slightly lower than that obtained without pre-mixing (Table 3, entry 1). These observations prompted us to consider the possibility of asymmetric fluorine transfer occurring not from the fluorinated alkaloid, but rather directly from NFSI. Although in contrast to other literature precedent, this pathway was also alluded to in the recent publication by Gouverneur and co-workers for reactions performed at low temperatures.[30]

We suggested that a chiral environment may be formed via associative complexation of the cinchona alkaloid with the substrate, perhaps through hydrogen bonding of the quinuclidine nitrogen with the pendent nucleophile. However, since fluorination of the alkaloid has been shown to be rapid and would prevent this hydrogen bonding, formation of a chiral environment by this fluorinated species should also be considered.

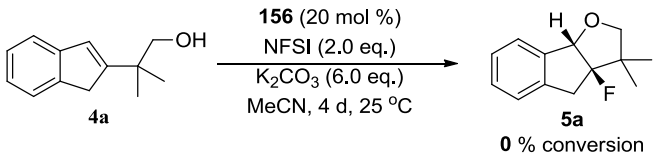
This proposal was investigated by employing a quaternised alkaloid, in order to remove the possibility of hydrogen bonding with the substrate. DHCD was employed as a probe, since we envisioned complications due to dimethylation of $(DHQ)_2PHAL$. We chose to *N*-methylate the alkaloid so as not to introduce excessive steric crowding around the quinuclidine core. The quaternised alkaloid was synthesised according to a modified literature procedure by addition of methyl iodide to DHCD in MeOH (Scheme 18).[31] After standing overnight, complete conversion to product was observed by mass spectrometry, with excellent

chemoselectivity for *N*-alkylation over *O*-alkylation. An anion transfer was then carried out to form the chloride salt, in order to avoid potential oxidation of the iodide ion by NFSI. This was achieved in 2 hours by addition of silver chloride to the quaternised alkaloid in water at 40 °C. The anion transfer was indicated by change in decomposition temperature from 115 °C to 160 °C.



Scheme 18 - Synthesis of methylated DHCD

As DHCD has been shown to be at its most effective when employed in a catalytic quantities, 20 mol % of methylated alkaloid was employed, in combination with 2.0 equivalents of NFSI (Scheme 19).

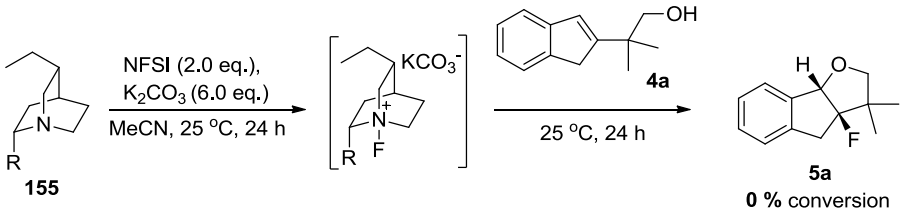


Scheme 19 - Reaction with methylated catalyst

After 4 days, no conversion to product was observed by ^{1}H NMR. Whilst any conversion to product would have indicated that the reaction is not mediated by a hydrogen bonded associative complex, no conversion could only indicate that an unblocked quinuclidine

nitrogen is essential for catalysis of the fluorocyclization reaction. Whether this is necessary due to the requirement of the nitrogen lone pair for hydrogen bonding, or whether it is crucial to the reaction that the nitrogen is fluorinated, was still undetermined.

It should be noted that, when $(DHQ)_2PHAL$ is combined with excess NFSI, both quinuclidine nitrogen atoms may undergo fluorination, thus inhibiting the potential for hydrogen bonding. Similarly, once fluorinated, the mono-alkaloid DHCD would be unable to engage in hydrogen bonding. If hydrogen bonding is important for the catalysed reaction, we proposed that pre-formed, fluorinated DHCD would be ineffective at mediating the reaction. We tested this suggestion by performing a reaction in which a stoichiometric amount of fluorinated DHCD was pre-formed by mixing with an excess of NFSI and stirring for 24 hours prior to substrate addition (Scheme 20).



Scheme 20 - Fluorocyclization with pre-formed N-F reagent and excess NFSI

After 24 hours, no conversion to product was observed, compared to a 13 % conversion when the fluorinated alkaloid is not pre-formed, therefore verifying our predication that the fluorinated alkaloid is ineffective at mediating the fluorocyclization. However, it should be remembered that the same reaction with $(DHQ)_2PHAL$ produced an excellent result, which could be explained by the higher reactivity of a bis-fluorinated species relative to a mono-fluorinated species. To further investigate the mechanism of the reaction with the

unprotected mono-alkaloid, again an NMR experiment was conducted to deduce the timescale of fluorination of the alkaloid. As opposed to $(DHQ)_2PHAL$, after stirring equal amounts of DHCD and NFSI for 5 minutes in deuterated acetonitrile, ^{19}F NMR indicated that only partial fluorination of the alkaloid had occurred. Fluorination was not complete after 30 minutes of stirring, but full transfer was observed within 24 hours (Figure 4). This indicated that rather than instant fluorination of the alkaloid, as had been assumed, the reaction with DHCD as a catalyst could in fact have non-fluorinated catalyst present for up to a day. We envisage that the reason for the much slower fluorination of DHCD is likely to be due to a problem with the extremely poor solubility of this specific alkaloid.

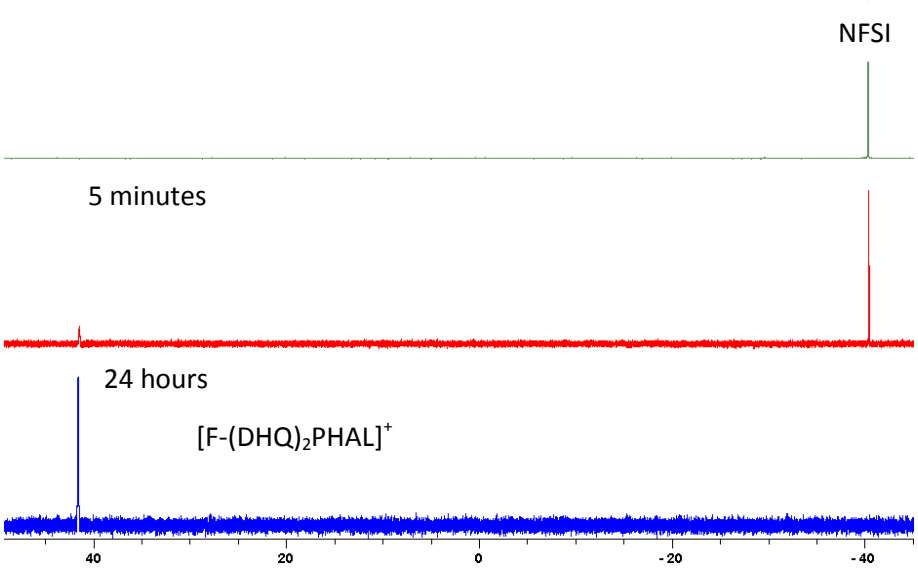


Figure 4 - NMR experiment indicating fluorination of $(DHQ)_2PHAL$

We believe that these findings provide considerable support for the direct transfer of fluorine from NFSI in a mono-alkaloid system, with a chiral environment provided by a hydrogen bonded associative complex of the alkaloid with the substrate. We propose that the importance of employing a large excess of NFSI could be due to making the reaction zero order in NFSI. The result obtained in Scheme 20 suggests that when complete fluorination of

the alkaloid has occurred, the DHCD mediated reaction will shut down. The success of DHCD at mediating the fluorocyclization can then be explained by the very slow fluorination of this alkaloid.

However, our findings support no firm conclusions for the bis-alkaloid (or capped mono-alkaloid) systems at this time. The fact that the reaction delivers broadly the same result whether the alkaloid is pre-mixed or not with 2 or more equivalents of NFSI suggests that bis-fluorinated alkaloids are capable of mediating the reaction, perhaps due to increased reactivity. The discrepancy in conversions when 1 or 2 equivalents of NFSI are employed with 20 mol % of $(DHQ)_2PHAL$ could be explained by the concentration of NFSI appearing in the rate equation and therefore benefiting from a rate acceleration. Therefore a fundamental change in mechanism from mono-alkaloids (association H-bond mechanism) to bis-alkaloids (bis-fluorinated reagent) is possible, which is accounted for by the speculated higher reactivity of a bis-fluorinated species. On the other hand, since both fluorine and transfer to the alkaloid and the reaction itself were found to be very fast, it is entirely feasible in an *in situ* reaction for the bis-alkaloid to be initially participating in an associative H-bond mechanism, before difluorination occurs. These two pathways could be complementary, with the same level of enantioselectivity being coincidental. Indeed, the fact that the stoichiometric reaction is successful with just 1 equivalent of NFSI indicated that either one quinuclidine was fluorinated on all the $(DHQ)_2PHAL$ or both quinuclidines were fluorinated on half the $(DHQ)_2PHAL$, or somewhere inbetween. In the first case, one quinuclidine would be available for association, with fluorine delivered from the other. In the second case, there would be an equilibrium between bis-fluorinated/non-fluorinated and mono-fluorinated, with fluorine delivered from the equilibrium amount of bis-fluorinated. Further investigations would be required to probe the mechanism further.

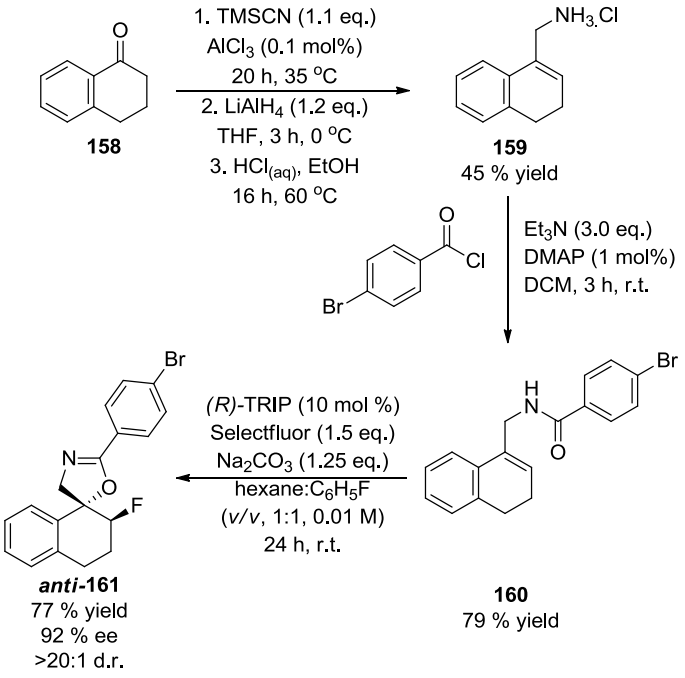
The only question remaining concerns the contrasting trend in conversions observed by increasing the loading of $(DHQ)_2PHAL$ or DHCD. As this conversion trend appears to be dependent on the presence or absence of a free hydroxyl moiety in the cinchona alkaloid, we envisage that dimerization of the unprotected mono-alkaloids, via hydrogen bonding of the quinuclidine nitrogen of one molecule with the hydroxyl moiety of another catalyst molecule, may be a possibility. The probability of homo-alkaloid complex formation would increase with increased alkaloid concentration, therefore reducing the amount of catalyst available to associate with the substrate and resulting in the poorer conversions observed.

5.2.4 Phase-transfer approach

Following mediocre success using cinchona alkaloids, we wished to explore the latest technique for asymmetric fluorination, which is by phase-transfer catalysis.[28] The proposed mechanism involves deprotonated chiral phosphate anions first replace the tetrafluoroborate counterions of Selectfluor to form a new chiral Selectfluor species, which is soluble in apolar solvents (see Chapter 4). The resultant solubilised fluorinating reagent can now react with the substrate to furnish the fluorinated product in good yields with excellent enantioselectivity. Upon fluorination a chiral phosphate is liberated which can then replace further tetrafluoroborate anions and can hence be employed in catalytic quantities. The attraction of this phase-transfer approach is that the racemic uncatalyzed background reaction is totally suppressed as the dicationic Selectfluor will be completely insoluble. This mechanism implies that as long as the fluorinating agent can be brought into solution, any substrate of sufficient reactivity could potentially undergo a reaction. Since we know that the carbocyclization substrates successfully react with Selectfluor in nitromethane, and are therefore sufficiently reactive, we deemed that this could be a viable method to achieve a novel asymmetric fluoro-carbocyclization.

5.2.4.1 Validation of literature results

The catalytic system was tested by validating a literature result reported by Toste for the fluorination of dihydronaphthalene **160** (Table 9). Before the control reaction could be performed, we needed to synthesise the starting material 4-bromo-*N*-((3,4-dihydronaphthalen-1-yl)methyl)benzamide **160**. This was achieved in a 2-step synthesis from 1-tetralone (Scheme 21). In the first step, TMSCN was first used to form the intermediate cyanohydrin, which was then reduced to the corresponding amine using $LiAlH_4$. Dehydration was accomplished using acid to furnish the required amine as hydrochloride salt. Finally, protection of the amine with the relevant benzoyl chloride afforded the desired amide in a good yield over the multi-step synthesis. The substrate was subjected to literature conditions using 10 mol % of (*R*)-TRIP to obtain the fluorocyclized product in comparable yields and ee to the reported value.

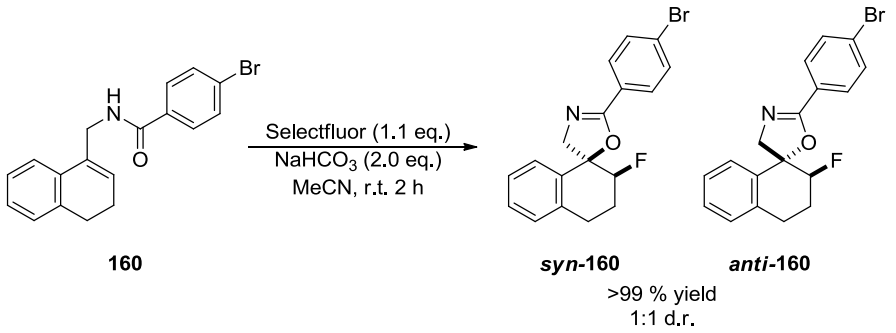


Scheme 21 - Synthesis of precursor for asymmetric fluorination followed by test reaction with (R)-TRIP

Reaction	Yield (%)[a]	ee (%)[b]	dr (%)[c]
Literature	84	93[d]	>20:1
Test	77	92	>20:1

Table 9 - Comparison of literature reaction with test reaction; [a] NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra; [b] Determined by chiral HPLC; [c] Determined from 19F NMR; [d] *(R)*-C_8TRIP

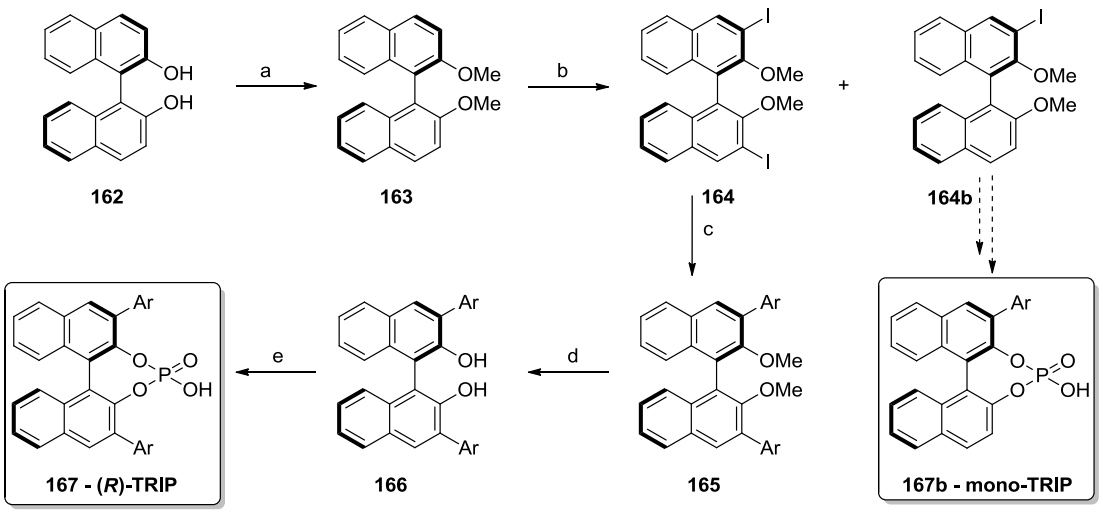
An interesting observation was made whilst performing this control reaction. When the reaction was run with a catalytic amount of (R)-TRIP present it very cleanly afforded the product in good yield with complete enantiosleectivity, with only one of the possible two diastereomers was formed. However, when the reaction was run without (*R*)-TRIP and in acetonitrile (required to solubilse Selectfluor) the product was recovered in a quantitative yield as a 1:1 mixture of diasteromers. This meant that the effect of the chiral anion was not just to control enantioslectivity but also to control diastereoselectivity.



Scheme 22 - Racemic control reaction in absence of catalyst

While the catalyst is commercially available and can be bought in, it is expensive to do so and thus we synthesised it from (*R*)-BINOL according to the procedure of Klussmann *et al.*, (Scheme 23).[32] In the first step the commercially available (*R*)-Binol was protected using methyl iodide and potassium carbonate. Iodination was achieved using *n*-butyl lithium

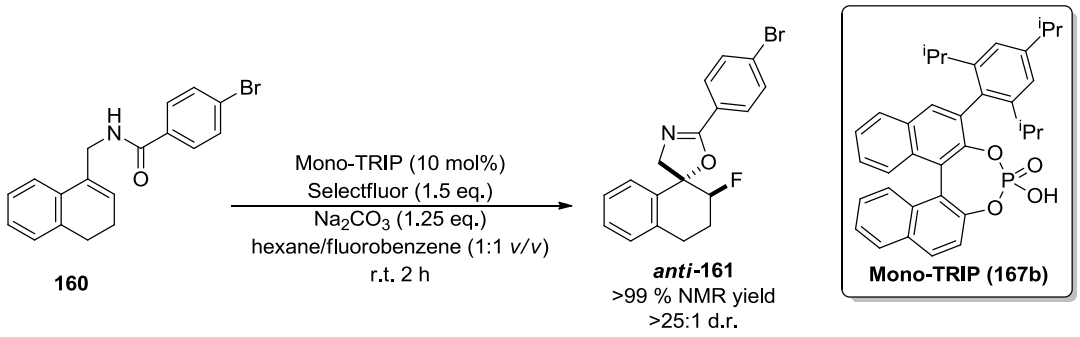
activated with TMEDA followed by quenching with iodine. However, the reaction was highly sensitive to the quality of TMEDA, with all but extremely pure samples stopping the reaction. Without the addition of TMEDA a significant amount of mono-iodinated compound was obtained. The dihalogenated compound was cross-coupled with the appropriate Grignard reagent (prepared by the reaction of the appropriate aryl bromide and magnesium in the usual way) using a catalytic amount of bis(triphenylphosphine)nickel(II) dichloride in refluxing ether. Following dimethylation using boron tribromide, the phosphoric acid was furnished by refluxing the intermediate dialcohol with phosphorous oxychloride.



Scheme 23 – Preparation of (*R*)-TRIP

Of further interest was the fluorocyclization of the dihydronaphthalene substrate mediated by the novel Mono-TRIP catalyst which was obtained as a side product in the synthesis of (*R*)-TRIP. The reaction was run in the same fluorobenzene/hexanes medium that Toste had used with (*R*)-C_8TRIP and whilst the catalyst is not enantiopure so no enantioenrichment was anticipated, we were intrigued to observe total diastereoselectivity. Using 3-fluoronitrobenzene as an internal NMR reference, the yield of the reaction was determined

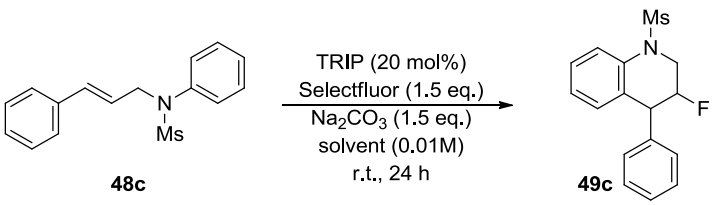
to be quantitative and the diastereoselectivity to be in excess of 25:1 in favour of the major diastereomer isolated from the equivalent reaction using (*R*)-TRIP. Whilst the reaction had been initially performed to identify whether the reaction was unique to the very bulky and hydrophobic (*R*)-TRIP catalyst or could be achieved using a somewhat simpler catalyst, it demonstrated that the diastereoselectivity of the reaction could be controlled by recemic phase-transfer catalysts.



Scheme 24 - Diastereoselective Fluorocyclization of dihydronaphthalene using Mono-TRIP

5.2.4.2 Asymmetric fluorocyclization by phase-transfer

With the literature results validated we next chose a test substrate on which to optimise an asymmetric reaction. We elected to use an acyclic substrate as this would simultaneously provide date on both the diastereoselectivity and enantioselectivity of the reaction. Also, the sulfonamide substrate was chosen as it was sufficiently polar to allow separation of the fluorocyclized product by chiral stationary phase HPLC. The general reaction is presented in Table 10 below.



Entry	Catalyst	Solvent	Yield	d.r.
A	Mono-TRIP	Hexane	0	-
B	Mono-TRIP	Hexane/benzene (1:1)	0	-
C	(*R*)-TRIP	Hexane	0	-
D	(*R*)-TRIP	Hexane/benzene (1:1)	0	-

Table 10 - Attempted phase-transfer catalyzed fluorocyclization of 3n

It seems that, when in a polar solvent that is capable of solubilising the parent fluorinating reagent, the reaction works very well but under phase transfer conditions the reaction simply does not occur. This was somewhat counterintuitive based on the mechanism proposed and it led us to scrutinise the mechanism further to see if there was another possibility. In Toste's later report he eluded to a possible transition state that would explain the observed enantioselectivity in which hydrogen-bonding of the phosphate counterion to the substrate N-H bond was the crucial step as outlined in the figure below.

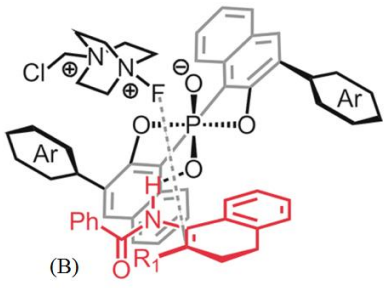
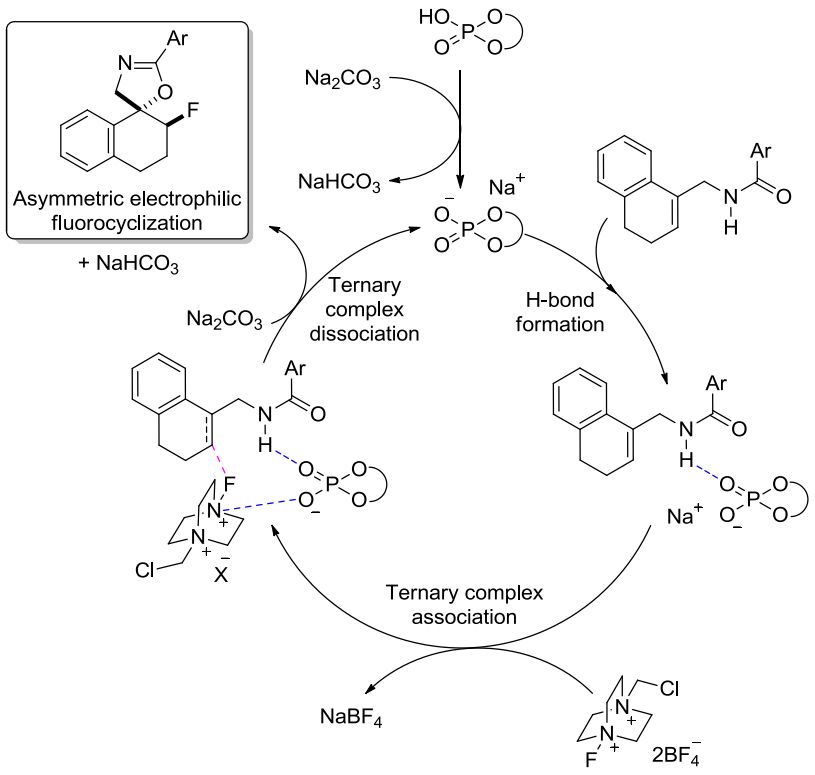


Figure 5 - Proposed transition state for fluorination of enamides

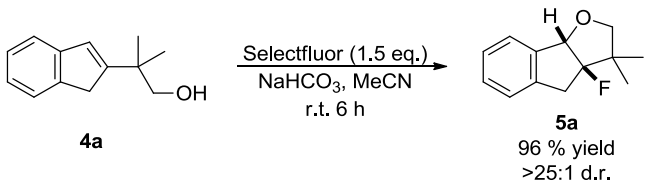
The critical difference between the enamide and dihydronaphthalene substrates of Toste and our own is the lack of an acidic N-H bond on the substrate close to the reacting site. Since under the reaction conditions dihydronaphthalene substrates bearing pendent amides were sufficiently reactive, we propose that it must be the lack of H-bonding site that explains

the lack of reactivity in our system. This tentatively led us to propose a slight variation of the mechanism that was described by Toste. Essentially, we feel the important step is an aggregation of the chiral phosphate to the acidic proton. This chiral associative complex then attracts a Selectfluor dication by ionic interactions and thus brings it into solution by the displacement of a tetrafluoroborate anion. Once fluorination has taken place, there is no longer a proton for which the phosphate to bind and the Selectfluor has lost a positive charge which causes the ternary complex to dissociate. The phosphate is catalytic in that it is then able to find a new substrate to bind to and mediate its fluorination. This postulated alternative mechanism is summarised in Scheme 25.



Scheme 25 - Proposed alternative mechanism for phase-transfer asymmetric fluorination

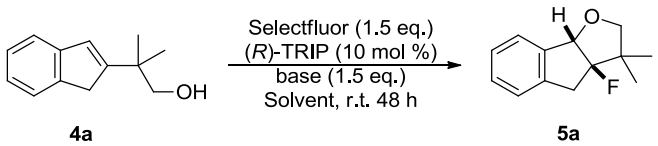
If this is the case then we reasoned that changing the pendent nucleophile to one that is capable of hydrogen bonding would make the reaction successful. This would provide evidence that the hydrogen-bonding of the substrate to the chiral anion is not simply necessary for enantioselectivity but also, crucially, for reactivity. We noticed that the pKa of the amide N-H is not too dissimilar from that of an alcohol, with the later being the less acidic of the two and therefore should be expected to have a weaker H-bond. Nevertheless, we would expect at least some effect from the possibility of forming a hydrogen bond. We chose the same indene system with a pendent alcohol nucleophile that previous optimization reactions had been run to achieve an asymmetric fluorocyclization. It was already known that the substrate reacted very efficiently with Selectfluor in acetonitrile and so we set out to optimise the reaction under phase-transfer conditions.



4a **5a**
96 % yield
>25:1 d.r.

Scheme 26 - Fluoroetherification of indene bearing pendent alcohol using Selectfluor

Using the same indene as the model substrate we explored solvent, concentration, base and temperature in an effort to achieve an asymmetric fluorocyclization under phase-transfer conditions. In a preliminary control experiment, the alcohol was reacted with Selectfluor in benzene in the presence of sodium carbonate without the addition of the phosphate (Table 11, entry 1). Gratifyingly, there was no reaction observed after 2 days stirring at room temperature. This confirmed that there would not be an uncatalyzed background that we needed to be concerned with.



4a **5a**

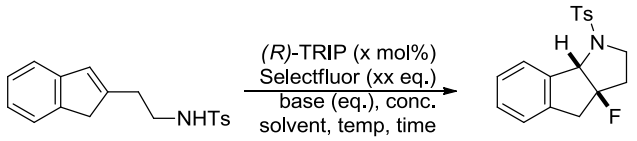
Entry	Solvent	Conc.	Base	Temp.	Yield (%)[a]	ee (%)[b]
1[c]	Benzene	0.01M	Na_2CO_3	r.t.	0	-
2	Benzene	0.01M	Na_2CO_3	r.t.	17	14
3	Toluene	0.01M	Na_2CO_3	r.t.	12	14
4	Benzene/hexane (1:1)	0.01M	Na_2CO_3	r.t.	20	14
5	Hexane	0.01M	Na_2CO_3	r.t.	28	14
6	Hexane/^{i}PrOH (9:1)	0.01M	Na_2CO_3	r.t.	<5	ND
7	Hexane	0.01M	$NaHCO_3$	r.t.	92	15
8	Hexane	0.01M	K_2CO_3	r.t.	17	6
9	Hexane	0.1M	Na_2CO_3	r.t.	85	0
10	Hexane	0.01M	Na_2CO_3	50 °C	35	16
11	Hexane	0.005M	Na_2CO_3	r.t.	17	28
12	Hexane	0.05M	Na_2CO_3	r.t.	92	12
13	Hexane	0.01M	Cs_2CO_3	r.t.	<5	ND
14	Hexane	0.005M	$NaHCO_3$	r.t.	73	14
15	Hexane	0.01M	Proton sponge	r.t.	<5	ND

Table 11 - Optimisation of asymmetric fluorocyclization using (R)-TRIP; [a] determined by ^{1}H NMR; [b] determined by stationary phase chiral HPLC; [c] in absence of *(R)*-TRIP

The solvent had essentially no effect on the determined ee, with a constant value of 14 %. However, as the reaction medium became more polar, the yield was diminished, culminating in no detected reaction when 10 % *iso*-propanol was added (entry 6). The least polar solvent, hexane, gave the best yield (entry 5) and so all further screening was performed in this solvent. Changing the base from Na_2CO_3 to the slightly less basic $NaHCO_3$ had a dramatic effect on the reaction (entry 7). The yield was a much improved 77 % but, to our disappointment, the level of enantioselectivity was not improved. Further changing the base to K_2CO_3 had a significant but negative effect with both a drop in yield and ee (entry 8). The

reaction was found to be highly concentration dependent as increasing the concentration by a factor of 10 led to a large increase in yield (entry 9). Unfortunately, this rate acceleration was also accompanied by a total loss of enantioselectivity. Temperature had little effect on the reaction as when it was ran at 50 °C the yield and ee were very comparable to when the reaction was performed at room temperature (entries 10 and 5 respectively). It was encouraging to observe an improvement in ee when the reaction was run under very dilute conditions with sodium carbonate as base (entry 11), however, this was accompanied by a very poor yield. Unfortunately, even the best conditions were not sufficiently successful from a synthetic standpoint.

A different substrate class was next investigated to examine if altering the acidity of the pendent nucleophile has a positive influence on the reaction. We elected to use sulfonamide **4l** as the model substrate as it is more acidic than an alcohol, and should therefore form a stronger hydrogen-bond, and has much greater steric bulk at the nucleophilic site to aid with enantio-differentiation. The results of these optimization studies are presented in Table 12.



4l **5l**

Entry	Solvent	Conc.	Base	Temp.	N-F$^+$ reagent	Additive	Yield (%)	ee (%)
1[a]	C_6H_6	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	0	-
2	C_6H_6	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	9	19
3	C_6H_{14}	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	10	20
4	C_6H_6/C_6H_{14} 1:1	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	34	18
5	C_6H_5F	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	7	20
6	$C_6H_{14}/C_6H_5CH_3$ 1:1	0.05M	$NaHCO_3$	r.t.	Selectfluor	-	36	20

7	C_6H_{14}/C_6H_5Me 1:1	0.01M	Na_2CO_3	r.t.	Selectfluor	-	39	12
8	C_6H_{14}/C_6H_5Me 1:1	0.01M	$NaHCO_3$	r.t.	NFCPT	-	80	0
9	Et_2O	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	<5	-
10	DCM	0.01M	$NaHCO_3$	r.t.	Selectfluor	-	<5	-
11	**C_6H_{14}/C_6H_5Me 2:1**	**0.05M**	**$NaHCO_3$**	**r.t.**	**Selectfluor**	**-**	**49**	**19**
12	C_6H_{14}/C_6H_5Me 1:2	0.05M	$NaHCO_3$	r.t.	Selectfluor	-	68	13
13	C_6H_{14}/C_6H_5Me 1:1	0.05M	$NaHCO_3$	r.t.	Selectfluor	3 ÅMS	<5	ND
14	C_6H_{14}/C_6H_5Me 1:1	0.05M	NaH_2PO_4	r.t.	Selectfluor	3 ÅMS	<5	ND
15	C_6H_{14}/C_6H_5Me 1:1	0.05M	K_2HPO_4	r.t.	Selectfluor	3 ÅMS	29	13
16	C_6H_{14}/C_6H_5Me 1:1	0.05M	K_3PO_4	r.t.	Selectfluor	3 ÅMS	<5	ND
17	C_6H_{14}/C_6H_5Me 1:1	0.05M	Imidazole	r.t.	Selectfluor	3 ÅMS	<5	ND
18	C_6H_{14}/C_6H_5Me 1:1	0.05M	CMD	r.t.	Selectfluor	3 ÅMS	28	0
19	C_6H_{14}/C_6H_5Me 2:1	0.05M	$NaHCO_3$	r.t.	Selectfluor	1% H_2O (*v/v*)	29	18

Table 12 - Optimisation of asymmetric fluorocyclization using (R)-TRIP; [a] Control reaction run in absence of (R)-TRIP

Optimization studies on the sulfonamide substrates presented a problem which was not encountered with the alcohol substrate. By introducing a sulfonamide motif, the inherent solubility of the substrate dramatically reduces. We propose that this accounts for the general poor reactivity, especially when using neat hexanes (entry 3). As with the study on the alcohol, we found that performing the reactions in the more solubilising aromatic solvents was detrimental and so an arene/hexane solvent mix was the compromise. The

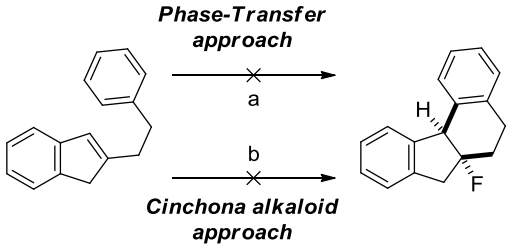
general trend was that of a slightly higher enantioselectivity with respect to the alcohol when using the tosyl protected amine. Of significant note was the importance that water seemed to have on the reaction. Solvents were used from the bottle, without pre-drying and it was observed that when molecular sieves were added a significant detrimental effect resulted (entry 11 vs 13). This was a surprising result as we would have anticipated that water would disrupt the necessary hydrogen-bonding required for the reaction to proceed. Unfortunately, we found that the addition of 1 % of water could not further improve the reaction and it was, therefore, concluded that the presence of a trace of moisture was very important for the reaction.

Whilst our studies did not reveal a synthetically useful procedure for asymmetric fluorocyclization they did confirm our prediction of H-bond requirement. The small but increased enantioselectivity using the more acidic sulfonamide substrate supports this hypothesis. We decided to return to the carbocyclization system and investigate alternative methods to achieve reactivity.

5.3 Asymmetric fluoro-carbocyclization

Attempts to apply the chiral counter-ion methodology of Toste and co-workers using a catalytic amount of chiral phosphate with Selectfluor in a non-polar solvent under phase-transfer conditions were unsuccessful, with no product detected. We postulate that this is either because there is no hydrogen-bonding site on the substrate to co-ordinate to the phosphate counter-ion or that a polar solvent is required to facilitate a fluoro-cyclization. We therefore quickly determined that a chiral reagent approach was necessary and turned our attention to previously described methods. Following our success utilizing cinchona

alkaloids for the asymmetric fluorocyclization of prochiral indole and indene substrates, we attempted to translate these conditions to our carbocyclization reaction.



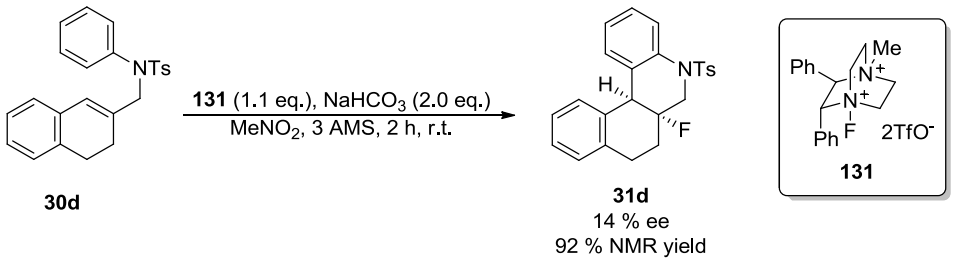
Scheme 27 - Unsuccessful asymmetric fluoro-carbocyclization; [a] (*R*)-TRIP (10 mol %), Selectfluor (1.5 eq.), Na_2CO_3 (1.25 eq.), hexane (0.05 M), 48 h, r.t. [b] $(DHQ)_2PHAL$ (100 mol %), NFSI (1.2 eq.), K_2CO_3 (6.0 eq.), MeCN, 16 h, r.t.

We formed the chiral fluorinating reagent *in situ* by premixing the bis-alkaloid $(DHQ)_2PHAL$ with a stoichiometric amount of achiral fluorinating reagent in the presence of a large excess of potassium carbonate according to the usual procedure.[11] Unfortunately, addition of the substrate to the solution containing the chiral reagent resulted in no formation of the fluoro-carbocyclized product, with recovery of starting material. We concluded that with our system we had found the limit for the reactivity of the current state-of-the-art in the literature. The solution we proposed was to depart from the literature and develop a new class of chiral fluorinating reagents that exhibited a similar reactivity profile to Selectfluor or the *N*-fluoro-2,6-dichloropyridinium triflate we had used for the development of the racemic series of the reaction.

5.3.1 Preliminary results

Preliminary investigations using the 2,3-diphenyl substituted chiral Selectfluor developed in Chapter 4 concerned the fluorocyclization of dihydronaphthalene **30d**. The same conditions were employed as for the racemic reaction, since nitromethane was found to be an effective

solvent for Selectfluor in the original optimisation. To our delight, we observed excellent reactivity, where none was found with other asymmetric systems, to achieve a 92 % NMR yield. We were also excited to obtain the product in a 14 % ee. Though low in itself, importantly it validated that asymmetric fluoro-carbocyclization was indeed possible using our novel fluorinating reagents. To demonstrate effectiveness of chiral Selectfluor at promoting the reaction, Figure 7 illustrates how clean the reaction is. This is the crude ^{19}F NMR, which contains just two signals arising from the internal standard and the fluorinated product. Of particular note, is the absence of any small peaks in the aromatic region, thus demonstrating the regioselectivity of the reagent. The chemical shift of the product at -140.0 ppm is characteristic of the compound by comparing to the reference compound prepared in Chapter 2. Finally, there is only one product peak, indicating that the perfect diastereoselectivity of the cyclization reaction was maintained.



30d

31d
14 % ee
92 % NMR yield

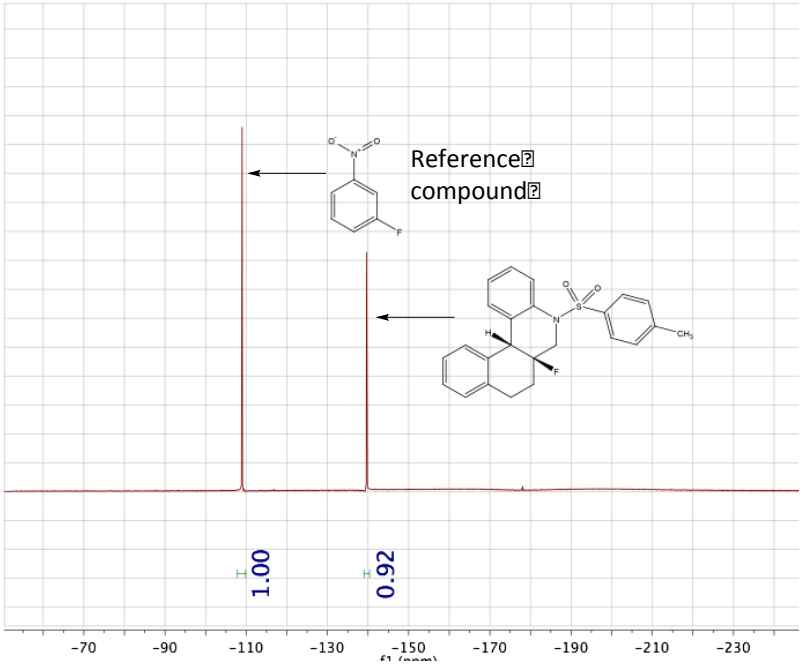
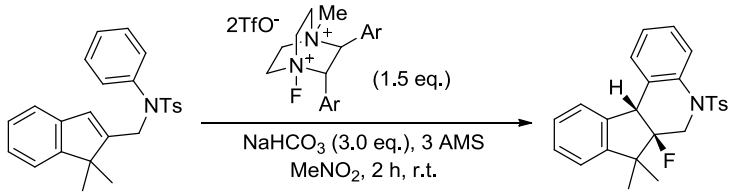


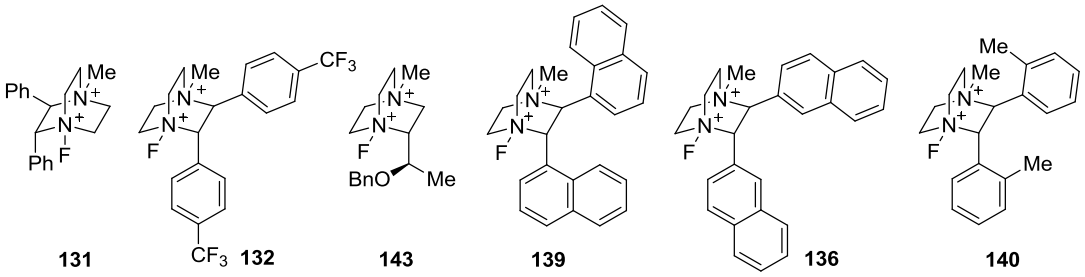
Figure 6 - ^{19}F NMR Spectra of fluoro-carbocyclised product referenced to 1-fluoro-3-nitrobenzene

5.3.2 Optimisation studies

With confirmation that the reaction had the potential to succeed asymmetrically, we decided to optimise the reaction using a substrate containing a gem-dimethyl group as we imagined that sterics could be an important factor in increasing facial selectivity. This speculation was based on the observation that in the heterocyclization reaction a substantial improvement in ee was observed when a gem-dimethyl group was present (46 % ee vs 19 % ee, Section 5.2). Optimisation studies were carried out either by *in situ* formation or direct use of the isolated fluorinating reagent. From the screening we found that the 2,3-disubstituted bis-para-CF_3 chiral Selectfluor **132** gave the best result with 60% ee and over 95% yield (Table 2, entry 2). The 2,3-disubstituted diphenyl and dinaphthyl chiral selectfluors showed similar reactivities with ee values between 32-36% (Table 2, entries 1, 4 and 7).



39a **40a**



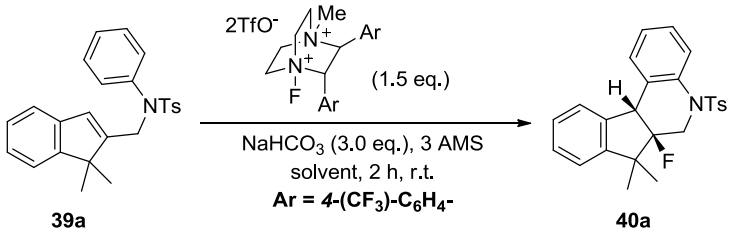
131 **132** **143** **139** **136** **140**

Entry	Chiral Selectfluor	Solvent	Base	Temp.	NMR yield (%)	ee (%)	Conc. (**39a**)
1	**(*R*,*R*)-131**	$MeNO_2$	$NaHCO_3$	r.t	63	32	5 mg/mL
2	**(*S*,*S*)-132**	**$MeNO_2$**	**$NaHCO_3$**	**r.t**	**>95**	**60**	**5 mg/mL**
3	**(*R*)-143**	$MeNO_2$	$NaHCO_3$	r.t	83	10	5 mg/mL
4	**(*S*,*S*)-139**	$MeNO_2$	$NaHCO_3$	r.t	18	32	5 mg/mL
5	**(*S*,*S*)-136**	$MeNO_2$	$NaHCO_3$	r.t	69	36	5 mg/mL
6	**(*S*,*S*)-140**	$MeNO_2$	$NaHCO_3$	r.t	44	55	5 mg/mL

Table 13 - Optimisation of chiral Selectfluors; triflate counterions omitted for clarity

Reactions with Selectfluor are normally only carried out in acetonitrile, or as we showed nitromethane, due to solubility issues. However, we postulated that we had increased the solubility of the fluorinating reagents by adding chirality. We therefore undertook re-optimisation of the reaction conditions to determine whether it would improve the enantioselectivities (Table 14). As we found that the *in situ* method is equally good as the isolated fluorinated reagent, we decided to proceed with the former method. Pleasingly, changing the solvent system improved the enantiomeric excess to values as high as 81% using THF as the solvent albeit at the cost in yield (Table 14, entry 4). 1,4-Dioxane was found to be the solvent of choice as it gave a stereoselectivity of 74% with a quantitative NMR yield (entry 5). We then went on to test different bases but found them to make little difference

to the ee and also decreased the yield of cyclised product (entries 9-12). Performing the reaction at 10°C and 50°C hardly changed the results of the reaction (entries 13-14) and further reduction in the temperature was not possible due to the melting point of the solvent. Finally, the reaction was also performed at different concentrations (entries 15-16). Despite an increase in enantioselectivity, the yield decreased to below 50%.

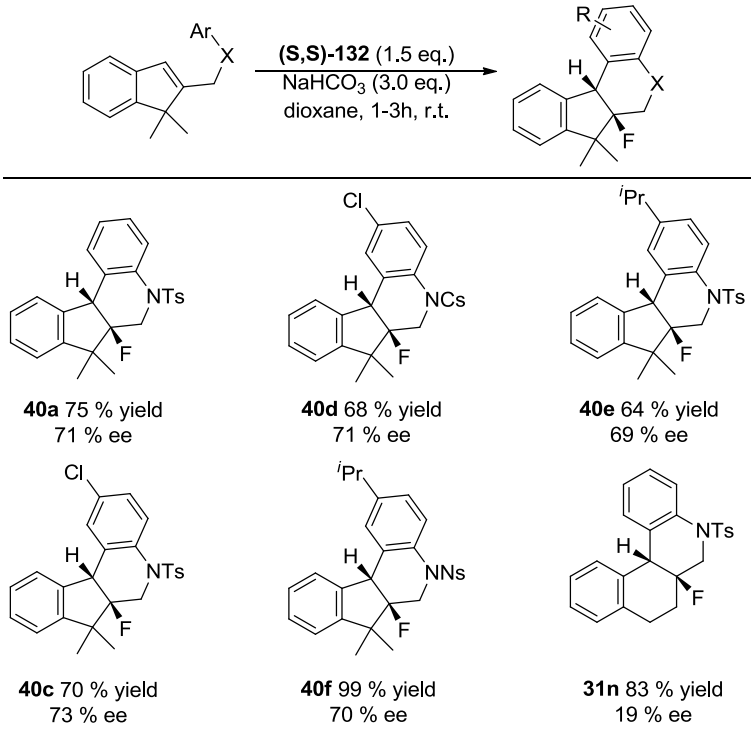


Entry	Chiral selectfluor	Solvent	Base	Temp.	NMR yield (%)	ee (%)	Conc.
1	6f	$MeNO_2$	$NaHCO_3$	r.t	>95	60	5 mg/mL
2	6f	DCM	$NaHCO_3$	r.t	14	77	5 mg/mL
3	6f	DCE	$NaHCO_3$	r.t	59	74	5 mg/mL
4	6f	THF	$NaHCO_3$	r.t	22	81	5 mg/mL
5	**6f**	**1,4-dioxane**	**$NaHCO_3$**	**r.t**	**>95**	**74**	**5 mg/mL**
6	6f	DMF	$NaHCO_3$	r.t	N/A	N/A	5 mg/mL
7	6f	Acetone	$NaHCO_3$	r.t	14	72	5 mg/mL
8	6f	MeCN	$NaHCO_3$	r.t	47	52	5 mg/mL
9	6f	1,4-dioxane	Na_2CO_3	r.t	62	76	5 mg/mL
10	6f	1,4-dioxane	K_2CO_3	r.t	39	76	5 mg/mL
11	6f	1,4-dioxane	Cs_2CO_3	r.t	23	79	5 mg/mL
12	6f	1,4-dioxane	No base	r.t	45	74	5 mg/mL
13	6f	1,4-dioxane	$NaHCO_3$	10	47	74	5 mg/mL
14	6f	1,4-dioxane	$NaHCO_3$	50	46	74	5 mg/mL
15	6f	1,4-dioxane	$NaHCO_3$	r.t	13	80	1 mg/mL
16	6f	1,4-dioxane	$NaHCO_3$	r.t	48	80	10 mg/mL

Table 14 - Further optimisation of fluorocyclisation reaction

5.3.3 Isolation of non-racemic fluoro-carbocyclized products

With the optimised conditions in hand we proceeded to isolate a range of carbocyclized products using **132** as the chiral fluorine source. The reaction was tolerant of various groups on the arene nucleophile, delivering the products in very good yields and high enantiomeric excesses. The electronics of the nucleophile could also be tuned by varying the sulfonyl protection of the aniline. Even the highly electron withdrawing nosyl group reacted smoothly to furnish the cyclized compound. Inclusion of gem-dimethyl functionality was demonstrated to be essential for achieving high levels of stereoselectivity with **31n** delivering a low enantiomeric excess.



Scheme 28 - Isolated yields. Cs = 4-chlorobenzenesulfonyl; Ns = 4-nitrobenzenesulfonyl

5.3.4 Determination of absolute configuration

The relative stereochemistry was readily assigned by comparison of the $^{3}J_{H\text{-}F}$ coupling constants with those obtained in the racemic series (Chapter 2). It was previously established that the products were formed with a syn relationship of the hydrogen and fluorine at the ring junction by obtaining x-ray crystallographic structures. In order to determine the absolute stereochemistry we attempted to grow crystals of the asymmetric fluorocyclized compounds. The first crystal analysed was **40c**, which unfortunately was found to have crystallized as its racemate, due to the sample not being enantiopure. In fact, the difficulty we experienced in growing suitable crystals is likely a consequence of the cyclized compounds preferring to form a racemic crystal, which is difficult due to the enantio-enrichment. Fortunately, we were able to obtain a single crystal of **40a**, which was enantiopure. The x-ray structure revealed the absolute stereochemistry to be (*R*,*R*) as illustrated in Figure 9.

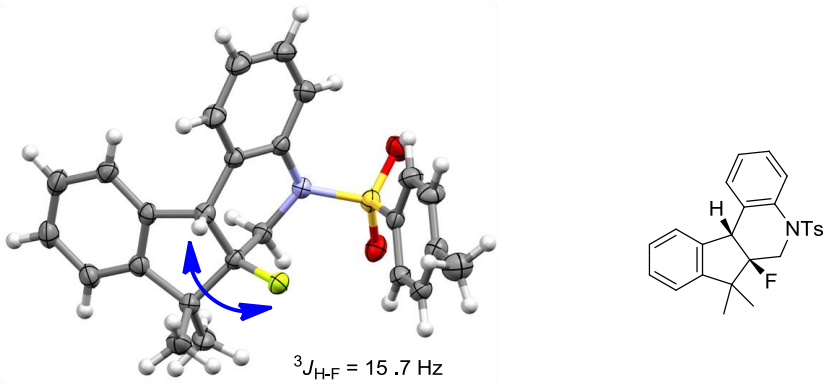


Figure 7 - Structure of 12a Confirming Absolute Stereochemistry

In order to confirm we had used the major enantiomer for structure determination we performed a single crystal chiral HPLC. Injecting the crystal into the HPLC revealed that the product was the major enantiomer. Hence we can conclude that the absolute

stereochemistry for **40a** is (6aR,11bR). The two spectra below depict the racemic reference (top) and the single crystal analysis (bottom).

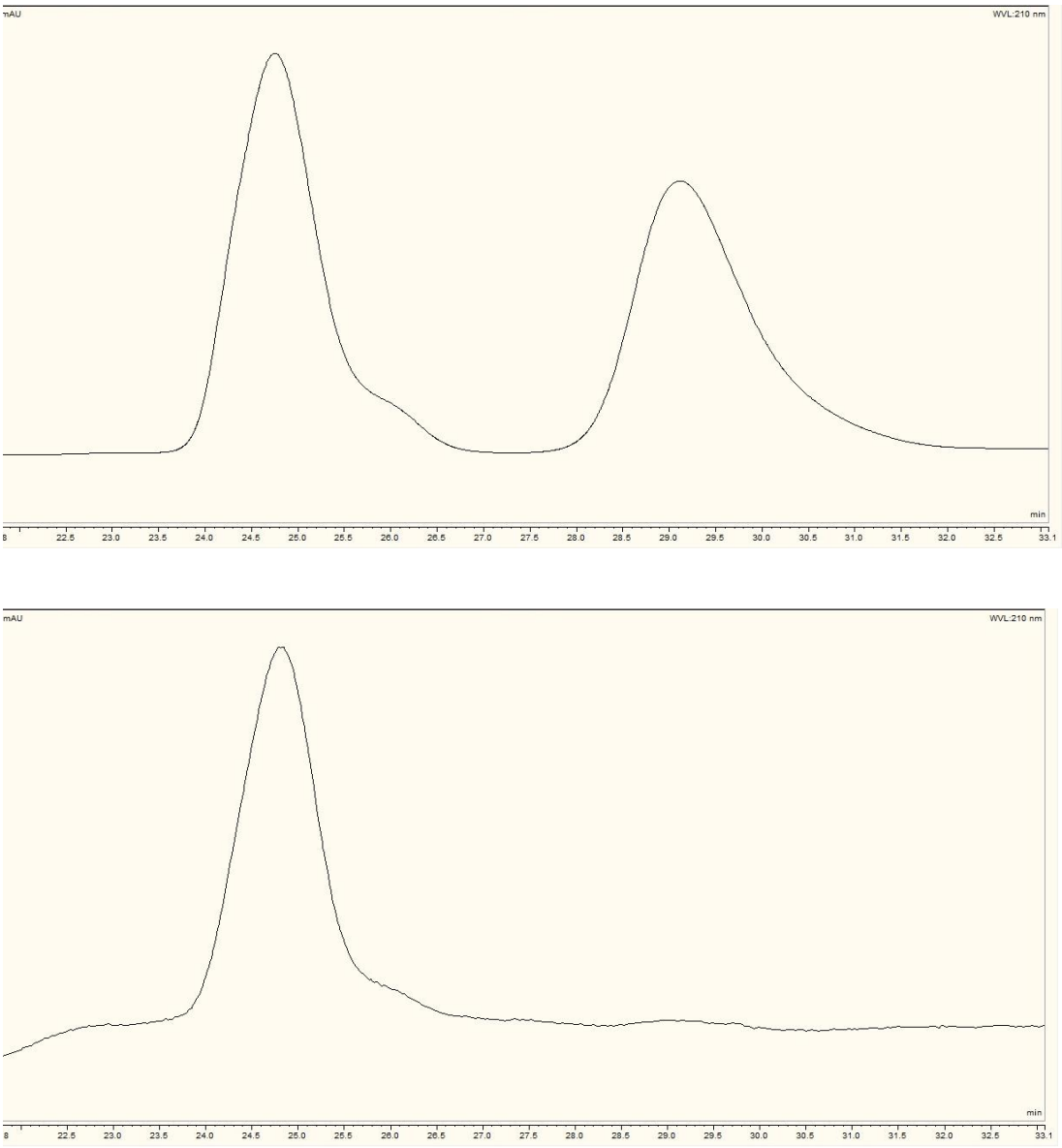
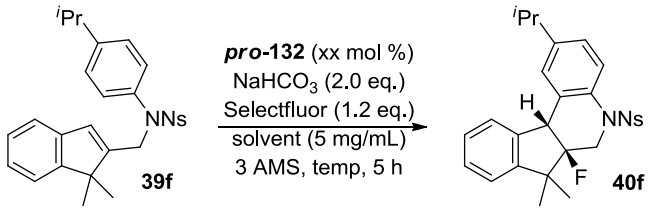


Figure 8 – HPLC traces of **40a**; top) racemic reference of **40a**, bottom) spectrum of single crystal of **(*R,R*)-40a**

5.3.5 Catalytic chiral Selectfluor

Finally, we investigated whether the reaction could be translated to a catalytic setting. Of course, the high molecular weight of the chiral Selectfluor reagents is somewhat prohibitive to their use and so development of a sub-stoichiometric reaction would be a significant advance. Taking inspiration from the phase-transfer work by Toste and co-workers[26] we considered the alternative approach. Instead of employing a chiral anion to bring the fluorine source into solution, we could use a chiral cation phase transfer reagent. Capitalising on the increased solubility of the chiral Selectfluor reagents, we proposed that we could find a solvent in which Selectfluor was insoluble but the chiral Selectfluor was soluble. Then, fluorine could be transferred to the catalyst, with the uncatalyzed background reaction being suppressed. We embarked on a short optimization study, seeking to take advantage of this solubility difference. Unfortunately, satisfactory conversion or selectivity could not be obtained, with only the highly solubilising nitromethane allowing an appreciable reaction. Moreover, of the small conversions that were detected, there was very poor selectivity, suggesting that the background Selectfluor reaction was essentially as competitive as the catalyzed reaction.

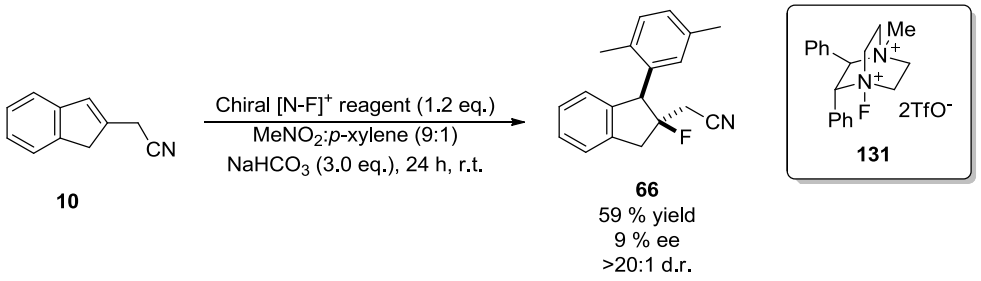


Entry	Solvent	Cat. mol %	Temp.	SM %[a]	Yield %[a]	ee %[b]
1	$MeNO_2$	25	20	31	27	10
2	Dioxane	25	20	84	<5	6
3	Dioxane	10	20	83	<5	7
4	DCE	25	20	77	<5	8

Table 15 - Catalytic asymmetric fluoro-carbocyclization reaction development; General conditions: 1h (7.5 mg), *pro*-**132** (xx mol %), solvent (1.5 mL), 3 ÅMS, $NaHCO_3$ (2.0 eq.), Selectfluor (1.2 eq.), 5 h; [a] ^1H NMR yield using 1-fluoro-3-nitrobenzene as an internal reference [b] calculated using chiral HPLC

5.4 Asymmetric fluoro-arylation

We also investigated the use of chiral fluorinating reagents for the fluoro-arylation reaction developed previously. Indene **10** was reacted with the prototype chiral Selectfluor reagent **(*R*,*R*)-131** under the optimised conditions of fluoro-arylation.



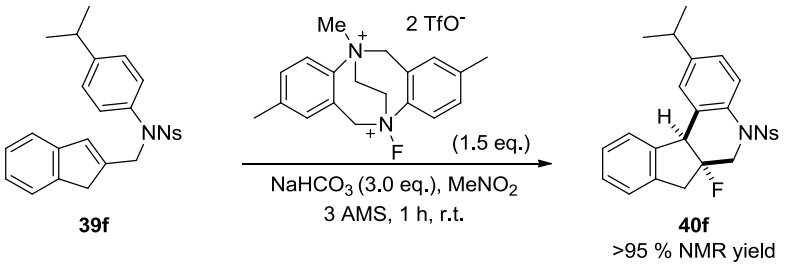
Scheme 29 - Asymmetric fluorination using chiral Selectfluor **131**

As an initial test reaction with these chiral Selectfluor derivatives, the reaction was pleasing as an ee was observed and a reasonable yield of 58 % was obtained. It should be noted that no report of the use of chiral fluorinating reagents of this class with their superior reactivity exist in the literature. Whilst the initial challenge of sufficient reactivity has been met, the reagent needs to be far more structurally complex to impart satisfactory enantioselectivity.

5.5 Tröger's base derived reagents

Finally, we were interested to perform some preliminary investigations using the Tröger's base type reagents that were developed in Chapter 4. We decided to study the reagent for its potential in asymmetric fluoro-carbocyclization by comparing it to the results obtained by the chiral Selectfluor type reagents. We first took the racemic reagent, which was prepared by an *in situ* fluorine transfer from *N*-fluoro-pentachloropyridinium triflate and validated its reactivity using the standard conditions for fluoro-carbocyclization developed in Chapter 2. Owing to the suspected high reactivity of this type of reagent we elected to use the most

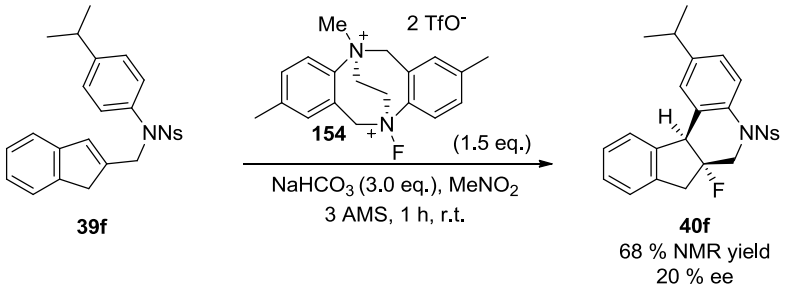
electron poor substrate which we had developed which was *4*-nitrobenzenesulfonyl protected aniline **39f**. We were delighted to observe excellent reactivity, delivering the product in excellent yield as assessed by ^{1}H NMR using 1-fluoro-3-nitrobenzene as an internal standard.



Scheme 30 – Racemic fluoro-carbocyclization of **39f** using Tröger's base type reagent; *Ns = 4-nitrobenzenesulfonyl*

Having determined this new class of reagents as suitable candidates for fluoro-carbocyclization we proceeded to investigate the chiral reagent to assess enantiocontrol. The results obtained from this preliminary study were promising, considering the structural simplicity of the reagent. The yield of the reaction was reasonable, considering the less than complete fluorine transfer to the pro- reagent. It is important to note that NMR studies of the *in situ* formed reagent confirmed the absence of unreacted *N*-fluoro-pentachloropyridinium triflate, thus suppressing background fluorination. The ee obtained was low, however, the library of chiral Selectfluors delivered vastly different results, providing encouragement that structural analogues of Tröger's base might be more fruitful. Indeed, the addition of a *p*-CF_3 group on the chiral Selectfluor was enough to increase the ee from 32 % to 60 %. Also, the speculated high reactivity of the reagent may indicate that a different class of lower reactivity substrates may be more appropriate to maximise the enantioselectivity. The absolute configuration of the product was assigned by comparison of

the results with those obtained using chiral Selectfluor, which were determined by single crystal X-ray analysis.



Scheme 31 – Asymmetric fluoro-carbocyclization of **39f** using Tröger's base derived reagent

We were unable to obtain an X-ray structure of the fluorinated Tröger's base reagent, however the structure of the methylated precursor is known and closely matches the molecular modelled (MM2) structure of the fluorinated derivative depicted in Figure 9. Considerations of such models could be helpful in designing future analogues of this reagent, by suggesting suitable sites for functionalization. It would seem reasonable to begin by investigating the substituents on the aromatic rings to provide a bias towards facial approach of the substrate.

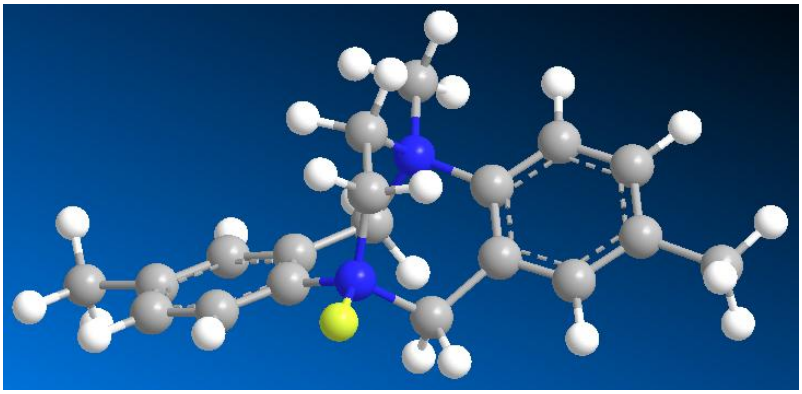


Figure 9 – Molecular modelled (MM2) structure of **154**

5.6 Conclusion

In conclusion, we have successfully developed novel asymmetric fluorocyclization methodology using indene and dihydronaphthalene substrates. We began by exploring indenes bearing pendant alcohol nucleophiles to initially simplify the ultimate goal of asymmetric fluoro-carbocyclization. This more reactive class of substrates was found to be sufficiently reactive with cinchona alkaloids derived asymmetric fluorinating reagents, which are the current state-of-the-art for chiral reagent driven asymmetric fluorination. Following mediocre results in both stoichiometric and catalytic modes, we performed extensive mechanistic work to shine light on a possible reaction mechanism. We also examined a recently reported chiral phase-transfer protocol for asymmetric fluorination to investigate its possible use in our reaction. Whilst the results obtained were generally poor it prompted us to suggest an alternative reaction pathway to that described in the literature. However, when we translated two approaches to the carbocyclization substrates we found a complete lack of reactivity and consequently we were focussed to depart from literature methods. This class of substrates offered the perfect testing ground for the library of chiral Selectfluors developed in Chapter 4, which were developed to be a more reactive class of reagents. To our delight the reactivity problem was solved, delivering excellent yields in all cases. Finally, enantioselectivity was found to be rather substrate dependant, as is so often the case in asymmetric fluorination, delivering the best results when a gem-dimethyl group was present on the indene substrate. For completeness, we were pleased to determine the absolute stereochemistry of the products by means of x-ray crystallography. An extension to the project that we looked at very briefly was the use of chiral Selectfluor in catalytic amounts. Whilst our preliminary data was unsatisfactory, this would be a valuable future area of research. Indeed, a catalytic mode would answer the main criticism of a reagent driven process which is the requirement for a stoichiometric amount of expensive chiral reagent. We concluded the chapter by briefly exploring Tröger's base derived chiral

fluorinating reagents. The initial results obtained were successful in that excellent yields were observed and whilst the ee values were low, they did validate the potential of this novel class of reagents. Much more research would be needed in order to determine the possibilities of such reagents, with both structural variation and substrate scope yet to be explored. It is likely that the high reactivity of this class of reagents would favour the use of substrates of lower reactivity, therefore complementing the chiral Selectfluor reagents and providing a spectrum of chiral fluorinating reagents as depicted in Figure 10.

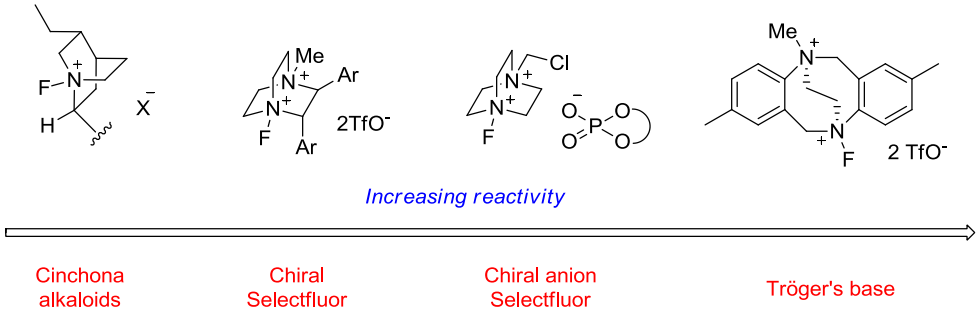


Figure 10 – Spectrum of chiral fluorinating reagents

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Chapter 6:

Experimental Section

6. Experimental Section

6.1 General information

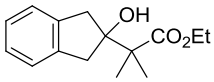
All NMR spectra were recorded on Bruker DPX200, DPX250, AV400, AVC500, AVB500 and DRX500 spectrometers. ^{1}H and ^{13}C NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$. The following abbreviations are used to describe multiplicities s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet br = broad, m = multiplet. NMR spectra were processed in Topspin 3.1. High resolution mass spectra (HRMS, *m*/*z*) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI) or on a Micromass GCT spectrometer using field ionization (EI/FI) or chemical ionization (CI). IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Absorptions are measured in wavenumbers and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were obtained using the ACD/ILab service. Weighing was perfomed with a 4 decimal place balance. All solvents were dried on a column of alumina prior to use. Optical rotations were measured using a Perkin-Elmer Model 341 Polarimeter.

6.2 Experimental data for Chapter 2

Details for the synthesis of compounds described in Chapter 2 are provided herein. See appendices for NMR images of novel compounds as well as X-ray crystallographic data.

6.2.1 Substrate synthesis (heterocyclization)

Ethyl 2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate (2)

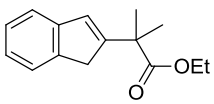


To a solution of diisopropylamine (5.72 mL, 40.8 mmol) in THF (80 mL) at 0 °C, was added ^{n}BuLi (2.5 M in hexanes, 16.4 mL, 40.8 mmol) and the reaction was stirred for 15 minutes before being cooled to -78 °C. Ethyl isobutyrate (5.36 mL, 40.0 mmol) was then added and the reaction was stirred for 20 minutes before the addition of 2-indanone (5.28g, 40.0 mmol) in THF (20 mL). The reaction was stirred for 2 hours before being warmed to 0 °C and quenched slowly with 1M HCl (50 mL). The product was then extracted into ether, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Hexane: EtOAc 1:0-4:1) afforded the title compound as a dark orange oil (5.38 g, 21.7 mmol, 54 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 6H), 2.97 (d, *J* = 16.6 Hz, 2H), 3.33 (d, *J* = 16.6 Hz, 2H), 3.56 (brs, 1H, O*H*), 4.23 (q, *J* = 7.1 Hz, 2H), 7.18-7.26 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 22.1, 43.4, 48.9, 61.0, 85.2, 124.8, 126.5, 141.1, 177.9.

Data consistent with literature values.[1]

Ethyl 2-(1H-inden-2-yl)-2-methylpropanoate (3)

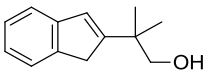


To a solution of ethyl 2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate (2.96 g, 11.9 mmol) in benzene (50 mL) was added phosphorus pentoxide (2.54 g, 17.9 mmol) and the reaction was refluxed for 3 hours. After this time the reaction was cooled to room temperature before filtration through silica gel (eluted with Petroleum ether: EtOAc 1:0-19:1) to afford the title compound as a dark orange oil (1.08 g, 4.69 mmol, 39 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3H), 1.54 (s, 6H), 3.43 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 6.69 (s, 1H), 7.15 (td, *J* = 7.3, 0.5 Hz, 1H), 7.24 (td, *J* = 7.4 Hz, *J* = 0.3 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.1, 25.2, 38.6, 44.6, 60.9, 120.6, 123.5, 124.3, 126.3, 126.6, 143.2, 144.6, 152.5, 176.0.

Data consistent with literature values.[1]

2-(1*H*-Inden-2-yl)-2-methylpropan-1-ol (4a)

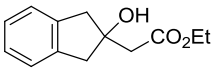


To a solution of ethyl 2-(1*H*-inden-2-yl)-2-methylpropanoate (1.03 g, 4.47 mmol) in ether (15 mL) at -78 °C was added DIBAL (1.0 M solution in hexanes, 12.1 mL, 12.1 mmol) and the reaction stirred for 1 hour and a further hour at room temperature before quenching with 1 M NaOH (5 mL) and extracting into DCM (2 x 30 mL). The aqueous layer was acidified with 3 M HCl and further extracted with DCM (30 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 19:1-1:1) afforded the title compound as a white solid (809 mg, 4.30 mmol, 96 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 6H), 1.58 (brs, 1H, O*H*), 3.41 (brs, 2H), 3.56 (d, *J* = 6.3 Hz, 2H), 6.67 (s, 1H), 7.15 (td, *J* = 7.5, *J* = 1.1 Hz, 1H), 7.24 (dd, *J* = 7.8 Hz, *J* = 0.5 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.8, 38.2, 39.1, 71.7, 120.4, 123.8, 124.1, 126.4, 127.0, 143.1, 144.9, 155.3.

Data consistent with literature values.[1]

Ethyl (2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetate (5)

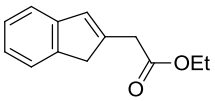


To a solution of diisopropylamine (1.43 mL, 10.2 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.5 M solution in THF, 4.1 mL, 10.2 mmol) and the reaction was stirred for 15 minutes before cooling to -78 °C. Ethyl acetate (0.98 mL, 10.0 mmol) was added dropwise and the reaction was stirred for 20 minutes before adding 2-indanone (1.32 g, 10.0 mmol) in THF (5 mL). The reaction was stirred for 2 hours before being warmed to 0 °C and quenched with 1 M HCl carefully before being extracted with ether, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 4:1) afforded the title compound as a colourless oil (1.52 g, 6.76 mmol, 68 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3H), 2.77 (s, 2H), 3.03 (d, *J* = 16.2 Hz, 2H), 3.17 (d, *J* = 16.2 Hz, 2H), 3.73 (brs, 1H, O*H*), 4.23 (q, *J* = 7.1 Hz, 2H), 7.16-7.23 (m, 4H, H_{Ar}); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 44.0, 46.6, 60.8, 79.5, 124.8, 126.7, 140.8, 173.0.

Data consistent with literature values.[2]

Ethyl 1*H*-inden-2-ylacetate (6)

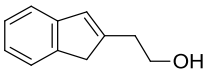


To a solution of ethyl 2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetate (1.38 g, 6.15 mmol) in benzene (150 mL) was added PTSA (118 mg, 0.62 mmol) and the reaction was refluxed overnight using Dean-Stark apparatus. After cooling to room temperature the reaction was concentrated *in vacuo* pressure and the crude residue purified by column chromatography (SiO_2, Petroleum ether: EtOAc 9:1) to afford the title compound as a colourless oil (516 mg, 2.50 mmol, 41 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.47 (s, 2H), 3.53 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.71 (s, 1H), 7.16 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 7.25 (td, *J* = 7.4 Hz, *J* = 0.4 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 37.1, 41.3, 60.9, 120.5, 123.5, 124.3, 126.3, 130.0, 141.1, 143.4, 144.8, 171.0.

Data consistent with literature values.[2]

2-(1*H*-Inden-2-yl)ethanol (4b)

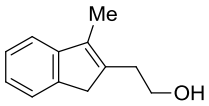


To a solution of ethyl 2-(1*H*-inden-2-yl)acetate (250 mg, 1.21 mmol) in ether (5 mL) at -78 °C was added DIBAL (1.0 M solution in hexanes, 3.27 mL, 3.27 mmol) and the reaction stirred for 1 hour and a further hour at room temperature before quenching with 1 M NaOH (5 mL) and extracting into ether (2 x 10 mL). The aqueous layer was acidified with 3 M HCl and further extracted with ether (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 2:1) afforded the title compound as a colourless solid (202 mg, 1.21 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (brs, 1H, O*H*), 2.78 (t, *J* = 6.4 Hz, 2H), 3.38 (s, 2H), 3.89 (t, *J* = 6.4 Hz, 2H), 6.65 (s, 1H), 7.15 (td, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 7.25 (td, *J* = 7.3 Hz, *J* = 0.4 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 7.4 Hz, *J* = 0.6 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 34.5, 41.2, 61.8, 120.2, 123.5, 124.0, 126.4, 128.4, 143.1, 145.2, 146.3.

Data consistent with literature values.[3]

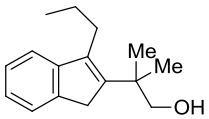
2-(3-Methyl-1*H*-inden-2-yl)ethanol (4c)



To a solution of 2-(1*H*-inden-2-yl)ethanol (100 mg, 0.61 mmol) in THF (1 mL) at -78 °C was added ^{n}BuLi (2.4 M solution in hexanes, 0.52 mL, 1.25 mmol) and the reaction was stirred for 20 minutes. Methyl iodide (38 µL, 0.61 mmol) was added dropwise and the reaction stirred overnight and allowed to warm to room temperature before quenching with ammonium chloride (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 4:1) afforded the title compound as a pale yellow oil (93 mg, 0.52 mmol, 86 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 2.76 (t, *J* = 6.7 Hz, 2H), 3.35 (d, *J* = 1.0 Hz, 2H), 3.81 (t, *J* = 6.7 Hz, 2H), 7.19 (td, *J* = 7.1 Hz, *J* = 1.8 Hz), 7.26-7.35 (m, 2H), 7.43 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 10.4, 32.0, 40.5, 62.1, 118.4, 123.2, 124.2, 126.2, 135.2, 138.2, 142.5, 147.0; **IR (ν, cm^{-1}):** 3350 (br, OH), 1607 (w, C=C), 1467 (m, $C=C_{Ar}$), 1043 (s, C-O); **HRMS (FI^{+}, m/z):** $[C_{12}H_{14}O]^{+}$ $(M)^{+}$ calc. 174.1045, found 174.1051.

2-Methyl-2-(3-propyl-1*H*-inden-2-yl)propan-1-ol (4d)

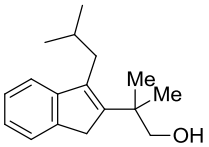


To a solution of 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol (200 mg, 1.06 mmol) in THF (4 mL) at -78 °C was added ^{n}BuLi (2.5 M solution in hexanes, 892 µL, 2.23 mmol) dropwise. After 30 minutes *n*-propyl bromide (101 µL, 1.11 mmol) was added and the reaction was allowed to warm to room temperature and stirred for 24 hours before being cooled to 0 °C and quenched by the addition of ammonium chloride (10 mL). The aqueous layer was extracted with DCM (3 x 20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Toluene: EtOAc 19:1) afforded the title compound as a yellow oil (56 mg, 0.24 mmol, 23 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.3 Hz, 3H), 1.36 (s, 6H), 1.57 (brs, 1H, O*H*), 1.67 (tq, *J* = 7.5 Hz, *J* = 7.4 Hz, 2H), 2.67-2.73 (m, 2H), 3.44 (s, 2H), 3.66 (s, 2H), 7.15-7.21 (m, 1H),

7.27-7.33 (m, 2H), 7.42 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.9, 23.0 , 25.8, 29.5, 40.0, 40.4, 72.1, 118.6, 123.1, 124.1, 126.1, 138.8, 142.2, 145.2, 147.2; **IR (ν, cm^{-1}):** 3393 (br, OH), 1605 (w, C=C), 1468 (m, C=C_{Ar}), 1042 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{16}H_{22}NaO]^+$ $(M+Na)^+$ calc. 253.1563, found 253.1564.

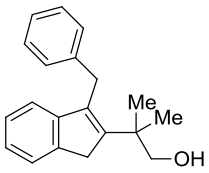
2-Methyl-2-[3-(2-methylpropyl)-1*H*-inden-2-yl]propan-1-ol (4e)



To a solution of 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol (100 mg, 0.53 mmol) in THF (2 mL) at -78 °C was added ^{n}BuLi (2.5 M solution in hexanes, 446 µL, 1.12 mmol). The reaction was stirred for 1 hour before isobutyl bromide (59 µL, 0.54 mmol) was added dropwise. The reaction was allowed to slowly warm to room temperature overnight before being quenched with ammonium chloride, extracted into DCM, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Toluene: EtOAc 19:1) afforded the product as a colourless oil (52 mg, 0.21 mmol, 40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.7 Hz, 6H), 1.36 (s, 6H), 1.43 (brs, 1H), 2.05-2.21 (m, 1H), 2.64 (d, *J* = 7.4 Hz, 2H), 3.46 (s, 2H), 3.65 (s, 2H), 7.16 (td, *J* = 7.2 Hz. *J* = 0.9 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.3 Hz); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.2, 26.2, 28.8, 35.6, 40.3, 40.4, 72.4, 119.5, 122.9, 124.0, 125.8, 138.0, 142.1, 146.1, 147.1; **IR (ν, cm^{-1}):** 3328 (br, O-H), 1604 (w, C=C), 1460 (w, C-C_{Ar}), 1047 (s, C-O); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{24}NaO]^+$ $(M+Na)^+$ calc. 267.1719, found 267.1714.

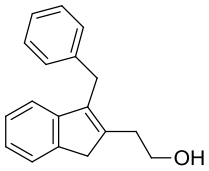
2-(3-Benzyl-1*H*-inden-2-yl)-2-methylpropan-1-ol (4f)



To a solution of 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol (100 mg, 0.53 mmol) in THF (2 mL) at -78 °C was added ^{n}BuLi (2.5 M solution in hexanes, 446 µL, 1.12 mmol). The reaction was stirred for 30 minutes before benzyl bromide (132 µL, 0.54 mmol) was added dropwise. The reaction was allowed to slowly warm to room temperature and stirred for 24 hours before being quenched with ammonium chloride (10 mL), extracted into DCM (3 x 10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Toluene: EtOAc 19:1) afforded the product as a colourless oil (141 mg, 0.51 mmol, 96 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 6H), 1.42 (brs, 1H, O*H*), 3.59 (s, 2H), 3.64 (s, 2H), 4.19 (s, 2H), 7.08-7.12 (m, 1H), 7.14-7.23 (m, 5H), 7.24-7.26 (m, 1H), 7.27-7.30 (m, 1H), 7.42-7.47 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.8, 32.4, 40.0, 40.7, 72.1, 119.3, 123.0, 124.2, 126.0, 126.2, 128.0, 128.5, 135.6, 139.7, 142.0, 147.3, 148.3; **IR (ν, cm^{-1}):** 3374 (br, OH), 1603 (w, C=C), 1494 (w, C=C_{Ar}), 1030 (s, C-OH); **HRMS (ESI^{+}, m/z):** $[C_{20}H_{22}ONa]^{+}$ $(M+Na)^{+}$ calc. 301.1563, found 301.1563.

2-(3-Benzyl-1*H*-inden-2-yl)ethanol (4g)

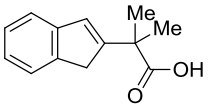


To a solution of 2-(1*H*-inden-2-yl)ethanol (200 mg, 1.22 mmol) in THF at -78 °C, was added ^{n}BuLi (1.2 M solution in hexanes, 2.13 mL, 2.56 mmol) dropwise and the reaction was stirred for 20 minutes before the addition of benzyl bromide (152 µL, 1.28 mmol). The reaction was stirred for 2 hours at -78 °C before warming to room temperature overnight. The reaction was quenched with ammonium chloride (10 mL) and extracted into DCM (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Toluene: EtOAc 1:0-19:1) followed by further column

chromatography (SiO_2, Petroleum ether: EtOAc 19:1- 1:1) afforded the title compound as a yellow solid (150 mg, 0.60 mmol, 49 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (brs, 1H, OH), 2.84 (t, *J* = 6.6 Hz, 2H), 3.47 (s, 2H), 3.84 (t, *J* = 6.7 Hz, 2H), 3.97 (s, 2H), 7.14 (td, *J* = 5.6 Hz, *J* = 1.5 Hz, 1H), 7.15 - 7.29 (m, 7H), 7.43 (dt, *J* = 7.1 Hz, *J* = 0.8 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 31.2, 32.2, 40.7, 62.3, 119.3, 123.3, 124.2, 126.0, 126.2, 128.3, 128.5, 137.8, 139.6, 140.3, 142.6, 146.1; **IR (ν, cm^{-1}):** 3348 (br, OH), 1602 (w, C=C), 1494 (m, C=C_{Ar}), 1466 (m, C=C_{Ar}), 1044 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{18}NaO]^+$ $(M+Na)^+$ calc. 273.1250, found 273.1251; **mp:** 58-61 °C.

2-(1*H*-Inden-2-yl)-2-methylpropanoic acid (4h)

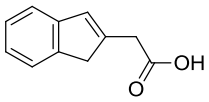


To a solution of ethyl 2-(1*H*-inden-2-yl)-2-methylpropanoate (700 mg, 3.04 mmol) in THF (2 mL) at room temperature was added 6M HCl and the reaction stirred for 72 hours before extracting into DCM (3 x 20 mL), drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 9:1) afforded the title compound as a yellow solid (186 mg, 0.92 mmol, 30 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 6H), 3.49 (s, 2H), 6.76 (s, 1H), 7.16 (td, *J* = 7.3 Hz, *J* = 0.9 Hz, 1H), 7.25 (td, *J* = 7.5 Hz, *J* = 0.4 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 11.42 (brs, 1H, COO*H*) ; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.4, 38.7, 44.5, 120.8, 123.5, 124.5, 126.3, 127.4, 143.1, 144.3, 151.4, 182.2.

Data consistent with literature values.[4]

1*H*-Inden-2-ylacetic acid (4i)

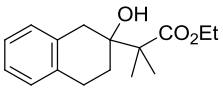


To a solution of ethyl 2-(1*H*-inden-2-yl)acetate (230 mg, 1.11 mmol) in THF (2 mL) at room temperature was added 1M NaOH and the reaction stirred for 1 hour before acidifying with 3 M HCl, extracting into DCM (3 x 20 mL), drying over $MgSO_4$ and evaporating under reduced pressure. Recrystallization from hot hexanes afforded the title compound as a white solid (180 mg, 1.03 mmol, 93 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49 (s, 2H), 3.59 (s, 2H), 6.76 (s, 1H), 7.17 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 11.28 (brs, 1H, COO*H*); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 36.6, 41.3, 120.7, 123.5, 124.6, 126.4, 130.7, 139.9, 143.4, 144.5, 177.2.

Data consistent with literature values.[3]

Ethyl 2-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylpropanoate (8)

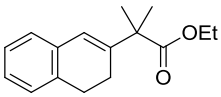


To a solution of diisopropylamine (2.86 mL, 20.4 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (2.5 M solution in hexanes, 8.2 mL, 20.4 mmol) and the reaction was left to stir for 15 minutes before cooling to -78 °C. Ethyl isobutyrate (2.69 mL, 20.0 mmol) was added dropwise and stirred for 20 minutes before *β*-tetralone (2.92 g, 20.0 mmol) was added as a solution in THF (10 mL). The reaction was stirred for a further 2 hours before warming to 0 °C and quenching with 1 M HCl slowly. The aqueous layer was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 19:1) afforded the title compound as a colourless oil (2.62 g, 10.0 mmol, 50 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 3H), 1.75 (td, *J* = 12.9 Hz, *J* = 5.6 Hz, 1H), 1.89-1.96 (m, 1H), 2.67 (dd, *J* = 16.6 Hz, *J* = 2.1 Hz, 1H), 2.75 (ddd, *J* = 16.4 Hz, *J* = 5.5 Hz, *J* = 2.2 Hz, 1H), 3.06 (d, *J* = 16.3 Hz, 1H), 3.11 (ddd, *J* = 15.9 Hz, *J* = 13.0 Hz, *J* = 5.5 Hz, 1H), 3.56 (brs, 1H, O*H*), 4.24 (q, *J* = 7.1 Hz, 2H), 7.04-7.15 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 21.0, 21.0, 25.8, 28.7, 36.9, 49.8, 61.0, 73.7, 125.7, 125.7, 128.4, 129.6, 134.5, 136.2, 178.3.

Data consistent with literature values.[5]

Ethyl 2-(3,4-dihydronaphthalen-2-yl)-2-methylpropanoate (9)

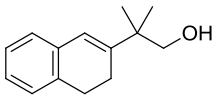


To a solution of ethyl 2-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylpropanoate (1.35 g, 5.14 mmol) in benzene (50 mL) was added phosphorous pentoxide (876 mg, 6.17 mmol) and the reaction was heated to 70 °C. After 1 hour the reaction was cooled to room temperature and filtered through silica gel (eluted with Petroleum ether: EtOAc 19:1) to afford the title compound as a colourless oil (1.15 g, 4.71 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 6H), 2.24 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 2H), 2.79 (dd, *J* = 7.7 Hz, *J* = 7.4 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 6.38 (s, 1H), 7.04-7.18 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 24.1, 25.1, 28.5, 47.7, 60.7, 121.2, 126.2, 126.4, 126.6, 127.0, 134.4, 134.9, 143.9, 176.5.

Data consistent with literature values.[5]

2-(3,4-Dihydronaphthalen-2-yl)-2-methylpropan-1-ol (4j)

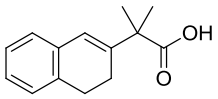


To a solution of ethyl 2-(3,4-dihydronaphthalen-2-yl)-2-methylpropanoate (690 mg, 2.82 mmol) in ether (20 mL) at -78 °C was added DIBAL (1 M solution in hexanes, 7.62 mL, 7.62 mmol) dropwise. The reaction was stirred for 1 hour at -78 °C and a further hour at room temperature before cooling to 0 °C and quenching with 1 M NaOH. After stirring for 30 minutes the aqueous layer was acidified with 3M HCl, extracted into ether (3 x 100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 4:1) afforded the title compound as a colourless oil (484 mg 2.39 mmol, 85 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 0.8 Hz, 6H), 2.29 (t, *J* = 8.0 Hz, 2H), 2.79 (t, 8.0 Hz, 2H), 3.35 (t, *J* = 4.5 Hz, 1H, O*H*), 3.52 (d, *J* = 4.9 Hz, 2H), 6.40 (s, 1H), 7.04-7.19 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.3, 23.7, 28.5, 41.3, 69.9, 123.1, 126.1, 126.5, 126.6, 127.0, 128.1, 134.6, 145.3.

Data consistent with literature values.[5]

2-(3,4-Dihydronaphthalen-2-yl)-2-methylpropanoic acid (4k)

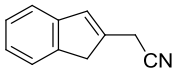


To a solution of ethyl 2-(3,4-dihydronaphthalen-2-yl)-2-methylpropanoate (991 mg, 4.06 mmol) in dry ethanol (10 mL) was added sodium hydroxide (178 mg, 4.46 mmol) and the reaction was heated at reflux for 24 hours. After cooling to room temperature the reaction was concentrated *in vacuo* to give an orange residue which was dissolved in water. The aqueous layer was first extracted with ether (25 mL) before acidifying with 3M HCl and extracting into ether (3 x 25 mL). The combined ether extracts were dried over $MgSO_4$ and evaporated under reduced pressure to afford the title compound as a yellow solid (367 mg, 1.70 mmol, 42 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 6H), 2.32 (td, *J* = 8.1 Hz, *J* = 1.0 Hz, 2H), 2.82 (t, *J* = 8.1 Hz, 2H), 6.44 (s, 1H), 7.04-7.18 (m, 4H), 10.50 (brs, 1H, COO*H*); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.0, 25.1, 28.4, 47.5, 122.0, 126.3, 126.5, 126.9, 127.0, 134.2, 134.9, 142.9, 182.4.

Data consistent with literature values.[6]

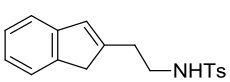
1*H*-Inden-2-ylacetonitrile (10)



To a suspension of NaH (60 % dispersion in mineral oil, 664 mg, 16.6 mmol) in THF (50 mL) at room temperature was added diethyl(cyanomethyl)phosphonate (2.61 mL, 16.6 mmol) dropwise. After 45 minutes 2-indanone (2.00 g, 15.1 mmol) was added carefully over 10 minutes and the reaction was heated for 2 hours at 40 °C before pouring onto ice water (25 mL), extracting into ether (3 x 50 mL), drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 19:1) afforded the title compound as a yellow solid (2.21 g, 14.2 mmol, 94 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.44 (s, 2H), 3.58 (d, *J* = 0.6 Hz, 2H), 6.86-6.88 (m, 1H), 7.22 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 7.30 (td, *J* = 7.3 Hz, *J* = 0.4 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.9, 40.7, 117.2, 121.1, 123.7, 125.2, 126.7, 131.0, 136.1, 142.8, 143.8; **IR (ν, cm^{-1}):** 2935 (w, C≡N), 1463 (w, C-C_{Ar}); **HRMS (ESI$^+$, m/z):** $[C_{11}H_9NNa]^+$ $(M+Na)^+$ calc. 178.0627, found 178.0631.

***N*-[2-(1*H*-Inden-2-yl)ethyl]-4-methylbenzenesulfonamide (4l)**

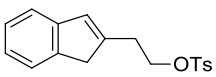


To a suspension of lithium aluminium hydride (57 mg, 1.5 mmol) in

ether (5 mL) at 0 °C was added 2-(1H-inden-2-yl)acetonitrile (100 mg, 0.64 mmol) as a solution in ether (1 mL) and the reaction was warmed to room temperature and stirred for 30 minutes before cooling to 0 °C. The reaction was quenched carefully with 1 % KOH and stirred for 15 minutes before filtering through Celite (ether), drying over $MgSO_4$ and concentrating *in vacuo*. After redissolving in DCM (mL), triethylamine (178 µL, 1.28 mmol), tosyl chloride (135 mg, 0.71 mmol) and DMAP (10 mg) were added at 0 °C and the reaction was stirred for 2 hours at room temperature. The reaction was concentrated *in vacuo* and purified by column chromatography directly (SiO_2, Petroleum ether: EtOAc 9:1) to afford the title compound as a brown solid (35 mg, 0.11 mmol, 17 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 2.65 (t, *J* = 6.7 Hz, 2H), 3.17 (s, 2H), 3.22 (q, *J* = 6.5 Hz, 2H), 4.53 (t, *J* = 5.9 Hz, 1H), 6.50 (s, 1H), 7.14 (td, *J* = 7.1 Hz, *J* = 1.7 Hz, 1H), 7.22-7.28 (m, 4H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 31.1, 40.7, 42.1, 120.3, 123.5, 124.3, 126.4, 127.1, 128.9, 129.7, 136.7, 142.9, 143.5, 144.7, 145.2; **IR (ν, cm^{-1}):** 3268 (m, NH), 1597 (w, C=C), 1459 (w, $C=C_{Ar}$), 1312 (s, S=O), 1094 (m, C-N), 660 (S, S-N) ; **HRMS (ESI$^+$, m/z):** $[C_{18}H_{19}NNaO_2S]^+$ $(M+Na)^+$ calc. 336.1092, found 336.1092; **mp:** 90-91 °C.

2-(1*H*-Inden-2-yl)ethyl 4-methylbenzenesulfonate (8)

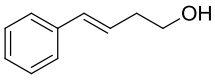


To a solution of 2-(1*H*-inden-2-yl)ethanol (400 mg, 2.50 mmol) in DCM (10 mL) at 0 °C was added triethylamine (697 µL, 3.00 mmol) and tosyl chloride (572 mg, 3.00 mmol). After stirring at 0 °C for 3 hours, TLC analysis showed that the reaction was not complete. DMAP (3 mg, 0.03 mmol) was therefore added and the reaction stirred for a further hour before quenching with sodium carbonate (10 mL) and extracting into DCM (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2,

Petroleum ether: EtOAc 9:1) afforded the title compound as a white solid (642 mg, 2.04 mmol, 82 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 2.84 (t, *J* = 6.6 Hz, 2H), 3.20 (s, 2H), 4.27 (t, *J* = 6.6 Hz, 2H), 6.51 (s, 1H), 7.14 (td, *J* = 7.1 Hz, *J* = 1.9 Hz, 1H), 7.21-7.28 (m, 4H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 30.6, 41.0, 69.1, 120.3, 123.4, 124.2, 126.4, 127.9, 129.1, 129.8, 132.9, 143.0, 143.7, 144.8, 153.5; **IR (ν, cm^{-1}):** 1594 (w, C=C), 1460 (w, C-C_{Ar}), 1355 (s, S=O), 1184 (s, S=O), 975 (s, C-O), 663 (s, S-O); **HRMS (ESI^+, m/z):** $[C_{18}H_{18}NaO_3S]^+$ $(M+Na)^+$ calc. 337.0869, found 338.0860; **mp:** 84-85 °C.

(*E*)-4-Phenylbut-3-en-1-ol (15)

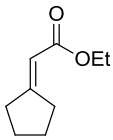


To a solution of trans-styrylacetic acid (500 mg, 3.08 mmol) in THF (5 mL) at 0 °C was added lithium aluminium hydride (140 mg, 3.70 mmol) portionwise. After stirring for 20 minutes the reaction was warmed to room temperature and stirred for a further 40 minutes before quenching with 1 % KOH at 0 °C. After stirring for 30 minutes the reaction mixture was filtered through celite (THF), dried over $MgSO_4$ and evaporated. Purification by column chromatography (SiO_2, EtOAc/PE 1:3) afforded the title compound as a colourless oil (390 mg, 2.63 mmol, 85 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (qd, *J* = 6.6 Hz, *J* = 1.2 Hz, 2H), 3.77 (t, *J* = 6.3 Hz, 2H), 6.22 (dt, *J* = 15.8 Hz, *J* = 7.1 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 7.23 (tt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.36-7.40 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 36.4, 62.0, 126.1, 126.3, 127.3, 128.5, 132.8, 137.2.

Data consistent with literature values.[7]

Ethyl 2-cyclopentylideneacetate (19)

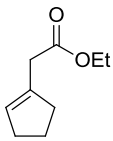


To a suspension of sodium hydride (60 % *w/w*, 440 mg, 11.0 mmol) in THF (25 ml) at 0 °C was added triethylphosphonoacetate (2.18 mL, 11.0 mmol) dropwise. The reaction was warmed to room temperature and stirred for 30 minutes before the addition of cyclopentanone (885 µL, 10.0 mmol) as a solution in THF (5 mL). The reaction was further stirred for 2 hours before quenching with water and diluting with ether (50 ml). The aqueous layer was extracted with ether (3 x 50 ml), dried over $MgSO_4$ and evaporated. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (1.26 g, 8.19 mmol, 82 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3H), 1.65 (tt, *J* = 6.9 Hz, *J* = 6.8 Hz, 2H), 1.74 (tt, *J* = 6.9 Hz, *J* = 6.8 Hz, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.79 (tt, *J* = 2.2 Hz, *J* = 2.1 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.4, 25.5, 26.4, 32.6, 35.9, 59.4, 111.7, 166.9, 169.1.

Data consistent with literature values.[8]

Ethyl 2-(cyclopent-1-en-1-yl)acetate (20)



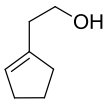
To a solution of diisopropylamine (1.25 mL, 8.92 mmol) in THF (20 ml) at 0 °C was added ^{n}BuLi (2.4M in hexanes, 3.55 mL, 8.52 mmol) and the reaction was stirred for 15 minutes before cooling to -78 °C. Ethyl 2-cyclopentylideneacetate (1.25 g, 8.11 mmol) was added as a solution in THF (6 mL) over a period of 10 minutes. The reaction was further stirred for 20 minutes before the addition of ammonium chloride (20 mL) over a period of 20 minutes. The reaction was warmed to room temperature and poured onto water (40 mL) and ether (50 mL). The aqueous layer was extracted with ether (3 x 50 mL),

dried over $MgSO_4$ and evaporated. Further purification was not required (1.25 g, 8.11 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3H), 1.83-1.95 (m, 2H), 2.29-2.37 (m, 4H), 3.11 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.54 (brs, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 23.4, 32.5, 35.1, 37.1, 60.5, 128.1, 136.6, 171.5.

Data consistent with literature values.[9]

2-(Cyclopent-1-en-1-yl)ethanol (21)

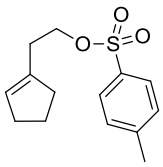


To a solution of ethyl 2-(cyclopent-1-en-1-yl)acetate (1.25 g, 8.11 mmol) in ether (30 mL) at -78 °C was added DIBAL (1.2M in toluene, 18.2 mL, 21.9 mmol). The reaction was stirred for 1 hour at -78 °C and a further hour at room temperature before cooling to 0 °C and quenching with 1M NaOH (20 mL). After stirring for 30 minutes the aqueous layer was acidified with 3M HCl and extracted with ether (3 x 50 mL). The combined ether extracts were dried over $MgSO_4$ and evaporated. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded the title compound as a colourless oil (738 mg, 6.58 mmol, 81 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (tt, *J* = 7.1 Hz, *J* = 6.6 Hz, 2H), 2.24-2.40 (m, 6H), 3.72 (t, *J* = 6.2 Hz, 2H), 5.47 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.3, 32.5, 34.4, 34.9, 60.5, 126.3, 140.8.

Data consistent with literature values.[10]

2-(Cyclopent-1-en-1-yl)ethyl 4-methylbenzenesulfonate (23)

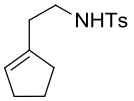


To a solution of 2-(cyclopent-1-en-1-yl)ethanol (327 mg, 2.92 mmol) in DCM (40 mL) at 0 °C was added triethylamine (814 µL, 5.84 mmol) followed by tosyl chloride (611 mg, 3.21 mmol). The reaction was stirred for 3 hours at room temperature before quenching with NH_4Cl (50 mL) and extracting into DCM. The combined organic extracts were washed with NH_4Cl (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (739 mg, 2.77 mmol, 95 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76-1.85 (m, 2H), 2.12-2.18 (m, 2H), 2.23-2.30 (m, 2H), 2.42 (td, *J* = 6.9 Hz, *J* = 1.0 Hz, 2H), 2.46 (s, 3H), 4.13 (t, *J* = 6.9 Hz, 2H), 5.34-5.37 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 23.1, 30.5, 32.5, 35.0, 68.8, 126.5, 127.9, 129.8, 133.2, 138.6, 144.7.

Data consistent with literature values.[11]

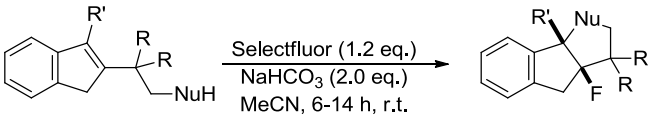
***N*-(2-(Cyclopent-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide (24)**



To a suspension of freshly powdered KOH (202 mg, 3.60 mmol) in dry dioxane (20 mL) was added tosyl amide (616 mg, 3.60 mmol) and the reaction was heated to reflux for 1 hour. 2-(Cyclopent-1-en-1-yl)ethyl 4-methylbenzenesulfonate (639 mg, 2.40 mmol) was added as a solution in dry dioxane (5 mL) at reflux and the reaction stirred for a further 3 hours before cooling to room temperature. The reaction was poured onto water (50 mL), extracted with ethyl acetate (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (188 mg, 0.71 mmol, 30 % yield).

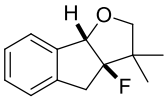
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.81 (tt, *J* = 8.4 Hz, *J* = 6.6 Hz, 2H), 2.04-2.10 (m, 2H), 2.22 (td, *J* = 6.6 Hz, *J* = 0.9 Hz, 2H), 2.25-2.31 (m, 2H), 2.44 (s, 3H), 3.06 (dd, *J* = 12.6 Hz, *J* = 6.6 Hz, 2H), 4.35 (t, *J* = 4.3 Hz, 1H, N*H*), 5.34 (brs, 1H, C=C*H*), 7.32 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 21.5, 23.2, 30.7, 32.4, 34.4, 40.8, 126.9, 127.1, 129.7, 136.8, 140.1, 143.3; **IR (ν, cm^{-1}):** 3281 (br, N-H), 1598 (w, C=C), 1422 (w, C-C_{Ar}), 1325 (s, S=O), 1159 (s, S=O), 666 (m, N-S); **HRMS (ESI$^+$, m/z):** $[C_{14}H_{19}NNaO_2S]^+$ $(M+Na)^+$ calc. 288.1029, found 288.1022.

6.2.2 General procedure for fluoro-heterocyclization



To a solution of substrate (50 mg, 1.0 eq.) in acetonitrile (2 mL) was added sodium bicarbonate (2.0 eq.) and Selectfluor® (1.2 eq.) and the reaction was stirred for 6-14 hours at room temperature. The reaction was poured onto water (5 mL) before extraction into DCM (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification was performed by column chromatography on silica gel.

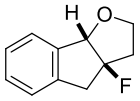
3*a*-Fluoro-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5a)



Prepared according to general procedure using 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by column chromatography (SiO_2, 9:1 Petroleum ether: EtOAc) afforded the title compound as a colourless oil (96 % yield, >25:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.93 (s, 3H), 1.22 (d, *J* = 3.6 Hz, 3H), 3.15 (dd, *J* = 26.0 Hz, *J* = 17.4 Hz, 1H), 3.40 (dd, *J* = 17.4 Hz, *J* = 10.6 Hz, 1H), 3.64 (d, *J* = 8.4 Hz, 1H), 3.86 (dd, *J* = 8.4 Hz, 1.7 Hz, 1H), 5.48 (d, *J* = 22.2 Hz, 1H), 7.18 (dd, *J* = 6.5 Hz, *J* = 1.1 Hz, 1H), 7.25-7.33 (m, 2H), 7.40 (dd, *J* = 6.5 Hz, *J* = 2.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.2 (d, *J* = 12.0 Hz), 21.7 (d, *J* = 3.2 Hz), 37.4 (d, *J* = 29.2 Hz), 44.6 (d, *J* = 20.8 Hz), 80.3, 91.2 (d, *J* = 28.2 Hz), 112.4 (d, *J* = 195.8 Hz), 124.4, 125.2, 127.6, 129.1, 140.2 (d, *J* = 7.0 Hz), 141.0 (d, *J* = 4.4 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -158.9 (m); **IR (ν, cm^{-1}):** 1469 (w, C=C_{Ar}), 1057 (s, C-O), 1036 (s, C-O); **HRMS (FI$^+$, m/z):** $[C_{13}H_{15}FO]^+$ $(M)^+$ calc. 206.1105, found 206.1107.

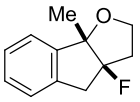
3*a*-Fluoro-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5b)



Prepared according to general procedure using 2-(1*H*-inden-2-yl)ethanol. Purification by column chromatography (SiO_2, 4:1 Petroleum ether: EtOAc) afforded the title compound as a colourless oil (58 % yield, >25:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.08 (ddt, *J* = 25.7 Hz, *J* = 13.6 Hz, *J* = 8.1 Hz, 1H), 2.51 (dddd, *J* = 23.7 Hz, *J* = 13.6 Hz, *J* = 6.2 Hz, *J* = 4.6 Hz, 1H), 3.39 (dd, *J* = 20.7 Hz, 16.7 Hz, 1H), 3.42 (dd, *J* = 33.8 Hz, *J* = 16.7 Hz, 1H), 3.88 (td, *J* = 8.1 Hz, *J* = 4.6 Hz, 1H), 4.11 (td, *J* = 8.6 Hz, *J* = 6.3 Hz, 1H), 5.47 (d, *J* = 20.2 Hz, 1H), 7.18-7.22 (m, 1H), 7.27-7.32 (m, 2H), 7.38-7.42 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 39.5 (d, *J* = 24.7 Hz), 41.4 (d, *J* = 27.4 Hz), 68.2, 90.8 (d, *J* = 26.7 Hz), 110.5 (d, *J* = 192.4 Hz), 125.0 (d, *J* = 0.9 Hz), 125.6, 127.8, 129.1, 139.4 (d, *J* = 5.4 Hz), 139.7 (d, *J* = 7.3 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -151.3 (m); **IR (ν, cm^{-1}):** 1462 (w, C=C_{Ar}), 1045 (s, C-F), 966 (m, C-O); **HRMS (FI$^+$, m/z):** $[C_{11}H_{11}OF]^+$ $(M)^+$ calc. 178.0794, found 178.0790.

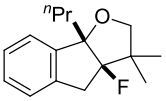
3*a*-Fluoro-8*b*-methyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5c)



Prepared according to general procedure using 2-(3-methyl-1*H*-inden-2-yl)ethanol. Purification by column chromatography (Petroleum ether: EtOAc 19:1) afforded the title compound as a colourless oil (76 % yield, >25:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.52 (d, *J* = 3.5 Hz, 3H), 2.15 (dddd, *J* = 20.9 Hz, *J* = 13.8 Hz, *J* = 7.2 Hz, *J* = 6.1 Hz, 1H), 2.51 (dddd, *J* = 26.5 Hz, *J* = 13.6 Hz, *J* = 7.3 Hz, *J* = 7.2 Hz, 1H), 3.34 (dd, *J* = 23.5 Hz, *J* = 16.3 Hz, 1H), 3.36 (s, 1H), 3.53 (dt, *J* = 8.8 Hz, *J* = 7.2 Hz, 1H), 4.03 (ddd, *J* = 8.8 Hz, *J* = 7.5 Hz, *J* = 6.0 Hz, 1H), 7.15-7.37 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.3 (d, *J* = 9.5 Hz), 40.0 (d, *J* = 25.6 Hz), 41.1 (d, *J* = 27.3 Hz), 65.5 (d, *J* = 2.0 Hz), 92.8 (d, *J* = 21.7 Hz), 108.9 (d, *J* = 199.6 Hz), 124.0, 124.8 (d, *J* = 2.0 Hz), 127.9, 128.8, 137.2 (d, *J* = 8.0 Hz), 144.3 (d, *J* = 4.2 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -158.5; **IR (ν, cm^{-1}):** 1478 (w, C=C_{Ar}), 1068 (m, C-F), 1022 (m, C-O); **HRMS (FI^+, m/z):** $[C_{12}H_{13}OF]^+$ $(M)^+$ calc. 192.0950, found 192.0949.

3*a*-Fluoro-3,3-dimethyl-8*b*-propyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5d)

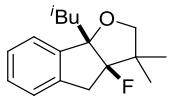


Prepared according to general procedure using 2-methyl-2-(3-propyl-1*H*-inden-2-yl)propan-1-ol. Purification by column chromatography (Petroleum ether: EtOAc 19:1) afforded the title compound as a colourless oil (96 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 1.14 (d, *J* = 4.9 Hz, 3H), 1.15-1.24 (m, 1H), 1.38-1.53 (m, 1H), 1.90 (ddd, *J* = 7.4 Hz, *J* = 7.3 Hz, *J* = 2.1 Hz, 2H), 3.09 (dd, *J* = 22.3 Hz, *J* = 16.7 Hz, 1H), 3.32 (d, *J* = 8.5 Hz, 1H), 3.32 (d, *J* = 16.5 Hz, 1H), 3.75 (dd, *J* = 8.4 Hz, *J* = 1.4 Hz, 1H), 7.10-7.15 (m, 1H), 7.23-7.33 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.7, 16.8 (d, *J* = 3.2 Hz), 19.9 (d, *J* = 15.3 Hz), 22.8 (d, *J* = 3.3 Hz), 37.4 (d, *J* = 36.8 Hz), 37.6, 45.6 (d, *J* = 21.8 Hz), 78.4, 96.1 (d, *J* = 21.7 Hz), 111.4 (d, *J* = 203.0 Hz), 123.7 (d, *J* = 1.7 Hz), 124.2, 127.4, 128.6, 138.8 (d, *J* = 9.0 Hz), 143.6 (d, *J* = 5.0 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ

= -167.0; **IR (ν, cm^{-1}):** 1463 (m, C=C$_{Ar}$), 1040 (s, C-F), 1036 (s, C-O); **HRMS (FI$^+$, m/z):** [$C_{16}H_{21}OF$]$^+$ (M)$^+$ calc. 248.1576, found 248.1583.

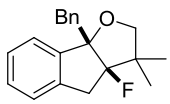
3*a*-Fluoro-3,3-dimethyl-8*b*-(2-methylpropyl)-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5e)



Prepared according to general procedure using 2-methyl-2-[3-(2-methylpropyl)-1*H*-inden-2-yl]propan-1-ol. Purification by column chromatography (SiO_2, 9:1 Petroleum ether: EtOAc) afforded the title compound as a colourless oil (83 % yield, >25:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.78 (s, 3H), 0.83 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 4.9 Hz, 3H), 1.74-1.85 (m, 3H), 3.11 (dd, *J* = 21.7 Hz, *J* = 16.7 Hz, 1H), 3.27-3.34 (m, 2H), 3.74 (dd, *J* = 8.5 Hz, *J* = 1.4 Hz, 1H), 7.10-7.15 (m, 1H), 7.24-7.28 (m, 2H), 7.31-7.35 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.0 (d, *J* = 15.5 Hz), 22.8 (d, *J* = 3.4 Hz), 23.7, 23.8 (d, *J* = 2.6 Hz), 25.1, 37.2 (d, *J* = 28.4 Hz), 43.3 (d, *J* = 8.7 Hz), 45.3 (d, *J* = 21.6 Hz), 78.4, 96.3 (d, *J* = 21.2 Hz), 111.7 (d, *J* = 203.8 Hz), 123.8 (d, *J* = 1.8 Hz), 124.8, 127.3, 128.6, 138.6 (d, *J* = 9.0 Hz), 143.7 (d, *J* = 4.9 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -166.0; **IR (ν, cm^{-1}):** 1460 (w, C=C$_{Ar}$), 1048 (s, C-F), 1022 (s, C-O); **HRMS (FI$^+$, m/z):** [$C_{17}H_{23}OF$]$^+$ (M)$^+$ calc. 262.1733, found 262.1732.

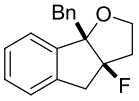
8*b*-Benzyl-3*a*-fluoro-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5f)



Prepared according to general procedure using 2-(3-benzyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by column chromatography (SiO_2, 9:1 Petroleum ether: EtOAc) afforded the title compound as a colourless oil (73 % yield, 10:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.77 (s, 3H), 1.18 (d, *J* = 4.6 Hz, 1H), 2.91 (dd, *J* = 21.8 Hz, *J* = 16.5 Hz, 1H), 3.00 (dd, *J* = 13.7 Hz, *J* = 1.6 Hz, 1H), 3.24 (d, *J* = 16.5 Hz, 1H), 3.34 (dd, *J* = 13.7 Hz, *J* = 2.8 Hz, 1H), 3.45 (d, *J* = 8.4 Hz, 1H), 3.91 (dd, *J* = 8.4 Hz, *J* = 1.0 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 7.03-7.14 (m, 5H), 7.16-7.24 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.5 (d, *J* = 14.8 Hz), 22.9 (d, *J* = 3.9 Hz), 36.7 (d, *J* = 27.9 Hz), 40.6 (d, *J* = 11.2 Hz), 45.7 (d, *J* = 21.5 Hz), 78.6, 95.9 (d, *J* = 20.6 Hz), 111.8 (d, *J* = 203.5 Hz), 123.5 (d, *J* = 1.7 Hz), 125.1, 126.1, 126.9, 127.5, 128.6, 131.3, 136.3 (d, *J* = 1.4 Hz), 138.5 (d, *J* = 9.0 Hz), 142.8 (d, *J* = 4.8 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -165.6; **IR (ν, cm^{-1}): 1469 (w, C-C_{Ar}), 1092 (m, C-O), 1036 (m, C-F); HRMS (ESI$^+$, m/z):** $[C_{20}H_{21}FNaO]^+$ $(M+Na)^+$ calc. 319.1469, found 319.1466.

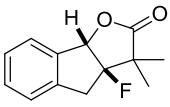
8*b*-Benzyl-3*a*-fluoro-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (5g)



Prepared according to general procedure using 2-(3-benzyl-1*H*-inden-2-yl)ethanol. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 19:1) afforded the title compound as a colourless oil (90 % yield, >25:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.03-2.18 (m, 1H), 2.43-2.57 (m, 1H), 3.05 (t, *J* = 16.6 Hz, 1H), 3.06 (dd, *J* = 13.5 Hz, *J* = 0.9 Hz, 1H), 3.25 (d, *J* = 15.9 Hz, 1H), 3.33 (dd, *J* = 13.5 Hz, *J* = 2.3 Hz, 1H), 3.60 (td, *J* = 8.1 Hz, *J* = 6.1 Hz, 1H), 4.14 (td, *J* = 8.5 Hz, *J* = 6.1 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 7.05-7.27 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 40.0 (d, *J* = 25.5 Hz), 40.1 (d, *J* = 8.0 Hz), 40.5 (d, *J* = 26.3 Hz), 66.0, 94.7 (d, *J* = 20.4 Hz), 109.5 (d, *J* = 200.6 Hz), 124.6 (d, *J* = 1.8 Hz), 125.6, 126.2, 127.5, 127.5, 128.7, 131.1, 136.1, 137.4 (d, *J* = 8.7 Hz), 142.2 (d, *J* = 4.6 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -159.8; **IR (ν, cm^{-1}):** 1496 (w, C=C_{Ar}), 1477 (w, C=C_{Ar}), 1088 (s, C-F), 947 (m, C-O); **HRMS (FI$^+$, m/z):** $[C_{18}H_{17}OF]^+$ $(M)^+$ calc. 268.1263, found 268.1263.

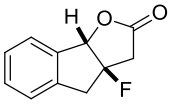
3*a*-Fluoro-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (5h)



Prepared according to general procedure using 2-(1*H*-inden-2-yl)-2-methylpropanoic acid. Purification by column chromatography (SiO_2, 4:1 Petroleum ether: EtOAc) afforded the title compound as a colourless oil (70 % yield, >20:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.22 (s, 3H), 1.42 (d, *J* = 4.1 Hz, 3H), 3.30 (dd, *J* = 23.7 Hz, *J* = 17.5 Hz, 1H), 3.42 (t, *J* = 18.0 Hz, 1H), 5.74 (d, *J* = 16.0 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.39 (td, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.2 (d, *J* = 12.7 Hz), 20.9, 38.5 (d, *J* = 28.1 Hz), 45.5 (d, *J* = 21.6 Hz), 86.9 (d, *J* = 28.6 Hz), 107.5 (d, *J* = 200.7 Hz), 124.9, 126.5, 128.0, 130.6, 136.3 (d, *J* = 3.5 Hz), 141.4 (d, *J* = 2.6 Hz), 179.1 (d, *J* = 6.8 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -163.9; **IR (ν, cm^{-1}):** 1780 (s, C=O), 1466 (w, C=C_{Ar}), 1109 (m, O-C(O)), 1026 (m, C-F), 991 (M, C-O); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{13}FNaO_2]^+$ $(M+Na)^+$ calc. 243.0792, found 243.0792.

3*a*-Fluoro-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (5i)

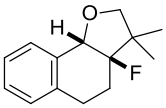


Prepared according to general procedure using 1*H*-inden-2-ylacetic acid. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 4:1) afforded the title compound as a colourless oil (42 % yield, 10:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ =2.81 (dd, *J* = 24.5 Hz, *J* = 18.8 Hz, 1H), 3.16 (dd, *J* = 24.1 Hz, *J* = 18.8 Hz, 1H), 3.42 (dd, *J* = 16.7 Hz, *J* = 5.4 Hz, 1H), 3.53 (t, *J* = 18.5 Hz, 1H), 5.96 (d, *J* = 18.2 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.39 (td, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 40.5 (d, *J* = 27.0 Hz), 41.3 (d, *J* = 26.5 Hz), 90.3 (d, *J* = 27.6 Hz), 104.0 (d, *J* = 196.3 Hz), 125.4, 126.2, 128.5, 130.5, 136.5 (d, *J* = 5.9 Hz), 138.7 (d, *J* = 5.6 Hz), 173.6 (d, *J* = 1.8 Hz); **^{19}F NMR (376.6**

MHz, $CDCl_3$): δ = -150.7; **IR (ν, cm^{-1}):** 1765 (s, C=O), 1464 (w, C=C_{Ar}), 1166 (m, O-C(O)), 1008 (s, C-F), 952 (w, C-O); **HRMS (ESI$^+$, m/z):** $[C_{11}H_9FNaO_2]^+$ $(M+Na)^+$ calc. 215.0479, found 215.0482.

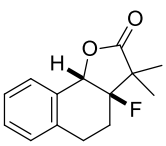
3*a*-Fluoro-3,3-dimethyl-2,3,3*a*,4,5,9*b*-hexahydronaphtho[1,2-*b*]furan (5j)



Prepared according to general procedure using 2-(3,4-dihydronaphthalen-2-yl)-2-methylpropan-1-ol. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 19:1) afforded the title compound as a colourless oil (59 % yield, 10:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.87 (s, 3H), 1.20 (d, *J* = 3.1 Hz, 3H), 1.63 (dddd, *J* = 40.9 Hz, *J* = 14.3 Hz, *J* = 13.0 Hz, *J* = 4.4 Hz, 1H), 2.17 (ddt, *J* = 20.1 Hz, *J* = 14.3 Hz, 3.5 Hz, 1H), 2.74 (dt, *J* = 14.9 Hz, *J* = 3.8 Hz, 1H), 2.85 (ddd, *J* = 15.1 Hz, *J* = 12.9 Hz, *J* = 3.9 Hz, 1H), 3.75 (d, *J* = 8.2 Hz, 1H), 3.92 (dd, *J* = 8.3 Hz, *J* = 1.4 Hz, 1H), 4.83 (d, *J* = 29.2 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.22 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 7.27 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.2 (d, *J* = 10.4 Hz), 22.8 (d, *J* = 3.4 Hz), 26.1 (d, *J* = 1.0 Hz), 26.8, 27.1, 44.3 (d, *J* = 19.7 Hz), 79.3, 81.8 (d, *J* = 31.6 Hz), 104.6 (d, *J* = 182.8 Hz), 126.2, 126.6, 127.0, 127.2, 136.2 (d, *J* = 69.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -154.4; **IR (ν, cm^{-1}):** 1470 (w, C-C_{Ar}), 1054 (s, C-F), 1050 (m, C-O); **HRMS (FI$^+$, m/z):** $[C_{14}H_{17}OF]^+$ $(M)^+$ calc. 220.1263, found 220.1270.

3*a*-Fluoro-3,3-dimethyl-3*a*,4,5,9*b*-tetrahydronaphtho[1,2-*b*]furan-2(3*H*)-one (5k)

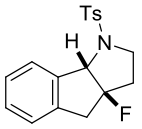


Prepared according to general procedure using 2-(3,4-dihydronaphthalen-2-yl)-2-methylpropanoic acid. Purification by column chromatography (SiO_2,

Petroleum ether: EtOAc 1:9) afforded the title compound as colourless solid (64 % yield, 20:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ =1.20 (s, 3H), 1.44 (d, *J* = 3.6 Hz, 3H), 1.72 (dddd, *J* = 41.0 Hz, *J* = 14.4 Hz, *J* = 13.0 Hz, *J* = 4.8 Hz, 1H), 2.17-2.28 (m, 1H), 2.82 (ddd, *J* = 16.3 Hz, *J* = 4.8 Hz, *J* = 2.7 Hz, 1H), 2.99 (ddd, *J* = 16.3 Hz, *J* = 13.0 Hz, *J* = 4.3 Hz, 1H), 5.35 (d, *J* = 16.3 Hz, 1H), 7.19-7.23 (m, 1H), 7.29- 7.33 (m, 2H), 7.47-7.51 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.7, 19.7 (d, *J* = 11.1 Hz), 24.5 (d, *J* = 2.8 Hz), 26.6 (d, *J* = 25.1 Hz), 46.5 (d, *J* = 20.9 Hz), 77.0 (d, *J* = 30.8 Hz), 98.3 (d, *J* = 192.3 Hz), 127.0, 128.2, 128.9, 129.5, 129.9 (d, *J* = 1.8 Hz), 136.3, 178.2 (d, *J* = 8.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -170.7; **IR (ν, cm^{-1}):** 1786 (s, C=O), 1460 (w, C=C_{Ar}), 1109 (m, O-C(O)), 993 (m, C-F), 959 (w, C-O); **HRMS (ESI^{+}, m/z):** $[C_{14}H_{15}FNaO_2]^+$ $(M+Na)^+$ calc. 257.0948, found 257.0946; **mp:** 110-111 °C.

3*a*-Fluoro-1-[(4-methylphenyl)sulfonyl]-1,2,3,3*a*,4,8*b*-hexahydroindeno[1,2-*b*]pyrrole (5l)

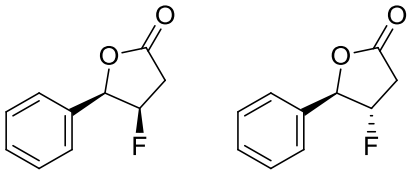


Prepared according to general procedure using *N*-[2-(1*H*-inden-2-yl)ethyl]-4-methylbenzenesulfonamide. Purification by column chromatography (SiO_2, Petroleum ether: EtOAc 4:1) afforded the title compound as a pale yellow solid (36 % yield, >25:1 d.r.).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.03 (dddd, *J* = 35.0 Hz, *J* = 13.7 Hz, *J* = 11.5 Hz, *J* = 8.3 Hz, 1H), 2.22 (dddt, *J* = 18.2 Hz, *J* = 14.0 Hz, *J* = 6.4 Hz, *J* = 1.3 Hz, 1H), 2.46 (s, 3H), 3.16 (dd, *J* = 16.1 Hz, *J* = 2.0 Hz, 1H), 3.28 (dd, *J* = 19.1 Hz, *J* = 16.1 Hz, 1H), 3.38 (ddd, *J* = 11.4 Hz, *J* = 9.4 Hz, *J* = 6.4 Hz, 1H), 3.60 (ddd, *J* = 7.9 Hz, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H), 5.13 (d, *J* = 20.7 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.28-7.39 (m, 4H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.82 (m, 1H), 7.88 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 35.4 (d, *J* = 24.7 Hz), 39.4 (d, *J* = 24.4 Hz), 48.8, 72.9 (d, *J* = 24.2), 109.4 (d, *J* = 195.5 Hz), 124.9, 126.8, 127.9, 128.1, 128.8, 129.7, 133.5, 137.7 (d, *J* = 6.6 Hz), 139.9 (d, *J* = 8.5), 143.9; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.2; **IR (ν, cm^{-1}):** 1597 (w, C=C_{Ar}), 1461 (w, C=C_{Ar}), 1340 (m, S=O), 1160 (s,

S=O), 1093 (s, C-N), 1038 (s, C-F), 661 (s, N-S); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{18}FNNaO_2S]^+$ $(M+Na)^+$ calc. 354.0934, found 354.0929; **mp:** 129-133 °C.

4-Fluoro-5-phenyldihydrofuran-2(3*H*)-one (16)



Prepared according to the general procedure starting from *trans*-styrylacetic acid. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded the title compound as a colourless oil (mixture of diastereomers, syn:anti 1.49:1, 68 % yield).

Syn diastereomer (major conformational isomer): **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.73-2.96 (m, 2H), 5.23 (ddt, *J* = 53.4 Hz, *J* = 5.3 Hz, *J* = 1.2 Hz, 1H), 5.76 (d, *J* = 21.3 Hz, 1H), 7.17-7.20 (m, 1H), 7.29-7.47 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 34.1 (d, *J* = 23.8 Hz), 85.6 (d, *J* = 25.9 Hz), 93.8 (d, *J* = 185.6 Hz), 124.7, 129.2, 129.3, 135.1 (d, *J* = 9.0 Hz), 173.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -170.8; **IR (ν, cm^{-1}):** 1789 (s, C=O), 1454 (w, C=C), 1150 (s, C-O), 1028 (s, C-F), 954 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{10}H_9FNaO_2]^+$ $(M+Na)^+$ calc. 203.0479, found 203.0483.

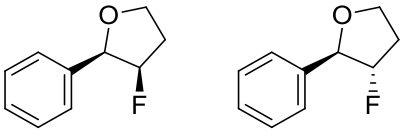
Minor conformational isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.73-2.93 (m, 2H), 3.02 (ddd, *J* = 39.7, *J* = 18.6, *J* = 4.6 Hz, 1H), 5.00 (dd, *J* = 52.0 Hz, *J* = 4.5 Hz, 1H), 5.62 (d, *J* = 21.5 Hz, 1H), 7.29-7.47 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 38.7 (d, *J* = 24.7 Hz), 66.9 (d, *J* = 25.3 Hz), 90.8 (d, *J* = 185.2 Hz), 125.2, 128.5, 129.0, 135.5 (d, *J* = 9.9 Hz), 170.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -167.3.

Anti diastereomer (major conformational isomer): **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.94-3.04 (m, 2H), 5.39 (dtd, *J* = 52.8 Hz, *J* = 3.4 Hz, *J* = 1.8 Hz, 1H), 5.54 (dd, *J* = 26.3 Hz, *J* = 3.2 Hz, 1H),

7.22 (d, *J* = 7.5 Hz, 1H), 7.31-7.47 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 37.2 (d, *J* = 25.5 Hz), 84.2 (d, *J* = 21.0 Hz), 89.8 (d, *J* = 188.3 Hz), 126.6, 128.5, 129.0, 132.1 (d, *J* = 4.2 Hz), 173.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -189.2; **IR (ν, cm^{-1}):** 1791 (s, C=O), 1455 (w, C-C_{Ar}), 1149 (s, C-O), 1023 (s, C-F), 993 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{10}H_9FNaO_2]^+$ $(M+Na)^+$ calc. 203.0479, found 203.0485.

Minor conformational isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.94-3.02 (m, 2H), 5.30 (ddd, *J* = 53.3 Hz, *J* = 11.8 Hz, *J* = 6.0 Hz, 1H), 5.47 (dd, *J* = 13.2 Hz, 6.3 Hz, 1H), 7.31-7.47 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 39.1 (d, *J* = 23.6 Hz), 64.0 (d, *J* = 21.4 Hz), 84.8 (d, *J* = 188.1 Hz), 126.8, 128.3, 128.5, 133.8 (d, *J* = 4.6 Hz), 170.4; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -187.3.

3-Fluoro-2-phenyltetrahydrofuran (17)

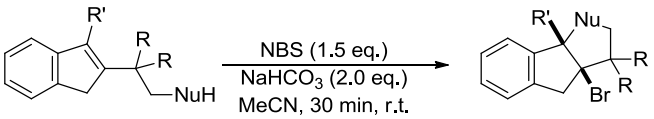


Prepared according to the general procedure from (E)-4-phenylbut-3-en-1-ol Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (mixture of diastereomers, 1.16:1 syn:anti, 41 % yield).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.01-2.28 (m, 2H), 4.14 (ddd, *J* = 10.9 Hz, *J* = 8.4 Hz, *J* = 5.9 Hz, 1H), 4.30 (td, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 5.08 (ddt, *J* = 54.6 Hz, *J* = 4.6 Hz, *J* = 1.1 Hz, 1H), 5.16 (d, *J* = 25.5 Hz, 1H), 7.27-7.40 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 32.1 (d, *J* = 21.0 Hz), 67.5, 85.9 (d, *J* = 25.4 Hz), 99.4 (d, *J* = 180.5 Hz), 125.4, 127.7, 128.5, 139.4 (d, *J* = 10.5 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -173.1; **IR (ν, cm^{-1}):** 1453 (w, C-C_{Ar}), 1065 (s, C-F), 972 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{10}H_{11}FNaO]^+$ $(M+Na)^+$ calc. 189.0686, found 189.0689.

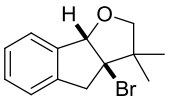
Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.26-2.45 (m, 2H), 4.06 (ddd, *J* = 11.1 Hz, *J* = 5.7 Hz, *J* = 4.4 Hz, 1H), 4.31 (dd, *J* = 16.0 Hz, *J* = 8.2 Hz, 1H), 4.84 (dd, *J* = 28.5 Hz, *J* = 2.9 Hz, 1H), 5.21 (dddd, *J* = 53.4 Hz, *J* = 4.3 Hz, *J* = 3.0 Hz, 1.3 Hz, 1H), 7.29-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 33.8 (d, *J* = 22.0 Hz), 66.7, 84.3 (d, *J* = 19.3 Hz), 93.9 (d, *J* = 185.3 Hz), 127.0, 127.8, 128.1, 136.0 (d, *J* = 4.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -187.0; **IR (ν, cm^{-1}):** 1454 (w, C-C_{Ar}), 1083 (s, C-F), 996 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{10}H_{11}FNaO]^+$ $(M+Na)^+$ calc. 189.0686, found 189.0688.

6.2.3 General procedure for bromo-heterocyclization



To a solution of substrate (25 mg) in acetonitrile at room temperature was added sodium bicarbonate (2.0 eq.) followed by *N*-bromosuccinimide (1.5 eq.). The reaction was stirred for 30 minutes before diluting with DCM (10 mL) and washing with water (5 mL). The aqueous layer was extracted twice more with DCM before drying over $MgSO_4$ and evaporating under reduced pressure. The crude residue was purified by flash chromatography.

3*a*-Bromo-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (26a)

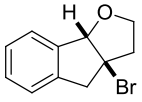


Prepared according to the general procedure from 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (94 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 3H), 1.45 (s, 3H), 3.42 (d, *J* = 17.8 Hz, 1H), 3.72 (d, *J* = 17.8 Hz, 1H), 3.74 (d, *J* = 8.3 Hz, 1H), 3.80 (d, *J* = 8.3 Hz, 1H), 5.51 (s, 1H), 7.24 (d, *J* = 7.3 Hz,

1H), 7.29 (dd, *J* = 7.3 Hz, *J* = 7.2 Hz, 1H), 7.34 (dtd, *J* = 7.3 Hz, *J* = 7.2 Hz, *J* = 1.4 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.2, 28.0, 45.7, 46.7, 78.6, 79.1, 93.1, 124.7, 126.0, 127.6, 129.5, 140.0, 142.0; **IR (ν, cm^{-1}):** 1463 (w, C-C_{Ar}), 1030 (m, C-O), 756 (s, C-Br); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{15}BrNaO]^+$ $(M+Na)^+$ calc. 289.0918, found 289.0916.

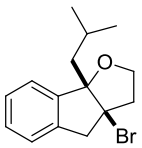
3*a*-Bromo-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (26b)



Prepared according to the general procedure from 2-(1*H*-inden-2-yl)acetic acid. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (75 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (ddd, *J* = 15.9 Hz, *J* = 8.3 Hz, *J* = 7.8 Hz, 1H), 2.65 (ddd, *J* = 13.6 Hz, *J* = 6.1 Hz, *J* = 3.8 Hz, 1H), 3.63 (d, *J* = 16.9 Hz, 1H), 3.72 (d, *J* = 16.9 Hz, 1H), 3.94 (ddd, *J* = 11.6 Hz, *J* = 7.8 Hz, *J* = 4.0 Hz, 1H), 4.16 (td, *J* = 8.6 Hz, *J* = 6.1 Hz, 1H), 5.69 (s, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.28-7.34 (m, 2H), 7.39-7.42 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 44.9, 48.5, 67.0, 68.5, 96.0, 124.5, 125.3, 127.8, 129.2, 139.6, 140.9; **IR (ν, cm^{-1}):** 1461 (w, C-C_{Ar}), 1043 (s, C-O), 750 (s, C-Br); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{11}BrNaO]^+$ $(M+Na)^+$ calc. 260.9885, found 260.9891.

3*a*-Bromo-8*b*-isobutyl-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (26e)

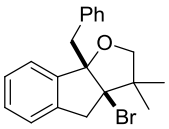


Prepared according to the general procedure from 2-(3-isobutyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (94 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.4 Hz, 3H), 0.80 (s, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.33 (s, 3H), 1.86-1.95 (m, 1H), 1.99-2.04 (m, 2H), 3.32 (d, *J* = 8.4 Hz, 1H), 3.52 (d, *J* = 17.2 Hz,

1H), 3.64 (d, *J* = 17.2 Hz, 1H), 3.78 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 4.5 Hz, *J* = 3.1 Hz, 1H), 7.24 (d, *J* = 5.8 Hz, 1H), 7.26 (t, *J* = 5.5 Hz, 1H), 7.34-7.38 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.3, 23.5, 24.3, 25.2, 28.1, 46.0, 47.3, 49.6, 78.1, 86.0, 97.5, 123.0, 124.7, 127.2, 128.6, 140.1, 144.3; **IR (ν, cm^{-1}):** 1459 (w, C-C_{Ar}), 1075 (s, C-O), 749 (s, C-Br); **HRMS (ESI$^+$, m/z):** $[C_{15}H_{19}BrNaO]^+$ $(M+Na)^+$ calc. 317.0511, found 317.0514.

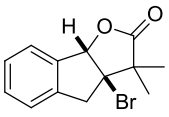
8*b*-Benzyl-3*a*-bromo-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (26f)



Prepared according to the general procedure from 2-(3-benzyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (99 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3H), 1.39 (s, 3H), 2.95 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 8.3 Hz, 1H), 3.60 (d, *J* = 17.2 Hz, 1H), 3.66 (d, *J* = 13.8 Hz, 1H), 3.70 (d, *J* = 17.2 Hz, 1H), 3.95 (d, *J* = 8.3 Hz, 1H), 6.21 (d, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.18 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 7.20-7.29 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.2, 27.7, 45.7, 47.5, 47.5, 78.1, 86.1, 96.4, 122.6, 125.6, 126.4, 126.5, 127.6, 128.5, 131.4, 137.5, 139.9, 142.8; **IR (ν, cm^{-1}):** 1470 (w, C-C_{Ar}), 1032 (s, C-O), 701 (s, C-Br); **HRMS (ESI$^+$, m/z):** $[C_{20}H_{21}BrNaO]^+$ $(M+Na)^+$ calc. 379.0668, found 379.0661.

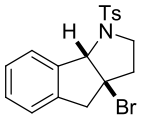
3*a*-Bromo-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (26h)



Prepared according to the general procedure from 2-(1*H*-inden-2-yl)-2-methylpropanoic acid. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (75 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3H), 1.53 (s, 3H), 3.47 (d, *J* = 17.4 Hz, 1H), 3.59 (d, *J* = 17.4 Hz, 1H), 5.68 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.43 (dd, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.9, 26.9, 46.2, 48.3, 73.5, 89.5, 125.1, 127.2, 127.9, 130.8, 135.6, 142.8, 176.8; **IR (ν, cm^{-1}):** 1779 (s, C=O), 1464 (w, C-C_{Ar}), 1120 (m, O-C_{ester}), 963 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{13}BrNaO_2]^+$ $(M+Na)^+$ calc. 302.9991, found 302.9986.

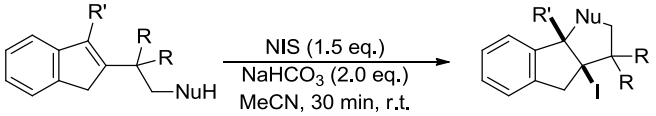
3*a*-Bromo-3,3-dimethyl-1-tosyl-1,2,3,3*a*,4,8*b*-hexahydroindeno[1,2-*b*]pyrrole (26l)



Prepared according to the general procedure from N-(2-(1*H*-inden-2-yl)ethyl)-4-methylbenzenesulfonamide. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (94 % yield, >25:1 d.r.).

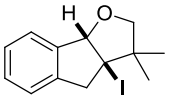
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16-2.34 (m, 2H), 2.46 (s, 3H), 3.42 (d, *J* =16.2 Hz, 1H), 3.51 (ddd, *J* = 11.6 Hz, *J* = 9.2 Hz, *J* = 6.2 Hz, 1H), 3.53 (d, *J* = 16.2 Hz, 1H), 3.64 (ddd, *J* = 9.2 Hz, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 5.32 (s, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.28 (td, *J* = 7.4 Hz, *J* = 0.5 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.83-7.88 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 41.0, 46.3, 48.9, 66.5, 77.8, 124.4, 126.4, 128.1, 128.2, 128.8, 129.7, 133.3, 138.1, 141.6, 143.9; **IR (ν, cm^{-1}):** 1598 (w, C-C_{Ar}), 1478 (w, C-C_{Ar}), 1346 (s, S=O), 1161 (s, S=O), 1103 (m, C-N), 747 (m, N-S), 662 (s, C-Br); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{18}BrNNaO_2S]^+$ $(M+Na)^+$ calc. 414.0134, found 414.0125.

6.2.4 General procedure for iodo-heterocyclization



To a solution of substrate (25 mg) in acetonitrile at room temperature was added sodium bicarbonate (2.0 eq.) followed by *N*-iodosuccinimide (1.5 eq.). The reaction was stirred for 30 minutes before being purified directly by flash chromatography on silica gel.

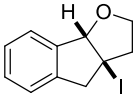
3*a*-Iodo-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (27a)



Prepared according to the general procedure from 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (93 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 3H), 1.48 (s, 3H), 3.53 (d, *J* = 18.0 Hz, 1H), 3.71 (d, *J* = 8.2 Hz, 1H), 3.76 (d, *J* = 18.0 Hz, 1H), 3.78 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.28-7.37 (m, 2H), 7.45 (dd, *J* = 7.3 Hz, *J* = 0.9 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.4, 32.7, 46.4, 50.1, 62.3, 75.4, 95.0, 124.7, 126.1, 127.6, 129.5, 139.8, 142.1; **IR (ν, cm^{-1}):** 1461 (w, C-C_{Ar}), 1028 (s, C-O), 754 (s, C-I); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{15}INaO]^+$ $(M+Na)^+$ calc. 337.0060, found 337.0063.

3*a*-Iodo-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (27b)

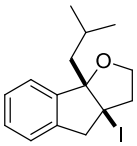


Prepared according to the general procedure from 2-(1*H*-inden-2-yl)ethanol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (83 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17-2.26 (m, 1H), 2.67 (ddd, *J* = 13.7 Hz, *J* = 6.2 Hz, *J* = 4.3 Hz, 1H), 3.67 (d, *J* = 17.1 Hz, 1H), 3.82 (d, *J* = 17.1 Hz, 1H), 3.91 (ddd, *J* = 8.5 Hz, *J* = 7.1 Hz, *J* = 4.2 Hz, 1H), 4.11 (td, *J* = 8.5 Hz, *J* = 6.3 Hz, 1H), 5.83 (s, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.25-7.33 (m, 2H), 7.39-7.43 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 42.1, 47.3, 51.8, 68.3, 98.4, 124.3,

125.2, 127.7, 129.1, 139.8, 140.9; **IR (ν, cm^{-1}):** 1476 (w, C-C_{Ar}), 1040 (m, C-O), 749 (s, C-I); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{11}INaO]^+$ $(M+Na)^+$ calc. 308.9747, found 308.9751.

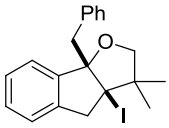
3*a*-Iodo-8*b*-isobutyl-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (27e)



Prepared according to the general procedure from 2-(3-isobutyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (71 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.43 (s, 3H), 2.00-2.13 (m, 3H), 3.40 (d, *J* = 8.4 Hz, 1H), 3.75 (d, *J* = 8.2 Hz, 1H), 3.76 (d, *J* = 4.5 Hz, 1H), 7.07-7.11 (m, 1H), 7.21-7.27 (m, 2H), 7.39-7.43 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.1, 23.8, 25.3, 34.2, 47.3, 50.3, 53.4, 73.1, 77.1, 97.2, 123.1, 124.5, 127.2, 128.6, 141.1, 143.3; **IR (ν, cm^{-1}):** 1468 (w, C-C_{Ar}), 1044 (s, C-O), 758 (s, C-I); **HRMS (ESI$^+$, m/z):** $[C_{15}H_{19}INaO]^+$ $(M+Na)^+$ calc. 365.0373, found 365.0375.

8*b*-Benzyl-3*a*-iodo-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (27f)

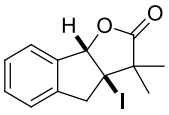


Prepared according to the general procedure from 2-(3-benzyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (52 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3H), 1.49 (s, 3H), 3.06 (d, *J* = 13.7 Hz, 1H), 3.41 (d, *J* = 8.5 Hz, 1H), 3.67 (d, *J* =13.7 Hz, 1H), 3.83 (d, 17.6 Hz, 1H), 3.88 (d, *J* = 8.5 Hz, 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 6.25 (d, *J* = 7.8 Hz, 1H), 6.92 (td, *J* = 7.6 Hz, *J* = 0.7 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.17 (td, *J* = 7.4 Hz, *J* = 1.0 Hz, 1H), 7.27-7.30 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.8, 34.2, 47.7, 50.2, 52.9, 72.9, 76.9, 96.1, 122.6, 125.5, 126.4, 126.5, 127.7, 128.6, 131.3,

138.3, 141.0, 141.5; **IR (ν, cm^{-1}):** 1495 (w, C-C_{Ar}), 1455 (w, C-C_{Ar}), 1030 (s, C-O), 701 (s, C-I); **HRMS (ESI$^+$, m/z):** $[C_{20}H_{21}INaO]^+$ $(M+Na)^+$ calc. 427.0529, found 427.0514.

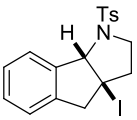
3*a*-Iodo-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (27h)



Prepared according to the general procedure from 2-(1*H*-inden-2-yl)-2-methylpropanoic acid. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (86 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3H), 1.54 (s, 3H), 3.56 (d, *J* = 17.6 Hz, 1H), 3.63 (d, *J* = 17.6 Hz, 1H), 5.77 (s, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.43 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.2, 31.2, 49.0, 49.2, 55.3, 91.2, 125.1, 127.2, 127.9, 130.8, 135.7, 142.9, 174.9; **IR (ν, cm^{-1}):** 1777 (s, C=O), 1462 (w, C-C_{Ar}), 1116 (s, O-C), 951 (s, C-O), 732 (m, C-I); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{13}INaO_2]^+$ $(M+Na)^+$ calc. 350.9852, found 350.9842.

3*a*-Iodo-1-tosyl-1,2,3,3*a*,4,8*b*-hexahydroindeno[1,2-*b*]pyrrole (27l)

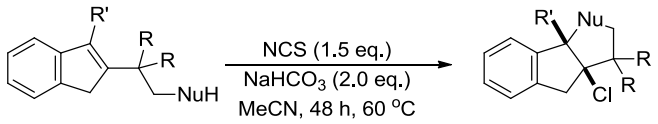


Prepared according to the general procedure from *N*-(2-(1*H*-inden-2-yl)ethyl)-4-methylbenzenesulfonamide. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.05 (ddd, *J* = 14.1 Hz, *J* = 11.6 Hz, *J* = 7.3 Hz, 1H), 2.30 (dd, *J* = 14.0 Hz, *J* = 5.7 Hz, 1H), 2.46 (s, 3H), 3.50 (d, *J* = 16.4 Hz, 1H), 3.54 (ddd, *J* = 11.6 Hz, *J* = 9.4 Hz, *J* = 5.7 Hz, 1H), 3.61-3.65 (m, 1H), 3.69 (d, *J* = 16.8 Hz, 1H), 5.44 (s, 1H), 7.14 (d, *J* =7.2 Hz, 1H), 7.27 (td, *J* = 7.6 Hz, *J* = 1.1 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 41.4, 43.7, 49.3, 49.8, 80.0, 124.1, 126.3, 128.1, 128.3,

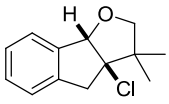
128.7, 129.8, 133.5, 138.5, 142.0, 143.9; **IR (ν, cm^{-1}):** 1598 (w, C-C_{Ar}), 1460 (w, C-C_{Ar}), 1345 (s, S=O), 1161 (s, S=O), 1100 (m, C-N), 747 (s, N-S), 662 (s, C-I); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{18}INNaO_2S]^+$ $(M+Na)^+$ calc. 461.9995, found 461.9991.

6.2.5 General procedure for chloro-heterocyclization



To a solution of substrate (25 mg) in acetonitrile in a sealed vial at room temperature was added sodium bicarbonate (2.0 eq.) followed by *N*-chlorosuccinimide (1.5 eq.). The reaction was stirred for 48 hours at 60 °C before being purified directly by flash chromatography on silica gel.

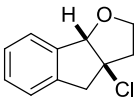
3*a*-Chloro-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (28a)



Prepared according to the general procedure from 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (71 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.40 (s, 3H), 3.26 (d, *J* = 17.5 Hz, 1H), 3.63 (d, *J* = 17.5 Hz, 1H), 3.73 (d, *J* = 8.5 Hz, 1H), 3.84 (d, *J* = 8.5 Hz, 1H), 5.41 (s, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.34 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.3, 25.2, 45.1, 45.5, 79.9, 84.2, 92.9, 124.7, 126.0, 127.6, 129.4, 140.1, 141.9; **IR (ν, cm^{-1}):** 1596 (w, C-C_{Ar}), 1462 (w, C-C_{Ar}), 1112 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{15}ClNaO]^+$ $(M+Na)^+$ calc. 245.0704, found 245.0709.

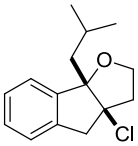
3*a*-Chloro-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (28b)



Prepared according to the general procedure from 2-(1*H*-inden-2-yl)ethanol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (38 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (ddd, *J* = 13.4 Hz, *J* = 8.7 Hz, *J* = 7.4 Hz, 1H), 2.54 (ddd, *J* = 13.3 Hz, *J* = 6.1 Hz, *J* = 3.9 Hz, 1H), 3.55 (s, 2H), 3.94 (ddd, *J* = 8.2 Hz, *J* = 7.7 Hz, 4.0 Hz, 1H), 4.17 (td, *J* = 8.7 Hz, 6.1 Hz, 1H), 5.52 (s, 1H), 7.16-7.20 (m, 1H), 7.28-7.34 (m, 2H), 7.38-7.42 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 43.8, 47.1, 68.4, 76.2, 95.1, 124.7, 125.4, 127.8, 129.1, 139.4, 140.7; **IR (ν, cm^{-1}):** 1595 (w, C-C_{Ar}), 1463 (w, C-C_{Ar}), 1108 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{11}ClNaO]^+$ $(M+Na)^+$ calc. 217.0391, found 217.0395.

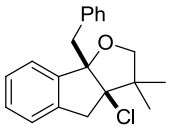
3*a*-Chloro-8*b*-isobutyl-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (28e)



Prepared according to the general procedure from 2-(3-isobutyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (99 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.5 Hz, 3H), 0.77 (s, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.24 (s, 3H), 1.80-1.92 (m, 1H), 1.94 (d, *J* = 7.0 Hz, 1H), 1.95 (d, *J* = 4.2 Hz, 1H), 3.31 (d, *J* = 8.4 Hz, 1H), 3.31 (d, *J* =17.0 Hz, 1H), 3.55 (d, *J* = 17.0 Hz, 1H), 3.77 (d, *J* = 8.4 Hz, 1H), 7.07-7.11 (m, 1H), 7.23-7.27 (m, 2H), 7.32-7.37 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.5, 23.7, 24.0, 24.7, 25.3, 44.2, 47.2, 78.3, 88.1, 97.7, 123.1, 124.7, 127.2, 128.5, 139.4, 144.6; **IR (ν, cm^{-1}):** 1596 (w, C-C_{Ar}), 1465 (w, C-C_{Ar}), 1109 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{15}H_{19}ClNaO]^+$ $(M+Na)^+$ calc. 273.1017, found 273.1021.

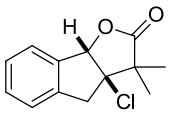
8*b*-Benzyl-3*a*-chloro-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan (28f)



Prepared according to the general procedure from 2-(3-benzyl-1*H*-inden-2-yl)-2-methylpropan-1-ol. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless solid (41 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (s, 3H), 1.29 (s, 3H), 2.91 (d, *J* = 13.8 Hz, 1H), 3.33 (d, *J* = 17.0 Hz, 1H), 3.42 (d, *J* = 8.4 Hz, 1H), 3.55 (d, *J* = 2.6 Hz, 1H), 3.59 (s, 1H), 3.94 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.15-7.20 (m, 3H), 7.22-7.26 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.7, 24.3, 43.7, 44.5, 47.4, 78.3, 88.2, 96.7, 122.8, 125.5, 126.3, 126.5, 127.6, 128.5, 131.4, 137.0, 139.2, 143.3; **IR (ν, cm^{-1}):** 1592 (w, C-C_{Ar}), 1461 (w, C-C_{Ar}), 1112 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{20}H_{21}ClNaO]^+$ $(M+Na)^+$ calc. 335.1173, found 335.1176.

3*a*-Chloro-3,3-dimethyl-3,3*a*,4,8*b*-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (28h)

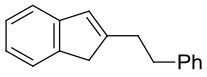


Prepared according to the general procedure from 2-(1*H*-inden-2-yl)-2-methylpropanoic acid. Purification by flash chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (72 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3H), 1.50 (s, 3H), 3.32 (d, *J* = 17.3 Hz, 1H), 3.51 (d, *J* = 17.2 Hz, 1H), 5.57 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.42 (td, *J* = 7.4 Hz, *J* = 1.0 Hz, 1H), 7.56 (d, *J* =7.5 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.8, 24.4, 44.9, 47.9, 79.7, 89.0, 125.1, 127.2, 127.9, 130.7, 135.5, 142.7, 171.6; **IR (ν, cm^{-1}):** 1593 (w, C-C_{Ar}), 1463 (w, C-C_{Ar}), 1109 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{13}ClNaO_2]^+$ $(M+Na)^+$ calc. 259.0496, found 259.0499.

6.2.6 Substrate synthesis (carbocyclization)

2-Phenethyl-1*H*-indene (30a)

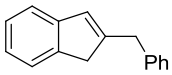


To a flask containing ether (100 mL) in an ambient temperature water bath was added magnesium turnings (729 mg, 30.0 mmol). To the flask was added (2-bromoethyl)benzene (4.10 mL, 30.0 mmol) followed by 1 crystal of iodine. After approx 2 hours all the magnesium had been consumed. β-indanone (2.72 g, 20.0 mmol) was added as a solution in ether (10 mL) over a period of 10 minutes and the reaction was left to stir at room temperature overnight. The excess Grignard reagent was destroyed by the addition of saturated NH_4Cl solution and the product was extracted into ether (3 x 50 mL). The combined ethereal extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was redissolved in benzene (150 mL) and was refluxed under Dean-Stark conditions for 3 hours in the presence of PTSA (380 mg, 2.00 mmol, 10 mol%). The reaction was cooled to room temperature and quenched with $NaHCO_3$. After 30 minutes of stirring the product was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a white solid (1.22 g, 5.60 mmol, 28 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81-2.88 (m, 2H), 2.94-3.01 (m, 2H), 3.36 (s, 2H), 6.58 (s, 1H), 7.14 (td, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 7.20-7.29 (m, 4H), 7.29-7.36 (m, 3H), 7.41 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 33.0, 35.4, 41.2, 120.0, 123.4, 123.7, 126.0, 126.3, 126.6, 128.3, 128.4, 141.9, 143.1, 145.5, 149.8.

Data consistent with literature values.[12]

2-Benzyl-1*H*-indene (30b)

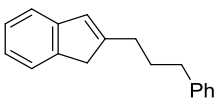


To a solution of 2-indanone (1.32 g, 10.0 mmol) in ether (50 mL) at room temperature was added benzyl magnesium chloride (1.5 M sln in THF, 10 mL, 15.0 mmol) and the reaction was stirred overnight before being cooled to 0 °C and quenched with 1M HCl. The product was extracted into ether (2 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a yellow solid which was used directly in the next step. To a solution of 2-benzyl-2,3-dihydro-1H-inden-2-ol (200 mg, 0.89 mmol) in benzene (5 mL) was added phosphorous pentoxide (152 mg, 1.07 mmol) and the reaction heated at reflux for 1 hour. After cooling to room temperature the crude reaction mixture was poured onto silica gel and eluted with EtOAc/PE 1:49 to afford the title compound as a colourless oil (56 mg, 0.27 mmol, 30 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.35 (s, 2H), 3.89 (s, 2H), 6.59 (s, 1H), 7.14-7.51 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 38.0, 40.9, 120.3, 123.5, 123.9, 126.3, 126.3, 127.9, 128.5, 128.9, 140.1, 143.5, 145.4, 149.3.

Data consistent with literature values.[13]

2-(3-Phenylpropyl)-1*H*-indene (1c)



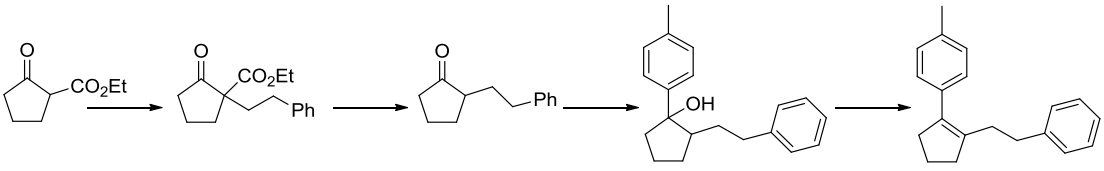
To a flame dried 2-necked 100 mL flask containing ether (50 mL) in an ambient temperature water bath at room temperature was added magnesium (146 mg, 6.00 mmol) followed by (3-bromopropyl)benzene (1.19 g, 6.00 mmol) and a single crystal of iodine. The reaction was stirred until all the magnesium was consumed (approx 3 hours). After which, 2-indanone (661 mg, 5.00 mmol) was added as a solution in ether (5 mL) over 10 minutes. The reaction was stirred overnight before

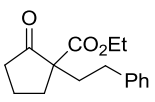
quenching with NH_4Cl and extracting into ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the alcohol intermediate as a white solid. Dehydration was achieved by addition of P_2O_5 (227 mg, 1.60 mmol) to a solution of the alcohol intermediate in benzene (20 mL) at room temperature. After stirring for 2 hours the reaction was quenched with water and the product extracted into ethyl acetate. The combined organic fractions were washed with $NaHCO_3$ then brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a yellow oil (91 mg, 0.39 mmol, 8 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (tt, *J* = 7.7 Hz, *J* = 7.7 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.7 Hz, 2H), 3.33 (s, 2H), 6.55 (s, 1H), 7.12 (td, *J* = 7.3 Hz, *J* = 1.0 Hz, 1H), 7.19-7.24 (m, 1H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.6, 30.7, 35.6, 41.0, 119.9, 123.4, 123.6, 125.8, 126.2, 126.4, 128.3, 128.5, 142.2, 143.1, 145.6, 150.3.

Data consistent with literature values.[14]

1-Methyl-4-(2-phenethylcyclopent-1-en-1-yl)benzene (30d)



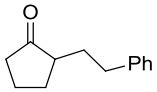


To a solution of ethyl 2-oxocyclopentanecarboxylate (1.00 g, 6.40 mmol) in toluene (25 mL) was added NaH (60 % dispersion in mineral oil, 282 mg, 7.04 mmol) and the reaction stirred for 30 minutes before the addition of (2-bromoethyl)benzene

(1.05 mL, 7.68 mmol). The reaction was subsequently heated at reflux for 96 hours before cooling to room temperature and quenching with NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (614 mg, 2.36 mmol, 37 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.7 Hz, 3H), 1.86 (ddd, *J* = 13.6 Hz, *J* = 12.3 Hz, *J* = 4.8 Hz, 1H), 1.92-2.11 (m, 3H), 2.21-2.36 (m, 2H), 2.38-2.77 (m, 4H), 4.19 (q, *J* = 7.7 Hz, 2H), 7.16-7.23 (m, 3H), 7.25-7.32 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.1, 19.6, 31.2, 33.0, 35.8, 37.9, 60.4, 61.5, 126.0, 128.4, 128.4, 141.4, 170.8, 214.6.

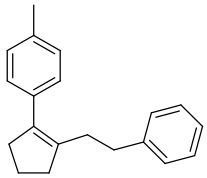
Data consistent with literature values.[15]



A solution of ethyl 2-oxo-1-phenethylcyclopentanecarboxylate (600 mg, 2.31 mmol) in 3M HCl (50 mL) was heated at reflux for 24 hours before cooling to room temperature and extracting into ether (3 x 50 mL). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (154 mg, 0.82 mmol, 35 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50-1.64 (m, 2H), 1.70-1.85 (m, 1H), 1.97-2.20 (m, 4H), 2.21-2.37 (m, 2H), 2.61-2.79 (m, 2H), 7.16-7.24 (m, 3H), 7.25-7.32 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.7, 29.7, 31.4, 33.6, 38.2, 48.4, 125.9, 128.4, 128.4, 141.6, 221.3.

Data consistent with literature values.[16]

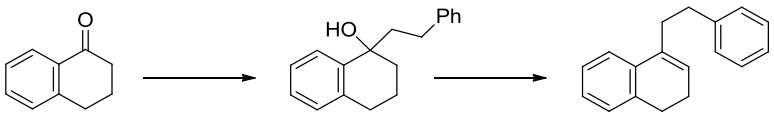


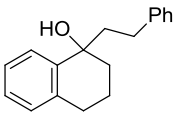
To a solution of 2-phenethylcyclopentanone (150 mg, 0.80 mmol) in ether (5 mL) at room temperature was added p-tolylmagnesium bromide (0.5M sln in ether, 3.2 mL, 1.60 mmol) and the reaction was stirred for 1

hour before quenching with NH_4Cl. The aqueous phase was extracted into ether, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the intermediate tertiary alcohol as a colourless oil which was employed directly in the next step. The intermediate 2-phenethyl-1-(*p*-tolyl)cyclopentanol was diluted in toluene (10 mL) and heated to 100 °C before the addition of PTSA (15 mg, 0.08 mmol). Stirring was continued for 2 hours before cooling to room temperature and concentrating *in vacuo*. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (131 mg, 0.50 mmol, 62 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88-1.98 (m, 2H), 2.35 (s, 3H), 2.52-2.60 (m, 4H), 2.72 (t, *J* = 6.9 Hz, 2H), 2.80 (t, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.16-7.23 (m, 3H), 7.25-7.32 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.1, 22.1, 31.4, 33.9, 34.6, 37.0, 37.7, 125.8, 127.4, 128.3, 128.3, 128.7, 135.8, 135.8, 136.0, 137.8, 142.3; **IR (ν, cm^{-1}):** 1605 (m, C=C), 1496 (m, C-C_{Ar}), 1454 (m, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{20}H_{22}$] calc. 262.1721, found 262.1726.

4-Phenethyl-1,2-dihydronaphthalene (30e)

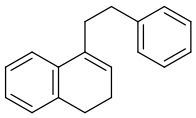




To a flame dried flask fitted with a reflux condenser containing ether (15 mL) was added magnesium turnings (182 mg, 7.5 mmol) and a single crystal of iodine. The reaction was stirred until the iodine colour began to disappear, at which point (2-bromoethyl)benzene (1.02 mL, 7.5 mmol) was added slowly so as to maintain a steady reflux. Once all the magnesium had been consumed (2-3 hours), 1-tetralone (665 µL, 5.0 mmol) was added as a solution in ether (3 mL) dropwise over about 10 minutes. The

reaction was stirred for a further 10 minutes before carefully quenching with NH_4Cl and extracting into ether (3 x 25 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1-phenethyl-1,2,3,4-tetrahydronaphthalen-1-ol as a colourless oil (862 mg, 3.42 mmol, 68 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84-2.01 (m, 3H), 2.10-2.31 (m, 3H), 2.59-2.69 (m, 1H), 2.71-2.92 (m, 4H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.16-7.37 (m, 7H), 7.60 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.8, 29.8, 30.6, 36.1, 44.3, 72.4, 125.7, 126.2, 126.3, 127.2, 128.3, 128.4, 129.0, 136.8, 142.1, 142.4; **IR (ν, cm^{-1}):** 3356 (br, O-H), 1484 (w, C-C_{Ar}), 1449 (w, C-C_{Ar}); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{20}NaO]^+$ $(M+Na)^+$ calc. 275.1406, found 275.1409.

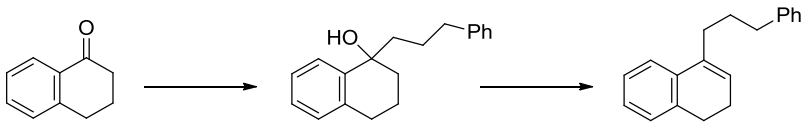


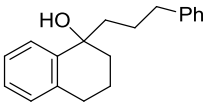
To a solution of 1-phenethyl-1,2,3,4-tetrahydronaphthalen-1-ol (830 mg, 3.29 mmol) in toluene (50 mL) at 100 °C was added PTSA monohydrate (63 mg, 0.33 mmol) and stirring was continued for 2 hours before cooling to room temperature. The reaction was directly poured onto a pad of silica (6 inch) pre-packed with petroleum ether. The silica was washed with EtOAc/PE (1:49) to afford the title compound as a colourless oil (578 mg, 2.47 mmol, 75 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22-2.30 (m, 2H), 2.73-2.81 (m, 4H), 2.85-2.92 (m, 2H), 5.87 (t, *J* = 4.5 Hz, 1H), 7.17-7.21 (m, 2H), 7.22-7.29 (m, 4H), 7.30-7.38 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.1, 28.4, 34.8, 35.0, 122.5, 125.3, 125.8, 126.4, 126.6, 127.7, 128.3, 128.5, 134.8, 135.8, 136.8, 142.3.

Data consistent with literature values.[17]

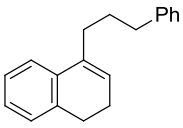
4-(3-Phenylpropyl)-1,2-dihydronaphthalene (30f)





To a flame dried flask fitted with a reflux condenser containing ether (15 mL) was added magnesium turnings (182 mg, 7.5 mmol) and a single crystal of iodine. The reaction was stirred until the iodine colour began to disappear, at which point (3-bromopropyl)benzene (1.14 mL, 7.5 mmol) was added slowly so as to maintain a steady reflux. Once all the magnesium had been consumed (2-3 hours), 1-tetralone (665 µL, 5.0 mmol) was added as a solution in ether (3 mL) dropwise over about 10 minutes. The reaction was stirred for a further 10 minutes before carefully quenching with NH_4Cl and extracting into ether (3 x 25 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1-phenethyl-1,2,3,4-tetrahydronaphthalen-1-ol as a colourless oil (934 mg, 3.53 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54-1.67 (m, 1H), 1.71-2.10 (m, 8H), 2.56-2.88 (m, 4H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.16-7.34 (m, 7H), 7.51 (dd, *J* = 7.9 Hz, *J* = 1.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.7, 26.1, 29.9, 36.1, 36.3, 42.0, 72.4, 125.7, 126.2, 126.3, 127.1, 128.3, 128.5, 128.9, 136.8, 142.2, 142.4; **IR (v, cm^{-1}):** 3379 (br, O-H), 1487 (w, C-C_{Ar}), 1452 (w, C-C_{Ar}); **HRMS (ESI$^+$, m/z):** $[C_{19}H_{22}NaO]^+$ $(M+Na)^+$ calc. 289.1563, found 289.1553.

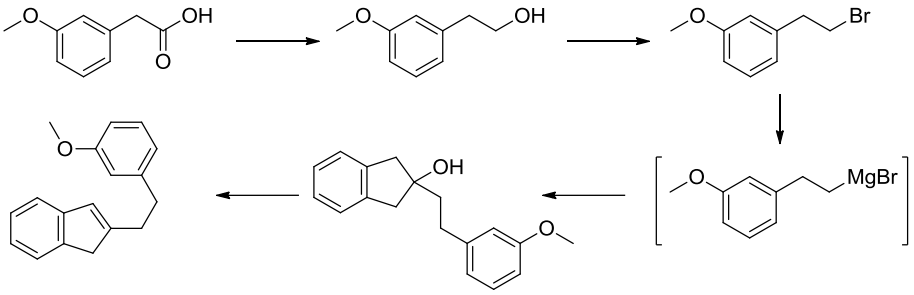


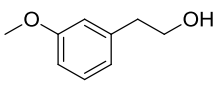
To a solution of 1-(3-phenylpropyl)-1,2,3,4-tetrahydronaphthalen-1-ol (900 mg, 3.40 mmol) in toluene (50 mL) at 100 °C was added PTSA monohydrate (65 mg, 0.34 mmol) and stirring was continued for 2 hours before cooling to room temperature. The reaction was directly poured onto a pad of silica (6 inch) pre-packed

with petroleum ether. The silica was washed with EtOAc/PE (1:49) to afford the title compound as a colourless oil (537 mg, 2.16 mmol, 64 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86-1.97 (m, 2H), 2.34-2.32 (m, 2H), 2.52 (t, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 7.7 Hz, 2H), 2.77 (t, *J* = 8.1 Hz, 2H), 5.90 (t, *J* = 4.5 Hz, 1H), 7.14-7.26 (m, 7H), 7.28-7.35 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.1, 28.5, 30.1, 32.2, 35.7, 122.6, 125.0, 125.7, 126.3, 126.5, 127.6, 128.3, 128.5, 134.9, 136.2, 136.8, 142.5; **IR (ν, cm^{-1}):** 1602 (w, C=C), 1487 (m, C-C_{Ar}), 1452 (m, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{19}H_{20}$] calc. 248.1565, found 248.1574.

2-(3-Methoxyphenethyl)-1*H*-indene (30g)

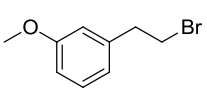




To a suspension of $LiAlH_4$ (1.14 g, 30.1 mmol) in THF (40 mL) at 0 °C was added 3-methoxyphenylacetic acid (5.0 g, 30.1 mmol) portionwise followed by stirring at room temperature for 24 hours. The reaction was quenched with 1 % KOH, filtered through celite and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 3:7) afforded 2-(3-methoxyphenyl)ethanol as a colourless liquid (3.95 g, 26.0 mmol, 86 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85 (t, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 3.83-3.90 (m, 2H), 6.77-6.81 (m, 2H), 6.83 (d, *J* = 7.7 Hz, 1H), 7.22-7.26 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 39.2, 55.2, 63.5, 111.8, 114.8, 121.3, 129.6, 140.1, 159.8.

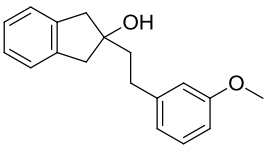
Data consistent with literature values.[18]



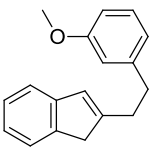
To a solution of 2-(3-methoxyphenyl)ethanol (3.50 g, 23.0 mmol) in ether (25 mL) at room temperature was added phosphorous tribromide (2.81 mL, 29.9 mmol) and the reaction was stirred overnight. After pouring onto ice-water the product was extracted into chloroform, washed with $NaHCO_3$, dried over Na_2SO_4 and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1-(2-bromoethyl)-3-methoxybenzene as a colourless liquid (1.98 g, 9.21 mmol, 40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16 (t, *J* = 7.7 Hz, 2H), 3.58 (t, *J* = 7.7 Hz, 2H), 3.82 (s, 3H), 6.76-6.78 (m, 1H), 6.80-6.82 (m, 1H), 6.82-6.84 (m, 1H), 7.23-7.28 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 32.7, 39.5, 55.2, 112.2, 114.5, 121.0, 129.6, 140.4, 159.8.

Data consistent with literature values.[19]



To a flask containing ether (100 mL) in an ambient temperature water bath was added magnesium turnings (224 mg, 9.21 mmol), followed by 1-(2-bromoethyl)-3-methoxybenzene (1.98 g, 9.21 mmol) as a solution in ether (10 mL). The reaction was activated by the addition of a single crystal of iodine and was left to stir for 6 hours, after which, all the magnesium had been consumed. Next, β-indanone (811 mg, 6.14 mmol) was added as a solution in ether (10 mL) dropwise. The reaction was stirred overnight before quenching with NH_4Cl (25 mL) and stirring for a further 30 minutes. The aqueous layer was extracted with ether (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was used in the next step without isolation or further purification.

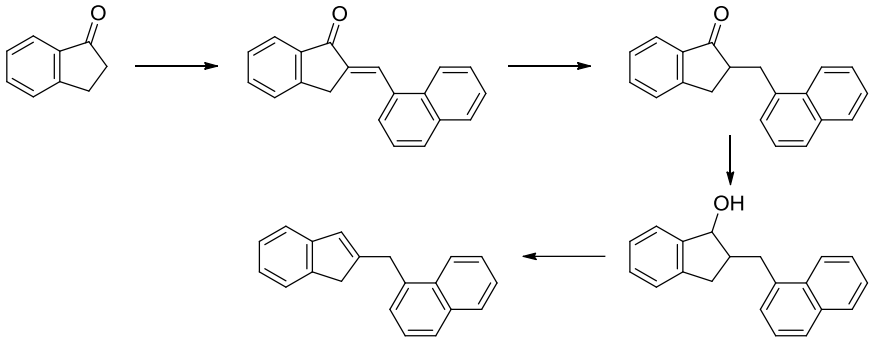


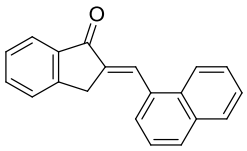
To a solution of crude 2-(3-methoxyphenethyl)-2,3-dihydro-1H-inden-2-ol obtained from the Grignard reaction in benzene (150 mL) was added PTSA

(175 mg, 0.92 mmol) and the reaction was heated at reflux under Dean-Stark conditions for 3 hours. After cooling to room temperature, the acid was quenched with $NaHCO_3$ (50 mL) and stirred for 30 minutes. The product was extracted into EtOAc (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless liquid (461 mg, 1.84 mmol, 20 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80-2.86 (m, 2H), 2.91-2.97 (m, 2H), 3.35 (s, 2H), 3.81 (s, 3H), 6.57 (s, 1H), 6.77 (dd, *J* = 8.1 Hz, *J* = 2.5 Hz, 1H), 6.79-6.82 (m, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 7.13 (td, *J* =7.4 Hz, *J* =1.3 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* =7.3 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 32.9, 35.4, 41.2, 55.1, 111.2, 114.1, 120.0, 120.7, 123.4, 123.7, 126.3, 126.6, 129.3, 143.0, 143.5, 145.5, 149.8, 159.7; **IR (ν, cm^{-1}):** 1601 (m, C=C), 1490 (m, C-C_{Ar}), 1461 (m, C-C_{Ar}), 1051 (m, C-O); **HRMS (FI$^+$):** [$C_{18}H_{18}O$] calc. 250.1358, found 250.1360.

1-((1*H*-inden-2-yl)methyl)naphthalene (30h)



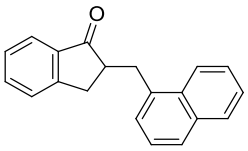


To a mixture of ethanol (10 mL) and KOH (3 g in 30 mL water) at room temperature was added 1-indanone (1.32 g, 10.0 mmol) followed by 1-naphthaldehyde (1.36 mL, 10.0 mmol). After stirring overnight the resulting solid was filtered and washed with water. The residue was redissolved in ethanol

(10 mL) and NaOH (15 g in 30 mL water) and stirred at room temperature for 2 hours before the solid was again filtered and washed with water. The residue was dissolved in DCM and washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. After recrystallising from hexane the title compound was obtained as a yellow solid (1.84 g, 6.79 mmol, 68 % yield).

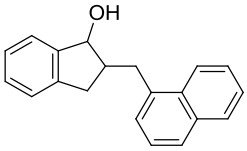
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (d, *J* = 1.4 Hz, 2H), 7.45 (td, *J* = 7.4 Hz, *J* = 0.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.53-7.60 (m, 3H), 7.61 (td, *J* = 7.4 Hz, *J* = 1.0 Hz, 1H), 7.79 (d, *J* =7.2 Hz, 1H), 7.89-7.92 (m, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.46 (t, *J* = 2.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 32.0, 124.1, 124.5, 125.2, 126.2, 126.3, 126.8, 127.0, 127.7, 128.7, 129.9, 130.9, 132.3, 133.7, 134.6, 137.2, 138.3, 150.0, 193.9.

Data consistent with literature values.[20]

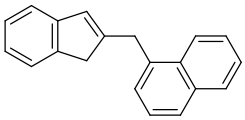


To a suspension of 2-(naphthalen-1-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (805 mg, 2.98 mmol) in ethanol (20 mL) at room temperature was added Pd/C (10 wt %, 319 mg, 0.30 mmol). An atmosphere of hydrogen was applied and the reaction stirred for 2 hours before filtering through celite and evaporating under reduced pressure to afford the title compound as a colourless oil (805 mg, 2.98 mmol, quant. yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82-3.18 (m, 3H), 3.13-3.29 (m, 1H), 4.06 (dd, *J* = 14.1 Hz, *J* = 3.3 Hz, 1H), 7.35-7.65 (m, 7H), 7.79 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H), 7.81-7.93 (m, 2H), 8.17-8.24 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 33.3, 35.1, 48.7, 124.1, 124.6, 125.9, 126.2, 126.7, 127.0, 127.1, 127.8, 127.9, 129.4, 132.3, 134.5, 135.3, 136.3, 137.0, 154.1, 208.4; **IR (ν, cm^{-1}):** 1769, 1494, 1439; **HRMS (ESI$^+$, m/z):** $[C_{20}H_{16}NaO]^+$ $(M+Na)^+$ calc. 295.1093, found 295.1097.



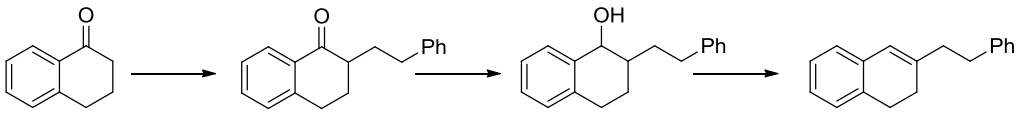
To a solution of 2-(naphthalen-1-ylmethyl)-2,3-dihydro-1H-inden-1-one (805 mg, 2.98 mmol) in methanol (25 mL) at room temperature was added $NaBH_4$ (225 mg, 5.96 mmol) and the reaction stirred for 1 hour. After cooling to 0 °C the reaction was quenched with 1 M HCl and extracted into EtOAc. After drying over $MgSO_4$ the solvent was evaporated under reduced pressure to afford the title compound as a white solid (721 mg, 2.63 mmol, 88 % yield).

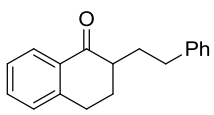


To a solution of 2-(naphthalen-1-ylmethyl)-2,3-dihydro-1H-inden-1-ol (700 mg, 2.55 mmol) in benzene (50 mL) was added P_2O_5 (435 mg, 3.06 mmol) and the reaction stirred at room temperature for 1 hour. The reaction was poured onto ice-water, extracted into EtOAc, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (551 mg, 2.15 mmol, 84 % yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.35 (s, 2H), 4.28 (s, 2H), 6.41-6.46 (m, 1H), 7.03-8.13 (m, 11H)**; IR (ν, cm^{-1}):** 1610 (w, C=C), 1509 (w, C-C_{Ar}), 1460 (w, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{20}H_{16}$] calc. 256.1252, found 256.1251.

3-Phenethyl-1,2-dihydronaphthalene (30i)



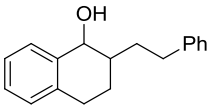


To a solution of potassium *tert*-butoxide (102 mg, 0.91 mmol) in DMSO (9 mL) was added 1-tetralone (905 µL, 6.8 mmol) and styrene (265 µL, 2.3 mmol) and the reaction heated at 40 °C for 15 h. The reaction was quenched with water (5 mL) and extracted into DCM (3 x 15 mL). The combined organic fractions were washed

with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 2-phenethyl-3,4-dihydronaphthalen-1(2*H*)-one as a colourless oil (550 mg, 2.20 mmol, 96 % yield).

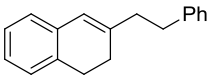
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75-1.87 (m, 1H), 1.90-2.04 (m, 1H), 2.25-2.40 (m, 2H), 2.47-2.58 (m, 1H), 2.69-2.87 (m, 2H), 2.98-3.05 (m, 2H), 7.16-7.35 (m, 7H), 7.47 (t, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 28.4, 28.5, 31.3, 33.1, 46.8, 125.9, 126.6, 127.4, 128.4, 128.5, 128.7, 132.5, 133.1, 142.0, 143.9, 200.2.

Data consistent with literature values.[21]



To a solution of 2-phenethyl-3,4-dihydronaphthalen-1(2*H*)-one (538 mg, 2.15 mmol) in methanol (10 mL) was added $NaBH_4$ (163 mg, 4.30 mmol) and the reaction stirred for 1 hour. Water was added and then extracted into EtOAc (3 x 25 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 2-phenethyl-1,2,3,4-tetrahydronaphthalen-1-ol as a colourless oil (524 mg, 2.08 mmol, 97 % yield).

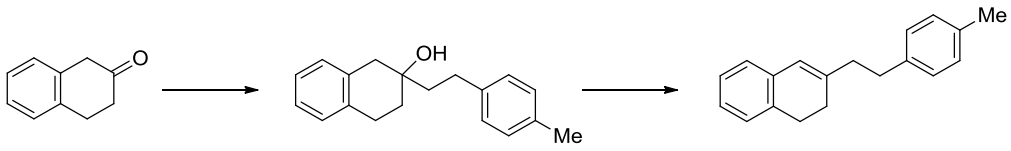
Mixture of diastereomers (1:1.5 syn:anti); **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.48-1.89 (m, 4H), 1.95-2.22 (m, 2H), 2.64-2.95 (m, 4H), 4.48 (d, *J* = 7.0 Hz, $1H_{anti}$), 4.71 (s, $1H_{syn}$), 7.08-7.54 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.9 (syn), 24.5 (anti), 27.5 (anti), 29.1 (syn), 33.3 (syn), 33.3 (anti), 33.4 (anti), 33.4 (syn), 38.9 (syn), 41.4 (anti), 69.9 (syn), 73.3 (anti), 125.7 (syn), 125.8 (anti), 126.2 (syn), 126.3 (anti), 127.4 (anti), 128.0 (syn), 128.4 (anti), 128.4 (syn), 128.4 (syn), 128.4 (anti), 128.5 (anti), 128.7 (anti), 129.1 (syn), 130.0 (syn), 126.8 (anti), 137.0 (syn), 138.6 (syn), 138.7 (anti), 142.4 (anti), 142.6 (syn); **IR (ν, cm^{-1}):** 3348, 1494, 1454; **HRMS (ESI$^+$, m/z):** $[C_{18}H_{20}NaO]^+$ $(M+Na)^+$ calc. 275.1406, found 275.1402.

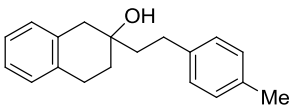


To a solution of 2-phenethyl-1,2,3,4-tetrahydronaphthalen-1-ol (506 mg, 2.00 mmol) in toluene (30 mL) at 100 °C was added PTSA (38 mg, 0.20 mmol) and the reaction stirred for 2 hours. After cooling to room temperature the reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (381 mg, 1.63 mmol, 81 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (t, *J* = 8.1 Hz, 2H), 2.52 (t, *J* = 8.0 Hz, 2H), 2.80-2.89 (m, 4H), 6.26 (s, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 7.07-7.18 (m, 3H), 7.19-7.28 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 27.5, 28.2, 34.3, 39.4, 122.6, 125.4, 125.9, 126.1, 126.4, 127.2, 128.4, 128.4, 134.4, 134.8, 141.4, 142.0; **IR (ν, cm^{-1}):** 1607, 1454; **HRMS (FI$^+$):** [$C_{18}H_{18}$] calc. 234.1409, found 234.1408.

3-(4-Methylphenethyl)-1,2-dihydronaphthalene (30j)

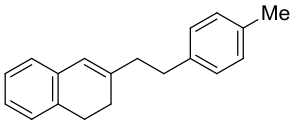




To a 50 mL flame dried flask containing ether (20 mL) fitted with a reflux condenser was added magnesium turnings (122 mg, 5.02 mmol) and a single crystal of iodine. Once the colour began to disappear, 1-(2-bromoethyl)-4-methylbenzene (1.00 g, 5.02 mmol) was added in a single portion. The reaction quickly reached reflux and was left to stir for 2 hours before the addition of 2-tetralone (489 mg, 3.35 mmol) as a solution in ether (3 mL). The reaction was stirred for 20 minutes before quenching with NH_4Cl solution and extracting into ether. The ether layer was further washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by

column chromatography (SiO_2, EtOAc/PE 1:9) afforded 2-(4-methylphenethyl)-1,2,3,4-tetrahydronaphthalen-2-ol as a yellow oil (199 mg, 0.75 mmol, 22 % yield).

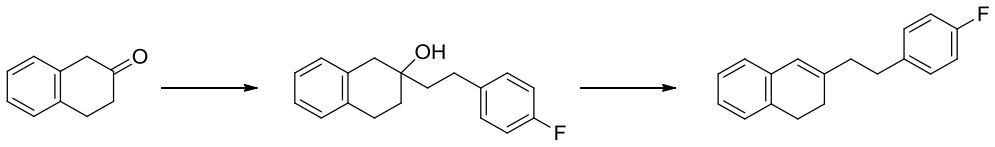
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82-1.92 (m, 3H), 1.95 (dtd, *J* = 13.2 Hz, *J* = 5.8 Hz, *J* = 1.6 Hz, 1H), 2.33 (s, 3H), 2.76-2.90 (m, 4H), 2.94 (d, *J* = 16.6 Hz, 1H), 3.04 (ddd, *J* = 17.2 Hz, *J* = 9.1 Hz, *J* = 6.3 Hz, 1H), 7.06-7.18 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.0, 26.1, 29.1, 33.8, 42.1, 43.4, 70.9, 125.9, 126.0, 128.2, 128.7, 129.1, 129.7, 134.3, 135.3, 135.4, 139.3; **IR (ν, cm^{-1}):** 3405, 1453; **HRMS (ESI$^+$, m/z):** $[C_{19}H_{22}NaO]^+$ $(M+Na)^+$ calc. 289.1563, found 289.1564.

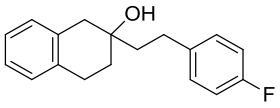


To a solution of 2-(4-methylphenethyl)-1,2,3,4-tetrahydronaphthalen-2-ol (175 mg, 0.66 mmol) in toluene (10 mL) at 100 °C was added PTSA monohydrate (12 mg, 0.066 mmol) and the reaction was stirred for 90 minutes before cooling to room temperature. The reaction was directly poured onto a large pad of silica packed with PE and eluted with EtOAc/PE 1:49 to afford the title compound as a colourless oil (37 mg, 0.15 mmol, 23 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (t, *J* = 8.0 Hz, 2H), 2.34 (s, 3H), 2.49 (t, *J* = 8.0 Hz, 2H), 2.81 (t, *J* = 6.5 Hz, 2H), 2.83 (t, *J* = 6.5 Hz, 2H), 6.25 (s, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 7.06-7.18 (m, 7H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.0, 27.5, 28.1, 33.8, 39.5, 122.5, 125.4, 126.1, 126.4, 127.1, 128.2, 129.0, 134.4, 134.9, 135.3, 138.9, 141.5; **IR (ν, cm^{-1}):** 1610, 1459; **HRMS (FI$^+$):** $[C_{19}H_{20}]$ calc. 248.1565, found 248.1559.

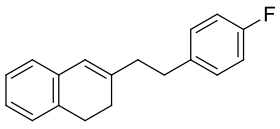
3-(4-Fluorophenethyl)-1,2-dihydronaphthalene (30k)





To a 50 mL flame dried flask containing ether (20 mL) fitted with a reflux condenser was added magnesium turnings (180 mg, 7.39 mmol) and a single crystal of iodine. Once the colour began to disappear, 1-(2-bromoethyl)-4-fluorobenzene (1.50 g, 7.39 mmol) was added in a single portion. The reaction quickly reached reflux and was left to stir for 2 hours before the addition of 2-tetralone (720 mg, 4.93 mmol) as a solution in ether (3 mL). The reaction was stirred for 20 minutes before quenching with NH_4Cl and extracting into ether. The ether layer was further washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a yellow oil (346 mg, 1.28 mmol, 26 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81-1.91 (m, 3H), 1.95 (dt, *J* = 13.4 Hz, *J* = 5.8 Hz, 1H), 2.77-2.99 (m, 6H), 3.04 (ddd, *J* = 17.2 Hz, *J* = 8.9 Hz, *J* = 6.6 Hz, 1H), 6.98 (t, *J* = 8.6 Hz, 2H), 7.06-7.11 (m, 1H), 7.11-7.21 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.1, 28.8, 33.9, 42.2, 43.4, 70.8, 115.1 (d, *J* = 21.3 Hz), 126.0 (d, *J* = 11.3 Hz), 128.7, 129.6, 129.7, 129.7, 134.1, 135.4, 138.0 (d, *J* = 3.1 Hz), 161.2 (d, *J* = 243.8 Hz); **IR (ν, cm^{-1}):** 3400 (br, O-H), 1554 (w, C-C_{Ar}), 1087 (m, C-F); **HRMS (FI$^+$):** [$C_{18}H_{19}FO$] calc. 270.1420, found 270.1418.

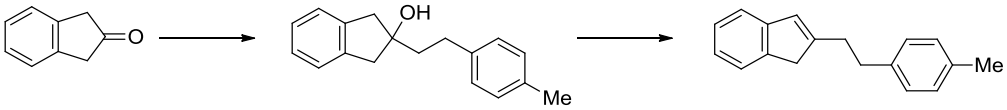


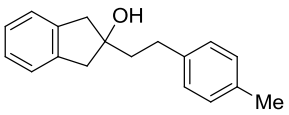
To a solution of 2-(4-fluorophenethyl)-1,2,3,4-tetrahydronaphthalen-2-ol (320 mg, 1.18 mmol) in toluene (25 mL) at 100 °C was added PTSA monohydrate (23 mg, 0.12 mmol) and the reaction was stirred for 90 minutes before cooling to room temperature. The reaction was directly poured onto a 6 inch pad of silica packed with PE and eluted with EtOAc/PE 1:49 to afford the title compound as a white solid (161 mg, 0.64 mmol, 54 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (t, *J* = 8.0 Hz, 2H), 2.49 (t, *J* = 7.8 Hz, 2H), 2.80-2.86 (m, 4H), 6.22 (s, 1H), 6.95-7.21 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 27.5, 28.1, 33.4, 39.4,

115.0 (d, *J* = 21.0 Hz), 122.8, 125.4, 126.2, 126.4, 127.2, 129.7 (d, *J* = 7.7 Hz), 134.4, 134.7, 137.5 (d, *J* = 2.9 Hz), 141.0, 161.3 (d, *J* = 243.4 Hz); **IR (ν, cm^{-1}):** 1601 (w, C=C), 1486 (w, C-C_{Ar}), 1453 (w, C-C_{Ar}), 1093 (m, C-F); **HRMS (FI$^+$):** [$C_{18}H_{17}F$] calc. 252.1314, found 252.1313.

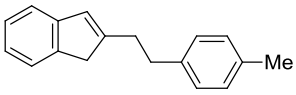
2-(4-Methylphenethyl)-1*H*-indene (30l)





To a 50 mL flame dried flask containing ether (20 mL) fitted with a reflux condenser was added magnesium turnings (122 mg, 5.02 mmol) and a single crystal of iodine. Once the colour began to disappear, 1-(2-bromoethyl)-4-methylbenzene (1.00 g, 5.02 mmol) was added in a single portion. The reaction quickly reached reflux and was left to stir for 2 hours before the addition of 2-indanone (443 mg, 3.35 mmol) as a solution in ether (3 mL). The reaction was stirred for 20 minutes before quenching with NH_4Cl solution and extracting into ether. The ether layer was further washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 2-(4-methylphenethyl)-2,3-dihydro-1*H*-inden-2-ol as a yellow oil (156 mg, 0.62 mmol, 18 % yield).

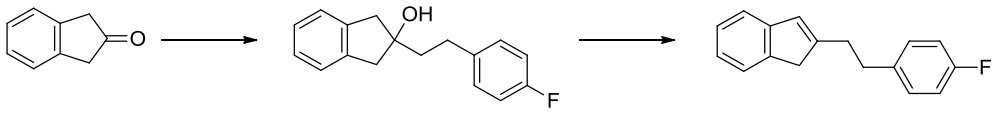
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (brs, 1H, O*H*), 2.05-2.13 (m, 2H), 2.34 (s, 3H), 2.79-2.86 (m, 2H), 3.01 (d, *J* = 16.2 Hz, 2H), 3.13 (d, *J* = 16.2 Hz, 2H), 7.09-7.17 (m, 4H), 7.17-7.22 (m, 2H), 7.22-7.28 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.0, 30.7, 42.7, 47.1, 82.4, 125.1, 126.7, 128.2, 129.1, 135.3, 139.2, 141.2; **IR (ν, cm^{-1}):** 3996, 1482, 1459; **HRMS (ESI$^+$, m/z):** $[C_{18}H_{20}NaO]^+$ $(M+Na)^+$ calc. 275.1406, found 275.1406.

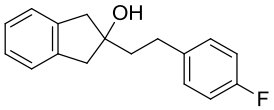


To a solution of 2-(4-methylphenethyl)-2,3-dihydro-1*H*-inden-2-ol (150 mg, 0.59 mmol) in toluene (15 mL) at 100 °C was added PTSA monohydrate (11 mg, 0.06 mmol) and the reaction was stirred for 90 minutes before cooling to room temperature. The reaction was directly poured onto a 6 inch pad of silica packed with petroleum ether and eluted with EtOAc/PE 1:49 to afford the title compound as a colourless oil (52 mg, 0.22 mmol, 38 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 2.78-2.85 (m, 2H), 2.90-2.96 (m, 2H), 3.35 (s, 2H), 6.57 (s, 1H), 7.10-7.18 (m, 5H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.0, 33.2, 34.9, 41.2, 120.0, 123.4, 123.7, 126.2, 126.5, 128.2, 129.1, 135.4, 138.8, 143.1, 145.6, 150.0; **IR (ν, cm^{-1}):** 1648, 1486, 1453; **HRMS (FI^{+}):** [$C_{18}H_{18}$] calc. 234.1409, found 234.1411.

2-(4-Fluorophenethyl)-1*H*-indene (30m)

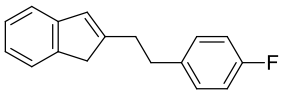




To a 50 mL flame dried flask containing THF (20 mL) fitted with a reflux condenser was added magnesium turnings (180 mg, 7.39 mmol) and a single crystal of iodine. Once the colour began to disappear, 1-(2-bromoethyl)-4-fluorobenzene (1.50 g, 7.39 mmol) was added in a single portion. The reaction quickly reached reflux and was left to stir for 2 hours before the addition of 2-indanone (652 mg, 4.93 mmol) as a solution in ether (3 mL). The reaction was stirred for 20 minutes before quenching with NH_4Cl solution and extracting into ether. The ether layer was further washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by

column chromatography (SiO_2, EtOAc/PE 1:9) afforded 2-(4-fluorophenethyl)-2,3-dihydro-1*H*-inden-2-ol as a yellow oil (296 mg, 1.15 mmol, 23 % yield).

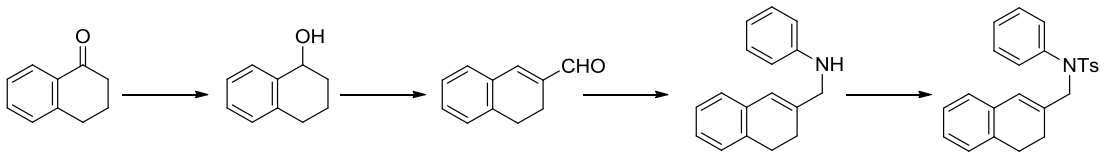
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (brs, 1H, O*H*), 2.05-2.10 (m, 2H), 2.80-2.87 (m, 2H), 3.00 (d, *J* = 16.2 Hz, 2H), 3.12 (d, *J* = 16.2 Hz, 2H), 6.95-7.03 (m, 2H), 7.16-7.29 (m, 6H), **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.3, 42.7, 47.1, 82.3, 115.2 (d, *J* = 20.9 Hz), 125.2, 126.7, 129.7 (d, *J* = 7.7 Hz), 137.9 (d, *J* = 3.1 Hz), 141.1, 161.2 (d, *J* = 243.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -117.7 (tt, *J* = 8.9 Hz, *J* = 5.5 Hz, 1F); **IR (ν, cm^{-1}):** 3369, 1482, 1459, 1054; **HRMS (ESI$^+$, m/z):** $[C_{17}H_{17}FNaO]^+$ $(M+Na)^+$ calc. 279.1156, found 279.1151.

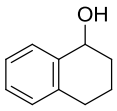


To a solution of 2-(4-fluorophenethyl)-2,3-dihydro-1*H*-inden-2-ol (280 mg, 1.09 mmol) in toluene (25 mL) at 100 °C was added PTSA monohydrate (21 mg, 0.11 mmol) and the reaction was stirred for 90 minutes before cooling to room temperature. The reaction was directly poured onto a large pad of silica packed with PE and eluted with EtOAc/PE 1:49 to afford the title compound as a white solid (98 mg, 0.41 mmol, 38 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80 (t, *J* = 7.8 Hz, 2H), 2.93 (t, *J* = 7.8 Hz, 2H), 3.33 (s, 2H), 6.54 (s, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 5.6 Hz, 1H), 7.19 (t, *J* = 5.8 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 33.1, 34.5, 41.2, 115.1 (d, *J* = 21.2 Hz), 120.1, 123.4, 123.8, 126.3, 126.8, 129.6 (d, *J* = 7.8 Hz), 137.4 (d, *J* = 3.3 Hz), 143.0, 145.4, 149.4, 161.2 (d, *J* = 243.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -117.5 (tt, *J* = 8.6 Hz, *J* = 5.8 Hz, 1F); **IR (ν, cm^{-1}):** 1600, 1460, 1092; **HRMS (FI$^+$):** $[C_{17}H_{15}F]$ calc. 238.1158, found 238.1152; **mp:** 82-83 °C.

_N_-((3,4-dihydronaphthalen-2-yl)methyl)-4-methyl-_N_-phenylbenzenesulfonamide (30n)

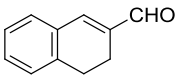




To a solution of 1-tetralone (8.00 g, 54.8 mmol) in methanol (100 mL) was added $NaBH_4$ (2.07 g, 54.8 mmol) in a single portion. The reaction was stirred for 1 hour before concentrating to about 15 mL under reduced pressure. The reaction was diluted with water (50 mL) and extracted into ether (3 x 100 mL). The combined ethereal extracts were washed with brine (100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1,2,3,4-tetrahydronaphthalen-1-ol as a pale yellow oil (8.07 g, 54.5 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73-2.08 (m, 5H), 2.69-2.80 (m, 1H), 2.80-2.90 (m, 1H), 4.79 (t, *J* = 5.0 Hz, 1H), 7.09-7.16 (m, 1H), 7.18-7.26 (m, 2H), 7.42-7.48 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.8, 29.2, 32.3, 68.1, 126.2, 127.6, 128.7, 129.0, 137.1, 138.8.

Data consistent with literature values.[22]

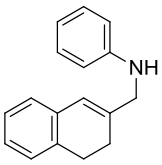


To a solution of 1,2,3,4-tetrahydronaphthalen-1-ol (1.00 g, 6.75 mmol) in DMF (2.5 mL) at 0 °C was added $POCl_3$ (1.5 mL) slowly. The reaction was stirred for 1 hour before warming to room temperature and stirring for a further hour. Finally, the reaction was heated at 100 °C overnight. After cooling to room temperature, the reaction was quenched with water and made basic with 3M NaOH. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic fractions washed with brine (100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column

chromatography (SiO_2, EtOAc/PE 0:1 to 1:9) afforded 3,4-dihydronaphthalene-2-carbaldehyde as a yellow oil (964 mg, 6.09 mmol, 90 % yield).

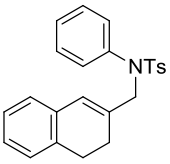
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (t, *J* = 8.2 Hz, 2H), 2.89 (t, *J* = 8.2 Hz, 2H), 7.19-7.35 (m, 5H), 9.68 (s, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.3, 27.0, 127.0, 128.1, 128.9, 130.6, 132.2, 138.2, 139.3, 145.8, 192.9.

Data consistent with literature values.[23]



To a solution of 3,4-dihydronaphthalene-2-carbaldehyde (791 mg, 5.0 mmol) in 2,2,2-trifluoroethanol (10 mL) at 40 °C was added aniline (456 µL, 5.0 mmol) and the reaction stirred for 5 minutes before the addition of $NaBH_4$ (227 mg, 6.0 mmol) in one portion. Stirring was continued for 30 minutes before filtering off the solid and washing the filtrand with a further 10 mL of 2,2,2-trifluoroethanol. Following evaporation under reduced pressure, purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded *N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline as a colourless oil (232 mg, 0.99 mmol, 20 % yield).

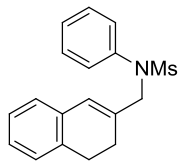
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (t, *J* = 8.0 Hz, 2H), 2.87 (t, *J* = 8.0 Hz, 2H), 3.90 (s, 2H), 4.02 (brs, 1H, N*H*), 6.47 (s, 1H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.74 (tt, *J* = 7.3 Hz, *J* = 0.8 Hz, 1H), 7.02 (d, *J* = 6.5 Hz, 1H), 7.11-7.18 (m, 3H), 7.20 (td, *J* = 7.9 Hz, *J* = 0.9 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.5, 28.0, 49.6, 113.0, 117.6, 123.1, 125.9, 126.5, 126.7, 127.3, 129.2, 134.2, 134.8, 138.7, 148.2; **IR (v, cm^{-1}):** 3436, 1612, 1485, 1453; **HRMS (FI$^+$):** [$C_{17}H_{17}N$] calc. 235.1361, found 235.1369.



To a solution of *N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (235 mg, 1.0 mmol) in DCM (5 mL) at room temperature was added sequentially Et_3N (209 µL, 1.5 mmol), tosyl chloride (250 mg, 1.3 mmol) and DMAP (5 mg). The reaction was stirred for 24 hours before the addition of 1M HCl. The acid layer was extracted with DCM and the organic fraction further washed with 1M HCl, $NaHCO_3$ solution and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19 to 1:4) afforded the title compound as a white solid (355 mg, 0.91 mmol, 91 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (t, *J* = 8.1 Hz, 2H), 2.45 (s, 3H), 2.69 (t, *J* = 8.1 Hz, 2H), 4.30 (s, 2H), 6.13 (s, 1H), 6.83-6.89 (m, 1H), 7.02-7.11 (m, 5H), 7.20-7.31 (m, 5H), 7.51 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 24.6, 27.8, 56.2, 125.9, 126.3, 126.9, 127.0, 127.3, 127.7, 127.8, 128.7, 128.8, 129.4, 133.7, 135.1, 135.2, 135.2, 138.7, 143.5; **IR (ν, cm^{-1}):** 1596, 1491, 1453, 1346, 1163; **HRMS (ESI$^+$, m/z):** $[C_{24}H_{23}NNaO_2S]^+$ $(M+Na)^+$ calc. 412.1342, found 412.1328; **mp:** 129-131 °C.

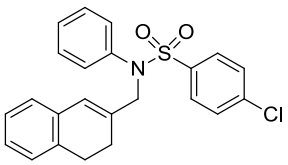
***N*-((3,4-dihydronaphthalen-2-yl)methyl)-*N*-phenylmethanesulfonamide (30o)**



To a solution of *N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (200 mg, 0.85 mmol) in DCM (2 mL) at -20 °C was added Et_3N (130 µL, 1.27 mmol) followed by methane sulfonyl chloride (99 µL, 0.94 mmol). The reaction was stirred overnight and allowed to warm to room temperature before the addition of NH_4Cl solution. The aqueous phase was extracted with DCM and the organic fraction washed with brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:3) afforded the title compound as a white solid (185 mg, 0.59 mmol, 69 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31-2.46 (m, 2H), 2.67-2.78 (m, 2H), 2.95 (s, 3H), 4.45 (s, 2H), 6.23 (s, 1H), 6.87-6.97 (m, 1H), 7.03-7.16 (m, 3H), 7.24-7.53 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.6, 27.8, 37.4, 56.2, 126.0, 126.4, 126.9, 127.2, 127.3, 128.1, 128.4, 129.4, 133.6, 135.0, 135.2, 138.8; **IR (ν, cm^{-1}):** 1595, 1491, 1453, 1324, 1150; **HRMS (ESI$^+$, m/z):** $[C_{18}H_{19}NNaO_2S]^+$ $(M+Na)^+$ calc. 336.1029, found 336.1020; **mp:** 110-111 °C.

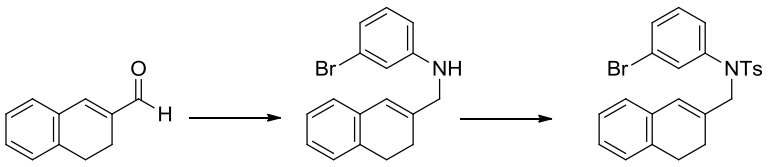
4-Chloro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)-*N*-phenylbenzenesulfonamide (30p)

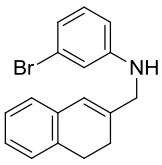


To a solution of *N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (200 mg, 0.85 mmol) in DCM (5 mL) at room temperature was added sequentially Et_3N (347 µL, 2.49 mmol), 4-chlorobenzene-1-sulfonyl chloride (359 mg, 1.70 mmol) and DMAP (5 mg). The reaction was stirred for 24 hours before the addition of NH_4Cl solution. The aqueous phase was extracted with DCM and the organic fraction further washed with NH_4Cl solution, $NaHCO_3$ solution and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (300 mg, 0.73 mmol, 86 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (t, *J* = 7.9 Hz, 2H), 2.70 (t, *J* = 7.9 Hz, 2H), 4.30 (s, 2H), 6.14 (s, 1H), 6.81-6.93 (m, 1H), 6.98-7.15 (m, 5H), 7.21-7.35 (m, 3H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.6, 27.7, 56.4, 126.0, 126.4, 127.2, 127.2, 127.3, 128.1, 128.6, 129.0, 129.1, 129.2, 133.6, 134.7, 135.1, 136.6, 138.3, 139.2; **IR (ν, cm^{-1}):** 1586, 1490, 1453, 1351, 1164; **HRMS (ESI$^+$, m/z):** $[C_{23}H_{20}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 432.0795, found 432.0785; **mp:** 140-142 °C.

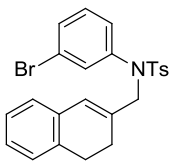
_N_-(3-Bromophenyl)-_N_-((3,4-dihydronaphthalen-2-yl)methyl)-4-methylbenzenesulfonamide (30q)





To a solution of 3,4-dihydronaphthalene-2-carbaldehyde (791 mg, 5.0 mmol) in 2,2,2-trifluoroethanol (10 mL) at 40 °C was added 3-bromoaniline (544 µL, 5.0 mmol) and the reaction stirred for 5 minutes before the addition of $NaBH_4$ (227 mg, 6.0 mmol) in one portion. Stirring was continued for 30 minutes before filtering off the solid and washing the filtrand with a further 10 mL of TFE. Following evaporation under reduced pressure, purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (184 mg, 0.59 mmol, 12 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (t, *J* = 7.9 Hz, 2H), 2.86 (t, *J* = 8.0 Hz, 2H), 3.87 (s, 2H), 4.24 (brs, 1H, N*H*), 6.44 (s, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.81 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.97-7.06 (m, 2H), 7.09-7.19 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.4, 27.9, 49.3, 111.6, 115.6, 120.4, 123.2, 123.3, 126.0, 126.5, 126.8, 127.3, 130.5, 134.0, 134.7, 137.8, 149.4; **IR (ν, cm^{-1}):** 3421 (br, N-H), 1732 (w, C=C), 1482 (w, C-C_{Ar}), 1453 (w, C-C_{Ar}); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{16}BrNNa]^+$ $(M+Na)^+$ calc. 336.0358, found 336.0352.

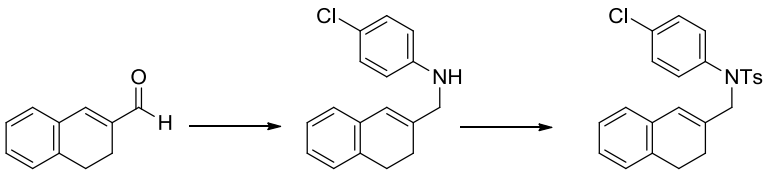


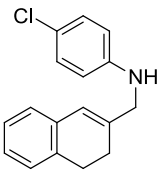
To a solution of 3-bromo-*N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (164 mg, 0.52 mmol) in DCM (5 mL) at room temperature was added sequentially Et_3N (217 µL, 1.56 mmol), tosyl chloride (199 mg, 1.04 mmol) and DMAP (5 mg). The reaction was stirred for 24 hours before the addition of 1M HCl. The acid layer was extracted with DCM and the organic fraction further washed with 1M HCl,

$NaHCO_3$ and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (86 mg, 0.18 mmol, 35 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (t, *J* = 8.1 Hz, 2H), 2.46 (s, 3H), 2.71 (t, *J* = 8.2 Hz, 2H), 4.25 (s, 2H), 6.14 (s, 1H), 6.86-6.89 (m, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.03-7.10 (m, 3H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 24.6, 27.7, 56.2, 122.0, 126.0, 126.4, 127.2, 127.2, 127.3, 127.4, 127.7, 129.6, 130.0, 130.9, 131.6, 133.5, 134.6, 134.7, 135.0, 140.2, 143.9; **IR (ν, cm^{-1}):** 1587 (w, C=C), 1353 (s, S=O), 1164 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{24}H_{22}BrNNaO_2S]^+$ $(M+Na)^+$ calc. 490.0447, found 490.0441.

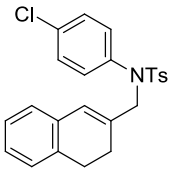
_N_-(4-chlorophenyl)-_N_-((3,4-dihydronaphthalen-2-yl)methyl)-4-methylbenzenesulfonamide (30R)





To a pestle and motor was added 4-chloroaniline (638 mg, 5.0 mmol) and 3,4-dihydronaphthalene-2-carbaldehyde (791 mg, 5.0 mmol) and the mixture was ground for 15 minutes until a consistent pale yellow oil was obtained. To the resultant imine was directly charged $NaBH_4$ (189 mg, 5.0 mmol) and PTSA monohydrate (951 mg, 5.0 mmol) and grinding was rapidly continued. The reaction was further ground for 20 minutes before dissolving in DCM and quenching with $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a pale yellow oil (918 mg, 3.40 mmol, 68 % yield).

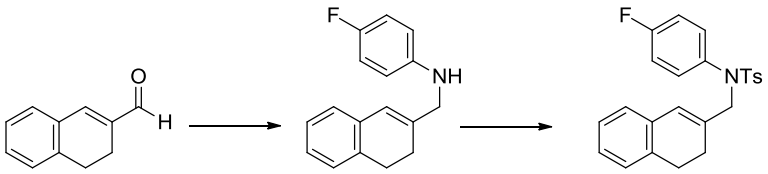
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (t, *J* = 8.2 Hz, 2H), 2.86 (t, *J* = 8.2 Hz, 2H), 3.87 (s, 2H), 4.08 (brs, 1H, N*H*), 6.44 (s, 1H), 6.59 (d, *J* = 8.8 Hz, 2H), 7.02 (dd, *J* = 6.2 Hz, *J* = 1.4 Hz, 1H), 7.10-7.19 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.4, 27.9, 49.5, 114.0, 122.1, 123.3, 125.9, 126.5, 126.8, 127.3, 129.0, 134.0, 134.7, 138.1, 146.7; **IR (ν, cm^{-1}):** 3423 (br, N-H), 1598 (m, C=C), 1453 (w, C-C_{Ar}), 1032 (m, C-Cl); **HRMS (FI^+):** [$C_{17}H_{16}ClN$] calc. 269.0971, found 269.0969.

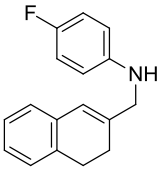


To a solution of 4-chloro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (559 mg, 2.07 mmol) in DCM (15 mL) at room temperature was added sequentially Et_3N (866 µL, 6.21 mmol), tosyl chloride (790 mg, 4.14 mmol) and DMAP (10 mg). The reaction was stirred for 24 hours before the addition of NH_4Cl. The acid layer was extracted with DCM and the organic fraction further washed with NH_4Cl, and $NaHCO_3$ before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (765 mg, 1.80 mmol, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (t, *J* = 8.1 Hz, 2H), 2.46 (s, 3H), 2.70 (t, *J* = 8.1 Hz, 2H), 4.27 (s, 2H), 6.13 (s, 1H), 6.85-6.90 (m, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.03-7.13 (m, 3H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 24.6, 27.7, 56.1, 126.0, 126.4, 127.3, 127.3, 127.3, 127.7, 129.1, 129.6, 129.9, 133.5, 133.6, 134.7, 134.8, 135.0, 137.3, 143.8; **IR (ν, cm^{-1}):** 1598 (w, C=C), 1488 (m, C-C_{Ar}), 1347 (s, S=O), 1161 (s, S=O), 1015 (m, C-Cl); **HRMS (ESI^+, m/z):** $[C_{24}H_{22}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 446.0952, found 446.0966.

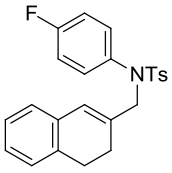
_N_-((3,4-dihydronaphthalen-2-yl)methyl)-_N_-(4-fluorophenyl)-4-methylbenzenesulfonamide (30s)





To a pestle and mortar was added 4-fluoroaniline (474 µL, 5.00 mmol) and 3,4-dihydronaphthalene-2-carbaldehyde (791 mg, 5.00 mmol) and the mixture was ground for 15 minutes until a consistent pale yellow oil was obtained. To the resultant imine was directly charged $NaBH_4$ (189 mg, 5.00 mmol) and PTSA monohydrate (951 mg, 5.00 mmol) and grinding was rapidly continued. The reaction was further ground for 20 minutes before dissolving in DCM and quenching with $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 4-fluoro-_N_-((3,4-dihydronaphthalen-2-yl)methyl)aniline as a pale yellow oil (996 mg, 3.93 mmol, 79 % yield).

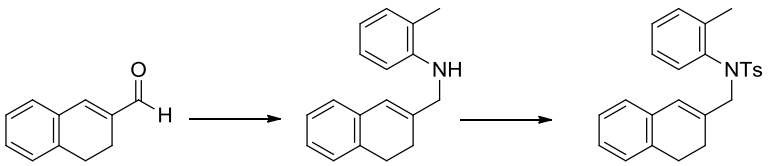
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, *J* = 8.2 Hz, 2H), 2.87 (t, *J* = 8.2 Hz, 2H), 3.86 (s, 2H), 3.86 (brs, 1H, N*H*), 6.46 (s, 1H), 6.58-6.64 (m, 2H), 6.87-6.94 (m, 2H), 7.03 (dd, *J* = 6.2 Hz, *J* = 1.3 Hz, 1H), 7.11-7.20 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.5, 28.0, 50.1, 113.8 (d, *J* = 7.3 Hz), 115.6 (d, *J* = 22.3 Hz), 123.2, 125.9, 126.5, 126.8, 127.3, 134.1, 134.8, 138.2, 144.5, 155.9 (d, *J* = 235.3 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -128.3 (tt, *J* = 8.2 Hz, *J* = 4.2 Hz, 1F); **IR (ν, cm^{-1}):** 3425, 1612, 1485, 1453, 1110; **HRMS (FI$^+$):** [$C_{17}H_{16}FN$] calc. 253.1267, found 253.1264.

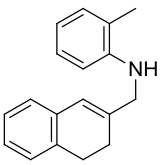


To a solution of 4-fluoro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (497 mg, 1.96 mmol) in DCM (15 mL) at room temperature was added sequentially Et_3N (820 µL, 5.88 mmol), tosyl chloride (748 mg, 3.92 mmol) and DMAP (10 mg). The reaction was stirred for 24 hours before the addition of NH_4Cl solution. The acid layer was extracted with DCM and the organic fraction further washed with NH_4Cl solution, and $NaHCO_3$ solution before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (733 mg, 1.80 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ =2.37 (t, *J* = 8.2 Hz, 2H), 2.46 (s, 3H), 2.71 (t, *J* = 8.2 Hz, 2H), 4.27 (s, 2H), 6.12 (s, 1H), 6.83-6.90 (m, 1H), 6.91-6.98 (m, 2H), 6.98-7.04 (m, 2H), 7.04-7.12 (m, 3H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 24.7, 27.7, 56.4, 115.8 (d, *J* = 22.4 Hz), 126.0, 126.4, 127.2, 127.3, 127.7, 129.5, 130.4, 130.5, 133.5, 134.6 (d, *J* = 3.3 Hz), 134.8, 134.9, 135.0, 143.7, 161.7 (d, *J* = 248.1 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -113.5 (tt, *J* = 7.0 Hz, *J* = 6.0 Hz, 1F); **IR (ν, cm^{-1}):** 1599, 1453, 1347, 1163, 1091; **HRMS (ESI$^+$, m/z):** $[C_{24}H_{22}FNNaO_2S]^+$ $(M+Na)^+$ calc. 430.1247, found 430.1239; **mp:** 95-96 °C.

***N*-((3,4-dihydronaphthalen-2-yl)methyl)-4-methyl-*N*-(o-tolyl)benzenesulfonamide (30t)**

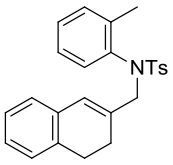




To a pestle and motor was added *o*-toluidine (536 µL, 5.0 mmol) and 3,4-dihydronaphthalene-2-carbaldehyde (791 mg, 5.0 mmol) and the mixture was ground for 15 minutes until a consistent pale yellow oil was obtained. To the resultant imine was directly charged $NaBH_4$ (189 mg, 5.0 mmol) and PTSA

monohydrate (951 mg, 5.0 mmol) and grinding was rapidly continued. The reaction was further ground for 20 minutes before dissolving in DCM and quenching with $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a pale yellow oil (654 mg, 2.62 mmol, 52 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3H), 2.38 (t, *J* = 8.1 Hz, 2H), 2.90 (t, *J* = 8.1 Hz, 2H), 3.90 (brs, 1H, N*H*), 3.97 (s, 2H), 6.48 (s, 1H), 6.65-6.75 (m, 2H), 7.04 (d, *J* = 6.5 Hz, 1H), 7.09-7.21 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 17.6, 25.5, 28.0, 49.5, 110.2, 117.1, 121.9, 123.0, 125.9, 126.5, 126.7, 127.2, 127.3, 130.1, 134.2, 134.8, 138.8, 146.1; **IR (ν, cm^{-1}):** 3449 (br, N-H), 1605 (m,, C=C), 1450 (m, C-C_{Ar}); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{20}N]^+$ $(M+H)^+$ calc. 250.1590, found 250.1582.

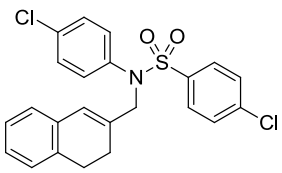


To a solution of *N*-((3,4-dihydronaphthalen-2-yl)methyl)-2-methylaniline (625 mg, 2.51 mmol) in DCM (15 mL) at room temperature was added sequentially Et_3N (1.05 mL, 7.53 mmol), tosyl chloride (956 mg, 5.01 mmol) and DMAP (10 mg). The reaction was stirred for 24 hours before the addition of NH_4Cl. The acid layer was extracted with DCM and the organic fraction further washed with NH_4Cl, and $NaHCO_3$ before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (503 mg, 1.25 mmol, 50 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30-2.57 (m, 2H), 2.39 (s, 3H), 2.47 (s, 3H), 2.64-2.85 (m, 2H), 3.94 (d, *J* = 13.3 Hz, 1H), 4.47 (d, *J* = 13.3 Hz, 1H), 6.04 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.81-6.87 (m, 1H), 7.01-7.12 (m, 4H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.1

Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.6, 21.6, 25.2, 27.8, 29.7, 57.4, 126.0, 126.1, 126.3, 127.1, 127.3, 127.4, 127.9, 128.1, 128.1, 129.4, 131.5, 133.7, 134.9, 135.0, 135.6, 138.0, 139.8, 143.5; **IR (ν, cm^{-1}):** 1598 (w, C=C), 1491 (w, C-C_{Ar}), 1453 (w, C-C_{Ar}), 1343 (s, S=O), 1158 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{25}H_{25}NNaO_2S]^+$ $(M+Na)^+$ calc. 426.1498, found 426.1485.

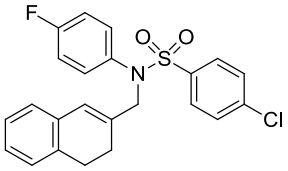
4-Chloro-*N*-(4-chlorophenyl)-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)benzenesulfonamide (30u)



To a solution of 4-chloro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (330 mg, 1.22 mmol) in DCM (10 mL) at room temperature was added sequentially Et_3N (510 µL, 3.66 mmol), 4-chlorobenzene-1-sulfonyl chloride (516 mg, 2.45 mmol) and DMAP (5 mg). The reaction was stirred for 24 hours before the addition of NH_4Cl. The aqueous phase was extracted with DCM and the organic fraction further washed with NH_4Cl, $NaHCO_3$ and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (477 mg, 1.07 mmol, 88 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (t, *J* = 8.1 Hz, 2H), 2.70 (t, *J* = 8.1 Hz, 2H), 4.27 (s, 2H), 6.13 (s, 1H), 6.85-6.91 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.04-7.12 (m, 3H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.6, 27.7, 56.3, 126.1, 126.4, 127.3, 127.4, 127.6, 129.0, 129.3, 129.3, 129.8, 133.4, 133.9, 134.2, 135.0, 136.3, 136.8, 139.5; **IR (ν, cm^{-1}):** 1583 (w, C=C), 1488 (m, C-C_{Ar}), 1352 (s, S=O), 1165 (s, S=O), 1031 (m, C-Cl), 1013 (m, C-Cl); **HRMS (ESI$^+$, m/z):** $[C_{23}H_{19}Cl_2NNaO_2S]^+$ $(M+Na)^+$ calc. 466.0406, found 466.0392; **mp:** 134-135 °C.

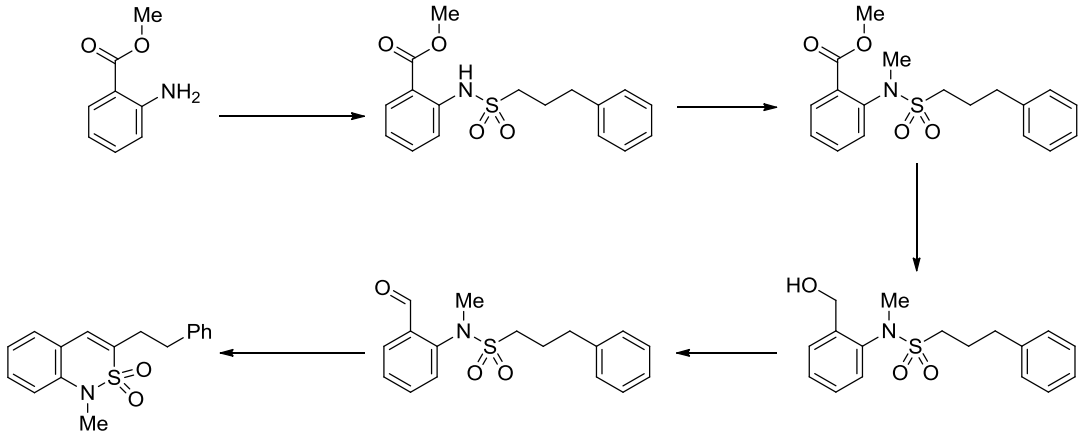
4-chloro-N-(4-fluorophenyl)-N-((3,4-dihydronaphthalen-2-yl)methyl)benzenesulfonamide (30v)

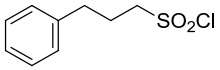


To a solution of 4-fluoro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)aniline (476 mg, 1.88 mmol) in DCM (15 mL) at room temperature was added sequentially Et_3N (786 µL, 5.64 mmol), 4-chlorobenzene-1-sulfonyl chloride (793 mg, 3.76 mmol) and DMAP (5 mg). The reaction was stirred for 24 hours before the addition of NH_4Cl. The aqueous phase was extracted with DCM and the organic fraction further washed with NH_4Cl, $NaHCO_3$ and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (652 mg, 1.52 mmol, 81 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (t, *J* = 8.1 Hz, 2H), 2.71 (t, *J* = 8.1 Hz, 2H), 4.27 (s, 2H), 6.12 (s, 1H), 6.85-6.90 (m, 1H), 6.93-7.04 (m, 4H), 7.04-7.13 (m, 3H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.6, 27.7, 56.6, 116.0 (d, *J* = 22.6 Hz), 126.0, 126.4, 127.3, 127.5, 129.1, 129.3, 130.4, 130.5, 133.4, 134.2 (d, *J* = 3.7 Hz), 134.3, 135.0, 136.4, 139.5, 161.7 (d, *J* = 248.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -112.9 (m, 1F); **IR (ν, cm^{-1}):** 1585 (w, C=C), 1476 (w, C-C_{Ar}), 1352 (s, S=O), 1166 (s, S=O), 1093 (m, C-F), 1013 (m, C-Cl); **HRMS (ESI$^+$, m/z):** $[C_{23}H_{19}ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 450.0701, found 450.0692.

1-Methyl-3-phenethyl-1H-benzo[*c*][1,2]thiazine 2,2-dioxide (38)



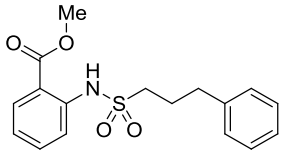


To a solution of (3-bromopropyl)benzene (4.00 mL, 26.2 mmol) in water (31 mL) was added sodium sulphite (3.31 g, 26.2 mmol) and sodium iodide (196 mg, 1.31 mmol) and the reaction was heated at reflux for 24 hours. After cooling to room temperature the water was removed under reduced pressure to afford a white residue which was dried under high vacuum and used in the next step without purification.

The crude residue was suspended in a mixture of toluene (150 mL) and DMF (1.0 mL) and thionyl chloride (4.75 mL, 65.5 mmol) was added in a single portion. The reaction was heated at 90 °C for 3 hours, after which the majority of solid had dissolved, leaving the sodium bromide and sodium iodide from the previous reaction. The reaction was cooled and concentrated *in vacuo* to remove the toluene and excess thionyl chloride. Purification by column chromatography (SiO_2, EtAOc/PE 1:9) afforded 3-phenylpropane-1-sulfonyl chloride as a colourless liquid (3.64 g, 16.7 mmol, 64 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36-2.45 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 3.62-3.68 (m, 2H), 7.20-7.24 (m, 2H), 7.25-7.31 (m, 1H), 7.33-7.39 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.8, 33.3, 64.5, 126.9, 128.4, 128.9, 139.0.

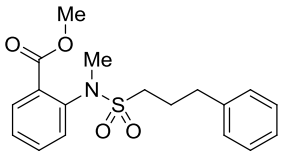
Data consistent with literature values.[24]



To a solution of 3-phenylpropane-1-sulfonyl chloride (1.00 g, 4.58 mmol) in DCM (30 mL) at 0 °C was added Et_3N (702 µL, 5.03 mmol) and methyl 2-aminobenzoate (593 µL, 4.58 mmol). The reaction was stirred overnight before quenching with water and washing with 1M HCl. The organic phase was further washed with 1M HCl, $NaHCO_3$ and brine before drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2,

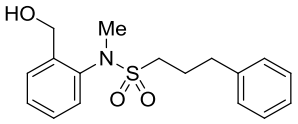
EtOAc/PE 1:9) afforded methyl 2-(3-phenylpropylsulfonamido)benzoate as a colourless oil (1.23 g, 3.69 mmol, 81 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12-2.21 (m, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 3.13-3.19 (m, 2H), 3.96 (s, 3H), 7.08-7.15 (m, 3H), 7.17-7.23 (m, 1H), 7.24-7.30 (m, 2H), 7.53 (ddd, *J* = 8.3 Hz, *J* = 6.0 Hz, *J* = 1.5 Hz, 1H), 7.72 (dd, *J* = 8.4 Hz, *J* = 0.5 Hz, 1H), 8.07 (dd, *J* = 8.1 Hz, *J* = 1.6 Hz, 1H), 10.49 (s, 1H, N*H*); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.9, 33.8, 51.2, 52.6, 115.1, 117.8, 122.6, 126.4, 128.3, 128.6, 131.6, 134.9, 139.9, 141.0, 169.4; **IR (ν, cm^{-1}):** 3195 (br, N-H), 1338 (s, S=O), 1150 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{19}NNaO_4S]^+$ $(M+Na)^+$ calc. 356.0927, found 356.0912.



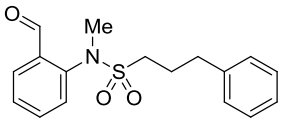
To a solution of methyl 2-(3-phenylpropylsulfonamido)benzoate (1.23 g, 3.69 mmol) in MeCN (10 mL) at room temperature was added K_2CO_3 (1.02 g, 7.38 mmol) and methyl iodide (459 µL, 7.38 mmol). The reaction was stirred overnight before quenching with water and extracting into EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded methyl 2-(*N*-methyl-3-phenylpropylsulfonamido)benzoate (993 mg, 2.86 mmol, 77 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14-2.24 (m, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 3.06-3.12 (m, 2H), 3.34 (s, 3H), 3.91 (s, 3H), 7.16-7.21 (m, 2H), 7.21-7.27 (m, 1H), 7.29-7.34 (m, 2H), 7.36 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz, 1H), 7.42 (td, *J* = 7.7 Hz, *J* = 1.2 Hz, 1H), 7.53 (td, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H), 7.90 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.0, 34.3, 39.4, 51.2, 52.4, 126.3, 128.2, 128.5, 128.6, 130.7, 131.0, 131.3, 132.8, 140.4, 166.5; **IR (ν, cm^{-1}):** 1726 (s, C=O), 1336 (s, S=O), 1143 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{21}NNaO_4S]^+$ $(M+Na)^+$ calc. 370.1083, found 370.1075.



To a solution of methyl 2-(*N*-methyl-3-phenylpropylsulfonamido)benzoate (810 mg, 2.34 mmol) in ether (20 mL) at -78 °C was added DIBAL (1M sln in hexane, 9.40 mL, 9.35 mmol) and the reaction was stirred for 1 hour before slowly warming to room temperature. The reaction was stirred for a further hour before quenching with NH_4Cl and extracting into ether. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 3:17) afforded *N*-(2-(hydroxymethyl)phenyl)-*N*-methyl-3-phenylpropane-1-sulfonamide as a colourless oil (667 mg, 2.09 mmol, 89 % yield).

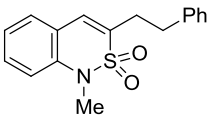
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18-2.29 (m, 2H), 2.69-2.89 (m, 3H, C*H*$_2$ + O*H*), 3.04-3.19 (m, 2H), 3.27 (s, 3H), 4.67 (brs, 2H), 7.08 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz, 1H), 7.17-7.22 (m, 2H), 7.22-7.27 (m, 1H), 7.27-7.36 (m, 3H), 7.39 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.60 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.9, 34.2, 40.0, 48.7, 61.1, 126.5, 127.0, 128.5, 128.7, 129.1, 129.3, 131.6, 139.2, 140.1, 141.3; **IR (ν, cm^{-1}):** 3505 (br, O-H), 1328 (s, S=O), 1138 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{21}NNaO_3S]^+$ $(M+Na)^+$ calc. 342.1134, found 342.1122.



To a solution of pyridine (1.98 mL, 24.5 mmol) in DCM (50 mL) at room temperature was added freshly powdered CrO_3 (1.22 g, 12.2 mmol). The flask was fitted with a $CaCl_2$ drying tube and the reaction was left to stir for 15 minutes before *N*-(2-(hydroxymethyl)phenyl)-*N*-methyl-3-phenylpropane-1-sulfonamide (650 mg, 2.04 mmol) was added as a solution in DCM (10 mL) in a single portion. The drying tube was replaced and the reaction stirred for a further 15 minutes before filtering off the solid. The residue was washed with DCM and the combined DCM filtrate was washed with dilute $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and evaporation under reduced pressure, purification by column chromatography (SiO_2, EtAOc/PE 1:19) afforded *N*-(2-

formylphenyl)-*N*-methyl-3-phenylpropane-1-sulfonamide as a colourless oil (504 mg, 1.59 mmol, 78 % yield).

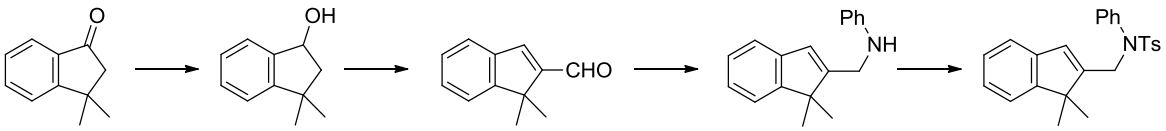
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15-2.25 (m, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 3.04-3.11 (m, 2H), 3.39 (s, 3H), 7.15-7.20 (m, 2H), 7.22-7.28 (m, 1H), 7.29-7.35 (m, 3H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.63 (td, *J* = 7.7 Hz, *J* = 1.7 Hz, 1H), 8.00 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.8, 34.2, 39.5, 48.8, 126.5, 127.4, 128.5, 128.7, 128.7, 129.6, 134.6, 134.7, 140.0, 143.0, 189.7; **IR (ν, cm^{-1}):** 1692 (s, C=O), 1337 (s, S=O), 1147 (s, S=O); **HRMS (ESI^+, m/z):** $[C_{17}H_{19}NNaO_3S]^+$ $(M+Na)^+$ calc. 340.0978, found 340.0966.

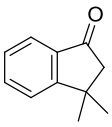


To a solution of *N*-(2-formylphenyl)-*N*-methyl-3-phenylpropane-1-sulfonamide (480 mg, 1.51 mmol) in MeCN (48 mL) at room temperature was added Cs_2CO_3 (987 mg, 3.03 mmol). The reaction was heated at reflux overnight before cooling to room temperature and diluting with DCM. The organic layer was washed with $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 1-methyl-3-phenethyl-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide as a white solid (125 mg, 0.42 mmol, 28 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.98-3.03 (m, 2H), 3.06-3.11 (m, 2H), 3.51 (s, 3H), 6.80 (s, 1H), 7.13-7.17 (m, 2H), 7.21-7.25 (m, 1H), 7.25-7.34 (m, 5H), 7.43 (ddd, *J* = 8.3 Hz, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 30.4, 31.7, 34.9, 116.0, 121.2, 122.8, 126.4, 128.5, 128.6, 129.3, 130.2, 130.9, 135.5, 139.9, 140.2; **IR (ν, cm^{-1}):** 1603 (w, C=C), 1310 (s, S=O), 1144 (s, S=O); **HRMS (ESI^+, m/z):** $[C_{17}H_{17}NNaO_2S]^+$ $(M+Na)^+$ calc. 322.0872, found 322.0861; **mp:** 104-105 °C.

_N_-((1,1-dimethyl-1_H_-inden-2-yl)methyl)-4-methyl-_N_-phenylbenzenesulfonamide (39a)

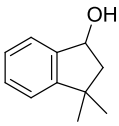




A solution of 3-methylcrotonic acid (1.90 g, 19.0 mmol) in benzene (10 mL) was added slowly to $AlCl_3$ (7.60 g, 57.0 mmol) in an ambient temperature oil bath and the mixture was heated to reflux for 5 hours before pouring onto iced HCl (1M). The organic layer was washed with Na_2CO_3 solution, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one as a colourless oil (2.70 g, 16.9 mmol, 89 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 6H), 2.61 (s, 2H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 6.6 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 29.7, 38.6, 52.9, 123.4, 123.5, 127.4, 135.0, 135.3, 163.9, 206.0.

Data consistent with literature values.[25]

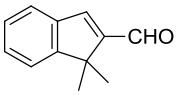


To a solution of 3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one (2.65 g, 16.5 mmol) in MeOH (50 mL) at room temperature was added $NaBH_4$ (688 mg, 18.2 mmol). The reaction was stirred for 30 minutes before quenching with 1M HCl. The aqueous layer was extracted with ether (3 x 100 mL) and the combined ether layers washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded 3,3-dimethyl-2,3-dihydro-1*H*-inden-1-ol as a colourless oil (2.13 g, 13.1 mmol, 79 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.43 (s, 3H), 1.86 (dd, *J* = 13.0 Hz, 6.1 Hz, 1H), 1.94 (brs, 1H, O*H*), 2.42 (dd, *J* = 13.0 Hz, *J* = 7.0 Hz, 1H), 5.29 (t, *J* = 6.6 Hz, 1H), 7.23 (d, *J* = 7.1

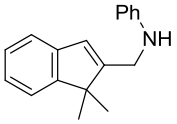
Hz, 1H), 7.29 (td, *J* = 7.4 Hz, 1.4 Hz, 1H), 7.34 (td, *J* = 7.4 Hz, 1.3 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 29.9, 30.0, 42.3, 52.0, 74.5, 122.3, 124.1, 127.0, 128.6, 143.7, 151.9.

Data consistent with literature values.[26]



To a solution of 3,3-dimethyl-2,3-dihydro-1*H*-inden-1-ol (1.20 g, 7.40 mmol) in DMF (3.7 mL) at 0 °C was added $POCl_3$ (2.44 mL) and the reaction was heated at 100 °C for 6 hours before cooling to room temperature and pouring onto iced water. The aqueous phase was basified with 3M NaOH and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 1,1-dimethyl-1*H*-indene-2-carbaldehyde as a colourless oil (407 mg, 2.36 mmol, 32 % yield).

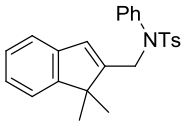
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 6H), 7.24-7.28 (m, 1H), 7.31-7.36 (m, 2H), 7.48 (dt, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 7.49 (s, 1H), 9.87 (s, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.5, 48.8, 121.8, 124.4, 127.3, 129.1, 139.0, 146.7, 154.4, 157.8, 188.2; **IR (ν, cm^{-1}):** 1691, 1533; **HRMS (ESI$^+$, m/z):** $[C_{12}H_{12}NaO]^+$ $(M+Na)^+$ calc. 195.0780, found 195.0779.



In a mortar and pestle was added 1,1-dimethyl-1*H*-indene-2-carbaldehyde (400 mg, 2.32 mmol) and aniline (212 μL, 2.32 mmol) and the mixture was ground for 15 minutes to afford a sticky yellow oil. To the resulting imine was added $NaBH_4$ (88 mg, 2.32 mmol) and PTSA (441 mg, 2.32 mmol) simultaneously. Grinding was continued for 5 minutes before dissolving in DCM (30 mL), washing with $NaHCO_3$ solution, brine, drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column

chromatography (SiO_2, EtOAc/PE 1:19) afforded *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)aniline as a colourless oil (253 mg, 1.01 mmol, 44 % yield).

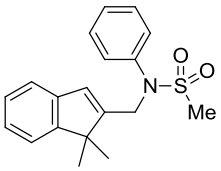
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 6H), 4.08 (brs, 1H, N*H*), 4.09 (d, *J* = 1.6 Hz, 2H), 6.59 (s, 1H), 6.69 (d, *J* = 7.9 Hz, 2H), 6.75 (t, *J* = 7.9 Hz, 1H), 7.17-7.28 (m, 5H), 7.35 (d, *J* = 6.9 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.4, 41.5, 49.7, 113.0, 117.6, 120.8, 121.0, 124.0, 124.6, 126.6, 129.3, 141.9, 148.2, 153.9, 155.5; **IR (ν, cm^{-1}):** 3420, 1602; **HRMS (FI$^+$):** [$C_{18}H_{19}N$] calc. 249.1517, found 249.1518.



To a solution of *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)aniline (240 mg, 0.96 mmol) in DCM (10 mL) at room temperature was added Et_3N (401 µL, 2.88 mmol), DMAP (10 mg) and tosyl chloride (367 mg, 1.92 mmol). The reaction was stirred for 24 hours before quenching with water. The organic layer was washed with NH_4Cl solution (2 x 30 mL), $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (316 mg, 0.78 mmol, 82 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 6H), 2.45 (s, 3H), 4.52 (s, 2H), 6.40 (s, 1H), 7.08-7.19 (m, 5H), 7.20-7.32 (m, 6H), 7.51 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 24.1, 47.8, 50.0, 121.0, 121.0, 125.0, 126.4, 127.6, 127.8, 128.3, 128.4, 128.7, 129.5, 134.9, 139.2, 141.3, 143.5, 150.8, 154.0; **IR (ν, cm^{-1}):** 1596, 1346, 1120; **HRMS (ESI$^+$, m/z):** $[C_{25}H_{25}NNaO_2S]^+$ $(M+Na)^+$ calc. 426.1498, found 426.1482; **mp:** 104-106 °C.

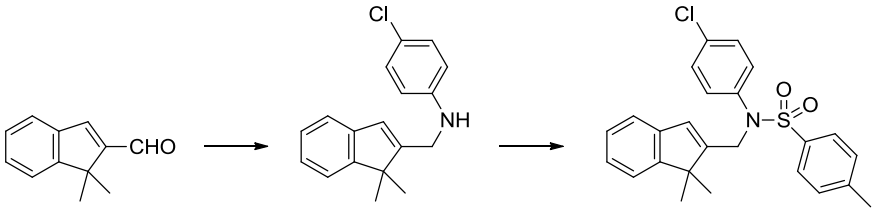
_N_-((1,1-dimethyl-1_H_-inden-2-yl)methyl)-_N_-phenylmethanesulfonamide (39b)

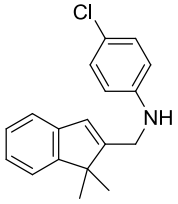


To a solution of *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)aniline (290 mg, 1.16 mmol) in DCM (5 mL) at -20 °C was added Et_3N (243 µL, 1.75 mmol) followed by methane sulfonyl chloride (99 µL, 1.28 mmol). The reaction was stirred for 24 hours and allowed to warm to room temperature before being quenched with water and stirred for a further 30 minutes before acidifying with 1M HCl. The aqueous phase was extracted into DCM and the organic layer washed successively with 1M HCl, and brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:3) afforded the title compound as a colourless oil (34 mg, 0.10 mmol, 9 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 6H), 2.97 (s, 3H), 4.70 (s, 2H), 6.51 (s, 1H), 7.05-7.45 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.1, 42.5, 48.0, 50.6, 121.2, 120.9, 125.3, 126.1, 127.9, 127.4, 128.7, 128.9, 134.6, 141.4, 150.3, 154.8; **IR (ν, cm^{-1}):** 1601, 1453; **HRMS (ESI$^+$, m/z):** $[C_{19}H_{21}NNaO_2S]^+$ $(M+Na)^+$ calc. 350.1185, found 350.1180.

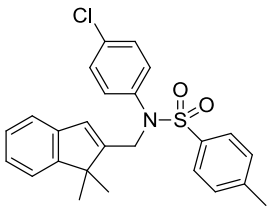
_N_-(4-chlorophenyl)-_N_-((1,1-dimethyl-1_H_-inden-2-yl)methyl)-4-methylbenzenesulfonamide (39c)





In a mortar and pestle was added 1,1-dimethyl-1*H*-indene-2-carbaldehyde (381 mg, 2.20 mmol) and 4-chloroaniline (282 mg, 2.20 mmol) and the

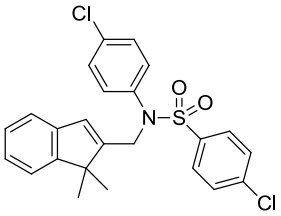
mixture was ground for 15 minutes to afford a sticky yellow oil. To the resulting imine was added $NaBH_4$ (84 mg, 2.20 mmol) and PTSA (421 mg, 2.20 mmol) simultaneously. Grinding was continued for 5 minutes before dissolving in DCM (30 mL), washing with $NaHCO_3$, brine, drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 4-chloro-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)aniline as a colourless oil (119 mg, 0.42 mmol, 19 % yield). The product contained a small amount of inseparable starting aldehyde but was used directly in the next step without further purification.



To a solution of 4-chloro-*N*-((1,1-dimethyl-1H-inden-2-yl)methyl)aniline (346 mg, 1.22 mmol) in DCM (10 mL) at room temperature was added Et_3N (511 µL, 3.67 mmol), DMAP (10 mg) and tosyl chloride (466 mg, 2.45 mmol). The reaction was stirred for 24 hours before quenching with water. The organic layer was washed with NH_4Cl solution (2 x 30 mL), $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (197 mg, 0.45 mmol, 37 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 6H), 2.46 (s, 3H), 4.48 (d, *J* = 1.2 Hz, 2H), 6.36 (s, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.13-7.19 (m, 3H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.24-7.28 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 21.6, 24.1, 47.7, 50.0, 121.0, 121.1, 125.2, 126.5, 127.7, 128.8, 128.9, 129.4, 129.6, 133.3, 134.5, 137.6, 141.0, 143.8, 150.2, 153.9; **IR (ν, cm^{-1}):** 1489, 1455, 1349, 1056; **HRMS (ESI$^+$, m/z):** $[C_{25}H_{24}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 460.1108, found 460.1119; **mp:** 133-134 °C.

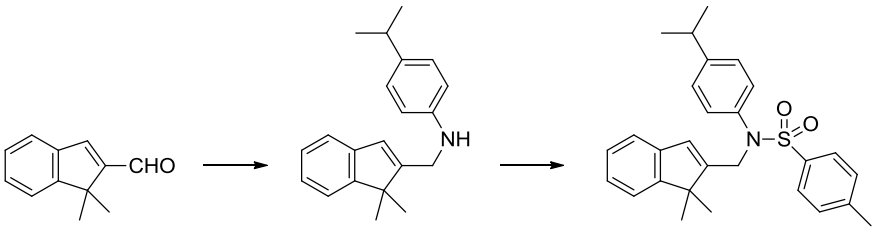
4-Chloro-*N*-(4-chlorophenyl)-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)benzenesulfonamide (39d)

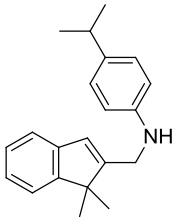


To a solution of 4-chloro-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)aniline (360 mg, 1.28 mmol) in DCM (5 mL) at room temperature was added Et_3N (357 µL, 2.56 mmol), 4-chlorobenzenesulfonyl chloride (403 mg, 1.91 mmol) and DMAP (5 mg). The reaction was stirred for 24 hours before being quenched with water, stirred for a further 30 minutes and acidified with 1M HCl. The aqueous phase was extracted into DCM and the organic layer washed successively with 1M HCl, $NaHCO_3$ solution and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (374 mg, 0.82 mmol, 64 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 6H), 4.49 (d, *J* = 1.3 Hz, 2H), 6.38 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.14-7.21 (m, 3H), 7.23-7.29 (m, 3H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.1, 47.9, 50.0, 121.1, 121.2, 125.3, 126.6, 129.1, 129.1, 129.2, 129.4, 129.5, 133.7, 136.0, 137.3, 139.6, 140.9, 149.8, 153.8; **IR (v, cm^{-1}):** 1586, 1352, 1165; **HRMS (ESI$^+$, m/z):** $[C_{24}H_{21}Cl_2NNaO_2S]^+$ $(M+Na)^+$ calc. 480.0562, found 480.0549; **mp:** 120-121 °C.

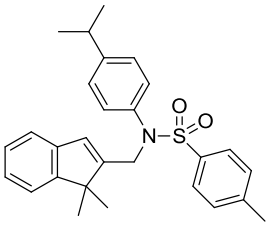
_N_-((1,1-dimethyl-1_H_-inden-2-yl)methyl)-_N_-(4-isopropylphenyl)-4-methylbenzenesulfonamide (39e)





In a pestle and mortar was added 1,1-dimethyl-1*H*-indene-2-carbaldehyde (739 mg, 4.29 mmol) and 4-isopropylaniline (1.17 mL, 8.58 mmol) and the mixture was ground for 15 minutes to obtain a sticky paste. To the resultant imine was added simultaneously PTSA (816 mg, 4.29 mmol) and sodium borohydride (162 mg, 4.29 mmol) and grinding was continued vigorously for 10 minutes before dissolving in DCM and transferring into a separating funnel. The organic layer was washed with $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-isopropylaniline as a pale yellow oil (776 mg, 2.66 mmol, 62 % yield).

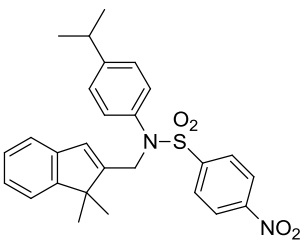
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 6H), 1.38 (s, 6H), 2.85 (sept, *J* = 6.8 Hz, 1H), 3.90 (brs, 1H, N*H*), 4.07 (d, *J* = 1.7 Hz, 2H), 6.61 (s, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.17-7.31 (m, 3H), 7.35 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.3, 24.4, 33.2, 41.9, 49.7, 113.0, 120.8, 121.0, 123.9, 124.6, 126.6, 127.1, 138.1, 142.0, 146.3, 154.0, 155.9; **IR (ν, cm^{-1}):** 3417 (br, N-H), 1615 (m, C=C); **HRMS (ESI$^+$, m/z):** $[C_{21}H_{26}N]^+$ $(M+H)^+$ calc. 292.2060, found 292.2060.



To a solution of *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-isopropylaniline (378 mg, 1.30 mmol) in DCM (5 mL) at room temperature was added Et_3N (542 µL, 3.89 mmol), 4-toluenesulfonyl chloride (494 mg, 2.59 mmol) and DMAP (20 mg). The reaction was stirred for 24 hours before being quenched with water and stirred for a further 30 minutes before acidifying with 1M HCl. The aqueous phase was extracted into DCM and the organic layer washed successively with 1M HCl, $NaHCO_3$ solution and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (332 mg, 0.75 mmol, 57 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.9, 6H), 1.30 (s, 6H), 2.46 (s, 3H), 2.86 (sept, *J* = 6.9 Hz, 1H), 4.48 (d, *J* = 1.2 Hz, 2H), 6.42 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.12-7.20 (m, 3H), 7.25-7.31 (m, 3H), 7.52 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 23.9, 24.1, 33.6, 48.0, 49.9, 120.9, 121.1, 124.9, 126.4, 126.7, 127.8, 128.1, 128.2, 129.4, 135.2, 136.7, 141.5, 143.4, 148.3, 151.1, 154.1; **IR (ν, cm^{-1}):** 1598, 1343, 1162; **HRMS (ESI$^+$, m/z):** $[C_{28}H_{31}NNaO_2S]^+$ $(M+Na)^+$ calc. 468.1968, found 468.1947; **mp:** 167-169 °C.

_N_-((1,1-dimethyl-1_H_-inden-2-yl)methyl)-_N_-(4-isopropylphenyl)-4-nitrobenzenesulfonamide (39f)

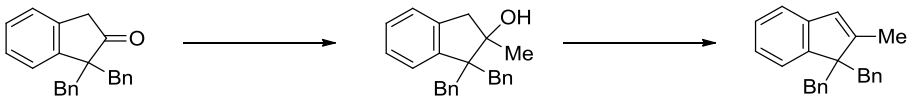


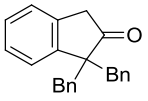
To a solution of *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-isopropylaniline (355 mg, 1.22 mmol) in DCM (5 mL) at room temperature was added Et_3N (509 µL, 3.65 mmol), 4-nitrobenzenesulfonyl chloride (545 mg, 2.46 mmol) and DMAP (20 mg). The reaction was stirred for 24 hours before being quenched with water and stirred

for a further 30 minutes before acidifying with 1M HCl. The aqueous phase was extracted into DCM and the organic layer washed successively with 1M HCl, $NaHCO_3$ solution and finally brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 3:17) afforded the title compound as a white solid (369 mg, 0.77 mmol, 63 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 7.0 Hz, 6H), 1.31 (s, 6H), 2.87 (sept, *J* = 7.0 Hz, 1H), 4.53 (d, *J* = 1.1 Hz, 2H), 6.45 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 7.11-7.22 (m, 5H), 7.27-7.30 (m, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 8.34 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.8, 24.1, 33.7, 48.4, 50.0, 121.1, 121.1, 124.1, 125.2, 126.6, 127.2, 128.0, 128.7, 128.9, 135.7, 141.1, 143.9, 149.1, 150.1, 150.2, 154.0; **IR (ν, cm^{-1}):** 1666, 1529, 1348, 1310, 1166; **HRMS (ESI$^+$, m/z):** $[C_{27}H_{28}N_2NaO_4S]^+$ $(M+Na)^+$ calc. 499.1662, found 499.1647; **mp:** 191-193 °C.

1,1-Dibenzyl-2-methyl-1*H*-indene (42)



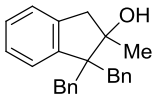


To a 5 mL flask at room temperature containing 2-indanone (1.32 g, 10.0 mmol) was added aliquat 336 (442 mg, 1.0 mmol) and freshly ground KOH (561 mg, 10.0 mmol). The solid mixture was stirred to obtain a yellow paste like consistency before benzyl bromide (2.38 mL, 20.0 mmol) was added rapidly. **Caution the benzyl bromide starts to reflux after ~10 seconds**. The reaction was stirred for 30 minutes, after which it had cooled to room temperature, and was then diluted with DCM and washed with water. The aqueous layer was extracted with DCM (2 x 30 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification

by column chromatography (SiO_2, EtOAc/PE 1:19) afforded 1,1-dibenzyl-1H-inden-2(3H)-one as a colourless oil (1.09 g, 3.50 mmol, 70 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (s, 2H), 3.13 (d, *J* = 13.0 Hz, 2H), 3.35 (d, *J* = 13.0 Hz, 2H), 6.81-8.86 (m, 4H), 6.92-6.96 (m, 1H), 7.03-7.10 (m, 6H), 7.14-7.19 (m, 1H), 7.33-7.38 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 43.6, 45.3, 62.4, 124.5, 125.2, 126.3, 126.9, 127.4, 127.8, 130.2, 136.4, 137.1, 142.6, 220.4.

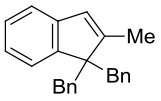
Data consistent with literature values.[27]



A 100 mL flask containing $CeCl_3.7H_2O$ (2.40 g, 6.44 mmol) was dried under vacuum at 150 °C for 6 hours before being cooled to room temperature. The flask was filled with argon and THF (20 mL) was added and the suspension was stirred overnight. 1,1-Dibenzyl-1*H*-inden-2(3H)-one (670 mg, 2.15 mmol) was added as a solution in THF (10 mL) and the suspension was further stirred for 30 minutes. Finally, MeMgBr (3M sln in THF, 2.15 mL, 6.44 mmol) was added dropwise and the reaction was stirred for 30 minutes before carefully quenching with 1M HCl and extracting into ether (3 x 30 mL). The combined ether layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1,1-dibenzyl-2-methyl-2,3-dihydro-1*H*-inden-2-ol as a colourless oil (508 mg, 1.55 mmol, 72 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3H), 1.85 (brs, 1H, O*H*), 2.71 (d, *J* = 16.4 Hz, 1H), 2.75 (d, *J* = 16.4 Hz, 1H), 2.83 (d, *J* = 13.7 Hz, 1H), 3.12 (d, *J* = 13.6 Hz, 1H), 3.23 (d, *J* = 13.8 Hz, 1H), 3.29 (d, *J* = 13.6 Hz, 1H), 6.74-6.82 (m, 3H), 7.09-7.27 (m, 6H), 7.28-7.31 (m, 1H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.51 (d, *J* = 7.1 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.3, 39.3, 41.2, 47.6, 58.2, 84.8, 125.0, 125.6, 126.1, 126.2, 126.3, 127.1, 127.5, 127.9, 130.8, 131.7, 138.2, 138.8,

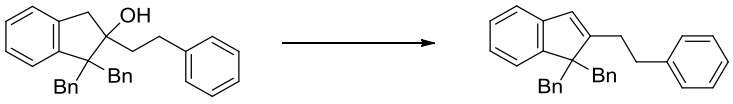
140.0, 147.9; **IR (ν, cm^{-1}):** 3524 (br, O-H); **HRMS (ESI$^+$, m/z):** $[C_{24}H_{24}NaO]^+$ $(M+Na)^+$ calc. 351.1719, found 351.1713.

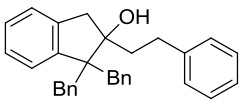


To a solution of 1,1-dibenzyl-2-methyl-2,3-dihydro-1*H*-inden-2-ol (500 mg, 1.52 mmol) in toluene (20 mL) at 100 °C was added PTSA (29 mg, 0.15 mmol) and the reaction was stirred for 2 hours before cooling to room temperature. The toluene was washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded 1,1-dibenzyl-2-methyl-1*H*-indene as a colourless oil (410 mg, 1.32 mmol, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (d, *J* = 1.5 Hz, 3H), 3.05 (d, *J* = 13.4 Hz, 2H), 3.38 (d, *J* = 13.4 Hz, 2H), 6.16 (s, 1H), 6.80 (dd, *J* = 7.4 Hz, *J* = 1.4 Hz, 4H), 6.94-6.98 (m, 1H), 7.02-7.12 (m, 6H), 7.12-7.16 (m, 2H), 7.22-7.27 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 119.9, 123.1, 123.5, 126.0, 126.6, 127.3, 128.1, 129.6, 137.3, 144.6, 148.0, 149.4; **IR (ν, cm^{-1}):** 1600 (w, C=C); **HRMS (FI$^+$):** $[C_{24}H_{22}]$ calc. 310.1721, found 310.1734.

1,1-Dibenzyl-2-phenethyl-1*H*-indene (44)

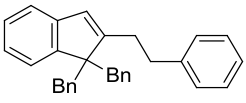




A 100 mL flask containing $CeCl_3.7H_2O$ (3.97 g, 10.5 mmol) was dried under vacuum at 150 °C for 6 hours before being cooled to room temperature. The flask was filled with argon and THF (20 mL) was added and the suspension was stirred overnight. 1,1-dibenzyl-1*H*-inden-2(3*H*)-one (1.09 g, 3.49 mmol) was added as a solution in THF (10 mL) and the suspension was further stirred for 30 minutes.

In a separate flask containing a solution of (2-bromoethyl)benzene (1.94 g, 10.5 mmol) in THF (20 mL) in an ambient temperature water bath was added magnesium (255 mg, 10.5 mmol) and the reaction was stirred until all the magnesium had been consumed (approx 1 hour). Once complete the Grignard reagent was transferred to the flask containing the ketone and added in a single portion. The reaction was stirred for 30 minutes before carefully quenching with 1M HCl and extracting into ether (3 x 30 mL). The combined ether layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1,1-dibenzyl-2-phenethyl-2,3-dihydro-1*H*-inden-2-ol as a colourless oil (1.13 g, 2.71 mmol, 78 % yield).

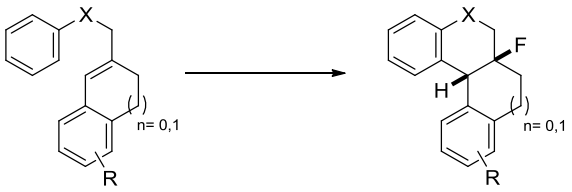
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (ddd, *J* = 13.6 Hz, *J* = 12.2 Hz, *J* = 5.0 Hz, 1H), 1.84 (brs, 1H, O*H*), 1.93 (ddd, *J* = 13.7 Hz, *J* = 12.2 Hz, *J* = 5.2 Hz, 1H), 2.56 (td, *J* = 12.7 Hz, *J* = 5.0 Hz, 1H), 2.75 (d, *J* = 16.2 Hz, 1H), 2.77 (d, *J* = 13.5 Hz, 1H), 2.86 (d, *J* = 16.1 Hz, 1H), 2.87-2.98 (m, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 3.25-3.34 (m, 2H), 6.65 (d, *J* = 7.2 Hz, 2H), 6.79 (d, *J* = 7.6 Hz, 1H), 7.06-7.12 (m, 4H), 7.12-7.19 (m, 2H), 7.21-7.26 (m, 2H), 7.26-7.32 (m, 4H), 7.33-7.40 (m, 2H), 7.56-7.61 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.7, 36.6, 39.3, 41.1, 44.8, 59.3, 86.9, 125.2, 125.7, 125.7, 126.1, 126.2, 126.4, 127.1, 127.4, 128.0, 128.3, 128.4, 130.9, 131.7, 138.0, 138.9, 139.9, 142.8, 147.8; **IR (ν, cm^{-1}):** 3369 (br, O-H), 1579 (w, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{31}H_{30}O$] calc. 418.2297, found 418.2299.



To a solution of 1,1-dibenzyl-2-phenethyl-2,3-dihydro-1*H*-inden-2-ol (1.00 g, 2.39 mmol) in toluene (40 mL) at 100 °C was added PTSA (100 mg) and the reaction was stirred for 2 hours before cooling to room temperature. The toluene was washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded 1,1-dibenzyl-2-phenethyl-1*H*-indene as a colourless oil (549 mg, 1.37 mmol, 57 % yield).

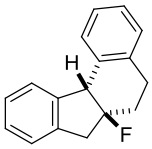
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59-2.78 (m, 4H), 2.91 (d, *J* = 13.5 Hz, 2H), 3.28 (d, *J* = 13.5 Hz, 2H), 6.16 (s, 1H), 6.63-6.68 (m, 4H), 6.87-7.08 (m, 10H), 7.15-7.21 (m, 3H), 7.24-7.30 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 29.9, 33.5, 43.2, 60.0, 120.2, 123.5, 123.6, 126.1, 126.1, 126.7, 127.4, 128.4, 128.6, 129.5, 130.7, 137.3, 142.3, 144.6, 148.0, 153.6; **IR (ν, cm^{-1}):** 1600 (w, C=C), 1554 (w, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{31}H_{28}$] calc. 400.2191, found 400.2198.

6.2.7 General procedure for fluoro-carbocyclization (cyclic substrates)



To the appropriate olefin (50 mg) in a 7.5 mL screw-top vial was added nitromethane (5 mL) and a few activated 3Å molecular sieves. The solution was left for 3 hours before $NaHCO_3$ (3.0 eq.) was added and the reaction was warmed to 40 °C. Once at 40 °C, *N*-fluoro-2,6-dichloropyridinium triflate (1.1 eq.) was added in one portion and the reaction was stirred for 1 hour before being filtered through a pipette of celite and eluted with ethyl acetate. The filtrate was concentrated *in vacuo* and purified directly by column chromatography (SiO_2).

6*a*-Fluoro-6,6*a*,7,11b-tetrahydro-5*H*-benzo[*c*]fluorene (31a)

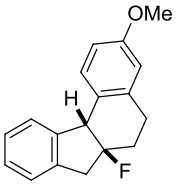


Prepared from 2-phenethyl-1*H*-indene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (92 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (dddd, *J* = 27.5 Hz, *J* = 13.8 Hz, *J* = 9.7 Hz, *J* = 5.1 Hz, 1H), 2.22 (tt, *J* = 13.3 Hz, *J* = 5.6 Hz, 1H), 2.73 (dt, *J* = 16.4 Hz, *J* = 5.8 Hz, 1H), 3.03 (ddd, *J* = 16.4

Hz, *J* = 9.5 Hz, *J* = 4.9 Hz, 1H), 3.18 (dd, *J* = 16.0 Hz, *J* = 14.2 Hz, 1H), 3.46 (dd, *J* = 21.0 Hz, *J* = 16.3 Hz, 1H), 4.52 (d, *J* = 21.6 Hz, 1H), 7.14-7.24 (m, 5H), 7.28 (td, *J* = 7.1 Hz, *J* = 1.3 Hz, 1H), 7.34-7.36 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.3 (d, *J* = 5.5 Hz), 30.7 (d, *J* = 24.2 Hz), 43.3 (d, *J* = 24.6 Hz), 53.1 (d, *J* = 24.6 Hz), 103.5 (d, *J* = 183.3 Hz), 124.7, 124.9, 126.3, 126.4, 126.9, 127.2, 128.6, 129.3, 135.2 (d, *J* = 3.4 Hz), 135.8, 139.3 (d, *J* = 4.5 Hz), 143.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -147.8 (ddddd, *J* = 27.5 Hz, *J* = 22.2 Hz, *J* = 20.5 Hz, *J* = 14.1 Hz, *J* = 12.6 Hz, 1F); **IR (ν, cm^{-1}):** 1480, 1414, 1025; **HRMS (FI$^+$):** [$C_{17}H_{15}F$] calc. 238.1158, found 238.1163.

6*a*-Fluoro-3-methoxy-6,6*a*,7,11*b*-tetrahydro-5*H*-benzo[*c*]fluorene + 6*a*-Fluoro-1-methoxy-6,6*a*,7,11*b*-tetrahydro-5*H*-benzo[*c*]fluorene (31g)

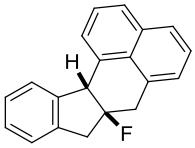


Prepared from 2-(3-methoxyphenethyl)-1H-indene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as separable regioisomers (99 % yield 2:1 para:ortho, >25:1 d.r.).

Para isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.03 (dddd, *J* = 27.6 Hz, *J* = 13.4 Hz, *J* = 9.7 Hz, *J* = 5.2 Hz, 1H), 2.19 (tt, *J* = 13.4 Hz, *J* = 5.5 Hz, 1H), 2.69 (dt, *J* = 16.5 Hz, *J* = 5.7 Hz, 1H), 3.00 (ddd, *J* = 16.5 Hz, *J* = 9.6 Hz, *J* = 4.9 Hz, 1H), 3.16 (dd, *J* = 16.2 Hz, *J* = 13.8 Hz, 1H), 3.43 (dd, *J* = 20.9 Hz, *J* = 16.4 Hz, 1H), 3.80 (s, 3H), 4.45 (d, *J* = 21.6 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.5 Hz, *J* = 2.7 Hz, 1H), 7.16-7.24 (m, 3H), 7.30-7.33 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 1H); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -148.5 (ddddd, *J* = 35.7 Hz, *J* = 22.4 Hz, *J* = 21.0 Hz, *J* = 14.2 Hz, *J* = 12.3 Hz, 1F); **IR (ν, cm^{-1}):** 1501 (w, C-C_{Ar}), 1413 (w, C-C_{Ar}), 1037 (m, C-F), 986 (m, C-O); **HRMS (FI$^+$):** [$C_{18}H_{17}OF$] calc. 268.1263, found 268.1271.

ortho isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.87-2.10 (m, 2H), 2.60-2.85 (m, 1H), 3.00 (ddd, *J* = 16.7 Hz, *J* = 11.0 Hz, *J* = 5.3 Hz, 1H), 3.12 (dd, *J* = 15.6 Hz, *J* = 3.6 Hz, 1H), 3.56 (dd, *J* = 19.6 Hz, *J* = 15.6 Hz, 1H), 3.92 (s, 3H), 4.80 (d, *J* = 19.7 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 7.08-7.26 (m, 5H); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -154.7 (m, 1F); **IR (ν, cm^{-1}):** 1470 (m, C-C_{Ar}), ,1439 (w, C-C_{Ar}), 1084 (s, C-F), 1054 (m, C-O); **HRMS (FI^+):** [$C_{18}H_{17}OF$] calc. 268.1263, found 268.1263.

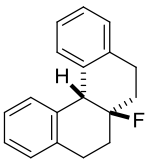
7*a*-Fluoro-7,7*a*,8,12*b*-tetrahydroindeno[1,2-*a*]phenalene (31h)



Prepared from 1-((1H-inden-2-yl)methyl)naphthalene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (60 % yield, 3.9:1 syn:anti).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 3.23 (dd, *J* = 15.5 Hz, *J* = 10.3 Hz, 1H), 3.37 (dd, *J* = 31.4 Hz, *J* = 16.8 Hz, 1H), 3.43-3.58 (m, 2H), 4.88 (d, *J* = 17.0 Hz, 1H), 7.20-7.39 (m, 5H), 7.43-7.66 (m, 3H), 7.75-7.88 (m, 2H); **^{13}C NMR (100.6 MHz, CD_2Cl_2):** δ = 36.8 (d, *J* = 25.5 Hz), 43.2 (d, *J* = 23.2 Hz), 53.0 (d, *J* = 23.2Hz), 102.1 (d, *J* = 187.8 Hz), 124.5, 125.2, 125.8, 125.9, 126.5, 126.6, 127.0, 127.2, 127.5, 128.2, 128.5 (d, *J* = 1.9 Hz), 131.6 (d, *J* = 3.1 Hz), 132.2 (d, *J* = 1.4 Hz), 133.6, 139.1 (d, *J* = 5.4 Hz), 143.2 (d, *J* = 6.4 Hz); **^{19}F NMR (376.6 MHz, CD_2Cl_2):** δ = -153.2 (m, 1F); **IR (ν, cm^{-1}):** 1460 (w, C-C_{Ar}), 1417 (w, C-C_{Ar}), 1049 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{20}H_{15}FNa]^+$ $(M+Na)^+$ calc. 297.1050, found 297.1049.

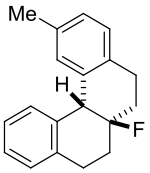
6*a*-Fluoro-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*c*]phenanthrene (31i)



Prepared from 3-phenethyl-1,2-dihydronaphthalene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:99) afforded the title compound as a colourless oil (93 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (ddd, *J* = 14.0 Hz, *J* = 9.8 Hz, *J* = 6.5 Hz, 1H), 1.95 (ddd, *J* = 14.0 Hz, *J* = 9.0 Hz, *J* = 6.6 Hz, 1H), 2.26 (dt, *J* = 14.6 Hz, *J* = 5.8 Hz, 1H), 2.30 (dt, *J* = 14.3 Hz, *J* = 5.8 Hz, 1H), 2.83 (dt, *J* = 16.5 Hz, *J* = 5.9 Hz, 2H), 3.10 (ddd, *J* = 16.3 Hz, *J* = 8.2 Hz, *J* = 7.0 Hz, 2H), 4.19 (d, *J* = 14.7 Hz, 1H), 7.07-7.14 (m, 2H), 7.17-7.29 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.7 (d, *J* = 5.5 Hz), 33.1 (d, *J* = 23.9 Hz), 48.7 (d, *J* = 24.6 Hz), 95.9 (d, *J* = 174.3 Hz), 125.9, 126.6, 128.3, 129.8, 136.4, 136.4; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -142.4 (m, 1F); **IR (ν, cm^{-1}):** 1491, 1452, 1062; **HRMS (FI$^+$):** [$C_{18}H_{17}F$] calc. 252.1314, found 252.1312.

6*a*-Fluoro-2-methyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*c*]phenanthrene (31j)

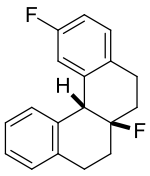


Prepared from 3-(4-methylphenethyl)-1,2-dihydronaphthalene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:99) afforded the title compound as a colourless oil (61 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81-1.96 (m, 2H), 2.16-2.30 (m, 2H), 2.30 (s, 3H), 2.76 (dt, *J* = 16.4 Hz, *J* = 6.0 Hz, 1H), 2.81 (dt, *J* = 16.4 Hz, *J* = 6.1 Hz, 1H), 2.97-3.11 (m, 2H), 4.13 (d, *J* = 14.6 Hz, 1H), 6.89 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.06-7.10 (m, 2H), 7.15-7.24 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.2, 26.2 (d, *J* = 5.5 Hz), 26.7 (d, *J* = 5.6 Hz), 33.1 (d, *J* = 23.8 Hz), 33.1 (d, *J* = 23.8 Hz), 48.7 (d, *J* = 24.2 Hz), 96.0 (d, *J* = 173.7 Hz), 125.8, 126.5, 127.4, 128.1, 128.2, 129.7, 130.4, 133.2, 135.3, 136.1 (d, *J* = 5.3 Hz), 136.4, 136.5 (d, *J* = 5.6 Hz); **^{19}F**

NMR (376.6 MHz, $CDCl_3$): δ = -142.8 (tq, *J* = 26.1 Hz, *J* = 14.8 Hz, 1F); **IR (ν, cm^{-1}):** 1492, 1456, 1063; **HRMS (FI^+):** [$C_{19}H_{19}F$] calc. 266.1471, found 266.1469.

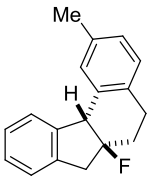
2,6*a*-Difluoro-6,6*a*,7,11*b*-tetrahydro-5*H*-benzo[*c*]fluorine (31k)



Prepared from 3-(4-fluorophenethyl)-1,2-dihydronaphthalene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (11 % yield, 7:1 syn:anti).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78-1.93 (m, 2H), 2.17-2.30 (m, 2H), 2.73-2.84 (m, 2H), 2.96-3.09 (m, 2H), 4.11 (d, *J* = 14.6 Hz, 1H), 6.76 (dd, *J* = 10.0 Hz, *J* = 2.6 Hz, 1H), 6.90 (td, *J* = 8.3 Hz, *J* = 2.6 Hz, 1H), 7.05-7.08 (m, 1H), 7.11-7.23 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.1 (d, *J* = 5.6 Hz), 26.5 (d, *J* = 5.5 Hz), 32.8 (d, *J* = 23.9 Hz), 33.3 (d, *J* = 23.9 Hz), 48.7 (d, *J* = 24.8 Hz), 95.6 (d, *J* = 174.5 Hz), 113.5 (d, *J* = 20.9 Hz), 116.2 (d, *J* = 21.7 Hz), 126.0, 126.8, 128.4, 129.4 (d, *J* = 7.8 Hz), 129.7, 131.9 (d, *J* = 2.7 Hz), 135.5 (d, *J* = 4.7 Hz), 136.3, 138.7 (t, *J* = 6.3 Hz), 161.2 (d, *J* = 243.2 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -116.9 (m, 1F), -142.9 (m, 1F); **IR (ν, cm^{-1}):** 1494 (w, C-C_{Ar}), 1452 (w, C-C_{Ar}), 1091 (m, C-F), 1063 (m, C-F); **HRMS (FI^+):** [$C_{18}H_{16}F_2$] calc. 270.1220, found 270.1220.

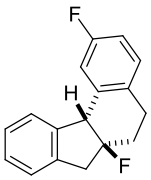
6*a*-Fluoro-2-methyl-6,6*a*,7,11*b*-tetrahydro-5*H*-benzo[*c*]fluorine (31l)



Prepared from 2-(4-methylphenethyl)-1*H*-indene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (81 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (dddd, *J* = 21.9 Hz, *J* = 13.8 Hz, *J* = 9.4 Hz, *J* = 5.1 Hz, 1H), 2.16-2.25 (m, 1H), 2.39 (s, 3H), 2.70 (dt, *J* = 16.4 Hz, *J* = 5.9 Hz, 1H), 2.98 (ddd, *J* = 16.4 Hz, *J* = 9.3 Hz, *J* = 5.0 Hz, 1H), 3.19 (dd, *J* = 16.2 Hz, *J* = 14.8 Hz, 1H), 3.44 (dd, *J* = 21.1 Hz, *J* = 16.4 Hz, 1H), 4.47 (d, *J* = 21.8 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.18-7.25 (m, 3H), 7.27 (s, 1H), 7.36-7.39 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.2, 25.9 (d, *J* = 5.9 Hz), 30.9 (d, *J* = 23.9 Hz), 43.3 (d, *J* = 24.8 Hz), 53.1 (d, *J* = 24.4 Hz), 103.7 (d, *J* = 183.1 Hz), 124.7, 124.9, 126.8, 127.2, 127.3, 128.5, 129.8, 132.6, 135.1 (d, *J* = 3.1 Hz), 135.7, 139.4 (d, *J* = 4.0 Hz), 143.1 (d, *J* = 4.9 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -147.8 (m, 1F); **IR (ν, cm^{-1}):** 1493, 1454, 1058; **HRMS (FI^+):** [$C_{18}H_{17}F$] calc. 252.1314, found 252.1311.

2,6*a*-Difluoro-6,6*a*,7,11*b*-tetrahydro-5*H*-benzo[*c*]fluorine (31m)

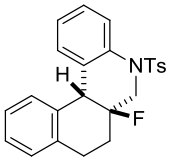


Prepared from 2-(4-fluorophenethyl)-1*H*-indene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (60 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (dddd, *J* = 27.6 Hz, *J* = 14.0 Hz, *J* = 9.7 Hz, *J* = 5.1 Hz, 1H), 2.18-2.27 (m, 1H), 2.70 (dt, *J* = 16.3 Hz, *J* = 5.6 Hz, 1H), 2.98 (ddd, *J* = 16.2 Hz, *J* = 9.6 Hz, *J* = 4.8 Hz, 1H), 3.18 (dd, *J* = 16.2 Hz, *J* = 14.3 Hz, 1H), 3.46 (dd, *J* = 21.0 Hz, *J* = 14.3 Hz, 1H), 4.47 (d, *J* = 21.4 Hz, 1H), 6.90 (td, *J* = 8.5 Hz, *J* = 2.7 Hz, 1H), 7.12 (dd, *J* = 8.4 Hz, *J* = 6.0 Hz, 1H), 7.16 (dd, *J* = 9.6 Hz, *J* = 2.5 Hz, 1H), 7.20-7.26 (m, 3H), 7.33-7.37 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.6 (d, *J* = 5.6 Hz), 30.8 (d, *J* = 23.9 Hz), 43.3 (d, *J* = 24.7 Hz), 53.2 (d, *J* = 24.7 Hz), 103.1 (d, *J* = 183.9 Hz), 113.5 (d, *J* = 21.4 Hz), 115.6 (d, *J* = 21.4 Hz), 124.5, 125.1, 127.0, 127.5, 129.9 (d, *J* = 8.0 Hz), 131.4 (d, *J* = 2.7 Hz), 137.1 (dd, *J* = 6.9 Hz, *J* = 3.2 Hz), 139.3 (d, *J* = 4.4 Hz), 142.3 (d, *J* = 5.1 Hz), 161.4 (d, *J* = 243.6 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -

117.0 (dd, *J* = 15.1 Hz, *J* = 8.2 Hz, 1F), -148.5 (m, 1F); **IR (ν, cm^{-1}):** 1493, 1454, 1089, 1058; **HRMS (FI^{+}):** [$C_{17}H_{14}F_2$] calc. 256.1064, found 256.1068.

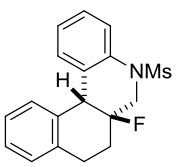
6*a*-Fluoro-5-tosyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31n)



Prepared from *N*-((3,4-dihydronaphthalen-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (52 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (dddd, *J* = 27.9 Hz, *J* = 14.1 Hz, *J* = 9.7 Hz, *J* = 6.7 Hz, 1H), 2.05-2.17 (m, 1H), 2.37 (s, 3H), 2.77 (dt, *J* = 16.9 Hz, *J* = 5.4 Hz, 1H), 2.99 (ddd, *J* = 16.9 Hz, *J* = 9.2 Hz, *J* = 7.0 Hz, 1H), 3.36 (d, *J* = 14.8 Hz, 1H), 3.51 (dd, *J* = 26.4 Hz, *J* = 14.8 Hz, 1H), 4.53 (dd, *J* = 22.2 Hz, *J* = 14.8 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 7.03-7.23 (m, 6H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 25.8 (d, *J* = 5.1 Hz), 30.8 (d, *J* = 24.2 Hz), 46.1 (d, *J* = 25.0 Hz), 54.8 (d, *J* = 29.2 Hz), 97.0 (d, *J* = 181.7 Hz), 124.5, 125.7, 126.1, 127.0, 127.1, 127.8, 128.6, 129.3, 129.5, 129.9, 132.0 (d, *J* = 5.8 Hz), 133.1 (d, *J* = 2.8 Hz), 135.4, 136.3, 136.3, 143.8; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -140.0 (m, 1F); **IR (ν, cm^{-1}):** 1492, 1458, 1351, 1165, 1065; **HRMS (ESI^{+}, m/z):** $[C_{24}H_{22}FNNaO_2S]^{+}$ $(M+Na)^{+}$ calc. 430.1247, found 430.1234.

6*a*-Fluoro-5-(methylsulfonyl)-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31o)

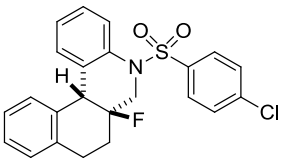


Prepared from *N*-((3,4-dihydronaphthalen-2-yl)methyl)-*N*-phenylmethanesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded the

title compound as a colourless oil (82 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (dddd, *J* = 19.4 Hz, *J* = 14.1 Hz, *J* = 8.5 Hz, *J* = 6.1 Hz, 1H), 2.37 (ddt, *J* = 20.1 Hz, *J* = 14.1 Hz, *J* = 6.2 Hz, 1H), 2.63 (s, 3H), 2.93 (dt, *J* = 16.3 Hz, *J* = 6.1 Hz, 1H), 3.12 (ddd, *J* = 16.8 Hz, *J* = 8.3 Hz, *J* = 6.4 Hz, 1H), 3.42 (dd, *J* = 31.6 Hz, *J* = 14.8 Hz, 1H), 4.18 (d, *J* = 15.4 Hz, 1H), 4.28 (td, *J* = 14.8 Hz, *J* = 1.5 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 7.10-7.15 (m, 1H), 7.19-7.28 (m, 4H), 7.33-7.39(m, 1H), 7.93 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.8 (d, *J* = 5.4 Hz), 31.2 (d, *J* = 23.7 Hz), 36.7 (d, *J* = 4.5 Hz), 46.1 (d, *J* = 24.6 Hz), 50.8 (d, *J* = 26.1 Hz), 93.9 (d, *J* = 178.8 Hz), 121.4, 123.9, 125.5, 126.3, 126.9, 127.0, 127.3 (d, *J* = 1.7 Hz), 127.3, 130.7, 134.7 (d, *J* = 8.4 Hz), 135.1, 135.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -139.4 (m, 1F); **IR (ν, cm^{-1}):** 1489, 1460, 1342, 1155, 1062; **HRMS (ESI^+, m/z):** $[C_{18}H_{18}FNNaO_2S]^+$ $(M+Na)^+$ calc. 354.0934, found 354.0925.

5-((4-Chlorophenyl)sulfonyl)-6*a*-fluoro-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31p)

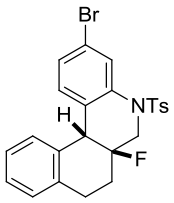


Prepared from 4-chloro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)-*N*-phenylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (84 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.83 (dddd, *J* = 23.9 Hz, *J* = 14.5 Hz, *J* = 8.7 Hz, *J* = 6.6 Hz, 1H), 2.15 (tt, *J* = 13.4 Hz, *J* = 6.0 Hz, 1H), 2.80 (dt, *J* = 16.8 Hz, *J* = 6.2 Hz, 1H), 3.02 (dt, *J* = 16.8 Hz, *J* = 7.6 Hz, 1H), 3.48-3.59 (m, 2H), 4.46 (dd, *J* = 20.8 Hz, *J* = 14.5 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 7.11-7.15 (m, 1H), 7.15 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.25-7.29 (m, 2H), 7.31 (td, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H), 7.47-7.53 (m, 2H), 7.84 (dd, *J* = 8.2 Hz, *J* = 0.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.6 (d, *J* =

5.6 Hz), 31.5 (d, *J* = 23.9 Hz), 46.9 (d, *J* = 24.8 Hz), 54.6 (d, *J* = 28.3 Hz), 96.9 (d, *J* = 181.1 Hz), 124.7, 126.3, 126.8, 127.5, 128.4, 128.9, 129.0, 129.6, 129.8, 130.4, 131.6 (d, *J* = 4.9 Hz), 133.8 (d *J* = 4.3 Hz), 135.6, 136.2, 137.8; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -138.9 (m, 1F); **IR (ν, cm^{-1}):** 1477, 1459, 1356, 1167, 1064; **HRMS (ESI^+, m/z):** $[C_{23}H_{19}ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 450.0701, found 450.0695.

3-Bromo-6*a*-fluoro-5-tosyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine and **1-bromo-6*a*-fluoro-5-tosyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31q)**



Prepared from *N*-(3-bromophenyl)-*N*-((3,4-dihydronaphthalen-2-yl)methyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (67 % yield, >25:1 d.r.).

Mixture of ortho and para isomers (1:1.3)

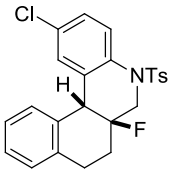
Para isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.79 (dddd, *J* = 25.3 Hz *J* = 14.3 Hz, *J* = 9.1 Hz, *J* = 6.6 Hz, 1H), 2.10-2.22 (m, 1H), 2.37 (s, 3H), 2.79 (dt, *J* = 16.8 Hz, *J* = 5.8 Hz, 1H), 2.93-3.05 (m, 1H), 4.42 (d, *J* = 14.3 Hz, 1H), 3.48 (dd, *J* = 27.9 Hz, *J* = 14.6 Hz, 1H), 4.46 (dd, *J* = 20.5 Hz, *J* = 14.6 Hz, 1H), 6.54 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.07-7.22 (m, 4H), 7.32 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 25.9 (d, *J* = 4.9 Hz), 30.9 (d, *J* = 24.2 Hz), 46.0 (d, *J* = 24.9 Hz), 54.0 (d, *J* = 28.4 Hz), 96.1 (d, *J* = 181.5 Hz), 121.2, 126.3, 126.7, 127.1, 127.7, 128.4, 128.6, 129.3, 129.4, 129.6, 133.1, 134.0, 135.3, 135.8, 137.4, 144.1; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -138.1 (m, 1F).

Ortho isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.11-2.22 (m, 1H), 2.32 (s, 3H), 2.34-2.50 (m, 1H), 2.92-3.06 (m, 1H), 3.16 (dt, *J* = 16.4 Hz, *J* = 6.4 Hz, 1H), 3.71 (dd, *J* = 35.6 Hz, *J* = 13.8 Hz,

1H), 4.07 (ddd, *J* = 17.7 Hz, *J* = 13.9 Hz, *J* = 2.2 Hz, 1H), 4.54 (d, *J* = 10.9 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 7.07-7.22 (m, 6H), 7.43 (dd, *J* = 8.1 Hz, *J* = 0.9 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 27.3 (d, *J* = 7.7 Hz), 32.0 (d, *J* = 22.6 Hz), 47.7 (d, *J* = 23.2 Hz), 51.1 (d, *J* = 25.8 Hz), 94.0 (d, *J* = 178.2 Hz), 121.2, 126.5, 126.8, 127.1, 127.7, 128.2, 128.6, 128.7, 129.4, 131.0, 133.0, 134.1, 134.5, 134.7, 137.5, 143.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -139.9 (m, 1F).

IR (ν, cm^{-1}): 1459 (w, C-C_{Ar}), 1353 (m, S=O), 1165 (s, S=O), 1090 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{24}H_{21}BrFNNaO_2S]^+$ $(M+Na)^+$ calc. 508.0353, found 508.0349.

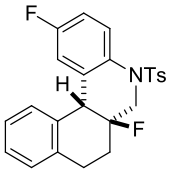
2-Chloro-6*a*-fluoro-5-tosyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31r)



Prepared from *N*-(4-chlorophenyl)-*N*-((3,4-dihydronaphthalen-2-yl)methyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (dddd, *J* = 27.5 Hz, *J* = 14.4 Hz, *J* = 9.6 Hz, *J* = 6.7 Hz, 1H), 2.05-2.18 (m, 1H), 2.37 (s, 3H), 2.78 (dt, *J* = 16.6 Hz, *J* = 5.6 Hz, 1H), 2.98 (ddd, *J* = 17.0 Hz, *J* = 9.4 Hz, *J* = 6.8 Hz, 1H), 3.31 (d, *J* = 14.4 Hz, 1H), 3.49 (dd, *J* = 26.9 Hz, *J* = 14.8 Hz, 1H), 4.50 (dd, *J* = 22.1 Hz, *J* = 14.8 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.12-7.23 (m, 4H), 7.26 (dd, *J* = 8.5 Hz, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 25.8 (d, *J* = 5.0 Hz), 30.7 (d, *J* = 23.9 Hz), 46.1 (d, *J* = 25.0 Hz), 54.6 (d, *J* = 28.8 Hz), 96.6 (d, *J* = 182.1 Hz), 125.8, 126.3, 127.1, 127.2, 128.0, 128.8, 129.2, 129.6, 129.7, 131.3, 132.3 (d, *J* = 2.3 Hz), 133.8 (d, *J* = 6.3 Hz), 134.9, 135.2, 136.0, 144.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -140.3 (m, 1F); **IR (ν, cm^{-1}):** 1486 (m, C-C_{Ar}), 1352 (s, S=O), 1164 (s, S=O), 1058 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{24}H_{21}ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 464.0858, found 464.0852.

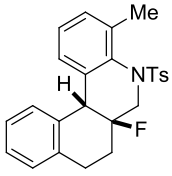
2,6*a*-Difluoro-5-tosyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31s)



Prepared from *N*-((3,4-dihydronaphthalen-2-yl)methyl)-*N*-(4-fluorophenyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (52 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (dddd, *J* = 31.2 Hz, *J* = 14.3 Hz, *J* = 10.4 Hz, *J* = 6.5 Hz, 1H), 2.00-2.12 (m, 1H), 2.38 (s, 3H), 2.74 (ddd, *J* = 17.1 Hz, *J* = 6.3 Hz, *J* = 4.0 Hz, 1H), 2.96 (ddd, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz, 1H), 3.11 (d, *J* = 15.1 Hz, 1H), 3.47 (dd, *J* = 24.9 Hz, *J* = 15.1 Hz, 1H), 4.59 (dd, *J* = 24.3 Hz, *J* = 15.2 Hz, 1H), 6.40 (dd, *J* = 9.1 Hz, *J* = 2.8 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.99 (td, *J* = 8.5 Hz, *J* = 2.9 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.17-7.24 (m, 3H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.74 (dd, *J* = 8.9 Hz, *J* = 5.1 Hz, 1H), **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 25.5 (d, *J* = 4.8 Hz), 30.5 (d, *J* = 30.5 Hz), 45.9 (d, *J* = 25.4 Hz), 55.7 (d, *J* = 29.7 Hz), 97.6 (d, *J* = 182.7 Hz), 114.6 (d, *J* = 22.9 Hz), 115.5, 115.8 (d, *J* = 1.9 Hz), 126.2, 127.1, 127.2, 127.3, 128.9, 129.6, 130.1, 131.7 (d, *J* = 1.4 Hz), 132.2 (d, *J* = 2.7 Hz), 135.3, 136.3, 144.0, 160.8 (d, *J* = 246.3 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -115.0 (td, *J* = 8.8 Hz, *J* = 5.6 Hz, 1F), -140.1 (m, 1F); **IR (ν, cm^{-1}):** 1486, 1351, 1164, 1089, 1061; **HRMS (FI$^+$):** [$C_{24}H_{21}F_2NO_2S$] calc. 425.1261, found 425.1266.

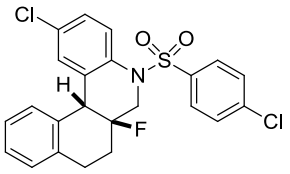
6*a*-Fluoro-4-methyl-5-tosyl-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31t)



Prepared from *N*-((3,4-dihydronaphthalen-2-yl)methyl)-4-methyl-*N*-(o-tolyl)benzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (27 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25-1.39 (m, 1H), 1.80-1.90 (m, 1H), 2.40 (s, 3H), 2.56 (s, 3H), 2.63 (dd, *J* = 17.1 Hz, *J* = 6.4 Hz, 1H), 2.82-2.97 (m, 1H), 2.90 (d, *J* = 15.9 Hz, 1H), 3.33 (dd, *J* = 21.1 Hz, *J* = 15.9 Hz, 1H), 4.74 (dd, *J* = 27.7 Hz, *J* = 15.8 Hz, 1H), 6.27 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 7.11-7.17 (m, 2H), 7.17-7.22 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.4, 21.5, 24.8 (d, *J* = 3.8 Hz), 29.7 (d, *J* = 15.0 Hz), 45.1 (d, *J* = 25.4 Hz), 58.4 (d, *J* = 30.5 Hz), 99.0 (d, *J* = 184.0 Hz), 125.1, 125.7, 127.0, 127.5, 127.7, 129.0, 129.7, 130.4, 131.4, 131.4, 135.2, 135.4, 137.2, 137.9, 138.3 (d, *J* = 9.4 Hz), 144.1; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -141.5 (m, 1F); **IR (ν, cm^{-1}):** 1454 (w, C-C_{Ar}), 1351 (m, S=O), 1164 (s, S=O), 1060 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{25}H_{24}FNNaO_2S]^+$ $(M+Na)^+$ calc. 444.1404, found 444.1393.

2-Chloro-5-((4-chlorophenyl)sulfonyl)-6*a*-fluoro-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31u)

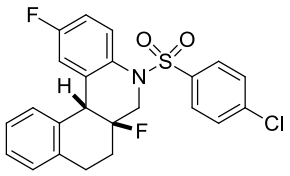


Prepared from 4-chloro-*N*-(4-chlorophenyl)-*N*-((3,4-dihydronaphthalen-2-yl)methyl)benzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (46 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (dddd, *J* = 23.4 Hz, *J* = 13.9 Hz, *J* = 8.3 Hz, *J* = 6.8 Hz, 1H), 2.16 (tt, *J* = 13.3 Hz, *J* = 6.0 Hz, 1H), 2.81 (dt, *J* = 17.0 Hz, *J* = 6.2 Hz, 1H), 3.01 (dt, *J* = 17.0 Hz, *J* = 7.6 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.51 (dd, *J* = 29.6 Hz, *J* = 14.7 Hz, 1H), 4.43 (dd, *J* = 21.1 Hz, *J* = 14.7 Hz, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.25-7.32 (m, 3H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.1 (d, *J* = 5.6 Hz), 30.9 (d, *J* = 23.6 Hz), 46.5 (d, *J* = 24.7 Hz), 53.9 (d, *J* = 28.2 Hz), 96.1 (d, *J* = 181.6 Hz), 125.6, 126.6, 127.3, 128.2,

128.4, 128.7, 129.1, 129.3, 129.9, 131.4, 132.6 (d, *J* = 4.0 Hz), 132.9 (d, *J* = 5.1 Hz), 134.4, 134.9, 137.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -139.6 (m, 1F); **IR (ν, cm^{-1}):** 1476 (w, C-C_{Ar}), 1357 (s, S=O), 1167 (s, S=O), 1054 (m, C-F); **HRMS (FI^+):** [$C_{23}H_{18}Cl_2FNO_2S$] calc. 461.0419, found 461.0413.

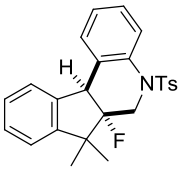
5-((4-Chlorophenyl)sulfonyl)-2,6*a*-difluoro-5,6,6*a*,7,8,12*b*-hexahydrobenzo[*k*]phenanthridine (31v)



Prepared from 4-chloro-*N*-((3,4-dihydronaphthalen-2-yl)methyl)-*N*-(4-fluorophenyl)benzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (35 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (dddd, *J* = 27.2 Hz, *J* = 14.3 Hz, *J* = 9.3 Hz, *J* = 6.6 Hz, 1H), 2.05-2.14 (m, 1H), 2.77 (dt, *J* = 16.9 Hz, *J* = 5.8 Hz, 1H), 2.98 (ddd, *J* = 16.9 Hz, *J* = 9.1 Hz, *J* = 6.7 Hz, 1H), 3.28 (d, *J* = 14.9 Hz, 1H), 3.50 (dd, *J* = 27.4 Hz, *J* = 15.0 Hz, 1H), 4.51 (dd, *J* = 22.9 Hz, *J* = 15.0 Hz, 1H), 6.52 (dd, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 7.01 (td, *J* = 8.5 Hz, *J* = 2.8 Hz, 1H), 7.09 (t, *J* = 7.1 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.79 (dd, *J* = 9.0 Hz, *J* = 5.1 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.7 (d, *J* = 5.2 Hz), 30.6 (d, *J* = 24.3 Hz), 46.3 (d, *J* = 25.0 Hz), 55.0 (d, *J* = 29.2 Hz), 97.1 (d, *J* = 181.8 Hz), 114.8 (d, *J* = 22.6 Hz), 116.3 (d, *J* = 23.7 Hz), 126.5, 126.9 (d, *J* = 8.6 Hz), 127.4, 128.4, 128.8, 129.3, 129.6, 131.8 (d, *J* = 2.7 Hz), 131.9 (d, *J* = 2.8 Hz), 134.9 (t, *J* = 7.0 Hz), 135.0, 137.3, 139.7, 160.7 (d, *J* = 246.8 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -114.9 (td, *J* = 8.3 Hz, *J* = 5.2 Hz, 1F), -139.3 (m, 1F); **IR (ν, cm^{-1}):** 1486 (w, C-C_{Ar}), 1356 (s, S=O), 1167 (s, S=O), 1091 (m, C-F), 1060 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{23}H_{18}ClF_2NNaO_2S]^+$ $(M+Na)^+$ calc. 468.0607, found 468.0600.

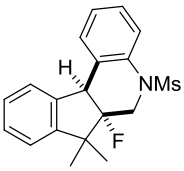
6*a*-Fluoro-7,7-dimethyl-5-tosyl-6,6*a*,7,11*b*-tetrahydro-5*H*-indeno[2,1-*c*]quinoline (40a)



Prepared from *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:17) afforded the title compound as a colourless oil (96 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 3.4 Hz, 3H), 1.37 (s, 3H), 2.35 (s, 3H), 3.28 (dd, *J* = 37.2 Hz, *J* = 14.7 Hz, 1H), 4.30 (d, *J* = 15.7 Hz, 1H), 4.83 (ddd, *J* = 14.8 Hz, *J* = 12.3 Hz, *J* = 0.7 Hz, 1H), 7.12-7.21 (m, 6H), 7.21-7.27 (m, 2H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.0, 21.6, 24.4 (d, *J* = 9.5 Hz), 46.9 (d, *J* = 20.7 Hz), 47.6 (d, *J* = 22.3 Hz), 47.8 (d, *J* = 20.7 Hz), 101.2 (d, *J* = 200.3 Hz), 122.2, 122.4, 124.2, 124.4, 126.9, 127.3, 127.4, 127.9 (d, *J* = 3.2 Hz), 128.2, 129.2, 130.3, 135.5, 136.7, 139.3 (d, *J* = 8.0 Hz), 143.5, 147.7 (d, *J* = 3.2 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -169.4 (dt, *J* = 36.6 Hz, *J* = 12.6 Hz, 1F); **IR (ν, cm^{-1}):** 1346, 1142, 1027; **HRMS (ESI$^+$, m/z):** $[C_{25}H_{24}FNNaO_2S]^+$ $(M+Na)^+$ calc. 356.0927, found 356.0912; **HPLC:** Chiralpak IA, 98/2 hexanes/isopropanol, 1mL/min, 19.2 min + 22.0 min, dissolved in isopropanol.

6*a*-Fluoro-7,7-dimethyl-5-(methylsulfonyl)-6,6*a*,7,11*b*-tetrahydro-5*H*-indeno[2,1-*c*]quinoline (40b)

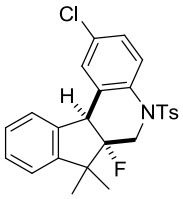


Prepared from *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-*N*-phenylmethanesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:17) afforded the title compound as a colourless oil (79 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 3.4 Hz, 3H), 1.42 (s, 3H), 2.91 (s, 3H), 3.15 (dd, *J* = 38.9 Hz, *J* = 15.0 Hz, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.69 (ddd, *J* = 15.2 Hz, *J* = 10.1 Hz, *J* = 1.7

Hz, 1H), 7.15-7.21 (m, 3H), 7.24-7.29 (m, 1H), 7.30-7.35 (m, 2H), 7.52-7.57 (m, 1H), 7.96-8.01 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.9, 24.8 (d, *J* = 9.6 Hz), 37.8 (d, *J* = 9.6 Hz), 47.2-47.6 (m, 2C), 100.7 (d, *J* = 196.6 Hz), 122.4, 122.6, 123.8 (d, *J* = 1.5 Hz), 125.1, 126.6, 127.4, 128.0, 128.3, 131.1, 135.4, 139.1 (d, *J* = 10.1 Hz), 147.2 (d, *J* = 5.1 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -173.4 (m, 1F); **IR (ν, cm^{-1}):** 1379, 1159, 1037; **HRMS (ESI$^+$):** [$C_{19}H_{20}FNNaO_2S$] $(M+Na)^+$ calc. 368.1091, found 368.1077.

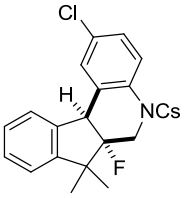
2-Chloro-6*a*-fluoro-7,7-dimethyl-5-tosyl-6,6*a*,7,11*b*-tetrahydro-5*H*-indeno[2,1-*c*]quinoline (40c)



Prepared from *N*-(4-chlorophenyl)-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (99 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 3.4 Hz, 3H), 1.34 (s, 3H), 2.35 (s, 3H), 3.23 (dd, *J* = 37.2 Hz, *J* = 15.0 Hz, 1H), 4.21 (d, *J* = 15.5 Hz, 1H), 4.78 (ddd, *J* = 14.8 Hz, *J* = 12.6 Hz, *J* = 1.1 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.13-7.20 (m, 5H), 7.22-7.28 (m, 2H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.1, 21.6, 24.3 (d, *J* = 9.5 Hz), 46.9 (d, *J* = 20.7 Hz), 47.6 (d, *J* = 20.0 Hz), 47.8 (d, *J* = 18.9 Hz), 101.0 (d, *J* = 199.1 Hz), 122.5, 123.5, 124.0, 127.4, 127.5, 127.9 (d, *J* = 3.1 Hz), 128.5, 128.7, 129.3, 129.8, 129.9, 134.2, 136.2, 138.5 (d, *J* = 8.4 Hz), 143.8, 147.6 (d, *J* = 3.9 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -168.7 (m, 1F); **IR (ν, cm^{-1}):** 1347, 1162, 1035; **HRMS (ESI$^+$):** [$C_{25}H_{23}ClFNNaO_2S$] $(M+Na)^+$ calc. 478.1014, found 478.1006; **HPLC:** Chiralpak IA, 95/5 hexanes/isopropanol, 1 mL/min, 13.6 min + 17.1 min, sample dissolved in isopropanol.

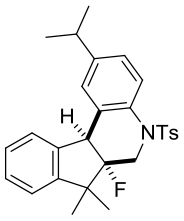
2-Chloro-5-((4-chlorophenyl)sulfonyl)-6*a*-fluoro-7,7-dimethyl-6,6*a*,7,11*b*-tetrahydro-5*H*-indeno[2,1-*c*]quinoline (40d)



Prepared from 4-chloro-*N*-(4-chlorophenyl)-*N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)benzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (99 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 3.4 Hz, 3H), 1.36 (s, 3H), 3.25 (dd, *J* = 38.0 Hz, *J* = 15.0 Hz, 1H), 4.24 (d, *J* = 15.3 Hz, 1H), 4.77 (ddd, *J* = 15.0 Hz, *J* = 12.0 Hz, *J* = 1.2 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.19 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.22-7.30 (m, 2H), 7.34-7.39 (m, 3H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.8, 24.4 (d, *J* = 9.5 Hz), 46.7 (d, *J* = 20.2 Hz), 47.6 (d, *J* = 14.9 Hz), 47.8 (d, *J* = 16.0 Hz), 100.8 (d, *J* = 199.1 Hz), 122.5, 123.8, 124.0 (d, *J* = 1.5 Hz), 128.5, 128.9, 129.0, 129.4, 129.4, 130.1, 130.4, 133.7, 137.4, 138.3 (d, *J* = 8.8 Hz), 139.5, 147.4 (d, *J* = 4.2 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -168.7 (m, 1F); **IR (ν, cm^{-1}):** 1352, 1165, 1014; **HRMS (ESI$^+$):** $[C_{23}H_{20}Cl_2FNNaO_2S]$ $(M+Na)^+$ calc. 498.0468, found 498.0474; **HPLC:** Chiralpak IA, 95/5 hexanes/isopropanol, 1 mL/min, 13.8 min + 15.9 min, sample dissolved in isopropanol/hexane 1:9.

6*a*-Fluoro-2-isopropyl-7,7-dimethyl-5-tosyl-6,6*a*,7,11*b*-tetrahydro-5*H*-indeno[2,1-*c*]quinoline (40e)

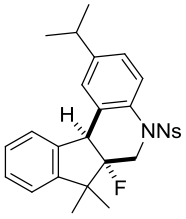


Prepared from *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-*N*-(4-isopropylphenyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9)

afforded the title compound as a colourless oil (99 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 3.3 Hz, 3H), 1.37 (s, 3H), 2.36 (s, 3H), 2.92 (sept, *J* = 6.2 Hz, 1H), 3.23 (dd, *J* = 37.5 Hz, *J* = 14.9 Hz, 1H), 4.31 (d, *J* = 15.4 Hz, 1H), 4.77 (ddd, *J* = 14.9 Hz, *J* = 10.5 Hz, *J* = 1.4 Hz, 1H), 7.06-7.28 (m, 8H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.8, 21.6, 24.0, 24.1, 24.4 (d, *J* = 9.2 Hz), 33.4, 46.7 (d, *J* = 20.6 Hz), 47.6 (d, *J* = 22.2 Hz), 47.9 (d, *J* = 20.6 Hz), 100.9 (d, *J* = 199.5 Hz), 121.8, 122.3, 124.0, 125.5, 126.4, 127.2, 127.7 (d, *J* = 2.6 Hz), 128.1, 128.1, 129.1, 133.0, 136.9, 139.4 (d, *J* = 8.7 Hz), 143.3, 144.9, 147.7 (d, *J* = 4.4 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -170.4 (m, 1F); **IR (ν, cm^{-1}):** 2963, 1457, 1347, 1027; **HRMS (ESI^{+}, m/z):** $[C_{28}H_{30}FNNaO_2S]^{+}$ $(M+Na)^{+}$ calc. 486.1873, found 486.1868; **HPLC:** Chiralpak IA, 95/5 hexanes/isopropanol, 1 mL/min, 13.8 min + 15.9 min, sample dissolved in EtOAc/hexane 1:9.

6*a*-Fluoro-2-isopropyl-7,7-dimethyl-5-((4-nitrophenyl)sulfonyl)-6,6*a*,7,11*b*-tetrahydro-5*H*-indeno[2,1-*c*]quinoline (40f)

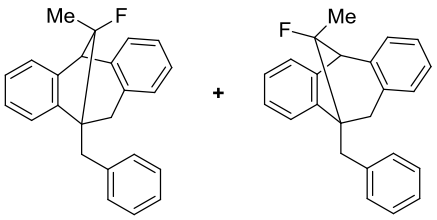


Prepared from *N*-((1,1-dimethyl-1H-inden-2-yl)methyl)-*N*-(4-isopropylphenyl)-4-nitrobenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:17) afforded the title compound as a colourless oil (98 % yield, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 3.4 Hz, 3H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.38 (s, 3H), 2.97 (sept, *J* = 6.6 Hz, 1H), 3.26 (dd, *J* = 38.9 Hz, *J* = 14.8 Hz, 1H), 4.28 (d, *J* = 14.8 Hz, 1H), 4.72 (ddd, *J* = 15.1 Hz, *J* = 11.1 Hz, *J* = 1.3 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.12-7.21 (m, 3H), 7.22-7.27 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.4, 23.9, 24.0, 24.6 (d, *J* = 9.3 Hz), 33.5, 46.5

(d, *J* = 20.2 Hz), 47.6 (d, *J* = 23.8 Hz), 48.1 (d *J* = 24.7 Hz), 100.9 (d, *J* = 199.0 Hz), 122.4, 123.9 (d, *J* = 1.3 Hz), 123.5, 124.1, 125.9, 127.4, 128.3, 128.6, 129.0 (d, *J* = 3.7 Hz), 132.0, 138.9 (d, *J* = 9.4 Hz), 140.7, 144.9 (d, *J* = 2.0 Hz), 146.3, 147.3 (d, *J* = 4.5 Hz), 149.9; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -169.7 (m, 1F); **HRMS (ESI$^+$):** $[C_{27}H_{27}FN_2NaO_4S]$ $(M+Na)^+$ calc. 517.1568, found 517.1566; **IR (ν, cm^{-1}):** 1530, 1348, 1311, 1165, 1079; **HPLC:** Chiralpak IC, 80/20 hexanes/isopropanol, 1mL/min, 18.5 min + 33.0 min, sample dissolved in DCM/hexane 1:3.

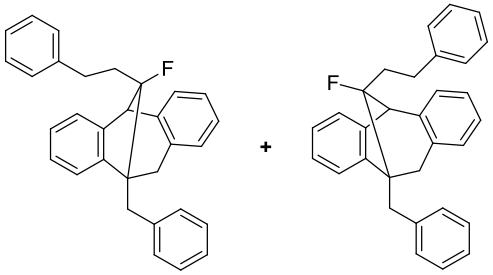
10-Benzyl-12-fluoro-12-methyl-10,11-dihydro-5*H*-5,10-methanodibenzo[*a*,*d*][7]annulene (43)



Prepared from 1,1-dibenzyl-2-phenethyl-1*H*-indene according to the general procedure (44 mg, 0.13 mmol, 83 % yield).

Data for major isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.06 (d, *J* = 22.3 Hz, 3H), 2.78 (dd, *J* = 17.1 Hz, *J* = 4.6 Hz, 1H), 3.16-3.31 (m, 3H), 3.85 (d, *J* = 8.3 Hz, 1H), 6.79-7.41 (m, 13H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 17.4 (d, *J* = 26.7 Hz), 38.2 (d, *J* = 3.2 Hz), 39.3 (d, *J* = 5.0 Hz), 52.7 (d, *J* = 18.6 Hz), 58.1 (d, *J* = 21.8 Hz), 107.9 (d, *J* = 186.9 Hz), 121.9, 123.1, 126.1, 126.2, 126.6, 127.0, 127.1, 127.1, 128.1, 128.2, 131.5, 134.8, 137.7, 137.8, 145.6, 147.0; **IR (ν, cm^{-1}):** 1594 (w, C-C_{Ar}), 1546 (w, C-C_{Ar}), 1030 (m, C-F); **HRMS (FI$^+$):** $[C_{24}H_{21}F]$ calc. 328.1627, found 328.1631.

10-Benzyl-12-fluoro-12-phenethyl-10,11-dihydro-5*H*-5,10-methanodibenzo[*a*,*d*][7]annulene (45)

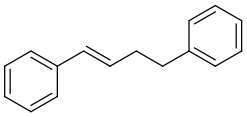


Prepared from 1,1-dibenzyl-2-phenethyl-1*H*-indene according to the general procedure (46 mg, 0.11 mmol, 88 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51-1.71 (m, 1H, major + minor isomer), 1.88-2.11 (m, 1H, major + minor isomer), 2.51-2.69 (m, 1H, major + minor isomer), 2.85-3.04 (m, 2H, major + minor isomer), 3.22-3.45 (m, 3H, major + minor isomer), 4.17-4.22 (m, 1H, major + minor isomer), 6.88-7.54 (m, 18 H, major + minor isomer); **^{13}C NMR (100.6 MHz, $CDCl_3$, major isomer):** δ = 29.5 (d, *J* = 3.8 Hz), 31.4 (d, *J* = 23.9 Hz), 38.2 (d, *J* = 3.6 Hz), 39.5 (d, *J* = 4.8 Hz), 53.2 (d, *J* = 18.5 Hz), 54.5 (d, *J* = 21.9 Hz), 109.6 (d, *J* = 191.3 Hz), 122.1, 123.2, 125.8, 126.0, 126.3, 126.6, 127.1, 127.1, 128.2, 128.2, 128.3, 128.3, 128.4, 128.5, 129.5, 131.4, 137.9, 141.8, 145.6, 146.7; **^{19}F NMR (376.5 MHz, $CDCl_3$):** δ = -171.9 (dddd, *J* = 39.7 Hz, *J* = 8.8 Hz, *J* = 7.2 Hz, *J* = 4.1 Hz, 1F, major isomer), -172.9 (dd, *J* = 37.1 Hz, *J* = 7.7 Hz, 1F, minor isomer); **IR (ν, cm^{-1}):** 1591 (w, C-C_{Ar}), 1549 (w, C-C_{Ar}), 1046 (m, C-F); **HRMS (FI^{+}):** [$C_{31}H_{27}F$] calc. 418.2097, found 418.2099.

6.2.8 Substrate synthesis (acyclic carbocyclizations)

But-1-ene-1,4-diyldibenzene (46a)



To a suspension of benzyltriphenylphosphonium bromide (2.00 g, 4.62 mmol) in THF (40 mL) at -78 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.89 mL, 4.62 mmol) and the reaction stirred at room temperature for 15 minutes. Hydrocinnamaldehyde (406 µL, 3.08 mmol) in THF (2 mL) was added at -78 °C and the reaction stirred for 24 hours at room temperature before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions dried

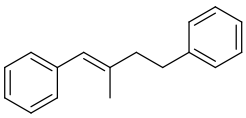
over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:99) afforded the title compound as a colourless oil (497 mg, 2.39 mmol, 78 % yield, 2.3:1 E:Z).

E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.55 (dd, *J* = 14.9 Hz, *J* = 7.1 Hz, 2H), 2.80 (dt, *J* = 8.5 Hz, *J* = 7.3 Hz, 2H), 6.28 (dt, *J* = 15.8 Hz, *J* = 6.8 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 7.19-7.37 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 34.9, 35.9, 125.9, 126.0, 126.9, 128.4, 128.5, 128.7, 130.0, 130.3, 137.7, 141.8.

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.62-2.72 (m, 2H), 2.76-2.85 (m, 2H), 5.72 (dt, *J* = 11.7 Hz, *J* = 7.1 Hz, 1H), 6.46 (d, *J* = 11.6 Hz, 1H), 7.18-7.38 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.4, 36.1, 125.9, 126.6, 128.1, 128.4, 128.5, 128.7, 129.4, 131.8, 137.5, 141.7.

Data consistent with literature values.[28]

(2-methylbut-1-ene-1,4-diyl)dibenzene (46b)



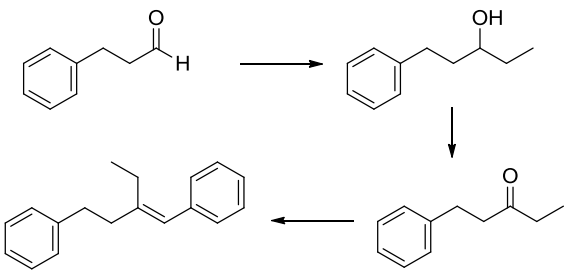
To a suspension of benzyltriphenylphosphonium bromide (2.00 g, 4.62 mmol) in THF (40 mL) at -78 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.89 mL, 4.62 mmol) and the reaction stirred at room temperature for 15 minutes. Benzylacetone (462 µL, 3.08 mmol) in THF (2 mL) was added at -78 °C and the reaction stirred for 24 hours at room temperature before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:99) afforded the title compound as a colourless oil (163 mg, 0.73 mmol, 24 % yield, 1:1.8 E:Z).

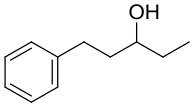
E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.94 (d, *J* = 1.1 Hz, 3H), 2.47-2.53 (m, 2H), 2.84-2.90 (m, 2H), 6.29 (s, 1H), 7.14-7.39 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.0, 34.7, 42.6, 125.4, 125.8, 125.9, 128.0, 128.3, 128.5, 128.8, 138.3, 138.5, 142.1.

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.97 (d, *J* = 1.4 Hz, 3H), 2.54-2.60 (m, 2H), 2.80-2.87 (m, 2H), 6.36 (s, 1H), 7.14-7.39 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.2, 34.3, 34.5, 125.9, 126.0, 126.3, 128.1, 128.3, 128.4, 128.5, 138.3, 138.5, 142.0.

Data consistent with literature values.[28]

(2-Ethylbut-1-ene-1,4-diyl)dibenzene (46c)

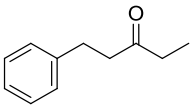




To a solution of hydrocinnamaldehyde (1.58 mL, 12.0 mmol) in ether (15 mL) was added ethylmagnesium bromide (2.5 M sln in ether, 7.2 mL, 18.0 mmol) slowly. The reaction was exothermic and reached reflux after 5 minutes. The reaction was further stirred for 30 minutes before quenching with NH_4Cl, extracting with ether, drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1-phenylpentan-3-ol as a colourless oil (1.72 g, 10.5 mmol, 88 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3H), 1.45 (brs, 1H, O*H*), 1.45-1.62 (m, 2H), 1.69-1.88 (m, 2H), 2.64-2.74 (m, 1H), 2.77-2.87 (m, 1H), 3.58 (tt, *J* = 7.7 Hz, *J* = 4.4 Hz, 1H), 7.18-7.25 (m, 3H), 7.27-7.33 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 9.8, 30.3, 32.1, 38.6, 72.7, 125.8, 128.4, 128.4, 142.2.

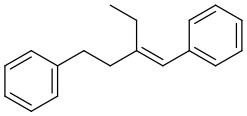
Data consistent with literature values.[29]



To a solution of pyridine (10.1 mL, 125 mmol) in DCM (100 mL) at room temperature was added freshly powdered chromium trioxide (6.2 g, 62.1 mmol) in one portion. The flask was fitted with a calcium chloride drying tube and the reaction was left to stir for 15 minutes before 1-phenylpentan-3-ol (1.70 g, 10.4 mmol) was added as a solution in DCM (10 mL) in one portion. The drying tube was replaced and the reaction stirred for a further 15 minutes before filtering off the solid. The residue was washed with DCM (3 x 50 mL) and the combined DCM filtrate was washed with dilute $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and evaporation under reduced pressure, purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 1-phenylpentan-3-one as a colourless oil (1.57 g, 9.70 mmol, 93 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.3 Hz, 3H), 2.42 (q, *J* = 7.3 Hz, 2H), 2.74 (t, *J* = 7.7 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H), 7.17-7.24 (m, 3H), 7.26-7.33 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 7.8, 29.8, 36.1, 43.9, 126.1, 128.3, 128.5, 141.2, 210.7.

Data consistent with literature values.[30]



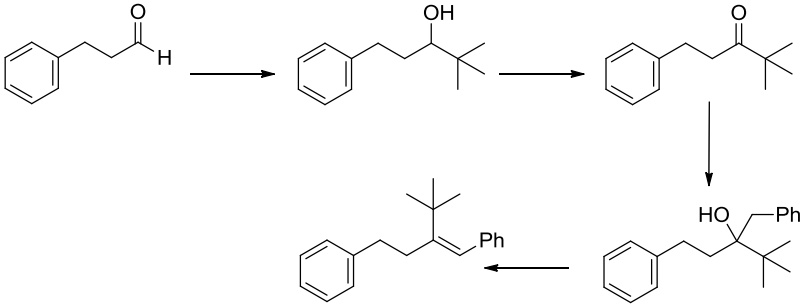
To a solution of diethyl benzylphosphonate (964 µL, 4.62 mmol) in THF at 0 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.89 mL, 4.62 mmol) and the reaction was stirred for 20 minutes before the addition of 1-phenylpentan-3-one (500 mg, 3.08 mmol) as a solution in THF (2 mL). The reaction was stirred at room temperature for 24 hours before quenching with NH_4Cl, extracting into ether (3 x 25 mL), drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, toluene/PE 1:49) afforded the title compound as a colourless oil (61 mg, 0.26 mmol, 8 % yield, 1.4:1 E:Z).

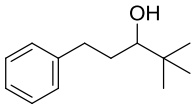
E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.18 (t, *J* = 7.4 Hz, 3H), 2.24-2.37 (m, 2H), 2.53-2.61 (m, 2H), 2.75-2.82 (m, 2H), 6.34 (s, 1H), 7.15-7.37 (m, 10H).

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.13 (t, *J* = 7.5 Hz, 3H), 2.24-2.37 (m, 2H), 2.46-2.53 (m, 2H), 2.82-2.89 (m, 2H), 6.27 (s, 1H), 7.15-7.37 (m, 10H).

IR (ν, cm^{-1}): 1606 (w, C=C), 1491 (m, C-C_{Ar}), 1449 (w, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{18}H_{20}$] calc. 236.1565, found 236.1569.

(2-(*tert*-Butyl)but-1-ene-1,4-diyl)dibenzene (46d)

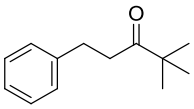




To a solution of hydrocinnamaldehyde (1.58 mL, 12.0 mmol) in ether (15 mL) was added *tert*-butylmagnesium bromide (1.6 M sln in ether, 11.3 mL, 18.0 mmol) slowly. The reaction was exothermic and reached reflux after 5 minutes. The reaction was further stirred for 30 minutes before quenching with NH_4Cl, extracting with ether, drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 4,4-dimethyl-1-phenylpentan-3-ol as a colourless oil (1.64 g, 8.51 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 9H), 1.44 (brs, 1H, O*H*), 1.60 (dddd, *J* = 14.0 Hz, *J* = 10.7 Hz, *J* = 9.6 Hz, *J* = 5.0 Hz, 1H), 1.86 (dddd, *J* = 13.8 Hz, *J* = 9.8 Hz, *J* = 6.8 Hz, *J* = 1.7 Hz, 1H), 2.64 (ddd, *J* = 13.7 Hz, *J* = 9.7 Hz, *J* = 6.9 Hz, 1H), 2.94 (ddd, *J* = 13.7 Hz, *J* = 10.1 Hz, *J* = 5.0 Hz, 1H), 3.24 (d, *J* = 10.4 Hz, 1H), 7.18-7.33 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.7, 33.4, 33.4, 35.0, 79.4, 125.8, 128.4, 128.5, 142.5.

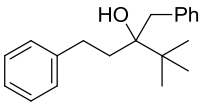
Data consistent with literature values.[31]



To a solution of pyridine (8.0 mL, 99.8 mmol) in DCM (100 mL) at room temperature was added freshly powdered chromium trioxide (4.99 g, 49.9 mmol) in one portion. The flask was fitted with a calcium chloride drying tube and the reaction was left to stir for 15 minutes before 4,4-dimethyl-1-phenylpentan-3-ol (1.60 g, 8.32 mmol) was added as a solution in DCM (10 mL) in one portion. The drying tube was replaced and the reaction stirred for a further 15 minutes before filtering off the solid. The residue was washed with DCM (3 x 50 mL) and the combined DCM filtrate was washed with dilute $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and evaporation under reduced pressure, purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded 4,4-dimethyl-1-phenylpentan-3-one as a colourless oil (1.44 g, 7.58 mmol, 91 % yield).

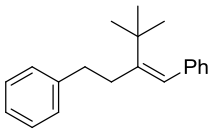
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9H), 2.78-2.84 (m, 2H), 2.86-2.91 (m, 2H), 2.17-2.23 (m, 3H), 7.26-7.32 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.3, 30.1, 38.5, 44.1, 126.0, 128.4, 128.4, 141.6, 215.0.

Data consistent with literature values.[31]



To a solution of 4,4-dimethyl-1-phenylpentan-3-one (300 mg, 1.58 mmol) in ether (5 mL) at room temperature was added benzylmagnesium bromide (1.5 M sln in ether, 1.37 mL, 2.05 mmol). The reaction was stirred for 30 minutes before quenching with NH_4Cl and extracting into ether (3 x 20 mL). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (392 mg, 1.39 mmol, 88 % yield).

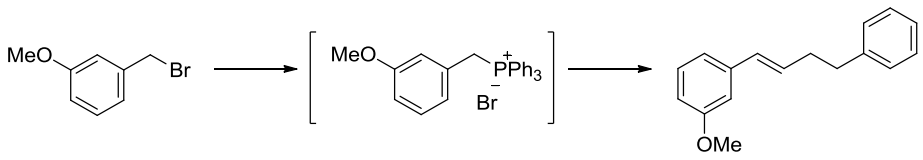
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 9H), 1.41 (brs, 1H, O*H*), 1.81 (td, *J* = 12.6 Hz, *J* = 5.2 Hz, 1H), 1.91 (td, *J* = 13.9 Hz, *J* = 4.9 Hz, 1H), 2.10 (td, *J* = 12.8 Hz, *J* = 5.1 Hz, 1H), 2.47 (td, *J* = 12.8 Hz, *J* = 5.0 Hz, 1H), 2.84 (d, *J* = 13.5 Hz, 1H), 3.02 (d, *J* = 13.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 7.16 (tt, *J* = 7.3 Hz, *J* = 1.0 Hz, 1H), 7.21-7.33 (m, 3H), 7.34-7.38 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.7, 31.5, 37.9, 39.1, 41.7, 125.7, 126.5, 128.2, 128.3, 128.4, 130.8, 138.5, 142.8; **IR (ν, cm^{-1}):** 3510 (br, O-H), 1454 (w, C-C_{Ar}); **HRMS (ESI$^+$, m/z):** $[C_{20}H_{26}NaO]^+$ $(M+Na)^+$ calc. 305.1876, found 305.1872.

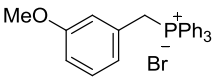


To a solution of 3-benzyl-4,4-dimethyl-1-phenylpentan-3-ol (367 mg, 1.30 mmol) in toluene (25 mL) at 100 °C was added PTSA (25 mg, 0.13 mmol) and the reaction was stirred for 2 hours before cooling to room temperature, diluting with EtOAc (50 mL) and washing with $NaHCO_3$. The organic fraction was washed further with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (169 mg, 0.64 mmol, 49 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H), 2.58 (s, 4H), 6.50 (s, 1H), 7.00 (d, *J* = 7.4 Hz, 2H), 7.12-7.41 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 29.5, 30.9, 36.1, 37.3, 123.3, 125.7, 126.0, 128.0, 128.2, 128.3, 128.6, 139.5, 142.7, 150.7; **IR (ν, cm^{-1}):** 1602 (w, C=C), 1494 (m, C-C_{Ar}), 1453 (w, C-C_{Ar}); **HRMS (FI$^+$):** $[C_{20}H_{24}]$ calc. 264.1878, found 264.1888.

1-Methoxy-3-(4-phenylbut-1-en-1-yl)benzene (46e)

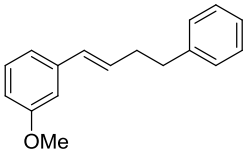




To a suspension of triphenylphosphine (5.00 g, 19.1 mmol) in toluene (50 mL) was added benzyl bromide (2.27 mL, 19.1 mmol) and the reaction was heated at reflux for 3 hours before cooling to room temperature and collecting the white precipitate by filtration. The white solid was washed successively with toluene and pentane and dried under vacuum to afford (3-methoxybenzyl)triphenylphosphonium bromide in quantitative yield.

^{1}H NMR (400 MHz, MeOD): δ = 3.56 (s, 3H), 4.92 (d, *J* = 15.1 Hz, 2H), 6.50-6.54 (m, 1H), 6.60-6.65 (m, 1H), 6.87-6.92 (m, 1H), 7.15 (td, *J* = 8.0 Hz, *J* = 0.6 Hz, 1H), 7.64-7.79 (m, 12H), 7.88-7.96 (m, 3H); **^{13}C NMR (100.6 MHz, MeOD):** δ = 29.8 (d, *J* = 48.3 Hz), 54.7, 114.9 (d, *J* = 3.8 Hz), 116.3 (d, *J* = 5.2 Hz), 123.3 (d, *J* = 5.8 Hz), 129.0 (d, *J* = 8.6 Hz), 130.1 (d, *J* = 3.4 Hz), 130.3 (d, *J* = 12.5 Hz), 134.4 (d, *J* = 9.8 Hz), 135.4 (d, *J* = 3.1 Hz), 160.4 (d, *J* = 3.2 Hz); **^{31}P NMR (162.0 MHz, MeOD):** δ = 23.0.

Data consistent with literature values.[32]



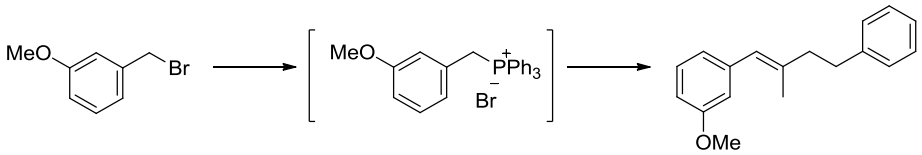
To a solution of (3-methoxybenzyl)triphenylphosphonium bromide (2.00 g, 4.32 mmol) in THF (40 mL) at -78 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.70 mL, 4.32 mmol) and the reaction stirred for 15 minutes at room temperature before being cooled back down to -78 °C. Hydrocinnamaldehyde (380 µL, 2.88 mmol) was added as a solution in THF (2 mL) and the reaction was warmed to room temperature and stirred overnight. After quenching with NH_4Cl, the aqueous phase was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, toluene/PE 3:7) afforded the title compound as a colourless oil (521 mg, 2.19 mmol, 76 % yield, 1.9:1 E:Z).

E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.52-2.60 (m, 2H), 2.76-2.86 (m, 2H), 3.83 (s, 3H), 6.28 (dt, *J* = 15.8 Hz, *J* = 6.7 Hz, 1H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.80 (d, *J* = 6.4 Hz, 1H), 6.89-6.92 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 7.19-7.35 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 34.9, 35.8, 55.2, 111.4, 112.5, 118.7, 125.9, 128.4, 128.5, 129.5, 139.2, 141.7, 159.8.

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.65-2.74 (m, 2H), 2.76-2.86 (m, 2H), 3.81 (s, 3H), 5.73 (dt, *J* = 11.7 Hz, *J* = 7.1 Hz, 1H), 6.44 (d, *J* = 11.7 Hz, 1H), 6.76-6.82 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 7.19-7.35 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.4, 36.0, 55.2, 112.1, 114.3, 121.3, 125.9, 129.1, 129.3, 130.3, 130.3, 132.1, 138.9, 141.0, 159.4.

Data consistent with literature values.[33]

1-Methoxy-3-(2-methyl-4-phenylbut-1-en-1-yl)benzene (46f)



To a solution of (3-methoxybenzyl)triphenylphosphonium bromide (2.00 g, 4.32 mmol) in THF (40 mL) at -78 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.70 mL, 4.32 mmol) and the reaction stirred for 15 minutes at room temperature before being cooled back down to -78 °C. Benzylacetone (432 µL, 2.88 mmol) was added as a solution in THF (2 mL) and the reaction was warmed to room temperature and stirred overnight. After quenching with NH_4Cl, the aqueous phase was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, toluene/PE 3:7) afforded the title compound as a colourless oil (441 mg, 1.75 mmol, 61 % yield, 1:1.6 E:Z).

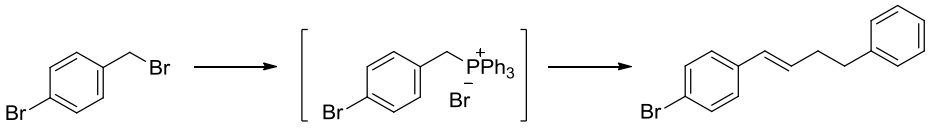
Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.96 (d, *J* = 1.1 Hz, 3H), 2.48-2.54 (m, 2H), 2.82-2.91 (m, 2H), 3.84 (s, 3H), 6.28 (s, 1H), 6.73-6.81 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.18-7.39 (m,

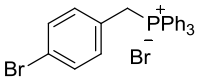
6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.1, 34.7, 42.6, 55.2, 111.4, 114.4, 121.4, 125.3, 125.9, 128.3, 128.5, 129.0, 138.6, 139.9, 142.1, 159.3.

E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.98 (d, *J* = 1.4 Hz, 3H), 2.56-2.62 (m, 2H), 2.82-2.91 (m, 2H), 3.81 (s, 3H), 6.35 (s, 1H), 6.73-6.81 (m, 3H), 7.18-7.39 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.2, 34.3, 34.5, 55.2, 111.7, 114.0, 121.0, 125.9, 126.2, 128.3, 128.4, 129.1, 138.8, 139.8, 141.9, 159.4.

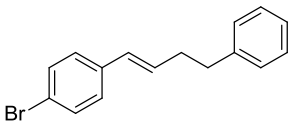
IR (ν, cm^{-1}): 1599 (m, C=C), 1490 (w, C-C_{Ar}), 1454 (w, C-C_{Ar}), 1048 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{20}NaO]^+$ $(M+Na)^+$ calc. 275.1406, found 275.1417.

1-Bromo-4-(4-phenylbut-1-en-1-yl)benzene (46g)





To a suspension of triphenylphosphine (5.00 g, 19.1 mmol) in toluene (50 mL) was added 1-bromo-4-(bromomethyl)benzene (4.76 g, 19.1 mmol) and the reaction was heated at reflux for 5 hours before cooling to room temperature and collecting the white precipitate by filtration. The white solid was washed successively with toluene and pentane and dried under vacuum to afford (4-bromobenzyl)triphenylphosphonium bromide in quantitative yield.



To a solution of (4-bromobenzyl)triphenylphosphonium bromide (2.00 g, 3.90 mmol) in THF (30 mL) at -78 °C was added NaH (60% dispersion in mineral oil, 156 mg, 3.90 mmol) and the reaction stirred for 30 minutes at room temperature before being cooled back down to -78 °C. Hydrocinnamaldehyde (343 µL,

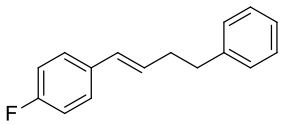
2.60 mmol) was added as a solution in THF (2 mL) and the reaction was warmed to room temperature and stirred overnight. After quenching with NH_4Cl, the aqueous phase was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, toluene/PE 3:7) afforded the title compound as a colourless oil (554 mg, 1.93 mmol, 74 % yield, 1.7:1 E:Z).

E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.52-2.60 (m, 2H), 2.76-2.86 (m, 2H), 6.28 (dt, *J* = 15.8 Hz, *J* = 6.5 Hz, 1H), 6.35-6.39 (m, 1H), 7.07-7.13 (m, 1H), 7.19-7.28 (m, 4H), 7.29-7.37 (m, 2H), 7.41-7.48 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 34.9, 35.7, 120.6, 126.0, 127.6, 128.4, 128.5, 128.5, 131.6, 132.6, 136.6, 141.6.

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.61-2.68 (m, 2H), 2.76-2.86 (m, 2H), 5.76 (dt, *J* = 11.6 Hz, *J* = 7.2 Hz, 1H), 6.39-6.42 (m, 1H), 7.04-7.11 (m, 1H), 7.19-7.28 (m, 4H), 7.29-7.37 (m, 2H), 7.37-7.48 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.4, 35.9, 120.5, 126.0, 128.4, 129.3, 130.3, 130.8, 131.3, 131.3, 136.4, 141.5.

IR (ν, cm^{-1}): 1487 (m, C=C), 1447 (w, C-C_{Ar}); **HRMS (FI^+):** [$C_{16}H_{15}Br$] calc. 286.0357, found 286.0353.

1-Fluoro-4-(4-phenylbut-1-en-1-yl)benzene (46h)



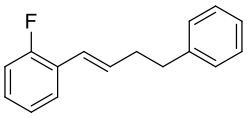
To a suspension of triphenyl(3-phenylpropyl)phosphonium bromide (1.00 g, 2.17 mmol) in THF (15 mL) at 0 °C was added ^{n}BuLi (1.6 M sln in hexanes, 1.36 mL, 2.17 mmol) and the reaction stirred at room temperature for 15 minutes. 4-Fluorobenzaldehyde (153 µL, 1.45 mmol) in THF (2 mL) was added and the reaction stirred overnight before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2,

EtOAc/PE 1:49) afforded the title compound as a colourless oil (279 mg, 1.23 mmol, 85 % yield, 1:4.0 E:Z).

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.58-2.68 (m, 2H), 2.74-2.84 (m, 2H), 5.70 (dt, *J* = 11.6 Hz, *J* = 7.2 Hz, 1H), 6.41 (d, *J* = 11.6 Hz, 1H), 6.96-7.04 (m, 2H), 7.16-7.25 (m, 5H), 7.27-7.33 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.3, 36.0, 115.0 (d, *J* = 21.2 Hz), 125.9, 126.0, 128.3, 128.4, 128.5, 130.2 (d, *J* = 8.0 Hz), 131.7 (d, *J* = 1.1 Hz), 141.5, 161.4 (d, *J* = 247.0 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -115.6.

Data consistent with literature values.[33b]

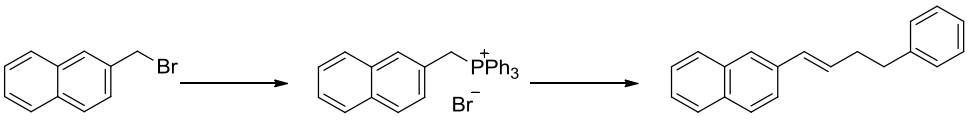
1-Fluoro-2-(4-phenylbut-1-en-1-yl)benzene (46i)

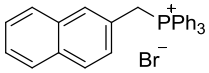


To a suspension of triphenyl(3-phenylpropyl)phosphonium bromide (1.00 g, 2.17 mmol) in THF (15 mL) at 0 °C was added ^{n}BuLi (1.6 M sln in hexanes, 1.36 mL, 2.17 mmol) and the reaction stirred at room temperature for 15 minutes. 2-Fluorobenzaldehyde (153 µL, 1.45 mmol) in THF (2 mL) was added and the reaction stirred overnight before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (327 mg, 1.45 mmol, 99 % yield, 1:10.1 E:Z).

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.53-2.62 (m, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 5.85 (dt, *J* = 11.6 Hz, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 11.5 Hz, 1H), 7.01-7.11 (m, 2H), 7.16-7.25 (m, 5H), 7.26-7.32 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.7, 35.8, 115.3 (d, *J* = 22.3 Hz), 122.0 (d, *J* = 3.2 Hz), 123.5 (d, *J* = 3.7 Hz), 125.9, 128.2, 128.4, 128.4 (d, *J* = 8.5 Hz), 128.5, 130.4 (d, *J* = 3.7 Hz), 133.9, 141.6, 160.0 (d, *J* = 246.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -115.3; **IR (ν, cm^{-1}):** 1574 (w, C=C), 1486 (m, C-C_{Ar}), 1452 (m, C-C_{Ar}); **HRMS (FI^+):** [$C_{16}H_{15}F$] calc. 226.1158, found 226.1154.

2-(4-Phenylbut-1-en-1-yl)naphthalene (46j)

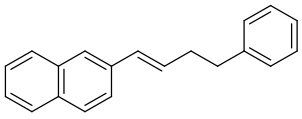




To a suspension of triphenylphosphine (4.75 g, 18.1 mmol) in toluene (50 mL) was added 2-(bromomethyl)naphthalene (4.00 g, 18.1 mmol) and the reaction was heated at reflux for 5 hours before cooling to room temperature and collecting the white precipitate by filtration. The white solid was washed successively with toluene and pentane and dried under vacuum to afford (naphthalen-2-ylmethyl)triphenylphosphonium bromide in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.13 (d, *J* = 15.1 Hz, 2H), 7.09 (dt, *J* = 8.5 Hz, *J* = 1.8 Hz, 1H), 7.45-7.54 (m, 3H), 7.58-7.62 (m, 1H), 7.65-7.78 (m, 13H), 7.82-7.86 (m, 1H), 7.88-7.94 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.0 (d, *J* = 47.9 Hz), 118.2 (d, *J* = 86.0 Hz), 125.1 (d, *J* = 9.5 Hz), 127.0, 127.2 (d, *J* = 1.5 Hz), 127.7 (d, *J* = 1.4 Hz), 127.8 (d, *J* = 1.5 Hz), 128.0 (d, *J* = 4.0 Hz), 128.8 (d, *J* = 2.5 Hz), 130.4 (d, *J* = 12.6 Hz), 131.0 (d, *J* = 7.3 Hz), 133.3 (d, *J* = 2.9 Hz), 133.5 (d, *J* = 3.2 Hz), 134.4 (d, *J* = 9.7 Hz), 135.5 (d, *J* = 3.0 Hz); **^{31}P NMR (162.0 MHz, MeOD):** δ = 22.8.

Data consistent with literature values.[34]



To a suspension of (naphthalen-2-ylmethyl)triphenylphosphonium bromide (2.00 g, 4.14 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.59 mL, 4.14 mmol) and the reaction stirred at room temperature for 15 minutes. Hydrocinnamaldehyde (364 µL, 2.76 mmol) in THF (2 mL) was added and the reaction stirred overnight before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic

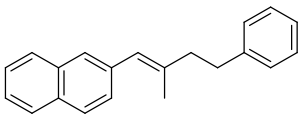
fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (712 mg, 2.76 mmol, 99 % yield, 2.3:1).

E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.59-2.68 (m, 2H), 2.83-2.92 (m, 2H), 6.44 (dt, *J* = 15.8 Hz, *J* = 6.8 Hz, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 7.22-7.40 (m, 5H), 7.40-7.53 (m, 2H), 7.61 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1H), 7.71 (s, 1H), 7.78-7.86 (m, 3H);); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 35.0, 35.9, 123.6, 125.5, 125.5, 125.9, 126.2, 127.7, 127.9, 128.1, 128.4, 128.5, 130.5, 130.5, 132.3, 133.7, 135.2, 141.8.

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.75-2.83 (m, 2H), 2.83-2.92 (m, 2H), 5.84 (dt, *J* = 11.6 Hz, *J* = 7.1 Hz, 1H), 6.64 (d, *J* = 11.6 Hz, 1H), 7.22-7.40 (m, 5H), 7.40-7.53 (m, 3H), 7.68 (s, 1H), 7.78-7.86 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.6, 36.1, 123.6, 125.7, 126.0, 126.1, 127.2, 127.4, 127.6, 127.6, 128.0, 128.4, 128.6, 129.5, 132.2, 133.3, 135.1, 141.7.

Data consistent with literature values.[35]

2-(2-Methyl-4-phenylbut-1-en-1-yl)naphthalene (46k)



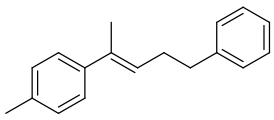
To a suspension of (naphthalen-2-ylmethyl)triphenylphosphonium bromide (2.00 g, 4.14 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (1.6 M sln in hexanes, 2.59 mL, 4.14 mmol) and the reaction stirred at room temperature for 15 minutes. Benzylacetone (414 µL, 2.76 mmol) in THF (2 mL) was added and the reaction stirred overnight before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (239 mg, 0.88 mmol, 32 % yield, 1:1.6).

Z isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.01 (d, *J* = 1.2 Hz, 3H), 2.52-2.58 (m, 2H), 2.89 (dd, *J* = 16.1 Hz, *J* = 8.3 Hz, 2H), 6.43 (s, 1H), 7.18-7.86 (m, 12H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.1, 34.8, 42.7, 125.4, 125.4, 125.9, 125.9, 125.9, 127.4, 127.6, 127.8, 128.3, 128.4, 128.5, 131.9, 133.4, 136.0, 138.9, 142.1.

E isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.03 (d, *J* = 1.4 Hz, 3H), 2.63 (dd, *J* = 8.7 Hz, *J* = 5.8 Hz, 2H), 2.87-2.94 (m, 2H), 6.49 (s, 1H), 7.18-7.86 (m, 12H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 24.2, 34.3, 34.7, 125.4, 126.0, 126.4, 126.7, 127.0, 127.2 ,127.3, 127.5, 127.5, 127.6, 127.8, 131.9, 133.5, 135.8, 139.0, 141.9.

IR (ν, cm^{-1}): 1599 (w, C=C), 1495 (m, C-C_{Ar}), 1454 (m, C-C_{Ar}); **HRMS (FI^+):** [$C_{21}H_{20}$] calc. 272.1565, found 272.1563.

1-Methyl-4-(5-phenylpent-2-en-2-yl)benzene (46l)

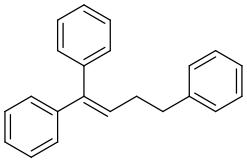


To a suspension of triphenyl(3-phenylpropyl)phosphonium bromide (1.00 g, 2.17 mmol) in THF (15 mL) at 0 °C was added ^{n}BuLi (2.4 M sln in hexanes, 0.90 mL, 2.17 mmol) and the reaction stirred at room temperature for 15 minutes. 4'-Methylacetophenone (194 µL, 1.45 mmol) in THF (2 mL) was added and the reaction stirred for 24 hours before quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (264 mg, 1.12 mmol, 77 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (d, *J* = 1.0 Hz, 3H), 2.34 (dt, *J* = 7.9 Hz, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 2.68 (t, *J* = 7.4 Hz, 2H), 5.51 (td, *J* = 7.3 Hz, *J* = 1.3 Hz, 1H), 7.02-7.06 (m, 2H), 7.12-7.18 (m, 4H), 7.24-7.32 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.1, 25.7, 31.0, 36.4,

125.7, 126.4, 127.8, 128.2, 128.5, 128.7, 136.0, 136.7, 139.0, 142.1; **IR (ν, cm^{-1}):** 1610 (w, C=C), 1496 (w, C-C_{Ar}), 1453 (w, C-C_{Ar}); **HRMS (FI^{+}):** [$C_{18}H_{20}$] calc. 236.1565, found 236.1565.

But-1-ene-1,1,4-triyltribenzene (46m)

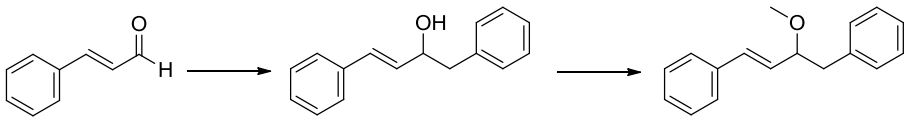


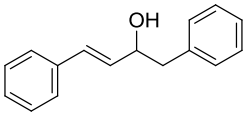
To a suspension of (3-phenylpropyl)triphenylphosphonium bromide (2.00 g, 4.34 mmol) in THF (25 mL) at 0 °C was added ^{n}BuLi (2.5 M sln in hexanes, 1.74 mL, 4.34 mmol) and the reaction stirred for 15 minutes before the addition of benzophenone (527 mg, 2.89 mmol). The reaction was stirred for 24 hours before quenching with NH_4Cl and extracting into ether (3 x 25 mL). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (342 mg, 1.20 mmol, 42 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (dt, *J* = 7.8 Hz, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 6.14 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.29-7.40 (m, 11H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 31.7, 36.2, 125.8, 126.9, 126.9, 127.2, 128.1, 128.1, 128.3, 128.5, 128.8, 129.8, 140.1, 141.7, 142.2, 142.7.

Data consistent with literature values.[36]

(*E*)-(3-Methoxybut-1-ene-1,4-diyl)dibenzene (46n)



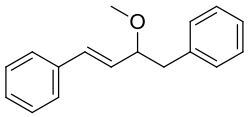


To a solution of cinnamaldehyde (755 µL, 6.0 mmol) in ether (20 mL) at -78 °C was added benzylmagnesium bromide (1.5 M sln in ether, 6.0 mL, 9.0 mmol). The reaction was stirred for 1 hour before warming to room temperature

and quenching with NH_4Cl. The aqueous layer was extracted with ether (3 x 20 mL) and the combined ethereal extracts washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded the title compound as a colourless oil (404 mg, 1.80 mmol, 30 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (brs, 1H, O*H*), 2.91 (dd, *J* = 13.5 Hz, *J* = 7.9 Hz, 1H), 3.00 (dd, *J* = 13.5 Hz, *J* = 5.0 Hz, 1*J* = 12.5 Hz, *J* = 6.5 Hz, 1H), 6.31 (dd, *J* = 15.8 Hz, *J* = 6.3 Hz, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 7.24-7.43 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 44.2, 73.5, 126.5, 126.7, 127.7, 128.6, 128.6, 129.6, 130.4, 131.4, 136.7, 137.7.

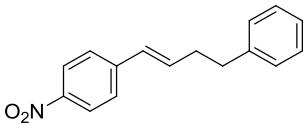
Data consistent with literature values.[37]



To a solution of (*E*)-1,4-diphenylbut-3-en-2-ol (365 µL, 1.63 mmol) in THF (7 mL) at room temperature was added NaH (60 % dispersion in mineral oil, 98 mg, 2.44 mmol) and the reaction was stirred for 30 minutes before the addition of methyl iodide (152 µL, 2.44 mmol). The reaction was heated to 40 °C and stirred for 1 hour before quenching with water, extracting into EtOAc, washing with brine, drying over $MgSO_4$ and evaporating under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (312 mg, 1.31 mmol, 80 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.89 (dd, *J* = 13.7 Hz, *J* = 6.0 Hz, 1H), 3.03 (dd, *J* = 13.8 Hz, *J* = 7.0 Hz, 1H), 3.33 (s, 3H), 3.97 (dd, *J* = 13.7 Hz, *J* = 6.8 Hz, 1H), 6.11 (dd, *J* = 15.9 Hz, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 7.20-7.41 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 42.5, 56.5, 83.3, 126.2, 126.5, 127.7, 128.2, 128.6, 129.6, 129.6, 132.4, 136.6, 138.2; **IR (ν, cm^{-1}):** 1602 (w, C=C), 1495 (w, C-C_{Ar}), 1452 (w, C-C_{Ar}), 1091 (s, C-O), 968 (m, C-O); **HRMS (FI$^+$):** [$C_{17}H_{18}O$] calc. 238.1358, found 238.1356.

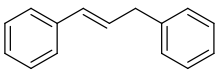
1-Nitro-4-(4-phenylbut-1-en-1-yl)benzene (46o)



To a suspension of (3-phenylpropyl)triphenylphosphonium bromide (2.00 g, 4.34 mmol) in THF (25 mL) at 0 °C was added ^{n}BuLi (2.5 M sln in hexanes, 1.74 mL, 4.34 mmol) and the reaction stirred for 15 minutes before the addition of *p*-nitrobenzaldehyde (437 mg, 2.89 mmol). The reaction was stirred for 24 hours before quenching with NH_4Cl and extracting into ether (3 x 25 mL). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (558 mg, 2.20 mmol, 76 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (dt, *J* = 7.8 Hz, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.8 Hz, 2H), 5.92 (dt, *J* = 11.7 Hz, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 11.7 Hz, 1H), 7.17-7.30 (m, 5H), 7.32 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.6, 35.7, 123.5, 126.2, 127.8, 128.4, 128.5, 128.5, 129.3, 135.6, 141.0, 144.2; **IR (ν, cm^{-1}):** 1595 (m, C=C), 1512 (s, N=O), 1454 (w, C-C_{Ar}), 1339 (s, N=O); **HRMS (ESI^{+}, m/z):** $[C_{16}H_{15}NNaO_2]^{+}$ $(M+Na)^{+}$ calc. 276.0995, found 276.0988.

Prop-1-ene-1,3-diyldibenzene (46p)



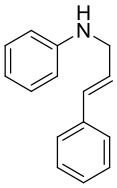
To a solution of cinnamyl alcohol (481 mg, 3.58 mmol) in THF (12mL) in a sealed tube at room temperature was added phenylboronic acid (547 mg, 4.49 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.0078 mmol). The reaction was immediately placed into a preheated oil bath at 80 °C and stirred for 6 hours before cooling to room temperature. The crude reaction mixture was poured onto a 1 inch pad of silica, eluted with ether and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:99) afforded the title compound as a colourless liquid (637 mg, 3.28 mmol, 92 % yield).

Only *E*- isomer observed.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (d, *J* = 6.6 Hz, 2H), 6.39 (dt, *J* = 15.8 Hz, *J* = 6.5 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 7.20-7.42 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 39.4, 126.1, 126.2, 127.1, 128.5, 128.5, 128.7, 129.2, 131.1, 137.5, 140.2.

Data consistent with literature values.[38]

_N_-Cinnamylaniline (48a)

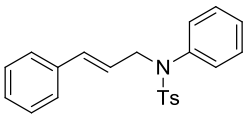


To a solution of cinnamylaldehyde (629 µL, 5.0 mmol) in TFE (10 mL) at 40 °C was added aniline (456µL, 5.0 mmol) and the reaction was stirred for 5 minutes before the addition of $NaBH_4$ (227 mg, 6.0 mmol) in one portion. The reaction was left to stir for 30 minutes before filtering off the solid and washing with a further 5 mL TFE. The solvent was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, EtOAc/PE 1:9) to afford the title compound as a pale yellow oil (891 mg, 4.26 mmol, 85 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (brs, 1H, N*H*), 3.96 (dd, *J* = 5.7 Hz, *J* = 1.2 Hz, 2H), 6.35 (dt, *J* = 15.9 Hz, *J* = 5.7 Hz, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.69 (dd, *J* = 8.6 Hz, *J* = 0.7 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 7.21 (dd, *J* = 8.5 Hz, *J* = 7.3 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 46.2, 113.0, 117.6, 126.3, 127.0, 127.5, 128.6, 129.3, 131.5, 136.8, 148.0.

Data consistent with literature values.[39]

_N_-Cinnamyl-4-methyl-_N_-phenylbenzenesulfonamide (48b)

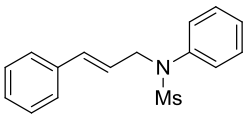


To a solution of *N*-cinnamylaniline (209 mg, 1.0 mmol) in THF (5 mL) at room temperature was added DMAP (147 mg, 1.2 mmol) and tosyl chloride (286 mg, 1.5 mmol) and the reaction was stirred for 48 hours. To the reaction was added saturated $NaHCO_3$ solution (10 mL) and stirring was continued for 30 minutes. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic fractions dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (211 mg, 0.58 mmol, 58 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 4.34 (dd, *J* = 6.6 Hz, *J* = 1.2 Hz, 2H), 6.11 (dt, *J* = 15.9 Hz, *J* = 6.6 Hz, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 7.06-7.11 (m, 2H), 7.18-7.32 (m, 10H), 7.53 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 53.3, 124.1, 126.4, 127.7, 127.8, 127.8, 128.5, 128.9, 128.9, 129.4, 133.7, 135.7, 136.3, 139.2, 143.4.

Data consistent with literature values.[40]

_N_-cinnamyl-_N_-phenylmethanesulfonamide (48c)

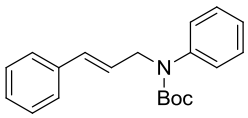


To a solution of *N*-cinnamylaniline (150 mg, 0.72 mmol) in DCM (5 mL) at -20 °C was added triethylamine (110 µL, 0.79 mmol). Methanesulfonyl chloride (83 µL, 1.08 mmol) was added slowly and then the reaction was left to warm to room temperature and stirred for 24 hours. The reaction was quenched with water, and extracted into DCM (50mL). The DCM fraction was washed with 1M NaOH and brine before being dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:3) afforded the title compound as a white solid (196 mg, 0.68 mmol, 95 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.96 (s, 3H), 4.46 (dd, *J* = 6.7 Hz, *J* = 1.3 Hz, 2H), 6.22 (dt, *J* = 15.8 Hz, *J* = 6.7 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 7.21-7.42 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 38.4, 53.5, 124.0, 126.5, 128.0, 128.1, 128.6 ,128.6, 129.5, 134.2, 136.2, 139.4.

Data consistent with literature values.[40]

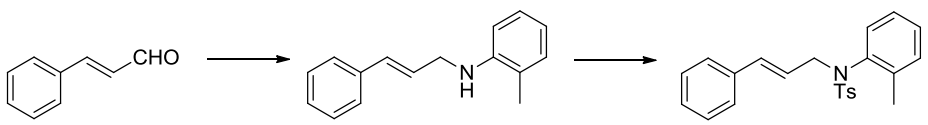
tert-Butyl cinnamyl(phenyl)carbamate (48d)

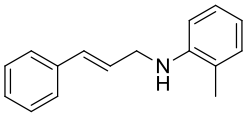


To a solution of *N*-cinnamylaniline (209 mg, 1.0 mmol) in chloroform (5 mL) at room temperature was added di-*tert*-butyl dicarbonate (327 mg, 1.5 mmol) and the reaction stirred for 24 hours. The crude reaction mixture was concentrated *in vacuo* and directly purified by column chromatography (SiO_2, EtOAc/PE 1:19) to afford a yellow oil. The oil was further dissolved into ethyl acetate (50 mL) and washed rapidly with 1M HCl (2 x 25 mL) before drying over $MgSO_4$ and evaporating under reduced pressure. A final purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (219 mg, 0.71 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 4.37-4.40 (m, 2H), 6.31 (dtd, *J* = 15.8 Hz, *J* = 5.9 Hz, *J* = 1.3 Hz, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 7.16-7.38 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 28.3, 52.5, 80.4, 125.7, 125.8, 126.4, 126.5, 127.5, 128.5, 128.7, 131.8, 136.8, 142.8, 154.6; **IR (ν, cm^{-1}):** 1694 (s, C=O), 1597 (w, C=C), 1495 (m, C-C_{Ar}), 1451 (m, C-C_{Ar}), 1277 (s, C-N), 1164 (s, C-O); **HRMS (ESI^+, m/z):** $[C_{20}H_{23}NaO_2]^+$ $(M+Na)^+$ calc. 332.1621, found 332.1615.

_N_-cinnamyl-4-methyl-_N_-(_o_-tolyl)benzenesulfonamide (48e)

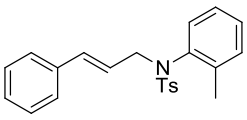




To a solution of cinnamylaldehyde (629 µL, 5.0 mmol) in TFE (10 mL) at 40 °C was added *o*-toluidine (536µL, 5.0 mmol) and the reaction was stirred for 5 minutes before the addition of $NaBH_4$ (227 mg, 6.0 mmol) in one portion. The reaction was left to stir for 30 minutes before filtering off the solid and washing with a further 5 mL TFE. The solvent was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, EtOAc/PE 1:19) to afford the title compound as a pale yellow oil (531 mg, 2.38 mmol, 48 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H), 4.01 (dd, *J* = 5.9 Hz, *J* = 1.2 Hz, 2H), 6.40 (dt, *J* = 15.9 Hz, *J* = 5.9 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.69-6.78 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.16 (td, *J* = 8.0 Hz, *J* = 0.9 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.39-7.44 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 17.6, 46.2, 110.1, 117.3, 122.1, 126.4, 127.1, 127.2, 127.6, 128.6, 130.1, 131.7, 136.8, 145.9.

Data consistent with literature values.[41]

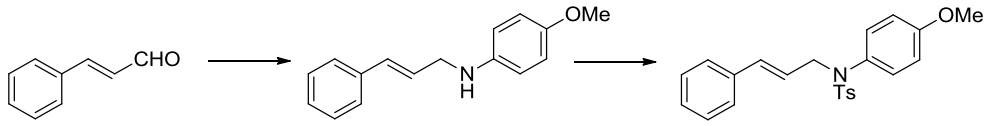


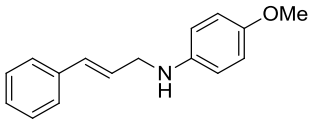
To a solution of *N*-cinnamyl-2-methylaniline (500 mg, 2.24 mmol) in DCM (10 mL) at room temperature was added DMAP (10 mg), Et_3N (937 µL, 6.72 mmol) and tosyl chloride (854 mg, 4.48 mmol) and the reaction was stirred for 24 hours. To the reaction was added saturated NH_4Cl solution (40 mL) and stirring was continued for 30 minutes. The aqueous layer was extracted with DCM (50 mL) and the organic fraction was further washed with NH_4Cl, $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (479 mg, 1.27 mmol, 57 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 2.46 (s, 3H), 4.06 (dd, *J* = 14.0 Hz, *J* = 7.6 Hz, 1H), 4.78 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 6.12 (dt, *J* = 15.7 Hz, *J* = 7.0 Hz, 1H), 6.29 (d, *J* = 15.9 Hz,

1H), 6.65 (d, *J* = 7.9 Hz, 1H), 7.05 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 7.17-7.34 (m, 9H), 7.63 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 18.6, 21.6, 54.3, 123.7, 126.2, 126.4, 127.8, 127.9, 128.4, 128.5, 128.5, 129.5, 131.4, 134.1, 136.3, 136.4, 138.1, 140.0, 143.4; **IR (ν, cm^{-1}):** 1598 (w, C=C), 1492 (w, C-C_{Ar}), 1449 (w, C-C_{Ar}), 1344 (s, S=O), 1157 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{23}H_{23}NNaO_2S]^+$ $(M+Na)^+$ calc. 400.1342, found 400.1332.

***N*-cinnamyl-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (48f)**

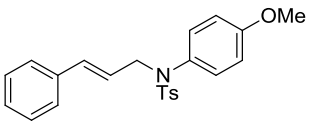




To a solution of cinnamylaldehyde (629 µL, 5.0 mmol) in TFE (10 mL) at 40 °C was added *p*-anisidine (616 mg, 5.0 mmol) and the reaction was stirred for 10 minutes before the addition of $NaBH_4$ (227 mg, 6.0 mmol) in one portion. The reaction was left to stir for 30 minutes before filtering off the solid and washing with a further 5 mL TFE. The solvent was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, EtOAc/PE 1:9) to afford the title compound as a white solid (931 mg, 3.89 mmol, 78 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.35 (brs, 1H, N*H*), 3.77 (s, 3H), 3.91 (dd, *J* = 5.8 Hz, *J* = 1.4 Hz, 2H), 6.36 (dt, *J* = 15.9 Hz, *J* = 5.7 Hz, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.65-6.70 (m, 2H), 6.80-6.86 (m, 2H), 7.23-7.28 (m, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.38-7.42 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 47.2, 55.8, 114.5, 114.9, 126.3, 127.3, 127.5, 128.6, 131.5, 136.9, 142.2, 152.3.

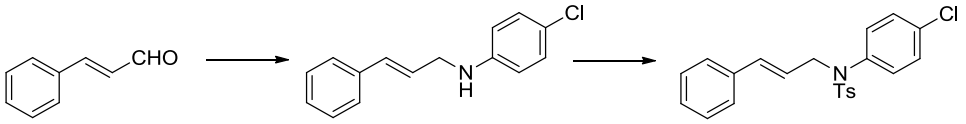
Data consistent with literature values.[42]

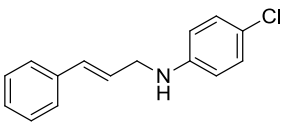


To a solution of *N*-cinnamyl-4-methoxyaniline (900 mg, 3.76 mmol) in DCM (20 mL) at room temperature was added DMAP (20 mg), Et_3N (1.57 mL, 11.3 mmol) and tosyl chloride (1.43 g, 7.52 mmol) and the reaction was stirred for 24 hours. To the reaction was added water (10 mL) and stirring was continued for 30 minutes. The aqueous layer was acidified with NH_4Cl and extracted with DCM (50 mL) and the organic fraction was further washed with NH_4Cl, $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless solid (1.39 g, 3.53 mmol, 94 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 3.78 (s, 3H), 4.30 (dd, *J* = 6.7 Hz, *J* = 1.0 Hz, 2H), 6.11 (dt, *J* = 15.9 Hz, *J* = 6.7 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.19-7.31 (m, 7H), 7.54 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 53.6, 55.3, 114.1, 124.2, 126.4, 127.8, 127.8, 128.5, 129.4, 130.2, 131.7, 133.7, 135.7, 136.4, 143.3, 159.0; **IR (ν, cm^{-1}):** 1600 (w, C=C), 1448 (w, C-C_{Ar}), 1344 (m, S=O), 1159 (s, S=O), 1032 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{23}H_{23}NNaO_3S]^+$ $(M+Na)^+$ calc. 416.1291, found 416.1282.

***N*-(4-chlorophenyl)-*N*-cinnamyl-4-methylbenzenesulfonamide (48g)**



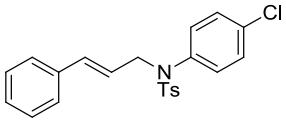


To a pestle and motor was added 4-chloroaniline (1.26 g, 10.0 mmol) and cinnamaldehyde (1.26 mL, 10.0 mmol) and the mixture was ground for 10 minutes until a consistent yellow powder was obtained. To the resultant imine was directly charged $NaBH_4$ (378 mg, 10.0 mmol) and PTSA monohydrate (1.90 g, 10.0 mmol) and grinding was rapidly continued. The reaction was further ground for 20 minutes

before dissolving in DCM and quenching with $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a white solid (1.73 g, 7.08 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (dd, *J* = 5.8 Hz, *J* = 1.2 Hz, 2H), 4.00 (brs, 1H, N*H*), 6.31 (dt, *J* = 15.9 Hz, *J* = 5.8 Hz, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 15.9 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.24-7.28 (m, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.35-7.40 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 46.3, 114.2, 126.3, 126.4, 127.7, 128.4, 128.6, 129.1, 131.8, 136.6, 146.4.

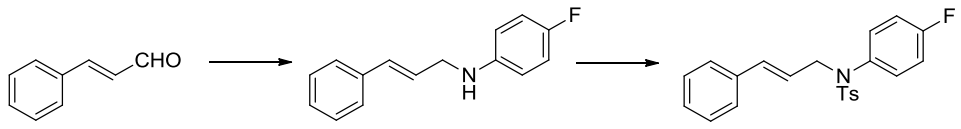
Data consistent with literature values.[43]

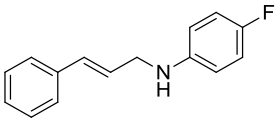


To a solution of 4-chloro-*N*-cinnamylaniline (100 mg, 0.41 mmol) in DCM (2 mL) at room temperature was added DMAP (5 mg), Et_3N (171 µL, 1.23 mmol) and tosyl chloride (156 mg, 0.82 mmol) and the reaction was stirred for 24 hours. To the reaction was added water (10 mL) and stirring was continued for 30 minutes. The aqueous layer was acidified with NH_4Cl and extracted with DCM (50 mL) and the organic fraction was further washed with NH_4Cl, $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (131 mg, 0.33 mmol, 80 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 4.31 (dd, *J* = 6.7 Hz, *J* = 1.1 Hz, 2H), 6.07 (dt, *J* = 15.8 Hz, *J* = 6.8 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.21-7.32 (m, 9H), 7.52 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 53.2, 123.6, 126.4, 127.7, 128.0, 128.5, 129.2, 129.6, 130.1, 133.7, 134.2, 135.2, 136.1, 137.7, 143.7; **IR (ν, cm^{-1}):** 1598 (w, C=C), 1489 (m, C-C_{Ar}), 1449 (w, C-C_{Ar}), 1348 (s, S=O), 1162 (s, S=O); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{20}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 420.0795, found 420.0793.

_N_-cinnamyl-_N_-(4-fluorophenyl)-4-methylbenzenesulfonamide (48h)

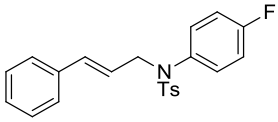




To a pestle and motor was added 4-fluoroaniline (947 µL, 10.0 mmol) and cinnamaldehyde (1.26 mL, 10.0 mmol) and the mixture was ground for 10 minutes until a consistent yellow powder was obtained. To the resultant imine was directly charged $NaBH_4$ (378 mg, 10.0 mmol) and PTSA monohydrate (1.90 g, 10.0 mmol) and grinding was rapidly continued. The reaction was further ground for 20 minutes before dissolving in DCM and quenching with $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a pale yellow solid (1.70 g, 7.50 mmol, 75 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (brs, 1H, N*H*), 3.92 (dd, *J* = 5.8 Hz, *J* = 1.4 Hz, 2H), 6.34 (dt, *J* = 15.8 Hz, *J* = 5.8 Hz, 1H), 6.60-6.65 (m, 2H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.93 (t, *J* = 8.7 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 46.9, 113.9 (d, *J* = 7.4 Hz), 115.7 (d, *J* = 22.4 Hz), 126.3, 126.8, 127.6, 128.6, 131.7, 136.8, 144.3 (d, *J* = 1.5 Hz), 155.9 (d, *J* = 234.9 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -127.7 (tt, *J* = 8.5 Hz, *J* = 4.5 Hz, 1F).

Data consistent with literature values.[43]

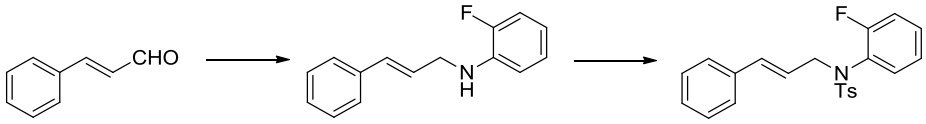


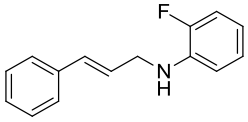
To a solution of *N*-cinnamyl-4-fluoroaniline (500 mg, 2.20 mmol) in DCM (15 mL) at room temperature was added DMAP (20 mg), Et_3N

(920 µL, 6.60 mmol) and tosyl chloride (839 mg, 4.40 mmol) and the reaction was stirred for 24 hours. To the reaction was added water (10 mL) and stirring was continued for 30 minutes. The aqueous layer was acidified with NH_4Cl and extracted with DCM (50 mL) and the organic fraction was further washed with NH_4Cl, $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (772 mg, 2.02 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 4.31 (dd, *J* = 6.7 Hz, *J* = 0.8 Hz, 2H), 6.09 (dt, *J* = 15.8 Hz, *J* = 6.7 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.97 (t, *J* = 8.6 Hz, 2H), 7.01-7.08 (m, 2H), 7.19-7.33 (m, 7H), 7.53 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 53.5, 115.9 (d, *J* = 22.5 Hz), 123.8, 126.4, 127.7, 127.9, 128.5, 129.5, 130.8 (d, *J* = 8.7 Hz), 134.1, 135.0 (d, *J* = 2.8 Hz), 135.3, 136.2, 143.7, 161.8 (d, *J* = 247.6 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -115.6 (m, 1F); **IR (ν, cm^{-1}):** 1599 (w, C=C), 1449 (w, C-C_{Ar}), 1347 (s, S=O), 1162 (s, S=O), 1091 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calc. 404.1091, found 404.1076.

***N*-cinnamyl-*N*-(2-fluorophenyl)-4-methylbenzenesulfonamide (48i)**



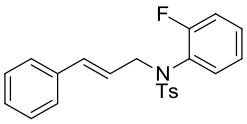


To a pestle and motor was added 2-fluoroaniline (965 µL, 10.0 mmol) and cinnamaldehyde (1.26 mL, 10.0 mmol) and the mixture was ground for 10 minutes until a consistent yellow powder was obtained. To the resultant imine was directly charged $NaBH_4$ (378 mg, 10.0 mmol) and PTSA monohydrate (1.90 g, 10.0 mmol) and grinding was rapidly continued. The reaction was further ground for 20 minutes before dissolving in DCM and quenching with $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic layers dried over $MgSO_4$ and

evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:48) afforded the title compound as a pale yellow oil (1.62 g, 7.12 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.00 (dd, *J* = 5.7 Hz, *J* = 1.1 Hz, 2H), 4.16 (brs, 1H, N*H*), 6.35 (dt, *J* = 15.8 Hz, *J* = 5.8 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.66-6.70 (m, 1H), 6.78 (td, *J* = 8.2 Hz, *J* = 1.2 Hz, 1H), 6.98-7.02 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.23-7.29 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 45.8, 112. 4 (d, *J* = 3.2 Hz), 114.4 (d, *J* = 18.5 Hz), 116.8 (d, *J* = 7.1 Hz), 124.6 (d, *J* = 3.6 Hz), 126.4, 126.5, 127.6, 128.6, 131.7, 136.5 (d, *J* = 11.3 Hz), 136.7, 151.6 (d, *J* = 238.6 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -116.8 (m, 1F).

Data consistent with literature values.[41]

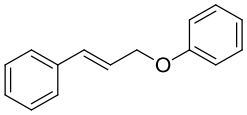


To a solution of *N*-cinnamyl-2-fluoroaniline (500 mg, 2.20 mmol) in DCM (15 mL) at room temperature was added DMAP (20 mg), Et_3N (920 µL, 6.60 mmol) and tosyl chloride (839 mg, 4.40 mmol) and the reaction was stirred for 24 hours. To the reaction was added water (10 mL) and stirring was continued for 30 minutes. The aqueous layer was acidified with NH_4Cl and extracted with DCM (50 mL) and the organic fraction was further washed with NH_4Cl, $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 3:17) afforded the title compound as a white solid (525 mg, 1.38 mmol, 63 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 4.34 (d, *J* = 6.8 Hz, 2H), 6.13 (dt, *J* = 15.6 Hz, *J* = 6.8 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.99-7.05 (m, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.18-7.33 (m, 8H), 7.63 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 52.9 (d, *J* = 3.1 Hz), 116.5

(d, *J* = 20.2 Hz), 123.9, 124.4 (d, *J* = 3.8 Hz), 126.2 (d, *J* = 11.6 Hz), 126.5, 127.6, 127.8, 128.5, 129.5, 130.1 (d, *J* = 8.1 Hz), 132.8, 134.0, 136.3, 136.4, 143.6, 159.7 (d, *J* = 252.4 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -118.6 (m, 1F); **IR (ν, cm^{-1}):** 1495 (m, C-C_{Ar}), 1450 (w, C-C_{Ar}), 1348 (s, S=O), 1162 (s, S=O), 1091 (s, C-F); **HRMS (ESI^+, m/z):** $[C_{22}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calc. 404.1091, found 404.1074.

(Cinnamyloxy)benzene (48j)

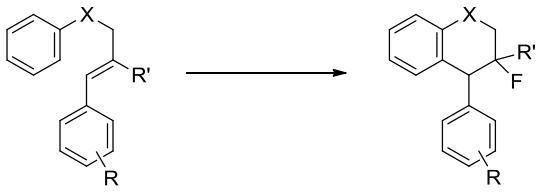


To a solution of phenylboronic acid (488 mg, 4.0 mmol) in DCM (15 mL) at room temperature was added copper(II) acetate monohydrate (400 mg, 2.0 mmol), DMAP (489 mg, 4.0 mmol) and 10 activated 3 Å molecular sieves. The solution was stirred for 10 minutes before the addition of Cinnamyl alcohol (268 mg, 2.0 mmol). The reaction was stirred for 24 hours before being filtered through a 1 inch plug of silica, eluted with DCM and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 3:97) afforded the title compound as a white solid (70 mg, 0.33 mmol, 17 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (dd, *J* = 5.8 Hz, *J* = 1.4 Hz, 2H), 6.45 (dt, *J* = 15.9 Hz, *J* = 5.8 Hz, 1H), 6.76 (d, *J* = 16.0 Hz, 1H), 6.96-7.03 (m, 3H), 7.25-7.39 (m, 5H), 7.41-7.46 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 68.6, 114.8, 120.9, 124.5, 126.6, 127.9, 128.6, 129.5, 133.0, 136.5, 158.6.

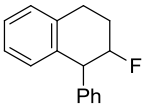
Data consistent with literature values.[44]

6.2.9 General procedure for fluoro-carbocyclization (acyclic substrates)



To the appropriate olefin (50 mg) in a 7 mL screw-top vial was added nitromethane (5 mL) and a few activated 3Å molecular sieves. The solution was left for 3 hours before $NaHCO_3$ (3.0 eq.) was added and the reaction was warmed to 40 °C. Once at 40 °C, *N*-fluoro-2,6-dichloropyridinium triflate (1.1 eq.) was added in one portion and the reaction was stirred for 1 hour before being filtered through a pipette of celite and eluted with ethyl acetate. The filtrate was concentrated *in vacuo* and purified directly by column chromatography (SiO_2).

2-Fluoro-1-phenyl-1,2,3,4-tetrahydronaphthalene (47a)



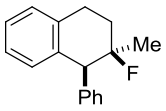
Prepared from but-1-ene-1,4-diyldibenzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:4) afforded the title compound as a colourless oil (94 % yield).

1:1 mixture of inseparable diastereosiomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98-2.34 (m, 4H), 2.89-3.03 (m, 2H), 3.05-3.16 (m, 1H), 3.17-3.28 (m, 1H), 4.33-4.38 (m, 1H), 4.38-4.44 (m, 1H), 5.01 (dddd, *J* = 44.2 Hz, *J* = 6.7 Hz, *J* = 6.0 Hz, *J* = 3.4 Hz, 1H), 5.12 (dddd, *J* = 43.0 Hz, *J* = 8.0 Hz, *J* = 4.2 Hz, *J* = 2.4 Hz, 1H), 6.90-6.96 (m ,2H), 7.09-7.25 (m, 10H), 7.26-7.38 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.6 (d, *J* = 8.2 Hz), 25.7 (d, *J* = 8.2 Hz), 25.8 (d, *J* = 20.6 Hz), 26.3 (d, *J* = 20.6 Hz), 49.9 (d, *J* = 18.9 Hz), 51.5 (d, *J* = 21.8 Hz), 90.6 (d, *J* = 178.2 Hz), 94.2 (d, *J* = 175.4 Hz), 126.2, 126.3, 126.5, 126.6, 126.8, 126.9, 128.0, 128.4, 128.5, 128.5, 129.4, 130.4, 130.6, 135.9, 136.0 (d, *J* = 1.2 Hz), 136.1 (d, *J* = 4.1 Hz), 136.4 (d, *J* = 4.3 Hz), 141.1, 142.9 (d, *J* = 6.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -175.7 (ddddd, *J* = 45.7 Hz, *J* = 28.4 Hz, *J* = 17.4 Hz, *J* = 7.7 Hz, *J* = 2.3 Hz, 1F); -188.0 (dtd, *J* =

49.4 Hz, *J* = 26.5 Hz, *J* = 4.8 Hz, 1F); **IR (ν, cm^{-1}):** 1493 (m, C-C_{Ar}), 1450 (m, C-C_{Ar}), 1029 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{16}H_{15}FNa]^+$ $(M+Na)^+$ calc. 249.1050, found 249.1046.

2-Fluoro-2-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene (47b)

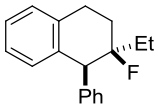


Prepared from (2-methylbut-1-ene-1,4-diyl)dibenzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:4) afforded the title compound as a colourless oil (59 % yield).

3:1 syn:anti mixture of inseparable diastereosiomers.

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.39 (d, *J* = 21.3, 3H), 1.95-2.08 (m, 1H), 2.22-2.33 (m, 1H), 2.87 (dt, *J* = 16.9 Hz, *J* = 5.5 Hz, 1H), 3.27 (ddd, *J* = 16.9 Hz, *J* = 10.1 Hz, *J* = 6.1 Hz, 1H), 4.06 (d, *J* = 25.6 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 7.02-7.39 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.9 (d, *J* = 25.5 Hz), 26.2 (d, *J* = 7.2 Hz), 33.3 (d, *J* = 22.5 Hz), 55.0 (d, *J* = 20.0 Hz), 93.7 (d, *J* = 176.5 Hz), 126.0, 126.2, 126.8, 127.8, 128.3, 130.4, 131.2 (d, *J* = 2.2 Hz), 135.6, 137.9 (d, *J* = 2.2 Hz), 141.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -157.6 (m, 1F); **IR (ν, cm^{-1}):** 1493 (m, C-C_{Ar}), 1451 (m, C-C_{Ar}), 1029 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{17}FNa]^+$ $(M+Na)^+$ calc. 263.1206, found 263.1199.

2-Ethyl-2-fluoro-1-phenyl-1,2,3,4-tetrahydronaphthalene (47c)



Prepared from (2-Ethylbut-1-ene-1,4-diyl)dibenzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:4) afforded the title compound as a colourless oil (50 % yield).

2.7:1 syn:anti mixture of inseparable diastereosiomers

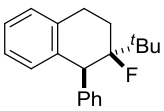
Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.99 (t, *J* = 7.5 Hz, 3H), 1.57-1.78 (m, 2H), 1.83-1.97 (m, 1H), 2.19-2.27 (m, 1H), 2.86 (dt, *J* = 17.0 Hz, *J* = 5.9 Hz, 1H), 3.21 (ddd, *J* = 17.0

Hz, *J* = 8.9 Hz, *J* = 6.3 Hz, 1H), 4.15 (d, *J* = 23.5 Hz, 1H), 7.01-7.32 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 7.7 (d, *J* = 6.8 Hz), 26.1 (d, *J* = 8.3 Hz), 29.0 (d, *J* = 22.7 Hz), 30.5 (d, *J* = 24.6 Hz), 53.1 (d, *J* = 20.0 Hz), 95.8 (d, *J* = 178.4 Hz), 126.0, 126.1, 126.6, 127.8, 128.2, 130.5, 131.1 (d, *J* = 2.3 Hz), 135.7, 138.1 (d, *J* = 2.7 Hz), 141.1; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.0 (m, 1F).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.97 (t, *J* = 7.4 Hz, 3H), 1.23-1.42 (m, 2H), 1.97-2.15 (m, 2H), 2.97 (ddd, *J* = 17.2 Hz, *J* = 6.5 Hz, *J* = 3.4 Hz, 1H), 3.13 (ddd, *J* = 17.2 Hz, *J* = 10.7 Hz, *J* = 6.8 Hz, 1H), 4.30 (d, *J* = 14.6 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 7.01-7.32 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 6.8 (d, *J* = 5.1 Hz), 25.5 (d, *J* = 6.5 Hz), 26.6 (d, *J* = 22.2 Hz), 30.2 (d, *J* = 23.0 Hz), 54.6 (d, *J* = 25.7 Hz), 97.3 (d, *J* = 174.0 Hz), 126.1, 126.1, 127.8, 128.1, 128.3, 130.1, 130.8, 135.3, 137.4, 142.3 (d, *J* = 10.4 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.0 (m, 1F).

IR (ν, cm^{-1}): 1494 (m, C-C_{Ar}), 1451 (m, C-C_{Ar}), 1031 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{18}H_{19}FNNa]^+$ $(M+Na)^+$ calc. 277.1363, found 277.1365.

2-(*tert*-Butyl)-2-fluoro-1-phenyl-1,2,3,4-tetrahydronaphthalene (47d)



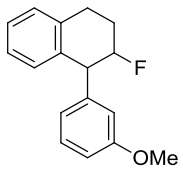
Prepared from (2-(tert-butyl)but-1-ene-1,4-diyl)dibenzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:4) afforded the title compound as a colourless oil (50 % yield).

12.5:1 syn:anti mixture of inseparable diastereosiomers

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.04 (s, 9H), 1.97-2.13 (m, 1H), 2.23-2.35 (m, 1H), 2.83-2.93 (m, 1H), 3.14-3.25 (m, 1H), 4.57 (d, *J* = 12.7 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.02-7.42 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.3 (d, *J* = 5.1 Hz), 26.9 (d, *J* = 8.8 Hz), 28.5 (d, *J* = 25.4 Hz), 39.0 (d, *J* = 23.3 Hz), 50.2 (d, *J* = 21.0 Hz), 98.9 (d, *J* = 183.7 Hz),

126.0, 126.1, 126.4, 127.7, 127.9, 130.4 (d, *J* = 1.4 Hz), 130.8 (d, *J* = 2.5 Hz), 136.3, 139.7 (d, *J* = 3.3 Hz), 143.1 (d, *J* = 5.4 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -155.7 (dt, *J* = 23.3 Hz, *J* = 12.7 Hz, 1F); **IR (ν, cm^{-1}):** 1491 (m, C-C_{Ar}), 1449 (m, C-C_{Ar}), 1046 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{20}H_{23}FNa]^+$ $(M+Na)^+$ calc. 305.1676, found 305.1671.

2-Fluoro-1-(3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (47e)



Prepared from 1-methoxy-3-(4-phenylbut-1-en-1-yl)benzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 2:3) afforded the title compound as a colourless oil (39 % yield).

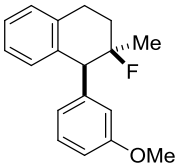
1:1 syn:anti mixture of separable diastereosiomers

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.03-2.22 (m, 2H), 2.90-3.00 (m, 1H), 3.01-3.11 (m, 1H), 3.78 (s, 3H), 4.31 (dd, *J* = 17.0 Hz, *J* = 5.6 Hz, 1H), 4.99 (dddd, *J* = 48.8 Hz, *J* = 7.8 Hz, *J* = 5.6 Hz, *J* = 2.6 Hz, 1H), 6.66-6.68 (m, 1H), 6.69-6.73 (m, 1H), 6.80 (ddd, *J* = 8.3 Hz *J* = 2.5 Hz, *J* = 0.7 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 7.07-7.12 (m, 1H), 7.16-7.19 (m, 2H), 7.23 (t, *J* = 7.8 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.6 (d, *J* = 8.1 Hz), 25.8 (d, *J* = 20.1 Hz), 51.4 (d, *J* = 21.9 Hz), 55.2, 94.1 (d, *J* = 175.2 Hz), 111.8, 115.5, 121.7, 126.3, 126.5, 128.4, 129.4, 130.5, 135.7, 135.9 (d, *J* = 4.2 Hz), 144.5 (d, *J* = 6.8 Hz), 159.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -175.6 (ddddd, *J* = 45.0 Hz, *J* = 27.7 Hz, *J* = 17.2 Hz, *J* = 7.8 Hz, *J* = 1.9 Hz, 1F); **IR (ν, cm^{-1}):** 1453 (m, C-C_{Ar}), 1436 (m, C-C_{Ar}), 1048 (s, C-F), 1022 (m, C-O); **HRMS (ESI^+, m/z):** $[C_{17}H_{17}FNaO]^+$ $(M+Na)^+$ calc. 279.1156, found 279.1151.

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.95-2.14 (m, 1H), 2.20-2.32 (m, 1H), 2.90 (dt, *J* = 17.0 Hz, *J* = 6.4 Hz, 1H), 3.13-3.24 (m, 1H), 3.78 (s, 3H), 4.33 (dd, *J* = 24.1 Hz, *J* = 4.2 Hz, 1H), 5.09 (dddd, *J* = 49.4 Hz, *J* = 7.9 Hz, *J* = 4.3 Hz, *J* = 2.4 Hz, 1H), 6.71-6.73 (m, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 7.06-7.12 (m, 1H), 7.16-7.20 (m, 2H), 7.23 (t, *J* = 7.9 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.7 (d, *J* = 8.3 Hz), 26.3 (d, *J* = 20.4 Hz), 49.9 (d, *J* = 19.0 Hz), 55.1,

90.5 (d, *J* = 178.1 Hz), 112.0, 116.5 (d, *J* = 1.4 Hz), 123.0, 126.2, 126.6, 128.4, 128.8, 130.3, 135.9, 136.1 (d, *J* = 4.3 Hz), 142.6 (d, *J* = 1.2 Hz), 159.3; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -187.9 (dtd, *J* = 49.3 Hz, *J* = 26.6 Hz, *J* = 5.1 Hz, 1F); **IR (ν, cm^{-1}):** 1452 (m, C-C_{Ar}), 1436 (m, C-C_{Ar}), 1048 (s, C-F), 1018 (m, C-O); **HRMS (ESI^+, m/z):** $[C_{17}H_{17}FNaO]^+$ $(M+Na)^+$ calc. 279.1156, found 279.1148.

2-Fluoro-1-(3-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene (47f)



Prepared from 1-methoxy-3-(2-methyl-4-phenylbut-1-en-1-yl)benzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 2:3) afforded the title compound as a colourless oil (86 % yield).

2.3:1 syn:anti mixture of inseparable diastereosiomers.

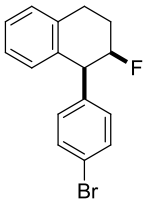
Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.40 (d, *J* = 21.2 Hz, 3H), 1.95 (dddd, *J* = 29.7 Hz, *J* = 13.6 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz, 1H), 2.27 (ddt, *J* = 13.6 Hz, *J* = 5.6 Hz, *J* = 4.9 Hz, 1H), 2.82-2.91 (m, 1H), 3.26 (ddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 6.2 Hz, 1H), 3.78 (s, 3H), 4.03 (d, *J* = 25.6 Hz, 1H), 6.72-6.75 (m, 1H), 6.76-6.81 (m, 2H), 6.84 (dd, *J* = 8.2 Hz, *J* = 2.1 Hz, 1H), 7.02-7.07 (m, 1H), 7.13-7.20 (m, 3H), 7.24 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.9 (d, *J* = 25.3 Hz), 26.1 (d, *J* = 7.4 Hz), 33.3 (d, *J* = 22.5 Hz), 55.0 (d, *J* = 20.0 Hz), 55.1, 93.7 (d, *J* = 176.9 Hz), 112.0, 117.1 (d, *J* = 2.0 Hz), 123.8 (d, *J* = 1.7 Hz), 126.0, 126.2, 128.3, 128.6, 130.3, 135.5, 137.7 (d, *J* = 1.8 Hz), 142.5, 159.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -157.6 (m, 1F).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.27 (d, *J* = 22.3 Hz, 3H), 2.01-2.20 (m, 2H), 2.96 (ddd, *J* = 17.2 Hz, *J* = 6.2 Hz, *J* = 3.6 Hz, 1H), 3.15 (ddd, *J* = 17.2 Hz, *J* = 10.5 Hz, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 4.26 (d, *J* = 15.5 Hz, 1H), 6.23-6.65 (m, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.76-6.81 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 7.08 (td, *J* = 7.5 Hz, *J* =0.4 Hz, 1H), 7.13-7.20 (m, 3H); **^{13}C**

NMR (100.6 MHz, $CDCl_3$): δ = 25.6 (d, *J* = 18.9 Hz), 25.7 (d, *J* = 6.1 Hz), 30.3 (d, *J* = 22.0 Hz), 55.1, 55.1 (d, *J* = 25.1 Hz), 95.9 (d, *J* = 169.8 Hz), 111.4, 116.6, 122.6, 126.1, 126.2, 128.4, 128.9, 129.3, 135.0, 135.3, 137.0, 159.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -141.7 (m, 1F).

IR (ν, cm^{-1}): 1489 (m, C-C_{Ar}), 1452 (m, C-C_{Ar}), 1048 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{18}H_{19}FNaO]^+$ $(M+Na)^+$ calc. 293.1312, found 293.1310.

1-(4-Bromophenyl)-2-fluoro-1,2,3,4-tetrahydronaphthalene (47g)



Prepared from 1-bromo-4-(4-phenylbut-1-en-1-yl)benzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:4) afforded the title compound as a colourless oil (72 % yield).

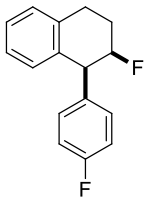
1.3:1 syn:anti mixture of inseparable diastereosiomers.

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.04-2.15 (m, 1H), 2.15-2.27 (m, 1H), 2.91 (dt, *J* = 17.0 Hz, *J* = 6.4 Hz, 1H), 4.34 (dd, *J* = 18.6 Hz, *J* = 4.2 Hz, 1H), 5.06 (dddd, *J* = 48.8 Hz, *J* = 8.0 Hz, *J* = 4.4 Hz, *J* = 2.4 Hz, 1H), 6.82-6.90 (m, 1H), 6.98-7.06 (m, 2H), 7.07-7.15 (m, 1H), 7.17-7.23 (m, 2H), 7.41-7.48 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.6 (d, *J* = 8.4 Hz), 26.1 (d, *J* = 20.4 Hz), 49.3 (d, *J* = 19.1 Hz), 90.3 (d, *J* = 178.1 Hz), 120.9, 126.3, 126.8, 128.6, 130.2, 131.1, 131.7, 135.8 (d, *J* = 1.2 Hz), 135.9, 140.0 (d, *J* = 1.1 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -188.1 (dtd, *J* = 49.2 Hz, *J* = 26.5 Hz, *J* = 5.0 Hz, 1F).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.94-2.15 (m, 2H), 2.96 (dt, *J* = 17.0 Hz, *J* = 6.7 Hz, 1H), 3.02-3.12 (m, 1H), 4.29 (dd, *J* = 14.0 Hz, *J* = 6.1 Hz, 1H), 4.91 (dddd, *J* = 48.7 Hz, *J* = 7.3 Hz, *J* = 6.2 Hz, *J* = 3.4 Hz, 1H), 6.82-6.90 (m, 1H), 6.98-7.06 (m, 2H), 7.07-7.15 (m, 1H), 7.17-7.23 (m, 2H), 7.41-7.48 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.8 (d, *J* = 8.7 Hz), 26.1 (d, *J* = 19.9 Hz), 51.1 (d, *J* = 22.0 Hz), 94.0 (d, *J* = 175.8 Hz), 120.8, 126.4, 126.7, 128.5, 130.4, 131.1, 132.3 (d, *J* = 1.2 Hz), 135.7, 135.8, 141.9 (d, *J* = 6.5 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -175.7 (ddddd, *J* = 48.3 Hz, *J* = 25.1 Hz, *J* = 16.7 Hz, *J* = 7.2 Hz, *J* = 2.7 Hz, 1F).

IR (ν, cm^{-1}): 1482 (s, C-C_{Ar}), 1451 (w, C-C_{Ar}), 1048 (m, C-F), 875 (s, C-Br); **HRMS (FI^+):** [$C_{16}H_{14}BrF$] calc. 304.0263, found 304.0263.

2-Fluoro-1-(4-fluorophenyl)-1,2,3,4-tetrahydronaphthalene (47h)



Prepared from 1-fluoro-4-(4-phenylbut-1-en-1-yl)benzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:3) afforded the title compound as a colourless oil (94 % yield).

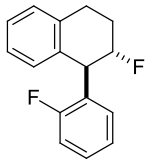
1.3:1 syn:anti mixture of inseparable diastereosiomers

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.05-2.29 (m, 2H), 2.91 (dt, *J* = 17.0 Hz, *J* = 6.4 Hz, 1H), 3.14-3.25 (m, 1H), 4.36 (dd, *J* = 23.6 Hz, *J* = 4.2 Hz, 1H), 5.07 (dddd, *J* = 49.3 Hz, *J* = 7.9 Hz, *J* = 4.3 Hz, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.98-7.06 (m, 2H), 7.07-7.16 (m, 3H), 7.18-7.24 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.7 (d, *J* = 8.7 Hz), 26.1 (d, *J* = 20.7 Hz), 49.1 (d, *J* = 18.9 Hz), 90.5 (d, *J* = 177.3 Hz), 114.8 (d, *J* = 21.3 Hz), 126.3, 126.7, 128.5, 130.3, 130.8 (d, *J* = 8.1 Hz), 135.9, 136.2 (d, *J* = 4.1 Hz), 136.7, 161.8 (d, *J* = 245.3 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -116.3 (tt, *J* = 8.5 Hz, *J* = 5.6 Hz, 1F), -188.1 (dtd, *J* = 49.2 Hz, *J* = 26.1 Hz, *J* = 5.1 Hz, 1F).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.95-2.29 (m, 2H), 2.97 (dt, *J* = 17.0 Hz, *J* = 6.6 Hz, 1H), 3.03-3.13 (m, 1H), 4.32 (dd, *J* = 16.6 Hz, *J* = 6.0 Hz, 1H), 4.94 (dddd, *J* = 48.8 Hz, *J* = 7.4 Hz, *J* = 6.0 Hz, *J* = 3.3 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.98-7.06 (m, 2H), 7.07-7.16 (m, 3H), 7.18-7.24 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.8 (d, *J* = 9.0 Hz), 25.9 (d, *J* = 20.2 Hz), 50.8 (d, *J* = 21.8 Hz), 94.2 (d, *J* = 175.5 Hz), 115.4 (d, *J* = 21.3 Hz), 126.4, 126.6, 128.5, 130.4, 132.0 (dd, *J* = 8.1 Hz, *J* = 1.3 Hz), 135.8, 136.0 (d, *J* = 5.0 Hz), 136.7 (d, *J* = 1.3 Hz), 161.8 (d, *J* = 245.3 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -116.1 (tt, *J* = 8.5 Hz, *J* = 5.5 Hz, 1F), -175.7 (ddddd, *J* = 48.0 Hz, *J* = 26.0 Hz, *J* = 16.3 Hz, *J* = 7.2 Hz, *J* = 1.8 Hz, 1F).

IR (ν, cm^{-1}): 1507 (s, C-C_{Ar}), 1452 (w, C-C_{Ar}), 1096 (m, C-F), 1017 (m, C-F); **HRMS (FI$^+$):** [$C_{16}H_{14}F_2$] calc. 244.1064, found 244.1063.

2-Fluoro-1-(2-fluorophenyl)-1,2,3,4-tetrahydronaphthalene (47i)



Prepared from 1-fluoro-2-(4-phenylbut-1-en-1-yl)benzene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:4) afforded the title compound as a colourless oil (89 % yield).

1:1.4 syn:anti mixture of inseparable diastereosiomers

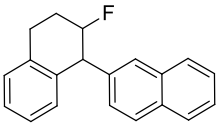
Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.08-2.21 (m, 2H), 2.96 (dt, *J* = 16.9 Hz, *J* = 6.5 Hz, 1H), 3.04-3.13 (m, 1H), 4.64 (dd, *J* = 16.4 Hz, *J* = 5.7 Hz, 1H), 5.07 (dddd, *J* = 48.6 Hz, *J* = 7.3 Hz, *J* = 5.7 Hz, *J* = 2.9 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 7.04-7.08 (m, 1H), 7.08-7.14 (m, 2H), 7.18-7.21 (m, 2H), 7.23-7.29 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.6 (d, *J* = 8.6 Hz), 26.1 (d, *J* = 20.0 Hz), 45.0 (dd, *J* = 22.8 Hz, *J* = 1.3 Hz), 89.6 (d, *J* = 177.0 Hz), 115.5 (d, *J* = 22.1 Hz), 124.2 (d, *J* = 3.4 Hz), 126.4, 126.6, 128.5, 128.6 (d, *J* = 8.6 Hz), 129.5 (dd, *J* = 14.0 Hz, *J* = 6.6 Hz), 129.9 (d, *J* = 7.9 Hz), 132.4 (d, *J* = 2.5 Hz), 135.2 (d, *J* = 4.5 Hz), 135.9, 161.0 (d, *J* = 246.6 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -117.7 (m, 1F), -176.5 (m, 1F).

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.00-2.14 (m, 1H), 2.28-2.37 (m, 1H), 2.89 (dt, *J* = 16.9 Hz, *J* = 5.8 Hz, 1H), 3.21 (ddd, *J* = 16.9 Hz, *J* = 9.4 Hz, *J* = 6.0 Hz, 1H), 4.81 (dd, *J* = 26.9 Hz, *J* = 4.0 Hz, 1H), 5.13 (dddd, *J* = 49.4 Hz, *J* = 7.1 Hz, *J* = 4.1 Hz, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.98-7.03 (m, 1H), 7.04-7.08 (m, 1H), 7.08-7.14 (m, 1H), 7.18-7.21 (m, 2H), 7.23-7.29 (m, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.1 (d, *J* = 7.5 Hz), 26.7 (d, *J* = 20.8 Hz), 41.6 (dd, *J* = 19.3 Hz, *J* = 2.7 Hz), 92.3 (dd, *J* = 175.3 Hz, *J* = 1.4 Hz), 114.9 (d, *J* = 22.9 Hz), 123.7 (d, *J* = 3.6 Hz), 126.3, 126.6, 128.0 (dd, *J* = 13.4 Hz, *J* = 1.7 Hz), 128.4 (d, *J* = 8.6 Hz), 128.5, 131.2 (d, *J* = 4.2 Hz), 132.4 (d, *J* = 2.5 Hz), 135.3 (d, *J* = 2.9 Hz), 136.4, 161.4 (d, *J* =

245.1 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -118.8 (m, 1F), -190.2 (dddt, *J* = 49.0 Hz, *J* = 33.0 Hz, *J* = 26.6 Hz, *J* = 6.8 Hz, 1F).

IR (ν, cm^{-1}): 1489 (m, C-C_{Ar}), 1453 (m, C-C_{Ar}), 1091 (m, C-F), 1020 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{16}H_{14}F_2Na]^+$ $(M+Na)^+$ calc. 267.0956, found 267.0956.

2-Fluoro-1,2,3,4-tetrahydro-1,2'-binaphthalene (47j)

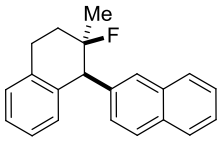


Prepared from 2-(4-phenylbut-1-en-1-yl)naphthalene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:5) afforded the title compound as a colourless oil (93 % yield).

1:1 syn:anti mixture of inseparable diastereosiomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00-2.40 (m, 4H), 2.95 (dt, *J* = 17.1 Hz, *J* = 6.1 Hz, 1H), 3.03 (d, *J* = dt, *J* = 17.1 Hz, *J* = 6.6 Hz, 1H), 3.08-3.18 (m, 1H), 3.21-3.32 (m, 1H), 4.51 (dd, *J* = 17.0 Hz, *J* = 5.9 Hz, 1H), 4.53 (dd, *J* = 24.8 Hz, *J* = 4.1 Hz, 1H), 5.08 (dddd, *J* = 48.7 Hz, *J* = 7.7 Hz, *J* = 6.1 Hz, *J* = 2.9 Hz, 1H), 5.19 (dddd, *J* = 49.2 Hz, *J* = 7.7 Hz, *J* = 4.1 Hz, *J* = 2.2 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 7.07-7.14 (m, 2H), 7.19-7.29 (m, 5H), 7.33 (dt, *J* = 8.5 Hz, *J* = 1.5 Hz, 1H), 7.45-7.52 (m, 4H), 7.60 (s, 1H), 7.63 (s, 1H), 7.76-7.88 (m, 6H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.6 (d, *J* = 8.0 Hz), 25.9 (d, *J* = 8.7 Hz), 26.2 (d, *J* = 19.7 Hz), 26.5 (d, *J* = 20.8 Hz), 50.1 (d, *J* = 18.8 Hz), 51.8 (d, *J* = 21.7 Hz), 90.8 (d, *J* = 177.8 Hz), 94.0 (d, *J* = 175.3 Hz), 125.7, 125.8, 125.9, 126.2, 126.3, 126.4, 126.6, 126.7, 127.0, 127.5, 127.6, 127.6, 127.8, 127.8, 128.3, 128.5, 128.5, 128.6, 128.8 (d, *J* = 2.2 Hz), 129.3, 130.4, 130.7, 132.4, 132.5, 133.3, 133.4, 135.9, 136.1 (d, *J* = 1.1 Hz), 136.1 (d, *J* = 5.1 Hz), 136.3 (d, *J* = 3.4 Hz), 138.7, 140.2 (d, *J* = 6.2 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -175.4 (ddddd, *J* = 51.1 Hz, *J* = 26.5 Hz, *J* = 17.2 Hz, *J* = 6.8 Hz, *J* = 1.7 Hz, 1F), -188.5 (dtd, *J* = 49.4 Hz, *J* = 28.3 Hz, *J* = 5.1 Hz, 1F); **IR (ν, cm^{-1}):** 1492 (w, C-C_{Ar}), 1451 (w, C-C_{Ar}), 1019 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{20}H_{17}FNa]^+$ $(M+Na)^+$ calc. 299.1206, found 299.1196.

2-Fluoro-2-methyl-1,2,3,4-tetrahydro-1,2'-binaphthalene (47k)



Prepared from 2-(2-methyl-4-phenylbut-1-en-1-yl)naphthalene according to the general procedure. Purification by column chromatography (SiO_2, toluene/PE 1:5) afforded the title compound as a colourless oil (94 % yield).

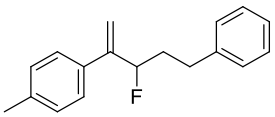
2.0:1 syn:anti mixture of inseparable diastereosiomers

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.43 (d, *J* = 21.2 Hz, 3H), 2.01-2.15 (m, 1H), 2.28-2.38 (m, 1H), 2.91 (dt, *J* = 16.9 Hz, *J* = 5.1 Hz, 1H), 3.33 (ddd, *J* = 17.0 Hz, *J* = 10.6 Hz, *J* = 5.9 Hz, 1H), 4.23 (d, *J* = 26.9 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 7.03 (t, *J* = 7.1 Hz, 1H), 7.15-7.29 (m, 2H), 7.31 (dt, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 7.45-7.52 (m, 2H), 7.68 (s, 1H), 7.77-7.88 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.0 (d, *J* = 25.3 Hz), 26.1 (d, *J* = 6.9 Hz), 33.6 (d, *J* = 22.6 Hz), 55.1 (d, *J* = 20.1 Hz), 94.0 (d, *J* = 175.9 Hz), 125.7, 125.8, 126.0, 126.3, 127.4, 127.6, 127.8, 128.4, 129.2 (d, *J* = 3.6 Hz), 130.2, 130.4, 132.5, 133.1, 135.8, 137.7 (d, *J* = 1.7 Hz), 139.9; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -158.4 (m, 1F).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.29 (d, *J* = 22.5 Hz, 3H), 1.93-2.27 (m, 2H), 3.04 (ddd, *J* = 17.3 Hz, *J* = 6.1 Hz, *J* = 4.1 Hz, 1H), 3.22 (ddd, *J* = 17.3 Hz, *J* = 10.1 Hz, *J* = 6.9 Hz, 1H), 4.48 (d, *J* = 15.5 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.15-7.29 (m, 3H), 7.45-7.52 (m, 2H), 7.58 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.77-7.88 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.5 (d, *J* = 24.6 Hz), 25.9 (d, *J* = 7.2 Hz), 30.6 (d, *J* = 22.1 Hz), 55.3 (d, *J* = 25.4 Hz), 96.0 (d, *J* = 185.3 Hz), 125.8, 126.1, 126.2, 126.3, 127.5, 127.6, 127.9, 128.5, 129.1, 130.9, 132.3, 133.1, 135.3, 137.1, 138.6; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -141.0 (m, 1F).

IR (ν, cm^{-1}): 1493 (m, C-C_{Ar}), 1451 (m, C-C_{Ar}), 1019 (w, C-F); **HRMS (ESI$^+$, m/z):** $[C_{21}H_{19}FNa]^+$ $(M+Na)^+$ calc. 313.1363, found 313.1364.

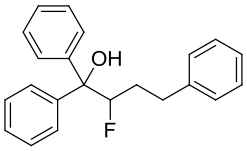
1-(3-Fluoro-5-phenylpent-1-en-2-yl)-4-methylbenzene (47l)



Prepared from pent-3-ene-1,4-diyldibenzene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a colourless oil (57 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90-2.10 (m, 2H), 2.37 (s, 3H), 2.67-2.86 (m, 2H), 5.36 (ddd, *J* = 47.8 Hz, *J* = 7.9 Hz, *J* = 4.1 Hz, 1H), 5.38-5.42 (m, 2H), 7.12-7.32 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.1, 31.2 (d, *J* = 3.8 Hz), 36.1 (d, *J* = 22.6 Hz), 93.5 (d, *J* = 174.2 Hz), 113.7 (d, *J* = 10.9 Hz), 126.0, 126.7, 128.4, 128.5, 129.2, 135.6 (d, *J* = 3.1 Hz), 137.7, 141.2, 147.1 (d, *J* = 16.4 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -180.2 (ddd, *J* = 47.8 Hz, *J* = 27.7 Hz, *J* = 21.2 Hz, 1F); **IR (ν, cm^{-1}):** 1598 (w, C=C), 1496 (m, C-C_{Ar}), 1454 (m, C-C_{Ar}), 1032 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{19}FNa]^+$ $(M+Na)^+$ calc. 277.1363, found 277.1356.

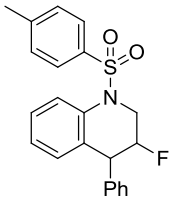
2-Fluoro-1,1,4-triphenylbutan-1-ol (47m)



Prepared from pent-3-ene-1,4-diyldibenzene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:97) afforded the title compound as a colourless oil (37 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (ddddd, *J* = 40.0 Hz, *J* = 14.7 Hz, *J* = 9.5 Hz, *J* = 8.1 Hz, *J* = 2.1 Hz, 1H), 2.07-2.22 (m, 1H), 2.65 (dt, *J* = 13.5 Hz, *J* = 8.7 Hz, 1H), 2.65 (s, 1H, O*H*), 2.88 (ddd, *J* = 13.8 Hz, *J* = 9.6 Hz, *J* = 4.8 Hz, 1H), 5.39 (ddd, *J* = 47.2 Hz, *J* = 10.1 Hz, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 6.9 Hz, 2H), 7.18-7.39 (m, 11H), 7.53 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 30.5 (d, *J* = 21.2 Hz), 31.6 (d, *J* = 3.4 Hz), 79.0 (d, *J* = 20.7 Hz), 95.1 (d, *J* = 178.3 Hz), 125.8, 126.0, 126.7 (d, *J* = 1.4 Hz), 127.2, 127.4, 128.2, 128.3, 128.4, 128.5, 141.2, 142.9 (d, *J* = 4.3 Hz), 144.6; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -190.2 (ddd, *J* = 47.4 Hz, *J* = 40.0 Hz, *J* = 13.5 Hz, 1F); **IR (ν, cm^{-1}):** 3510 (br, O-H), 1454 (w, C-C_{Ar}); **HRMS (FI$^+$):** $[C_{22}H_{21}FO]$ calc. 320.1577, found 320.1579.

3-Fluoro-4-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (49b)



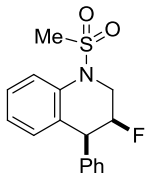
Prepared from *N*-Cinnamyl-4-methyl-*N*-phenylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (78 % yield).

2.4:1 syn:anti mixture of separable diastereosiomers.

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.42 (s, 3H), 3.93-4.04 (m, 2H), 4.23 (ddd, *J* = 18.4 Hz, *J* = 14.1 Hz, *J* = 3.7 Hz, 1H), 4.65 (dddd, *J* = 48.3 Hz, *J* = 7.9 Hz, *J* = 6.5 Hz, *J* = 3.6 Hz, 1H), 6.68-6.71 (m, 2H), 6.81 (d, *J* = 7.7 Hz, 1H), 7.05 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 7.17-7.26 (m, 6H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.95 (dd, *J* = 8.4 Hz, *J* = 1.0 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 47.7 (d, *J* = 26.1 Hz), 50.1 (d, *J* = 22.4 Hz), 88.9 (d, *J* = 181.0 Hz), 125.5, 127.3, 127.5, 127.5, 128.6, 128.8, 129.4 (d, *J* = 5.5 Hz), 129.7, 130.7, 136.0, 136.3, 141.0 (d, *J* = 3.7 Hz), 144.1; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -177.5 (dddd, *J* = 48.2 Hz, *J* = 20.6 Hz, *J* = 18.5 Hz, *J* = 7.0 Hz, 1F); **IR (ν, cm^{-1}):** 1490 (w, C-C_{Ar}), 1454 (w, C-C_{Ar}), 1353 (s, S=O), 1166 (s, S=O), 1041 (w, C-F); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calc. 404.1091, found 404.1078.

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.44 (s, 3H), 3.61 (dd, *J* = 29.1 Hz, *J* = 2.9 Hz, 1H), 4.07 (ddd, *J* = 31.7 Hz, *J* = 14.5 Hz, *J* = 3.4 Hz, 1H), 4.24 (td, *J* = 14.8 Hz, *J* = 4.0 Hz, 1H), 5.02 (ddtd, *J* = 49.8 Hz, *J* = 3.8 Hz, *J* = 3.5 Hz, *J* = 1.0 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.86-6.92 (m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.21-7.33 (m, 6H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.5, 47.6 (d, *J* = 19.6 Hz), 49.6 (d, *J* = 25.2 Hz), 88.6 (d, *J* = 180.7 Hz), 123.9, 125.5, 127.4, 127.6, 128.4, 129.5, 129.5, 129.9, 129.9, 130.2 (d, *J* = 3.2 Hz), 136.0, 136.0, 138.0, 143.9; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = 185.0 (dddd, *J* = 49.8 Hz, *J* = 31.1 Hz, *J* = 29.5 Hz, *J* = 15.3 Hz, 1F); **IR (ν, cm^{-1}):** 1488 (w, C-C_{Ar}), 1454 (w, C-C_{Ar}), 1348 (s, S=O), 1163 (s, S=O), 1080 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calc. 404.1091, found 404.1080.

3-Fluoro-1-(methylsulfonyl)-4-phenyl-1,2,3,4-tetrahydroquinoline (49c)



Prepared from *N*-cinnamyl-*N*-phenylmethanesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded the title compound as a white solid (92 % yield).

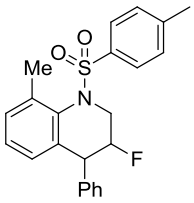
1.8:1 syn:anti mixture of separable diastereosiomers

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 3.04 (s, 3H), 3.74 (dd, *J* = 36.4 Hz, *J* = 14.8 Hz, 1H), 4.32 (dd, *J* = 36.1 Hz, *J* = 3.9 Hz, 1H), 4.76 (ddd, *J* = 14.8 Hz, *J* = 8.6 Hz, *J* = 4.1 Hz, 1H), 5.04 (dtd, *J* = 48.4 Hz, *J* = 4.0 Hz, *J* = 0.9 Hz, 1H), 7.01-7.06 (m, 1H), 7.06 (td, *J* = 7.1 Hz, *J* = 1.1 Hz, 1H), 7.19-7.41 (m, 5H), 7.98 (dd, *J* = 8.5 Hz, *J* = 0.9 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 37.8 (d, *J* = 8.7 Hz), 48.7, 49.2 (d, *J* = 21.2 Hz), 86.8 (d, *J* = 179.6 Hz), 121.9, 128.0, 128.5, 128.9, 129.0, 130.1, 130.9, 136.6, 138.9, 141.4; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -189.7 (dtd, *J* = 48.4 Hz, *J* = 36.2 Hz, *J* = 8.5 Hz, 1F).

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.97 (s, 3H), 3.58 (dd, *J* = 36.5 Hz, *J* = 15.1 Hz, 1H), 4.45 (d, *J* = 18.1 Hz, 1H), 4.53 (dddd, *J* = 15.1 Hz, *J* = 6.9 Hz, *J* = 4.3 Hz, *J* = 1.3 Hz, 1H), 4.97 (dddd, *J* = 47.4 Hz, *J* = 4.1 Hz, *J* = 2.8 Hz, *J* = 1.1 Hz, 1H), 7.01-7.09 (m, 2H), 7.13 (td, *J* = 7.4 Hz, *J* = 1.0 Hz, 1H), 7.19-7.41 (m, 5H), 8.03 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 37.9 (d, *J* = 8.6 Hz), 48.5 (d, *J* = 23.0 Hz), 48.9, 89.8 (d, *J* = 179.6 Hz), 121.4, 125.2, 126.5, 127.5, 127.6, 128.2, 131.9, 136.5, 138.9, 141.3; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -175.6 (dddd, *J* = 47.4 Hz, *J* = 37.1 Hz, *J* = 18.3 Hz, *J* = 8.4 Hz, 1F).

IR (ν, cm^{-1}): 1488 (m, C-C_{Ar}), 1454 (m, C-C_{Ar}), 1339 (s, S=O), 1154 (s, S=O), 1040 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{16}H_{16}FNNaO_2S]^+$ $(M+Na)^+$ calc. 328.0778, found 328.0770.

3-Fluoro-8-methyl-4-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (49e)

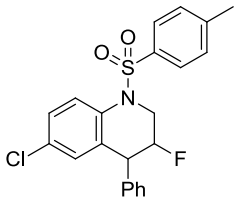


Prepared from *N*-cinnamyl-4-methyl-*N*-(*o*-tolyl)benzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (77 % yield).

1:1.3 syn:anti mixture of separable diastereosiomers.

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.52 (s, 3H), 2.61 (s, 3H), 3.79 (dd, *J* = 28.3 Hz, *J* = 15.7 Hz, 1H), 4.39-4.54 (m, 2H), 5.14 (dd, *J* = 53.2 Hz, *J* = 6.4 Hz, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 6.92 (brs, 2H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.25-7.37 (m, 6H), 7.56 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.6, 21.6, 46.9 (d, *J* = 19.2 Hz), 52.5 (d, *J* = 28.0 Hz), 93.4 (d, *J* = 178.0 Hz), 125.1, 127.1, 127.5, 127.5, 128.8, 129.8, 129.8, 130.0, 130.5, 134.3, 136.0 (d, *J* = 3.6 Hz), 136.8, 138.1, 144.3; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -179.3 (m, 1F); **IR (ν, cm^{-1}):** 1494 (w, C-C_{Ar}), 1455 (w, C-C_{Ar}), 1351 (s, S=O), 1162 (s, S=O), 1062 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{23}H_{22}FNNaO_2S]^+$ $(M+Na)^+$ calc. 418.1247, found 418.1233.

6-Chloro-3-fluoro-4-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (49g)



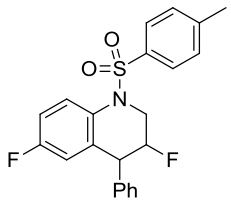
Prepared from *N*-(4-chlorophenyl)-*N*-cinnamyl-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (95 % yield).

1:5.8 syn:anti mixture of separable diastereosiomers.

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.45 (s, 3H), 3.48 (dd, *J* = 30.1 Hz, *J* = 2.8 Hz, 1H), 4.04 (ddd, *J* = 33.2 Hz, *J* = 14.7 Hz, *J* = 3.3 Hz, 1H), 4.24 (td, *J* = 15.0 Hz, *J* = 3.3 Hz, 1H), 5.01 (ddt, *J* = 49.7 Hz, *J* = 3.4 Hz, *J* = 3.4 Hz, 1H), 6.66 (dd, *J* = 2.4 Hz, *J* = 0.6 Hz, 1H), 6.89 (d, *J* = 7.1 Hz, 2H), 7.24 (dd, *J* = 8.7 Hz, *J* = 2.3 Hz, 1H), 7.26-7.31 (m, 5H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 47.5 (d, *J* = 19.2 Hz), 49.8

(d, *J* = 24.8 Hz), 88.5 (d, *J* = 181.0 Hz), 125.4, 127.4, 127.8 (d, *J* = 1.7 Hz), 128.6, 129.1, 129.6, 129.7, 129.8, 131.1, 132.2 (d, *J* = 3.2 Hz), 134.6, 135.6, 137.1, 144.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -184.8 (m, 1F); **IR (ν, cm^{-1}):** 1479 (w, C-C_{Ar}), 1349 (s, S=O), 1162 (s, S=O), 1086 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{19}ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 438.0701, found 438.0696.

3,6-Difluoro-4-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (49h)

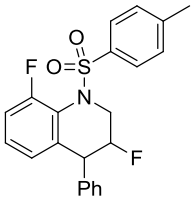


Prepared from *N*-cinnamyl-*N*-(4-fluorophenyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (73 % yield).

1:3.7 syn:anti mixture of separable diastereosiomers.

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.46 (s, 3H), 3.31 (dd, *J* = 31.0 Hz, *J* = 2.0 Hz, 1H), 4.08 (ddd, *J* = 34.0 Hz, *J* = 14.9 Hz, *J* = 3.8 Hz, 1H), 4.18 (ddd, *J* = 33.0 Hz, *J* = 14.9 Hz, *J* = 2.6 Hz, 1H), 5.03 (ddt, *J* = 50.1 Hz, *J* = 3.5 Hz, *J* = 3.1 Hz, 1H), 6.37 (ddd, *J* = 9.2 Hz, *J* = 3.0 Hz, *J* = 0.8 Hz, 1H), 6.85-6.89 (m, 2H), 6.99 (tdd, *J* = 8.5 Hz, *J* = 3.1 Hz, *J* = 0.4 Hz, 1H), 7.24-7.32 (m, 5H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.84 (dd, *J* = 9.1 Hz, *J* = 5.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 47.5 (d, *J* = 19.5 Hz), 50.3 (d, *J* = 24.4 Hz), 89.3 (d, *J* = 180.7 Hz), 114.5 (d, *J* = 22.1 Hz), 115.7 (d, *J* = 24.0 Hz), 126.6 (d, *J* = 8.5 Hz), 127.3, 127.8, 128.6, 129.6, 129.7 (d, *J* = 2.7 Hz), 131.7 (d, *J* = 2.7 Hz), 133.6 (dd, *J* = 7.7 Hz, *J* = 2.9 Hz), 135.7, 137.0, 144.1, 160.6 (d, *J* = 246.0 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -115.3 (m, 1F), -183.7 (m, 1F); **IR (ν, cm^{-1}):** 1487 (w, C-C_{Ar}), 1454 (w, C-C_{Ar}), 1351 (s, S=O), 1165 (s, S=O), 1080 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{19}F_2NNaO_2S]^+$ $(M+Na)^+$ calc. 422.0997, found 422.0981.

3,8-Difluoro-4-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (49i)

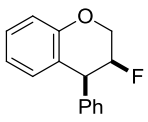


Prepared from *N*-cinnamyl-*N*-(2-fluorophenyl)-4-methylbenzenesulfonamide according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (10 % yield).

1:4.6 syn:anti mixture of separable diastereosiomers.

Anti diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 3.26 (s, 3H), 3.43 (d, *J* = 32.3 Hz, 1H), 3.72 (ddt, *J* = 24.8 Hz, *J* = 14.9 Hz, *J* = 1.2 Hz, 1H), 4.36 (ddd, *J* = 30.6 Hz, *J* = 15.0 Hz, *J* = 5.8 Hz, 1H), 5.32 (ddt, *J* = 52.1 Hz, *J* = 5.8 Hz, *J* = 1.9 Hz, 1H), 6.49-6.52 (m, 1H), 6.94-7.54 (m, 9H), 7.77 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.6, 47.0 (dd, *J* = 19.1 Hz, *J* = 1.7 Hz), 51.1 (d, *J* = 27.7 Hz), 92.6 (d, *J* = 179.4 Hz), 115.5 (d, *J* = 20.9 Hz), 123.5 (d, *J* = 3.4 Hz), 125.3, 127.5 (d, *J* = 1.3 Hz), 128.2, 128.7, 129.0, 129.8, 129.9 (d, *J* = 3.2 Hz), 136.5 (d, *J* = 4.3 Hz), 137.0 (d, *J* = 3.6 Hz), 137.9, 144.2, 157.5 (d, *J* = 253.1 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -116.8 (m, 1F), -180.8 (m, 1F); **IR (ν, cm^{-1}):** 1496 (w, C-C_{Ar}), 1477 (w, C-C_{Ar}), 1357 (s, S=O), 1166 (s, S=O), 1087 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{22}H_{19}F_2NNaO_2S]^+$ $(M+Na)^+$ calc. 422.0997, found 422.0981.

3-Fluoro-4-phenylchroman (49j)



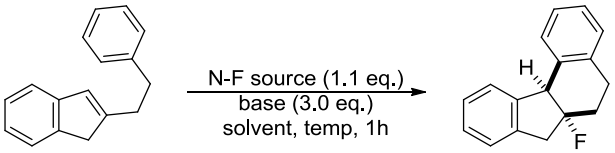
Prepared from (cinnamyloxy)benzene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a colourless oil (17 % yield).

Only syn diastereomer recovered

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.27 (ddt, *J* = 30.5 Hz, *J* = 11.9 Hz, *J* = 1.3 Hz, 1H), 4.39 (dd, *J* = 29.4 Hz, *J* = 3.8 Hz, 1H), 4.46 (ddd, *J* = 12.0 Hz, *J* = 8.3 Hz, *J* = 4.5 Hz, 1H), 5.04 (dtd, *J* = 47.6 Hz, *J* = 4.3 Hz, *J* = 1.3 Hz, 1H), 6.81-6.84 (m, 1H), 6.85 (td, *J* = 7.7 Hz, *J* = 0.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.18 (td, *J* = 7.5 Hz, *J* = 2.0 Hz, 1H), 7.22-7.27 (m, 2H), 7.30-

7.39 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 46.0 (d, *J* = 19.6 Hz), 66.3 (d, *J* = 22.3 Hz), 86.1 (d, *J* = 182.1 Hz), 116.4, 121.1, 121.8 (d, *J* = 2.5 Hz), 127.4, 128.3, 128.3, 130.3, 130.3, 139.0, 153.8; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -198.1 (dtd, *J* = 47.1 Hz, *J* = 30.5 Hz, *J* = 7.9 Hz, 1F); **IR (ν, cm^{-1}):** 1466 (C-C_{Ar}), 1091 (m, C-F), 1005 (w, C-O); **HRMS (ESI^+, m/z):** $[C_{15}H_{13}FNaO]^+$ $(M+Na)^+$ calc. 251.0843, found 251.0847.

6.2.10 Optimisation Table 5

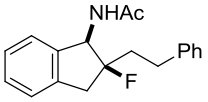


30a **31a**

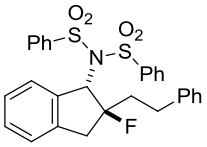
Entry[a]	N-F Source[b]	Solvent	Temp.	Ratio[c] **1a**:**2a**:**3a**:**4a**:**5a**	Yield **2a** [%][d]
1	**A**	MeCN	r.t.	0:**29**:63:0:8	26
2	**A**	MeCN	0 °C	0:**26**:69:0:5	-
3	**A**	MeCN	-40 °C	81:**3**:14:0:2	-
4[e]	**A**	MeCN	r.t.	19:**22**:49:0:10	-
5	**B**	MeCN	r.t.	56:**10**:0:33:1	-
6[f]	**A**	$MeNO_2$	r.t.	0:**93**:0:0:7	59
7[f]	**C**	$MeNO_2$	r.t.	0:**96**:0:0:4	89
8[f]	**C**	$MeNO_2$	0 °C	0:**86**:0:0:14	72
9[f]	**C**	$MeNO_2$	40 °C	0:**98**:0:0:2	92

A = Selectfluor, B = NFSI, C = *N*-fluoro-2,6-dichloropyridinium triflate; General conditions: **30a** (50 mg), solvent (5 mL), 3 ÅMS, base (3.0 eq.), N-F reagent (1.1 eq.), temp. 1h [a] ratio of product to starting material or fluoro-Ritter product [b] isolated yield [c] remainder was fluoro-Ritter product (**30b**) [d] dibenzenesulfonimide incorporation (**30c**).

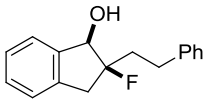
To a solution of indene **30a** (50 mg) in solvent (5 mL) in a 7.5 mL screw-top vial was added 3 ÅMS (about 10) and the solution was stirred gently for 3 hours. To the vial was added base (3.0 eq.) and $N\text{-}F^+$ reagent (1.1 eq.) and the reaction was stirred vigorously for 1 hour before filtering through a celite pipette. The crude reaction was concentrated *in vacuo* and analyzed by ^{1}H NMR before being purified by column chromatography (SiO_2, EtAOc/PE 1:49).



32a

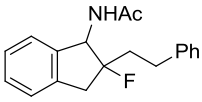


32b



32c

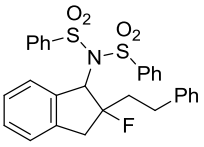
***N*-(2-fluoro-2-phenethyl-2,3-dihydro-1*H*-inden-1-yl)acetamide (32a) – fluoro-Ritter product**



To a solution of 2-phenethyl-1*H*-indene (100 mg, 0.45 mmol) in acetonitrile (10 mL) over molecular sieves was added $NaHCO_3$ solution (76 mg, 0.91 mmol) and Selectfluor (241 mg, 0.68 mmol). The reaction was stirred for 2 hours before diluting with EtOAc and washing with water. The organic phase was further washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 3:7) afforded the title compound as a colourless oil (63 mg, 0.21 mmol, 47 % yield).

Data for major isomer: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 2.15 (s, 3H), 2.15 (dddd, *J* = 29.3 Hz, *J* = 14.5 Hz, *J* = 11.3 Hz, *J* = 6.1 Hz, 1H), 2.27-2.39 (m, 1H), 2.81-2.93 (m, 2H), 3.10 (dd, *J* = 36.6 Hz, *J* = 17.2 Hz, 1H), 3.26 (dd, *J* = 21.2 Hz, *J* = 17.2 Hz, 1H), 5.60 (dd, *J* = 23.4 Hz, *J* = 9.6 Hz, 1H), 6.08 (d, *J* = 9.6 Hz, 1H, N*H*), 7.20-7.28 (m, 7H), 7.29-7.34 (m, 2H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 23.4, 30.3 (d, *J* = 4.3 Hz), 37.6 (d, *J* = 23.5 Hz), 41.4 (d, *J* = 24.1 Hz), 59.4 (d, *J* = 17.3 Hz), 106.2 (d, *J* = 182.0 Hz), 123.9, 125.0, 126.1, 127.3, 128.3, 128.3, 128.5, 138.7, 140.7, 141.2, 170.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ = -166.4 (ddddd, *J* = 36.6 Hz, *J* = 29.4 Hz, *J* = 23.8 Hz, *J* = 21.8 Hz, *J* = 13.8 Hz, 1F); **IR (ν, cm^{-1}):** 3280, 1653, 1049; **HRMS (ESI$^+$):** m/z calc. for $C_{19}H_{20}FNNaO$ ($[M+Na]^+$): 320.1421, found 320.1413.

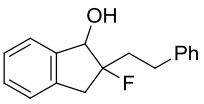
_N_-(2-fluoro-2-phenethyl-2,3-dihydro-1_H_-inden-1-yl)-_N_-(phenylsulfonyl)benzenesulfonamide (32b)



To a solution of 2-phenethyl-1*H*-indene (70 mg, 0.32 mmol) in $MeNO_2$ (5 mL) over 3 ÅMS was added $NaHCO_3$ (53 mg, 0.64 mmol) and NFSI (151 mg, 0.48 mmol). The reaction was stirred for 2 hours before diluting with EtOAc and washing with water. The organic layer was further washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:4) afforded the title compound as a colourless oil (21 mg, 0.039 mmol, 12 % yield).

Data for major isomer: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 1.70-1.89 (m, 2H), 2.54-2.68 (m, 2H), 3.18 (dd, *J* = 16.7 Hz, *J* = 8.7 Hz, 1H), 3.75 (dd, *J* = 22.3 Hz, *J* = 16.7 Hz, 1H), 5.47 (d, *J* = 6.1 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.23-7.29 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.55-7.59 (m, 3H), 7.66-7.73 (m, 3H), 8.16 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 29.5 (d, *J* = 5.7 Hz), 41.9 (d, *J* = 25.0 Hz), 70.3 (d, *J* = 18.1 Hz), 99.4 (d, *J* = 200.0 Hz), 125.1, 125.4, 126.1, 126.9, 128.3, 128.3, 128.4, 128.9, 129.0, 129.1, 129.6, 133.4, 134.1, 135.7, 139.2, 140.5, 140.6, 141.0, 141.4; **^{19}F {1H} NMR (376 MHz, $CDCl_3$):** δ = -154.7; **IR (ν, cm^{-1}):** 1372, 1170, 1046; **HRMS (ESI$^+$):** m/z calc. for $C_{29}H_{26}FNNaO_4S_2$ ($[M+Na]^+$): 558.1179, found 558.1161.

2-Fluoro-2-phenethyl-2,3-dihydro-1_H_-inden-1-ol (*32c*)



To a solution of 2-phenethyl-1*H*-indene (100 mg, 0.45 mmol) in a $MeNO_2/H_2O$ mixture (9:1 *v/v*, 10 mL) was added $NaHCO_3$ (76 mg, 0.91 mmol) and Selectfluor (241 mg, 0.68 mmol). The reaction was stirred for 2 hours before diluting with EtOAc and washing with water. The organic phase was further washed with

brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (12 mg, 0.047 mmol, 10 % yield).

Data for major isomer: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 2.17 (dddd, *J* = 28.3 Hz, *J* = 14.3 Hz, *J* = 12.0 Hz, *J* = 5.3 Hz, 1H), 2.37 (brs, 1H, O*H*), 2.47 (dddd, *J* = 16.1 Hz, *J* = 14.4 Hz, *J* = 11.9 Hz, *J* = 4.8 Hz, 1H), 2.87 (ddd, *J* = 13.5 Hz, *J* = 12.0 Hz, *J* = 5.3 Hz, 1H), 2.96-3.09 (m, 2H), 3.28 (dd, *J* = 20.3 Hz, *J* = 17.1 Hz, 1H), 4.96 (dd, *J* = 16.4 Hz, *J* = 6.8 Hz, 1H), 7.18-7.36 (m, 8H), 7.45-7.49 (m, 1H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 30.3 (d, *J* = 3.9 Hz), 37.5 (d, *J* = 23.7 Hz), 40.7 (d, *J* = 24.2 Hz), 79.7 (d, *J* = 19.2 Hz), 105.1 (d, *J* = 180.7 Hz), 124.4, 125.0, 126.1, 127.4, 128.3, 128.5, 128.6, 138.0, 141.5, 142.5; **^{19}F {1H} NMR (376 MHz, $CDCl_3$):** δ = -172.6; **IR (ν, cm^{-1}):** 3378, 1052, 1049; **HRMS (ESI^+):** m/z calc. for $C_{17}H_{17}FNaO$ ($[M+Na]^+$): 279.1156, found 279.1155.

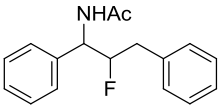
6.3 Experimental data for Chapter 3

Details for the synthesis of compounds described in Chapter 3 are provided herein. See appendices for NMR images of novel compounds as well as X-ray crystallographic data.

6.3.1 General procedure for fluoro-amidation

To a solution of olefin (50 mg) in MeCN (2 mL) at room temperature was added $NaHCO_3$ (2.0 eq.) followed by Selectfluor (1.5 eq.). The reaction was stirred for 12 hours before being poured onto water (5 mL), extracted into DCM (3 x 10 mL), drying over $MgSO_4$ and evaporated under removed pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:1) afforded the title compound.

_N_-(2-fluoro-1,3-diphenylpropyl)acetamide (50)

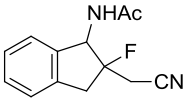


Prepared from (*E*)-prop-1-ene-1,3-diyldibenzene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:1) afforded the title compound as a white solid (43 mg, 0.16 mmol, 62 % yield, d.r. 1:1).

Syn isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.03 (s, 3H), 2.94 (td, *J* = 14.5 Hz, *J* = 4.4 Hz, 1H), 3.05 (td, *J* = 14.5 Hz, *J* = 8.5 Hz, 1H), 4.98 (dddd, *J* = 47.0 Hz, *J* = 8.5 Hz, *J* = 5.1 Hz, *J* = 3.2 Hz, 1H), 5.15 (ddd, *J* = 27.7 Hz, *J* = 9.1 Hz, *J* = 2.8 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H, N*H*), 7.25-7.42 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.1, 38.1 (d, *J* = 21.9 Hz), 54.9 (d, *J* = 18.1 Hz), 96.3 (d, *J* = 178.3 Hz), 126.6, 127.0, 127.5, 128.5, 128.5, 129.4, 137.1 (d, *J* = 4.8 Hz), 140.1, 169.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -193.0 (dddd, *J* = 47.0 Hz, *J* = 31.0 Hz, *J* = 28.7 Hz. *J* = 16.1 Hz, 1F); **IR (ν, cm^{-1}):** 3303 (br, N-H), 1650 (s, C=O), 1455 (w, C-C_{Ar}), 1295 (m, N-C_{amide}), 1056 (m, C-N), 1034 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{18}FNNaO]^+$ $(M + Na)^+$ calc. 294.1265, found 294.1257.

Anti isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.93 (d, *J* = 0.8 Hz, 3H), 2.73 (td, *J* = 15.1 Hz, *J* = 9.5 Hz, 1H), 2.95 (ddd, *J* = 35.6 Hz, *J* = 14.8 Hz, *J* = 2.8 Hz, 1H), 4.97 (dddd, *J* = 48.2 Hz, *J* = 9.5 Hz, *J* = 5.0 Hz, *J* = 3.5 Hz, 1H), 5.10 (ddd, *J* = 21.8 Hz, *J* = 8.8 Hz, *J* = 5.0 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 1H, N*H*), 7.21-7.45 (m, 10H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.1, 38.0 (d, *J* = 21.0 Hz), 55.8 (d, *J* = 21.9 Hz), 95.5 (d, *J* = 177.4 Hz), 126.6, 127.7, 128.3, 128.4, 128.5, 129.3, 137.4 (d, *J* = 1.9 Hz), 138.5, 169.1; **^{19}F NMR 376.6 MHz, $CDCl_3$):** δ = -190.3 (dddd, *J* = 48.2 Hz, *J* = 35.6 Hz, *J* = 21.8 Hz, *J* = 17.2 Hz, 1F); **IR (ν, cm^{-1}):** 3338 (br, N-H), 1650 (s, C=O), 1455 (w, C-C_{Ar}), 1265 (m, N-C_{amide}), 1070 (m, C-N), 1032 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{18}FNNaO]^+$ $(M + Na)^+$ calc. 294.1265, found 294.1255.

_N_-(2-(cyanomethyl)-2-fluoro-2,3-dihydro-1_H_-inden-1-yl)acetamide (51)

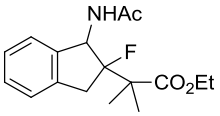


Prepared from 2-(1H-inden-2-yl)acetonitrile according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:2) afforded the title compound as a white solid (60 mg, 0.26 mmol, 41 % yield, d.r. 1:2.5 anti:syn).

Syn isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.06 (s, 3H), 3.09 (dd, *J* = 18.2 Hz, *J* = 17.3 Hz, 1H), 3.14 (dd, *J* = 25.6 Hz, *J* = 17.2 Hz, 1H), 3.28 (dd, *J* = 24.0 Hz, *J* = 17.3 Hz, 1H), 3.35 (s, 1H), 5.58 (dd, *J* = 24.1 Hz, *J* = 9.3 Hz, 1H), 6.89 (d, *J* = 6.9 Hz, 1H, N*H*), 7.21-7.26 (m, 1H), 7.28-7.34 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.0, 24.3 (d, *J* = 26.7 Hz), 41.0 (d, *J* = 23.8 Hz), 58.6 (d, *J* = 17.2 Hz), 102.0 (d, *J* = 188.8 Hz), 116.4 (d, *J* = 4.8 Hz), 123.6, 125.1, 127.4, 128.4, 138.1, 140.2, 170.9; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -163.2 (m, 1F); **IR (ν, cm^{-1}):** 3249 (br, N-H), 2978 (w, C≡N), 1649 (s, C=O), 1461 (w, C-C_{Ar}), 1283 (m, N-C_{amide}), 1122 (m, C-N), 1055 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{13}FN_2NaO]^+$ $(M + Na)^+$ calc. 255.0904, found 255.0901.

Anti isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.96 (d, *J* = 0.9 Hz, 3H), 3.00 (ddd, *J* = 33.4 Hz, *J* = 17.3 Hz, *J* = 0.6 Hz, 1H), 3.05 (dd, *J* = 28.1 Hz, *J* = 17.3 Hz, 1H), 3.36 (dd, *J* = 26.5 Hz, *J* = 17.3 Hz, 1H), 3.41 (dd, *J* = 30.6 Hz, *J* = 17.3 Hz, 1H), 5.49 (dd, *J* = 18.6 Hz, *J* = 8.5 Hz, 1H), 6.69 (d, *J* = 4.3 Hz, 1H, N*H*), 7.31-7.39 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.0, 23.5 (d, *J* = 24.8 Hz), 41.5 (d, *J* = 24.8 Hz), 60.8 (d, *J* = 32.4 Hz), 78.2, 102.9 (d, *J* = 186.2 Hz), 125.0, 125.2, 127.7, 129.1, 139.3, 139.4, 170.2; **^{19}F NMR 376.6 MHz, $CDCl_3$):** δ = -145.1 (m, 1F); **IR (ν, cm^{-1}):** 3286 (br, N-H), 2978 (w, C≡N), 1657 (s, C=O), 1464 (w, C-C_{Ar}), 1294 (m, C-N_{amide}), 1045 (s, C-F), 1023 (m, C-N); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{13}FN_2NaO]^+$ $(M + Na)^+$ calc. 255.0904, found 255.0903.

Ethyl 2-(1-acetamido-2-fluoro-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate (52)

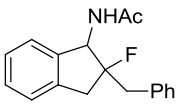


Prepared from ethyl 2-(1H-inden-2-yl)-2-methylpropanoate according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:1) afforded the title compound as a white solid (19 mg, 0.030 mmol, 14 % yield, d.r. 1:4 syn:anti).

Syn isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.23 (t, *J* = 7.1 Hz, 3H), 1.37 (s, 6H), 2.01 (s, 3H), 3.16 (dd, *J* = 25.0 Hz, *J* = 17.7 Hz, 1H), 3.48 (dd, *J* = 36.4 Hz, *J* = 17.7 Hz, 1H), 4.06-4.18 (m, 2H), 5.95 (dd, *J* = 24.3 Hz, *J* = 9.6 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H, N*H*), 7.13-7.18 (m, 1H), 7.23-7.30 (m, 3H); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -169.0 (ddd, *J* = 35.6 Hz, *J* = 24.1 Hz, *J* = 24.1 Hz, 1F); **IR (ν, cm^{-1}):** 3279 (br, N-N), 1723 (s, C=O_{ester}), 1654 (s, C=O_{amide}), 1272 (s, N-C_{amide}), 1150 (s, O-C_{ester}), 1032 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{22}FNNaO_3]^+$ $(M+Na)^+$ calc. 330.1476, found 330.1476.

Alcohol product d.r. = >25:1 anti:syn: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.22 (t, *J* = 7.1 Hz, 3H), 1.43 (s, 3H), 1.46 (s, 3H), 3.10 (dd, *J* = 23.5 Hz, *J* = 17.7 Hz, 1H), 3.47 (d, *J* = 6.8 Hz, 1H, O*H*), 3.98-4.16 (m, 3H), 4.98 (dd , *J* = 15.9 Hz, *J* = 6.8 Hz, 1H), 7.23-7.45 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 13.7, 20.6 (d, *J* = 4.8 Hz), 22.1 (d, *J* = 3.2 Hz), 39.5 (d, *J* = 25.6 Hz), 46.8 (d, *J* = 20.8 Hz), 60.9, 79.6 (d, *J* = 36.8 Hz), 108.3 (d, *J* = 179.0 Hz), 125.5, 125.9, 127.3, 129.4, 141.9, 142.9, 175.4 (d, *J* = 8.0 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -152.3 (ddd, *J* = 39.0 Hz, *J* = 22.9 Hz, *J* = 14.9 Hz, 1F); **IR (ν, cm^{-1}):** 3494 (br, O-H), 1707 (s, C=O), 1474 (w, C-C_{Ar}), 1148 (m, C-O_{ester}), 1062 (s, C-F), 1024 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{15}H_{19}FNaO_3]^+$ $(M+Na)^+$ calc. 289.1210, found 289.1215.

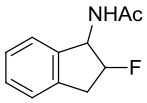
_N_-(2-benzyl-2-fluoro-2,3-dihydro-1_H_-inden-1-yl)acetamide (53)



Prepared from 2-benzyl-1*H*-indene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:1) afforded the title compound as a colourless oil (24 mg, 0.085 mmol, 35 % yield, d.r. >25:1 syn:anti).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.88 (dd, *J* = 20.1 Hz, *J* = 17.2 Hz, 1H), 3.16 (dd, *J* = 29.0 Hz, *J* = 14.1 Hz, 1H), 3.21 (dd, *J* = 37.6 Hz, *J* = 17.3 Hz, 1H), 3.29 (dd, *J* = 15.2 Hz, *J* = 14.3 Hz, 1H), 4.08 (dd, *J* = 14.3 Hz, *J* = 7.1 Hz, 1H), 5.59 (dd, *J* = 24.8 Hz, *J* = 9.5 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H, N*H*), 7.16-7.39 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.1, 40.6 (d, *J* = 23.5 Hz), 40.7 (d, *J* = 23.6 Hz), 58.9 (d, *J* = 17.8 Hz), 106.5 (d, *J* = 183.2 Hz), 123.6, 124.9, 126.7, 127.0, 127.9, 128.2, 130.3, 136.5 (d, *J* = 3.2 Hz), 139.0, 141.4; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -164.6 (ddddd, *J* = 37.9 Hz, *J* = 28.9 Hz, *J* = 24.8 Hz, *J* = 20.1 Hz, *J* = 15.4 Hz, 1F); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{18}FNNaO]^+$ $(M+Na)^+$ calc. 306.1265, found 306.1269.

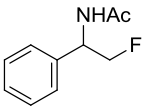
_N_-(2-fluoro-2,3-dihydro-1_H_-inden-1-yl)acetamide (55)



Prepared from indene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:1) afforded the title compound as a colourless oil (27 mg, 0.14 mmol, 33 % yield, only syn isomer recovered).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.08-3.30 (m, 2H), 5.32 (dm, *J* = 54.3 Hz, 1H), 5.52 (ddd, *J* = 27.3 Hz, *J* = 8.8 Hz, *J* = 4.0 Hz, 1H), 6.84 (brs, 1H, N*H*), 7.24-7.33 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.4, 37.9 (d, *J* = 22.4 Hz), 57.1 (d, *J* = 17.6 Hz), 95.8 (d, *J* = 179.0 Hz), 124.1, 125.1, 127.5, 128.4, 139.8, 140.9, 170.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -196.3 (dddd, *J* = 53.9 Hz, *J* = 39.0 Hz, *J* = 27.1 Hz, *J* = 26.4 Hz, 1F); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{12}FNNaO]^+$ $(M+Na)^+$ calc. 216.0795, found 216.0799.

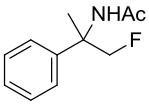
***N*-(2-fluoro-1-phenylethyl)acetamide (57)**



Prepared from styrene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:2) afforded the title compound as a colourless oil (31 mg, 0.17 mmol, 35 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H), 4.48-4.69 (m, 2H), 5.16-5.28 (m, 1H), 7.18 (brs, 1H), 7.28-7.42 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.4, 53.5 (d, *J* = 19.8 Hz), 85.3 (d, *J* = 173.7 Hz), 117.7, 127.4, 128.1, 129.0, 139.1 (d, *J* = 5.0 Hz), 170.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -223.5 (td, *J* = 47.3 Hz, *J* = 20.3 Hz, 1F); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{12}FNNaO]^+$ $(M+Na)^+$ calc. 216.0795, found 216.0799.

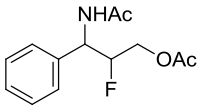
***N*-(1-fluoro-2-phenylpropan-2-yl)acetamide (59)**



Prepared from α-methyl-styrene according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 3:2) afforded the title compound as a colourless oil (39 mg, 0.20 mmol, 47 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 1.8 Hz, 3H), 1.93 (s, 3H), 4.63 (dd, *J* = 28.6 Hz, *J* = 9.0 Hz, 1H), 4.75 (dd, *J* = 29.2 Hz, *J* = 9.0 Hz, 1H), 6.85 (brs, 1H, N*H*), 7.25-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.1 (d, *J* = 4.1 Hz), 58.8 (d, *J* = 17.7 Hz), 87.5 (d, *J* = 177.0 Hz), 117.7, 126.0, 127.4, 128.7, 143.1 (d, *J* = 3.7 Hz), 169.9; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -223.2 (t, *J* = 47.9 Hz, 1F).

3-Acetamido-2-fluoro-3-phenylpropyl acetate (61)



Prepared from cinnamyl acetate according to the general procedure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9 to 3:2) afforded the title compound as a colourless oil (12 mg, 0.048 mmol, 17 % yield, d.r. 1.4:1 syn:anti).

Anti isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.92 (s, 3H), 2.03 (s, 3H), 4.06 (ddd, *J* = 21.2 Hz, *J* = 12.6 Hz, *J* = 6.8 Hz, 1H), 4.20 (ddd, *J* = 28.3 Hz, *J* = 12.6 Hz, *J* = 2.0 Hz, 1H), 4.95 (dtd, *J* = 48.5 Hz, *J* = 6.6 Hz, *J* = 2.0 Hz, 1H), 5.19 (ddd, *J* = 18.4 Hz, *J* = 8.6 Hz, *J* = 6.6 Hz, 1H), 7.10 (d, *J* = 5.3 Hz, 1H, N*H*), 7.33-7.43 (m, 5H); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -195.3 (dddd, *J* = 48.2 Hz, *J* = 27.5 Hz, *J* = 20.7 Hz, *J* = 18.9 Hz, 1F); **IR (ν, cm^{-1}):** 3324 (br, N-H), 1734 (s, C=O_{ester}), 1651 (s, C=O_{amide}), 1456 (w, C-C_{Ar}), 1245 (s, N-C_{amide}), 1117 (m, O-C_{ester}), 1079 (m, C-O), 1044 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{16}FNNaO_3]^+$ $(M + Na)^+$ calc. 276.1006, found 276.1006.

Syn isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.96 (s, 3H), 2.05 (s, 3H), 4.10 (ddd, *J* = 20.2 Hz, *J* = 12.6 Hz, *J* = 6.8 Hz, 1H), 4.22 (ddd, *J* = 27.5 Hz, *J* = 12.6 Hz, *J* = 2.8 Hz, 1H), 4.95 (dddd, *J* = 48.0 Hz, *J* = 6.6 Hz, *J* = 4.8 Hz, *J* = 3.0 Hz, 1H), 5.27 (ddd, *J* = 24.0 Hz, *J* = 8.8 Hz, *J* = 4.6 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 1H, N*H*), 7.31-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.3, 22.4, 53.6 (d, *J* = 19.2 Hz), 63.8 (d, *J* = 22.4 Hz), 93.2 (d, *J* = 179.0 Hz), 100.0, 127.5, 128.2, 129.1, 170.0, 170.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -198.6 (dddd, *J* = 47.8 Hz, *J* = 26.4 Hz, *J* = 23.0 Hz, *J* = 20.7 Hz, 1F); **IR (ν, cm^{-1}):** 3254 (br, N-H), 1732 (s, C=O_{ester}), 1651 (s, C=O_{amide}), 1427 (w, C-C_{Ar}), 1239 (s, N-C_{amide}), 1117 (O-C_{ester}), 1079 (m, C-O), 1049 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{16}FNNaO_3]^+$ $(M + Na)^+$ calc. 276.1006, found 276.1008.

Expected alcohol **61b**, syn (isomers inseparable by column chromatography, 4:1 syn:anti): **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.08 (s, 3H), 2.63 (brs, 1H, O*H*), 4.04 (ddd, *J* = 22.5 Hz, *J* = 12.6 Hz, *J* = 6.1 Hz, 1H), 4.25 (ddd, *J* = 25.5 Hz, *J* = 12.6 Hz, *J* = 2.8 Hz, 1H), 4.78 (dddd, *J* = 48.3 Hz, *J* =

12.9 Hz, *J* = 6.3 Hz, *J* = 3.0 Hz, 1H), 4.89 (ddd, *J* = 14.7 Hz, *J* = 6.6 Hz, *J* = 1.8 Hz, 1H), 7.31-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.7, 63.0 (d, *J* = 22.4 Hz), 73.4 (d, *J* = 20.8 Hz), 93.8 (d, *J* = 179.0 Hz), 126.8, 128.5, 128.8, 138.2 (d, *J* = 4.8 Hz), 170.6; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -195.8 (dddd, *J* = 48.2 Hz, *J* = 25.2 Hz, *J* = 22.9 Hz, *J* = 14.9 Hz, 1F).

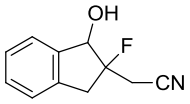
Anti: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.08 (s, 3H), 2.57 (d, *J* = 2.8 Hz, 1H, O*H*), 4.27 (ddd, *J* = 28.0 Hz, *J* = 12.6 Hz, *J* = 2.5 Hz, 1H), 4.42 (ddd, *J* = 22.2 Hz, *J* = 12.9 Hz, *J* = 6.3 Hz, 1H), 4.69-4.87 (m, 1H), 4.94 (ddd, *J* = 11.1 Hz, *J* = 5.6 Hz, *J* = 2.3 Hz, 1H), 7.31-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.7, 62.6 (d, *J* = 20.8 Hz), 73.3 (d, *J* = 20.8 Hz), 93.2 (d, *J* = 166.2 Hz), 126.4, 128.5, 128.7, 138.2 (d, *J* = 4.8 Hz), 170.6; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -193.6 (dddd, *J* = 47.0 Hz, *J* = 26.7 Hz, *J* = 22.9 Hz, *J* = 11.5 Hz, 1F).

IR (ν, cm^{-1}): 3448 (br, O-H), 1739 (s, C=O), 1454 (w, C-C_{Ar}), 1231 (s, O-C_{ester}), 1051 (m, C-O), 1042 (s, C-F); **HRMS (ESI^+, m/z):** $[C_{11}H_{13}FNaO_3]^+$ $(M + Na)^+$ calc. 235.0741, found 235.0750.

Rearranged alcohol **61c** (syn:anti 11:1): **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.01 (brs, 1H, O*H*), 2.15 (s, 3H), 3.56 (ddd, *J* = 23.0 Hz, *J* = 13.1 Hz, *J* = 5.3 Hz, 1H), 3.68 (ddd, *J* = 21.4 Hz, *J* = 12.6 Hz, *J* = 3.3 Hz, 1H), 4.76 (dddd, *J* = 48.0 Hz, *J* = 6.8 Hz, *J* = 5.1 Hz, *J* = 3.5 Hz, 1H), 6.07 (dd, *J* = 15.7 Hz, *J* = 7.1 Hz, 1H), 7.33-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.1, 61.4 (d, *J* = 24.0 Hz), 73.9 (d, *J* = 19.2 Hz), 94.1 (d, *J* = 180.6 Hz), 121.9, 127.3, 128.8, 128.9, 170.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -197.7 (dddd, *J* = 48.2 Hz, *J* = 22.9 Hz, *J* = 21.8 Hz, *J* = 16.1 Hz, 1F); **IR (ν, cm^{-1}):** 3438 (br, O-H), 1738 (s, C=O), 1455 (w, C-C_{Ar}), 1231 (s, O-C_{ester}), 1030 (s, C-F), 1026 (s, C-O); **HRMS (ESI^+, m/z):** $[C_{11}H_{13}FNaO_3]^+$ $(M + Na)^+$ calc. 235.0741, found 235.0750.

Anti: **^{19}F NMR 376.6 MHz, $CDCl_3$):** δ = -198.4 (dddd, *J* = 48.2 Hz, *J* = 24.1 Hz, *J* = 24.1 Hz, *J* = 13.8 Hz, 1F).

2-(2-Fluoro-1-hydroxy-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (62)

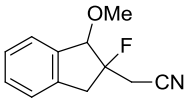


To a solution of 2-(1*H*-inden-2-yl)acetonitrile (50 mg, 0.32 mmol) in acetonitrile:water 9:1 (2 mL) at room temperature was added $NaHCO_3$ (54 mg, 0.64 mmol) followed by Selectfluor (171 mg, 0.48 mmol). The reaction was stirred for 12 hours before being poured onto water (5 mL), extracted into DCM (3 x 10 mL), drying over $MgSO_4$ and evaporated under removed pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:3) afforded the title compound as a white solid (29 mg, 0.15 mmol, 47 % yield, d.r. 1:1.5 anti:syn).

Anti isomer: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 2.34 (d, *J* = 5.7 Hz, 1H, O*H*), 2.90 (dd, *J* = 24.6 Hz, *J* = 17.0 Hz, 1H), 3.07 (dd, *J* = 17.3 Hz, *J* = 17.0 Hz, 1H), 3.35 (dd, *J* = 20.5 Hz, *J* = 2.2 Hz, 1H), 5.24 (dd, *J* = 15.8 Hz, *J* = 5.4 Hz, 1H), 7.25-7.44 (m, 4H), **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 23.3 (d, *J* = 24.8 Hz), 40.8 (d, *J* = 23.8 Hz), 79.6 (d, *J* = 31.5 Hz), 102.5 (d, *J* = 189.8 Hz), 116.5 (d, *J* = 2.9 Hz), 125.0, 125.3, 128.0, 129.8, 138.3, 140.4 (d, *J* = 2.9 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -151.6 (ddddd, *J* = 24.4 Hz, *J* = 20.7 Hz, *J* = 20.5 Hz, *J* = 18.1 Hz, *J* = 16.1 Hz, 1F); **IR (ν, cm^{-1}):** 3408 (br, O-H), 2975 (w, C≡N), 1463 (w, C-C_{Ar}), 1060 (s, C-O), 1057 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{11}FNNaO]^+$ $(M+Na)^+$ calc. 214.0639, found 214.0642.

Syn isomer: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 2.36 (dd, *J* = 11.7 Hz, *J* = 3.5 Hz, 1H, O*H*), 3.00 (d, *J* = 21.8 Hz, *J* = 17.0 Hz, 1H), 3.14 (dd, *J* = 16.7 Hz, *J* = 11.0 Hz, 1H), 3.24 (dd, *J* = 33.4 Hz, *J* = 17.0 Hz, 1H), 3.42 (dd, *J* = 19.8 Hz, *J* = 17.0 Hz, 1H), 5.04 (dd, *J* = 16.4 Hz, *J* = 11.7 Hz, 1H), 7.25-7.29 (m, 1H), 7.32-7.35 (m, 2H), 7.45-7.47 (m, 1H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 24.2 (d, *J* = 30.5 Hz), 40.1 (d, *J* = 22.9 Hz), 78.6 (d, *J* = 18.1 Hz), 100.6 (d, *J* = 187.9 Hz), 115.5 (d, *J* = 8.6 Hz), 124.5, 125.2, 128.0, 129.3, 136.6, 140.8; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -167.6 (dddddd, *J* = 40.2 Hz, *J* = 22.1 Hz, *J* = 20.1 Hz, *J* = 16.6 Hz, *J* = 11.2 Hz, *J* = 4.0 Hz, 1F); **IR (ν, cm^{-1}):** 3420 (br, O-H), 2975 (w, C≡N), 1463 (w, C-C_{Ar}), 1060 (m, C-O), 1057 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{11}H_{10}FNNaO]^+$ $(M+Na)^+$ calc. 214.0639, found 214.0643.

2-(2-Fluoro-1-methoxy-2,3-dihydro-1H-inden-2-yl)acetonitrile (63)



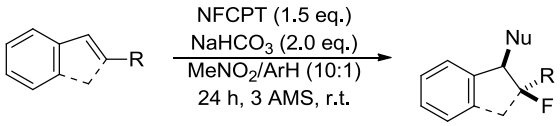
To a solution of 2-(1*H*-inden-2-yl)acetonitrile (50 mg, 0.32 mmol) in acetonitrile/methanol 9:1 (2 mL) at room temperature was added $NaHCO_3$ (54 mg, 0.64 mmol) followed by Selectfluor (171 mg, 0.48 mmol). The reaction was stirred for 12 hours before being poured onto water (5 mL), extracted into DCM (3 x 10 mL), drying over $MgSO_4$ and evaporated under removed pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a white solid (20 mg, 0.097 mmol, 30 % yield, d.r. 1:1 syn:anti).

Anti isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.91 (d, *J* = 1.9 Hz, 1H), 2.94 (s, 1H), 3.16 (t, *J* = 16.7 Hz, 1H), 3.50 (dd, *J* = 17.8 Hz, *J* = 16.7 Hz, 1H), 3.67 (d, *J* = 0.6 Hz, 3H), 4.65 (d, *J* = 9.1 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 7.3 Hz, *J* = 1.3 Hz, 1H), 7.35 (td, *J* = 7.6 Hz, *J* = 1.3 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.0 (d, *J* = 28.6 Hz), 40.7 (d, *J* = 23.8 Hz), 58.9 (d, *J* = 1.9 Hz), 85.6 (d, *J* = 16.2 Hz), 99.5 (d, *J* = 199.3 Hz), 115.6 (d, *J* = 5.7 Hz), 125.4, 125.7, 127.7, 129.7, 137.7 (d, *J* = 3.8 Hz), 138.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -166.5 (ttd, *J* = 18.0 Hz, *J* = 18.0 Hz, *J* = 9.2 Hz, 1F); **IR (ν, cm^{-1}):** 2936 (w, C≡N), 1463 (w, C-C_{Ar}), 1094 (s, C-O), 1060 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{12}H_{12}FNNaO]^+$ $(M+Na)^+$ calc. 228.0795, found 228.0786.

Syn isomer: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 2.86 (dd, *J* = 24.6 Hz, *J* = 17.1 Hz, 1H), 3.02 (dd, *J* = 18.9 Hz, *J* = 17.1 Hz, 1H), 3.28 (d, *J* = 3.4 Hz, 1H), 3.32 (d, *J* =4.1 Hz, 1H), 3.55 (s, 3H), 4.76 (d, *J* = 15.1 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.35 (td, *J* = 7.3 Hz, *J* = 0.9 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.2 (d, *J* = 24.0 Hz), 40.9 (d, *J* = 23.6 Hz), 57.8, 87.2 (d, *J* = 28.7 Hz), 102.7 (d, *J* = 189.6 Hz), 116.4 (d, *J* = 2.2 Hz), 125.4, 125.7, 127.4, 129.6, 138.6 (d, *J* = 2.0 Hz), *J* = 138.6 (d, *J* = 3.1 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -151.8 (dddt, *J* = 24.6 Hz, *J* = 19.9 Hz, *J* = 19.8 Hz, *J* = 15.2 Hz, 1F); **IR (ν, cm^{-1}):** 2940 (w, C≡N),

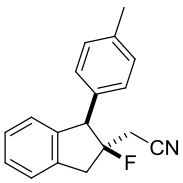
1464 (w, C-C_{Ar}), 1093 (s, C-O), 1048 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{12}H_{12}FNNaO]^+$ $(M+Na)^+$ calc. 228.0795, found 228.0789.

6.3.2 General procedure for fluoro-arylation



A solution of $MeNO_2$:arene (*v*/*v*, 9:1, 5 mL) was prepared and 10 activated 3Å molecular sieves were added. This was then left to stir for 12 h. To the solution, the substrate (50 mg, 1.0 eq.) was added, followed by sodium bicarbonate (3.0 eq.) and then NFCPT (1.5 eq.) and the reaction was stirred for 24 h at room temperature. The crude reaction mixture was filtered through a pad of Celite and then evaporated under reduced pressure. Purification was performed by flash chromatography on silica gel.

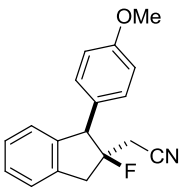
2-(2-Fluoro-1-(*p*-tolyl)-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (64)



Prepared according to the general procedure using 2-(1*H*-inden-2-yl)acetonitrile as the indene and with toluene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 20:1) afforded the title compound as a clear crystal (67 mg, 0.25 mmol, 78 % yield, d.r. 11:1 syn:anti, *p:o* >20:1). Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.41 (s, 3H), 2.88 (dd, *J* = 36.3 Hz, *J* = 17.1 Hz, 1H), 2.91 (dd, *J* = 27.8 Hz, *J* = 17.1 Hz, 1H), 3.46 (dd, *J* = 52.7 Hz, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 17.8 Hz, 1H), 4.44 (d, *J* = 26.7 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 7.1 Hz, *J* = 1.0, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.2, 25.2 (d, *J* = 32.7 Hz), 42.8 (d, *J* = 24.2

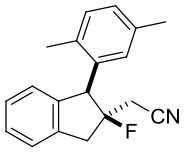
Hz), 58.6 (d, *J* = 19.8 Hz), 101.6 (d, *J* = 193.2 Hz), 116.1 (d, *J* = 10.5 Hz), 124.8, 125.2, 127.5, 127.8, 129.3, 130.3 (d, *J* = 1.1 Hz), 131.9 (d, *J* = 3.2), 137.8, 138.9, 142.6; **^{19}F NMR (376.6 (MHz, $CDCl_3$):** δ = -156.9 (ddddd, *J* = 32.1 Hz, *J* = 26.5 Hz, *J* = 22.7 Hz, *J* = 18.3 Hz, *J* = 9.9 Hz, 1F); **IR (ν, cm^{-1}):** 2361 (m, C≡N), 1460 (m, C=C_{Ar}), 1050 (s, C-F); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{16}FNNa]^+$ $(M+Na)^+$ calc. 288.1159, found 288.1151; **mp:** 93-95°C.

2-(2-Fluoro-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (65)



Prepared according to the general procedure using 2-(1*H*-inden-2-yl)acetonitrile as the indene and with anisole as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 20:1) afforded the title compound as a yellow oil (73 mg, 0.26 mmol, 81 % yield, d.r. 10:1 syn:anti, *p:o* 5:1). Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.88 (dd, *J* = 37.8 Hz, *J* = 16.8 Hz 1H), 2.90 (dd, *J* = 28.8 Hz, *J* = 16.8 Hz, 1H), 3.39–3.60 (m, 2H), 3.85 (s, 3H), 4.41 (d, *J* = 26.6 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.18 (dd, *J* = 8.7 Hz, *J* = 1.1, 2H), 7.21–7.39 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.2 (d, *J* = 32.6 Hz), 42.7 (d, *J* = 24.2 Hz), 55.3, 58.2 (d, *J* = 19.8 Hz), 101.7 (d, *J* = 192.7 Hz), 114.0, 116.1 (d, *J* = 10.6 Hz), 124.8, 125.2, 126.9 (d, *J* = 3.2 Hz), 127.5, 127.8, 131.5 (d, *J* = 1.1 Hz), 138.8, 142.8, 159.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -157.1 (ddddd, *J* = 32.7 Hz, *J* = 26.3 Hz, *J* = 21.6 Hz, *J* = 18.4 Hz, *J* = 9.1 Hz, 1F); **IR (ν, cm^{-1}):** 2361 (m, C≡N), 1461 (m, C=C_{Ar}), 1109 (m, C-F), 1033 (m, C-O); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{16}FNNaO]^+$ $(M+Na)^+$ calc. 304.1108, found 304.1102.

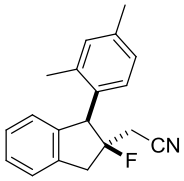
2-(1-(2,5-Dimethylphenyl)-2-fluoro-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (66)



Prepared according to the general procedure using 2-(1*H*-inden-2-yl)acetonitrile as the indene and with *p*-xylene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 20:1) afforded the title compound as a pale yellow oil (69 mg, 0.25 mmol, 77 % yield, d.r. 10:1 syn:anti).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.25 (s, 3H), 2.47 (s, 3H), 2.89 (dd, *J* = 31.8 Hz, *J* = 16.9 Hz, 1H), 2.92 (dd, *J* = 28.2 Hz, *J* = 16.9 Hz, 1H), 3.35-3.60 (m, 2H), 4.77 (d, *J* = 26.5 Hz, 1H), 6.81 (s, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.9, 21.0, 26.0 (d, *J* = 32.1 Hz), 42.8 (d, *J* = 24.1 Hz), 53.7 (d, *J* = 19.7 Hz), 102.0 (d, *J* = 195.2 Hz), 116.1 (d, *J* = 9.2 Hz), 124.7, 125.3, 127.7, 128.6, 130.3, 131.3 (d, *J* = 4.1 Hz), 133.5, 134.2, 135.5, 138.8, 142.8, 143.4; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.5 (m, 1F); **IR (ν, cm^{-1}):** 2341 (m, C≡N), 1460 (m, C=C_{Ar}), 1049 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{19}H_{18}FNNa]^+$ $(M+Na)^+$ calc. 302.1315, found 302.1311.

2-(1-(2,4-Dimethylphenyl)-2-fluoro-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (67)

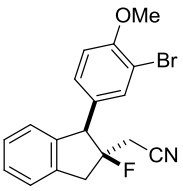


Prepared according to the general procedure using 2-(1*H*-inden-2-yl)acetonitrile as the indene and with *m*-xylene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 20:1 increasing to 10:1 after two column volumes) afforded the title compound as a yellow oil (65 mg, 0.23 mmol, 72 % yield, d.r. >20:1 syn:anti, *p:o* >20:1).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.35 (s, 3H), 2.52 (s, 3H), 2.89 (dd, *J* = 34.9 Hz, *J* = 16.9 Hz, 1H), 2.92 (dd, *J* = 28.9 Hz, *J* = 16.9 Hz, 1H), 3.44 (dd, *J* = 37.4 Hz, *J* = 16.8 Hz, 1H), 3.48 (dd, *J* = 29.8 Hz, *J* = 16.7 Hz, 1H), 4.76 (d, *J* = 26.2 Hz, 1H), 6.90 (dd, *J* = 8.0

Hz, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 2H), 7.12 (s, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.3, 21.0, 26.0 (d, *J* = 32.1 Hz), 42.7 (d, *J* = 23.8 Hz), 53.5.6 (d, *J* = 19.6 Hz), 102.0 (d, *J* = 194.8 Hz), 116.0 (d, *J* = 9.0 Hz), 124.7, 125.3, 126.9, 127.6, 127.7, 130.6 (d, *J* = 4.2 Hz), 130.8, 131.2, 137.4, 137.5, 138.8, 143.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.6 (m, 1F); **IR (ν, cm^{-1}):** 2342 (m, C≡N), 1460 (m, C=C_{Ar}), 1049 (m, C-F); **HRMS (ESI^+, m/z):** $[C_{19}H_{18}FNNa]^+$ $(M+Na)^+$ calc. 302.1315, found 302.1313.

2-(1-(3-Bromo-4-methoxyphenyl)-2-fluoro-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (68)

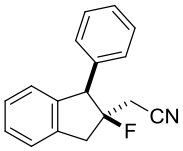


To a vial containing 5ml of $MeNO_2$, 2-bromo anisole (181mg, 0.97 mmol, 3.0 eq.) was added followed by 10 activated 3Å molecular sieves. The mixture was left to stir for 12 hours. 2-(1*H*-Inden-2-yl)acetonitrile (50 mg, 0.32 mmol, 1.0 eq.) was then added followed by $NaHCO_3$ (81 mg, 0.97 mmol, 3.0 eq.). Once dissolved, 2,6-dichloro-1-fluoropyridinium tetrafluoroborate (153 mg, 0.4 8mmol, 1.5 eq.) was added and the reaction left to stir for 24 h. The reaction was then filtered through a celite filter to remove the base and molecular sieves. The crude reaction mixture was evaporated under reduced pressure and the crude residue purified by flash column chromatography (SiO_2, petroleum ether/ EtOAc 5:1) afforded the title compound as a yellow oil (49 mg, 0.14 mmol, 42 % yield, d.r. >20:1 syn:anti, *p:o* >20:1).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.87 (dd, *J* = 39.8 Hz, *J* = 16.9 Hz 1H), 2.91 (dd, *J* = 26.3 Hz, *J* = 16.8 Hz, 1H), 3.44 (dd, *J* = 54.1 Hz, *J* = 16.8 Hz, 1H), 3.45 (d, *J* = 16.6 Hz, 1H), 3.93 (s, 3H) 4.38 (d, *J* = 26.0 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 7.17 (dt, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H), 7.26 (t, *J* =7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 6.5 Hz, 1H), 7.43 (t, *J* = 1.52 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** 25.3 (d, *J* = 32.7 Hz),

42.7 (d, *J* = 24.3 Hz), 56.3, 57.8 (d, *J* = 19.8 Hz), 101.6 (d, *J* = 193.4 Hz), 111.7, 111.8, 115.8, 124.9, 125.1, 127.7, 128.1, 128.6 (d, *J* = 3.2 Hz), 130.6 (d, *J* = 1.2 Hz), 135.0 (d, *J* = 1.5 Hz), 138.7, 142.2, 155.7; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.7 (ddddd, *J* = 31.9 Hz, *J* = 26.1 Hz, *J* = 21.8 Hz, *J* = 18.4 Hz, *J* = 9.8 Hz, 1F); **IR (ν, cm^{-1}):** 2341 (s, C≡N), 1498 (s, C=C_{Ar}), 1461 (w, C=C_{Ar}), 1054 (m, C-F), 1020 (m, C-O), 745 (m C-Br); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{15}BrFNNaO]^+$ $(M+Na)^+$ calc. 382.0213, found 384.0188.

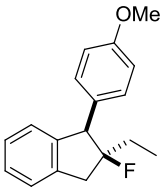
2-(2-Fluoro-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (69)



Prepared according to the general procedure using 2-(1*H*-inden-2-yl)acetonitrile as the indene and with benzene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 20:1 increasing to 10:1 after two column volumes) afforded the title compound as a yellow oil (13 mg, 0.052 mmol, 16 % yield, d.r. >20:1 syn:anti).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.90 (dd, *J* = 41.9 Hz, *J* = 16.9 Hz, 1H), 2.91 (dd, *J* = 33.2 Hz, *J* = 16.9 Hz, 1H), 3.44 (dd, *J* = 27.4 Hz, *J* = 17.0 Hz, 1H), 3.50 (dd, *J* = 18.5 Hz, *J* = 17.0 1H), 4.46 (d, *J* = 26.4 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 7.24-7.27 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.38-7.42 (m, 3H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.2 (d, *J* = 32.7 Hz), 42.7 (d, *J* = 24.0 Hz), 58.9 (d, *J* = 19.9 Hz), 101.6 (d, *J* = 193.1 Hz), 116.0 (d, *J* = 11.5 Hz), 124.8, 125.2, 127.5, 127.9, 128.0, 128.5, 130.4 (d, *J* = 1.3 Hz), 135.0 (d, *J* = 3.1 Hz), 138.8, 142.4; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -156.9 (ddddd, *J* = 31.9 Hz, *J* = 26.2 Hz, *J* = 22.9 Hz, *J* = 18.8 Hz, *J* = 9.2 Hz, 1F); **IR (ν, cm^{-1}):** 2361 (m, C≡N), 1455 (m, C=C_{Ar}), 1049 (m, C-F); **HRMS (FI$^+$):** $[C_{17}H_{14}NF]$ calc. 251.1110, found 251.1107.

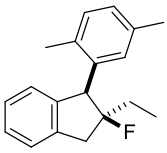
2-Ethyl-2-fluoro-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene (71)



Prepared according to the general procedure using 2-ethyl-1*H*-indene as the indene and with anisole as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ toluene: 4:1) afforded the title compound as a yellow oil (43 mg, 0.16 mmol, 46 % yield, d.r. >20:1 syn:anti, *p:o* 5:1).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.08 (td, *J* = 7.3 Hz, *J* = 0.9 Hz, 3H), 1.74-1.88 (m, 1H), 1.92-2.04 (m, 1H), 3.15 (dd, *J* = 35.1 Hz, *J* = 16.7 Hz, 1H), 3.31 (dd, *J* = 20.9 Hz, *J* = 16.8 Hz, 1H), 3.85 (s, 3H), 4.25 (d, *J* = 27.7 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 8.7 (d, *J* = 5.6 Hz), 29.1 (d, *J* = 24.7 Hz), 42.2 (d, *J* = 25.5 Hz), 55.2, 59.0 (d, *J* = 20.6 Hz), 106.9 (d, *J* = 185.0 Hz), 113.5, 124.7, 125.1, 126.8, 127.1, 129.3 (d, *J* = 3.4 Hz), 131.6 (d, *J* = 1.2 Hz), 140.5, 144.5, 158.8; **^{19}F (NMR 376.6 MHz, $CDCl_3$):** δ = -162.4 (m, 1F); **IR (v, cm^{-1}):** 1512 (s, C=C_{Ar}), 1460 (w, C=C_{Ar}), 1036 (m, C-F), 975 (w, C-O); **HRMS (ESI$^+$, m/z):** $[C_{18}H_{19}FNaO]^+$ $(M+Na)^+$ calc. 293.1312, found 293.1310.

1-(2,5-Dimethylphenyl)-2-ethyl-2-fluoro-2,3-dihydro-1*H*-indene (72)

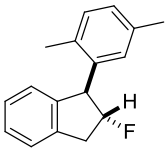


Prepared according to the general procedure using 2-ethyl-1*H*-indene as the indene and with *p*-xylene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 99:1) afforded the title compound as a yellow oil (32 mg, 0.12 mmol, 34 % yield, d.r. >20:1 syn:anti).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.06 (t, *J* = 7.34 Hz, 3H), 1.76-2.00 (m, 2H), 2.24 (s, 3H), 2.42 (s, 3H), 3.15 (dd, *J* = 33.0 Hz, *J* = 16.8 Hz, 1H), 3.30 (dd, *J* = 20.5 Hz, *J* = 16.8 Hz, 1H), 4.60 (d, *J* = 26.3 Hz, 1H), 6.88 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.02

(d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 8.5 (d, *J* = 4.8 Hz), 20.0, 21.1, 30.0 (d, *J* = 24.4 Hz), 42.2 (d, *J* = 25.3 Hz), 54.5 (d, *J* = 20.6 Hz), 107.0 (d, *J* = 187.9 Hz), 124.5, 125.1, 126.9, 127.8, 129.8, 131.6 (d, *J* = 4.7 Hz), 134.1, 135.0, 135.6 (d, *J* = 1.7 Hz), 140.6, 142.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -163.2 (m, 1F); **IR (ν, cm^{1}):** 1504 (s, C=C_{Ar}), 1460 (s, C=C_{Ar}), 1087 (w, C-F); **HRMS (ESI$^+$, m/z):** $[C_{19}H_{21}FNa]^+$ $(M+Na)^+$ calc. 291.1519, found 259.1515.

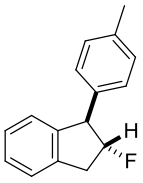
1-(2,5-Dimethylphenyl)-2-fluoro-2,3-dihydro-1*H*-indene (73)



Prepared according to the general procedure using indene and with *p*-xylene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 99:1) afforded the title compound as a yellow oil (37 mg, 0.15 mmol, 36 % yield, d.r. 3.5:1 anti:syn).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.28 (s, 3H), 2.45 (s, 3H), 3.33 (dd, *J* = 34.5 Hz, *J* = 4.3 Hz, 1H), 3.35 (d, *J* = 24.7 Hz, 1H), 4.73 (dd, *J* = 29.7 Hz, *J* = 4.7 Hz, 1H), 5.46 (dtd, *J* = 53.3 Hz, *J* = 4.4 Hz, *J* = 1.1 Hz, 1H), 6.95 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.25-7.34 (m, 2H), 7.39 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.6, 21.1, 38.6 (d, *J* = 22.6 Hz), 39.7 (d, *J* = 23.5 Hz), 94.9 (d, *J* = 185.9 Hz), 124.9, 125.5, 127.0, 127.1, 127.9, 130.0, 130.8, 133.7, 134.9 (d, *J* = 4.0 Hz), 135.1, 140.6, 143.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -186.3 (m, 1F); **IR (ν, cm^{-1}):** 1504 (m, C=C_{Ar}), 1458 (m, C=C_{Ar}), 1039 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{17}H_{17}FNa]^+$ $(M+Na)^+$ calc. 263.1206, found 263.1205.

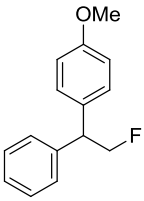
2-Fluoro-1-(*p*-tolyl)-2,3-dihydro-1*H*-indene (74)



Prepared according to the general procedure using indene and with toluene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 99:1) afforded the title compound as a yellow oil (39 mg, 0.17 mmol, 40 % yield, d.r. 5:1 anti:syn, *p:o* 7:1).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.41 (s, 3H), 3.20-3.42 (m, 2H), 4.45 (dd, *J* = 30.1 Hz, *J* = 4.4 Hz, 1H), 5.39 (dddd, *J* = 53.3 Hz, *J* = 4.7 Hz, *J* = 3.0 Hz, *J* = 1.8 Hz, 1H), 7.07-7.43 (m, 8H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.2, 39.6 (d, *J* = 23.0 Hz), 56.2 (d, *J* = 19.8 Hz), 96.6 (d, *J* = 185.4 Hz), 124.9, 125.2, 127.0, 127.2, 129.0, 130.1, 134.1 (d, *J* = 4.4 Hz), 136.9, 140.7, 143.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -187.8 (dddd, *J* = 53.0 Hz, *J* = 34.6 Hz, *J* = 30.4 Hz, *J* = 25.3 Hz, 1F); **IR (ν, cm^{-1}):** 1459 (w, C=C_{Ar}), 1038 (m, C-F); **HRMS (ESI$^+$, m/z):** $[C_{16}H_{15}FNa]^+$ $(M+Na)^+$ calc. 249.1050, found 249.1052.

1-(2-Fluoro-1-phenylethyl)-4-methoxybenzene (76)

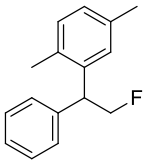


Prepared according to the general procedure using styrene and with anisole as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 99:1) afforded the title compound as a clear oil (26 mg, 0.11 mmol, 23 % yield, *p:o* >20:1).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 3.80 (s, 3H), 4.37 (dt, *J* = 16.6 Hz, *J* = 7.0 Hz, 1H), 4.90 (ddd, *J* = 47.2 Hz, *J* = 7.0 Hz, *J* = 2.2 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.23-7.27 (m, 1H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 50.4 (d, *J* = 19.3 Hz), 55.2, 85.4 (d, *J* = 174.8 Hz), 114.0, 126.8, 128.2, 128.6, 129.3, 132.4 (d, *J* = 5.4 Hz), 140.6 (d, *J* = 4.8 Hz), 158.5; **^{19}F NMR (376.6 MHz,**

$CDCl_3$): δ = -214.4 (m, 1F); **IR (ν, cm^{-1}):** 1512 (m, C=C_{Ar}), 1034 (m, C-F), 1019 (w, C-O); **HRMS (FI^+):** [$C_{15}H_{15}FO$] calc. 230.1107, found 230.1114.

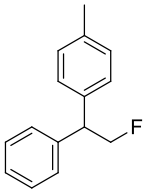
2-(2-Fluoro-1-phenylethyl)-1,4-dimethylbenzene (77)



Prepared according to the general procedure using styrene and with *p*-xylene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ toluene 4:1) afforded the title compound as a clear oil (51 mg, 0.22 mmol, 47 % yield).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.22 (s, 3H), 2.34 (s, 3H), 4.55 (dt, *J* = 16.0 Hz, *J* = 7.1 Hz, 1H), 4.91 (dd, *J* = 47.2 Hz, *J* = 6.9 Hz, 2H), 7.00 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 7.21-7.26 (m, 3H), 7.28-7.34 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.3, 21.2, 47.4 (d, *J* = 19.6 Hz), 85.2 (d, *J* = 175.2 Hz), 126.8, 127.6, 127.7, 128.5, 128.6, 130.7, 133.5, 135.5, 137.9 (d, *J* = 4.3 Hz), 140.0; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -213.6 (td, *J* = 47.3 Hz, *J* = 16.3 Hz, 1F); **IR (ν, cm^{-1}):** 1497 (m, C=C_{Ar}), 1452 (m, C=C_{Ar}), 1060 (w, C-F); **HRMS (FI^+):** [$C_{16}H_{17}F$] calc. 228.1314, found 228.1311.

1-(2-Fluoro-1-phenylethyl)-4-methylbenzene (78)

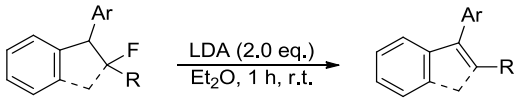


Prepared according to the general procedure using styrene and with toluene as the arene. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 99:1) afforded the title compound as a yellow oil (53 mg, 0.25 mmol, 52 % yield, *p:o* 6.2:1).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.36 (s, 3H), 4.41 (dt, *J* = 16.4 Hz, *J* = 6.9 Hz, 1H), 4.94 (dd, *J* = 47.1 Hz, *J* =6.9 Hz, 2H), 7.15-7.39 (m, 9H); **^{13}C NMR (100.6**

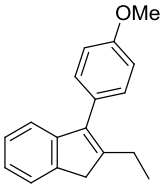
MHz, $CDCl_3$): δ = 21.0, 50.9 (d, *J* = 19.6 Hz), 85.4 (d, *J* = 174.9 Hz), 126.9, 128.2, 128.3, 128.6, 129.4, 136.6, 137.3 (d, *J* = 5.1 Hz), 140.5 (d, *J* = 4.7 Hz); **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -214.4 (td, *J* = 47.3 Hz, *J* = 16.6 Hz, 1F); **IR (ν, cm^{-1}):** 1495 (m, C=C_{Ar}), 1453 (m, C=C_{Ar}), 1012 (s, C-F); **HRMS (FI^+):** [$C_{15}H_{15}F$] calc. 214.1158, found 214.1156.

6.3.3 General procedure for dehydrofluorination



To a solution of substrate (30 mg, 1.0 eq.) in Et_2O (5 mL) was added LDA (2.0 M solution in THF/ heptane/ ethylbenzene, 2.0 eq.) and the reaction was stirred for 1 h at room temperature before being poured onto water (10 mL), extracted into Et_2O (3 x 10 mL) and then dried over $MgSO_4$. The solution was evaporated under reduced pressure and then purification was performed by flash chromatography on silica gel.

2-Ethyl-3-(4-methoxyphenyl)-1*H*-indene (80)

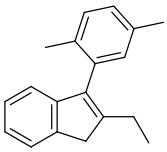


Prepared according to the general procedure using 2-ethyl-2-fluoro-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether / Et_2O 50:1) afforded the title compound as clear liquid (0.084 mmol, 60 % yield).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.19 (t, *J* = 7.7 Hz, 3H,), 2.54 (q, *J* = 7.7 Hz, 2H), 3.48 (s, 2H), 3.88 (s, 3H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.17 (td, *J* = 6.9 Hz, *J* = 1.7 Hz, 1H), 7.20-7.26 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.7, 22.1, 39.9, 55.3, 113.8, 119.4, 125.5, 123.9, 126.1, 127.9, 130.2, 137.6,

142.5, 146.2, 146.6, 158.6; **IR (ν, cm^{-1}):** 1510 (s, C=C_{Ar}), 1462 (m, C=C_{Ar}), 1034 (m, C-O); **HRMS (FI$^+$):** [$C_{18}H_{18}O$] calc. 250.1358, found 250.1353.

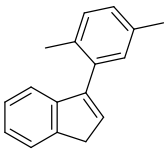
3-(2,5-Dimethylphenyl)-2-ethyl-1*H*-indene (81)



Prepared according to the general procedure using 1-(2,5-dimethylphenyl)-2-ethyl-2-fluoro-2,3-dihydro-1*H*-indene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether/ Et_2O 99:1) afforded the title compound as clear liquid (0.032 mmol, 33 % yield).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.11 (t, *J* = 7.6 Hz, 3H), 2.10 (s, 3H), 2.32-2.38 (m, 2H), 2.35 (s, 3H), 3.50 (s, 2H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.98 (s, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.17 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 7.16-7.22 (m, 2H), 7.46 (d, *J* = 7,2 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 14.2, 19.3, 19.9, 22.3, 39.7, 119.6, 123.3, 123.7, 126.1, 128.0, 129.8, 130.4, 133.8, 134.9, 135.1, 138.8, 142.3, 146.4, 146.9; **IR (ν, cm^{-1}):** 1459 (w, C=C_{Ar}); **HRMS (FI$^+$):** [$C_{19}H_{20}$] calc. 248.1565, found 248.1574.

3-(2,5-Dimethylphenyl)-1*H*-indene (82)

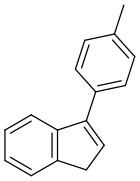


Prepared according to the general procedure using 1-(2,5-dimethylphenyl)-2-fluoro-2,3-dihydro-1*H*-indene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether/ Et_2O 50:1) afforded the title compound as a clear liquid (0.15 mmol, 82 % yield).

Data for major diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.26 (s, 3H), 2.40 (s, 3H), 3.58 (d, *J* = 1.2 Hz, 2H), 6.46 (t, *J* = 1.2 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.19 (d, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.26-7.34 (m, 2H), 7.58 (d, *J* = 6.9 Hz, 1H); **^{13}C NMR (100.6**

MHz, $CDCl_3$): δ = 18.7, 19.9, 37.3, 119.5, 122.8, 123.6, 125.1, 127.2, 129.0, 129.1, 130.3, 132.2, 134.0, 134.6, 142.9, 144.1, 144.3; **IR (ν, cm^{-1}):** 2963 (m, $C=H_{Alkene}$), 1457 (m, $C=C_{Ar}$); **HRMS (FI^+):** [$C_{17}H_{16}$] calc. 220.1252, found 220.1256.

3-(*p*-Tolyl)-1*H*-indene (83)

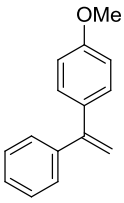


Prepared according to the general procedure using 2-fluoro-1-(*p*-tolyl)-2,3-dihydro-1*H*-indene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether/ Et_2O 99:1) afforded the title compound as clear liquid (0.24 mmol, 99 % yield, *p:o* 4:1).

Data for major isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.47 (s, 3H), 3.55 (d, *J* = 2.1 Hz, 2H), 6.61 (t, *J* = 2.2 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.28-7.35 (m, 1H), 7.38 (t, *J* = 7.1 Hz, 1H), 7.55-7.61 (m, 1H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* =7.5 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.2, 38.2, 120.4, 124.1, 124.8, 126.2, 127.6, 129.3, 130.5, 133.3, 137.3, 144.1, 144.8, 145.1.

Data consistent with literature values.[45]

1-Methoxy-4-(1-phenylvinyl)benzene (84)



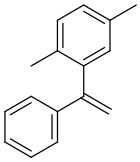
Prepared according to the general procedure using 1-(2-fluoro-1-phenylethyl)-4-methoxybenzene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether/ Et_2O 24:1) afforded the title compound as white solid (0.05 mmol, 73 % yield, *p:o* 6:1).

Data for major diastereoisomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 3.84 (s, 3H), 5.37 (d, *J* = 1.2 Hz, 1H), 5.41 (d, *J* = 1.2 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.32-7.40 (m,

5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 55.2, 112.9, 113.5, 127.6, 128.1, 128.3, 129.4, 134.0, 141.8, 149.5, 159.3.

Data consistent with literature values.[46]

1,4-Dimethyl-2-(1-phenylvinyl)benzene (24)

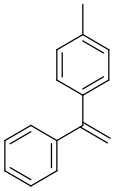


Prepared according to the general procedure using 2-(2-fluoro-1-phenylethyl)-1,4-dimethylbenzene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether/ Et_2O 99:1) afforded the title compound as clear liquid (0.10 mmol, 55 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3H), 2.36 (s, 3H), 5.20 (d, *J* = 1.1 Hz, 1H), 5.77 (d, *J* = 1.1 Hz, 1H), 7.05-7.11 (m, 3H), 7.26-7.37 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.6, 20.9, 114.7, 126.5, 127.5, 128.2, 128.3, 130.0, 130.7, 132.9, 135.0, 140.7, 141.4, 149.5.

Data consistent with literature values.[47]

1-Methyl-4-(1-phenylvinyl)benzene (25)



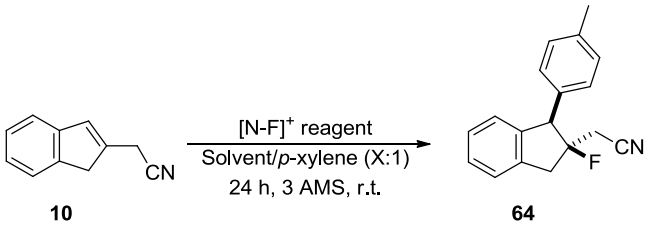
Prepared according to the general procedure using 1-(2-fluoro-1-phenylethyl)-4-methylbenzene as the substrate. Purification by flash chromatography (SiO_2, petroleum ether/ Et_2O 99:1) afforded the title compound as colourless oil (0.11 mmol, 73 % yield, *p:o* >20:1).

Data for major diastereoisomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.39 (s, 3H), 5.43 (d, *J* = 1.3 Hz, 1H), 5.46 (d, *J* = 1.3 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.32-7.39 (m,

5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.2, 113.6, 127.6, 128.1, 128.3, 128.9, 137.5, 138.6, 141.7, 149.9.

Data consistent with literature values.[48]

6.3.4 Optimisation Table 4



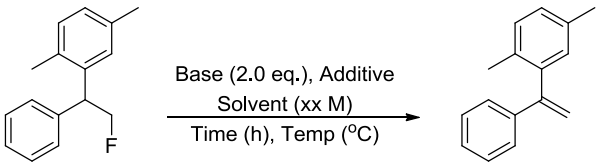
10 **64**

Entry	[N-F]$^+$ reagent (eq.) [a]	Solvent	Ratio[b]	Additive (eq.)	Temp. (°C)	Yield (%)[c]	d.r.[f]
1	Selectfluor (1.1)	$MeNO_2$	4:1	None	r.t.	40	>20:1
2	Selectfluor (1.1)	$MeNO_2$	4:1	$NaHCO_3$ (2.0)	r.t.	42	>20:1
3	NFCPT (1.1)	$MeNO_2$	4:1	$NaHCO_3$ (2.0)	r.t.	78	>20:1
4	NFCPT (1.1)	THF	4:1	$NaHCO_3$ (2.0)	r.t.	<5[d]	ND
5	NFCPT (1.1)	Dioxane	4:1	$NaHCO_3$ (2.0)	r.t.	9[d]	ND
6	Selectfluor (1.1)	DMF	4:1	$NaHCO_3$ (2.0)	r.t.	<5[d]	ND
7	NFCPT (1.1)	EtOAc	4:1	$NaHCO_3$ (2.0)	r.t.	<5[d]	ND
8	NFCPT (1.1)	Et_2O	4:1	$NaHCO_3$ (2.0)	r.t.	<5[d]	ND
9	NFCPT (1.1)	DCM	4:1	$NaHCO_3$ (2.0)	r.t.	52	>20:1
10	NFCPT (1.1)	DCE	4:1	$NaHCO_3$ (2.0)	r.t.	52	>20:1
11	NFCPT (1.1)	*p*-xylene	-	$NaHCO_3$ (2.0)	r.t.	<5[d]	ND
12	Selectfluor (1.1)	MeCN	4:1	$NaHCO_3$ (2.0)	r.t.	8[e]	ND
13	NFCPT (1.1)	$MeNO_2$	4:1	$NaHCO_3$ (2.0)	50	64	>20:1
14	NFCPT (1.1)	DCE	4:1	$NaHCO_3$ (2.0)	50	47	>20:1
15	NFCPT (1.1)	$MeNO_2$	1:1	$NaHCO_3$ (2.0)	r.t.	61	>20:1
16	NFCPT (1.1)	$MeNO_2$	2:1	$NaHCO_3$ (2.0)	r.t.	71	>20:1
17	NFCPT (1.1)	$MeNO_2$	10:1	$NaHCO_3$ (2.0)	r.t.	81	>20:1
18	NFCPT (1.1)	$MeNO_2$	20:1	$NaHCO_3$ (2.0)	r.t.	78	>20:1
19	**NFCPT (1.5)**	**$MeNO_2$**	**10:1**	**$NaHCO_3$ (2.0)**	**r.t.**	**82**	**>20:1**
20	NFCPT (1.5)	$MeNO_2$	10:1	K_2CO_3 (2.0)	r.t.	57	>20:1

Table 1 - Optimisation of the fluorination of Indene 1; *a) NFCPT = N-Fluoro-2,6-dichloropyridinium triflate, b) Ratio of solvent to p-xylene, c) NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra, d) Significant amount of starting material observed, e) Significant amount of fluoro-Ritter and fluoro-hydrin product observed, f) Determined by ^{19}F NMR, ND = not determined.*

A solution of solvent (*v*/*v*, 5 mL) was prepared and 10 activated 3Å molecular sieves were added. This was then left to stir for 12 h. To the solution, indene **10** (50 mg, 1.0 eq.) was added, followed by sodium bicarbonate (3.0 eq.) and then fluorinating reagent (1.5 eq.) and the reaction was stirred for 24 h at room temperature. The crude reaction mixture was filtered through a pad of Celite and then evaporated under reduced pressure. The yield and d.r. were determined by ^{1}H NMR and ^{19}F NMR using 1-fluoro-3-nitrobenzene as an internal reference.

6.3.5 Optimisation Table 11



76 **78**

Entry	Base	Additive	Solvent	Temp. (°C)	Time (h)	Yield[a]
1	TBD[b]	LiOTF	DCM-d_2	r.t.	24	<5[c]
2	TBD[b]	LiOTF	DCM-d_2	40	24	<5[c]
3	TBD[b]	LiOTF	MeCN-d_3	82	24	14[c]
4	TBD[b]	LiOTF	Toluene-d_8	110	24	8[c]
5	TBD[b]	BF_3	Toluene-d_8	110	24	0
6	**LDA**	**None**	**Et_2O**	**r.t.**	**4**	**55[d]**

Table 2 - Optimisation of the elimination step; *a) NMR yield obtained by adding 1.0 eq. m-fluoro-nitrobenzene prior to obtaining spectra, b) TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene, c) Significant amount of starting material remaining, d) Isolated yield*

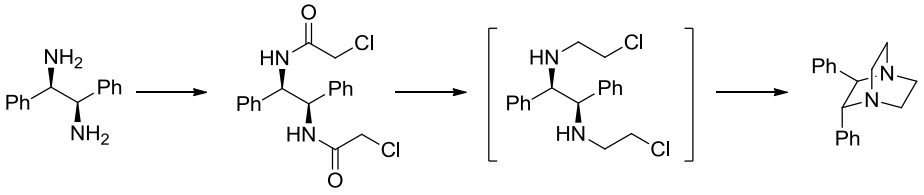
To a solution of substrate (10 mg, 1.0 eq.) in solvent (1 mL) was added base (2.0 eq.) and the reaction was stirred before being poured onto water (10 mL), extracted into Et_2O (3 x 10 mL) and then dried over $MgSO_4$. The solution was evaporated under reduced pressure and the yield was determined by ^1H NMR and ^{19}F NMR using 1-fluoro-3-nitrobenzene as an internal reference.

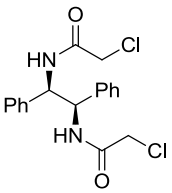
6.4 Experimental data for Chapter 4

Details for the synthesis of compounds described in Chapter 4 are provided herein. See appendices for NMR images of novel compounds as well as X-ray crystallographic data.

6.4.1 Synthesis of chiral DABCOs

(2*R*,3*R*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (109)

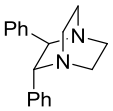




To a solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (1.0 eq) in DCM (40 mL) at 0 °C was added Et_3N (5.0 eq.), DMAP (3 mol %) and chloroacetyl chloride (5.0 eq.) The reaction was stirred at room temperature for 3 hours before quenching with water (15 mL) and acidifying with 1M HCl. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic phases dried over $MgSO_4$ and evaporated under reduced pressure. Purification by trituation with acetonitrile afforded *N*,*N'*-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (1.69 g, 98 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.06 (s, 4H), 5.17-5.19 (m, 2H), 7.14-7.20 (m, 10H), 9.01-9.03 (m, 2H, N*H*); **^{13}C NMR (100.6 MHz, DMSO-d_6):** δ = 46.4, 58.3, 128.0, 128.3, 128.8, 140.5, 166.4.

Data consistent with literature values.[49]



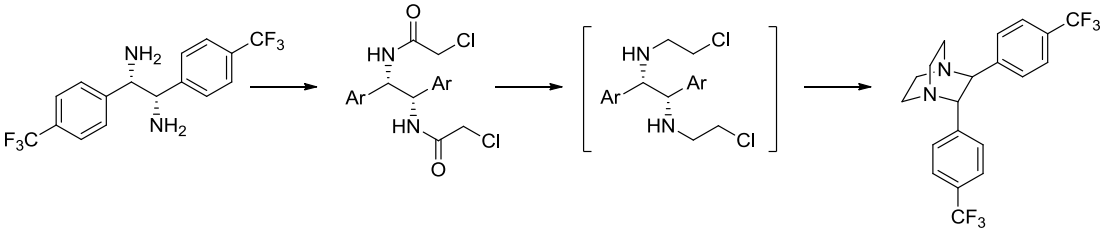
To a solution of *N*,*N*′-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(2-chloroacetamide) (1.0 eq) in THF (0.1 M) at 0 °C was added BH_3•THF (1M solution in THF, 4.0 eq) and the reaction was heated at reflux for 12 hours before cooling to 0 °C and quenching with methanol. The mixture was concentrated *in vacuo* and acidified with 1 M HCl. The aqueous phase was washed with ether and the organic layer discarded. Following the addition of 3 M NaOH to achieve pH14, the diamine was extracted into EtOAc and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The intermediate was used directly in the next step without further purification.

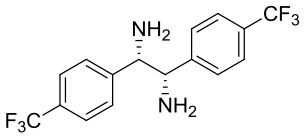
A solution of diamine in DMF (0.2 M) was heated at reflux for 5 hours before cooling to room temperature and concentrating *in vacuo*. The crude mixture was dissolved in water, and basified with 3 M NaOH. The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 97:3) afforded (2*R*,3*R*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane as a pale yellow solid (1.45 g, 65 % yield *over 2 steps*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59-2.64 (m, 2H), 2.76-2.83 (m, 2H), 2.99-3.04 (m, 4H), 4.18 (s, 2H), 7.27-7.48 (m, 10H, ArH); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 41.1, 49.5, 62.4, 127.1, 127.7, 128.4, 141.2; **mp:** 74-76 °C; **$[\alpha]^{22}_D$** -93.9 (*c* 0.50, MeOH).

Data consistent with literature values.[49]

(2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane (110)

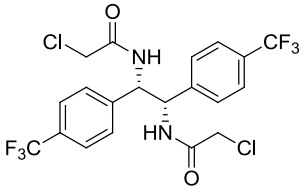




To a solution of (1*R*,2*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (2.20 g, 10.0 mmol) in DMSO (50 mL) was added aryl aldehyde (24.0 mmol). The resulting mixture was stirred overnight at room temperature before being poured onto water (150 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. To the resultant diimine intermediate in THF (100 mL) was added 37 % HCl (3.0 mL) and the reaction was stirred for 3 hours to obtain a precipitate. The solid was filtered and washed with THF to afford analytically pure dihydrochloride salt. To the salt was added ethyl acetate, saturated aqueous $NaHCO_3$ solution and some NaOH (3M) and the two layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried and evaporated under recduced pressure to afford the product as a white solid (97 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (brs, 4H, NH_2), 4.17 (s, 2H), 7.39 (d, *J* = 8.1 Hz, 4H), 7.56 (d, *J* = 8.1 Hz, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 61.6, 121.9 (q, *J* = 271.8 Hz, CF_3), 125.3 (q, *J* = 3.2 Hz), 127.3, 129.5 (q, *J* = 32.4 Hz), 147.1; **^{19}F{1H} NMR (376.6 MHz, CDCl3):** δ = -63.1; **$[\alpha]^{25}_D$** -34.5 (c 0.06, MeOH).

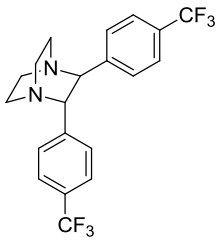
Data consistent with literature values.[50]



To a solution of diamine (1.0 eq) in DCM (40 mL) at 0 °C was added Et_3N (5.0 eq.), DMAP (3 mol %) and chloroacetyl chloride

(5.0 eq.) The reaction was stirred at room temperature for 3 hours before quenching with water (15 mL) and acidifying with 1M HCl. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic phases dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtAOc/PE 1:1) afforded *N,N'*-((1*S*,2*S*)-1,2-bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (420 mg, 34 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.06 (d, *J* = 13.1 Hz, 2H), 4.09 (d, *J* = 13.1 Hz, 2H), 5.36-5.41 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 4H), 7.61 (d, *J* = 8.1 Hz, 4H), 9.00-9.06 (m, 2H, N*H*); **^{13}C NMR (100.6 MHz, DMSO-d_6):** δ = 42.5, 56.6, 124.2 (q, *J* = 271.6 Hz, CF_3), 125.0 (q, *J* = 3.7 Hz), 127.9 (q, *J* = 31.6 Hz), 128.2, 144.0, 165.8; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = -60.9 (CF_3); **IR (ν, cm^{-1}):** 3302 (NH), 1650 (NCO); **HRMS (ESI$^+$):** *m/z* calc. for $C_{20}H_{16}Cl_2F_6N_2O_2$ ([M+Na]$^+$) 523.0385, found 523.0391; **mp:** 274-278 °C; The optical rotation could not be determined due to problems with solubility.



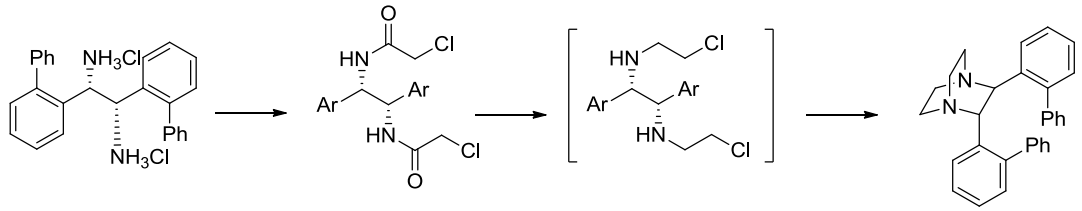
To a solution of *N,N'*-((1*S*,2*S*)-1,2-bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) (1.0 eq) in THF (0.1 M) at 0 °C was added BH_3•THF (1M solution in THF, 4.0 eq) and the reaction was heated at reflux for 12 hours before cooling to 0 °C and quenching with methanol. The mixture was concentrated *in vacuo* and acidified with 1 M HCl. The aqueous phase was washed with DCM and the organic layer discarded. Following the addition of 3 M NaOH to achieve pH14, the reduced product was extracted into DCM and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The intermediate was used directly in the next step without further purification.

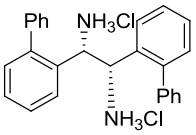
A solution of diamine in DMF (0.2 M) was heated at reflux for 5 hours before cooling to room temperature and concentrating *in vacuo*. The crude mixture was dissolved in water, and basified with 3 M NaOH. The aqueous phase was extracted with $CHCl_3$ and the

combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 97:3) afforded (2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane as a pale yellow oil (176 mg, 41 % yield *over 2 steps*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61-2.73 (m, 4H), 2.98-3.02 (m, 4H), 4.14 (s, 2H), 7.57 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 8.4 Hz, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 41.2, 49.4, 62.1, 124.1 (q, *J* = 272.4 Hz, CF_3), 125.3 (q, *J* = 4.0 Hz), 128.0, 129.6 (q, *J* = 32.6 Hz), 145.0; **^{19}F {1H} NMR (376 MHz, $CDCl_3$):** δ = -62.5 (CF3); **IR (ν, cm^{-1}):** 3695, 3584, 3055; **HRMS (ESI$^+$):** *m/z* calc. for $C_{20}H_{18}F_6N_2$ $[M+H]^+$ 401.1447, found 401.1448; **$[\alpha]^{23}_D$** +25.0 (c 0.26, DCM).

(2*S*,3*S*)-2,3-di([1,1'-biphenyl]-2-yl)-1,4-diazabicyclo[2.2.2]octane (111)

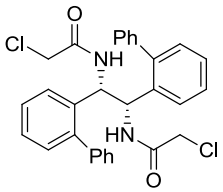




To a solution of (1*R*,2*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (1.00 g, 4.09 mmol) in DMSO (80 mL) was added *2*-phenyl-benzaldehyde (1.79 g, 9.81 mmol). The resulting mixture was stirred overnight at room temperature before being poured onto water (150 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. To the resultant diimine intermediate in THF (100 mL) was added 37 % HCl (3.0 mL) and the reaction was stirred for 3 hours before concentrating *in vacuo*. The resultant solid was dissolved in water (25 mL) and washed with ether. The aqueous layer was then made basic with 3M NaOH and extracted with EtOAc. The organic layer was further

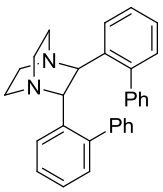
washed with 1M NaOH and then extracted with 1M HCl. The aqueous layer was evaporated under reduced pressure to afford the dihydrochloride salt as a pale yellow solid (590 mg, 1.35 mmol, 33 % yield).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.92 (s, 2H), 6.95-7.18 (m, 10H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.39-7.49 (m, 6H), 9.31 (brs, 6H); **^{13}C NMR (125.8 MHz, DMSO-d_6):** δ = 53.5, 127.4, 127.5, 128.0, 128.3, 128.8, 129.4, 129.9, 131.0, 139.0, 141.8; **IR (ν, cm^{-1}):** 3374; **HRMS (ESI$^+$, m/z):** $[C_{26}H_{25}N_2]^+$ $(M+H)^+$ calc. 365.2012, found 365.2007; **mp:** 216-218 °C.



To a suspension of the dihydrochloride salt (450 mg, 1.03 mmol) in DCM (20 mL) at 0 °C was added Et_3N (1.15 mL, 8.14 mmol) followed by DMAP (10 mg) and chloroacetyl chloride (328 μL, 4.12 mmol). The reaction was stirred overnight before quenching with water (50 mL) and extracting into DCM (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 2:3) afforded *N,N'*-((1*S*,2*S*)-1,2-di([1,1'-biphenyl]-2-yl)ethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (330 mg, 0.64 mmol, 62 % yield).

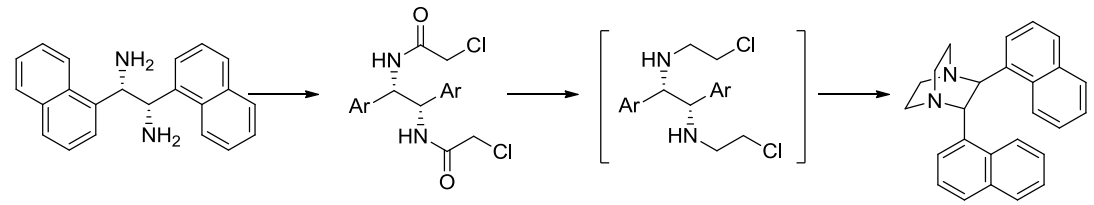
^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.01 (d, *J* = 12.8 Hz, 2H), 4.04 (d, *J* = 12.8 Hz, 2H), 5.34-5.42 (m, 2H), 6.76-7.10 (m, 10H), 7.12-7.16 (m, 2H), 7.23-7.35 (m, 6H), 8.74-8.81 (m, 2H, N*H*); **^{13}C NMR (125.8 MHz, DMSO-d_6):** δ = 42.7, 54.1, 126.4, 126.9, 127.4, 127.5, 127.7, 129.3, 129.3, 136.1, 140.1, 141.1, 165.2; **IR (ν, cm^{-1}):** 3295, 1678, 1644, 1530, 1262; **HRMS (ESI$^+$):** m/z calc. for $C_{30}H_{26}Cl_2N_2NaO_2$ ($[M+Na]^+$): 539.1264, found 539.1250; **mp:** 210-212 °C; **$[\alpha]^{22}_D$** -7.6 (c 0.20, MeOH).

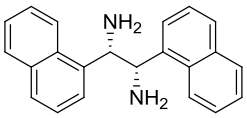


To a solution of *N*,*N*'-(1*S*,2*S*)-1,2-bis([1,1'-biphenyl]-2-yl)ethane-1,2-diyl)bis(2-chloroacetamide) (630 mg, 1.22 mmol) in THF (20 mL) at 0 °C was added dropwise BH_3·THF (1M in THF, 5.0 mL, 4.88 mmol) and the reaction was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and MeOH was added dropwise and stirred for 5 hours at room temperature. Then the solvent was concentrated, HCl (1M) was added and the mixture was stirred at the same temperature for 12 hours. NaOH (3M) was added to bring the reaction mixture to pH 14 and the aqueous layer was extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to furnish the crude diamine, which was used in the next step without purification. The crude product (478 mg) was dissolved in dimethylformamide (15 mL) and heated at 150 °C for 12 hours. The solvent was concentrated under reduced pressure and the residue was dissolved in water. The aqueous phase was treated with 3M NaOH to reach pH 14 and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 99:1) afforded (2*S*,3*S*)-2,3-di([1,1'-biphenyl]-2-yl)-1,4-diazabicyclo[2.2.2]octane as a colourless oil (128 mg, 25% yield *over 2 steps*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (ddd, *J* = 9.6 Hz, 7.1 Hz, 3.4 Hz, 2H), 2.55-2.63 (m, 2H), 2.70-2.85 (m, 4H), 4.23 (s, 2H), 6.92 (d, *J* = 7.5 Hz, 2H), 7.03-7.13 (m, 7H), 7.31-7.36 (m, 9H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 40.2, 49.1, 57.3, 125.9, 126.7, 126.9, 126.9, 127.6, 129.7, 130.7, 136.7, 141.8, 144.7; **IR (ν, cm^{-1}):** 2938, 1477, 1074; **HRMS (ESI$^+$):** m/z calc. for $C_{30}H_{29}N_2$ ($[M+H]^+$): 417.2325, found 417.2321; **$[\alpha]^{22}_D$** +98 (c 0.25, MeOH).

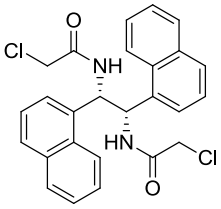
(2*S*,3*S*)-2,3-di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octane (112)





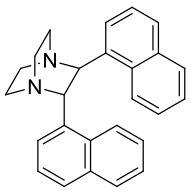
To a solution of (1*R*,2*R*)-1,2- bis(2-hydroxylphenyl)-1,2-diaminoethane (2.20 g, 10.0 mmol) in DMSO (50 mL) was added aryl aldehyde (24.0 mmol). The resulting mixture was stirred overnight at room temperature before being poured onto water (150 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. To the resultant diimine intermediate in THF (100 mL) was added 37 % HCl (3.0 mL) and the reaction was stirred for 3 hours to obtain a precipitate. The solid was filtered and washed with THF to afford analytically pure dihydrochloride salt. To the salt was added ethyl acetate, saturated aqueous $NaHCO_3$ solution and some NaOH (3M) and the two layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried and evaporated under reduced pressure to afford the product as a white solid (2.34 g, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (brs, 4H, N*H*$_2$), 5.14 (s, 2H), 7.48-7.55 (m, 4H), 7.60 (td, *J* = 7.0 Hz, *J* = 1.2 Hz, 2H), 7.80 (dd, *J* = 8.0 Hz, *J* = 7.1 Hz, 4H), 7.89 (d, *J* = 7.8 Hz, 2H), 8.33 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, CDCl3):** δ = 54.3, 22.8, 124.1, 125.4, 125.4, 125.9, 127.6, 129.1, 130.8, 133.9, 139.6; **IR (ν, cm^{-1}):** 2869, 1454, 1067; **$[\alpha]^{22}_D$** value of dihydrochloride salt is +266.0 (*c* 0.56, H_2O); **Elemental analysis:** Calc. for dihydrochloride salt $C_{22}H_{22}Cl_2N_2$: C, 68.57; H, 5.75; N, 7.27; found: C, 68.58; H, 5.77; N, 7.34.



To a solution of diamine (1.0 eq) in DCM (40 mL) at 0 °C was added Et_3N (5.0 eq.), DMAP (3 mol %) and chloroacetyl chloride (5.0 eq.) The reaction was stirred at room temperature for 3 hours before quenching with water (15 mL) and acidifying with 1M HCl. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic phases dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:1) afforded *N,N'*-((1*S*,2*S*)-1,2-di(naphthalen-1-yl)ethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (3.15 g, 90 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04 (d, *J* = 16.1 Hz, 2H), 4.11 (d, *J* = 16.1 Hz, 2H), 6.73 (brs, 2H), 7.22 (t, *J* = 6.0 Hz, 2H), 7.25-7.37 (m, 2H), 7.45-7.54 (m, 6H), 7.65 (d, *J* = 6.5 Hz, 2H), 7.76 (d, *J* = 6.5 Hz, 2H), 8.23 (brs, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 42.4, 51.6, 121.7, 123.8, 124.1, 124.9, 126.0, 128.0, 128.1, 130.0, 132.4, 132.9, 165.9; **IR (ν, cm^{-1}):** 3268, 1654, 1541, 776; **HRMS (ESI$^+$):** *m/z* calc. for $C_{26}H_{22}Cl_2N_2O_2$ $[M+Na]^+$ 487.0951, found 487.0959; **mp:** 164-166 °C; **$[\alpha]^{22}_D$** +367 (*c* 0.28, MeOH).

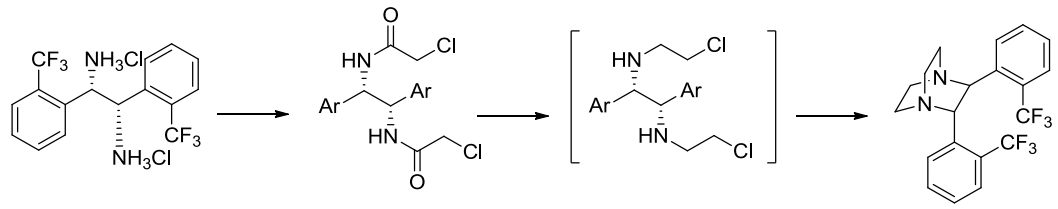


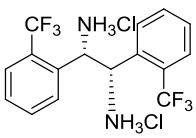
To a solution of *N,N'*-((1*S*,2*S*)-1,2-di(naphthalen-1-yl)ethane-1,2-diyl)bis(2-chloroacetamide) (1.0 eq) in THF (0.1 M) at 0 °C was added BH_3•THF (1M solution in THF, 4.0 eq) and the reaction was heated at reflux for 12 hours before cooling to 0 °C and quenching with methanol. The mixture was concentrated *in vacuo* and acidified with 1 M HCl. The aqueous phase was washed with ether and the organic layer discarded. Following the addition of 3 M NaOH to achieve pH14, the reduced product was extracted into EtOAc and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The intermediate was used directly in the next step without further purification.

A solution of diamine in DMF (0.2 M) was heated at reflux for 5 hours before cooling to room temperature and concentrating *in vacuo*. The crude mixture was dissolved in water, and basified with 3 M NaOH. The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 97:3) afforded (2*S*,3*S*)-2,3-di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octane as a pale yellow solid (683 mg, 51 % yield *over 2 steps*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69-2.75 (m, 2H), 2.88-3.00 (m, 2H), 3.00-3.10 (m, 2H), 3.49-3.59 (m, 2H), 5.37 (s, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.54 (ddd, *J* = 8.0 Hz, *J* = 6.9 Hz, *J* = 1.0 Hz, 2H), 7.68 (ddd, *J* = 8.5 Hz, *J* = 6.8 Hz, *J* = 1.2 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H), 8.53 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 41.4, 49.3, 55.6, 123.1, 124.6, 124.6, 125.6, 126.5, 128.6, 128.9, 133.3, 134.4, 134.5; **IR (ν, cm^{-1}):** 2932, 2868, 2360, 2341, 771; **HRMS (ESI$^+$):** *m/z* calc. for $C_{26}H_{24}N_2$ $[M+H]^+$: 365.2012, found 365.2008; **mp:** 105-107 °C; **$[\alpha]^{22}_D$** +64 (*c* 0.5, MeOH).

(2*S*,3*S*)-2,3-bis(2-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane (113)

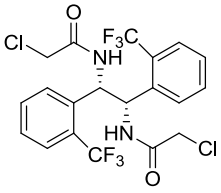




To a solution of (1*R*,2*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (1.00 g, 4.09 mmol) in DMSO (80 mL) was added *2*-(trifluoromethyl)benzaldehyde (1.30 mL, 9.82 mmol). The resulting mixture was stirred overnight at room temperature before being poured onto water (150 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with water,

dried over $MgSO_4$ and evaporated under reduced pressure. To the resultant diimine intermediate in THF (100 mL) was added 37 % HCl (3.0 mL) and the reaction was stirred for 3 hours before concentrating *in vacuo*. The resultant solid was dissolved in water (25 mL) and washed with ether. The aqueous layer was then made basic with 3M NaOH and extracted with EtOAc. The organic layer was further washed with 1M NaOH and then extracted with 1M HCl. The aqueous layer was evaporated under reduced pressure to afford the dihydrochloride salt as a pale yellow solid (920 mg, 2.18 mmol, 53 % yield).

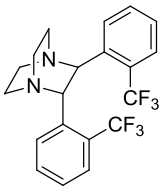
^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52 (s, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.71 (t, *J* = 7.7 Hz, 2H), 8.07 (d, *J* = 7.9 Hz, 2H), 9.46 (brs, 6H); **^{13}C NMR (125.8 MHz, DMSO-d_6):** δ = 52.1, 123.6 (q, *J* = 274.7 Hz), 126.5 (q, *J* = 5.5 Hz), 127.5 (q, *J* = 29.7 Hz), 130.2, 130.3, 131.5, 133.1; **^{19}F {1H} NMR (376.5 MHz, CD_3CN):** δ = -55.9; **IR (ν, cm^{-1}):** 3546; **HRMS (ESI$^+$, m/z):** $[C_{16}H_{15}F_6N_2]^+$ $(M+H)^+$ calc. 349.1134, found 349.1134; **mp:** 198 °C.



To a suspension of the dihydrochloride salt (700 mg, 1.65 mmol) in DCM (20 mL) at 0 °C was added Et_3N (1.84 mL, 13.2 mmol) followed by DMAP (10 mg) and chloroacetyl chloride (527 µL, 6.62 mmol). The reaction was stirred overnight before quenching with water (50 mL) and extracting into DCM (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 2:3) afforded *N,N'*-((1*S*,2*S*)-1,2-bis(2-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (743 mg, 1.48 mmol, 90 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (d, *J* = 15.1 Hz, 2H), 4.12 (d, *J* = 15.1 Hz, 2H), 5.97-6.05 (m, 2H), 6.93 (d, *J* = 5.6 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 2H), 8.08 (d, *J* = 7.9 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 42.3, 55.0, 123.5 (q, *J* = 272.2 Hz), 126.2 (q, *J* = 6.0 H), 128.7, 128.8, 129.7, 133.0, 136.1, 166.5; **^{19}F {1H} NMR (376.5 MHz, $CDCl_3$):** δ = -58.5; **IR (ν, cm^{-1}):** 3296, 1662, 1311, 1112; **HRMS (ESI$^+$):** m/z calc. for

$C_{20}H_{16}Cl_2F_6N_2NaO_2$ ([M+Na]$^+$): 523.0385, found 523.0383; **mp:** 70-72 °C; **[α]$^{22}_D$** +257 (c 0.165, MeOH).

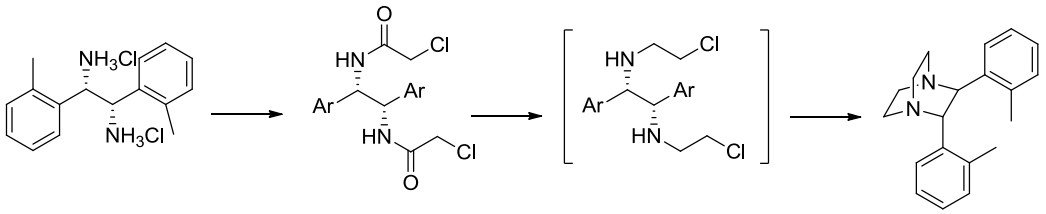


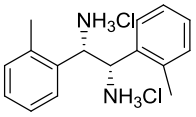
To a solution of *N*,*N*'-(1*S*,2*S*)-1,2-bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) (740 mg, 1.48 mmol) in THF (22 mL) at 0 ºC was added dropwise BH_3·THF (1M in THF, 6.0 mL, 5.92 mmol) and the reaction was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and MeOH was added dropwise and stirred for 5 hours at room temperature. Then the solvent was evaporated under reduced pressure, HCl (1M) was added and the mixture was stirred at the same temperature for 12 hours. NaOH (3M) was added to bring the reaction mixture to pH 14, which was then extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated to furnish the crude diamine, which was used in the next step with no further purification. The crude product (759 mg) was dissolved in dimethylformamide (23 mL) and heated at 150 ºC for 12 hours. The solvent was concentrated under reduced pressure and the residue was dissolved in water. The aqueous phase was treated with 3M NaOH to reach pH 14 and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 99.5:0.5) afforded (2*S*,3*S*)-2,3-bis(2-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane as a colourless oil (295 mg, 50% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.64 (ddd, *J* = 9.3 Hz, 8.3 Hz, 3.7 Hz, 2H), 2.91-3.01 (m, 2H), 3.04-3.15 (m, 2H), 3.37 (ddt, *J* = 8.8 Hz, 3.2 Hz, 2.4 Hz, 2H), 4.92 (s, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 39.9, 49.9, 56.2, 124.5 (q, *J* = 274.9 Hz, CF_3), 127.4 (q, *J* = 6.4 Hz), 127.8, 127.9, 130. 6 (q, *J* = 29.2 Hz), 131.4, 136.6; **^{19}F {1H} NMR (376.5 MHz, $CDCl_3$):** δ = -58.1; **IR (ν,**

cm^{-1}): 1690, 1380, 1210; **HRMS (ESI$^+$):** m/z calc. for $C_{20}H_{19}F_6N_2$ ([M+H]$^+$): 401.1447, found 401.1444; **[α]$^{22}_D$** +21 (c 0.15, MeOH).

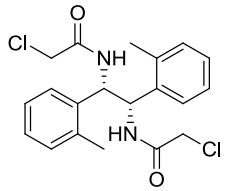
(2*S*,3*S*)-2,3-di-o-tolyl-1,4-diazabicyclo[2.2.2]octane (114)





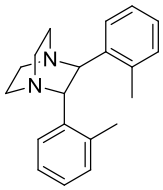
To a solution of (1*R*,2*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (1.00 g, 4.09 mmol) in DMSO (80 mL) was added *o*-tolualdehyde (1.14 mL, 9.81 mmol). The resulting mixture was stirred overnight at room temperature before being poured onto water (150 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. To the resultant diimine intermediate in THF (100 mL) was added 37 % HCl (3.0 mL) and the reaction was stirred for 3 hours before concentrating *in vacuo*. The resultant solid was dissolved in water (25 mL) and washed with ether. The aqueous layer was then made basic with 3M NaOH and extracted with EtOAc. The organic layer was further washed with 1M NaOH and then extracted with 1M HCl. The aqueous layer was evaporated under reduced pressure to afford the dihydrochloride salt as a pale yellow solid (609 mg, 1.94 mmol, 48 % yield).

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 2.17 (s, 6H), 5.33 (s, 2H), 7.01 (d, *J* = 7.3 Hz, 2H), 7.12 (td, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 9.22 (s, 6H); **^{13}C NMR (100.6 MHz, DMSO-d$_6$):** δ = 19.6, 53.2, 126.7, 127.6, 129.4, 130.9, 133.3, 136.8; **IR (ν, cm^{-1}):** 3430; **HRMS (ESI$^+$, m/z):** $[C_{16}H_{21}N_2]^+$ (M+H)$^+$ calc. 241.1699, found 241.1709.



To a suspension of the dihydrochloride salt (600 mg, 1.92 mmol) in DCM (50 mL) at 0 °C was added Et_3N (2.14 mL, 15.4 mmol) followed by DMAP (10 mg) and chloroacetyl chloride (617 µL, 7.68 mmol). The reaction was stirred overnight before quenching with water (50 mL) and extracting into DCM (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 2:3) afforded *N,N'*-((1*S*,2*S*)-1,2-di-o-tolylethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (509 mg, 1.29 mmol, 67 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98 (s, 6H), 4.03 (d, *J* = 15.1 Hz, 2H), 4.09 (d, *J* = 15.1 Hz, 2H), 5.64-5.71 (m, 2H), 6.97 (d, *J* = 7.5 Hz, 2H), 7.13 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.39 (brs, 2H, N*H*), 7.50 (d, *J* = 7.7 Hz, 2H); **^{13}C NMR (125.8 MHz, $CDCl_3$):** δ = 19.2, 42.5, 54.9, 126.5, 126.6, 128.1, 130.7, 136.3, 136.4, 166.7; **IR (ν, cm^{-1}):** 3261, 1651, 1537, 1243; **HRMS (ESI$^+$):** m/z calc. for $C_{20}H_{22}Cl_2N_2NaO_2$ ([M+Na]$^+$): 415.0951, found 415.0958; **mp:** 174-176 °C; **$[\alpha]^{22}_D$** +90 (c 0.20, MeOH).

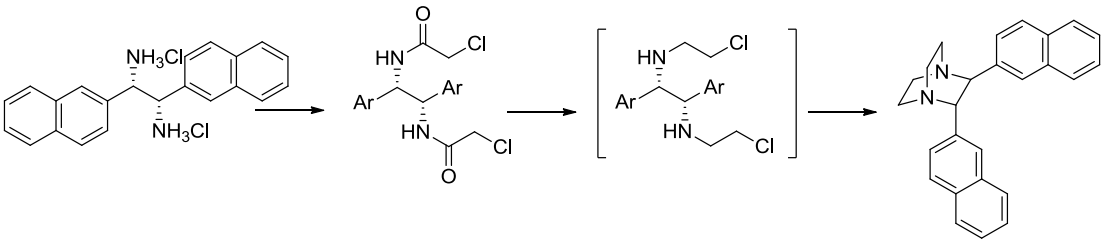


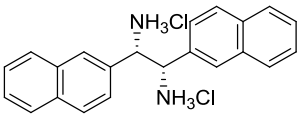
To a solution of *N,N'*-((1*S*,2*S*)-1,2-di-o-tolylethane-1,2-diyl)bis(2-chloroacetamide) (500 mg, 1.28 mmol) in THF (15 mL) at 0 °C was added dropwise BH_3·THF (1M in THF, 5.1 mL, 5.10 mmol) and the reaction was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and MeOH was added dropwise and stirred for 5 hours at room temperature. Then the solvent was concentrated, HCl (1M) was added and the mixture was stirred at the same temperature for 12 hours. NaOH (3M) was added to bring the reaction mixture to pH 14 and was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to furnish the crude diamine, which was used in the next step with no further purification. The crude product (343 mg) was dissolved in DMF (12 mL) and heated at 150 °C for 12 hours. The solvent was concentrated under reduced

pressure and the residue was dissolved in water. The aqueous phase was treated with 3M NaOH to reach pH 14 and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 99:1) afforded (2*S*,3*S*)-2,3-di-o-tolyl-1,4-diazabicyclo[2.2.2]octane as an oil (147 mg, 40% yield *over 2 steps*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55-2.65 (m, 2H), 2.64 (s, 6H), 2.85-3.01 (m, 4H), 3.21-3.31 (m, 2H), 4.65 (s, 2H), 7.17-7.25 (m, 4H), 7.26-7.31 (m, 2H), 7.38-7.43 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 19.9, 40.5, 49.6, 55.9, 124.9, 125.3, 127.2, 131.3, 136.9, 139.0; **IR (ν, cm^{-1}):** 2937, 1458, 1075; **HRMS (ESI$^+$):** m/z calc. for $C_{20}H_{25}N_2$ ($[M+H]^+$): 293.2012, found 293.2004; **$[\alpha]^{22}_D$** +111 (c 0.15, MeOH).

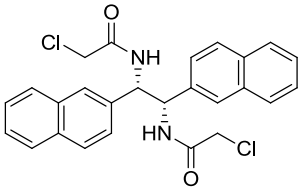
(2*S*,3*S*)-methyl-2,3-di(naphthalen-2-yl)-1,4-diazabicyclo[2.2.2]octane (115)





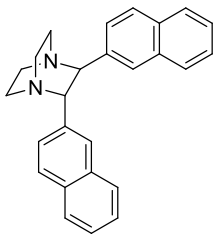
To a suspension of (1*R*,2*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (1.57 g, 6.43 mmol) in ethanol (24 mL) was added *2*-naphthaldehyde (2.40 g, 15.4 mmol). After a few minutes the solution became clear and after 2-3 hours a white solid precipitated. The solid was collected by vacuum filtration, washed with ethanol and dried. The solid was dissolved in THF (75 mL) and 36 % HCl (2.5 mL) was added dropwise. The solution was stirred for 3 hours to obtain the dihydrochloride salt as a white precipitate, which was used without purification (1.86 g, 4.82 mmol, 75 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.40 (s, 2H), 7.46-7.51 (m, 4H), 7.54 (dd, *J* = 8.7 Hz, *J* = 1.5 Hz, 2H), 7.74-7.84 (m, 6H), 7.99 (s, 2H), 9.46 (brs, 6H); **^{13}C NMR (100.6 MHz, DMSO-d_6):** δ = 57.3, 126.0, 127.1, 127.4, 128.0, 128.4, 128.6, 129.3, 131.2, 132.6,133.1; **IR (v, cm^{-1}):** 3595; **HRMS (ESI^{+}, m/z):** $[C_{22}H_{21}N_2]^+$ $(M+H)^+$ calc. 313.1699, found 313.1699; **mp:** 215-216 °C.



To a suspension of the dihydrochloride salt (1.20 g, 3.11 mmol) in DCM (50 mL) at 0 °C was added Et_3N (3.47 mL, 24.9 mmol) followed by DMAP (10 mg) and chloroacetyl chloride (992 µL, 12.5 mmol). The reaction was stirred overnight before quenching with water (100 mL) and extracting into DCM (3 x 300 mL) – **Note: product is very insoluble**. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by trituation (MeCN) afforded *N,N*'-((1S,2S)-1,2-di(naphthalen-2-yl)ethane-1,2-diyl)bis(2-chloroacetamide) as a white solid (1.44 g, 3.11 mmol, 99 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.08 (d, *J* = 13.0 Hz, 2H), 4.13 (d, *J* = 13.0 Hz, 2H), 5.51-5.60 (m, 2H), 7.39-7.50 (m, 6H), 7.71-7.83 (m, 8H), 9.02-9.10 (m, 2H); **^{13}C NMR (100.6 MHz, DMSO-d_6):** δ = 43.2, 57.7, 126.0, 126.4, 126.6, 126.9, 127.9, 128.1, 128.1, 132.6, 133.0, 137.5, 166.2; **IR (v, cm^{-1}):** 3398, 1645; **HRMS (ESI^{+}, m/z):** $[C_{26}H_{22}Cl_2N_2NaO_2]^+$ $(M+Na)^+$ calc. 487.0951, found 487.0949; **mp:** 249-251 °C.



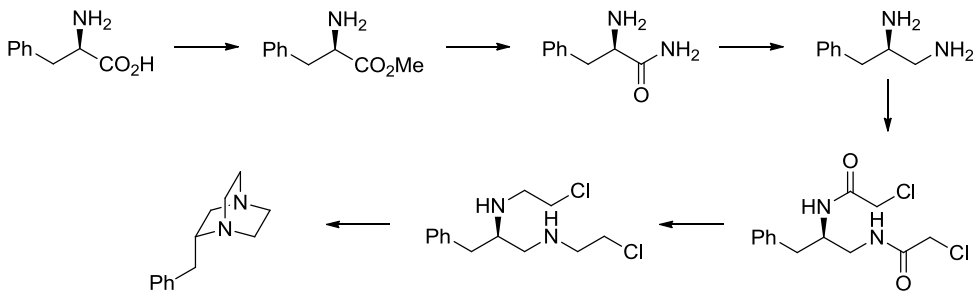
To a solution of *N,N*'-((1*S*,2*S*)-1,2-di(naphthalen-2-yl)ethane-1,2-diyl)bis(2-chloroacetamide) (1.43 g, 3.07 mmol) in THF (0.1 M) at 0 °C was added BH_3•THF (1M solution in THF, 12.3 mL, 12.3 mmol) and the reaction was heated at reflux for 12 hours before cooling to 0 °C and quenching with methanol. The mixture was concentrated *in vacuo* to dryness and acidified

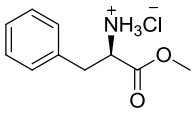
with 1 M HCl. The aqueous phase was washed with ether and the organic layer discarded. Following the addition of 3 M NaOH to achieve pH14, the reduced product was extracted into EtOAc and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The intermediate was used directly in the next step without further purification.

A solution of diamine in DMF (0.2 M) was heated at reflux for 5 hours before cooling to room temperature and concentrating *in vacuo*. The crude mixture was dissolved in water, and basified with 3 M NaOH. The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH 97:3) afforded (2*S*,3*S*)-2,3-di(naphthalen-2-yl)-1,4-diazabicyclo[2.2.2]octane as a white solid (470 mg, 1.29 mmol, 42 % yield *over 2 steps*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65-2.75 (m, 2H), 2.81-2.93 (m, 2H), 3.02-3.19 (m, 4H), 4.47 (s, 2H), 7.44-7.53 (m, 4H), 7.70 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 2H), 7.78-7.84 (m, 2H), 7.84-7.90 (m, 4H), 7.93 (s, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 41.3, 49.6, 62.5, 125.8, 125.9, 126.1, 126.7, 127.6, 128.1, 128.1, 132.7, 133.3, 138.8; **IR (ν, cm^{-1}):** 3052 (m, C-H), 2935 (m, C-H), 2866 (m, C-H), 858 (m, C-N), 809 (m, C-C); **HRMS (ESI$^+$, m/z):** $[C_{26}H_{25}N_2]^+$ $(M+H)^+$ calc. 365.2012, found 365.2000.

(2*R*)-2-Benzyl-1,4-diazabicyclo[2.2.2]octane (122)

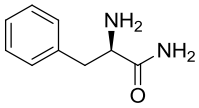




To a solution of L-Phenylalanine (20.0 g, 121 mmol) in methanol (200 ml) at 0 °C was added thionyl chloride (22.0 ml, 303 mmol) dropwise over 10 minutes. The reaction was warmed to room temperature and stirred overnight before evaporating to dryness. The resulting semi-solid was treated with ether (200 ml) and the solvent evaporated under reduced pressure to afford the title compound as a white solid (quantitative yield, 26.1 g, 121 mmol).

^{1}H NMR (400 MHz, DMSO): δ = 3.11 (dd, *J* = 13.9 Hz, *J* = 7.9 Hz, 1H), 3.26 (dd, *J* = 13.9 Hz, *J* = 5.5 Hz, 1H), 3.61 (s, 3H), 4.18 (dd, *J* = 7.8 Hz, *J* = 5.4 Hz, 1H), 7.21-7.28 (m, 3H), 7.28-7.34 (m, 2H), 8.93 (brs, 3H, N*H*$_3$); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 36.6, 53.3, 54.2, 128.1, 129.4, 130.2, 135.7, 170.1.

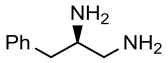
Data consistent with literature values.[51]



To a solution of *L*-Phenylalanine methyl ester hydrochloride in chloroform (200 ml) was added saturated $NaHCO_3$ solution until pH paper indicated the solution to be basic. The free amine was extracted with chloroform (2 x 200 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting L-Phenylalanine methyl ester was dissolved in toluene (300 ml) and to this solution was added saturated ammonium hydroxide solution (150 ml). The reaction was stirred at room temperature for 24 hours before being evaporated to dryness under reduced pressure. The crude product did not require further purification (19.5 g, 119 mmol, 98 %).

^{1}H NMR (400 MHz, DMSO): δ = 1.90 (brs, 2H, N*H*$_2$), 2.59 (dd, *J* = 13.4 Hz, 8.3 Hz, 1H), 2.92 (dd, *J* = 13.4 Hz, *J* = 5.1 Hz, 1H), 3.34 (dd, *J* = 8.3 Hz, 5.1 Hz, 1H), 6.96 (brs, 1H), 7.16-7.30 (m, 5H), 7.32 (brs, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 42.0, 57.1, 126.9, 128.9, 130.2, 139.8, 177.6.

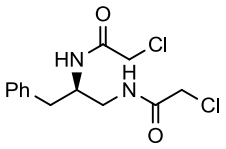
Data consistent with literature values.[52]



To a solution of $LiAlH_4$ (13.9 g, 365 mmol) in THF (250 ml) at 0 °C in a 1L flask was carefully added (*R*)-2-amino-3-phenylpropanamide (17.7 g, 108 mmol) and the reaction was heated at reflux for 8 hours before being cooled to 0 °C and quenched with 1 % KOH (dropwise addition). The reaction mixture was then filtered through a pad of cellite and washed with THF. The solvent was evaporated under reduced pressure and the product purified by vacuum distillation (0.25 mmHg, 86-88 °C) to afford the title compound as a colourless liquid (10.0 g, 67 mmol, 55 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (brs, 4H, N*H*$_2$), 2.50 (ddd, *J* = 19.7 Hz, *J* = 12.6 Hz, *J* = 7.7 Hz, 2H), 2.77 (ddd, *J* = 12.6 Hz, 6.7 Hz, 4.2 Hz, 2H), 2.90-2.97 (m, 1H), 7.15-7.22 (m, 3H), 7.28 (tt, *J* = 7.3 Hz, *J* = 1.1 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 42.3, 48.2, 55.1, 126.2, 128.5, 129.2, 139.2.

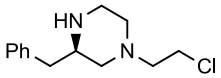
Data consistent with literature values.[53]



To a solution of (R)-3-phenylpropane-1,2-diamine (1.00 g, 6.67 mmol) in DCM (100 ml) at 0 °C was added triethylamine (4.65 ml, 33.4 mmol), DMAP (41 mg) and chloroacetal chloride (1.59 ml, 20.0 mmol) dropwise. The reaction was warmed to room temperature and stirred for 3 hours before quenching with $NaHCO_3$ (100 ml), stirred for 1 hour, extracted into DCM (2 x 100 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was redissolved in DCM (200 ml), washed with 2M HCl (2 x 100 ml), then water (100 ml), dried over $MgSO_4$ and evaporated under reduced pressure to afford the title compound as a brown solid (1.93 g, 6.40 mmol, 96 % yield).

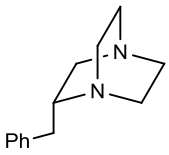
An analytically pure sample was obtained by column chromatography (SiO_2, EtOAc/PE 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (dd, *J* = 13.8 Hz, *J* = 7.5 Hz, 1H), 2.98 (dd, *J* = 13.8 Hz, *J* = 6.3 Hz, 1H), 3.39-3.50 (m, 2H), 4.01 (d, *J* = 3.1 Hz, 2H), 4.05 (d, *J* = 1.3 Hz, 2H), 4.27-4.35 (m, 1H), 6.98 (brs, 1H, NH), 7.00 (brs, 1H, NH), 7.22 (d, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 38.4, 42.4, 42.5, 43.3, 51.7, 127.1, 128.9, 129.1, 136.4, 166.7, 167.2; **IR (ν, cm^{-1}):** 3055 (NH), 2987 (NH), 1673 (NC=O); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{16}Cl_2N_2NaO_2]^+$ $(M+Na)^+$ calc. 325.0481, found 325.0474.



To a solution of (R)-N,N'-(3-phenylpropane-1,2-diyl)bis(2-chloroacetamide) (200 mg, 0.66 mmol) in THF (5 ml) at 0 °C was added BH_3.THF (1M, 2.64 ml, 2.64 mmol). The reaction was heated at reflux overnight before being cooled to room temperature and quenched with methanol. After 30 minutes the solution was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, MeOH/$CHCl_3$ 1:19) afforded the title compound as a pale yellow oil (144 mg, 0.60 mmol, 91 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (dd, *J* = 12.0 Hz, *J* = 9.8 Hz, 1H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.74 (t, *J* = 11.9 Hz, 2H), 2.88 (td, *J* = 12.1 Hz, *J* = 6.1 Hz, 1H), 2.98 (t, *J* = 11.7 Hz, 1H), 3.03-3.18 (m, 2H), 3.39 (dt, *J* = 13.1 Hz, *J* = 3.8 Hz, 2H), 3.43 (t, *J* = 6.7 Hz, 2H), 7.16-7.30 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 36.7, 40.6, 43.3, 49.2, 54.1, 56.5, 58.9, 127.2, 128.9, 129.2, 135.3; **IR (ν, cm^{-1}):** 3054 (NH); **HRMS (ESI$^+$, m/z):** $[C_{13}H_{20}ClN_2]^+$ $(M+H)^+$ calc. 239.1310, found 239.1310.

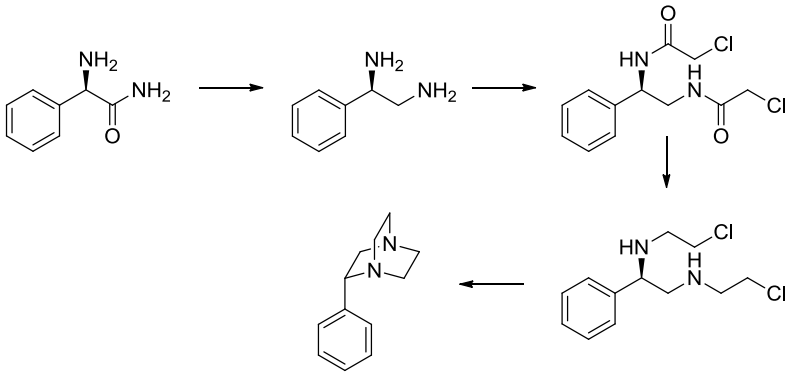


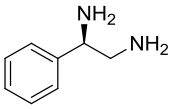
(*R*)-3-benzyl-1-(2-chloroethyl)piperazine (100 mg, 0.42 mmol) in DMF (5 ml) was heated to reflux and stirred overnight before being cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in 1M NaOH (5 ml), extracted into chloroform (3 x 15 ml), dried over $MgSO_4$ and evaporated.

Purification by flash chromatography (SiO_2, 1:9 MeOH/$CHCl_3$) afforded the product as a yellow oil (34 mg, 0.17 mmol, 40 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45 (ddd, *J* = 13.1 Hz, *J* = 6.7 Hz, *J* = 1.9 Hz, 1H), 2.64-2.81 (m, 6H), 2.81-2.86 (m, 1H), 2.86 (dd, *J* = 8.9 Hz, *J* = 1.9 Hz, 1H), 2.90 (td, *J* = 9.2 Hz, 1.8 Hz, 1H), 2.92-2.98 (m, 1H), 2.98-3.04 (m, 1H), 3.07-3.14 (m, 1H), 7.19-7.23 (m, 3H), 7.27-7.32 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 39.8, 40.9, 46.1, 47.3, 49.8, 53.8, 56.3, 126.3, 128.5, 128.9, 138.8; **HRMS (ESI$^+$, m/z):** $[C_{13}H_{19}N_2]^+$ $(M+H)^+$ calc. 203.1544, found 203.1543.

(2*R*)-2-Phenyl-1,4-diazabicyclo[2.2.2]octane (123)



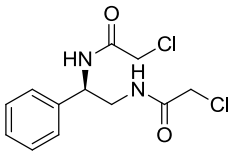


(*R*)-1-phenylethane-1,2-diamine was prepared following a 2 step procedure. To a solution of (*R*)-(-)-2-phenylglycine methyl ester hydrochloride (8.5 g, 51.52 mmol) in toluene (100 mL) was added an aqueous solution of NH_4OH (28% in water, 50 mL) and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the solid obtained was dried, affording 7.09 g (92% conversion) of (*R*)-2-amino-2-phenylacetamide. To a suspension of lithium aluminium hydride ($LiAlH_4$) (5.4 g, 141.80 mmol) in tetrahydrofuran (150 mL) at 0 °C was added portionwise (*R*)-2-amino-2-phenylacetamide (7.09 g, 47.26 mmol). The reaction was stirred at 0 °C for 10 minutes and then heated at reflux overnight. The mixture was cooled to 0 °C and then quenched by the careful addition of water and NaOH (1M). The mixture was stirred

for 10 minutes until a white precipitate was observed, filtered through celite and evaporated. The residue was purified by distillation affording (*R*)-1-phenylethane-1,2-diamine as a colourless oil (2.02 g, 13.4 mmol, 26 % yield).

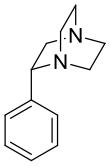
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (brs, 4H, NH_2), 2.73 (dd, *J* = 12.6 Hz, *J* = 5.3 Hz, 1H), 2.83 (dd, *J* = 12.6 Hz, *J* = 5.3 Hz, 1H), 3.82 (dd, *J* = 6.8 Hz, *J* = 5.5 Hz, 1H), 7.19-7.23 (m, 1H), 7.27-7.31 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 49.7, 58.0, 126.2, 126.2, 128.2, 128.2, 128.2, 143.9; **$[\alpha]^{22}_D$** -28.5 (*c* 0.5, MeOH).

Data consistent with literature values.[54]



(*R*)-1-Phenylethane-1,2-diamine (3.10 g, 22.8 mmol) was dissolved in dichloromethane (120 mL) and 4-dimethylaminopyridine (95 mg, 0.775 mmol), triethylamine (16 mL, 114 mmol) and chloroacetyl chloride (5.4 mL, 68.40 mmol) were added sequentially at 0 °C. The solution was stirred at room temperature overnight. Water and HCl (1M) were added, and the mixture stirred for 15 minutes then extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexane:ethyl acetate, from 1:1 to 3:7) affording (2.96 g, 10.2 mmol, 45 % yield) of (*R*)-*N,N*'-(1-phenylethane-1,2-diyl)bis(2-chloroacetamide).

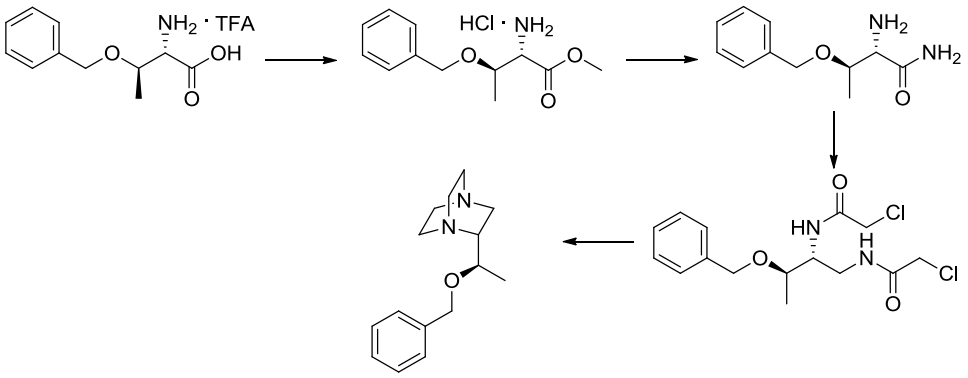
^{1}H NMR (400 MHz, MeOD): δ = 3.58 (dd, *J* = 8.3 Hz, *J* = 6.0 Hz, 2H), 4.02 (s, 2H), 4.06 (s, 2H), 5.13 (dd, *J* = 8.1 Hz, *J* = 6.2 Hz, 1H), 7.26-7.31 (m, 1H), 7.34-7.37 (m, 4H); **^{13}C NMR (100.6 MHz, MeOD):** δ = 43.2, 43.4, 45.5, 55.3, 127.9, 127.9, 129.0, 129.9, 129.9, 140.6, 169.2, 170.1; **IR (ν, cm^{-1}):** 3312, 1642, 1533, 1262; **HRMS (ESI$^+$, m/z):** $[C_{12}H_{14}Cl_2N_2O_2]^+$ $(M+Na)^+$ calc. 311.0325, found 311.0326; **elemental analysis:** for $C_{12}H_{14}Cl_2N_2O_2$: C, 49.84; H, 4.88; N, 9.69. Found: C, 49.76; H, 4.87; N, 9.62; **$[\alpha]^{22}_D$** -50 (*c* 0.53, MeOH); **mp**: 112-113 °C;

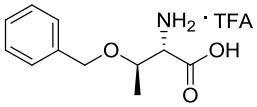


To a solution of (*R*)-*N,N'*-(1-phenylethane-1,2-diyl)bis(2-chloroacetamide) (500 mg, 1.73 mmol) in THF (22 mL) at 0 °C was added dropwise BH3.THF (1M in THF, 7 mL, 6.95 mmol) and the reaction was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and MeOH was added dropwise and stirred for 12 hours at room temperature. Then the solvent was concentrated, HCl (2M) was added and the mixture was stirred at the same temperature for 12 more hours. NaOH (3M) was added to bring the reaction mixture to pH 14 and was extracted with dichloromethane. The combined organic extracts were dried, filtered and evaporated to give 411 mg of a crude, which was used in the next step with no further purification. The crude product (411 mg) was dissolved in dimethylformamide (25 mL) and heated at 150 °C for 12 hours. The solvent was concentrated under reduced pressure; water and NaOH 3M were added until reach pH 14 and extracted with dichloromethane. The combined organic extracts were dried, filtered and evaporated. Purification by flash chromatography (SiO_2, 1:19 MeOH/$CHCl_3$) afforded the product as a yellow oil (65 mg, 0.35 mmol, 20 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48-2.54 (m, 1H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.67-2.74 (m, 3H), 2.85-2.97 (m, 3H), 3.29 (dd, *J* = 9.6 Hz, *J* = 9.6 Hz, 1H), 3.83 (t, *J* = 8.6 Hz, 1H), 7.13-7.17 (m, 1H), 7.23-7.28 (m, 4H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 40.9, 46.4, 47.1, 49.2, 52.9, 56.4, 126.5, 126.8, 126.8, 128.1, 128.1, 141.2; **IR (ν, cm^{-1}):** 2869, 1454, 1067; **HRMS (ESI$^+$, m/z):** $[C_{12}H_{17}N_2]^+$ $(M+H)^+$ calc. 189.1386, found 189.1390; **mp**: 64-65 °C; **$[\alpha]^{22}_D$** -82 (*c* 0.11, MeOH).

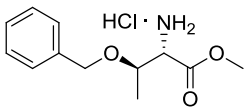
(2*R*)-2-((*R*)-1-(benzyloxy)ethyl)-1,4-diazabicyclo[2.2.2]octane (124)





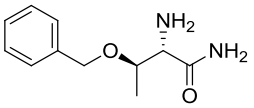
To a solution of Boc-*O*-benzyl-*L*-threonine (25.0 g, 80.8 mmol) in DCM (125 mL) at 0 °C was added TFA (62 mL, 808 mmol) and the solution was warmed to room temperature and stirred for 24 hours. The reaction was concentrated *in vacuo* and the residue co-evaporated with toluene (3 times) to furnish the TFA salt as a white solid (26.2 g, 80.8 mmol, quantitative yield).

^{1}H NMR (250 MHz, MeOD): δ = 1.36 (d, *J* = 6.5 Hz, 3H), 3.77 (d, *J* = 3.8 Hz, 1H), 4.03 (dq, *J* = 6.5 Hz, 3.8 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H) 4.66 (d, *J* = 11.7 Hz, 1H), 7.22-7.41 (m, 5H); **^{13}C NMR (63 MHz, MeOD):** δ = 17.1, 59.7, 72.4, 73.9, 128.9, 129.1, 129.4, 139.1, 171.2; **IR (*v*, cm^{-1}):** 2938, 1670, 1499, 1195, 1141, 1066; **HRMS (ESI)$^{+}$:** *m/z* calc. for $C_{11}H_{15}NNaO_3$ $[M+Na]^+$: 232.0944, found 232.0953; **mp:** 77-78 °C; **$[\alpha]^{20}_D$** -20.4 (c = 0.41, MeOH).



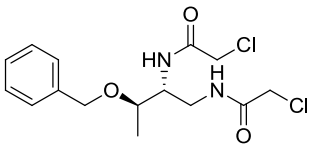
To a solution of (*2S,3R*)-2-amino-3-(benzyloxy)butanoic acid trifluoroacetate (26.0 g, 80.5 mmol) in methanol (150 mL) was added thionyl chloride (14.6 mL, 201 mmol) dropwise over 10 minutes at 0 °C. The reaction was warmed to room temperature and stirred for 24 hours before evaporating to dryness. The resulting semi-solid was treated with diethyl ether (200 mL) to afford a solid which was collected by filtration, washed with diethyl ether and dried under high vacuum to furnish the hydrochloride salt as a slightly green solid (20.9 g, 80.5 mmol, quant.).

^{1}H NMR (250MHz, MeOD): δ = 1.37 (d, *J* = 6.5 Hz, 3H), 3.74 (s, 3H), 4.10 (d, *J* = 2.6 Hz, 1H), 4.18 (dq, *J* = 6.4 Hz, *J* = 3.2 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 7.26-7.41 (m, 5H); **^{13}C NMR (63 MHz, MeOD):** δ = 16.4, 54.0, 59.1, 72.0, 72.8, 129.0, 129.3, 129.4, 138.6, 169.2; **IR (ν, cm^{-1}):** 2874, 1749, 1586, 1498, 1454, 1388, 1304, 1238, 1067; **HRMS (ESI)$^{+}$:** *m/z* calc. for $C_{12}H_{18}NO_3$ $[M+H]^+$: 224.1281, found 224.1279; **mp:** 100-101 °C; **$[\alpha]^{20}_D$** -34.4 (c = 0.50, MeOH).



To a solution of (*2S,3R*)-methyl-2-amino-3-(benzyloxy)butanoate hydrochloride (20.9 g, 80.5 mmol) in chloroform (100 mL) was added saturated aqueous $NaHCO_3$ (100 mL) and the solution was further basified with NaOH pellets to achieve pH 12. The aqueous layer was extracted with chloroform (3 x 200 mL), the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give a brown oil (17.5 g). The free amine was dissolved in toluene (8 mL) and saturated aqueous NH_4OH (38 mL) was added. The reaction was stirred in a sealed tube at room temperature for 24 hours, then at 60 °C for 24 hours. After evaporation of the solvent under reduced pressure, the brown residue was dissolved in chloroform (200 ml) and washed with 0.1 M aqueous Na_2CO_3 solution. The aqueous layer was washed with chloroform (3 x 200 ml) and the organic layers were combined, dried over $MgSO_4$ and evaporated to dryness to afford (*2S,3R*)-2-amino-3-(benzyloxy)butanamide as a brown solid (11.8 g, 56.7 mmol, 70 %).

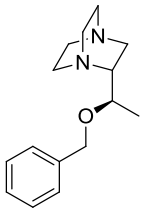
^{1}H NMR (400 MHz, MeOD): δ = 1.24 (d, *J* = 6.1 Hz, 3H), 3.32 (brs, 1H), 3.89 (brs, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 7.23-7.40 (m, 5H); **^{13}C NMR (100.6 MHz, MeOD):** δ = 16.8, 60.5, 72.4, 77.5, 128.8, 129.0, 129.5, 140.0, 178.6; **IR (ν, cm^{-1}):** 3399 (NH), 1673 (NC=O), 1454, 1378, 1071; **HRMS (ESI)$^{+}$:** *m/z* calc. for $C_{11}H_{17}N_2O_2$ $[M+H]^+$: 209.1285, found 209.1282; **mp:** 66-67 °C; **$[\alpha]^{20}_D$** -49.2 (c = 0.25, MeOH).



(*2S,3R*)-2-amino-3-(benzyloxy)butanamide (9.36 g, 45.0 mmol) was dissolved in THF (70 mL) over activated molecular sieves under argon and cooled to 0 °C. BH_3·THF (1 M solution in THF, 225 mL, 225 mmol) was added dropwise and the solution was stirred under reflux conditions for 24 hours. After cooling to 0 °C, methanol (15 mL) was added carefully and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated and the residue treated with 6 M HCl (20 mL) for 2 hours under stirring. The solvent was removed, 1 M NaOH (100 mL) was added to the residue and the aqueous layer was extracted with chloroform (4 x 80 mL). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure to afford a brown oil (8.30 g).

The crude amine (7.88 g, 40.6 mmol) was dissolved in dichloromethane (200 mL) under argon and cooled to 0 °C. Triethylamine (28.3 mL, 207 mmol) followed by DMAP (248 mg, 2.07 mmol) and chloroacetyl chloride (9.70 mL, 122 mmol) were added and the dark solution was stirred at room temperature for 8 hours. After quenching with aqueous $NaHCO_3$ (100 mL) and stirring for 1 hour at room temperature, the layers were separated and the aqueous layer extracted with DCM (3 x 100 mL). The combined organic layers were washed with 1 M HCl and water, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (DCM/MeOH: 99/1) afforded (*2S,3R*)-*N*,*N*'-(3-benzyloxybutane-1,2-diyl)bis(2-chloroacetamide) as a colourless oil (7.27 g, 20.93 mmol, 48 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.3 Hz, 3H), 3.35-3.65 (m, 2H), 3.75 (qd, *J* = 6.2, *J* = 2.0 Hz, 1H), 3.98 (s, 2H), 4.00-4.15 (m, 1H), 4.07 (s, 2H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 6.97-7.14 (m, 2H), 7.28-7.43 (m, 5H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 16.3, 42.4, 42.5, 42.6, 53.5, 70.7, 73.4, 127.9, 128.0, 128.5, 137.6, 166.6, 167.0; **IR (ν, cm^{-1}):** 3316, 1662, 1540, 1261, 1022; **HRMS (ESI)$^+$:** *m/z* calc. for $C_{15}H_{20}Cl_2N_2NaO_3$ [*M*+Na]$^+$: 369.0743, found 369.0730; **$[\alpha]^{20}_D$** -22.4 (c = 0.25, $CHCl_3$).

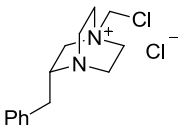


To a solution of (*2S,3R*)-*N*,*N*'-(3-benzyloxybutane-1,2-diyl)bis(2-chloroacetamide) (2.77 g, 7.98 mmol) in THF (160 mL) over activated molecular sieves at 0 °C was added BH_3·THF (1 M solution in THF, 32 mL, 31.9 mmol) dropwise and the reaction was stirred under reflux overnight. After cooling to room temperature, MeOH (40 mL) was added and stirring was continued for 3 hours. The solvent was evaporated under reduced pressure and the crude product was dissolved in chloroform and washed with 0.1 M Na_2CO_3. The aqueous layer was washed with chloroform (3 x 100 mL), the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to furnish the crude diamine (2.08 g) as a yellow oil. Dry DMF (25 mL) was added and the solution was stirred at 110 °C overnight. After cooling to room temperature and evaporation of the solvent under reduced pressure purification by column chromatography ($CHCl_3$/MeOH: 99.5/0.5 – 98/2 with 0.5 % NH_4OH (25 %)) afforded (2*R*)-2-((*R*)-1-(benzyloxy)ethyl)-1,4-diazabicyclo[2.2.2]octane as a yellow oil (840 mg, 3.41 mmol, 43 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.1 Hz, 3H), 2.27 (dd, *J* = 12.6, *J* = 7.2 Hz, 1H), 2.46-2.97 (m, 10H), 3.32-3.53 (m, 1H) 4.53 (d, *J* = 12.5 Hz, 1H) 4.65 (d, *J* = 12.5 Hz, 1H), 7.14-7.40 (m, 5H); **^{13}C NMR (63 MHz, $CDCl_3$):** δ = 16.2, 41.8, 46.4, 47.3, 49.7, 50.6, 60.4, 70.4, 73.3, 127.5, 127.9, 128.3, 138.8; **IR (ν, cm^{-1}):** 2936, 1685, 1261, 1064; **HRMS (ESI)$^+$:** *m/z* calc. for $C_{15}H_{23}N_2O$ [*M*+H]$^+$: 247.1805, found 247.1803; **$[\alpha]^{20}_D$** -14.2 (c = 0.15, $CHCl_3$).

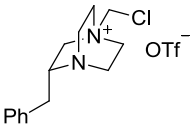
6.4.2 Chloromethylation of mono-substituted DABCOs

(*R*)-3-Benzyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (125)



(*R*)-2-Benzyl-1,4-diazabicyclo[2.2.2]octane (300 mg, 1.48 mmol) was dissolved in DCM (5 ml) and left under argon, without stirring, for 120 hours. Removal of the solvent under reduced pressure afforded the product as a solid (426 mg, 99%).

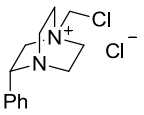
^{1}H NMR (400 MHz, MeOD): δ = 2.91 (dd, *J* = 13.8 Hz, *J* = 7.8 Hz, 1H), 3.03 (dd, *J* = 13.8 Hz, *J* = 7.1 Hz, 1H), 3.15-3.22 (m, 2H), 3.29 (t, *J* = 7.8 Hz, 2H), 3.40-3.66 (m, 7H), 5.18 (d, *J* = 9.9 Hz, 1H), 5.23 (d, *J* = 9.9 Hz, 1H), 7.22-7.28 (m, 1H), 7.29-7.35 (m, 4H); **^{13}C NMR (100.6 MHz, MeOD):** δ = 37.6, 39.3, 46.6, 50.9, 51.9, 55.6, 56.9, 68.1, 126.9, 128.7, 129.2, 137.1; **HRMS (ESI)$^{+}$:** *m/z* calc. for $C_{14}H_{20}ClN_2$ $[M]^+$: 251.1306, found 251.1310.



To a solution of (*R*)-3-benzyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane chloride (166 mg, 0.66 mmol) in acetonitrile (5 ml) at room temperature was added sodium trifluoromethanesulfonate (113 mg, 0.66 mmol) and the reaction was stirred for 24 hours before filtering and concentrating in vacuo. Recrystallizing from ether afforded the title compound (136 mg, 59% yield).

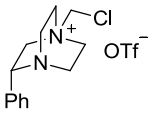
^{1}H NMR (400 MHz, CD_3CN): δ = 2.83 (dd, *J* = 14.4, *J* = 7.0 Hz, 1H), 2.92 (dd, *J* = 13.9, *J* = 8.0 Hz, 1H), 2.98-3.22 (m, 4H), 3.28-3.48 (m, 6H), 3.50-3.56 (m, 1H), 4.97 (d, *J* = 7.6 Hz, 2H), 7.23-7.34 (m, 5H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 38.0, 39.9, 47.2, 51.6, 52.8, 56.0, 57.5, 69.1, 120.4 (q, *J*= 320 Hz), 127.7, 129.5, 129.5, 130.2, 130.2, 138.5; **^{19}F {1H} NMR (376.6 MHz, CD_3CN):** δ = -79.2 (OTf); **IR (neat) (ν, cm^{-1}):** 1276, 1169, 1029; **HRMS (ESI):** m/z calcd for $C_{14}H_{20}ClN_2$ (M)+: 251.1310, found 251.1310; **$[\alpha]^{22}_D$** +30 (c 0.29, MeOH).

(*R*)-3-Phenyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (126)



(*R*)-2-Phenyl-1,4-diazabicyclo[2.2.2]octane (60 mg, 0.32 mmol) was dissolved in DCM (0.7 ml) and acetone (0.7 mL) and stirred under argon for 120 hours. The precipitate was filtered and washed with cold dichloromethane and diethyl ether affording (3*R*)-1-(chloromethyl)-3-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride **194** (62 mg, 72%).

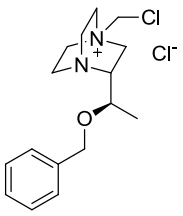
^{1}H NMR (500 MHz, CD_3CN): δ = 2.94-3.01 (m, 1H), 3.04-3.09 (m, 1H), 3.35 (dt, *J* = 13.5 Hz, *J* = 8.8 Hz, 1H), 3.43-3.55 (m, 2H), 3.62-3.67 (m, 3H), 3.87 (t, *J* = 10.4 Hz, 1H), 4.20 (ddd, *J* = 12.3 Hz, *J* = 9.5 Hz, *J* = 3.0 Hz, 1H), 4.51 (t, *J* = 9.0 Hz, 1H), 5.53 (d, *J* = 9.6 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.41-7.47 (m, 4H); **^{13}C NMR (125.8 MHz, CD_3CN):** δ = 40.6, 46.8, 51.7, 52.6, 56.4, 56.7, 68.9, 127.9, 127.9, 129.0, 129.7, 129.7, 138.8; **IR (neat) (ν, cm^{-1}):** 2957, 1658, 1097; **HRMS (FI):** *m/z* calcd for $C_{13}H_{18}ClN_2$ ([M]+): 237.1153, found 237.1157; **mp:** 147-148 °C; **$[\alpha]^{22}_D$** -17 (*c* 0.57, MeOH); **elemental analysis:** calc. for $C_{13}H_{18}Cl_2N_2$: C, 57.15; H, 6.64; N, 10.25; found: C, 56.93; H, 6.75; N, 10.14.



A solution of (3*R*)-1-(chloromethyl)-3-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (200 mg, 0.84 mmol) and sodium trifluoromethanesulfonate (145 mg, 0.84 mmol) in acetonitrile (12 mL) was stirred for 46 hours at room temperature. The solvent was concentrated under reduced pressure, 3 mL of dry acetonitrile was added and the suspension was filtered. The solid was rinsed twice with acetonitrile (2 x 5 mL) and the filtrate was concentrated under reduced pressure to afford the title compound as a solid (282 mg, 99%).

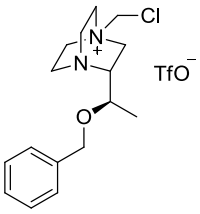
^{1}H NMR (400 MHz, CD_3CN): δ = 2.95-3.04 (m, 1H), 3.07-3.14 (m, 1H), 3.27-3.39 (m, 3H), 3.40-3.51 (m, 4H), 4.05 (ddd, *J* = 12.1 Hz, *J* = 9.5 Hz, *J* = 2.7 Hz, 1H), 4.50 (t, *J* = 9.0 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 7.34-7.46 (m, 5H); **^{13}C NMR (125.8 MHz, CD_3CN):** δ = 40.6, 46.7, 52.1, 53.1, 56.4, 57.1, 69.3, 121.5 (q, *J* = 320 Hz), 127.6, 127.6, 129.1, 129.8, 129.8, 138.6; **^{19}F {1H} NMR (376.6 MHz, CD_3CN):** δ = -79.3 (s, OTf); **IR (neat) (ν, cm^{-1}):** 1249, 1156, 1028; **HRMS (FI):** *m/z* calcd for $C_{13}H_{18}ClN_2$ ([M]+): 237.1153, found 237.1150; **mp:** 60-63 °C; **[α]$^{22}_{D}$** -11 (*c* 0.94, MeOH).

(1*R*)-3-((*R*)-1-(benzyloxy)ethyl)-1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (127)



(2*R*)-2-((*R*)-1-(benzyloxy)ethyl)-1,4-diazabicyclo[2.2.2]octane (602 mg, 2.48 mmol) was dissolved in DCM (20 mL) and left at room temperature under argon, without stirring, for 108 hours. Removal of the solvent under reduced pressure afforded (2*R*)-2-((*R*)-1-(Benzyloxy)ethyl)-1-(chloromethyl)-1,4-diaza-bicyclo[2.2.2]octane chloride as a white solid (757 mg, 2.29 mmol, 93 %).

^{1}H NMR (500 MHz, acetone): δ = 1.29 (d, *J* = 6.3 Hz, 3H), 3.08-3.16 (m, 1H), 3.33 (t, *J* = 7.7 Hz, 2H), 3.35-3.41 (m, 1H), 3.56-3.72 (m, 3H), 3.73-3.85 (m, 2H), 3.85-3.99 (m, 2H), 4.06 (ddd, *J* = 11.7, *J* = 9.3, *J* = 3.0 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 5.94 (d, *J* = 9.5 Hz, 1H), 5.99 (d, *J* = 9.5 Hz, 1H), 7.22-7.30 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR (63 MHz, acetone):** δ = 16.6, 42.3, 48.3, 51.5, 52.1, 53.8, 59.6, 68.8, 72.4, 74.7, 128.3, 128.7, 129.2, 139.9; **IR (ν, cm^{-1}):** 3404, 1456, 1276, 1069; **HRMS (ESI)$^{+}$:** *m/z* calc. for $C_{16}H_{24}ClN_2O$ [*M*+H]$^{+}$: 295.1572, found 295.1572; **[α]$^{20}_{D}$** -13.3 (c = 0.12, MeOH).



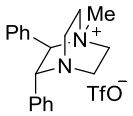
To a solution of (2*R*)-2-((*R*)-1-(benzyloxy)ethyl)-1-(chloromethyl)-1,4-diaza-bicyclo[2.2.2]octane chloride (180 mg, 0.54 mmol) in acetonitrile (4.2 mL) at room temperature was added sodium triflate (94 mg, 0.54 mmol) and the reaction was stirred overnight. The precipitation was filtered off and washed with acetonitrile and the filtrate was evaporated under reduced pressure to give furnish crude product (209 mg). Recrystallization in diethyl ether/methanol afforded the triflate salt as a white solid (159 mg, 0.36 mmol, 66 %).

^{1}H NMR (250 MHz, CD_3CN): δ = 1.24 (d, *J* = 6.4 Hz, 3H), 2.89-3.07 (m, 1H), 3.08-3.56 (m, 10H), 3.64 (quin, *J* = 5.9 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.86-5.05 (m, 2H), 7.23-7.46 (m, 5H); **^{13}C NMR (63 MHz, CD_3CN):** δ = 16.3, 42.2, 47.9, 52.0, 52.9, 54.3, 59.2, 69.4, 72.3, 74.5, 128.7, 128.8, 129.5, 139.7; **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = -79.3 (OTf); **IR (ν, cm^{-1}):** 2361, 2342, 1468, 1257, 1164, 1031; **HRMS (ESI)$^{+}$:** *m/z* calc. for $C_{16}H_{24}ClN_2O$ [*M*+H]$^{+}$: 295.1572, found 295.1572; **$[\alpha]^{20}_{D}$** -6.6 (c = 0.15, MeOH).

6.4.3 General procedure for methylation of chiral DABCOs

To a solution of chiral DABCO (1.0 eq.) in dichloromethane (0.02 M) at -78 °C, methyl trifluoromethanesulfonate (1.0 eq.) in dichloromethane (0.2 M) was added dropwise (10 min addition time) at the same temperature and the reaction mixture was stirred for 4 hours at -78 °C. The solvent was evaporated under reduced pressure before ether was added and the resulting solid was recovered by filtration and dried under high vacuum to afford the triflate salt.

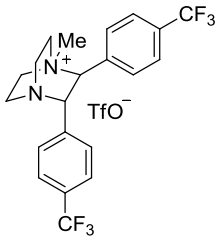
(2*R*,3*R*)-1-methyl-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (128)



To a solution of (2*R*,3*R*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (1.0 eq) in Et_2O (0.02 M) at 0 °C was added methyl triflate (1.0 eq.) dropwise. The reaction was stirred for 3 hours, after which the precipitate was collected under vacuum filtration. The resulting solid was washed with ether and acetone to afford the triflate salt as a white solid (800 mg, 97 % yield).

^{1}H NMR (500 MHz, CD_3CN): δ = 2.60 (s, 3H), 3.07-3.19 (m, 3H), 3.38-3.49 (m, 2H), 3.50-3.59 (m, 2H), 3.75 (t, *J* = 11.3 Hz, 1H), 4.75 (d, *J* = 9.6 Hz, 1H), 4.81 (d, *J* = 9.6 Hz, 1H), 7.27-7.39 (m, 5H), 7.55-7.63 (m, 3H), 7.76-7.81 (m, 2H); **^{13}C NMR (125.8 MHz, CD_3CN):** δ = 40.8, 47.1, 50.0, 50.7, 58.4, 63.4, 72.6, 122.0 (q, *J* = 320 Hz, OTf), 128.1, 129.2, 129.7, 130.9, 130.9, 131.4, 132.3, 137.8; mp 197-199 °C; **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = -79.3; **IR (ν, cm^{-1}):** 1469, 1272, 1153, 1030, 992, 708; **HRMS (ESI$^+$):** *m/z* calc. for $C_{19}H_{23}N_2$ $[M]^+$ 279.1856, found 279.1853; **mp:** 197-199 °C; **$[\alpha]^{22}_D$** -85.7 (*c* 0.27, MeOH).

(2*S*,3*S*)-1-methyl-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (129)

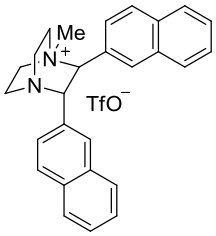


To a solution of (2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane (1.0 eq) in Et_2O (0.02 M) at 0 °C was added methyl triflate (1.0 eq.) dropwise. The reaction was stirred for 3 hours, after which the precipitate was collected under vacuum filtration. The resulting solid was washed with ether and acetone to afford the triflate salt as a white solid (143 mg, 92 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.71 (s, 3H), 3.04-3.13 (m, 1H), 3.15-3.24 (m, 1H), 3.25-3.32 (m, 1H), 3.45-3.63 (m, 3H), 3.68 (ddt, *J* = 12.4 Hz, *J* = 9.5 Hz, *J* = 3.2 Hz, 1H), 3.85 (ddt, *J* = 12.4

Hz, *J* = 10.5 Hz, *J* = 2.9 Hz, 1H), 4.93 (d, *J* = 9.6 Hz, 1H), 5.00 (d, *J* = 9.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 40.8, 46.9, 50.0, 50.7, 58.4, 62.9, 71.2, 121.6 (q, *J* = 320.5 Hz, OTf), 124.7 (q, *J* = 270.2 Hz, CF_3), 125.0 (q, *J* = 271.1 Hz, CF_3), 126.4 (q, *J* = 3.9 Hz), 127.7 (q, *J* = 3.7 Hz), 128.8, 128.8, 130.5 (q, *J* = 32.1 Hz), 133.4 (q, *J* = 33.3 Hz), 135.4, 142.1; **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = -62.5 (CF_3), -79.3 (TfO); **IR (ν, cm^{-1}):** 3095, 2955; **mp:** 182-83 °C; **$[\alpha]^{22}_D$** +43.0 (c 0.30, MeOH); **Elemental analysis:** Calc. for $C_{22}H_{21}F_9N_2O_3S$: C, 46.81; H,3.75; N, 4.96. Found: C, 46.74; H, 3.70; N, 4.61.

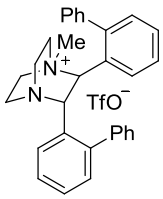
(2*S*,3*S*)-1-methyl-2,3-di(naphthalen-2-yl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (130)



Prepared according to the general procedure to afford the triflate salt as a white solid (430 mg, 0.81 mmol, 96 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.71 (s, 3H), 3.16-3.28 (m, 3H), 3.47-3.59 (m, 2H), 3.60-3.69 (m, 1H), 3.69-3.78 (m, 1H), 3.88-3.99 (m, 1H), 5.11 (d, *J* = 9.6 Hz, 1H), 5.15 (d, *J* = 9.6 Hz, 1H), 7.49-7.55 (m, 3H), 7.65-7.70 (m, 2H), 7.83-7.95 (m, 5H), 7.99-8.05 (m, 1H), 8.06-8.11 (m, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 8.50 (s, 1H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 40.5, 46.8, 49.7, 50.3, 58.1, 63.3, 72.2, 121.7 (q, *J* = 321.1 Hz, CF_3), 126.1, 126.4, 127.1, 127.2, 127.9, 128.0, 128.3, 128.3, 128.3, 128.6, 128.7, 129.0, 129.0, 129.2, 130.3, 133.4, 133.5, 133.8, 134.8, 134.9; **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = -79.3; **IR (ν, cm^{-1}):** 1255, 1029, 819; **HRMS (ESI$^+$, m/z):** $[C_{27}H_{27}N_2]^+$ $(M)^+$ calc. 379.2169, found 379.2165; **mp:** 213-214 °C.

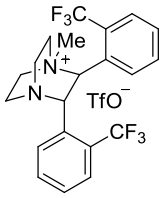
(2*S*,3*S*)-2,3-di([1,1'-biphenyl]-2-yl)-1-methyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (131)



Prepared according to the general procedure to afford the triflate salt as a white solid (139 mg, 78% yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.35 (s, 3H), 2.93-3.07 (m, 2H), 3.15-3.47 (m, 6H), 4.68 (d, *J* = 9.5 Hz, 1H), 4.80 (d, *J* = 9.5 Hz, 1H), 7.06-7.66 (m, 18H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 40.2, 47.8, 49.7, 50.1, 59.5, 62.6, 67.8, 121.7 (q, *J* = 321.1 Hz, OTf), 128.0, 128.5, 128.7, 128.8, 128.9, 129.4, 129.4, 129.8, 130.1, 130.3, 130.5, 130.6, 131.8, 132.0, 132.9, 133.2, 140.3, 141.4, 145.7, 147.3; **^{19}F {1H} NMR (376.5 MHz, CD_3CN):** δ = -79.3 (TfO); **IR (ν, cm^{-1}):** 1257, 1029, 702; **HRMS (ESI^{+}):** m/z calc. for $C_{31}H_{31}N_2$ ($[M]^{+}$): 431.2482, found 431.2475; **mp:** 208-210 °C; **$[\alpha]^{22}_{D}$** +47 (c 0.26, MeOH).

(2*S*,3*S*)-1-methyl-2,3-bis(2-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (132)

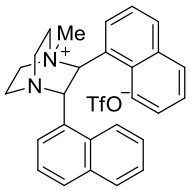


Prepared according to the general procedure to afford the triflate salt as a white solid (139 mg, 98% yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.70 (s, 3H), 3.14 (ddd, *J* = 10.0 Hz, 8.3 Hz, 3.9 Hz, 1H), 3.37-3.56 (m, 3H), 3.64-3.71 (m, 1H), 3.77-3.94 (m, 3H), 5.03 (d, *J* = 9.8 Hz, 1H), 5.14 (d, *J* = 9.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 8.5, 8.3 Hz, 3H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 40.2, 48.7, 50.0, 51.2, 60.7, 62.9, 66.9, 124.5 (q, *J* = 274.0 Hz, CF_3), 125.0 (q, *J* = 274.8 Hz, CF_3), 128.3 (q, *J* = 5.6 Hz), 129.1 (q, *J* = 6.4 Hz), 130.2, 130.3 (q, *J* = 29.8 Hz), 130.8, 131.5, 131.6 (q, *J* = 29.6 Hz), 133.0, 133.1, 133.4, 134.9; **^{19}F {1H} NMR (376.5 MHz, CD_3CN):** δ

= -55.3, -58.7, -79.2; **IR (ν, cm^{-1}):** 1225, 1054, 985; **HRMS (ESI$^+$):** m/z calc. for $C_{21}H_{21}F_6N_2$ ([M]$^+$): 415.1603, found 415.1601; **mp:** 99-101 °C; **[α]$^{22}_D$** -3.7 (c 0.25, MeOH).

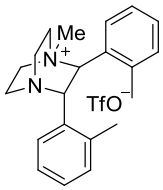
(2*S*,3*S*)-1-methyl-2,3-di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (133)



To a solution of (2*S*,3*S*)-2,3-di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octane (1.0 eq) in Et_2O (0.02 M) at 0 °C was added methyl triflate (1.0 eq.) dropwise. The reaction was stirred for 3 hours, after which the precipitate was collected under vacuum. The resulting solid was washed with ether and acetone to afford the triflate salt as a white solid (150 mg, 95 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.55 (s, 3H), 3.02 (ddd, *J* = 13.7 Hz, *J* = 9.5 Hz, *J* = 2.3 Hz, 1H), 3.16-3.29 (m, 2H), 3.42 (ddd, *J* = 13.6 Hz, *J* = 9.3 Hz, *J* = 7.8 Hz, 1H), 3.54 (dt, *J* = 11.7 Hz, *J* = 9.0 Hz, 1H), 3.80-3.91 (m, 1H), 4.07-4.19 (m, 2H), 5.59 (d, *J* = 10.1 Hz, 1H), 6.06 (d, *J* = 10.1 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.44-7.54 (m, 2H), 7.58-7.64 (m, 2H), 7.70 (d, *J* = 6.7 Hz, 1H), 7.71 (d, *J* = 6.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.85 (ddd, *J* = 8.6 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 7.4 Hz, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 8.85 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 40.5, 46.6, 48.9, 50.2, 58.8, 61.7, 63.4, 121.7 (q, *J* = 321.1 Hz, CF_3), 122.9, 124.0, 125.0, 125.0, 125.9, 126.0, 126.7, 127.2, 127.3, 128.5, 129.0, 129.2, 130.1, 130.2, 131.0, 132.6, 132.9, 133.7, 134.7, 134.8; **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = -79.3 (TfO); **IR (ν, cm^{-1}):** 2932, 2868, 2360; **HRMS (ESI$^+$):** *m/z* calc. for $C_{27}H_{27}N_2$ [M]$^+$: 379.2169, found 379.2165; **mp:** 210-212 °C; **[α]$^{22}_D$** = +303.6 (c 0.52, MeOH).

(2*S*,3*S*)-1-methyl-2,3-di-o-tolyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (134)

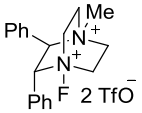


To a solution of (2*S*,3*S*)-2,3-di-o-tolyl-1,4-diazabicyclo[2.2.2]octane (147 mg, 0.50 mmol) in DCM (20 mL) at -78 °C, methyl triflate (40 µL, 0.45 mmol) in dichloromethane (5 mL) was added dropwise (10 min addition time) at the same temperature and the reaction mixture was stirred for 4 hours at -78 °C. The solvent was evaporated under reduced pressure before ether was added and the resulting solid was recovered by filtration and dried under high vacuum to afford the triflate salt as a white solid (197 mg, 86% yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.39 (s, 3H), 2.57 (s, 3H), 2.64 (s, 3H), 3.01 (ddd, *J* = 9.5 Hz, 6.6 Hz, 2.2 Hz, 1H), 3.15-3.25 (m, 2H), 3.36 (ddd, *J* = 10.3 Hz, 7.1 Hz, 6.8 Hz, 1H), 3.49-3.59 (m, 1H), 3.68-3.76 (m, 1H), 3.78-3.85 (m, 1H), 3.92 (ddt, *J* = 9.5 Hz, 3.2 Hz, 3.0 Hz, 1H), 4.78 (d, *J* = 10.1 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 7.19-7.30 (m, 4H), 7.35-7.41 (m, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.92-7.95 (m, 1H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 19.8, 21.0, 40.5, 47.6, 48.8, 50.9, 59.5, 62.8, 65.9, 121.7 (q, *J* = 321.1 Hz, CF_3), 126.3, 126.9, 128.6, 129.1, 129.5, 129.8, 132.0, 132.6, 133.3, 134.1, 140.4, 141.2; **^{19}F {1H} NMR (376.5 MHz, CD_3CN):** δ = -79.3 (TfO); **IR (ν, cm^{-1}):** 1465, 1257, 1029; **HRMS (ESI$^+$):** m/z calc. for $C_{21}H_{27}N_2$ ($[M]^+$): 307.2169, found 307.2154; **mp:** 89-91 °C; **$[\alpha]^{22}_D$** +38 (c 0.175, MeOH).

6.4.4 Isolation of chiral Selectfluor using F_2 gas

(2*R*,3*R*)-1-fluoro-4-methyl-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (135)

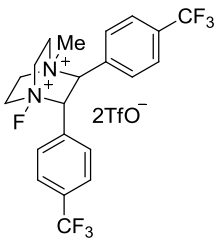


A solution of triflate salt (1.0 eq) and sodium trifluoromethanesulfonate (1.0 eq) in acetonitrile (0.02 M) was prepared in a small PTFE reactor. The mixture was purged with N_2 and cooled to -35 °C. Elemental F_2 as a homogeneous 1:9 (*v/v*) mixture

with N_2 was introduced at a flow rate of 15 mL/min into the rapidly stirred mixture via PTFE tubing at -35 °C (**Caution: Poison, corrosive, toxic)**. The reaction was monitored by ^{19}F NMR. Once fluorination was complete, the mixture was purged with N_2 and allowed to warm to room temperature, before filtration to remove sodium fluoride, and the solution was evaporated under reduced pressure. Purification by recrsytallisation (Et_2O/MeOH 4:1) afforded the title compound as a pale yellow solid (140 mg, 97 % yield).

^{1}H NMR (500 MHz, CD_3CN): δ = 2.95 (s, 3H), 4.24 (t, *J* = 11.9 Hz, 1H), 4.42-4.49 (m, 1H), 4.55 (dt, *J* = 11.8, *J* = 8.9 Hz, 1H), 4.70-4.82 (m, 3H), 5.02 (q, *J* = 9.9 Hz, 1H), 5.30-5.37 (m, 1H), 6.03 (d, *J* = 10.9 Hz, 1H), 6.54 (d, *J* = 10.9 Hz, 1H), 7.58-7.61 (m, 4H), 7.65-7.69 (m, 2H), 7.85-7.96 (m, 4H); **^{13}C NMR (125.8 MHz, CD_3CN):** δ = 50.9, 53.5 (d, *J* = 9.9 Hz), 53.6, 58.8 (d, *J* = 5.6 Hz), 59.9 (d, *J* = 15.4 Hz), 74.5, 77.8 (d, *J* = 14.3 Hz), 122.0 (q, *J* = 320 Hz, OTf), 122.5, 122.5, 125.3, 131.4, 131.6, 132.8, 134.5, 134.8; **^{19}F{1H} NMR (470.4 MHz, CD_3CN):** δ = +35.4 (s, $[N\text{-}F]^+$), -79.7 (s, TfO^-); **IR (ν, cm^{-1}):** 1469, 1279, 1153, 1032, 756, 640; **HRMS (ESI$^+$):** *m/z* calc. for $C_{19}H_{22}FN_2$ $[M]^+$ 297.1761, found 297.1762; **mp:** 174-176 °C; **$[\alpha]^{22}_D$** -21.7 (*c* 1.00, MeOH); **Elemental analysis:** Calc. for $C_{21}H_{23}F_7N_2O_6S_2$: C, 42.28; H, 3.89; N, 4.70. Found: C, 42.38; H, 4.01; N, 4.66.

(2*S*,3*S*)-1-fluoro-4-methyl-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (136)

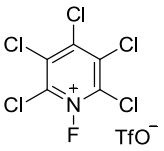


A solution of triflate salt (1.0 eq) and sodium trifluoromethanesulfonate (1.0 eq) in acetonitrile (0.02 M) was prepared in a small PTFE reactor. The mixture was purged with N_2 and cooled to -35 °C. Elemental F_2 as a homogeneous 1:9 (*v/v*) mixture with N_2 was introduced at a flow rate of 15 mL/min into the rapidly stirred mixture via PTFE tubing at -35 °C (**Caution: Poison,**

corrosive, toxic). The reaction was monitored by ^{19}F NMR. Once fluorination was complete, the mixture was allowed to warm to room temperature, before filtration to remove sodium fluoride, and the solution was evaporated under reduced pressure. Purification by recrsytallisation (Et_2O/MeOH 4:1) afforded the desired product as a pale yellow solid (115 mg, 97 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 3.03 (s, 3H), 4.30-4.36 (m, 1H), 4.51 (d, *J* = 21.8 Hz, 1H), 4.61 (dd, *J* = 19.8 Hz, *J* = 10.3 Hz, 1H), 4.76-4.86 (m, 3H), 5.09 (q, *J* = 10.0 Hz, 1H), 5.41 (q, *J* = 11.4 Hz, 1H), 6.22 (d, *J* = 10.5 Hz, 1H), 6.71 (d, *J* = 10.7 Hz, 1H) 7.90 (m, 4H), 8.09-8.20 (m, 4H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 51.2, 53.9, 53.9 (d, *J* = 6.6 Hz), 59.2 (d, *J* = 5.2 Hz), 60.2 (d, *J* = 15.3 Hz), 73.2, 76.3 (d, *J* = 14.2 Hz), 121.8 (q, *J* = 320.3 Hz, OTf), 124.2 (q, *J* = 272.4 Hz), 124.3 (q, *J* = 272.1 Hz), 126.3, 128.1 (q, *J* = 3.6 Hz), 128.4 (q, *J* = 3.5 Hz), 129.0, 133.9, 133.9, 135.2 (q, *J* = 28.7 Hz), 135.4 (q, *J* = 29.0 Hz); **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = +36.6 ($[N\text{-}F]^+$), -63.9 (CF_3), -64.0 (CF_3), -79.3 (TfO); **IR (ν, cm^{-1}):** 3095, 2955; **mp:** 147-150 °C, **$[\alpha]^{22}_D$** +74.5 (*c* 0.53, MeOH); **Elemental analysis:** Calc. for $C_{23}H_{21}F_{13}N_2O_6S_2$: C, 37.71; H, 2.89; N, 3.82. Found: C, 37.43; H, 2.76; N, 3.90.

***N*-Fluoropentachloropyridinium trifluoromethanesulfonate (138)**



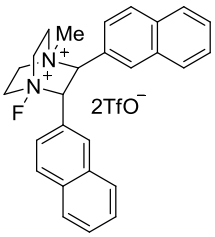
Pentachloropyridine (10.0 g, 39.8 mmol) and triflic acid (5.00 mL, 56.9 mmol) were mixed in trifluoroacetic acid (160 mL). The mixture was purge with nitrogen for 20 min and cooled using an ice bath before 10 % F_2/N_2 (3.0 eq) was passed through the mixture at a rate of 30 mL/min at 5 °C for 15 hours (**Caution: Poison, corrosive, toxic)**. After the reaction, the mixture was purged with nitrogen for 30 min, and the solvent was evaporated under reduced pressure. Ether (50 mL) was slowly added to the oily residue and the resulting white precipitate formed was collected by filtration and washed with EtOAc (15 mL) to afford the title compound as a white solid.

^{13}C NMR (125.8 MHz, CD_3CN): δ = 135.4, 142.0, 156.0; **^{19}F {1H} NMR (376 MHz, CD_3CN):** δ = +46.5 ($[N\text{-}F]^+$), -79.3 (OTf); **mp:** 123-124 °C; **Elemental analysis:** $C_6Cl_5F_4NO_3S$: C 17.18; N 3.34. Found: C 17.07; N 3.41.

6.4.5 General procedure for preparation of chiral Selectfluor by *in situ* fluorination using fluorine transfer

An *in situ* sample of the fluorinated reagent was prepared by mixing the corresponding methyl triflate salt (1.0 eq.) with *N*-fluoropentachloropyridinium triflate (1.0 eq.) and $NaHCO_3$ (2.0 eq.) in CD_3CN. Filtration through a cotton wool pipette afforded the *in situ* prepared reagent which displayed the following characteristic data.

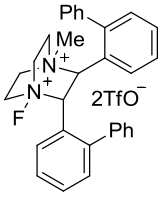
(2*S*,3*S*)-1-fluoro-4-methyl-2,3-di(naphthalen-2-yl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (140)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +35.9 ($[N\text{-}F]^+$), -79.3 (OTf).

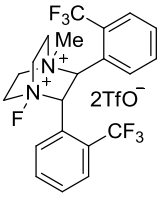
(2*S*,3*S*)-2,3-di([1,1'-biphenyl]-2-yl)-1-fluoro-4-methyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (141)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +36.5 ($[N\text{-}F]^+$), -79.3 (OTf).

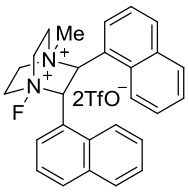
(2*S*,3*S*)-1-fluoro-4-methyl-2,3-bis(2-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (142)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +37.3 (q, *J* = 13.2 Hz, 1F, $[N\text{-}F]^+$), -55.1 (s, 3F, CF_3), -56.5 (d, *J* = 13.2 Hz, 3F), -79.3 (OTf).

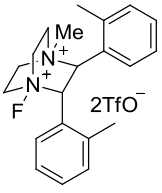
(2*S*,3*S*)-1-fluoro-4-methyl-2,3-di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (143)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +35.1 ($[N\text{-}F]^+$), -79.3 (OTf).

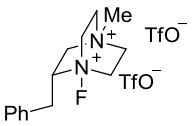
(2*S*,3*S*)-1-fluoro-4-methyl-2,3-di-o-tolyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (144)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +33.6 ($[N\text{-}F]^+$), -79.3 (OTf).

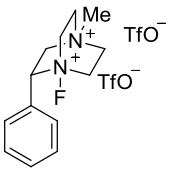
(2*R*)-2-Benzyl-1-fluoro-4-methyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (139)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +29.7 ($[N\text{-}F]^+$), -79.3 (OTf).

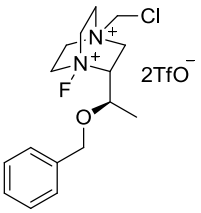
(2*R*)-1-fluoro-4-methyl-2-phenyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (145)



Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +31.0 ($[N\text{-}F]^+$), -79.3 (OTf).

(2*R*)-2-((R)-1-(benzyloxy)ethyl)-4-(chloromethyl)-1-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(trifluoromethanesulfonate) (146)



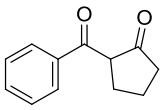
Prepared *in situ* according to the general procedure which displayed the following characteristic data.

^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +33.1 ($[N\text{-}F]^+$), -79.3 (OTf).

6.4.6 Reactivity of chiral Selectfluors

6.4.6.1 Synthesis of compounds

2-Benzoylcyclopentanone (147)



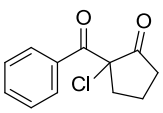
To a solution of LiHMDS (1.0 M sln in THF, 20 mL, 20.0 mmol) in THF (100 mL) at -10 °C was added cyclopentanone (1.77 mL, 20.0 mmol). The reaction was stirred for 30 minutes before the addition of benzoyl chloride (1.16 mL, 10.0 mmol) as a solution in THF (10 mL). Stirring was continued at -10 °C for 14 hours, during which the reaction was allowed to warm to room temperature. The reaction was quenched with 1M HCl, extracted into ether, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtAOc/PE 1:9) afforded the title compound as a colourless oil (1.21 g, 6.43 mmol, 64 % yield).

Data given for enol form (enol/keto 2.25:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (tt, *J* = 7.7 Hz, *J* = 7.3 Hz, 2H), 2.53 (t, *J* = 7.8 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 7.47-7.55 (m, 3H), 7.77-7.82 (m, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 21.3, 28.4, 37.6, 109.3, 128.1, 128.3, 131.0, 134.6, 168.6, 210.5.

Data consistent with literature values.[55]

2-Benzoyl-2-chlorocyclopentanone (148)

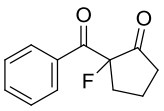


To a solution of 2-benzoylcyclopentanone (50 mg, 0.27 mmol) in MeCN (2 mL) at room temperature was added $NaHCO_3$ (27 mg, 0.32 mmol) and NCS (39 mg, 0.29 mmol). The reaction was stirred overnight before diluting with water and extracting into ether. The combined ether layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2,

EtOAc/PE 1:9) afforded the title compound as a colourless oil (39 mg, 0.18 mmol, 68 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.01-2.12 (m, 1H), 2.13-2.25 (m, 1H), 2.49-2.59 (m, 3H), 3.02 (dt, *J* = 14.1 Hz, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.67 (tt, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 8.01-8.05 (m, 2H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 19.2, 35.9, 39.0, 75.5, 129.0, 130.3, 134.1, 134.4, 194.6, 208.8; **IR (v, cm^{-1}):** 1756 (s, C=O), 1671 (s, C=O); **HRMS (ESI^+, m/z):** $[C_{12}H_{11}ClNaO_2]^+$ $(M+Na)^+$ calc. 245.0340, found 245.0340.

2-Benzoyl-2-fluorocyclopentanone (149)



To a solution of 2-benzoylcyclopentanone (50 mg, 0.27 mmol) in MeCN (2 mL) at room temperature was added $NaHCO_3$ (27 mg, 0.32 mmol) and Selectfluor (104 mg, 0.29 mmol). The reaction was stirred overnight before diluting with water and extracting into ether. The combined ether layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:9) afforded the title compound as a colourless oil (44 mg, 0.21 mmol, 80 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.03-2.23 (m, 2H), 2.44 (dddd, *J* = 23.1 Hz, *J* = 14.3 Hz, *J* = 9.9 Hz, *J* = 7.9 Hz, 1H), 2.53 (t, *J* = 7.8 Hz, 2H), 2.79 (dddd, *J* = 14.0 Hz, *J* = 13.1 Hz, *J* = 7.3 Hz, *J* = 4.9 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 7.70 (tt, *J* = 7.4 Hz, *J* = 1.3 Hz, 1H), 8.02-8.08 (m, 2H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 17.9 (d, *J* = 5.1 Hz), 34.7 (d, *J* = 20.1 Hz), 36.0, 102.6 (d, *J* = 202.4 Hz), 129.2, 130.1 (d, *J* = 6.3 Hz), 134.5, 134.7 (d, *J* = 4.0 Hz), 197.6 (d, *J* = 27.6 Hz), 210.7 (d, *J* = 17.1 Hz); **^{19}F NMR (376.5 MHz, CD_3CN):** δ = -157.9 (dd, *J* = 23.5 Hz, *J* = 13.1 Hz, 1F).

Data consistent with literature values.[56]

6.4.5.2 General procedure for reactivity study

To a 1.75 mL screw-top vial containing CD_3CN (0.75 mL) was added NCS* (0.10 mmol), electrophilic fluorinating reagent[#] (0.10 mmol) and $NaHCO_3$ (0.20 mmol) and stirring was commenced to ensure complete solubilisation of the halogenating reagents. Finally, 2-benzoylcyclopentanone (0.10 mmol) was added as a solution in CD_3CN (0.25 mL) (A stock solution was prepared for increased accuracy – 2.0 mmol in 5.0 mL CD_3CN). The reaction was stirred in the dark for 24 hours before filtering through a cotton wool pipette and obtaining a ^1H NMR directly without purification. A typical spectra obtained in this way is illustrated below.

* NCS was purified by recrystallization prior to use in the following way. To a flask containing toluene (50 mL) was added NCS (~10 g) and the flask was heated at reflux for 10 minutes. The majority of the solid dissolved after this time, with a small amount of NCS and the corresponding NHS remaining. The partially dissolved suspension was subjected to a hot filtration to remove the insoluble impurities and the filtrate was left to cool. After 48 hours of being undisturbed at room temperature the resulting colourless crystals were collected by filtration and washed with a minimum of toluene.

[#] The fluorinating reagents were recrystallized prior to use according to our recent publication, except the alkaloid based reagent, which was recrystallized according to the literature.

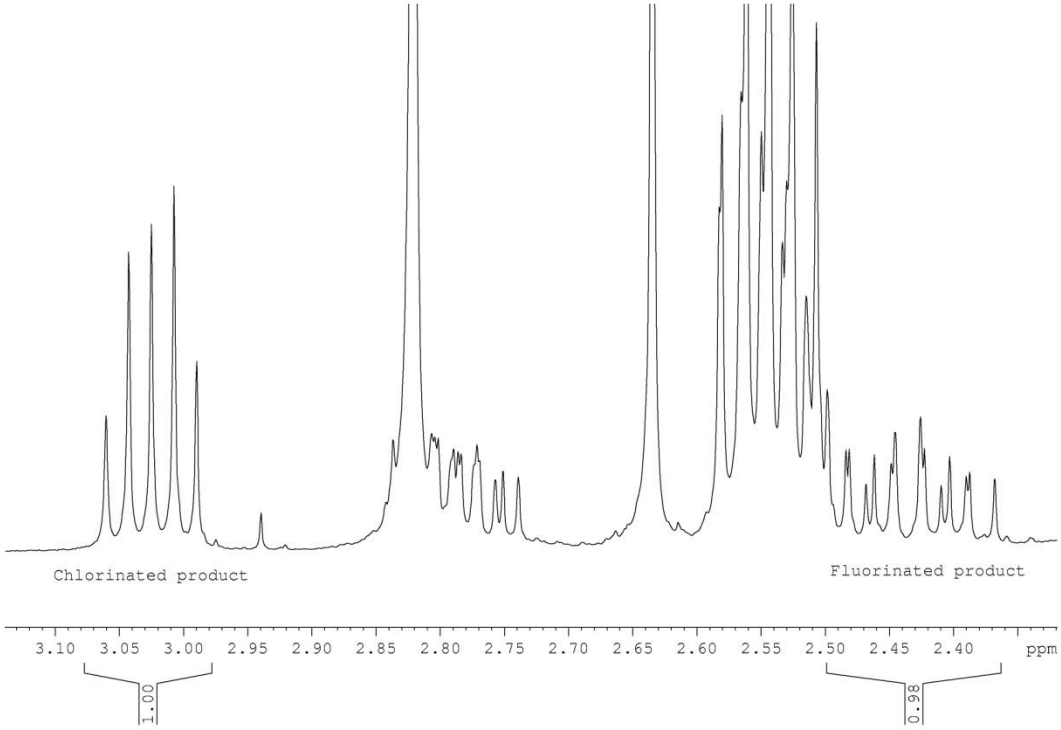
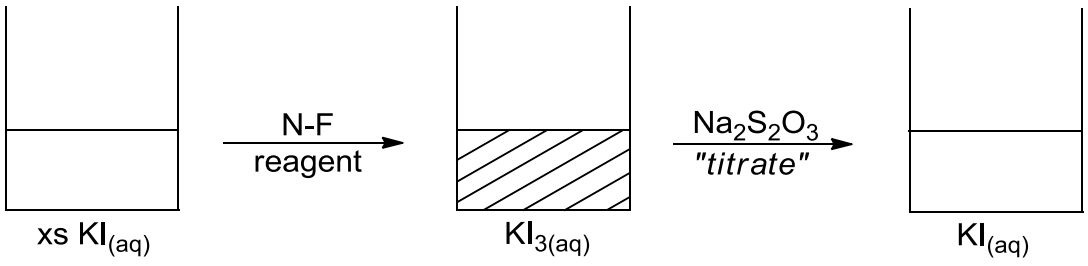


Figure 1 – Example of ^{1}H NMR spectra obtained on a 400 MHz spectrometer from a competition reaction. This is the spectrum obtained from Selectfluor II reagent, showing a 1:0.98 ratio of chlorinated product to fluorinated product.

6.4.7 Purity of fluorinating reagents

6.4.7.1 General iodometric titration procedure



Stock solutions required

Sodium thiosulfate (2 mM) – to a 500 mL volumetric flask add $Na_2S_2O_3$ (158.11 mg, 1.000 mmol) and make up to 500 mL with water.

Charged Fluorinating reagents (4 mM) – to a 100 mL volumetric flask add N-F reagent (0.400 mmol) and make up to 100 mL with water.

Neutral Fluorinating reagents (40 mM) – to a 25 mL volumetric flask add N-F reagent (1.000 mmol) and make up to 25 mL with acetonitrile.

Titration procedure

The F^+ purity can be determined by following the following procedure:

For charged reagents:

1. To a flask containing water (approx 2 mL) with magnetic stirring add excess (with respect to the F^+ reagent) KI (approx 15 mg)

2. Add 10.00 mL of the fluorinating reagent stock solution in water (solution turns brown)

3. Begin to titrate against the stock thiosulfate solution using an accurately calibrated burette (will require 20.0 mL if reagent is 100 % pure).

4. Towards the end-point (as solution begins to turn colourless) add 4 drops of starch solution (solution turns blue)

5. Titrate until blue colour disappears

6. F^+ purity is calculated by: $\frac{titrate\ (mL)}{20\ (mL)}$

For neutral reagents:

1. To a flask containing water (approx 5 mL) with magnetic stirring add excess (with respect to the F^+ reagent) KI (approx 15 mg)

2. Add 1.00 mL of the fluorinating reagent stock solution in acetonitrile (solution turns brown)

3. Begin to titrate against the stock thiosulfate solution using an accurately calibrated burette (will require 20.0 mL if reagent is 100 % pure).

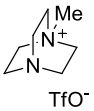
4. Towards the end-point (as solution begins to turn colourless) add 4 drops of starch solution (solution turns blue)

5. Titrate until blue colour disappears

6. F^+ purity is calculated by: $\frac{titrate\ (mL)}{20\ (mL)}$

6.4.7.2 Synthesis of compounds for NMR technique

1-Methyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (150)

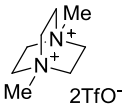


To a solution of DABCO (1.00 g, 8.91 mmol) in DCM (150 mL) at -78 °C was added MeOTf (910 µL, 8.02 mmol) slowly over 1 minute. The reaction was stirred for 2 hours before slowly warming to room temperature overnight. After evaporation to dryness the residue was suspended in ether (150 mL) and stirred vigorously for 20 minutes before collecting the solid under filtration and washing with ether (3 x 50 mL). Drying under high vacuum afforded the title compound as a white solid (2.20 g, 8.00 mmol, 99 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.95 (s, 3H), 3.09-3.16 (m, 6H), 3.18-3.26 (m, 6H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 45.4, 52.0, 54.7, 121.8 (q, *J* = 320.1 Hz); **^{19}F NMR (376.6 MHz, CD_3CN):** δ = -79.3.

Data consistent with literature values.[57]

1,4-Dimethyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(triflate) (151)



To a solution of DABCO (500 mg, 4.46 mmol) in DCM (20 mL) at 0 °C was added MeOTf (1.51 mL, 13.4 mmol) slowly over 1 minute. The reaction was stirred for 1 hour before being added slowly to ether (150 mL) with stirring. The precipitate was filtered and washed with ether before being dried under high vacuum to afford the title compound as a white solid (1.91 g, 4.46 mmol, 99 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 3.28 (s, 6H), 3.89 (m, 12H); **^{13}C NMR (100.6 MHz, CD_3CN):** δ = 53.1, 53.7, 121.5 (q, *J* = 320.0 Hz); **^{19}F NMR (376.6 MHz, CD_3CN):** δ = -79.3.

Data consistent with literature values.[58]

6.4.7.3 General procedure for "NMR titration" using internal reference

To a solution of 1,4-Dimethyl-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(triflate) (22.0 mg, 0.050 mmol) in CD_3CN (1.0 mL) add $NaHCO_3$ (16.8 mg, 0.20 mmol) followed by fluorinating reagent (0.050 mmol). Filter through a cotton wool pipette and obtain a ^{1}H NMR. Purity is assessed by comparison of integrals.

6.4.7.4 General procedure for "NMR titration" using F^+ acceptor

To a solution of 1-methyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (27.6 mg, 0.100 mmol) in CD_3CN (1.0 mL) add $NaHCO_3$ (16.8 mg, 0.20 mmol) followed by fluorinating reagent (0.050 mmol). Stir for 1 hour before filtering through a cotton wool pipette and obtain a ^{1}H NMR. Purity is assessed by comparison of the integrals according to the main text.

^{1}H NMR reference data for fluorinated F^{+} acceptor:

^{1}H NMR (400 MHz, CD_3CN): δ = 3.39 (s, 3H), 4.25-4.35 (m, 6H), 4.69-4.80 (m, 6H).

Data consistent with literature values.[57]

6.4.7.5 Purification of common reagents

6.4.7.5.1 Purification of Selectfluor

To a flask containing 'crude' Selectfluor™ (approx 1 g) add MeOH (30 mL) and heat to reflux then slowly add MeCN at reflux until dissolution occurs (approx 12 mL). Set the flask to one side and allow to cool before placing in a freezer for 48 hours and collecting the crystals under vacuum filtration and drying under high vacuum for 1 hour.

6.4.7.5.2 Purification of NFSI

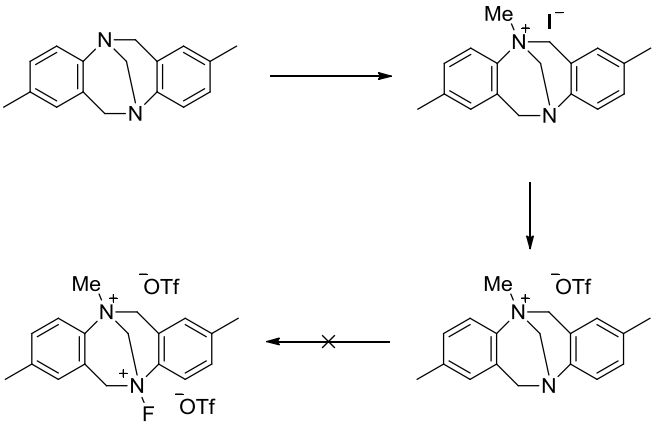
To a flask containing 'crude' NFSI (approx 1 g) add EtOH (approx 25 mL) and heat at reflux until complete dissolution occurs. Set the flask to one side and allow to cool to room temperature and stand for 24 hours before collecting the crystals under vacuum filtration and drying under high vacuum for 1 hour.

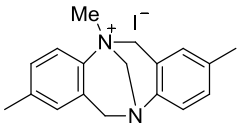
6.4.7.5.3 Purification of *N*-fluoropyridinium type reagents

Reagents of this type can be purified by suspending the 'crude' reagent (approx 1 g) in dry EtOAc (20 mL) and stirring for 10 minutes. Filter off the white solid and wash with EtOAc. Dry the resultant solid under high vacuum for 1 hour.

6.4.7 Troger's base derived reagents

2,5,8-Trimethyl-6,12-dihydro-5*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-5-ium trifluoromethanesulfonate (154)

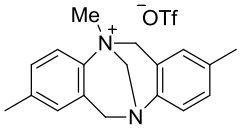




To a solution of 2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (250 mg, 1.0 mmol) in THF (2 mL) at room temperature was added methyl iodide (93 µL, 1.5 mmol) and the reaction was stirred for 24 hours. The precipitated solid was filtered under vacuum and washed with THF to afford the title compound as a white solid (390 mg, 1.0 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3H), 2.26 (s, 3H), 4.16 (s, 3H), 4.16-4.21 (m, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 5.06 (dd, *J* = 15.5 Hz, *J* = 1.5 Hz, 1H), 5.36 (dd, *J* = 11.4 Hz, *J* = 1.8 Hz, 1H), 5.48 (dd, *J* = 11.2 Hz, *J* = 1.4 Hz, 1H), 5.77 (d, *J* = 15.4 Hz, 1H), 6.83-6.87 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.23-7.28 (m, 1H), 8.08 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.8, 21.0, 52.4, 57.4, 68.0, 78.4, 121.2, 127.2, 124.3, 127.1, 127.2, 128.2, 130.5, 130.7, 136.0, 138.7, 139.6, 141.2.

Data consistent with literature values.[59]

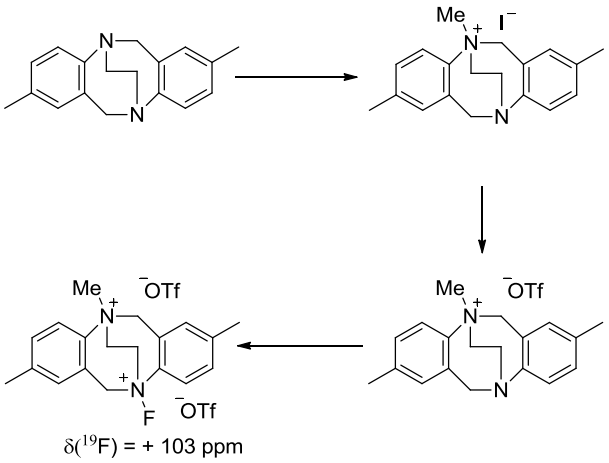


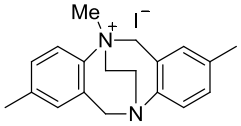
To a solution of 2,5,8-Trimethyl-6,12-dihydro-5H-5,11-methanodibenzo[b,f][1,5]diazocin-5-ium iodide (390 mg, 1.0 mmol) in acetone (10 mL) was added AgOTf (257 mg, 1.0 mmol) and the reaction was stirred for 14 hours before filtering through celite to remove the silver iodide. Evaporation of acetone afforded the title compound as an off-white solid (410 mg, 1.0 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3H), 2.26 (s, 3H), 4.16 (s, 3H), 4.16-4.21 (m, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 5.06 (dd, *J* = 15.5 Hz, *J* = 1.5 Hz, 1H), 5.36 (dd, *J* = 11.4 Hz, *J* = 1.8 Hz, 1H), 5.48 (dd, *J* = 11.2 Hz, *J* = 1.4 Hz, 1H), 5.77 (d, *J* = 15.4 Hz, 1H), 6.83-6.87 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.23-7.28 (m, 1H), 8.08 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.8, 21.0, 52.4, 57.4, 68.0, 78.4, 121.2, 127.2, 124.3, 127.1, 127.2, 128.2, 130.5, 130.7, 136.0, 138.7, 139.6, 141.2; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -78.3.

Data consistent with literature values.[59]

5-Fluoro-2,8,11-trimethyl-5,6,11,12-tetrahydro-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine-5,11-diium bis(trifluoromethanesulfonate) (159)

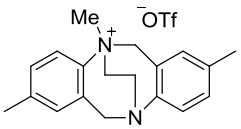




To a solution of 2,8-dimethyl-6,12-dihydro-5,11-ethanodibenzo[b,f][1,5]diazocine (264 mg, 1.0 mmol) in THF (2 mL) was added methyl iodide (93 µL, 1.5 mmol) and the reaction was stirred for 24 hours. The precipitate was filtered and washed with THF before drying under high vacuum to afford the title compound as a pale yellow solid (120 mg, 0.30 mmol, 30 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.20 (s, 3H), 3.71-3.81 (m, 1H), 4.00-4.13 (m, 1H), 4.43 (s, 3H), 4.38-4.50 (m, 2H), 4.79 (d, *J* = 17.3 Hz, 1H), 5.22 (dd, *J* = 13.3 Hz, *J* = 5.3 Hz, 1H), 5.24 (d, *J* = 15.5 Hz, 1H), 6.33 (d, *J* = 15.3 Hz, 1H), 6.84 (d, *J* = 13.3 Hz, 2H), 6.93-7.00 (m, 2H), 7.09-7.15 (m, 1H), 7.94 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.5, 20.6, 49.7, 59.2, 60.2, 69.1, 70.3, 122.0, 127.1, 128.0, 130.0, 130.3, 130.7, 131.5, 133.5, 135.4, 140.6, 142.1, 145.3.

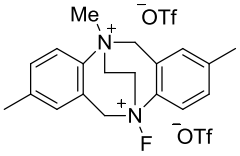
Data consistent with literature values.[60]



To a solution of 2,5,8-Trimethyl-6,12-dihydro-5H-5,11-ethanodibenzo[b,f][1,5]diazocin-5-ium iodide (120 mg, 0.30 mmol) in acetone (5 mL) was added AgOTf (77 mg, 0.3 mmol) and the reaction was stirred for 14 hours before filtering through celite to remove the silver iodide. Evaporation of acetone afforded the title compound as an off-white solid (125 mg, 0.3 mmol, 98 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.20 (s, 3H), 3.71-3.81 (m, 1H), 4.00-4.13 (m, 1H), 4.43 (s, 3H), 4.38-4.50 (m, 2H), 4.79 (d, *J* = 17.3 Hz, 1H), 5.22 (dd, *J* = 13.3 Hz, *J* = 5.3 Hz, 1H), 5.24 (d, *J* = 15.5 Hz, 1H), 6.33 (d, *J* = 15.3 Hz, 1H), 6.84 (d, *J* = 13.3 Hz, 2H), 6.93-7.00 (m, 2H), 7.09-7.15 (m, 1H), 7.94 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 20.5, 20.6, 49.7, 59.2, 60.2, 69.1, 70.3, 122.0, 127.1, 128.0, 130.0, 130.3, 130.7, 131.5, 133.5, 135.4, 140.6, 142.1, 145.3; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -78.3.

Data consistent with literature values.[60]



Prepared *in situ* according to the general procedure for *in situ* fluorination using *N*-fluoro-pentachloropyridinium triflate which displayed the following characteristic data.

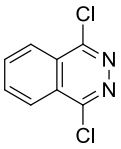
^{19}F {1H} NMR (376 MHz, CD_3CN): δ = +103.0 ($[N\text{-}F]^+$), -79.3 (OTf).

6.5 Experimental data for Chapter 5

Details for the synthesis of compounds described in Chapter 5 are provided herein. See appendices for NMR images of novel compounds as well as X-ray crystallographic data.

6.5.1 Synthesis of cinchona alkaloid analogues

1,4-Dichlorophthalazine (152)

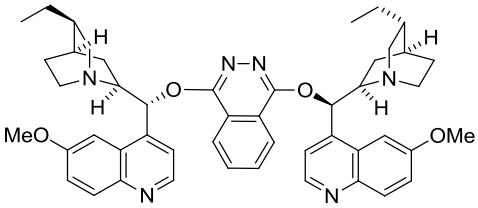


Phosphoryl chloride (22.5 mL) and 2,3-dihydrophthalazine-1,4-dione (4.25 g, 26.2 mmol) were refluxed for 4 hours before cooling to 0 °C and diluting with DCM (100 mL). The pH was slowly brought to 7.0 by the careful addition of 1M NaOH followed by saturation with $NaHCO_3$. The aqueous layer was extracted into DCM (3 x 100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, Petroluem ether: EtOAc 8:1) afforded the title compound as a white solid (2.61 g, 13.1 mmol, 50 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 6.1 Hz, *J* = 3.0 Hz, 2H), 8.29 (dd, *J* = 5.8 Hz, *J* = 3.0 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 125.9, 127.2, 134.6, 155.1.

Data consistent with literature values.[61]

$(DHQ)_2PHAL$ (154)



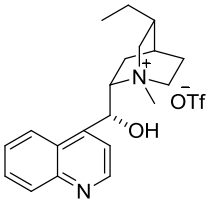
To quinine (9.68 g, 29.8 mmol) in EtOH (500 mL), was added palladium (10 % on charcoal, 250 mg, 0.03 mmol) and the reaction stirred under a hydrogen atmosphere for 2 days. The reaction was then filtered through a Celite plug (EtOH). Recrystallisation from EtOAc afforded dihydroquinine as a white solid (8.45 g, 25.9 mmol, 87 % yield).

To a suspension of potassium carbonate (4.37 g, 31.6 mmol) in toluene (100 mL) was added dihydroquinine (6.92 g, 21.2 mmol) followed by 1,4-dichlorophthalazine (2.10 g, 10.5 mmol). The reaction was heated to reflux (135 °C oil bath temperature) under Dean-Stark conditions for 2 hours before the addition of KOH pellets (1.77 g, 31.6 mmol). The reflux was continued for 12 hours with azeotropic removal of water before cooling to room temperature. Water (50 mL) was added and the product was extracted into EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Recrystallisation from EtOAc afforded the title compound as a white solid (4.01 g, 5.15 mmol, 49 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.6 Hz, 3H), 1.25-1.37 (m, 2H), 1.37-1.47 (m, 2H), 1.68-1.76 (m, 1H), 1.76-1.84 (m, 3H), 2.33 (ddd, *J* = 13.9 Hz, *J* = 4.4 Hz, *J* = 2.5 Hz, 1H), 2.55 (ddd, *J* = 13.2 Hz, *J* = 11.3 Hz, *J* = 4.7 Hz, 1H), 3.01 (dd, *J* = 13.6 Hz, *J* = 9.5 Hz, 1H), 3.13 (dddd, *J* = 13.9 Hz, *J* = 10.1 Hz, *J* = 5.4 Hz, *J* = 2.2 Hz, 1H), 3.48 (dd, *J* = 13.2 Hz, *J* = 6.9 Hz, 1H), 3.92 (s, 3H), 7.02 (d, *J* = 6.0 Hz, 1H), 7.36 (dd, *J* = 9.1 Hz, *J* = 2.5 Hz, 1H), 7.45 (d, *J* = 4.4 Hz, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.95 (dd, *J* = 6.0 Hz, *J* = 3.2 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 8.33 (dd, *J* = 6.0 Hz, *J* = 3.2 Hz, 1H), 8.65 (d, *J* = 4.7 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 12.1, 23.6, 25.4, 27.7, 28.6, 37.5, 42.8, 55.7, 58.5, 60.0, 76.3, 102.0, 118.5, 121.9, 122.5, 122.8, 127.3, 131.5, 132.3, 144.7, 144.8, 147.4, 156.4, 157.7.

Data consistent with literature values.[62]

_N_-Methyldihydrocinchonidine triflate (156)

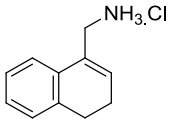


To a solution of dihydrocinchonidine (250 mg, 0.84 mmol) in DCM (100 mL) at 0 °C was added methyl iodide (53 µL, 0.84 mmol). The reaction was stirred for 24 hours before the addition of excess potassium carbonate. The reaction was stirred for 10 minutes and then filtered. To the filtrate was added silver triflate (216 mg, 0.84 mmol) and the reaction was stirred for a further 24 hours before being filtered through a pad of celite. After evaporation of the solvent, the residue was redissolved in acetonitrile and further filtered through celite to afford the product as an off-white solid (388 mg, 0.84 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3H), 1.15-1.30 (m, 2H), 1.28-1.36 (m, 1H), 1.85-1.94 (m, 1H), 1.97-2.06 (m, 1H), 2.07-2.12 (m, 1H), 2.21 (dd, *J* = 13.6 Hz, *J* = 7.9 Hz, 1H), 2.30 (dddd, *J* = 12.6 Hz, *J* = 11.4 Hz, *J* = 5.4 Hz, *J* = 3.5 Hz, 1H), 2.98 (ddd, *J* = 12.6 Hz, *J* = 5.4 Hz, *J* = 3.2 Hz, 1H), 3.38 (tdd, *J* = 11.9 Hz, *J* = 5.4 Hz, *J* = 1.3 Hz, 1H), 3.42 (dd, *J* = 9.8 Hz, *J* = 8.5 Hz, 1H), 3.69 (dd, *J* = 12.6 Hz, *J* = 10.7 Hz, 1H), 3.80 (s, 3H), 4.92 (dddd, *J* =12.9 Hz, *J* = 11.5 Hz, *J* = 4.8 Hz, *J* = 3.4 Hz, 1H), 6.50 (d, *J* = 6.3 Hz, 1H), 7.40 (d, *J* = 6.6 Hz, 1H), 7.65 (ddd, *J* = 8.5 Hz, *J* = 6.9 Hz, *J* = 1.3 Hz, 1H), 7.72 (ddd, *J* = 8.5 Hz, *J* = 6.9 Hz, *J* = 1.3 Hz, 1H), 7.87 (d, *J* = 4.41 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 8.14 (dd, *J* = 8.2 Hz, *J* = 1.0 Hz, 1H), 8.95 (d, *J* = 4.4 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 11.5, 20.7, 24.2, 26.0, 27.0, 37.0, 50.5, 55.6, 64.2, 69.5, 69.7, 120.7, 122.5, 124.9, 127.7, 129.5, 131.0, 145.4, 148.4, 150.6; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -79.3 (s, 3F); **HRMS (ESI$^+$, m/z):** $[C_{20}H_{27}N_2O]^+$ $(M)^+$ calc. 311.2118, found 311.2115; **IR (ν, cm^{-1}):** 3164 (br, O-H), 1462 (w, C=C_{Ar}), 1129 (m, C-N), 1071 (m, C-O); **mp:** Decomposed at 220 °C.

6.5.2 Phase-transfer fluorocyclization method

(3,4-Dihydronaphthalen-1-yl)methanamine hydrochloride (159)

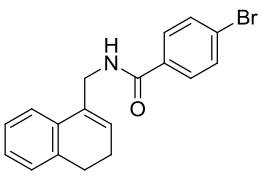


To a flask containing 1-tetralone (1.97 mL, 16.2 mmol) and $AlCl_3$ (3 mg, 0.02 mmol) was added TMSCN (1.4 mL, 17.8 mmol) (**caution; danger very toxic**) and the reaction was heated at 35 °C and stirred for 20 h. The reaction was then cooled to 0 °C and diluted with THF (30 mL) before the portion wise addition of $LiAlH_4$ (740 mg, 19.4 mmol). The reaction was stirred for 10 min before warming to room temperature and stirring was continued for 3 h before quenching with $Na_2SO_4.10H_2O$. After 1 h, the reaction was filtered, washed with Et_2O, concentrated under reduced pressure and redissolved in EtOH (100 mL). Conc. HCl (10 mL) was added and the reaction heated at 60 °C for 16 h. The crude residue was suspended in Et_2O, filtered and the filtrand was further washed with DCM. The solid was dried under reduced pressure to afford the title compound as a white solid (1.42 g, 7.26 mmol, 45 % yield).

^{1}H NMR (400 MHz, CD_3OD): δ = 2.31-2.41 (m, 2H), 2.81 (t, *J* = 8.0 Hz, 2H), 4.01 (s, 2H), 6.27 (s, 1H), 7.18-7.31 (m, 4H); **^{13}C NMR (100.6 MHz, CD_3OD):** δ = 23.0, 27.6, 40.6, 122.1, 126.9, 128.1, 128.1, 130.3, 130.5, 131.9, 136.8.

Data consistent with literature values.[63]

4-Bromo-*N*-((3,4-dihydronaphthalen-1-yl)methyl)benzamide (160)



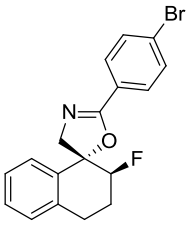
To a solution of (3,4-dihydronaphthalen-1-yl)methanamine hydrochloride (300 mg, 1.53 mmol) in DCM (15 mL) was added Et_3N (640 µL, 4.59 mmol). The reaction mixture became homogeneous and then 4-bromobenzoyl chloride (505 mg, 2.30 mmol) was added followed by DMAP (0.1 eq.). The reaction was stirred at room temperature for 3 h before quenching with NH_4Cl (30

mL) and extracting into DCM (3x25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (SiO_2, petroleum ether/ DCM/ EtOAc 13:4:3) afforded the title compound as a white solid (412 mg, 1.20 mmol, 79 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30-2.38 (m, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 4.48 (dd, *J* = 5.1 Hz, *J* = 0.8 Hz, 2H), 6.13 (t, *J* = 4.3 Hz, 1H), 6.13 (brs, 1H, N*H*), 7.16-7.24 (m, 3H), 7.25-7.30 (m, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.1, 27.9, 42.5, 122.6, 126.1, 126.8, 127.4, 127.9, 128.6, 128.7, 131.8, 132.8, 132.8, 133.3, 136.4, 166.4.

Data consistent with literature values.[64]

(1*R*,2*S*)-2'-(4-Bromophenyl)-2-fluoro-3,4-dihydro-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazole] (161)



Into an oven dried flask containing a stirrer bar, powdered Na_2CO_3 (4 mg, 0.039 mmol) was added 4-bromo-*N*-((tetrahydro-2*H*-pyran-2-yl)methyl)benzamide (10.2 mg, 0.03 mmol) was then added followed by the catalyst (*R*)-TRIP, (2.2 mg, 0.003 mmol, 10 mol %). To this mixture was added a hexane/ fluorobenzene mix (*v/v*, 1:1, 3 mL). To this solution was added Selectfluor (16 mg, 0.045 mmol) and the reaction was left to stir at room temperature for 24 h. The reaction was quenched with $Na_2S_2O_3$, stirred for 10 min and then extracted into DCM. The product was dried over $MgSO_4$, filtered and then evaporated under reduced pressure. Purification by column chromatography (SiO_2, petroleum ether/ EtOAc 19:1) afforded the title compound as a an off white solid (77 % yield, 92 % ee, d.r >20:1 anti:syn).

Anti isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.06-2.20 (m, 1H), 2.28-2.42 (m, 1H), 2.96-3.09

(m, 2H), 4.06 (dd, *J* = 15.1 Hz, *J* = 2.5 Hz, 1H), 4.56 (d, *J* = 15.1 Hz, 1H), 5.07 (ddd, *J* = 50.1 Hz, *J* = 11.0 Hz, *J* = 3.4 Hz, 1H), 7.13-7.19 (m, 1H), 7.25-7.34 (m, 3H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 26.1 (d, *J* = 19.3 Hz), 26.4 (d, *J* = 10.4 Hz), 64.3 (d, *J* = 7.1 Hz), 87.0 (d, *J* = 20.4 Hz), 92.0 (d, *J* = 182.8 Hz), 126.4, 126.4, 126.5 (d, *J* = 3.0 Hz), 127.5, 128.3, 128.6, 130.0, 131.8, 134.8 (d, *J* = 1.0 Hz), 137.6 (d, *J* = 4.8 Hz), 162.8; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -193.2 (dd, *J* = 50.2 Hz, *J* = 17.4 Hz, 1F).

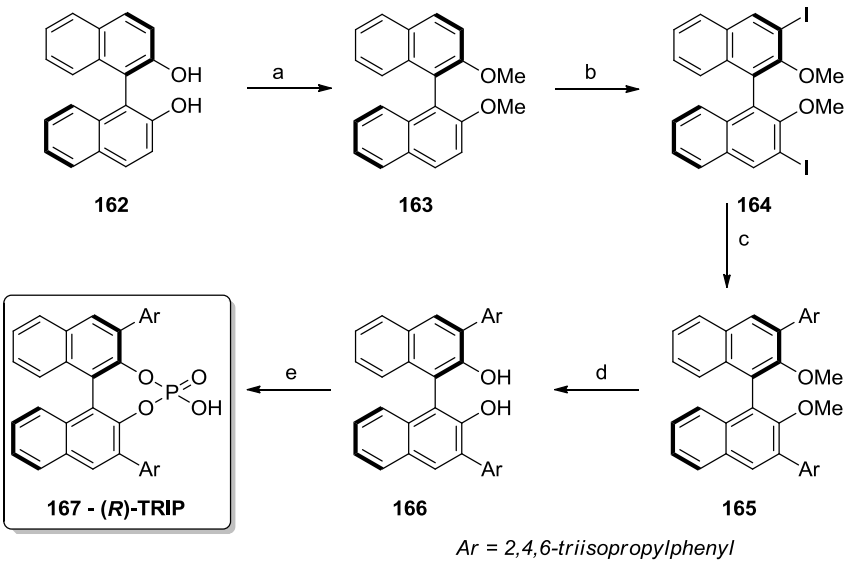
Data consistent with literature values.[64]

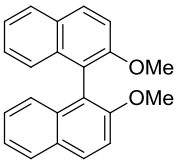
Syn isomer can be formed from the reaction with Selectfluor in acetonitrile as follows.

To a solution of 4-bromo-*N*-((tetrahydro-2*H*-pyran-2-yl)methyl)benzamide (25 mg, 0.073 mmol) in acetonitrile (2 mL) was added $NaHCO_3$ (12 mg, 0.15 mmol) followed by Selectfluor (28 mg, 0.08 mmol). The reaction was stirred for 2 hours before diluting with DCM (25 mL) and washing with water then brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/PE 1:19 to 1:9) afforded the title compound as a colourless oil (99 % yield, 1:1 mixture of diastereomers).

Syn diastereomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.10-2.27 (m, 1H), 2.38-2.50 (m, 1H), 2.91 (dt, *J* = 17.2 Hz, *J* = 6.8 Hz, 1H), 3.09-3.20 (m, 1H), 4.19-4.32 (m, 2H), 4.86 (ddd, *J* = 48.7 Hz, *J* = 8.8 Hz, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.24-7.33 (m ,2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 25.2 (d, *J* = 20.1 Hz), 25.7 (d, *J* = 9.2 Hz), 65.1, 85.7 (d, 17.5 Hz), 91.7 (d, *J* = 184.4 Hz), 126.0, 126.9, 127.0, 127.6, 128.8, 128.9, 130.3, 131.9, 135.6, 135.8, 163.5; **^{19}F NMR (376.6 MHz, $CDCl_3$):** δ = -193.6 (dd, *J* = 48.7 Hz, *J* = 25.6 Hz, 1F).

(*R*)-TRIP (167)



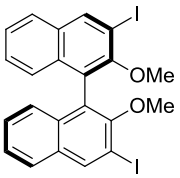


A 250-mL two-necked round-bottom flask containing BINOL (5.00 g, 17.3 mmol) was equipped with a magnetic stirrer bar, an addition funnel and a reflux condenser with argon inlet. To this was added 160 mL dried acetone followed by K_2CO_3 (7.88 g, 57.1 mmol) and then MeI (4.35 mL, 69.2 mmol). The mixture was stirred at reflux for 24 h before removing the solvent under reduced pressure. The crude residue was dissolved in water (180 mL), stirred for 2 h and then the solid was collected in a funnel and washed with water. The solid was left to dry for 14 h under high vacuum. The title compound was collected as a pale yellow solid (5.08 g, 16.2 mmol, 93 % yield.)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 6H), 7.08 (d, *J* = 8.5 Hz, 2H), 7.24 (ddd, *J* = 8.5 Hz, *J* = 7.2 Hz, *J* = 1.0 Hz, 2H), 7.36 (ddd, *J* = 8.1 Hz, *J* = 7.8 Hz, *J* = 0.8 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 8.04 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 56.9, 114.3, 119.6, 123.9, 125.3, 126.7, 128.3, 129.5, 129.8, 134.3, 155.3.

Data consistent with literature values.[65]

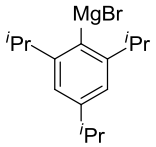
(*R*)-3,3'-Diiodo-2,2'-dimethoxy-1,1'-binaphthalene (27)[69]



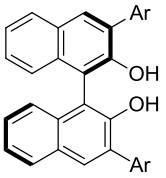
To a solution of (*R*)-2,2'-Dimethoxy-1,1'-binaphthalene (1.00 g, 3.18 mmol) in THF (30 mL) at -78 °C under argon was added BuLi (1.6 M, 7.0 mL, 11.11 mmol) and the mixture was stirred for 30 min. The reaction was then warmed to 0 °C and stirred for a further 1.5 h. Upon completion of this time, the mixture was cooled back to -78 °C and iodine was added (3.07 g, 12.1 mmol) in a single portion. The reaction was stirred for a further 0.5 h before warming to room temperature Na_2SO_3 (100 mL) was added and the reaction stirred for 1 h. The product was extracted into EtOAc (3 x 50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 19:1) afforded the title compound as a pale yellow foam (100 mg, 0.17 mmol, 6 % yield).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 3.42 (s, 6H), 7.08 (d, *J* = 8.5 Hz, 2H), 7.24-7.32 (m, 2H), 7.38-7.45 (m, 2H), 7.81 (d, *J* =8.3 Hz, 2H), 8.54 (s, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 61.8, 118.2, 126.5, 126.7, 127.4, 127.6, 128.0, 132.3, 133.8, 133.9, 153.3.

Data consistent with literature values.[66]



To a 100 mL 2-necked round-bottomed flask fitted with a reflux condenser was added Et_2O (5 mL) followed by magnesium turnings (1.26 g, 52.0 mmol, 2.0 eq.) and 2 crystals of iodine. 2-Bromo-1,3,5-triisopropylbenzene (7.67 g, 26.0 mmol) was added as a solution in Et_2O (30 mL) along with 0.1 mL dibromoethane so as to maintain a steady reflux. Following complete addition, the reaction was placed into a pre-heated oil bath and refluxed for 24 h. The crude reaction mixture was filtered through a short pad of cotton wool and washed with Et_2O (17 mL) to afford the title compound as a 0.5 M solution in ether.

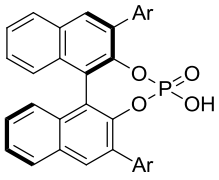


To a solution of (*R*)-3,3'-Diiodo-2,2'-dimethoxy-1,1'-binaphthalene (78 mg, 0.14 mmol) in ether (5 mL) was added $NiCl_2(PPh_3)_2$ (9.0 mg, 0.01 mmol, 10 mol %). After complete addition, (2,4,6-triisopropylphenyl)magnesium bromide **34** (0.5 M in Et_2O, 1.38 mL, 0.69 mmol) was added and the reaction heated to reflux for 6 h. Following this, the mixture was cooled to 0 °C, quenched with 1 M HCl (5mL) and then the product was then extracted into Et_2O, filtered through a short silica plug and dried over $MgSO_4$, before being evaporated under reduced pressure. The crude mixture was carried forward to the next step without further purification.

Into a 50 mL round bottomed flask with magnetic stirrer, under argon, the crude material was added. The material was dissolved in DCM (10 mL) and then cooled to 0 °C. To the solution was added BBr_3 (93 µl, 0.97 mmol). The resulting solution was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with water (30 mL), and the aqueous layer extracted with DCM (3 x 30 mL). $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash chromatography (SiO_2, petroleum ether/ EtOAc 98:2) afforded the title compound as a pale yellow solid (87 mg, 0.13 mmol, 91 % yield (over 2 steps)).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.9 Hz, 6H), 1.07 (d, *J* = 6.8 Hz, 6H), 1.09 (d, *J* = 6.8 Hz, 6H), 1.16 (d, *J* = 6.8 Hz, 6H), 1.29 (d, *J* = 6.9 Hz, 12H), 2.67 (sept, *J* = 6.9 Hz, 2H), 2.81 (sept, *J* = 6.9 Hz, 2H), 2.94 (sept, *J* = 6.9 Hz, 2H), 5.01 (s, 2H, O*H*), 7.22 (s, 2H), 7.23 (s, 2H), 7.36-7.48 (m, 6H), 7.86 (s, 2H), 7.95 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.8, 24.0, 24.1, 24.1, 24.4, 24.4, 30.9, 30.9, 34.4, 113.1, 121.2, 121.3, 123.8, 124.6, 126.7, 128.3, 129.1, 129.2, 130.5, 130.7, 133.5, 147.8, 147.8, 149.2, 150.7.

Data consistent with literature values.[64]

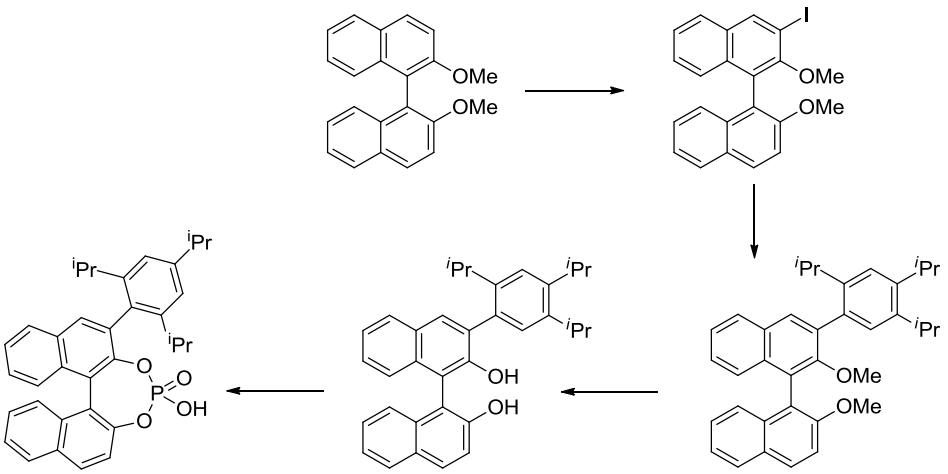


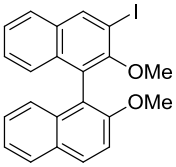
To a 10-mL round bottomed flask under argon, with reflux condenser attached, containing (3*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (87 mg, 0.13 mmol) pyridine (5 mL) was added. To this solution was added $POCl_3$ (23 µl, 0.25 mmol) and the resulting mixture was heated to 90 °C for 14 h. After this time the reaction was cooled to room temperature and subsequently quenched with water (1 mL). The resulting brownish slurry was heated to reflux and hydrolysed for 1 h. The reaction was again cooled to room temperature and EtOAc (30 mL) was added. HCl (40 mL) was then added to the mixture and the organic layer was extracted with two further portions of HCl (2 x 30 mL). The resulting organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound as a white solid (70 mg, 0.093 mmol, 74 % yield). (**Note;** The aqueous medium should be clearly acidic (pH = 1- 2) throughout the workup steps to maintain the product in its free acid form).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 6H), 1.06 (d, *J* = 6.4 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H), 1.18 (d, *J* = 6.7 Hz, 6H), 1.25-1.31 (m, 12H), 2.58-2.74 (m, 2H), 2.87-2.97 (m, 2H) 3.36-3.59 (m, 2H), 7.03 (s, 2H), 7.08 (s, 2H), 7.32-7.37 (m, 4H), 7.49-7.56 (m, 2H), 7.90 (s, 2H), 7.93 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 22.8, 23.3, 23.9, 24.1, 25.0, 26.6, 30.8, 31.0, 34.2, 120.3, 121.1, 121.9, 125.7, 126.3, 127.3, 128.2, 131.0, 131.2, 132.1, 132.2, 132.2, 132.6, 147.4, 148.0, 148.5; **^{31}P NMR (400 MHz, $CDCl_3$):** δ = 4.17.

Data consistent with literature values.[64]

Mono-TRIP (167b)

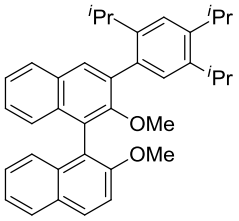




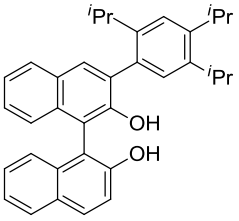
To a solution of 2,2'-Dimethoxy-1,1'-binaphthalene (1.00 g, 3.18 mmol) in THF (30 mL) at -78 °C under argon was added BuLi (1.6 M, 7.0 mL, 11.11 mmol) and the mixture was stirred for 30 min. The reaction was then warmed to 0 °C and stirred for a further 1.5 h. Upon completion of this time, the mixture was cooled back to -78 °C and iodine was added (3.07 g, 12.1 mmol) in a single portion. The reaction was stirred for a further 0.5 h before warming to room temperature Na_2SO_3 (100 mL) was added and the reaction stirred for 1 h. The product was extracted into EtOAc (3 x 50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc/PE 1:19) afforded the title compound as a pale yellow foam (713 mg, 1.62 mmol, 51 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3H), 3.81 (s, 3H), 7.07-7.16 (m, 2H), 7.21-7.30 (m, 2H), 7.34 (td, *J* = 7.9 Hz, *J* = 0.9 Hz, 1H), 7.40 (td, *J* = 8.0 Hz, *J* = 0.8 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 8.51 (s, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 56.5, 60.8, 92.6, 113.3, 118.6, 123.7, 125.0, 125.4, 125.7, 125.8, 126.7, 126.8, 126.9, 127.9, 128.9, 130.1, 132.4, 133.8, 134.0, 139.1, 154.4, 154.8; **HRMS**

(FI$^+$): [$C_{22}H_{17}O_2I$] calc. 440.0273, found 440.0283.



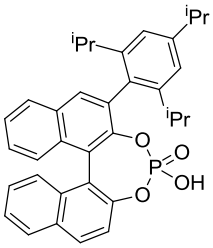
To a solution of 3-iodo-2,2'-dimethoxy-1,1'-binaphthalene (700 mg, 1.59 mmol) in ether (10 mL) was added $NiCl_2(PPh_3)_2$ (105 mg, 0.16 mmol, 10 mol%). After complete addition, (2,4,6-triisopropylphenyl)magnesium bromide (0.5 M in Et_2O, 15.9 mL, 7.95 mmol) was added and the reaction heated to reflux for 6 h. Following this, the mixture was cooled to 0 °C, quenched with 1 M HCl (5mL) and then the product was then extracted into Et_2O, filtered through a short silica plug and dried over $MgSO_4$, before being evaporated under reduced pressure. The crude mixture was carried forward to the next step without further purification.



Into a 50 mL round bottomed flask with magnetic stirrer, under argon, the crude material was added. The material was dissolved in DCM (30 mL) and then cooled to 0 °C. To the solution was added BBr_3 (1.23 mL, 11.1 mmol). The resulting solution was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with water (50 mL), and the aqueous layer extracted with DCM (3 x 50 mL). $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc/PE 1:49) afforded the title compound as a pale yellow solid (605 mg, 1.24 mmol, 78 % yield (over 2 steps)).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.7 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.34 (d, *J* = 6.9 Hz, 6H), 2.75 (sept, *J* = 6.8 Hz, 1H), 2.78 (sept, *J* = 6.9 Hz, 1H), 2.99 (sept, *J* = 6.9 Hz, 1H), 4.99 (brs, 1H, O*H*), 5.10 (brs, 1H, O*H*), 7.17 (s, 2H),

7.23 (d, *J* = 8.3 Hz, 1H), 7.26-7.31 (m, 2H), 7.32-7.45 (m, 4H), 7.83 (s, 1H), 7.88-7.93 (m, 2H), 7.97 (d, *J* = 8.9 Hz, 1H); **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ = 23.9, 23.9, 24.0, 24.4, 24.4, 30.9, 31.0, 34.3, 111.2, 112.8, 117.6, 121.3, 121.3, 123.7, 124.2, 124.4, 124.4, 126.9, 127.2, 128.3, 128.3, 129.2, 129.3, 129.4, 129.8, 130.7, 131.4, 133.3, 133.4, 147.7, 147.8, 149.4, 151.2, 152.0; **IR (ν, cm^{-1}):** 3520 (m, O-H), 1463 (w, C-C_{Ar}); **HRMS (FI$^+$):** [$C_{35}H_{36}O_2$] calc. 488.2715, found 488.2730.

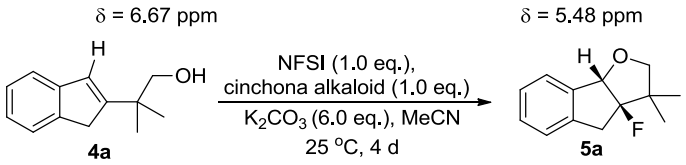


To a 10-mL round bottomed flask under argon, with reflux condenser attached, containing 3-(2,4,5-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (605 mg, 1.24 mmol), pyridine (5 mL) was added. To this solution was added $POCl_3$ (231 µl, 2.48 mmol) and the resulting mixture was heated to 90 °C for 14 h. After this time the reaction was cooled to room temperature and subsequently quenched with water (2 mL). The resulting brownish slurry was heated to reflux and hydrolysed for 1 h. The reaction was again cooled to room temperature and EtOAc (50 mL) was added. HCl (40 mL) was then added to the mixture and the organic layer was extracted with two further portions of HCl (2 x 30 mL). The resulting organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound as a white solid (663 mg, 1.20 mmol, 97 % yield). (**Note;** The aqueous medium should be clearly acidic (pH = 1- 2) throughout the workup steps to maintain the product in its free acid form).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 2.59 (sept, *J* = 6.8 Hz, 1H), 2.69 (sept, *J* = 6.7 Hz, 1H), 2.92 (sept, *J* = 6.9 Hz, 1H), 7.07 (d, *J* = 1.3 Hz, 1H), 7.09 (brs, 1H, O*H*), 7.13 (d, *J* = 1.1 Hz, 1H), 7.28-7.39 (m, 4H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.48-7.53 (m, 2H), 7.89 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.9 Hz, 1H), **^{13}C**

NMR (100.6 MHz, $CDCl_3$): δ = 23.0, 23.5, 23.9, 24.1, 24.9, 26.6, 31.0, 31.0, 34.2, 120.4, 120.6 (d, *J* = 2.8 Hz), 121.1, 121.2 (d, *J* = 1.7 Hz), 121.7 (d, *J* = 1.9 Hz), 125.6, 125.9, 126.3, 126.7, 127.1, 127.2, 128.1, 128.5, 130.9, 131.0, 131.2, 131.8, 131.9, 132.1 (d, *J* = 3.8 Hz), 132.5, 132.6, 145.7 (d, *J* = 9.1 Hz), 146.6 (d, *J* = 8.9 Hz), 147.2, 147.7, 148.5; **^{31}P NMR (400 MHz, $CDCl_3$):** δ = 4.76; **HRMS (ESI^-, m/z):** $[C_{35}H_{34}O_4P]^-$ $(M-H)^-$ calc. 549.2200, found 549.2205.

6.5.3 Optimisation Table 1

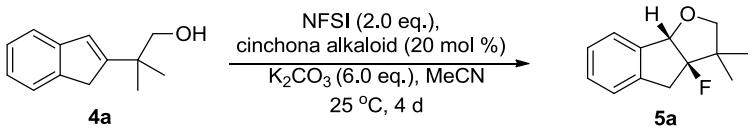


Entry[a]	Cinchona Alkaloid	Conversion[b] (%)	ee[c] (%)
1	Quinine	9	30
2	Quinidine	14	15(-)
3	DHQ	15	34
4	DHQD	<5	14(-)
5	Cinchonine	11	7(-)
6	Cinchonidine	14	14
7	DHCD	<5	18
8	$(DHQ)_2$PHAL	41	45
9	$(DHQD)_2$PHAL	78	25
10	$(DHQ)_2$PYR	70	0
11	$(DHQ)_2$AQN	<5	-[d]
12	BQ	45	27
13	BQ[e]	45	26
14	BQd	56	12
15	DHQB	60	38
16	DHQDB	24	21
17	None	9	0

Table 3 - Cinchona alkaloid screening; [a] alcohol 4 (1.0 eq.), NFSI (1.0 eq.), cinchona alkaloid (1.0 eq.), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b] Determined by ^{1}H NMR; [c] Determined by stationary phase chiral HPLC; [d] ee not obtained; [e] Under atmosphere of argon

To a solution of **4a** (20 mg) in acetonitrile (2 mL) at room temperature was added cinchona alkaloid (1.0 eq.), K_2CO_3 (6.0 eq.) and NFSI (1.0 eq.). The reaction was stirred for 4 days before diluting in DCM and washing with water. The aqueous layer was extracted with DCM, and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The conversion of the reaction was determined by comparison of the ^{1}H NMR signals of the indene and the product. The ee was determined by chiral stationary phase HPLC.

6.5.4 Optimisation Table 4



4a **5a**

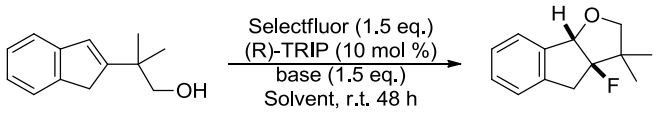
Entry[a]	Cinchona Alkaloid	Conversion[b] (%)	ee[c] (%)
1	Quinine	37	31
2	Quinidine	54	12 (-)
3	DHQ	45	42
4	DHQD	32	5(-)
5	Cinchonine	56	34 (-)
6	Cinchonidine	53	30
7	DHCD	47	43
8	$(DHQ)_2$PHAL	59	46
9	$(DHQD)_2$PHAL	59	12
10	$(DHQ)_2$PYR	54	0
11	$(DHQ)_2$AQN	36	11 (-)
12	$(DHQD)_2$AQN	32	48
13	BQ	41	12
14	BQd	65	8
15	Hydroquinine 9-phenanthryl ether	30	8
16	DHQB	40	16
17	DHQDB	31	15

18	None	32	0

Table 4 - Catalytic cinchona alkaloid screening; [a]alcohol 4 (1.0 eq.), NFSI (2.0 eq.), catalyst (20 mol %), K_2CO_3 (6.0 eq.), MeCN (0.05 M), in air, 25 °C, 4 days; [b]Determined by ^{1}H NMR; [c]Determined by stationary phase chiral HPLC

To a solution of **4a** (20 mg) in acetonitrile (2 mL) at room temperature was added cinchona alkaloid (20 mol %), K_2CO_3 (6.0 eq.) and NFSI (1.0 eq.). The reaction was stirred for 4 days before diluting in DCM and washing with water. The aqueous layer was extracted with DCM, and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The conversion of the reaction was determined by comparison of the ^{1}H NMR signals of the indene and the product. The ee was determined by chiral stationary phase HPLC.

6.5.5 Optimisation Table 11



4a **5a**

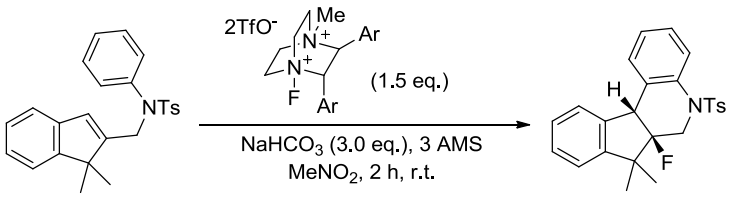
Entry	Solvent	Conc.	Base	Temp.	Yield (%)[a]	ee (%)[b]
1[c]	Benzene	0.01M	Na_2CO_3	r.t.	0	-
2	Benzene	0.01M	Na_2CO_3	r.t.	17	14
3	Toluene	0.01M	Na_2CO_3	r.t.	12	14
4	Benzene/hexane (1:1)	0.01M	Na_2CO_3	r.t.	20	14
5	Hexane	0.01M	Na_2CO_3	r.t.	28	14
6	Hexane/^{i}PrOH (9:1)	0.01M	Na_2CO_3	r.t.	<5	ND
7	Hexane	0.01M	$NaHCO_3$	r.t.	92	15
8	Hexane	0.01M	K_2CO_3	r.t.	17	6
9	Hexane	0.1M	Na_2CO_3	r.t.	85	0
10	Hexane	0.01M	Na_2CO_3	50 °C	35	16
11	Hexane	0.005M	Na_2CO_3	r.t.	17	28
12	Hexane	0.05M	Na_2CO_3	r.t.	92	12
13	Hexane	0.01M	Cs_2CO_3	r.t.	<5	ND

14	Hexane	0.005M	$NaHCO_3$	r.t.	73	14
15	Hexane	0.01M	Proton sponge	r.t.	<5	ND

Table 5 - Optimisation of asymmetric fluorocyclization using (R)-TRIP; [a] determined by ^{1}H NMR; [b] determined by stationary phase chiral HPLC; [c] in absence of *(R)*-TRIP

To a solution of **4a** (5 mg) in solvent at room temperature was added (*R*)-TRIP (10 mol %) followed by base (1.5 eq.) and finally Selectfluor (1.5 eq.). The reaction was stirred for 48 hours before diluting in DCM and washing with water. The aqueous layer was extracted with DCM, and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The conversion of the reaction was determined by ^{1}H NMR using 1-fluoro-3-nitrobenzene as an internal standard. The ee was determined by chiral stationary phase HPLC.

6.5.6 Optimisation Table 13



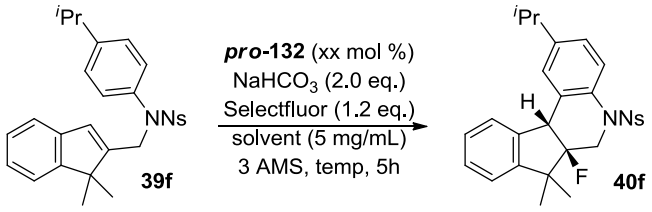
39a **40a**

Entry	Chiral Selectfluor	Solvent	Base	Temp.	NMR yield (%)	ee (%)	Conc.
1	**(*R*,*R*)-131**	$MeNO_2$	$NaHCO_3$	r.t	63	32	5 mg/mL
2	**(*S*,*S*)-132**	**$MeNO_2$**	**$NaHCO_3$**	**r.t**	**>95**	**60**	**5 mg/mL**
3	**(*R*)-143**	$MeNO_2$	$NaHCO_3$	r.t	83	10	5 mg/mL
4	**(*S*,*S*)-139**	$MeNO_2$	$NaHCO_3$	r.t	18	32	5 mg/mL
5	**(*S*,*S*)-136**	$MeNO_2$	$NaHCO_3$	r.t	69	36	5 mg/mL
6	**(*S*,*S*)-140**	$MeNO_2$	$NaHCO_3$	r.t	44	55	5 mg/mL

Table 6 - Optimisation of Chiral Selectfluors

To a solution of **39a** (5 mg) in nitromethane (1 mL) over 3 AMS was added $NaHCO_3$ (3.0 eq.) and chiral Selectfluor (1.5 eq.). The reaction was stirred for 2 hours before filtering through a cotton wool pipette and eluting with ethyl acetate. The solvent was removed under reduced pressure the crude residue was dry-loaded onto a short pad of silica and eluted with EtOAc/PE 1:4. The yield was calculated by ^{1}H NMR using 1-fluoro-3-nitrobenzene as an internal reference. The ee was calculated using chiral stationary phase HPLC.

6.5.7 Optimisation Table 15

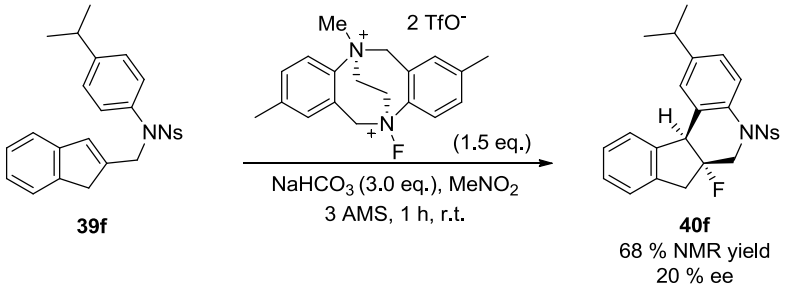


Entry	Solvent	Cat. mol %	Temp.	SM %[a]	Yield %[a]	ee %[b]
1	$MeNO_2$	25	20	31	27	10
2	Dioxane	25	20	84	<5	6
3	Dioxane	10	20	83	<5	7
4	DCE	25	20	77	<5	8

Table 7 - Catalytic asymmetric fluoro-carbocyclization reaction development; General conditions: 1h (7.5 mg), *pro*-**132** (xx mol %), solvent (1.5 mL), 3 ÅMS, $NaHCO_3$ (2.0 eq.), Selectfluor (1.2 eq.), 5 h; [a] ^{1}H NMR yield using 1-fluoro-3-nitrobenzene as an internal reference [b] calculated using chiral HPLC

To a solution of **39f** (5 mg) in solvent (5 mg/mL) over 3 AMS was added $NaHCO_3$ (2.0 eq.) and chiral Selectfluor (1.2 eq.). The reaction was stirred for 5 hours before filtering through a cotton wool pipette and eluting with ethyl acetate. The solvent was removed under reduced pressure the crude residue was dry-loaded onto a short pad of silica and eluted with EtOAc/PE 1:4. The yield was calculated by ^{1}H NMR using 1-fluoro-3-nitrobenzene as an internal reference. The ee was calculated using chiral stationary phase HPLC.

6.5.8 Troger's base derived reagents



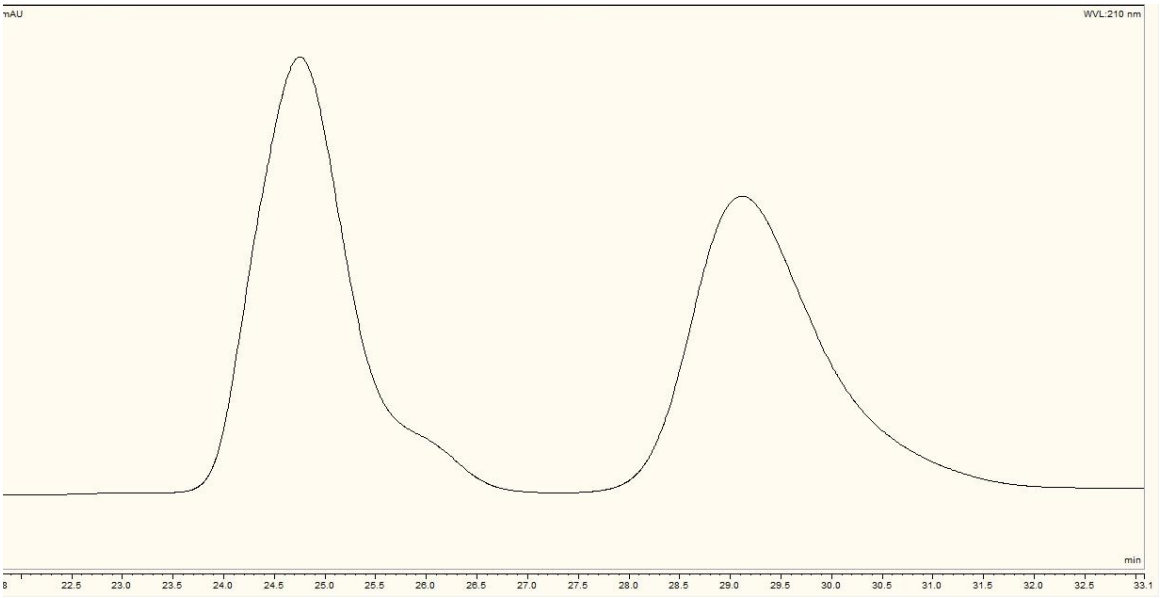
39f

40f
68 % NMR yield
20 % ee

To a vial containing nitromethane over 3 AMS (5 mg/mL) was added *pro*-reagent (1.5 eq.), $NaHCO_3$ and *N*-fluoro-pentachloropyridinium triflate (1.5 eq.). The reaction was stirred for 30 minutes before the addition of **39f** (1.0 eq.). The reaction was further stirred for 1 hour before filtering through a cotton wool pipette and evaporated under reduced pressure. The crude reaction residue was dry-loaded onto a short plug of silica and eluted with EtOAc/PE 3:7. The NMR yield was calculated using 1-fluoro-3-nitrobenzene as an internal reference and the ee was calculated using chiral stationary phase HPLC.

6.5.9 Determination of absolute configuration

The absolute configuration was determined by X-ray crystallographic analysis of (6a*R*,11b*R*)-**40a**. The single crystal used for data collection was run by chiral stationary phase HPLC to confirm its identity as the major enantiomer. The two spectra below depict the racemic reference (top) and the single crystal analysis (bottom).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24.0
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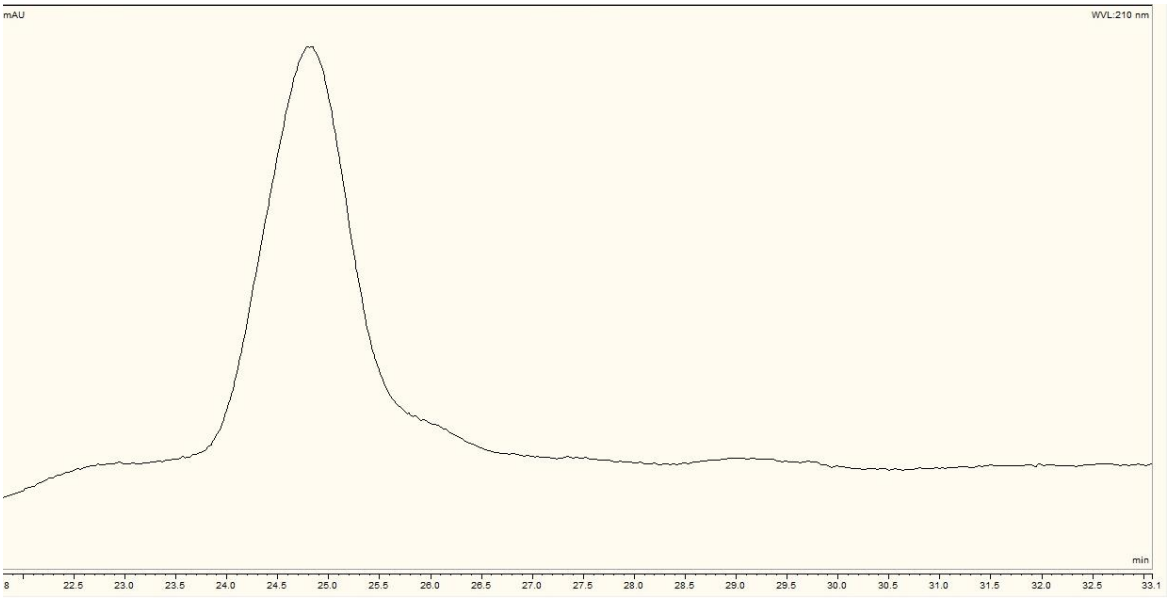
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27.5
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29.0
29.5
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30.5
31.0
31.5
32.0
32.5
33.1

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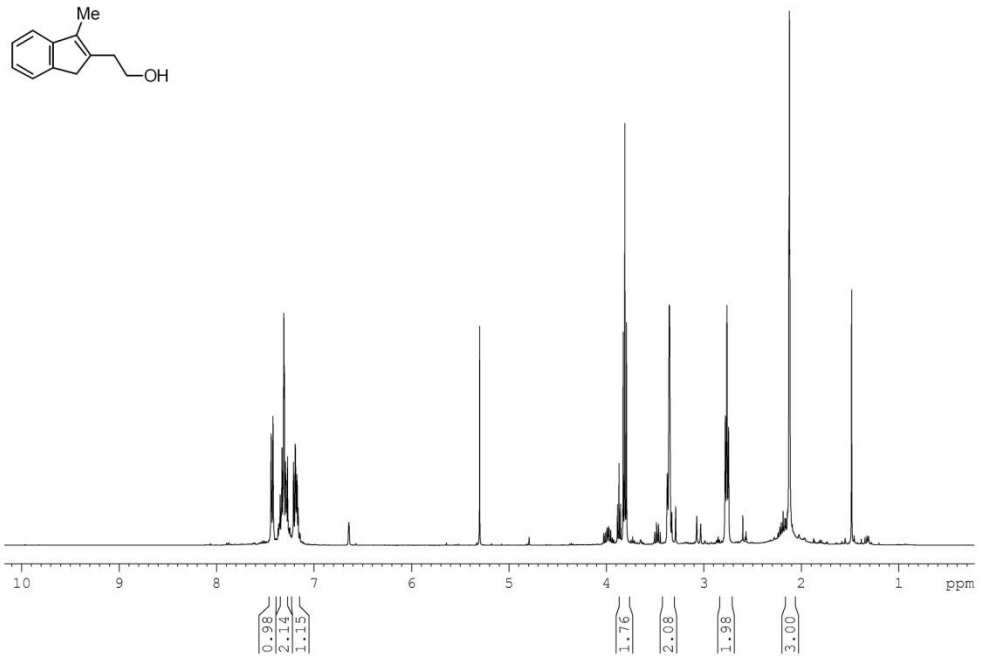
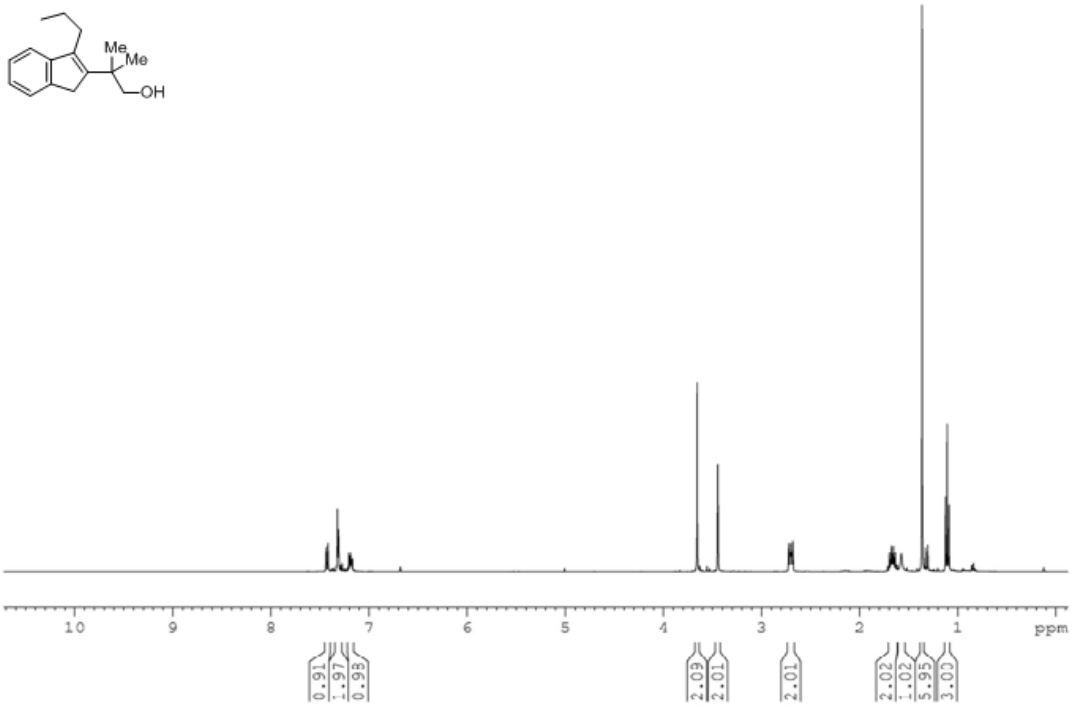
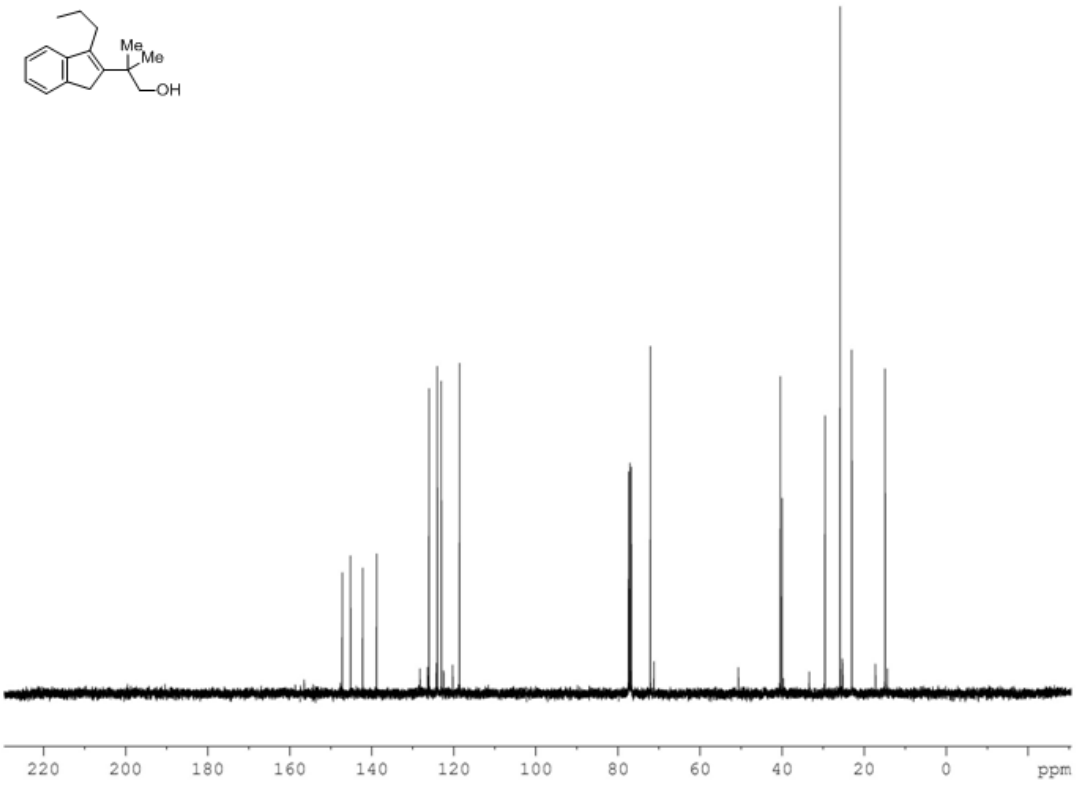
Appendices

Appendix i: NMR spectra of novel compounds



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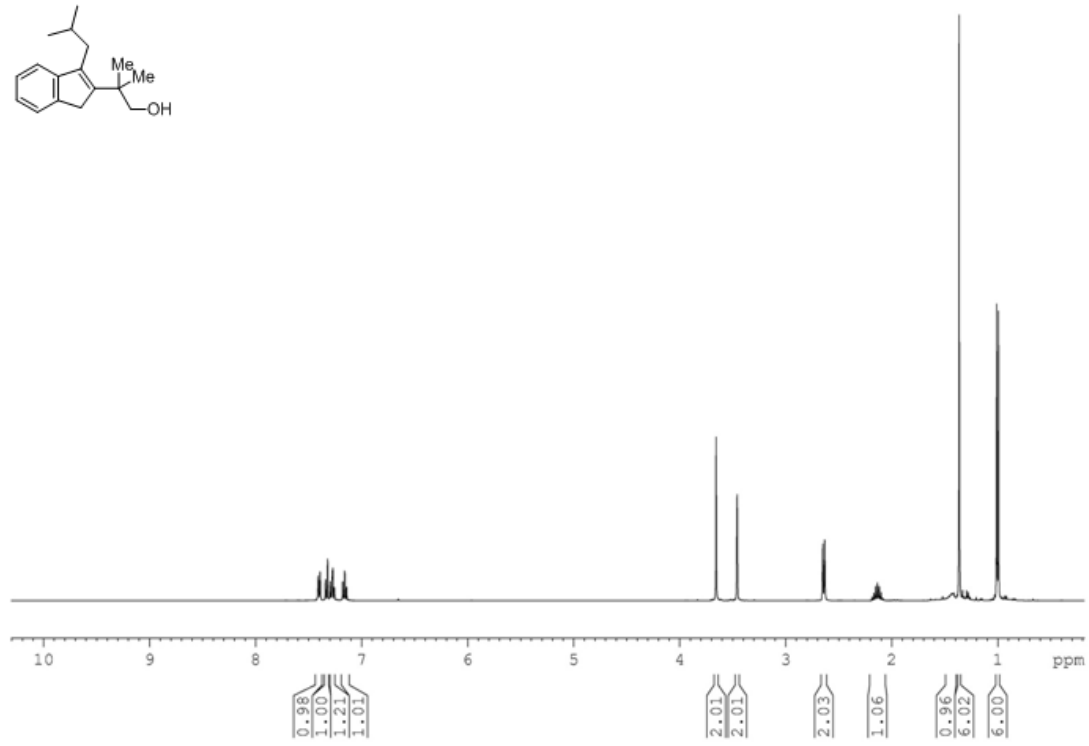
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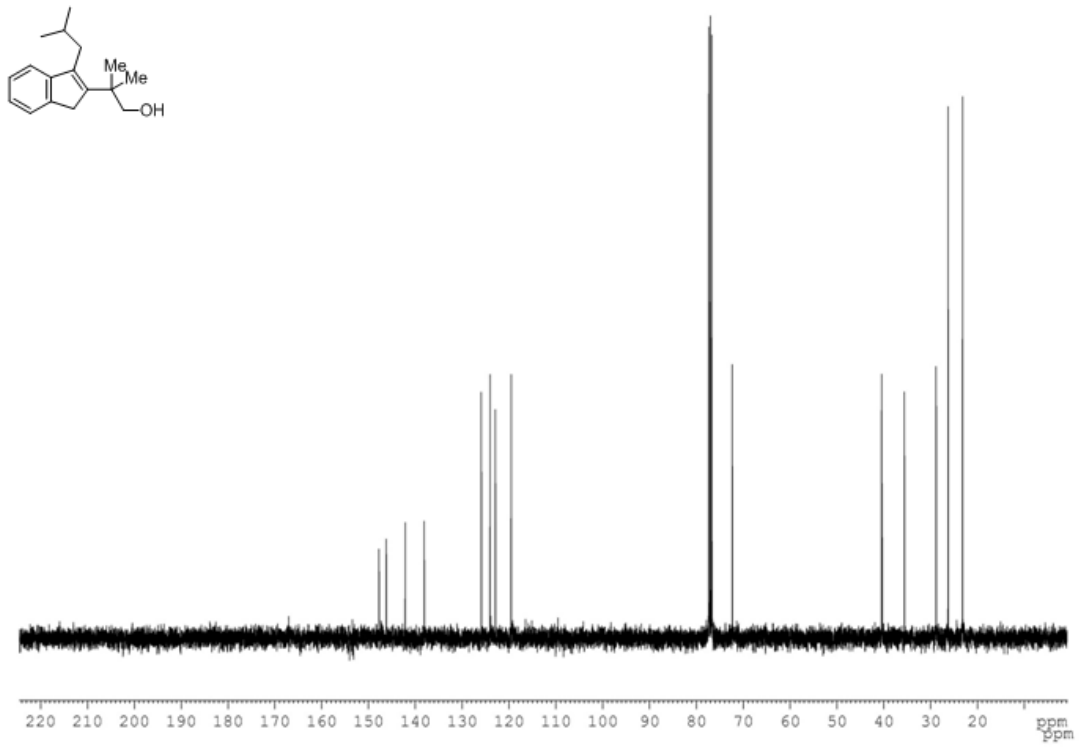
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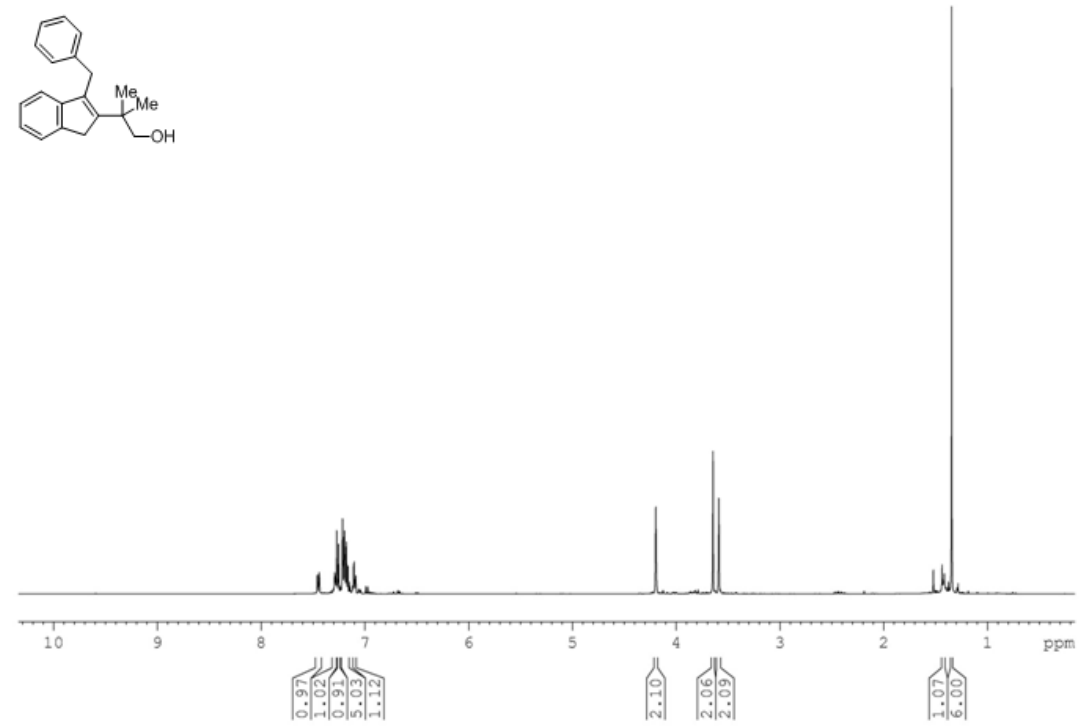
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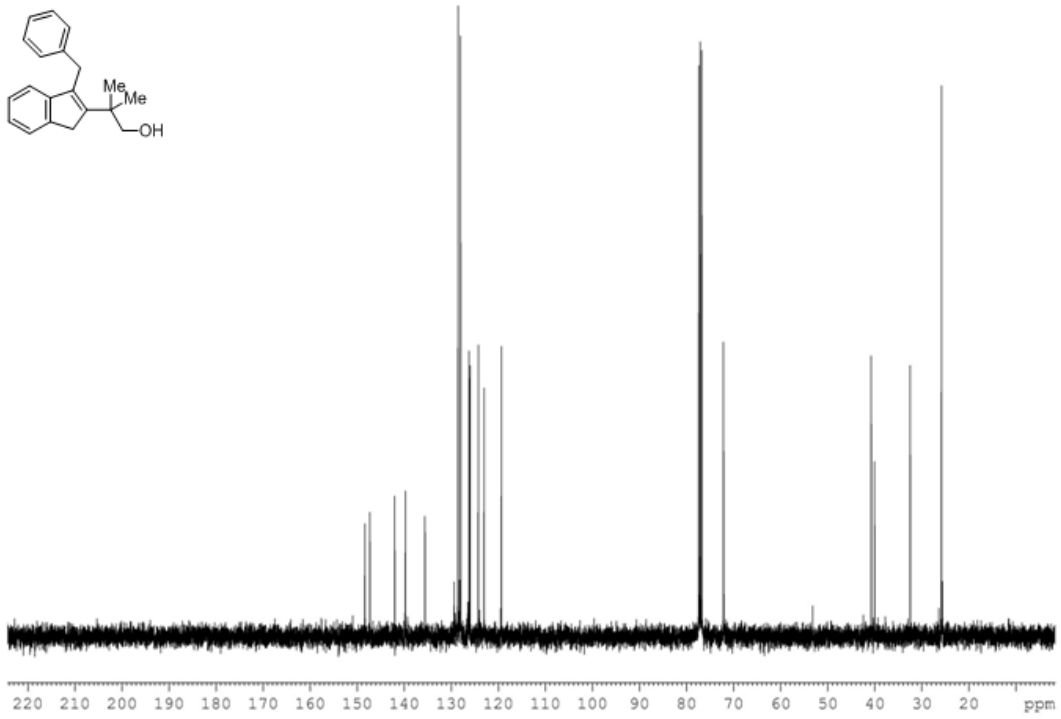
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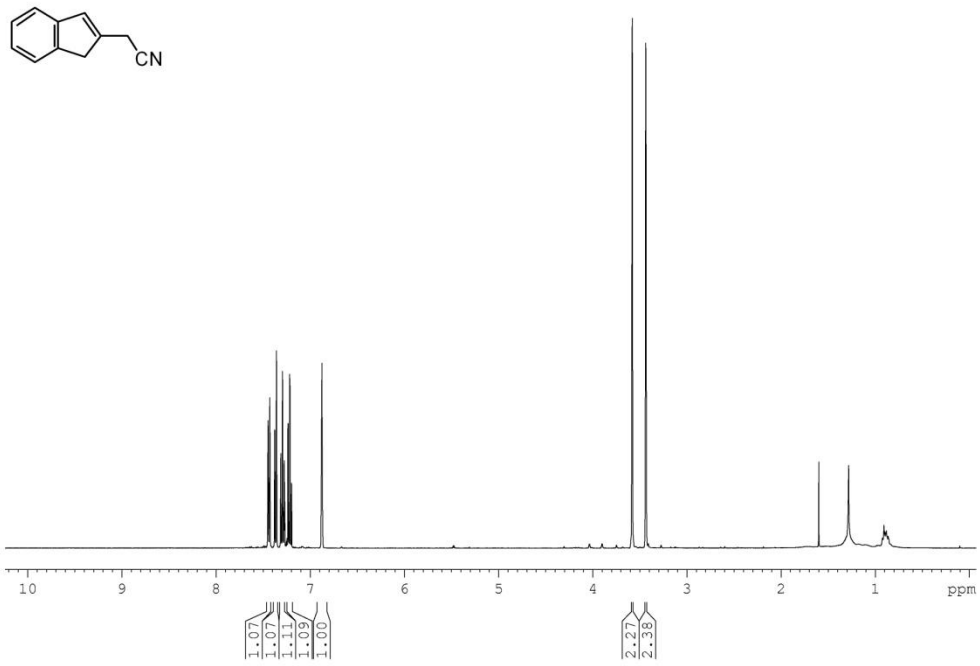
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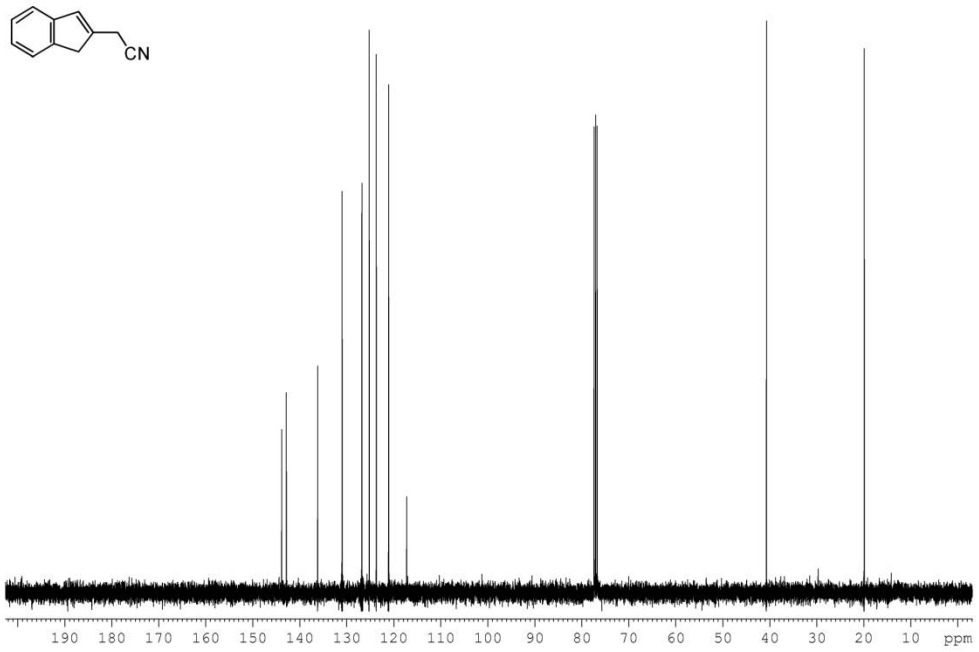
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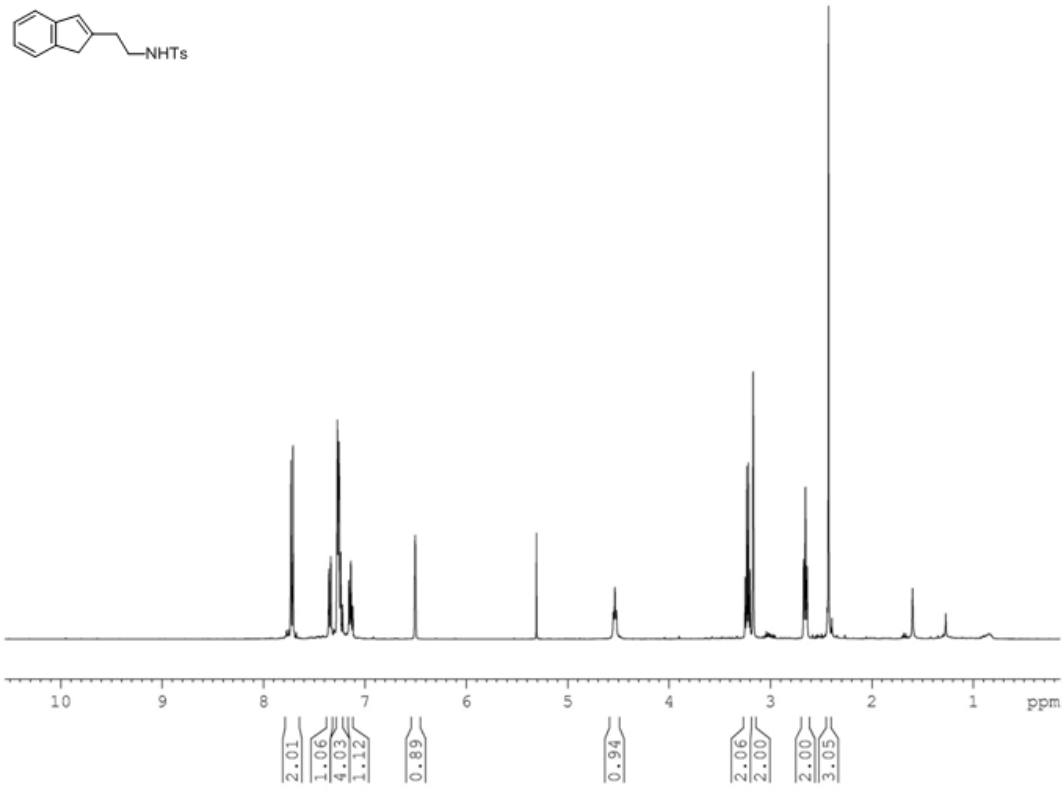
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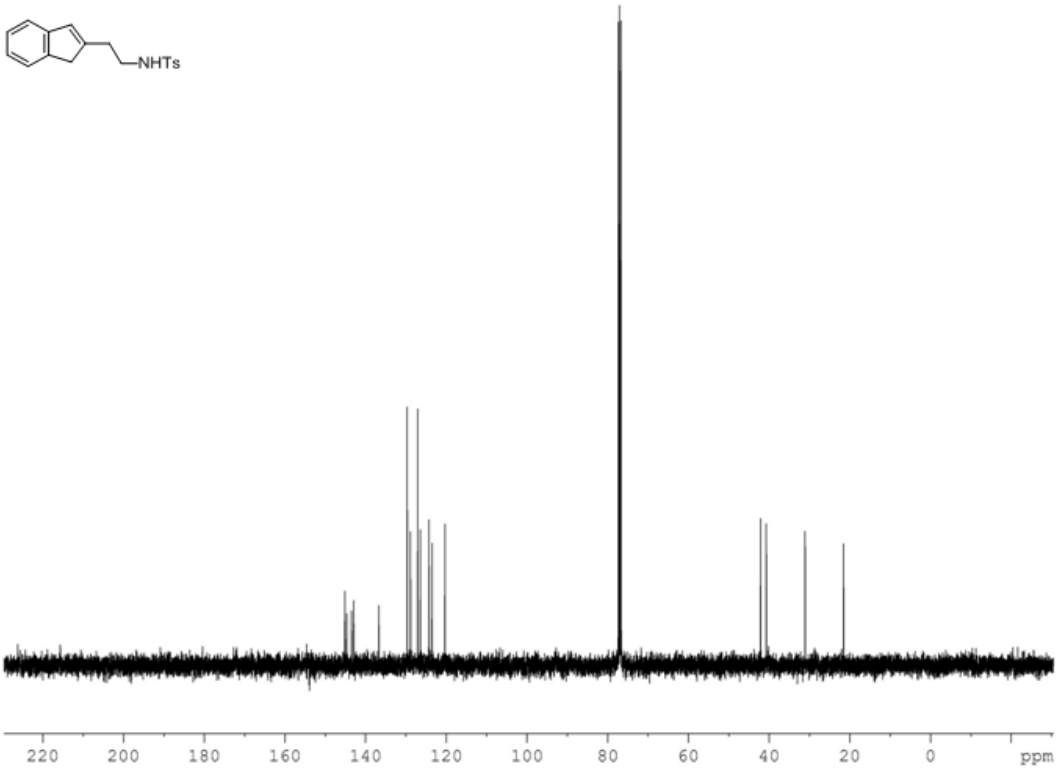
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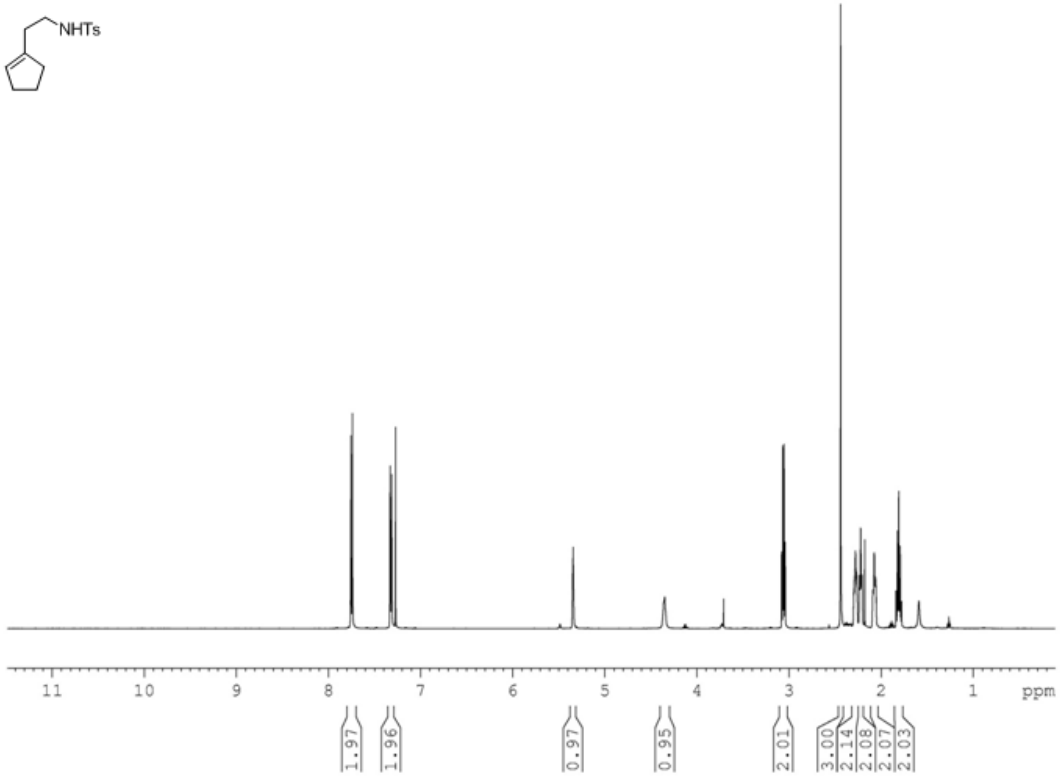
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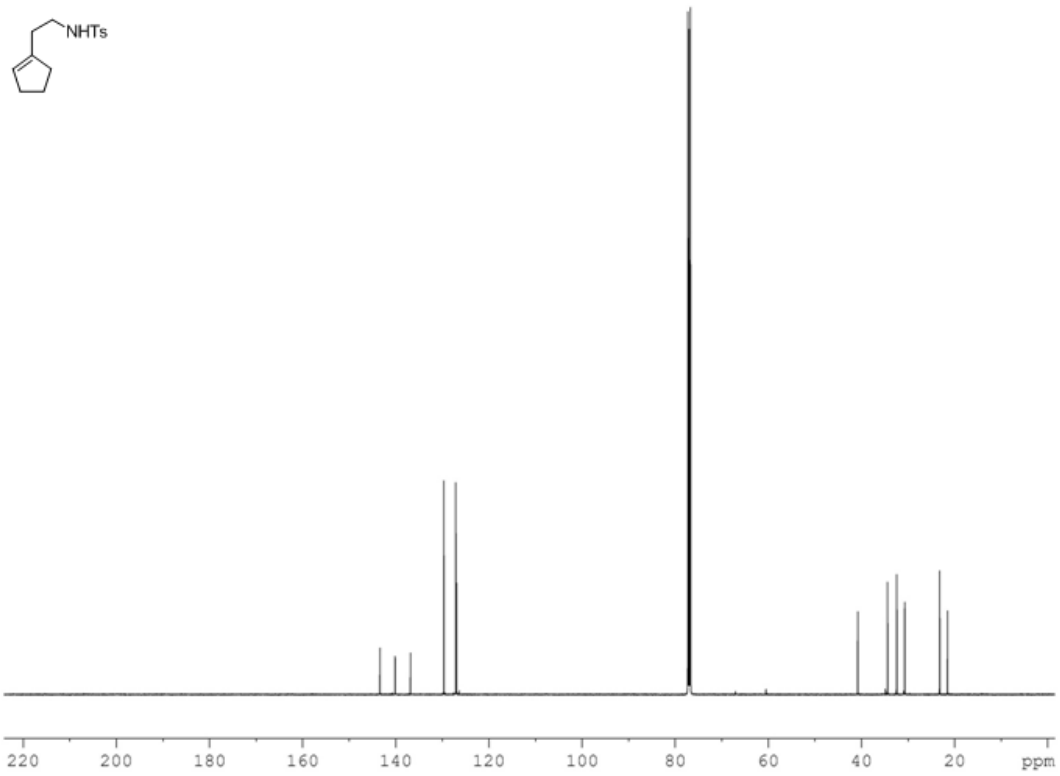
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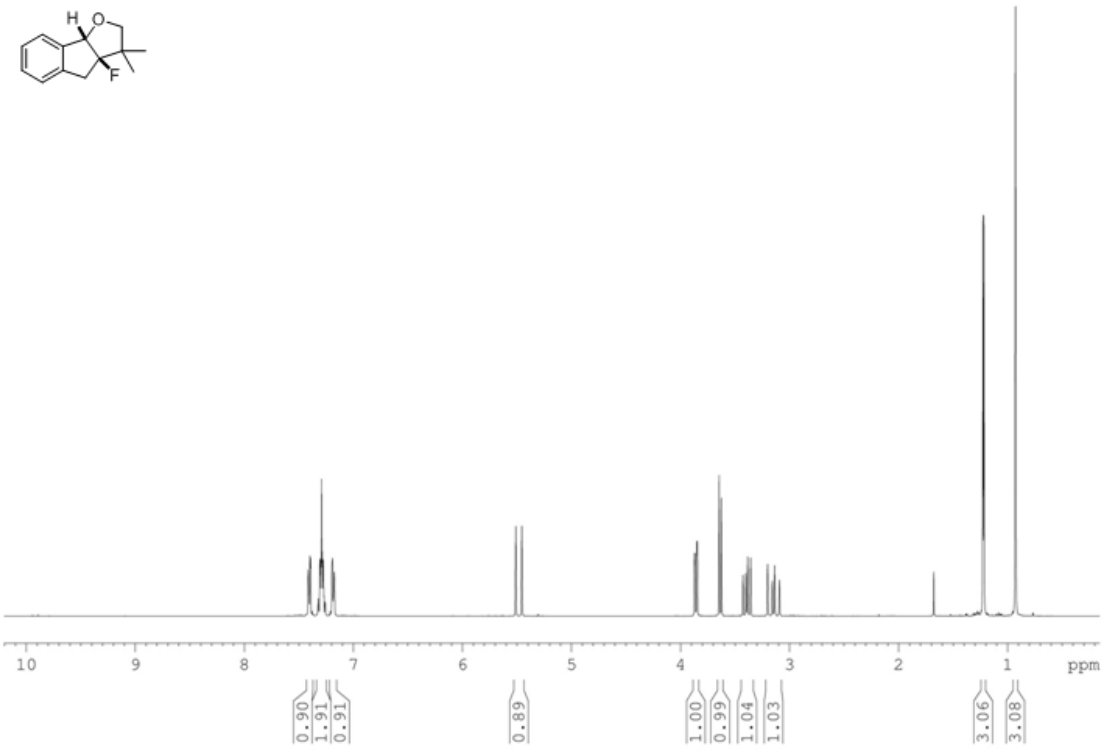
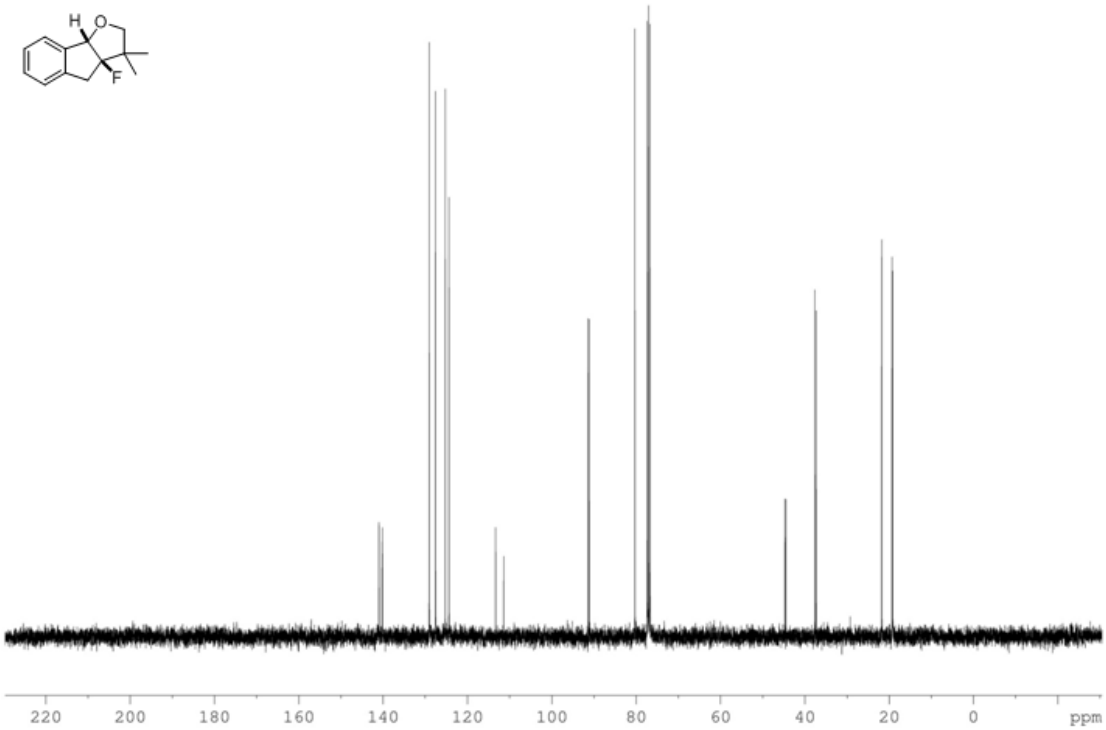
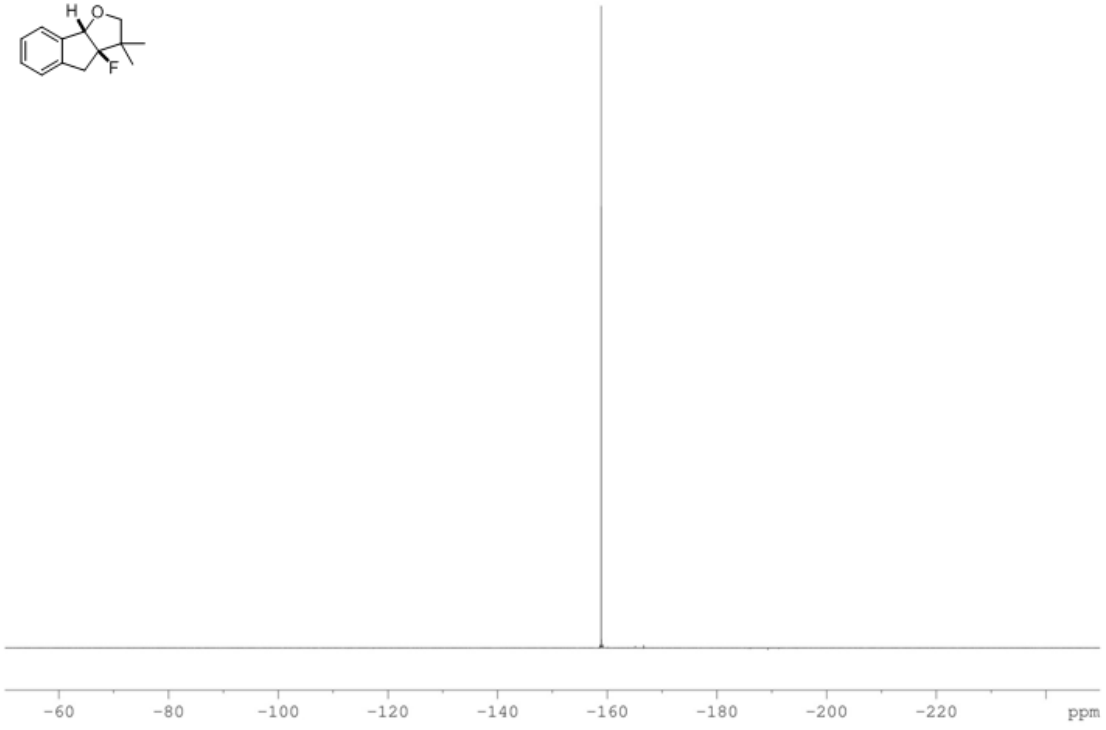
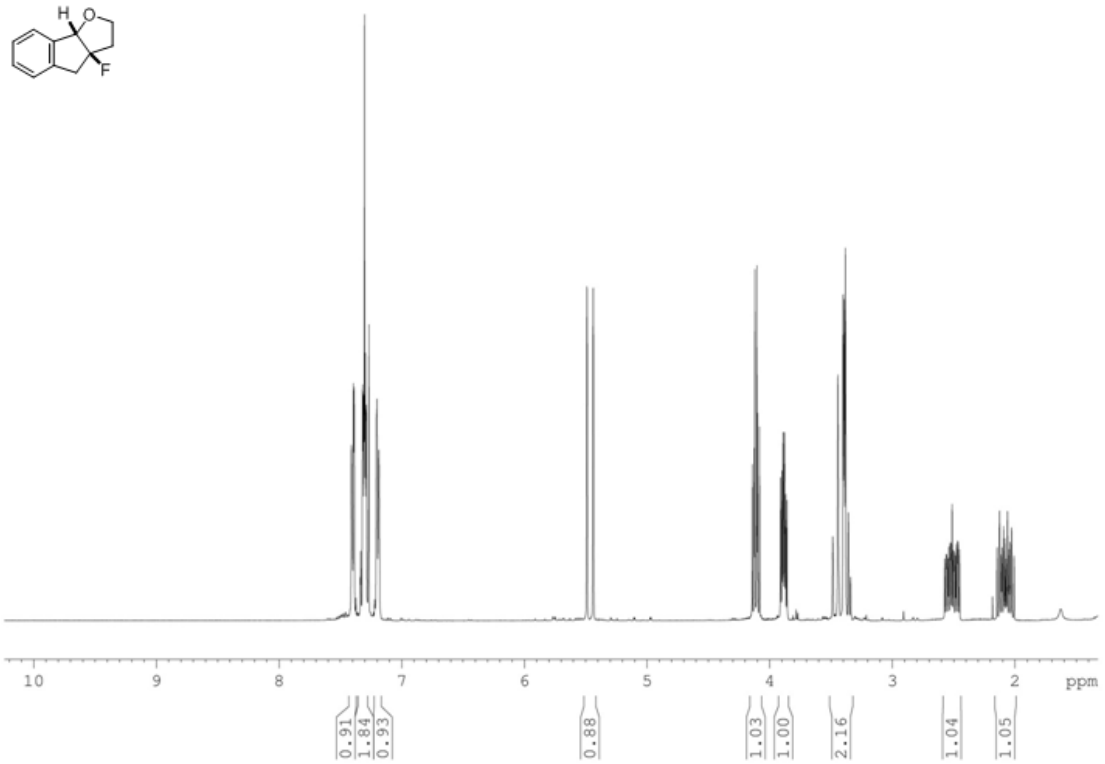
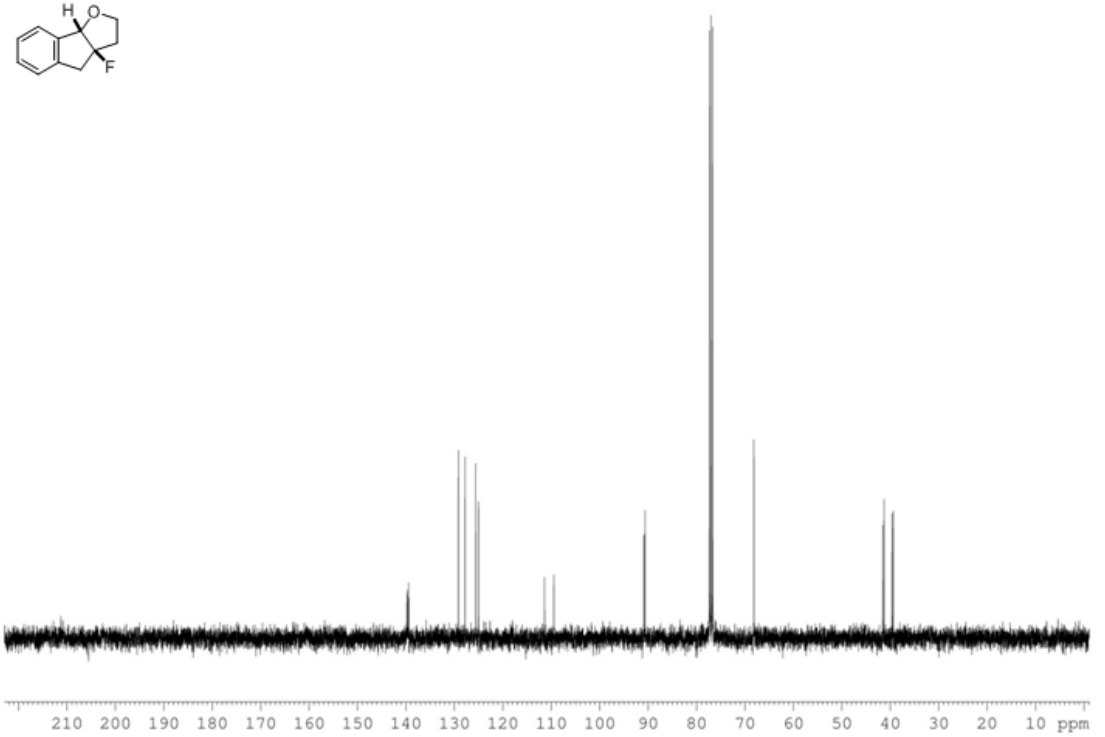
20
ppm

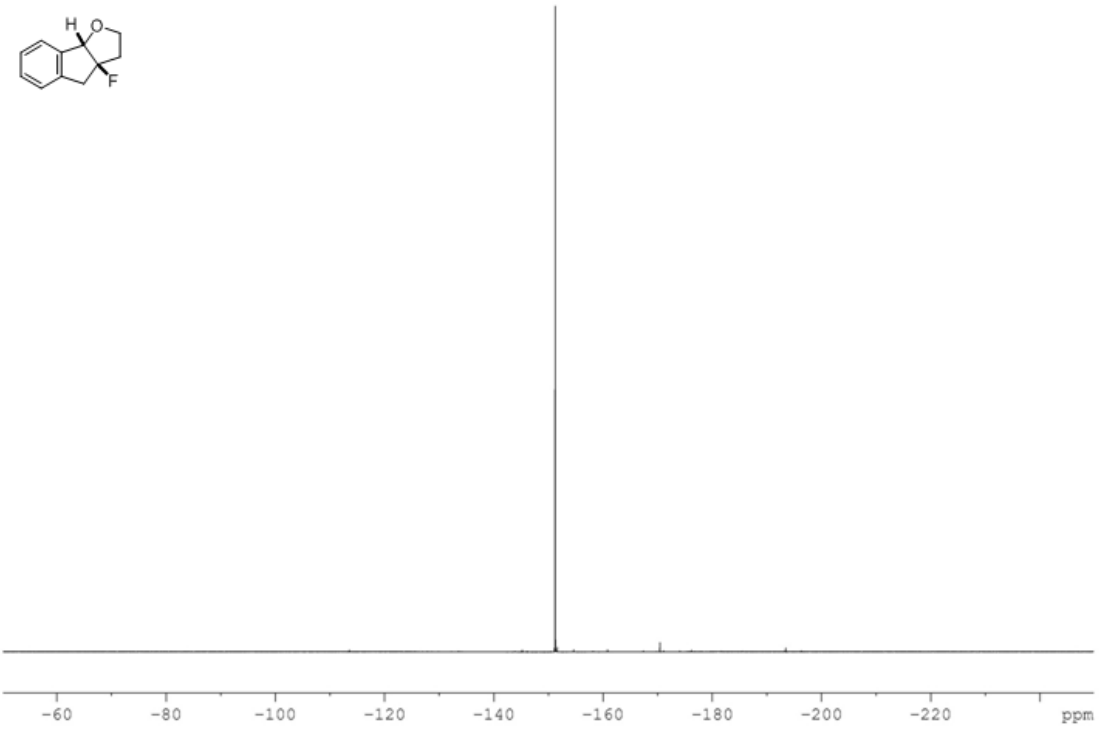

H
O
F
10
9
8
7
6
5
4
3
2
1
ppm
0.90
1.91
0.91
0.89
1.00
0.99
1.04
1.03
3.06
3.08

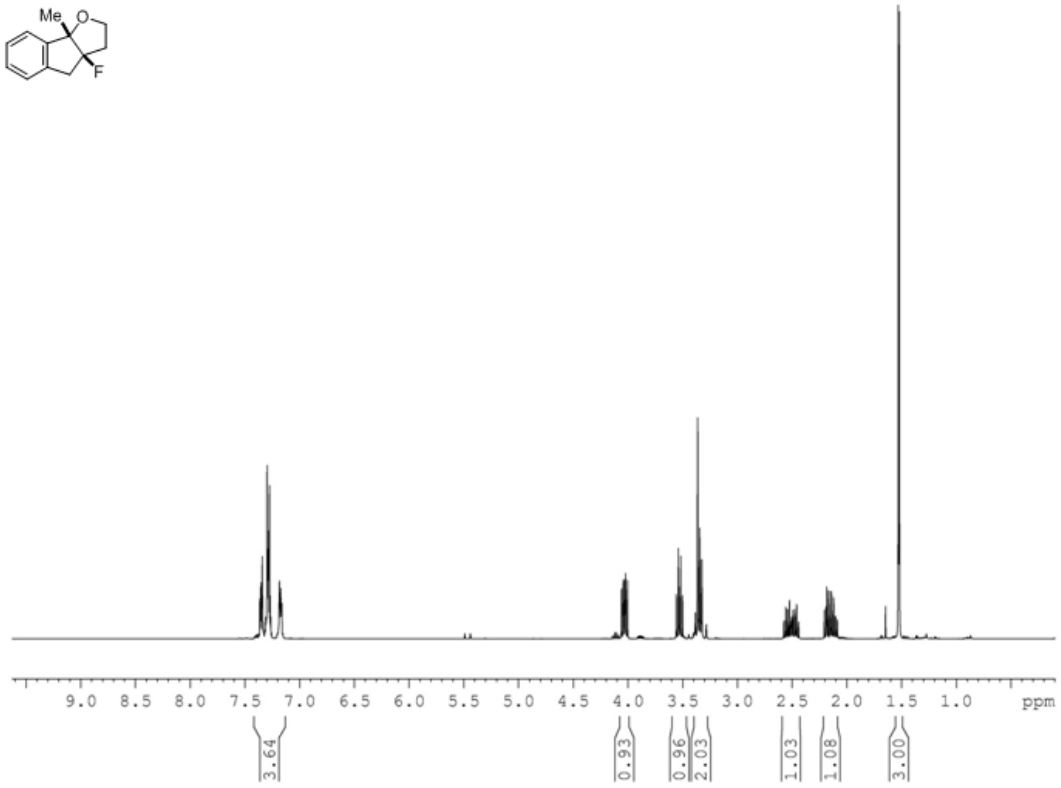

H
O
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

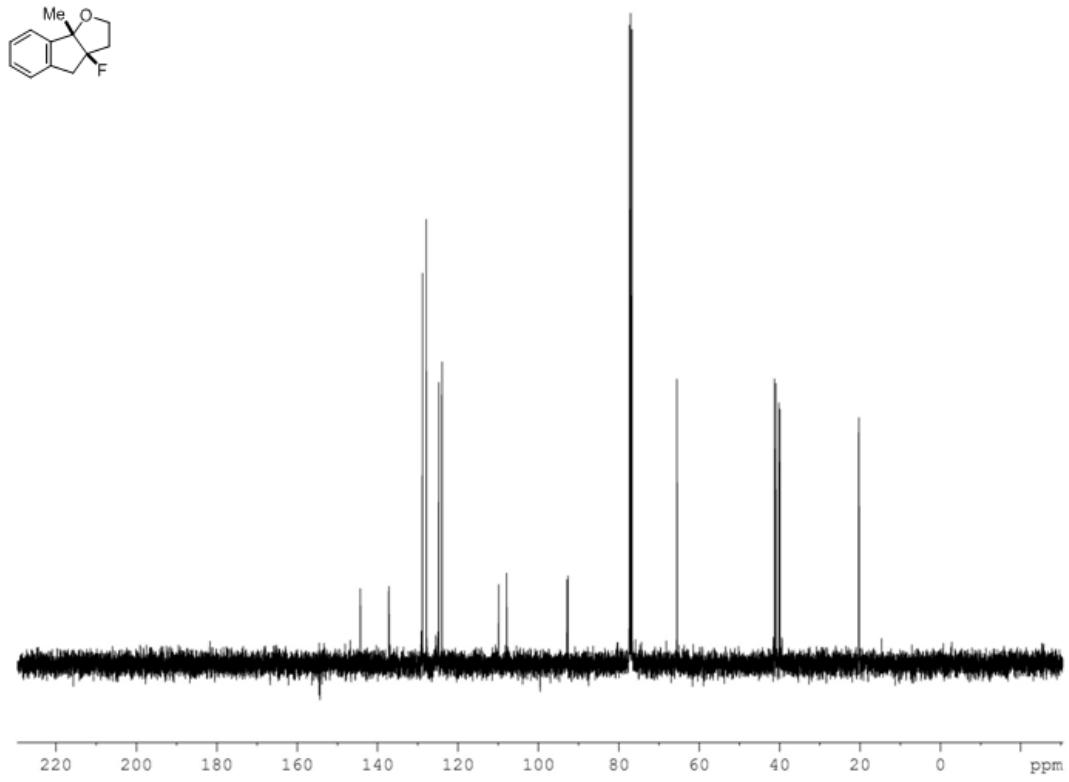

H
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

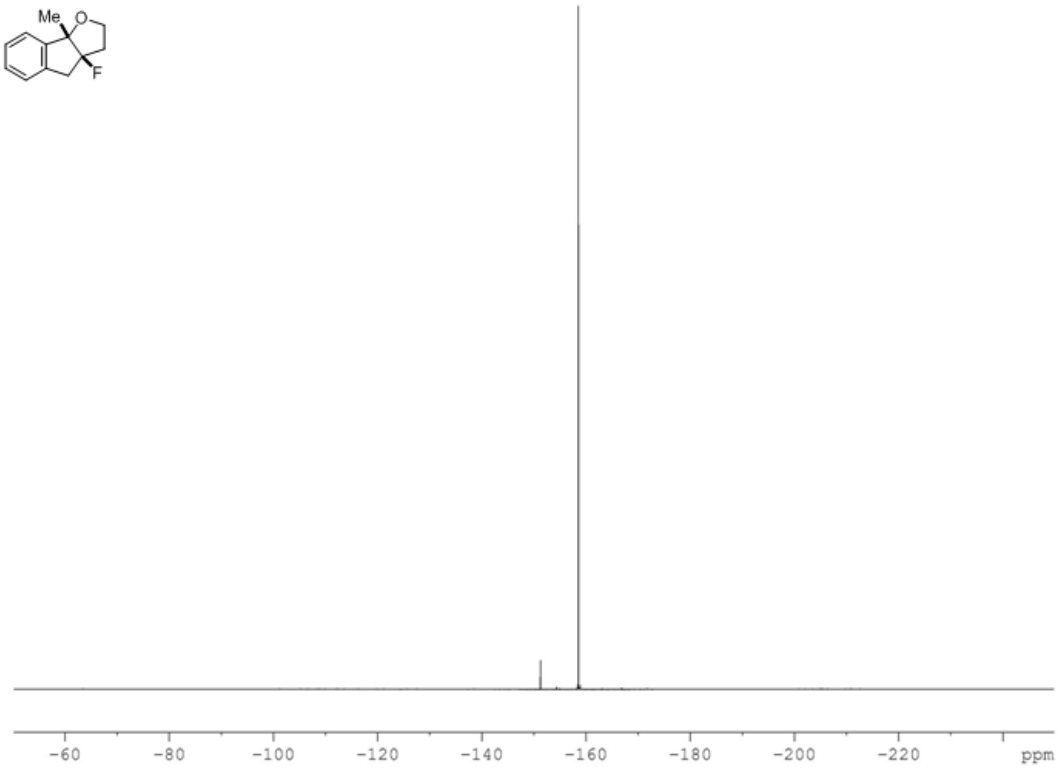

H
O
F
10
9
8
7
6
5
4
3
2
ppm
0.91
1.84
0.93
0.88
1.03
1.00
2.16
1.04
1.05

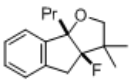

H
O
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

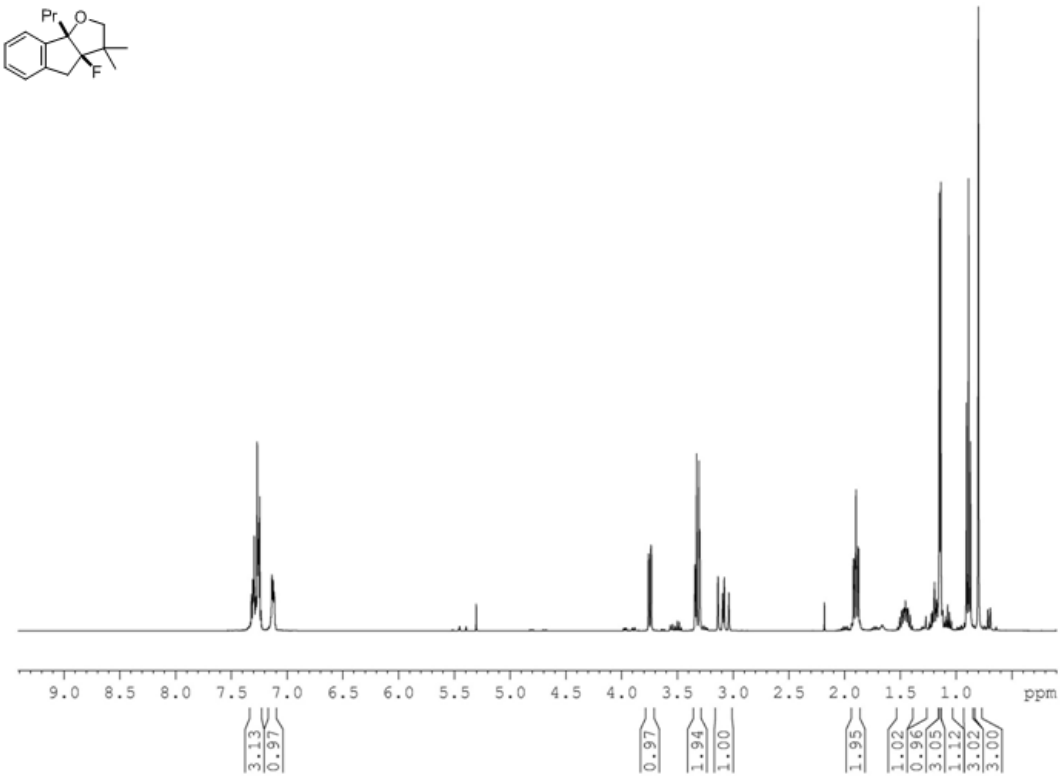

H
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm


Me
O
F
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
3.64
0.93
0.96
2.03
1.03
1.08
3.00

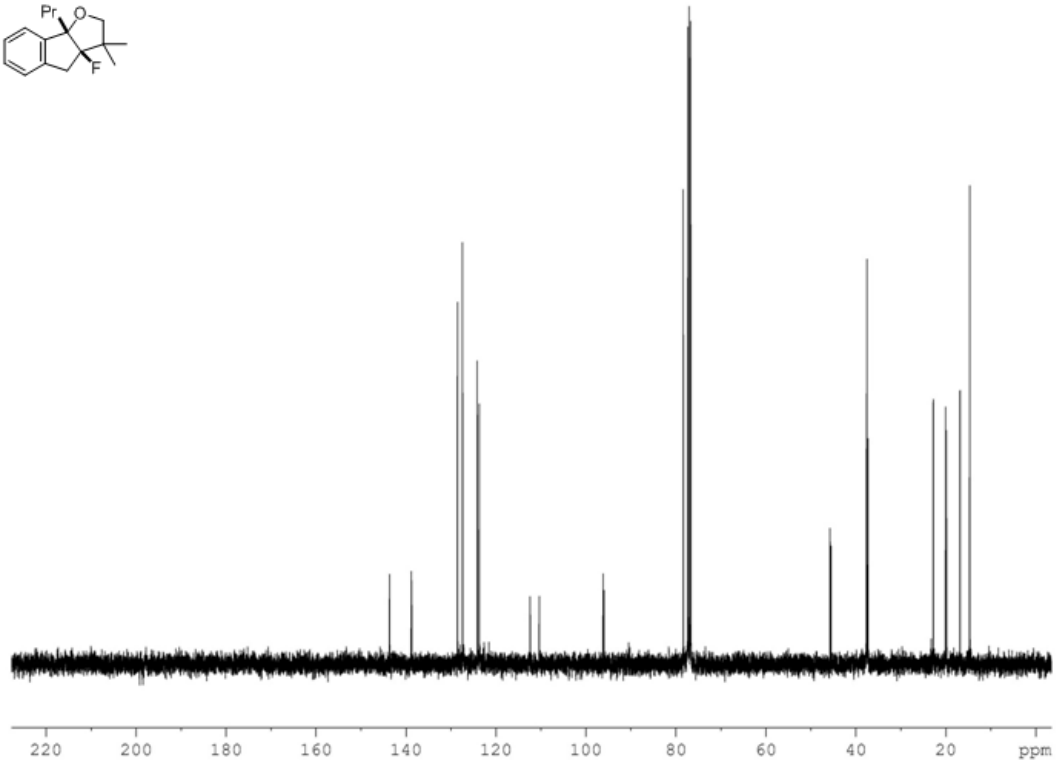

Me
O
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

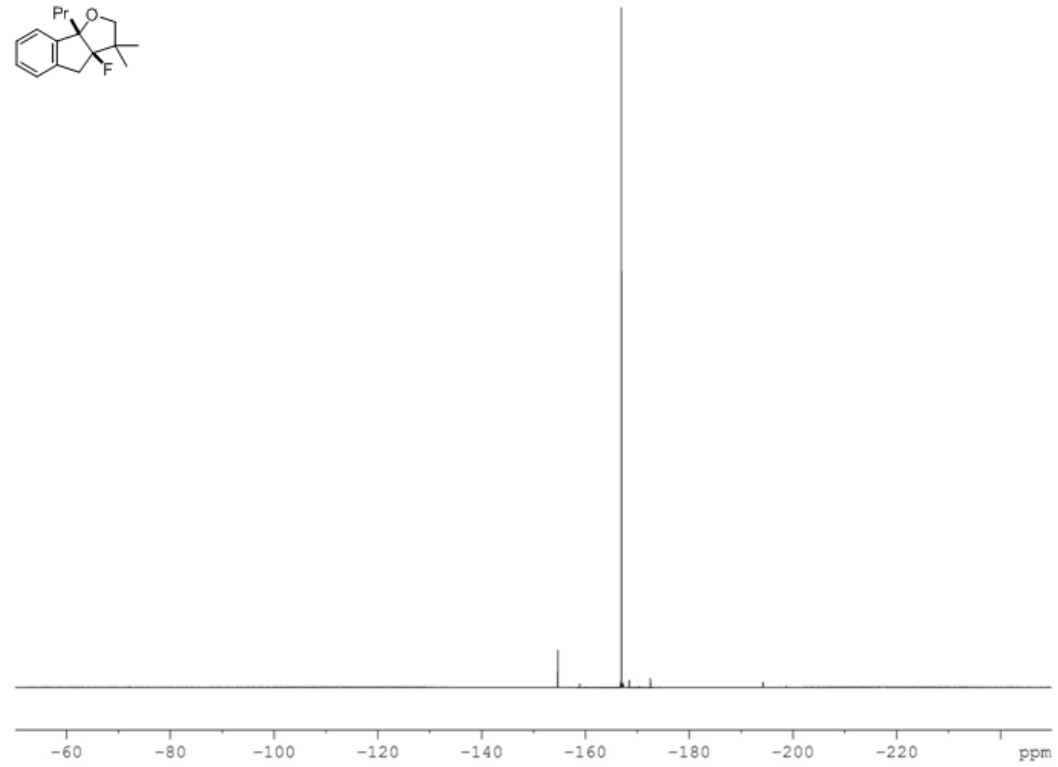

Me
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

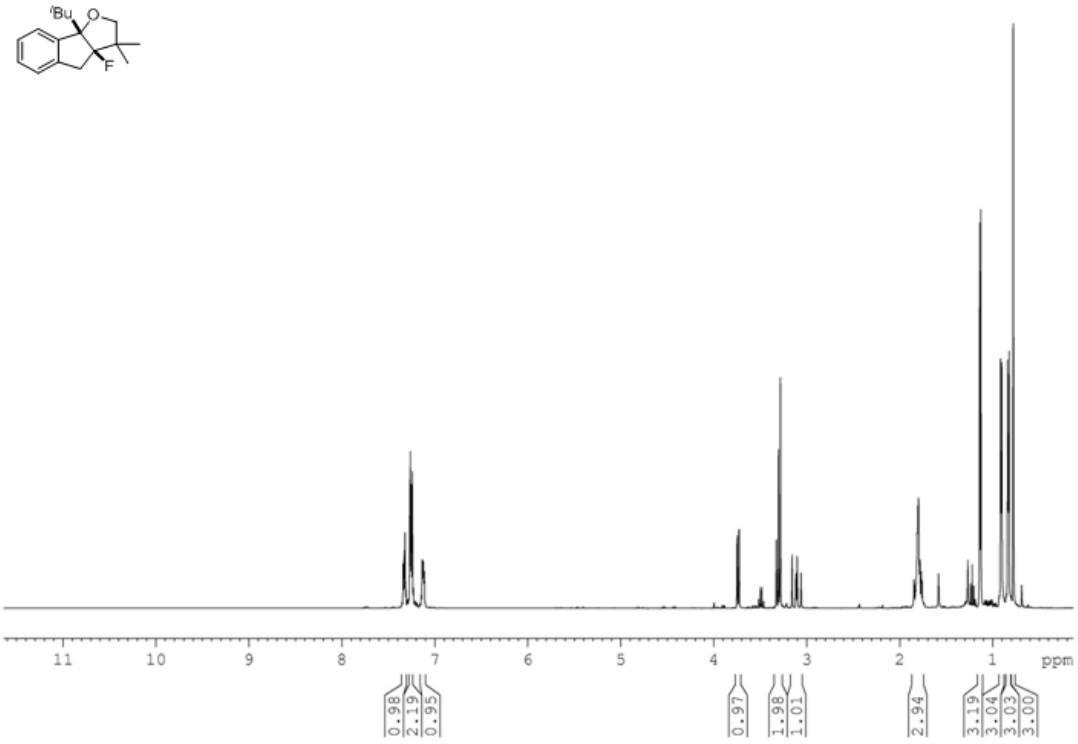

Pr
O
F

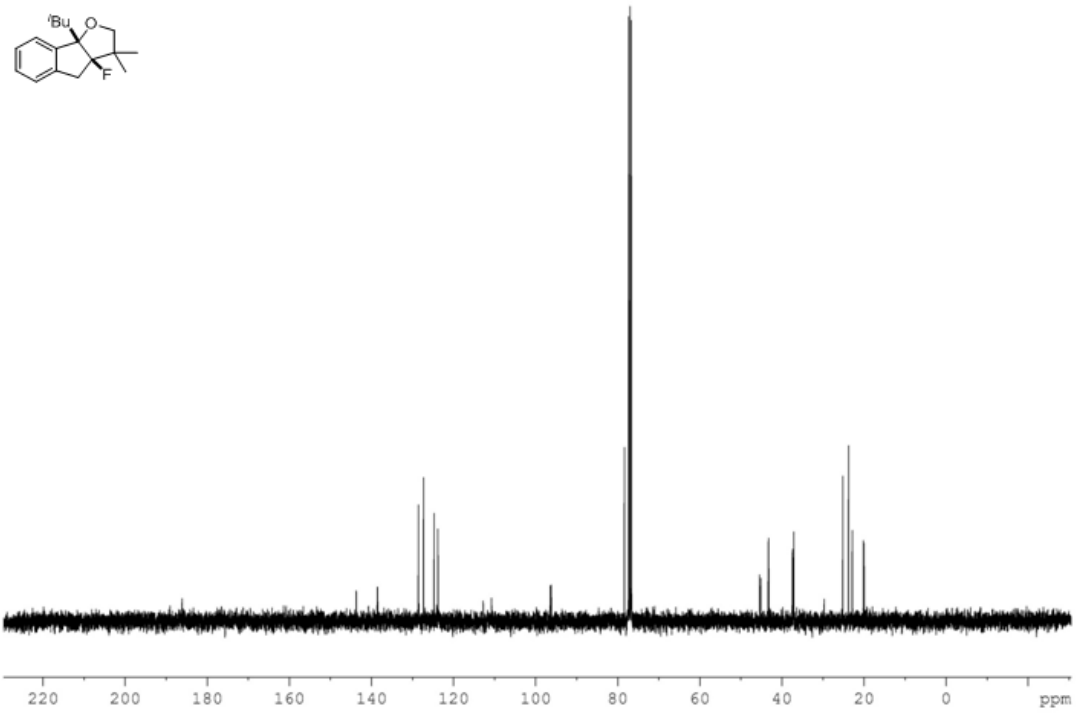

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
3.13
0.97
0.97
1.94
1.00
1.95
1.02
0.96
3.05
1.12
3.02
3.00

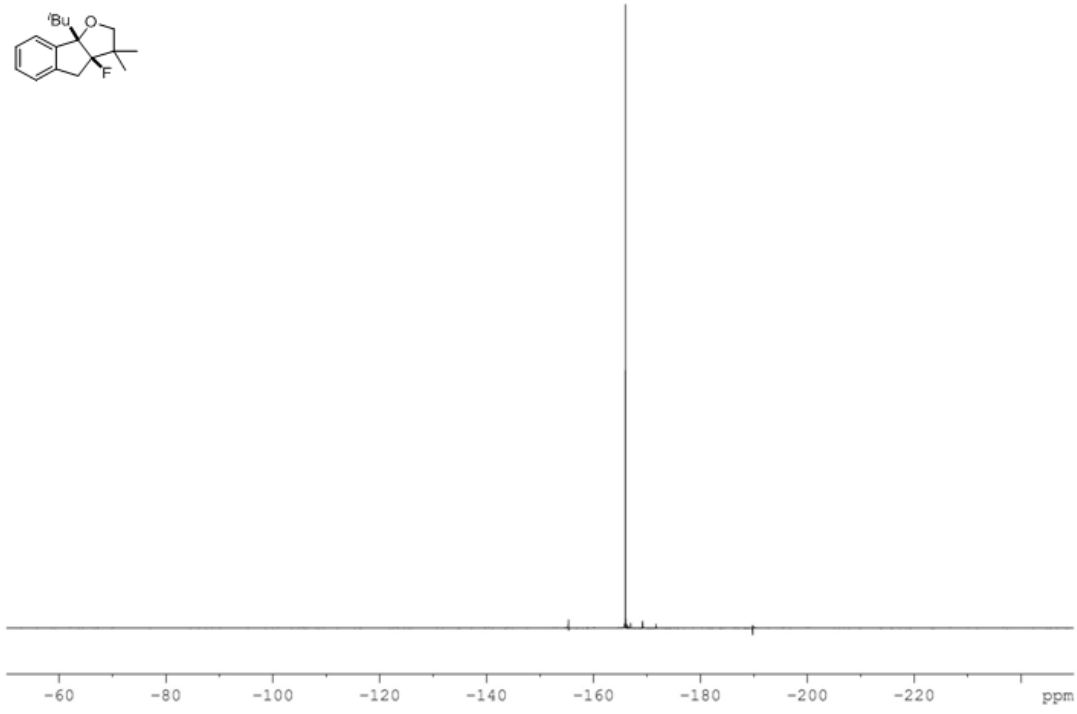
Pr
O
F

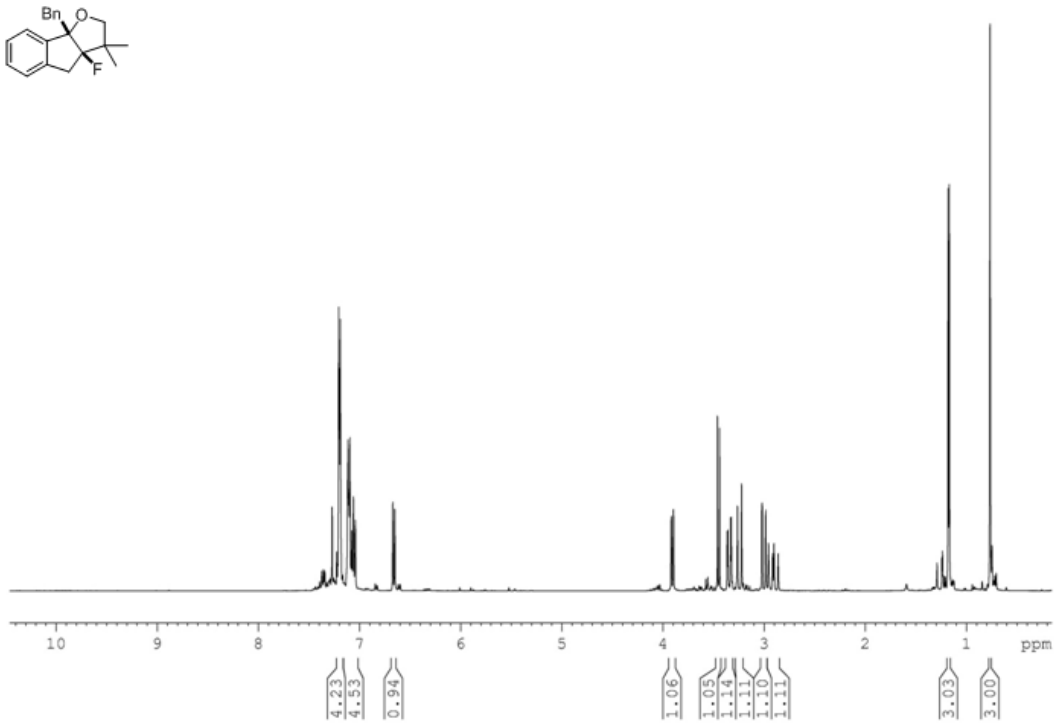

220 200 180 160 140 120 100 80 60 40 20 ppm

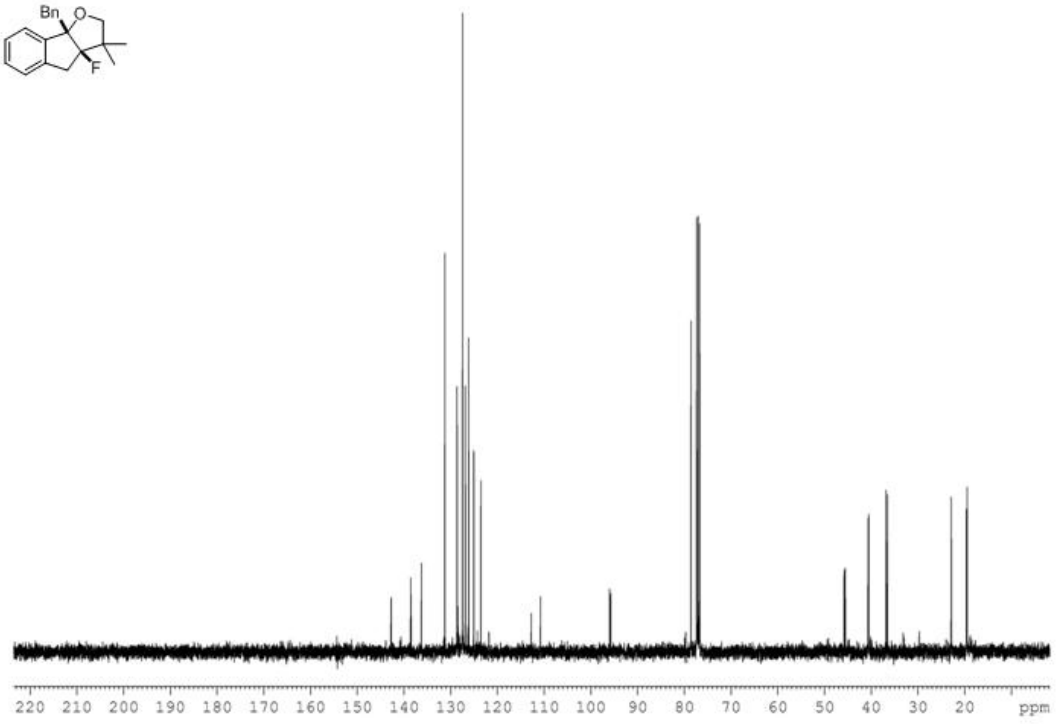

Pr
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

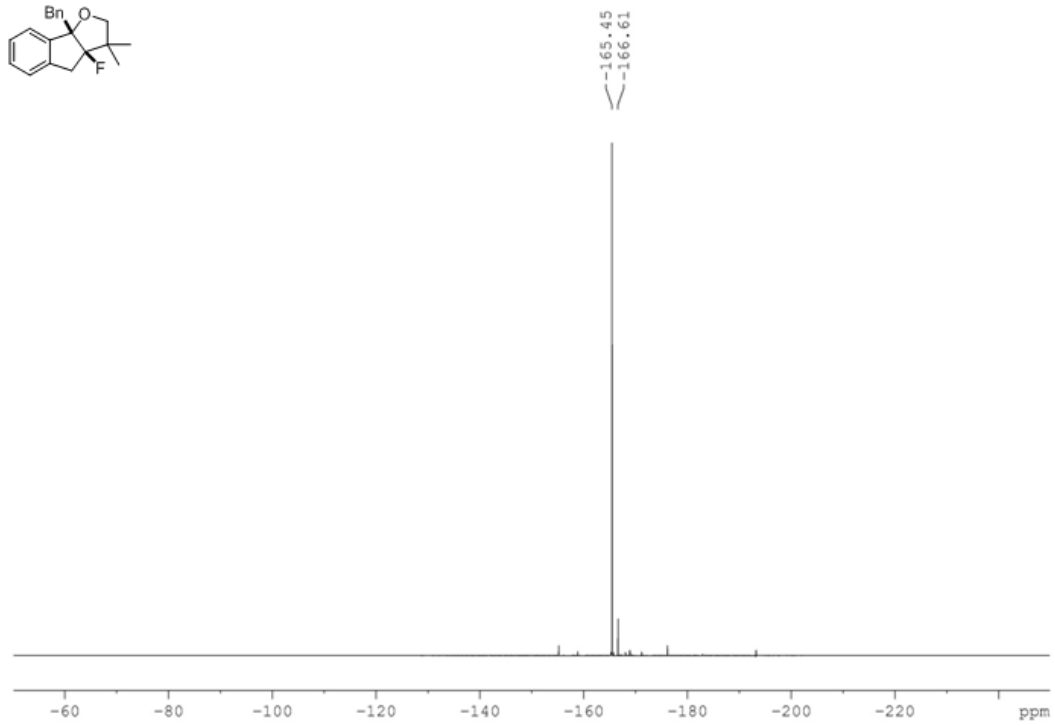

tBu
O
F
11
10
9
8
7
6
5
4
3
2
1
ppm
0.98
2.19
0.95
0.97
1.98
1.01
2.94
3.19
3.04
3.03
3.00

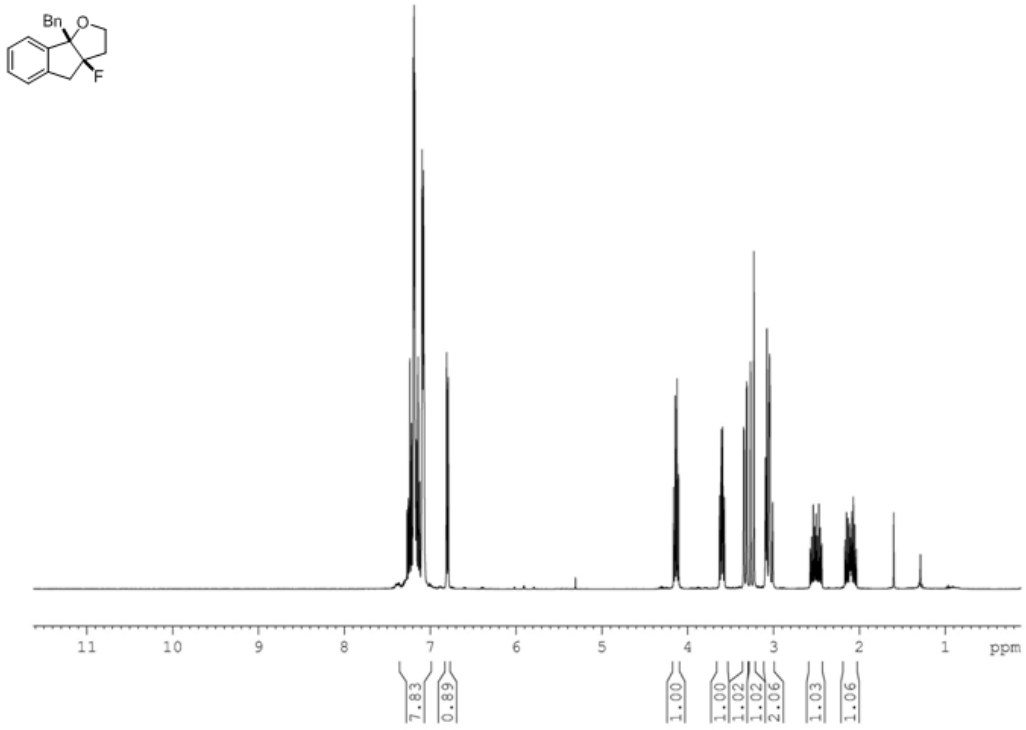

tBu
O
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

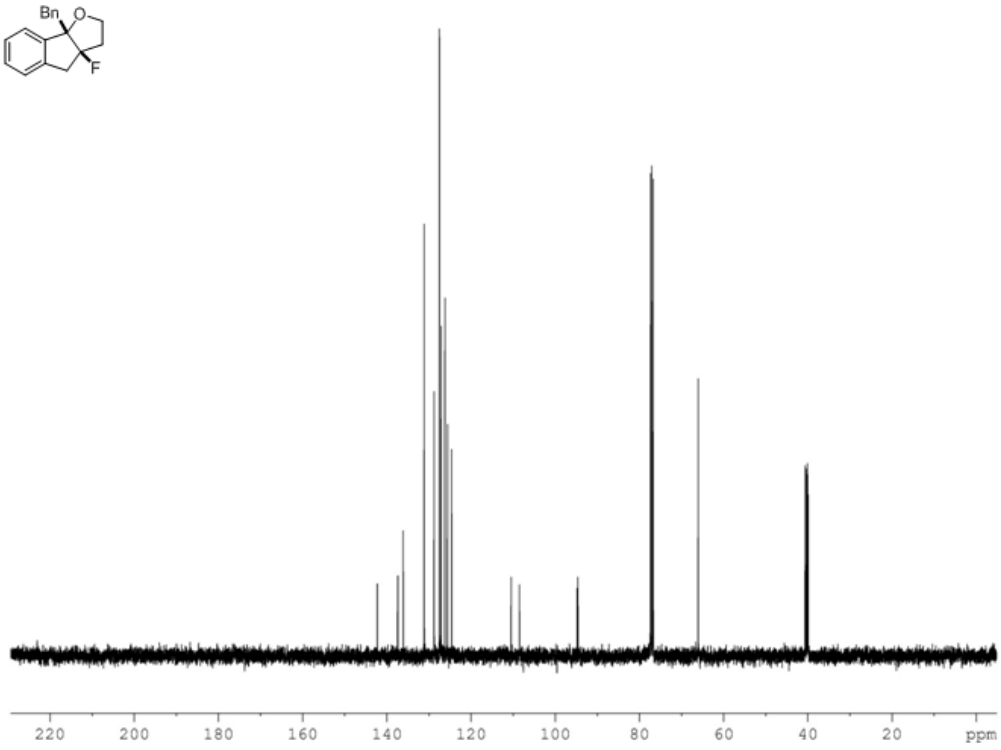

tBu
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

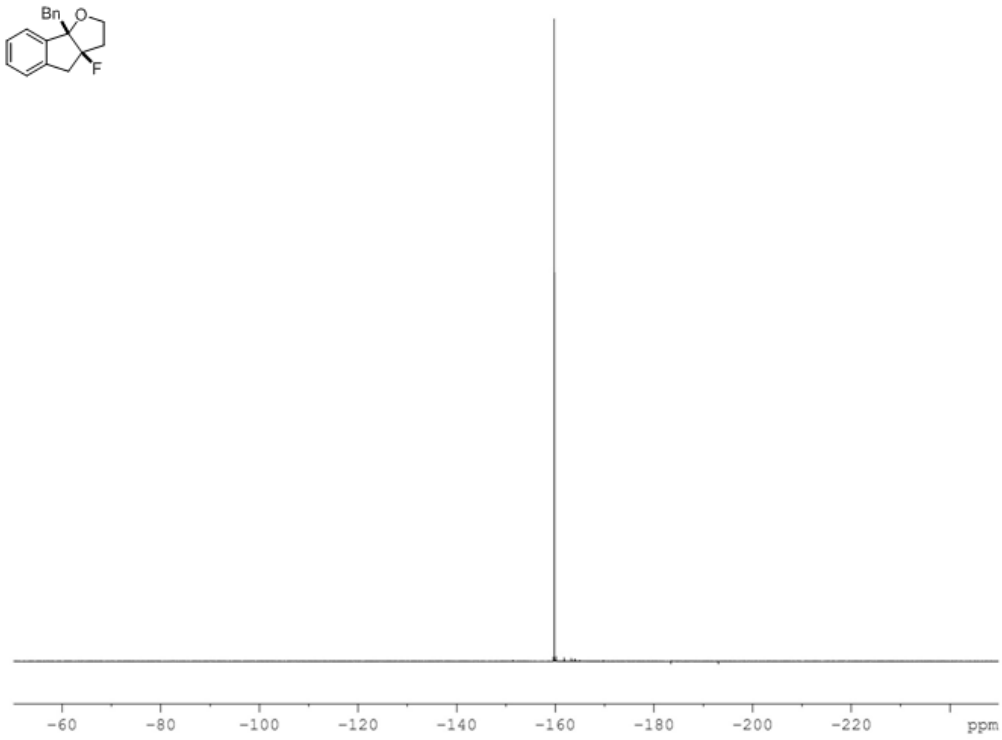

Bn
O
F
10
9
8
7
6
5
4
3
2
1
ppm
4.23
4.53
0.94
1.06
1.05
1.14
1.11
1.10
1.11
3.03
3.00

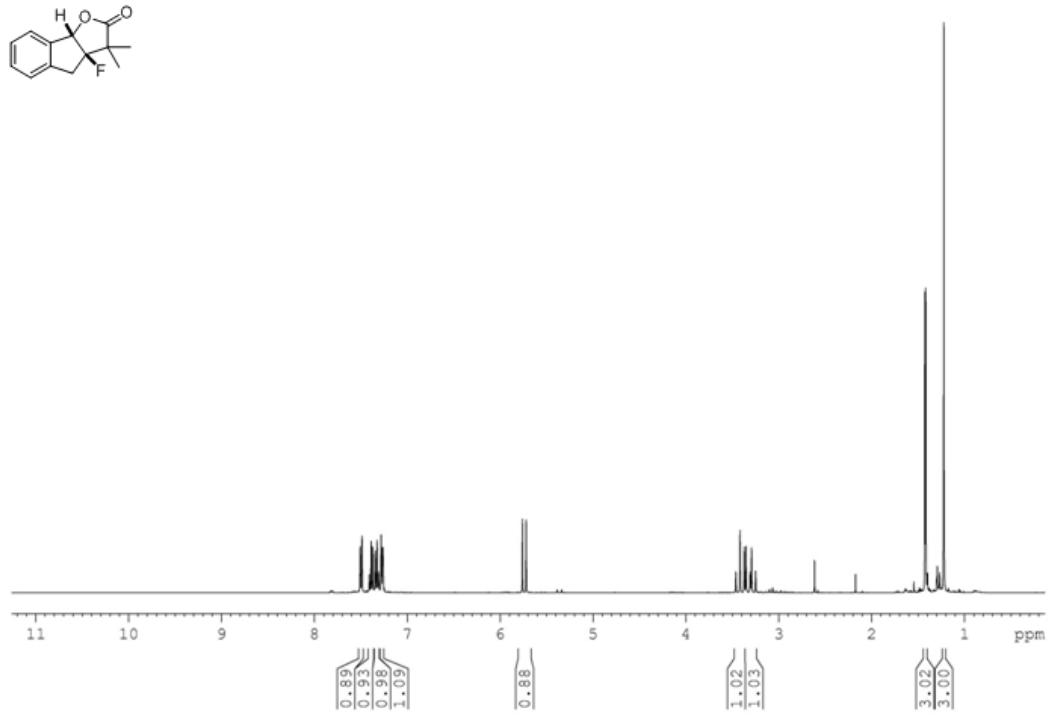

Bn
O
F
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

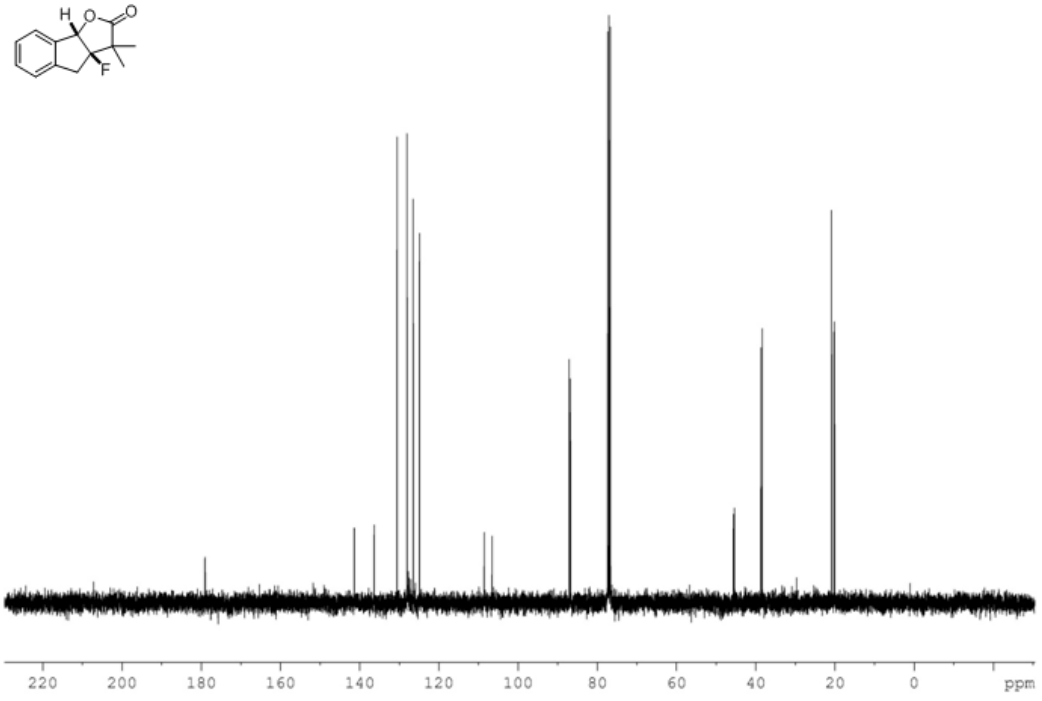

Bn
O
F
-165.45
-166.61
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

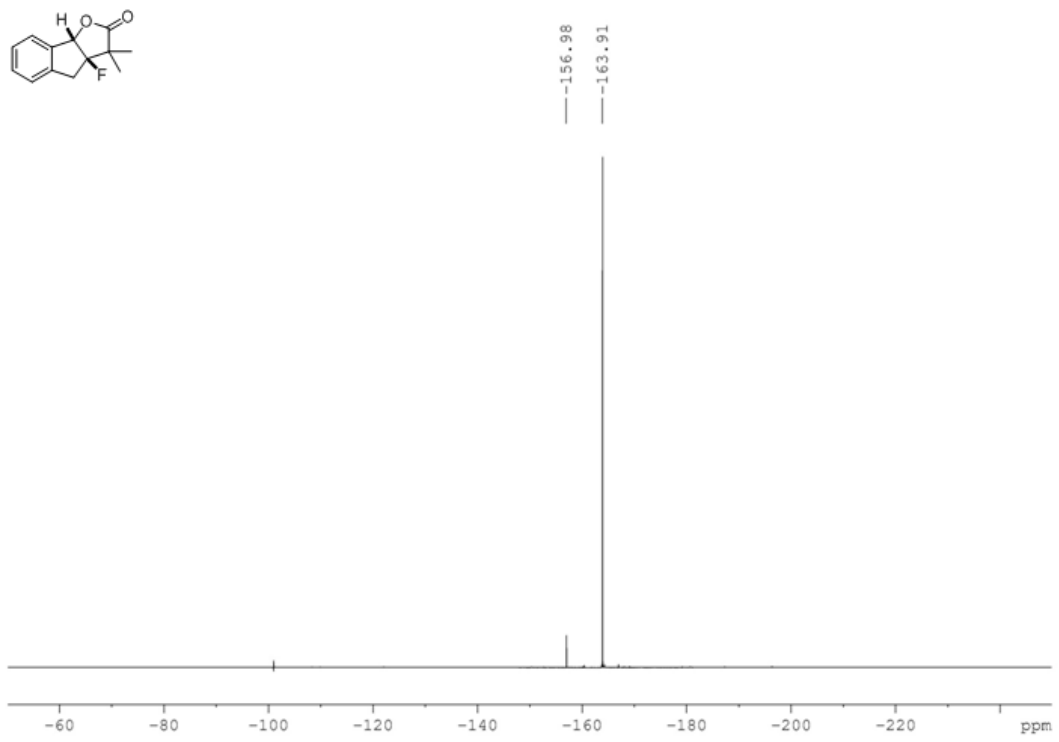

Bn
O
F
11
10
9
8
7
6
5
4
3
2
1
ppm
7.83
0.89
1.00
1.00
1.02
1.02
2.06
1.03
1.06

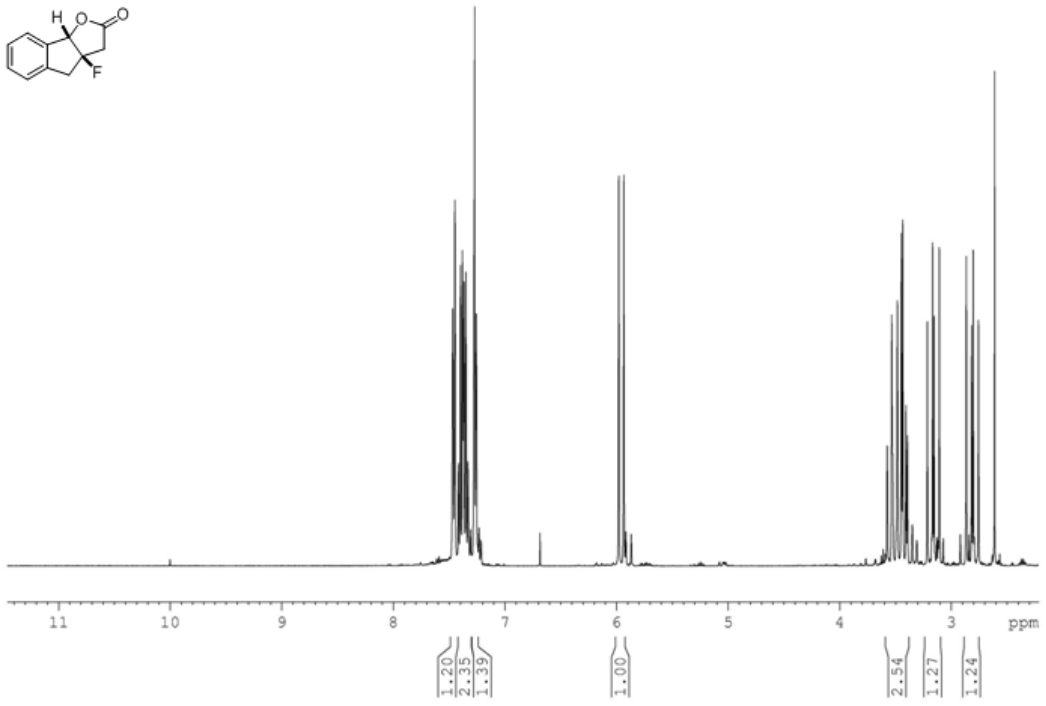

Bn
O
F
220
200
180
160
140
120
100
80
60
40
20
ppm

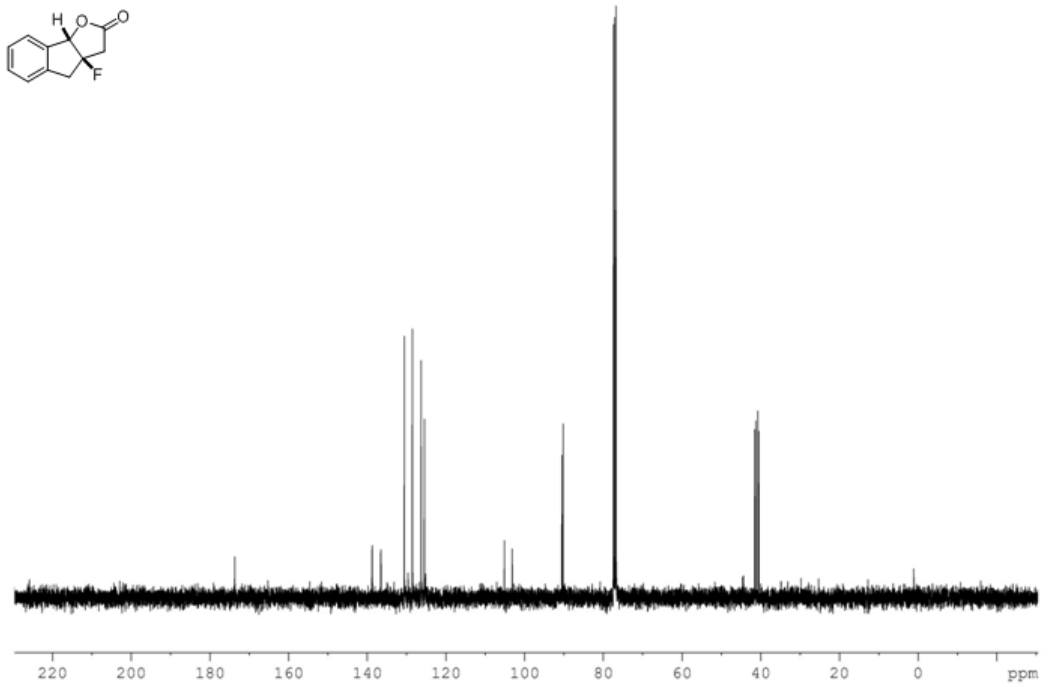

Bn
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

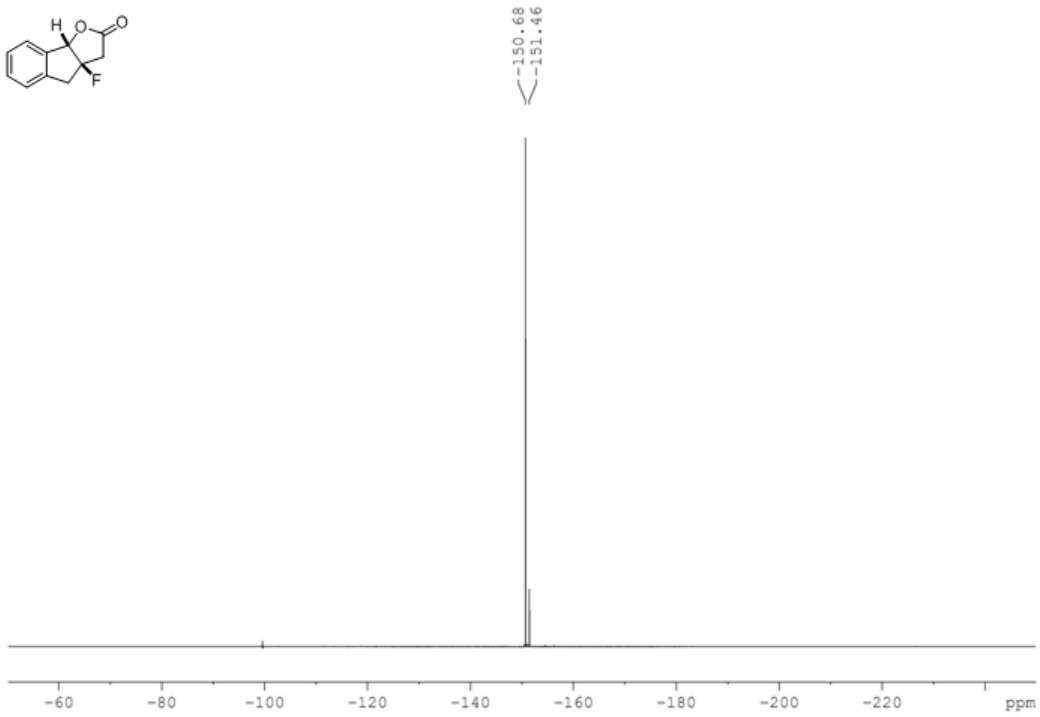

H
O
O
F
11
10
9
8
7
6
5
4
3
2
1
ppm
0.89
0.93
0.98
1.09
0.88
1.02
1.03
3.02
3.00

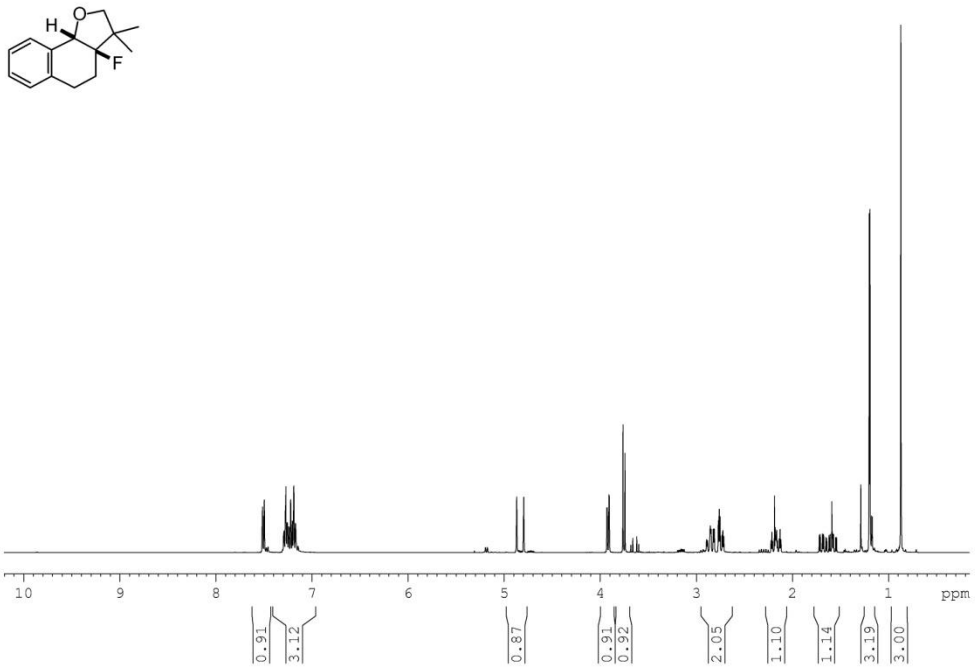

H
O
O
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

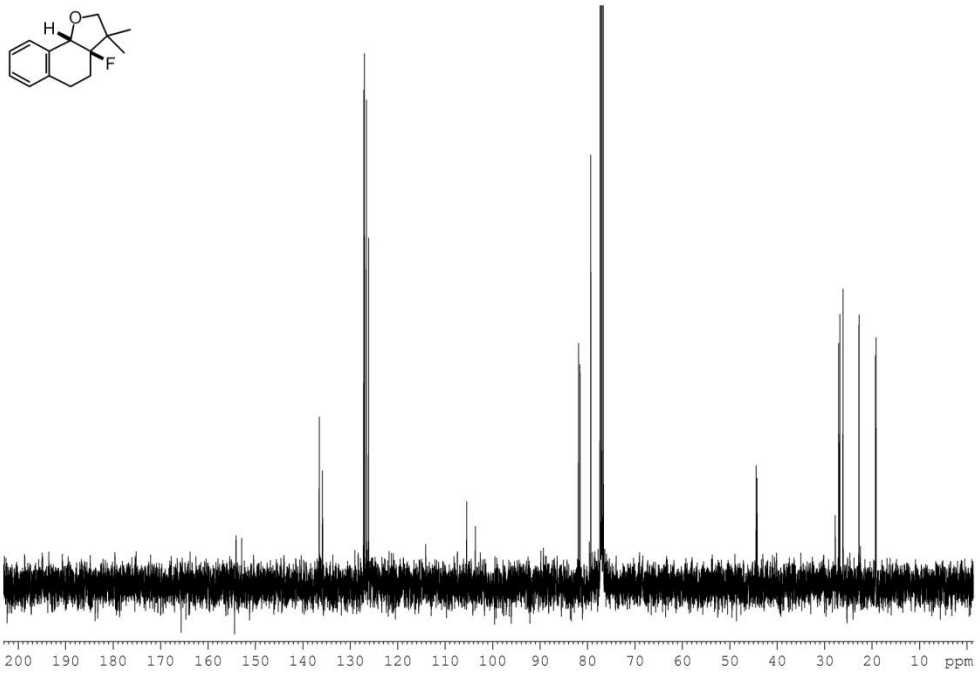

H
O
O
F
-156.98
-163.91
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

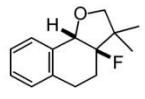

H
O
O
F
11
10
9
8
7
6
5
4
3
ppm
1.20
2.35
1.39
1.00
2.54
1.27
1.24

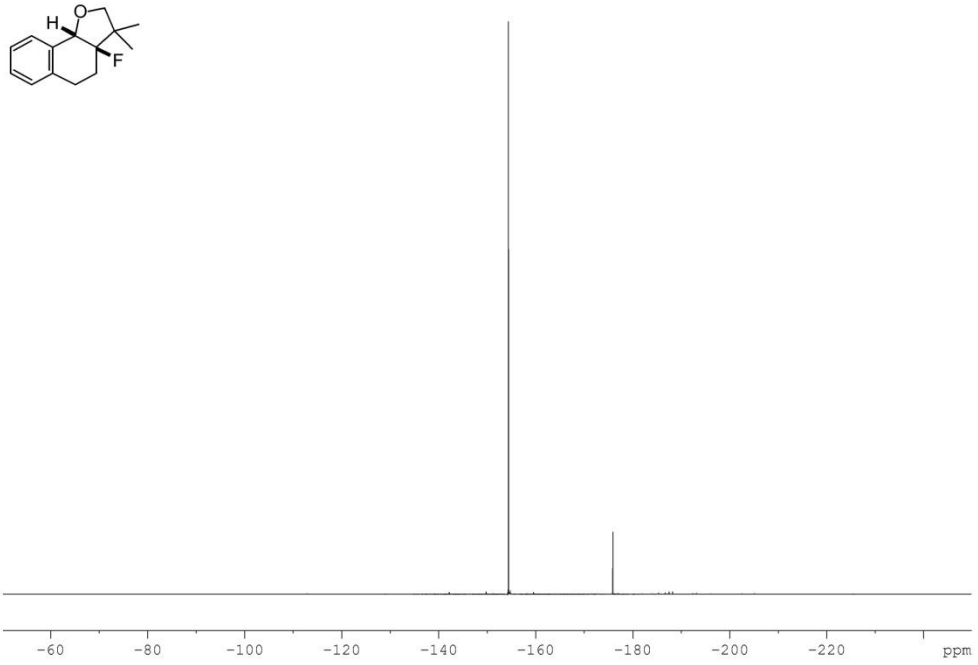

H
O
O
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

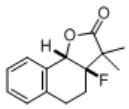

H
O
O
F
-150.68
-151.46
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

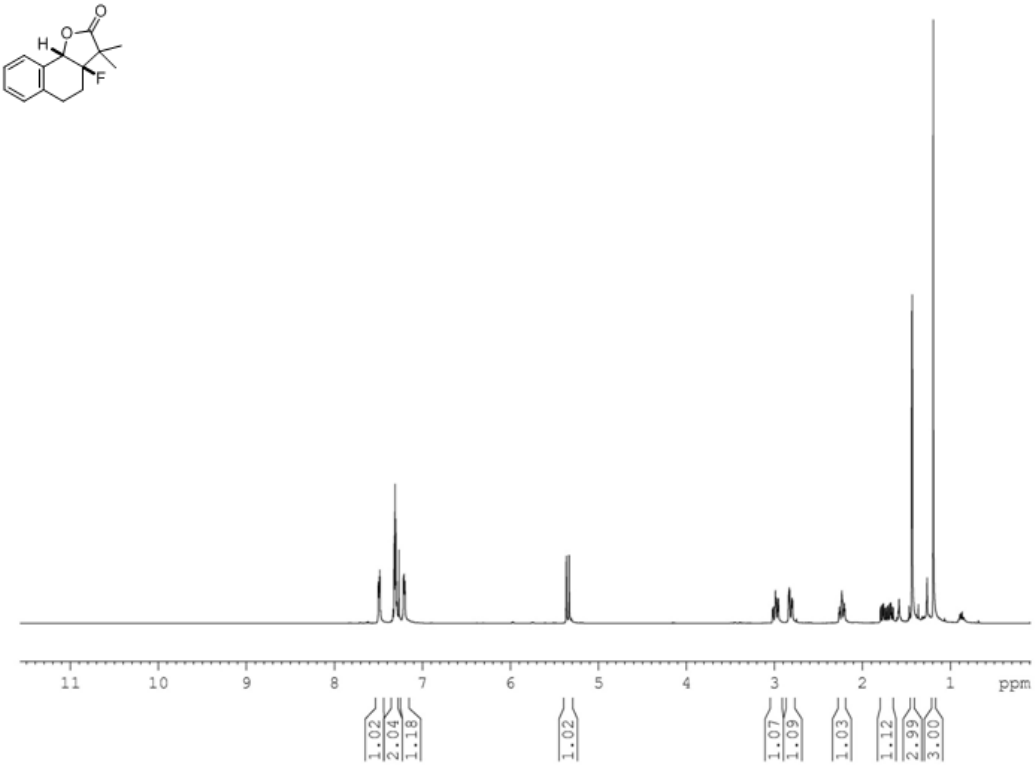

H
O
F
10
9
8
7
6
5
4
3
2
1
ppm
0.91
3.12
0.87
0.91
0.92
2.05
1.10
1.14
3.19
3.00

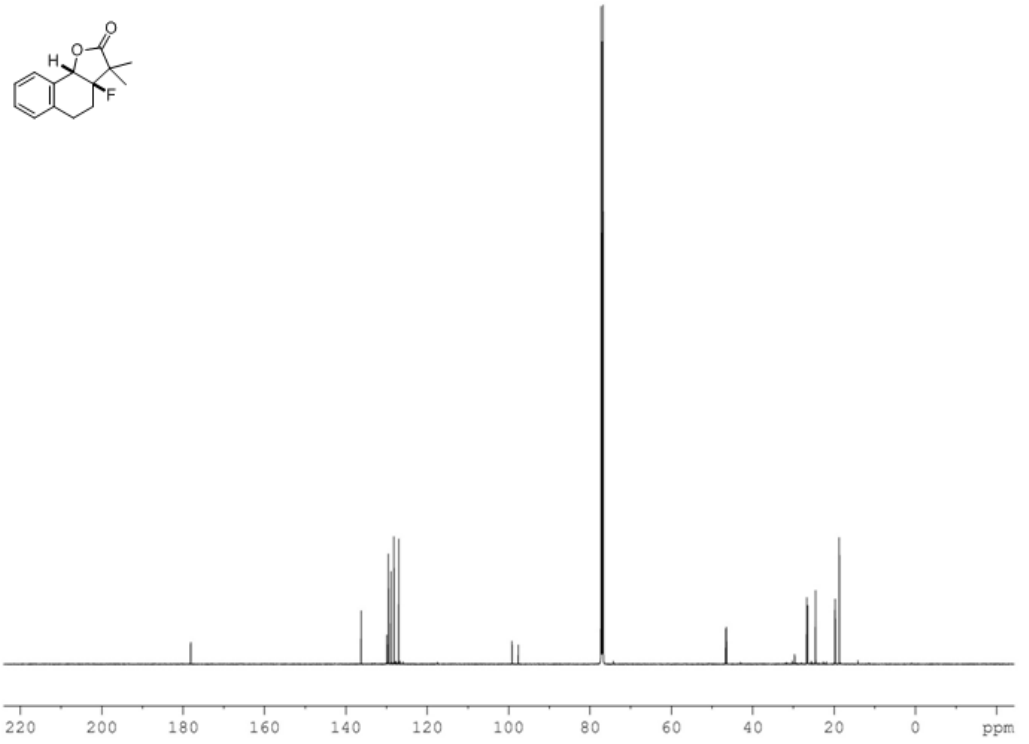

H
O
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

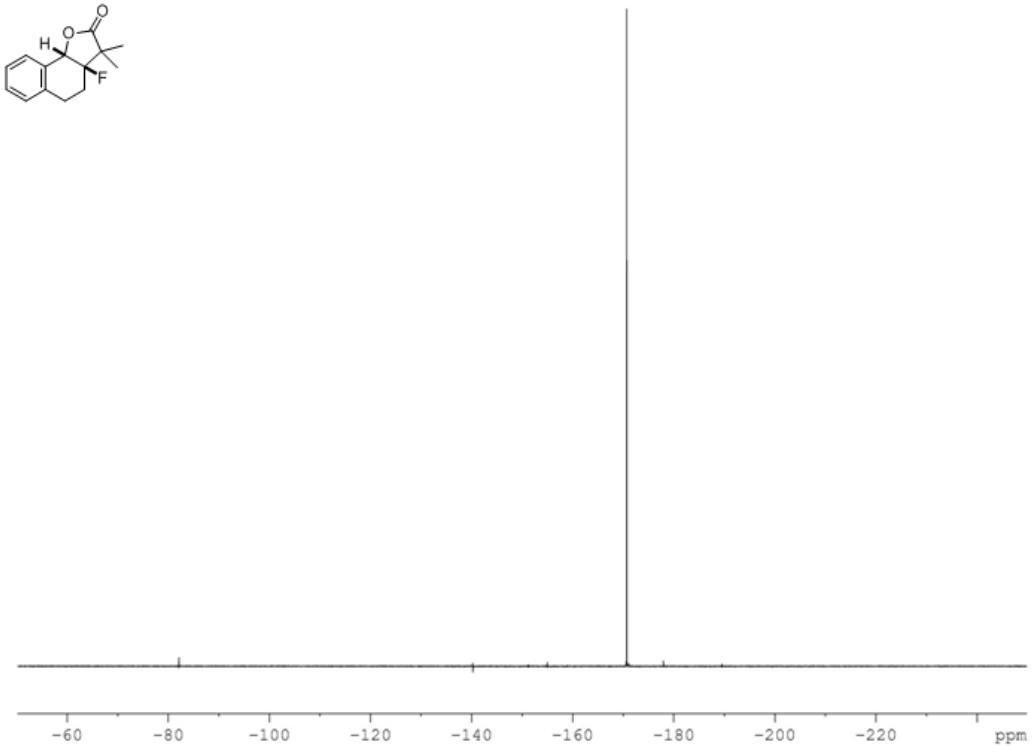

H
O
F

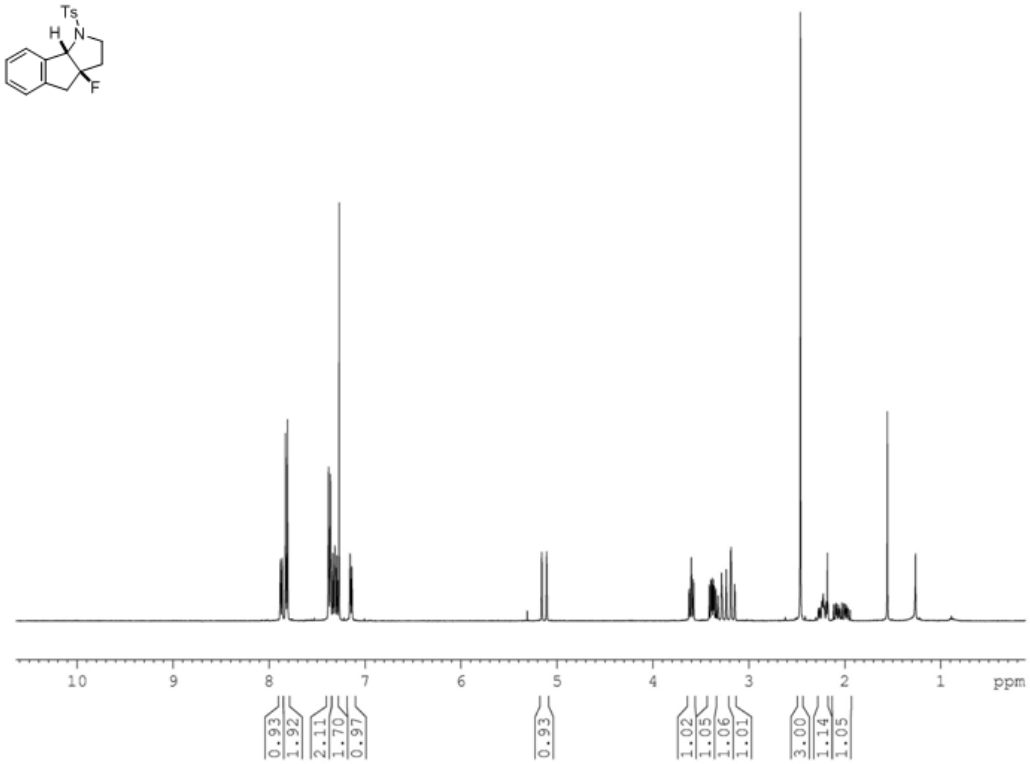

-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

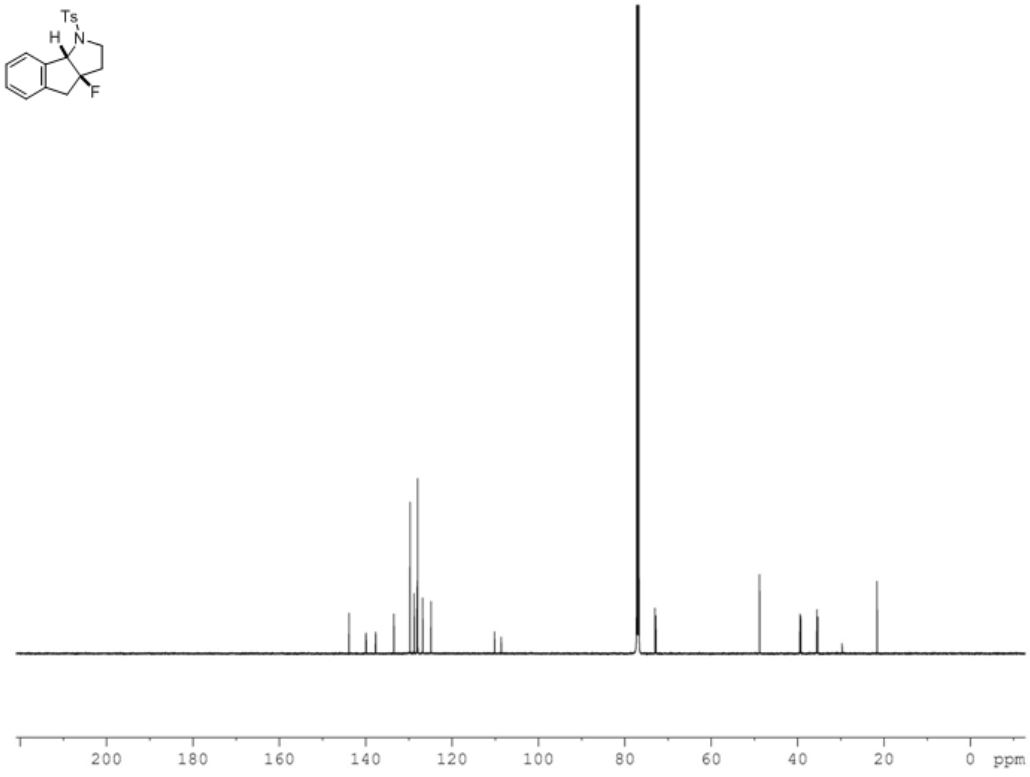

H
O
O
F

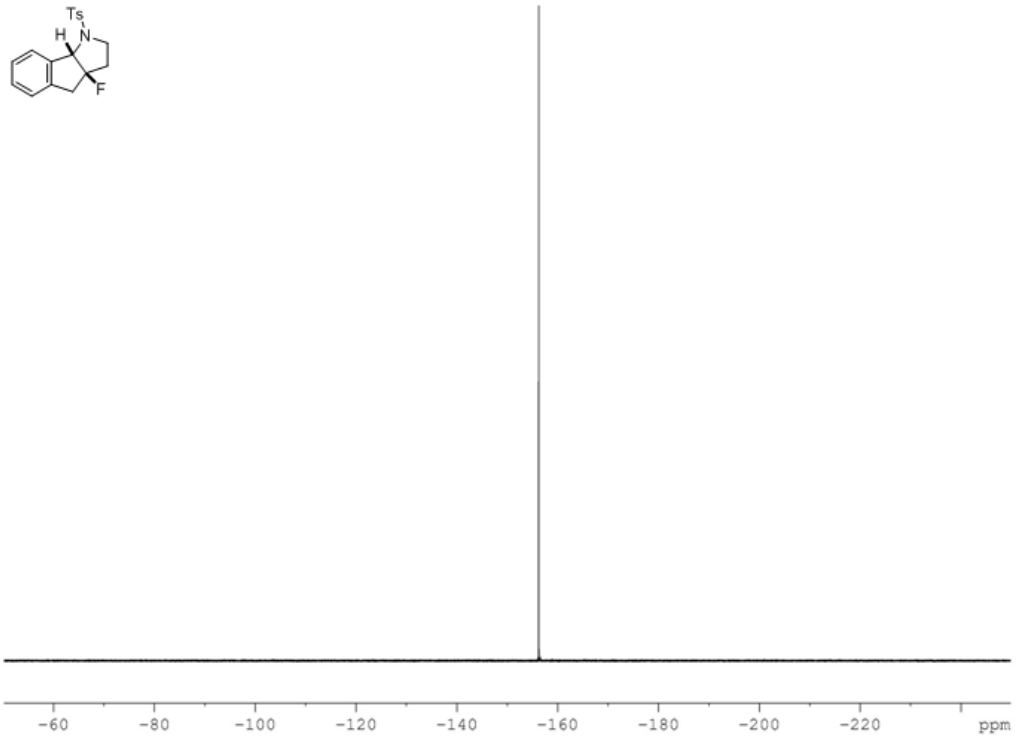

11
10
9
8
7
6
5
4
3
2
1
ppm
1.02
2.04
1.18
1.02
1.07
1.09
1.03
1.12
2.99
3.00

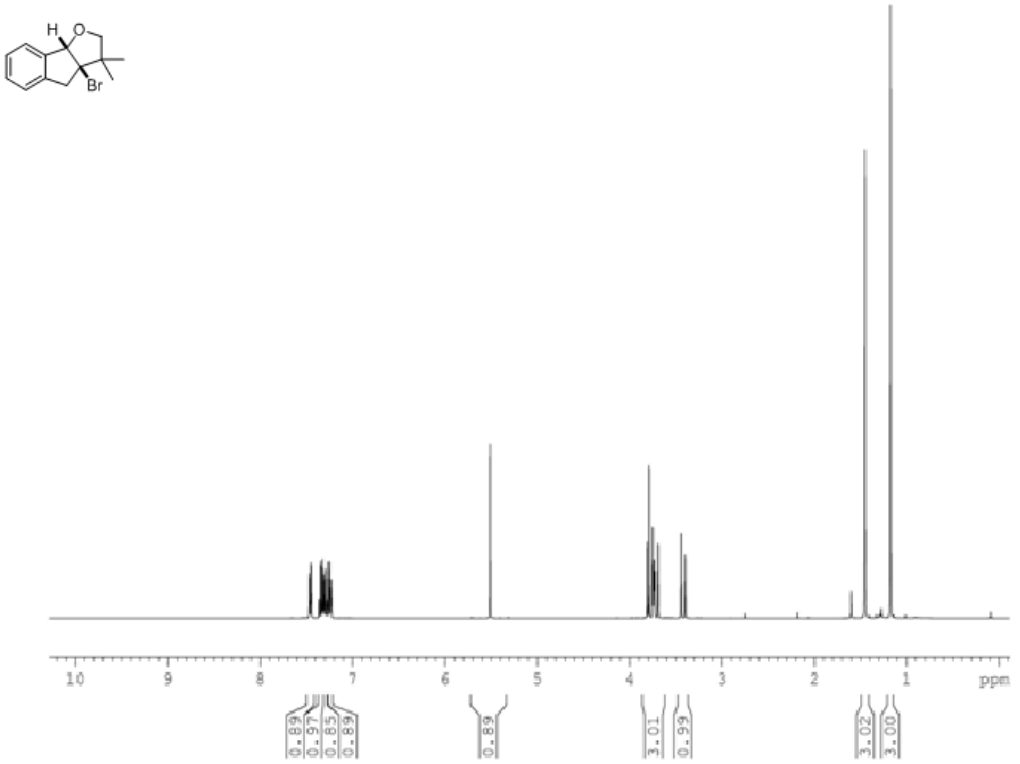

O
H
O
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

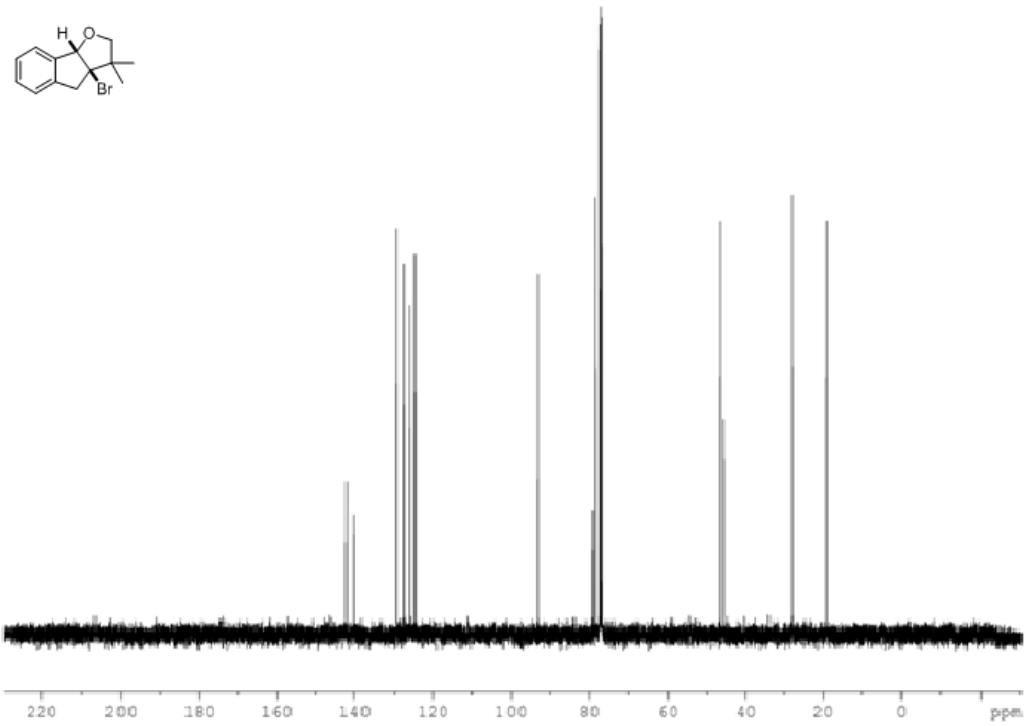

O
H
O
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

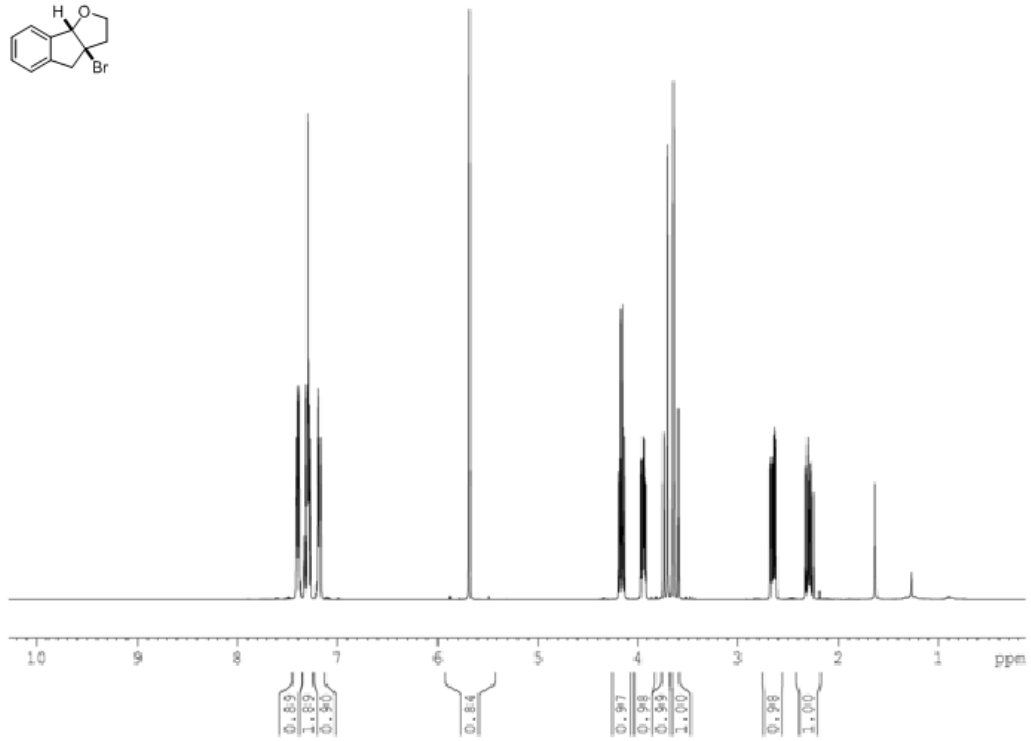

Ts
H
N
F
10
9
8
7
6
5
4
3
2
1
ppm
0.93
1.92
2.11
1.70
0.97
0.93
1.02
1.05
1.06
1.01
3.00
1.14
1.05

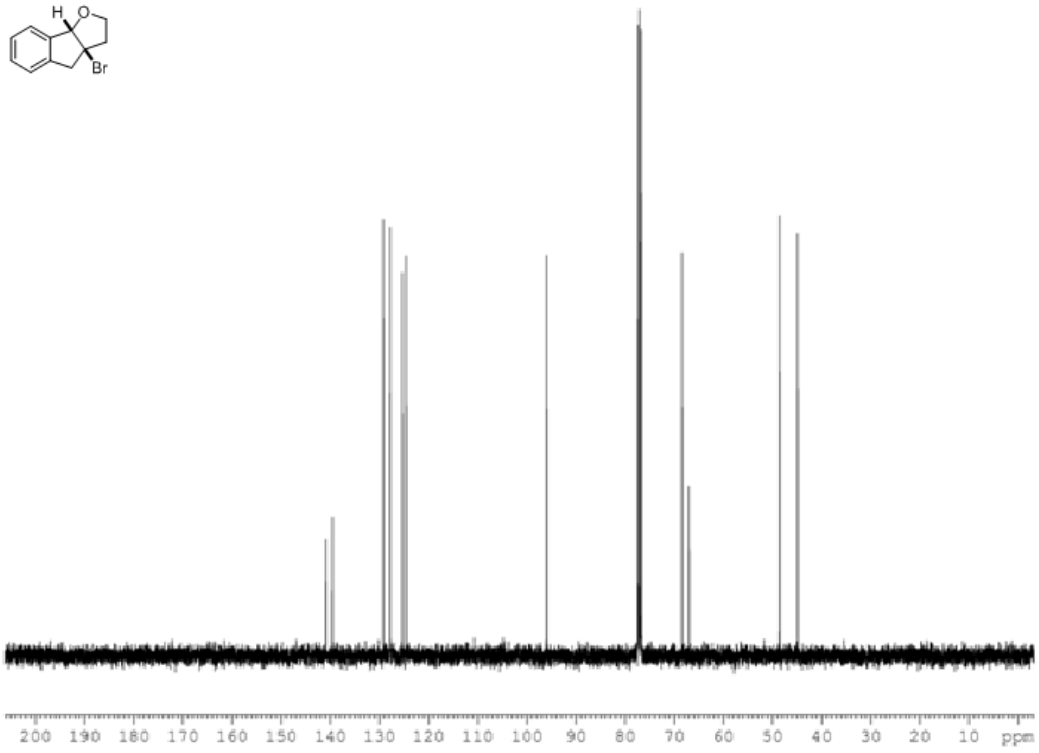

Ts
H
N
F
200
180
160
140
120
100
80
60
40
20
0
ppm

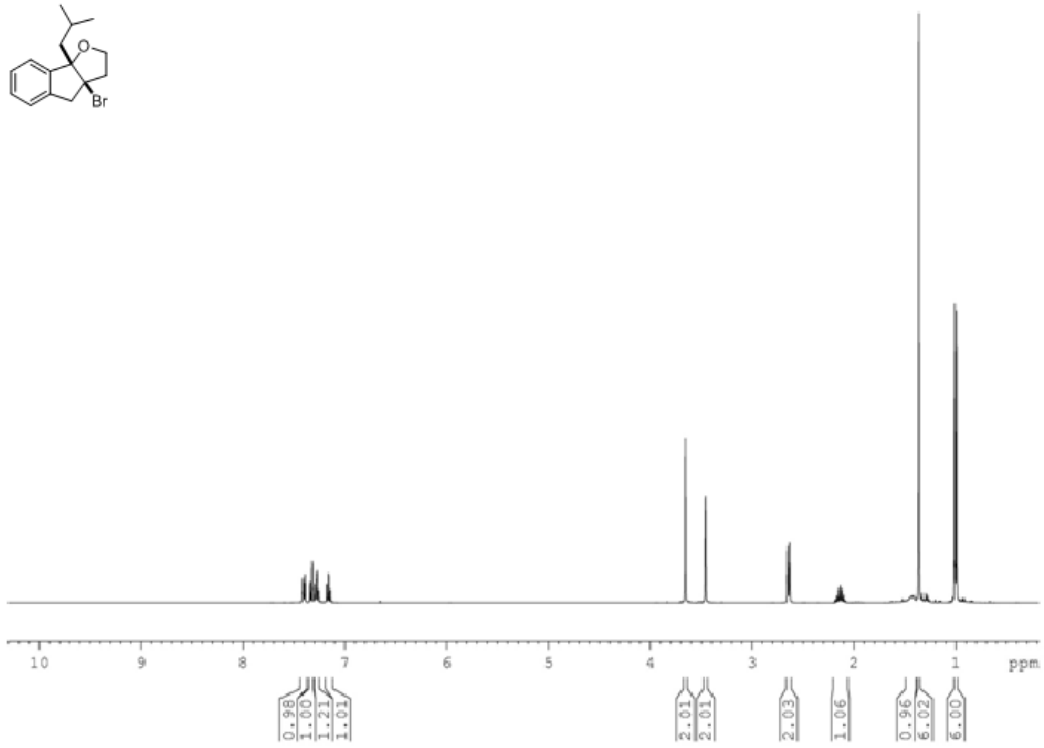

Ts
H
N
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

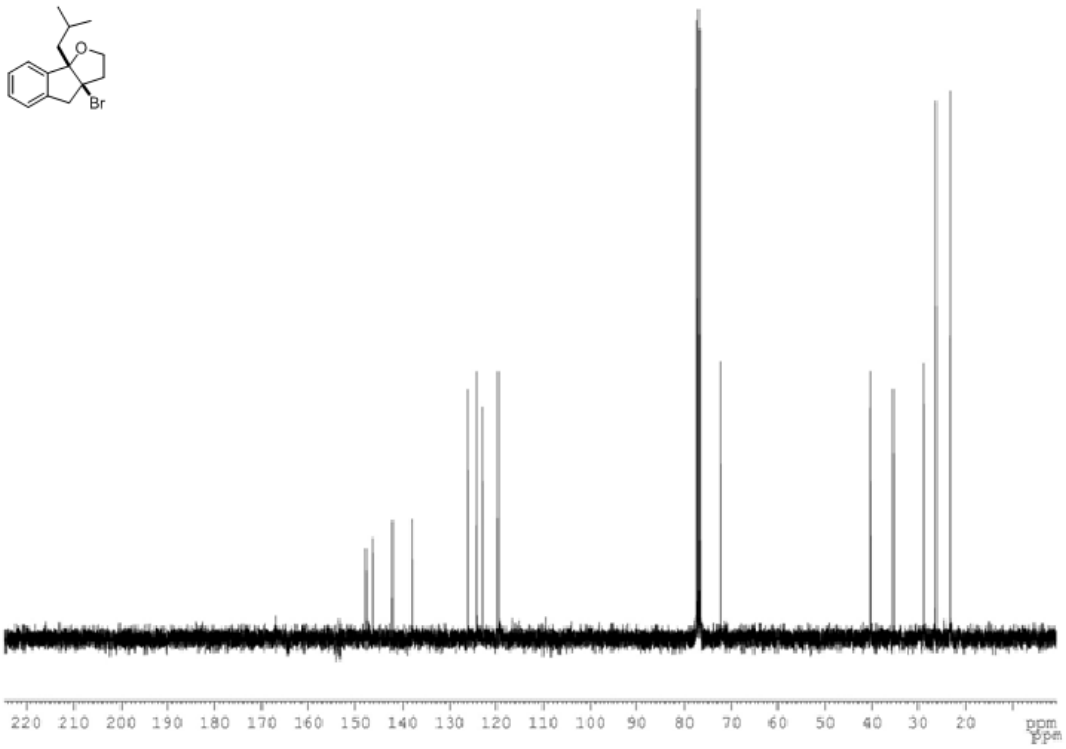

H
O
Br
10
9
8
7
6
5
4
3
2
1
ppm
0.89
0.97
0.85
0.89
0.89
3.01
0.99
3.02
3.00

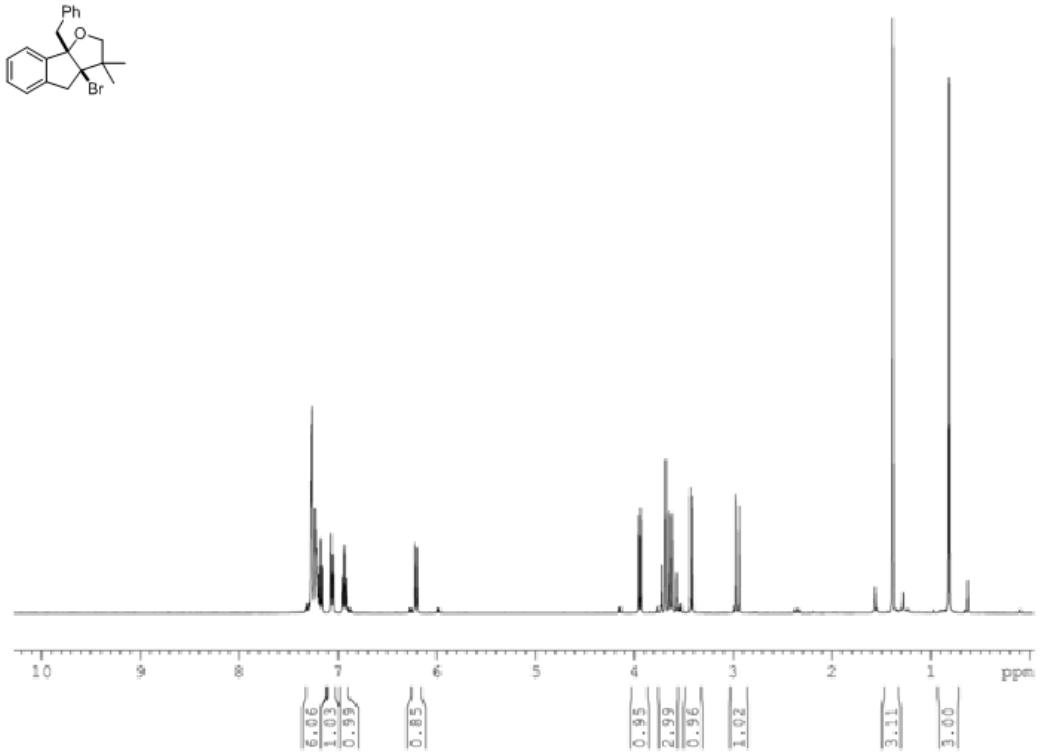

H
O
Br
220
200
180
160
140
120
100
80
60
40
20
0
ppm

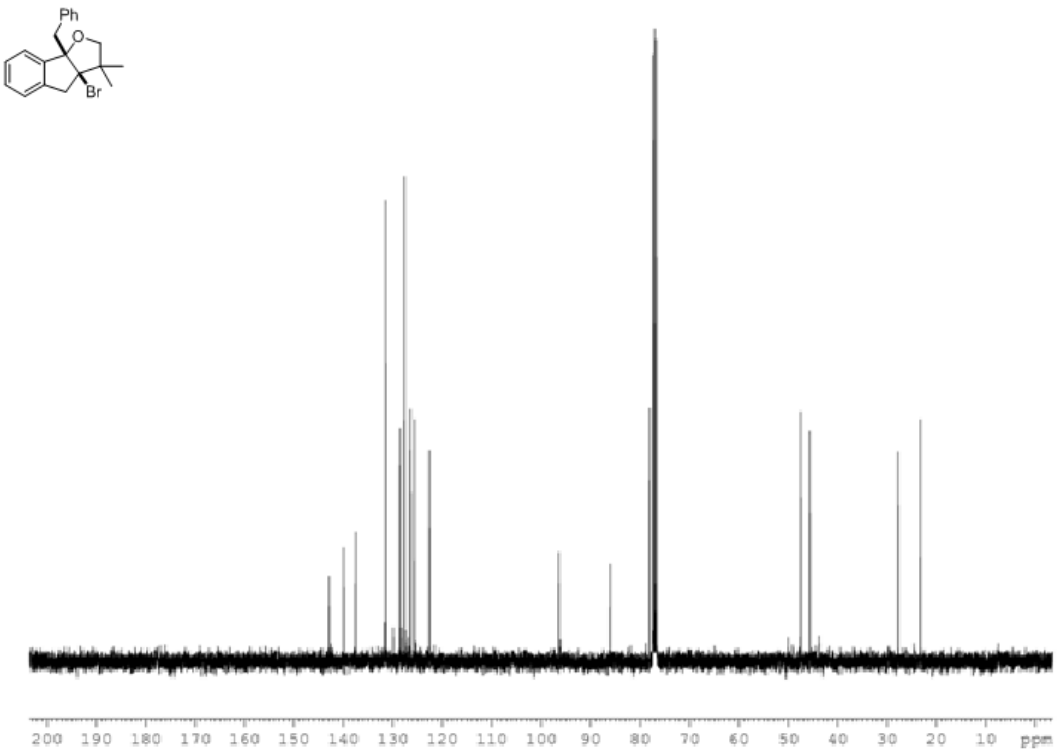

H
O
Br
10
9
8
7
6
5
4
3
2
1
ppm
0.89
1.89
0.90
0.84
0.97
0.98
0.99
1.00
0.98
1.00

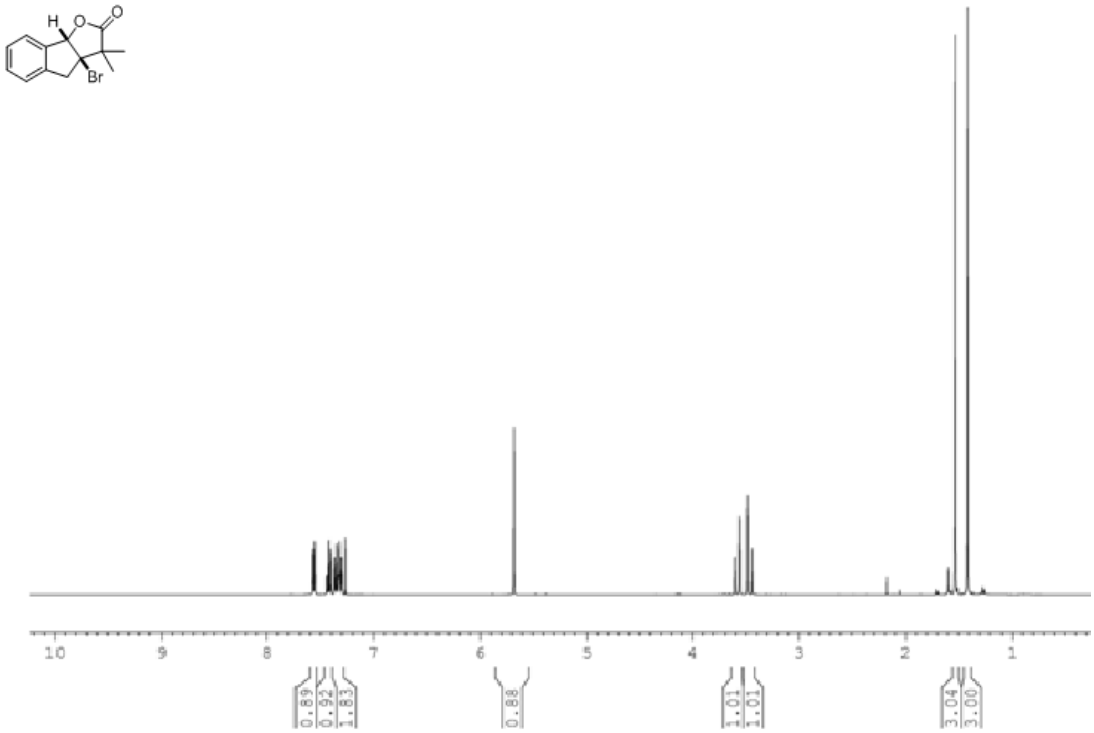

H
O
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

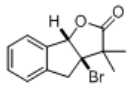

O
Br
10 9 8 7 6 5 4 3 2 1 ppm
0.98
1.00
1.21
1.04
2.01
2.01
2.03
1.06
0.96
6.02
6.00

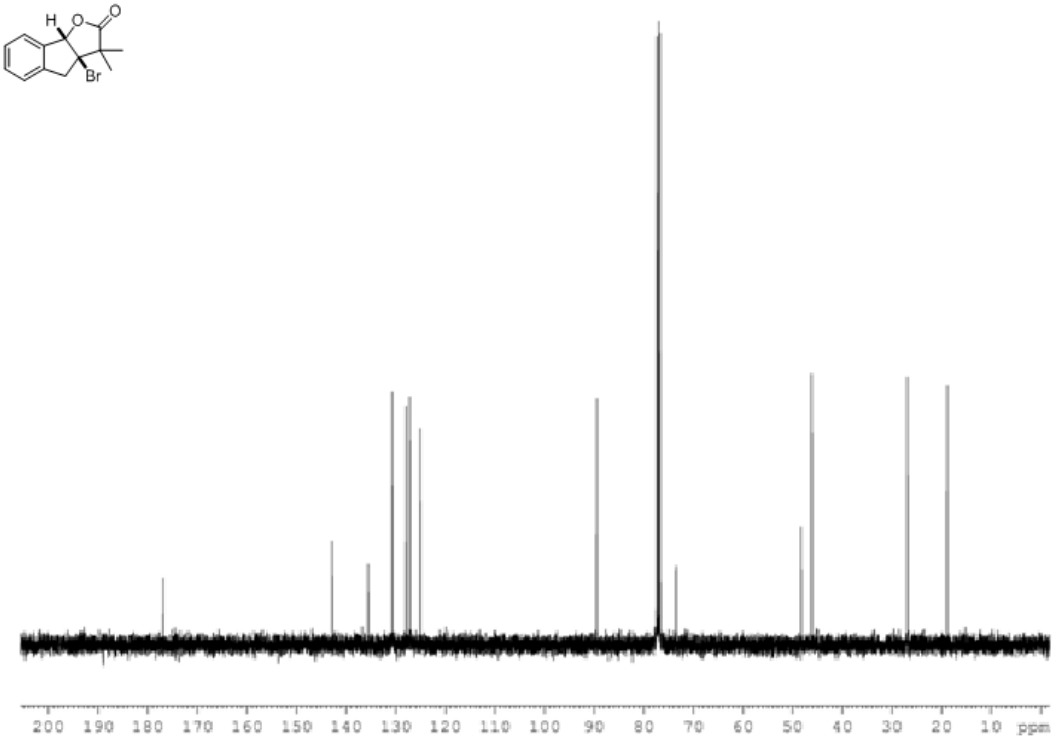

O
Br
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

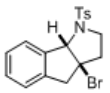

Ph
O
Br
10 9 8 7 6 5 4 3 2 1
ppm
6.06
1.03
0.99
0.85
0.95
2.99
0.96
1.02
3.11
3.00

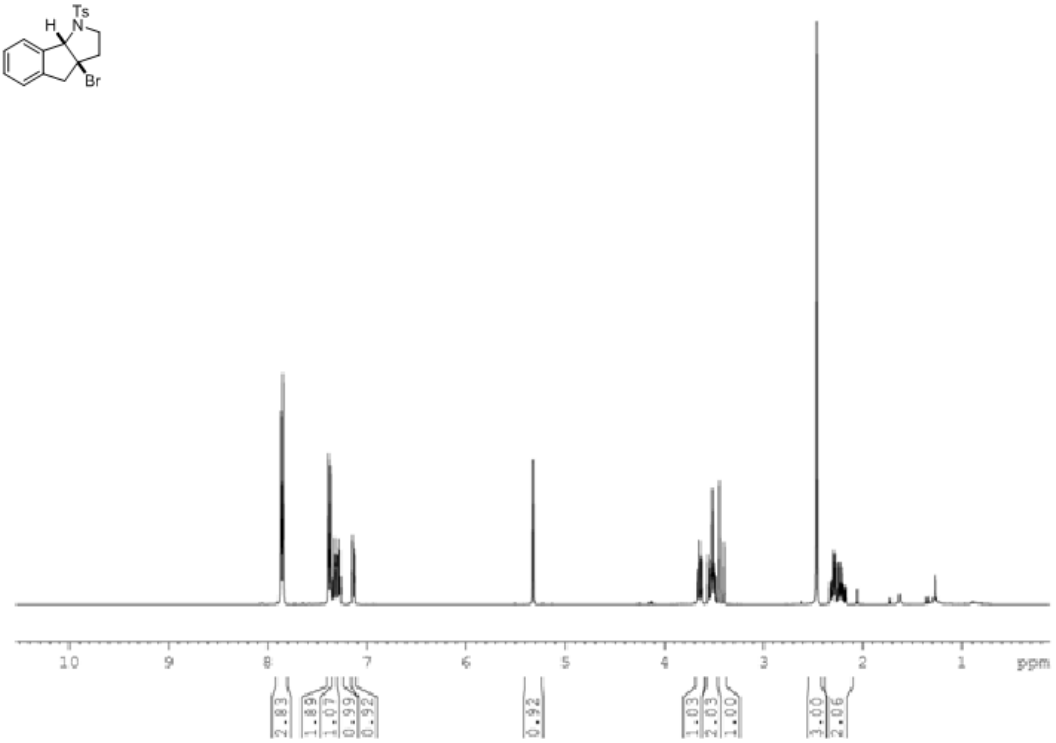

Ph
O
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

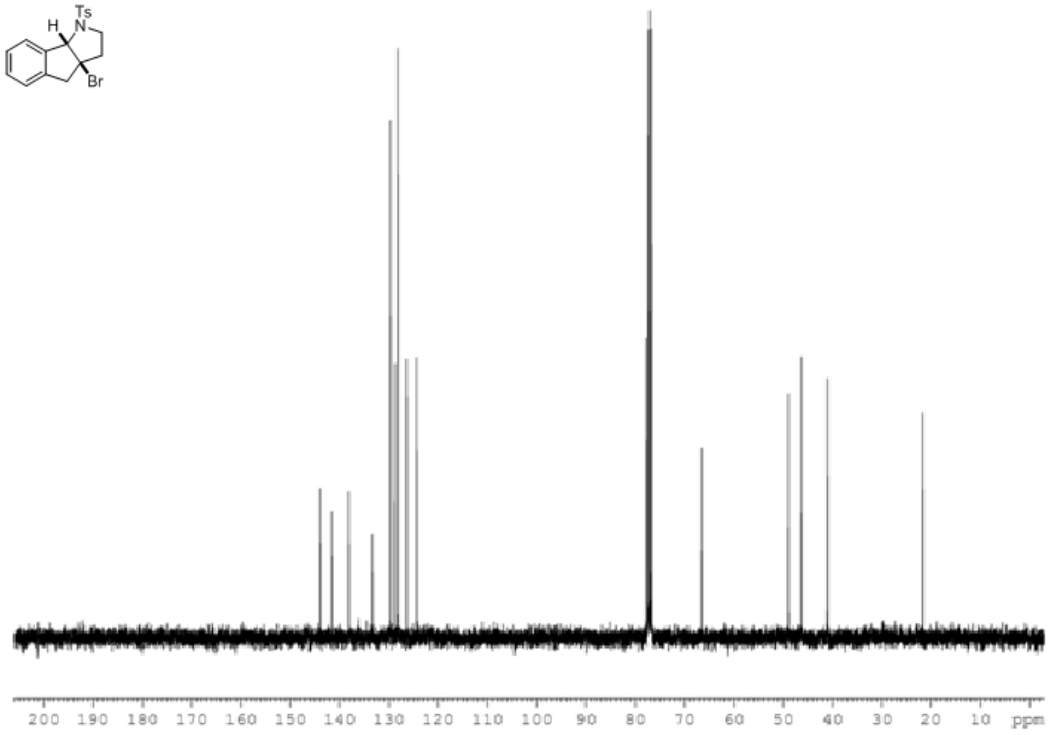

H
O
O
Br
10 9 8 7 6 5 4 3 2 1
0.89
0.92
1.83
0.88
1.01
1.01
3.04
3.00

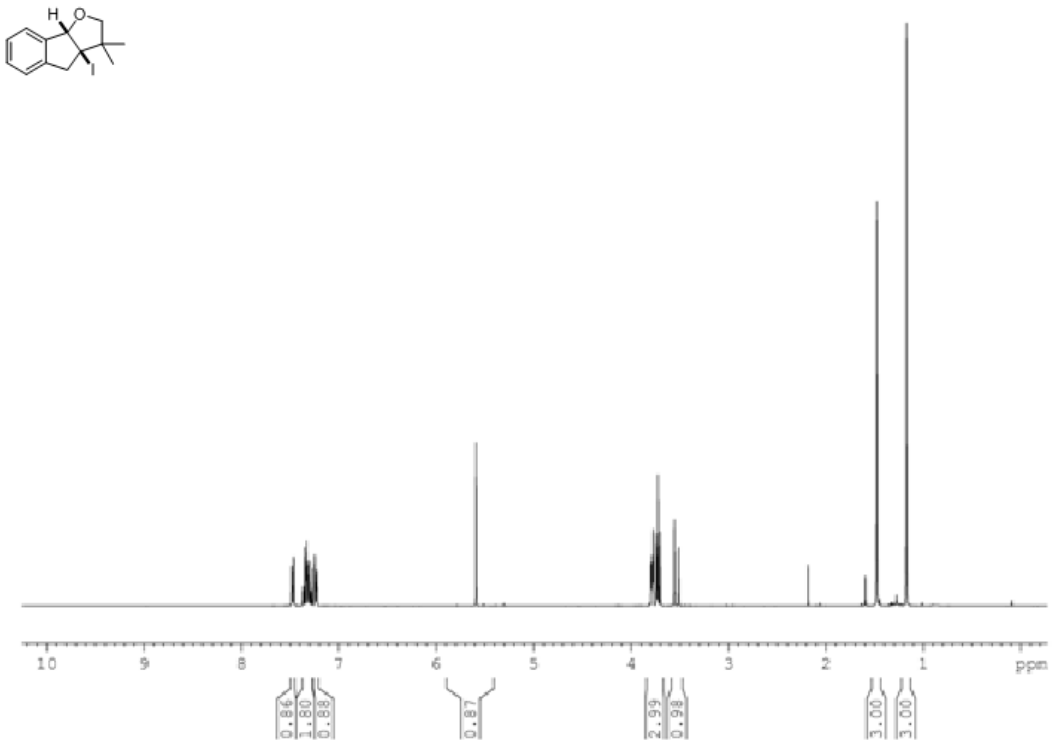

H
O
O
Br

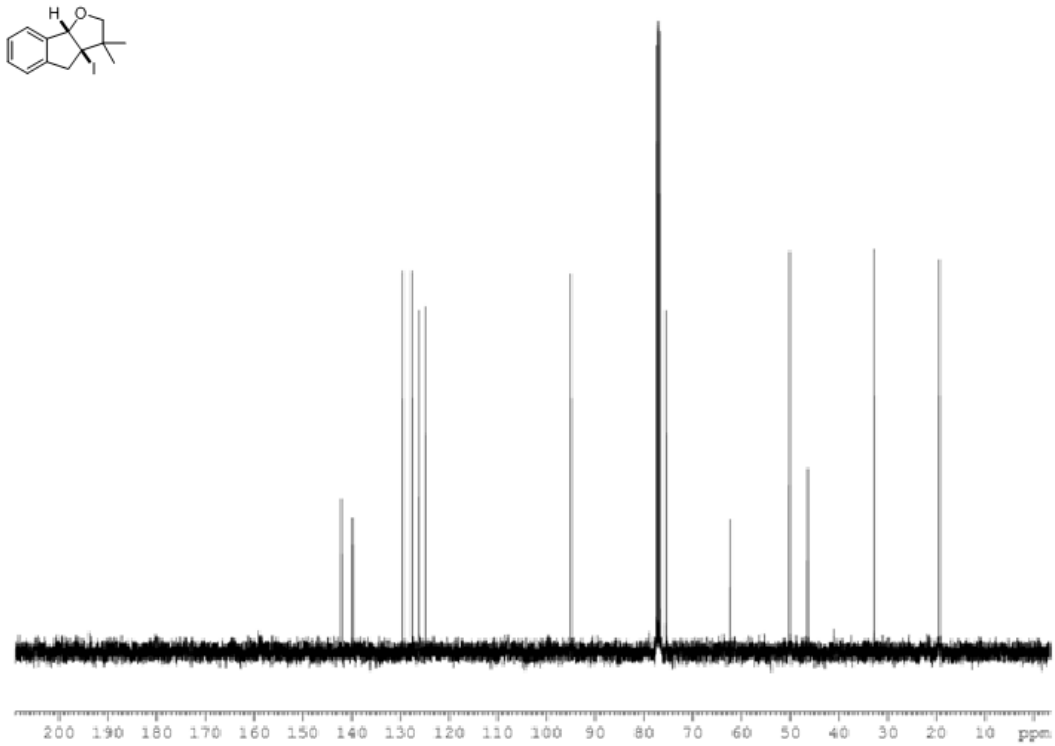

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

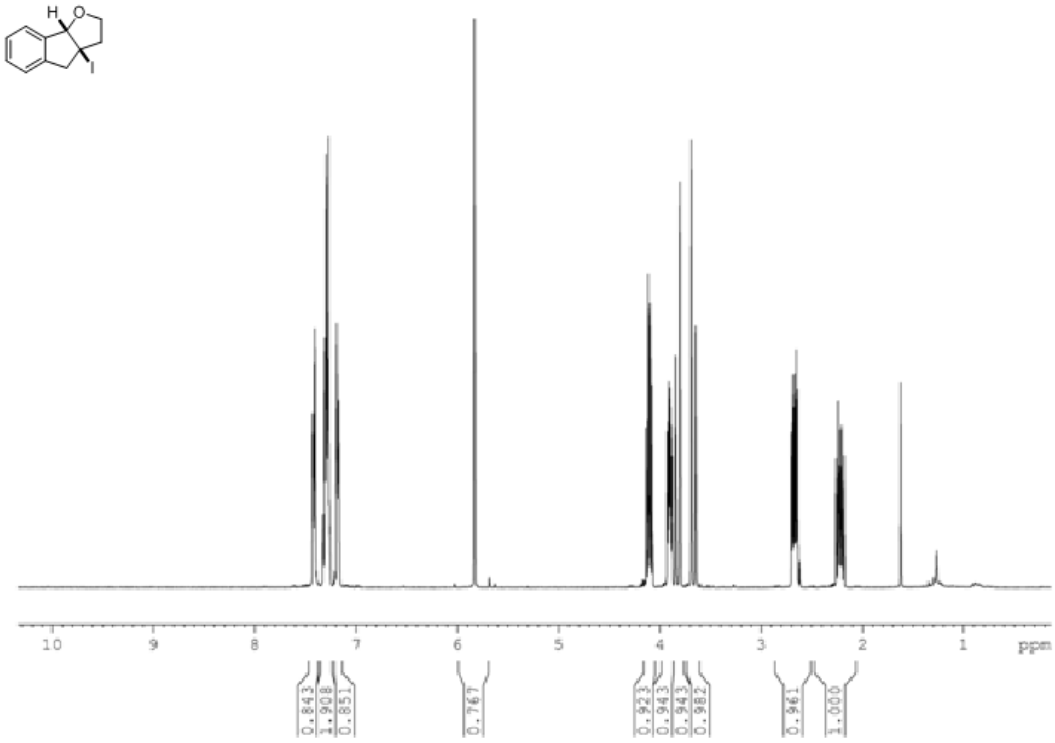

Ts
H
N
Br

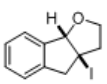

10 9 8 7 6 5 4 3 2 1 ppm
2.83
1.89
1.07
0.99
0.92
0.92
1.03
2.03
1.00
3.00
2.06

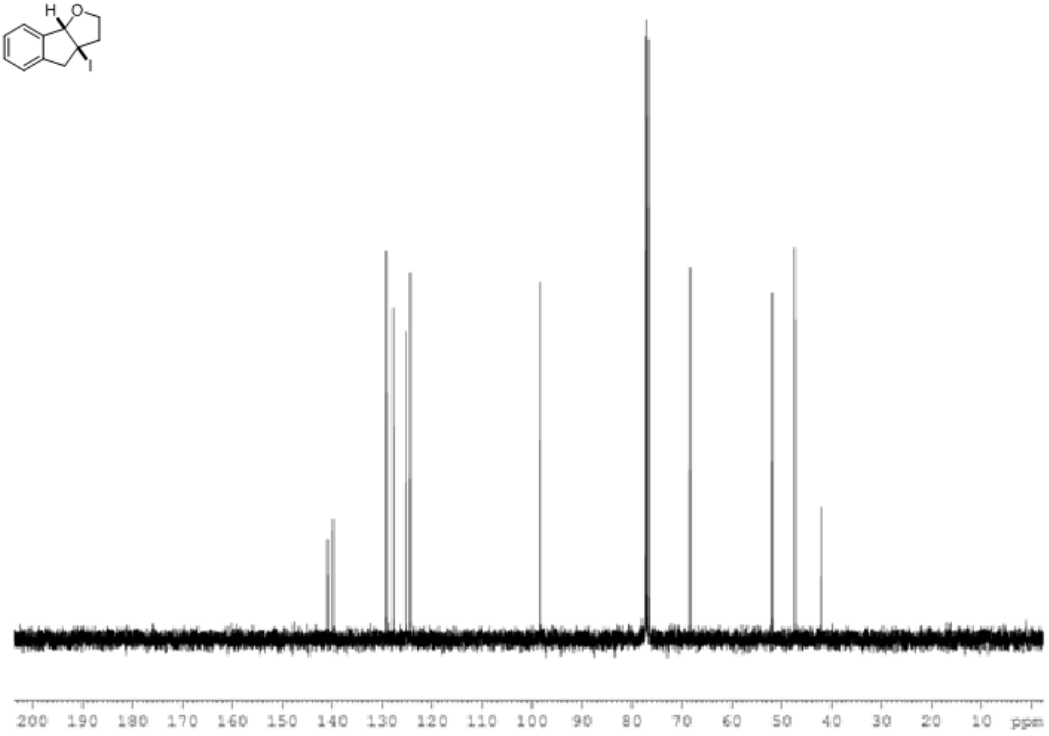

Ts
H
N
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

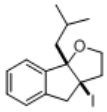

H
O
I
10 9 8 7 6 5 4 3 2 1 ppm
0.86
1.80
0.88
0.87
2.99
0.98
3.00
3.00

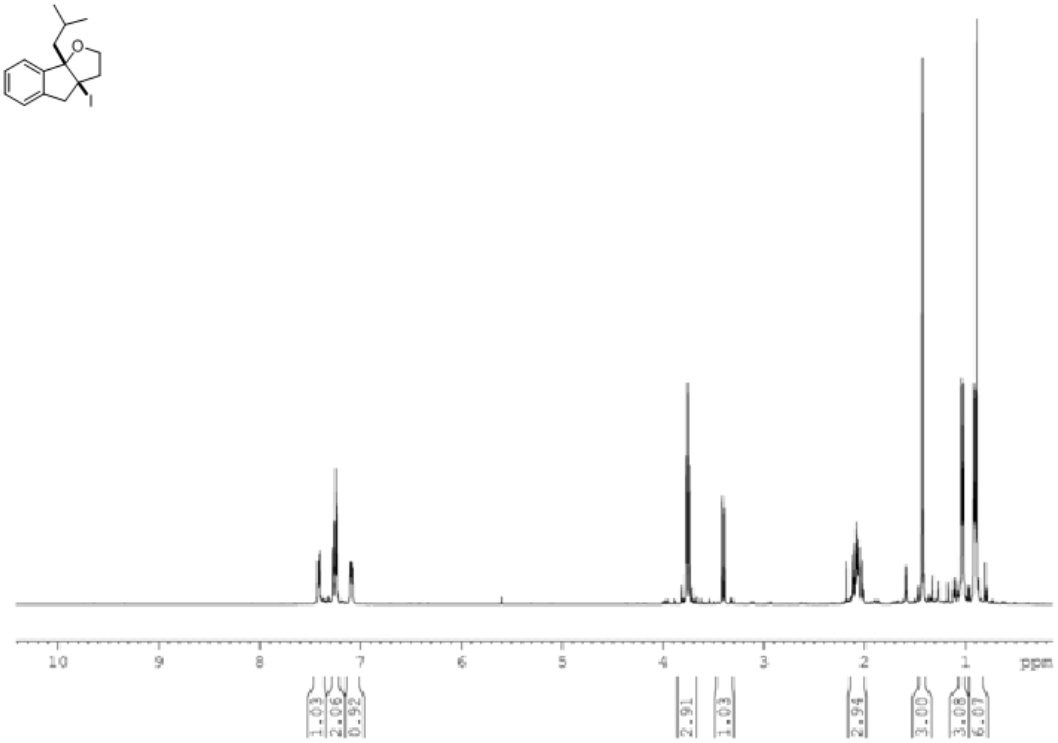

H
O
I
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

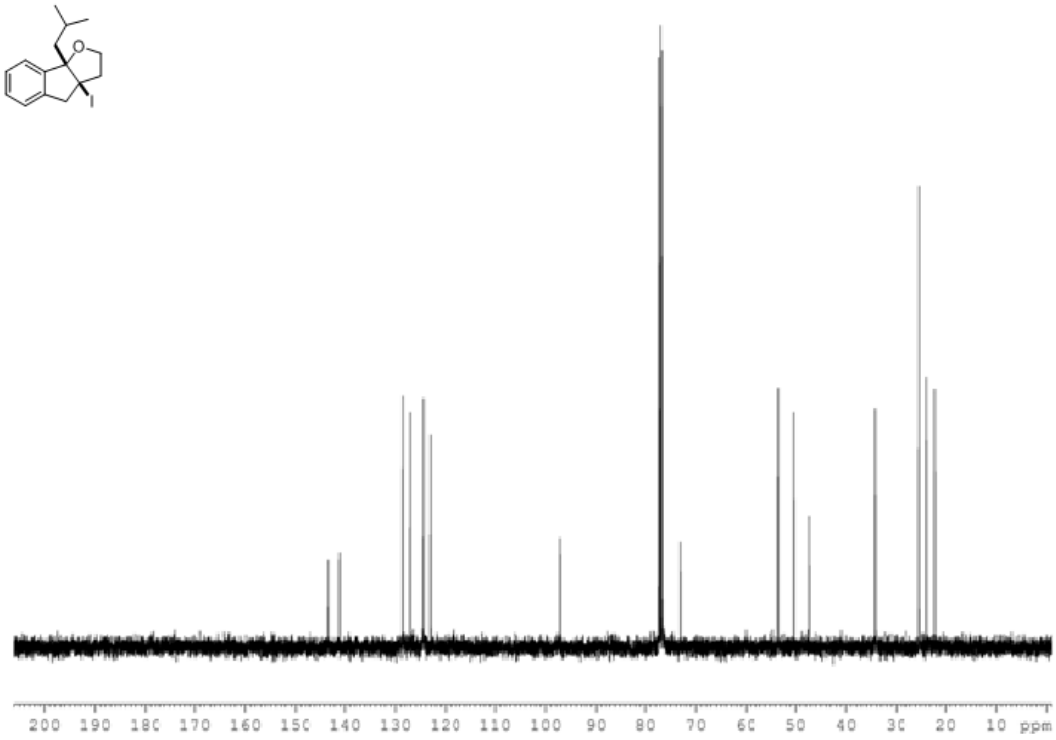

H
O
I
10 9 8 7 6 5 4 3 2 1 ppm
0.843
1.908
0.851
0.767
0.923
0.943
0.945
0.982
0.961
1.000

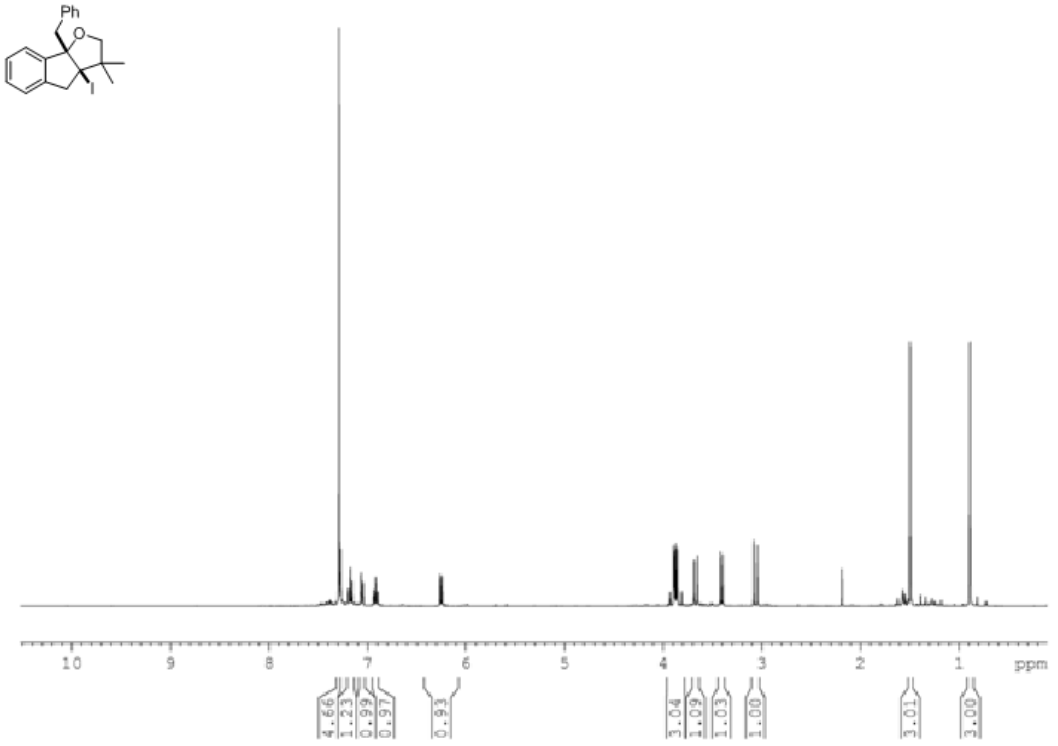

H
O
I

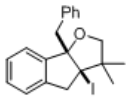

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

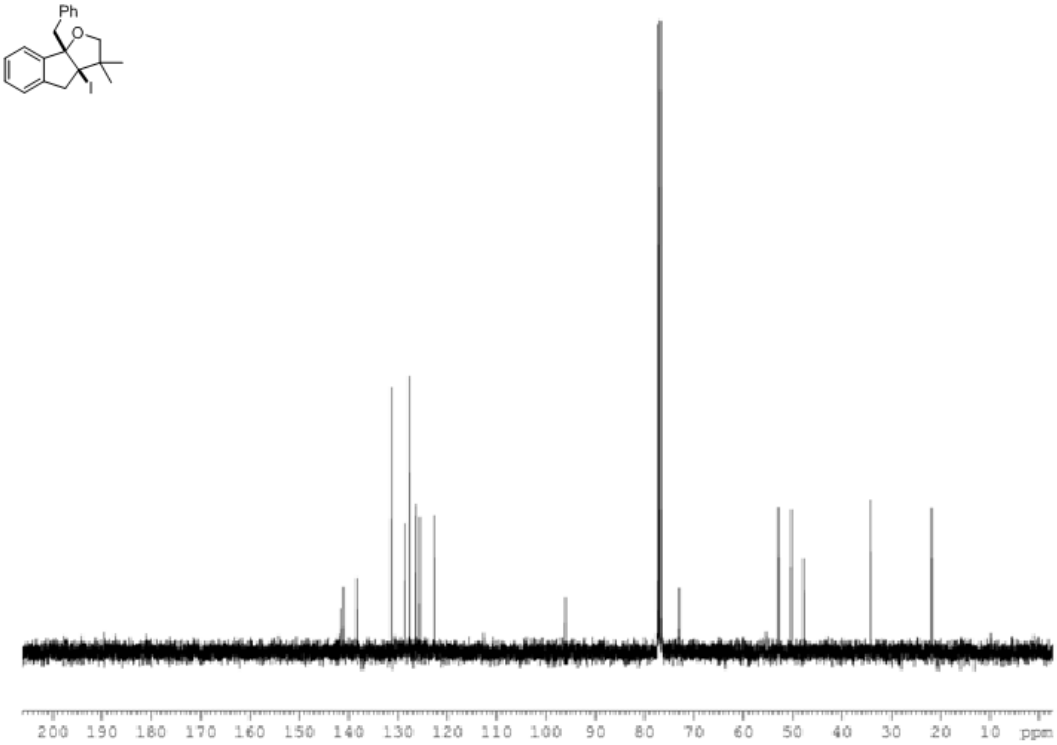

O
I

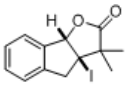

10 9 8 7 6 5 4 3 2 1 ppm
1.03
2.06
0.92
2.91
1.03
2.94
3.00
3.08
6.07

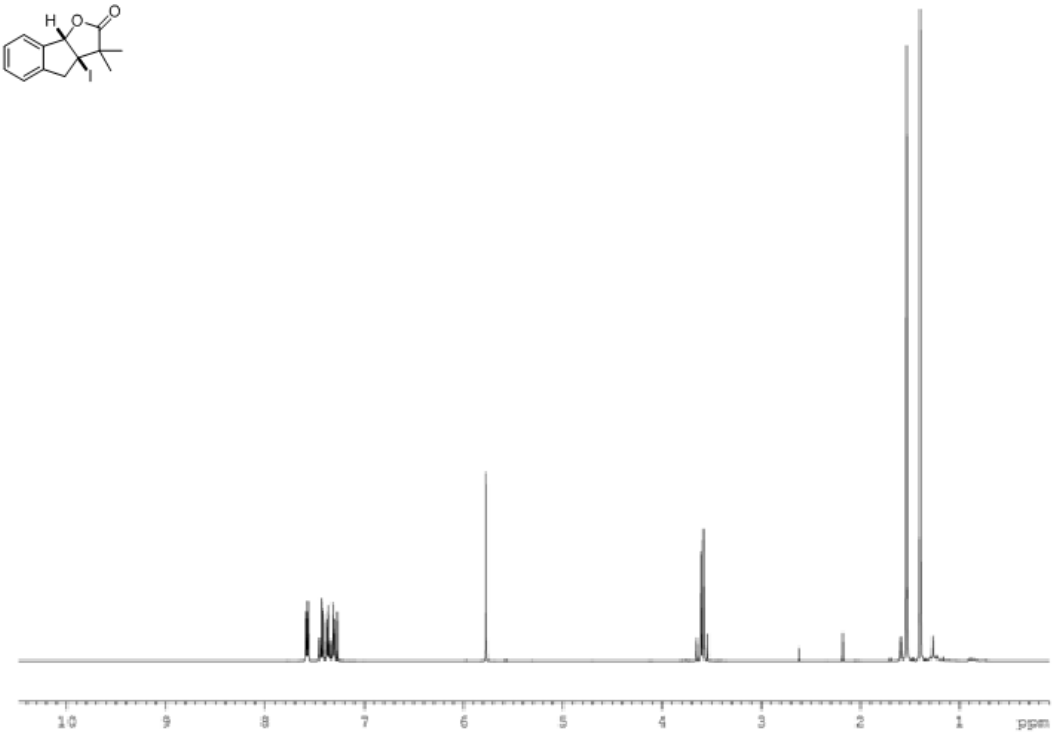

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

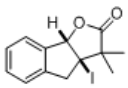

Ph
10 9 8 7 6 5 4 3 2 1 ppm
4.66
1.23
0.99
0.97
0.93
3.04
1.09
1.03
1.00
3.01
3.00

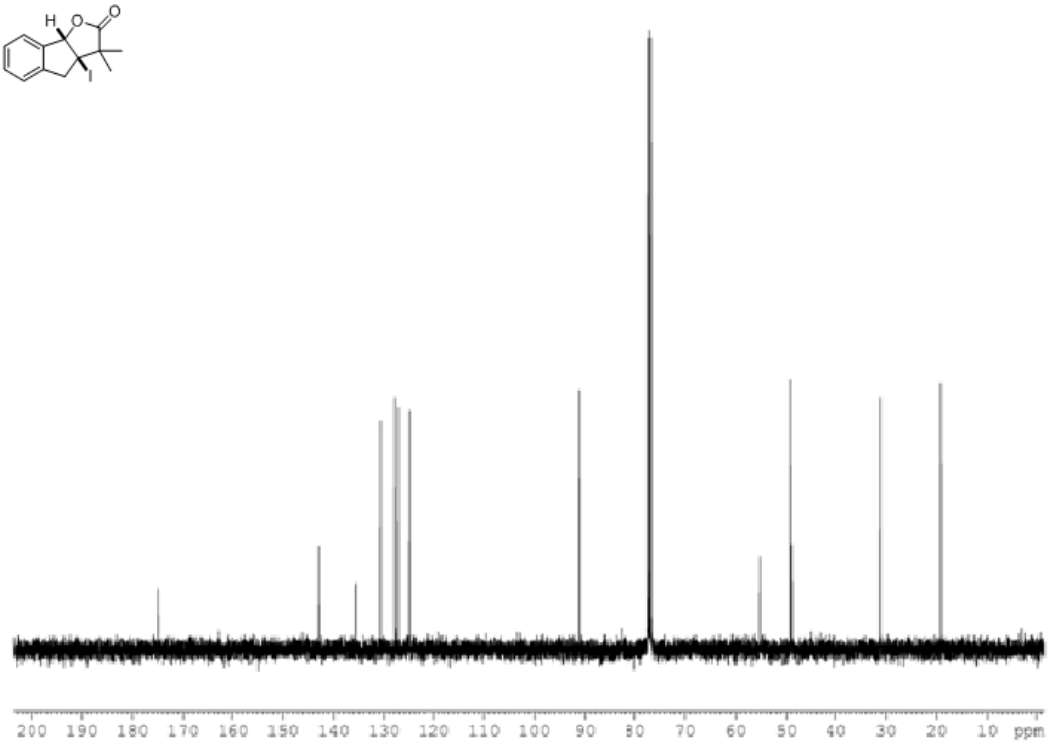

Ph
O
I

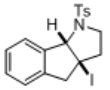

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

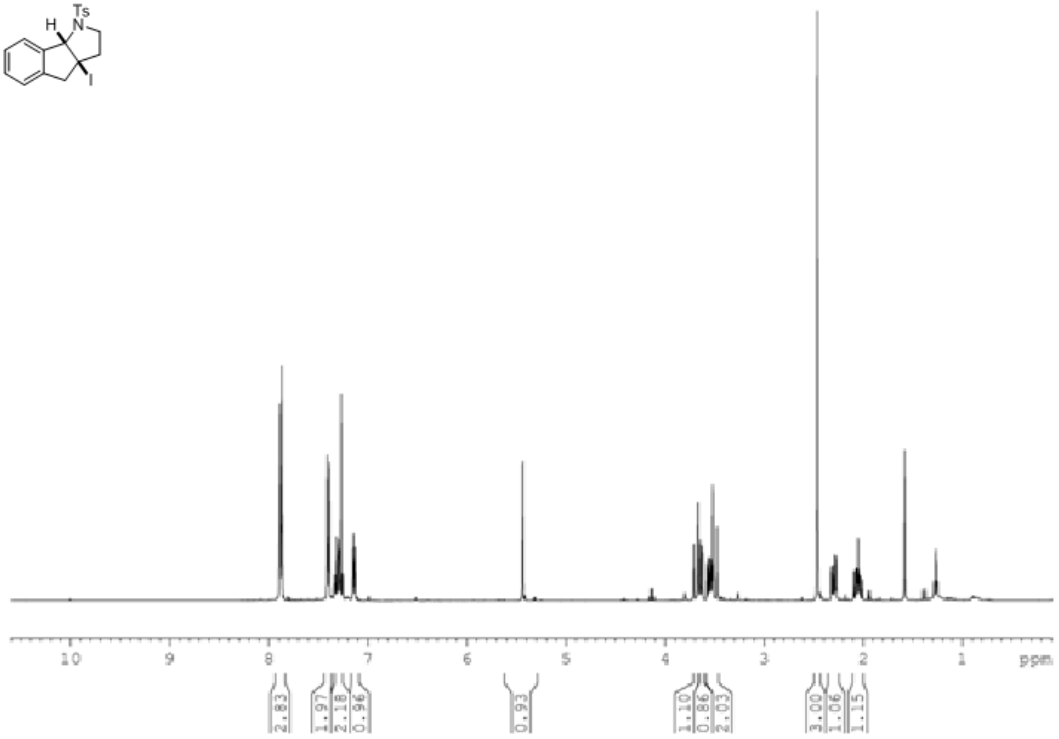

H
O
O
I

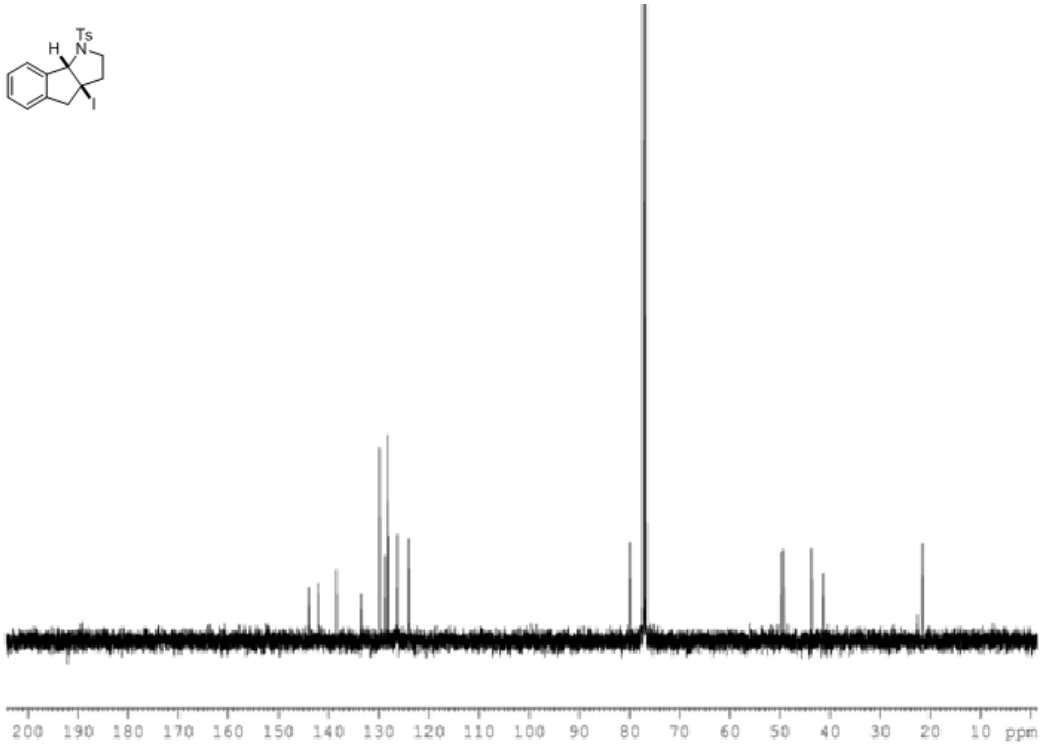

10 9 8 7 6 5 4 3 2 1 ppm

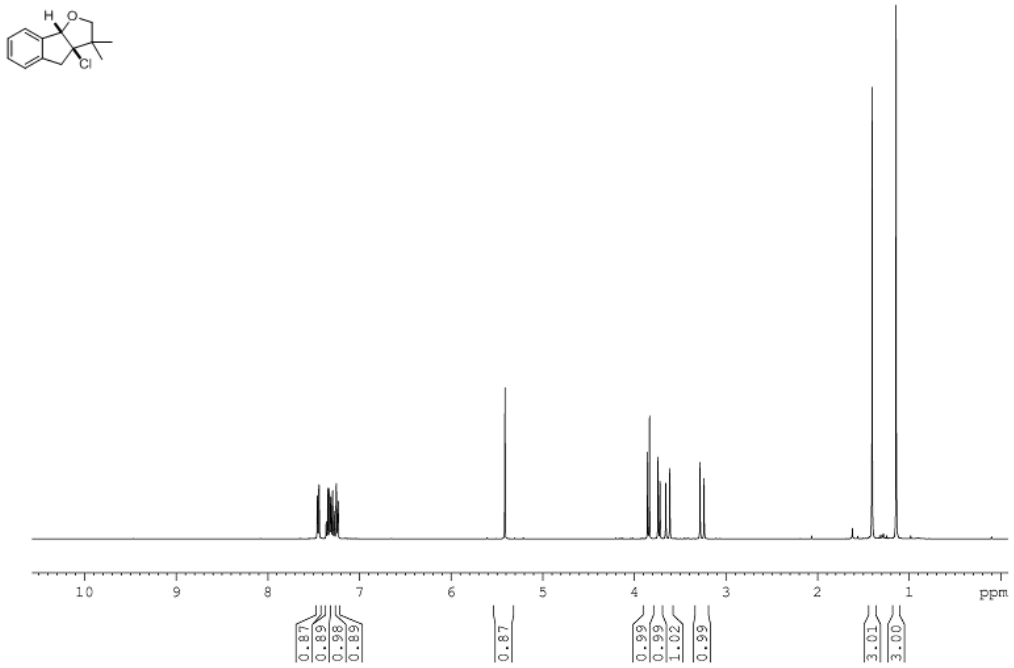

H
O
O
I

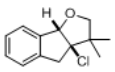

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

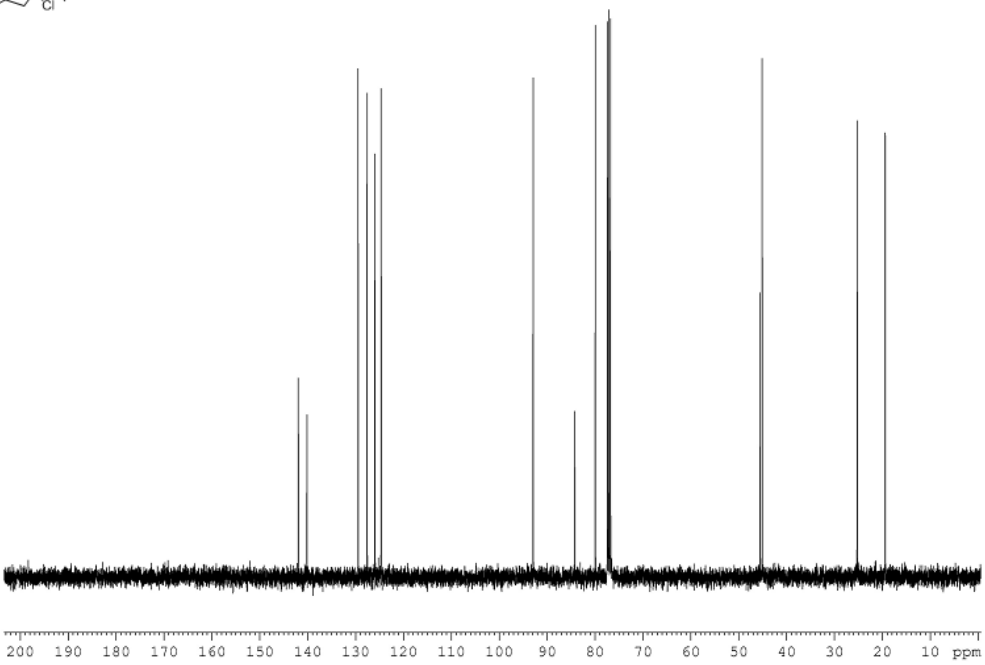

Ts
H
N
I


10 9 8 7 6 5 4 3 2 1 ppm
2.83
1.97
1.68
2.16
0.98
0.93
1.10
0.86
2.03
3.00
1.06
1.15

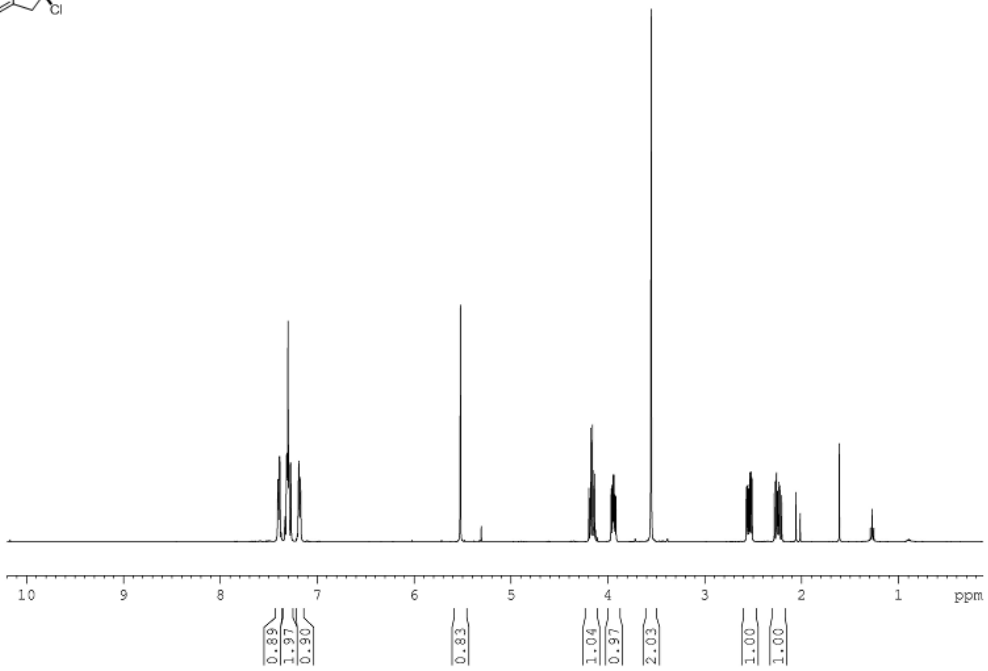

Ts
N
H
I
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

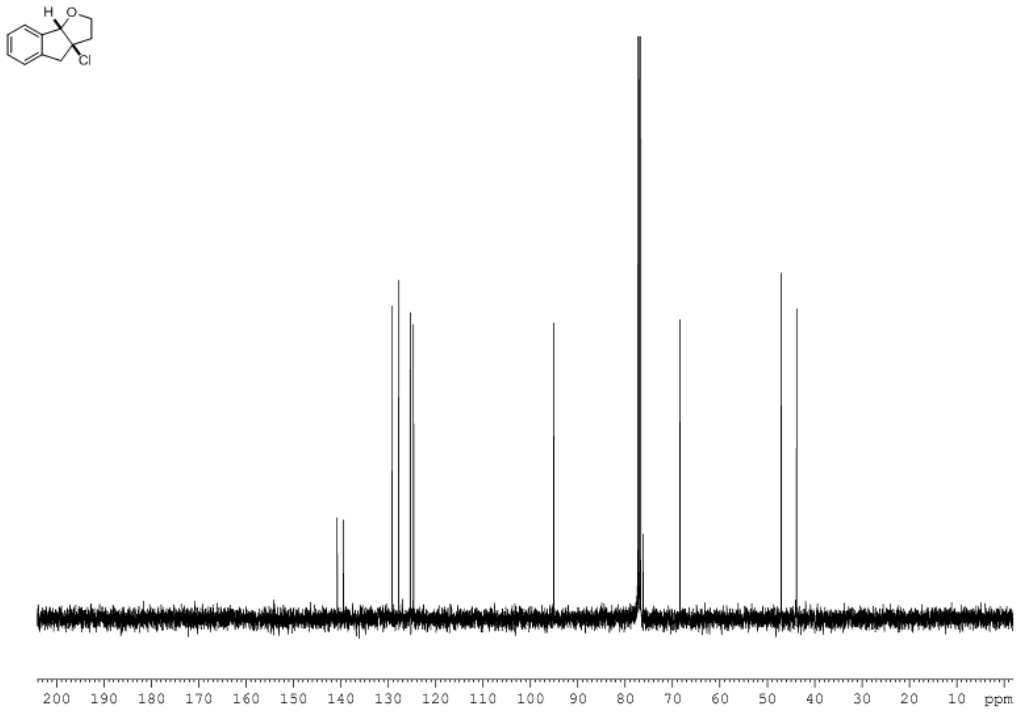

H
O
Cl
10 9 8 7 6 5 4 3 2 1 ppm
0.87
0.89
0.98
0.89
0.87
0.99
0.99
1.02
0.99
3.01
3.00

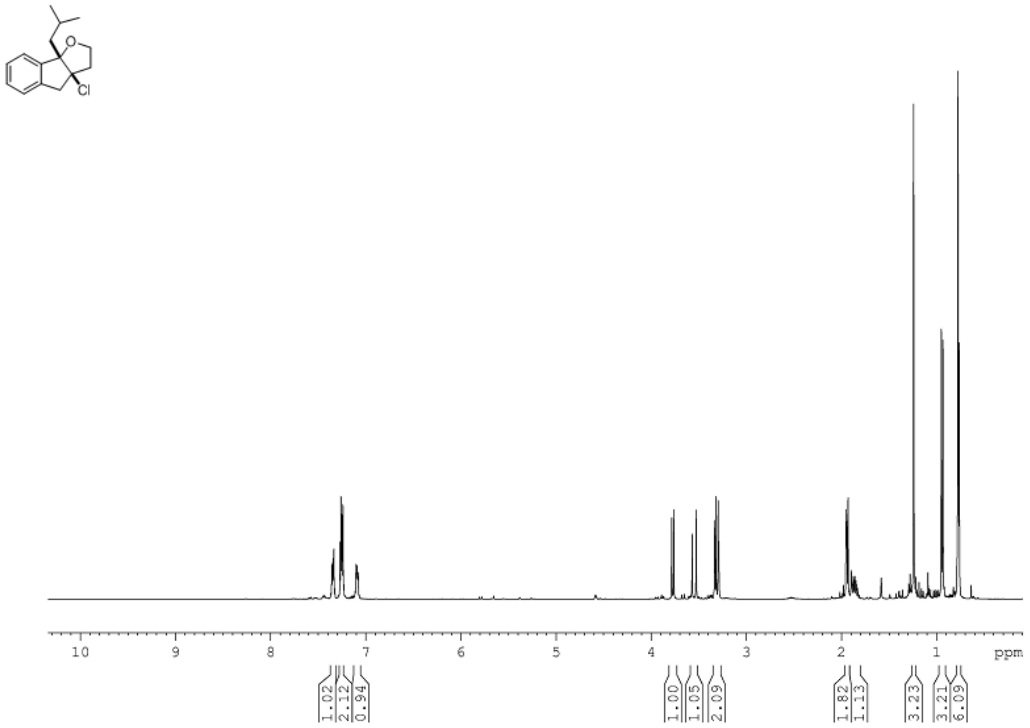

H
O
Cl

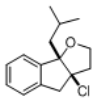

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

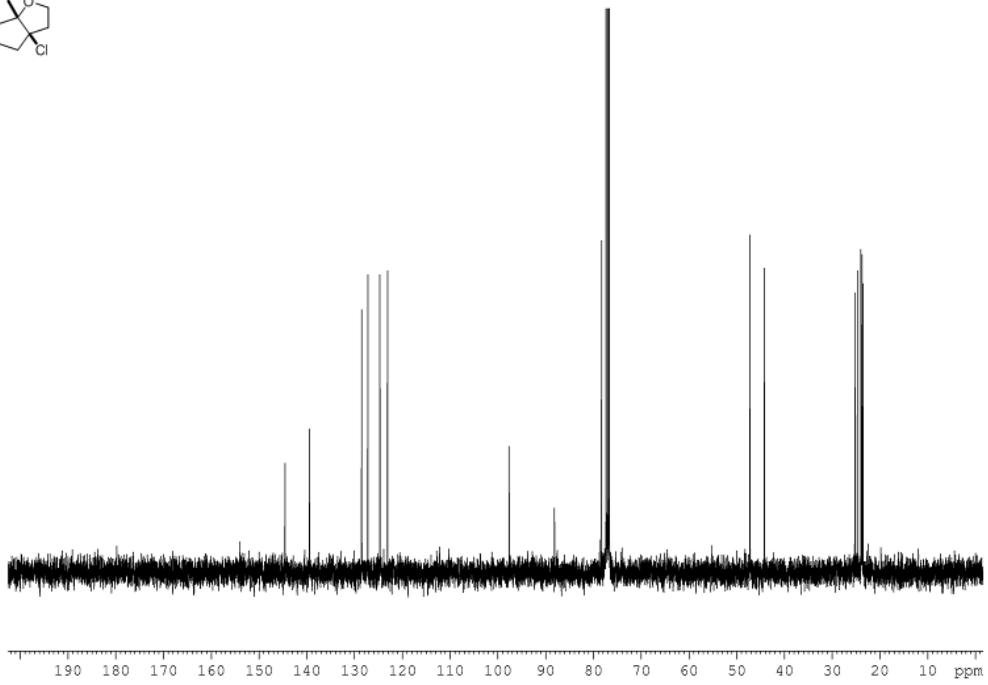
H
O
Cl

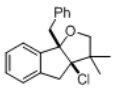

10 9 8 7 6 5 4 3 2 1 ppm
0.89
1.97
0.90
0.83
1.04
0.97
2.03
1.00
1.00

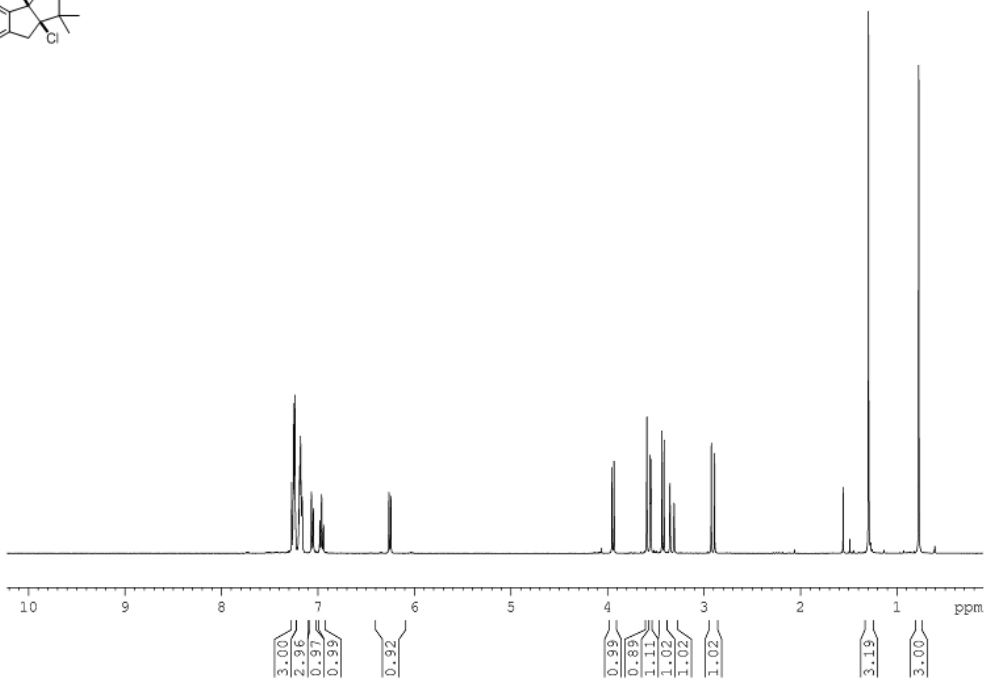

H
O
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

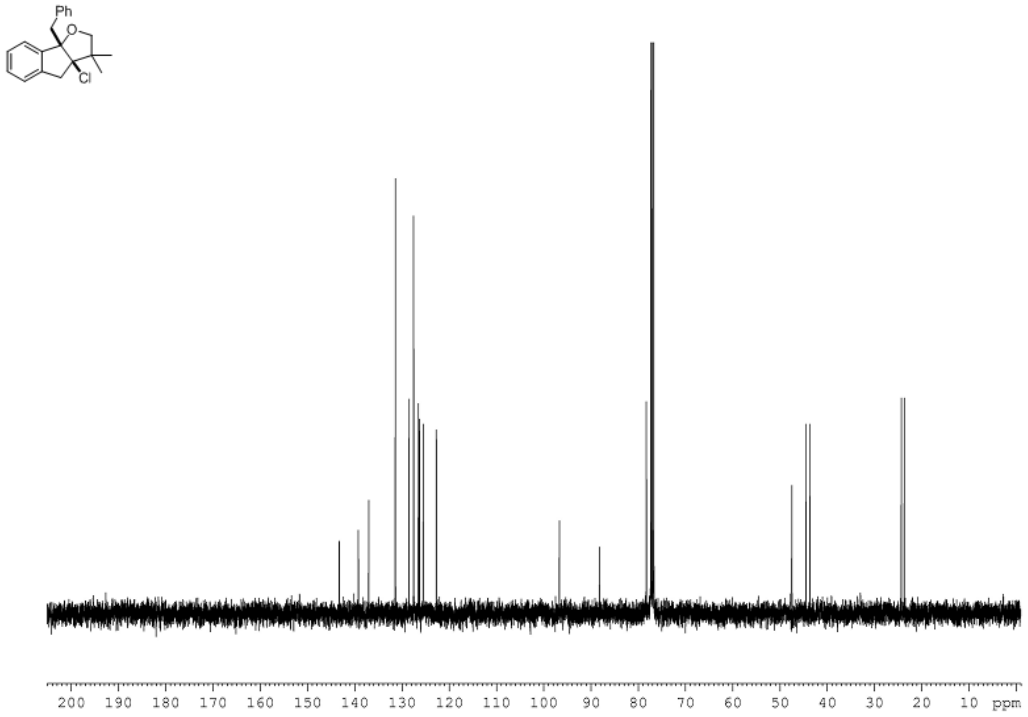

O
Cl
10 9 8 7 6 5 4 3 2 1 ppm
1.02
2.12
0.94
1.00
1.05
2.09
1.82
1.13
3.23
3.21
6.09

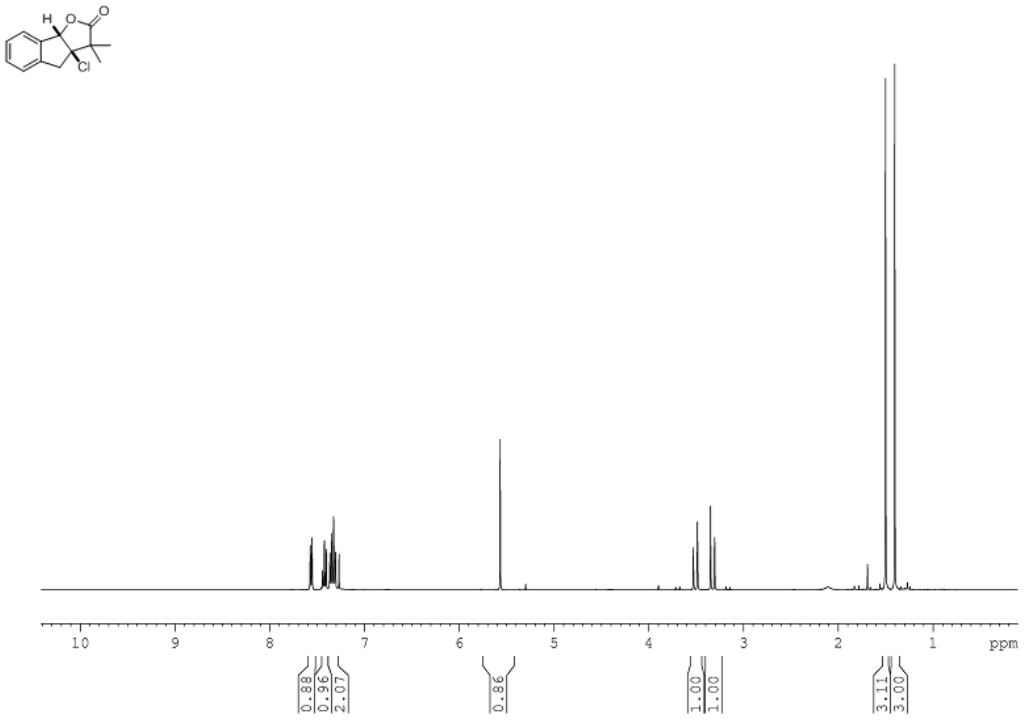

O
Cl

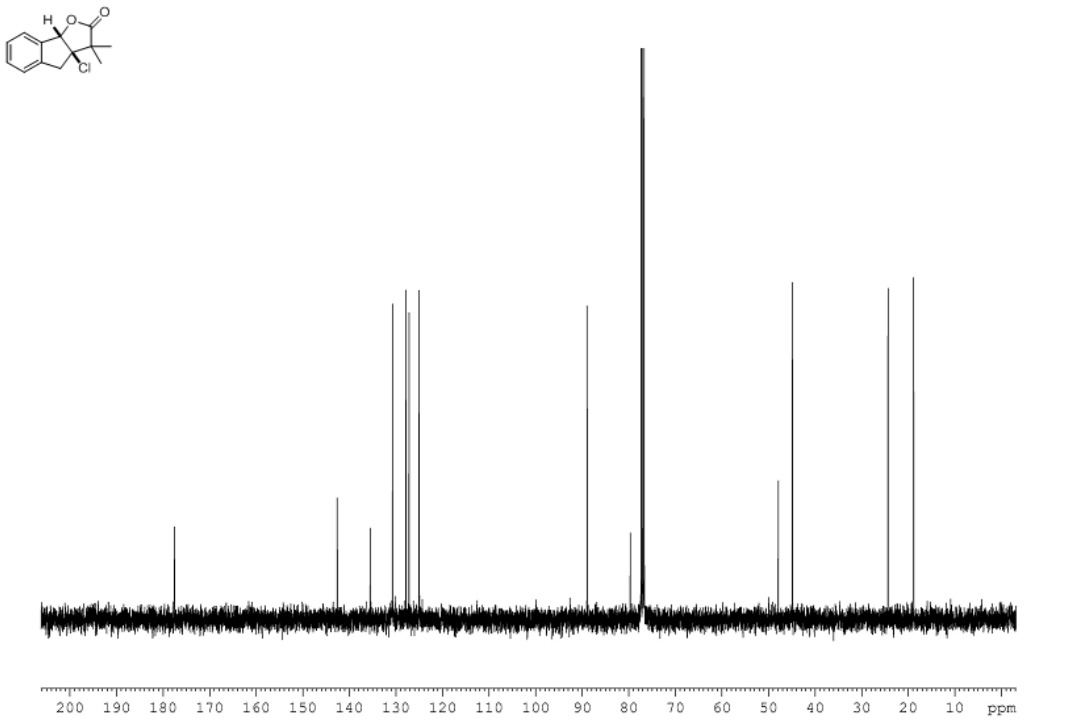

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

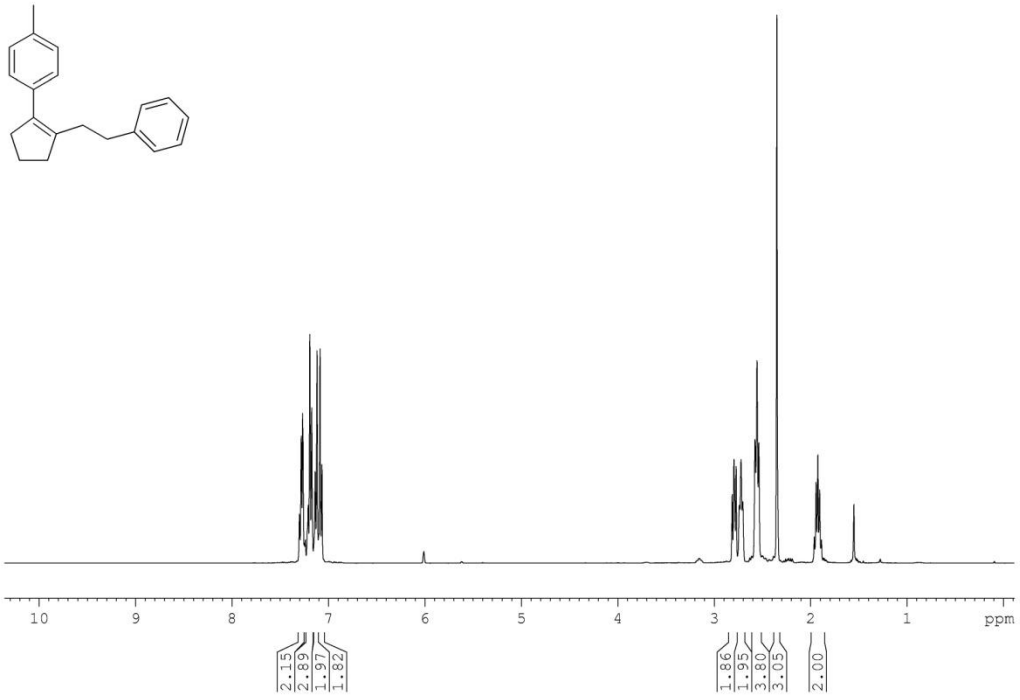

Ph
O
Cl

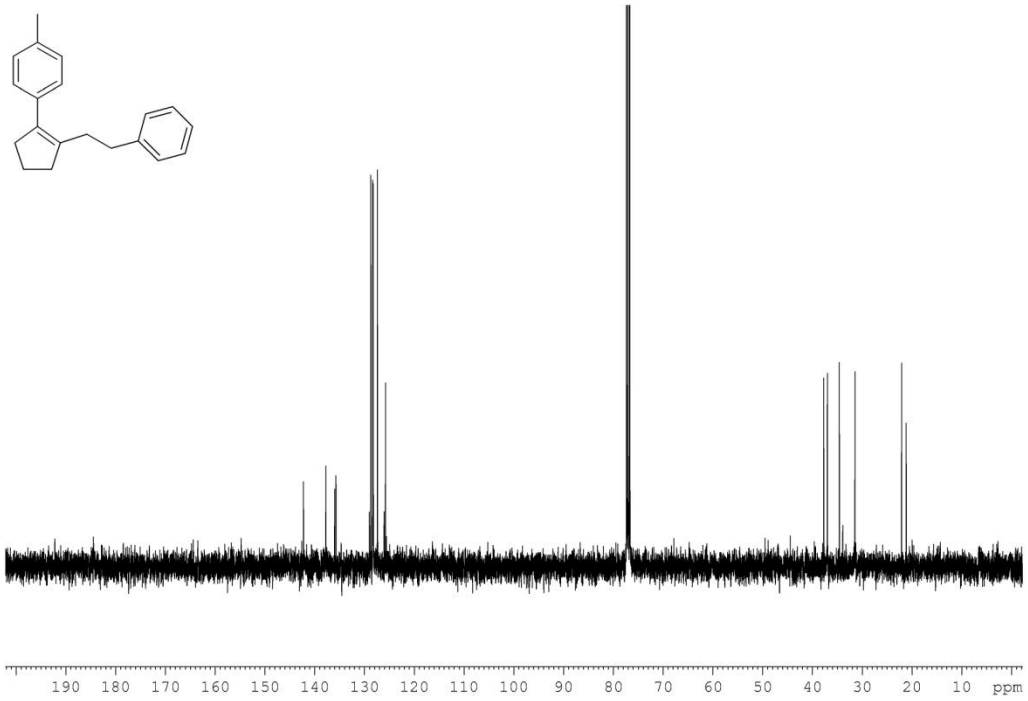

10 9 8 7 6 5 4 3 2 1 ppm
3.00
2.96
0.97
0.99
0.92
0.99
0.89
1.11
1.02
1.02
1.02
3.19
3.00

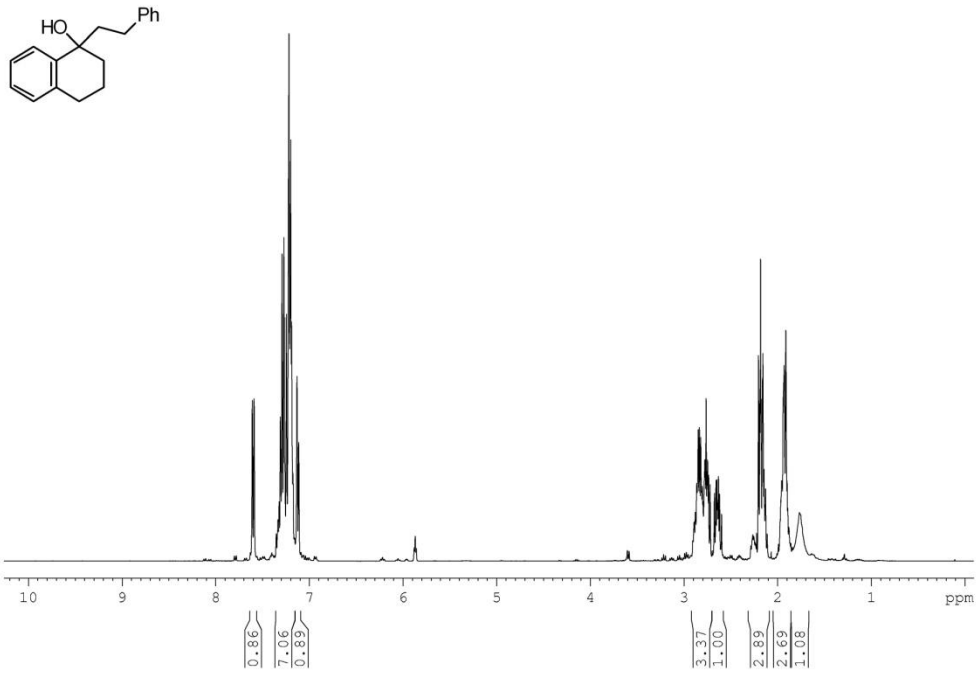

Ph
O
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

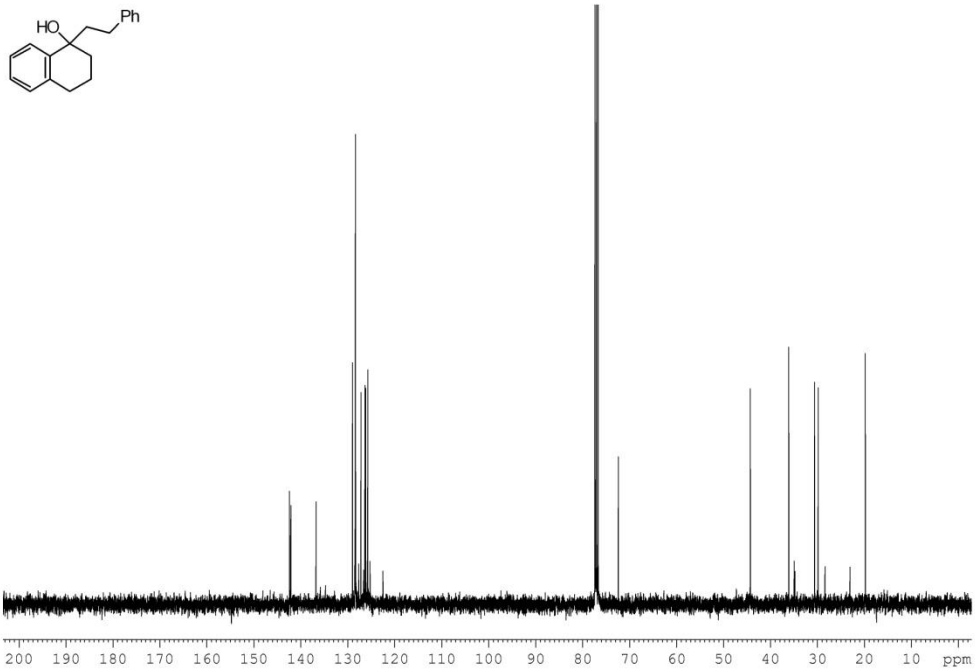

H
O
O
Cl
10 9 8 7 6 5 4 3 2 1 ppm
0.88
0.96
2.07
0.86
1.00
1.00
3.11
3.00

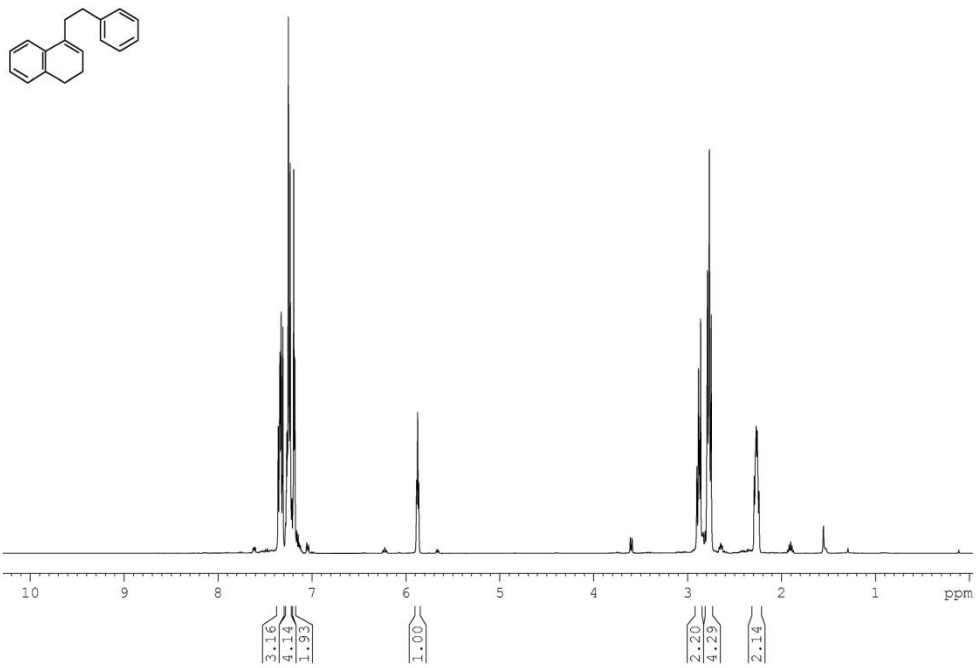

H
O
O
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

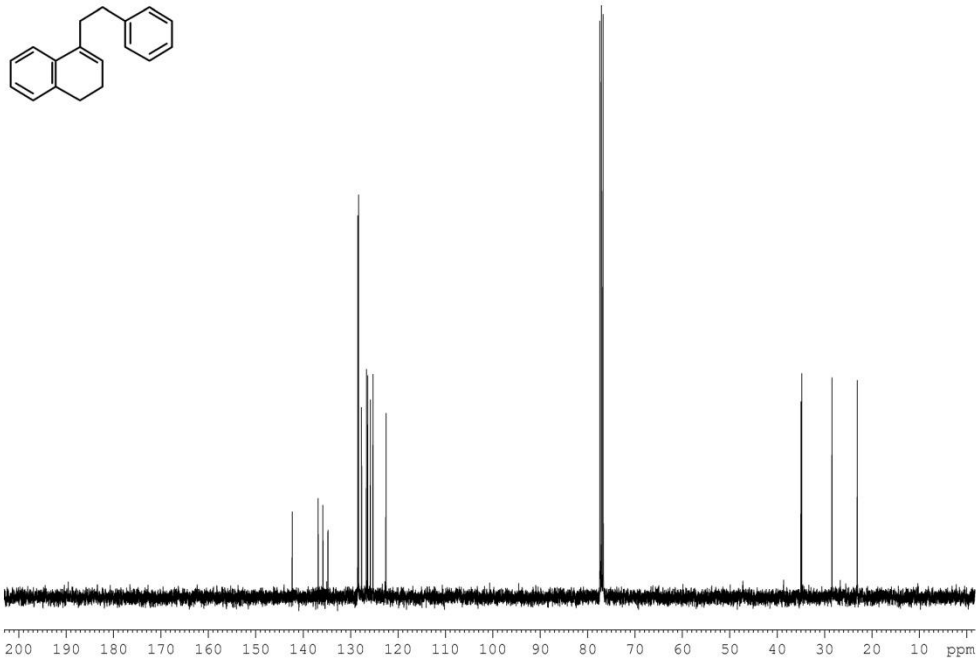

10 9 8 7 6 5 4 3 2 1 ppm
2.15
2.89
1.97
1.82
1.86
1.95
3.80
3.05
2.00

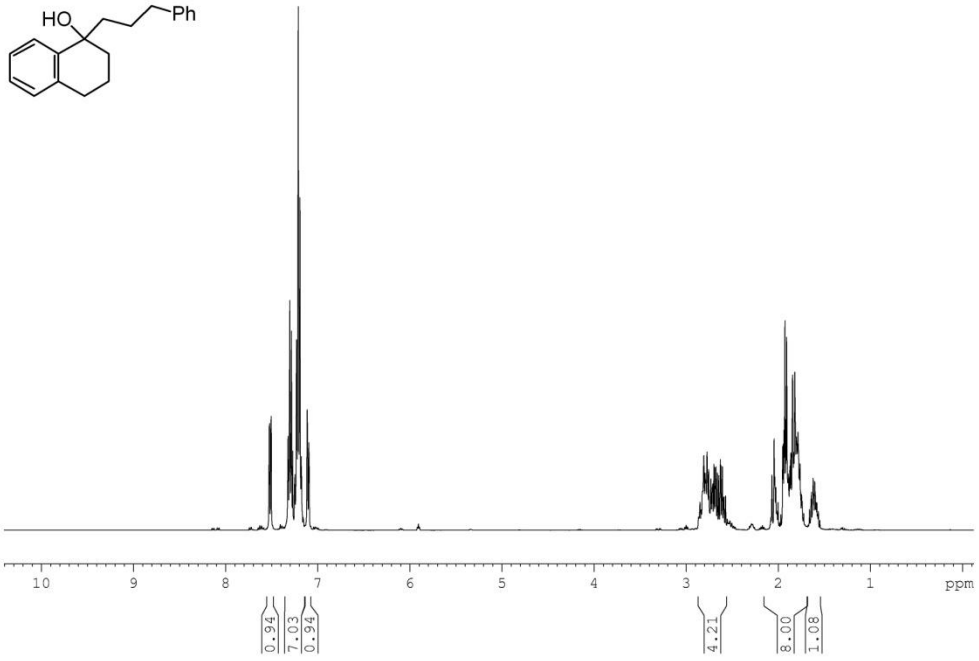

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

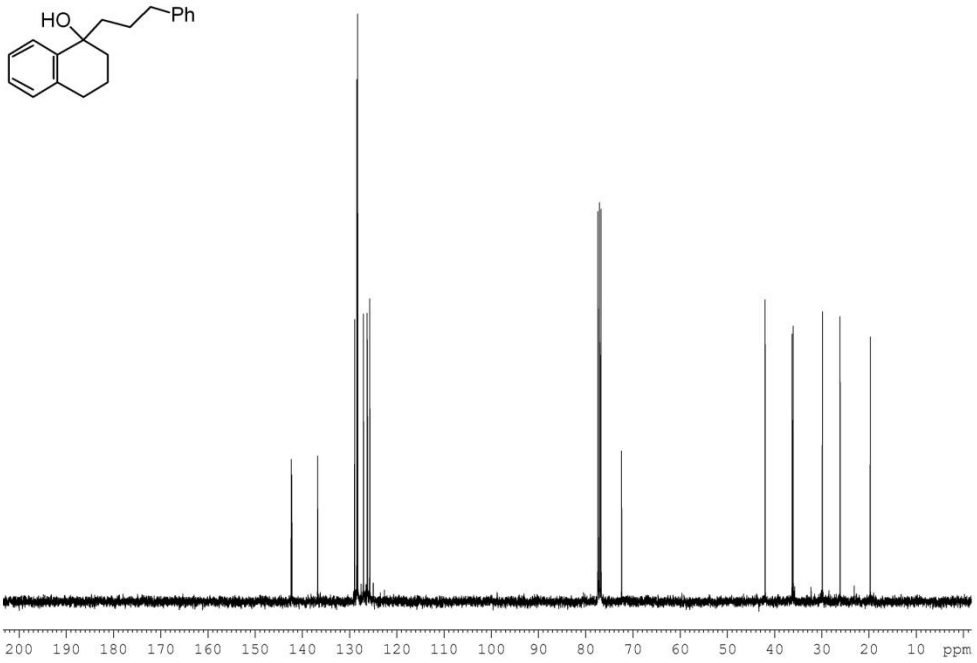

HO
Ph
10 9 8 7 6 5 4 3 2 1 ppm
0.86
7.06
0.89
3.37
1.00
2.89
2.69
1.08

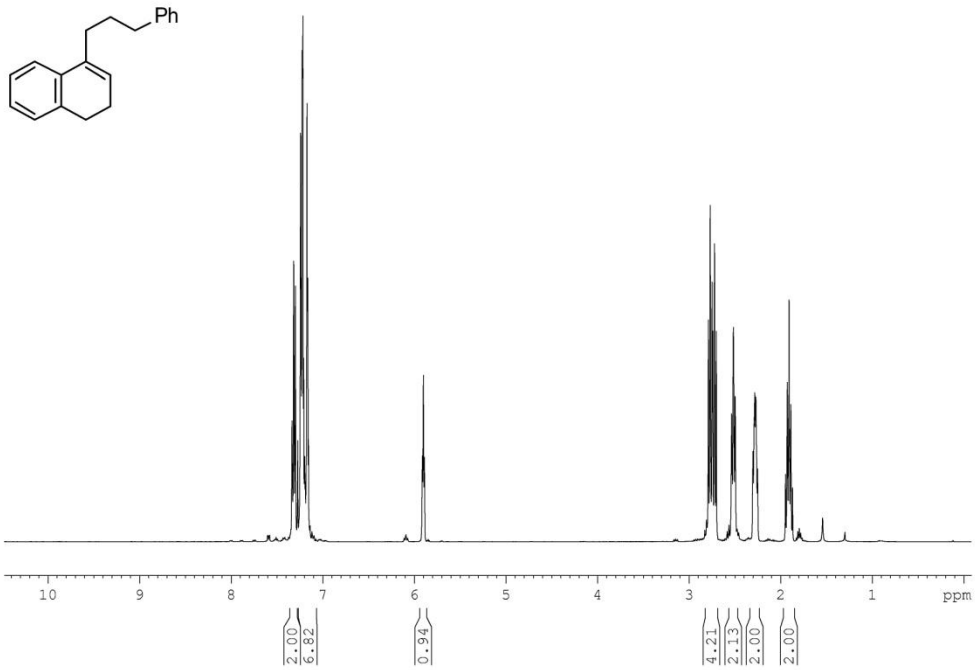

HO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

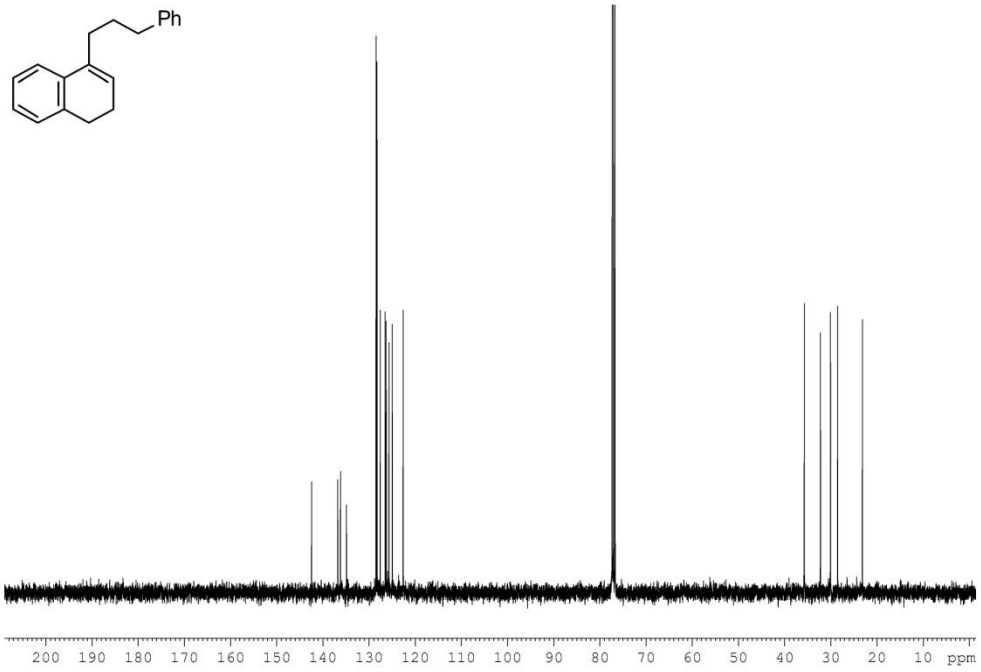

10 9 8 7 6 5 4 3 2 1 ppm
3.16
4.14
1.93
1.00
2.20
4.29
2.14

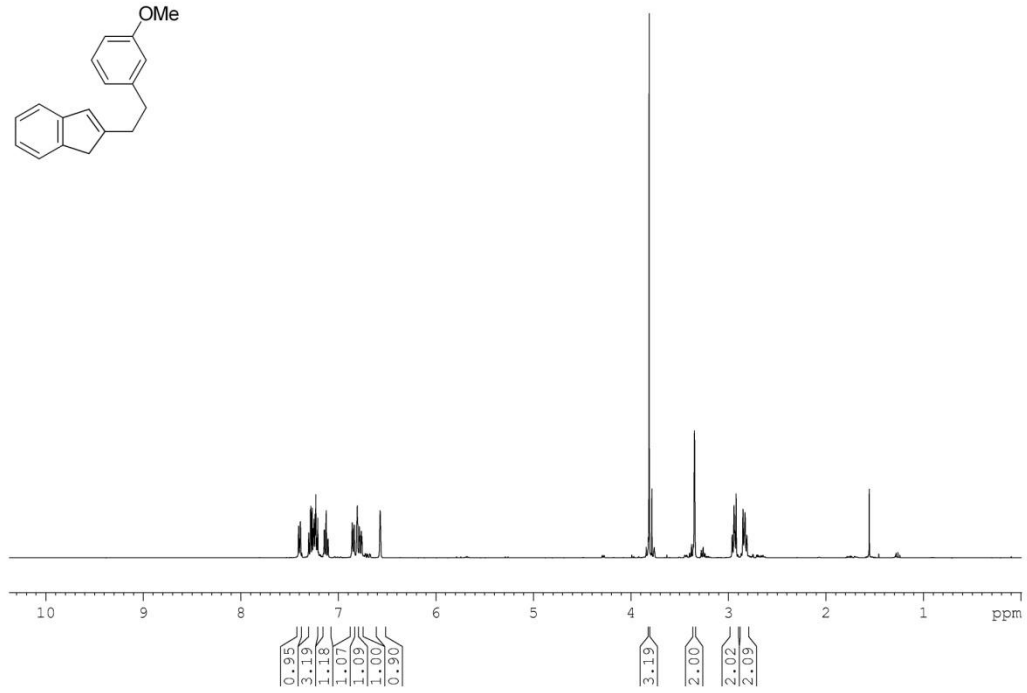

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

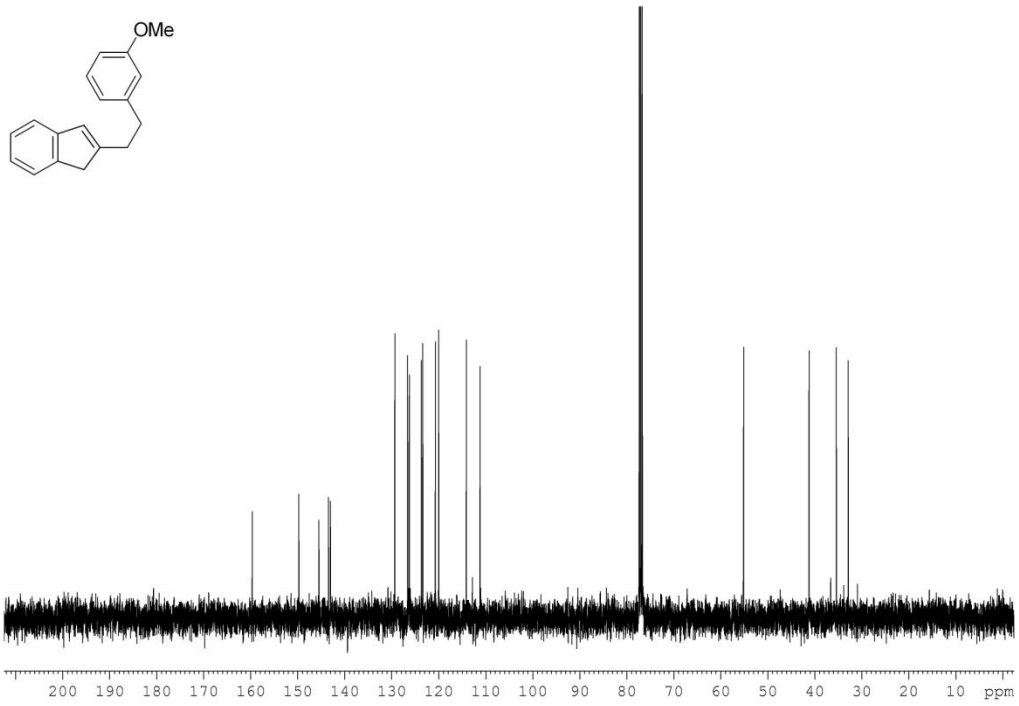

HO
Ph
10 9 8 7 6 5 4 3 2 1 ppm
0.94
7.03
0.94
4.21
8.00
1.08

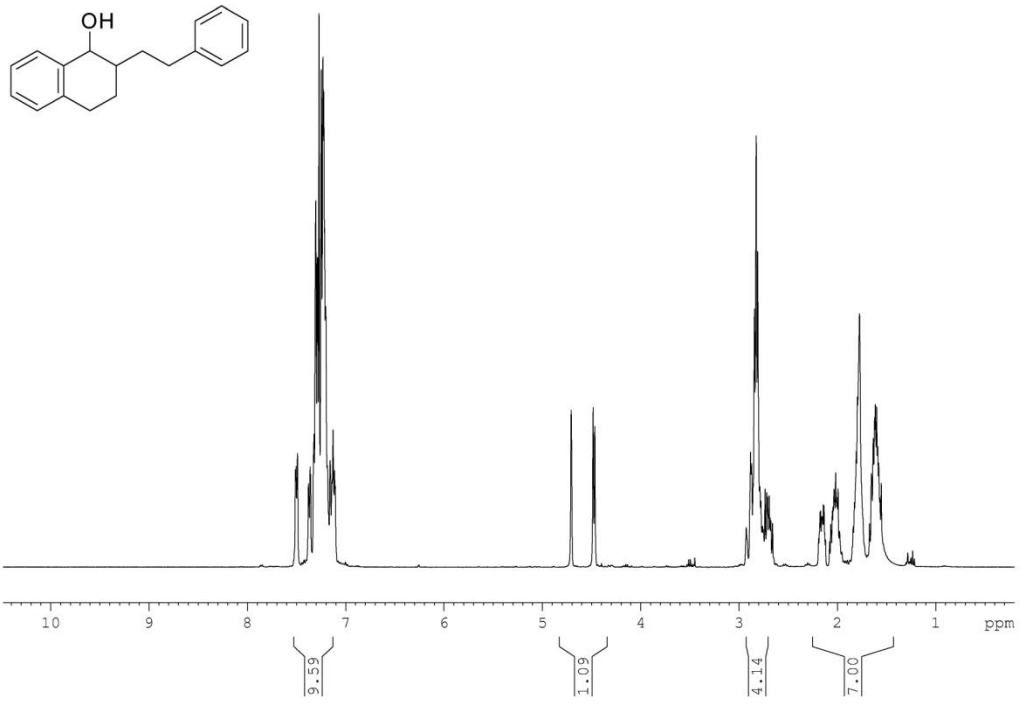

HO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

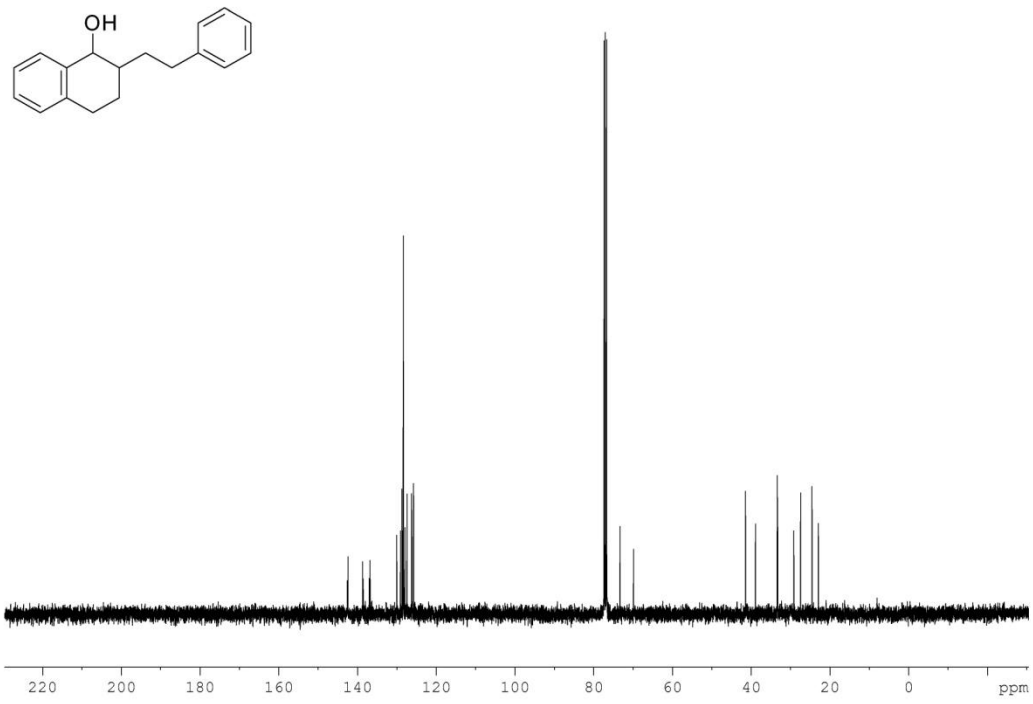

Ph
10 9 8 7 6 5 4 3 2 1 ppm
2.00
6.82
0.94
4.21
2.13
2.00
2.00

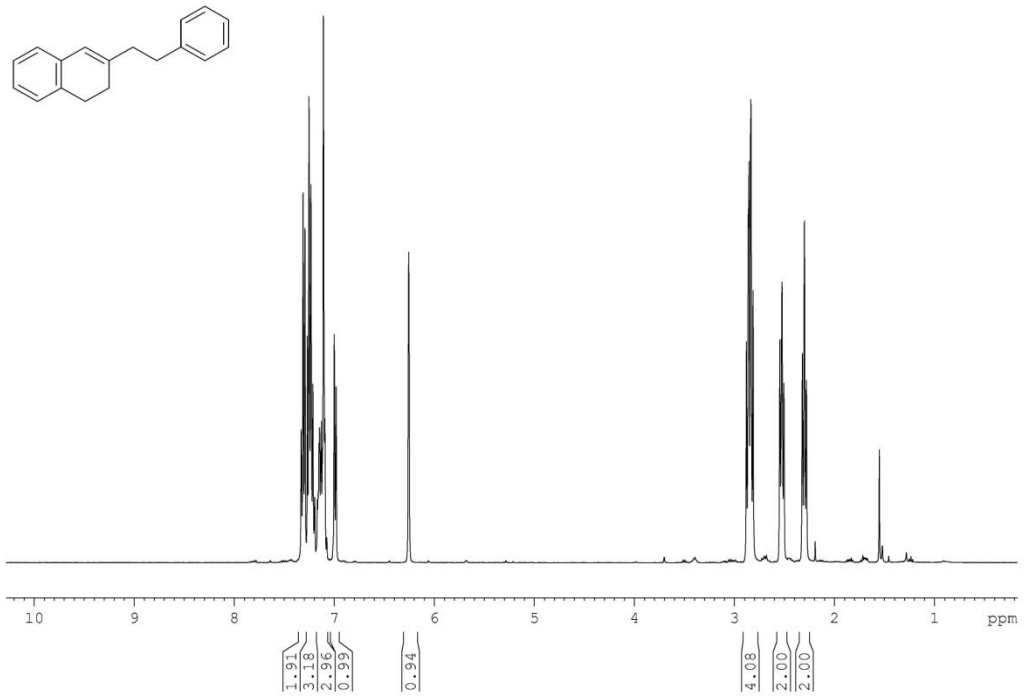

Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

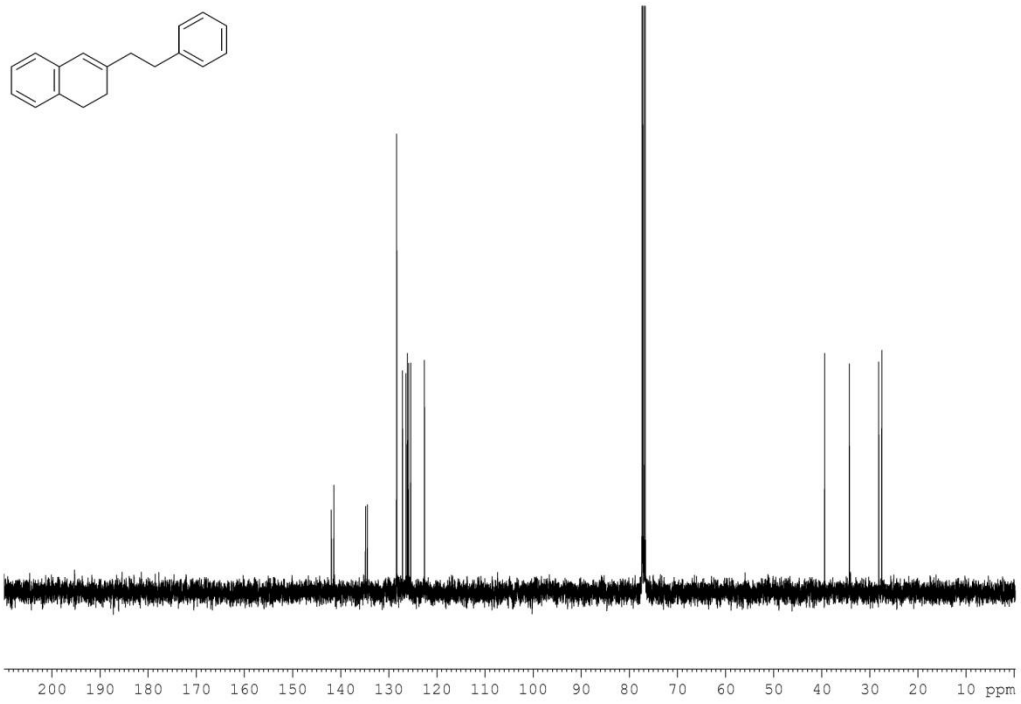

OMe
10 9 8 7 6 5 4 3 2 1 ppm
0.95
3.19
1.18
1.07
1.09
1.00
0.90
3.19
2.00
2.02
2.09

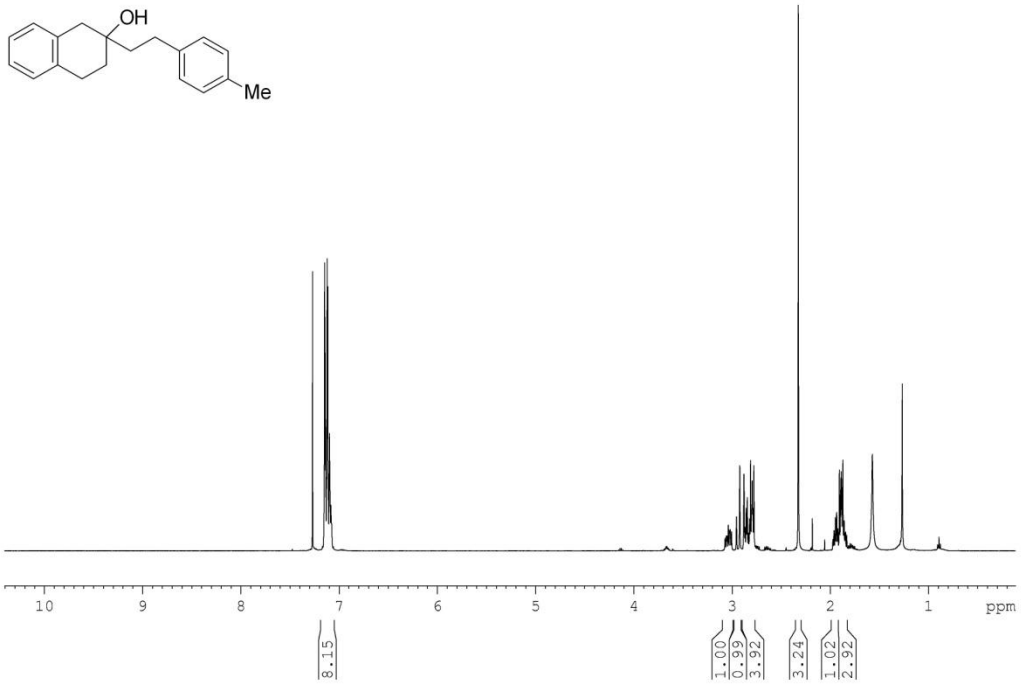

OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

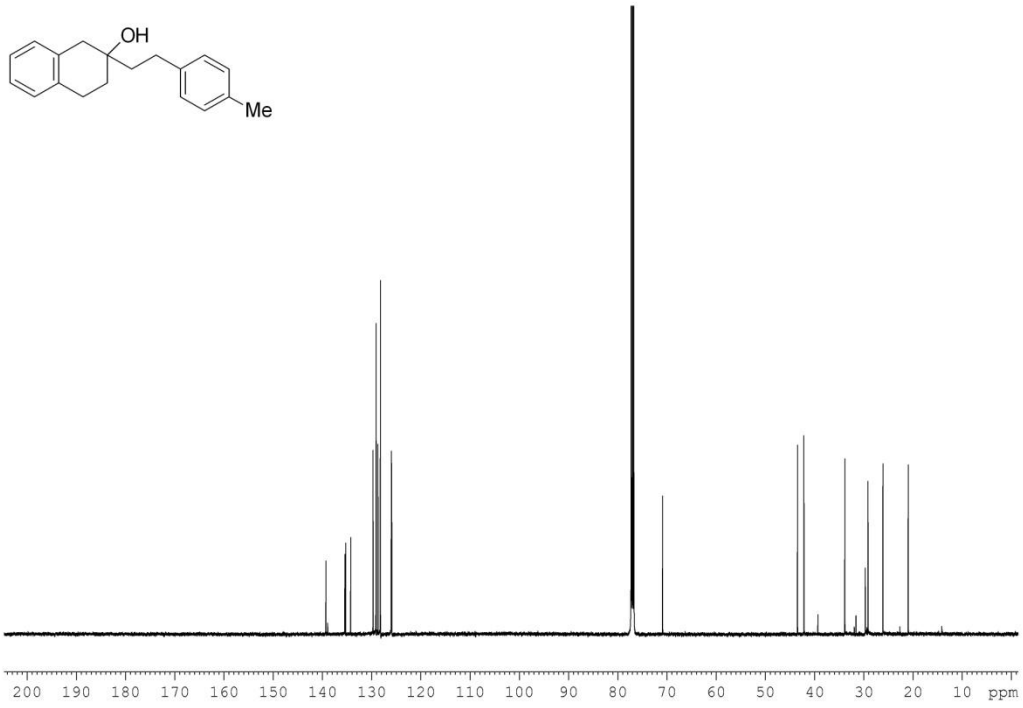

OH
10 9 8 7 6 5 4 3 2 1 ppm
9.59
1.09
4.14
7.00

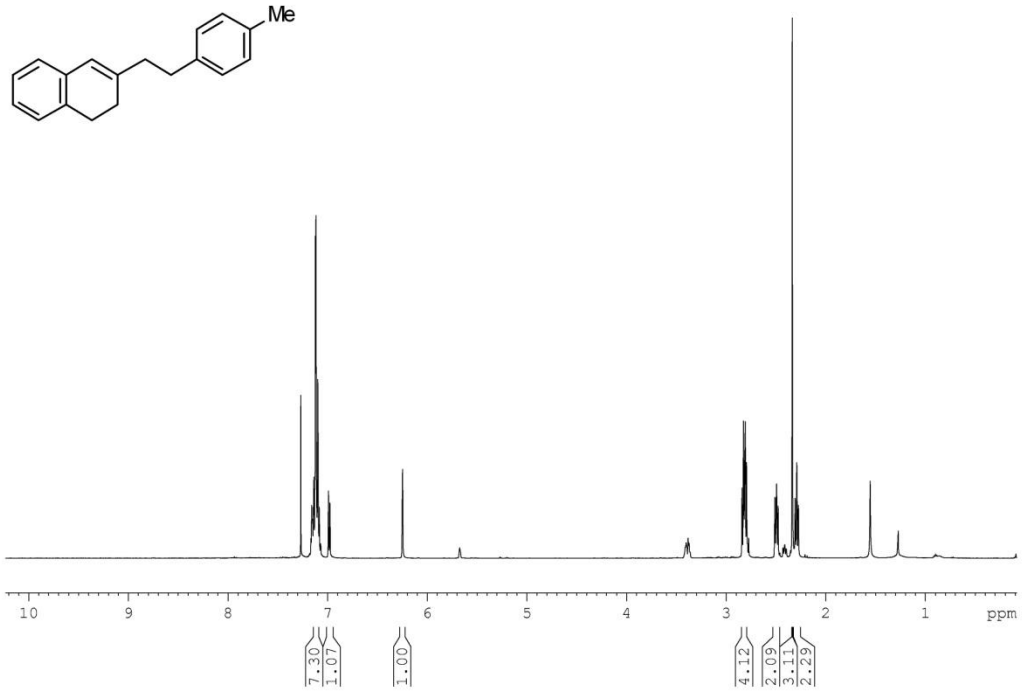

OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

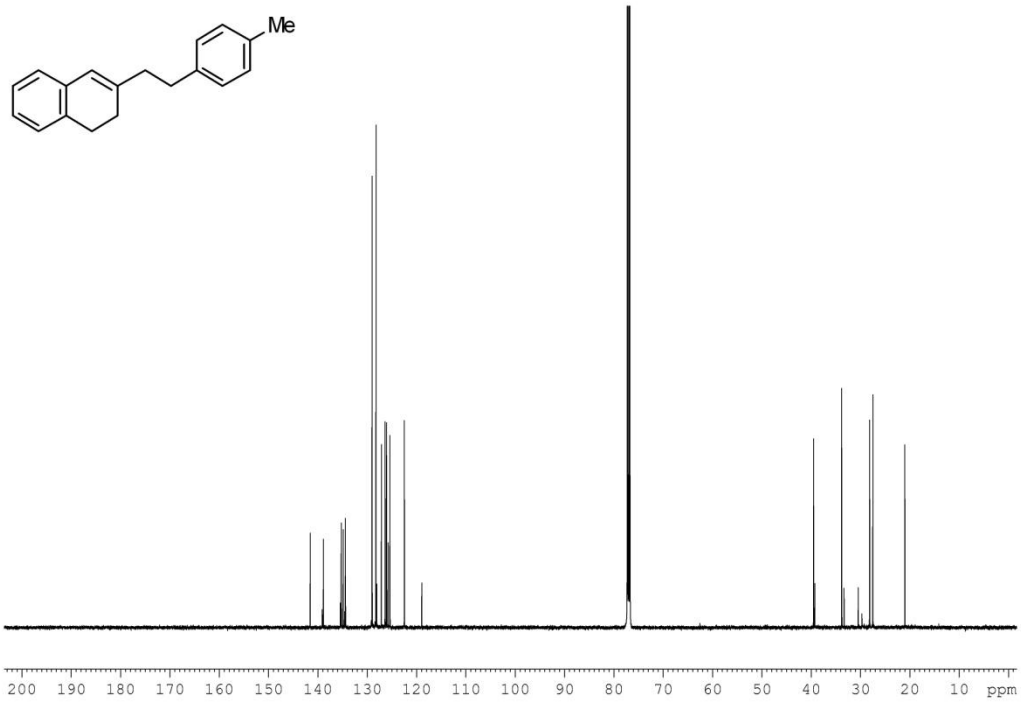

10
9
8
7
6
5
4
3
2
1
ppm
1.91
3.18
2.96
0.99
0.94
4.08
2.00
2.00

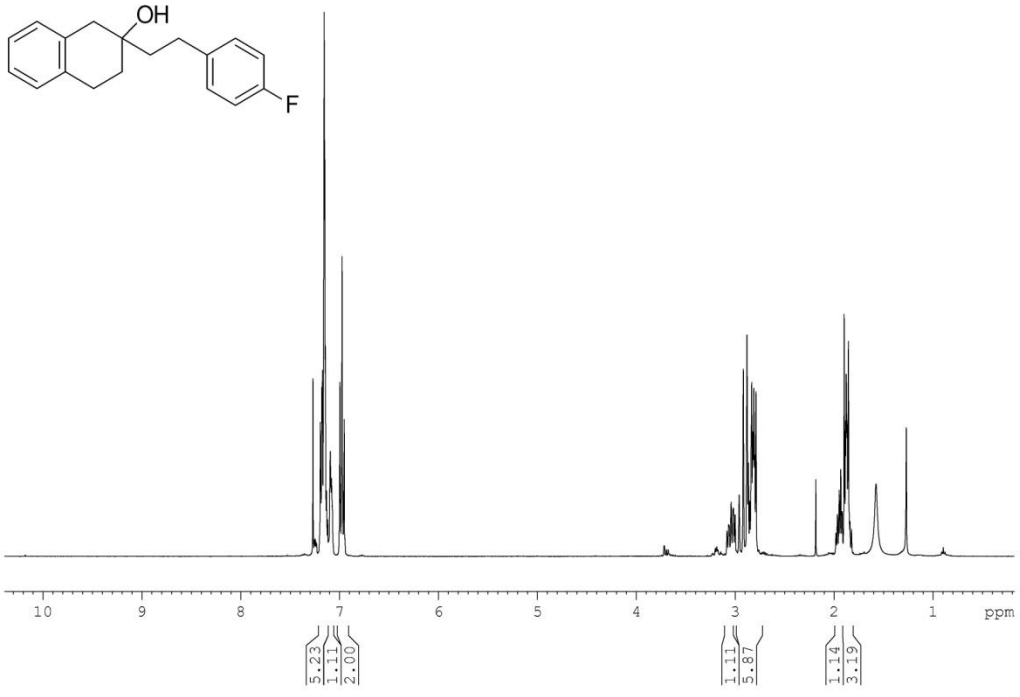

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

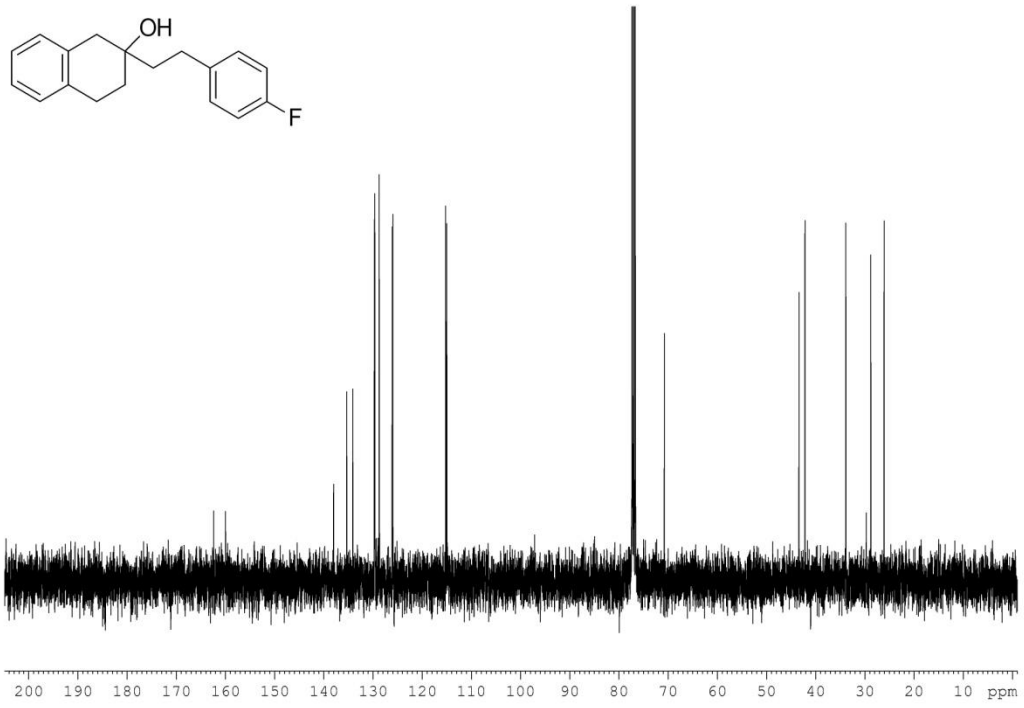

OH
Me
10 9 8 7 6 5 4 3 2 1 ppm
8.15
1.00
0.99
3.92
3.24
1.02
2.92

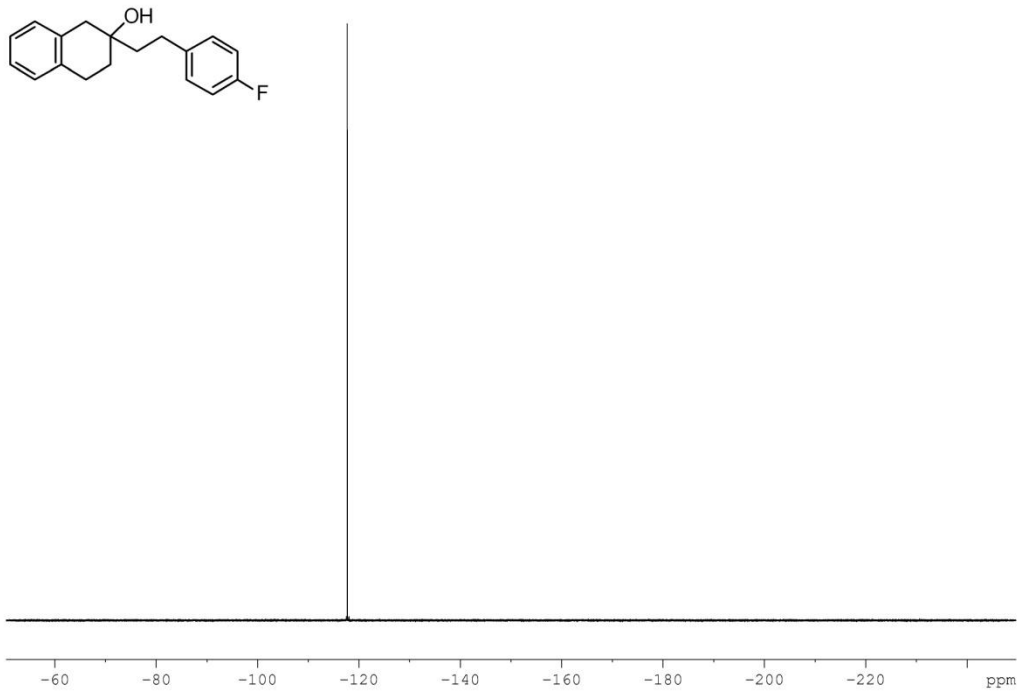

OH
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

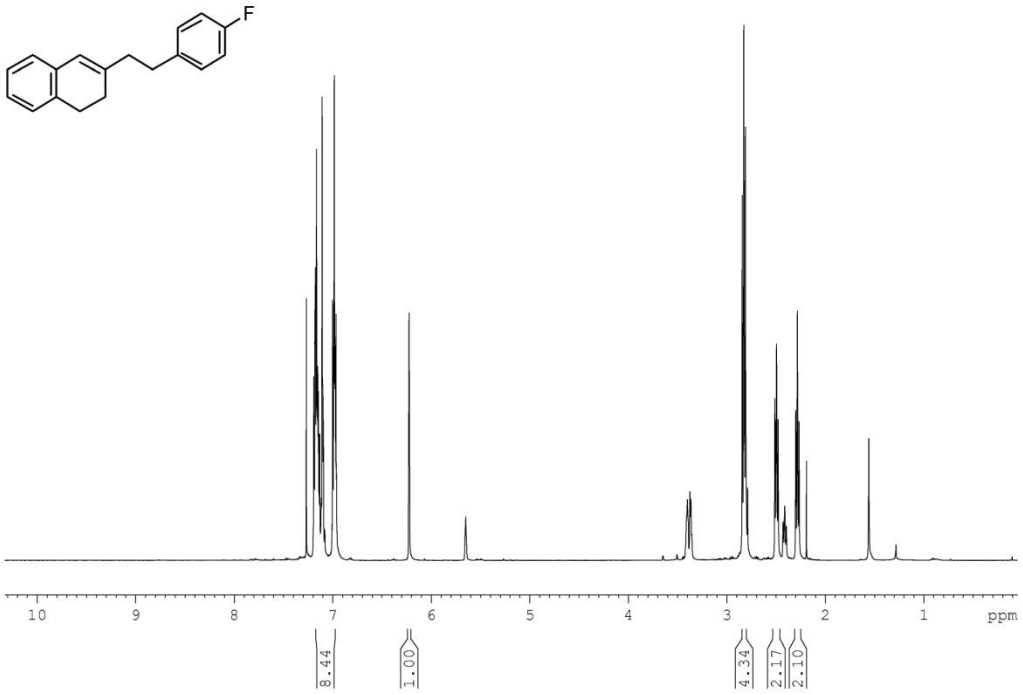

Me
10 9 8 7 6 5 4 3 2 1 ppm
7.30
1.07
1.00
4.12
2.09
3.11
2.29

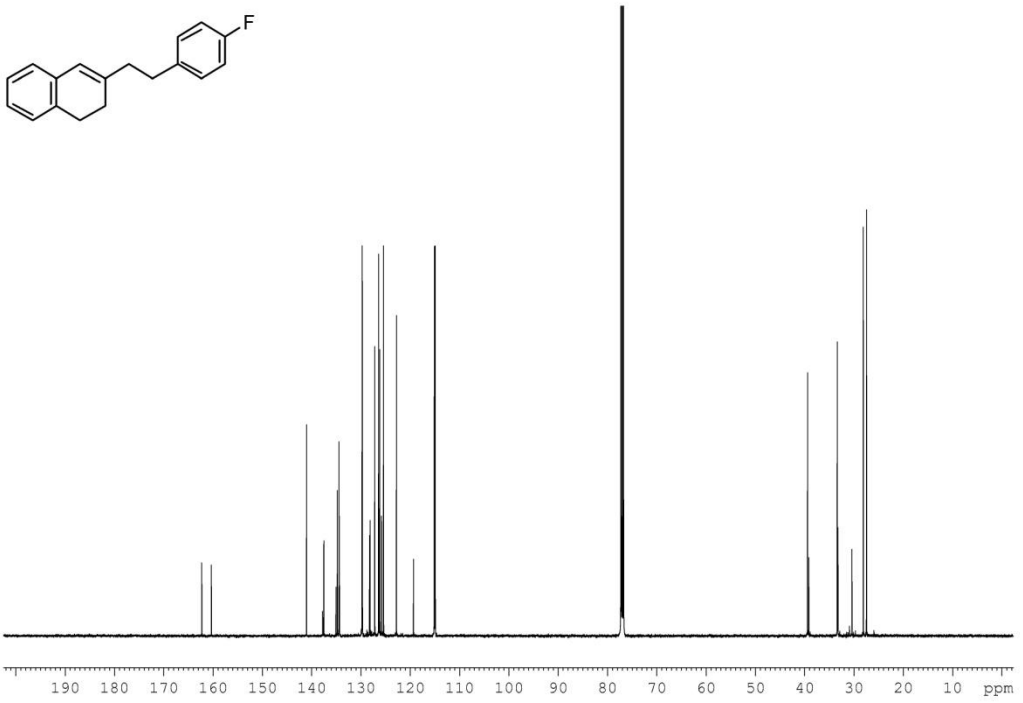

Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

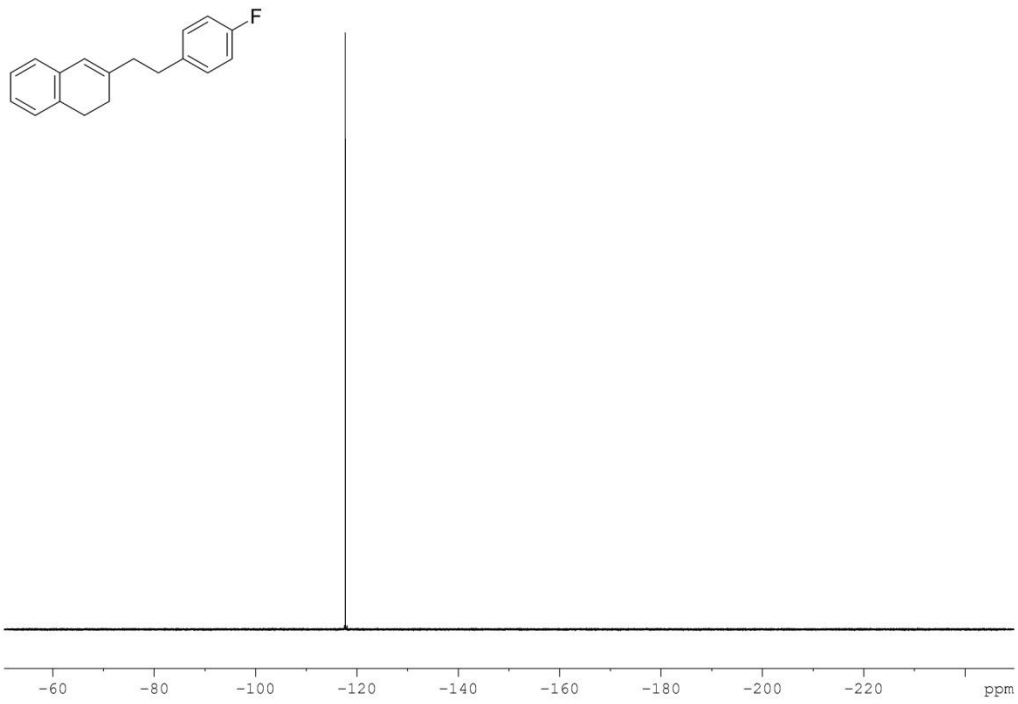

OH
F
10 9 8 7 6 5 4 3 2 1 ppm
5.23
1.11
2.00
1.11
5.87
1.14
3.19

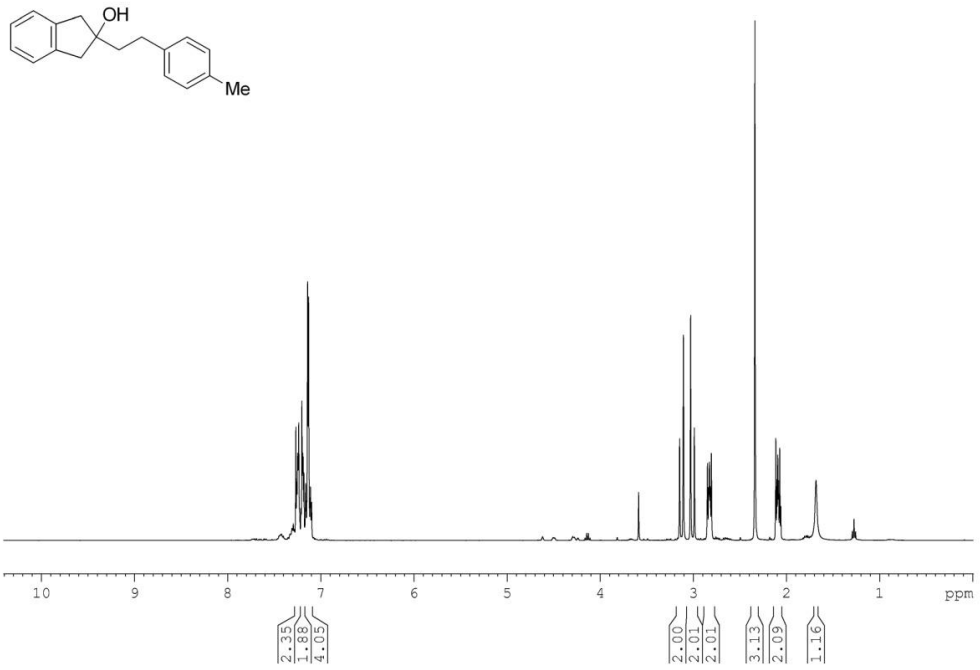

OH
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

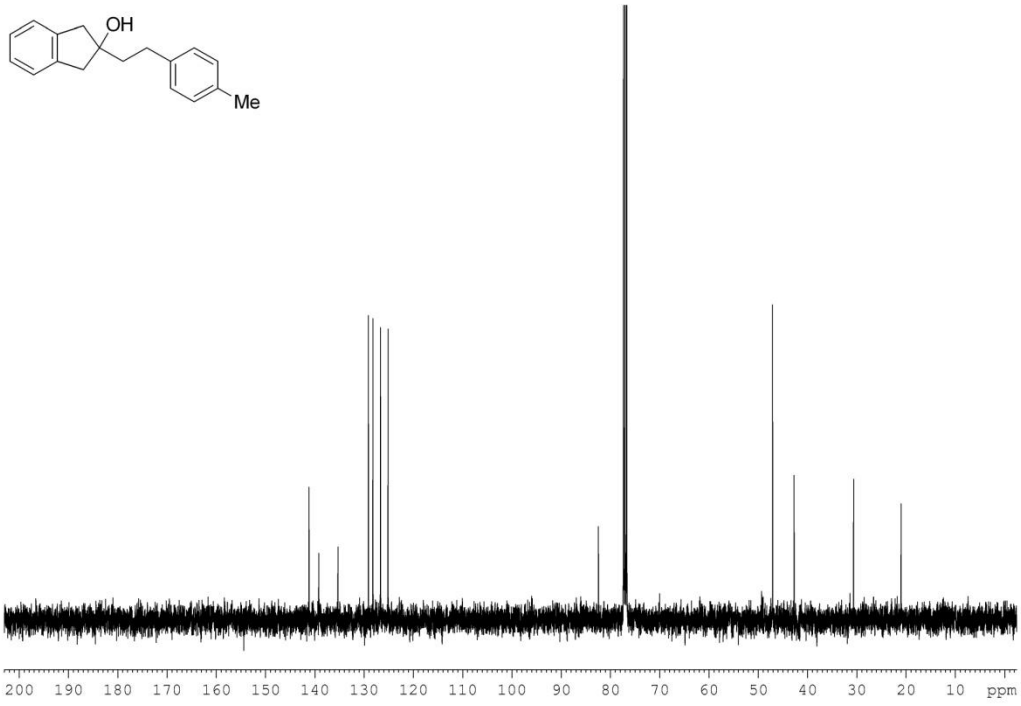

OH
F
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

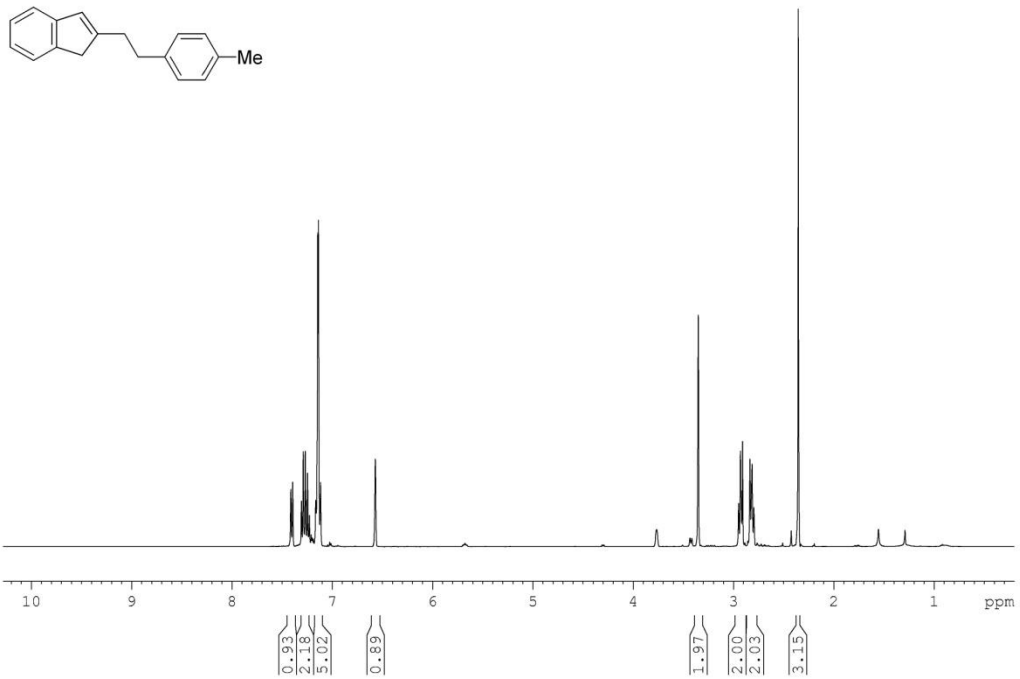

F
10
9
8
7
6
5
4
3
2
1
ppm
8.44
1.00
4.34
2.17
2.10

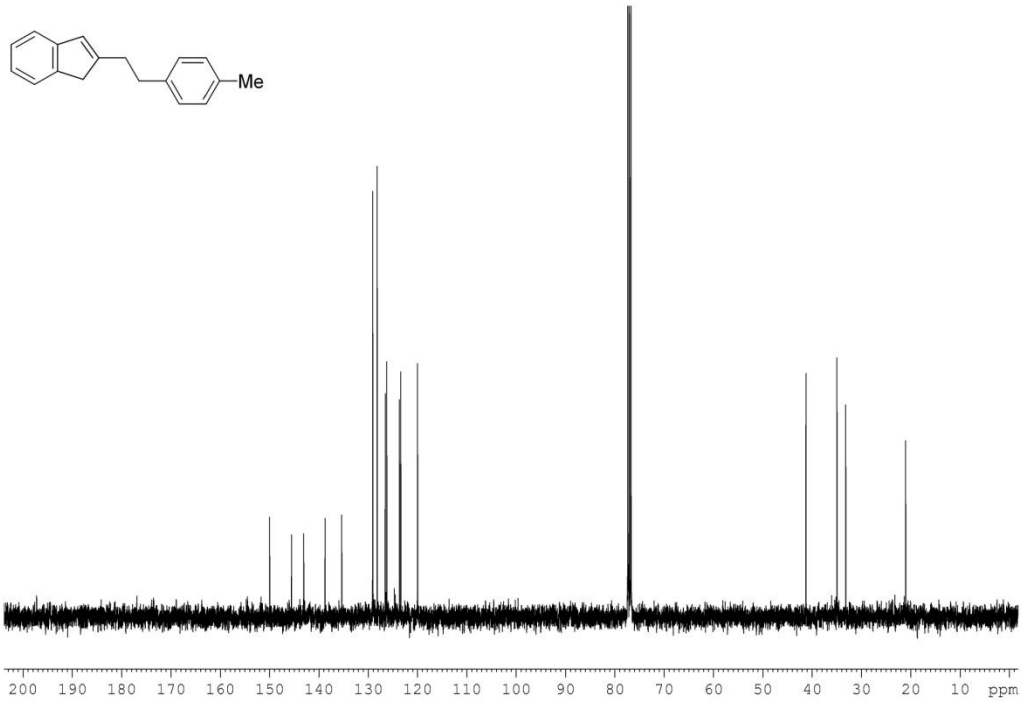

F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

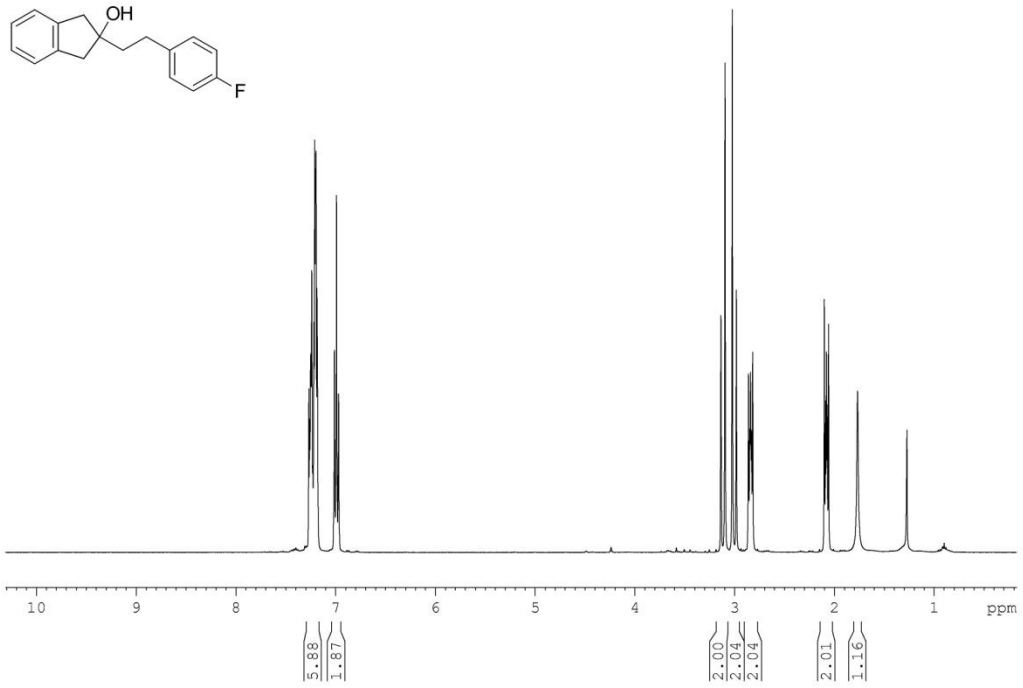

F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

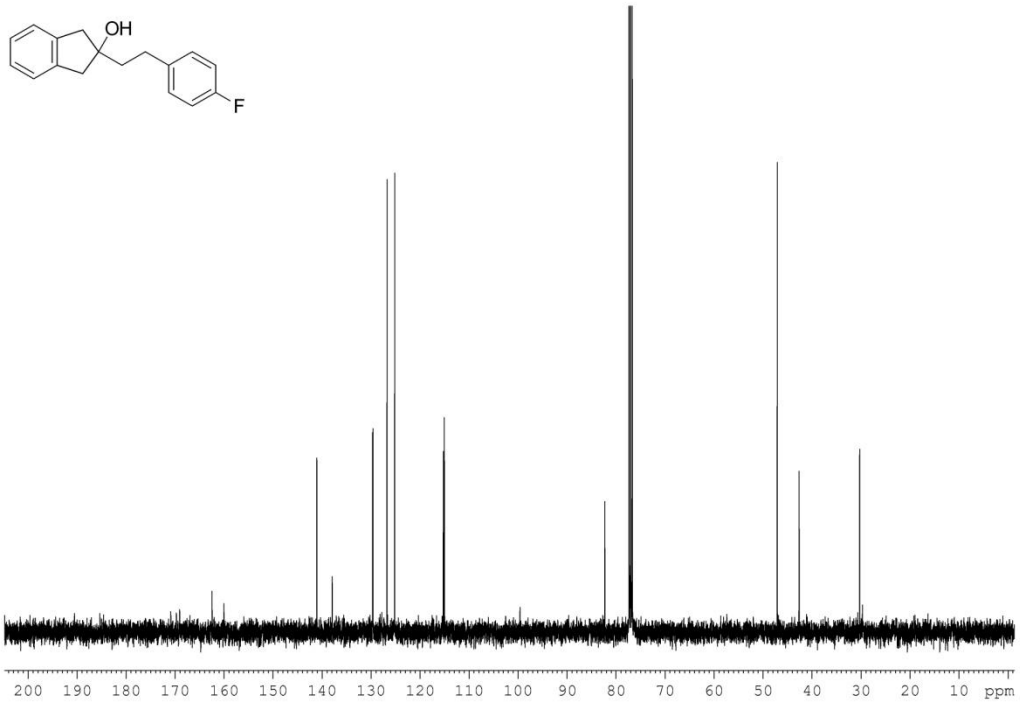

OH
Me
10
9
8
7
6
5
4
3
2
1
ppm
2.35
1.88
4.05
2.00
2.01
2.01
3.13
2.09
1.16

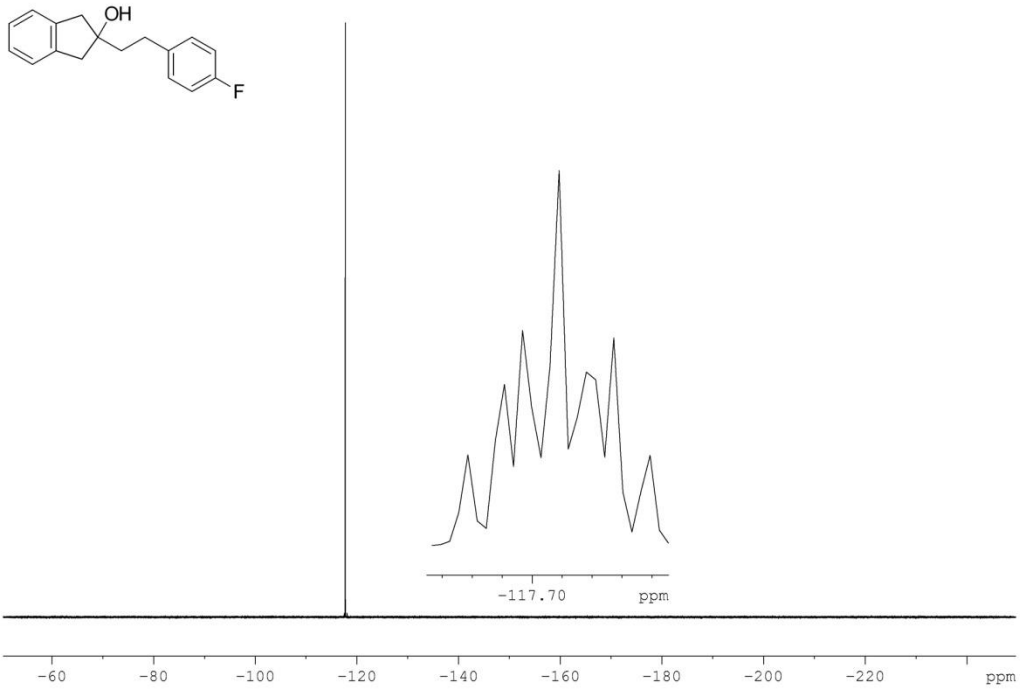

OH
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

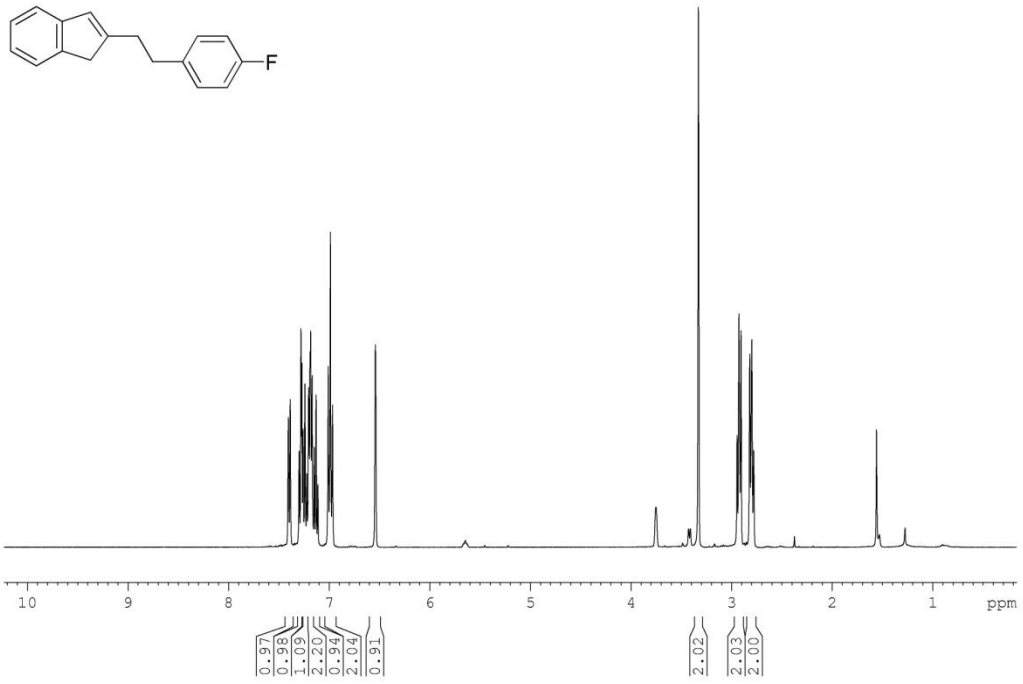

Me
10 9 8 7 6 5 4 3 2 1 ppm
0.93
2.18
5.02
0.89
1.97
2.00
2.03
3.15

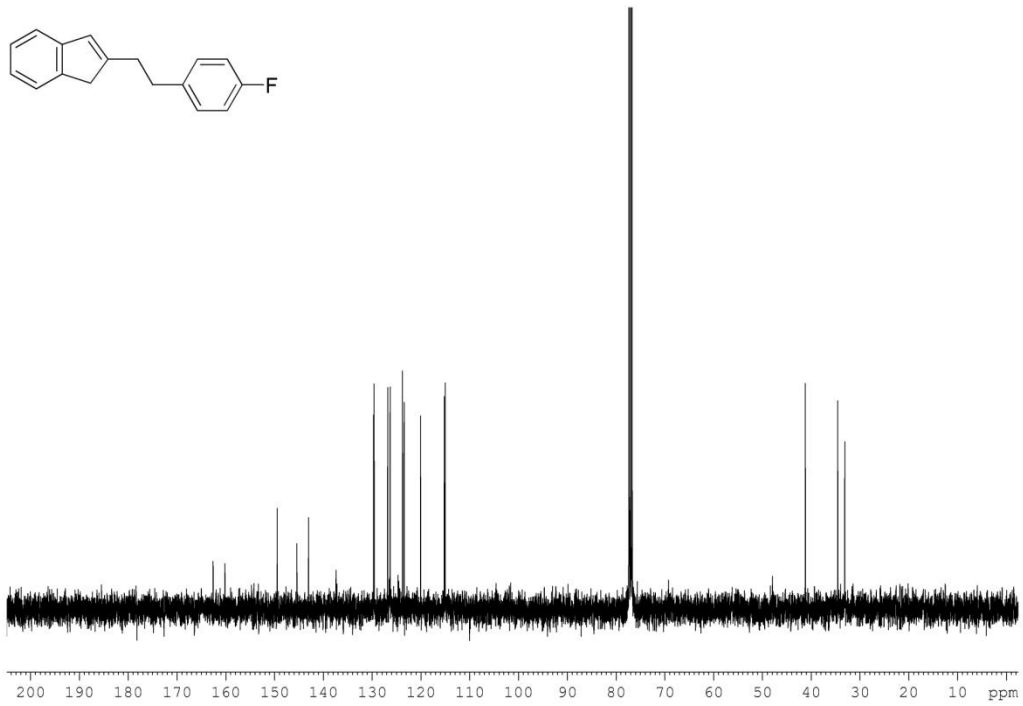

Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

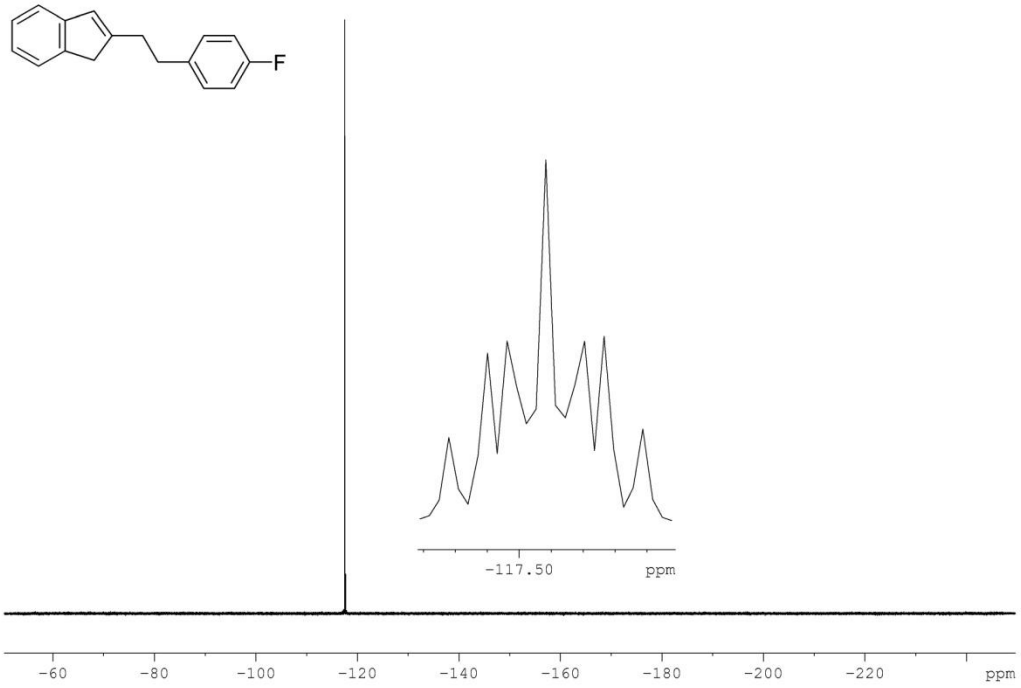

OH
F
10 9 8 7 6 5 4 3 2 1 ppm
5.88
1.87
2.00
2.04
2.04
2.01
1.16

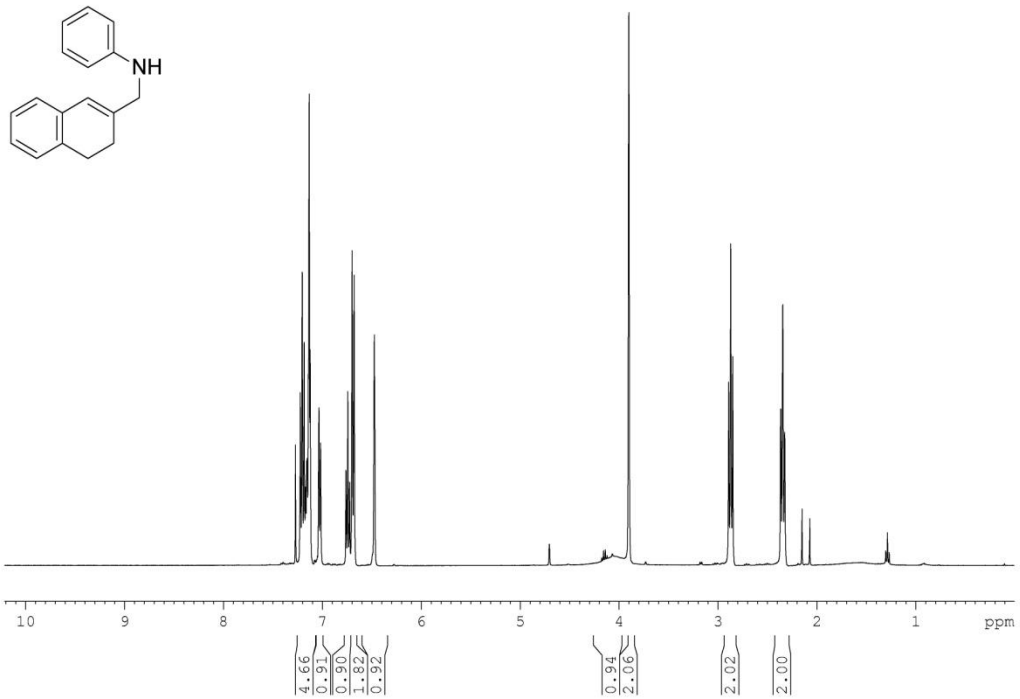

OH
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

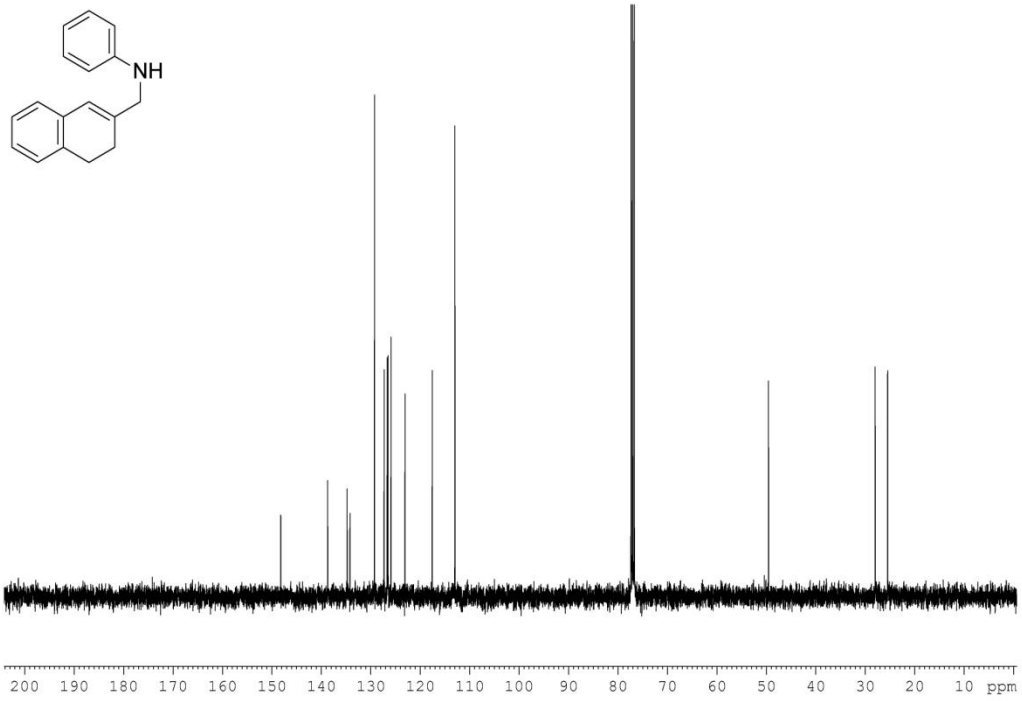

OH
F
-117.70
ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

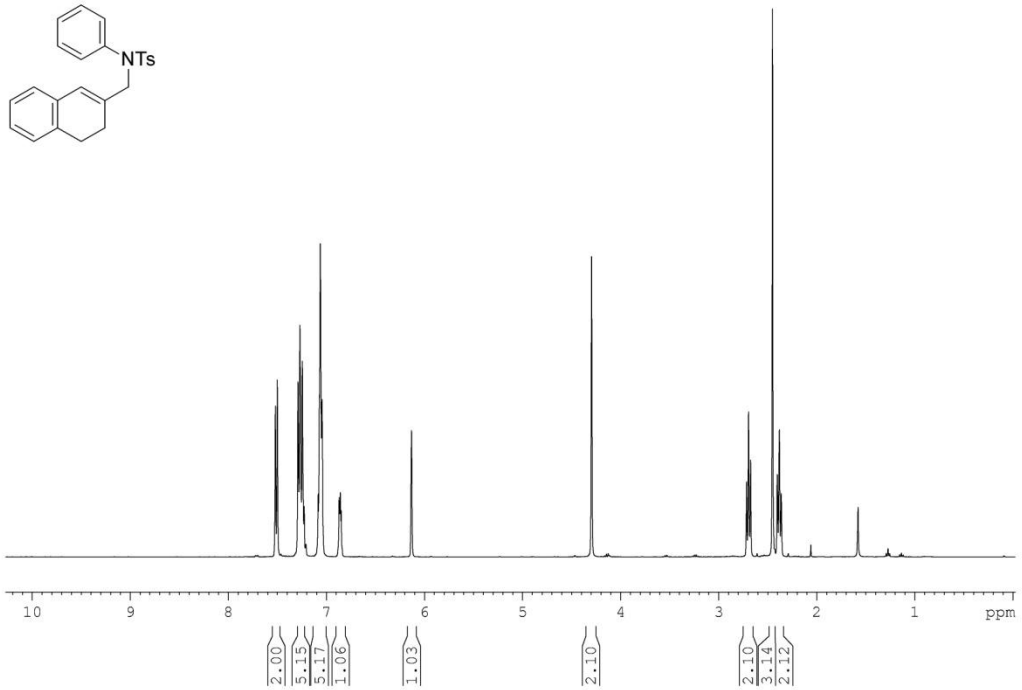

F
10
9
8
7
6
5
4
3
2
1
ppm
0.97
0.98
1.09
2.20
0.94
2.04
0.91
2.02
2.03
2.00

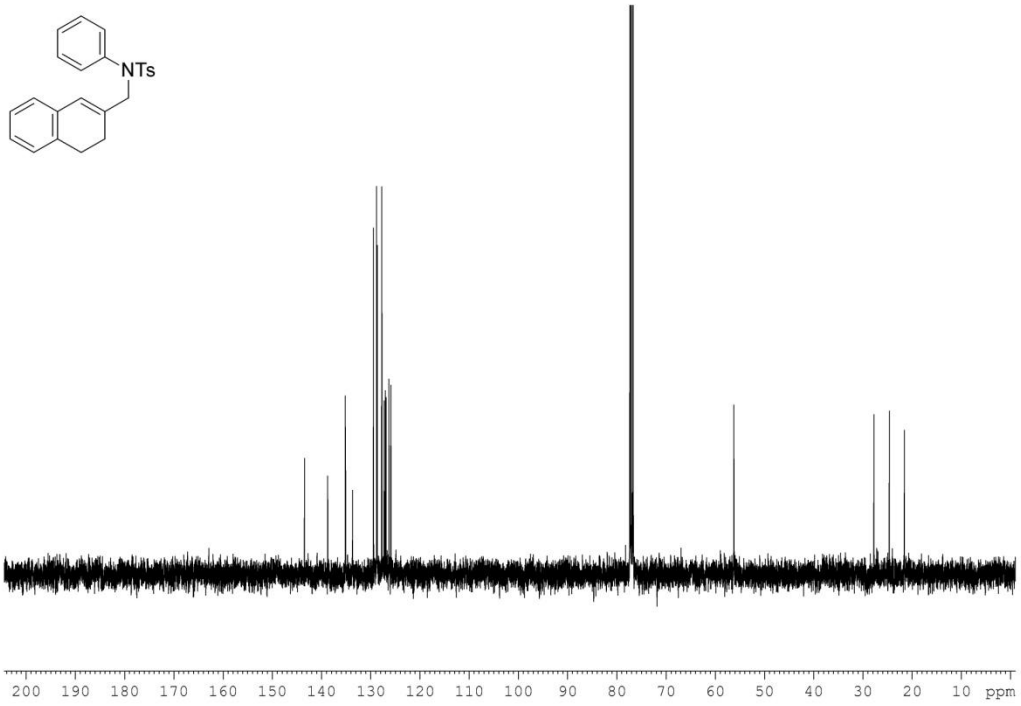

F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

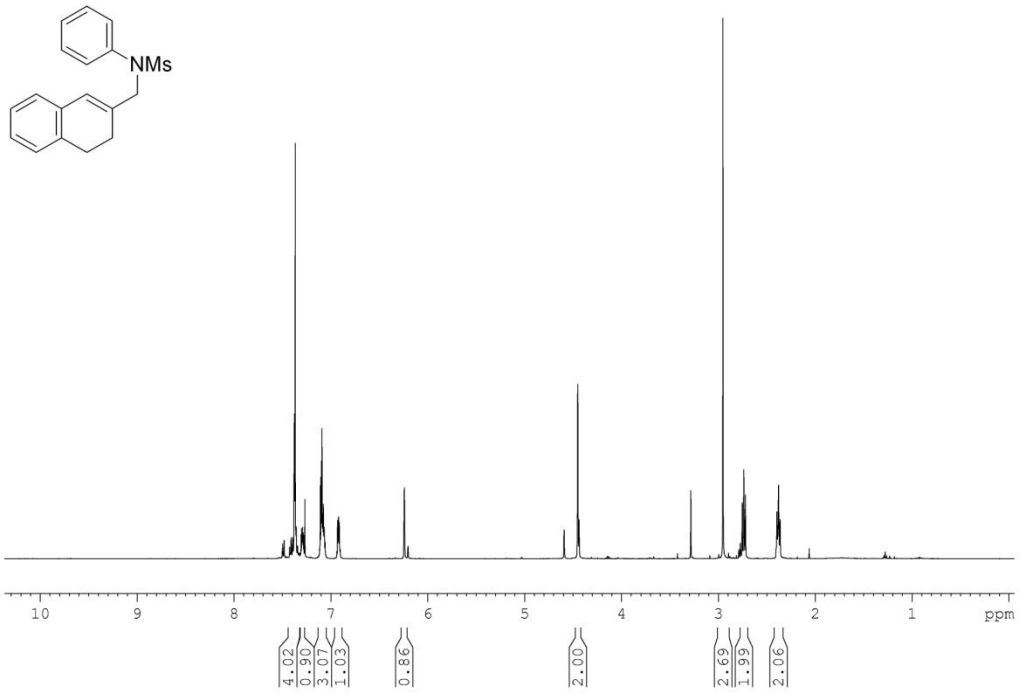

F
-117.50
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

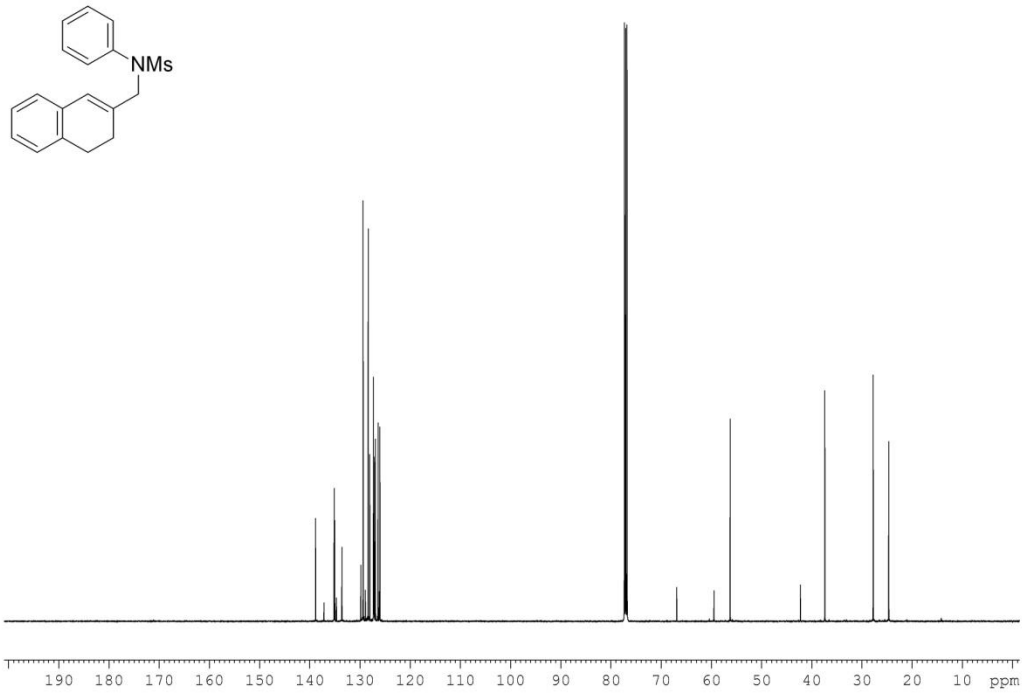

NH
10
9
8
7
6
5
4
3
2
1
ppm
4.66
0.91
0.90
1.82
0.92
0.94
2.06
2.02
2.00

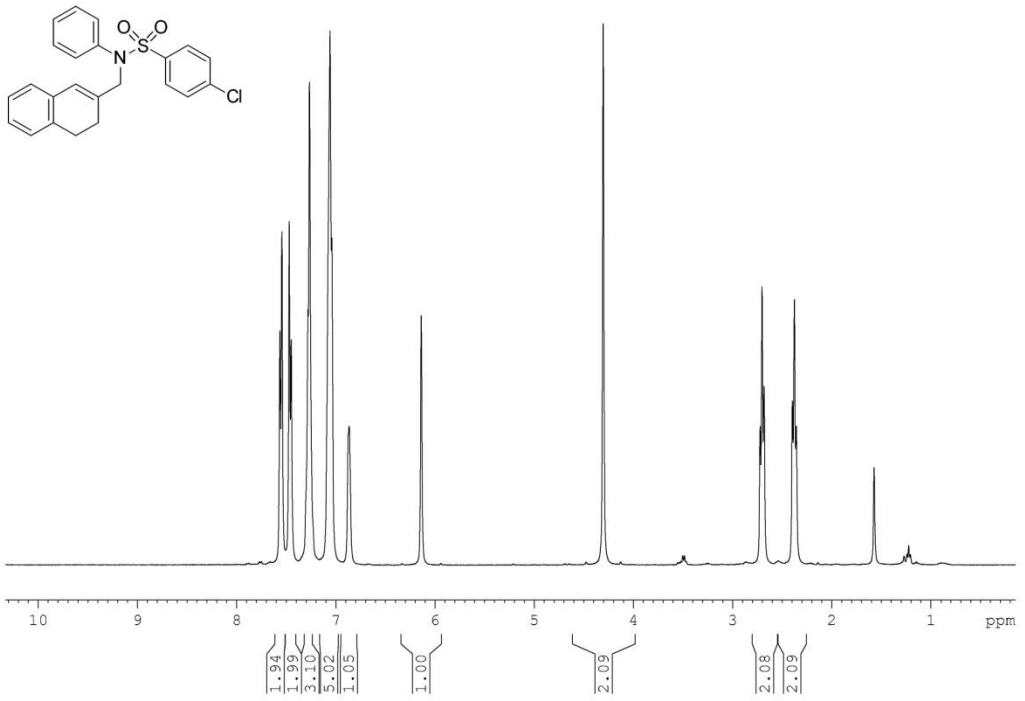

NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

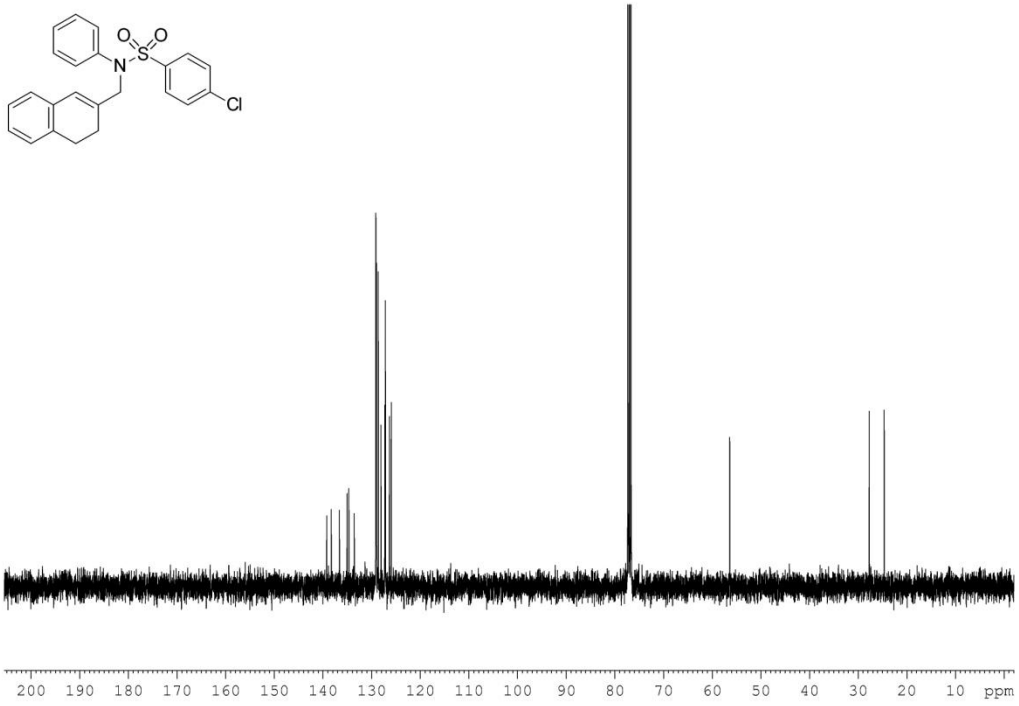

NTs
10 9 8 7 6 5 4 3 2 1 ppm
2.00
5.15
5.17
1.06
1.03
2.10
2.10
3.14
2.12

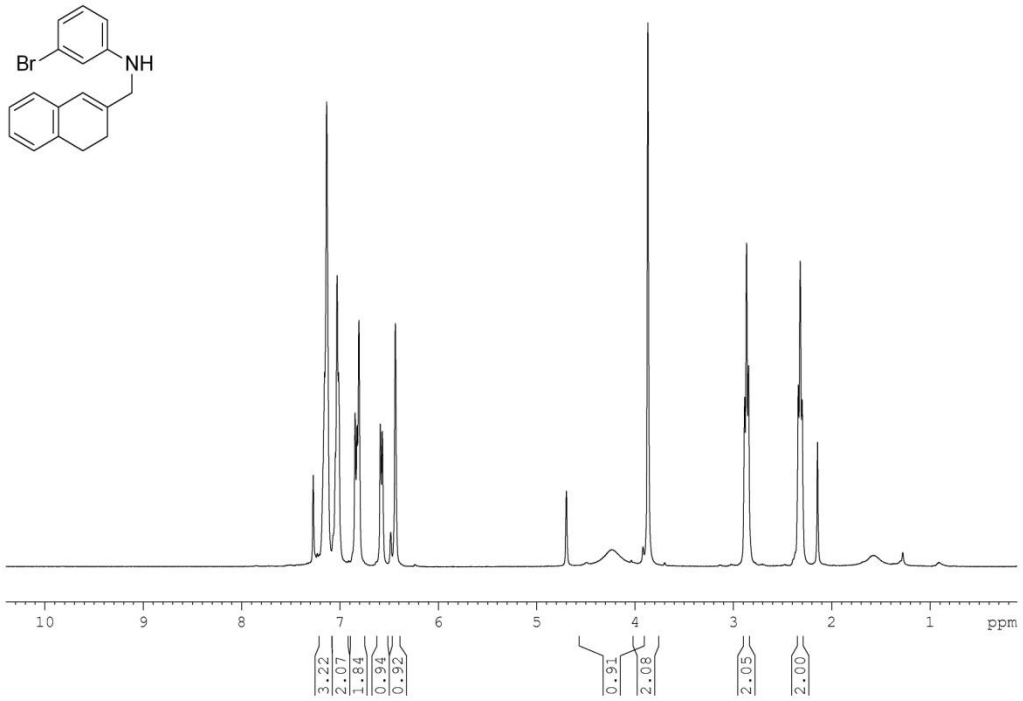

NTs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

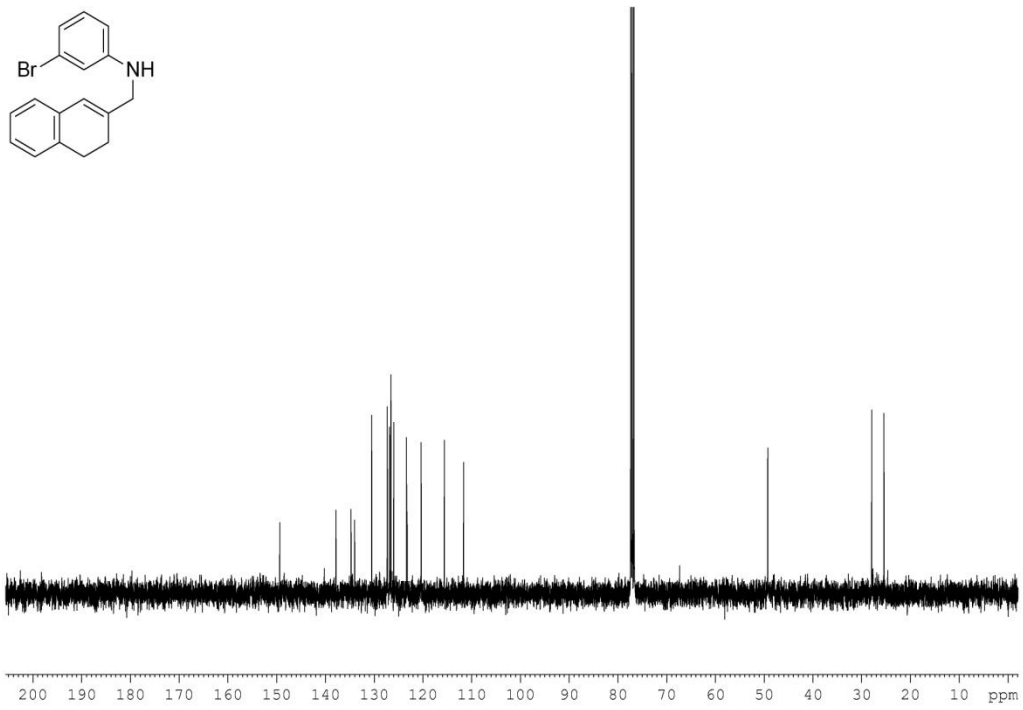

NMs
10 9 8 7 6 5 4 3 2 1 ppm
4.02
0.90
3.07
1.03
0.86
2.00
2.69
1.99
2.06

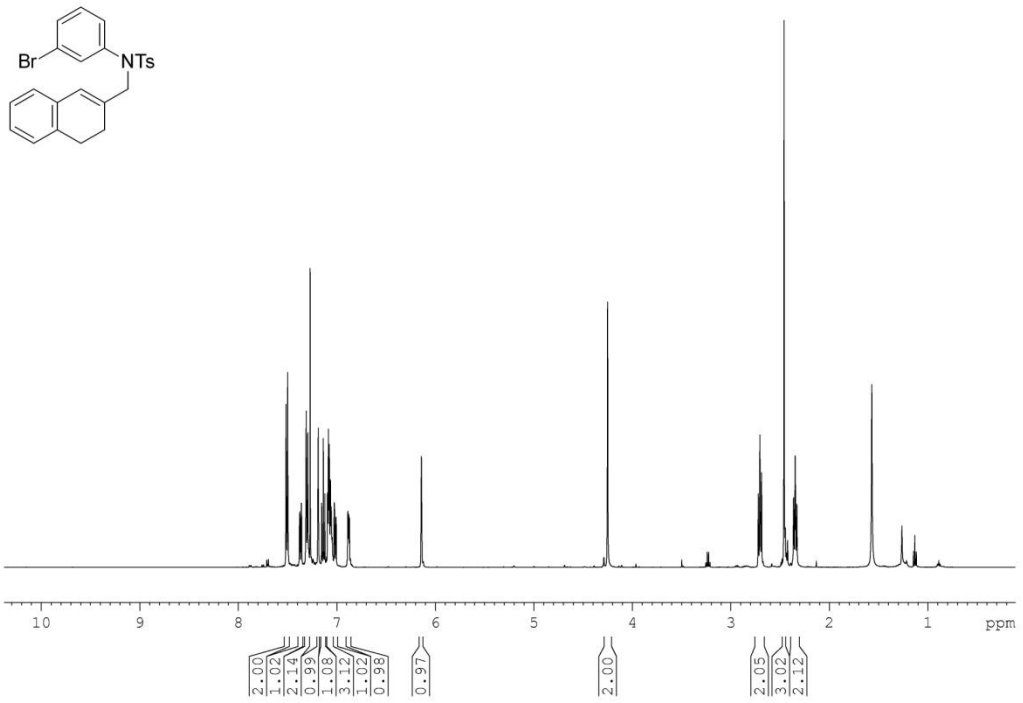

NMs
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

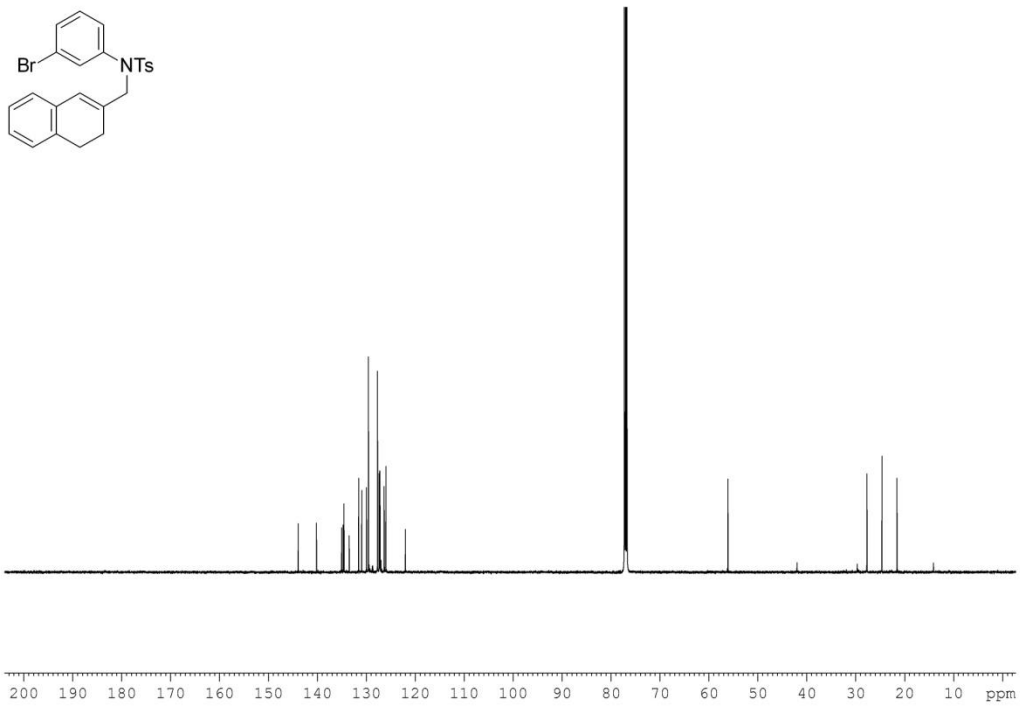

O
O
N
S
Cl
10 9 8 7 6 5 4 3 2 1 ppm
1.94
1.99
3.10
5.02
1.05
1.00
2.09
2.08
2.09

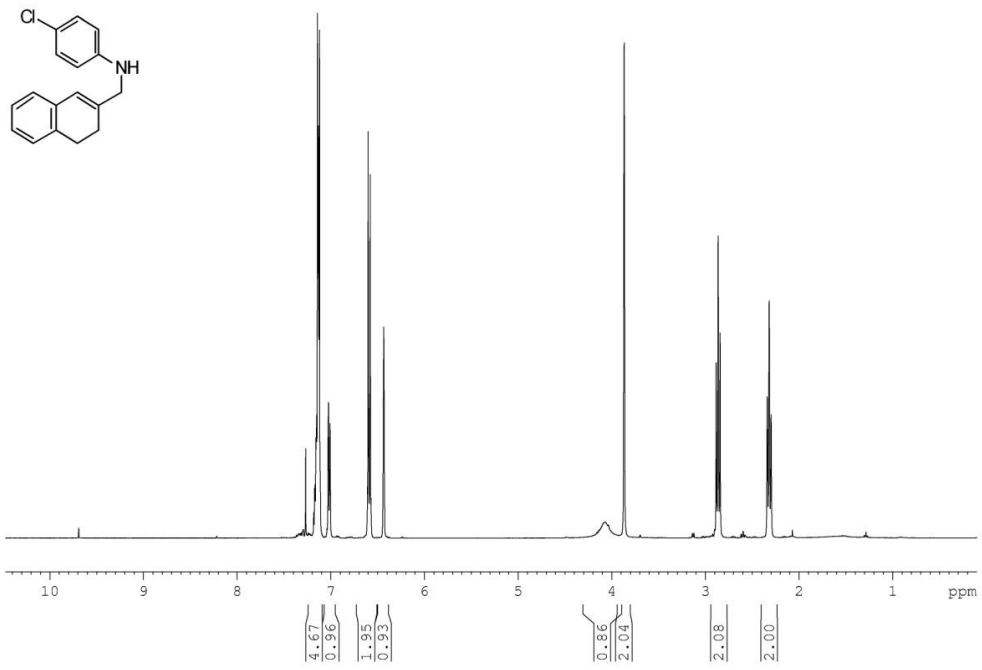

O
O
N
S
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

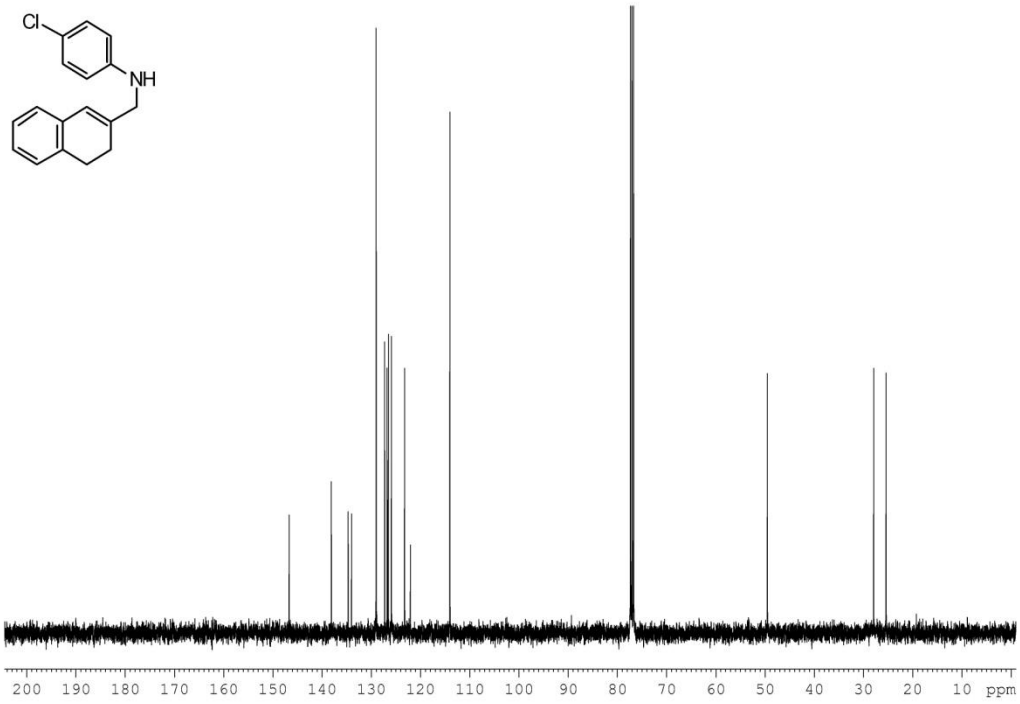

Br
NH
10 9 8 7 6 5 4 3 2 1 ppm
3.22
2.07
1.84
0.94
0.92
0.91
2.08
2.05
2.00

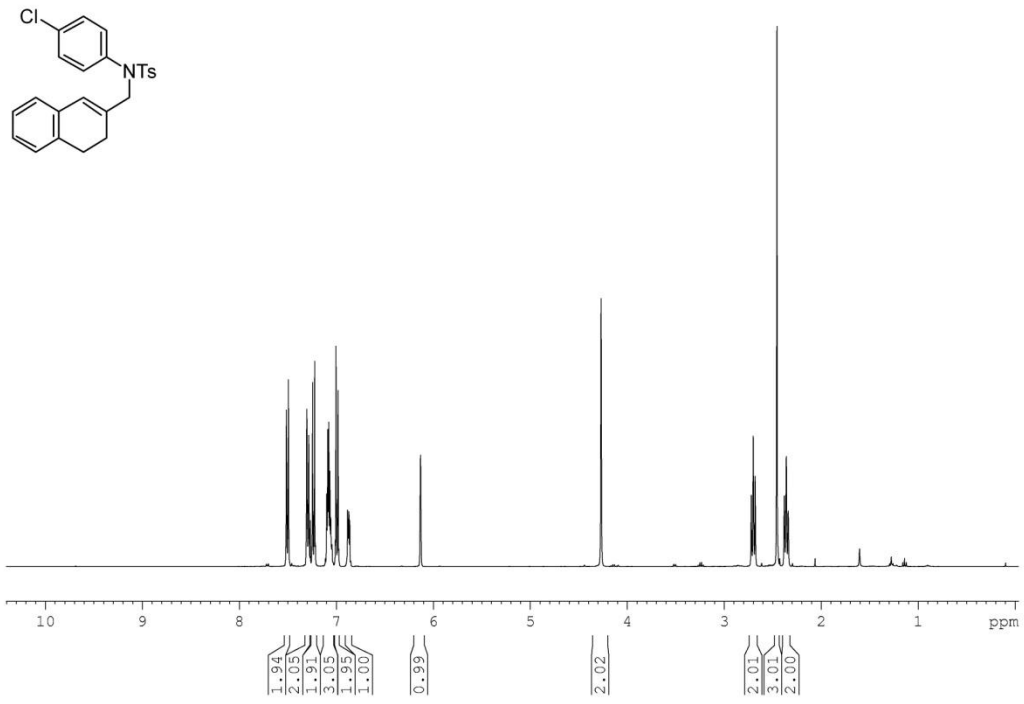

Br
NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

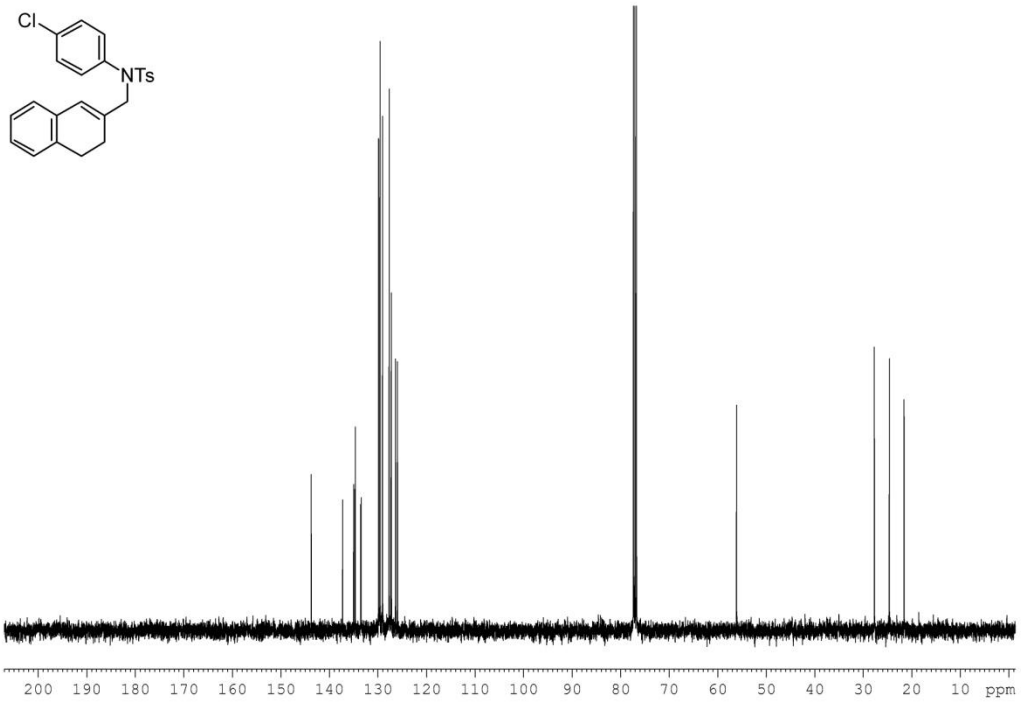

Br
NTs
10 9 8 7 6 5 4 3 2 1 ppm
2.00
1.02
2.14
0.99
1.08
3.12
1.02
0.98
0.97
2.00
2.05
3.02
2.12

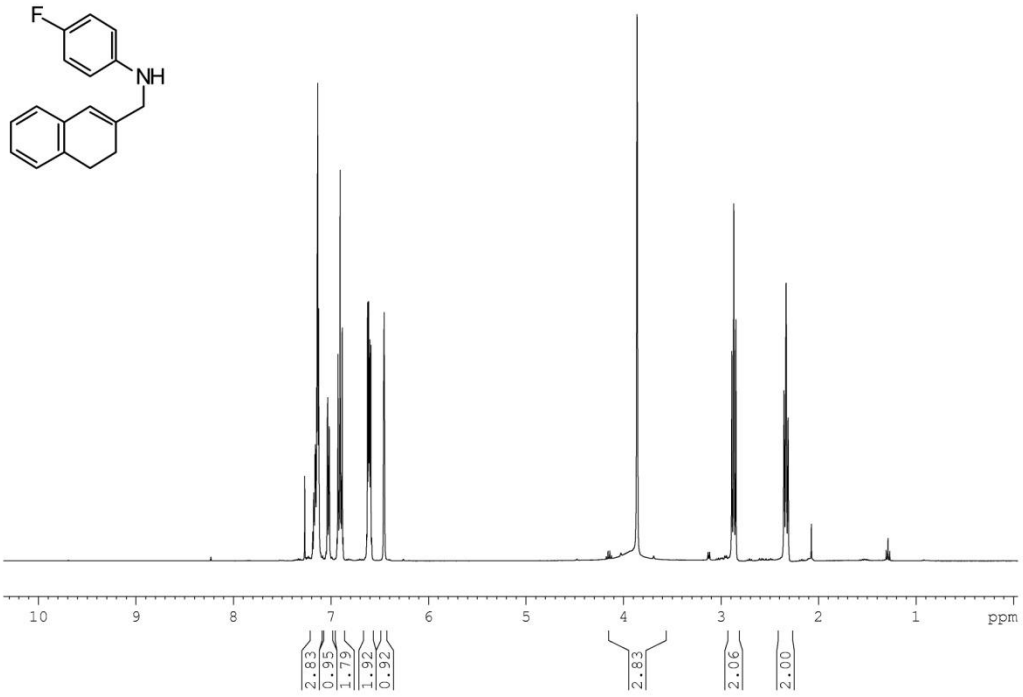

Br
NTs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

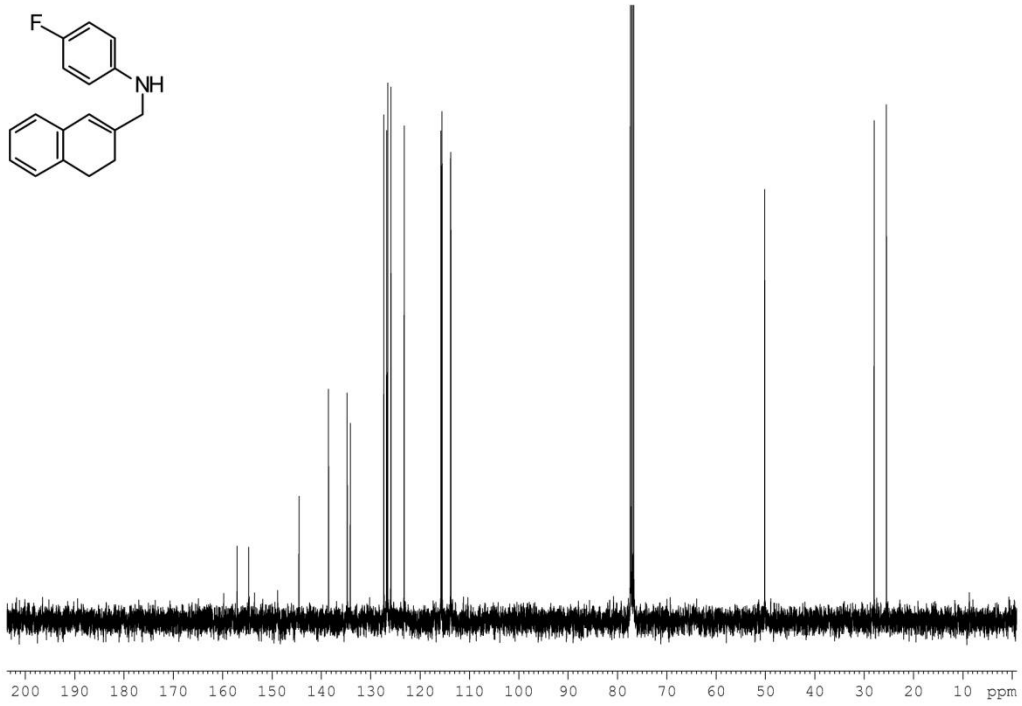

Cl
NH
10 9 8 7 6 5 4 3 2 1 ppm
4.67
0.96
1.95
0.93
0.86
2.04
2.08
2.00

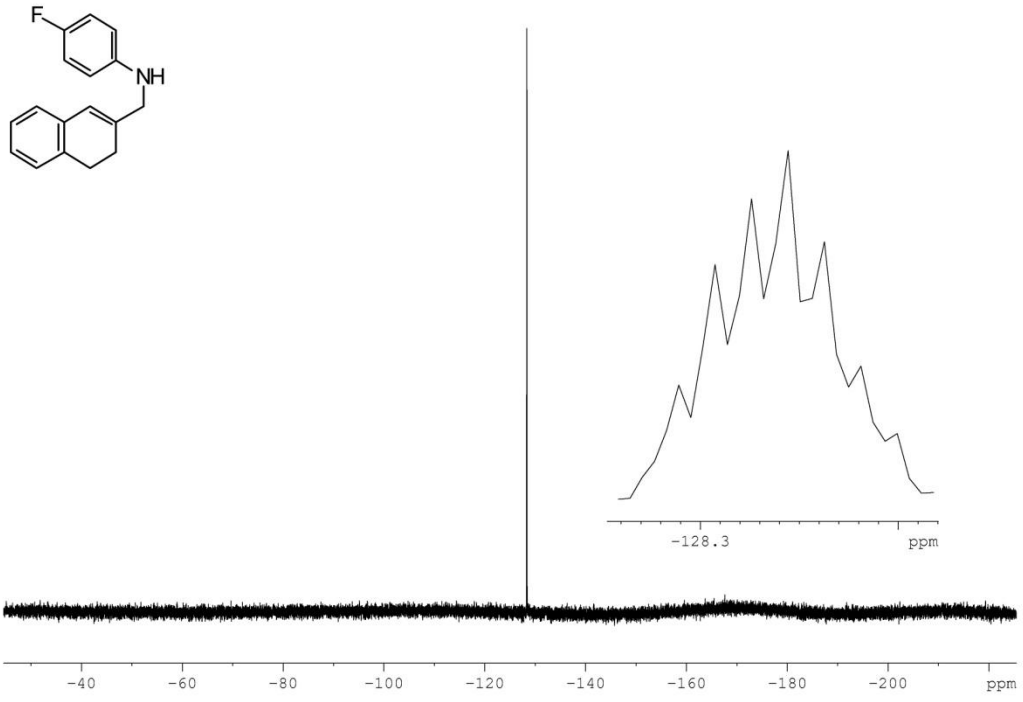

Cl
NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

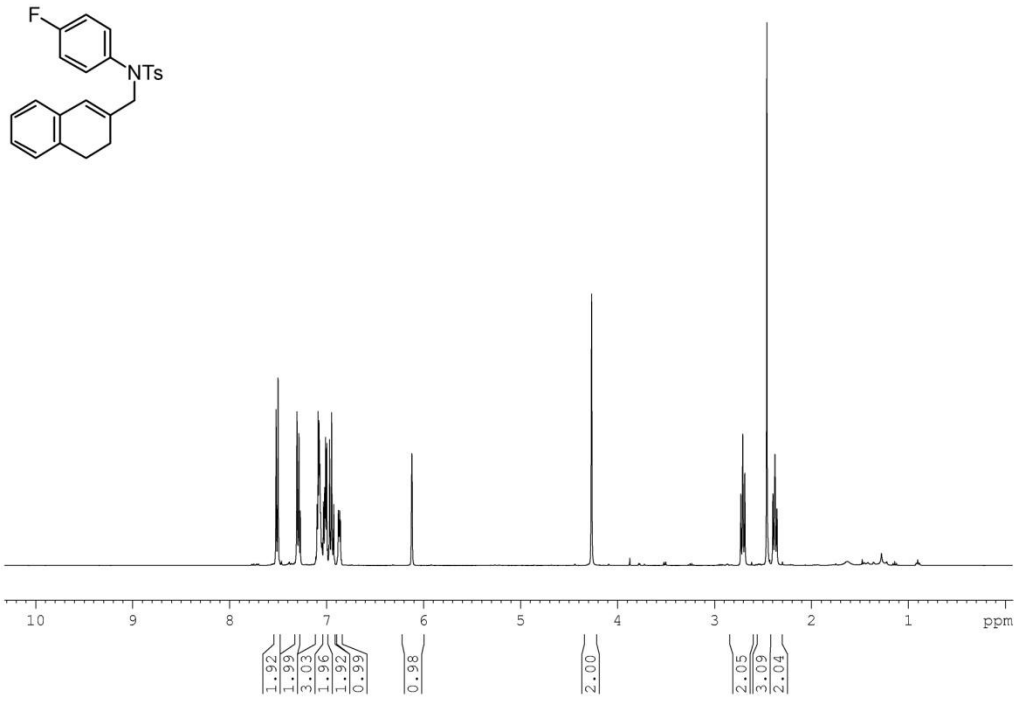

Cl
NTs
10 9 8 7 6 5 4 3 2 1 ppm
1.94
2.05
1.91
3.05
1.95
1.00
0.99
2.02
2.01
3.01
2.00

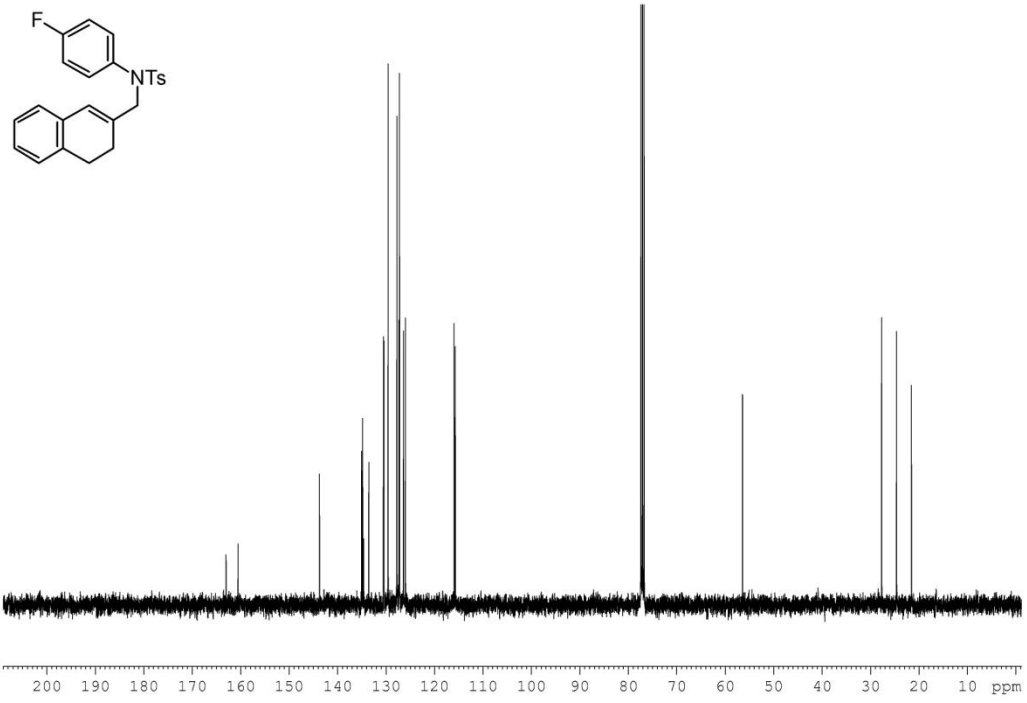

Cl
NTs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

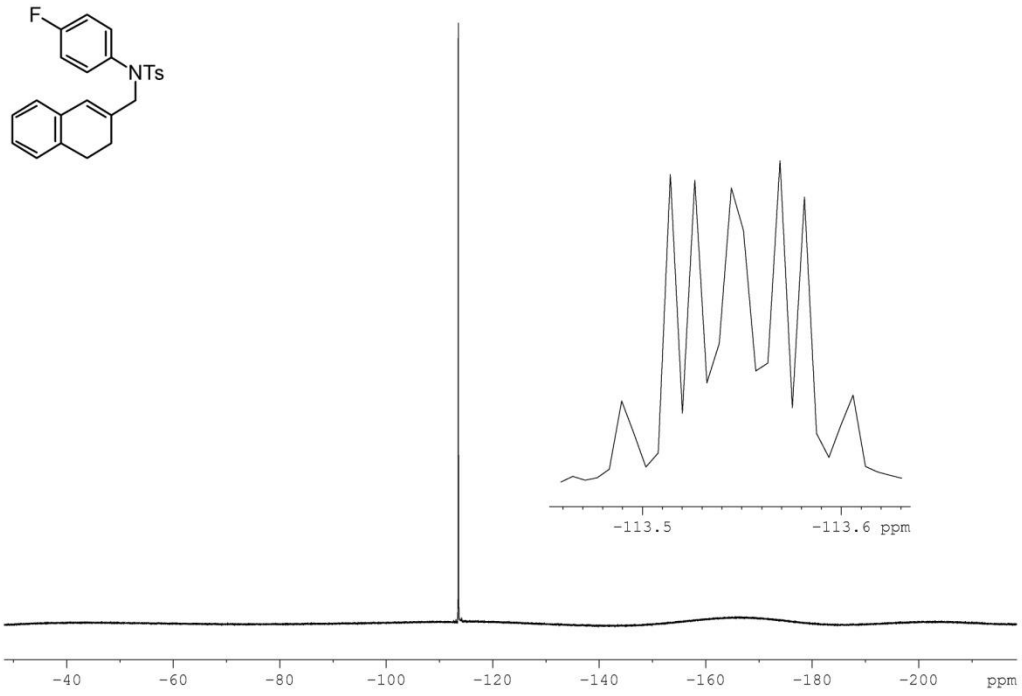

F
NH
10 9 8 7 6 5 4 3 2 1 ppm
2.83
0.95
1.79
1.92
0.92
2.83
2.06
2.00

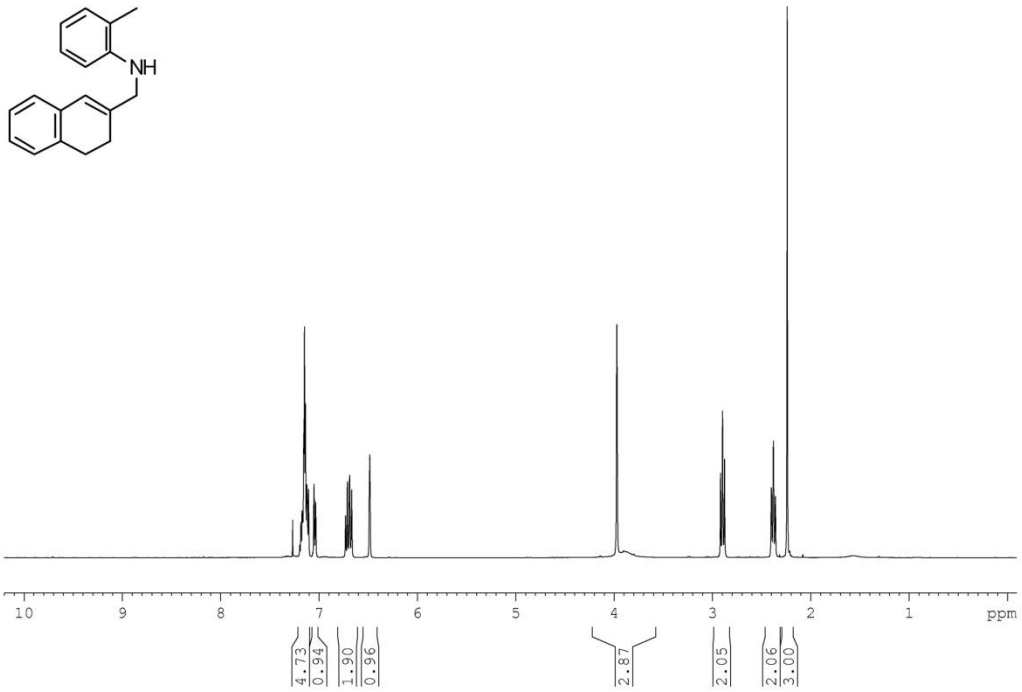

F
NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

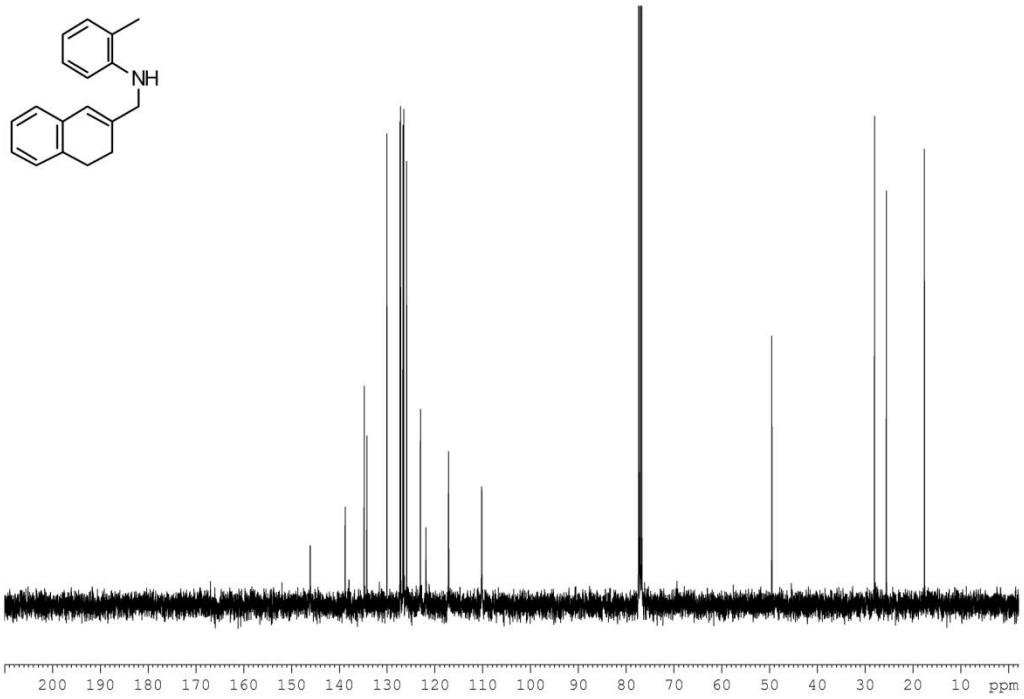

F
NH
-128.3
ppm
-40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

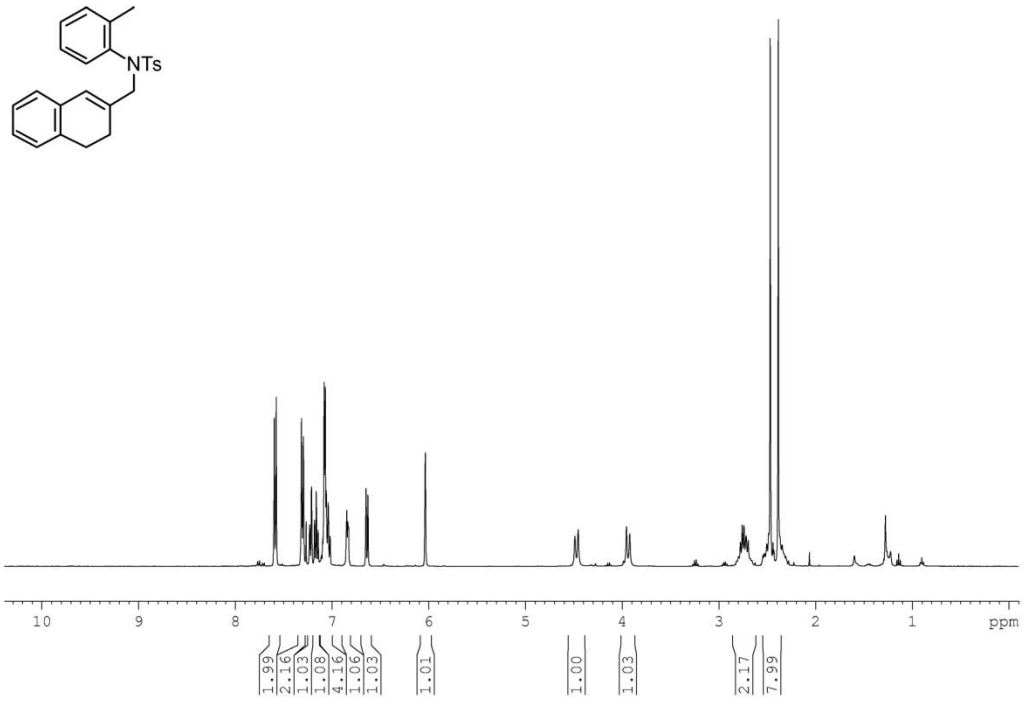

F
NTs
10
9
8
7
6
5
4
3
2
1
ppm
1.92
1.99
3.03
1.96
1.92
0.99
0.98
2.00
2.05
3.09
2.04

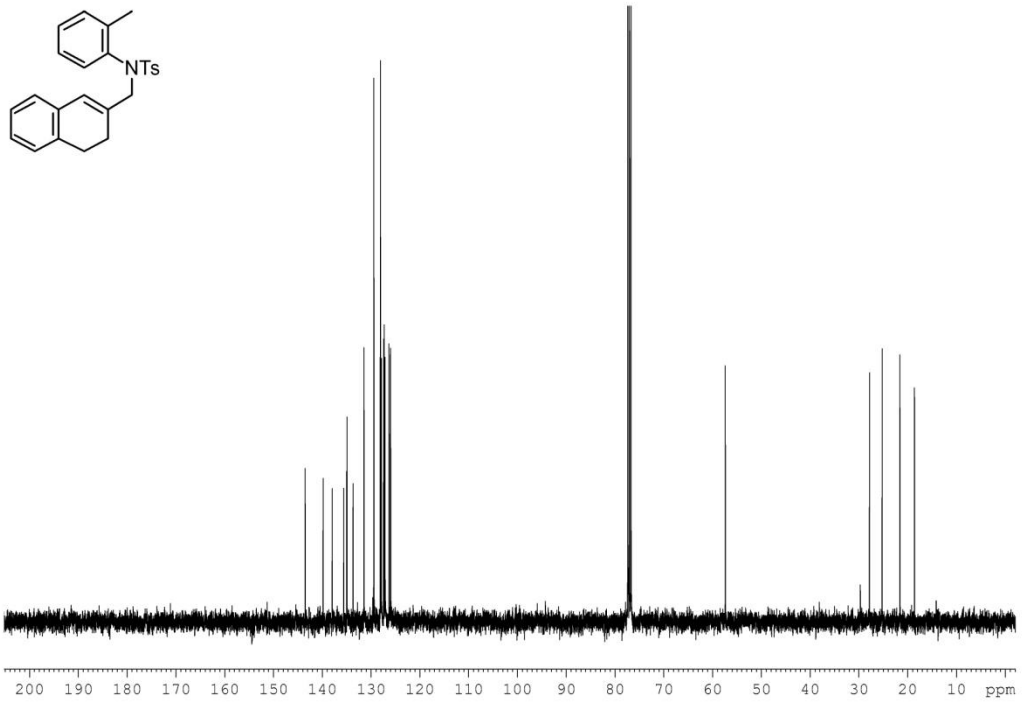

F
NTs
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

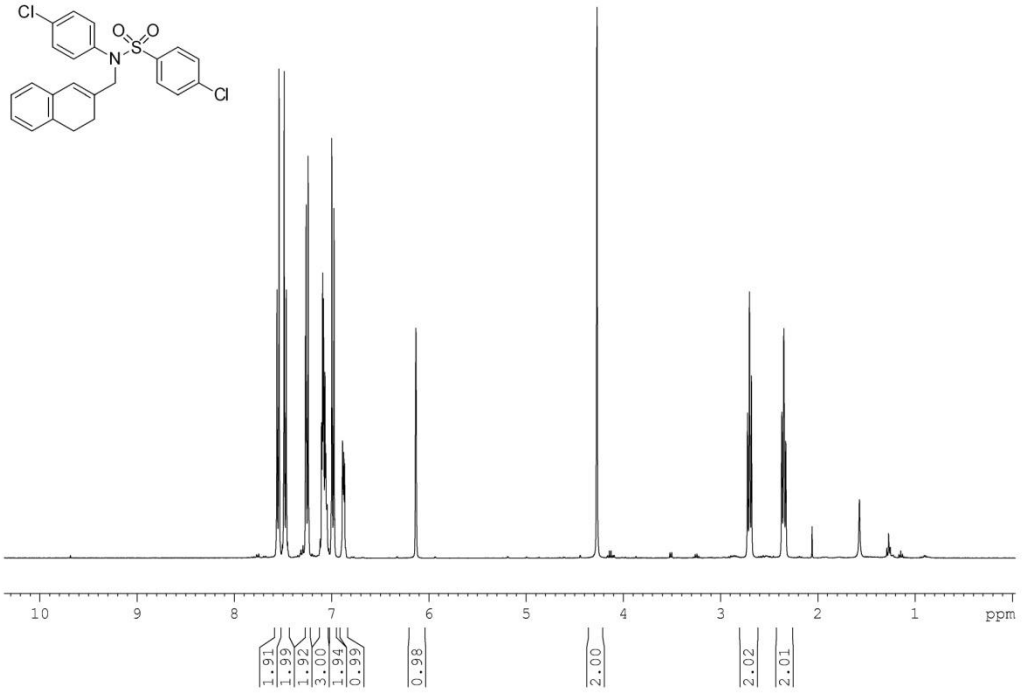

F
NTs
-113.5
-113.6 ppm
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

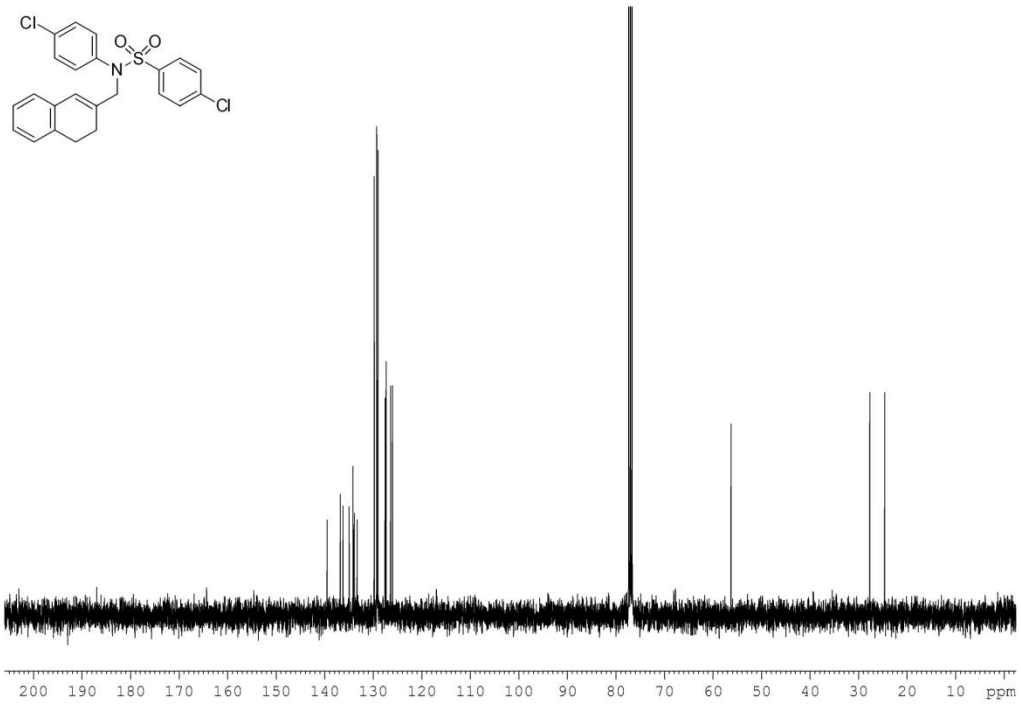

NH
10
9
8
7
6
5
4
3
2
1
ppm
4.73
0.94
1.90
0.96
2.87
2.05
2.06
3.00

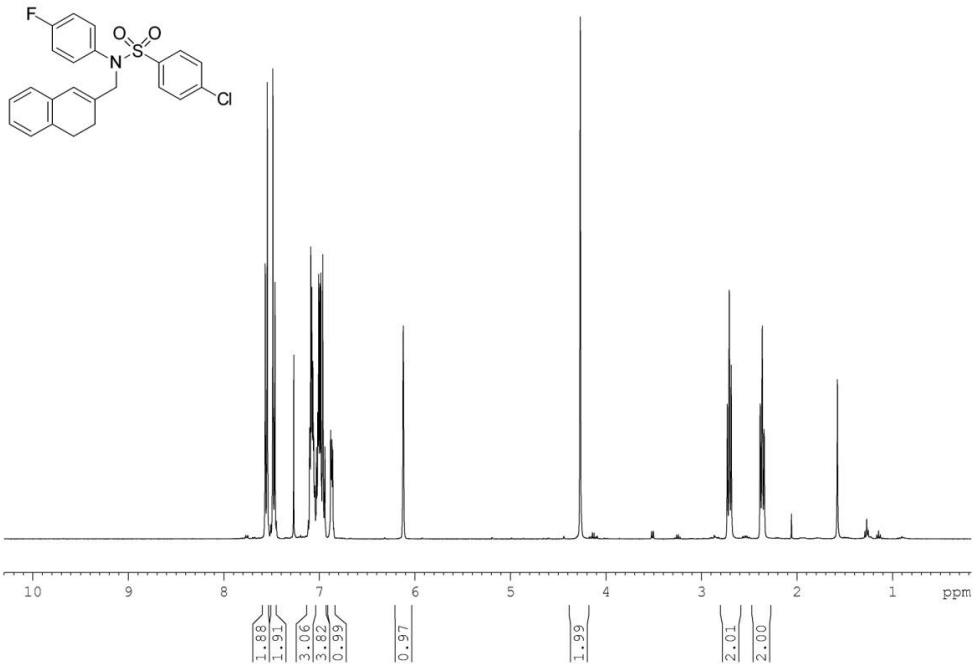

NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

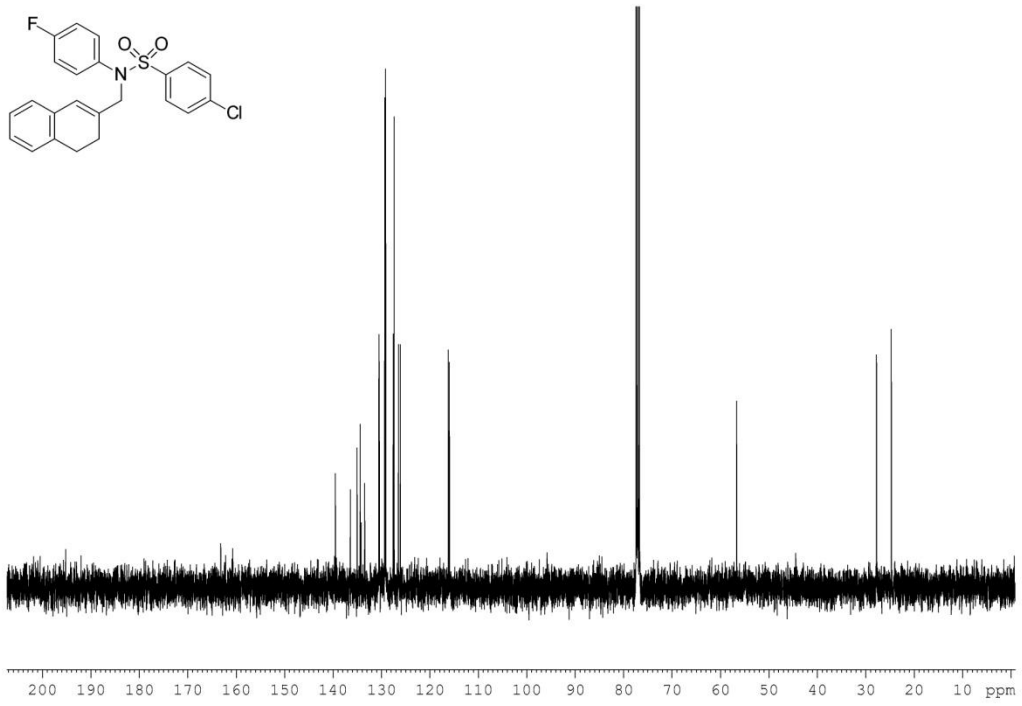

NTs
10 9 8 7 6 5 4 3 2 1 ppm
1.99
2.16
1.03
1.08
4.16
1.06
1.03
1.01
1.00
1.03
2.17
7.99

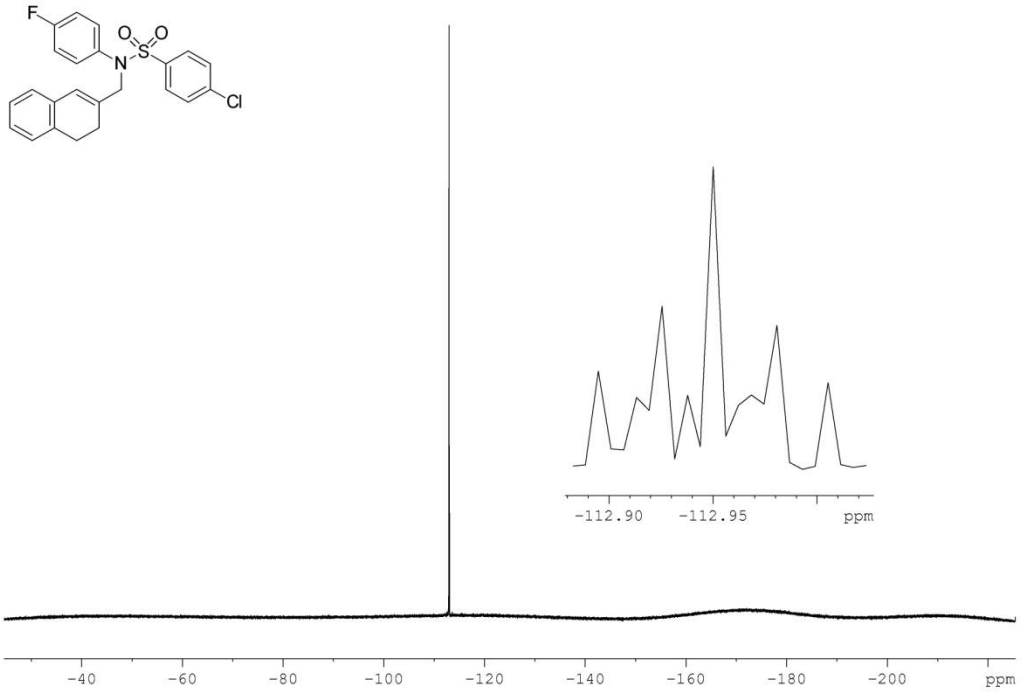

NTs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

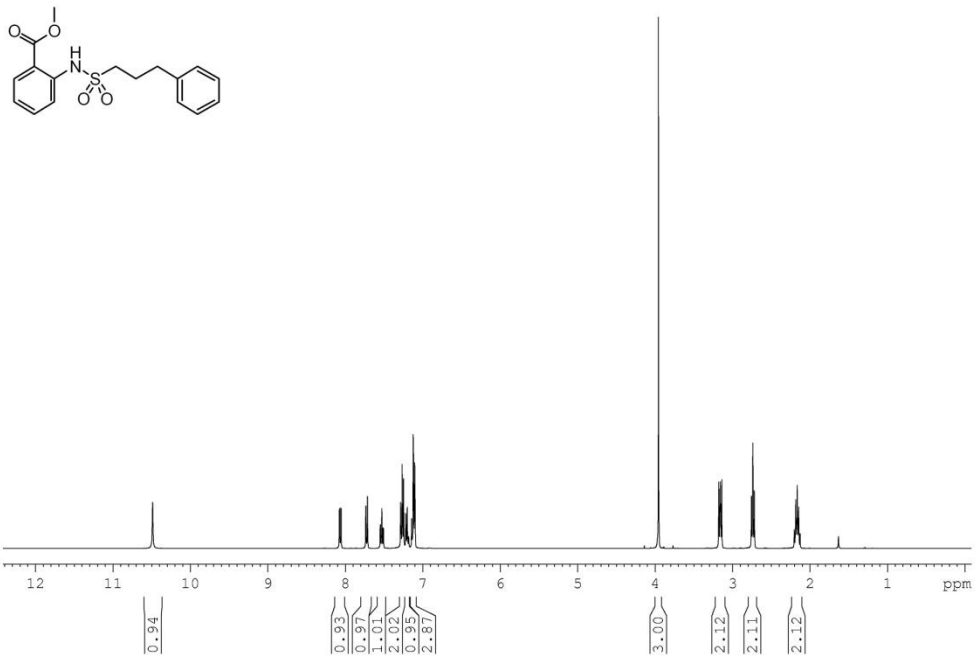

Cl
O
O
N
S
Cl
10 9 8 7 6 5 4 3 2 1 ppm
1.91
1.99
1.92
3.00
1.94
0.99
0.98
2.00
2.02
2.01

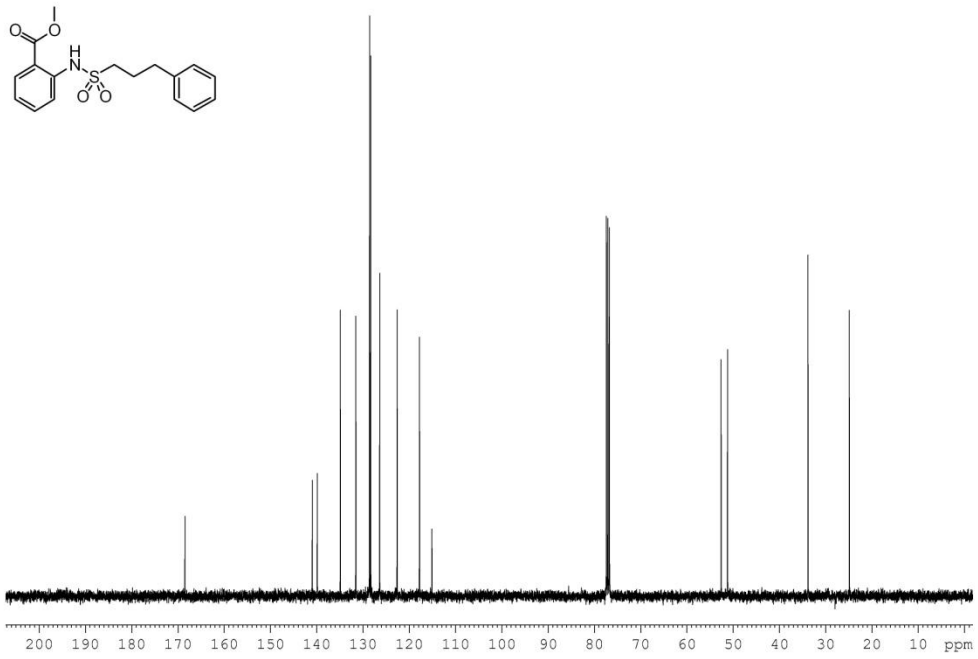

Cl
O
S
O
N
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

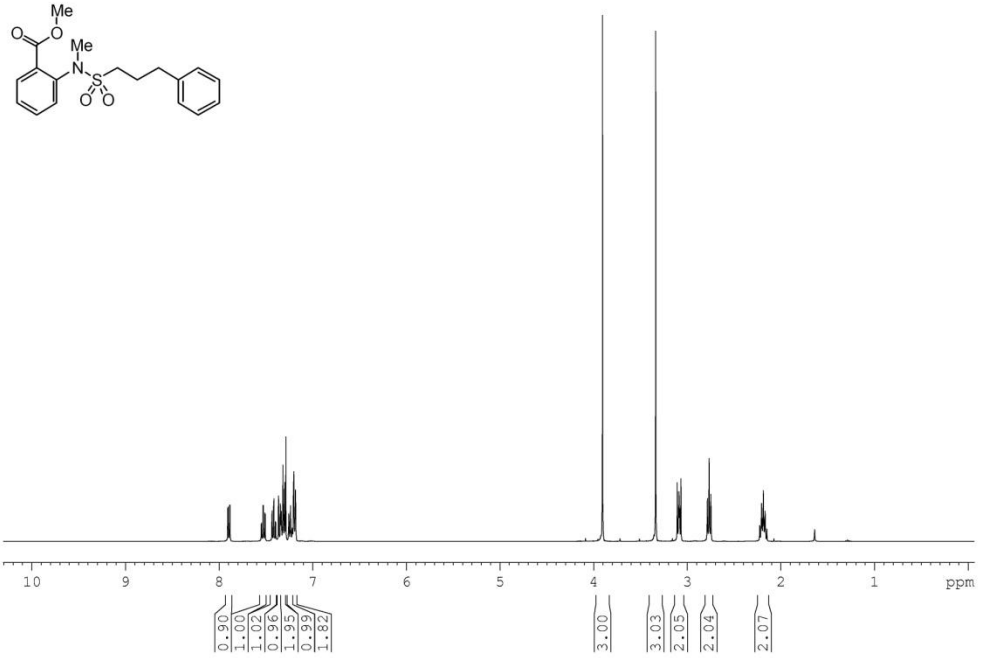

F
O
S
O
N
Cl
10 9 8 7 6 5 4 3 2 1 ppm
1.88
1.91
3.06
3.82
0.99
0.97
1.99
2.01
2.00

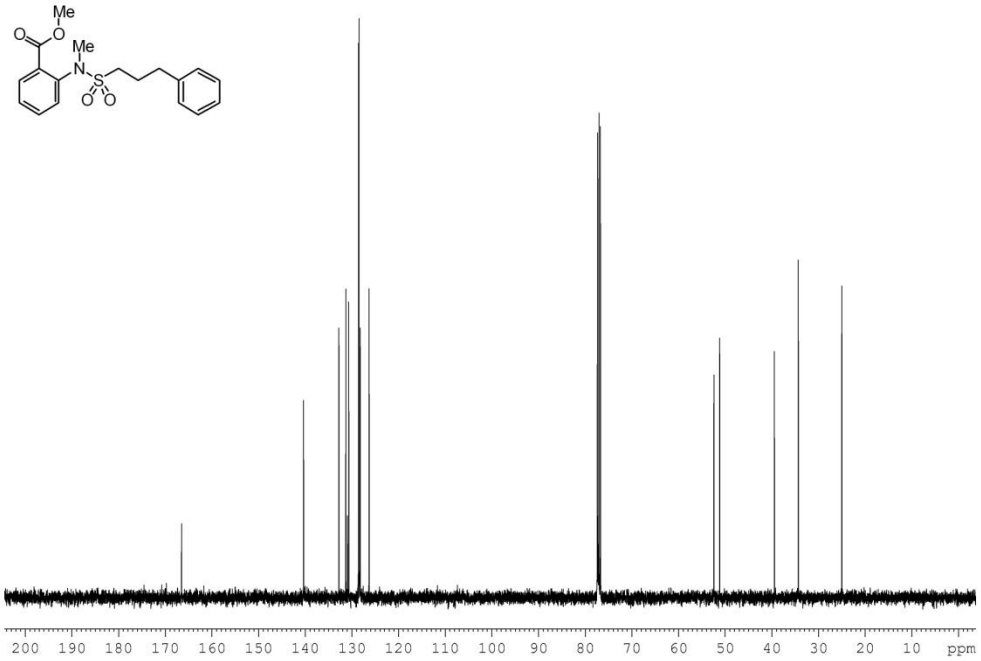

F
O
O
N
S
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

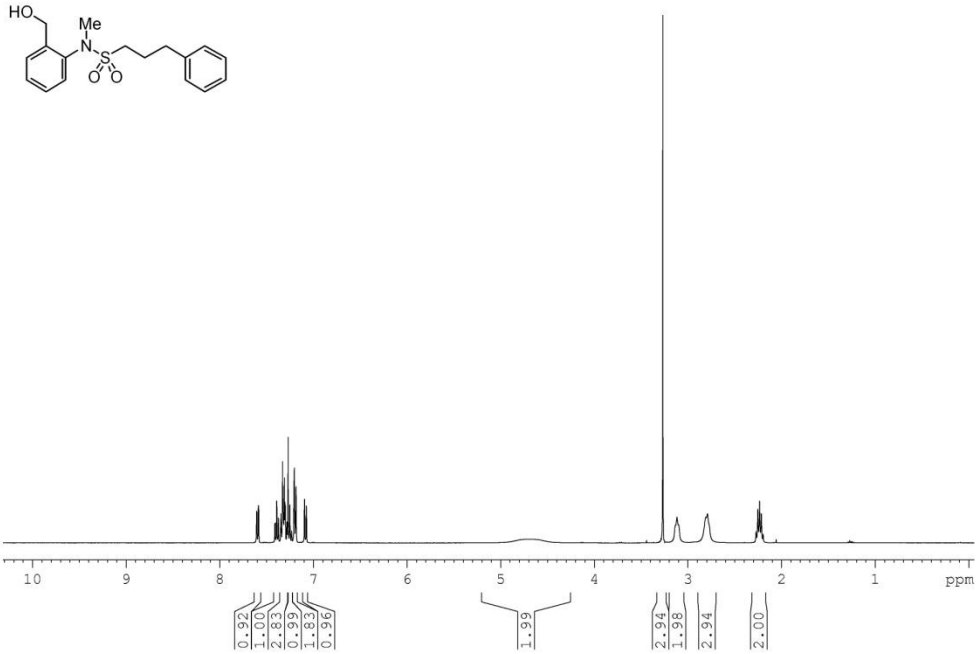

F
O
O
N
S
Cl
-112.90
-112.95
ppm
-40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

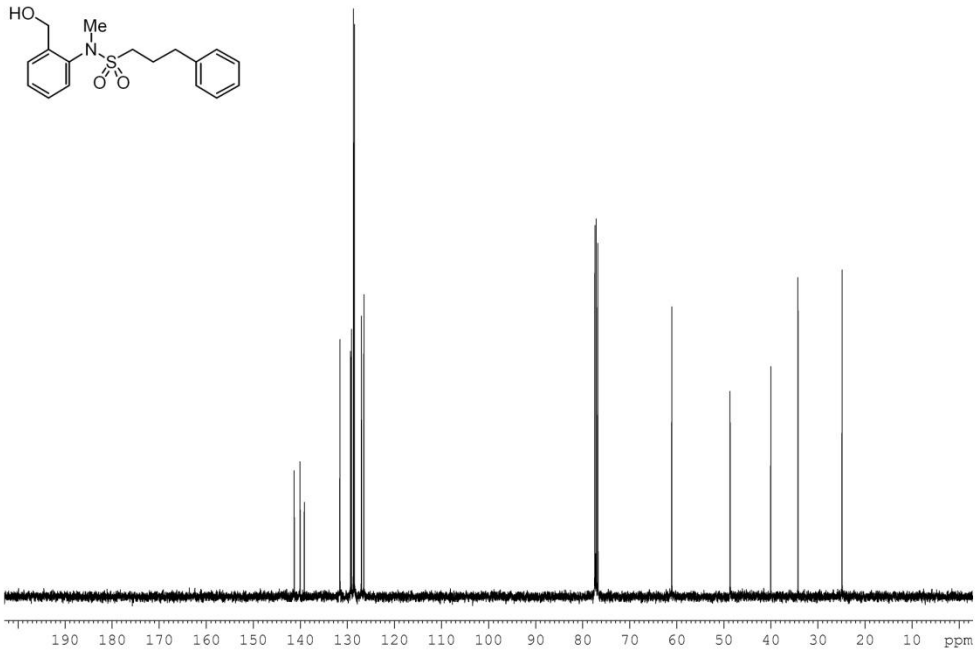

12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.94
0.93
0.97
1.01
2.02
0.95
2.87
3.00
2.12
2.11
2.12

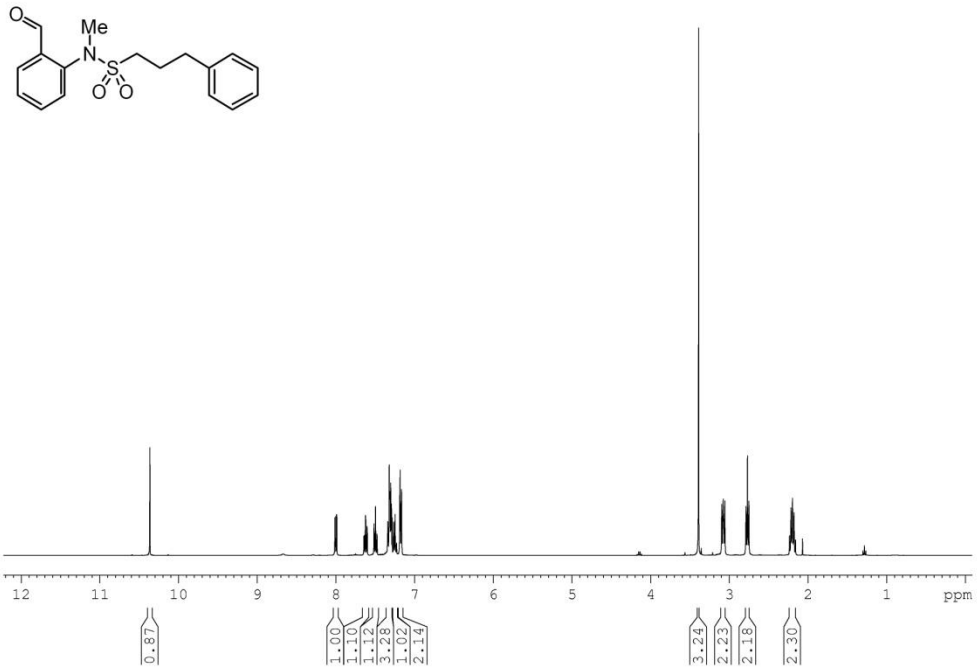

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

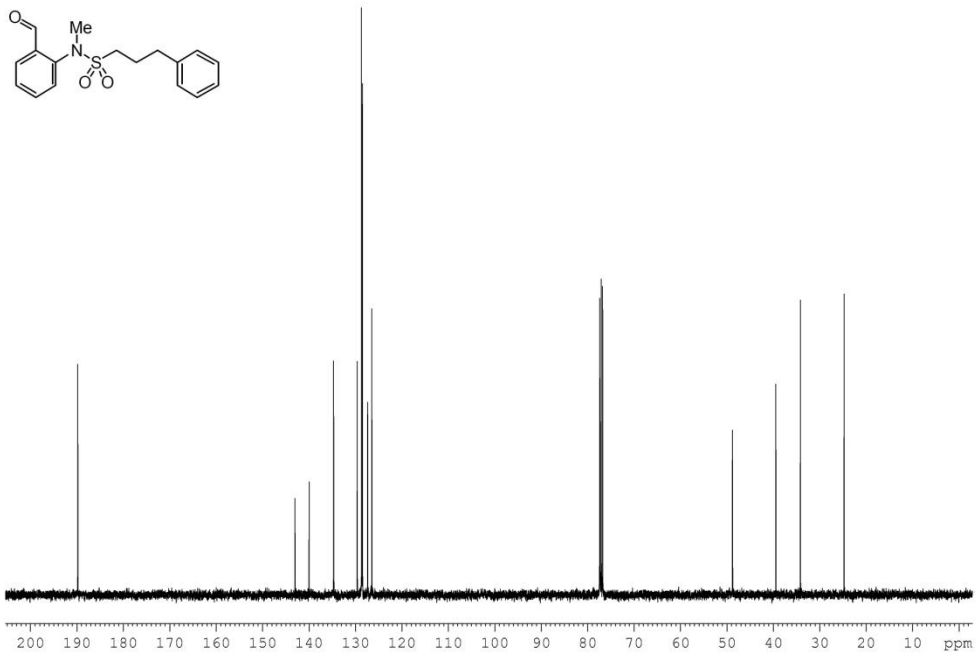

Me
O
O
Me
N
S
O
O
10
9
8
7
6
5
4
3
2
1
ppm
0.90
1.00
1.02
0.96
1.95
0.99
1.82
3.00
3.03
2.05
2.04
2.07

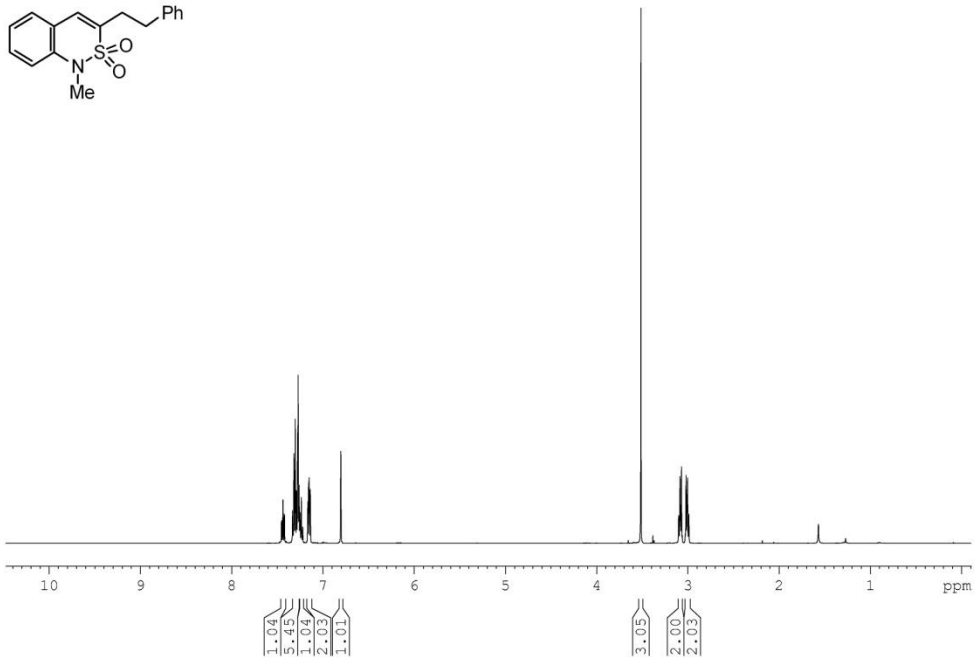

Me
O
O
Me
N
S
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

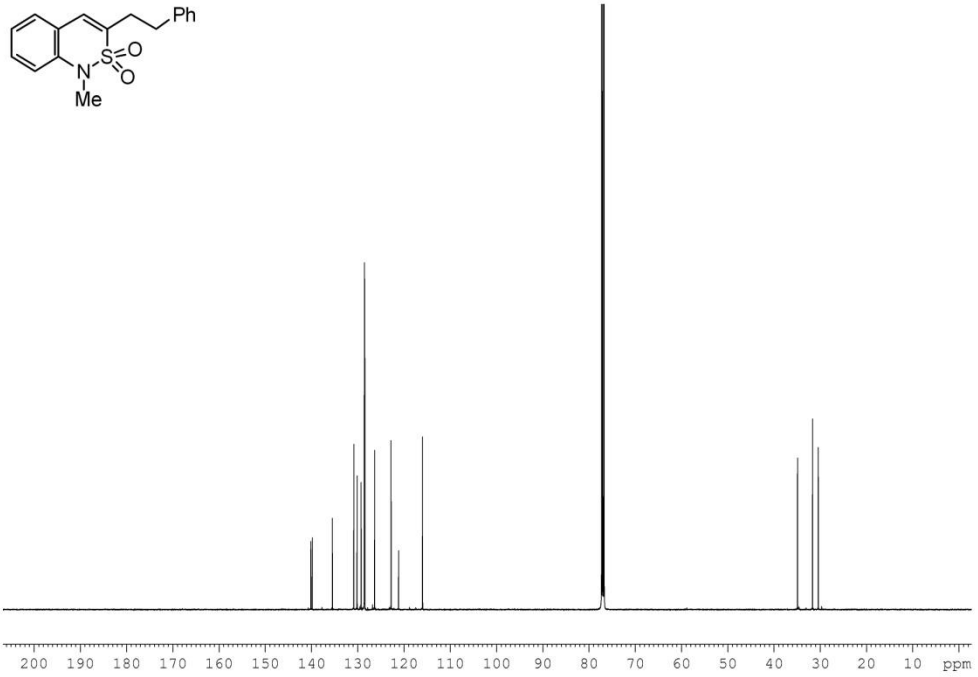

HO
Me
N
S
O
O
10
9
8
7
6
5
4
3
2
1
ppm
0.92
1.00
2.83
0.99
1.83
0.96
1.99
2.94
1.98
2.94
2.00

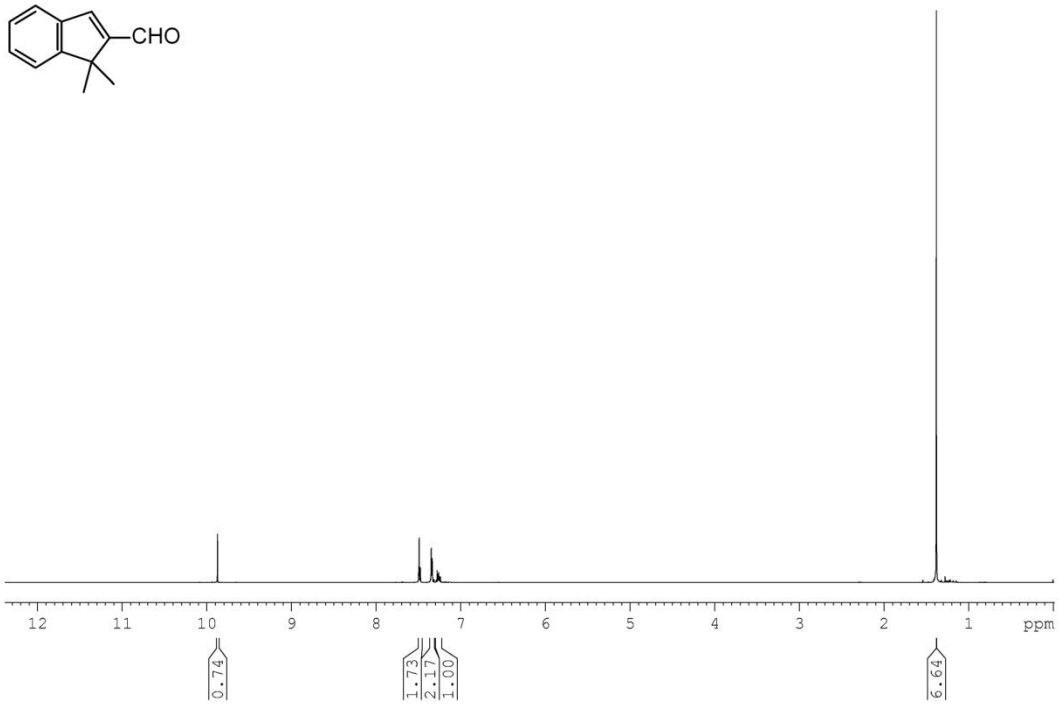

HO
Me
N
S
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

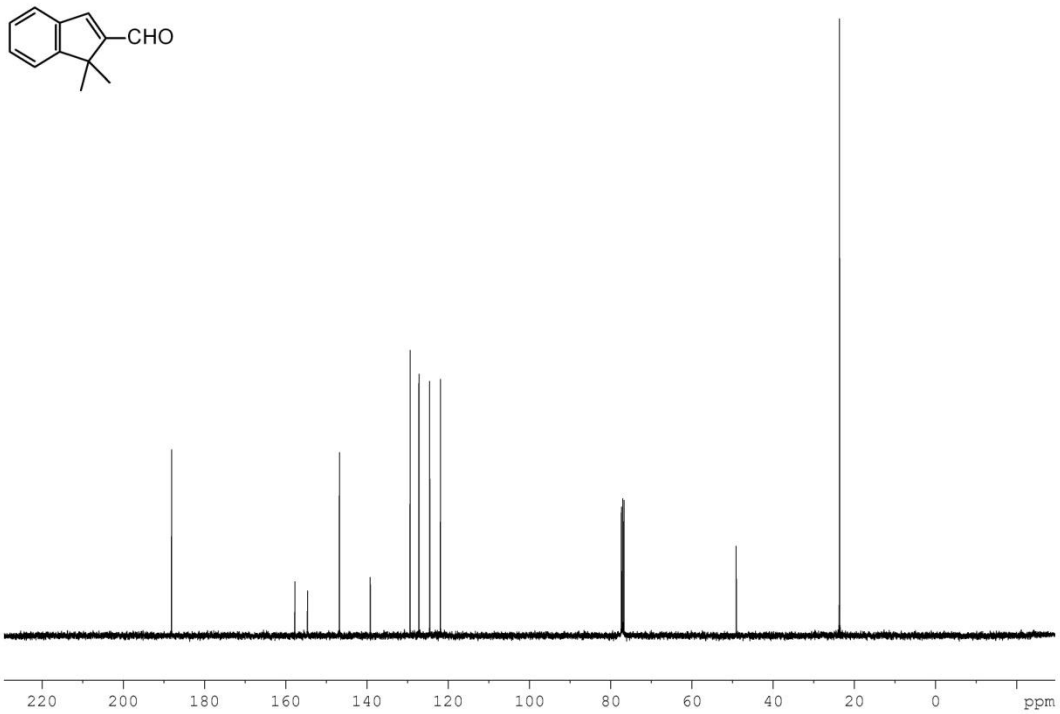

O
Me
N
S
O
O
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.87
1.00
1.10
1.12
3.28
1.02
2.14
3.24
2.23
2.18
2.30

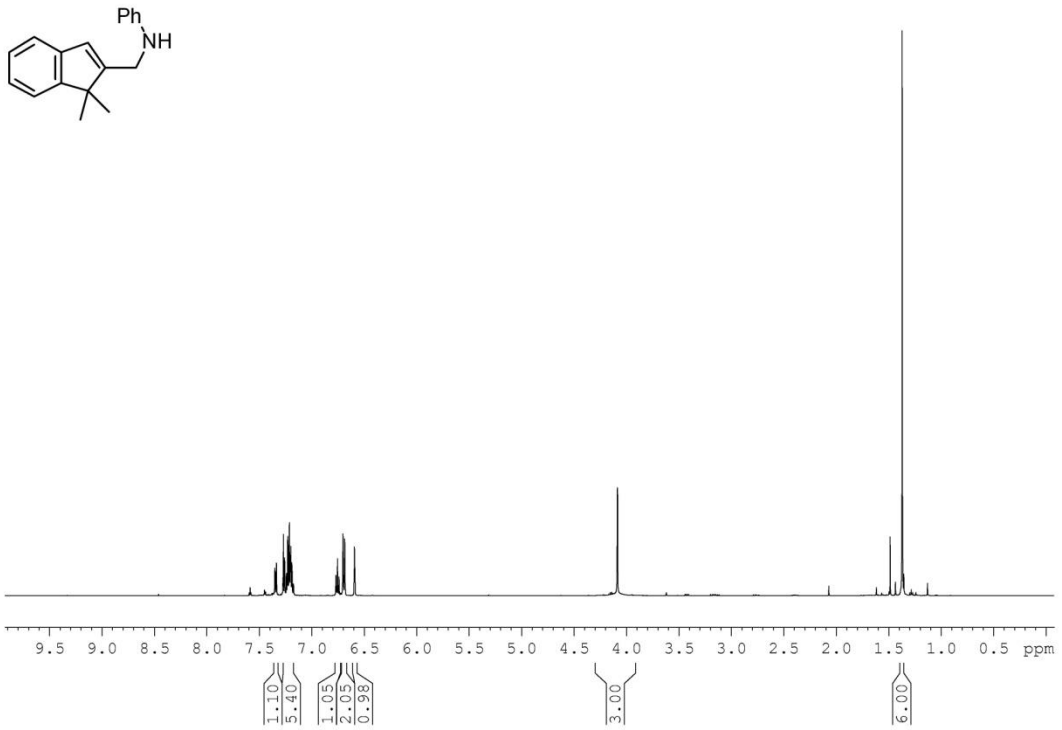

O
Me
N
S
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

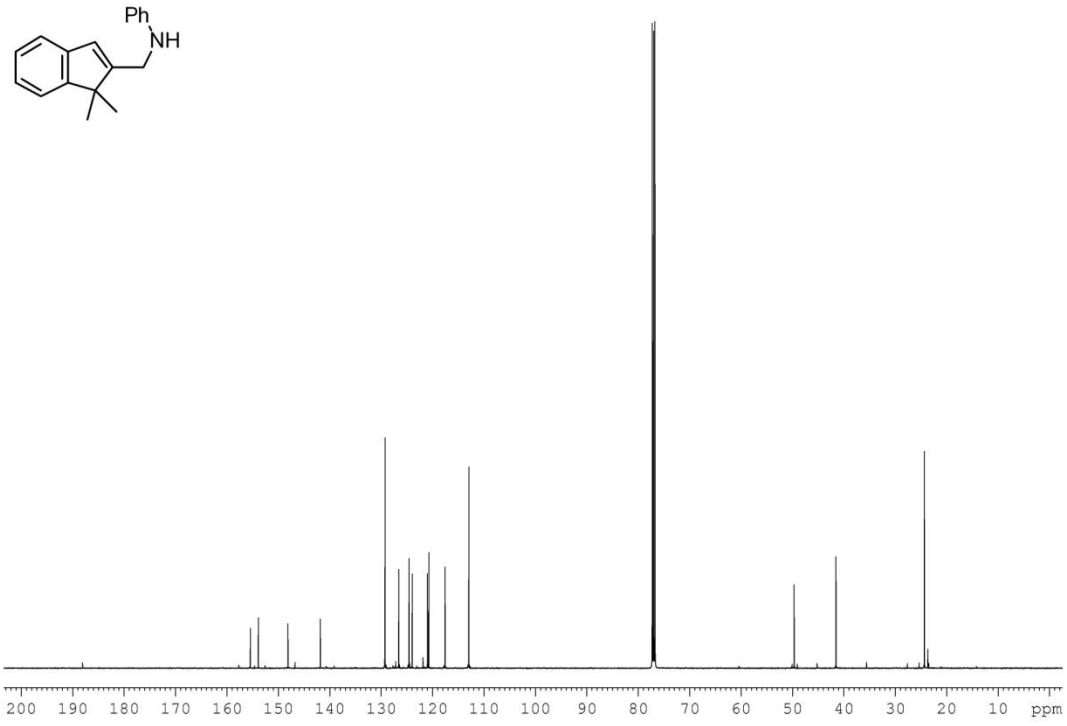

Ph
O
S
O
N
Me
10
9
8
7
6
5
4
3
2
1
ppm
1.04
5.45
1.04
2.03
1.01
3.05
2.00
2.03

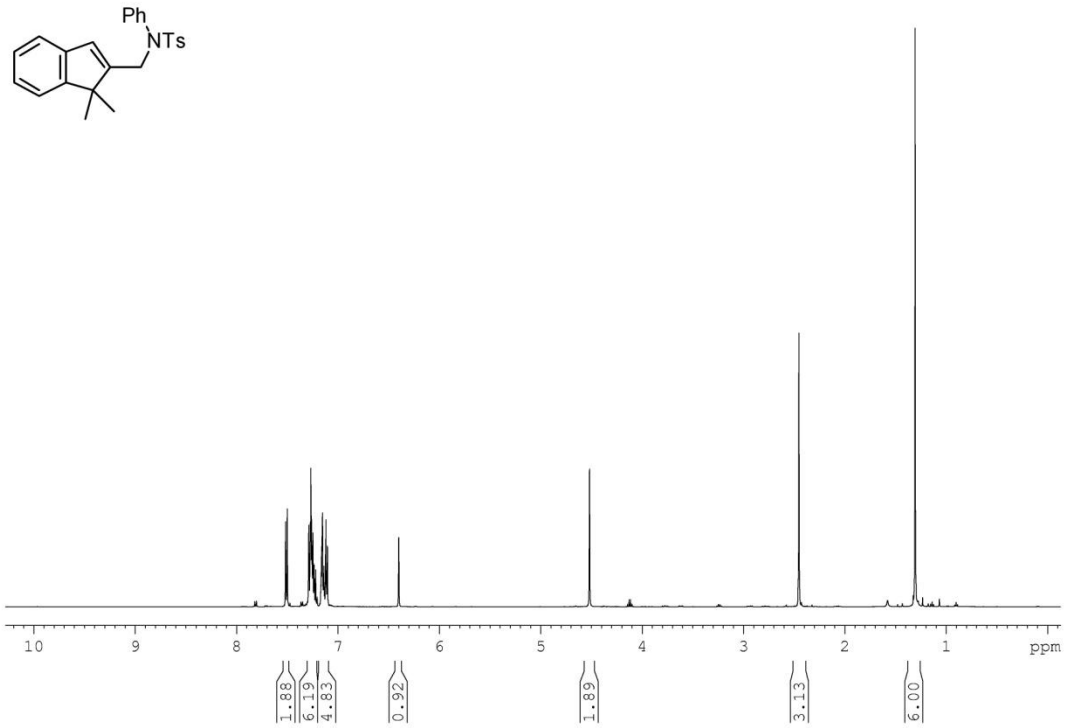

Ph
O
S
O
N
Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

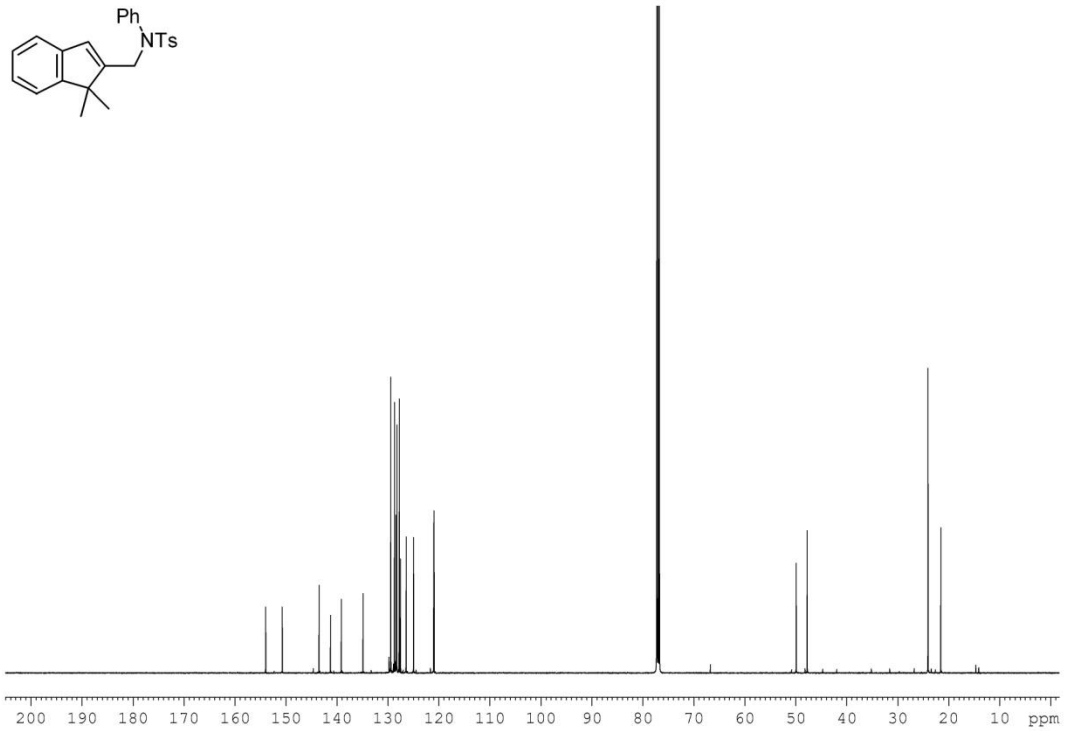

CHO
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.74
1.73
2.17
1.00
6.64

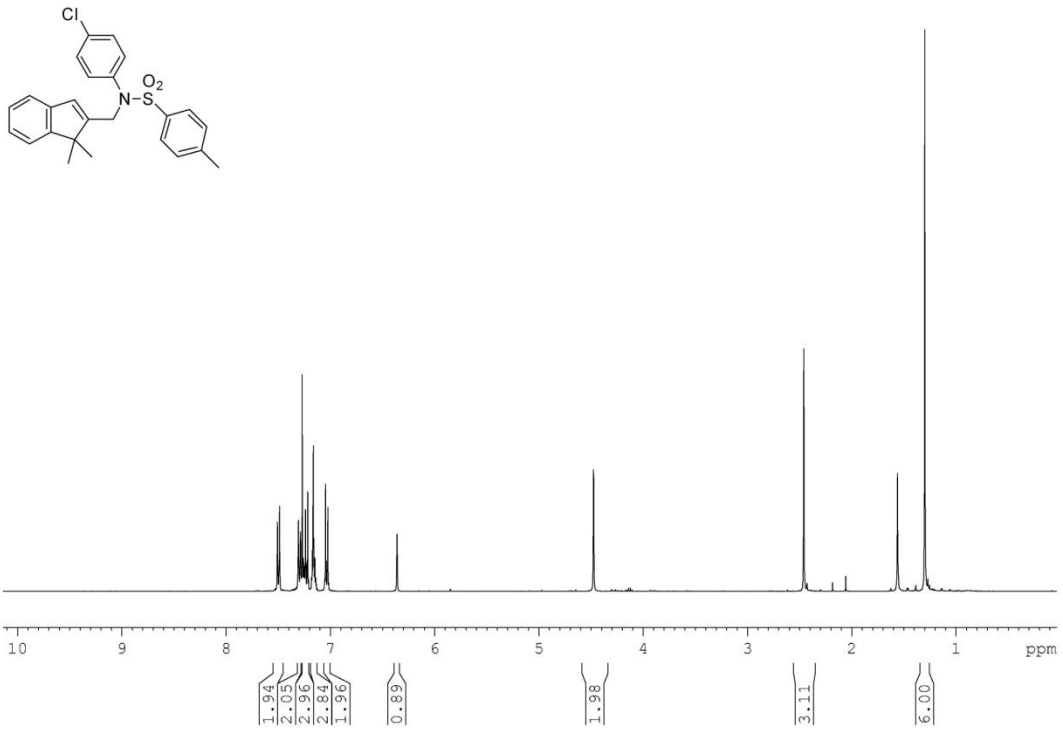

CHO
220
200
180
160
140
120
100
80
60
40
20
0
ppm

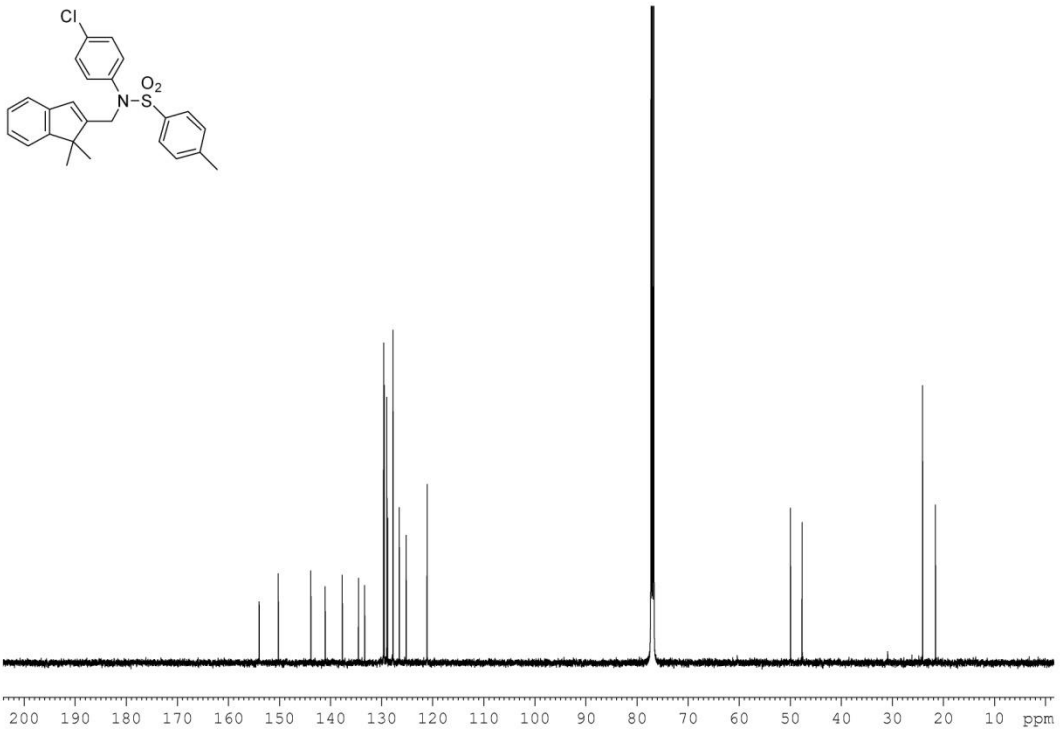

Ph
NH
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.10
5.40
1.05
2.05
0.98
3.00
6.00

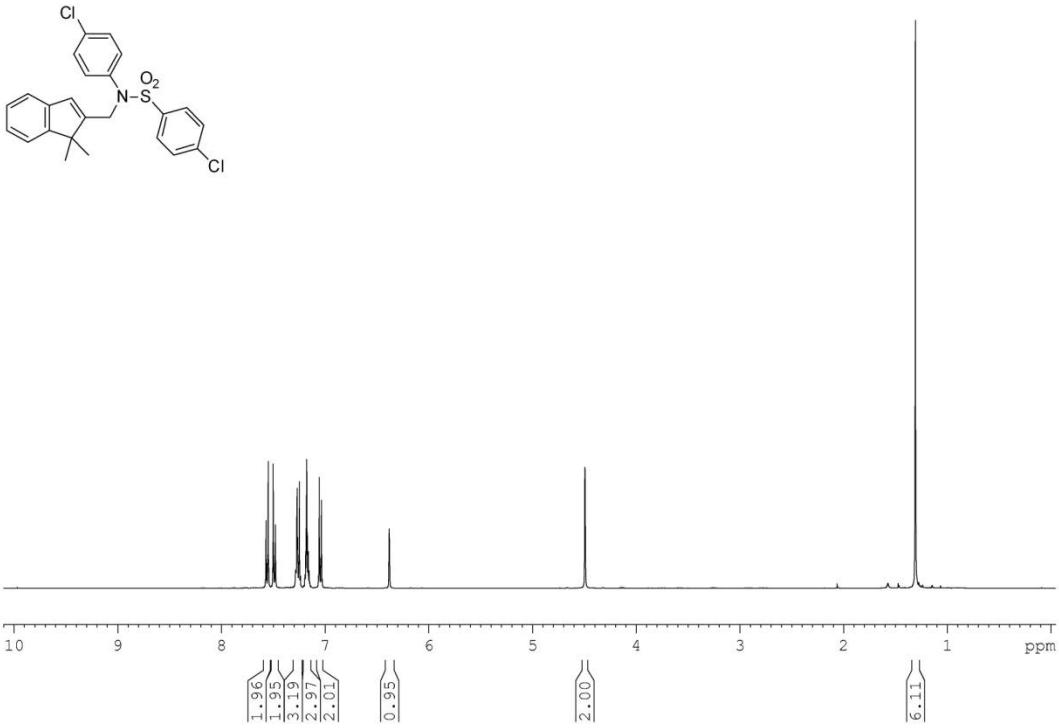

Ph
NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

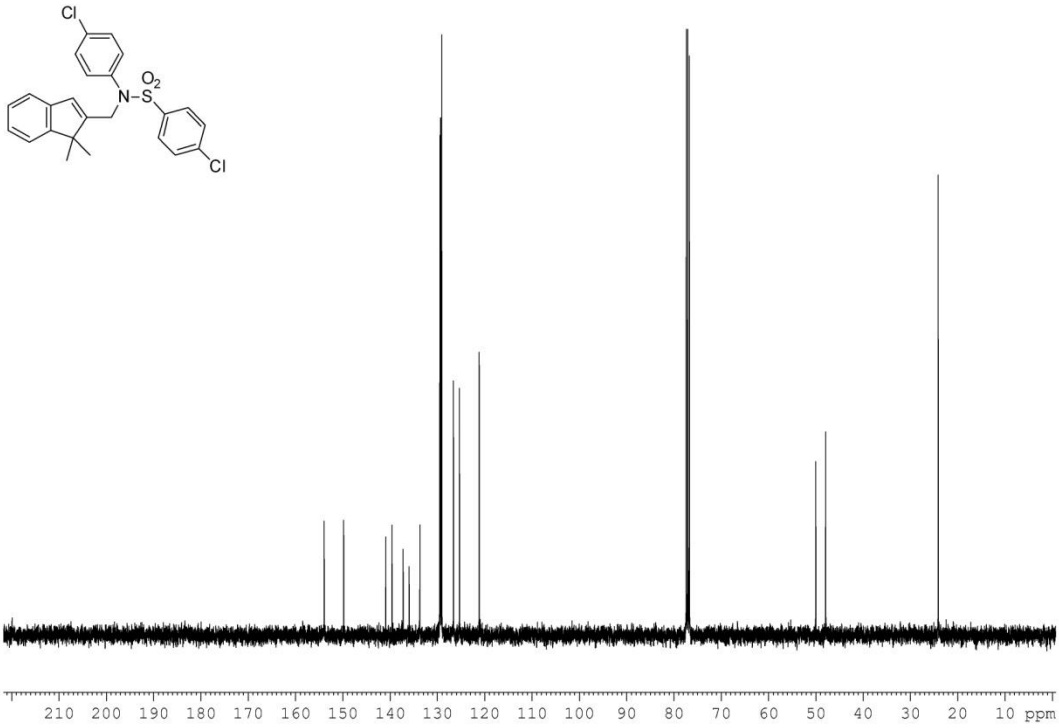

Ph
NTs
10
9
8
7
6
5
4
3
2
1
ppm
1.88
6.19
4.83
0.92
1.89
3.13
6.00

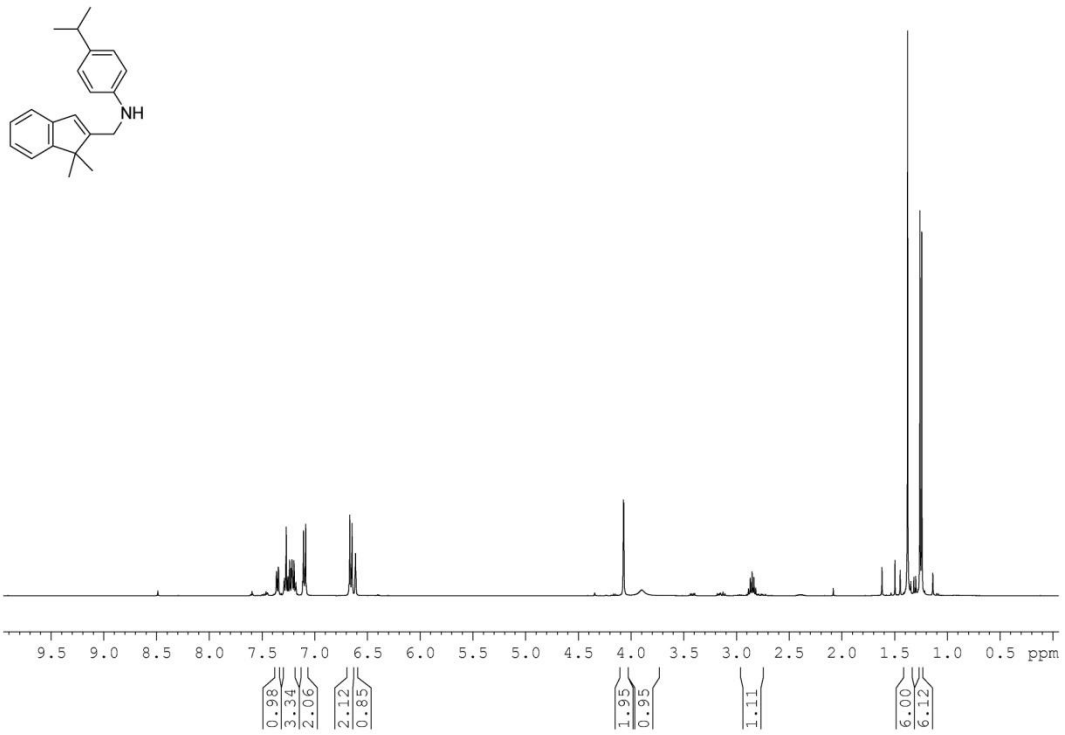

Ph
NTs
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

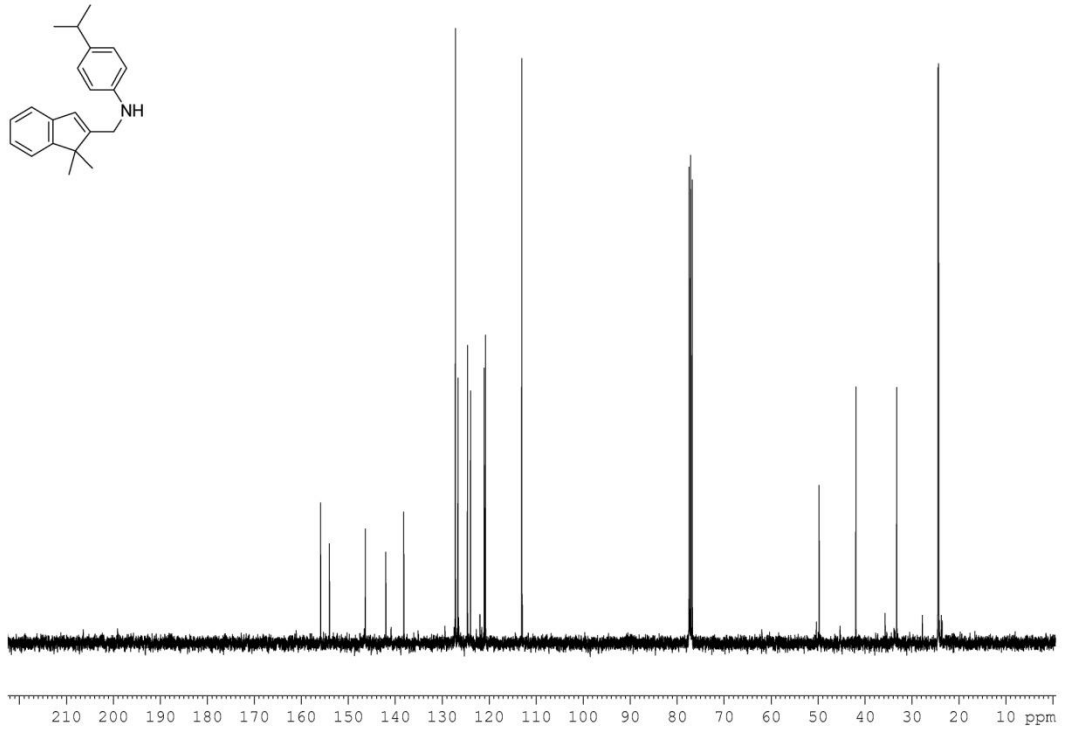

Cl
O2
N-S
10
9
8
7
6
5
4
3
2
1
ppm
1.94
2.05
2.96
2.84
1.96
0.89
1.98
3.11
6.00

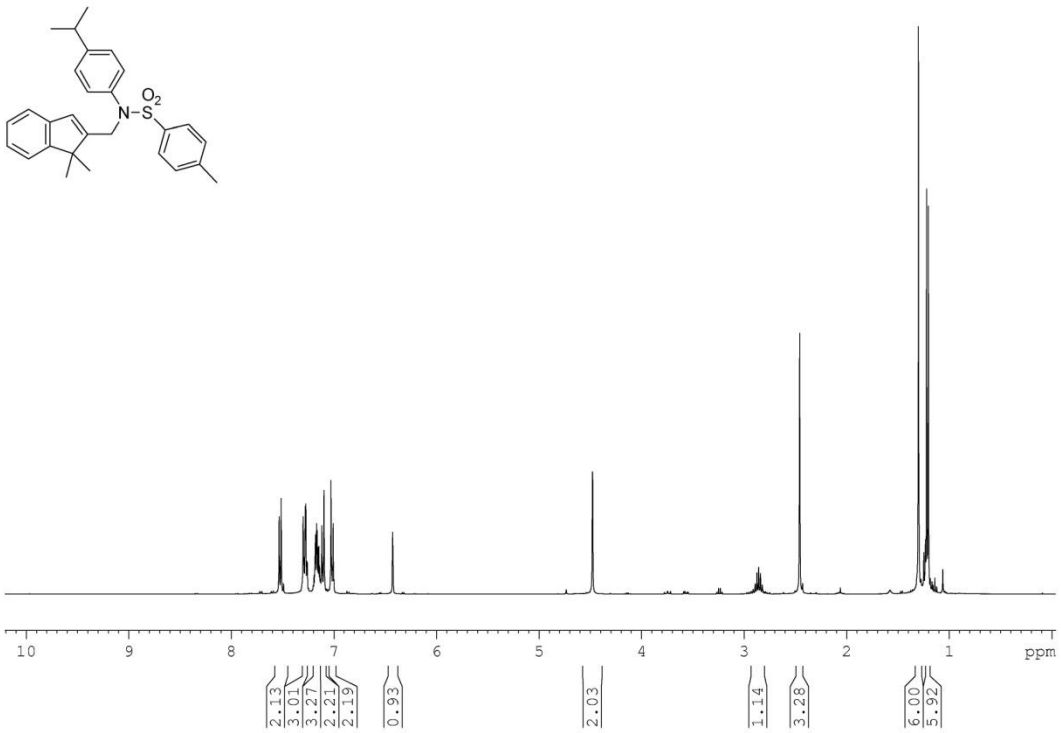

Cl
O2
N-S
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

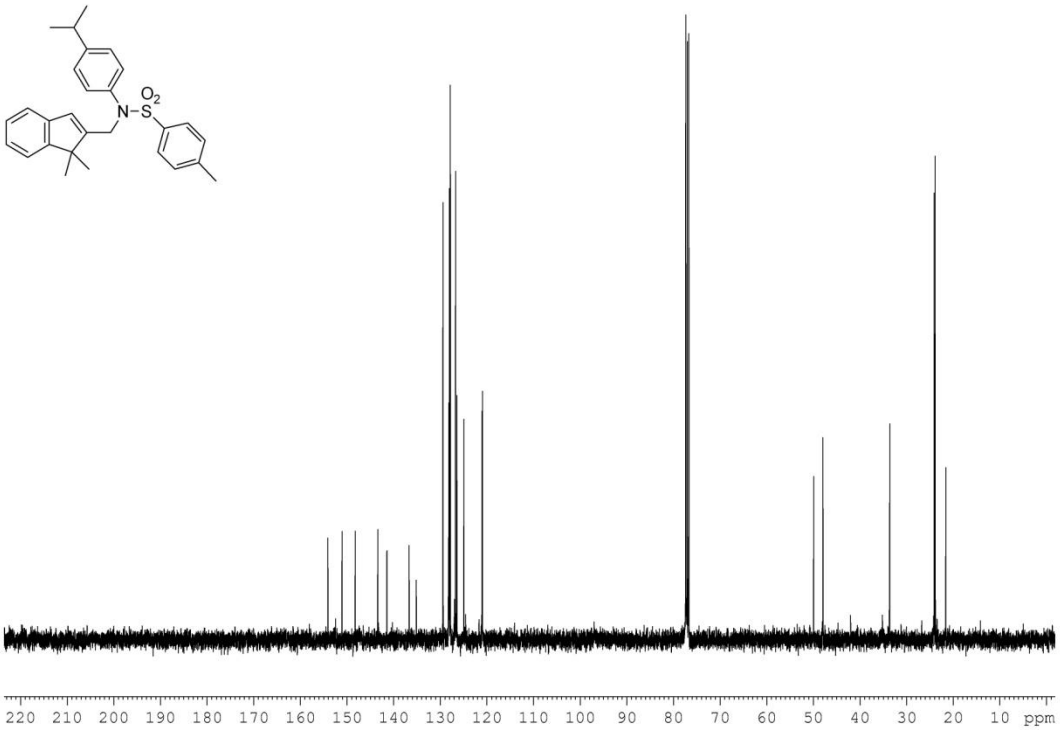

Cl
N
S
O2
Cl
10
9
8
7
6
5
4
3
2
1
ppm
1.96
1.95
3.19
2.97
2.01
0.95
2.00
6.11

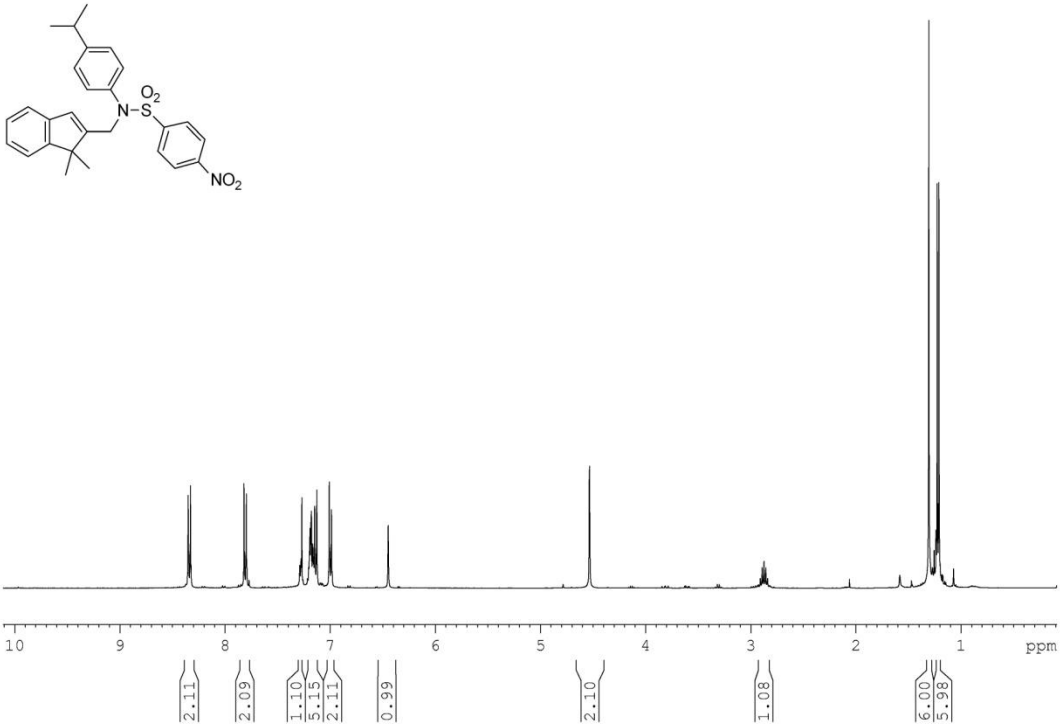

Cl
N
S
O2
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

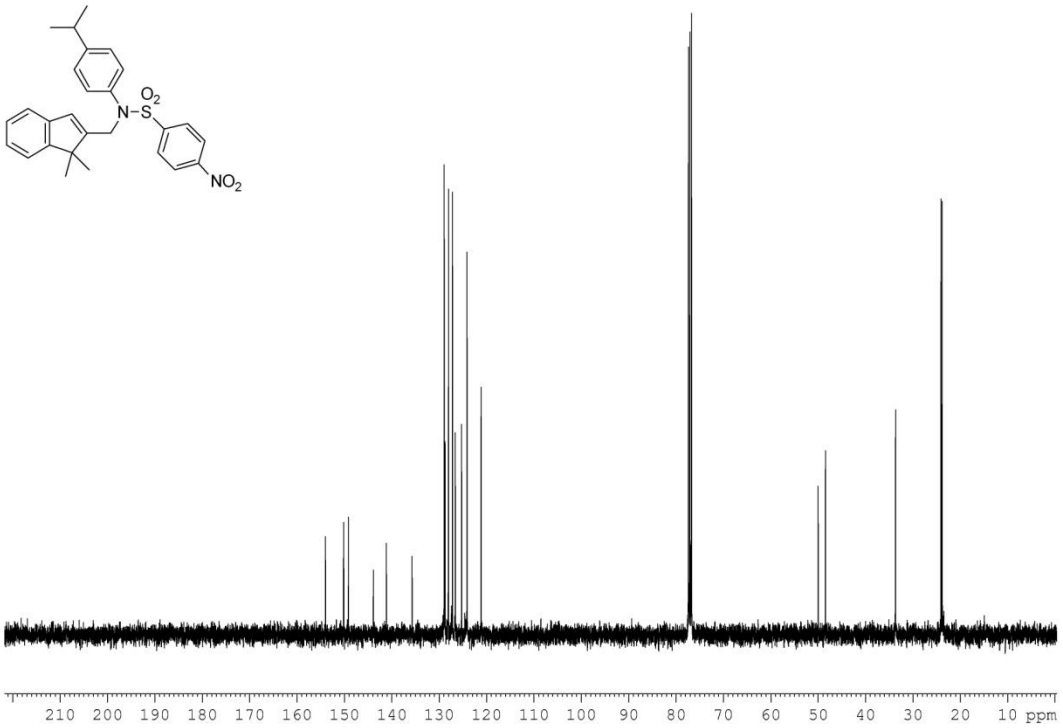

NH
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.98
3.34
2.06
2.12
0.85
1.95
0.95
1.11
6.00
6.12

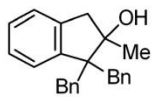

NH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

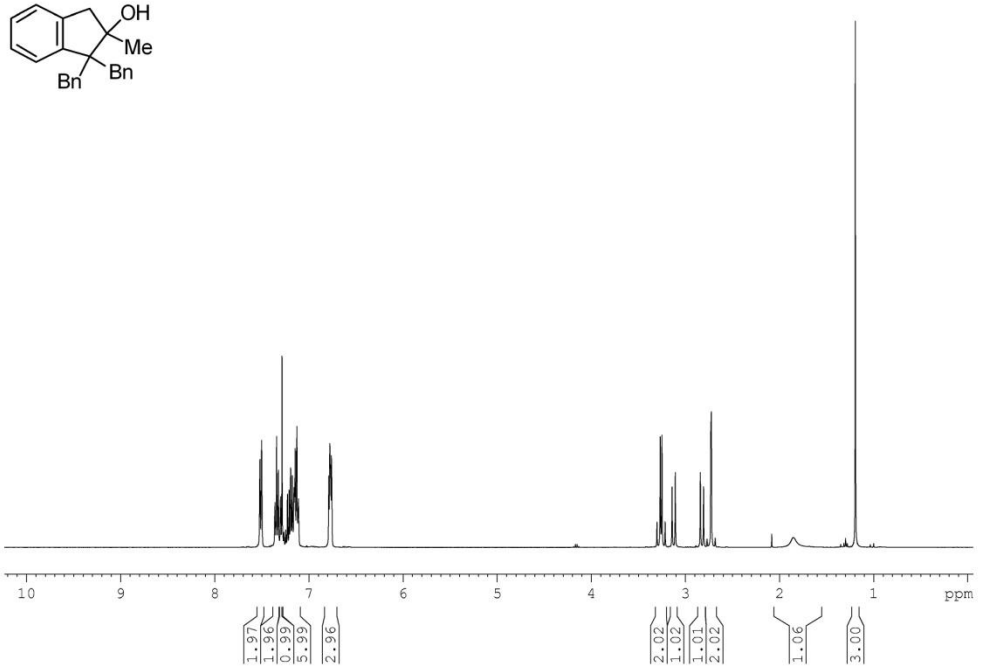

O2
N-S
10 9 8 7 6 5 4 3 2 1 ppm
2.13
3.01
3.27
2.21
2.19
0.93
2.03
1.14
3.28
6.00
5.92

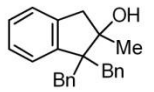

O2
N-S
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

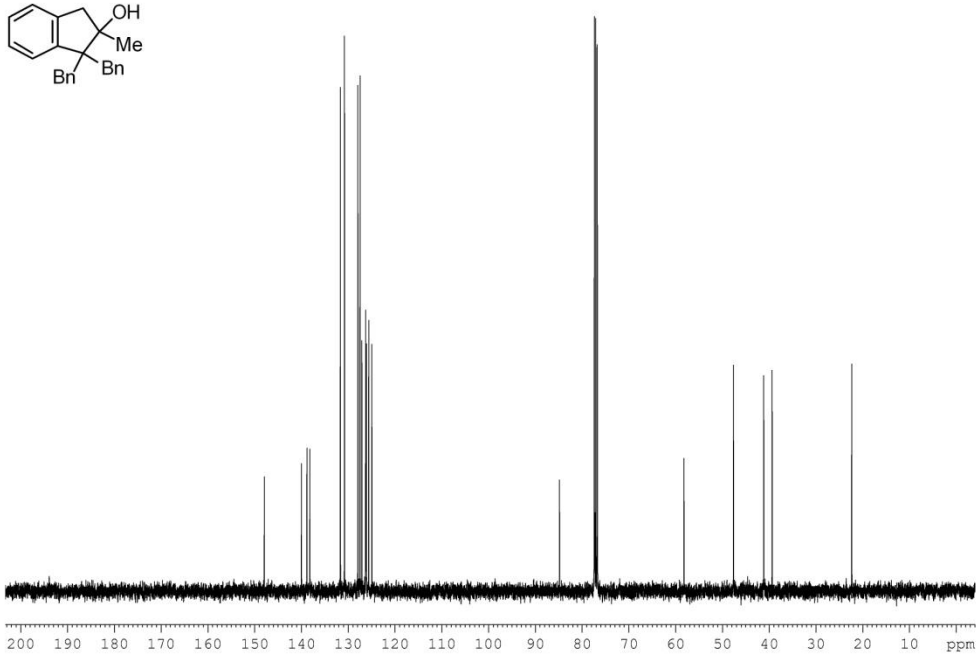

O2
N-S
NO2
10
9
8
7
6
5
4
3
2
1
ppm
2.11
2.09
1.10
5.15
2.11
0.99
2.10
1.08
6.00
5.98

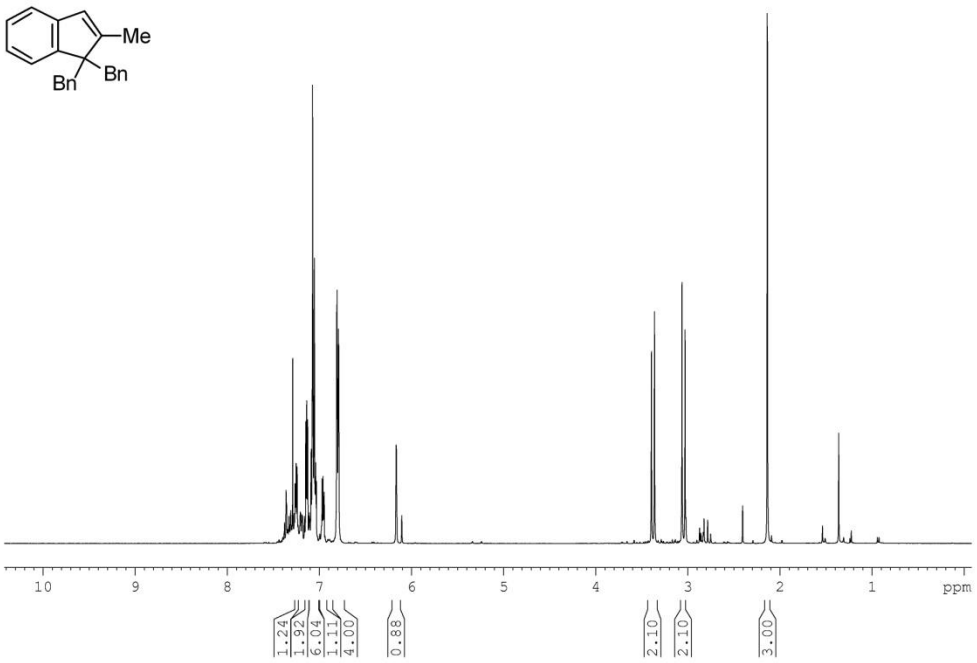

O2
N-S
NO2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

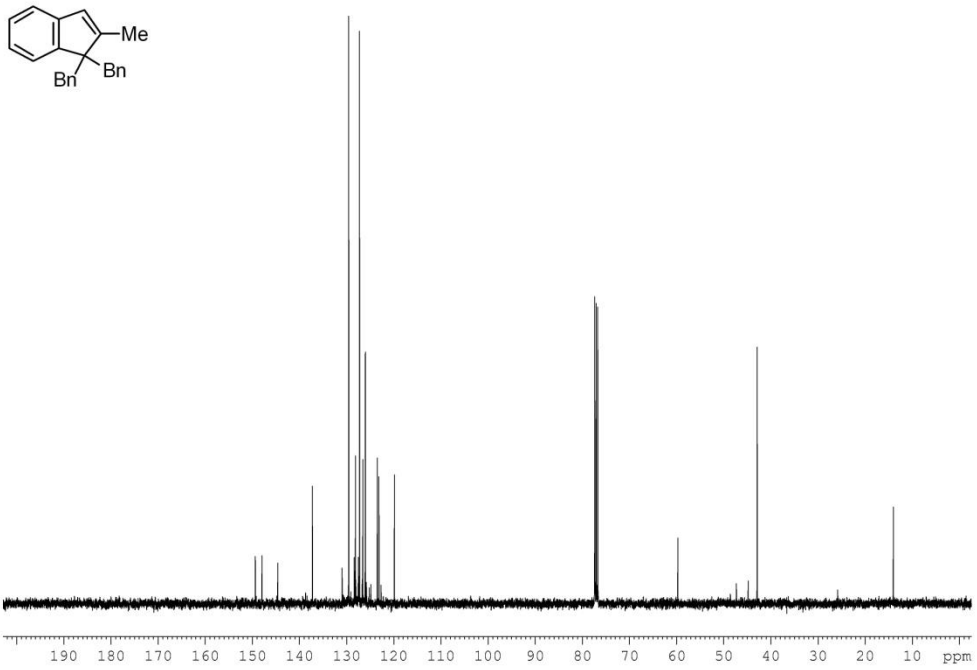

OH
Me
Bn
Bn

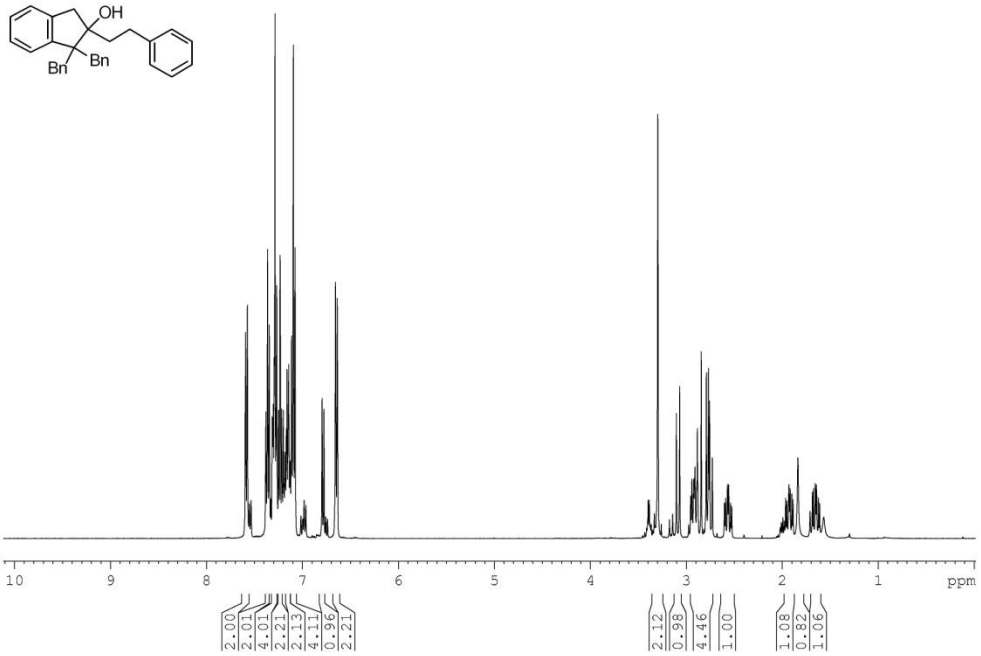

10
9
8
7
6
5
4
3
2
1
ppm
1.97
1.96
0.99
5.99
2.96
2.02
1.02
1.01
2.02
1.06
3.00

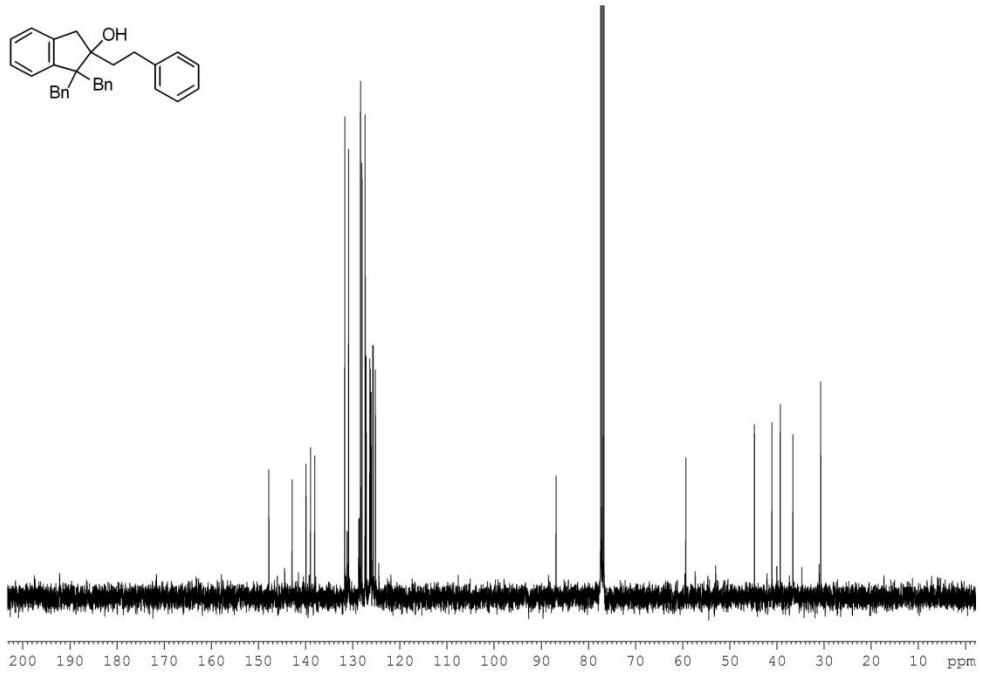

OH
Me
Bn
Bn

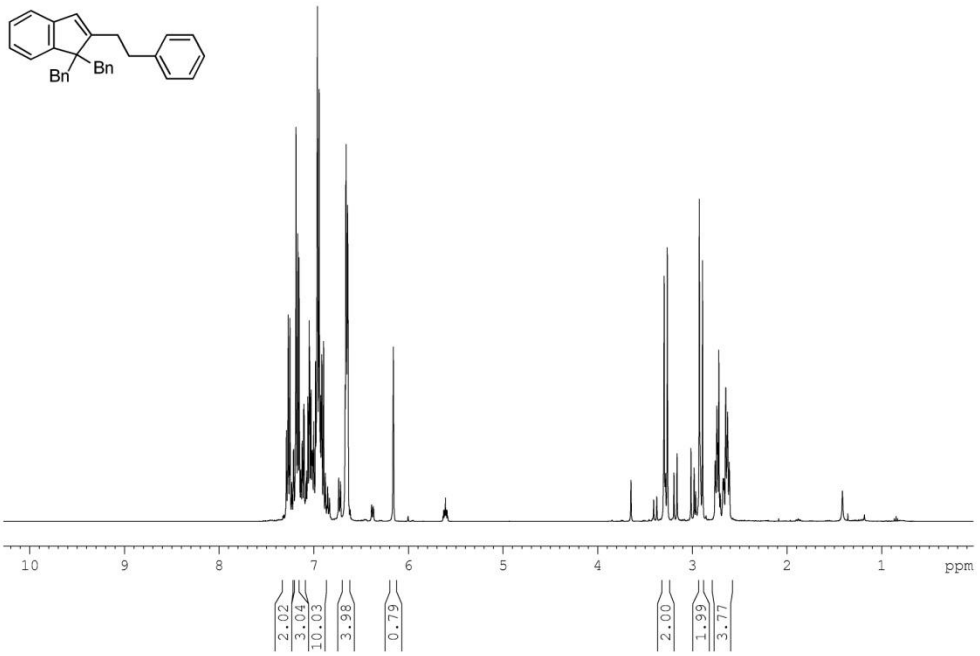

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

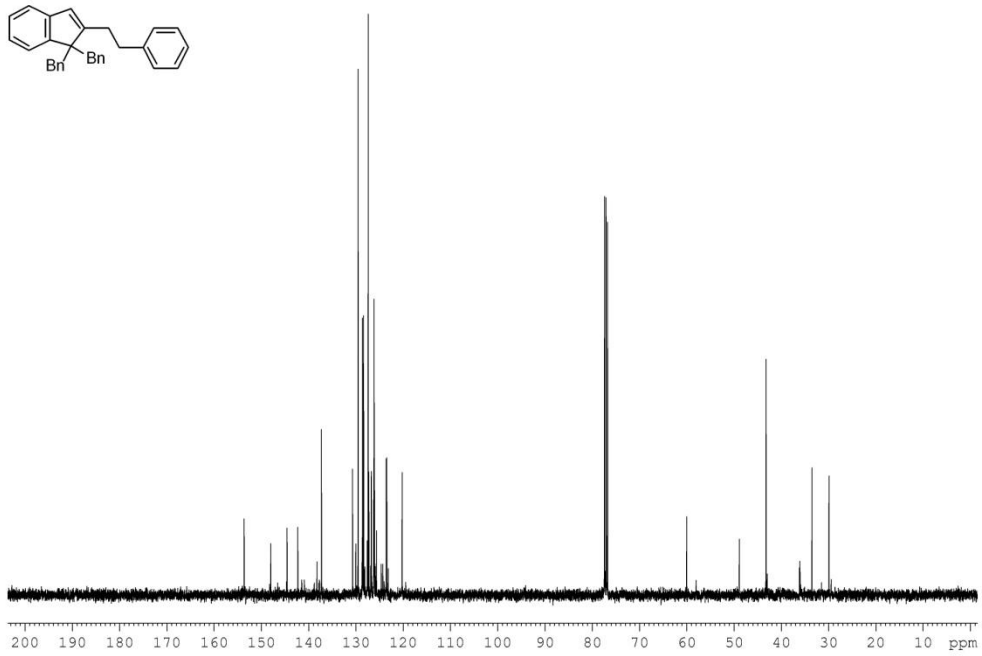

Me
Bn
Bn
10
9
8
7
6
5
4
3
2
1
ppm
1.24
1.92
6.04
1.11
4.00
0.88
2.10
2.10
3.00

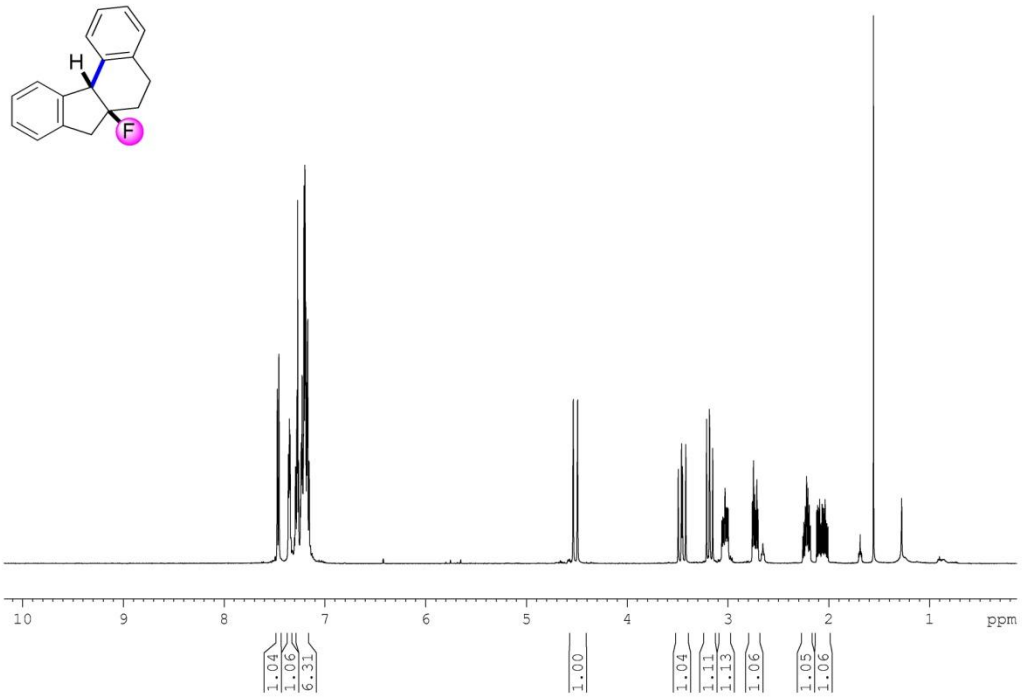

Me
Bn
Bn
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

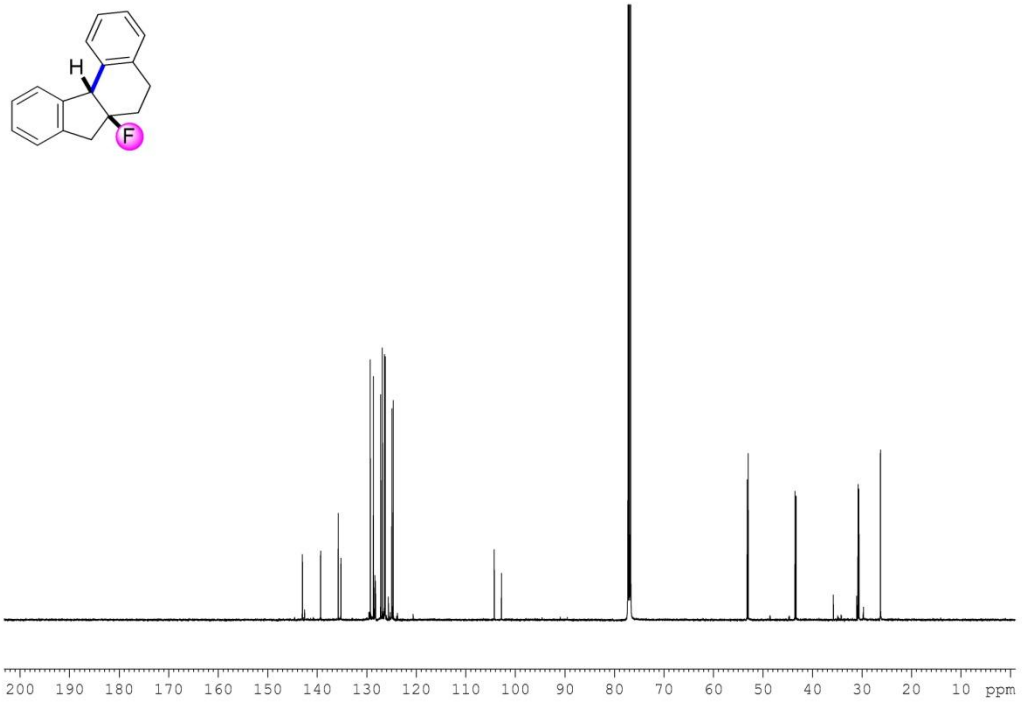

OH
Bn
Bn
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.01
4.01
2.21
2.13
4.11
0.96
2.21
2.12
0.98
4.46
1.00
1.08
0.82
1.06

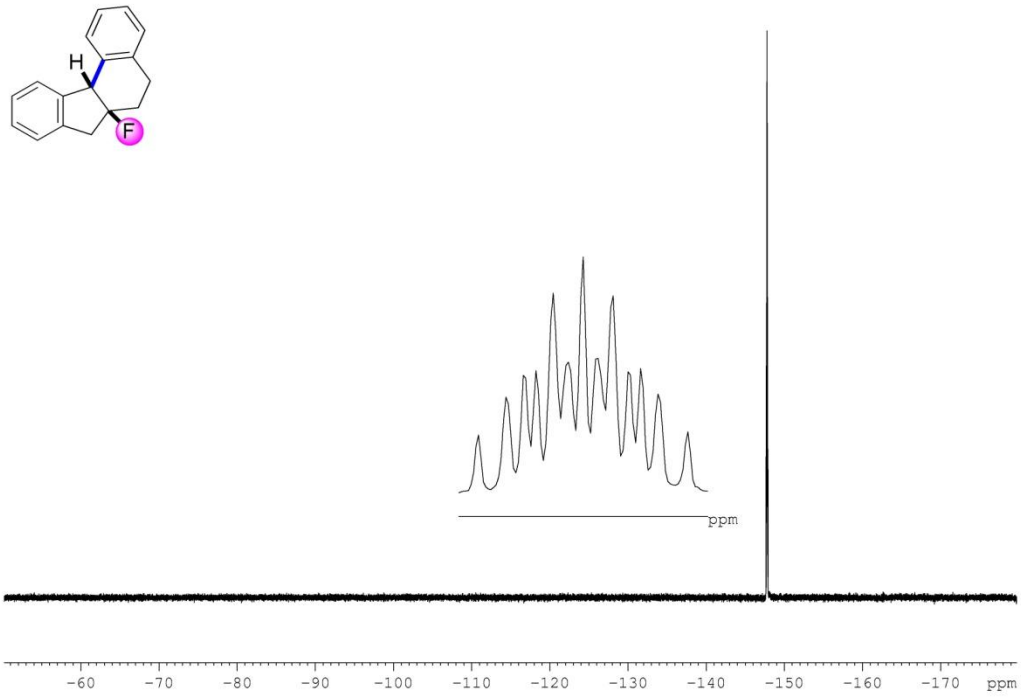

OH
Bn
Bn
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

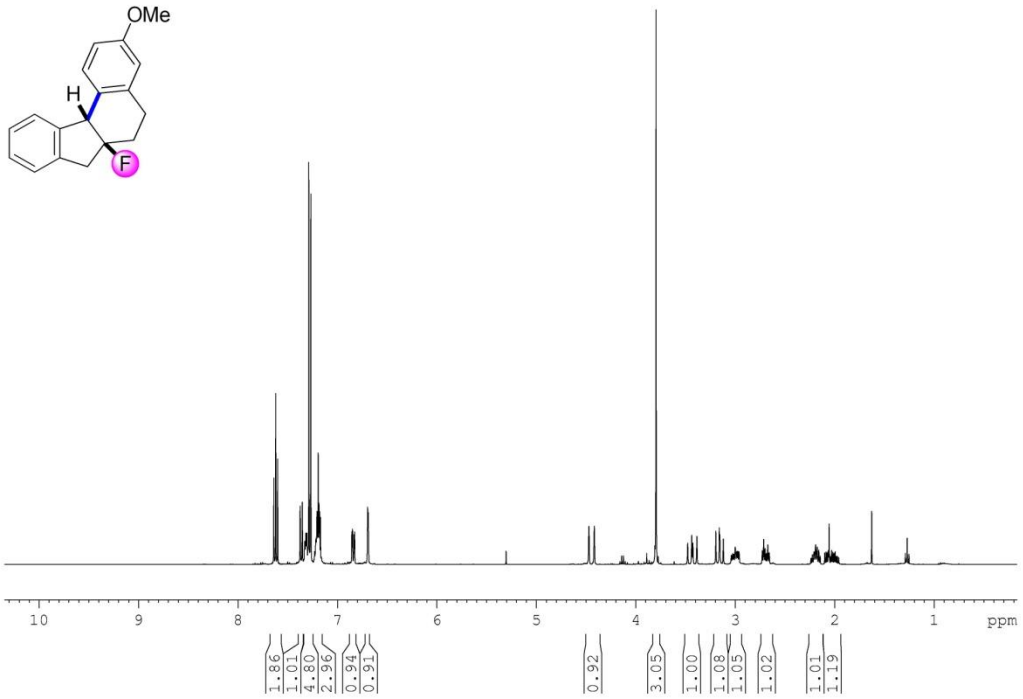

Bn
Bn
10
9
8
7
6
5
4
3
2
1
ppm
2.02
3.04
10.03
3.98
0.79
2.00
1.99
3.77

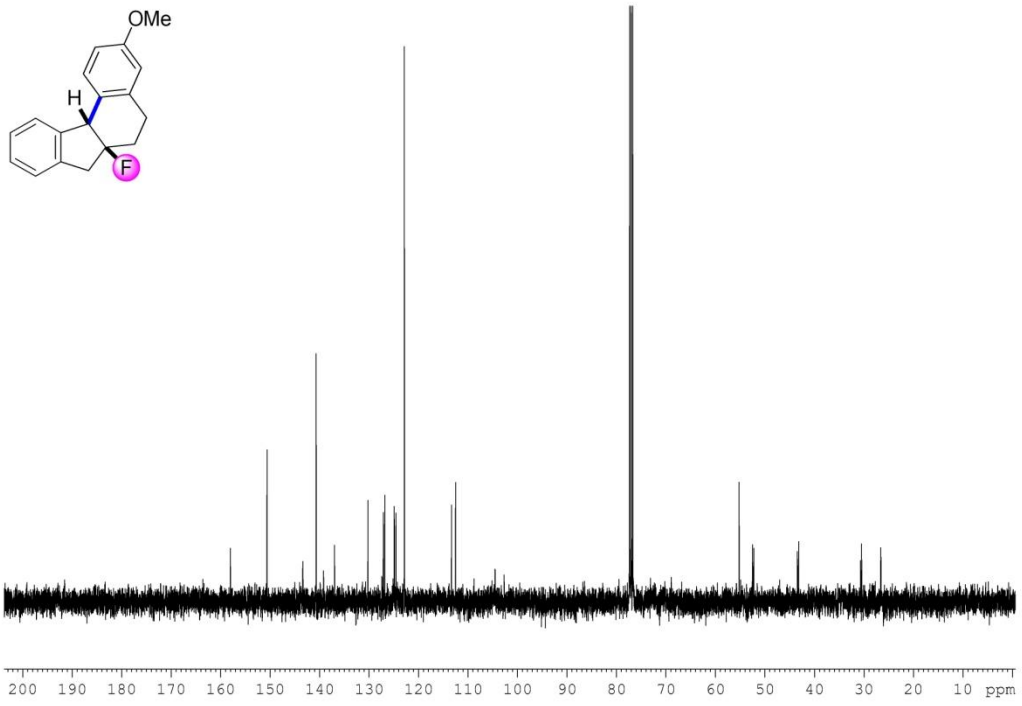

Bn
Bn
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

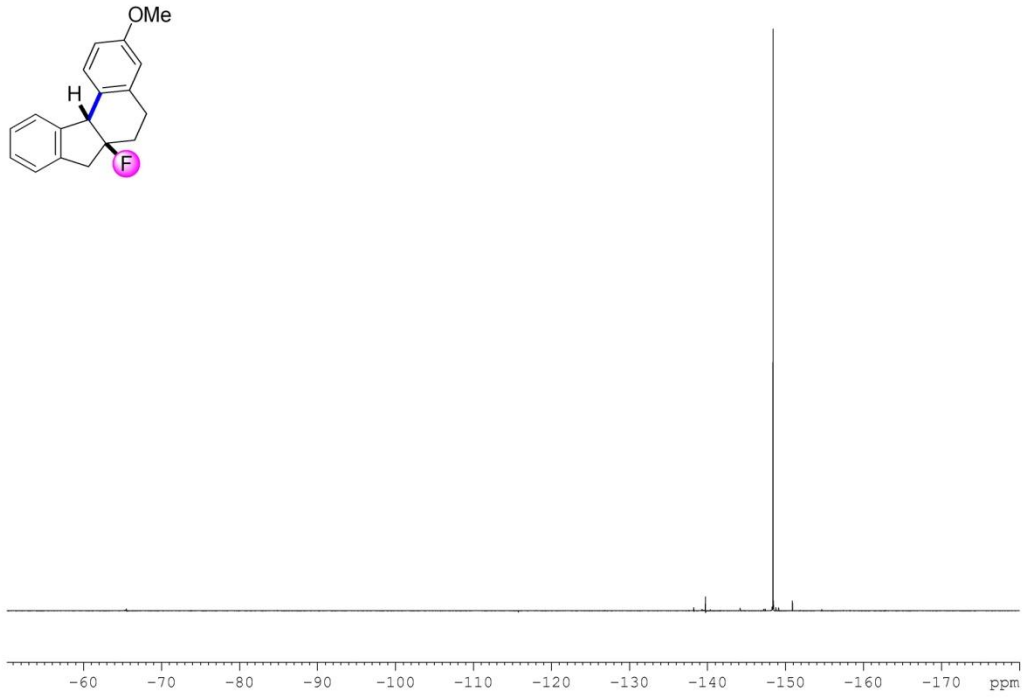

H
F
10
9
8
7
6
5
4
3
2
1
ppm
1.04
1.06
6.31
1.00
1.04
1.11
1.13
1.06
1.05
1.06

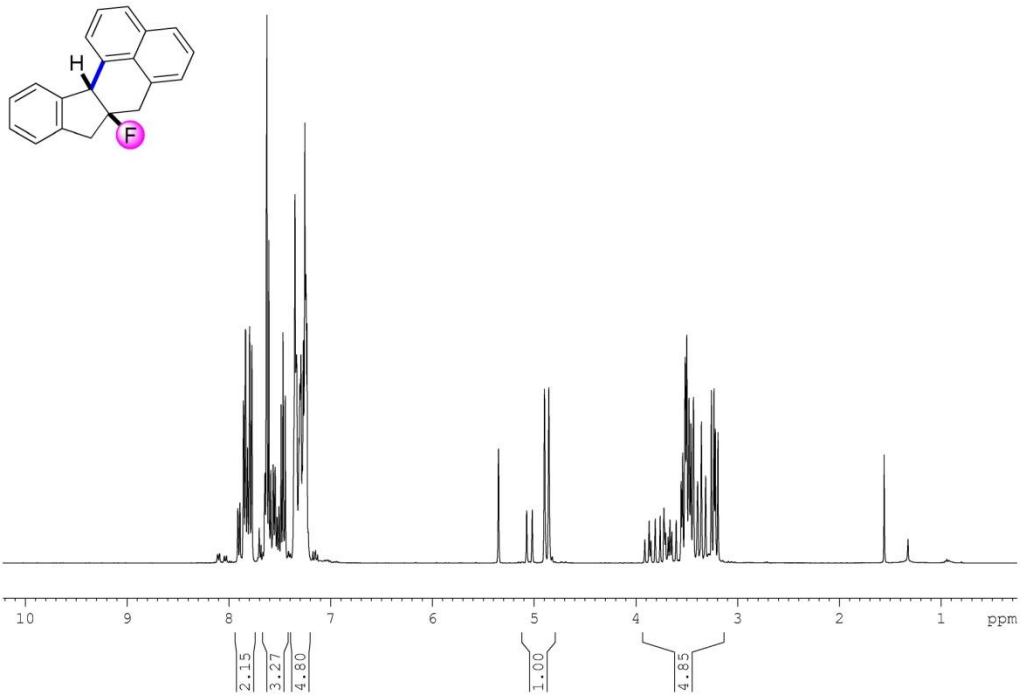

H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

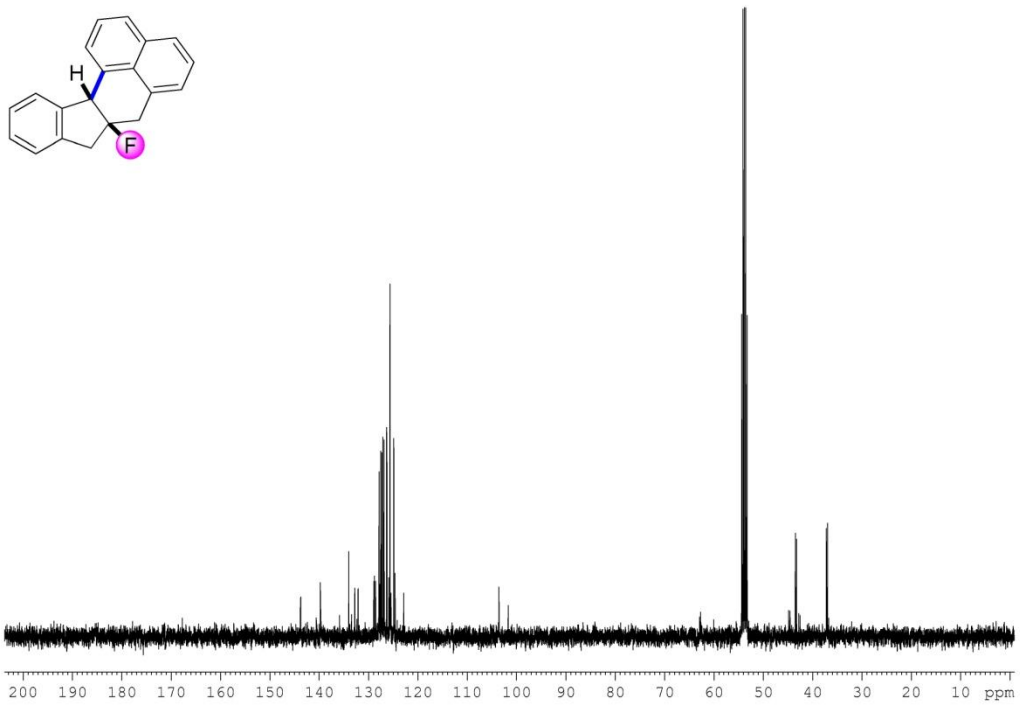

H
F
ppm
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm

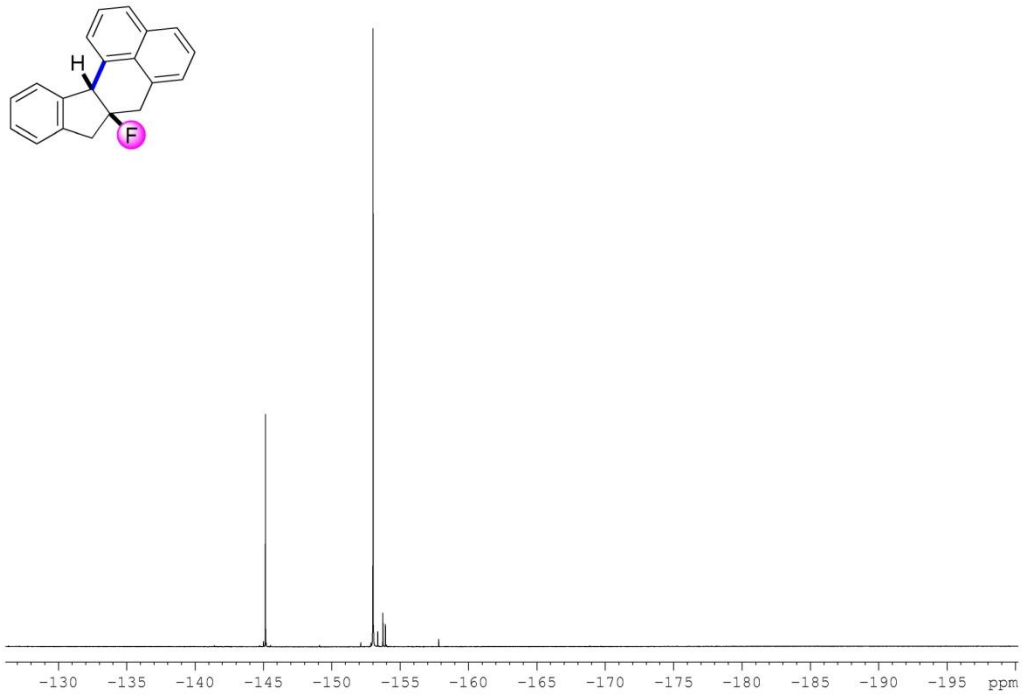

OMe
H
F
10
9
8
7
6
5
4
3
2
1
ppm
1.86
1.01
4.80
2.96
0.94
0.91
0.92
3.05
1.00
1.08
1.05
1.02
1.01
1.19

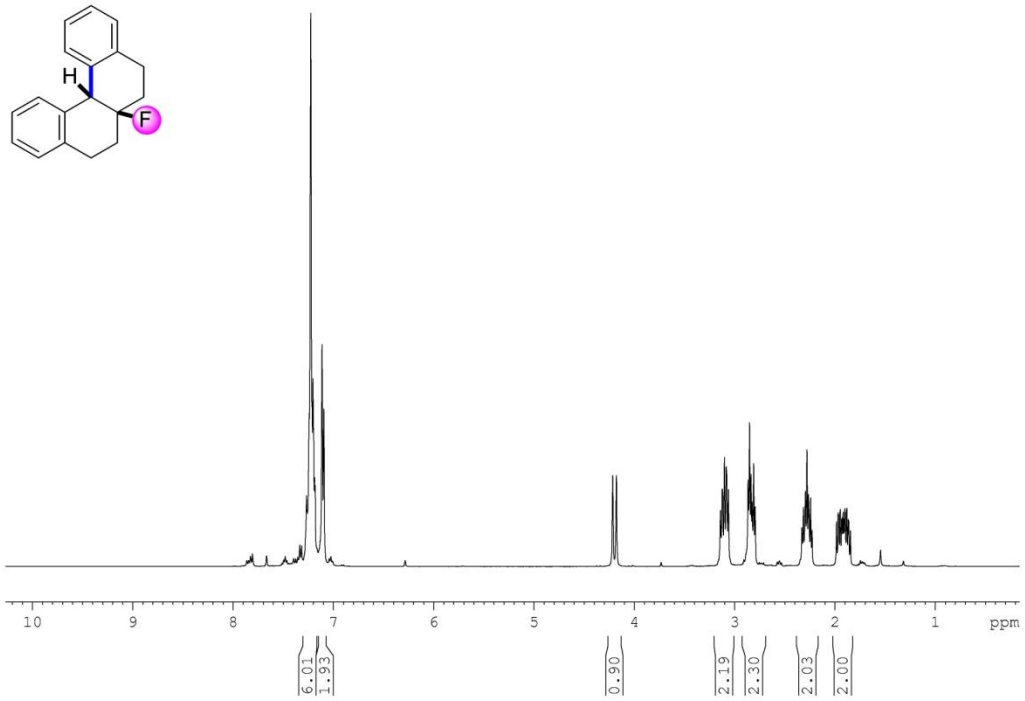

OMe
H
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

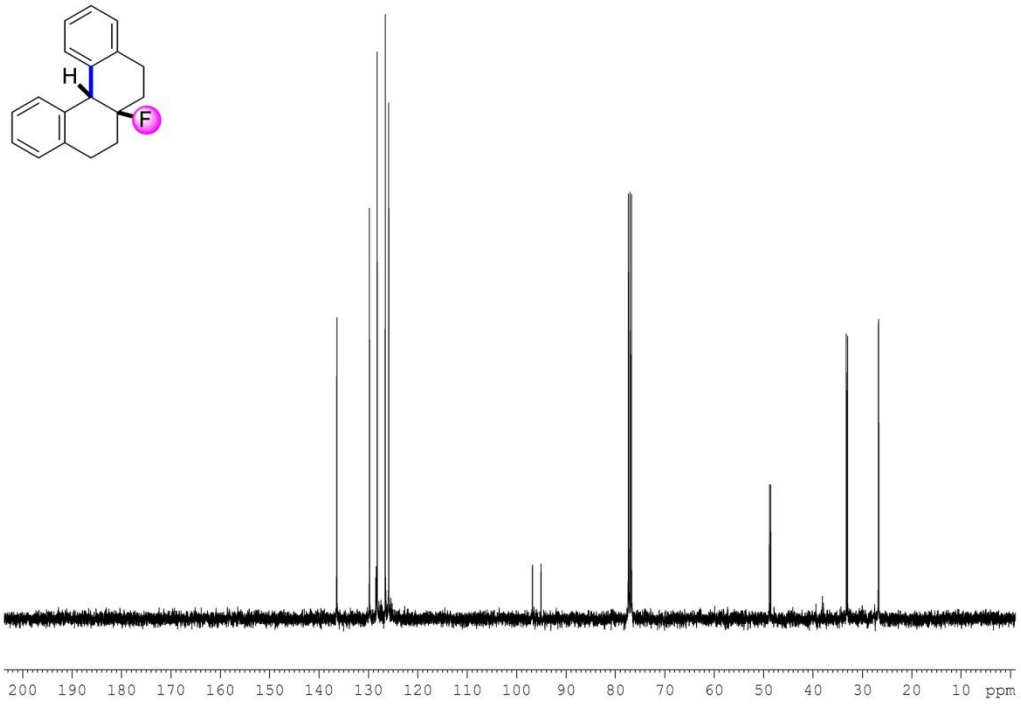

OMe
H
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 ppm

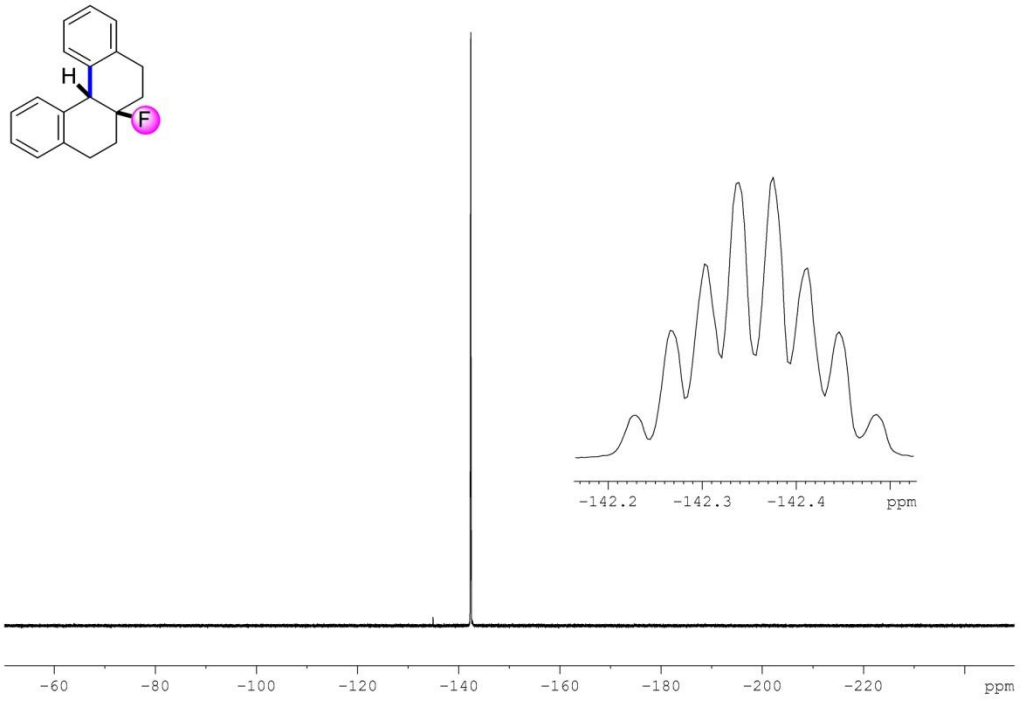

H
F
10
9
8
7
6
5
4
3
2
1
ppm
2.15
3.27
4.80
1.00
4.85

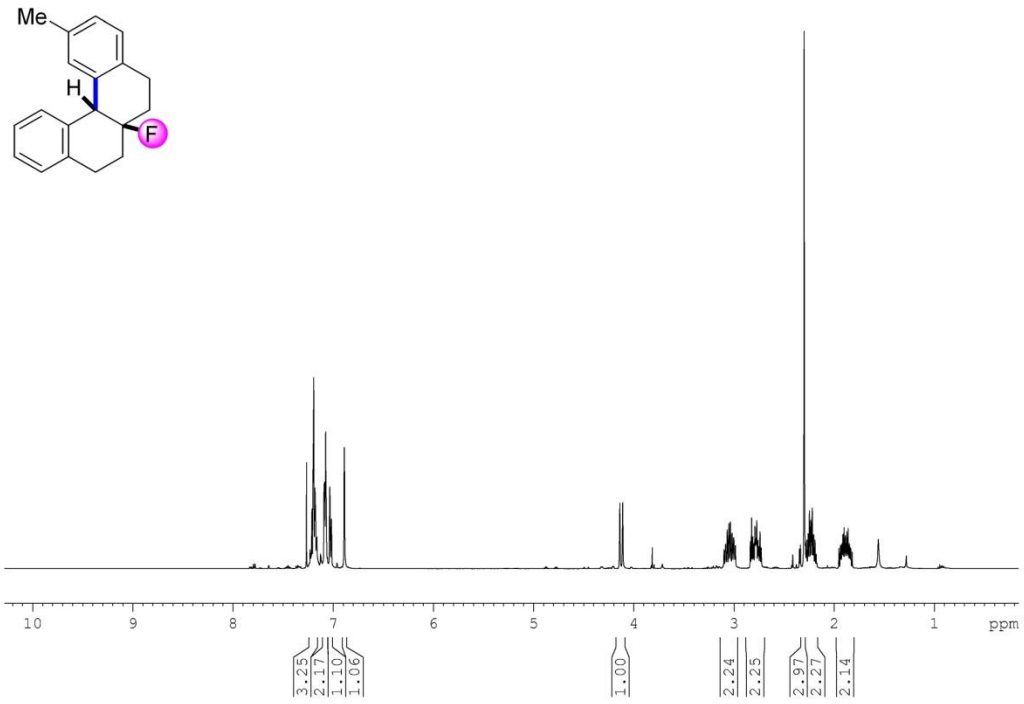

H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

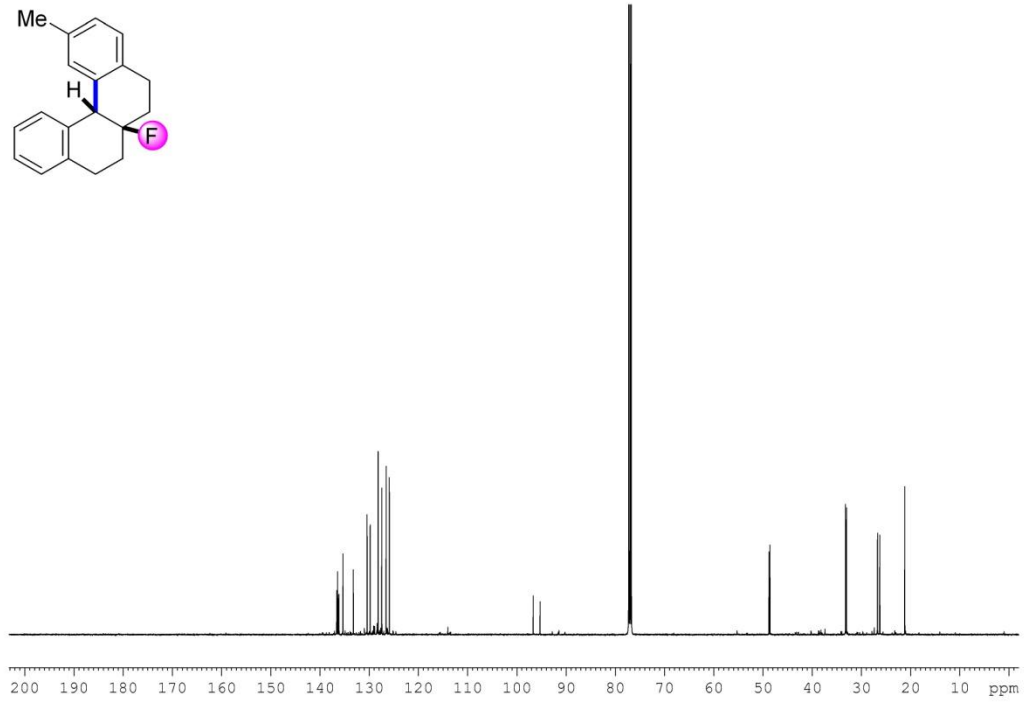

H
F
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
ppm

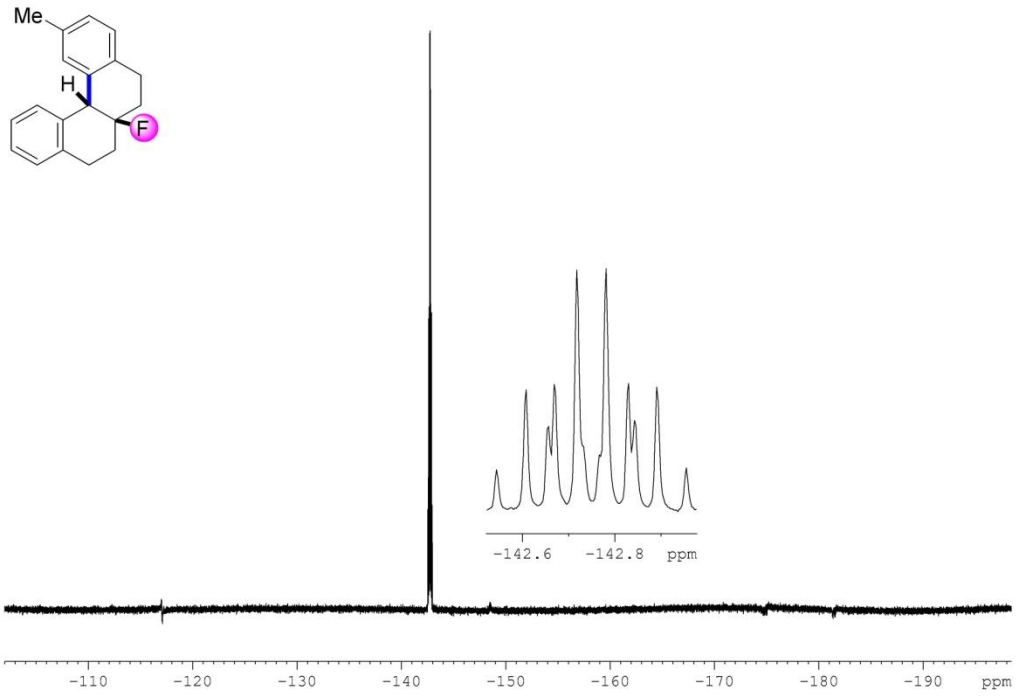

H
F
10
9
8
7
6
5
4
3
2
1
ppm
6.01
1.93
0.90
2.19
2.30
2.03
2.00

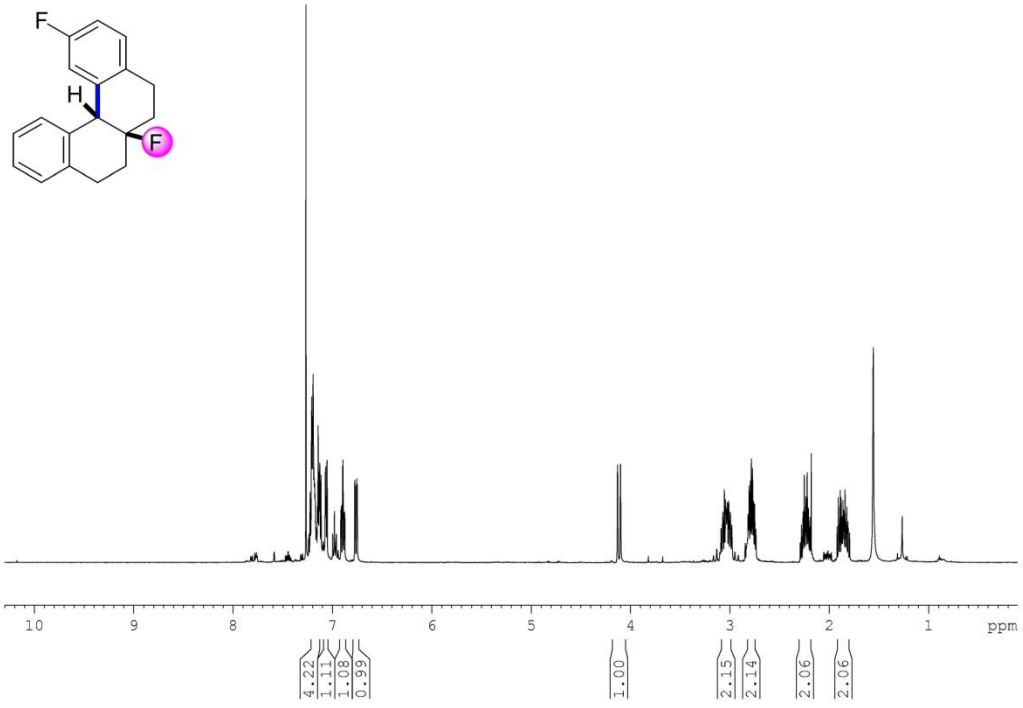

H
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


H
F
-142.2 -142.3 -142.4 ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

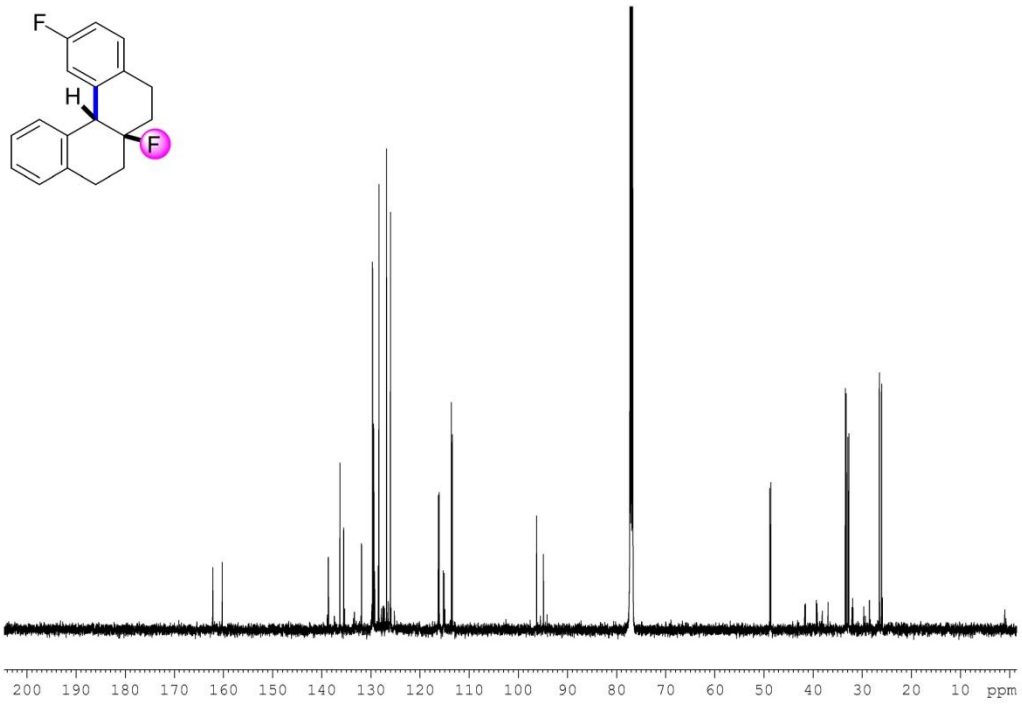

Me
H
F
10
9
8
7
6
5
4
3
2
1
ppm
3.25
2.17
1.10
1.06
1.00
2.24
2.25
2.97
2.27
2.14

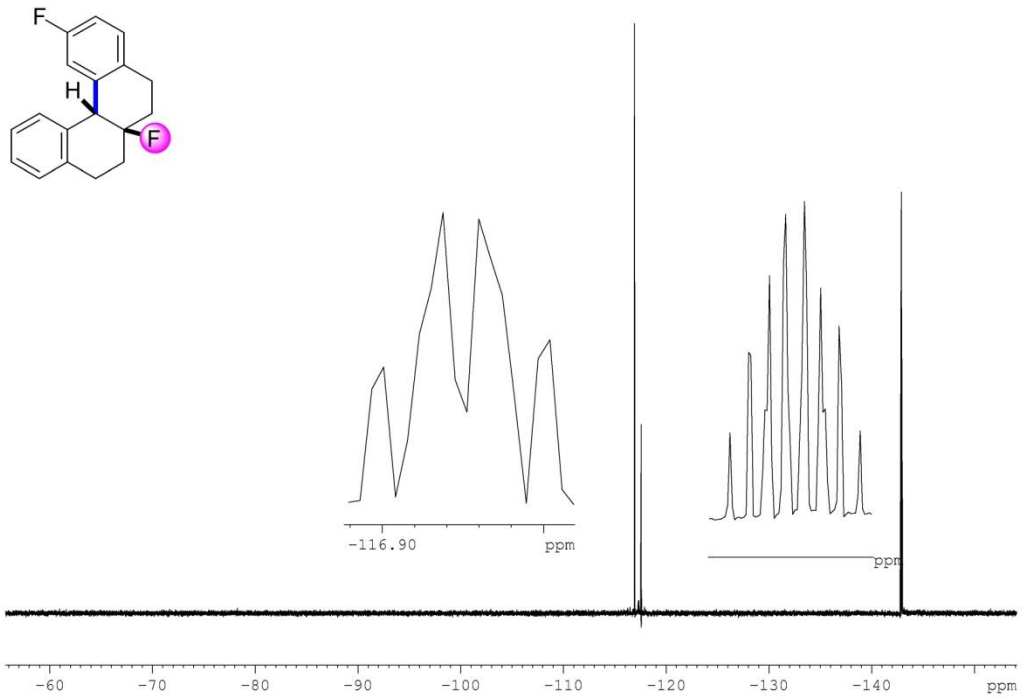

Me
H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

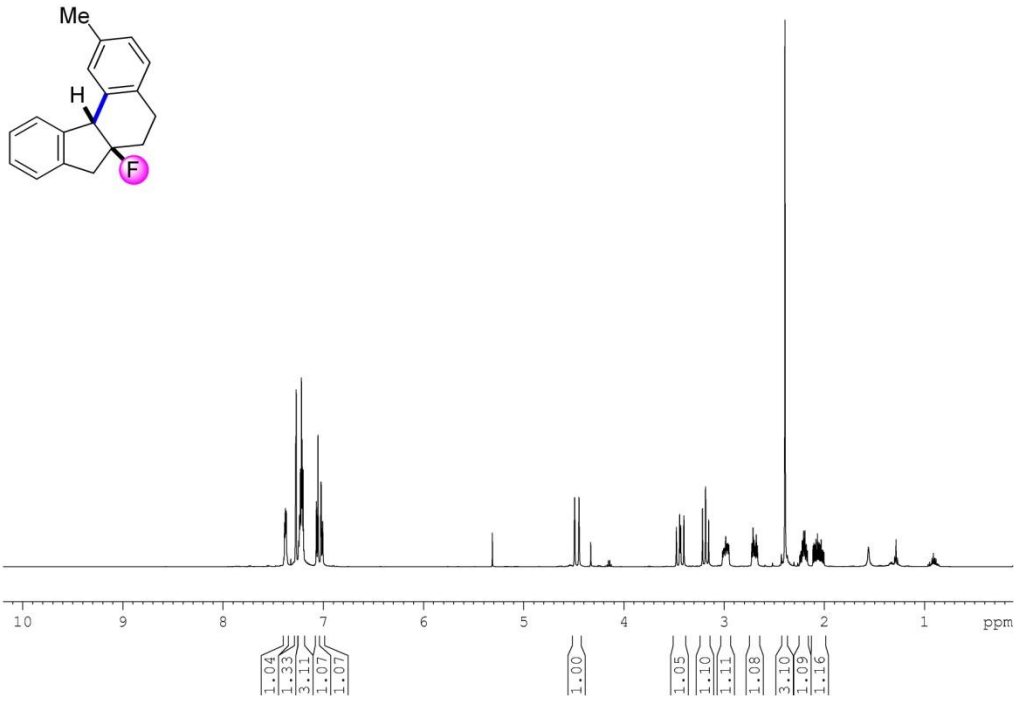

Me
H
F
-142.6
-142.8
ppm
-110
-120
-130
-140
-150
-160
-170
-180
-190
ppm

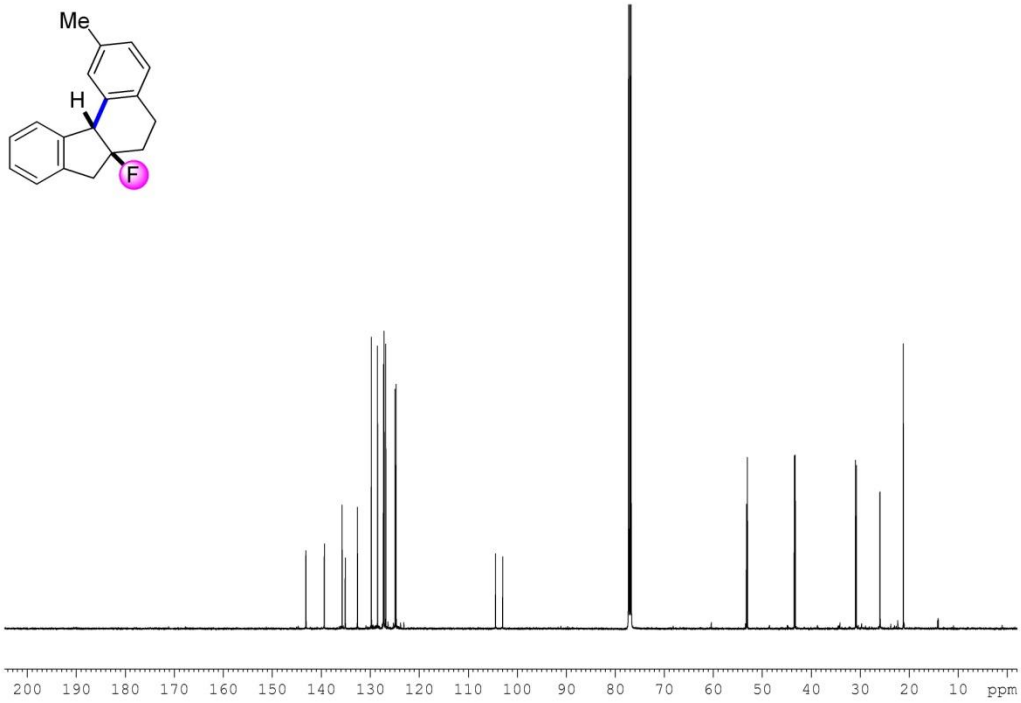

F
H
F
10
9
8
7
6
5
4
3
2
1
ppm
4.22
1.11
1.08
0.99
1.00
2.15
2.14
2.06
2.06

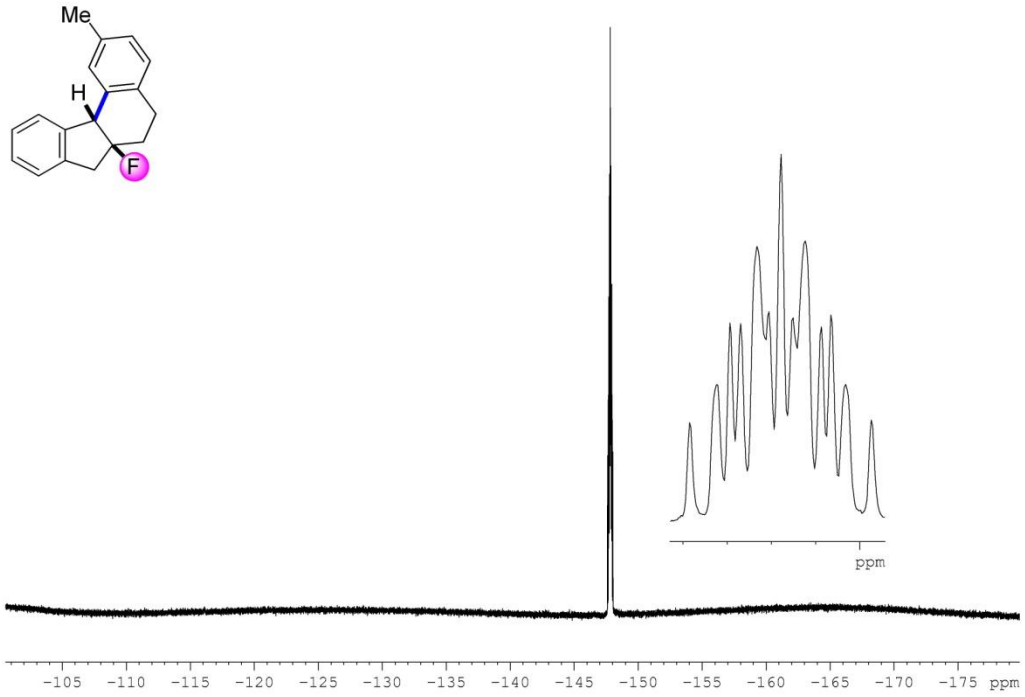
c

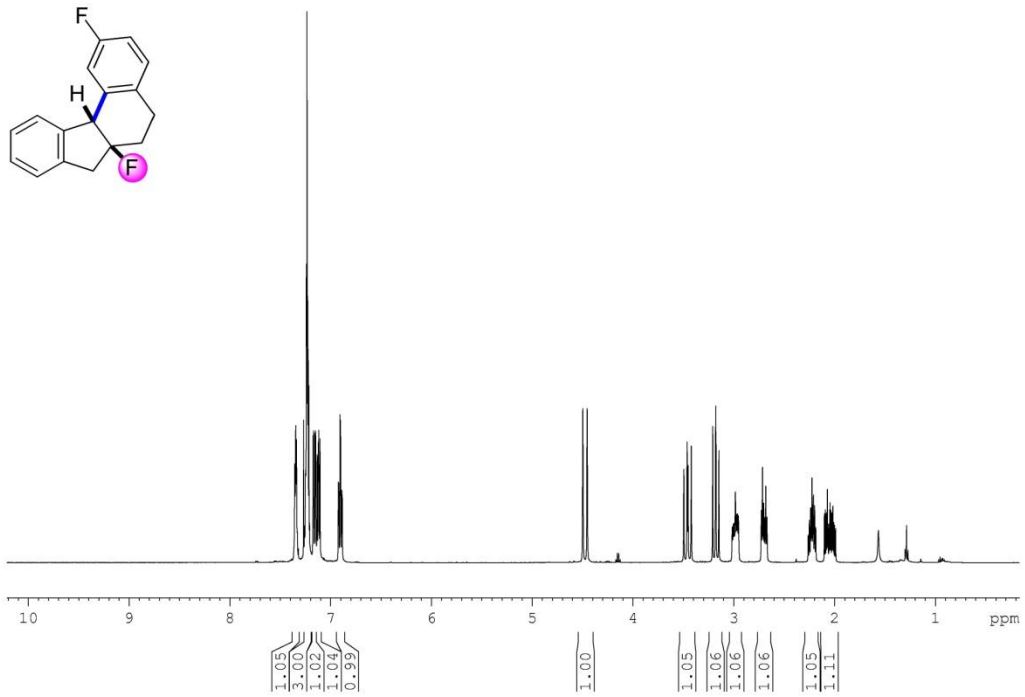

F
H
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

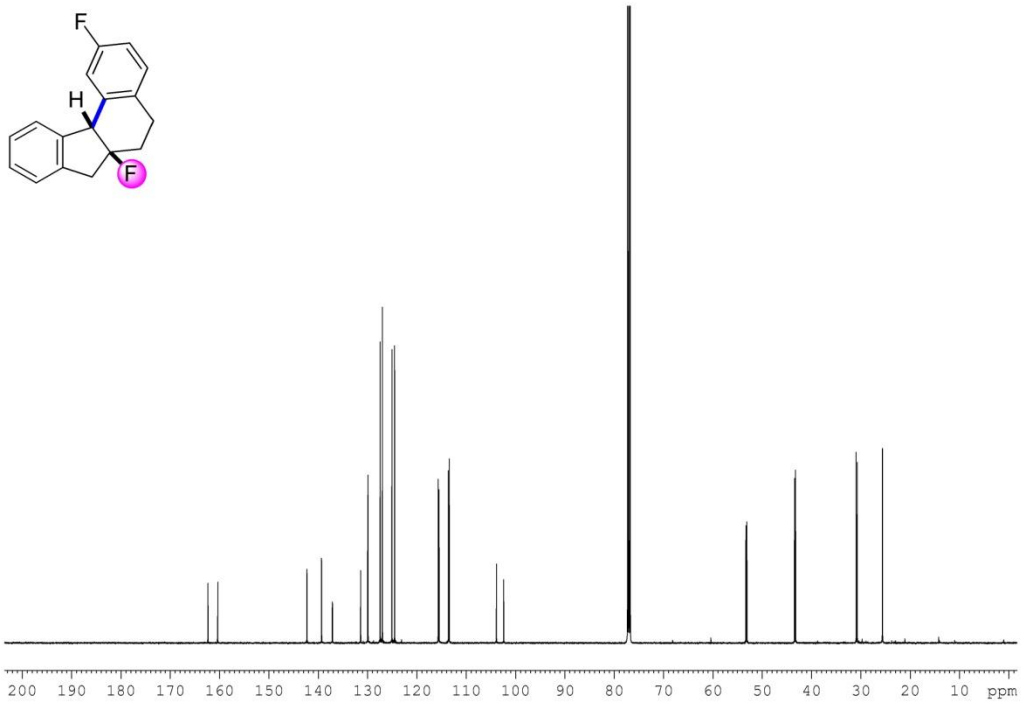

F
H
F
-116.90
ppm
ppm
-60 -70 -80 -90 -100 -110 -120 -130 -140 ppm

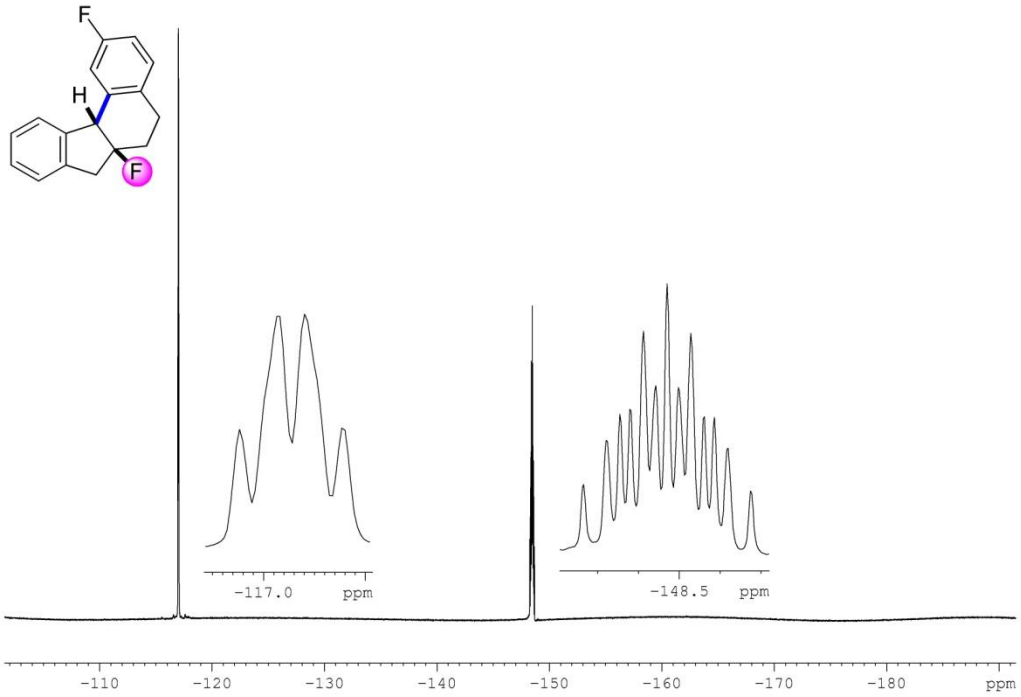

Me
H
F
10
9
8
7
6
5
4
3
2
1
ppm
1.04
1.33
3.11
1.07
1.07
1.00
1.05
1.10
1.11
1.08
3.10
1.09
1.16

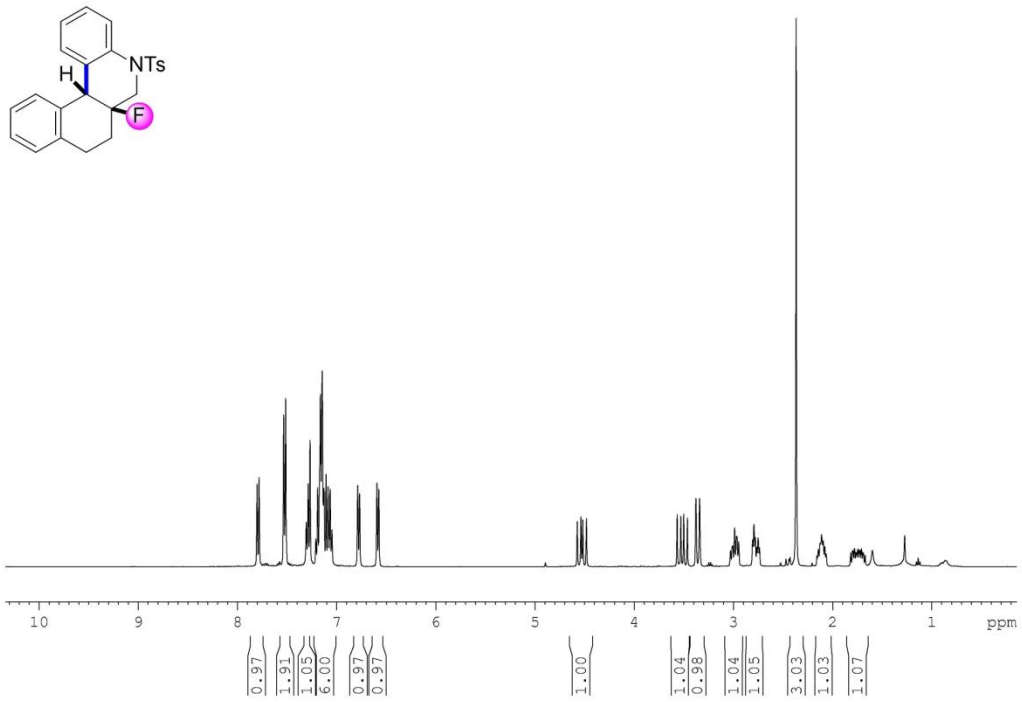

Me
H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

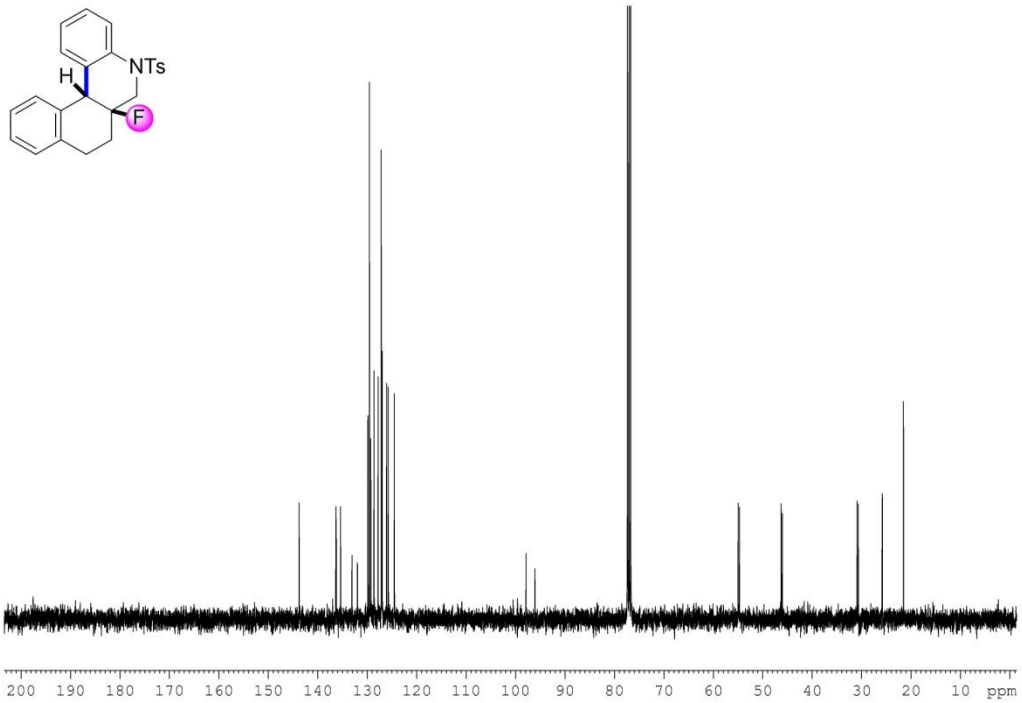

Me
H
F
ppm
-105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 ppm

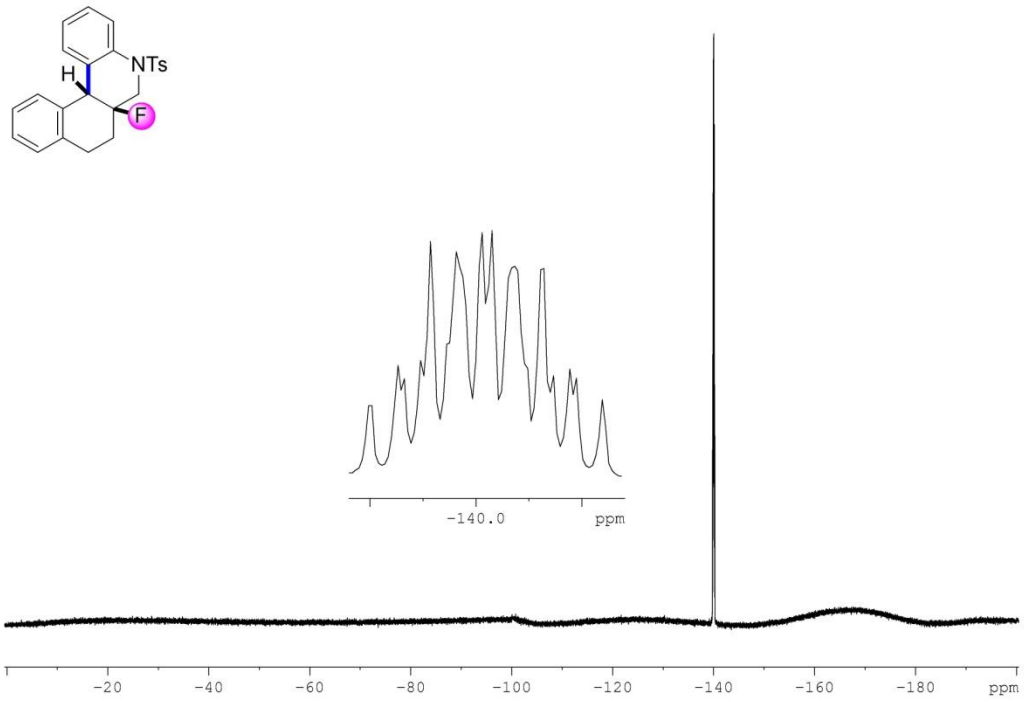

F
H
F
10 9 8 7 6 5 4 3 2 1 ppm
1.05
3.00
1.02
1.04
0.99
1.00
1.05
1.06
1.06
1.06
1.05
1.11

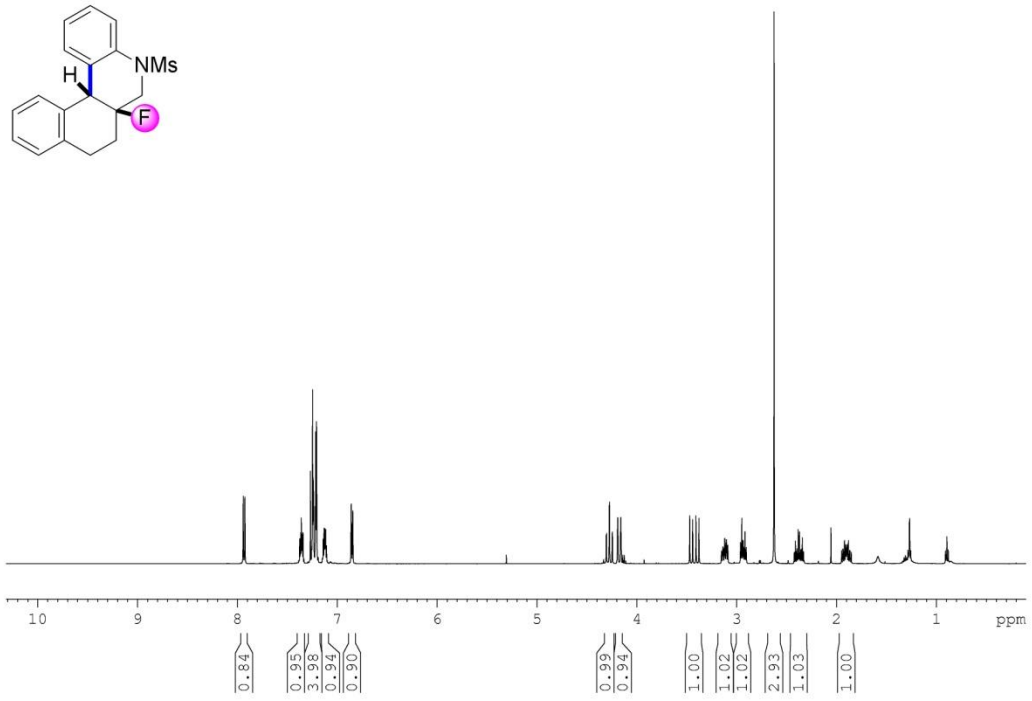

F
H
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

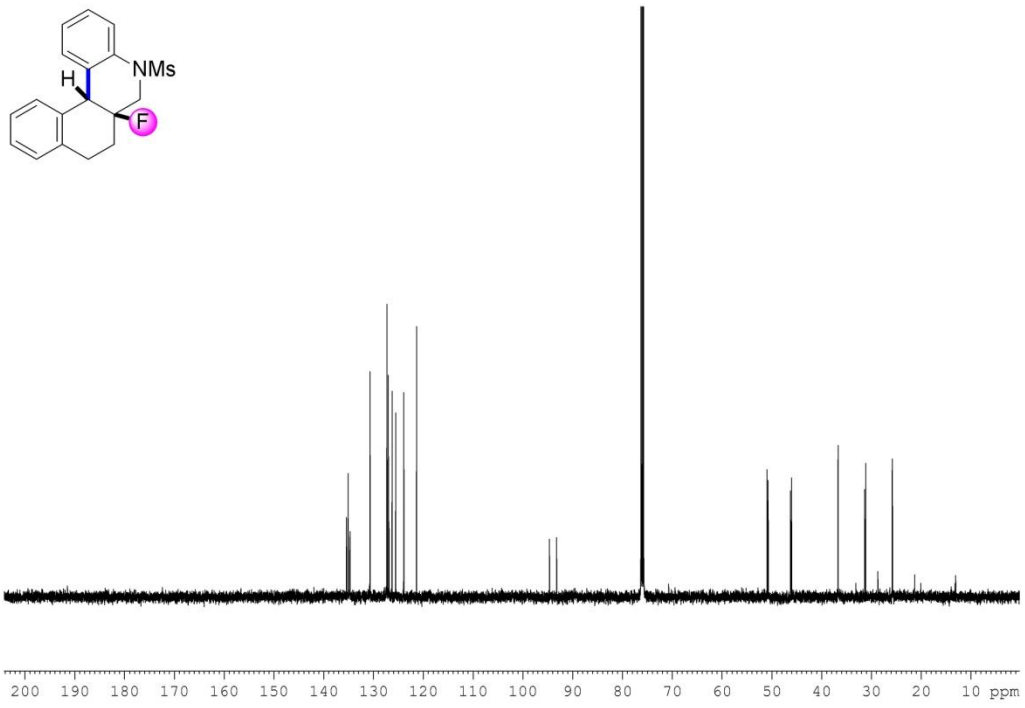

F
H
F
-117.0 ppm
-148.5 ppm
-110 -120 -130 -140 -150 -160 -170 -180 ppm

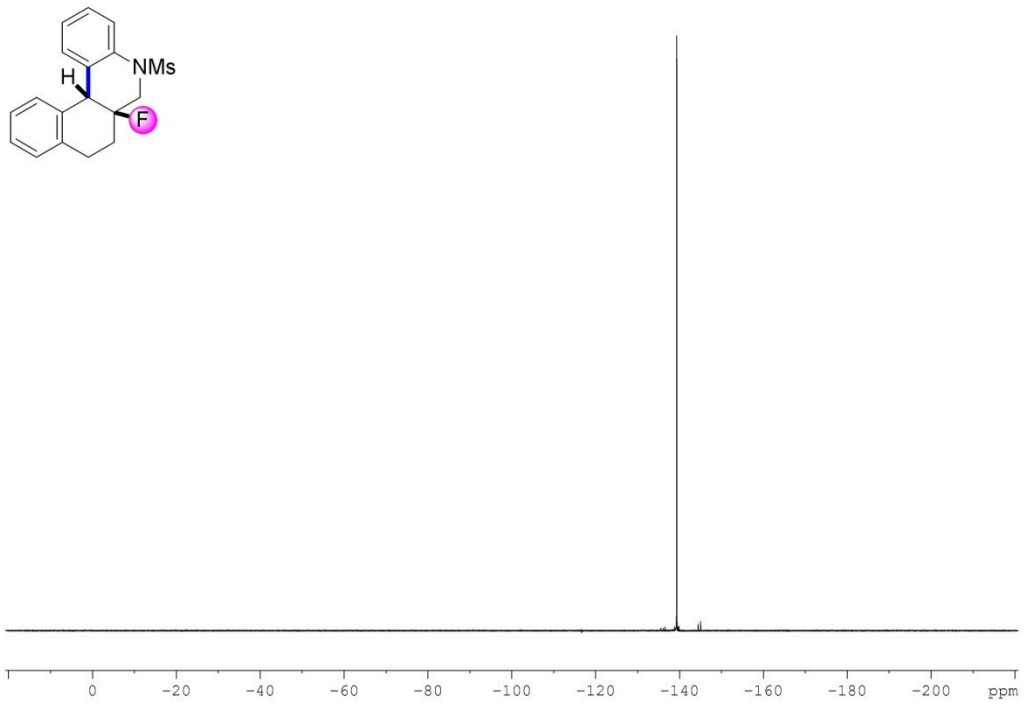

NTs
H
F
10
9
8
7
6
5
4
3
2
1
ppm
0.97
1.91
1.05
6.00
0.97
0.97
1.00
1.04
0.98
1.04
1.05
3.03
1.03
1.07

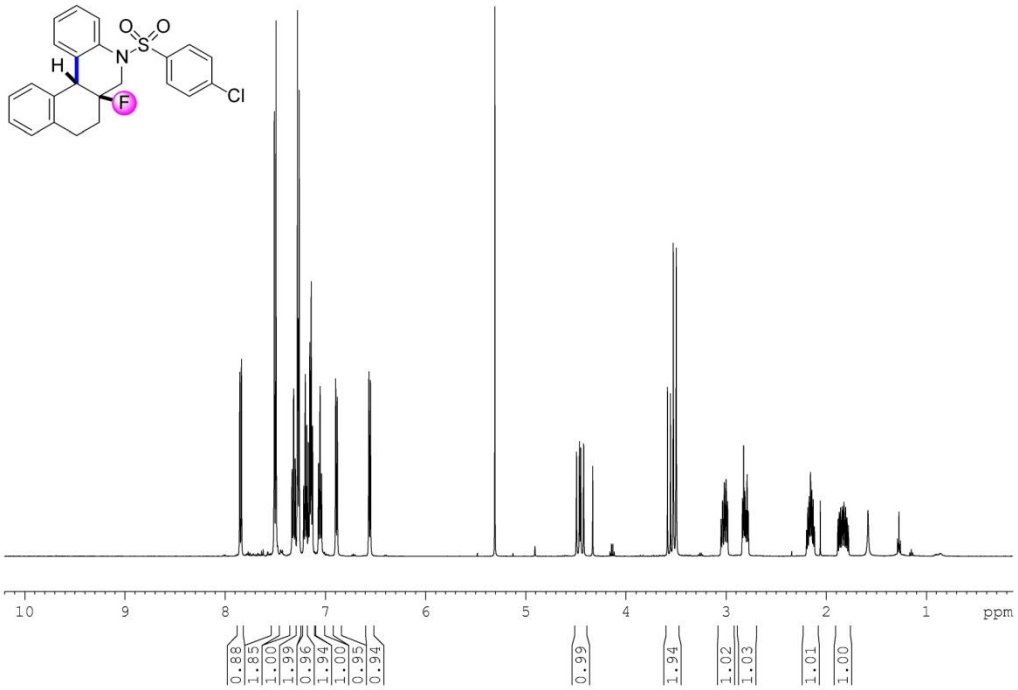

NTs
H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

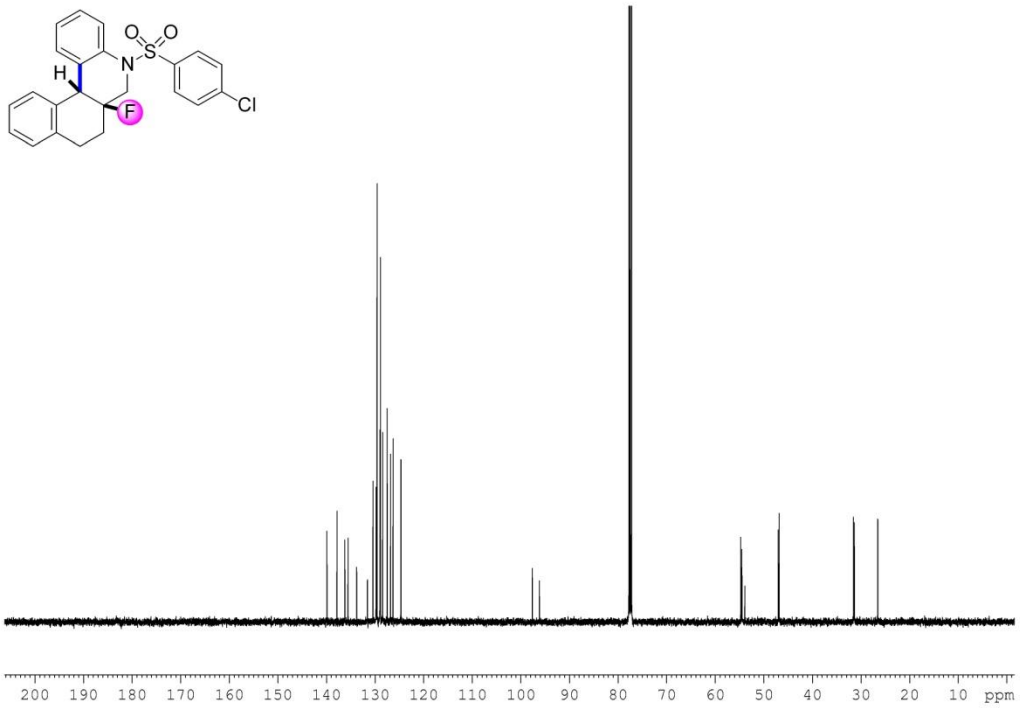

NTs
H
F
-140.0
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

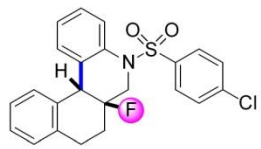

NMs
H
F
10
9
8
7
6
5
4
3
2
1
ppm
0.84
0.95
3.98
0.94
0.90
0.99
0.94
1.00
1.02
1.02
2.93
1.03
1.00

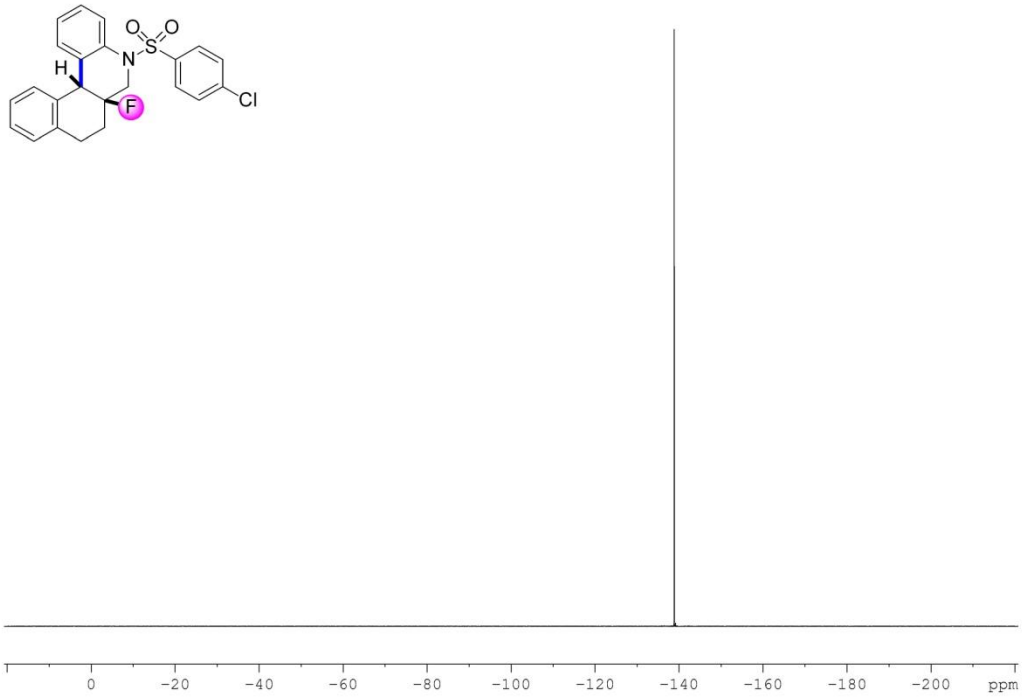

NMs
H
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


NMs
H
F
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

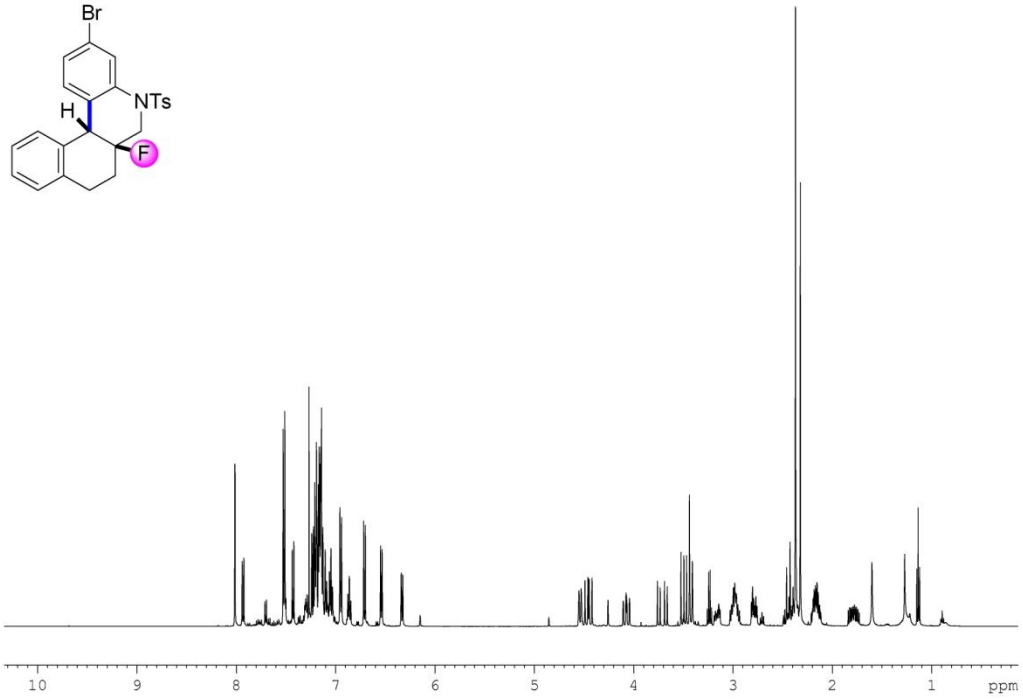

O
O
S
N
H
F
Cl
10
9
8
7
6
5
4
3
2
1
ppm
0.88
1.85
1.00
1.99
0.96
1.94
1.00
0.95
0.94
0.99
1.94
1.02
1.03
1.01
1.00

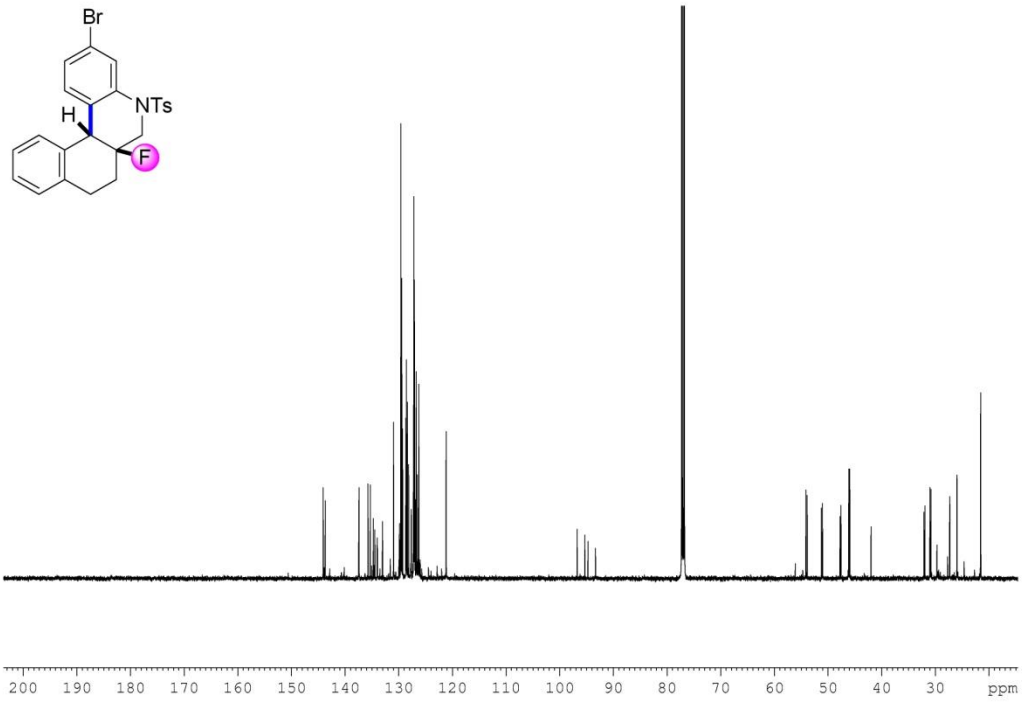

O
O
S
N
H
F
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

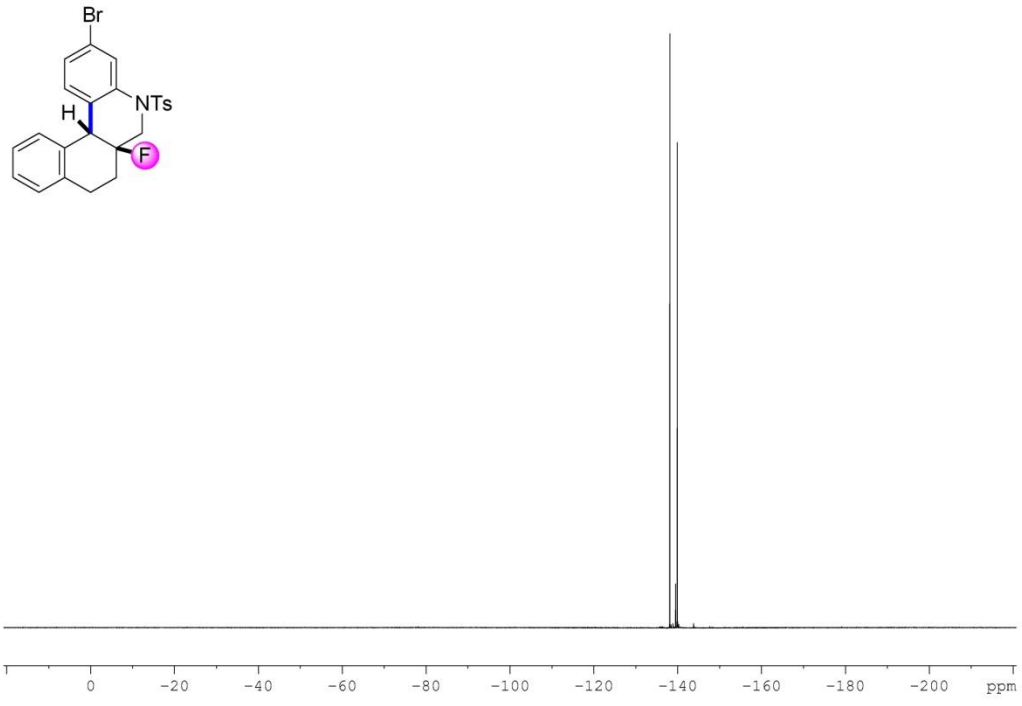

O
O
S
N
H
F
Cl

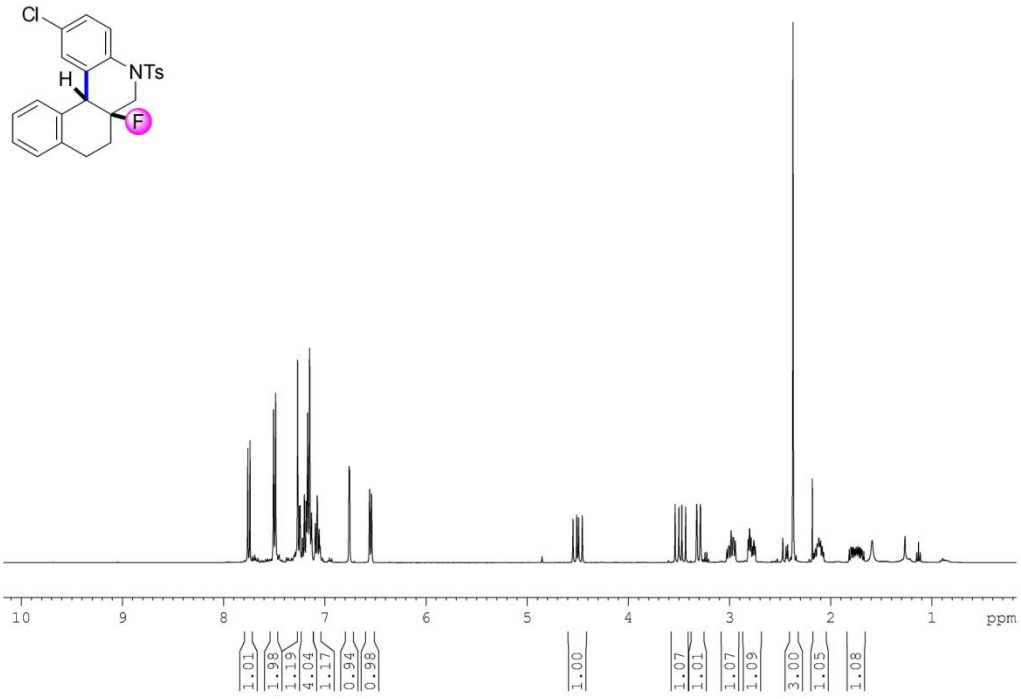

0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

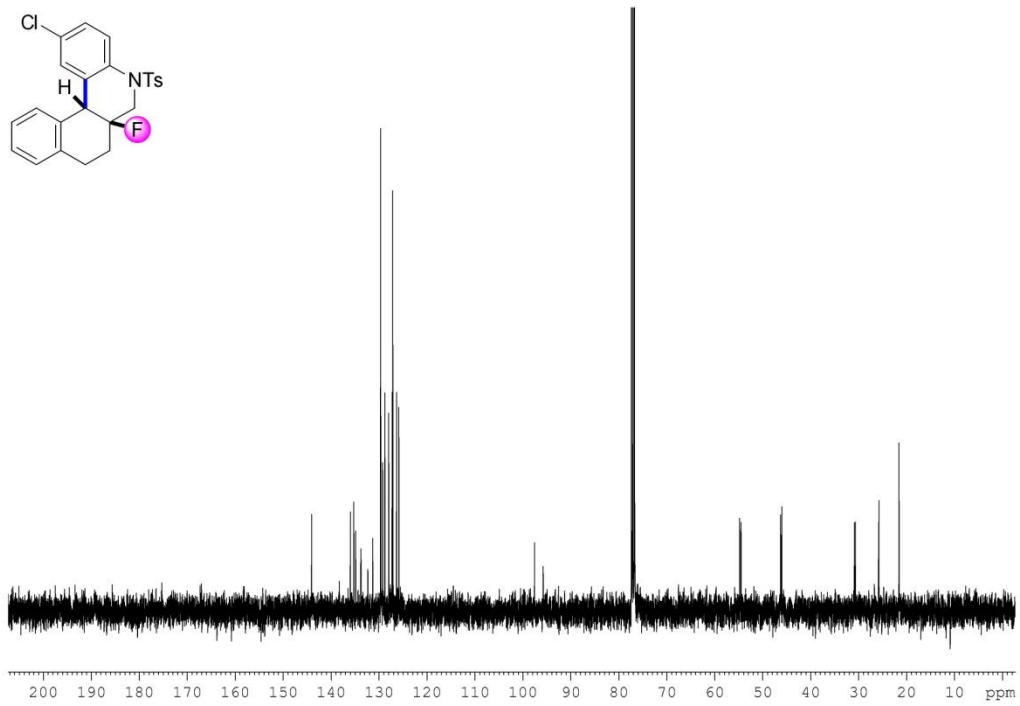
Br
NTs
H
F

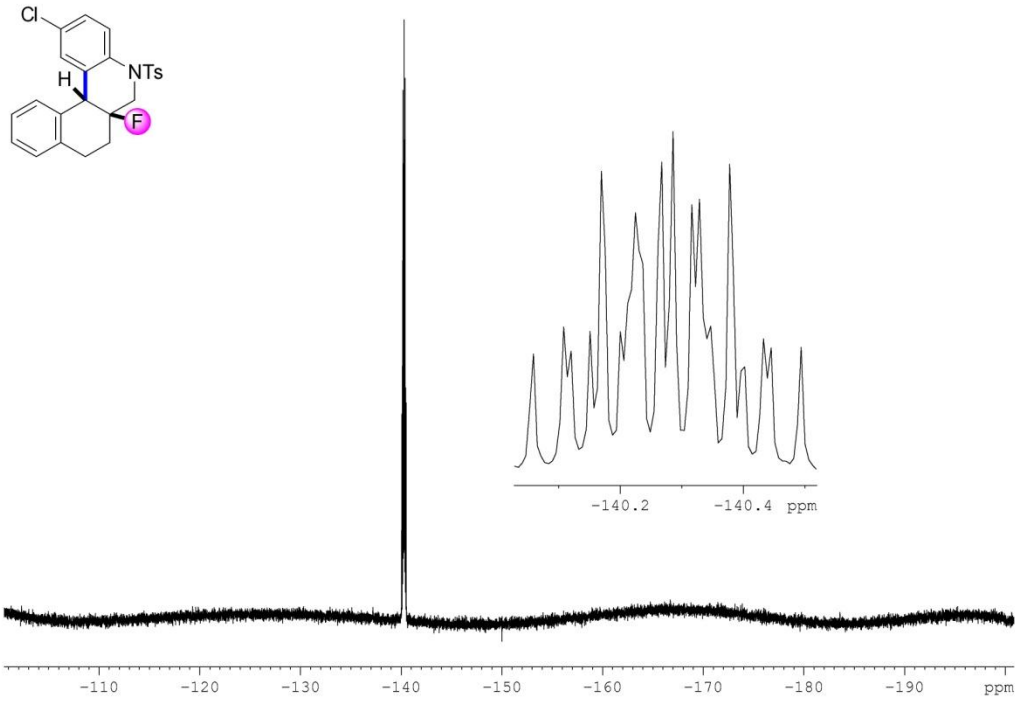

10
9
8
7
6
5
4
3
2
1
ppm

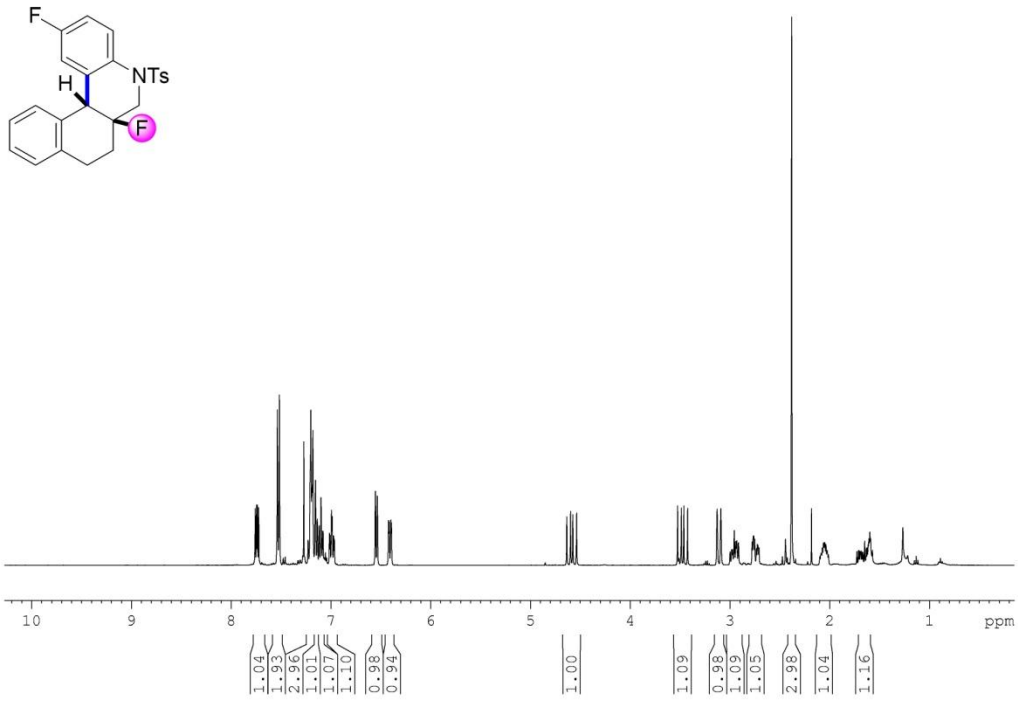

Br
NTs
H
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

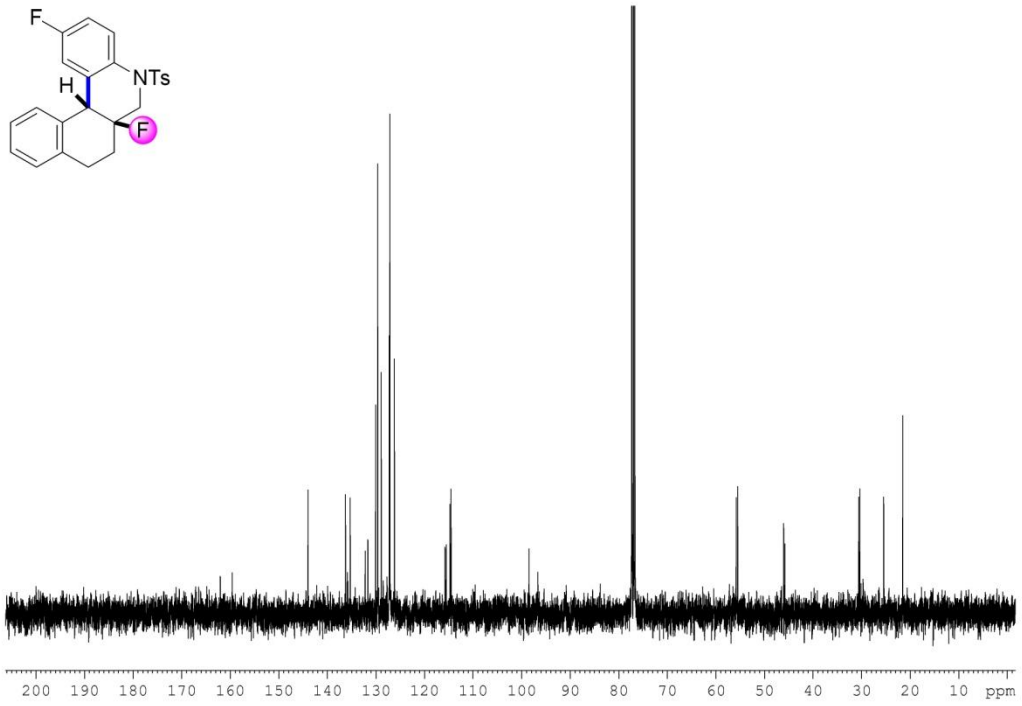

Br
NTs
H
F
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

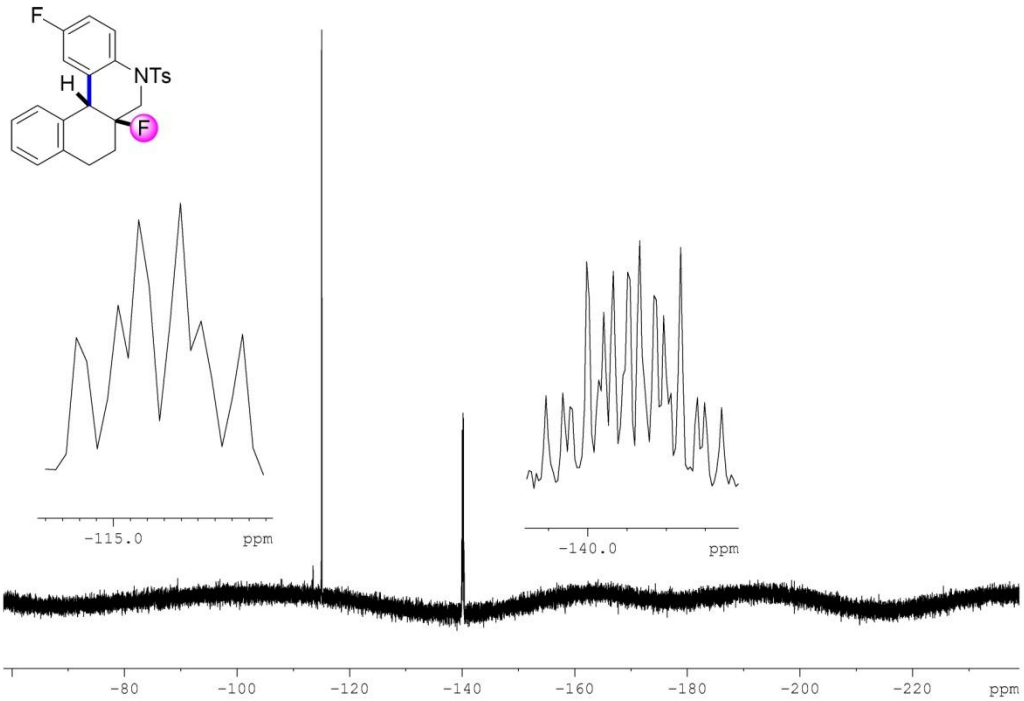

Cl
NTs
H
F
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.98
1.19
4.04
1.17
0.94
0.98
1.00
1.07
1.01
1.07
1.09
3.00
1.05
1.08

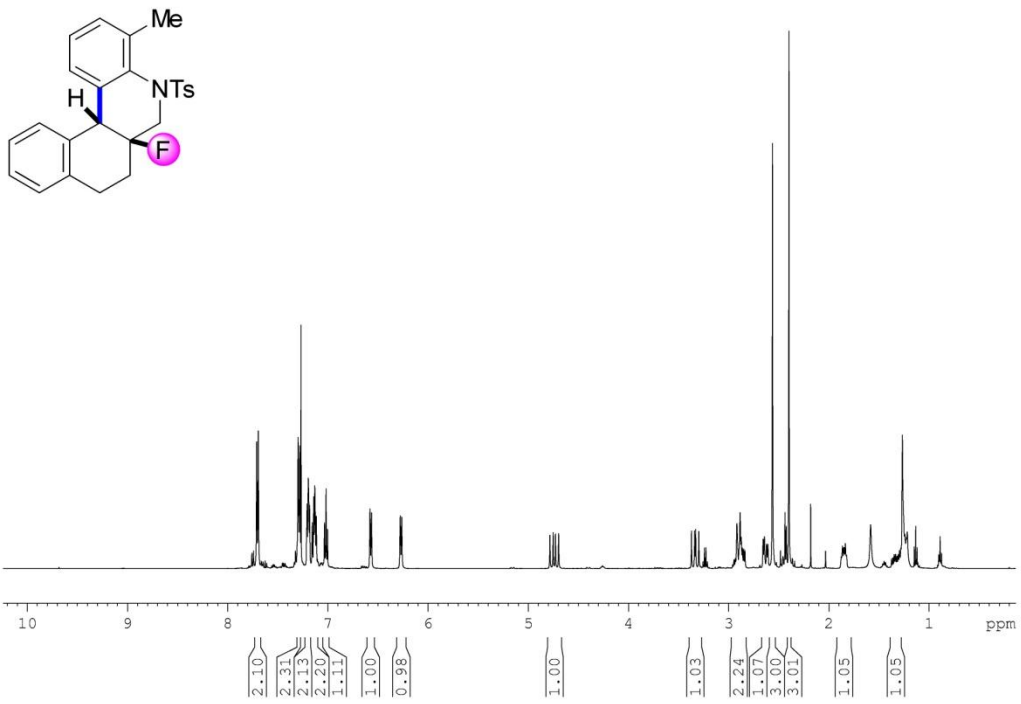

Cl
NTs
H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

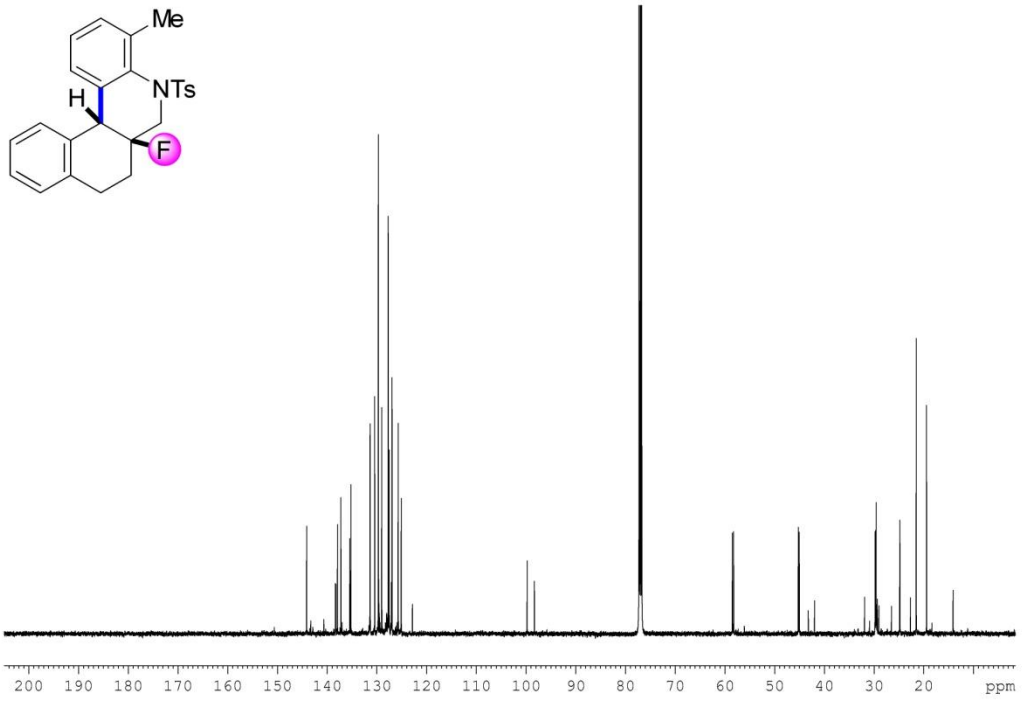

Cl
H
NTs
F
-140.2
-140.4 ppm
-110
-120
-130
-140
-150
-160
-170
-180
-190
ppm

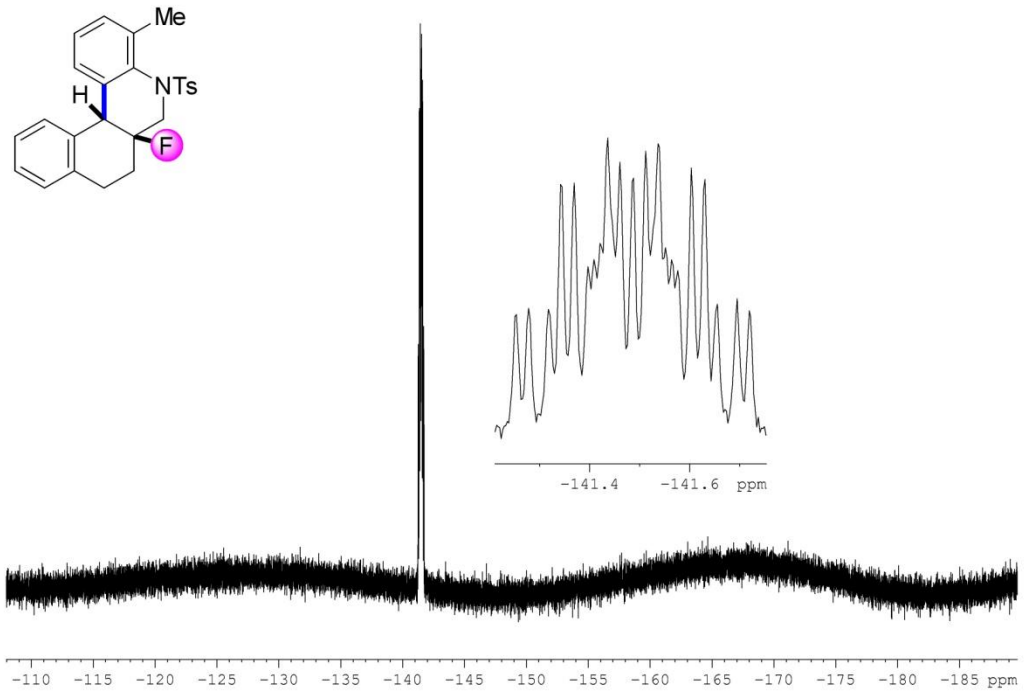

F
H
NTs
F
10
9
8
7
6
5
4
3
2
1
ppm
1.04
1.93
2.96
1.01
1.07
1.10
0.98
0.94
1.00
1.09
0.98
1.09
1.05
2.98
1.04
1.16

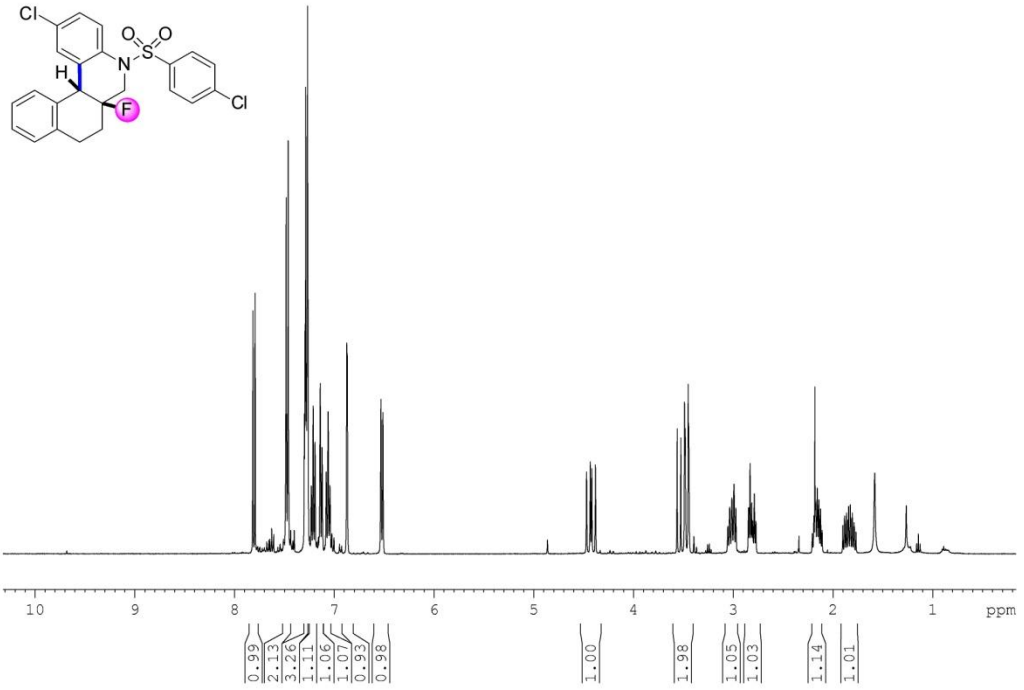

F
H
NTs
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

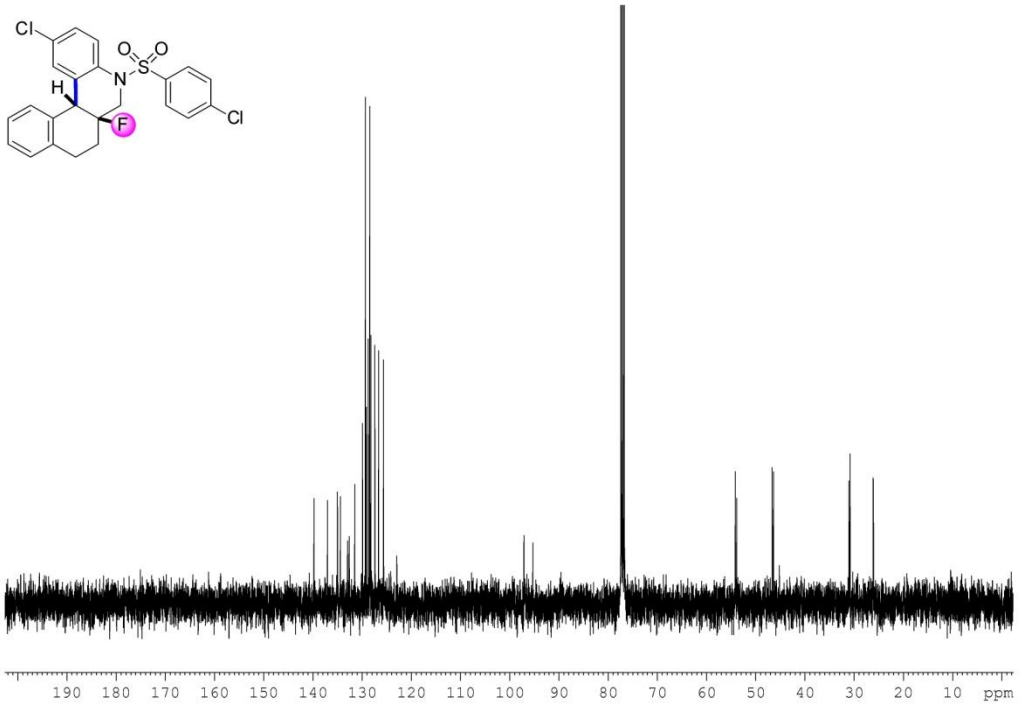

F
H
NTs
F
-115.0 ppm
-140.0 ppm
-80 -100 -120 -140 -160 -180 -200 -220 ppm

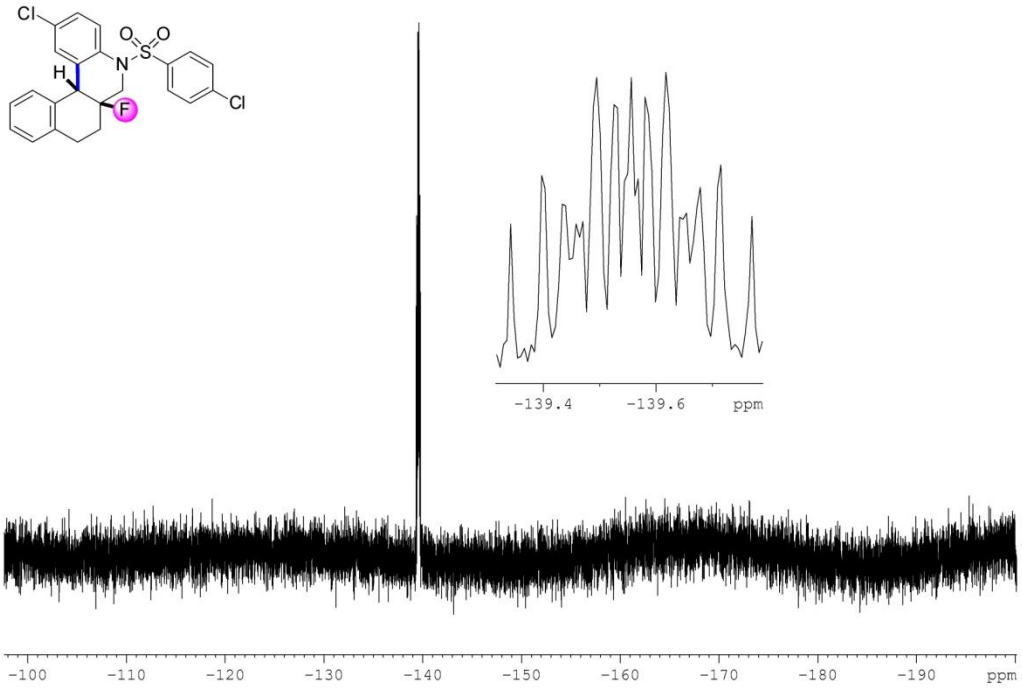

Me
NTs
H
F
10
9
8
7
6
5
4
3
2
1
ppm
2.10
2.31
2.13
2.20
1.11
1.00
0.98
1.00
1.03
2.24
1.07
3.00
3.01
1.05
1.05

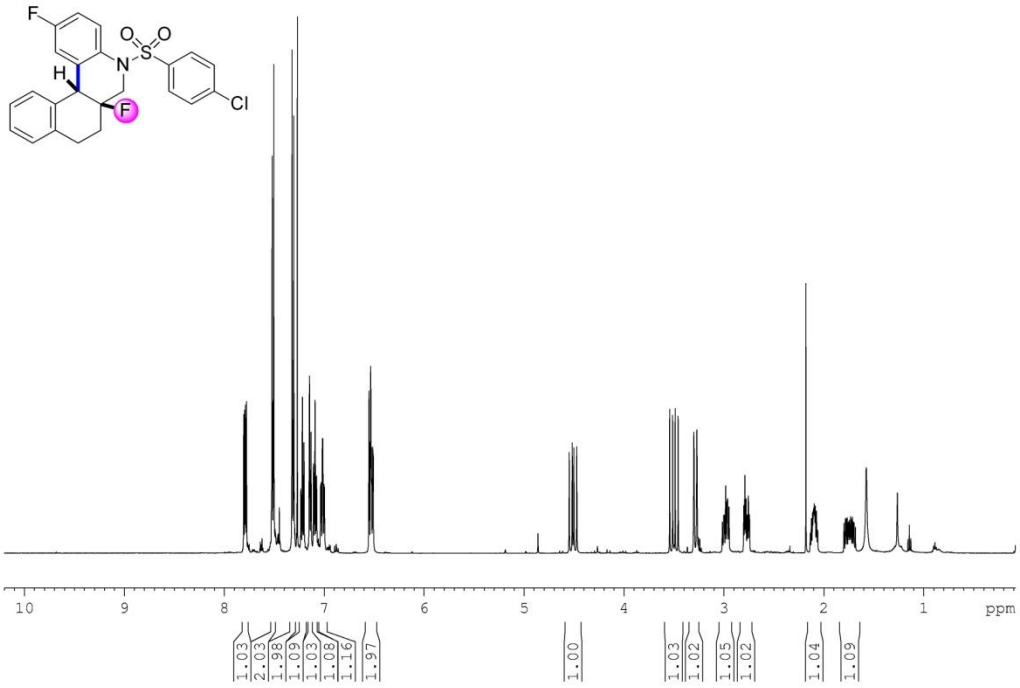

Me
NTs
H
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

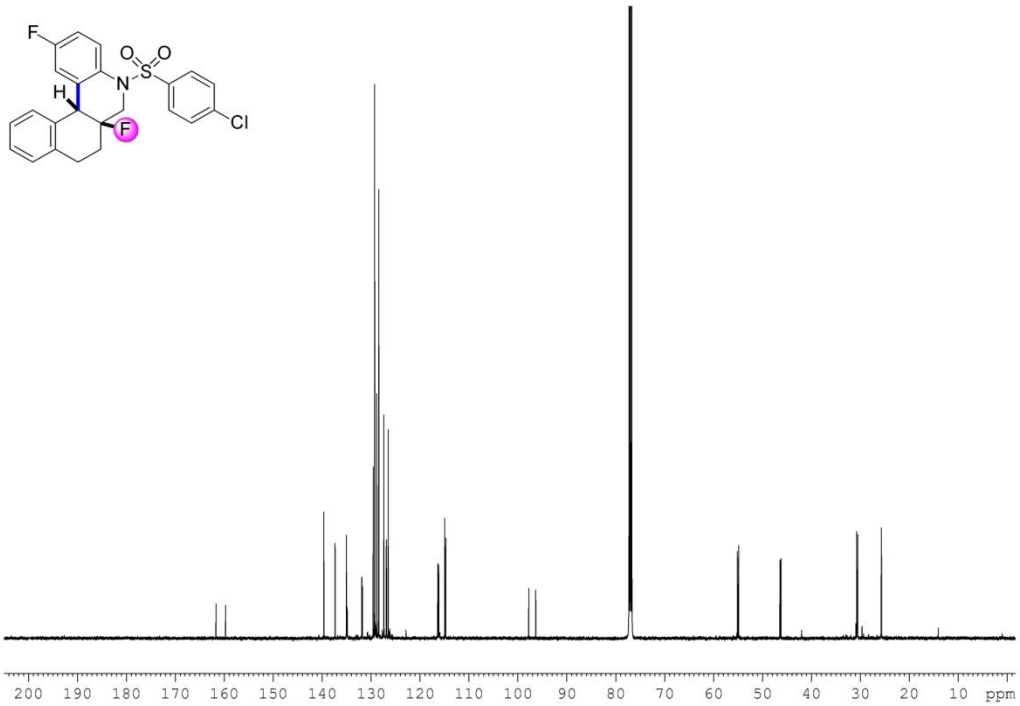

Me
NTs
H
F
-141.4
-141.6 ppm
-110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 ppm

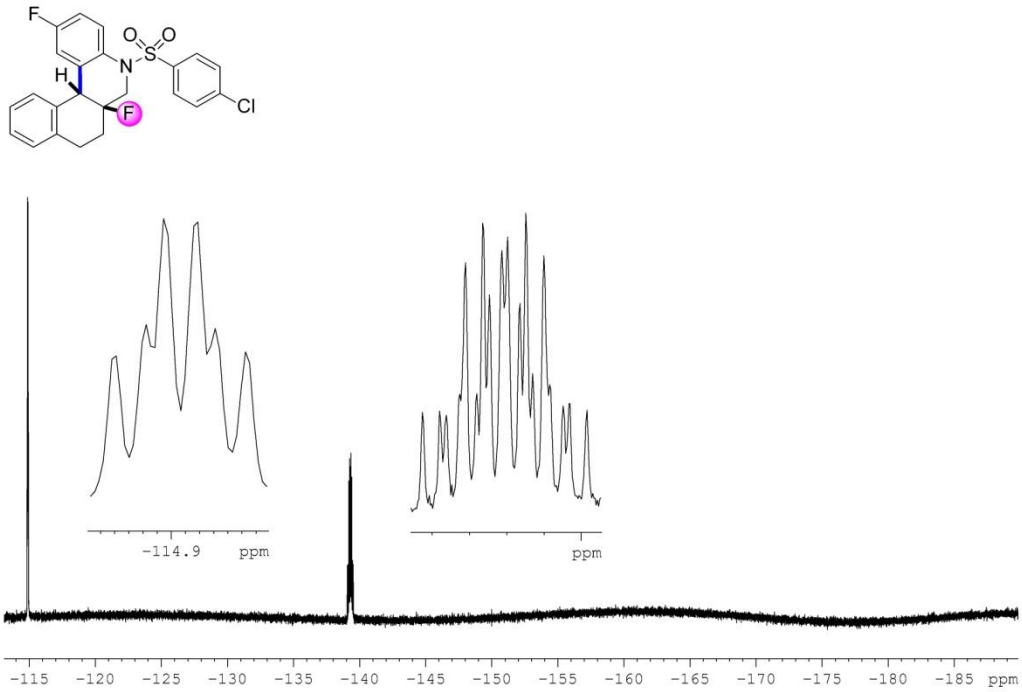

Cl
O
O
S
N
H
F
Cl
10 9 8 7 6 5 4 3 2 1 ppm
0.99
2.13
3.26
1.11
1.06
1.07
0.93
0.98
1.00
1.98
1.05
1.03
1.14
1.01

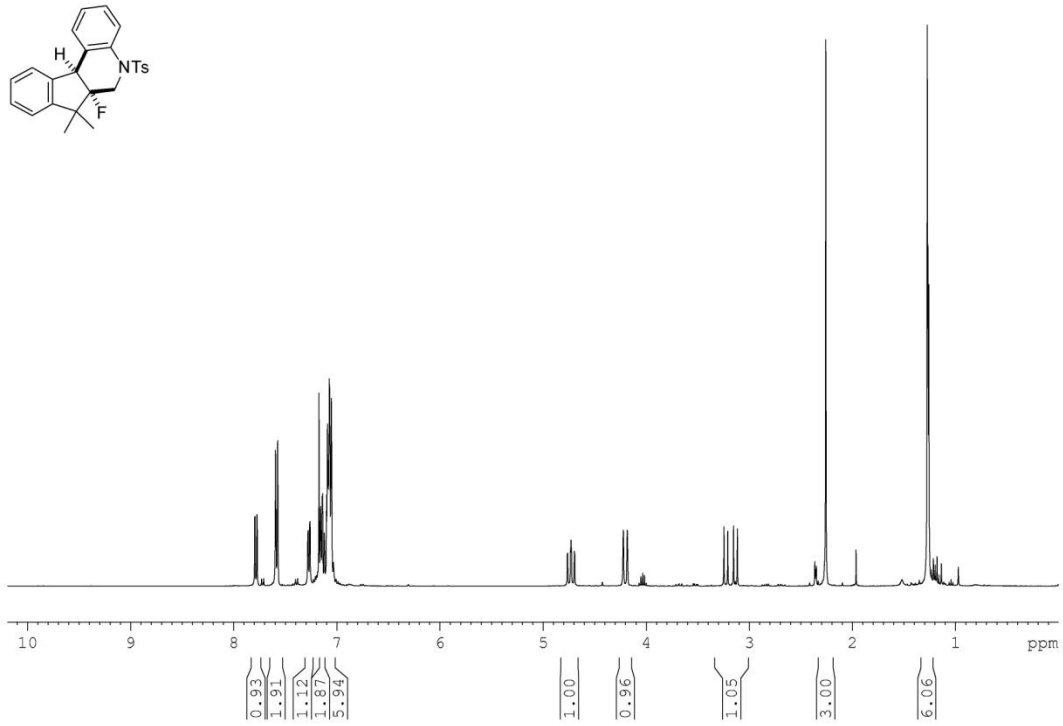

Cl
O
O
S
N
H
F
Cl
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

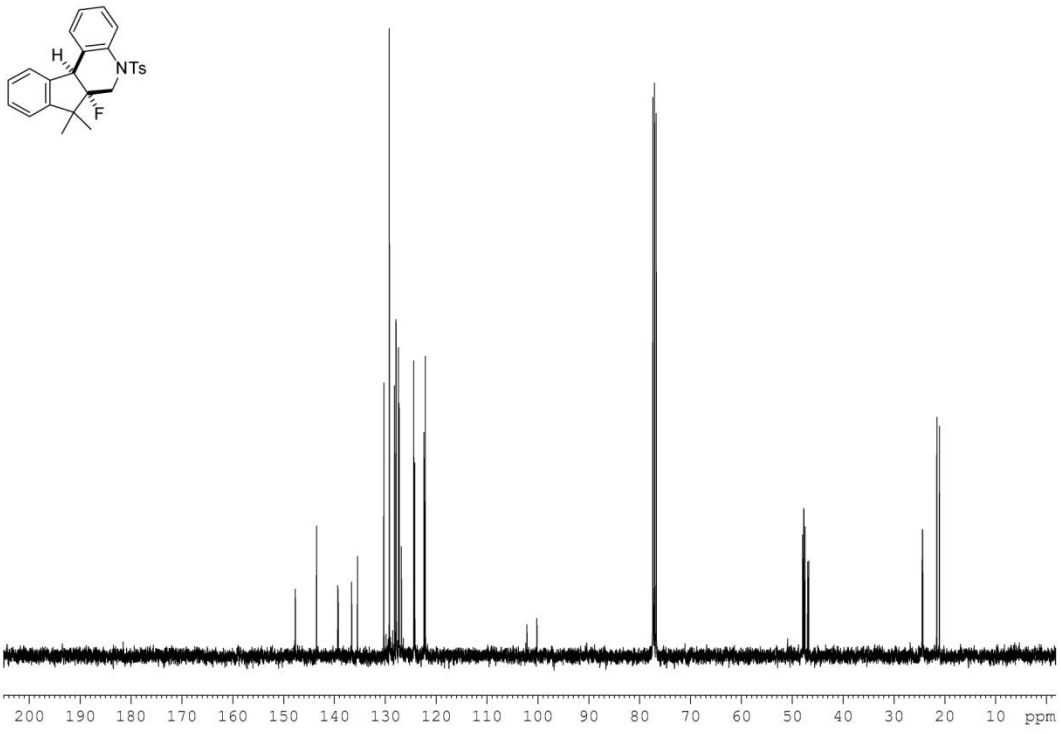

Cl
O
O
S
N
H
F
Cl
-139.4
-139.6
ppm
-100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

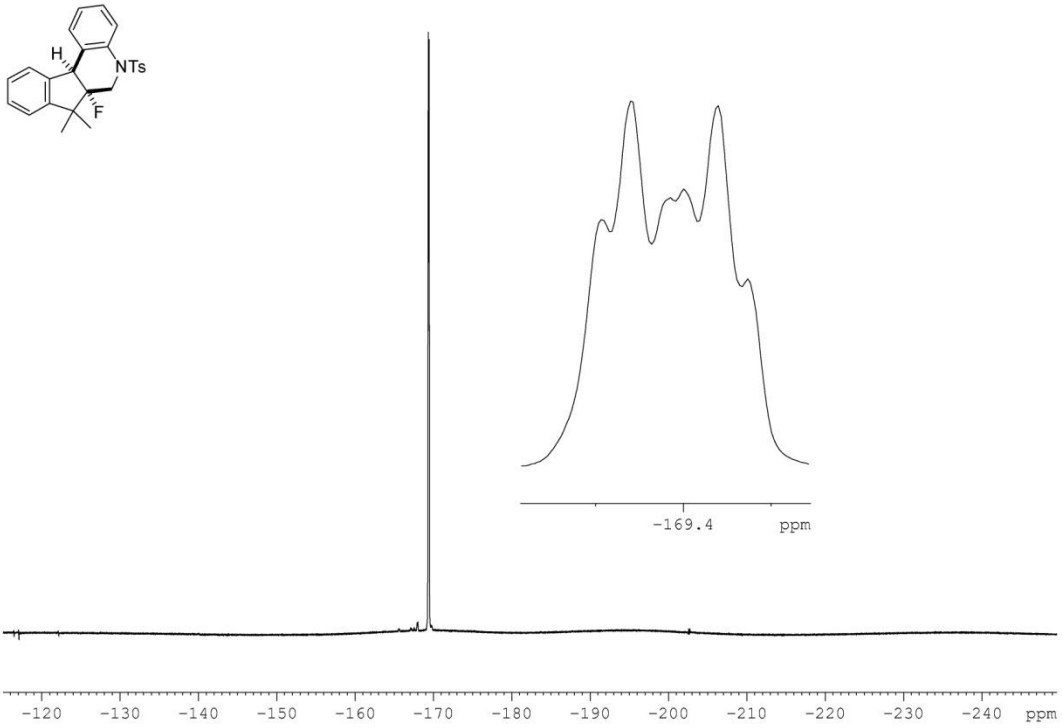

F
O
O
S
N
H
F
Cl
10
9
8
7
6
5
4
3
2
1
ppm
1.03
2.03
1.98
1.09
1.03
1.08
1.16
1.97
1.00
1.03
1.02
1.05
1.02
1.04
1.09

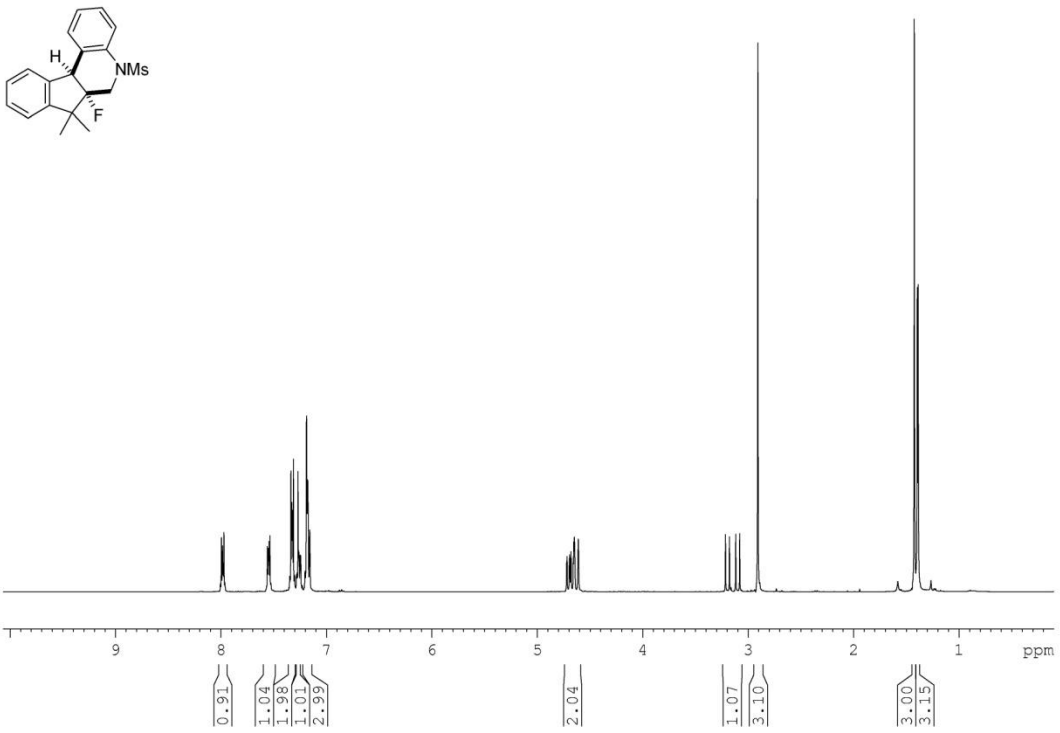

F
O
O
S
N
H
F
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

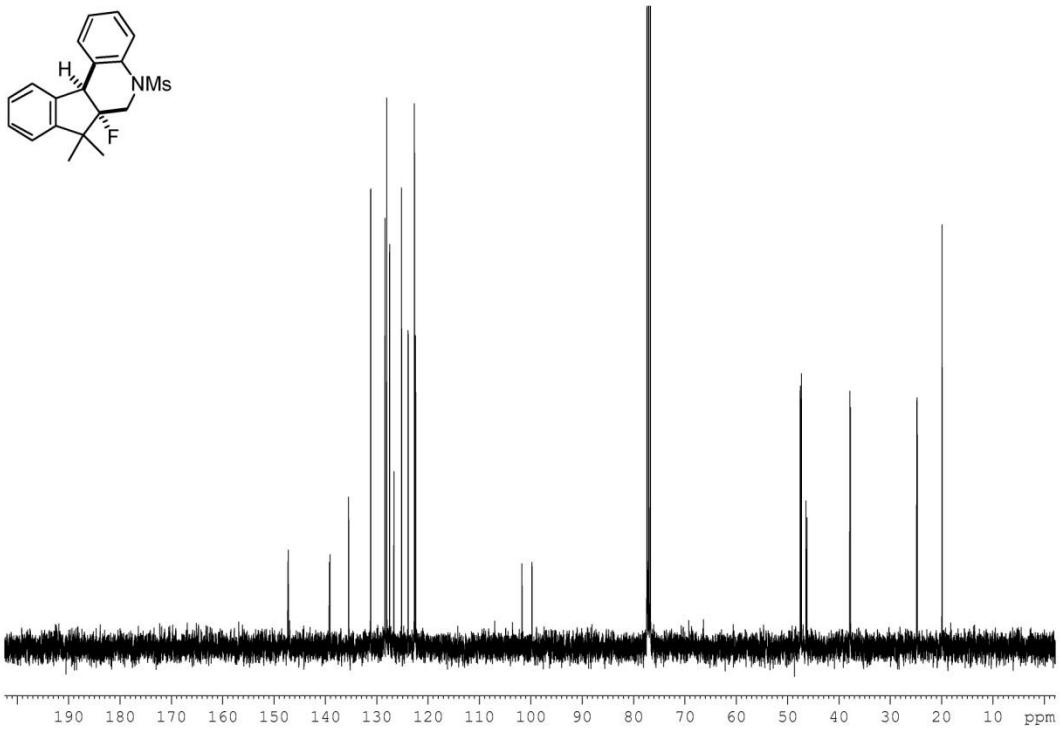

F
O
O
S
N
H
F
Cl
-114.9
ppm
ppm
-115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 ppm

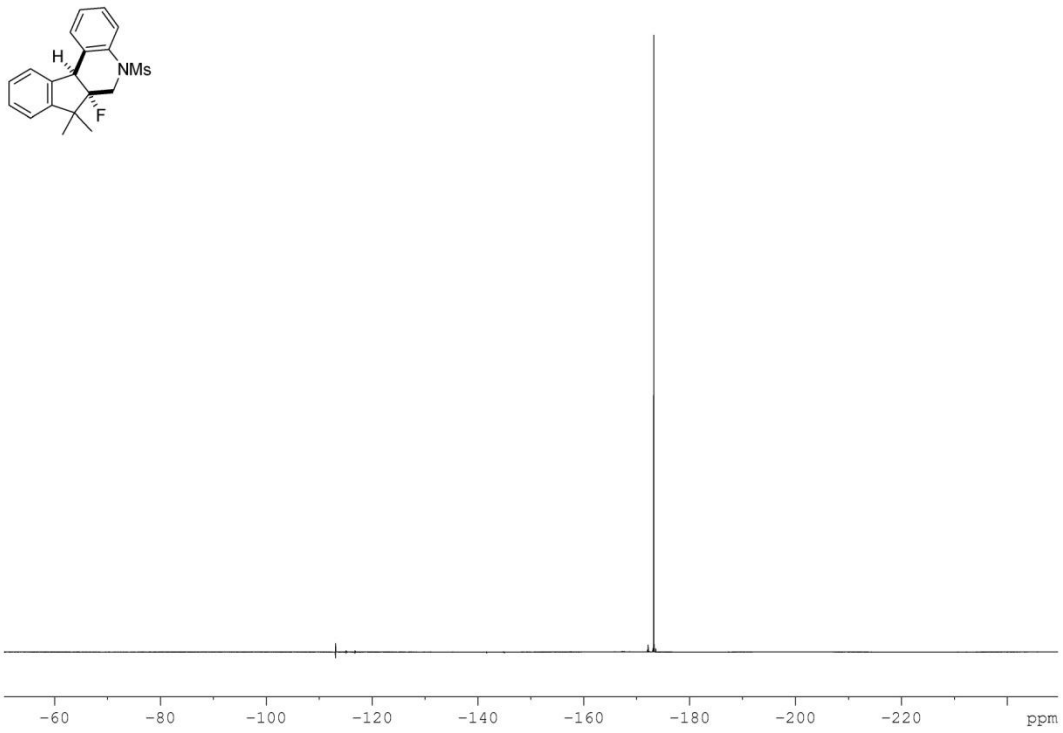

H
NTs
F
10 9 8 7 6 5 4 3 2 1 ppm
0.93
1.91
1.12
1.87
5.94
1.00
0.96
1.05
3.00
6.06

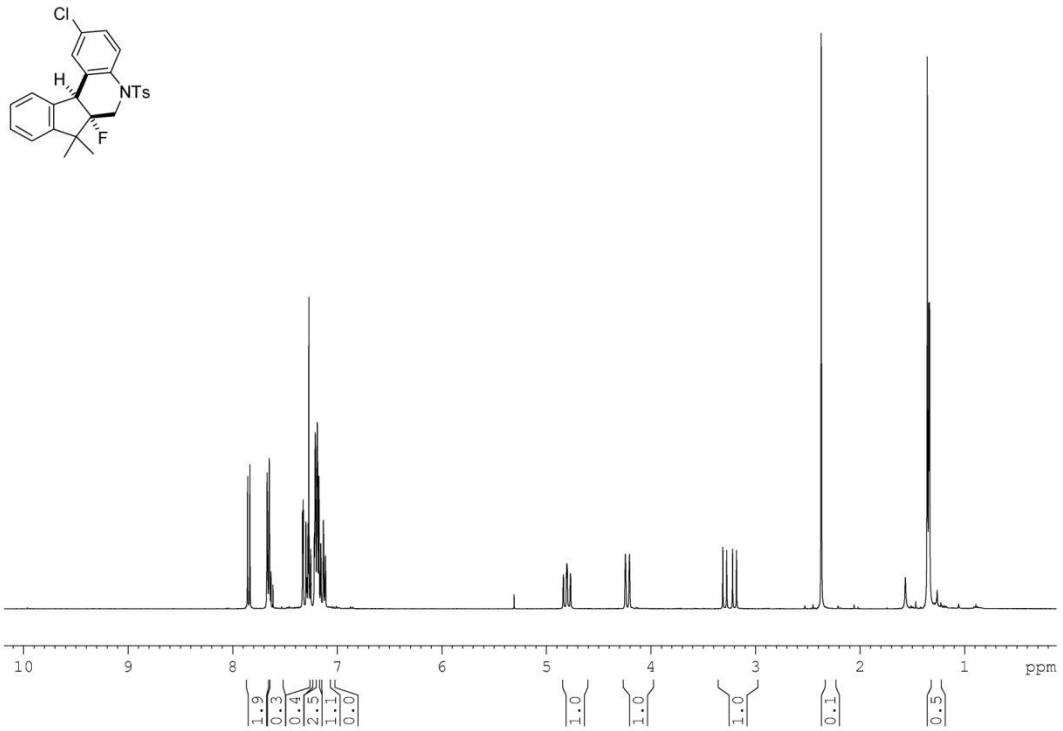

H
NTs
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

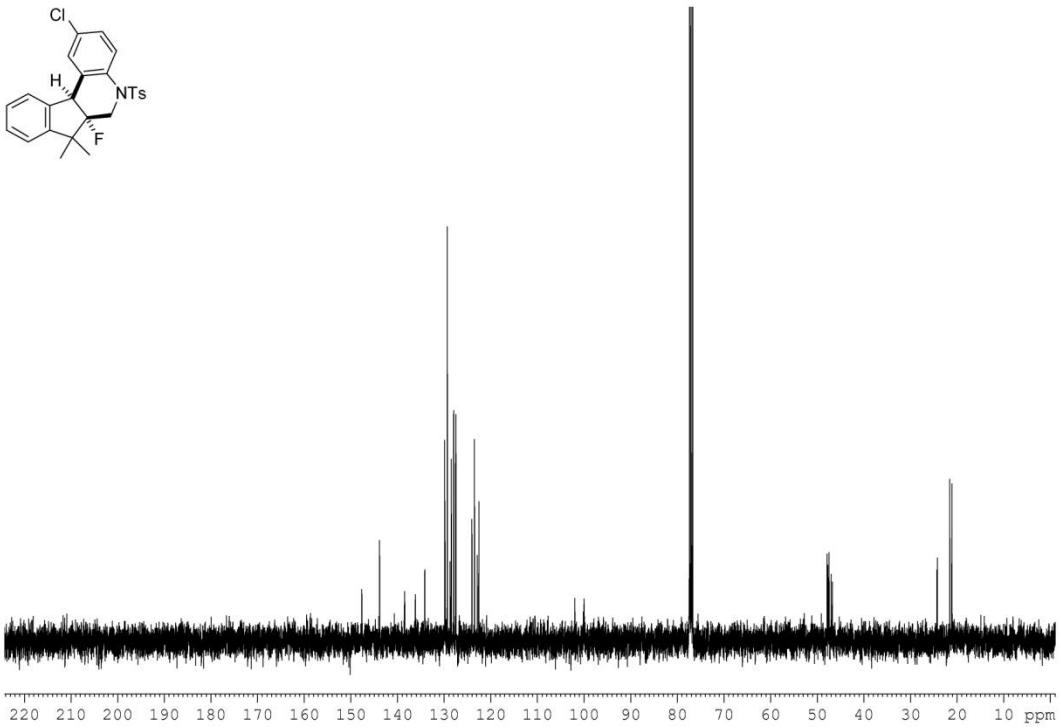

H
NTs
F
-169.4
ppm
-120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 ppm

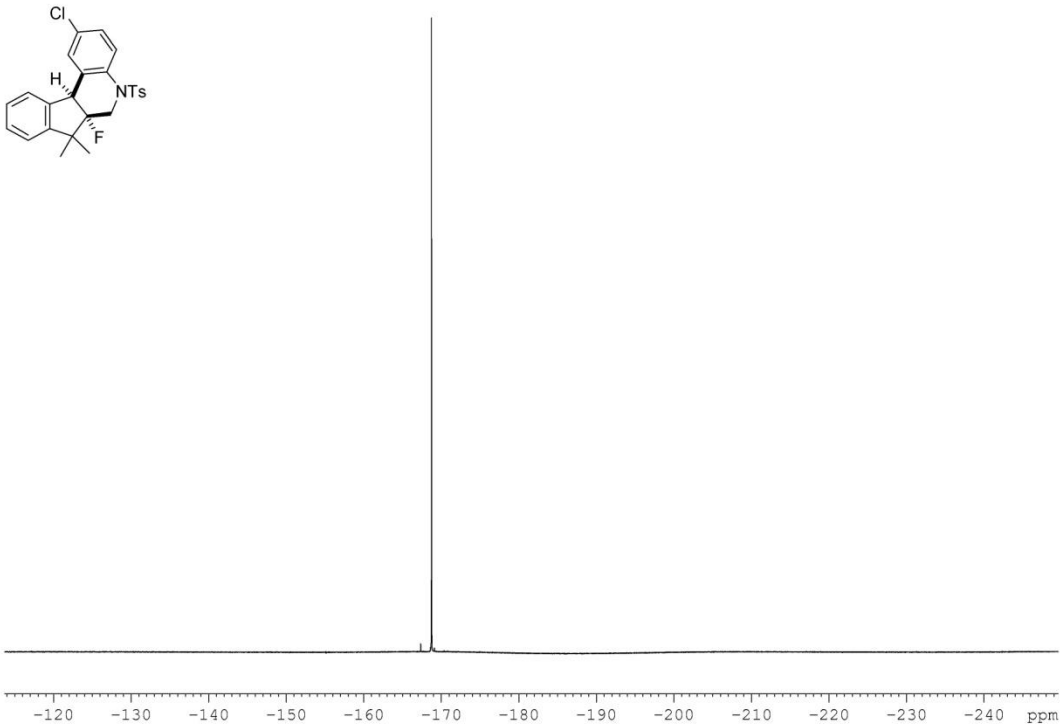

H
NMs
F
9
8
7
6
5
4
3
2
1
ppm
0.91
1.04
1.98
1.01
2.99
2.04
1.07
3.10
3.00
3.15

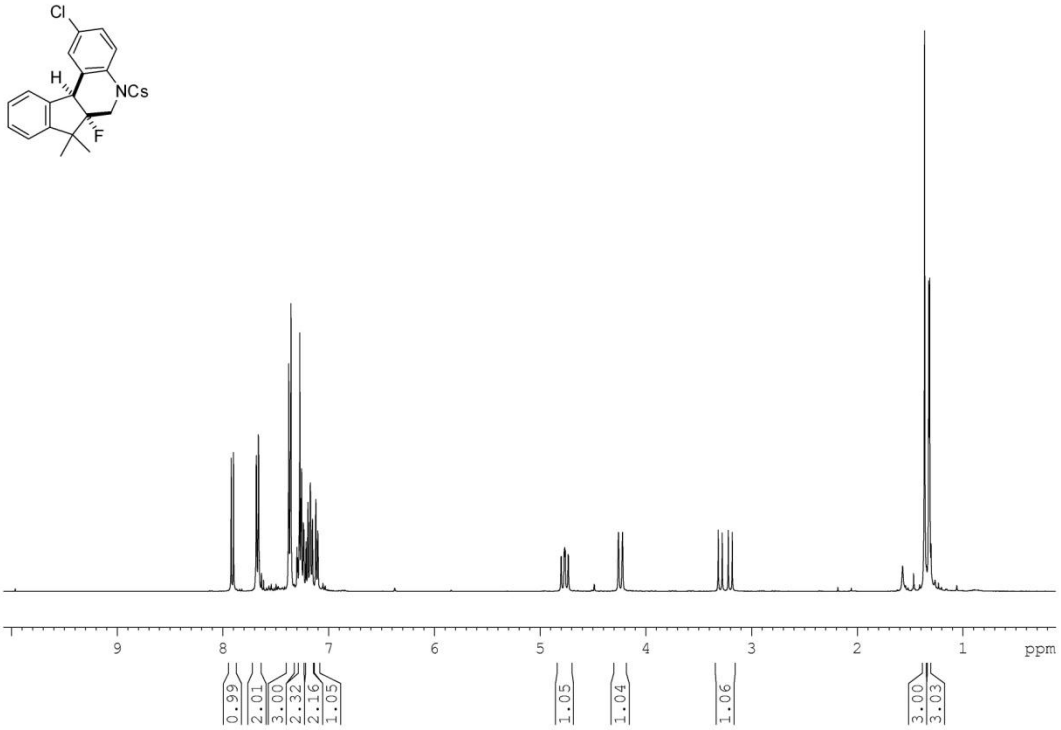

H
NMs
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

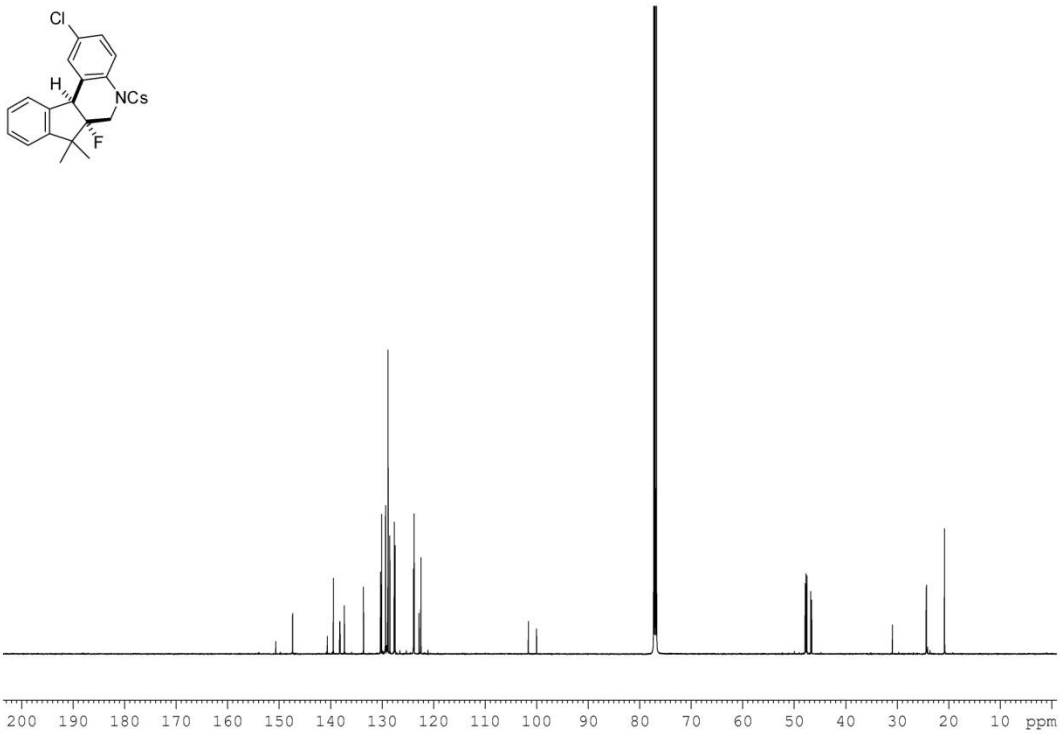

H
NMs
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

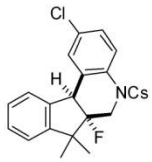

Cl
H
NTs
F
10
9
8
7
6
5
4
3
2
1
ppm
1.9
0.3
0.4
2.5
1.1
0.0
1.0
1.0
1.0
0.1
0.5

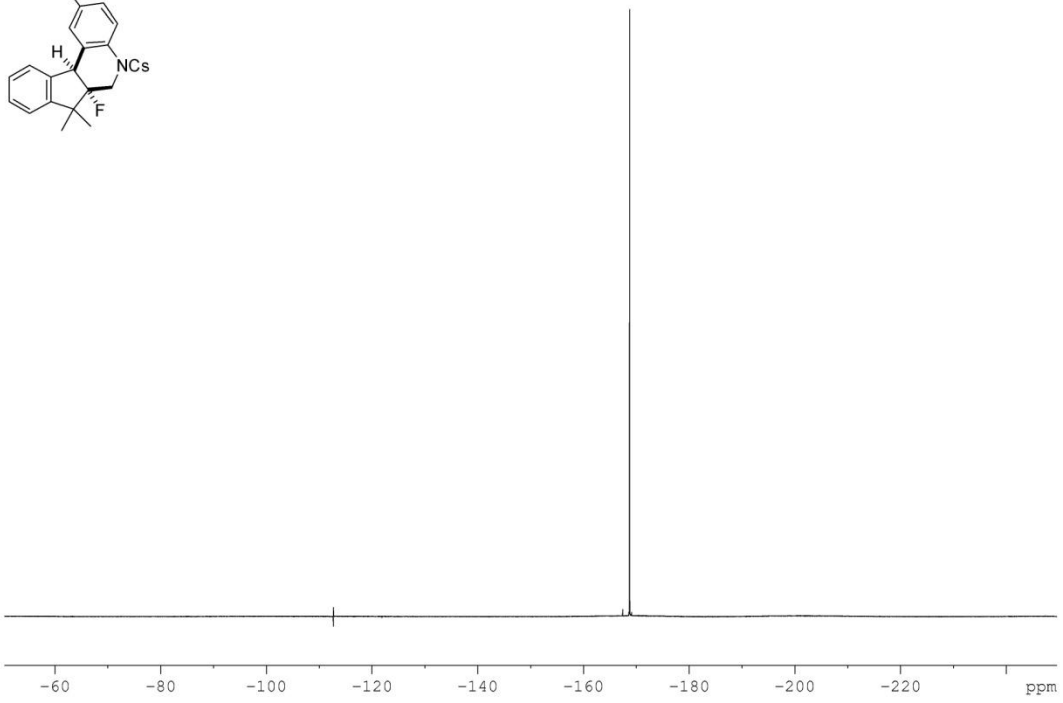

Cl
H
NTs
F
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

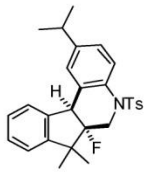

Cl
H
NTs
F
-120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 ppm

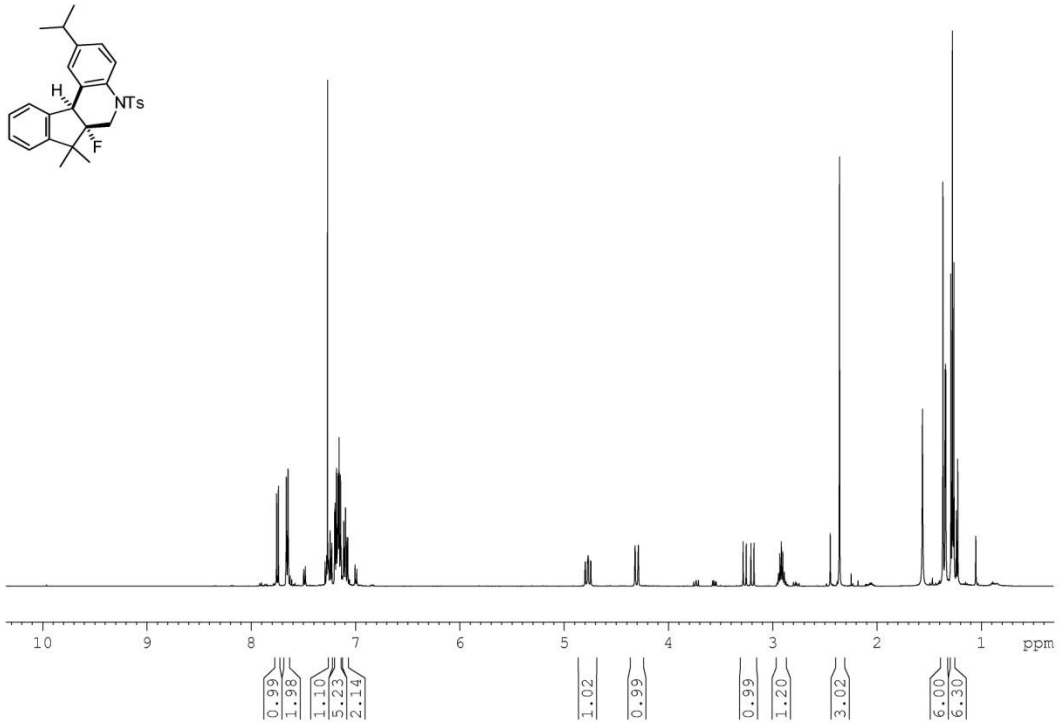

Cl
H
NCs
F
9
8
7
6
5
4
3
2
1
ppm
0.99
2.01
3.00
2.32
2.16
1.05
1.05
1.04
1.06
3.00
3.03

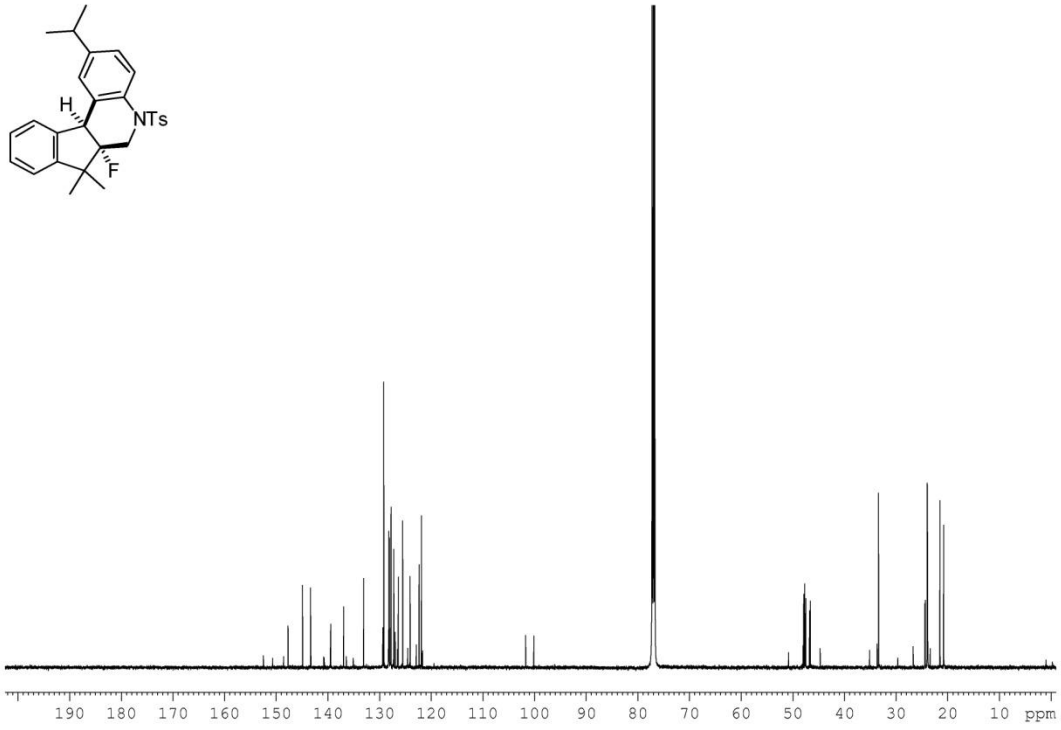

Cl
H
NCs
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

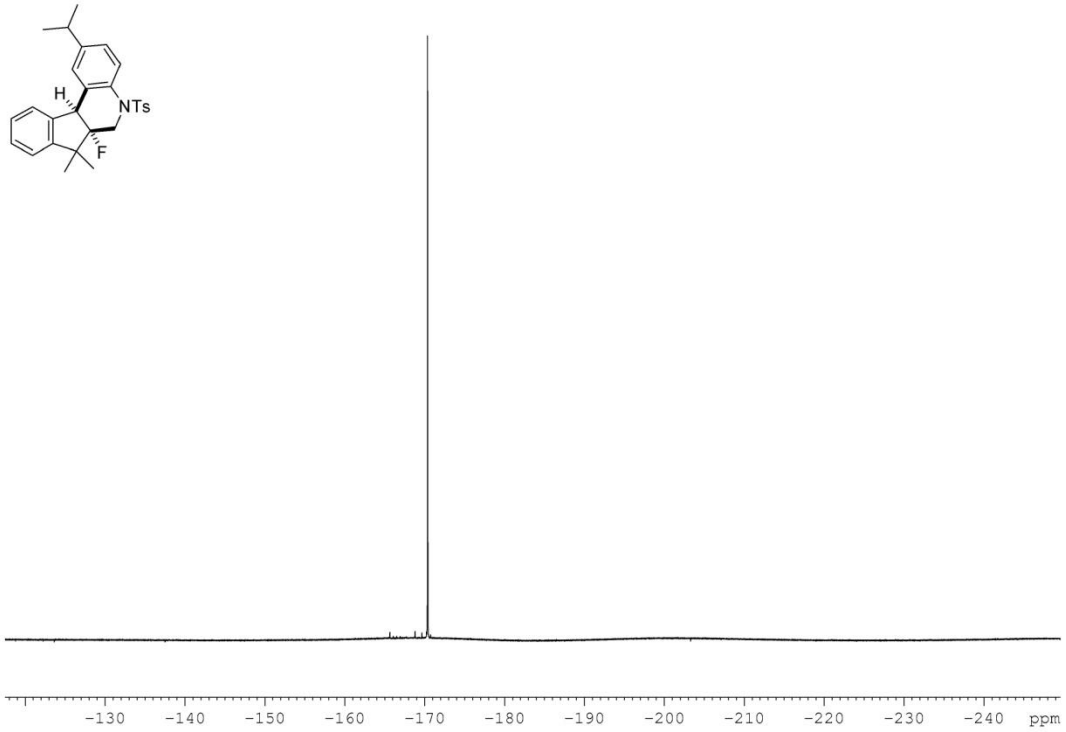

Cl
H
NCs
F

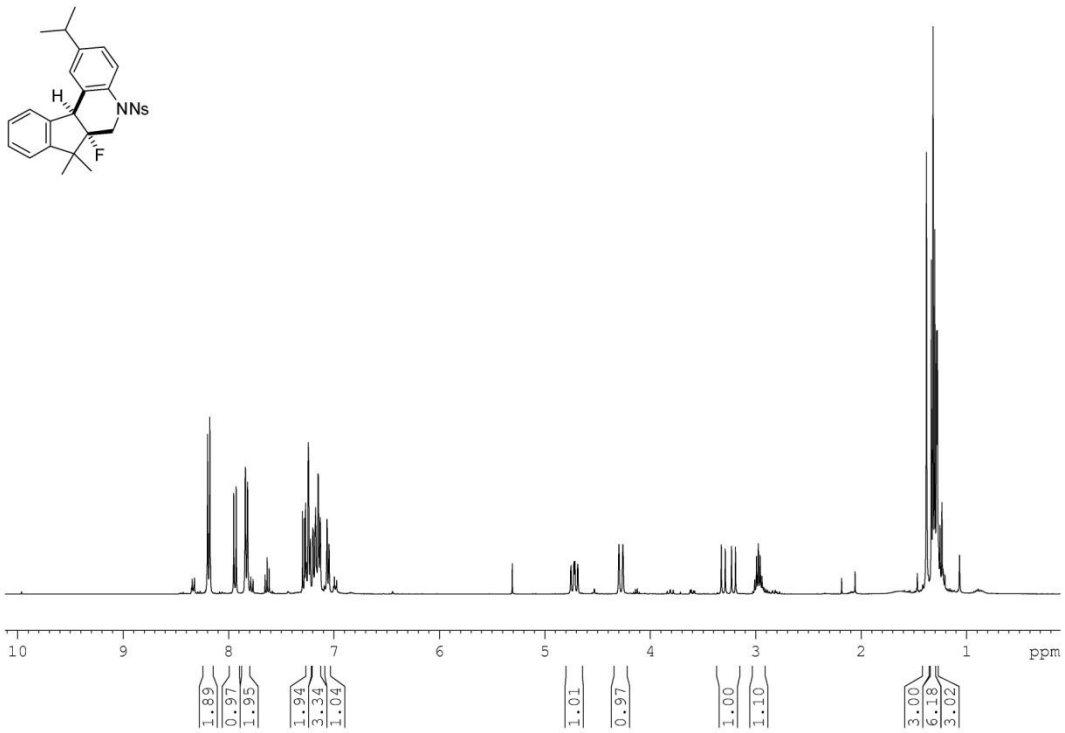

-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

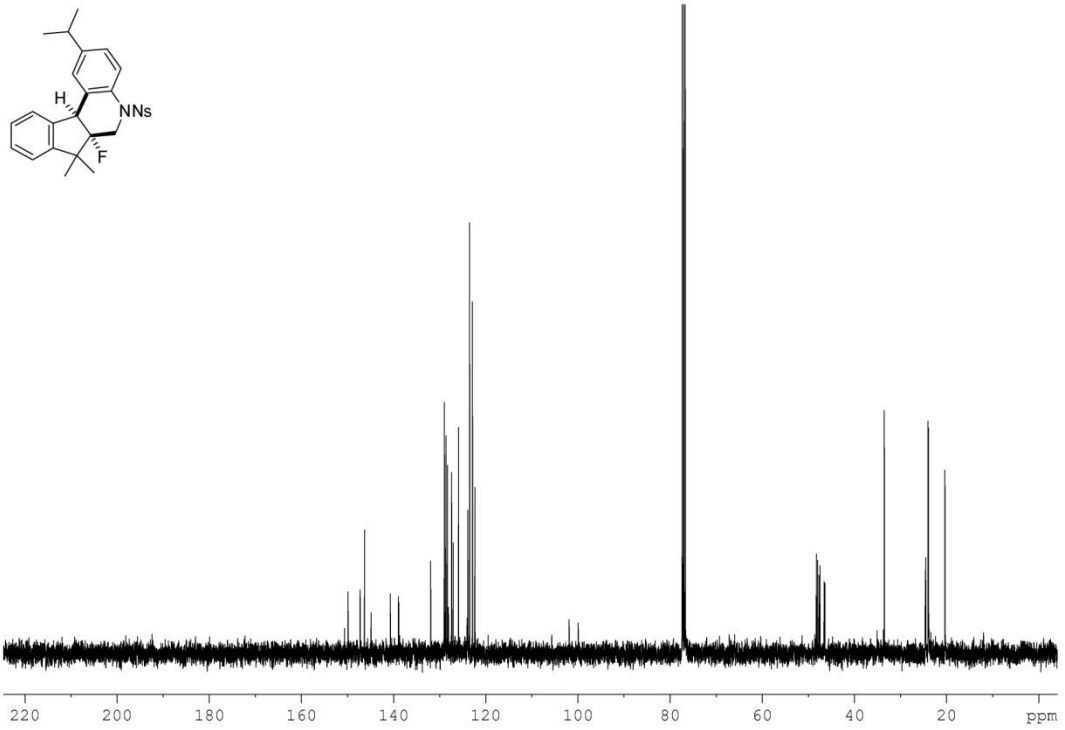

H
NTs
F

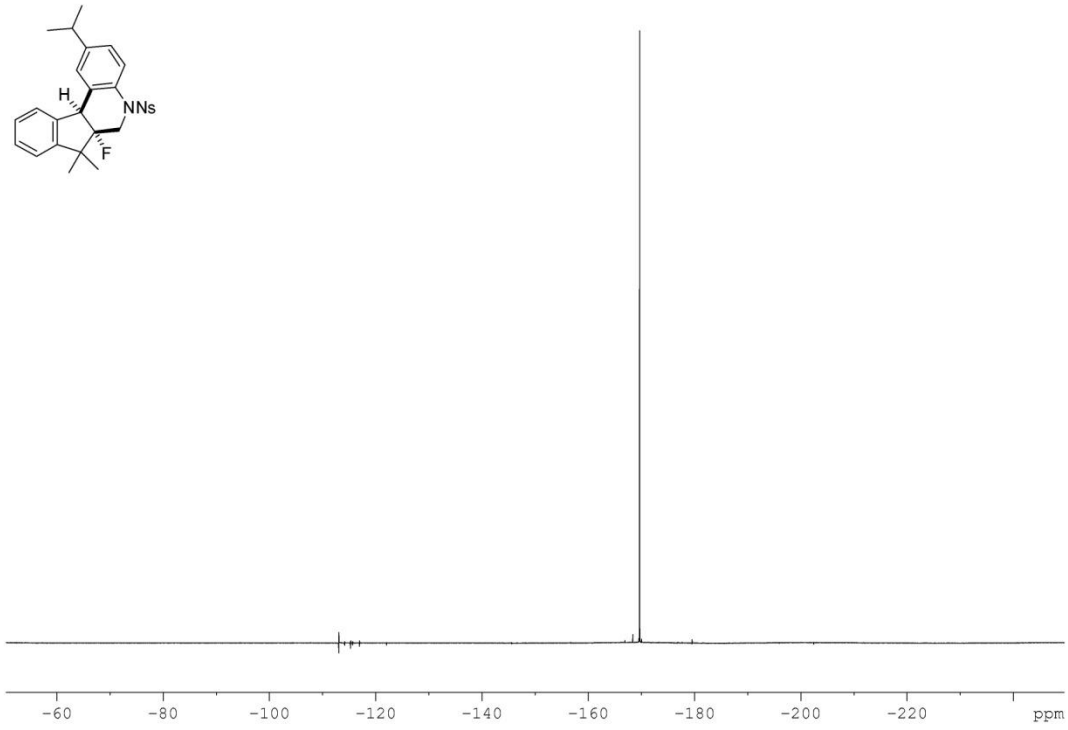

10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.98
1.10
5.23
2.14
1.02
0.99
0.99
1.20
3.02
6.00
6.30

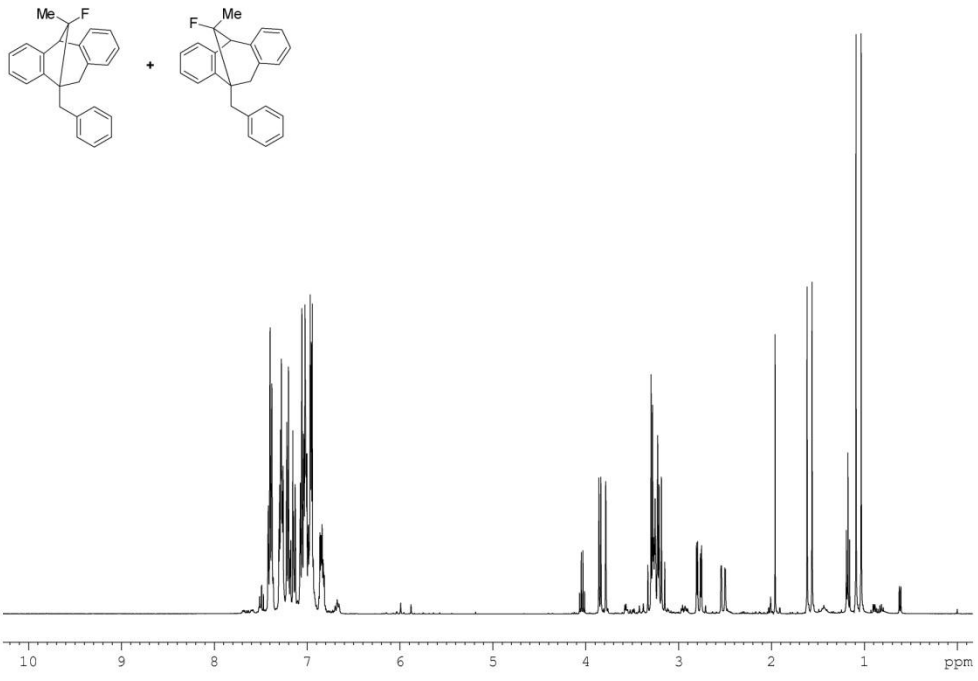

H
NTs
F
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

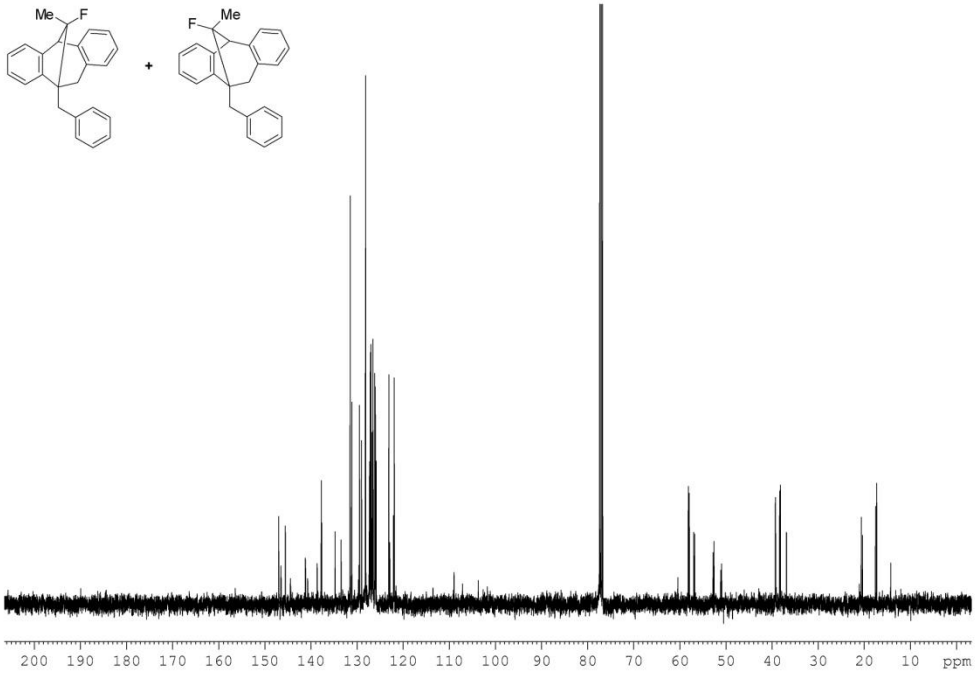

H
NTs
F
-130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 ppm

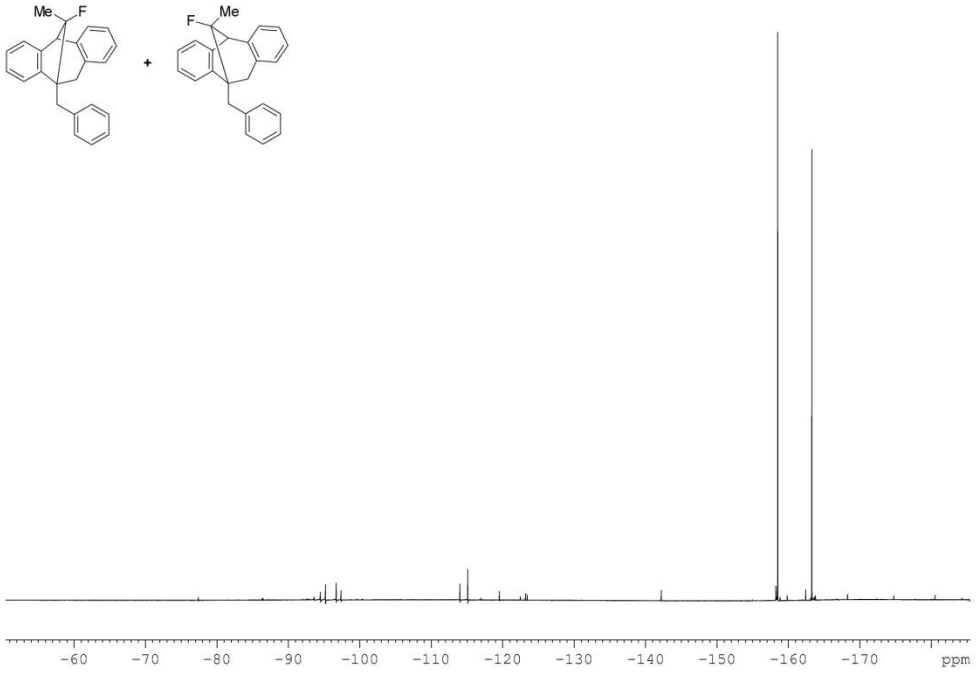

H
NNs
F
10
9
8
7
6
5
4
3
2
1
ppm
1.89
0.97
1.95
1.94
3.34
1.04
1.01
0.97
1.00
1.10
3.00
6.18
3.02

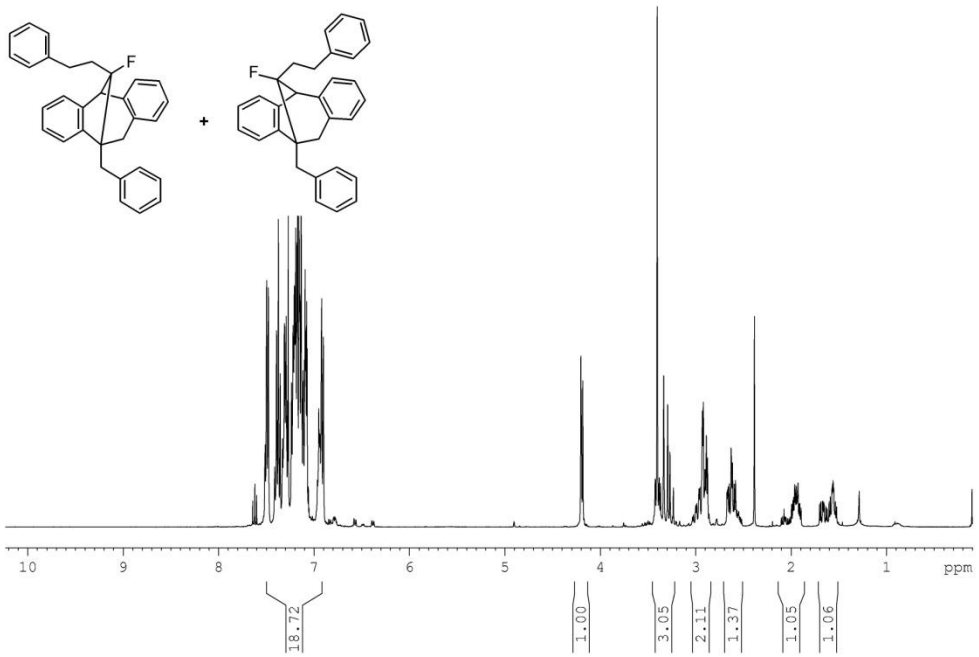

H
NNs
F
220
200
180
160
140
120
100
80
60
40
20
ppm

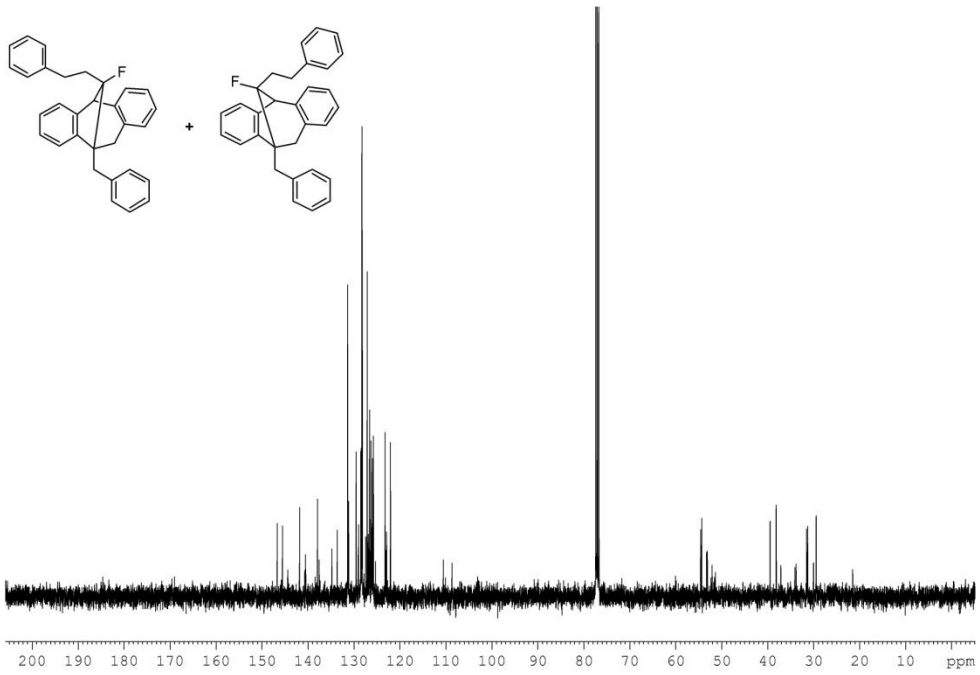

H
NNs
F
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

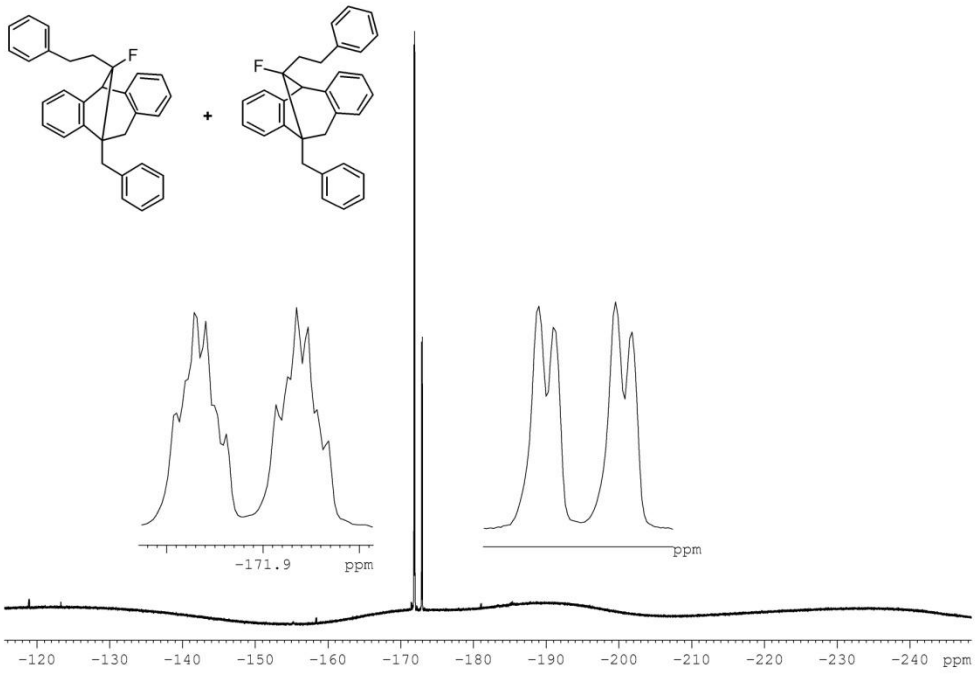

Me
F
+
F
Me
10
9
8
7
6
5
4
3
2
1
ppm

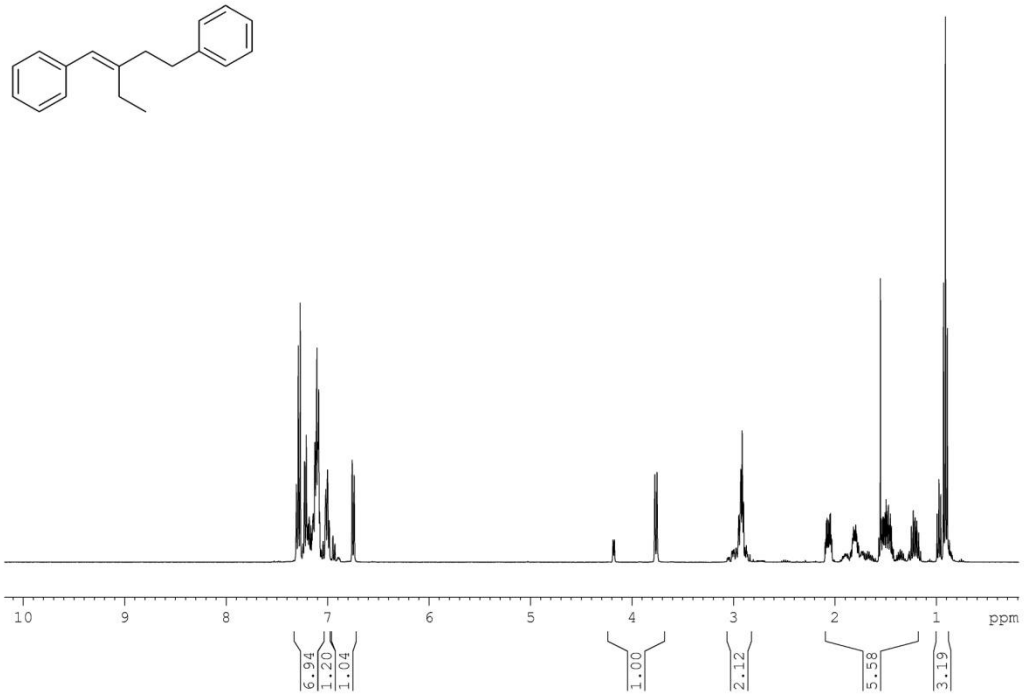

Me
F
+
F
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

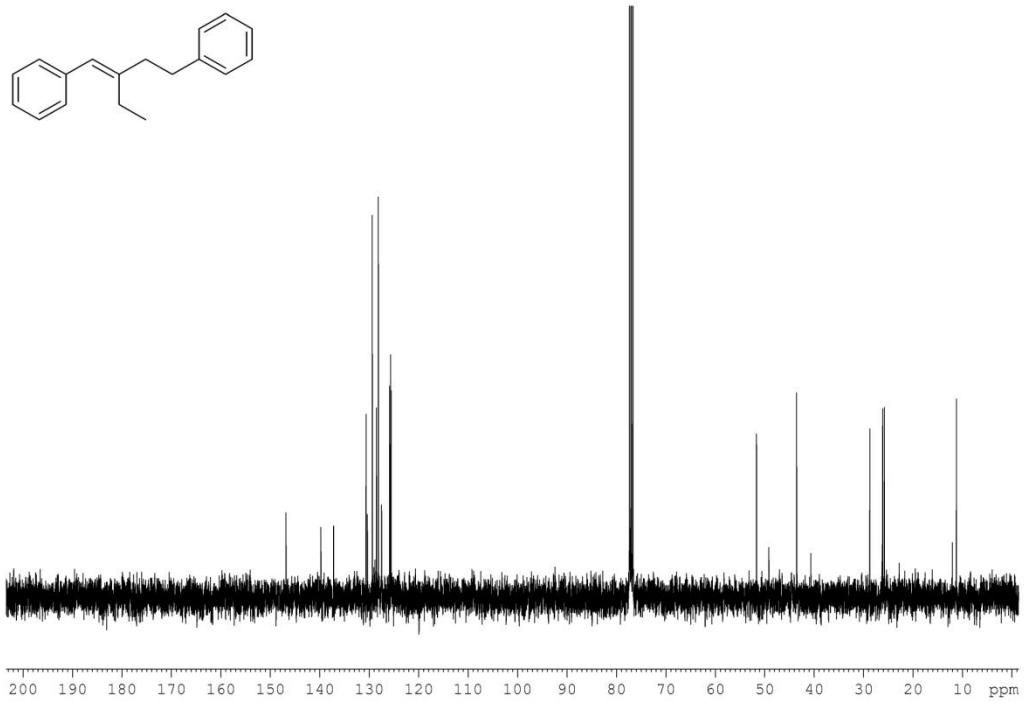

Me
F
+
F
Me
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 ppm

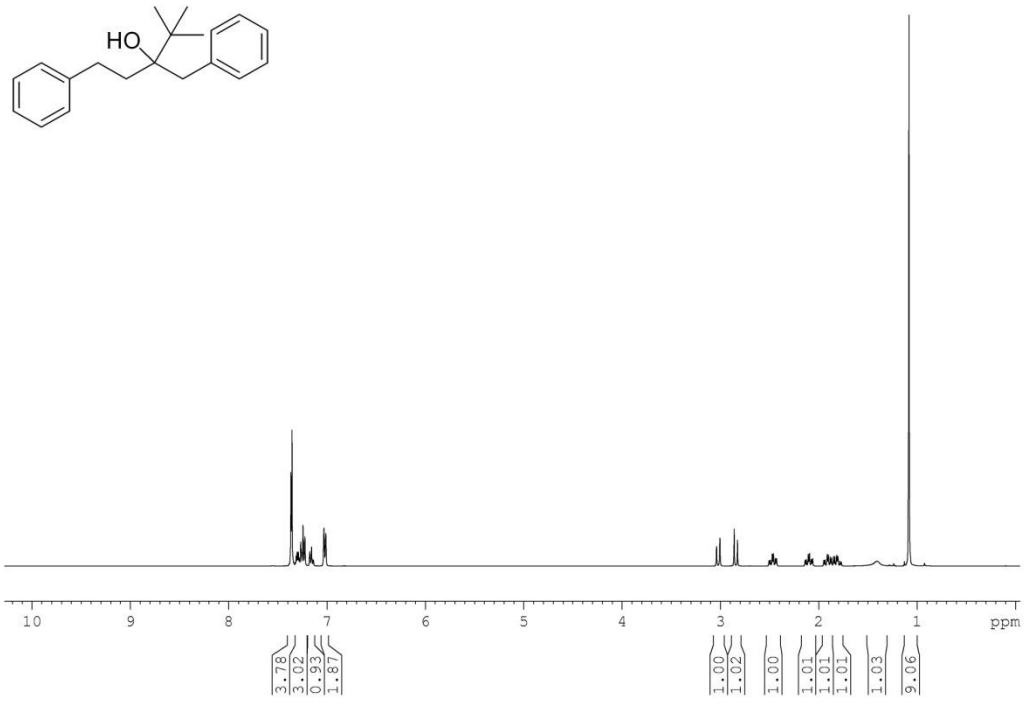

F
+
F
10
9
8
7
6
5
4
3
2
1
ppm
18.72
1.00
3.05
2.11
1.37
1.05
1.06

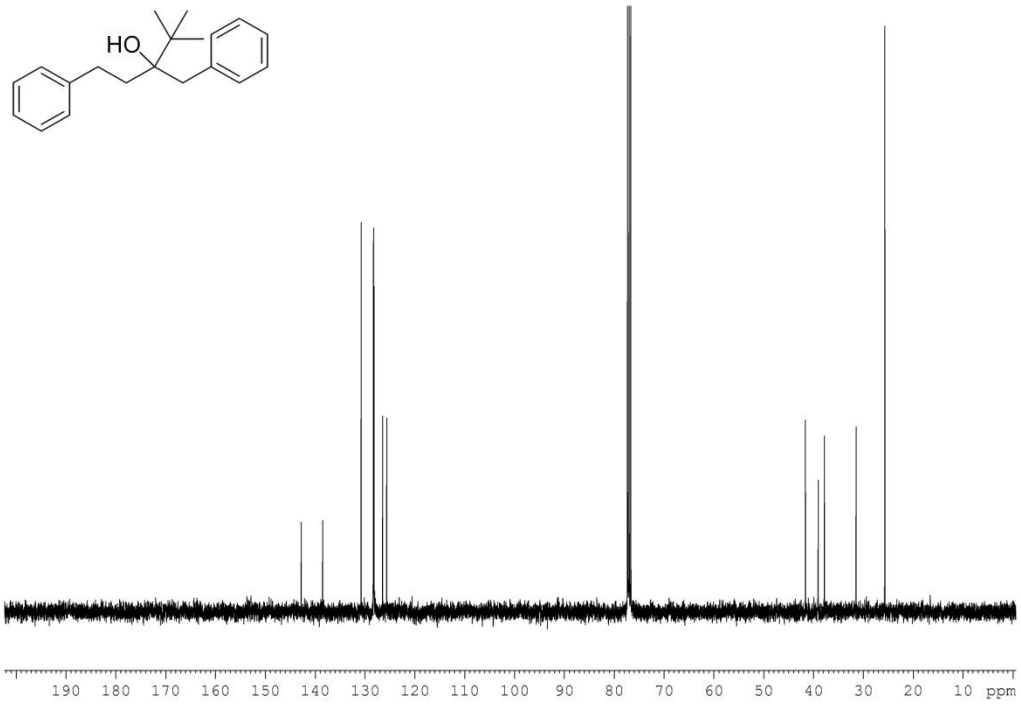

F
+
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

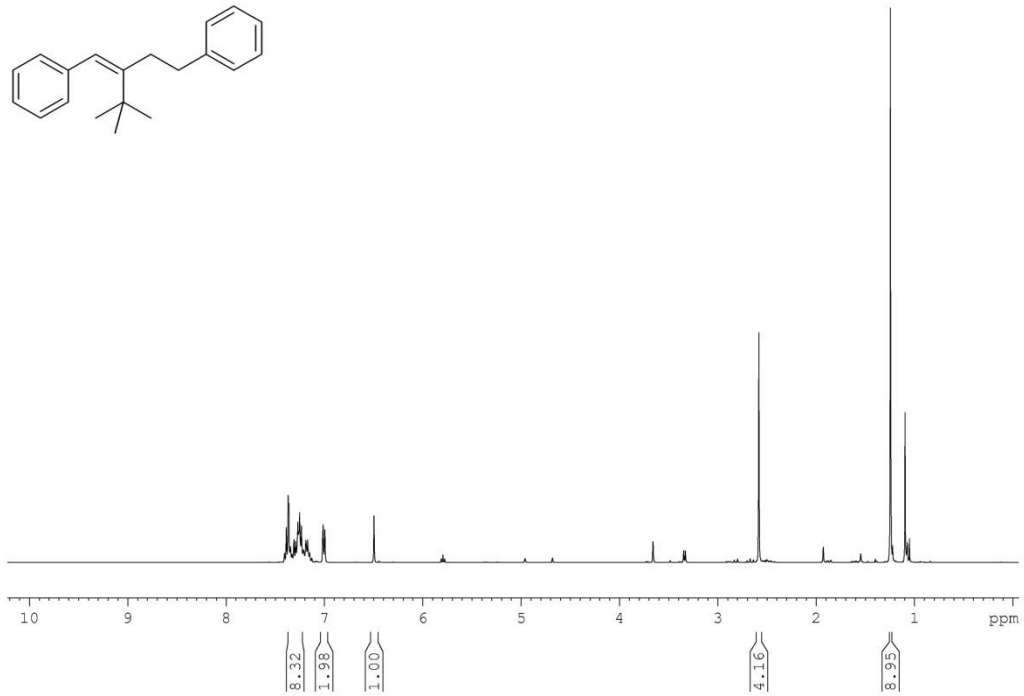

F
+
F
-171.9
ppm
ppm
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
ppm

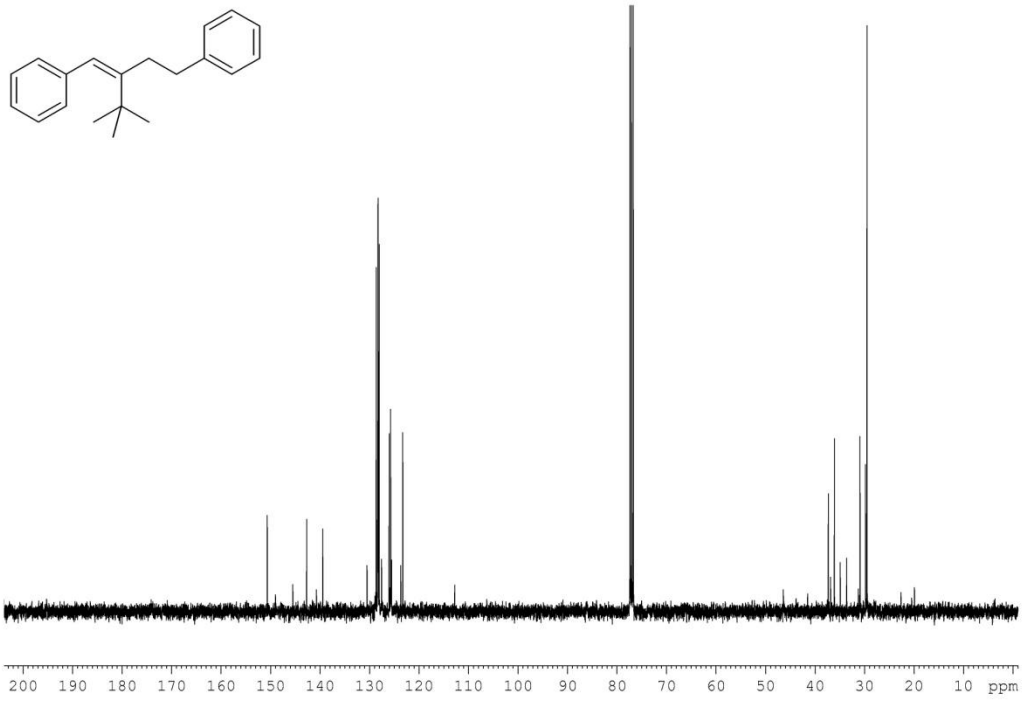

10
9
8
7
6
5
4
3
2
1
ppm
6.94
1.20
1.04
1.00
2.12
5.58
3.19

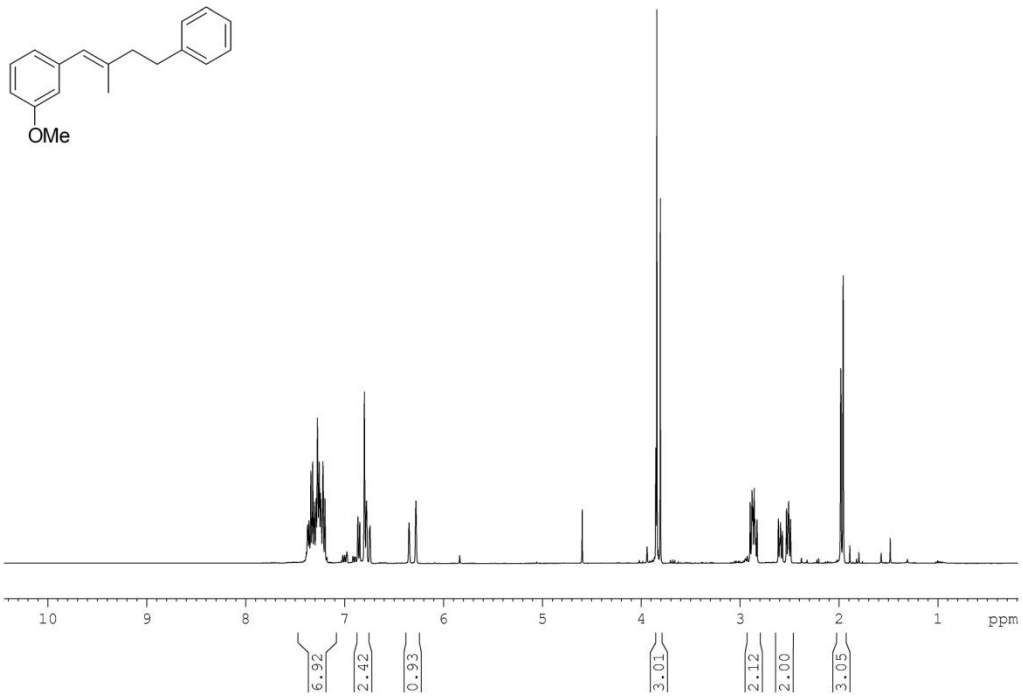

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

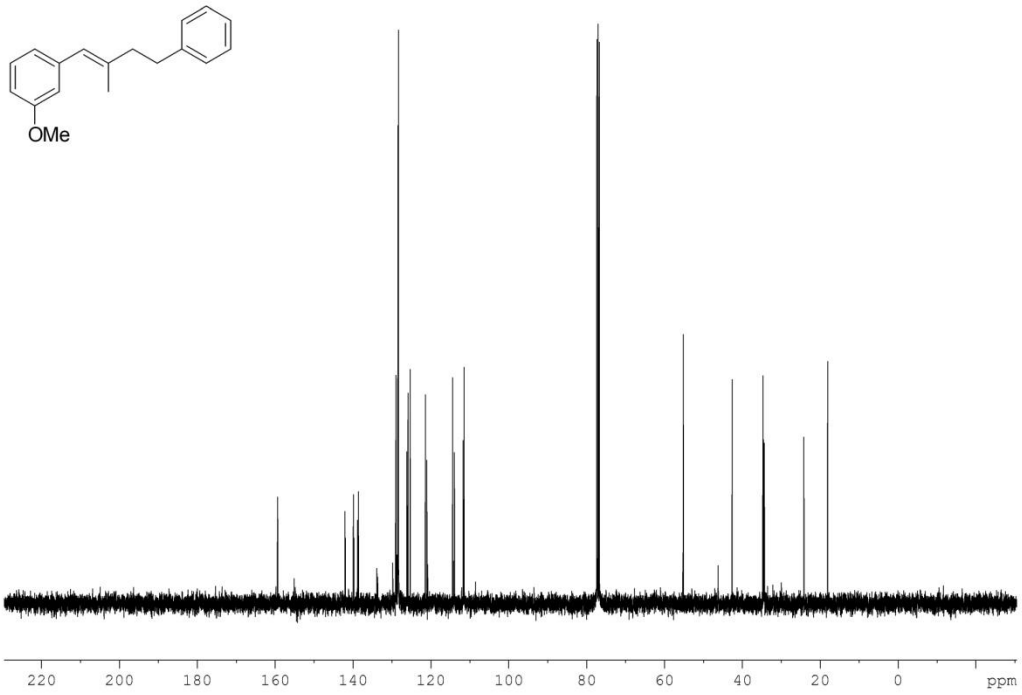

HO
10 9 8 7 6 5 4 3 2 1 ppm
3.78
3.02
0.93
1.87
1.00
1.02
1.00
1.01
1.01
1.01
1.03
9.06

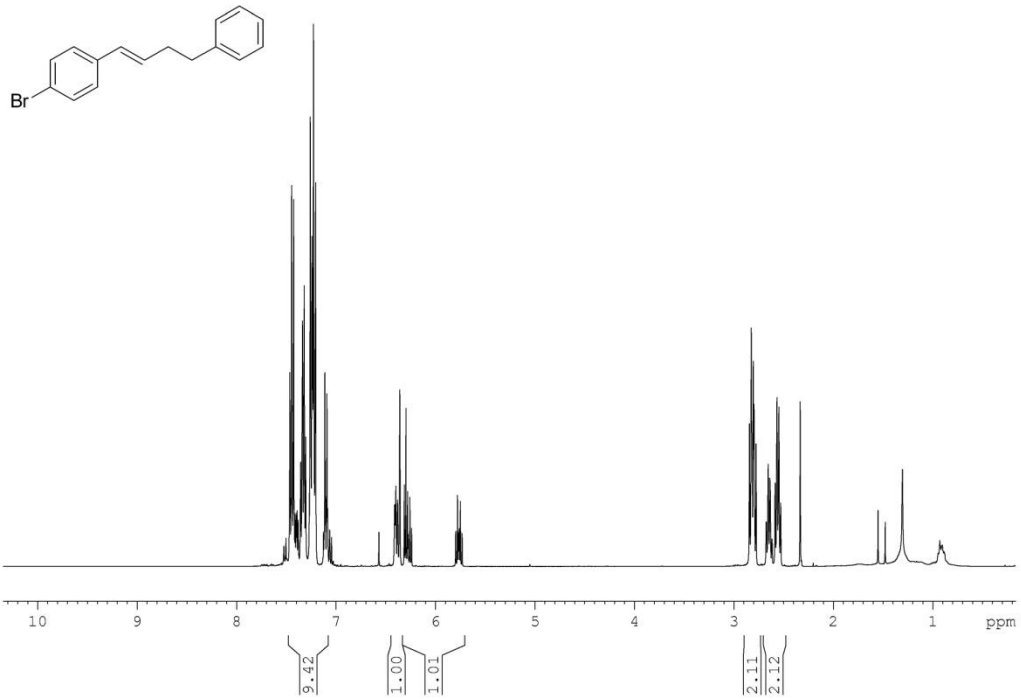

HO
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

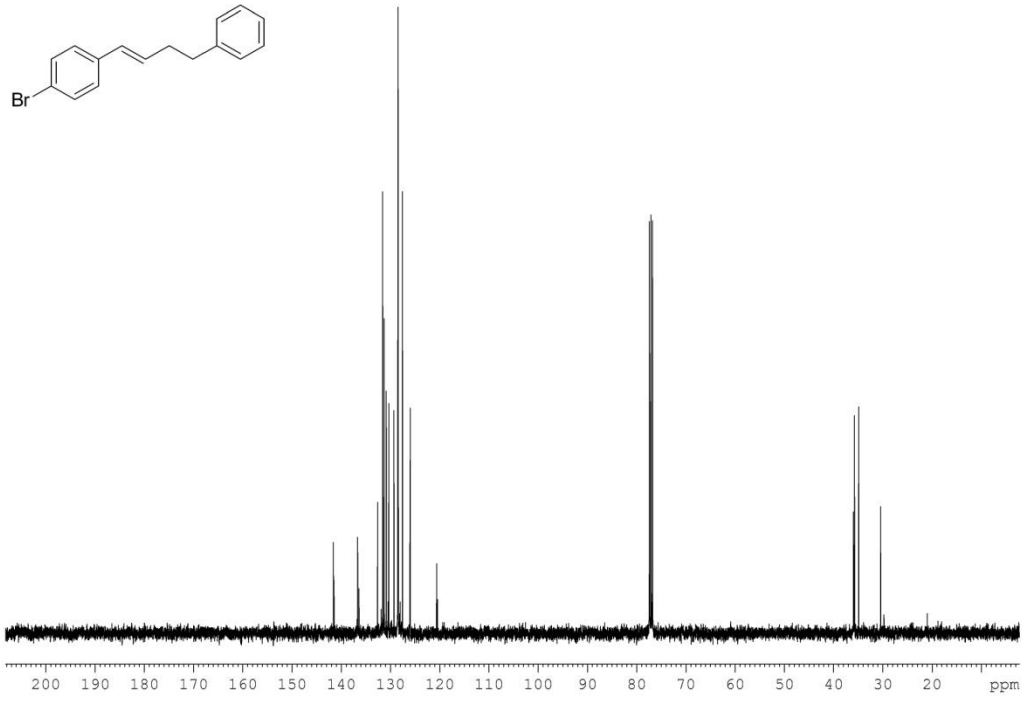

10 9 8 7 6 5 4 3 2 1 ppm
8.32
1.98
1.00
4.16
8.95

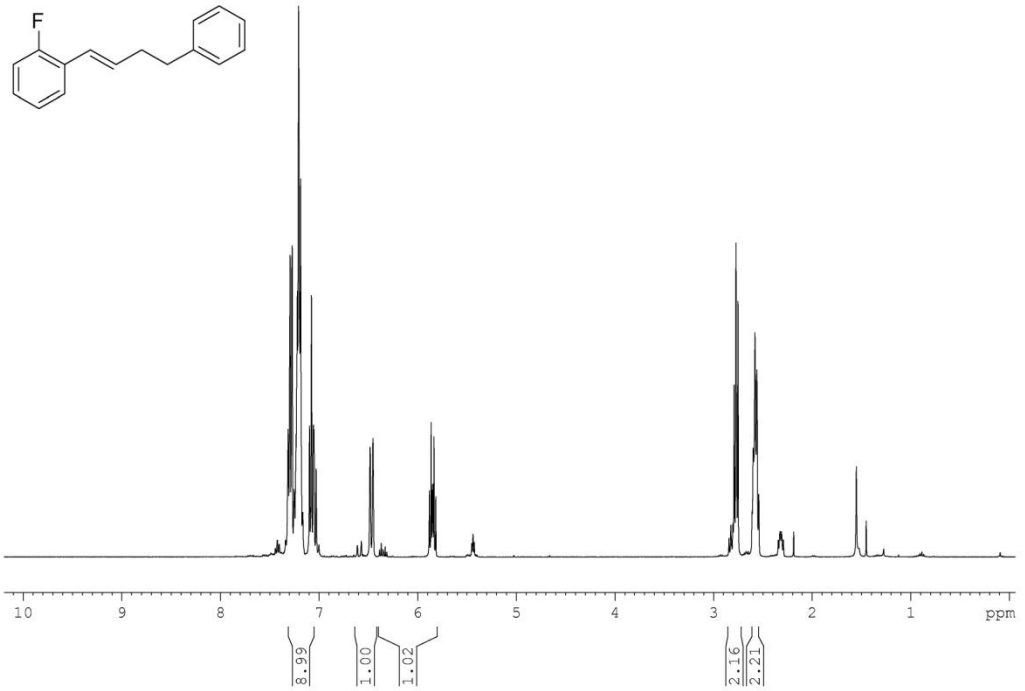

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

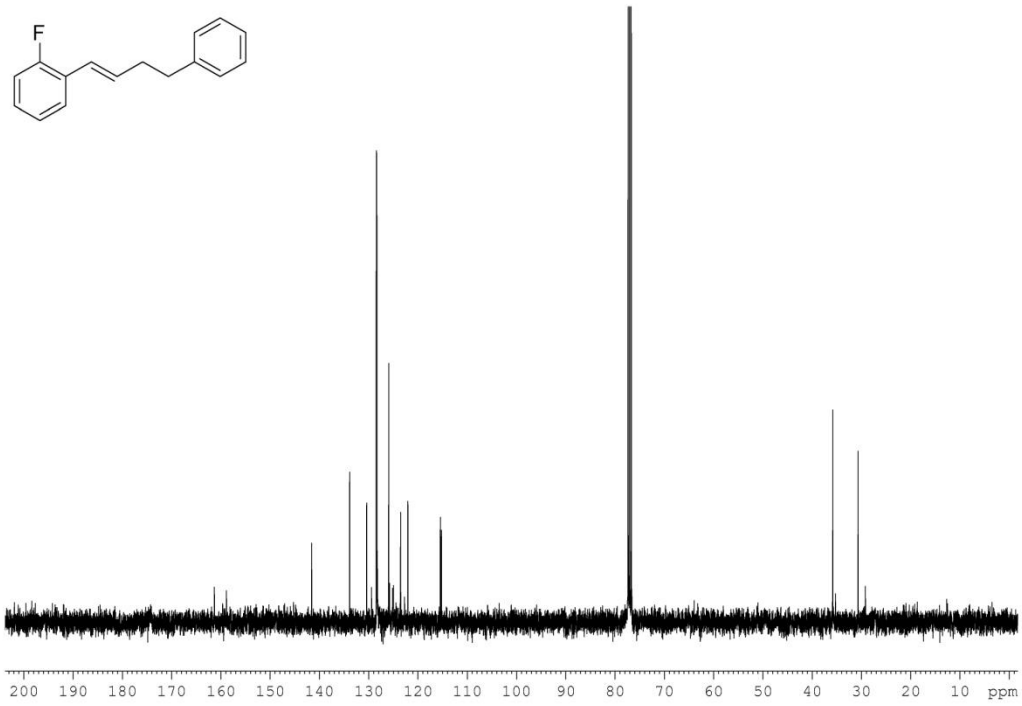

OMe
10 9 8 7 6 5 4 3 2 1 ppm
6.92
2.42
0.93
3.01
2.12
2.00
3.05

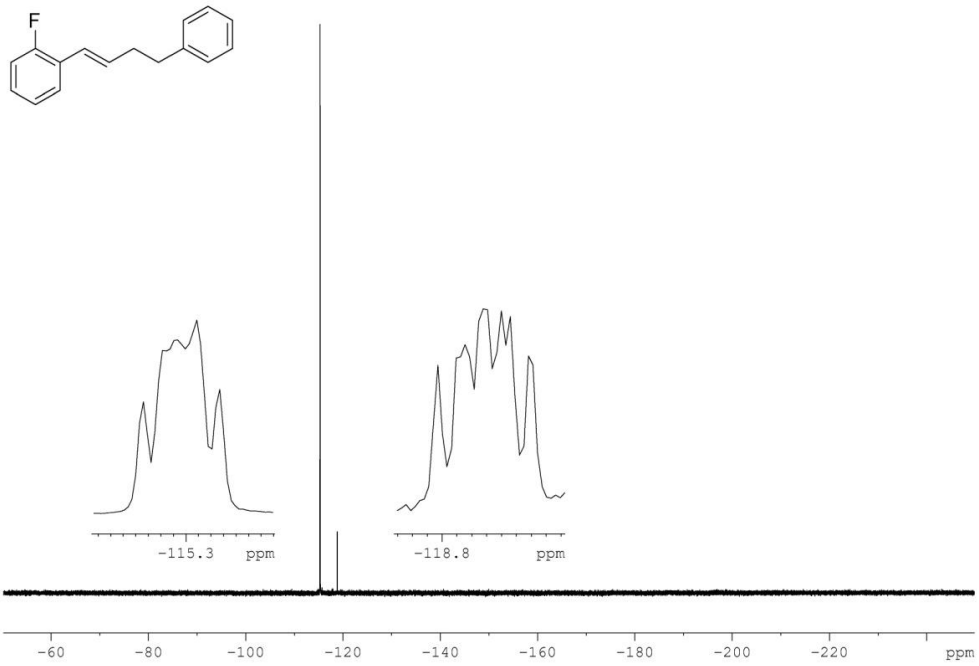

OMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm

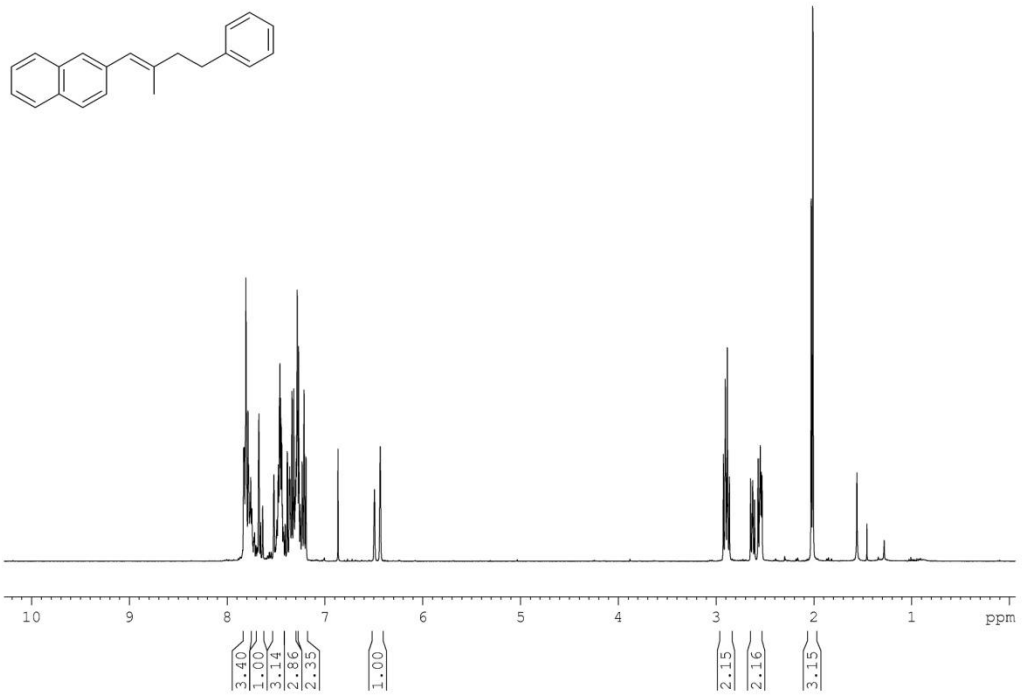

Br
10
9
8
7
6
5
4
3
2
1
ppm
9.42
1.00
1.01
2.11
2.12

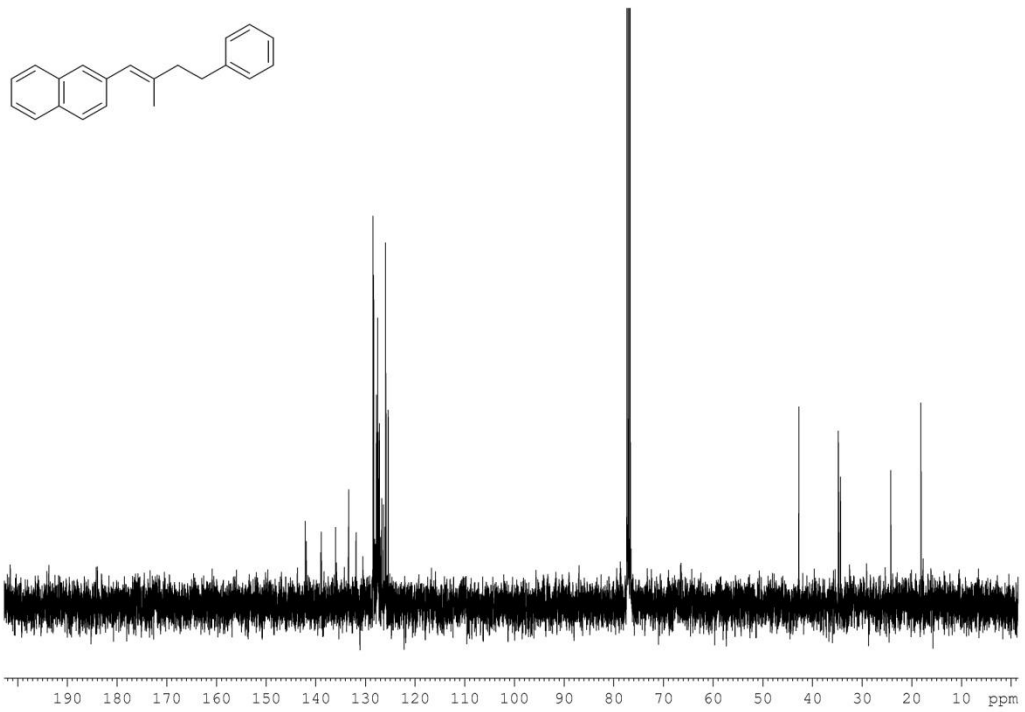

Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

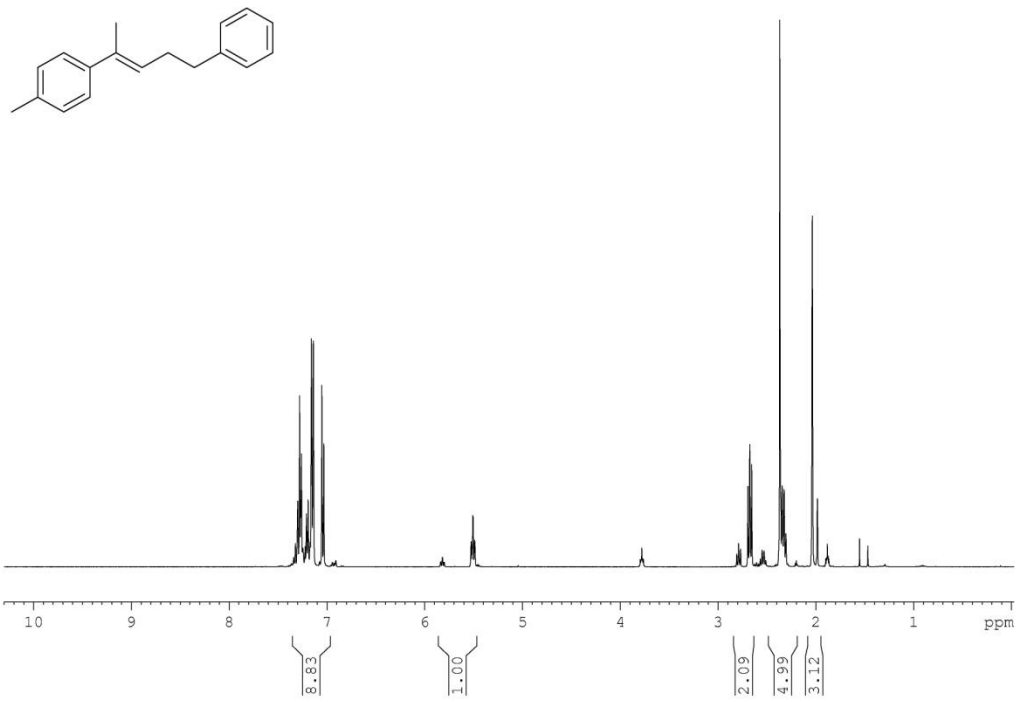

F
10 9 8 7 6 5 4 3 2 1 ppm
8.99
1.00
1.02
2.16
2.21

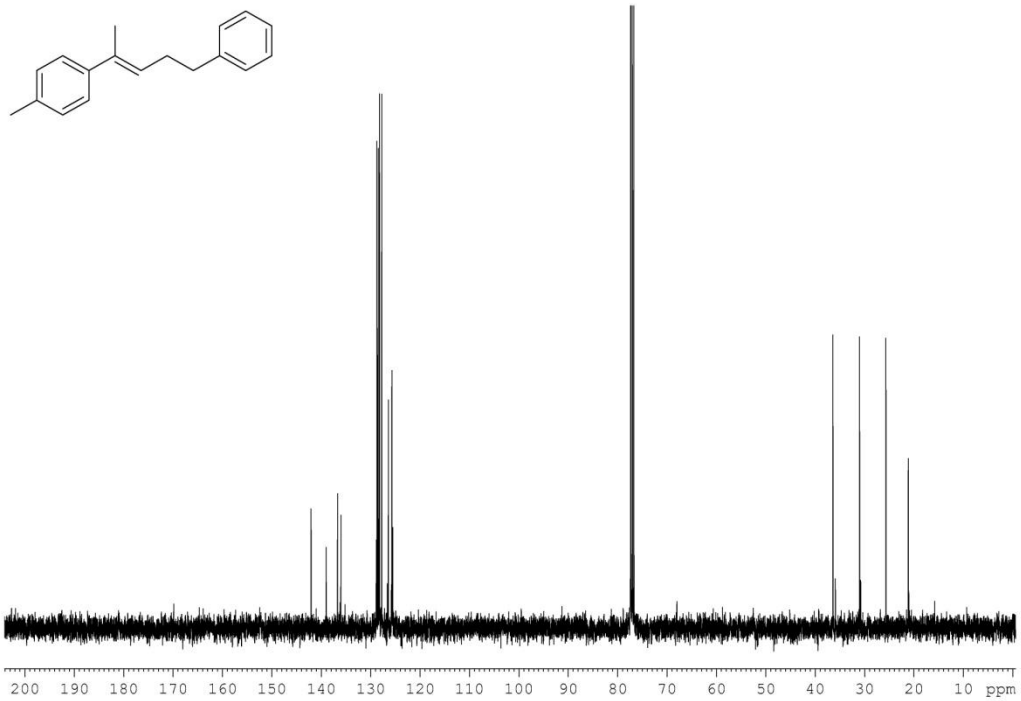

F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

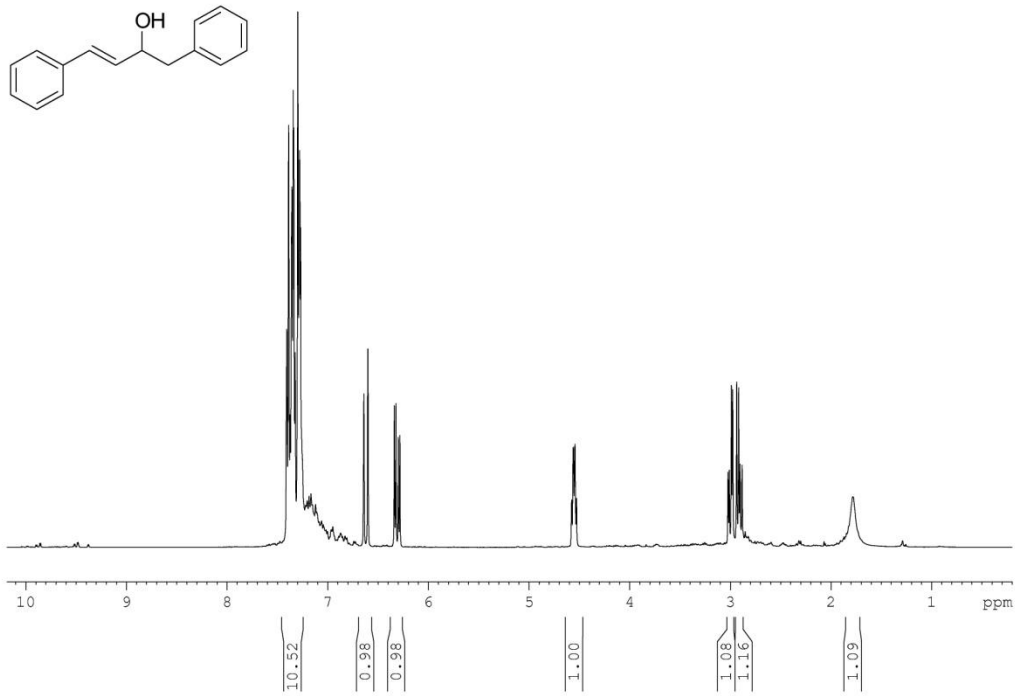

F
-115.3 ppm
-118.8 ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

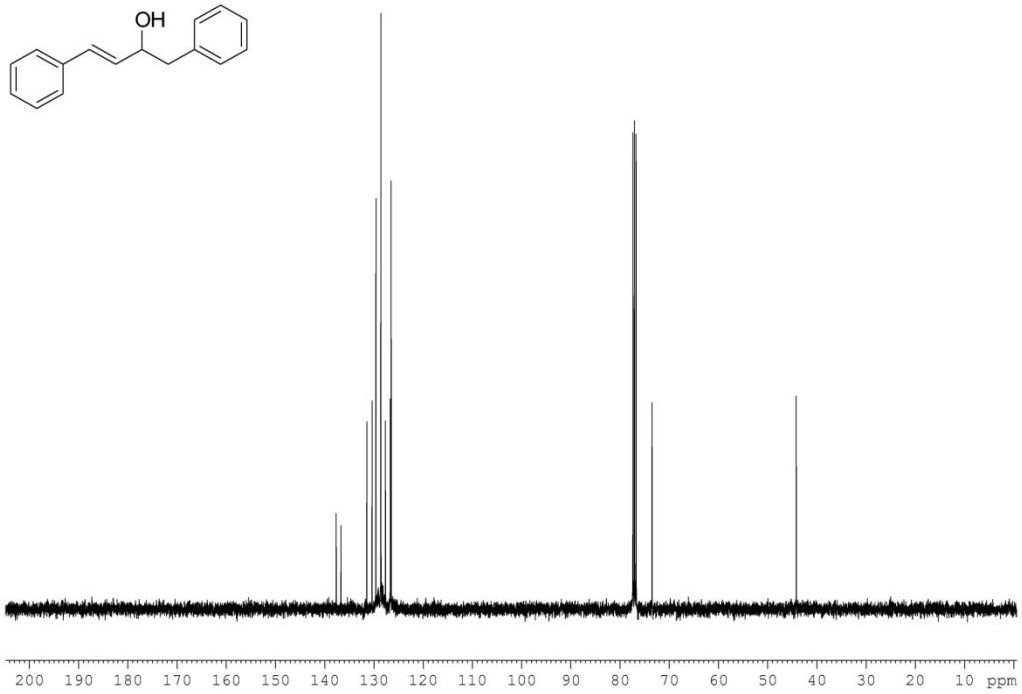

10
9
8
7
6
5
4
3
2
1
ppm
3.40
1.00
3.14
2.86
2.35
1.00
2.15
2.16
3.15

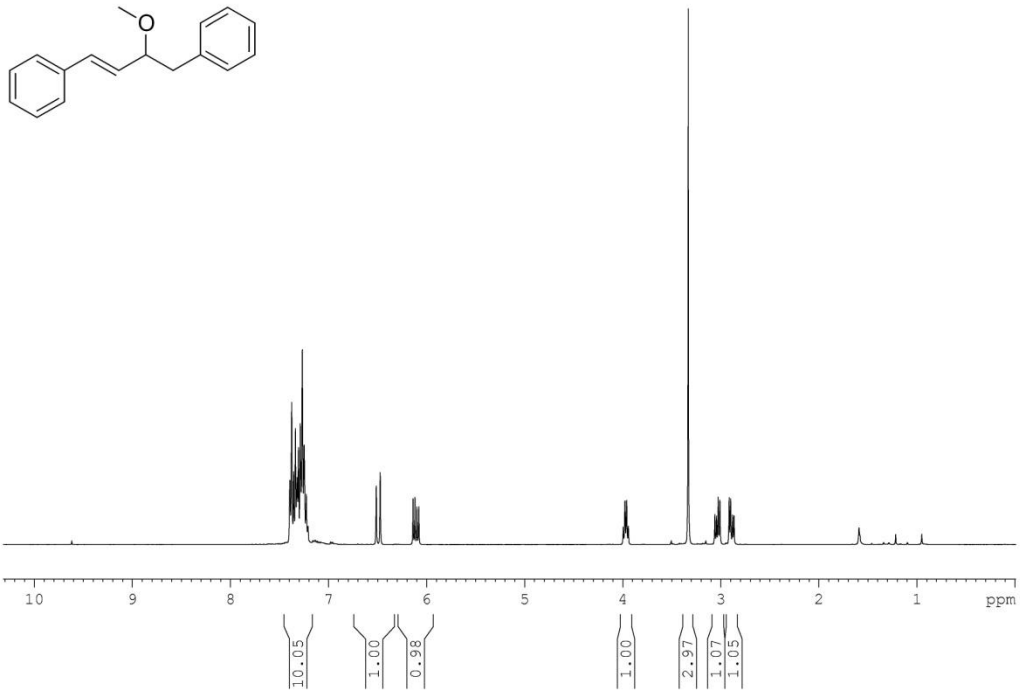

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

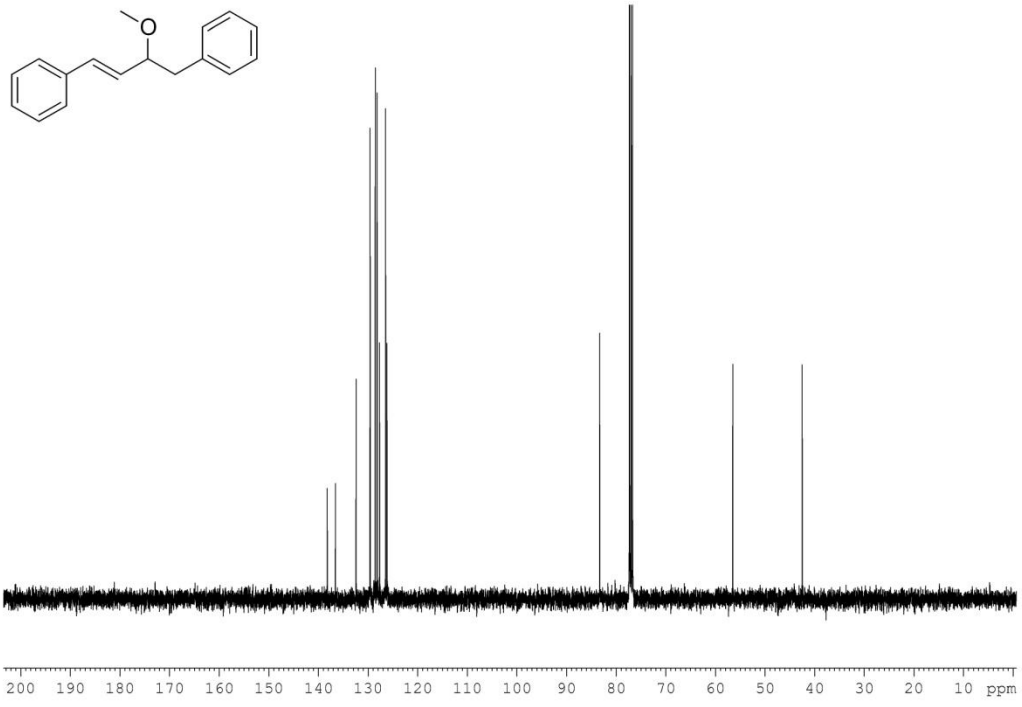

10
9
8
7
6
5
4
3
2
1
ppm
8.83
1.00
2.09
4.99
3.12

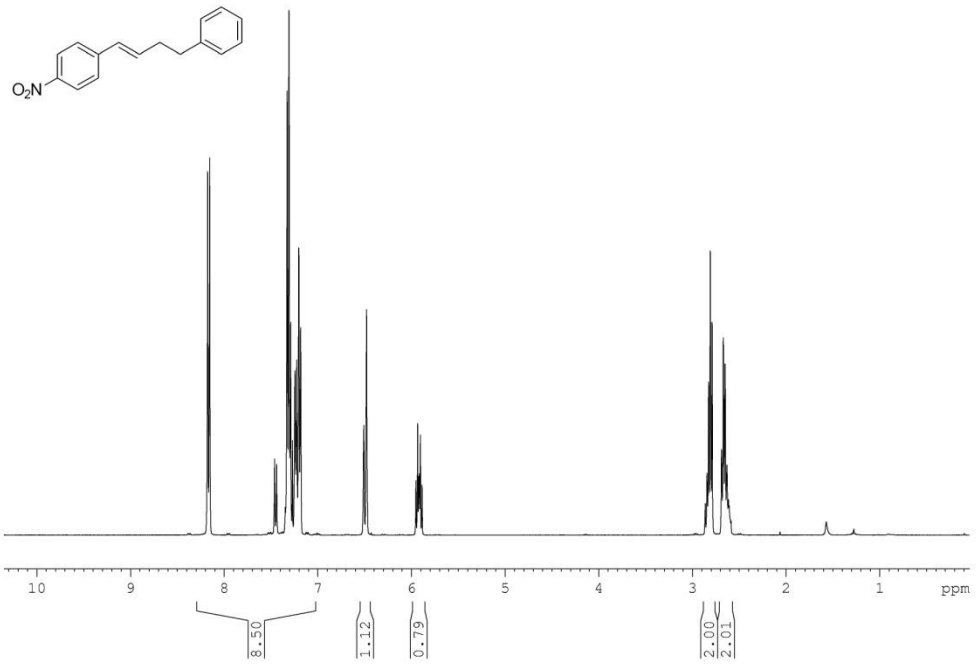

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

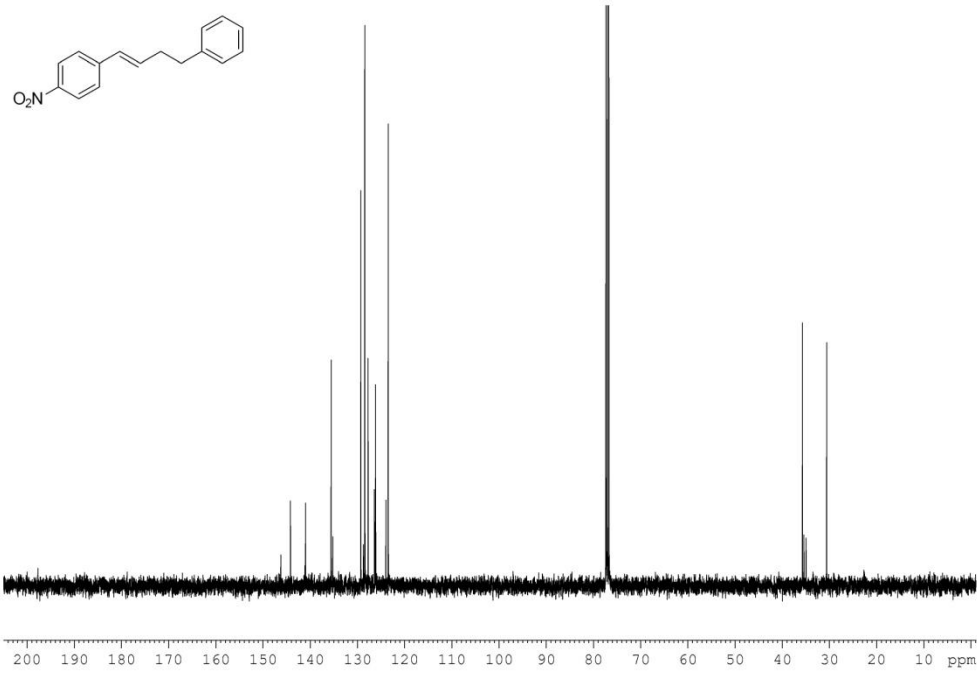

OH
10
9
8
7
6
5
4
3
2
1
ppm
10.52
0.98
0.98
1.00
1.08
1.16
1.09

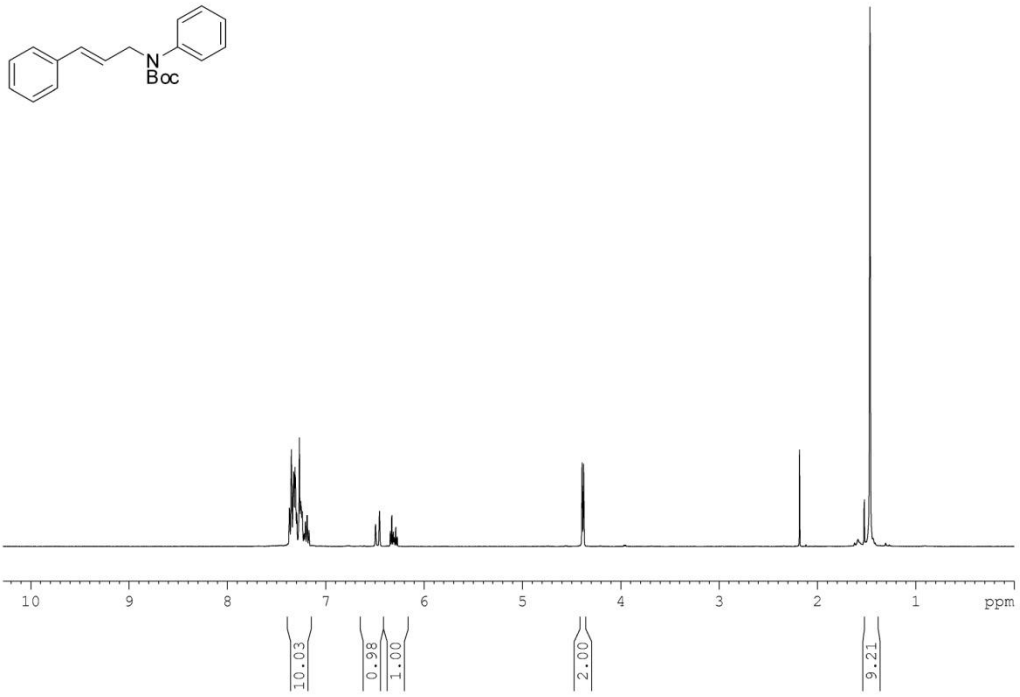

OH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

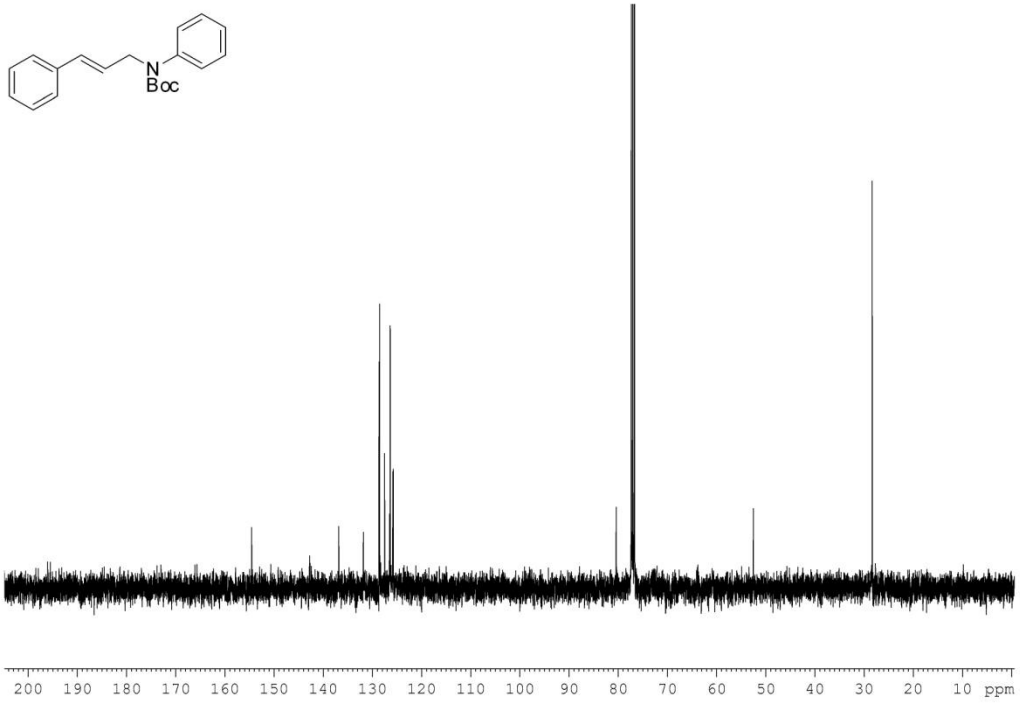

O
10
9
8
7
6
5
4
3
2
1
ppm
10.05
1.00
0.98
1.00
2.97
1.07
1.05


O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O2N
10
9
8
7
6
5
4
3
2
1
ppm
8.50
1.12
0.79
2.00
2.01


O2N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


N
Boc
10
9
8
7
6
5
4
3
2
1
ppm
10.03
0.98
1.00
2.00
9.21


N
Boc
200
190
180
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150
140
130
120
110
100
90
80
70
60
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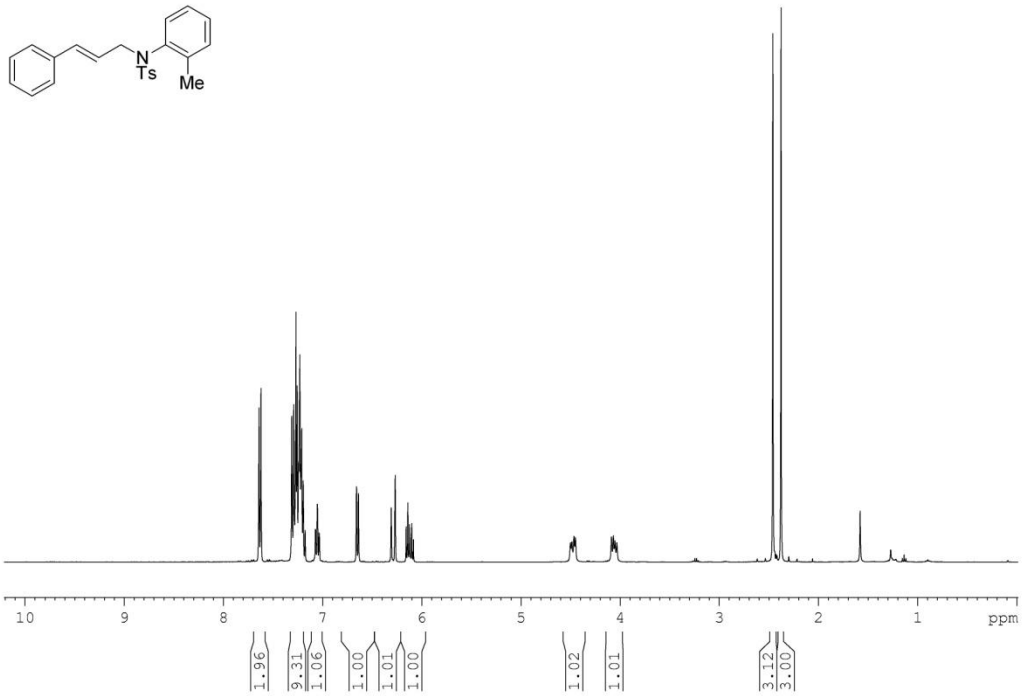
40
30
20
10
ppm


N
Ts
Me
10
9
8
7
6
5
4
3
2
1
ppm
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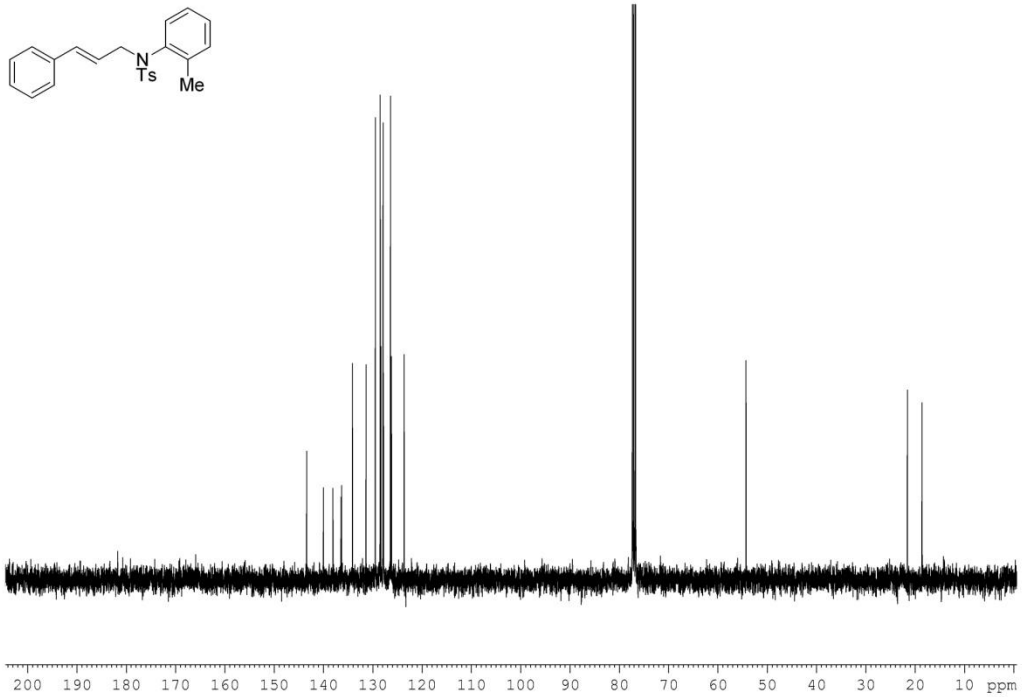
9.31
1.06
1.00
1.01
1.00
1.02
1.01
3.12
3.00


N
Ts
Me
200
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180
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150
140
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120
110
100
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70
60
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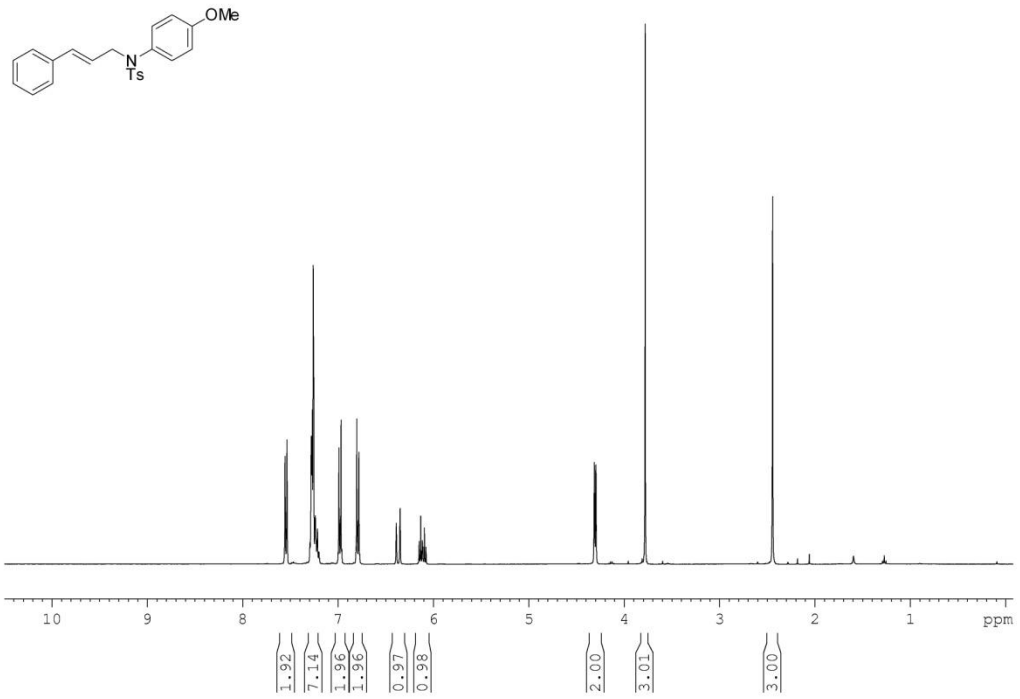
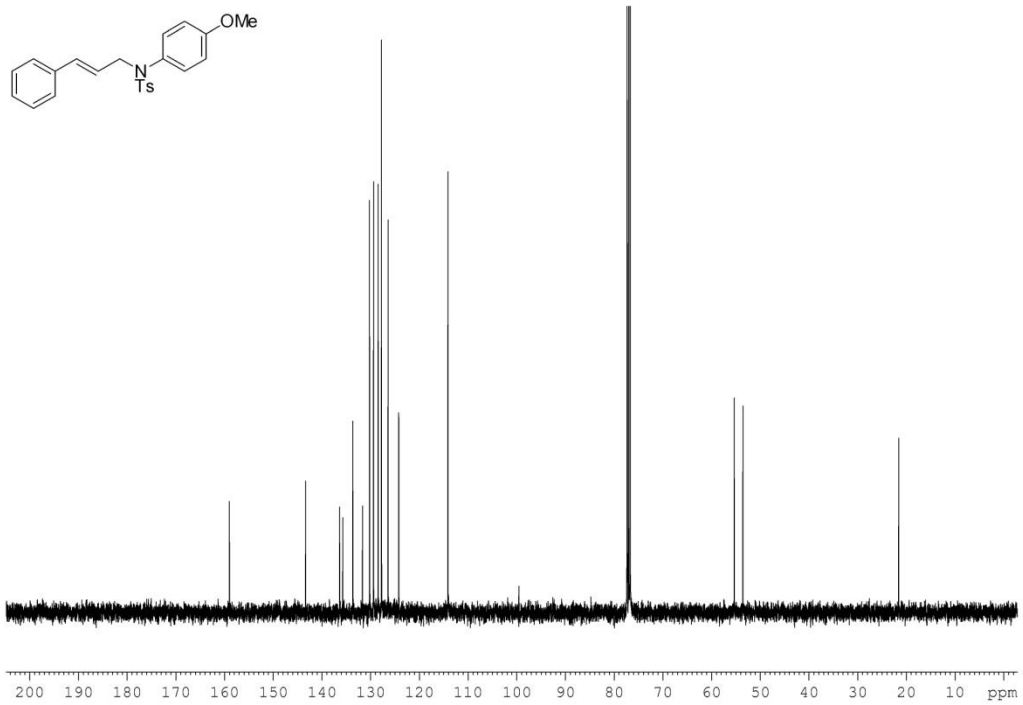
30
20
10
ppm


OMe
N
Ts
10
9
8
7
6
5
4
3
2
1
ppm
1.92
7.14
1.96
1.96
0.97
0.98
2.00
3.01
3.00


OMe
N
Ts
200
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180
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150
140
130
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110
100
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70
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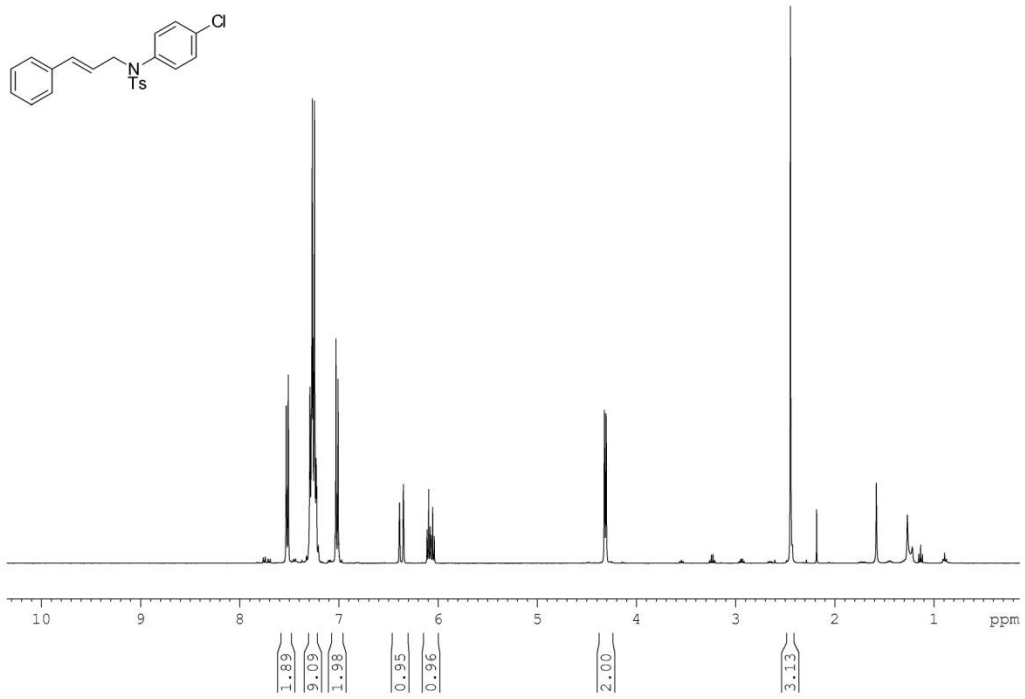
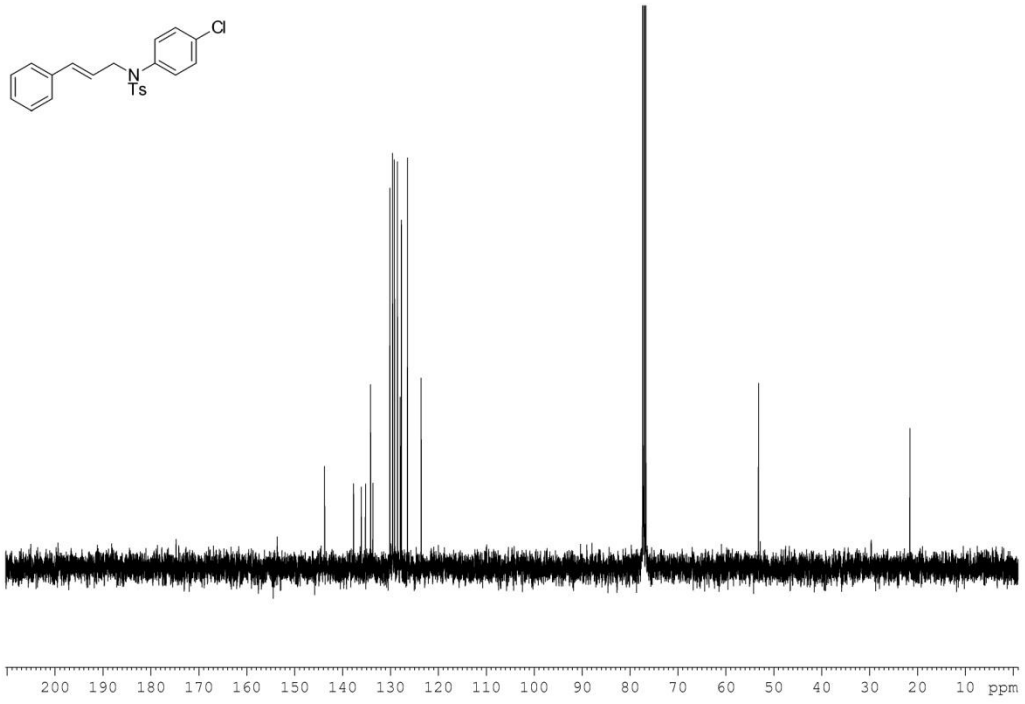
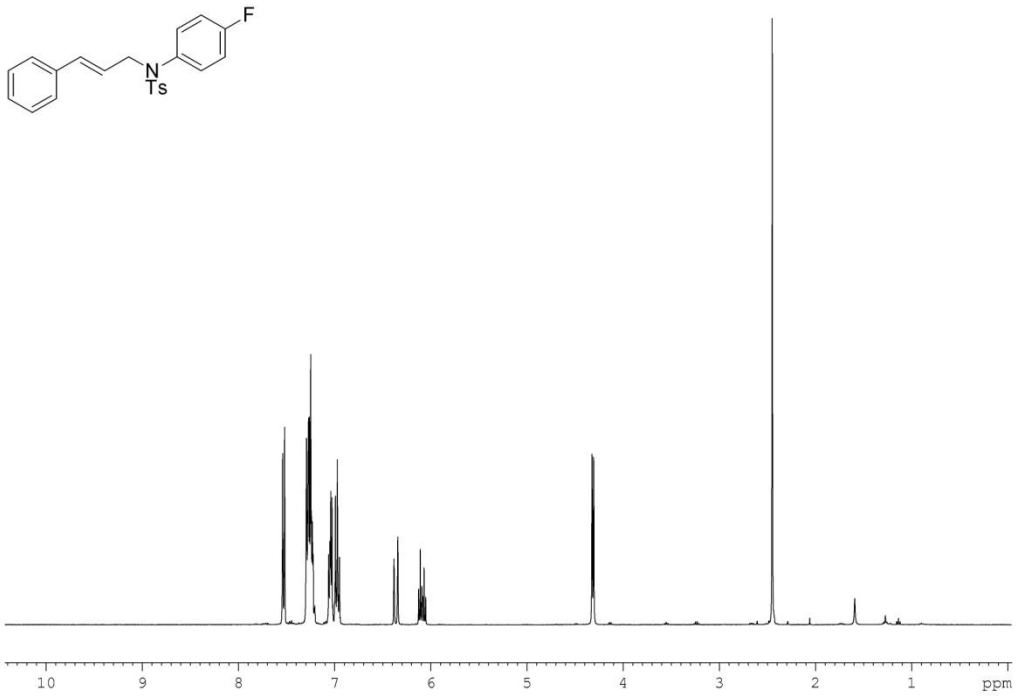
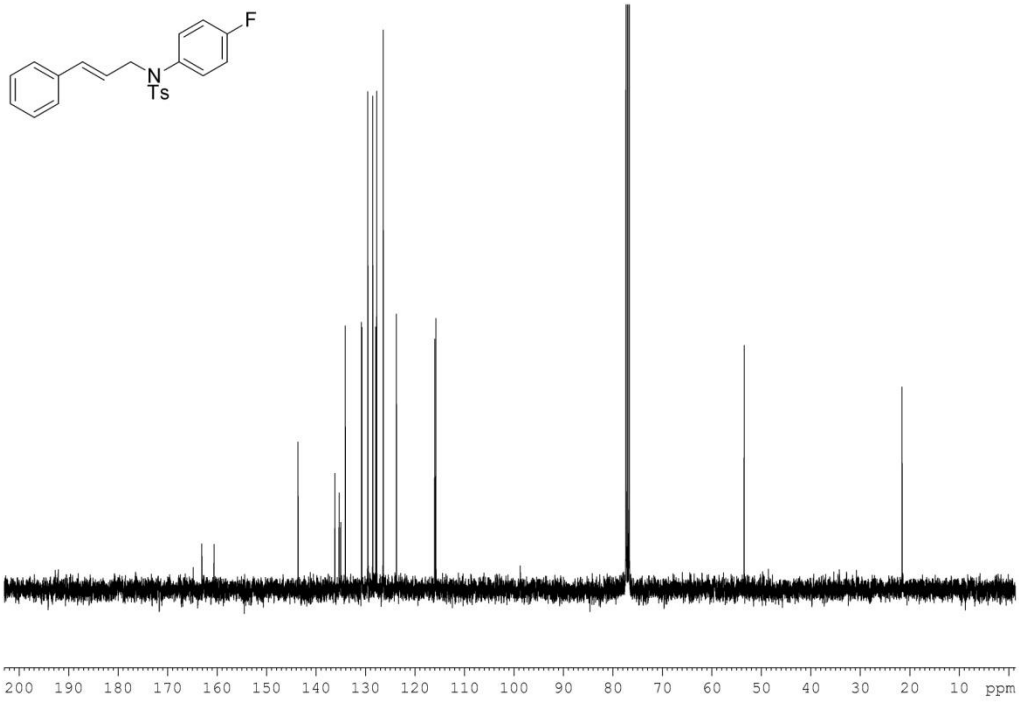
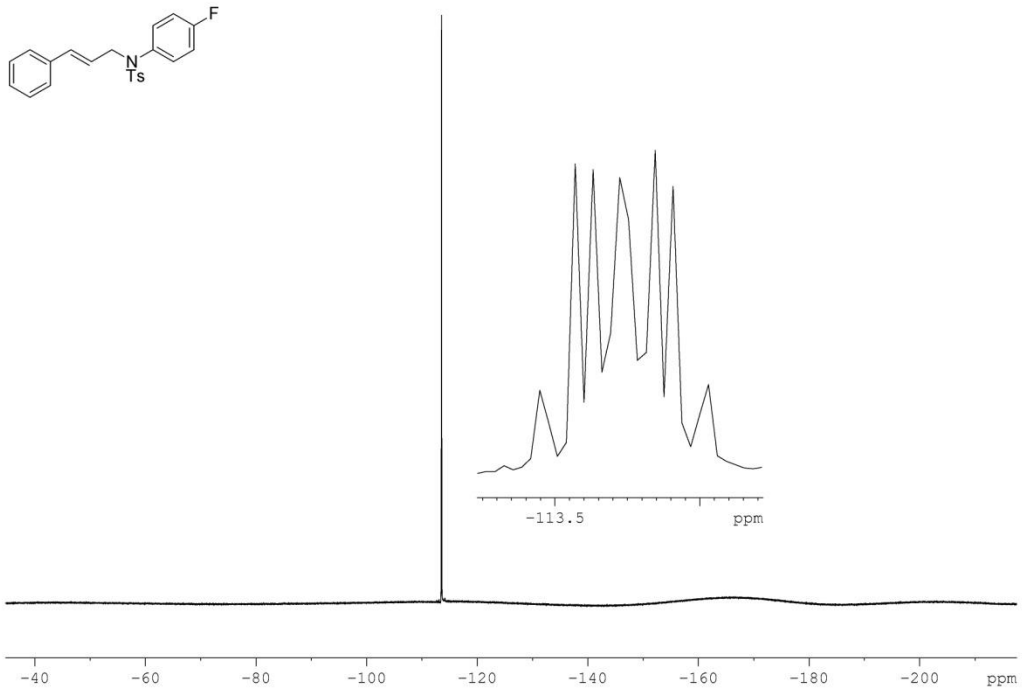
30
20
10
ppm

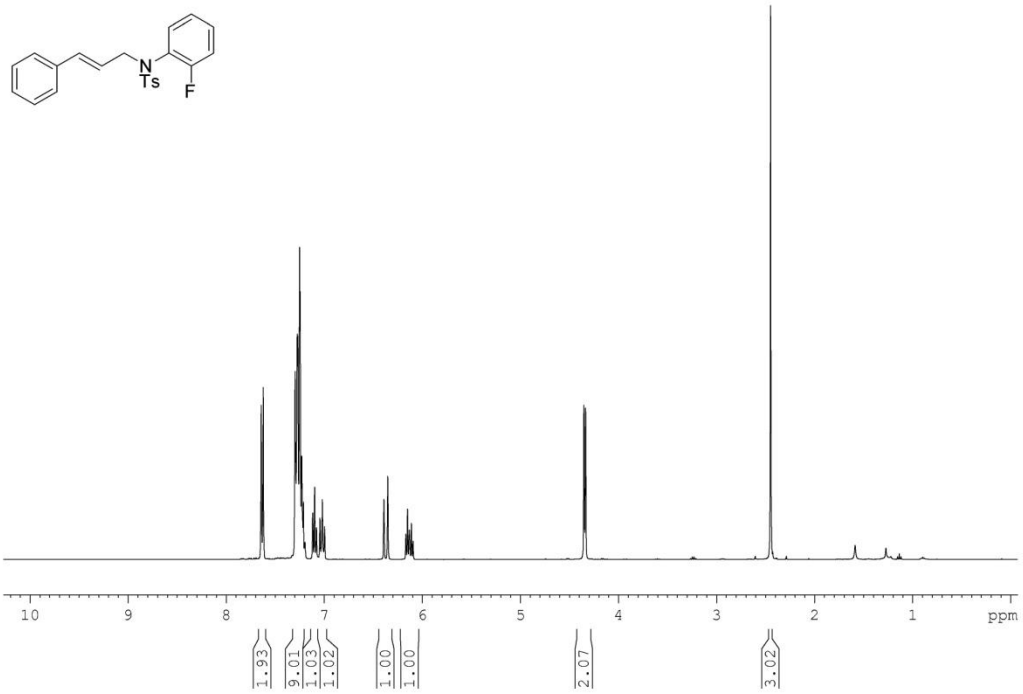

Cl
N
Ts
10
9
8
7
6
5
4
3
2
1
ppm
1.89
9.09
1.98
0.95
0.96
2.00
3.13

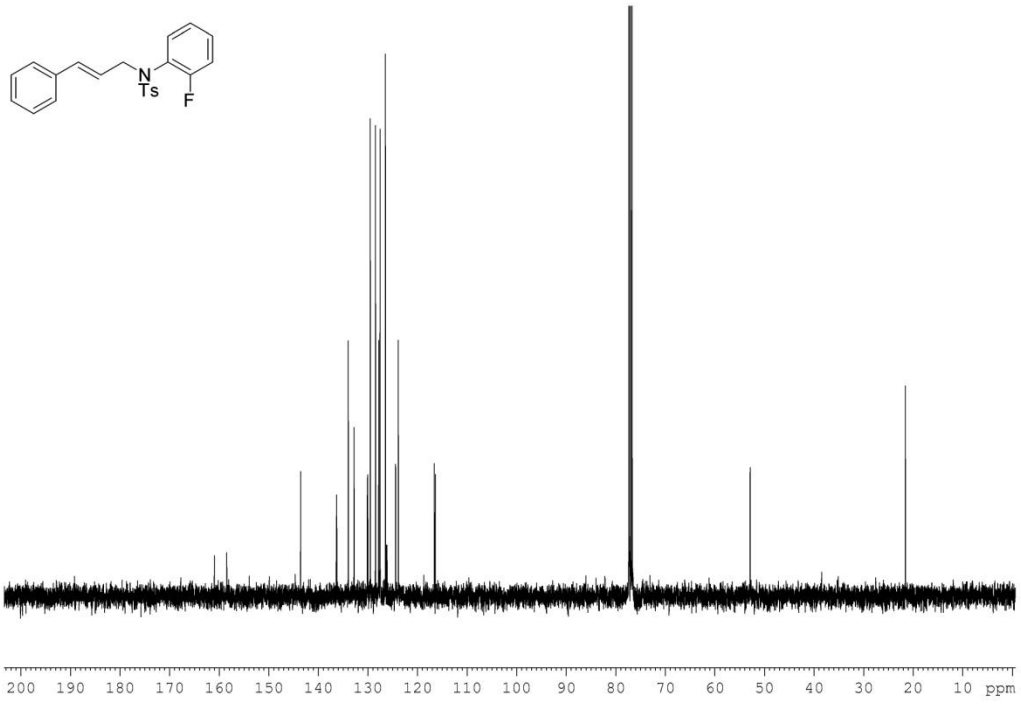

Cl
N
Ts
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

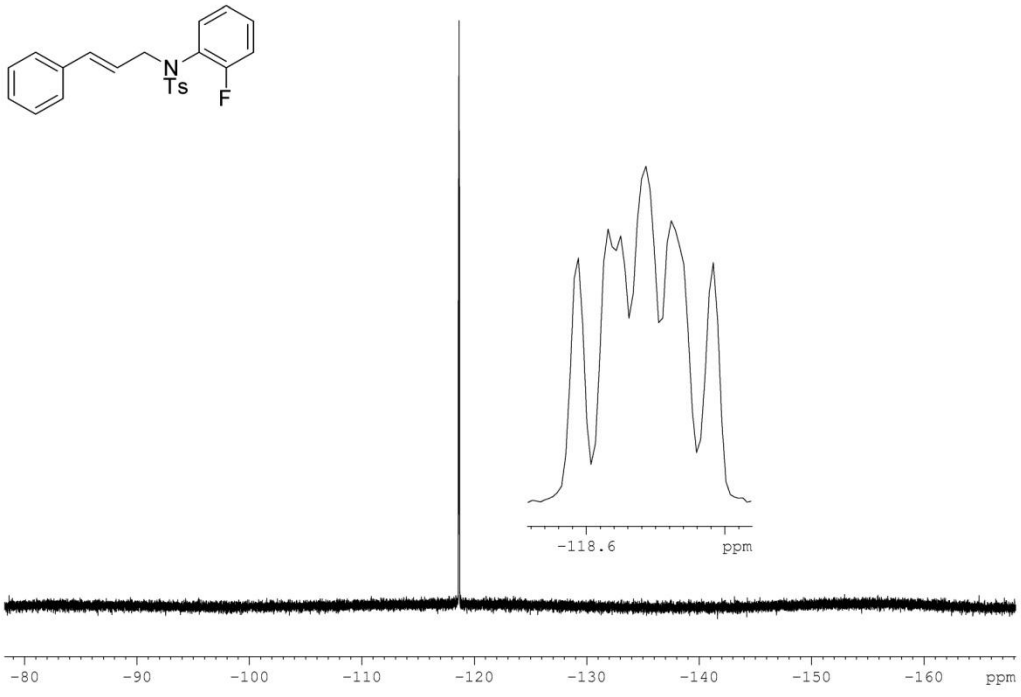

F
N
Ts
10
9
8
7
6
5
4
3
2
1
ppm

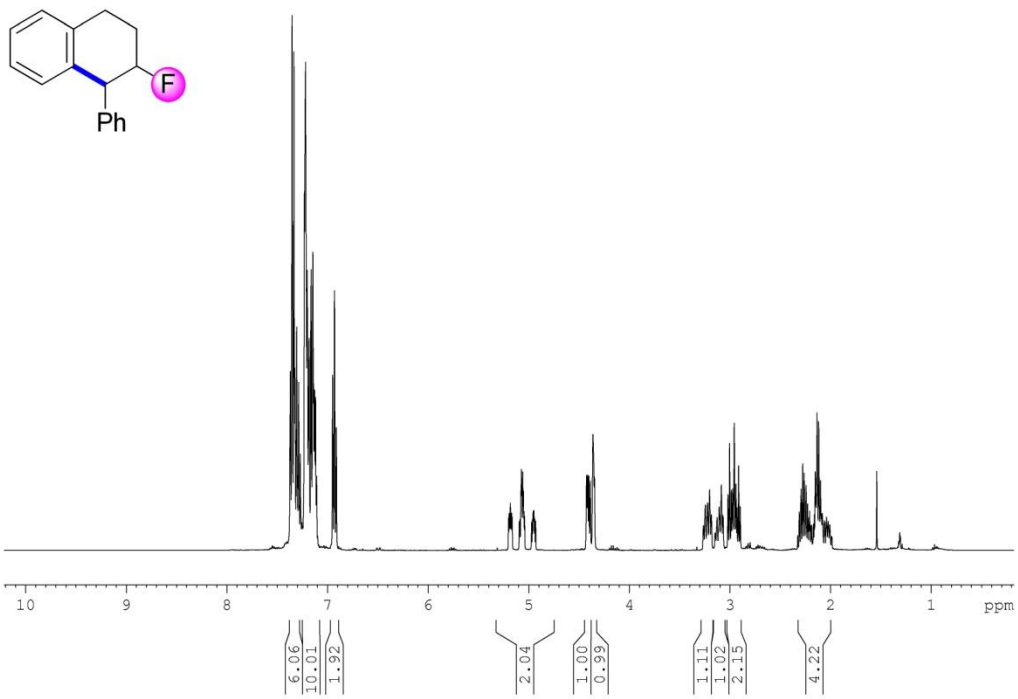

F
N
Ts
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

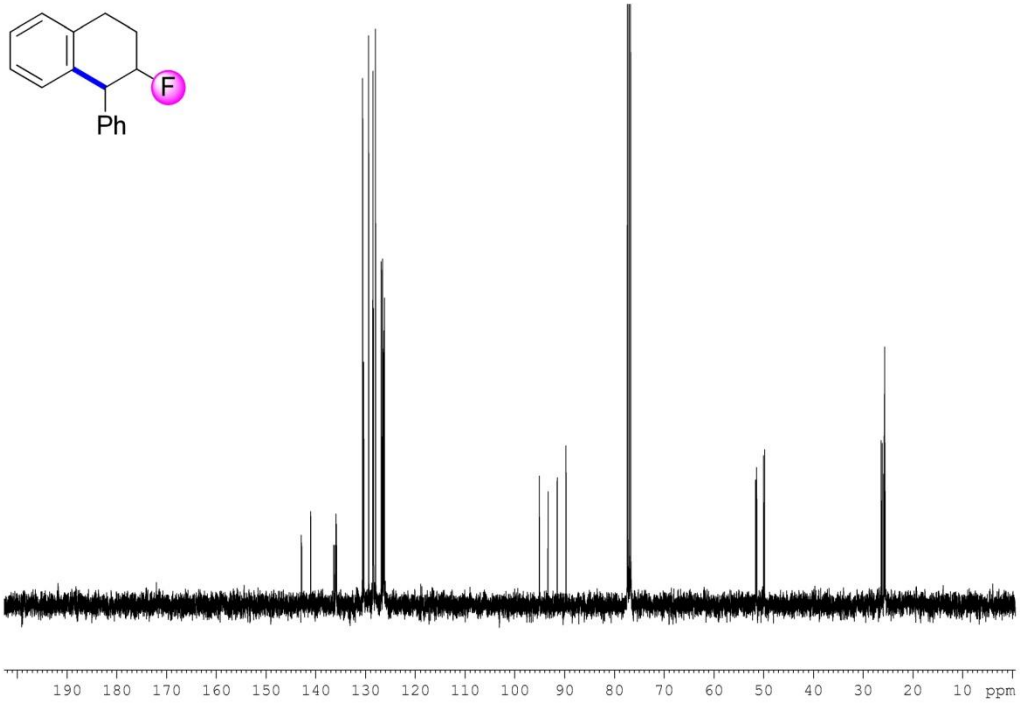

F
N
Ts
-113.5
ppm
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

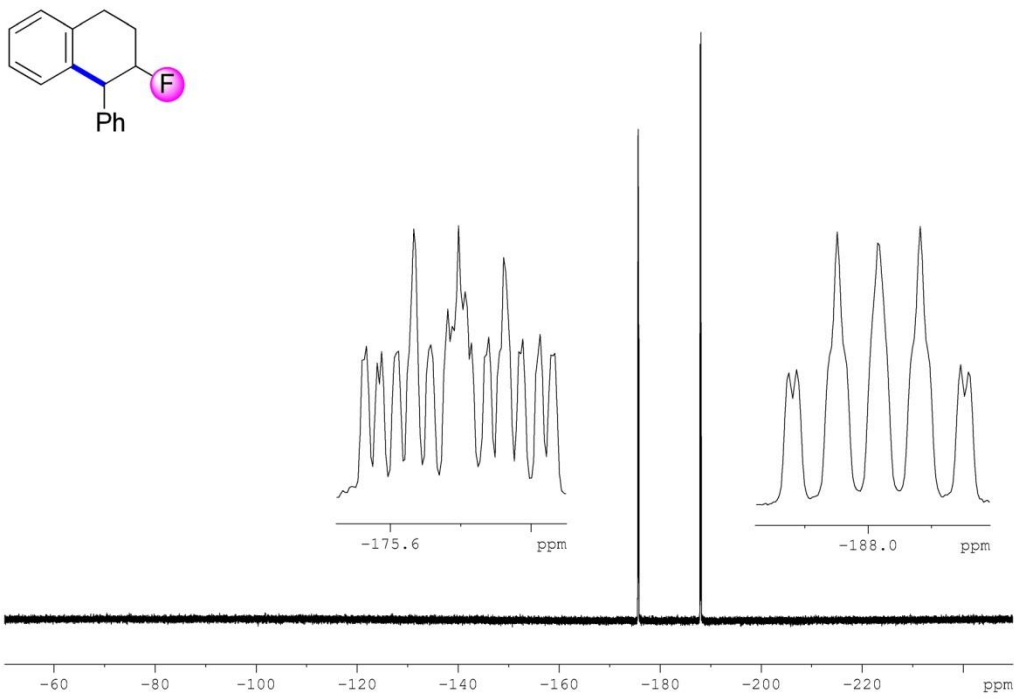

N
Ts
F
10
9
8
7
6
5
4
3
2
1
ppm
1.93
9.01
1.03
1.02
1.00
1.00
2.07
3.02

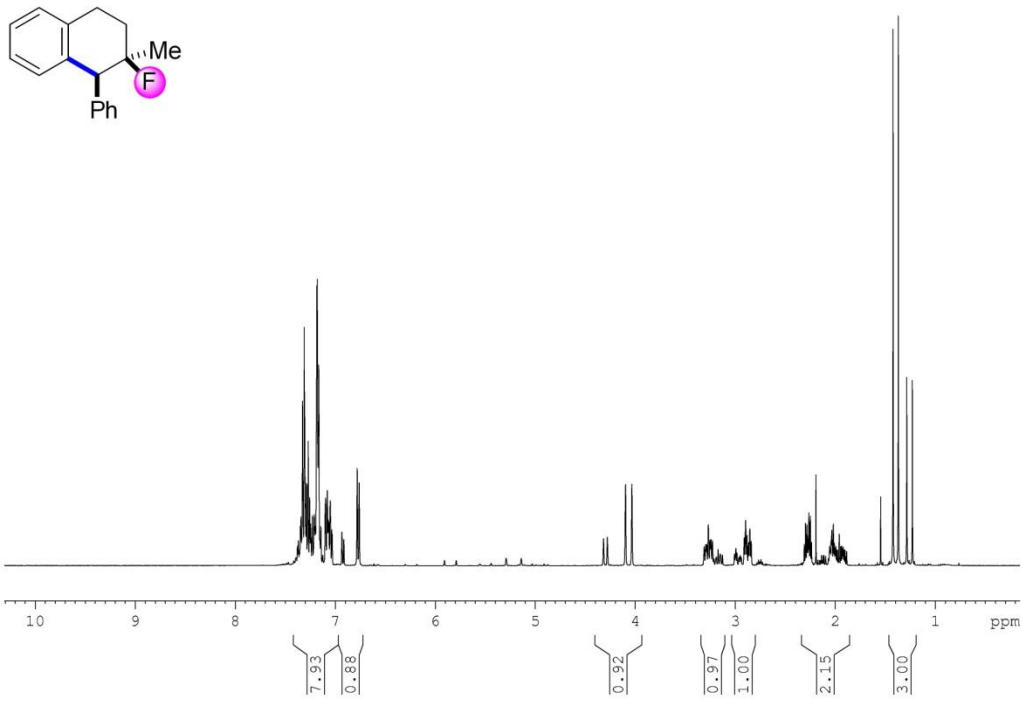

N
Ts
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


N
Ts
F
-118.6
ppm
-80 -90 -100 -110 -120 -130 -140 -150 -160 ppm

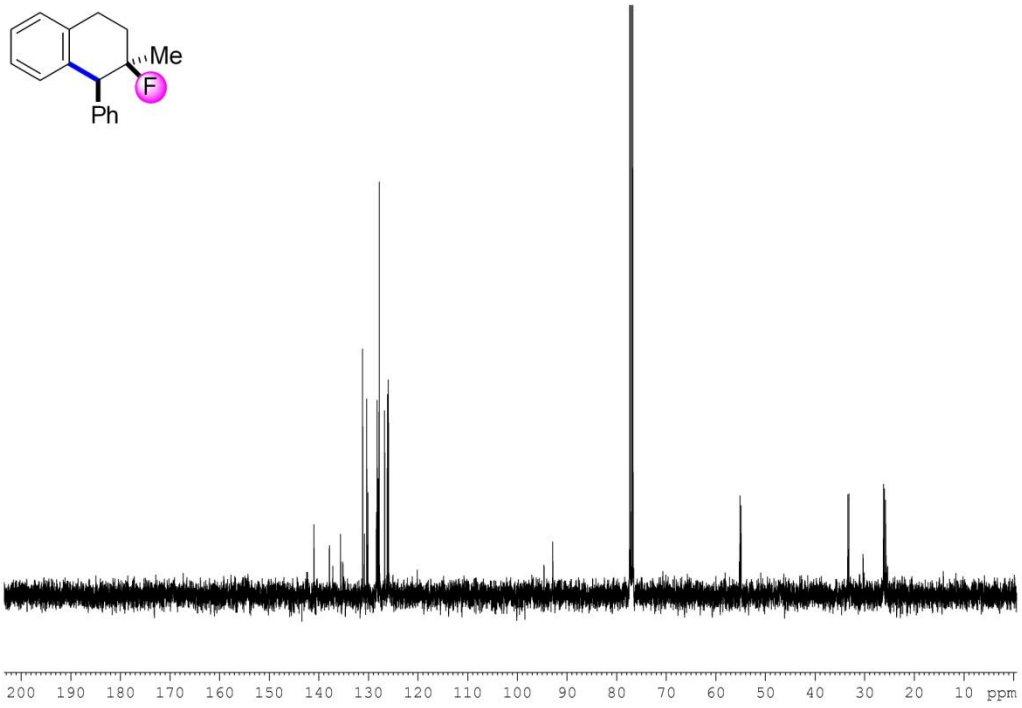

F
Ph
10
9
8
7
6
5
4
3
2
1
ppm
6.06
10.01
1.92
2.04
1.00
0.99
1.11
1.02
2.15
4.22

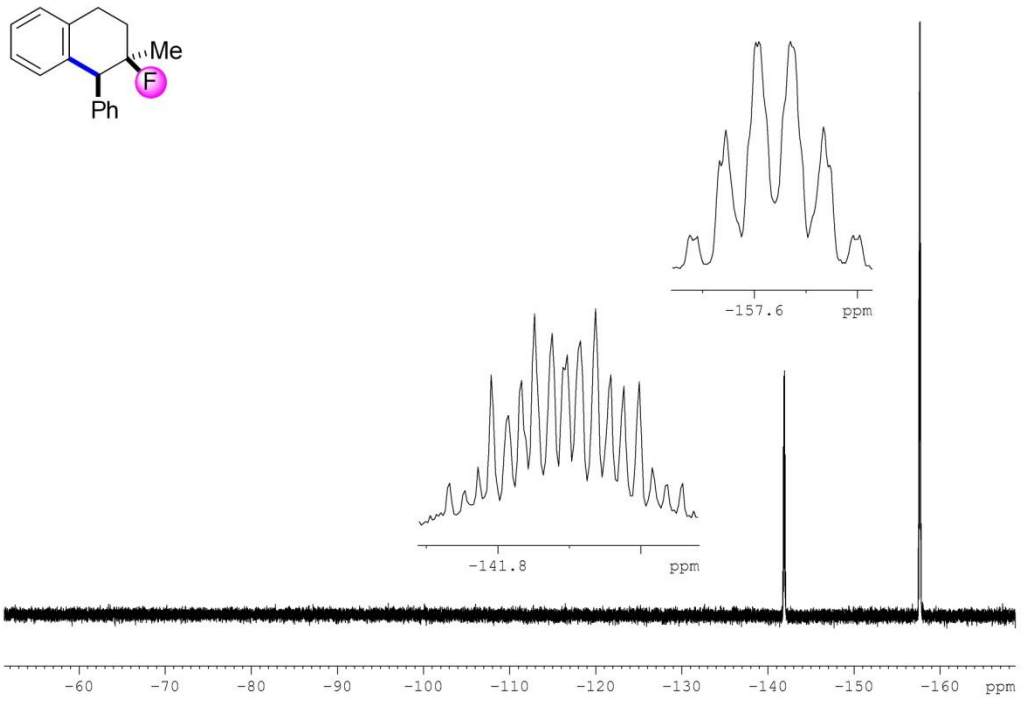

F
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

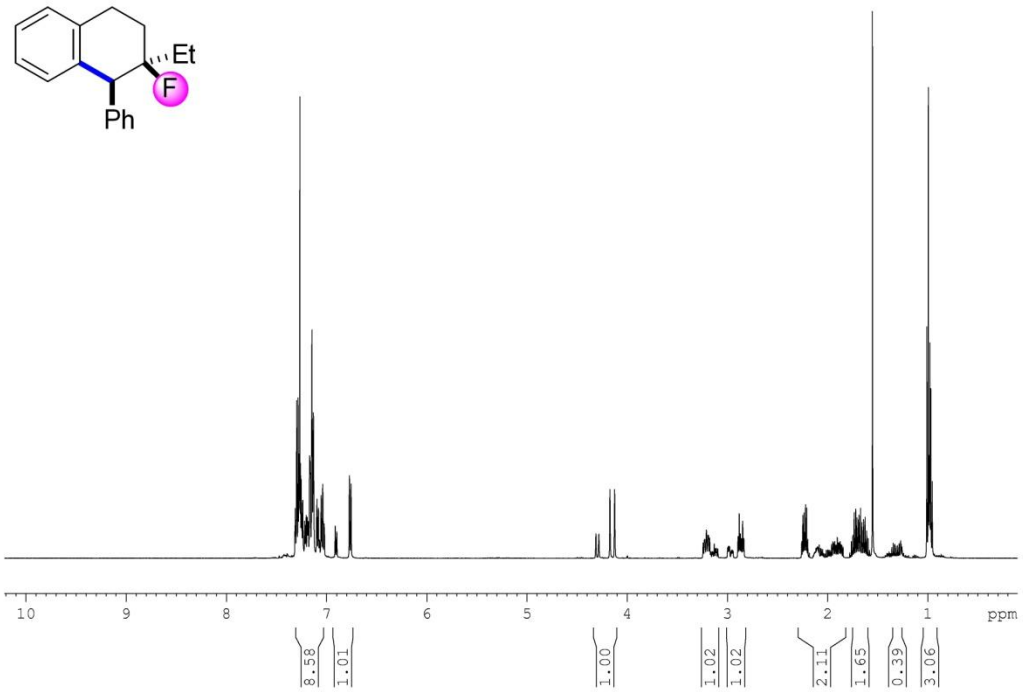

F
Ph
-175.6
ppm
-188.0
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm


Me
F
Ph
10
9
8
7
6
5
4
3
2
1
ppm
7.93
0.88
0.92
0.97
1.00
2.15
3.00

cl


Me
F
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Me
F
Ph
-157.6
ppm
-141.8
ppm
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 ppm


Et
F
Ph
10
9
8
7
6
5
4
3
2
1
ppm
8.58
1.01
1.00
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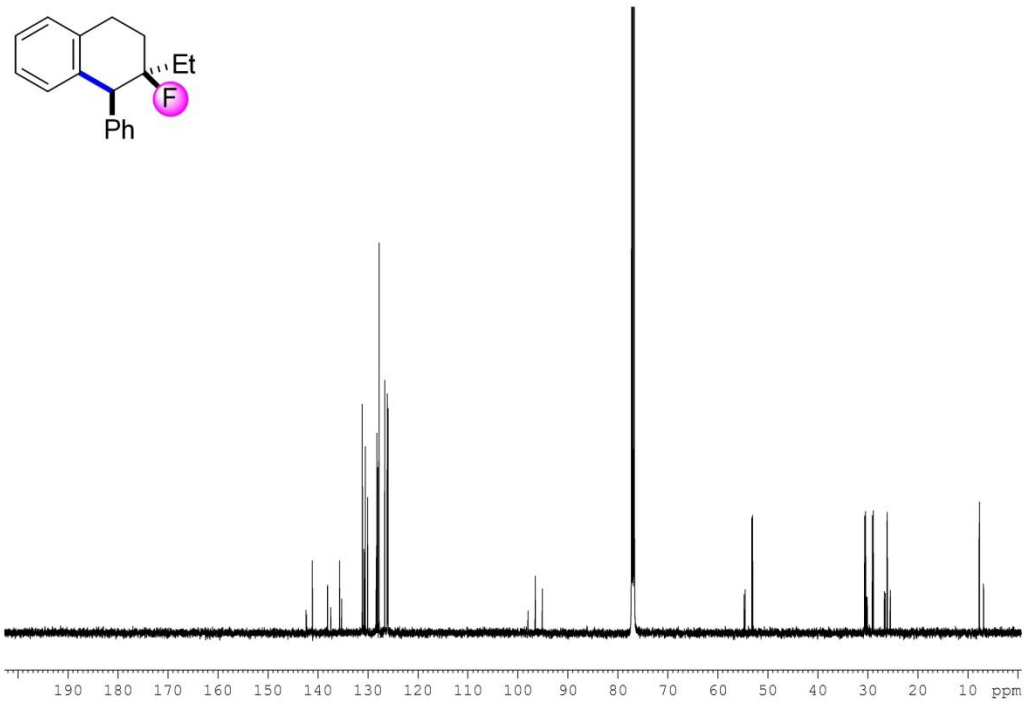
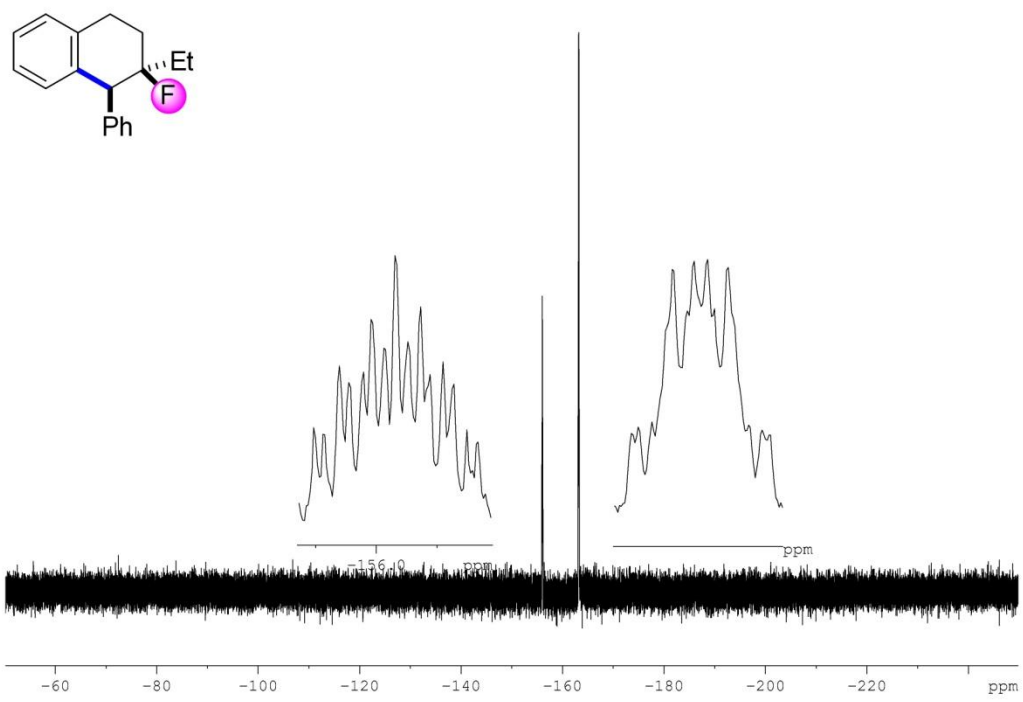
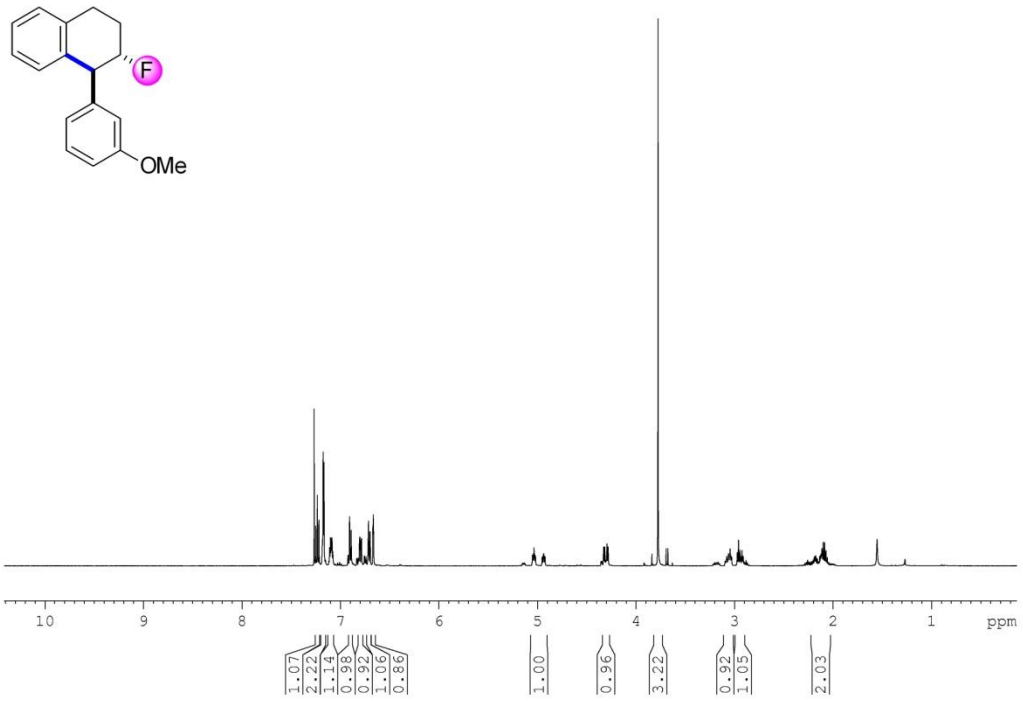
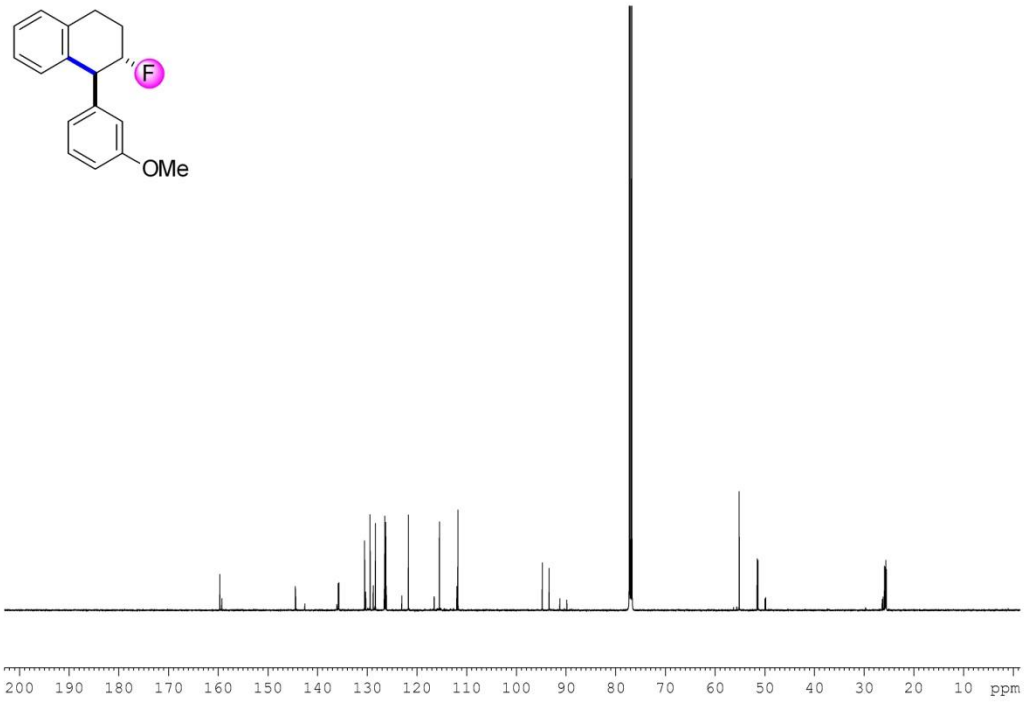
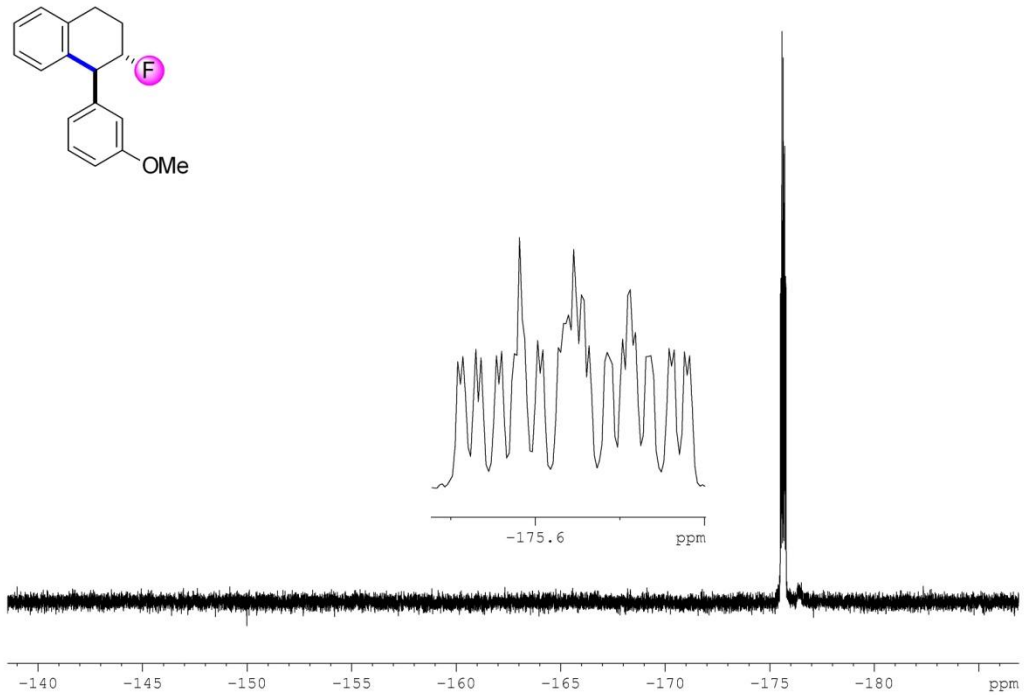
0.39
3.06

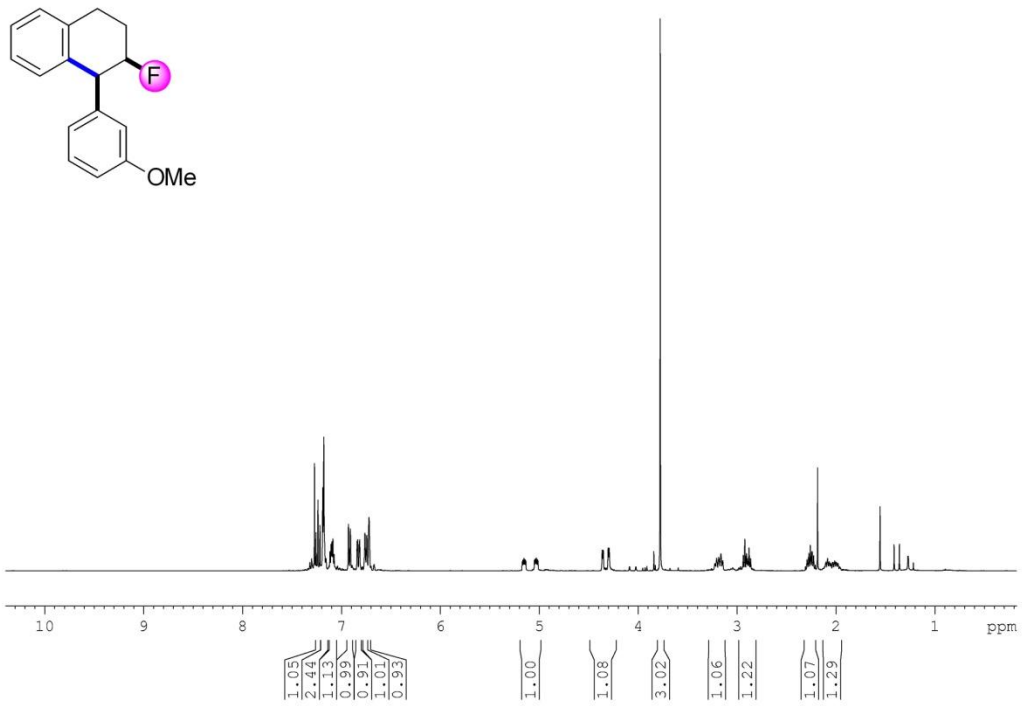

Et
F
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

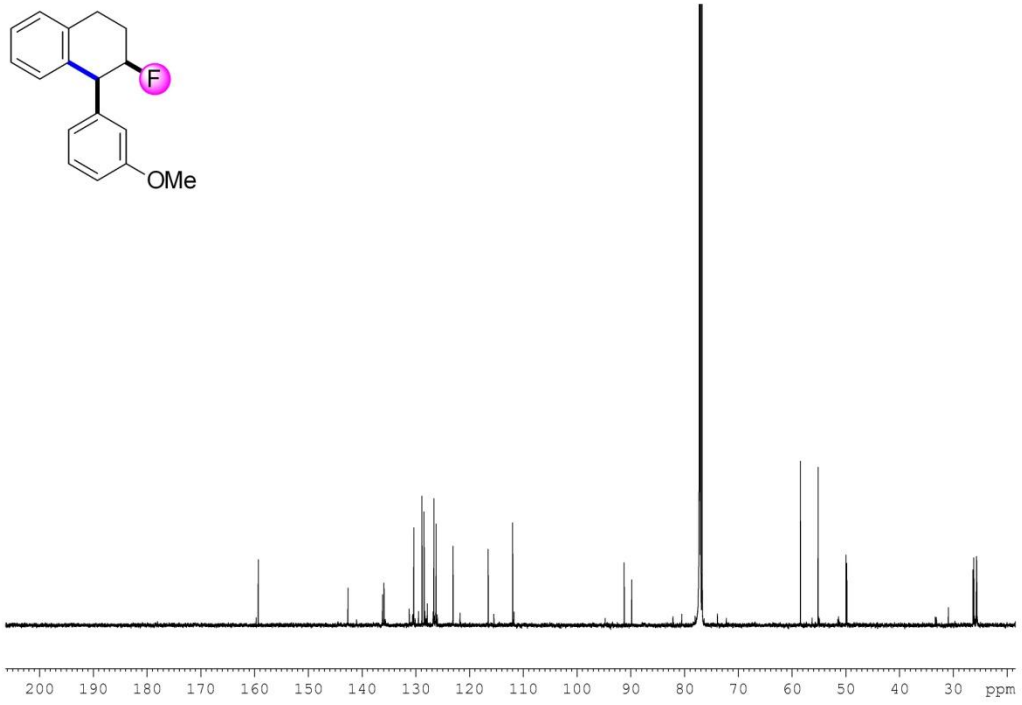

Et
F
Ph
-156.19
ppm
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

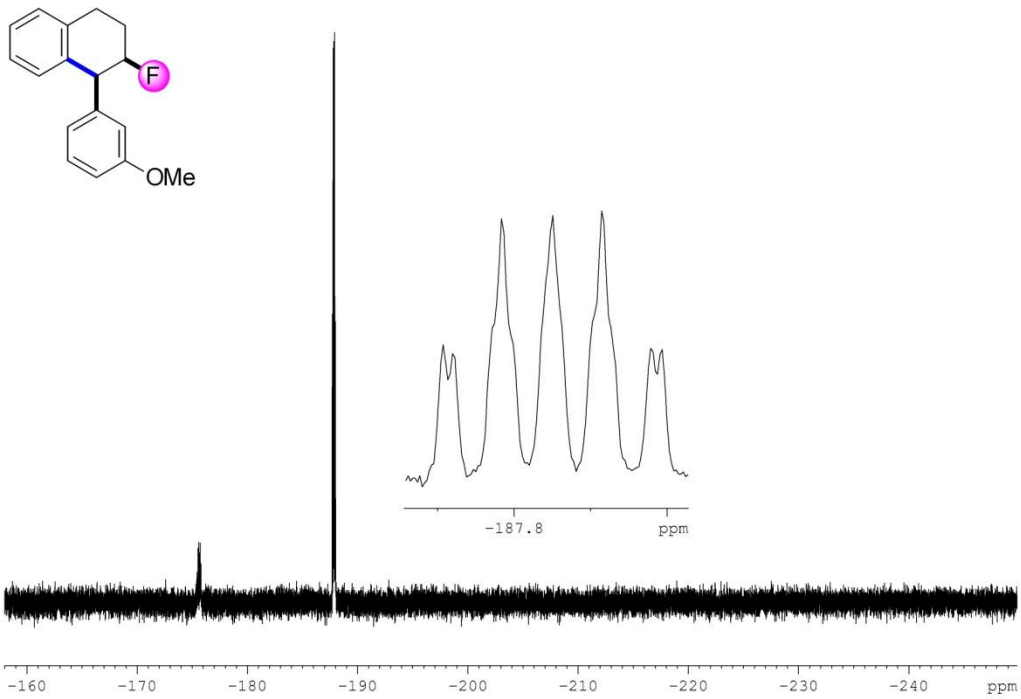

F
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.07
2.22
1.14
0.98
0.92
1.06
0.86
1.00
0.96
3.22
0.92
1.05
2.03

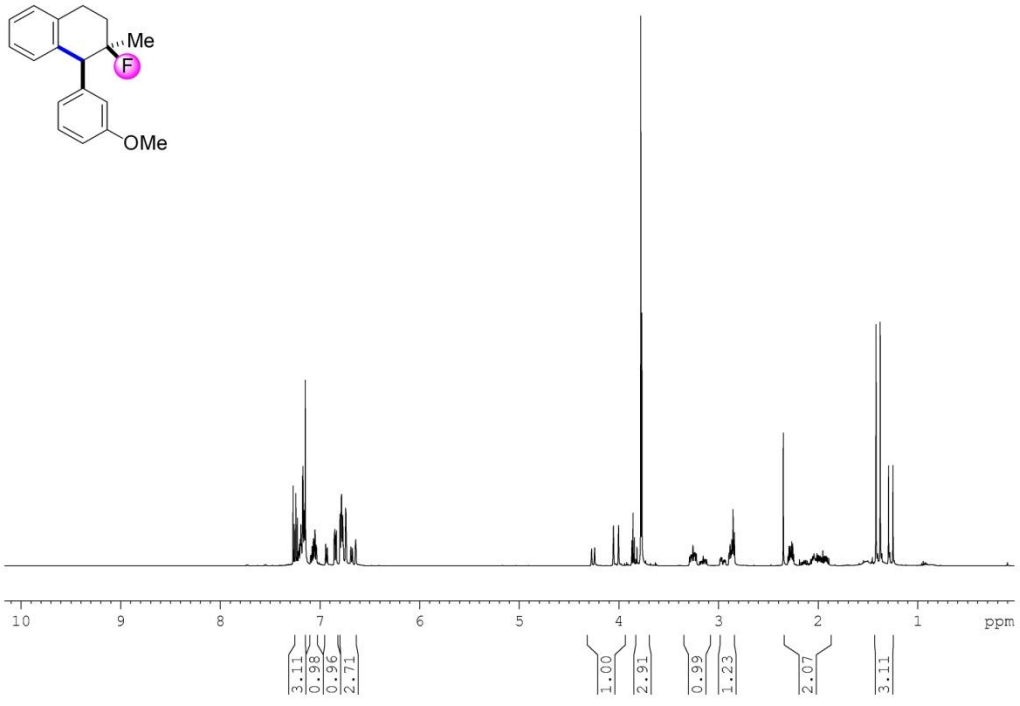

F
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

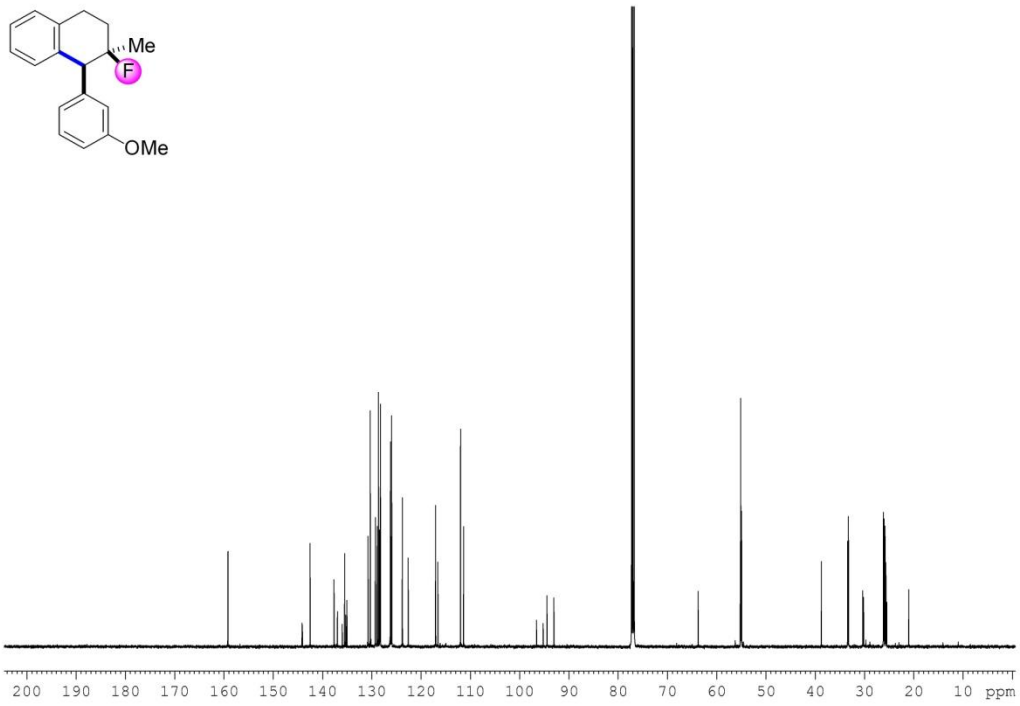

F
OMe
-175.6
ppm
-140 -145 -150 -155 -160 -165 -170 -175 -180 ppm

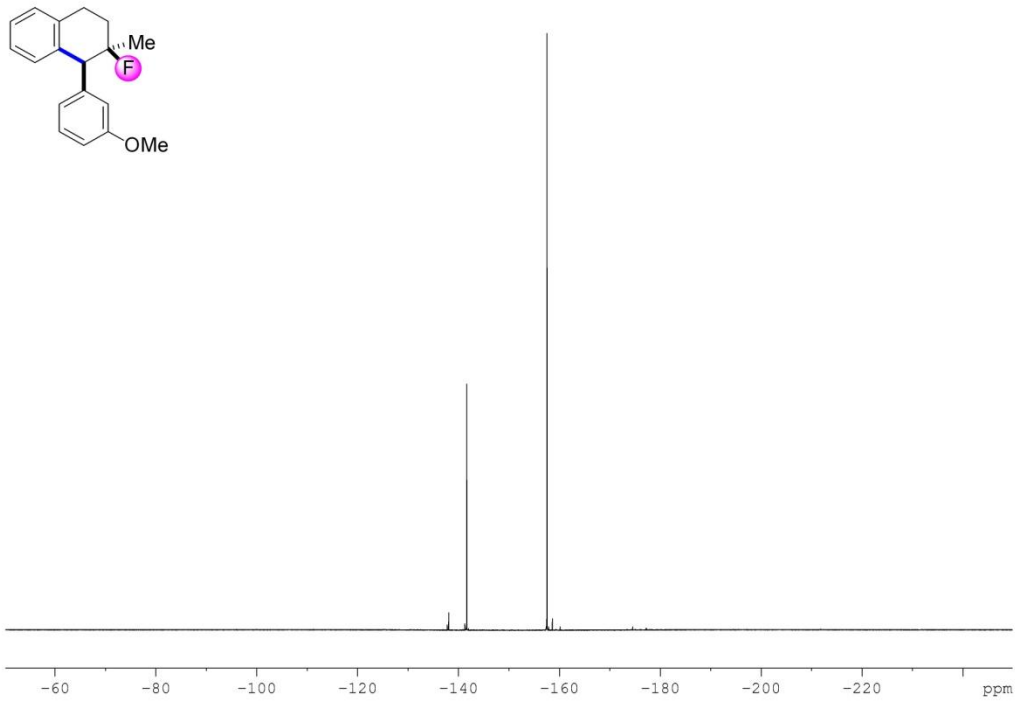

F
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.05
2.44
1.13
0.99
0.91
1.01
0.93
1.00
1.08
3.02
1.06
1.22
1.07
1.29

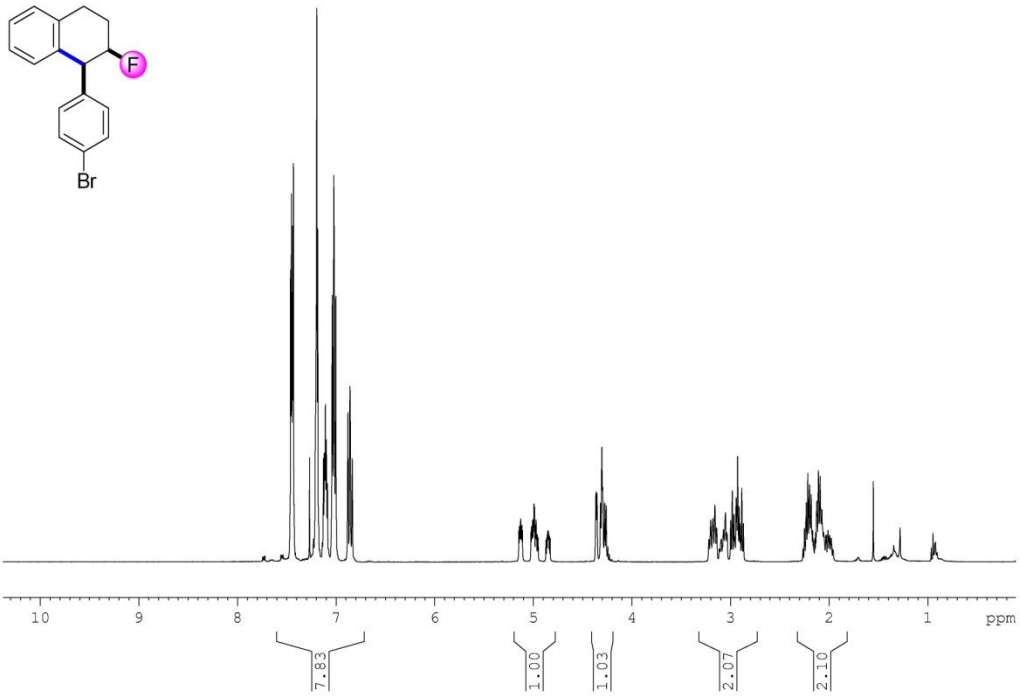

F
OMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

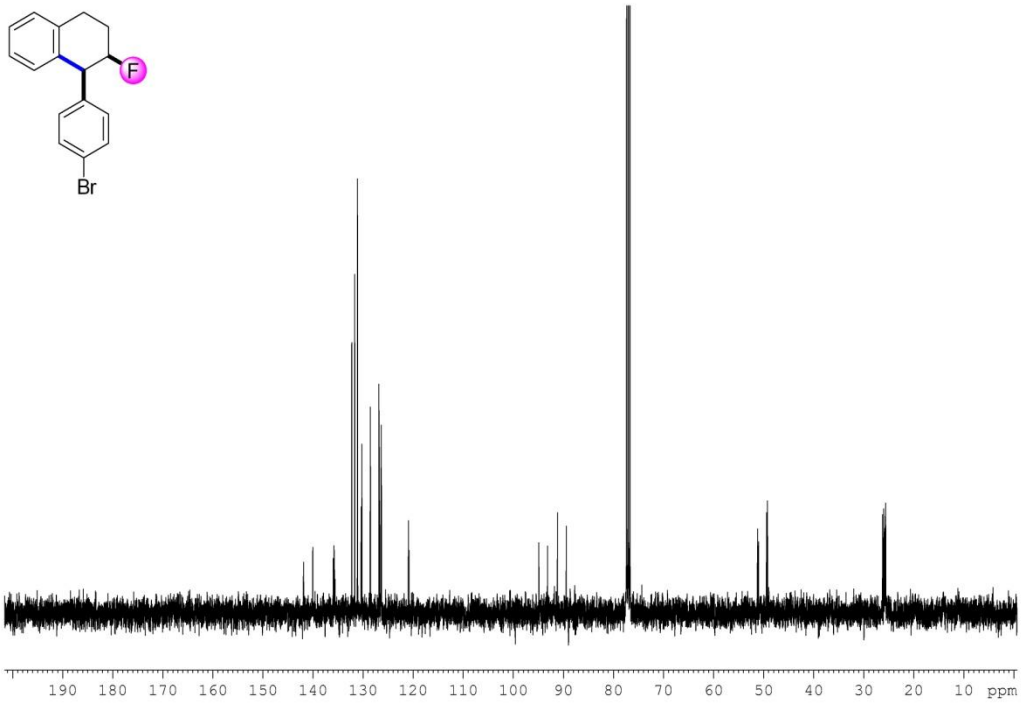

F
OMe
-187.8
ppm
-160
-170
-180
-190
-200
-210
-220
-230
-240
ppm

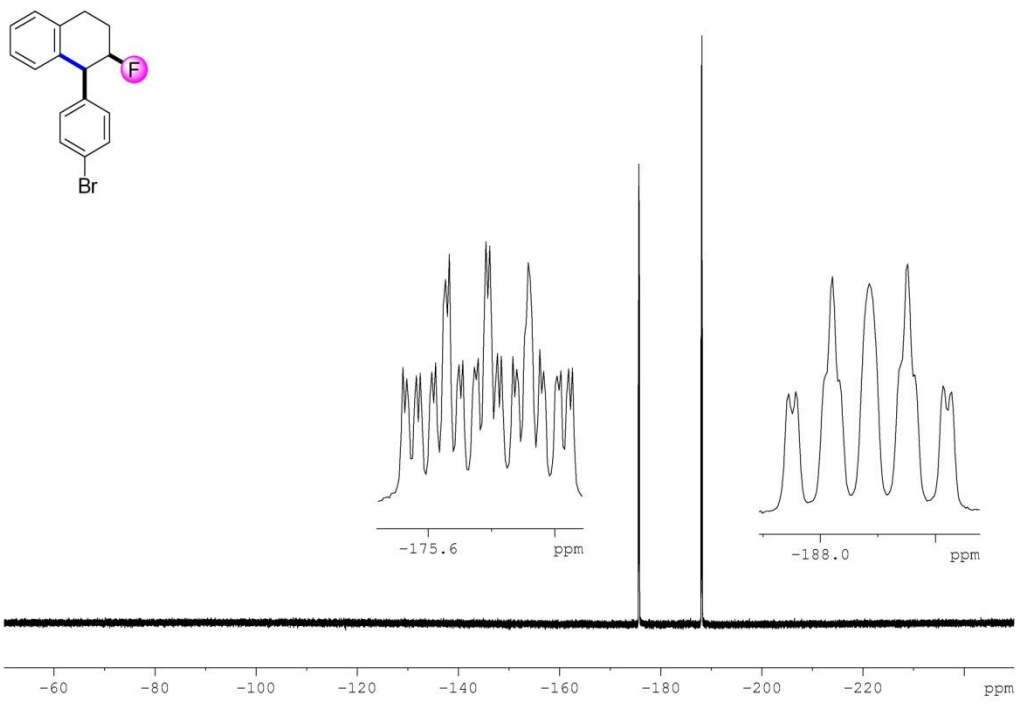

Me
F
OMe
10
9
8
7
6
5
4
3
2
1
ppm
3.11
0.98
0.96
2.71
1.00
2.91
0.99
1.23
2.07
3.11

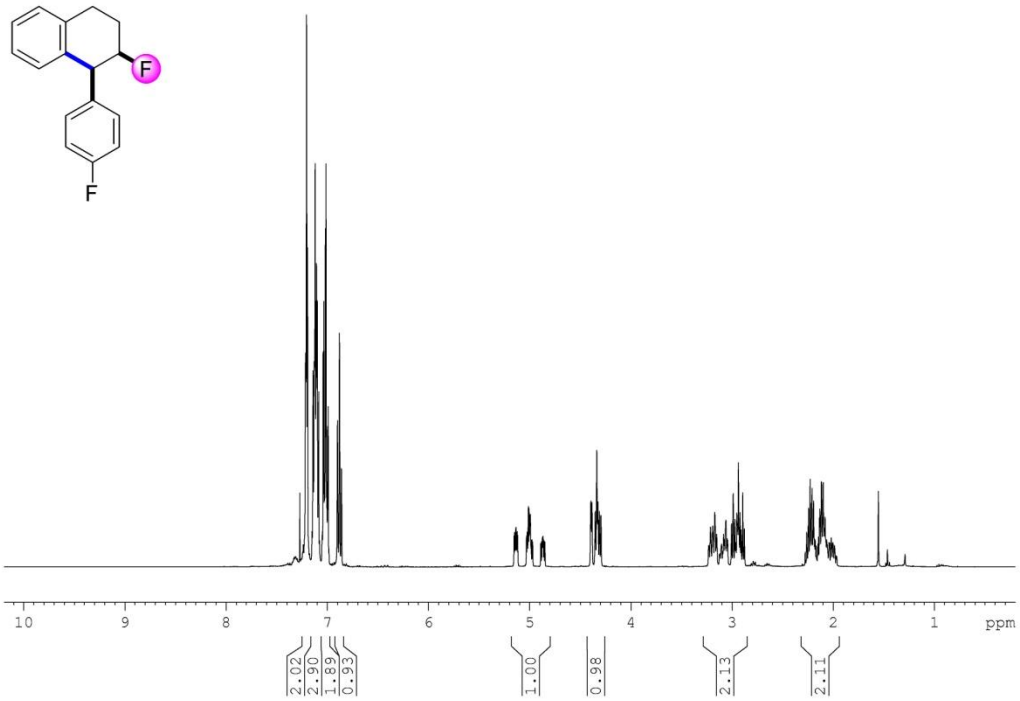

Me
F
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

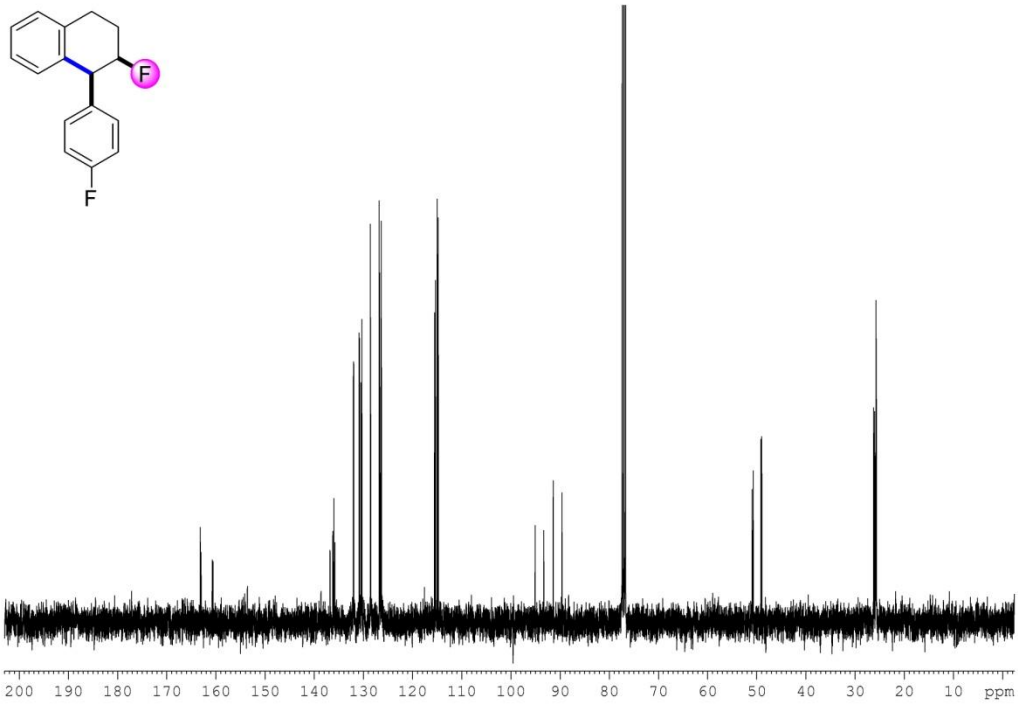

Me
F
OMe
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

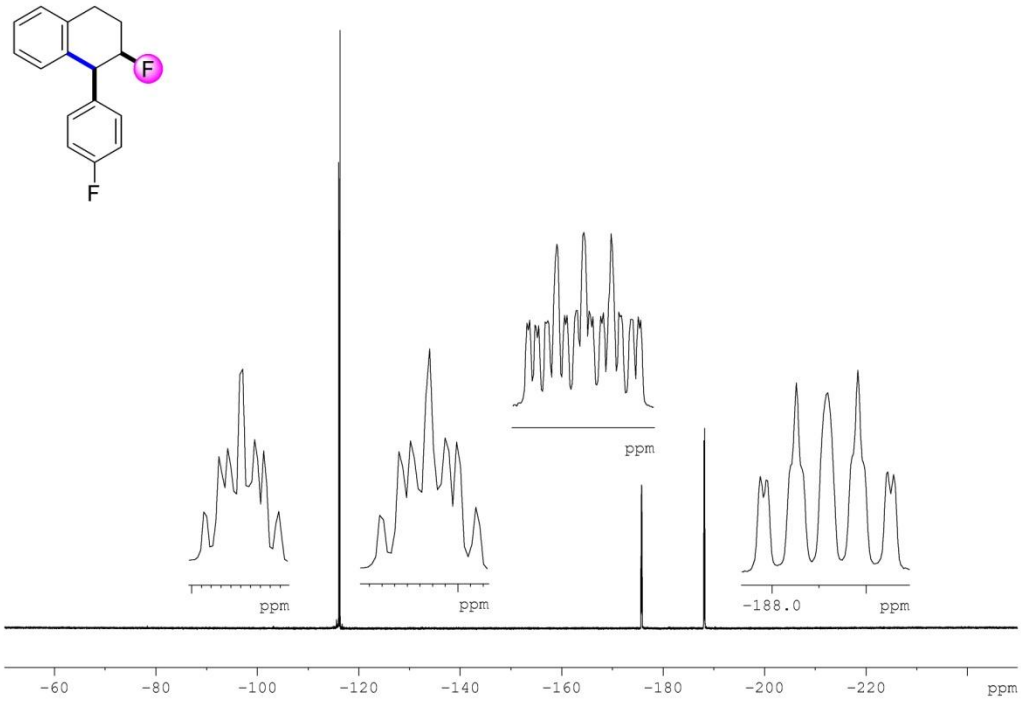

F
Br
10
9
8
7
6
5
4
3
2
1
ppm
7.83
1.00
1.03
2.07
2.10

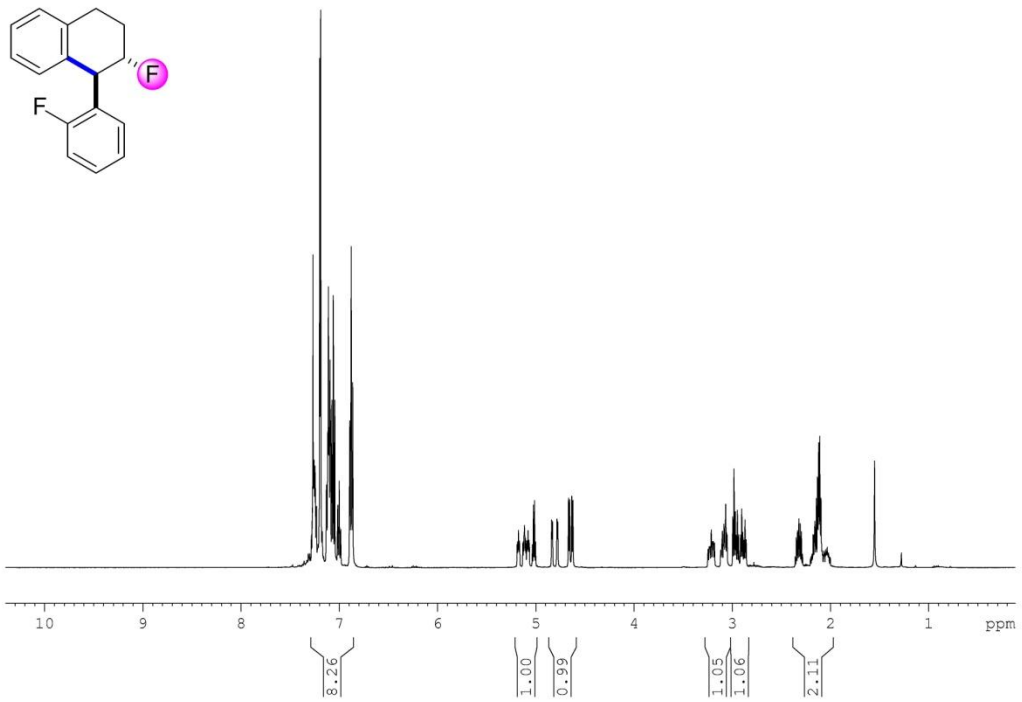

F
Br
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

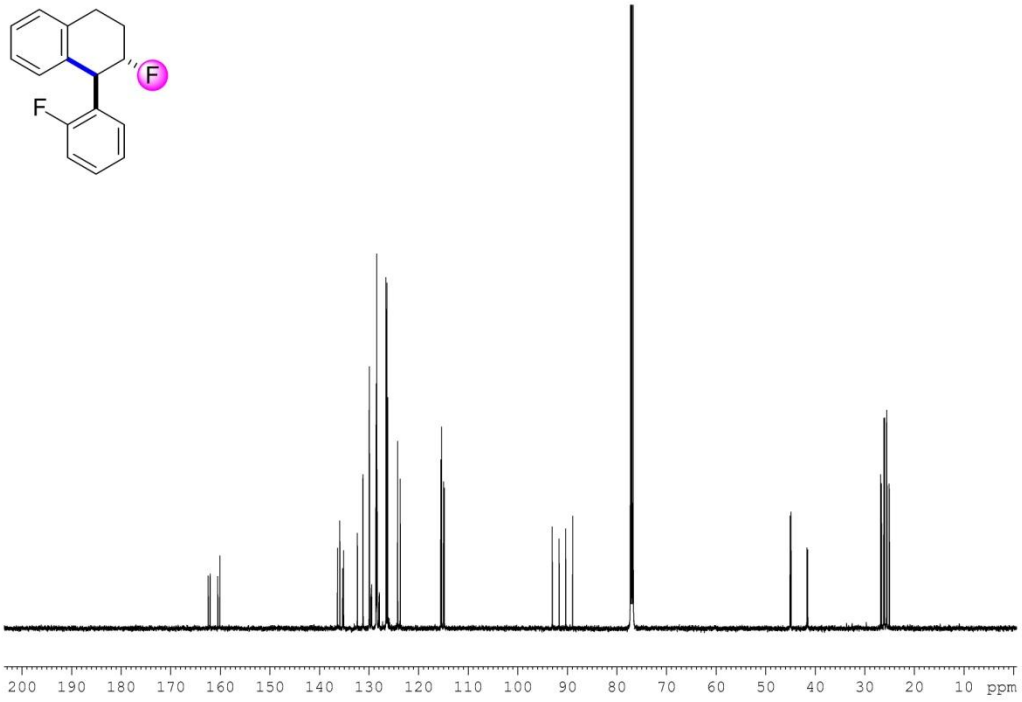

F
Br
-175.6
ppm
-188.0
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

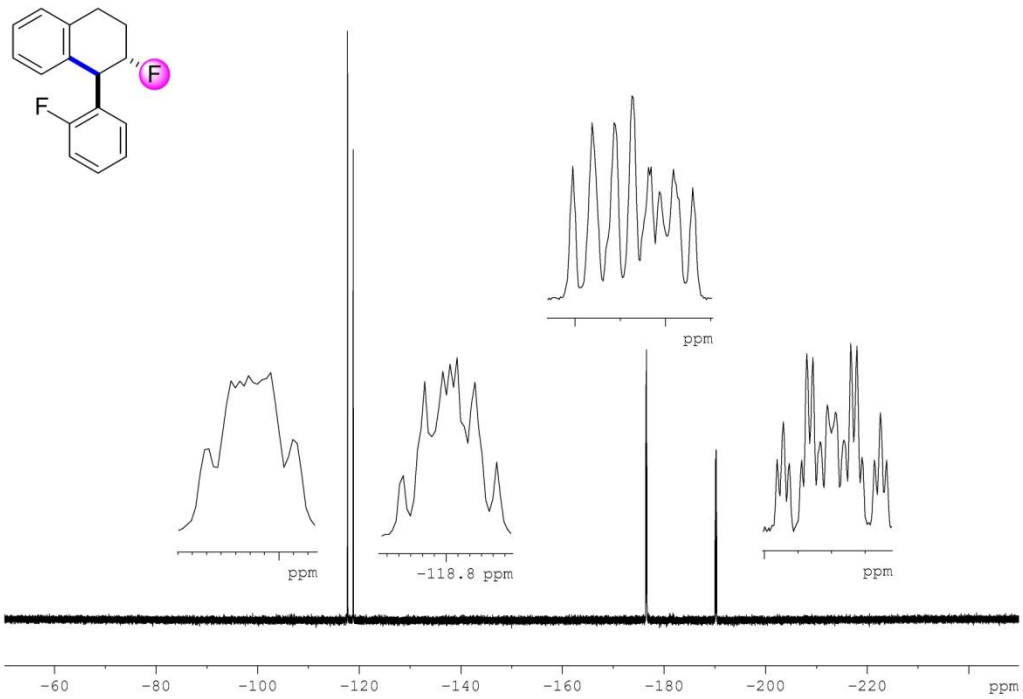

F
F
10
9
8
7
6
5
4
3
2
1
ppm
2.02
2.90
1.89
0.93
1.00
0.98
2.13
2.11

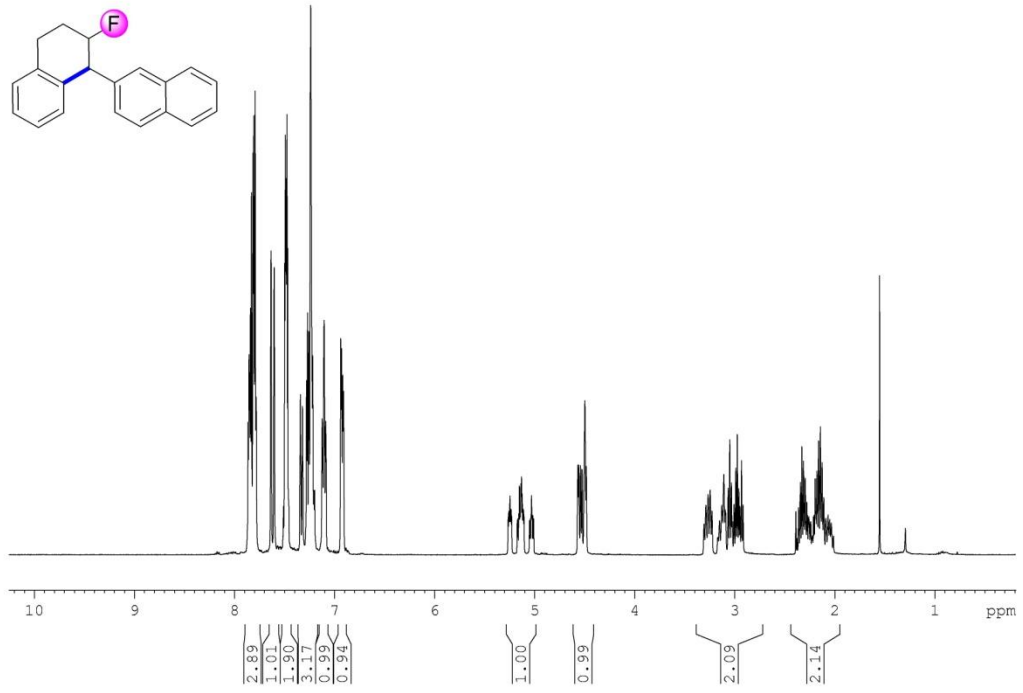

F
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

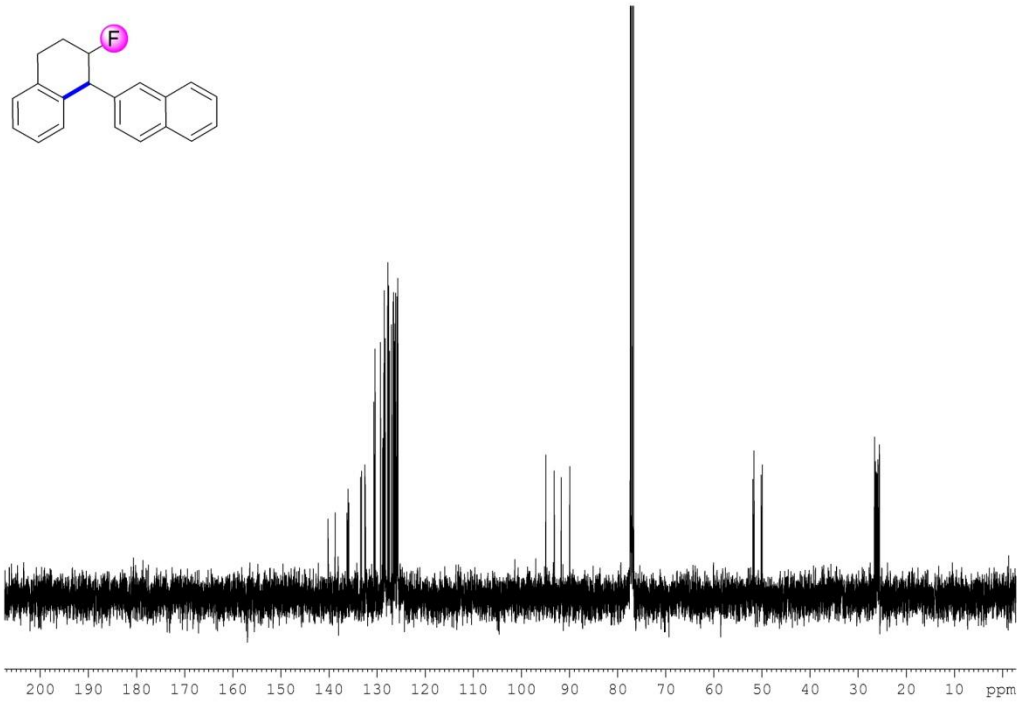

F
F
ppm
ppm
ppm
-188.0
ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

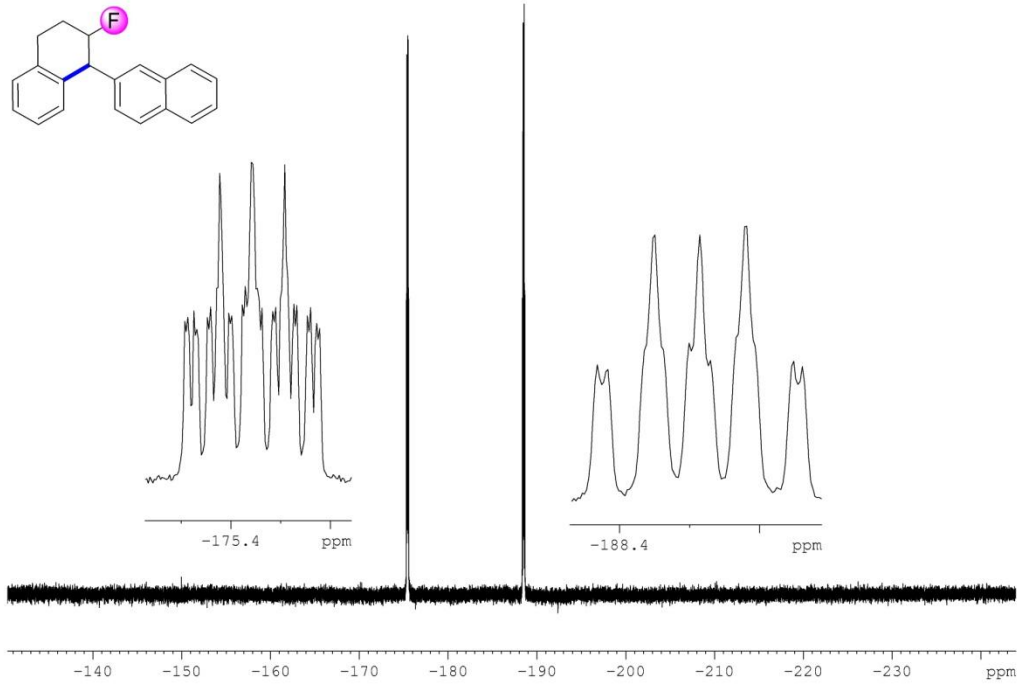

F
F
10
9
8
7
6
5
4
3
2
1
ppm
8.26
1.00
0.99
1.05
1.06
2.11

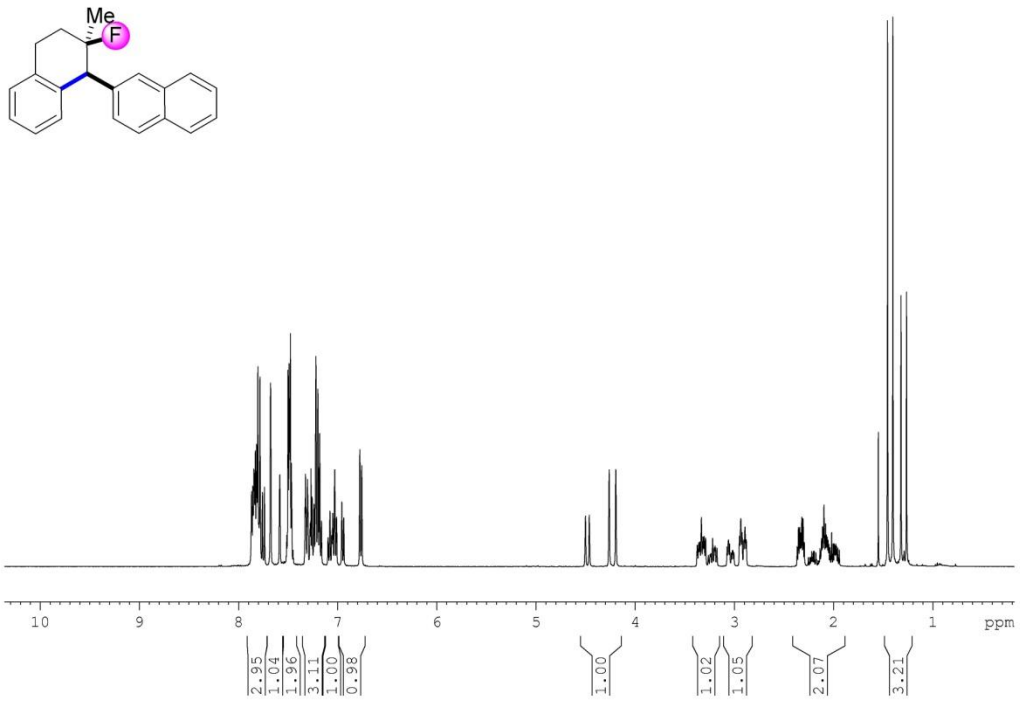

F
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

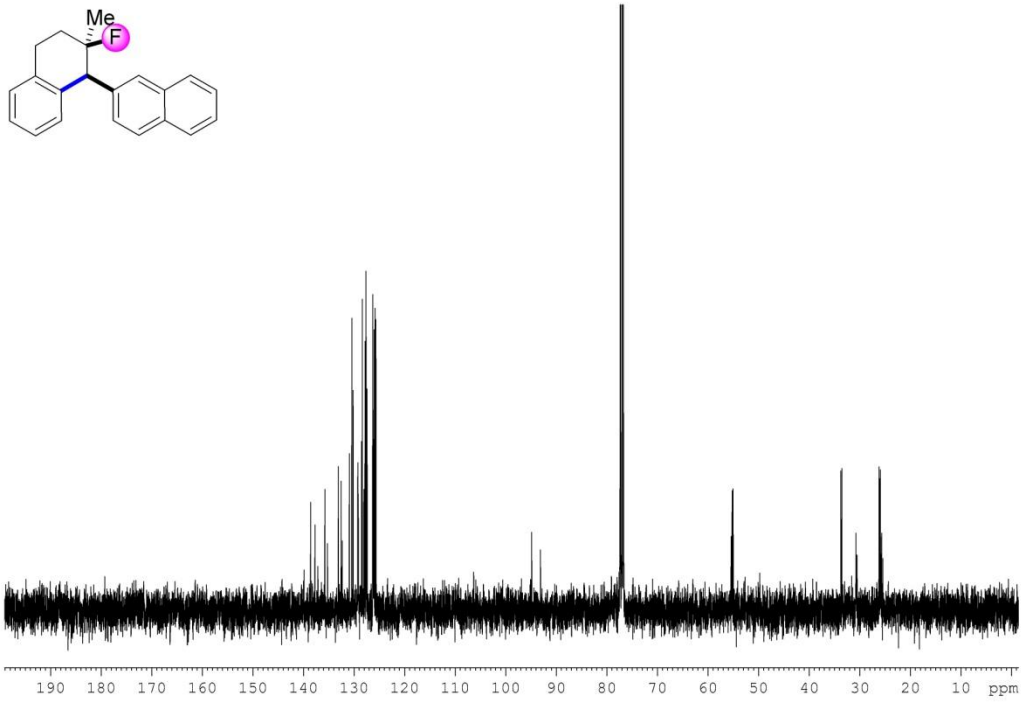

F
F
ppm
ppm
-118.8 ppm
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

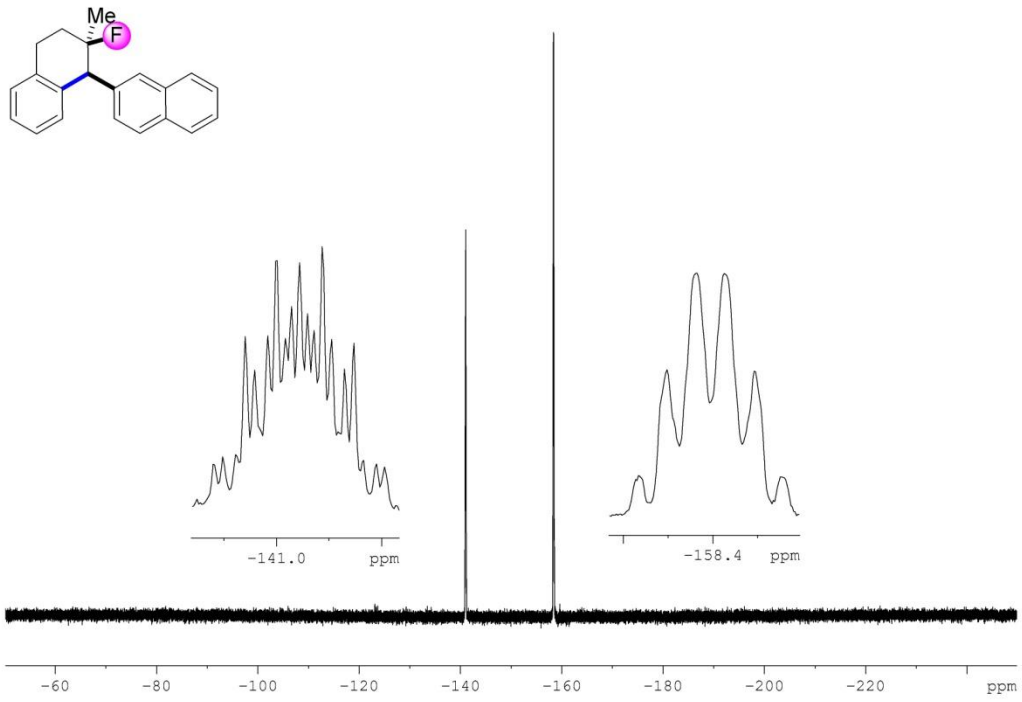

F
10
9
8
7
6
5
4
3
2
1
ppm
2.89
1.01
1.90
3.17
0.99
0.94
1.00
0.99
2.09
2.14

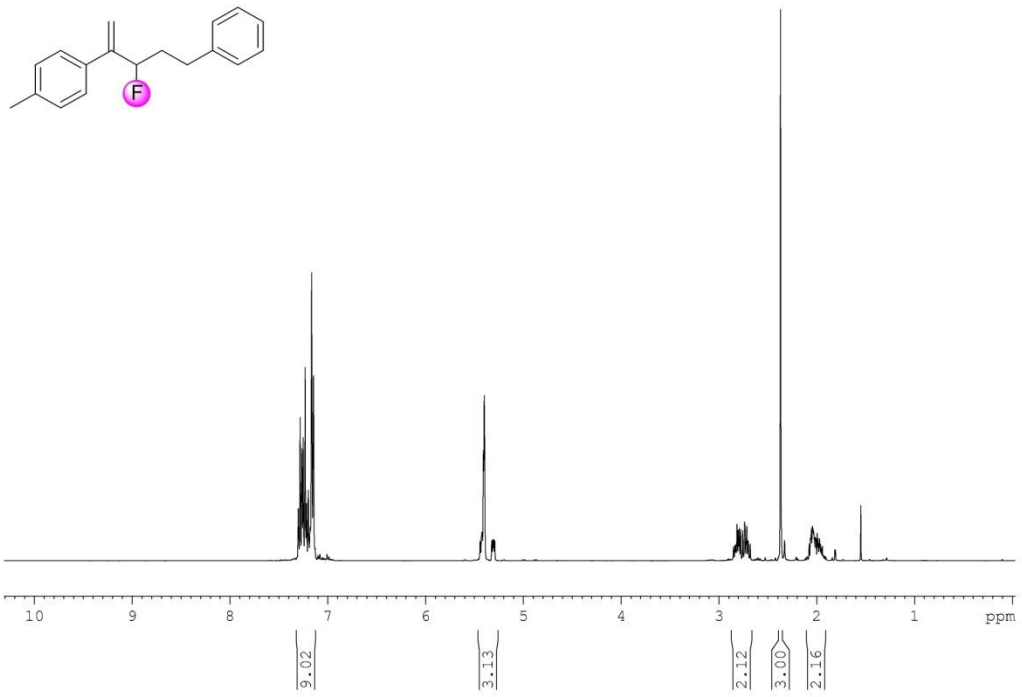

F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

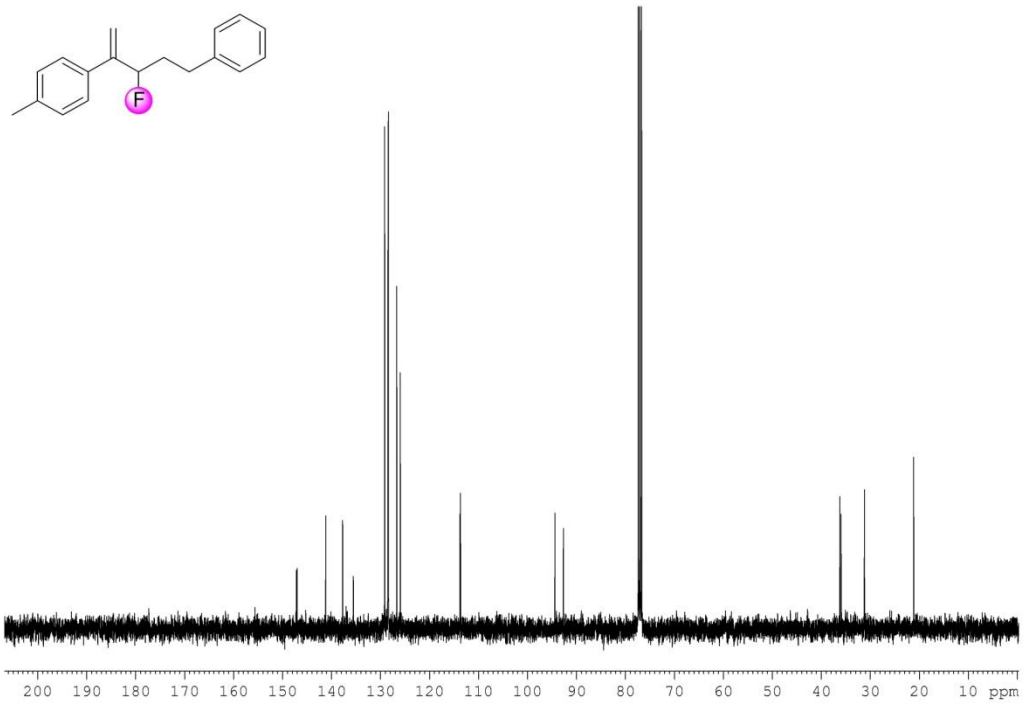

F
-175.4 ppm
-188.4 ppm
-140 -150 -160 -170 -180 -190 -200 -210 -220 -230 ppm

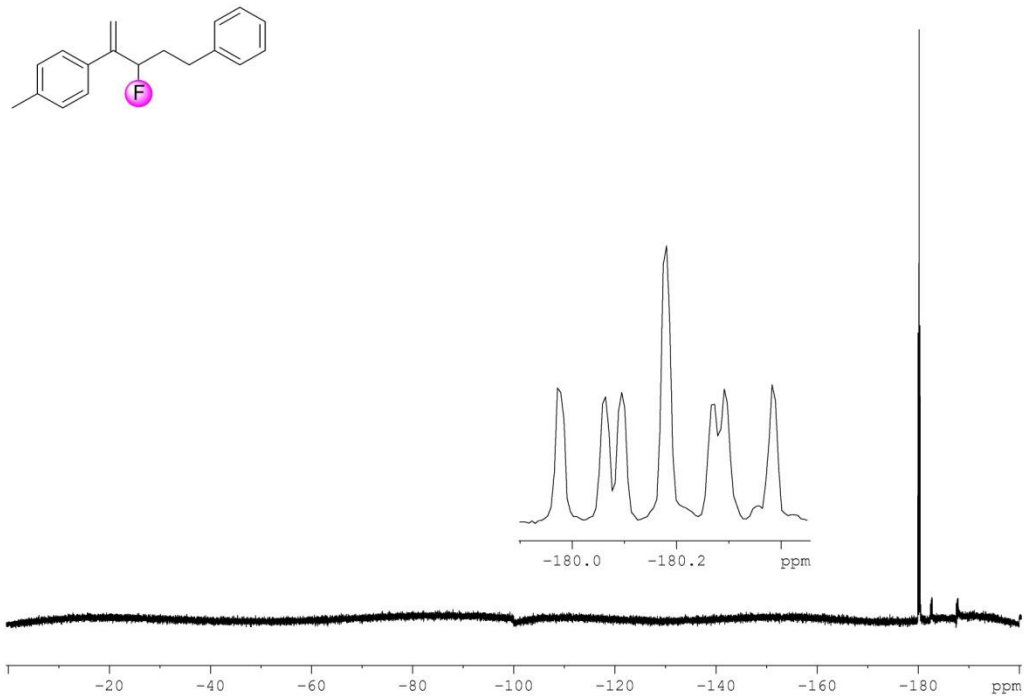

Me
F
10
9
8
7
6
5
4
3
2
1
ppm
2.95
1.04
1.96
3.11
1.00
0.98
1.00
1.02
1.05
2.07
3.21

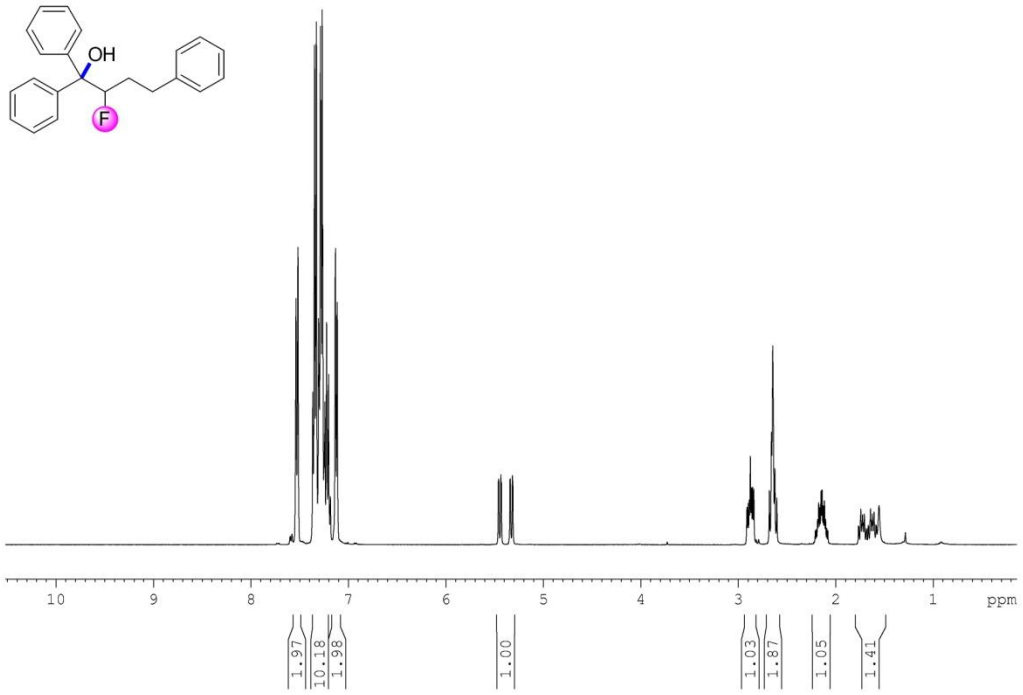

Me
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

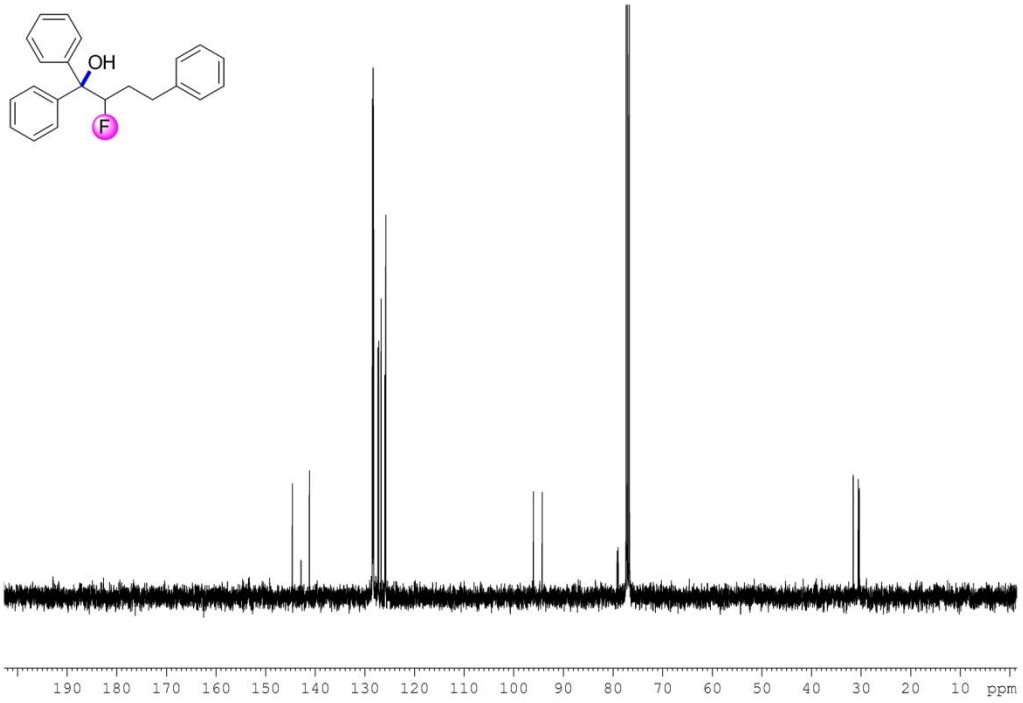

Me
F
-141.0
ppm
-158.4
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

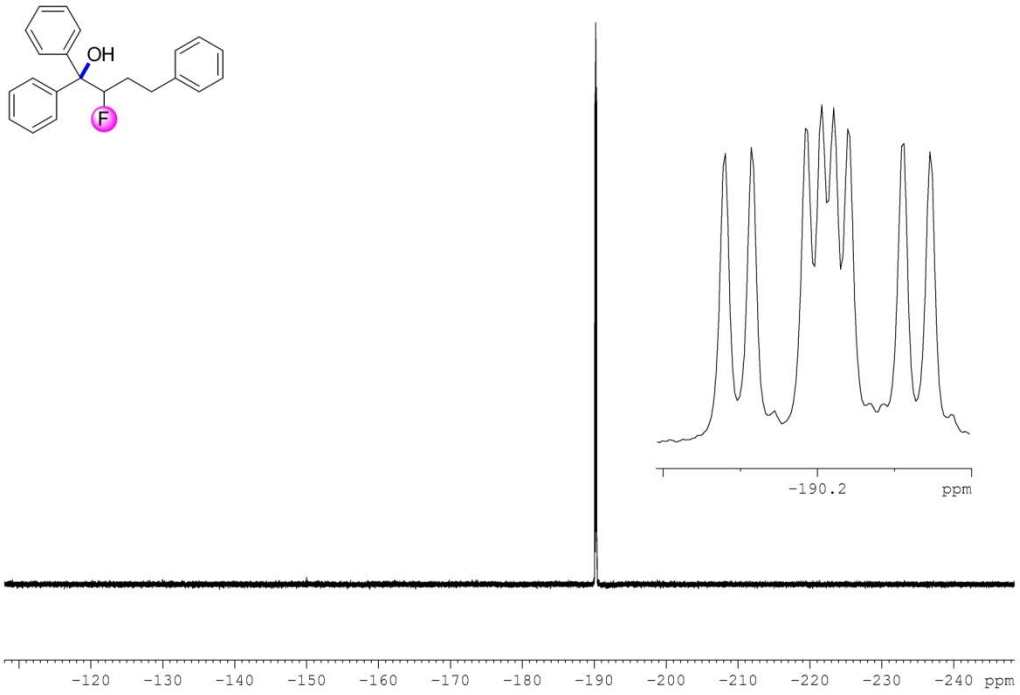

F
10
9
8
7
6
5
4
3
2
1
ppm
9.02
3.13
2.12
3.00
2.16

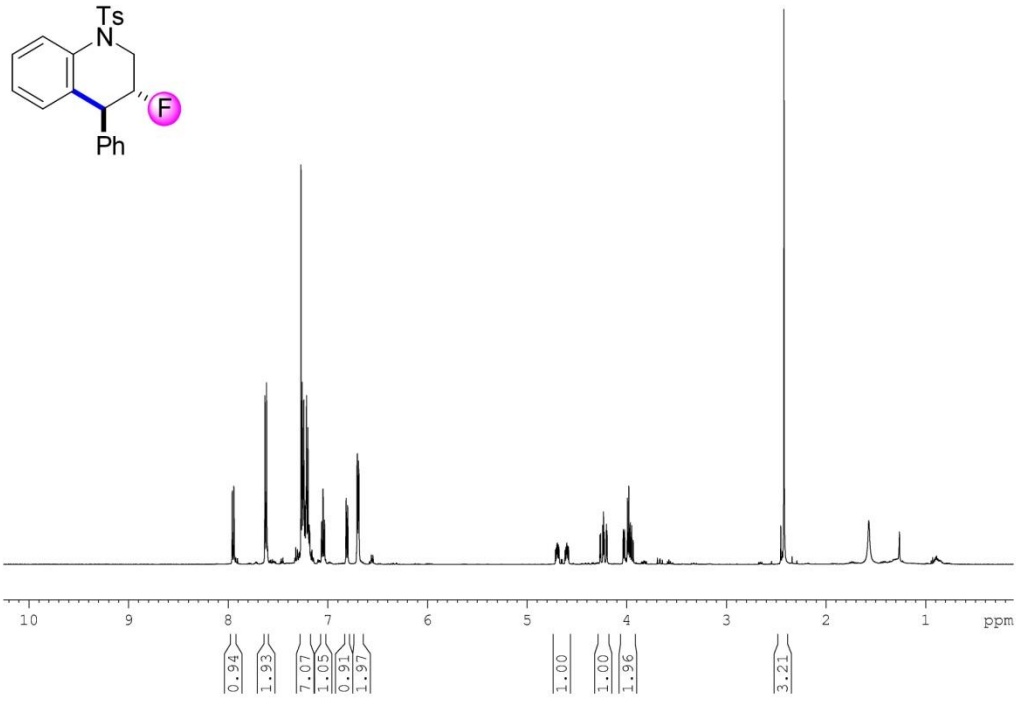

F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

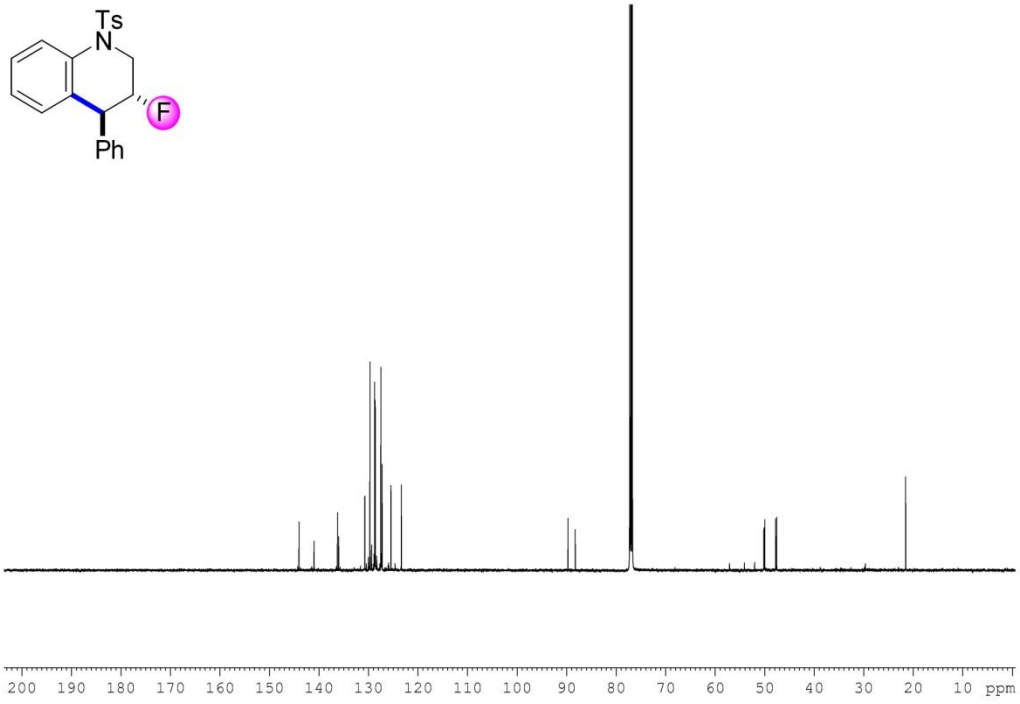

F
-180.0
-180.2
ppm
-20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

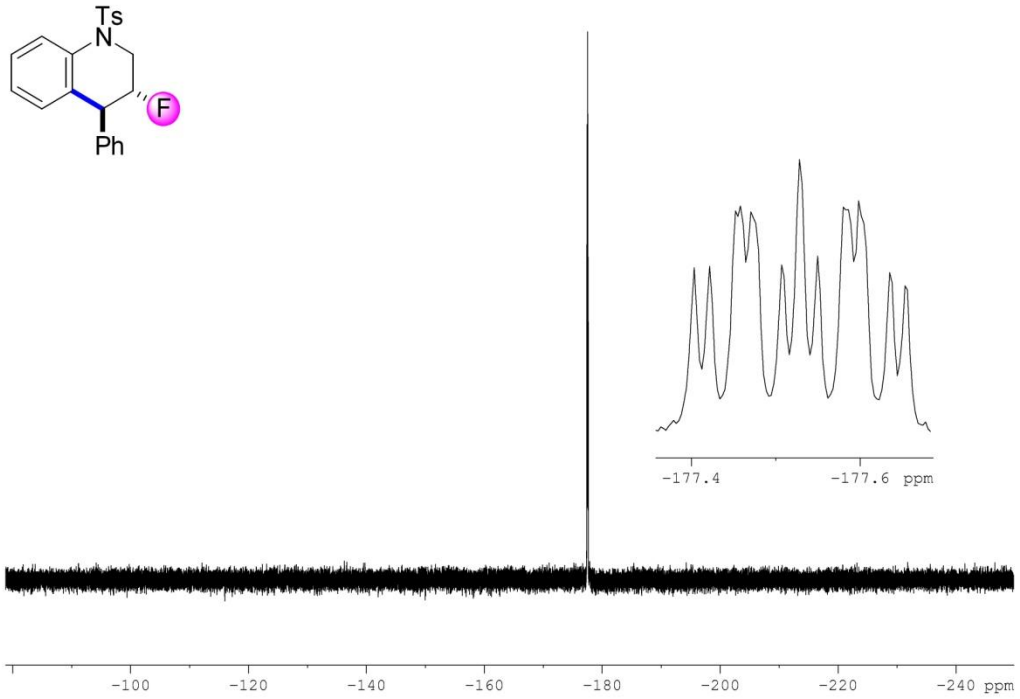

OH
F
10
9
8
7
6
5
4
3
2
1
ppm
1.97
10.18
1.98
1.00
1.03
1.87
1.05
1.41

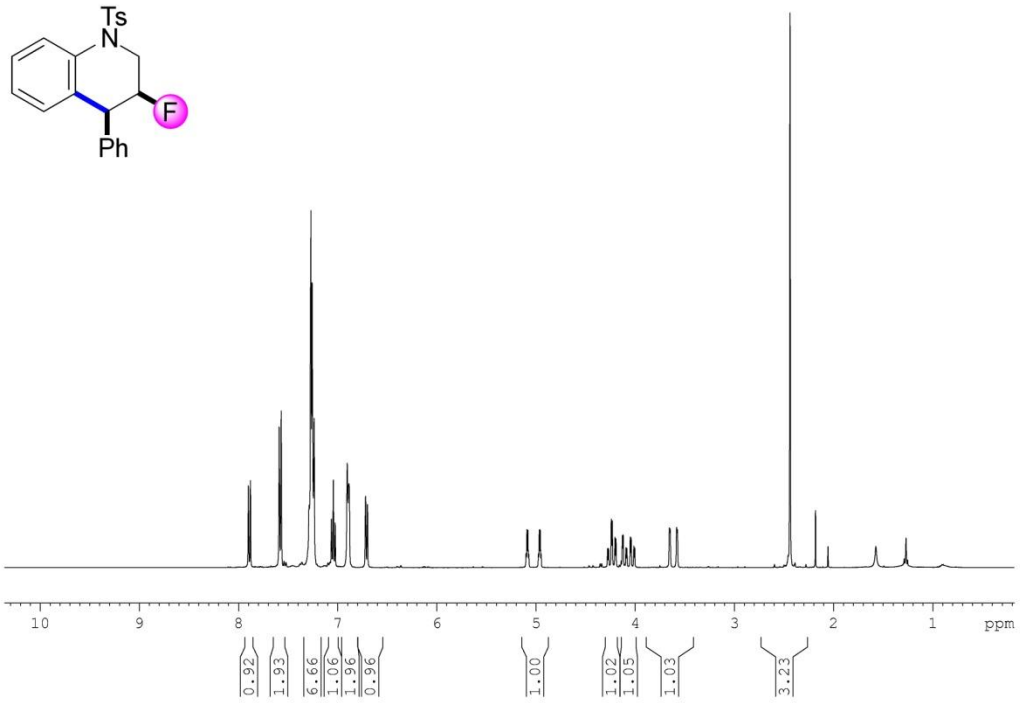

OH
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

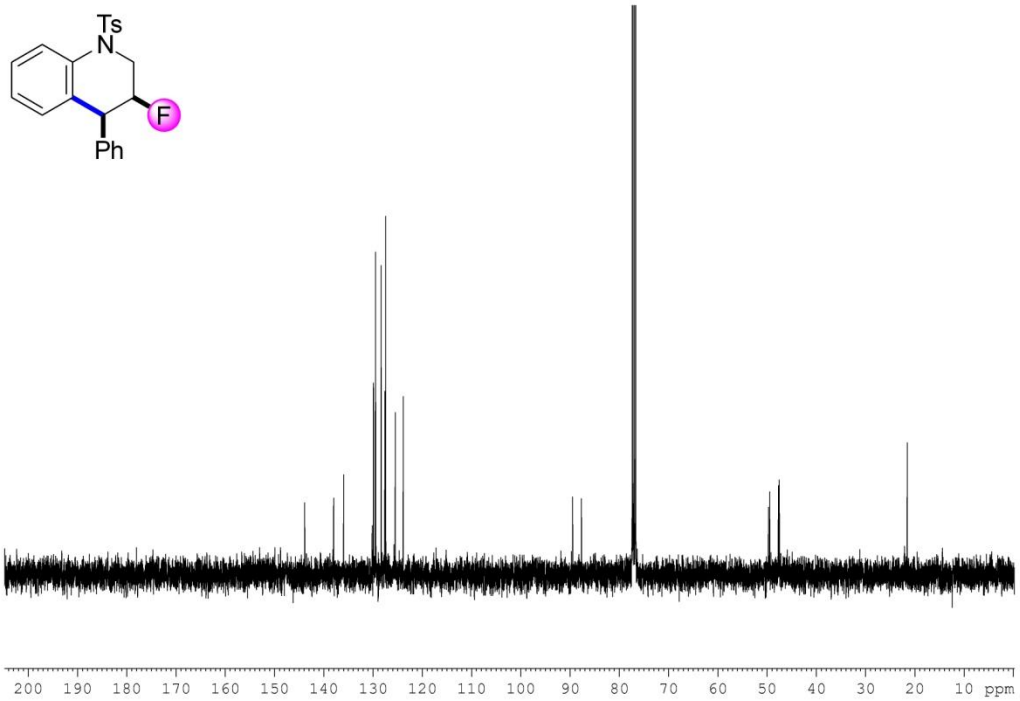

OH
F
-190.2
ppm
-120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 ppm

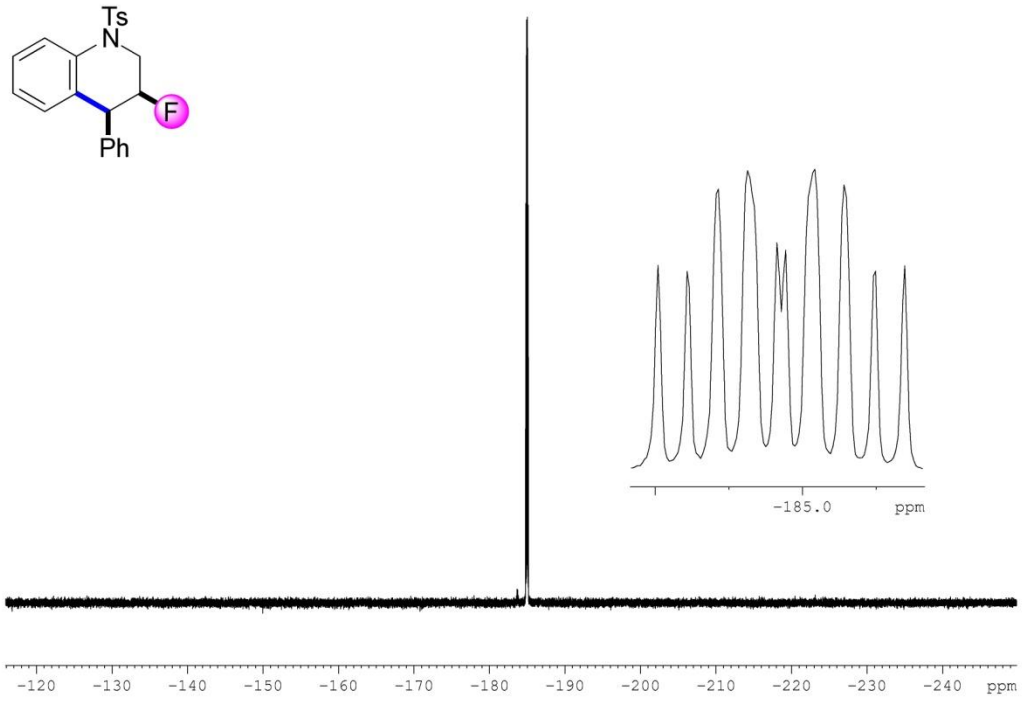

Ts
N
F
Ph
10 9 8 7 6 5 4 3 2 1 ppm
0.94
1.93
7.07
1.05
0.91
1.97
1.00
1.00
1.96
3.21

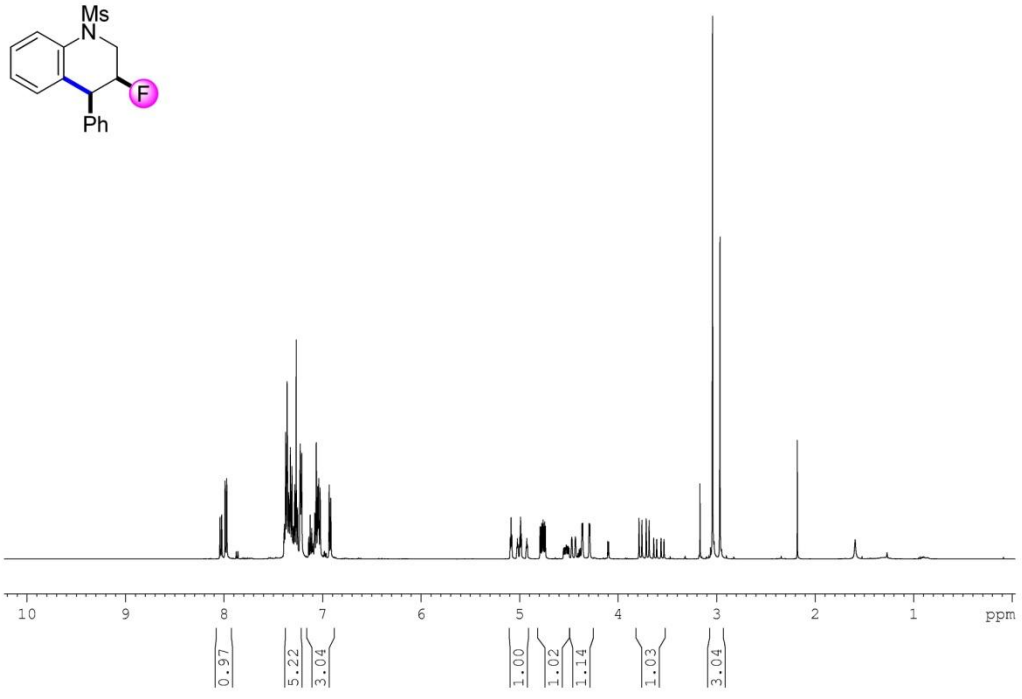

Ts
N
F
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

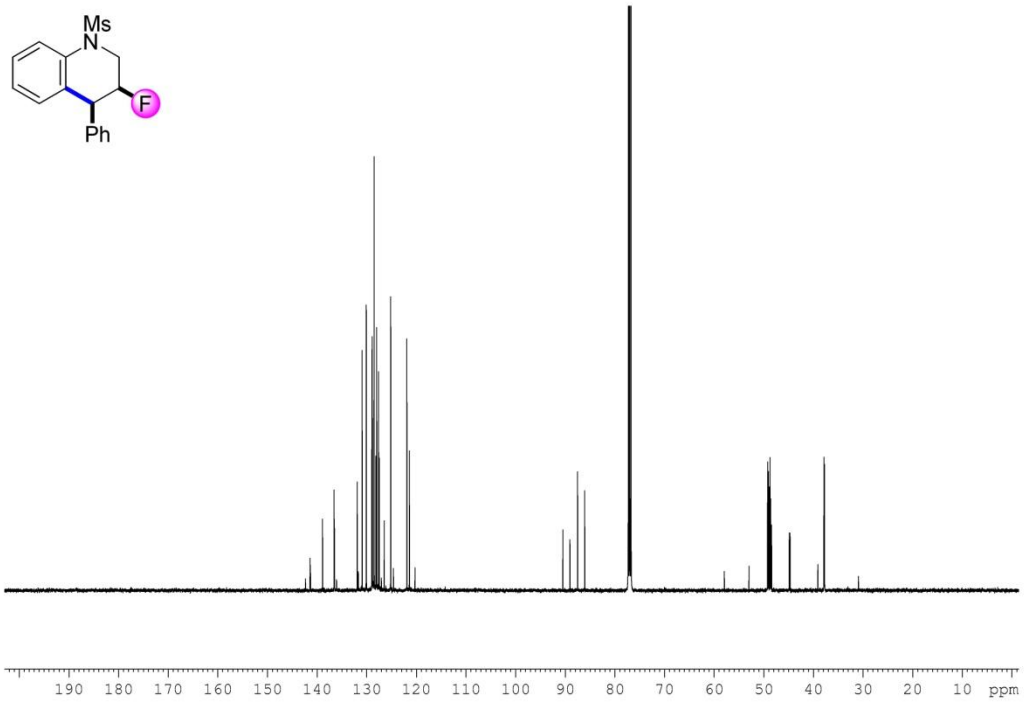

Ts
N
F
Ph
-177.4
-177.6 ppm
-100 -120 -140 -160 -180 -200 -220 -240 ppm

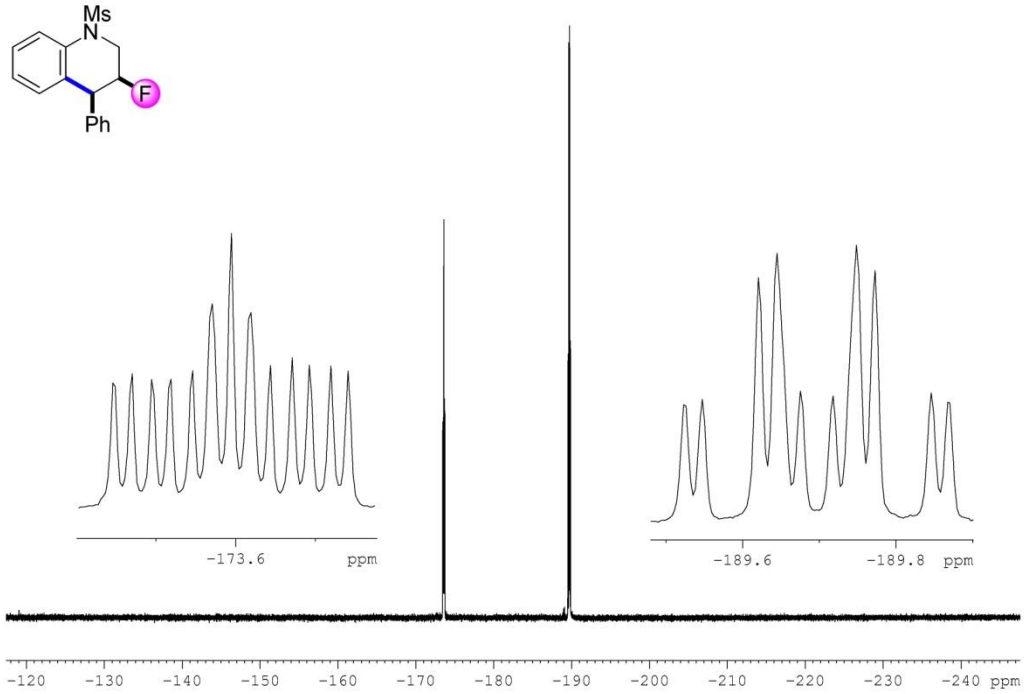

Ts
N
F
Ph
10
9
8
7
6
5
4
3
2
1
ppm
0.92
1.93
6.66
1.06
1.96
0.96
1.00
1.02
1.05
1.03
3.23

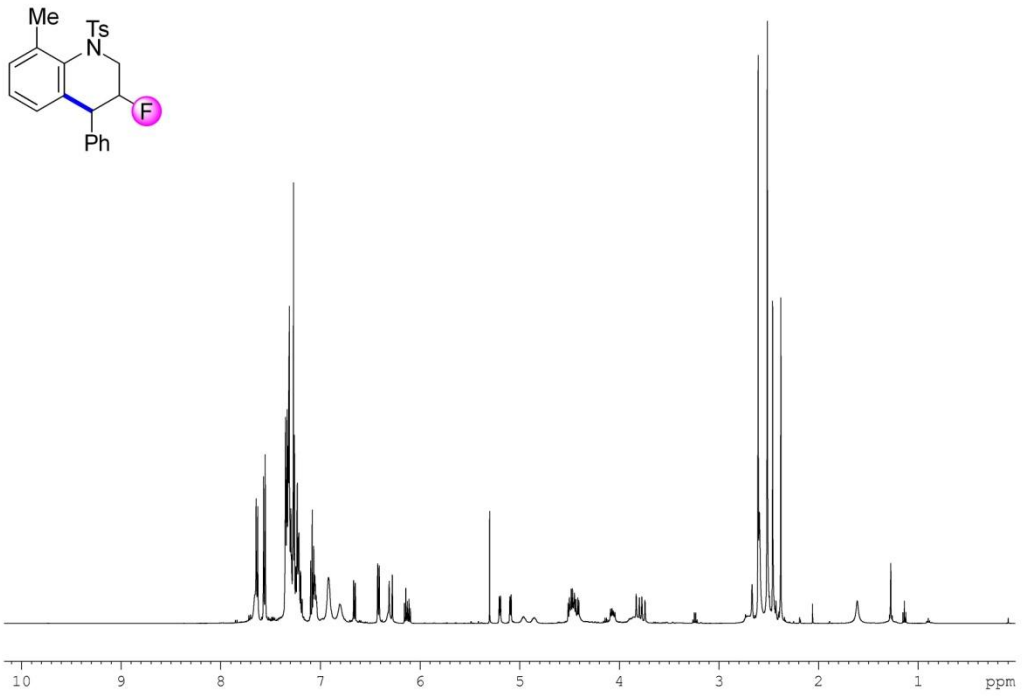

Ts
N
F
Ph
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

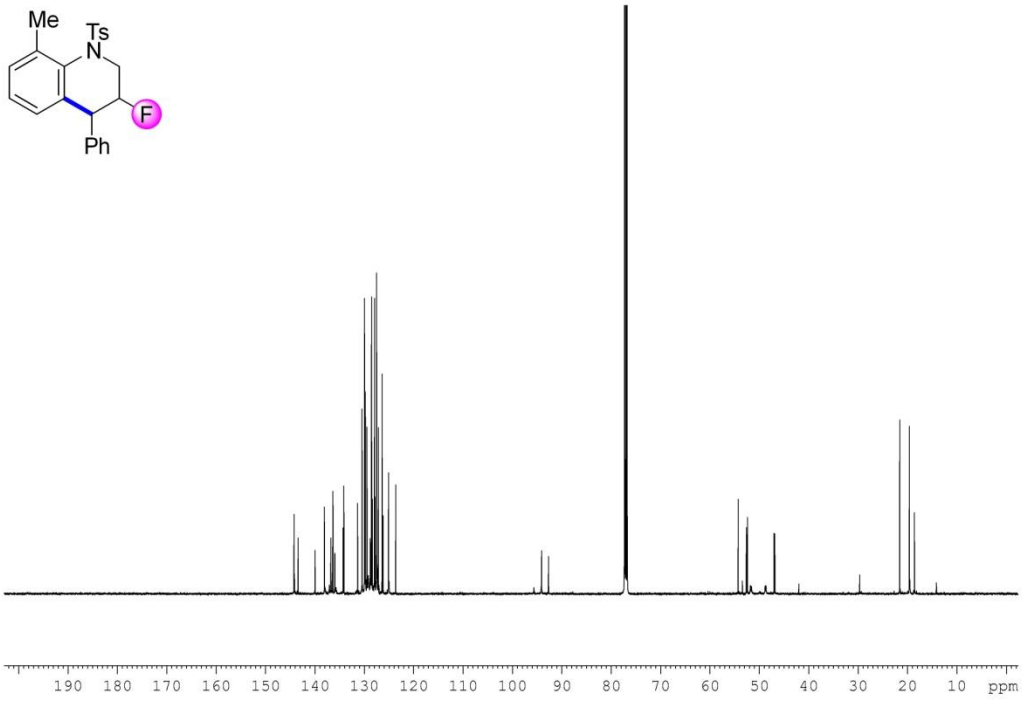

Ts
N
F
Ph
-185.0
ppm
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
ppm

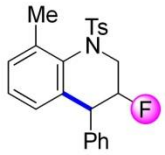

Ms
N
F
Ph
10
9
8
7
6
5
4
3
2
1
ppm
0.97
5.22
3.04
1.00
1.02
1.14
1.03
3.04


Ms
N
F
Ph
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Ms
N
F
Ph
-173.6 ppm
-189.6 -189.8 ppm
-120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 ppm

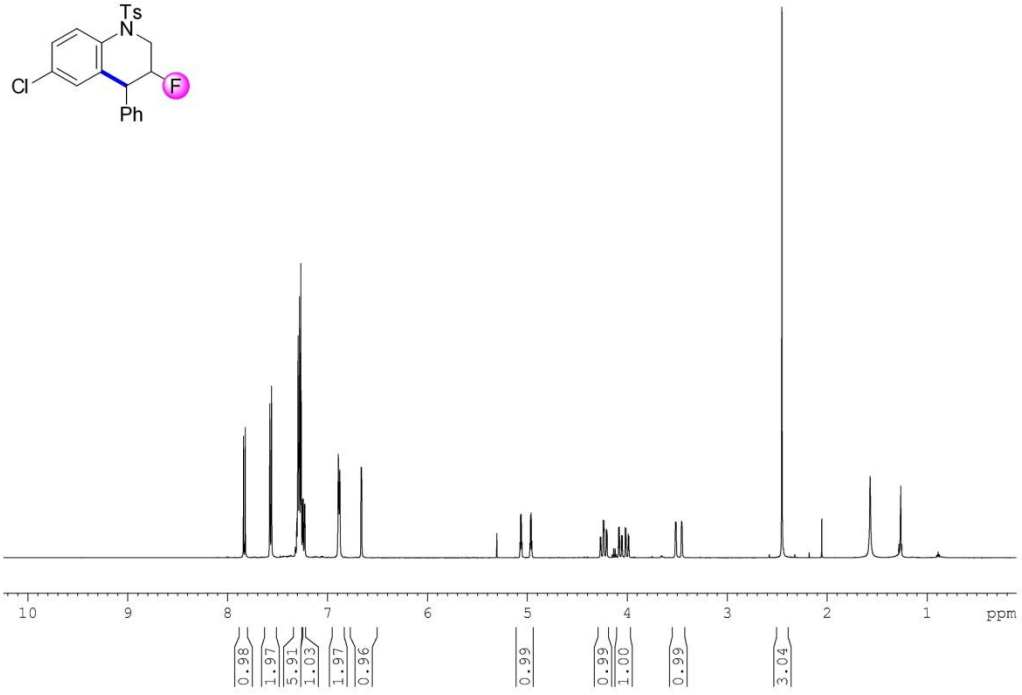

Me
Ts
N
F
Ph
10
9
8
7
6
5
4
3
2
1
ppm

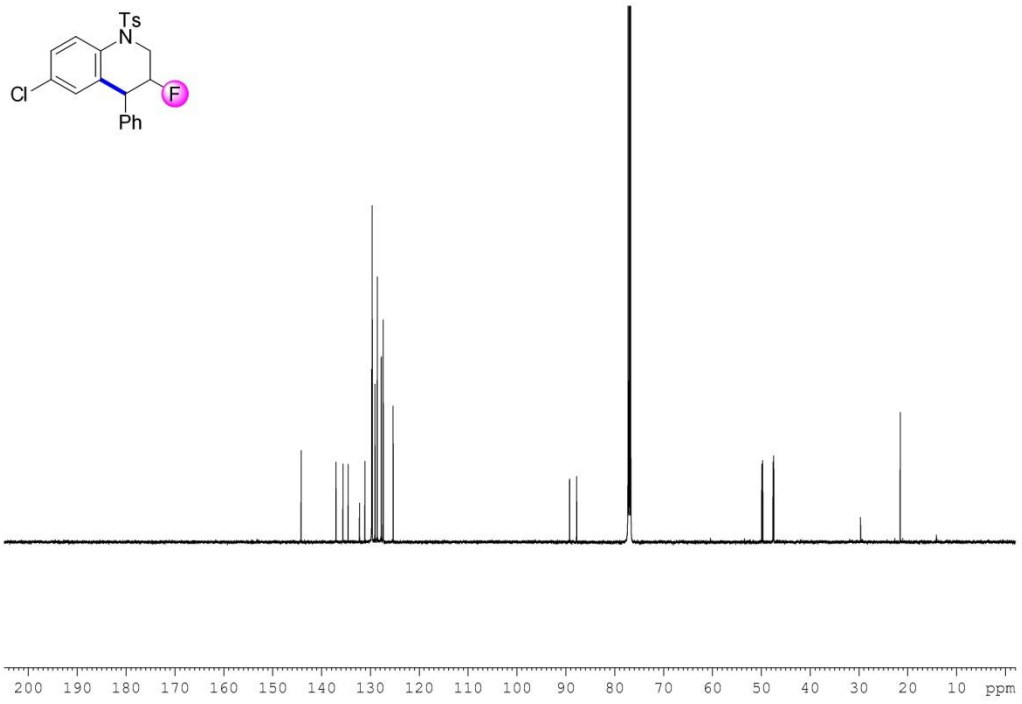

Me
Ts
N
F
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

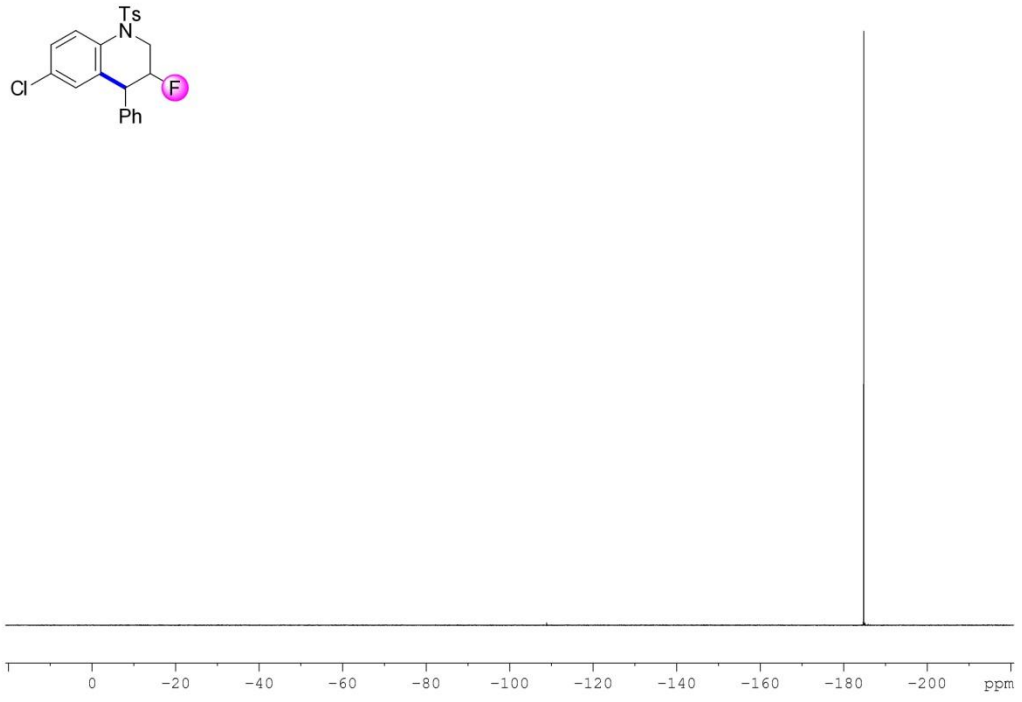

Me
Ts
N
F
Ph

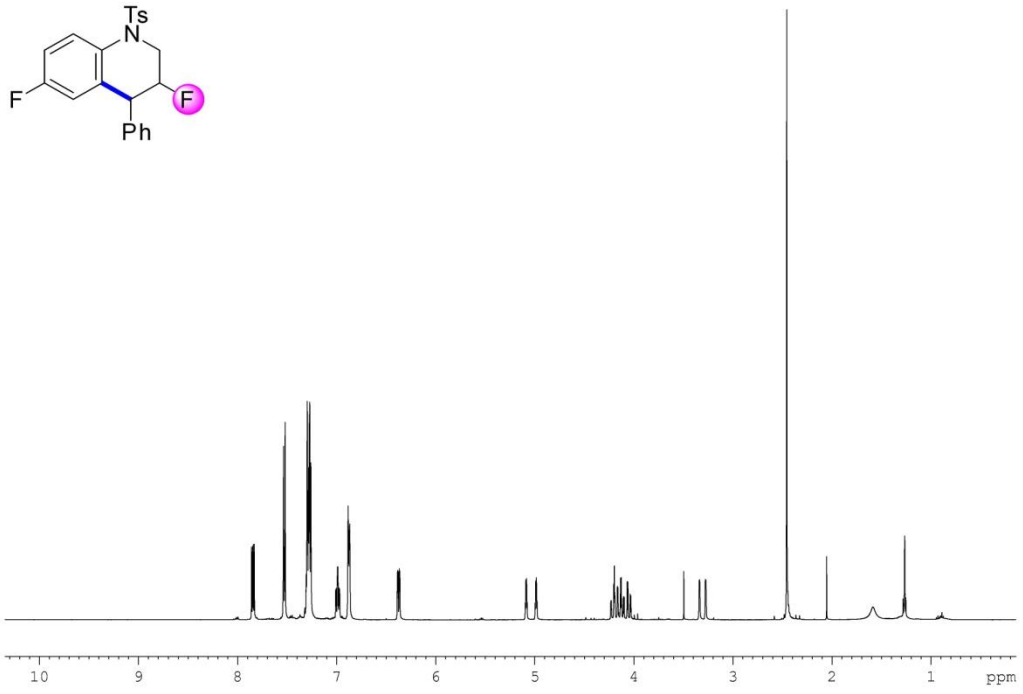
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

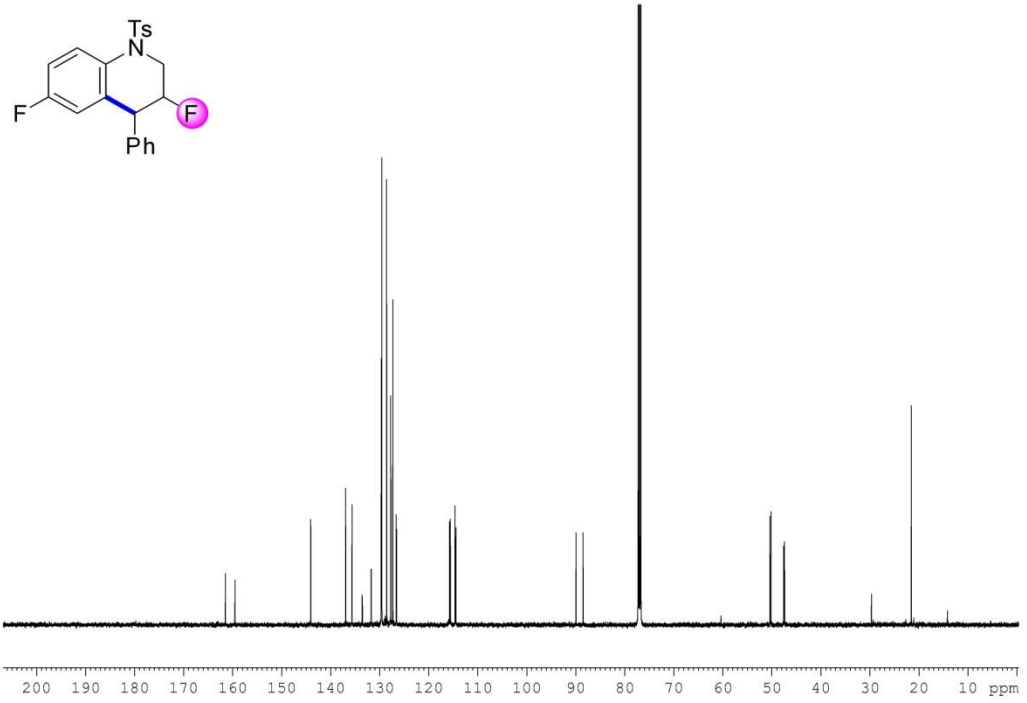
Ts
N
Cl
F
Ph

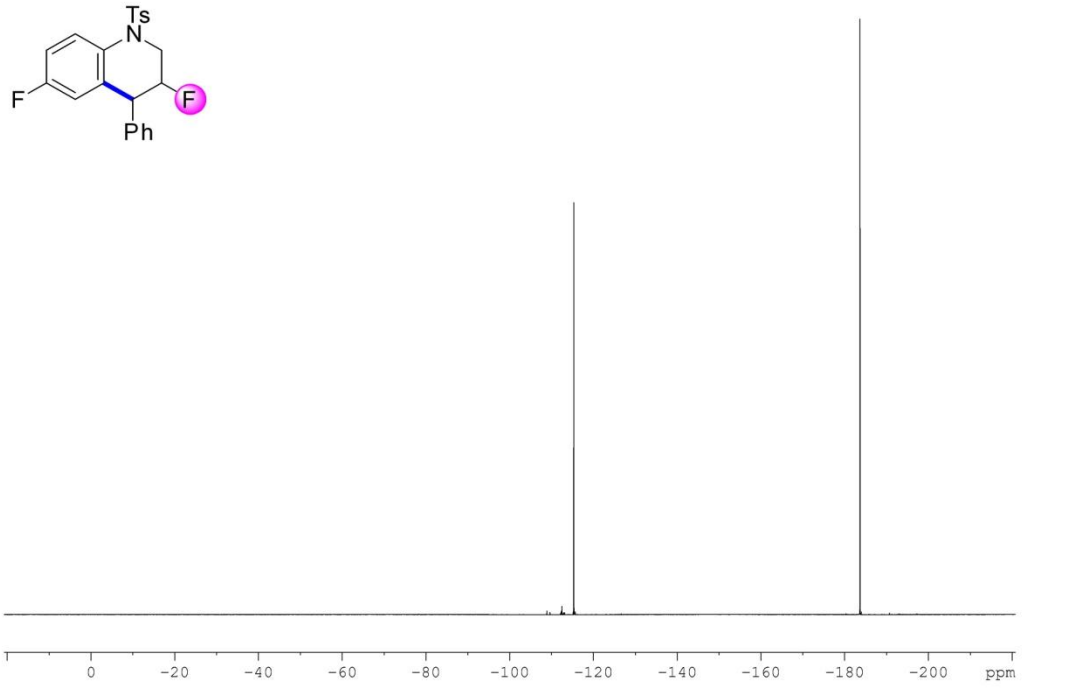

10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.97
5.91
1.03
1.97
0.96
0.99
0.99
1.00
0.99
3.04

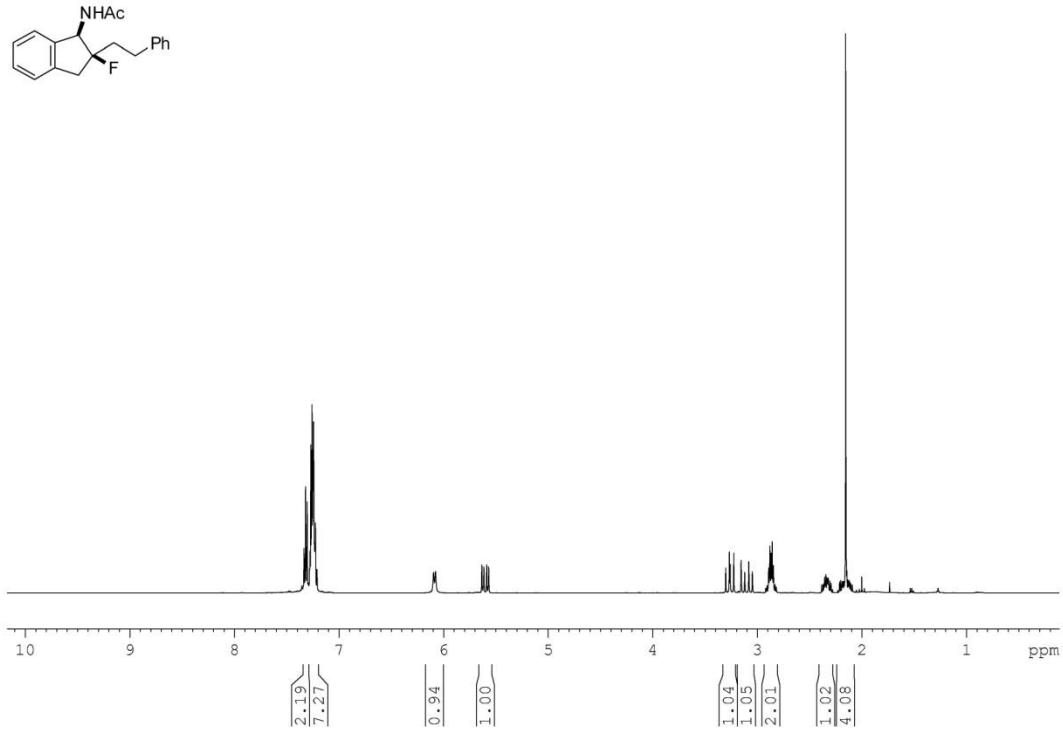

Ts
N
Cl
F
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

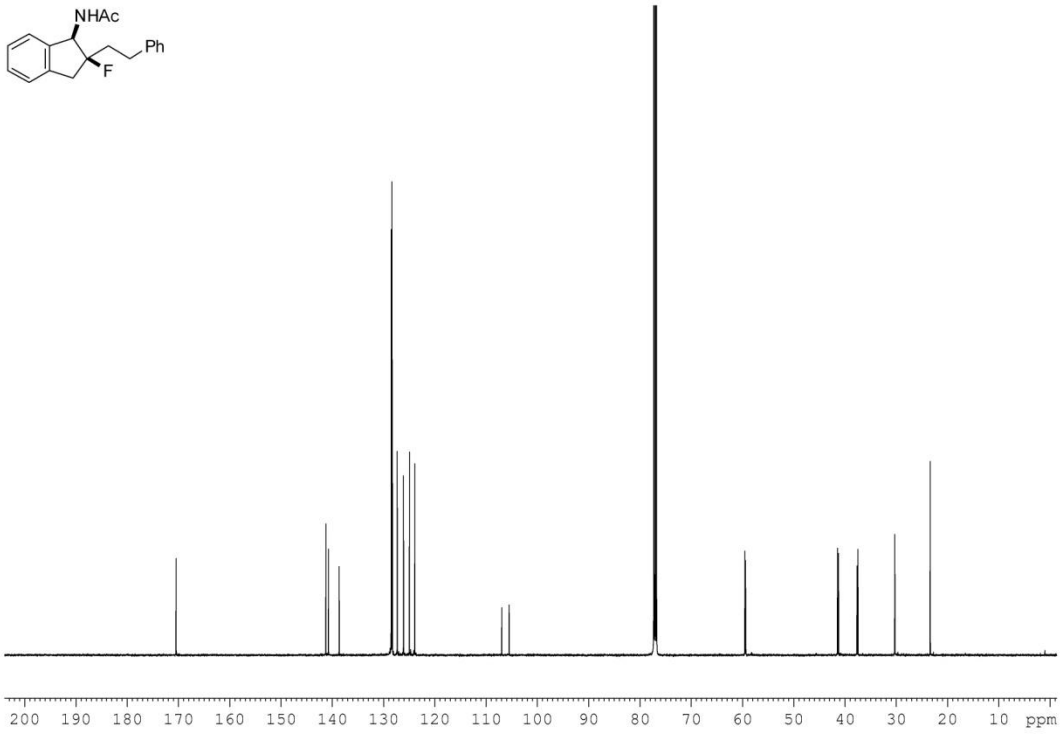

Ts
N
Cl
F
Ph
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

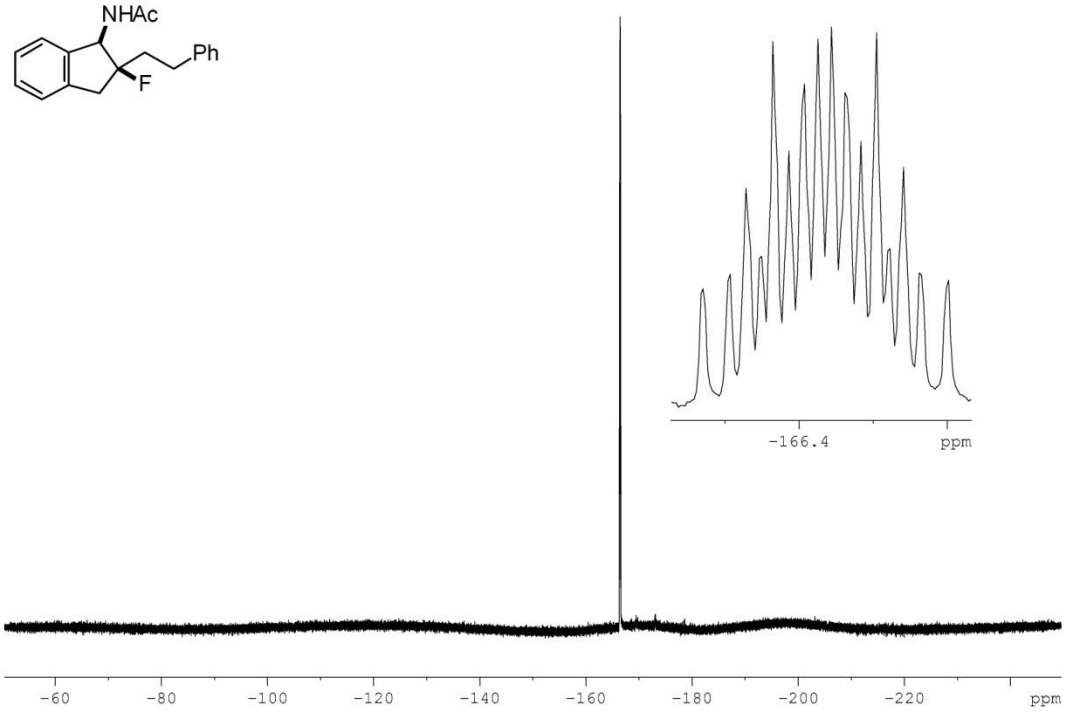

Ts
N
F
F
Ph
10
9
8
7
6
5
4
3
2
1
ppm

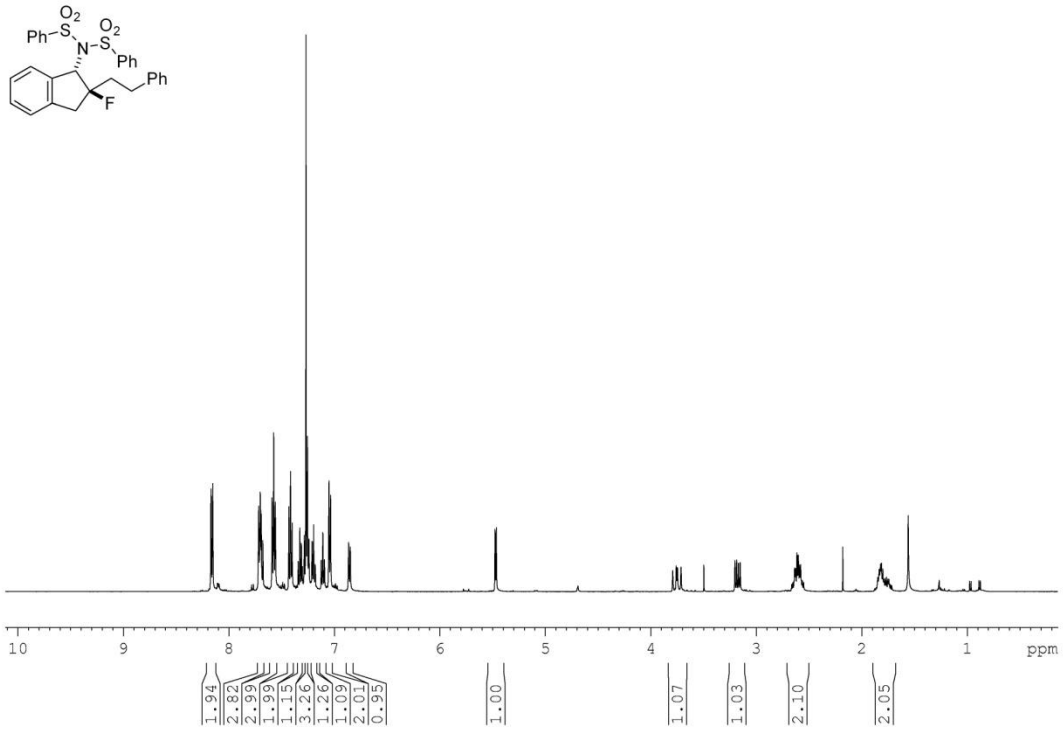

Ts
N
F
F
Ph
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

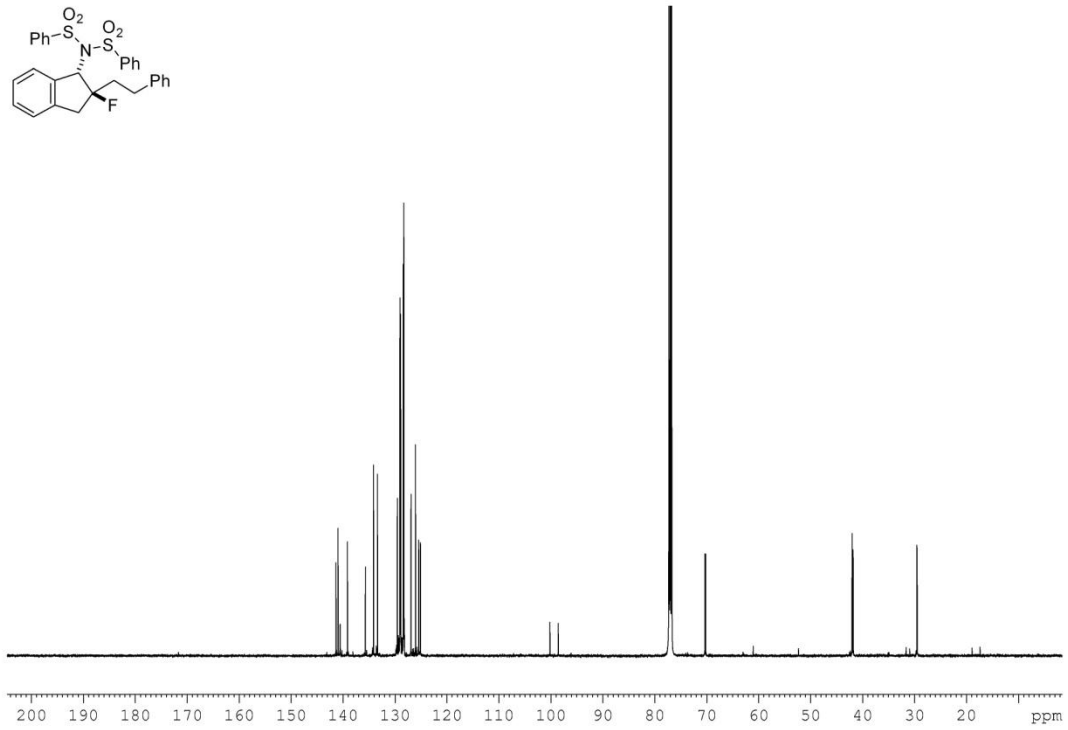

Ts
N
F
F
Ph
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

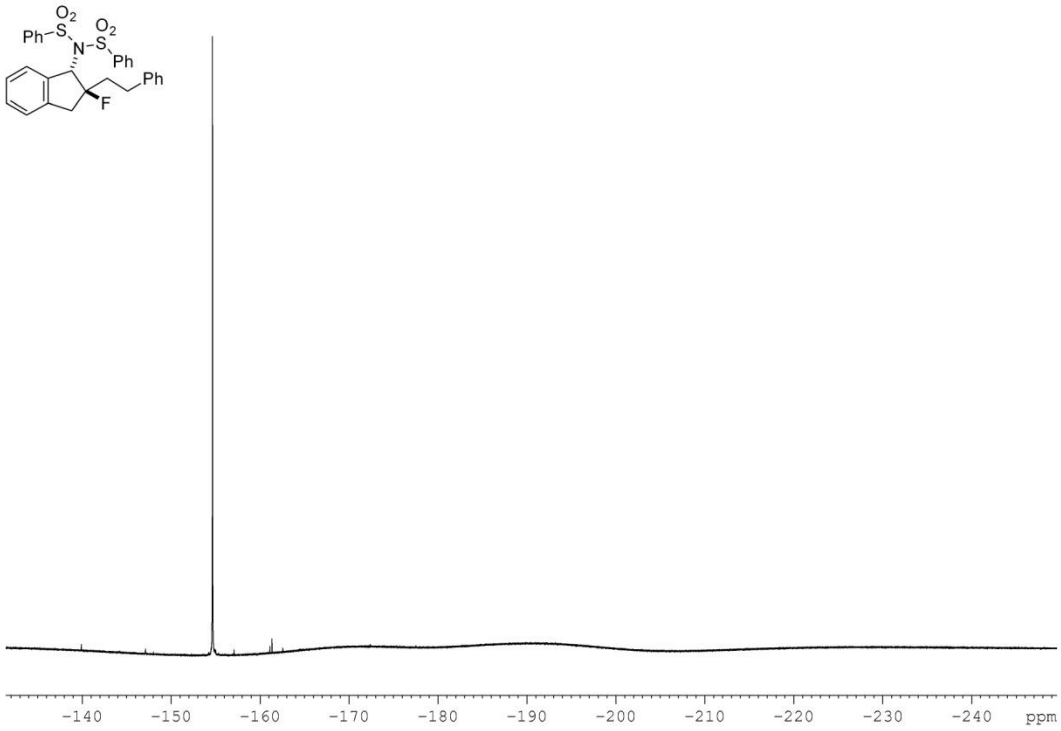

NHAc
Ph
F
10
9
8
7
6
5
4
3
2
1
ppm
2.19
7.27
0.94
1.00
1.04
1.05
2.01
1.02
4.08

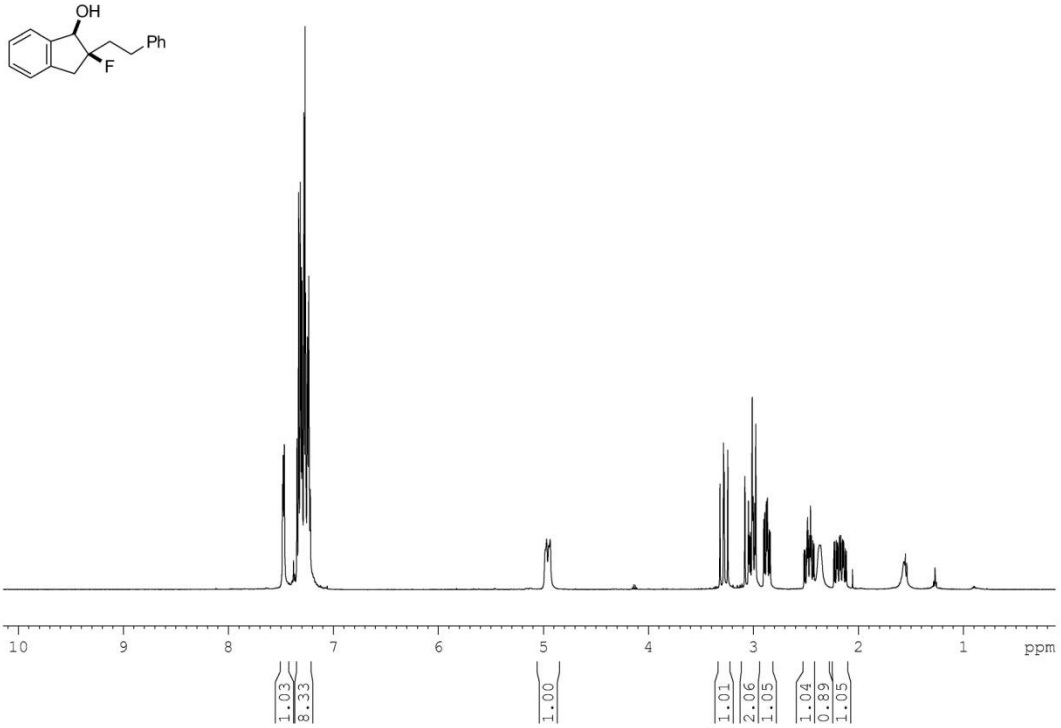

NHAc
Ph
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

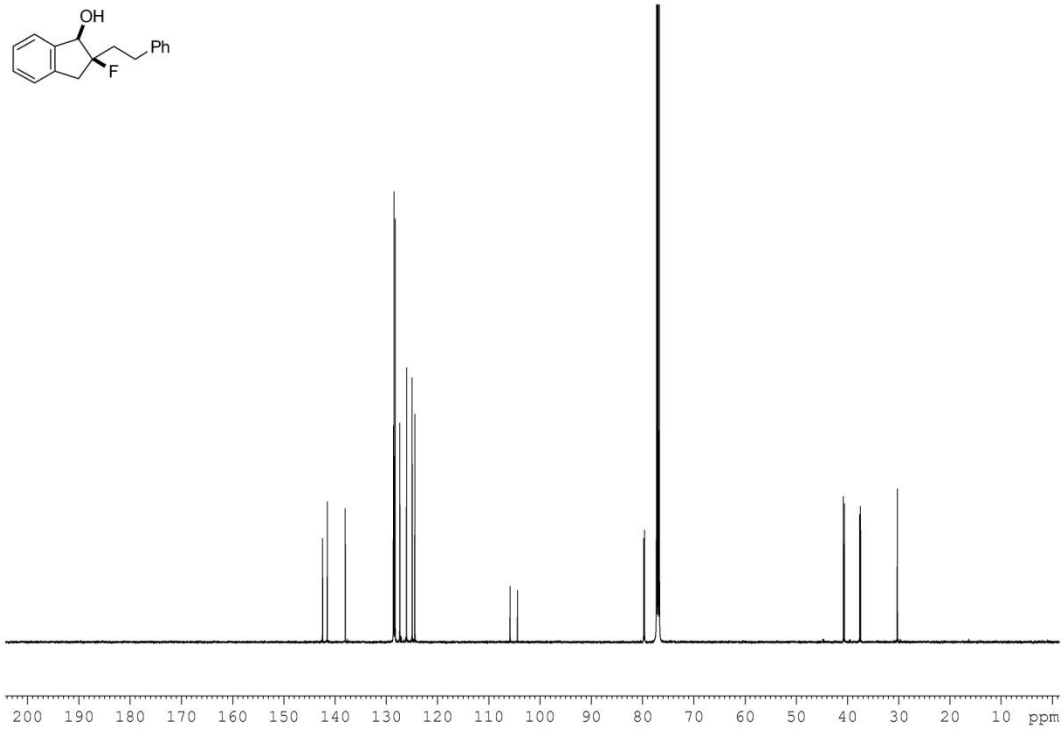

NHAc
Ph
F
-166.4
ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

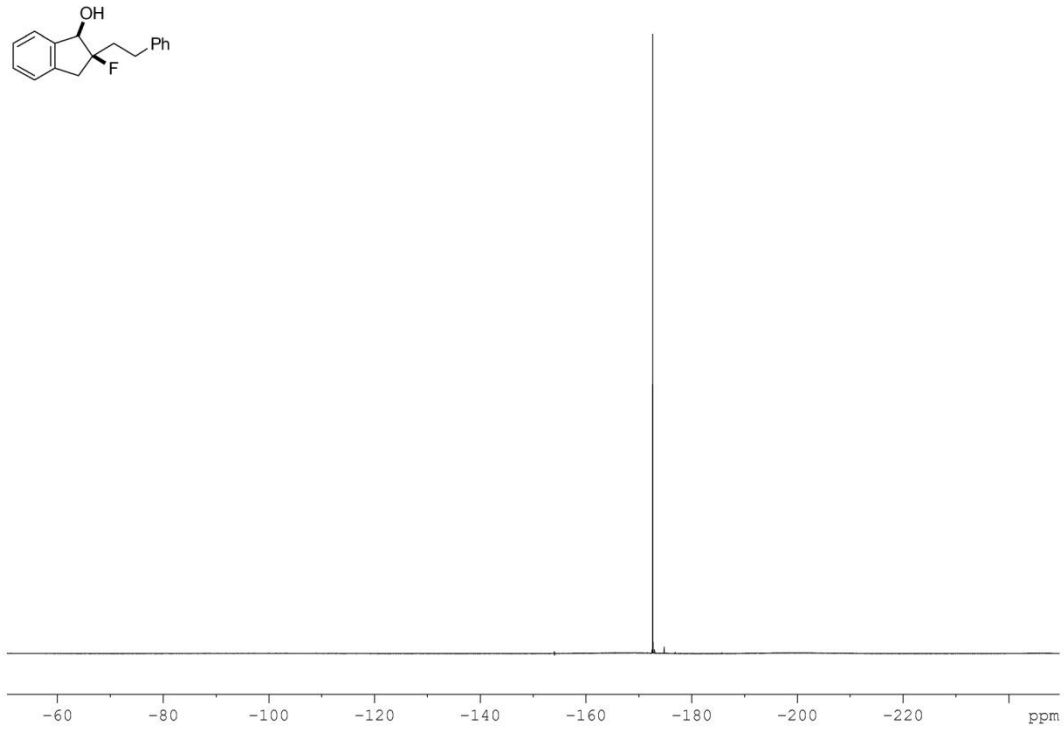

Ph
S
O2
O2
N
S
Ph
Ph
F
10
9
8
7
6
5
4
3
2
1
ppm
1.94
2.82
2.99
1.99
1.15
3.26
1.26
1.09
2.01
0.95
1.00
1.07
1.03
2.10
2.05

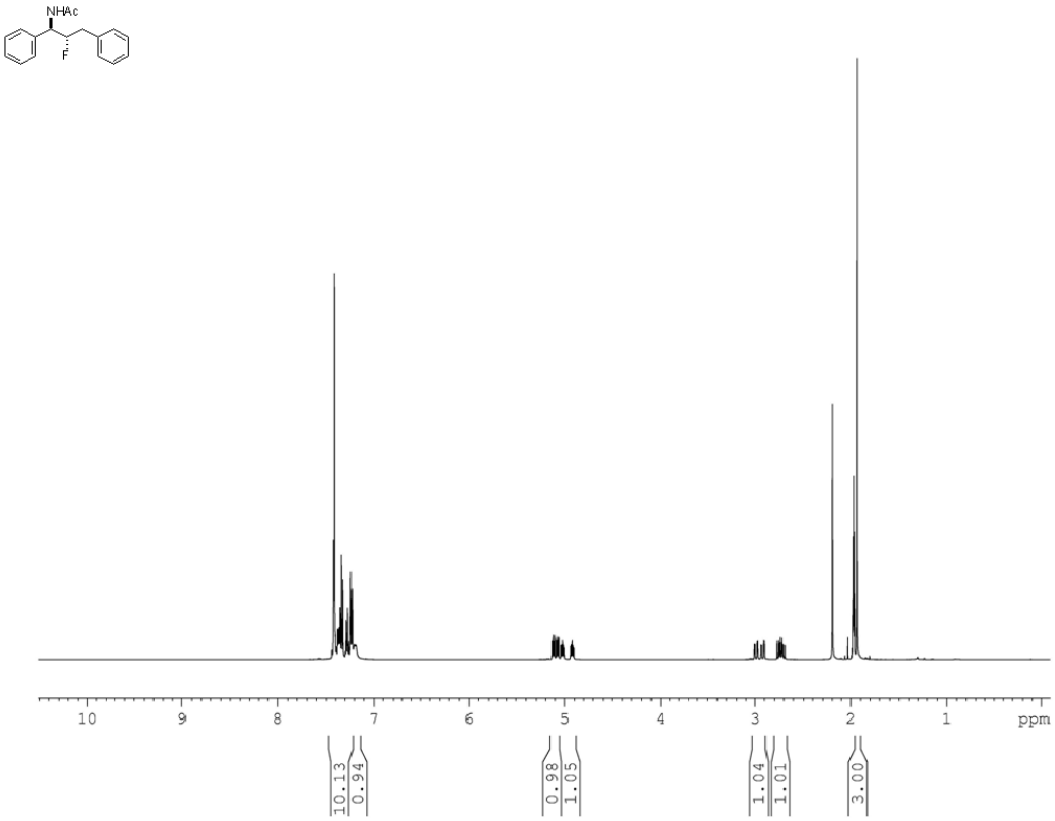

Ph
S
O2
O2
N
S
Ph
Ph
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

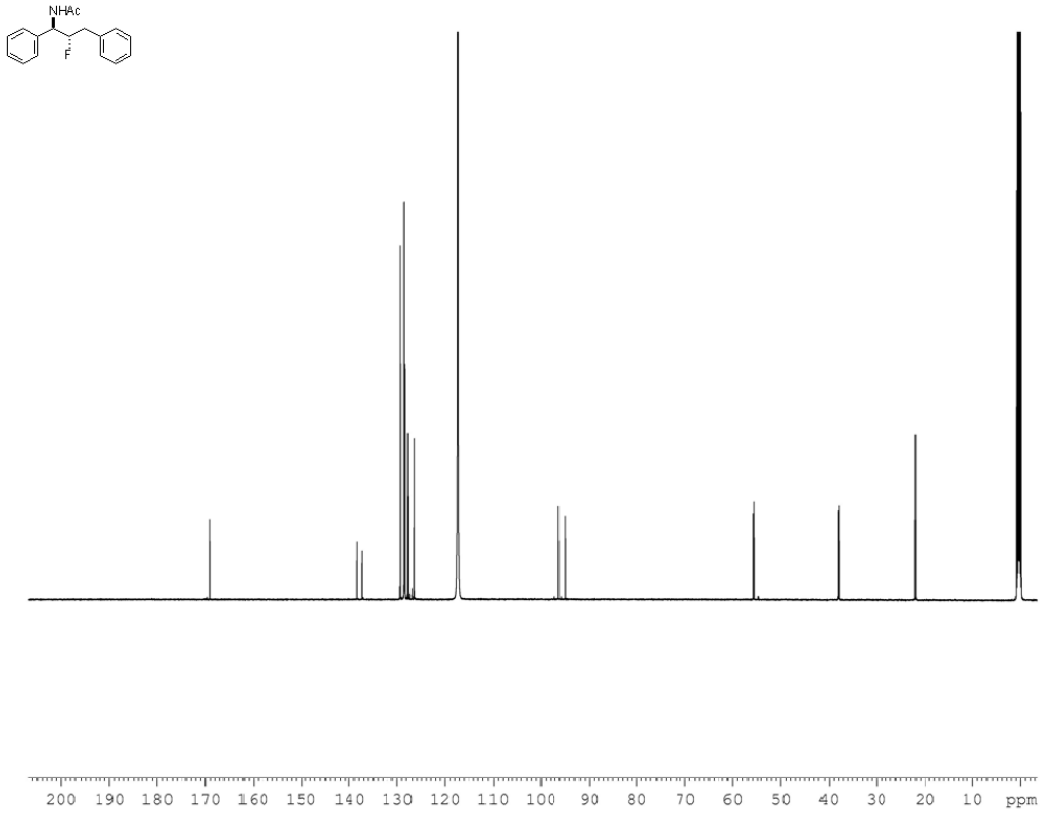

O2
Ph
S
N
S
O2
Ph
Ph
F
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
ppm

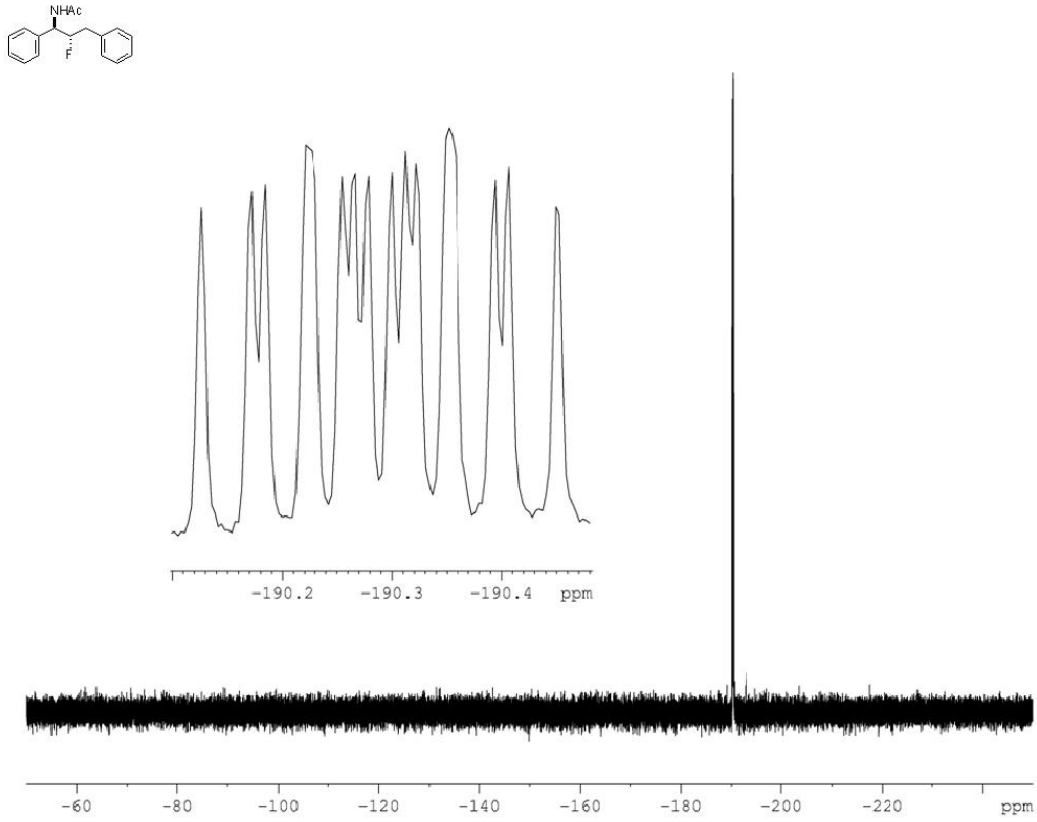

OH
Ph
F
10
9
8
7
6
5
4
3
2
1
ppm
1.03
8.33
1.00
1.01
2.06
1.05
1.04
0.89
1.05

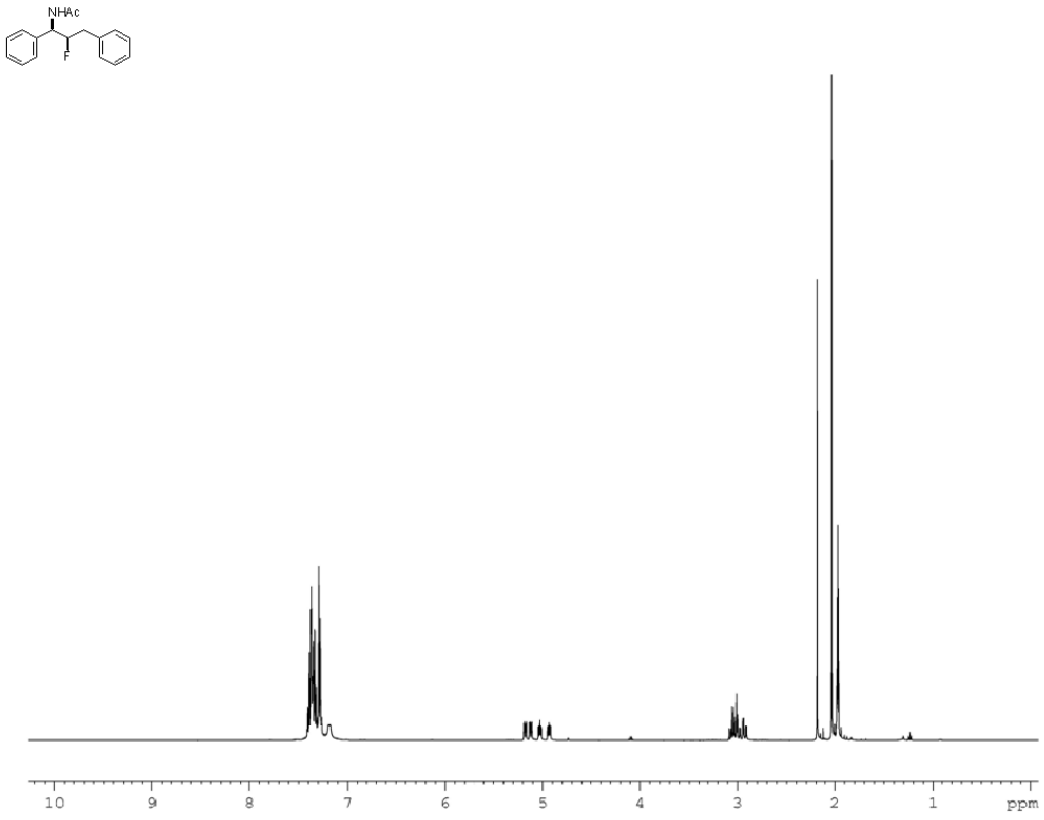

OH
Ph
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

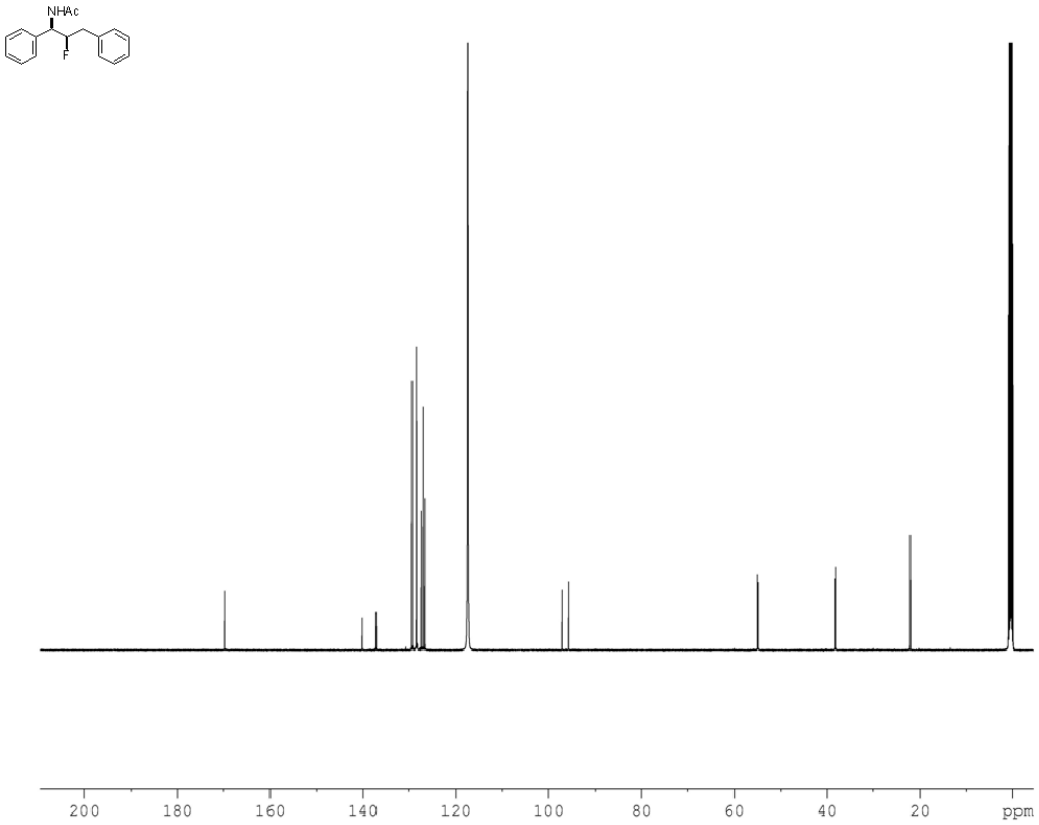

OH
Ph
F
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

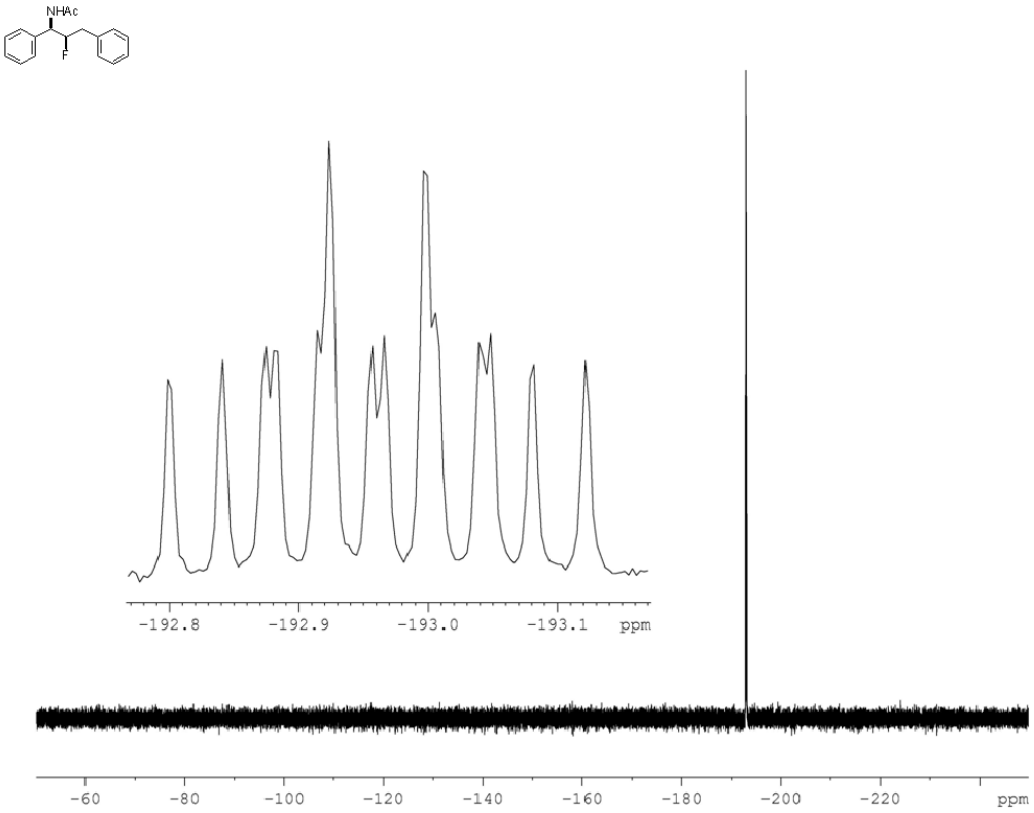

NHAc
F
10
9
8
7
6
5
4
3
2
1
ppm
10.13
0.94
0.98
1.05
1.04
1.01
3.00

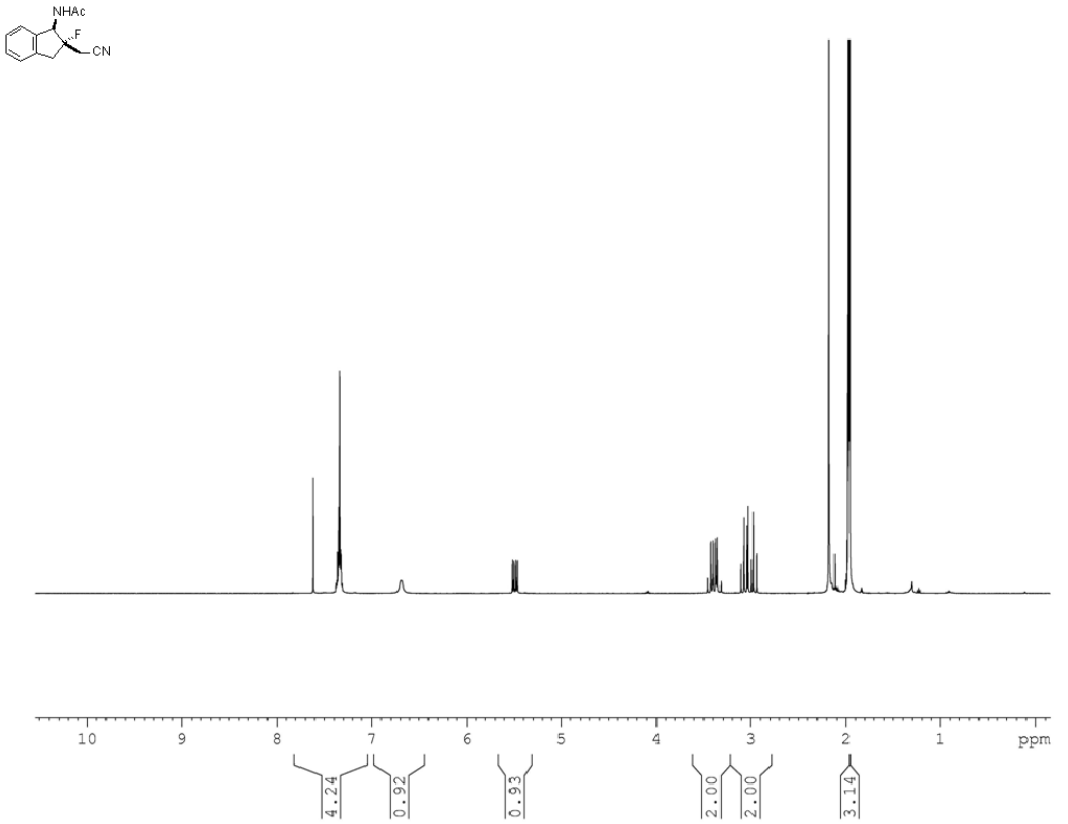

NHAc
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

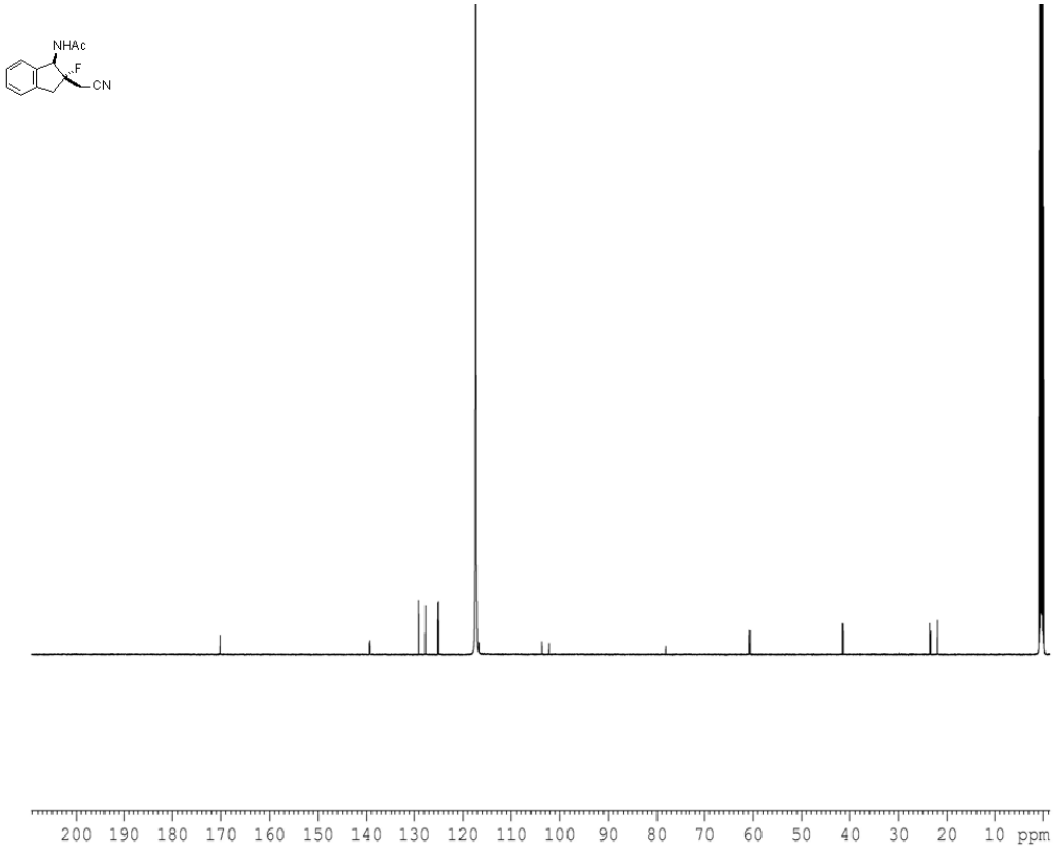

NHAc
F
-190.2
-190.3
-190.4
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

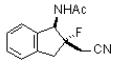

NHAc
F
10
9
8
7
6
5
4
3
2
1
ppm

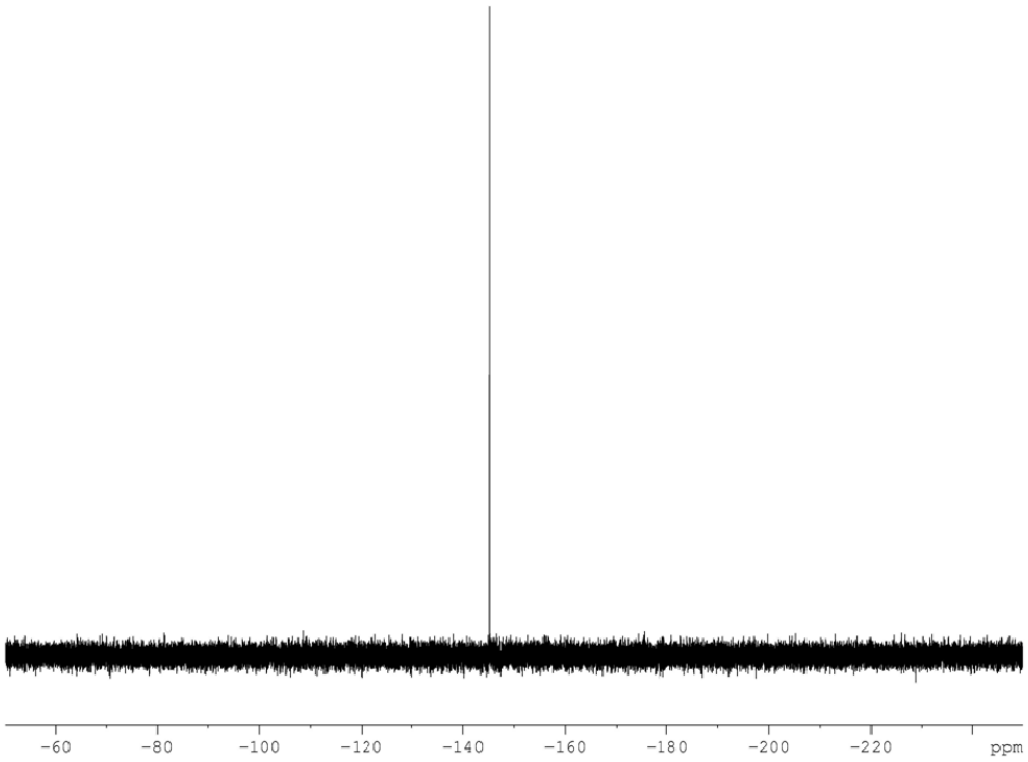

NHAc
F
200
180
160
140
120
100
80
60
40
20
ppm


NHAc
F
-192.8
-192.9
-193.0
-193.1
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

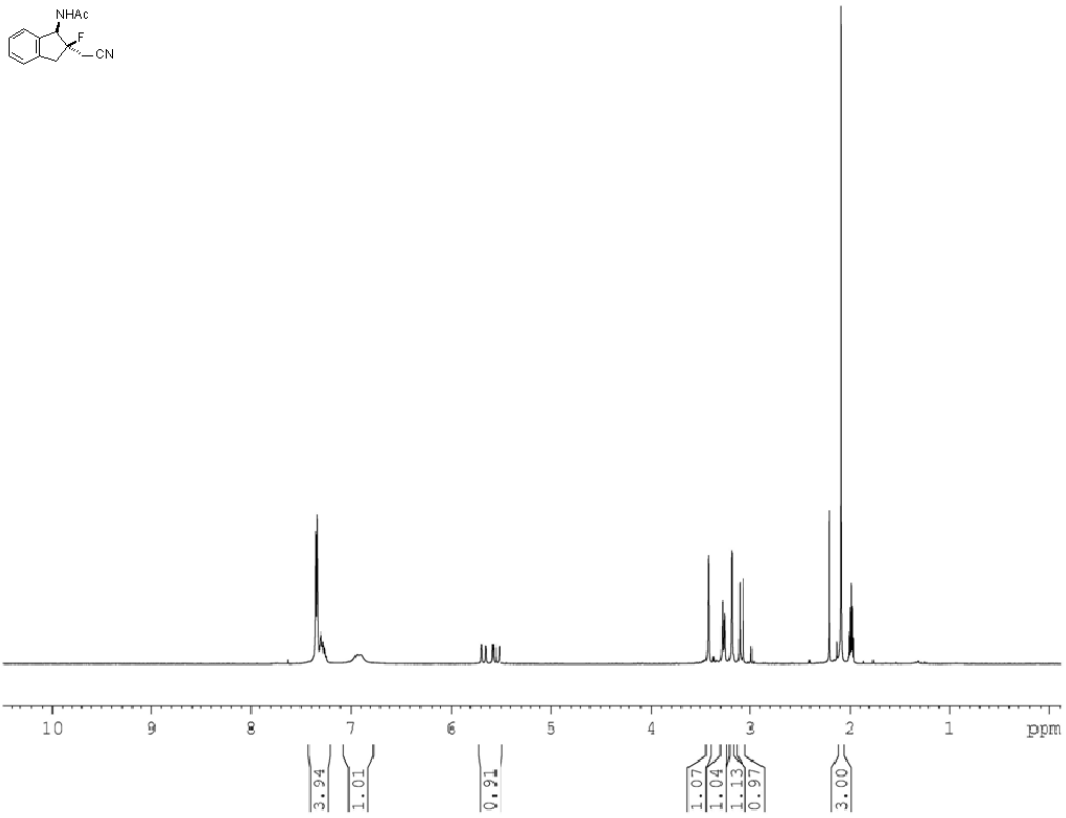

NHAc
F
CN
10
9
8
7
6
5
4
3
2
1
ppm
4.24
0.92
0.93
2.00
2.00
3.14

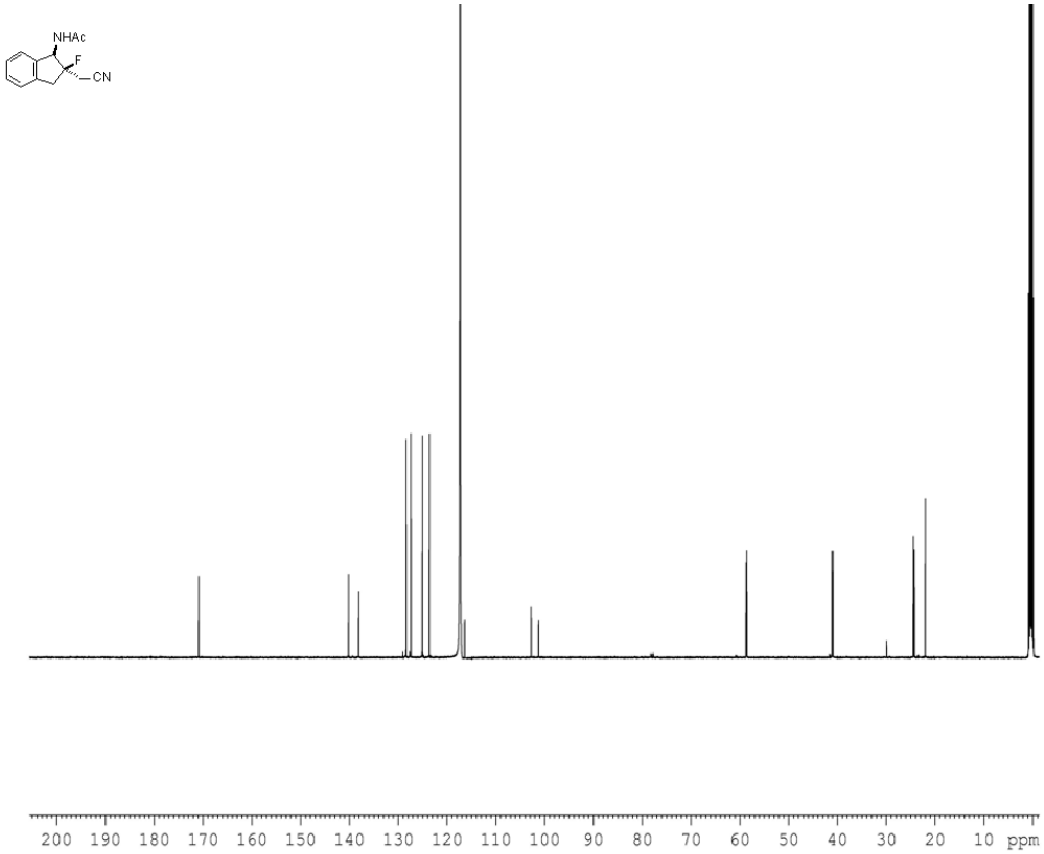

NHAc
F
CN
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

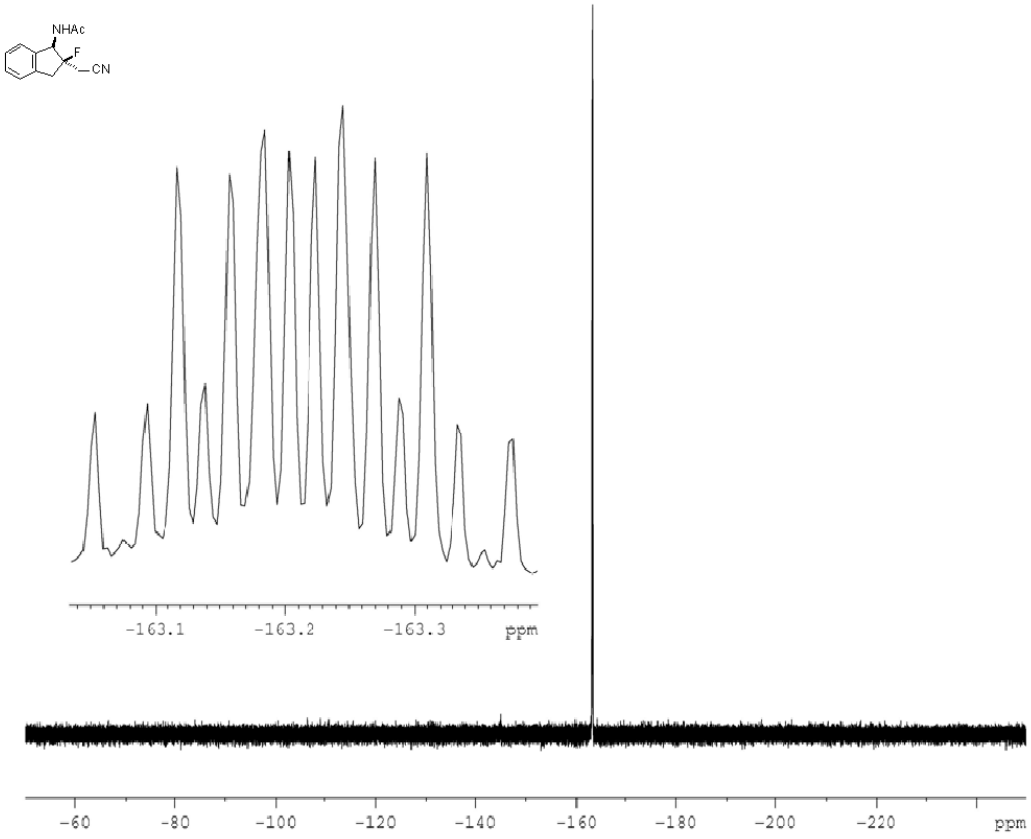

NHAc
F
CN

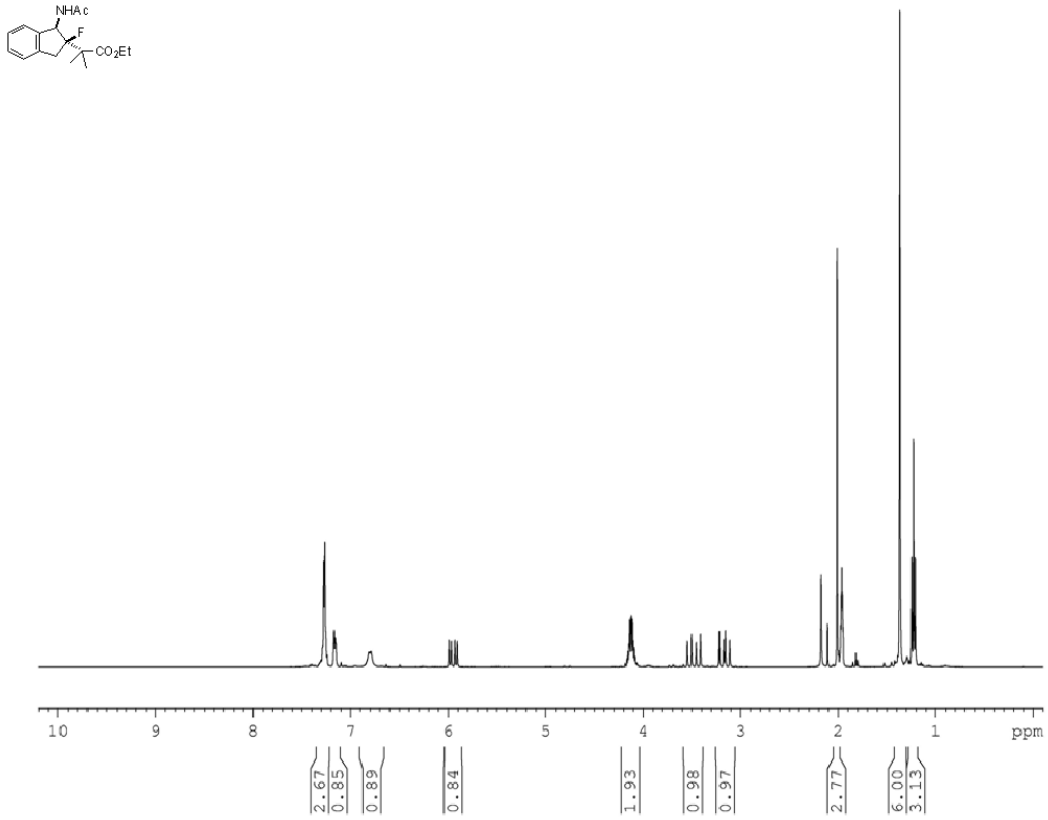

-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

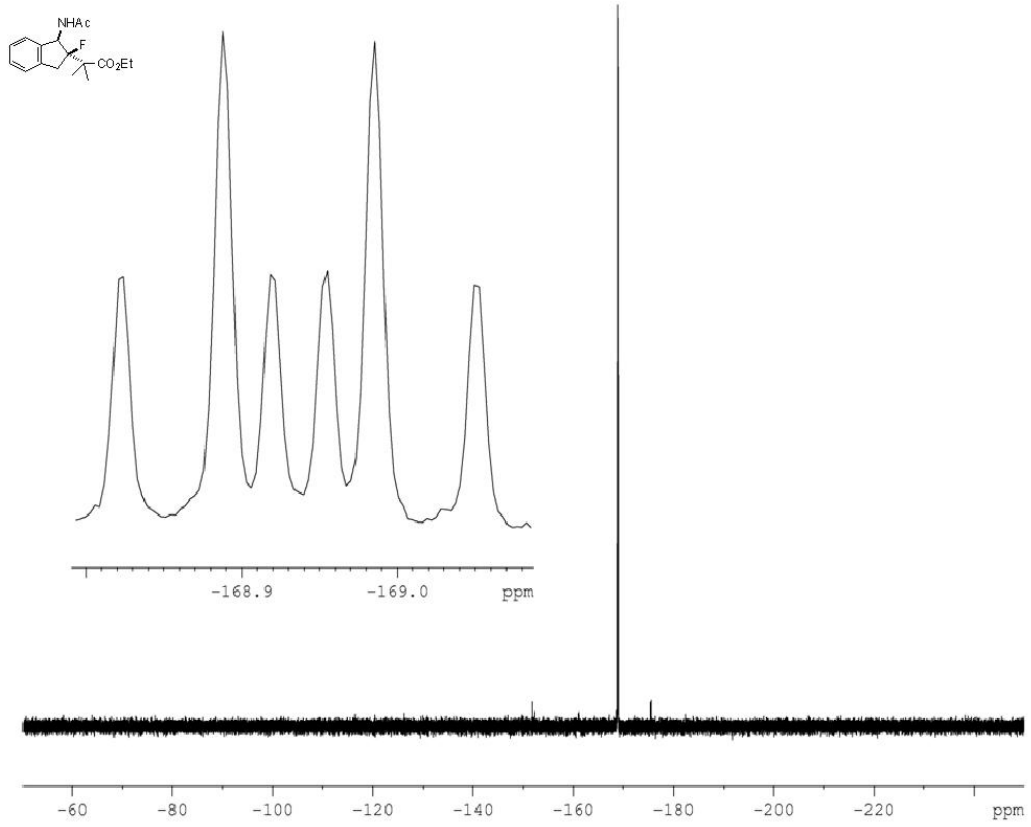
NHAc
F
CN

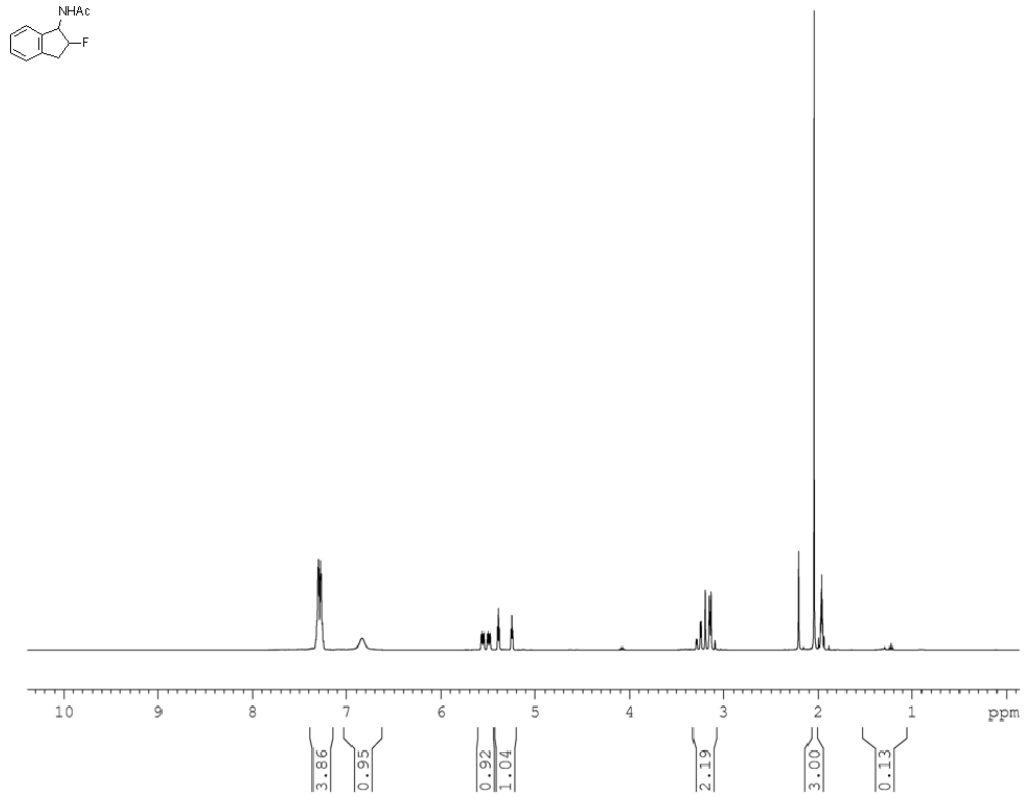

10
9
8
7
6
5
4
3
2
1
ppm
3.94
1.01
0.91
1.07
1.04
1.13
0.97
3.00

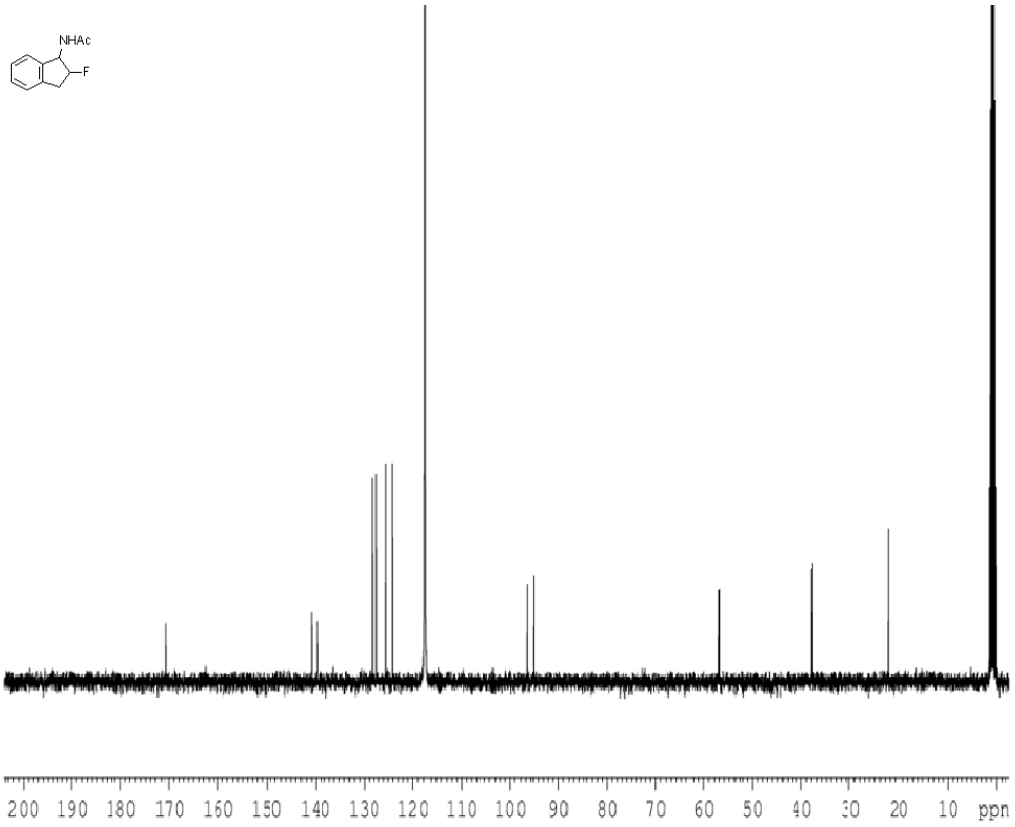

NHAc
F
CN
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

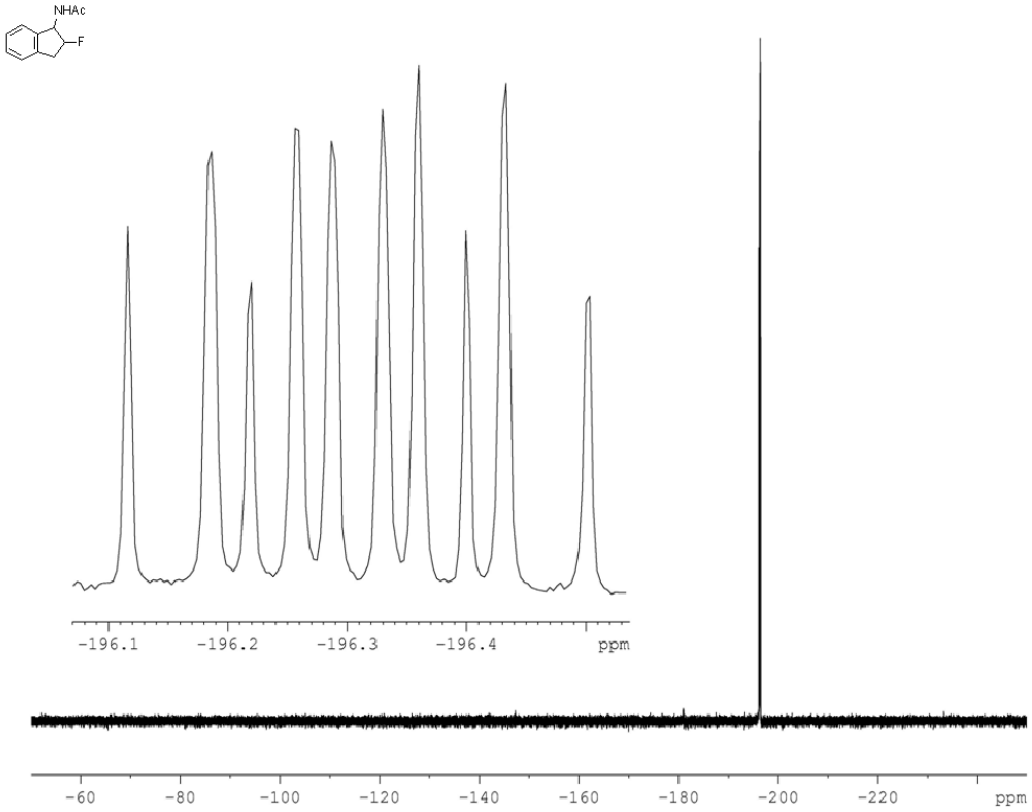

NHAc
F
CN
-163.1
-163.2
-163.3
ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

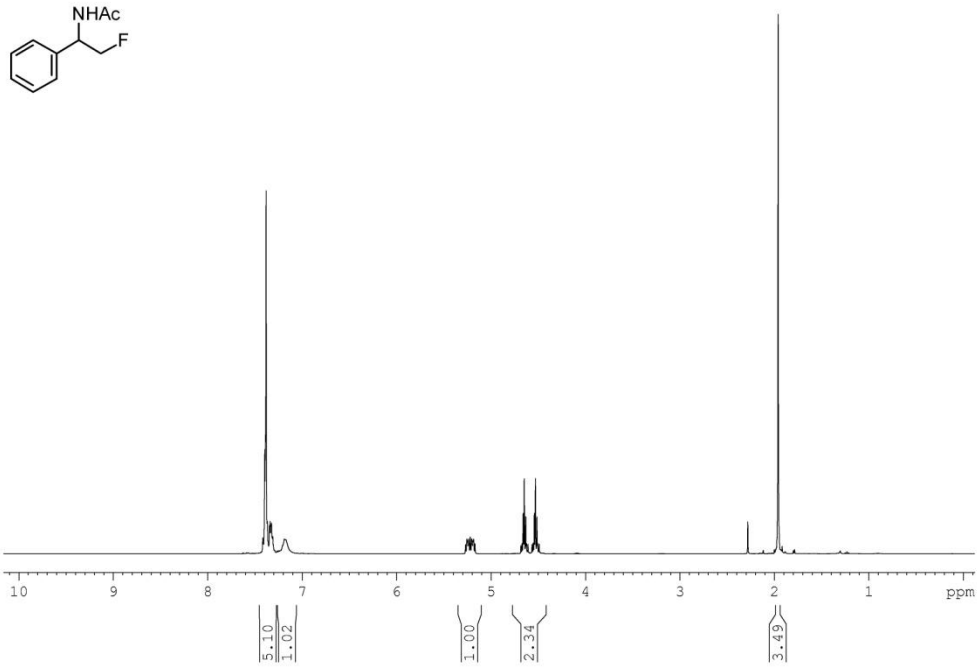

NHAc
F
CO2Et
10
9
8
7
6
5
4
3
2
1
ppm
2.67
0.85
0.89
0.84
1.93
0.98
0.97
2.77
6.00
3.13

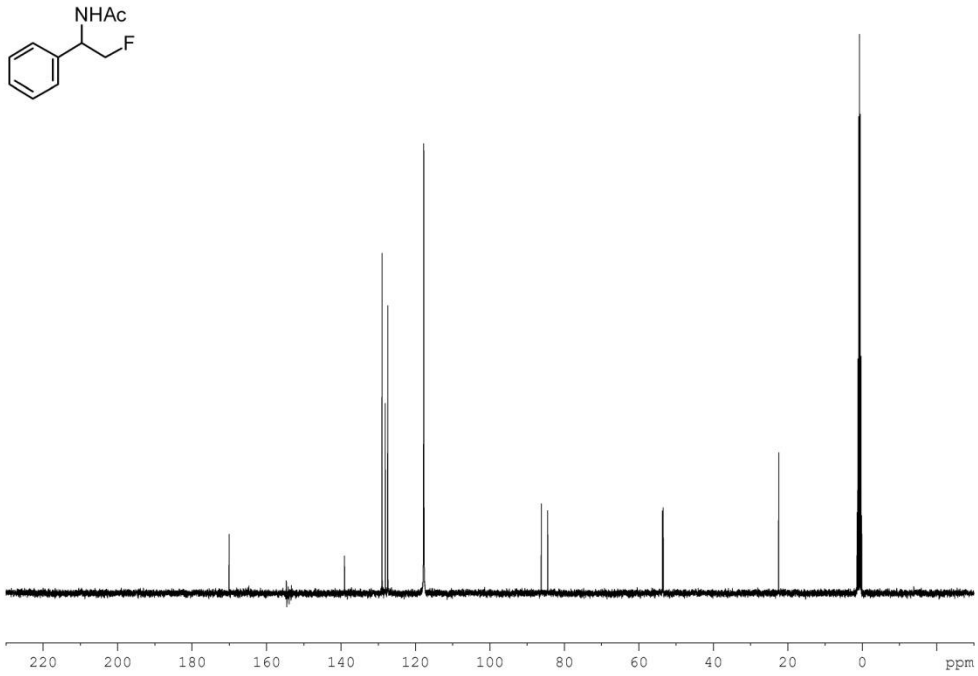

NHAc
F
CO2Et
-168.9
-169.0
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

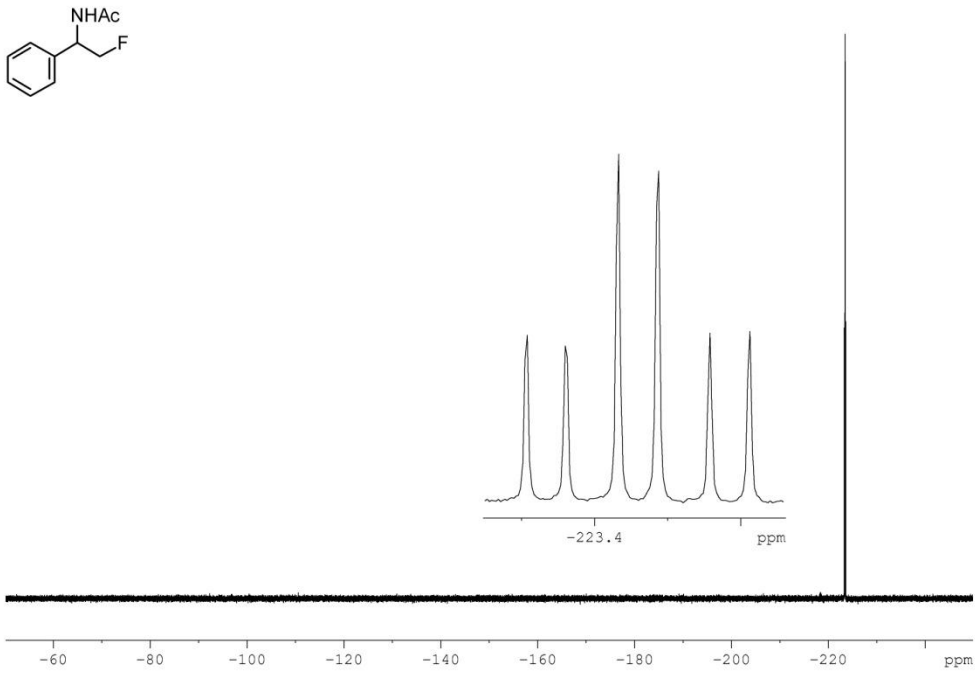

NHAc
F
10
9
8
7
6
5
4
3
2
1
ppm
3.86
0.95
0.92
1.04
2.19
3.00
0.13

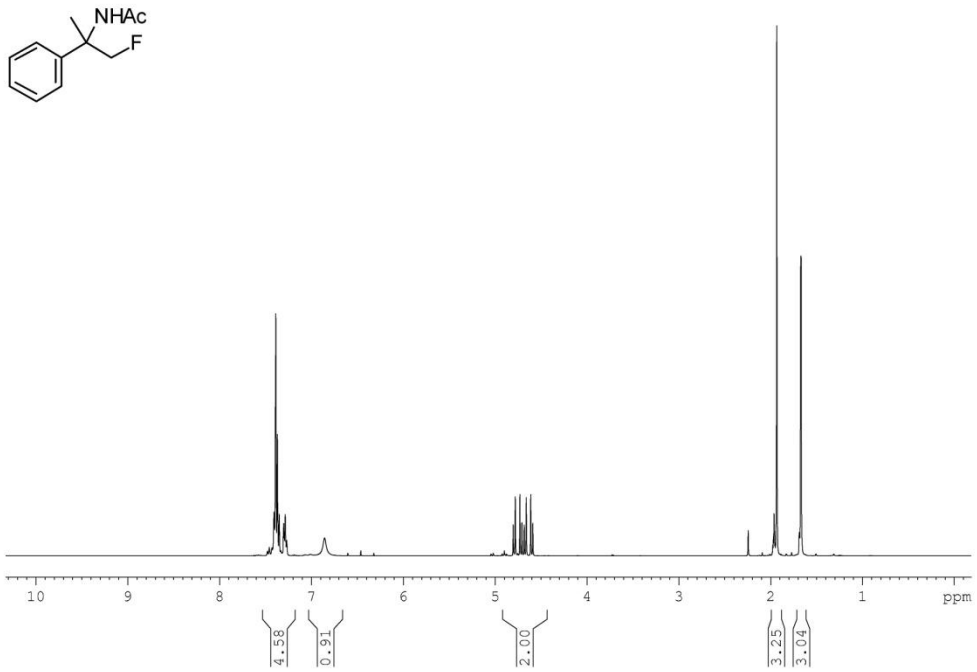

NHAc
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

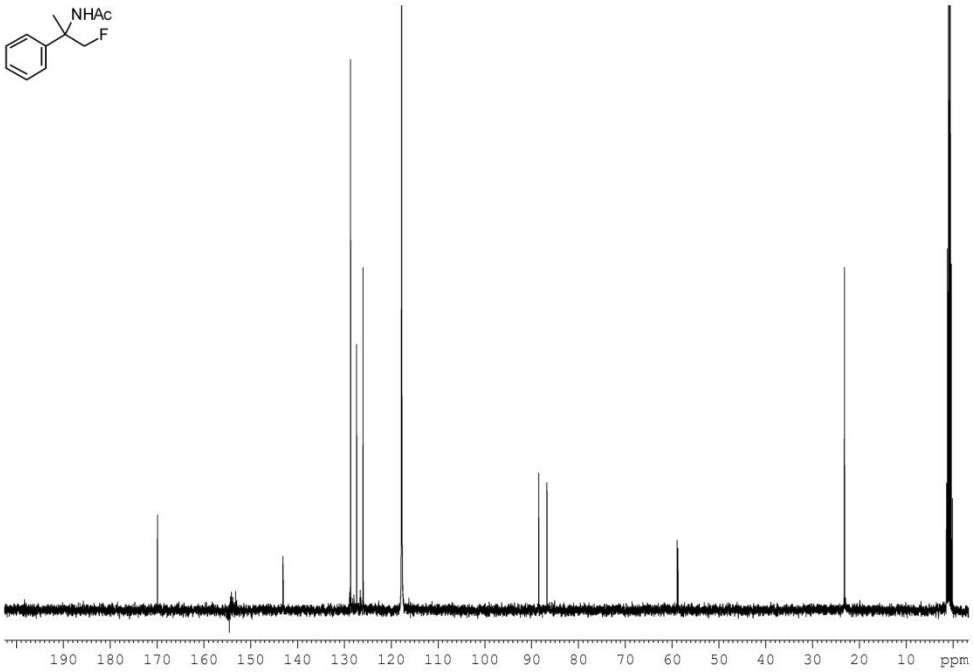

NHAc
F
-196.1
-196.2
-196.3
-196.4
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

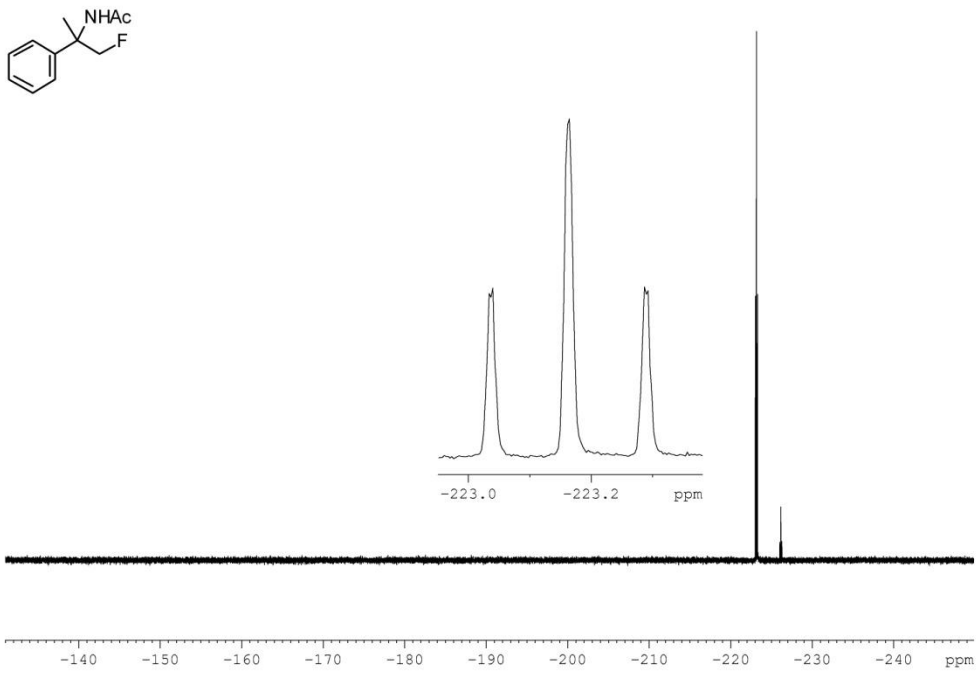

NHAc
F
10
9
8
7
6
5
4
3
2
1
ppm
5.10
1.02
1.00
2.34
3.49

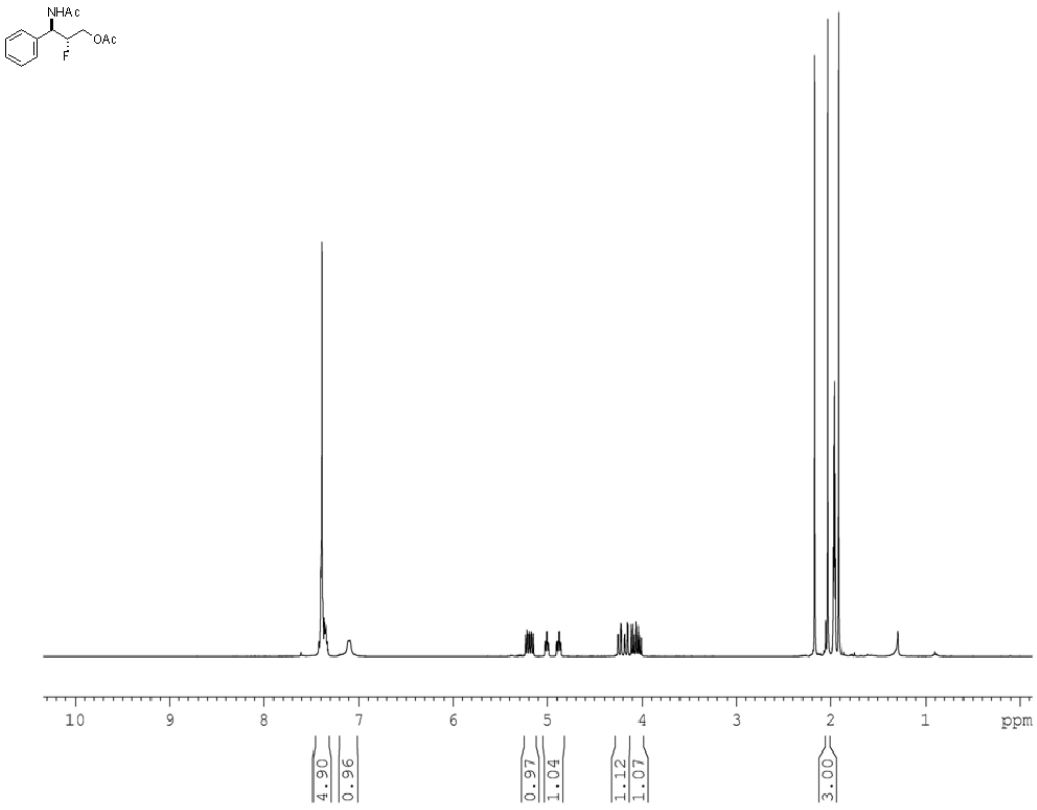

NHAc
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

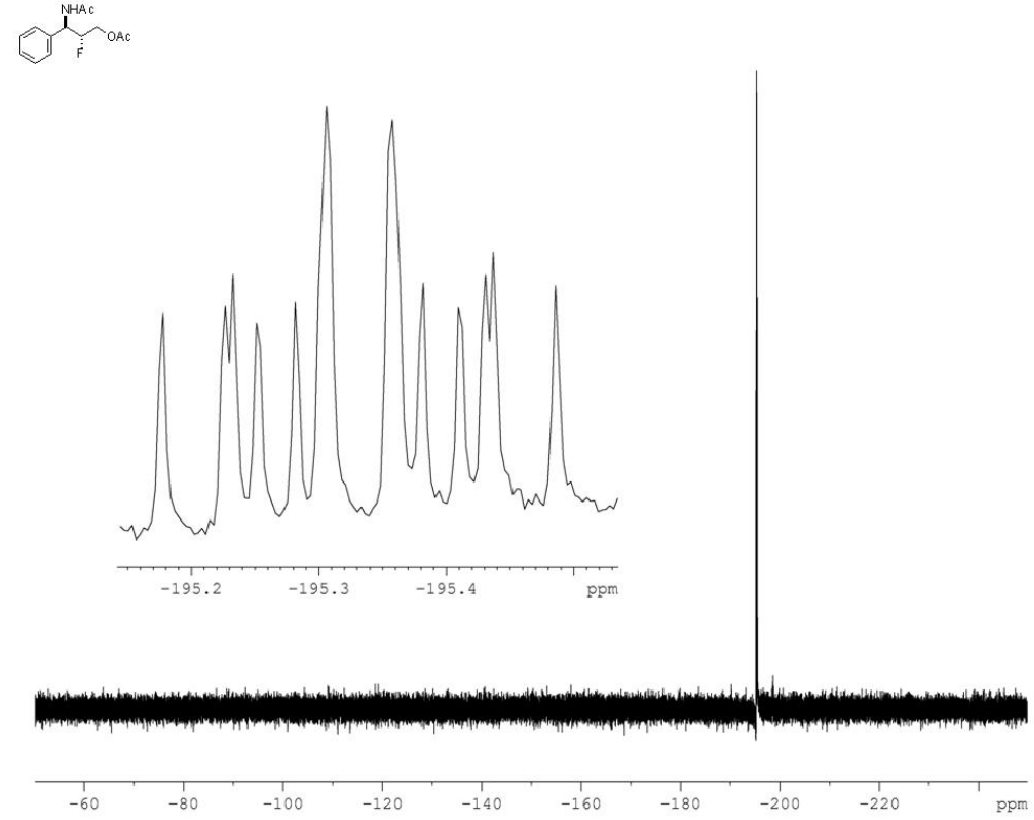

NHAc
F
-223.4
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

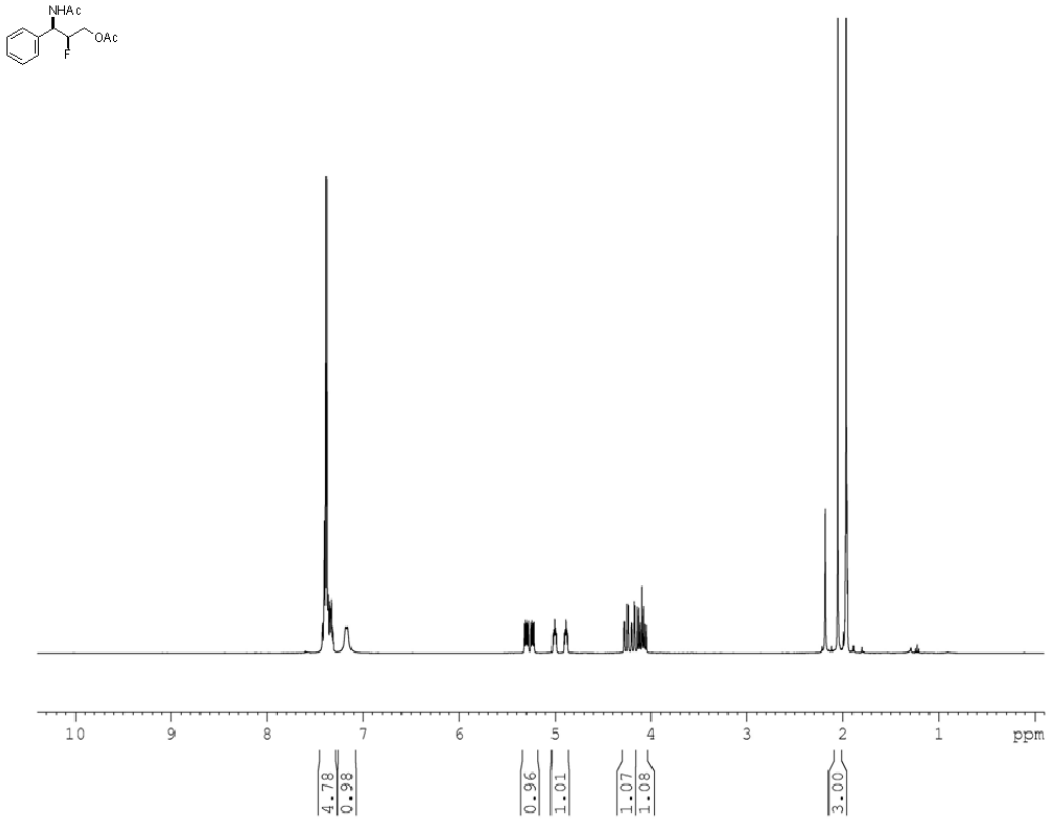

NHAc
F
10
9
8
7
6
5
4
3
2
1
ppm
4.58
0.91
2.00
3.25
3.04

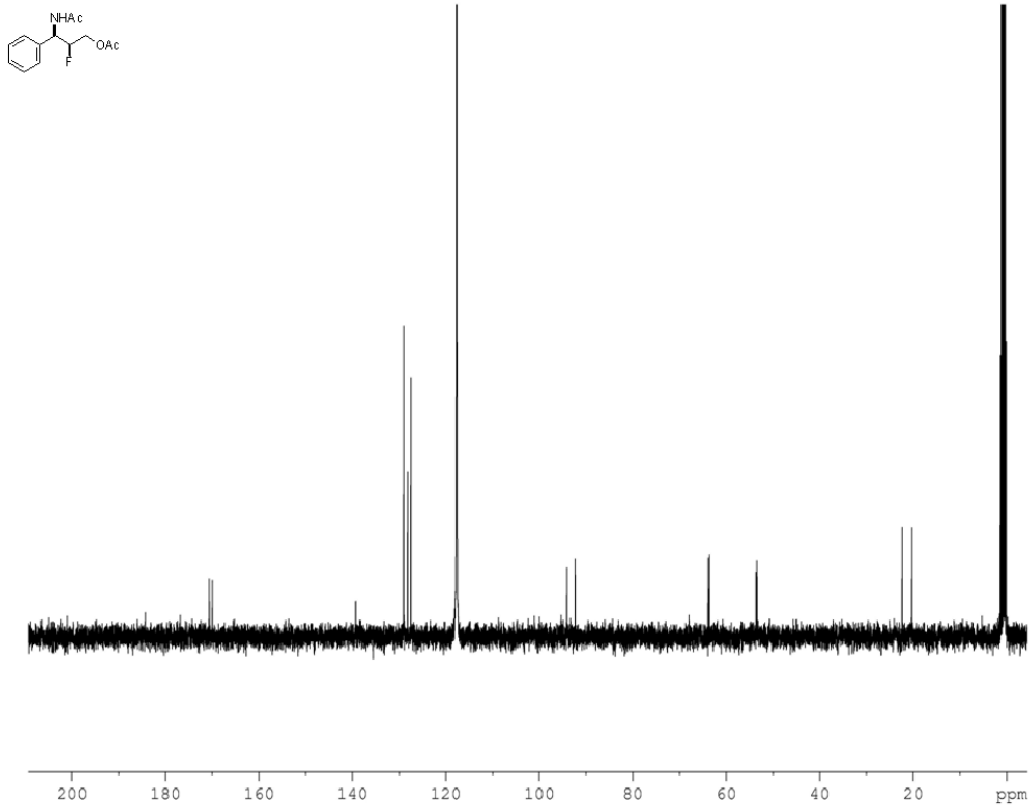

NHAc
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

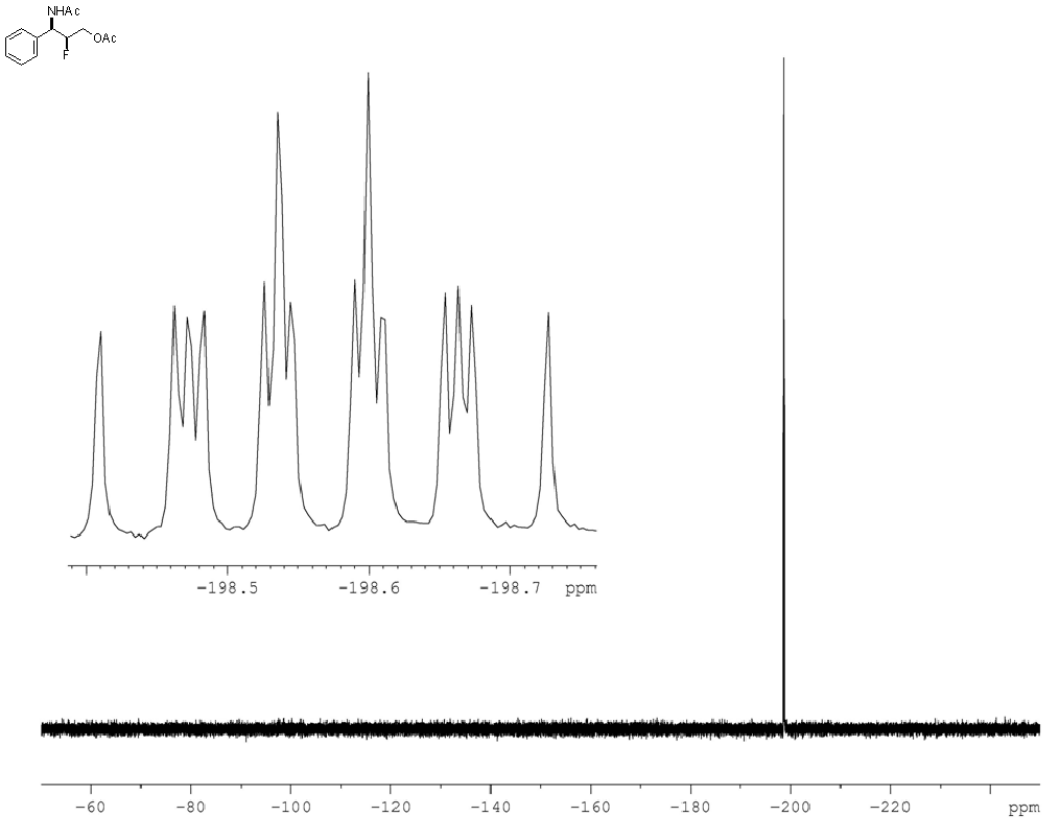

NHAc
F
-223.0
-223.2
ppm
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
ppm

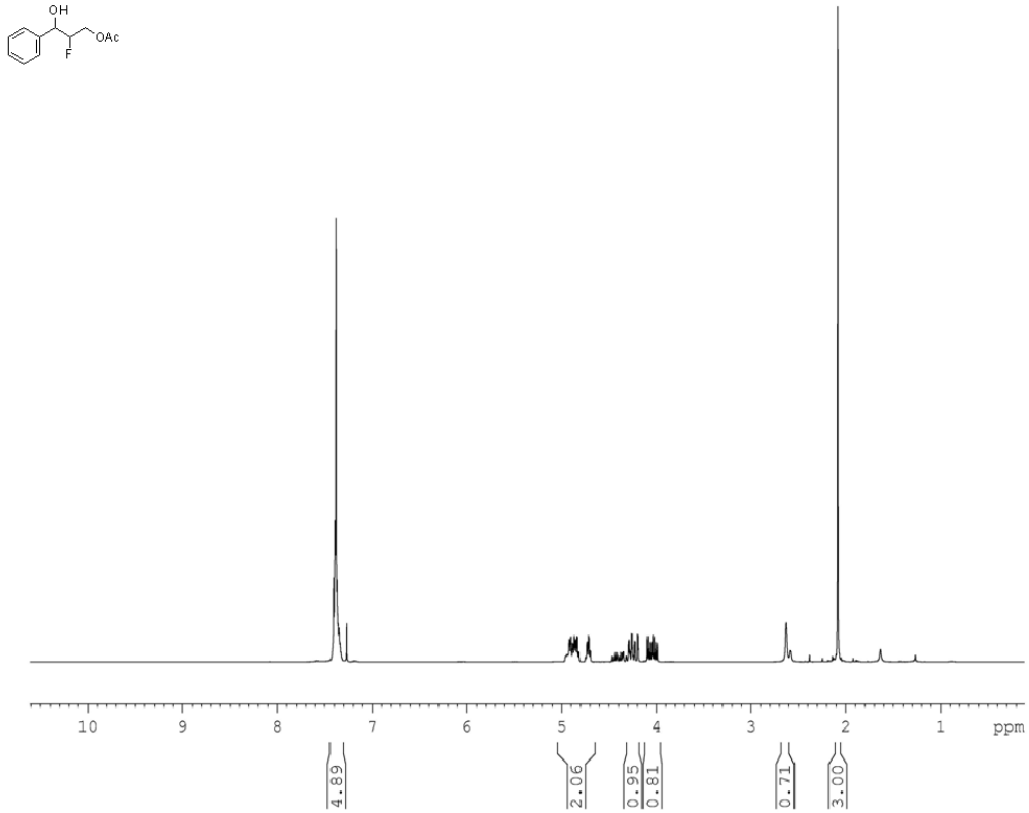

NHAc
OAc
F
10
9
8
7
6
5
4
3
2
1
ppm
4.90
0.96
0.97
1.04
1.12
1.07
3.00

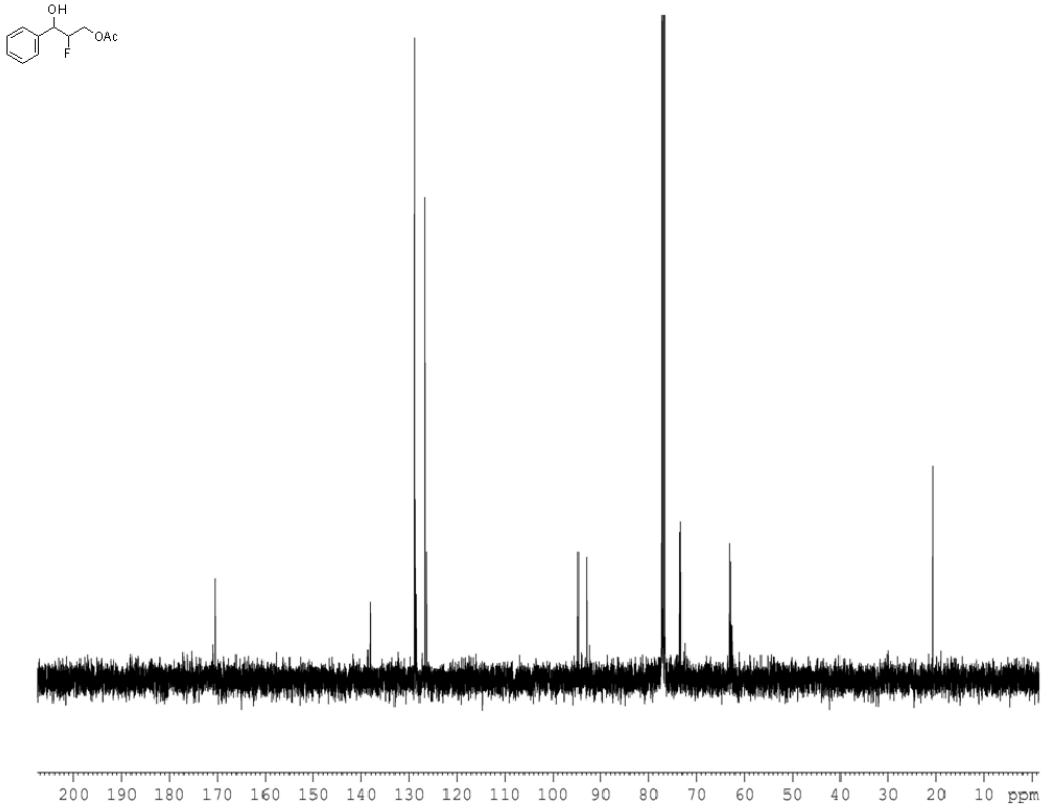

NHAc
OAc
F
-195.2
-195.3
-195.4
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

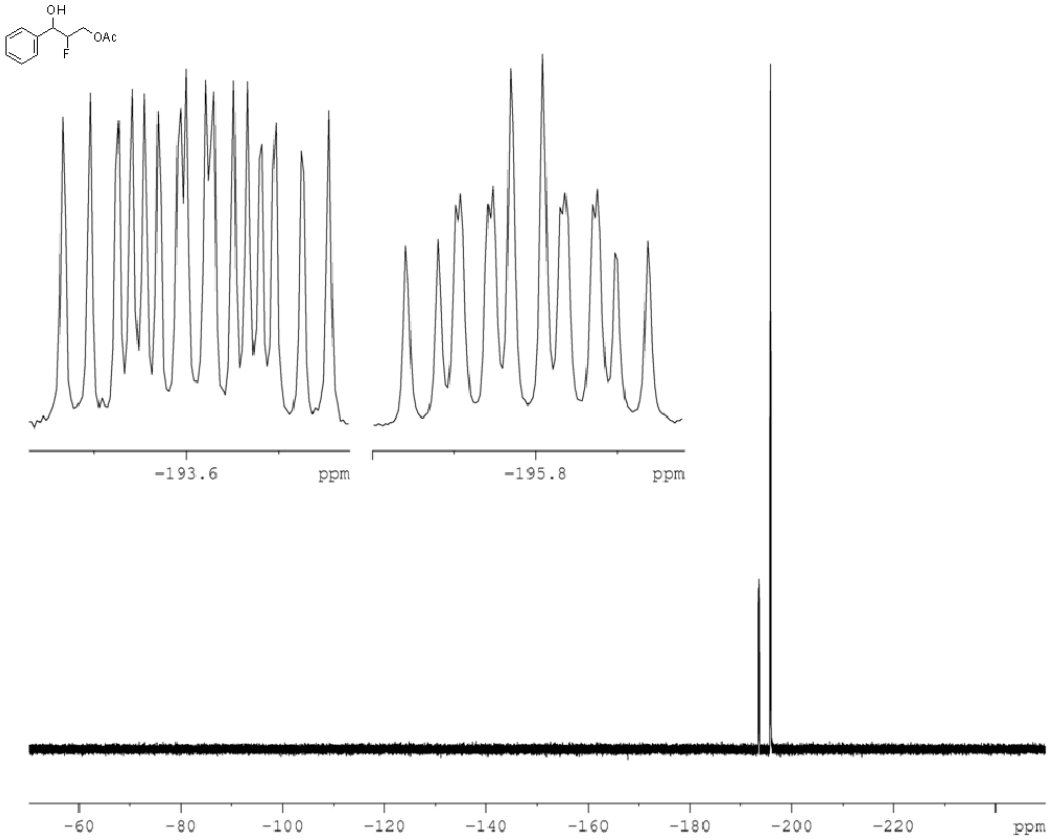

NHAc
OAc
F
10
9
8
7
6
5
4
3
2
1
ppm
4.78
0.98
0.96
1.01
1.07
1.08
3.00

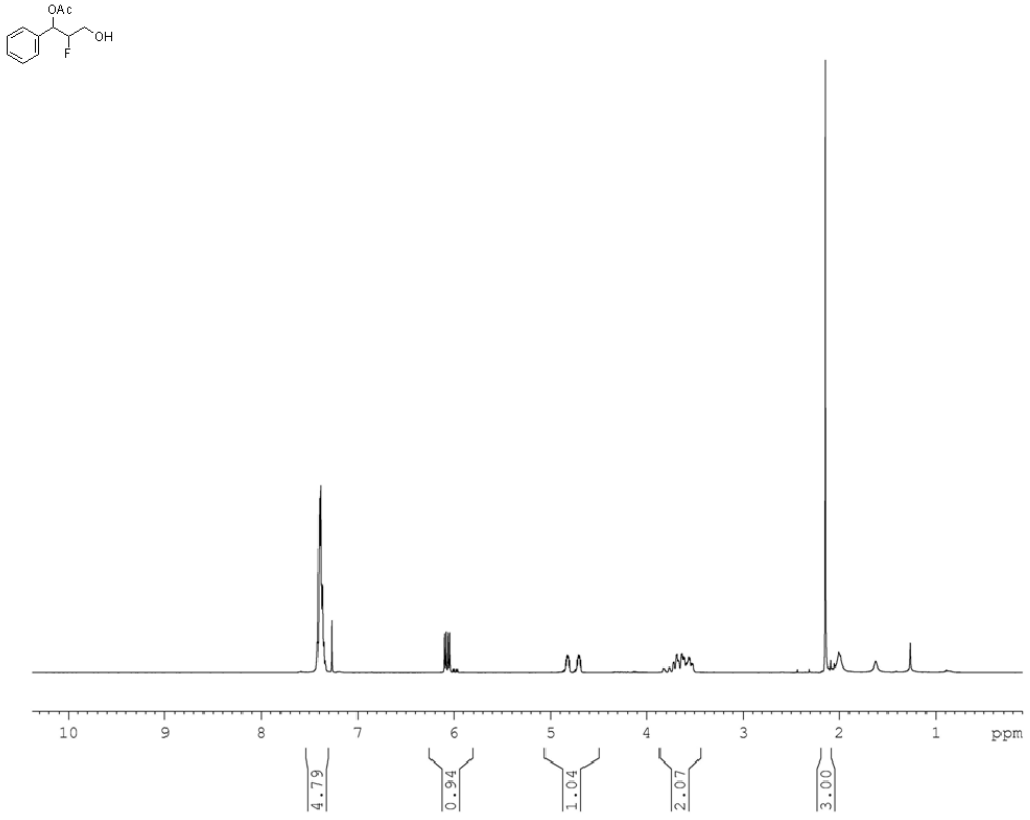

NHAc
OAc
F
200
180
160
140
120
100
80
60
40
20
ppm

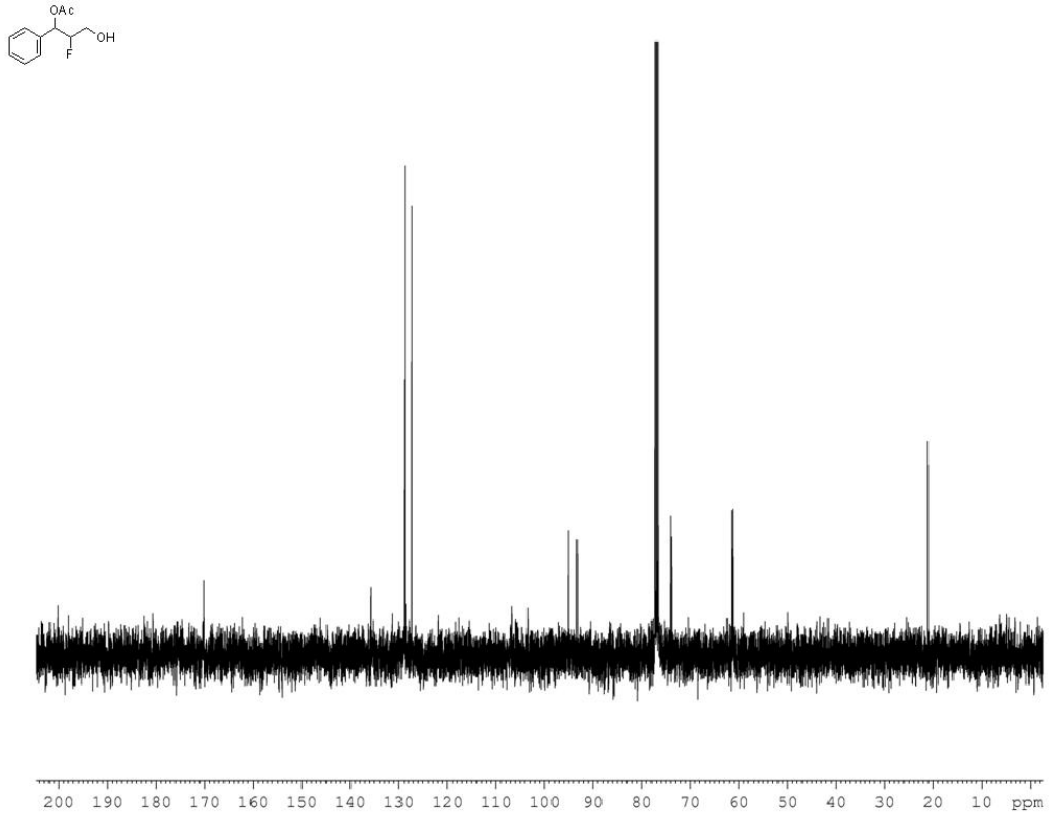

NHAc
OAc
F
-198.5
-198.6
-198.7
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

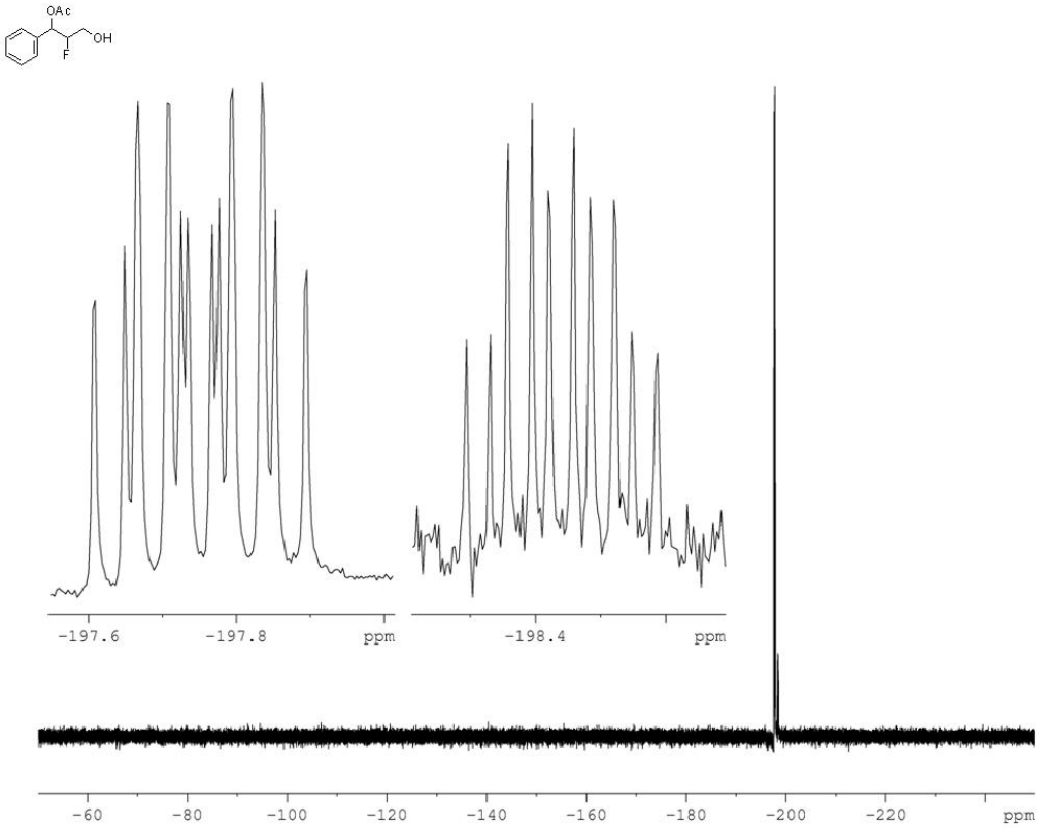

OH
OAc
F
10
9
8
7
6
5
4
3
2
1
ppm
4.89
2.06
0.95
0.81
0.71
3.00

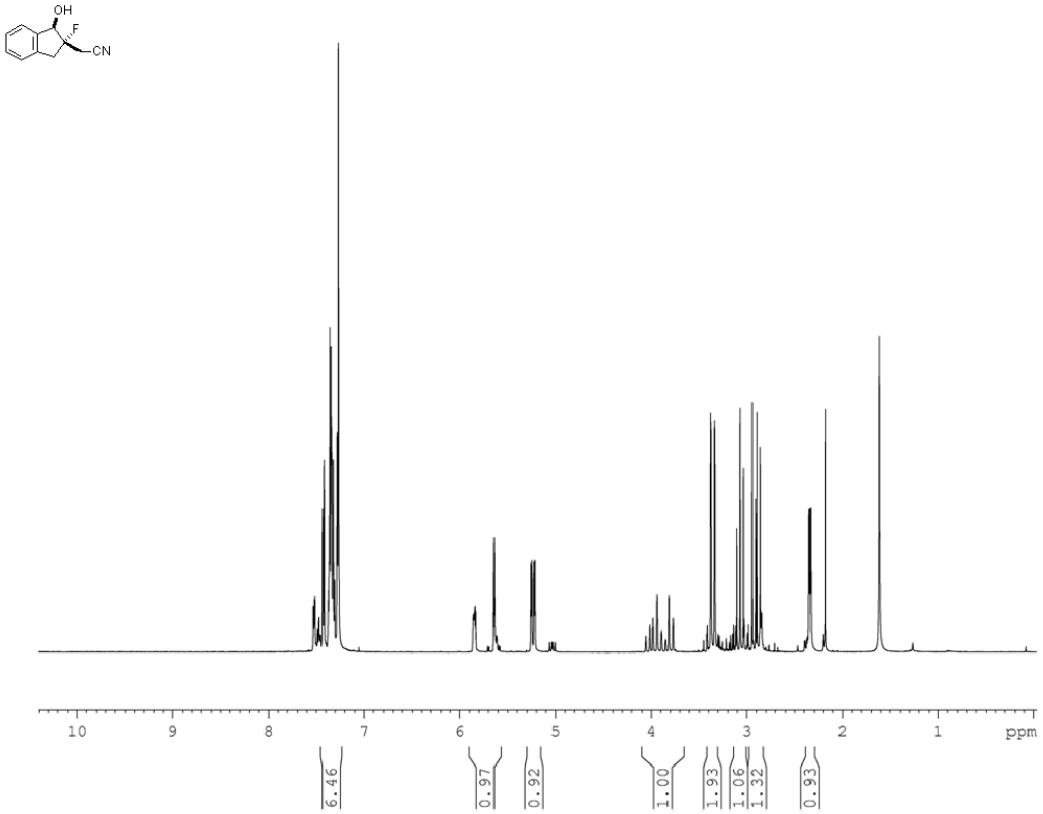

OH
OAc
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

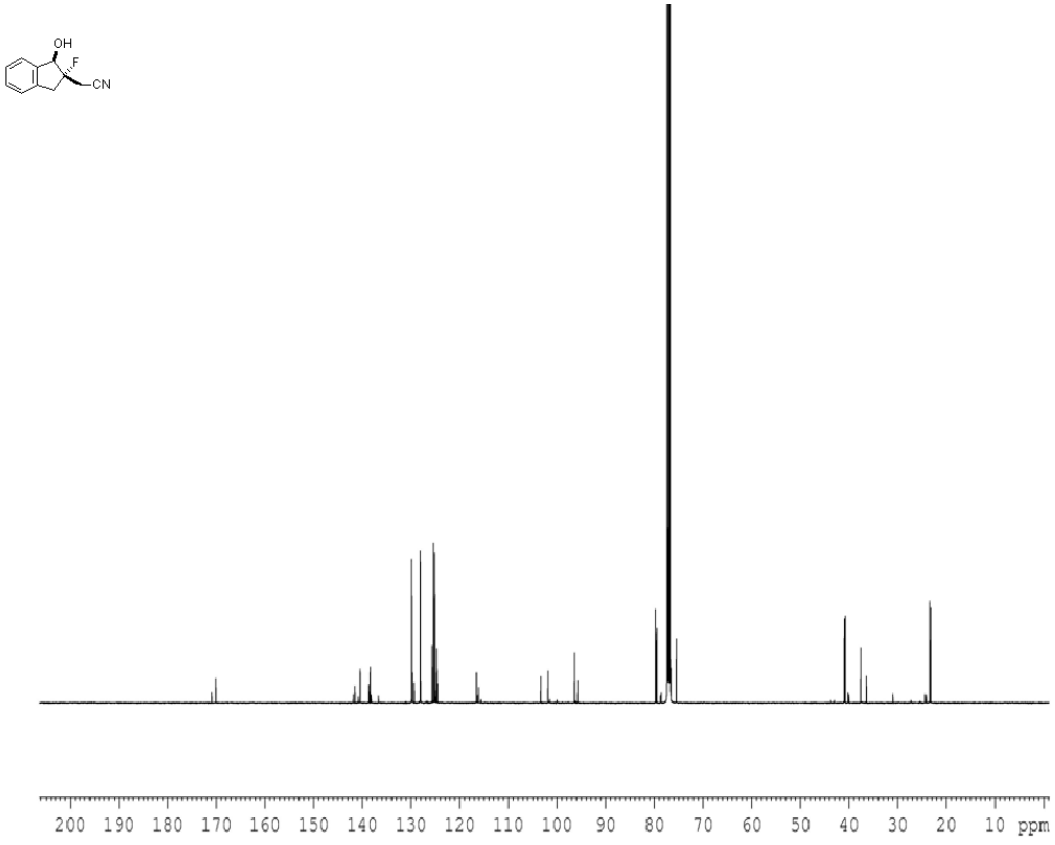

OH
OAc
F
-193.6
ppm
-195.8
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

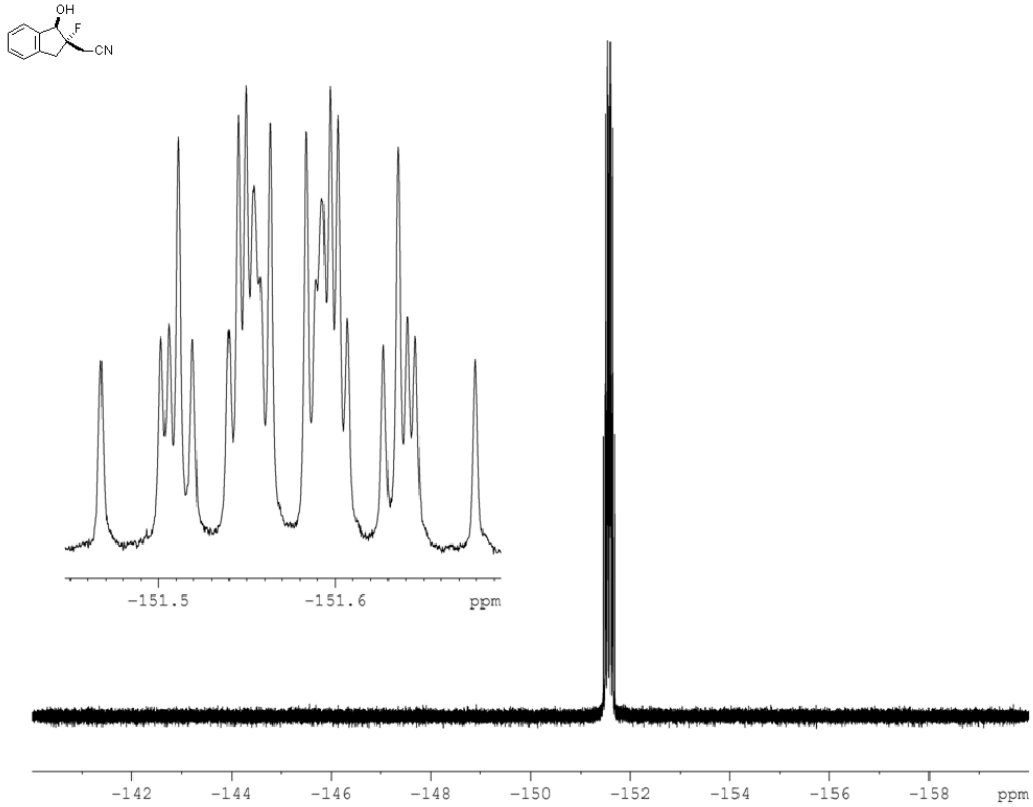

OAc
OH
F
10
9
8
7
6
5
4
3
2
1
ppm
4.79
0.94
1.04
2.07
3.00

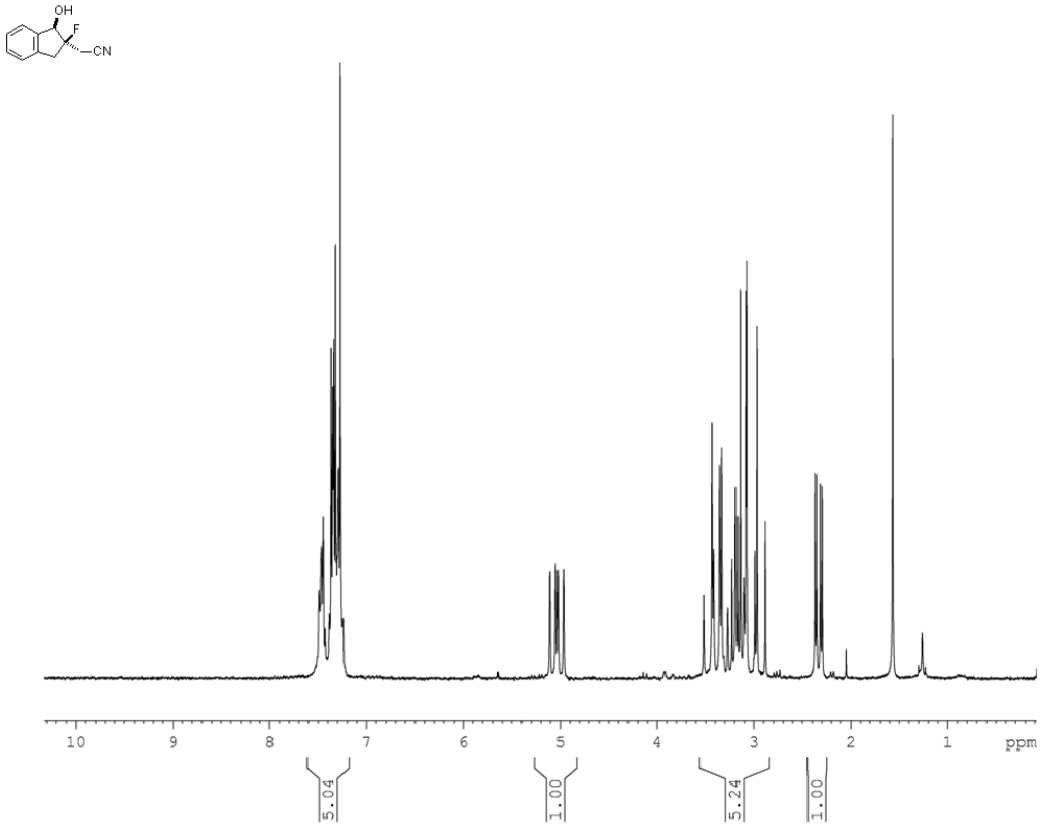

OAc
OH
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OAc
OH
F
-197.6
-197.8
ppm
-198.4
ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

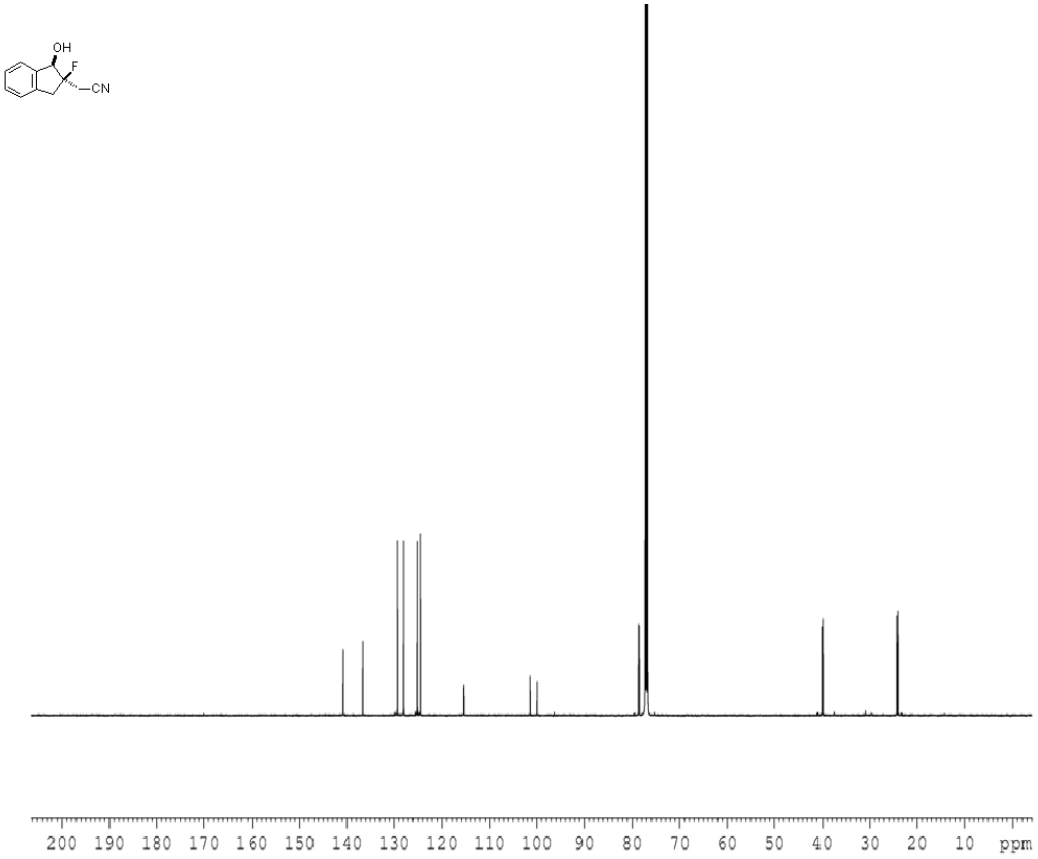

OH
F
CN
10
9
8
7
6
5
4
3
2
1
ppm
6.46
0.97
0.92
1.00
1.93
1.06
1.32
0.93

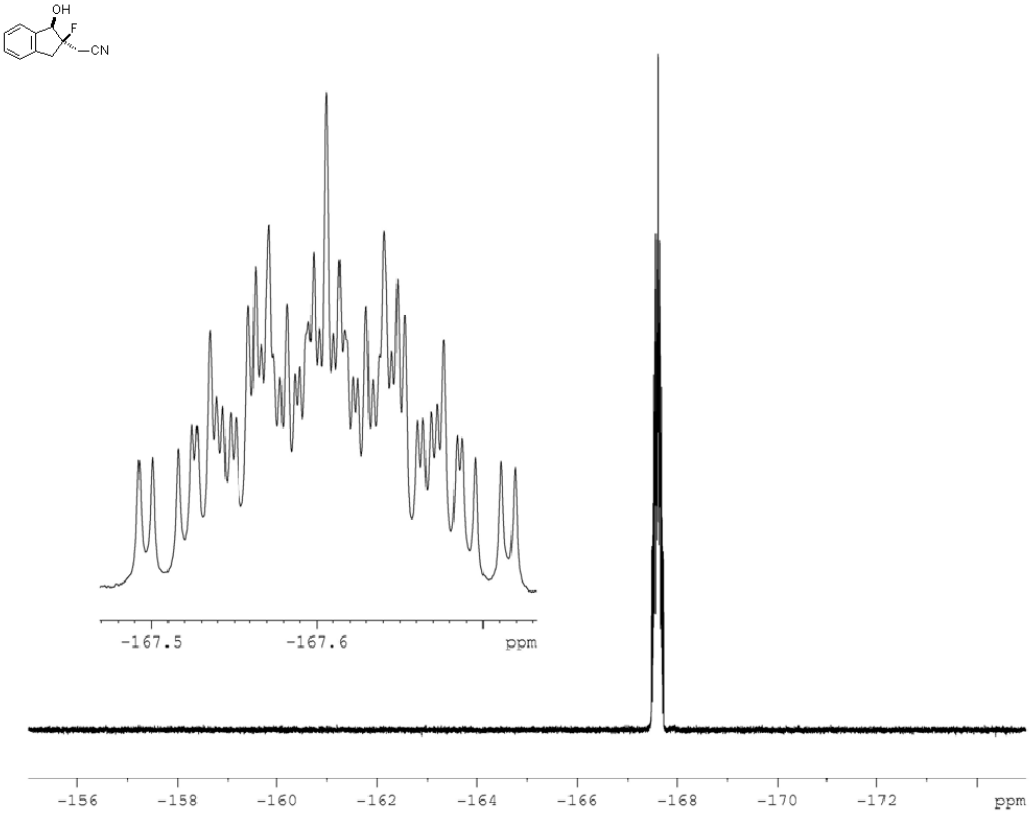

OH
F
CN
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

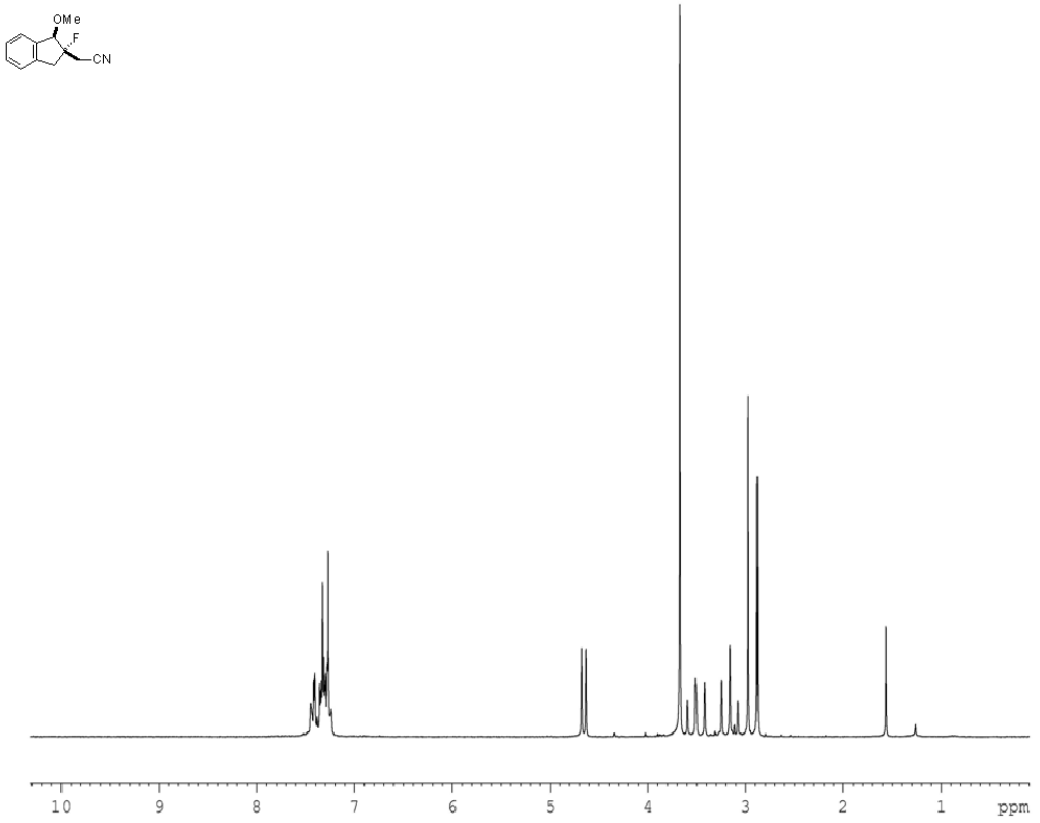

OH
F
CN
-151.5
-151.6
ppm
-142
-144
-146
-148
-150
-152
-154
-156
-158
ppm

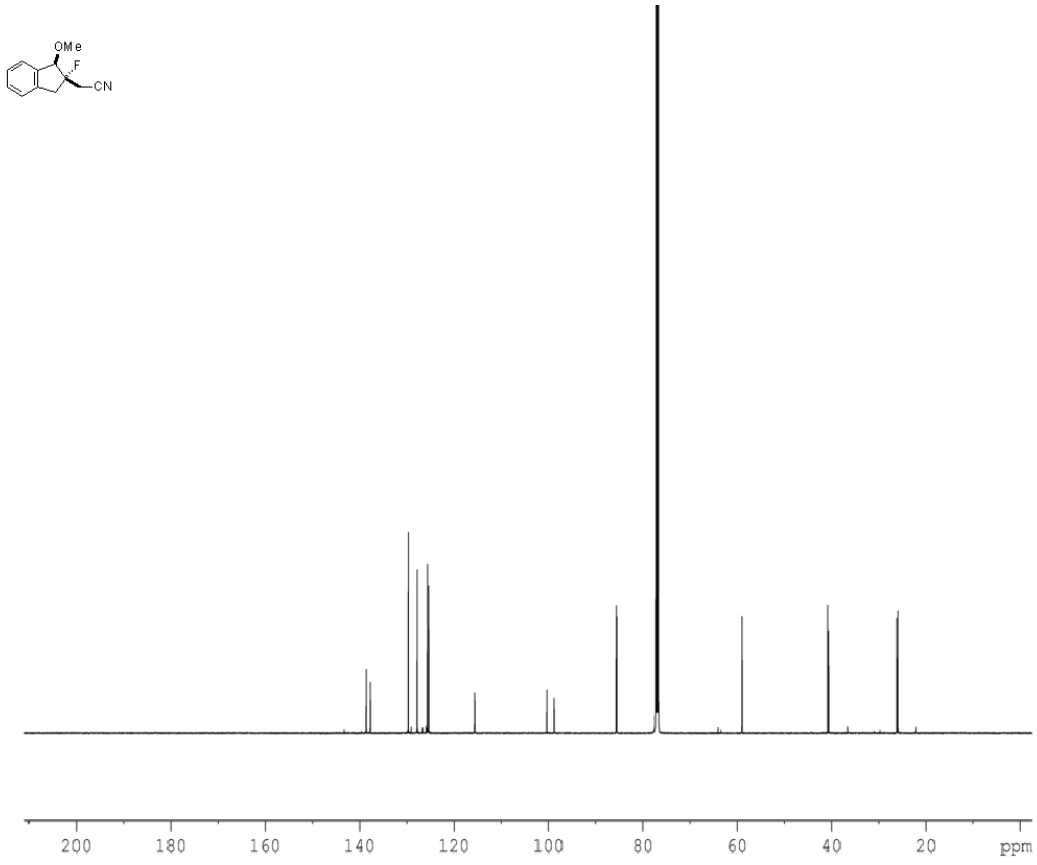

OH
F
CN
10
9
8
7
6
5
4
3
2
1
ppm
5.04
1.00
5.24
1.00

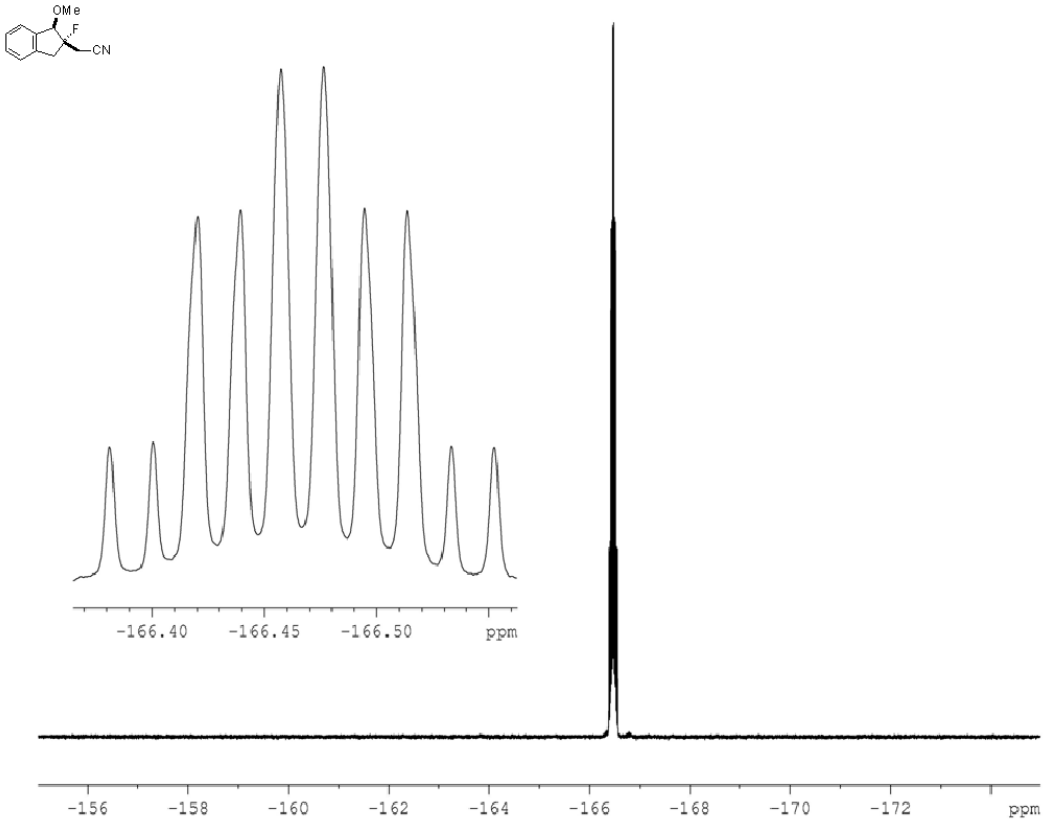
cc

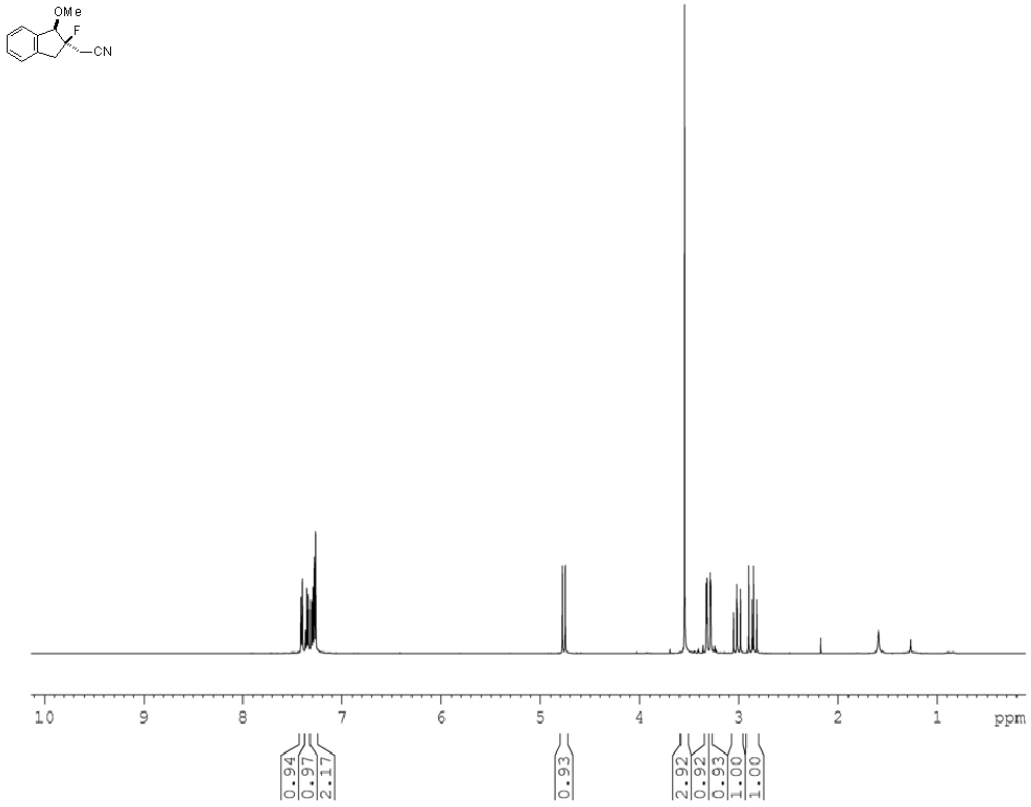

OH
F
CN
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

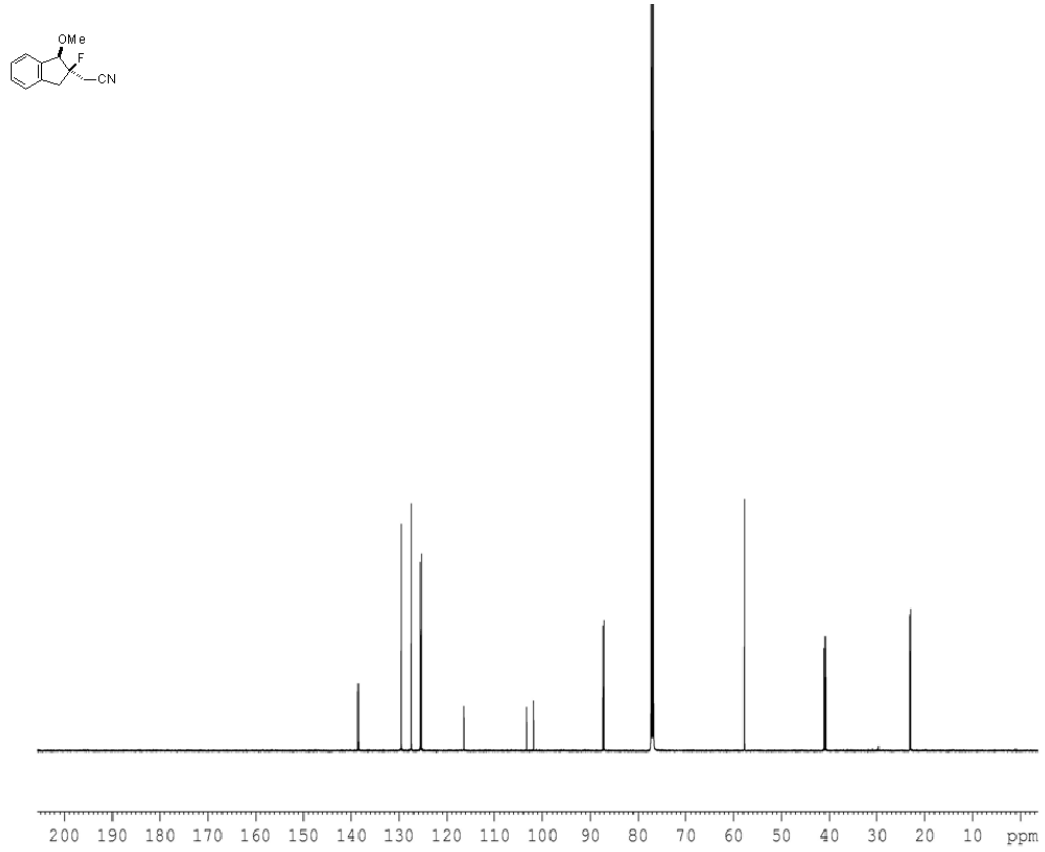

OH
F
CN
-167.5
-167.6
ppm
-156 -158 -160 -162 -164 -166 -168 -170 -172 ppm

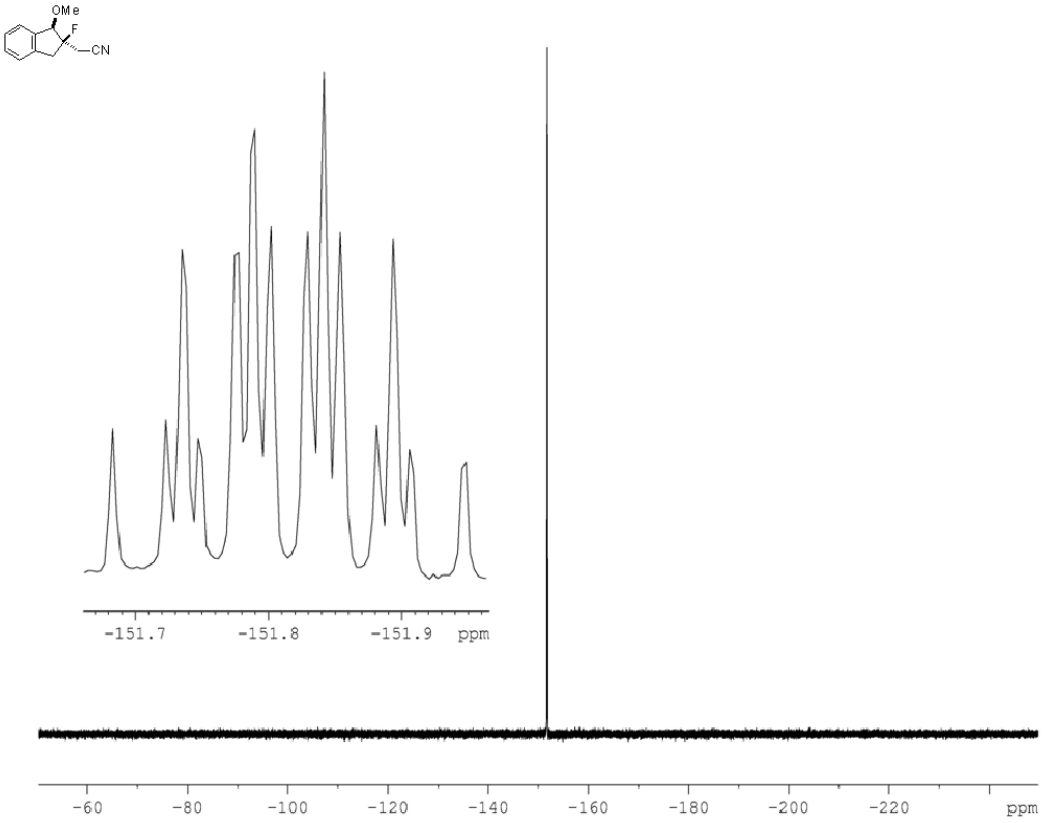

OMe
F
CN
10
9
8
7
6
5
4
3
2
1
ppm

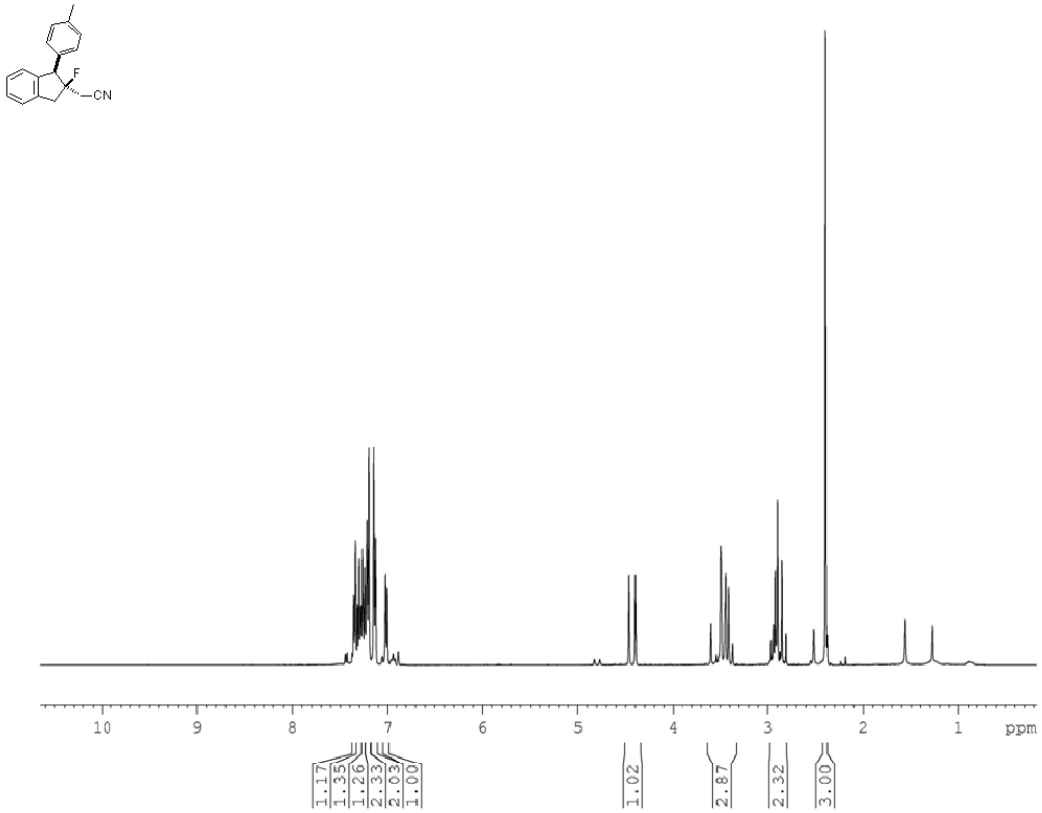

OMe
F
CN
200
180
160
140
120
100
80
60
40
20
ppm

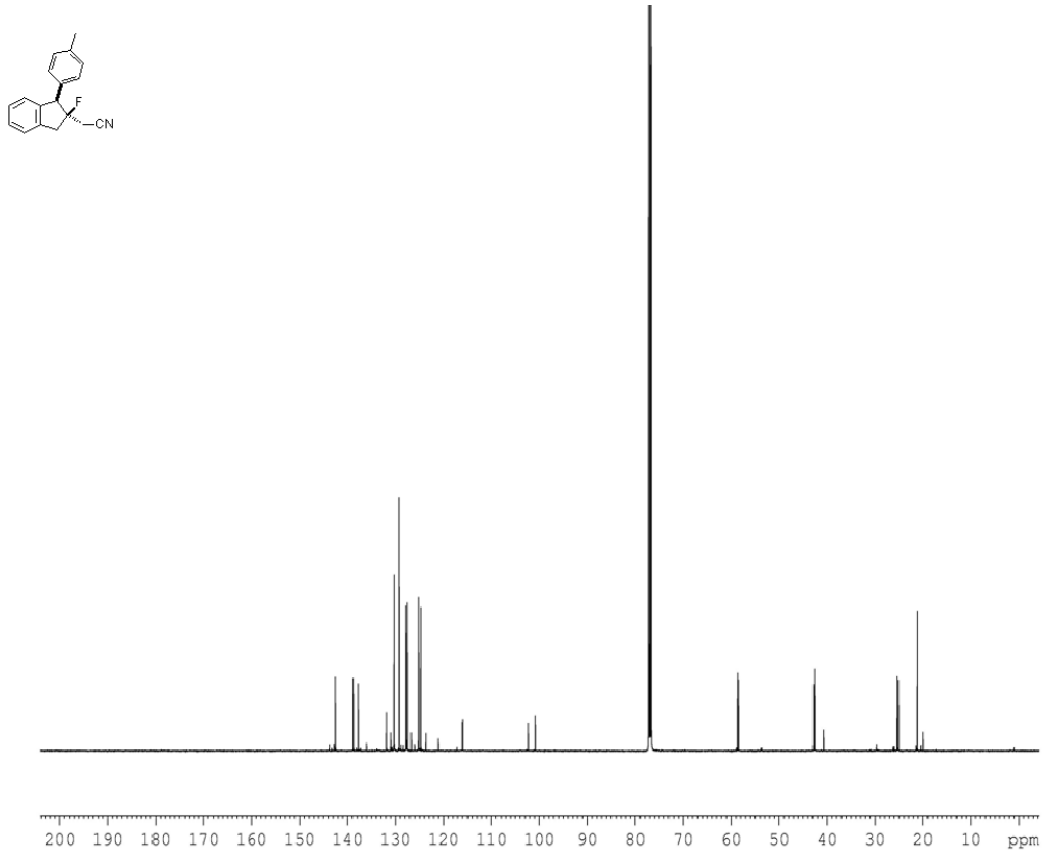

OMe
F
CN
-166.40
-166.45
-166.50
ppm
-156
-158
-160
-162
-164
-166
-168
-170
-172
ppm

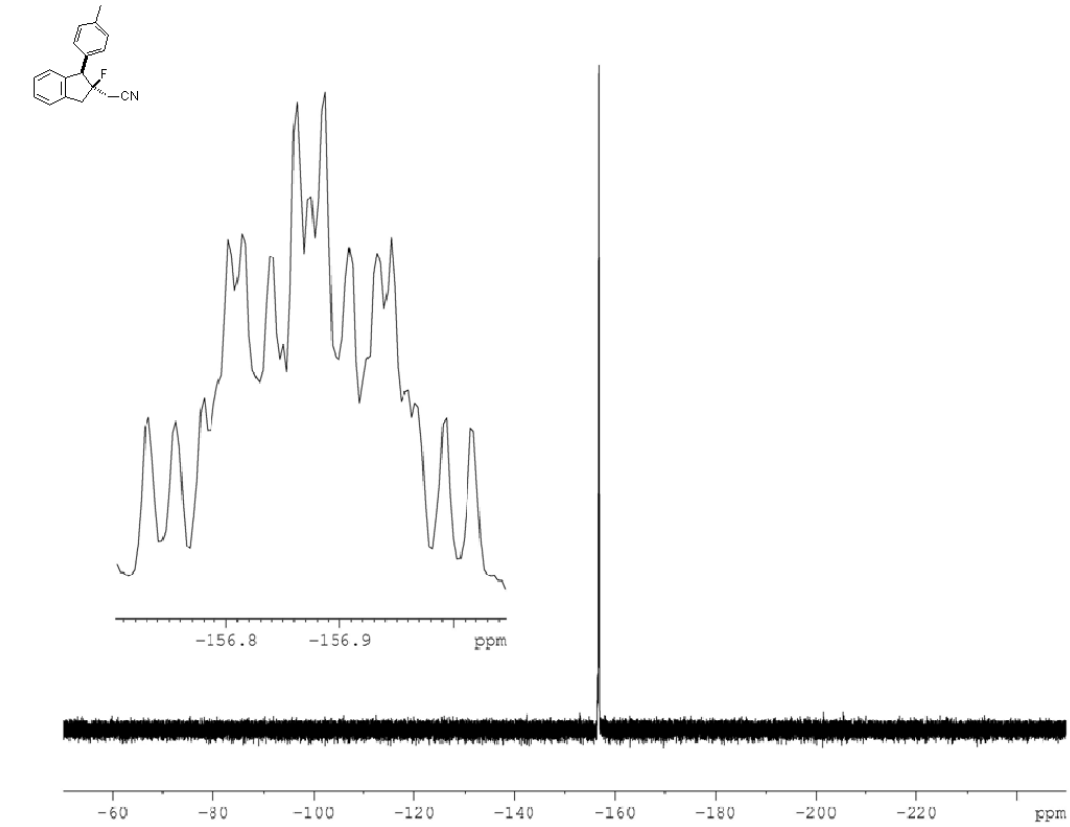

OMe
F
CN
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.97
2.17
0.93
2.92
0.92
0.93
1.00
1.00

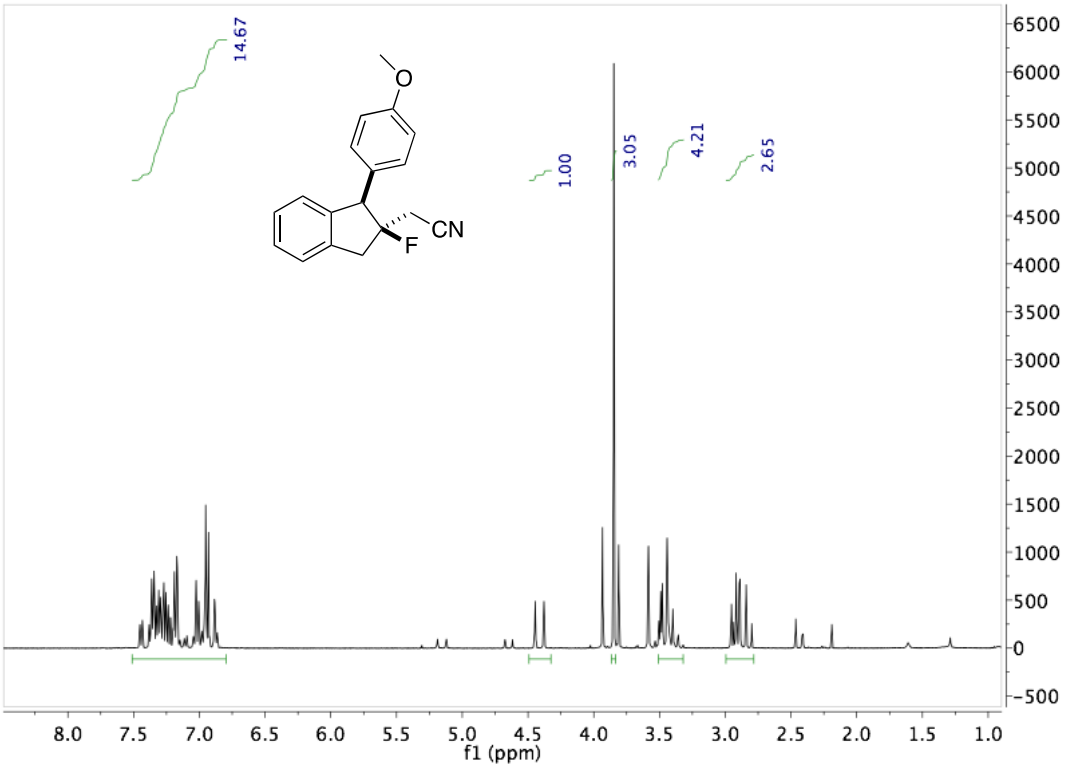

OMe
F
CN
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

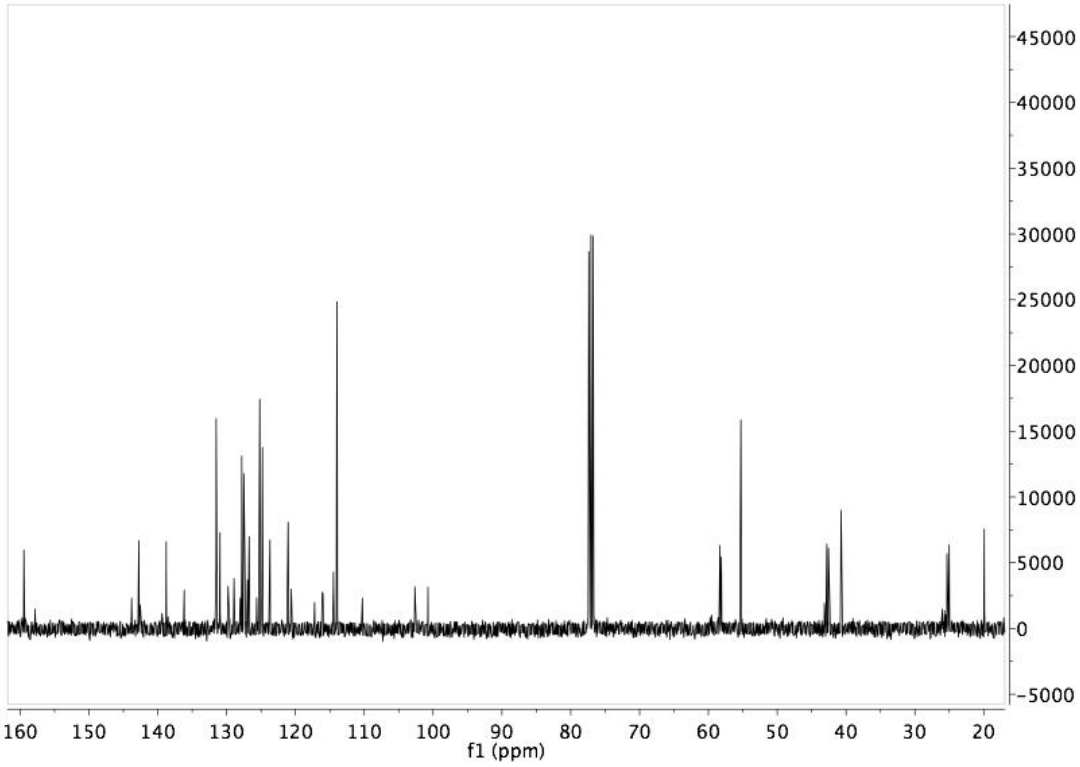

OMe
F
CN
-151.7 -151.8 -151.9 ppm
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

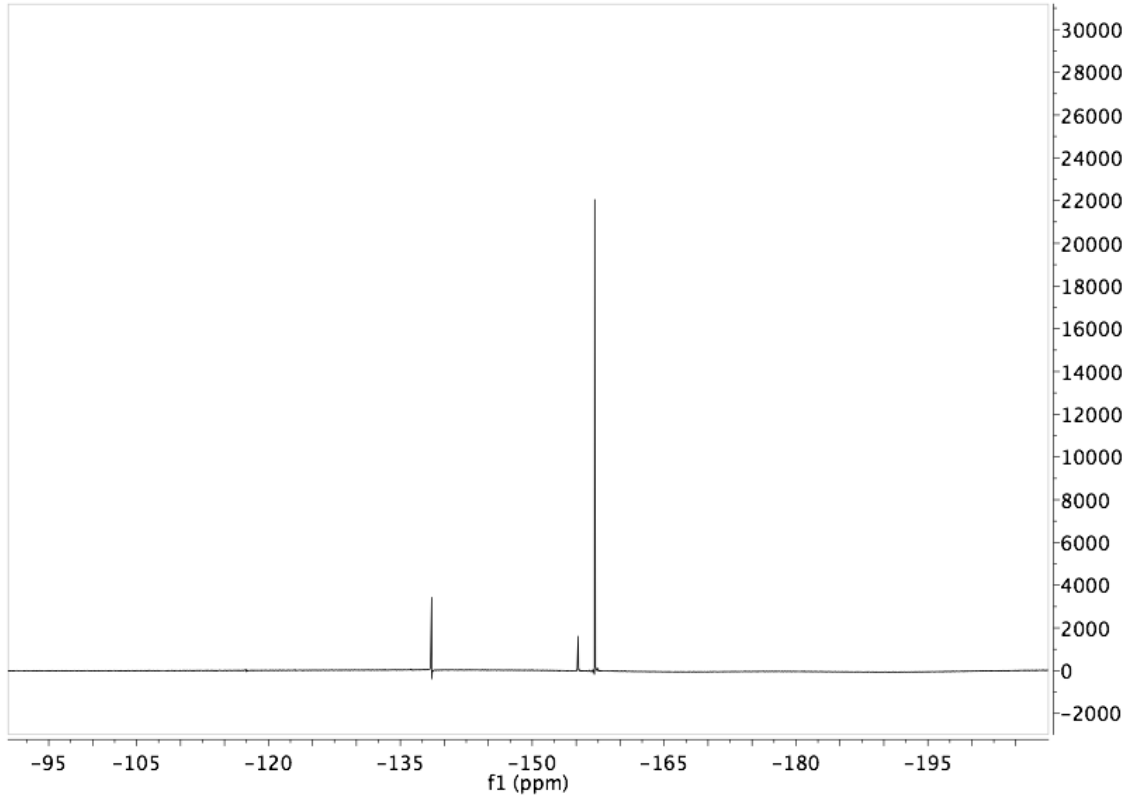

F
CN
10 9 8 7 6 5 4 3 2 1 ppm
1.17
1.35
1.26
2.33
2.03
1.00
1.02
2.87
2.32
3.00

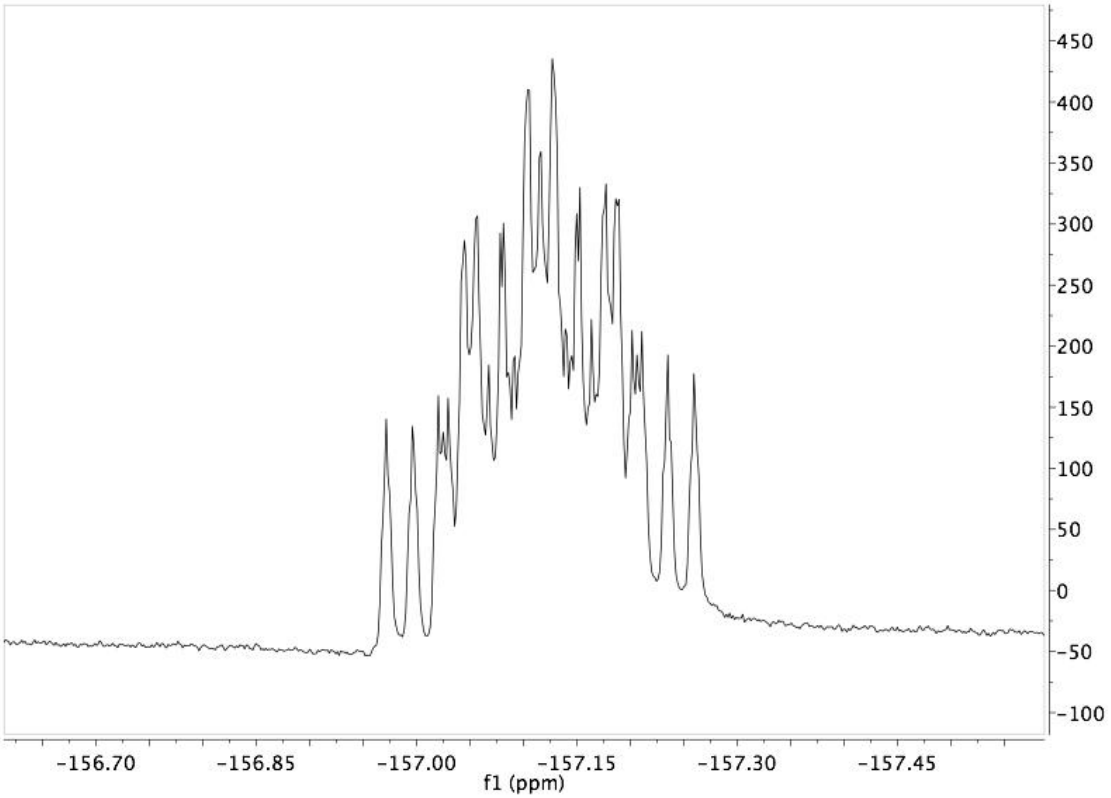

F
CN
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

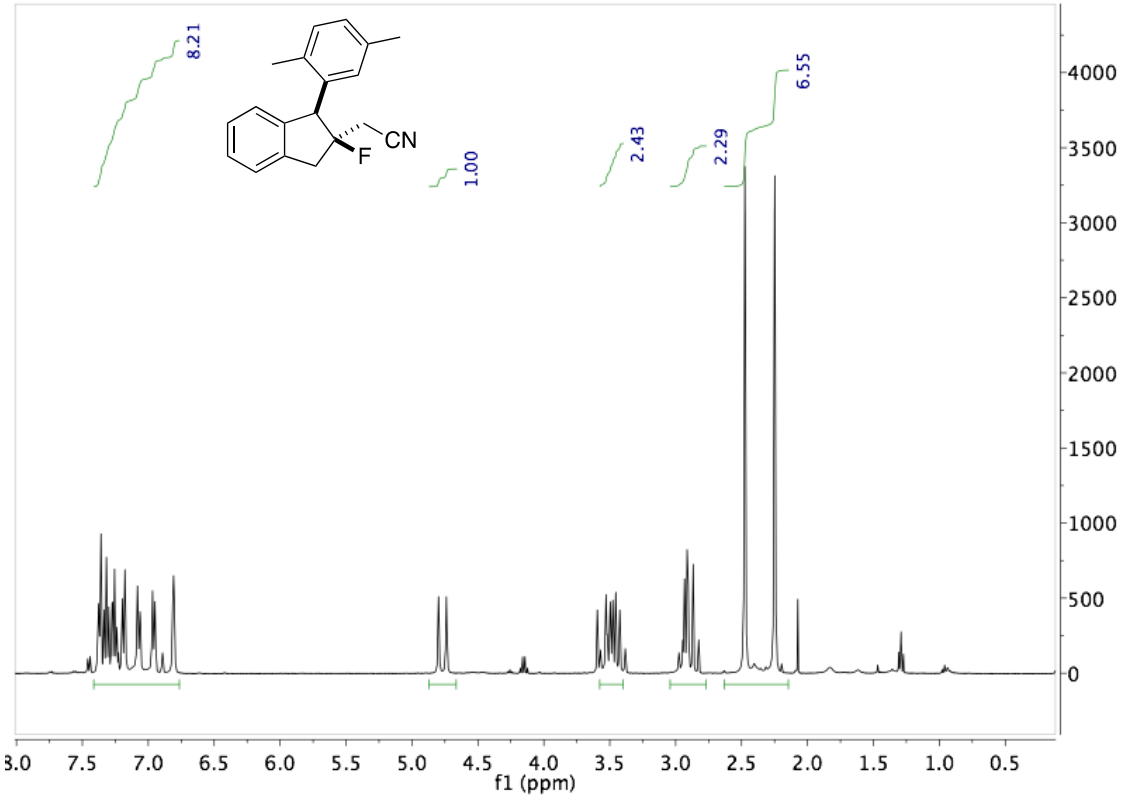

F
CN
-156.8
-156.9
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

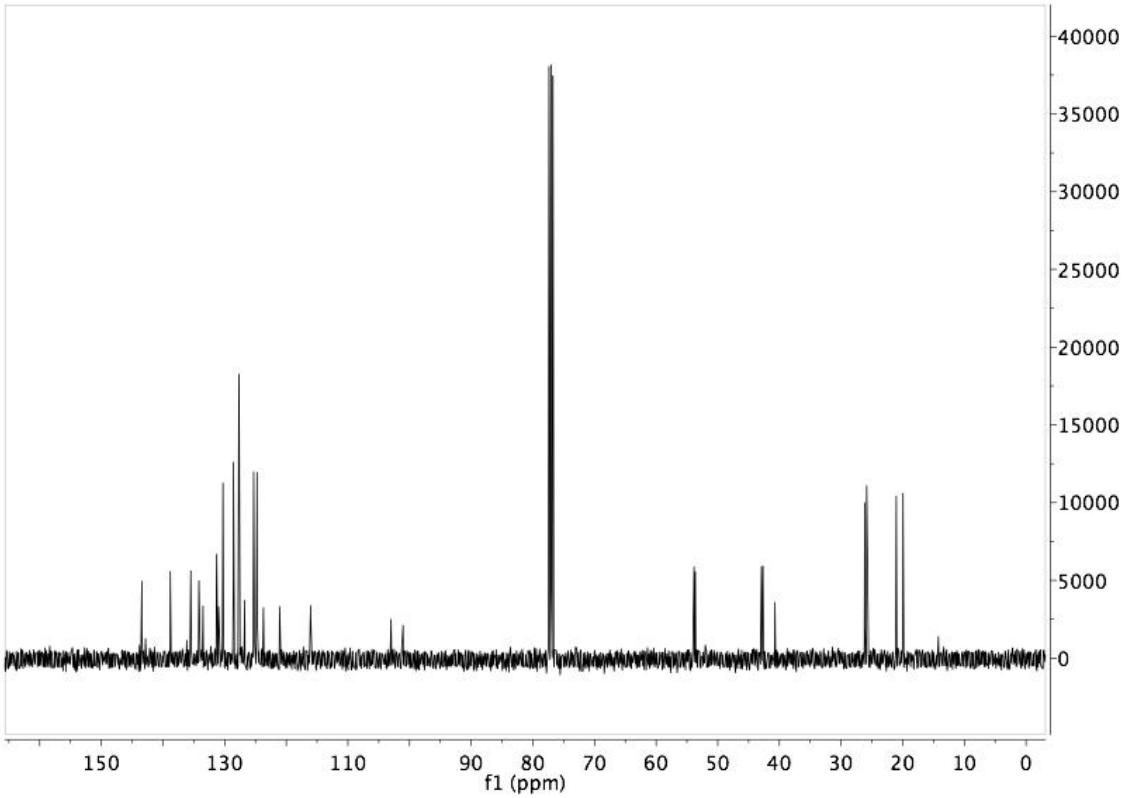

14.67
1.00
3.05
4.21
2.65
O
F
CN
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

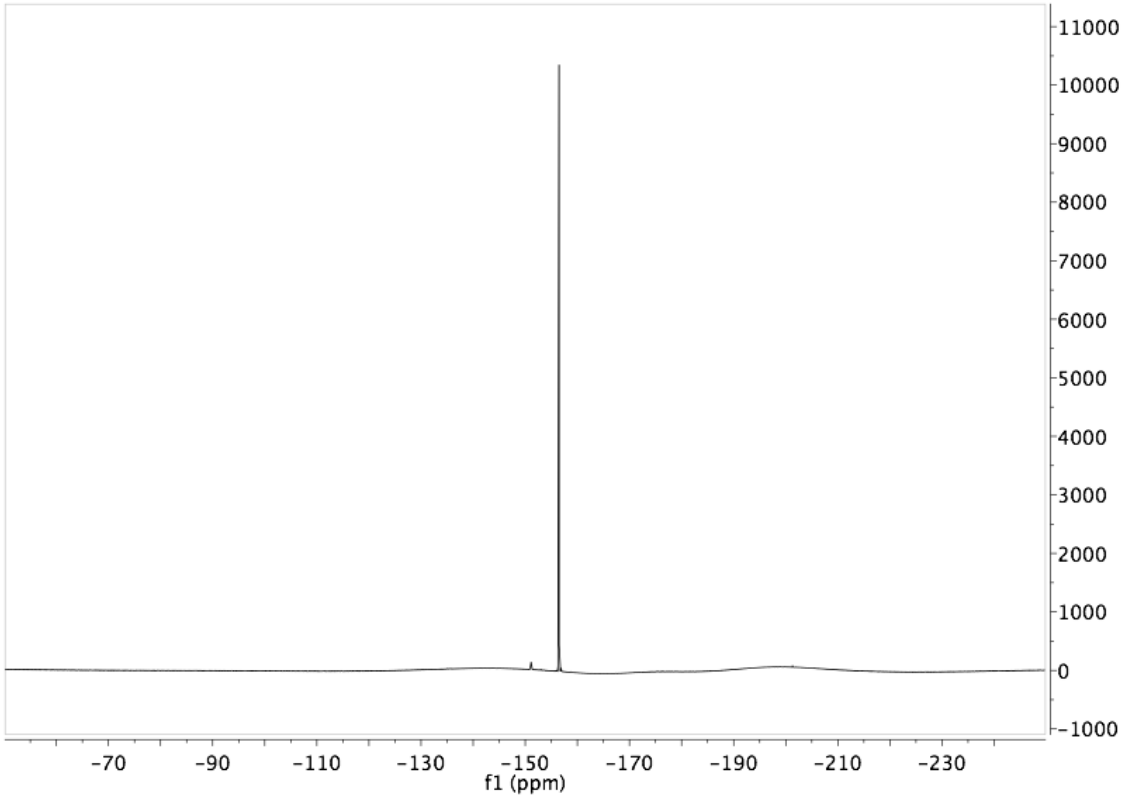

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

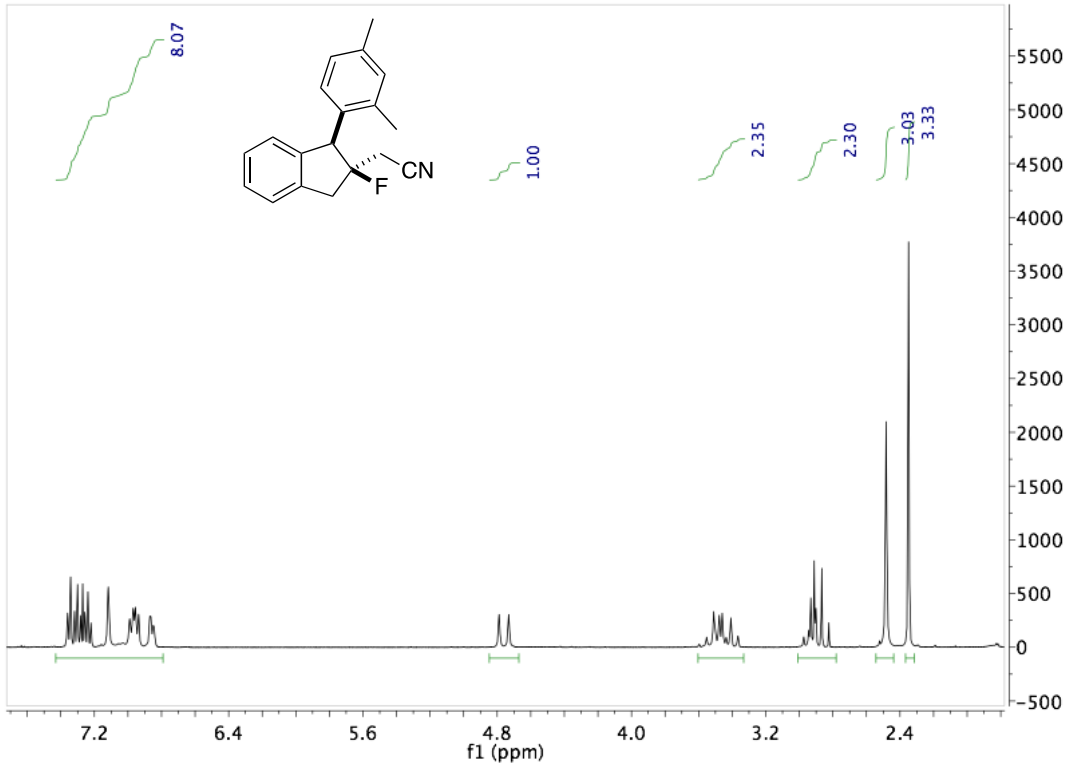

30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-95 -105 -120 -135 -150 -165 -180 -195
f1 (ppm)

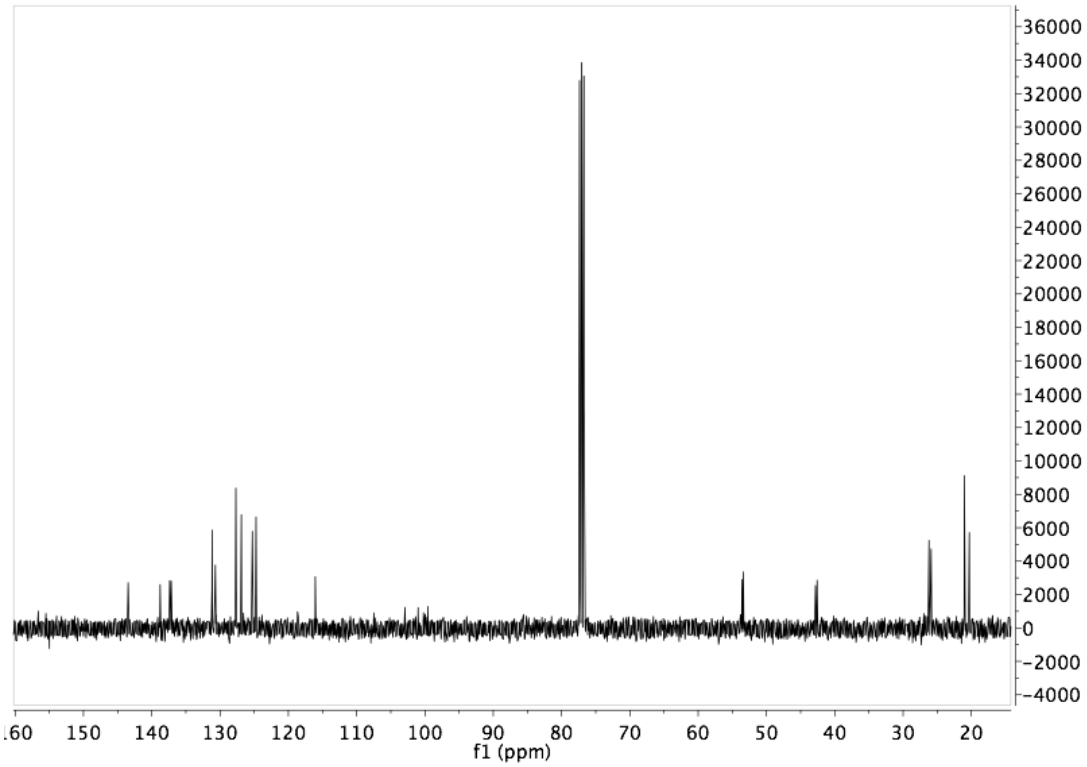

450
400
350
300
250
200
150
100
50
0
-50
-100
-156.70
-156.85
-157.00
-157.15
-157.30
-157.45
f1 (ppm)

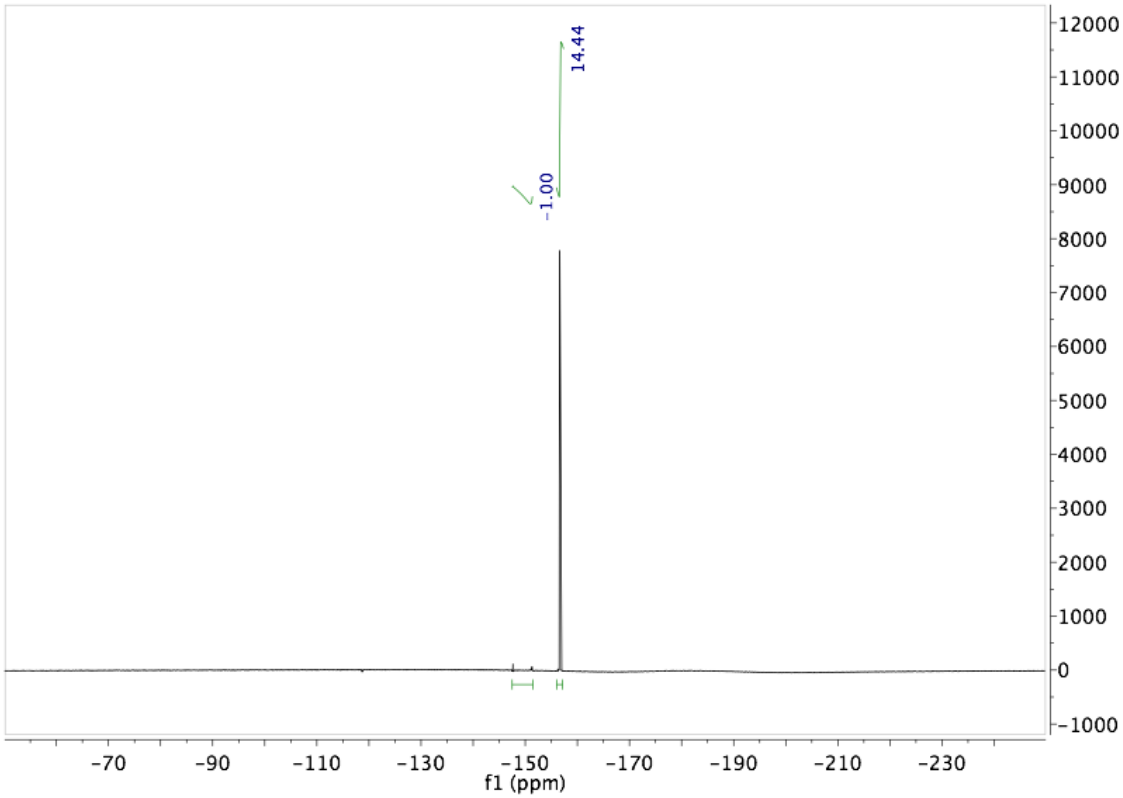

8.21
1.00
2.43
2.29
6.55
CN
F
4000
3500
3000
2500
2000
1500
1000
500
0
3.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

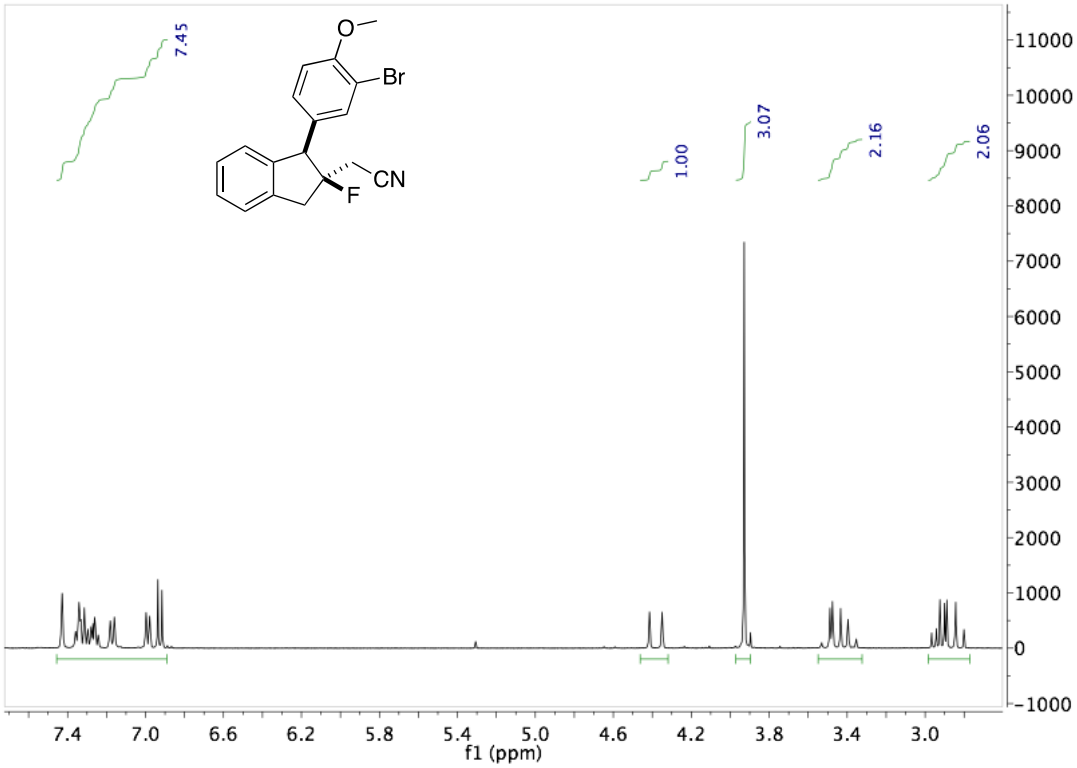

40000
35000
30000
25000
20000
15000
10000
5000
0
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

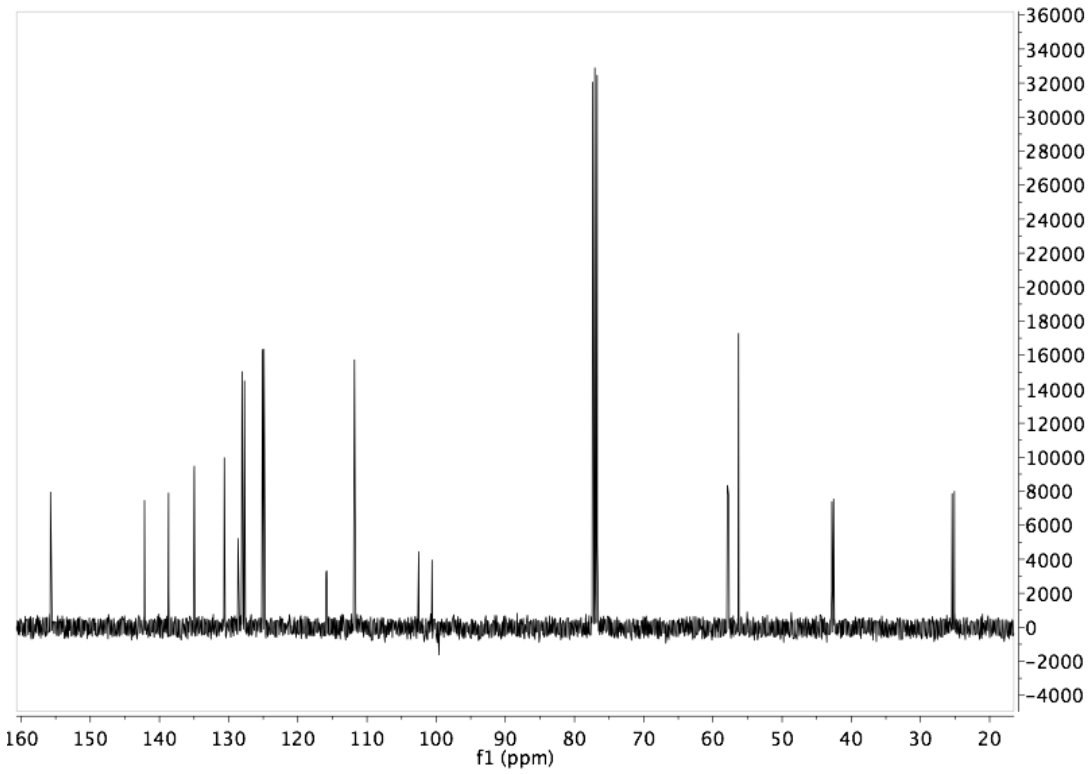

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

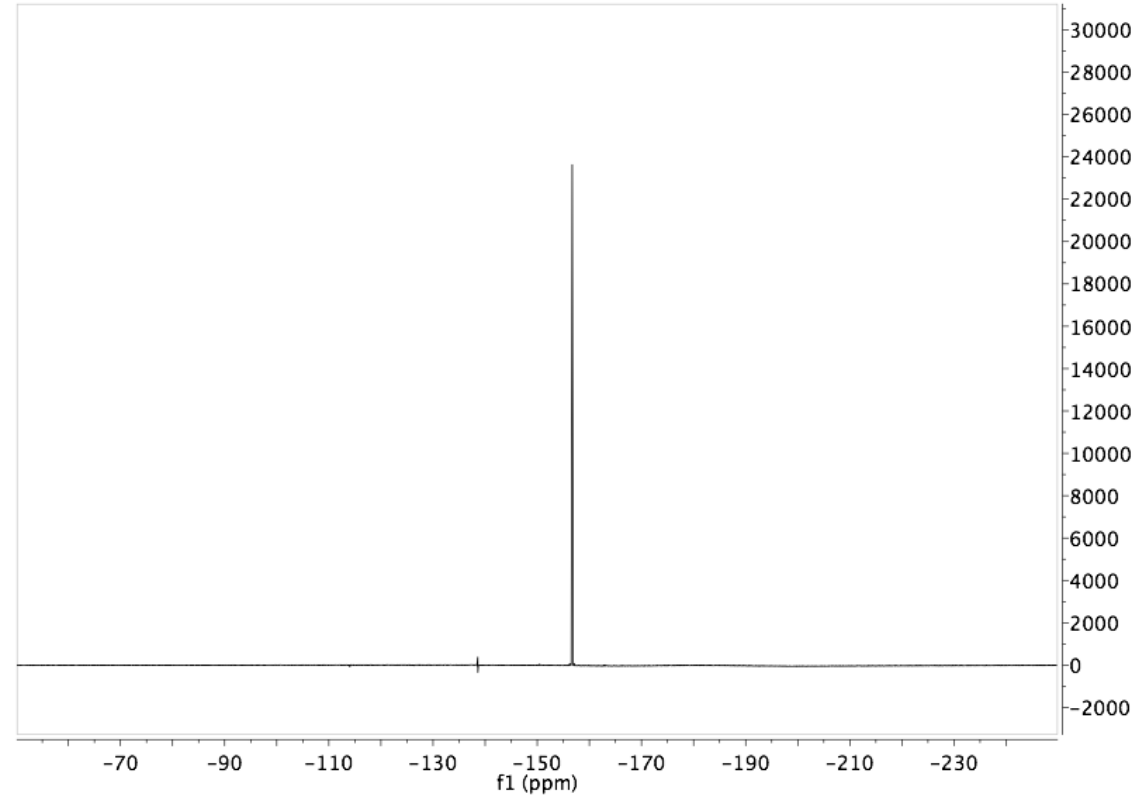

8.07
1.00
2.35
2.30
3.03
3.33
CN
F
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
7.2
6.4
5.6
4.8
4.0
3.2
2.4
f1 (ppm)

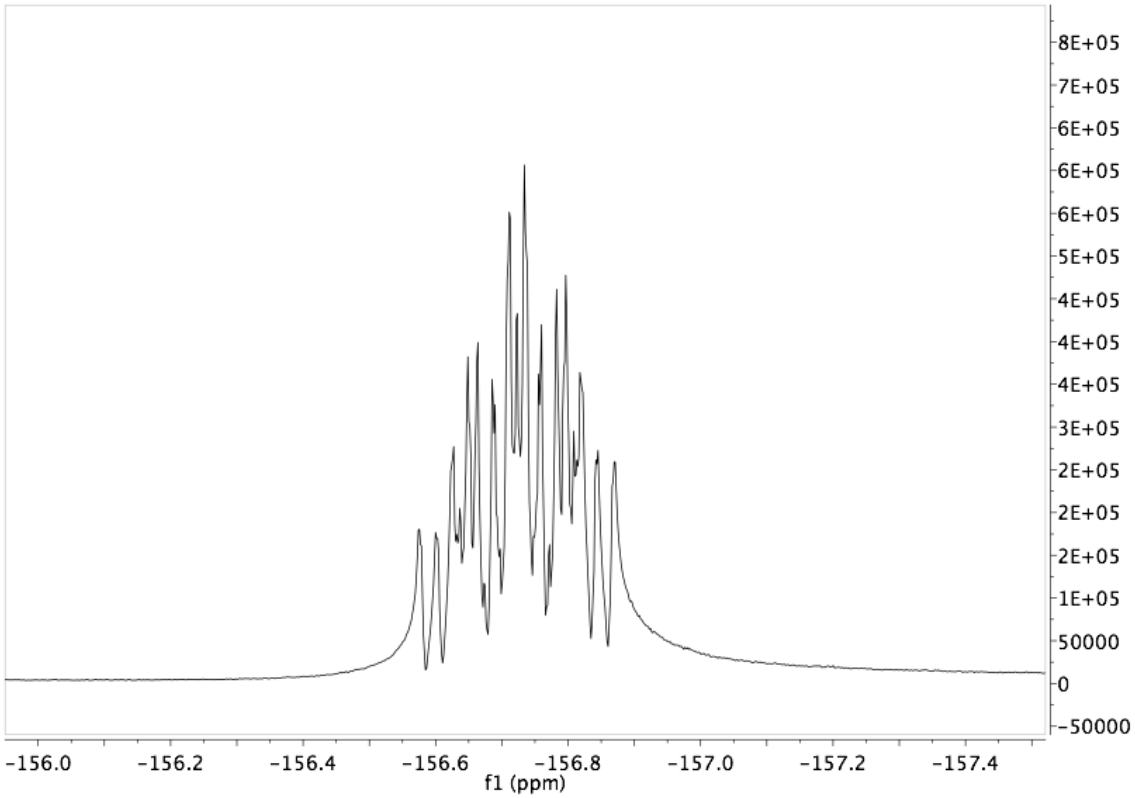

36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

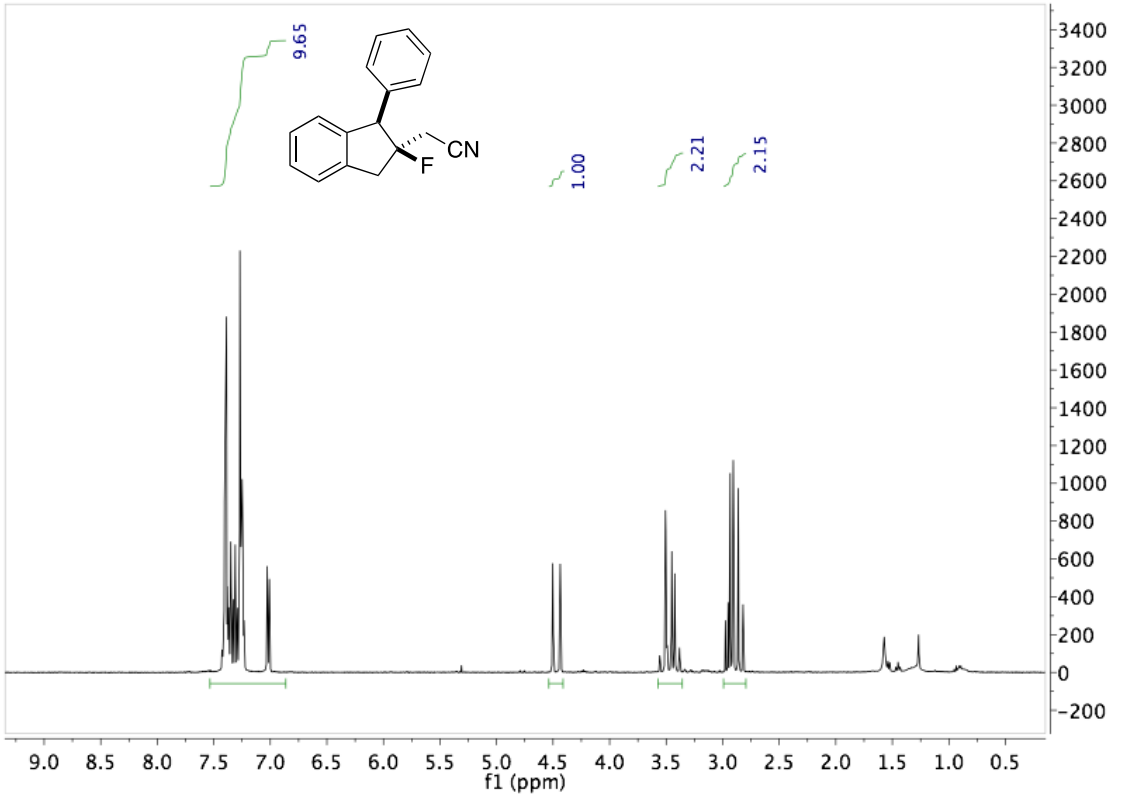

14.44
1.00
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

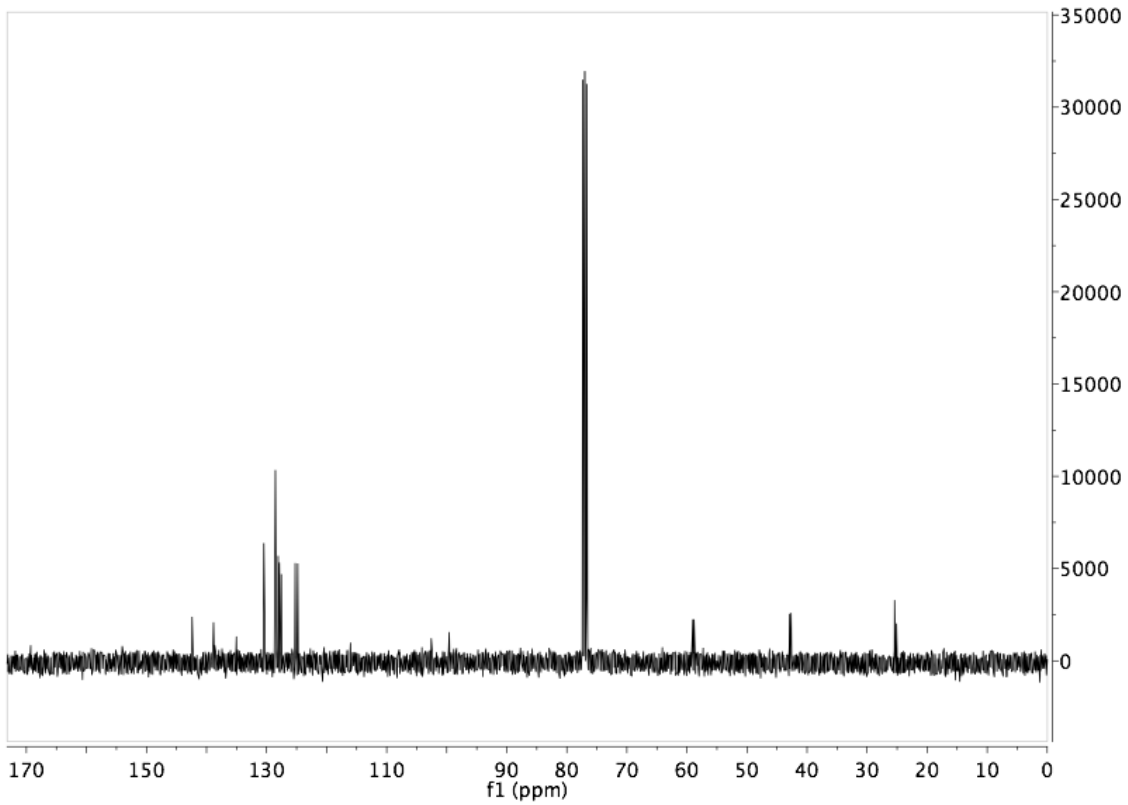

7.45
O
Br
CN
F
1.00
3.07
2.16
2.06
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
f1 (ppm)

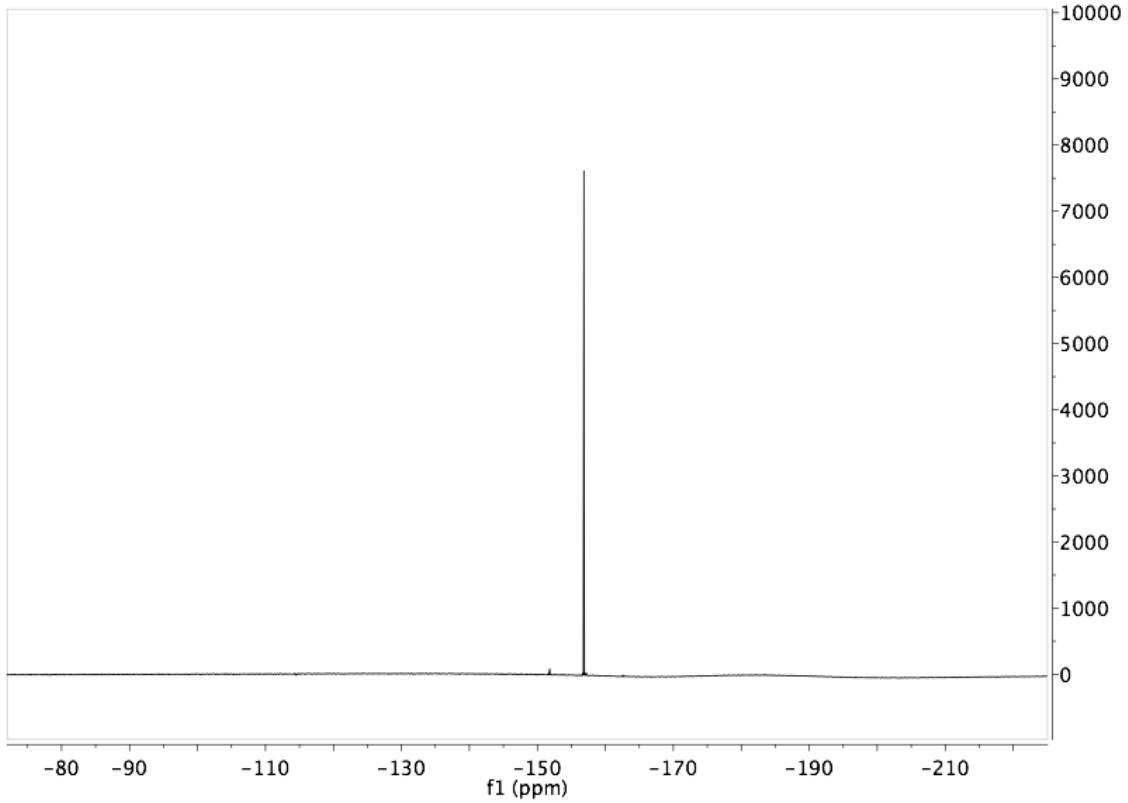

36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

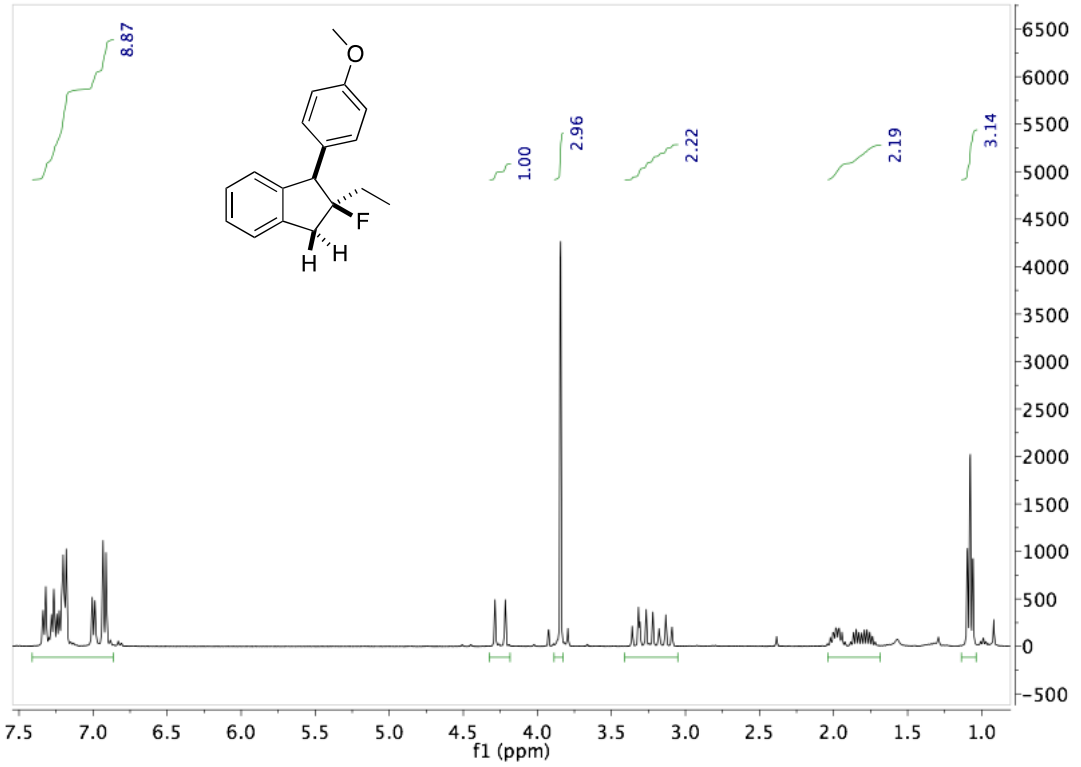

30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-70 -90 -110 -130 -150 -170 -190 -210 -230
f1 (ppm)

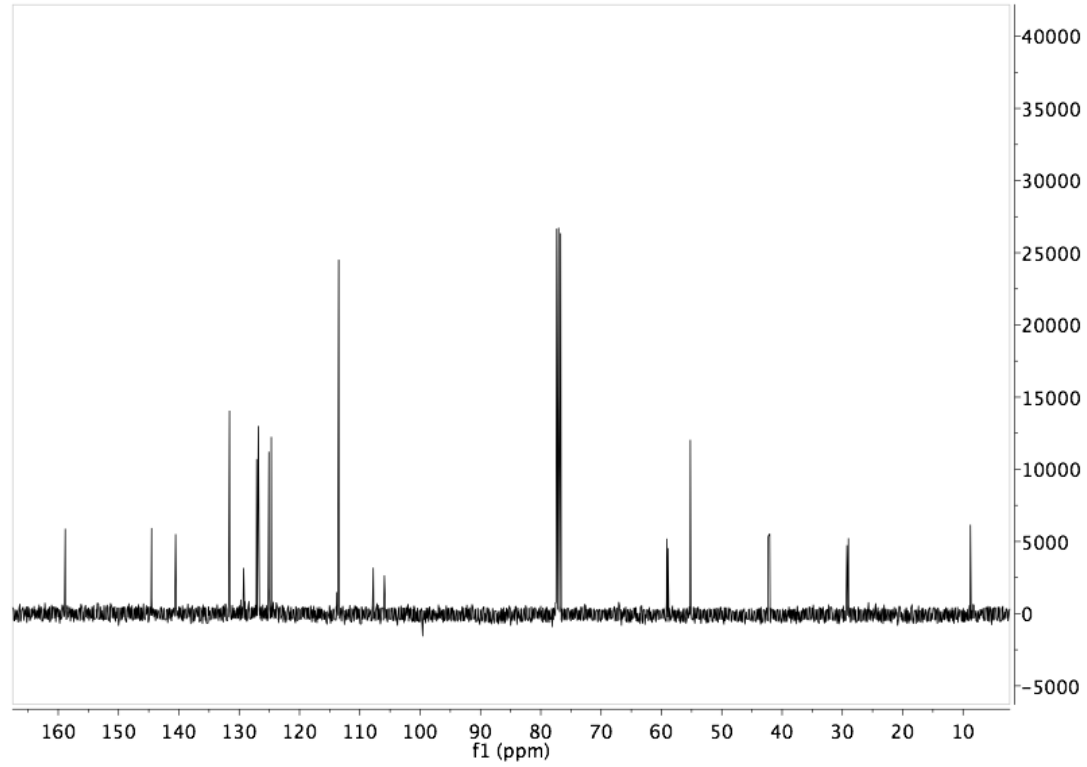

8E+05
7E+05
6E+05
6E+05
6E+05
5E+05
4E+05
4E+05
4E+05
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
-50000
-156.0
-156.2
-156.4
-156.6
-156.8
-157.0
-157.2
-157.4
f1 (ppm)

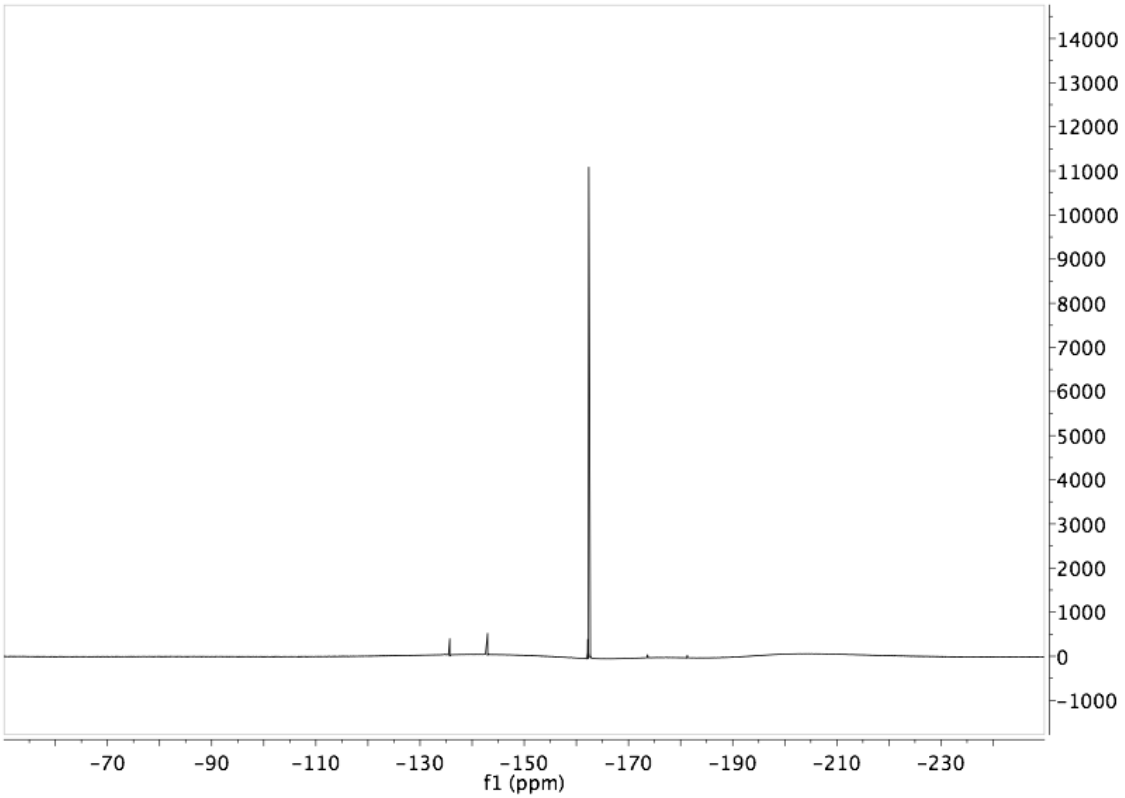

9.65
1.00
2.21
2.15
F
CN
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

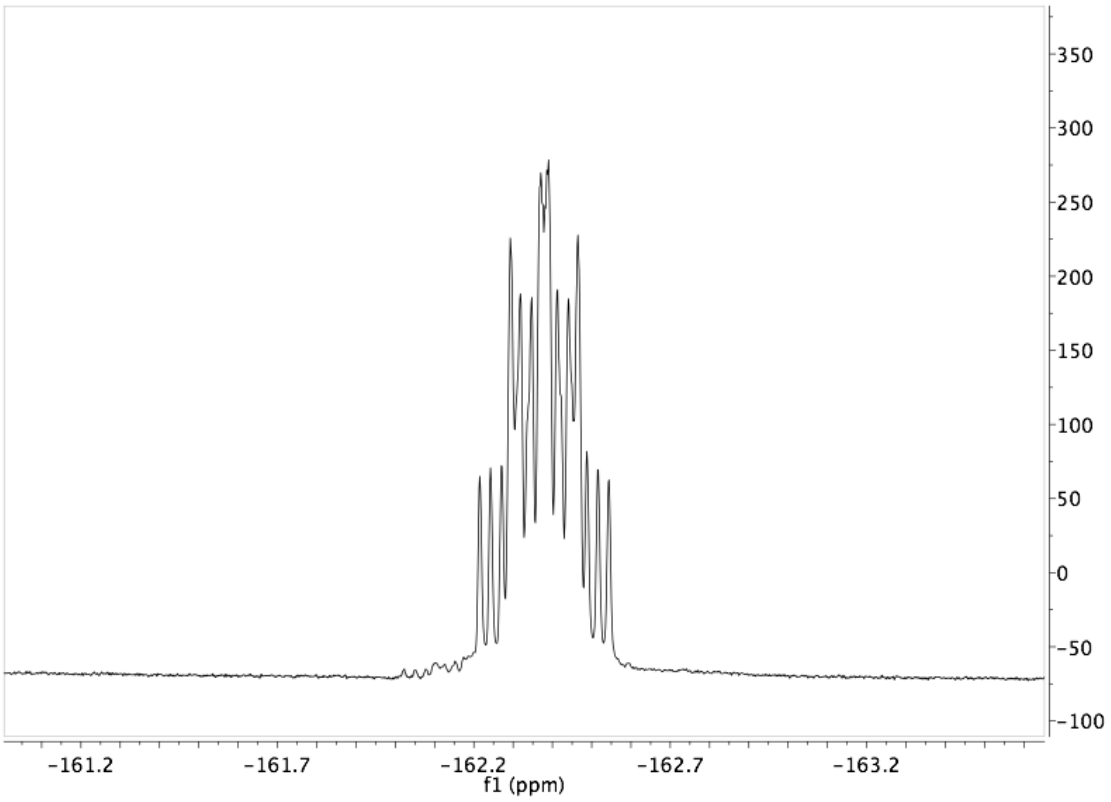

35000
30000
25000
20000
15000
10000
5000
0
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

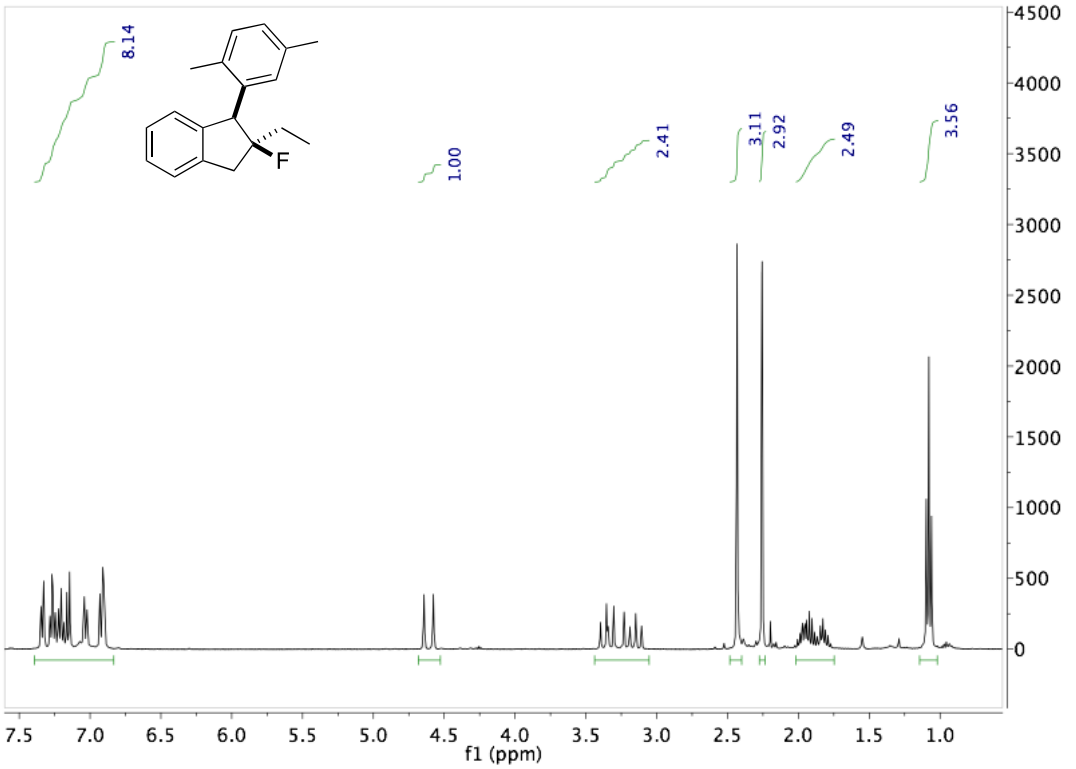

10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-80
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)

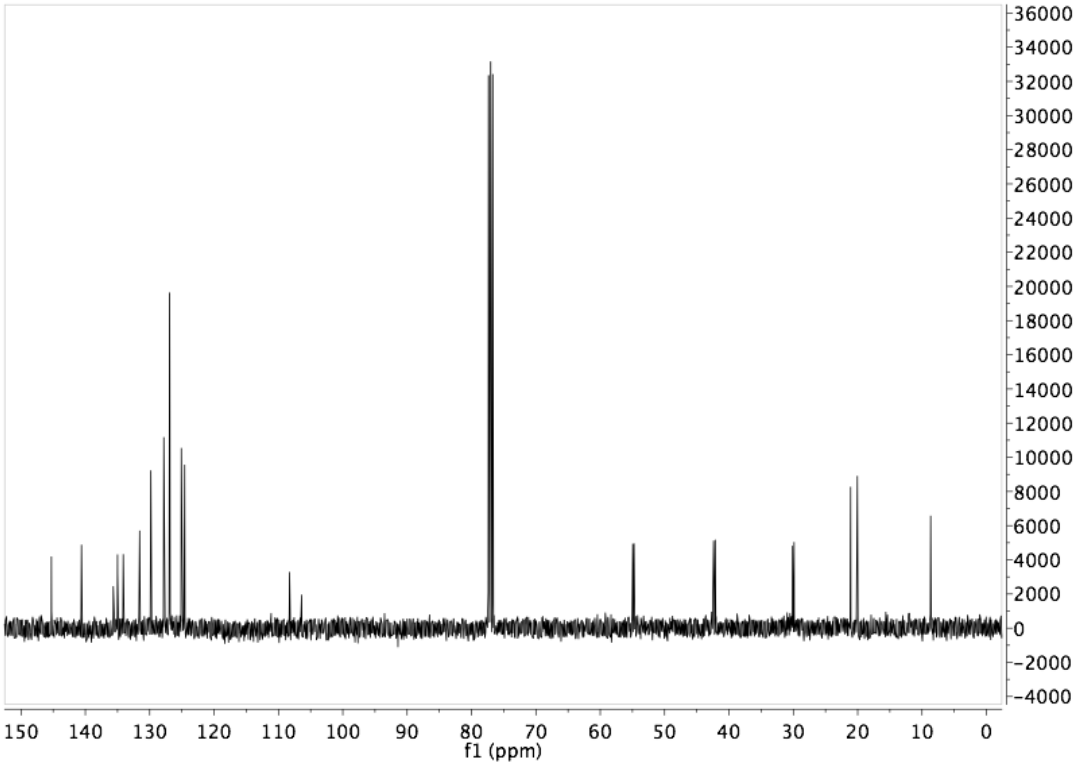

8.87
1.00
2.96
2.22
2.19
3.14
O
F
H
H
f1 (ppm)

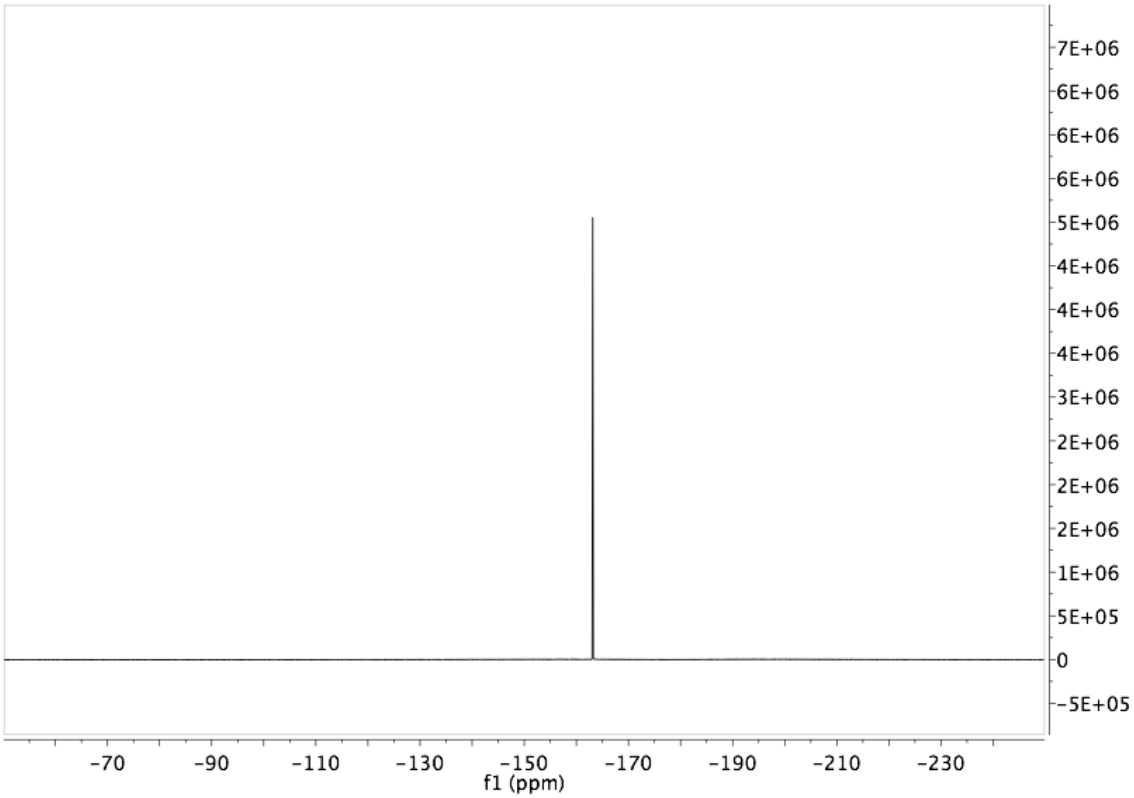

f1 (ppm)

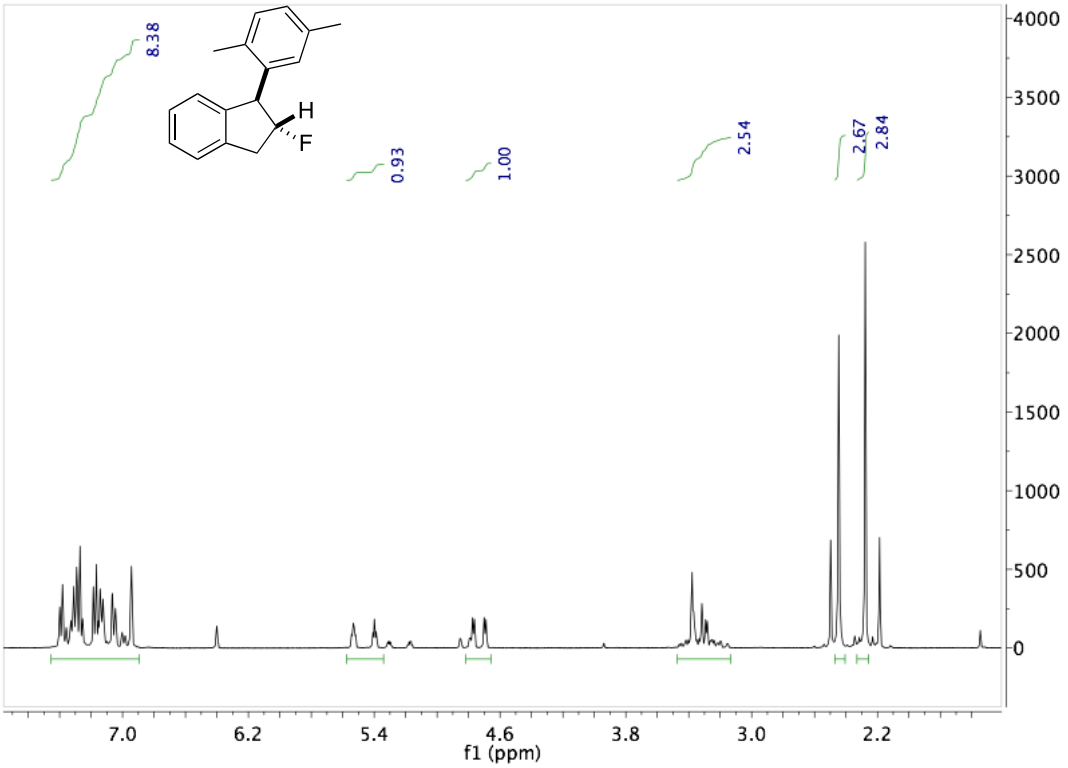

14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

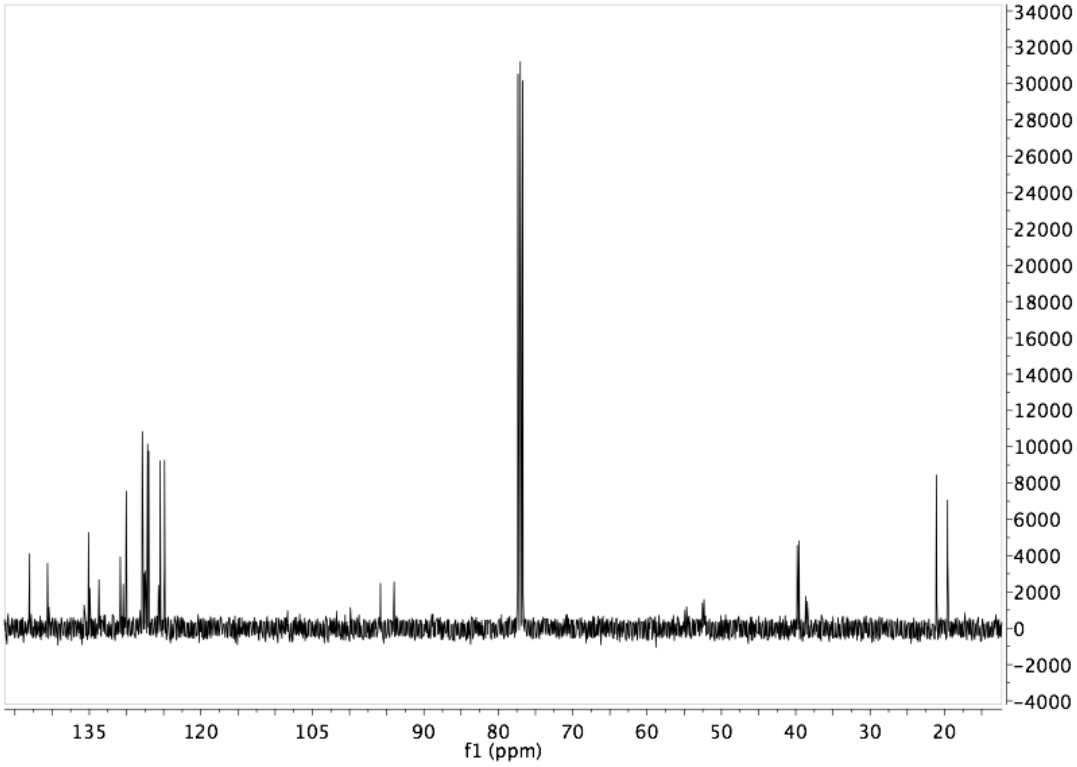

350
300
250
200
150
100
50
0
-50
-100
-161.2
-161.7
-162.2
-162.7
-163.2
f1 (ppm)

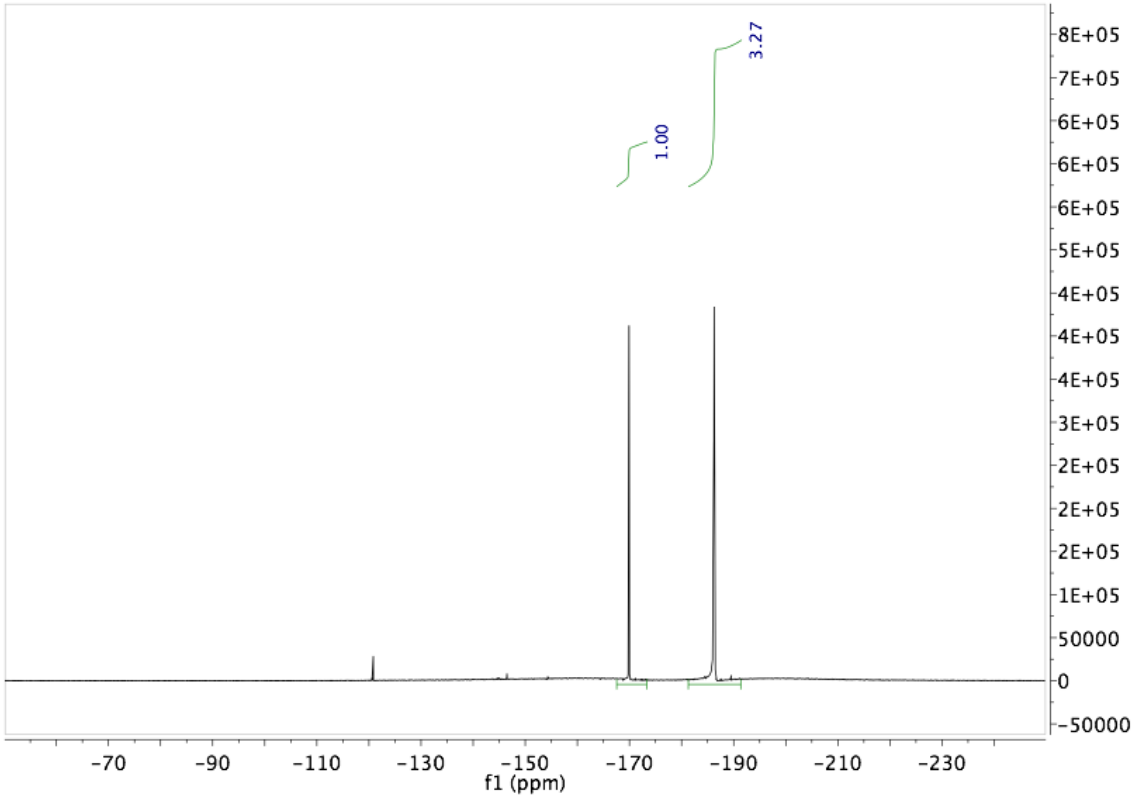

8.14
1.00
2.41
3.11
2.92
2.49
3.56
F
4500
4000
3500
3000
2500
2000
1500
1000
500
0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

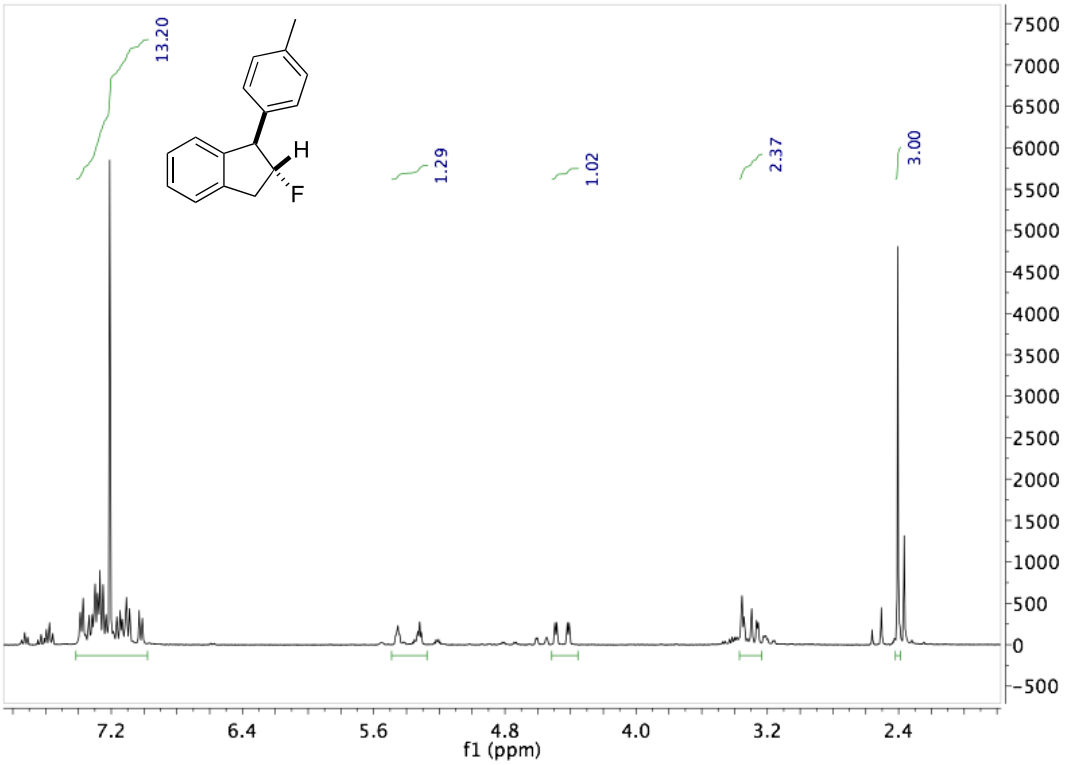

36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

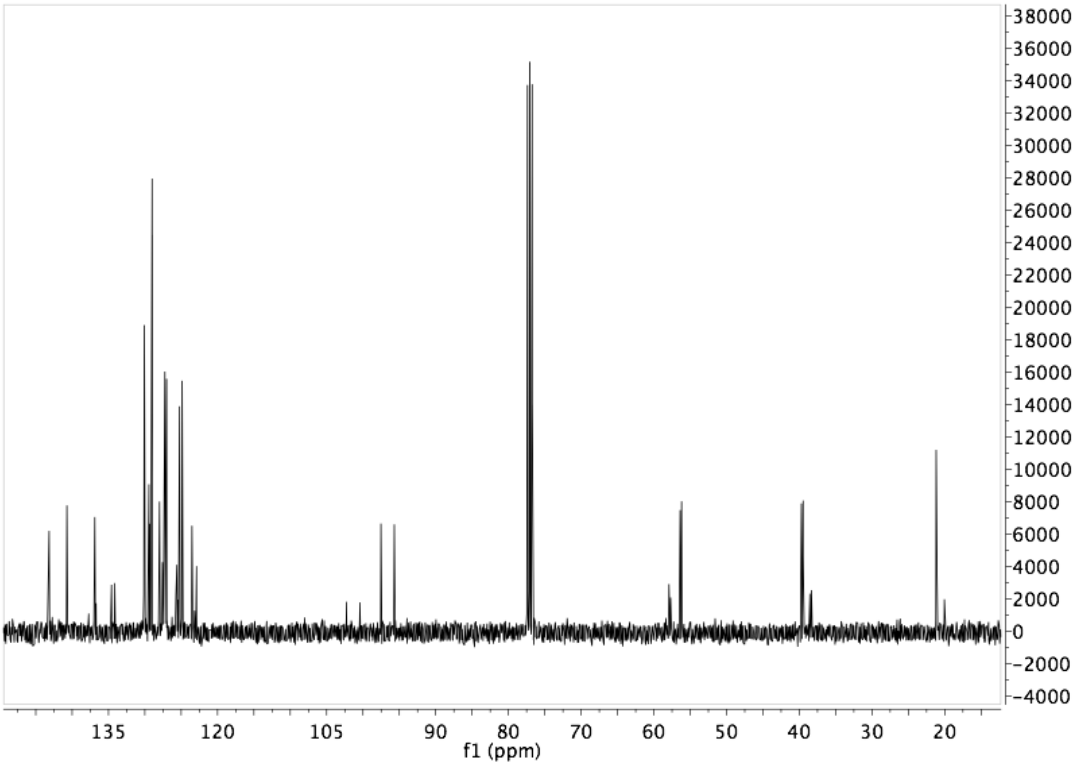

7E+06
6E+06
6E+06
6E+06
5E+06
4E+06
4E+06
4E+06
3E+06
2E+06
2E+06
2E+06
1E+06
5E+05
0
-5E+05
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

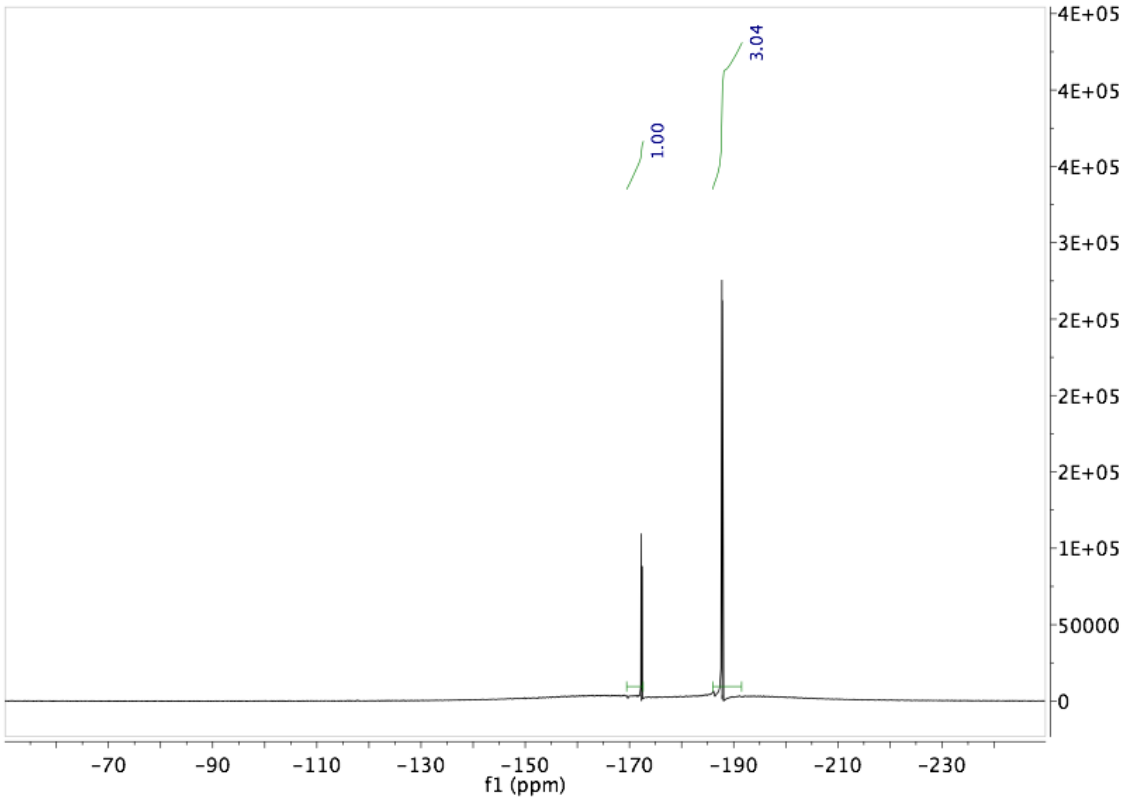

8.38
0.93
1.00
2.54
2.67
2.84
H
F
4000
3500
3000
2500
2000
1500
1000
500
0
7.0
6.2
5.4
4.6
3.8
3.0
2.2
f1 (ppm)

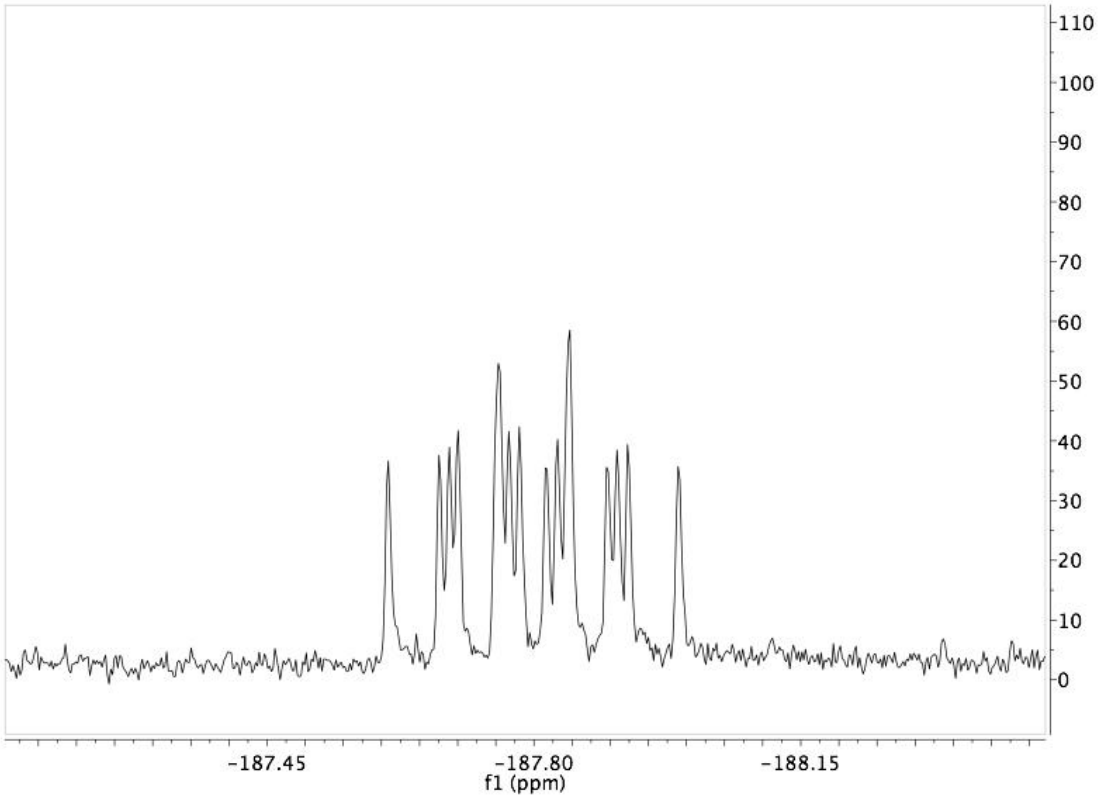

34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
135
120
105
90
80
70
60
50
40
30
20
f1 (ppm)

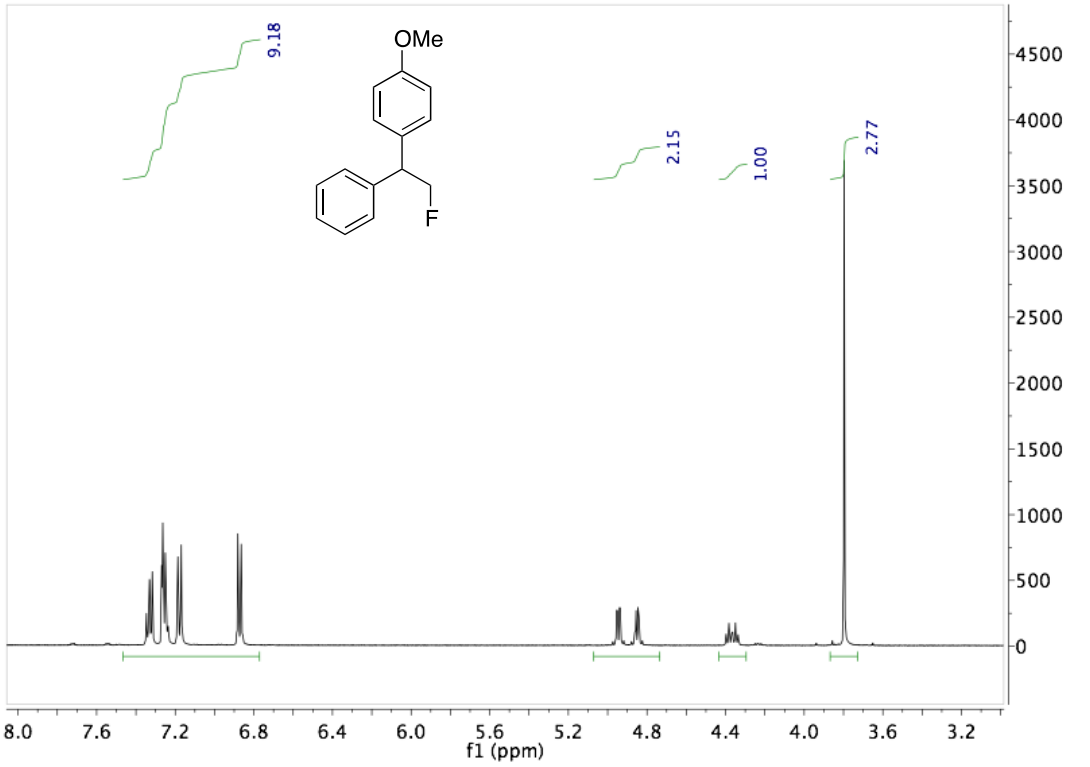

3.27
1.00
8E+05
7E+05
6E+05
6E+05
6E+05
5E+05
4E+05
4E+05
4E+05
4E+05
3E+05
2E+05
2E+05
2E+05
2E+05
1E+05
50000
0
-50000
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

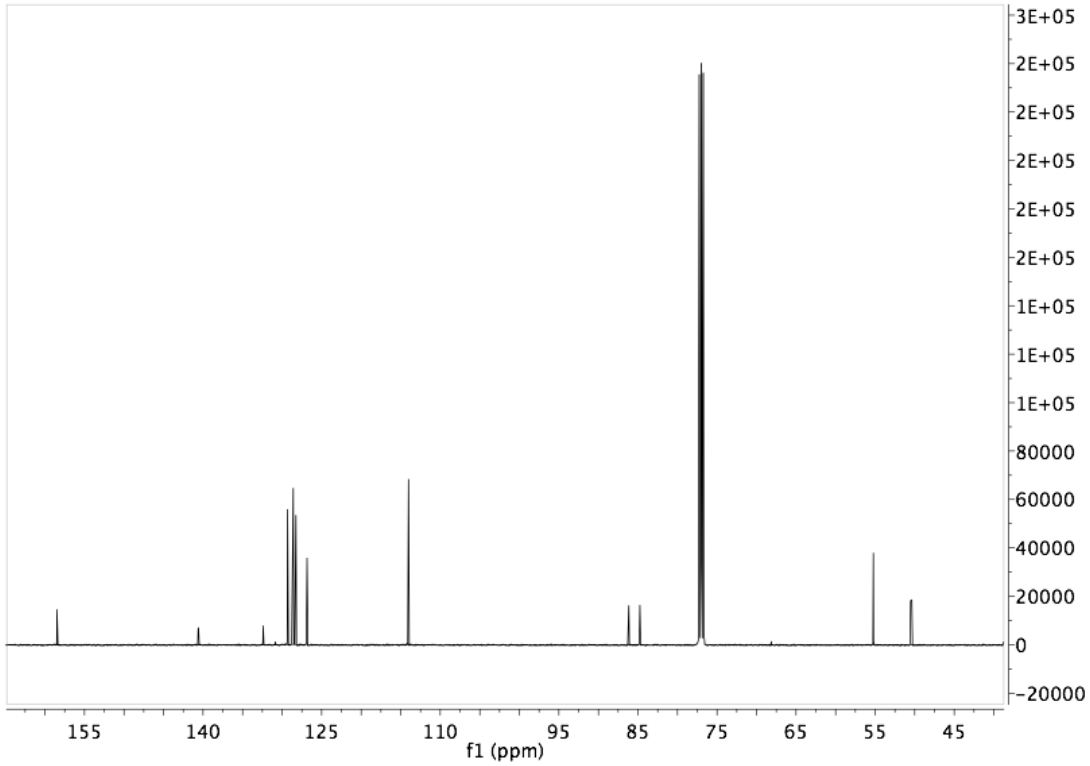

13.20
1.29
1.02
2.37
3.00
H
F
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
7.2
6.4
5.6
4.8
4.0
3.2
2.4
f1 (ppm)

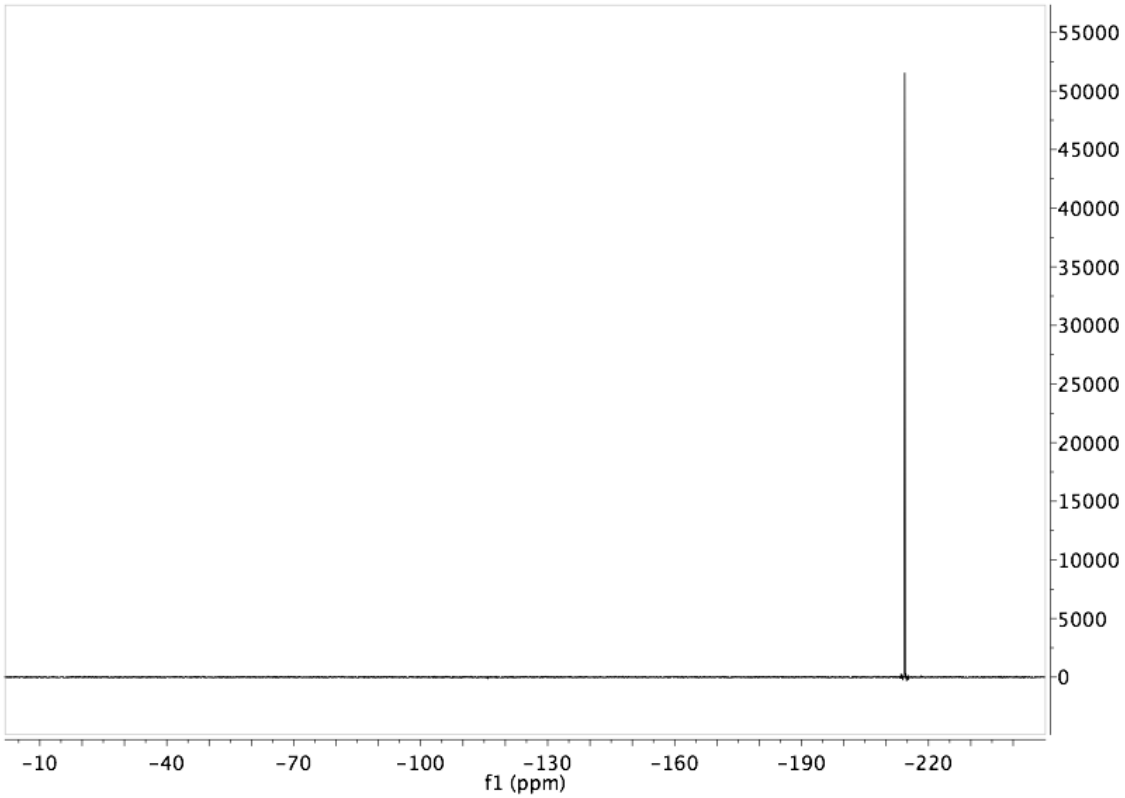

38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
135
120
105
90
80
70
60
50
40
30
20
f1 (ppm)

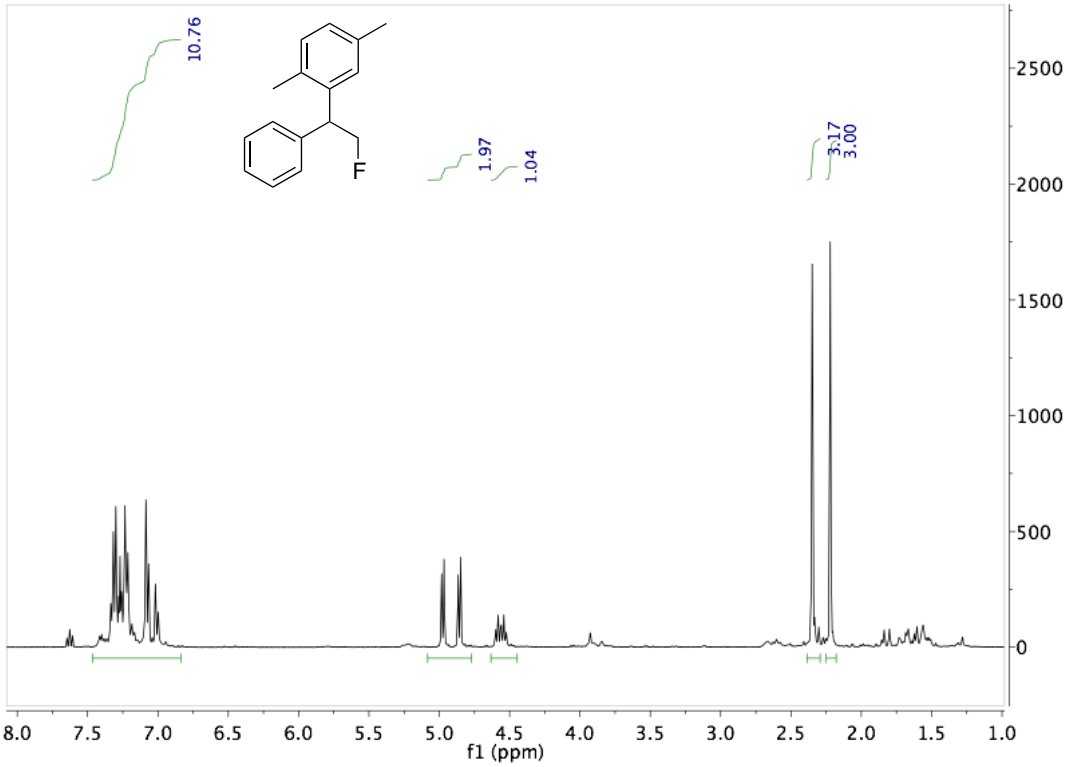

4E+05
4E+05
4E+05
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
1.00
3.04
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

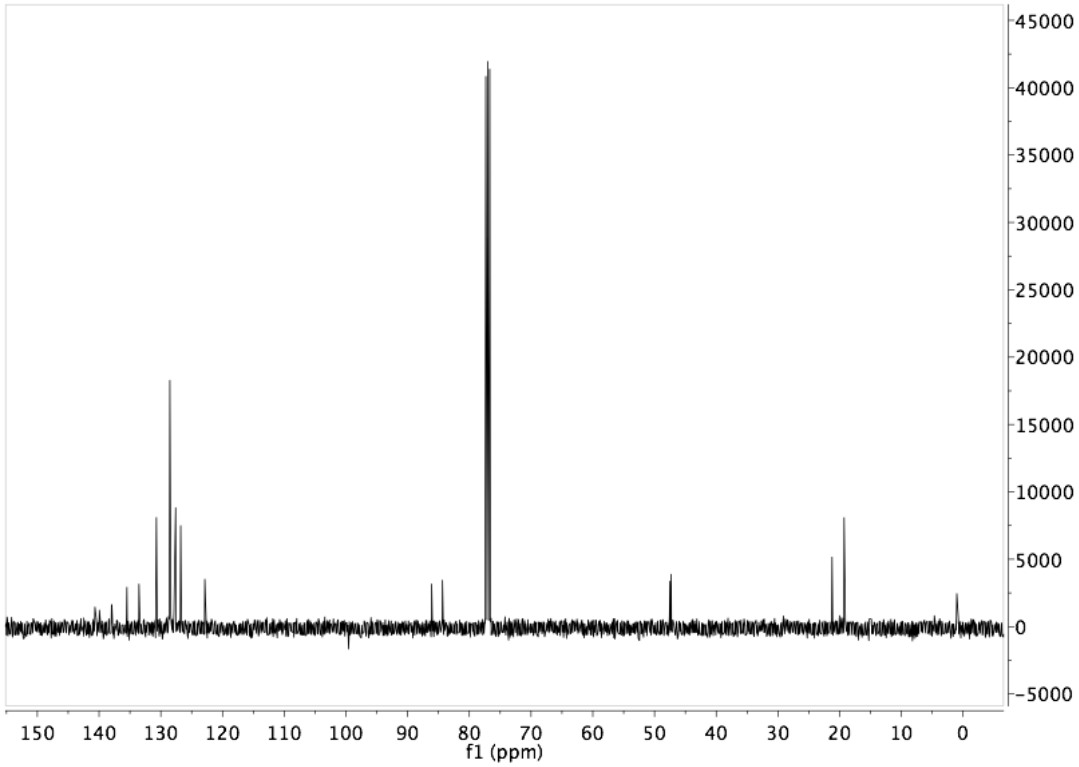

110
100
90
80
70
60
50
40
30
20
10
0
-187.45
-187.80
-188.15
f1 (ppm)

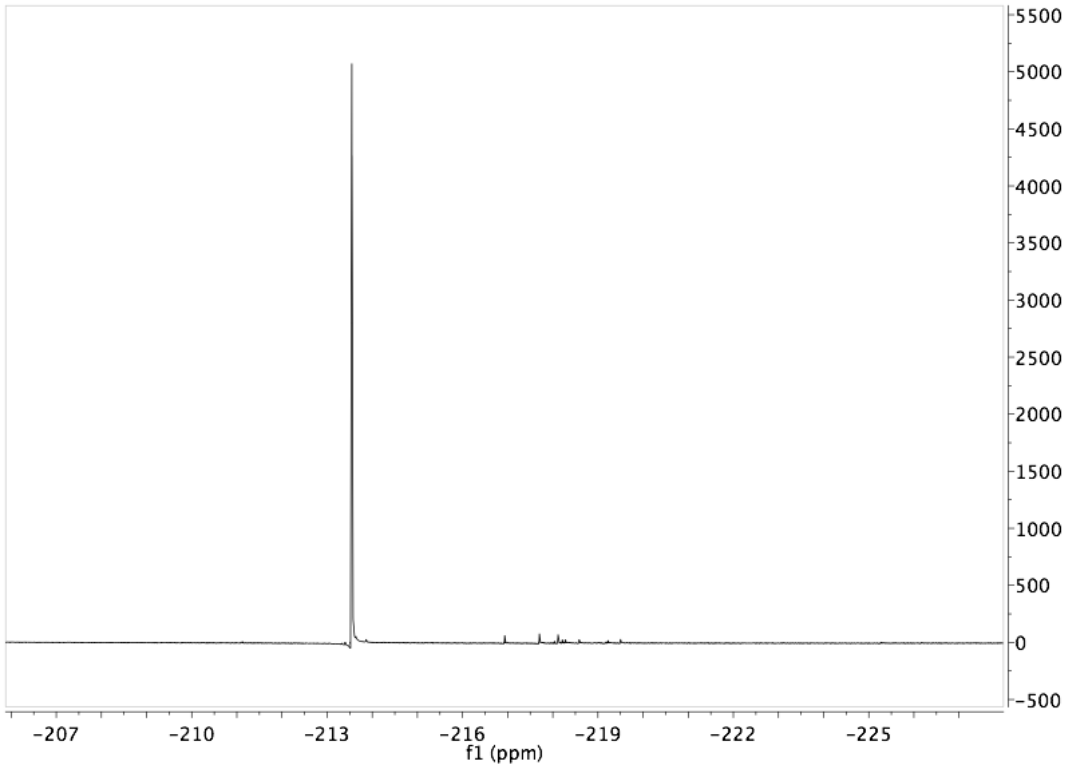

9.18
OMe
2.15
1.00
2.77
F
4500
4000
3500
3000
2500
2000
1500
1000
500
0
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
f1 (ppm)

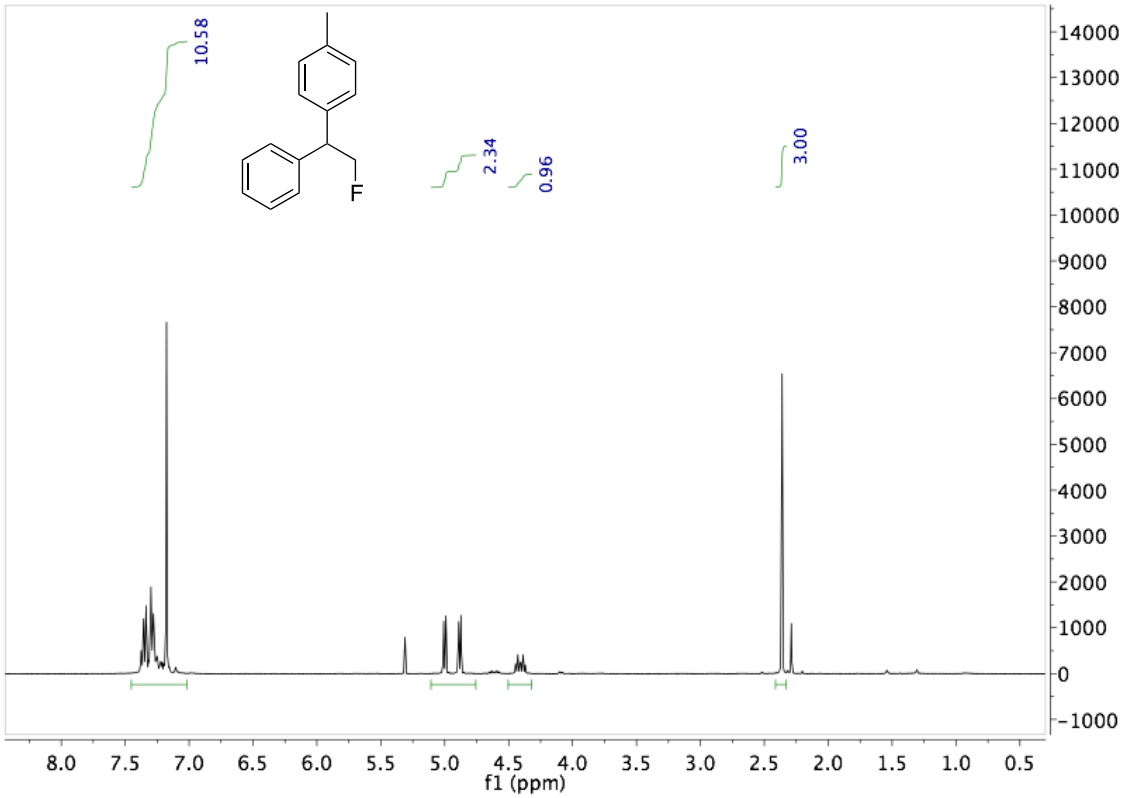

3E+05
2E+05
2E+05
2E+05
2E+05
2E+05
2E+05
1E+05
1E+05
1E+05
80000
60000
40000
20000
0
-20000
155
140
125
110
95
85
75
65
55
45
f1 (ppm)

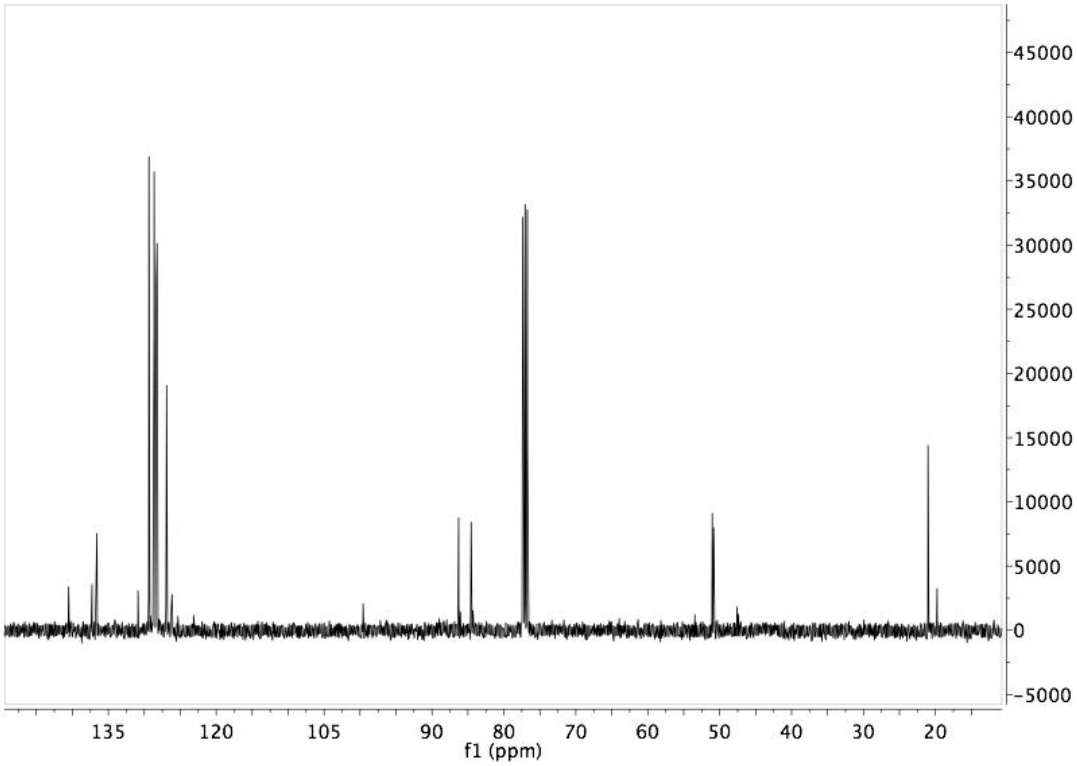

55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-10
-40
-70
-100
-130
-160
-190
-220
f1 (ppm)

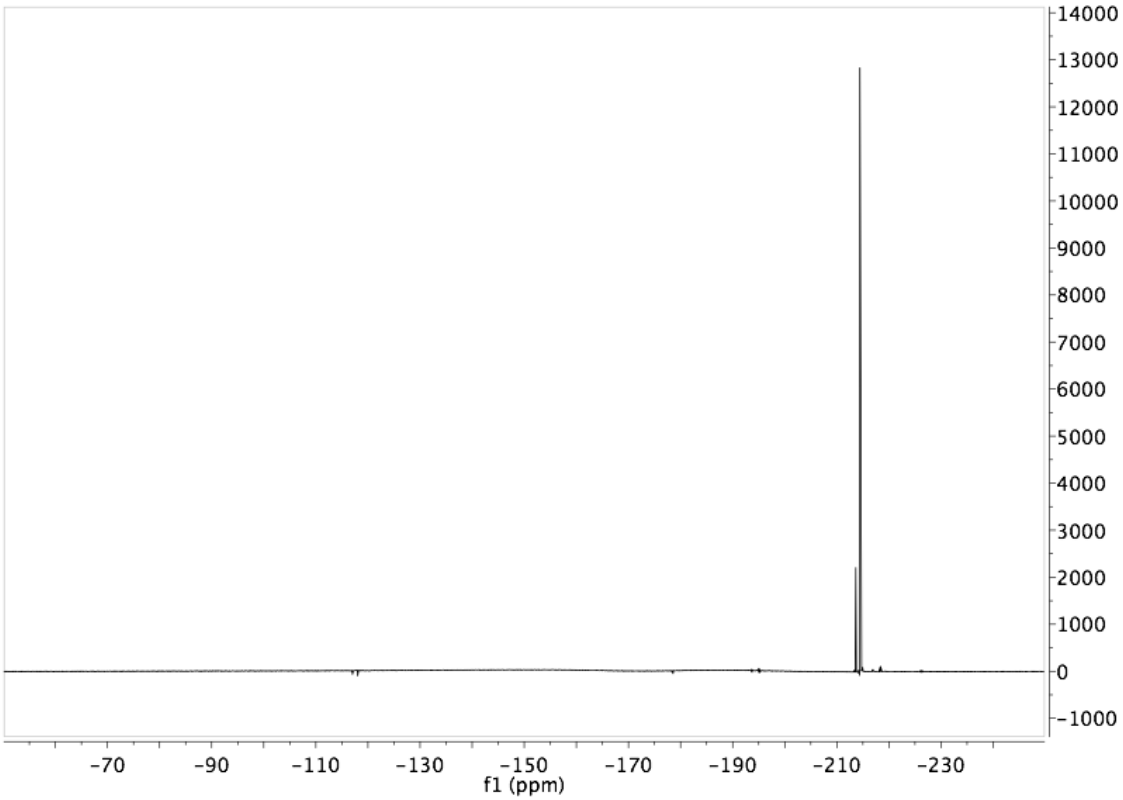

10.76
1.97
1.04
3.17
3.00
F
2500
2000
1500
1000
500
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

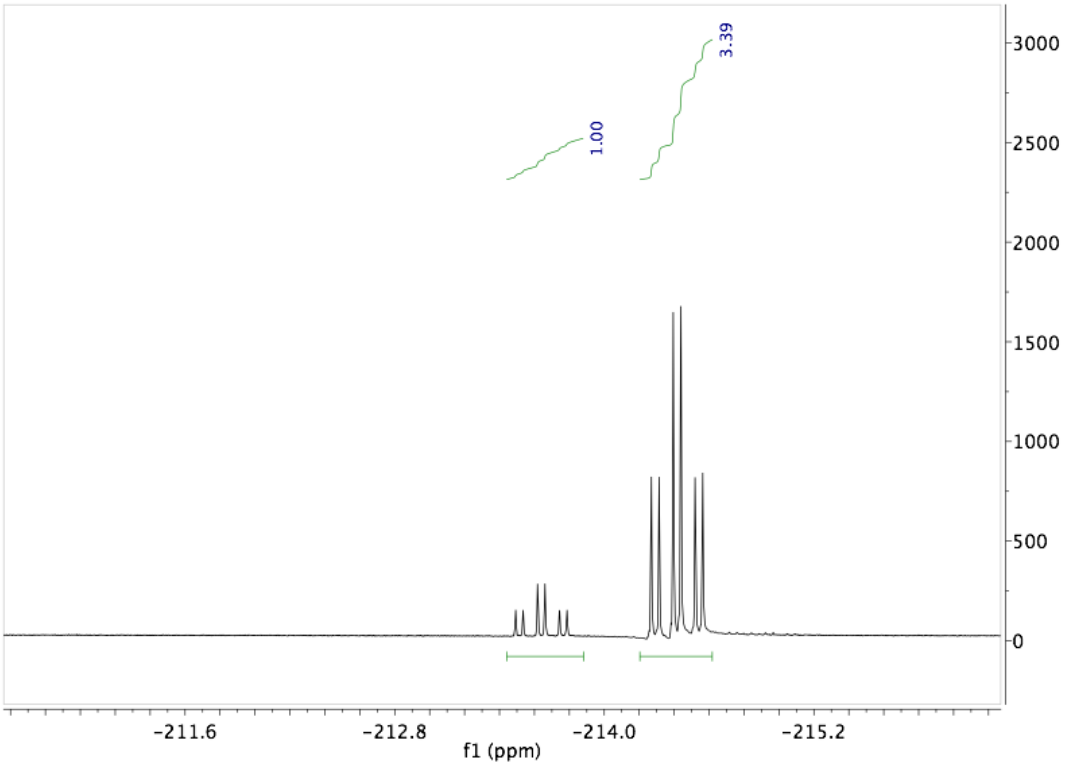

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

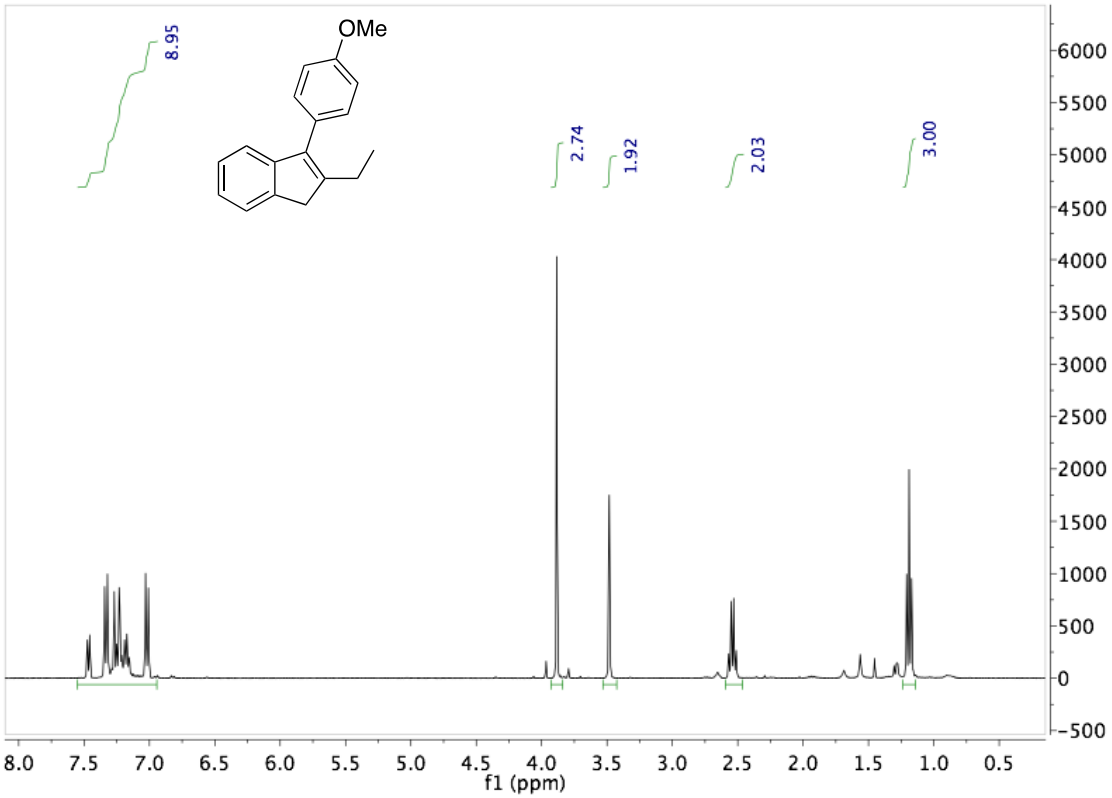

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-207 -210 -213 -216 -219 -222 -225
f1 (ppm)

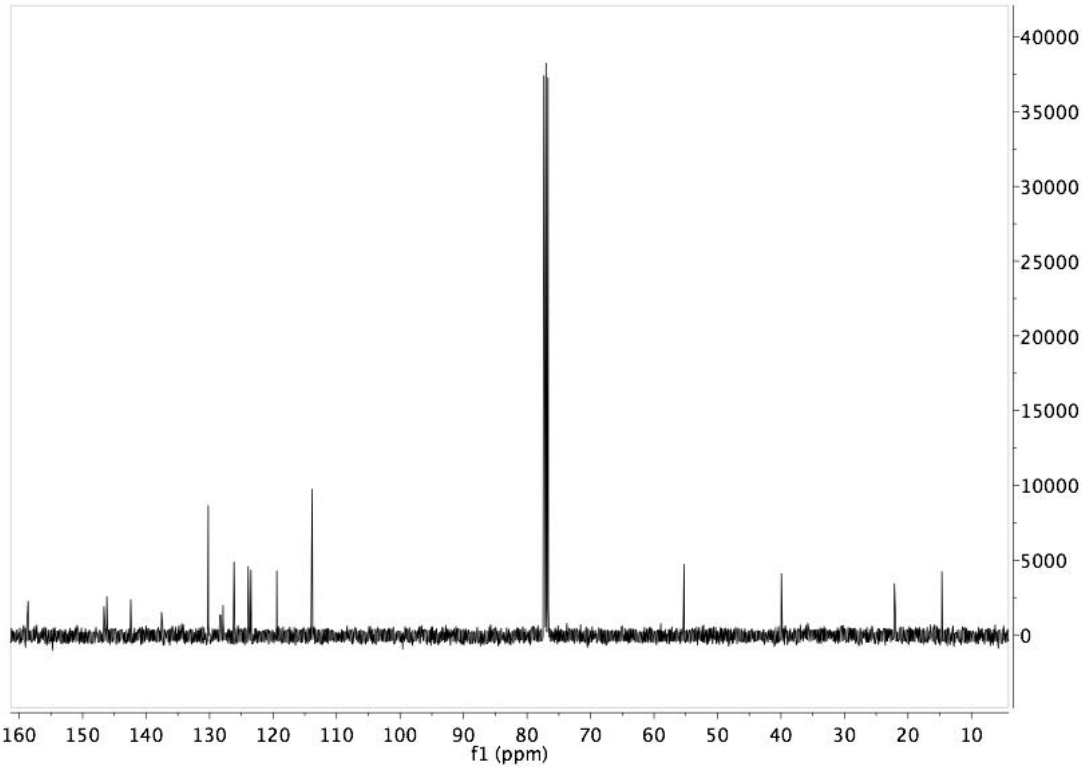

10.58
2.34
0.96
3.00
F
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

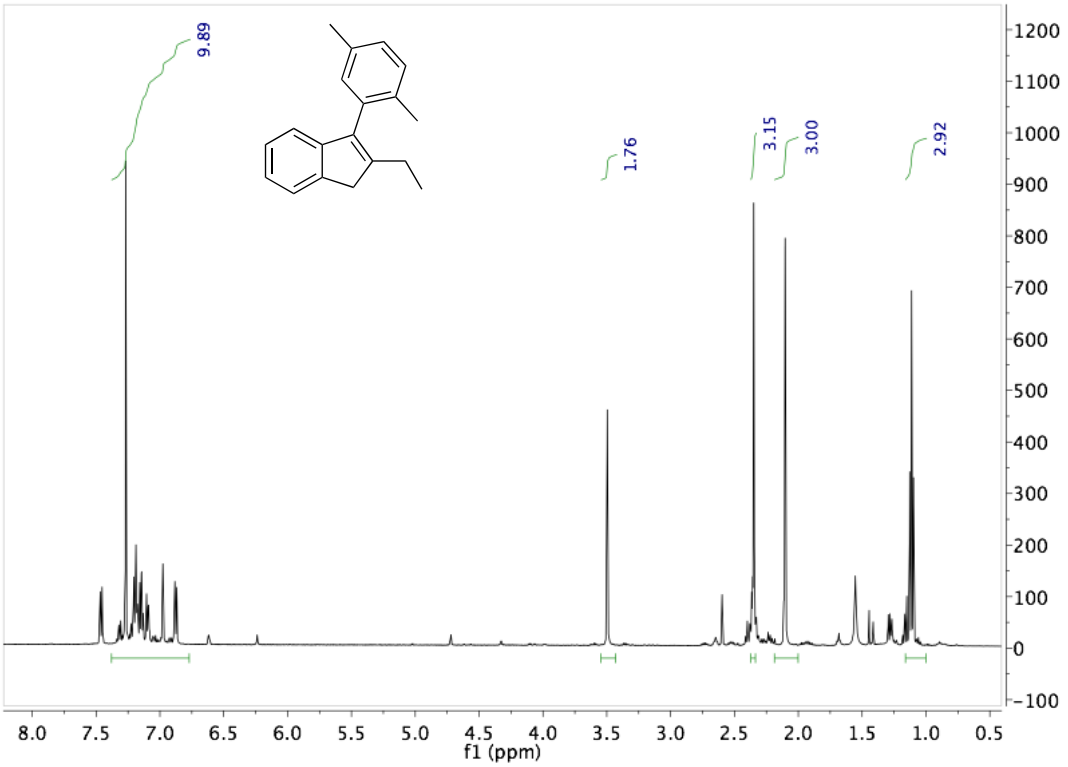

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
135 120 105 90 80 70 60 50 40 30 20
f1 (ppm)

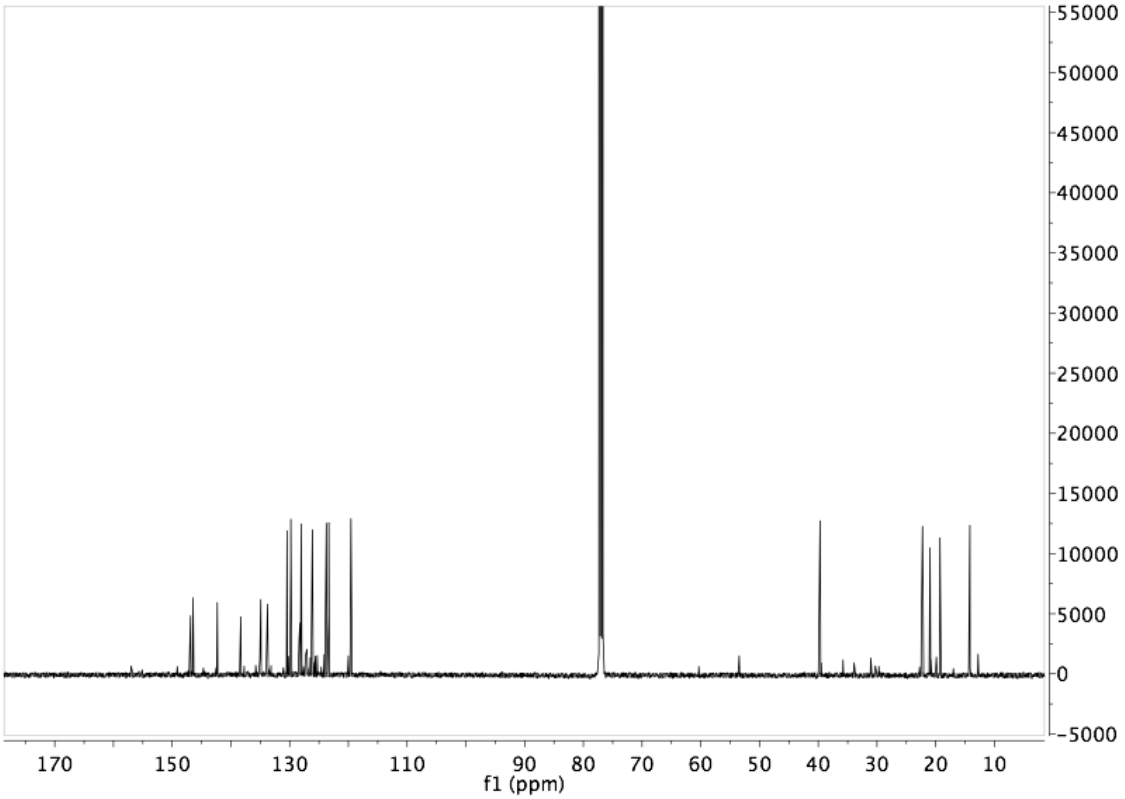

14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

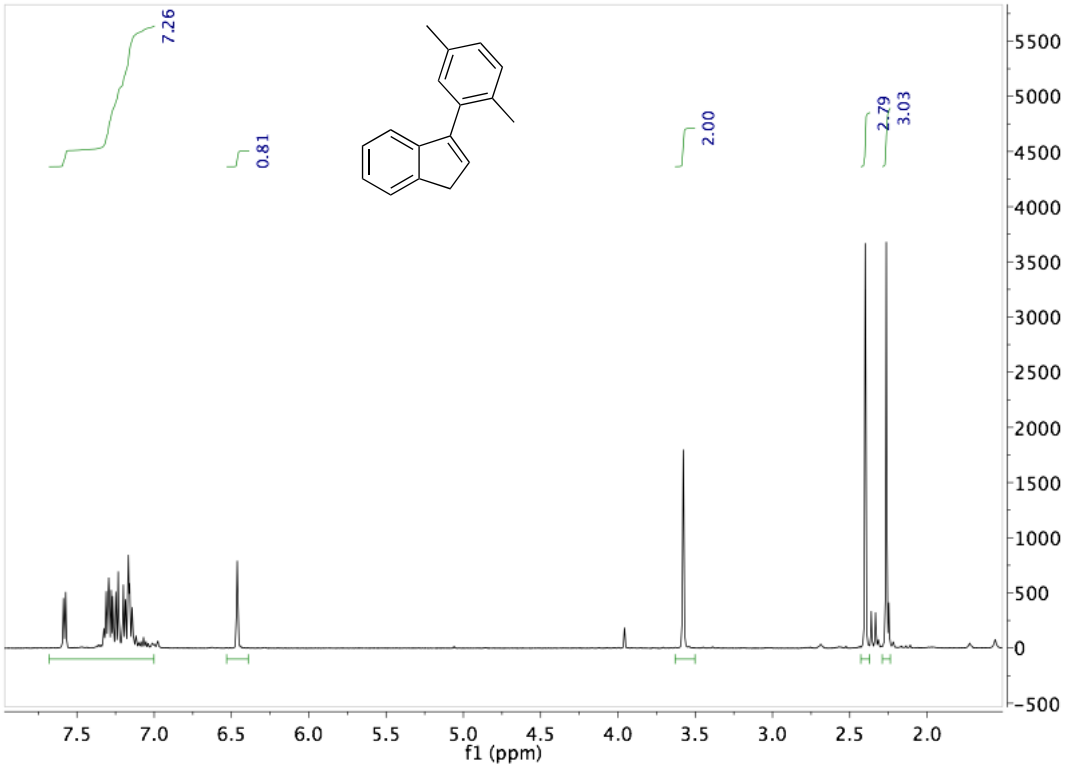

3.39
1.00
3000
2500
2000
1500
1000
500
0
-211.6
-212.8
-214.0
-215.2
f1 (ppm)

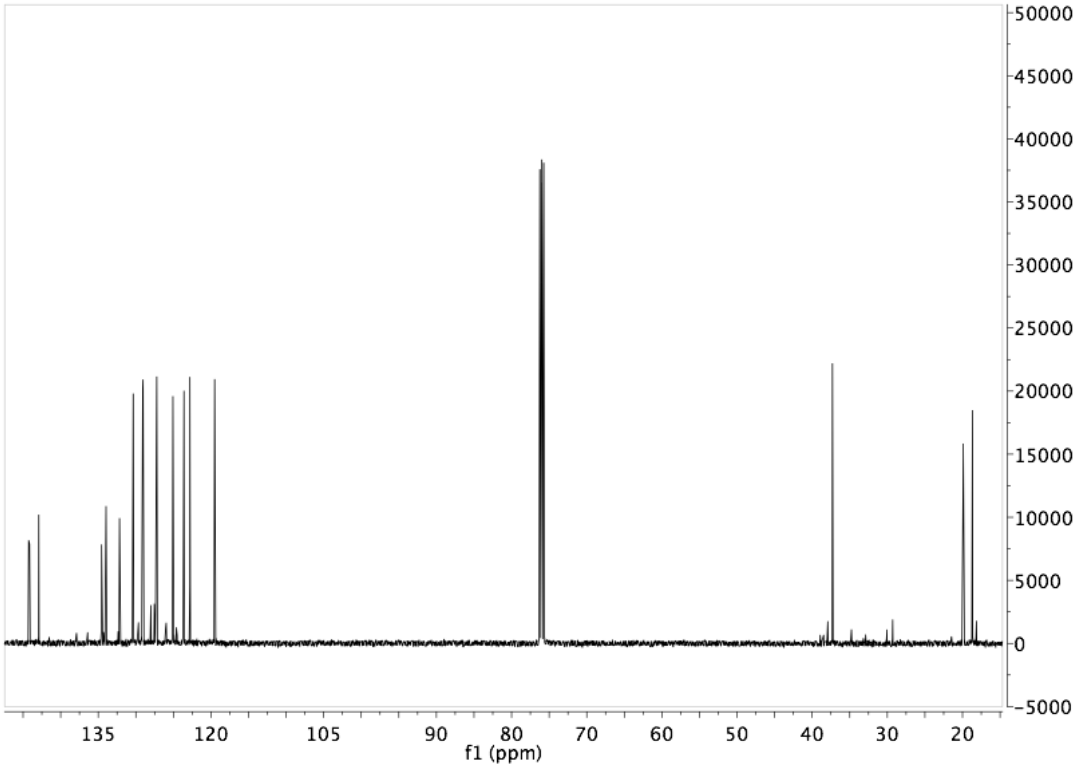

OMe
8.95
2.74
1.92
2.03
3.00
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

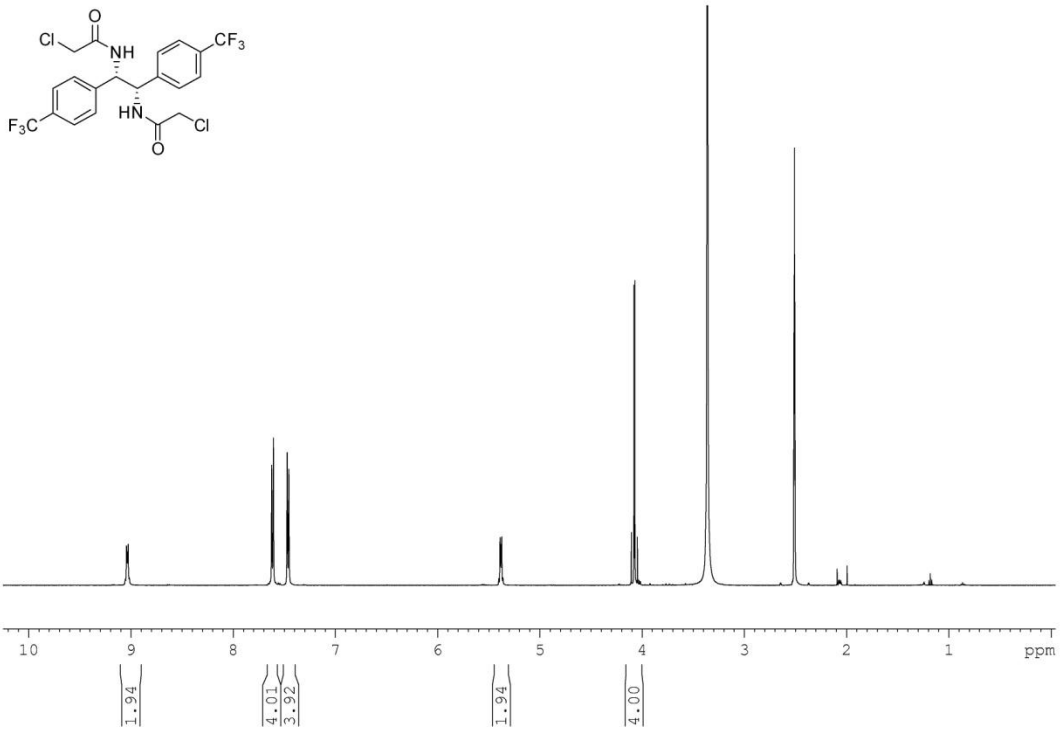

40000
35000
30000
25000
20000
15000
10000
5000
0
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

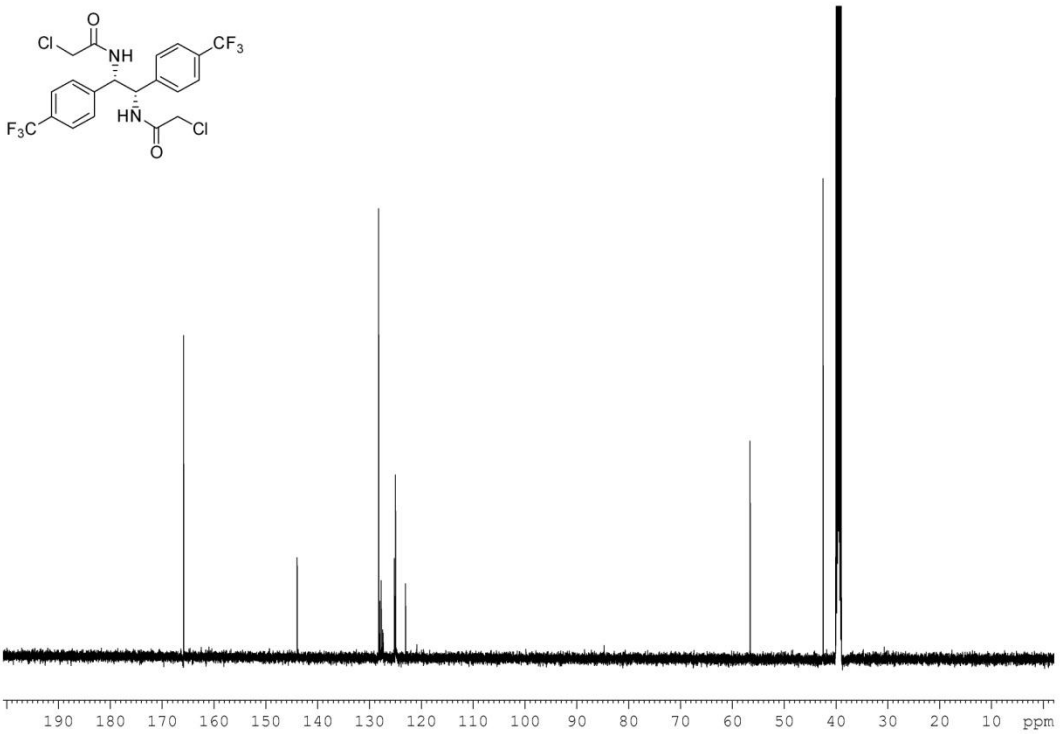

9.89
1.76
3.15
3.00
2.92
f1 (ppm)

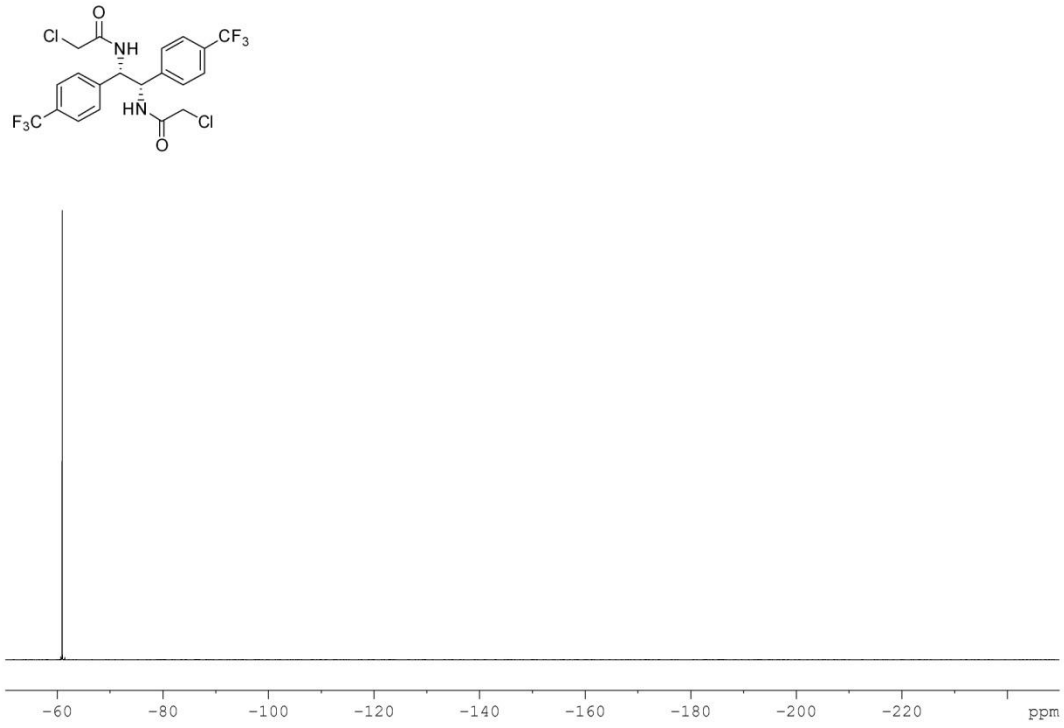

f1 (ppm)

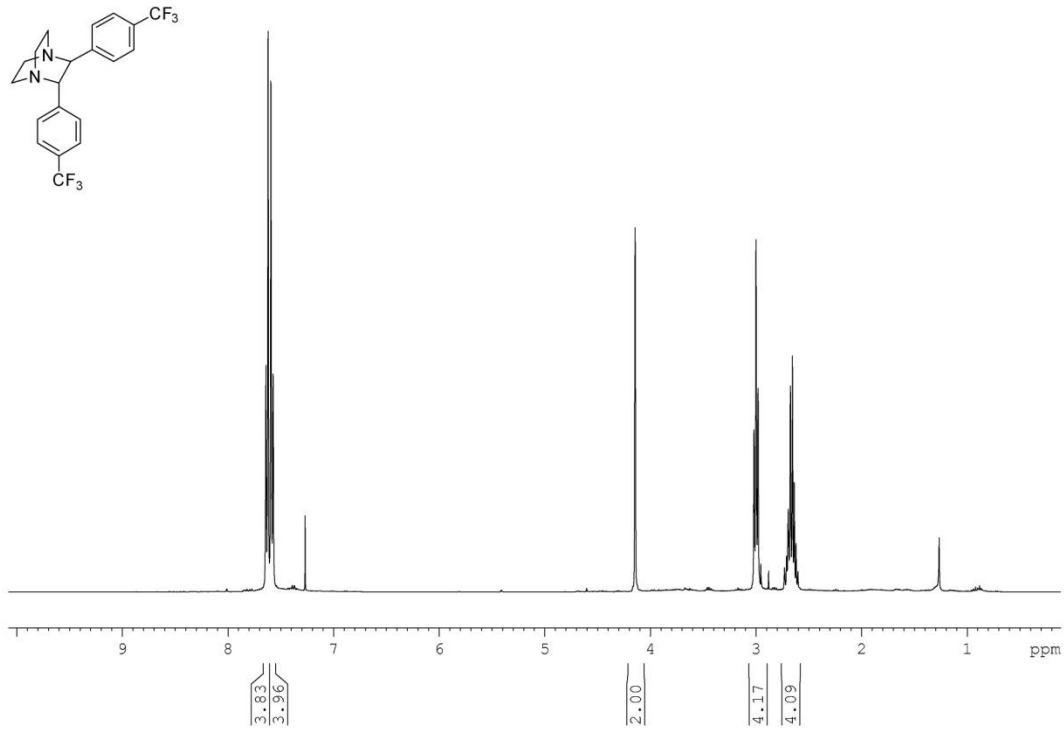

7.26
0.81
2.00
2.79
3.03
f1 (ppm)

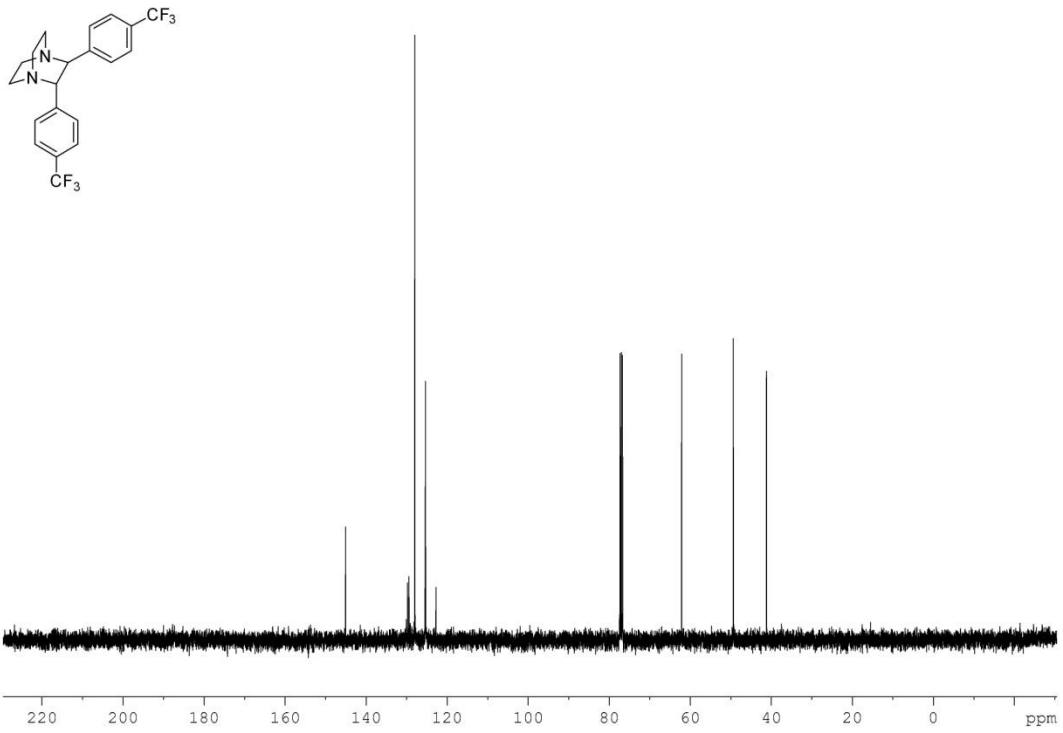

f1 (ppm)

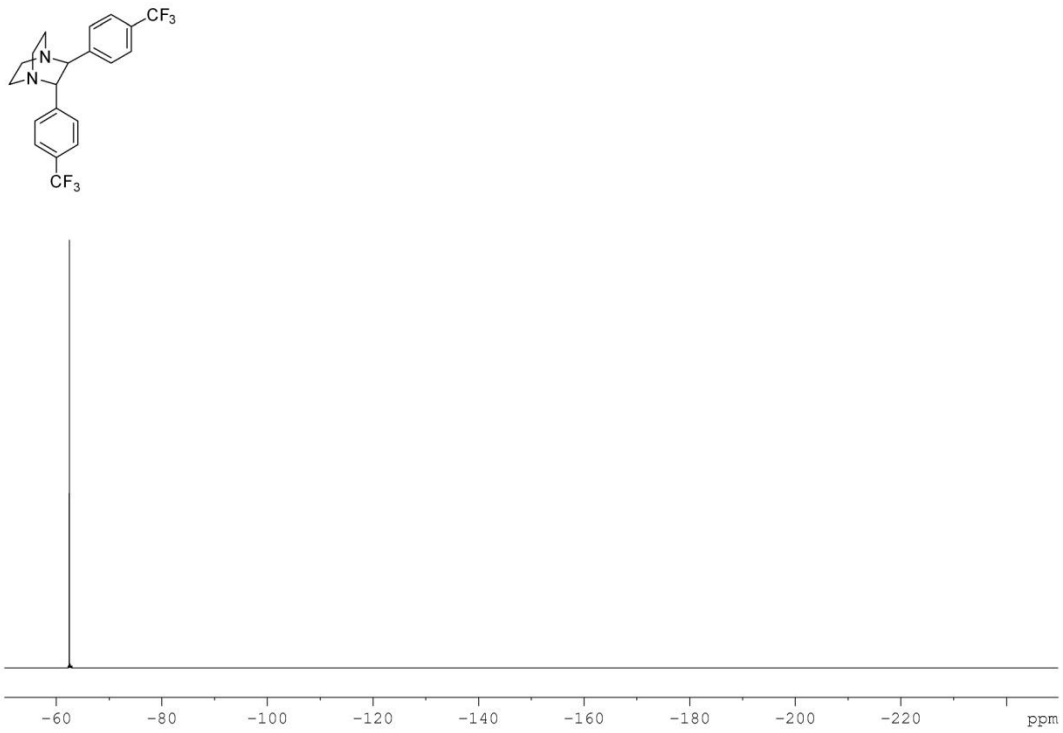

Cl
O
NH
CF3
F3C
HN
Cl
O
10
9
8
7
6
5
4
3
2
1
ppm
1.94
4.01
3.92
1.94
4.00

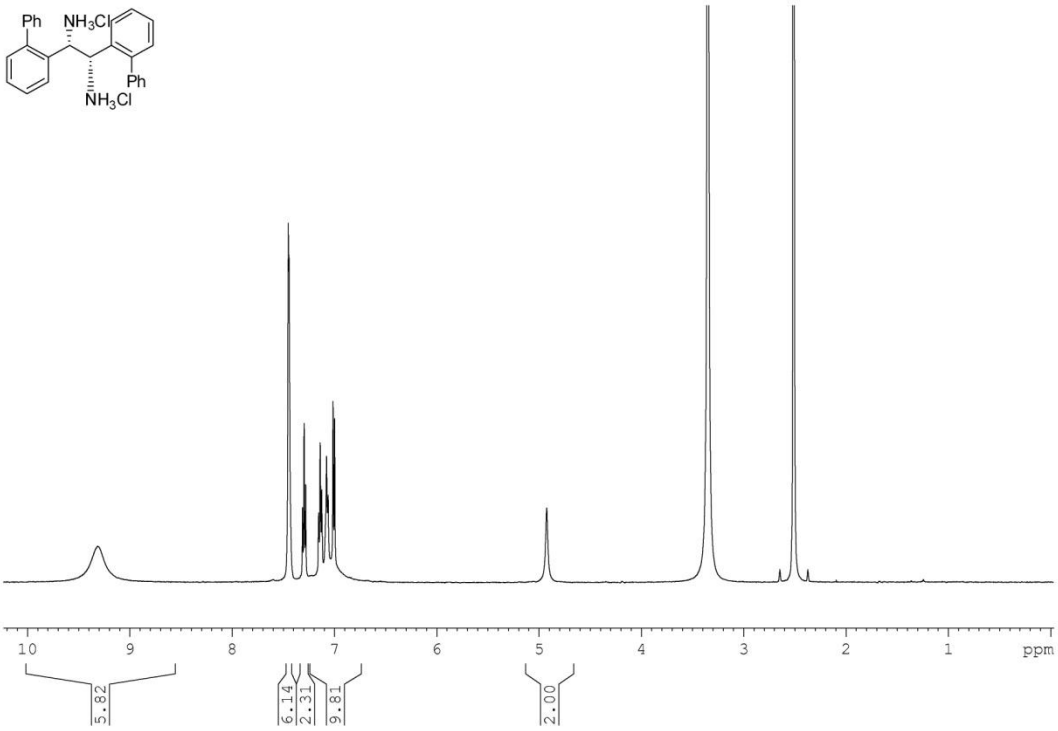

Cl
O
NH
CF3
F3C
HN
Cl
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

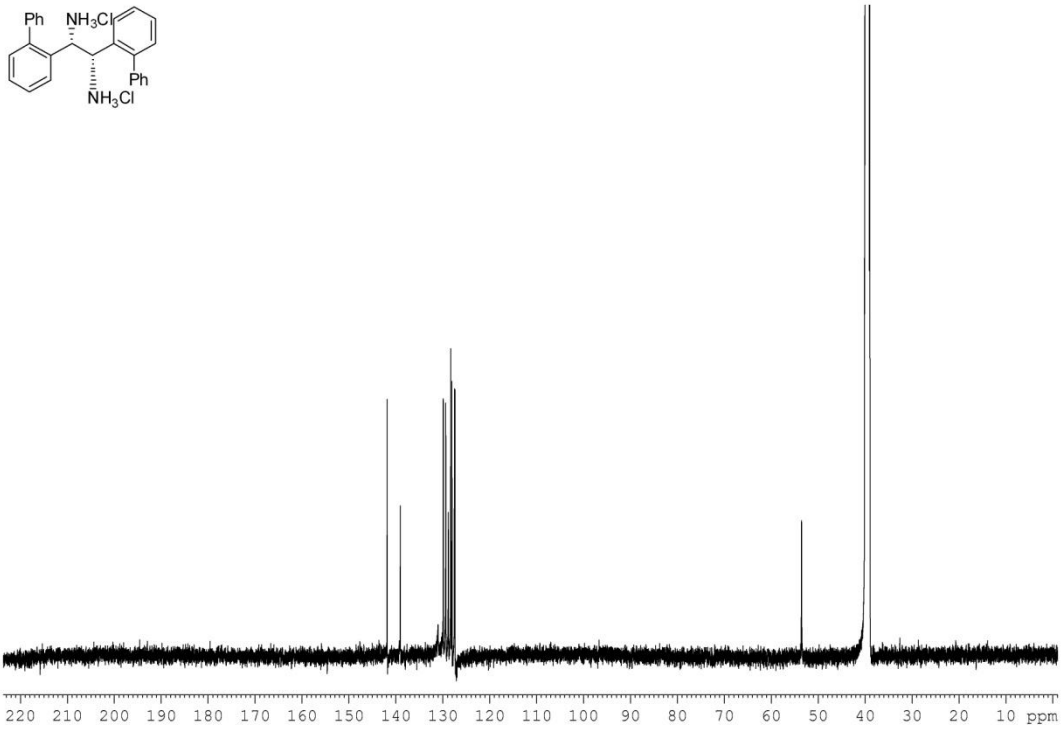

Cl
O
NH
CF3
F3C
HN
Cl
O
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

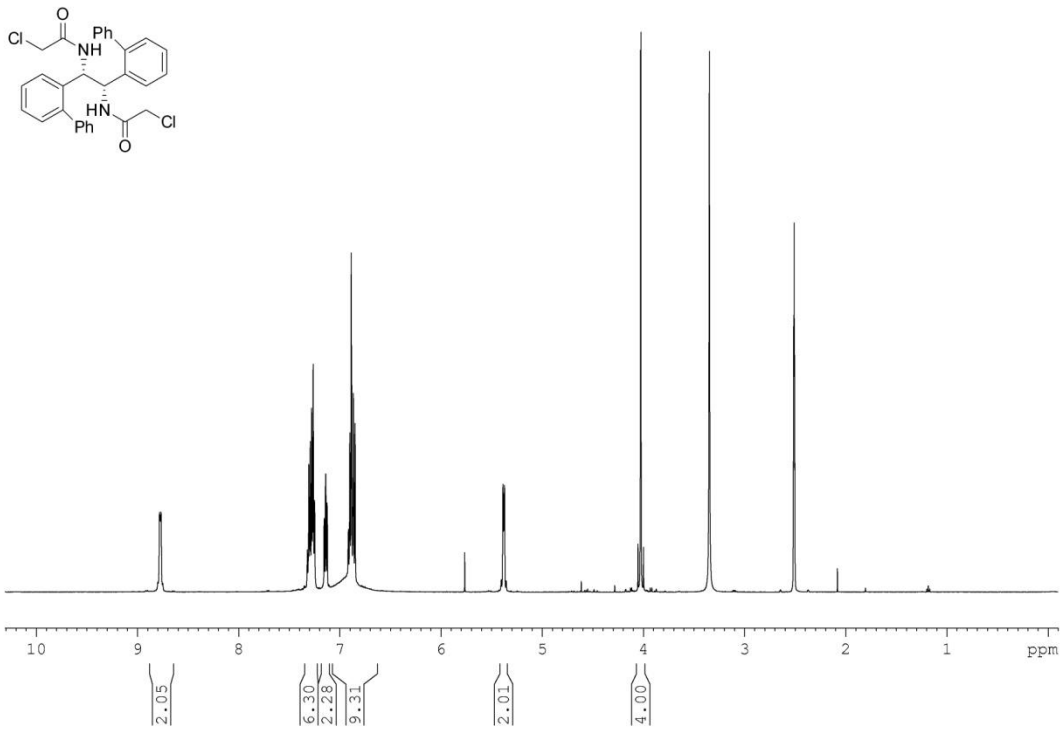

CF3
N
N
CF3
9
8
7
6
5
4
3
2
1
ppm
3.83
3.96
2.00
4.17
4.09

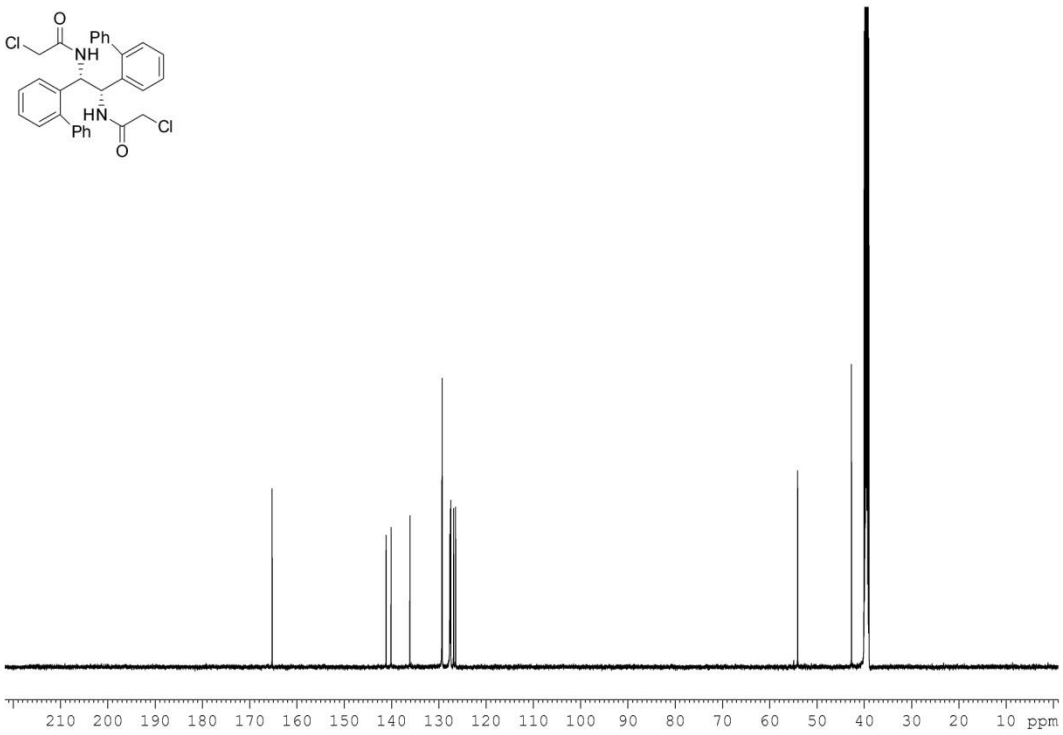

CF3
N
N
CF3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

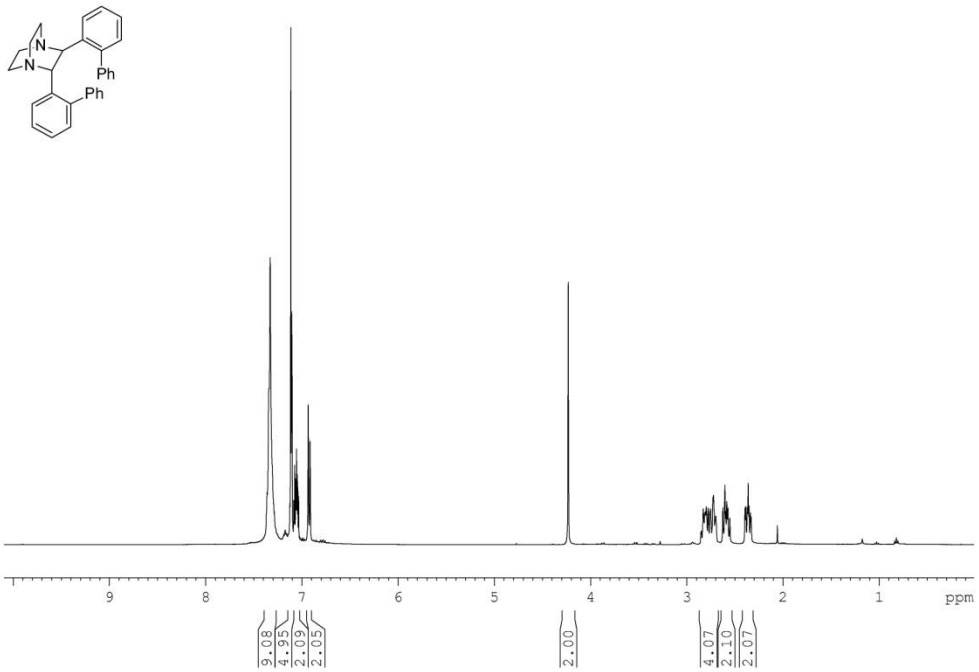

CF3
N
N
CF3
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

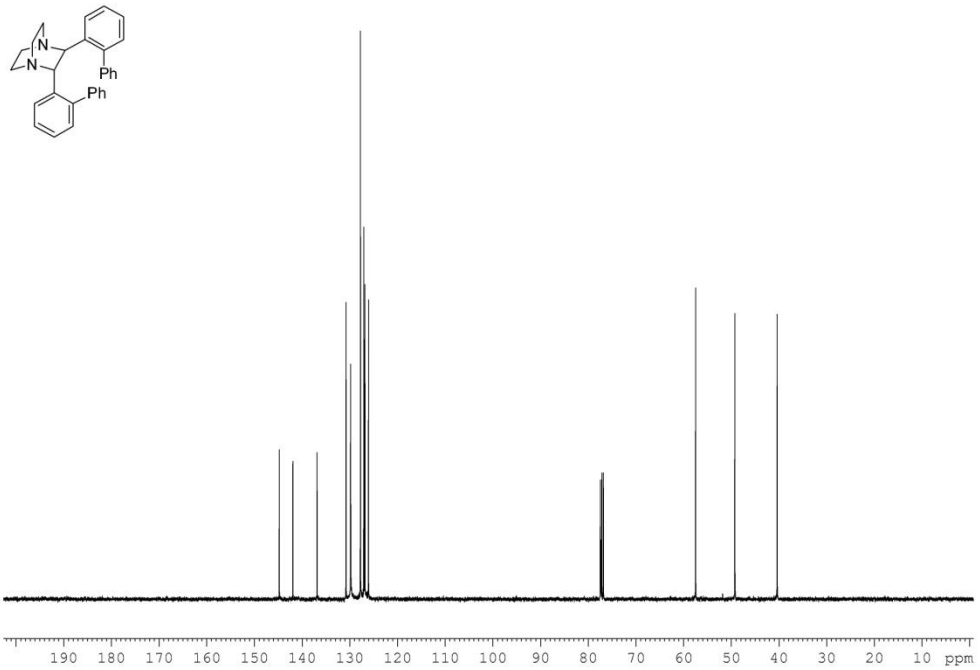

Ph
NH3Cl
Ph
NH3Cl
10
9
8
7
6
5
4
3
2
1
ppm
5.82
6.14
2.31
9.81
2.00

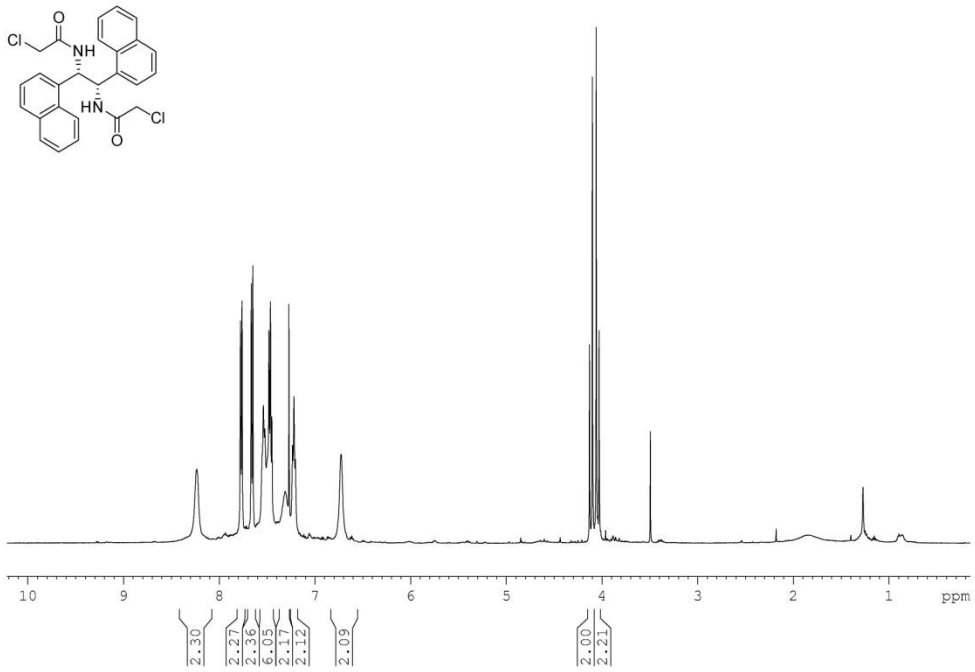

Ph
NH3Cl
Ph
NH3Cl
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

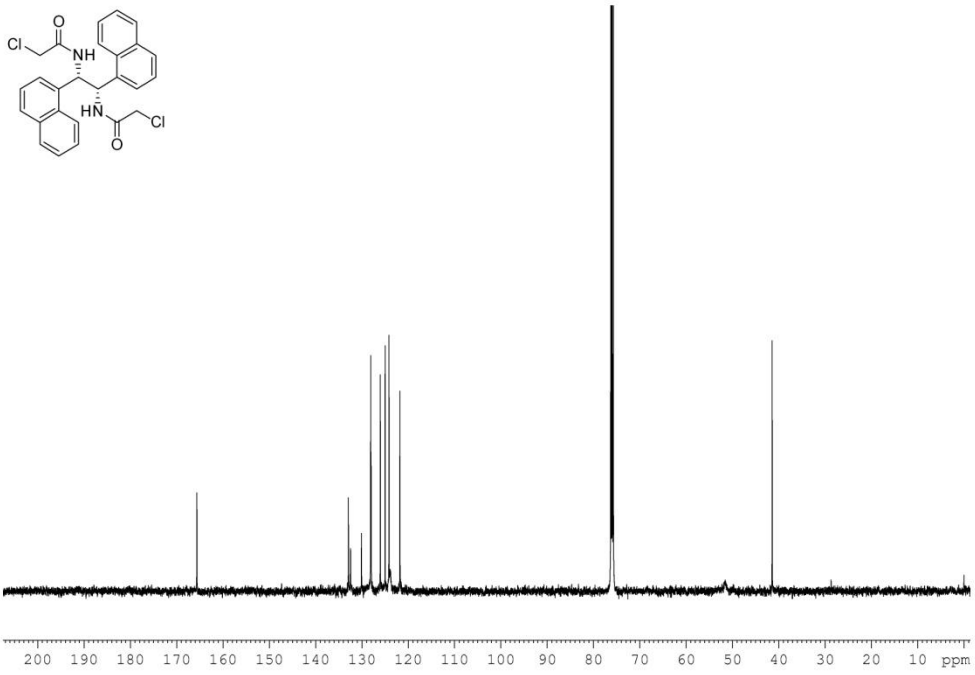

O
Cl
Ph
NH
HN
Cl
Ph
O
10
9
8
7
6
5
4
3
2
1
ppm
2.05
6.30
2.28
9.31
2.01
4.00

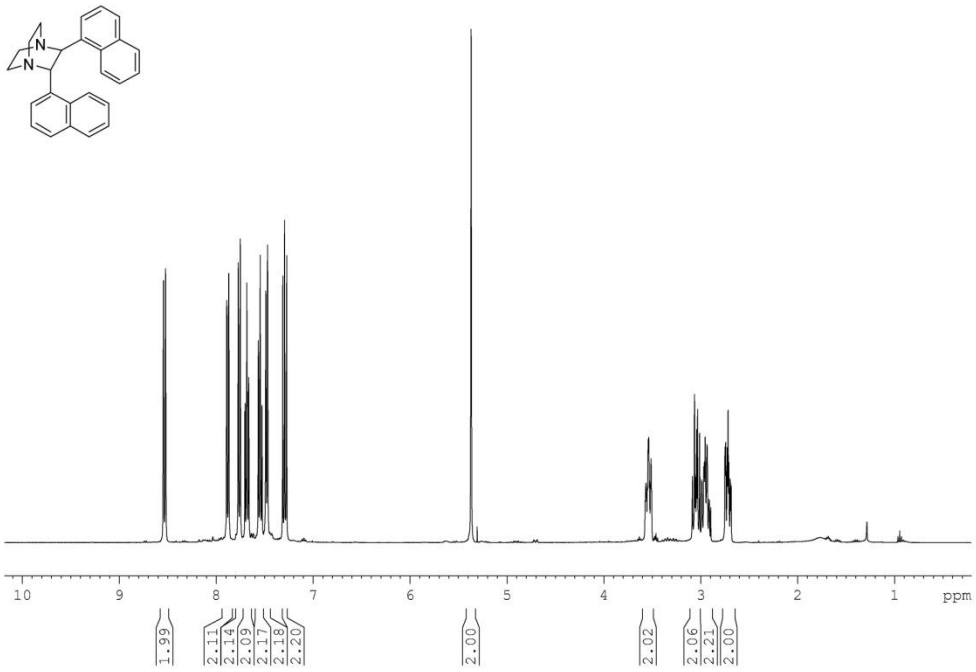

O
Cl
Ph
NH
HN
Cl
Ph
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

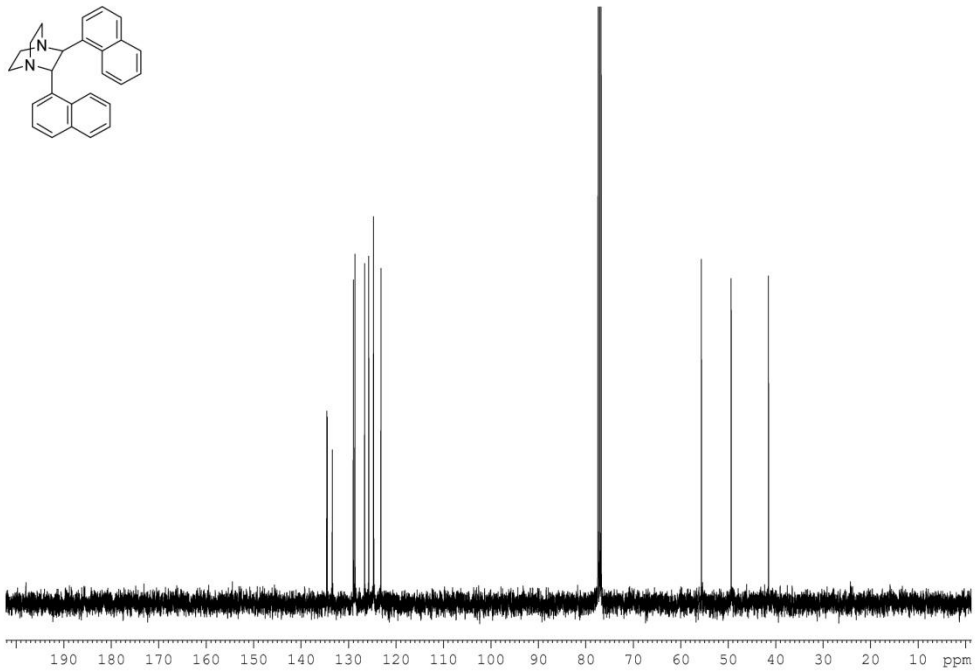

N
N
Ph
Ph
9
8
7
6
5
4
3
2
1
ppm
9.08
4.95
2.09
2.05
2.00
4.07
2.10
2.07

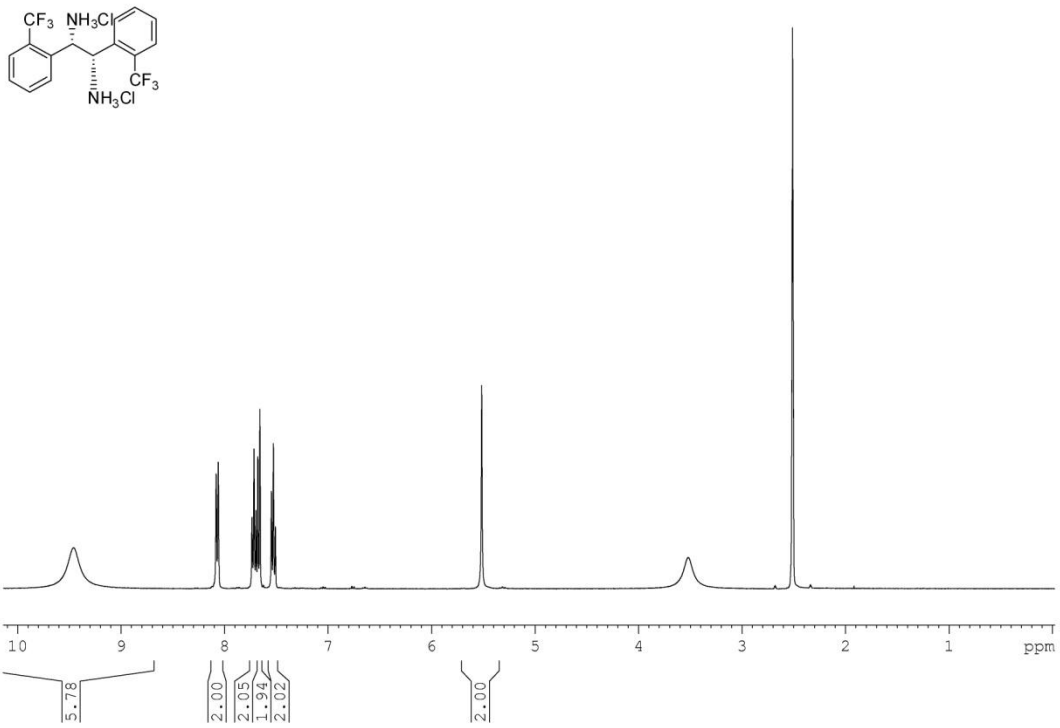

N
N
Ph
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

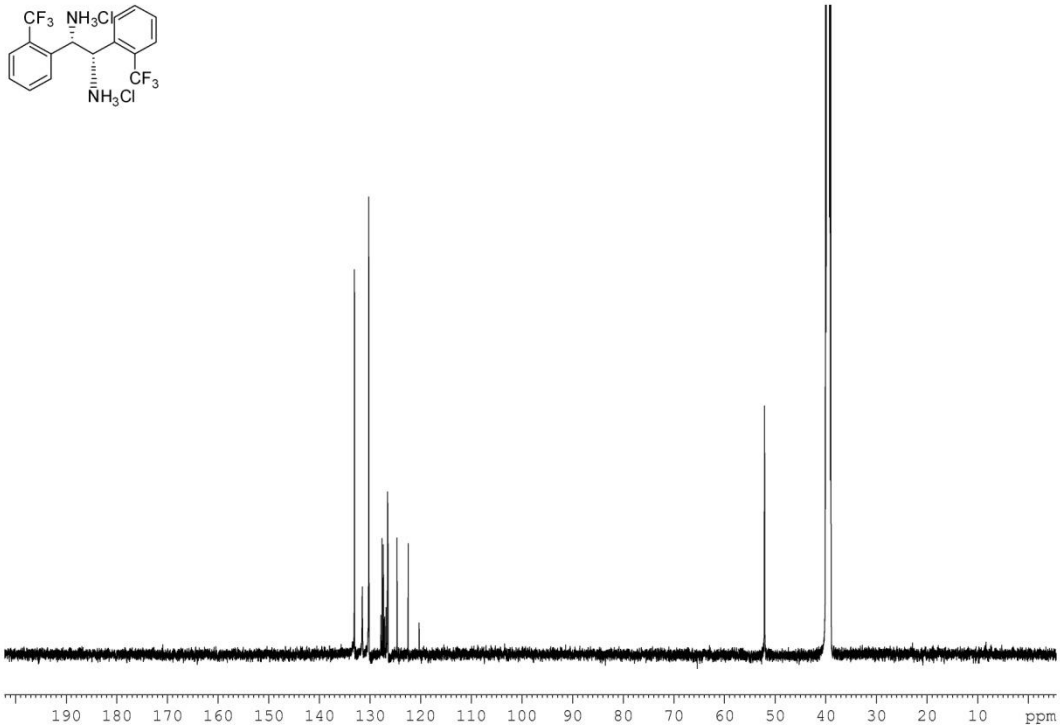

Cl
O
NH
HN
Cl
O
10 9 8 7 6 5 4 3 2 1 ppm
2.30
2.27
2.36
6.05
2.17
2.12
2.09
2.00
2.21

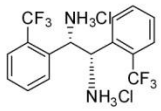

Cl
O
NH
HN
Cl
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

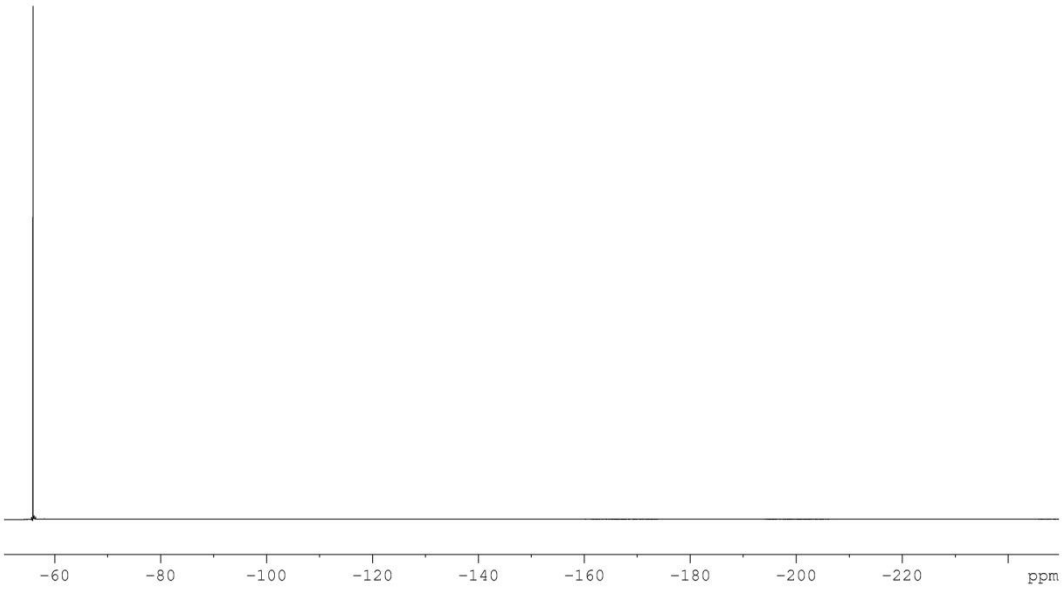

10
9
8
7
6
5
4
3
2
1
ppm
1.99
2.11
2.14
2.09
2.17
2.18
2.20
2.00
2.02
2.06
2.21
2.00


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

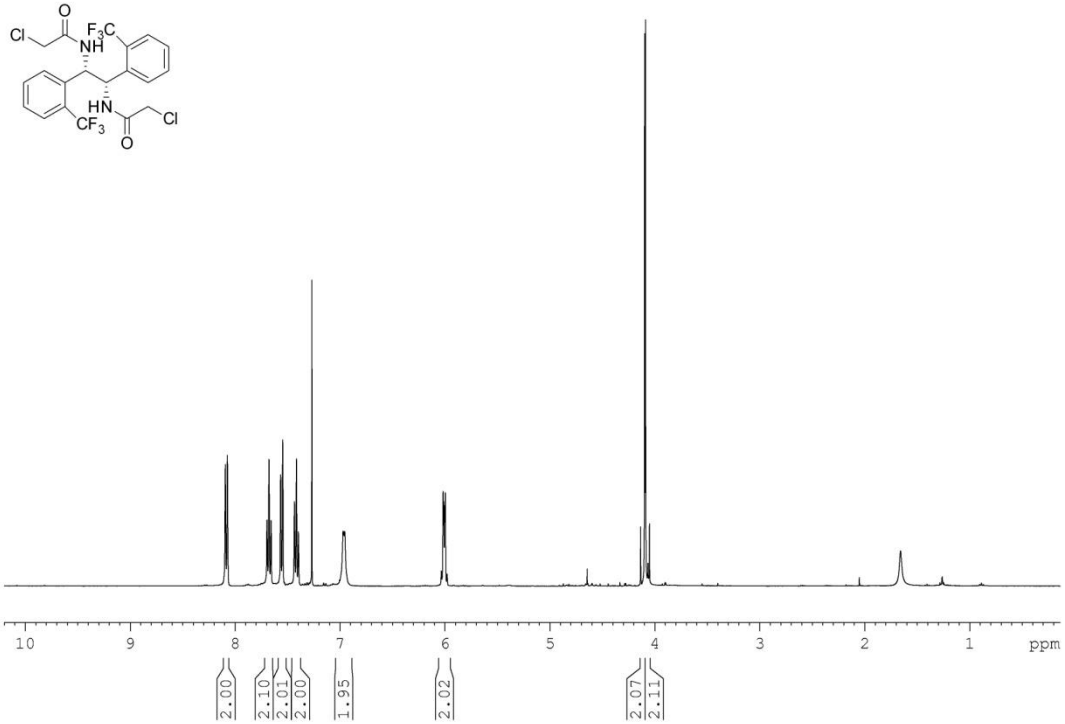

CF3
NH3Cl
CF3
NH3Cl
10
9
8
7
6
5
4
3
2
1
ppm
5.78
2.00
2.05
1.94
2.02
2.00

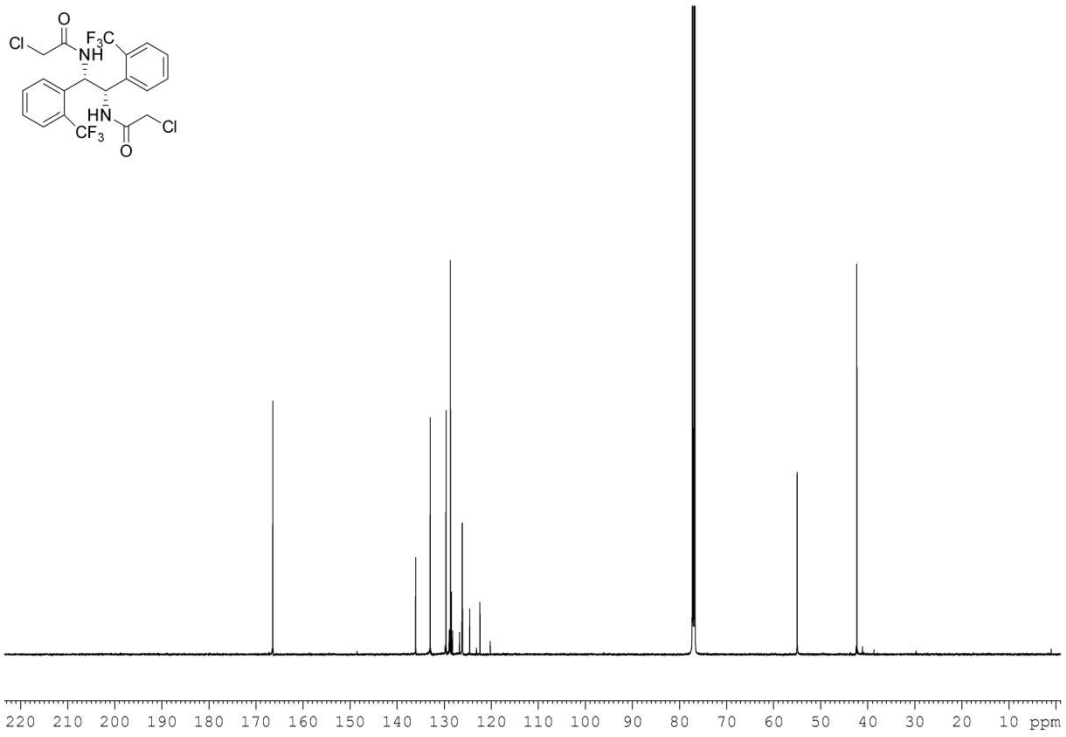

CF3
NH3Cl
CF3
NH3Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

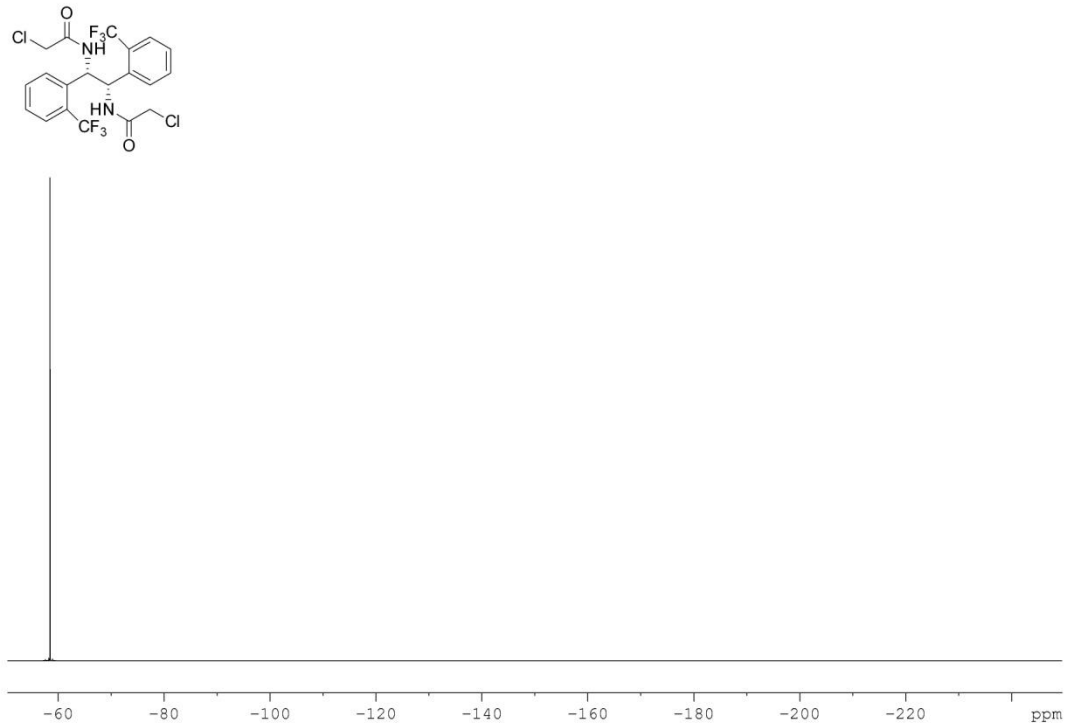

CF3
NH3Cl
CF3
NH3Cl

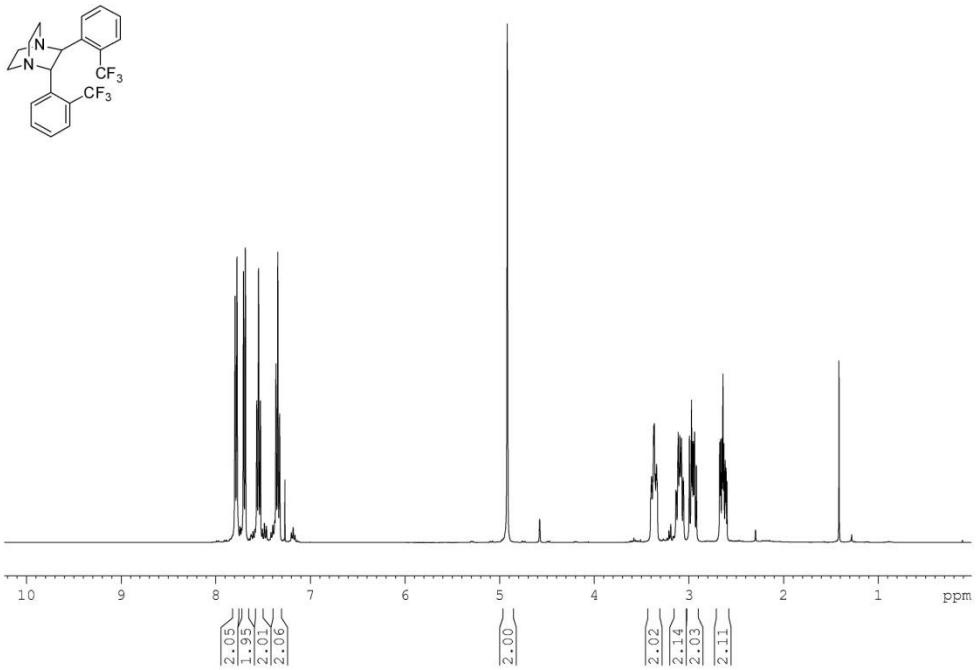

-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

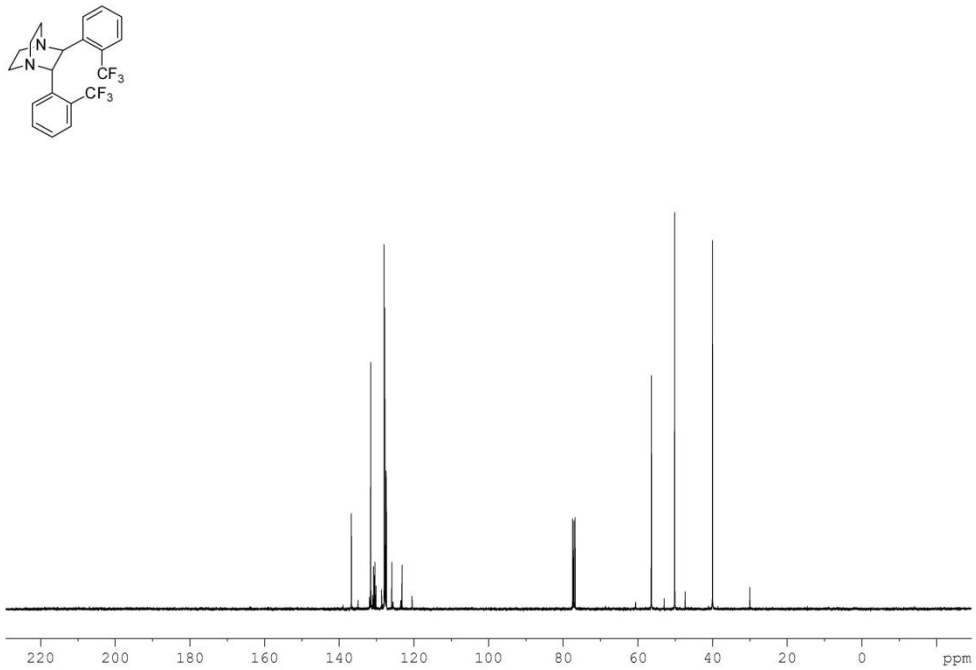
O
Cl
NH
F3C
HN
CF3
Cl
O

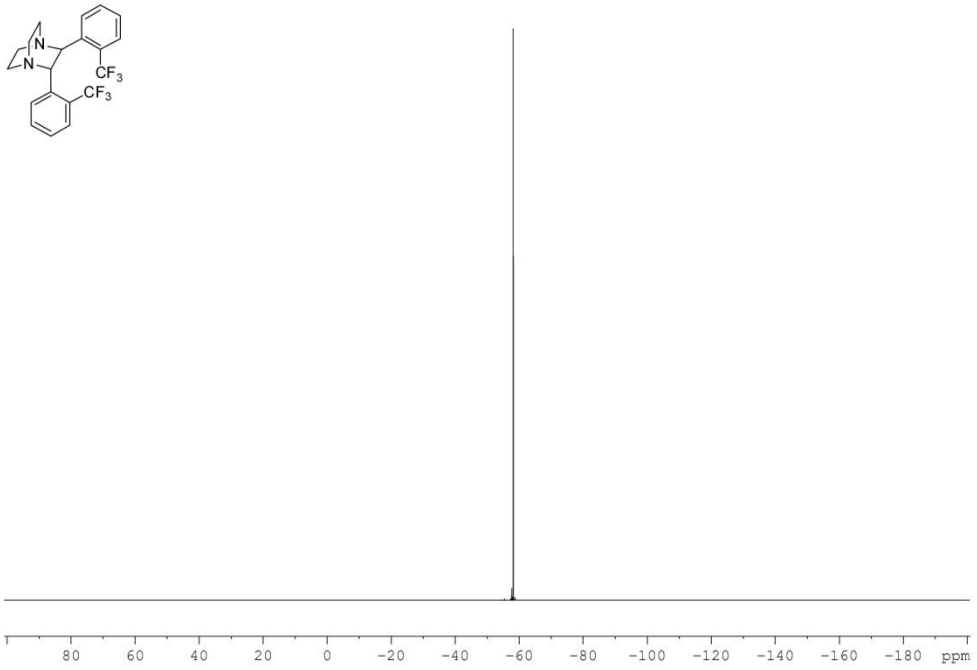

10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.10
2.01
2.00
1.95
2.02
2.07
2.11

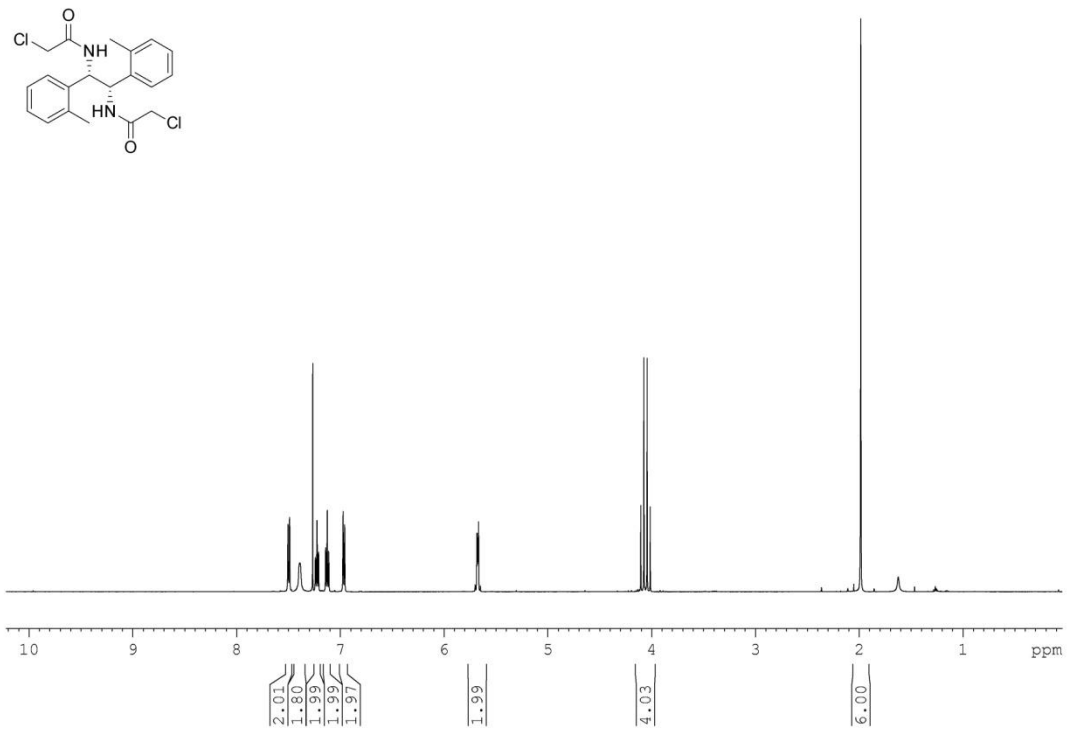

Cl
O
NH
F3C
HN
CF3
O
Cl
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

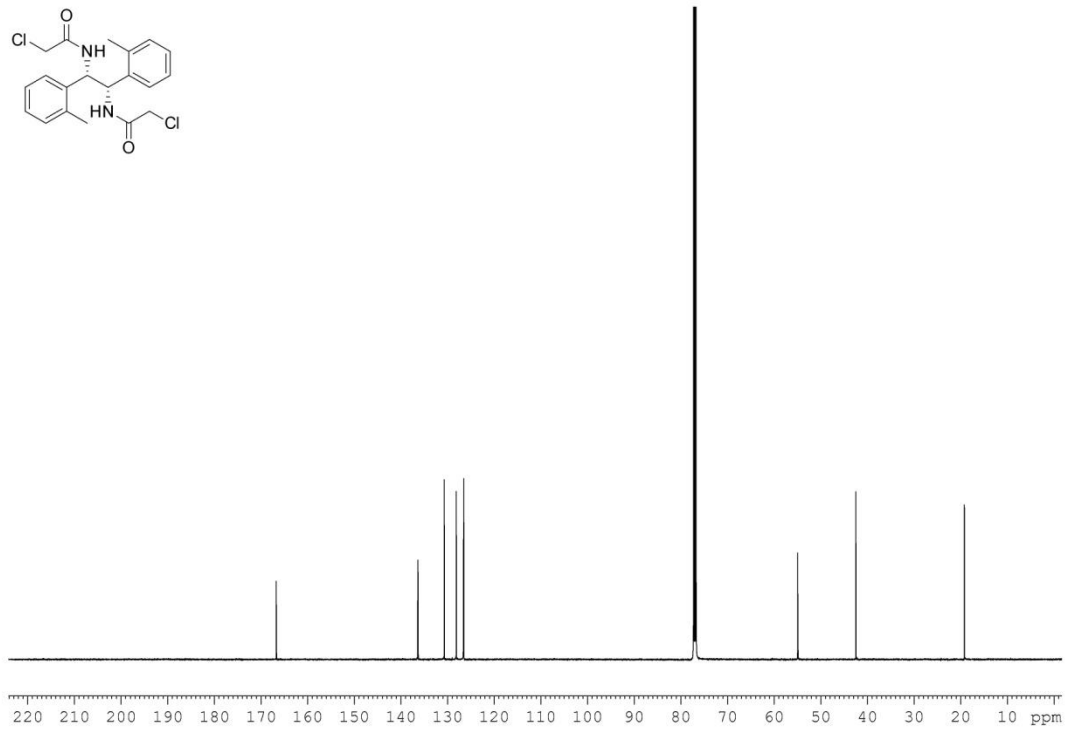

Cl
O
NH
F3C
HN
CF3
O
Cl
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

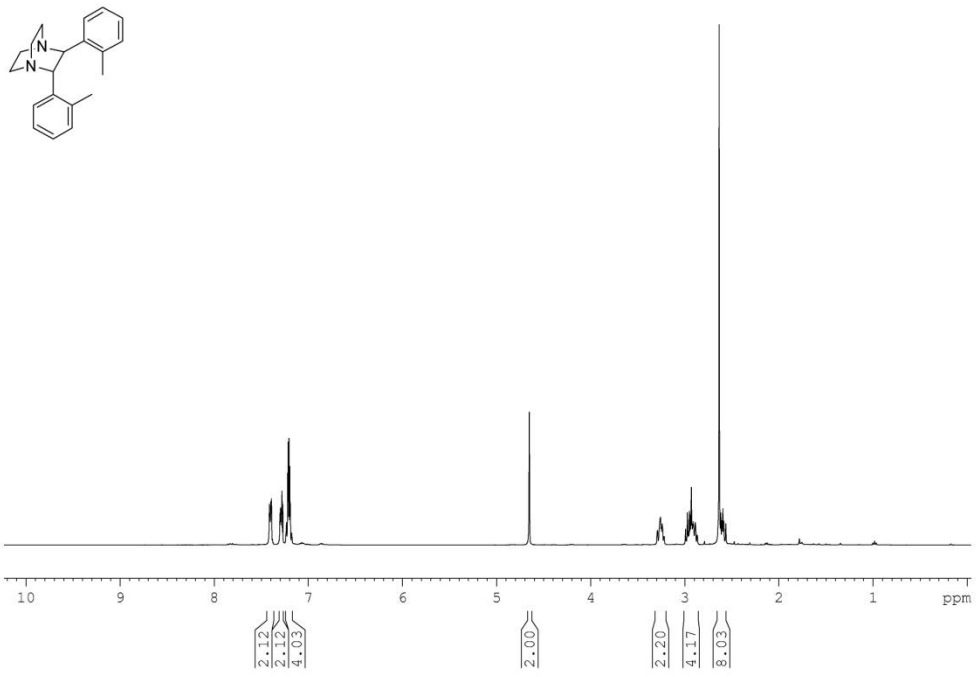

N
N
CF3
CF3
10
9
8
7
6
5
4
3
2
1
ppm
2.05
1.95
2.01
2.06
2.00
2.02
2.14
2.03
2.11

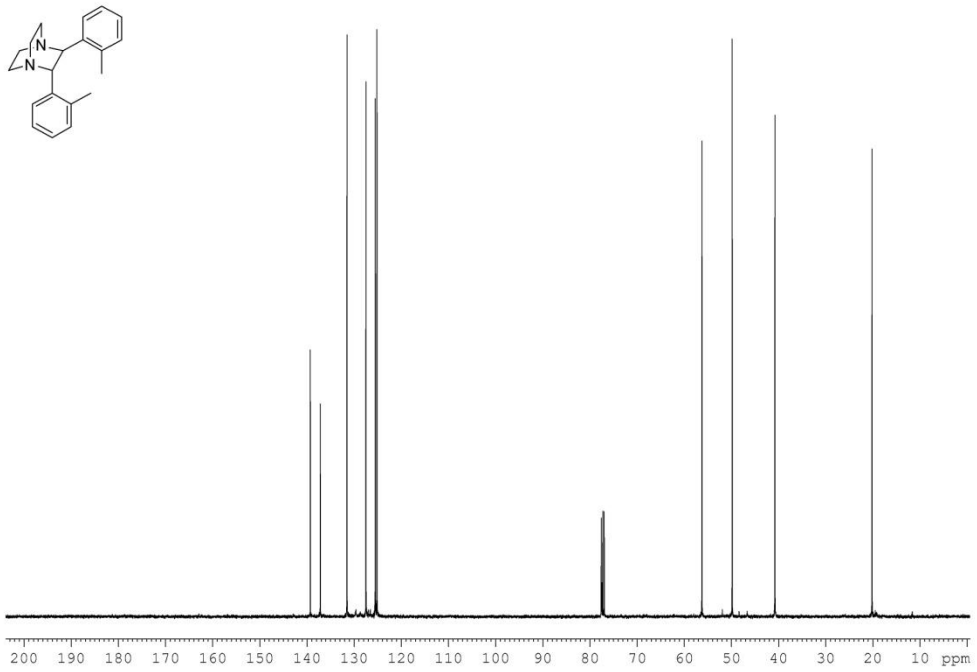

N
N
CF3
CF3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

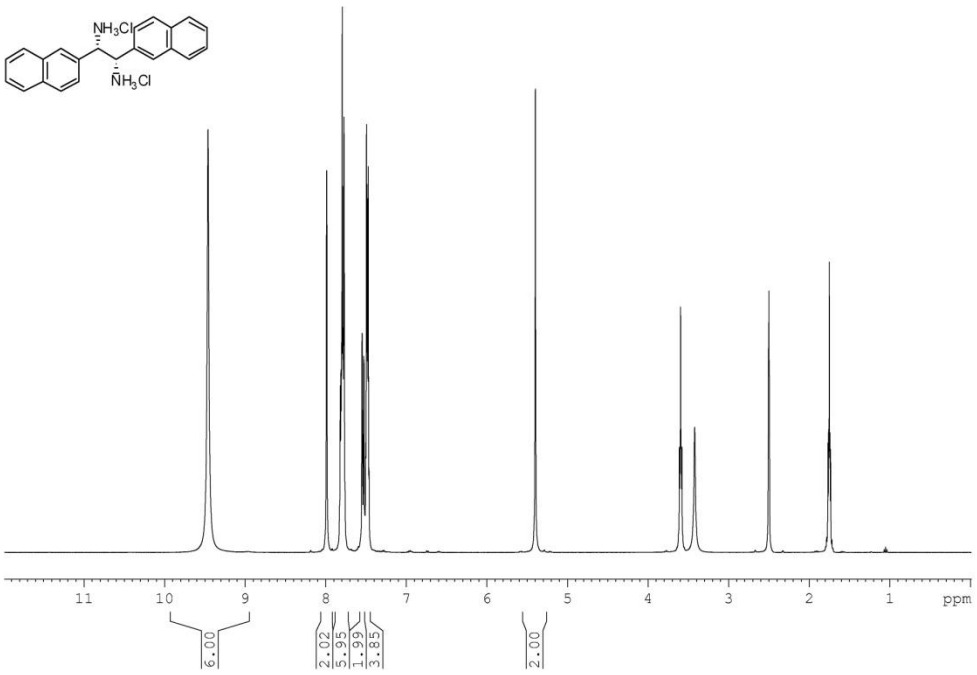

N
N
CF3
CF3
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

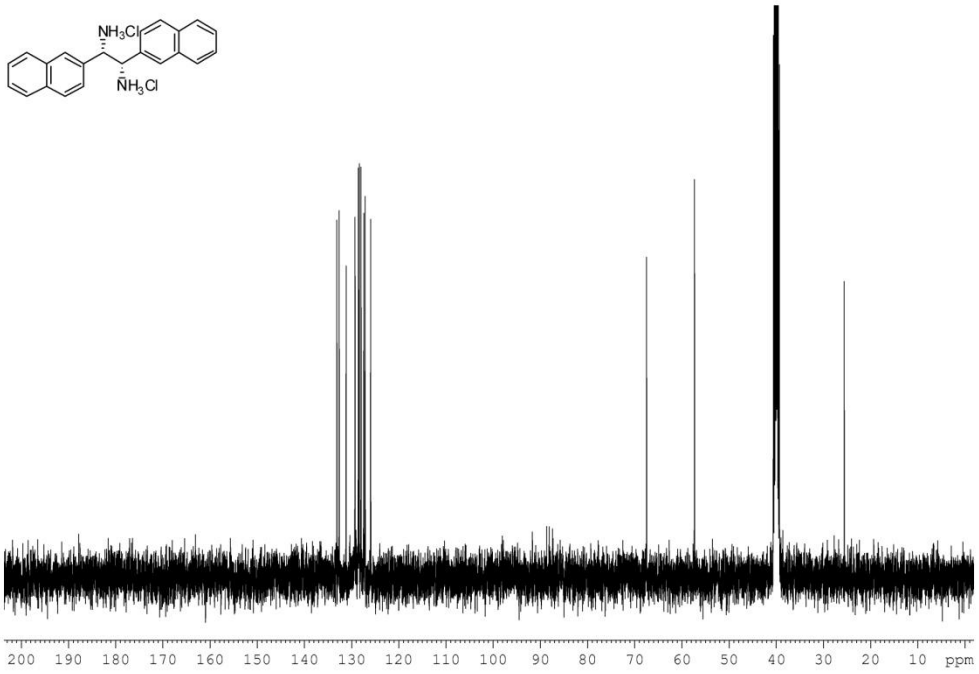

O
Cl
NH
HN
Cl
O
10
9
8
7
6
5
4
3
2
1
ppm
2.01
1.80
1.99
1.99
1.97
1.99
4.03
6.00

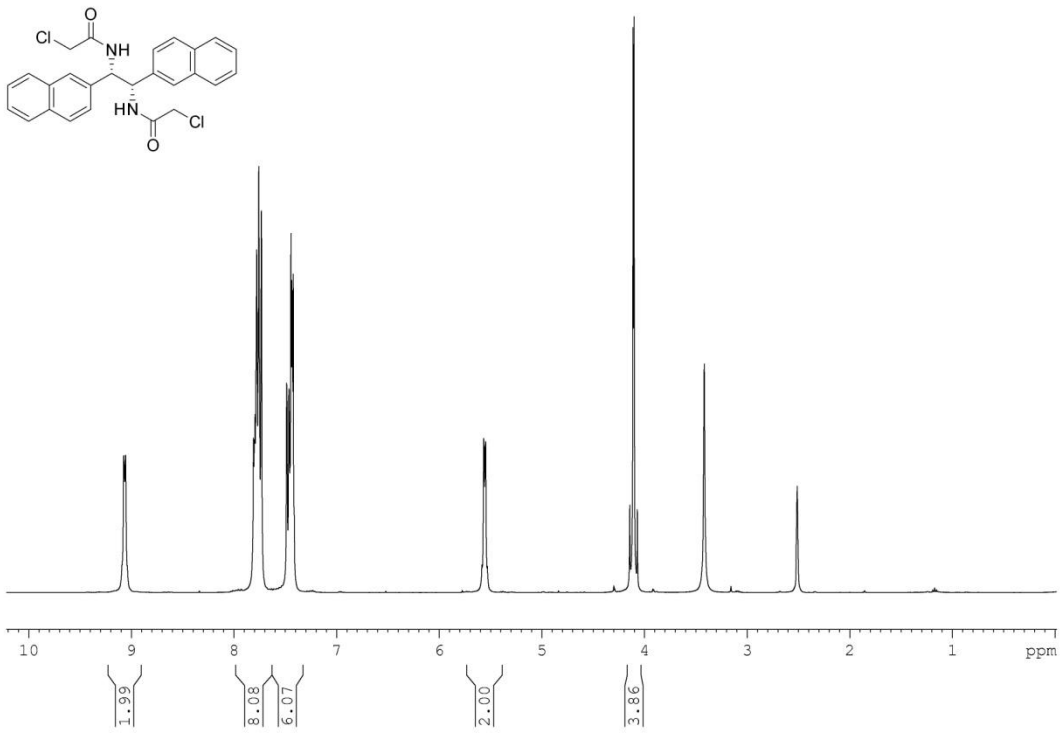

Cl
O
NH
HN
Cl
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

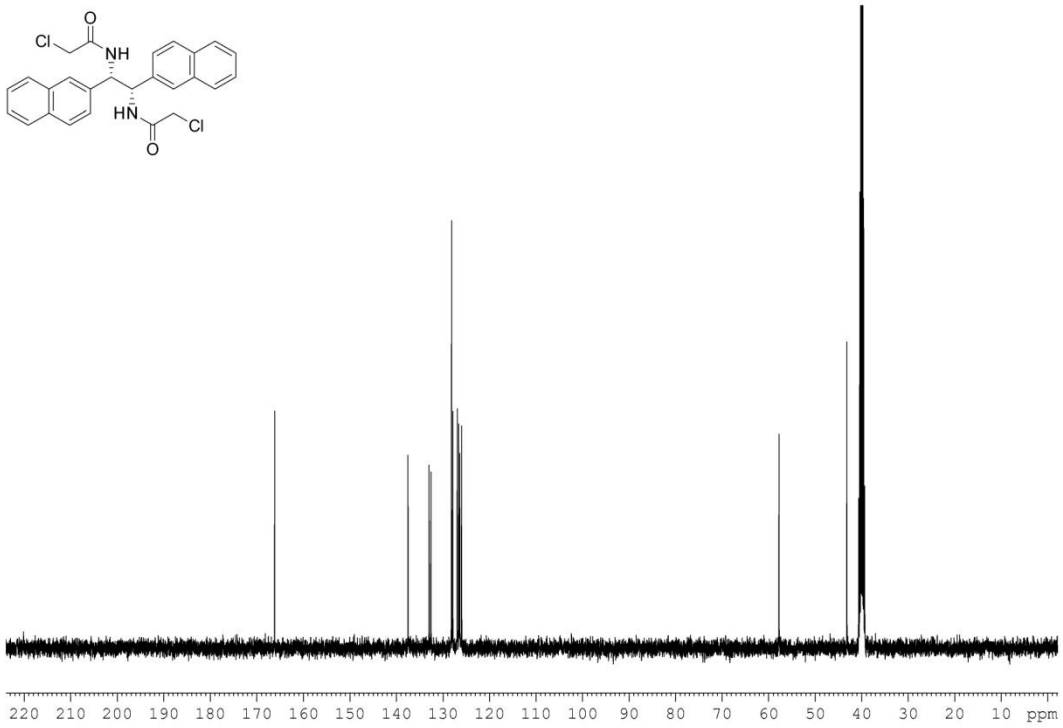

N
N
10 9 8 7 6 5 4 3 2 1 ppm
2.12
2.12
4.03
2.00
2.20
4.17
8.03

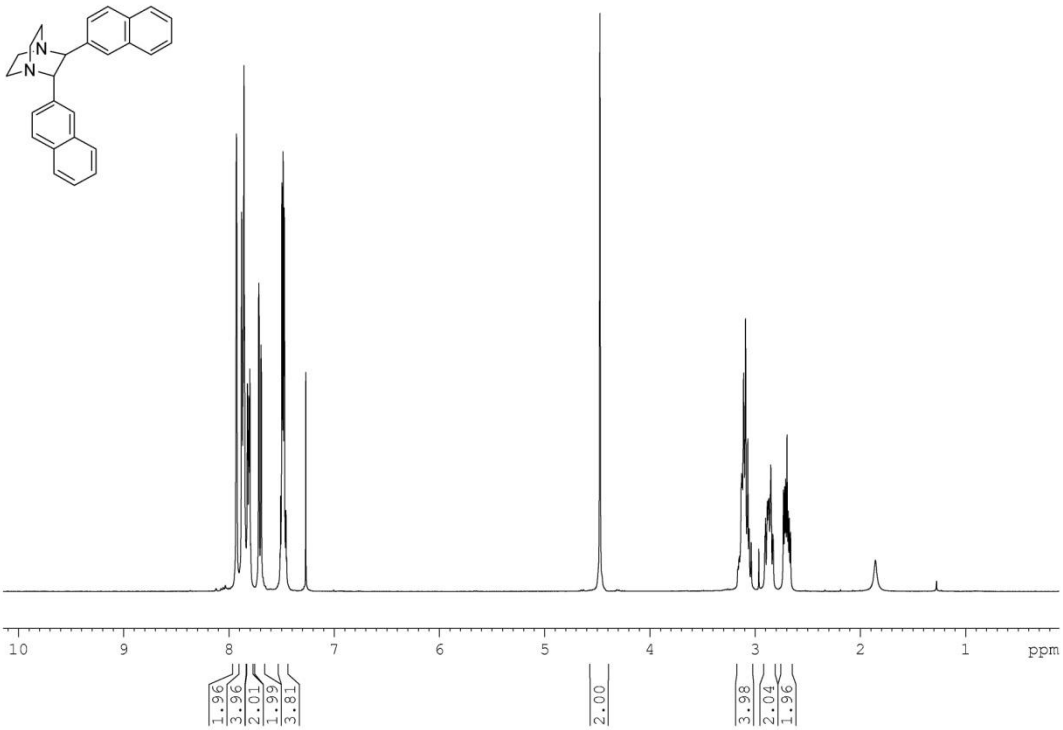

N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

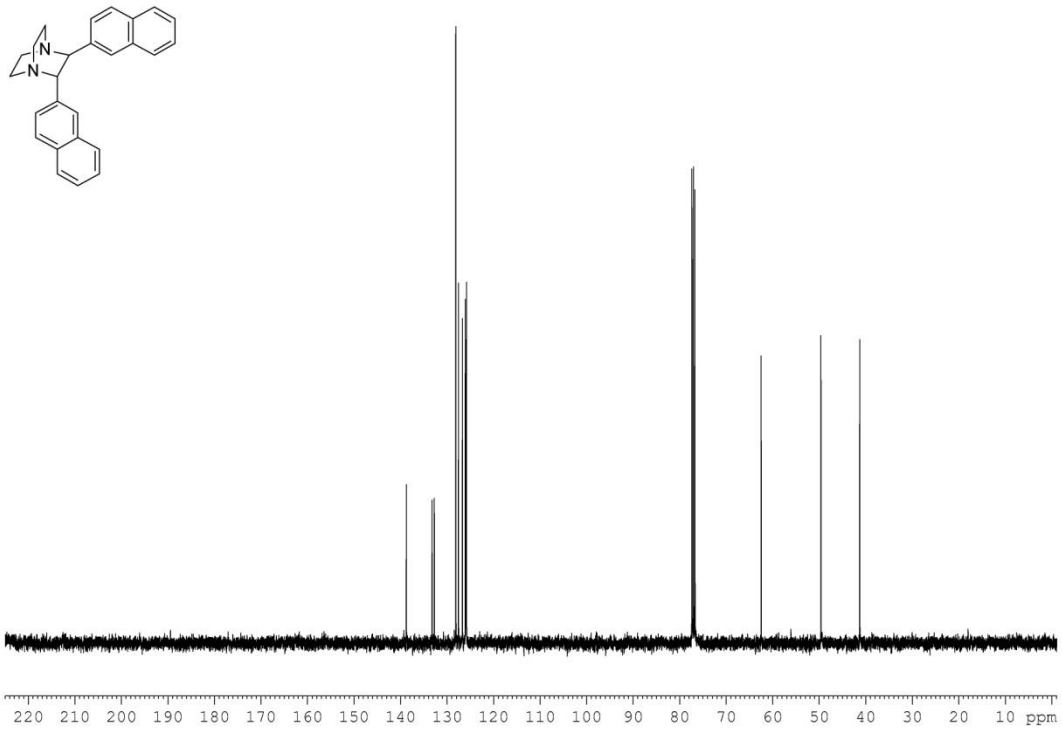

NH3Cl
NH3Cl
11 10 9 8 7 6 5 4 3 2 1 ppm
6.00
2.02
5.95
1.99
3.85
2.00

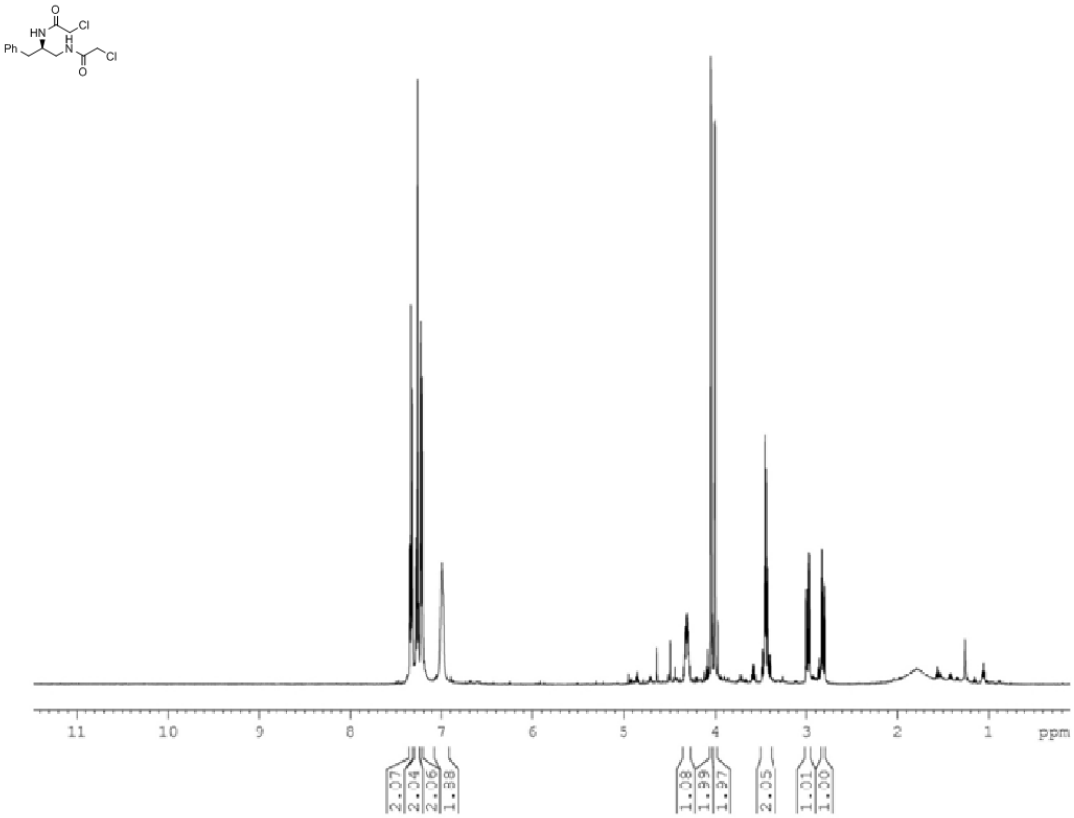

NH3Cl
NH3Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

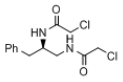

O
Cl
NH
HN
Cl
O
10 9 8 7 6 5 4 3 2 1 ppm
1.99
8.08
6.07
2.00
3.86

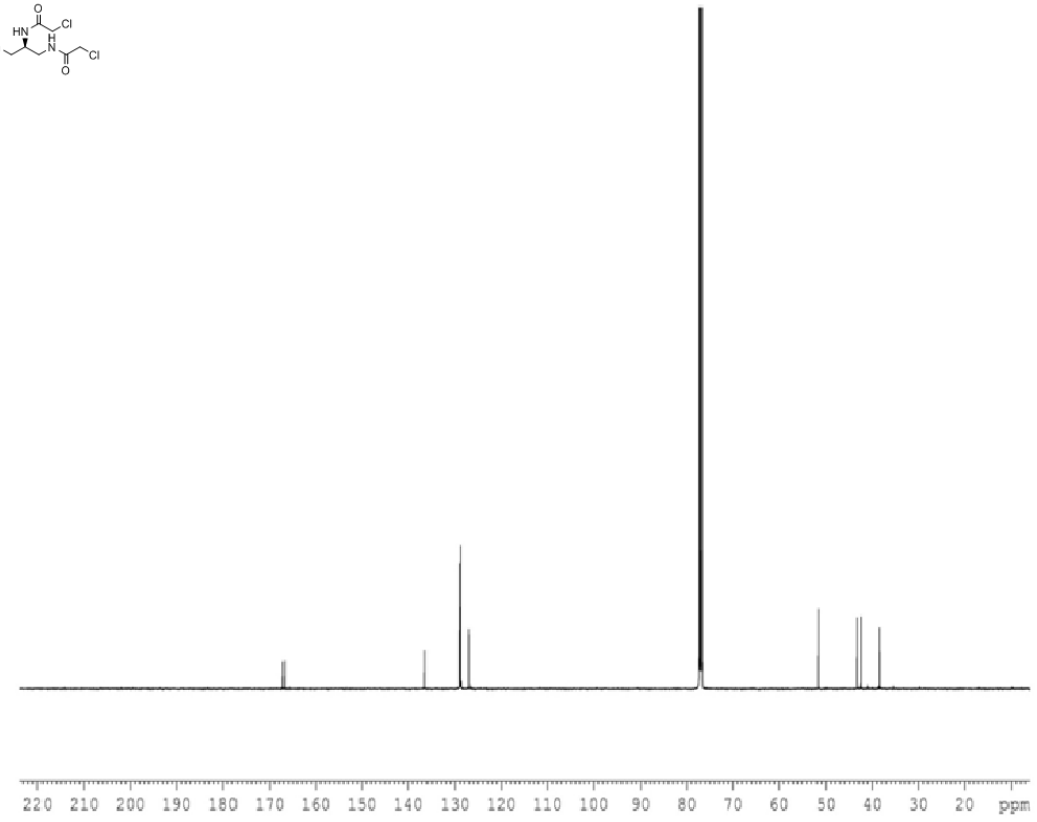

Cl
O
NH
HN
Cl
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

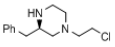

N
N
10 9 8 7 6 5 4 3 2 1 ppm
1.96
3.96
2.01
1.99
3.81
2.00
3.98
2.04
1.96

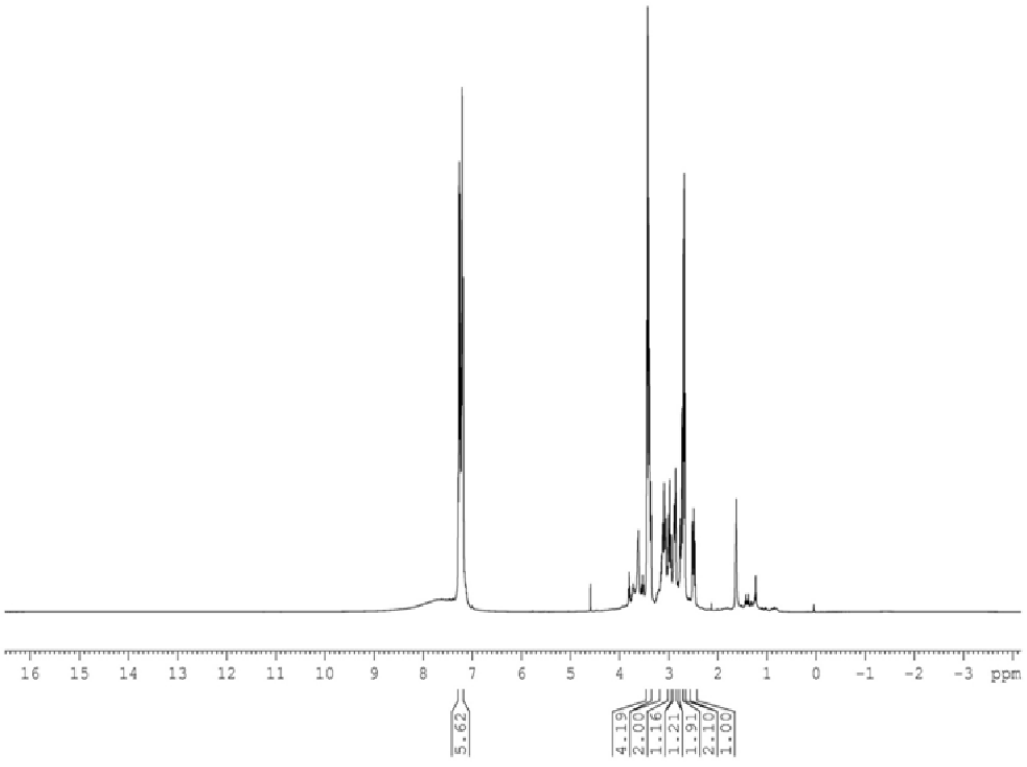

N
N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

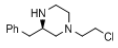

HN
Cl
Ph
N
H
Cl
O
O
11 10 9 8 7 6 5 4 3 2 1 ppm
2.07
2.04
2.06
1.88
1.08
1.99
1.97
2.05
1.01
1.00

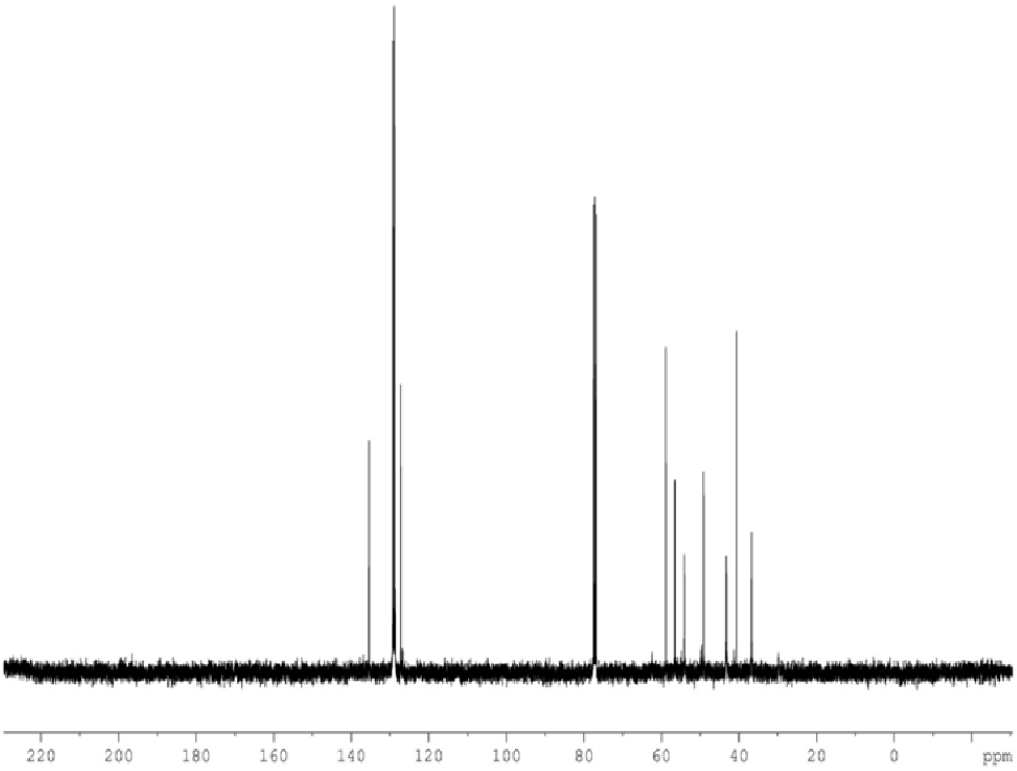

O
HN
Cl
Ph
N
Cl
O


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

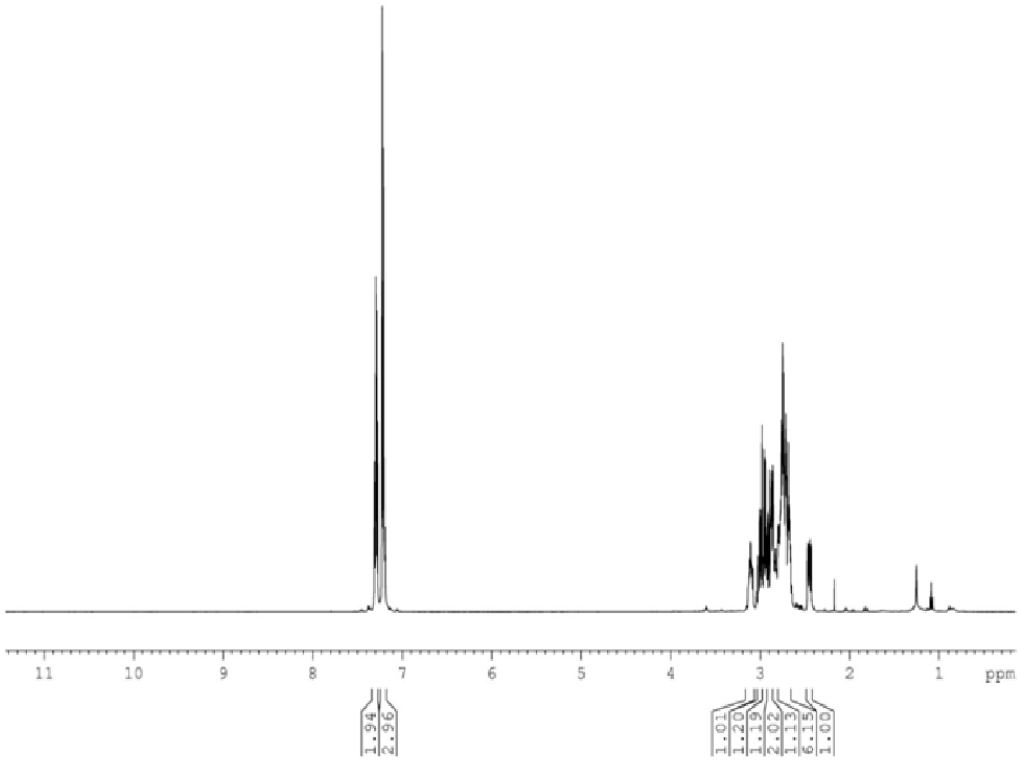

HN
Ph
N
Cl

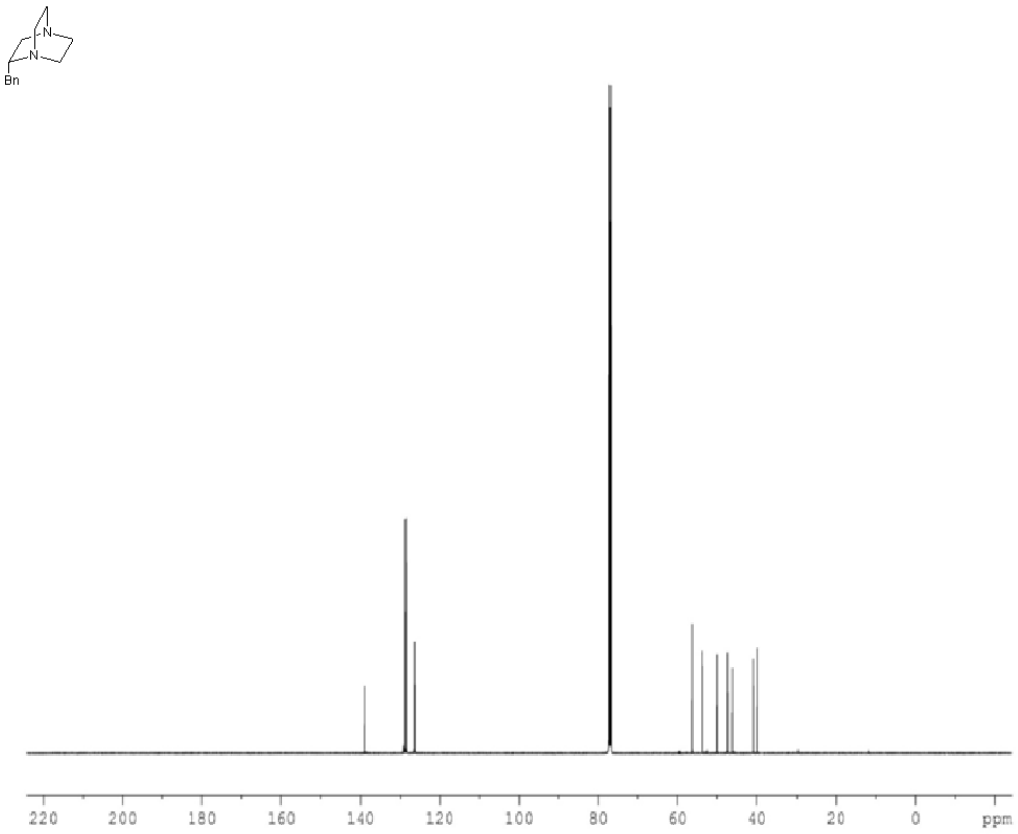

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
5.62
4.19
2.00
1.16
1.21
1.91
2.10
1.00

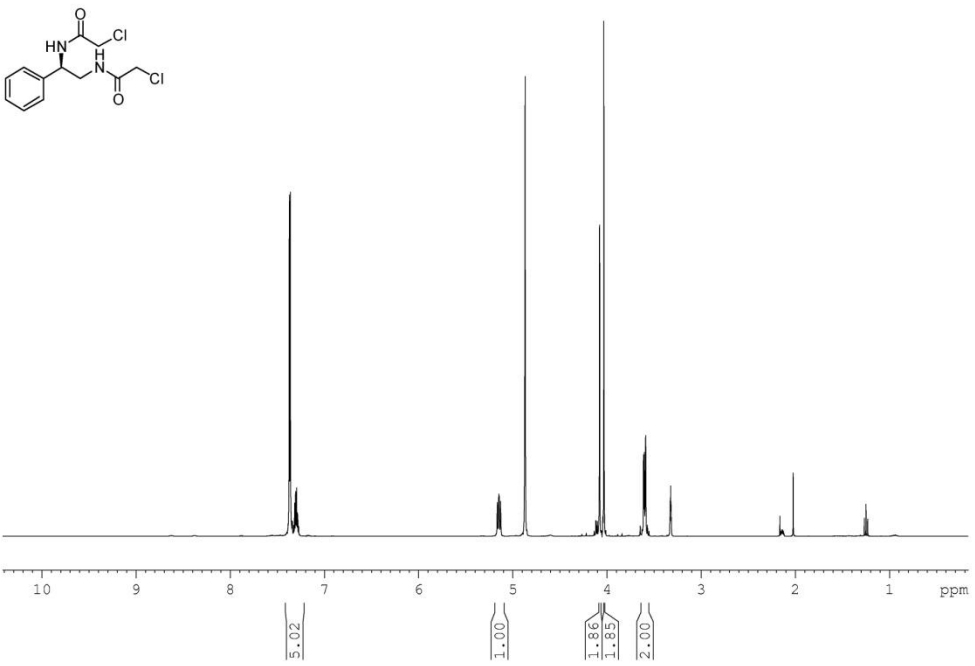

HN
Ph
N
Cl


220
200
180
160
140
120
100
80
60
40
20
0
ppm

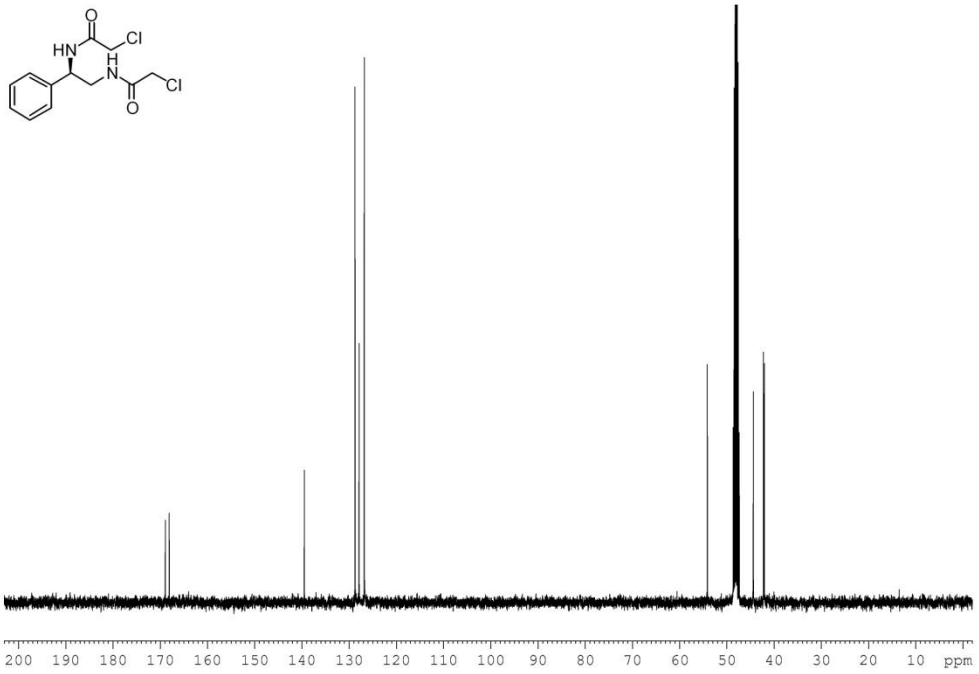
N
N
Bn

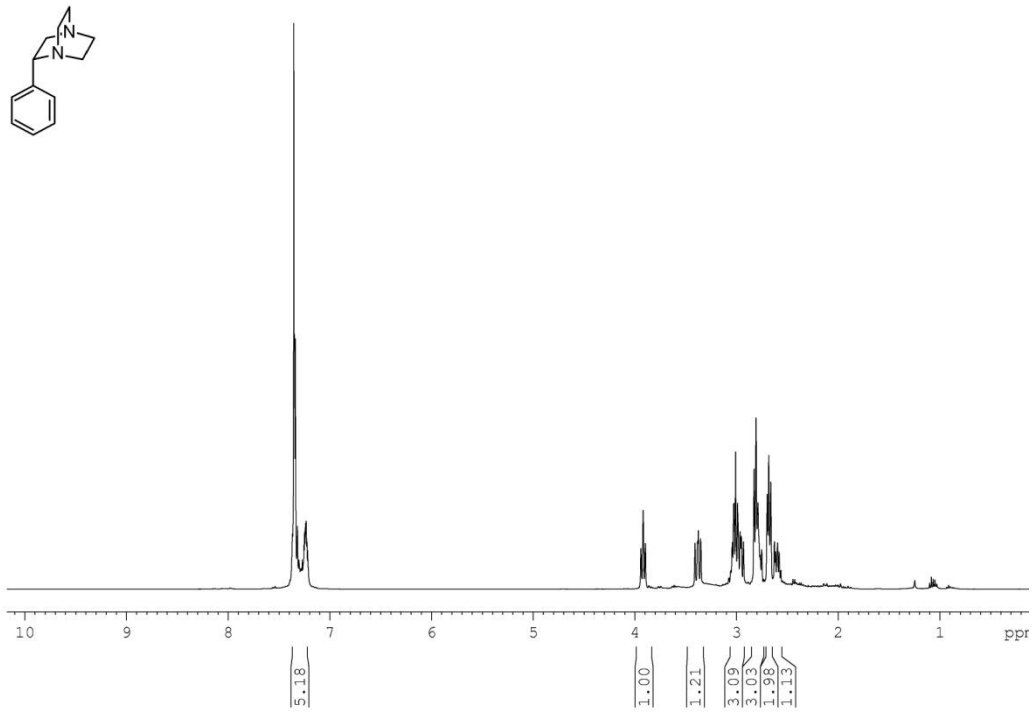

11
10
9
8
7
6
5
4
3
2
1
ppm
1.94
2.96
1.01
1.20
1.19
2.02
1.13
6.15
1.00

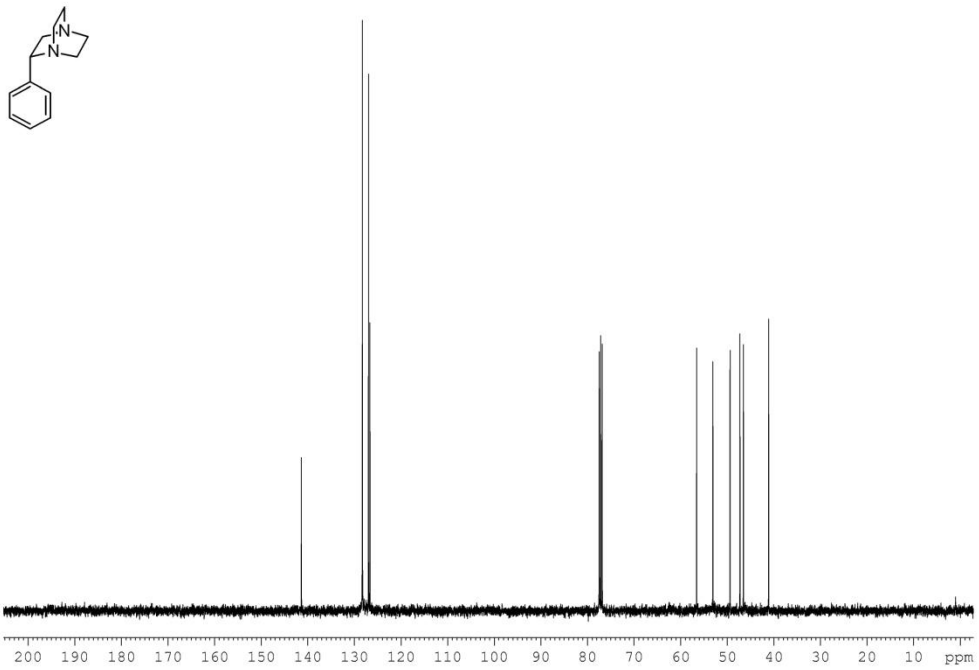

Bn
220
200
180
160
140
120
100
80
60
40
20
0
ppm

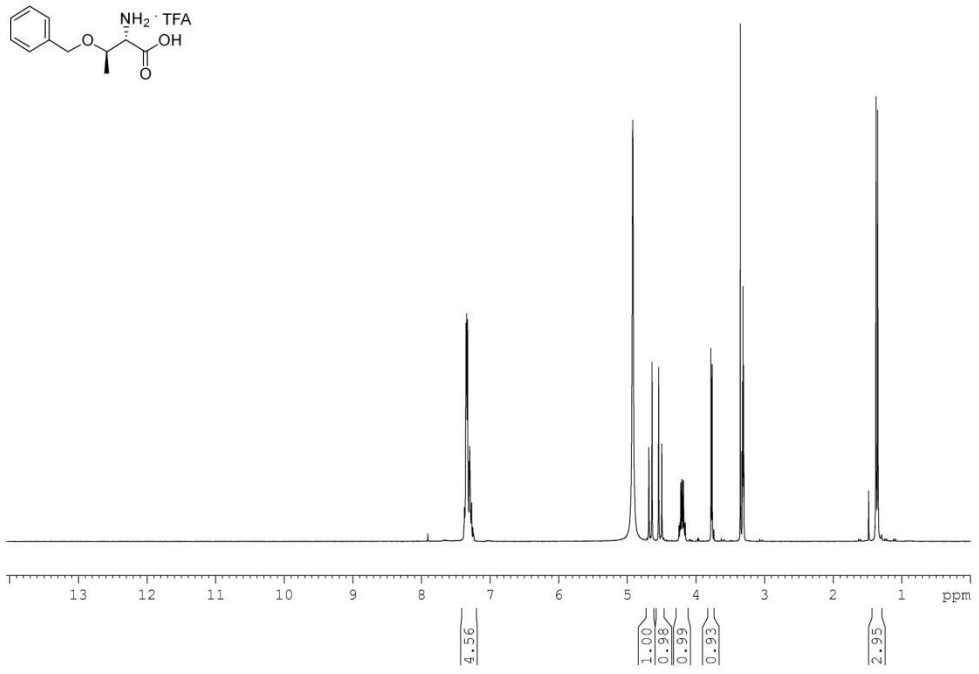

HN
Cl
H
N
Cl
O
O
10
9
8
7
6
5
4
3
2
1
ppm
5.02
1.00
1.86
1.85
2.00

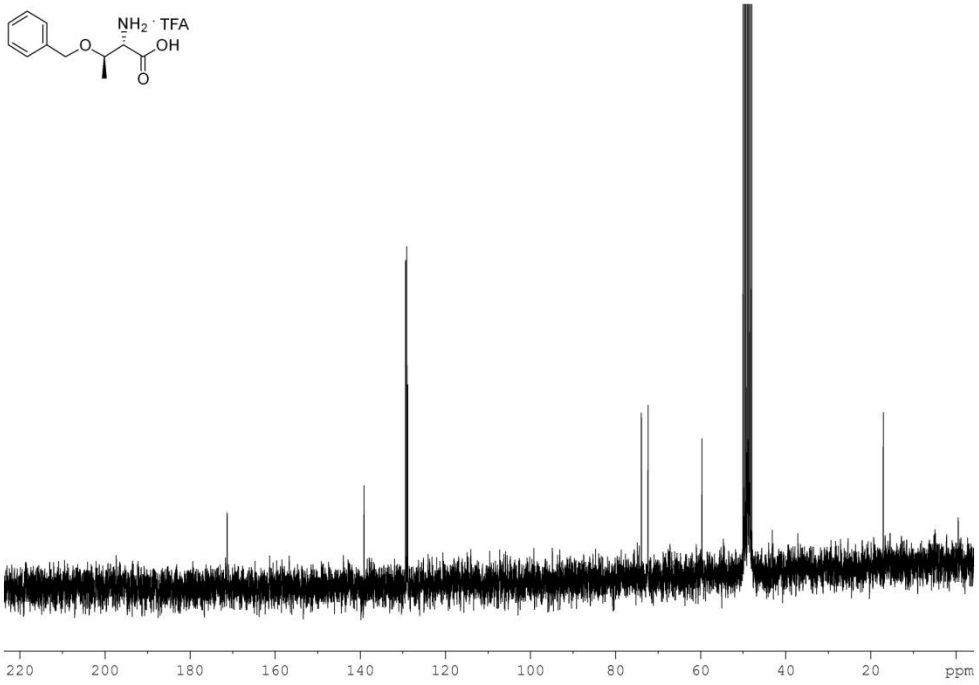
ccl

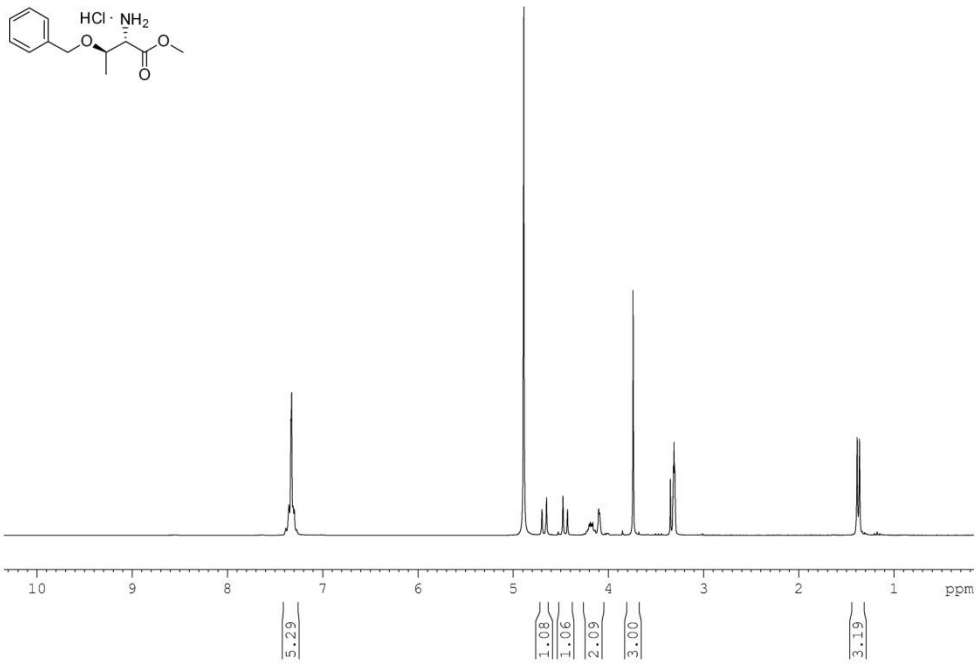

HN
Cl
H
N
Cl
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

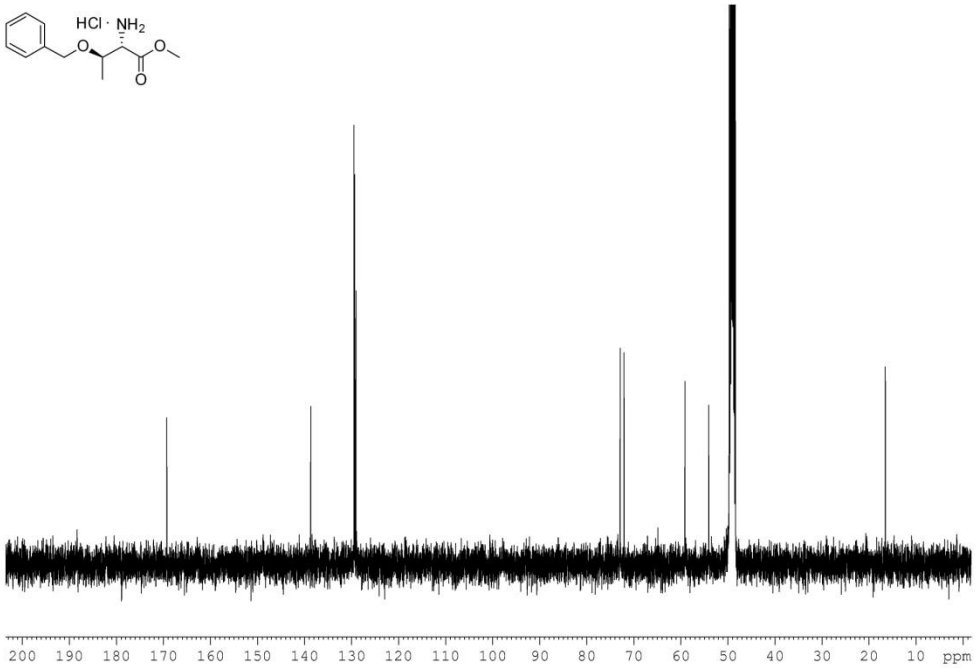

N
N
10 9 8 7 6 5 4 3 2 1 ppr
5.18
1.00
1.21
3.09
3.03
1.98
1.13

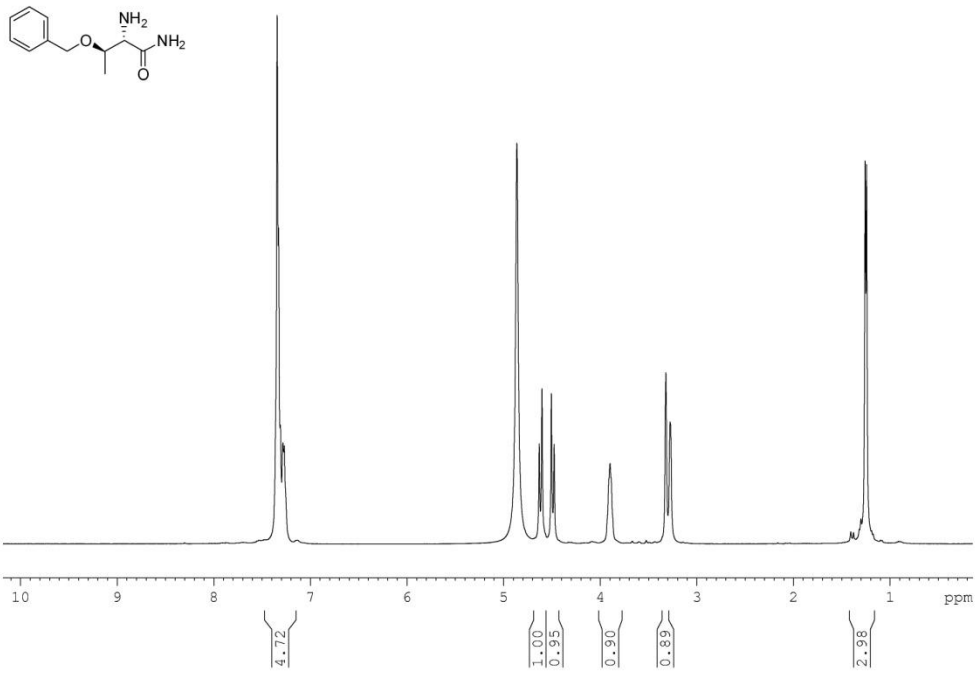

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

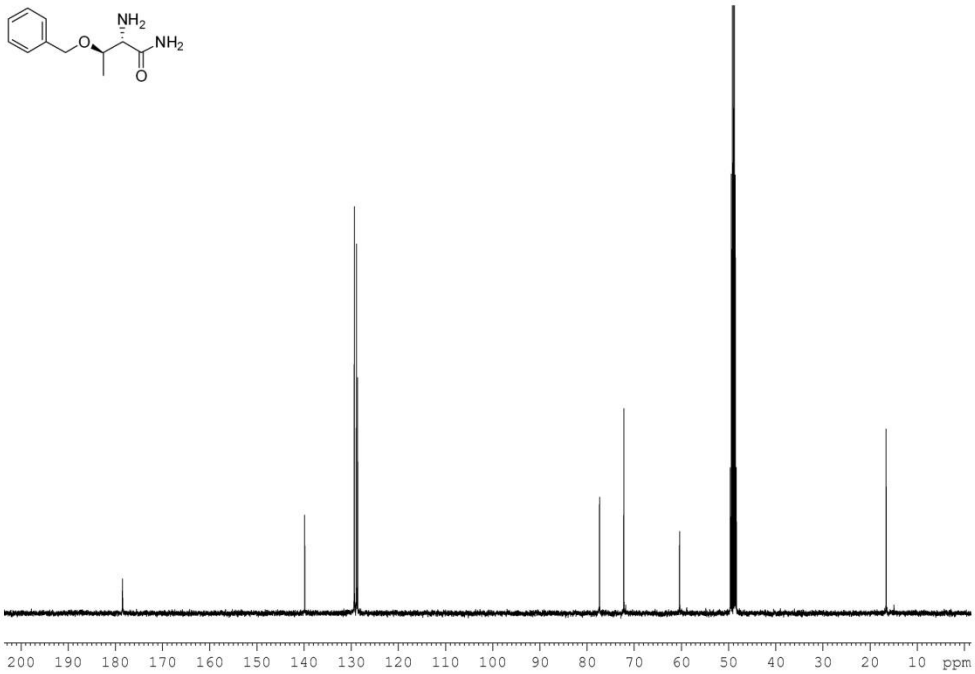

NH2 · TFA
OH
O
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
4.56
1.00
0.98
0.99
0.93
2.95

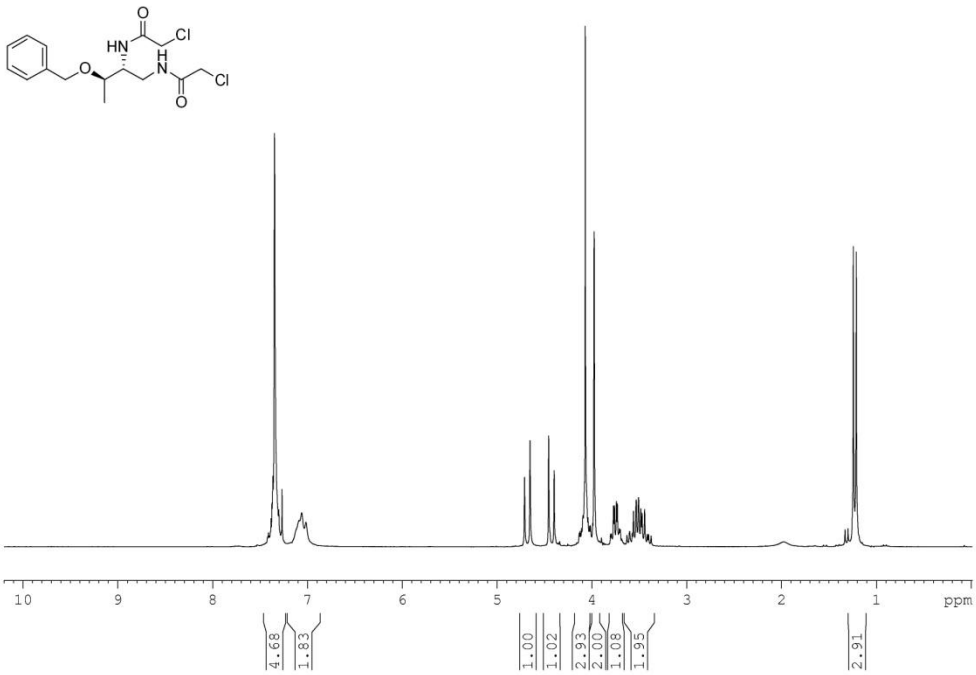

NH2 · TFA
OH
O
220
200
180
160
140
120
100
80
60
40
20
ppm

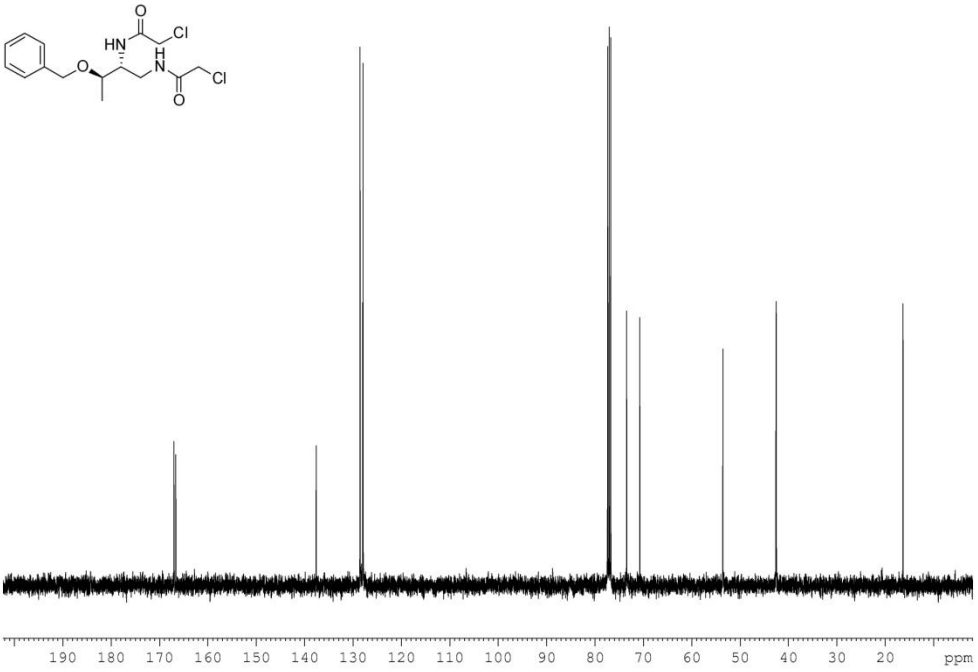

HCl · NH2
O
O
O
10
9
8
7
6
5
4
3
2
1
ppm
5.29
1.08
1.06
2.09
3.00
3.19

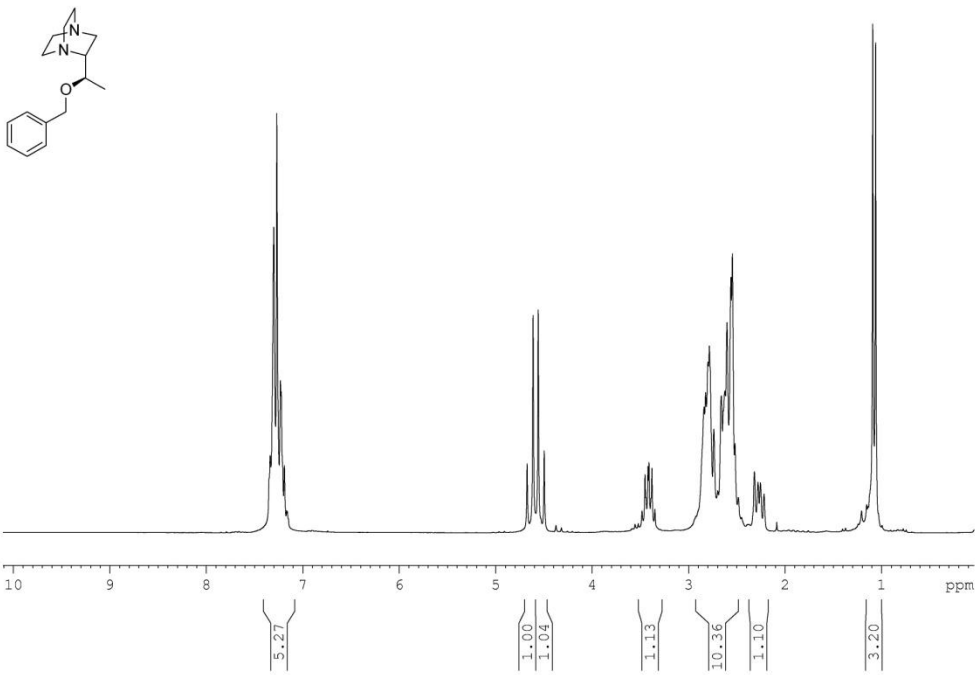

HCl · NH2
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

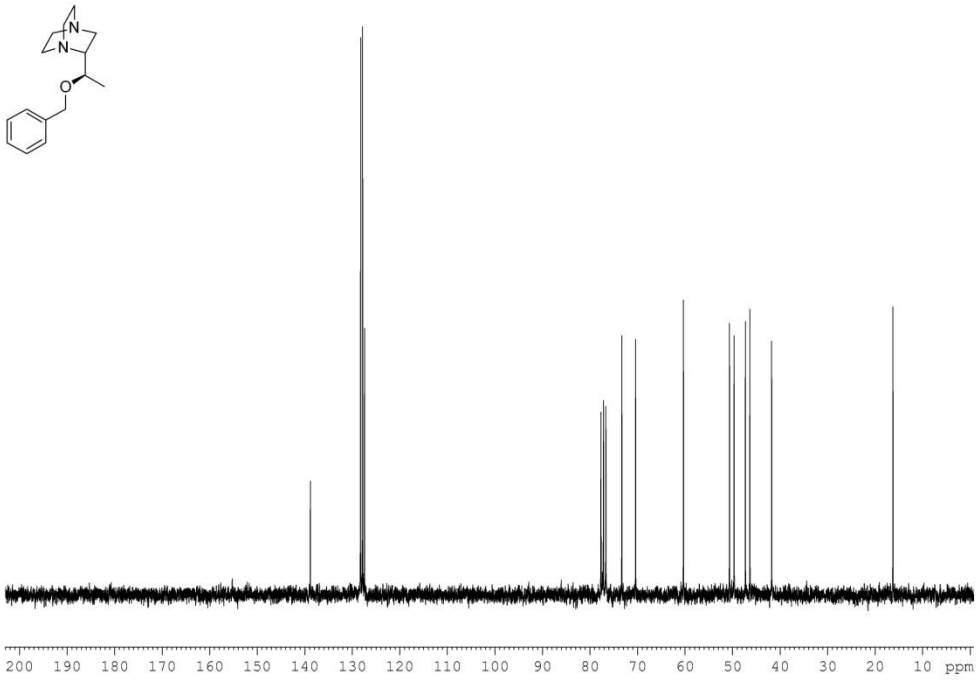

NH2
NH2
O
10 9 8 7 6 5 4 3 2 1 ppm
4.72
1.00
0.95
0.90
0.89
2.98

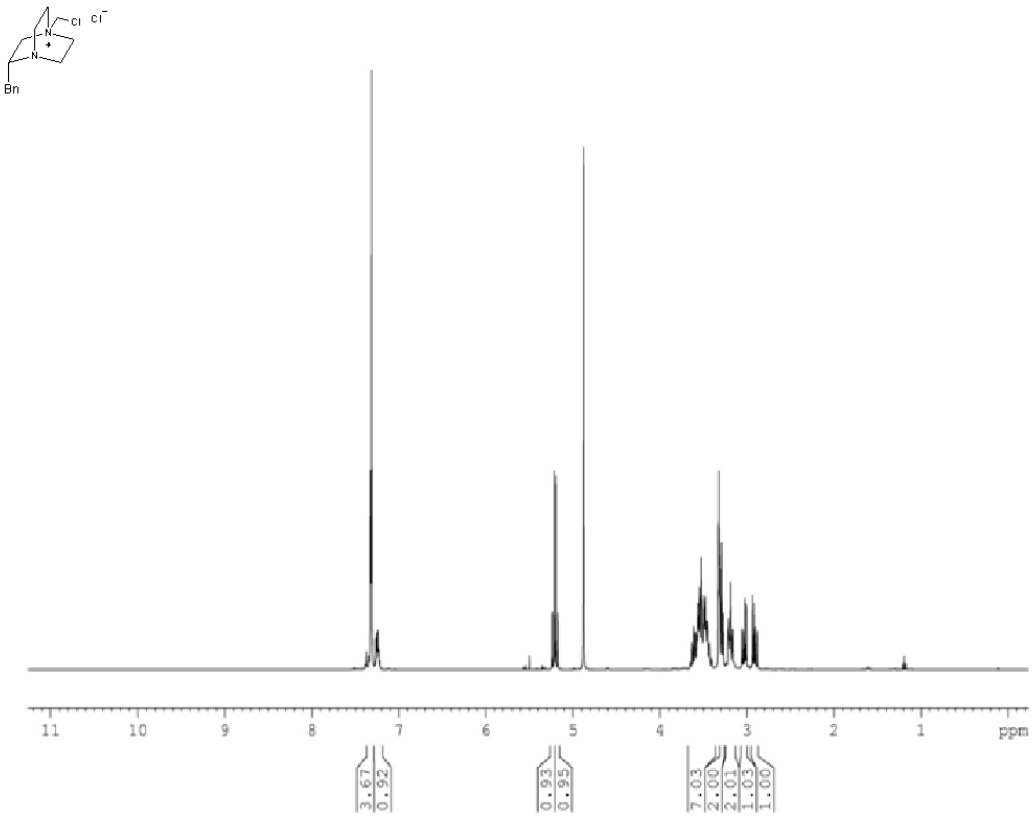

NH2
NH2
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

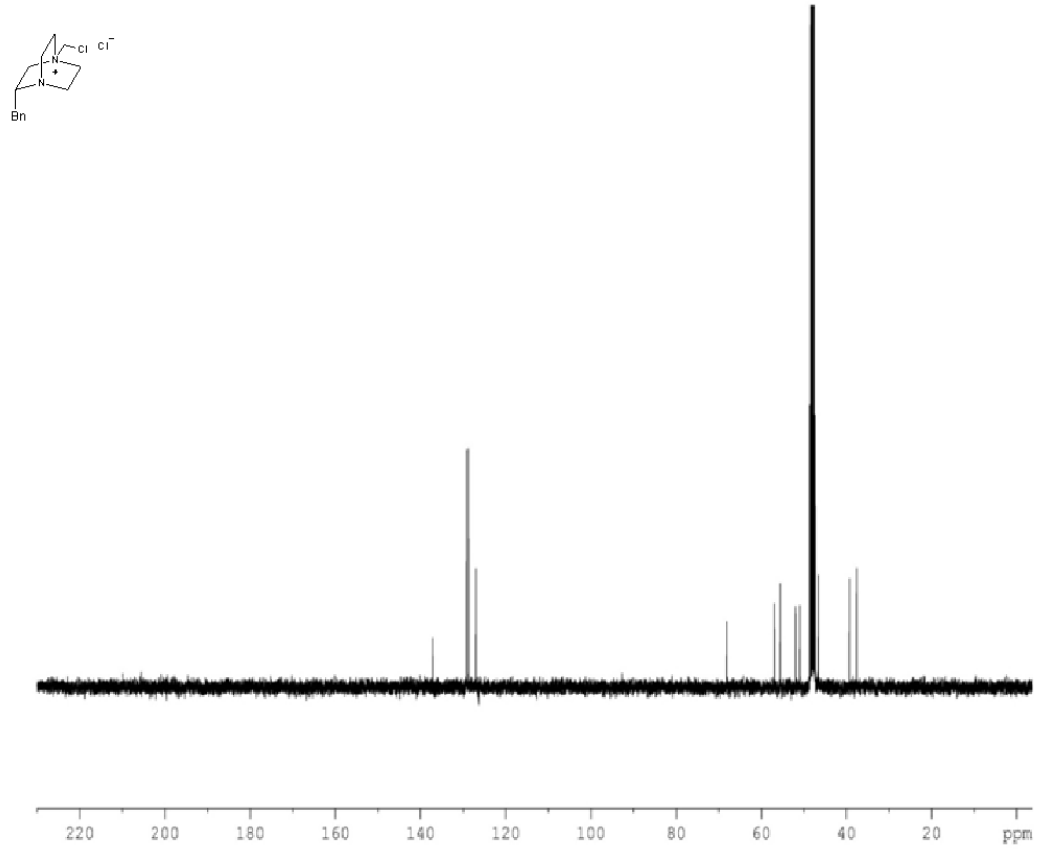

O
HN
Cl
H
N
Cl
O
O
10 9 8 7 6 5 4 3 2 1 ppm
4.68
1.83
1.00
1.02
2.93
2.00
1.08
1.95
2.91

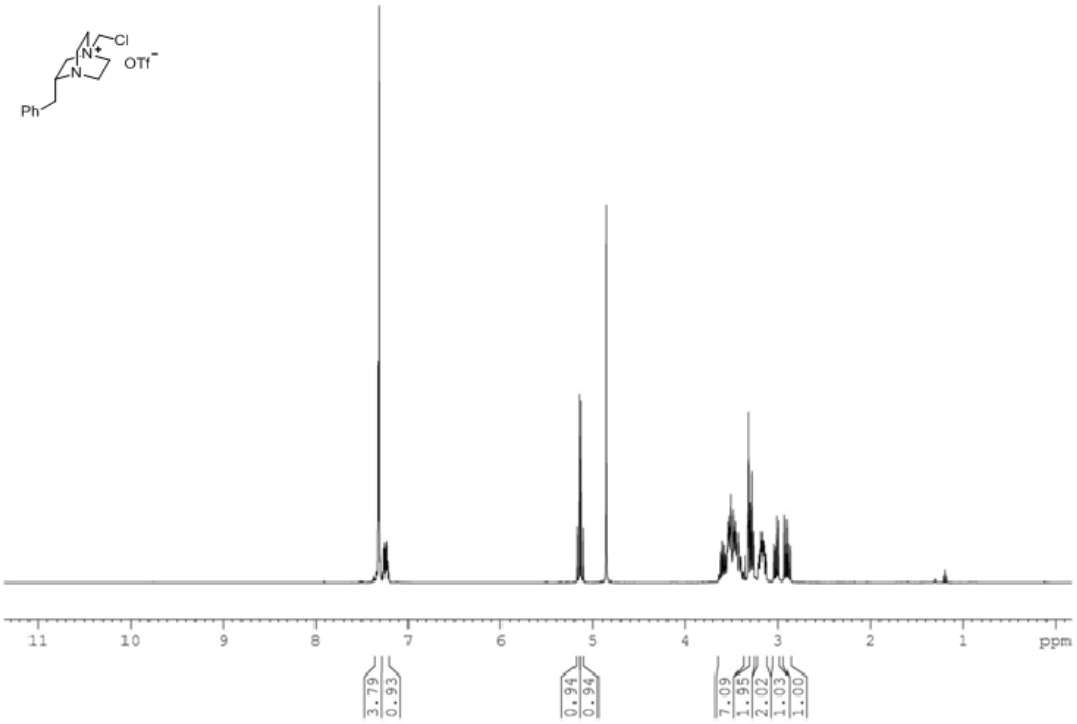

O
HN
Cl
O
H
N
Cl
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

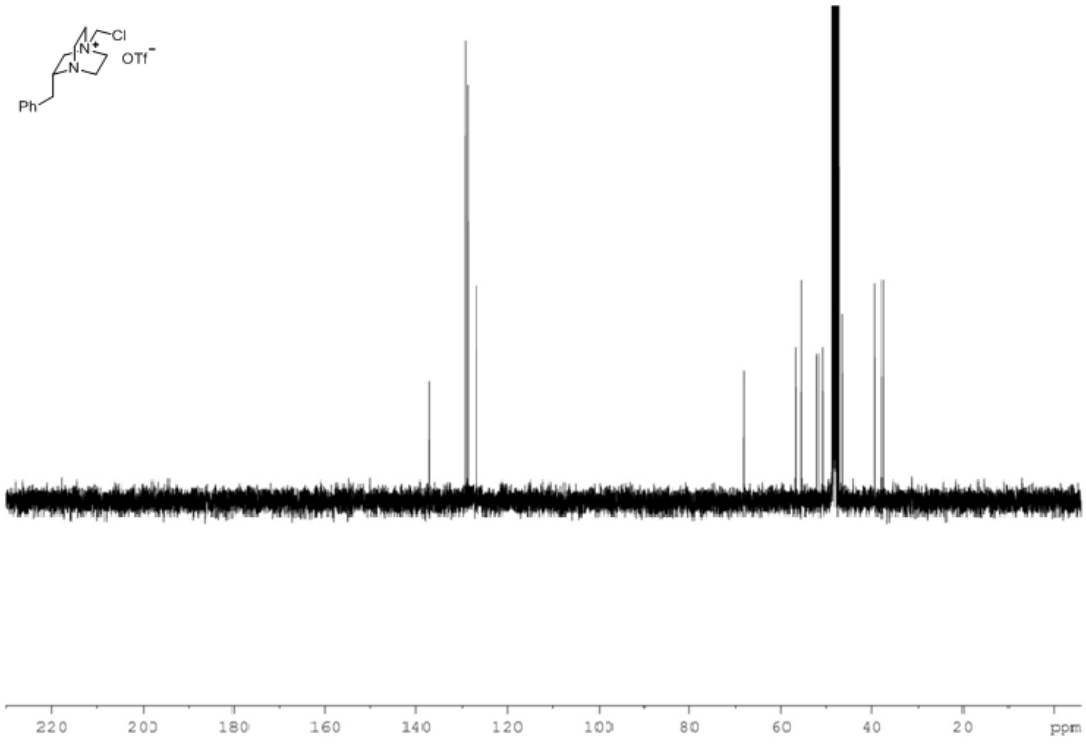

N
N
O
10 9 8 7 6 5 4 3 2 1 ppm
5.27
1.00
1.04
1.13
10.36
1.10
3.20

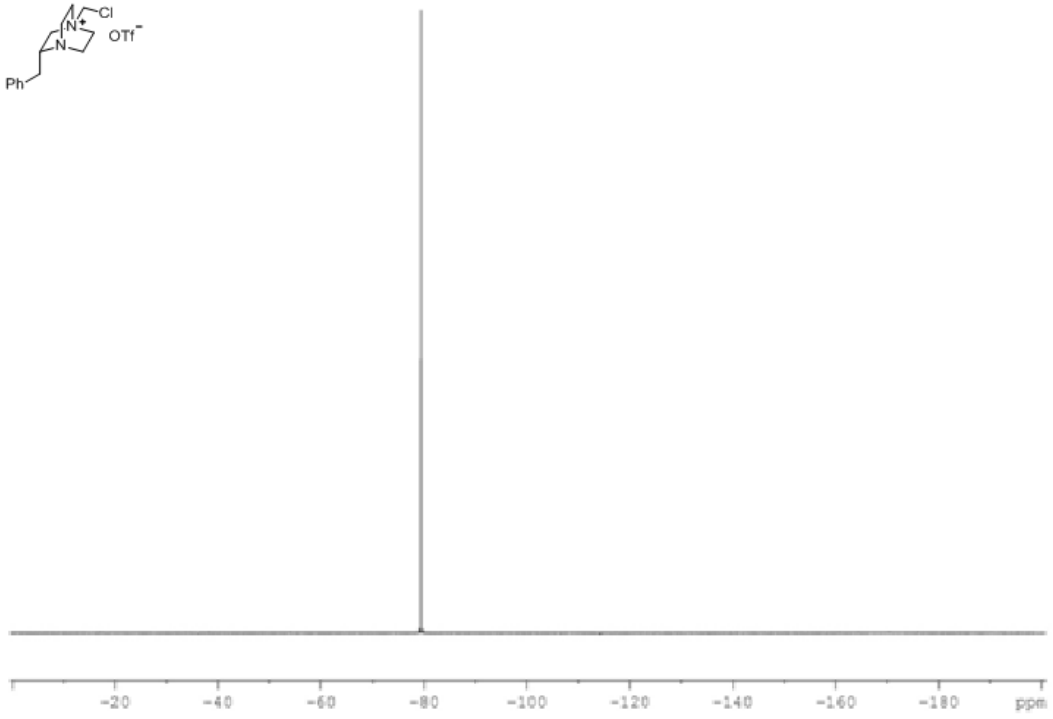

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

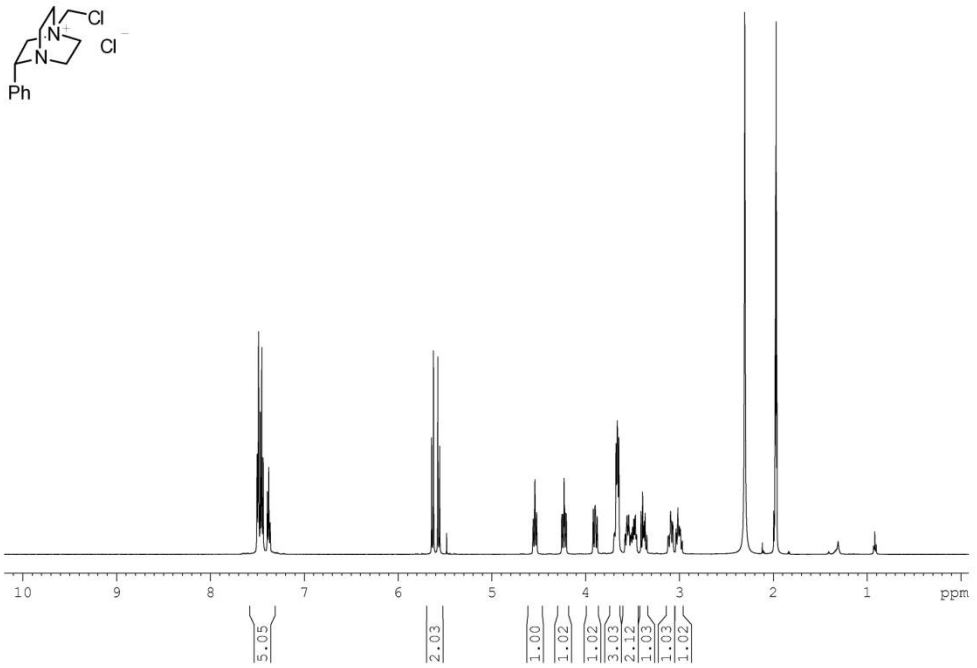

Cl
Cl⁻
Bn
11 10 9 8 7 6 5 4 3 2 1 ppm
3.67
0.92
0.93
0.95
7.03
2.00
2.01
1.03
1.00

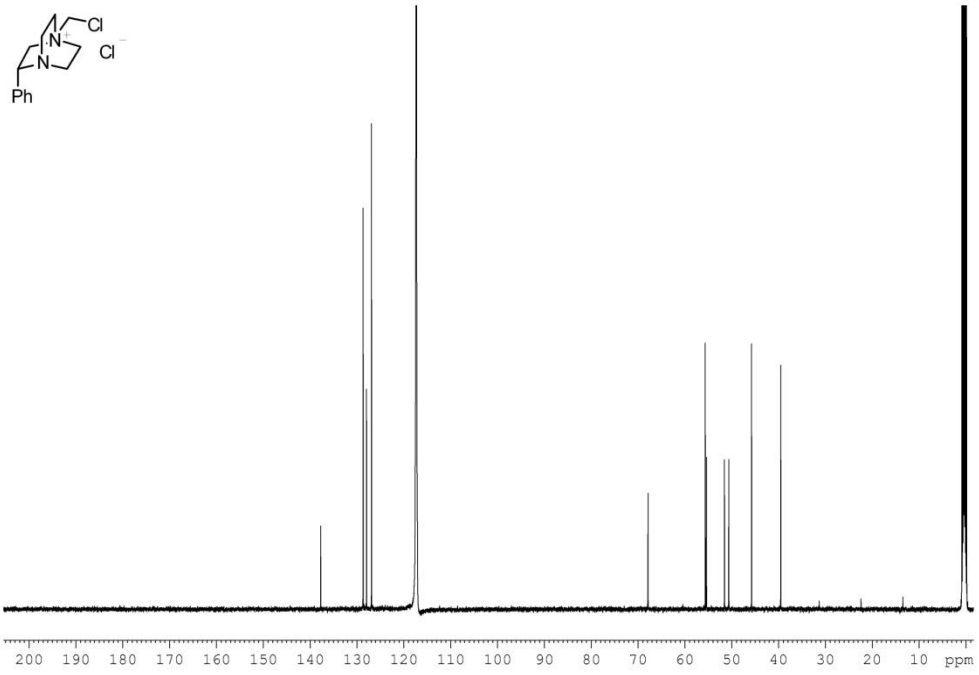

Cl
Cl⁻
N
N
Bn
220
200
180
160
140
120
100
80
60
40
20
ppm

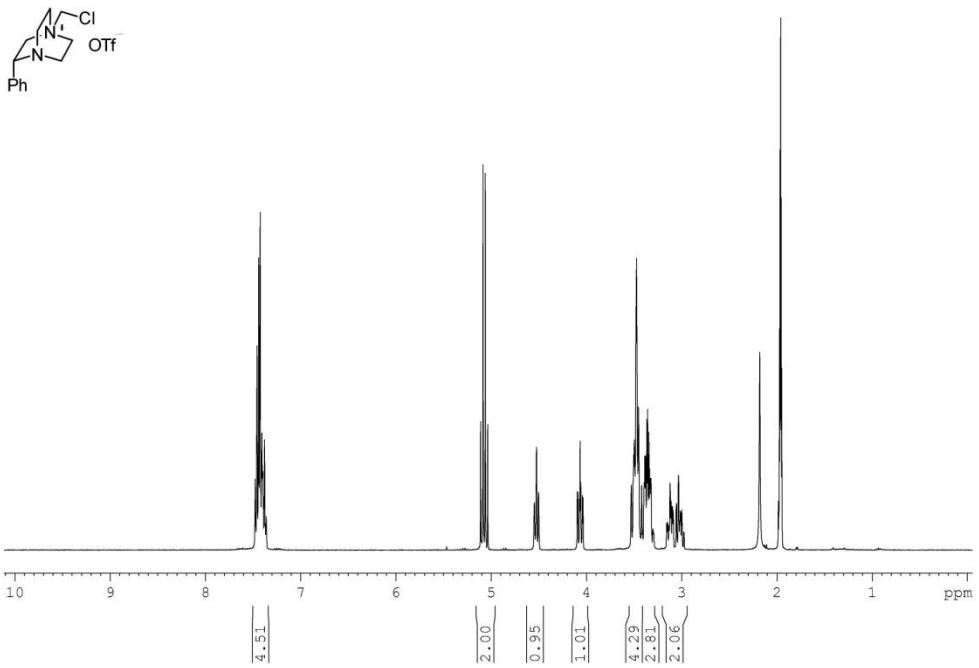

Cl
N
OTf⁻
N
Ph
11
10
9
8
7
6
5
4
3
2
1
ppm
3.79
0.93
0.94
0.94
7.09
1.95
2.02
1.03
1.00

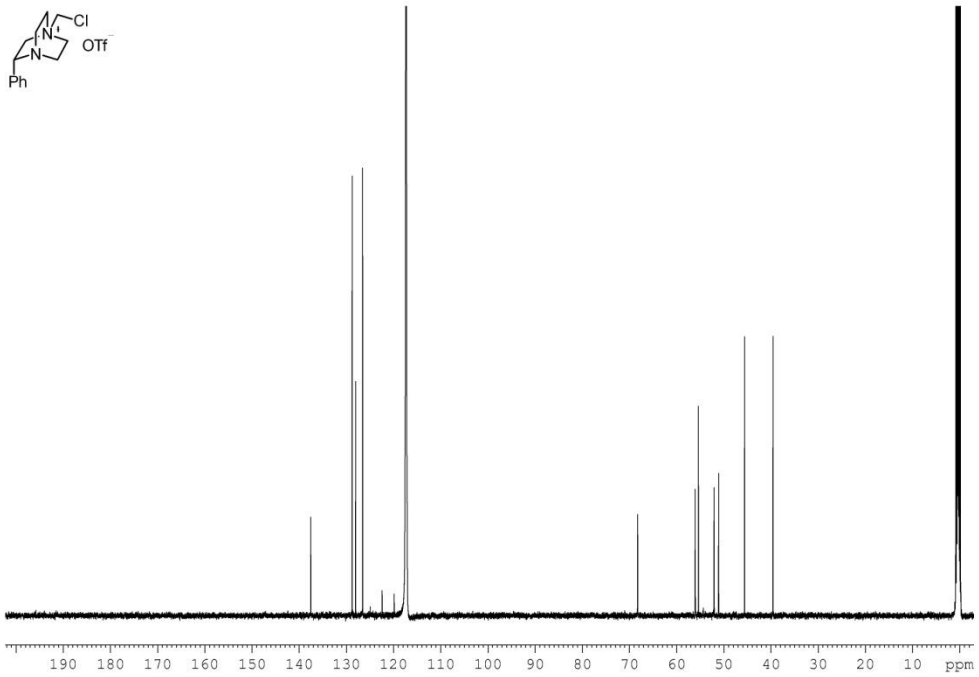

Cl
OTf
Ph
220
200
180
160
140
120
100
80
60
40
20
ppm

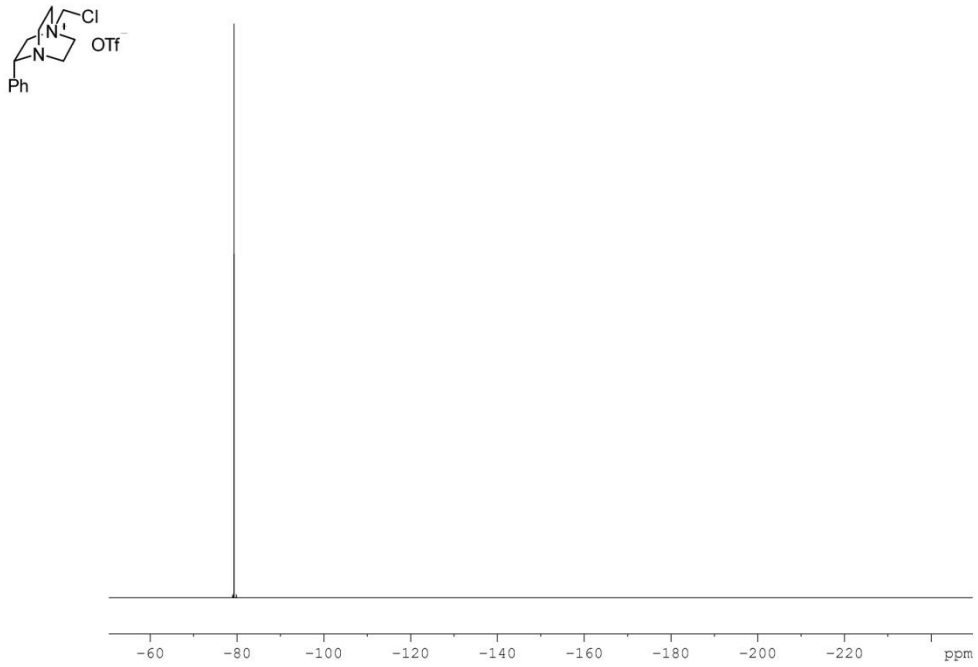

Cl
OTf
Ph
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

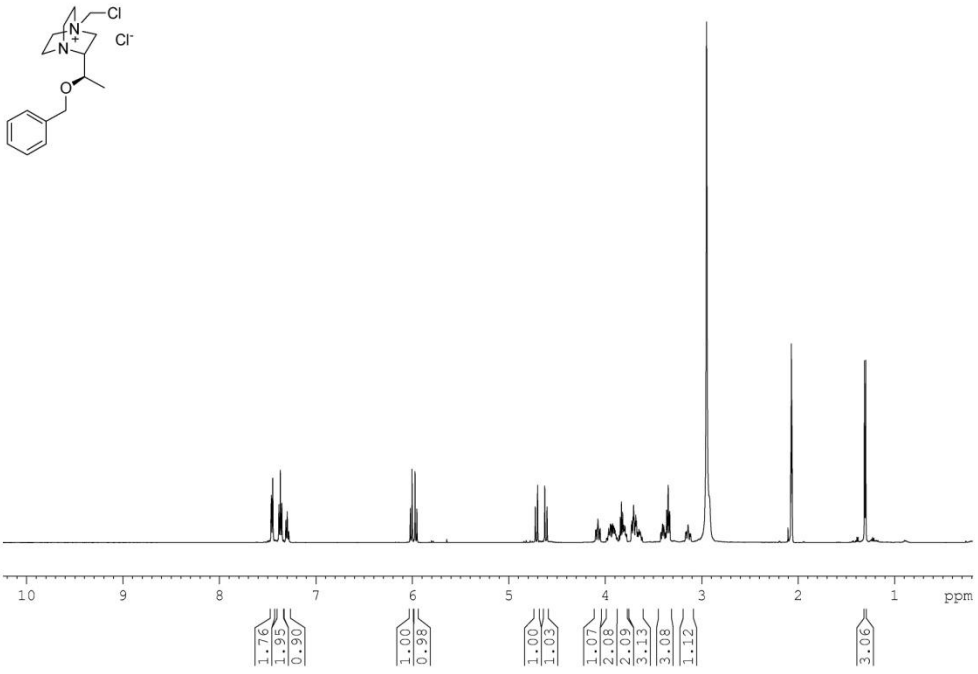

Cl
Cl
N
N
Ph
10
9
8
7
6
5
4
3
2
1
ppm
5.05
2.03
1.00
1.02
1.02
3.03
2.12
1.03
1.03
1.02

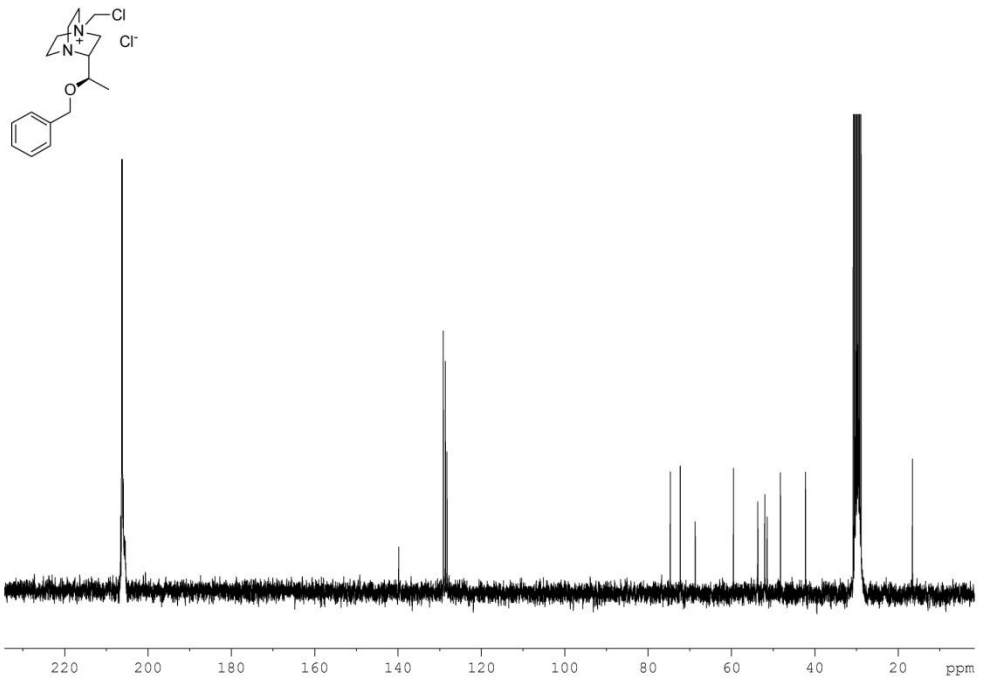

Cl
Cl
N
N
Ph
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

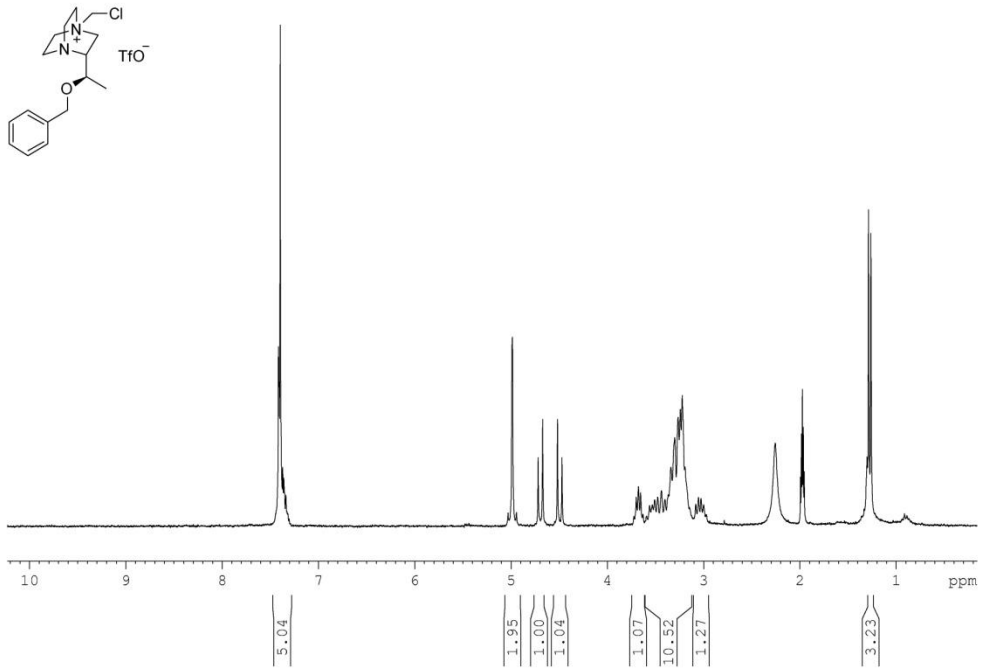

Cl
N
N
OTf
Ph
10
9
8
7
6
5
4
3
2
1
ppm
4.51
2.00
0.95
1.01
4.29
2.81
2.06

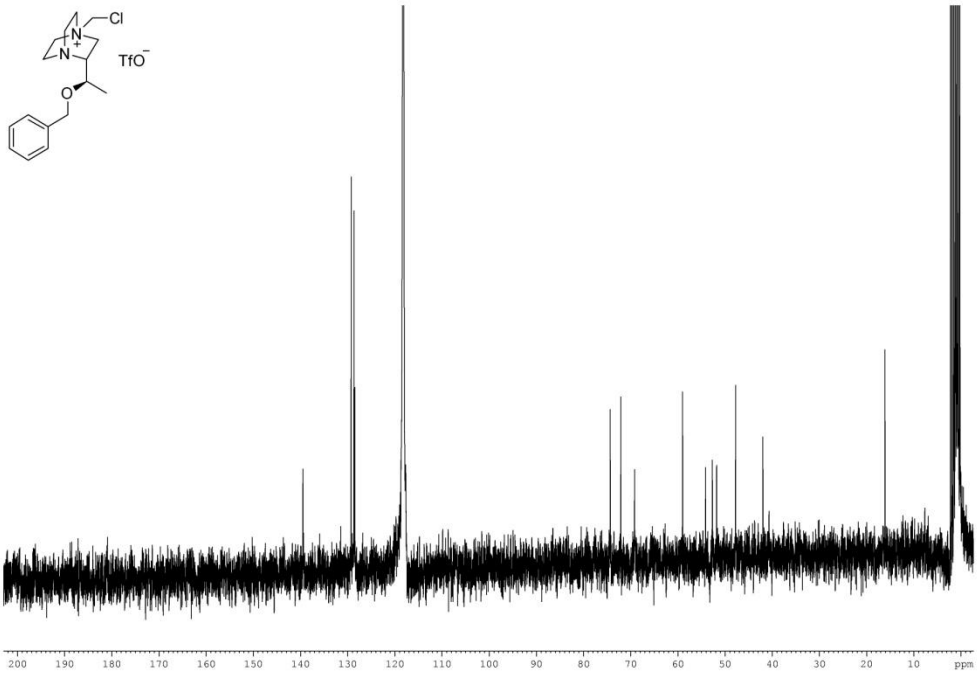

Cl
N
N
OTf
Ph
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

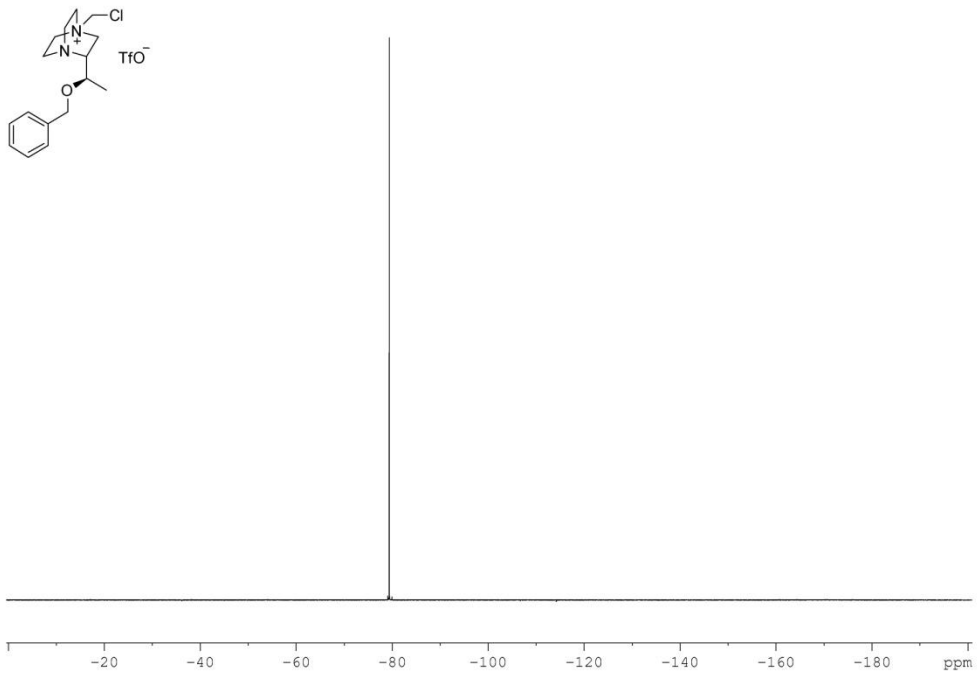

Cl
OTf
Ph
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

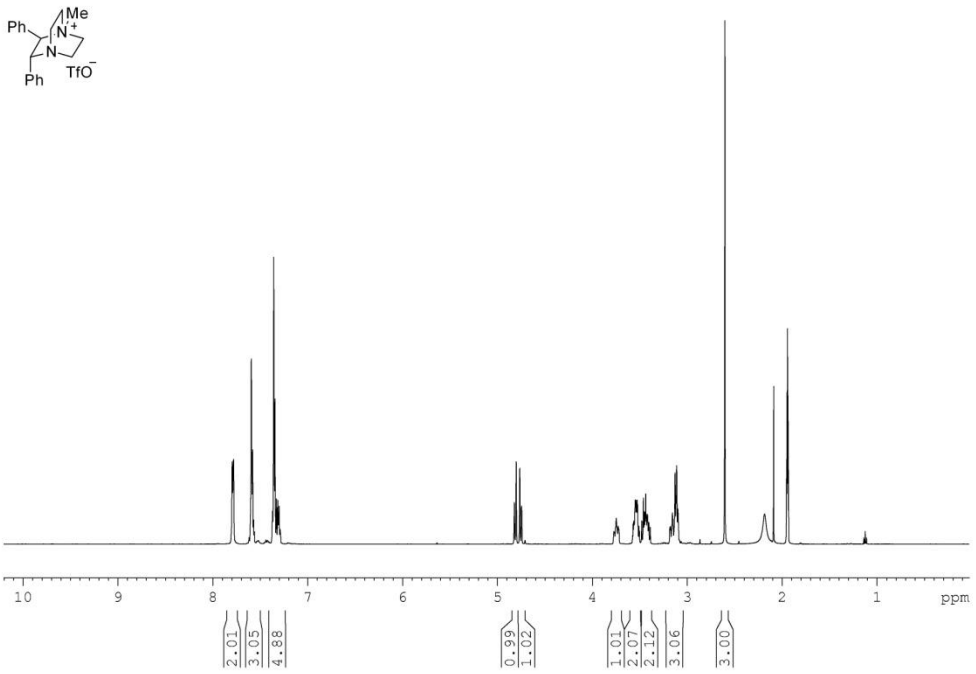

Cl
Cl-
O
10
9
8
7
6
5
4
3
2
1
ppm
1.76
1.95
0.90
1.00
0.98
1.00
1.03
1.07
2.08
2.09
3.13
3.08
1.12
3.06

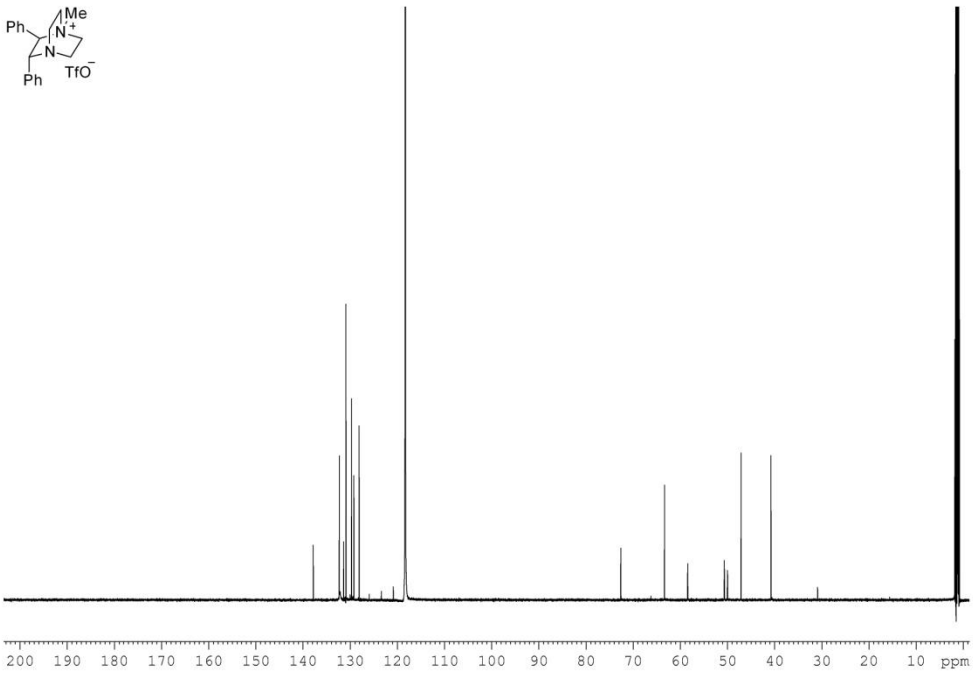

Cl
Cl⁻
N
N
O
220
200
180
160
140
120
100
80
60
40
20
ppm

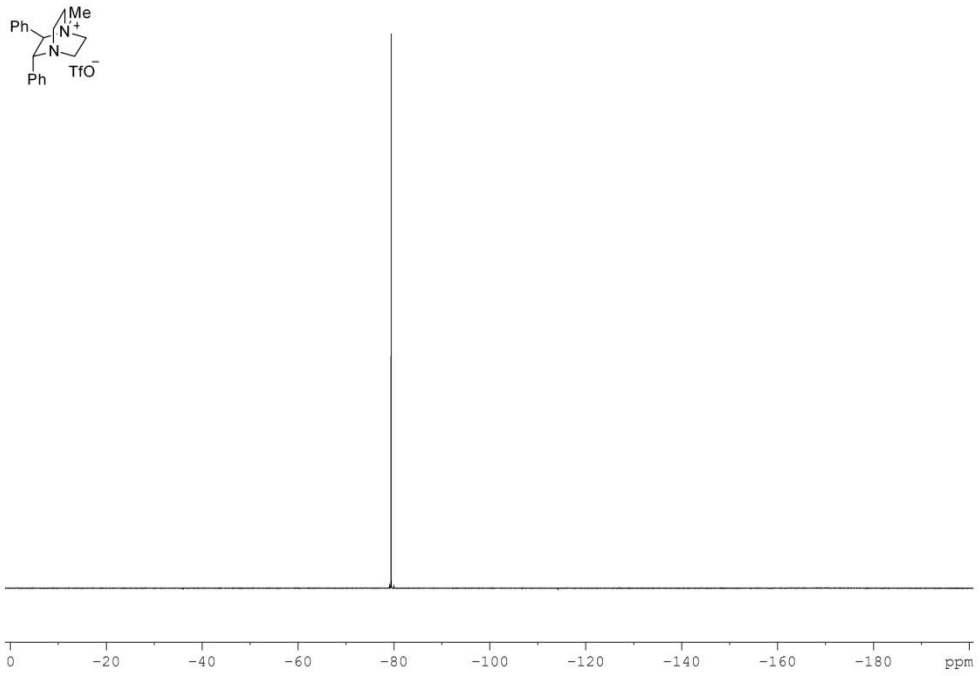

Cl
TfO⁻
N
N
O
10
9
8
7
6
5
4
3
2
1
ppm
5.04
1.95
1.00
1.04
1.07
10.52
1.27
3.23

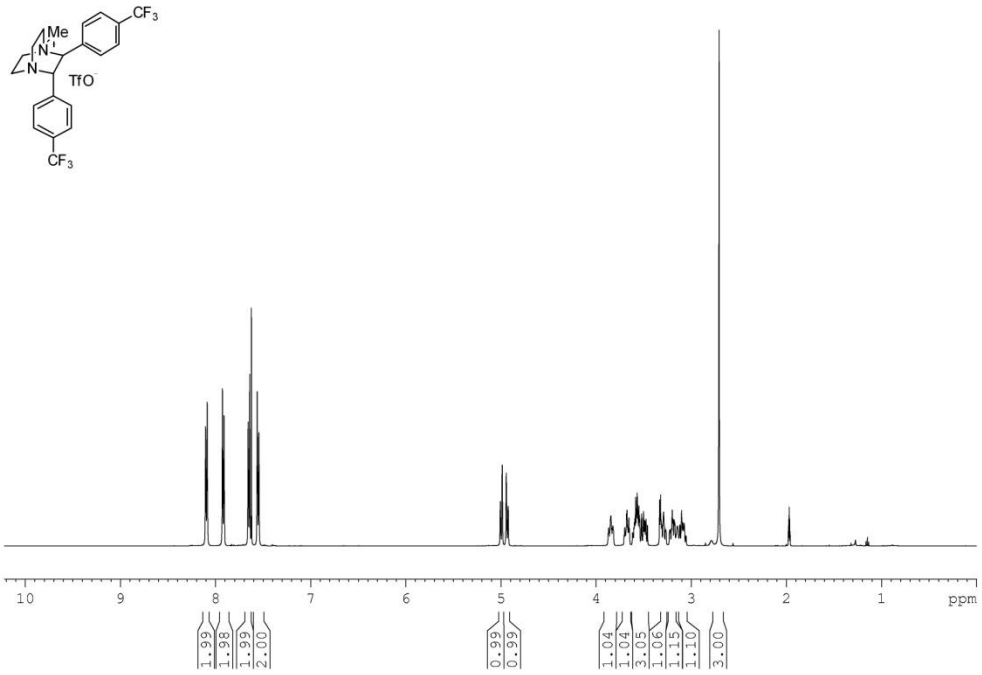

Cl
N
N
TfO⁻
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

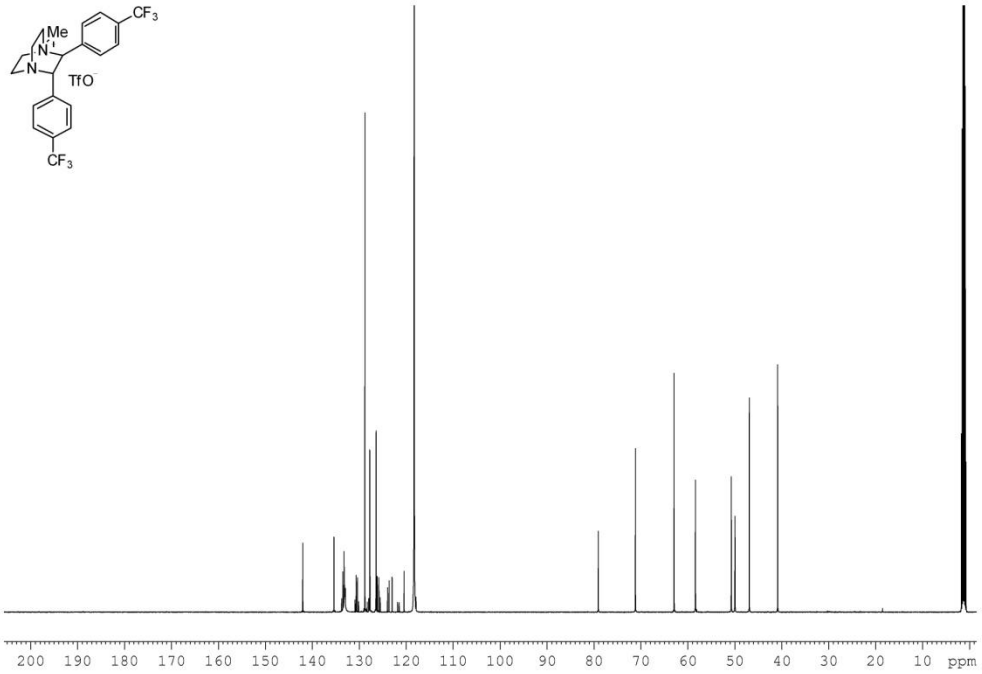

Cl
N
N
TfO⁻
O
-20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

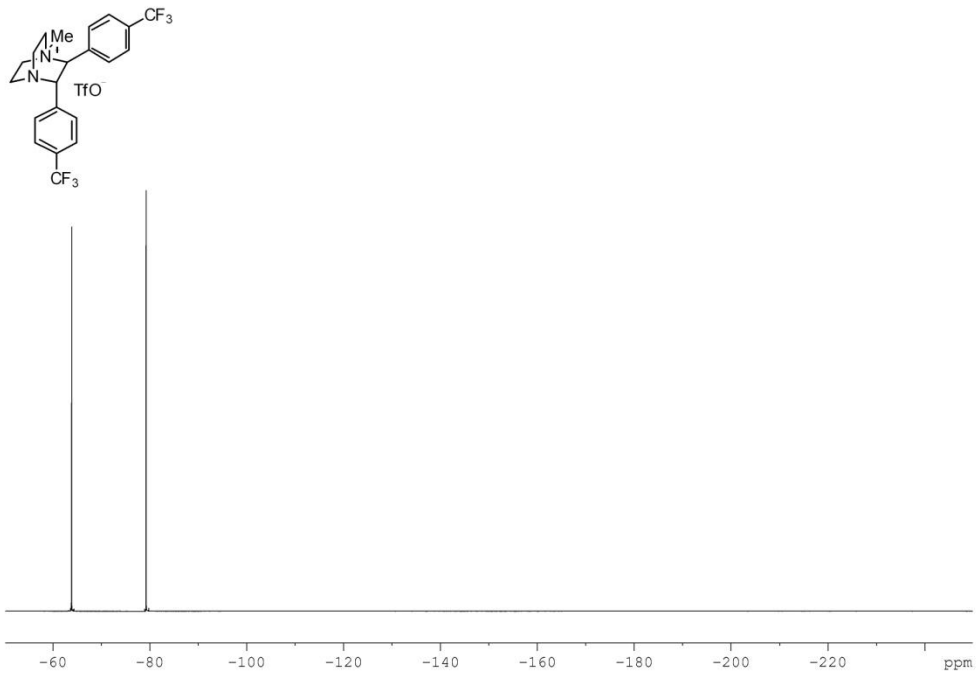

Ph
Me
N+
N
Ph
TfO−
10
9
8
7
6
5
4
3
2
1
ppm
2.01
3.05
4.88
0.99
1.02
1.01
2.07
2.12
3.06
3.00

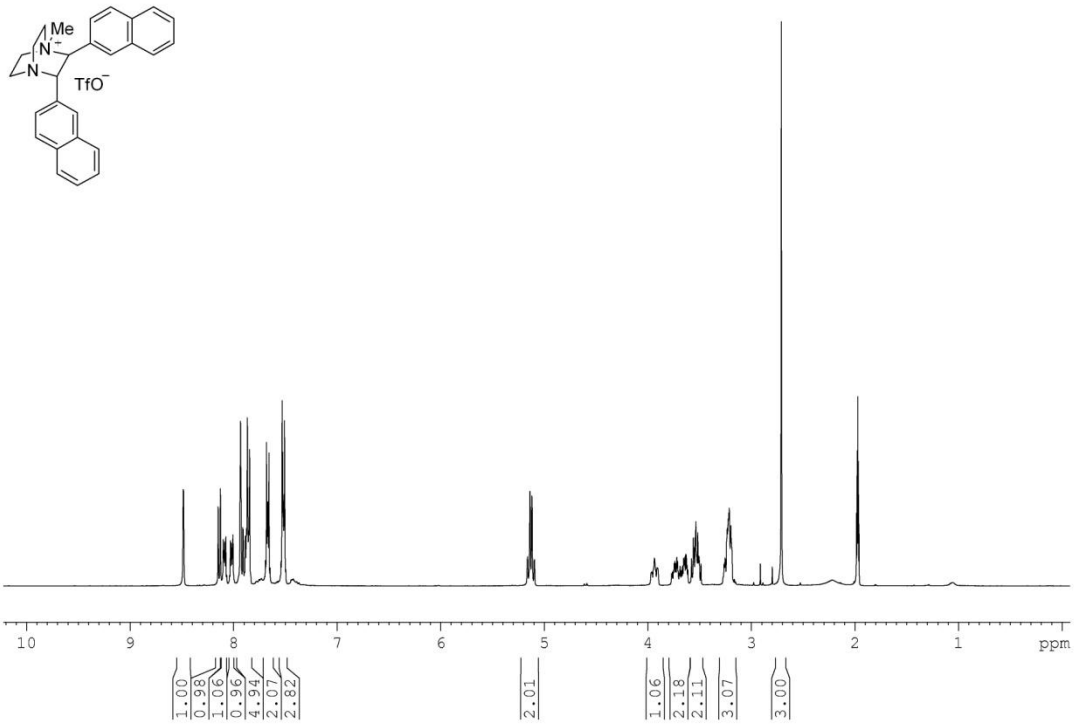

Ph
Me
N+
N
Ph
TfO−
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

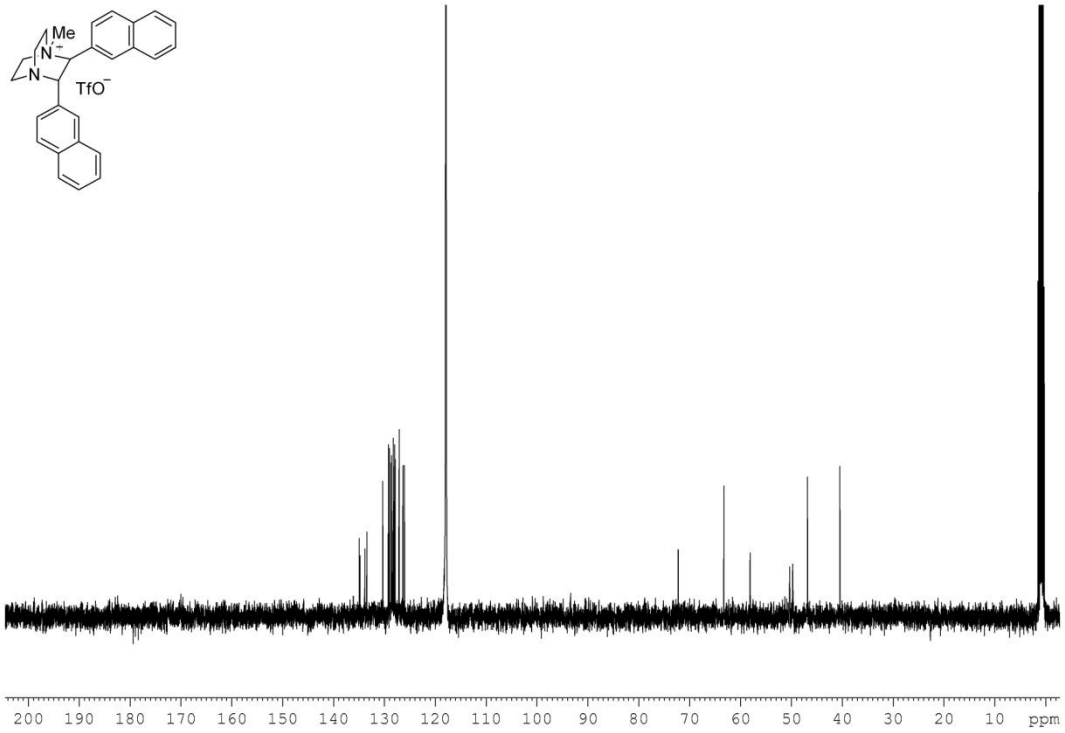

Me
Ph
N+
N
TfO−
Ph
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

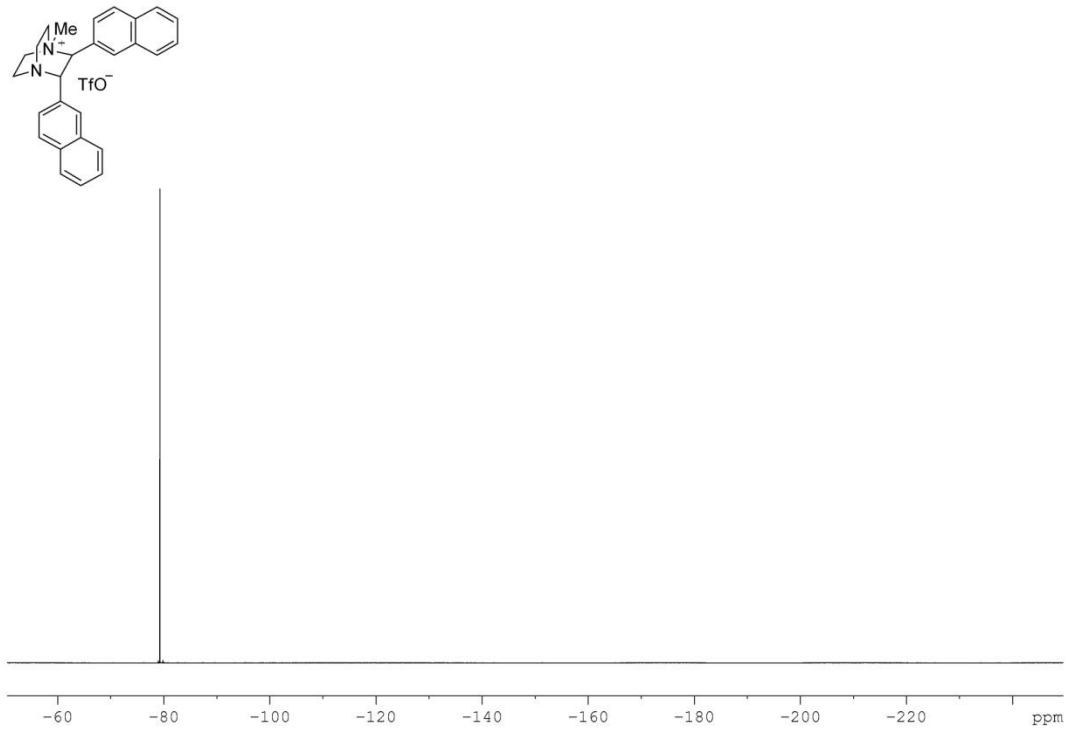

CF3
Me
N+
N
TfO−
CF3
10
9
8
7
6
5
4
3
2
1
ppm
1.99
1.98
1.99
2.00
0.99
0.99
1.04
1.04
3.05
1.06
1.15
1.10
3.00

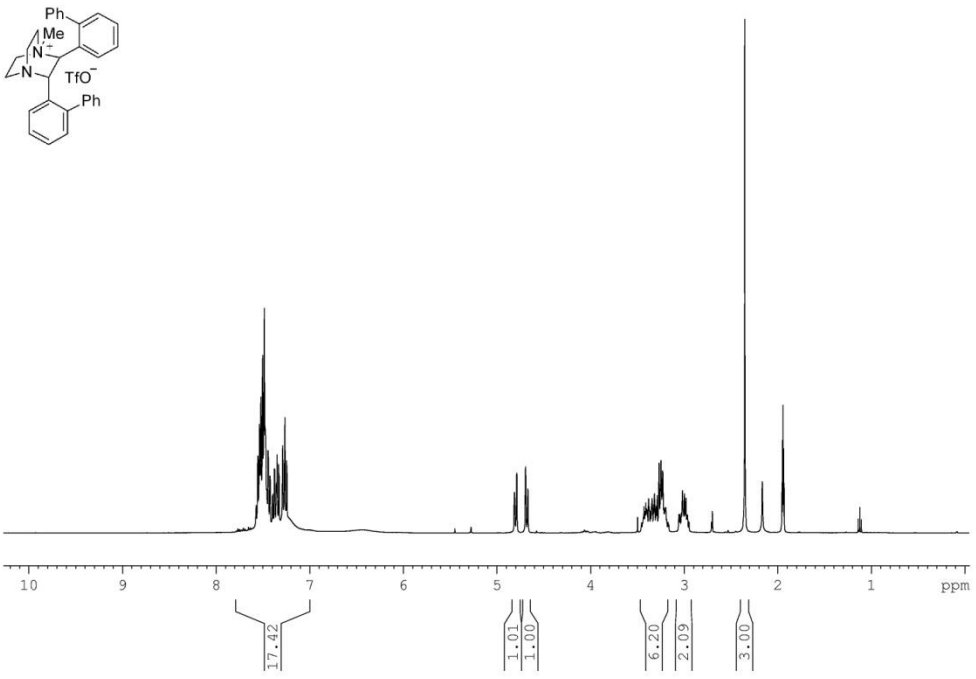

Me
N
N
TfO
CF3
CF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

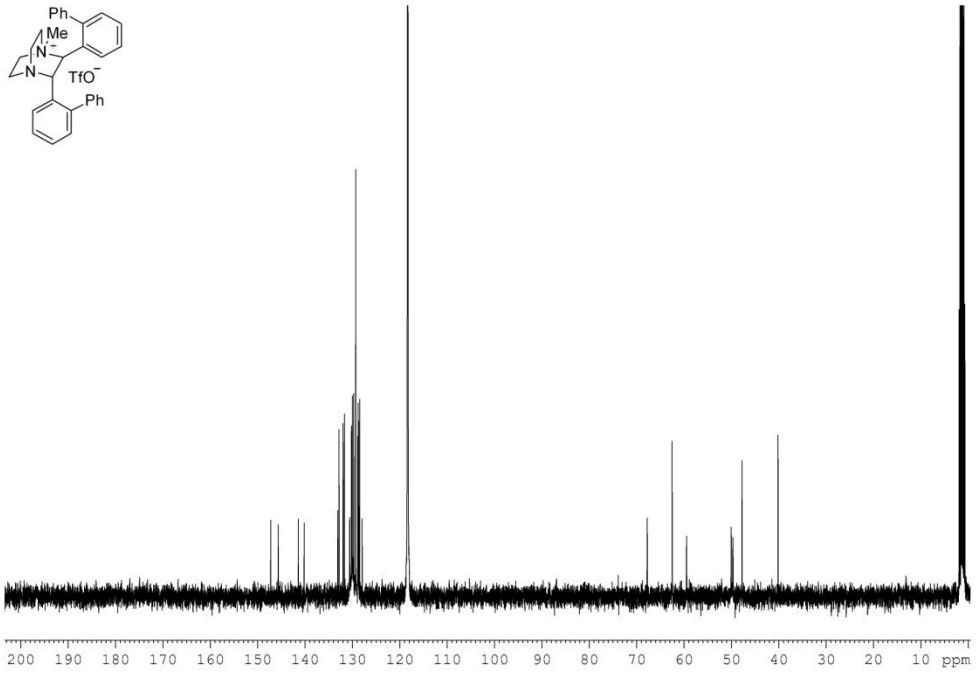

Me
N
N
TfO
CF3
CF3
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

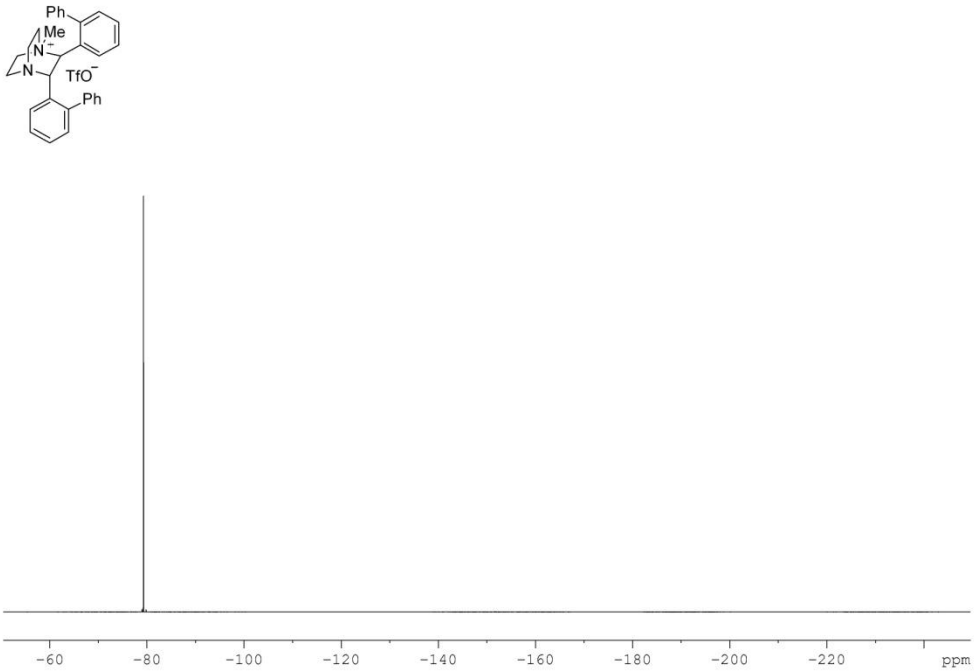

Me
N
N
TfO⁻
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.98
1.06
0.96
4.94
2.07
2.82
2.01
1.06
2.18
2.11
3.07
3.00

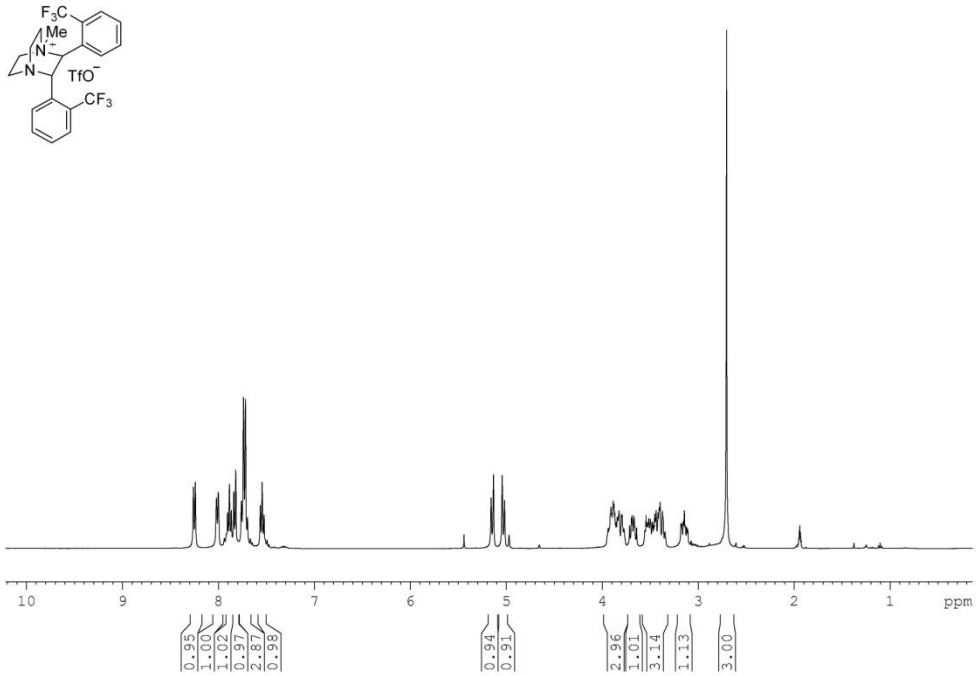

Me
N
N
TfO⁻
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

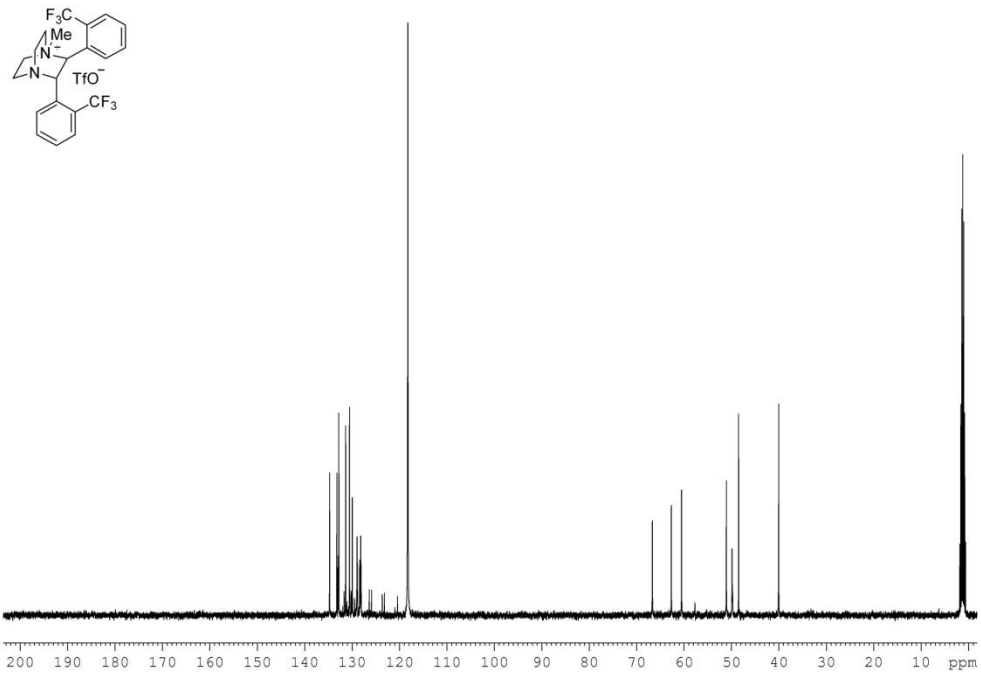

Me
N
N
TfO⁻
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

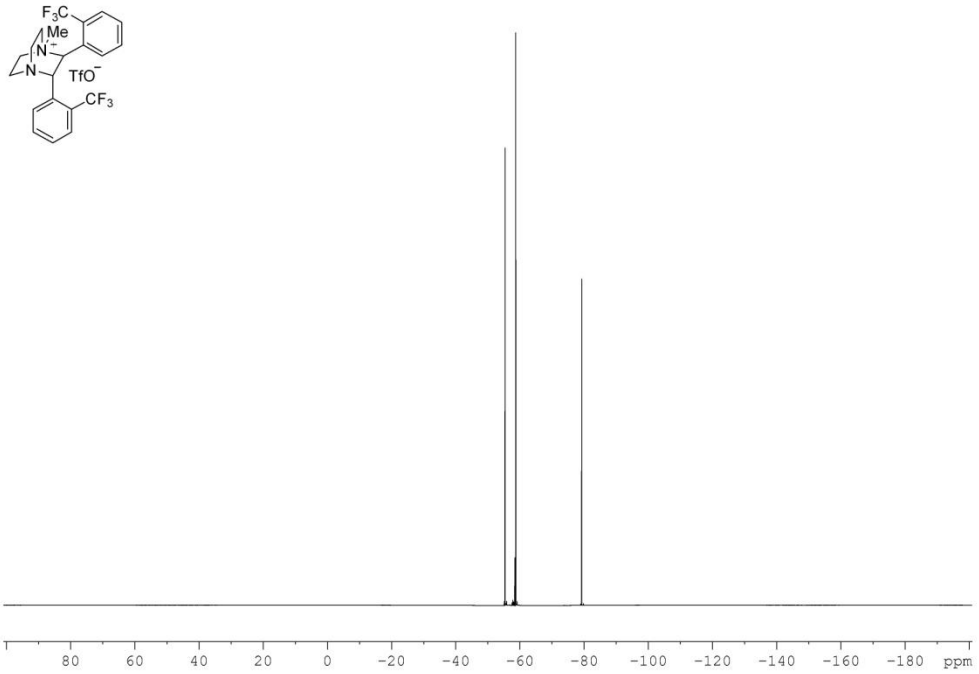

Ph
Me
N
N
TfO⁻
Ph
10
9
8
7
6
5
4
3
2
1
ppm
17.42
1.01
1.00
6.20
2.09
3.00

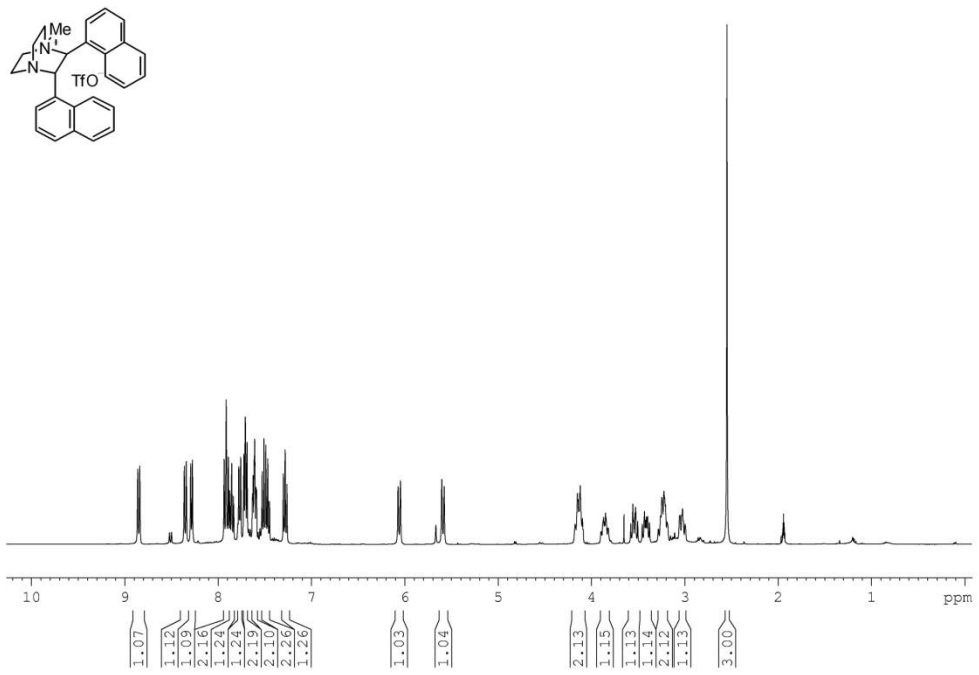

Ph
Me
N
N
TfO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

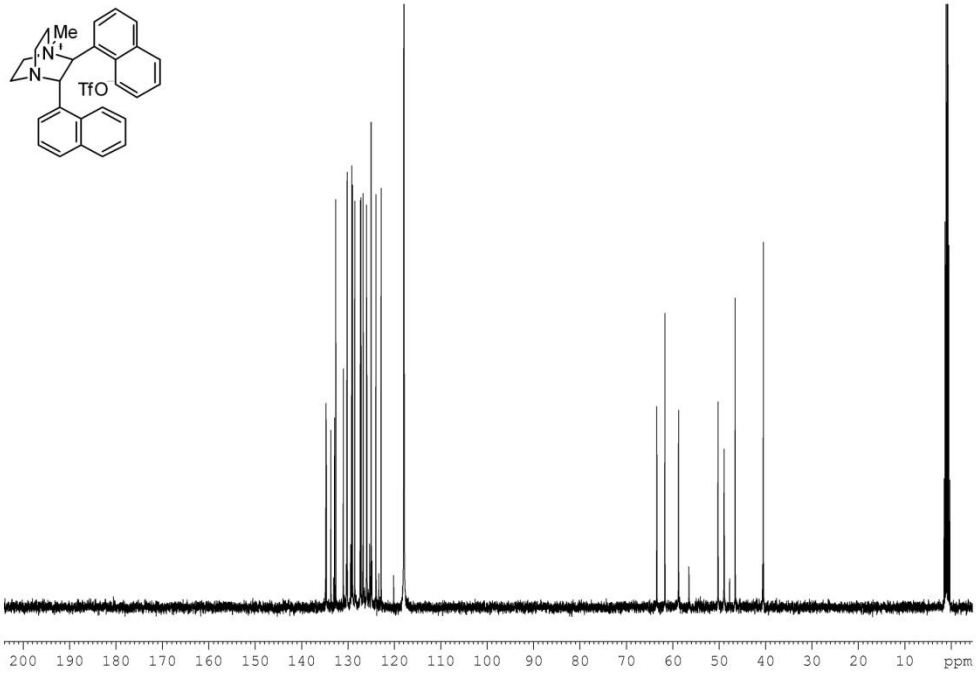

Ph
Me
N
N
TfO
Ph
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

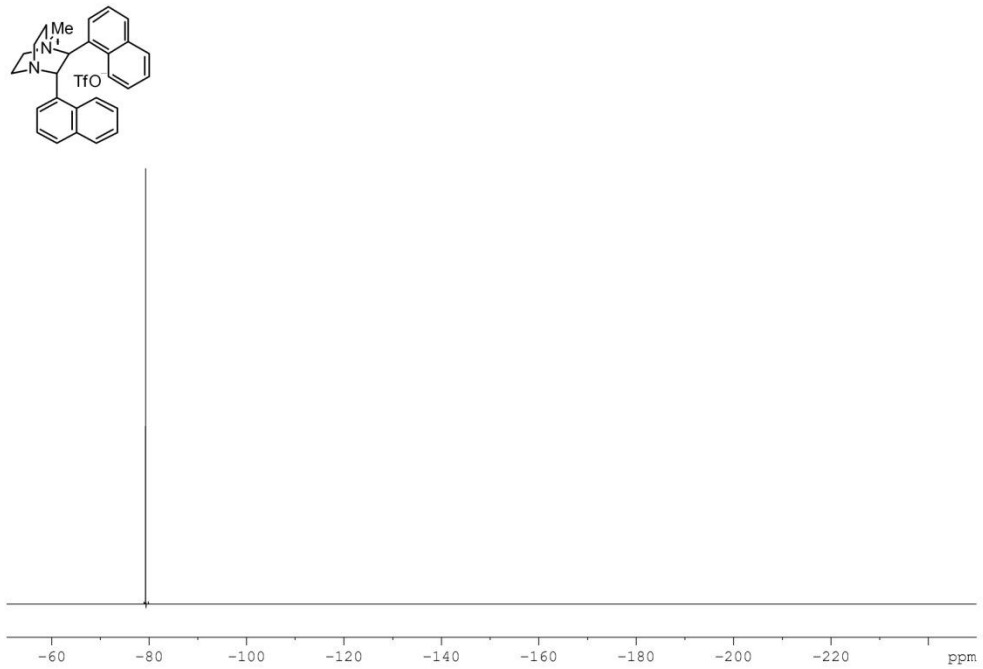

F3C
Me
N+
N
TfO−
CF3
10 9 8 7 6 5 4 3 2 1 ppm
0.95 1.00 1.02 0.97 2.87 0.98
0.94 0.91
2.96 1.01 3.14 1.13 3.00

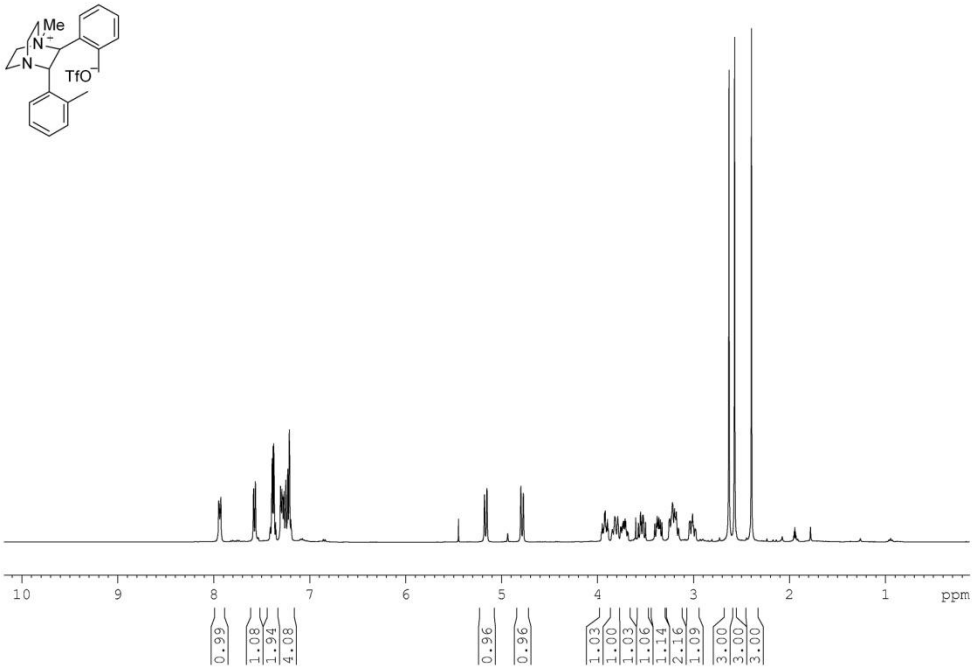

F3C
Me
N+
N
TfO−
CF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

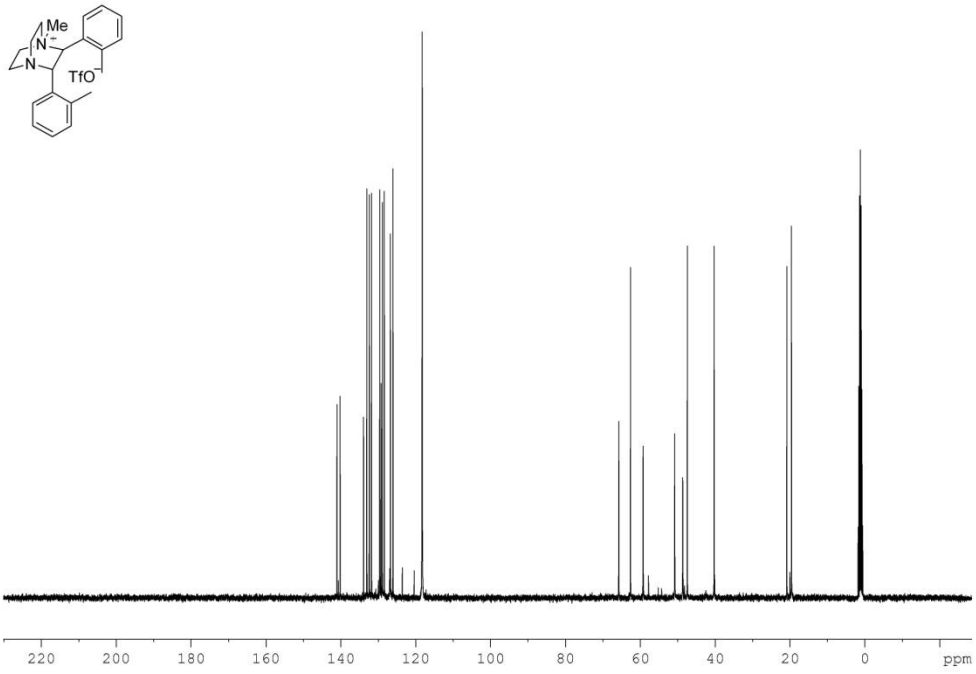

F3C
Me
N+
N
TfO−
CF3
80
60
40
20
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
ppm

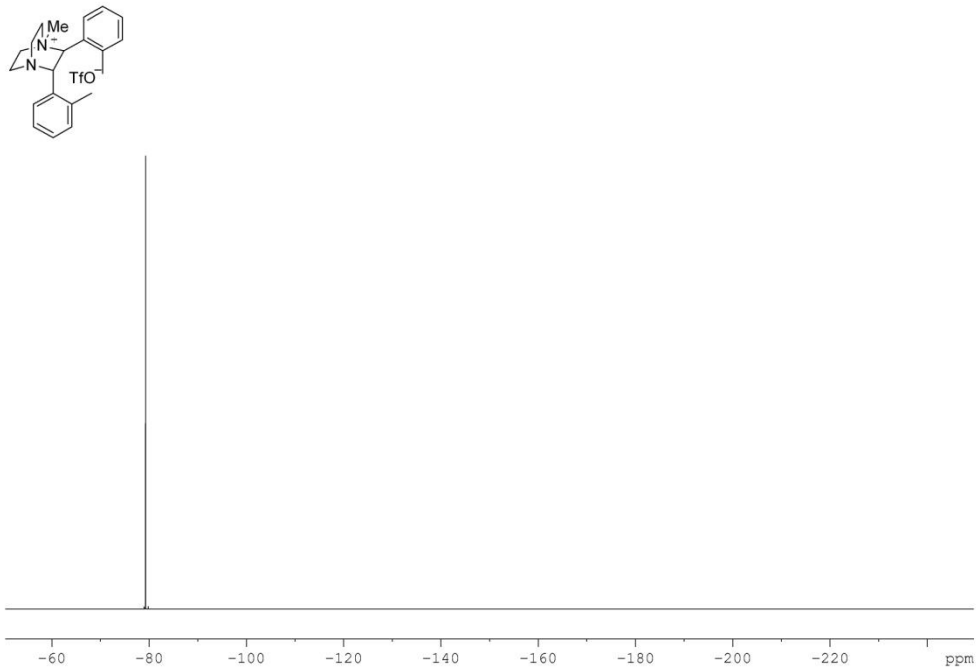

Me
N+
N
TfO
10
9
8
7
6
5
4
3
2
1
ppm
1.07
1.12
1.09
2.16
1.24
1.24
2.19
2.10
2.26
1.26
1.03
1.04
2.13
1.15
1.13
1.14
2.12
1.13
3.00

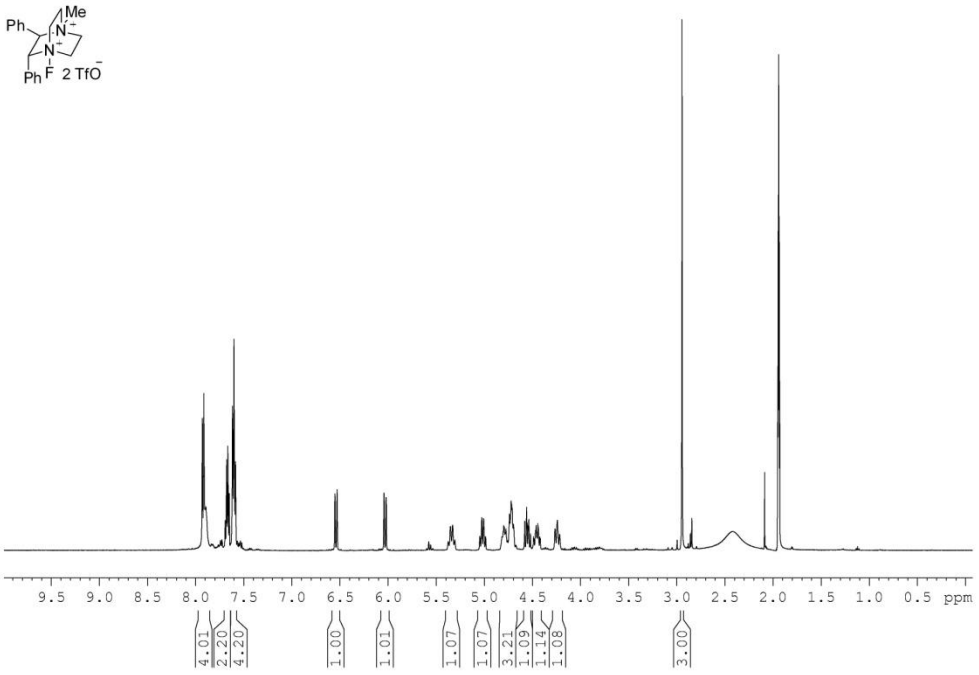

Me
N
N
TfO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

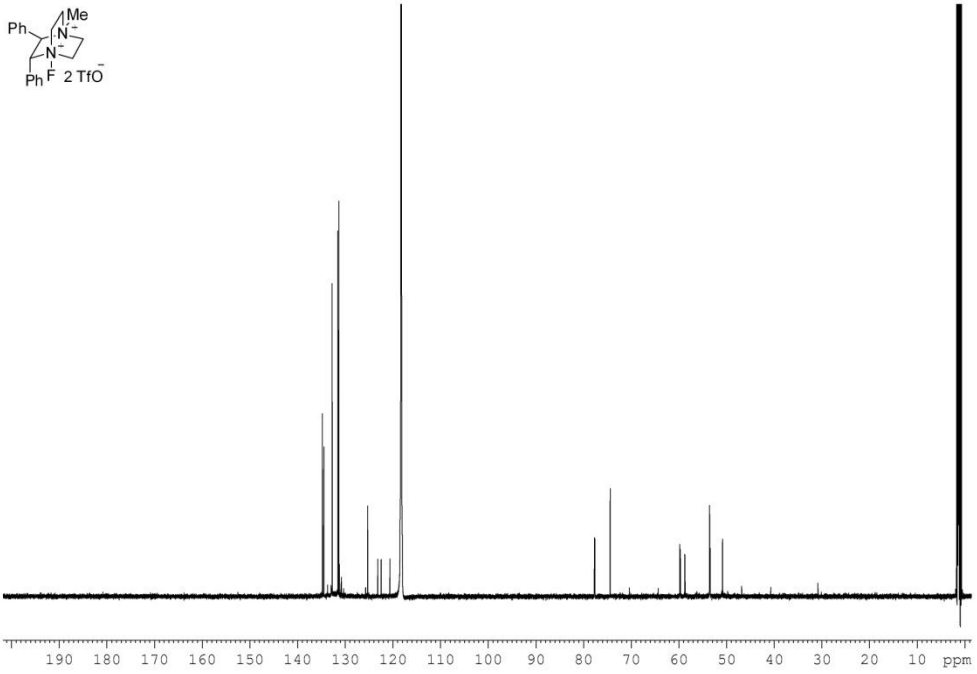

Me
N
N
TfO
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

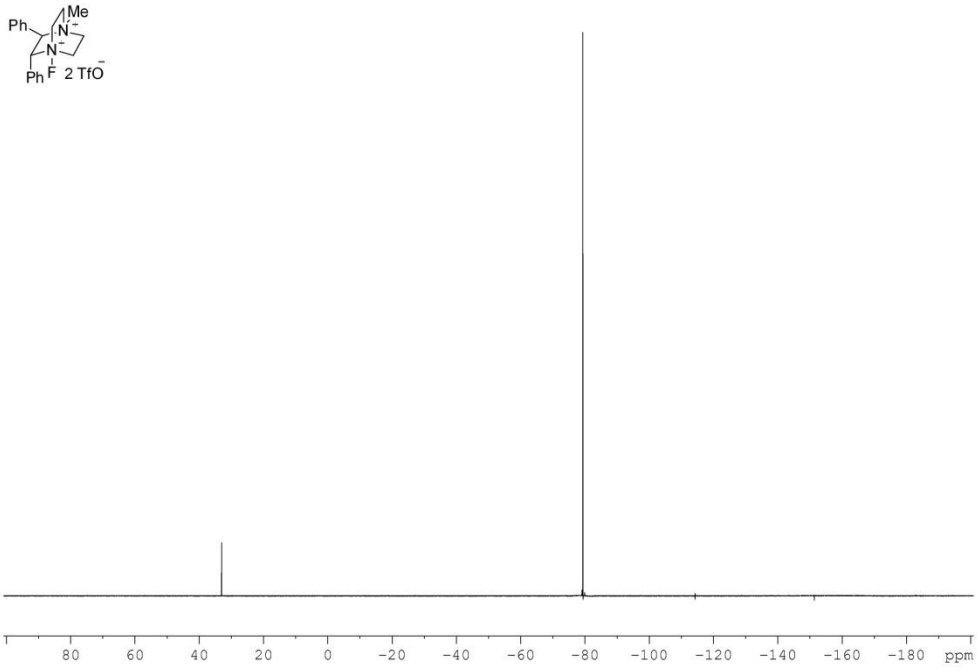

Me
N
N
TfO
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.08
1.94
4.08
0.96
0.96
1.03
1.00
1.03
1.06
1.14
2.16
1.09
3.00
3.00
3.00

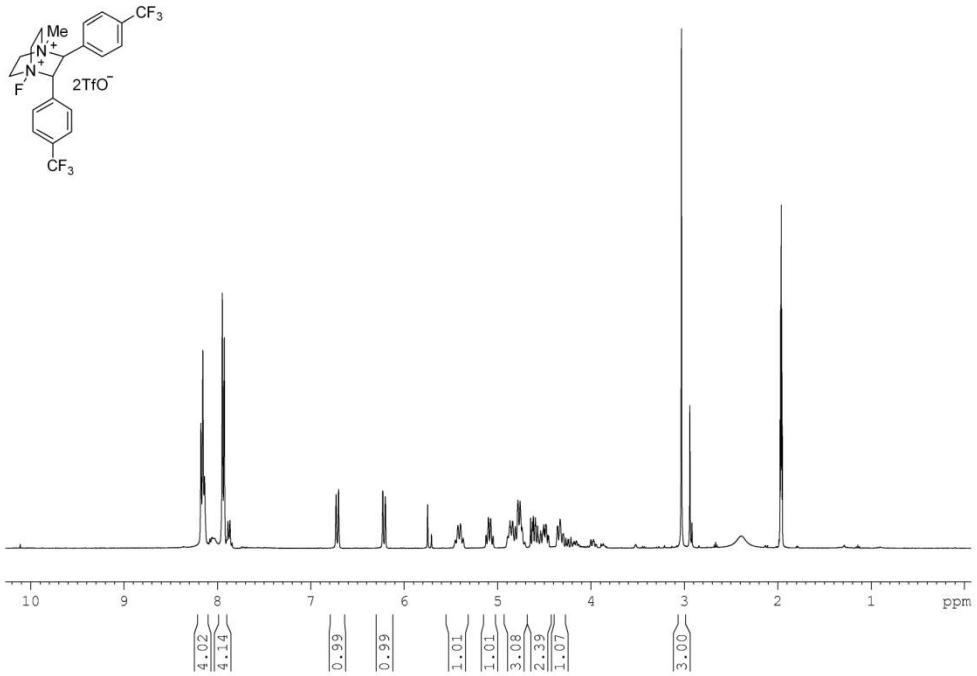

Me
N
N
TfO
220
200
180
160
140
120
100
80
60
40
20
0
ppm

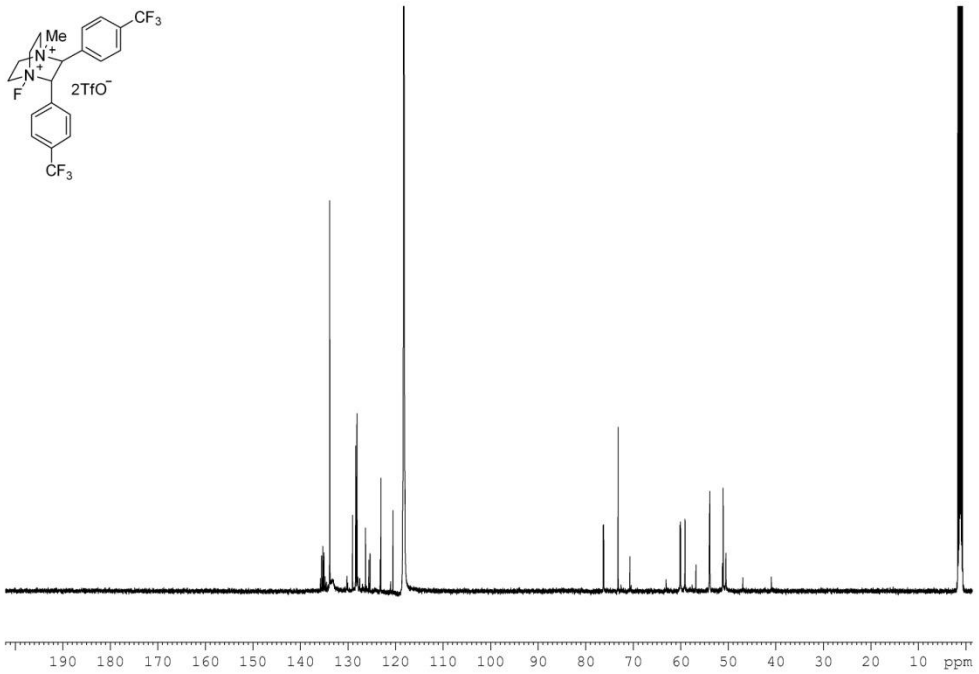

Me
N
N
TfO
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

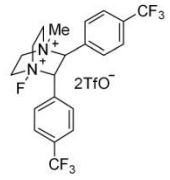

Ph
Me
N
N
Ph
F
2 TfO
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.01
2.20
4.20
1.00
1.01
1.07
1.07
3.21
1.09
1.14
1.08
3.00

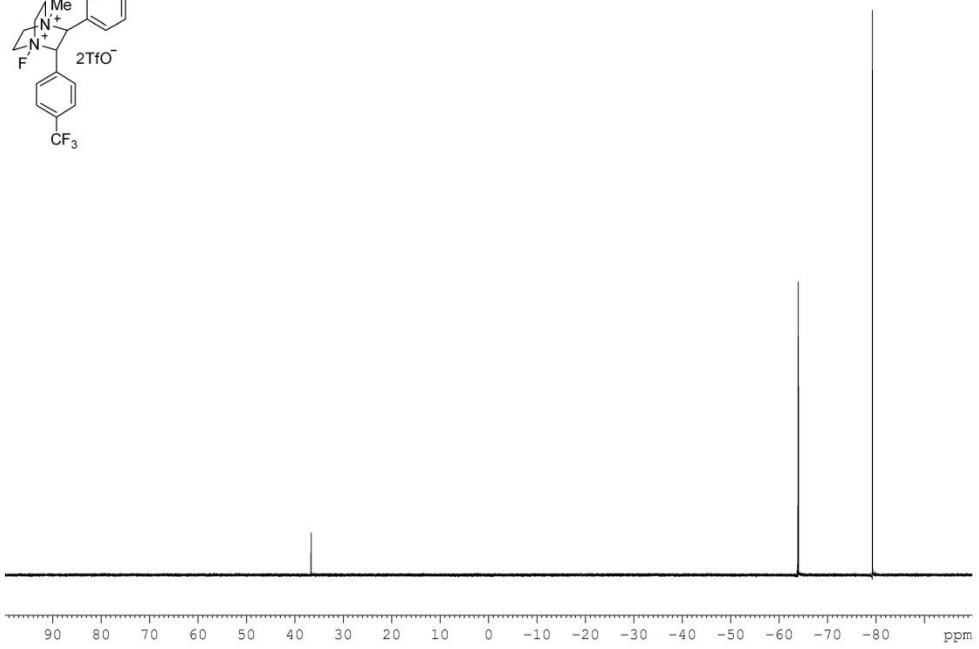

Ph
Me
N
N
Ph
F
2 TfO
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Ph
Me
N
N
Ph
F
2 TfO
80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

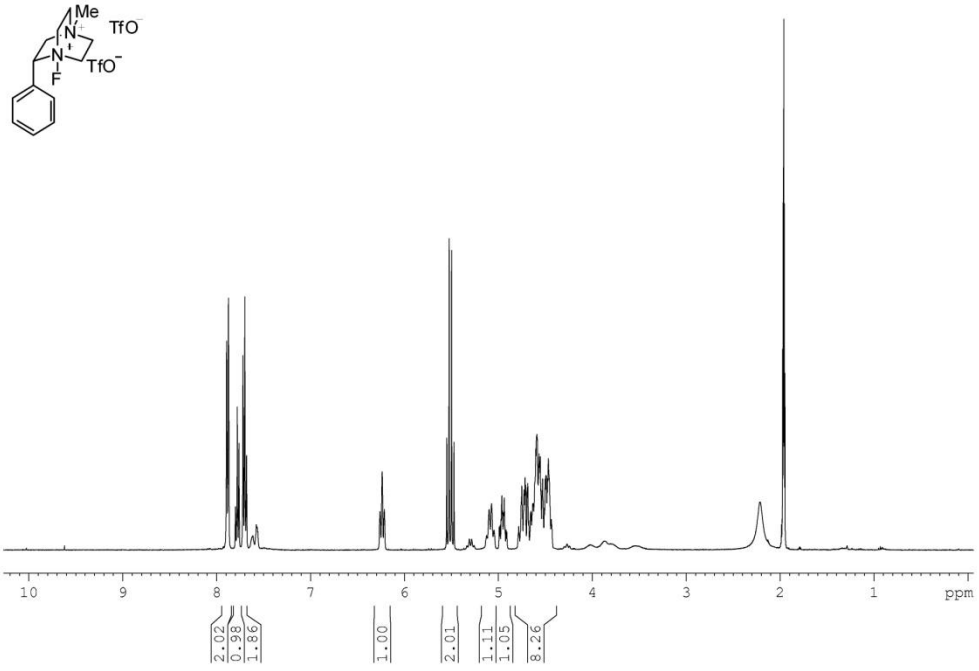

Me
N+
N+
F
2TfO−
CF3
CF3
10
9
8
7
6
5
4
3
2
1
ppm
4.02
4.14
0.99
0.99
1.01
1.01
3.08
2.39
1.07
3.00

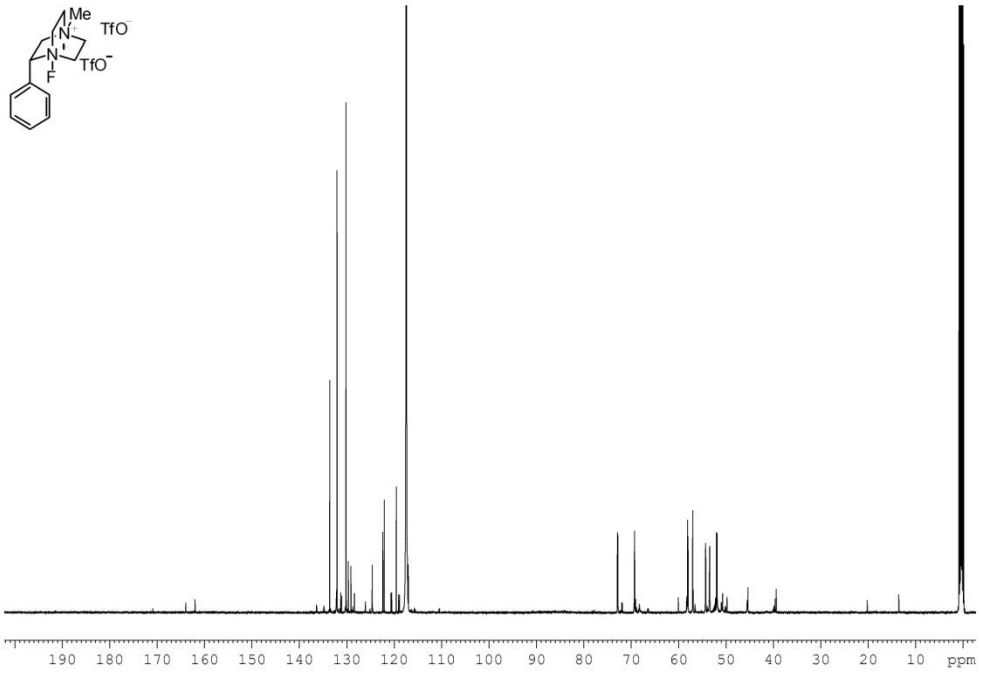

Me
N+
N+
F
2TfO−
CF3
CF3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

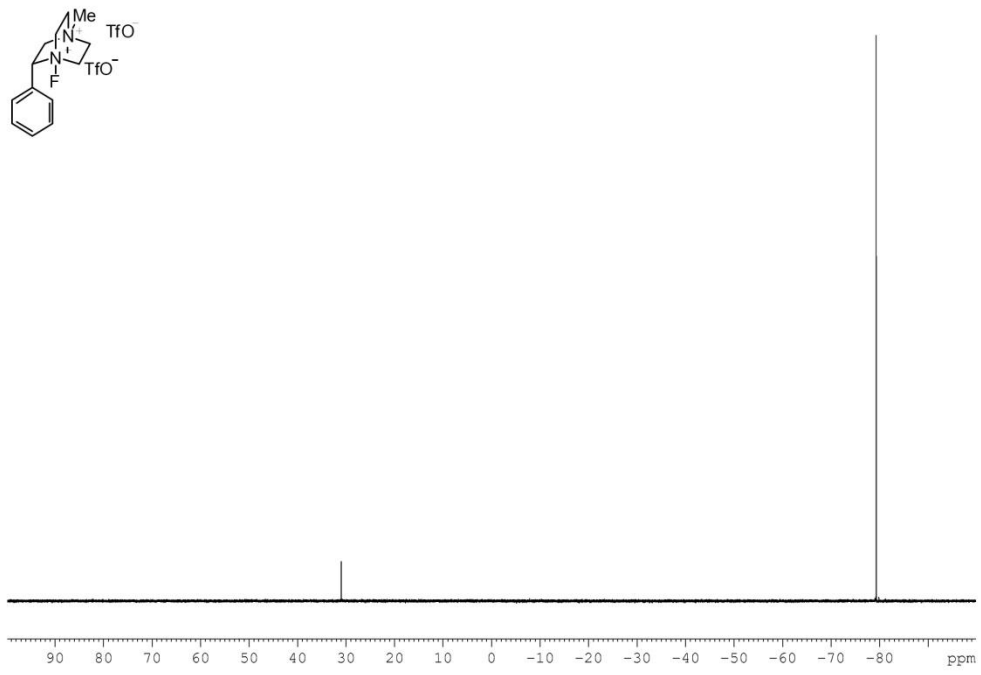

Me
N+
N+
F
2TfO−
CF3
CF3

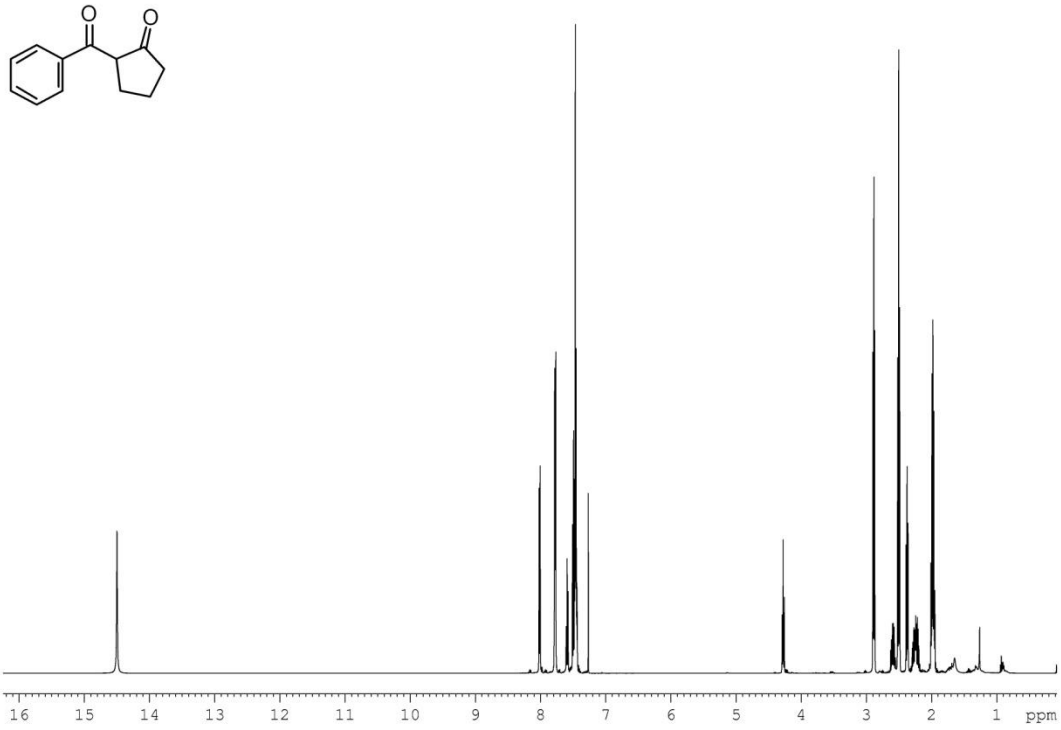

90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 ppm

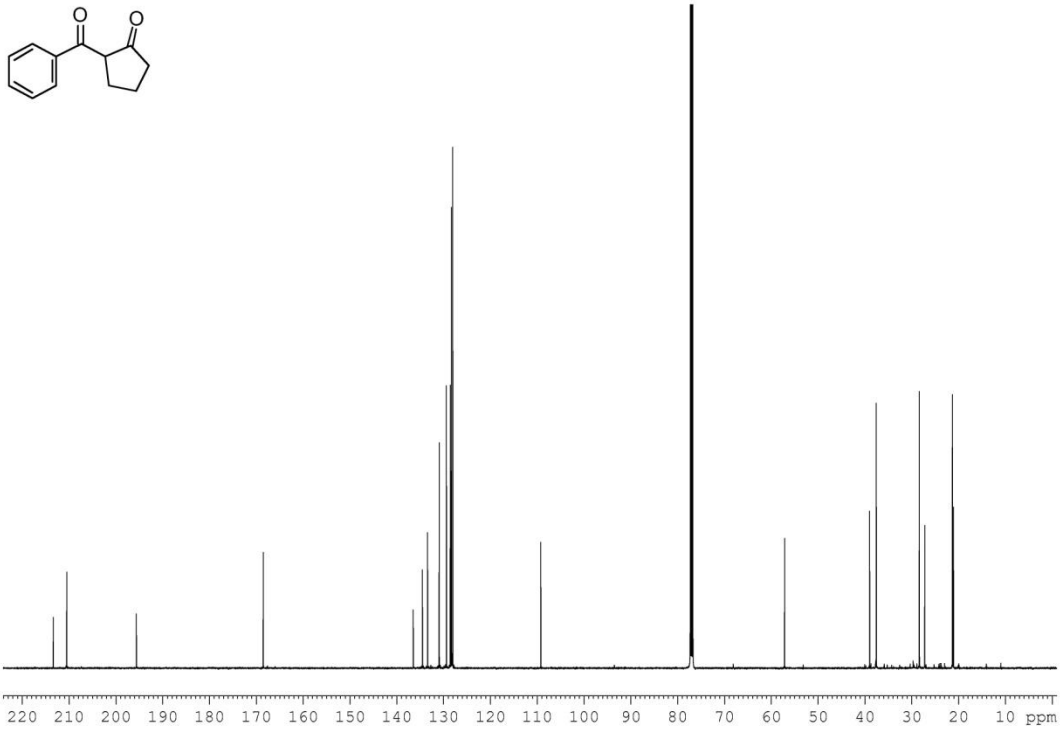
Me
N+
N+
F
TfO−
TfO−

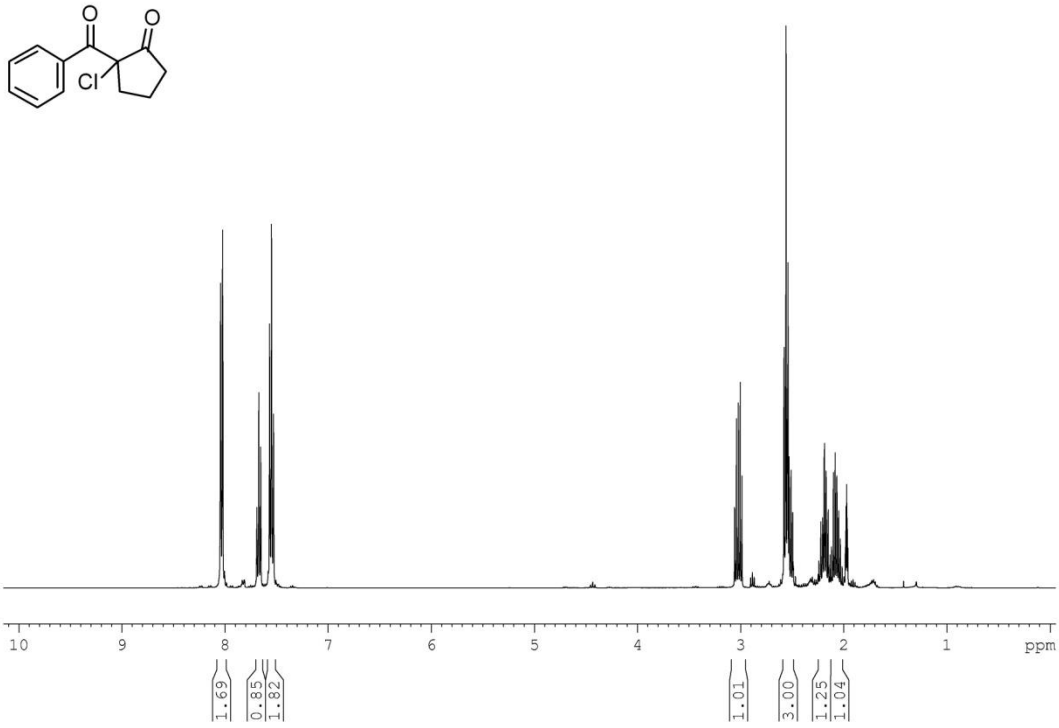

10 9 8 7 6 5 4 3 2 1 ppm
2.02
0.98
1.86
1.00
2.01
1.11
1.05
8.26

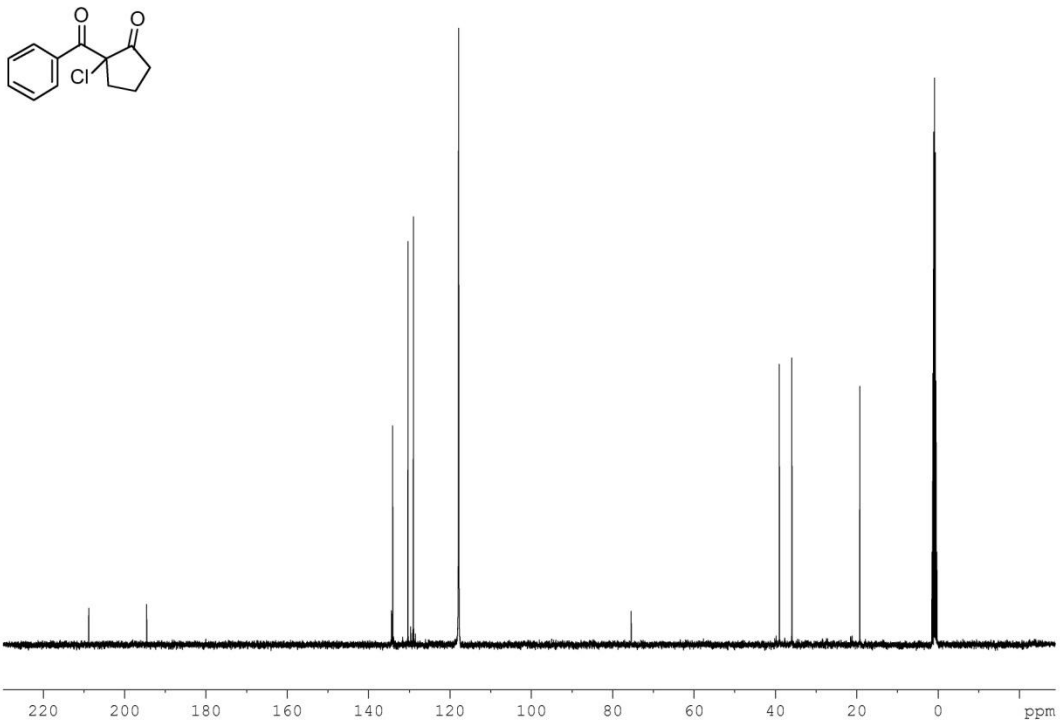

Me
TfO⁻
TfO⁻
F
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

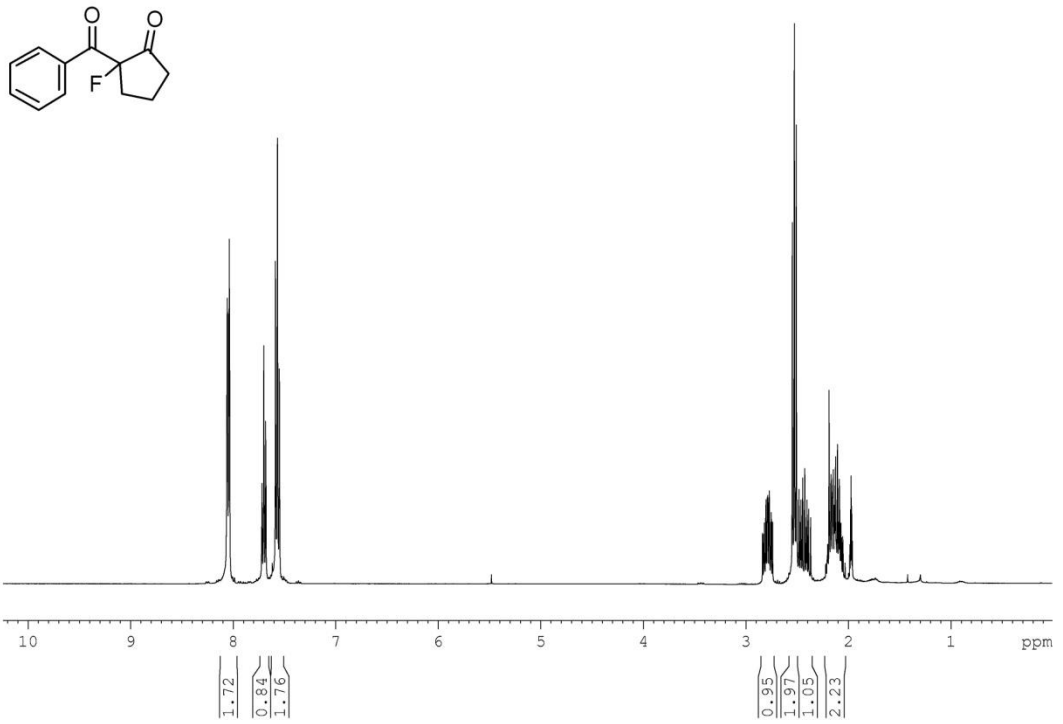

Me
TfO⁻
TfO⁻
F
90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 ppm

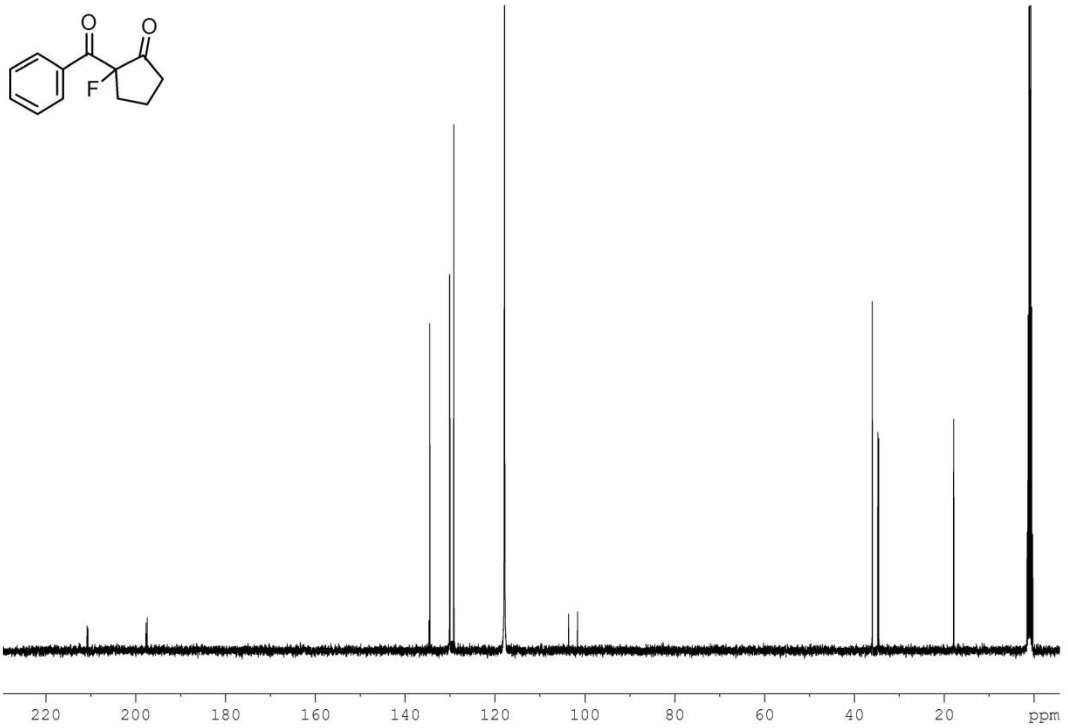

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

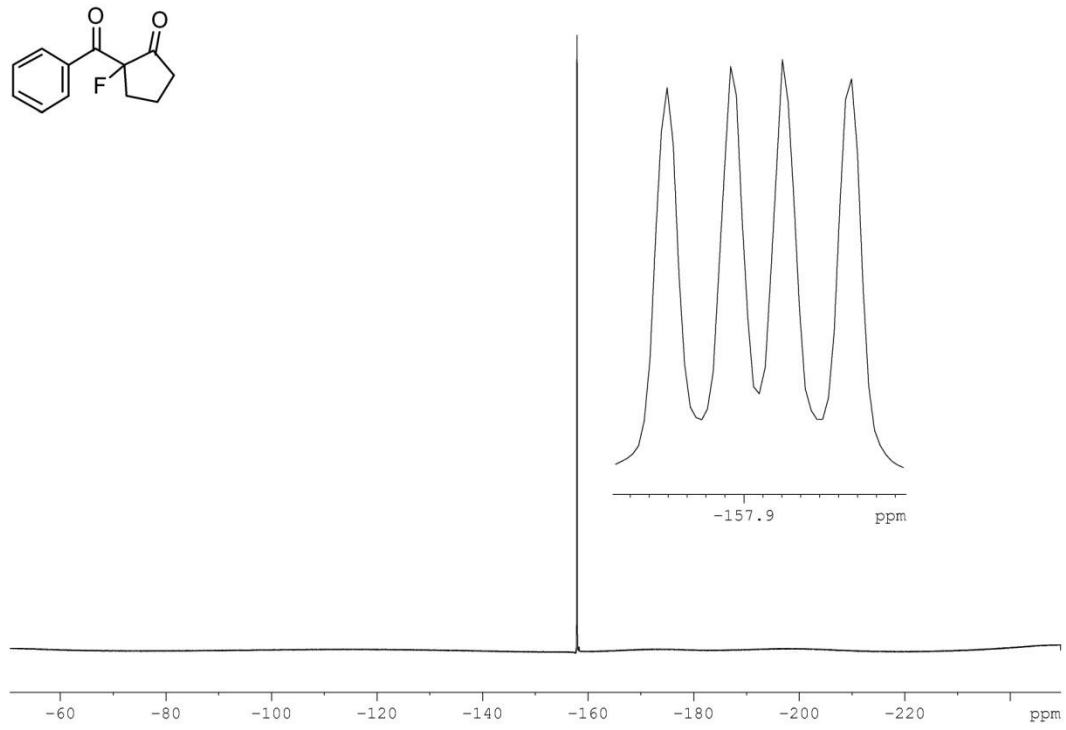

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

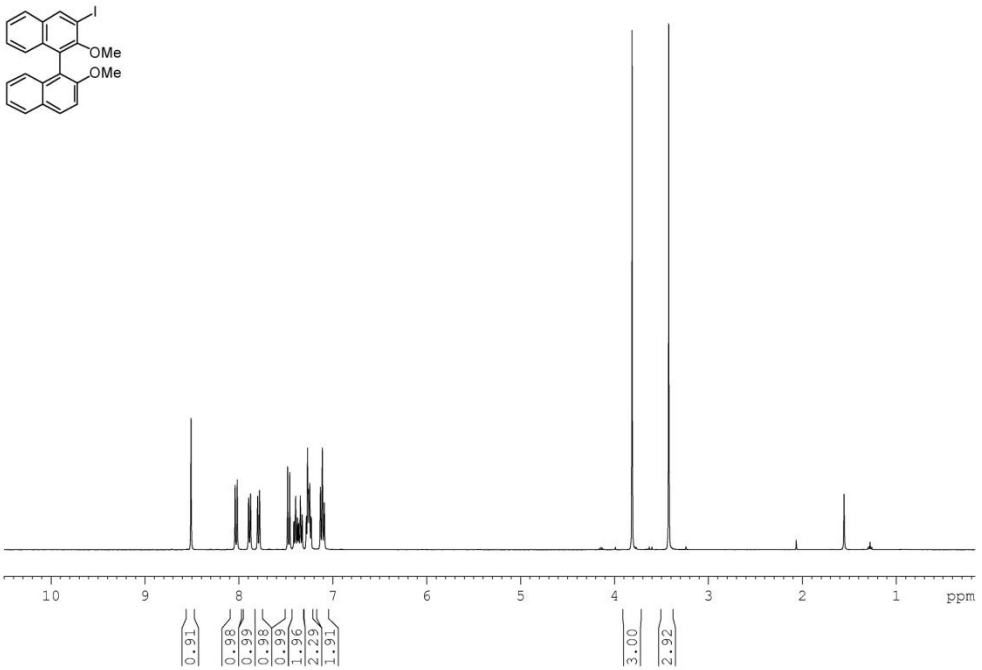

O
O
Cl
10
9
8
7
6
5
4
3
2
1
ppm
1.69
0.85
1.82
1.01
3.00
1.25
1.04

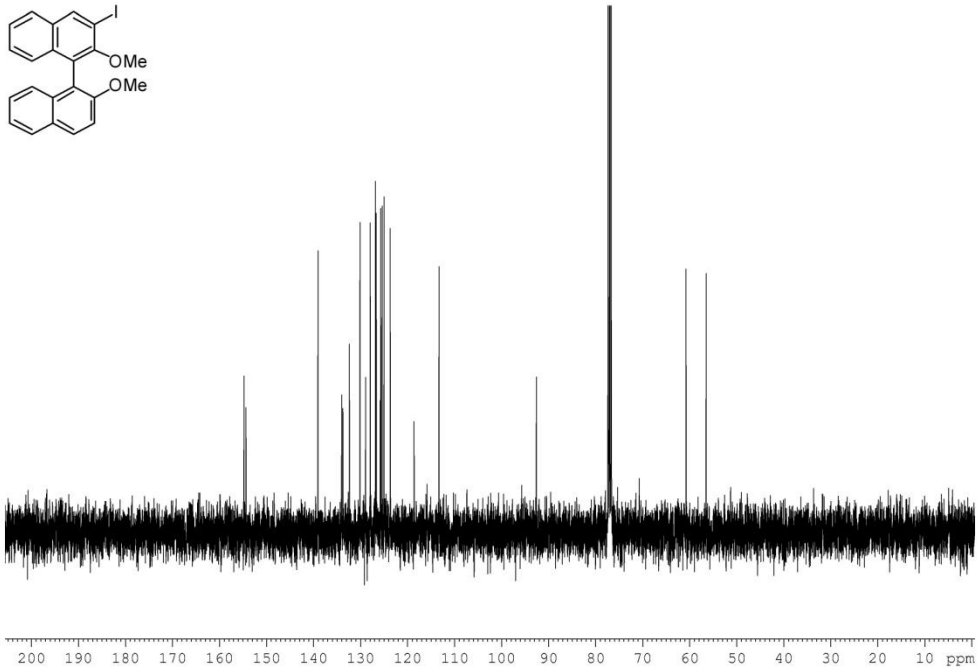

O
O
Cl
220
200
180
160
140
120
100
80
60
40
20
0
ppm

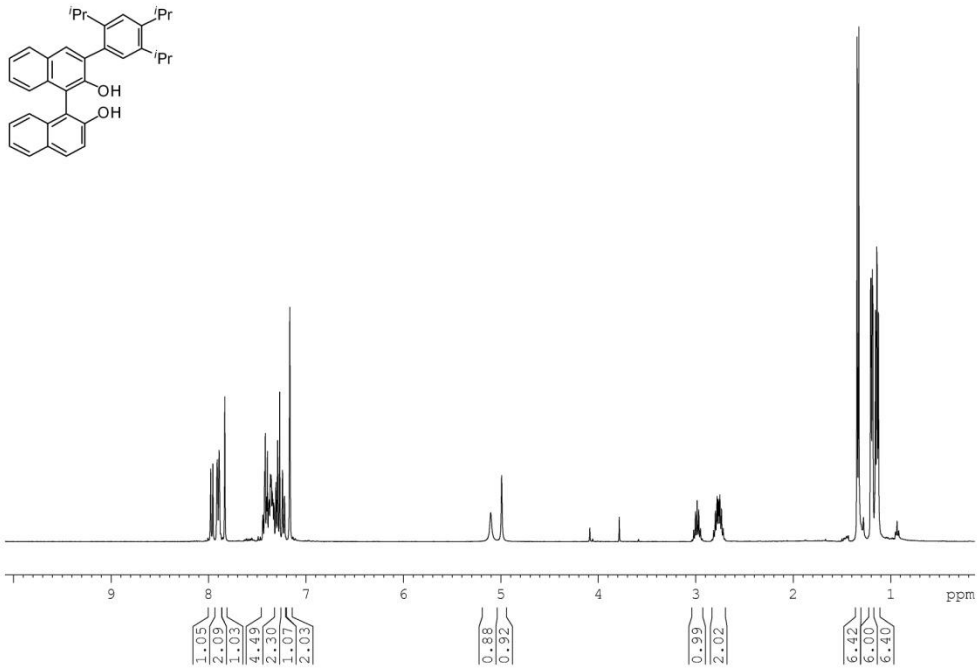

O
O
F
10
9
8
7
6
5
4
3
2
1
ppm
1.72
0.84
1.76
0.95
1.97
1.05
2.23

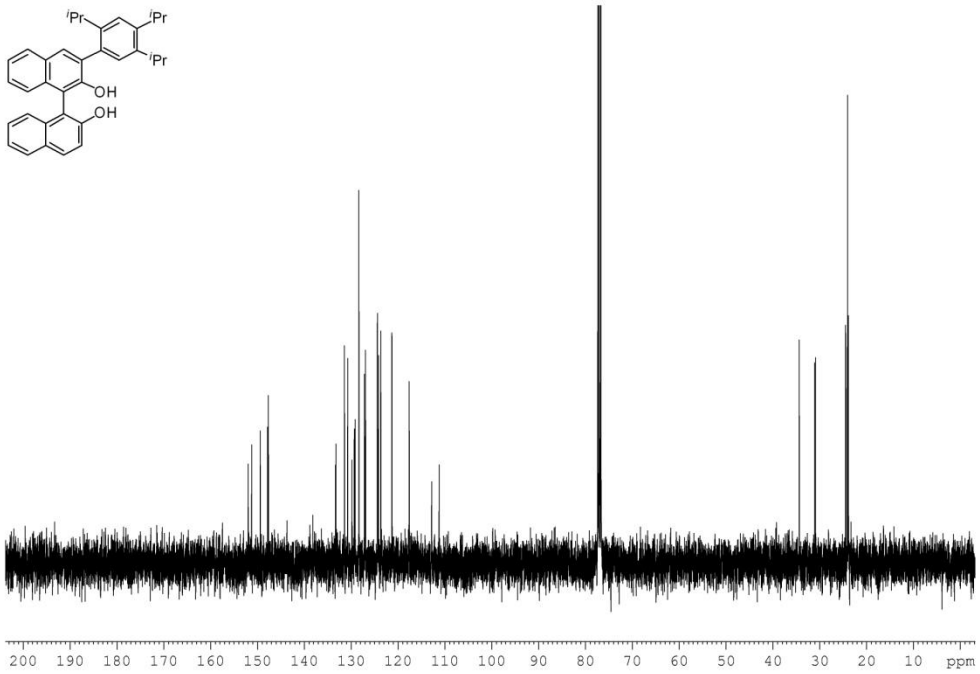

O
O
F
220
200
180
160
140
120
100
80
60
40
20
ppm

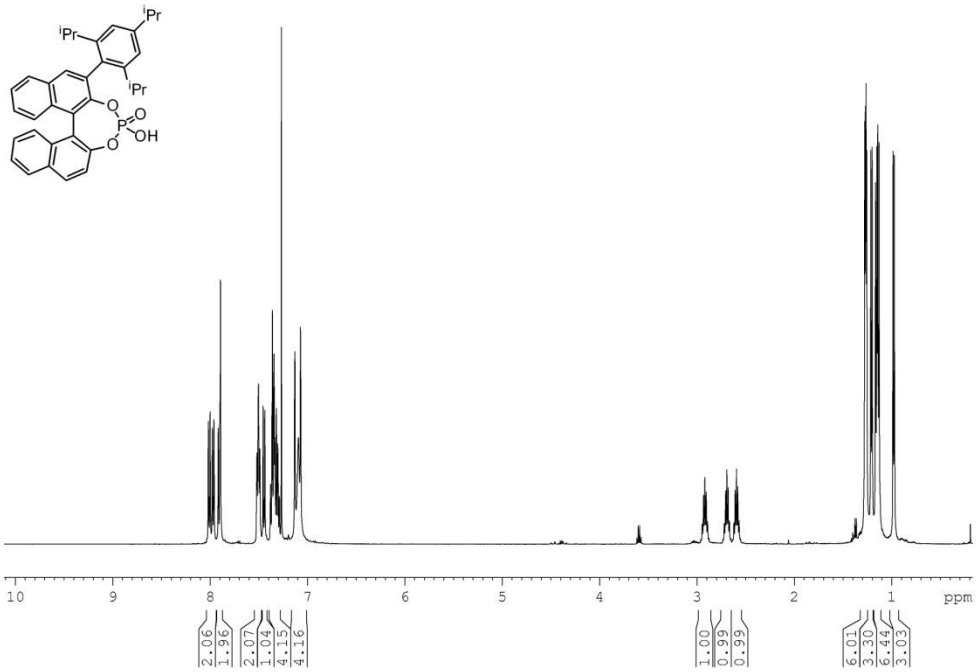

O
O
F
-157.9
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

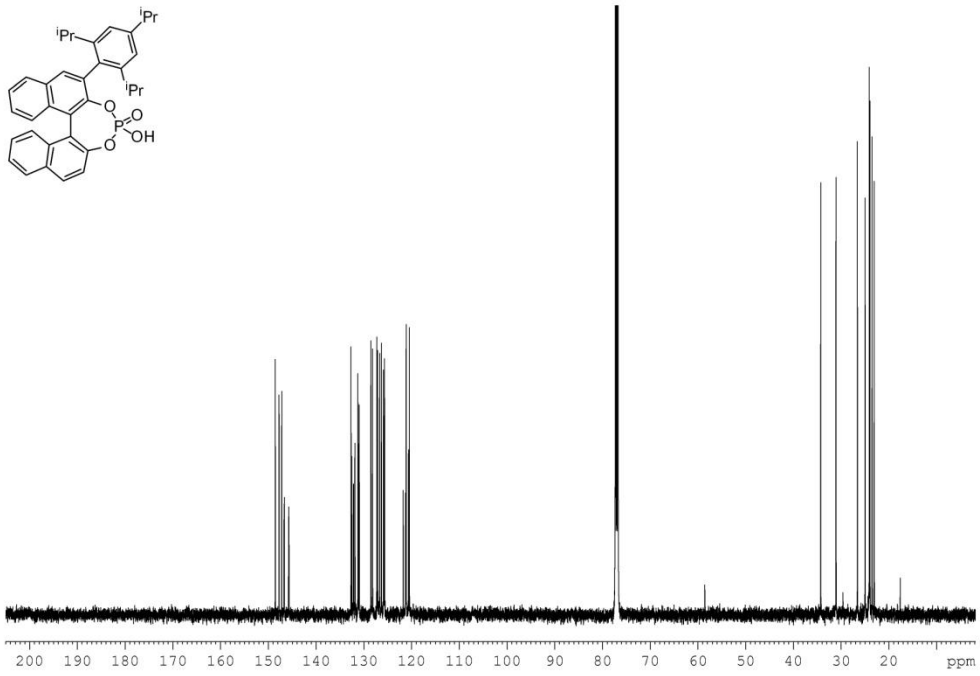

I
OMe
OMe
10
9
8
7
6
5
4
3
2
1
ppm
0.91
0.98
0.99
0.98
0.99
1.96
2.29
1.91
3.00
2.92

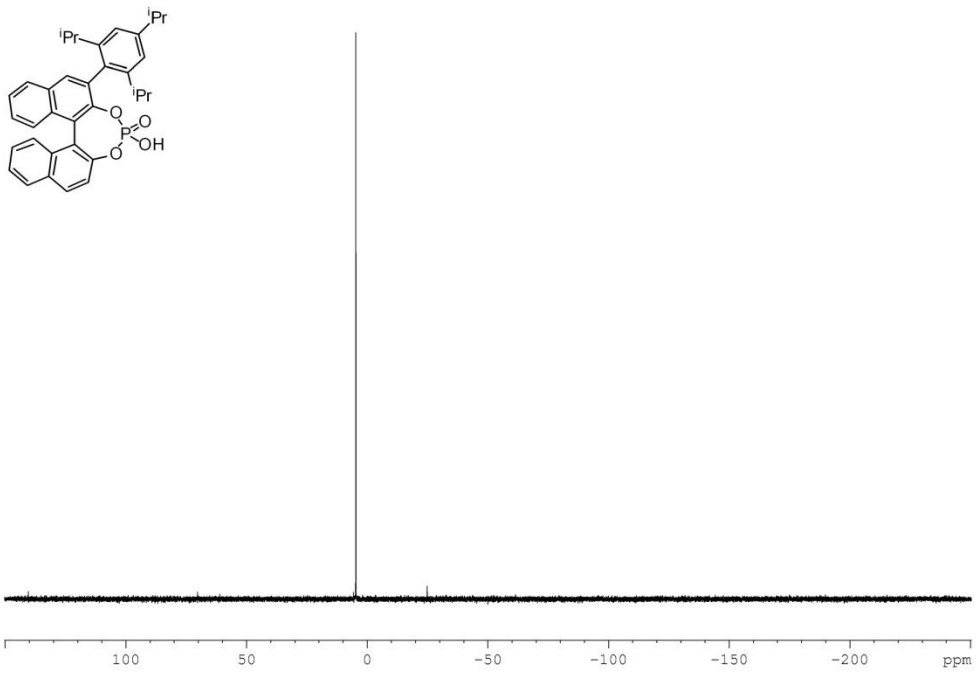

I
OMe
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


iPr
iPr
iPr
OH
OH
9 8 7 6 5 4 3 2 1 ppm
1.05
2.09
1.03
4.49
2.30
1.07
2.03
0.88
0.92
0.99
2.02
6.42
6.00
6.40


iPr
iPr
iPr
OH
OH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


iPr
iPr
iPr
O
O
P
O
OH
10 9 8 7 6 5 4 3 2 1 ppm
2.06
1.96
2.07
1.04
4.15
4.16
1.00
0.99
0.99
6.01
3.30
6.44
3.03

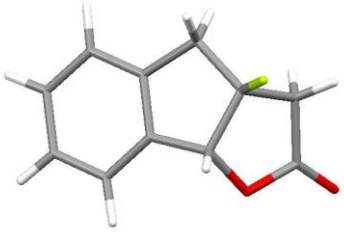

iPr
iPr
iPr
O
P
O
OH
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


iPr
iPr
iPr
O
P
O
OH
O
100 50 0 -50 -100 -150 -200 ppm

Appendix ii: X-ray Crystallography data

X-ray crystallographic structures were determined by single X-ray diffraction. The structures were solved with Superflip [Palatinus & Chapuis, *J. Appl. Crystallogr.,* **2007**, *40*, 786–790] and refined with CRYSTALS [Betteridge *et al.*, *J. Appl. Crystallogr.,* **2003**, 36, 1487; Cooper, et al., *J. Appl. Crystallogr.,* **2010**, 43, 1100.] including the Flack x parameter [Flack, *Acta Crystallogr.,* **1983**, A39, 876–881; Thompson & Watkin, *J. Appl. Crystallogr.*, **2011**, 44, 1017–1022.] which refined to -0.012(13) for **40a** (unrestrained).

Crystal Data for compound 5i



a = 9.1957(5) Å α = 90°
b = 10.4042(5) Å β = 107.388(2)°
c = 9.6070(6) Å γ = 90°

Volume	877.14(8) Å³	Crystal Class	monoclinic
Space group	P 2_1/a	Z =	3
Formula	$C_{14.67}$ H_{12} $F_{1.33}$ $O_{2.67}$	M_r	256.25
Cell determined from	1766 reflections	Cell θ range =	5 - 26°
Temperature	150K		
Shape	block		
Colour	yellow	Size	0.20 × 0.20 × 0.20 mm
D_x	1.46 Mg m^{-3}	F000	400.000
μ	0.113 mm^{-1}		
Absorption correction	multi-scan		

T_{min}	0.98	T_{max}	0.98

Data Collection

Diffractometer	KAPPACCD
Scan type	ω scans
Reflections measured	9419
Independent reflections	3223
Rint	0.0503
θ_{max}	25.9901
h =	-11 → 11
k =	-12 → 12
l =	-11 → 11

Refinement

$\Delta\rho_{min}$ =	-0.28 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.24 e $Å^{-3}$
Reflections used	3223
Cutoff: I >	-3.00σ(I)
Parameters refined	127
S =	0.96
R-factor	0.056
weighted R-factor	0.127
Δ/σ_{max}	0.0003
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.059 \times P)^2 + 0.648 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
F1	0.41891(9)	0.59457(9)	0.38724(10)	0.0441	1.0000
C2	0.54376(14)	0.64447(12)	0.34860(14)	0.0281	1.0000
C3	0.63890(17)	0.72550(15)	0.47202(17)	0.0404	1.0000
C4	0.78178(15)	0.65174(13)	0.54063(14)	0.0327	1.0000
O5	0.78798(11)	0.54666(9)	0.46027(10)	0.0355	1.0000
C6	0.65125(14)	0.53467(12)	0.33586(13)	0.0284	1.0000
C7	0.68072(14)	0.55700(11)	0.19327(14)	0.0262	1.0000

C8	0.58529(14)	0.65304(12)	0.11510(13)	0.0276	1.0000
C9	0.48599(16)	0.70762(13)	0.19917(14)	0.0336	1.0000
C10	0.58836(15)	0.68519(13)	0.02431(14)	0.0331	1.0000
C11	0.68934(17)	0.62154(14)	0.08219(15)	0.0378	1.0000
C12	0.78535(17)	0.52624(14)	0.00332(16)	0.0389	1.0000
C13	0.78197(15)	0.49206(13)	0.13556(15)	0.0329	1.0000
O14	0.88243(12)	0.67794(12)	0.64903(11)	0.0462	1.0000
H31	0.66234(17)	0.80765(15)	0.44001(17)	0.0511	1.0000
H32	0.58522(17)	0.75377(15)	0.54244(17)	0.0535	1.0000
H61	0.61049(14)	0.45626(12)	0.34838(13)	0.0324	1.0000
H91	0.49956(16)	0.79982(13)	0.20091(14)	0.0461	1.0000
H92	0.37690(16)	0.68552(13)	0.15503(14)	0.0451	1.0000
H101	0.51965(15)	0.75121(13)	0.07675(14)	0.0423	1.0000
H111	0.69108(17)	0.63937(14)	0.18097(15)	0.0435	1.0000
H121	0.85282(17)	0.47932(14)	0.04895(16)	0.0485	1.0000
H131	0.85141(15)	0.42376(13)	0.19493(15)	0.0414	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.0309(5)	0.0565(6)	0.0515(5)	0.0095(4)	0.0222(4)	-0.0016(4)
C2	0.0242(6)	0.0339(7)	0.0288(6)	0.0014(5)	0.0121(5)	-0.0018(5)
C3	0.0372(8)	0.0422(8)	0.0393(8)	-0.0106(6)	0.0075(6)	0.0050(6)
C4	0.0308(7)	0.0428(7)	0.0265(7)	0.0005(6)	0.0117(5)	-0.0024(6)
O5	0.0331(5)	0.0425(6)	0.0288(5)	0.0018(4)	0.0062(4)	0.0072(4)
C6	0.0289(7)	0.0286(6)	0.0278(7)	0.0017(5)	0.0085(5)	-0.0003(5)
C7	0.0270(6)	0.0256(6)	0.0266(6)	-0.0022(5)	0.0087(5)	-0.0031(5)
C8	0.0262(6)	0.0294(6)	0.0268(6)	-0.0008(5)	0.0074(5)	-0.0046(5)
C9	0.0337(7)	0.0365(7)	0.0312(7)	0.0036(5)	0.0108(6)	0.0063(5)
C10	0.0327(7)	0.0356(7)	0.0292(7)	0.0013(5)	0.0062(5)	-0.0067(6)
C11	0.0417(8)	0.0475(8)	0.0263(7)	-0.0050(6)	0.0134(6)	-0.0144(6)
C12	0.0368(8)	0.0460(8)	0.0392(8)	-0.0135(6)	0.0193(6)	-0.0077(6)
C13	0.0313(7)	0.0314(7)	0.0374(7)	-0.0058(5)	0.0122(6)	-0.0017(5)
O14	0.0365(6)	0.0695(7)	0.0301(5)	-0.0051(5)	0.0060(4)	-0.0031(5)

Distances

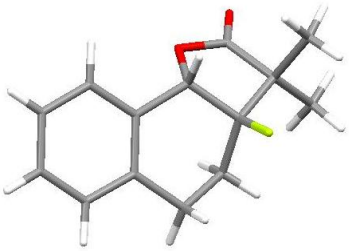
F1	C2	1.4071(14)Å		C2	C3	1.5040(19)Å
C2	C6	1.5393(18)Å		C2	C9	1.5228(18)Å
C3	C4	1.494(2)Å		C3	H31	0.955Å
C3	H32	0.994Å		C4	O5	1.3493(17)Å
C4	O14	1.1997(17)Å		O5	C6	1.4584(15)Å
C6	C7	1.4919(18)Å		C6	H61	0.921Å
C7	C8	1.3924(18)Å		C7	C13	1.3926(18)Å
C8	C9	1.4997(18)Å		C8	C10	1.3889(18)Å
C9	H91	0.967Å		C9	H92	0.992Å
C10	C11	1.385(2)Å		C10	H101	0.967Å
C11	C12	1.392(2)Å		C11	H111	0.972Å
C12	C13	1.390(2)Å		C12	H121	0.989Å
C13	H131	1.010Å				

Angles

F1	C2	C3	109.09(11)°	F1	C2	C6	109.94(10)°
C3	C2	C6	104.04(10)°	F1	C2	C9	109.01(10)°
C3	C2	C9	117.28(11)°	C6	C2	C9	107.25(10)°
C2	C3	C4	106.71(11)°	C2	C3	H31	112.462°
C4	C3	H31	110.400°	C2	C3	H32	114.352°
C4	C3	H32	113.707°	H31	C3	H32	99.216°
C3	C4	O5	110.23(11)°	C3	C4	O14	127.94(13)°
O5	C4	O14	121.81(13)°	C4	O5	C6	111.39(10)°
C2	C6	O5	106.75(10)°	C2	C6	C7	104.76(10)°
O5	C6	C7	112.98(10)°	C2	C6	H61	110.558°
O5	C6	H61	104.691°	C7	C6	H61	116.790°
C6	C7	C8	110.41(11)°	C6	C7	C13	128.07(12)°
C8	C7	C13	121.47(12)°	C7	C8	C9	111.61(11)°
C7	C8	C10	120.12(12)°	C9	C8	C10	128.26(12)°
C2	C9	C8	104.32(10)°	C2	C9	H91	113.883°
C8	C9	H91	106.782°	C2	C9	H92	109.036°
C8	C9	H92	112.495°	H91	C9	H92	110.243°
C8	C10	C11	118.77(13)°	C8	C10	H101	118.368°

C11	C10	H101	122.863°		C10	C11	C12	120.95(13)°
C10	C11	H111	120.627°		C12	C11	H111	118.345°
C11	C12	C13	120.82(13)°		C11	C12	H121	119.360°
C13	C12	H121	119.745°		C7	C13	C12	117.87(13)°
C7	C13	H131	120.100°		C12	C13	H131	122.022°

Crystal Data for compound 5k



a = 8.1980(2) Å α = 69.1448(11)°

b = 8.6538(2) Å β = 65.1714(11)°

c = 9.5021(2) Å γ = 75.9896(10)°

Volume	568.30(2) Å³	Crystal Class	Triclinic
Space group	P -1	Z =	2
Formula	C_{14} H_{15} F_1 O_2	M_r	234.27
Cell determined from	2320 reflections	Cell θ range =	5 - 27°
Temperature	150K		
Shape	block		
Colour	colourless	Size	0.35 × 0.40 × 0.45 mm
D_x	1.37 Mg m^{-3}	F000	248.000
μ	0.101 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.50	T_{max}	0.97

Data Collection

Diffractometer	KAPPACCD
Scan type	ω scans
Reflections measured	8352
Independent reflections	2569
Rint	0.0145

θ_{max}	27.4112
h =	-10 → 10
k =	-10 → 11
l =	-12 → 12

Refinement

$\Delta\rho_{min}$ =	-0.23 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.35 e $Å^{-3}$
Reflections used	2569
Cutoff: I >	-3.00σ(I)
Parameters refined	154
S =	0.94
R-factor	0.041
weighted R-factor	0.097
Δ/σ_{max}	0.0003
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.057 \times P)^2 + 0.190 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
F1	0.01435(9)	0.68284(8)	0.88283(8)	0.0253	1.0000
C2	0.10648(14)	0.67008(13)	0.79248(12)	0.0192	1.0000
C3	0.15113(13)	0.49122(13)	0.85022(12)	0.0190	1.0000
O4	0.31383(10)	0.50938(9)	0.81484(9)	0.0219	1.0000
C5	0.40135(14)	0.66428(13)	0.81171(12)	0.0207	1.0000
C6	0.29495(14)	0.76937(13)	0.83480(13)	0.0213	1.0000
C7	0.30636(16)	0.94903(14)	0.72945(15)	0.0276	1.0000
C8	0.37507(16)	0.76301(15)	1.01524(14)	0.0281	1.0000
O9	0.54368(10)	0.70445(10)	0.79343(10)	0.0274	1.0000
C10	0.00743(14)	0.37002(13)	0.77244(12)	0.0208	1.0000
C11	0.15689(14)	0.42050(14)	0.65151(13)	0.0235	1.0000
C12	0.29093(16)	0.29929(16)	0.59344(15)	0.0297	1.0000
C13	0.26262(17)	0.13336(16)	0.65326(16)	0.0329	1.0000
C14	0.09877(18)	0.08398(15)	0.77192(15)	0.0315	1.0000

C15	0.03526(16)	0.20201(14)	0.83155(14)	0.0263	1.0000
C16	0.19171(15)	0.60043(15)	0.58745(14)	0.0279	1.0000
C17	0.01681(14)	0.71802(14)	0.61569(13)	0.0235	1.0000
H31	0.18579(13)	0.44984(13)	0.96732(12)	0.0226	1.0000
H73	0.43189(16)	1.00055(14)	0.76285(15)	0.0408	1.0000
H72	0.23177(16)	1.01560(14)	0.73960(15)	0.0398	1.0000
H71	0.26779(16)	0.95487(14)	0.61466(15)	0.0397	1.0000
H83	0.50193(16)	0.80899(15)	1.04609(14)	0.0418	1.0000
H82	0.30771(16)	0.82868(15)	1.03327(14)	0.0420	1.0000
H81	0.36924(16)	0.64794(15)	1.08656(14)	0.0405	1.0000
H121	0.40597(16)	0.33080(16)	0.51206(15)	0.0372	1.0000
H131	0.35683(17)	0.05222(16)	0.61101(16)	0.0399	1.0000
H141	0.07857(18)	0.02884(15)	0.81235(15)	0.0388	1.0000
H151	0.14951(16)	0.16878(14)	0.91711(14)	0.0319	1.0000
H162	0.25978(15)	0.61630(15)	0.64267(14)	0.0342	1.0000
H161	0.26442(15)	0.62759(15)	0.47054(14)	0.0341	1.0000
H171	0.04304(14)	0.83416(14)	0.58380(13)	0.0289	1.0000
H172	0.04688(14)	0.71225(14)	0.55045(13)	0.0272	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.0274(3)	0.0277(3)	0.0288(4)	-0.0078(3)	-0.0171(3)	-0.0051(3)
C2	0.0194(5)	0.0223(5)	0.0198(5)	-0.0056(4)	-0.0101(4)	-0.0042(4)
C3	0.0172(5)	0.0221(5)	0.0182(5)	-0.0037(4)	-0.0076(4)	-0.0045(4)
O4	0.0185(4)	0.0230(4)	0.0271(4)	-0.0076(3)	-0.0098(3)	-0.0041(3)
C5	0.0190(5)	0.0242(5)	0.0175(5)	-0.0057(4)	-0.0052(4)	-0.0035(4)
C6	0.0211(5)	0.0227(5)	0.0223(5)	-0.0077(4)	-0.0095(4)	-0.0016(4)
C7	0.0307(6)	0.0221(5)	0.0330(6)	-0.0072(5)	-0.0163(5)	-0.0006(4)
C8	0.0279(6)	0.0341(6)	0.0251(6)	-0.0143(5)	-0.0088(5)	-0.0013(5)
O9	0.0198(4)	0.0340(4)	0.0302(4)	-0.0098(3)	-0.0110(3)	-0.0020(3)
C10	0.0211(5)	0.0235(5)	0.0207(5)	-0.0071(4)	-0.0108(4)	-0.0009(4)
C11	0.0200(5)	0.0313(6)	0.0224(5)	-0.0097(4)	-0.0103(4)	-0.0010(4)
C12	0.0213(5)	0.0437(7)	0.0296(6)	-0.0183(5)	-0.0120(5)	0.0039(5)
C13	0.0344(6)	0.0385(7)	0.0375(7)	-0.0224(5)	-0.0237(5)	0.0127(5)

C14	0.0436(7)	0.0243(6)	0.0369(7)	-0.0118(5)	-0.0262(6)	0.0041(5)
C15	0.0303(6)	0.0249(6)	0.0274(6)	-0.0067(4)	-0.0147(5)	-0.0029(4)
C16	0.0189(5)	0.0346(6)	0.0262(6)	-0.0069(5)	-0.0038(4)	-0.0074(4)
C17	0.0221(5)	0.0240(5)	0.0214(5)	-0.0018(4)	-0.0069(4)	-0.0068(4)

Distances

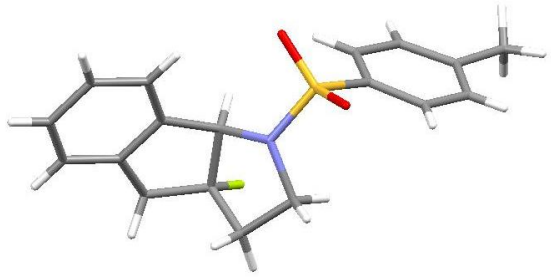
F1	C2	1.4043(11)Å		C2	C3	1.5270(14)Å
C2	C6	1.5390(14)Å		C2	C17	1.5155(14)Å
C3	O4	1.4677(12)Å		C3	C10	1.5022(14)Å
C3	H31	0.973Å		O4	C5	1.3551(13)Å
C5	C6	1.5241(14)Å		C5	O9	1.2015(13)Å
C6	C7	1.5258(15)Å		C6	C8	1.5424(15)Å
C7	H73	0.981Å		C7	H72	0.987Å
C7	H71	0.985Å		C8	H83	0.976Å
C8	H82	0.979Å		C8	H81	0.988Å
C10	C11	1.3977(15)Å		C10	C15	1.3975(16)Å
C11	C12	1.3989(16)Å		C11	C16	1.5070(16)Å
C12	C13	1.3814(19)Å		C12	H121	0.961Å
C13	C14	1.3861(19)Å		C13	H131	0.964Å
C14	C15	1.3847(16)Å		C14	H141	0.941Å
C15	H151	0.972Å		C16	C17	1.5258(15)Å
C16	H162	0.969Å		C16	H161	0.985Å
C17	H171	0.991Å		C17	H172	0.983Å

Angles

F1	C2	C3	108.45(8)°		F1	C2	C6	110.65(8)°
C3	C2	C6	102.59(8)°		F1	C2	C17	107.44(8)°
C3	C2	C17	111.59(8)°		C6	C2	C17	115.92(9)°
C2	C3	O4	103.07(7)°		C2	C3	C10	116.56(8)°
O4	C3	C10	110.51(8)°		C2	C3	H31	109.143°
O4	C3	H31	107.291°		C10	C3	H31	109.758°
C3	O4	C5	109.79(8)°		O4	C5	C6	110.70(8)°
O4	C5	O9	121.46(10)°		C6	C5	O9	127.84(10)°
C2	C6	C5	100.68(8)°		C2	C6	C7	115.93(9)°

C5	C6	C7	111.24(9)°		C2	C6	C8	110.57(9)°
C5	C6	C8	107.71(9)°		C7	C6	C8	110.11(9)°
C6	C7	H73	109.967°		C6	C7	H72	111.262°
H73	C7	H72	107.982°		C6	C7	H71	111.332°
H73	C7	H71	106.921°		H72	C7	H71	109.225°
C6	C8	H83	110.286°		C6	C8	H82	109.174°
H83	C8	H82	109.008°		C6	C8	H81	111.935°
H83	C8	H81	107.494°		H82	C8	H81	108.885°
C3	C10	C11	121.22(10)°		C3	C10	C15	118.62(10)°
C11	C10	C15	119.99(10)°		C10	C11	C12	118.44(11)°
C10	C11	C16	121.11(10)°		C12	C11	C16	120.43(10)°
C11	C12	C13	121.17(11)°		C11	C12	H121	119.886°
C13	C12	H121	118.928°		C12	C13	C14	120.22(11)°
C12	C13	H131	119.645°		C14	C13	H131	120.125°
C13	C14	C15	119.46(11)°		C13	C14	H141	120.489°
C15	C14	H141	120.053°		C10	C15	C14	120.71(11)°
C10	C15	H151	118.916°		C14	C15	H151	120.362°
C11	C16	C17	112.19(9)°		C11	C16	H162	108.145°
C17	C16	H162	108.924°		C11	C16	H161	109.718°
C17	C16	H161	109.118°		H162	C16	H161	108.673°
C2	C17	C16	110.67(9)°		C2	C17	H171	108.839°
C16	C17	H171	110.530°		C2	C17	H172	108.467°
C16	C17	H172	109.691°		H171	C17	H172	108.584°

Crystal Data for compound 5l



a = 8.7189(2) Å α = 90°

b = 9.4126(2) Å β = 90°

c = 19.5276(4) Å γ = 90°

Volume	1602.58(6) Å³	Crystal Class	Orthorhombic
Space group	P 2_1 2_1 2_1	Z =	4
Formula	C_{18} H_{18} F_1 N_1 O_2 S_1	M_r	331.41
Cell determined from	2007 reflections	Cell θ range =	5 - 27°
Temperature	150K		
Shape	block		
Colour	yellow	Size	0.30 × 0.30 × 0.30 mm
D_x	1.37 Mg m^{-3}	F000	696.000
μ	0.221 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.90	T_{max}	0.94

Data Collection

Diffractometer	KAPPACCD
Scan type	ω scans
Reflections measured	9419
Independent reflections	2076
Rint	0.0174
θ_{max}	27.4820
h =	-11 → 11
k =	-12 → 12
l =	-25 → 25

Refinement

$\Delta\rho_{min}$ =	-0.30 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.29 e $Å^{-3}$
Reflections used	2076
Cutoff: I >	-3.00σ(I)
Parameters refined	208
S =	0.96
R-factor	0.039
weighted R-factor	0.087
Δ/σ_{max}	0.0017
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.057 \times P)^2 + 0.425 \times P + 0.000 + 0.000 \times \sin\theta]$,

$$P = 0.333 \times \max(F_{obs}^2, 0) + 0.667 \times F_{calc}^2$$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
S1	0.27339(6)	0.37136(6)	0.64196(3)	0.0261	1.0000
O2	0.20442(19)	0.50476(18)	0.66004(8)	0.0317	1.0000
O3	0.2086(2)	0.24139(18)	0.66581(9)	0.0373	1.0000
N4	0.2724(2)	0.36533(18)	0.55889(8)	0.0247	1.0000
C5	0.2875(2)	0.4975(2)	0.51858(10)	0.0233	1.0000
C6	0.1377(3)	0.5526(2)	0.49032(11)	0.0244	1.0000
C7	0.1483(3)	0.5709(2)	0.41963(11)	0.0299	1.0000
C8	0.3083(3)	0.5376(3)	0.39469(11)	0.0368	1.0000
C9	0.3751(3)	0.4526(3)	0.45356(12)	0.0306	1.0000
F10	0.53245(16)	0.48203(19)	0.46236(8)	0.0471	1.0000
C11	0.3544(3)	0.2923(3)	0.45014(12)	0.0328	1.0000
C12	0.3516(3)	0.2452(2)	0.52464(12)	0.0330	1.0000
C13	0.0212(3)	0.6160(3)	0.38270(13)	0.0411	1.0000
C14	-0.1147(3)	0.6431(2)	0.41681(14)	0.0432	1.0000
C15	-0.1243(3)	0.6271(2)	0.48751(14)	0.0375	1.0000
C16	0.0020(3)	0.5813(2)	0.52459(13)	0.0287	1.0000
C17	0.4655(3)	0.3761(3)	0.67068(10)	0.0261	1.0000
C18	0.5456(3)	0.5032(3)	0.66967(12)	0.0340	1.0000
C19	0.6919(3)	0.5085(3)	0.69816(13)	0.0392	1.0000
C20	0.7572(3)	0.3893(3)	0.72797(11)	0.0380	1.0000
C21	0.6775(3)	0.2629(3)	0.72601(12)	0.0369	1.0000
C22	0.5315(3)	0.2540(3)	0.69719(11)	0.0303	1.0000
C23	0.9100(3)	0.4018(4)	0.76390(14)	0.0565	1.0000
H51	0.3430(2)	0.5703(2)	0.54387(10)	0.0281	1.0000
H81	0.3678(3)	0.6237(3)	0.38926(11)	0.0448	1.0000
H82	0.3069(3)	0.4886(3)	0.35189(11)	0.0439	1.0000
H111	0.4341(3)	0.2469(3)	0.42484(12)	0.0395	1.0000
H112	0.2587(3)	0.2710(3)	0.42807(12)	0.0412	1.0000
H121	0.4577(3)	0.2412(2)	0.54255(12)	0.0412	1.0000
H122	0.2959(3)	0.1545(2)	0.53072(12)	0.0399	1.0000

H131	0.0234(3)	0.6254(3)	0.33587(13)	0.0515	1.0000
H141	-0.2029(3)	0.6724(2)	0.39298(14)	0.0515	1.0000
H151	-0.2192(3)	0.6448(2)	0.51163(14)	0.0443	1.0000
H161	-0.0049(3)	0.5679(2)	0.57189(13)	0.0351	1.0000
H181	0.4995(3)	0.5862(3)	0.65075(12)	0.0405	1.0000
H191	0.7466(3)	0.5922(3)	0.69591(13)	0.0484	1.0000
H211	0.7202(3)	0.1881(3)	0.74429(12)	0.0462	1.0000
H221	0.4796(3)	0.1725(3)	0.69619(11)	0.0351	1.0000
H231	0.9222(3)	0.3209(4)	0.79436(14)	0.0880	1.0000
H232	0.9100(3)	0.4842(4)	0.79309(14)	0.0866	1.0000
H233	0.9953(3)	0.4020(4)	0.73330(14)	0.0864	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	0.0267(3)	0.0270(3)	0.0245(2)	-0.0002(2)	-0.0014(2)	0.0000(2)
O2	0.0314(9)	0.0333(9)	0.0305(8)	-0.0062(7)	-0.0011(7)	0.0076(8)
O3	0.0382(10)	0.0363(9)	0.0374(9)	0.0077(7)	-0.0008(8)	-0.0075(8)
N4	0.0272(9)	0.0212(8)	0.0256(8)	-0.0021(7)	-0.0034(7)	0.0054(9)
C5	0.0216(10)	0.0221(10)	0.0263(9)	-0.0034(8)	-0.0015(9)	-0.0018(9)
C6	0.0266(11)	0.0181(10)	0.0286(10)	-0.0014(8)	-0.0038(9)	-0.0024(9)
C7	0.0378(13)	0.0215(10)	0.0304(11)	0.0021(9)	-0.0054(10)	-0.0044(10)
C8	0.0455(15)	0.0378(13)	0.0271(11)	0.0003(10)	0.0094(11)	-0.0056(11)
C9	0.0207(11)	0.0373(13)	0.0337(11)	-0.0055(10)	0.0026(10)	-0.0054(10)
F10	0.0220(7)	0.0604(10)	0.0591(9)	-0.0127(8)	0.0083(7)	-0.0065(7)
C11	0.0299(13)	0.0357(12)	0.0327(12)	-0.0093(10)	-0.0004(11)	0.0060(11)
C12	0.0372(13)	0.0276(11)	0.0342(12)	-0.0087(10)	-0.0043(10)	0.0089(11)
C13	0.0609(18)	0.0268(12)	0.0355(12)	0.0047(11)	-0.0182(12)	0.0016(13)
C14	0.0448(15)	0.0250(12)	0.0598(17)	-0.0011(12)	-0.0262(13)	0.0055(12)
C15	0.0300(12)	0.0225(10)	0.0598(15)	-0.0037(12)	-0.0087(11)	0.0039(11)
C16	0.0275(12)	0.0205(10)	0.0382(12)	-0.0011(9)	-0.0016(10)	0.0021(9)
C17	0.0278(11)	0.0311(11)	0.0195(8)	-0.0011(9)	-0.0027(8)	0.0018(11)
C18	0.0343(13)	0.0316(12)	0.0360(11)	-0.0013(11)	-0.0058(10)	-0.0010(11)
C19	0.0331(13)	0.0453(14)	0.0393(12)	-0.0049(12)	-0.0030(10)	-0.0045(12)
C20	0.0285(12)	0.0632(16)	0.0224(9)	-0.0073(11)	0.0015(9)	0.0100(13)

C21	0.0388(14)	0.0475(14)	0.0245(10)	0.0033(11)	0.0016(10)	0.0204(12)
C22	0.0366(13)	0.0317(11)	0.0227(10)	0.0013(10)	0.0010(10)	0.0056(11)
C23	0.0284(13)	0.102(3)	0.0392(14)	-0.0045(16)	-0.0044(11)	0.0101(17)

Distances

S1	O2	1.4363(17)Å		S1	O3	1.4258(17)Å
S1	N4	1.6230(17)Å		S1	C17	1.767(2)Å
N4	C5	1.478(3)Å		N4	C12	1.484(3)Å
C5	C6	1.510(3)Å		C5	C9	1.541(3)Å
C5	H51	0.973Å		C6	C7	1.394(3)Å
C6	C16	1.386(3)Å		C7	C8	1.510(4)Å
C7	C13	1.389(4)Å		C8	C9	1.517(4)Å
C8	H81	0.968Å		C8	H82	0.955Å
C9	F10	1.410(3)Å		C9	C11	1.521(3)Å
C11	C12	1.521(3)Å		C11	H111	0.954Å
C11	H112	0.960Å		C12	H121	0.990Å
C12	H122	0.990Å		C13	C14	1.383(4)Å
C13	H131	0.919Å		C14	C15	1.391(4)Å
C14	H141	0.940Å		C15	C16	1.386(3)Å
C15	H151	0.967Å		C16	H161	0.934Å
C17	C18	1.386(3)Å		C17	C22	1.385(3)Å
C18	C19	1.392(3)Å		C18	H181	0.952Å
C19	C20	1.386(4)Å		C19	H191	0.922Å
C20	C21	1.378(4)Å		C20	C23	1.511(3)Å
C21	C22	1.395(4)Å		C21	H211	0.873Å
C22	H221	0.891Å		C23	H231	0.972Å
C23	H232	0.963Å		C23	H233	0.953Å

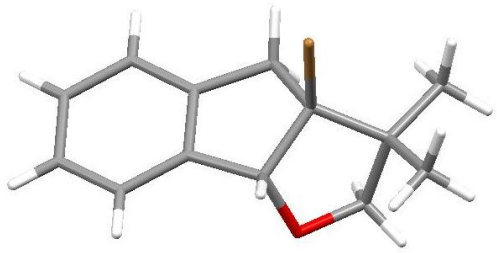
Angles

O2	S1	O3	120.25(10)°		O2	S1	N4	105.91(9)°
O3	S1	N4	107.12(10)°		O2	S1	C17	107.27(11)°
O3	S1	C17	107.08(11)°		N4	S1	C17	108.85(10)°
S1	N4	C5	120.15(13)°		S1	N4	C12	118.33(14)°
C5	N4	C12	111.09(16)°		N4	C5	C6	114.00(17)°

N4	C5	C9	104.60(17)°		C6	C5	C9	102.82(17)°
N4	C5	H51	111.497°		C6	C5	H51	111.941°
C9	C5	H51	111.398°		C5	C6	C7	110.30(19)°
C5	C6	C16	129.00(19)°		C7	C6	C16	120.7(2)°
C6	C7	C8	110.8(2)°		C6	C7	C13	119.9(2)°
C8	C7	C13	129.3(2)°		C7	C8	C9	102.68(18)°
C7	C8	H81	110.925°		C9	C8	H81	108.582°
C7	C8	H82	111.766°		C9	C8	H82	114.409°
H81	C8	H82	108.385°		C5	C9	C8	106.83(19)°
C5	C9	F10	109.15(18)°		C8	C9	F10	111.2(2)°
C5	C9	C11	104.44(19)°		C8	C9	C11	116.4(2)°
F10	C9	C11	108.4(2)°		C9	C11	C12	104.43(19)°
C9	C11	H111	112.368°		C12	C11	H111	112.076°
C9	C11	H112	109.274°		C12	C11	H112	110.780°
H111	C11	H112	107.901°		N4	C12	C11	102.47(17)°
N4	C12	H121	107.730°		C11	C12	H121	109.540°
N4	C12	H122	112.001°		C11	C12	H122	111.972°
H121	C12	H122	112.582°		C7	C13	C14	119.4(2)°
C7	C13	H131	122.009°		C14	C13	H131	118.603°
C13	C14	C15	120.6(2)°		C13	C14	H141	121.104°
C15	C14	H141	118.285°		C14	C15	C16	120.3(2)°
C14	C15	H151	121.083°		C16	C15	H151	118.604°
C6	C16	C15	119.1(2)°		C6	C16	H161	120.339°
C15	C16	H161	120.526°		S1	C17	C18	119.67(18)°
S1	C17	C22	119.44(19)°		C18	C17	C22	120.8(2)°
C17	C18	C19	119.1(2)°		C17	C18	H181	120.030°
C19	C18	H181	120.822°		C18	C19	C20	121.0(3)°
C18	C19	H191	119.000°		C20	C19	H191	119.970°
C19	C20	C21	118.7(2)°		C19	C20	C23	119.6(3)°
C21	C20	C23	121.6(3)°		C20	C21	C22	121.6(2)°
C20	C21	H211	118.062°		C22	C21	H211	120.364°
C17	C22	C21	118.7(2)°		C17	C22	H221	119.677°
C21	C22	H221	121.626°		C20	C23	H231	108.649°
C20	C23	H232	109.701°		H231	C23	H232	105.622°

C20	C23	H233	113.371°		H231	C23	H233	107.466°
H232	C23	H233	111.670°					

Crystal Data for compound 26a



a = 12.1851(3) Å α = 90°

b = 6.32610(10) Å β = 94.0133(10)°

c = 15.2992(3) Å γ = 90°

Volume	1176.43(4) Å³	Crystal Class	Monoclinic
Space group	P 1 2_1/n 1	Z =	4
Formula	C_{13} H_{15} Br_1 O_1	M_r	267.17
Cell determined from	0 reflections	Cell θ range =	0 - 0°
Temperature	150K		
Shape	?		
Colour	colourless	Size	0.30 × 0.30 × 0.30 mm
D_x	1.51 Mg m^{-3}	F000	544.000
μ	3.465 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.28	T_{max}	0.35

Data Collection

Diffractometer	KAPPACCD
Scan type	2θ/ω scans
Reflections measured	14322
Independent reflections	2668
Rint	0.0190
θ_{max}	27.4478
h =	-15 → 15

k = -8 → 8

l = -19 → 19

Refinement

$\Delta\rho_{min}$ = -0.46 e Å^{-3}

$\Delta\rho_{max}$ = 0.42 e Å^{-3}

Reflections used 2668

Cutoff: I > -3.00σ(I)

Parameters refined 136

S = 0.94

R-factor 0.034

weighted R-factor 0.070

Δ/σ_{max} 0.0007

Refinement on F^2

w = $1/[\sigma^2(F_{obs}^2) + (0.038 \times P)^2 + 0.915 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
Br1	.893576(15)	0.78934(4)	.534999(14)	0.0358	1.0000
C2	0.74362(14)	0.6832(3)	0.50655(11)	0.0211	1.0000
C3	0.66358(15)	0.8686(3)	0.51845(11)	0.0245	1.0000
C4	0.63067(14)	0.8416(3)	0.61088(11)	0.0226	1.0000
C5	0.65821(14)	0.6411(3)	0.64274(11)	0.0223	1.0000
C6	0.71324(14)	0.5168(3)	0.57452(11)	0.0231	1.0000
O7	0.63605(11)	0.3789(2)	0.52587(8)	0.0292	1.0000
C8	0.62574(16)	0.4422(3)	0.43516(12)	0.0291	1.0000
C9	0.73099(15)	0.5648(3)	0.41871(11)	0.0247	1.0000
C10	0.7193(2)	0.7060(4)	0.33831(14)	0.0379	1.0000
C11	0.82428(18)	0.4050(4)	0.40906(14)	0.0360	1.0000
C12	0.63260(16)	0.5785(3)	0.72603(12)	0.0290	1.0000
C13	0.57789(18)	0.7210(4)	0.77660(13)	0.0337	1.0000
C14	0.55132(16)	0.9223(3)	0.74541(13)	0.0324	1.0000
C15	0.57796(15)	0.9850(3)	0.66249(12)	0.0275	1.0000
H31	0.69629(15)	1.0036(3)	0.50915(11)	0.0300	1.0000

H32	0.59765(15)	0.8477(3)	0.47778(11)	0.0287	1.0000
H61	0.77653(14)	0.4354(3)	0.59828(11)	0.0264	1.0000
H81	0.56230(16)	0.5328(3)	0.42320(12)	0.0342	1.0000
H82	0.61657(16)	0.3168(3)	0.39829(12)	0.0350	1.0000
H102	0.7025(2)	0.6207(4)	0.28544(14)	0.0565	1.0000
H101	0.7874(2)	0.7838(4)	0.33456(14)	0.0567	1.0000
H103	0.6612(2)	0.8076(4)	0.34394(14)	0.0560	1.0000
H113	0.80738(18)	0.3196(4)	0.35839(14)	0.0536	1.0000
H112	0.89315(18)	0.4752(4)	0.40033(14)	0.0532	1.0000
H111	0.83456(18)	0.3118(4)	0.45968(14)	0.0533	1.0000
H121	0.65163(16)	0.4440(3)	0.74776(12)	0.0344	1.0000
H131	0.55961(18)	0.6800(4)	0.83233(13)	0.0417	1.0000
H141	0.51447(16)	1.0166(3)	0.77990(13)	0.0395	1.0000
H151	0.56005(15)	1.1212(3)	0.64113(12)	0.0327	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	0.02328(12)	0.04329(14)	0.04055(13)	0.00083(9)	0.00038(8)	0.00760(8)
C2	0.0166(8)	0.0241(9)	0.0224(8)	0.0005(7)	0.0007(6)	-0.0001(6)
C3	0.0284(9)	0.0217(8)	0.0235(8)	0.0024(7)	0.0028(7)	0.0048(7)
C4	0.0198(8)	0.0257(9)	0.0219(8)	-0.0019(7)	-0.0012(6)	-0.0007(7)
C5	0.0206(8)	0.0255(9)	0.0204(8)	-0.0004(7)	-0.0012(6)	-0.0022(7)
C6	0.0246(8)	0.0210(8)	0.0236(8)	0.0025(7)	0.0005(7)	0.0017(7)
O7	0.0367(7)	0.0228(7)	0.0282(7)	-0.0012(5)	0.0041(5)	-0.0042(6)
C8	0.0303(10)	0.0295(10)	0.0270(9)	-0.0036(8)	-0.0007(7)	-0.0008(8)
C9	0.0249(9)	0.0264(9)	0.0229(8)	0.0001(7)	0.0022(7)	0.0030(7)
C10	0.0466(13)	0.0414(12)	0.0261(10)	0.0065(9)	0.0058(9)	0.0071(10)
C11	0.0367(11)	0.0379(12)	0.0345(10)	-0.0028(9)	0.0088(8)	0.0111(9)
C12	0.0333(10)	0.0293(10)	0.0241(9)	0.0019(8)	-0.0008(7)	-0.0040(8)
C13	0.0358(11)	0.0450(12)	0.0206(9)	-0.0028(8)	0.0039(8)	-0.0080(9)
C14	0.0300(10)	0.0381(11)	0.0294(9)	-0.0100(8)	0.0050(8)	-0.0004(8)
C15	0.0248(9)	0.0288(10)	0.0285(9)	-0.0042(8)	0.0005(7)	0.0020(7)

Distances

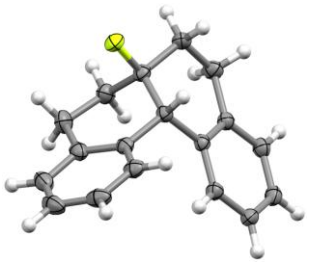
Br1	C2	1.9667(17)Å		C2	C3	1.545(2)Å
C2	C6	1.543(2)Å		C2	C9	1.537(2)Å
C3	C4	1.506(2)Å		C3	H31	0.957Å
C3	H32	0.990Å		C4	C5	1.391(3)Å
C4	C15	1.389(3)Å		C5	C6	1.502(2)Å
C5	C12	1.391(2)Å		C6	O7	1.449(2)Å
C6	H61	0.976Å		O7	C8	1.441(2)Å
C8	C9	1.534(3)Å		C8	H81	0.969Å
C8	H82	0.975Å		C9	C10	1.519(3)Å
C9	C11	1.536(3)Å		C10	H102	0.982Å
C10	H101	0.970Å		C10	H103	0.965Å
C11	H113	0.955Å		C11	H112	0.967Å
C11	H111	0.974Å		C12	C13	1.389(3)Å
C12	H121	0.937Å		C13	C14	1.390(3)Å
C13	H131	0.933Å		C14	C15	1.389(3)Å
C14	H141	0.932Å		C15	H151	0.942Å

Angles

Br1	C2	C3	107.40(12)°		Br1	C2	C6	110.29(11)°
C3	C2	C6	104.80(14)°		Br1	C2	C9	113.24(12)°
C3	C2	C9	116.61(14)°		C6	C2	C9	104.05(14)°
C2	C3	C4	103.68(14)°		C2	C3	H31	112.777°
C4	C3	H31	112.432°		C2	C3	H32	108.406°
C4	C3	H32	108.497°		H31	C3	H32	110.718°
C3	C4	C5	111.01(15)°		C3	C4	C15	128.59(17)°
C5	C4	C15	120.38(16)°		C4	C5	C6	110.03(15)°
C4	C5	C12	121.11(17)°		C6	C5	C12	128.84(17)°
C2	C6	C5	104.52(14)°		C2	C6	O7	104.01(13)°
C5	C6	O7	111.51(14)°		C2	C6	H61	112.964°
C5	C6	H61	113.388°		O7	C6	H61	109.980°
C6	O7	C8	109.69(13)°		O7	C8	C9	106.30(14)°
O7	C8	H81	111.130°		C9	C8	H81	109.583°
O7	C8	H82	109.253°		C9	C8	H82	112.291°

H81	C8	H82	108.301°		C2	C9	C8	97.85(14)°
C2	C9	C10	114.79(16)°		C8	C9	C10	113.46(17)°
C2	C9	C11	112.04(15)°		C8	C9	C11	108.42(17)°
C10	C9	C11	109.71(16)°		C9	C10	H102	110.236°
C9	C10	H101	108.320°		H102	C10	H101	111.076°
C9	C10	H103	110.328°		H102	C10	H103	109.145°
H101	C10	H103	107.701°		C9	C11	H113	109.333°
C9	C11	H112	111.489°		H113	C11	H112	106.702°
C9	C11	H111	112.132°		H113	C11	H111	108.126°
H112	C11	H111	108.858°		C5	C12	C13	118.22(18)°
C5	C12	H121	121.217°		C13	C12	H121	120.567°
C12	C13	C14	120.85(18)°		C12	C13	H131	118.894°
C14	C13	H131	120.251°		C13	C14	C15	120.75(18)°
C13	C14	H141	120.117°		C15	C14	H141	119.126°
C4	C15	C14	118.67(19)°		C4	C15	H151	120.352°
C14	C15	H151	120.979°					

Crystal Data for compound 31i



a = 8.7701(3) Å α = 90°

b = 14.9783(5) Å β = 111.1576(15)°

c = 10.5859(3) Å γ = 90°

Volume	1296.84(7) Å³	Crystal Class	monoclinic
Space group	P $2_1/n$	Z =	4
Formula	C_{18} H_{17} F_1	M_r	252.33
Cell determined from	3055 reflections	Cell θ range =	5 - 27°
Temperature	150K		
Shape	block		
Colour	clear_pale_colourless	Size	0.34 × 0.38 × 0.48 mm
D_x	1.29 Mg m^{-3}	F000	536.000

μ	0.083 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.76	T_{max}	0.97

Data Collection

Diffractometer	multi-scan
Scan type	ω scans
Reflections measured	19912
Independent reflections	2961
Rint	0.0227
θ_{max}	27.4708
h =	-11 → 11
k =	-19 → 19
l =	-13 → 13

Refinement

$\Delta\rho_{min}$ =	-0.35 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.25 e $Å^{-3}$
Reflections used	2961
Cutoff: I >	-3.00σ(I)
Parameters refined	172
S =	0.98
R-factor	0.065
weighted R-factor	0.116
Δ/σ_{max}	0.0003
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.053 \times P)^2 + 0.529 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
F1	0.58849(9)	0.62483(6)	0.64235(8)	0.0319	1.0000
C2	0.44884(16)	0.61742(9)	0.68123(13)	0.0256	1.0000
C3	0.39466(15)	0.52011(9)	0.66070(13)	0.0231	1.0000
C4	0.22756(15)	0.50977(9)	0.67570(12)	0.0228	1.0000

C5	0.17882(16)	0.42697(9)	0.70905(13)	0.0257	1.0000
C6	0.02638(17)	0.41565(10)	0.71940(14)	0.0282	1.0000
C7	0.08143(17)	0.48665(10)	0.69406(14)	0.0292	1.0000
C8	0.03501(17)	0.56880(10)	0.65997(14)	0.0282	1.0000
C9	0.11906(16)	0.58171(9)	0.65134(13)	0.0250	1.0000
C10	0.16424(18)	0.67496(9)	0.62141(15)	0.0307	1.0000
C11	0.31867(17)	0.67762(9)	0.58748(14)	0.0283	1.0000
C12	0.52619(16)	0.45878(9)	0.75253(13)	0.0257	1.0000
C13	0.53950(17)	0.37149(10)	0.71085(15)	0.0308	1.0000
C14	0.6584(2)	0.31364(11)	0.79168(17)	0.0385	1.0000
C15	0.7651(2)	0.34280(12)	0.91700(17)	0.0428	1.0000
C16	0.75570(19)	0.42947(12)	0.95810(16)	0.0382	1.0000
C17	0.63836(17)	0.48900(10)	0.87640(14)	0.0300	1.0000
C18	0.6468(2)	0.58579(11)	0.91870(15)	0.0377	1.0000
C19	0.50443(19)	0.64285(10)	0.82981(14)	0.0318	1.0000
H31	0.37957(15)	0.50586(9)	0.56571(13)	0.0278	1.0000
H51	0.25127(16)	0.37598(9)	0.72569(13)	0.0306	1.0000
H61	0.00437(17)	0.35732(10)	0.74533(14)	0.0337	1.0000
H71	0.18592(17)	0.47954(10)	0.70071(14)	0.0351	1.0000
H81	0.11122(17)	0.61891(10)	0.63919(14)	0.0351	1.0000
H101	0.18228(18)	0.71184(9)	0.70142(15)	0.0369	1.0000
H102	0.07123(18)	0.70111(9)	0.54590(15)	0.0376	1.0000
H111	0.36015(17)	0.73962(9)	0.59435(14)	0.0346	1.0000
H112	0.29410(17)	0.65706(9)	0.49235(14)	0.0320	1.0000
H131	0.46509(17)	0.35232(10)	0.62443(15)	0.0357	1.0000
H141	0.6661(2)	0.25443(11)	0.76053(17)	0.0457	1.0000
H151	0.8476(2)	0.30340(12)	0.97485(17)	0.0506	1.0000
H161	0.83322(19)	0.45079(12)	1.04325(16)	0.0464	1.0000
H181	0.6525(2)	0.58982(11)	1.01180(15)	0.0457	1.0000
H182	0.7507(2)	0.61094(11)	0.91530(15)	0.0453	1.0000
H191	0.53679(19)	0.70639(10)	0.83949(14)	0.0383	1.0000
H192	0.40875(19)	0.63533(10)	0.85908(14)	0.0382	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.0256(4)	0.0376(5)	0.0341(5)	0.0026(3)	0.0127(3)	-0.0060(3)
C2	0.0231(6)	0.0288(7)	0.0270(7)	0.0000(5)	0.0115(5)	-0.0034(5)
C3	0.0227(6)	0.0245(7)	0.0223(6)	-0.0001(5)	0.0082(5)	-0.0013(5)

C4	0.0221(6)	0.0259(7)	0.0193(6)	-0.0015(5)	0.0061(5)	-0.0012(5)
C5	0.0248(7)	0.0254(7)	0.0253(7)	-0.0004(5)	0.0072(5)	-0.0006(5)
C6	0.0262(7)	0.0302(7)	0.0273(7)	0.0016(5)	0.0086(5)	-0.0057(6)
C7	0.0223(7)	0.0382(8)	0.0267(7)	-0.0014(6)	0.0084(5)	-0.0032(6)
C8	0.0246(7)	0.0314(7)	0.0278(7)	-0.0002(6)	0.0085(5)	0.0028(6)
C9	0.0254(7)	0.0257(7)	0.0223(6)	-0.0003(5)	0.0069(5)	-0.0007(5)
C10	0.0314(7)	0.0257(7)	0.0350(8)	0.0020(6)	0.0120(6)	0.0023(6)
C11	0.0295(7)	0.0246(7)	0.0297(7)	0.0032(5)	0.0095(6)	-0.0020(5)
C12	0.0231(7)	0.0290(7)	0.0276(7)	0.0037(5)	0.0123(5)	0.0003(5)
C13	0.0284(7)	0.0308(8)	0.0382(8)	0.0027(6)	0.0182(6)	0.0010(6)
C14	0.0387(8)	0.0302(8)	0.0547(10)	0.0100(7)	0.0266(8)	0.0067(6)
C15	0.0344(8)	0.0494(10)	0.0473(10)	0.0230(8)	0.0182(7)	0.0136(7)
C16	0.0299(8)	0.0521(10)	0.0316(8)	0.0120(7)	0.0099(6)	0.0054(7)
C17	0.0267(7)	0.0376(8)	0.0265(7)	0.0051(6)	0.0106(6)	0.0013(6)
C18	0.0358(8)	0.0432(9)	0.0273(7)	-0.0029(6)	0.0031(6)	-0.0040(7)
C19	0.0353(8)	0.0293(7)	0.0279(7)	-0.0035(6)	0.0078(6)	-0.0047(6)

Distances

F1	C2	1.4302(15)Å		C2	C3	1.5241(18)Å
C2	C11	1.5110(19)Å		C2	C19	1.5176(19)Å
C3	C4	1.5377(17)Å		C3	C12	1.5199(18)Å
C3	H31	0.989Å		C4	C5	1.3981(18)Å
C4	C9	1.3986(19)Å		C5	C6	1.3906(19)Å
C5	H51	0.968Å		C6	C7	1.383(2)Å
C6	H61	0.982Å		C7	C8	1.384(2)Å
C7	H71	0.950Å		C8	C9	1.4002(19)Å
C8	H81	0.976Å		C9	C10	1.5161(19)Å
C10	C11	1.5218(19)Å		C10	H101	0.975Å
C10	H102	0.994Å		C11	H111	0.991Å
C11	H112	0.999Å		C12	C13	1.398(2)Å
C12	C17	1.4002(19)Å		C13	C14	1.388(2)Å
C13	H131	0.956Å		C14	C15	1.389(2)Å
C14	H141	0.957Å		C15	C16	1.381(2)Å
C15	H151	0.963Å		C16	C17	1.400(2)Å
C16	H161	0.967Å		C17	C18	1.511(2)Å
C18	C19	1.526(2)Å		C18	H181	0.971Å

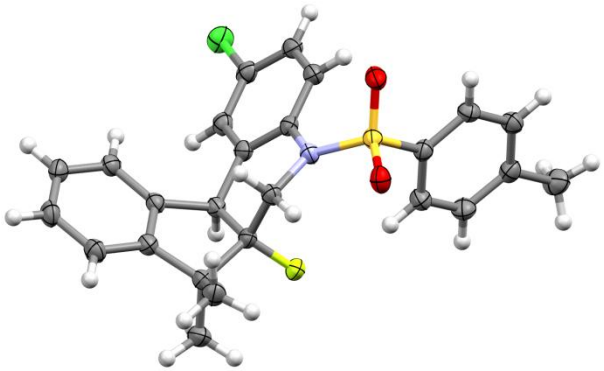
C18	H182	0.998Å		C19	H191	0.988Å
C19	H192	1.000Å				

Angles

F1	C2	C3	106.77(10)°		F1	C2	C11	106.68(10)°
C3	C2	C11	110.75(11)°		F1	C2	C19	106.89(11)°
C3	C2	C19	110.78(11)°		C11	C2	C19	114.51(12)°
C2	C3	C4	109.95(11)°		C2	C3	C12	111.18(11)°
C4	C3	C12	113.87(10)°		C2	C3	H31	105.765°
C4	C3	H31	107.487°		C12	C3	H31	108.177°
C3	C4	C5	120.33(12)°		C3	C4	C9	120.91(12)°
C5	C4	C9	118.71(12)°		C4	C5	C6	121.22(13)°
C4	C5	H51	120.354°		C6	C5	H51	118.429°
C5	C6	C7	120.02(13)°		C5	C6	H61	119.941°
C7	C6	H61	120.039°		C6	C7	C8	119.28(13)°
C6	C7	H71	120.629°		C8	C7	H71	120.086°
C7	C8	C9	121.42(13)°		C7	C8	H81	120.033°
C9	C8	H81	118.528°		C4	C9	C8	119.34(12)°
C4	C9	C10	122.45(12)°		C8	C9	C10	118.17(12)°
C9	C10	C11	113.29(11)°		C9	C10	H101	108.250°
C11	C10	H101	108.121°		C9	C10	H102	109.311°
C11	C10	H102	109.993°		H101	C10	H102	107.704°
C2	C11	C10	110.80(11)°		C2	C11	H111	109.932°
C10	C11	H111	109.981°		C2	C11	H112	108.360°
C10	C11	H112	110.074°		H111	C11	H112	107.624°
C3	C12	C13	119.60(12)°		C3	C12	C17	121.20(12)°
C13	C12	C17	119.17(13)°		C12	C13	C14	121.26(14)°
C12	C13	H131	118.483°		C14	C13	H131	120.250°
C13	C14	C15	119.33(15)°		C13	C14	H141	119.804°
C15	C14	H141	120.871°		C14	C15	C16	119.99(14)°
C14	C15	H151	120.485°		C16	C15	H151	119.507°
C15	C16	C17	121.22(15)°		C15	C16	H161	120.157°
C17	C16	H161	118.592°		C12	C17	C16	118.95(14)°
C12	C17	C18	122.03(12)°		C16	C17	C18	118.78(13)°
C17	C18	C19	114.39(12)°		C17	C18	H181	109.845°
C19	C18	H181	108.771°		C17	C18	H182	107.408°
C19	C18	H182	108.718°		H181	C18	H182	107.481°
C2	C19	C18	112.57(12)°		C2	C19	H191	108.793°

C18	C19	H191	109.587°		C2	C19	H192	107.525°
C18	C19	H192	109.711°		H191	C19	H192	108.555°

Crystal Data for compound 40c



a = 10.2414(3) Å α = 118.760(4)°

b = 11.0578(4) Å β = 103.118(3)°

c = 11.3029(6) Å γ = 91.124(3)°

Volume	1080.33(9) Å³	Crystal Class	triclinic
Space group	P -1	Z =	2
Formula	C_{25} H_{23} Cl_1 F_1 N_1 O_2 S_1	M_r	455.98
Cell determined from	11142 reflections	Cell θ range =	4 - 75°
Temperature	150K		
Shape	block		
Colour	clear_pale_colourless	Size	0.13 × 0.22 × 0.31 mm
D_x	1.40 Mg m^{-3}	F000	476.000
μ	2.731 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.50	T_{max}	0.70

Data Collection

Diffractometer	multi-scan
Scan type	ω scans
Reflections measured	18223
Independent reflections	4365
Rint	0.0430
$θ_{max}$	75.3152

cccx

h =	-12 → 12
k =	-13 → 13
l =	-13 → 12

Refinement

$\Delta\rho_{min}$ =	-0.31 e Å^{-3}
$\Delta\rho_{max}$ =	0.38 e Å^{-3}
Reflections used	3734
Cutoff: I >	-3.00σ(I)
Parameters refined	280
S =	0.99
R-factor	0.034
weighted R-factor	0.090
Δ/σ_{max}	0.0006
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.056 \times P)^2 + 0.495 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
Cl1	0.70543(4)	0.82200(4)	0.87266(4)	0.0378	1.0000
C2	0.69327(16)	0.66105(17)	0.72329(16)	0.0287	1.0000
C3	0.62896(16)	0.54280(18)	0.71033(17)	0.0298	1.0000
C4	0.61923(16)	0.41508(17)	0.59215(17)	0.0289	1.0000
C5	0.67371(15)	0.40432(16)	0.48521(16)	0.0246	1.0000
N6	0.66516(13)	0.27465(13)	0.36244(13)	0.0265	1.0000
S7	0.62549(4)	0.12294(4)	0.35062(4)	0.0262	1.0000
O8	0.64295(12)	0.01918(11)	0.21920(12)	0.0329	1.0000
O9	0.49613(11)	0.11397(12)	0.37718(12)	0.0333	1.0000
C10	0.74870(15)	0.12510(15)	0.48955(16)	0.0261	1.0000
C11	0.70695(16)	0.07023(16)	0.56474(16)	0.0278	1.0000
C12	0.80269(16)	0.05900(16)	0.66599(16)	0.0293	1.0000
C13	0.93971(17)	0.10498(17)	0.69581(17)	0.0301	1.0000
C14	1.04311(18)	0.0964(2)	0.80875(19)	0.0418	1.0000
C15	0.97897(16)	0.16032(18)	0.61918(18)	0.0335	1.0000
C16	0.88525(16)	0.16975(17)	0.51568(18)	0.0313	1.0000
C17	0.68174(16)	0.27636(16)	0.23743(16)	0.0259	1.0000

C18	0.80936(15)	0.37271(16)	0.27392(16)	0.0252	1.0000
F19	0.91924(9)	0.31630(9)	0.31946(9)	0.0301	1.0000
C20	0.80527(15)	0.51990(15)	0.39028(15)	0.0243	1.0000
C21	0.74045(15)	0.52443(16)	0.49997(16)	0.0246	1.0000
C22	0.74979(16)	0.65225(16)	0.61980(16)	0.0274	1.0000
C23	0.73417(15)	0.58322(15)	0.30425(16)	0.0247	1.0000
C24	0.74874(15)	0.51003(16)	0.16879(16)	0.0263	1.0000
C25	0.82653(16)	0.38916(17)	0.14865(17)	0.0279	1.0000
C26	0.77025(19)	0.25821(18)	0.00570(17)	0.0353	1.0000
C27	0.97684(17)	0.4328(2)	0.16851(19)	0.0359	1.0000
C28	0.69721(17)	0.55249(17)	0.07245(17)	0.0318	1.0000
C29	0.62837(17)	0.66712(18)	0.11271(18)	0.0339	1.0000
C30	0.61046(17)	0.73716(17)	0.24645(18)	0.0310	1.0000
C31	0.66433(16)	0.69699(15)	0.34436(17)	0.0272	1.0000
H31	0.58922(16)	0.54662(18)	0.78049(17)	0.0361	1.0000
H41	0.57351(16)	0.33606(17)	0.58293(17)	0.0345	1.0000
H111	0.61638(16)	0.04095(16)	0.54686(16)	0.0333	1.0000
H121	0.77227(16)	0.01855(16)	0.71303(16)	0.0347	1.0000
H141	1.12601(18)	0.0774(2)	0.78488(19)	0.0632	1.0000
H142	1.06184(18)	0.1837(2)	0.89345(19)	0.0646	1.0000
H143	1.01042(18)	0.0266(2)	0.82607(19)	0.0643	1.0000
H151	1.06973(16)	0.19016(18)	0.63746(18)	0.0397	1.0000
H161	0.91187(16)	0.20567(17)	0.46456(18)	0.0381	1.0000
H171	0.68744(16)	0.18362(16)	0.16925(16)	0.0291	1.0000
H172	0.60277(16)	0.30749(16)	0.19899(16)	0.0296	1.0000
H201	0.89953(15)	0.56651(15)	0.43753(15)	0.0278	1.0000
H221	0.79923(16)	0.73308(16)	0.63112(16)	0.0323	1.0000
H263	0.78758(19)	0.27749(18)	0.06582(17)	0.0522	1.0000
H262	0.81516(19)	0.17982(18)	0.00072(17)	0.0529	1.0000
H261	0.67351(19)	0.23310(18)	0.01546(17)	0.0514	1.0000
H271	0.98285(17)	0.4566(2)	0.09806(19)	0.0535	1.0000
H272	1.01528(17)	0.5151(2)	0.26119(19)	0.0524	1.0000
H273	1.02614(17)	0.3557(2)	0.15722(19)	0.0530	1.0000
H281	0.70853(17)	0.50346(17)	0.01952(17)	0.0381	1.0000
H291	0.59187(17)	0.69752(18)	0.04687(18)	0.0409	1.0000
H301	0.56158(17)	0.81345(17)	0.27214(18)	0.0354	1.0000
H311	0.65327(16)	0.74690(15)	0.43632(17)	0.0333	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	0.0482(3)	0.0366(2)	0.0241(2)	0.01150(17)	0.00992(17)	0.01249(18)
C2	0.0303(8)	0.0335(8)	0.0235(8)	0.0152(7)	0.0063(6)	0.0119(6)
C3	0.0303(8)	0.0406(9)	0.0289(8)	0.0228(7)	0.0131(6)	0.0144(7)
C4	0.0286(8)	0.0337(8)	0.0349(8)	0.0229(7)	0.0136(7)	0.0101(6)
C5	0.0236(7)	0.0281(8)	0.0275(8)	0.0171(7)	0.0082(6)	0.0096(6)
N6	0.0319(7)	0.0251(7)	0.0283(7)	0.0160(6)	0.0122(5)	0.0066(5)
S7	0.0263(2)	0.0253(2)	0.0308(2)	0.01742(17)	0.00653(15)	0.00394(14)
O8	0.0410(6)	0.0254(6)	0.0317(6)	0.0152(5)	0.0064(5)	0.0036(5)
O9	0.0267(6)	0.0392(6)	0.0429(7)	0.0284(6)	0.0069(5)	0.0035(5)
C10	0.0277(8)	0.0228(7)	0.0293(8)	0.0143(6)	0.0075(6)	0.0060(6)
C11	0.0253(8)	0.0291(8)	0.0303(8)	0.0155(7)	0.0082(6)	0.0026(6)
C12	0.0331(8)	0.0300(8)	0.0276(8)	0.0156(7)	0.0106(7)	0.0064(6)
C13	0.0316(8)	0.0292(8)	0.0286(8)	0.0136(7)	0.0082(7)	0.0098(6)
C14	0.0344(9)	0.0567(11)	0.0379(10)	0.0274(9)	0.0070(8)	0.0118(8)
C15	0.0251(8)	0.0369(9)	0.0411(9)	0.0214(8)	0.0087(7)	0.0045(7)
C16	0.0296(8)	0.0327(8)	0.0390(9)	0.0226(7)	0.0112(7)	0.0055(6)
C17	0.0298(8)	0.0268(8)	0.0254(8)	0.0152(6)	0.0093(6)	0.0072(6)
C18	0.0251(7)	0.0302(8)	0.0269(8)	0.0183(7)	0.0088(6)	0.0105(6)
F19	0.0282(5)	0.0375(5)	0.0352(5)	0.0246(4)	0.0116(4)	0.0138(4)
C20	0.0242(7)	0.0268(8)	0.0256(8)	0.0156(6)	0.0076(6)	0.0044(6)
C21	0.0240(7)	0.0302(8)	0.0253(8)	0.0179(7)	0.0066(6)	0.0073(6)
C22	0.0288(8)	0.0295(8)	0.0267(8)	0.0169(7)	0.0055(6)	0.0065(6)
C23	0.0246(7)	0.0259(7)	0.0280(8)	0.0168(6)	0.0072(6)	0.0019(6)
C24	0.0269(7)	0.0281(8)	0.0283(8)	0.0167(7)	0.0090(6)	0.0047(6)
C25	0.0314(8)	0.0319(8)	0.0285(8)	0.0190(7)	0.0130(6)	0.0099(6)
C26	0.0461(10)	0.0355(9)	0.0288(8)	0.0167(7)	0.0159(7)	0.0137(7)
C27	0.0336(9)	0.0483(10)	0.0397(9)	0.0286(8)	0.0183(7)	0.0135(8)
C28	0.0381(9)	0.0352(9)	0.0281(8)	0.0195(7)	0.0106(7)	0.0078(7)
C29	0.0381(9)	0.0357(9)	0.0367(9)	0.0258(8)	0.0075(7)	0.0082(7)
C30	0.0329(8)	0.0264(8)	0.0395(9)	0.0201(7)	0.0115(7)	0.0079(6)
C31	0.0290(8)	0.0243(8)	0.0310(8)	0.0147(7)	0.0109(6)	0.0034(6)

Distances

Cl1	C2	1.7430(16)Å		C2	C3	1.380(2)Å
C2	C22	1.383(2)Å		C3	C4	1.381(2)Å
C3	H31	0.955Å		C4	C5	1.399(2)Å
C4	H41	0.932Å		C5	N6	1.419(2)Å

C5	C21	1.400(2)Å		N6	S7	1.6523(13)Å
N6	C17	1.4698(19)Å		S7	O8	1.4295(12)Å
S7	O9	1.4349(12)Å		S7	C10	1.7670(16)Å
C10	C11	1.387(2)Å		C10	C16	1.390(2)Å
C11	C12	1.385(2)Å		C11	H111	0.920Å
C12	C13	1.391(2)Å		C12	H121	0.937Å
C13	C14	1.506(2)Å		C13	C15	1.394(2)Å
C14	H141	0.946Å		C14	H142	0.951Å
C14	H143	0.954Å		C15	C16	1.383(2)Å
C15	H151	0.922Å		C16	H161	0.924Å
C17	C18	1.514(2)Å		C17	H171	0.955Å
C17	H172	0.978Å		C18	F19	1.4121(17)Å
C18	C20	1.532(2)Å		C18	C25	1.558(2)Å
C20	C21	1.515(2)Å		C20	C23	1.523(2)Å
C20	H201	0.982Å		C21	C22	1.391(2)Å
C22	H221	0.956Å		C23	C24	1.392(2)Å
C23	C31	1.391(2)Å		C24	C25	1.518(2)Å
C24	C28	1.388(2)Å		C25	C26	1.527(2)Å
C25	C27	1.537(2)Å		C26	H263	0.980Å
C26	H262	0.973Å		C26	H261	0.966Å
C27	H271	0.965Å		C27	H272	0.981Å
C27	H273	0.969Å		C28	C29	1.392(2)Å
C28	H281	0.950Å		C29	C30	1.387(2)Å
C29	H291	0.962Å		C30	C31	1.390(2)Å
C30	H301	0.945Å		C31	H311	0.950Å

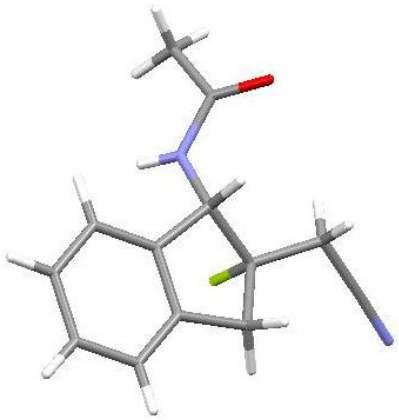
Angles

Cl1	C2	C3	119.56(12)°		Cl1	C2	C22	119.97(13)°
C3	C2	C22	120.47(15)°		C2	C3	C4	119.71(14)°
C2	C3	H31	121.786°		C4	C3	H31	118.497°
C3	C4	C5	120.70(15)°		C3	C4	H41	119.240°
C5	C4	H41	120.036°		C4	C5	N6	122.03(14)°
C4	C5	C21	119.27(14)°		N6	C5	C21	118.69(13)°
C5	N6	S7	122.77(10)°		C5	N6	C17	118.24(12)°
S7	N6	C17	118.81(10)°		N6	S7	O8	105.80(7)°
N6	S7	O9	110.84(7)°		O8	S7	O9	117.98(7)°
N6	S7	C10	104.50(7)°		O8	S7	C10	109.92(7)°
O9	S7	C10	107.01(7)°		S7	C10	C11	118.07(12)°

S7	C10	C16	121.08(12)°		C11	C10	C16	120.64(14)°
C10	C11	C12	119.50(14)°		C10	C11	H111	120.113°
C12	C11	H111	120.384°		C11	C12	C13	121.03(15)°
C11	C12	H121	117.879°		C13	C12	H121	121.093°
C12	C13	C14	120.90(15)°		C12	C13	C15	118.33(15)°
C14	C13	C15	120.76(15)°		C13	C14	H141	111.248°
C13	C14	H142	109.527°		H141	C14	H142	107.064°
C13	C14	H143	111.097°		H141	C14	H143	109.573°
H142	C14	H143	108.201°		C13	C15	C16	121.51(15)°
C13	C15	H151	119.002°		C16	C15	H151	119.483°
C10	C16	C15	118.97(15)°		C10	C16	H161	119.842°
C15	C16	H161	121.190°		N6	C17	C18	110.50(12)°
N6	C17	H171	108.320°		C18	C17	H171	109.712°
N6	C17	H172	109.399°		C18	C17	H172	109.844°
H171	C17	H172	109.036°		C17	C18	F19	106.66(12)°
C17	C18	C20	110.11(12)°		F19	C18	C20	110.59(12)°
C17	C18	C25	113.07(12)°		F19	C18	C25	110.63(12)°
C20	C18	C25	105.83(12)°		C18	C20	C21	114.66(12)°
C18	C20	C23	100.90(11)°		C21	C20	C23	116.04(12)°
C18	C20	H201	107.122°		C21	C20	H201	107.953°
C23	C20	H201	109.722°		C5	C21	C20	122.12(13)°
C5	C21	C22	119.35(14)°		C20	C21	C22	118.52(14)°
C2	C22	C21	120.49(15)°		C2	C22	H221	120.632°
C21	C22	H221	118.826°		C20	C23	C24	109.77(13)°
C20	C23	C31	129.31(14)°		C24	C23	C31	120.92(14)°
C23	C24	C25	111.57(13)°		C23	C24	C28	120.29(14)°
C25	C24	C28	128.13(14)°		C18	C25	C24	99.85(12)°
C18	C25	C26	113.90(13)°		C24	C25	C26	113.28(13)°
C18	C25	C27	110.22(13)°		C24	C25	C27	110.04(13)°
C26	C25	C27	109.25(13)°		C25	C26	H263	108.084°
C25	C26	H262	110.997°		H263	C26	H262	108.425°
C25	C26	H261	111.931°		H263	C26	H261	107.974°
H262	C26	H261	109.314°		C25	C27	H271	108.309°
C25	C27	H272	110.232°		H271	C27	H272	108.547°
C25	C27	H273	109.597°		H271	C27	H273	109.396°
H272	C27	H273	110.712°		C24	C28	C29	118.89(15)°
C24	C28	H281	120.258°		C29	C28	H281	120.852°
C28	C29	C30	120.64(15)°		C28	C29	H291	119.763°

C30	C29	H291	119.597°		C29	C30	C31	120.74(15)°
C29	C30	H301	120.067°		C31	C30	H301	119.194°
C23	C31	C30	118.48(15)°		C23	C31	H311	121.399°
C30	C31	H311	120.120°					

Crystal Data for compound 51



a = 13.2311(5) Å α = 90°

b = 10.6329(5) Å β = 90.645(2)°

c = 8.5241(4) Å γ = 90°

Volume	1199.14(9) Å³	Crystal Class	monoclinic
Space group	C c	Z =	4
Formula	C_{13} H_{13} F_1 N_2 O_1	M_r	232.26
Cell determined from	1244 reflections	Cell θ range =	5 - 27°
Temperature	150K		
Shape	block		
Colour	colourless	Size	0.20 × 0.20 × 0.20 mm
D_x	1.29 Mg m^{-3}	F000	488.000
μ	0.094 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.73	T_{max}	0.98

Data Collection

Diffractometer	KAPPACCD
Scan type	ω scans
Reflections measured	4233

Independent reflections	1354
Rint	0.0172
θ_{max}	27.4777
h =	-16 → 17
k =	-13 → 13
l =	-11 → 11

Refinement

$\Delta\rho_{min}$ =	-0.13 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.15 e $Å^{-3}$
Reflections used	1354
Cutoff: I >	-3.00σ(I)
Parameters refined	154
S =	0.97
R-factor	0.029
weighted R-factor	0.074
Δ/σ_{max}	0.0002
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.045 \times P)^2 + 0.309 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
F1	0.77999(11)	0.31439(9)	0.49133(14)	0.0275	1.0000
C2	0.72544(15)	0.30492(15)	0.6324(2)	0.0234	1.0000
C3	0.74227(14)	0.42895(15)	0.72273(19)	0.0216	1.0000
N4	0.84443(13)	0.47594(13)	0.71460(18)	0.0236	1.0000
C5	0.91462(15)	0.45099(15)	0.8248(2)	0.0237	1.0000
O6	0.89780(12)	0.38476(12)	0.94047(15)	0.0283	1.0000
C7	1.01591(16)	0.51065(19)	0.7989(2)	0.0351	1.0000
C8	0.66418(14)	0.51447(15)	0.64746(19)	0.0233	1.0000
C9	0.59021(15)	0.44347(17)	0.5723(2)	0.0263	1.0000
C10	0.61321(15)	0.30511(17)	0.5883(2)	0.0291	1.0000
C11	0.50907(16)	0.5015(2)	0.4965(2)	0.0342	1.0000
C12	0.50412(17)	0.6318(2)	0.4979(2)	0.0372	1.0000
C13	0.57854(17)	0.70280(18)	0.5730(2)	0.0343	1.0000

C14	0.65987(16)	0.64479(16)	0.6490(2)	0.0293	1.0000
C15	0.76617(16)	0.18983(16)	0.7181(2)	0.0273	1.0000
C16	0.74990(15)	0.07394(17)	0.6275(2)	0.0305	1.0000
N17	0.73611(16)	0.01473(16)	0.5546(3)	0.0433	1.0000
H31	0.72704(14)	0.41460(15)	0.83316(19)	0.0266	1.0000
H72	1.06753(16)	0.44895(19)	0.8156(2)	0.0537	1.0000
H71	1.02693(16)	0.57699(19)	0.8713(2)	0.0552	1.0000
H73	1.02118(16)	0.53989(19)	0.6923(2)	0.0534	1.0000
H102	0.57479(15)	0.26936(17)	0.6755(2)	0.0356	1.0000
H101	0.59920(15)	0.25552(17)	0.4931(2)	0.0346	1.0000
H111	0.45698(16)	0.4527(2)	0.4451(2)	0.0419	1.0000
H121	0.44847(17)	0.6741(2)	0.4451(2)	0.0454	1.0000
H131	0.57348(17)	0.79315(18)	0.5777(2)	0.0424	1.0000
H141	0.71031(16)	0.69411(16)	0.6979(2)	0.0363	1.0000
H152	0.83762(16)	0.20038(16)	0.7352(2)	0.0322	1.0000
H151	0.73393(16)	0.18349(16)	0.8179(2)	0.0344	1.0000
H41	0.86031(13)	0.52079(13)	0.63624(18)	0.0295	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.0313(5)	0.0306(5)	0.0208(4)	-0.0011(4)	0.0038(4)	0.0007(4)
C2	0.0266(8)	0.0229(8)	0.0208(7)	0.0002(6)	0.0027(6)	-0.0016(6)
C3	0.0233(8)	0.0219(7)	0.0196(7)	0.0004(6)	0.0024(6)	-0.0019(6)
N4	0.0263(7)	0.0248(6)	0.0197(6)	0.0018(5)	-0.0003(5)	-0.0044(5)
C5	0.0294(8)	0.0214(7)	0.0204(7)	-0.0051(6)	-0.0021(6)	-0.0004(6)
O6	0.0349(6)	0.0284(6)	0.0217(5)	-0.0001(5)	-0.0013(4)	0.0025(5)
C7	0.0330(9)	0.0358(10)	0.0364(9)	-0.0011(8)	-0.0068(8)	-0.0098(8)
C8	0.0245(7)	0.0269(8)	0.0186(6)	0.0021(6)	0.0032(6)	0.0017(6)
C9	0.0241(7)	0.0286(8)	0.0263(8)	0.0003(6)	0.0032(6)	0.0001(7)
C10	0.0271(8)	0.0254(9)	0.0349(9)	-0.0001(6)	-0.0024(7)	-0.0028(6)
C11	0.0242(8)	0.0426(10)	0.0357(9)	0.0003(8)	-0.0012(7)	0.0035(7)
C12	0.0336(9)	0.0417(11)	0.0364(9)	0.0049(8)	0.0017(7)	0.0136(8)
C13	0.0420(10)	0.0298(8)	0.0313(8)	0.0026(7)	0.0037(7)	0.0118(8)
C14	0.0381(9)	0.0258(8)	0.0239(7)	-0.0003(7)	0.0025(6)	0.0019(7)

C15	0.0320(8)	0.0222(8)	0.0276(8)	0.0008(6)	-0.0016(7)	-0.0005(6)
C16	0.0269(8)	0.0255(9)	0.0389(9)	0.0002(7)	-0.0004(7)	0.0018(6)
N17	0.0390(9)	0.0320(8)	0.0589(11)	-0.0106(8)	-0.0013(8)	0.0013(7)

Distances

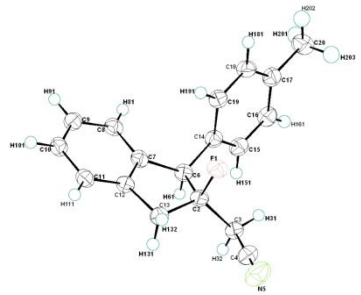
F1	C2	1.4133(17)Å		C2	C3	1.542(2)Å
C2	C10	1.528(2)Å		C2	C15	1.520(2)Å
C3	N4	1.443(2)Å		C3	C8	1.514(2)Å
C3	H31	0.977Å		N4	C5	1.340(2)Å
N4	H41	0.849Å		C5	O6	1.234(2)Å
C5	C7	1.501(2)Å		C7	H72	0.957Å
C7	H71	0.948Å		C7	H73	0.963Å
C8	C9	1.387(2)Å		C8	C14	1.387(2)Å
C9	C10	1.508(2)Å		C9	C11	1.391(3)Å
C10	H102	0.982Å		C10	H101	0.983Å
C11	C12	1.386(3)Å		C11	H111	0.964Å
C12	C13	1.391(3)Å		C12	H121	0.969Å
C13	C14	1.394(3)Å		C13	H131	0.964Å
C14	H141	0.942Å		C15	C16	1.469(2)Å
C15	H152	0.962Å		C15	H151	0.958Å
C16	N17	1.143(3)Å				

Angles

F1	C2	C3	106.96(12)°		F1	C2	C10	107.12(13)°
C3	C2	C10	104.85(13)°		F1	C2	C15	106.52(13)°
C3	C2	C15	113.60(13)°		C10	C2	C15	117.23(14)°
C2	C3	N4	113.71(13)°		C2	C3	C8	102.02(12)°
N4	C3	C8	114.00(13)°		C2	C3	H31	108.496°
N4	C3	H31	107.687°		C8	C3	H31	110.795°
C3	N4	C5	122.66(14)°		C3	N4	H41	118.189°
C5	N4	H41	119.146°		N4	C5	O6	122.91(15)°
N4	C5	C7	115.20(15)°		O6	C5	C7	121.89(15)°
C5	C7	H72	108.990°		C5	C7	H71	110.465°
H72	C7	H71	108.003°		C5	C7	H73	110.464°

H72	C7	H73	107.602°		H71	C7	H73	111.215°
C3	C8	C9	110.10(14)°		C3	C8	C14	128.62(15)°
C9	C8	C14	121.28(16)°		C8	C9	C10	110.39(15)°
C8	C9	C11	120.64(17)°		C10	C9	C11	128.97(17)°
C2	C10	C9	102.60(14)°		C2	C10	H102	108.849°
C9	C10	H102	109.911°		C2	C10	H101	112.102°
C9	C10	H101	114.354°		H102	C10	H101	108.811°
C9	C11	C12	118.41(18)°		C9	C11	H111	121.054°
C12	C11	H111	120.529°		C11	C12	C13	120.85(18)°
C11	C12	H121	119.673°		C13	C12	H121	119.479°
C12	C13	C14	120.83(18)°		C12	C13	H131	120.740°
C14	C13	H131	118.371°		C8	C14	C13	117.99(17)°
C8	C14	H141	122.096°		C13	C14	H141	119.902°
C2	C15	C16	111.94(14)°		C2	C15	H152	108.756°
C16	C15	H152	108.407°		C2	C15	H151	108.896°
C16	C15	H151	110.092°		H152	C15	H151	108.683°
C15	C16	N17	178.5(2)°					

Crystal Data for compound 64



Compound **64** was crystallised by slow evaporation from chloroform.

Crystal data

a = 6.0278(2) Å α = 90°

b = 17.2296(8) Å β = 102.2555(18)°

c = 14.1013(6) Å γ = 90°

Volume 1431.14(10) Å³

Space group	P 1 2_1/n 1
Formula	C_{18} H_{16} F_1 N_1
Cell determined from	2605 reflections
Temperature	150K
Shape	block
Colour	colourless
D_x	1.23 Mg m^{-3}
μ	0.081 mm^{-1}
Absorption	multi-scan correction
Crystal Class	Monoclinic
Z =	4
M_r	265.33
Cell θ range =	5 - 26°
Size	0.18 × 0.24 × 0.30 mm
F000	560.000
T_{min}	0.91

Data Collection

Diffractometer	KAPPACCD
Scan type	ω scans
Reflections measured	9551
Independent reflections	2903
Rint	0.0336
θ_{max}	26.3884
h =	-7 → 7
k =	0 → 21
l =	0 → 17

Refinement

$\Delta\rho_{min}$ =	-0.29 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.36 e $Å^{-3}$
Reflections used	2901
Cutoff: I >	-3.00σ(I)
Parameters refined	181
S =	1.05
R-factor	0.070
weighted R-factor	0.133
Δ/σ_{max}	0.0005

Refinement on	F^2
w =	$w' \times [1 - (\Delta F_{obs} / 6 \times \Delta F_{est})^2]^2$
w' =	$[P_0T_0'(x) + P_1T_1'(x) + ...P_{n-1}T_{n-1}'(x)]^{-1}$, where P_i are the coefficients of a Chebychev series in $t_i(x)$, and x = $F_{calc}^2/F_{calc}^2{}_{max}$.
P_0 - P_{n-1} =	85.2 140. 87.1 38.1 9.29

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
F1	0.33165(16)	0.81051(6)	0.40486(7)	0.0368	1.0000
C2	0.5085(3)	0.80477(10)	0.48849(12)	0.0325	1.0000
C3	0.7310(3)	0.81346(11)	0.45435(13)	0.0352	1.0000
C4	0.7519(3)	0.88962(12)	0.41181(15)	0.0444	1.0000
N5	0.7636(4)	0.94937(12)	0.37812(17)	0.0644	1.0000
C6	0.4866(3)	0.72567(10)	0.53726(12)	0.0320	1.0000
C7	0.3172(3)	0.74404(10)	0.59962(11)	0.0318	1.0000
C8	0.1903(3)	0.69301(10)	0.64292(12)	0.0335	1.0000
C9	0.0529(3)	0.72307(11)	0.70173(12)	0.0359	1.0000
C10	0.0421(3)	0.80248(11)	0.71634(12)	0.0367	1.0000
C11	0.1681(3)	0.85347(11)	0.67249(12)	0.0357	1.0000
C12	0.3060(3)	0.82338(10)	0.61409(12)	0.0330	1.0000
C13	0.4605(3)	0.86576(10)	0.56014(13)	0.0365	1.0000
C14	0.4396(3)	0.65694(10)	0.46945(12)	0.0313	1.0000
C15	0.6151(3)	0.60659(10)	0.46046(13)	0.0341	1.0000
C16	0.5773(3)	0.54428(10)	0.39734(13)	0.0370	1.0000
C17	0.3620(3)	0.52931(10)	0.34133(13)	0.0371	1.0000
C18	0.1859(3)	0.57911(11)	0.35129(13)	0.0377	1.0000
C19	0.2231(3)	0.64186(10)	0.41369(13)	0.0354	1.0000
C20	0.3210(4)	0.46161(12)	0.27284(16)	0.0505	1.0000
H32	0.8556(3)	0.80601(11)	0.51059(13)	0.0429	1.0000
H31	0.7409(3)	0.77410(11)	0.40642(13)	0.0407	1.0000
H61	0.6363(3)	0.71665(10)	0.58154(12)	0.0370	1.0000
H81	0.1984(3)	0.63890(10)	0.63369(12)	0.0392	1.0000
H91	-0.0349(3)	0.68833(11)	0.73225(12)	0.0426	1.0000
H101	-0.0508(3)	0.82181(11)	0.75702(12)	0.0433	1.0000
H111	0.1591(3)	0.90665(11)	0.68265(12)	0.0419	1.0000
H131	0.6045(3)	0.88074(10)	0.60343(13)	0.0442	1.0000
H132	0.3954(3)	0.91247(10)	0.52922(13)	0.0440	1.0000
H151	0.7677(3)	0.61318(10)	0.49890(13)	0.0410	1.0000

H161	0.6989(3)	0.50828(10)	0.39127(13)	0.0442	1.0000
H181	0.0376(3)	0.57111(11)	0.31457(13)	0.0448	1.0000
H191	0.0993(3)	0.67627(10)	0.41937(13)	0.0425	1.0000
H202	0.1644(4)	0.45972(12)	0.23960(16)	0.0757	1.0000
H203	0.4088(4)	0.46531(12)	0.22366(16)	0.0770	1.0000
H201	0.3549(4)	0.41187(12)	0.30672(16)	0.0756	1.0000

Atomic displacement parameters ($Å^2$)

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.0294(5)	0.0433(6)	0.0336(5)	0.0026(4)	-0.0022(4)	0.0008(4)
C2	0.0248(8)	0.0403(9)	0.0299(8)	0.0001(7)	0.0004(6)	-0.0008(7)
C3	0.0278(8)	0.0428(9)	0.0349(8)	-0.0026(7)	0.0061(7)	-0.0024(7)
C4	0.0374(10)	0.0480(11)	0.0506(11)	-0.0027(9)	0.0159(8)	-0.0056(8)
N5	0.0655(13)	0.0487(11)	0.0874(15)	0.0080(10)	0.0354(11)	-0.0065(9)
C6	0.0261(8)	0.0377(9)	0.0305(8)	0.0010(7)	0.0024(6)	0.0019(7)
C7	0.0272(8)	0.0409(9)	0.0247(8)	-0.0010(7)	0.0000(6)	0.0017(7)
C8	0.0332(8)	0.0356(9)	0.0293(8)	-0.0002(7)	0.0011(7)	-0.0011(7)
C9	0.0319(9)	0.0456(10)	0.0289(8)	0.0021(7)	0.0034(7)	-0.0043(7)
C10	0.0339(9)	0.0475(10)	0.0280(8)	-0.0034(7)	0.0050(7)	0.0010(7)
C11	0.0356(9)	0.0382(9)	0.0320(8)	-0.0060(7)	0.0039(7)	-0.0009(7)
C12	0.0284(8)	0.0389(9)	0.0297(8)	-0.0013(7)	0.0016(6)	-0.0020(7)
C13	0.0337(9)	0.0372(9)	0.0389(9)	-0.0029(7)	0.0086(7)	-0.0025(7)
C14	0.0277(8)	0.0352(9)	0.0306(8)	0.0024(7)	0.0051(6)	0.0003(7)
C15	0.0285(8)	0.0371(9)	0.0366(9)	0.0043(7)	0.0064(7)	0.0016(7)
C16	0.0356(9)	0.0345(9)	0.0426(10)	0.0032(8)	0.0117(7)	0.0043(7)
C17	0.0423(10)	0.0332(8)	0.0377(9)	0.0013(7)	0.0127(8)	-0.0040(7)
C18	0.0308(8)	0.0427(10)	0.0380(9)	-0.0008(8)	0.0039(7)	-0.0059(7)
C19	0.0278(8)	0.0413(10)	0.0367(9)	-0.0013(7)	0.0062(7)	0.0018(7)
C20	0.0534(12)	0.0439(11)	0.0542(12)	-0.0104(9)	0.0116(10)	-0.0065(9)

Geometric parameters (Å, °)

F1	C2	1.4153(18)Å		C2	C3	1.526(2)Å
C2	C6	1.545(2)Å		C2	C13	1.527(2)Å
C3	C4	1.459(3)Å		C3	H32	0.978Å
C3	H31	0.968Å		C4	N5	1.142(3)Å
C6	C7	1.516(2)Å		C6	C14	1.511(2)Å
C6	H61	0.994Å		C7	C8	1.389(2)Å
C7	C12	1.386(2)Å		C8	C9	1.391(2)Å
C8	H81	0.944Å		C9	C10	1.387(3)Å
C9	H91	0.959Å		C10	C11	1.389(3)Å
C10	H101	0.943Å		C11	C12	1.389(2)Å

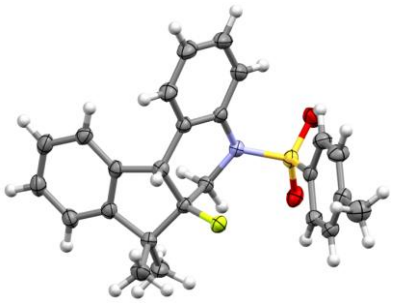
C11	H111	0.931Å		C12	C13	1.510(2)Å
C13	H131	0.984Å		C13	H132	0.959Å
C14	C15	1.395(2)Å		C14	C19	1.397(2)Å
C15	C16	1.382(2)Å		C15	H151	0.970Å
C16	C17	1.393(2)Å		C16	H161	0.978Å
C17	C18	1.395(3)Å		C17	C20	1.501(3)Å
C18	C19	1.382(2)Å		C18	H181	0.944Å
C19	H191	0.970Å		C20	H202	0.961Å
C20	H203	0.960Å		C20	H201	0.981Å

Angles

F1	C2	C3	106.69(13)°		F1	C2	C6	108.19(12)°
C3	C2	C6	113.01(14)°		F1	C2	C13	106.75(13)°
C3	C2	C13	116.36(14)°		C6	C2	C13	105.45(13)°
C2	C3	C4	112.11(15)°		C2	C3	H32	107.843°
C4	C3	H32	109.445°		C2	C3	H31	109.878°
C4	C3	H31	108.636°		H32	C3	H31	108.876°
C3	C4	N5	178.6(2)°		C2	C6	C7	101.87(13)°
C2	C6	C14	115.60(14)°		C7	C6	C14	118.16(14)°
C2	C6	H61	105.401°		C7	C6	H61	107.554°
C14	C6	H61	107.363°		C6	C7	C8	128.64(16)°
C6	C7	C12	110.57(15)°		C8	C7	C12	120.74(16)°
C7	C8	C9	118.66(17)°		C7	C8	H81	121.020°
C9	C8	H81	120.313°		C8	C9	C10	120.58(17)°
C8	C9	H91	119.354°		C10	C9	H91	120.070°
C9	C10	C11	120.68(16)°		C9	C10	H101	119.412°
C11	C10	H101	119.903°		C10	C11	C12	118.71(17)°
C10	C11	H111	119.921°		C12	C11	H111	121.371°
C7	C12	C11	120.63(16)°		C7	C12	C13	110.38(15)°
C11	C12	C13	128.98(16)°		C2	C13	C12	102.96(14)°
C2	C13	H131	108.960°		C12	C13	H131	111.815°
C2	C13	H132	113.162°		C12	C13	H132	113.500°
H131	C13	H132	106.476°		C6	C14	C15	120.07(15)°
C6	C14	C19	121.97(15)°		C15	C14	C19	117.96(16)°
C14	C15	C16	121.13(16)°		C14	C15	H151	121.602°
C16	C15	H151	117.261°		C15	C16	C17	121.04(16)°
C15	C16	H161	121.651°		C17	C16	H161	117.297°
C16	C17	C18	117.79(16)°		C16	C17	C20	121.01(17)°
C18	C17	C20	121.20(18)°		C17	C18	C19	121.42(17)°

C17	C18	H181	120.508°		C19	C18	H181	118.067°
C14	C19	C18	120.65(16)°		C14	C19	H191	118.870°
C18	C19	H191	120.480°		C17	C20	H202	110.515°
C17	C20	H203	111.874°		H202	C20	H203	106.565°
C17	C20	H201	112.116°		H202	C20	H201	106.827°
H203	C20	H201	108.663°					

Crystal Data for 40a (single enantiomer)



a = 9.2633(3) Å α = 90°
b = 10.9330(3) Å β = 111.499(4)°
c = 11.4738(4) Å γ = 90°

Volume	1081.17(7) Å³	Crystal Class	monoclinic
Space group	P 2_1	Z =	2
Formula	C_{25} H_{24} F_1 N_1 O_2 S_1	M_r	421.53
Cell determined from	8816 reflections	Cell θ range =	4 - 76°
Temperature	150K		
Shape	prism		
Colour	clear_pale_colourless	Size	0.05 × 0.10 × 0.21 mm
D_x	1.29 Mg m^{-3}	F000	444.000
μ	1.575 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.83	T_{max}	0.92

Data Collection

Diffractometer	multi-scan
Scan type	ω scans
Reflections measured	18159
Independent reflections	4403
Rint	0.0317
θ_{max}	76.6035
h =	-11 → 11
k =	-13 → 13
l =	-14 → 14

Refinement

$\Delta\rho_{min}$ =	-0.56 e $Å^{-3}$
$\Delta\rho_{max}$ =	0.41 e $Å^{-3}$
Reflections used	3924
Cutoff: I >	-3.00σ(I)
Parameters refined	272
S =	1.00
R-factor	0.031
weighted R-factor	0.073
Δ/σ_{max}	0.0005
Flack parameter	-0.012(13)
Refinement on	F^2
w =	$1/[\sigma^2(F_{obs}^2) + (0.043 \times P)^2 + 0.203 \times P + 0.000 + 0.000 \times \sin\theta]$, $P = 0.333 \times \max(F_{obs}^2,0) + 0.667 \times F_{calc}^2$

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
S1	0.54646(5)	0.50000(7)	0.26800(4)	0.0278	1.0000
O2	0.41116(15)	0.56882(14)	0.19727(12)	0.0340	1.0000
O3	0.54382(16)	0.36909(13)	0.25854(13)	0.0365	1.0000
N4	0.68543(17)	0.54853(14)	0.22075(14)	0.0255	1.0000
C5	0.84198(19)	0.50563(19)	0.28122(15)	0.0262	1.0000
C6	0.9628(2)	0.59067(17)	0.31457(16)	0.0265	1.0000
C7	0.9362(2)	0.72536(17)	0.28650(16)	0.0259	1.0000
C8	0.9806(2)	0.77215(17)	0.17843(16)	0.0263	1.0000
C9	0.8803(2)	0.86619(17)	0.11600(17)	0.0285	1.0000
C10	0.7589(2)	0.89010(17)	0.17386(17)	0.0289	1.0000
C11	0.7668(2)	0.76602(17)	0.24113(15)	0.0248	1.0000
C12	0.6660(2)	0.66754(16)	0.15726(16)	0.0259	1.0000

F13	0.71722(12)	0.77858(11)	0.34248(9)	0.0306	1.0000
C14	0.5983(2)	0.9203(2)	0.07839(19)	0.0388	1.0000
C15	0.8127(3)	0.9952(2)	0.26970(19)	0.0409	1.0000
C16	0.8985(2)	0.92463(18)	0.01532(17)	0.0340	1.0000
C17	1.0179(2)	0.8874(2)	0.02289(19)	0.0386	1.0000
C18	1.1157(2)	0.7926(2)	0.0379(2)	0.0384	1.0000
C19	1.0977(2)	0.73360(18)	0.13941(18)	0.0321	1.0000
C20	1.1150(2)	0.54839(19)	0.37425(19)	0.0363	1.0000
C21	1.1471(3)	0.4251(2)	0.3983(2)	0.0424	1.0000
C22	1.0263(3)	0.3424(2)	0.3628(2)	0.0432	1.0000
C23	0.8748(2)	0.38086(19)	0.30375(19)	0.0360	1.0000
C24	0.5969(2)	0.53634(16)	0.42734(17)	0.0271	1.0000
C25	0.5383(2)	0.64291(18)	0.45929(17)	0.0295	1.0000
C26	0.5757(2)	0.67074(18)	0.58476(18)	0.0332	1.0000
C27	0.6718(2)	0.59555(19)	0.67928(18)	0.0334	1.0000
C28	0.7285(2)	0.4896(2)	0.64414(17)	0.0381	1.0000
C29	0.6919(2)	0.45915(18)	0.51950(18)	0.0348	1.0000
C30	0.7140(3)	0.6293(2)	0.8149(2)	0.0474	1.0000
H71	0.9933(2)	0.77201(17)	0.36156(16)	0.0302	1.0000
H122	0.5558(2)	0.68967(16)	0.12766(16)	0.0306	1.0000
H121	0.6971(2)	0.65993(16)	0.08574(16)	0.0303	1.0000
H143	0.5207(2)	0.9182(2)	0.11858(19)	0.0565	1.0000
H142	0.5670(2)	0.8648(2)	0.00522(19)	0.0565	1.0000
H141	0.6012(2)	1.0030(2)	0.04729(19)	0.0570	1.0000
H153	0.7343(3)	1.0055(2)	0.30642(19)	0.0599	1.0000
H152	0.8211(3)	1.0690(2)	0.22532(19)	0.0611	1.0000
H151	0.9125(3)	0.9777(2)	0.33751(19)	0.0604	1.0000
H161	0.8296(2)	0.98726(18)	0.02634(17)	0.0416	1.0000
H171	1.0332(2)	0.9272(2)	0.09147(19)	0.0461	1.0000
H181	1.1957(2)	0.7641(2)	0.0100(2)	0.0452	1.0000
H191	1.1623(2)	0.66791(18)	0.18075(18)	0.0389	1.0000
H201	1.1958(2)	0.60806(19)	0.39935(19)	0.0444	1.0000
H211	1.2560(3)	0.4005(2)	0.4407(2)	0.0496	1.0000
H221	1.0483(3)	0.2560(2)	0.3789(2)	0.0519	1.0000
H231	0.7919(2)	0.32332(19)	0.27620(19)	0.0425	1.0000
H251	0.4725(2)	0.69437(18)	0.39453(17)	0.0350	1.0000
H261	0.5338(2)	0.74258(18)	0.60692(18)	0.0413	1.0000
H281	0.7950(2)	0.4367(2)	0.70685(17)	0.0465	1.0000

H291	0.7307(2)	0.38547(18)	0.49639(18)	0.0417	1.0000
H303	0.7151(3)	0.5585(2)	0.8650(2)	0.0729	1.0000
H302	0.6456(3)	0.6897(2)	0.8276(2)	0.0723	1.0000
H301	0.8156(3)	0.6618(2)	0.8486(2)	0.0728	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	0.0271(2)	0.0297(2)	0.0297(2)	0.00255(19)	0.01386(16)	0.00554(18)
O2	0.0232(6)	0.0461(8)	0.0320(6)	0.0002(6)	0.0091(5)	-0.0024(6)
O3	0.0453(8)	0.0281(7)	0.0410(7)	-0.0054(6)	0.0217(6)	-0.0111(6)
N4	0.0244(7)	0.0255(7)	0.0294(7)	0.0013(6)	0.0130(6)	-0.0002(6)
C5	0.0278(8)	0.0282(9)	0.0274(7)	0.0016(8)	0.0158(7)	0.0037(8)
C6	0.0266(9)	0.0295(9)	0.0260(9)	0.0035(7)	0.0126(7)	0.0033(7)
C7	0.0229(9)	0.0290(9)	0.0235(8)	-0.0012(7)	0.0059(7)	-0.0009(7)
C8	0.0233(8)	0.0269(9)	0.0288(8)	-0.0020(7)	0.0098(7)	-0.0057(7)
C9	0.0287(9)	0.0276(9)	0.0309(9)	-0.0013(8)	0.0131(8)	-0.0037(7)
C10	0.0293(9)	0.0268(9)	0.0339(9)	0.0027(7)	0.0155(8)	0.0013(7)
C11	0.0256(9)	0.0275(9)	0.0242(8)	0.0003(7)	0.0126(7)	0.0018(7)
C12	0.0235(9)	0.0289(9)	0.0259(8)	0.0008(7)	0.0097(7)	0.0003(7)
F13	0.0374(6)	0.0303(5)	0.0310(5)	-0.0012(4)	0.0206(5)	0.0002(4)
C14	0.0354(10)	0.0384(12)	0.0453(11)	0.0165(9)	0.0181(9)	0.0121(9)
C15	0.0547(12)	0.0275(9)	0.0479(10)	-0.0032(10)	0.0277(9)	0.0003(10)
C16	0.0358(10)	0.0317(10)	0.0366(9)	0.0055(9)	0.0158(8)	-0.0029(8)
C17	0.0435(11)	0.0411(11)	0.0381(10)	0.0019(9)	0.0230(9)	-0.0087(9)
C18	0.0363(11)	0.0427(12)	0.0447(11)	-0.0058(9)	0.0248(9)	-0.0064(9)
C19	0.0268(10)	0.0316(9)	0.0401(10)	-0.0051(8)	0.0148(8)	-0.0024(8)
C20	0.0301(10)	0.0429(11)	0.0361(10)	0.0097(9)	0.0125(8)	0.0066(9)
C21	0.0375(11)	0.0487(13)	0.0442(11)	0.0152(11)	0.0188(9)	0.0164(10)
C22	0.0518(13)	0.0353(11)	0.0521(13)	0.0131(10)	0.0305(11)	0.0168(10)
C23	0.0443(11)	0.0300(10)	0.0425(11)	0.0050(8)	0.0263(9)	0.0045(9)
C24	0.0252(9)	0.0301(9)	0.0304(9)	-0.0001(7)	0.0155(7)	-0.0023(7)
C25	0.0282(9)	0.0303(10)	0.0330(9)	0.0049(8)	0.0145(8)	0.0051(7)
C26	0.0355(11)	0.0319(10)	0.0377(10)	0.0010(8)	0.0201(8)	0.0056(8)
C27	0.0312(10)	0.0388(11)	0.0318(9)	0.0007(8)	0.0135(8)	-0.0002(8)
C28	0.0396(10)	0.0404(11)	0.0323(9)	0.0068(9)	0.0109(8)	0.0124(10)
C29	0.0384(10)	0.0327(10)	0.0365(10)	0.0012(8)	0.0175(8)	0.0070(8)
C30	0.0541(14)	0.0523(13)	0.0333(10)	-0.0021(10)	0.0132(10)	0.0067(11)

Distances

S1	O2	1.4317(14)Å		S1	O3	1.4348(14)Å
S1	N4	1.6565(15)Å		S1	C24	1.7586(18)Å
N4	C5	1.438(2)Å		N4	C12	1.470(2)Å
C5	C6	1.397(3)Å		C5	C23	1.401(3)Å
C6	C7	1.508(3)Å		C6	C20	1.401(3)Å
C7	C8	1.531(2)Å		C7	C11	1.527(2)Å
C7	H71	0.973Å		C8	C9	1.395(3)Å
C8	C19	1.382(3)Å		C9	C10	1.523(2)Å
C9	C16	1.384(3)Å		C10	C11	1.549(3)Å
C10	C14	1.526(3)Å		C10	C15	1.542(3)Å
C11	C12	1.516(2)Å		C11	F13	1.4047(19)Å
C12	H122	0.981Å		C12	H121	0.968Å
C14	H143	0.986Å		C14	H142	0.989Å
C14	H141	0.976Å		C15	H153	0.971Å
C15	H152	0.972Å		C15	H151	0.985Å
C16	C17	1.391(3)Å		C16	H161	0.939Å
C17	C18	1.385(3)Å		C17	H171	0.954Å
C18	C19	1.394(3)Å		C18	H181	0.960Å
C19	H191	0.944Å		C20	C21	1.386(3)Å
C20	H201	0.954Å		C21	C22	1.379(3)Å
C21	H211	0.983Å		C22	C23	1.381(3)Å
C22	H221	0.970Å		C23	H231	0.953Å
C24	C25	1.390(3)Å		C24	C29	1.387(3)Å
C25	C26	1.385(3)Å		C25	H251	0.953Å
C26	C27	1.392(3)Å		C26	H261	0.951Å
C27	C28	1.391(3)Å		C27	C30	1.505(3)Å
C28	C29	1.384(3)Å		C28	H281	0.952Å
C29	H291	0.958Å		C30	H303	0.961Å
C30	H302	0.963Å		C30	H301	0.946Å

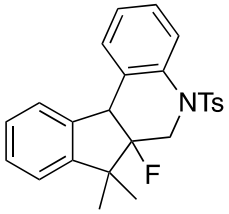
Angles

O2	S1	O3	119.61(9)°		O2	S1	N4	105.66(8)°
O3	S1	N4	106.77(8)°		O2	S1	C24	108.32(8)°
O3	S1	C24	107.14(9)°		N4	S1	C24	109.01(8)°
S1	N4	C5	120.33(12)°		S1	N4	C12	118.50(12)°
C5	N4	C12	116.53(14)°		N4	C5	C6	118.73(17)°

N4	C5	C23	121.26(17)°		C6	C5	C23	119.99(17)°
C5	C6	C7	122.64(16)°		C5	C6	C20	118.45(17)°
C7	C6	C20	118.89(17)°		C6	C7	C8	115.33(15)°
C6	C7	C11	115.11(15)°		C8	C7	C11	100.04(14)°
C6	C7	H71	109.227°		C8	C7	H71	108.762°
C11	C7	H71	107.818°		C7	C8	C9	109.63(15)°
C7	C8	C19	129.53(17)°		C9	C8	C19	120.84(17)°
C8	C9	C10	111.23(15)°		C8	C9	C16	120.45(17)°
C10	C9	C16	128.32(17)°		C9	C10	C11	99.17(14)°
C9	C10	C14	113.94(15)°		C11	C10	C14	113.73(15)°
C9	C10	C15	109.98(15)°		C11	C10	C15	110.71(15)°
C14	C10	C15	109.03(16)°		C7	C11	C10	106.24(14)°
C7	C11	C12	109.06(14)°		C10	C11	C12	113.58(14)°
C7	C11	F13	110.68(13)°		C10	C11	F13	110.90(14)°
C12	C11	F13	106.42(14)°		N4	C12	C11	112.27(14)°
N4	C12	H122	108.223°		C11	C12	H122	111.437°
N4	C12	H121	108.890°		C11	C12	H121	107.096°
H122	C12	H121	108.847°		C10	C14	H143	110.217°
C10	C14	H142	112.444°		H143	C14	H142	110.217°
C10	C14	H141	108.186°		H143	C14	H141	108.359°
H142	C14	H141	107.271°		C10	C15	H153	107.332°
C10	C15	H152	108.182°		H153	C15	H152	110.383°
C10	C15	H151	112.482°		H153	C15	H151	108.361°
H152	C15	H151	110.070°		C9	C16	C17	118.86(18)°
C9	C16	H161	119.564°		C17	C16	H161	121.572°
C16	C17	C18	120.57(18)°		C16	C17	H171	120.154°
C18	C17	H171	119.280°		C17	C18	C19	120.72(19)°
C17	C18	H181	121.164°		C19	C18	H181	118.091°
C8	C19	C18	118.55(19)°		C8	C19	H191	119.822°
C18	C19	H191	121.627°		C6	C20	C21	121.46(19)°
C6	C20	H201	117.341°		C21	C20	H201	121.187°
C20	C21	C22	119.18(19)°		C20	C21	H211	118.057°
C22	C21	H211	122.759°		C21	C22	C23	120.9(2)°
C21	C22	H221	119.447°		C23	C22	H221	119.657°
C5	C23	C22	120.0(2)°		C5	C23	H231	119.190°
C22	C23	H231	120.805°		S1	C24	C25	118.88(14)°
S1	C24	C29	120.51(14)°		C25	C24	C29	120.60(17)°
C24	C25	C26	119.01(17)°		C24	C25	H251	119.280°

C26	C25	H251	121.710°		C25	C26	C27	121.68(17)°
C25	C26	H261	119.198°		C27	C26	H261	119.122°
C26	C27	C28	117.87(17)°		C26	C27	C30	120.71(18)°
C28	C27	C30	121.41(18)°		C27	C28	C29	121.62(18)°
C27	C28	H281	119.691°		C29	C28	H281	118.690°
C24	C29	C28	119.22(18)°		C24	C29	H291	119.889°
C28	C29	H291	120.891°		C27	C30	H303	111.261°
C27	C30	H302	112.897°		H303	C30	H302	109.014°
C27	C30	H301	110.913°		H303	C30	H301	105.473°
H302	C30	H301	106.927°					

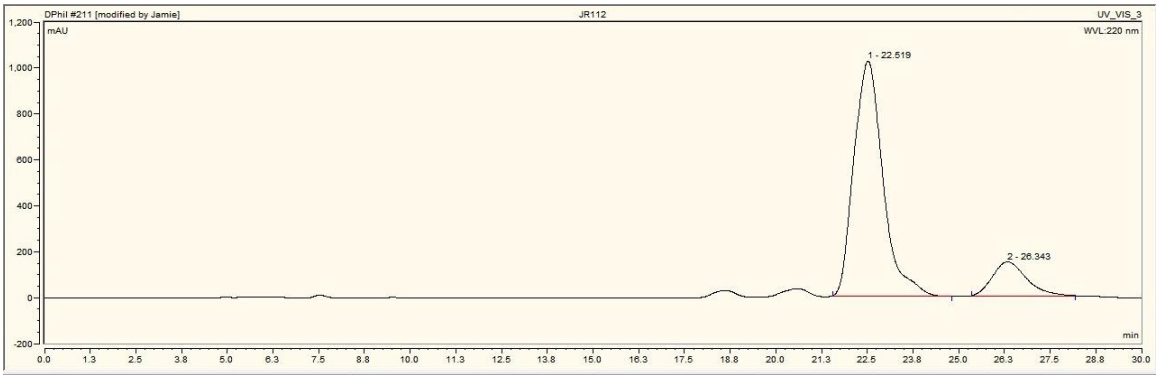
Appendix iii: HPLC traces



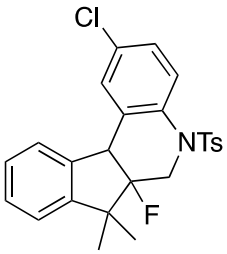
IA 98/2 1ml/min 19.2 min + 22.0 min

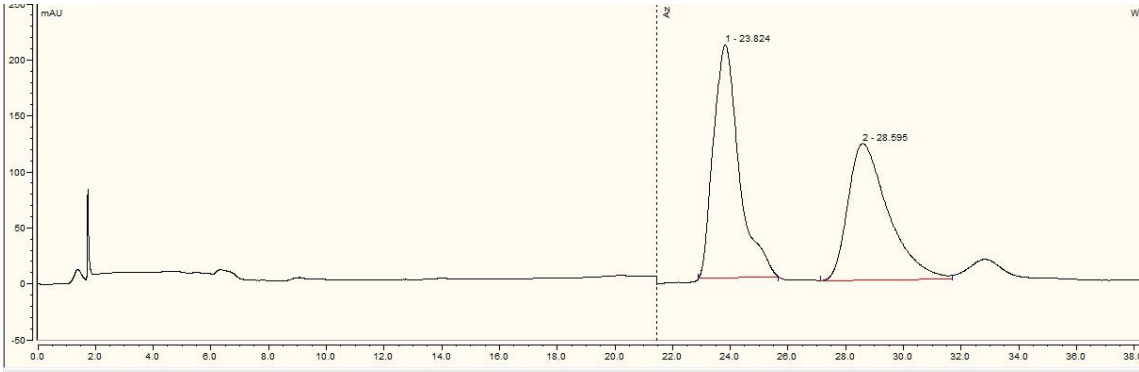
in iPA

71 % ee



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	22.519	943.1786	n.a.	BMB*	1022.874	85.63	2.46
2	n.a.	26.343	158.2890	n.a.	BMB*	147.154	14.37	n.a.
Total:			#########	0.0000		1170.028	100.00	



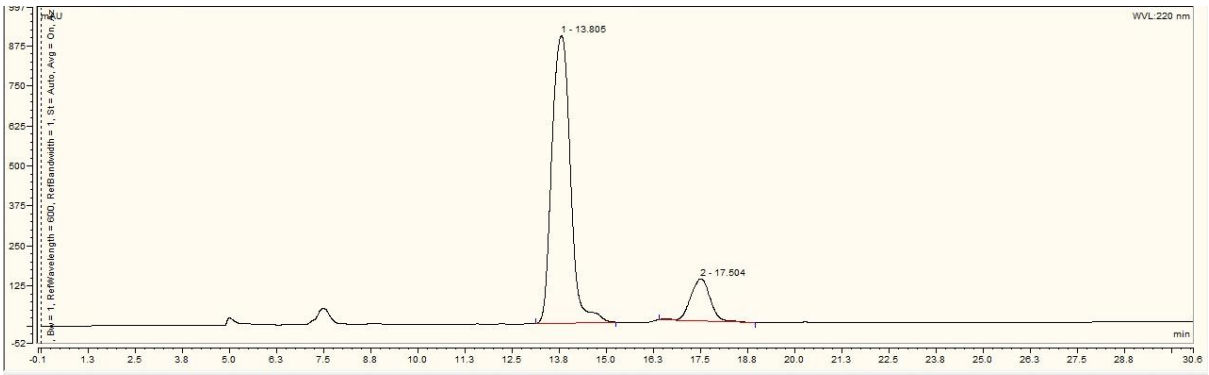


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23.824	214.5962	n.a.	BMB*	208.076	51.92	2.38
2	n.a.	28.595	198.7224	n.a.	BM *	122.042	48.08	n.a.
Total:			413.3185	0.0000		330.118	100.00	

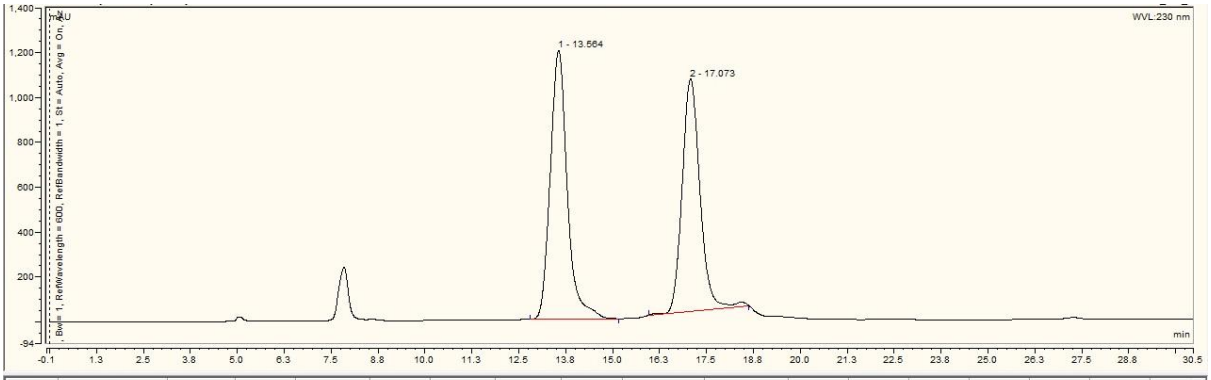
IA 95/5 1mL/min 13.6 min + 17.1 min

dissolved in iPA

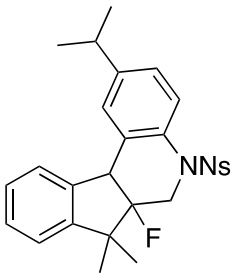
73 % ee



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	13.805	511.2246	n.a.	BMB*	898.309	86.50	3.99
2	n.a.	17.504	79.7686	n.a.	BMB*	131.889	13.50	n.a.
Total:			590.9932	0.0000		1030.198	100.00	



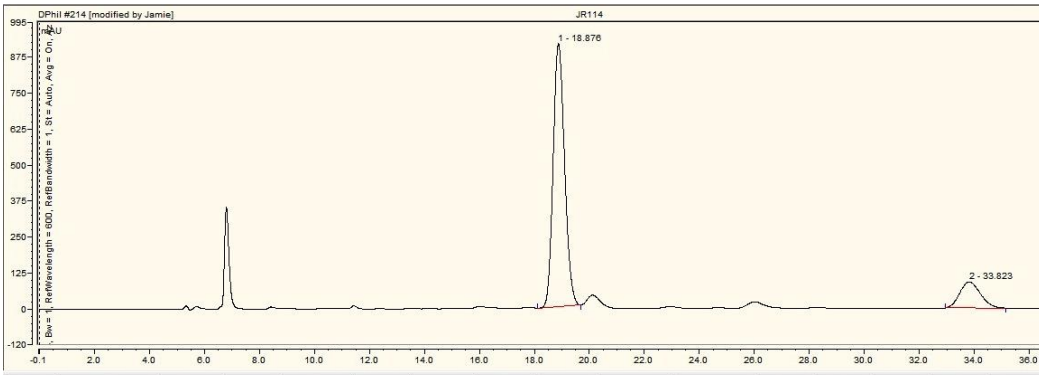
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	13.564	630.9995	n.a.	BMB*	1197.276	52.56	4.31
2	n.a.	17.073	569.5033	n.a.	BMB*	1034.637	47.44	n.a.
Total:			#########	0.0000		2231.913	100.00	



IC 80/20 1ml/min 18.5 min + 33.0 min

in 25% DCM/75% hexane

70 % ee



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	18.876	439.2900	n.a.	BMB*	910.829	84.87	13.97
2	n.a.	33.823	78.3179	n.a.	BMB*	90.681	15.13	n.a.
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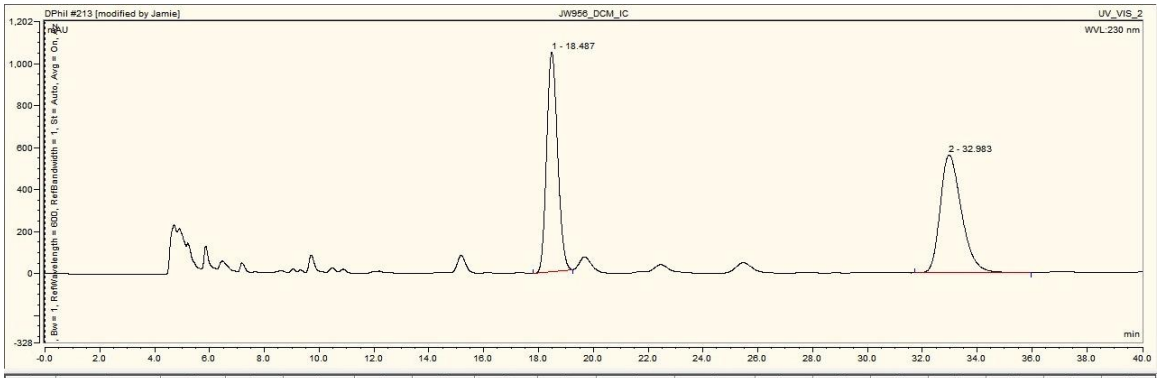

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	18.487	482.7306	n.a.	BMB*	1045.332	48.81	13.63
2	n.a.	32.983	506.1789	n.a.	BMB*	561.423	51.19	n.a.
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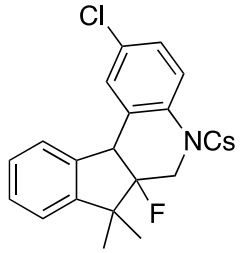
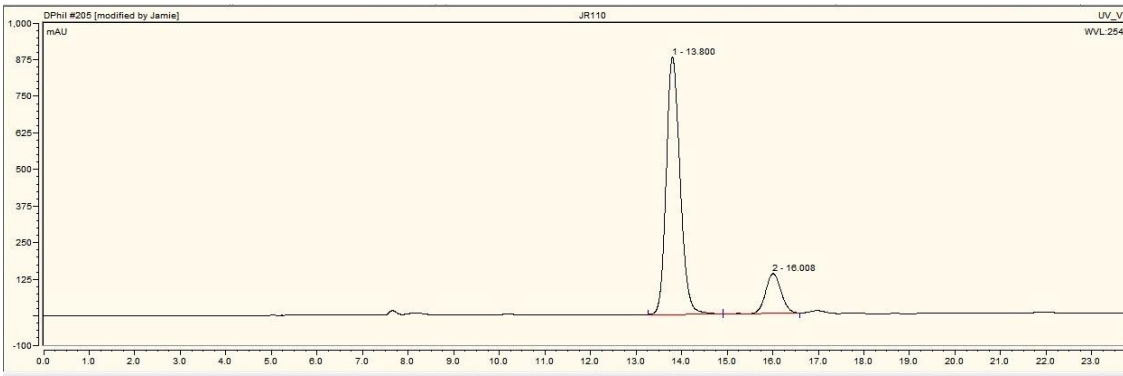


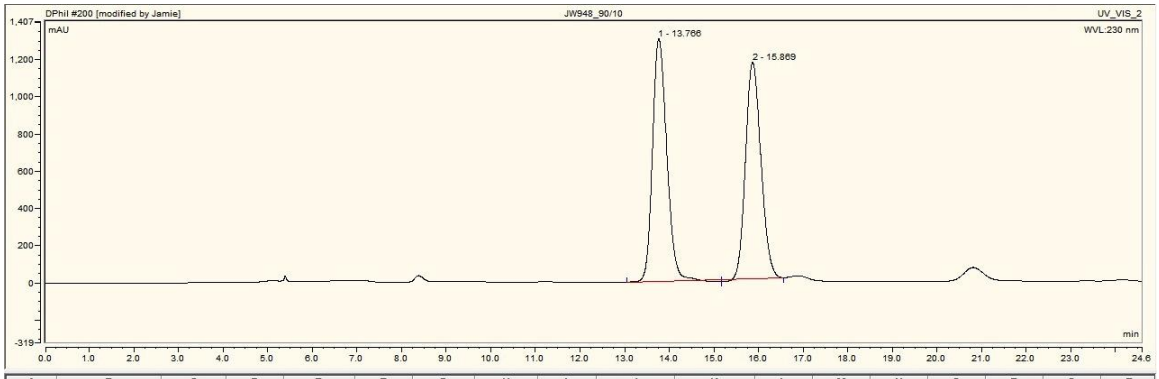
IA 95/5 13.8 min + 15.9 min 1ml/min

in 10% EtOAc/90% hexane

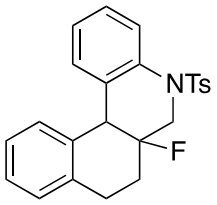
71 % ee



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	13.800	307.9777	n.a.	BMb*	877.148	85.56	3.82
2	n.a.	16.008	51.9959	n.a.	bMB*	135.361	14.44	n.a.
Total:			359.9736	0.0000		1012.509	100.00	



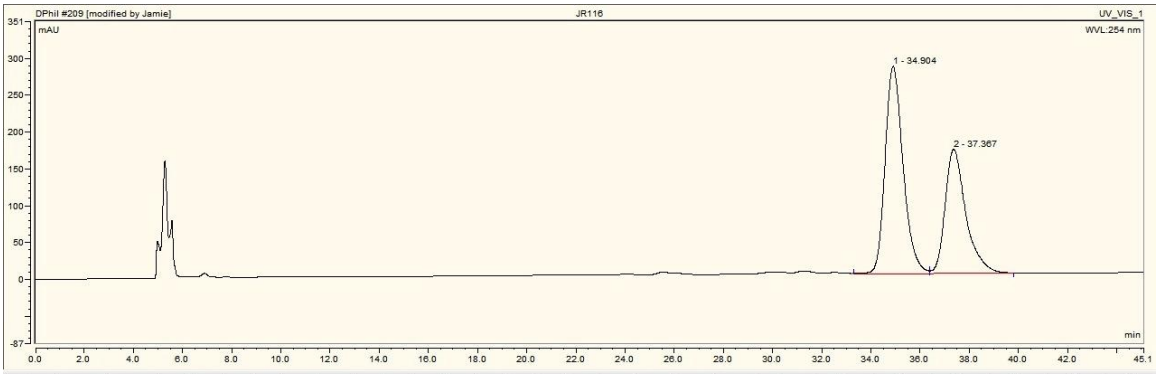
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	13.766	476.8884	n.a.	BM *	1300.475	50.75	3.47
2	n.a.	15.869	462.7893	n.a.	MB*	1160.424	49.25	n.a.
Total:			939.6777	0.0000		2460.899	100.00	



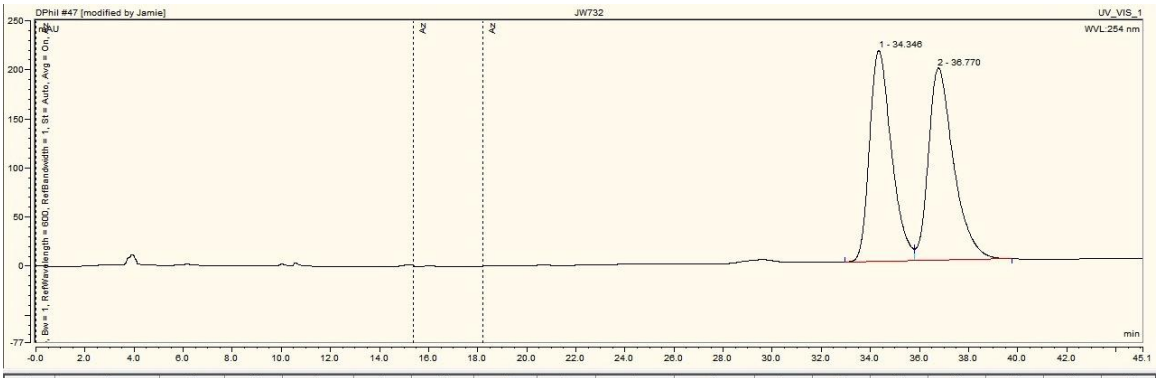
IC 90/10 1ml/min 34.3 min + 36.8 min

in iPA

19 % ee



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	34.904	237.9970	n.a.	BM	281.038	59.30	1.80
2	n.a.	37.367	163.3615	n.a.	MB	168.029	40.70	n.a.
Total:			401.3585	0.0000		449.067	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	34.346	223.3495	n.a.	BM	214.696	48.82	1.42
2	n.a.	36.770	234.1555	n.a.	MB	195.692	51.18	n.a.
Total:			457.5050	0.0000		410.388	100.00	

Synthetic Methods

DOI: 10.1002/anie.201304845

Asymmetric Electrophilic Fluorocyclization with Carbon Nucleophiles**

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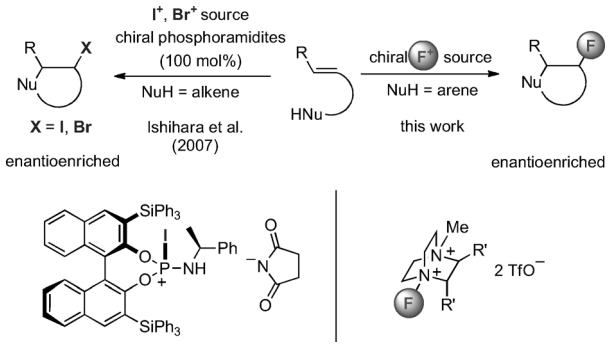
The electrophilic halogenation reaction of olefins coupled with cascade carbocyclization is an iconic biomimetic process for the construction of complex molecules.[1] In 2007, Ishihara and co-workers reported the first example of enantioselective iodocarbocyclization of polyenes with *N*-iodosuccinimide, a reaction promoted by stoichiometric quantities of a chiral phosphoramidite nucleophile.[2] This system was less effective for bromo- and chlorocarbocyclizations. Indeed, the enantiopurity of the products was significantly lower with *N*-bromosuccinimide, and the reaction did not proceed in the presence of *N*-chlorosuccinimide. As a matter of fact, the identification of competent electrophilic halogen sources which allow high-yielding product formation is not trivial, and conceptual advances to control enantioselectivity of these complex processes are in high demand. Since 2007, progress has been slow and in line with the well-recognized challenges associated with halocyclizations involving carbon nucleophiles.[3]

To the best of our knowledge, the synthesis of enantioenriched fluorinated carbocycles from prochiral polyenes is limited to the recent contribution of Gagné and co-workers who reported a unique transformation using a chiral dicationic platinum catalyst.[4] However, this transition-metal-catalyzed process is characterized by a stereoretentive electrophilic fluorination of a cyclized cationic platinum/alkyl intermediate and is therefore distinct from a mechanistic scenario in which a fluorinated cation is formed prior to π cyclization. Herein, we disclose the first metal-free fluorination/carbocyclization process for the synthesis of fluorinated carbocyclic products from prochiral precursors. A new class of chiral N-F reagents based on the dicationic structural core of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor) allowed access to enantioenriched fluorocyclized products (Scheme 1).



Scheme 1. Metal-free asymmetric halocyclization with a C nucleophile. Tf = trifluoromethanesulfonyl.

In the first instance, we focused our efforts towards developing a non-enantioselective version of the envisioned transformation, since cation–π cyclizations induced by an electrophilic fluorine source are not known (Table 1).[5] The prototypical structure selected for validation and optimization studies was the indene **1a** bearing a 2-phenylethyl substituent at the C2 position. The pendant phenyl group was chosen as a C nucleophile to encourage chemo- and regioselective electrophilic fluorination at the carbon–carbon double bond. The resulting intermediate would undergo aryl cyclization leading to the tetracyclic fluorinated product **2a**.

When **1a** was reacted with 1.1 equivalents of Selectfluor in acetonitrile in the presence of an excess $NaHCO_3$ (3 equiv), **2a** was formed together with the product **3a**, which arises from competitive capture of the fluorinated carbocationic intermediate by the reaction solvent, acetonitrile (Table 1).[6] Under these reaction conditions, **2a** was isolated in 26% yield (entry 1). Varying the reaction temperature or the nature of the base did not prove beneficial (entries 2–4). *N*-Fluorobenzenesulfonimide (NFSI) was less satisfactory than Selectfluor as this fluorinating agent led predominantly to **4a**, thus resulting from regioselective net NFSI addition across the double bond. The formation of **4a** with NFSI encouraged us to reconsider Selectfluor. The replacement of acetonitrile

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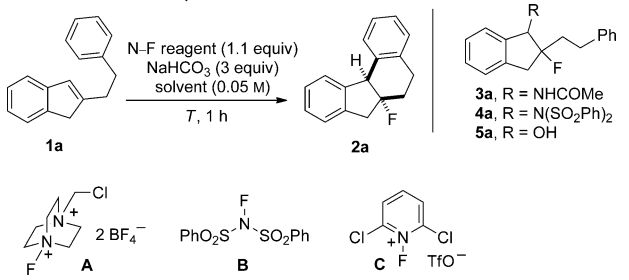
Table 1: Fluorocarbocyclization of indene **1a**.



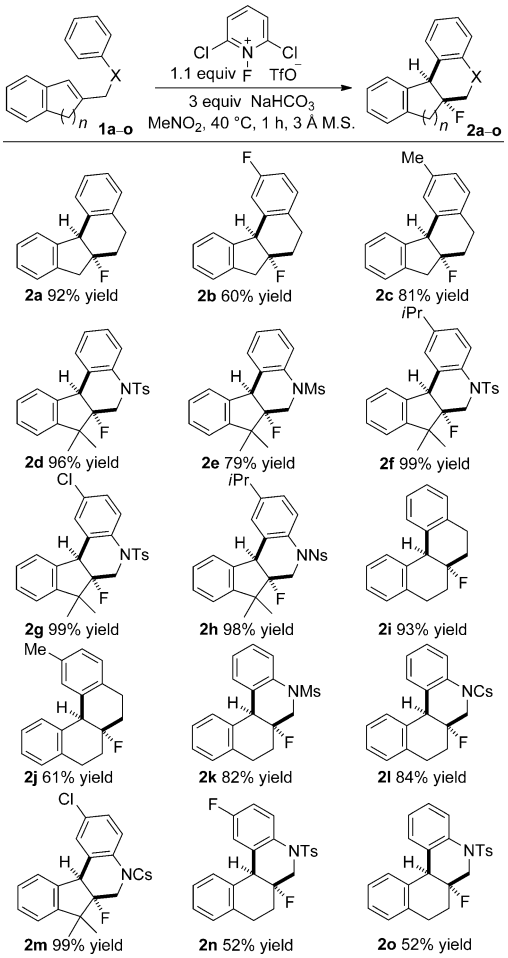
Entry[a]	N-F Source[b]	Solvent	T [°C]	**1a**/**2a**/**3a**/**4a**/**5a**[c]	**2a** Yield [%][d]
1	**A**	MeCN	RT	0:29:63:0:8	26
2	**A**	MeCN	0	0:26:69:0:5	–
3	**A**	MeCN	−40	81:3:14:0:2	–
4[e]	**A**	MeCN	RT	19:22:49:0:10	–
5	**B**	MeCN	RT	56:10:0:33:1	–
6[f]	**A**	$MeNO_2$	RT	0:93:0:0:7	59
7[f]	**C**	$MeNO_2$	RT	0:96:0:0:4	89
8[f]	**C**	$MeNO_2$	0	0:86:0:0:14	72
9[f]	**C**	$MeNO_2$	40	0:98:0:0:2	92

[a] General conditions: **1a** (50 mg), solvent (5 mL), $NaHCO_3$ (3.0 equiv), N-F reagent (1.1 equiv), 1 h. [b] **A** = Selectfluor, **B** = *N*-fluorobenzenesulfonimide (NFSI), **C** = *N*-fluoro-2,6-dichloropyridinium triflate. [c] Determined by integration of the ^{1}H NMR signals using 1-fluoro-3-nitrobenzene as an internal reference. [d] Yield of isolated product. [e] Reaction performed with 3 equivalents of K_2CO_3. [f] Reaction performed in the presence of molecular sieves (3 Å).

with nitromethane was found to be effective, thus delivering **2a** in 59% yield. The reaction was further optimized using *N*-fluoro-2,6-dichloropyridinium triflate in nitromethane at 40°C. Under these optimal reaction conditions, **2a** was obtained in 92% yield. The use of freshly activated 3 Å molecular sieves (M.S.) was found to be critical to suppress the formation of undesired fluorohydrin **5a**.[7]

A series of variously C2-substituted indenes and 1,2-dihydronaphthalenes effectively participated in the fluorocarbon-cyclization (Scheme 2).[8] The reaction tolerates substitution of the aryl C nucleophile at the *para*-position with fluoro, chloro, and alkyl groups. Substrates with N-sulfonylanilines acting as C nucleophiles also underwent successful fluorocyclization to afford a range of novel fluorinated tetrahydro-5*H*-indeno[2,1-*c*]quinolines and hexahydrobenzo[*k*]phenanthridines which were isolated in yields ranging from 52% to 99%. All products were formed exclusively as the corresponding *syn* diastereomers. The stereochemical assignment was based on the vicinal scalar coupling constant between the fluorine and the hydrogen located at the ring junction. These coupling constants were of the order of 15 Hz for **2d–o** and 21 Hz for **2a–c**.[8] Single-crystal X-ray crystallographic analysis of **2i** [$^3J(F^{6a},H^{12b}) = 14.7$ Hz] revealed its nonplanar helical structure and confirmed that the fluorine substituent is disposed *syn* to the hydrogen atom at C12b (Figure 1).[8]

Our next goal was the development of an asymmetric variant of this reaction. Preliminary experiments revealed the limitations of currently available strategies for (catalytic) asymmetric electrophilic fluorination, many of which were



Scheme 2. Fluorocarbocyclization of indenes and 1,2-dihydronaphtalenes. Cs = 4-chlorobenzenesulfonyl, Ms = methanesulfonyl, Ns = 4-nitrobenzenesulfonyl.

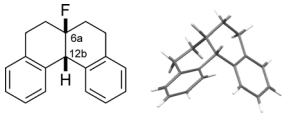


Figure 1. Structure of 6a-fluoro-5,6,6a,7,8,12b-hexahydrobenzo[*c*]phenanthrene (**2i**) from single-crystal X-ray diffraction data.

developed in the context of fluorocyclization with heteroatom nucleophiles. The reaction of **1a** with chiral N-F reagents derived from cinchona alkaloids (type A[9]; Figure 2) failed to proceed.[8] This result contrasts with the ability of these reagents to promote asymmetric fluoroheterocyclization of more nucleophilic substrates, including allylsilanes[10] and indoles.[11] The recovery of **1a** upon treatment with type A N-F reagents highlights the difference of reactivity between N-F reagents derived from quinuclidine and 1,4-diazabicyclo[2.2.2]octane (DABCO). We next considered chiral anion phase-transfer catalysis.[12] This catalytic manifold was applied by Toste and co-workers to Selectfluor, a cationic reagent insoluble in nonpolar media.[13] In the presence of bulky chiral phosphate (10 mol%), anion exchange with tetrafluoroborate

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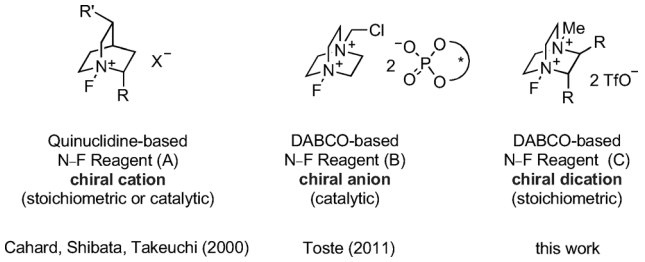
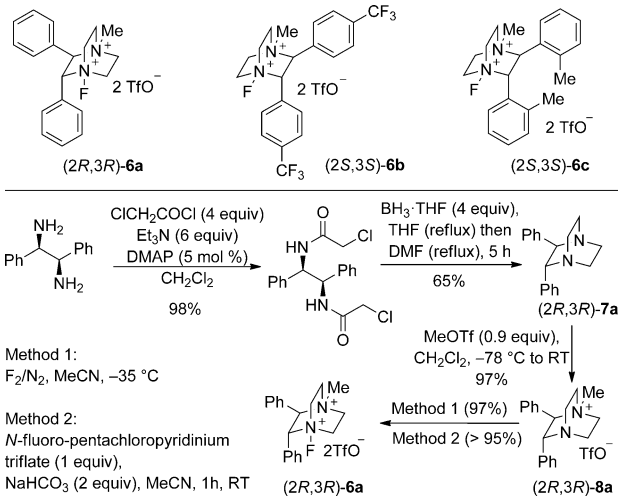


Figure 2. Chiral N-F reagents of types A, B, and C.

brings the N-F reagent into solution, thus allowing catalytic asymmetric fluoroheterocyclization of various substrates inclusive of 1,2-dihydronaphthalenes. Conceptually, this catalytic system relies on in situ formation of chiral Selectfluor of type B (Figure 2), in which the stereogenic elements are located on the anionic component. In the present reaction, we found that no reaction occurred when **1a** was reacted with 1.5 equivalents of Selectfluor, 1.25 equivalents of $NaHCO_3$, and 10 mol% of the chiral phosphonic acid (*R*)-TRIP (3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate) in hexanes. The use of nitromethane instead of hexanes induced fluorocarbocyclization, but as expected, this polar solvent afforded **2a** as a racemate. Similarly, the indene **1d** did not react upon treatment at room temperature for 24 hours with Selectfluor (1.5 equiv), $NaHCO_3$ (1.5 equiv), and 10 mol% of (*R*)-TRIP using hexanes, hexanes/fluorobenzene (1:1), or fluorobenzene as solvent.[8]

At this point, we considered a new approach to access enantioenriched fluorocarbocycles resulting from cation–π cyclization induced by an electrophilic fluorine source. Our studies in the racemic series informed us that the critical components necessary to convert **1a** into **2a** are the combined used of nitromethane as the solvent and either Selectfluor or *N*-fluoro-2,6-dichloropyridinium triflate as the fluorine source. These considerations led us to design a new class of chiral N-F reagents (type C; Figure 2) which are based on the structural core of Selectfluor with the stereogenic elements on the dicationic DABCO core. These chiral Selectfluor derivatives are predicted to be more reactive than the type A N-F reagents and offer a platform to investigate how solubility, reactivity, and enantiocontrol can be tuned by varying the R substituents of the DABCO core.

To this end, the chiral N-F reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c**, substituted with phenyl, *p*-(trifluoromethyl)phenyl, and *o*-toluoyl groups, respectively, were prepared (Scheme 3). The chiral DABCO (2*R*,3*R*)-**7a** was a necessary precursor to access (2*R*,3*R*)-**6a**. This compound was assembled from the corresponding enantiopure vicinal diamine using a protocol disclosed by Oi and Sharpless.[14] N-Quaternization of (2*R*,3*R*)-**7a** performed with methyl triflate afforded (2*R*,3*R*)-**8a** in 97% yield. The subsequent fluorination was achieved using fluorine gas (10% *v/v* in N_2) in acetonitrile (Method 1). Extensive optimization varying the amount of F_2, the reaction temperature, and the concentration was essential to identify reaction conditions which suppressed indiscriminate fluorination of the aryl groups. The best reaction conditions offered (2*R*,3*R*)-**6a** in 97% yield. Pleasingly, (2*R*,3*R*)-**6a** could also be prepared at room temperature in acetonitrile using commercially available *N*-fluoropentachloropyridinium triflate[15] in the presence of sodium bicarbonate (Method 2). This latter protocol is advantageous as it allows in situ formation of chiral Selectfluor reagents of type C[8] as an alternative to the use of isolated reagents. The chiral N-F reagents (2*S*,3*S*)-**6b** and (2*S*,3*S*)-**6c** were prepared in comparable yields by applying the same reaction sequence.[8]



Scheme 3. Chiral reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c**. DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

Asymmetric fluorocyclization of **1d** was carried out in the presence of the chiral N-F reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c** (Table 2).[8] For this study, the reaction solvent was reconsidered since we suspected that the solubility profile of the chiral reagents **6a–c** might differ from that of Selectfluor. All reagents mediated the conversion of **1d** into the enantioenriched **2d** when the reaction was performed in nitromethane, with each giving drastically different reactivity and enantioselectivity (entries 1–3). The reagent (2*S*,3*S*)-**6b** with the *para*-electron-withdrawing CF_3 substituents on the aryl rings was the most reactive, as **1d** was entirely converted into **2d** (entry 2). Collectively, these experiments demonstrate that one can tailor the reactivity of this new class of chiral reagents by varying the steric and electronic properties of the substituents located at C2 and C3. Pleasingly, (2*S*,3*S*)-**6b** was also the most effective for enantiocontrol as **2d** was formed in 60% *ee*. The reagents (2*R*,3*R*)-**6a** and (2*S*,3*S*)-**6c** gave *ee* values of 32% and 55%, respectively. Based on this lead result, all subsequent reactions were performed with (2*S*,3*S*)-**6b**. The reaction solvent had an influence on yield and *ee* value (entry 4–10). The compound **2d** was obtained with 81% *ee* in THF but with a significant decrease in yield (entry 6). 1,4-Dioxane afforded **2d** in 88% yield and 74% *ee* (entry 7). The nature of the inorganic base had no effect on the *ee* value but substituting $NaHCO_3$ with K_2CO_3 or Cs_2CO_3 was detrimental to the yield (entries 12 and 13). Notably, the *ee* value was found to be 74% when the reaction was performed at either 50 °C or 10 °C (entries 14 and 15). Thus, under the optimized reaction conditions, treating **1d** with

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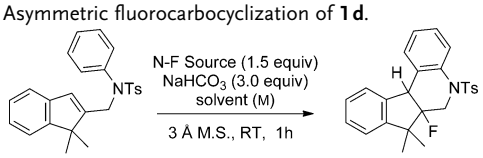
Table 2: Asymmetric fluorocarbocyclization of **1d**.



1d *syn*-**2d**

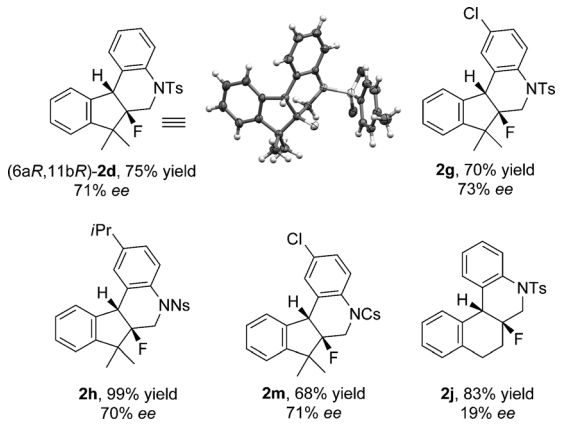
Entry	Solvent	N-F Source	**1d** Recovery [%][a]	Yield [%][a]	*ee* [%][b]
1	$MeNO_2$	(2*R*,2*R*)-**6a**	18	63	−32
2	$MeNO_2$	(2*S*,2*S*)-**6b**	<5	>95	60
3[c]	$MeNO_2$	(2*S*,2*S*)-**6c**	38	44	55
4	CH_2Cl2	(2*S*,2*S*)-**6b**	65	14	77
5	DCE	(2*S*,2*S*)-**6b**	30	59	74
6	THF	(2*S*,2*S*)-**6b**	6	22	81
7	1,4-dioxane	(2*S*,2*S*)-**6b**	<5	88	74
8	DMF	(2*S*,2*S*)-**6b**	92	0	–
9	acetone	(2*S*,2*S*)-**6b**	50	14	72
10	MeCN	(2*S*,2*S*)-**6b**	26	37	52
11[d]	1,4-dioxane	(2*S*,2*S*)-**6b**	38	62	76
12[e]	1,4-dioxane	(2*S*,2*S*)-**6b**	47	39	76
13[f]	1,4-dioxane	(2*S*,2*S*)-**6b**	67	23	79
14[g]	1,4-dioxane	(2*S*,2*S*)-**6b**	39	46	74
15[h]	1,4-dioxane	(2*S*,2*S*)-**6b**	34	47	74
16[i]	1,4-dioxane	(2*S*,2*S*)-**6b**	84	13	80
17[j]	1,4-dioxane	(2*S*,2*S*)-**6b**	32	48	80

[a] Determined by ^{1}H NMR spectroscopy using 1-fluoro-3-nitrobenzene as internal reference. [b] Determined by HPLC on a chiral stationary phase. [c] N-F Reagent prepared in situ. [d] $NaHCO_3$ replaced with Na_2CO_3 (3 equiv). [e] $NaHCO_3$ replaced with K_2CO_3 (3 equiv). [f] $NaHCO_3$ replaced with Cs_2CO_3 (3 equiv). [g] Reaction at 50°C. [h] Reaction at 10°C. [i] Concentration: 0.0025 M. [j] Concentration: 0.025 M. DCE = 1,2-dichloroethane.

3 equivalents of $NaHCO_3$ and 1.5 equivalents of (2*S*,3*S*)-**6b** in 1,4-dioxane at room temperature for 1 hour afforded (+)-**2d** in 62% yield and 76% *ee*.

A series of enantioenriched fluorotetrahydro-5*H*-indeno-[2,1-*c*]quinolines was obtained by applying this protocol, with yields reaching 99% and *ee* values averaging 71%. Hexahydrobenzo[*k*]phenanthridine (**2j**) was formed in 83% yield with a diminished *ee* value of 19%, thus indicating that structural variation of the substrate can have a dramatic influence on the *ee* value (Scheme 4). The absolute configuration of **2d** was assigned as (6a*R*,11b*R*) by single-crystal X-ray crystallographic analysis,[8,16] which also confirmed the *syn* stereochemistry at the ring junction [$^3J(F^{6a},H^{11b}) = 15.7$ Hz]. This fluorocarbocyclization process is a unique example of asymmetric synthesis leading to enantioenriched fluorine-containing helical molecular motifs.

The fluorocarbocyclization presented herein generates various tetracyclic molecules possessing a carbon–fluorine quaternary stereocenter. These compounds would be difficult to access using alternative approaches. The design and preparation of a new class of chiral Selectfluor N-F reagents led to the successful development of an asymmetric variant of this fluorocarbocyclization reaction. These reagents, which are soluble in 1,4-dioxane or THF, are readily synthesized from chiral DABCO derivatives and commercially available *N*-fluoro-pentachloropyridinium triflate. Their preparation is



Scheme 4. Synthesis of enantioenriched fluorotetrahydro-5*H*-indeno-[2,1-*c*]quinolones. Structure of (6a*R*,11b*R*)-**2d** from single-crystal X-ray diffraction data.[17]

operationally simple using shelf-stable *N*-fluoropyridinium salts, which require no special handling procedures. These novel N-F reagents, with their dicationic chiral DABCO core, may find applications for the asymmetric fluorination of other substrates which are problematic using currently available strategies. Since the solubility profile of this new class of chiral N-F reagents can be tuned through variation of the substituents located on the DABCO core, it should be possible to adapt these chiral dicationic salts for use in phase-transfer catalysis.[18] Probing these principles with an eye towards the development of catalytic asymmetric fluorocarbocyclization and other challenging transformations is the subject of a current study in our laboratory.

Experimental Section

General procedure for asymmetric fluorocarbocyclization with (2*S*,3*S*)-**6b** prepared in situ: *N*-fluoro-pentachloropyridinium triflate (1.5 equiv) was added to a solution of pro-reagent (2*S*,3*S*)-**8b** (1.5 equiv) and $NaHCO_3$ (3.0 equiv) in 1,4-dioxane (2.5 mL) over 3 Å molecular sieves at room temperature and the reaction was stirred overnight. The prochiral indene was added and the reaction was stirred for 1–3 h before being concentrated in vacuo. Purification by silica gel column chromatography (EtOAc/petroleum ether) afforded the enantioenriched fluorocarbocyclized products.

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