New Catalytic Routes to Sulfonyl Fluorides

Terry Shing-Bong Lou



Magdalen College,

University of Oxford

Trinity Term, 2020

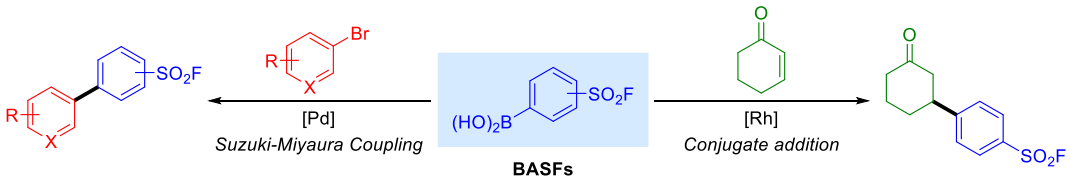
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

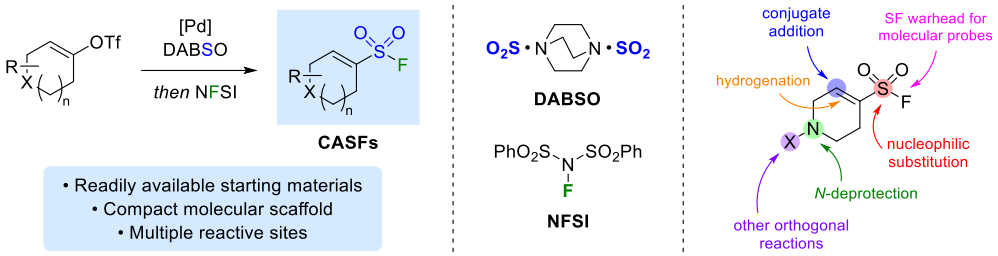
In this thesis, new methodologies towards the synthesis of sulfonyl fluorides through various approaches are documented. These approaches include the development of novel bi- or multifunctional sulfonyl fluoride reagents, and their derivatisations into structurally diverse sulfonyl fluorides and sulfonyl-containing compounds. During the study, the serendipitous formation of a symmetrical dialkenyl sulfone from the corresponding triflate led to further investigation on the cross-electrophilic sulfonylative cross-coupling.

Chapter 1 provides an overview of the project: including a general introduction to functional groups with the sulfonyl (–SO_2–) moiety, and the use of SO_2 in transition metal catalysis for the synthesis of sulfonyl-containing compounds; the properties, the applications and the synthesis of sulfonyl fluorides are then broadly discussed; the aims of this research are also addressed.

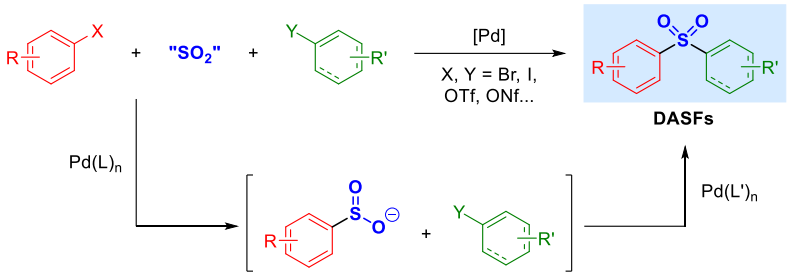
Chapter 2 describes the practical preparation of *ortho*-, *meta*-, and *para*-sulfonyl fluoride substituted phenylboronic acids (abbr. BASFs). Their applications in the Pd-catalysed Suzuki-Miyaura cross-coupling reactions and the Rh-catalysed conjugate addition are also documented, which demonstrate the versatility of these reagents to incorporate benzenesulfonyl fluorides onto target molecules.[1]



Chapter 3 details the development of an efficient one-pot cyclic alkenylsulfonyl fluorides (abbr. CASFs) synthesis using a Pd catalyst, DABSO as the SO_2 source, and NFSI as the electrophilic fluorine source. The orthogonal derivatisations of these multifunctional sulfonyl fluorides are also presented.[2]



Chapter 4 discusses the development of a sulfonylative cross-coupling between two different electrophiles, using DABSO and two different Pd catalysts for sulfination and sulfonylation, respectively, thus forming unsymmetrical diary sulfones (abbr. DASFs). Initial optimisation results have proven the feasibility of this process, and further investigation is needed.

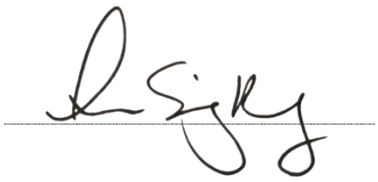


Chapter 5 summarises the research and discusses the potential for future work.

Chapter 6 presents the experimental data and procedures.

Declaration

I hereby declare that this report represents my own work after matriculation for the degree of Doctor of Philosophy and is entirely my work except where specifically indicated. This report has not been previously included in a thesis, dissertation or report for a degree, diploma or any other qualification at the University of Oxford or elsewhere.



Terry Shing-Bong LOU

31st August 2020

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The Willis group has always been awesome. I am thankful to have known all of you, and in particular to Charlieee, Loïc, Janette and Jonny for proofreading this thesis. Thanks also go to Alyn and Rob for setting a high standard of how good post-docs should be; Tim and Thomas for the men's talk and support; Tony for being a good friend and giving up the initials "TL" to well-deserved owner; Zexin for his trust and listening to my late-night philosophical harangue; Xinlan for being a great fumehood neighbour to work with; Tilby and Janette for bringing lots of joy to the group; Charlieee for being a trustworthy and literally the best buddy I have met in Oxford; Antoine, Jonny and Dan for being part of the best drinking crew – Magdalen Formal II was great fun and it was one of the most memorable nights I have ever had.

I will forever be grateful to my parents, Michael and Isabella. I am so blessed to have them waiting for me, with love and patience to skype every weekend, and to come home. Thank you for everything. I would also like to thank all my friends, especially those in Hong Kong. Keeping long-distance friendships is not easy. Thanks for bearing with me and my tight schedule to meetup.

Lastly, I would like to express my deep gratitude to the Croucher Foundation and Magdalen College for their generous financial support in the first three years and final year of my DPhil study, respectively, which has brought a young scientist one big step closer to realising his dream in science.

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Abbreviations

Å	Ångström (10^{-10} metre)
Ac	acetate
Ad	adamantyl
app.	apparent
aq.	aqueous
Ar	aryl
Asp	aspartate
ATP	adenosine triphosphate
BASF	boronic acid sulfonyl fluoride
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br.	broad
Bu	butyl
CASF	cyclic alkenylsulfonyl fluoride
cat	catecholate
cat.	catalyst *or* catalytic
Cbz	carboxybenzyl
CI	chemical ionisation
COSY	correlation spectroscopy
COVID-19	coronavirus disease
COX	cyclooxygenase
CuAAC	copper(I)-catalysed azide-alkyne cycloaddition
Cy	cyclohexyl
d	doublet *or* deuterated
D_0°	bond dissociation energies
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DASF	diaryl sulfone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DG	directing group

decomp.	decomposition
DIBAL	diisobutylaluminium hydride
dioxane	1,4-dioxane
DIPEA	*N*,*N*-diisopropylethylamine (Hünig's base)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPhil	Doctor of Philosophy
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
er	enantiomeric ratio
EI	electron ionisation
eq.	equation
equiv	equivalent(s)
ESF	ethenesulfonyl fluoride
ESI	electrospray ionisation
Et	ethyl
FITC	fluorescein isothiocyanate
Fs	fluorosulfate
Fsp^3	fraction of sp^3-hybridised carbons
g	gram *or* gas
gem	geminal
GST	glutathione S-transferase
h	hour(s)
Halex	halogen exchange
Het	heteroaromatic
HFIP	hexafluoroisopropanol
His	histidine
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence

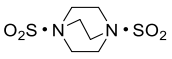
Hz	Hertz
i	iso
IC_{50}	half maximal inhibitory concentration
IPA	2-propanol (isopropyl alcohol)
IR	infrared
J	coupling constant
l	liquid
L	litre *or* ligand
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	metal *or* molar *or* mega (10^6)
m	metre *or* milli (10^{-3}) *or* multiplet
m	*meta*
m/z	mass to charge ratio
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mol	mole
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
n	nano (10^{-9})
n	normal
NBS	*N*-bromosuccinimide
NCD	nitrogen chemiluminescence detector
Nf	nonafluorobutanesulfonyl (nonafly)
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl (nosyl)
Nuc	nucleophile
o	*ortho*
[O]	oxidant
o/n	overnight

P	partition coefficient
p	*para*
PBSF	perfluorobutanesulfonyl fluoride
PET	positron emission tomography
PFP	pentafluorophenyl
PFSD	perfluorinated sulfonyl dicyanomethide
PG	protecting group
Ph	phenyl
Phe	phenylalanine
PI3K	phosphoinositide 3-kinase
pin	pinacolate
ppb	parts per billion
ppm	parts per million
Pr	propyl
PRMT	protein arginine *N*-methyltransferase
q	quartet
quant.	quantitative
quint	quintet
R	alkyl *or* generic group/substituent
RCC	radiochemical conversion
R_F	perfluoroalkyl
R_f	retardation factor
rot	rotamer
rt	room temperature
s	singlet *or* solid
SAM	*S*-adenosyl methionine
SAR	structure-activity relationship
sat.	saturated
Ser	serine
sext	sextet
SF	sulfonyl fluoride
SGC	Structural Genomics Consortium
SMC	Suzuki-Miyaura cross-coupling
S_N2	bimolecular nucleophilic substitution

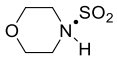
S_NAr	nucleophilic aromatic substitution
SuFEx	sulfur(VI) fluoride exchange
T	temperature
t	triplet
t	tertiary *or* time
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (trifly)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TL	Terry Lou
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl (tosyl)
UV	ultraviolet
V	volt
v/v	volume per volume
w/w	weight per weight
wt	weight
X	(pseudo)halide *or* heteroatom (unless stated otherwise)
Y	(pseudo)halide *or* heteroatom (unless stated otherwise)
$[\alpha]$	specific rotation
δ	chemical shift
μ	micro (10^{-6})
μW	microwave
ν	frequency
τ	retention time

Chemical Structures

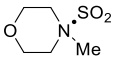
SO_2-amine Lewis adducts



DABSO



MOSO

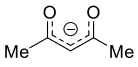


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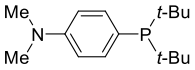


TIMSO

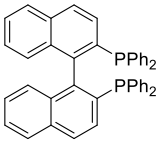
Ligands



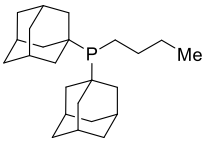
acac



AmPhos



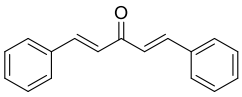
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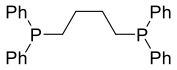
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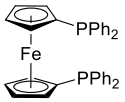
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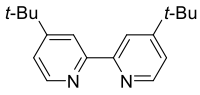
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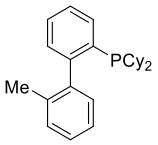
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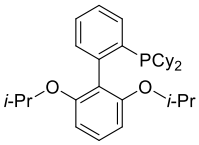
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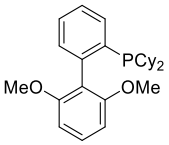
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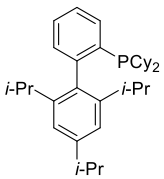
MePhos



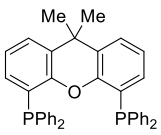
RuPhos



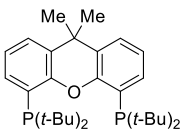
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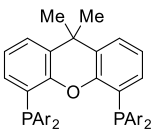
XPhos

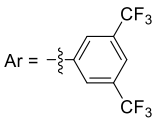


XantPhos



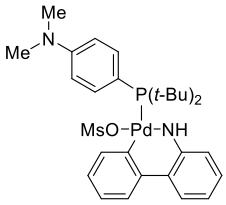
t-Bu-XantPhos



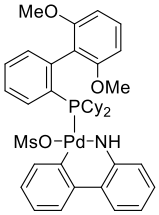


bis-CF_3-XantPhos (**L1**)

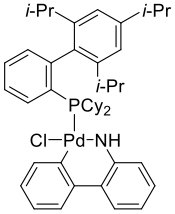
Buchwald palladacycles



AmPhos-Pd-G3

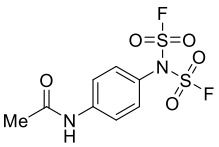


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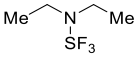


XPhos-Pd-G2

Fluorine-containing compounds



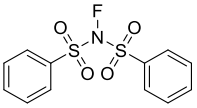
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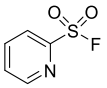
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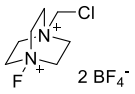
ESF



NFSI

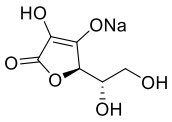


Pyfluor

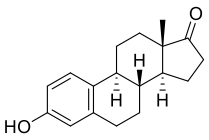


Selectfluor®

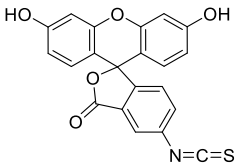
Other compounds



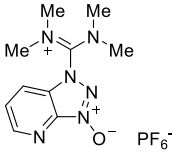
sodium ascorbate



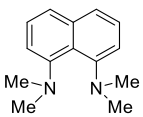
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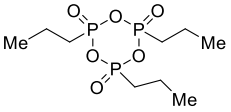
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Chapter 1 Introduction

1.1 Sulfonyl-Containing Functional Groups

Sulfur, a non-metallic element, which can adopt various oxidation and hybridisation states, is a key player in organic chemistry. From mercaptans in garlic, which give its distinctive smell, to sulfa drugs for treating bacterial infections, sulfur-containing compounds are ubiquitous in our daily life.

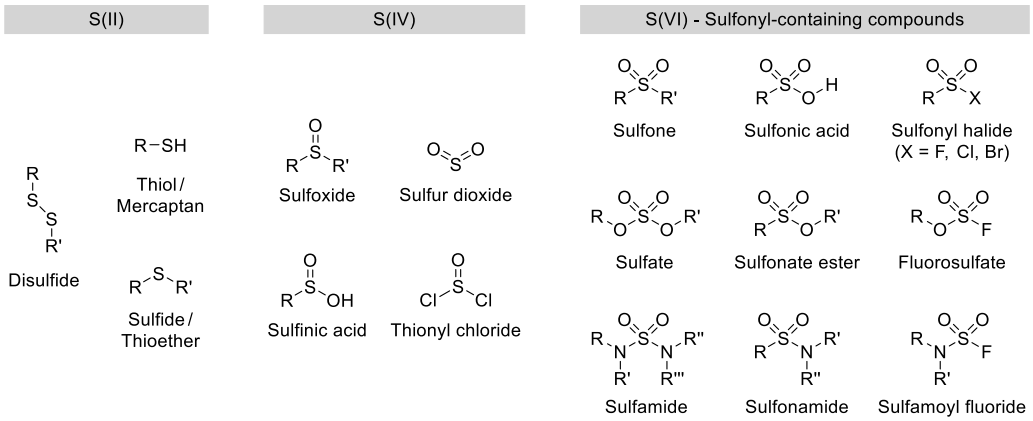


Figure 1-1. Examples of sulfur-containing functional groups.

In particular, organic compounds with the –SO_2– moiety, known as the sulfonyl group, have seen wide application in the modern world. For instance, sulfones, sulfonamides and sulfamides are common motifs found in drug candidates and pharmaceutical products.[3-5] Sulfonylureas, such as flazasulfuron, are used in agriculture as herbicides.[6] In material chemistry, polysulfones and polysulfates often exhibit excellent mechanical properties,[7-8] and polysulfonamides can be fabricated into durable membranes for reverse osmosis.[9] The sulfonyl moiety is also found in chemicals used as food additives, such as saccharin, an artificial sweetener.[10] Furthermore, sulfonyl-containing compounds are often encountered in synthetic chemistry as reagents or intermediates.[11-13]

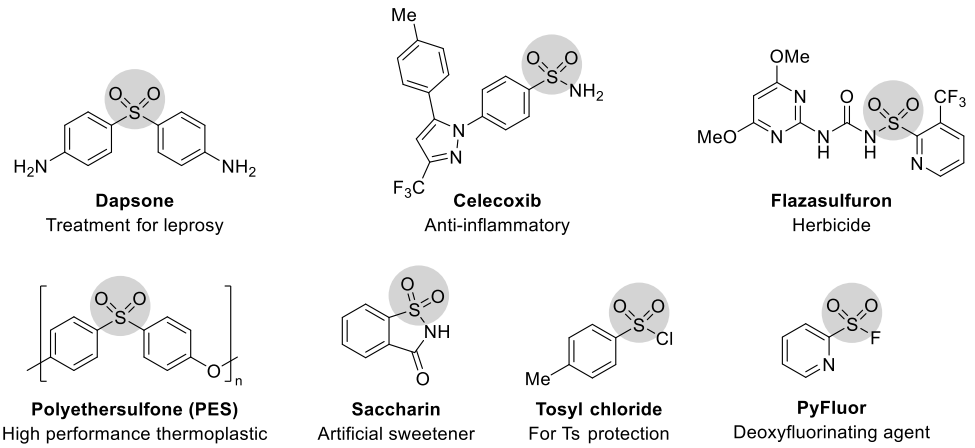


Figure 1-2. Examples of sulfonyl-containing compounds with their applications.

Common strategies for the synthesis of sulfonyl moieties are shown in **Scheme 1-1**. Firstly, the classical way to install a sulfonyl group onto aromatic compounds is through electrophilic aromatic substitution, using either sulfuric acid (sulfonation) or chlorosulfonic acid (chlorosulfonation) for the syntheses of sulfonic acids and sulfonyl chlorides respectively (**Scheme 1-1a**).[14-15] These products can then be further derivatised into other sulfonyl functional groups, such as sulfones, sulfonyl fluorides, sulfonate esters and sulfonamides through deoxyhalogenation or substitution reactions. A major drawback of this method lies in the limitation of electrophilic aromatic substitution reactions in general, which often suffer from poor conversion with electron-deficient substrates, and are limited by the regioselectivity of the reaction, which is governed by the relative position and identity of substituents on the aromatic ring.[15] The use of strong acids also deters the presence of any acid-sensitive functional groups. Therefore, this approach is often only used for simple aromatic substrates.

Secondly, sulfides can serve as the precursor to sulfones (**Scheme 1-1b**). Through oxidation, sulfides are first converted into sulfoxides, a S(IV) intermediate, which can further be oxidised into sulfones, with the oxidation state of sulfur being +6. Alternatively, thiols can be oxidised to sulfonic acids, or through oxidative chlorination to form sulfonyl

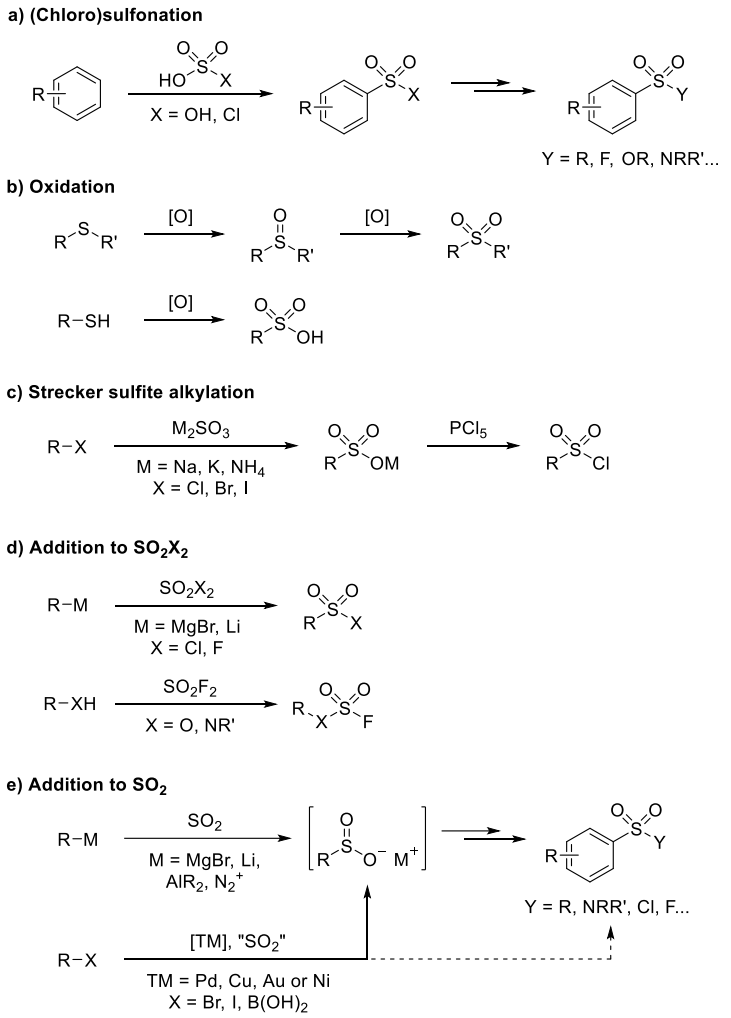
chlorides. These preparations benefit from the vast availability of sulfides and thiols. However, these S(II) compounds are often malodorous. The use of strong oxidants or chlorinating agents also limit the tolerance to various functional groups, hence narrowing the scope of sulfonyl-containing compounds that can be accessed.

Thirdly, treatment of alkyl halides with ammonium or alkali metal sulfites in aqueous alcohol results in the corresponding sulfonate salts (**Scheme 1-1c**).[16-17] This nucleophilic substitution reported by Strecker in 1868 can be followed by subsequent deoxychlorination, using phosphorus pentachloride to form aliphatic sulfonyl chlorides, which are capable precursors for further derivatisation.[18]

Fourthly, sulfuryl halides can be used for the introduction of sulfonyl moieties to organic compounds (**Scheme 1-1d**). As well as being an efficient chlorinating agent, sulfuryl chloride (SO_2Cl_2) can also undergo chlorosulfonation with organometallic reagents, such as Grignard and organolithium reagents, under specific conditions, forming the corresponding sulfonyl chlorides.[19] On the other hand, unlike SO_2Cl_2, the fluorine analogue – sulfuryl fluoride (SO_2F_2) is a hydrolytically stable gas. A recent report by Sammis also demonstrated the Grignard addition to SO_2F_2 to form sulfonyl fluorides and their derivatives.[20] SO_2F_2 also readily reacts with phenols or secondary amines in the presence of base, hence forming fluorosulfates or sulfamoyl fluorides respectively.[21] Alternatively, 4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF), a crystalline reagent, was developed as an alternative to the gaseous SO_2F_2 for the formation of these compounds.[22]

Lastly, given the structural composition of a sulfonyl moiety (–SO_2–), sulfur dioxide has been used to incorporate this motif into organic compounds, either as a gas or in the form of a surrogate (**Scheme 1-1e**).[23] Traditionally, the reaction mixtures for the

sulfination process would be bubbled with SO_2 gas, which requires a large excess of SO_2;[19, 24-25] otherwise SO_2 gas could be condensed into the reaction mixture as a liquid when cooled below −10 °C.[26-27] Sulfur dioxide has been shown to react with diazonium compounds[28-29] or various organometallic reagents, e.g. Grignard reagents[19, 25-26] or organolithium reagents, [27, 30] to form sulfinate salts, which could further be functionalised into different sulfonyl-containing compounds through substitution or oxidation. However, SO_2 gas is inconvenient to operate, in combination with the safety concern of using pyrophoric organometallic reagents or potentially explosive diazonium salts, this has not proven a popular approach for sulfination or sulfonylation.

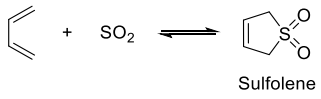


Scheme 1-1. Synthetic strategies for sulfonyl functional groups.

In recent years, the development of sulfur dioxide surrogates, such as inorganic metabisulfite salts or amine-SO_2 Lewis adducts, has enabled the use of SO_2 in the form of solid reagents, which can be easily weighed out stoichiometrically, hence avoiding the handling of gaseous reagent. Furthermore, employment of these sulfur dioxide surrogates in transition metal catalysis precludes the use of reactive organometallics or strong oxidants. This allows mild conditions to be used. Therefore, this catalytic sulfination approach represents an attractive method to access various sulfonyl functional groups. See the following section for further discussion.

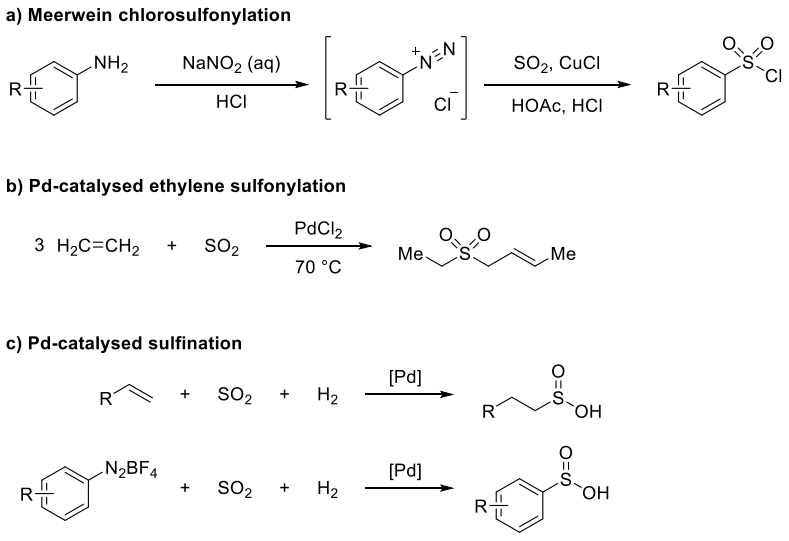
1.2 Sulfur Dioxide in Transition Metal Catalysis

Sulfur dioxide (SO_2) is a colourless toxic gas that can be found in the atmosphere at a very low concentration, in parts per billion (ppb) level. Since its discovery in the ancient world, humans have been using SO_2 to preserve food, and it is still a prominent preservative (E220) for dried fruits and wine. While naturally released during volcanic eruption, SO_2 is also a by-product in the smelting of sulfur-containing ores and the combustion of sulfur-contaminated fossil fuels. Despite being a known major air pollutant and contributor to acid rain formation, SO_2 is produced industrially through the combustion of sulfur or gypsum, as it is used for the manufacture of sulfuric acid by the contact process and other chemicals. In organic chemistry, SO_2 has also been used for accessing sulfur-containing compounds for decades through pericyclic reactions, such as cheletropic additions (**Scheme 1-2**),[23, 31] and combinations with organometallic reagents (see **Scheme 1-1e**).



Scheme 1-2. Cheletropic addition for sulfolene formation.

Whilst the palladium-catalysed carbonylation has advanced and matured significantly since the first reports by Heck in the 1970s,[32-36] gaseous SO_2 has not been a popular reagent in transition metal catalysis,[37-38] this is in spite of the similarity in electronic structures and reactivities between CO and SO_2.[39] In 1957, Meerwein reported the modified Sandmeyer reaction for the synthesis of arylsulfonyl chlorides using aryldiazonium salts, SO_2, acetic acid and hydrochloric acid with a copper catalyst (**Scheme 1-3a**).[28] This reaction was recently improved by Ley using flow techniques, hence minimising the potential hazard of using diazonium salts.[29] In 1968, Klein reported the first palladium-catalysed reaction using SO_2 and ethylene (**Scheme 1-3b**).[40] Among the handful of reports, Keim described the use of SO_2 with a palladium catalyst for the formation of sulfinic acids from alkenes or aryldiazonium salts (**Scheme 1-3c**).[41-42] This has provided the basis for recent advancement in the palladium-catalysed sulfination chemistry.



Scheme 1-3. Examples of transition metal-catalysed reactions using SO_2 gas.

The employment of SO_2 gas often involved the use of a pressurised gas cylinder, either to fill up the headspace of reaction chambers, for the dissolution of SO_2 to form a

solution, or to condense SO_2 into the reaction. These operations are inconvenient and require specialised pressure-resistant equipment, which account for the limited usage of SO_2 gas in modern syntheses. Sulfolene mentioned above (**Scheme 1-2**) is capable of undergoing the retro-cheletrophic reaction to form 1,3-butadiene and SO_2 at high temperature. Since it is a stable crystalline solid, it is often used as a convenient source of butadiene, but it has also been utilised as a reagent for SO_2.[43]

In 2010, the Willis laboratory reported the first example of using a SO_2 surrogate in transition metal-catalysed sulfonylation reactions, where the Lewis adduct of DABCO and SO_2 (later termed DABSO) was demonstrated to be a viable SO_2 surrogate. Despite its discovery by Santos and Mello in 1988,[44] this was the first application of DABSO in synthesis. Being a bench-stable solid, DABSO is easy to handle and allows for stoichiometric usage of SO_2 in reactions. Since then, the Willis group has developed various transformations using DABSO, including the addition of organometallic reagents (such as organolithium and Grignard reagents) for sulfinate formation,[45-49] palladium-catalysed reactions with aryl iodides,[50-52] bromides[49] and boronic acids,[53-54] copper-catalysed three-component synthesis of sulfones[55] and sulfonamides,[56] and more recently the sulfination of (hetero)aryl boronic acids using a nickel catalyst.[57] Wu, Ball and other researchers have also reported sulfonylation processes using DABSO.[58-63]

a) **b)**

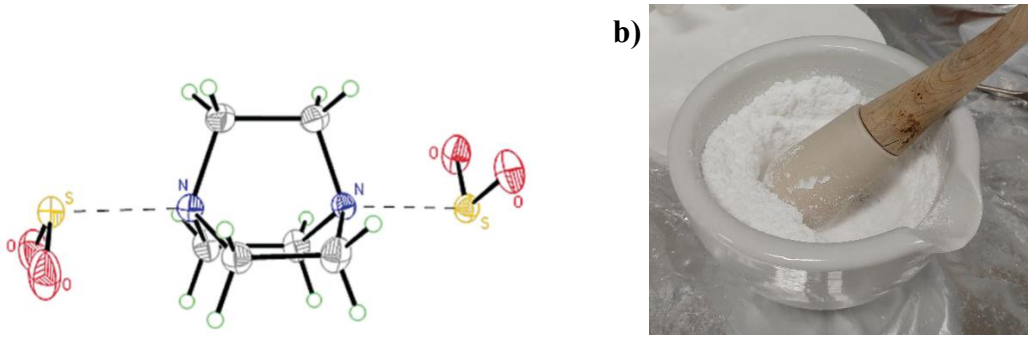
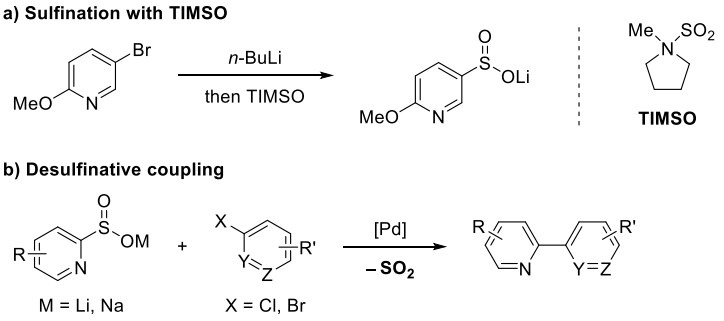


Figure 1-3. (a) X-ray crystal structure of DABSO;[64] (b) a sample of DABSO.

Other amine-SO_2 adducts have also been synthesised in the Willis laboratory. For instance, the *N*-methylpyrrolidine-SO_2 adduct (TIMSO, named after Dr. Tim Markovic) was used as a traceless SO_2 surrogate for the preparation of pyridine sulfinates, where the amine could be removed *in vacuo* which simplified purification (**Scheme 1-4a**).[65] The resulting pyridine sulfinates could then undergo a palladium-catalysed desulfinative coupling with (hetero)aryl halides.[65-66] Such $C(sp^2)$–$C(sp^2)$ bond coupling would otherwise be difficult to achieve using the Suzuki-Miyaura coupling or other methods (**Scheme 1-4b**). In the coupling, SO_2 is extruded from the sulfinates as a by-product and provides an entropic driving force to the reaction. A modification was later made using heterocyclic allylsulfones in place of sulfinates for simpler purifications, which also involves the expulsion of SO_2.[67]



Scheme 1-4. (a) TIMSO as a reagent for sulfinate synthesis;
(b) SO_2 extruded from desulfinative coupling.

Whilst metal sulfites (M_2SO_3) and metabisulfites ($M_2S_2O_5$) are known to react with Brønsted acids to liberate SO_2, these inorganic salts are also often referred to as SO_2 surrogates. They have been employed for the *ex-situ* generation of SO_2 gas in a two-chamber setup,[68] or the *in-situ* release of SO_2 to a reaction.[69-70] In particular, $Na_2S_2O_5$ and $K_2S_2O_5$ have been used by Toste,[71] Shavnya,[72] Wu[69-70, 73] and others for the formation of sulfinates and other sulfonylated products in gold-, copper- and palladium-catalysed reactions or radical processes.

1.3 Properties of Sulfonyl Fluorides

Sulfonyl fluorides having been forgotten for decades, have recently been revived.[21] These have been used for almost a century of history, with the first sulfonyl fluoride synthesised by treating toluene with fluorosulfonic acid in 1921 by Oderberger Chemischen Werke, a German chemical company.[74] In 1927, Steinkopf published the first account on the preparations and the reactivities of aryl sulfonyl fluorides, wherein he noted their resistance to hydrolysis and oxidation, and the milder reactivities relative to sulfonyl chlorides.[74] With very little attention from organic chemists since the mid-twentieth century, sulfonyl fluorides were reinvigorated only in the last few years, and these intrinsic properties were highly appreciated.

Sulfonyl fluorides are often compared with sulfonyl chlorides, as they both belong to the family of sulfonyl halides. While sulfonyl chlorides are excellent electrophiles, the fluoride counterpart only reacts with nucleophiles under specific conditions.[74-76] Such difference in reactivity is also observed between sulfuryl fluoride (SO_2F_2) and sulfuryl chloride (SO_2Cl_2) – the fluoride analogue is inert towards hydrolysis even when heated at 150 °C in a sealed tube, while the chloride reacts rapidly with water to give hydrogen chloride and sulfuric acid.[77] The stability and inertness of sulfonyl fluoride can be attributed to the exceptional strength of a S–F bond. This can be exemplified by the homolytic bond dissociation energies of S–Cl bond (43 ± 10 kcal mol^{-1}) and S–F bond (84 ± 10 kcal mol^{-1}) in sulfuryl chloride fluoride (SO_2ClF),[78] which suggests the ClO_2S–F bond is significantly stronger than the FO_2S–Cl bond. A similar trend is also observed when comparing the S–F bonds (81 ± 2 kcal mol^{-1}) in SO_2F_2 with the S–Cl bonds (46 ± 4 kcal mol^{-1}) in SO_2Cl_2.[78-79] Such difference in bond strength accounts for the relative reactivity between the two sulfuryl halides, as well as between sulfonyl fluorides and chlorides.

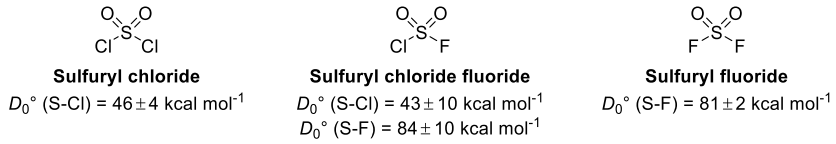


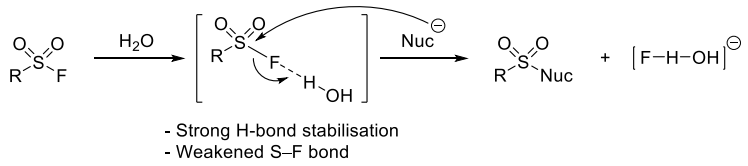
Figure 1-4. Homolytic bond dissociation energies of selected sulfuryl halides.

On the other hand, the +6 oxidation state of sulfur in sulfonyl fluorides also contributes to their inertness. Sulfur centres with lower oxidation states, e.g. S(II) and S(IV), are more prone to substitution.[77] For instance, sulfuryl fluoride (SO_2F_2) is soluble in water and only slowly undergoes hydrolysis, unless in basic solution;[80-82] whereas thionyl fluoride (SOF_2) hydrolyses readily to give hydrogen fluoride and sulfur dioxide.[77] The shorter S–F bond length in SO_2F_2 (1.530 Å) than that in SOF_2 (1.583 Å) suggests the S–F bond in the S(VI) compound is stronger, and therefore more stable. As a result, being S(VI) compounds with a strong S–F bond, sulfonyl fluorides are expected to be more stable than sulfinyl or sulfenyl fluorides, or sulfonyl chlorides.

When comparing the reactivities of sulfonyl fluorides and chlorides, one of the major differences is their hydrolytic stability and tolerance to aqueous acids.[81-82] While sulfonyl chlorides are useful synthetic intermediates for accessing different sulfonyl-containing functional groups, their hydrolysis and decomposition remain a key constraint to access more complicated substrates. On the other hand, the stability of sulfonyl fluorides under aqueous conditions are appreciated in their application to synthetic chemistry[83-85] and chemical biology.[7, 86-91]

In fact, water plays an important role in controlling the "on-and-off" reactivity of sulfonyl fluorides through fluoride stabilisation. Being the most electronegative element, fluorine forms some of the strongest hydrogen bonds.[92] For example, the hydrogen bond energy of bifluoride (FHF^-) was found to be an exceptional 39 kcal mol^{-1}, which is

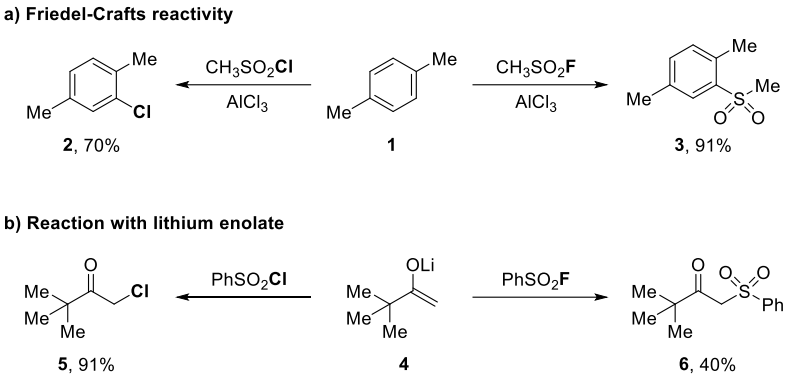
comparable to a single covalent bond.[93] Therefore, through the formation of F–HX hydrogen bonding, fluoride could be stabilised in the presence of water as a leaving group. This provides the enthalpic driving force for nucleophilic substitution or the exchange of fluoride. In other words, the "on-water" reaction switches on the otherwise inert sulfonyl fluoride for substitution (**Scheme 1-5**). Using this strategy, Lewis acids have also been demonstrated to facilitate the nucleophilic substitution on sulfonyl fluorides.[94-95]



Scheme 1-5. "On-water" nucleophilic substitution of sulfonyl fluorides.

Another notable difference between sulfonyl fluorides and chlorides in organic reactions, is sulfonyl fluorides' resistance to reduction. In sulfonyl chlorides, with a larger covalent radius, the chlorine centre is more polarisable (softer). This results in the plausible nucleophilic attack at the chlorine centre, with the S–Cl bond being cleaved homolytically to form a sulfonyl radical, or heterolytically for SO_2 extrusion.[21, 96-97] Such reductions often lead to undesirable sulfinate ester or chlorinated (instead of sulfonylated) side products. In contrast, fluorine has a small covalent radius and low polarisablility, along with being the most electronegative atom, nucleophilic attack at the fluorine centre of sulfonyl fluorides is unlikely. The high electronegativity of fluorine also ensures the heterolytic cleavage of the S–F bond, with fluoride anion (F^-) being the leaving group. As a result, sulfonyl fluorides are far less prone to reductions relative to their chloride counterpart. For instance, in the Friedel-Crafts sulfonylation of *p*-xylene (**1**) using $AlCl_3$ (**Scheme** 1-6**a**), reaction with methanesulfonyl chloride delivered 2,5-dimethylchlorobenzene (**2**) in 70% yield; sulfone product **3** was obtained in 91% yield when methanesulfonyl fluoride was employed.[98] Another example is the reaction with

lithium enolate **4** (**Scheme 1-6b**) – using benzenesulfonyl chloride gave the *α*-chloroketone **5** at 91% yield; and using benzenesulfonyl fluoride produced sulfonylated product **6** at 40% yield, and the low yield was attributed to the acidity of the *β*-keto sulfone **6**.[99] These examples highlighted the benefit of using sulfonyl fluorides in chemical synthesis over sulfonyl chlorides.



Scheme 1-6. Comparison of reactivity between sulfonyl chlorides and fluorides.

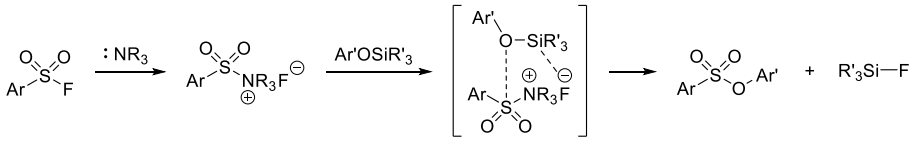
1.4 Applications of Sulfonyl Fluorides

1.4.1 Sulfonyl Fluorides in Azo Dyes

In the first report on sulfonyl fluorides by Steinkopf in 1927, he described the preparations and the properties of azo dyes that contain sulfonyl fluoride groups.[74] Due to the tolerance to acid and the resistance to reduction and substitution, nitro-substituted arylsulfonyl fluorides could survive the reduction to anilines, and subsequent diazotisations. Sulfonyl fluorides have continued to play a role in azo dye chemistry since then.[75, 100] Of note, in 1979, Hyatt reported the use of ethenesulfonyl fluoride in the preparation of azo dyes, and their downstream transformation into different sulfonyl derivatives.[101]

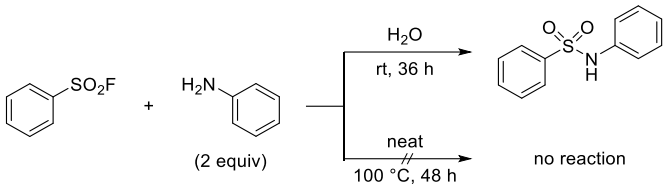
1.4.2 SuFEx Click Chemistry

In 1976, Hall reported the first reaction between alkoxytrimethylsilanes and benzenesulfonyl fluoride to form sulfonate esters.[102] The neat reaction was mediated by TBAF and required long reaction times of up to three weeks. Gembus reported a similar, yet much more efficient reaction between tosyl fluoride and silyl ethers catalysed by DBU in 2008.[103] He proposed that the sulfonyl fluorides would first react with the tertiary base, forming an activated sulfonyl ammonium fluoride salt intermediate, which would then activate the silyl ethers to form sulfonate esters (**Scheme 1-7**). However, without experimental backup, the exact mechanism is yet to be studied. The scope of the DBU-catalysed reaction was later expanded by Sharpless and Qin using various β-aryl ethenesulfonyl fluorides and TBS ethers.[104] The reaction between silyl ethers and sulfur(VI) fluorides later represents a classical example of the "SuFEx" reaction.



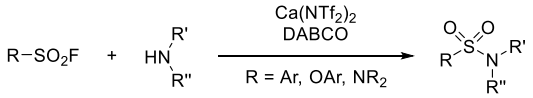
Scheme 1-7. SuFEx between silyl ethers and sulfonyl fluoride.

In 2014, Sharpless published a thorough review on the sulfur(VI)-fluoride exchange (SuFEx), where he proposed such reactivity would be the next candidate for click chemistry.[21] The key feature of sulfur(VI)-fluoride compounds, such as sulfonyl fluorides, is the exceptional strength of the S–F bonds, which account for their stability (see **Section 1.3**). On the other hand, the electronegativity of fluorine enables the formation of strong hydrogen bonds with acids or protic solvents, or bonding with silicon to form the strongest single covalent bond. The formation of these strong interactions provides driving force to the substitution (or exchange) of fluoride,[105-106] hence functionalising the otherwise inert sulfur(VI)-fluorides (**Scheme 1-8**).[21] This has been compared to the waking of Sleeping Beauty by a kiss, and hence is sometimes referred to as the "sleeping beauty" reactivity.[107]



Scheme 1-8. SuFEx reaction promoted by hydrogen bonding.[21]

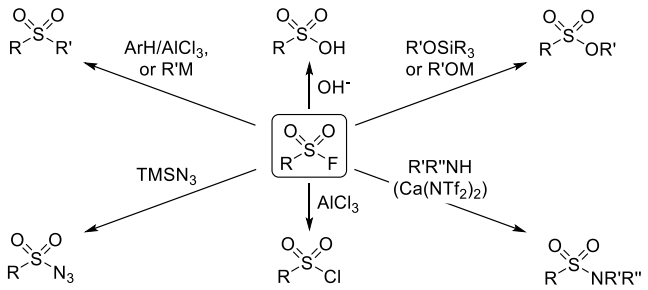
Examples of SuFEx reactions include the aforementioned base-catalysed reaction between silyl ethers and sulfonyl fluorides, which was also extended to sulfuryl fluoride (SO_2F_2) for the formation of fluorosulfates, and to fluorosulfates to form sulfates;[8, 21] the DBU-catalysed synthesis of sulfonyl azides from arylsulfonyl fluorides and trimethylsilyl azide has also been presented.[108] A recent report by Ball describes the activation of sulfur(VI) fluorides using a Lewis acid (calcium triflimide, $Ca(NTf_2)_2$) and DABCO, which represents an efficient transformation to sulfonamides and related compounds (**Scheme 1-9**).[94-95]



Scheme 1-9. Lewis acid-catalysed SuFEx with amines.

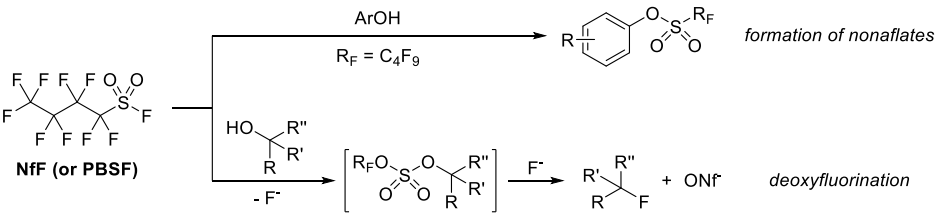
1.4.3 Sulfonyl Fluorides as Reagents in Synthesis

The SuFEx reactivity of sulfonyl fluorides allows them to be electrophilic precursors to various sulfonyl-containing functional groups (**Scheme 1-10**), such as sulfonamides, sulfonate esters, and sulfonyl azides, as previously mentioned. Sulfonyl fluorides can also react with carbon nucleophiles for the formation of sulfones through the electrophilic substitution of arenes[98] or the nucleophilic substitution by organometallic reagents,[99, 109-110] which would otherwise be challenging using sulfonyl chlorides due to competing chlorination (see **Scheme 1-6**). Halogen exchange (Halex) reaction enables the conversion of sulfonyl fluorides into reactive sulfonyl chlorides, albeit under harsh conditions using $AlCl_3$ in refluxing DCE.[111]



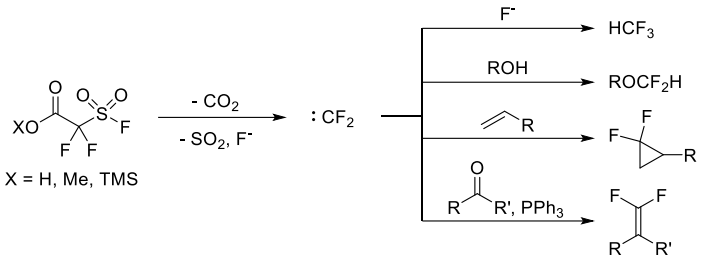
Scheme 1-10. Derivatisation of sulfonyl fluorides.

In particular, reactions between electron-deficient sulfonyl fluorides and alcohols, phenols or silyl ethers lead to the formation of activated sulfonate esters,[112] which are good leaving groups for substitutions or eliminations, and are efficient electrophilic substrates for transition-metal catalysis.[113-115] For instance, nonafluorobutanesulfonyl fluoride (NfF or PBSF) reacts with phenols or enols to form aryl or alkenyl nonaflates (–ONf). When aliphatic alcohols are employed, the lability of resulting nonaflates allows subsequent substitution by the F^- generated from the sulfonyl fluoride, hence producing alkyl fluorides as the final products (**Scheme 1-11**).[116-117] In the presence of base, the elimination of NfOH is also possible, which forms olefin products.[117] Likewise, 2-pyridinesulfonyl fluoride (PyFluor) efficiently converts primary and secondary alcohols to the corresponding fluorides with minimal elimination, thus making it a potent deoxyfluorinating agent.[118]



Scheme 1-11. NfF for nonaflate formation and deoxyfluorination.

Furthermore, (fluorosulfonyl)difluoroacetate derivatives were used for the *in-situ* generation of difluorocarbene through the elimination of CO_2, SO_2 and fluoride, and subsequently react with different partners, thus forming various di- or trifluoromethylated products (**Scheme 1-12**).[119-122]



Scheme 1-12. Sulfonyl fluorides as difluorocarbene precursors.

1.4.4 Application in Chemical Biology

Since their discovery in the early twentieth century, sulfonyl fluorides have been of constant interest in the field of medicinal chemistry and chemical biology. In fact, the antibiotic property of 4-(fluorosulfonyl)benzoic acid (abbr. 4-FSB) was described by Steinkopf in the first sulfonyl fluoride report in 1927.[74] Later reports suggested 4-FSB was also effective at inhibiting glutathione S-transferases (GSTs), and subsequently was used as an affinity label for the study of the enzyme.[123-125]

The stability to water represents the key feature of sulfonyl fluorides' application in chemical biology studies, where aqueous or semi-aqueous media are often used to mimic physiological conditions. Their inertness also ensures the sulfonyl fluoride group remains unreactive until being activated under specific conditions.[87] On another hand, sulfonyl fluorides would become reactive in the binding pockets of proteins. These sites are often rich in hydrogen bonds, which can activate the fluoride, and hold the electrophilic sulfonyl fluoride in close spatial proximity to nucleophilic residuals, such as serine. As a result, the binding sites would be covalently modified into a sulfonate ester or sulfonamide from reactions of alcohol and amine respectively, which will no longer accept their ordinary substrates, hence inhibiting the proteins.[86] For example, phenylmethylsulfonyl fluoride (PMSF)[89, 126-127] and 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF)[7] are established irreversible inhibitors for serine protease, and

commonly used for the preparation of cell lysates; 5'-*p*-fluorosulfonylbenzoyl adenosine (FSBA) is an adenosine derivate which targets the lysine residue of ATP-binding kinases (**Figure 1-5**).[128-129]

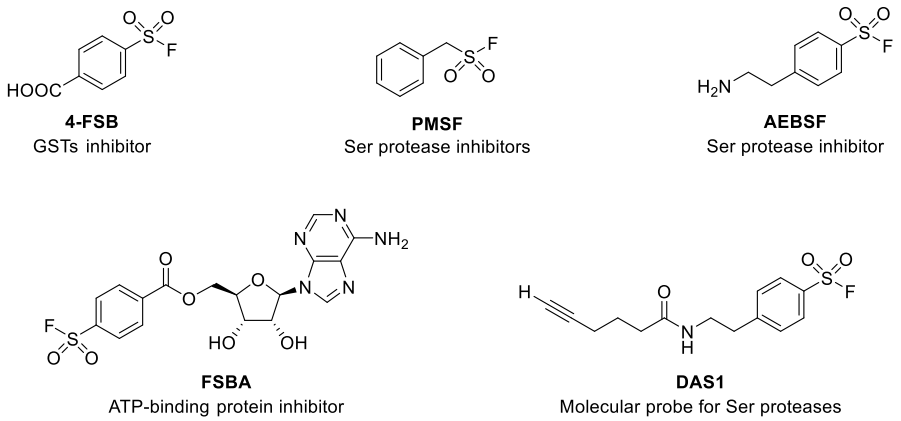
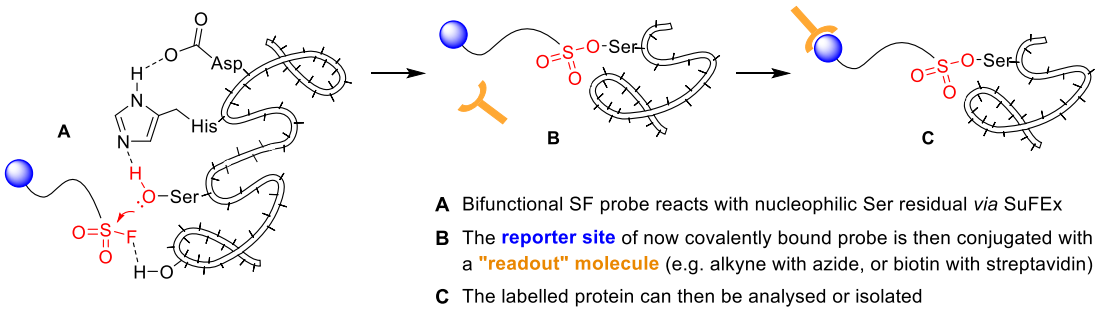


Figure 1-5. Examples of sulfonyl fluorides as protein inhibitors and molecular probes.

By carrying a second reactive functional group, sulfonyl fluorides can also serve as activity-based protein probes, with the "reporter site" being capable for further transformation, as illustrated in **Scheme 1-13**. For instance, DAS1 developed by Weerapana resembles AEBSF for its binding activity to serine protease, and carries a pendant terminal alkyne as a "click" handle for the copper(I)-catalysed alkyne-azide cycloaddition.[88, 130]



Scheme 1-13. Illustration of sulfonyl fluoride probes targeting serine proteases.

1.4.5 Fluorine-18 Radioactive Labelling

With the advancement in positron emission tomography (PET) for medical imaging, fluorine-18 (^{18}F) has become the most popular radioisotope for radiolabelling due to its favourable physical and chemical properties.[131] With a half-life of 110 minutes, ^{18}F-radiolabelling has to be efficient and specific. Two main approaches are adopted for ^{18}F-labelling – direct fluorination of the target molecules, and indirect fluorination by reacting the target molecules with a prosthetic compound carrying a radioactive ^{18}F.

Exploiting the water resistance and the robust "on-water" synthesis of sulfonyl fluorides, Inkster and co-workers designed a series of bifunctional [^{18}F]benzenesulfonyl fluoride derivatives as potential prosthetic compounds for radiolabelling.[132] An optimisation of the radiosynthesis of [^{18}F]sulfonyl fluorides was conducted by Fraser *et al*, and demonstrated the stability of the radiolabelled sulfonyl fluorides in the presence of water and other nucleophilic functional groups.[133]

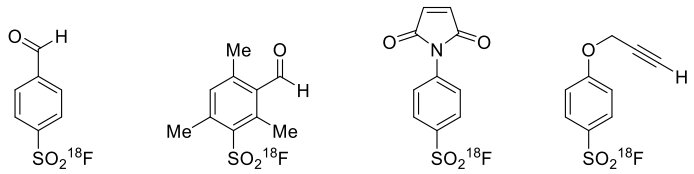
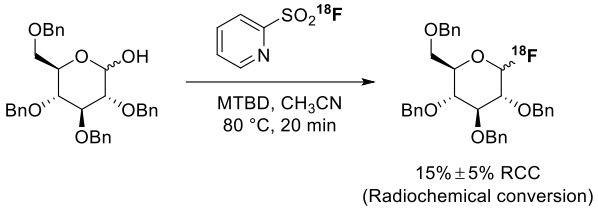


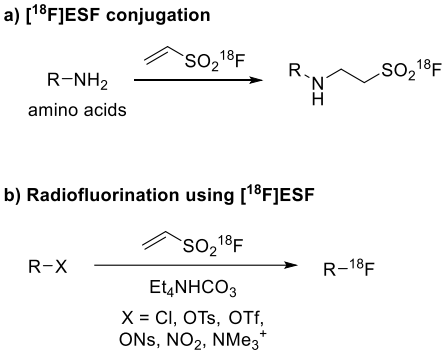
Figure 1-6. Examples of bifunctional [^{18}F]sulfonyl fluorides as potential ^{18}F labelling agents.[132]

In Doyle's report of using PyFluor to convert alcohols into fluorides, they demonstrated the radiosynthesis of [^{18}F]PyFluor.[118] The radiolabelled sulfonyl fluoride reagent was then applied to the deoxy-radiofluorination of a protected D-gluopyranose and gave promising results (**Scheme 1-14**). This represents an alternative approach to radiolabel biomolecules that are inaccessible *via* conventional radiofluorination methods.[134-135]



Scheme 1-14. Application of [^{18}F]PyFluor to deoxy-radiofluorination.

In 2018, Fraser considered the ^{18}F-labelled ethenesulfonyl fluoride ([^{18}F]ESF) as a potent prosthetic reagent for bioconjugations and radiolabelled amino groups through conjugate addition (**Scheme 1-15a**).[136] It was also shown that [^{18}F]ESF could be stored on inert silica cartridges for convenient shipment between laboratories and medical facilities, and acted as a [^{18}F]fluoride source upon hydrolysis with tetraethylammonium bicarbonate (Et_4NHCO_3) (**Scheme 1-15b**). Compared with other [^{18}F]fluoride sources, [^{18}F]ESF does not require azeotropic drying prior to [^{18}F]fluorination, hence making it an advantageous radiofluoride relay reagent.[137]



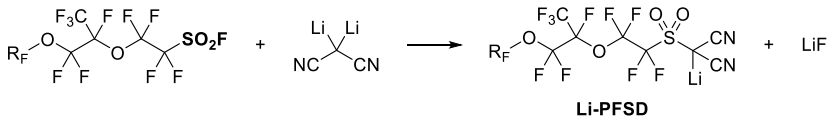
Scheme 1-15. Application of [^{18}F]ESF.

1.4.6 Lithium-ion Battery

A recent report by Xing and Li shows that *p*-toluenesulfonyl fluoride was a potent electrolyte additive to enhance the cyclic performance (the turnover number) of lithium ion batteries using a Ni-rich cathode, with high energy density charging up to 4.35 V.[138]

The sulfonyl fluoride was susceptible to both oxidation and reduction in the cell, and hence forming a protective interphase film on both the graphite anode and the Ni-rich cathode. Such a film would reduce the impedance on the electrode/electrolyte interphase, the decomposition of electrolyte, and the dissolution of metal ions from the cathode. Therefore, this maintains the integrity of the cell and retains its capacity when cycling at high voltage.[138]

In 2012, Angell and co-workers described the use of methanesulfonyl fluoride as solvent in high voltage lithium cell. The methanesulfonyl fluoride-based electrolyte has a benefit of low viscosity, and thus enhanced conductivity.[139] It also demonstrated the capability of such an electrolyte to form a solid electrolyte interface at a graphite electrode, hence improving the cell performance.[140] Furthermore, Jin reported the use of perfluorinated sulfonyl fluoride as a precursor to lithium perfluorinated sulfonyl dicyanomethide (Li-PFSD), which is used for the preparation of perfluorinated ionomer membranes and electrolyte (**Scheme 1-16**).[141]



Scheme 1-16. Perfluorinated sulfonyl fluoride as precursor to Li-PFSD ionomer.

1.5 Synthesis of Sulfonyl Fluorides

1.5.1 Fluorosulfonation

The first synthesis of sulfonyl fluorides reported by Steinkopf was achieved by treating aromatic hydrocarbons with fluorosulfonic acid.[74] Fluorosulfonic acid also reacted with benzenesulfonyl chloride to yield the corresponding fluoride. With the high

risk of preparing and handling the acid, and the necessity of using metallic apparatus due to its glass-etching property, chemists were indifferent to this process and sulfonyl fluorides remained rather inaccessible until the discovery of the more convenient method of chloride-fluoride exchange by Davies and Dick. Lately, in 2019, Sammis and coworkers reported the fluorosulfonation of Grignard reagents using sulfuryl fluoride. Nonetheless, this method involved the *ex-situ* generation of sulfuryl fluoride gas which is inconvenient to operate.[20]

1.5.2 Chloride-Fluoride Exchange – The Classical Approach

The classical approach for sulfonyl fluoride synthesis is through the chloride-fluoride exchange of sulfonyl chloride. Initially reported by Davies and Dick in 1931, aryl sulfonyl chlorides were refluxed in aqueous potassium fluoride solution to yield the corresponding sulfonyl fluorides.[76] It was found that the presence of water was crucial for the reaction as *p*-toluenesulfonyl chloride remained unreacted after 5 days of heating in refluxing benzene with dry zinc fluoride, but the addition of water resulted in complete conversion in an hour. Given the insolubility of sulfonyl chlorides in water, hydrolysis to sulfonates was common, especially for high-melting sulfonyl chlorides.[76] Therefore, later syntheses adopted a biphasic approach which involved refluxing a water-organic mixture.[18, 142]

This method was further extended to aliphatic sulfonyl fluorides by the same laboratory in 1932,[18] and an anhydrous procedure was also described for water-sensitive substrates, which involved heating the neat mixture of sulfonyl chlorides and zinc fluoride in a platinum flask. While the use of metallic apparatus was costly and heating a neat mixture to reflux was potentially dangerous, phase-transfer catalysis approaches were introduced as an alternative. In 1977, Bianchi and Cate reported the use of 18-crown-6 with potassium fluoride in acetonitrile to convert sulfonyl chlorides into fluorides, and

demonstrated good yields for water-sensitive substrates.[143] The "naked" fluoride was considered to be more basic and nucleophilic, hence promoting the chloride-fluoride exchange to take place at ambient temperature.

Due to the strong driving force for the formation of H–F hydrogen bonds, the presence of bifluoride anion $(F–H–F)^-$ along with fluoride is almost inevitable, particularly in aqueous and acidic medium.[93, 144] Following Dick's discovery, the combination of potassium fluoride and hydrofluoric acid was used by Beaman and Robins for the preparation of purinesulfonyl fluorides in 1961.[145] Potassium bifluoride (KHF_2), a safer alternative to HF/KF, was used by Brown in 1972.[146] Sharpless in 2014 advocated for the use of aqueous KHF_2 for the chloride-fluoride exchange. The "on-water" biphasic synthesis using saturated aqueous KHF_2 solution delivered various aryl and alkyl sulfonyl fluorides in excellent to quantitative yield, representing a robust and reliable method of sulfonyl fluoride synthesis.[21, 147]

1.5.3 Substitution of Sulfonate Esters

While sulfonyl chlorides are reactive substrates for nucleophilic substitution, the high reactivity also leads to challenges in their preparation and storage, hence limiting their availability. Pentafluorophenyl (PFP) sulfonate esters were introduced by Caddick as an alternative to sulfonyl chlorides.[148-149] With pentafluorophenolate being a good leaving group, the activated sulfonate esters are susceptible to nucleophilic substitution. In 2018, Vedovato and Willis showed that the PFP sulfonate ester of *p*-bromobenzene could be substituted by fluoride ion using KF in methanol, producing the corresponding sulfonyl fluoride in 78% yield.[54]

1.5.4 Oxidative Chlorination-Fluorination of Thiols

While some simple sulfonyl chlorides are commercially available, more complex sulfonyl chlorides often require on-site preparations. And even so, isolation could also be challenging as they are prone to hydrolysis and decomposition in work-up and purification. As a result, sulfonyl fluorides could be prepared by the *in-situ* generation of reactive sulfonyl chlorides, followed by quenching with fluoride; and a conventional way to access sulfonyl chlorides is the chlorination of thiols, which was described in the early twentieth century.[150-152]

Beaman and Robins reported the first synthesis of heterocyclic compounds carrying sulfonyl fluorides in 1961 using this approach. This was achieved by treating the methanolic solution of mercaptopurines with KF, aqueous hydrofluoric acid and chlorine gas at 0 °C.[145] The method was later improved by Brown and Hoskins for the preparation of pyrimidine sulfonyl fluorides in 1972, where KHF_2 was employed to avoid the use of hydrofluoric acid.[146] In 2006, Wright and Hallstrom developed a more general synthesis of sulfonyl fluorides from heteroaryl thiols using bleach (aqueous NaOCl) and KHF_2.[153]

1.5.5 Deoxychlorination-Fluorination of Sulfonates and Sulfonic Acids

Another approach for the *in-situ* generation of sulfonyl chlorides is through the deoxychlorination of sulfonates and their conjugate acids. Aryl sulfonic acids are easily accessible through the sulfonation of arenes and are more stable relative to sulfonyl chlorides, making them better precursors to sulfonyl fluorides. Kim and Jang reported the one-pot procedure of sulfonyl fluoride synthesis using trichloroacetonitrile (Cl_3CCN) and PPh_3 for the deoxychlorination, and tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride [TBAF(*t*-BuOH)$_4$], a fluoride source with good solubility in organic solvent and low hygroscopicity, for subsequent fluorination.[154] A similar strategy was

adopted by Qin, who reported the combination of cyanuric chloride, catalytic TBAB and KHF_2 for sulfonyl fluoride synthesis from various sulfonate salts and sulfonic acids.[155]

1.5.6 Deoxyfluorination

While the aforementioned methods either go through *in-situ* generated sulfonyl chloride intermediates or sulfonyl chloride alternatives, a more straight-forward approach of deoxyfluorination was reported by Casida[156] and Liskamp[157] in 2003 and 2009, respectively. These syntheses made use of diethylaminosulfur trifluoride (DAST) as the deoxyfluorinating agent and directly converted sodium sulfonate salts into the corresponding sulfonyl fluorides in useful yields.

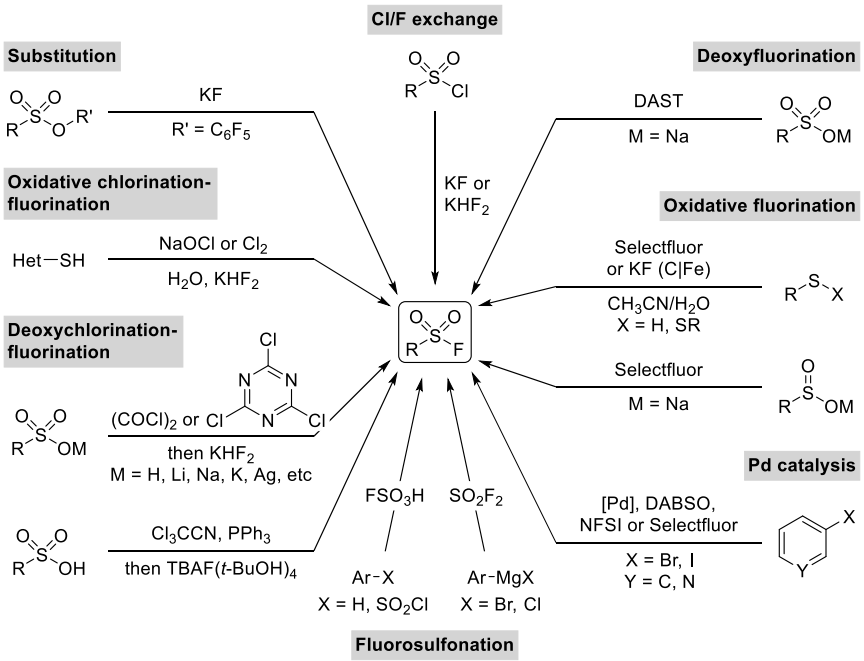
1.5.7 Oxidative Fluorination

Aside from deoxyfluorination, another approach without going through sulfonyl chloride intermediates – oxidative fluorination, was adopted by Kirihara in 2011 and 2014, using Selectfluor and thiols or disulfides.[158-159] However, the use of super-stoichiometric (6.5–7.5 equiv) Selectfluor was considered to be wasteful and expensive for large-scale preparation. In 2019, the Noël laboratory reported the first electrochemical synthesis of sulfonyl fluorides, which converted thiols or disulfides into sulfonyl fluorides using anodic oxidation and cheap KF as the fluoride source.[160]

Apart from the oxidation of S(II) compounds (e.g. thiols and disulfides), oxidative fluorination of sulfinate salts was also achieved using Selectfluor, in which the S(IV) compounds were oxidised to S(VI) in sulfonyl fluorides. This was first reported in 1996 by Banks,[161] who invented Selectfluor. This approach was later adopted by Willis and Ball to oxidatively fluorinate aryl sulfinates generated *in-situ*.[49, 62, 162]

1.5.8 Palladium Catalysis

With the advancement in using sulfur dioxide surrogates in transition metal-catalysed cross coupling pioneered by the Willis[50-51, 53, 163] and Toste[71] groups in recent years, Willis and Ball separately reported the preparation of (hetero)aryl sulfonyl fluorides in 2017 through the palladium-catalysed sulfination of aryl bromides or iodides, followed by electrophilic fluorination using Selectfluor or the cheaper *N*-fluorobenzenesulfonimide (NFSI).[49, 62] Compared with previously mentioned methods, the palladium catalysis approach did not rely on the use of sulfur-containing substrates, but instead introduced the sulfonyl (–SO_2–) moiety with SO_2 surrogates onto (hetero)aryl halides, which are widely commercially available. The palladium catalysis only requires mild conditions without the use of strong oxidising agents, acids or bases, hence allowing good functional group tolerance for the pre-installation of reactive handles onto the substrates.

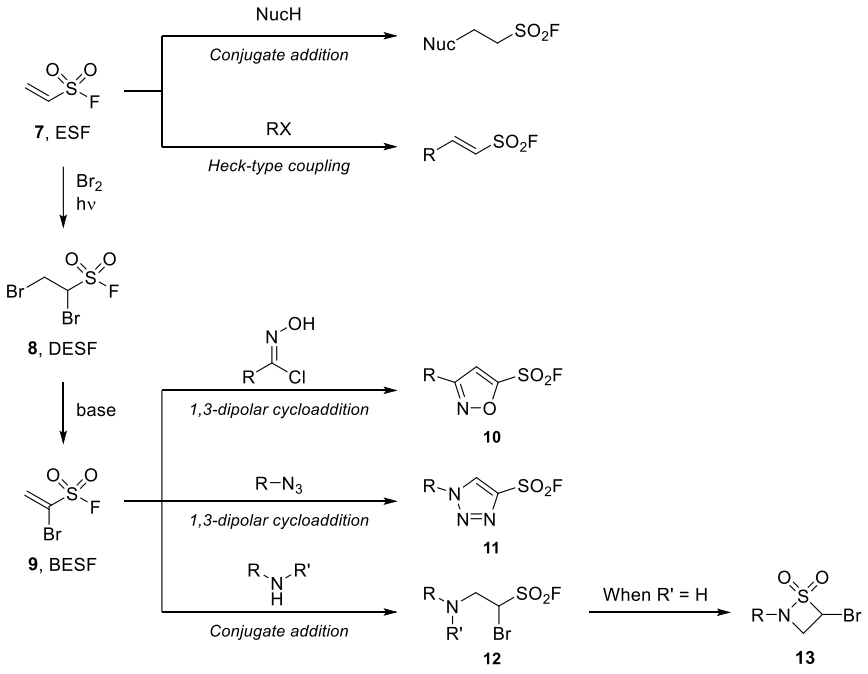


Scheme 1-17. Established synthetic routes to sulfonyl fluorides.

1.5.9 Bifunctional Sulfonyl Fluoride Reagents

Apart from the syntheses mentioned, which focused on the transformation of different functional groups into sulfonyl fluorides, a few bifunctional sulfonyl fluoride reagents with low molecular weights were developed.[21, 164-167] These small molecules enable the ligation of the sulfonyl fluoride functional group to pre-functionalised molecules through a second reactive site. **Scheme 1-18** illustrates three examples, *viz.* ethenesulfonyl fluoride (**7**, ESF), 1,2-dibromoethane-1-sulfonyl fluoride (**8**, DESF) and 1-bromoethene-1-sulfonyl fluoride (**9**, BESF).

ESF can undergo conjugate addition with nucleophiles or couple with aryl halides in Heck-type reactions, hence installing a sulfonyl fluoride handle with an ethyl or ethylene linkage.[101, 104, 164, 168-170] DESF serves as a stable precursor to BESF, which can be used for the preparation of fluorosulfonyl heterocycles.[165, 167] BESF can undergo 1,3-dipolar cycloaddition with nitrile oxides (generated *in-situ* from *N*-hydroxybenzimidoyl chlorides) to form 5-fluorosulfonyl isoxazoles (**10**),[166] or with azides to form

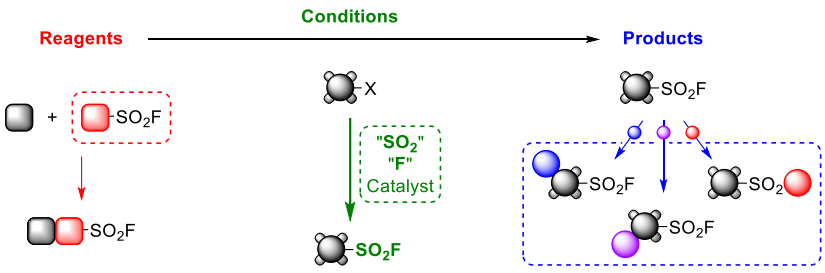


Scheme 1-18. Examples of bifunctional sulfonyl fluoride reagents and their transformations.

4-fluorosulfonyl triazoles (**11**).[167] BESF is also capable to take part in conjugate addition with amines. When primary amines were employed, the resulting 2-amino-1-bromo-ethanesulfonyl fluoride **12** could further cyclise to form 4-bromo-β-sultams **13**.[165]

1.6 Research Aims

The primary objective of this research was to develop novel methodologies for sulfonyl fluoride synthesis through transition metal catalysis. A chemical methodology comprises three major components as shown in a chemical equation: (i) reagents, (ii) conditions, and (iii) products. This research firstly focused on the invention of new sulfonyl fluoride-based reagents, and demonstrating their use for convenient access to sulfonyl fluoride functional groups. Secondly, with the established use of sulfur dioxide surrogates in the Willis group, this research aimed to develop a general and efficient synthesis of sulfonyl fluorides with multiple reactive sites through catalytic SO_2 fixation. Thirdly, upon the preparation of multifunctional sulfonyl fluorides, we explored the functionalisation of different reaction handles, hence producing structurally diverse sulfonyl fluorides and their derivatives.



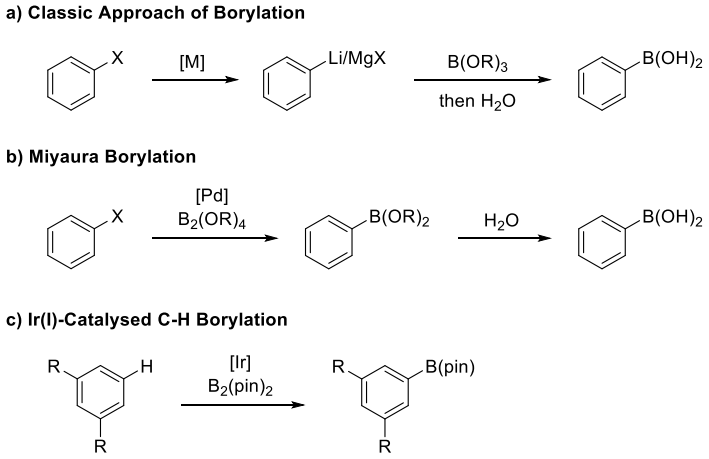
Scheme 1-19. The three approaches for the development of novel methodology.

Chapter 2 Arylsulfonyl Fluoride Boronic Acids (BASF): Preparation and Coupling Reactivity

2.1 Applications and Preparations of Boronic Acids

Boronic acids are useful nucleophilic substrates for coupling reactions, such as the Suzuki-Miyaura cross-coupling (SMC) and the Chan-Lam coupling. They are capable to transfer an aryl or alkyl residue to a transition metal through transmetallation. This allows boronic acids to be used as nucleophilic coupling partners and avoids the use of more reactive, sometimes pyrophoric, and toxic organometallics, like organotin and organozinc reagents. With the advantages of their ease of preparation, enhanced reactivity and high atom economy, boronic acids gained their popularity over other organoboron reagents and became the reagents of choice for wide applications in coupling reactions.

The most common way to access boronic acids is through the addition of an organometallic compound, such as an organolithium or Grignard reagents, to borate esters, e.g. triisopropyl borate or trimethyl borate, followed by hydrolysis (**Scheme 2-1a**). Another common strategy for boronic acid preparation is through Miyaura borylation of



Scheme 2-1. Common strategies for boronic acid synthesis.

aryl (pseudo)halides with diboronyl esters, such as B_2pin_2 or B_2cat_2, followed by hydrolysis (**Scheme 2-1b**), or alternatively with tetrahydroxydiboron ($B_2(OH)_4$).[171-172] On the other hand, borylation can be achieved across aromatic C–H bonds through iridium catalysis as reported by Smith, Hartwig and Miyaura to deliver pinacol boronates (**Scheme 2-1c**).[173-176]

2.2 Project Outline

2.2.1 Origin of the Project

While fluorosulfonyl aryl halides have been used as the electrophilic substrates in Heck and Suzuki-Miyaura cross-coupling reactions,[169, 177-178] the corresponding sulfonyl fluoride-substituted aryl boronic acids have not been reported. The tolerance of sulfonyl fluoride functional group was well-demonstrated in the presence of a palladium catalyst or under various metal-mediated processes when aryl halides carrying a sulfonyl fluoride substituent were employed. It was postulated that aryl **b**oronic **a**cids substituted with **s**ulfonyl **f**luorides (abbr. **BASF**s) would be capable for coupling reactivity while maintaining the sulfonyl fluoride group. As the nucleophilic substrates in cross-coupling reactions, BASFs would benefit from being able to deliver sulfonyl fluoride group in combination with a vast selection of commercially available aryl halides as the electrophilic coupling partner, hence making them versatile reagents for accessing fluorosulfonyl aryl moieties.

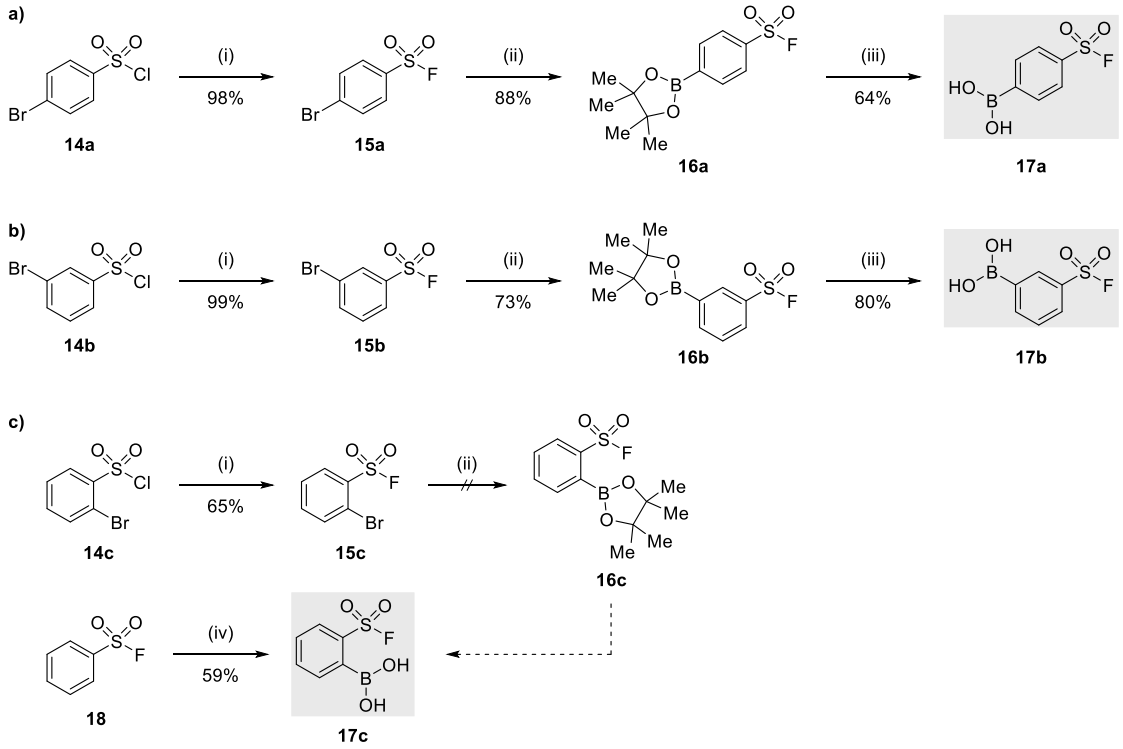
2.2.2 Project Aims

This project was divided into two parts: firstly, the development of synthetic strategies for the preparation of the different regioisomers of benzenesulfonyl fluoride boronic acids (BASFs); secondly, employing BASFs in coupling reactions to demonstrate the coupling

reactivity of boronic acids without influencing the sulfonyl fluoride functional group, therefore proving their usefulness as general reagents for the incorporation of an arylsulfonyl fluoride moiety.

2.3 Synthesis of Arylsulfonyl Fluoride Boronic Acids

The synthesis of *para*-benzenesulfonyl fluoride boronic acid began with commercially available *para*-bromobezenesulfonyl chloride (**14a**) (**Scheme 2-2a**). A chloride to fluoride was achieved using KHF_2 in aqueous acetonitrile at room temperature, converting the sulfonyl chloride into *para*-bromobenzenesulfonyl fluoride **15a** in quantitative yield. It was followed by the Miyaura borylation of **15a** using $B_2(pin)_2$ with $Pd(dppf)Cl_2$ to convert the bromide into a pinacol boronate **16a** in 88% yield. The targeted



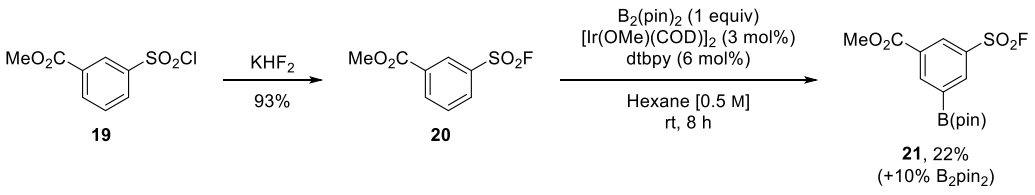
(i) KHF_2 (2.3 equiv), CH_3CN/H_2O (2:1) [0.6 M], rt, 6 h
(ii) $B_2(pin)_2$ (1.1 equiv), $Pd(dppf)Cl_2$ (3 mol%), KOAc (3 equiv), 1,4-dioxane [0.33 M], 80 °C, 2 h
(iii) NH_4OAc (5 equiv), $NaIO_4$ (4 equiv), Acetone/H_2O (1:1) [0.05 M], rt, 24 h
(iv) LDA (1.2 equiv), B(O*i*-Pr)$_3$ (2.4 equiv), THF [1 M], -78 °C, 30 min, then aq. HCl, rt, 30 min

Scheme 2-2. Synthesis of benzenesulfonyl fluoride boronic acids **17**.

boronic acid was obtained upon hydrolysis of the boronic ester **16a** using ammonium acetate and sodium periodate. The crude product was purified by trituration using a hexane/dichloromethane mixture, followed by pentane to deliver BASF **17a** in 64% yield. The *meta*-substituted BASF **17b** was synthesised from *meta*-bromobenzenesulfonyl chloride (**14b**) through an identical 3-step pathway with an overall 58% yield (**Scheme 2-2b**).

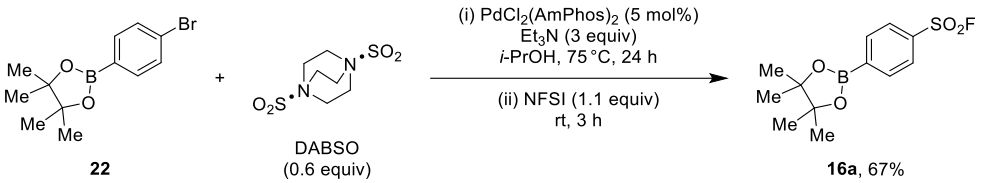
While *ortho*-bromobenzenesulfonyl fluoride **15c** was prepared from the corresponding sulfonyl chloride with a good 65% yield, it failed to deliver the boronic ester **16c** in the Miyaura borylation, with starting material recovered. In sight of Barbasiewicz's report,[179] the synthesis of *ortho*-substituted BASF was achieved through a one-pot operation of *ortho*-lithiation of commercially available benzenesulfonyl fluoride **18** using LDA, followed by *in-situ* quenching with triisopropyl borate and hydrolysis of the boronate directly with aqueous HCl to deliver the *ortho*-benzenesulfonyl fluoride boronic acid **17c** in a moderate 59% yield (**Scheme 2-2c**).

An attempt at an iridium-catalysed C-H borylation was also made using an Ir(I) catalyst with methyl *meta*-(fluorosulfonyl)benzoate **20** (**Scheme 2-3**), aiming for the preparation of a multifunctional BASF reagent. The transformation delivered an inseparable mixture of $B_2(pin)_2$ (*ca.* 10%) and the target boronic ester **21** in a poor 22% yield. No further investigation was made as it was thought that this would not be a synthetically useful approach for the preparation of the targeted BASF reagent.



Scheme 2-3. Attempt for Ir(I)-catalysed C-H borylation.

The synthesis presented in **Scheme 2-2** allowed for the preparation of BASF reagents in gram-scale and making use of commercially available starting materials featuring a sulfonyl chloride or fluoride moiety. It was then demonstrated in **Scheme 2-4** that catalytic sulfination can be realised with a substrate bearing an intact boron-substituent (**22**). By employing the conditions for palladium-catalysed sulfination of aryl bromides,[49] followed by electrophilic fluorination using NFSI, sulfonyl fluoride-substituted pinacolate boronic ester **10a** could be prepared in a good 67% yield.



Scheme 2-4. Sulfonyl fluoride synthesis from 4-bromophenylboronic acid pinacol ester.

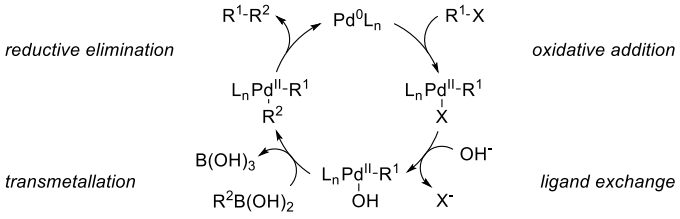
2.4 Application of BASF in Suzuki-Miyaura Cross-Coupling Reactions

2.4.1 Suzuki-Miyaura Coupling

First reported in 1979 by Akira Suzuki and Norio Miyaura, Suzuki-Miyaura coupling (SMC) is one of the most commonly used reactions in today's synthetic and medicinal chemistry,[180] and represents a convenient and reliable method for the formation of $C(sp^2)$–$C(sp^2)$ bond between an aryl or alkenyl (pseudo)halides and an organoboron species using a palladium catalyst.

For the SMC between an aryl halide and an arylboronic acid, the mechanism involves an oxidative addition of the electrophilic aryl halide to the palladium(0) catalyst. In the presence of water and base, halide was displaced by hydroxide to form an oxo-palladium species, followed by transmetallation with the nucleophilic boronic acid.[181] Finally,

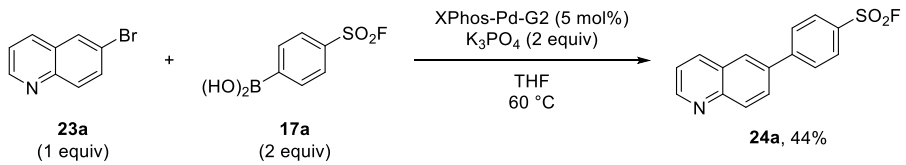
through reductive elimination, the coupled biaryl product was released and the active Pd(0) species was regenerated (**Scheme 2-5**).



Scheme 2-5. Mechanism of Suzuki-Miyaura coupling.

2.4.2 Optimisation of Suzuki-Miyaura Coupling

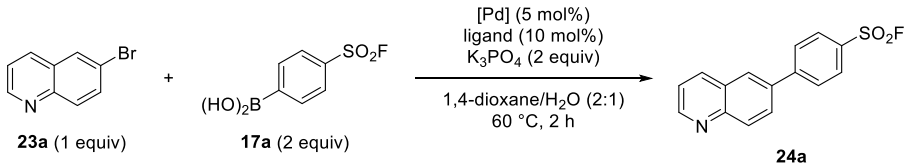
With the preparation of the three BASFs established, their reactivities in Suzuki-Miyaura cross-coupling were then demonstrated to show their application in coupling reactions. Despite the mature development in SMC reactions, the use of BASFs as the nucleophilic coupling partner is unprecedented. Two major challenges were foreseen regarding the use of BASFs in SMC – i) the reduced nucleophilicity, hence reactivity, of the boronic acid due to the strong electron-withdrawing property of a sulfonyl fluoride functional group, and ii) the hydrolytic instability of sulfonyl fluoride under basic conditions. The first attempt using 6-bromoquinoline (**23a**) and *para*-benezenesulfonyl fluoride boronic acid **17a** with XPhos-Pd-G2 precatalyst and potassium phosphate in THF resulted in a modest 44% yield (**Scheme 2-6**).



Scheme 2-6. Initial result of Suzuki-Miyaura Coupling.

An optimisation was carried out with the aforementioned substrates (**Table 2-1**). A range of phosphine ligands which are commonly used for SMC were evaluated in combination with $Pd(OAc)_2$ as the palladium source, K_3PO_4 as base and aqueous 1,4-dioxane as solvent, at 60 °C. Consumption of the aryl bromide starting material and the yields of the biaryl product were recorded after 2 hours. With the concern of sulfonyl fluoride being susceptible to hydrolysis under the reaction conditions, *i.e.* heating in the presence of base and water, yields were also recorded after 22 hours to measure any potential decomposition of the product or further conversion of the reactions when full conversion was not achieved in 2 hours.

Table 2-1. Ligand screening of Suzuki-Miyaura coupling.[a]



Entry	[Pd]	Ligand	Conversion[b]	Yield[c]	Yield[c] (22 h)
1	$Pd(OAc)_2$	XPhos	>99%	92%	85%
2	$Pd(OAc)_2$	SPhos	>99%	95%	85%
3	$Pd(OAc)_2$	RuPhos	>99%	96%	75%
4	$Pd(OAc)_2$	PCy_3	69%	69%	60%
5	$Pd(OAc)_2$	-	55%	40%	38%
6	$Pd(PPh_3)_4$	-	34%	29%	53%
7	$PdCl_2(AmPhos)_2$	-	>99%	99%	92%
8	XPhos-Pd-G2	-	94%	86%	78%

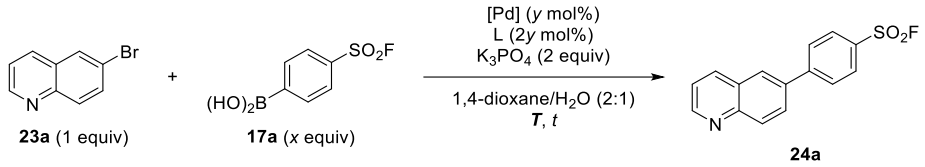
[a] Reaction conditions: ArBr (**23a**) (0.075 mmol, 1.0 equiv), $ArB(OH)_2$ (**17a**) (2.0 equiv), [Pd] (5 mol%), ligand (10 mol%), K_3PO_4 (1 M *aq*) (2.0 equiv), 1,4-dioxane [0.25 M], 60 °C, N_2. [b] Conversion determined by HPLC against internal standard based on the consumption of **23a**. [c] Yield determined by HPLC against internal standard.

It was found that with XPhos, SPhos, RuPhos and AmPhos (which was used as the $PdCl_2(AmPhos)_2$ preformed complex) all performed well, giving full conversion and good yields after 2 hours (entries 1–3 and 7). $Pd(OAc)_2$ alone or with PCy_3, and $Pd(PPh_3)_3$ gave moderate yields after 22 hours (entries 4–6). The precatalyst XPhos-Pd-G2 worked well but with a slower conversion and a lower yield when compared to the combination of $Pd(OAc)_2$ with XPhos (entry 8).

Following ligand evaluation, XPhos and AmPhos were further studied under various conditions (**Table 2-2**). By reducing the amount of BASF **17a** (entries 1 and 2) and the palladium loading (entries 3 and 4), and despite full conversion being achieved in the first hour of reaction, the yields dropped after 22 hours of reaction.

At lower temperatures, both ligands worked well at 40 °C (entries 5 and 6), and only XPhos was effective at room temperature after 24 hours of reaction while AmPhos delivered a low conversion possibly due to poor solubility (entries 7 and 8). Since an efficient conversion was achieved at 40 °C using XPhos with minimal decomposition observed over 22 hours, it was attempted to reduce the amount of BASF from 2.0 to 1.5 equivalents and this also resulted in good conversion. This provided a more attractive protocol for using BASF as a reagent in spite of the slight drop in the yield. Entries 10 and 11 show that both an inert atmosphere and the presence of water were crucial for effective conversion. Therefore, the following conditions were taken forward: 1 equiv of aryl halide substrate, 1.5 equiv of BASF **17a**, $Pd(OAc)_2$ as palladium source, XPhos as ligand, K_3PO_4 as base in aqueous 1,4-dioxane at 40 °C (entry 9).

Table 2-2. Optimisation of Suzuki-Miyaura coupling for milder conditions.[a]



Entry	L	**17a** (*x* equiv)	[Pd] (*y* mol%)	*T*	Time *t* [b]	Yield[c] (time *t*)	Yield[c] (22 h)
1	XPhos	1.5	5	60 °C	30 min	99%	68%
2	AmPhos	1.5	5	60 °C	15 min	99%	72%
3	XPhos	2.0	2	60 °C	1 h	95%	73%
4	AmPhos	2.0	2	60 °C	15 min	99%	76%
5	XPhos	2.0	5	40 °C	1 h	99%	**98%**
6	AmPhos	2.0	5	40 °C	2 h	99%	93%
7	XPhos	2.0	5	25 °C	24 h	99%	99%
8	AmPhos	2.0	5	25 °C	(1 h)[d]	10%	-[d]
9	**XPhos**	**1.5**	**5**	**40 °C**	**4 h**	**94%**	**93%**
10[e]	XPhos	1.5	5	40 °C	(22 h)[d]	-	43%
11[f]	XPhos	1.5	5	40 °C	(6 h)[d]	20%	-[d]

[a] Reaction conditions: ArBr (**23a**) (0.075 mmol, 1.0 equiv), $ArB(OH)_2$ (**17a**) (2.0 equiv), either $Pd(OAc)_2$ (5 mol%) with XPhos (10 mol%) or $PdCl_2(AmPhos)_2$ (5 mol%), K_3PO_4 (1 M *aq*) (2.0 equiv), 1,4-dioxane [0.25 M], 60 °C, N_2. [b] *t* indicates the time needed for 99% consumption of **23a**. [c] Yield determined by HPLC against internal standard. [d] Reaction terminated after time *t* regardless of conversion. [e] Reaction opened to air; 52% of **23a** remained. [f] Without H_2O; 80% of **23a** remained after 6 h.

2.4.3 Substrate Scope

Having the optimised set of conditions established, the substrate scope of the reaction was then investigated by employing a range of (hetero)aryl halide coupling partners with *para*-benzenesulfonyl fluoride boronic acid **17a** (**Table 2-3**). In addition to 6-bromo-quinoline (**23a**) which was used for optimisation and isolated in 91% yield, sterically demanding (**23b**), electron-rich (**23c**) and electron-deficient (**23d**) aryl bromides could be employed in good to excellent yields. A range of heterocycles were also successfully employed, including 3-bromoquinoline (**23e**), 4-bromopyrazole (**23f**) and 3-bromo-pyridine (**23g**) and 3-bromothiophene (**23h**).

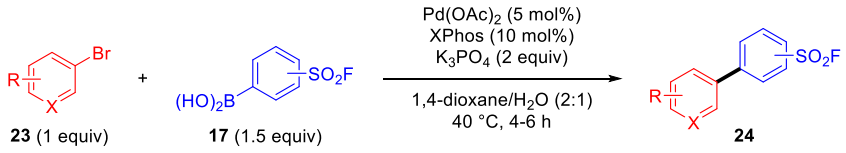
In order to demonstrate the potential application of this chemistry in discovery medicinal chemistry, more complex aryl halides from coupling-fragments of established value were employed. The incorporations of fragments from Sildenafil – for treating erectile dysfunction and pulmonary arterial hypertension (**23i**), Celecoxib – a selective cyclooxygenase-2 (COX-2) inhibitor (**23j**) and Omipalisib – a highly potent phosphorinositide 3-kinase (PI3K) inhibitor (**23k**), with *para*-benzenesulfonyl fluoride were successful.

Coupling using the other two regioisomers of the BASFs also proved viable. When the *meta*-substituted BASF **17b** was employed, products **24l** and **24m** were obtained in good yields. Product **24m** was prepared from using the corresponding aryl chloride instead of bromide as the electrophilic coupling partner. This showed the viability of using these less reactive electrophiles in cross coupling when an activating electron-withdrawing group is present. With *ortho*-substituted BASF **17c**, it was considerably more challenging to achieve coupling reactivity due to steric hindrance and potential intramolecular decomposition (due to the close spatial proximity of the boron and fluorine atoms and the thermodynamic driving force for the formation of strong B–F bond) under the reaction conditions. Rapid decomposition of the boronic acid **17c** was observed when the original set of conditions was employed. Coupling reactivity was restored under anhydrous conditions, using KF as base with increased catalyst loading in THF, first at 40 °C for half an hour, then at room temperature for 12 hours, yielding product **24n** in a modest 43% yield.

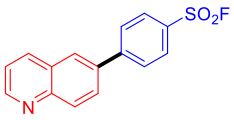
It was also demonstrated that the sulfonyl fluoride-bearing pinacolate ester **16a** could be used as substrate for the coupling reaction under the optimised conditions for the formation of **24a** with a good, but slightly compromised yield of 80% compared to the 91% when a boronic acid was used.

A list of low-yielding and unsuccessful examples is shown **Figure 2-1**. 4-Bromoisoxazole (**23o**) and 5-chlorobenzoxazole (**23p**) failed to deliver the target biaryl products despite rapid consumption of the aryl halides. Both 4-bromoaniline and 4-chloroaniline (**23q**) suffered from poor conversion with complex reaction mixtures. Products **24r** and **24s** were obtained in poor yields when 1-chloro-4-fluorobenzene and loratadine were employed respectively, likely due to the inertness of the aryl chlorides without an activating substituent. The conversions for the SMC of BASF **17a** with amoxapine (containing an isoxazole ring) (**23t**), and a fragment of a potent cognitive enhancer (with a highly basic amidine) (**23u**) were also poor.

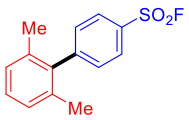
Table 2-3. Suzuki-Miyaura couplings of BASF.[a]



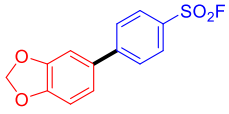
23 (1 equiv) + **17** (1.5 equiv) → **24**



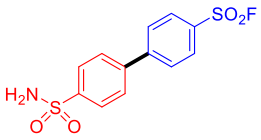
24a, 91%
(80% using Bpin ester)



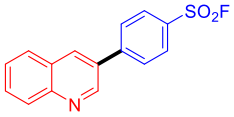
24b, 67%
(17% from ArCl)



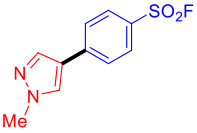
24c, 94%



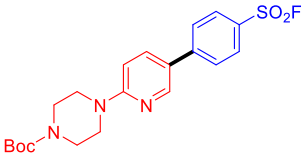
24d, 73%



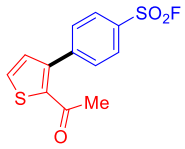
24e, 80%



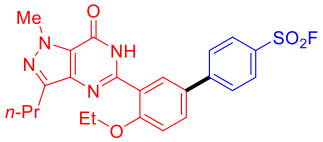
24f, 43%



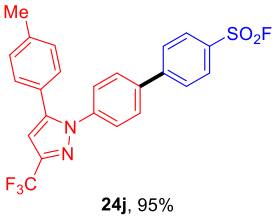
24g, 80%



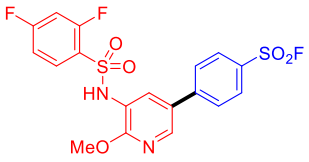
24h, 87%



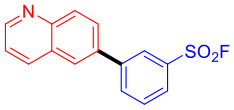
24i, 62%



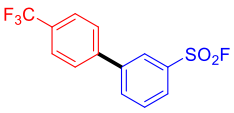
24j, 95%



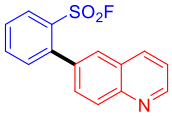
24k, 42%[b]



24l, 91%

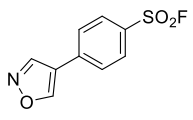


24m, 64%[c]

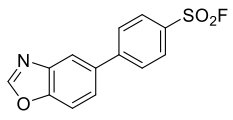


24n, 43%[d]

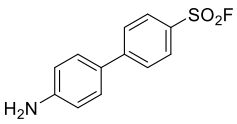
[a] Reaction conditions: Aryl halide **23** (1.0 equiv), BASF **17** (1.5 equiv), $Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), K_3PO_4 (1 M *aq*) (2.0 equiv), 1,4-dioxane [0.25 M], 40 °C, 4–6 h, N_2. [b] 24 hours. [c] Using aryl chloride substrate. [d] Aryl halide **23a** (1.0 equiv), BASF **17c** (1.5 equiv), $Pd(OAc)_2$ (20 mol%), XPhos (40 mol%), KF (3.3 equiv), THF [0.25 M], 40 °C, 0.5 h, then 25 °C, 12 h.



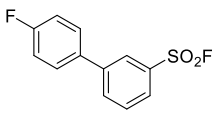
24o, 9% (from Br)



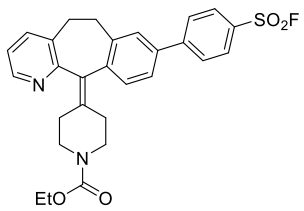
24p, 0% (from Cl)



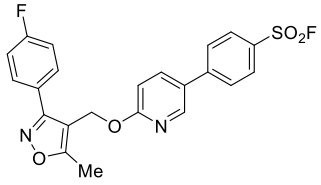
24q, -[a] (from Br or Cl)



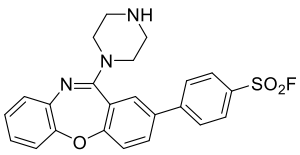
24r, 22% (from Cl)



24s, 26% (from Cl)



24t, -[a] (from Br)



24u, -[a] (from Cl)

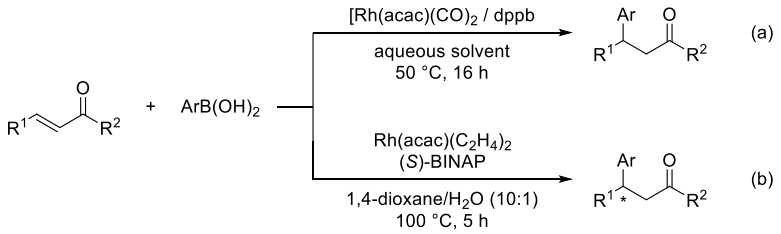
[a] Poor conversion.

Figure 2-1. Low yielding and unsuccessful examples in SMC.

2.5 Application of BASF in Rh(I)-Catalysed Conjugate Addition

2.5.1 Introduction

Conjugate addition to an electron deficient olefin, or α,β-unsaturated compound, represents a basic synthetic reaction for the formation of C–C bonds. In Miyaura's report from 1997,[182] the conjugate addition to α,β-unsaturated ketones could be achieved using aryl and alkenyl boronic acids as the nucleophile with a rhodium(I)-phosphine complex as catalyst, which provided a mild catalytic approach for such process without the use of reactive organometallics as nucleophiles (**Scheme 2-7a**). A later report by Hayashi and Miyaura in the next year demonstrated that the rhodium(I)-catalysed asymmetric conjugate addition could be realised with modified reaction conditions from Miyaura's original paper (**Scheme 2-7b**).[183]

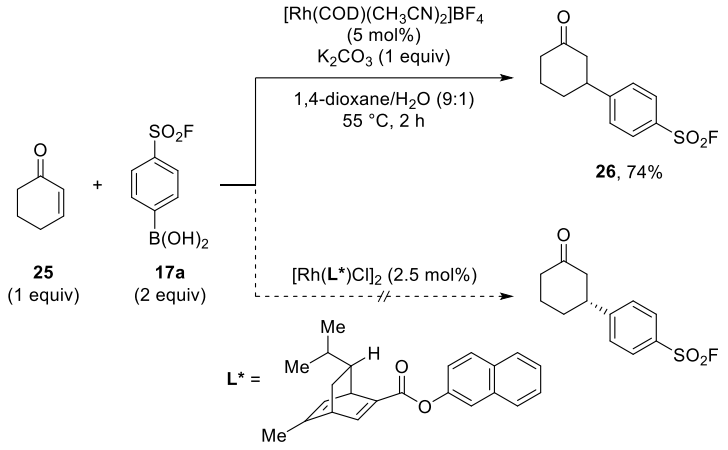


Scheme 2-7. First reports on racemic and asymmetric Rh(I)-catalysed conjugate addition.

2.5.2 Rh(I)-Catalysed Conjugate Addition using BASF

As illustrated in **Scheme 2-8**, Rh(I)-catalysed conjugate addition of *para*-substituted BASF **17a** to cyclohexanone (**25**) was realised by using simple commercially available $[Rh(COD)(CH_3CN)_2]BF_4$ as catalyst with K_2CO_3 as base in aqueous 1,4-dioxane at 55 °C. Full conversion was achieved in 2 hours and product **26** was isolated in a good 74% yield. An attempt for an asymmetric conjugate addition using a chiral Rh(I) catalyst (**L*** in **Scheme 2-8**) developed by Hayashi and previously reported by the Willis group,[184-186]

however, was unsuccessful with no conversion of the enone and decomposition of BASF **17a** being observed. No further attempt for the asymmetric addition was made as the success in the racemic addition had already demonstrated the compatibility of BASF **17a** in the rhodium-mediated reaction.



Scheme 2-8. Rhodium(I)-catalysed conjugate addition of BASF **17a** to cyclohexanone.

2.6 Project Summary

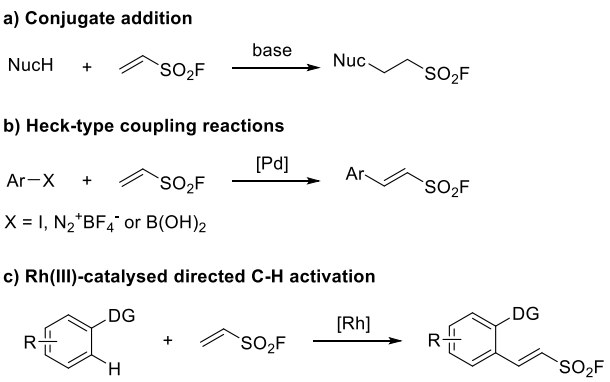
In conclusion, for this project, a series of *ortho*-, *meta*- and *para*-substituted benzenesulfonyl fluoride boronic acids (BASFs) were prepared from readily available starting materials for the first time. The employment of these electron-deficient boronic acids in Suzuki-Miyaura cross-coupling reactions, and a Rh(I)-catalysed conjugate addition, was also achieved. These reactions and syntheses showed the value of BASFs to open up new methods for the incorporation of the arylsulfonyl fluoride group. Therefore, it is envisioned that BASFs would prove their usefulness as reagents in the field of medicinal chemistry and chemical biology where sulfonyl fluorides are used as biologically compatible reactive handles.

Chapter 3 Cyclic Alkenylsulfonyl Fluorides (CASF): Palladium-Catalysed Synthesis and Functionalisation

3.1 Ethenesulfonyl Fluorides

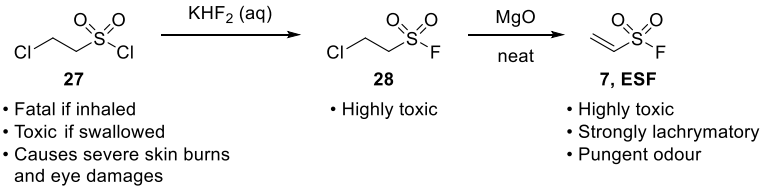
Ethenesulfonyl fluoride (ESF), the simplest example of an alkenylsulfonyl fluoride, was first documented by Hedrick in 1953, and which Hedrick anticipated it to be a new polymerisable fluorine compound for making plastics with improved properties.[168] Over a quarter of a century later, in 1979, Hyatt and co-workers reported the use of ESF in fluorosulfonylethylation of anilines to form sulfonamides. This led to the preparation of a series of azo dyes and heterocycles.[101]

Hyatt stated in 1979 that "Although ESF has been known for a number of years, the chemistry of this interesting difunctional compound has been little investigated." This statement still held years after Hyatt's report until 2014, when Sharpless reviewed the sulfur(VI)-fluoride exchange (SuFEx) reactions. He professed that sulfur(VI) fluorides could be candidates for the next "click reaction". Since then, Sharpless and others have reported the use of ESF for the incorporation of sulfonyl fluoride through conjugate addition,[21, 101] palladium-catalysed Heck-type coupling reactions using aryl iodides,[169] diazonium salts,[104] or boronic acids,[170] and rhodium(III)-catalysed directed C-H activation.[187-188]



Scheme 3-1. Common applications of ESF.

Due to the increased demand of having the sulfonyl fluoride warhead present in bioactive molecules or utilising this functionality to synthesise other sulfonyl containing compounds, ESF has gained in popularity amongst the medicinal chemistry and chemical biology communities. Whilst the versatility of ESF has been demonstrated for the incorporation of sulfonyl fluoride groups, unfortunately, there is a structural limitation to the fluorosulfonyl products; an ethyl or ethylene linker is inevitably added alongside with the sulfonyl fluoride moiety. Accompanying the high electrophilicity, ESF was also reported to be highly toxic and a lachrymator, which poses health and safety concerns for its use. In addition, the preparation of ESF includes the use of a starting material that is fatal if inhaled (**27**, 2-chloroethanesulfonyl chloride) (**Scheme 3-2**), which is clearly undesirable in modern day chemistry laboratories.



Scheme 3-2. Safety concern regarding the preparation of ESF.

3.2 Project Outline

3.2.1 Previous Work

In 2014, the Willis group reported the development of aryl iodide sulfination using a palladium catalyst and DABSO, as sulfur dioxide surrogate, to form aryl sulfinates.[51] Subsequently, in 2017, the Willis laboratory presented the synthesis of (hetero)arylsulfonyl fluorides through the Pd-catalysed sulfination of aryl bromides and subsequent electrophilic fluorination with NFSI.[49] Ball and co-workers also reported a similar strategy in accessing arylsulfonyl fluorides from aryl iodides later in the same year.[62] Alkenylsulfonyl fluorides, however, were not represented in these reports.

3.2.2 *Origin of the Project*

In view of the high reactivity and bifunctionality of ESF, it was thought that alkenylsulfonyl fluorides with customised alkene units would make attractive reagents for accessing structurally diverse sulfonyl fluorides carrying multiple reactive handles for further functionalisation.

Three-dimensional molecules have been gaining in popularity for biological applications. Having established the correlation between a high fraction of sp^3-hybridised carbons (Fsp^3), low lipophilicity (marked by log *P*)[189] and the likelihood of a small molecule being biologically active,[190-192] there is increasing demand for densely functionalised three-dimensional C(sp^3)-rich molecules for use in the pharmaceutical industry. We speculated that sulfonyl fluorides with sp^3-rich scaffolds would make interesting candidates for interdisciplinary applications.

Even though the previous reports on Pd-catalysed sulfonyl fluoride syntheses, using an SO_2-surrogate, presented an efficient strategy to access the sulfonyl fluoride functional groups, they are limited to aryl or heteroaryl substrates. As these partners are planar, the community's demand for C(sp^3)-rich molecules has not yet been addressed. **C**yclic **a**lkenyl**s**ulfonyl **f**luorides (abbr. **CASF**s), which have a rigid three-dimensional scaffold, contain multiple sp^3-carbon centres as well as several reaction handles for further derivatisations, were anticipated to be attractive reagents for potential applications in discovery medicinal chemistry and chemical biology.

3.2.3 *Project Aims*

This project aimed to deliver a general synthetic protocol for the preparation of alkenylsulfonyl fluorides through palladium catalysis. Alkenylsulfonyl fluorides, with

multiple functional groups present, were targeted to demonstrate reactivity with different reagents at several reactive sites, with the aim of establishing them to be versatile compact multifunctional reagents.

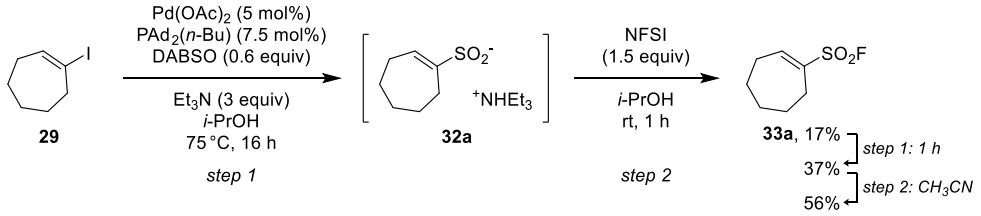
3.3 Optimisation of Reaction Conditions

When selecting the type of starting materials, the availability of substrates came into consideration, and therefore alkenyl halides or pseudohalides were preferred over alkenyl boronic acids or organometallic reagents. We first started with cycloheptenyl iodide (**29**), employing the conditions previously reported for the sulfination of aryl iodides,[51] followed by electrophilic fluorination using NFSI. A poor yield (17%) of the corresponding alkenylsulfonyl fluoride **33a** was obtained (**Scheme 3-3**).

As the alkenyl iodide starting material appeared to be fully consumed in the poor-yielding first reaction attempt, the reaction was repeated and monitored, at regular intervals by HPLC. Full conversion was achieved after one hour as all the starting material **29** had been consumed in the sulfination step (step 1, **Scheme 3-3**). The concentration of the sulfinate **32a** reduced over time after the first hour of sulfination. Prolonging the reaction time for the fluorination step (step 2) also reduced the yield of the final sulfonyl fluoride. The combination of excess base and protic alcoholic solvent likely led to the decomposition of the alkenyl sulfinate **32a** and sulfonyl fluoride **33a** under the reaction conditions. Therefore, higher yields were expected with minimal reaction time for full conversion. By shortening the reaction time for step 1 to one hour, the yield of **33a** was improved to 37%.

Considering the alkenylsulfonyl fluoride product **33a** is a good Michael acceptor and is susceptible for nucleophilic attack by isopropanol, the solvent was switched to prevent

this pathway. The volatiles were removed *in vacuo* after the one-hour sulfination before the addition of acetonitrile and NFSI for the fluorination step. These modifications produced the sulfonyl fluoride in an improved 56% yield.



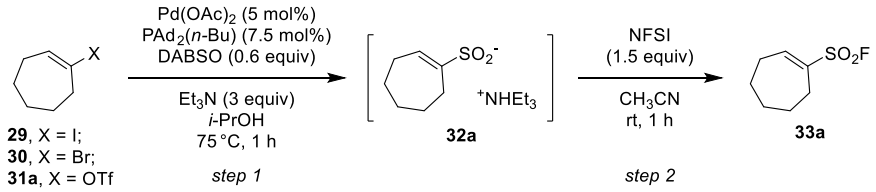
Scheme 3-3. Initial results for Pd-catalysed synthesis of cycloheptenylsulfonyl fluoride **33a**.

The reaction was further optimised based on these initial results (**Table 3-1**). Prolonged reaction time for the sulfination step proved to be detrimental to the yield (entries 2–4). Increasing the stoichiometry of DABSO to one equivalent gave a lower yield, which was attributed to the nucleophilicity of DABCO (entry 5). As a result, the sulfur dioxide adducts of other less nucleophilic amines were examined, including those of *N*-methylpyrrolidine (TIMSO) and *N*-methylmorpholine (NMSO). Unfortunately, these failed to improve the yield of the alkenylsulfonyl fluoride **33a** (entries 6–7). When isopropanol was replaced by a less nucleophilic alcohol, such as hexafluoro-2-propanol (HFIP) or *tert*-butanol, or when the ligand was switched to SPhos or MePhos, poor conversions were recorded with only trace amounts of alkenyl sulfinate observed after 24 to 48 hours of sulfination (entries 8–11). The preformed catalyst $PdCl_2(AmPhos)_2$, which was previously used in the sulfination of aryl bromides, was not as effective (entry 12).

Substrates with different leaving groups were then examined. Using $PdCl_2(AmPhos)_2$ as catalyst with cycloheptenyl bromide **30** delivered a 52% yield (entry 13). When NMSO was used in place of DABSO, a comparable 56% yield was obtained (entry 14). Employing alkenyl triflate **31a** with the combination of $Pd(OAc)_2$ and $PAd_2(n\text{-Bu})$

returned a 36% yield, whereas $PdCl_2(AmPhos)_2$ produced **33a** in 56% yield (entries 15–16). With similar yields obtained, alkenyl triflates were chosen for further investigation over the iodides and bromides, primarily because their preparation from the corresponding ketones was more convenient, and involved only one synthetic step in good yield.

Table 3-1. Optimisation for sulfination of aryl (pseudo)halide.[a]

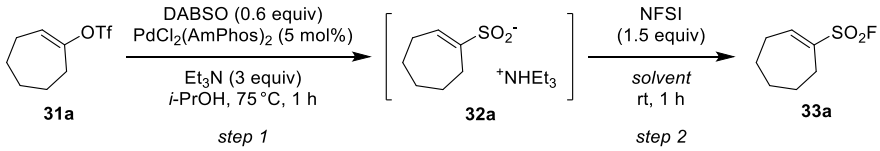


Entry	X	Variation in step 1	Conversion[b]	Yield of **33a**[c]
1	I	as above	-	56%
2	I	2 h	-	50%
3	I	24 h	-	0%
4	I	50 °C, 8 h	-	39%
5	I	DABSO (1 equiv)	-	53%
6	I	TIMSO (1.2 equiv)	-	33%
7	I	NMSO (1.2 equiv), 3 h	-	50%
8	I	HFIP, 48 h	68%[d]	-
9	I	*t*-BuOH, HCO_2Na (2.5 equiv), 24 h	84%[d]	-
10	I	SPhos instead of PAd_2(*n*-Bu), 24 h	83%[d]	-
11	I	MePhos instead of PAd_2(*n*-Bu), 24 h	89%[d]	-
12	I	$PdCl_2(AmPhos)_2$, 24 h	-	31%
13	Br	$PdCl_2(AmPhos)_2$, 1 h	-	52%
14	Br	$PdCl_2(AmPhos)_2$, NMSO(1.5 equiv), 4 h	-	56%
15	OTf	as above	-	36%
16	**OTf**	**$PdCl_2(AmPhos)_2$, 1 h**	**-**	**56%**

[a] Reaction condition: (step 1) Alkenyl (pseudo)halide (0.3 mmol, 1.0 equiv), DABSO (0.6 equiv), Et_3N (3.0 equiv), $Pd(OAc)_2$ (5 mol%), PAd_2(*n*-Bu) (7.5 mol%), *i*-PrOH [0.25 M], 75 °C, 1 h; (step 2) NFSI (1.5 equiv), CH_3CN [0.25 M], rt, 1 h. [b] Conversion determined by HPLC against internal standard based on the consumption of alkenyl (pseudo)halide; unless specified, conversion >95%. [c] Yield determined by ^{19}F-NMR spectroscopy with internal standard. [d] Less than 10% sulfinate was formed.

In light of the improvement in yield of the sulfonyl fluoride product **33a** when a solvent switch was performed, it was speculated that the role of solvent would have an impact in the fluorination step. As shown in **Table 3-2**, various solvents were evaluated for the electrophilic fluorination (entries 1–9), with ethyl acetate performing the best to give an isolated yield of 70%. While acetonitrile is a common solvent for electrophilic fluorination, it was thought that ethyl acetate provided a balance between the good solubility of NFSI, the sparing solubility of ammonium sulfinate and the poor solubility

Table 3-2. Optimisation for electrophilic fluorination.[a]



31a **32a** **33a**

Entry	Solvent for step 2	Yield of **33a**[b]
1	CH_3CN	56%
2	*i*-PrOH	54%
3	*i*-PrOH/CH_3CN (1:1)	46%
4	CH_2Cl_2	48%
5	THF	53%
6	**EtOAc**	**67% (70%)**[c]
7	DMF	61%
8	Et_2O	54%
9	Acetone	59%
10[d]	CH_3CN	53%
11[d]	EtOAc	67%
12[e]	EtOAc	65%
13[f]	EtOAc	40%
14[g]	EtOAc	55%
15[h]	EtOAc	68%

[a] Reaction condition: (step 1) Cycloheptenyl triflate **31a** (0.3 mmol, 1.0 equiv), DABSO (0.6 equiv), Et_3N (3.0 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), *i*-PrOH [0.25 M], 75 °C, 1 h; (step 2) NFSI (1.5 equiv), solvent [0.25 M], rt, 1 h. [b] Yield determined by ^{19}F-NMR spectroscopy with internal standard. [c] Isolated yield. [d] Step 1: 80 °C, 30 min. [e] Step 1: DABSO (1.0 equiv). [f] Step 1: DABSO (2.0 equiv). [g] Step 1: Cy_2NMe in place of Et_3N. [h] Step 1: DIPEA in place of Et_3N.

of by-products such as ammonium dibenzenesulfonimide, and therefore gave the best result.

With the optimal solvent for fluorination identified, we returned to the sulfination step and examined if any alteration would improve the yield further. By increasing the temperature to 80 °C, which is just below the boiling point of isopropanol, the reaction time could be shortened to 30 min, yet did not deliver a higher yield compared to that performed at 75 °C (entries 10–11). Increasing the amount of DABSO (entries 12–13), or replacing triethylamine with other organic bases, such as Cy_2NMe or DIPEA (entries 14–15), proved ineffective to further improve the yield of the sulfonyl fluoride.

Thus, the optimal conditions were identified for the sulfination step using alkenyl triflate as the substrate, 0.6 equiv of DABSO as the SO_2 source, $PdCl_2(AmPhos)_2$ as the catalyst, Et_3N as base in anhydrous isopropanol (which also acted as a reductant), at 75 °C; a solvent switch to EtOAc was performed upon full conversion to the sulfinate, followed by the addition of NFSI for the electrophilic fluorination at room temperature.

3.4 Substrate Scope of the Reaction

With the reaction conditions for the synthesis of alkenylsulfonyl fluorides from alkenyl triflates optimised, the substrate scope of the reaction was then investigated (**Table 3-5**). Initial attempts to apply the optimised conditions to cyclohexenyl triflate gave low and variable yields. It was then identified that cyclohexenylsulfonyl fluoride was too volatile for straight-forward isolation. Consequently, the scope of the reaction was first explored with the derivatives of cyclohexenyl triflate. With a phenyl (**Table 3-5**, **33b**) and a *tert*-butyl group (**33c**) substituted at the 4-position, which added bulk to the molecule and reduced the volatility of the products, the corresponding sulfonyl fluorides

were obtained in 71% and 70% yields, respectively. These yields were similar to the optimised cycloheptenyl sulfonyl fluoride (**33a**). However, longer reaction times were required for full conversion of the alkenyl triflates to the sulfinates (5.5 h for **31b** and 5 h at 80 °C for **31c**), which suggested the six-membered cyclohexenyl substrates were less reactive than the seven-membered counterpart.

Other 4-substituted cyclohexenyl triflate derivatives containing a range of functional groups were converted efficiently into alkenylsulfonyl fluorides. This included a geminal difluoro (**33d**), an ethyl ester (**33e**), a methoxy ether (**33f**), a *tert*-butyl carbamate (a Boc-protected primary amine) (**33g**) and a spiroacetal (dioxolane) (**33h**). Scaling up of the reaction was also proved viable by the gram-scale synthesis of **33h**. When one gram of alkenyl triflate **31h** (3.5 mmol) were subjected to the reaction conditions, a 73% yield was obtained with 0.57 g (2.57 mmol) of **33h** delivered. Pleasingly, the result was comparable to the 74% yield achieved from the reaction performed on 0.3 mmol scale.

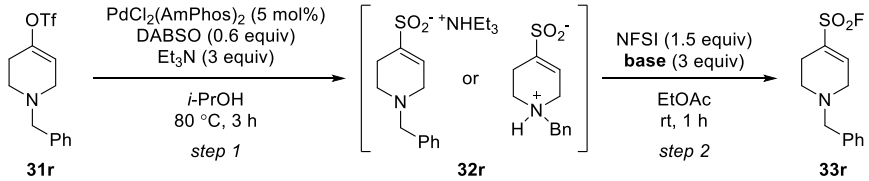
Cyclohexenyl substrates with substituents at the 3-position also performed well in the reaction and showed tolerance to electron-rich heteroaromatic substituents, namely 1-methylindole (**33i**) and 2-methylfuran (**33k**), delivering the CASFs in 52% and 69% yields respectively. 6-Methylcyclohexenyl triflate, on the other hand, reacted much slower in the sulfination step and required heating to 95 °C under microwave irradiation for 3 h to achieve full conversion, eventually producing **33l** in 43% yield. This modest yield was attributed to the increased steric demand (due to the substituent being adjacent to the reaction site), hindering the sulfination to take place.

Heterocyclic substrates were then examined. CASFs of a sulfone-containing heterocycle (**33m**) and a cyclic ether (**33n**) were generated in moderate yields (49% and 62%, respectively). Protected cyclic amines at the 4- or 5-positions (**33o–s**) were also

tolerated, with the sulfonamide-bearing CASF (**33s**) being delivered most efficiently in an excellent 90% yield. The X-ray crystal structure of **33s** displays a half-chair conformation; the expected conformation for cyclohexenes. The C–SO_2–F bond angle of 100.3°, relatively small for an sp^3-hybridised centre, resembles that of an arylsulfonyl fluoride.[193] The alkene C–C bond length (1.319(4) Å) is typical for a C=C double bond which suggested the olefin is not conjugated with the sulfonyl fluoride.

As basic amines are present in many natural products and drug molecules, it was desirable to apply the methodology to substrates with this functionality. The basic *N*-benzyl substituted CASF **33r**, however, was only obtained in trace amounts when the

Table 3-3. Base screening for the fluorination of basic CASF **33r**.[a]



Entry	Base	Yield[b]
1	no base added	14%
2	Et_3N	37%
3	DBU	36%
4	K_2CO_3	29%
5	Cs_2CO_3	27%
6	**DIPEA**	**53%**
7	Cy_2NMe	29%
8	Proton-Sponge	45%
9	*t*-BuOK	29%
10	DIPEA (1.5 equiv)	51%
11[c]	no base added	45%

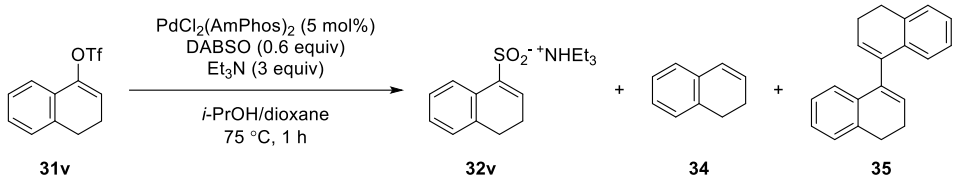
[a] Reaction conditions: (step 1) Alkenyl triflate **31r** (0.3 mmol, 1.0 equiv), DABSO (0.6 equiv), Et_3N (3.0 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), *i*-PrOH [0.25 M], 80 °C, N_2, 3 h; (step 2) base (3.0 equiv), NFSI (1.5 equiv), EtOAc [0.25 M], rt, 1 h. [b] Yield determined by ^{19}F-NMR spectroscopy with internal standard. [c] No solvent switch was performed; step 2: *i*-PrOH as solvent.

general procedure was followed. The basic nitrogen was thought to compete with Et_3N and became protonated, hence forming an insoluble salt that could not undergo the electrophilic fluorination effectively. To justify this, additional base was added after the solvent switch and prior to the addition of NFSI. **Table 3-3** summarises the results of adding different bases between solvent switch and fluorination, with DIPEA giving the best yield. Notably, when the solvent switch was not performed, **33r** was still obtained in 45% yield without additional base.

As for tetralone-derived alkenyl triflates, they were converted to the corresponding CASFs in modest yields following the original protocol (43% for **33u**; 48% for **33v**). For the reaction using triflate **31v**, the hydrodetriflation product (1,2-dihydronaphthalene, **34**) and dimer **35** were identified as the major side products in the sulfination step (**Table 3-4**). Since isopropanol acts as reductant in the reaction, as well as a potential source of proton for the hydrodetriflation, it was thought that reducing the amount of isopropanol, by employing a mixed solvent system, might suppress the by-product formation.

Since 1,4-dioxane had been previously used in the Willis laboratories for sulfination chemistry,[162] an isopropanol/dioxane co-solvent was investigated by varying the ratio between the two solvents (**Table 3-4**, entries 1–7). It was found that two parts of isopropanol to one part of dioxane gave the greatest amount of sulfinate (entry 3). Addition of sodium formate as a reductant was ineffective (entry 8). Increasing the amount of DABSO suppressed by-product formation, yet resulted in lower conversion (entries 9–10). Raising the temperature to 80 °C, with 1 equiv of DABSO, significantly reduced the formation of dimer **35**, whilst the formation of the sulfinate **32v** was increased (entry 11).

Table 3-4. Optimisation of solvent ratio for the sulfination of **31v**.[a]



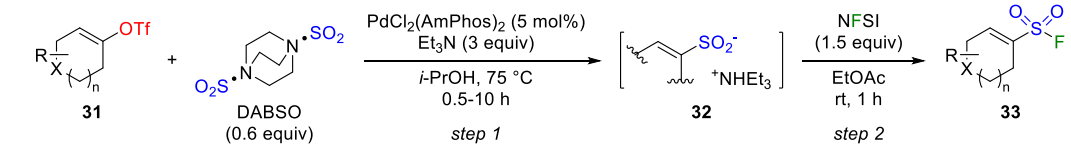
31v **32v** **34** **35**

Entry	*i*-PrOH/dioxane	Conversion[b]	**32v**[c]	**34**[c]	**35**[c]
1	1:0	97%	1.00	0.17	0.83
2	3:1	97%	1.34	0.25	0.44
3	2:1	93%	1.40	0.31	0.33
4	1:1	68%	1.00	0.19	0.22
5	1:2	26%	0.36	0.04	0.06
6	1:3	14%	0.22	0.03	0.04
7	1:10	0%	0	0	0
8[d]	2:1	16%	0.26	0.24	0.04
9[e]	2:1	79%	1.37	0.19	0.15
10[f]	2:1	56%	0.96	0.09	0.03
11[e,g]	**2:1**	**93%**	**1.56**	**0.23**	**0.21**

[a] Reaction conditions: Alkenyl triflate **31v** (0.3 mmol, 1.0 equiv), DABSO (0.6 equiv), Et_3N (3.0 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), *i*-PrOH/1,4-dioxane [0.25 M], 75 °C, N_2, 1 h. Acetophenone (0.3 mmol, 1.0 equiv) was added as internal standard after 1 h. [b] Conversion determined by HPLC against internal standard based on the consumption of **31v**. [c] Ratio of area under the curve against internal standard as determined by HPLC. [d] $NaHCO_2$ (2.5 equiv) added. [e] DABSO (1.0 equiv). [f] DABSO (2.0 equiv). [g] 80 °C.

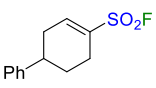
Using the new set of optimised conditions for the sulfination of tetralone-derived substrates, followed by the original fluorination procedure, CASF **33v** (**Table 3-5**) was obtained in 63% yield, and its regioisomer **33u** was obtained in 55% yield. Substituents on the aromatic ring were also tolerated, such as a methoxy group (**33w**) and a triflate (**33x**), with the corresponding CASFs formed in similar yields of 57% and 59% respectively. Interestingly, even though substrate **31x** consists of two different triflates in the same molecule, the aryl triflate remained intact and only the alkenyl triflate proved reactive under the conditions. The inertness of an aryl triflate under the reaction conditions was verified by the almost quantitative recovery of biphenyl triflate, with no sulfinate nor sulfonyl fluoride **33y** formed.

Table 3-5. Substrate scope of cyclic alkenylsulfonyl fluoride.[a]

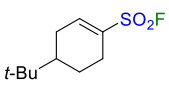




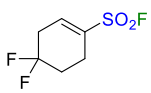
33a, 70%



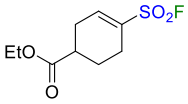
33b, 71%



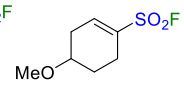
33c, 70%[b]



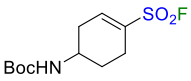
33d, 67%



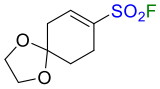
33e, 80%



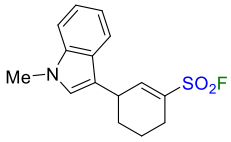
33f, 57%



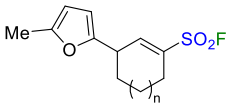
33g, 64%



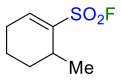
33h, 74%
(Gram-scale: 73%)



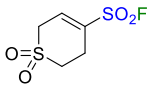
33i, 52%



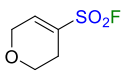
33j, n = 0, trace
33k, n = 1, 69%



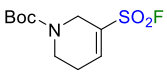
33l, 43%[c]



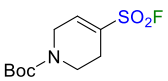
33m, 49%



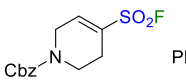
33n, 62%



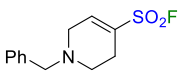
33o, 69%



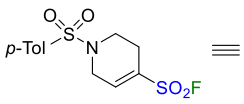
33p, 82%



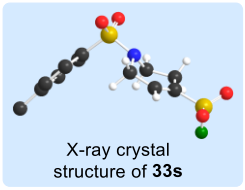
33q, 65%



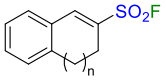
33r, 46%[c,d]
(53%)[b,d,f]



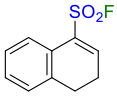
33s, 90%



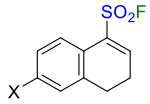
X-ray crystal
structure of **33s**



33t, n = 0, 0%
33u, n = 1, 43% (55%)[a]

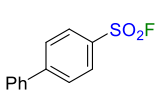


33v, 48%
(63%)[e]

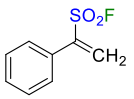


33w, X = OMe, 57%[e]
33x, X = OTf, 59%[e]

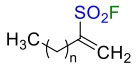
Low-yielding and unsuccessful examples:



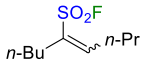
33y, 0%[g,h]



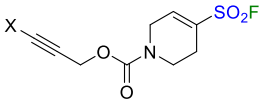
33z, trace
(from OTf or Br)



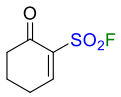
33aa, n = 6, trace (from Br)
33ab, n = 7, 11%[c,f]



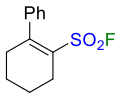
33ac, (*Z*)-alkene, trace
33ad, (*E*)-alkene, -[h]



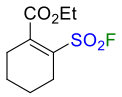
33ae, X = H, -[i]
33af, X = TMS 42%[f] (30%)[c]



33ag, 15%



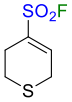
33ah, -[h]



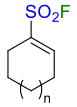
33ai, -[h]



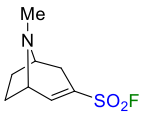
33aj, -[i]



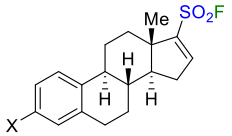
33ak, -[i]



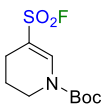
33al, n = 3, -[i]
33am, n = 7, -[i]



33an, 0%



33ao, X = OTf, 0%[i]
33ap, X = OMe, -[i]



33o', -[h]

[a] Reaction conditions: (step 1) Alkenyl triflate **31** (0.3 mmol, 1.0 equiv), DABSO (0.6 equiv), Et_3N (3.0 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), *i*-PrOH [0.25 M], 75 °C, N_2, 0.5–10 h; (step 2) NFSI (1.5 equiv), EtOAc [0.25 M], rt, 1 h. [b] Step 1: 80 °C. [c] Step 1: μW, 95 °C. [d] Step 2: DIPEA (3.0 equiv) was added after solvent switch. [e] Step 1: DABSO (1 equiv), Et_3N (3.0 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), *i*-PrOH/ 1,4-dioxane (2:1) [0.25 M], 80 °C, N_2, 0.5–1.5 h. [f] ^{19}F-NMR yield. [g] 96% recovery of biphenyl triflate. [h] Poor conversion in step 1. [i] Alkenyl triflate **31** was consumed but no sulfinate formation in step 1.

Other unsuccessful examples are also listed in **Table 3-5**. For acyclic substrates with terminal alkenes (**33z**–**ab**) and a *trans*-*Z*-alkene (**33ac**), the starting materials undergo rapid decomposition under the reaction conditions due to reduced steric strain and increased reactivity. Substrates with a terminal alkyne (**33ae**) failed to deliver the sulfinate in the first step possibly due to the coordination of the alkyne to the palladium catalyst; on the other hand, CASF bearing an internal alkyne (a trimethylsilylacetylene) **33af** was only generated in a useful 42% yield, which is significantly lower than other CASFs with a carbamate functional group (**33o-q**).

An α-keto CASF (**33ag**) was only generated in a poor 15% yield, and this was attributed to the instability of both the alkenyl sulfinate and the CASF product due to their high electrophilicity. 2-Substituted alkenyl triflates (**31ah**,**ai**) did not react in the Pd-catalysed sulfination because of the steric hinderance posed by the substituent adjacent to the reaction site. A 3,4,5,6-tetrahydropyridine (**33aj**) and a cyclic sulfide (**33ak**) failed to convert in the sulfinate step due to the possible coordination of the heteroatoms to the palladium. Conversions of substrates with ring sizes of five (**33j**,**t**), eight (**33al**) or twelve (**33am**) to sulfinates were ineffective due to dominance of side reactions, such as protodetriflation. This suggested that the defined conformation of an alkenyl triflate in a 6-membered or a 7-membered ring was essential for effective sulfination to take place.

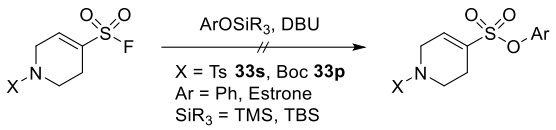
Triflates derived from natural products, such as tropinone (**31an**) (a bridged bicyclic compound with a basic amine) or estrone (**31ao**,**ap**) (a cyclopentenyl triflate with a disubstituted 5-position) were unsuccessful either. Lastly, an enamine substrate (**31o'**) did not convert to the corresponding sulfinate as the alkene was stabilised by the nitrogen through conjugation.

3.5 Functionalisation of Cyclic Alkenylsulfonyl Fluorides

With the substrate scope of the reaction established, a variety of functionalised CASFs were now available. These CASFs feature of multiple reactive sites, and the selective functionalisation of these sites was key to fully harnessing the potential of CASFs as useful reagents for accessing structurally diverse sulfonyl fluorides and related products. CASFs, as Michael acceptors, should undergo nucleophilic substitution at sulfur (1,2-addition) or conjugate addition at β-carbon (1,4-addition). Other reactivities, such as catalytic hydrogenation of the olefin and orthogonal transformations further away from the alkenylsulfonyl fluoride moiety were also investigated.

3.5.1 Nucleophilic Substitution (1,2-Addition on S)

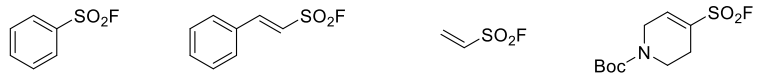
Sharpless professed the 1,2-addition on sulfur of sulfur(VI)-fluoride compounds as the next "click" reaction and called it the sulfur(VI) fluoride exchange (SuFEx).[21] Initial attempts of applying Sharpless' SuFEx reaction conditions to CASFs **33s** or **33p**, and TMS-protected phenol or 3-(*tert*-butyldimethylsilyloxy)estrone, in the presence of DBU, as the Lewis base, returned mainly starting materials (**Scheme 3-4**).



Scheme 3-4. Unsuccessful attempts of SuFEx with CASFs.

The poor reactivity of CASFs towards silyl ethers was thought to be attributed to reduced electrophilicity of the sulfur. **Scheme 3-5** shows the comparison of ^{19}F-NMR chemical shift between four sulfonyl fluorides. The fluorine shifts of benzenesulfonyl fluoride **18** (δ_F = 65.9 ppm) and 2-phenylethenesulfonyl fluoride (PhESF) (δ_F = 62.1 ppm), were significantly lower field than that of ethenesulfonyl fluoride (**7**, ESF) (δ_F = 56.8 ppm)

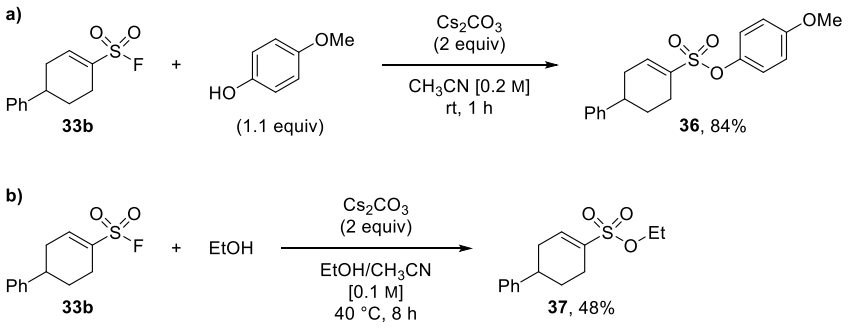
and CASF **33p** (δ_F = 54.2 ppm), meaning a more shielded environment for the fluorine in the alkenylsulfonyl fluorides. While the first two sulfonyl fluorides were known SuFEx substrates, the SuFEx reactivity of ESF was not reported. The upfield ^{19}F-NMR chemical shifts in ESF and CASF **33p** suggests the sulfonyl groups are less electron-withdrawing, which leaves more electron density around the fluorine atom, hence making the sulfur less electrophilic for SuFEx to take place.



18 δ_F = 65.9 ppm | PhESF δ_F = 62.1 ppm | ESF δ_F = 56.8 ppm | **33p** δ_F = 54.2 ppm

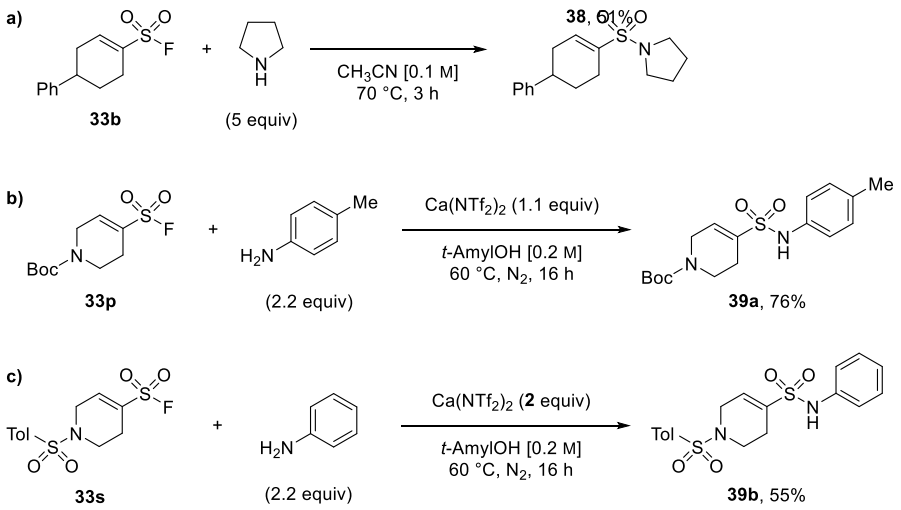
Scheme 3-5. Comparison of ^{19}F-NMR chemical shift.

Following the unsuccessful attempts of applying Sharpless' SuFEx chemistry to our CASFs using silyl ethers, it was felt that the direct addition of alcohols to the sulfonyl fluoride would be more convenient rather than pre-functionalising the alcohols prior to the transformation. This was achieved by the addition of Cs_2CO_3 base, in acetonitrile, at room temperature,[62] and was exemplified by the addition of *p*-methoxyphenol to **33b**, producing the corresponding sulfonate ester **36** in a good 84% yield (**Scheme 3-6a**). On the other hand, when aqueous ethanol was used as a co-solvent, the ethyl sulfonate ester **37** was obtained in 48% yield (**Scheme 3-6b**).



Scheme 3-6. Sulfonate ester synthesis from CASF.

Sulfonamide synthesis from CASF and amine nucleophile was also explored. As shown in **Scheme 3-7a**, a mixture of CASF **33b** and excess pyrrolidine in acetonitrile was heated to 70 °C for 3 hours, and the resulting sulfonamide **38** was obtained in a moderate 51% yield. Anilines, on the other hand, are less nucleophilic and activation of the sulfonyl fluoride was required. In 2018, Ball reported the use of $Ca(NTf_2)_2$ as Lewis acid for sulfonamide synthesis from sulfonyl fluorides,[94] in which divalent Lewis acids, such as $Ca(NTf_2)_2$ and $Ba(NTf_2)_2$ were found to be more effective than monovalent cationic salts; and triflimide counterion enabled good solubility of the Lewis acids. By adapting such strategy, alkenyl sulfonamides **39a** and **39b** were prepared in good yields in the presence of stoichiometric $Ca(NTf_2)_2$ (**Scheme 3-7b,c**). It is important to note that the sulfonamide in **33s** could also coordinate to the Lewis acid, thus an additional equivalent of $Ca(NTf_2)_2$ was needed to overcome this competition (**Scheme 3-7c**).

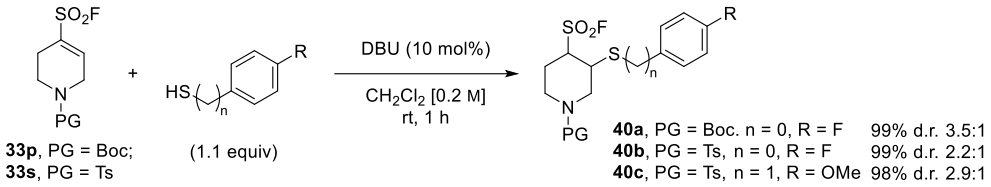


Scheme 3-7. Sulfonamide synthesis from CASFs.

3.5.2 Conjugate Addition (1,4-Addition on C)

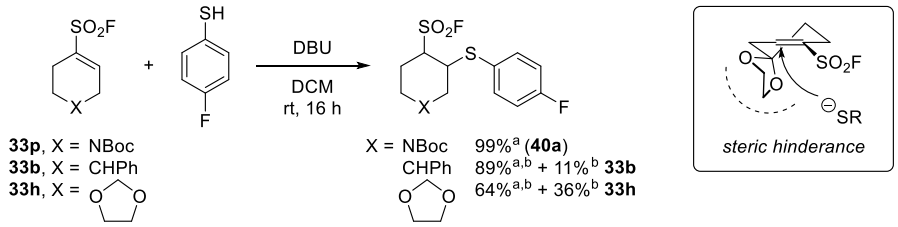
Being one of the two key reaction sites of CASFs, the electron-deficient olefin is susceptible to conjugate addition by soft nucleophiles at the β-C. (Despite the term "conjugate addition" being used, the alkene is not conjugated with the sulfonyl fluoride

as shown in the X-ray crystal structure in **Table 3-5**.) This was demonstrated by the addition of *p*-fluorothiophenol or *p*-methoxybenzylthiol to CASF **33p** or **33s** in the presence of DBU as catalytic base (**Scheme 3-8**). This gave the sulfa-Michael adducts **40a–c** in quantitative yields and poor diastereoselectivity.



Scheme 3-8. Conjugate addition of thiols and thiophenols to CASFs.

Efforts to improve the diastereoselectivity were attempted, yet were unsuccessful. During the study, it was observed that even though the diastereomeric ratio remained similar across different CASFs, the conversion of the conjugate addition varied. This was attributed to the extent of steric strain posed by different substituents at the 4-position, hindering the approach of the nucleophile (**Scheme 3-9**).



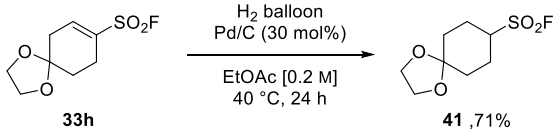
Scheme 3-9. Conversion of conjugate addition varied with CASF substrates. [a] Combined yield of diastereomers. [b] Yield determined by ^{19}F-NMR spectroscopy with internal standard.

The conjugate addition with other nucleophiles were also examined, but without much success. Reaction between CASFs and amine nucleophiles gave complex mixtures, likely due to other competing reactions, such as the nucleophilic substitution at S, and the subsequent conjugate addition to the resulting alkenyl sulfonamide side product. Employment of four types of organometallic reagents as nucleophiles was also attempted. Organocuprates and Grignard reagents remained unreactive to CASFs, while the reactions with aryl lithium or a lithium amide gave complex mixtures.

Whilst the versatility of ESF in conjugate addition was manifested, the conjugate addition to CASF was found to be significantly more challenging. Compared with ESF, the substituents at the α- and β-positions were thought to sterically hinder efficient conjugate additions to take place. In 2017, a report by Mayr and coworkers quantified the electrophilicities of different Michael acceptors.[194] The report showed that a substituent at either the α- or β-position reduces the electrophilicity parameter by a value of approximately 3–5, which correlates to a decrease in the rate constant of the Michael addition by a factor of 10^3–10^5. This suggested that CASFs would be significantly more inert towards conjugate additions compared to ESF or 2-arylethenesulfonyl fluoride. This revelation justified the difficulties faced in achieving conjugate addition to CASFs with various nucleophiles.

3.5.3 Hydrogenation

Hydrogenation of CASFs represents an efficient synthesis of functionalised saturated sulfonyl fluorides without the use of organometallic reagents or going through unstable sulfonyl chloride intermediates. As illustrated in **Scheme 3-10**, hydrogenation of CASF **33h** was realised using balloon pressure hydrogen and palladium on carbon. The conversion, however, was slow to progress and required three balloons of H_2 at the same time (to increase the pressure of hydrogen), 30 mol% of Pd/C and was heated to 40 °C for 24 h. Raising the reaction temperature further was avoided due to safety considerations.



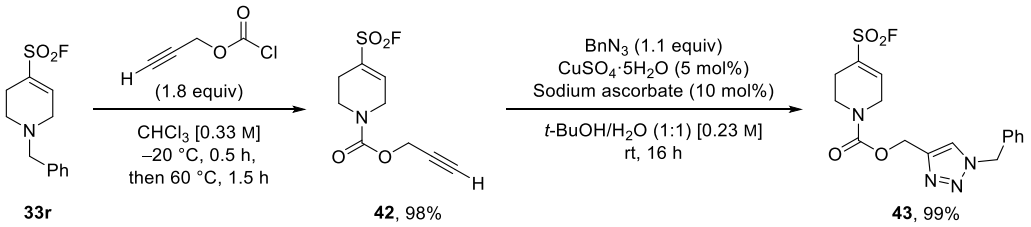
33h **41** ,71%

Scheme 3-10. Pd-catalysed hydrogenation of CASF.

3.5.4 N-Debenzylation / Acylation / CuAAC

In light of Chandrasekaran's work on *N*-dealkylation of tertiary amines,[195] CASF **33r** bearing a tertiary benzyl amine reacted with propagyl chloroformate to yield the propagyl carbamate **42** quantitatively (**Scheme 3-11**). This one-step reaction presents an efficient swap of a *N*-benzyl group to a terminal alkyne, which is a common motif utilised in "click" reactions.

To establish that the terminal alkyne could function as a "click handle" without the interference from the alkenylsulfonyl fluoride, the CASF featuring an alkyne (**42**) was subjected to the "click" copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) conditions.[196] The terminal alkyne underwent the click reaction with benzyl azide using a copper catalyst in a semi-aqueous medium, to produce the triazole adduct **43** in quantitative yield. This signifies the realisation of remote orthogonal functionalisation of a CASF without affecting the alkene or the sulfonyl fluoride moieties, and attests the ability of CASF to tolerate water.

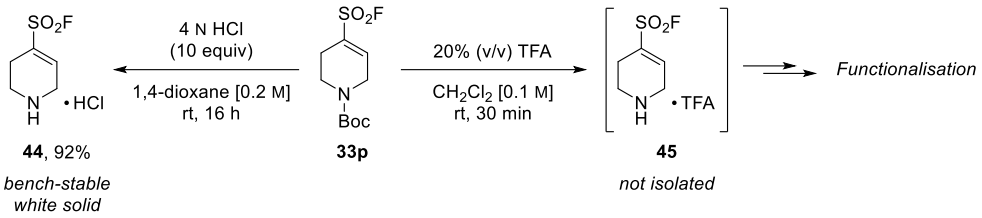


Scheme 3-11. *N*-Debenzylation/acylation and CuAAC of CASF.

3.5.5 N-Deprotection and Functionalisation

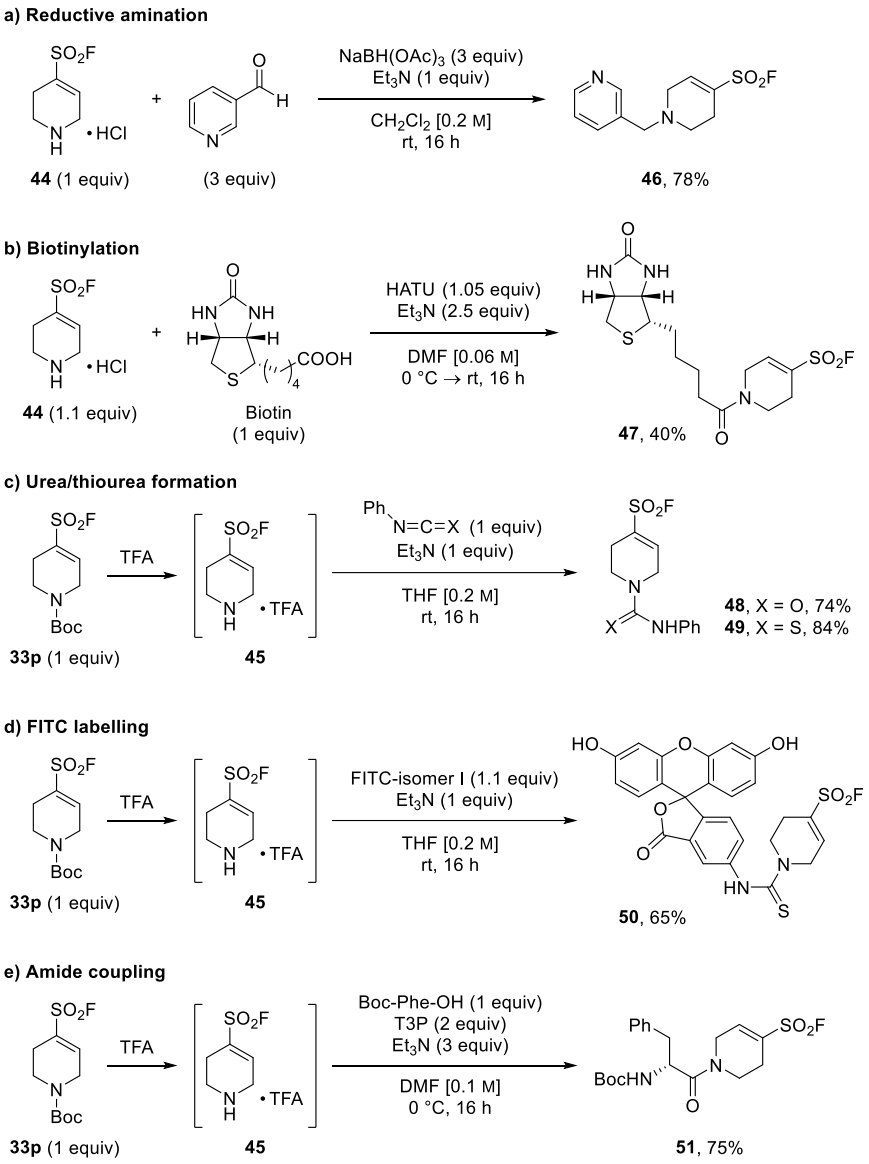
In order to demonstrate the capabilities of derivatisations orthogonal to the alkenylsulfonyl fluoride, the Boc protecting group of CASF **33p** was cleaved to free up the amine for further functionalisation (**Scheme 3-12**). The HCl salt of the free amine **44** was formed in 92% yield as a bench-stable white solid by treating **33p** with

4 N hydrochloric acid in dioxane. An alternate deprotection was achieved using 20% (v/v) trifluoroacetic acid (TFA) in dichloromethane to form the ammonium salt **45**, which could then be used directly in further functionalisation after the solvent and excess acid were removed *in vacuo*.



Scheme 3-12. Boc deprotection of CASF.

The deprotected secondary ammonium salts **44** and **45** could undergo various derivatisations with electrophiles. For instance, **44** underwent reductive amination with nicotinaldehyde in the presence of sodium triacetoxyborohydride to form the tertiary amine **46** in a good 78% yield, which also demonstrated the tolerance of CASF under a reductive environment (**Scheme 3-13a**). Biotin, a carboxylic acid, could be conjugated to **44** using HATU to form the biotinylated product **47** in a moderate 40% yield, which provided a handle for potential pulldown assays with streptavidin (**Scheme 3-13b**). Ammonium salt **45** was able to react with other electrophiles, such as isocyanates or isothiocyanates. Combination with phenyl isocyanate generated urea **48** in 74% yield, whereas reaction with phenyl isothiocyanate yielded thiourea **49** in 84% yield (**Scheme 3-13c**). Such reactivity was then exploited to label the CASF **45** with a fluorophore using fluorescein isothiocyanate (FITC) isomer I, forming the tagged product **50** in a good 65% yield (**Scheme 3-13d**). Furthermore, the amine could be condensed with amino acids using T3P as coupling agent as shown in **Scheme 3-13e**; the TFA salt **45** was coupled to Boc-protected phenylalanine (Boc-Phe-OH), giving the amide **51** in 75% yield.

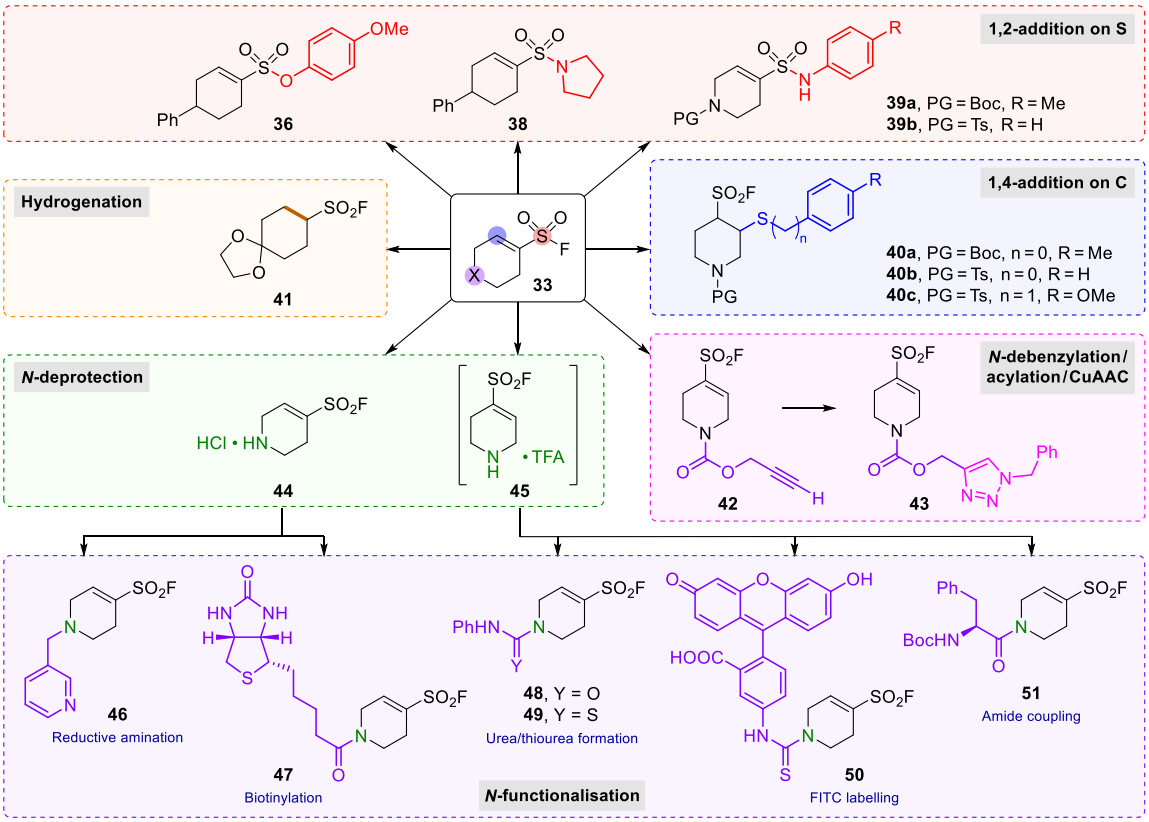


Scheme 3-13. *N*-Functionalisation of CASF **44** and **45**.

Despite being ambiphilic in nature (bearing both nucleophilic and electrophilic sites in the same molecule), the deprotected ammonium salts **44** and **45** demonstrated orthogonality to the alkenylsulfonyl fluoride and underwent the above derivatisations efficiently at either 0 °C or room temperature. For methods that required heat, or the use of strong bases or Lewis acids (such as nucleophilic aromatic substitution (S_NAr), the Buchwald-Hartwig amination and the Chan-Lam coupling), the reactions resulted in complex mixtures. This was attributed to the numerous plausible side reactions between the amine, alkene, sulfonyl fluoride and the reaction partners.

3.6 Project Summary

To conclude, a general and efficient synthesis of cyclic alkenylsulfonyl fluorides was developed using alkenyl triflates, which are readily accessible from the corresponding ketones, a commercially available Pd catalyst, DABSO and NFSI. The good functional group tolerance of the reaction enabled access to structurally diverse CASFs with various functionalities. It was then demonstrated that the different reactive sites could be derivatised in the presence of other reaction handles, including nucleophilic substitution (1,2-addition) at sulfur, conjugate addition (1,4-addition) to the alkene, Pd-catalysed hydrogenation of the olefin, Boc-deprotection, various *N*-functionalisation and a "click" CuAAC reaction. The successful CASF transformations presented in this project are summarised in **Scheme 3-14**.

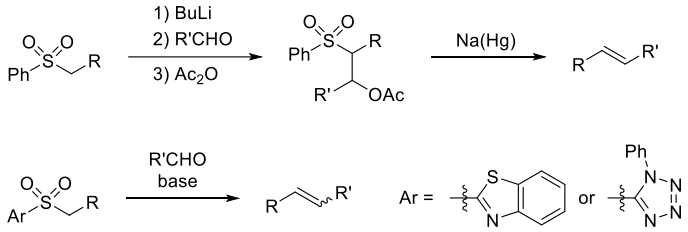


Scheme 3-14. Summary of functionalisation of CASFs.

Chapter 4 Unsymmetrical Diaryl Sulfones (DASF): Cross-Electrophilic Sulfonylative Cross-Coupling

4.1 Aryl Sulfones

Sulfones are a common sulfur-containing functional group containing a C–$S(O)_2$–C motif. Aryl, heteroaryl and alkenyl sulfones see wide applications across organic, medicinal and materials chemistry. For instance, phenyl sulfones are common substrates in the Julia olefination for the preparation of (*E*)-alkenes from aldehydes;[197] benzothiazole or tetrazole sulfones are also used in the modified Julia olefination[198] or the Julia–Kocienski olefination.[199]



Scheme 4-1. Julia olefination and its modifications.

Selected examples of aryl sulfones with pharmaceutical importance are shown in **Figure 4-1**, including Dapsone, which is used for treating leprosy,[200-201] 2-nitrophenyl phenyl sulfone (NPPS) and its derivatives, which are potent inhibitors for HIV-1 reverse transcriptase,[202-203] and bicalutamide (a.k.a. Casodex), an antiandrogen to treat prostate cancer.[204] Furthermore, aryl sulfones also display novel properties in polymer chemistry, such as polyethersulfone (PES), which is a thermoplastic demonstrating high rigidity and heat resistance.[205]

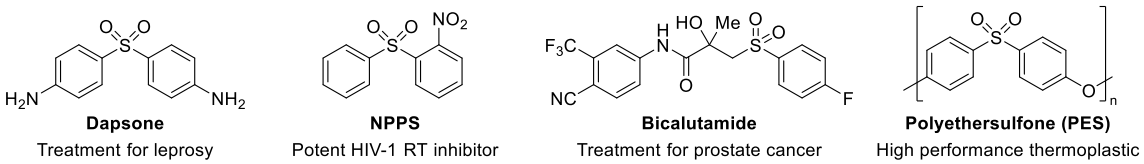
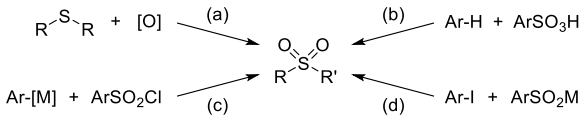


Figure 4-1. Pharmaceuticals and polymer featuring an aryl sulfone moiety.

Among various methods for the preparation of aryl sulfones, the oxidation of the corresponding sulfides represents one of the most straightforward syntheses (eq. a, **Scheme 4-2**),[206-207] yet is often limited by the commercial availability of sulfides, by the functional group tolerance due to the use of strong oxidising agents, e.g. *m*CPBA or hydrogen peroxide, as well as the selectivity between the formation of sulfones and sulfoxides. Another traditional approach to access aryl sulfones is through Friedel-Crafts-type sulfonylation of arenes (eq. b).[208] This method suffers from poor regioselectivity due to the inherent electronic and steric properties of the arene, and the poor conversion of electron-deficient substrates. Alternatively, the combination of organometallic reagents with arylsulfonyl chlorides is another approach to sulfones (eq. c),[209] but displays poor functional group tolerance, and is limited by the availability of reactive sulfonyl chlorides. Finally, recent advancements in transition metal-catalysed sulfonylation of aryl halides with sulfinate salts enables mild and efficient syntheses of aryl sulfones with good functional group tolerance (eq. d).[23, 45, 210-212]



Scheme 4-2. Conventional syntheses of aryl sulfones.

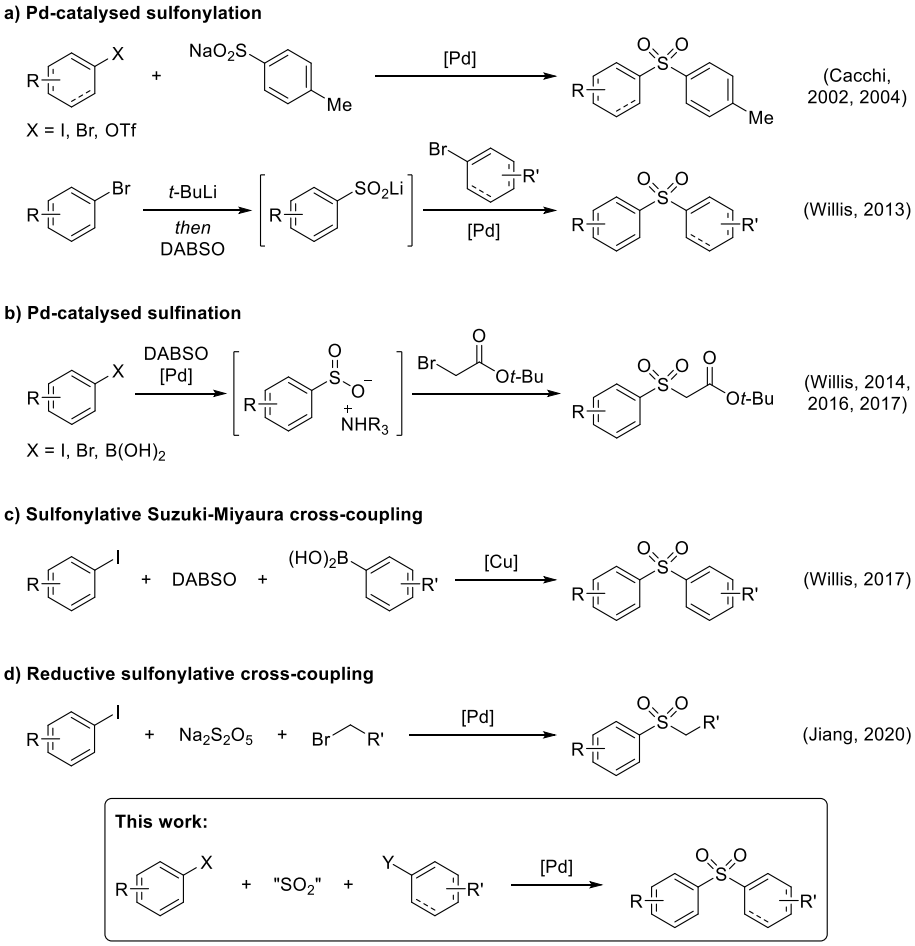
4.2 Project Outline

4.2.1 Previous Work and Origin of the Project

Cacchi and coworkers reported a palladium-catalysed unsymmetrical diary sulfone synthesis from a *p*-toluenesulfinate salt and (hetero)aryl halides or alkenyl triflates in 2002 and 2004 (**Scheme 4-3a**, top eq.).[210-211] As a result of the limited commercial availability of aryl sulfinate salts, Emmett and Willis improved the method in 2013 by generating the sulfinate salt *in-situ* using aryl lithium reagents and DABSO, followed by

the Pd-catalysed sulfonylation (*i.e.* sulfone formation) (**Scheme 4-3a**, bottom eq.).[45] The Willis group later developed Pd-catalysed sulfinations (*i.e.* sulfinate formation) using DABSO and aryl halides[49, 51] or boronic acids,[53] which avoided the use of reactive organometallic reagents (**Scheme 4-3b**). The formation of aryl-alkyl sulfones was achieved through a straightforward nucleophilic substitution (S_N2) between the aryl sulfinates and alkyl bromides. A similar approach was also reported by Toste using a gold(I) catalyst.[71]

In 2017, Chen and Willis developed a sulfonylative Suzuki-Miyaura cross-coupling for the formation of diaryl sulfones from aryl iodides, aryl boronic acids and DABSO with the aid of a copper(I) catalyst (**Scheme 4-3c**).[55] More recently, in 2020, the Jiang laboratory reported a reductive sulfonylative cross-coupling between aryl iodides and



Scheme 4-3. Previous work on sulfination and sulfonylation.

alkyl bromides using sodium metabisulfite ($Na_2S_2O_5$) as the source of sulfur dioxide and over-stoichiometric tin as a reductant. This was found to proceed through a radical mechanism (**Scheme 4-3d**).[213]

Whilst the preparation of sulfones from aryl halides and alkyl halides is well documented, the one-pot synthesis of unsymmetrical **di**aryl **s**ul**f**ones (abbr. **DASF**s) from two different aryl (pseudo)halides has not been reported. Since the formation of aryl sulfinates (sulfination) and their coupling with aryl halides (sulfonylation) have both been achieved independently using palladium catalysis, it was anticipated that a single set of conditions combining both reactions would be viable, thus achieving a one-pot sulfonylative cross-coupling between two electrophiles. With the benefit of the vast availability of aryl halides from commercial sources relative to arylboronic acids or sulfinate salts, we believed that the cross-electrophilic coupling would represent a convenient and attractive strategy for accessing unsymmetrical DASFs.

4.2.2 Project Aims

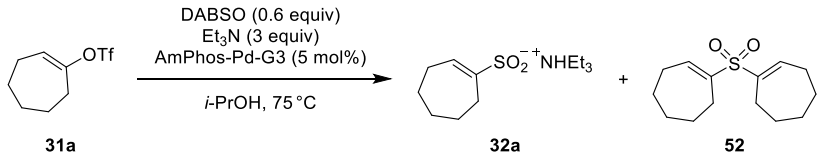
This project aimed to achieve a general synthesis of unsymmetrical diaryl sulfones using two different electrophiles and an SO_2 surrogate. Upon establishing a reaction scope, we planned to study the effect of varying combinations of electrophiles with different leaving groups on the sulfone formation and to investigate the reaction mechanism.

4.3 Initial Investigation

During optimisation of CASF synthesis (see **Chapter 3**), the symmetrical dialkenyl sulfone **52** was observed as the major product when AmPhos-Pd-G3 was used in place of $PdCl_2(AmPhos)_2$. This result represented the sulfonylative coupling between two

electrophiles (two molecules of cycloheptenyl triflate in this case), and this ignited our interest in the concept of sulfonylative cross-electrophilic coupling. Initial investigation into the formation of dicycloheptenyl sulfone showed up to 70% yield of the sulfone was obtained (**Table 4-1**). However, this reactivity was found to be substrate dependent; only cycloheptenyl triflate was converted to sulfone. Alternative alkenyl triflates delivered the corresponding alkenyl sulfinates as the major product instead of dialkenyl sulfones. Furthermore, aryl triflates showed no conversion under the reaction conditions, which demonstrates the potential challenges in accessing a broad scope of unsymmetrical sulfones with this catalytic system as shown in **Table 4-1**.

Table 4-1. Formation of symmetrical dicycloheptenyl sulfone.



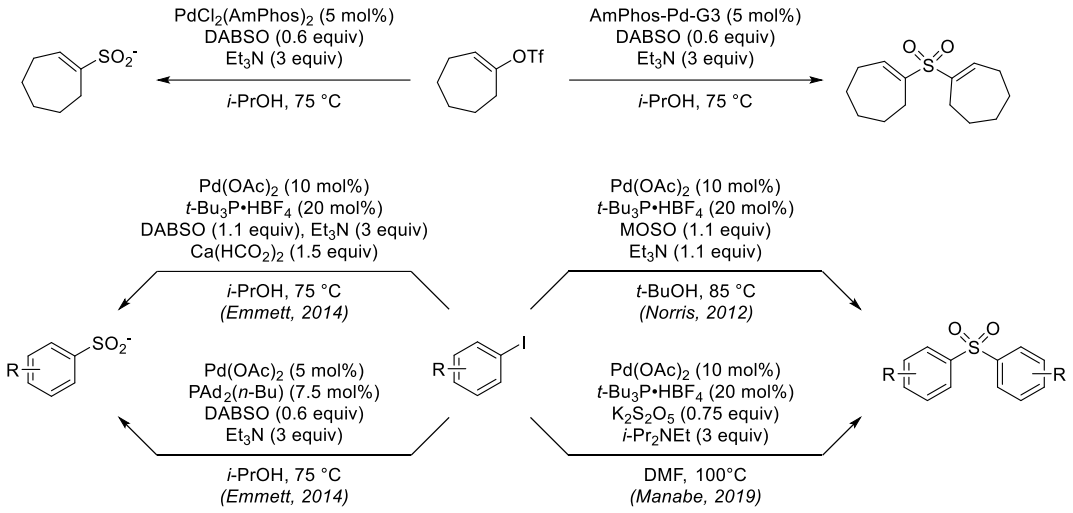
31a **32a** **52**

Entry	[**31a**] (M)	Reaction time	Yield of **32a**[b]	Yield of **52**[b]
1	0.25	1 h	8%	69% (66%)[c]
2	0.15	1 h	15%	59%
3	0.15	2 h	10%	69%
4	0.075	2.5 h	11%	70%

[a] Reaction conditions: Cycloheptenyl triflate **31a** (0.3 mmol, 1.0 equiv), DABSO (0.6 equiv), Et_3N (3.0 equiv), AmPhos-Pd-G3 (5 mol%), *i*-PrOH, 75 °C, 1–2.5 h. [b] HPLC yield. [c] Isolated yield.

Ed Emmett, a previous DPhil student in the Willis group, reported the sulfination of aryl iodides using DABSO, $Pd(OAc)_2$ and CataCXium® A (PAd_2(*n*-Bu)).[51] During the optimisation of this reaction, *t*-$Bu_3P{\cdot}HBF_4$ was also found to be an effective ligand to deliver *p*-tolyl sulfinate in the presence of calcium formate in 71% yield (**Scheme 4-4**).[162]

On the other hand, the same ligand delivered symmetrical diaryl sulfones when morpholine-SO_2 adduct (MOSO) was used as the source of SO_2, with 1.1 equivalents of Et_3N in *t*-BuOH. Ryan Norris, a previous Master's (Part II) student in the Willis group, investigated this reaction and found that DABSO was incompatible with the sulfone formation.[214] Given the similarity in the reaction conditions between the sulfination and the symmetrical sulfone formation, morpholine was thought to be the reductant and drove the selectivity from the formation of sulfinate to diaryl sulfone. In 2019, Manabe *et al.* also reported a similar symmetrical diaryl sulfone synthesis using the same ligand, potassium metabisulfite ($K_2S_2O_5$) as the SO_2 source with an excess of DIPEA.[215]



Scheme 4-4. Reported reactions for sulfinate and sulfone formation.

The proposed mechanism of the homo-coupling for Norris' system is shown in **Figure** 4-2. The aryl halide first undergoes oxidative addition to the active Pd(0) catalyst, followed by SO_2 insertion and ligand substitution to generate the ammonium sulfinate. The Pd(II) complex was reduced by morpholine to regenerate the Pd(0) catalyst (cycle A). Alternatively, after the oxidative addition, the halide of the aryl-palladium species could be substituted by the sulfinate formed *in-situ*, followed by reductive elimination to yield the diaryl sulfone and regenerating the active catalyst (cycle B).

With two competing pathways in a single catalytic system, it was envisioned that the cross coupling between two different electrophiles would be challenging, as the more reactive electrophile would preferentially undergo oxidative addition and be converted into sulfinate. The resulting sulfinate would then react with the aryl-palladium adduct from the more reactive electrophile to form the symmetrical sulfone. A trial experiment adapting Norris's conditions with two different electrophiles (*p*-tolyl triflate and 4-bromobiphenyl) was unsuccessful and did not deliver the desired unsymmetrical sulfone.

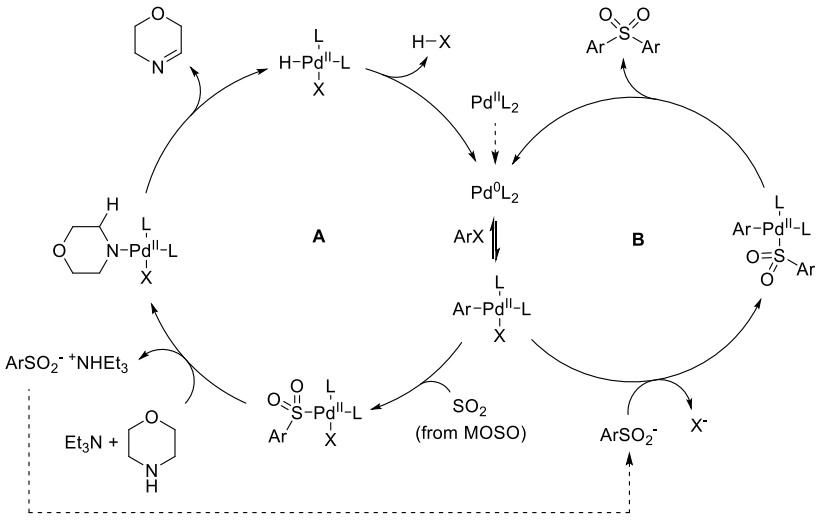


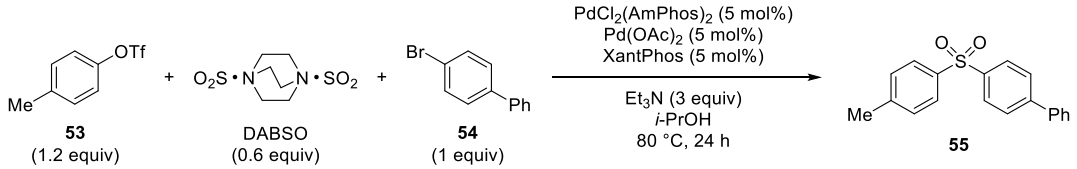
Figure 4-2. Proposed mechanism for symmetrical sulfone formation using MOSO.

With the substantial challenge of achieving the sulfonylative cross-electrophilic coupling using a single catalyst, we thought it would be more practical to adapt a dual-catalyst approach; one catalyst responsible for sulfinate formation and a second for sulfone coupling. While $PdCl_2(AmPhos)_2$ was used for the sulfination of aryl bromides,[49] aryl triflates did not react under the same conditions at 75 °C (**Table 3-5**). On the other hand, both aryl bromides and triflates are known substrates for the palladium-catalysed reaction with aryl sulfinates to form diaryl sulfones when XantPhos was used as the ligand, at an elevated temperature of 120 °C. Given the lower temperature required for sulfination, it was anticipated that when combining the two catalytic systems, aryl bromide would be

preferentially converted into the corresponding sulfinate. When the aryl bromide was fully consumed, the remaining aryl triflate would be the only electrophilic substrate for sulfonylation, hence achieving the cross-coupling.

The study began by using *p*-tolyl triflate (**53**) and 4-bromobiphenyl (**54**) as the substrates, DABSO as the SO_2 source, $PdCl_2(AmPhos)_2$ as the catalyst for sulfination, $Pd(OAc)_2$ and XantPhos for sulfone coupling, triethylamine as the base, isopropanol as the solvent and a temperature of 80 °C, which is just below the boiling point of isopropanol (*bp* 82 °C) and triethylamine (*bp* 89 °C) (**Table 4-2**). This gave a 41% yield by HPLC, of the cross-coupled product (entry 1). Whilst K_3PO_4 and Cs_2CO_3 were used in previously reported sulfonylations,[45, 210-211] the addition of either inorganic base resulted in diminished yields with only trace conversion (entry 2–4 and 6). Tetrabutylammonium chloride, a common additive for sulfonylations between aryl

Table 4-2. Initial optimisation for the synthesis of sulfone **55**.[a]



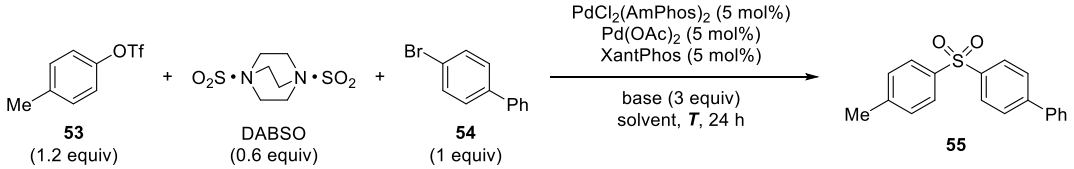
Entry	Variation	Yield[b]
1	as above	41%
2	K_3PO_4 (1.5 equiv) added	7%
3	K_3PO_4 (1.5 equiv) added, 100 °C	5%
4	Cs_2CO_3 (1.5 equiv) added	5%
5	*n*-Bu_4NCl (1.2 equiv) added	39%
6	Cs_2CO_3 (1.5 equiv) and *n*-Bu_4NCl (1.2 equiv) added	3%
7	*t*-Bu-XantPhos instead of XantPhos	3%
8	3-Pentanol instead of *i*-PrOH	28%
9	DIPEA instead of Et_3N	38%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.2 equiv), aryl bromide **54** (1.0 equiv), DABSO (0.6 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), $Pd(OAc)_2$ (5 mol%), XantPhos (5 mol%), Et_3N (3.0 equiv), *i*-PrOH [0.2 M], 80 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard.

halides and sulfinates, gave no improvement in the yield (entry 5–6). By replacing the two phenyl groups on XantPhos with *tert*-butyl groups, only trace amount of product was observed, suggesting the significance of ligand in the sulfonylation step (entry 7). Switching the solvent to 3-pentanol (*bp* 115 °C), a higher boiling alternative to isopropanol, gave a lower yield of 28%; and substituting Et_3N with DIPEA (*bp* 127 °C) resulted in a comparable 38% yield.

As unreacted aryl triflate **53** was observed after overnight heating, the reaction temperature was raised using either a sealed tube with isopropanol or the higher boiling 3-pentanol (**Table 4-3**) to drive the reaction to completion. As Et_3N and DIPEA gave similar yields (entry 1–2), the higher boiling DIPEA was chosen for further investigation to avoid potential complications due to vaporisation of the base. At 90 °C, both **53** and **54** were fully consumed in 24 hours in either isopropanol or 3-pentanol, but gave no improvement in yields (entry 3–4). The yield dropped slightly when the reaction was heated at 100 °C (entry 5–6). Therefore, further optimisation was performed at 90 °C.

Table 4-3. Optimisation at various temperatures.[a]

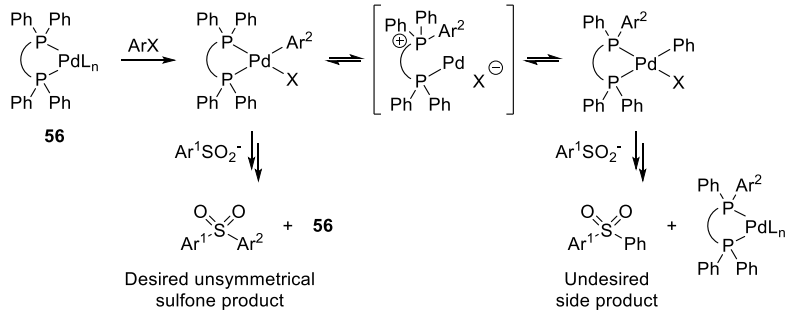


Entry	Base	Solvent	*T*	Yield[b]
1	Et_3N	*i*-PrOH	80 °C	41%
2	DIPEA	*i*-PrOH	80 °C	38%
3	DIPEA	*i*-PrOH	90 °C	39%
4	DIPEA	3-Pentanol	90 °C	40%
5	DIPEA	*i*-PrOH	100 °C	36%
6	DIPEA	3-Pentanol	100 °C	35%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.2 equiv), aryl bromide **54** (1.0 equiv), DABSO (0.6 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), $Pd(OAc)_2$ (5 mol%), XantPhos (5 mol%), Et_3N or DIPEA (3.0 equiv), *i*-PrOH or 3-pentanol [0.2 M], temperature *T*, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard.

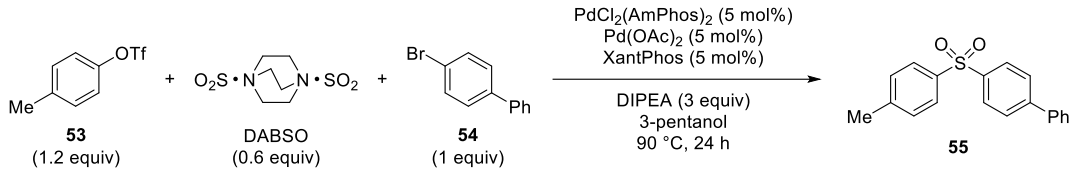
Further optimisation (**Table 4-4**) revealed that excess DABSO was detrimental to the formation of sulfone **55** (entry 2); and replacing DABSO with the morpholine analogue, MOSO, gave a slightly improved yield of 45% (entry 3). Increasing the amount of the aryl triflate **53** from 1.2 equiv to 2.0 equiv raised the yield to 51% (entry 4). Using the Buchwald palladacycle AmPhos-Pd-G3 instead of the precatalyst $PdCl_2(AmPhos)_2$ gave a similar yield (entry 5). Upon replacement of $PdCl_2(AmPhos)_2$ with 5 mol% of AmPhos and 5 mol% of $Pd(OAc)_2$ (10 mol% in total), comparable yields were obtained (entry 6–7).

A complex HPLC chromatogram was recorded for entry 1 in **Table 4-4**, with a few unidentified side products, and we believed that XantPhos contributed to the formation of some of them. The palladium-bound electron-rich ligand was reported to undergo an undesirable aryl-phenyl exchange as a side reaction (**Scheme 4-5**).[45, 216-218] An electron-deficient analogue of XantPhos with the two phenyl groups replaced by 3,5-bis(trifluoromethyl)-phenyl groups (*bis*-CF_3-XantPhos, **L1**) was used to suppress the side reaction in Emmett's Pd-catalysed sulfonylation. Using this analogue **L1** instead of the ordinary XantPhos gave a cleaner reaction profile with fewer side products, but did not significantly improve the yield, with a similar yield of 41% (entry 8).



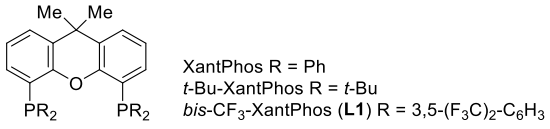
Scheme 4-5. Aryl-phenyl exchange of Pd-bound XantPhos ligand.

Table 4-4. Further optimisation for the formation of sulfone **55**.[a]



Entry	Variation	Yield[b]
1	as above	40%
2	1.2 equiv of DABSO	4%
3	MOSO (1.2 equiv) instead of DABSO	45%
4	2.0 equiv of aryl triflate **53**	51%
5	AmPhos-Pd-G3 instead of $PdCl_2(AmPhos)_2$	45%
6	Pd(OAc) (10 mol%), AmPhos (5 mol%), XantPhos (5 mol%)	39%
7	Pd(OAc) (10 mol%), AmPhos (10 mol%), XantPhos (5 mol%)	38%
8	Pd(OAc) (10 mol%), AmPhos (5 mol%), *bis*-CF_3-XantPhos (5 mol%)	41%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.2 equiv), aryl bromide **54** (1.0 equiv), DABSO (0.6 equiv), $PdCl_2(AmPhos)_2$ (5 mol%), $Pd(OAc)_2$ (5 mol%), XantPhos (5 mol%), DIPEA (3.0 equiv), 3-pentanol [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard.



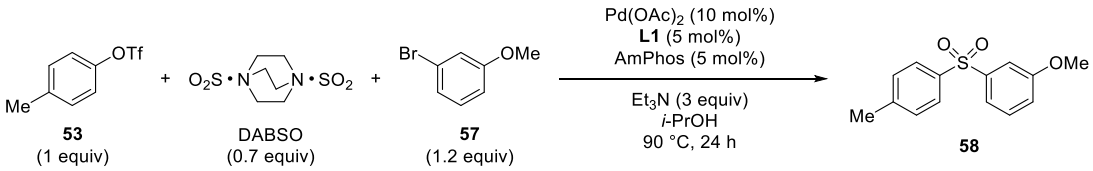
Given the similar polarity of phenyl, tolyl and biphenyl groups, separation of the unsymmetrical sulfone product **55** from other side products (including the symmetrical sulfones and those resulting from aryl-phenyl exchange with XantPhos) was unsuccessful using column chromatography techniques. As a result, a different combination of substrates was needed for further investigation.

4.4 Optimisation of Reaction Conditions

In light of the initial sulfonylative coupling results discussed above, *p*-tolyl triflate **53** and *m*-bromoanisole **57** were chosen to be the substrates. Investigation began with a slight excess of the bromide (1.2 equiv), DABSO (0.7 equiv), 10 mol% of $Pd(OAc)_2$ with

5 mol% of *bis*-CF_3-XantPhos (**L1**) and AmPhos each, and 3 equiv of Et_3N in isopropanol, sealed under nitrogen in a reaction tube, and heated to 90 °C, resulting in 13% yield (**Table 4-5**, entry 1). Using a slight excess of triflate gave a similar result (entry 2). Since AmPhos is air-sensitive and would degrade slowly during storage, the combination of $Pd(OAc)_2$ and AmPhos was replaced by the air-stable AmPhos-Pd-G3 precatalyst for consistency, which gave a similar HPLC yield of 15% and an isolated yield of 13% (entry 3). Therefore, the combination of $Pd(OAc)_2$ (5 mol%), **L1** (5 mol%) and AmPhos-Pd-G3 (5 mol%) was employed for further optimisation. Furthermore, substituting **L1** with XantPhos resulted in a similar yield, but produced a more complex mixture, which was consistent with the results discussed in the previous section (entry 4).

Table 4-5. Initial optimisation for the synthesis of sulfone **58**.[a]



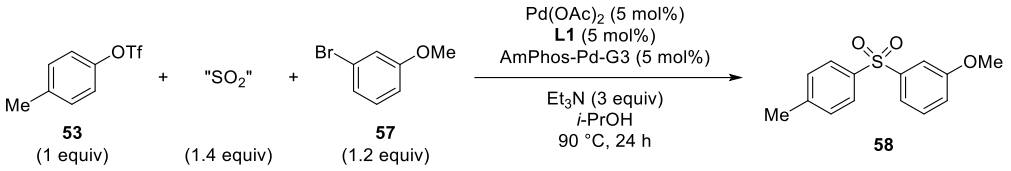
Entry	Variation	Yield[b]
1	as above	13%
2	ArBr (1 equiv), ArOTf (1.2 equiv), DABSO (0.6 equiv)	13%
3	**$Pd(OAc)_2$ (5 mol%), AmPhos-Pd-G3 (5 mol%) instead of AmPhos**	**15% (13%)[c]**
4	$Pd(OAc)_2$ (5 mol%), AmPhos-Pd-G3 (5 mol%) instead of AmPhos, XantPhos (5 mol%) instead of *bis*-CF_3-XantPhos (**L1**)	16%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), DABSO (0.7 equiv), $Pd(OAc)_2$ (10 mol%), **L1** (5 mol%), AmPhos (5 mol%), Et_3N (3.0 equiv), *i*-PrOH [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard. [c] Isolated yield.

Since we demonstrated in our initial study and previous studies that the source of SO_2 played a key role in sulfonylation, various SO_2 surrogates were examined (**Table 4-6**). Amine-SO_2 Lewis adducts, such as NMSO (*N*-methylmorpholine) and TIMSO (*N*-methylpyrrolidine) gave similar yields to DABSO, but interestingly, the morpholine-

SO_2 adduct MOSO did not give any conversion (entry 1–4). For inorganic SO_2 surrogates, only potassium metabisulfite yielded a trace amount of product (entry 5), and the sodium salts of metabisulfite and dithionite gave no conversion (entry 6–7).

Table 4-6. Optimisation of DASF formation with various SO_2 sources.[a]

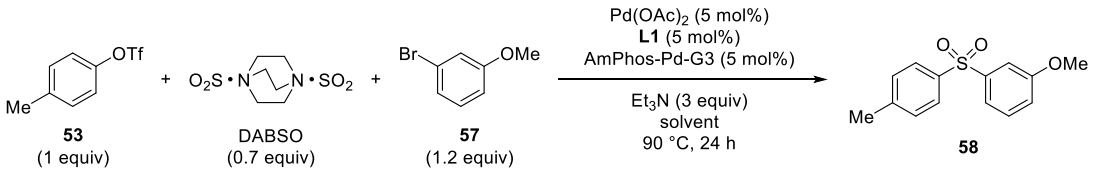


Entry	SO_2 source	Yield[b]
1	DABSO[c]	15%
2	MOSO	0%
3	NMSO	15%
4	TIMSO	14%
5	$K_2S_2O_5$	5%
6	$Na_2S_2O_5$	0%
7	$Na_2S_2O_4$	0%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), SO_2 source (1.4 equiv), $Pd(OAc)_2$ (5 mol%), **L1** (5 mol%), AmPhos-Pd-G3 (5 mol%), Et_3N (3.0 equiv), *i*-PrOH [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard. [c] 0.7 equiv.

Next, different solvents were evaluated (**Table 4-7**). While isopropanol gave a 15% yield (entry 1), other alcoholic solvents, including *n*-BuOH (a primary alcohol), 3-pentanol (a secondary alcohol) and *t*-BuOH (a tertiary alcohol) gave lower yields of 10–11% (entry 2–4). Polar aprotic solvent such as DMF yielded no product (entry 5). Among the three nonpolar solvents tested, *viz.* 1,4-dioxane, DCE and toluene, only 1,4-dioxane gave a trace amount of unsymmetrical sulfone **58** (entry 6–8). These results suggested the importance of alcoholic solvents for the process, and isopropanol remained the best choice of solvent despite the need of using a sealed tube to heat beyond its boiling point.

Table 4-7. Optimisation of DASF formation with various solvents.[a]



Entry	Solvent	Yield[b]
1	*i*-PrOH	15%
2	*n*-BuOH	10%
3	3-Pentanol	11%
4	*t*-BuOH	10%
5	DMF	0%
6	1,4-Dioxane	<5%
7	DCE	0%
8	Toluene	0%

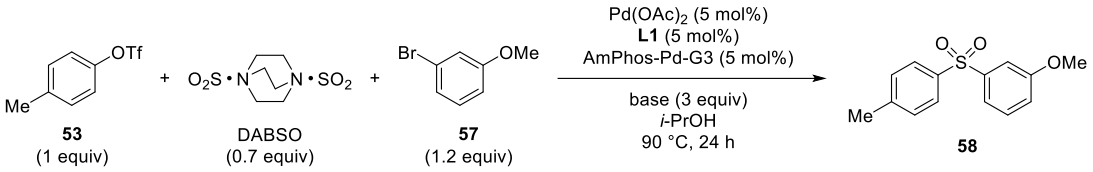
[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), DABSO (0.7 equiv), $Pd(OAc)_2$ (5 mol%), **L1** (5 mol%), AmPhos-Pd-G3 (5 mol%), Et_3N (3.0 equiv), solvent [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard.

We then explored the impact of different bases on the sulfone formation (**Table 4-8**). Tertiary amines such as Et_3N, DIPEA and Cy_2NMe gave similar yields (entry 1–2, 4). While Et_3N with MOSO gave no conversion (see above), using DIPEA with MOSO resulted in 7% yield, yet still lower than that obtained using DABSO (entry 3).

Morpholine, a secondary amine, did not give any conversion (entry 5), suggesting its presence was detrimental to the reaction when MOSO was employed. Lastly, no conversion was recorded with inorganic bases such as potassium phosphate and caesium carbonate (entry 6–7).

In the current dual-catalytic system, AmPhos-Pd-G3 contributed to the Pd-catalysed sulfination, and the Pd/**L1** system was responsible for the subsequent sulfonylation. Different palladium sources were screened for the Pd/**L1** system (**Table 4-9**), yet all the

Table 4-8. Optimisation of DASF formation with various bases.[a]



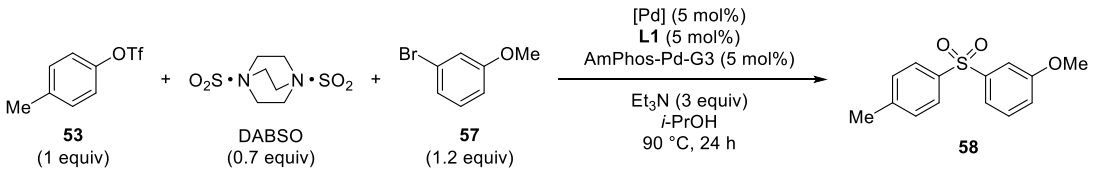
Entry	Base	Yield[b]
1	Et_3N	15%
2	DIPEA	15%
3	DIPEA[c]	7%
4	Cy_2NMe	13%
5	Morpholine	0%
6	K_3PO_4	0%
7	Cs_2CO_3	0%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), DABSO (0.7 equiv), $Pd(OAc)_2$ (5 mol%), **L1** (5 mol%), AmPhos-Pd-G3 (5 mol%), base (3.0 equiv), *i*-PrOH [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard. [c] MOSO (1.4 equiv) was used in place of DABSO.

selected Pd salts gave similar yields between 14% and 16%, suggesting the role of the counterion in the Pd salt was insignificant at this point of study.

Following the results from the palladium screening, the effect of varying the ratio of the two ligands was investigated (**Table 4-10**). Since the counterion was found to be unimportant, only one palladium source was used in this study (10 mol% of $Pd(OAc)_2$), and we varied the ratio between AmPhos and ligand **L1**. When the ratio was 1:1, 15% yield was recorded (entry 1). When using 7.5 mol% of **L1** and 2.5 mol% of AmPhos, the yield dropped to 12%, suggesting the reduced efficiency of the sulfination step (entry 2). Conversely, when using 2.5 mol% of **L1** and 7.5 mol% of AmPhos, only trace product was detected, with full consumption of aryl bromide (entry 3). This implied that the sulfonylation step was ineffective with only 2.5 mol% of active Pd/**L1** catalyst. When XantPhos was employed instead of **L1**, unsymmetrical sulfone product **58** was formed in

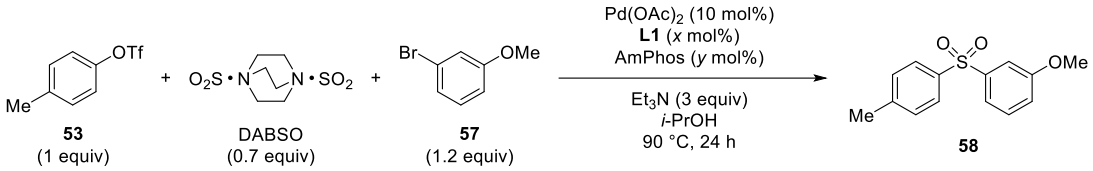
Table 4-9. Optimisation of DASF formation with various Pd sources.[a]



Entry	Pd source	Yield[b]
1	$Pd(OAc)_2$	15%
2	$Pd_2(dba)_3$	14%
3	$PdCl_2$	15%
4	$PdBr_2$	14%
5	$Pd(TFA)_2$	16%
6	$Pd(CH_3CN)_4(BF_4)_2$	15%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), DABSO (0.7 equiv), Pd source (5 mol%), **L1** (5 mol%), AmPhos-Pd-G3 (5 mol%), Et_3N (3.0 equiv), *i*-PrOH [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard.

Table 4-10. Optimisation of DASF formation with different ratios between ligands.[a]



Entry	**L1** (*x* mol%)	AmPhos (*y* mol%)	**L1**/AmPhos	Yield[b]
1	5	5	1:1	15%
2	7.5	2.5	3:1	12%
3	2.5	7.5	1:3	<5%
4[c]	5	5	1:1	16%
5[c]	2.5	7.5	1:3	14%
6[c]	1	9	1:9	12%

[a] Reaction conditions: Aryl triflate **53** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), DABSO (0.7 equiv), $Pd(OAc)_2$ (10 mol%), **L1** (*x* mol%), AmPhos (*y* mol%), Et_3N (3.0 equiv), *i*-PrOH [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard. [c] XantPhos was used in place of **L1**.

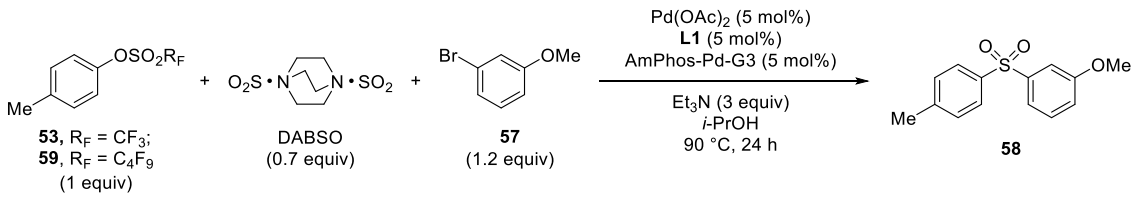
a comparable yield when the loading of XantPhos was reduced to 1 mol% (entry 4–6). This suggested that XantPhos made a more active catalyst with higher turnover numbers in spite of the undesirable aryl-phenyl transfer exchange side reaction.

As shown in **Table 4-11**, the reaction was further examined under different conditions. By increasing the amount of aryl bromide **57** to 2.0 equiv and DABSO to 1.2 equiv (*i.e.* 0.6 equiv with respect to aryl bromide), with complete consumption of the aryl bromide (which theoretically gave 2 equivalents of sulfinate), the yield of unsymmetrical sulfone **58** remained the same (entry 1–2). On the other hand, when using aryl bromide **57** as the limiting reagent and 2.0 equiv of aryl triflate **53**, the yield almost doubled to 26% (entry 3). With full consumption of aryl bromide in both cases, this implied that the sulfonylation between aryl sulfinate and aryl triflate was inefficient, and was therefore the bottleneck for the overall conversion to the desired sulfone. By changing the order of addition of reagents, we found that when the reaction was heated at 90 °C without *m*-bromoanisole (**57**) for 15 min, the reaction turned black without any conversion, and after the addition of the aryl bromide, no conversion was recorded either (entry 4).

Furthermore, using an aryl nonaflate in place of triflate gave a slightly higher yield of 18% (entry 5). In order to understand the reaction better, several control experiments were conducted. When *p*-tolyl nonaflate (**59**) was used in the presence of DABSO, Et_3N and AmPhos-Pd-G3, but without aryl bromide **57**, $Pd(OAc)_2$ and **L1**, no conversion was recorded, proving aryl nonaflates were not substrates for the Pd-catalysed sulfination (entry 6). When both *p*-tolyl nonaflate (**59**) and *m*-bromoanisole (**57**) were employed in the absence of $Pd(OAc)_2$ and **L1**, *i.e.* without the sulfonylation system, unsurprisingly, no sulfone product was observed (entry 7). Only aryl bromide was fully converted into sulfinate while aryl nonaflate remained unreacted. This proved that the presence of aryl nonaflate did not interfere with the sulfination of aryl bromide.

Finally, having both aryl nonaflate **59** and bromide **57** in the pot, but without AmPhos-Pd-G3, *i.e.* without the sulfination system, a complex mixture was obtained with trace amounts of the unsymmetrical sulfone **58** formed (entry 8). Symmetrical sulfones and sulfinates of both arenes were also observed. This result suggested the Pd/**L1** system catalysed not only sulfonylation, but also the sulfination of both the aryl nonaflate and the bromide in low yields. This accounted for the presence of the bitolyl sulfone in nearly all of the previous transformations; the tolyl triflate (or nonaflate in this case) was converted into sulfinate by Pd/**L1** (or Pd/XantPhos) system, which was then coupled with tolyl triflate using the same catalytic system. A more selective catalyst for sulfonylation is therefore needed.

Table 4-11. Further optimisation for the synthesis of sulfone **58**.[a]



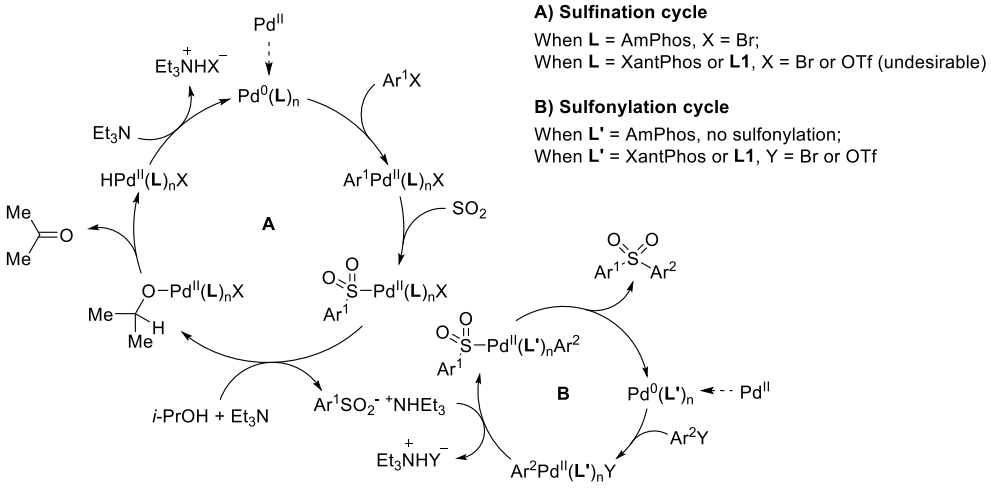
Entry	R_F	Variation	Yield[b]
1	CF_3	as above	15%
2	CF_3	ArBr (2.0 equiv), DABSO (1.2 equiv)	15%
3	CF_3	ArBr (1.0 equiv), ArOTf (2 equiv)	26%
4	CF_3	Reaction stirred for 15 min at 90 °C before adding ArBr	0%
5	C_4F_9	as above	18%
6	C_4F_9	without ArBr, $Pd(OAc)_2$ and **L1**	0%
7	C_4F_9	without $Pd(OAc)_2$ and **L1**	0%
8	C_4F_9	without AmPhos-Pd-G3	<5%

[a] Reaction conditions: Aryl triflate **53** or nonaflate **59** (0.2 mmol, 1.0 equiv), aryl bromide **57** (1.2 equiv), DABSO (0.7 equiv), $Pd(OAc)_2$ (5 mol%), **L1** (5 mol%), AmPhos-Pd-G3 (5 mol%), Et_3N (3.0 equiv), *i*-PrOH [0.2 M], 90 °C, 24 h. [b] Yield determined by HPLC against acetophenone as internal standard.

4.5 Proposed Mechanism

One plausible mechanism for the aforementioned dual-catalytic system is presented in **Scheme 4-6**. It was proposed that in the sulfination step (cycle A), the first electrophile (Ar^1X) undergoes oxidative addition to the first Pd(0) catalyst, followed by SO_2 insertion. Substitution by isopropanol released the aryl sulfinate. The Pd(II) complex was then reduced by the combination of isopropanol and triethylamine, regenerating the active Pd(0) species. The second electrophile (Ar^2Y) underwent oxidative addition to another Pd(0) catalyst for sulfonylation (cycle B). The leaving group was then substituted by the aryl sulfinate generated *in-situ* from cycle A to form an aryl-palladium-aryl sulfinate species. This was followed by reductive elimination to form the diaryl sulfone product and regenerating the Pd(0) catalyst.

From the evidence shown in **Table 4-11**, Pd/AmPhos only took part in cycle A, *i.e.* the sulfination cycle, and did not contribute to cycle B, *i.e.* the sulfonylation cycle, with aryl bromide being its substrate but not aryl triflate or nonaflate. The palladium catalyst ligated by XantPhos or *bis*-CF_3-XantPhos could take part in both cycles; and aryl bromide, triflate and nonaflate were all substrates for this catalyst in both steps.



Scheme 4-6. Proposed mechanism for the dual-catalytic sulfonylative coupling.

4.6 Project Summary and Outlook

Despite a general reaction protocol has yet to be established, it was envisaged that this project remained captivating and the work presented above provided useful information about the dual-catalytic approach. In particular, the Pd/AmPhos system selectively and efficiently converting aryl bromides into sulfinates in the presence of another aryl triflate or nonaflate was a promising finding.

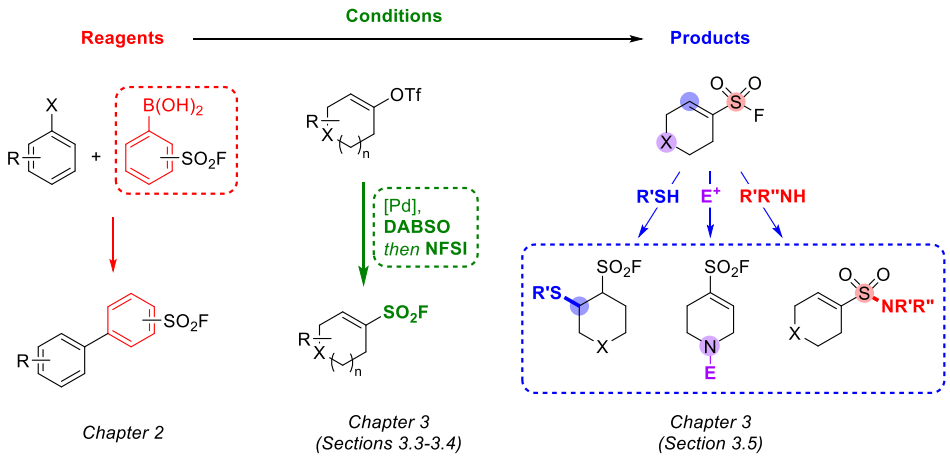
With the poor selectivity of XantPhos and *bis*-CF_3-XantPhos to perform sulfonylation, it was envisioned that modification to these ligands or the discovery of another class of ligands would enable accessing a catalyst that selectively catalyses sulfonylation, but not sulfination of the substrate. The catalyst would ideally be more selective towards certain electrophiles, such as aryl triflates or nonaflates. Alternatively, substrate selectivity may be promoted kinetically if the rate of the Pd/AmPhos-catalysed sulfination is significantly faster than the subsequent sulfonylation.

In conclusion, the one-pot three-component sulfonylative cross-coupling between two different electrophiles and SO_2 represented an attractive approach to access unsymmetrical diaryl sulfones with readily available starting materials. Despite the low yields obtained at this stage, results presented in this Chapter proved the feasibility of achieving the cross-electrophilic coupling using a dual-catalytic approach. A more extensive optimisation is needed in order to deliver a useful and efficient synthetic methodology, and the findings reported here would provide the foundation for further investigation.

Chapter 5 Conclusion and Future Work

Since the first report in the utilisation of DABSO for chemical synthesis by the Willis group, the employment of amine-sulfur dioxide Lewis adducts has enabled convenient access to the sulfonyl (–SO_2–) moiety without the need of using SO_2 gas. This has also opened up several branches of research in our group, such as the desulfinative cross-coupling of heteroaromatics,[65-67] and the syntheses of aza-analogues of sulfinic and sulfonic acid derivatives.[219-220]

The work presented in this thesis has demonstrated different approaches to the synthesis of sulfonyl fluorides. This includes the preparation of phenylboronic acids substituted with sulfonyl fluorides (BASFs), and their use as the nucleophilic substrates in metal catalysis, as elaborated in **Chapter 2**. Next, the synthesis of cyclic alkenylsulfonyl fluorides (CASFs) through the Pd-catalysed sulfination using DABSO and subsequent electrophilic fluorination was presented in **Chapter 3**. These sulfonyl fluorides with various reactive sites are considered to be compact multifunctional reagents. Their orthogonal reactivities were then demonstrated, leading to structurally diverse sulfonyl fluorides and sulfonic acid derivatives.



Scheme 5-1. Summary of different routes to sulfonyl fluorides presented in this thesis.

During the optimisation of CASF synthesis, we observed the sulfonylative homo-coupling of the substrate. This led us to the investigation of the cross-electrophilic sulfonylative cross-coupling for the formation of diary sulfones (DASFs). As discussed in **Chapter 4**, preliminary results attested the feasibility of employing a dual catalytic system to form an aryl sulfinate *in-situ*, followed by its coupling with a second electrophile. We expected a general and convenient synthesis could be established upon more extensive optimisation.

On the other hand, sulfur(VI) fluorides continue to attract interest and attention in chemical biology.[85-88] The chemical synthesis of biologically relevant sulfonyl fluorides, fluorosulfates, sulfamoyl fluorides, and their mono- or diaza analogues would allow establishing the structure-activity relationships (SAR) of these modified protein substrates, leading to their potential applications as covalent inhibitors or molecular probes. A collaborative project on the synthesis of fluorosulfonyl PRMT1 inhibitors is presented in the **Appendix**.

Chapter 6 Experimental Data and Procedures

6.1 General Considerations

Chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Fluorochem or Acros and used without further purification, except TMSCl which was distilled and NBS which was recrystalised from hot water prior to use, and DABSO which was prepared by literature method.[38] $PdCl_2(AmPhos)_2$ pre-catalyst (dichlorobis[di-*tert*-butyl(4-dimethylamino-phenyl)phosphine]palladium(II), CAS# 887919-35-9) was purchased from Alfa Aesar. Solvents were purchased from Sigma Aldrich, Fisher Scientific or Rathburn and used without further purification, with the exception of isopropanol (IPA) which was distilled from Drierite® (with indicator, 8 mesh) onto 4 Å molecular sieves which had been activated by heating under vacuum (0.1 mbar) at 250 °C for 12 h. "Petroleum ether" or "petrol" refers to the fraction of petroleum ether boiling in the range 40–60 °C.

Reactions were performed with continuous magnetic stirring, under an atmosphere of nitrogen (passed through a Drierite® filled tube), unless otherwise specified, all glassware was dried in an oven (150 °C, overnight) and allowed to cool under a flow of nitrogen prior to use. "Reaction tube" refers to a 10 mL CEM microwave reaction vial. Cooling between –20 °C and –78 °C was achieved using a dry ice/acetone bath. Flash column Chromatography was performed using Fluorochem Silicagel 60Å 40-63μ (particle size 0.040–0.063 nm) with the indicated eluents. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF254 pre-coated aluminum backed sheets and visualised either by UV fluorescence (254 nm) and/or staining with potassium permanganate solution.

NMR spectra were recorded, unless specified, at ambient temperature on a Bruker AVIIIHD 400 MHz or AVII 500 MHz spectrometer. Proton-decoupled spectra are denoted as $\{^1H\}$. Chemical shifts (δ) are reported in part per million (ppm) and referenced to the residual solvent peak(s). Coupling constants (*J*) are reported in Hertz (Hz). Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC and comparison with spectra of related compounds. Signal multiplicity are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br., broad; app., apparent.

Melting points were measured on a Leica Gallen III hot-stage microscope. Low resolution mass spectrometry (LRMS) was performed on a Fisons Platform spectrometer (ESI). High resolution mass spectrometry (HRMS) was performed *via* atmospheric pressure chemical ionisation (APCI), electron ionisation (EI) or electrospray ionisation (ESI) sources. *m/z* ratios are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula. Infrared (IR) spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer with an internal range of 600–4000 cm^{-1}. Optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter at 589 nm, 25 °C. $[\alpha]_D^T$ is expressed in deg cm^3 g^{-1} dm^{-1} and c is expressed in g/100 cm^3. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Dionex P680 chromatograph with a Dionex UVD170U detector (Daicel Chiralpak IC column).

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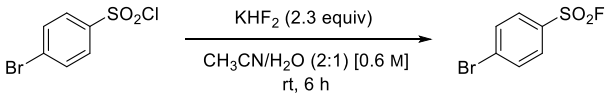
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6.2.1 Preparation of BASFs

General Procedure A: Synthesis of bromoarylsulfonyl fluorides as from the corresponding sulfonyl chlorides as exemplified by the preparation of 4-bromobenzenesulfonyl fluoride (15a)



To a solution of KHF_2 (7.0 g, 90 mmol, 2.3 equiv) in deionized water (20 mL) was added a solution of 4-bromobenzenesulfonyl chloride **14a** (10.0 g, 39.1 mmol, 1.0 equiv) in CH_3CN (40 mL). The reaction was stirred at ambient temperature for 24 h. The two phases were separated and the aqueous layer was extracted with EtOAc for three times. The combined organic extract was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the *sulfonyl fluoride* **15a** as a white solid (9.16 g, 98%);

mp 66–67 °C (EtOAc);

R_f 0.46 (10% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 2H, 2 × SCC*H*), 7.79 (d, *J* = 8.8 Hz, 2H, 2 × BrCC*H*);

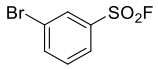
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.3, 132.1 (d, $^2J_{CF}$ = 25.6 Hz), 131.5, 130.0;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.4;

IR ν_{max} (neat)/cm^{-1} 3097, 1574, 1406, 1393, 1211, 825, 779, 736;

HRMS (EI$^+$) *m*/*z* calc. for $C_6H_4{}^{79}BrFO_2S^+$ $[M]^+$ 237.9094, found 237.9092.

3-Bromobenzenesulfonyl fluoride (15b)



Prepared according to General Procedure A using 3-bromobenzenesulfonyl chloride (2.0 g, 7.8 mmol, 1.0 equiv) and KHF_2 (1.4 g, 18 mmol, 2.3 equiv) to afford the corresponding *sulfonyl fluoride* **15b** as a pale yellow oil (1.78 g, 99%);

R_f 0.38 (10% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, *J* = 1.9 Hz, 1H, SCC*H*CBr), 7.98–7.94 (m, 1H, SCC*H*CH), 7.93–7.89 (m, 1H, BrCC*H*CH), 7.53 (td, *J* = 8.0, 1.1 Hz, 1H, SCCHC*H*);

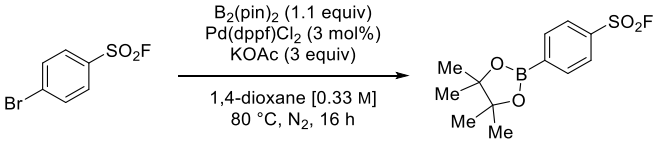
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.8, 134.8 (d, $^2J_{CF}$ = 25.8 Hz), 134.6, 131.4, 131.3, 127.1, 123.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.3;

IR ν_{max} (neat)/cm^{-1} 3091, 1410, 1209, 801, 786, 747;

HRMS (EI$^+$) *m*/*z* calc. for $C_6H_4{}^{79}BrFO_2S^+$ $[M]^+$ 237.9094, found 237.9077.

General Procedure B: Synthesis of benzenesulfonyl fluoride boronic acid pinacol esters from bromoarylsulfonyl fluoride as exemplified by the preparation of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (16a)



To a round bottom flask was charged 4-bromophenylsulfonyl fluoride **15a** (4.78 g, 20.0 mmol, 1.0 equiv), $B_2(pin)_2$ (5.59 g, 22.0 mmol, 1.1 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.49 g, 0.60 mmol, 3 mol%) and KOAc (5.88 g, 60.0 mmol, 3.0 equiv), evacuated and back-filled with N_2 for three times. Degassed anhydrous 1,4-dioxane (60 mL) was added and the reaction was stirred at 80 °C for 16 h, which was then cooled down to ambient temperature, concentrated *in vacuo*. The mixture was diluted with EtOAc, washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10–30% EtOAc in petrol) (see *note*), affording the *sulfonyl fluoride* **16a** as a white solid (5.06 g, 88%);

Alternatively, sulfonyl fluoride **2a** was prepared from 4-bromophenylboronic acid pinacol ester with Pd catalyst, DABSO and NFSI (Refer to General Procedure C).

mp 129–130 °C (Et_2O);

R_f 0.23 (10% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H, 2 × SCC*H*), 8.00–7.96 (m, 2H, 2 × BCC*H*), 1.36 (s, 12H, 4 × CH_3);

^{11}B {^{1}H} NMR (128 MHz, $CDCl_3$) δ 30.3;

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.8, 135.2 (d, $^2J_{CF}$ = 23.9 Hz), 127.4, 84.9, 25.0 (1C missing);

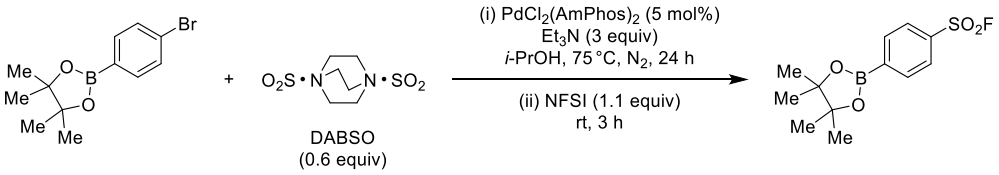
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 65.7;

IR ν_{max} (neat)/cm^{-1} 2976, 1396, 1357, 1213, 1140, 1080, 853, 768;

HRMS (ESI/APCI/EI) not found.

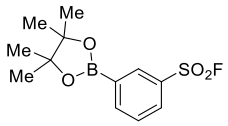
Note: The product is unstable towards silica gel, hence flash column chromatography should be done quickly to minimise decomposition of the product.

General Procedure C: Synthesis of fluorosulfonylarylboronic acid pinacol esters from bromophenylboronic acid pinacol ester, DABSO and NFSI as exemplified by the preparation of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (16a)



A reaction tube was charged with 4-bromophenylboronic acid pinacol ester (**22**) (85 mg, 0.30 mmol, 1.0 equiv), DABSO (72 mg, 0.30 mmol, 0.60 equiv) and $PdCl_2(AmPhos)_2$ (10.6 mg, 0.015 mmol, 0.050 equiv), sealed with a rubber septum, and evacuated and back-filled with N_2 for three times. Anhydrous degassed isopropanol (1.2 mL) and anhydrous triethylamine (0.13 mL, 0.90 mmol, 3.0 equiv) were added subsequently, and the reaction mixture stirred under positive pressure of N_2 in a preheated aluminum heating block at 75 °C for 24 h. After cooling to ambient temperature, NFSI (104 mg, 0.33 mmol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature for 3 h until completion. The reaction mixture was then diluted with EtOAc, filtered through a plug of Celite® and concentrated *in vacuo* to yield the crude product which was then purified by flash column chromatography (10–30% EtOAc in petrol), affording the *sulfonyl fluoride* **16a** as a white solid (57 mg, 67%) with spectroscopic data as shown above.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (16b)



Prepared according to General Procedure B using 3-bromobenzenesulfonyl fluoride **15b** (1.67 g, 7.0 mmol, 1.0 equiv), $B_2(pin)_2$ (1.96 g, 7.7 mmol, 1.1 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (172 mg, 0.21 mmol, 3 mol%), KOAc (2.06 g, 21 mmol, 3.0 equiv) and 1,4-dioxane (25 mL). The crude product was purified by quick flash column chromatography (5–20% EtOAc in petrol) to afford the corresponding *sulfonyl fluoride* **16b** as a white solid (1.47 g, 73%);

mp 83–85 °C (pentane);

R_f 0.21 (10% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (t, *J* = 1.4 Hz, 1H, Ar*H*), 8.17 (d, *J* = 7.4 Hz, 1H, Ar*H*), 8.07 (dt, *J* = 8.0, 1.6 Hz, 1H, Ar*H*), 7.62 (t, *J* = 7.7 Hz, 1H, Ar*H*), 1.36 (s, 12H, 4 × CH_3);

^{11}B {^{1}H} NMR (128 MHz, $CDCl_3$) δ 30.2;

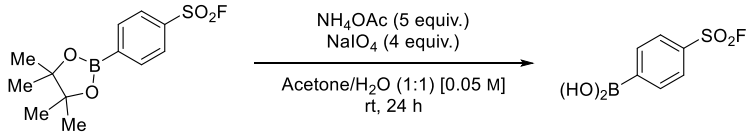
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.7, 134.6, 132.9 (d, $^2J_{CF}$ = 23.9 Hz), 130.7, 129.1, 84.9, 25.0 (1C missing);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 65.8;

IR ν_{max} (neat)/cm^{-1} 2980, 1600, 1406, 1353, 1208, 1142;

HRMS (ESI) not found.

General Procedure D: Synthesis of benzenesulfonyl fluoride boronic acids from the corresponding pinacolate boronic ester as exemplified by the preparation of 4-(fluorosulfonyl)phenylboronic acid (17a)



4-(Fluorosulfonyl)phenylboronic acid pinacol ester **16a** (1.2 g, 4.2 mmol, 1.0 equiv) was dissolved in acetone (20 mL). A solution of NH_4OAc (1.64 g, 21 mmol, 5.0 equiv) in water (20 mL) was then added, followed by $NaIO_4$ (3.64 g, 17 mmol, 4.0 equiv). The mixture was stirred rigorously at ambient temperature for 24 h, which was then concentrated *in vacuo* and extracted with EtOAc. The organic layer was washed with brine, and the combined aqueous extract was further extracted with EtOAc for three times. The combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resultant solid was then triturated with a 2:1 mixture of hexane/CH_2Cl_2, followed by pentane to afford the *boronic acid* **17a** as a white solid (0.55 g, 64%);

mp 240 °C (decomp.) (CH_2Cl_2);

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 2H, B(O*H*)$_2$), 8.14–8.07 (m, 4H, 4 × Ar*H*);

^{11}B {^{1}H} NMR (128 MHz, DMSO-d_6) δ 27.7;

^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 143.9 (br.), 135.5, 132.6 (d, $^2J_{CF}$ = 22.7 Hz), 127.1;

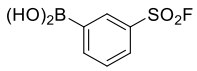
^{19}F {^{1}H} NMR (377 MHz, DMSO-d_6) δ 66.1;

IR ν_{max} (neat)/cm^{-1} 2160, 1405, 1349, 1304, 1209, 1108, 1075, 1015, 803, 785, 741;

LRMS (ESI$^-$) *m*/*z* 203.0 ([M−H]$^-$) ;

HRMS (ESI$^-$) *m*/*z* calc. for $C_6H_5BFO_4S^-$ [M−H]$^-$ 202.9991, found 202.9990.

3-(Fluorosulfonyl)phenylboronic acid (17b)



Prepared according to General Procedure D using 3-(fluorosulfonyl)phenylboronic acid pinacol ester **16b** (1.45 g, 5.1 mmol, 1.0 equiv), NH_4OAc (1.93 g, 25 mmol, 5.0 equiv), $NaIO_4$ (4.28 g, 20 mmol, 4.0 equiv), acetone (25 mL) and water (25 mL). The crude product was triturate with a 4:1 mixture hexane/CH_2Cl_2, followed by pentane to afford the *boronic acid* **17b** as a white solid (0.83 g, 80%);

mp 240 °C (decomp.) (CH_2Cl_2);

^{1}H NMR (400 MHz, DMSO-d_6) 8.58 (s, 2H, B(O*H*)$_2$), 8.46 (app. s, 1H, Ar*H*), 8.29 (d, J = 7.5 Hz, 1H, Ar*H*), 8.15 (ddd, J = 8.0, 2.2, 1.2 Hz, 1H, Ar*H*), 7.76 (t, J = 7.7 Hz, 1H, Ar*H*);

^{11}B {^{1}H} NMR (128 MHz, DMSO-d_6) δ 27.0;

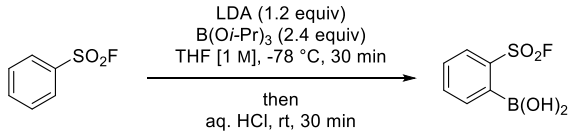
^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 142.0, 137.0, 133.3, 131.1 (d, $^2J_{CF}$ = 22.3 Hz), 129.72, 129.70;

^{19}F {^{1}H} NMR (377 MHz, DMSO-d_6) δ 66.4;

IR ν_{max} (neat)/cm^{-1} 1598, 1568, 1401, 1344, 1203, 1091, 841, 762, 721;

HRMS (ESI$^-$) *m*/*z* calc. for $C_6H_5BFO_4S^-$ [M−H]$^-$ 202.9991, found 202.9988.

General Procedure E: Synthesis of 2-(fluorosulfonyl)phenylboronic acid (17c) through subsequent directed *ortho*-metalation/borylation of benzenesulfonyl fluoride



Preparation of LDA solution

Diisopropylamine (0.92 mL, 6.6 mmol, 1.32 equiv) was dissolved in anhydrous THF (6 mL) under N_2 atmosphere and the solution was cooled to 0 °C. A solution of *n*-BuLi (2.4 M in hexane) (2.5 mL, 6.0 mmol, 1.2 equiv) was then added dropwise and the mixture was stirred at 0 °C for 15 min.

Ortho-lithiation/borylation

Under N_2 atmosphere, benzenesulfonyl fluoride **18** (0.60 mL, 5.0 mmol, 1 equiv) was dissolved in anhydrous THF (5 mL) and the solution was cooled to -78 °C. Triisopropyl borate (2.8 mL, 12 mmol, 2.4 equiv) was added to the solution, followed by the slow addition of LDA solution prepared as described above over 10 min and the reaction was stirred at −78 °C for 30 min. The reaction mixture was then warmed to ambient temperature, 10% (v/v) *aq*. HCl (9 mL) was added and the reaction was left stirring at ambient temperature for 30 min. The mixture was then diluted with EtOAc and the two phases were separated. The aqueous extract was further extracted with EtOAc for three times and the combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30–50% EtOAc in petrol). The resultant oil was then subsequently triturate with hexane, a 5:1 mixture hexane/CH_2Cl_2, followed by pentane to afford the *boronic acid* **17c** as a white solid (599 mg, 59%);

mp 70–72 °C (decomp.) (CH_2Cl_2);

R_f 0.27 (30% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H, Ar*H*), 8.01 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.78 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.67 (t, *J* = 7.4 Hz, 1H, Ar*H*), 5.58 (br. s, 2H, B(O*H*)$_2$)

^{11}B {^{1}H} NMR (128 MHz, $CDCl_3$) δ 28.7;

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.2, 135.9 (d, $^2J_{CF}$ = 21.6 Hz), 135.0, 131.2 (br.), 130.8, 129.4;

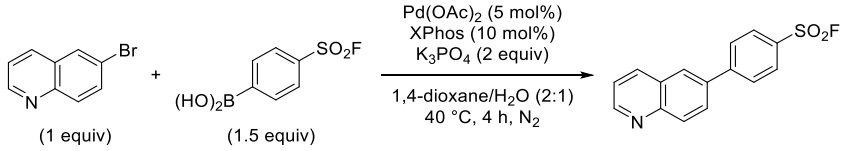
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 63.8;

IR ν_{max} (neat)/cm^{-1} 3387, 1394, 1332, 1207, 790, 763, 749;

HRMS (ESI^-) *m*/*z* calc. for $C_6H_5BFO_4S^-$ $[M-H]^-$ 202.9991, found 202.9991.

6.2.2 Suzuki-Miyaura Coupling (SMC) reactions using BASFs

General Procedure F: Synthesis of biarylsulfonyl fluorides through SMC between benzenesulfonyl fluoride boronic acids and aryl halides as exemplified by the preparation of 4-(quinolin-6-yl)benzenesulfonyl fluoride (24a)



A reaction tube was charged with 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv) and XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 for three times. Degassed 1,4-dioxane (0.8 mL), degassed 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 6-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv) were added subsequently, and the reaction mixture was stirred under positive pressure of N_2 in a preheated aluminum heating block at 40 °C for 4 h or until completion. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, dried with anhydrous $MgSO_4$, filtered over Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30–50% EtOAc in petrol), affording the *sulfonyl fluoride* **24a** as a white solid (52.5 mg, 91%);

mp 135–136 °C (CH_2Cl_2);

R_f 0.26 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 4.2, 1.7 Hz, 1H, Ar*H*), 8.28–8.23 (m, 2H, 2 × Ar*H*), 8.15–8.12 (m, 2H, 2 × Ar*H*), 8.07 (d, *J* = 2.1 Hz, 1H, Ar*H*), 7.99–7.93 (m, 3H, 3 × Ar*H*), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H, Ar*H*);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.6, 148.4, 147.9, 136.7, 136.6, 132.1 (d, $^2J_{CF}$ = 24.9 Hz), 130.9, 129.3, 128.7, 128.6, 128.5, 126.9, 122.2;

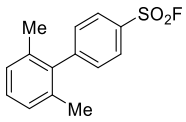
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.5;

IR ν_{max} (neat)/cm^{-1} 3071, 1591, 1406, 1212, 1193, 1097;

LRMS (ESI$^+$) *m*/*z* 288.0 ([M+H]$^+$) ;

HRMS (ESI$^+$) *m*/*z* calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0490.

2',6'-Dimethyl-[1,1'-biphenyl]-4-sulfonyl fluoride (24b)



Following General Procedure F, 2-bromo-1,3-dimethylbenzene (26.5 µL, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 4 h. Upon workup, the crude product was purified by flash column chromatography (0–10% EtOAc in petrol), affording the *sulfonyl fluoride* **24b** as a white solid (35.3 mg, 67%);

mp 133–134 °C ($CHCl_3$);

R_f 0.56 (10% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dtd, J = 8.2, 2.0, 0.4 Hz, 2H, 2 × Ar*H*), 7.44 (dtd, J = 8.6, 1.9, 0.9 Hz, 2H, 2 × Ar*H*), 7.23 (dd, J = 8.4, 6.7 Hz, 1H, Ar*H*), 7.16–7.13 (m, 2H, 2 × Ar*H*), 2.01 (s, 6H, 2 × CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.6, 139.4, 135.4, 131.6 (d, $^2J_{CF}$ = 24.6 Hz), 130.8, 128.9, 128.3, 127.9, 20.9;

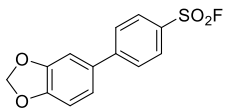
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.1;

IR ν_{max} (neat)/cm^{-1} 3088, 2966, 2923, 1590, 1464, 1403, 1208, 1179, 1163, 1092;

LRMS (ESI^+) not found;

HRMS (ESI) not found.

4-(Benzo[*d*][1,3]dioxol-5-yl)benzenesulfonyl fluoride (24c)



Following General Procedure F, 5-bromo-1,3-benzodioxole (24 µL, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 4 h. Upon workup, the crude product was purified by flash column chromatography (20% EtOAc in petrol), affording the *sulfonyl fluoride* **24c** as a white solid (51.9 mg, 93%);

mp 104–105 °C ($CHCl_3$);

R_f 0.45 (20% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dtd, *J* = 8.8, 2.0, 0.5 Hz, 2H, 2 × Ar*H*), 7.74 (dtd, *J* = 8.8, 2.1, 0.9 Hz, 2H, 2 × Ar*H*), 7.12 (dd, *J* = 8.0, 1.9 Hz, 1H, Ar*H*), 7.09 (dd, *J* = 1.9, 0.4 Hz, 1H, Ar*H*), 6.93 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.05 (s, 2H, OCH_2);

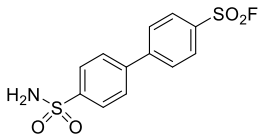
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.8, 148.4, 132.8, 131.0 (d, $^2J_{CF}$ = 24.6 Hz), 129.1, 127.9, 121.7, 109.1, 107.8, 101.8;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.5;

IR ν_{max} (neat)/cm^{-1} 3079, 2922, 1594, 1505, 1477, 1442, 1405, 1223, 1209, 1186, 1100, 1033;

HRMS (ESI) not found.

4'-Sulfamoyl-[1,1'-biphenyl]-4-sulfonyl fluoride (24d)



Following General Procedure F, 4-bromobenzenesulfonamide (47.2 mg, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 4 h. Upon workup, the crude product was purified by flash column chromatography (30–50% EtOAc in petrol), affording the *sulfonyl fluoride* **24d** as a white solid (46.0 mg, 73%);

mp 181–183 °C (EtOAc);

R_f 0.14 (30% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 8.14 (d, *J* = 8.1 Hz, 2H, 2 × Ar*H*), 8.02–7.95 (m, 4H, 4 × Ar*H*), 7.49 (s, 2H, NH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.4, 144.6, 140.7, 130.9 (d, $^2J_{CF}$ = 23.9 Hz), 129.2, 128.9, 128.1, 126.5;

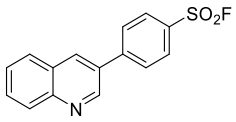
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.6;

IR ν_{max} (neat)/cm^{-1} 3367, 3263, 1594, 1404, 1329, 1215, 1153, 1097;

LRMS (ESI$^-$) *m*/*z* 313.9 ([M−H]$^-$);

HRMS (ESI$^-$) *m*/*z* calc. for $C_{12}H_9FNO_4S_2^-$ [M−H]$^-$ 313.9963, found 313.9961.

4-(Quinolin-3-yl)benzenesulfonyl fluoride (24e)



Following General Procedure F, 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 4 h. Upon workup, the crude product was purified by flash column chromatography (20–30% EtOAc in petrol), affording the *sulfonyl fluoride* **24e** as a white solid (45.8 mg, 80%);

mp 161–163 °C (CH_2Cl_2);

R_f 0.42 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, *J* = 2.4 Hz, 1H, Ar*H*), 8.39 (dd, *J* = 2.4, 0.8 Hz, 1H, Ar*H*), 8.21–8.14 (m, 3H, 3 × Ar*H*), 7.99–7.95 (m, 2H, 2 × Ar*H*), 7.95–7.92 (m, 1H, Ar*H*), 7.81 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, Ar*H*), 7.65 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, Ar*H*);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.1, 148.3, 145.5, 134.6, 132.5 (d, $^2J_{CF}$ = 25.4 Hz), 131.4, 130.7, 129.6, 129.5, 128.6, 128.4, 127.8, 127.8;

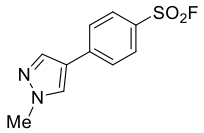
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.5;

IR ν_{max} (neat)/cm^{-1} 3060, 1595, 1403, 1216, 1097;

LRMS (ESI$^+$) *m*/*z* 288.0 ([M+H]$^+$);

HRMS (ESI$^+$) *m*/*z* calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0490.

4-(1-Methyl-1*H*-pyrazol-4-yl)benzenesulfonyl fluoride (24f)



Following General Procedure F, 4-bromo-1-methyl-1*H*-pyrazole (20.5 µL, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 6 h. Upon workup, the crude product was purified by flash column chromatography (50–75% EtOAc in petrol), affording the *sulfonyl fluoride* **24f** as a white solid (10.2 mg, 43%);

mp 85–86 °C ($CHCl_3$);

R_f 0.29 (50% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dt, *J* = 8.5, 1.9 Hz, 2H, 2 × Ar*H*), 7.85 (d, *J* = 0.9 Hz, 1H, H_3CNNC*H*), 7.75 (d, *J* = 0.8 Hz, 1H, H_3CNC*H*), 7.67 (dtd, *J* = 8.8, 2.1, 1.0 Hz, 2H, 2 × Ar*H*), 3.99 (s, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.5, 137.5, 130.0 (d, $^2J_{CF}$ = 24.3 Hz), 129.4, 128.3, 126.0, 121.1, 39.5;

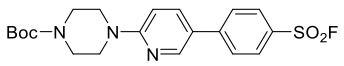
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.5;

IR ν_{max} (neat)/cm^{-1} 3101, 2948, 1597, 1564, 1402, 1206, 1192, 1097;

LRMS (ESI$^+$) *m*/*z* 241.0 ([M+H]$^+$);

HRMS (ESI$^+$) *m*/*z* calc. for $C_{10}H_{10}FN_2O_2S^+$ [M+H]$^+$ 241.0442, found 241.0443.

tert-Butyl 4-(5-(4-(fluorosulfonyl)phenyl)pyridin-2-yl)piperazine-1-carboxylate (24g)



Following General Procedure F, 4-Boc-1-(5-bromo-2-pyridyl)piperazine (68.4 mg, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 6 h. Upon workup, the crude product was purified by flash column chromatography (10–25% EtOAc in petrol), affording the *sulfonyl fluoride* **24g** as a white solid (67.3 mg, 80%);

mp 198–200 °C ($CHCl_3$);

R_f 0.42 (30% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 2.6, 0.7 Hz, 1H, Ar*H*), 8.04 (dt, *J* = 8.5, 2.1 Hz, 2H, 2 × Ar*H*), 7.77 (dd, *J* = 8.1, 1.9 Hz, 1H, Ar*H*), 7.75–7.72 (m, 2H, 2 × Ar*H*), 6.74 (dd, *J* = 9.0, 0.8 Hz, 1H, Ar*H*), 3.69–3.60 (m, 4H, 2 × NCNCH_2), 3.61–3.50 (m, 4H, 2 × C(O)NCH_2), 1.49 (s, 9H, C(CH_3)$_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3, 154.9, 147.0, 145.9, 136.3, 130.6 (d, $^2J_{CF}$ = 24.8 Hz), 129.3, 126.8, 123.4, 107.0, 80.3, 44.9, 43.3 (br.), 28.6;

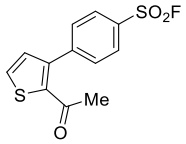
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.6;

IR ν_{max} (neat)/cm^{-1} 2981, 2923, 1673, 1605, 1589, 1424, 1403, 1243, 1212, 1190, 1172;

LRMS (ESI$^+$) *m*/*z* 422.0 ([M+H]$^+$);

HRMS (ESI$^+$) *m*/*z* calc. for $C_{20}H_{25}FN_3O_4S^+$ [M+H]$^+$ 422.1544, found 422.1548.

4-(2-Acetylthiophen-3-yl)benzenesulfonyl fluoride (24h)



Following General Procedure F, 2-acetyl-3-bromothiophene (41 mg, 0.20 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 6 h. Upon workup, the crude product was purified by flash column chromatography (10–25% EtOAc in petrol), affording the *sulfonyl fluoride* **24h** as an off-white solid (49.4 mg, 87%);

mp 127–129 °C ($CHCl_3$);

R_f 0.44 (30% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dt, *J* = 8.5, 1.8 Hz, 2H, 2 × Ar*H*), 7.66 (dtd, *J* = 8.8, 1.9, 0.8 Hz, 2H, 2 × Ar*H*), 7.61 (d, *J* = 5.1 Hz, 1H, SC*H*), 7.09 (d, *J* = 5.0 Hz, 1H, SCHC*H*), 2.39 (s, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.5, 144.3, 144.1, 138.9, 132.6 (d, $^2J_{CF}$ = 25.3 Hz), 131.9, 131.2, 130.7, 128.5, 29.9;

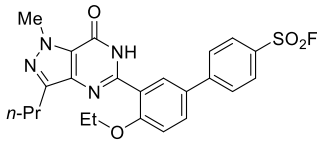
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.2;

IR ν_{max} (neat)/cm^{-1} 3105, 1672, 1402, 1274, 1209, 1186, 1095;

LRMS (ESI$^+$) *m*/*z* 285.0 ([M+H]$^+$);

HRMS (ESI$^+$) *m*/*z* calc. for $C_{12}H_{10}FO_3S_2^+$ [M+H]$^+$ 285.0050, found 285.0051.

4'-Ethoxy-3'-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-[1,1'-biphenyl]-4-sulfonyl fluoride (24i)



Following General Procedure F, 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (39.1 mg, 0.10 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (31 mg, 0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.050 equiv), XPhos (4.8 mg, 0.010 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.2 mL, 0.20 mmol, 2.0 equiv) and 1,4-dioxane (0.4 mL) were used and the reaction was heated at 40 °C for 6 h. Upon workup, the crude product was purified by flash column chromatography (35–70% EtOAc in petrol), affording the *sulfonyl fluoride* **24i** as a white solid (29.0 mg, 62%);

mp 176–178 °C ($CHCl_3$);

R*f* 0.26 (50% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H, N*H*), 8.67 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.08–8.00 (m, 2H, 2 × Ar*H*), 7.80 (dd, *J* = 8.9, 0.8 Hz, 2H, 2 × Ar*H*), 7.65 (dd, *J* = 8.6, 2.5 Hz, 1H, Ar*H*), 7.11 (d, *J* = 8.7 Hz, 1H, Ar*H*), 4.35–4.26 (m, 2H, OCH_2CH_3), 4.21 (s, 3H, NCH_3), 2.87 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 1.80 (sext, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_3$), 1.58 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 0.96 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$)

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 153.9, 147.8, 147.4, 146.9, 138.6, 132.2, 131.5 (d, $^2J_{CF}$ = 24.7 Hz), 131.2, 130.3, 129.3, 128.0, 124.7, 121.2, 113.9, 65.9, 38.4, 27.9, 22.5, 14.8, 14.2;

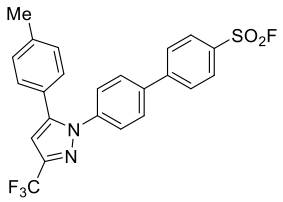
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.5;

IR ν_{max} (neat)/cm^{-1} 3310, 2959, 2932, 1697, 1593, 1566, 1486, 1473, 1406, 1213, 1159, 1031;

LRMS (ESI^+) *m*/*z* 471.2 ($[M+H]^+$);

HRMS (ESI^+) *m*/*z* calc. for $C_{23}H_{24}FN_4O_4S^+$ $[M+H]^+$ 471.1497, found 471.1496.

4'-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-4-sulfonyl fluoride (24j)



Following General Procedure F, 1-(4-bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (38.1 mg, 0.10 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (31 mg, 0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.050 equiv), XPhos (4.8 mg, 0.010 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.2 mL, 0.20 mmol, 2.0 equiv) and 1,4-dioxane (0.4 mL) were used and the reaction was heated at 40 °C for 6 h. Upon workup, the crude product was purified by flash column chromatography (0–10% EtOAc in petrol), affording the *sulfonyl fluoride* **24j** as an off-white solid (43.5 mg, 95%);

mp 121–123 °C ($CHCl_3$);

R*f* 0.41 (10% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (ddt, *J* = 103.1, 8.5, 2.0 Hz, 2H, 2 × Ar*H*), 7.82 (dtd, *J* = 8.9, 2.1, 0.8 Hz, 2H, 2 × Ar*H*), 7.62 (dt, *J* = 8.7, 2.5 Hz, 2H, 2 × Ar*H*), 7.47 (dt, *J* = 8.8, 2.2 Hz, 2H, 2 × Ar*H*), 7.19–7.15 (m, 4H, 4 × Ar*H*), 6.75 (s, 1H, F_3CCC*H*), 2.38 (s, 3H, C*H*$_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.3, 145.1, 143.8 (app. d, $^2J_{CF}$ = 38.9 Hz), 140.2, 139.6, 138.4, 132.1 (d, $^2J_{CF}$ = 24.7 Hz), 129.7, 129.2, 128.9, 128.3, 128.2, 126.3, 126.1, 121.4 (app. d, $^1J_{CF}$ = 269.5 Hz), 106.0, 21.5;

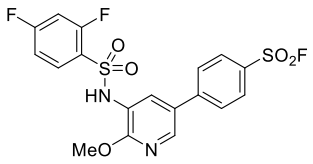
^{19}F NMR (377 MHz, $CDCl_3$) δ 66.5 (s, 1F), -62.3 (s, 3F);

IR ν_{max} (neat)/cm^{-1} 3061, 2925, 1595, 1472, 1408, 1376, 1236, 1213, 1161, 1133, 1097;

LRMS (ESI$^+$) *m*/*z* 461.0 ([M+H]$^+$);

HRMS (ESI$^+$) *m*/*z* calc. for $C_{21}H_{17}F_4N_2O_2S^+$ [M+H]$^+$ 461.0941, found 461.0938.

4-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)benzenesulfonyl fluoride (24k)



Following General Procedure F, *N*-(5-bromo-2-methoxypyridin-3-yl)-2,4-difluoro-benzenesulfonamide (37.9 mg, 0.10 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **17a** (31 mg, 0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.050 equiv), XPhos (4.8 mg, 0.010 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.2 mL, 0.20 mmol, 2.0 equiv) and 1,4-dioxane (0.4 mL) were used and the reaction was heated at 40 °C for 24 h. Upon workup, the crude product was purified by flash column chromatography (30–50% EtOAc in petrol), affording the *sulfonyl fluoride* **24k** as an off-white solid (19.4 mg, 42%);

mp 152–154 °C ($CHCl_3$);

R_f 0.52 (50% EtOAc in hexane) [UV];

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.3 Hz, 1H, Ar*H*), 8.08 (dt, *J* = 8.6, 2.0 Hz, 2H, 2 × Ar*H*), 7.99 (d, *J* = 2.3 Hz, 1H, Ar*H*), 7.91–7.86 (m, 1H, Ar*H*), 7.72 (d, *J* = 8.4 Hz, 2H, 2 × Ar*H*), 7.28 (br. s, 1H, N*H*), 6.98–6.93 (m, 2H, 2 × Ar*H*), 3.98 (s, 3H, CH_3);

^{13}C {^{1}H,^{19}F} NMR (126 MHz, $CDCl_3$) δ 166.4, 160.0, 155.0, 144.7, 140.9, 132.5, 129.4, 128.5, 127.9, 126.3, 123.5, 121.0, 112.2, 106.0, 54.6;

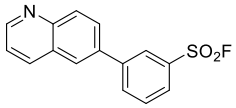
^{19}F NMR (377 MHz, $CDCl_3$) δ 66.4 (s, 1F), -98.5 (m, 1F), -103.8 (m, 1F);

IR ν_{max} (neat)/cm^{-1} 3285, 3103, 2929, 2856, 1602, 1480, 1407, 1347, 1213, 1178, 1149;

LRMS (ESI$^+$) *m*/*z* 459.0 ([M+H]$^+$) ;

HRMS (ESI$^+$) *m*/*z* calc. for $C_{18}H_{14}F_3N_2O_5S_2^+$ [M+H]$^+$ 459.0291, found 459.0291.

3-(Quinolin-6-yl)benzenesulfonyl fluoride (24l)



Following General Procedure F, 6-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv), 3-(fluorosulfonyl)phenylboronic acid **17b** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 4 h. Upon workup, the crude product was purified by flash column chromatography (50% EtOAc in petrol), affording the *sulfonyl fluoride* **24l** as a white solid (52.3 mg, 91%);

mp 111–113 °C ($CHCl_3$);

R_f 0.24 (30% EtOAc in hexane) [UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 4.2, 1.7 Hz, 1H, Ar*H*), 8.34 (t, *J* = 1.9 Hz, 1H, Ar*H*), 8.27–8.22 (m, 2H, 2 × Ar*H*), 8.12–8.08 (m, 1H, Ar*H*), 8.06–8.02 (m, 3H, 3 × Ar*H*), 7.96 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar*H*), 7.77 (t, *J* = 7.9 Hz, 1H, Ar*H*), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H, Ar*H*);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.4, 148.2, 142.5, 136.5, 136.4, 134.4, 134.1 (d, $^2J_{CF}$ = 24.6 Hz), 130.8, 130.5, 128.5 (2C), 127.4, 127.2, 126.5, 122.1;

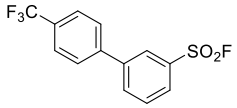
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.1;

IR ν_{max} (neat)/cm^{-1} 3067, 1593, 1480, 1404, 1208;

LRMS (ESI^+) *m*/*z* 288.0 ($[M+H]^+$);

HRMS (ESI^+) *m*/*z* calc. for $C_{15}H_{11}FNO_2S^+$ $[M+H]^+$ 288.0489, found 288.0489.

4'-(Trifluoromethyl)-[1,1'-biphenyl]-3-sulfonyl fluoride (24m)



Following General Procedure F, 4-chlorobenzotrifluoride (27 μL, 0.20 mmol, 1.0 equiv), 3-(fluorosulfonyl)phenylboronic acid **17b** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), XPhos (9.5 mg, 0.020 mmol, 0.10 equiv), 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and 1,4-dioxane (0.8 mL) were used and the reaction was heated at 40 °C for 6 h. Upon workup, the crude product was purified by flash column chromatography (5–20% EtOAc in petrol), affording the *sulfonyl fluoride* **24m** as an off-white solid (38.7 mg, 64%);

mp 50–51 °C ($CHCl_3$);

R_f 0.70 (30% EtOAc in hexane) [UV/$KMnO_4$];

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (t, *J* = 1.9 Hz, 1H, Ar*H*), 8.06 (dt, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 8.00 (dt, *J* = 7.8, 1.4 Hz, 1H, Ar*H*), 7.78–7.71 (m, 5H, 5 × Ar*H*);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.9, 141.9, 134.3, 134.2 (d, $^2J_{CF}$ = 24.6 Hz), 131.1 (app. d, $^2J_{CF}$ = 32.7 Hz), 130.6, 127.9, 127.8, 127.2, 126.4 (q, $^3J_{CF}$ = 3.7 Hz), 124.1 (app. d, $^1J_{CF}$ = 272.5 Hz);

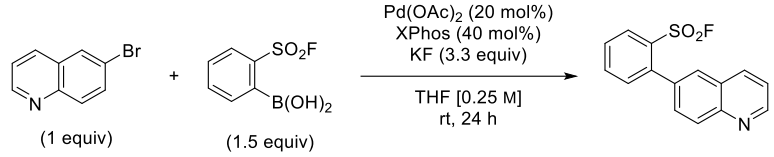
^{19}F NMR (377 MHz, $CDCl_3$) δ 66.1 (s, 1F), -62.7 (s, 3F);

IR ν_{max} (neat)/cm^{-1} 3076, 1619, 1409, 1325, 1210, 1167, 1125, 1071;

LRMS (ESI^-) *m*/*z* 339.1 ($[M+Cl]^-$);

HRMS (ESI^+) *m*/*z* calc. for $C_{13}H_8F_4O_2SNa^+$ $[M+Na]^+$ 327.0073, found 327.0080.

2-(Quinolin-6-yl)benzenesulfonyl fluoride (24n)



A reaction tube was charged with KF (48 mg, 0.83 mmol, 3.3 equiv), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol, 0.20 equiv) and XPhos (48 mg, 0.10 mmol, 0.40 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 for three times. Degassed anhydrous THF (0.25 mL) and 6-bromoquinoline (34 µL, 0.25 mmol, 1.0 equiv) were added subsequently, the mixture was stirred at ambient temperature for 5 min, then warmed to 40 °C and a solution of 2-(fluorosulfonyl)phenyl boronic acid **17c** (76 mg, 0.37 mmol, 1.5 equiv) in degassed THF (1 mL) was added over a period of 30 min. The reaction mixture was stirred at 40 °C for an additional 30 min, then stirred at ambient temperature for 12 h. The reaction was then diluted with EtOAc, filtered over Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40–50% EtOAc in petrol) to afford the *sulfonyl fluoride* **24n** as an off-white solid (30.5 mg, 43%);

mp 95–96 °C ($CHCl_3$);

R_f 0.31 (50% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 4.3, 1.7 Hz, 1H, Ar*H*), 8.23 (dd, *J* = 8.1, 1.3 Hz, 3H, 3 × Ar*H*), 8.21–8.17 (m, 2H, 2 × Ar*H*), 7.86–7.84 (m, 1H, Ar*H*), 7.81 (td, *J* = 7.6, 1.4 Hz, 1H, Ar*H*), 7.72 (ddd, *J* = 8.7, 2.0, 0.9 Hz, 1H, Ar*H*), 7.66 (ddt, *J* = 9.1, 7.7, 1.4 Hz, 1H, Ar*H*), 7.55 (dd, *J* = 7.7, 1.3 Hz, 1H, Ar*H*), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H, Ar*H*);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.3, 147.9, 142.3, 136.6, 136.3, 135.0, 133.3, 132.6 (d, $^2J_{CF}$ = 22.4 Hz), 130.5, 130.3, 129.4, 128.7, 128.4, 127.7, 122.0;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 67.5;

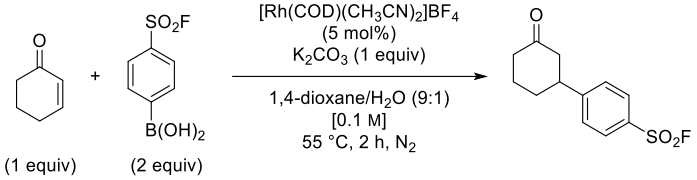
IR ν_{max} (neat)/cm^{-1} 3064, 1478, 1404, 1210, 763;

LRMS (ESI$^+$) *m*/*z* 288.0 ([M+H]$^+$);

HRMS (ESI$^+$) *m*/*z* calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0488.

6.2.3 Rh(I)-catalysed conjugate addition using BASF

Preparation of 4-(3-oxocyclohexyl)benzenesulfonyl fluoride (26)



A reaction tube was charged with 4-(fluorosulfonyl)phenylboronic acid **17a** (61 mg, 0.30 mmol, 2.0 equiv), $[Rh(COD)(CH_3CN)_2]BF_4$ (2.9 mg, 0.0075 mmol, 0.050 equiv) and K_2CO_3 (21 mg, 0.15 mmol, 1.0 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 for three times. Degassed 1,4-dioxane (1.35 mL), degassed water (0.15 mL, 0.40 mmol, 2.0 equiv) and 2-cyclohexen-1-one (14.5 µL, 0.15 mmol, 1.0 equiv) were added subsequently, and the reaction mixture was stirred under positive pressure of N_2 in a preheated aluminum heating block at 55 °C for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20–40% EtOAc in petrol), affording the *sulfonyl fluoride* **26** as a white solid (28.5 mg, 74%);

mp 61–62 °C (CH_2Cl_2);

R_f 0.38 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dt, J = 8.4, 2.0 Hz, 2H, 2 × Ar*H*), 7.48 (d, J = 8.2 Hz, 2H, 2 × Ar*H*), 3.15 (tt, J = 11.6, 4.0 Hz, 1H, C(O)CH_2CH), 2.62 (ddt, J = 14.0, 4.2, 1.9 Hz, 1H, C(O)CH_aH_bCH), 2.59–2.45 (m, 2H, C(O)CH_aH_bCH + $CHCH_2CH_cH_d$), 2.47–2.34 (m, 1H, $CHCH_2CH_cH_d$), 2.25–2.13 (m, 1H, C(O)C$H_eH_fCH_2$), 2.16–2.09 (m, 1H, $CHCH_gH_hCH_2$), 1.97–1.74 (m, 2H, $CHCH_gH_hCH_2$ + C(O)$CH_eH_fCH_2$);

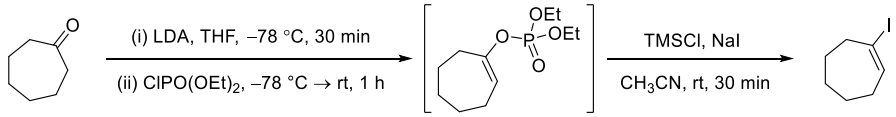
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 209.4, 152.8, 131.5 (d, $^2J_{CF}$ = 24.7 Hz), 129.1, 128.1, 48.2, 44.7, 41.1, 32.4, 25.4;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 66.1;

IR ν_{max} (neat)/cm^{-1} 2980, 2884, 1712, 1597, 1404, 1211, 1186, 804, 771;

HRMS (APCI$^+$) *m*/*z* calc. for $C_{12}H_{14}FO_3S^+$ $[M+H]^+$ 257.0642, found 257.0641.

6.2.4 Preparation of 1-iodocyclohept-1-ene (29)



According to the procedure of Lee and Wiemer,[221] a two-neck round bottom flask was charged with cycloheptanone (1.2 mL, 10 mmol, 1.0 equiv), and was evacuated and filled with N_2 three times. After the addition of anhydrous THF (10 mL), the mixture was cooled to −78 °C, followed by the addition of LDA (1.0 M in THF, 11 mL, 11 mmol, 1.1 equiv). The reaction was stirred at −78 °C for 30 min under a positive pressure of N_2. A solution of diethyl chlorophosphate (2.9 mL, 20 mmol, 2.0 equiv) in anhydrous THF (10 mL) was then added to the reaction. The reaction mixture was stirred at −78 °C for 30 min, then warmed up to ambient temperature and further stirred for a further hour. To the reaction mixture, sat. aq. NH_4Cl (30 mL) was added dropwise at 0 °C, and the THF was removed *in vacuo*, then the crude mixture extracted with ethyl acetate for three times. The combined organic layers were then dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification.

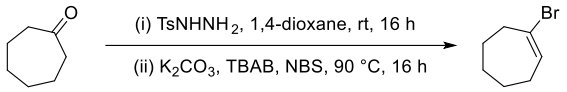
To the crude alkenyl phosphate was added NaI (4.5 g, 30 mmol, 3.0 equiv), then dried under vacuum (1 mbar) for an hour. The mixture was dissolved in anhydrous acetonitrile (25 mL), and TMSCl (3.8 mL, 30 mmol, 3.0 equiv) was added dropwise at room temperature. The reaction was stirred for 30 min under a positive pressure of N_2, which was then cooled to 0 °C and quenched by slow addition of sat. aq. NH_4Cl (2 mL). The mixture was diluted with Et_2O and filtered. The filtrate was then washed subsequently with sat. aq. $NaHCO_3$ and 10% (w/w) aq. $Na_2S_2O_3$, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (petrol), affording the corresponding alkenyl iodide **29** as a colourless oil (0.97 g, 44%) with spectroscopic data in accordance with the literature;[51]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (t, *J* = 6.6 Hz, 1H, C=C*H*), 2.78–2.72 (m, 2H, CHCH_2), 2.09–2.01 (m, 2H, CCH_2), 1.76–1.68 (m, 2H, Alk-CH_2), 1.58–1.50 (m, 4H, 2 × Alk-CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.0, 100.8, 45.1, 31.5, 31.1, 26.8, 26.5;

IR ν_{max} (neat)/cm^{-1} 2922, 2850, 1453, 1279, 1216, 1105, 1031.

6.2.5 Preparation of 1-bromocyclohept-1-ene (30)



According to the procedure of Ojha and Prabhu,[222] a solution of cycloheptanone (0.59 mL, 5.0 mmol, 1.0 equiv) and *p*-toluenesulfonyl hydrazide (0.93 g, 5.0 mmol, 1.0 equiv) in 1,4-dioxane (10 mL) was stirred at ambient temperature for 16 h, followed by the addition of K_2CO_3 (2.1 g, 15 mmol, 3.0 equiv), TBAB (4.8 g, 15 mmol, 3.0 equiv) and NBS (1.34 g, 7.5 mmol, 1.5 equiv). The mixture was heated to 90 °C and stirred for 16 h under a positive pressure of N_2. The reaction mixture was then cooled to room temperature and poured into a 1:1 mixture of petrol and EtOAc (100 mL). The solution was filtered through a plug of silica and concentrated *in vacuo* to yield the crude product which was then purified by flash column chromatography (petrol), affording the alkenyl bromide **30** as a colourless oil (237 mg, 27%) with spectroscopic data in accordance with the literature;[223]

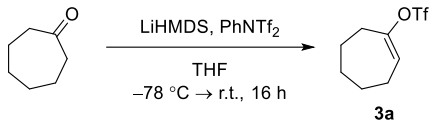
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (t, *J* = 6.5 Hz, 1H, C=C*H*), 2.71–2.64 (m, 2H, CHCH_2), 2.11–2.03 (m, 2H, CCH_2), 1.75–1.66 (m, 2H, Alk-CH_2), 1.66–1.52 (m, 4H, 2 × Alk-CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.5, 126.2, 40.7, 30.7, 29.2, 26.4, 26.3;

IR ν_{max} (neat)/cm^{-1} 2929, 2851, 1723, 1447, 1265, 1100, 1018, 730.

6.2.6 Preparation of alkenyl triflates

General Procedure G: Synthesis of alkenyl triflates from the corresponding ketone, LiHMDS and $PhNTf_2$ as exemplified by the preparation of 1-cyclohept-1-enyl trifluoromethanesulfonate (31a)



3a

A two-neck round bottom flask was charged with cycloheptanone (0.70 mL, 6.0 mmol, 1.0 equiv) and $PhNTf_2$ (2.36 g, 6.6 mmol, 1.1 equiv), then evacuated and back-filled with N_2 three times, followed by the addition of anhydrous THF (25 mL). The mixture was cooled to −78 °C, and LiHMDS (1 M in THF) (6.6 mL, 6.6 mmol, 1.1 equiv) was added slowly. The reaction was allowed to warm up gradually to ambient temperature over 16 h. To the reaction mixture, sat. aq. NH_4Cl solution (2 mL) was added, and was concentrated *in vacuo*. To the mixture was added Et_2O (20 mL) and 2 M aq. NaOH solution (10 mL), and the mixture was stirred vigorously for 15 minutes. The organic layer was separated and washed with 2 M aq. NaOH solution and brine, then dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to leave the crude product, which was then purified by flash column chromatography (petrol), affording the corresponding alkenyl triflate **31a** as a colourless oil (1.16 g, 79%) with spectroscopic data in accordance with the literature;[224]

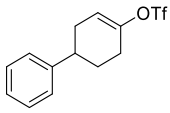
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, J = 6.4 Hz, 1H, OC=C*H*), 2.55–2.48 (m, 2H, OCCH_2), 2.20–2.12 (m, 2H, CHCH_2), 1.76–1.59 (m, 6H, 3 × Alk-CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.2, 123.2, 118.7 (q, $^1J_{CF}$ = 320.3 Hz), 33.3, 30.0, 26.5, 24.92, 24.87;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.0;

IR ν_{max} (neat)/cm^{-1} 2889, 1419, 1205, 1141, 990, 869.

4-Phenyl-1-cyclohexen-1-yl trifluoromethanesulfonate (31b)



Prepared according to General Procedure G using 4-phenylcyclohexan-1-one (1.74 g, 10 mmol). The crude product was purified by flash column chromatography (petrol) to afford the corresponding alkenyl triflate **31b** as a white crystalline solid (1.92 g, 63%) with spectroscopic data in accordance with the literature;[225]

mp 27–28 °C (hexane);

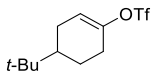
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 7.3 Hz, 2H, 2 × Ar*H*), 7.26–7.19 (m, 3H, 3 × Ar*H*), 5.86 (dt, J = 4.8, 2.1 Hz, 1H, OC=C*H*), 2.90–2.80 (m, 1H, ArC*H*), 2.62–2.27 (m, 4H, CCH_2 + C=CHCH_2), 2.14–2.02 (m, 1H, $CCH_2CH_aH_b$), 2.04–1.89 (m, 1H, $CCH_2CH_aH_b$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.1, 144.7, 128.8, 126.9, 126.8, 118.7 (q, $^{1}J_{CF}$ = 320.0 Hz), 118.3, 38.9, 31.7, 29.8, 28.0;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.0;

IR ν_{max} (neat)/cm^{-1} 3031, 2929, 1692, 1416, 1246, 1208, 1142, 1054, 1025.

4-(*tert*-Butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (31c)



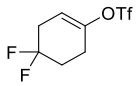
Prepared according to General Procedure G using 4-*tert*-butylcyclohexanone (0.46 g, 3.0 mmol). The crude product was purified by flash column chromatography (petrol) to afford the corresponding alkenyl triflate **31c** as a colourless oil (0.75 g, 87%) which solidified at -20 °C, with spectroscopic data in accordance with the literature;[226]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dt, *J* = 5.9, 2.4 Hz, 1H, OC=C*H*), 2.45–2.27 (m, 2H, CCH_2), 2.25–2.16 (m, 1H, $C(CH_3)_3CH$), 2.00–1.89 (m, 2H, C=CHCH_2), 1.44–1.25 (m, 2H, CCH_2CH_2), 0.89 (s, 9H, $C(CH_3)_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.4, 118.7 (q, $^{1}J_{CF}$ = 320.5 Hz), 118.6, 43.1, 32.2, 28.7, 27.3, 25.5, 24.2;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.1.

4,4-Difluorocyclohex-1-en-1-yl trifluoromethanesulfonate (31d)



Prepared according to General Procedure G using 4,4-difluorocyclohexan-1-one (0.67 g, 5.0 mmol). The crude product was purified by flash column chromatography (0–5% Et_2O in petrol) to afford the corresponding *alkenyl triflate* **31d** as a light yellow oil (0.96 g, 72%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70–5.65 (m, 1H, OC=C*H*), 2.70 (td, *J* = 13.4, 3.3 Hz, 2H, CHCH_2), 2.60 (t, *J* = 6.6 Hz, 2H, $CF_2CH_2CH_2$), 2.21 (tt, *J* = 13.4, 6.7 Hz, 2H, $CF_2CH_2CH_2$);

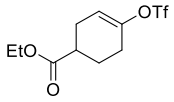
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.2, 120.5 (t, $^1J_{CF}$ = 241.1 Hz), 118.5 (q, $^1J_{CF}$ = 320.5 Hz), 113.8 (t, $^3J_{CF}$ = 5.9 Hz), 33.1 (t, $^2J_{CF}$ = 28.7 Hz), 30.1 (t, $^2J_{CF}$ = 25.8 Hz), 25.4 (t, $^3J_{CF}$ = 5.6 Hz);

^{19}F NMR (377 MHz, $CDCl_3$) δ −73.8 (s, 3F, CF_3), −98.6 (quint, $^3J_{H\text{-}F}$ = 13.2 Hz, 2F, CF_2);

IR ν_{max} (neat)/cm^{-1} 1694, 1418, 1382, 1247, 1206, 1141, 1122, 1086, 1066, 1041, 899, 863;

HRMS (APCI$^+$) found *m*/*z* 247.0034 $[M-F]^+$, $C_7H_7F_4O_3S$ requires *m*/*z* 247.0047.

Ethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate (31e)



Prepared according to General Procedure G using ethyl cyclohexanone-4-carboxylate (0.48 mL, 3.0 mmol). The crude product was purified by flash column chromatography (0–10% EtOAc in petrol) to afford the corresponding alkenyl triflate **31e** as a colourless oil (0.85 g, 94%) with spectroscopic data in accordance with the literature;[227]

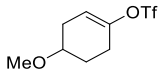
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (t, *J* = 3.6 Hz, 1H, OC=C*H*), 4.18 (q, *J* = 7.2 Hz, 2H, C(=O)OCH_2), 2.67–2.55 (m, 1H, C(=O)C*H*), 2.51–2.38 (m, 4H, C=CHCH_2 + CH=CCH_2), 2.21–2.10 (m, 1H, $SCCH_2CH_aH_b$), 2.01–1.86 (m, 1H, $SCCH_2CH_aH_b$), 1.28 (td, *J* = 7.2, 1.4 Hz, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.9, 148.4, 118.5 (q, $^1J_{CF}$ = 319.2 Hz), 116.9, 60.8, 37.8, 26.6, 26.1, 25.0, 14.2;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.0;

IR ν_{max} (neat)/cm^{-1} 2985, 2941, 1731, 1416, 1247, 1203, 1179, 1140, 1054, 1033, 872.

4-Methoxycyclohex-1-en-1-yl trifluoromethanesulfonate (31f)



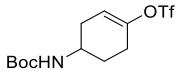
Prepared according to General Procedure G using 4-methoxycyclohexan-1-one (384 mg, 3.0 mmol). The crude product was purified by flash column chromatography (10–20% Et_2O in petrol) to afford the corresponding alkenyl triflate **31f** as a colourless oil (605 mg, 78%) with spectroscopic data in accordance with the literature;[228]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (q, J = 3.0, 2.3 Hz, 1H, OC=C*H*), 3.54–3.47 (m, 1H, OC*H*), 3.36 (s, 3H, OCH_3), 2.52–2.39 (m, 2H, CCH_2), 2.41–2.28 (m, 1H, C=CHCH_aH$_b$), 2.29–2.16 (m, 1H, C=CHCH$_a$$H_b$), 2.02–1.81 (m, 2H, CCH$_2CH_2$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 118.6 (q, $^1J_{CF}$ = 319.8 Hz), 115.6, 73.2, 56.3, 29.5, 26.9, 25.1;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.0.

4-((*tert*-Butoxycarbonyl)amino)cyclohex-1-en-1-yl trifluoromethanesulfonate (31g)



Prepared according to General Procedure G using *tert*-butyl (4-oxocyclohexyl)carbamate (639 mg, 3.0 mmol). The crude product was purified by flash column chromatography (10–20% EtOAc in petrol) to afford a creamy yellow solid which was then recrystallised from hot hexane to yield the corresponding alkenyl triflate **31g** as a white solid (336 mg, 32%) with spectroscopic data in accordance with the literature;[229]

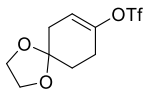
mp 75–77 °C (hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71–5.67 (m, 1H, OC=C*H*), 4.55–4.46 (m, 1H, N*H*), 3.87–3.79 (m, 1H, NHC*H*), 2.59–2.35 (m, 3H, CCH_2 + C=CHCH_aH$_b$), 2.11–1.96 (m, 2H, C=CHCH$_a$$H_b$ + CCH$_2$CH_cH$_d$), 1.83–1.73 (m, 1H, CCH$_2$CH$_c$$H_d$), 1.45 (s, 9H, C(C$H_3$)$_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.3, 148.4, 118.6 (q, $^1J_{CF}$ = 319.8 Hz), 116.3, 79.9, 44.4, 30.5, 28.5, 28.4, 25.9;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.0.

1,4-Dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (31h)



Prepared according to General Procedure G using 1,4-dioxaspiro[4.5]decan-8-one (2.0 g, 13 mmol). The crude product was purified by flash column chromatography (5–20% Et_2O in petrol) to afford the corresponding alkenyl triflate **31h** as a yellow oil (2.84 g, 76%) with spectroscopic data in accordance with the literature;[230]

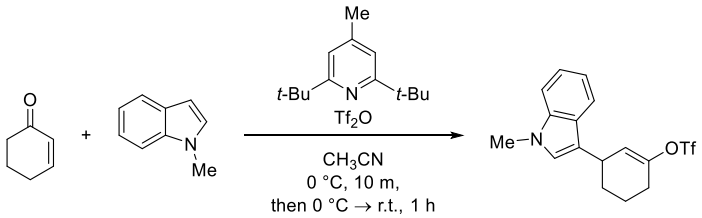
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69–5.63 (m, 1H, OC=C*H*), 4.25–3.69 (m, 4H, 2 × OCH_2), 2.57–2.51 (m, 2H, CH=CCH_2), 2.42–2.38 (m, 2H, CHCH_2), 1.90 (tt, J = 6.6, 0.8 Hz, 2H, CH=CCH$_2$CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.3, 118.6 (q, $^1J_{CF}$ = 320.2 Hz), 116.0, 106.2, 64.8, 34.3, 31.1, 26.5;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −76.0;

IR ν_{max} (neat)/cm^{-1} 2889, 1692, 1416, 1375, 1247, 1205, 1141, 1068, 1041, 1014.

3-(1-Methyl-1*H*-indol-3-yl)cyclohex-1-en-1-yl trifluoromethanesulfonate (31i)



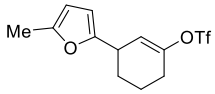
2,6-Di-*tert*-butyl-4-methylpyridine (0.74 g, 3.6 mmol, 1.2 equiv) was dissolved in acetonitrile (15 mL), followed by the addition of cyclohex-2-en-1-one (0.29 mL, 3.0 mmol, 1.0 equiv) and 1-methylindole (1.12 mL, 9.0 mmol, 3.0 equiv). The mixture was cooled to 0 °C and triflic anhydride (0.56 mL, 3.3 mmol, 1.1 equiv) was added with vigorous stirring. The reaction was stirred for 10 min at 0 °C, and sat. aq. $NaHCO_3$ solution (6 mL) was added. The mixture was stirred and allowed to warm up to ambient temperature over an hour, then diluted with water and extracted with CH_2Cl_2 three times. The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to leave the crude product, which was then purified by flash column chromatography (10–20% CH_2Cl_2 in petrol) without delay to afford the corresponding alkenyl triflate **31i** as a colourless oil (644 mg, 60%) with spectroscopic data in accordance with the literature;[231]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.25 (t, *J* = 7.1 Hz, 1H, Ar*H*), 7.13 (t, *J* = 7.0 Hz, 1H, Ar*H*), 6.82 (s, 1H, NC*H*), 5.98–5.94 (m, 1H, OC=C*H*), 3.99–3.92 (m, 1H, C=CHC*H*), 3.76 (s, 3H, NCH_3), 2.45–2.40 (m, 2H, CH=CCH_2), 2.05–1.96 (m, 1H, C=CHCHCH_aH_b), 1.92–1.83 (m, 1H, C=CHCHCH_aH_b), 1.82–1.75 (m, 2H, CCH_2CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.0, 137.4, 126.9, 126.6, 122.0, 121.8, 119.1, 118.9, 118.7 (app. d, $^{1}J_{CF}$ = 319.6 Hz), 116.8, 109.6, 32.9, 32.3, 29.0, 27.9, 20.6;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.1.

3-(5-Methylfuran-2-yl)cyclohex-1-en-1-yl trifluoromethanesulfonate (31k)



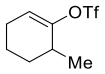
Prepared according to the procedure for compound **31i** as mentioned above using cyclohex-2-en-1-one (0.29 mL, 3.0 mmol), 2-methylfuran (0.81 mL, 9.0 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.74 g, 3.6 mmol), triflic anhydride (0.56 mL, 3.3 mmol) and acetonitrile (15 mL). The crude product was purified by flash column chromatography (10–20% CH_2Cl_2 in petrol) without delay to afford the corresponding alkenyl triflate **31s** as a yellow oil (196 mg, 21%) with spectroscopic data in accordance with the literature;[231]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 3.1, 0.8 Hz, 1H, Ar*H*), 5.87–5.85 (m, 2H, Ar*H* + OC=C*H*), 3.67–3.62 (m, 1H, C=CHC*H*), 2.39–2.34 (m, 2H, CH=CCH_2), 2.26 (s, 3H, CH_3), 1.96–1.81 (m, 2H, CHCH_2), 1.80–1.72 (m, 2H, CCH_2CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.1, 151.4, 150.7, 119.0, 118.7 (q, $^{1}J_{CF}$ = 320.3 Hz), 106.5, 106.1, 34.6, 27.7, 27.0, 20.4, 13.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.9.

6-Methylcyclohex-1-en-1-yl trifluoromethanesulfonate (31l)



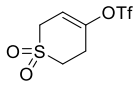
Prepared according to General Procedure G using 2-methylcyclohexan-1-one (0.37 mL, 3.0 mmol). The crude product was purified by flash column chromatography (petrol) to afford the corresponding alkenyl triflate **31l** as a colourless oil (388 mg, 53%) with spectroscopic data in accordance with the literature;[227]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (td, *J* = 4.1, 1.5 Hz, 1H, OC=C*H*), 2.59–2.49 (m, 1H, CH_3CH), 2.20–2.14 (m, 2H, C=CHCH_2), 2.07–1.89 (m, 1H, $CH_3CHCH_aH_b$), 1.71–1.61 (m, 1H, $CHCH_2CH_cH_d$), 1.61–1.52 (m, 1H, $CHCH_2CH_cH_d$), 1.51–1.42 (m, 1H, $CH_3CHCH_aH_b$), 1.14 (d, *J* = 6.9 Hz, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.5, 118.5 (q, $^{1}J_{CF}$ = 319.9 Hz), 118.3, 32.5, 31.6, 24.6, 19.4, 18.0;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −74.3.

1,1-Dioxido-3,6-dihydro-2*H*-thiopyran-4-yl trifluoromethanesulfonate (31m)



Prepared according to General Procedure G using tetrahydro-4*H*-thiopyran-4-one 1,1-dioxide (296 mg, 2.0 mmol). The crude product was purified by flash column chromatography (20–30% EtOAc in petrol) to afford the corresponding *alkenyl triflate* **31m** as a white solid (160 mg, 29%).

mp 81–83 °C (EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (tt, *J* = 4.5, 1.2 Hz, 1H, OC=C*H*), 3.79–3.76 (m, 2H, C=CHCH_2), 3.26 (tt, *J* = 6.7, 1.3 Hz, 2H, SCH_2CH_2), 3.10–3.01 (m, 2H, SCH_2CH_2);

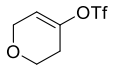
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.1, 118.5 (app. d, $^{1}J_{CF}$ = 320.6 Hz), 112.7, 48.7, 47.0, 28.2;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.4;

IR ν_{max} (neat)/cm^{-1} 2930, 2852, 1415, 1318, 1300, 1290, 1204, 1125, 1064, 1038;

HRMS (ESI/APCI) not found.

3,6-Dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (31n)



Prepared according to General Procedure G using tetrahydro-4*H*-pyran-4-one (0.46 mL, 5.0 mmol). The crude product was purified by flash column chromatography (5–20% Et_2O in pentane) to afford the corresponding alkenyl triflate **31n** as a colourless oil (678 mg, 58%) with spectroscopic data in accordance with the literature;[232]

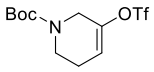
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.78 (m, 1H, OC=C*H*), 4.26 (app. q, *J* = 2.9 Hz, 2H, CHCH_2), 3.89 (t, *J* = 5.5 Hz, 2H, OCH_2CH$_2$), 2.49–2.42 (m, 2H, OCH$_2$CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 118.6 (q, $^1J_{CF}$ = 320.3 Hz), 117.1, 64.3, 64.1, 28.5;

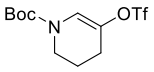
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.9;

IR ν_{max} (neat)/cm^{-1} 2846, 1695, 1416, 1357, 1248, 1203, 1138, 1064, 1008, 872.

Triflate 31o and 31o'



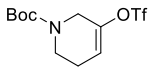
31o



31o'

Prepared according to General Procedure G using *tert*-butyl 3-oxopiperidine-1-carboxylate (0.60 g, 3.0 mmol). The crude product was purified by flash column chromatography (5–15% Et_2O in petrol) to afford the corresponding alkenyl triflate **31o** as a yellow oil (223 mg, 22%) and its regioisomer **3o'** as a yellow oil (416 mg, 42%) with spectroscopic data in accordance with the literature;[233]

tert-Butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate **(31o)**

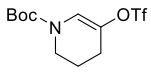


^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (t, *J* = 4.6 Hz, 1H, OC=C*H*), 4.08–3.99 (m, 2H, CCH_2N), 3.49 (t, *J* = 5.7 Hz, 2H, NCH_2CH_2), 2.34–2.26 (m, 2H, NCH_2CH_2), 1.47 (d, *J* = 1.5 Hz, 9H, C(CH_3)$_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.4, 144.9, 118.6 (app. d, $^1J_{CF}$ = 320.4 Hz), 117.4, 80.9, 44.4, 39.0, 28.5, 23.9;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.5.

tert-Butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydropyridine-1(2*H*)-carboxylate **(31o')**

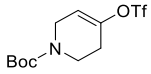


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (br. s, 0.4H, OC=CH^{rot1}), 7.06 (br. s, 0.6H, OC=CH^{rot2}), 3.56–3.47 (m, 2H, NCH_2), 2.43 (t, *J* = 6.4 Hz, 2H, CCH_2), 1.93 (quint, *J* = 6.1 Hz, 2H, NCH_2CH_2), 1.49 (app. d, *J* = 1.4 Hz, 9H, C(CH_3)$_3$) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.5, {134.3, 133.4}, {122.2, 121.8}, 118.7 (app. d, $^1J_{CF}$ = 321.0 Hz), 82.3, {41.8, 40.6}, 28.3, 25.4, {21.1, 20.8} (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.6.

tert-Butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (31p)



Prepared according to General Procedure G using *tert*-butyl 4-oxopiperidine-1-carboxylate (0.60 g, 3.0 mmol). The crude product was purified by flash column chromatography (10–20% Et_2O in petrol) to afford the corresponding alkenyl triflate **31p** as a low-melting white solid (0.59 g, 60%) with spectroscopic data in accordance with the literature;[234]

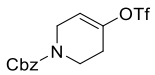
mp 27-28 °C (CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (br. s, 1H, OC=C*H*), 4.08–4.00 (m, 2H, CHCH_2), 3.62 (t, *J* = 5.8 Hz, 2H, CCH_2CH_2), 2.48–2.39 (m, 2H, CCH_2), 1.47 (app. d, *J* = 1.7 Hz, 9H, $C(CH_3)_3$) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.4, 147.0, 118.6 (q, $^1J_{CF}$ = 320.2 Hz), 115.6, 80.7, 41.9, 40.9, 39.9, {28.5, 28.2} (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.9.

1-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (31q)



Prepared according to General Procedure G using 1-benzyloxycarbonylpiperidin-4-one (2.33 g, 10.0 mmol). The crude product was purified by flash column chromatography (5–20% EtOAc in petrol) to afford the corresponding alkenyl triflate **31q** as a light brown oil (1.87 g, 51%) with spectroscopic data in accordance with the literature;[235]

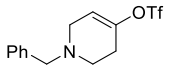
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5H, 5 × Ar*H*), 5.80 (br. s, 0.5H, OC=CH^{rot1}), 5.75 (br. s, 0.5H, OC=CH^{rot2}), 5.16 (s, 2H, ArCH_2), 4.13 (s, 2H, CHCH_2), 3.72 (t, *J* = 5.5 Hz, 2H, NCH_2CH_2), 2.47 (app. s, 2H, NCH_2CH_2) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.1, {147.0, 146.6}, 136.3, 128.7, 128.4, 128.2, 118.6 (q, $^1J_{CF}$ = 320.3 Hz), {115.9, 115.3}, 67.8, 42.0, 40.6, {28.3, 28.0} (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.7, −73.8 (recorded as a pair of rotamers);

HRMS (ESI$^+$) found *m*/*z* 366.0621 $[M+H]^+$, $C_{14}H_{15}F_3NO_5S^+$ requires *m*/*z* 366.0618.

1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (31r)



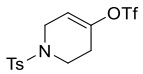
Prepared according to General Procedure G using 1-benzylpiperidin-4-one (1.13 g, 6.0 mmol). The crude product was purified by flash column chromatography (5–15% EtOAc in petrol) and filtered over basic alumina (10% EtOAc in petrol) to afford the corresponding alkenyl triflate **31r** as a yellow oil (1.81 g, 94%) with spectroscopic data in accordance with the literature;[236]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.31 (m, 4H, 4 × Ar*H*), 7.31–7.26 (m, 1H, Ar*H*), 5.73 (td, *J* = 3.5, 1.7 Hz, 1H, OC=C*H*), 3.63 (s, 2H, ArCH_2), 3.13 (q, *J* = 3.1 Hz, 2H, C=CHCH_2), 2.73 (t, *J* = 5.7 Hz, 2H, CCH_2CH_2N), 2.49–2.42 (m, 2H, CCH_2CH_2N);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.4, 137.8, 129.1, 128.6, 127.5, 118.7 (q, $^{1}J_{CF}$ = 320.7 Hz), 116.3, 61.4, 50.6, 49.2, 28.5;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.9.

1-Tosyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (31s)



Prepared according to General Procedure G using 1-tosylpiperidin-4-one (0.76 g, 3.0 mmol). The crude product was purified by flash column chromatography (0–15% EtOAc in petrol) to afford the corresponding alkenyl triflate **31s** as a white solid (498 mg, 43%) with spectroscopic data in accordance with the literature;[237]

mp 86–87 °C (EtOAc);

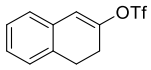
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2H, 2 × Ar*H*), 7.34 (d, *J* = 8.1 Hz, 2H, 2 × Ar*H*), 5.76–5.70 (m, 1H, OC=C*H*), 3.78 (app. q, *J* = 3.0 Hz, 2H, CHCH_2), 3.35 (t, *J* = 5.7 Hz, 2H, NCH_2CH_2), 2.52–2.45 (m, 2H, NCH_2CH_2), 2.44 (s, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.5, 144.4, 133.4, 130.1, 127.6, 118.0 (q, $^{1}J_{CF}$ = 320.6 Hz), 114.6, 43.5, 42.8, 28.0, 21.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.7;

LRMS (ESI^{+}) *m*/*z* 386.0 ([M+H]$^{+}$), 408.0 ([M+Na]$^{+}$).

3,4-Dihydronaphthalen-2-yl trifluoromethanesulfonate (31u)



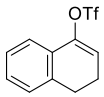
Prepared according to General Procedure G using 2-tetralone (0.40 mL, 3.0 mmol). The crude product was purified by flash column chromatography (0–0.25% Et_2O in petrol) to afford the corresponding alkenyl triflate **31u** as a colourless oil (670 mg, 80%) with spectroscopic data in accordance with the literature;[230]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 2H, 2 × Ar*H*), 7.18–7.15 (m, 1H, Ar*H*), 7.12–7.08 (m, 1H, Ar*H*), 6.50 (s, 1H, OC=C*H*), 3.08 (t, *J* = 8.4 Hz, 2H, ArCH_2), 2.72 (t, *J* = 8.4 Hz, 2H, OCCH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.1, 133.1, 131.2, 128.6, 127.7, 127.5, 127.2, 118.8 (q, $^1J_{CF}$ = 320.4 Hz), 118.7, 28.7, 26.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.6.

3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate (31v)



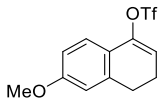
Prepared according to General Procedure G using 1-tetralone (1.46 g, 10.0 mmol) and $PhNTf_2$ (3.4 g, 9.5 mmol). The crude product was purified by vacuum distillation (***bp*** 100 °C, 5 mbar) using a Kugelrohr apparatus to afford the corresponding alkenyl triflate **31v** as a light yellow oil (2.06 g, 74%) with spectroscopic data in accordance with the literature;[238]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.16 (m, 4H, 4 × Ar*H*), 6.03 (t, *J* = 4.8 Hz, 1H, OC=C*H*), 2.88 (t, *J* = 8.2 Hz, 2H, ArCH_2), 2.56–2.49 (m, 2H, OC=CHCH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.5, 136.3, 129.3, 128.8, 127.9, 127.1, 121.4, 118.7 (app. d, $^1J_{CF}$ = 320.3 Hz), 117.9, 27.0, 22.5;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.7.

6-Methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (31w)



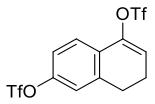
Prepared according to General Procedure G using 6-methoxy-1-tetralone (0.88 g, 5.0 mmol) and $PhNTf_2$ (1.78 g, 5.0 mmol). The crude product was purified by flash column chromatography (0–5% Et_2O in petrol) to afford the corresponding alkenyl triflate **31w** as a colourless oil (1.37 g, 89%) which solidified at -20 °C with spectroscopic data in accordance with the literature;[239]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.77 (dd, *J* = 8.5, 2.6 Hz, 1H, Ar*H*), 6.74–6.73 (m, 1H, Ar*H*), 5.87 (t, *J* = 4.8 Hz, 1H, OC=C*H*), 3.82 (s, 3H, OCH_3), 2.84 (t, *J* = 8.1 Hz, 2H, ArCH_2), 2.51–2.45 (m, 2H, OC=CHCH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.4, 146.5, 138.5, 122.9, 121.8, 118.8 (q, $^1J_{CF}$ = 320.2 Hz), 114.9, 114.4, 111.4, 55.4, 27.5, 22.4.;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −73.7.

3,4-Dihydronaphthalene-1,6-diyl bis(trifluoromethanesulfonate) (31x)



Prepared according to General Procedure G using 6-hydroxy-1-tetralone (486 mg, 3.0 mmol) and $PhNTf_2$ (2.07 g, 5.8 mmol). The crude product was purified by flash column chromatography (0–5% EtOAc in petrol) to afford the corresponding alkenyl triflate **31x** as a yellow oil (1.04 g, 84%) with spectroscopic data in accordance with the literature;[240]

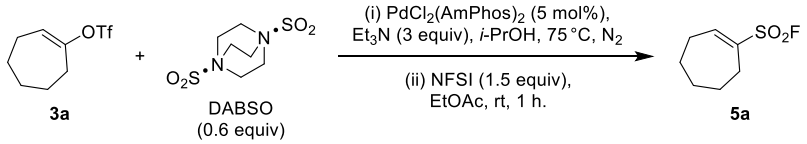
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.17 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar*H*), 7.12 (s, 1H, Ar*H*), 6.12 (t, *J* = 4.8 Hz, 1H, OC=C*H*), 2.92 (t, *J* = 8.2 Hz, 2H, ArCH_2), 2.57 (td, *J* = 8.2, 4.9 Hz, 2H, OC=CHCH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.5, 145.0, 139.1, 129.1, 123.2, 121.0, 119.9, 119.7, 118.8 (q, $^1J_{CF}$ = 320.7 Hz), 118.7 (q, $^1J_{CF}$ = 320.1 Hz), 26.9, 22.1;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ −72.8 (s, 3F), −73.6 (s, 3F).

6.2.7 Palladium-catalysed synthesis of CASFs

General Procedure H: Synthesis of alkenylsulfonyl fluorides from alkenyl triflates, DABSO and NFSI as exemplified by the preparation of cyclohept-1-ene-1-sulfonyl fluoride (33a)



A reaction tube was charged with 1-cyclohept-1-enyl triflate (**31a**) (73.2 mg, 0.30 mmol, 1.0 equiv), DABSO (43.2 mg, 0.18 mmol, 0.60 equiv) and $PdCl_2(AmPhos)_2$ (10.6 mg, 0.015 mmol, 0.050 equiv), sealed with a rubber septum, and evacuated and back-filled with N_2 for three times. Anhydrous degassed isopropanol (1.2 mL) and anhydrous triethylamine (0.13 mL, 0.90 mmol, 3.0 equiv) were added subsequently, and the reaction mixture was stirred under positive pressure of N_2 in a preheated aluminum heating block at 75 °C for 1 h. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*, followed by the addition of EtOAc (1.2 mL), then NFSI (142 mg, 0.45 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 h until completion. The reaction mixture was then diluted with EtOAc, filtered through a plug of silica and concentrated *in vacuo* to yield the crude product which was then purified by flash column chromatography (5–20% CH_2Cl_2 in petrol), affording the *alkenylsulfonyl fluoride* **33a** as a colourless oil (37.5 mg, 70%);

Note: As a general procedure, the first step (sulfination) was monitored by TLC and HPLC. As soon as the alkenyl triflates were fully consumed (0.5–10 h), the reactions were cooled to ambient temperature, followed by a solvent switch.

R_f 0.41 (20% CH_2Cl_2 in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 6.5 Hz, 1H, SC=C*H*), 2.69–2.61 (m, 2H, CHCH_2), 2.47–2.38 (m, 2H, CCH_2), 1.88–1.78 (m, 2H, Alk-CH_2), 1.73–1.59 (m, 4H, 2 × Alk-CH_2);

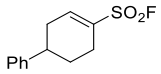
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.6 (d, $^3J_{CF}$ = 2.6 Hz), 138.4 (d, $^2J_{CF}$ = 20.8 Hz), 30.9, 28.8, 27.9, 25.8, 25.0;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 49.7;

IR ν_{max} (neat)/cm^{-1} 2930, 2858, 1449, 1394, 1227, 1194;

HRMS (APCI$^+$) found *m*/*z* 179.0531 $[M+H]^+$, $C_7H_{12}FO_2S^+$ requires *m*/*z* 179.0537.

1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-sulfonyl fluoride (33b)



Prepared according to General Procedure H using alkenyl triflate **31b** (92 mg, 0.30 mmol), with the first step heated for 5.5 h. The crude product was purified by flash column chromatography (0–10% Et_2O in petrol) to afford the *alkenylsulfonyl fluoride* **33b** as a white crystalline solid (51.0 mg, 71%);

mp 115–116 °C (CH_2Cl_2);

R_f 0.37 (15% Et_2O in hexane) [UV/$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 8.1, 6.7 Hz, 2H, 2 × Ar*H*), 7.30–7.18 (m, 4H, 3 × Ar*H* + SC=C*H*), 2.95–2.84 (m, 1H, ArC*H*), 2.76–2.53 (m, 3H, SCCH_2 + C=CHCH_aH$_b$), 2.52–2.39 (m, 1H, C=CHCH$_a$$H_b$), 2.23–2.14 (m, 1H, SCCH$_2$CH_aH$_b$), 1.98–1.83 (m, 1H, SCCH$_2$CH$_a$$H_b$);

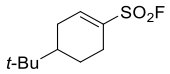
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.2, 143.9 (d, $^3J_{CF}$ = 2.1 Hz), 133.8, 128.9, 127.1, 126.8, 38.4, 33.5, 28.9, 24.2;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.7;

IR ν_{max} (neat)/cm^{-1} 2926, 1646, 1494, 1396, 1220, 1204;

HRMS (APCI$^+$) found *m*/*z* 241.0688 [M+H]$^+$, $C_{12}H_{14}FO_2S^+$ requires *m*/*z* 241.0693.

4-(*tert*-Butyl)cyclohex-1-ene-1-sulfonyl fluoride (33c)



Prepared according to General Procedure H using alkenyl triflate **31c** (86 mg, 0.30 mmol), with the first step heated to 80 °C for 5 h. The crude product was purified by flash column chromatography (2% Et_2O in petrol) to afford the *alkenylsulfonyl fluoride* **33c** as a white solid (46.1 mg, 70%);

mp 48–50 °C (hexane);

R_f 0.40 (5% Et_2O in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.11 (m, 1H, SC=C*H*), 2.69–2.58 (m, 1H, C(CH$_3$)$_3$C*H*), 2.49–2.32 (m, 2H, Alk-CH_2), 2.14–1.98 (m, 2H, Alk-CH_2), 1.42–1.21 (m, 2H, Alk-CH_2), 0.91 (s, 9H, C(CH_3)$_3$);

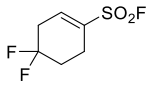
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.0, 133.7 (d, $^{2}J_{CF}$ = 22.6 Hz), 42.6, 32.3, 27.7, 27.1, 25.0, 23.3;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.6;

IR ν_{max} (neat)/cm^{-1} 2968, 1649, 1391, 1369, 1201, 1055;

HRMS (ESI/APCI) not found.

4,4-Difluorocyclohex-1-ene-1-sulfonyl fluoride (33d)



Prepared according to General Procedure H using alkenyl triflate **31d** (80 mg, 0.30 mmol), with the first step heated for 4 h. The crude product was purified by flash column chromatography (15–30% CH_2Cl_2 in petrol) to afford the *alkenylsulfonyl fluoride* **33d** as a light brown oil (40.2 mg, 67%);

R$_f$ 0.31 (33% CH_2Cl_2 in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03–6.96 (m, 1H, SC=C*H*), 2.86 (tt, *J* = 13.4, 3.1 Hz, 2H, C=CHC*H*$_2$), 2.78 (t, *J* = 6.0 Hz, 2H, $CF_2CH_2CH_2$), 2.23 (tt, *J* = 13.3, 6.6 Hz, 2H, CF_2CH_2);

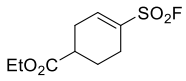
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.7 (td, $^{3}J_{CF}$ = 5.7, 2.5 Hz), 133.5 (d, $^{2}J_{CF}$ = 24.9 Hz), 120.4 (t, $^{1}J_{CF}$ = 241.7 Hz), 35.1 (t, $^{2}J_{CF}$ = 29.2 Hz), 29.6 (t, $^{2}J_{CF}$ = 25.4 Hz), 22.3 (t, $^{3}J_{CF}$ = 5.6 Hz);

^{19}F NMR (377 MHz, $CDCl_3$) δ 51.8 (s, 1F, SO_2F), −97.2 (quint d, *J* = 13.3, 2.6 Hz, 2F, CF_2);

IR ν_{max} (neat)/cm^{-1} 2953, 1654, 1403, 1378, 1265, 1205, 1150, 1121, 1086, 1059;

HRMS (APCI$^+$) found *m*/*z* 201.0189 [M+H]$^+$, $C_6H_8F_3O_2S^+$ requires *m*/*z* 201.0192.

Ethyl 4-(fluorosulfonyl)cyclohex-3-ene-1-carboxylate (33e)



Prepared according to General Procedure H using alkenyl triflate **31e** (91 mg, 0.30 mmol), with the first step heated for 4.5 h. The crude product was purified by flash column chromatography (5–10% EtOAc in petrol) to afford the *alkenylsulfonyl fluoride* **33e** as a colourless oil (57.0 mg, 80%);

R_f 0.27 (15% EtOAc in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 3.6 Hz, 1H, SC=C*H*), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.69–2.55 (m, 4H, C(=O)C*H* + C=CHCH_2 + SCC$H_a$$H_b$), 2.54–2.43 (m, 1H, SCC$H_a$$H_b$), 2.24–2.16 (m, 1H, SCC$H_2CH_c$$H_d$), 1.95–1.82 (m, 1H, SCC$H_2CH_c$$H_d$), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.7, 142.5 (d, $^3J_{CF}$ = 3.0 Hz), 133.5 (d, $^2J_{CF}$ = 23.8 Hz), 61.2, 37.4, 27.8, 24.3, 22.8, 14.3;

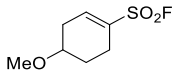
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.8;

IR ν_{max} (neat)/cm^{-1} 2984, 1728, 1398, 1252, 1202, 1180, 1033;

LRMS (ESI$^+$) *m*/*z* 237.0 ([M+H]$^+$), 259.0 ([M+Na]$^+$);

HRMS (APCI$^+$) found *m*/*z* 236.0516 [M]$^+$, $C_9H_{13}FO_4S^+$ requires *m*/*z* 236.0513.

4-Methoxycyclohex-1-ene-1-sulfonyl fluoride (33f)



Prepared according to General Procedure H using alkenyl triflate **31f** (78 mg, 0.30 mmol), with the first step heated for 4 h. The crude product was purified by flash column chromatography (1:4:15 EtOAc/CH_2Cl_2/hexane mixture) to afford the *alkenylsulfonyl fluoride* **33f** as a colourless oil (33.3 mg, 57%);

R_f 0.36 (1:4:8 EtOAc/CH_2Cl_2/hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (app. s, 1H, SC=C*H*), 3.66–3.51 (m, 1H, OC*H*), 3.37 (s, 3H, OCH_3), 2.67–2.53 (m, 2H, Alkyl-CH_2), 2.53–2.33 (m, 2H, Alkyl-CH_2), 2.05–1.84 (m, 2H, Alkyl-CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.5 (d, $^3J_{CF}$ = 2.4 Hz), 133.6 (d, $^2J_{CF}$ = 23.8 Hz), 72.4, 56.2, 31.5, 25.7, 20.8;

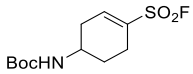
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.8;

IR ν_{max} (neat)/cm^{-1} 2934, 2829, 1397, 1202, 1100, 1055, 769;

LRMS (ESI$^+$) *m*/*z* 217.0 ([M+Na]$^+$);

HRMS (APCI$^+$) found *m*/*z* 194.0412 [M]$^+$, $C_7H_{11}FO_3S^+$ requires *m*/*z* 194.0407.

***tert*-Butyl (4-(fluorosulfonyl)cyclohex-3-en-1-yl)carbamate (33g)**



Prepared according to General Procedure H using alkenyl triflate **31g** (104 mg, 0.30 mmol), with the first step heated for 4 h. The crude product was purified by flash column chromatography (1:4:5 EtOAc/CH_2Cl_2/petrol mixture) to afford the *alkenylsulfonyl fluoride* **33g** as a white solid (53.5 mg, 64%);

mp 161–163 °C (CH_2Cl_2);

R_f 0.31 (1:4:5 EtOAc/CH_2Cl_2/hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.04 (m, 1H, SC=C*H*), 4.51 (br. s, 1H, N*H*), 3.85 (br. s, 1H, NC*H*), 2.76 (d, *J* = 19.2 Hz, 1H, SC=CHCH_aH$_b$), 2.67–2.50 (m, 2H, SCCH_2), 2.28–2.15 (m, 1H, SC=CHCH$_a$$H_b$), 2.12–2.01 (m, 1H, SCCH$_2$CH_cH$_d$), 1.81–1.67 (m, 1H, SCCH$_2$CH$_c$$H_d$), 1.45 (s, 9H, C(C$H_3$)$_3$);

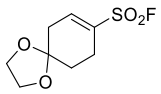
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.2, 141.9, 133.6, 80.1, 44.2, 32.5, 28.5, 27.5, 22.3;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.9;

IR ν_{max} (neat)/cm^{-1} 3359, 2981, 2938, 1676, 1529, 1398, 1370, 1316, 1301, 1178;

HRMS (APCI$^-$) found *m*/*z* 278.0870 [M–H]$^-$, $C_{11}H_{17}NO_4FS^-$ requires *m*/*z* 278.0868.

1,4-Dioxaspiro[4.5]dec-7-ene-8-sulfonyl fluoride (33h)



Prepared according to General Procedure H using alkenyl triflate **31h** (86 mg, 0.30 mmol), with the first step heated for 9 h. The crude product was purified by flash column chromatography (30–50% CH_2Cl_2 in petrol, then 10–30% Et_2O in petrol) to afford the *alkenylsulfonyl fluoride* **33h** as a white solid (49.5 mg, 74%);

Gram-scale synthesis:

An oven-dried two-neck round-bottom flask was charged with alkenyl triflate **31h** (1.01 g, 3.50 mmol, 1.0 equiv), DABSO (504 mg, 2.10 mmol, 0.60 equiv) and $PdCl_2(AmPhos)_2$ (124 mg, 0.175 mmol, 0.050 equiv), evacuated and filled with N_2 for three times. Anhydrous degassed isopropanol (12 mL) and triethylamine (1.45 mL, 10.5 mmol, 3.0 equiv) were added subsequently. The reaction mixture was heated under reflux under a N_2 atmosphere for 22 h or until completion. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*, followed by the addition of EtOAc (14 mL), then NFSI (1.32 g, 4.20 mmol, 1.5 equiv) was added in small portions. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with Et_2O, filtered through a plug of silica and concentrated *in vacuo* to yield the crude product which was then purified by flash column chromatography as stated above to afford **33h** (0.57 g, 73%);

mp 62–64 °C (Et_2O);

R_f 0.07 (50% CH_2Cl_2 in hexane), 0.39 (50% Et_2O in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (t, J = 3.2 Hz, 1H, SC=C*H*), 4.01 (s, 4H, 2 × OCH_2), 2.70 (t, J = 6.3 Hz, 2H, CH=CCH_2), 2.56 (t, J = 3.1 Hz, 2H, C=CHCH_2), 1.91 (t, J = 6.5 Hz, 2H, CH=CCH$_2$CH_2);

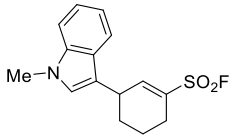
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.7 (d, $^3J_{CF}$ = 2.4 Hz), 133.5 (d, $^2J_{CF}$ = 23.7 Hz), 105.9, 64.9, 36.4, 30.6, 23.2;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.5;

IR ν_{max} (neat)/cm^{-1} 2894, 1650, 1400, 1372, 1201, 1121;

HRMS (APCI$^+$) found *m*/*z* 223.0431 $[M+H]^+$, $C_8H_{12}FO_4S^+$ requires *m*/*z* 223.0435.

3-(1-Methyl-1*H*-indol-3-yl)cyclohex-1-ene-1-sulfonyl fluoride (33i)



Prepared according to General Procedure H using alkenyl triflate **31i** (108 mg, 0.30 mmol), with the first step heated for 10 h. The crude product was purified by flash column chromatography (20–35% CH_2Cl_2 in petrol) to afford the *alkenylsulfonyl fluoride* **33i** as a light yellow oil (45.4 mg, 52%);

Alternatively, the first step was heated to 95 °C under microwave irradiation for 3 h, followed by fluorination and purification as described above to afford **5i** (46.0 mg, 52%).

R_f 0.27 (40% CH_2Cl_2 in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.3 Hz, 1H, Ar*H*), 7.28–7.23 (m, 2H, Ar*H* + SC=C*H*), 7.13 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.77 (s, 1H, NC*H*),
4.03–3.95 (m, 1H, SC=CHC*H*), 3.76 (s, 3H, NCH_3), 2.58–2.53 (m, 2H, SCCH_2), 2.15–2.03 (m, 1H, CHCH_aH$_b$), 1.97–1.77 (m, 3H, CHCH$_a$$H_b$ + SCCH$_2$CH_2);

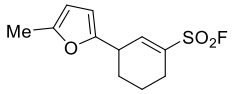
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.3, 137.3, 134.0 (d, $^2J_{CF}$ = 21.8 Hz)., 126.7, 126.5, 122.3, 119.4, 118.7, 114.8, 109.7, 33.5, 32.9, 28.4, 23.8, 20.1;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.8;

IR ν_{max} (neat)/cm^{-1} 3051, 2941, 2862, 1474, 1398, 1329, 1204, 738;

HRMS (ESI$^+$) found *m*/*z* 294.0960 [M+H]$^+$, $C_{15}H_{17}FNO_2S^+$ requires *m*/*z* 294.0959.

3-(5-Methylfuran-2-yl)cyclohex-1-ene-1-sulfonyl fluoride (33k)



Prepared according to General Procedure H using alkenyl triflate **31k** (93 mg, 0.30 mmol), with the first step heated for 9 h. The crude product was purified by flash column chromatography (10–25% CH_2Cl_2 in petrol) to afford the *alkenylsulfonyl fluoride* **33k** as a colourless oil (50.3 mg, 69%);

R_f 0.36 (25% CH_2Cl_2 in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.14 (m, 1H, SC=C*H*), 5.93 (d, *J* = 3.2 Hz, 1H, Ar*H*), 5.92–5.85 (m, 1H, Ar*H*), 3.75–3.65 (m, 1H, C=CHC*H*), 2.58–2.44 (m, 2H, SCCH_2), 2.27 (s, 3H, CH_3), 2.08–1.93 (m, 2H, CHCH_2), 1.87–1.75 (m, 2H, SCCH_2CH_2);

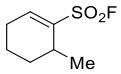
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.0, 151.9, 143.3, 134.9 (d, $^2J_{CF}$ = 22.5 Hz), 106.9, 106.2, 35.9, 26.3, 23.6, 20.1, 13.7.

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.6;

IR ν_{max} (neat)/cm^{-1} 2951, 2868, 1402, 1206, 1020, 944, 778;

HRMS (ESI$^-$) found *m*/*z* 243.0494 [M−H]$^-$, $C_{11}H_{12}O_3FS^-$ requires *m*/*z* 243.0497.

6-Methylcyclohex-1-ene-1-sulfonyl fluoride (33l)



Prepared according to General Procedure H using alkenyl triflate **31l** (73 mg, 0.30 mmol), with the first step heated to 95 °C under microwave irradiation for 3 h. The crude product was purified by flash column chromatography (10–30% CH_2Cl_2 in petrol) to afford the *alkenylsulfonyl fluoride* **33l** as a colourless oil (22.8 mg, 43%);

R_f 0.21 (20% CH_2Cl_2 in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 3.9 Hz, 1H, SC=C*H*), 2.85–2.77 (m, 1H, CH_3C*H*), 2.43–2.24 (m, 2H, C=CHCH_2), 1.86–1.61 (m, 4H, C=CHCH_2CH_2 + CH_3CHCH_2), 1.27 (dd, *J* = 7.0, 1.7 Hz, 3H, CH_3);

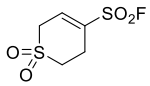
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.6 (d, $^3J_{CF}$ = 2.3 Hz), 138.7 (d, $^2J_{CF}$ = 19.0 Hz), 30.2, 28.8, 26.3, 19.7, 17.0;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 58.2;

IR ν_{max} (neat)/cm^{-1} 2944, 2880, 1399, 1202, 761, 729, 625;

HRMS (ESI/APCI) not found.

3,6-Dihydro-2*H*-thiopyran-4-sulfonyl fluoride 1,1-dioxide (33m)



Prepared according to General Procedure H using alkenyl triflate **31m** (84 mg, 0.30 mmol), with the first step heated for 1 h. The crude product was purified by flash column chromatography (20–40% EtOAc in petrol) to afford the *alkenylsulfonyl fluoride* **33m** as a creamy yellow solid (31.5 mg, 49%);

mp 113–115 °C (EtOAc);

R*f* 0.34 (40% EtOAc in hexane) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (t, *J* = 4.3 Hz, 1H, SC=C*H*), 3.96–3.88 (m, 2H, CHCH_2), 3.32–3.20 (m, 4H, 2 × CH_2);

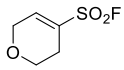
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.2, 134.2 (d, $^2J_{CF}$ = 27.0 Hz), 50.0, 46.5, 24.8;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 52.8;

IR ν_{max} (neat)/cm^{-1} 2964, 2922, 1406, 1326, 1292, 1206, 1170, 1126, 1059;

HRMS (ESI$^-$) found *m*/*z* 212.9697 [M−H]$^-$, $C_5H_6O_4FS_2^-$ requires *m*/*z* 212.9697.

3,6-Dihydro-2*H*-pyran-4-sulfonyl fluoride (33n)



Prepared according to General Procedure H using alkenyl triflate **31n** (70 mg, 0.30 mmol), with the first step heated for 3 h. The crude product was purified by flash column chromatography (20–50% CH_2Cl_2 in pentane) to afford the *alkenylsulfonyl fluoride* **33n** as a light yellow oil (31.0 mg, 62%);

R*f* 0.36 (50% CH_2Cl_2 in pentrol) [$KMnO_4$];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.13 (m, 1H, SC=C*H*), 4.39 (app. quint, *J* = 2.8 Hz, 2H, CHCH_2), 3.90 (t, *J* = 5.4 Hz, 2H, OCH_2CH$_2$), 2.61–2.55 (m, 2H, OCH$_2$CH_2);

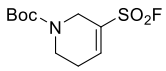
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 142.0 (d, $^3J_{CF}$ = 2.5 Hz), 131.6 (d, $^2J_{CF}$ = 25.7 Hz), 64.9, 63.3, 23.9;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 50.9;

IR ν_{max} (neat)/cm^{-1} 2872, 1653, 1434, 1399, 1279, 1237, 1200, 1129;

HRMS (APCI$^+$) found *m*/*z* 167.0170 [M+H]$^+$, $C_5H_8FO_3S^+$ requires *m*/*z* 167.0173.

***tert*-Butyl 5-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33o)**



Prepared according to General Procedure H using alkenyl triflate **31o** (99 mg, 0.30 mmol), with the first step heated for 1.5 h. The crude product was purified by flash column chromatography (50% CH_2Cl_2 in petrol, then 10–30% EtOAc in petrol) to afford the *alkenylsulfonyl fluoride* **33o** as a colourless oil which solidified at -20 °C (55.0 mg, 69%);

mp 43–45 °C (EtOAc);

R_f 0.36 (25% EtOAc in hexane) [$KMnO_4$/UV (weak)];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (app. s, 1H, SC=C*H*), 4.28 (s, 2H, CCH_2), 3.55 (t, *J* = 5.7 Hz, 2H, NCH_2CH_2), 2.52–2.40 (m, 2H, CHCH_2), 1.48 (s, 9H, C(CH_3)$_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.2, 143.1, 131.6, 81.3, 41.8, 38.4, 28.4, 25.8;

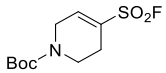
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 54.2;

IR ν_{max} (neat)/cm^{-1} 2978, 2935, 1740, 1699, 1616, 1407, 1207, 1157;

LRMS (ESI$^+$) *m*/*z* 288.0 ([M+Na]$^+$);

HRMS (ESI$^+$) found *m*/*z* 288.0676 [M+Na]$^+$, $C_{10}H_{16}NO_4FSNa^+$ requires *m*/*z* 288.0676.

***tert*-Butyl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33p)**



Prepared according to General Procedure H using alkenyl triflate **31p** (99 mg, 0.30 mmol), with the first step heated for 2 h. The crude product was purified by flash column chromatography (5–10% EtOAc in petrol) to afford the *alkenylsulfonyl fluoride* **33p** as a white solid (65.2 mg, 82%);

mp 56-58 °C (CH_2Cl_2);

R_f 0.36 (20% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (br. s, 1H, SC=C*H*), 4.22 (app. t, *J* = 3.0 Hz, 2H, CHCH_2), 3.64 (t, *J* = 5.5 Hz, 2H, NCH_2CH_2), 2.61–2.54 (m, 2H, CCH_2), 1.48 (s, 9H, C(CH_3)$_3$);

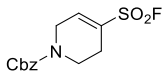
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.2, {140.6, 140.0}, 132.7 (br.), 81.2, {43.7, 43.3}, {40.1, 38.9}, 28.5, 24.2 (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.2;

IR ν_{max} (neat)/cm^{-1} 2978, 1697, 1403, 1367, 1241, 1203, 1165, 1118;

HRMS (APCI$^-$) found *m*/*z* 264.0710 [M−H]$^-$, $C_{10}H_{15}FNO_4S^-$ requires *m*/*z* 264.0711.

Benzyl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33q)



Prepared according to General Procedure H using alkenyl triflate **31q** (110 mg, 0.30 mmol), with the first step heated for 2 h. The crude product was purified by flash column chromatography (30–60% CH_2Cl_2 in petrol, followed by 4:2:1 petrol/CH_2Cl_2/Et_2O mixture) to afford the *alkenylsulfonyl fluoride* **33q** as a light yellow solid (58.0 mg, 65%);

mp 56–58 °C (CH_2Cl_2);

R_f 0.13 (50% CH_2Cl_2 in hexane), 0.41 (4:2:1 hexane/CH_2Cl_2/Et_2O) [$KMnO_4$/ UV (weak)];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5H, 5 × Ar*H*), 7.11 (br. s, 0.5H, SC=CH^{rot1}), 7.05 (br. s, 0.5H, SC=CH^{rot2}), 5.17 (s, 2H, ArCH_2), 4.30 (app. s, 2H, CHCH_2), 3.73 (t, *J* = 5.6 Hz, 2H, NCH_2CH_2), 2.60 (app. s, 2H, NCH_2CH_2) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.9, {140.1, 139.4}, 136.1, 132.8, 128.8, 128.5, 128.3, 68.0, 43.6, {39.9, 39.5}, {24.2, 24.0}(recorded as a pair of rotamers);

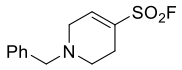
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.41, 51.36 (recorded as a pair of rotamers);

IR ν_{max} (neat)/cm^{-1} 2925, 1700, 1655, 1427, 1401, 1234, 1200, 1112;

LRMS (ESI^-) *m*/*z* 298.0 ($[M-H]^-$);

HRMS (ESI^-) found *m*/*z* 298.0555 $[M-H]^-$, $C_{13}H_{13}FNO_4S^-$ requires *m*/*z* 298.0555.

1-Benzyl-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (33r)



A reaction tube was charged with alkenyl triflate **31r** (96 mg, 0.30 mmol, 1.0 equiv), DABSO (43 mg, 0.18 mmol, 0.60 equiv) and $PdCl_2(AmPhos)_2$ (10.6 mg, 0.015 mmol, 0.050 equiv), sealed with a rubber septum, evacuated and filled with N_2 for three times. Anhydrous degassed isopropanol (1.2 mL) and anhydrous triethylamine (0.13 mL, 0.90 mmol, 3.0 equiv) were added subsequently. The septum was quickly replaced with a Teflon microwave cap, and the reaction was heated to 95 °C under microwave irradiation for 3 h. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*, followed by the addition of ethyl acetate (1.2 mL), DIPEA (0.16 mL, 0.90 mmol, 3.0 equiv) and then NFSI (142 mg, 0.45 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 h, and then diluted with EtOAc, filtered through a plug of silica and concentrated *in vacuo* to yield the crude product (53% NMR yield) which was then purified by flash column chromatography (10% EtOAc in petrol) to afford the *alkenylsulfonyl fluoride* **33r** as a yellow oil (35.5 mg, 46%);

R_f 0.18 (10% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H, 5 × Ar*H*), 7.08–7.03 (m, 1H, SC=C*H*), 3.66 (s, 2H, PhCH_2N), 3.27 (app. quint, *J* = 3.0 Hz, 2H, NCH_2CH), 2.74 (t, *J* = 5.5 Hz, 2H, NCH_2CH_2), 2.62–2.56 (m, 2H, CH=CCH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.7, 137.2, 132.3 (d, $^2J_{CF}$ = 24.7 Hz), 129.1, 128.7, 127.7, 61.8, 52.2, 48.4, 24.8;

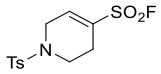
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.1;

IR ν_{max} (neat)/cm^{-1} 2919, 1404, 1207, 1159, 1029, 781, 736, 701, 652;

HRMS (ESI$^+$) found *m*/*z* 256.0802 [M+H]$^+$, $C_{12}H_{15}NO_2FS^+$ requires *m*/*z* 256.0802.

Note: When General Procedure H was followed, at 80 °C for 3 h, an NMR yield of 53% was obtained. The isolated product contained inseparable trace of unreacted **31r**. Heating to 95 °C under microwave irradiation ensured full conversion of **31r** without increasing the reaction time.

1-Tosyl-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (33s)



Prepared according to General Procedure H using alkenyl triflate **31s** (116 mg, 0.30 mmol), with the first step heated for 2 h. The crude product was purified by flash column chromatography (10–40% Et_2O in petrol) to afford the *alkenylsulfonyl fluoride* **33s** as a white solid (86.2 mg, 90%);

mp 176–178 °C (Et_2O);

R_f 0.18 (40% Et_2O in hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H, 2 × Ar*H*), 7.36 (d, *J* = 8.1 Hz, 2H, 2 × Ar*H*), 7.05–7.00 (m, 1H, SC=C*H*), 3.93 (app. quint, *J* = 2.9 Hz, 2H, CHCH_2), 3.35 (t, *J* = 5.6 Hz, 2H, NCH_2CH_2), 2.68–2.61 (m, 2H, NCH_2CH_2), 2.44 (s, 3H, CH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.7, 138.5 (d, $^3J_{CF}$ = 2.5 Hz), 132.8, 132.6 (d, $^2J_{CF}$ = 26.2 Hz), 130.2, 127.7, 44.9, 41.9, 24.2, 21.7;

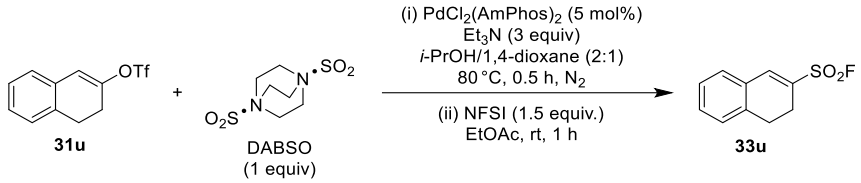
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.7;

IR ν_{max} (neat)/cm^{-1} 3657, 2980, 2889, 1381, 1250, 1206, 1162, 1073;

LRMS (ESI$^+$) *m*/*z* 320.0 ([M+H]$^+$), 342.0 ([M+Na]$^+$);

HRMS (ESI$^+$) found *m*/*z* 320.0421 [M+H]$^+$, $C_{12}H_{15}FNO_4S_2^+$ requires *m*/*z* 320.0421.

General Procedure I: Synthesis of alkenylsulfonyl fluorides from tetralone-derived alkenyl triflates, DABSO and NFSI as exemplified by the preparation of 3,4-dihydronaphthalene-2-sulfonyl fluoride (33u)



A reaction tube was charged with alkenyl triflate **31u** (83 mg, 0.30 mmol, 1.0 equiv), DABSO (72 mg, 0.30 mmol, 1.0 equiv) and $PdCl_2(AmPhos)_2$ (10.6 mg, 0.015 mmol, 0.050 equiv), sealed with a rubber septum, and evacuated and back-filled with N_2 for three times. Anhydrous degassed isopropanol (0.8 mL), 1,4-dioxane (0.4 mL) and triethylamine (0.13 mL, 0.90 mmol, 3.0 equiv) were added subsequently, and the reaction mixture was stirred under positive pressure of N_2 in a preheated aluminum heating block at 80 °C for 0.5 h. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*, followed by addition of EtOAc (1.2 mL), then NFSI (142 mg, 0.45 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 h until completion. The reaction mixture was then diluted with EtOAc, filtered through a plug of silica and concentrated *in vacuo* to yield the crude product, which was then purified by flash column chromatography (10–20% CH_2Cl_2 in petrol), affording the *alkenylsulfonyl fluoride* **33u** as a colourless oil (35.0 mg, 55%); Alternatively, when General Procedure H was followed with the first step (sulfination) heated for 0.5 h, **33u** was afforded in 43% yield (27.5 mg).

R_f 0.30 (20% CH_2Cl_2 in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H, SC=C*H*), 7.38 (dt, *J* = 7.4, 4.3 Hz, 1H, Ar*H*), 7.29 (d, *J* = 4.4 Hz, 2H, 2 × Ar*H*), 7.23 (dt, *J* = 7.4, 1.0 Hz, 1H, Ar*H*), 3.05 (t, *J* = 8.3 Hz, 2H, $SCCH_2CH_2$), 2.79 (t, *J* = 8.3 Hz, 2H, $SCCH_2CH_2$);

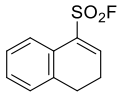
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.3 (d, $^3J_{CF}$ = 3.2 Hz), 136.2, 131.9, 130.4 (d, $^2J_{CF}$ = 24.7 Hz), 129.9, 129.8, 128.3, 127.6, 77.5, 77.2, 76.8, 27.3, 22.1;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 54.2

IR ν_{max} (neat)/cm^{-1} 3065, 3023, 2953, 2917, 2849, 1629, 1397, 1193, 1044;

HRMS (EI$^+$) found *m*/*z* 212.0304 [M]$^+$, $C_{10}H_9FO_2S^+$ requires *m*/*z* 212.0302.

3,4-Dihydronaphthalene-1-sulfonyl fluoride (33v)



Prepared according to General Procedure I using alkenyl triflate **31v** (83 mg, 0.30 mmol), with the first step heated for 1 h. The crude product was purified by flash column chromatography (5–20% CH_2Cl_2 in petrol) to afford the *alkenylsulfonyl fluoride* **33v** as a colourless oil (40.1 mg, 63%);

R_f 0.30 (20% CH_2Cl_2 in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 6.1, 3.0 Hz, 1H, Ar*H*), 7.45 (t, *J* = 4.9 Hz, 1H, SC=C*H*), 7.31 (dt, *J* = 7.9, 3.9 Hz, 2H, 2 × Ar*H*), 7.25–7.20 (m, 1H, Ar*H*), 2.89 (t, *J* = 8.1 Hz, 2H, SC=CHCH$_2$C*H*$_2$), 2.66–2.58 (m, 2H, SC=CHC*H*$_2$);

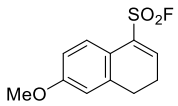
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.6 (d, $^3J_{CF}$ = 2.4 Hz), 135.7, 134.4 (d, $^2J_{CF}$ = 22.7 Hz), 129.7, 128.4, 127.5, 125.8, 124.9, 26.7, 23.8.

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 57.2;

IR ν_{max} (neat)/cm^{-1} 3072, 3028, 2951, 2894, 2840, 1400, 1221, 1201;

HRMS (EI$^+$) found *m*/*z* 212.0305 [M]$^+$, $C_{10}H_9FO_2S^+$ requires *m*/*z* 212.0302.

6-Methoxy-3,4-dihydronaphthalene-1-sulfonyl fluoride (33w)



Prepared according to General Procedure I using alkenyl triflate **31w** (92 mg, 0.30 mmol), with the first step heated for 1.5 h. The crude product was purified by flash column chromatography (0–3% EtOAc in petrol) to afford the *alkenylsulfonyl fluoride* **33w** as a yellow oil (41.3 mg, 57%) which solidified at -20 °C;

mp 41–42 °C (hexane);

R_f 0.25 (10% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.7, 2.5 Hz, 1H, Ar*H*), 7.29 (t, *J* = 4.9 Hz, 1H, SC=C*H*), 6.81 (dd, *J* = 8.7, 2.7 Hz, 1H, Ar*H*), 6.77 (d, *J* = 2.7 Hz, 1H, Ar*H*), 3.83 (s, 3H, OC*H*$_3$), 2.85 (t, *J* = 8.1 Hz, 2H, SC=CHCH$_2$C*H*$_2$), 2.62–2.54 (m, 2H, SC=CHC*H*$_2$);

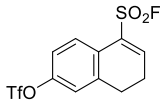
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.4, 141.6 (d, $^3J_{CF}$ = 2.6 Hz), 137.8, 134.0 (d, $^2J_{CF}$ = 22.7 Hz), 126.4, 118.6, 114.6, 111.9, 55.5, 27.2, 23.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 56.9;

IR ν_{max} (neat)/cm^{-1} 3070, 2946, 2840, 1607, 1566, 1500, 1399, 1256, 1205;

HRMS (APCI$^-$) found *m*/*z* 241.0337 $[M-H]^-$, $C_{11}H_{10}FO_3S^-$ requires *m*/*z* 241.0340.

5-(Fluorosulfonyl)-7,8-dihydronaphthalen-2-yl trifluoromethanesulfonate (33x)



Prepared according to General Procedure I using alkenyl triflate **31x** (108 mg, 0.25 mmol), with the first step heated for 0.5 h. The crude product was purified by flash column chromatography (40:1:1 to 20:1:1 petrol/CH_2Cl_2/EtOAc) to afford the *alkenylsulfonyl fluoride* **33x** as a yellow oil (53.0 mg, 59%) which solidified at -20 °C;

mp 32–34 °C (hexane);

R$_f$ 0.24 (18:1:1 hexane/CH_2Cl_2/EtOAc) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.8, 2.1 Hz, 1H, Ar*H*), 7.54 (t, *J* = 4.8 Hz, 1H, SC=C*H*), 7.22 (dd, *J* = 8.7, 2.7 Hz, 1H, Ar*H*), 7.18 (d, *J* = 2.6 Hz, 1H, Ar*H*), 2.95 (t, *J* = 8.2 Hz, 2H, SC=CHCH$_2$C*H*$_2$), 2.68 (tdd, *J* = 7.9, 4.8, 2.5 Hz, 2H, SC=CHC*H*$_2$);

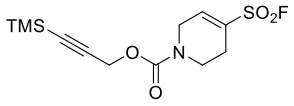
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.6, 146.0 (d, $^{3}J_{CF}$ = 2.3 Hz), 138.7, 133.4 (d, $^{2}J_{CF}$ = 24.6 Hz), 126.9, 126.1, 121.5, 120.3, 118.8 (app. d, $^{1}J_{CF}$ = 320.8 Hz), 26.7, 23.4;

^{19}F NMR (377 MHz, $CDCl_3$) δ 57.4 (s, 1F, SO_2F), -72.7 (s, 3F, SO_2CF_3);

IR ν_{max} (neat)/cm^{-1} 3079, 2956, 2922, 1602, 1579, 1461, 1406, 1250, 1203, 1138, 1114;

HRMS (ESI/CI) not found.

Prop-2-yn-1-yl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33af)



Prepared according to General Procedure H using the corresponding alkenyl triflate (116 mg, 0.30 mmol), with the first step heated for 6 h, affording the *alkenylsulfonyl fluoride* in 42% yield as determined by ^{19}F-NMR spectroscopy against $PhCF_3$ as internal standard. Alternatively, the first step was heated to 95 °C under microwave irradiation for 3 h, and crude product was purified by flash column chromatography (10:3:1 to 6:3:1 petrol/CH_2Cl_2/Et_2O) to afford the *alkenylsulfonyl fluoride* **33af** as a white solid (28.3 mg, 30%);

mp 70–71 °C (CH_2Cl_2);

R*f* 0.38 (6:3:1 hexane/CH_2Cl_2/Et_2O) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.05 (m, 1H, SC=C*H*), 4.75 (s, 2H, OCH_2), 4.38–4.25 (m, 2H, CHCH_2), 3.73 (t, *J* = 5.6 Hz, 2H, NC$H_2$$CH_2$), 2.69–2.55 (m, 2H, NCH_2CH_2), 0.18 (s, 9H, Si(CH_3)$_3$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.2, {139.9, 139.4}, 99.2, 92.5, 54.5, 43.7, {40.0, 39.7}, 30.5, {24.2, 24.0}, -0.2 (recorded as a pair of rotamers);

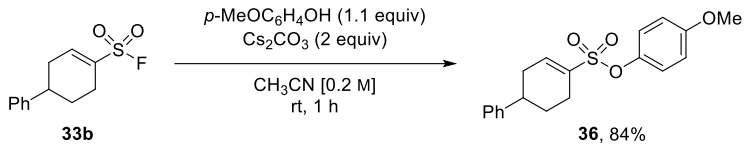
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.40, 51.38 (recorded as a pair of rotamers);

IR ν_{max} (neat)/cm^{-1} 2960, 2187, 1713, 1435, 1406, 1234, 1204, 1111;

HRMS (ESI) not found.

6.2.8 Derivatisation of CASFs

Nucleophilic addition of p-methoxyphenol for the preparation of 4-methoxy-phenyl 1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-sulfonate (36)



A sample vial was charged with alkenylsulfonyl fluoride **33b** (24.0 mg, 0.10 mmol, 1.0 equiv), *p*-methoxyphenol (13.6 mg, 0.11 mmol, 1.1 equiv), Cs_2CO_3 (65.2 mg, 0.20 mmol, 2.0 equiv) and CH_3CN (0.5 mL). The reaction was stirred at ambient temperature for 1 h, which was then diluted with hexane and directly purified by flash column chromatography (10–20% EtOAc in petrol), affording the *alkenyl sulfonate ester* **36** as a white solid (28.8 mg, 84%);

mp 58–60 °C (EtOAc);

R_f 0.46 (25% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 2H, 2 × Ar*H*), 7.27–7.22 (m, 1H, Ar*H*), 7.19 (d, *J* = 7.7 Hz, 2H, 2 × Ar*H*), 7.18–7.09 (m, 2H, 2 × Ar*H*), 6.90–6.87 (m, 3H, 2 × Ar*H* + SC=C*H*), 3.81 (s, 3H, OCH_3), 2.90–2.80 (m, 1H, PhC*H*), 2.74–2.52 (m, 3H, SC=CHCH_2 + SCCH$_2$CH_aH$_b$), 2.40–2.28 (m, 1H, SCCH$_2$CH$_a$$H_b$), 2.19–2.11 (m, 1H, SCC$H_aH_b$), 1.87 (dddd, *J* = 13.2, 11.5, 10.3, 5.6 Hz, 1H, SCCH$_a$$H_b$);

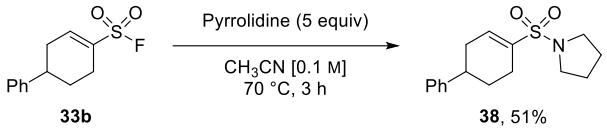
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.3, 144.6, 143.1, 141.7, 134.9, 128.9, 126.9, 126.8, 123.3, 114.8, 55.8, 38.5, 33.3, 29.1, 24.5;

IR ν_{max} (neat)/cm^{-1} 3028, 2931, 2839, 1502, 1365, 1251, 1191, 1167, 1149;

LRMS (ESI$^+$) *m*/*z* 367.0 ([M+Na]$^+$);

HRMS (ESI$^+$) found *m*/*z* 367.0975 [M+H]$^+$, $C_{19}H_{20}O_4SNa^+$ requires *m*/*z* 367.0975.

Nucleophilic addition of pyrrolidine for the preparation of 1-((1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)sulfonyl)pyrrolidine (38)



A reaction tube was charged with alkenylsulfonyl fluoride **33b** (24.0 mg, 0.10 mmol, 1.0 equiv), pyrrolidine (42 µL, 0.50 mmol, 5.0 equiv) and CH_3CN (1.0 mL). The reaction was heated to 70 °C and stirred for 3 h, which was then cooled to ambient temperature, diluted with hexane and directly purified by flash column chromatography (10–25% EtOAc in petrol), affording the *alkenyl sulfonamide* **38** as a white solid (14.8 mg, 51%);

mp 79–81 °C (EtOAc);

R_f 0.30 (25% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2H, 2 × Ar*H*), 7.26–7.19 (m, 3H, 3 × Ar*H*), 6.88–6.82 (m, 1H, SC=C*H*), 3.38–3.27 (m, 4H, 2 × NCH_2), 2.89–2.79 (m, 1H, PhC*H*), 2.64–2.48 (m, 2H, SC=CHCH_aH$_b$ + SCCH_cH$_d$), 2.47–2.32 (m, 2H, SC=CHCH$_a$$H_b$ + SCCH$_c$$H_d$), 2.13–2.03 (m, 1H, SCCH$_2$CH_aH$_b$), 1.96–1.88 (m, 4H, NCH$_2$CH_2), 1.88–1.79 (m, 1H, SCCH$_2$CH$_a$$H_b$);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.1, 137.3, 136.9, 128.8, 126.9, 126.7, 47.8, 38.8, 33.1, 29.4, 26.0, 24.6;

IR ν_{max} (neat)/cm^{-1} 2938, 2880, 1646, 1602, 1494, 1452, 1326, 1147;

LRMS (ESI$^+$) *m*/*z* 292.1 ([M+H]$^+$);

HRMS (ESI$^+$) found *m*/*z* 292.1365 [M+H]$^+$, $C_{16}H_{22}NO_2S^+$ requires *m*/*z* 292.1366.

General Procedure J: Synthesis of alkenyl sulfonamides using alkenylsulfonyl fluoride, anilines and Ca(NTf$_2$)$_2$ as exemplified by the preparation of *tert*-butyl 4-(*N*-(*p*-tolyl)sulfamoyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (39a)



A reaction tube was charged with alkenylsulfonyl fluoride **33p** (26.5 mg, 0.10 mmol, 1.0 equiv), *p*-toluidine (23.5 mg, 0.22 mmol, 2.2 equiv), Ca(NTf$_2$)$_2$ (66.0 mg, 0.11 mmol, 1.1 equiv) and *t*-amyl alcohol (0.5 mL), evacuated and back-filled with N_2 for three times. The reaction was heated at 60 °C for 16 h under N_2, which was then cooled to ambient temperature, diluted with EtOAc, washed subsequently with 1 M aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash column chromatography (20–40% EtOAc in petrol), affording the *alkenyl sulfonamide* **39a** as a light brown solid (26.6 mg, 76%);

mp 195–196 °C (EtOAc);

R$_f$ 0.60 (50% EtOAc in hexane) [$KMnO_4$/UV];

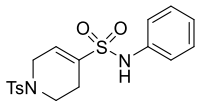
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.9 Hz, 2H, 2 × Ar*H*), 7.02 (d, *J* = 8.4 Hz, 2H, 2 × Ar*H*), 6.71 (br. s, 1H, N*H*), 6.54 (app. s, 1H, SC=C*H*), 4.02 (app. s, 2H, SC=CHC*H*$_2$), 3.49 (t, *J* = 5.6 Hz, 2H, SCCH$_2$C*H*$_2$), 2.39 (app. br. s, 2H, SCC*H*$_2$), 2.31 (s, 3H, ArC*H*$_3$), 1.44 (s, 9H, C(C*H*$_3$)$_3$) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.5, 136.3, 135.6, {135.3, 134.8}, 133.7, 130.2, 121.6, 80.7, {43.7, 43.1}, {40.4, 39.1}, 28.5, 24.2, 21.0 (recorded as a pair of rotamers);

IR ν_{max} (neat)/cm^{-1} 3241, 2976, 2926, 1697, 1674, 1511, 1334, 1282, 1241, 1157;

HRMS (ESI$^-$) found *m*/*z* 351.1385 [M–H]$^-$, $C_{17}H_{23}N_2O_4S^-$ requires *m*/*z* 351.1384.

***N*-Phenyl-1-tosyl-1,2,3,6-tetrahydropyridine-4-sulfonamide (39b)**



Prepared according to General Procedure J using alkenylsulfonyl fluoride **33p** (26.5 mg, 0.10 mmol, 1.0 equiv), aniline (20 μL, 0.22 mmol, 2.2 equiv), $Ca(NTf_2)_2$ (120 mg, 0.20 mmol, 2.0 equiv) and *t*-amyl alcohol (0.5 mL). The crude product was purified by flash column chromatography (20–40% EtOAc in petrol) to afford the *alkenyl sulfonamide* **39b** as a brown oil (21.4 mg, 55%);

R_f 0.21 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H, 2 × Ar*H*), 7.30 (t, *J* = 7.6 Hz, 4H, 4 × Ar*H*), 7.16 (tt, *J* = 7.4, 1.4 Hz, 1H, Ar*H*), 7.09 (dd, *J* = 8.5, 1.2 Hz, 2H, 2 × Ar*H*), 6.69 (tt, *J* = 3.2, 1.5 Hz, 1H, SC=C*H*), 6.45 (br. s, 1H, N*H*), 3.75 (dt, *J* = 3.2, 2.7 Hz, 2H, SC=CHCH_2), 3.21 (t, *J* = 5.6 Hz, 2H, SCCH_2CH_2), 2.50–2.44 (m, 2H, SCCH_2), 2.43 (s, 3H, ArCH_3);

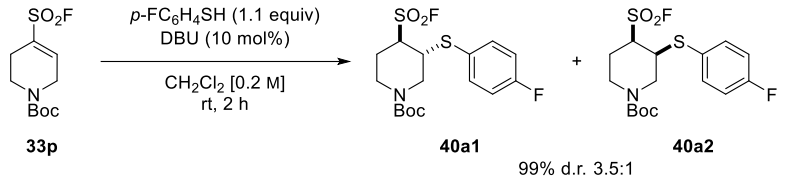
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.4, 136.7, 136.2, 133.2, 133.1, 130.1, 129.7, 127.7, 125.7, 121.0, 44.7, 42.2, 24.4, 21.7;

IR ν_{max} (neat)/cm^{-1} 3262, 2923, 2854, 1598, 1495, 1338, 1156;

LRMS (ESI$^+$) *m*/*z* 415.0 ([M+Na]$^+$);

HRMS (ESI$^+$) found *m*/*z* 393.0936 [M+H]$^+$, $C_{18}H_{20}N_2O_4S_2^+$ requires *m*/*z* 393.0937.

General Procedure K: Conjugate addition of thiols or thiophenols to alkenylsulfonyl fluorides as exemplified by the preparation of *tert*-butyl 3-((4-fluorophenyl)thio)-4-(fluorosulfonyl)piperidine-1-carboxylate (40a)

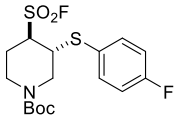


33p **40a1** **40a2**

99% d.r. 3.5:1

Alkenylsulfonyl fluoride **33p** (26.5 mg, 0.10 mmol, 1.0 equiv) and 4-fluorothiophenol (12 µL, 0.11 mmol, 1.1 equiv) were dissolved in CH_2Cl_2 in a sample vial and DBU (1.5 µL, 0.010 mmol, 0.10 equiv) was added as a solution in CH_2Cl_2 (0.1 mL). The reaction was stirred at ambient temperature for 2 h until completion, which was then directly purified by flash column chromatography (10–30% EtOAc in petrol), affording the *trans-sulfonyl fluoride* **40a1** as a white solid (8.7 mg, 22%) and *cis-sulfonyl fluoride* **40a2** as a white solid (30.4 mg, 77%);

tert-Butyl *trans*-3-((4-fluorophenyl)thio)-4-(fluorosulfonyl)piperidine-1-carboxylate (**40a1**)



mp 84–86 °C (EtOAc);

R_f 0.58 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (500 MHz, DMSO-d_6, 363 K) δ 7.59 (dd, J = 8.8, 5.3 Hz, 2H, 2 × ArC*H*), 7.24 (t, J = 8.8 Hz, 2H, 2 × ArC*H*), 4.33 (td, J = 9.2, 4.7 Hz, 1H, FO_2SCH), 3.95 (dd, J = 13.9, 4.2 Hz, 1H, NCH_aH_bCH), 3.78 (dt, J = 13.5, 4.8 Hz, 1H, $NCH_cH_dCH_2$), 3.43 (td, J = 8.6, 4.1 Hz, 1H, ArSC*H*), 3.27–3.13 (m, 2H, NCH_aH_bCH + $NCH_cH_dCH_2$), 2.39–2.30 (m, 1H, $NCH_2CH_eH_f$), 1.91 (dtd, J = 14.1, 9.7, 4.4 Hz, 1H, $NCH_2CH_eH_f$), 1.35 (s, 9H, $C(CH_3)_3$);

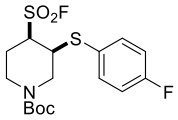
^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6, 363 K) δ 162.0 (d, $^1J_{CF}$ = 246.7 Hz), 153.0, 135.0 (d, $^3J_{CF}$ = 8.3 Hz), 126.9, 116.1 (d, $^2J_{CF}$ = 22.2 Hz), 79.2, 62.0 (d, $^2J_{CF}$ = 10.3 Hz), 46.4, 44.1, 40.3, 27.5, 25.2;

^{19}F {^{1}H} NMR (470 MHz, DMSO-d_6, 363 K) δ 54.4 (s, 1F, SO_2F), -113.0 (s, 1F, Ar*F*);

IR ν_{max} (neat)/cm^{-1} 2976, 2928, 1696, 1590, 1491, 1402, 1225, 1198, 1159, 1123;

HRMS (ESI$^+$) found m/z 416.0772 $[M+Na]^+$, $C_{16}H_{21}F_2NO_4S_2Na^+$ requires m/z 416.0772.

tert-Butyl *cis*-3-((4-fluorophenyl)thio)-4-(fluorosulfonyl)piperidine-1-carboxylate (**40a2**)



mp 89–91 °C (EtOAc);

R_f 0.39 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (500 MHz, DMSO-d_6, 363 K) δ 7.62–7.50 (m, 2H, 2 × ArC*H*), 7.22 (t, J = 9.1 Hz, 2H, 2 × ArC*H*), 4.75 (dt, J = 12.2, 3.2 Hz, 1H, FO_2SCH), 4.21–4.11 (m, 2H, NCH_aH_bCH + $NCH_cH_dCH_2$), 3.83–3.78 (m, 1H, ArSC*H*), 3.22 (d, J = 14.0 Hz, 1H, NCH_aH_bCH), 2.96 (ddd, J = 14.6, 12.3, 3.2 Hz, 1H, $NCH_cH_dCH_2$), 2.16–2.07 (m, 1H, $NCH_2CH_eH_f$), 1.95 (qd, J = 12.2, 4.7 Hz, 1H, $NCH_2CH_eH_f$), 1.41 (s, 9H, $C(CH_3)_3$);

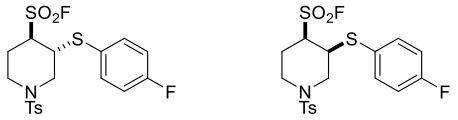
^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6, 363 K) δ 161.7 (d, $^1J_{CF}$ = 246.7 Hz), 153.6, 134.1, 128.3 (d, $^3J_{CF}$ = 3.0 Hz), 115.8 (d, $^2J_{CF}$ = 22.0 Hz), 78.9, 62.6 (d, $^2J_{CF}$ = 13.1 Hz), 46.5, 45.6, 41.0, 27.6, 22.5;

^{19}F {^{1}H} NMR (470 MHz, DMSO-d_6, 363 K) δ 54.4 (s, 1F, SO_2F), -113.8 (s, 1F, Ar*F*);

IR ν_{max} (neat)/cm^{-1} 2976, 2930, 2866, 1694, 1491, 1406, 1367, 1286, 1239, 1158;

HRMS (ESI$^+$) found m/z 416.0772 $[M+Na]^+$, $C_{16}H_{21}F_2NO_4S_2Na^+$ requires m/z 416.0772.

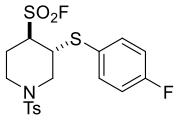
3-((4-Fluorophenyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (40b)



99% d.r. 2.2:1

Prepared according to General Procedure K using alkenylsulfonyl fluoride **33p** (49.8 mg, 0.156 mmol), 4-fluorothiophenol (18 μL, 0.17 mmol), DBU (2.2 μL, 0.015 mmol) and CH_2Cl_2 (0.75 mL). The crude product was purified by flash column chromatography (10–25% EtOAc in petrol), affording the *trans-sulfonyl fluoride* **40b1** as a white solid (48.0 mg, 69%) and *cis-sulfonyl fluoride* **40b2** as a white solid (21.8 mg, 31%);

trans-3-((4-Fluorophenyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (**40b1**)



mp 118–120 °C (EtOAc);

R*f* 0.45 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H, 2 × Ar*H*), 7.52 (dd, *J* = 8.8, 5.2 Hz, 2H, 2 × Ar*H*), 7.33 (d, *J* = 7.6 Hz, 2H, 2 × Ar*H*), 7.08 (t, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 3.59–3.52 (m, 2H, NCH_aH_bCH + ArSC*H*), 3.50–3.43 (m, 1H, FO_2SCH), 3.37–3.29 (m, 1H, NC$H_cH_dCH_2$), 3.18–3.11 (m, 1H, NCH_aH_bCH), 3.07 (ddd, *J* = 12.0, 7.4, 4.0 Hz, 1H, NCH_cH_dCH$_2$), 2.63–2.53 (m, 1H, NCH$_2$CH_eH_f), 2.44 (s, 3H, CH_3), 2.20 (dtd, *J* = 14.4, 7.2, 3.7 Hz, 1H, NCH$_2$CH_eH_f);

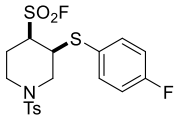
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.5 (d, $^1J_{CF}$ = 250.8 Hz), 144.5, 136.4 (d, $^3J_{CF}$ = 8.4 Hz), 133.2, 130.1, 127.6, 126.6 (d, $^4J_{CF}$ = 3.3 Hz), 117.0 (d, $^2J_{CF}$ = 22.1 Hz), 61.1 (d, $^2J_{CF}$ = 11.2 Hz), 48.5, 44.4, 42.9, 24.4, 21.7;

^{19}F NMR (377 MHz, $CDCl_3$) δ 54.5 (s, 1F, SO_2F), -110.9 (tt, *J* = 8.4, 5.3 Hz, 1F, Ar*F*);

IR ν_{max} (neat)/cm^{-1} 3065, 2926, 2857, 1590, 1491, 1404, 1226, 1199, 1165;

HRMS (ESI$^+$) found *m*/*z* 448.0518 [M+H]$^+$, $C_{18}H_{20}F_2NO_4S_3^+$ requires *m*/*z* 448.0517.

cis-3-((4-Fluorophenyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (**40b2**)



mp 104–105 °C (EtOAc);

R_f 0.32 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H, 2 × Ar*H*), 7.60 (dd, *J* = 8.8, 5.2 Hz, 2H, 2 × Ar*H*), 7.33 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.06 (t, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 3.89 (dd, *J* = 12.6, 4.2 Hz, 2H, NC$H_a$$H_b$$CH_2$ + NC$H_c$$H_d$CH), 3.64 (dtd, *J* = 11.4, 3.8, 1.2 Hz, 1H, FO_2SC*H*), 3.58 (qd, *J* = 3.8, 2.5, 1.7 Hz, 1H, ArSC*H*), 2.71 (dd, *J* = 12.6, 2.4 Hz, 1H, NC$H_c$$H_d$CH), 2.58 (td, *J* = 11.8, 3.1 Hz, 1H, NC$H_a$$H_b$$CH_2$), 2.43–2.34 (m, 1H,NC$H_2CH_e$$H_f$), 2.20 (ddd, *J* = 13.6, 3.5, 1.4 Hz, 1H, NCH_2C$H_e$$H_f$);

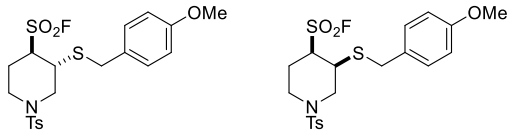
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{CF}$ = 250.2 Hz), 144.4, 137.3 (d, $^3J_{CF}$ = 8.6 Hz), 133.4, 130.1, 127.8, 127.7 (d, $^4J_{CF}$ = 3.2 Hz), 116.8 (d, $^2J_{CF}$ = 21.9 Hz), 63.2 (d, $^2J_{CF}$ = 15.0 Hz), 49.9, 47.0, 44.4, 23.7, 21.7;

^{19}F NMR (377 MHz, $CDCl_3$) δ 55.3 (s, 1F, SO_2F), -111.3 (tt, *J* = 8.4, 5.4 Hz, 1F, Ar*F*);

IR ν_{max} (neat)/cm^{-1} 2924, 2850, 1590, 1491, 1407, 1163;

HRMS (ESI$^+$) found *m*/*z* 448.0518 [M+H]$^+$, $C_{18}H_{20}F_2NO_4S_3^+$ requires *m*/*z* 448.0517.

3-((4-Methoxybenzyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (40c)

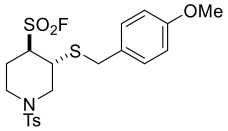


40c1 **40c2**

98% d.r. 2.9:1

Prepared according to General Procedure K using alkenylsulfonyl fluoride **33p** (47.9 mg, 0.150 mmol), 4-methoxybenzyl mercaptan (23 µL, 0.165 mmol), DBU (2.2 µL, 0.015 mmol) and CH_2Cl_2 (0.75 mL), and the reaction was stirred for 1 h. The crude product was purified by flash column chromatography (10–25% EtOAc in petrol), affording the *trans-sulfonyl fluoride* **40c1** as an off-white solid (51.7 mg, 73%) and *cis-sulfonyl fluoride* **40c2** as an off-white solid (17.8 mg, 25%);

trans-3-((4-Methoxybenzyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (**40c1**)



mp 79–81 °C (EtOAc);

bp 131 °C (decomp.);

R_f 0.41 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H, 2 × Ar*H*), 7.31 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 3.85 (d, *J* = 13.7 Hz, 1H, SCH_aH$_b$), 3.82 (s, 3H, OCH_3), 3.81 (d, *J* = 13.7 Hz, 1H, SCH$_a$$H_b$), 3.44 (dd, *J* = 12.7, 3.9 Hz, 1H, NCH_cH$_d$CH), 3.34 (td, *J* = 6.7, 4.8 Hz, 1H, FO$_2$SC*H*), 3.28 (dq, *J* = 8.2, 4.0, 3.5 Hz, 1H, NCH_eH$_f$CH$_2$), 3.18 (td, *J* = 6.8, 3.8 Hz, 1H, NCH$_2$C*H*), 2.98 (td, *J* = 12.6, 11.0, 5.2 Hz, 2H, NCH$_e$$H_fCH_2$ + NCH$_c$$H_d$CH), 2.55–2.47 (m, 1H, NCH$_2$CH_gH$_h$), 2.43 (s, 3H, CCH_3), 2.13 (dtd, *J* = 14.6, 7.3, 3.8 Hz, 1H, NCH$_2$CH$_g$$H_h$);

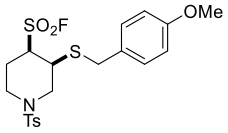
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3, 144.3, 133.1, 130.2, 130.1, 128.6, 127.7, 114.5, 62.1 (d, $^2J_{CF}$ = 10.0 Hz), 55.5, 49.3, 43.0, 39.8, 36.4, 24.6, 21.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 54.5;

IR ν_{max} (neat)/cm^{-1} 2976, 2928, 2870, 1696, 1491, 1402, 1279, 1225, 1198, 1159;

HRMS (ESI$^+$) found *m*/*z* 496.0692 [M+Na]$^+$, $C_{20}H_{24}FNO_5S_3Na^+$ requires *m*/*z* 496.0693.

cis-3-((4-Methoxybenzyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (**40c2**)



mp 143–145 °C (decomp.) (EtOAc);

R_f 0.31 (30% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H, 2 × Ar*H*), 7.32 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.29 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*), 3.86 (d, *J* = 13.5 Hz, 1H, SCH_aH$_b$), 3.82 (s, 3H, OCH_3), 3.80 (d, *J* = 13.4 Hz, 1H, SCH$_a$$H_b$), 3.74 (d, *J* = 12.6 Hz, 1H, NCH_cH$_d$CH$_2$), 3.60 (dd, *J* = 12.3, 4.3 Hz, 1H, NCH_eH$_f$CH), 3.50 (dt, *J* = 10.8, 3.1 Hz, 1H, FO$_2$SC*H*), 3.26 (dq, *J* = 5.0, 3.0, 2.2 Hz, 1H, NCH$_2$C*H*), 2.68 (dd, *J* = 12.3, 2.6 Hz, 1H, NCH$_e$$H_f$CH), 2.53 (td, *J* = 11.5, 3.0 Hz, 1H, NCH$_c$$H_dCH_2$), 2.43 (s, 3H, CC$H_3$), 2.42 (dd, *J* = 13.6, 10.8 Hz, 1H, NCH$_2$CH_gH$_h$), 2.15 (dd, *J* = 13.6, 3.8 Hz, 1H, NCH$_2$CH$_g$$H_h$);

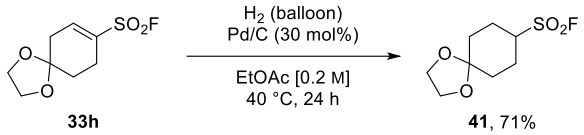
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.1, 144.3, 133.3, 130.5, 130.0, 128.7, 127.8, 114.3, 63.2 ($^2J_{CF}$ = 12.9 Hz), 55.5, 51.5, 44.2, 39.6, 36.3, 24.0, 21.7;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 54.6;

IR ν_{max} (neat)/cm^{-1} 2976, 2930, 2866, 1694, 1491, 1406, 1286, 1239, 1158;

HRMS (ESI$^+$) found *m*/*z* 496.0692 [M+Na]$^+$, $C_{20}H_{24}FNO_5S_3Na^+$ requires *m*/*z* 496.0693.

Pd-catalysed hydrogenation of alkenylsulfonyl fluoride for the preparation of 1,4-dioxaspiro[4.5]decane-8-sulfonyl fluoride (41)



A reaction tube was charged with alkenylsulfonyl fluoride **33h** (67 mg, 0.30 mmol, 1.0 equiv) and 10 wt% Pd on carbon (95 mg, 0.090 mmol, 0.30 equiv), which was evacuated and back-filled with H_2 for three times. EtOAc (1.5 mL) was bubbled with H_2 for 10 min and then added to the mixture. The reaction was heated at 40 °C for 24 h with three balloons of H_2 attached, which was then cooled to ambient temperature, diluted with EtOAc and filtered over Celite®. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (20:10:1 CH_2Cl_2/petrol/EtOAc mixture), affording the *sulfonyl fluoride* **41** as a white solid (47.8 mg, 71%);

mp 64–66 °C (EtOAc);

R*f* 0.53 (20:10:2.5 CH_2Cl_2/hexane/EtOAc) [Anisaldehyde–purple (hot) / brown (cooled)];

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (t, *J* = 2.1 Hz, 4H, 2 × OC*H*$_2$), 3.33 (ttd, *J* = 11.9, 3.8, 2.1 Hz, 1H, SC*H*), 2.36–2.24 (m, 2H, 2 × SCHC*H*$_a$H$_b$), 2.07 (tdd, *J* = 13.3, 11.9, 4.0 Hz, 2H, 2 × SCHCH$_a$*H*$_b$), 1.93 (dddd, *J* = 14.5, 5.4, 2.6, 1.4 Hz, 2H, 2 × CC*H*$_a$H$_b$), 1.62 (td, *J* = 13.5, 4.4 Hz, 2H, 2 × CCH$_a$*H*$_b$);

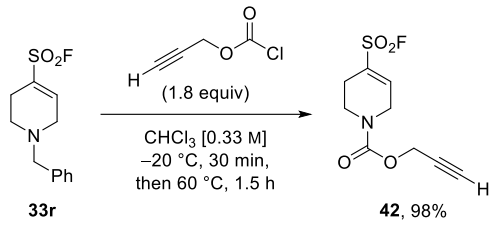
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 106.7, 64.8, 64.7, 59.4 (d, $^2J_{CF}$ = 13.6 Hz), 33.3, 24.3;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 42.7;

IR ν_{max} (neat)/cm^{-1} 2963, 2930, 2893, 1448, 1392, 1198, 1185, 1106;

HRMS (ESI/APCI) not found.

One-pot dealkylation/propagyloxycarbonylation with propargyl chloroformate for the preparation of prop-2-yn-1-yl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (42)



A reaction tube was charged with freshly synthesized alkenylsulfonyl fluoride **33r** (40.0 mg, 0.16 mmol, 1.0 equiv), evacuated and filled with N_2 for three times, followed by the addition of anhydrous $CHCl_3$ (0.45 mL). The solution was cooled to -20 °C and propargyl chloroformate (18.5 µL, 0.19 mmol, 1.2 equiv) was added. The reaction was stirred at -20 °C for 30 min, then heated to 60 °C for 30 min. Another portion of propargyl chloroformate (9.5 µL, 0.097 mmol, 0.60 equiv) was added and the reaction was stirred at 60 °C for 1 h, which was then cooled to ambient temperature and directly purified by flash column chromatography (15–25% EtOAc in petrol), affording the *sulfonyl fluoride* **42** as a colourless oil (37.2 mg, 98%);

R*f* 0.18 (20% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (br. s, 0.5H, SC=C*H*^{rot1}), 7.07 (br. s, 0.5H, SC=C*H*^{rot2}), 4.75 (d, *J* = 2.4 Hz, 2H, OC*H*$_2$), 4.31 (quint, *J* = 2.9 Hz, 2H, CHC*H*$_2$), 3.73 (t, *J* = 5.7 Hz, 2H, SCCH$_2$C*H*$_2$), 2.62 (br. s, 2H, SCC*H*$_2$), 2.50 (t, *J* = 2.4 Hz, 1H, OCH$_2$CC*H*) (recorded as a pair of rotamers);

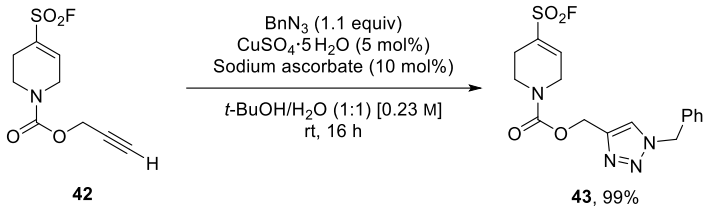
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.1, {139.9, 139.2}, 132.7, 77.9, 75.3, 53.7, 43.7, {40.0, 39.7}, {24.2, 24.0} (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.44, 51.40 (recorded as a pair of rotamers);

IR ν_{max} (neat)/cm^{-1} 3293, 2953, 2129, 1710, 1404, 1237, 1203;

HRMS (ESI/APCI) not found.

Copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) with alkenylsulfonyl fluoride 42 and benzyl azide for the preparation of (1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl 4-(fluorosulfonyl)-3,6-dihydro-pyridine-1(2*H*)-carboxylate (43)



A sample vial was charged with alkenylsulfonyl fluoride **42** (34.5 mg, 0.138 mmol, 1.0 equiv), $CuSO_4{\cdot}5H_2O$ (1.7 mg, 7.0 μmol, 0.050 equiv), sodium ascorbate (2.8 mg, 14 μmol, 0.10 equiv), *t*-butanol (0.3 mL) and deionised water (0.3 mL), followed by the addition of benzyl azide (19 μL, 0.15 mmol, 1.1 equiv), The reaction was stirred vigorously at ambient temperature for 16 h, which was then diluted with ethyl acetate and water. The two phases were separated and the aqueous phase was extracted with EtOAc for three times. The combined organic extract was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash column chromatography (50–70% EtOAc in petrol), affording the *sulfonyl fluoride* **43** as a yellow oil (52.7 mg, 99%);

R_f 0.46 (75% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H, NC=C*H*), 7.40–7.36 (m, 3H, 3 × Ar*H*), 7.30–7.27 (m, 2H, 2 × Ar*H*), 7.08 (br. s, 0.5H, SC=CH^{rot1}), 7.02 (br. s, 0.5H, SC=CH^{rot2}), 5.52 (s, 2H, PhCH_2), 5.24 (s, 2H, OCH_2), 4.27–4.23 (m, 2H, SC=CHCH_2), 3.68 (t, *J* = 5.6 Hz, 2H, NCH_2CH_2), 2.56 (br. s, 2H, NCH_2CH_2) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.8, 143.4, {139.8, 139.4}, 134.5, {132.9, 132.7}, 129.3, 129.0, 128.3, 124.0, 59.0, 54.4, 43.6, {40.0, 39.5}, {24.2, 23.9} (recorded as a pair of rotamers);

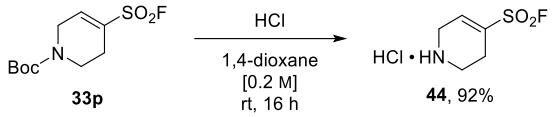
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.4;

IR ν_{max} (neat)/cm^{-1} 3142, 3066, 2953, 1704, 1432, 1402, 1280, 1236, 1202, 1113;

LRMS (ESI$^+$) *m*/*z* 403.0 ([M+Na]$^+$);

HRMS (ESI$^+$) found *m*/*z* 381.1028 [M+H]$^+$, $C_{16}H_{18}FN_4O_4S^+$ requires *m*/*z* 381.1027.

Boc deprotection using HCl in 1,4-dioxane for the preparation of 1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride hydrochloride (44)



A reaction tube was charged with alkenylsulfonyl fluoride **33p** (53.0 mg, 0.20 mmol, 1.0 equiv), evacuated and filled with N_2 for three times, followed by the addition of anhydrous 1,4-dioxane (0.5 mL) and hydrogen chloride solution (4 N in 1,4-dioxane) (0.5 mL). The reaction was stirred at ambient temperature for 16 h, and then filtered under vacuum. The residue was washed with Et_2O, affording the *alkenylsulfonyl fluoride* **44** as a white solid (37.2 mg, 92%);

mp 175 °C (decomp.) (EtOAc);

^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (dt, *J* = 2.9, 1.5 Hz, 1H, SC=C*H*), 4.07 (dt, *J* = 5.8, 2.6 Hz, 2H, CHCH_2), 3.52 (t, *J* = 6.1 Hz, 2H, CCH_2CH_2), 2.85 (tt, *J* = 6.1, 2.3 Hz, 2H, SCCH_2);

^{13}C {^{1}H} NMR (101 MHz, CD_3OD) δ 138.0, 133.2 (d, $^2J_{CF}$ = 27.7 Hz), 43.1, 41.0, 21.8;

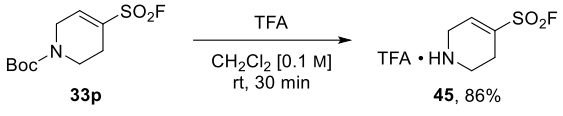
^{19}F {^{1}H} NMR (377 MHz, CD_3OD) δ 50.1;

IR ν_{max} (neat)/cm^{-1} 2963, 2730, 1658, 1542, 1450, 1392, 1209;

LRMS (ESI$^+$) *m*/*z* 166.0 ([M+H]$^+$);

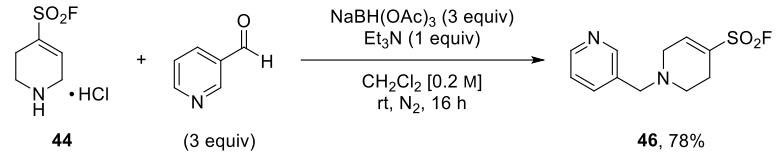
HRMS (ESI$^+$) found *m*/*z* 166.0333 [M+H]$^+$, $C_5H_9FNO_2S^+$ requires *m*/*z* 166.0333.

General Procedure L: Boc deprotection using TFA for the preparation of 1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride trifluoroacetate (45)



To a solution of alkenylsulfonyl fluoride **33p** (650 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (1.6 mL) was added trifluoroacetic acid (0.4 mL), which was stirred at ambient temperature for 30 min. Toluene (0.5 mL) was then added and the mixture was concentrated *in vacuo*. Another portion of toluene (0.5 mL) was added and upon removal of volatiles *in vacuo*, the *alkenylsulfonyl fluoride* **45** was obtained as an off-white solid (56.5 mg, 86%), which was used for subsequent functionalisation without further purification.

Reductive amination using alkenylsulfonyl fluoride 44, nicotinaldehyde and triacetoxyborohydride for the preparation of 1-(pyridin-3-ylmethyl)-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (46)



44 (3 equiv) **46**, 78%

A sample vial was charged with alkenylsulfonyl fluoride **44** (20.2 mg, 0.10 mmol, 1.0 equiv), nicotinaldehyde (32.1 mg, 0.30 mmol, 3.0 equiv) and $NaBH(OAc)_3$ (63.6 mg, 0.30 mmol, 3.0 equiv), evacuated and filled with N_2 for three times. A solution of Et_3N (14 µL, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was then added. The reaction was stirred at ambient temperature for 16 h, which was then diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The organic extract was dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography (50–100% EtOAc in petrol), affording the *alkenylsulfonyl fluoride* **46** as a red oil (20.0 mg, 78%);

R_f 0.17 (EtOAc) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 3.9, 2.6 Hz, 2H, 2 × Ar*H*), 7.69 (dt, *J* = 7.8, 2.0 Hz, 1H, Ar*H*), 7.29 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H, Ar*H*), 7.05 (tt, *J* = 3.3, 1.3 Hz, 1H, SC=C*H*), 3.67 (s, 2H, ArCH_2), 3.28 (quint, *J* = 3.0 Hz, 2H, CHCH_2), 2.74 (t, *J* = 5.5 Hz, 2H, CCH_2CH_2), 2.63–2.56 (m, 2H, CCH_2CH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.2, 149.3, 141.2 (d, $^3J_{CF}$ = 2.6 Hz), 136.7, 132.9, 132.4 (d, $^2J_{CF}$ = 24.9 Hz), 123.7, 59.0, 52.1, 48.3, 24.8;

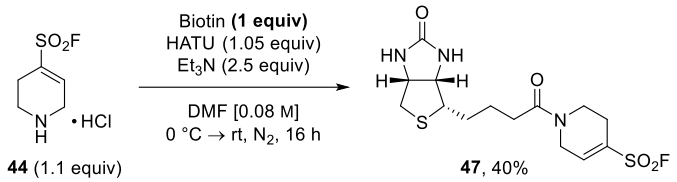
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.2;

IR ν_{max} (neat)/cm^{-1} 3055, 2922, 2850, 1652, 1577, 1400, 1205;

LRMS (ESI$^+$) *m*/*z* 257.0 ([M+H]$^+$);

HRMS (ESI$^+$) found *m*/*z* 257.0755 [M+H]$^+$, $C_{11}H_{14}FN_2O_2S^+$ requires *m*/*z* 257.0755.

Biotinylation of alkenylsulfonyl fluoride 44 for the preparation of 1-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoyl)-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (47)



A reaction tube was charged with biotin (32.9 mg, 0.135 mmol, 1.0 equiv) and HATU (53.2 mg, 0.14 mmol, 1.05 equiv), evacuated and filled with N_2 for three times. Anhydrous DMF (0.5 mL) and a solution of Et_3N (19 µL, 0.135 mmol, 1.0 equiv) in DMF (0.5 mL) was then added and was stirred at room temperature for 15 min. The reaction was then cooled to 0 °C, alkenylsulfonyl fluoride **44** (30.3 mg, 0.15 mmol, 1.1 equiv) was added, followed by a slow addition of a solution of Et_3N (28 µL, 0.20 mmol, 1.5 equiv) in DMF (0.75 mL) over 30 min. The reaction was warmed up to room temperature gradually and stirred for 16 h under an N_2 atmosphere. The mixture was diluted with EtOAc, washed with 1 M aq. HCl, water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash column chromatography (0–10% MeOH in CH_2Cl_2), affording the *alkenylsulfonyl fluoride* **47** as a white solid (21.2 mg, 40%);

mp 100–102 °C (EtOAc);

R_f 0.41 (10% MeOH in CH_2Cl_2) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (t, J = 3.1 Hz, 0.6H, SC=CH^{rot1}), 7.27 (t, J = 3.0 Hz, 0.4H, SC=CH^{rot2}), 6.42 (br. s, 1H, NH), 6.35 (br. s, 1H, NH), 4.39–4.34 (m, 0.8H, C=CHCH_2^{rot2}), 4.34–4.27 (m, 2.2H, C=CHCH_2^{rot1} + SCH_2CH), 4.14 (dd, J = 7.5, 4.5 Hz, 1H, SCHCH), 3.69 (t, J = 5.3 Hz, 0.8H, $SCCH_2CH_2^{rot2}$), 3.66 (t, J = 5.3 Hz, 1.2H, $SCCH_2CH_2^{rot1}$), 3.14–3.07 (m, 1H, SCH), 2.82 (dd, J = 12.5, 5.1 Hz, 1H, SCH_aH_b), 2.61–2.55 (m, 2.2H, SCH_AH_B + $SCCH_2^{rot1}$), 2.50–2.45 (m, 0.8H, $SCCH_2^{rot2}$), 2.39 (t, J = 7.6 Hz, 1.2H, C(=O)CH_2^{rot1}), 2.34 (d, J = 7.8 Hz, 0.8H, C(=O)CH_2^{rot2}), 1.68–1.57 (m, 1H, $SCHCH_cH_d$), 1.56–1.43 (m, 3H, $SCHCH_cH_d$ + $C(=O)CH_2CH_2$), 1.40–1.30 (m, 2H, $SCHCH_2CH_2$) (recorded as a pair of rotamers);

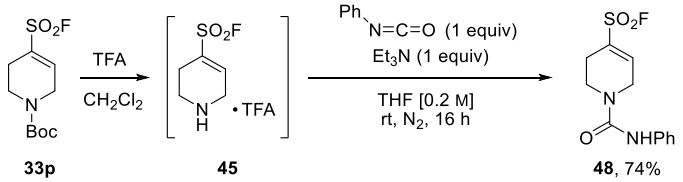
^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ {171.3, 171.1}, 162.7, {143.4, 142.8}, 130.4, 61.0, 59.2, 55.5, {44.6, 41.8}, {40.8, 36.7}, 39.9, {32.5, 32.1}, 28.3, 28.1, {24.6, 24.4}, {24.1, 23.3} (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, DMSO-d_6) δ 52.3, 52.2 (recorded as a pair of rotamers);

IR ν_{max} (neat)/cm^{-1} 3258, 2925, 2856, 1699, 1636, 1432, 1401, 1202;

HRMS (ESI$^+$) found m/z 392.1106 $[M+H]^+$, $C_{15}H_{23}FN_3O_4S_2^+$ requires m/z 392.1109.

Nucleophilic addition of alkenylsulfonyl fluoride 45 to phenyl isocyanate for the preparation of 1-(phenylcarbamoyl)-1,2,3,6-tetrahydro-pyridine-4-sulfonyl fluoride (48)



Following General Procedure L, alkenylsulfonyl fluoride **33p** (26.5 mg, 0.10 mmol, 1.0 equiv) was deprotected and was added with a solution of phenyl isocyanate (11 µL, 0.10 mmol, 1.0 equiv) and Et_3N (14 µL, 0.10 mmol, 1.0 equiv) in anhydrous THF (0.5 mL). The reaction was stirred at ambient temperature for 16 h, which was then diluted with EtOAc, filtered over Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30–45% EtOAc in petrol), affording the *alkenylsulfonyl fluoride* **48** as a white solid (20.9 mg, 74%);

mp 164 °C (decomp.) ($CHCl_3$);

R_f 0.43 (50% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4H, 4 × Ar*H*), 7.14–7.07 (m, 2H, Ar*H* + SC=C*H*), 6.37 (br. s, 1H, N*H*), 4.32 (quint, *J* = 2.9 Hz, 2H, C=CHCH_2), 3.72 (t, *J* = 5.6 Hz, 2H, SCH_2CH_2), 2.68 (tq, *J* = 5.0, 2.2 Hz, 2H, SCCH_2);

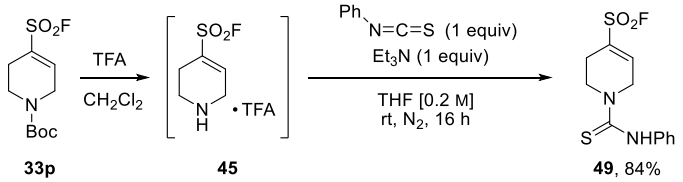
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.6, 139.5 (d, $^3J_{CF}$ = 2.5 Hz), 138.3, 133.2, 129.2, 124.1, 120.6, 44.0, 40.3, 24.3;

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.6;

IR ν_{max} (neat)/cm^{-1} 3303, 2923, 2855, 1633, 1594, 1531, 1447, 1397, 1199;

HRMS (ESI$^+$) found *m*/*z* 285.0704 [M+H]$^+$, $C_{12}H_{14}FN_2O_3S^+$ requires *m*/*z* 285.0704.

Nucleophilic addition of alkenylsulfonyl fluoride 45 to phenyl isothiocyanate for the preparation of 1-(phenylcarbamothioyl)-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (49)



Following General Procedure L, alkenylsulfonyl fluoride **33p** (26.5 mg, 0.10 mmol, 1.0 equiv) was deprotected and was added with a solution of phenyl isothiocyanate (12 µL, 0.10 mmol, 1.0 equiv) and Et_3N (14 µL, 0.10 mmol, 1.0 equiv) in anhydrous THF (0.5 mL). The reaction was stirred at ambient temperature for 16 h, which was then diluted with EtOAc, washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30–50% EtOAc in petrol), affording the *alkenylsulfonyl fluoride* **49** as a white solid (25.1 mg, 84%);

mp 110 °C (decomp.) (CH_2Cl_2);

R_f 0.58 (50% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.35 (m, 3H, N*H* + 2 × Ar*H*), 7.22 (tt, *J* = 7.4, 1.7 Hz, 1H, Ar*H*), 7.13 (d, *J* = 7.6 Hz, 2H, 2 × Ar*H*), 7.03–7.00 (m, 1H, SC=C*H*), 4.49 (quint, *J* = 2.9 Hz, 2H, C=CHCH_2), 4.02 (t, *J* = 5.6 Hz, 2H, SCCH_2CH_2), 2.73–2.68 (m, 2H, SCCH_2);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 184.8, 139.6, 138.8, 132.9 (d, $^2J_{CF}$ = 26.4 Hz), 129.7, 126.1, 123.2, 49.1, 45.6, 23.8;

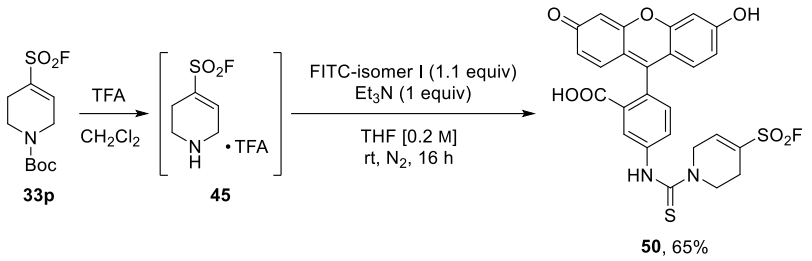
^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 52.0;

IR ν_{max} (neat)/cm^{-1} 3303, 2923, 2855, 1633, 1594, 1531, 1447, 1397, 1199;

LRMS (ESI$^+$) *m*/*z* 301.1 ([M+H]$^+$);

HRMS (ESI$^+$) found *m*/*z* 301.0476 [M+H]$^+$, $C_{12}H_{14}FN_2O_2S_2^+$ requires *m*/*z* 301.0475.

Nucleophilic addition of alkenylsulfonyl fluoride 45 to fluorescein isothiocyanate (FITC) isomer I for the preparation of 5-(4-(fluorosulfonyl)-1,2,3,6-tetrahydropyridine-1-carbothioamido)-2-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)benzoic acid (50)



Following General Procedure L, alkenylsulfonyl fluoride **33p** (26.5 mg, 0.10 mmol, 1.0 equiv) was deprotected and was added with FITC isomer 1 (42.8 mg, 0.11 mmol, 1.1 equiv) and a solution of Et_3N (14 μL, 0.10 mmol, 1.0 equiv) in anhydrous THF (0.5 mL). The reaction was stirred at ambient temperature for 16 h, which was then diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc for three times, and the combined organic extract was washed with brine and dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50–100% EtOAc in petrol), affording the *alkenylsulfonyl fluoride* **50** as an orange solid (36.0 mg, 65%);

mp 167–170 °C (decomp.) (EtOAc);

R*f* 0.38 (75% EtOAc in hexane) [$KMnO_4$/UV];

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (br. s, 2H, 2 × O*H*), 9.88 (s, 1H, N*H*), 7.96 (d, *J* = 1.9 Hz, 1H, Ar*H*), 7.78 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar*H*), 7.40–7.36 (m, 1H, SC=C*H*), 7.19 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.71–6.65 (m, 2H, 2 × Ar*H*), 6.61–6.55 (m, 4H, 4 × Ar*H*), 4.81 (t, *J* = 3.0 Hz, 2H, CHCH_2), 4.17 (t, *J* = 5.5 Hz, 2H, SCCH$_2$CH_2), 2.75–2.69 (m, 2H, SCCH_2);

^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 182.2, 168.9, 159.9, 152.3, 148.5, 143.3, 142.9, 132.5, 130.6, 129.4, 126.6, 124.0, 119.6, 113.1, 110.1, 102.7, 83.5, 49.0, 44.6, 24.1;

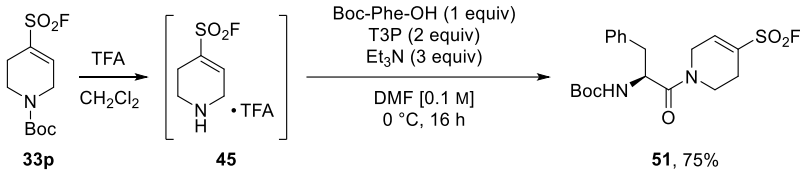
^{19}F {^{1}H} NMR (377 MHz, DMSO-d_6) δ 52.7;

IR ν_{max} (neat)/cm^{-1} 3067, 2924, 2592, 1726, 1589, 1452, 1397, 1203, 1175, 1111;

LRMS (ESI$^+$) *m*/*z* 555.0 ([M+H]$^+$);

HRMS (ESI$^+$) found *m*/*z* 555.0691 [M+H]$^+$, $C_{26}H_{20}FN_2O_7S_2^+$ requires *m*/*z* 555.0690.

Amide coupling between alkenylsulfonyl fluoride 45 and amino acid using T3P for the preparation of *tert*-butyl (*S*)-(1-(4-(fluorosulfonyl)-3,6-dihydropyridin-1(2*H*)-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (51)



Following General Procedure L, alkenylsulfonyl fluoride **33p** (39.8 mg, 0.15 mmol, 1.0 equiv) was deprotected and was added subsequently with anhydrous DMF (1.5 mL), Et_3N (63 µL, 0.45 mmol, 3.0 equiv) and Boc-Phe-OH (39.8 mg, 0.15 mmol, 1.0 equiv). The mixture was then cooled to 0 °C and T3P (50 wt% in EtOAc) (0.18 mL, 0.30 mmol, 2.0 equiv) was slowly added. The reaction was stirred at 0 °C for 16 h, which was then diluted with EtOAc and washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30–60% Et_2O in petrol), affording the *alkenylsulfonyl fluoride* **51** as a white solid (46.2 mg, 75%, >99% ***ee***);

mp 59–61 °C ($CHCl_3$);

$\mathbf{R}_f$ 0.33 (67% Et_2O in hexane) [$KMnO_4$/UV];

$[\alpha]_D^{25}$ +4.2° (c = 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.21 (m, 3H, 3 × Ar*H*), 7.21–7.14 (m, 2H, 2 × Ar*H*), 6.97 (br. s, 0.6H, SC=C*H*^{rot1}), 6.55 (s, 0.4H, SC=C*H*^{rot2}), 5.42 (d, *J* = 8.6 Hz, 0.4H, N*H*^{rot2}), 5.35 (d, *J* = 9.0 Hz, 0.6H, N*H*^{rot2}), 4.84 (td, *J* = 9.2, 5.4 Hz, 0.6H, C(=O)C*H*^{rot1}), 4.75 (td, *J* = 9.7, 5.3 Hz, 0.4H, C(=O)C*H*^{rot2}), 4.38–4.18 (m, 1.2H, C=CHC*H*$_2^{rot1}$), 4.07–3.96 (m, 0.8H, C=CHC*H*$_a$H$_b^{rot2}$ + NC*H*$_c$H$_d$CH$_2^{rot2}$), 3.55–3.45 (m, 0.4H, C=CHCH$_a$*H*$_b^{rot2}$), 3.47–3.32 (m, 1H, NCH$_c$*H*$_d$CH$_2^{rot2}$ + NC*H*$_c$H$_d$CH$_2^{rot1}$), 3.27 (dt, *J* = 13.9, 5.4 Hz, 0.6H, NCH$_c$*H*$_d$CH$_2^{rot1}$), 3.10 (dd, *J* = 12.9, 5.1 Hz, 0.4H, PhC*H*$_e$H$_f^{rot2}$), 3.04 (dd, *J* = 13.0, 5.6 Hz, 0.6H, PhC*H*$_e$H$_f^{rot1}$), 2.96 (dd, *J* = 12.9, 9.7 Hz, 0.6H, PhCH$_e$*H*$_f^{rot1}$), 2.89 (dd, *J* = 12.9, 10.3 Hz, 0.4H, PhCH$_e$*H*$_f^{rot2}$), 2.51–2.38 (m, 0.8H, SCC*H*$_2^{rot2}$), 2.38–2.29 (m, 0.6H, SCC*H*$_g$H$_h^{rot1}$), 1.67 (dd, *J* = 15.1, 7.1 Hz, 0.6H, SCCH$_g$*H*$_h^{rot1}$), 1.44 (s, 3.6H, C(C*H*$_3$)$_3^{rot2}$), 1.43 (s, 5.4H, C(C*H*$_3$)$_3^{rot1}$) (recorded as a pair of rotamers);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ {171.4, 171.0}, 155.2, 139.3, 138.3, {136.3, 136.0}, 129.4, {129.0, 128.9}, {127.7, 127.6}, 80.3, {52.0, 51.5}, {44.5, 42.1}, {41.6, 37.9}, {40.9, 40.6}, 28.5, {24.2, 23.6} (recorded as a pair of rotamers);

^{19}F {^{1}H} NMR (377 MHz, $CDCl_3$) δ 51.9, 51.1 (recorded as a pair of rotamers);

IR ν_{max} (neat)/cm^{-1} 3420, 3313, 3029, 2929, 1705, 1641, 1497, 1454, 1405, 1367, 1204, 1168;

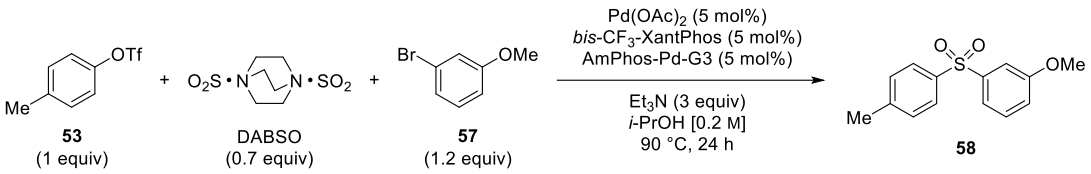
LRMS (ESI^+) *m*/*z* 413.2 ($[M+H]^+$);

HRMS (ESI^+) found *m*/*z* 435.1359 $[M+Na]^+$, $C_{19}H_{25}FN_2O_5SNa^+$ requires *m*/*z* 435.1360;

The ***ee*** was determined by HPLC using a Chiralpak IC column (90:10 hexane/*i*-PrOH); flow rate 1 mL/min; τ_{major} = 19.72 min, τ_{minor} = 37.49 min (>99:1 er, >99% ee).

6.2.9 Cross-electrophilic sulfonylative cross-coupling for DASF synthesis

Palladium-catalysed synthesis of 1-methoxy-3-tosylbenzene (58)



A reaction tube was charged with *m*-bromoanisole **57** (45 mg, 0.24 mmol, 1.2 equiv), DABSO (34 mg, 0.14 mmol, 0.70 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.050 equiv), *bis*-CF_3-XantPhos (11 mg, 0.010 mmol, 0.050 equiv) and AmPhos-Pd-G3 (6.4 mg, 0.010 mmol, 0.050 equiv), sealed with a microwave cap, evacuated and back-filled with Ar for three times through a needle. Degassed anhydrous isopropanol (1 mL), anhydrous triethylamine (83 µL, 0.60 mmol, 3.0 equiv) and *p*-tolyl triflate **53** (36 µL, 0.20 mmol, 1.0 equiv) were added subsequently, and the reaction mixture was stirred in the sealed reaction tube in a preheated aluminum heating block at 90 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, filtered over Celite® and concentrated *in vacuo*. The crude product was purified by preparative thin-layer chromatography (20% EtOAc in hexane), affording the diaryl sulfone **58** as an off-white solid (7.0 mg, 13%) with spectroscopic data in accordance with the literature;[241]

mp 73–75 °C ($CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H, 2 × Ar*H*), 7.49 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H, Ar*H*), 7.44 (dd, *J* = 2.6, 1.6 Hz, 1H, Ar*H*), 7.38 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.32–7.27 (m, 2H, 2 × Ar*H*), 7.06 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, Ar*H*), 3.84 (s, 3H, OCH_3), 2.40 (s, 3H, CCH_3);

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.1, 144.3, 143.3, 138.8, 130.5, 130.0, 127.9, 119.9, 119.5, 112.2, 55.8, 21.7;

LRMS (ESI^+) *m*/*z* 263.0 ($[M+H]^+$), 285.0 ($[M+Na]^+$).

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Appendix – Towards the Synthesis of PRMT1 Inhibitors

Protein Arginine *N*-Methyltransferase 1 (PRMT1)

Protein arginine *N*-methyltransferases (PRMTs) are a family of nine enzymes that catalyse the (i) mono-, (ii) symmetrical or (iii) asymmetrical di-methylation of the guanidium nitrogens of arginine residues on proteins, which are thus classified into three types, depending on their methylated products. PRMT1 belongs to type I and accounts for the majority of arginine asymmetric dimethylation, *i.e.* methylation on the same nitrogen twice. Such post-translational modification is important in cellular processes, such as gene transcription and DNA repair.[242-243] However, dysregulation of PRMT1 expressions has been associated with several diseases, such as breast cancers, prostate cancers, leukaemia and asthma.[243-247] Therefore, PRMT1 is considered to be a potential pharmaceutical target, and designing potent inhibitors to the enzyme is anticipated.

Design of Sulfur(VI) Fluoride-Based PRMT1 Inhibitor

S-Adenosyl methionine (SAM) is a biological methylating agent, which acts as a "CH_3^+" synthon for methyltransferases, including PRMTs. Some of the earliest examples of PRMT inhibitors resemble the structure of SAM, which hinder the binding of SAM to the enzyme, hence inhibiting the methylation. However, other SAM-dependent methyltransferases would also be indiscriminately inhibited, and therefore these SAM analogues often display poor specificity.[242] In 2015, Epizyme, a biopharmaceutical company, discovered that aryl pyrazoles containing an ethylenediamine were potent inhibitors to PRMT1, PRMT6 and PRMT8. The crystal structures of inhibitor-bound PRMT6 revealed that the diamine occupies the binding site for arginine side-chain of substrates.[248-249] Reported by Structural Genomics Consortium (SGC), aryl pyrroles with similar structures also displayed high potency for type I PRMTs.[250]

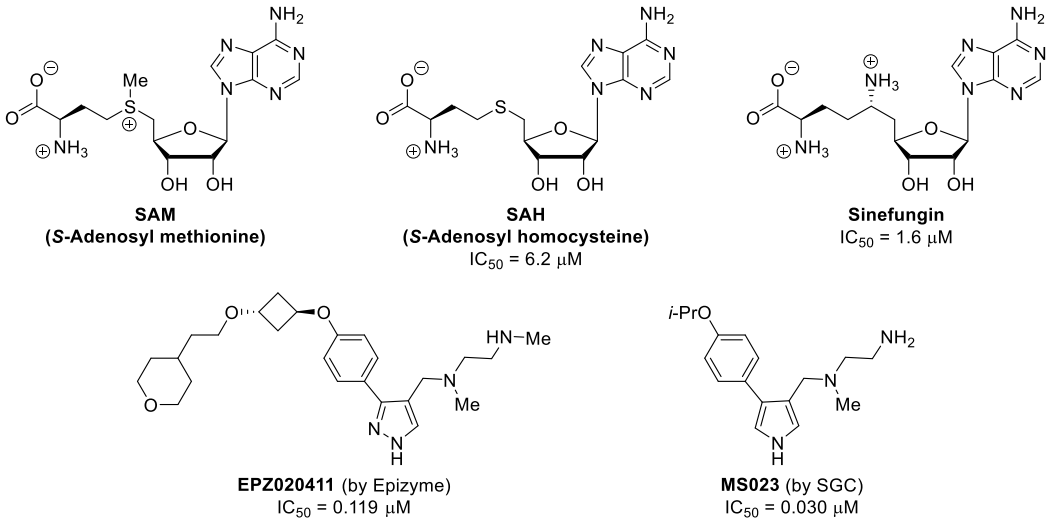


Figure A1. Structures of SAM and selected PRMT inhibitors.
(IC_{50} = half maximal inhibitory concentration with respect to PRMT1)

We established a collaboration with Prof. Paul Brennan from the SGC and the University of Oxford, and a series of PRMT1-selective inhibitors were designed (**Figure A2**), which consisted of a pyrazole core, an ethylenediamine, and an aromatic ring substituted with a sulfonyl fluoride or a fluorosulfate at either the *meta*- or *para*-position.

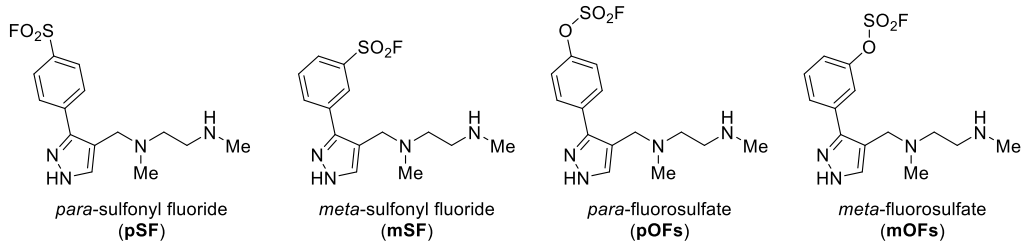


Figure A2. Designed PRMT1 inhibitors containing sulfur(VI) fluorides.

Synthetic Route

The synthetic route for the designed PRMT1 inhibitors is presented in **Scheme A1**. The synthesis of **A8** was modified from the procedures described in Epizyme's patent.[249]

Regarding the diamine fragment, *N*,*N*'-dimethylethylenediamine (**A1**) was protected with Boc_2O using an excess of the amine (2.5 equiv), producing the singly Boc-protected diamine **A2** in 66% yield upon distillation.

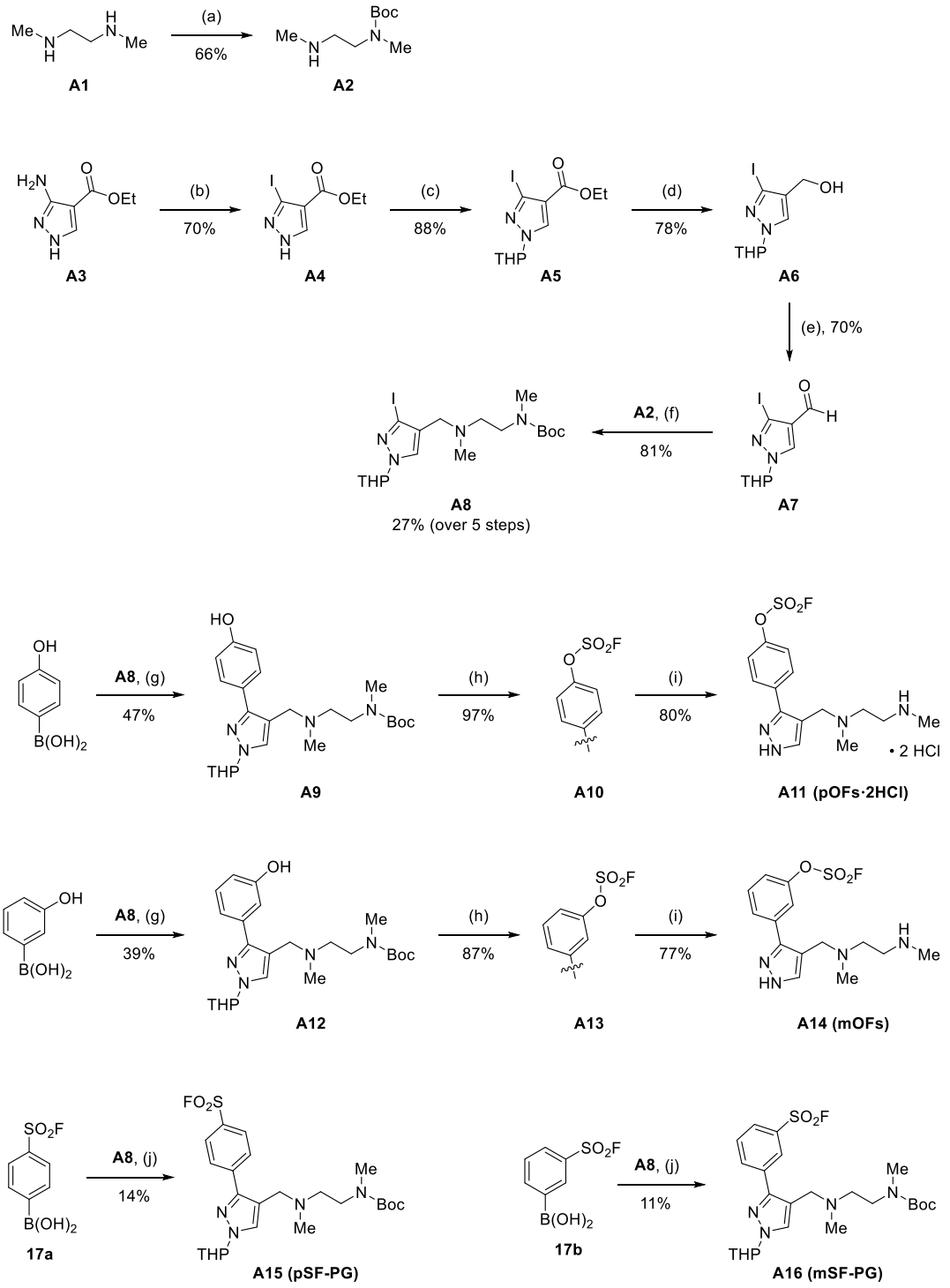
For the pyrazole fragment, starting from ethyl 3-aminopyrazole-4-carboxylate (**A3**), which is commercially available, the amino group of **A3** was diazotised using $NaNO_2$ and sulfuric acid, followed by substitution using KI to yield **A4**. The pyrazole was then protected with tetrahydropyran (THP) protecting group using 3,4-dihydropyran with 10 mol% tosylic acid, producing **A5**. Next, the ethyl ester was converted into an aldehyde. While the reduction of **A5** using 1 equiv of DIBAL at −78 °C (using dry ice-acetone bath) or −94 °C (using liquid N_2-hexane bath) resulted in a mixture of unreacted ester and over-reduced alcohol, 2 equiv of DIBAL was employed to fully convert **A5** into the corresponding alcohol **A6**. This was followed by a selective oxidation to the aldehyde **A7** using activated MnO_2. The aldehyde **A7** then underwent a reductive amination with the singly-Boc-protected diamine **A2** using sodium triacetoxyborohydride ($NaBH(OAc)_3$) to produce pyrazole **A8** in 27% yield over 5 steps.

Iodopyrazole **A8** was then used as the electrophilic coupling partner with various boronic acids in the Suzuki-Miyaura cross-coupling (SMC) reactions. First, **A8** was coupled with 4-hydroxyphenylboronic acid to form **A9**, using Buchwald precatalyst SPhos-Pd-G3 and K_3PO_4 in *n*-BuOH. The hydroxyl group was then converted into a fluorosulfate using [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF), giving **A10**. Subsequently, both THP and Boc protecting groups were cleaved using 4 N HCl in dioxane. The resulting HCl salt of **pOSF** was analytical pure by NMR upon trituration, and it was confirmed by nitrogen chemiluminescence detector (NCD) that **A11** was isolated as a dihydrochloride salt (**pOSF·2HCl**). The *meta*-substituted **mOFs** was prepared in an identical pathway using 3-hydroxyphenylboronic acid for the SMC. The

HCl salt of **A14** was dissolved in water and neutralised with sat. aq. $NaHCO_3$, and the neutral compound **A14** (*i.e.* **mOFs**) was obtained after extraction with CH_2Cl_2 and EtOAc.

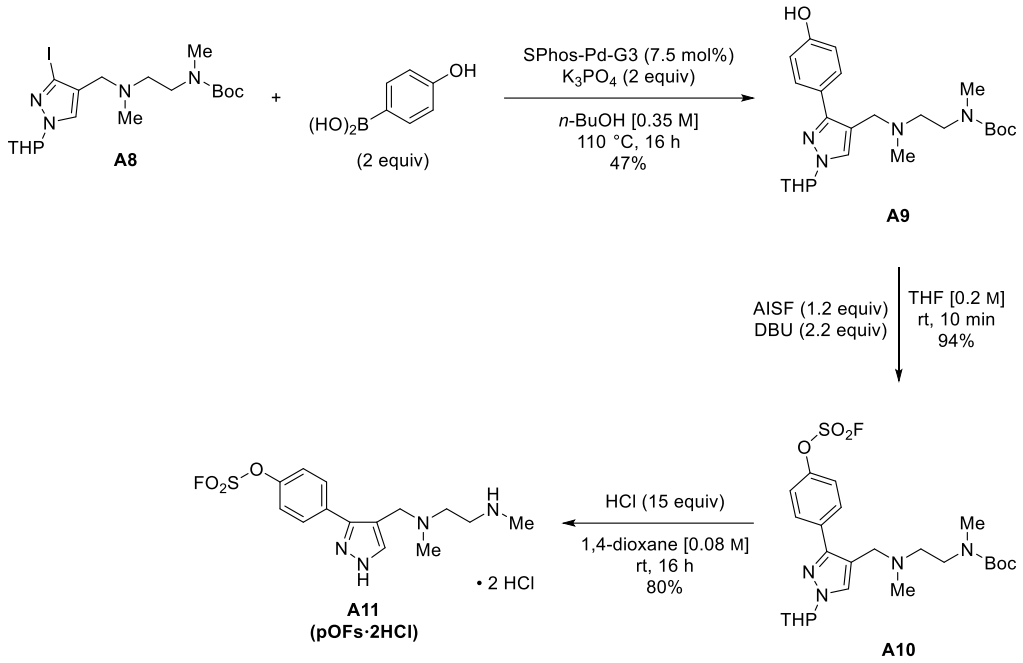
On the other hand, the preparations of the sulfonyl fluoride inhibitors **pSF** and **mSF** were significantly more challenging. After several failed attempts in the SMC step, it was found that **A15** and **A16** could be formed in poor yields using BASF **17a** or **17b**, $Pd(dppf)Cl_2$, and K_2CO_3 in 1,4-dioxane at 80 °C, respectively. The deprotections of **A15** and **A16** using HCl in dioxane were anticipated to yield targeting inhibitors **pSF** and **mSF**, respectively, but the experiment has not been conducted as the project was suspended due to the COVID-19 pandemic.

At the time of submission of this thesis, the IC_{50} of 4OFs against PRMT1 was determined by our collaborators from the SGC, at a value of 90 nM.



Scheme A1. Synthesis of S(VI)-F PRMT1 inhibitors. (a) **A1** (2.5 equiv), Boc_2O (1.0 equiv), CH_2Cl_2, 0 °C to rt, 16 h; (b) $NaNO_2$ (1.7 equiv), 50% (v/v) H_2SO_4, 0 °C, 30 min; then KI (3.0 equiv), 0 °C, 1 h; (c) 3,4-dihydropyran (1.2 equiv), TsOH (10 mol%), CH_2Cl_2, rt, 3 h; (d) DIBAL (2.0 equiv), CH_2Cl_2, −78 °C, 3 h; (e) MnO_2 (5.0 equiv), acetone, 50 °C, 16 h; (f) **A2** (1.2 equiv), **A7** (1.0 equiv), $NaBH(OAc)_3$ (2.0 equiv), $ClCH_2CH_2Cl$, rt, 1 h; (g) SPhos-Pd-G3 (7.5 mol%), K_3PO_4 (2.0 equiv), *n*-BuOH, 110 °C, 16 h; (h) AISF (1.2 equiv), DBU (2.2 equiv), THF, rt, 10 min; (i) 4 N HCl in dioxane (15 equiv), dioxane, rt, 16 h; (j) BASF **17a** or **b** (2.0 equiv), $Pd(dppf)Cl_2$ (10 mol%), K_2CO_3 (3.0 equiv), H_2O (1.5 equiv), dioxane, 80 °C, 24 h.

Preparation of 4-(4-((methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)phenyl sulfurofluoridate dihydrochloride (A11)



Suzuki-Miyaura cross-coupling

A reaction tube was charged with **A8** (382 mg, 0.80 mmol, 1.0 equiv), 4-hydroxyphenyl boronic acid (221 mg, 1.6 mmol, 2.0 equiv), SPhos-Pd-G3 (47 mg, 0.060 mmol, 0.075 equiv) and K_3PO_4 (339 mg, 1.6 mmol, 2.0 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 for three times. Degassed *n*-butanol (2 mL) was added, and the reaction mixture stirred under positive pressure of N_2 in a preheated aluminum heating block at 110 °C for 16 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, and the organic extract was washed with brine for three times, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (0–5% methanol in EtOAc), affording **A9** as a viscous yellow oil (167.5 mg, 47%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69–7.53 (m, 3H), 6.88–6.77 (m, 2H), 5.40–5.29 (m, 1H), 4.11–4.02 (m, 1H), 3.74–3.65 (m, 1H), 3.48–3.41 (m, 2H), 3.40–3.24 (m, 2H), 2.86–2.75 (m, 3H), 2.57–2.45 (m, 2H), 2.28–2.17 (m, 3H), 2.14–1.99 (m, 3H), 1.75–1.54 (m, 3H), 1.47–1.40 (m, 9H).

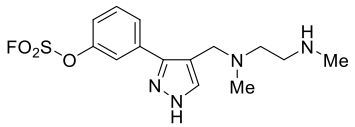
Fluorosulfonation of phenol

To a solution of **A9** (104 mg, 0.23 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added AISF (88 mg, 0.28 mmol, 1.2 equiv) and DBU (77 μL, 0.52 mmol, 2.2 equiv). The reaction was stirred at ambient temperature for 10 min. The mixture was diluted with EtOAc, and the organic extract was washed with water and brine for three times, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (0–5% methanol in CH_2Cl_2), affording **A10** as a viscous light yellow oil (120 mg, 97%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09–8.00 (m, 2H), 7.65–7.55 (m, 1H), 7.37 (app. d, *J* = 8.2 Hz, 2H), 5.38 (app. dd, *J* = 9.3, 3.0 Hz, 1H), 4.10–4.03 (m, 2H), 3.77–3.67 (m, 1H), 3.49–3.26 (m, 4H), 2.88–2.76 (m, 3H), 2.61–2.45 (m, 2H), 2.25 (s, 3H), 2.16–2.05 (m, 2H), 1.78–1.56 (m, 3H), 1.42 (app. d, *J* = 6.1 Hz, 9H); **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 37.6, 37.5 (recorded as a pair of rotamers).

Deprotection

To a solution of **A10** (78 mg, 0.15 mmol, 1.0 equiv) in 1,4-dioxane (1.2 mL) was added 4 N HCl solution in dioxane (0.6 mL). The reaction was stirred at ambient temperature for 16 h. The stirring was then stopped to allow the precipitate to settle. The supernatant was syringed out, and the remaining solid was triturated with Et_2O for three times to afford the dihydrochloride salt **A11** (**pOSF·2HCl**) as a white solid (71.4 mg, 80%); **^{1}H NMR** (400 MHz, D_2O) δ 8.06 (s, 1H), 7.78–7.74 (m, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 4.55 (s, 2H), 3.34 (s, 4H), 2.69 (s, 3H), 2.68 (s, 3H); **^{19}F {^{1}H} NMR** (377 MHz, D_2O) δ 37.9; **LRMS** (ESI^+) *m*/*z* 343.0 ($[M+H]^+$).

3-(4-((methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)phenyl sulfurofluoridate (A14)

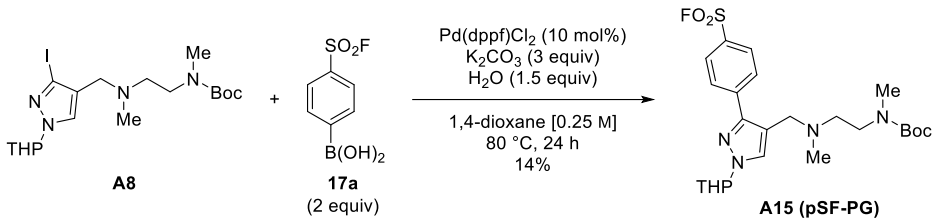


A12–14 was prepared in an identical 3-step pathway as in the synthesis of **A11**, using 3-hydroxyphenylboronic acid for the SMC. **A12** was isolated as a viscous yellow oil in 39% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.44–7.28 (m, 1H), 7.25–7.21 (m, 2H), 6.90–6.81 (m, 1H), 5.39 (app. dd, *J* = 7.0, 5.3 Hz, 1H), 4.12–4.05 (m, 1H), 3.74–3.67 (m, 1H), 3.51–3.30 (m, 4H), 2.95–2.85 (m, 3H), 2.69–2.44 (m, 2H), 2.17 (s, 3H), 2.14–2.01 (m, 3H), 1.74–1.57 (m, 3H), 1.51–1.37 (m, 9H).

A13 was isolated as a viscous colourless oil in 87% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.67–7.57 (m, 1H), 7.55–7.46 (m, 1H), 7.30–7.23 (m, 1H), 5.38 (app. dd, *J* = 9.4, 2.9 Hz, 1H), 4.13–4.04 (m, 1H), 3.72 (app. td, *J* = 11.2, 2.9 Hz, 1H), 3.53–3.26 (m, 4H), 2.84–2.75 (m, 3H), 2.61–2.46 (m, 2H), 2.27 (s, 3H), 2.19–2.02 (m, 3H), 1.78–1.58 (m, 3H), 1.45–1.37 (m, 9H); **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 37.7, 37.6 (recorded as a pair of rotamers).

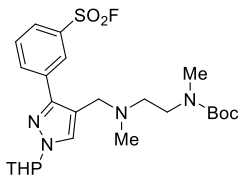
The HCl salt of **A14** obtained upon deprotection was dissolved in 0.1 M aq. HCl (5 mL), diluted with water (100 mL) and washed with Et_2O (100 mL × 3). The aqueous extract was then added with sat. aq. $NaHCO_3$ (50 mL) and subsequently extracted with CH_2Cl_2 (50 mL × 3) and EtOAc (50 mL × 4), until the aqueous layer became clear. The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the neutral **A14** as an off-white gummy solid in 77% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 2.4, 1.1 Hz, 1H), 7.81 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.28–7.21 (m, 1H), 3.44 (s, 2H), 2.73 (dd, *J* = 6.6, 5.0 Hz, 2H), 2.60 (dd, *J* = 6.6, 4.9 Hz, 2H), 2.39 (s, 3H), 2.28 (s, 3H); **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 37.6; **LRMS** (ESI^+) *m*/*z* 343.0 ($[M+H]^+$).

Preparation of *tert*-butyl (2-(((3-(4-(fluorosulfonyl)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (A15)



A reaction tube was charged with **A8** (239 mg, 0.50 mmol, 1.0 equiv), BASF **17a** (204 mg, 1.0 mmol, 2.0 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (41 mg, 0.050 mmol, 0.10 equiv) and K_2CO_3 (207 mg, 1.5 mmol, 3.0 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 for three times. Degassed 1,4-dioxane (2 mL) and degassed water (13.5 µL, 0.75 mmol, 1.5 equiv) were added, and the reaction mixture stirred under positive pressure of N_2 in a preheated aluminum heating block at 80 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, and The reaction mixture was then diluted with EtOAc, filtered over Celite® and concentrated *in vacuo* to yield the crude product which was then purified by flash column chromatography (33–67% EtOAc in hexane), followed by filtration through a plug of silica ($CHCl_3$), affording **A15** as a viscous yellow oil (37 mg, 14%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33–8.19 (m, 2H), 8.06–7.99 (m, 2H), 7.62 (s, 1H), 5.40 (dd, *J* = 8.9, 3.3 Hz, 1H), 4.13–4.04 (m, 1H), 3.78–3.67 (m, 1H), 3.45 (s, 2H), 3.35 (d, *J* = 32.3 Hz, 2H), 2.82 (s, 3H), 2.62–2.50 (m, 2H), 2.27 (s, 3H), 2.17–2.04 (m, 3H), 1.74–1.62 (m, 3H), 1.42 (s, 9H); **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.4, 66.3.

***tert*-butyl (2-(((3-(3-(fluorosulfonyl)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (A16)**



Following the procedure for the synthesis of **A15** as described above, using BASF **17b** instead of **17a**, **A16** was isolated as a viscous yellow oil in 11% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.40 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.68–7.57 (m, 2H), 5.39 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.13–4.05 (m, 1H), 3.72 (td, *J* = 11.1, 3.0 Hz, 1H), 3.43 (s, 2H), 3.40–3.30 (m, 2H), 2.84–2.77 (m, 3H), 2.61–2.51 (m, 2H), 2.28 (s, 3H), 2.18–2.03 (m, 3H), 1.76–1.59 (m, 3H), 1.41 (s, 9H); **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 65.76, 65.75 (recorded as a pair of rotamers).

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NMR Spectra

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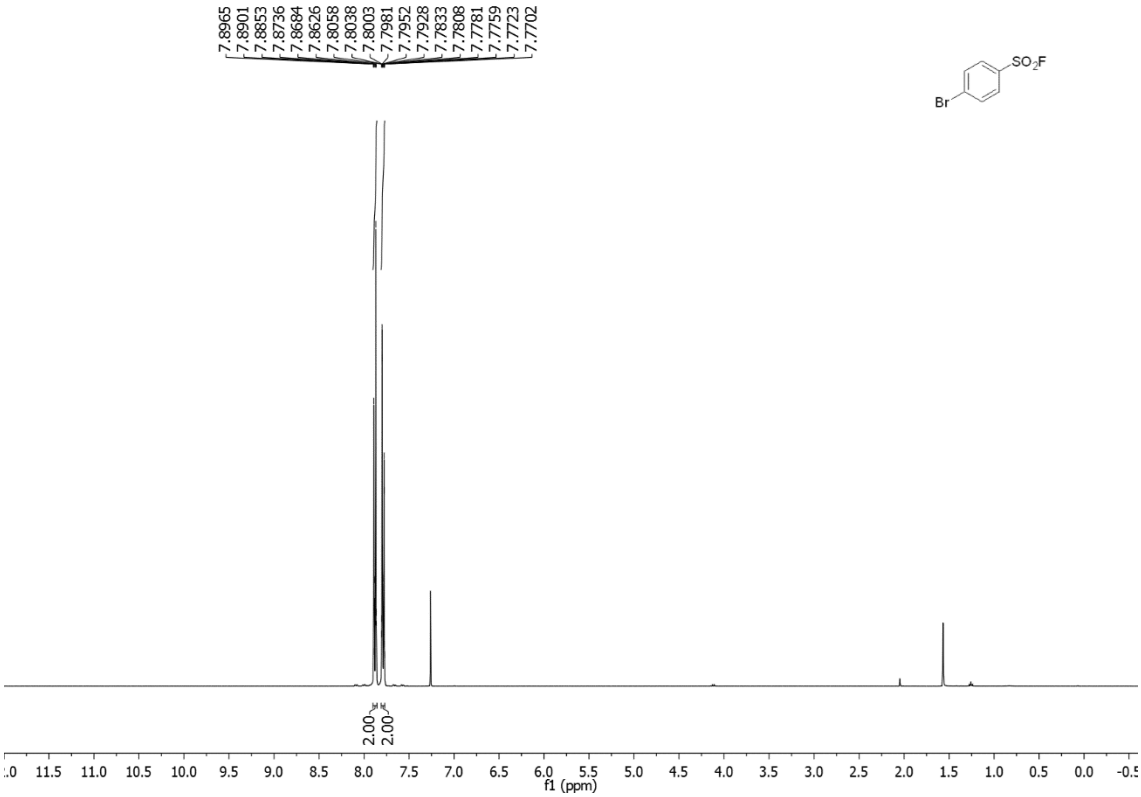
11 NMR Spectra of 1-Methoxy-3-tosylbenzene (**58**) 328

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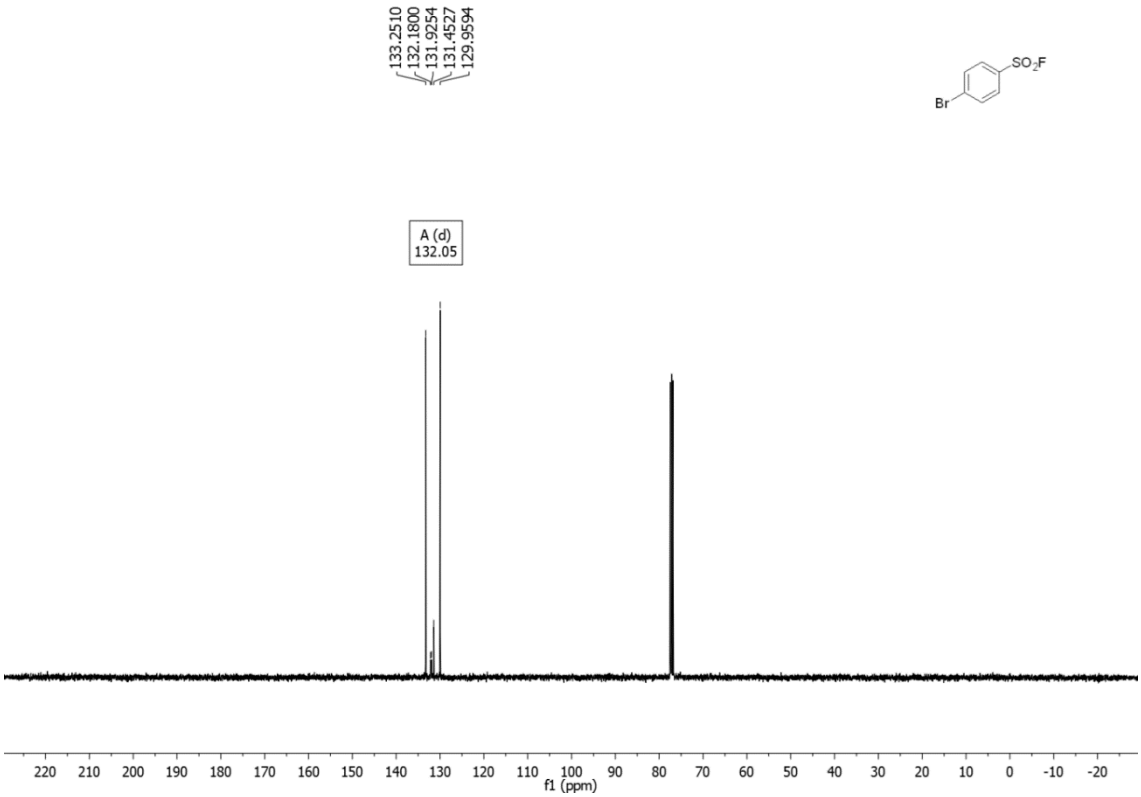
1 NMR Spectra of Bromobenzenesulfonyl fluorides

4-Bromobenzenesulfonyl fluoride (15a)

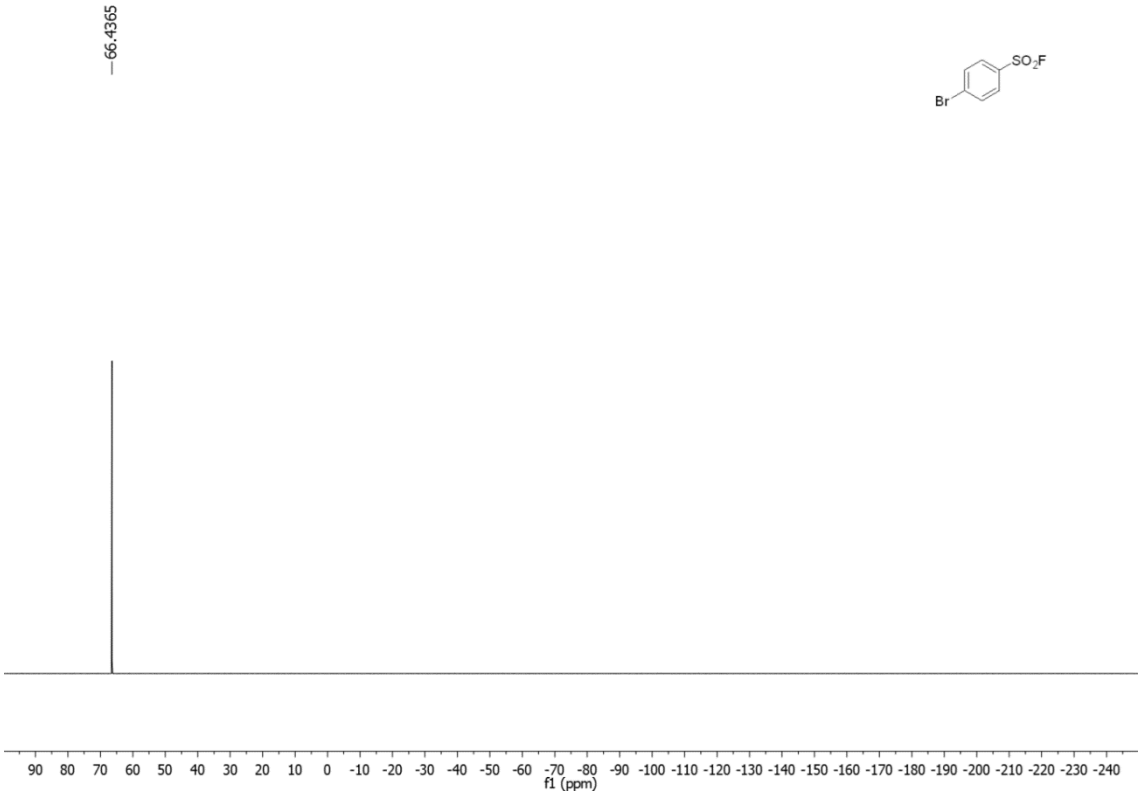
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

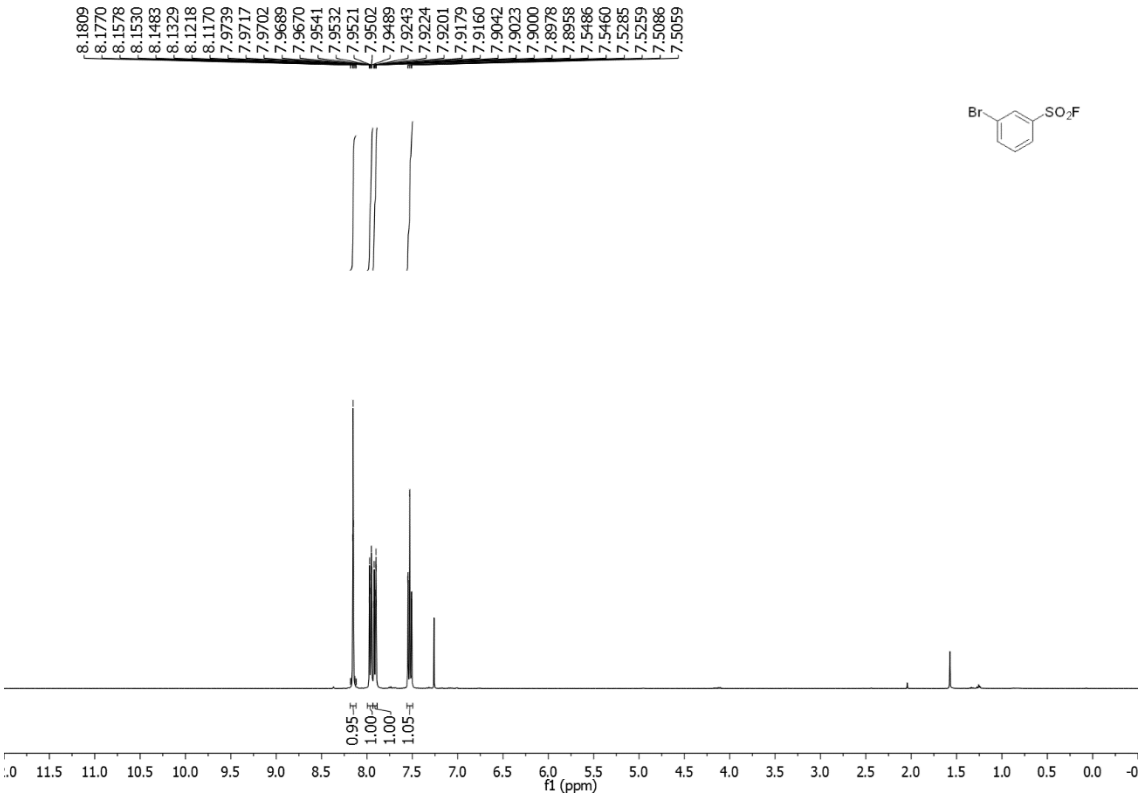


^{19}F-NMR Spectrum:

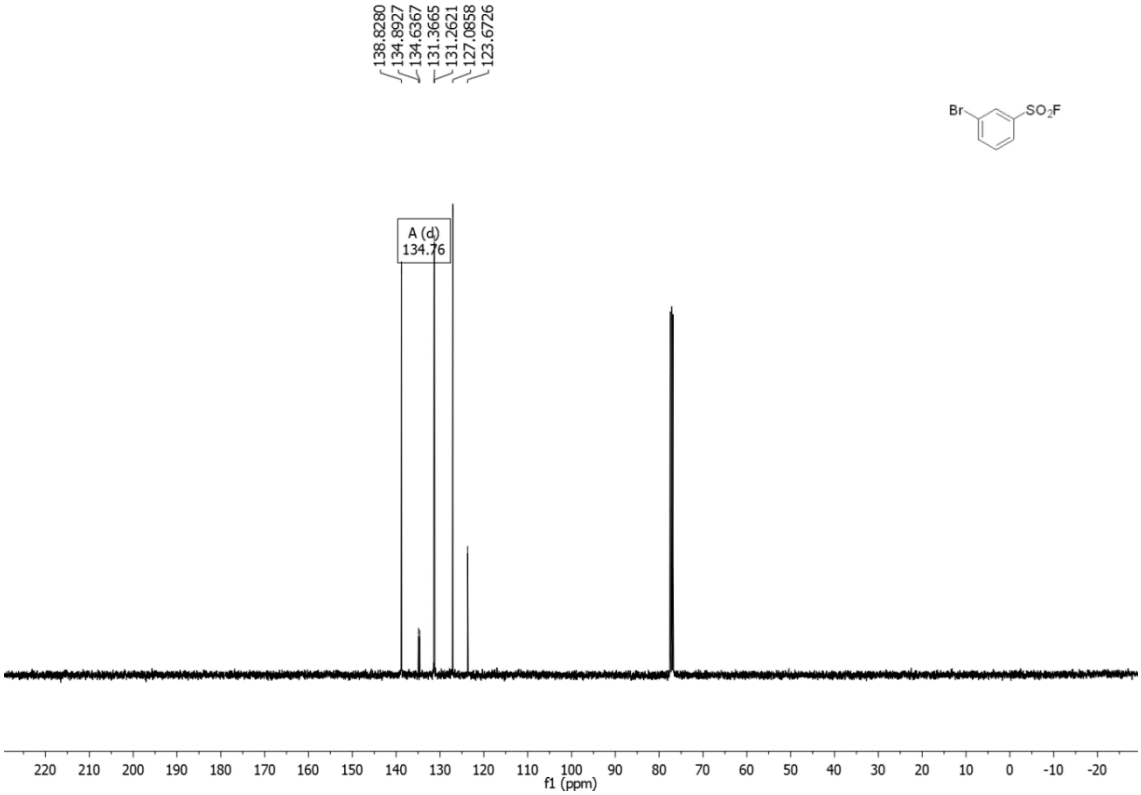


3-Bromobenzenesulfonyl fluoride (15b)

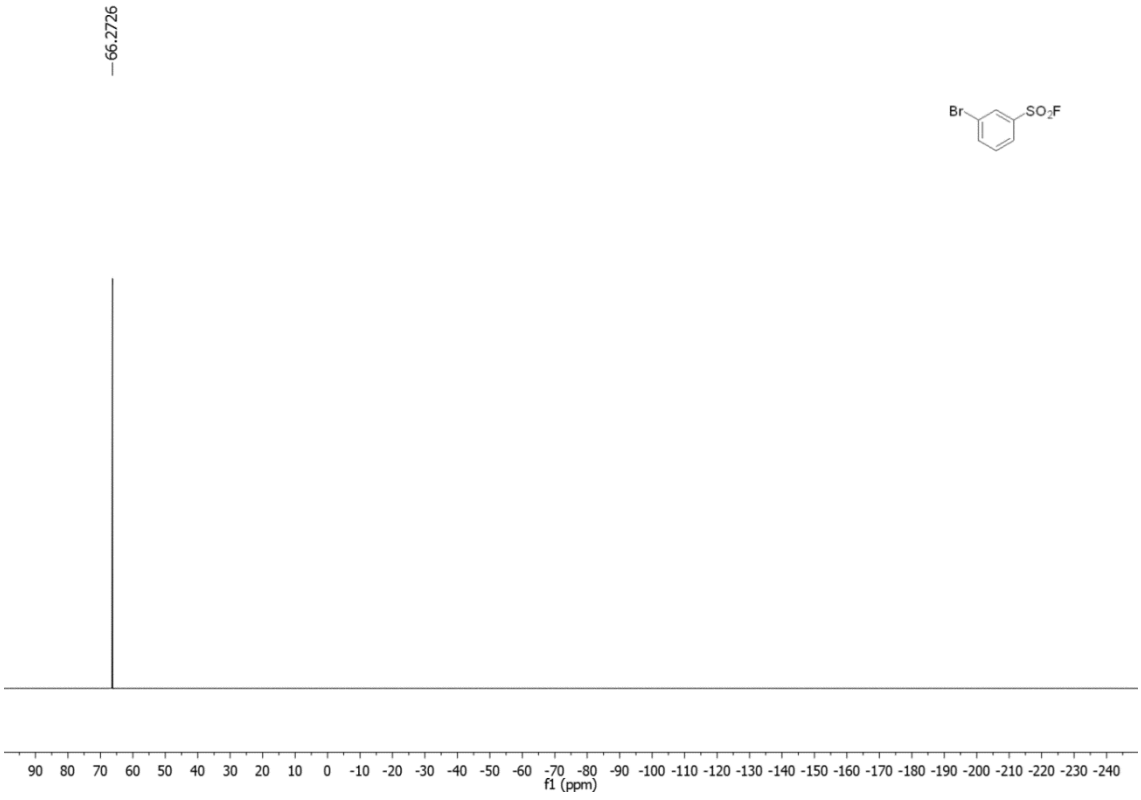
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:



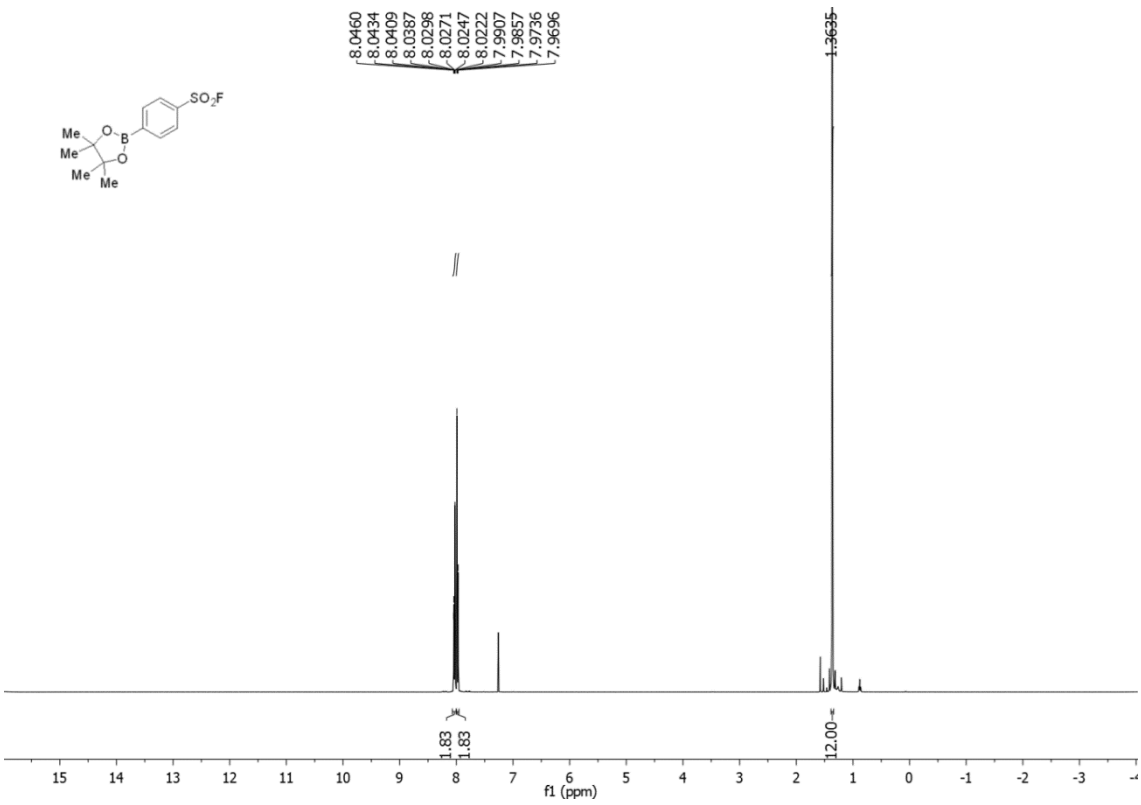
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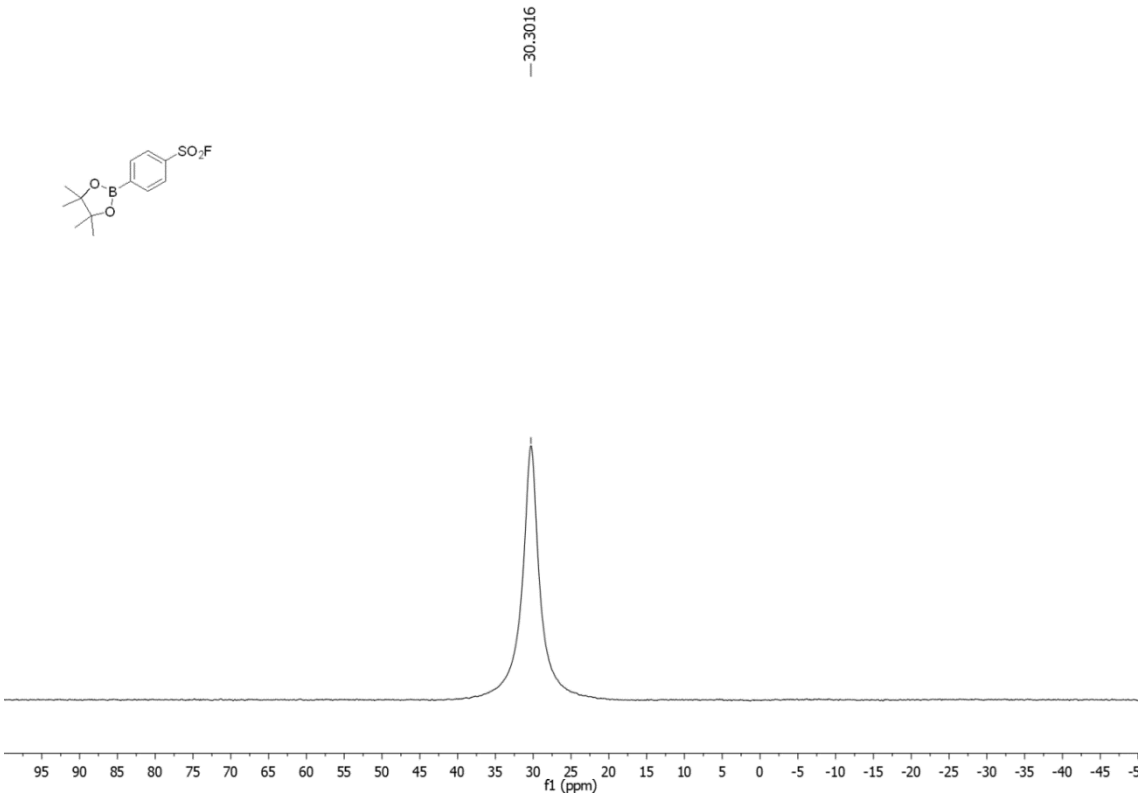
2 NMR Spectra of Arylsulfonyl fluoride boronic acid pinacol esters

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (16a)

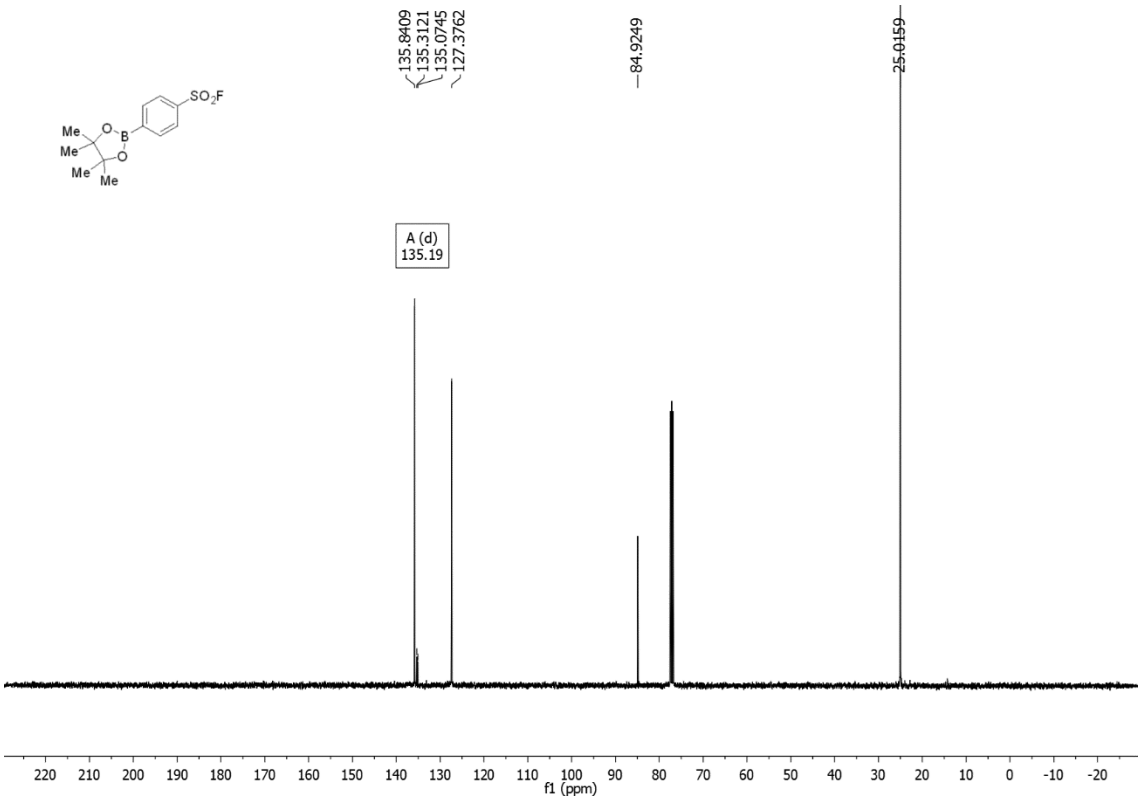
^{1}H-NMR Spectrum:



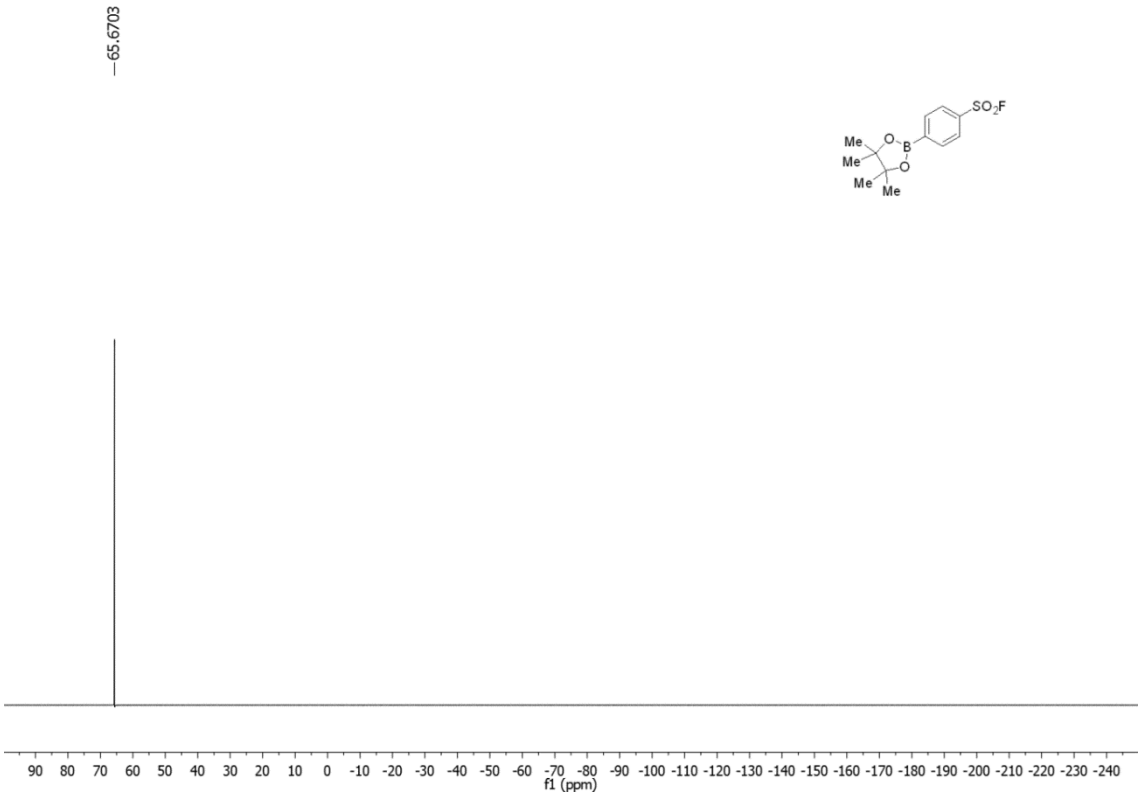
^{11}B-NMR Spectrum:



^{13}C-NMR Spectrum:

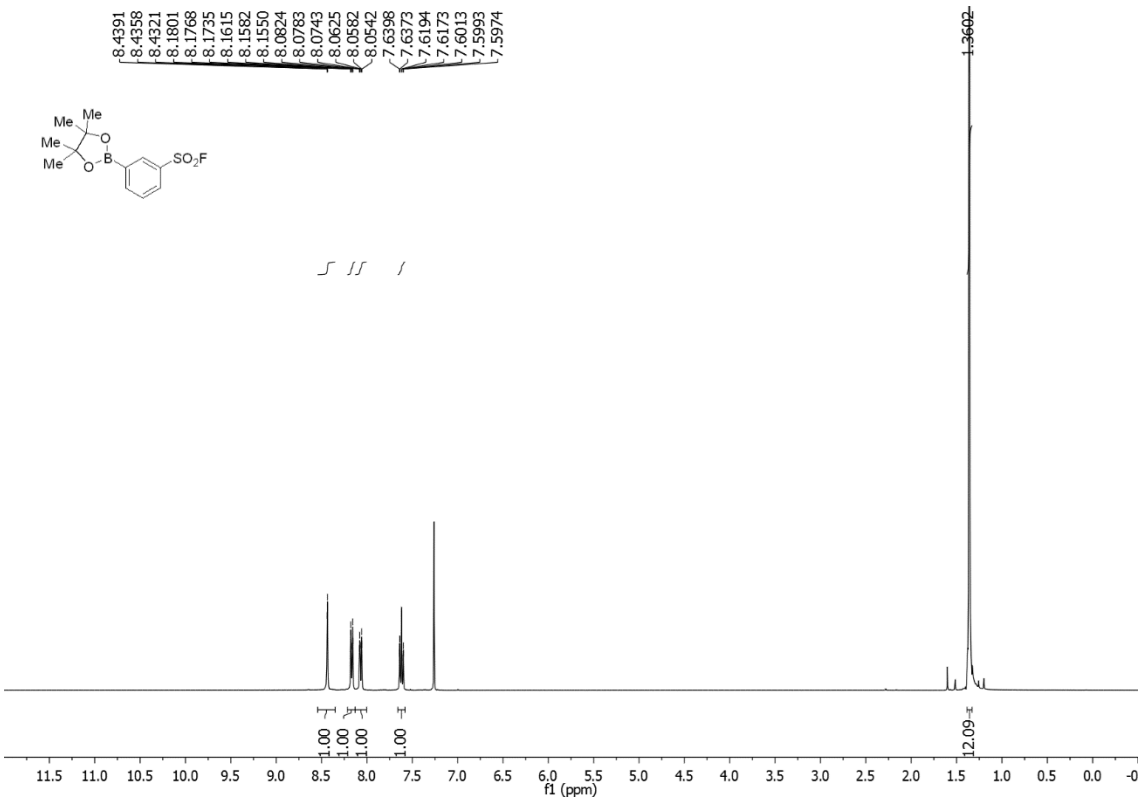


^{19}F-NMR Spectrum:

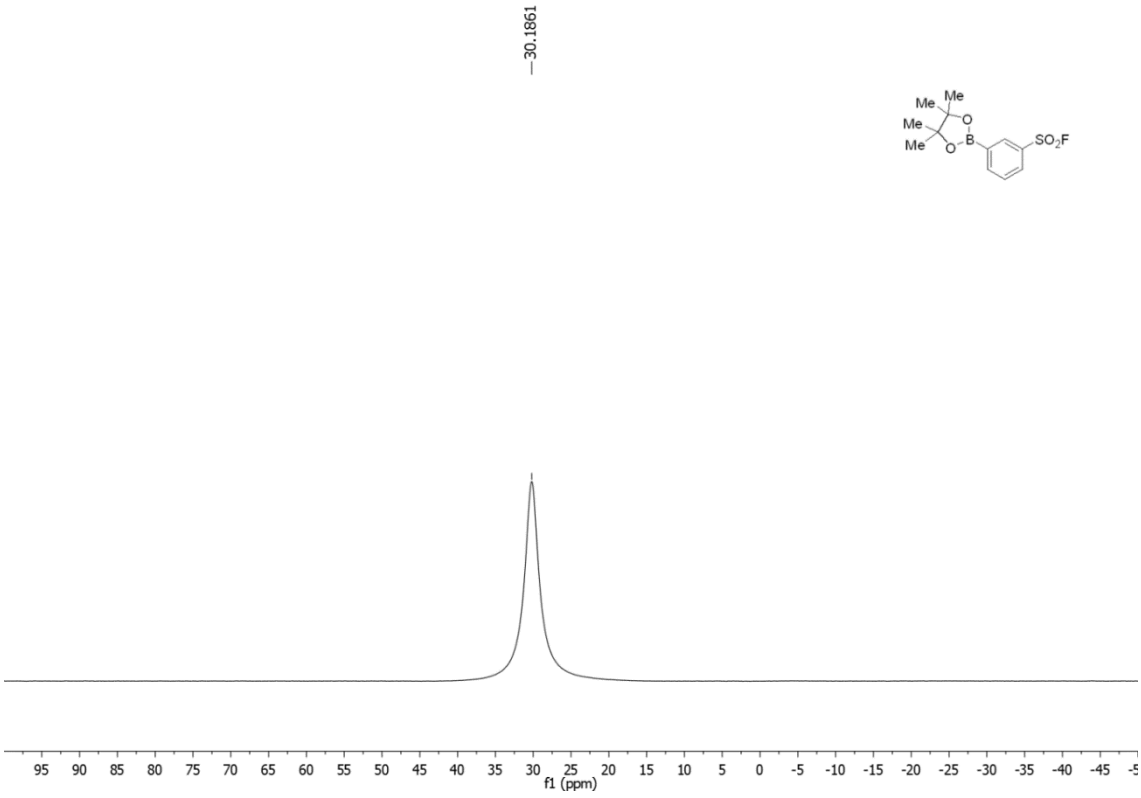


3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (16b)

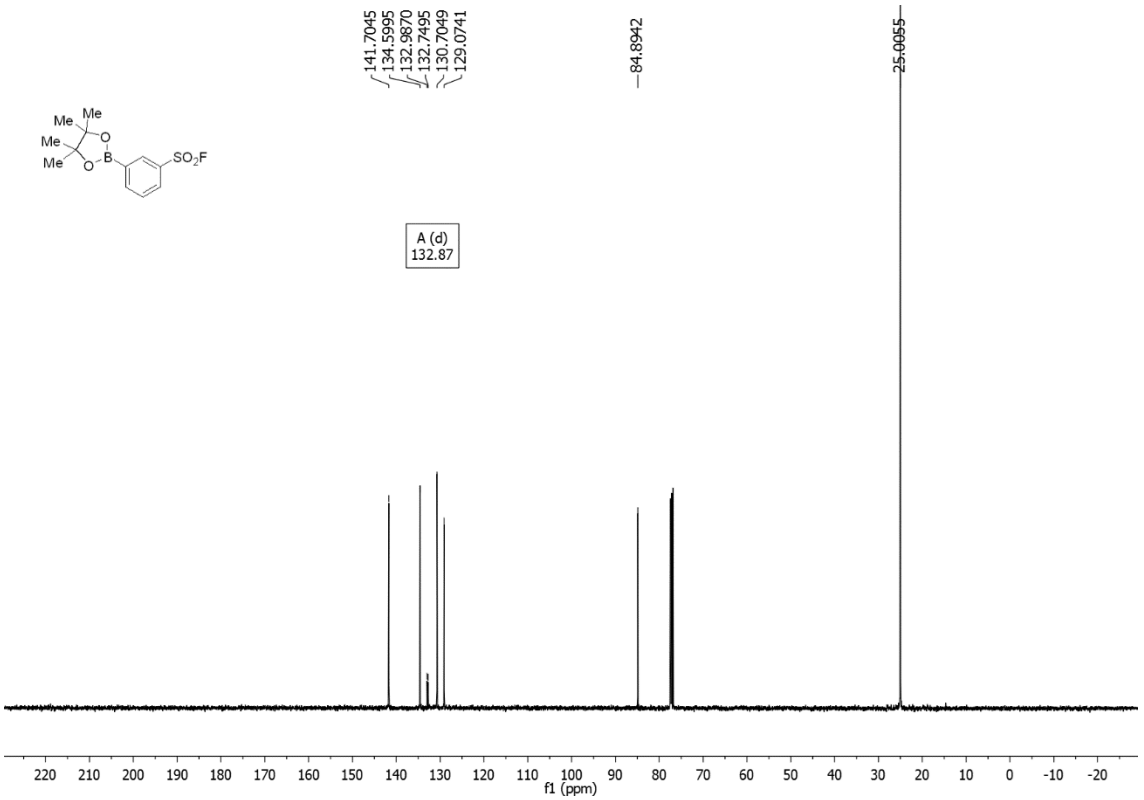
^{1}H-NMR Spectrum:



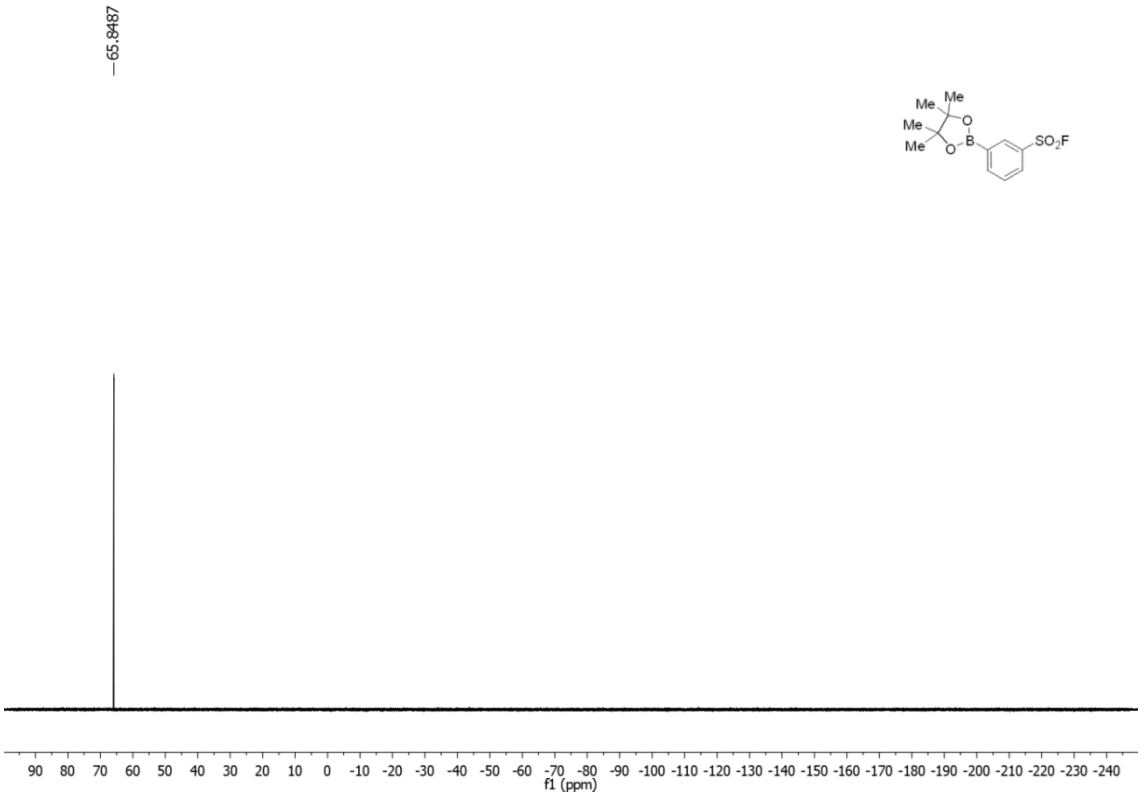
^{11}B-NMR Spectrum:



^{13}C-NMR Spectrum:



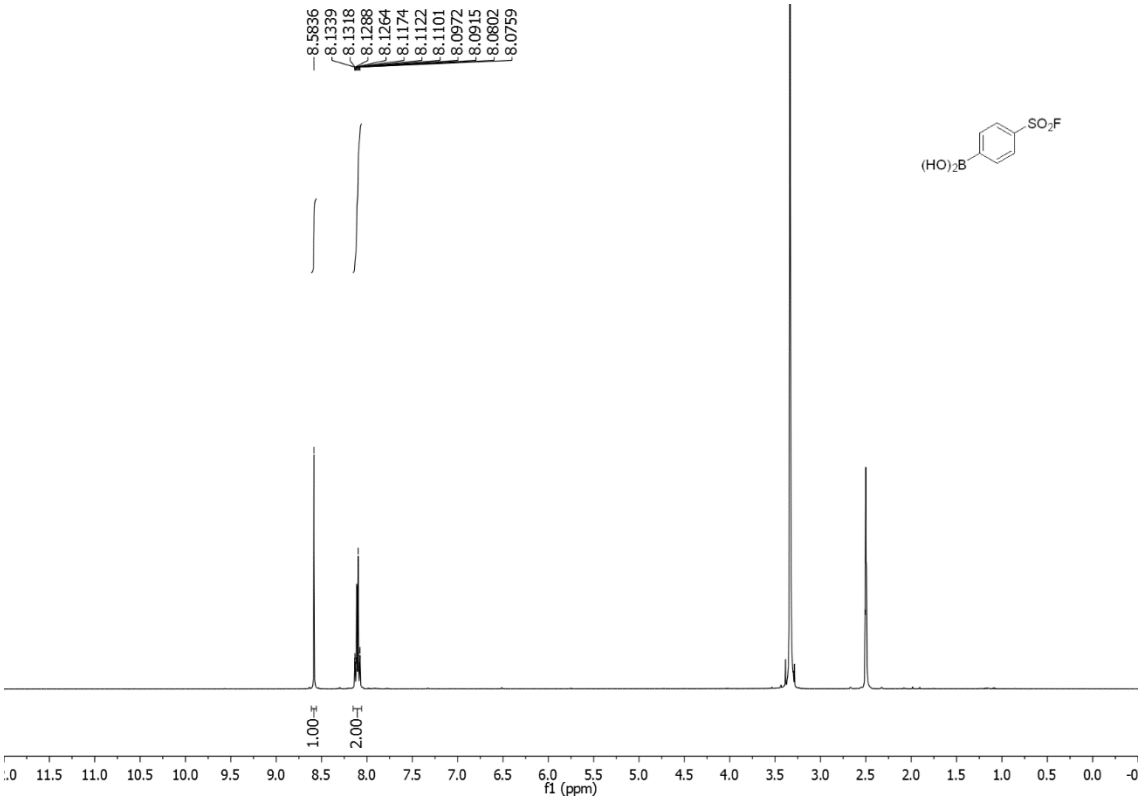
^{19}F-NMR Spectrum:



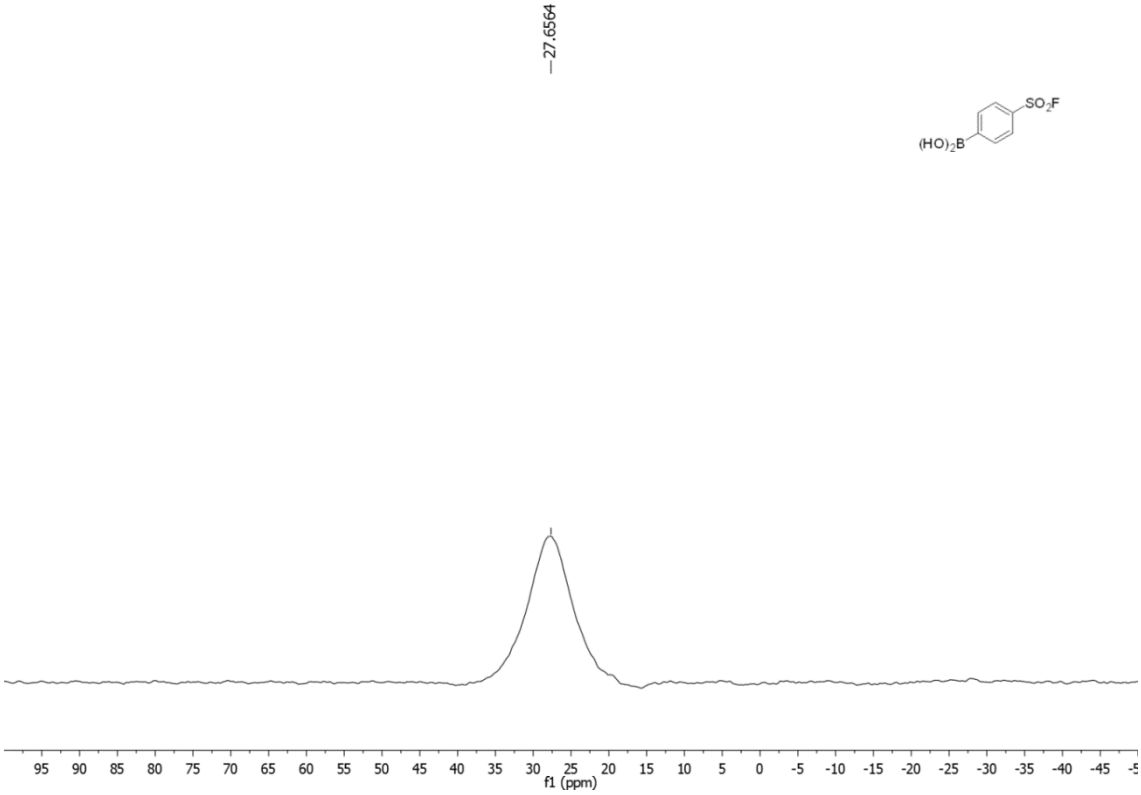
3 NMR Spectra of BASFs

4-(Fluorosulfonyl)phenylboronic acid (17a)

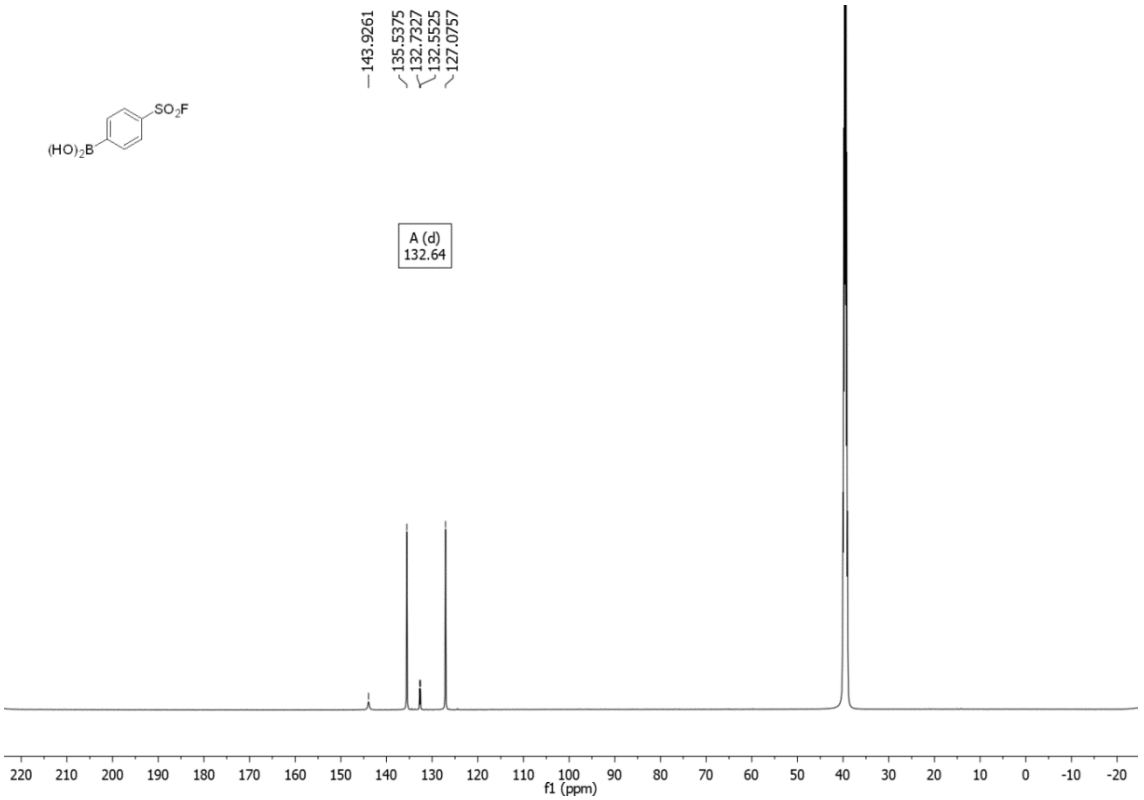
^{1}H-NMR Spectrum:



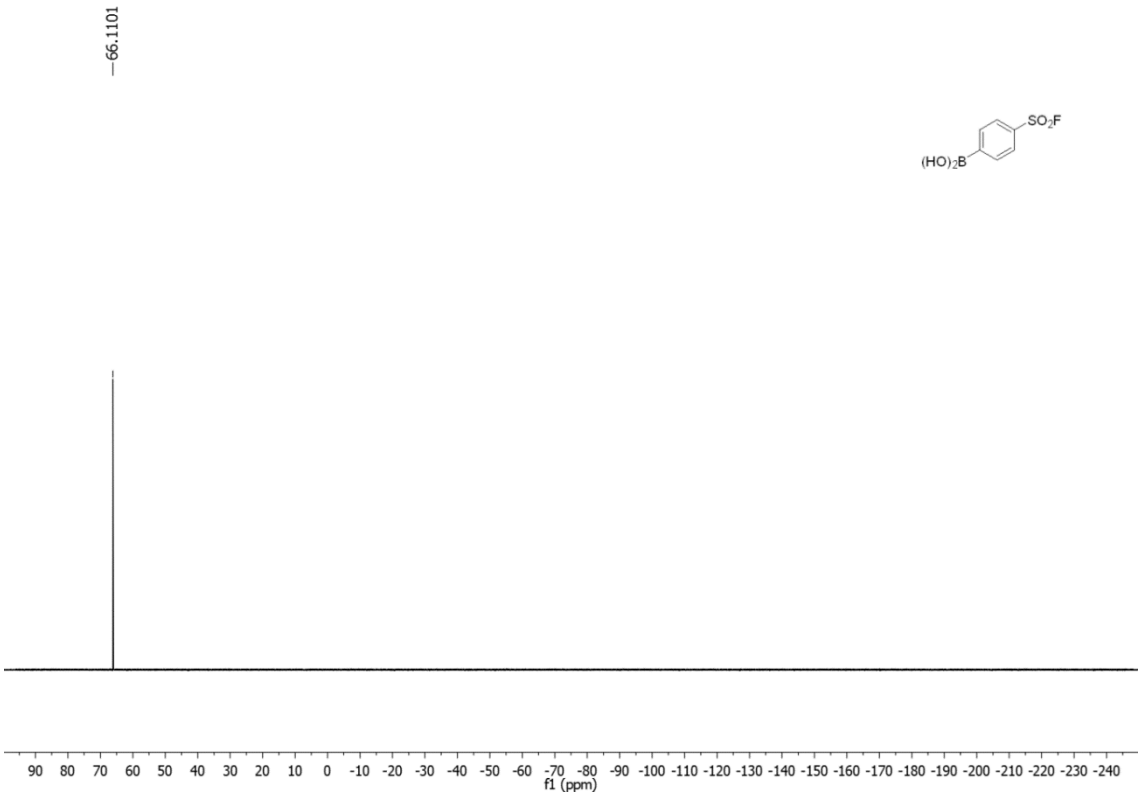
^{11}B-NMR Spectrum:



^{13}C-NMR Spectrum:

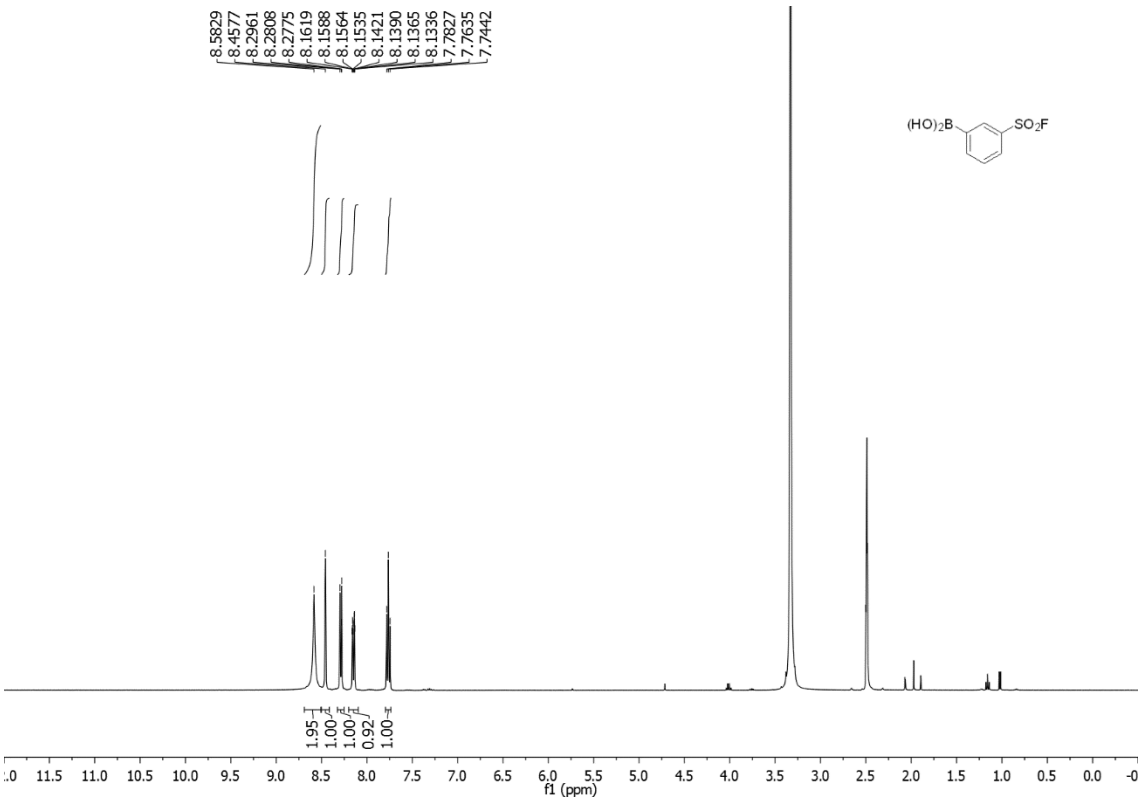


^{19}F-NMR Spectrum:

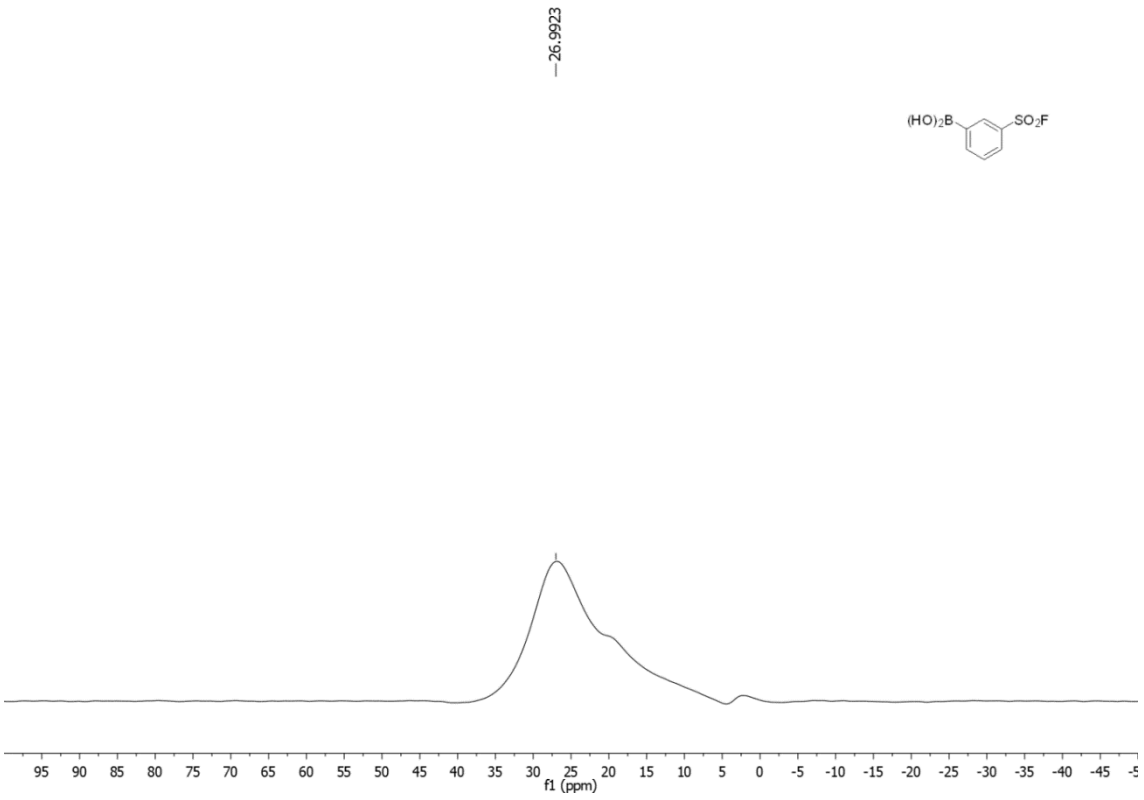


3-(Fluorosulfonyl)phenylboronic acid (17b)

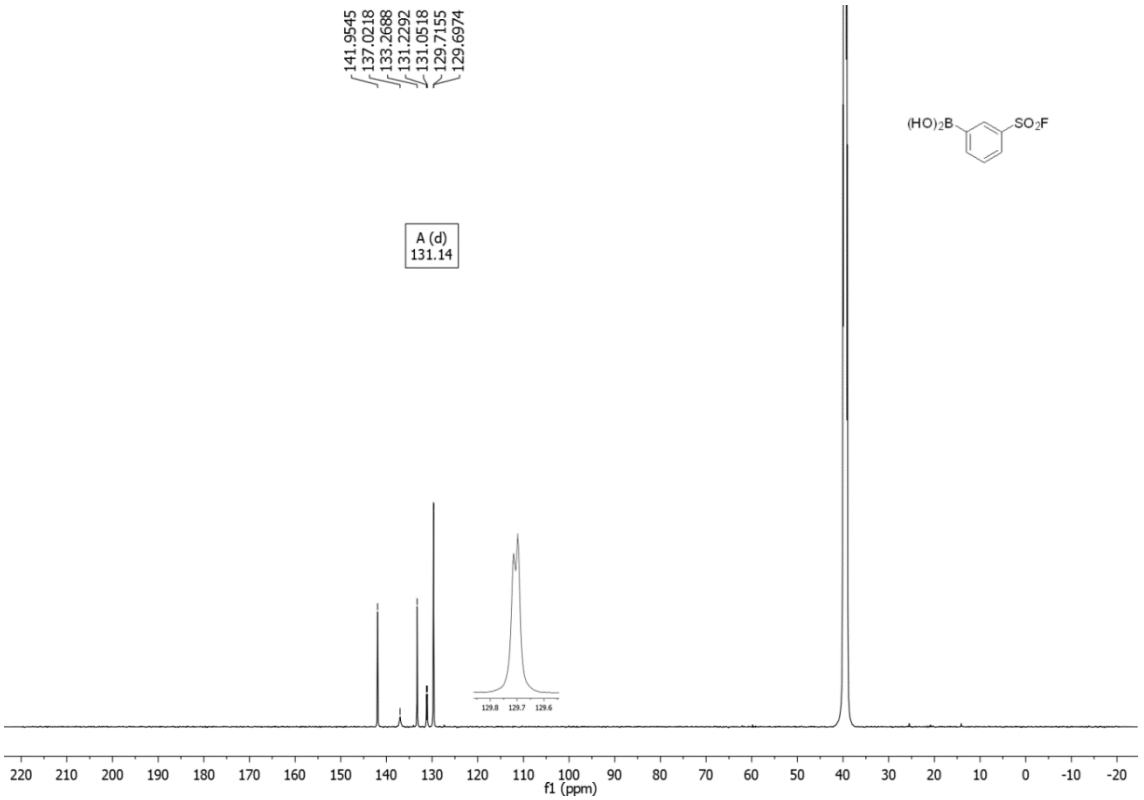
^{1}H-NMR Spectrum:



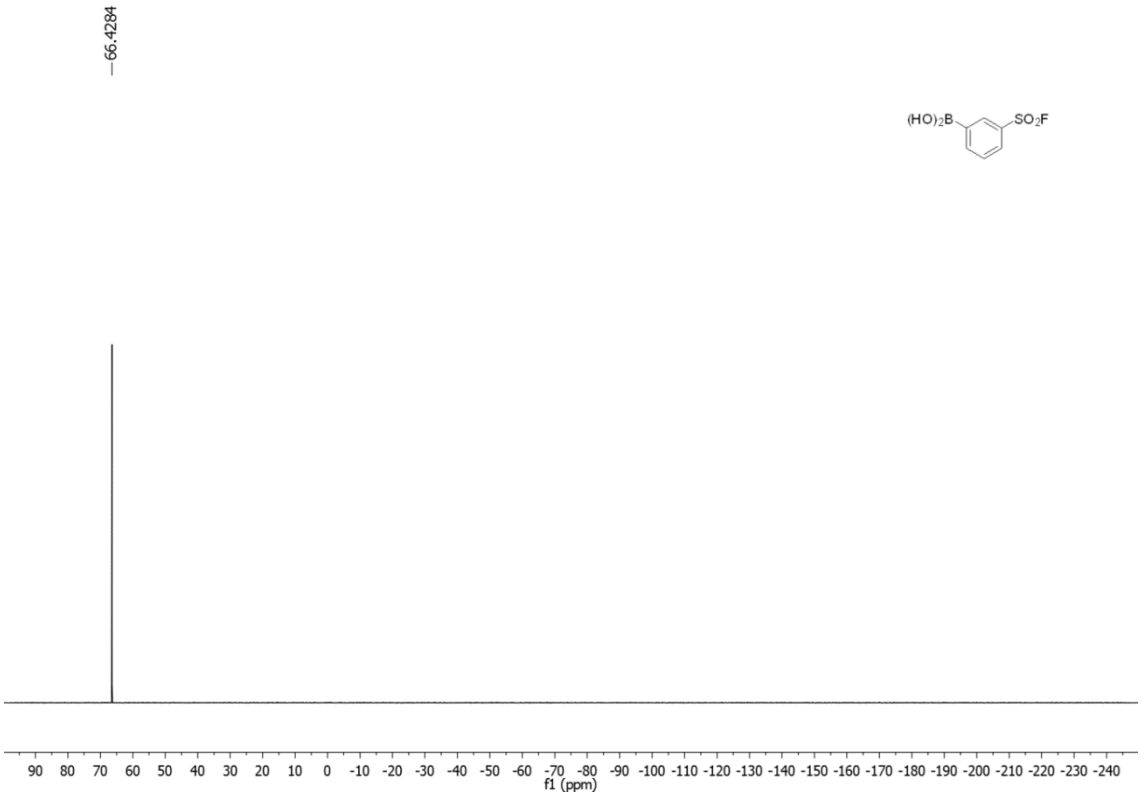
^{11}B-NMR Spectrum:



^{13}C-NMR Spectrum:

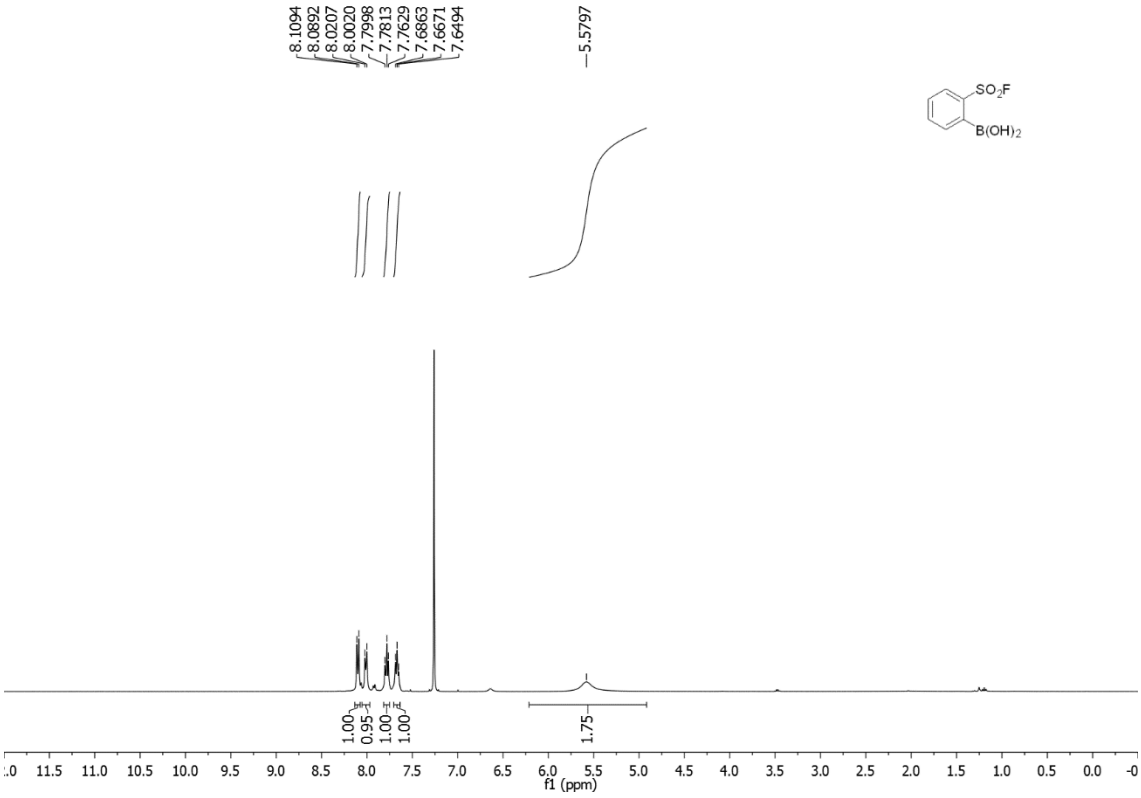


^{19}F-NMR Spectrum:

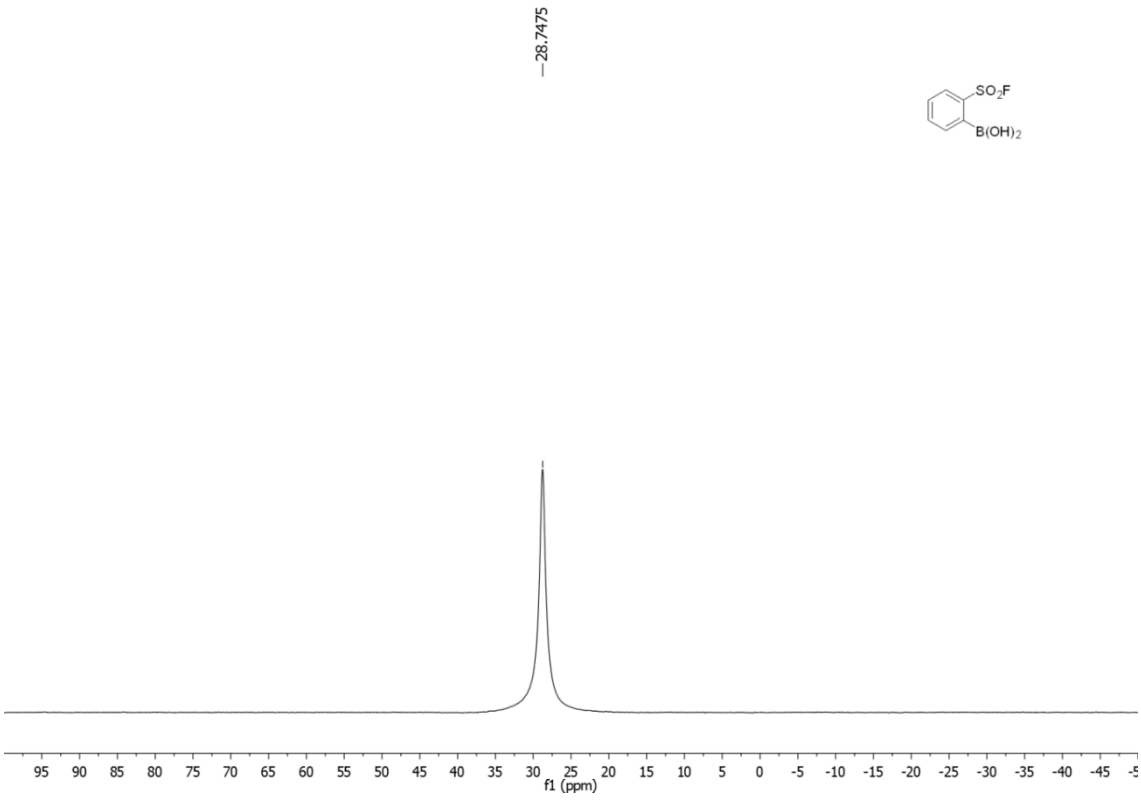


2-(Fluorosulfonyl)phenylboronic acid (17c)

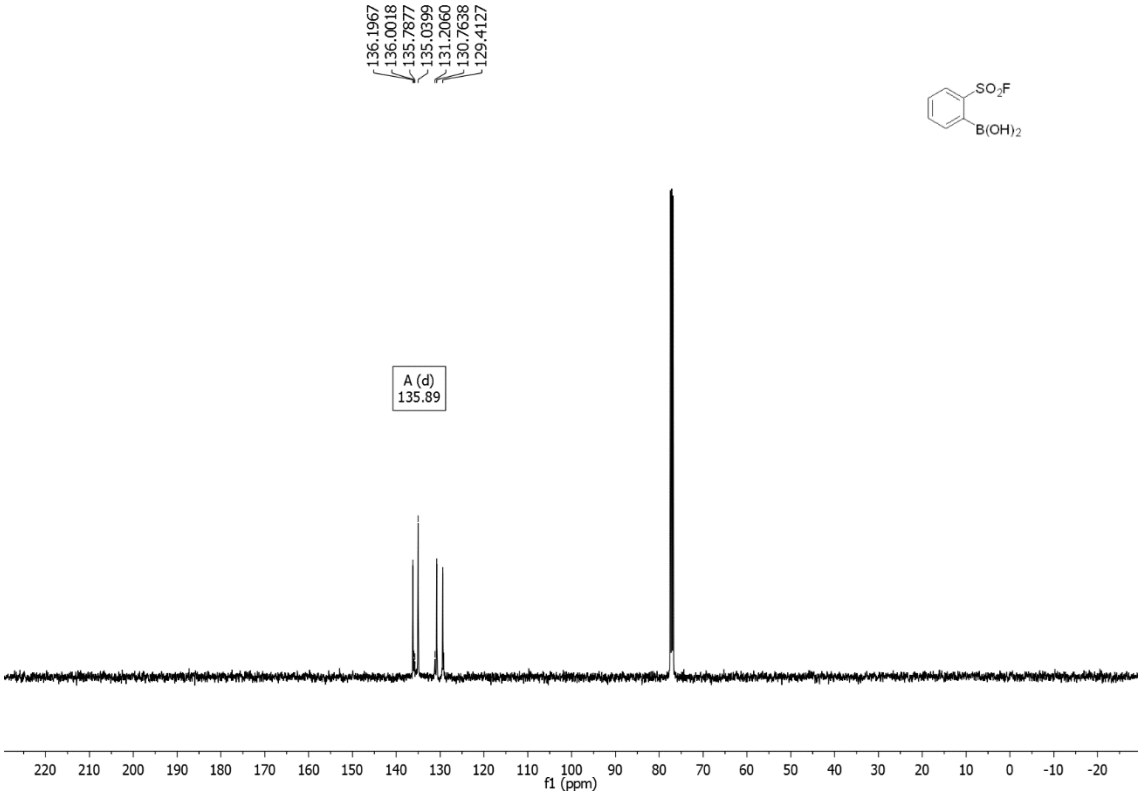
^{1}H-NMR Spectrum:



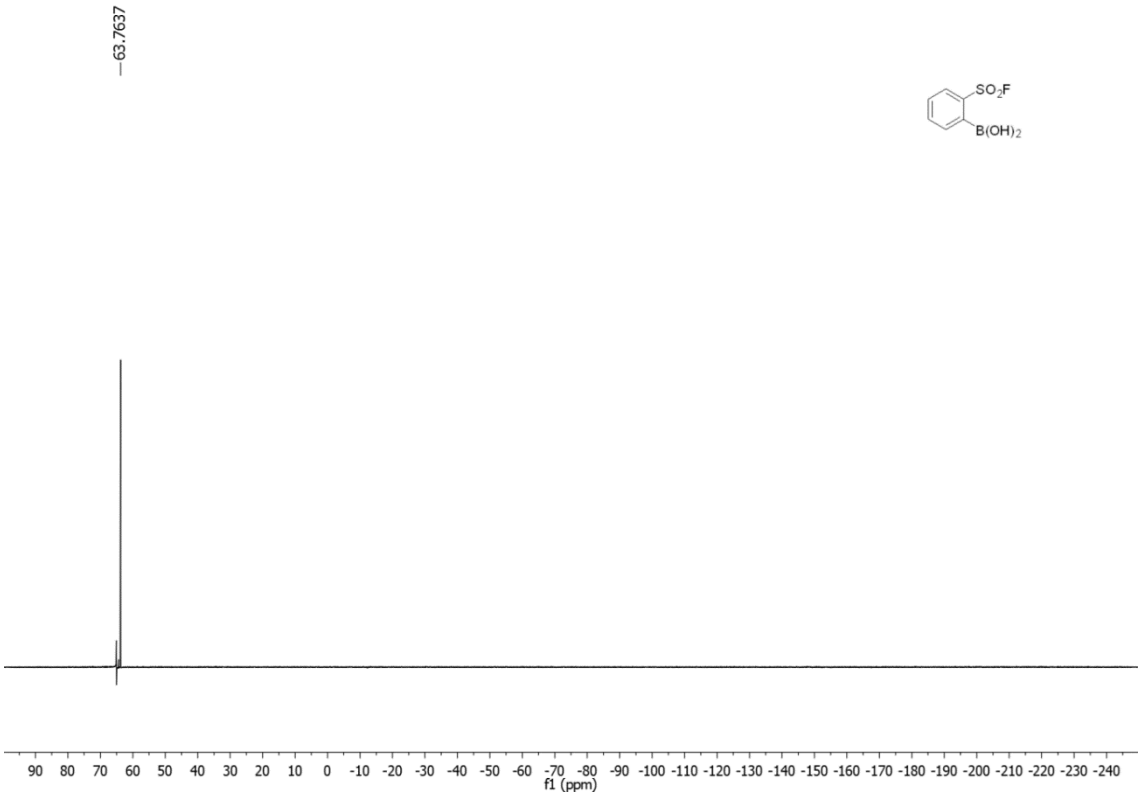
^{11}B-NMR Spectrum:



^{13}C-NMR Spectrum:



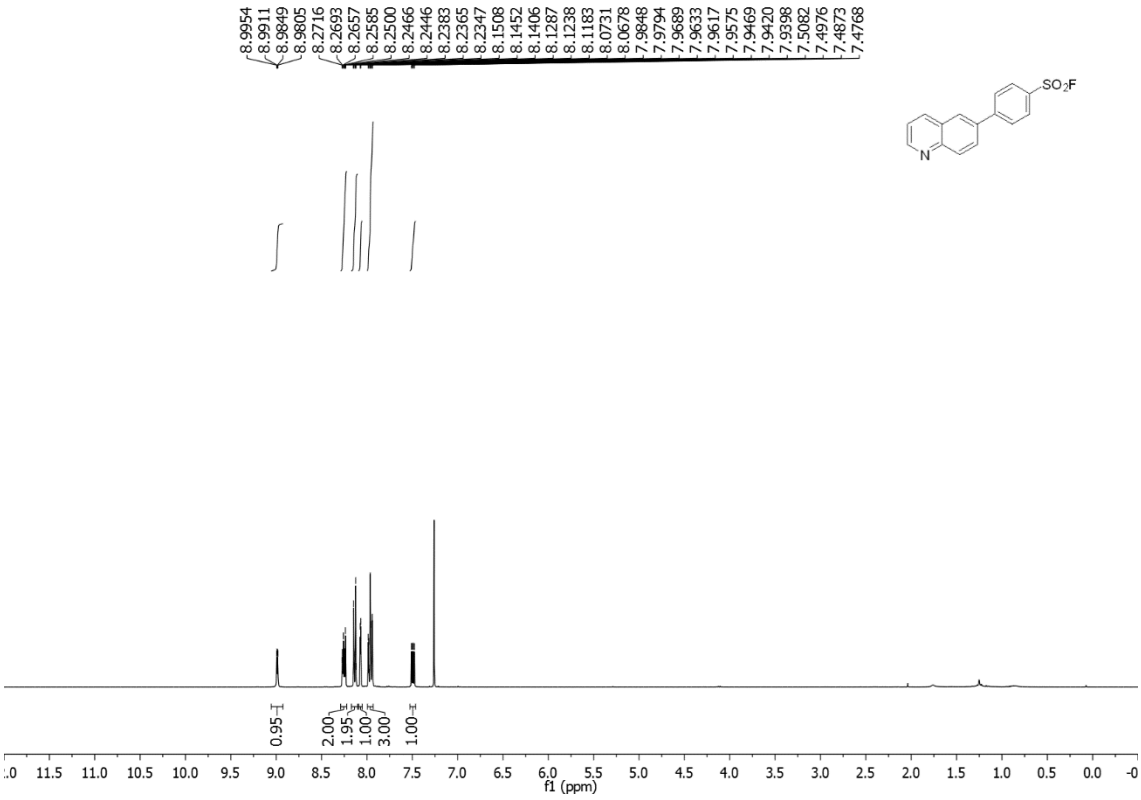
^{19}F-NMR Spectrum:



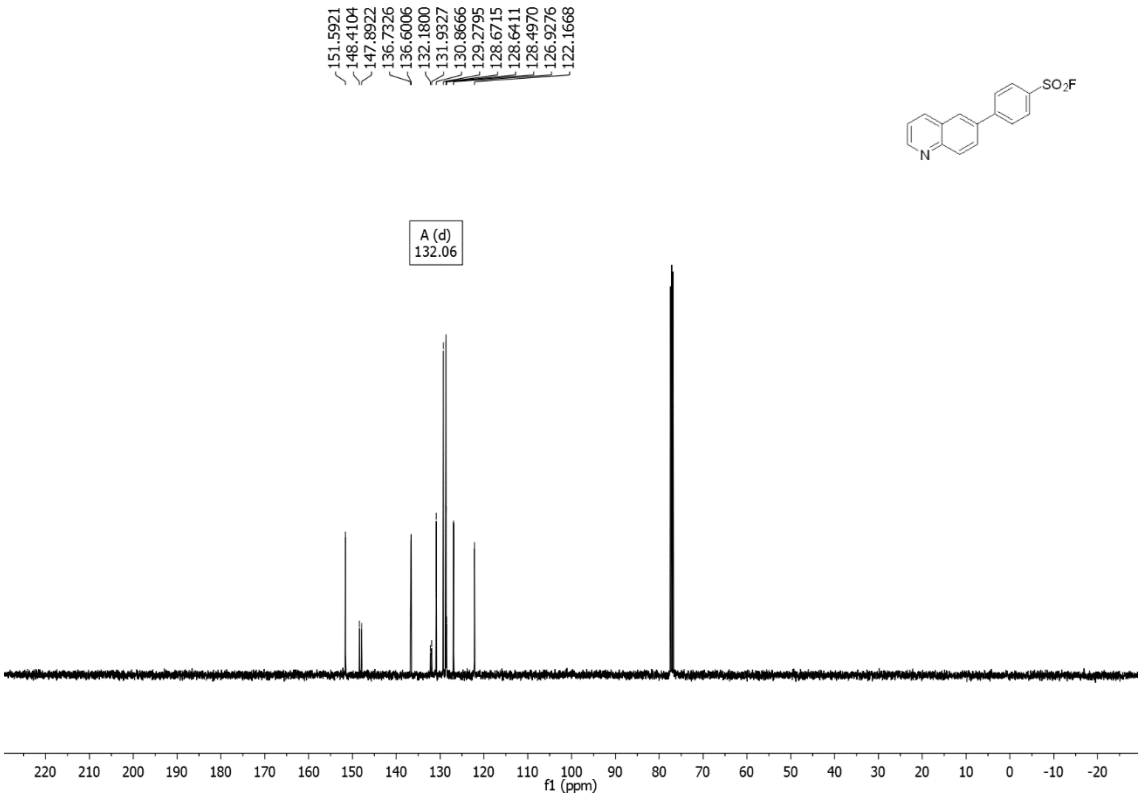
4 NMR Spectra of Suzuki-Miyaura Coupling Reaction Products

4-(Quinolin-6-yl)benzenesulfonyl fluoride (24a)

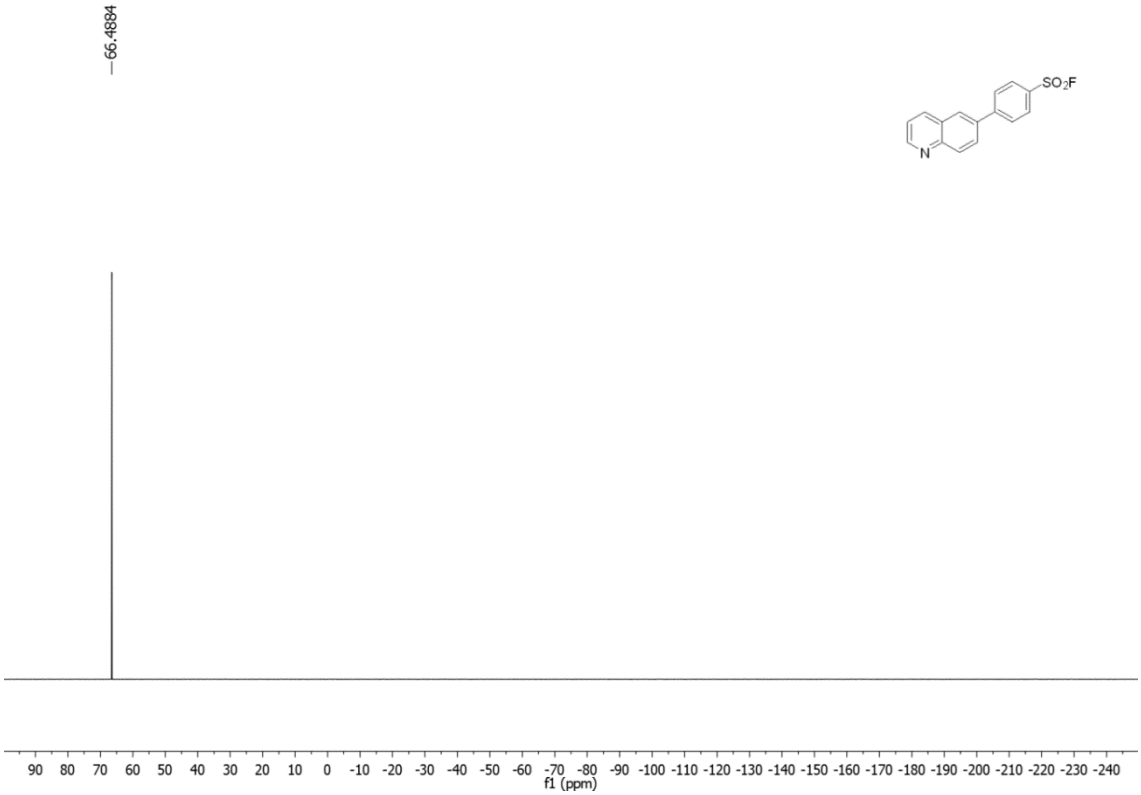
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

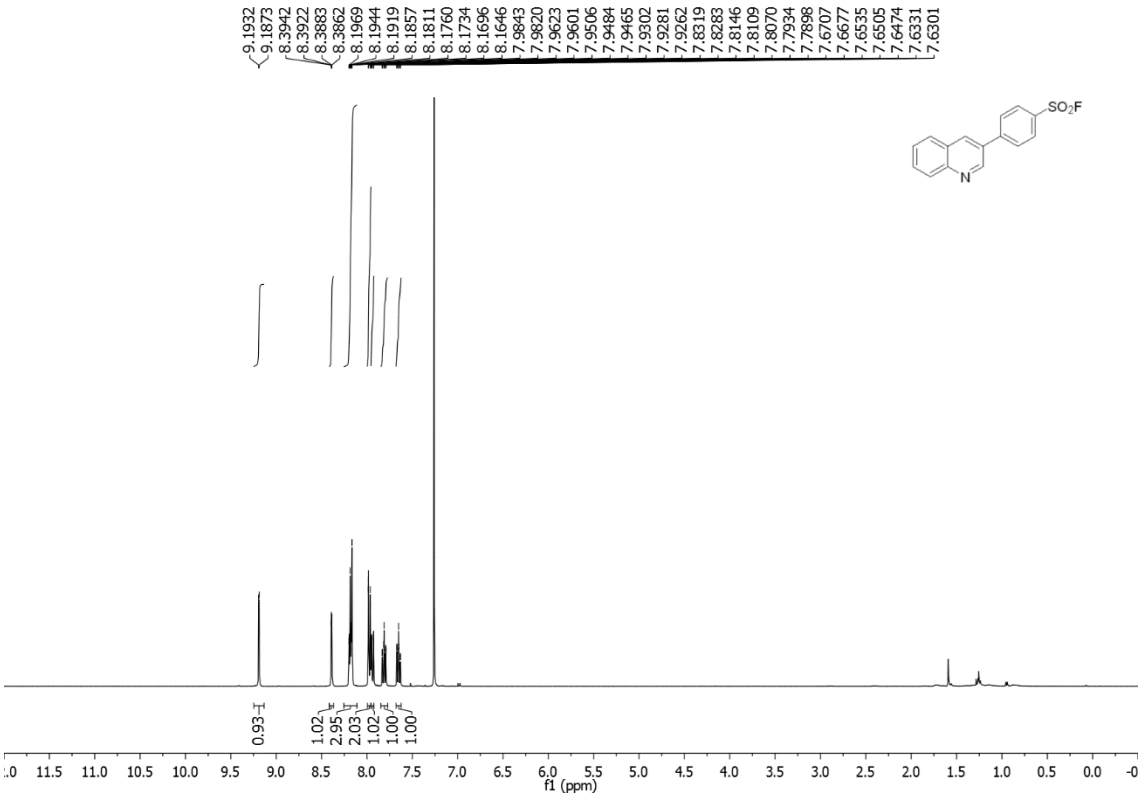


^{19}F-NMR Spectrum:

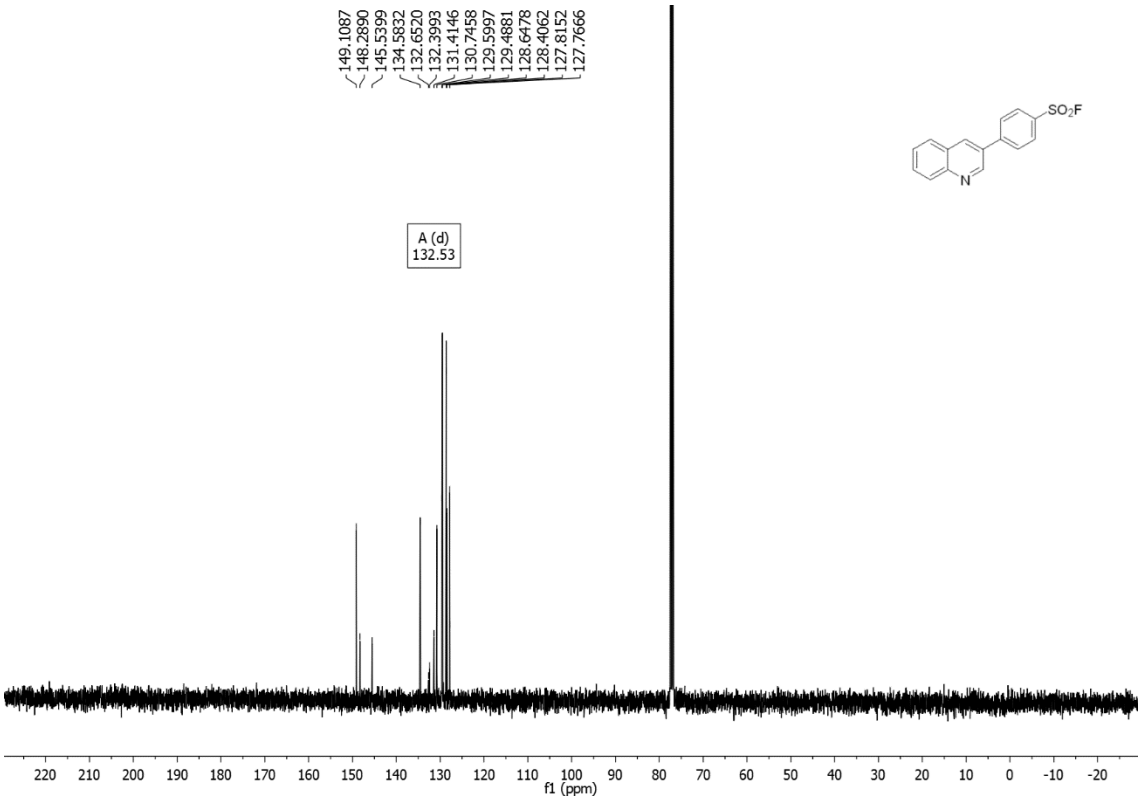


4-(Quinolin-3-yl)benzenesulfonyl fluoride (24b)

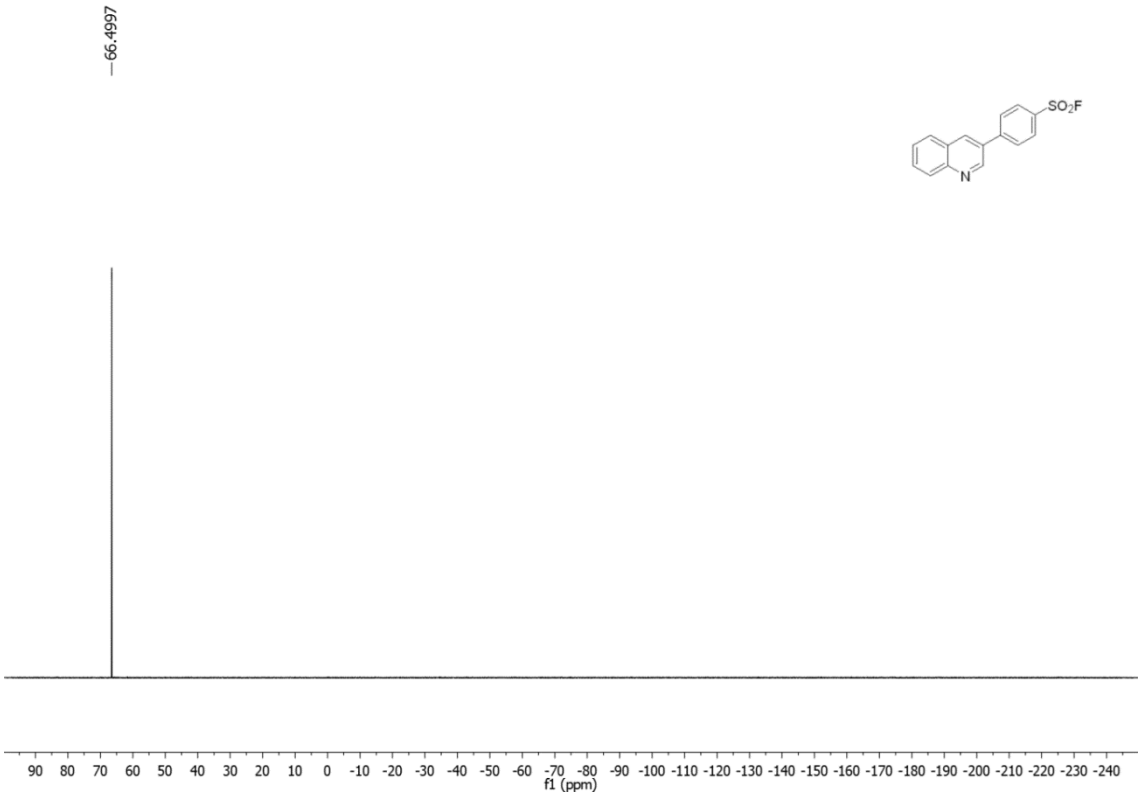
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

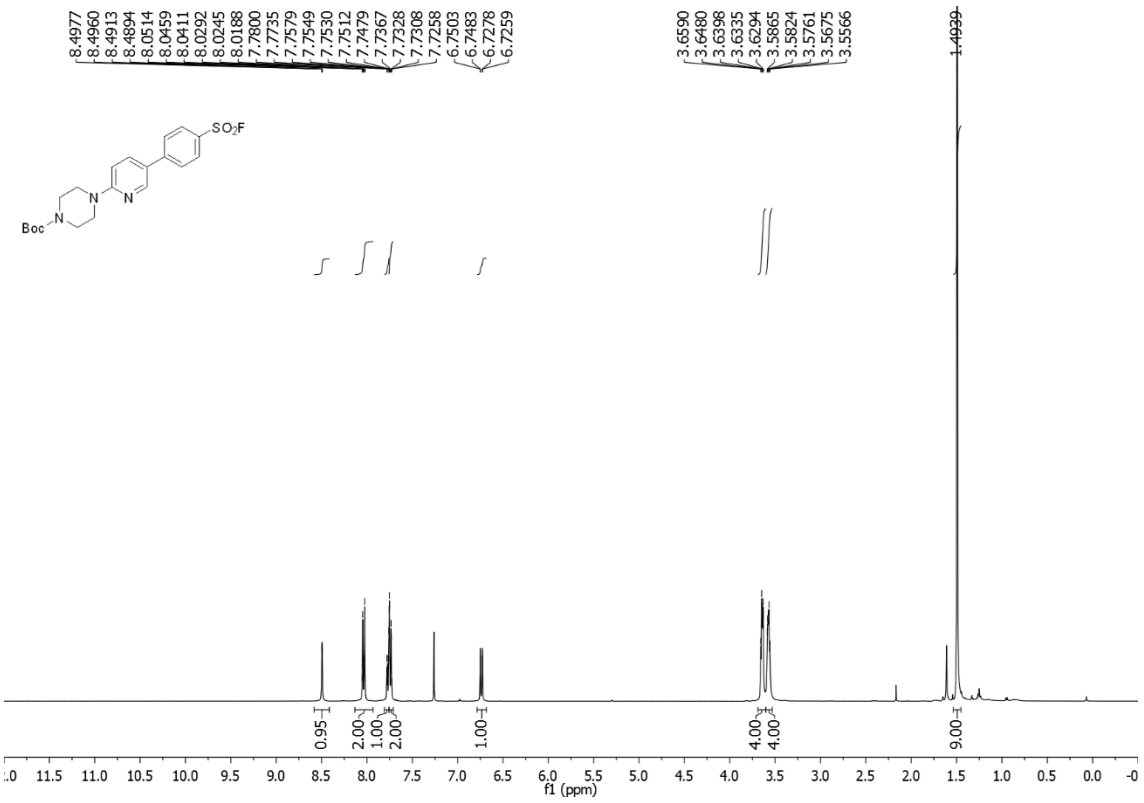


^{19}F-NMR Spectrum:

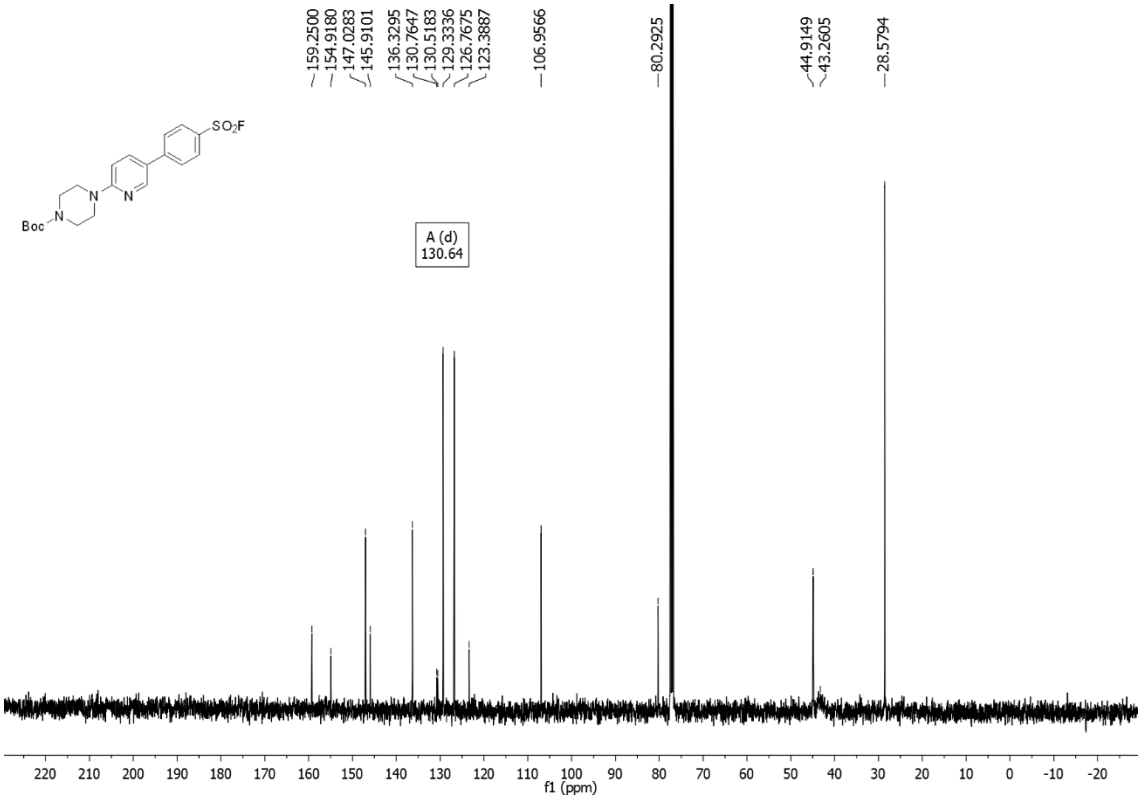


tert-Butyl 4-(5-(4-(fluorosulfonyl)phenyl)pyridin-2-yl)piperazine-1-carboxylate (24c)

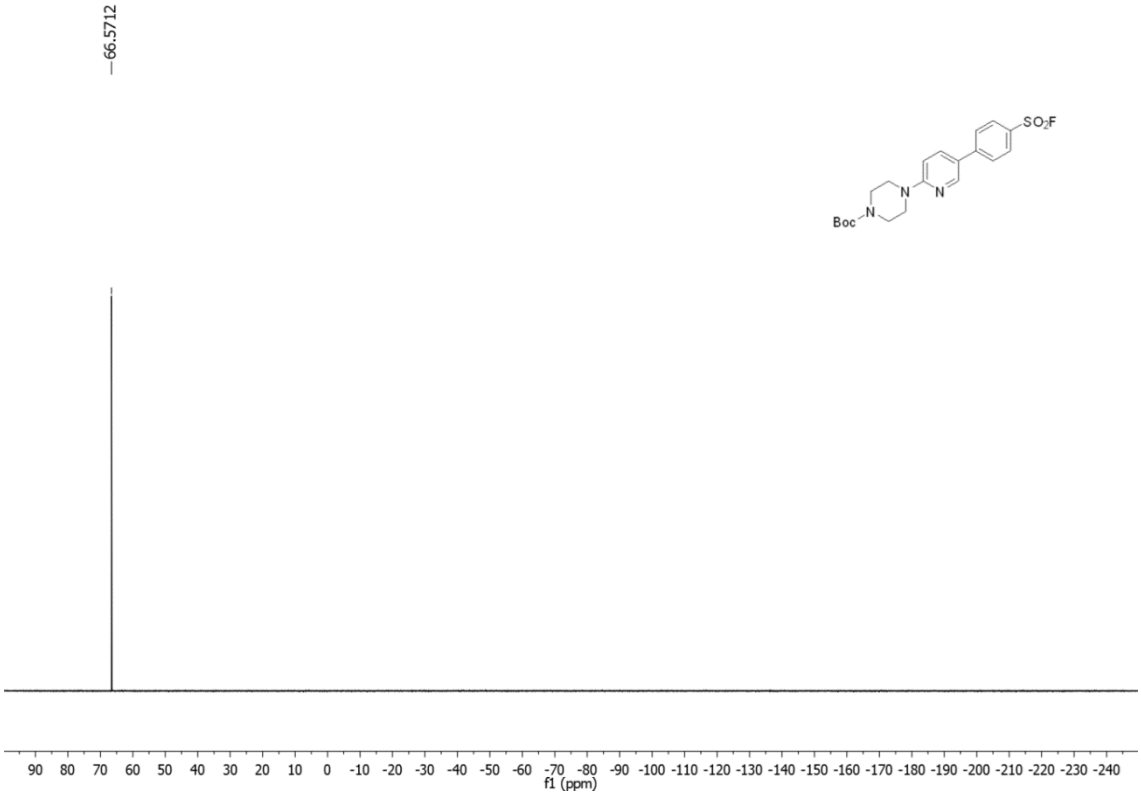
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

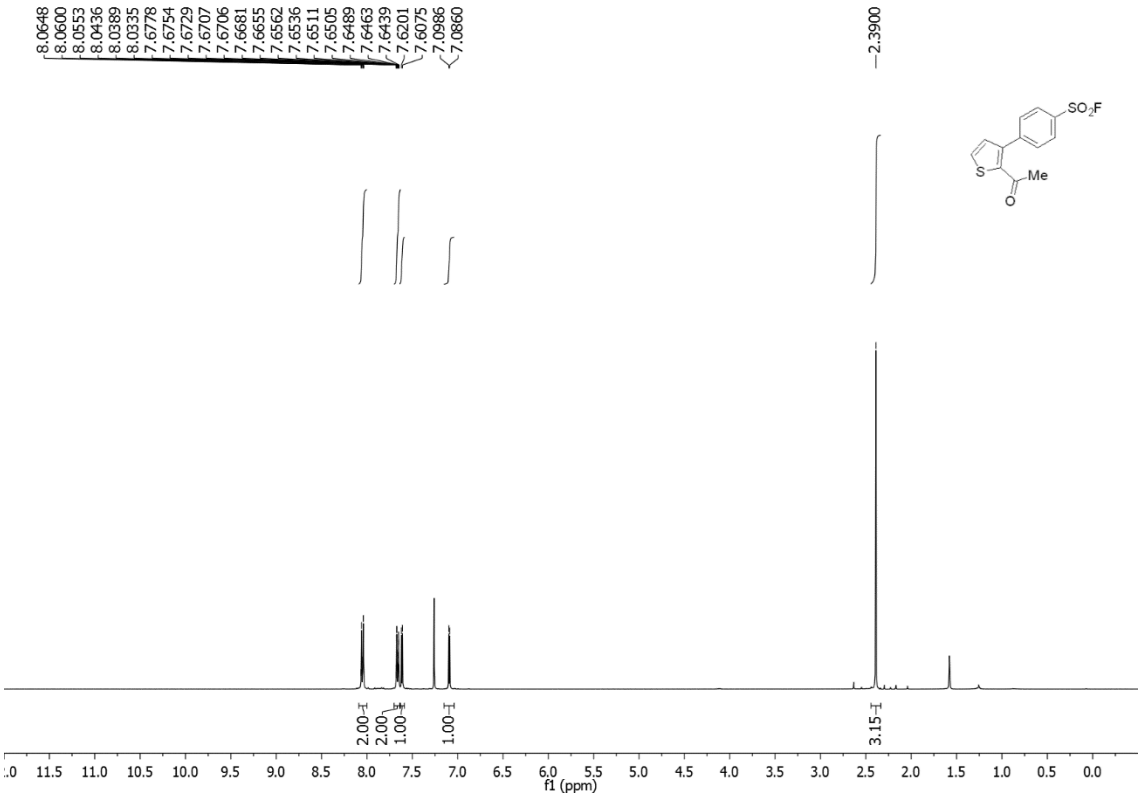


^{19}F-NMR Spectrum:

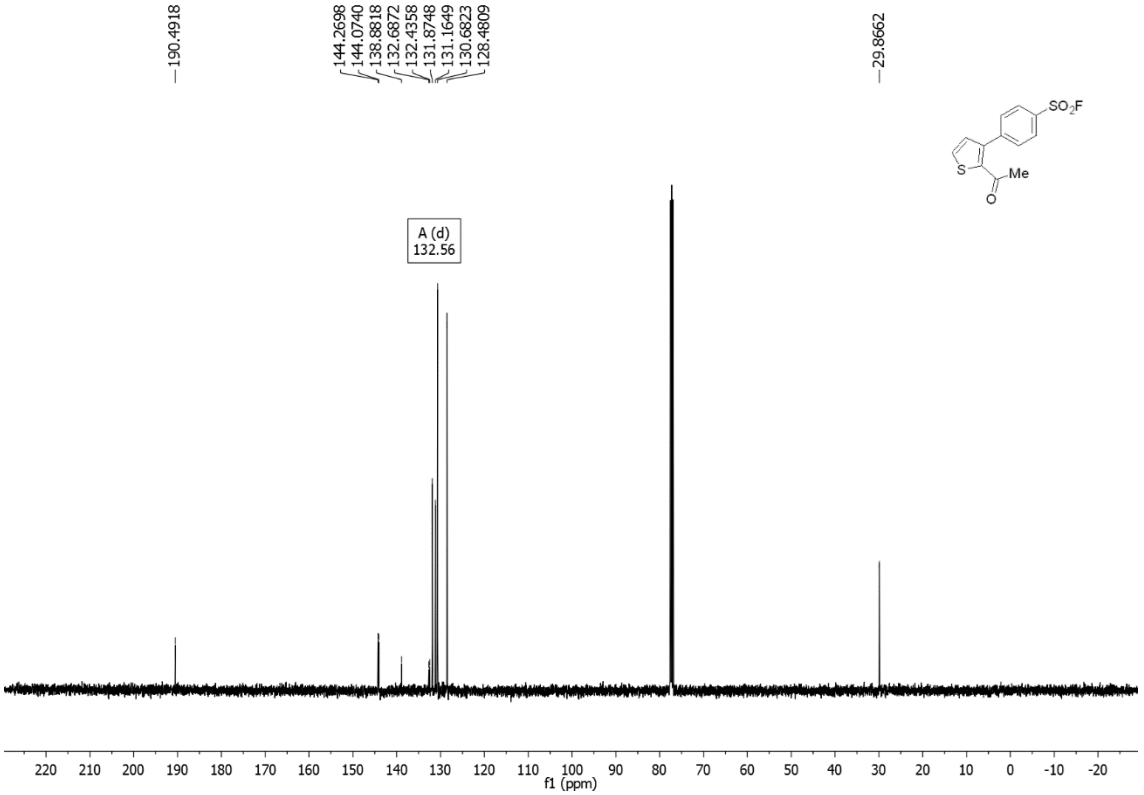


4-(2-Acetylthiophen-3-yl)benzenesulfonyl fluoride (24d)

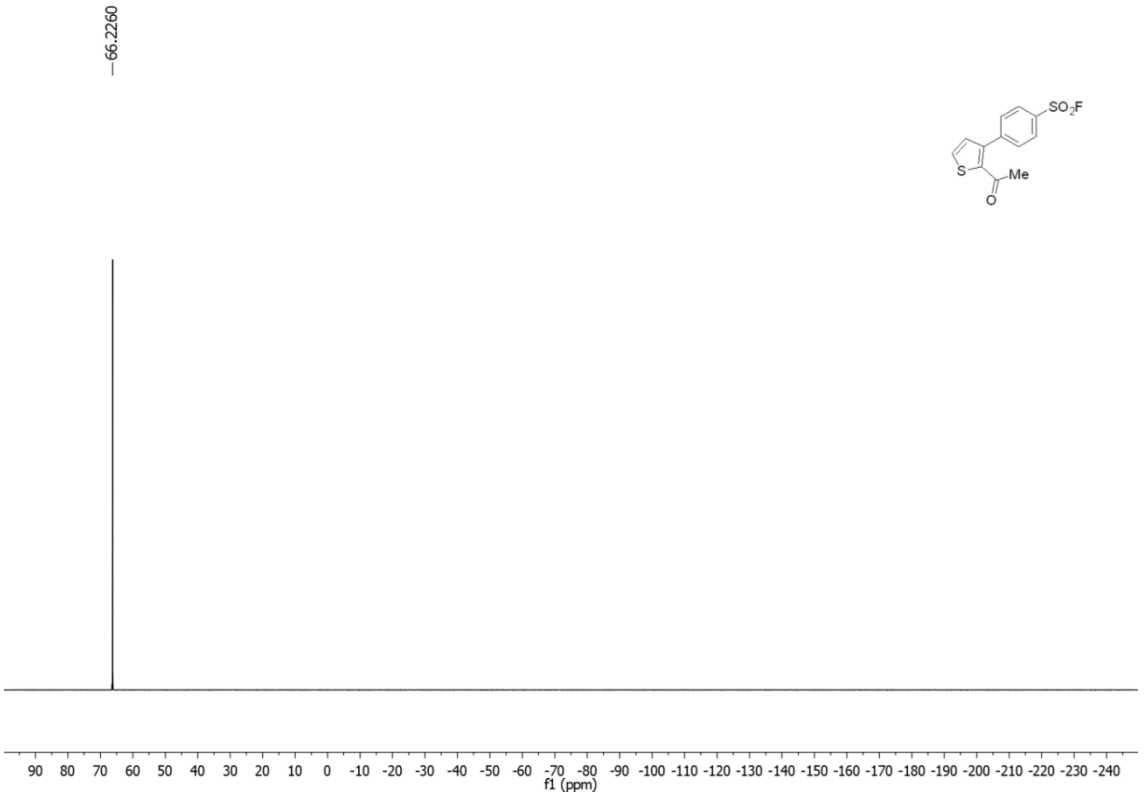
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

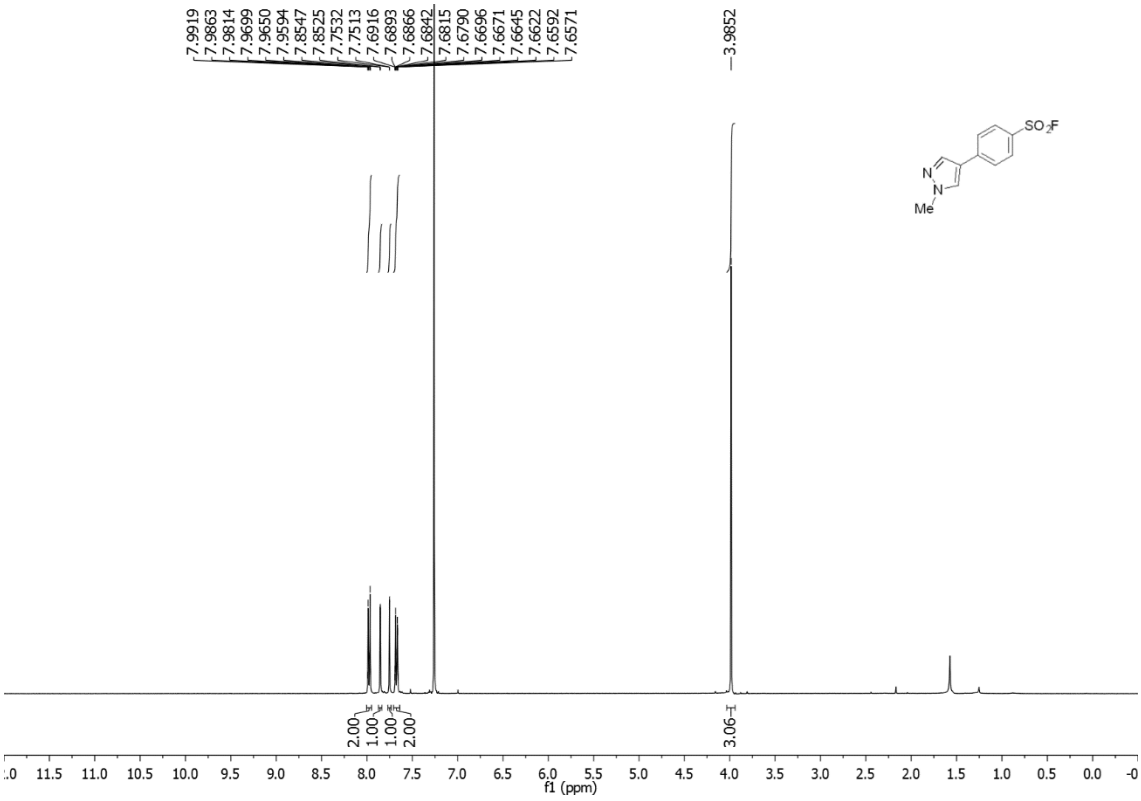


^{19}F-NMR Spectrum:

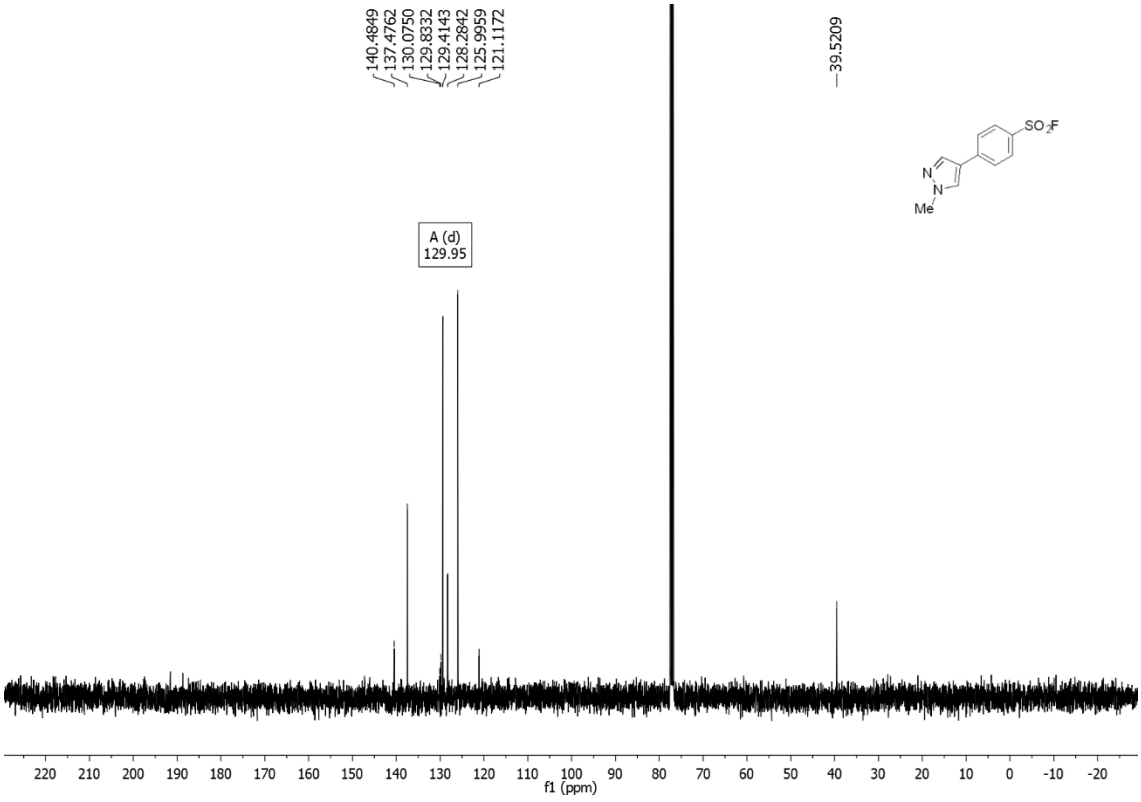


4-(1-Methyl-1*H*-pyrazol-4-yl)benzenesulfonyl fluoride (24e)

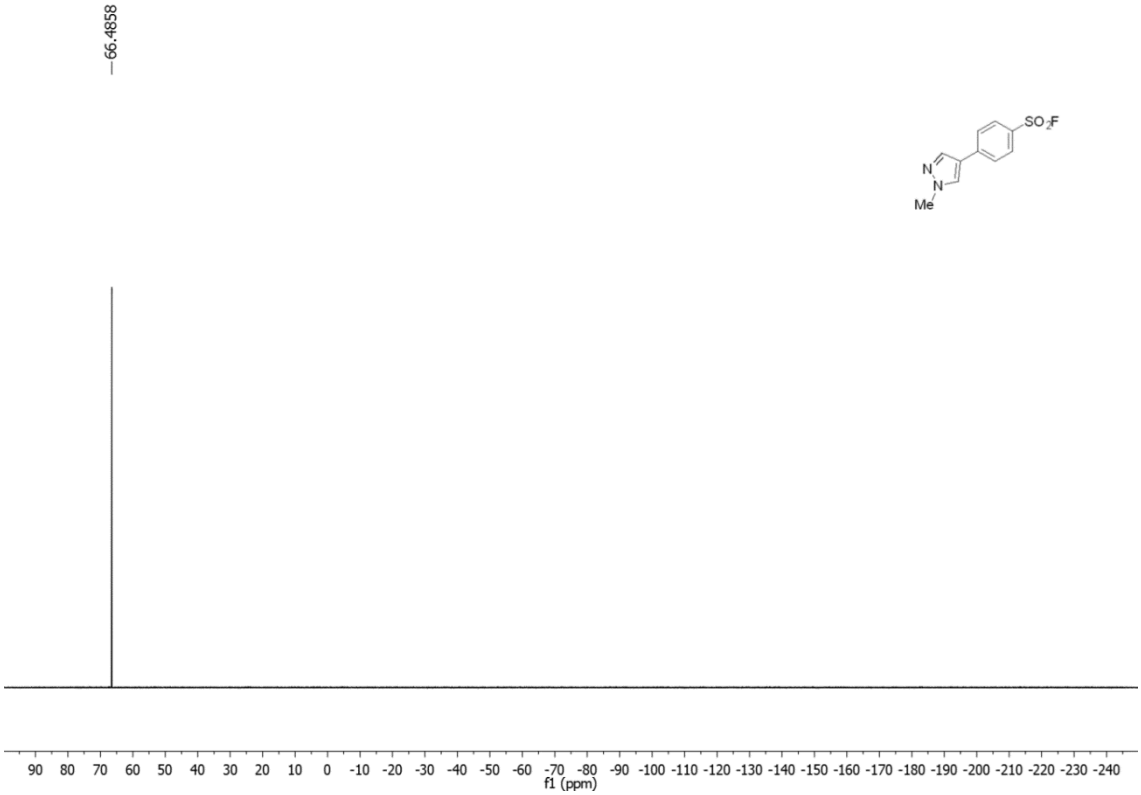
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

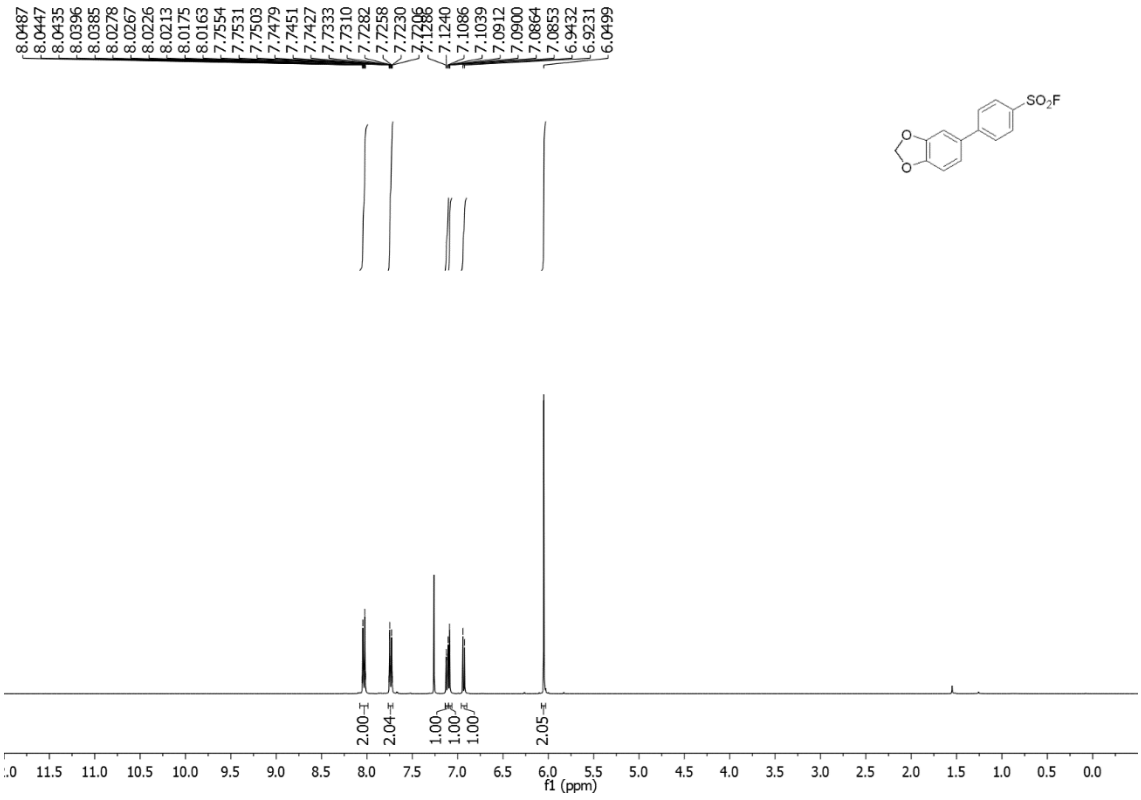


^{19}F-NMR Spectrum:

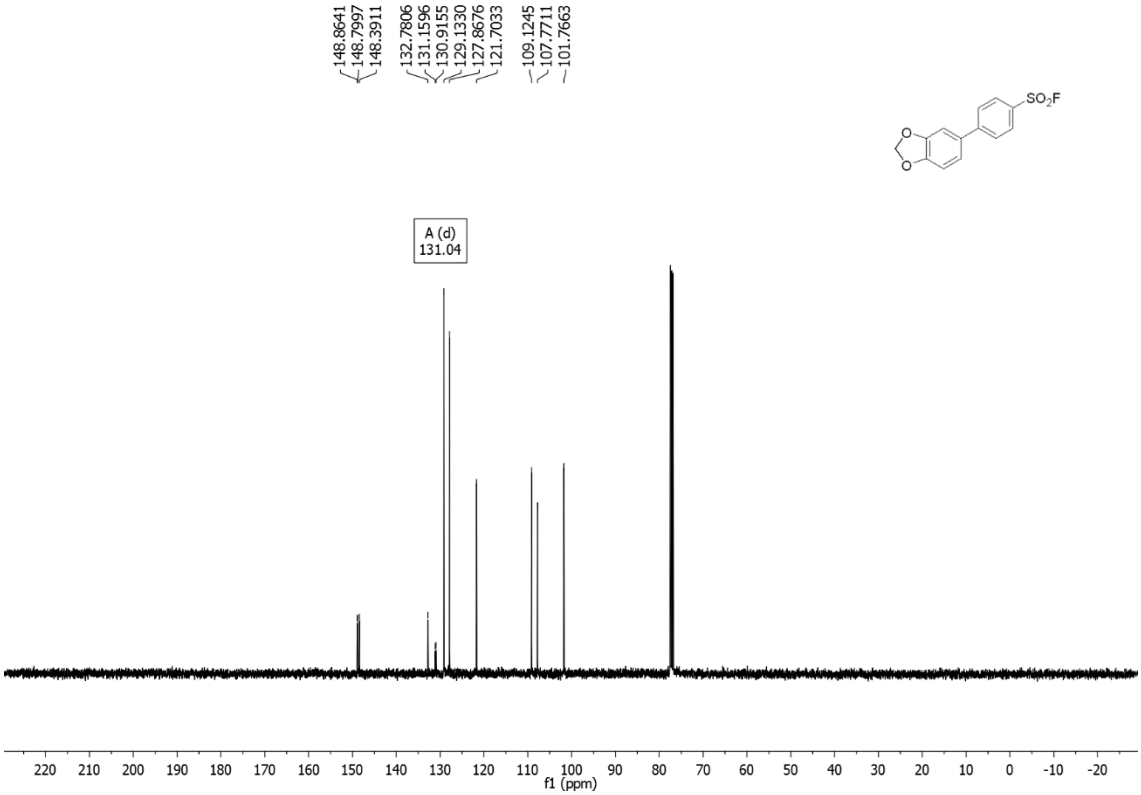


4-(Benzo[*d*][1,3]dioxol-5-yl)benzenesulfonyl fluoride (24f)

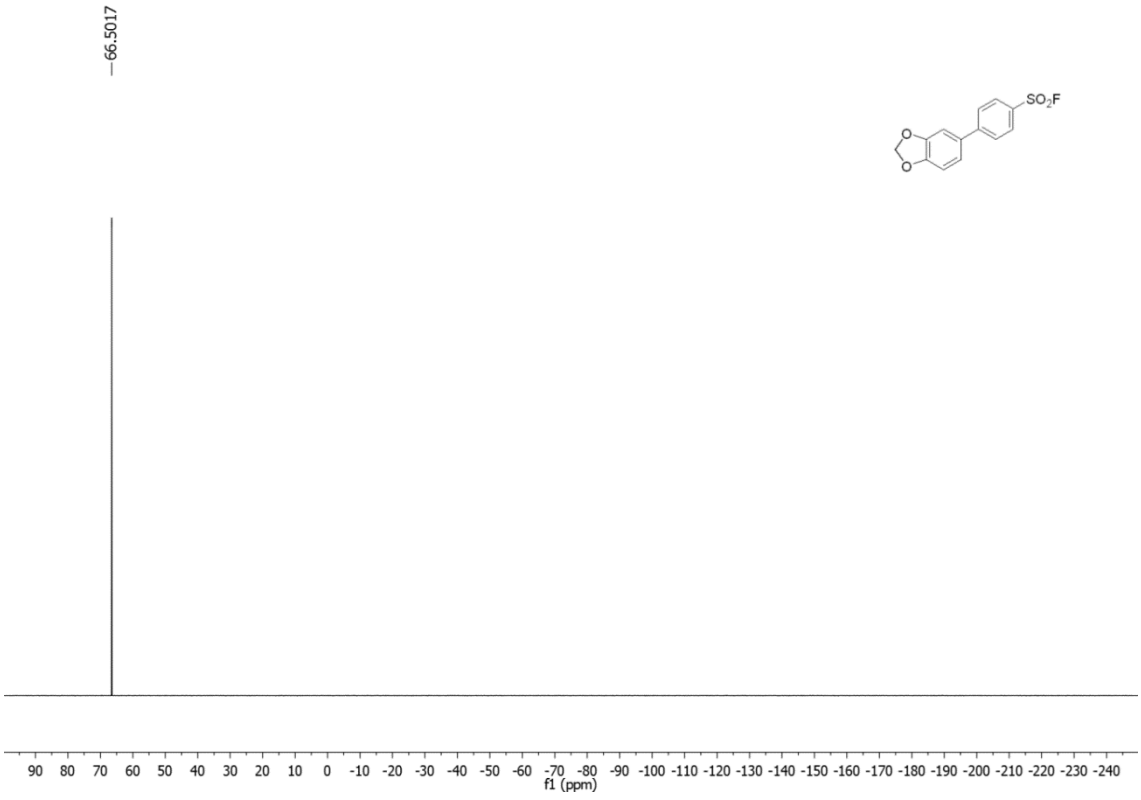
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

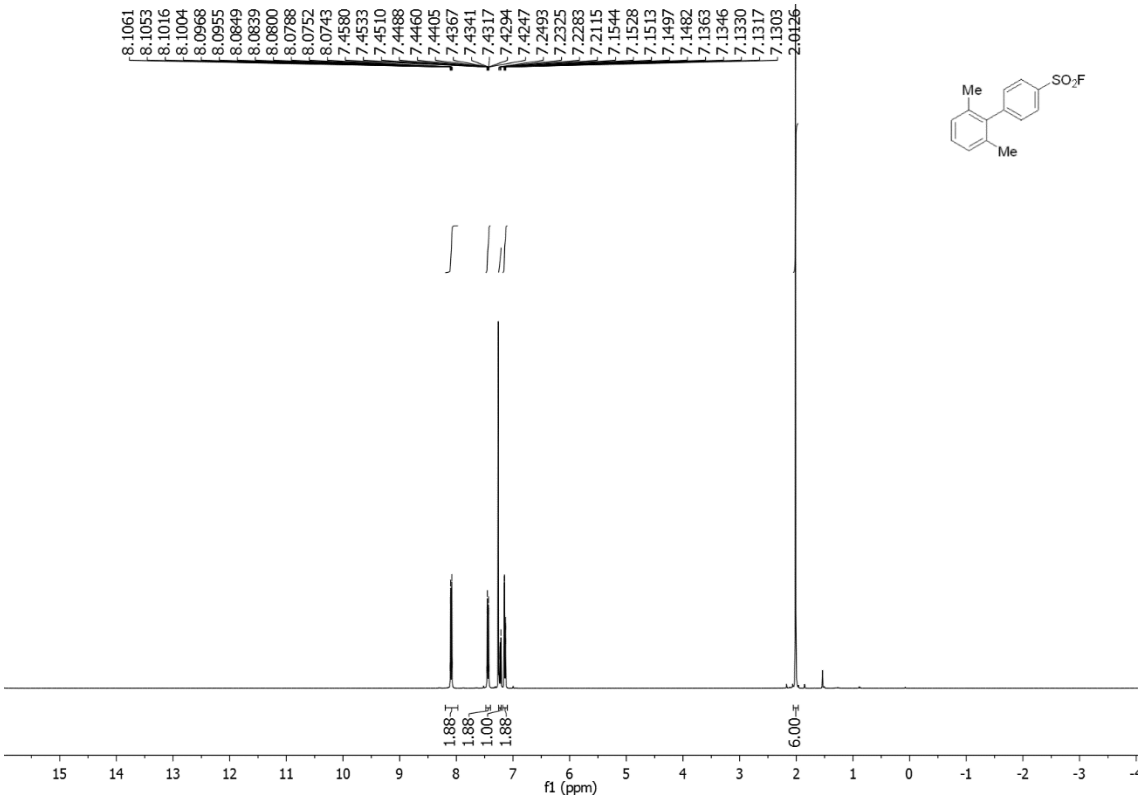


^{19}F-NMR Spectrum:

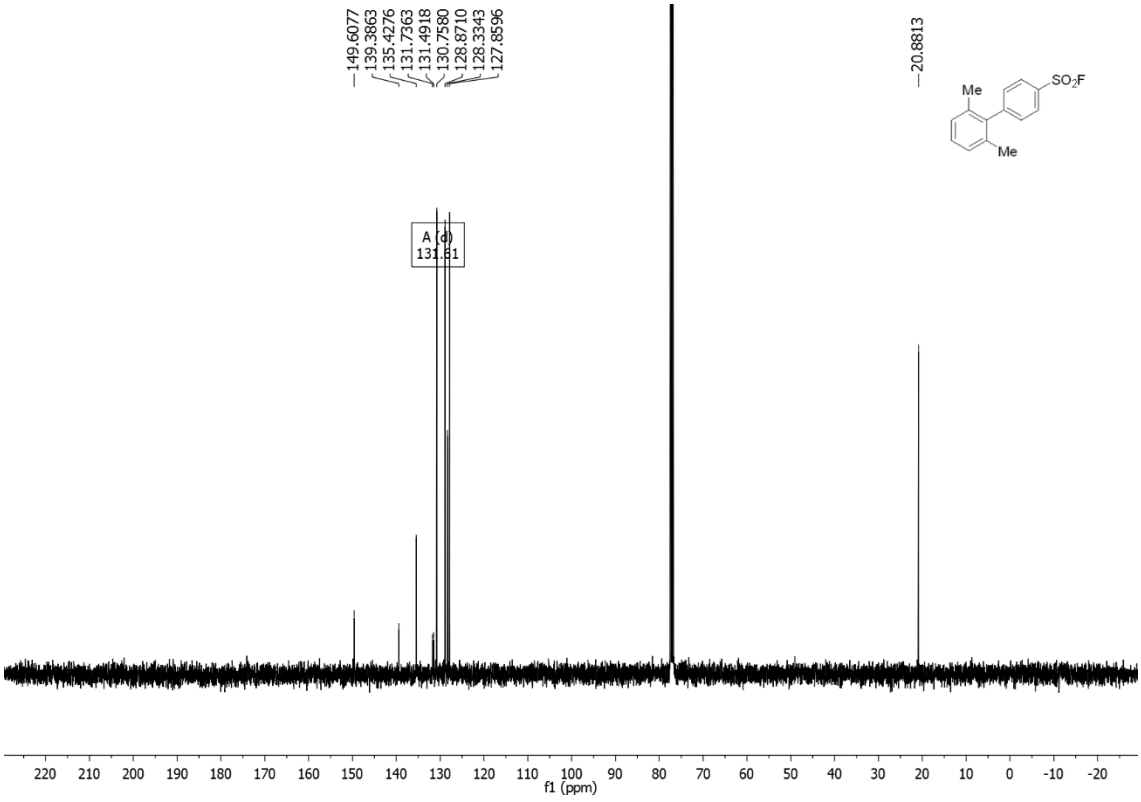


2',6'-Dimethyl-[1,1'-biphenyl]-4-sulfonyl fluoride (24g)

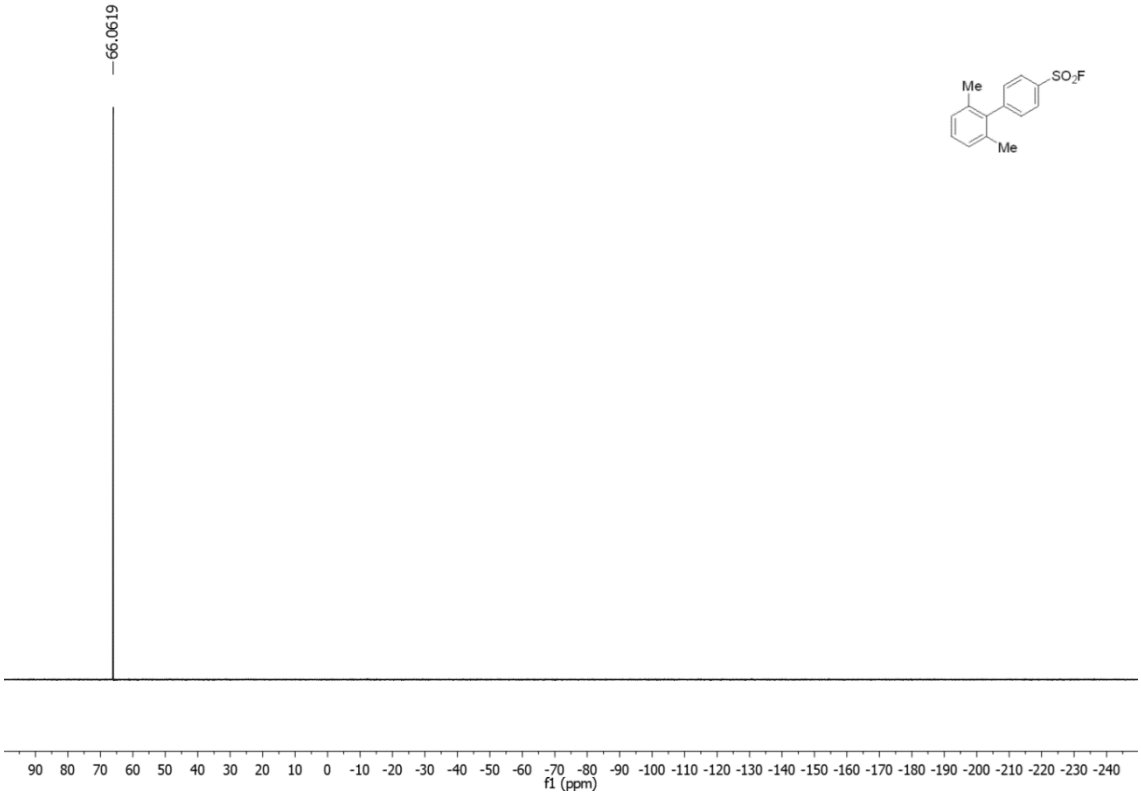
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

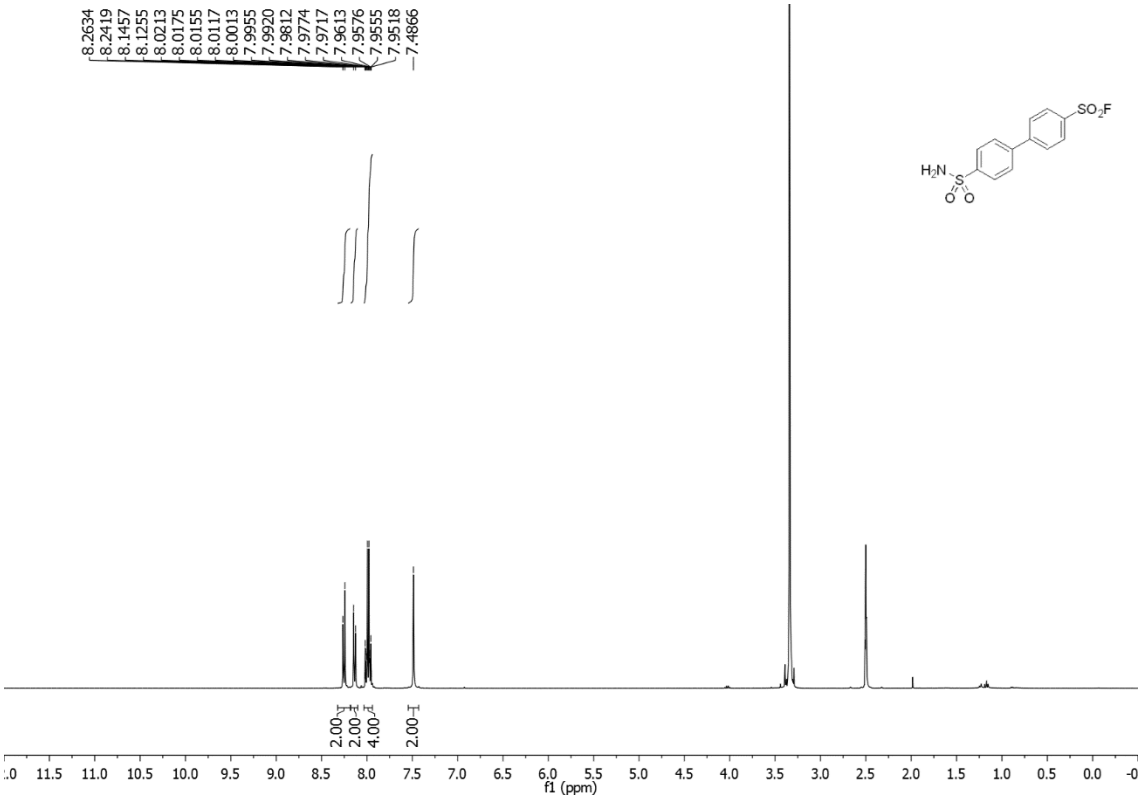


^{19}F-NMR Spectrum:

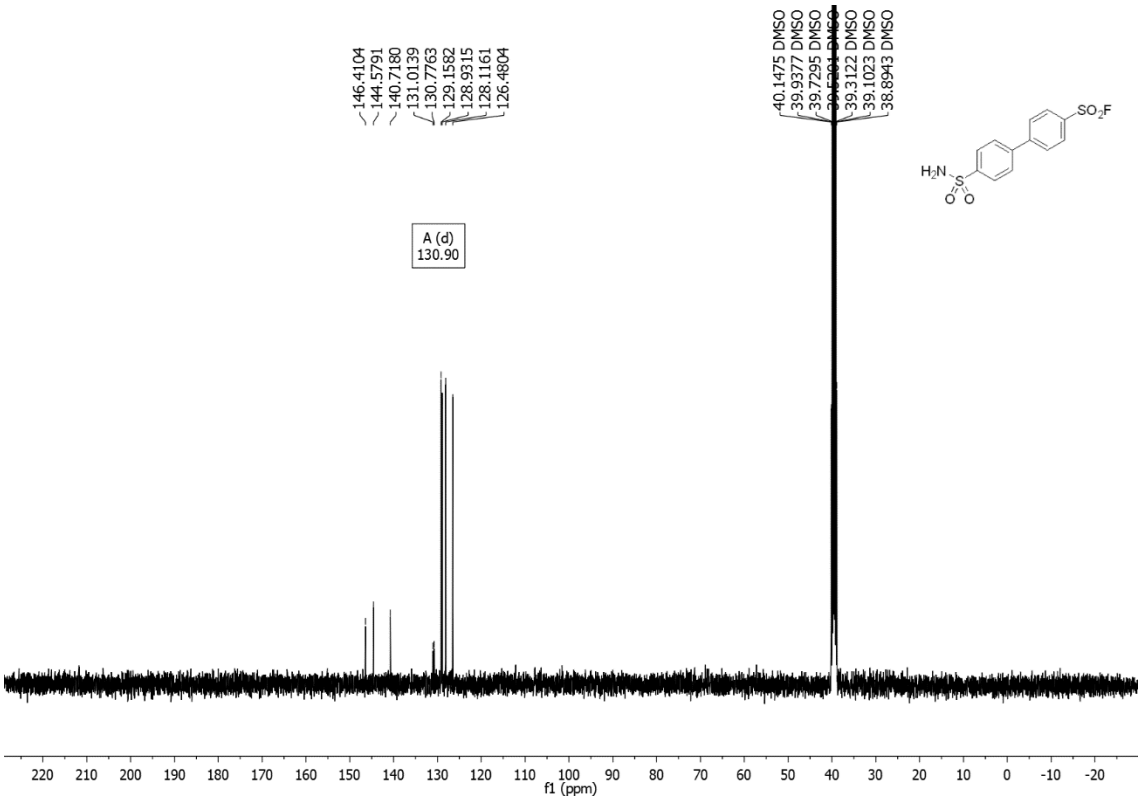


4'-Sulfamoyl-[1,1'-biphenyl]-4-sulfonyl fluoride (24h)

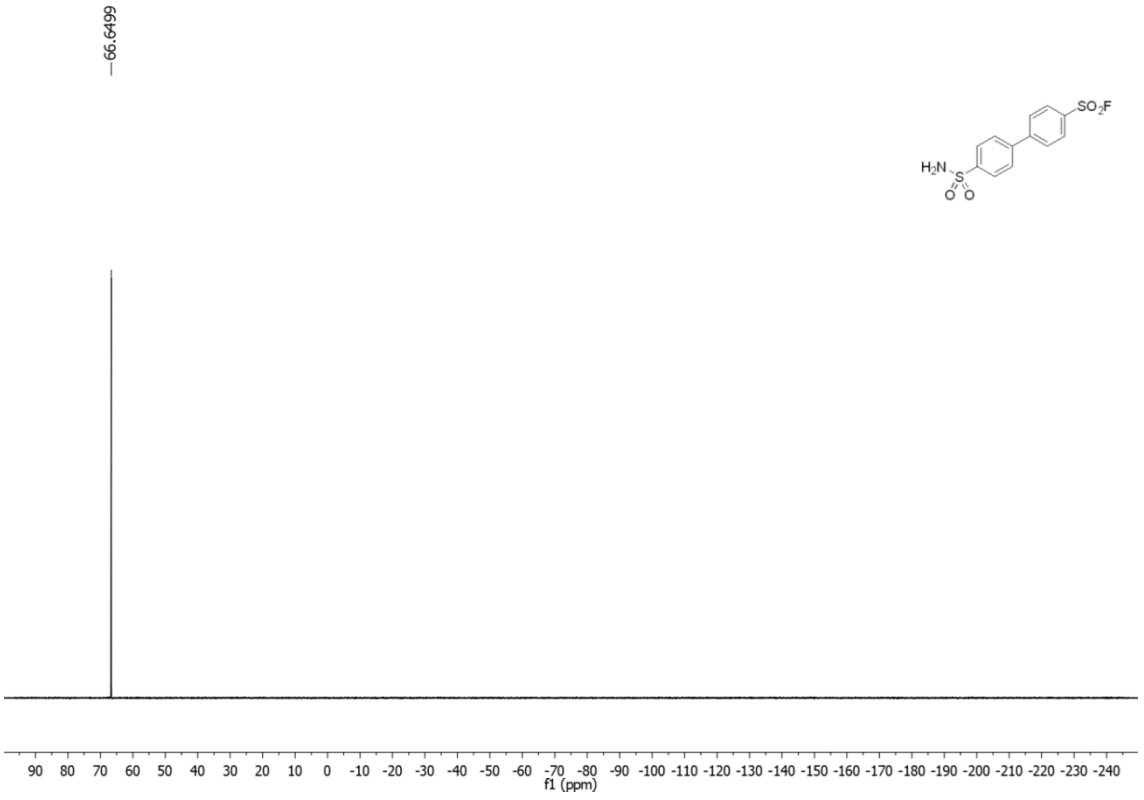
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

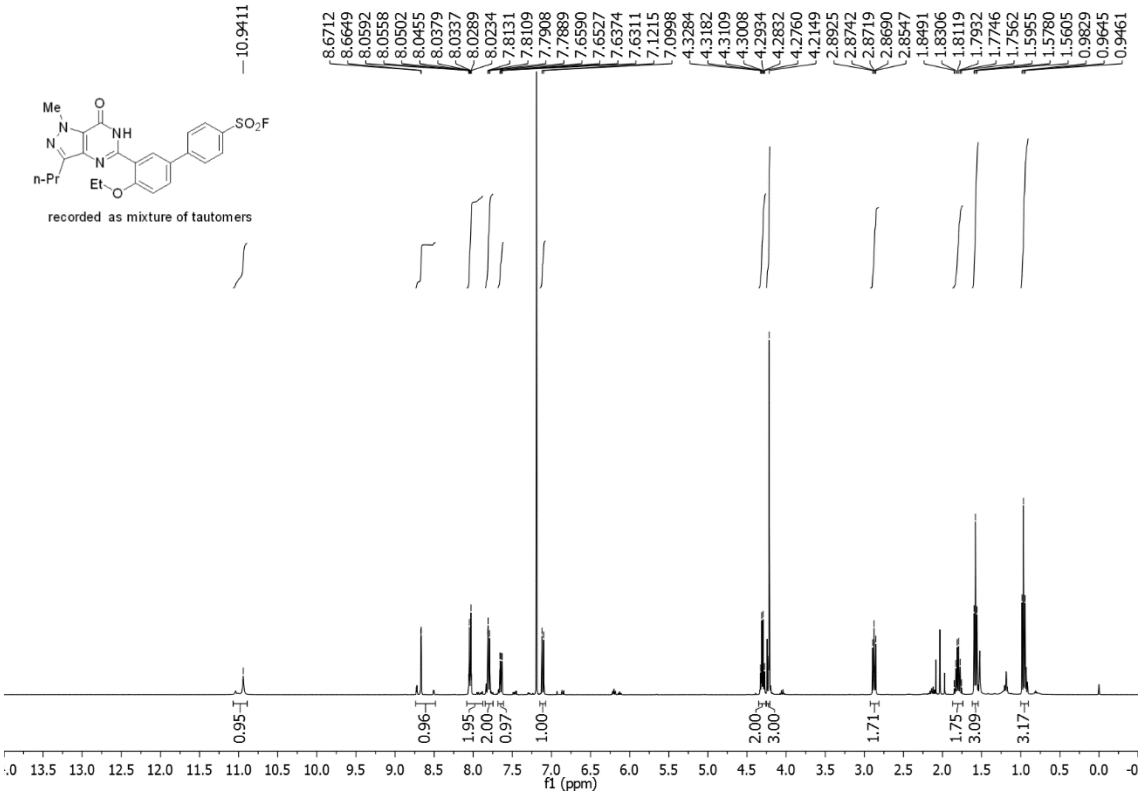


^{19}F-NMR Spectrum:

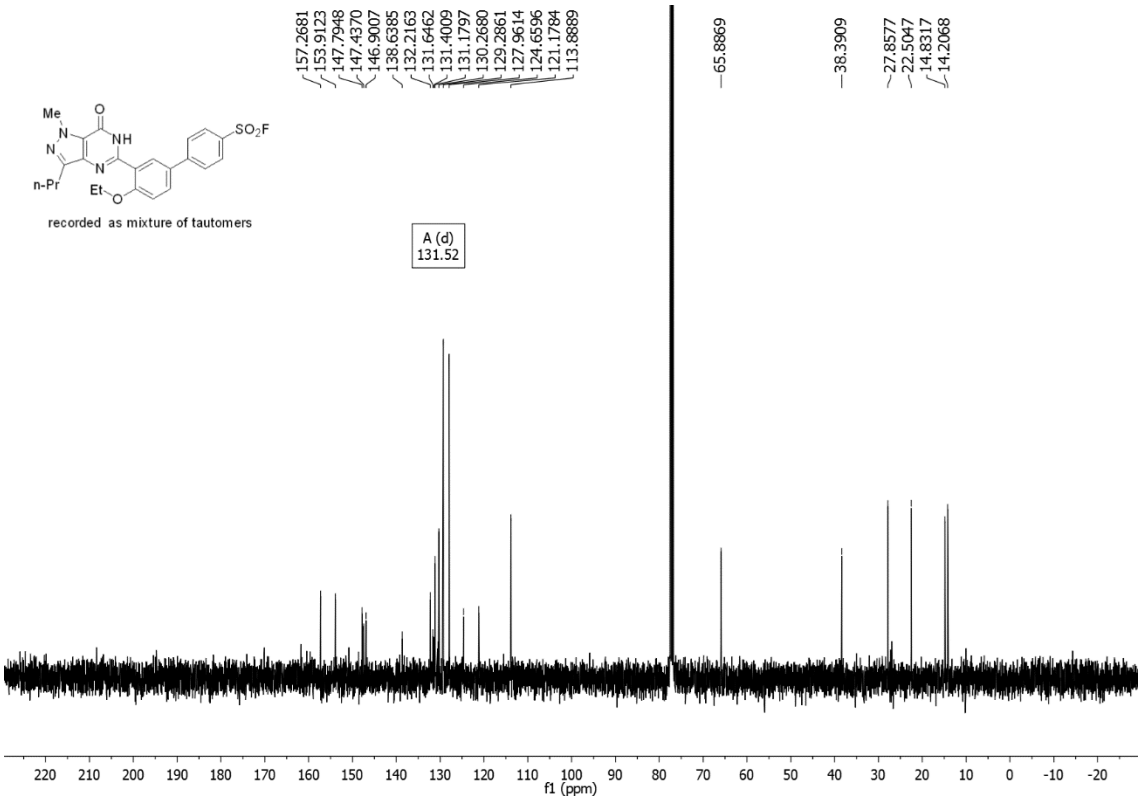


4'-Ethoxy-3'-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-[1,1'-biphenyl]-4-sulfonyl fluoride (24i)

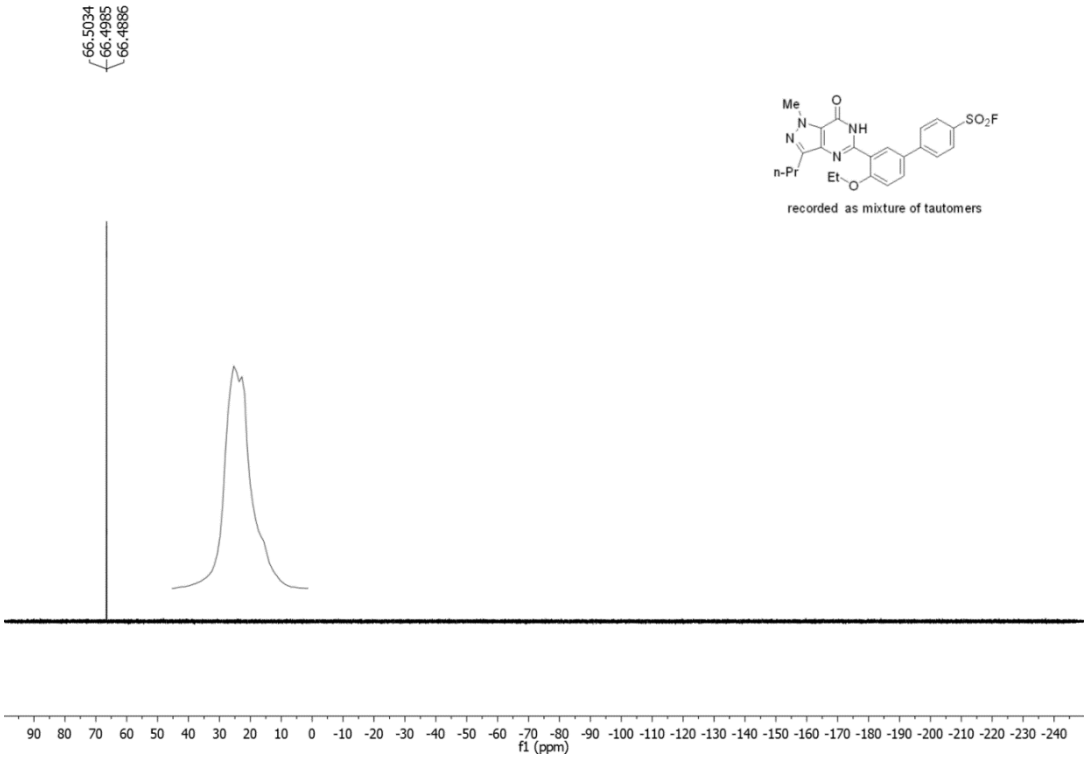
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

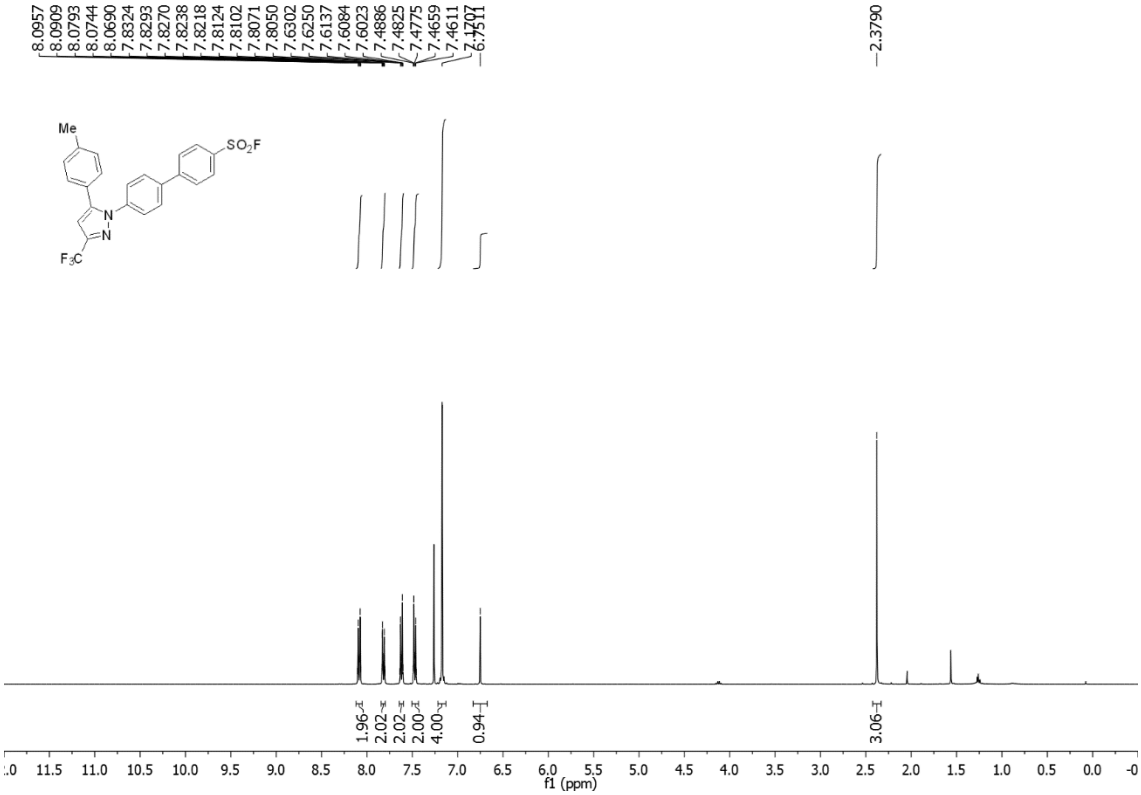


^{19}F-NMR Spectrum:

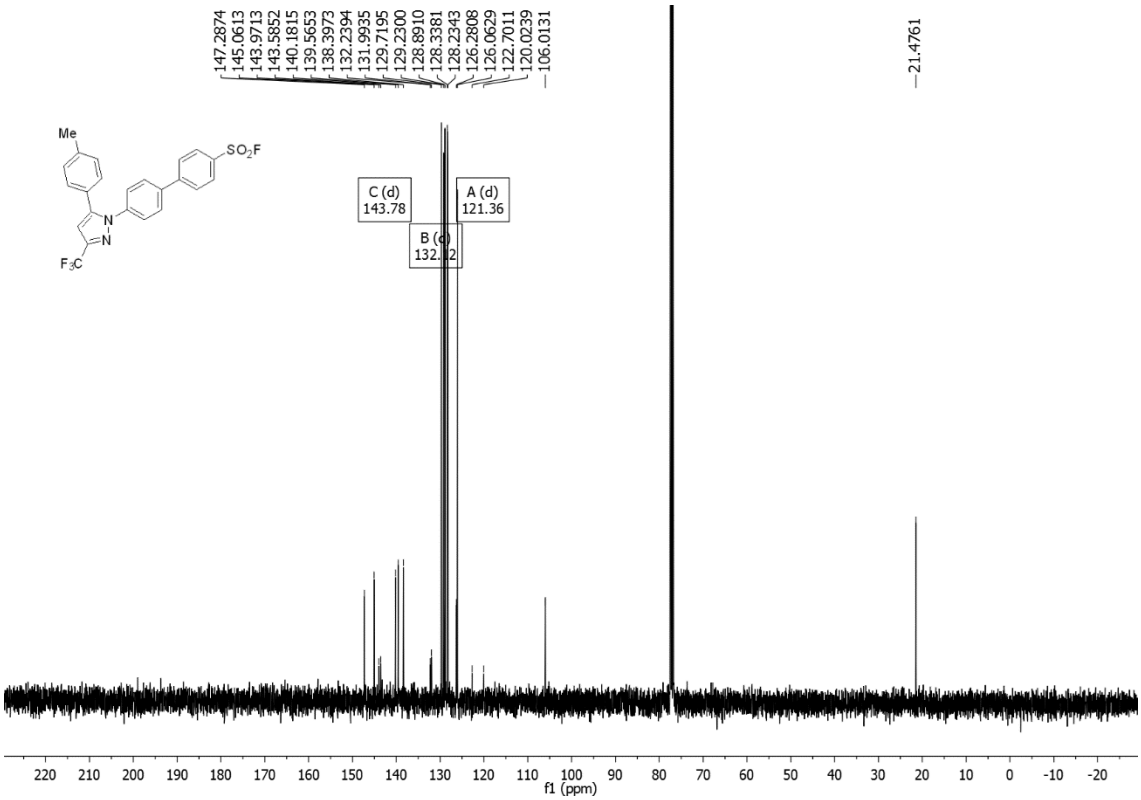


4'-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-4-sulfonyl fluoride (24j)

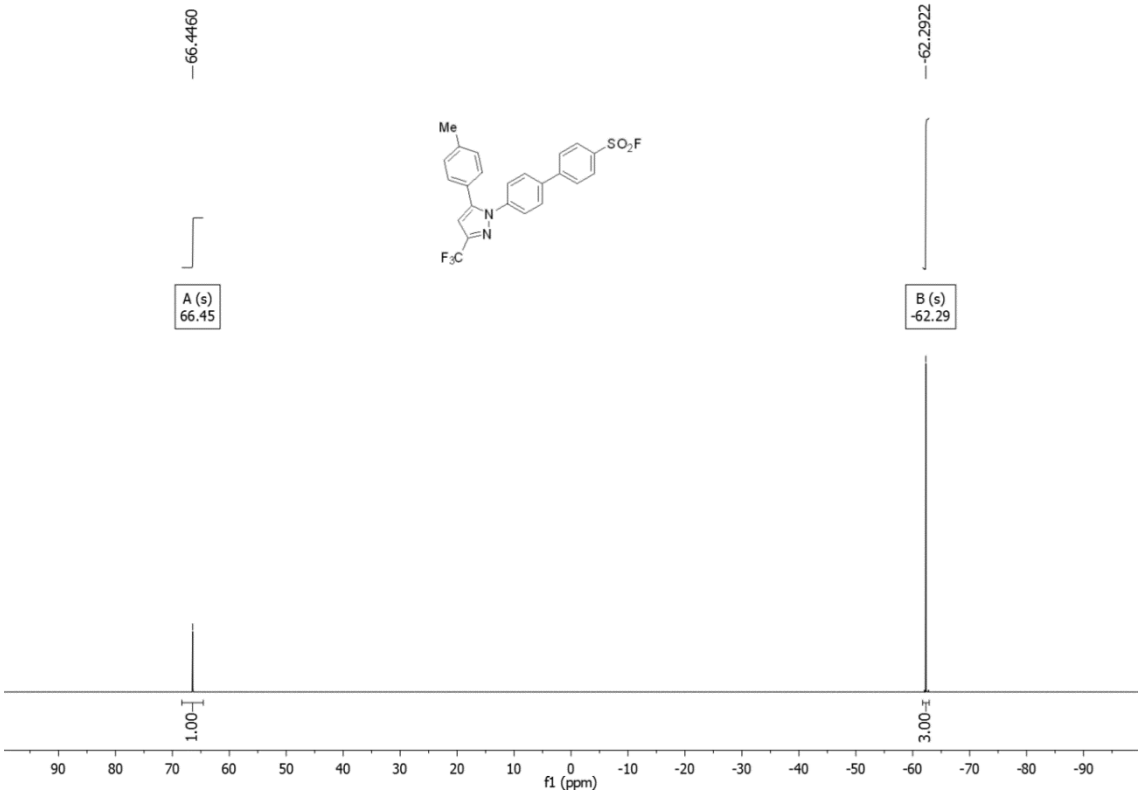
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

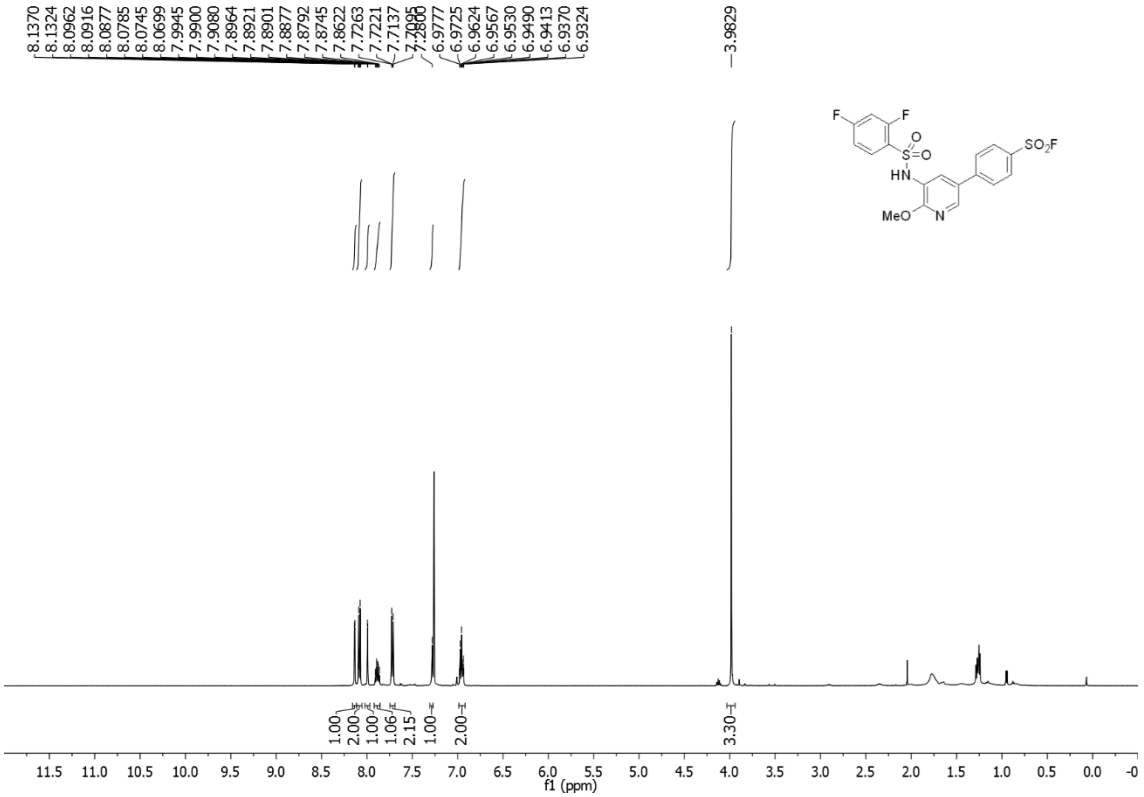


^{19}F-NMR Spectrum:

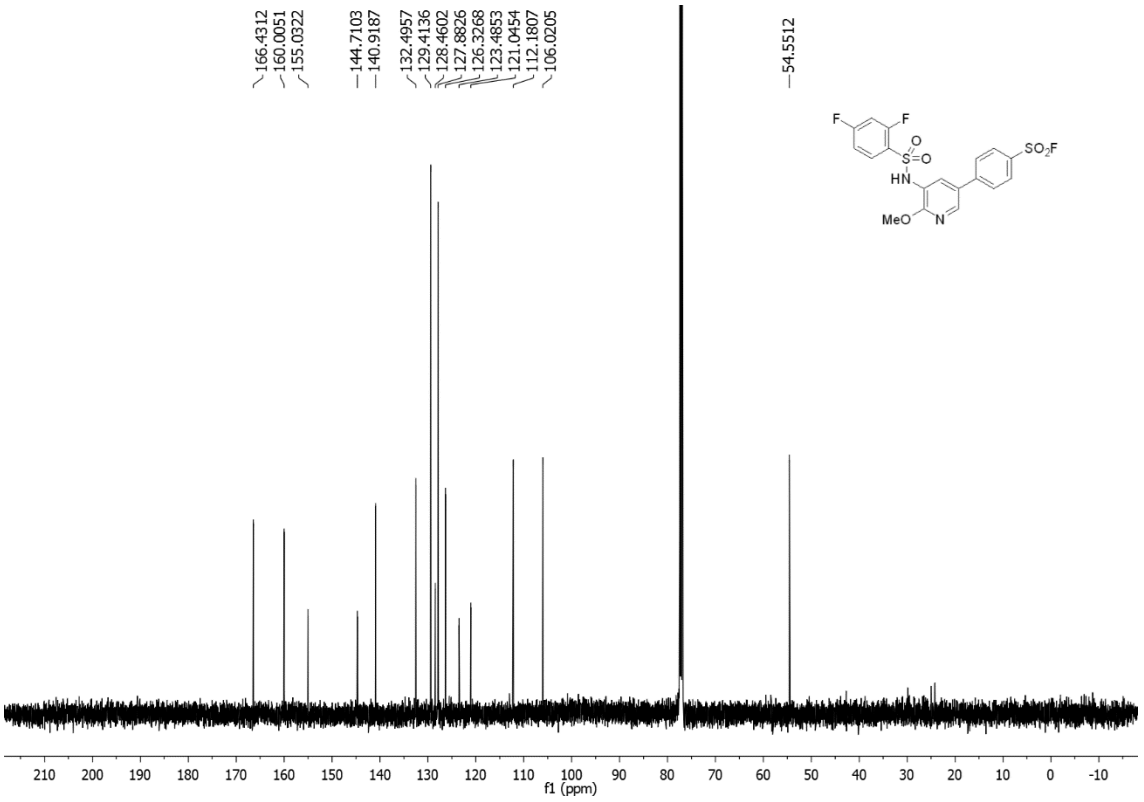


4-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)benzenesulfonyl fluoride (24k)

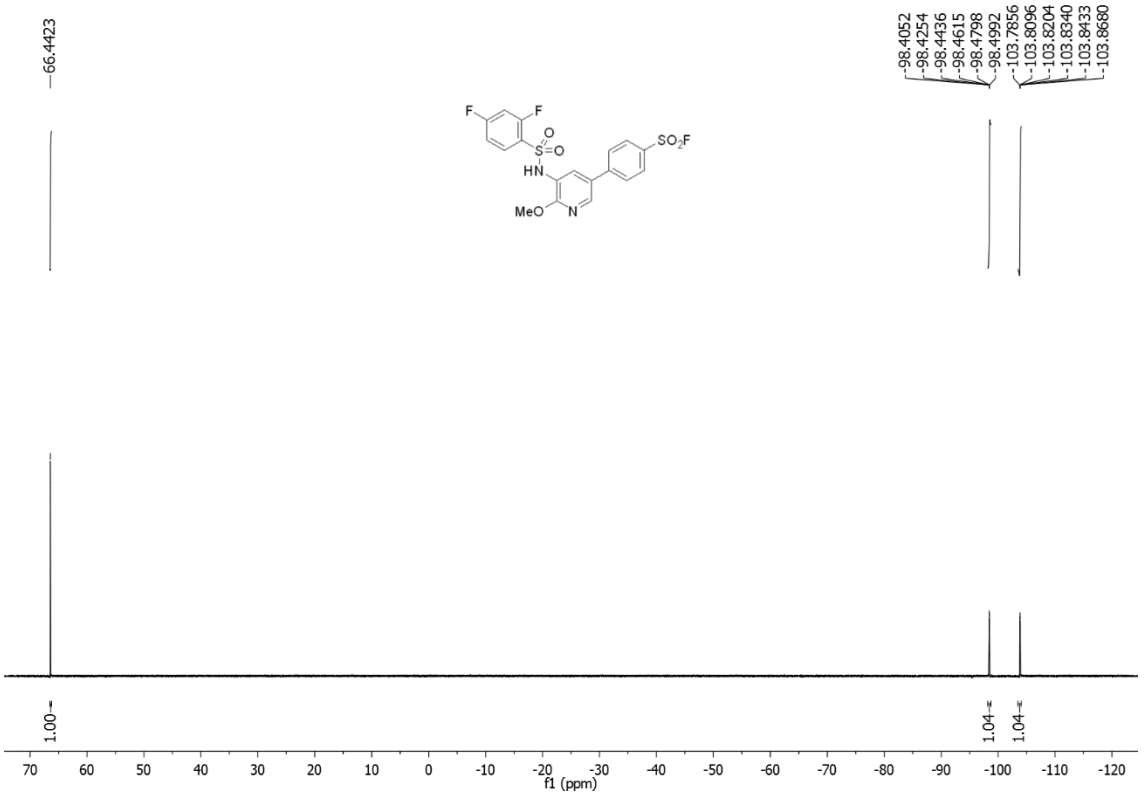
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

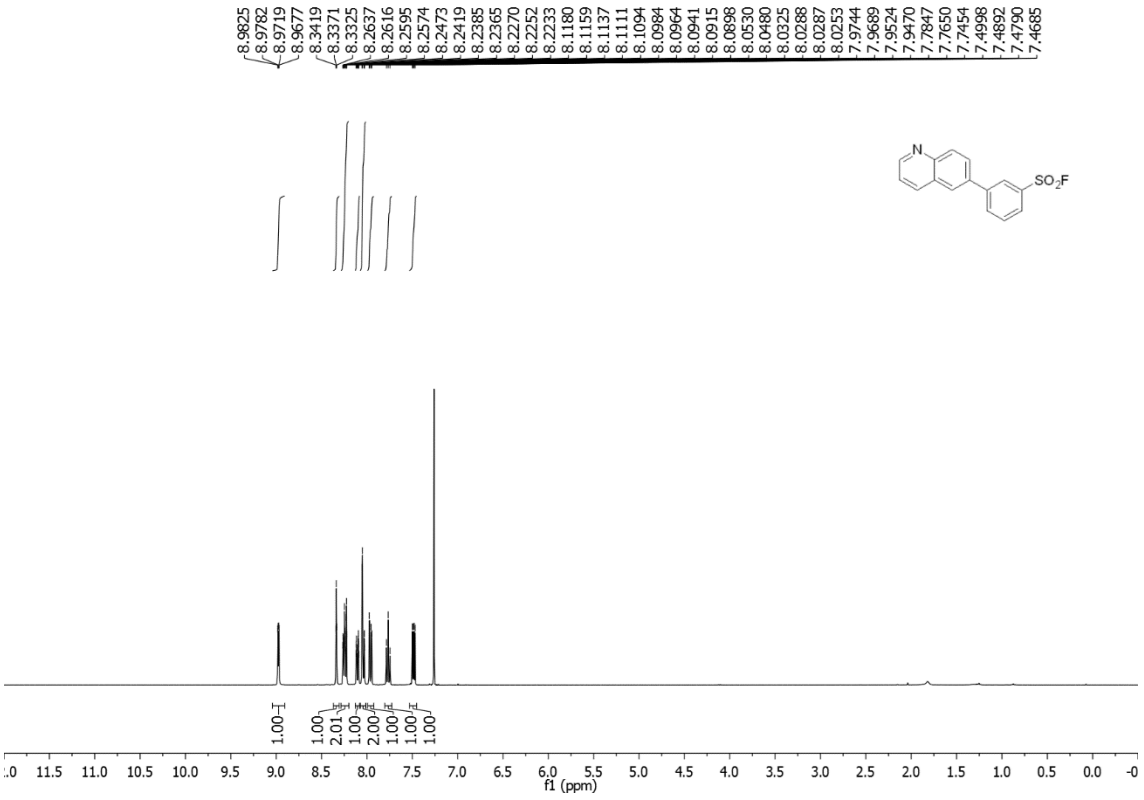


^{19}F-NMR Spectrum:

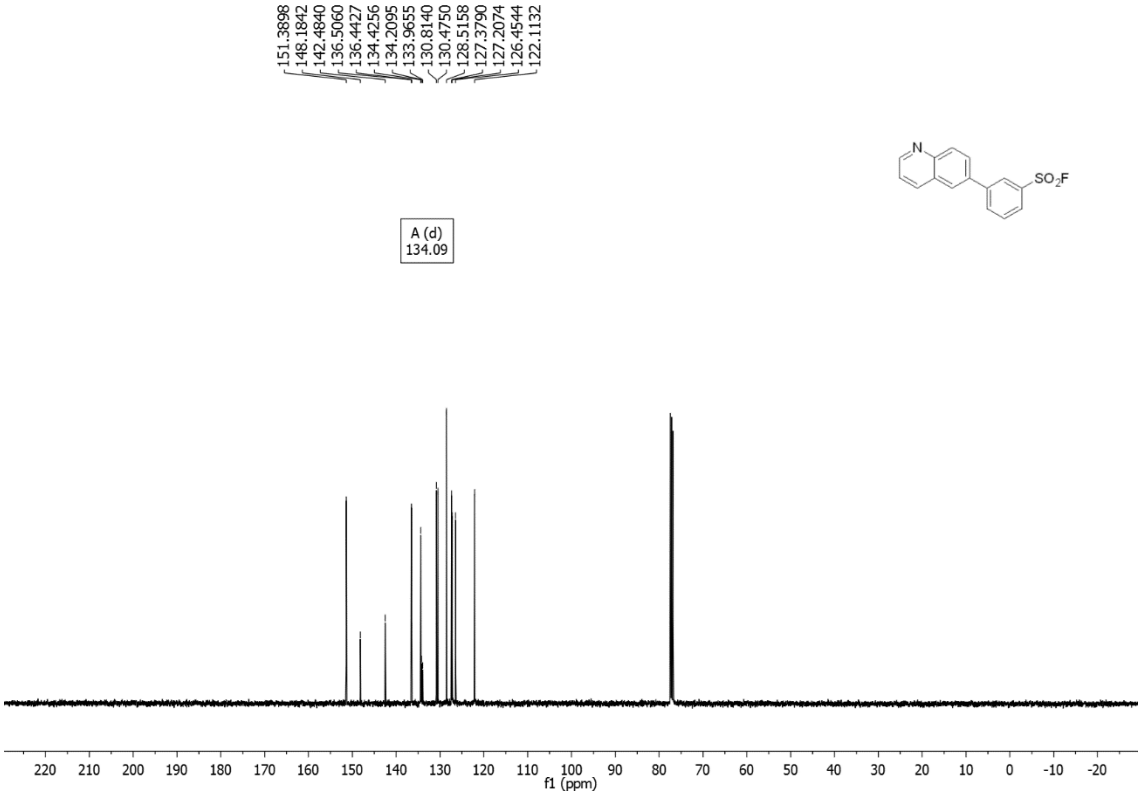


3-(Quinolin-6-yl)benzenesulfonyl fluoride (24l)

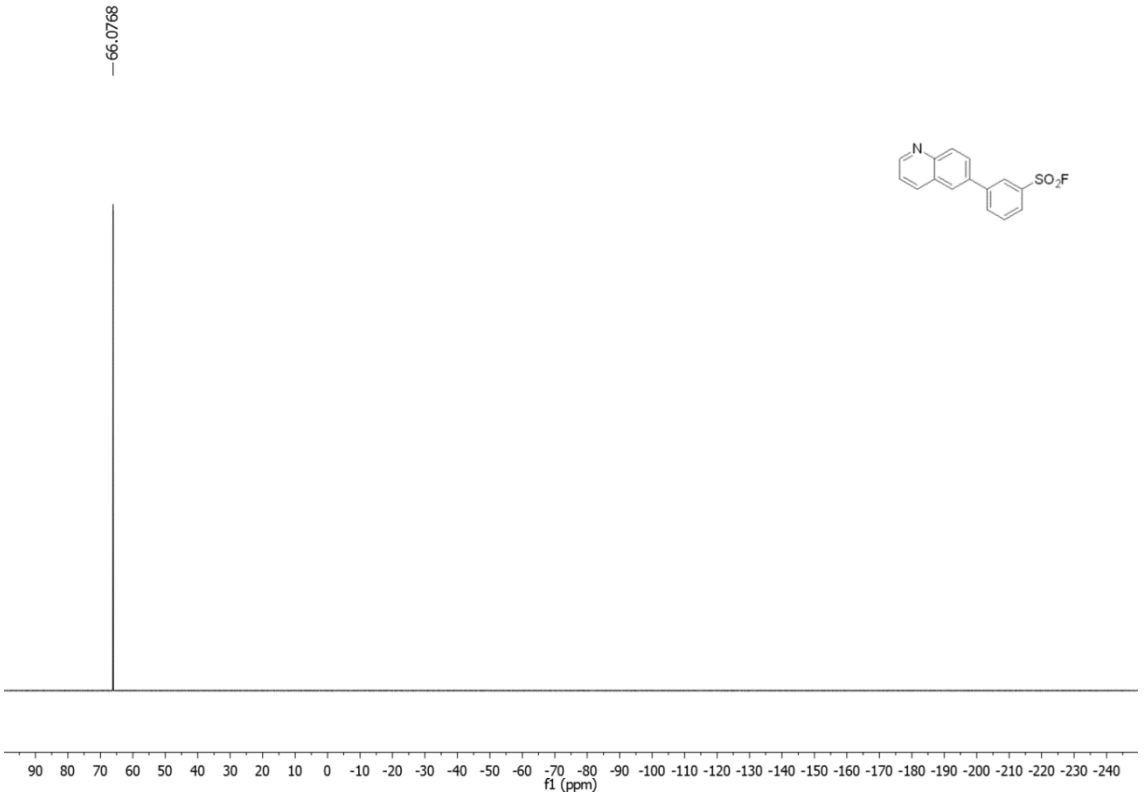
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

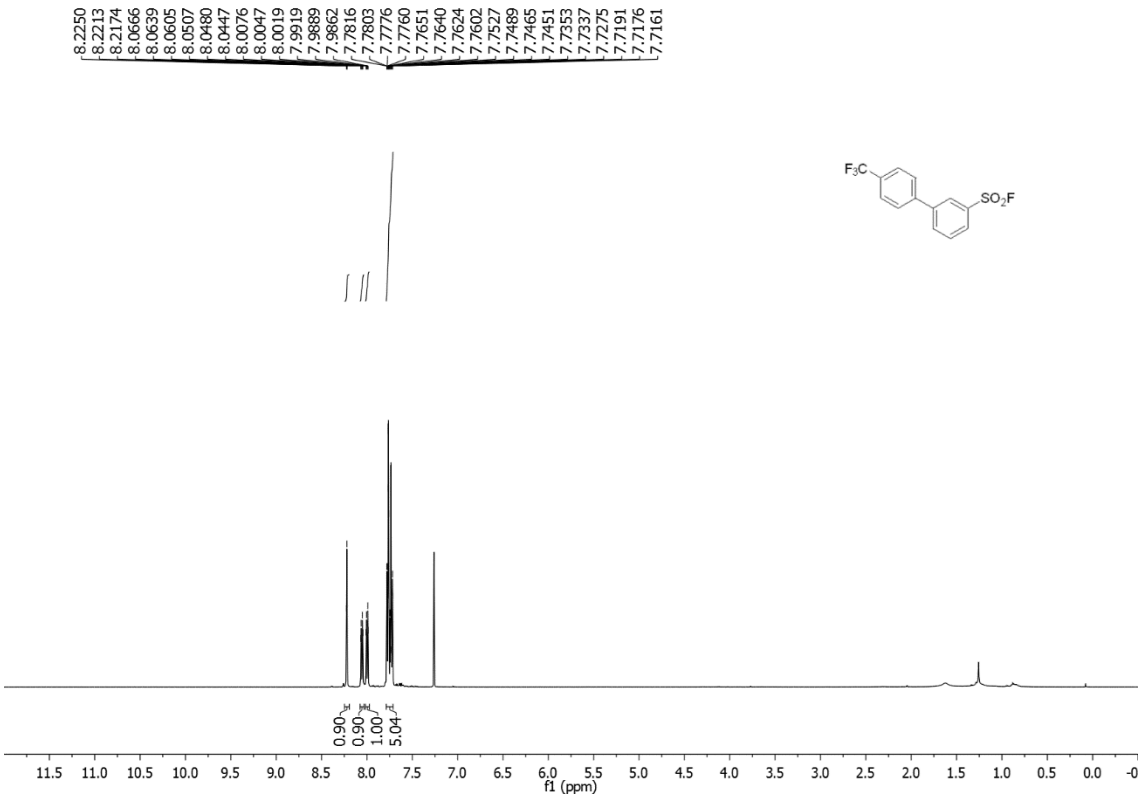


^{19}F-NMR Spectrum:

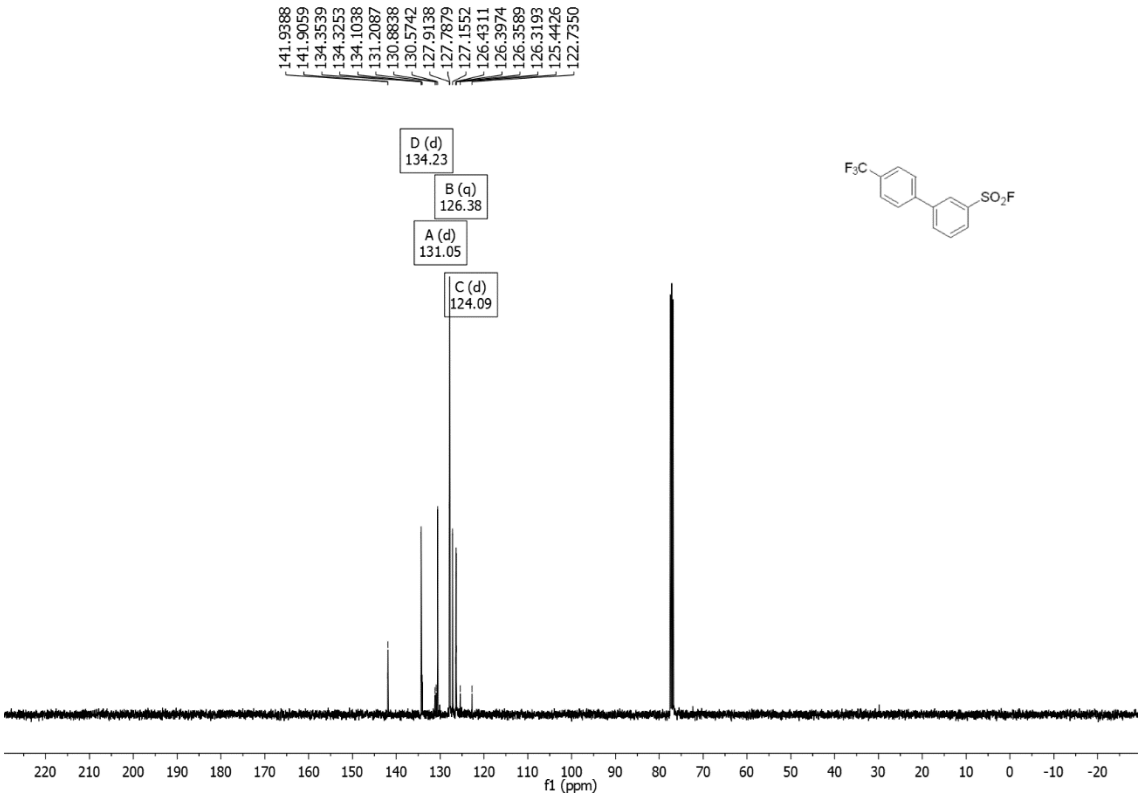


4'-(Trifluoromethyl)-[1,1'-biphenyl]-3-sulfonyl fluoride (24m)

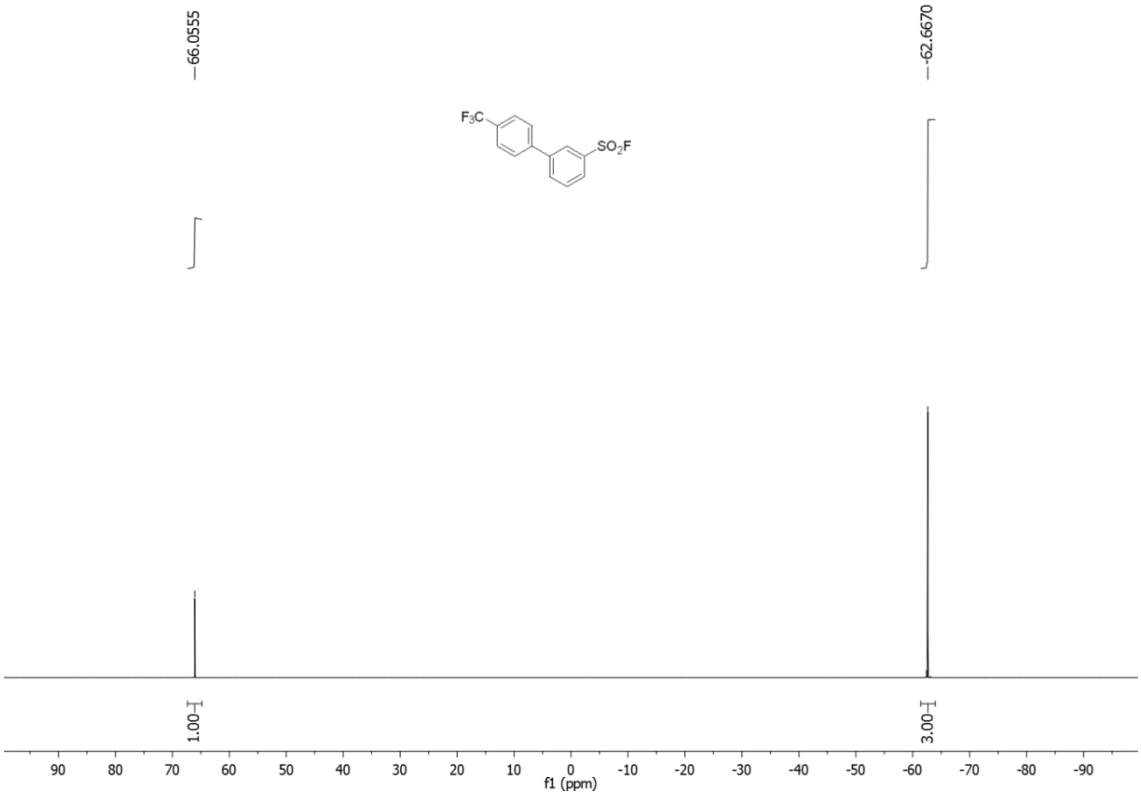
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

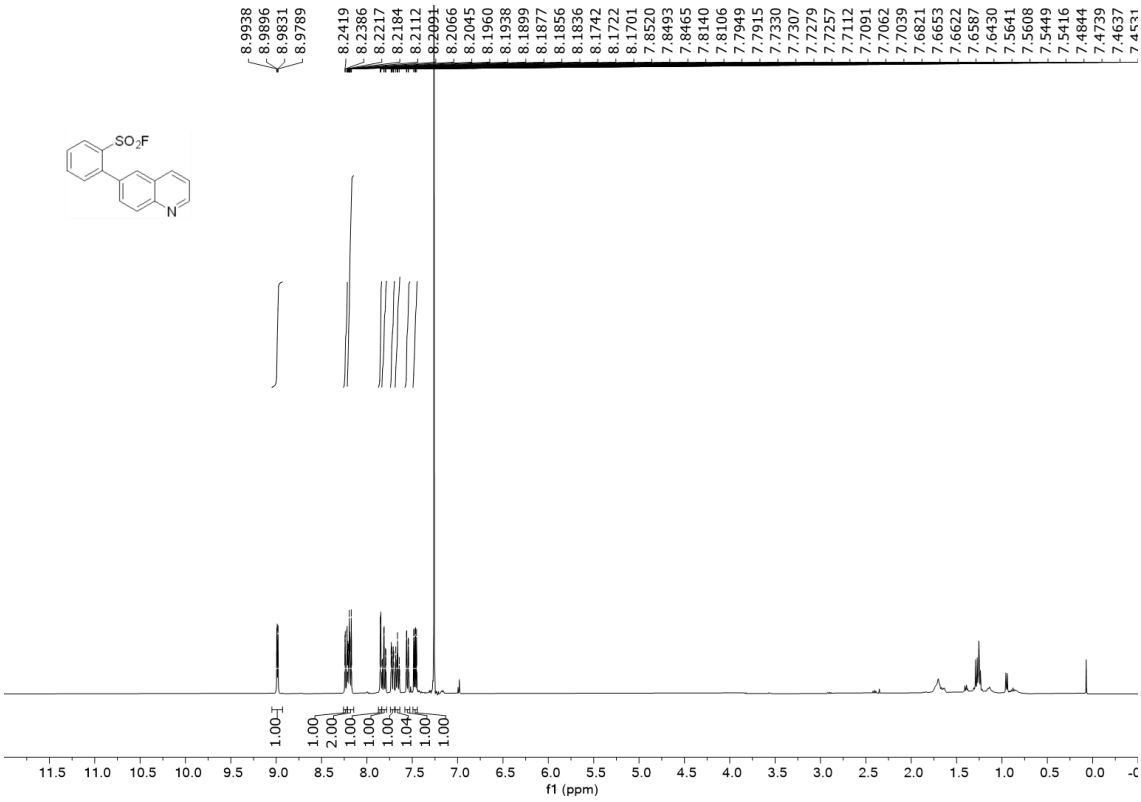


^{19}F-NMR Spectrum:

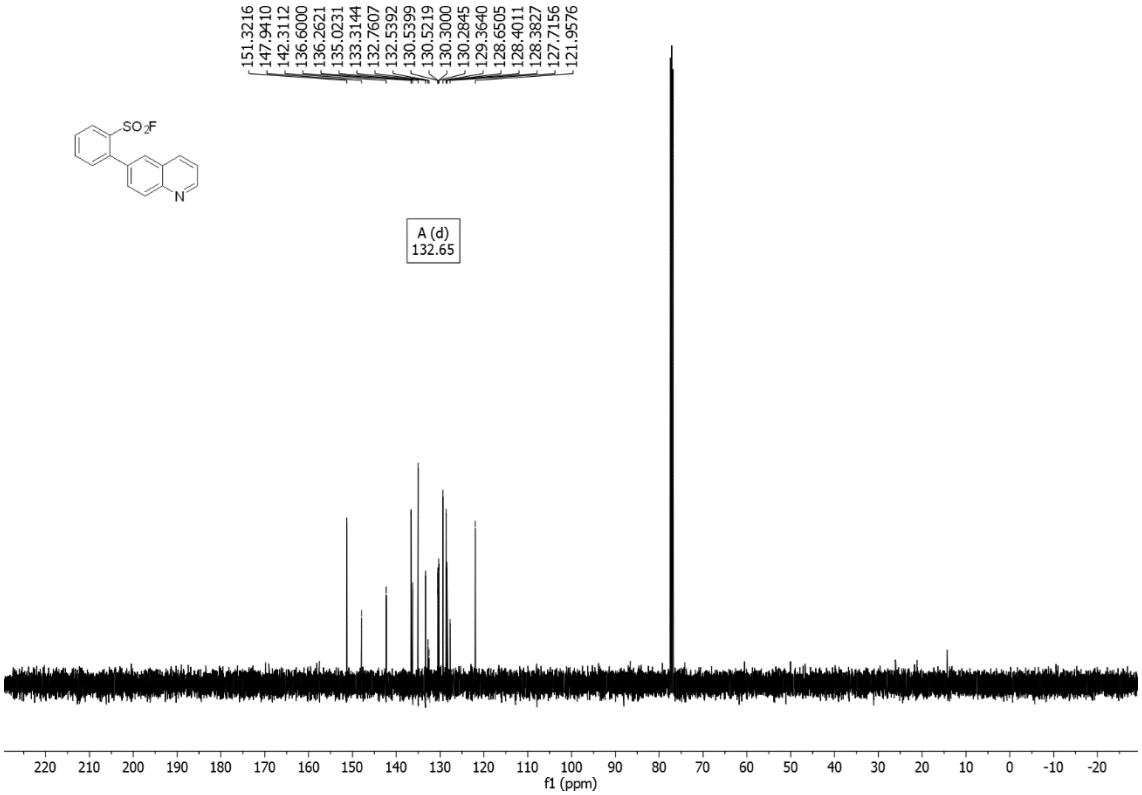


2-(Quinolin-6-yl)benzenesulfonyl fluoride (24n)

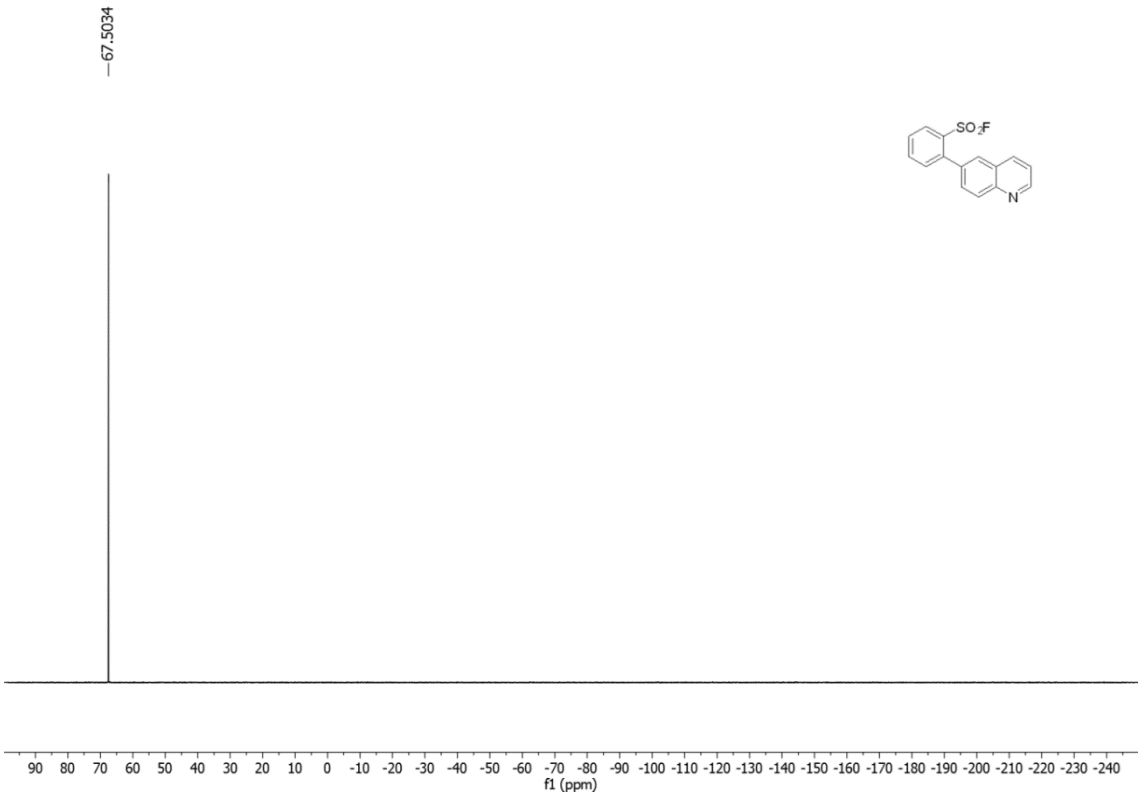
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

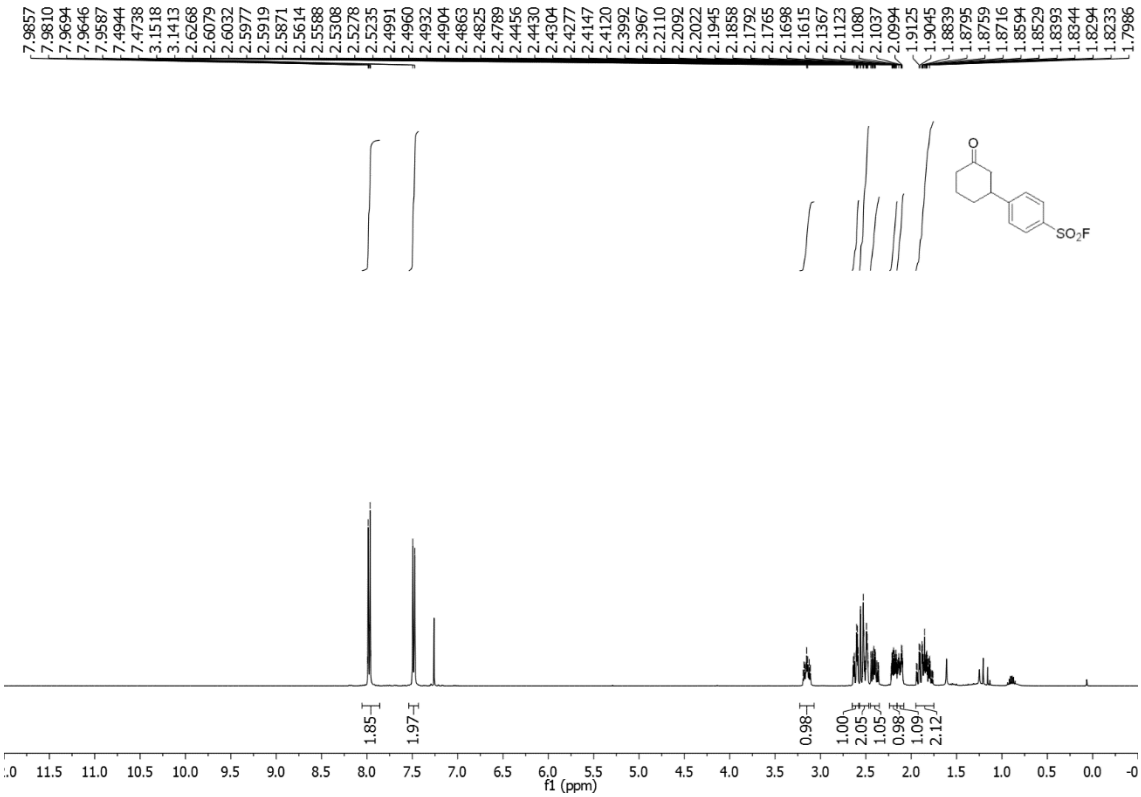


^{19}F-NMR Spectrum:

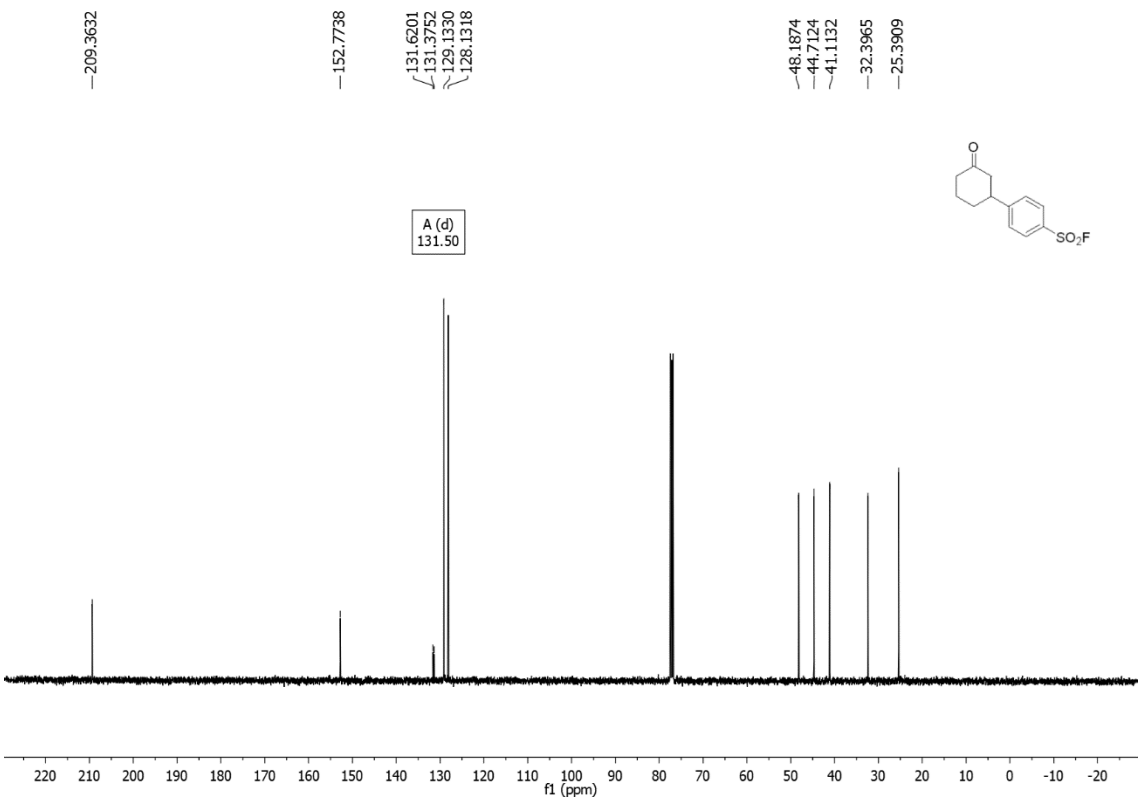


5 NMR Spectra of 4-(3-Oxocyclohexyl)benzenesulfonyl fluoride (26)

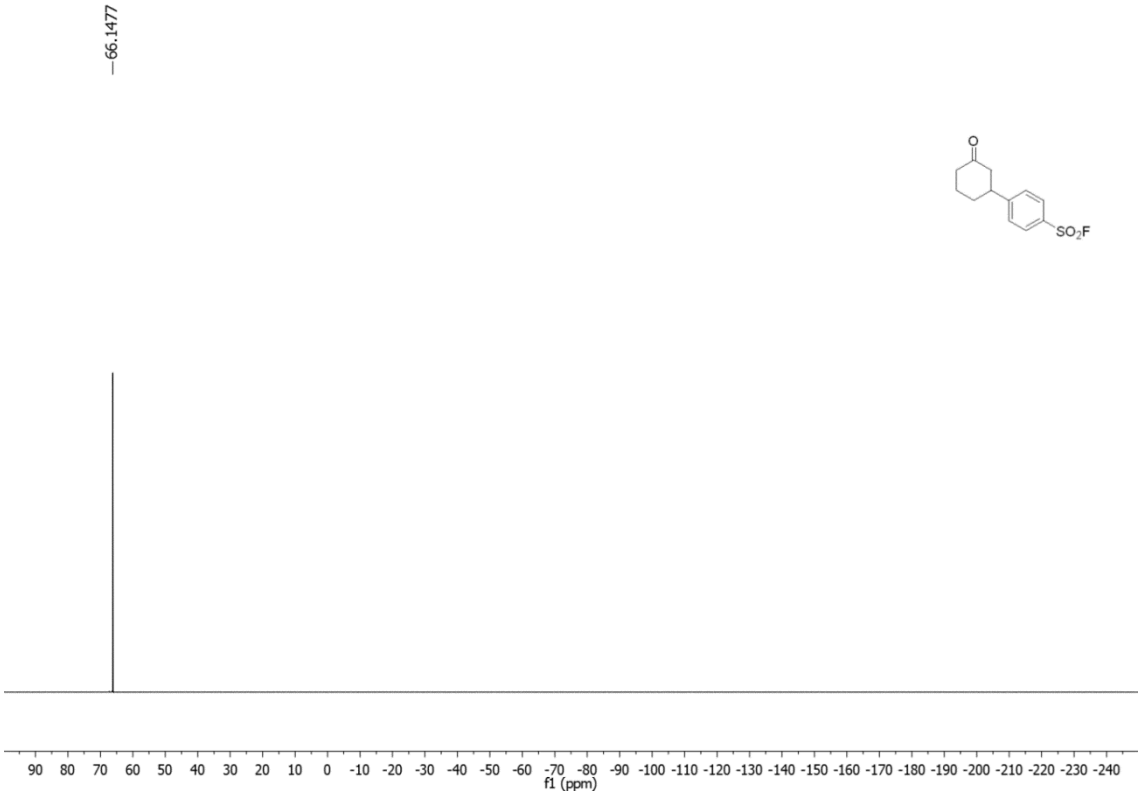
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

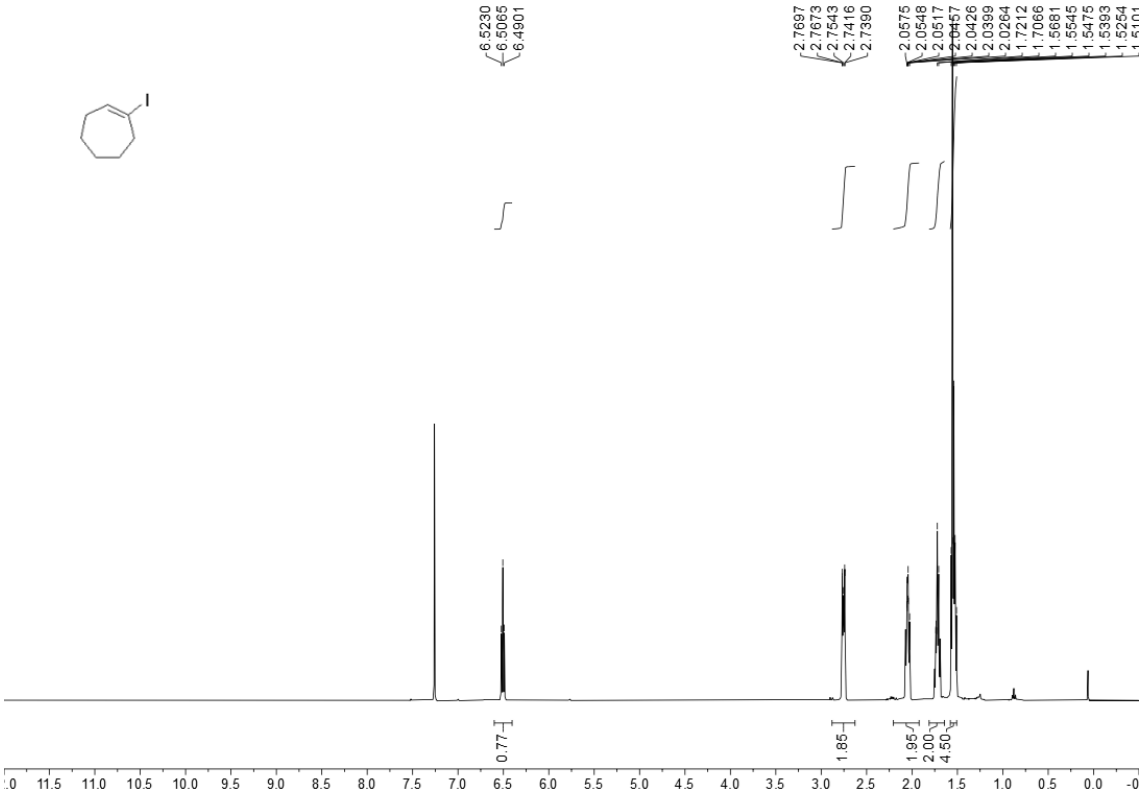


^{19}F-NMR Spectrum:

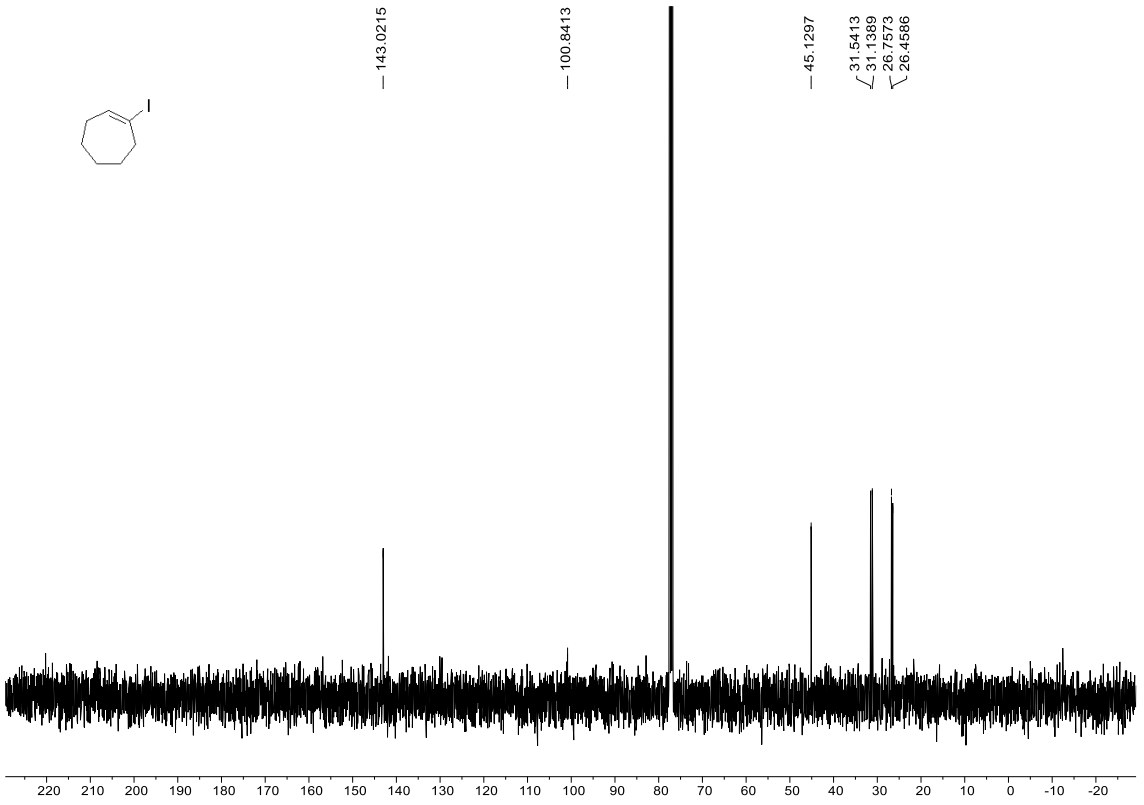


6 NMR Spectra of 1-Cyclohept-1-enyl iodide (29)

^{1}H-NMR Spectrum:

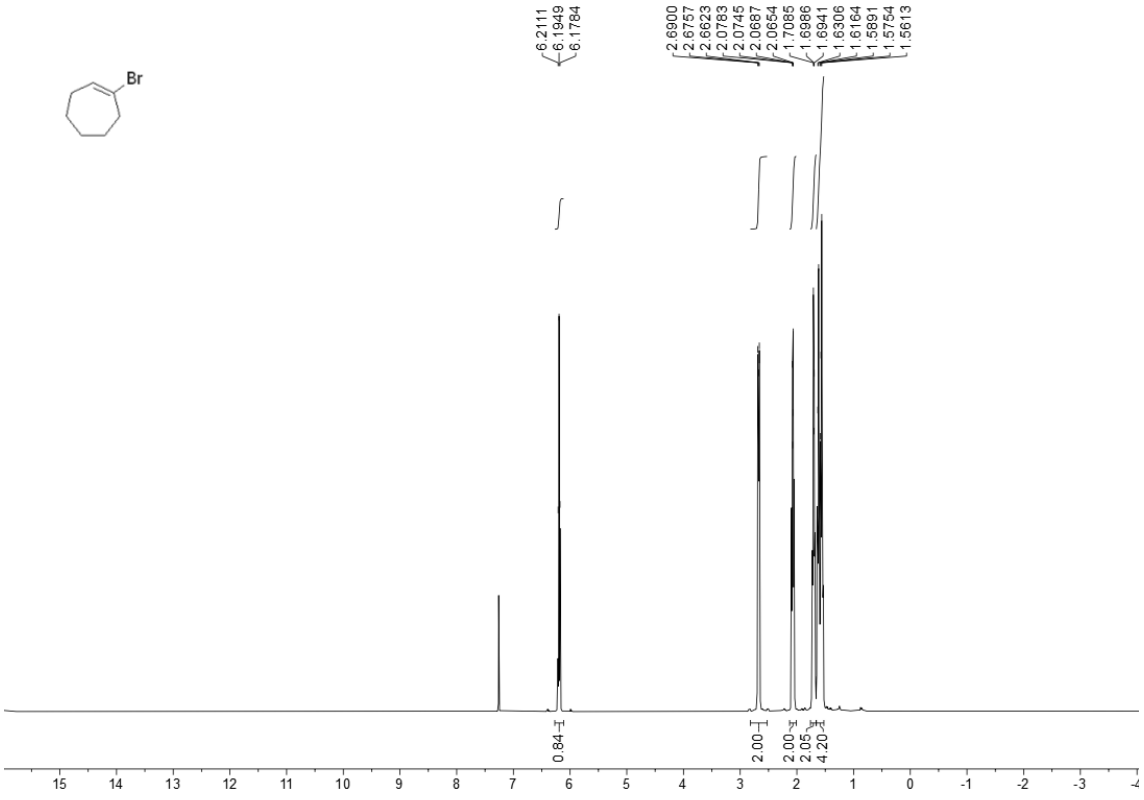


^{13}C-NMR Spectrum:

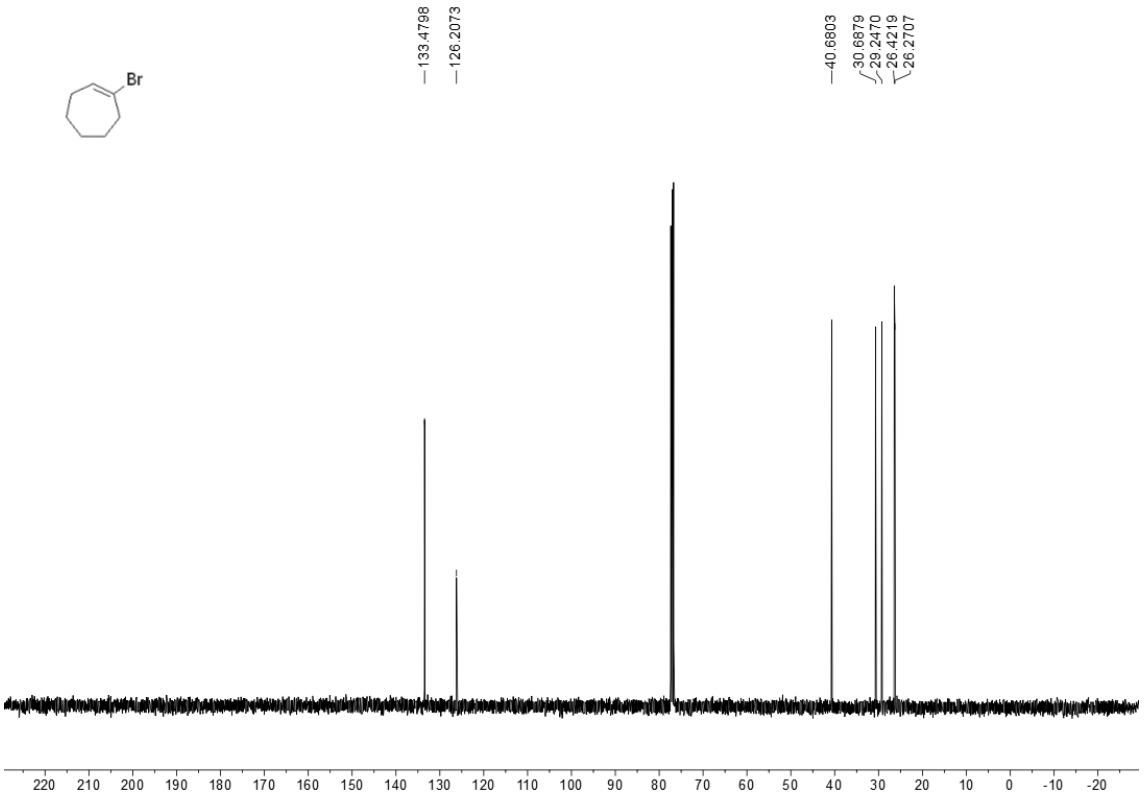


7 NMR Spectra of 1-Cyclohept-1-enyl bromide (30)

^{1}H-NMR Spectrum:



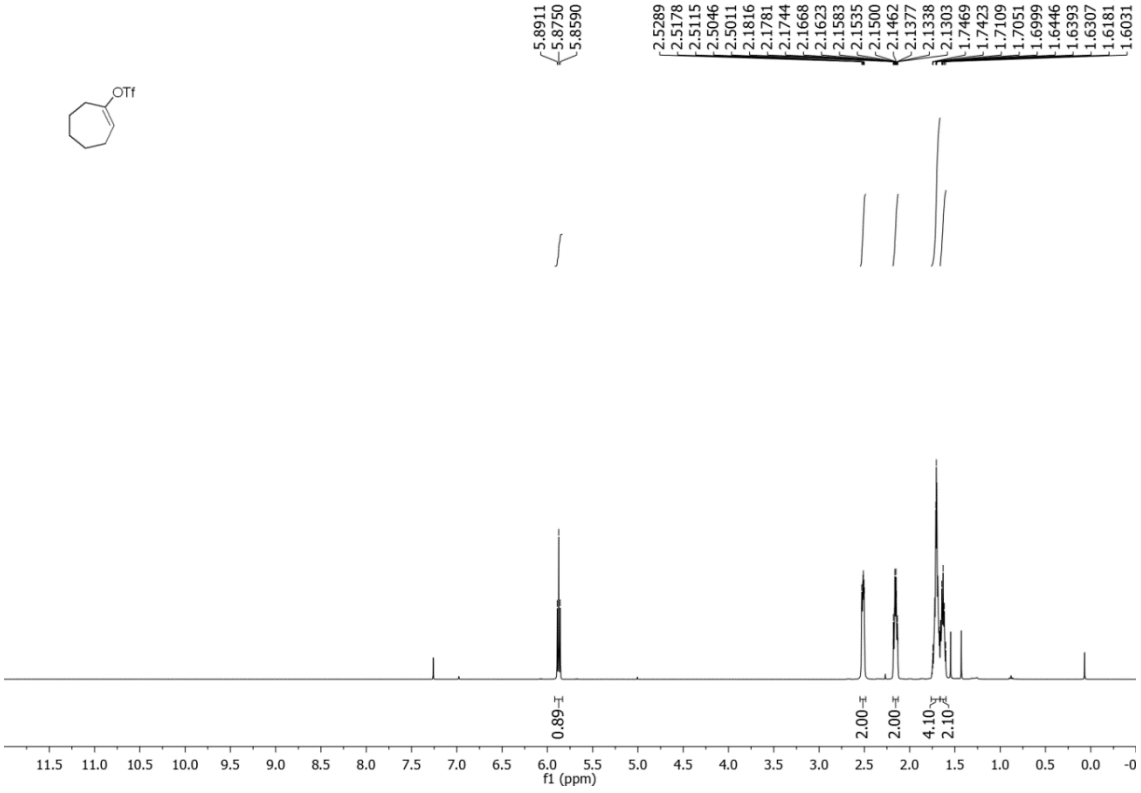
^{13}C-NMR Spectrum:



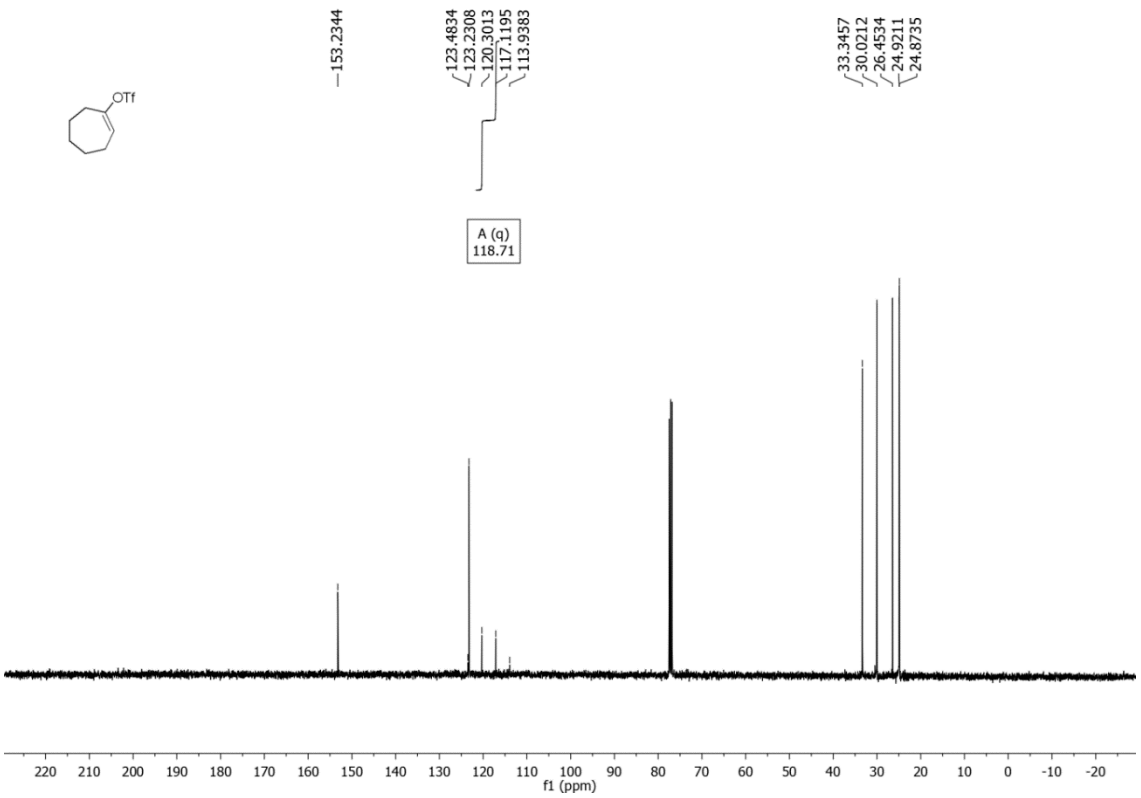
8 NMR Spectra of Alkenyl Triflates

1-Cyclohept-1-enyl trifluoromethanesulfonate (31a)

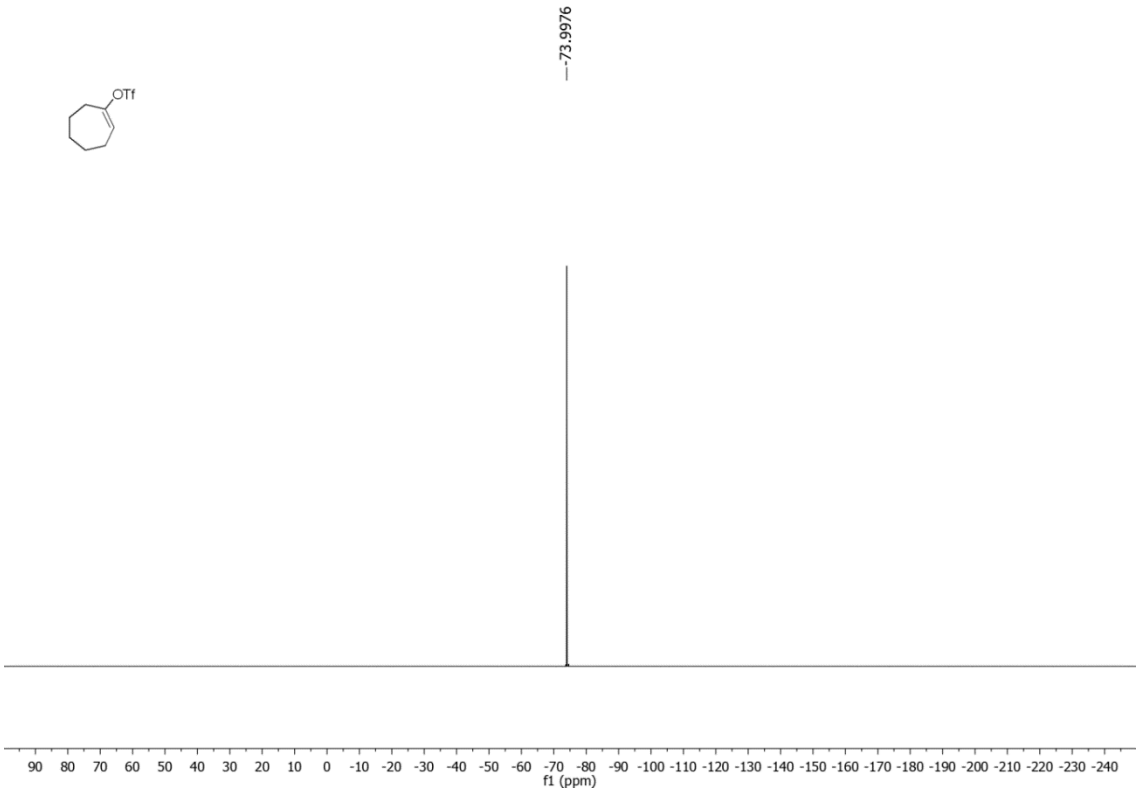
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

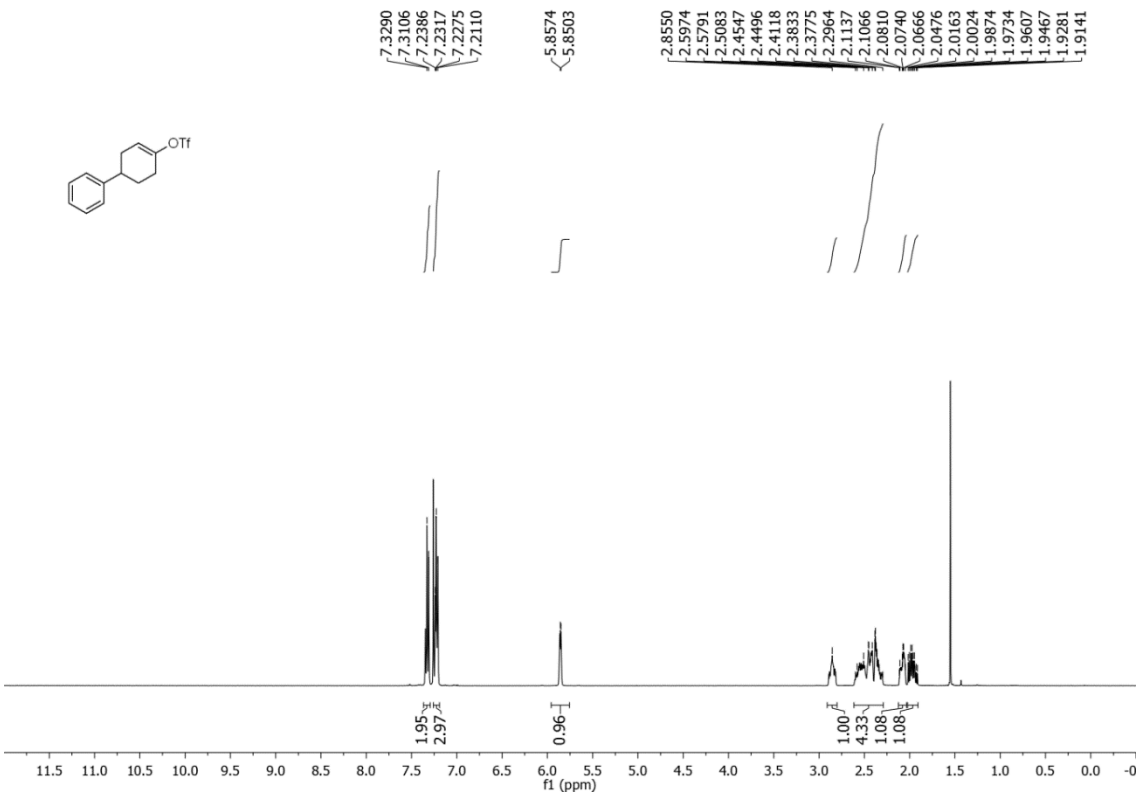


^{19}F-NMR Spectrum:

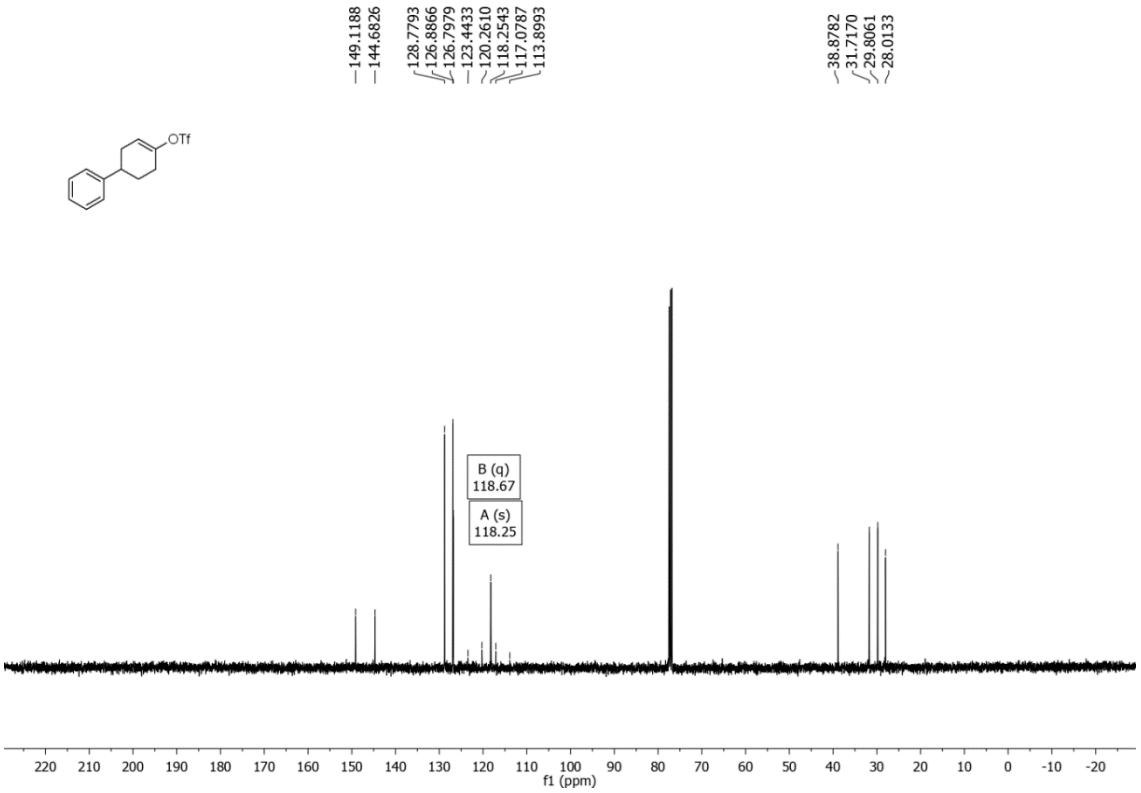


4-Phenyl-1-cyclohexen-1-yl trifluoromethanesulfonate (31b)

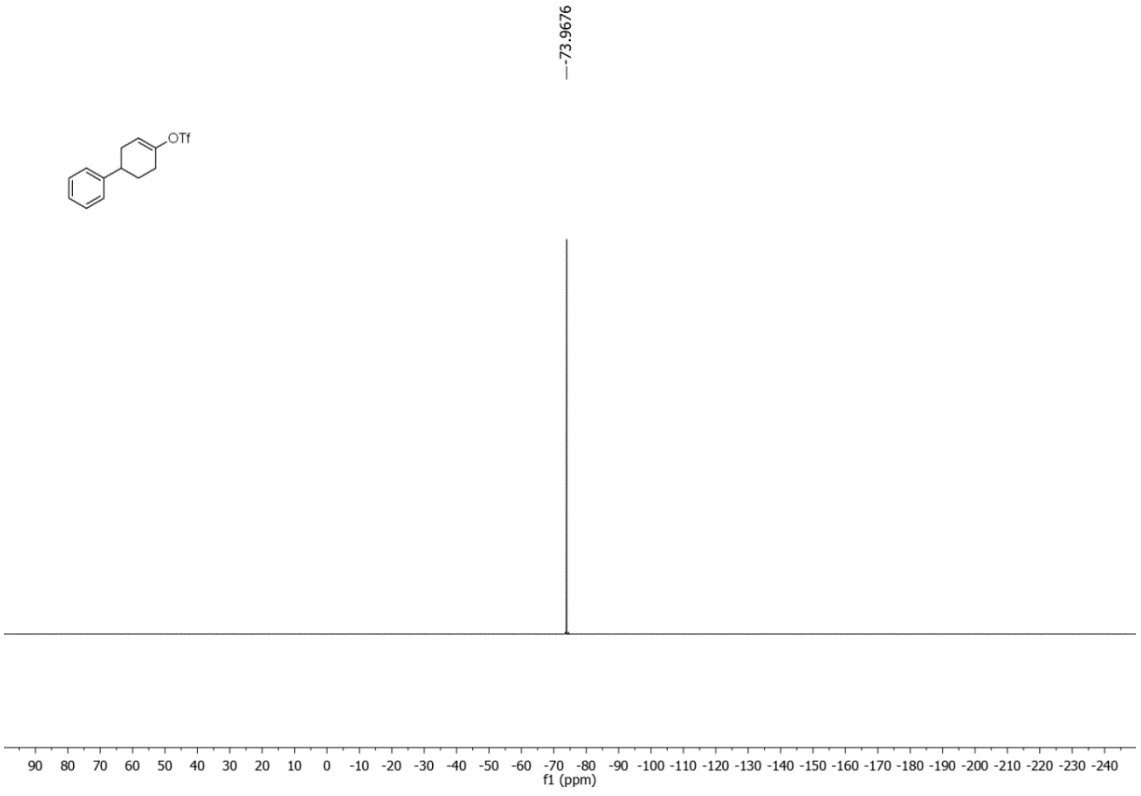
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

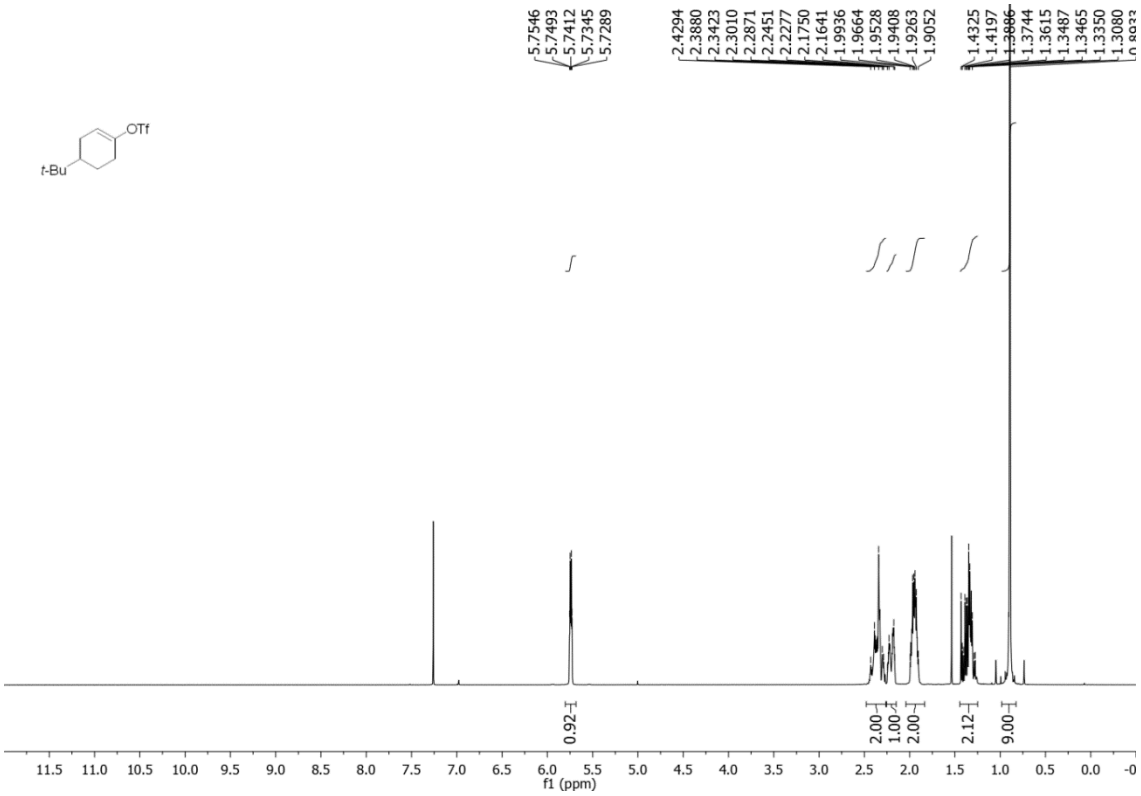


^{19}F-NMR Spectrum:

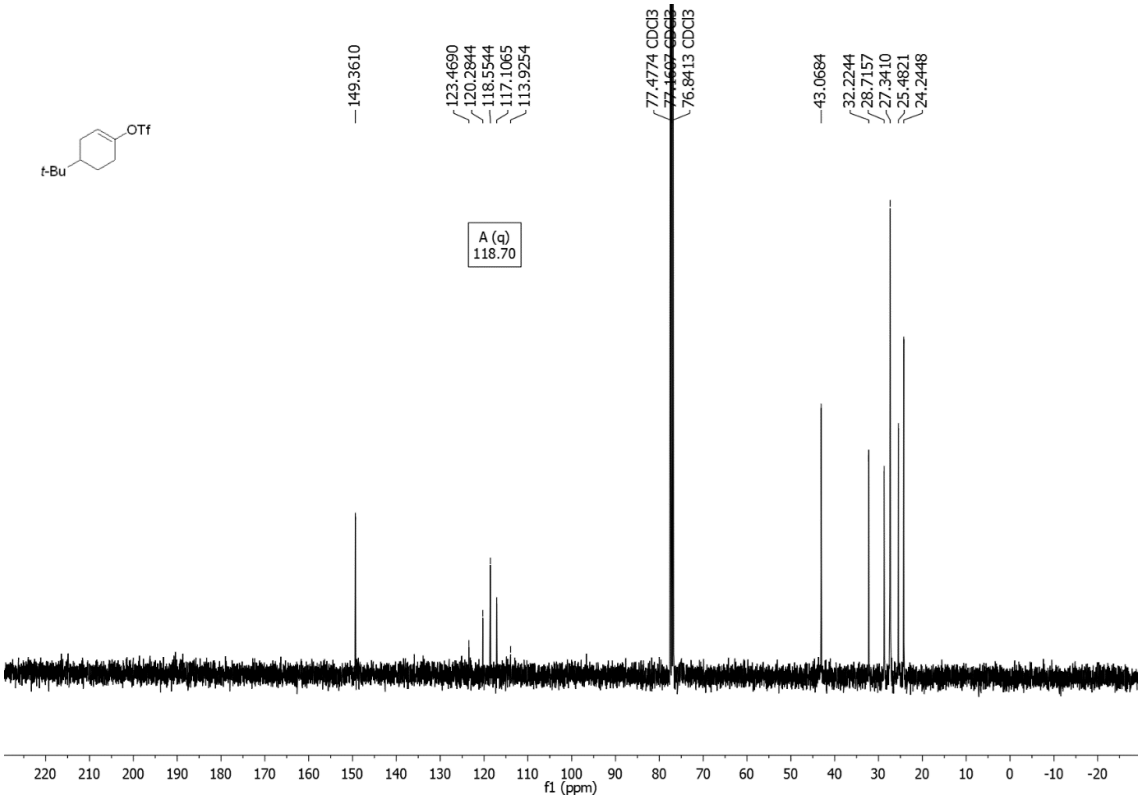


4-(*tert*-Butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (31c)

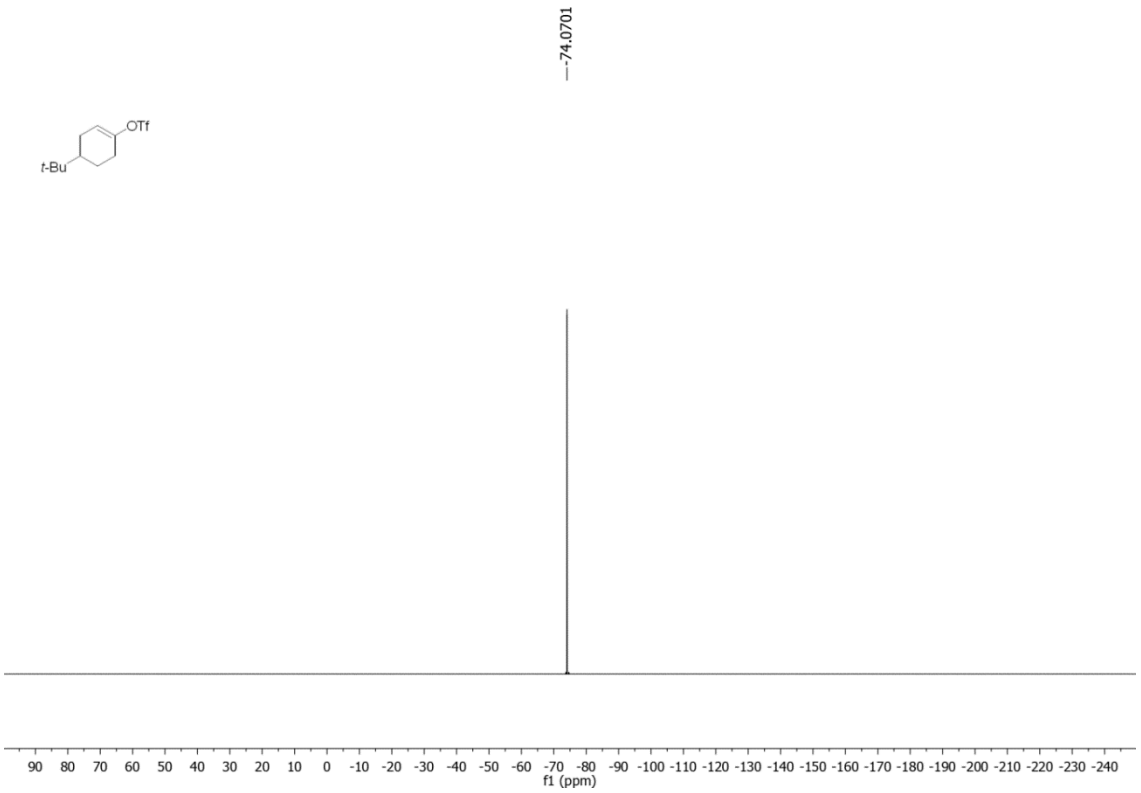
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

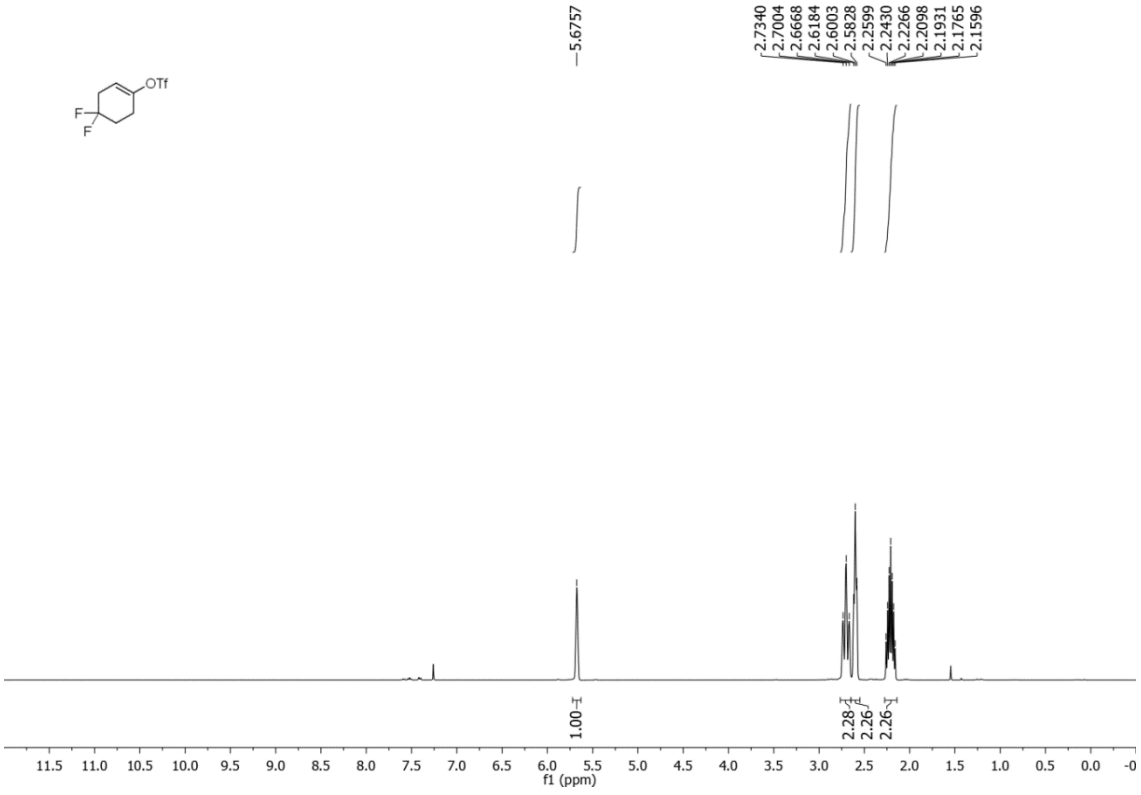


^{19}F-NMR Spectrum:

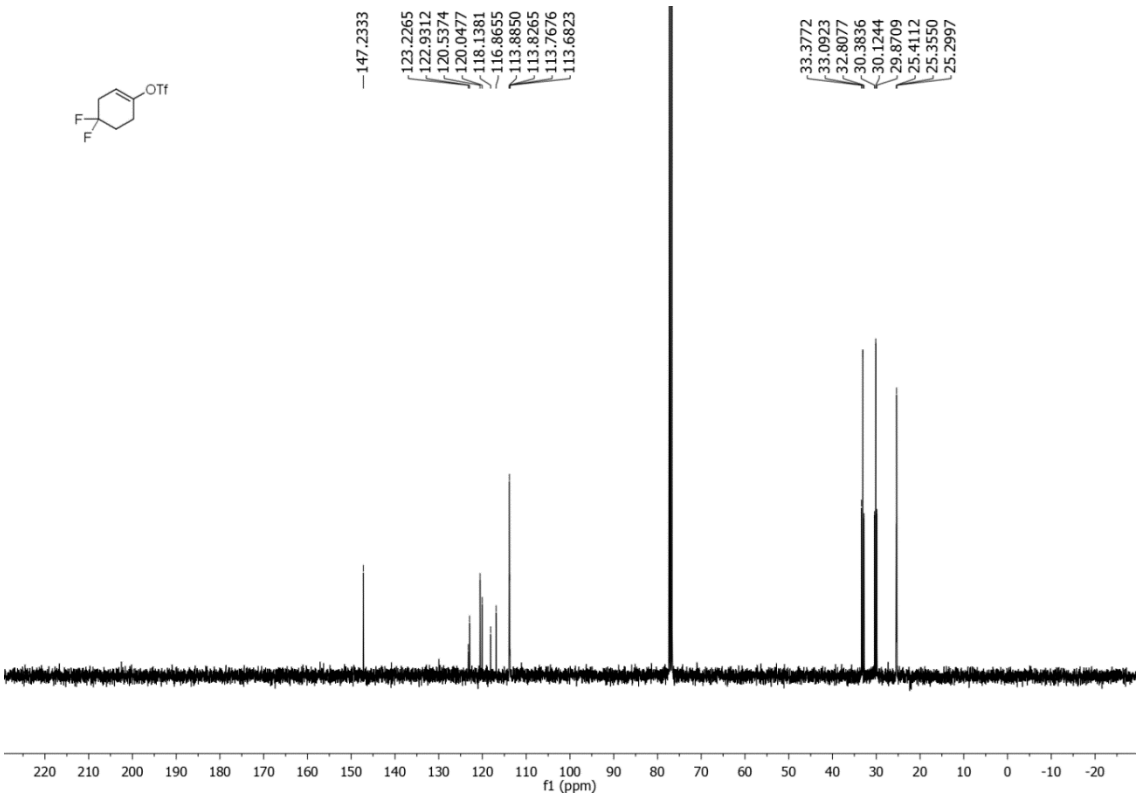


4,4-Difluorocyclohex-1-en-1-yl trifluoromethanesulfonate (31d)

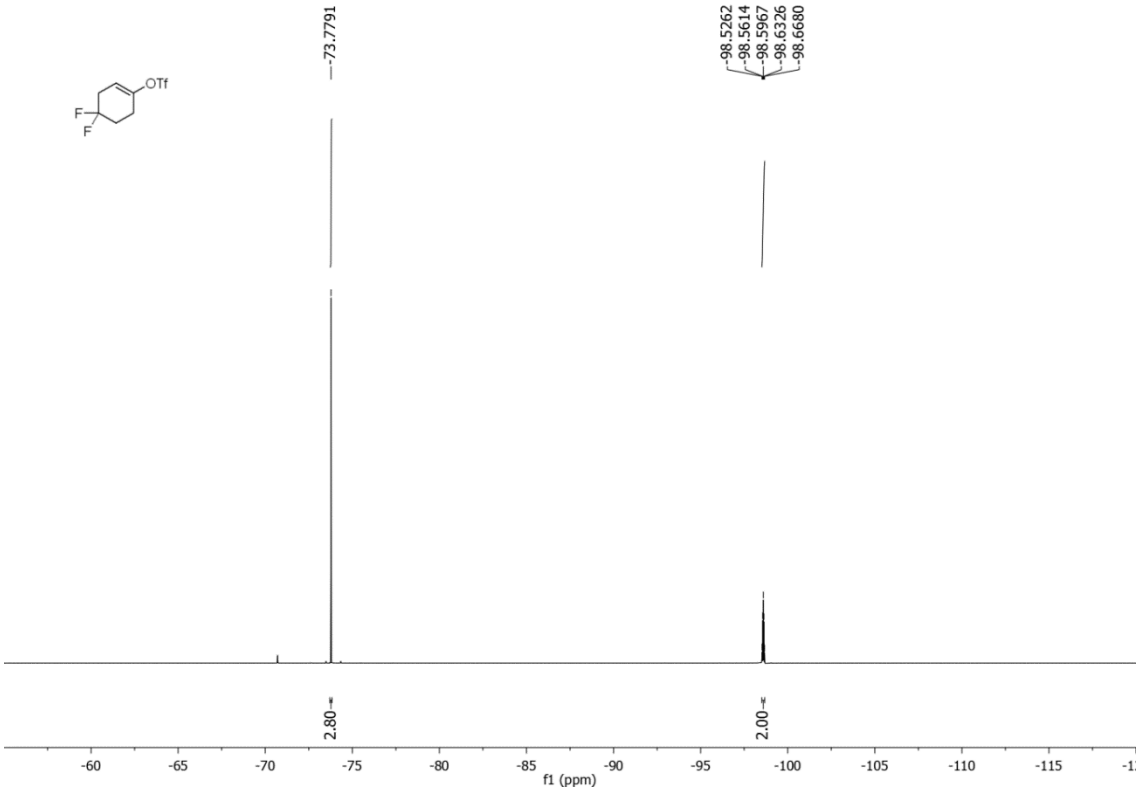
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

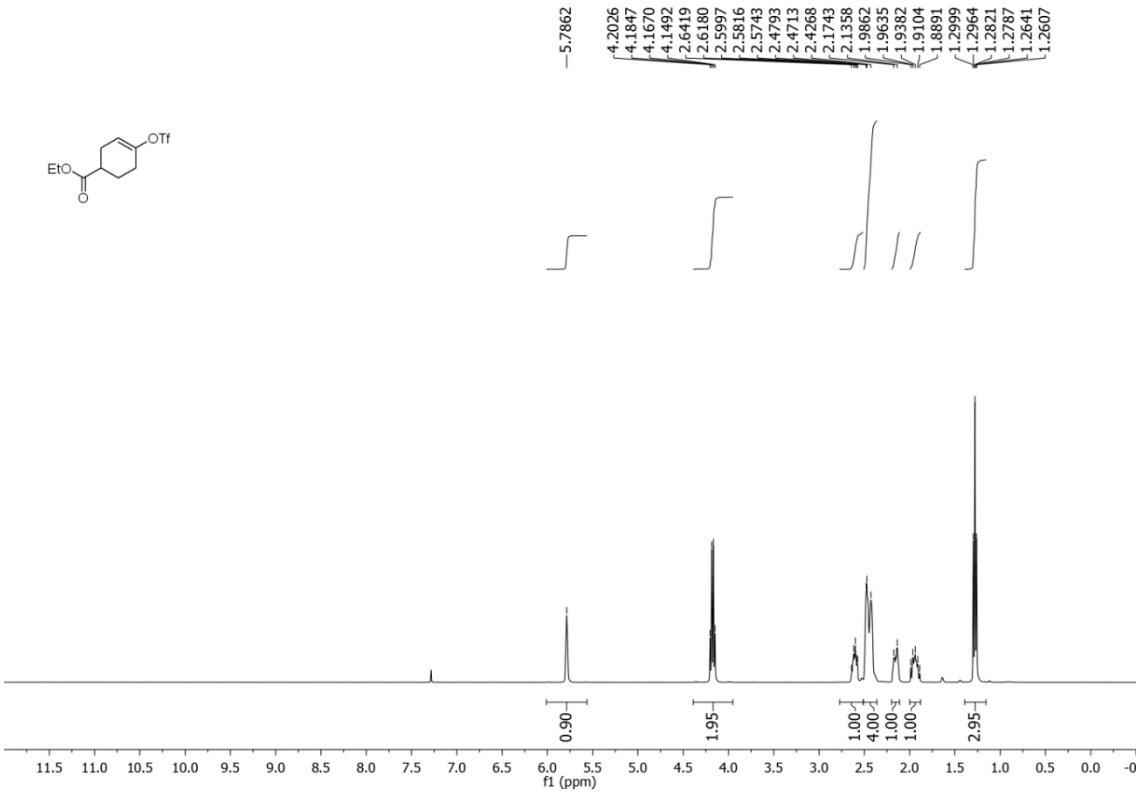


^{19}F-NMR Spectrum:

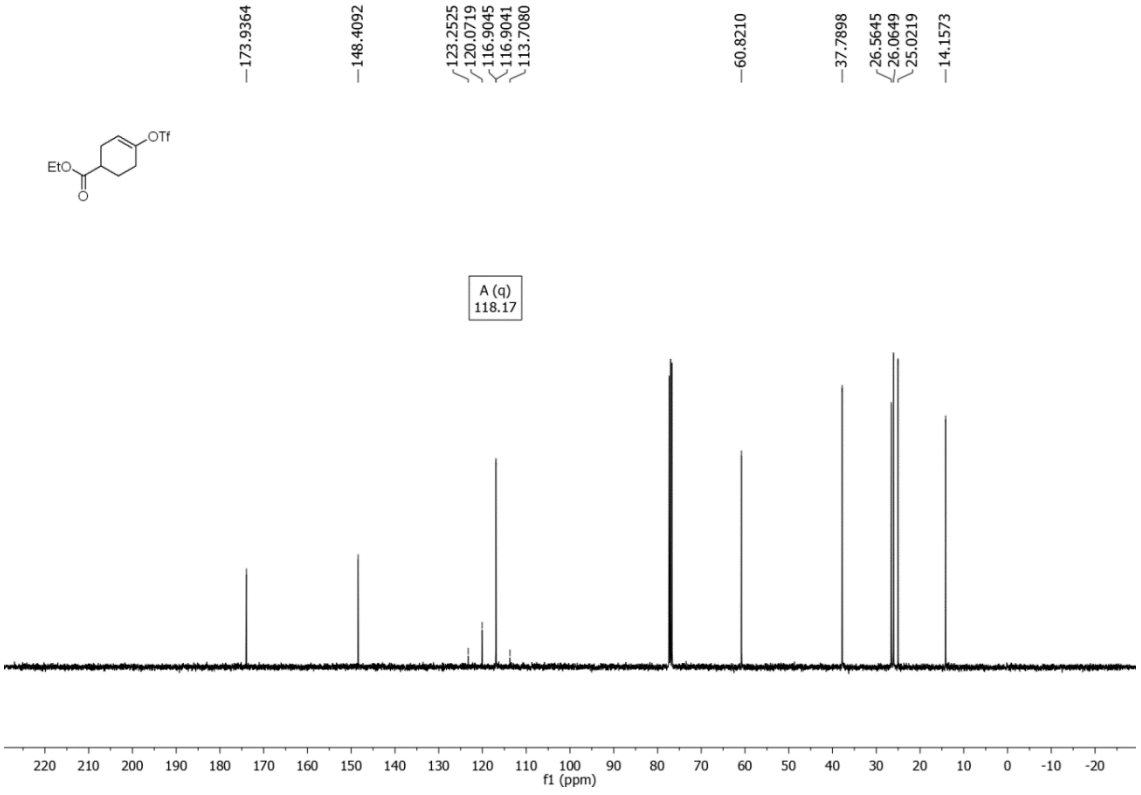


Ethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate (31e)

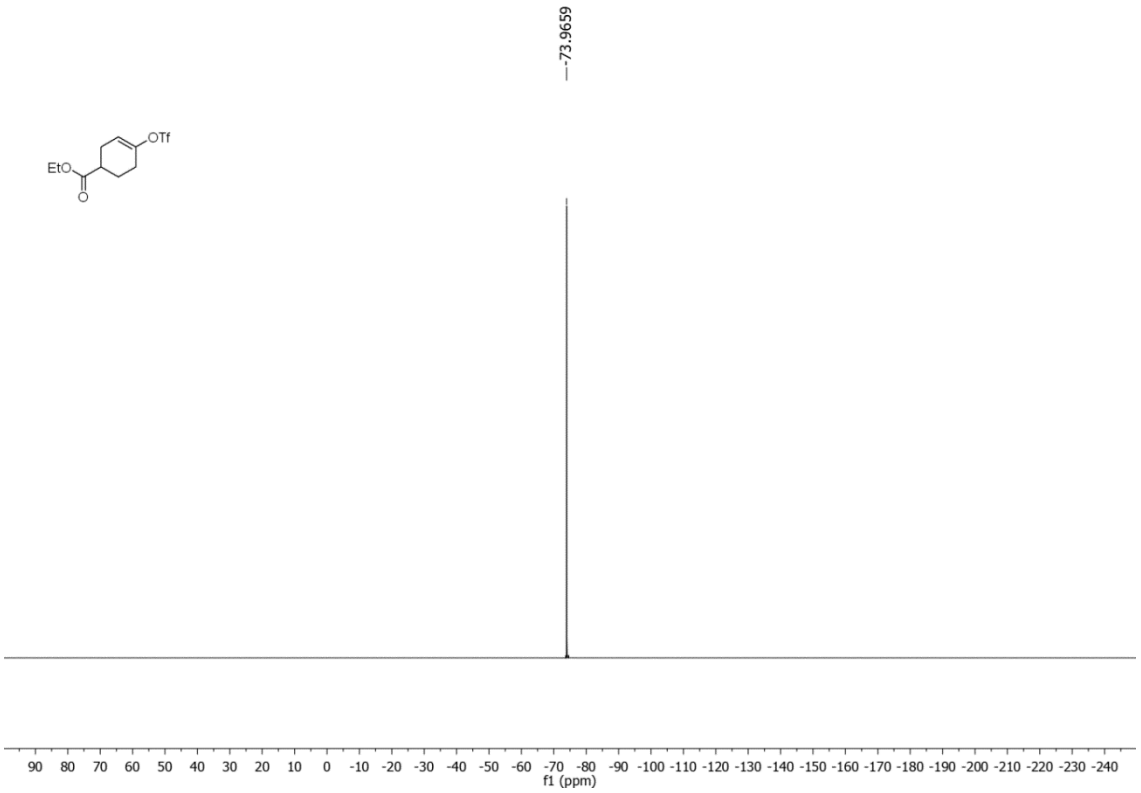
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

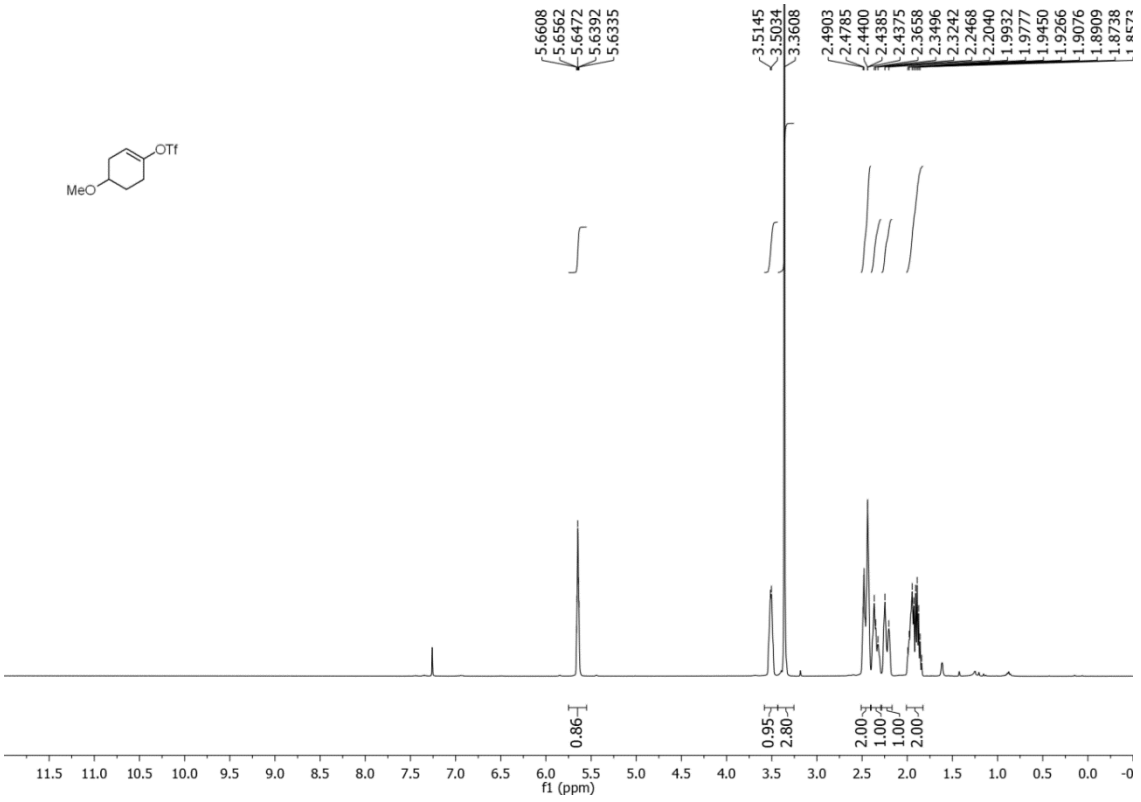


^{19}F-NMR Spectrum:

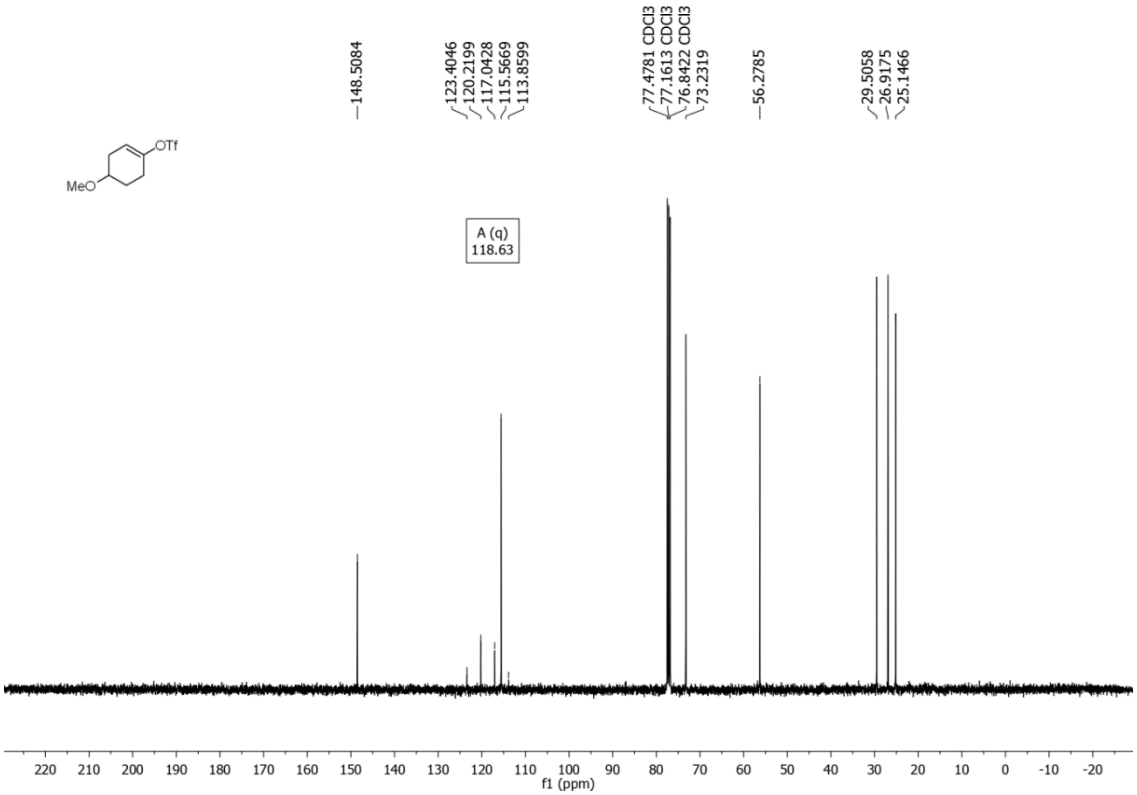


4-Methoxycyclohex-1-en-1-yl trifluoromethanesulfonate (31f)

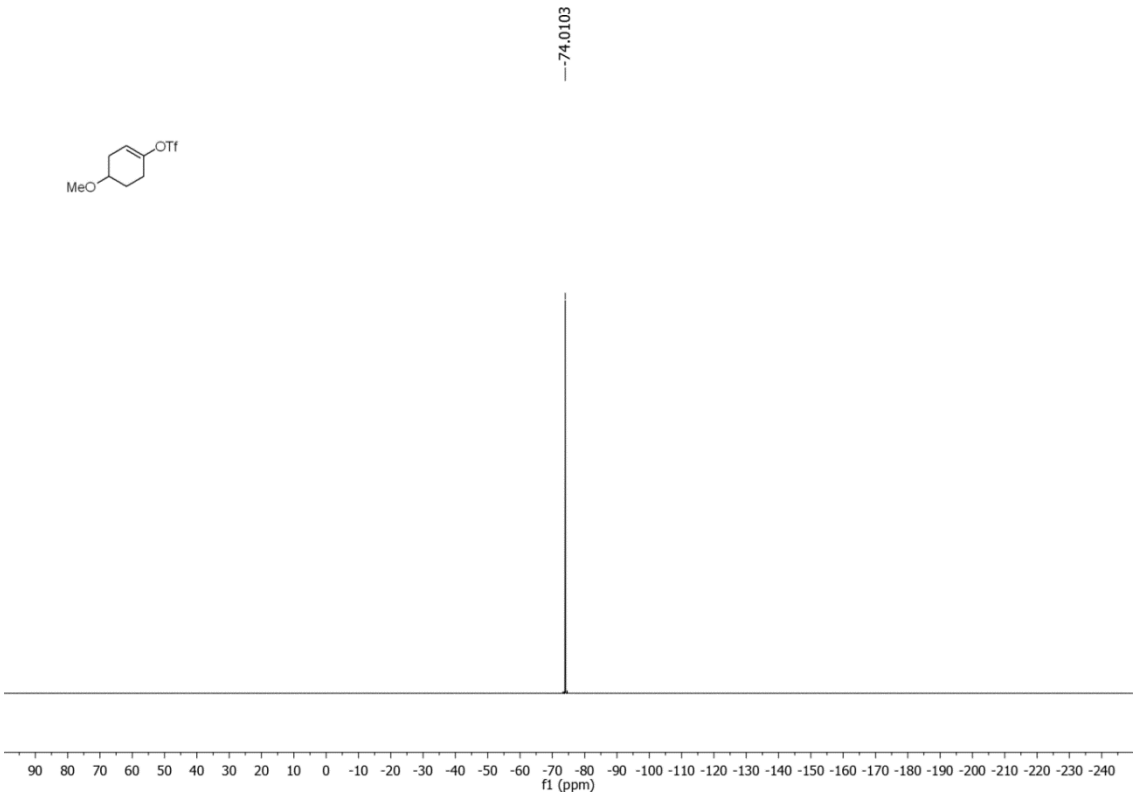
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

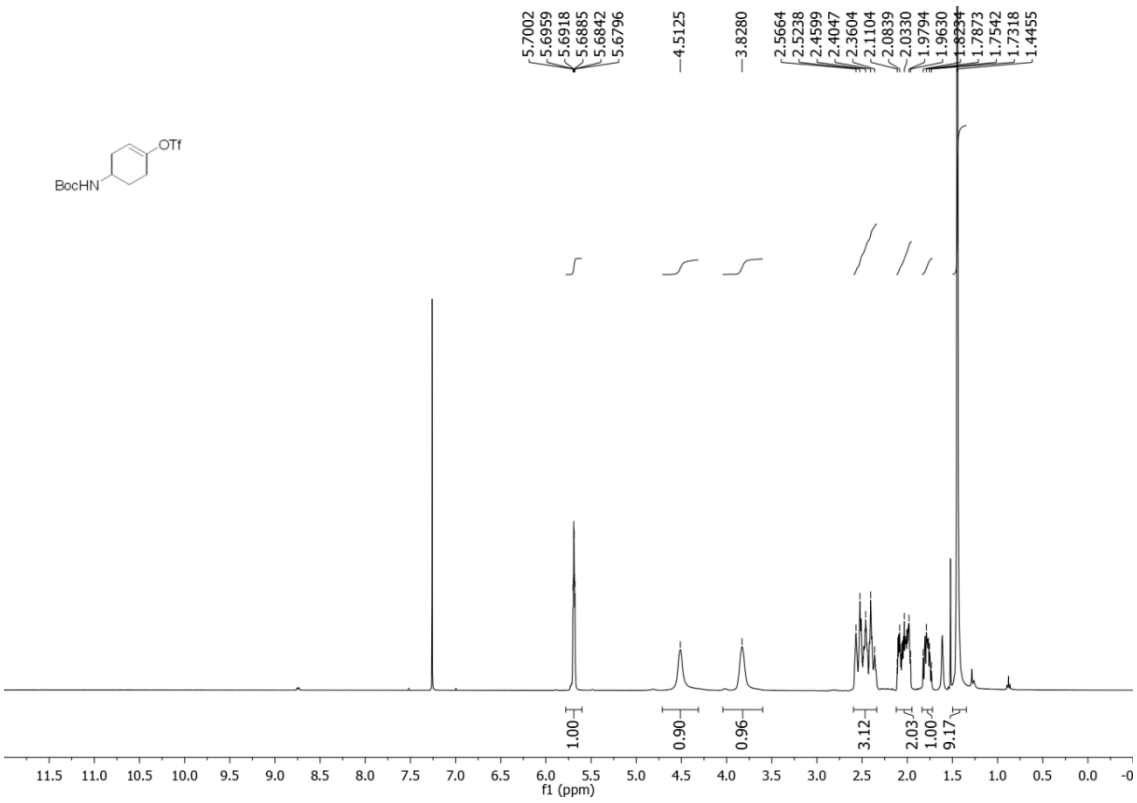


^{19}F-NMR Spectrum:

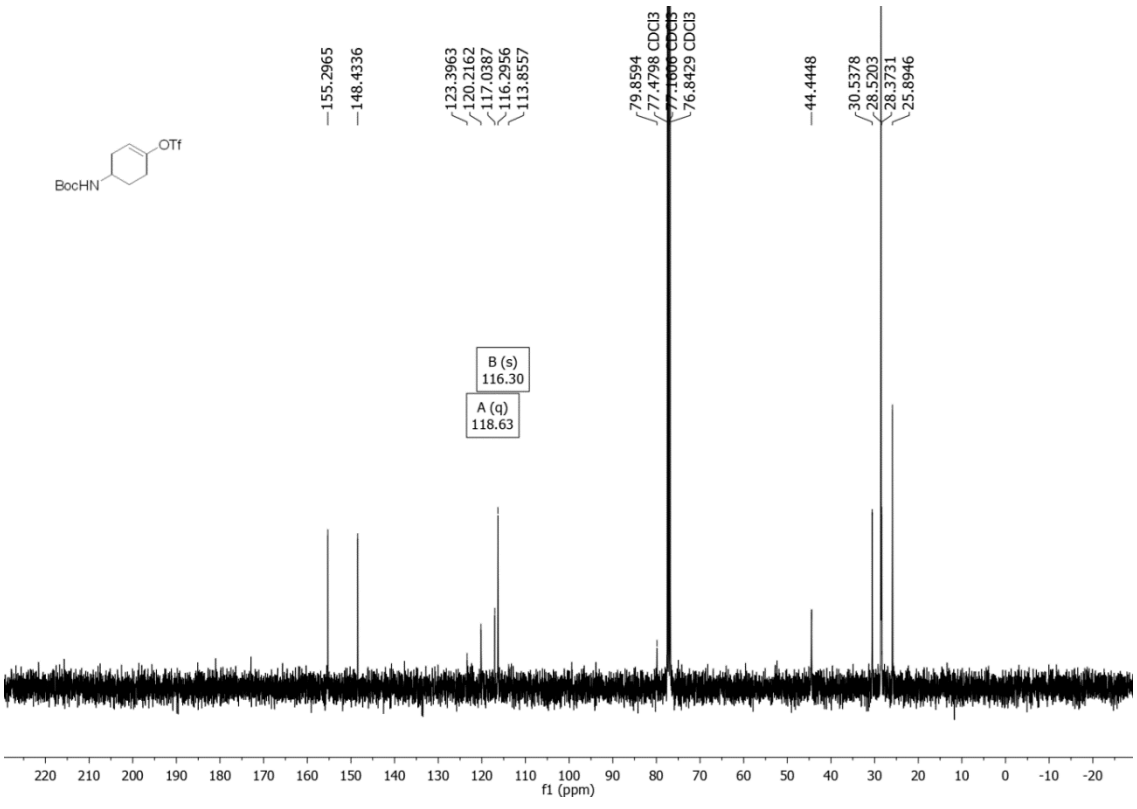


4-((*tert*-Butoxycarbonyl)amino)cyclohex-1-en-1-yl trifluoromethanesulfonate (31g)

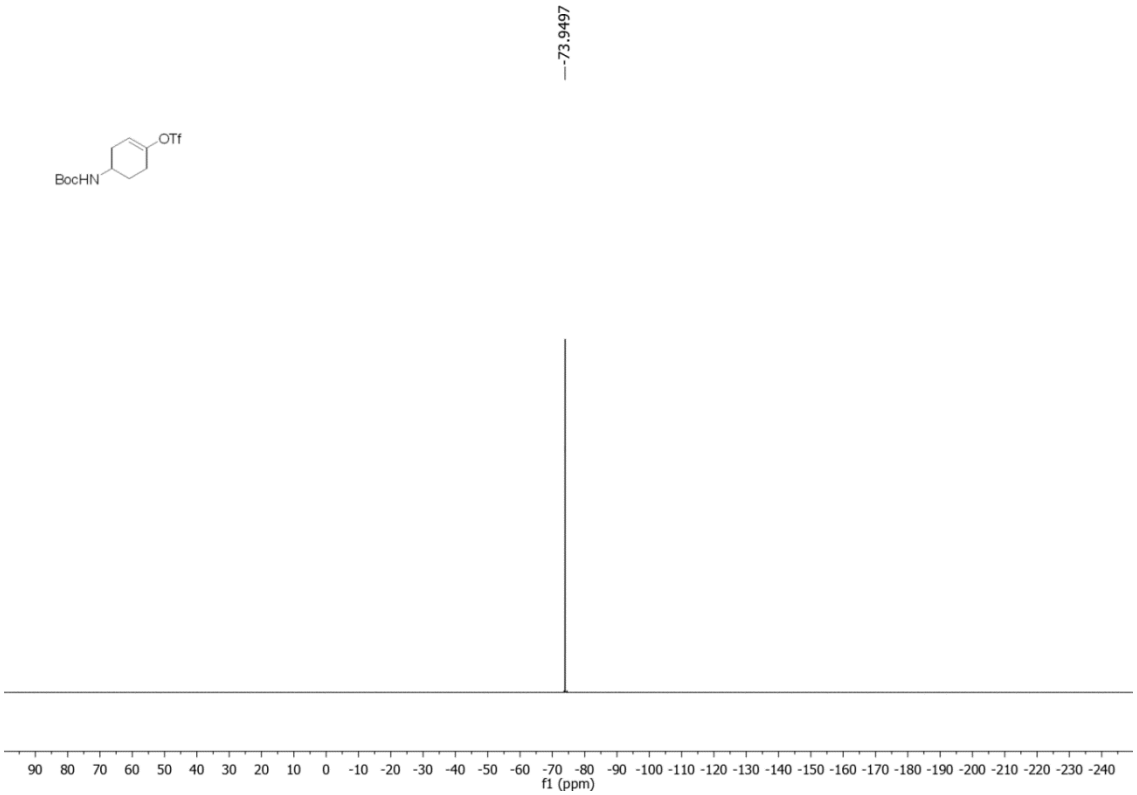
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

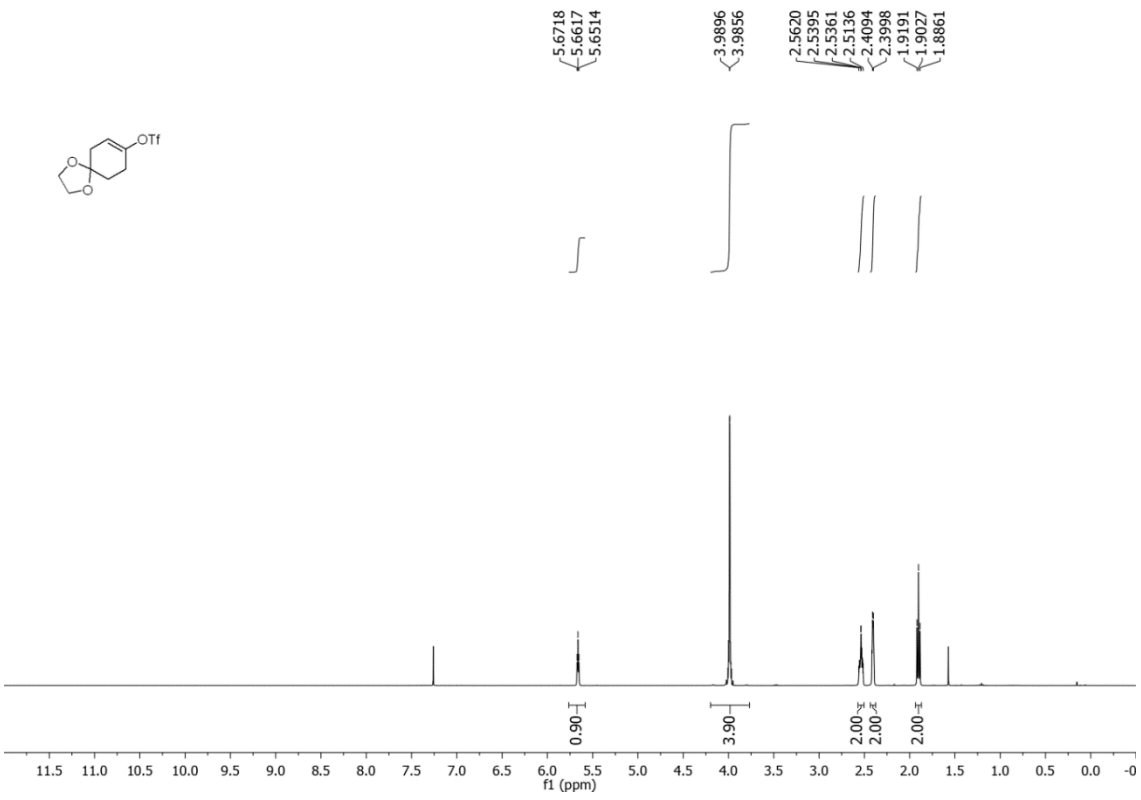


^{19}F-NMR Spectrum:

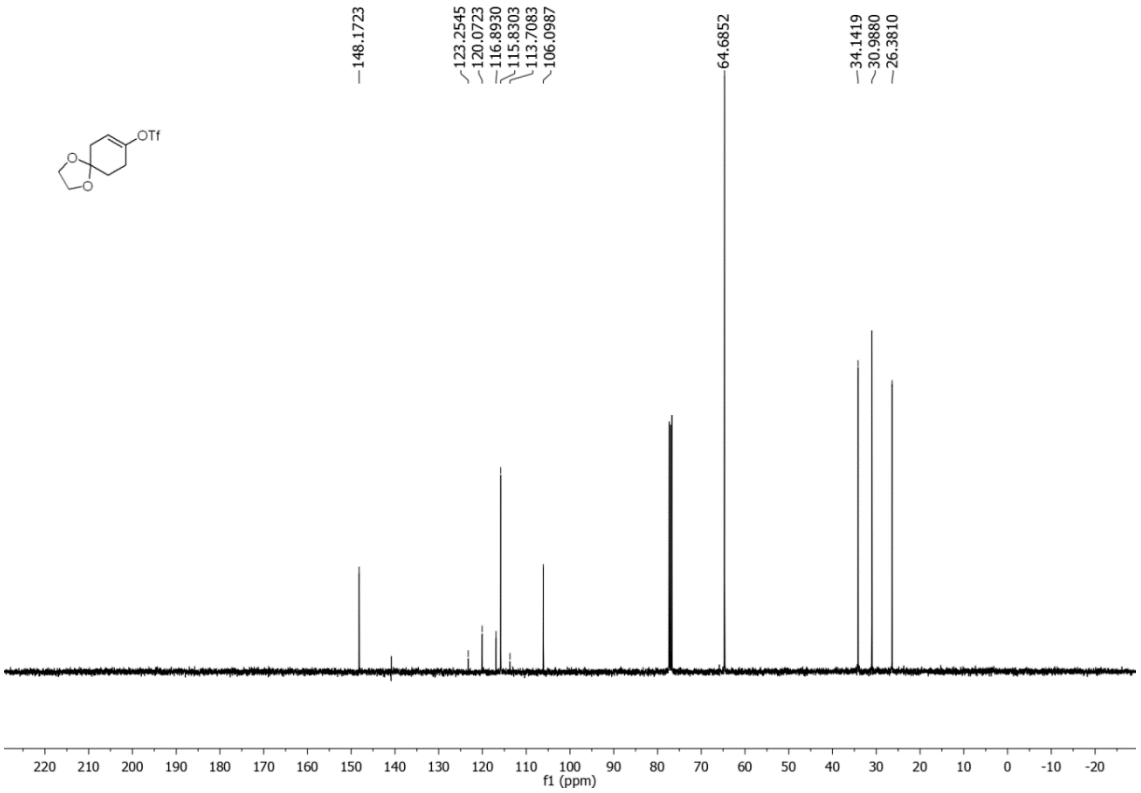


1,4-Dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (31h)

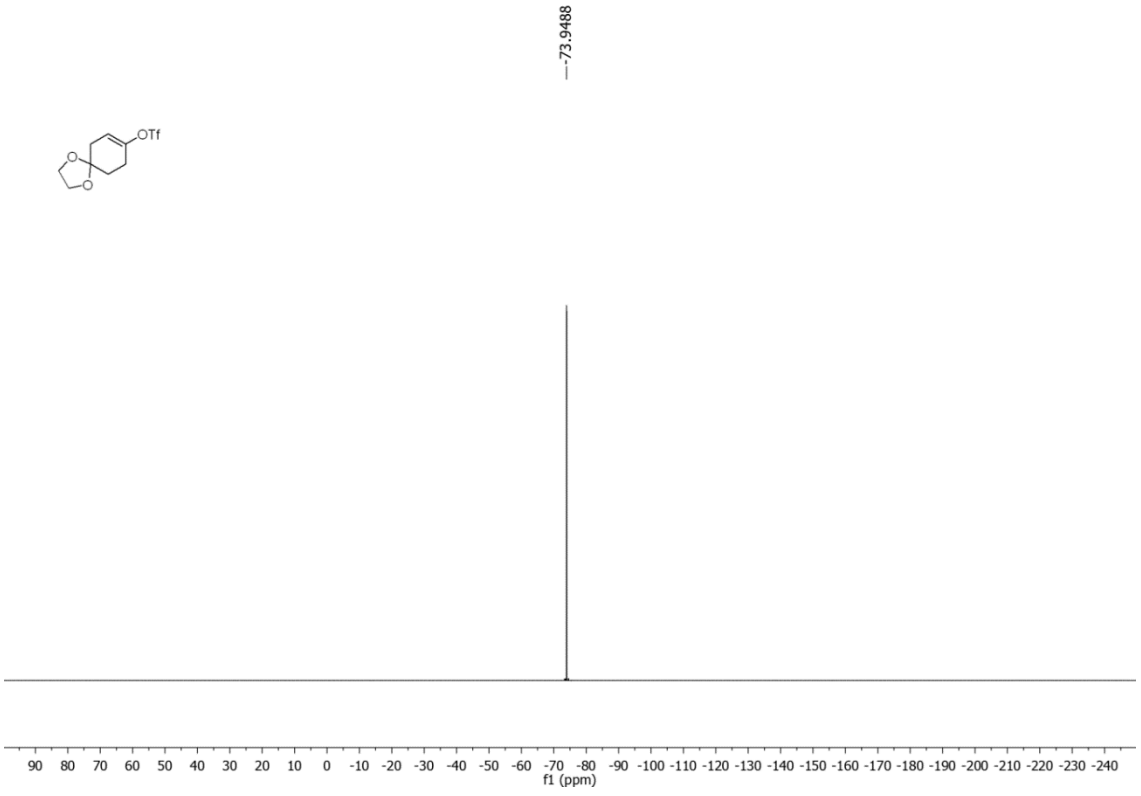
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

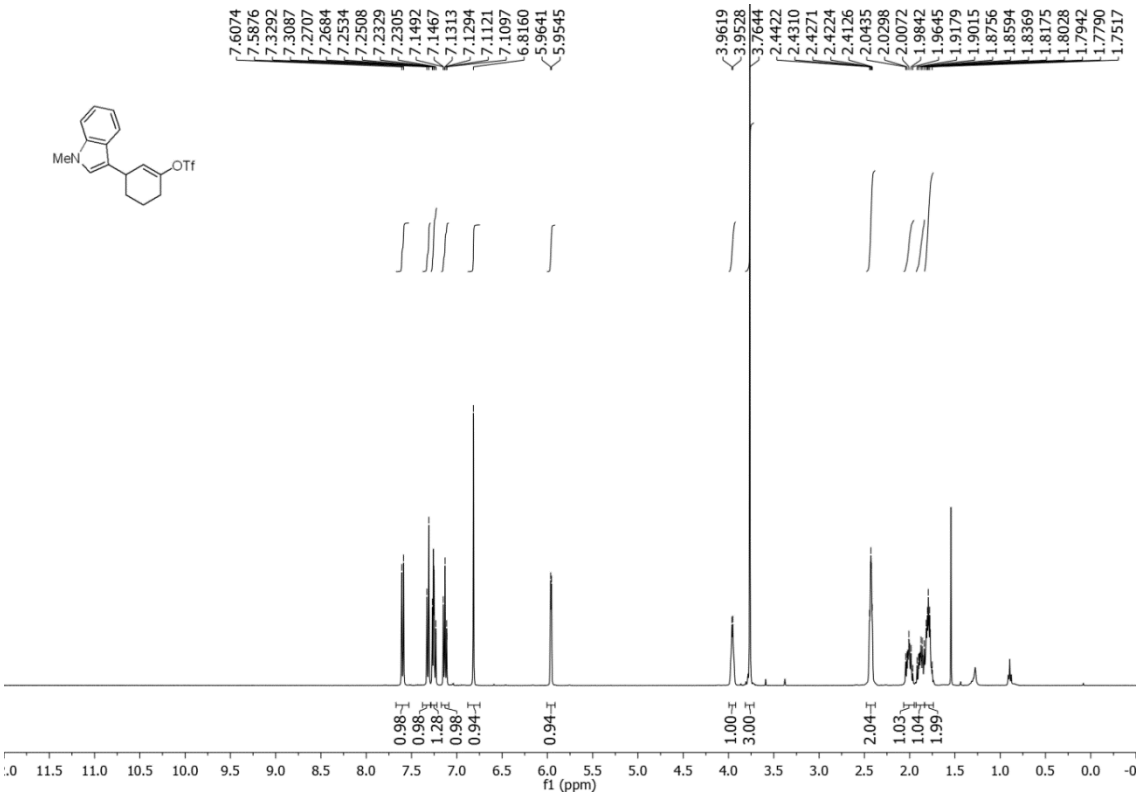


^{19}F-NMR Spectrum:

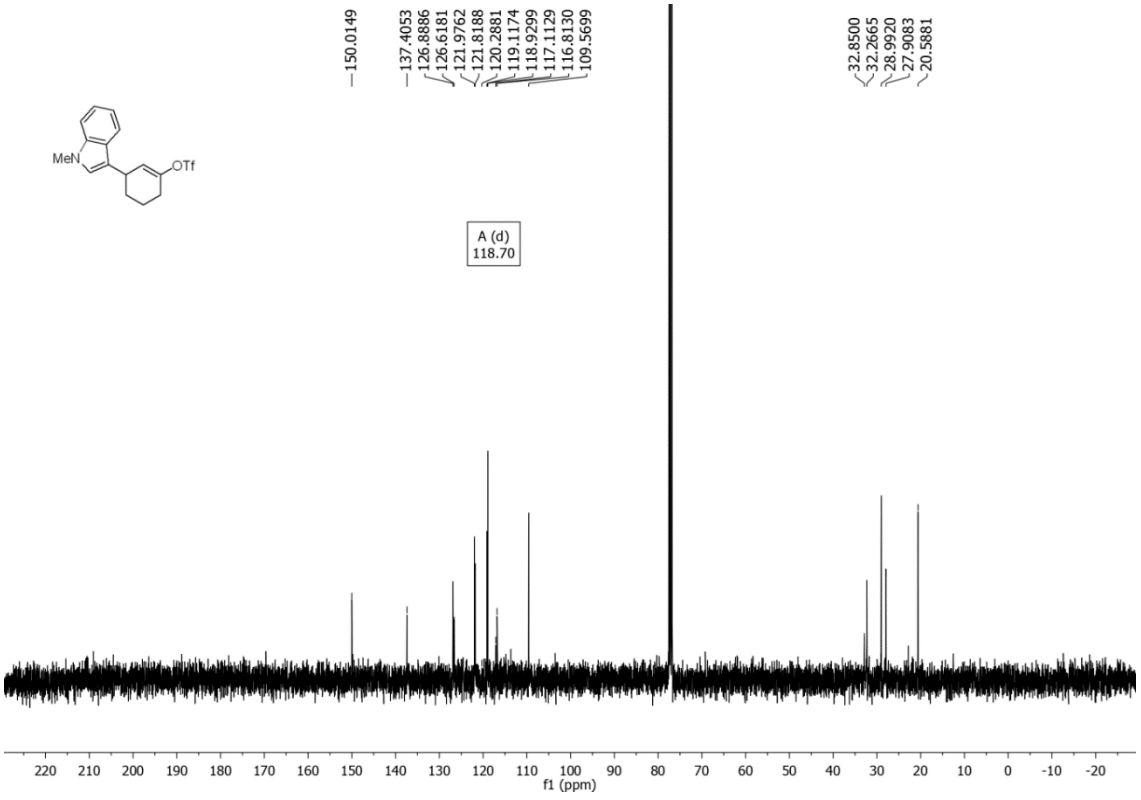


3-(1-Methyl-1*H*-indol-3-yl)cyclohex-1-en-1-yl trifluoromethanesulfonate (31i)

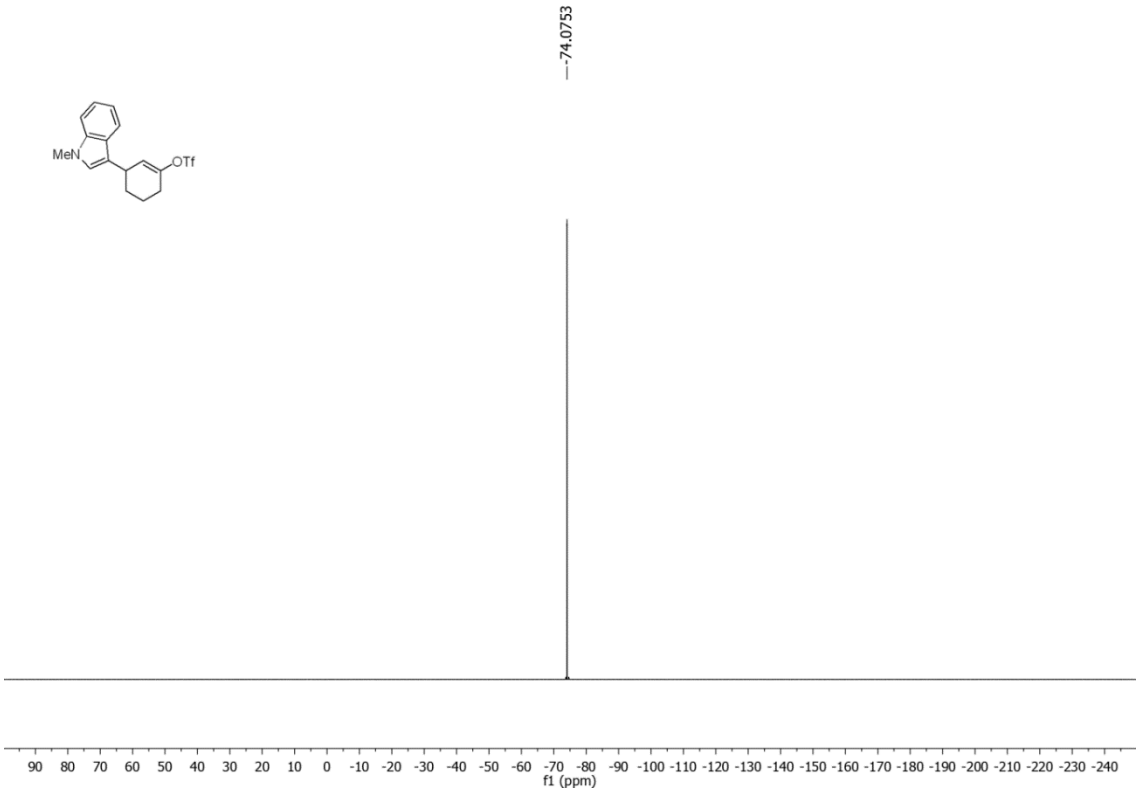
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

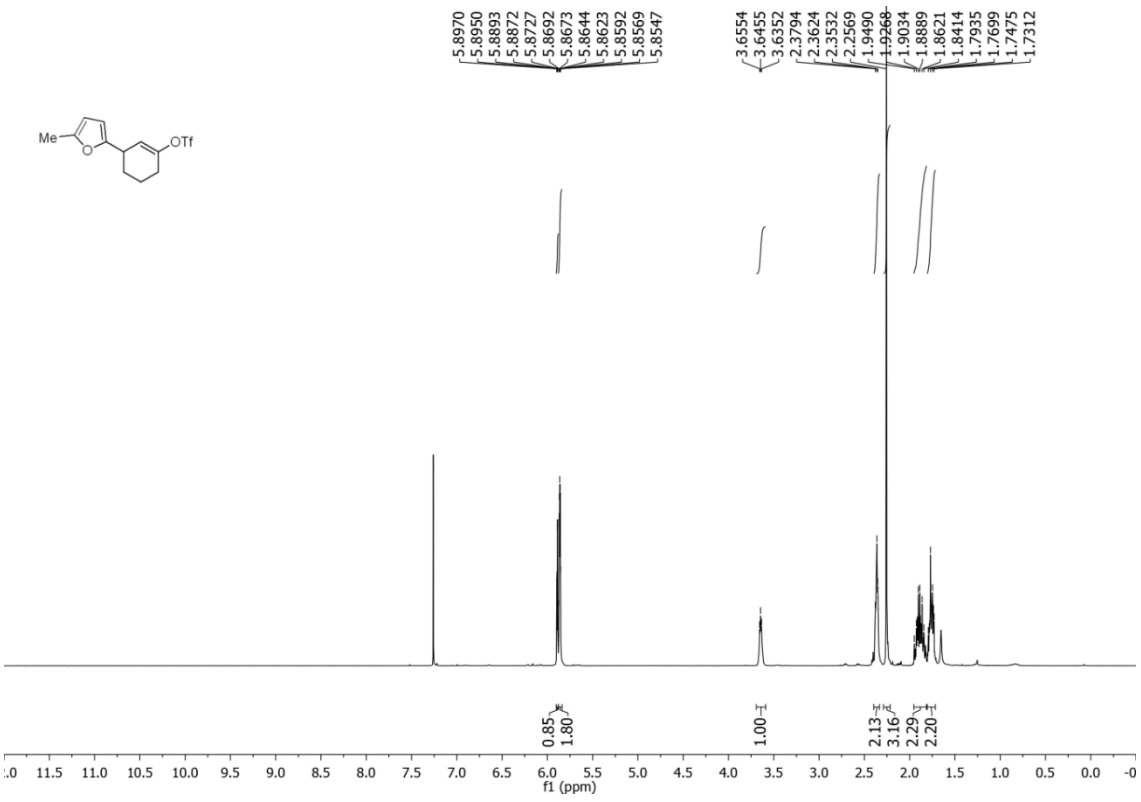


^{19}F-NMR Spectrum:

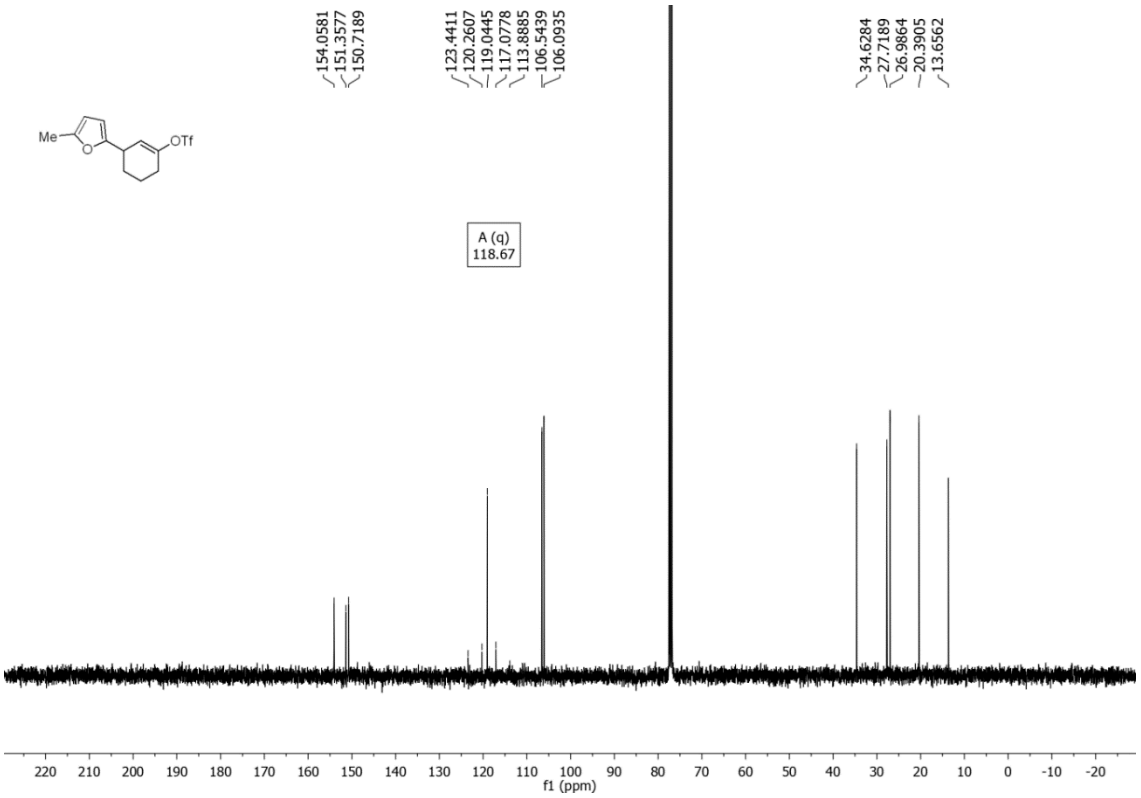


3-(5-Methylfuran-2-yl)cyclohex-1-en-1-yl trifluoromethanesulfonate (31k)

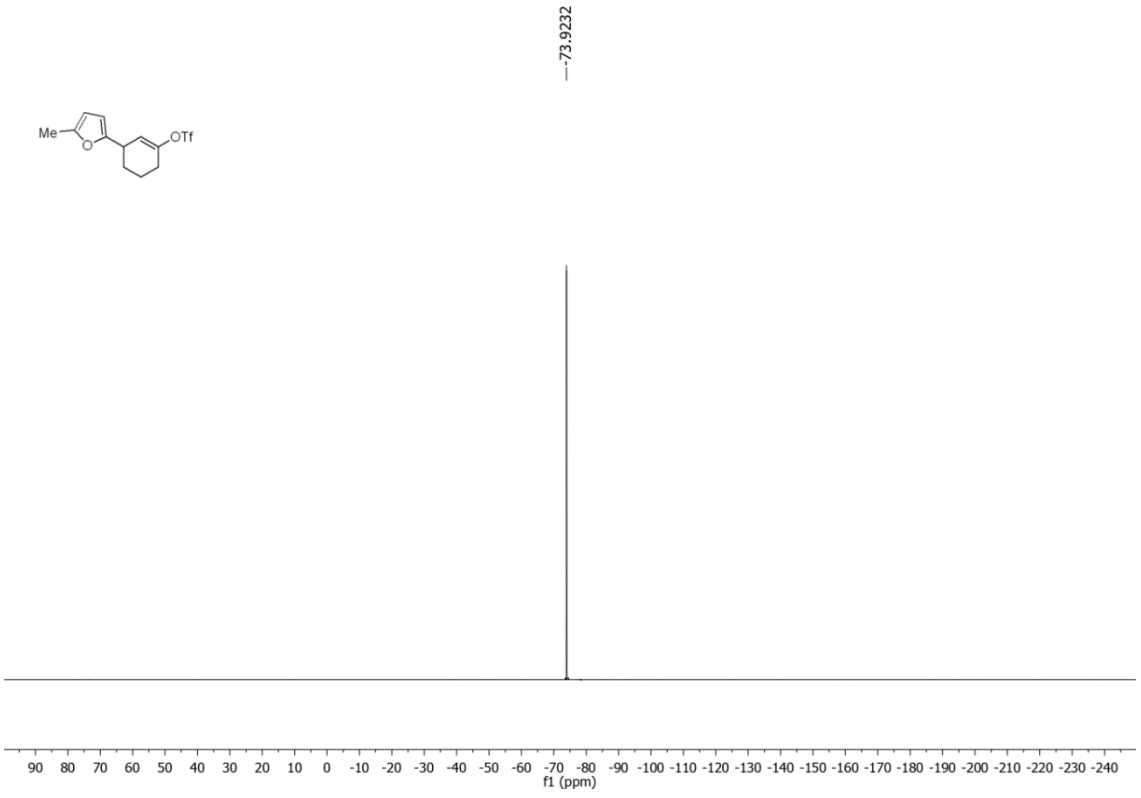
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

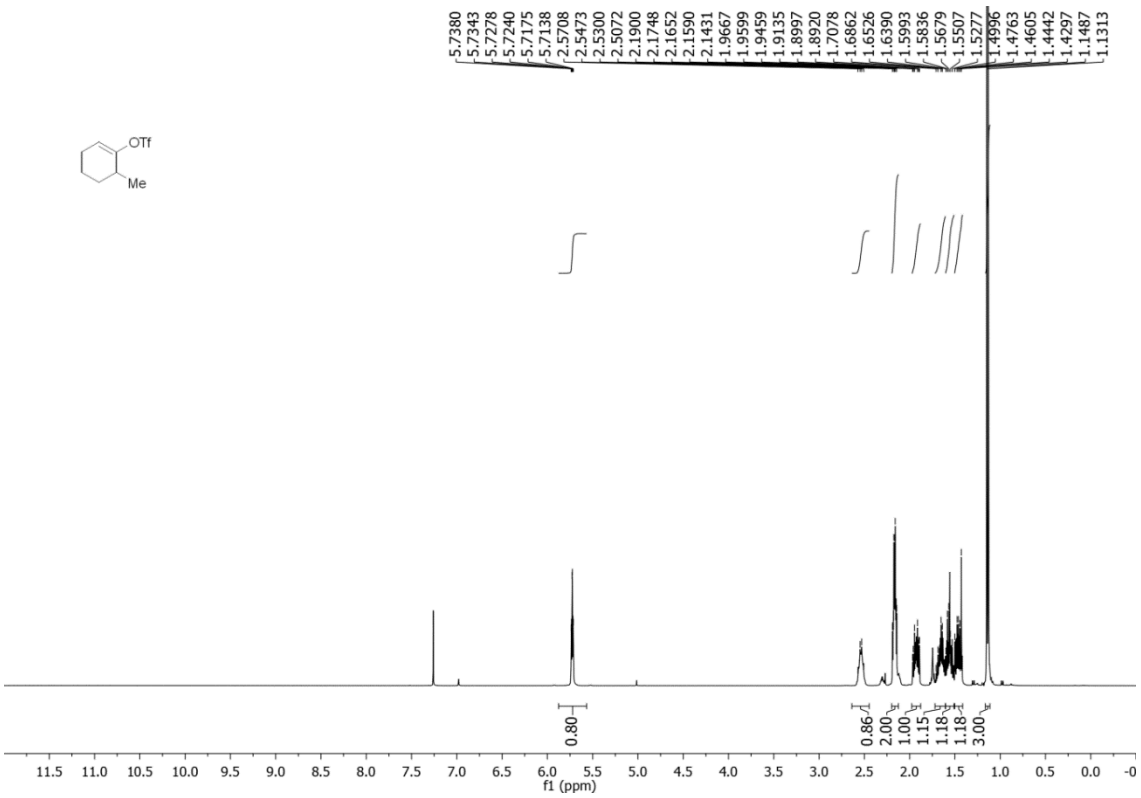


^{19}F-NMR Spectrum:

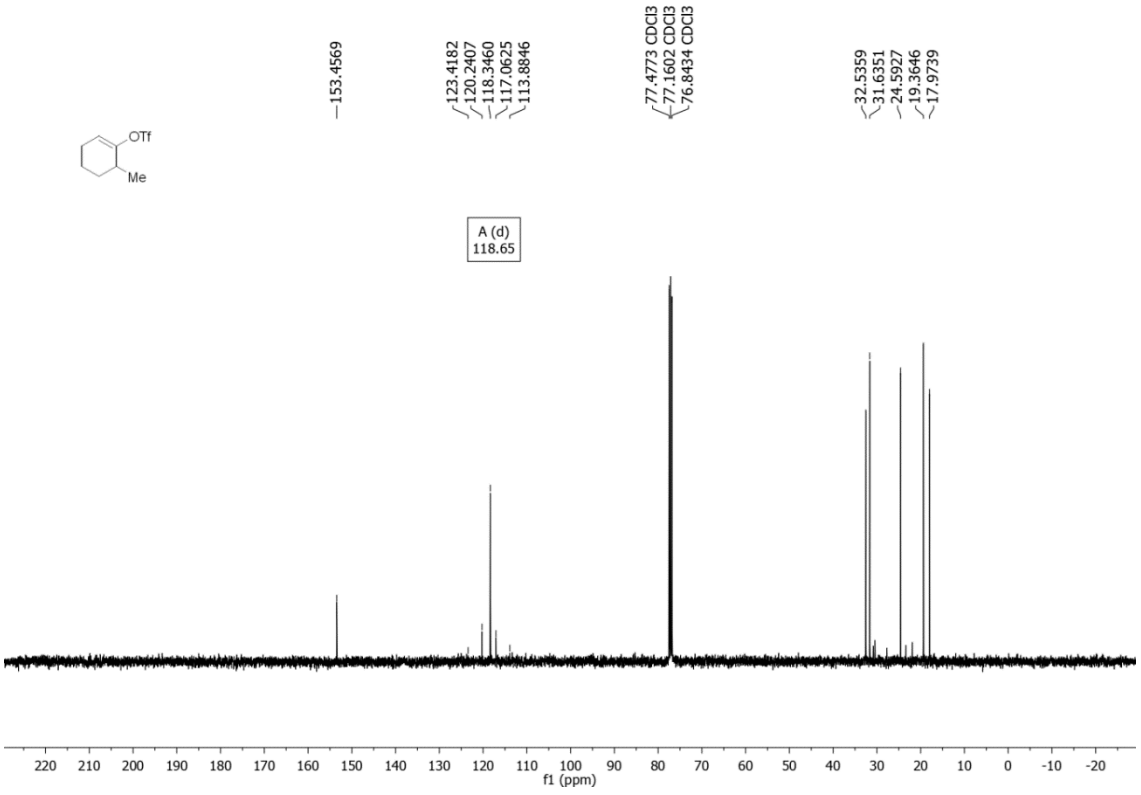


6-Methylcyclohex-1-en-1-yl trifluoromethanesulfonate (31l)

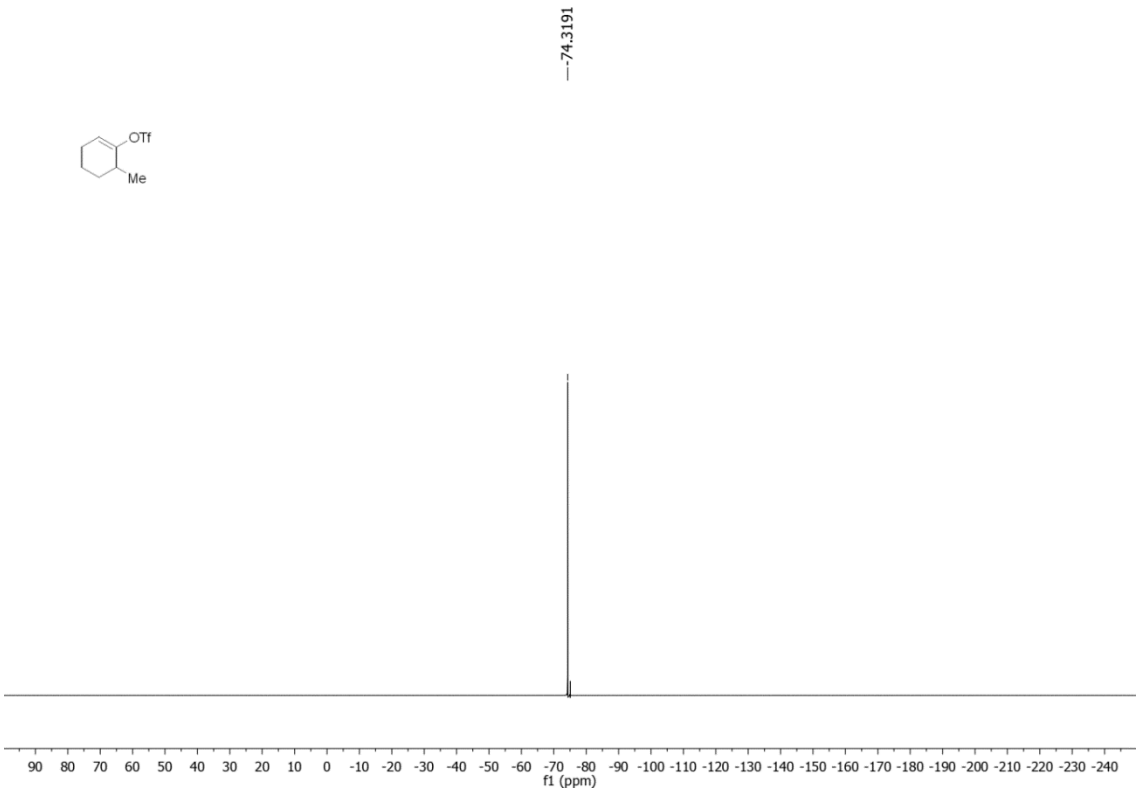
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

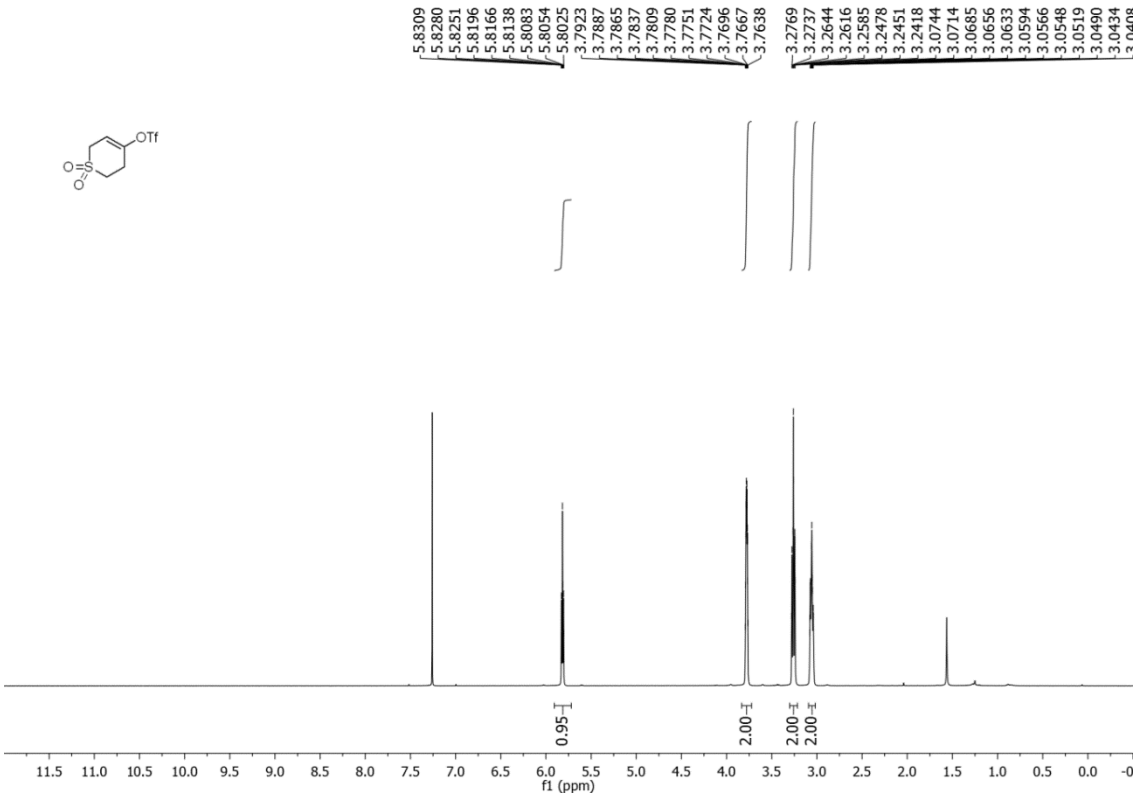


^{19}F-NMR Spectrum:

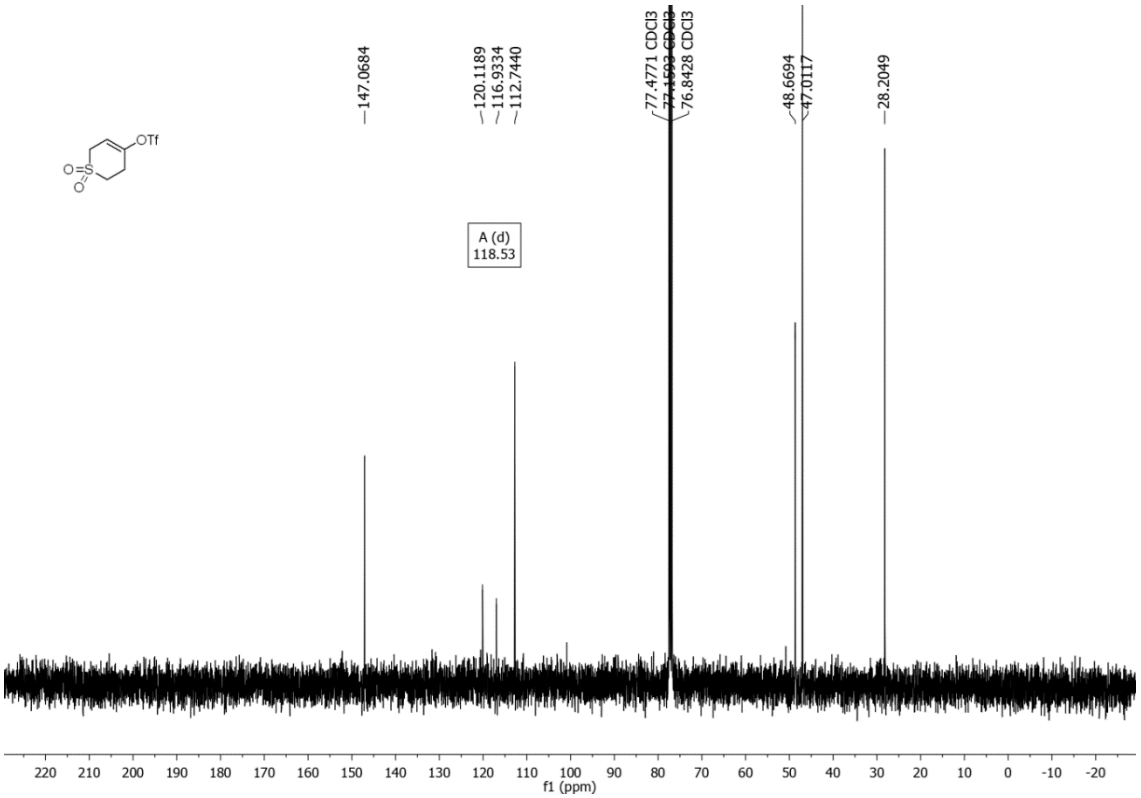


1,1-Dioxido-3,6-dihydro-2*H*-thiopyran-4-yl trifluoromethanesulfonate (31m)

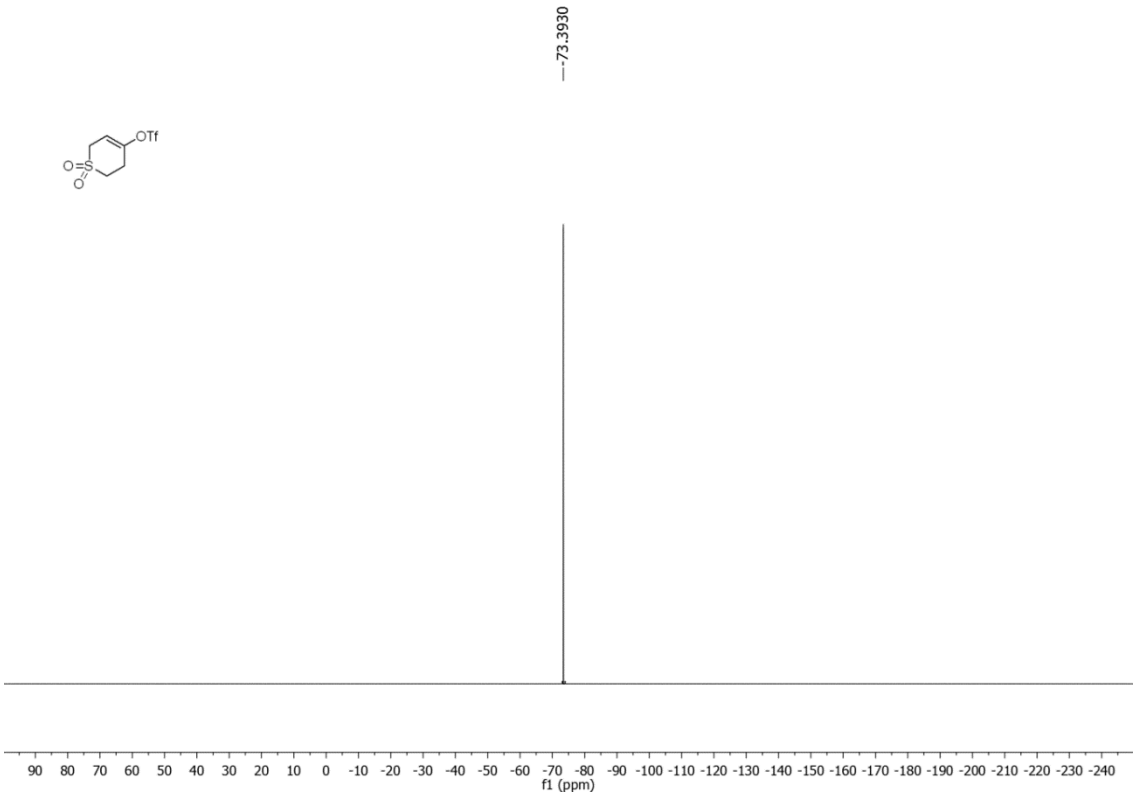
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

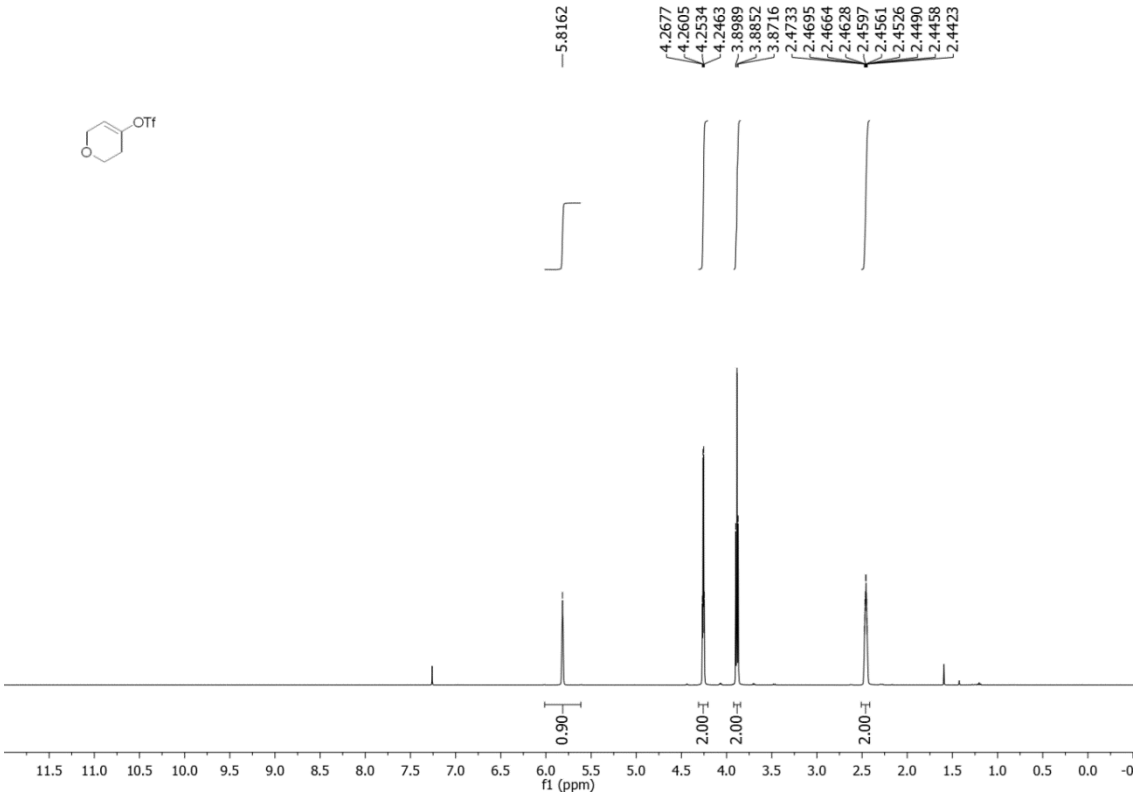


^{19}F-NMR Spectrum:

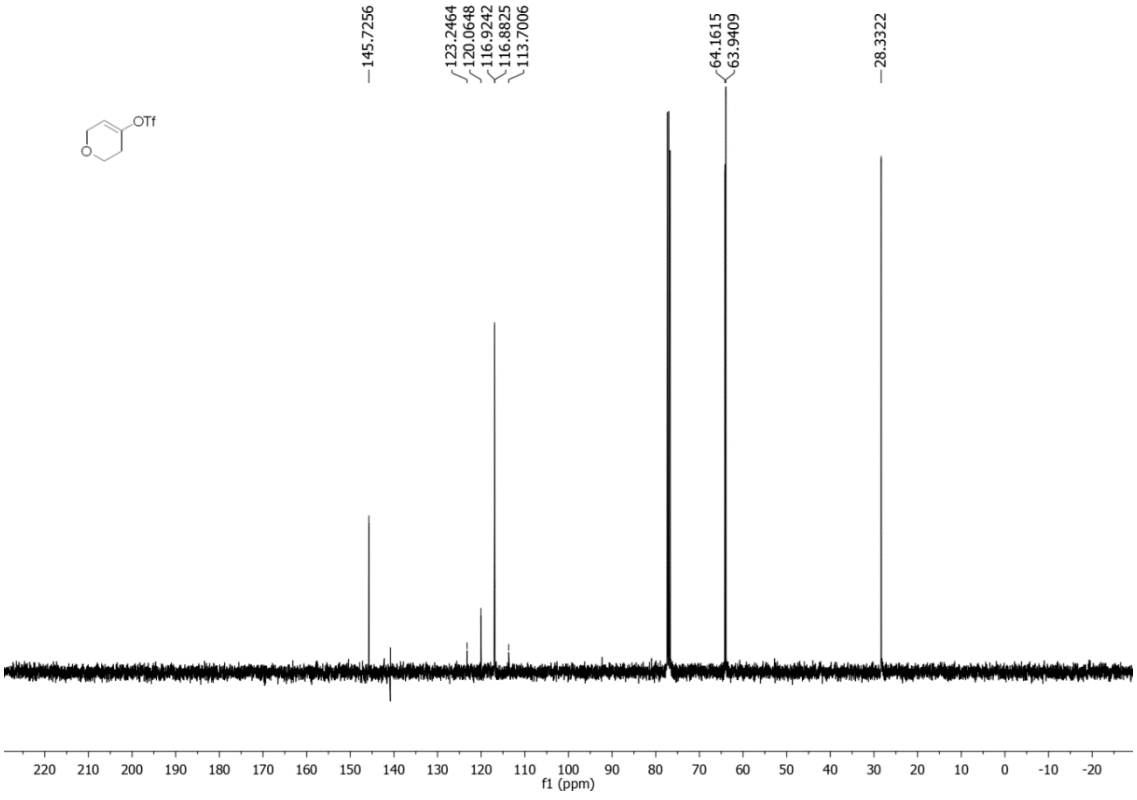


3,6-Dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (31n)

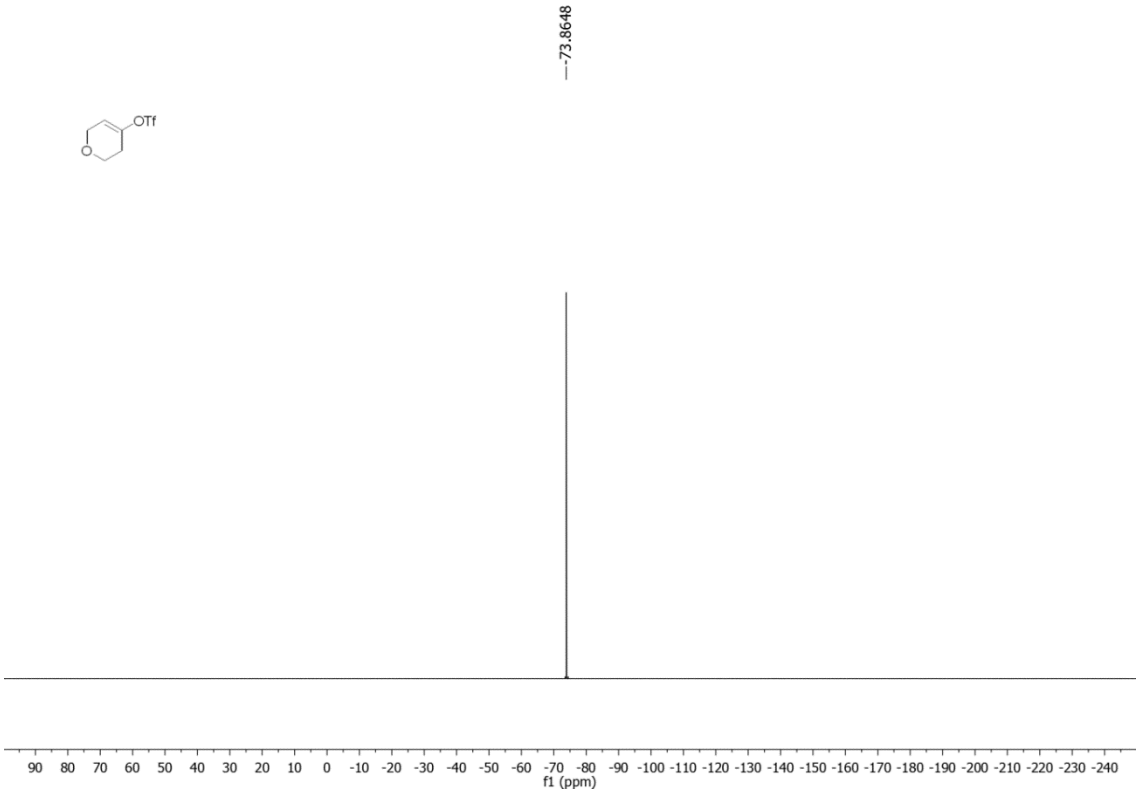
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

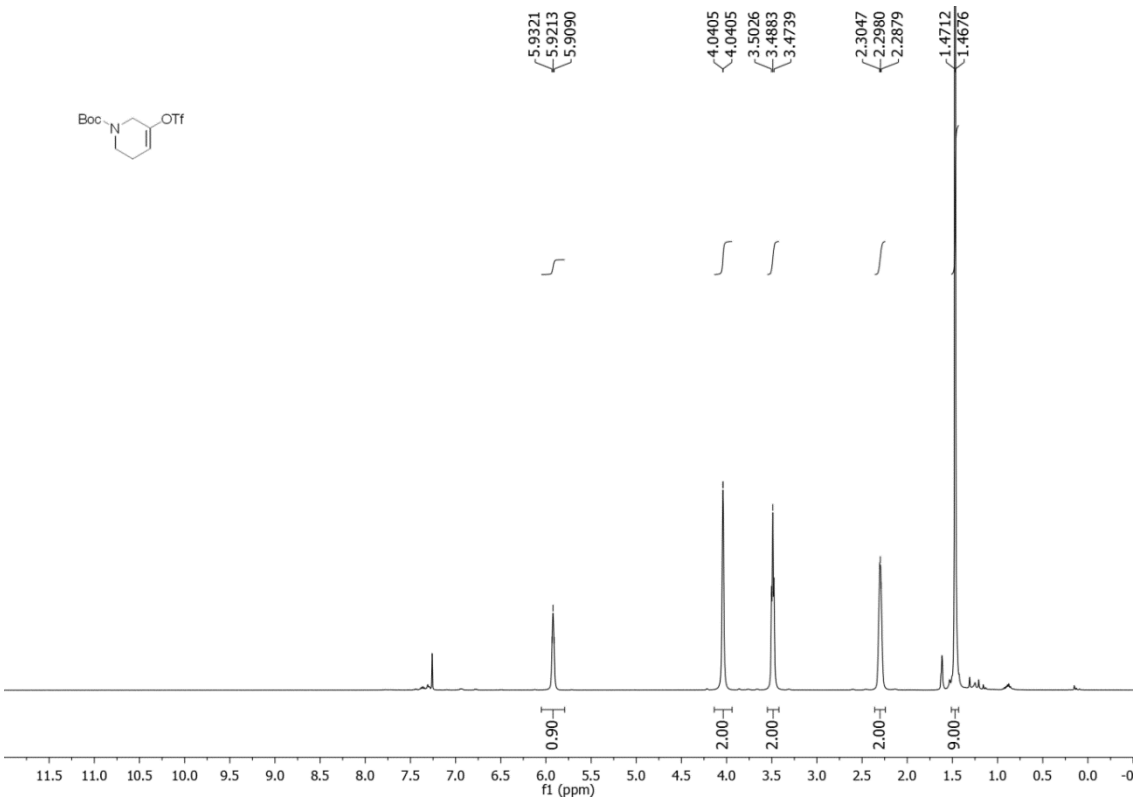


^{19}F-NMR Spectrum:

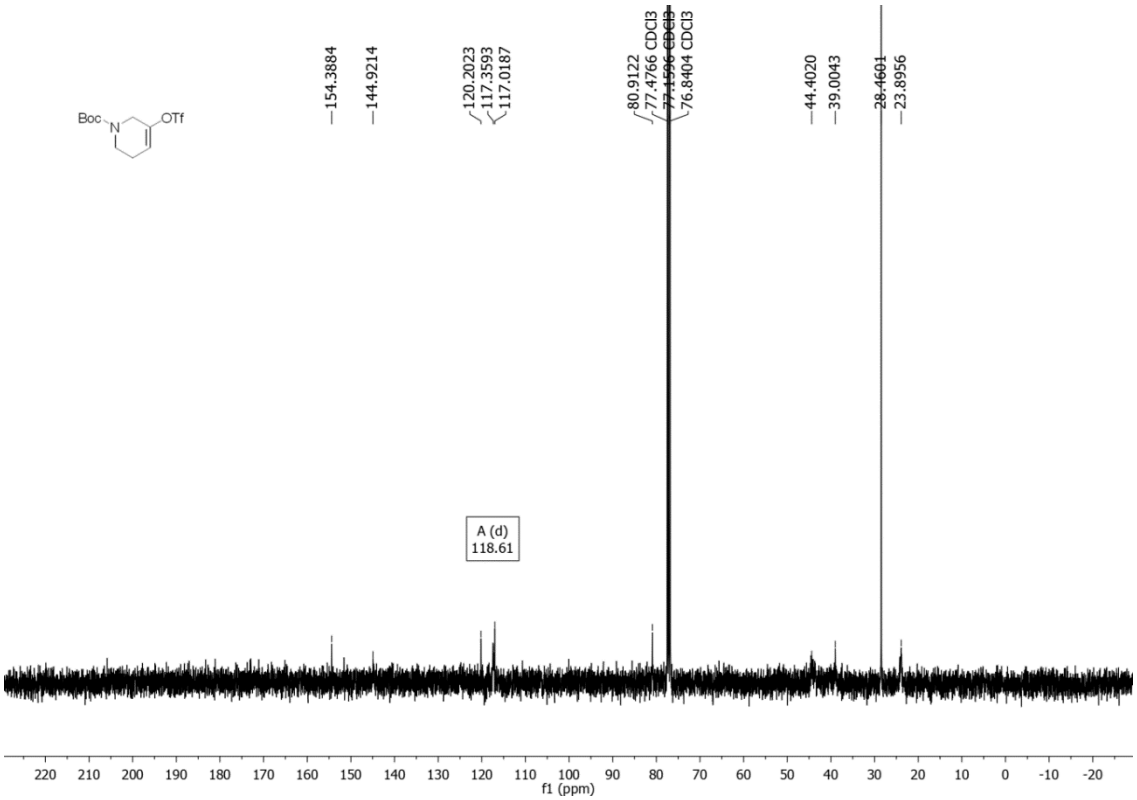


tert-Butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (31o)

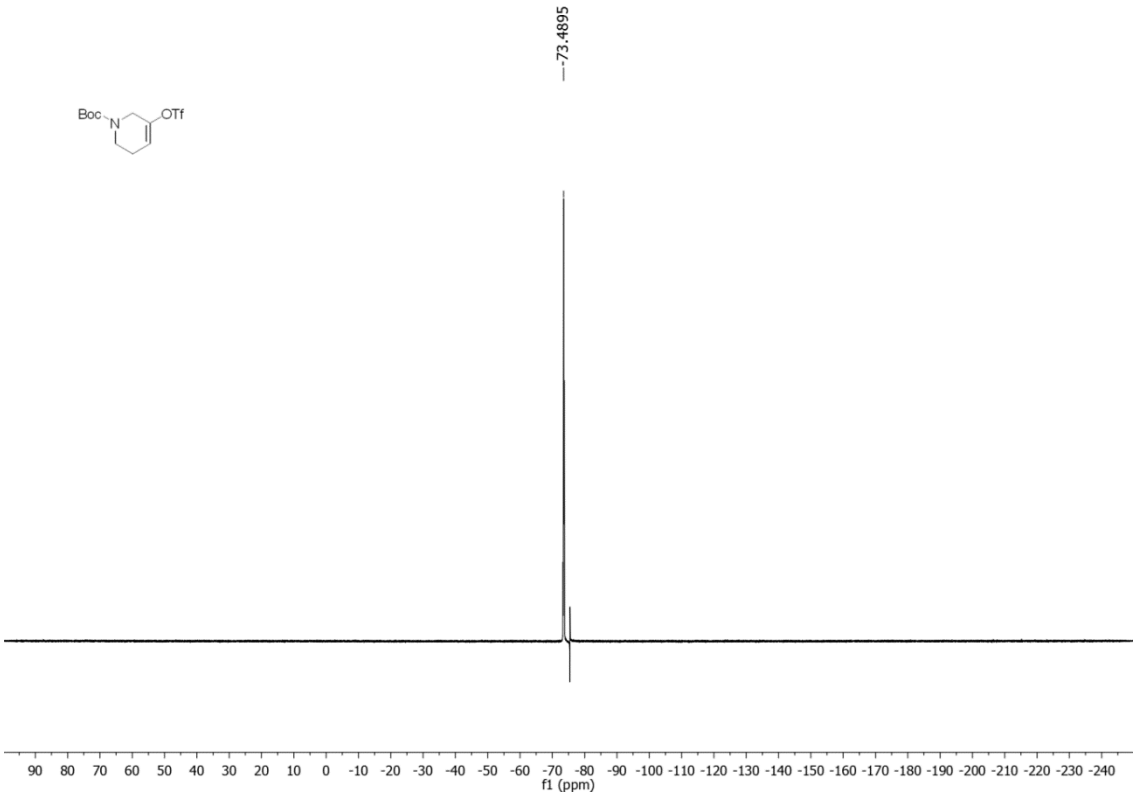
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

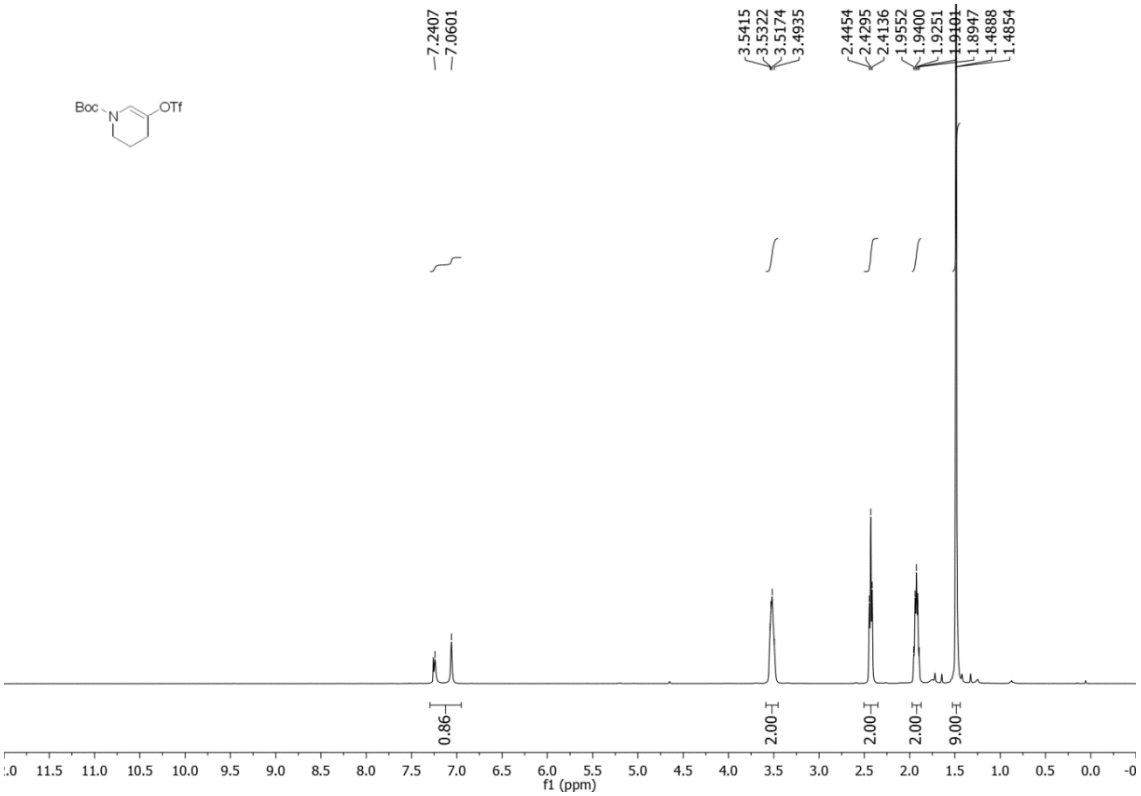


^{19}F-NMR Spectrum:

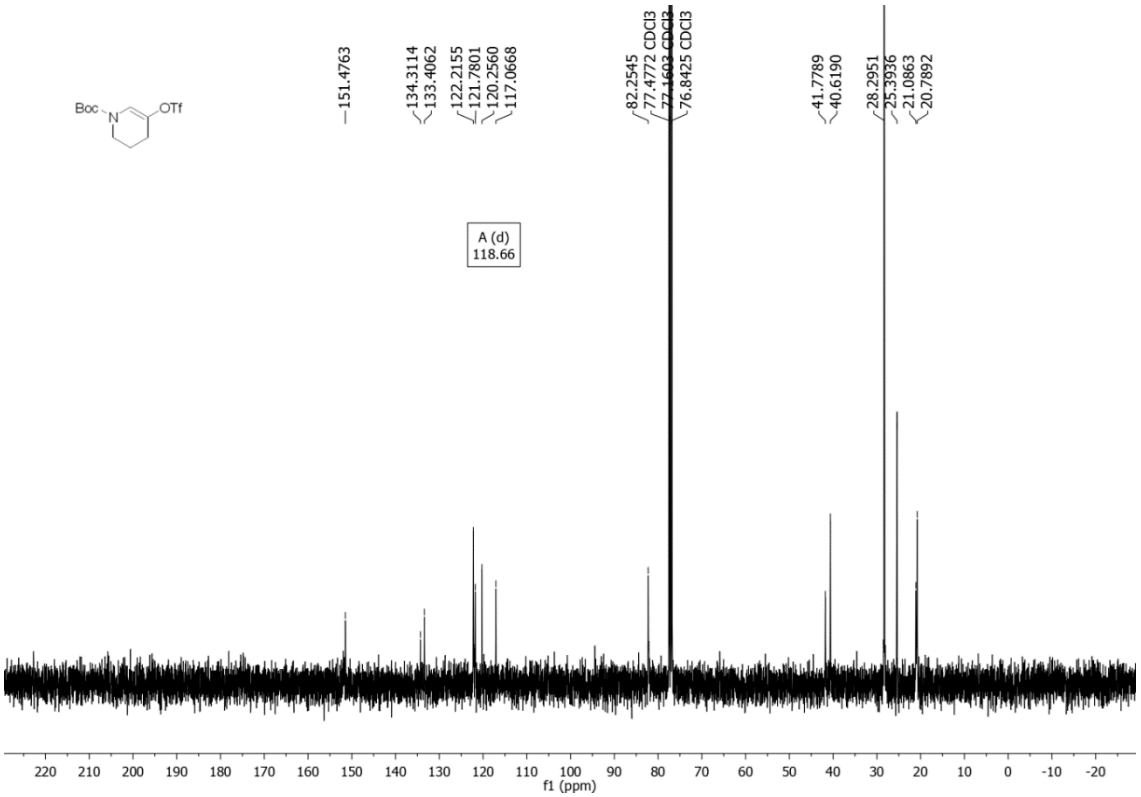


***tert*-Butyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydropyridine-1(*2H*)-carboxylate (31o')**

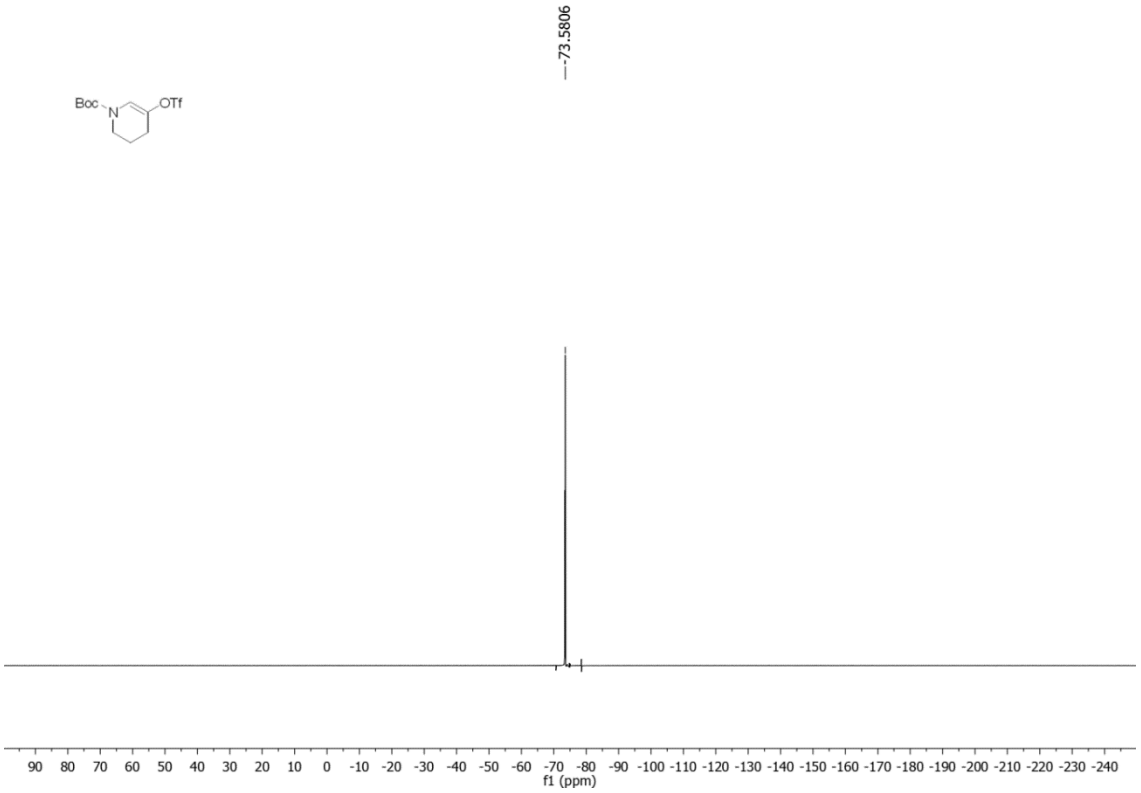
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

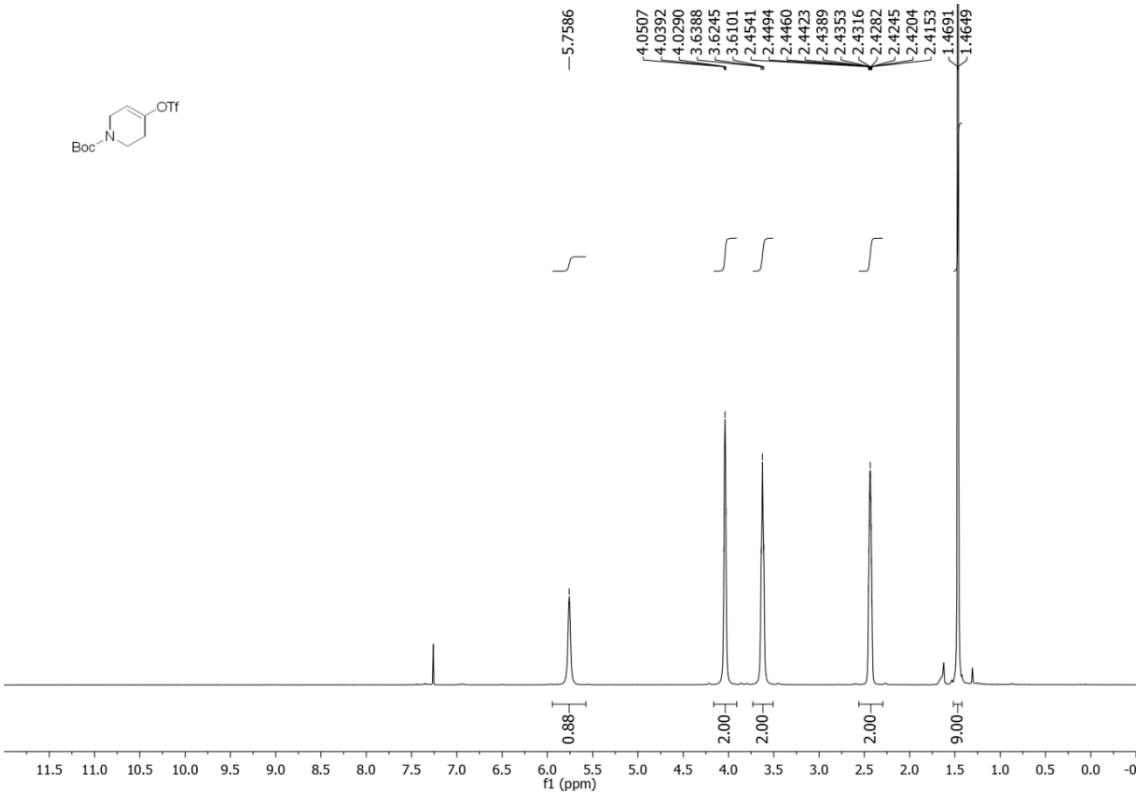


^{19}F-NMR Spectrum:

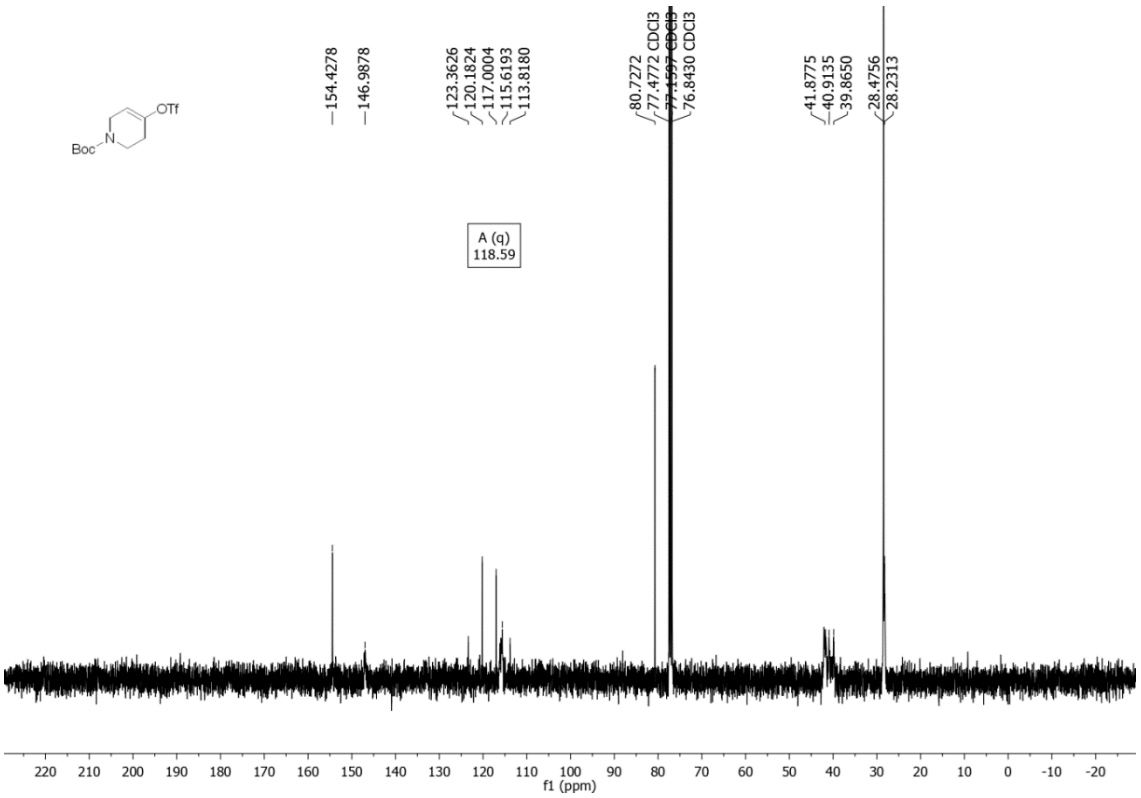


tert-Butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (31p)

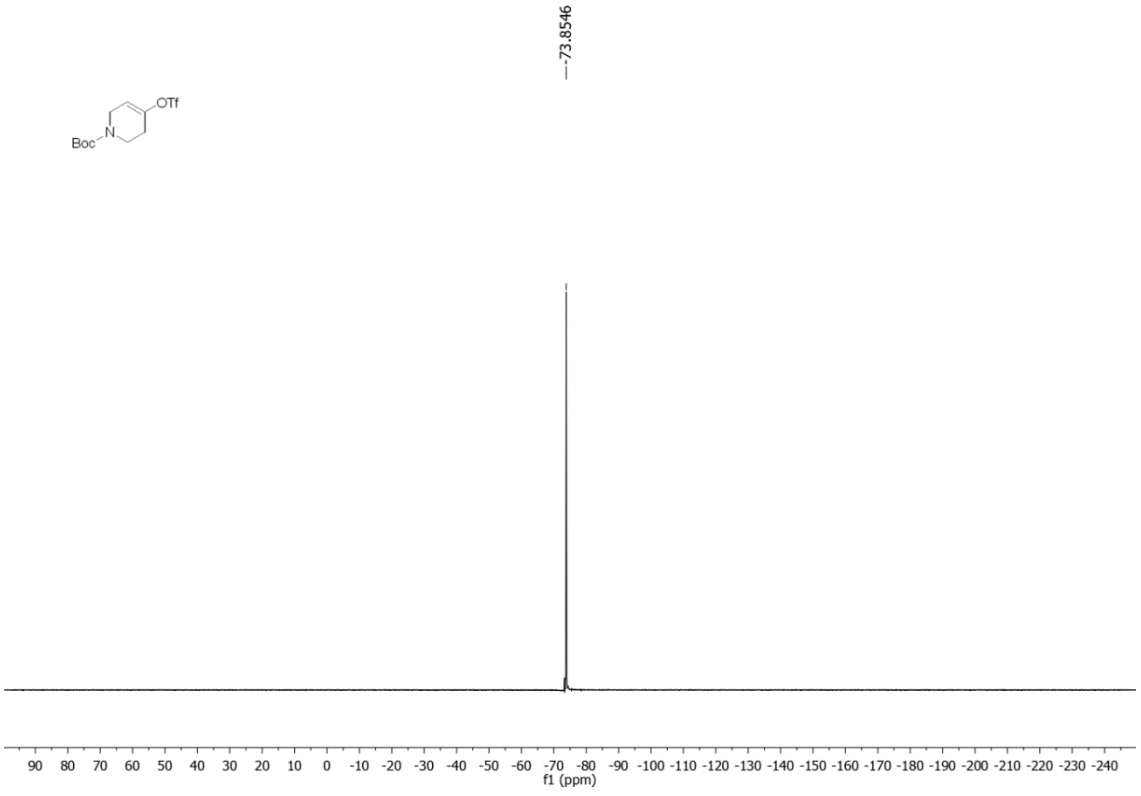
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

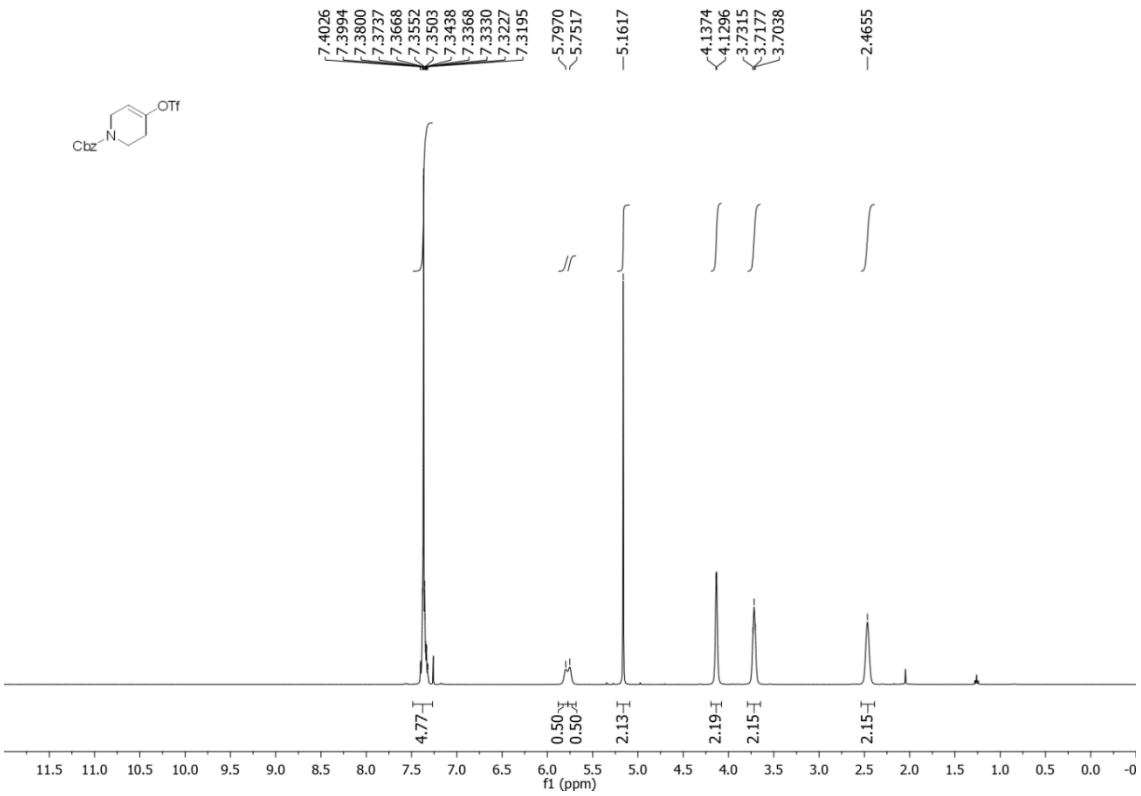


^{19}F-NMR Spectrum:

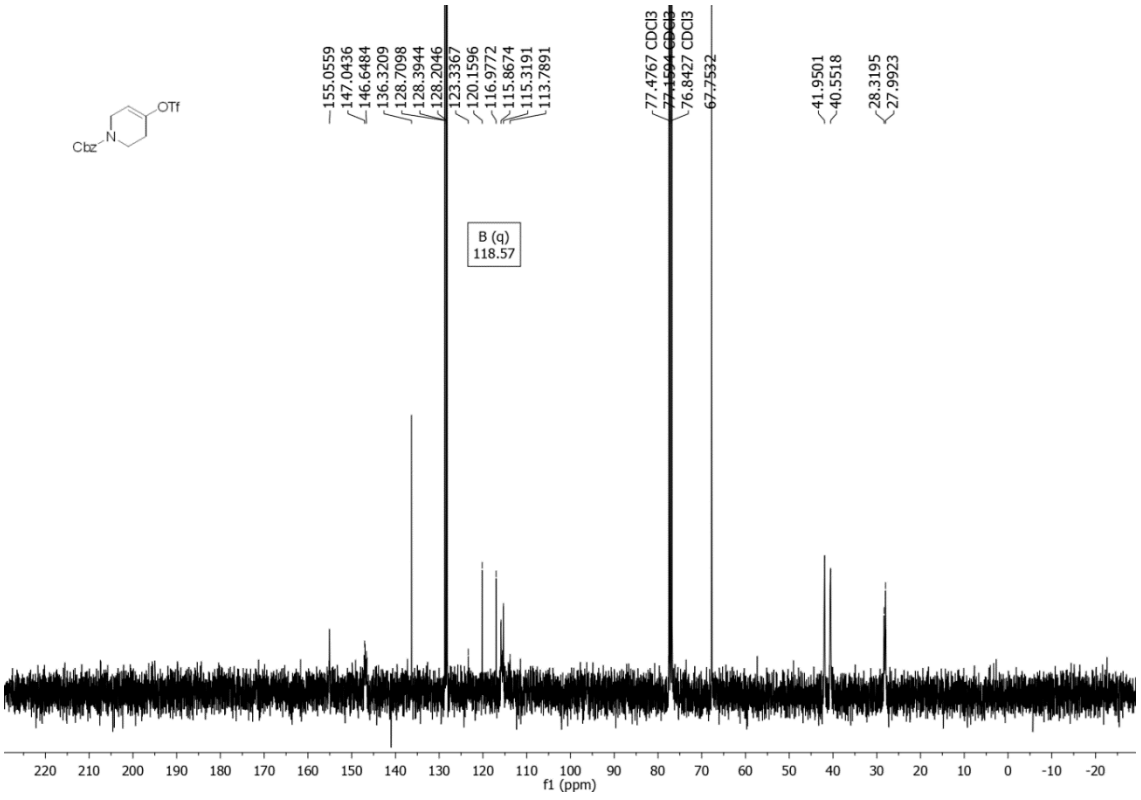


1-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (31q)

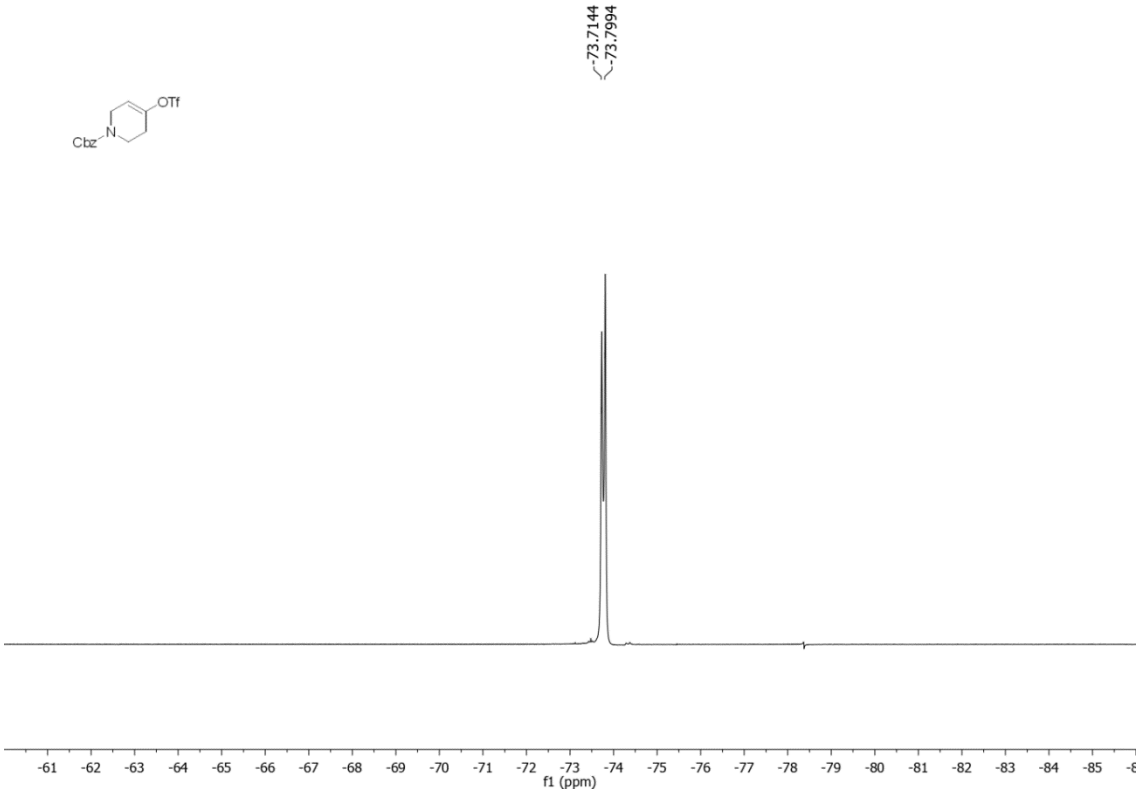
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

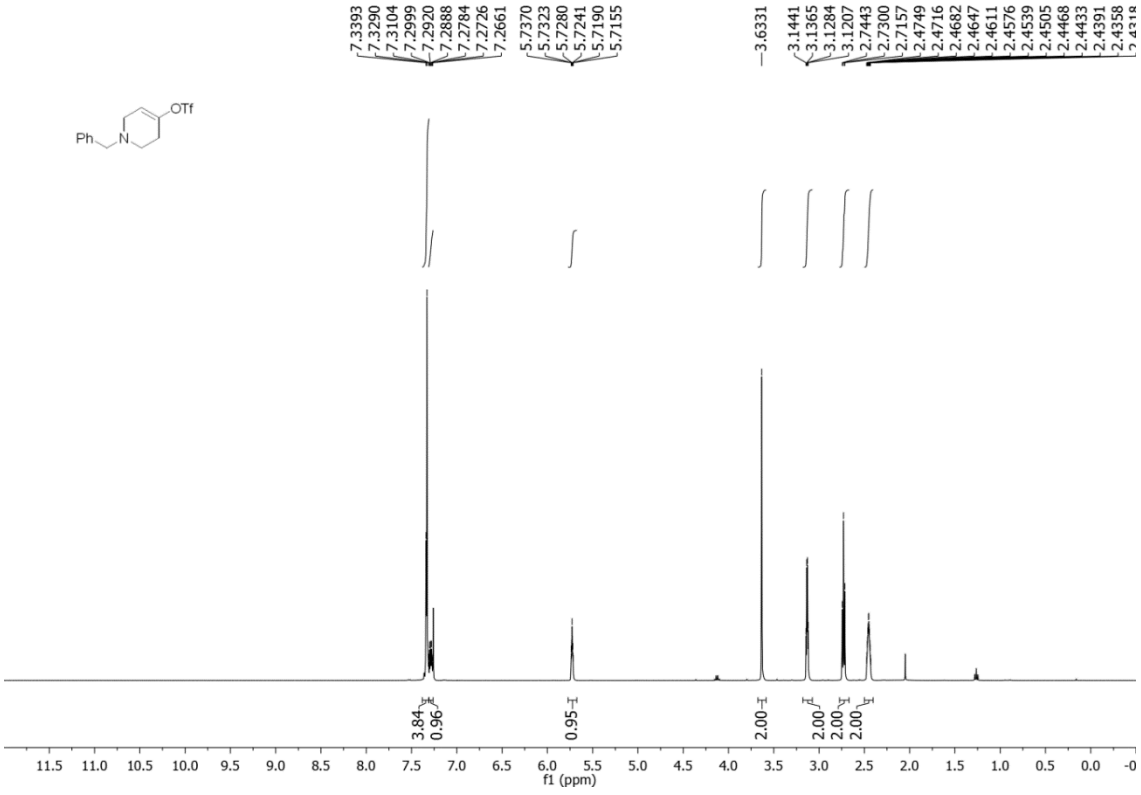


^{19}F-NMR Spectrum:

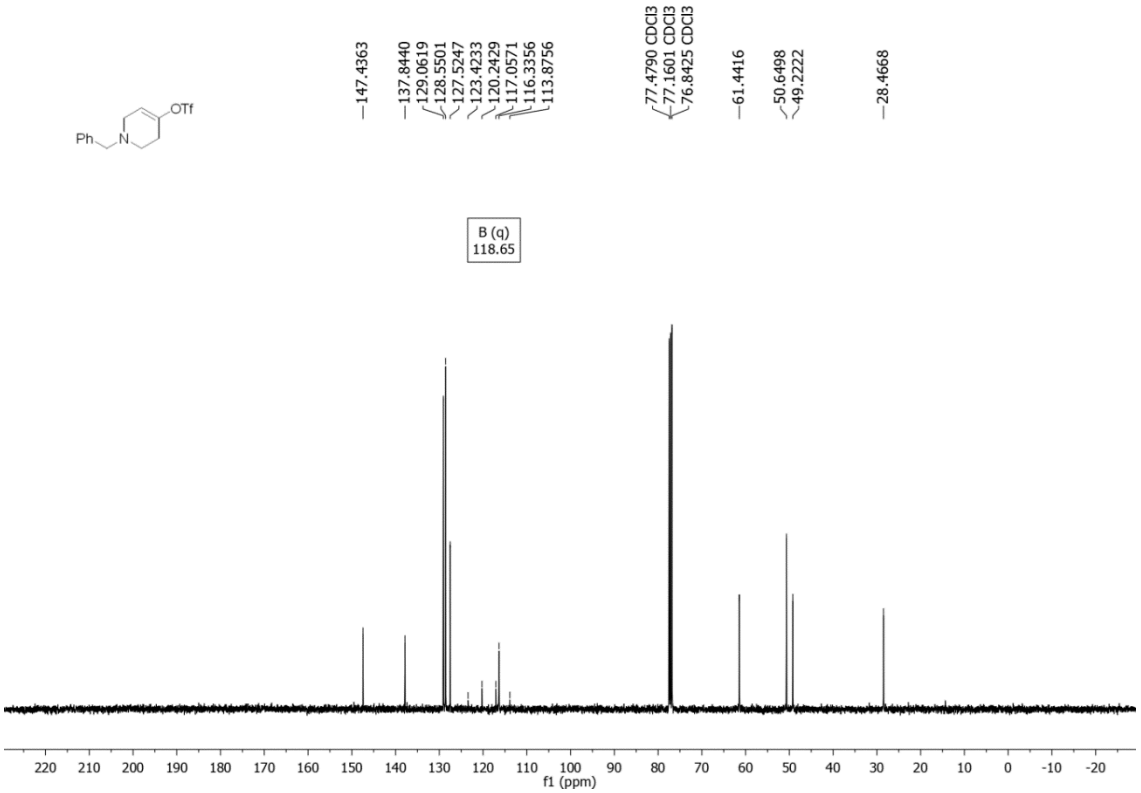


1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (31r)

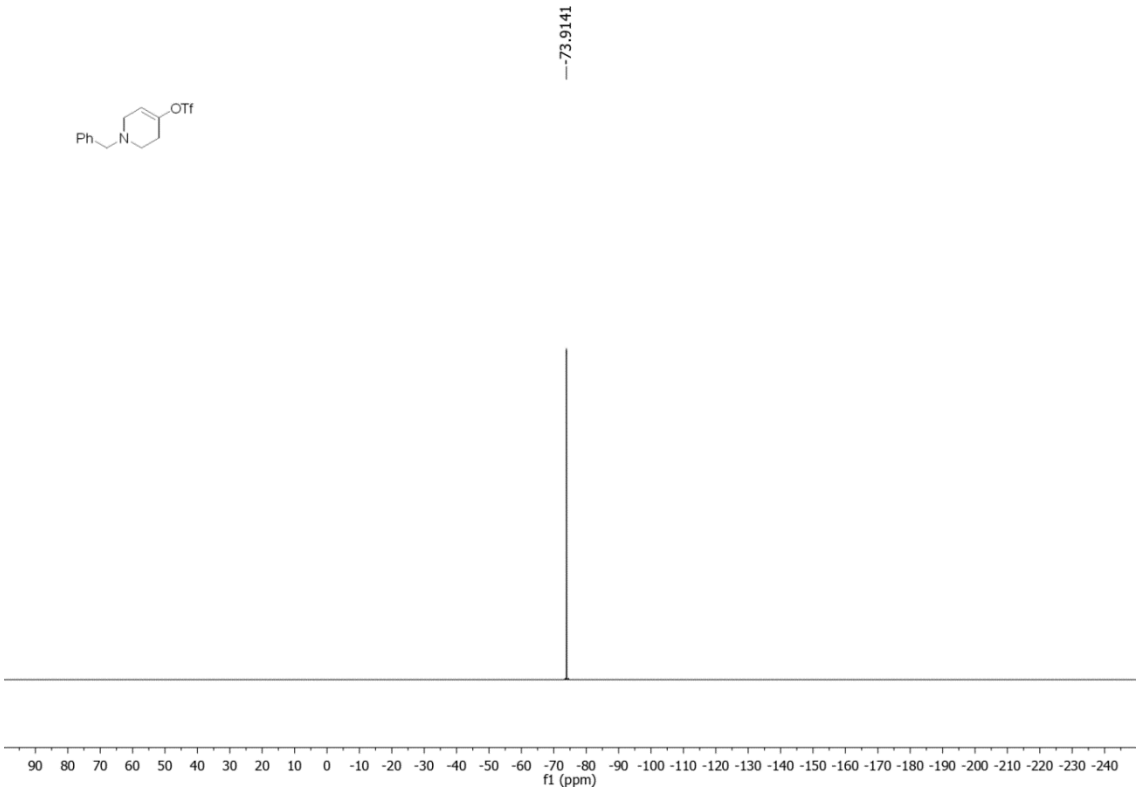
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

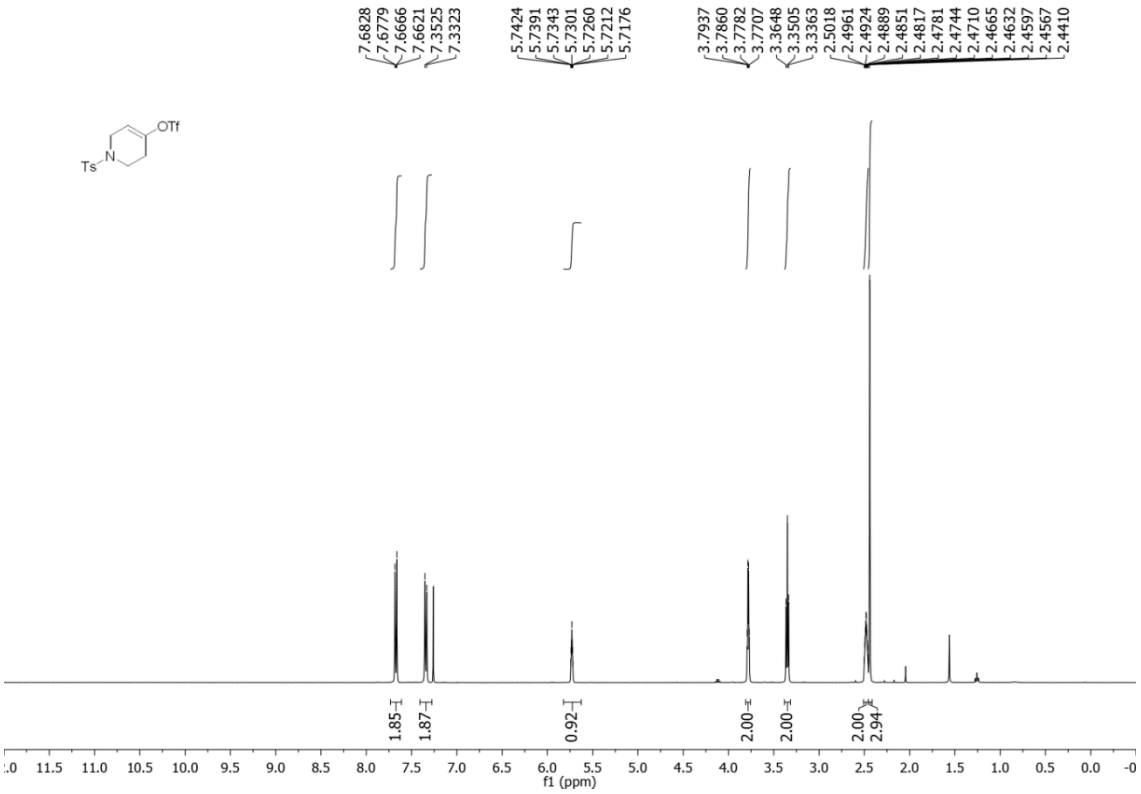


^{19}F-NMR Spectrum:

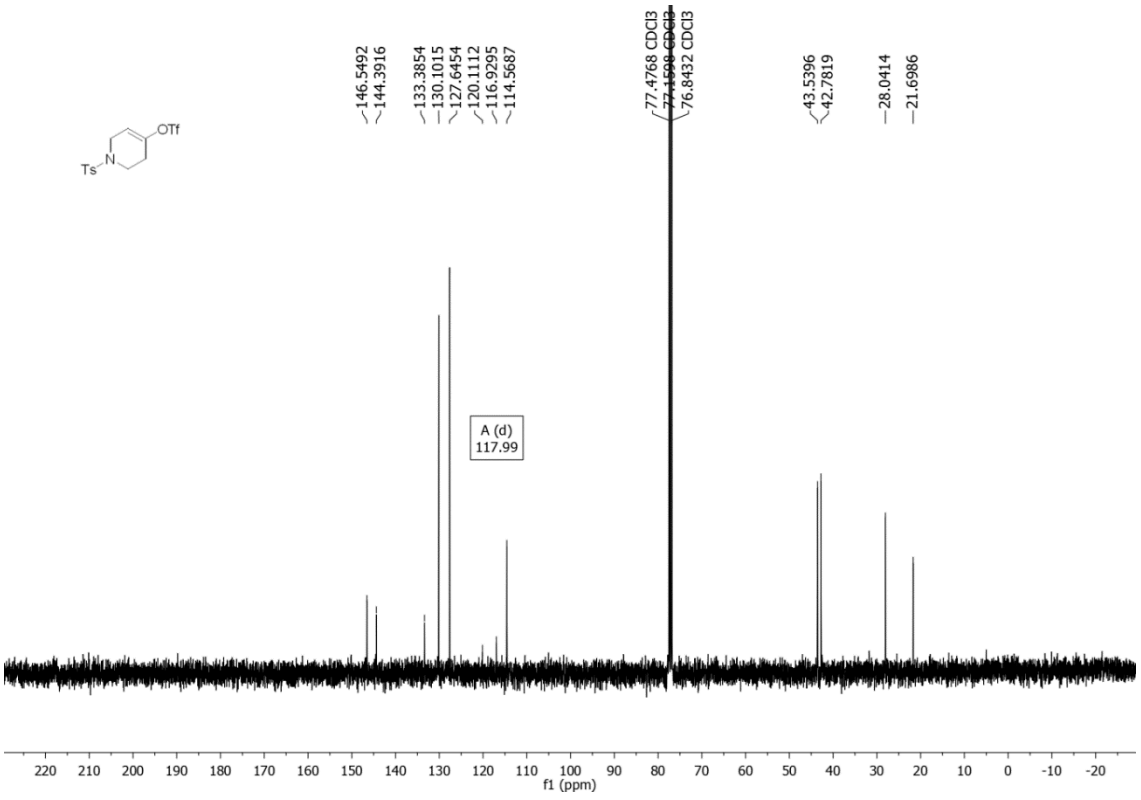


1-Tosyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (31s)

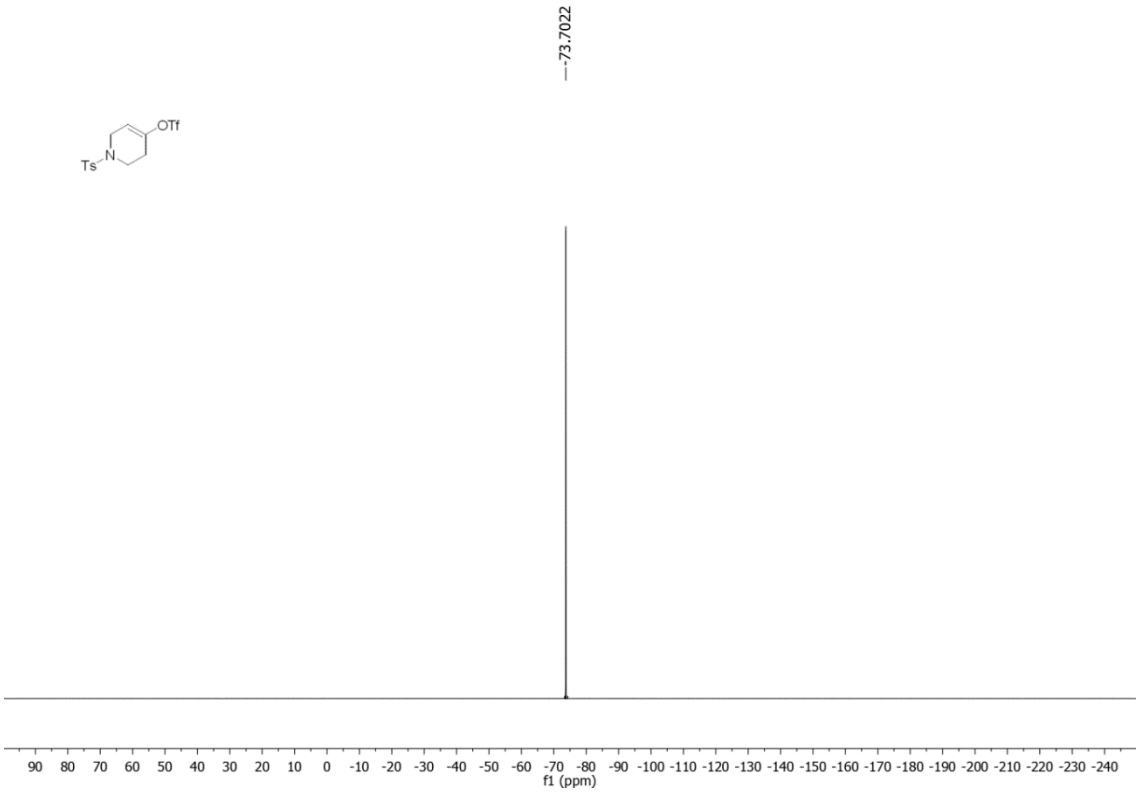
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

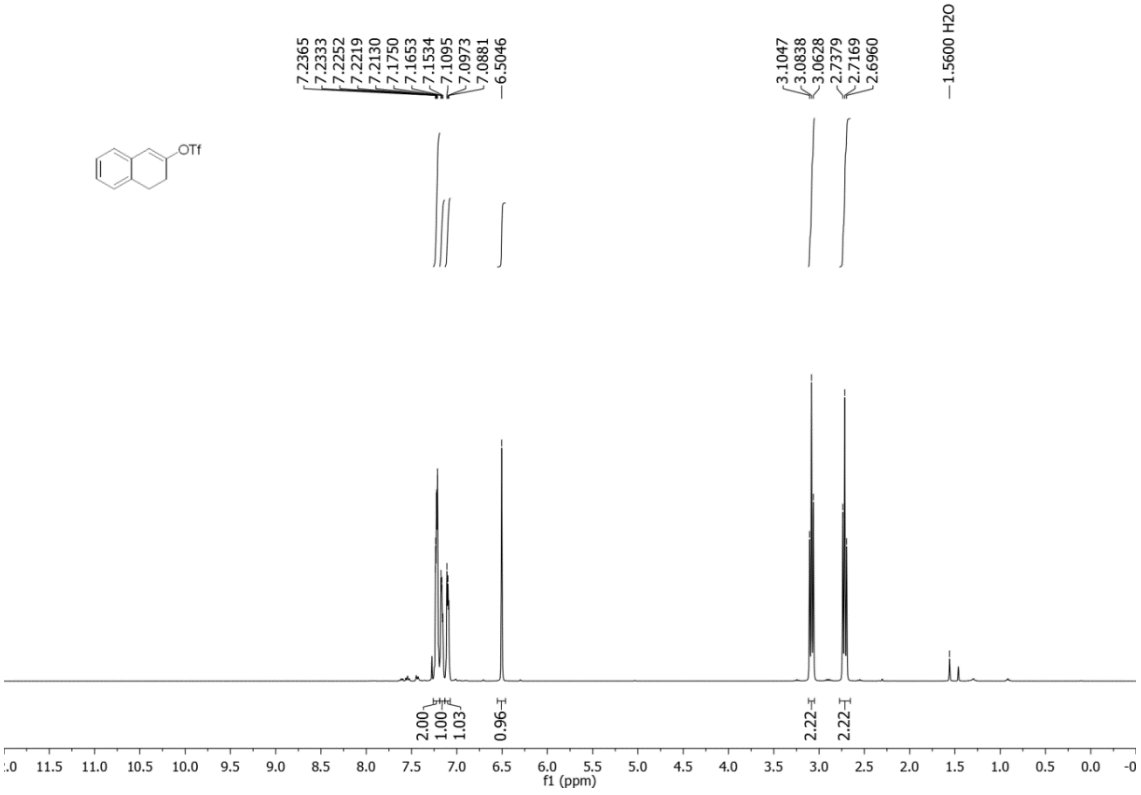


^{19}F-NMR Spectrum:

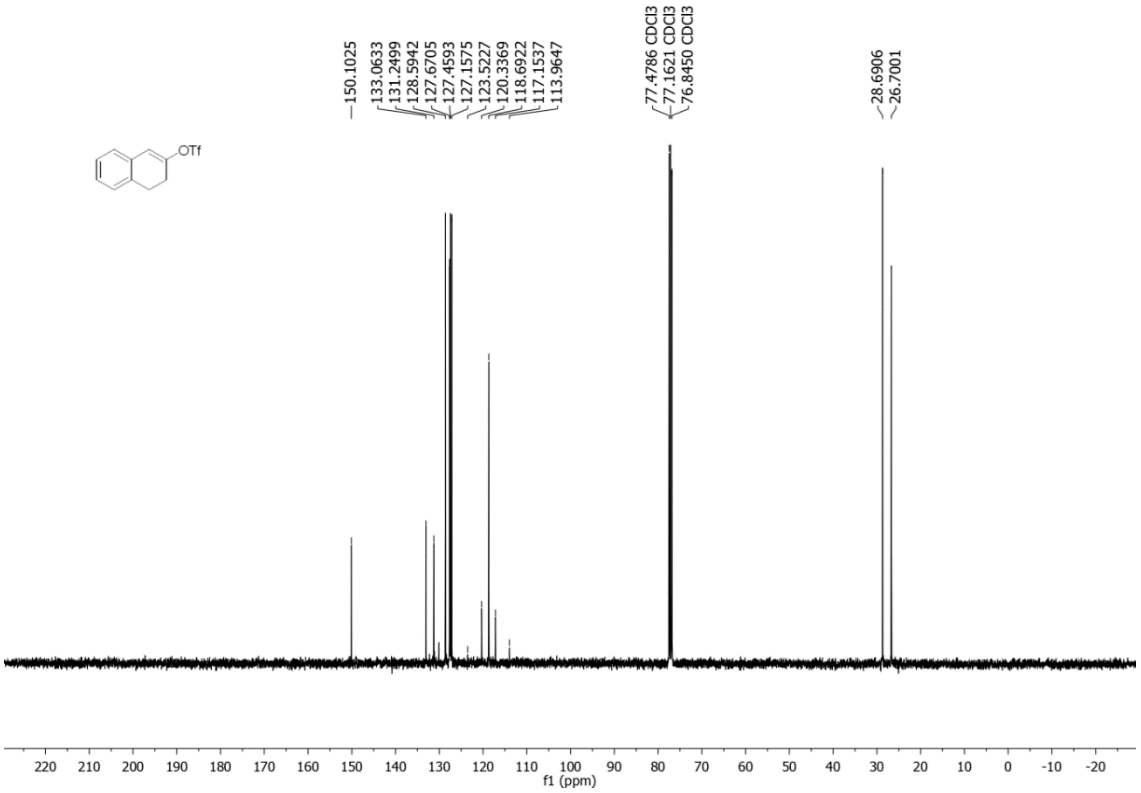


3,4-Dihydronaphthalen-2-yl trifluoromethanesulfonate (31u)

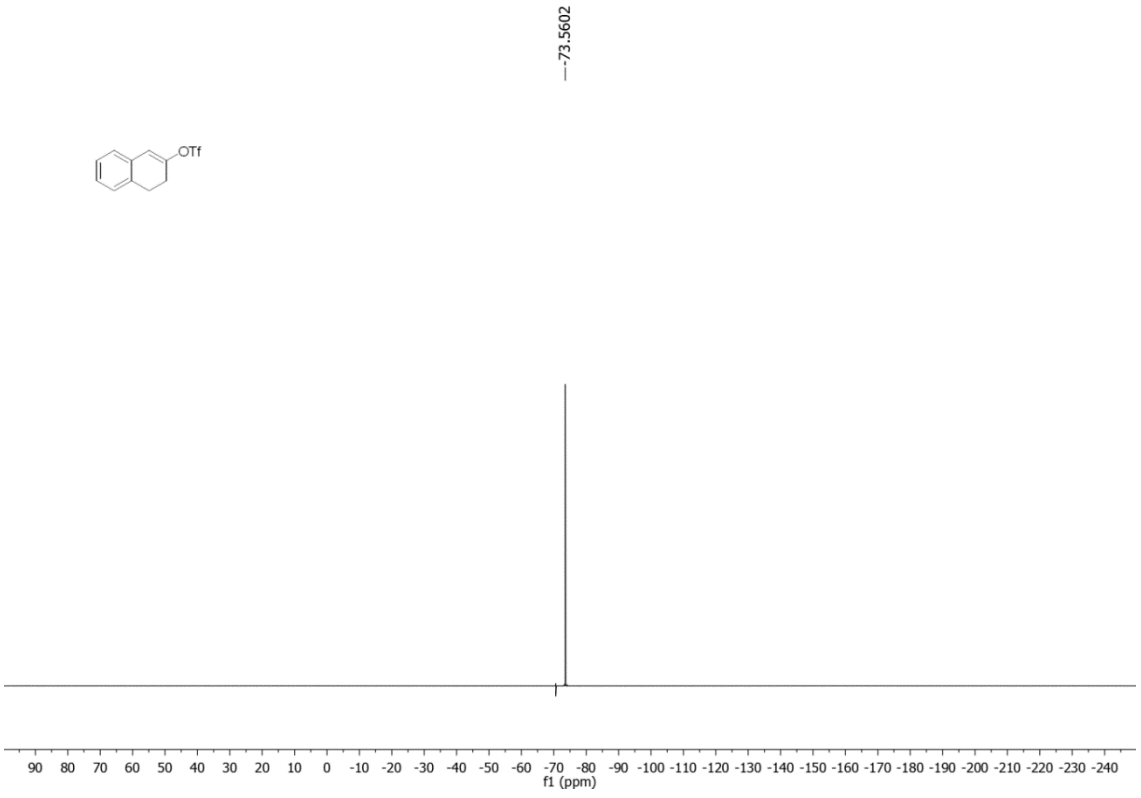
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

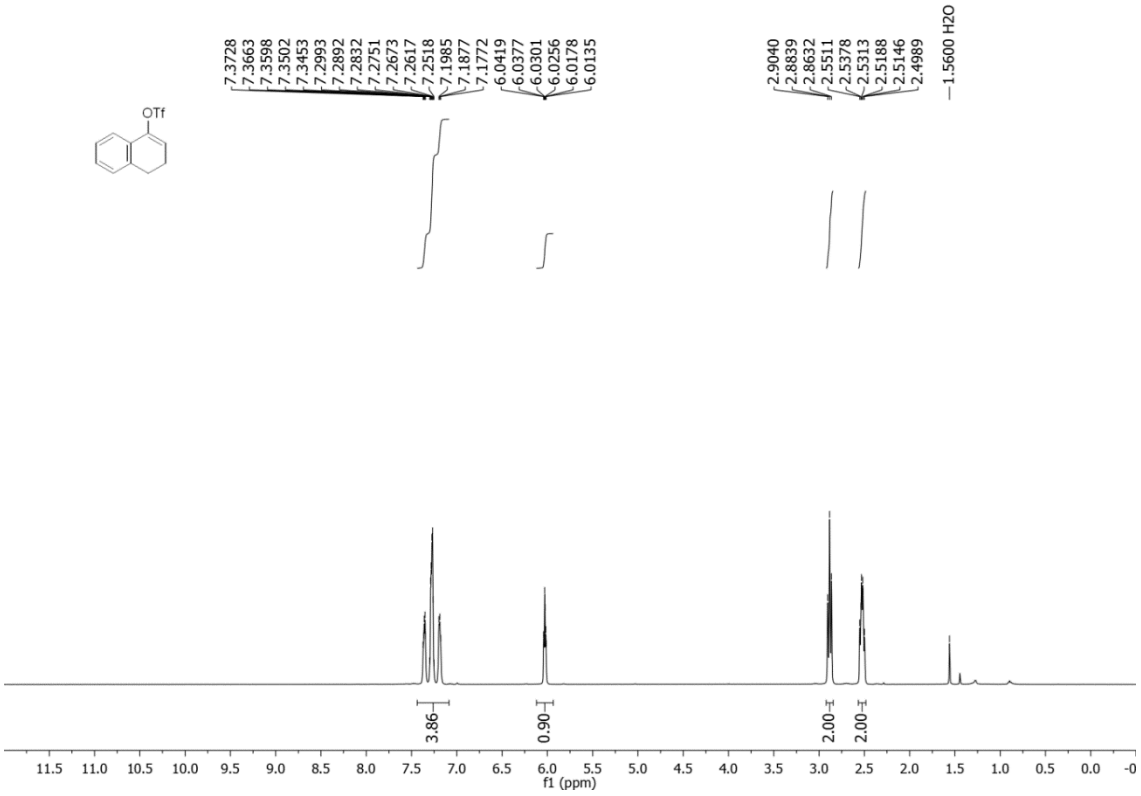


^{19}F-NMR Spectrum:

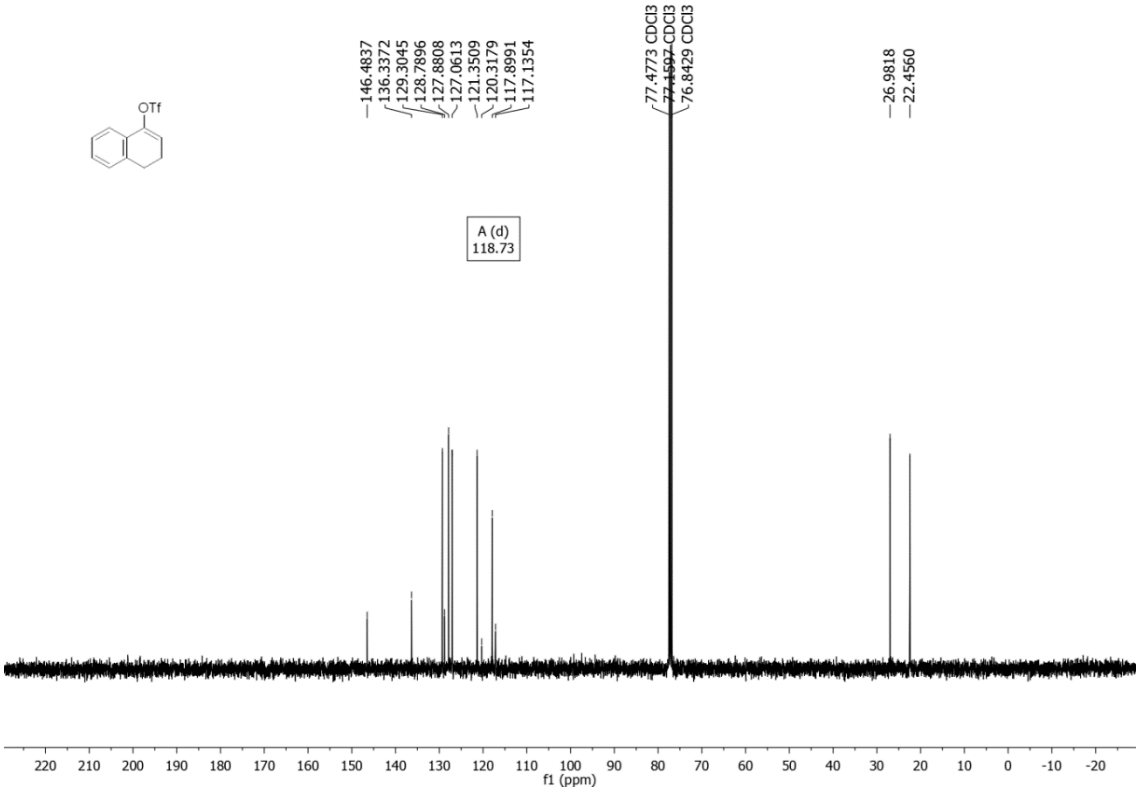


3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate (31v)

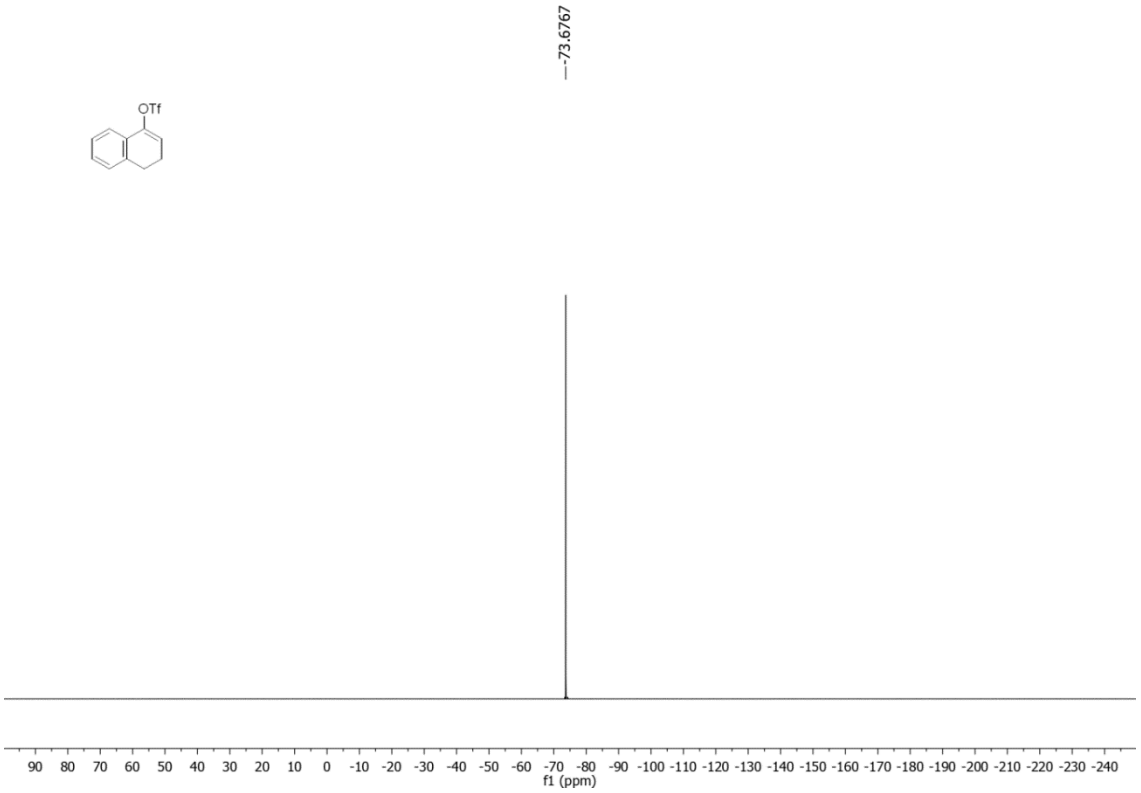
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

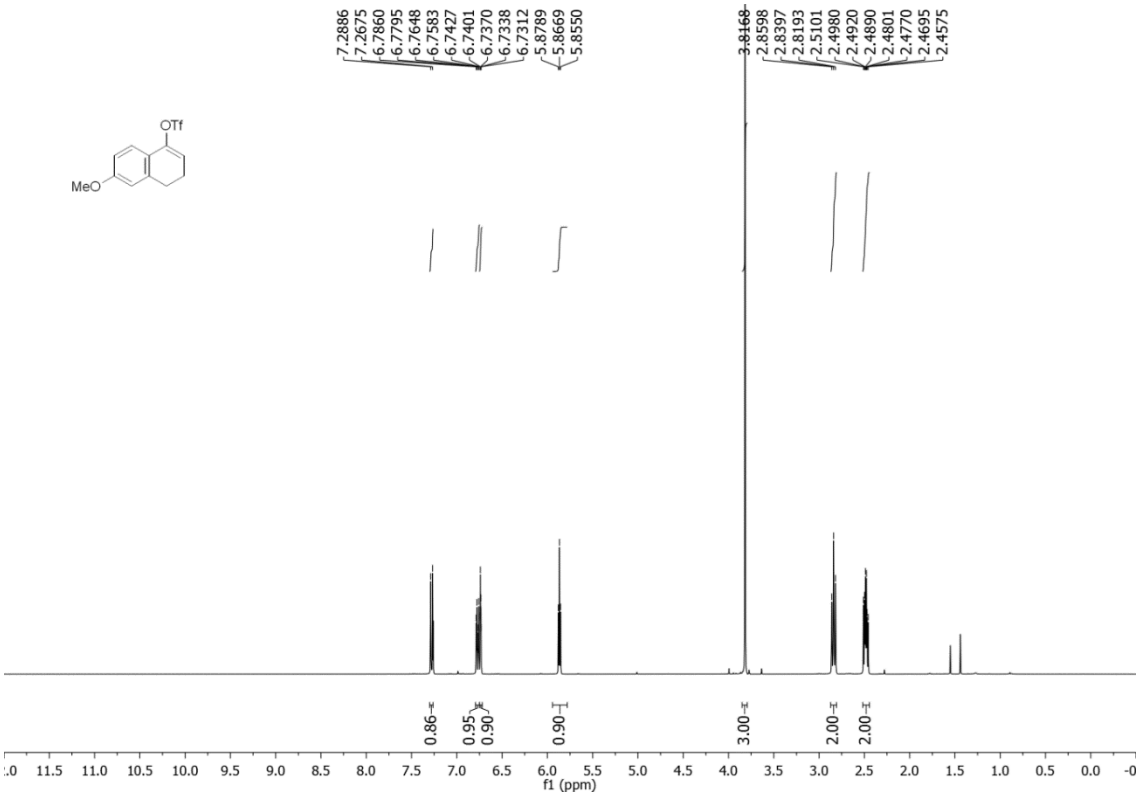


^{19}F-NMR Spectrum:

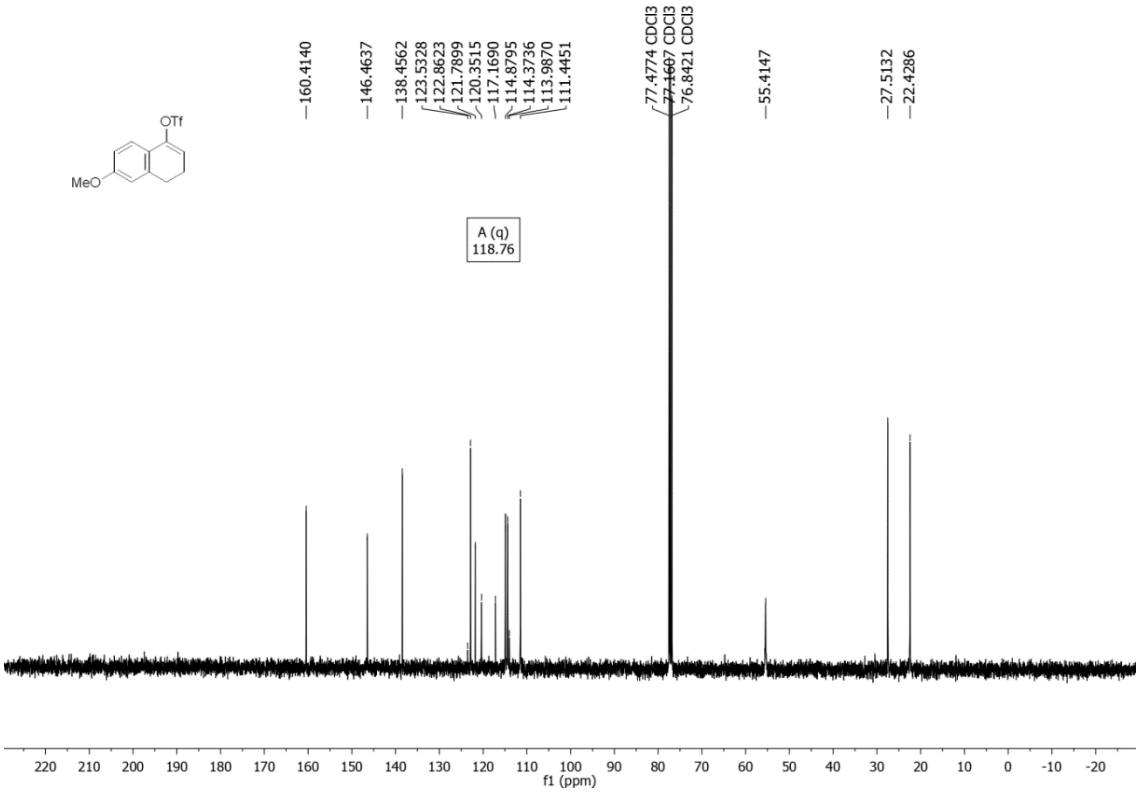


6-Methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (31w)

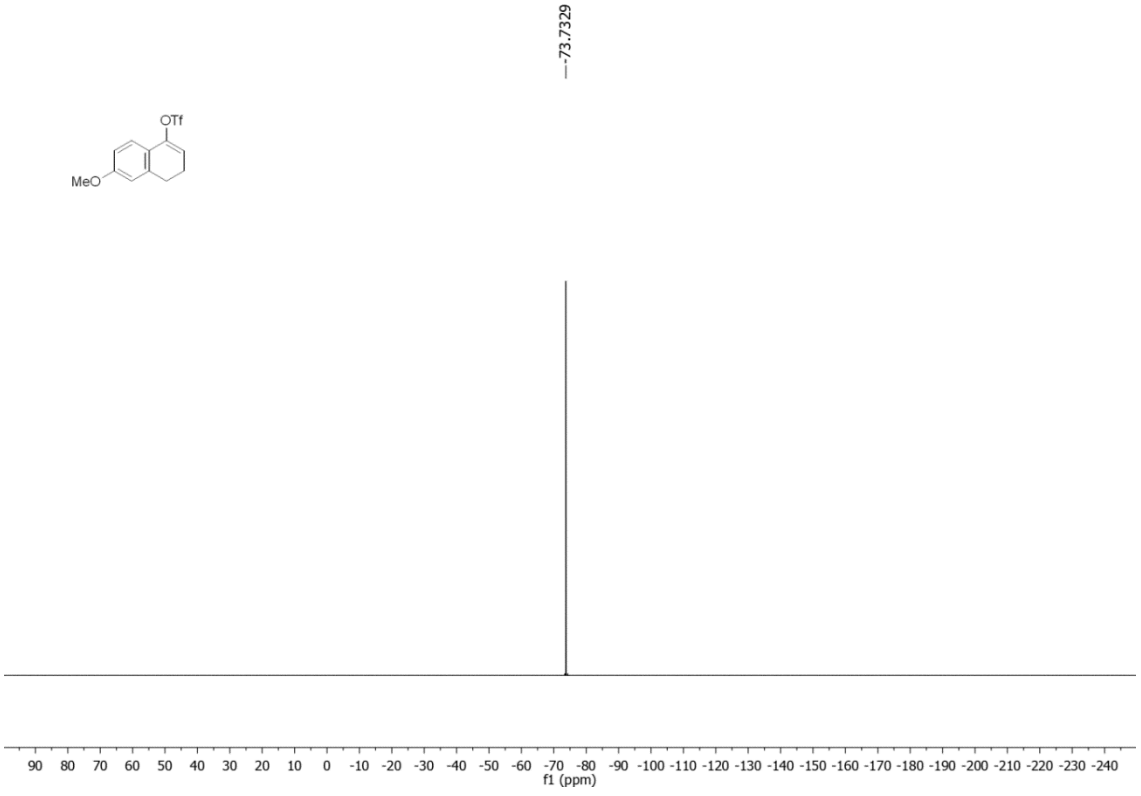
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

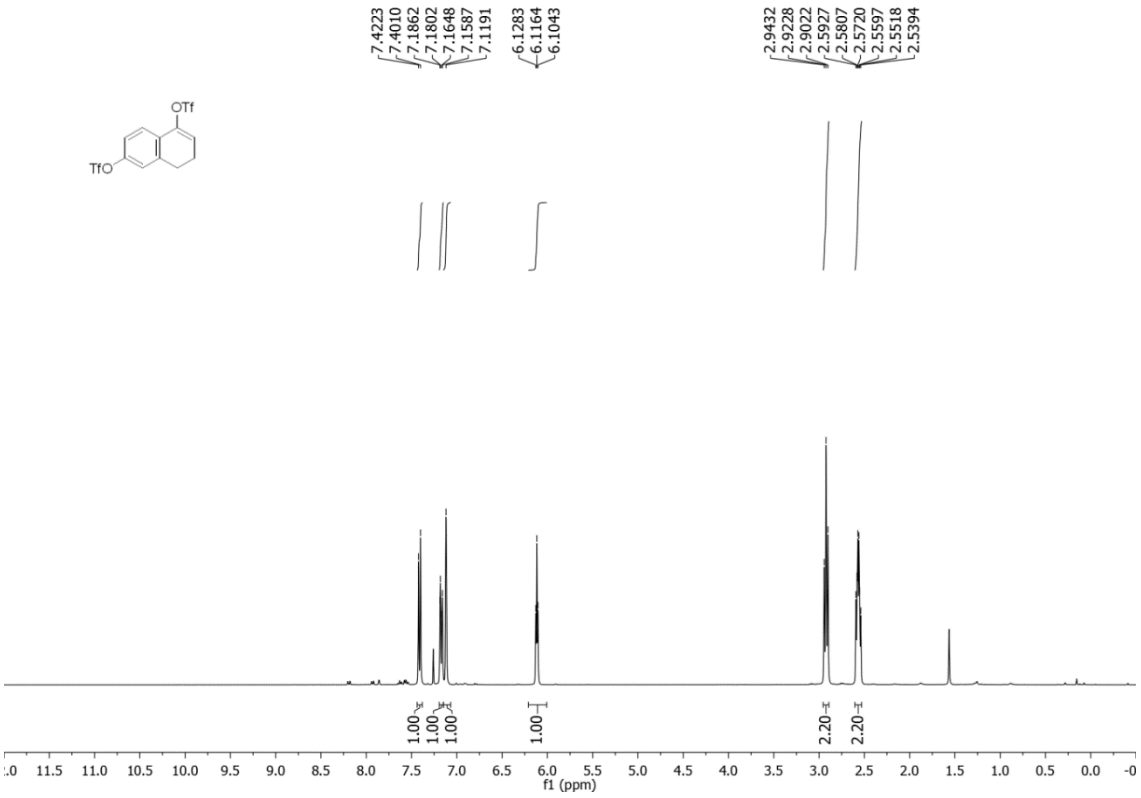


^{19}F-NMR Spectrum:

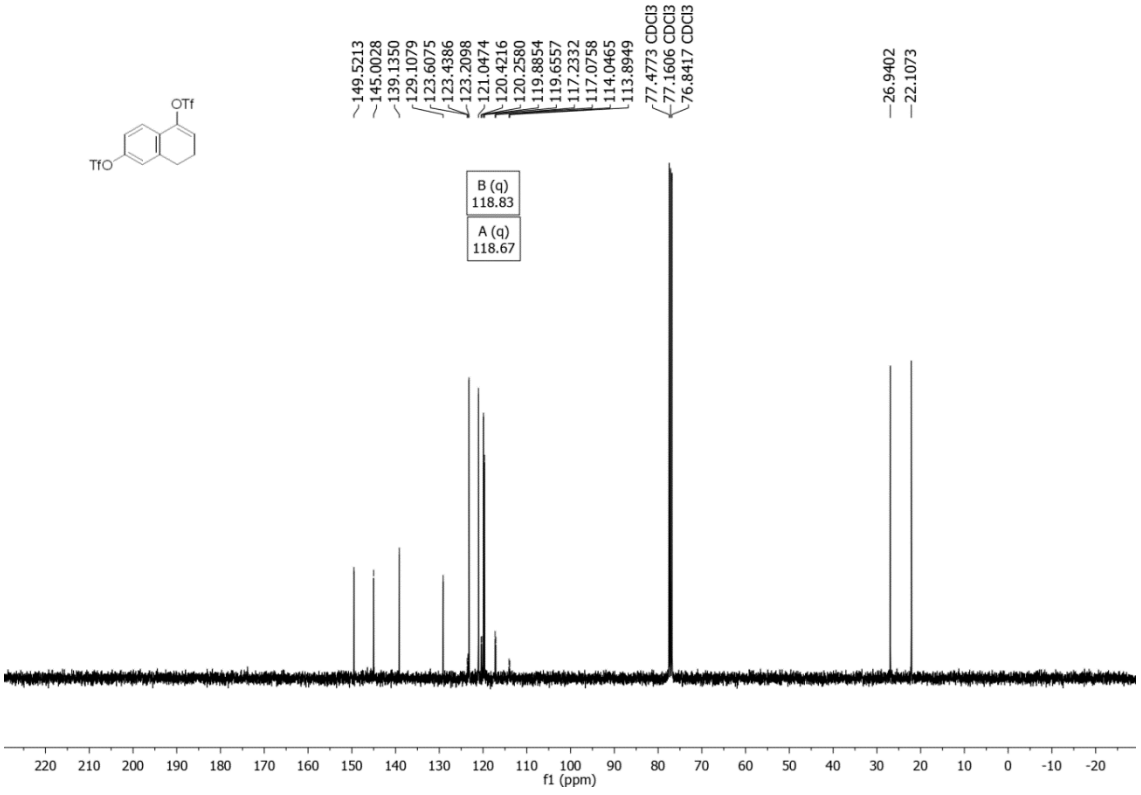


3,4-Dihydronaphthalene-1,6-diyl bis(trifluoromethanesulfonate) (31x)

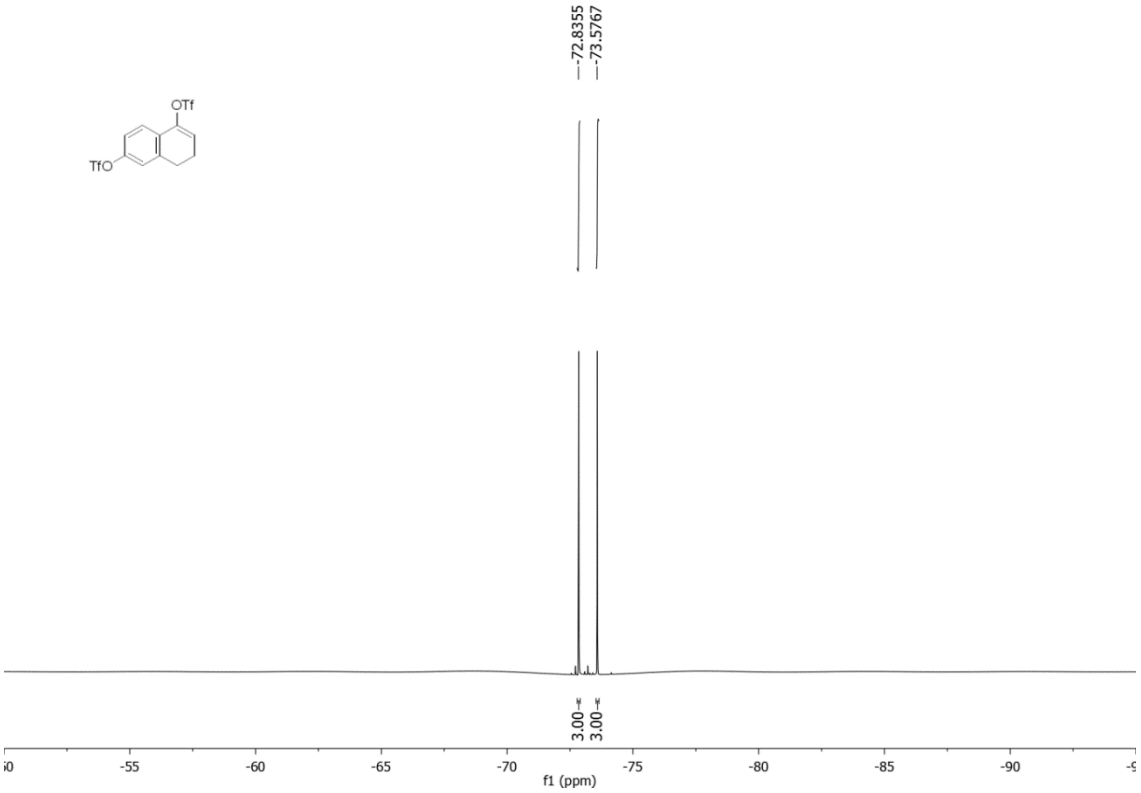
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:



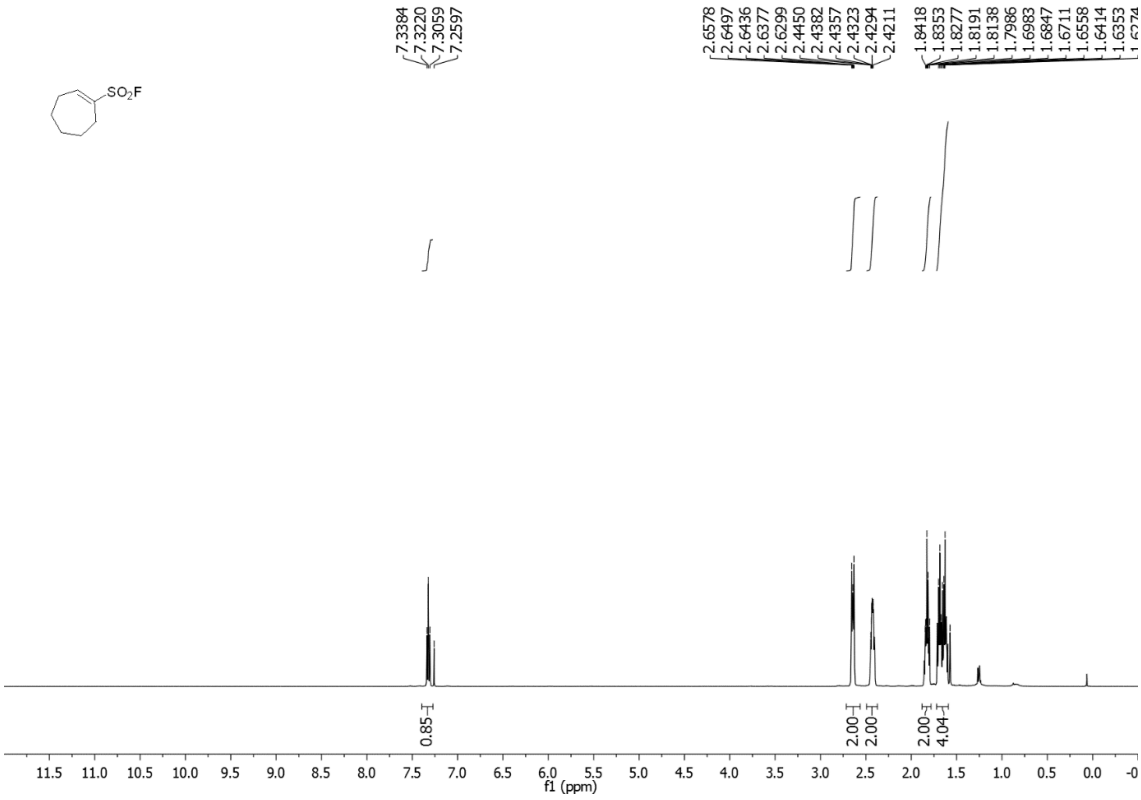
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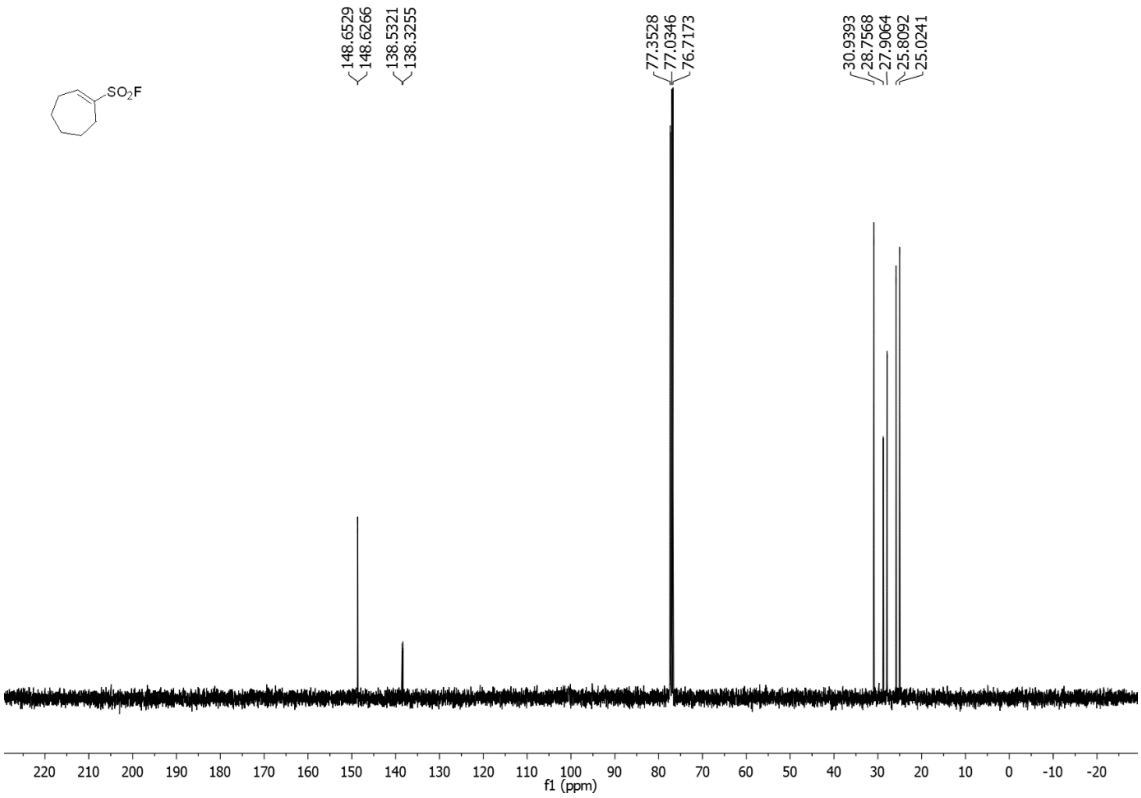
9 NMR Spectra of CASFs

Cyclohept-1-ene-1-sulfonyl fluoride (33a)

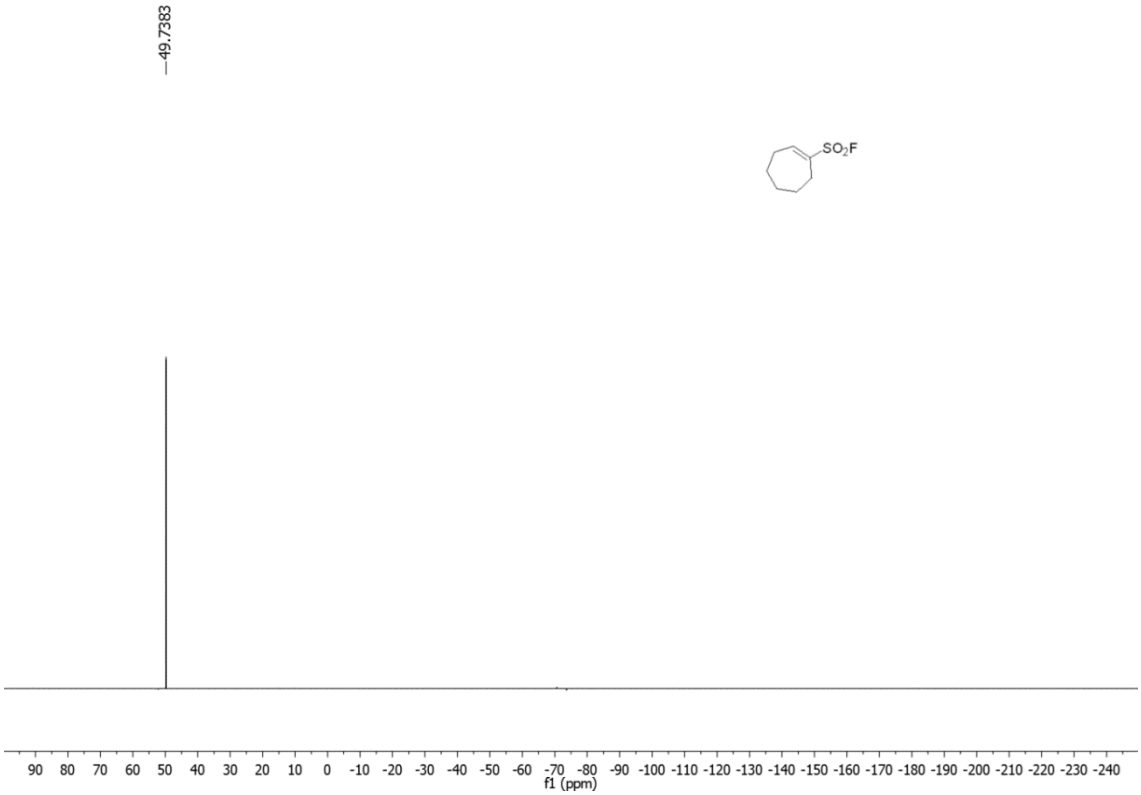
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

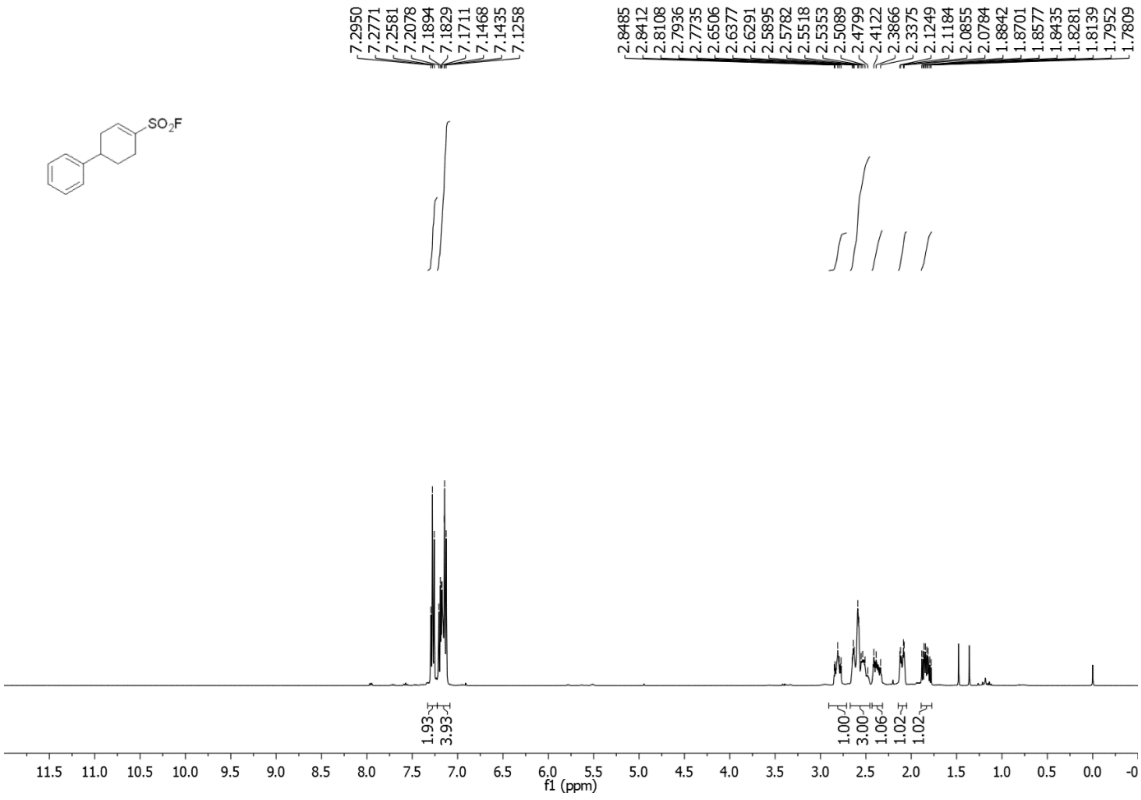


^{19}F-NMR Spectrum:

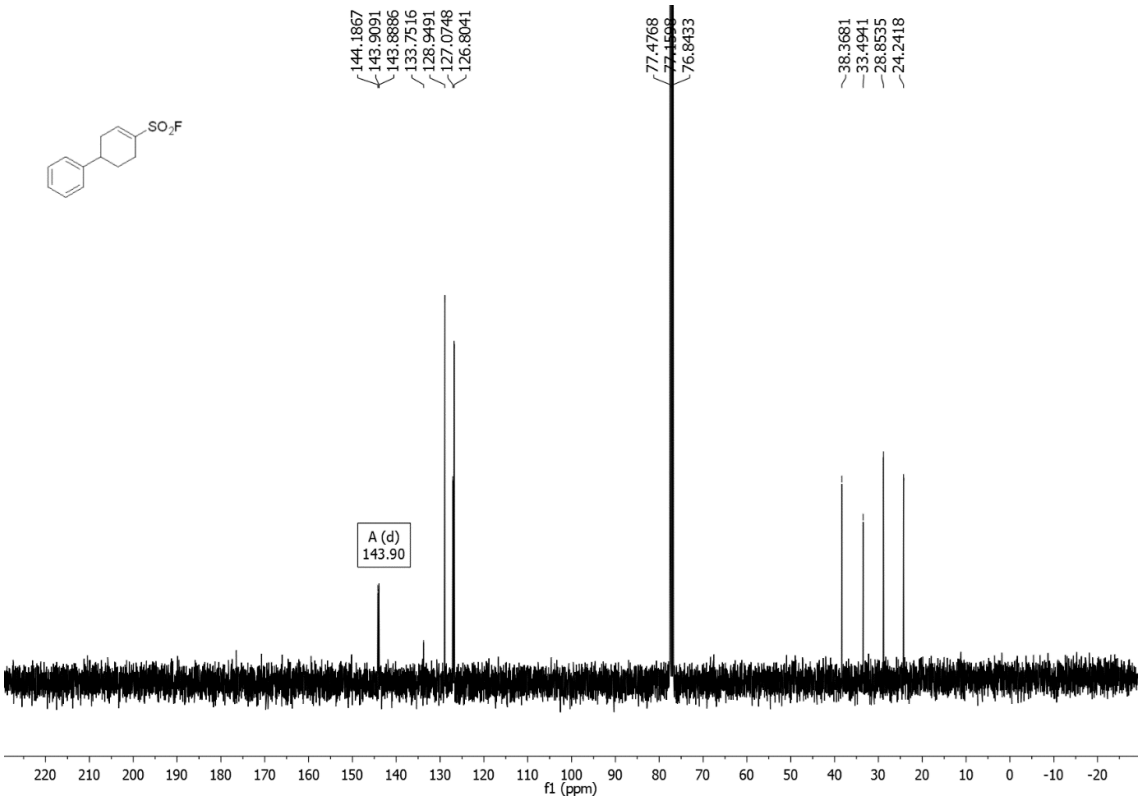


1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-sulfonyl fluoride (33b)

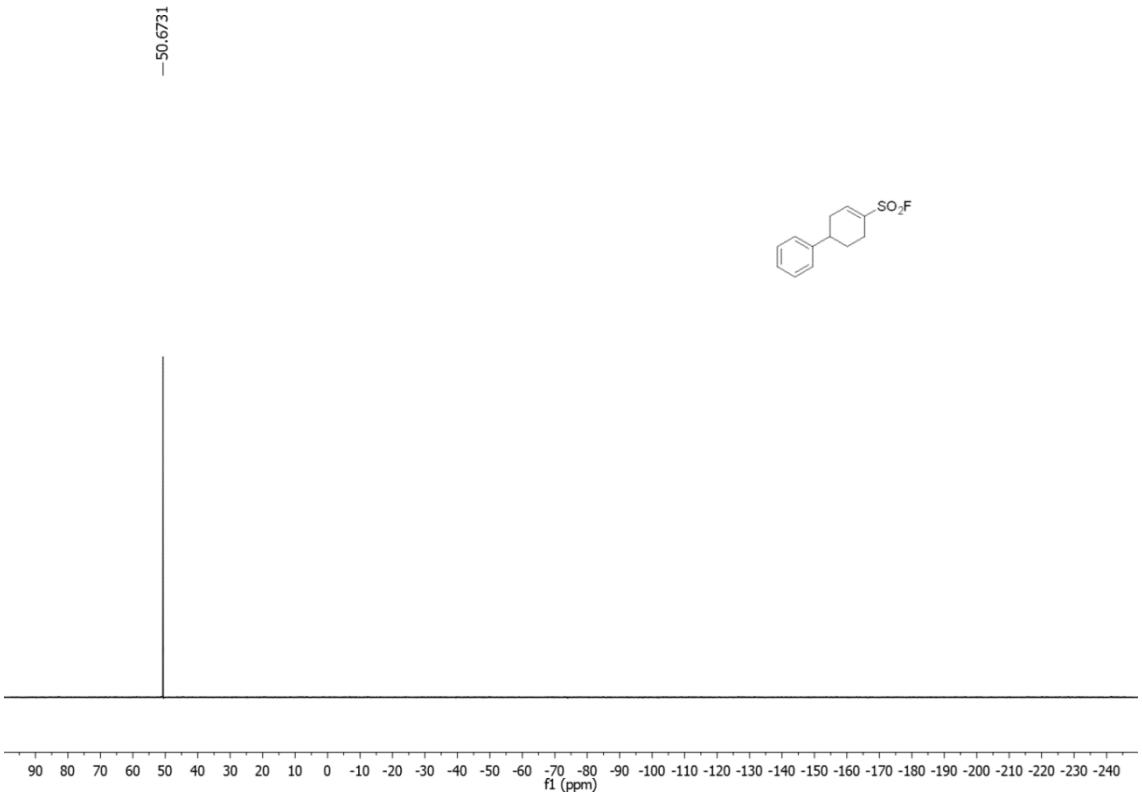
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

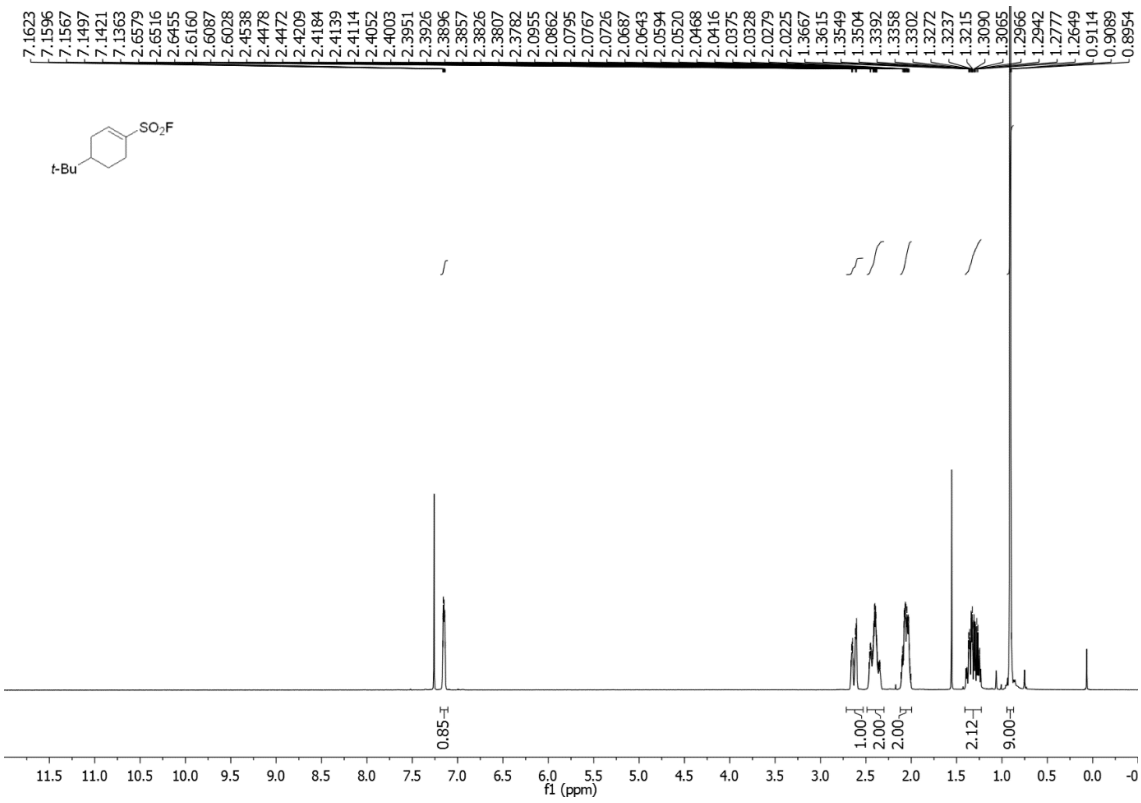


^{19}F-NMR Spectrum:

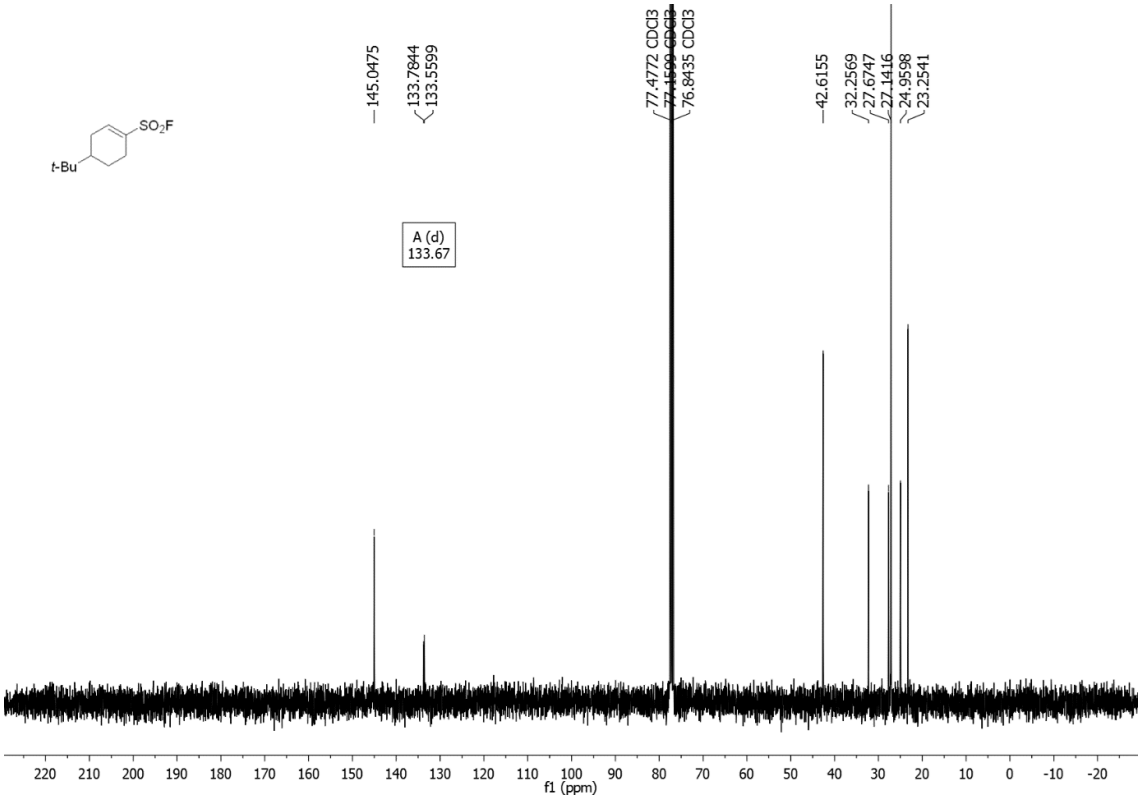


4-(*tert*-Butyl)cyclohex-1-ene-1-sulfonyl fluoride (33c)

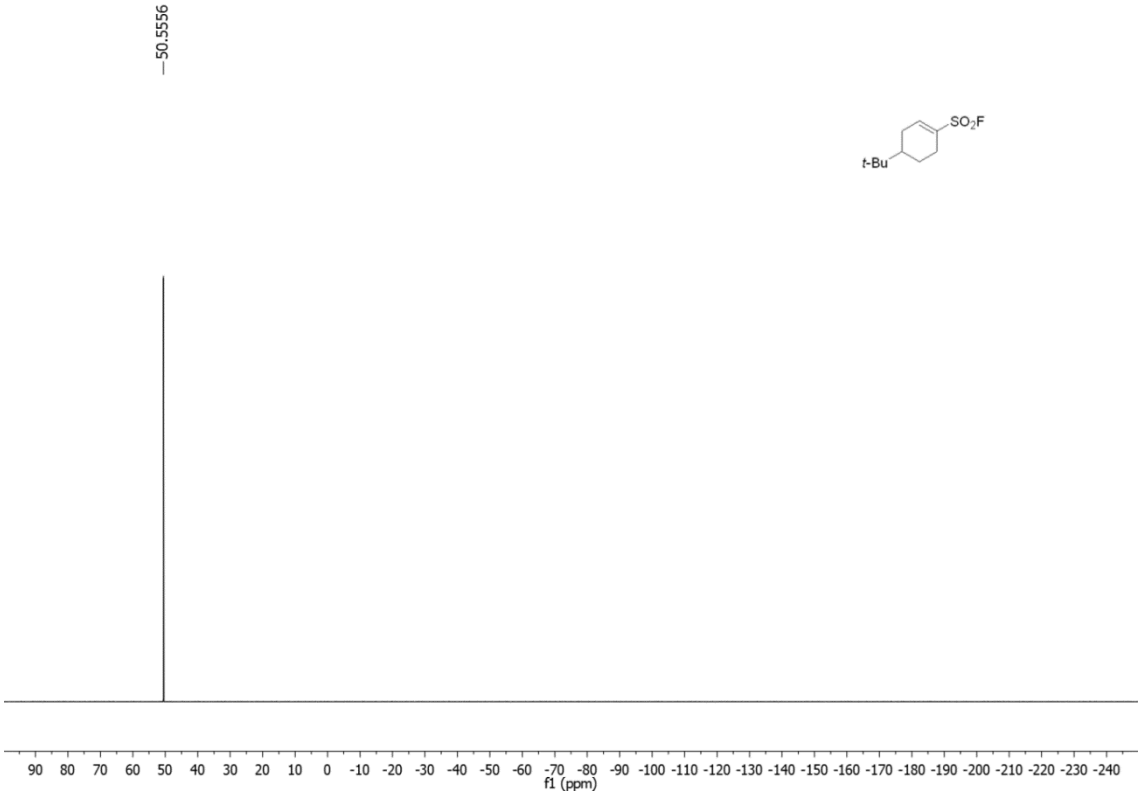
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

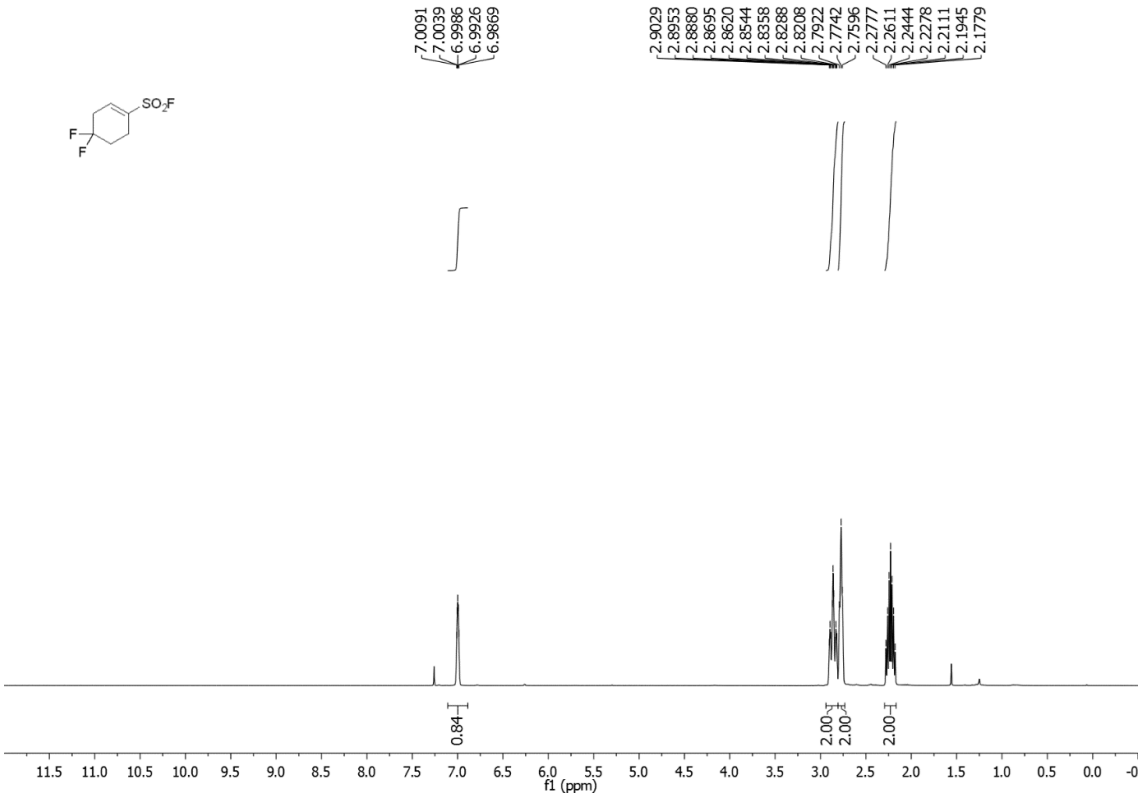


^{19}F-NMR Spectrum:

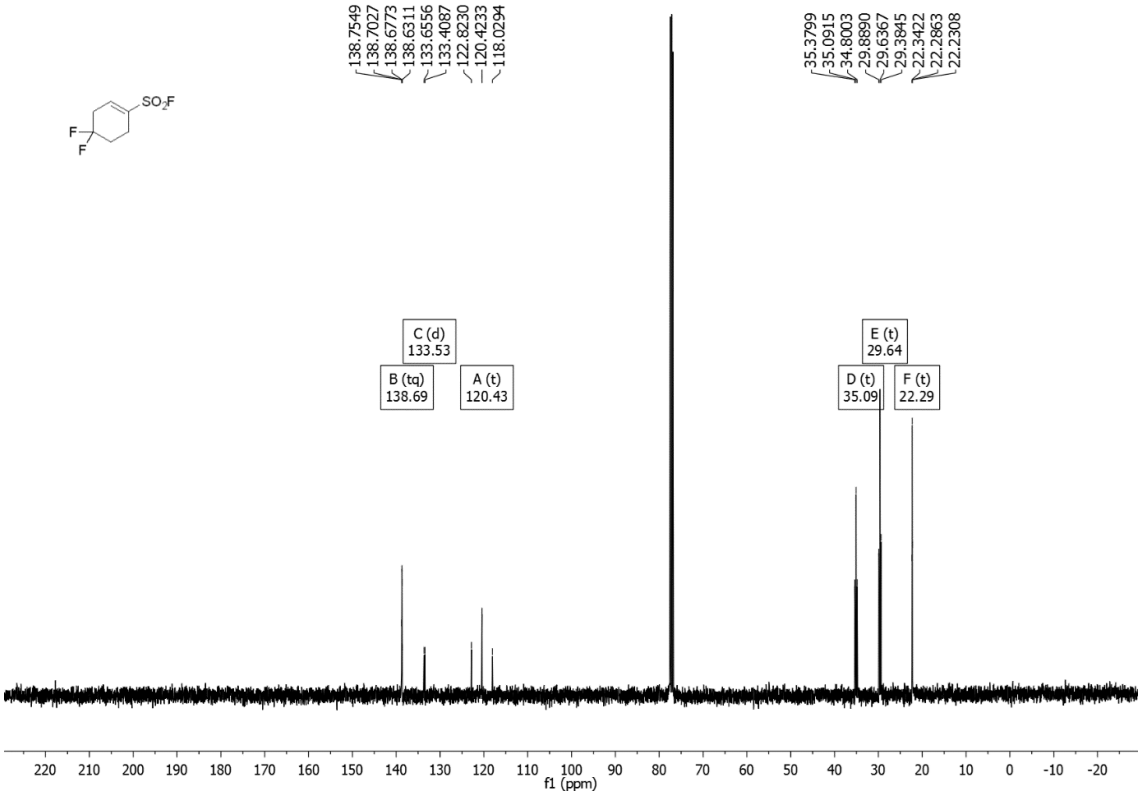


4,4-Difluorocyclohex-1-ene-1-sulfonyl fluoride (33d)

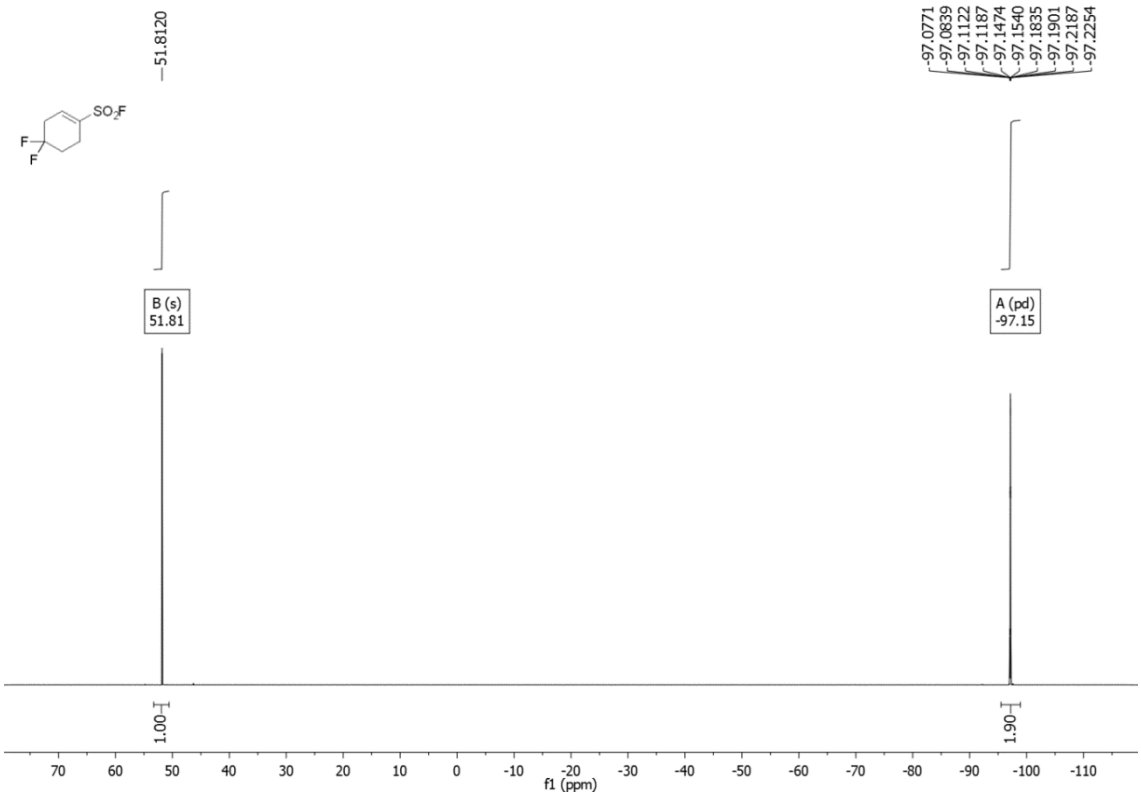
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

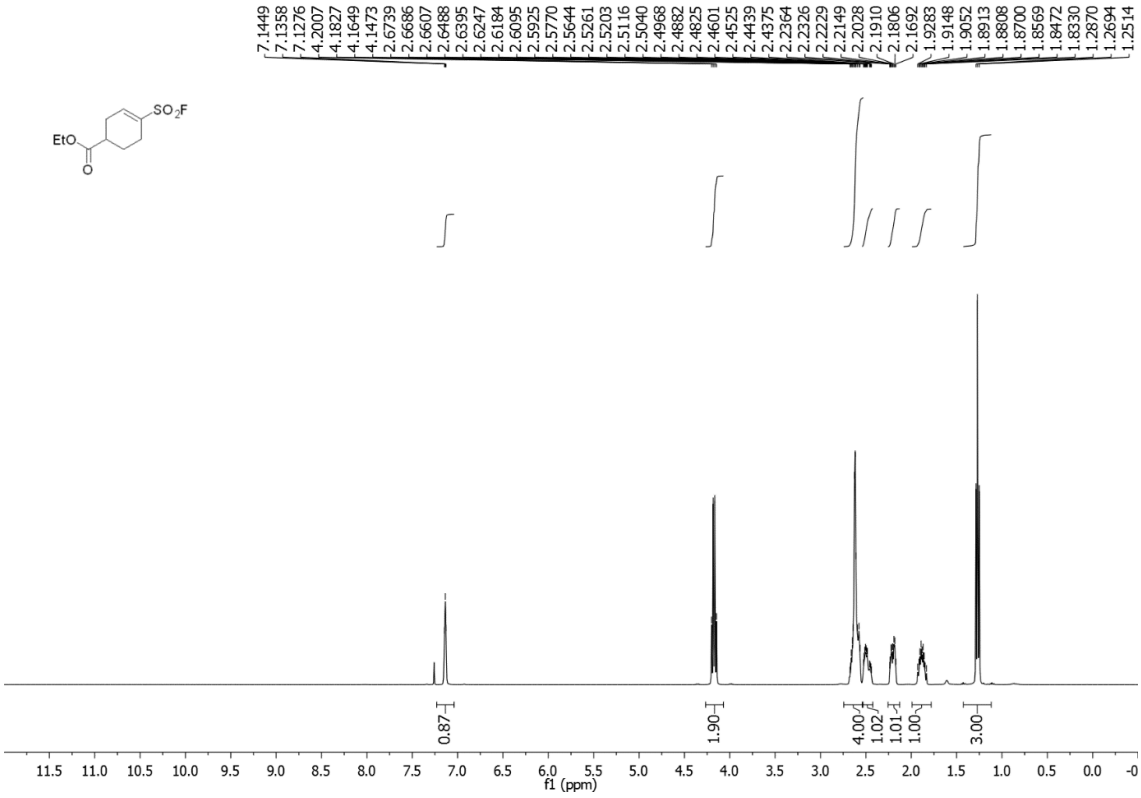


^{19}F-NMR Spectrum:

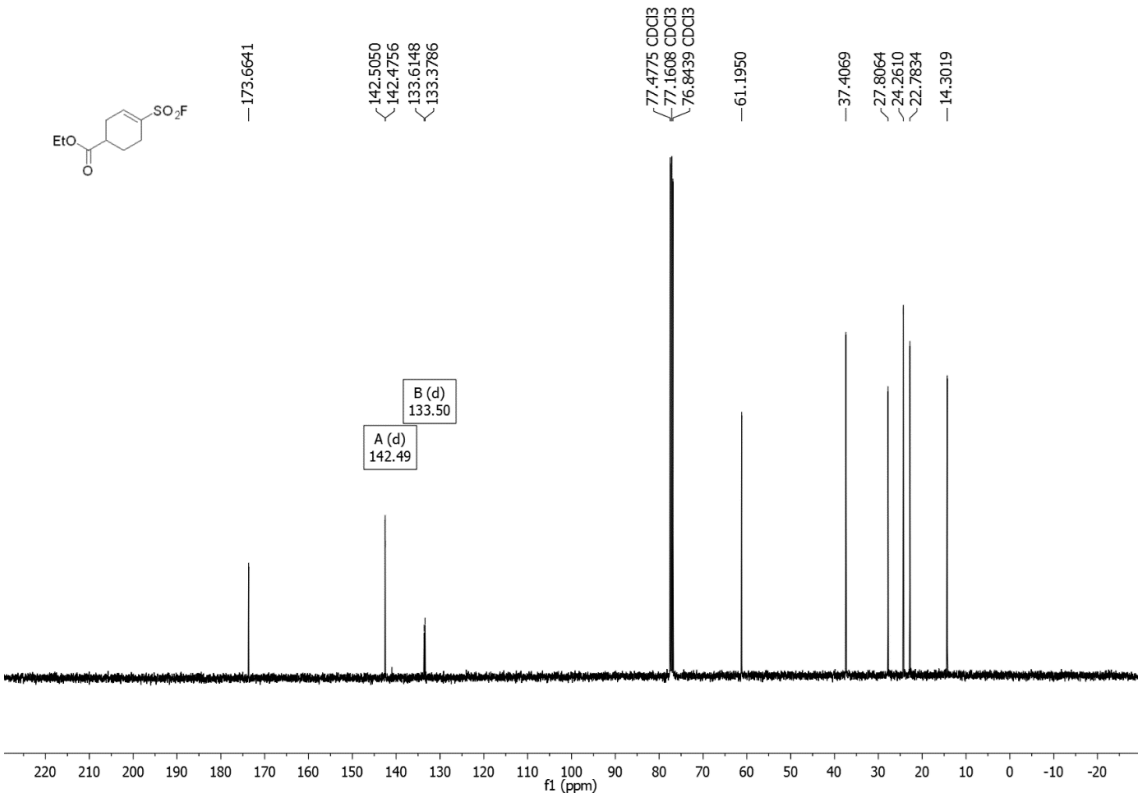


Ethyl 4-(fluorosulfonyl)cyclohex-3-ene-1-carboxylate (33e)

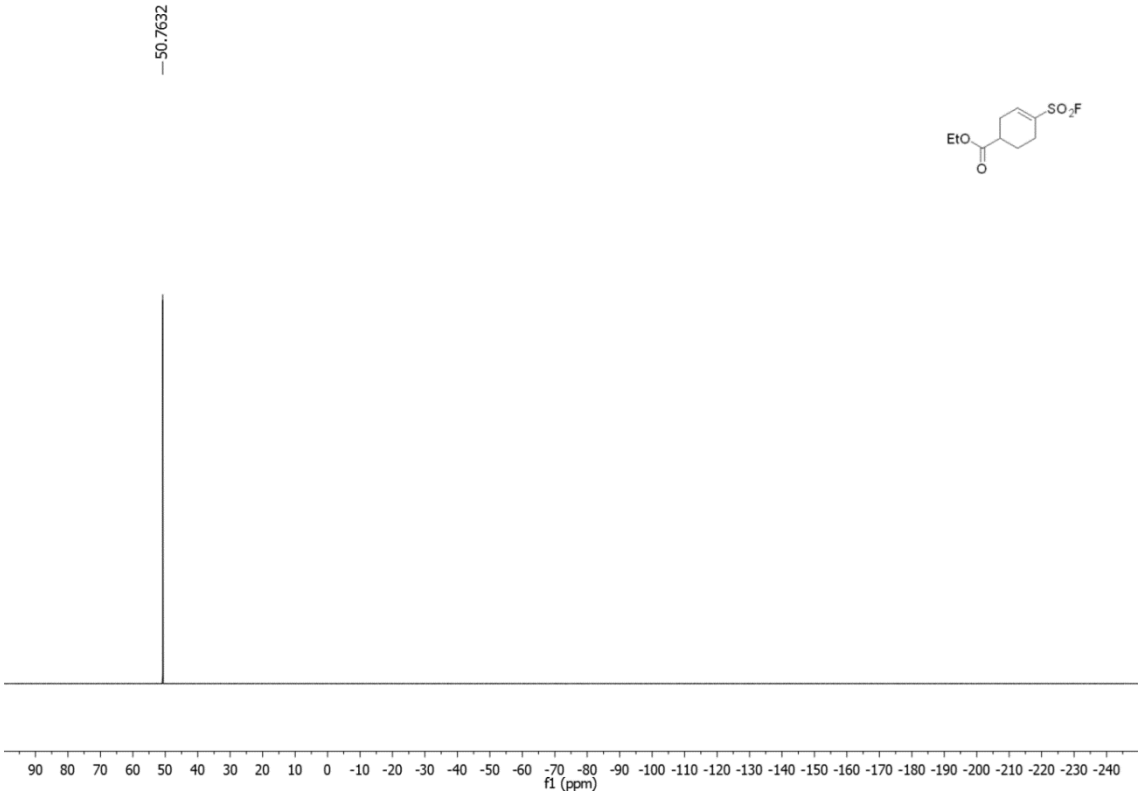
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

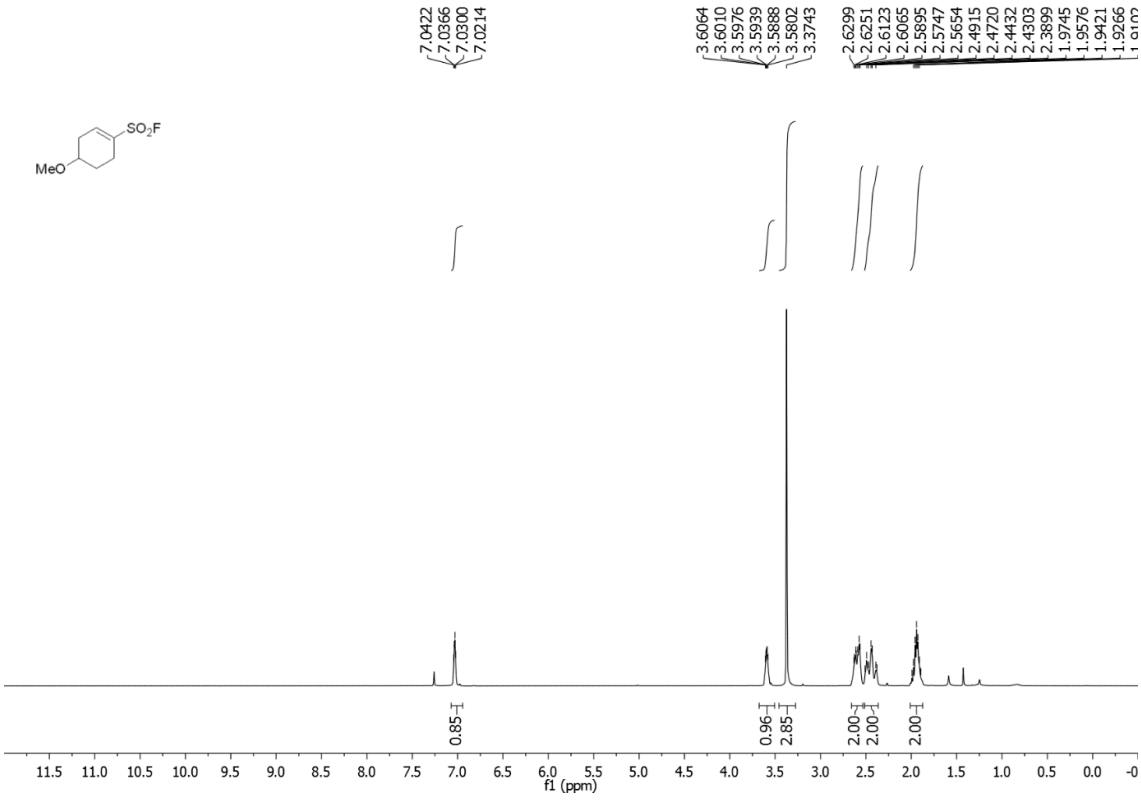


^{19}F-NMR Spectrum:

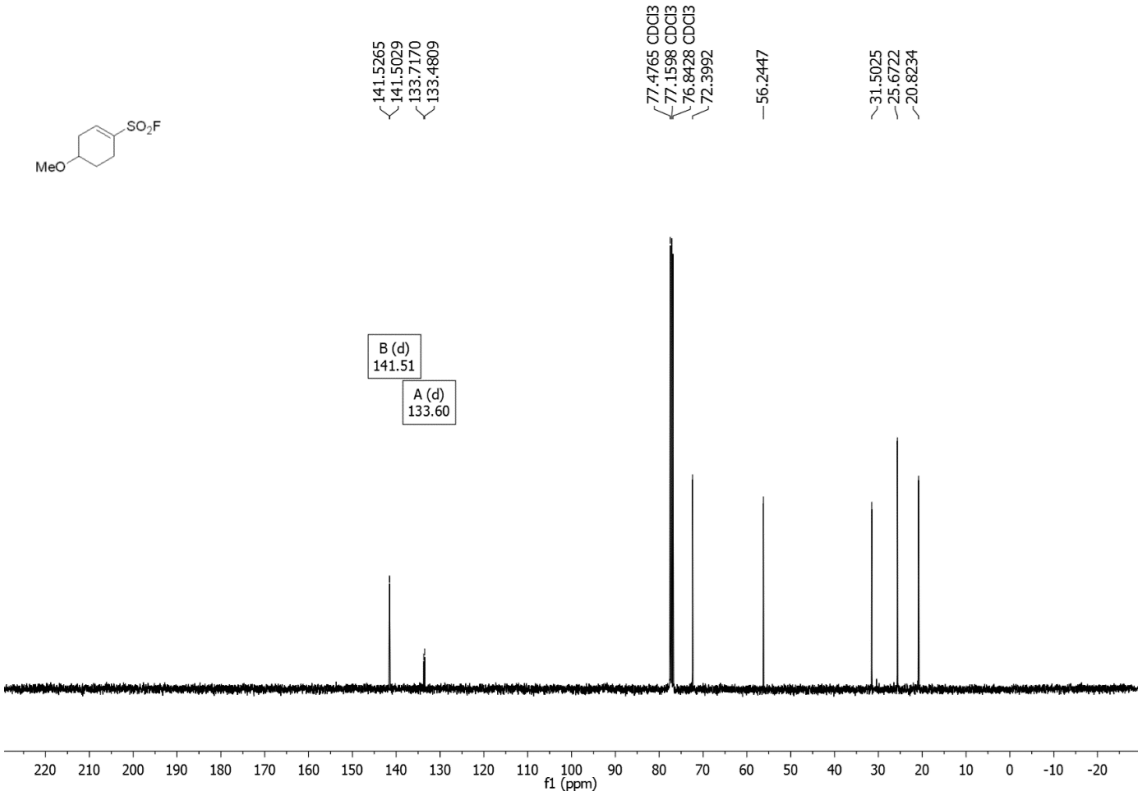


4-Methoxycyclohex-1-ene-1-sulfonyl fluoride (33f)

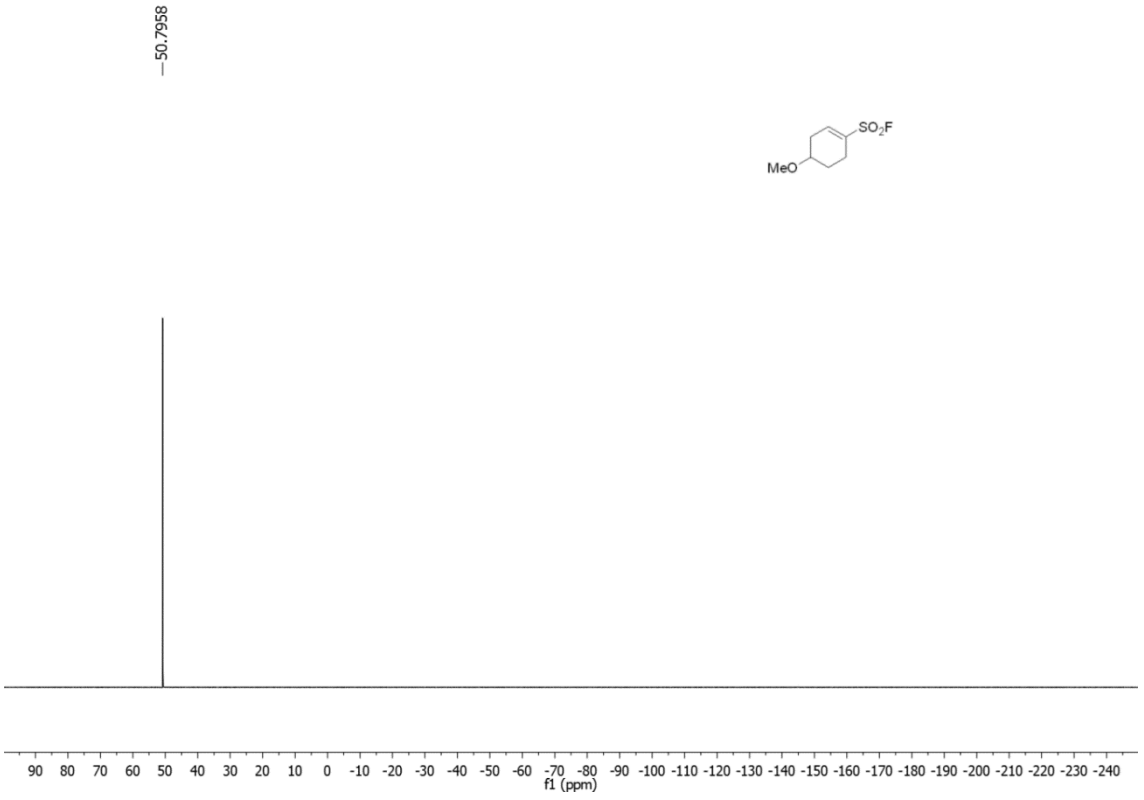
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

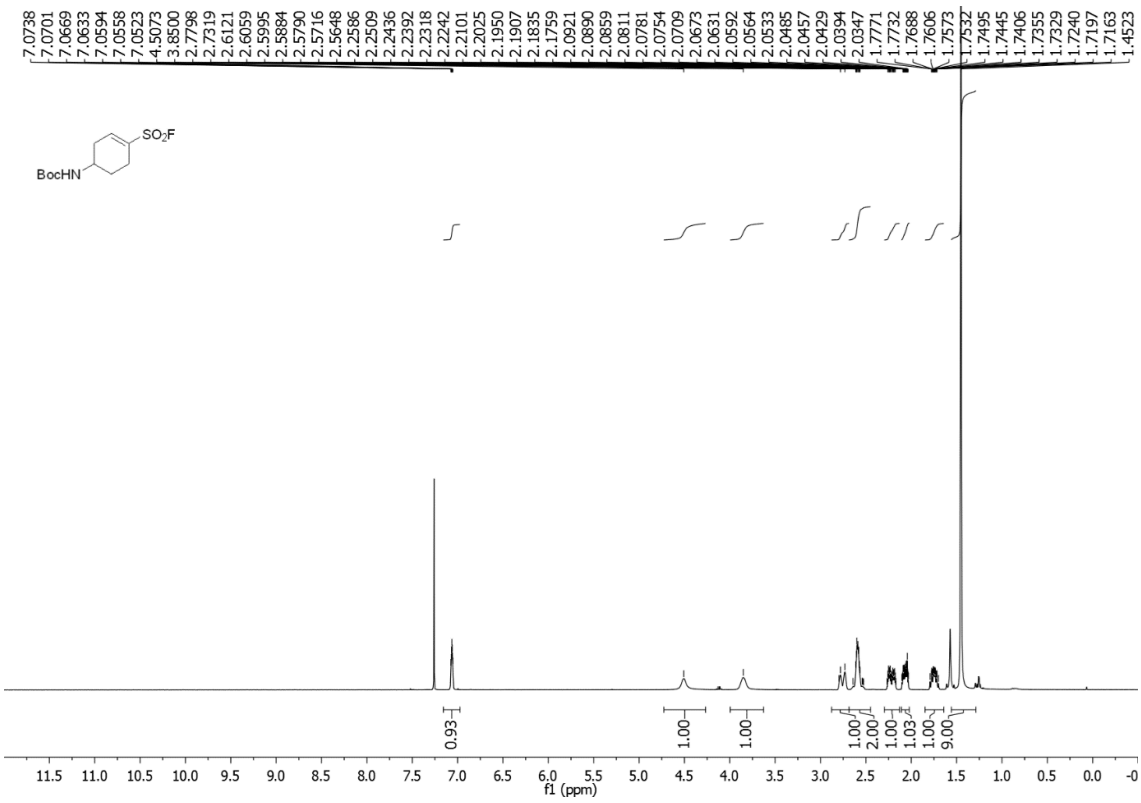


^{19}F-NMR Spectrum:

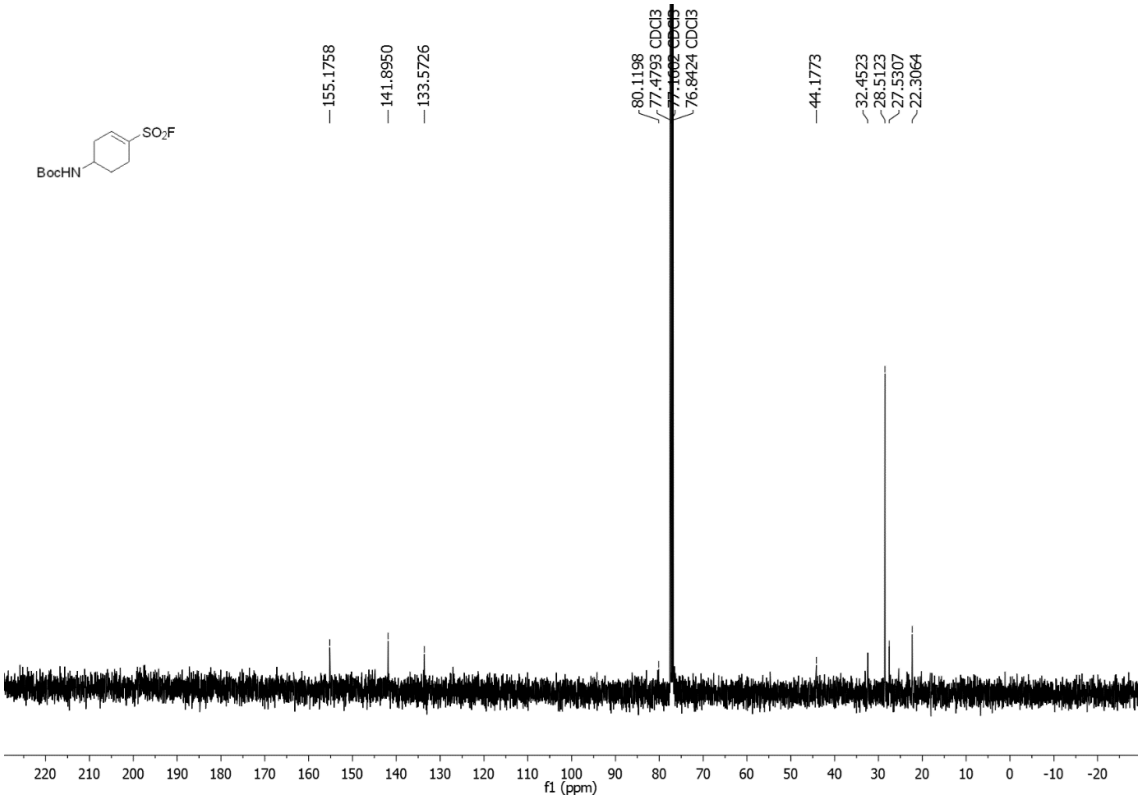


tert-Butyl (4-(fluorosulfonyl)cyclohex-3-en-1-yl)carbamate (33g)

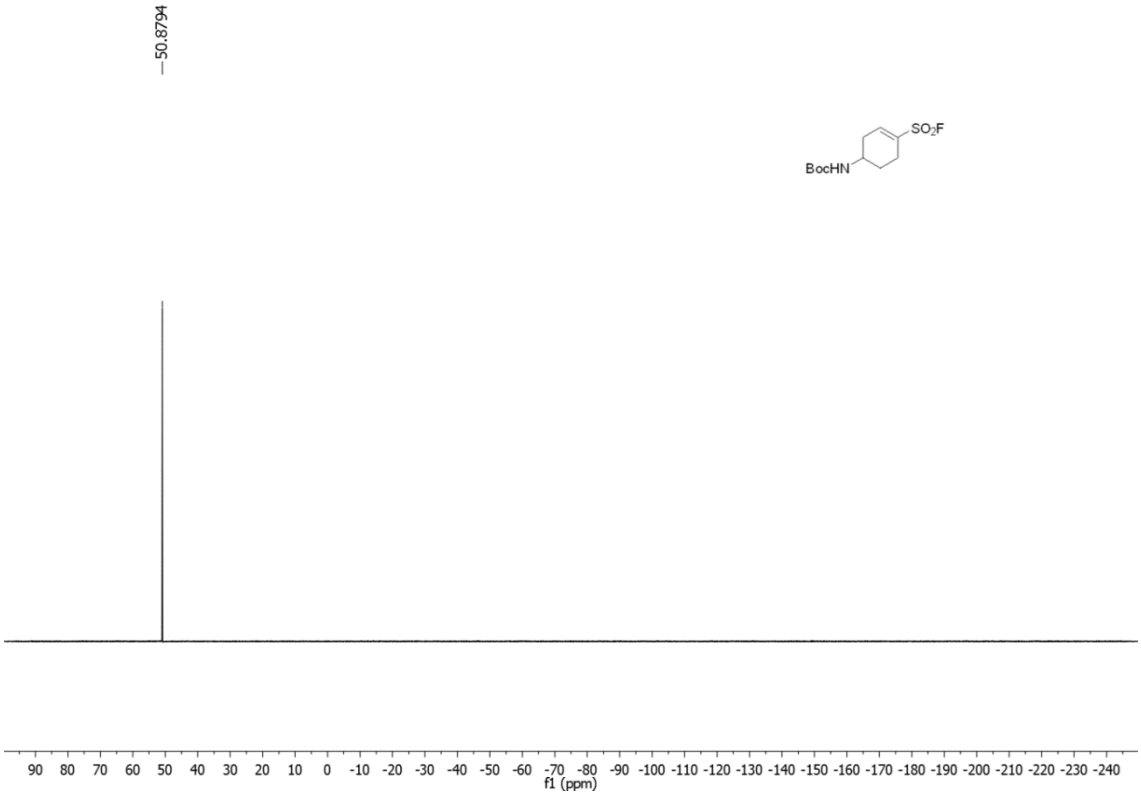
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

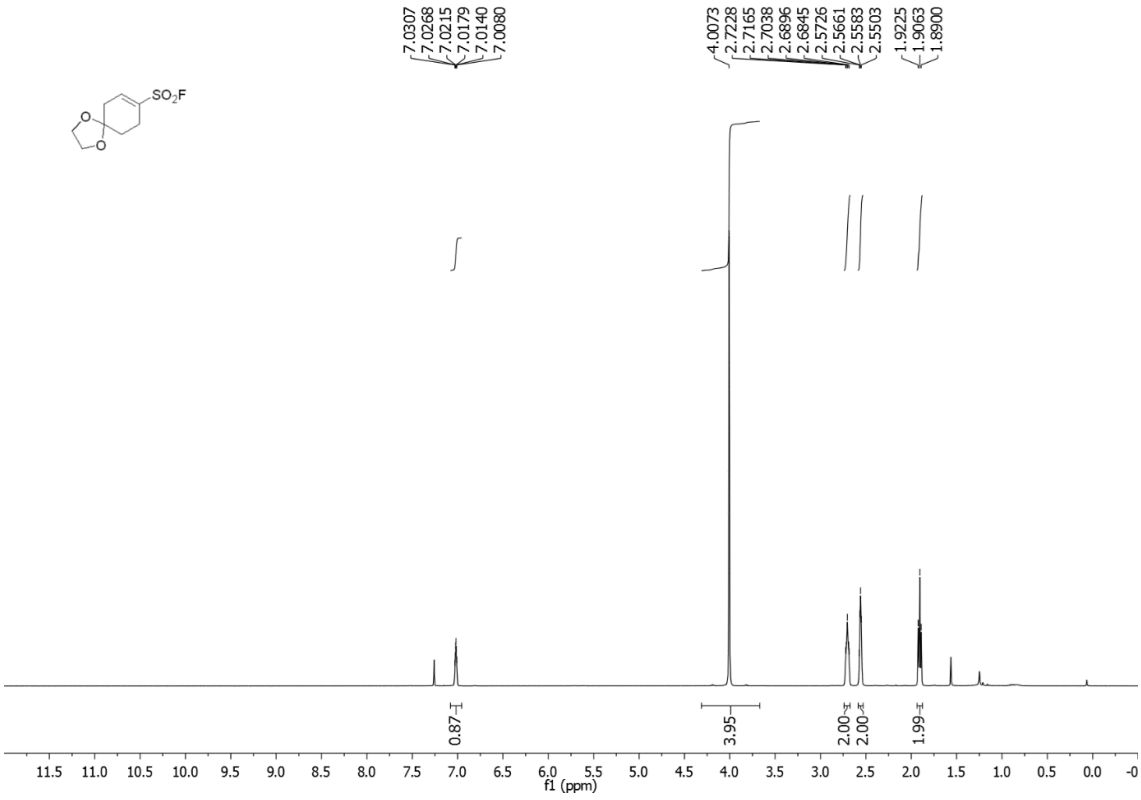


^{19}F-NMR Spectrum:

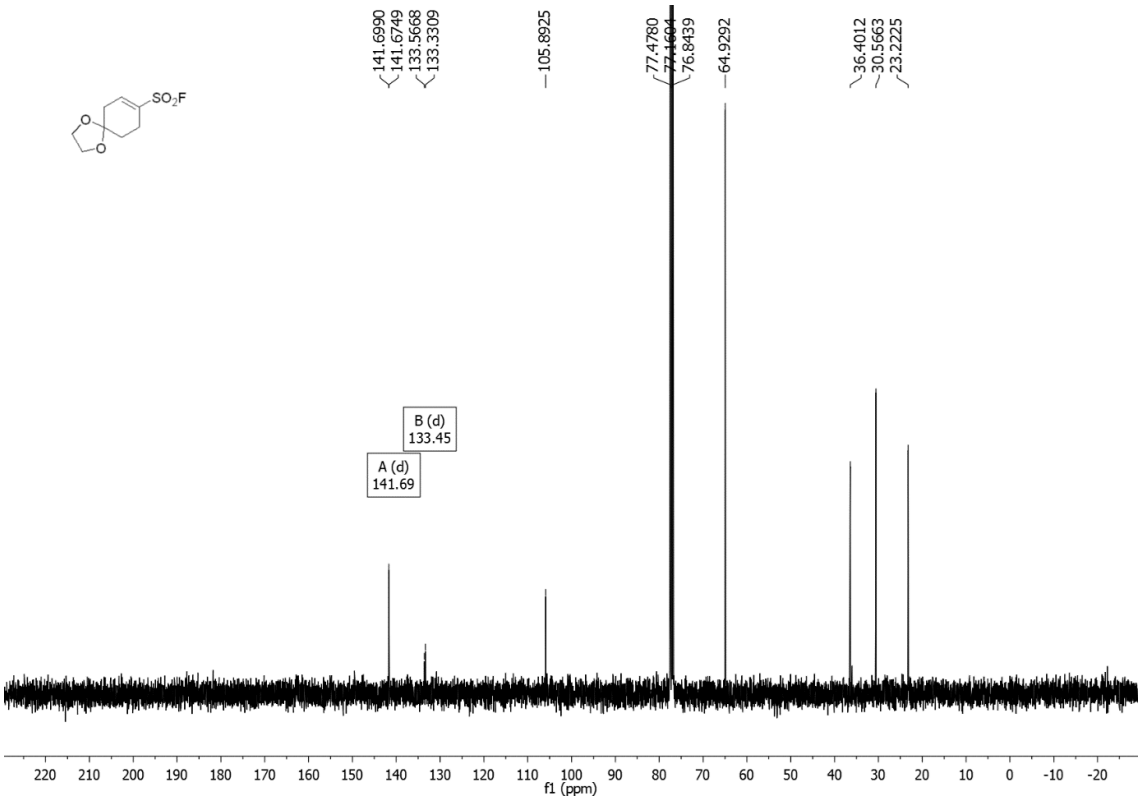


1,4-Dioxaspiro[4.5]dec-7-ene-8-sulfonyl fluoride (33h)

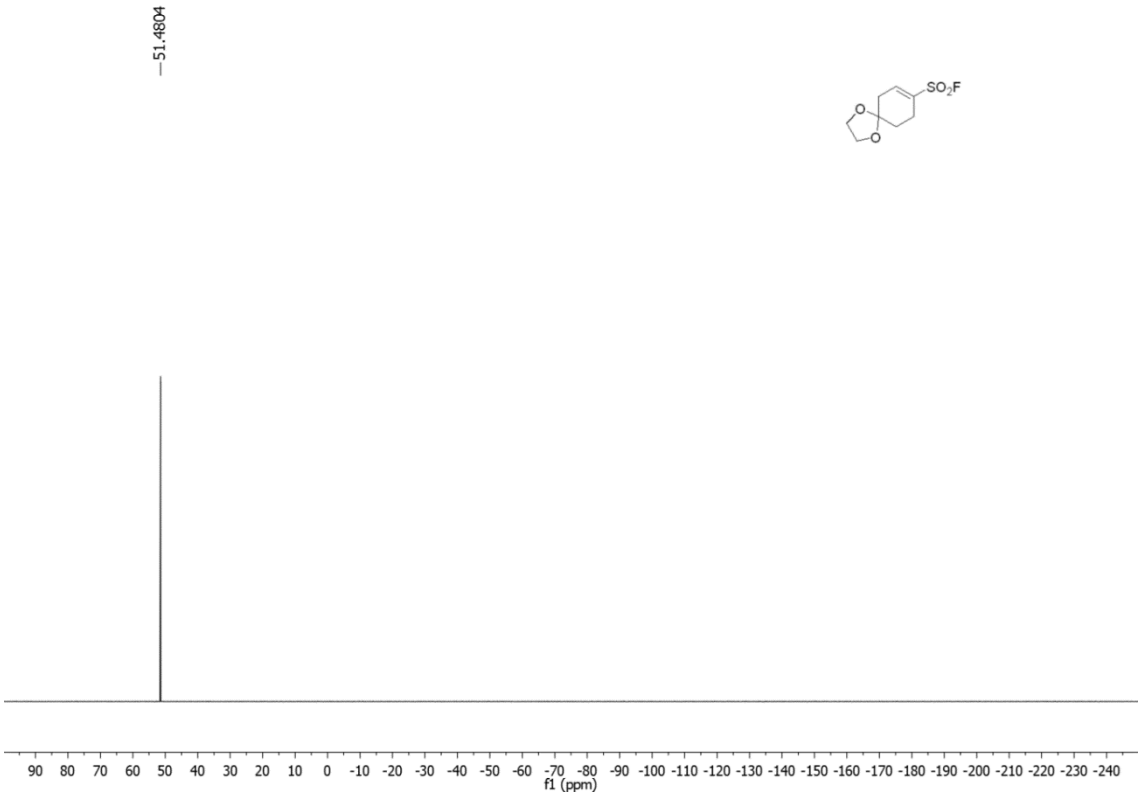
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

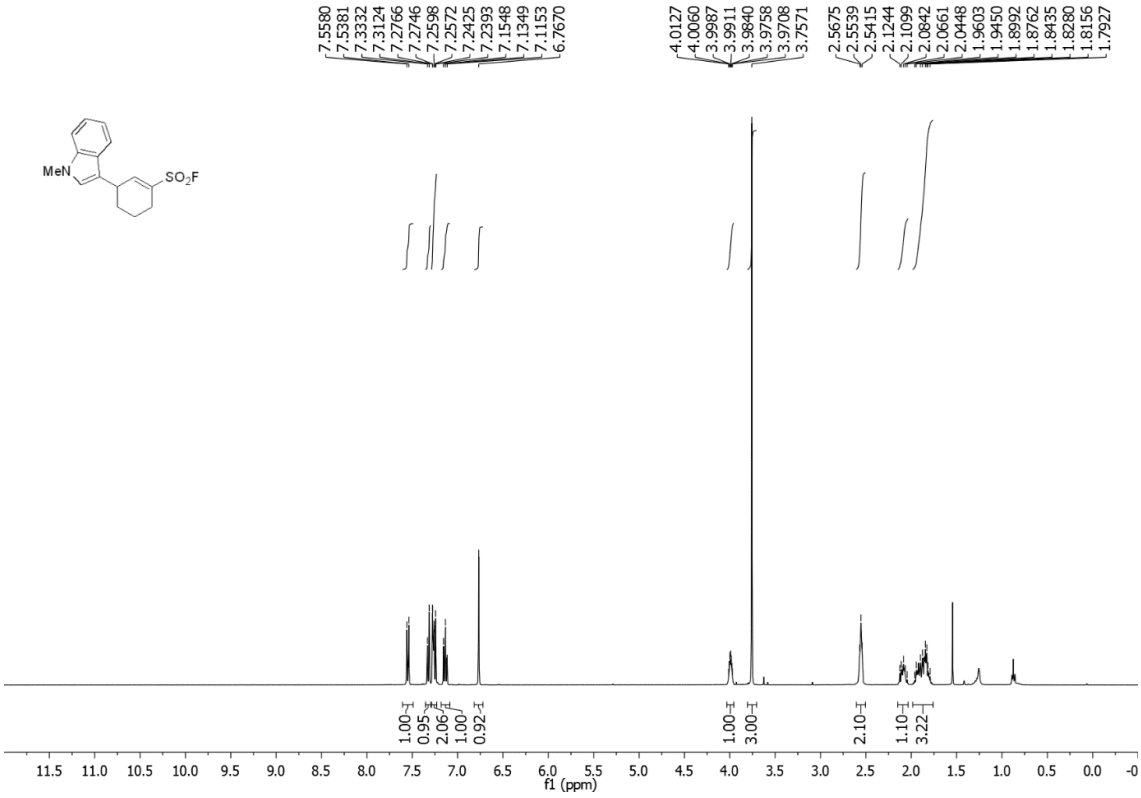


^{19}F-NMR Spectrum:

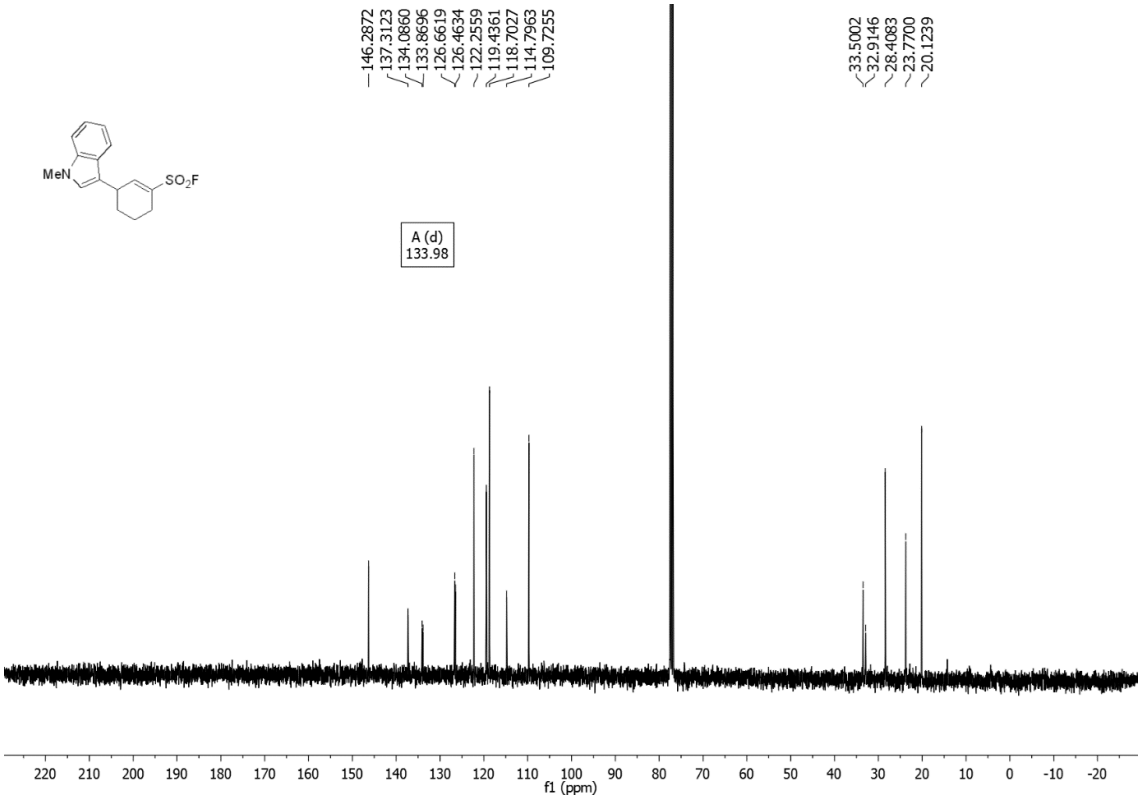


3-(1-Methyl-1*H*-indol-3-yl)cyclohex-1-ene-1-sulfonyl fluoride (33i)

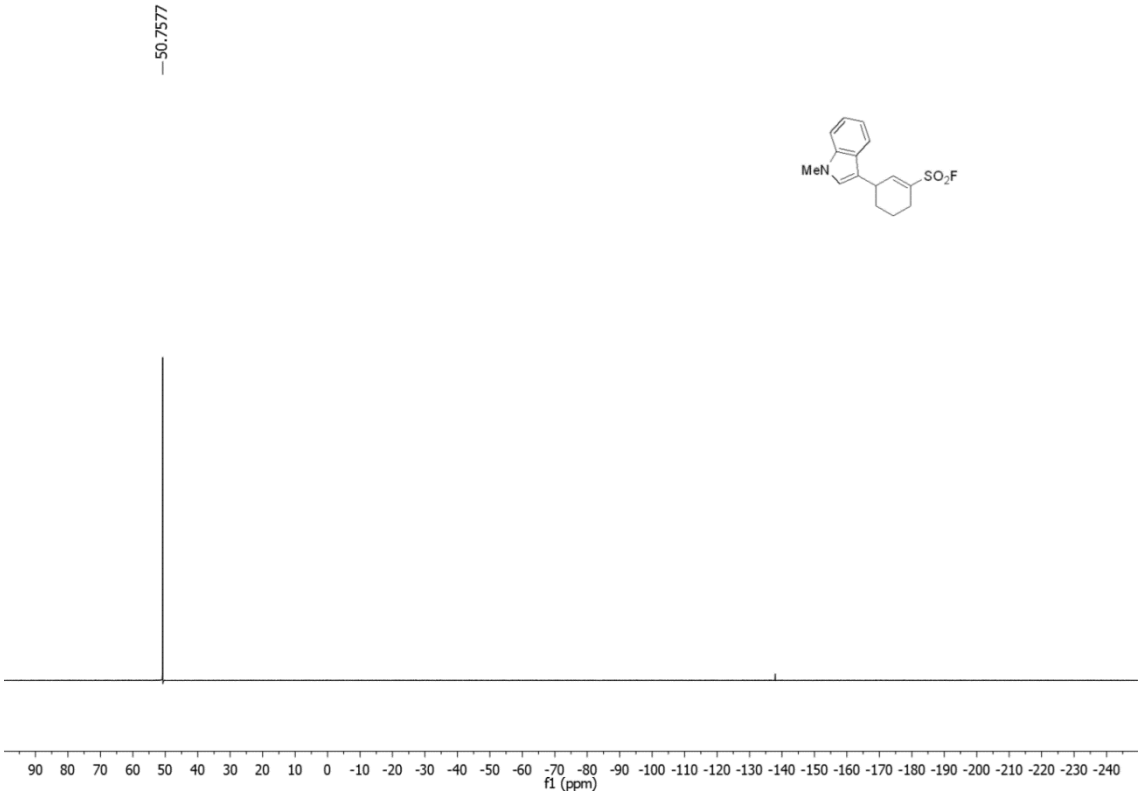
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

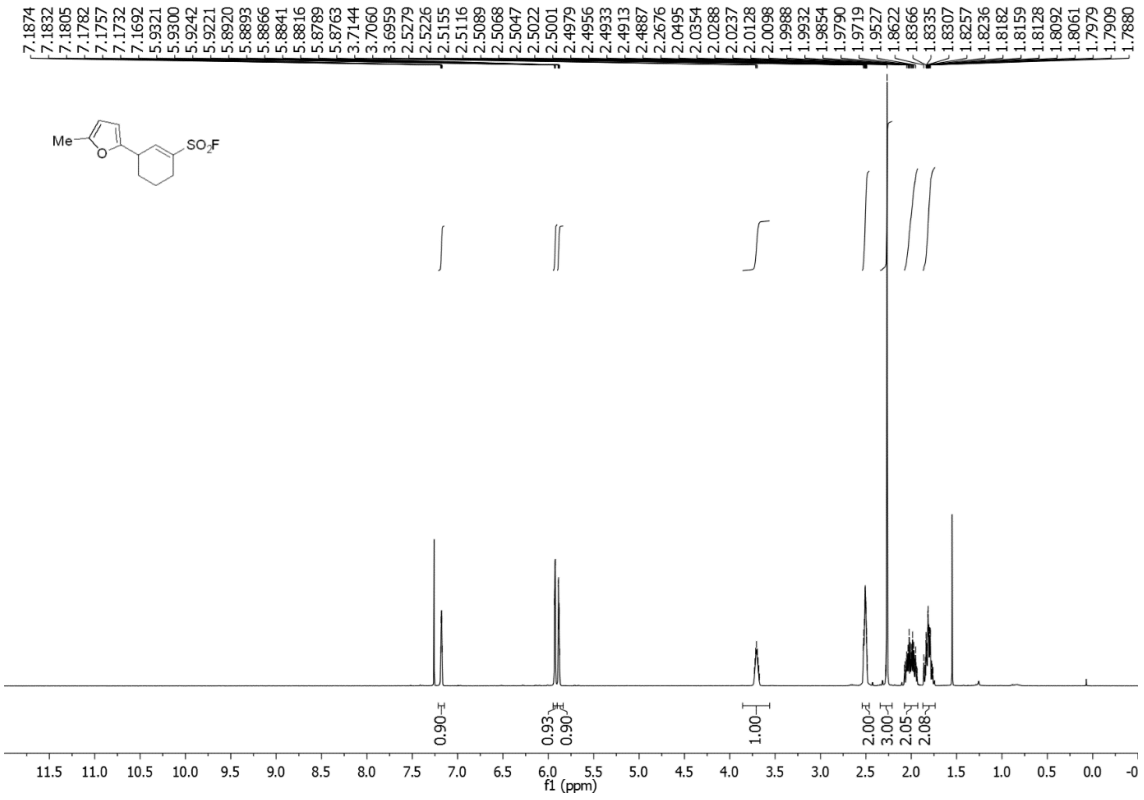


^{19}F-NMR Spectrum:

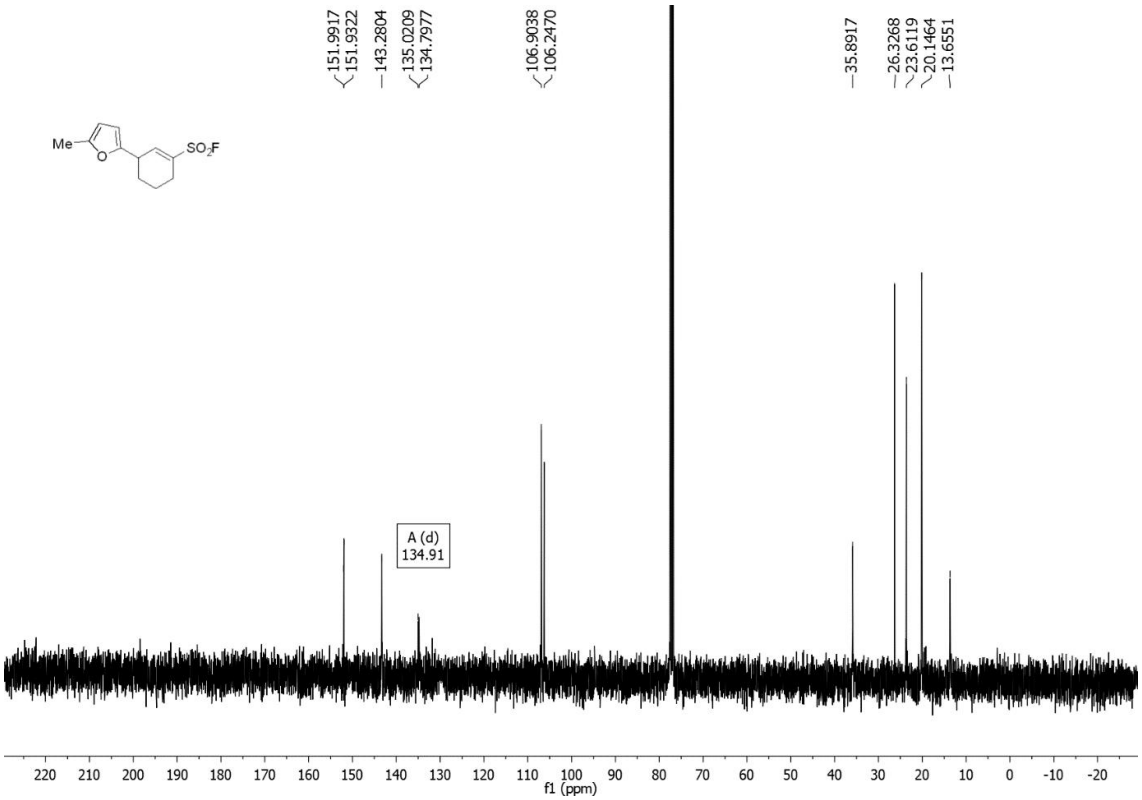


3-(5-Methylfuran-2-yl)cyclohex-1-ene-1-sulfonyl fluoride (33k)

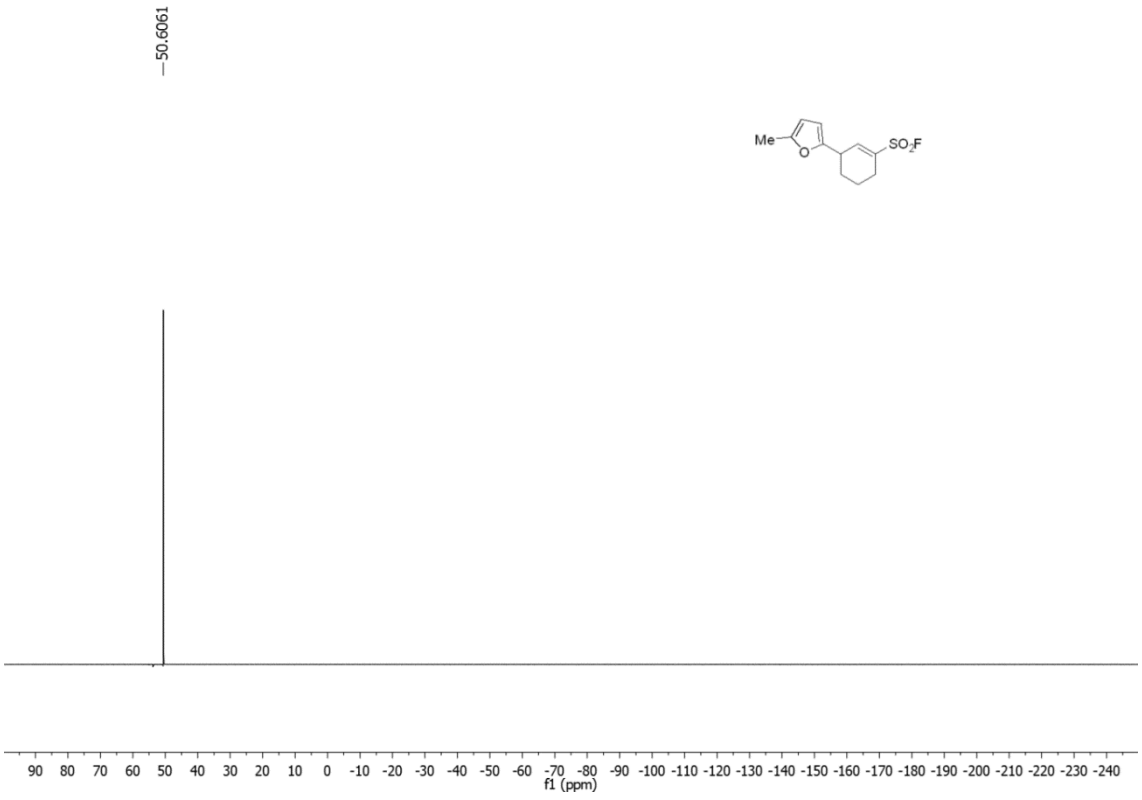
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

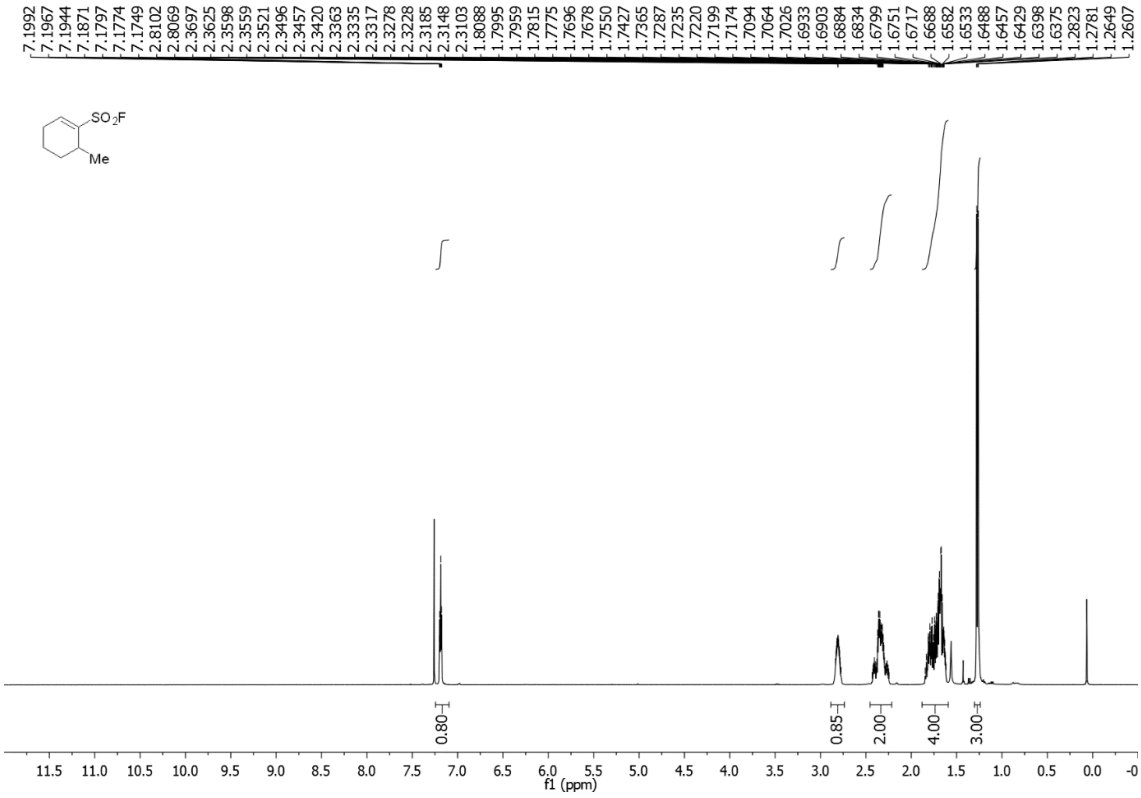


^{19}F-NMR Spectrum:

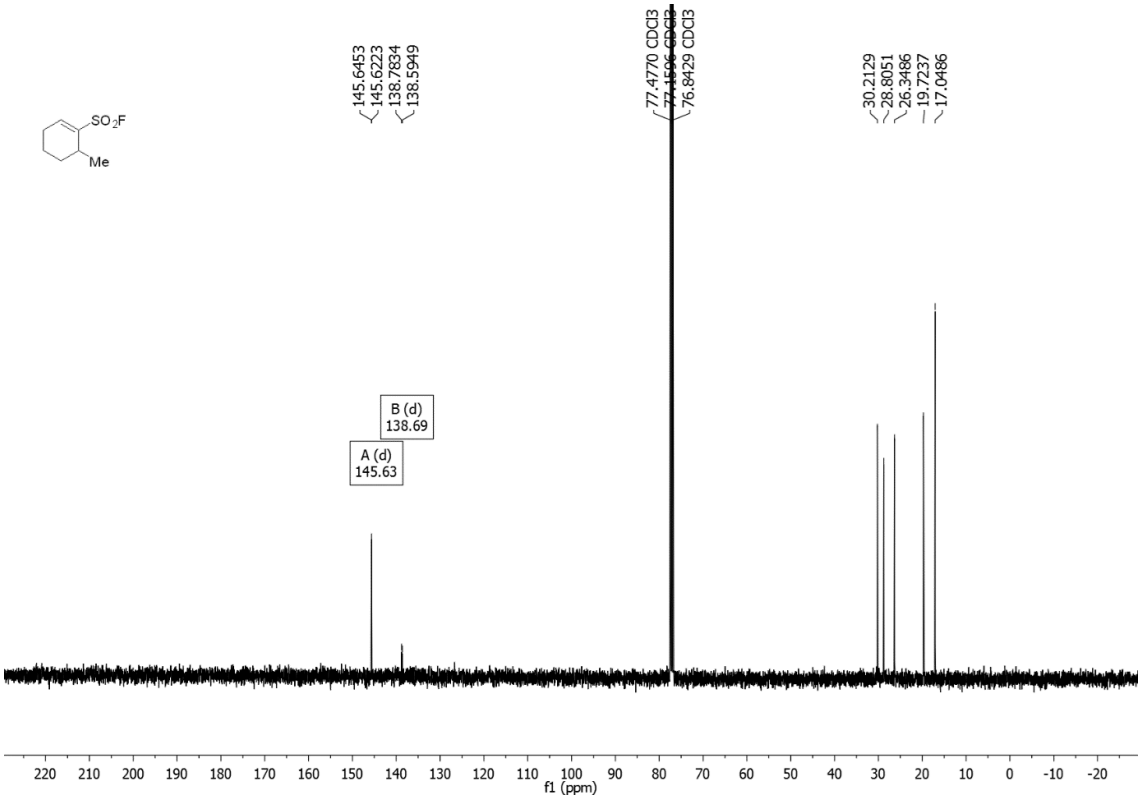


6-Methylcyclohex-1-ene-1-sulfonyl fluoride (33l)

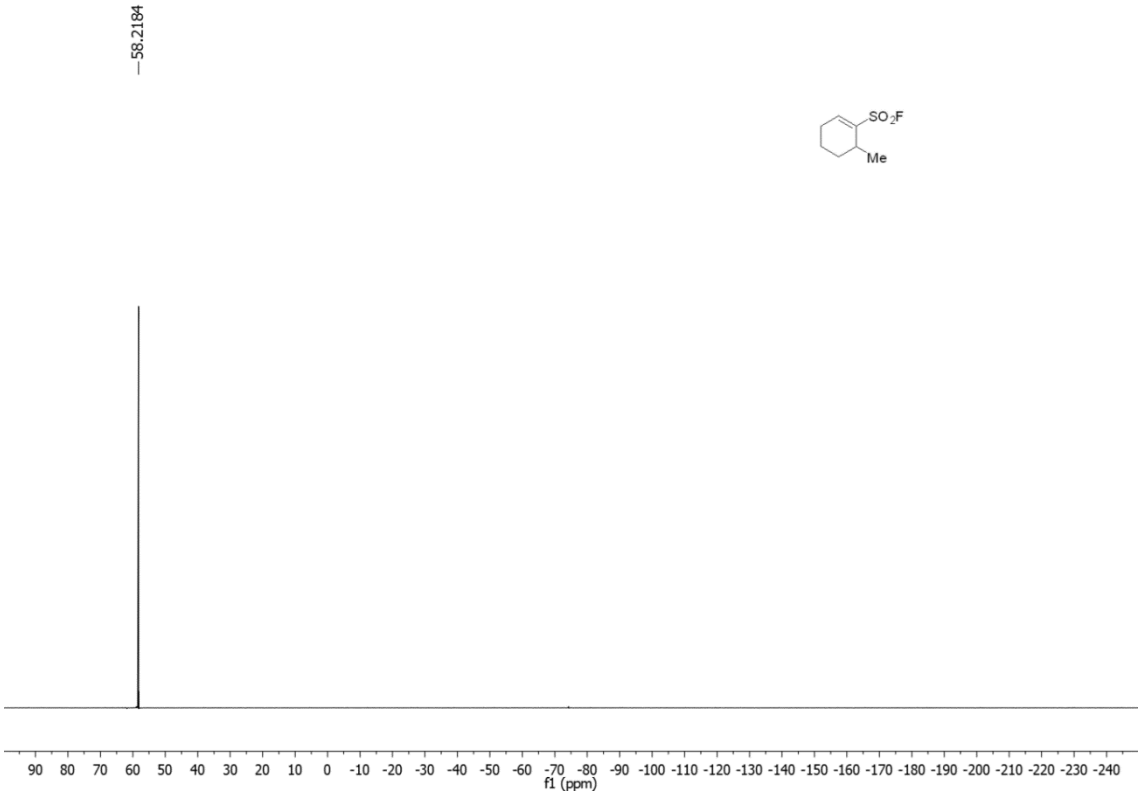
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

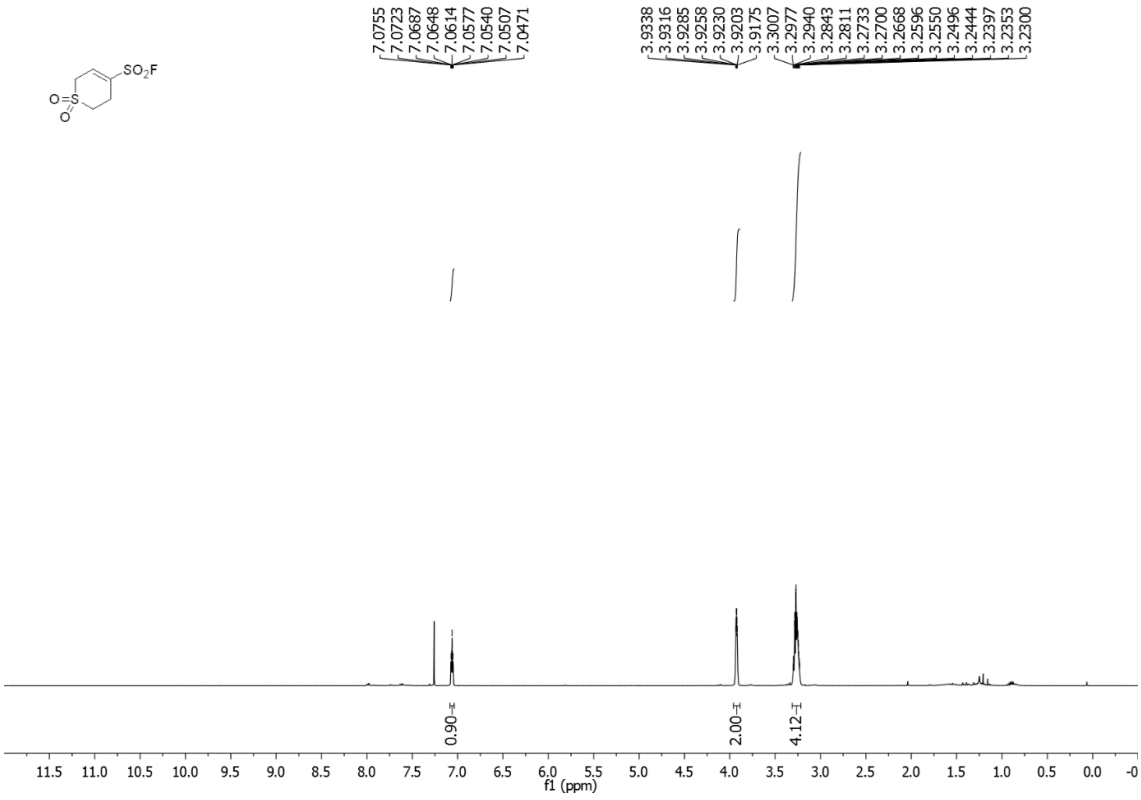


^{19}F-NMR Spectrum:

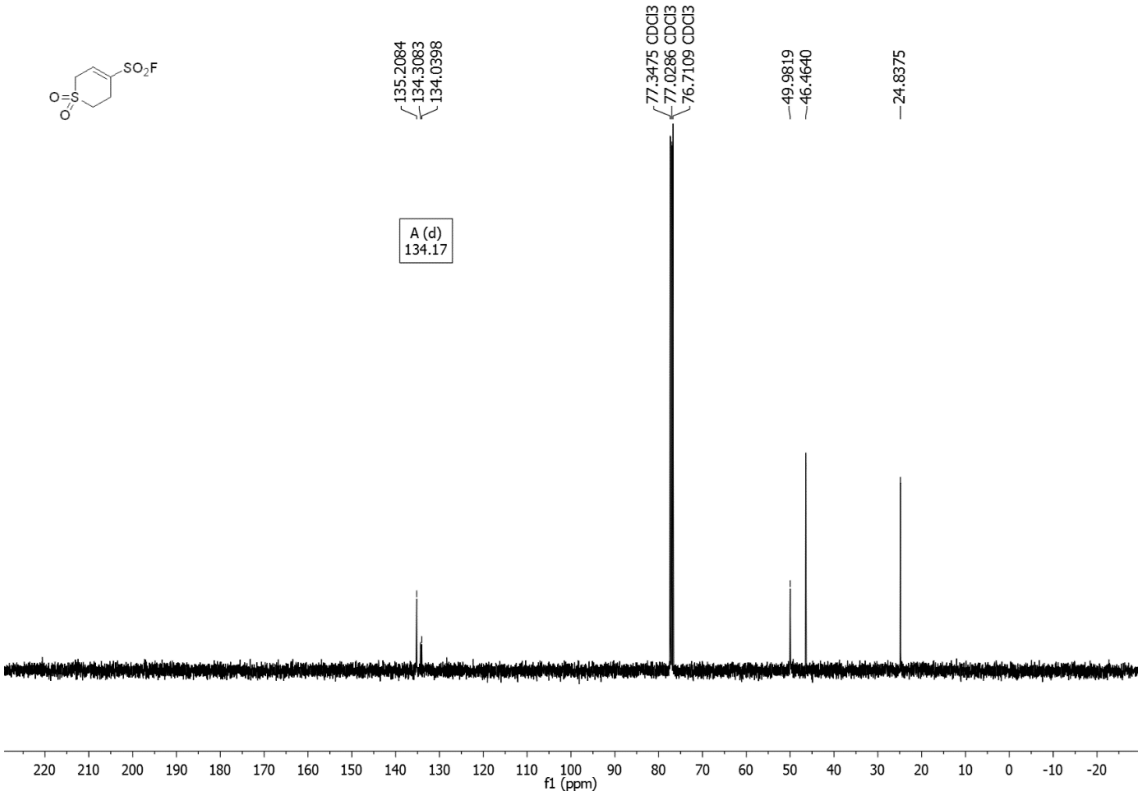


3,6-Dihydro-2*H*-thiopyran-4-sulfonyl fluoride 1,1-dioxide (33m)

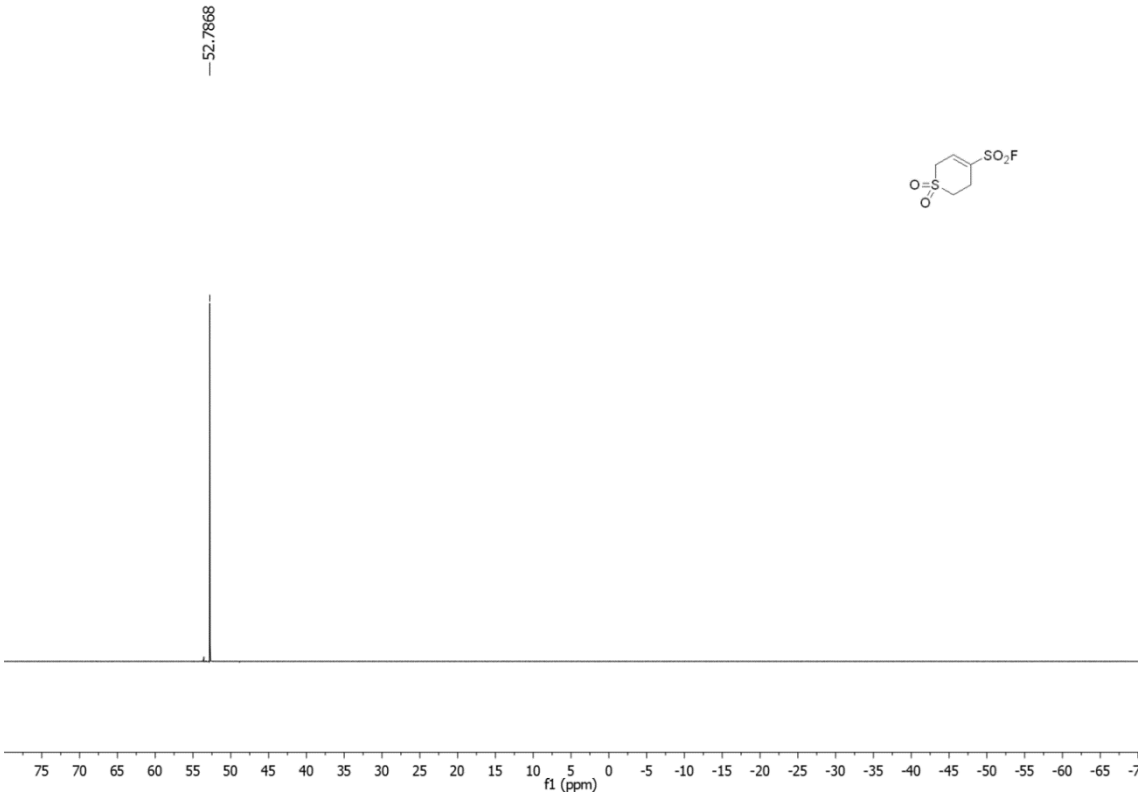
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

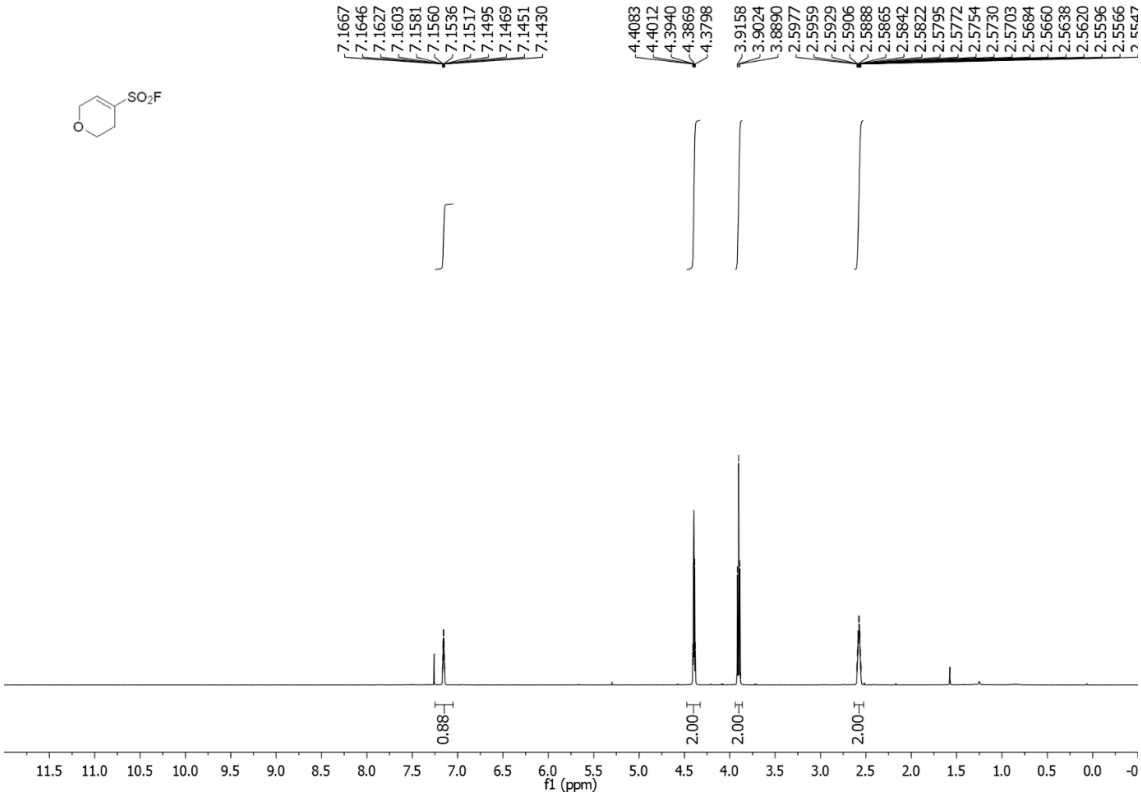


^{19}F-NMR Spectrum:

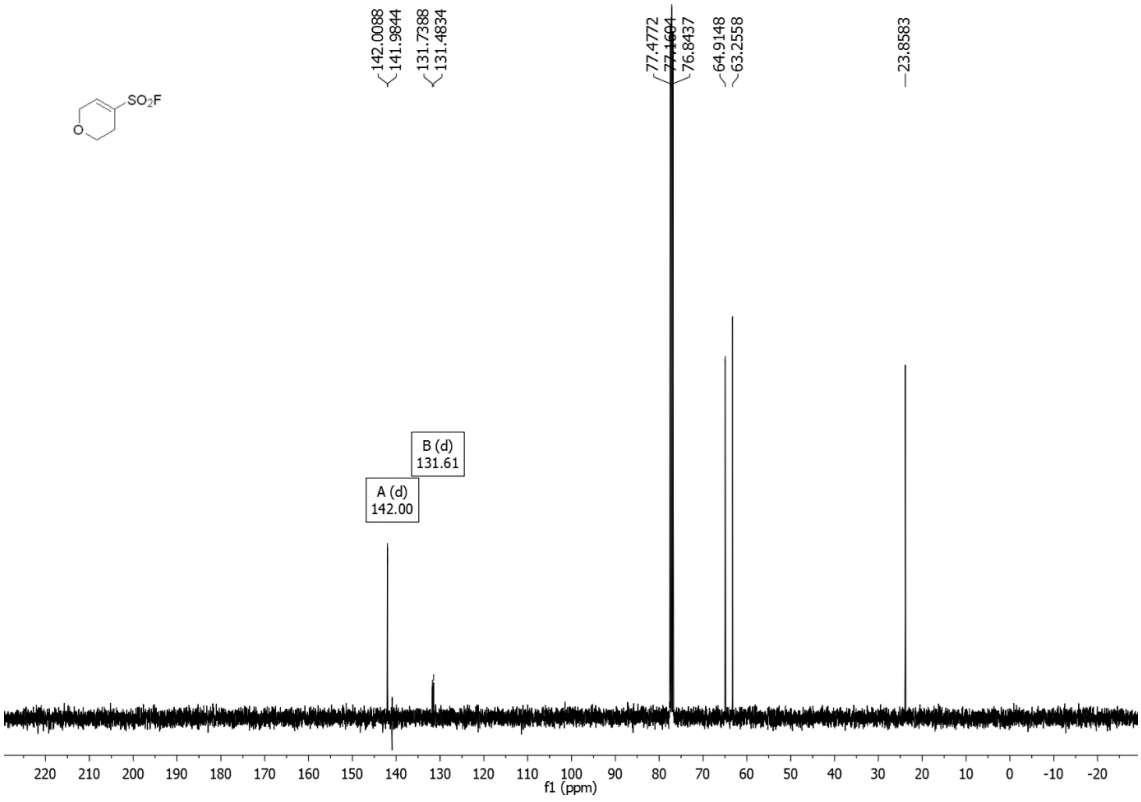


3,6-Dihydro-2*H*-pyran-4-sulfonyl fluoride (33n)

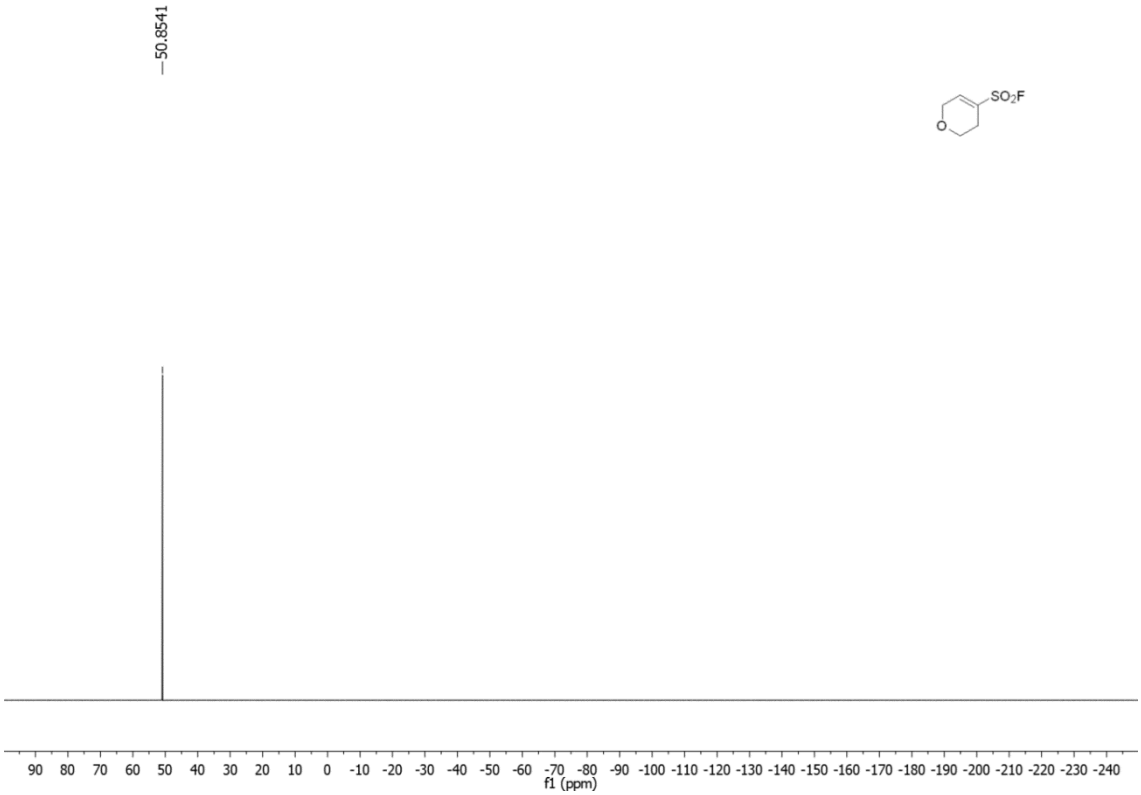
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

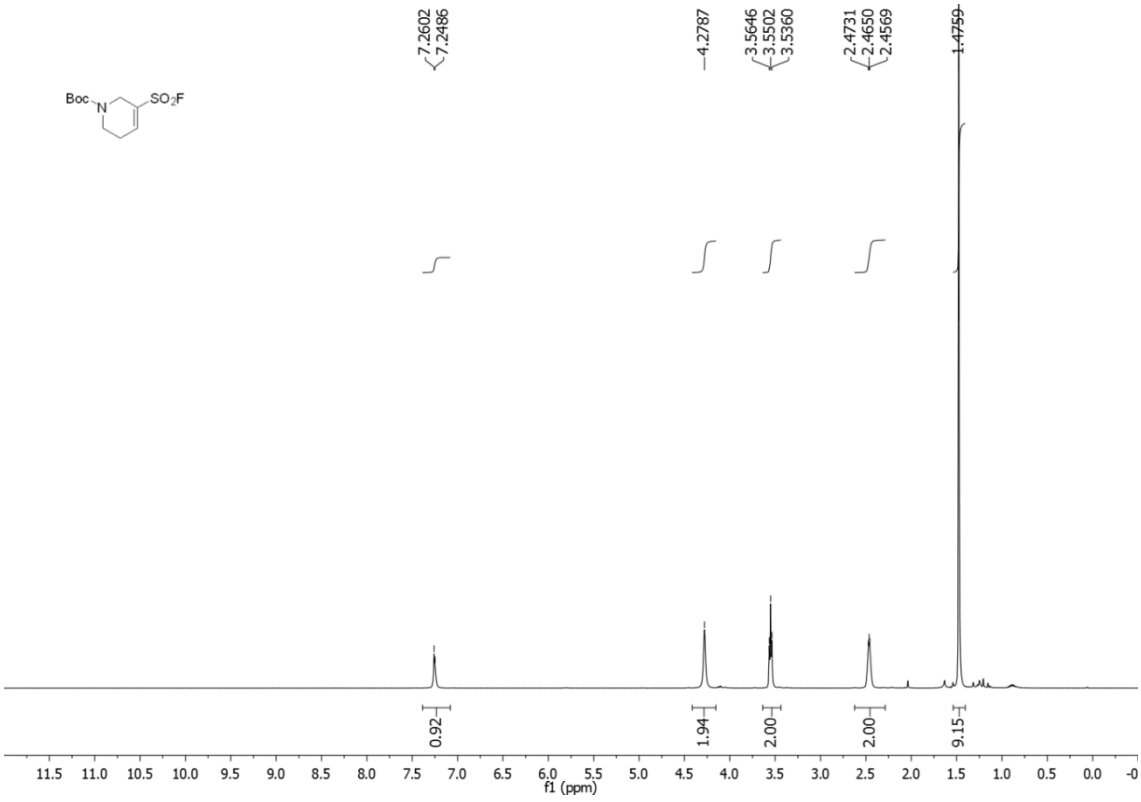


^{19}F-NMR Spectrum:

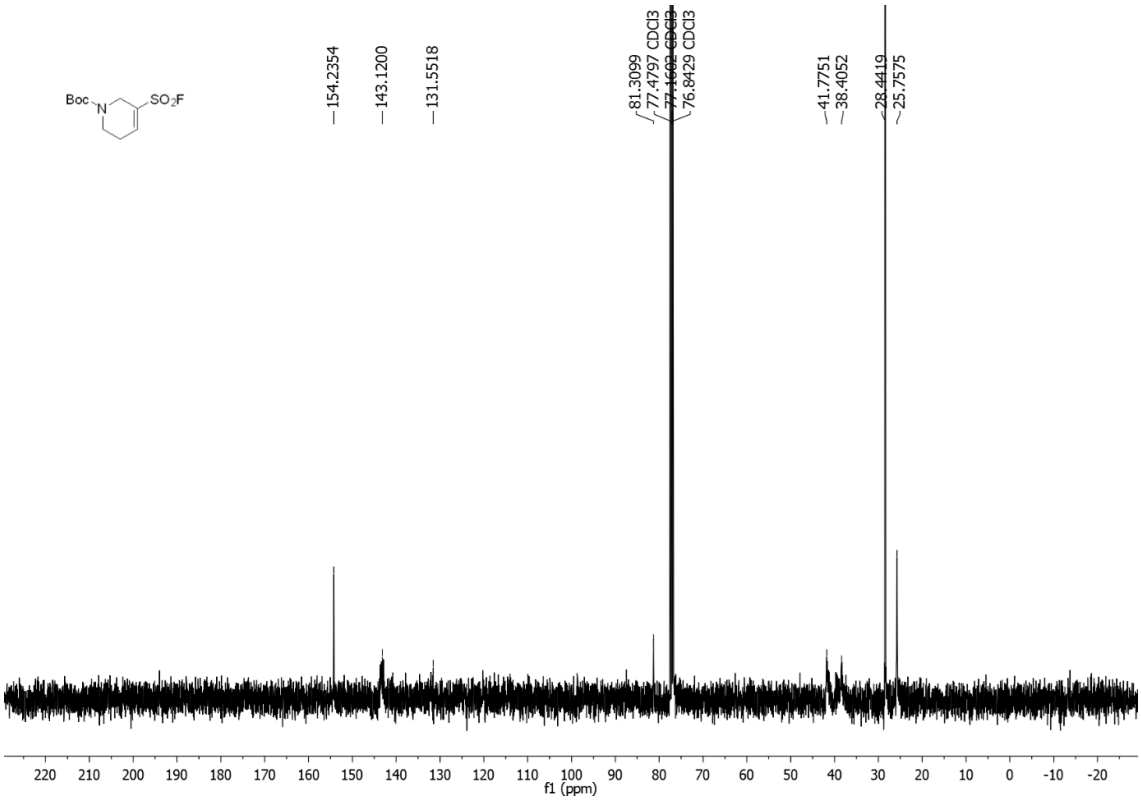


tert-Butyl 5-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33o)

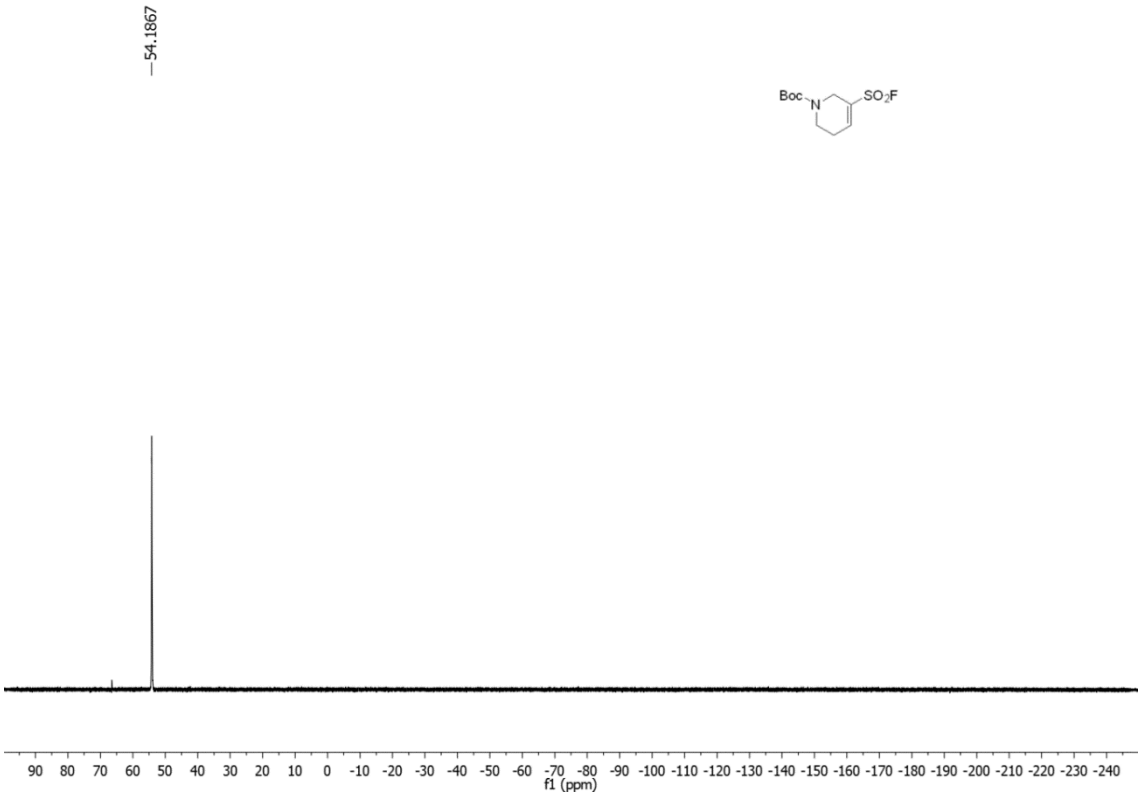
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

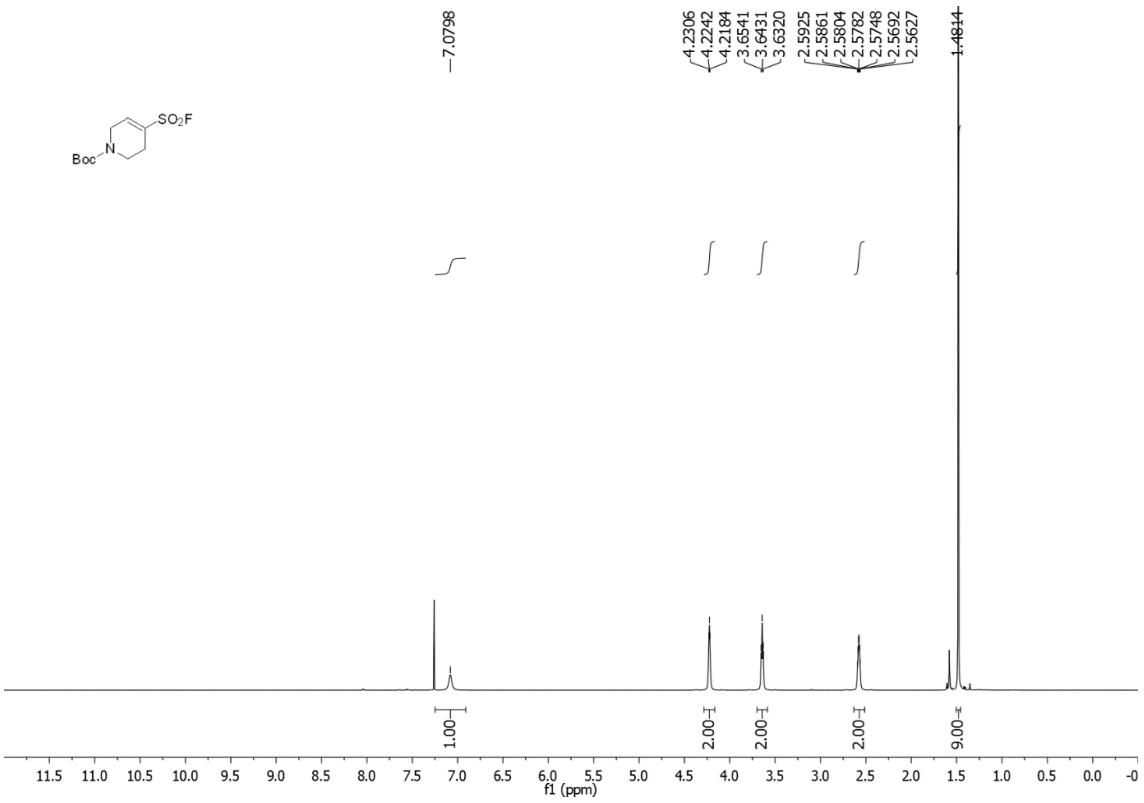


^{19}F-NMR Spectrum:

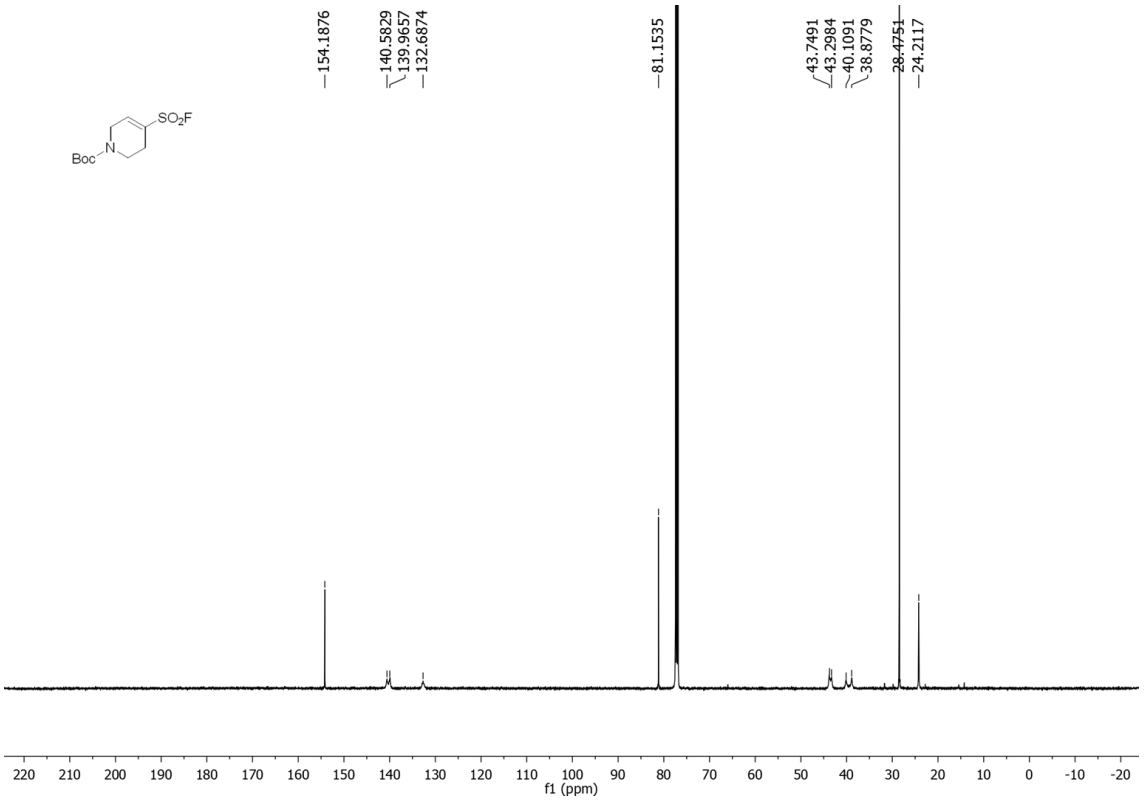


tert-Butyl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33p)

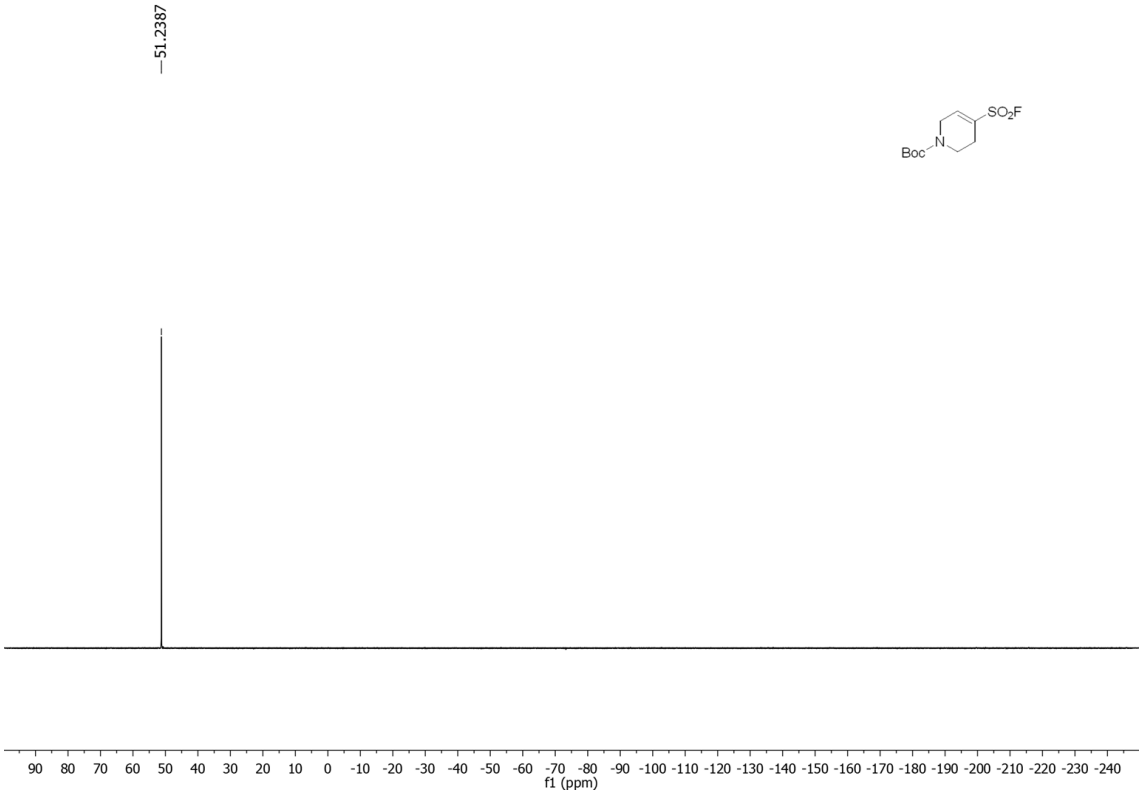
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

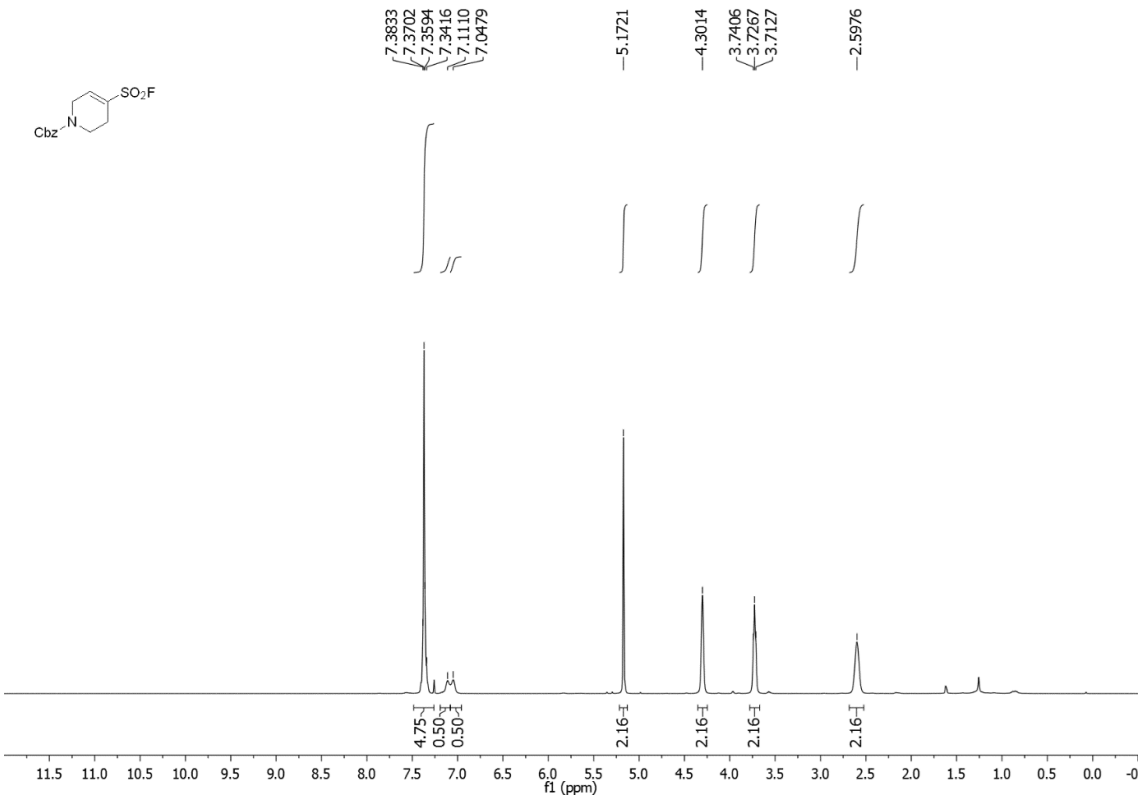


^{19}F-NMR Spectrum:

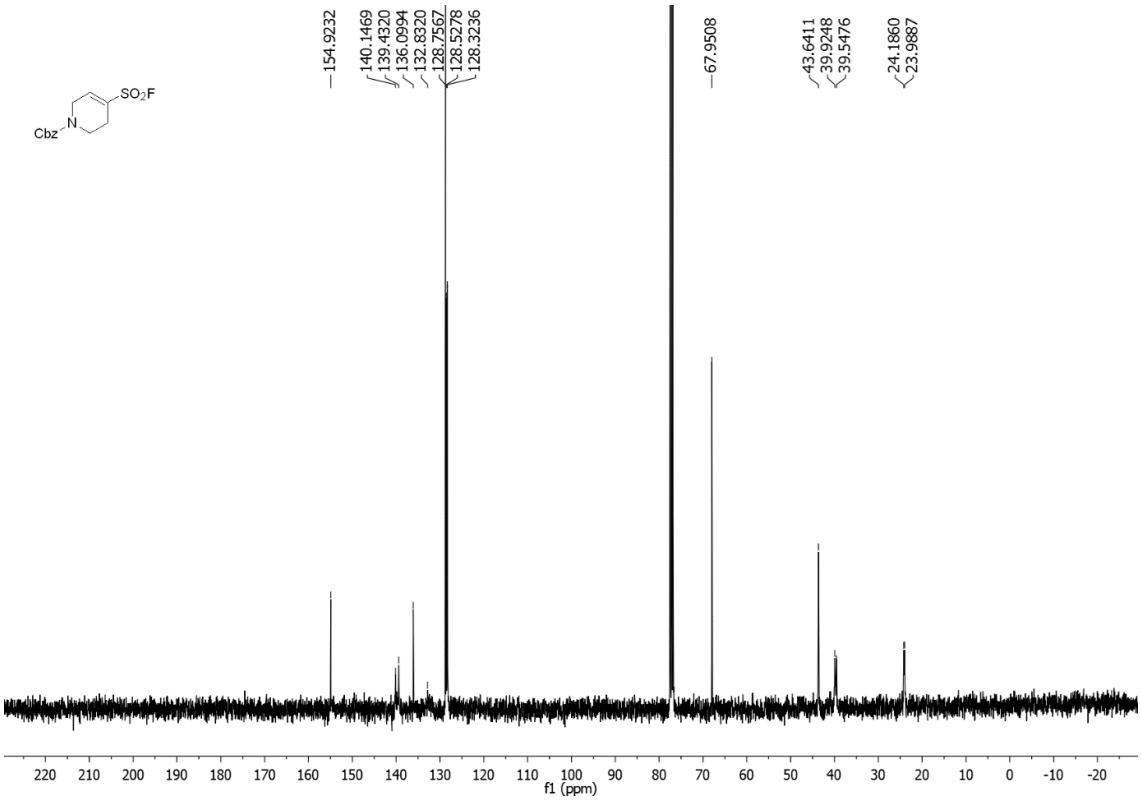


Benzyl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (33q)

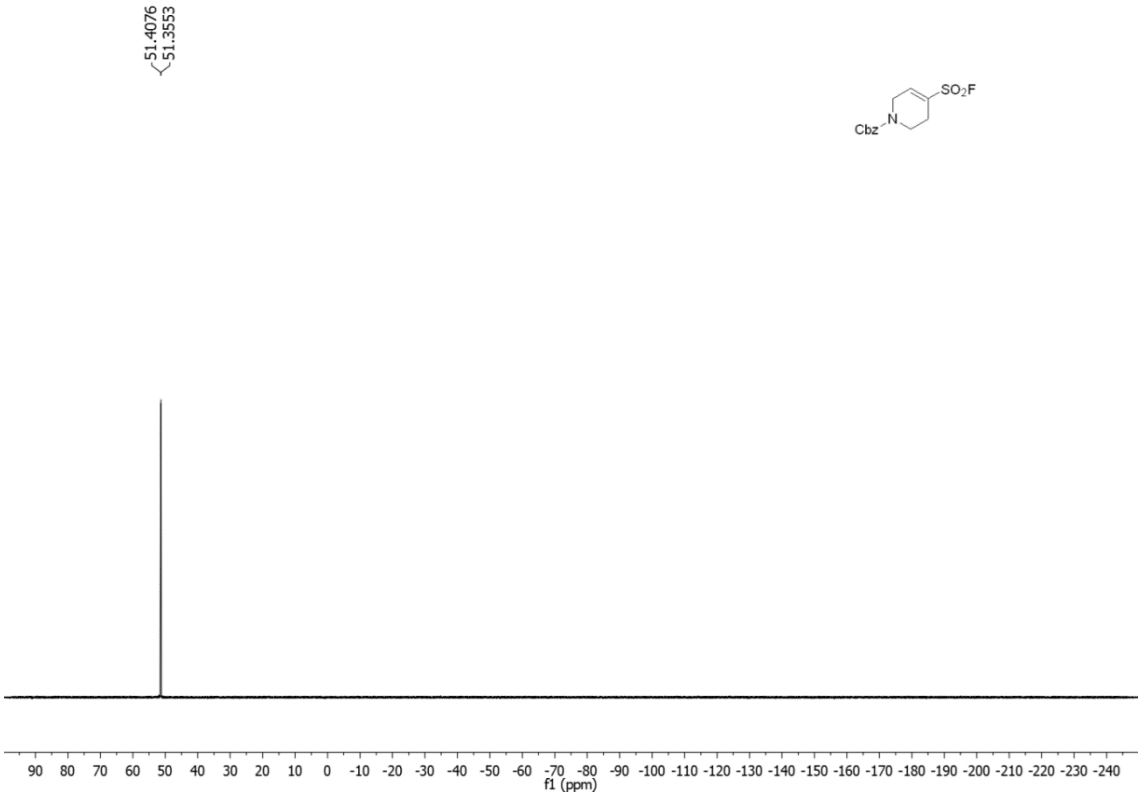
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

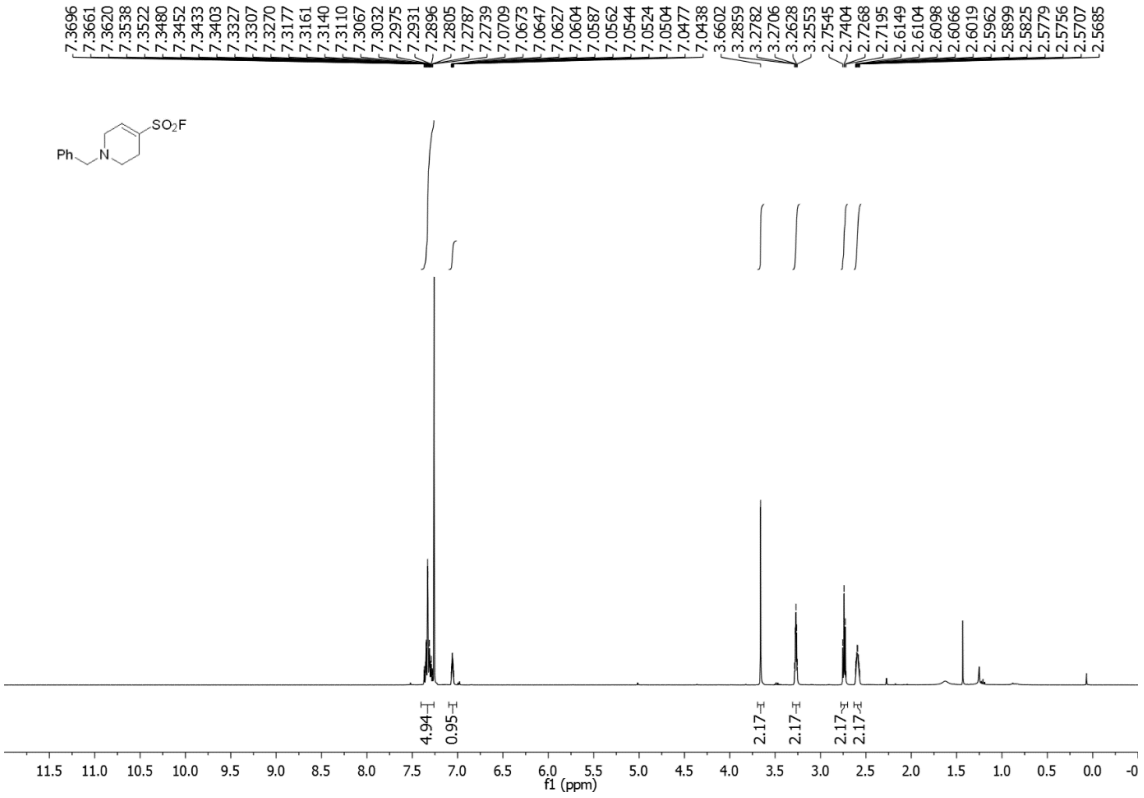


^{19}F-NMR Spectrum:

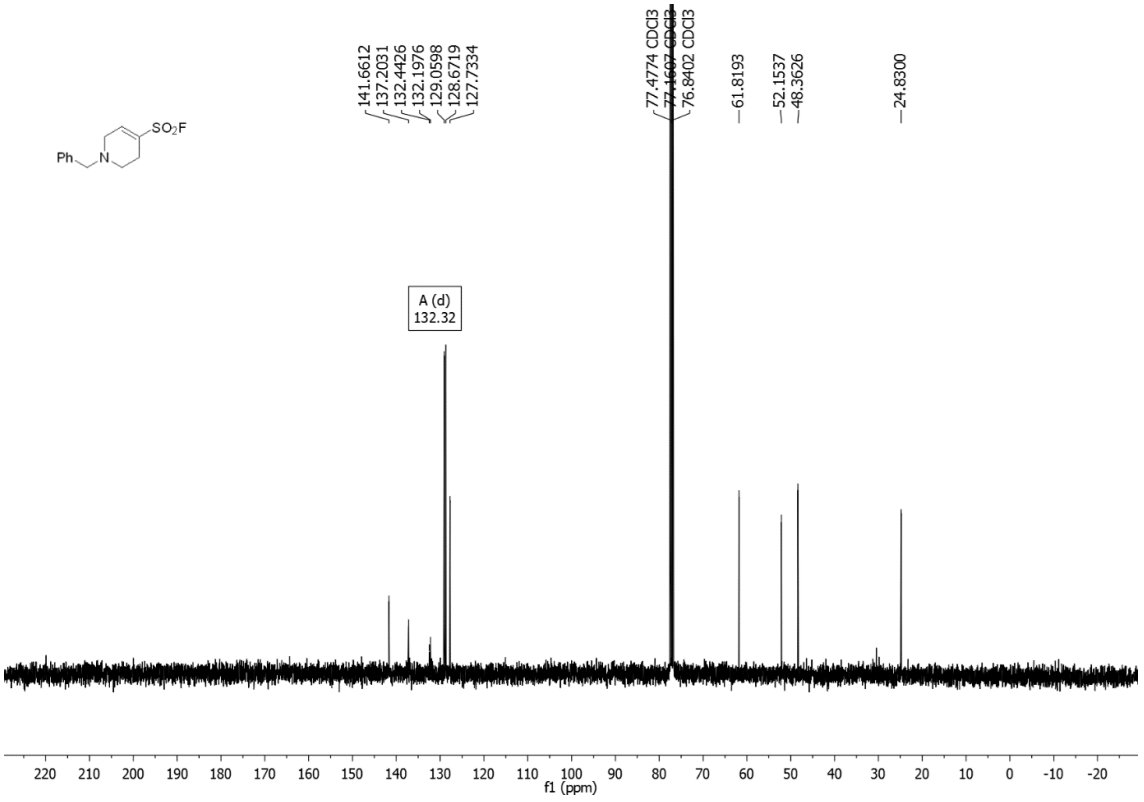


1-Benzyl-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (33r)

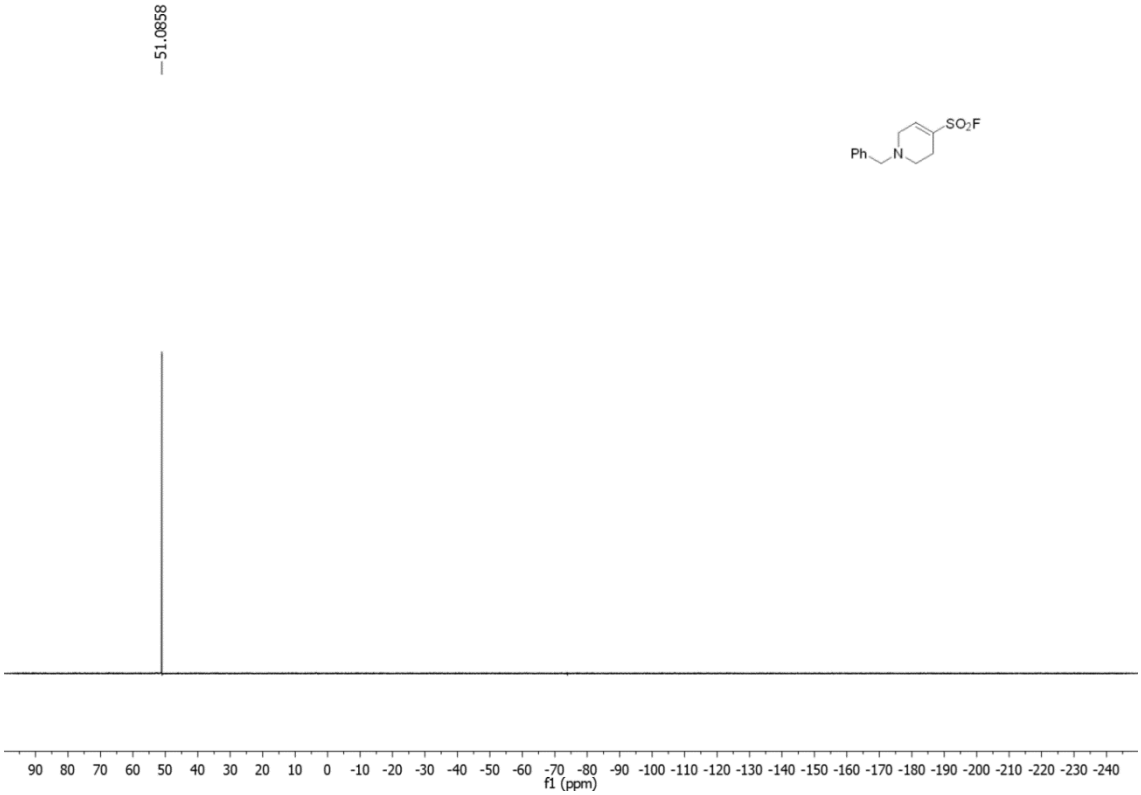
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

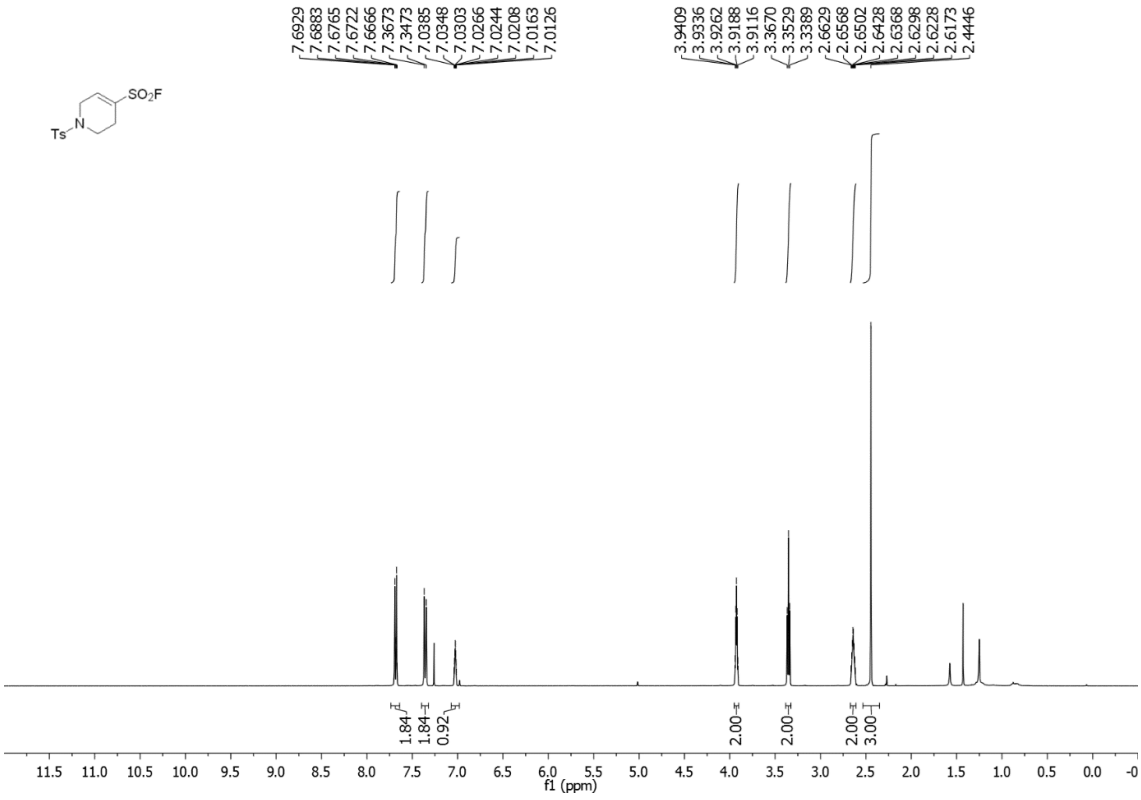


^{19}F-NMR Spectrum:

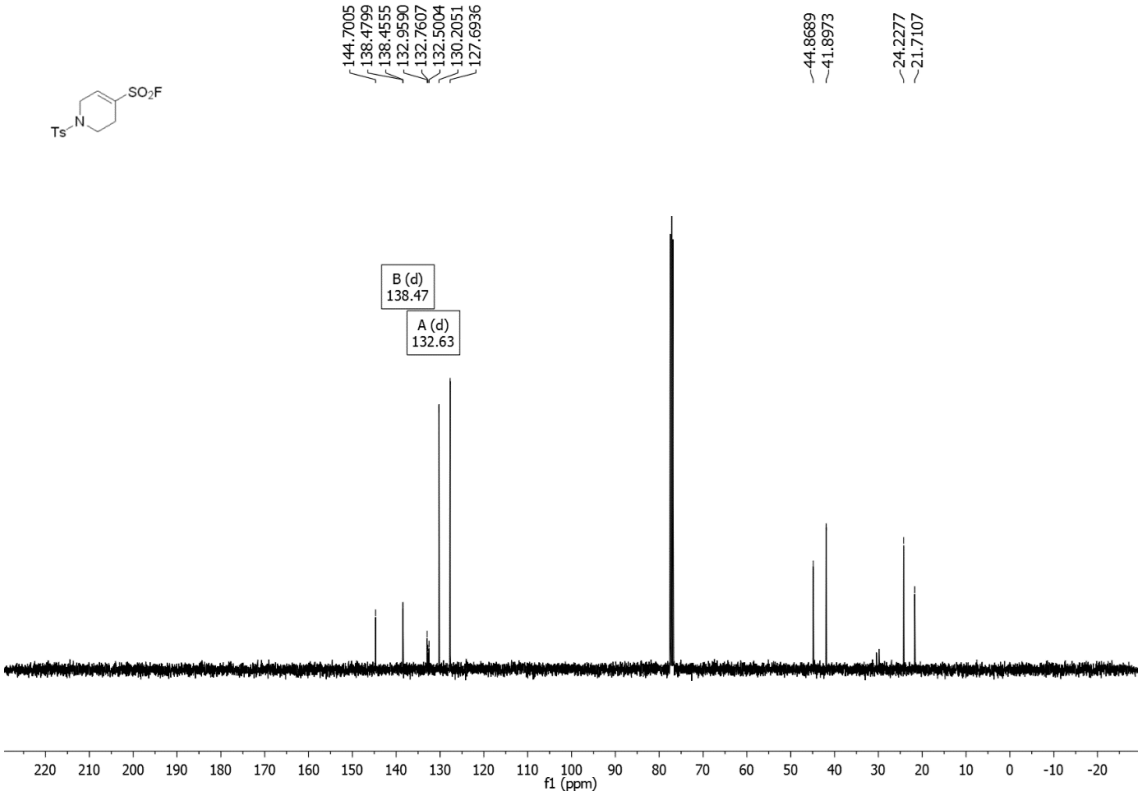


1-Tosyl-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (33s)

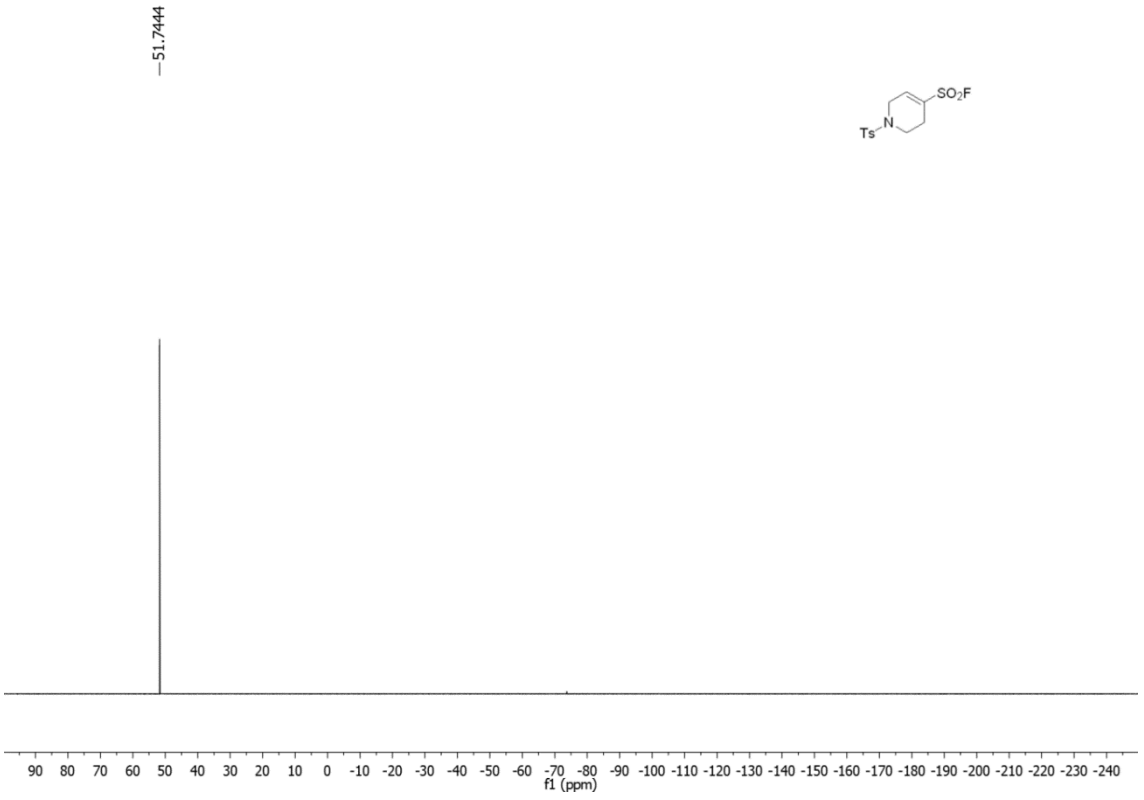
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

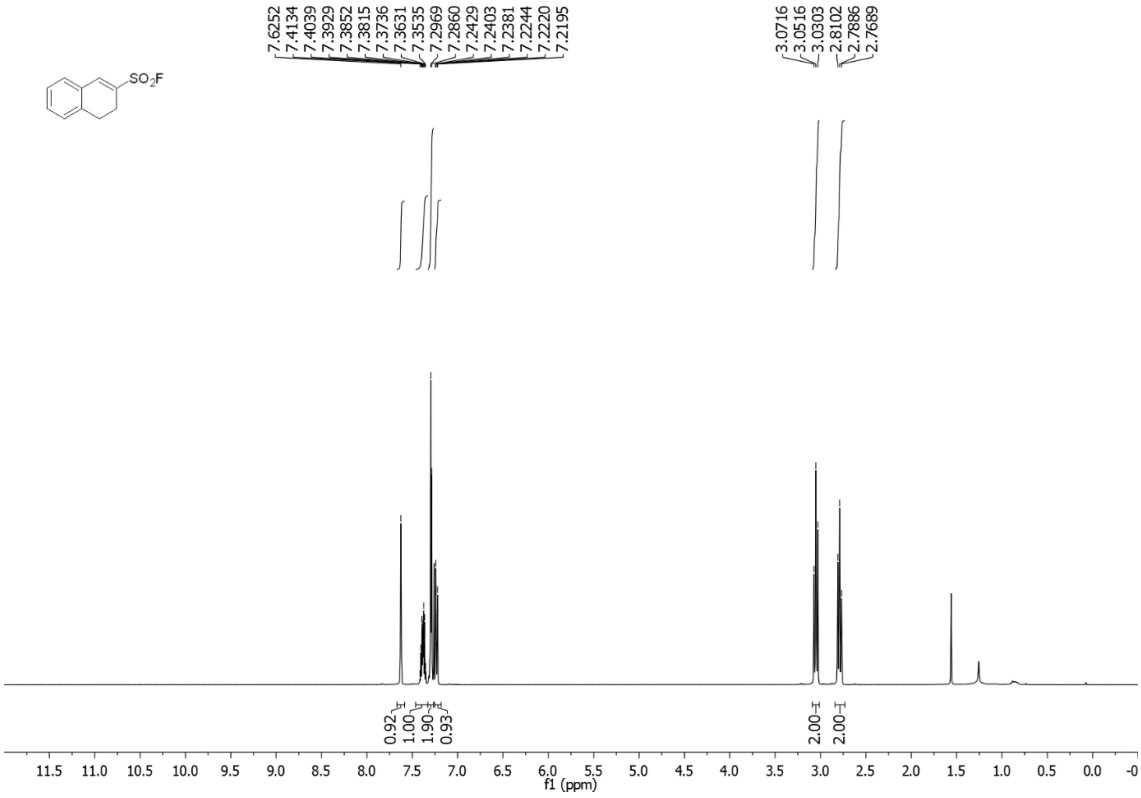


^{19}F-NMR Spectrum:

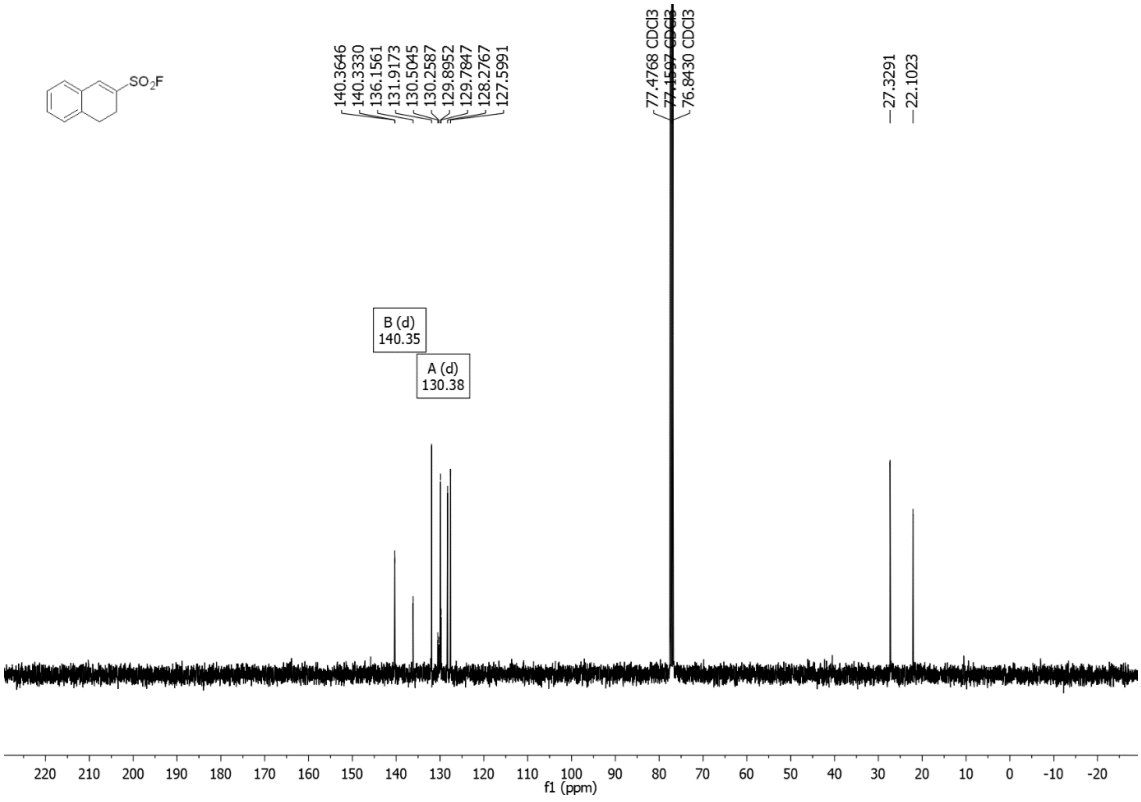


3,4-Dihydronaphthalene-2-sulfonyl fluoride (33u)

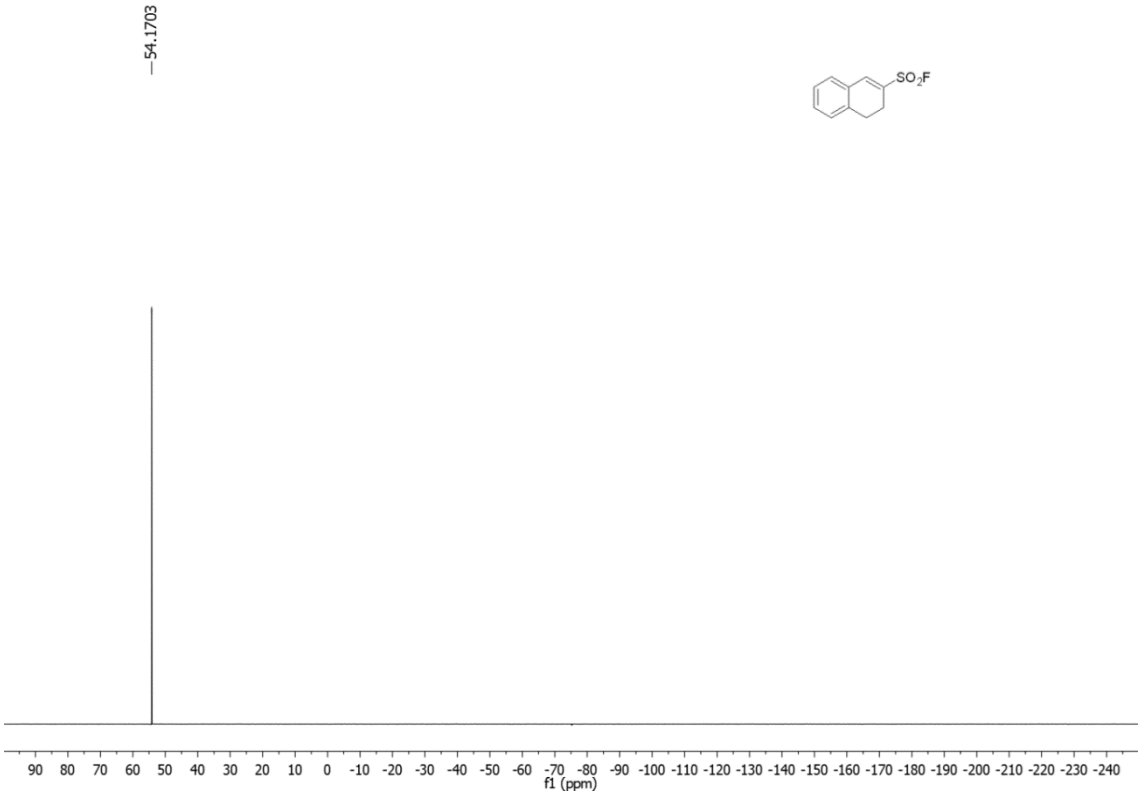
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

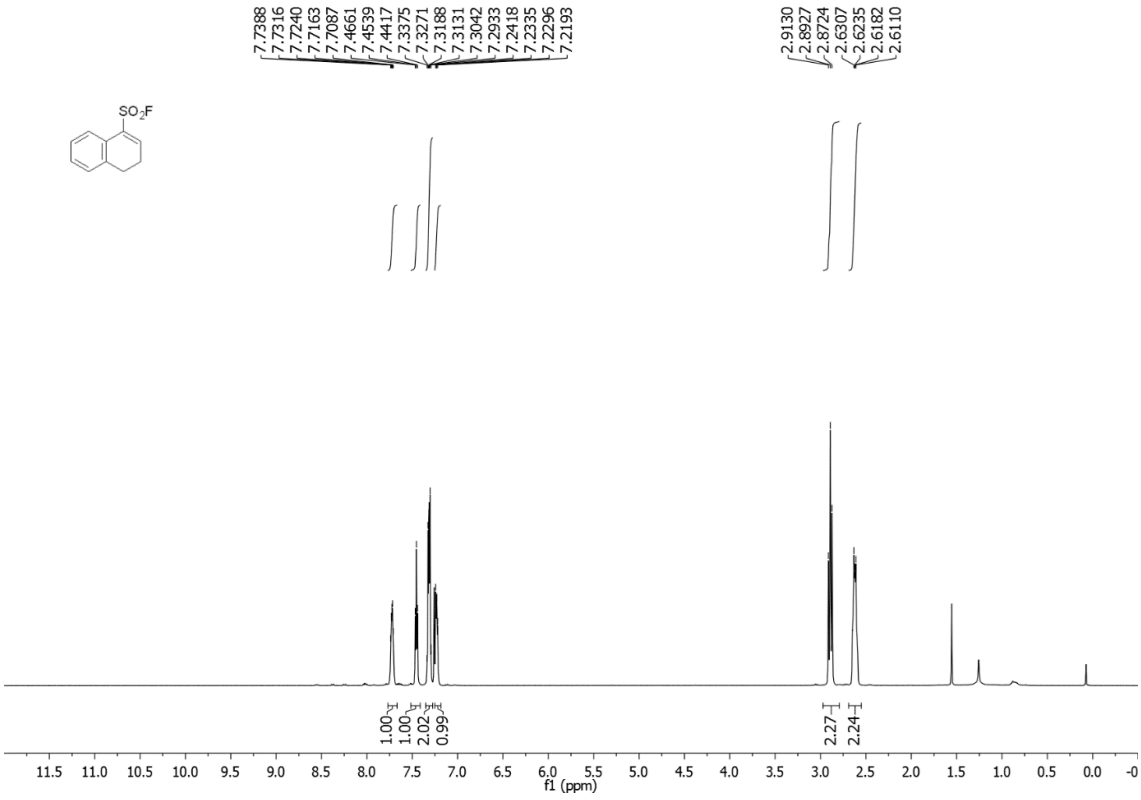


^{19}F-NMR Spectrum:

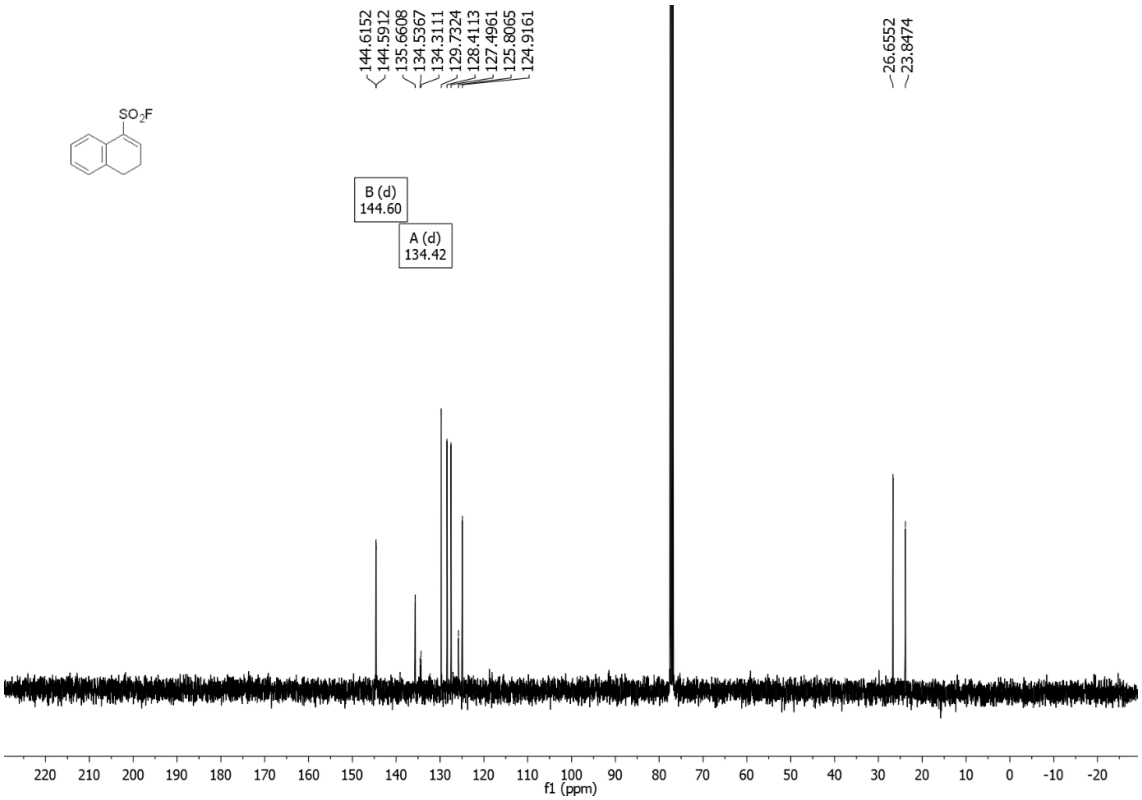


3,4-Dihydronaphthalene-1-sulfonyl fluoride (33v)

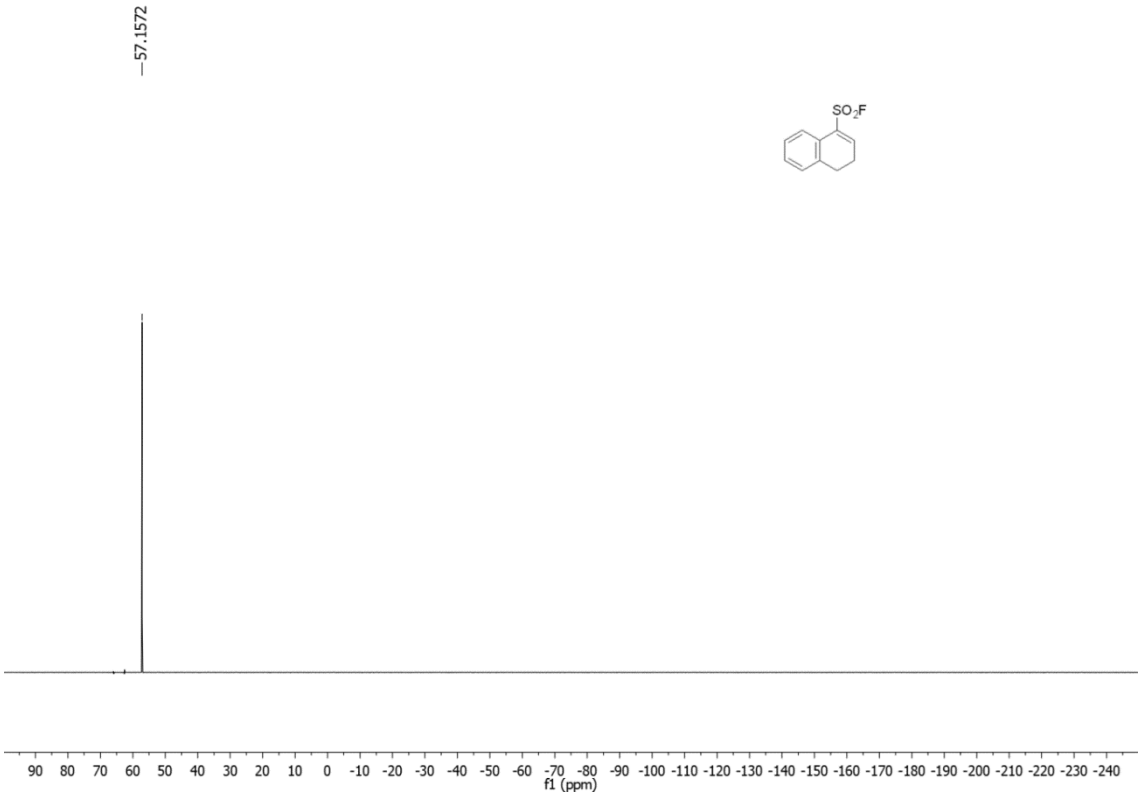
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

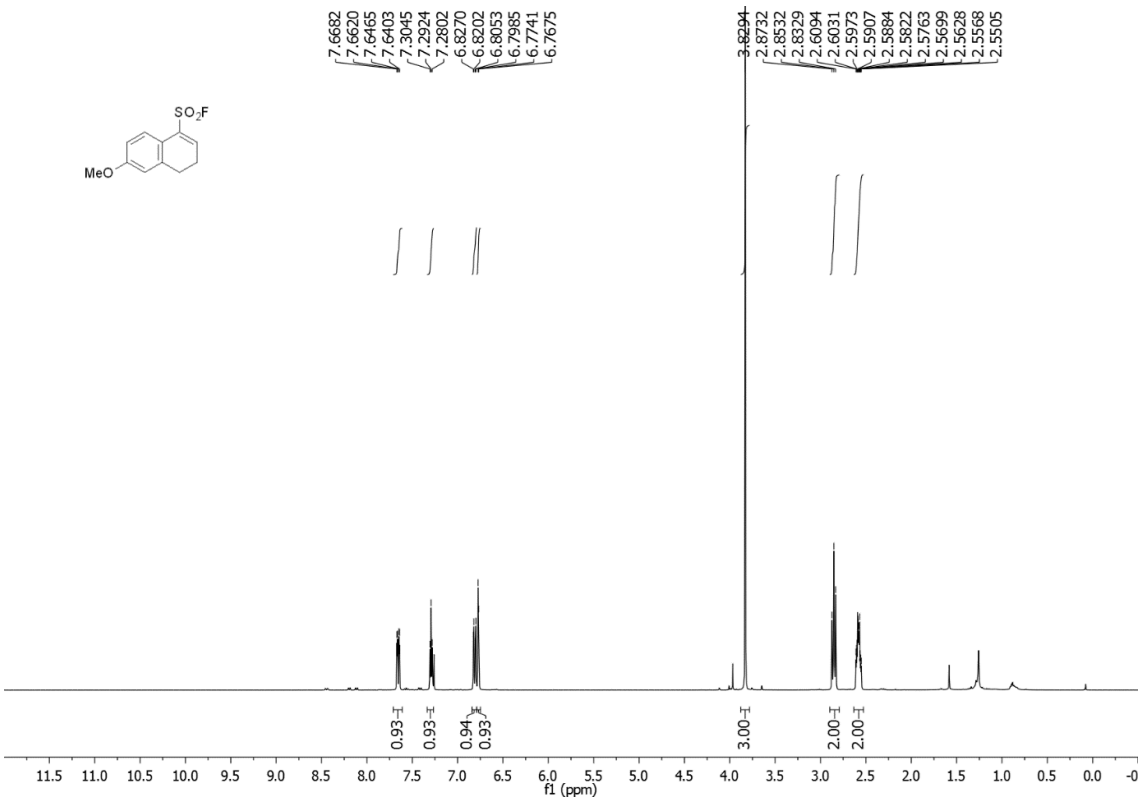


^{19}F-NMR Spectrum:

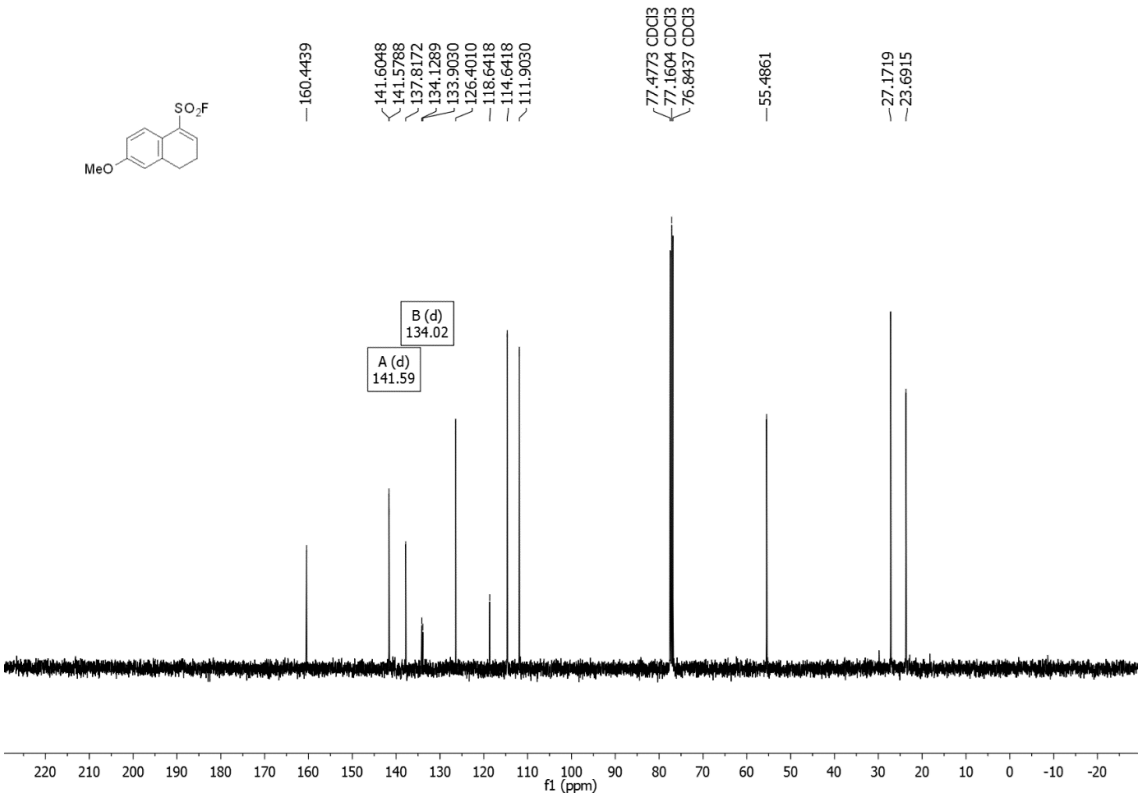


6-Methoxy-3,4-dihydronaphthalene-1-sulfonyl fluoride (33w)

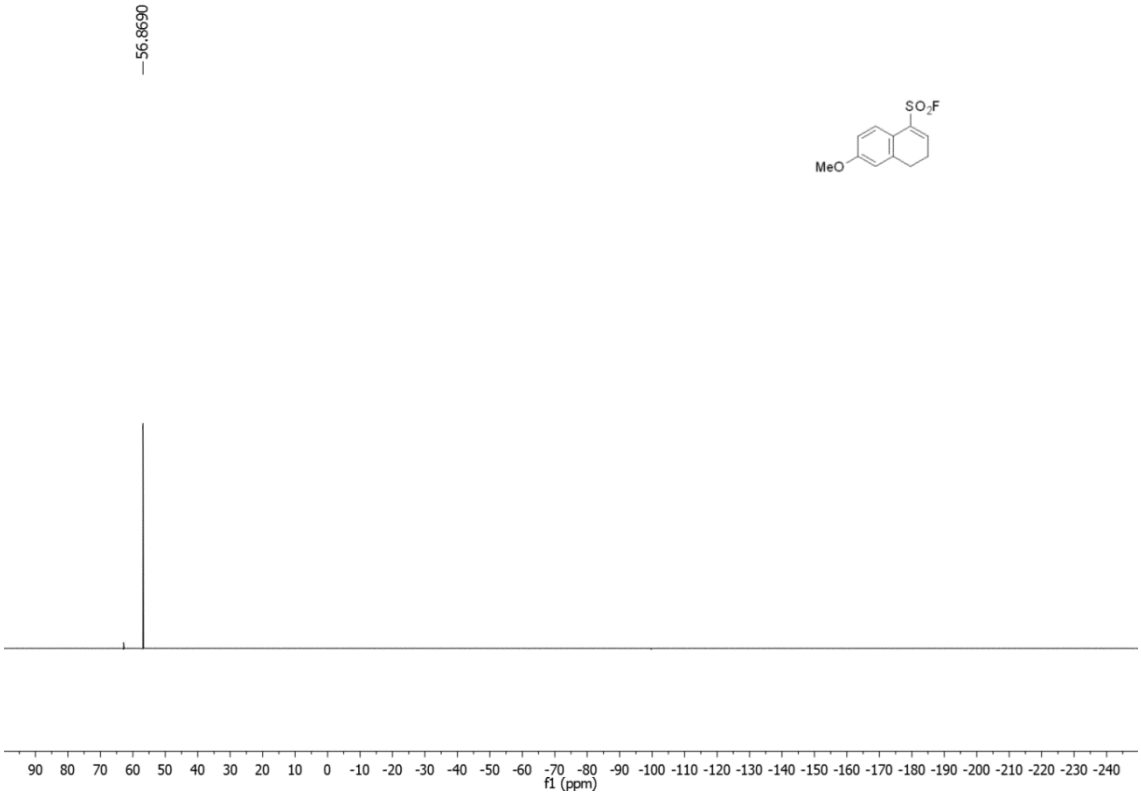
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

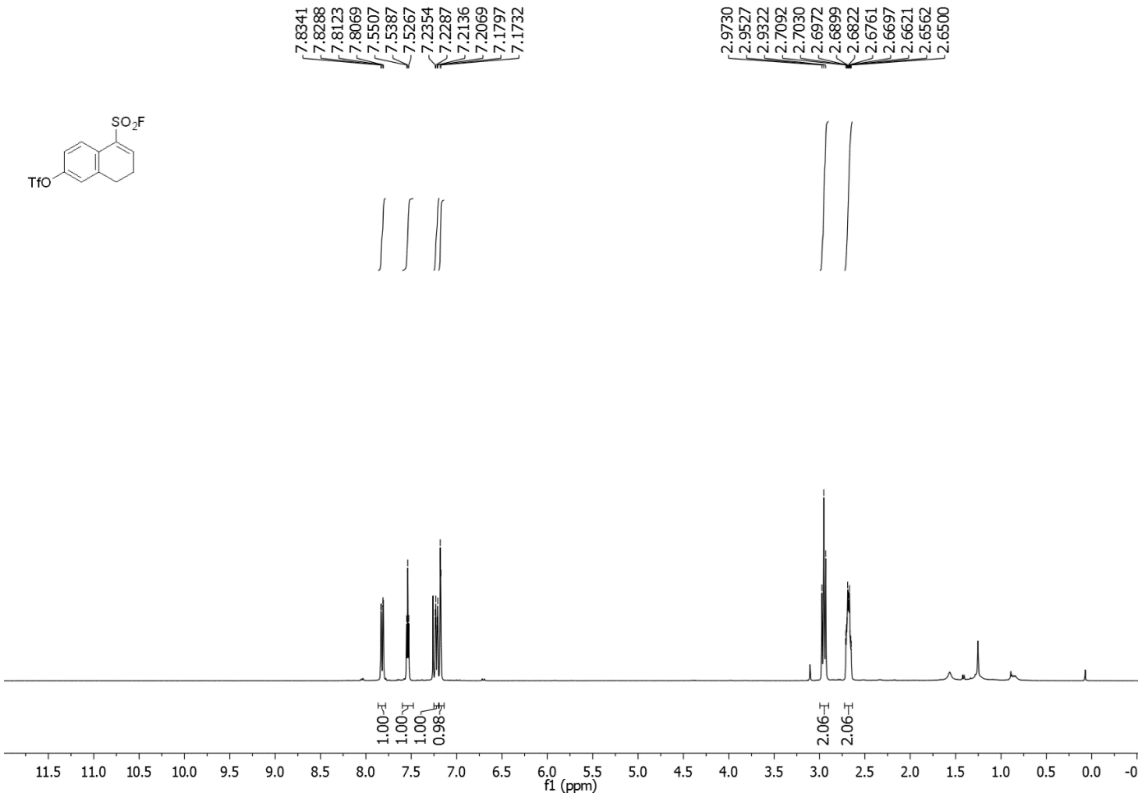


^{19}F-NMR Spectrum:

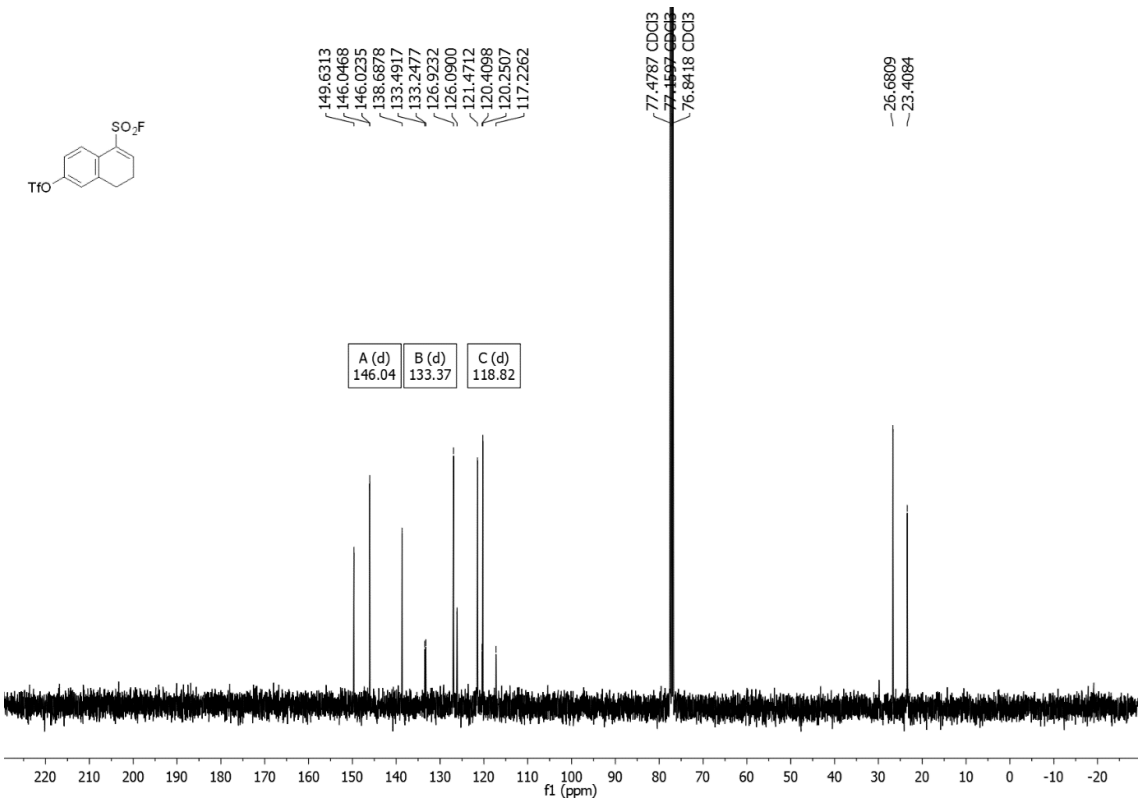


5-(Fluorosulfonyl)-7,8-dihydronaphthalen-2-yl trifluoromethanesulfonate (33x)

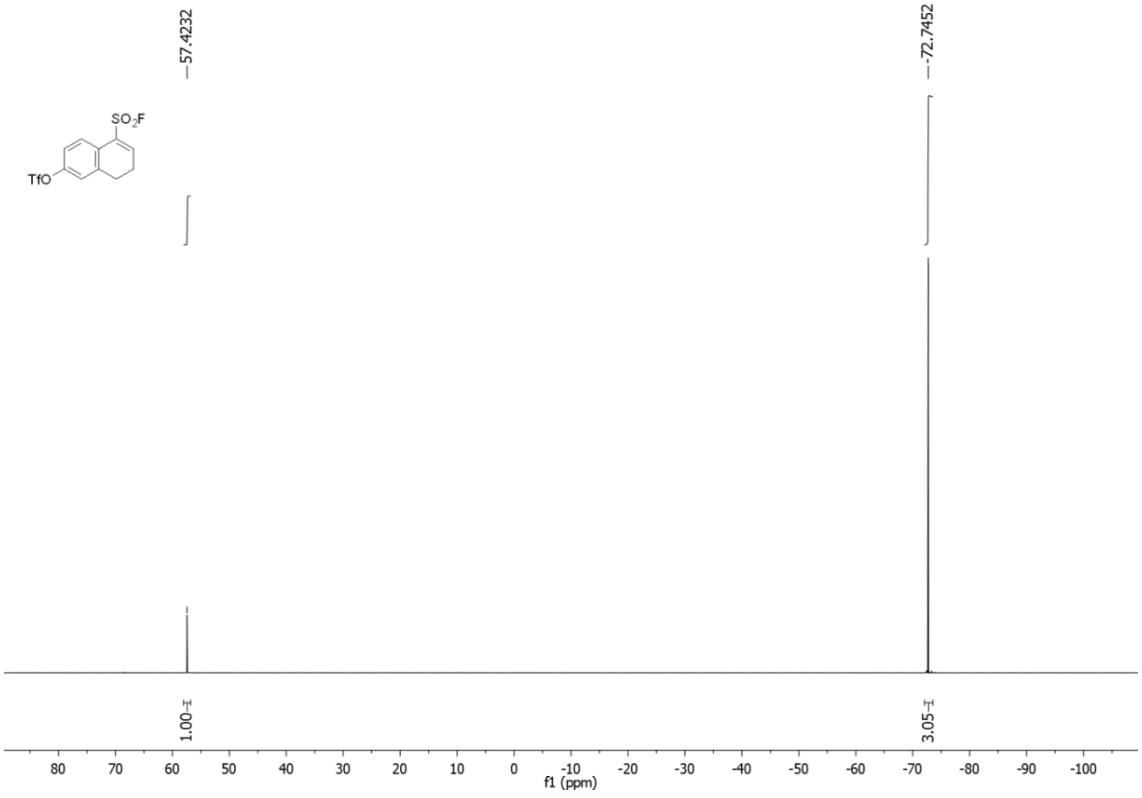
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:



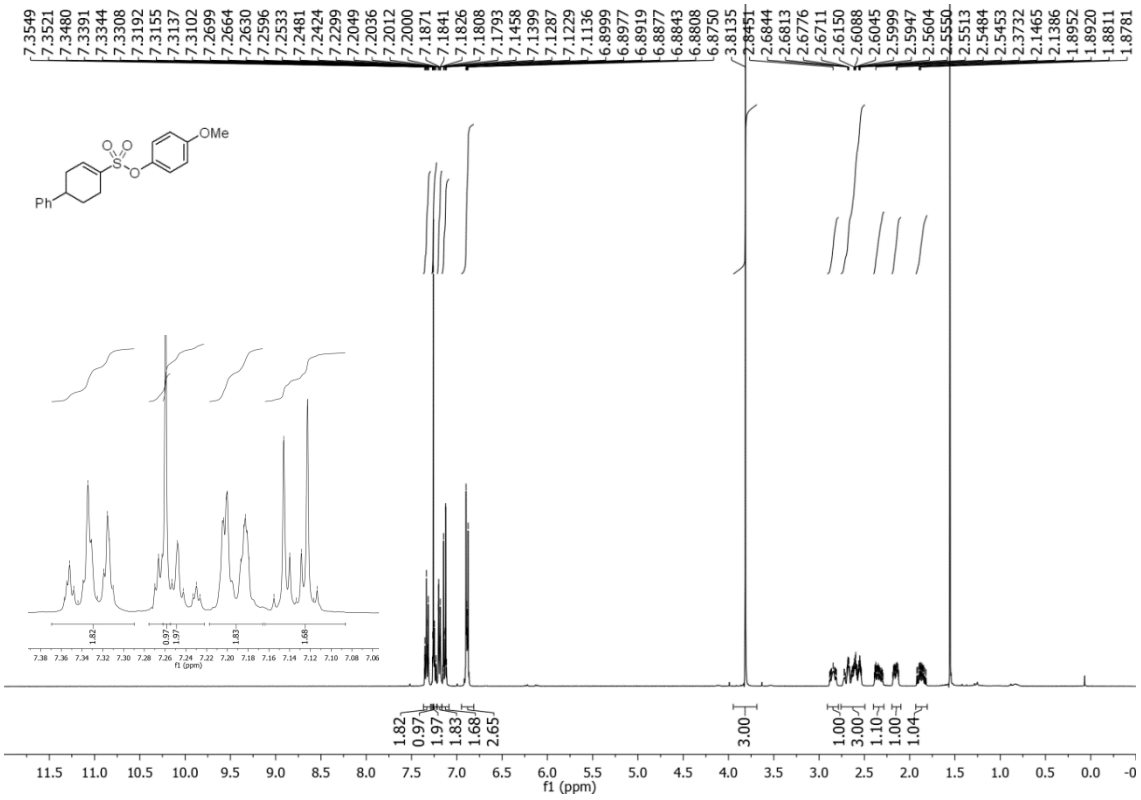
^{19}F-NMR Spectrum:



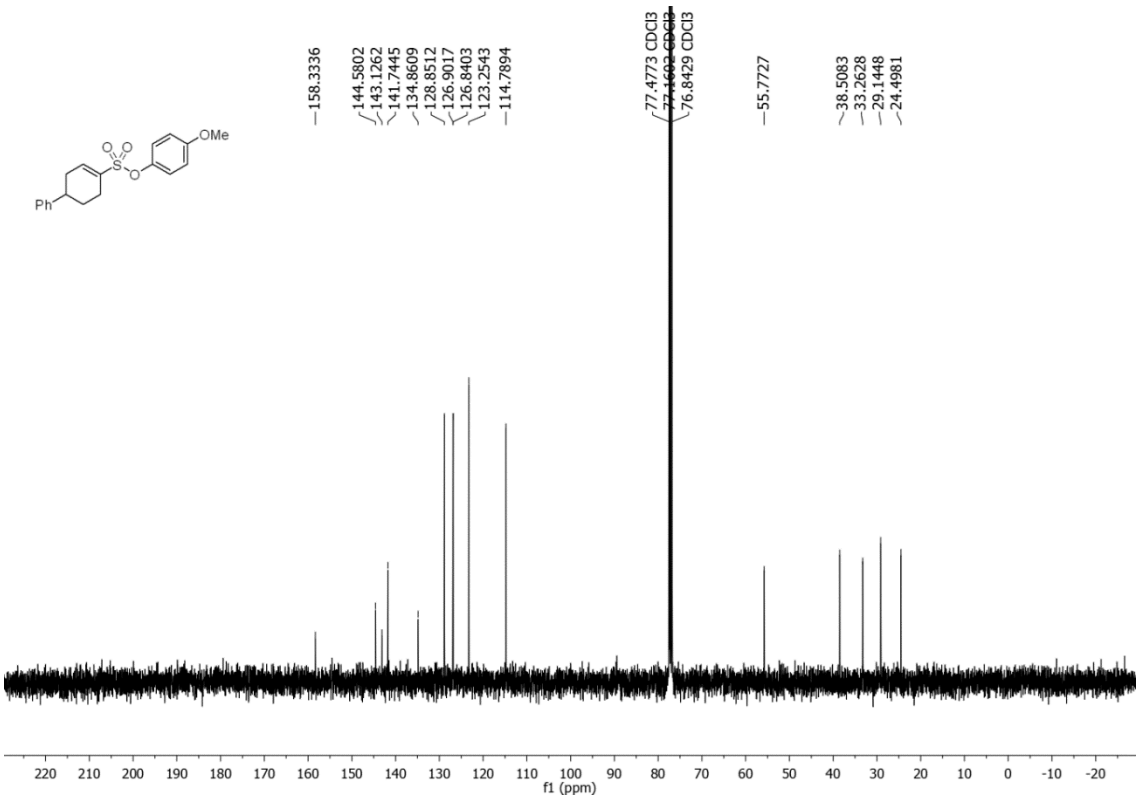
10 NMR Spectra of Derivatives of Alkenylsulfonyl Fluorides

4-Methoxyphenyl 1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-sulfonate (36)

^{1}H-NMR Spectrum:

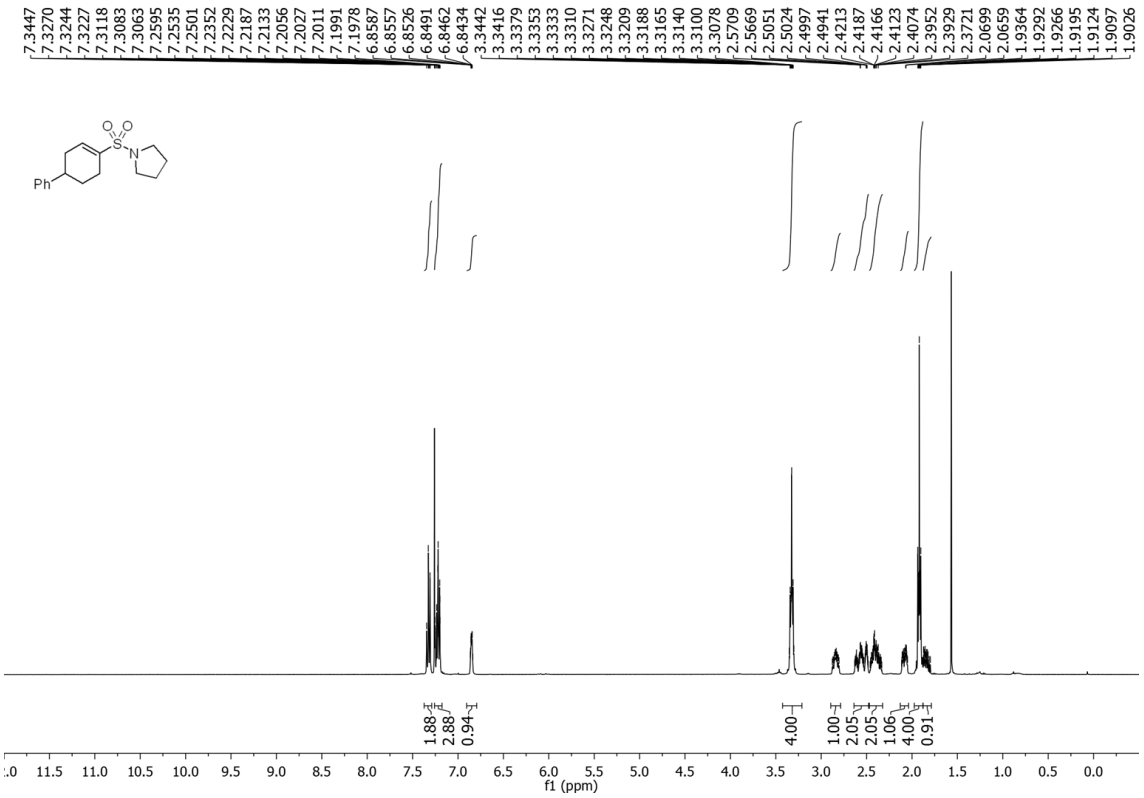


^{13}C-NMR Spectrum:

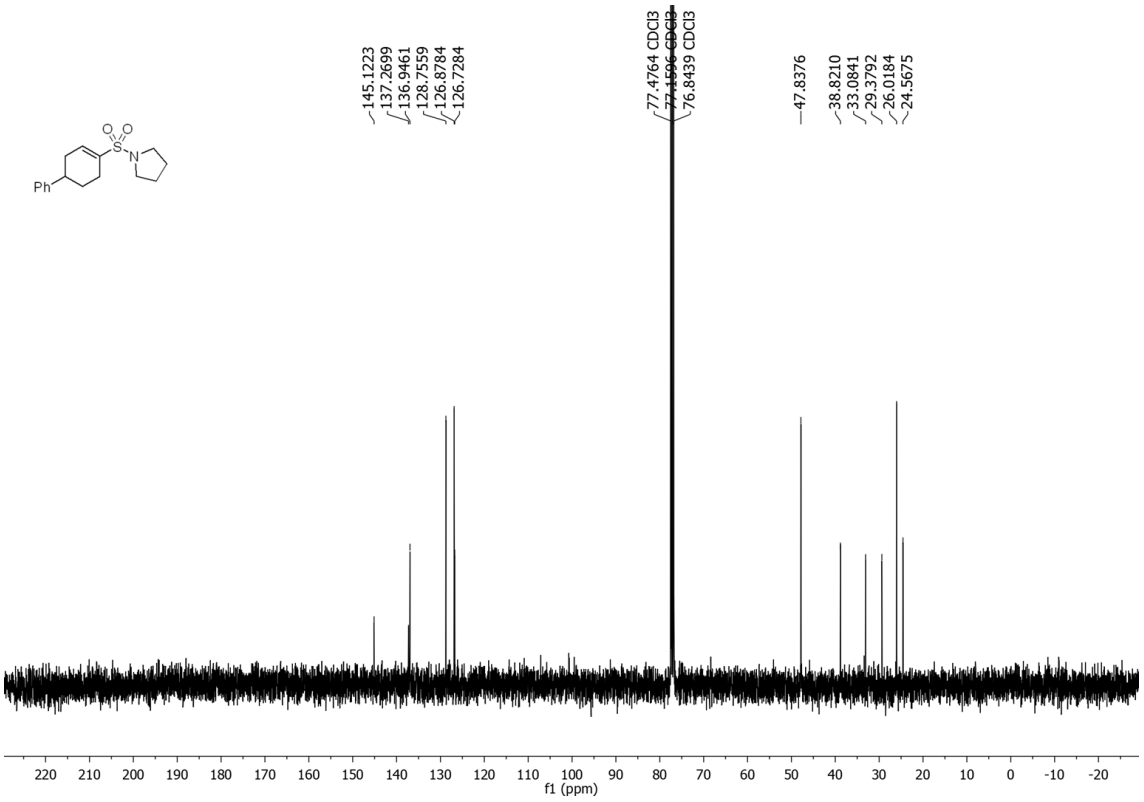


1-((1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-yl)sulfonyl)pyrrolidine (38)

^{1}H-NMR Spectrum:

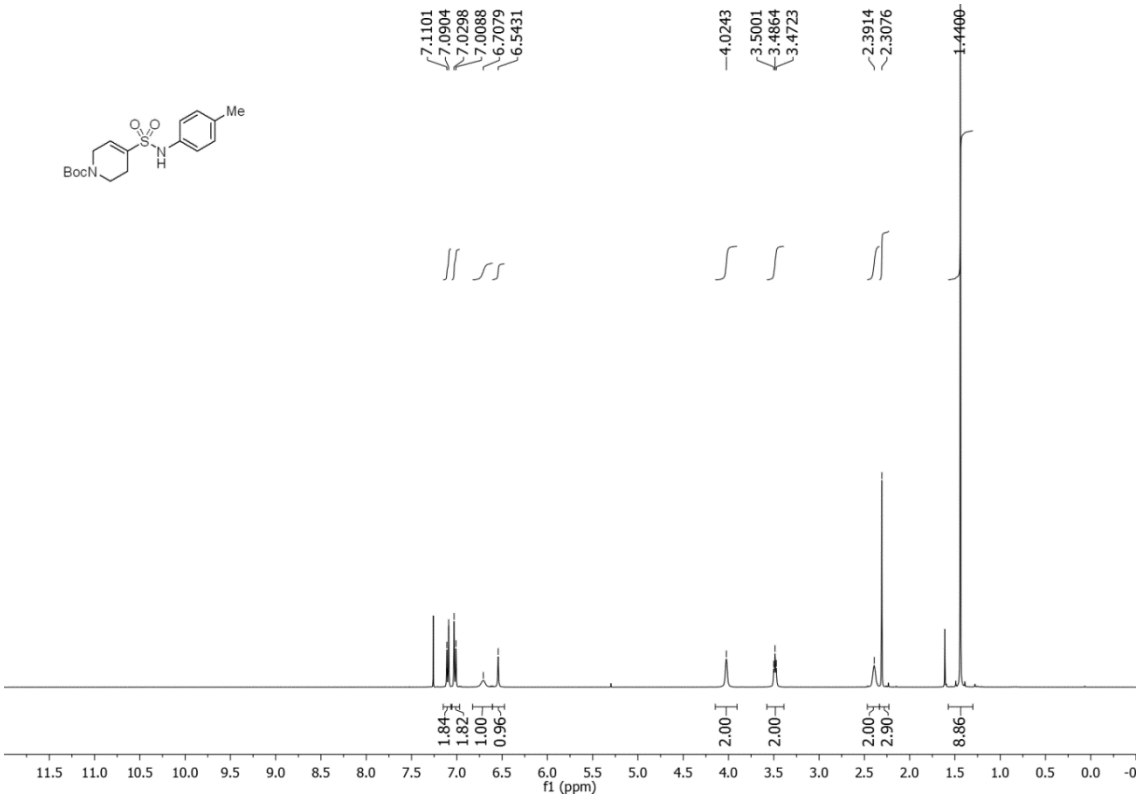


^{13}C-NMR Spectrum:

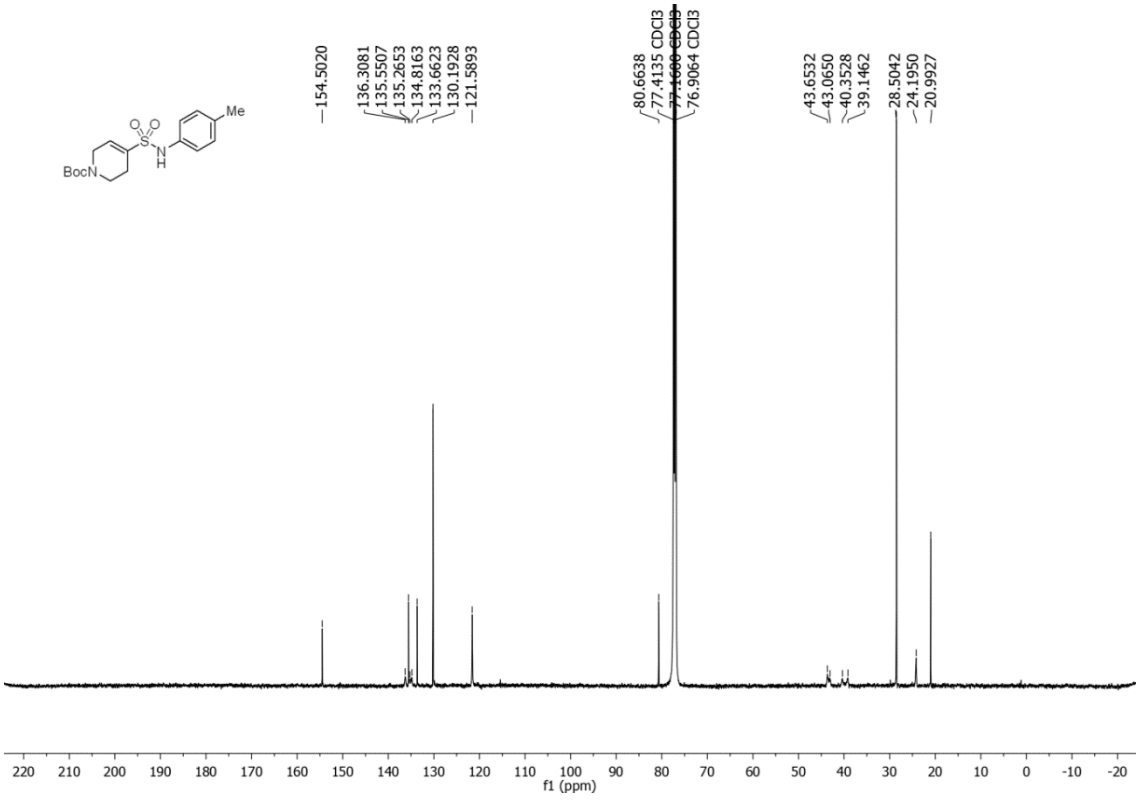


tert-Butyl 4-(_N_-(_p_-tolyl)sulfamoyl)-3,6-dihydropyridine-1(2_H_)-carboxylate (39a)

^{1}H-NMR Spectrum:

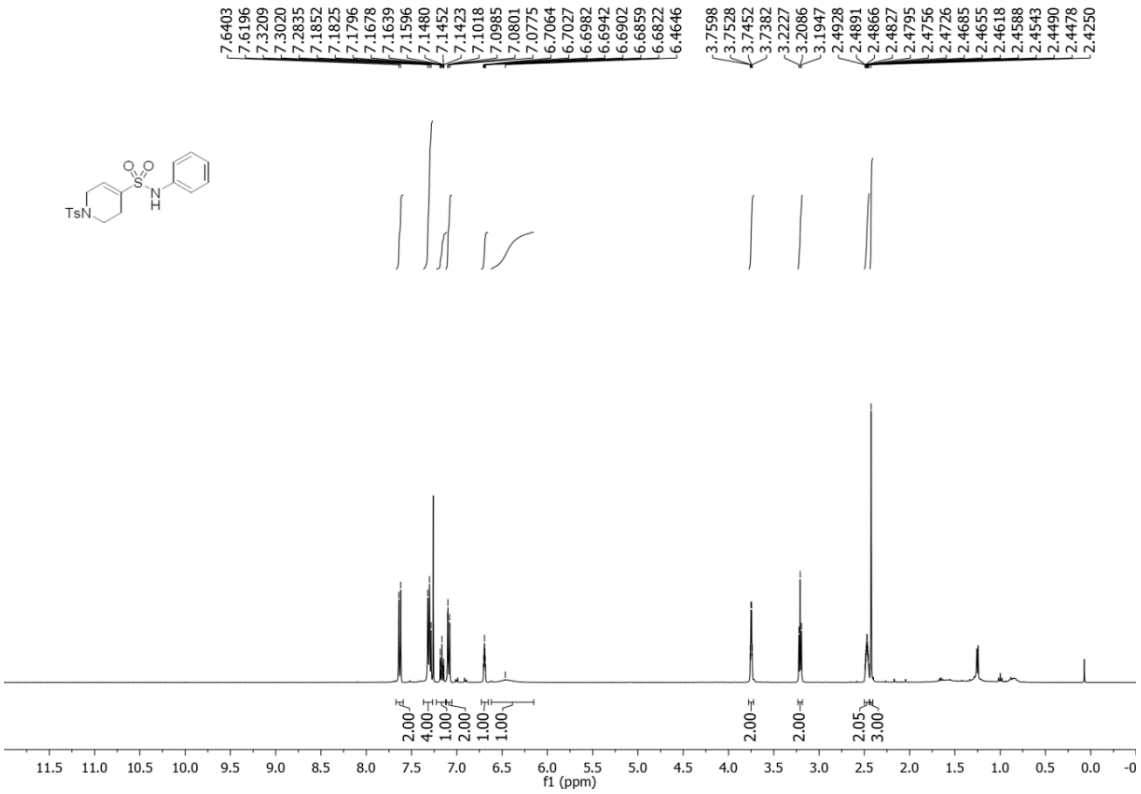


^{13}C-NMR Spectrum:

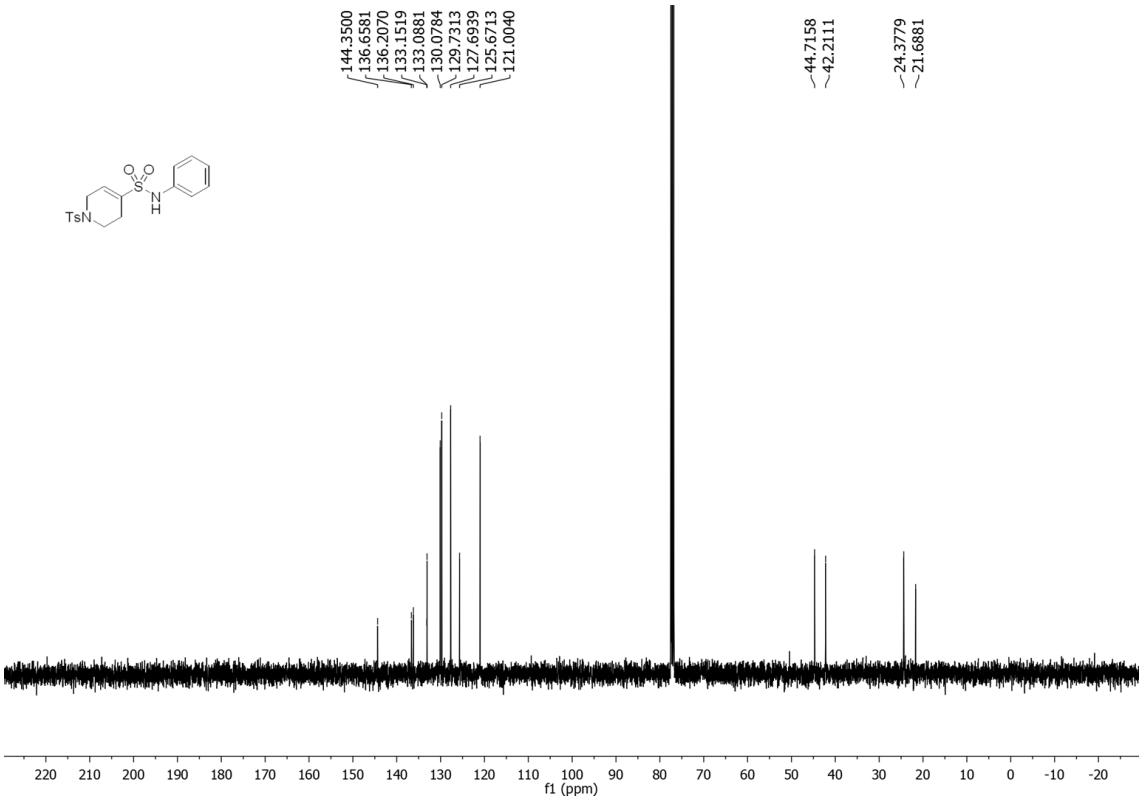


N-Phenyl-1-tosyl-1,2,3,6-tetrahydropyridine-4-sulfonamide (39b)

^{1}H-NMR Spectrum:

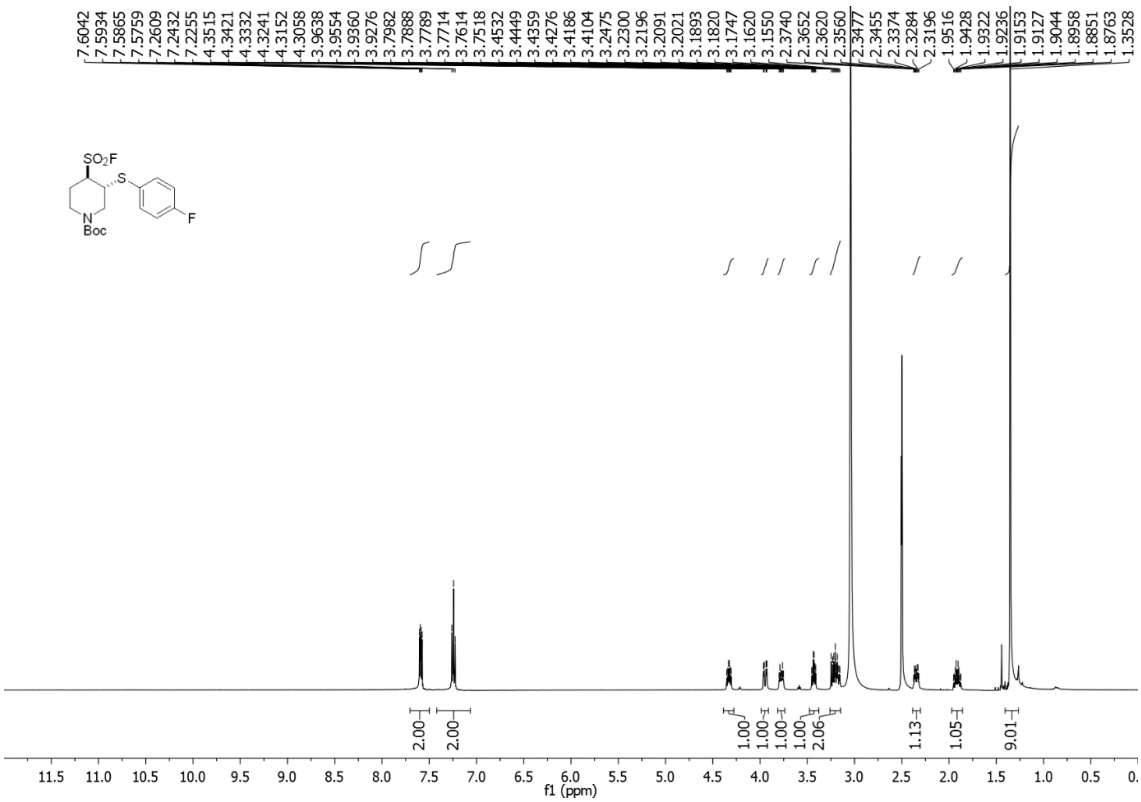


^{13}C-NMR Spectrum:

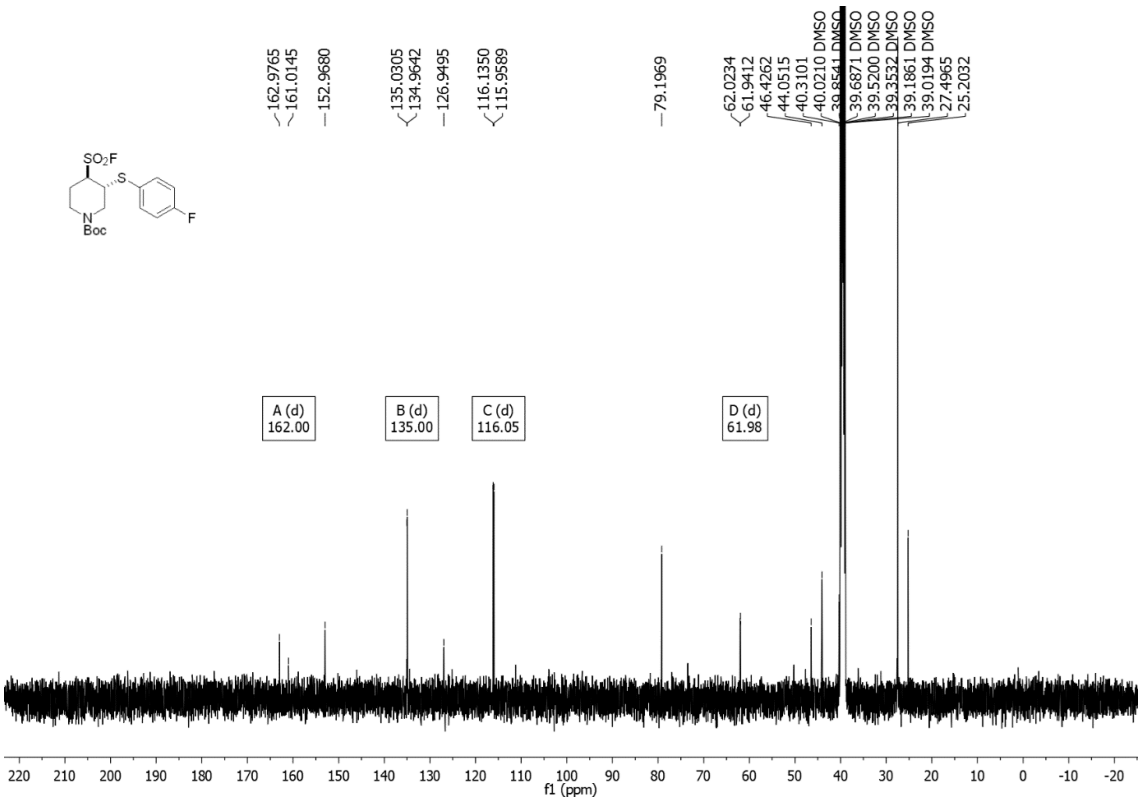


***cis-tert*-Butyl 3-((4-fluorophenyl)thio)-4-(fluorosulfonyl)piperidine-1-carboxylate (40a1)**

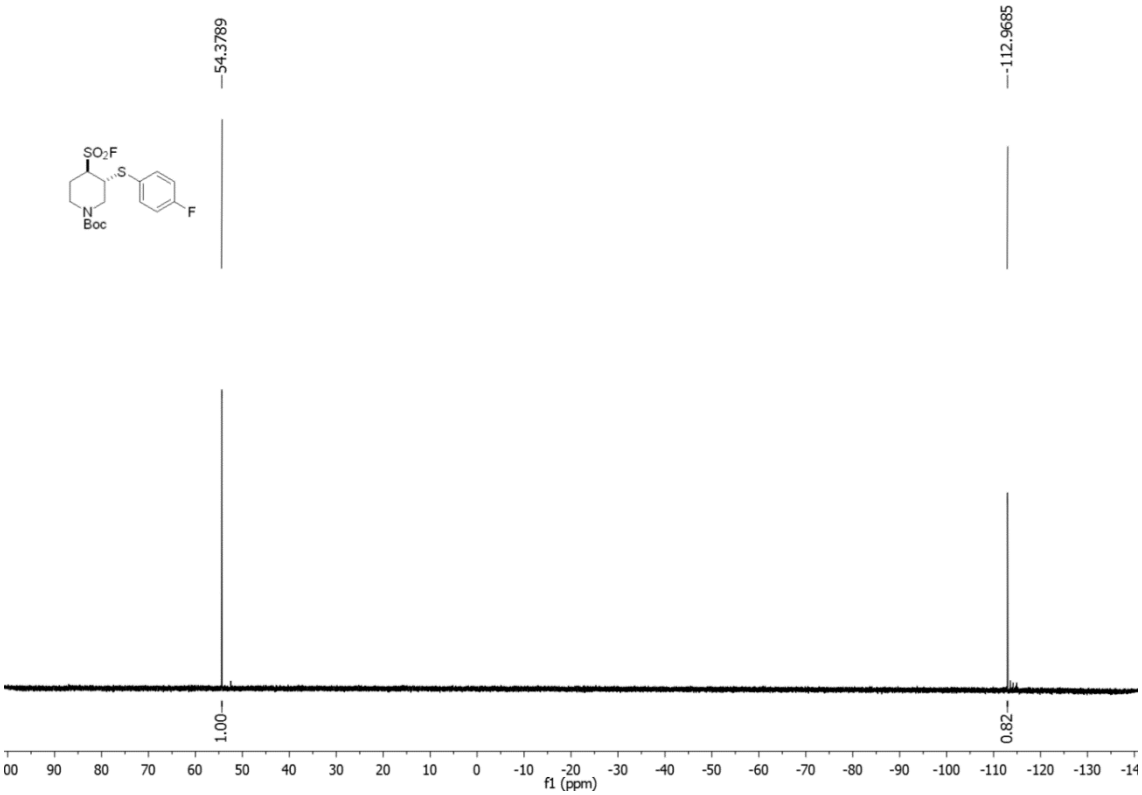
^{1}H- NMR Spectrum (363 K):



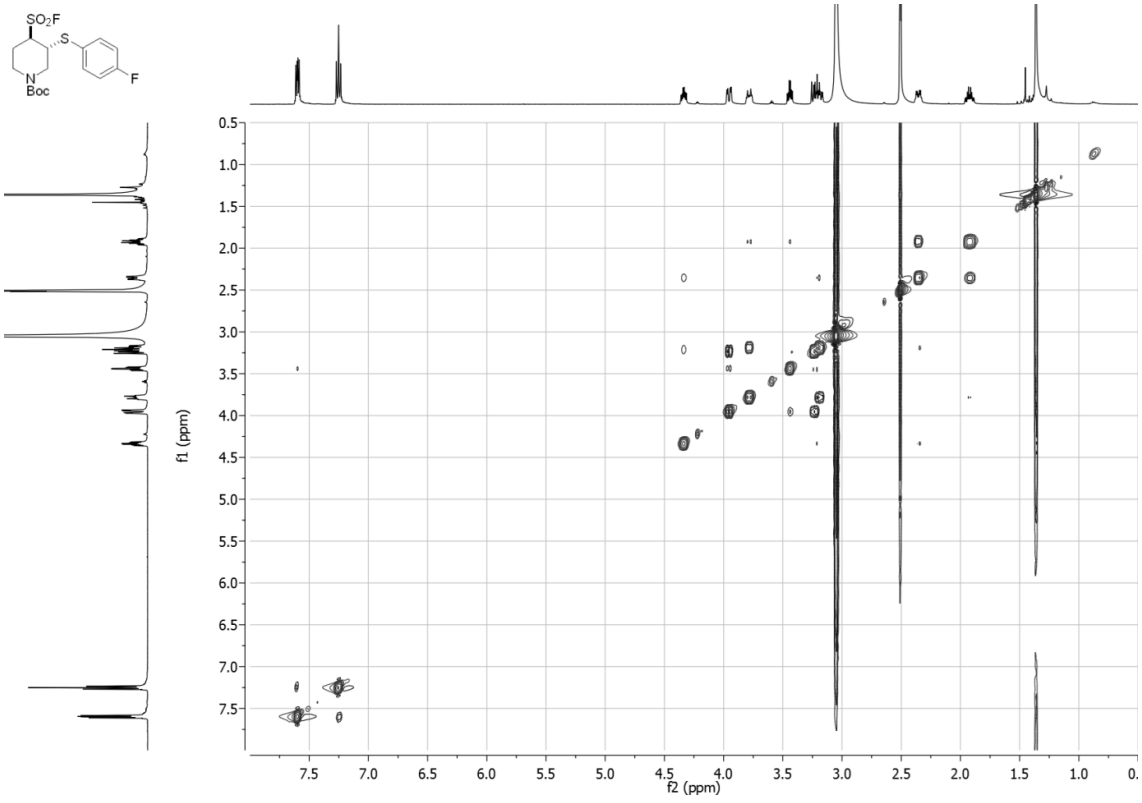
^{13}C- NMR Spectrum (363 K):



^{19}F-NMR Spectrum (363 K):

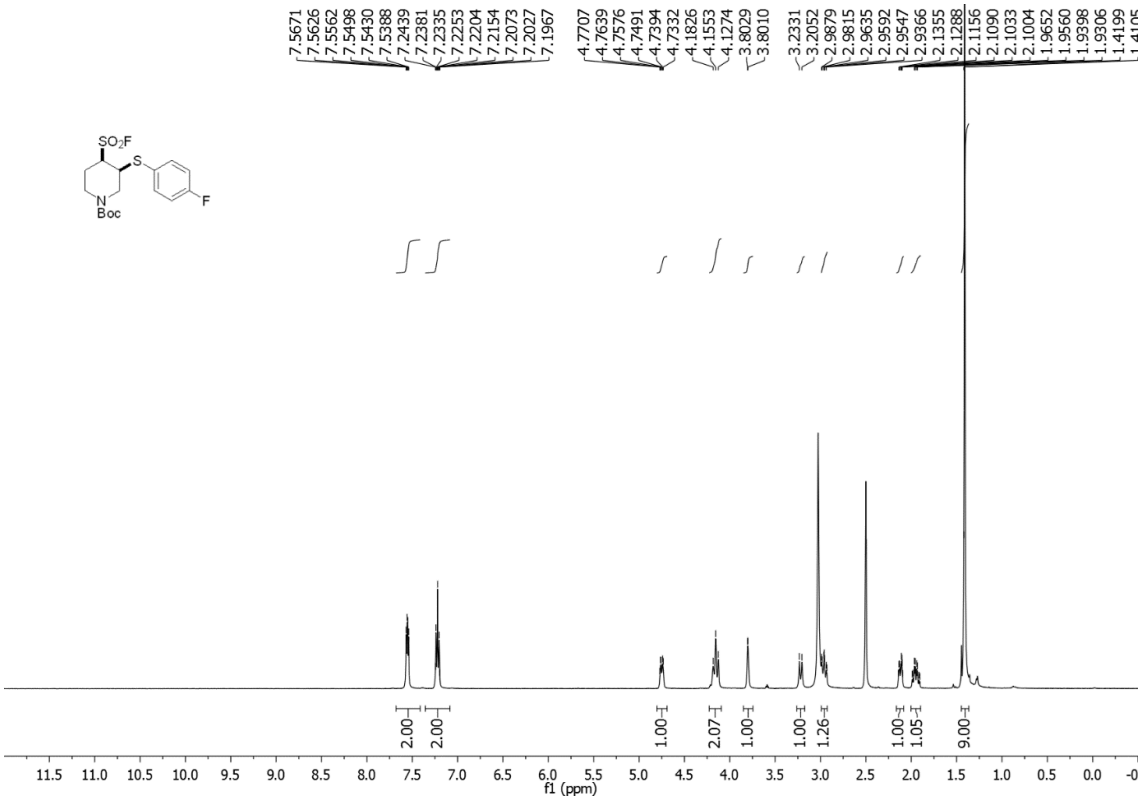


^{1}H-^{1}H NOESY NMR Spectrum (363 K):

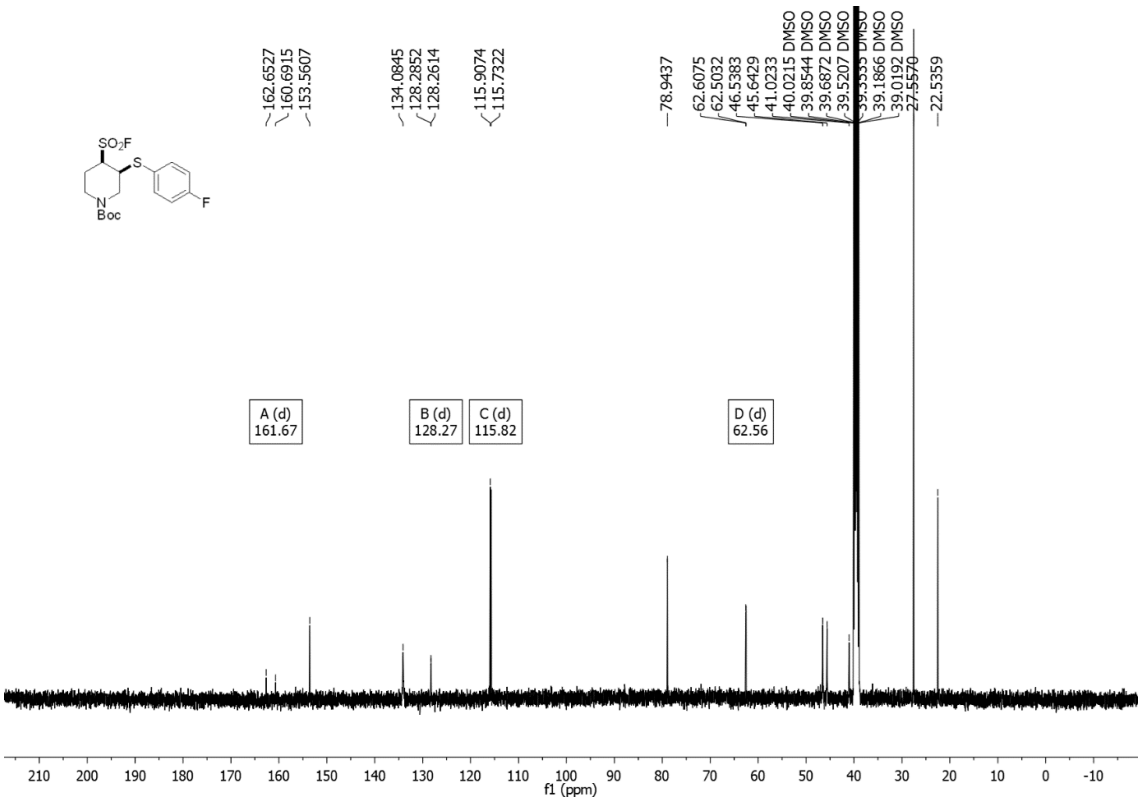


***trans-tert*-Butyl 3-((4-fluorophenyl)thio)-4-(fluorosulfonyl)piperidine-1-carboxylate (40a2)**

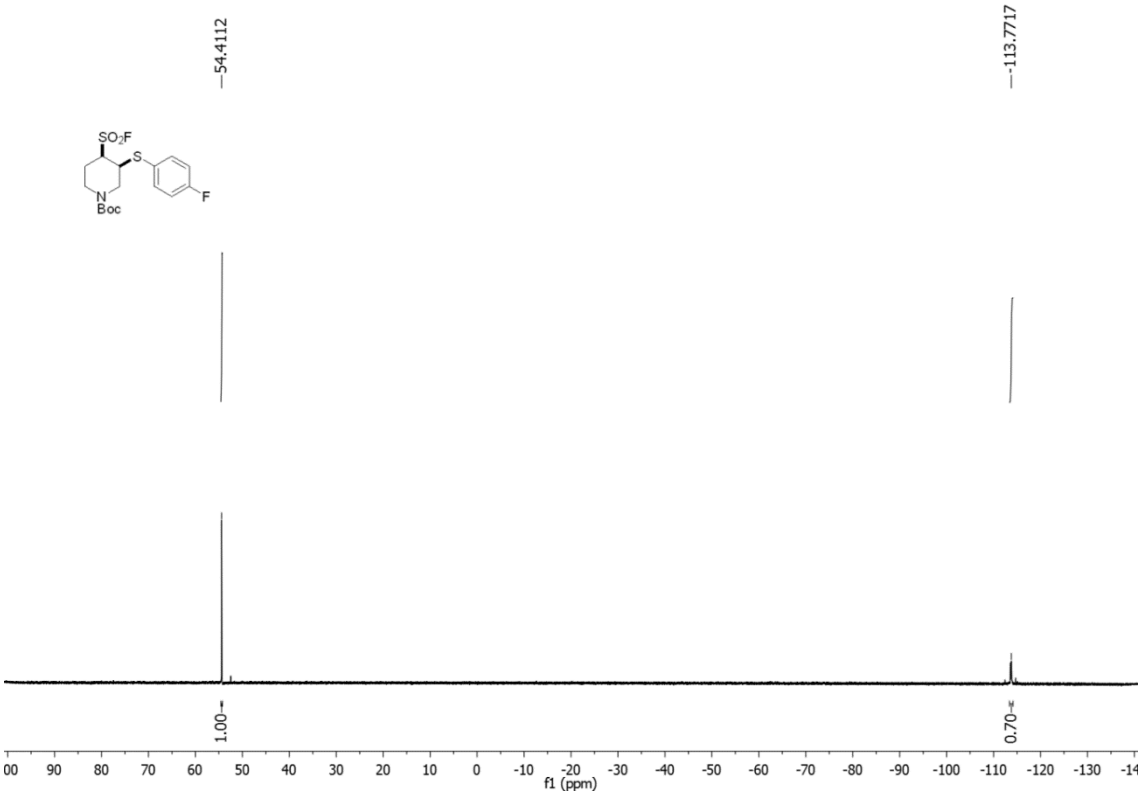
^{1}H- NMR Spectrum (363K):



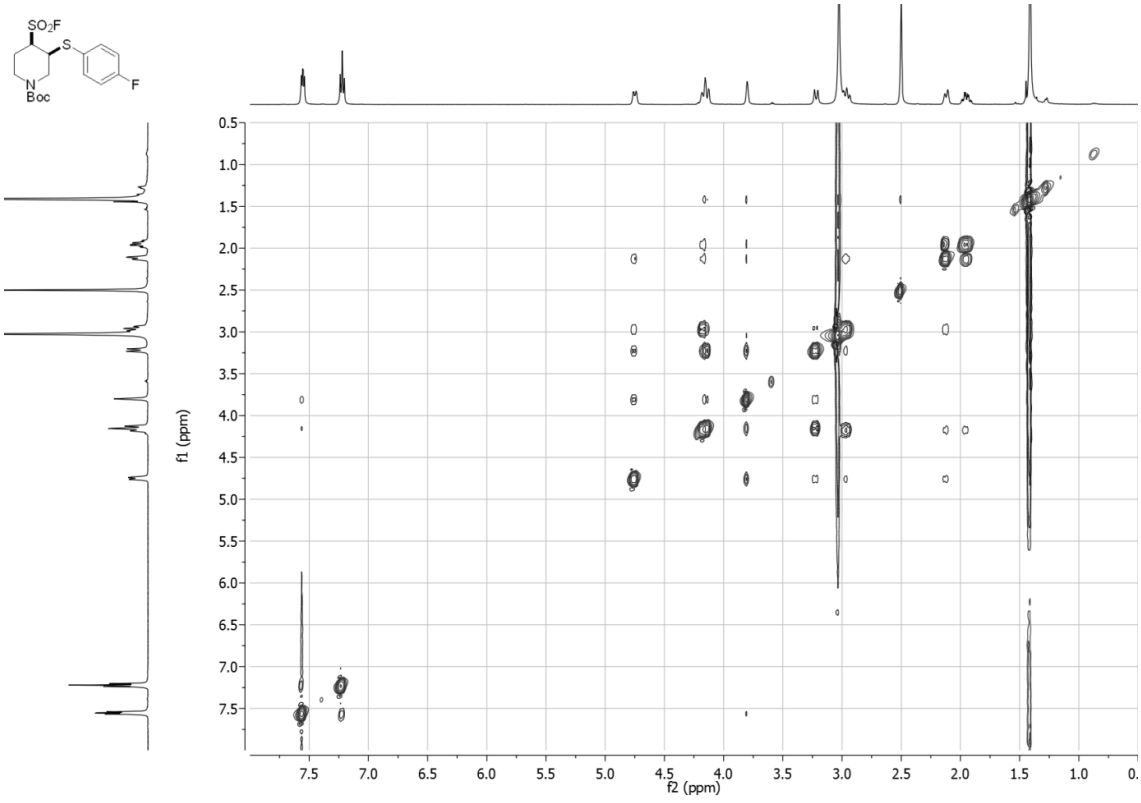
^{13}C- NMR Spectrum (363K):



^{19}F-NMR Spectrum (363K):

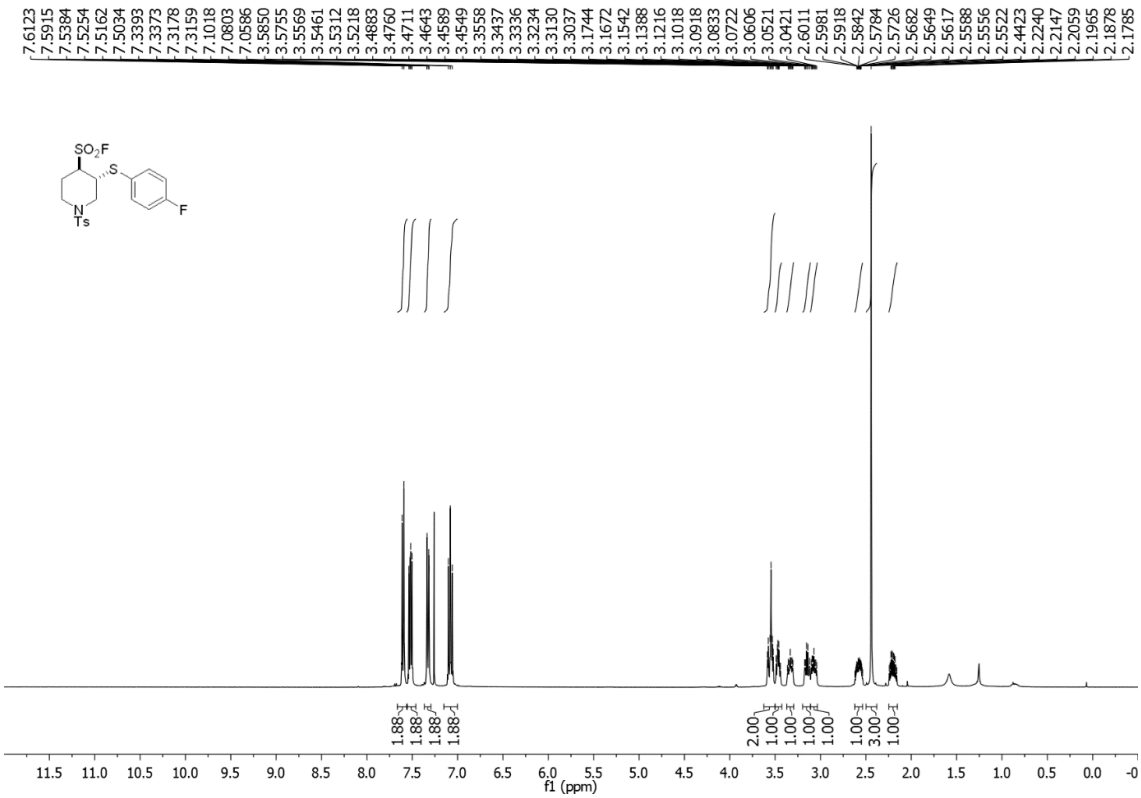


^{1}H-^{1}H NOESY NMR Spectrum (363 K):

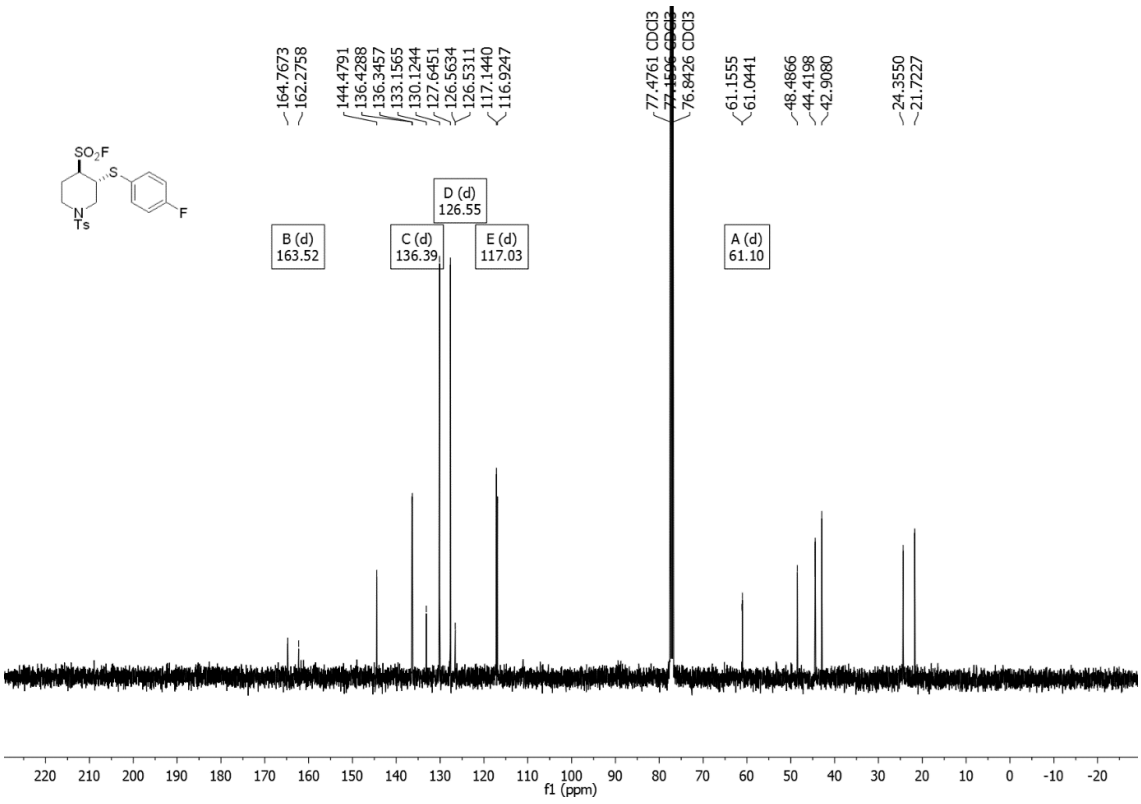


trans-3-((4-Fluorophenyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (40b1)

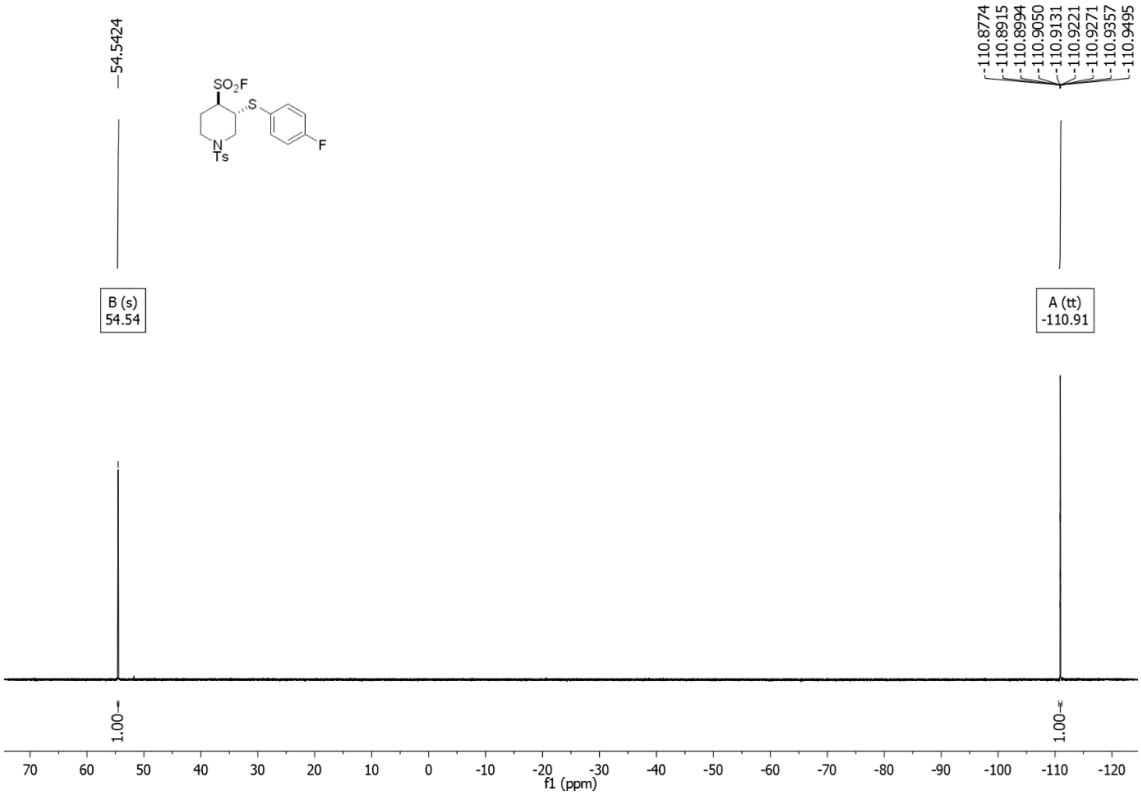
^{1}H-NMR Spectrum:



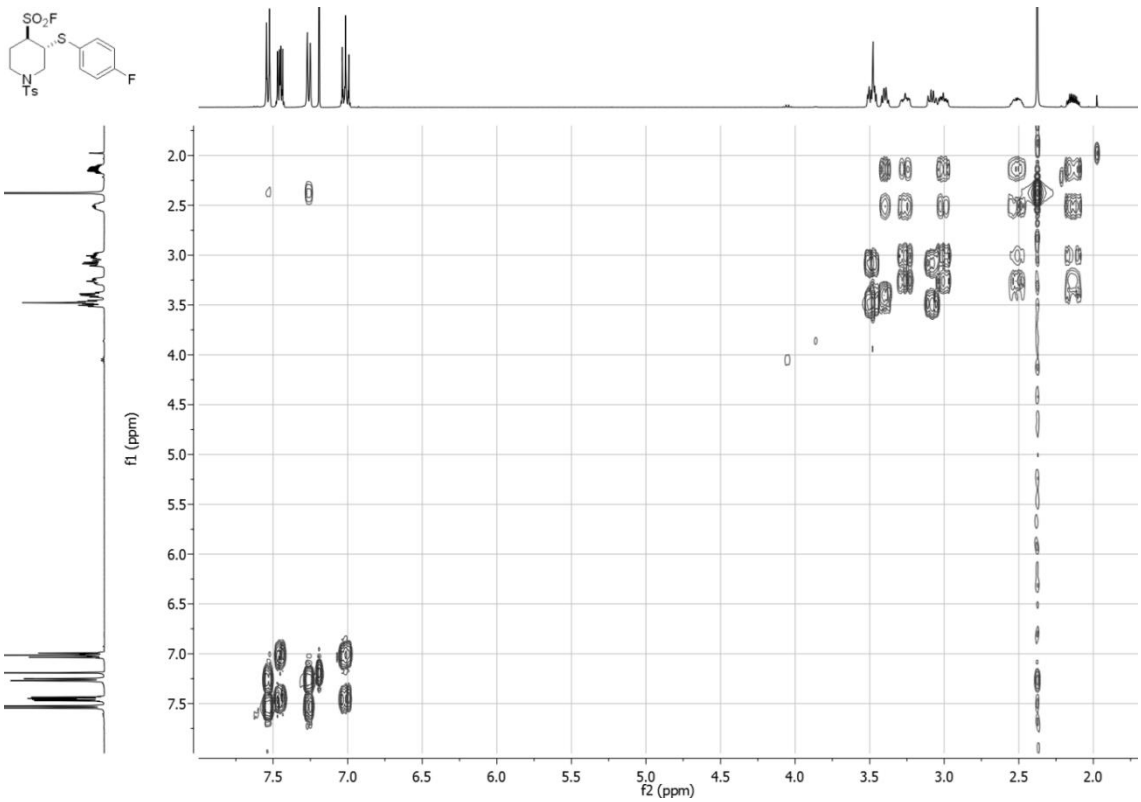
^{13}C-NMR Spectrum:



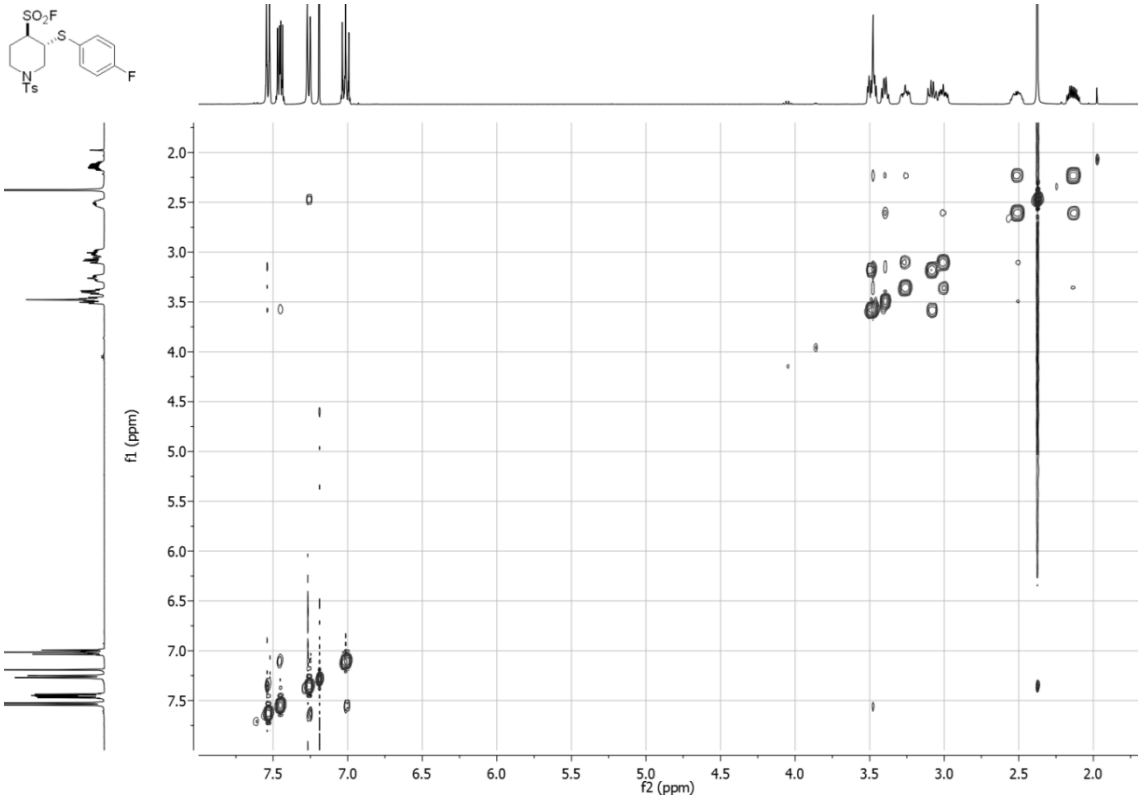
^{19}F-NMR Spectrum:



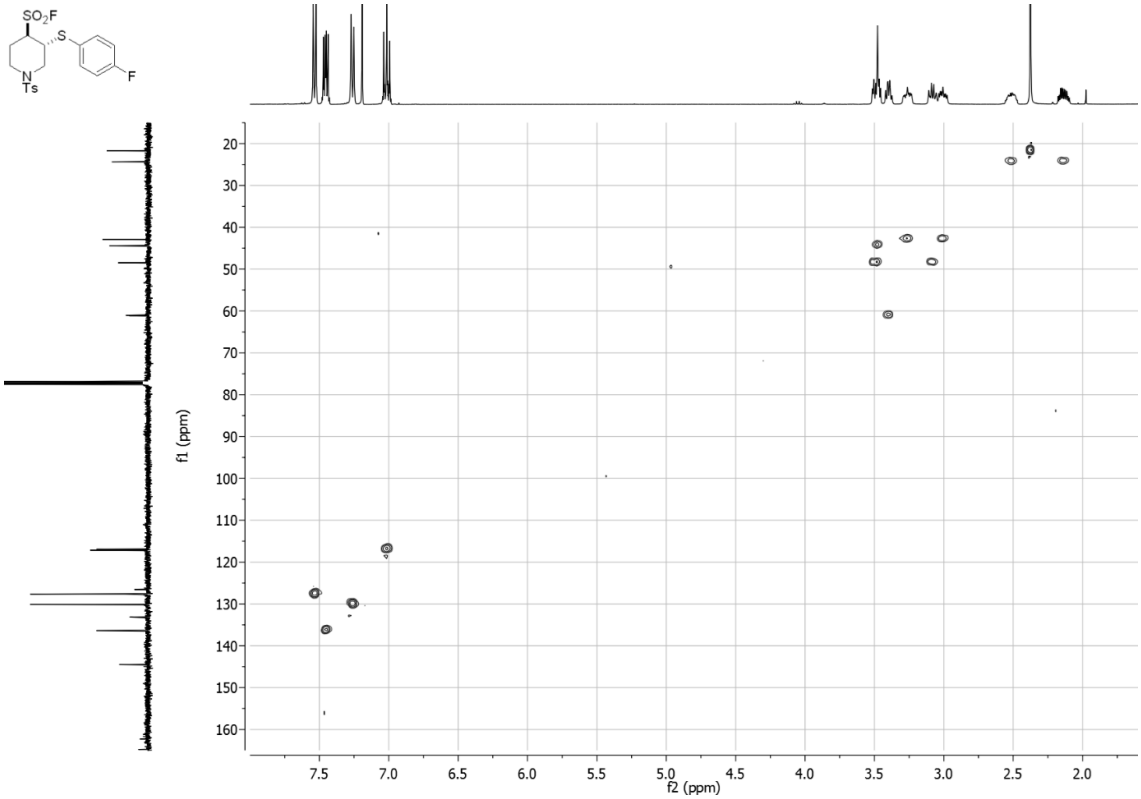
^{1}H-^{1}H COSY NMR Spectrum:



^{1}H-^{1}H NOESY NMR Spectrum:

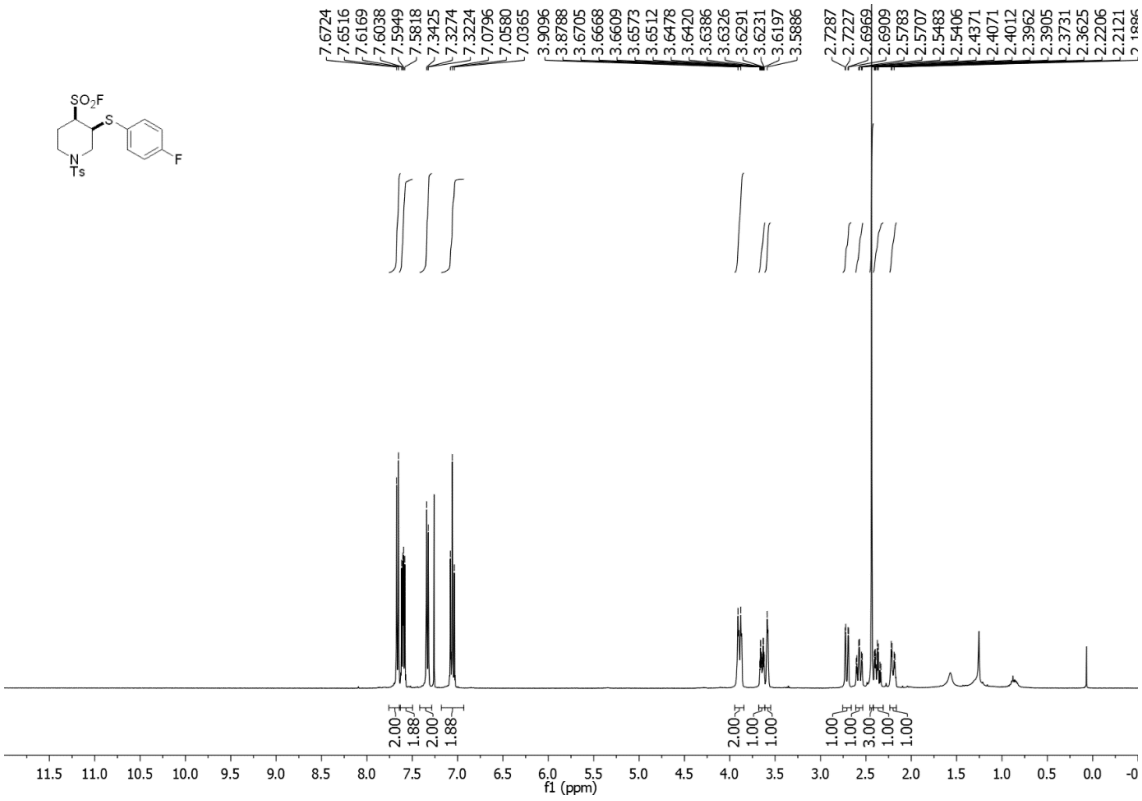


^{1}H-^{13}C HSQC NMR Spectrum:

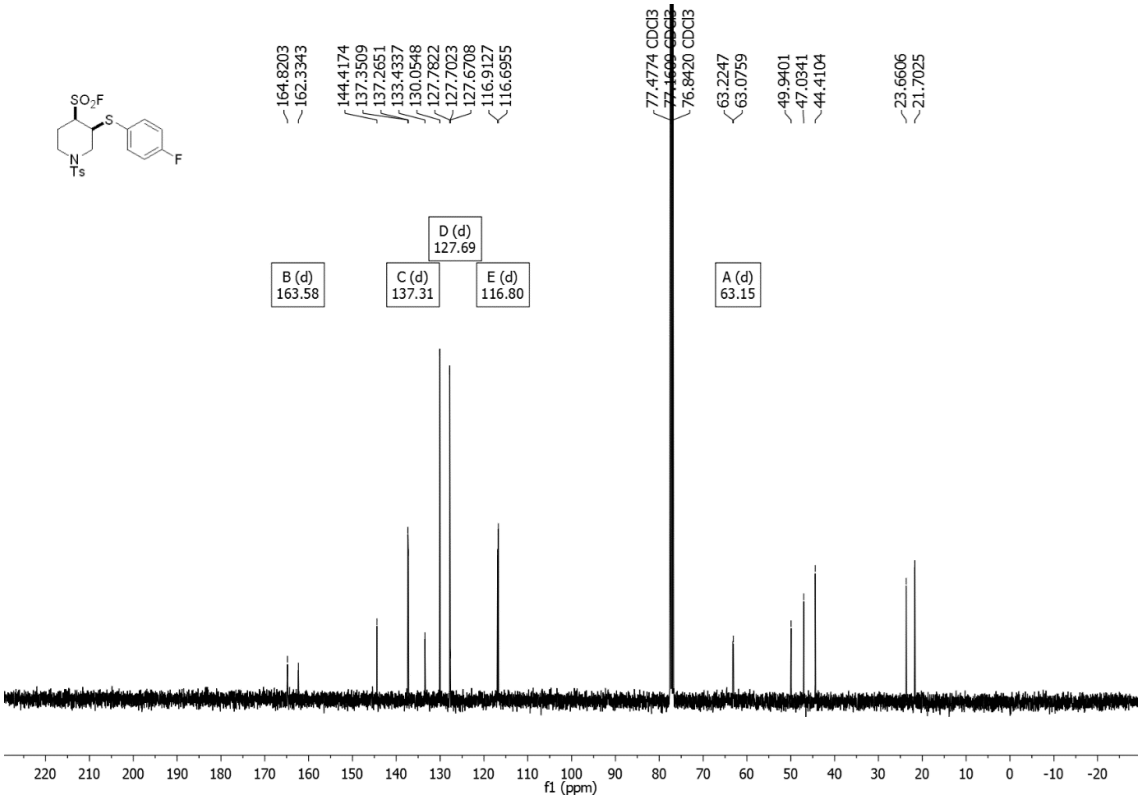


cis-3-((4-Fluorophenyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (40b2)

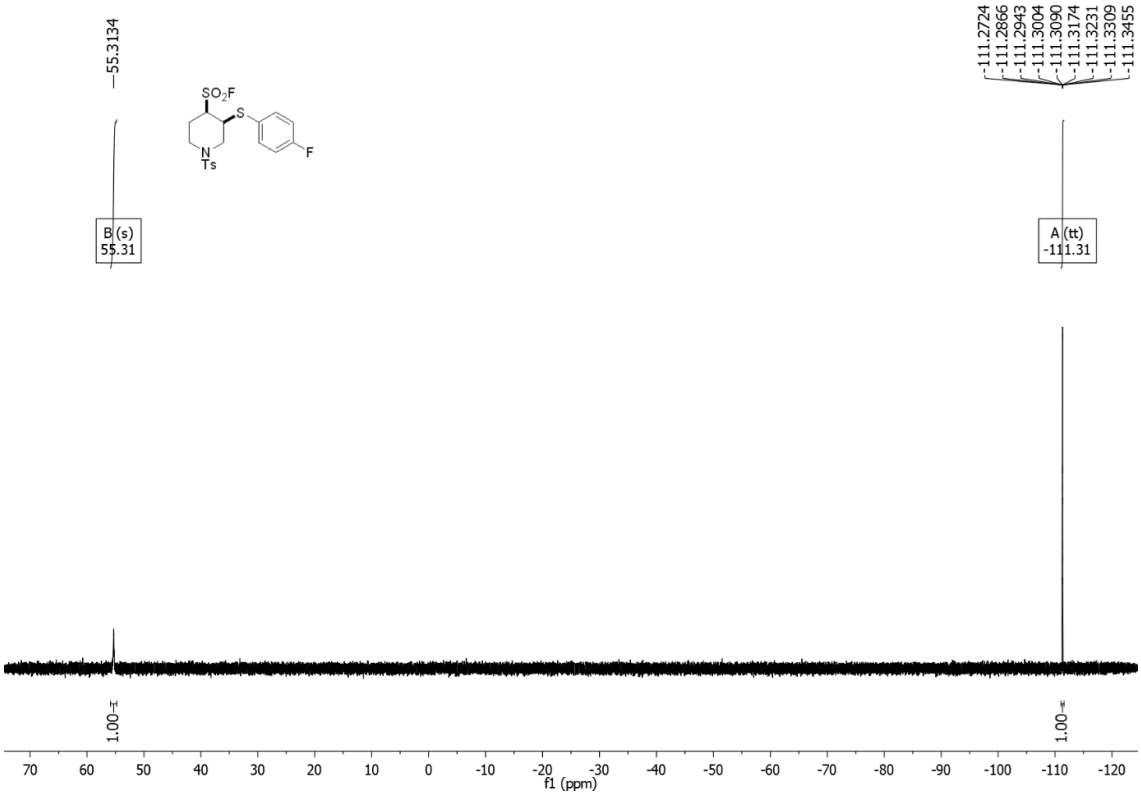
^{1}H-NMR Spectrum:



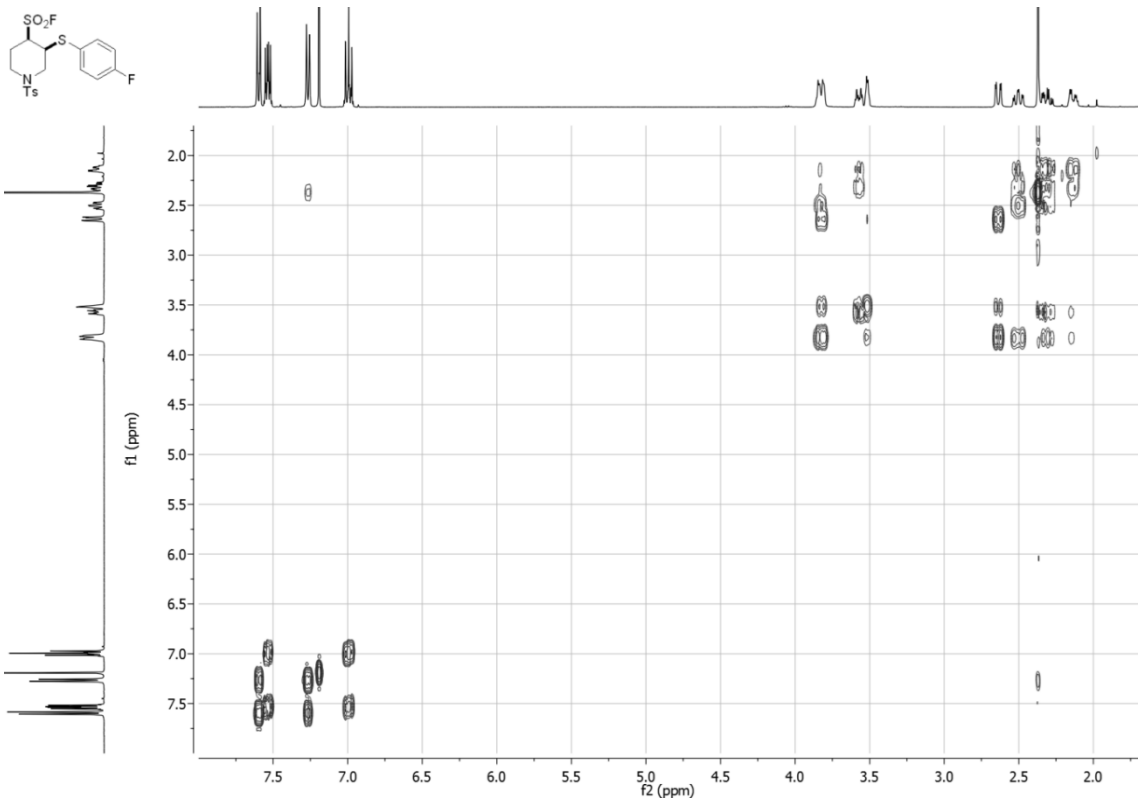
^{13}C-NMR Spectrum:



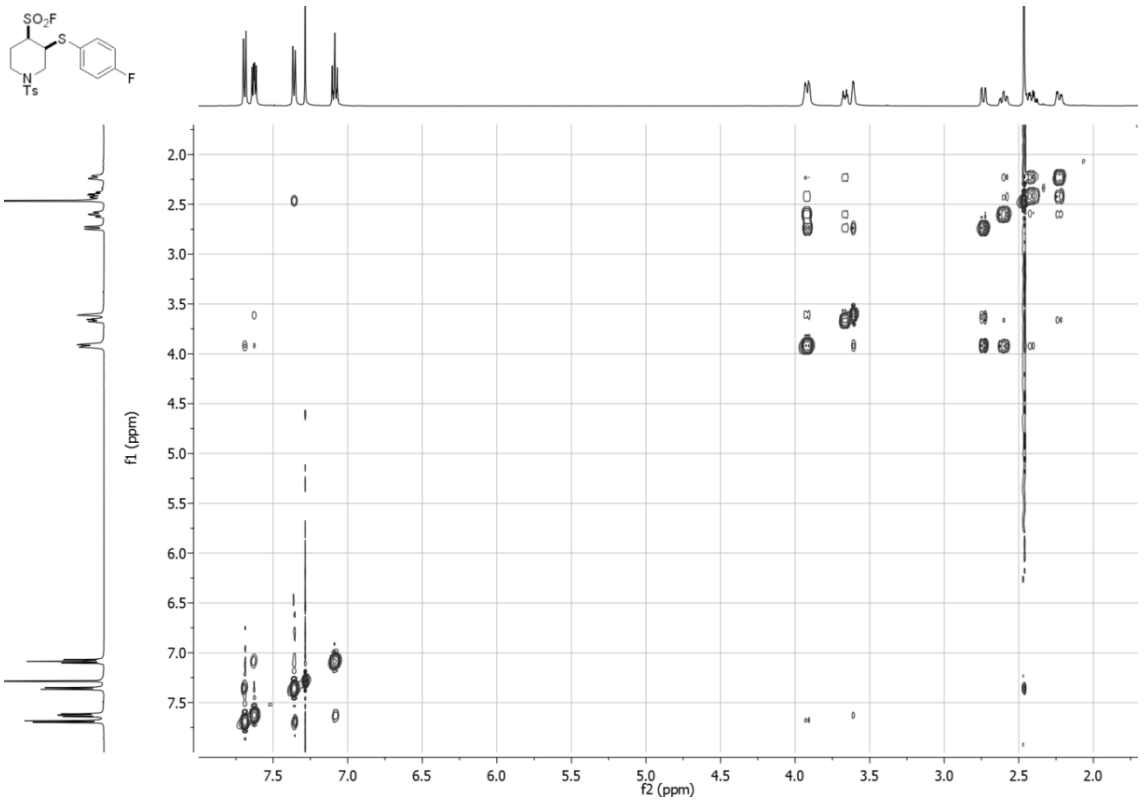
^{19}F-NMR Spectrum:



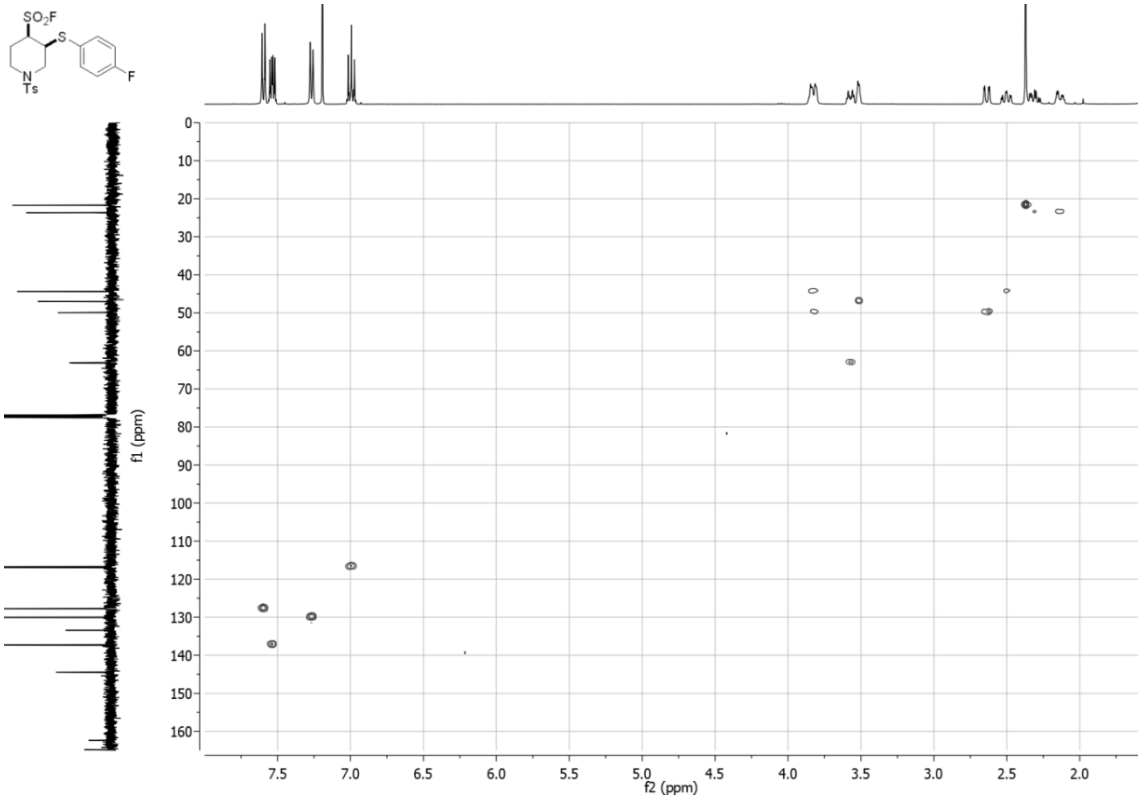
^{1}H-^{1}H COSY NMR Spectrum:



^{1}H-^{1}H NOESY NMR Spectrum:

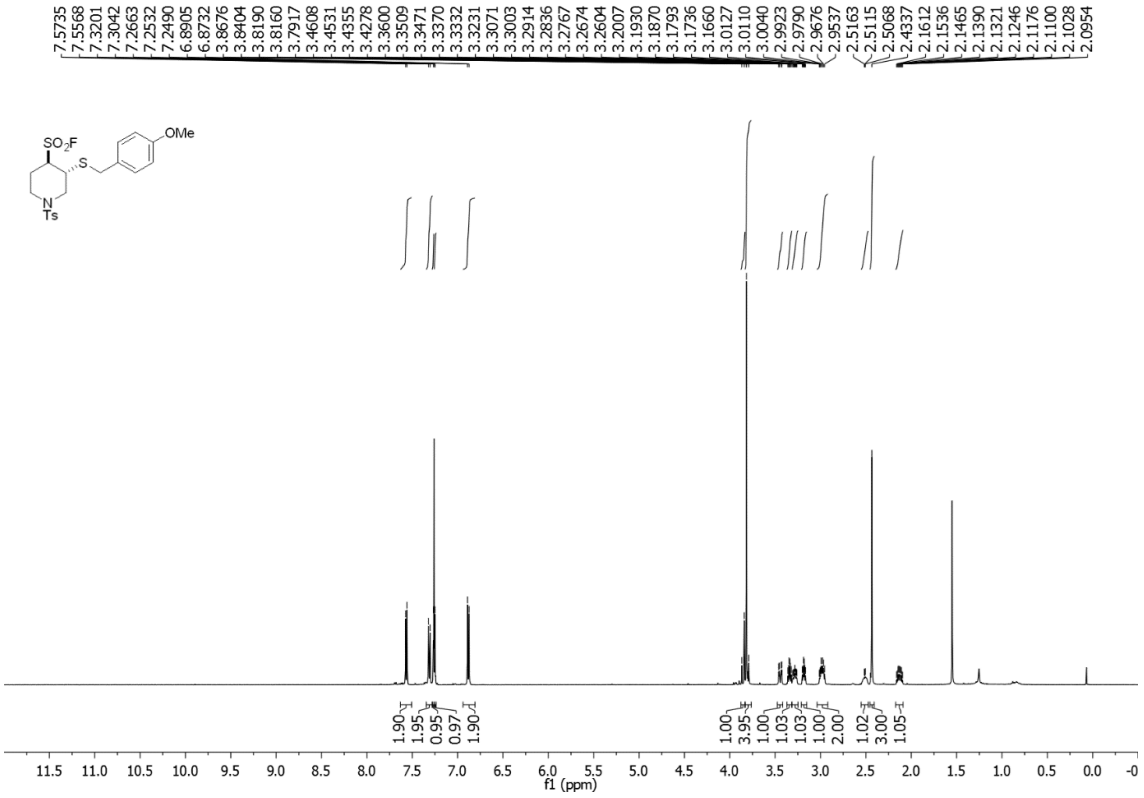


^{1}H-^{13}C HSQC NMR Spectrum:

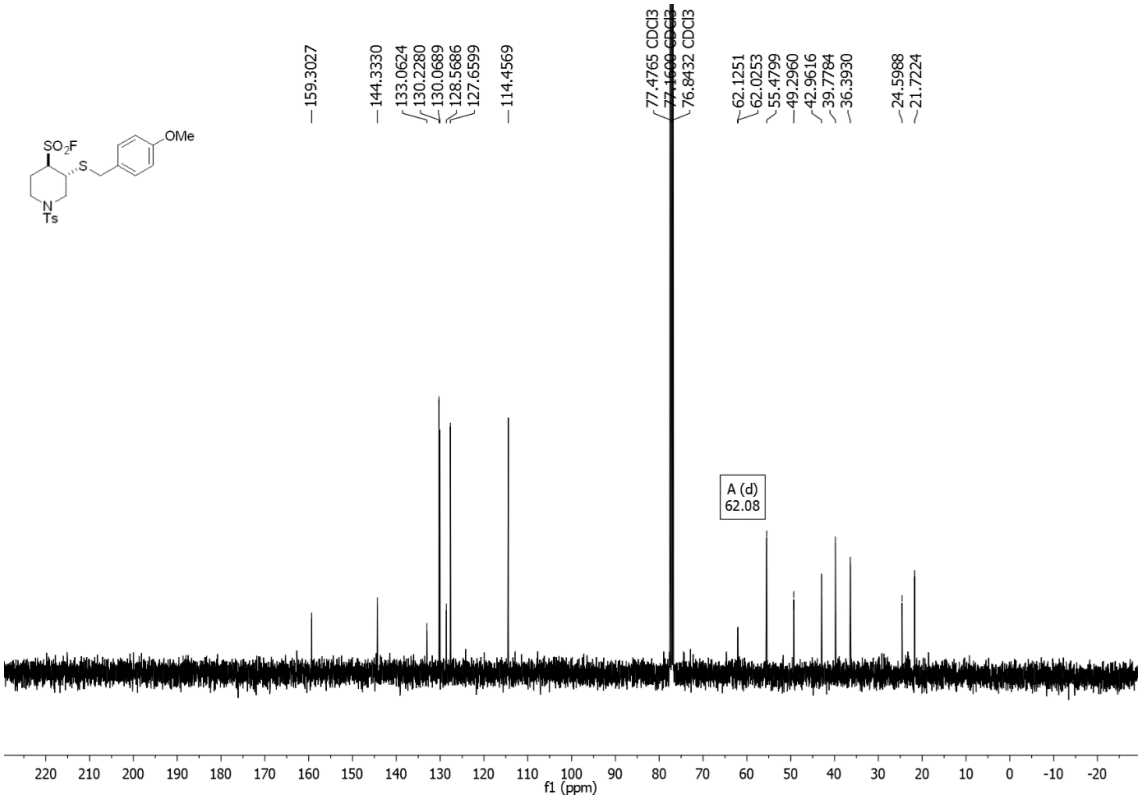


trans-3-((4-Methoxybenzyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (40c1)

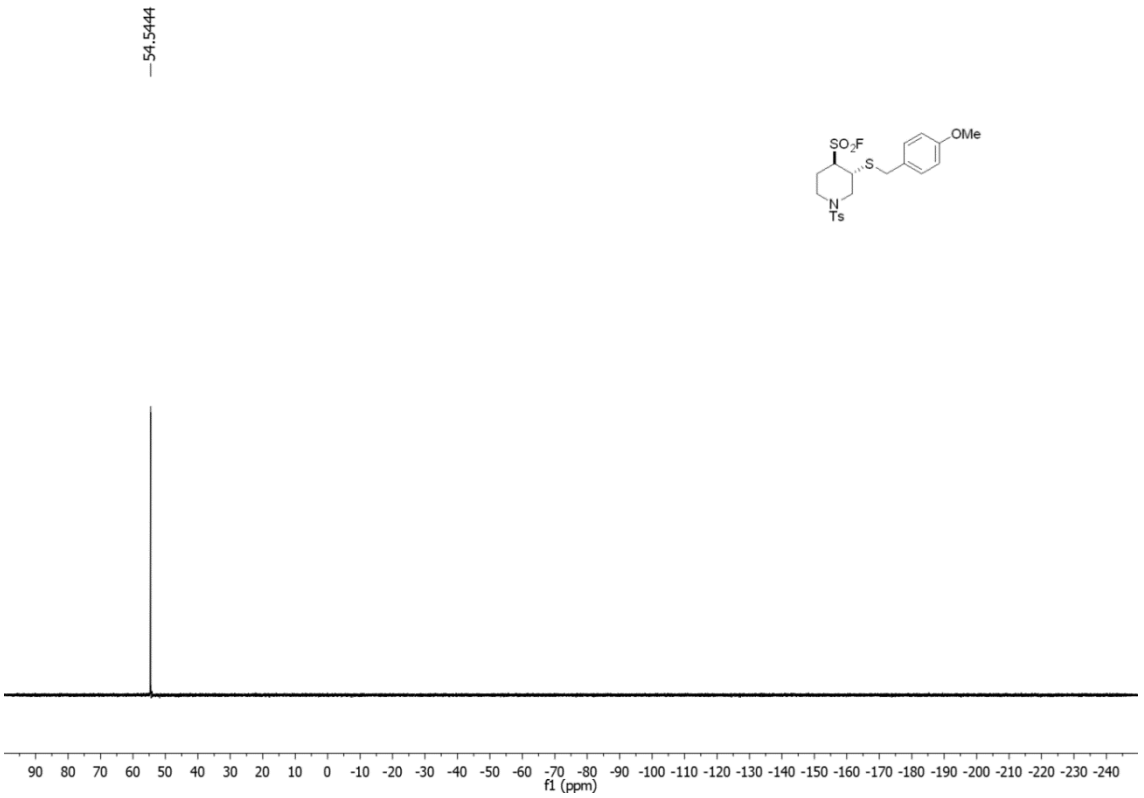
^{1}H-NMR Spectrum:



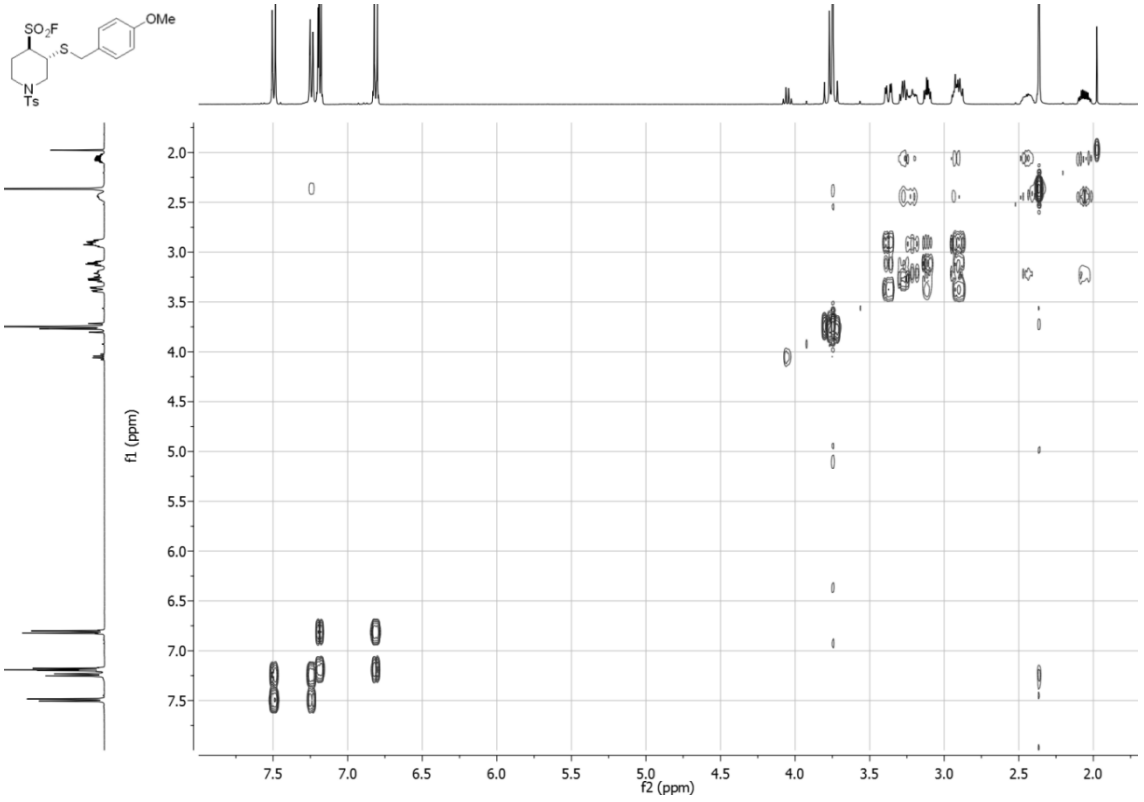
^{13}C-NMR Spectrum:



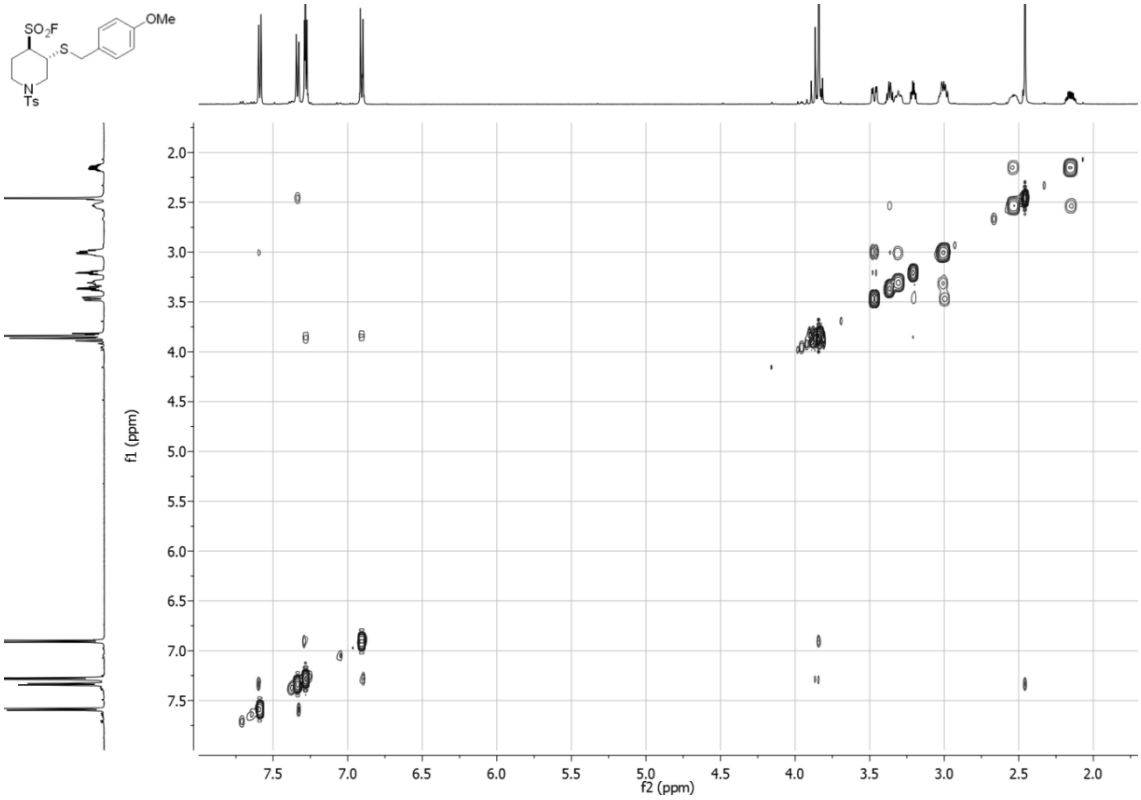
^{19}F-NMR Spectrum:



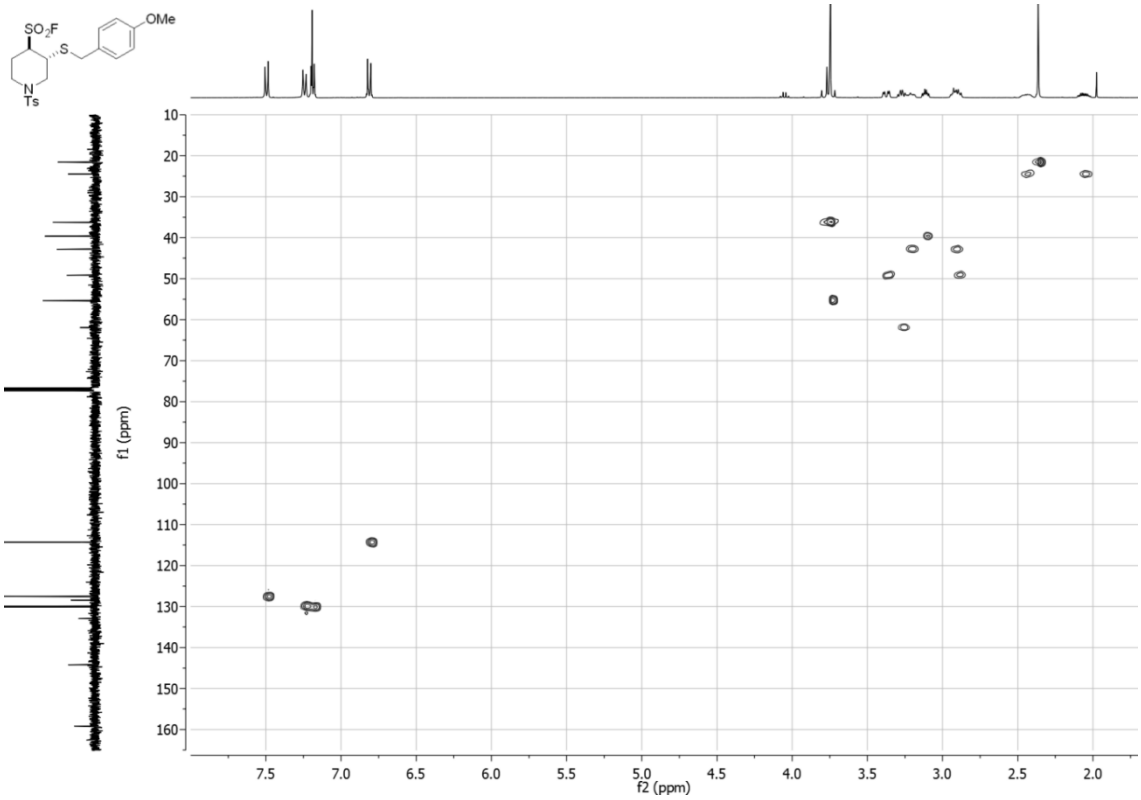
^{1}H-^{1}H COSY NMR Spectrum:



^{1}H-^{1}H NOESY NMR Spectrum:

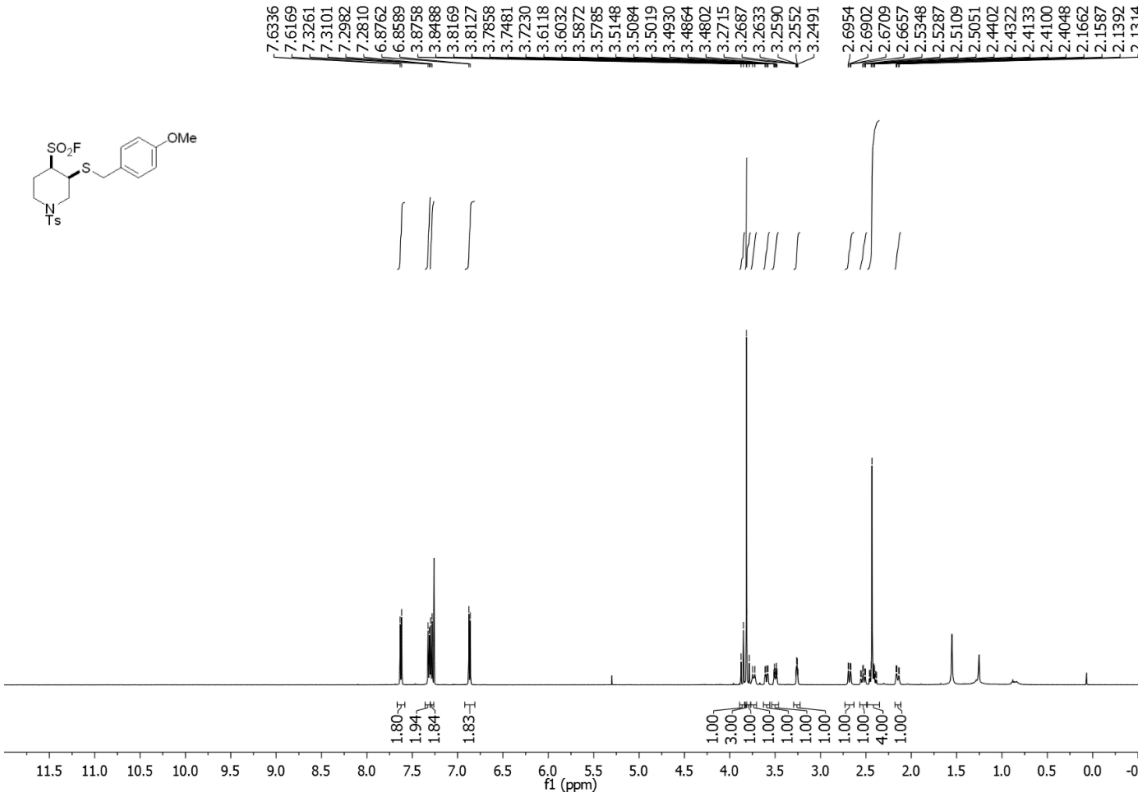


^{1}H-^{13}C HSQC NMR Spectrum:

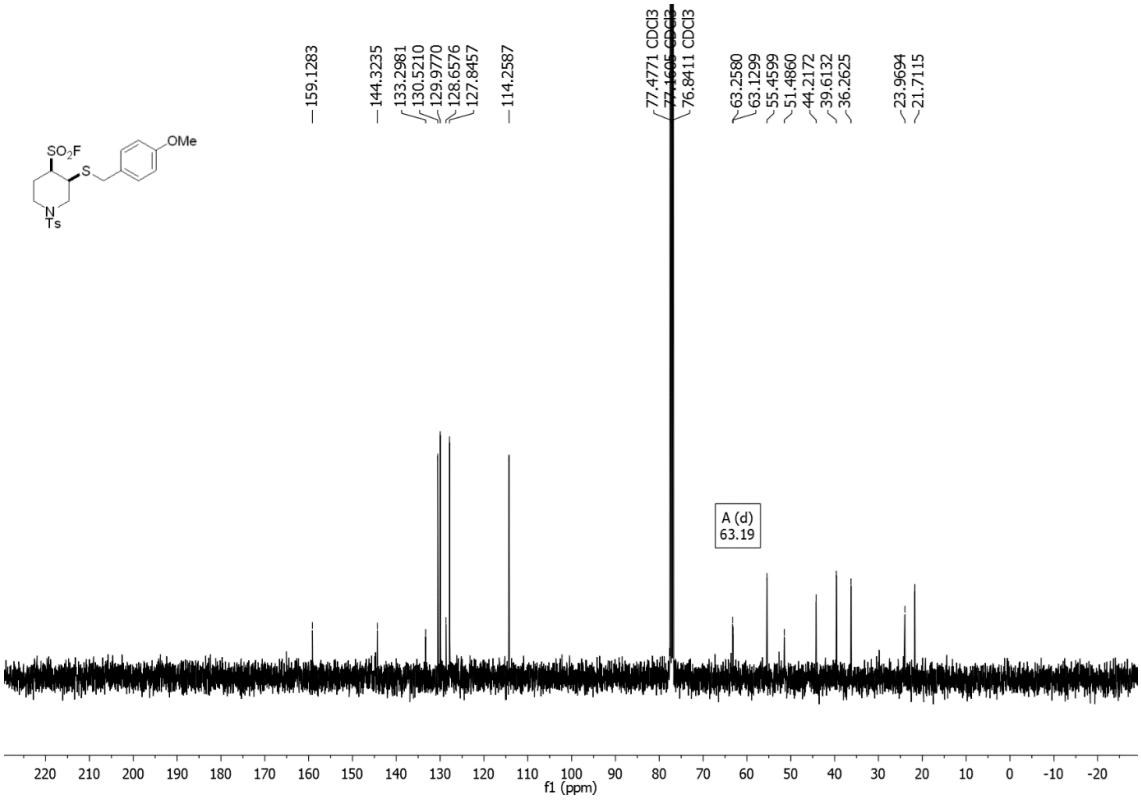


cis-3-((4-Methoxybenzyl)thio)-1-tosylpiperidine-4-sulfonyl fluoride (40c2)

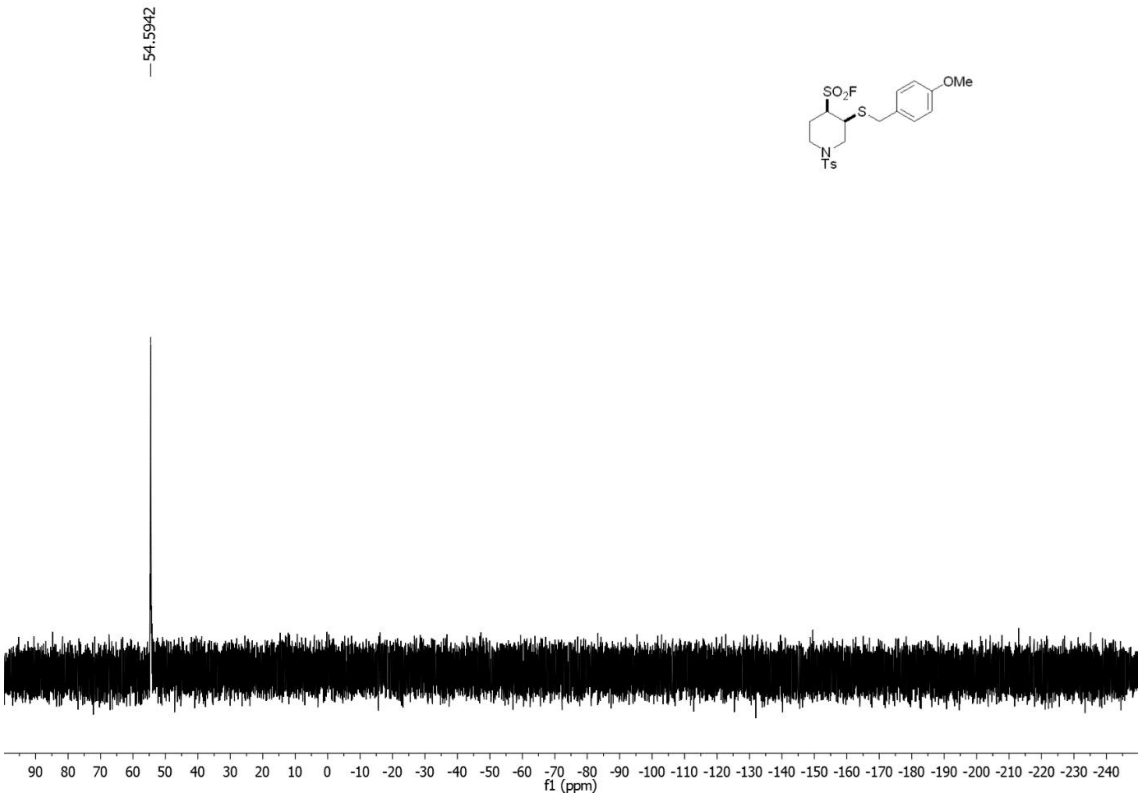
^{1}H-NMR Spectrum:



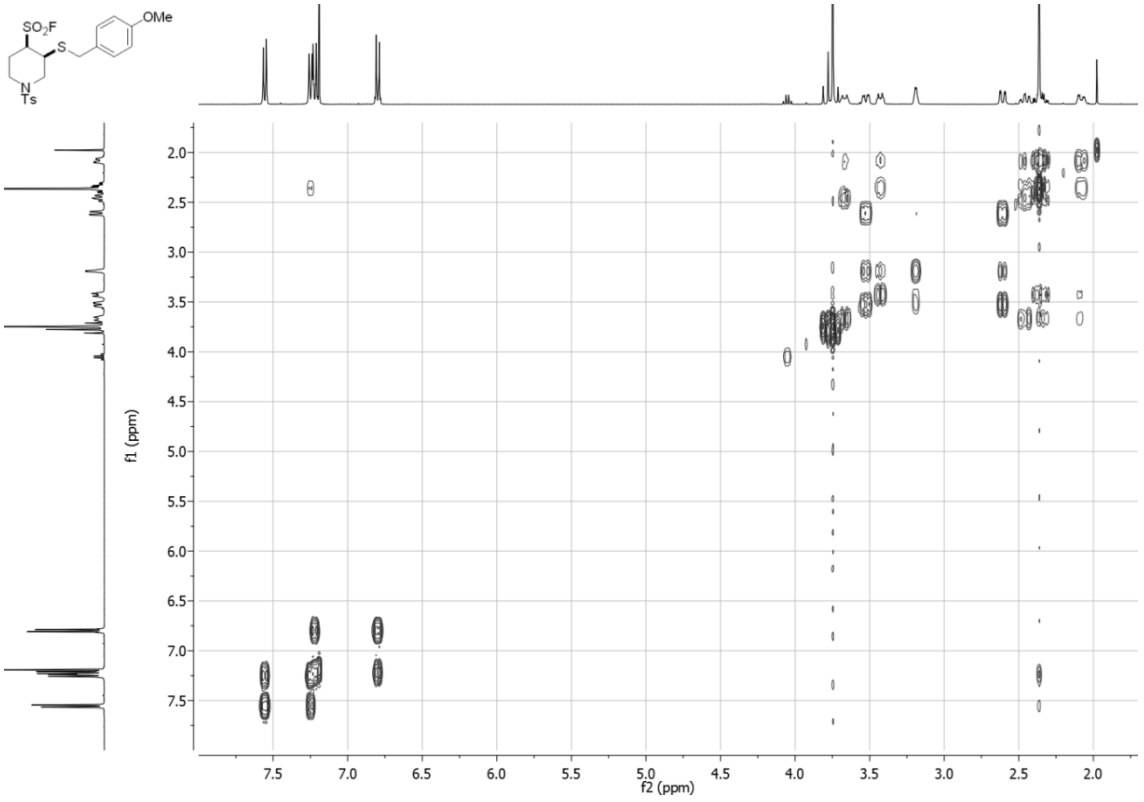
^{13}C-NMR Spectrum:



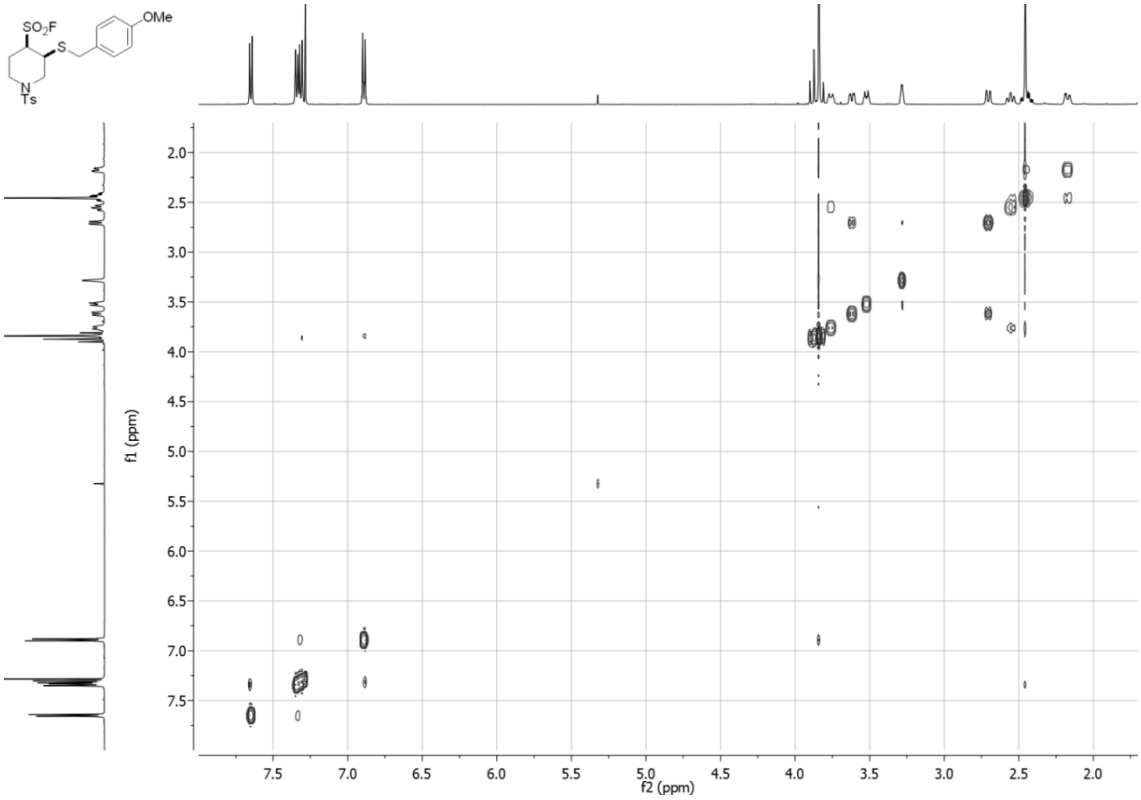
^{19}F-NMR Spectrum:



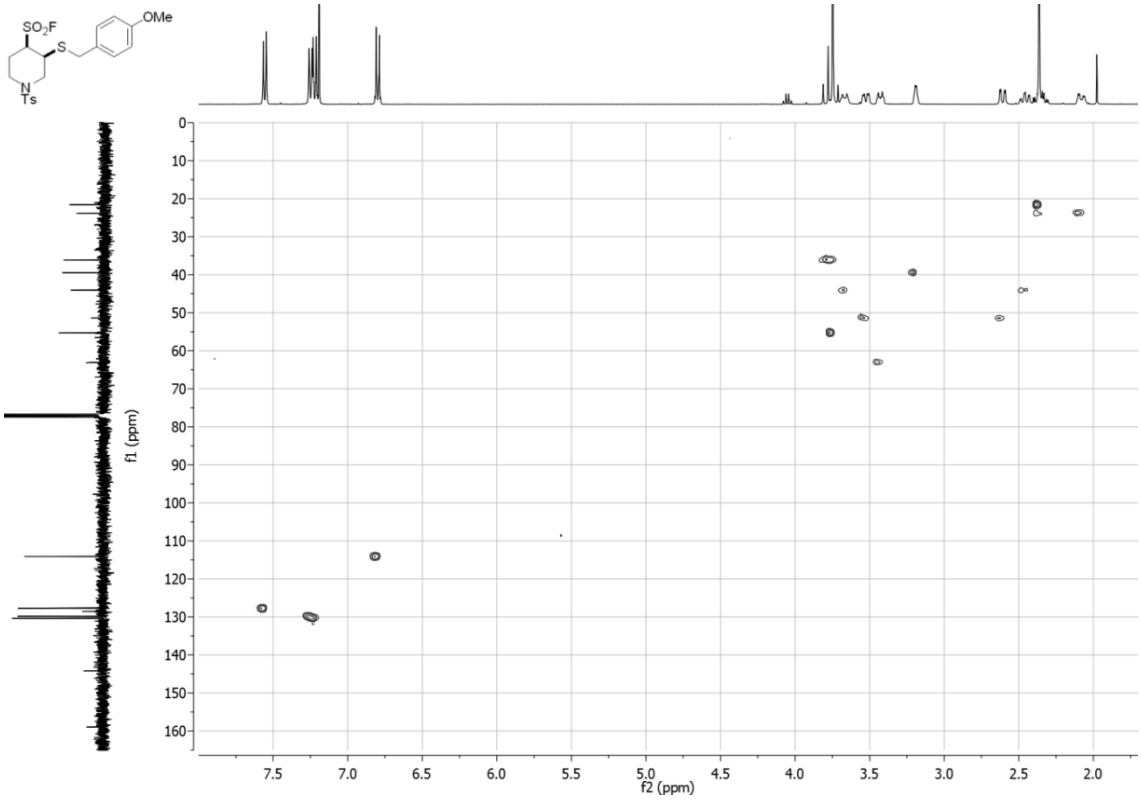
^{1}H-^{1}H COSY NMR Spectrum:



^{1}H-^{1}H NOESY NMR Spectrum:

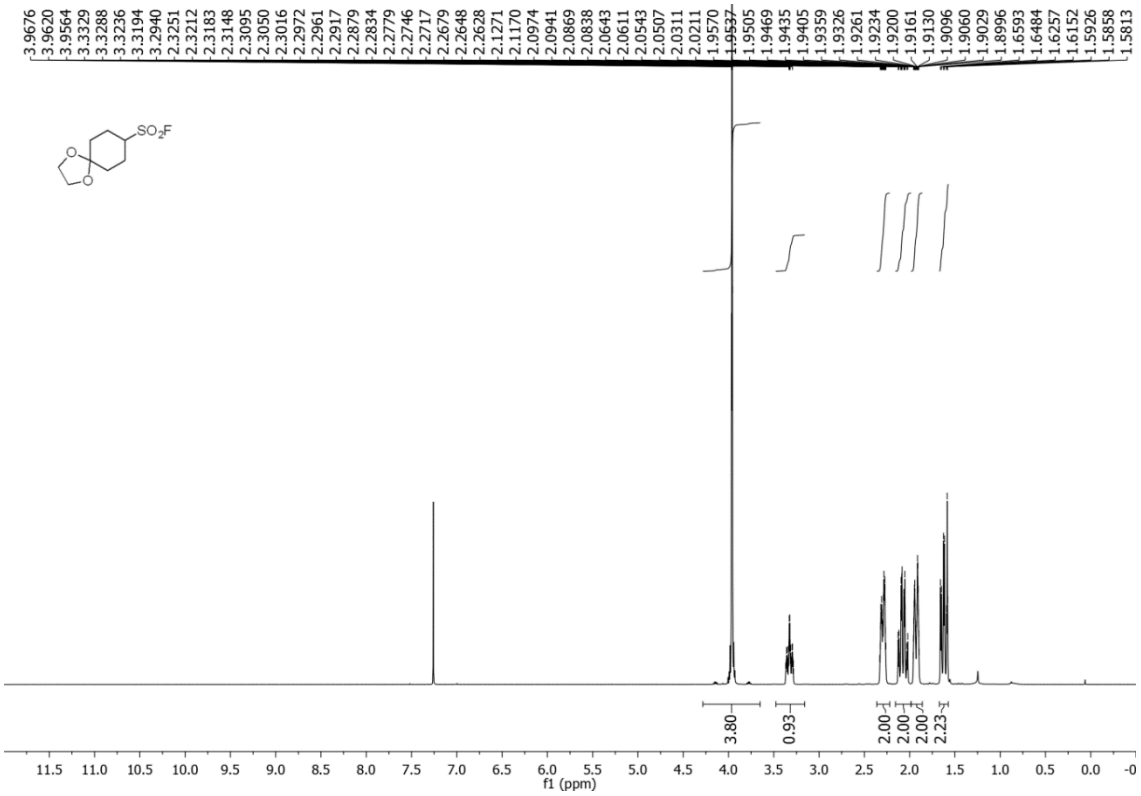


^{1}H-^{13}C HSQC NMR Spectrum:

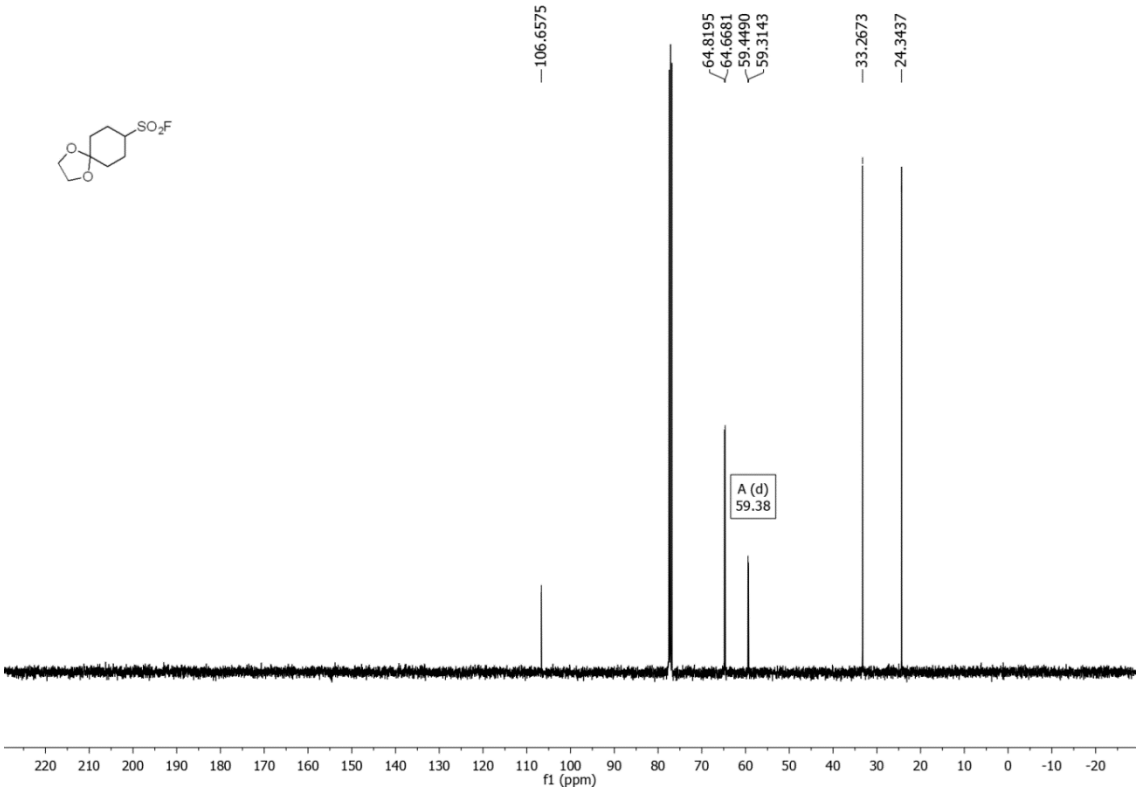


1,4-Dioxaspiro[4.5]decane-8-sulfonyl fluoride (41)

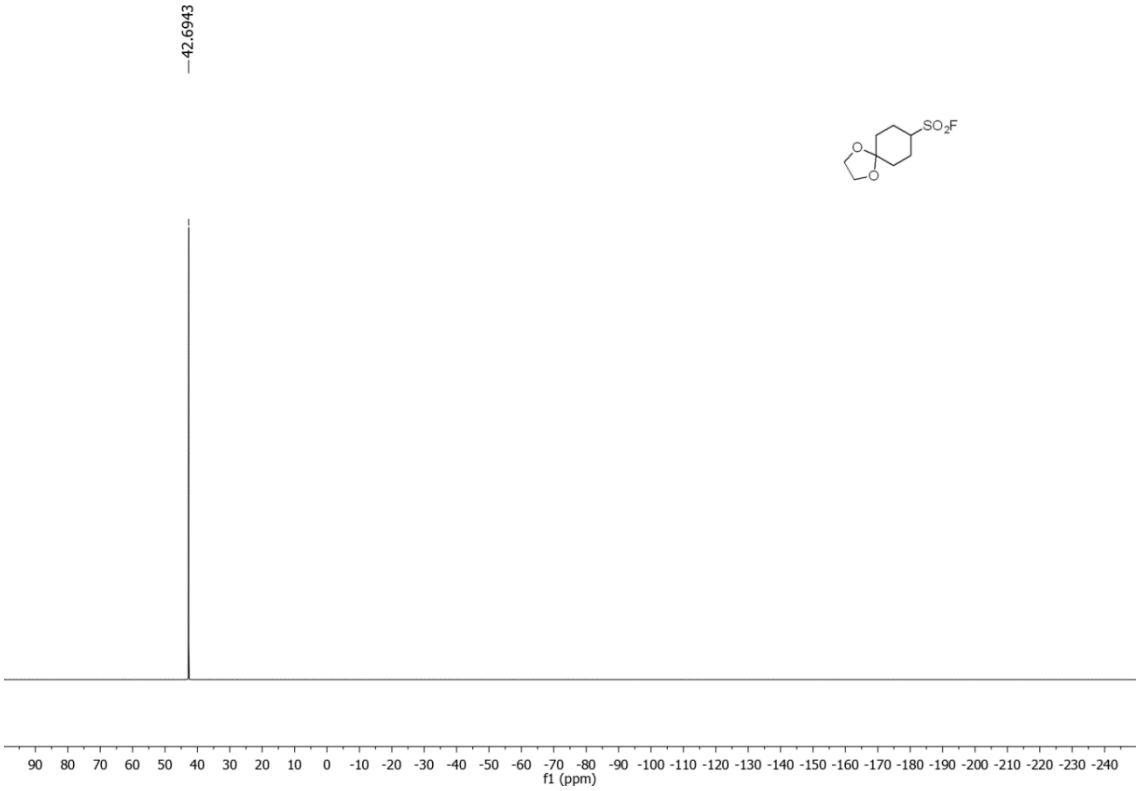
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

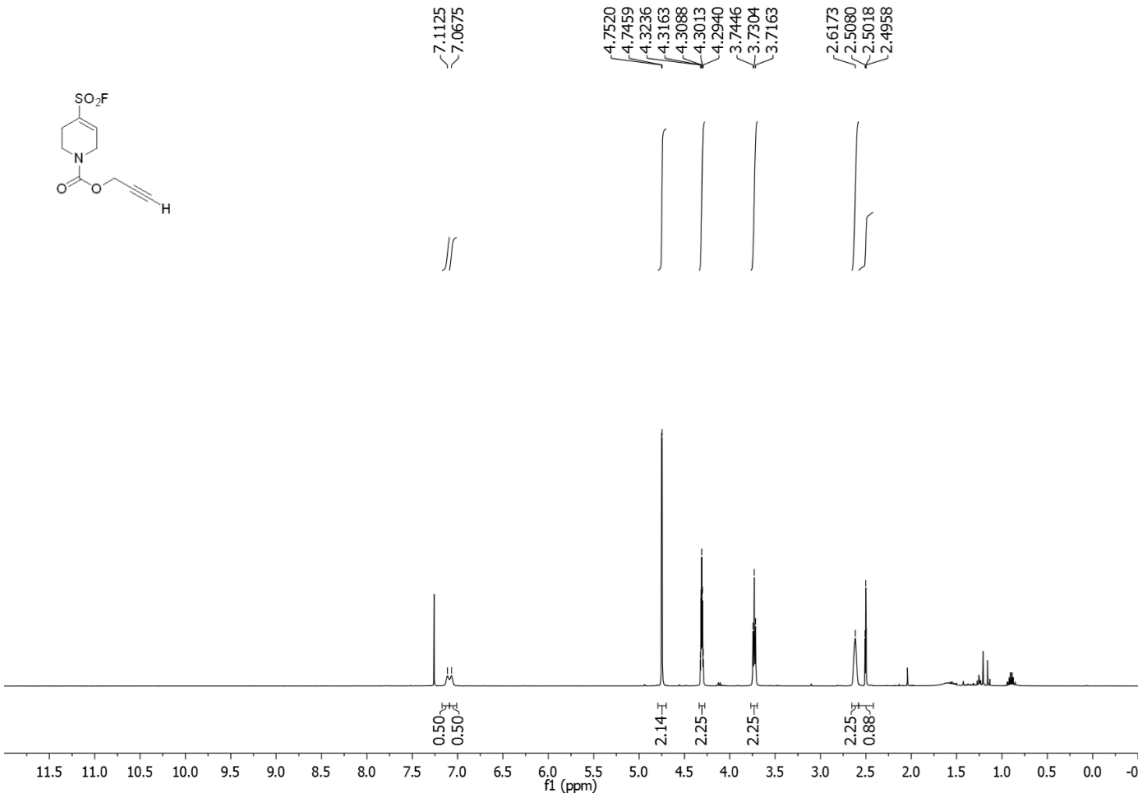


^{19}F-NMR Spectrum:

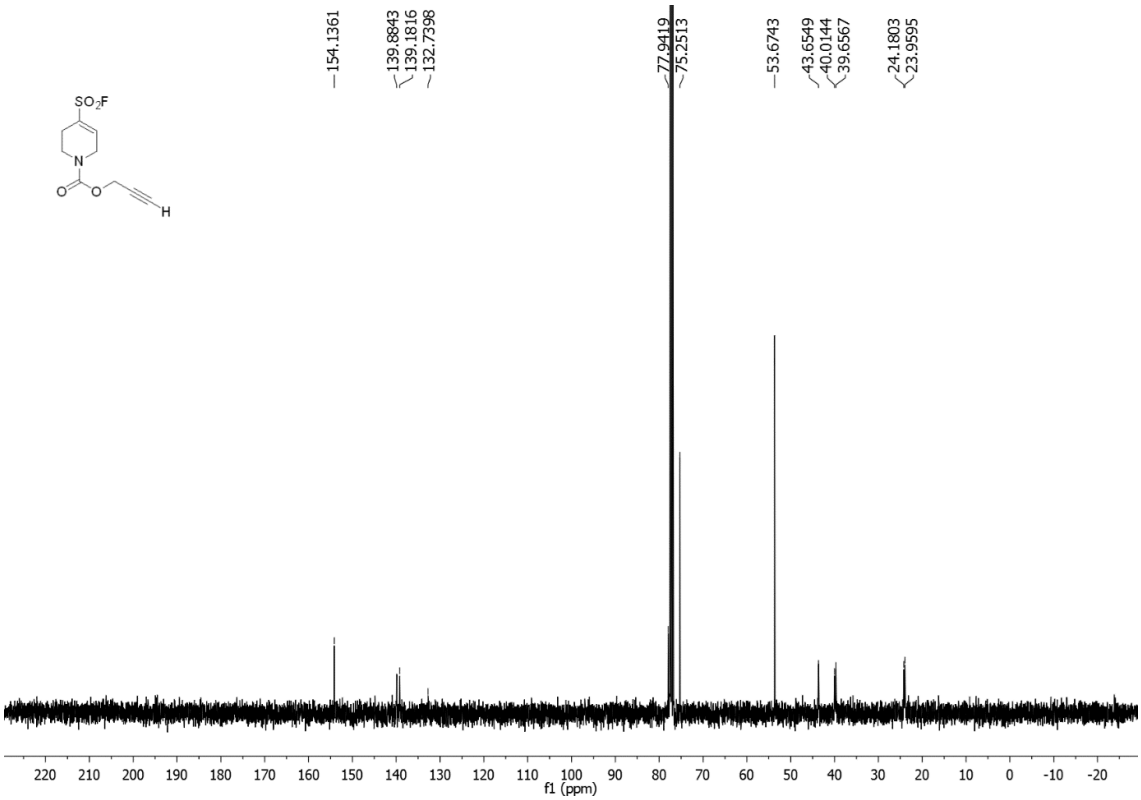


Prop-2-yn-1-yl 4-(fluorosulfonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (42)

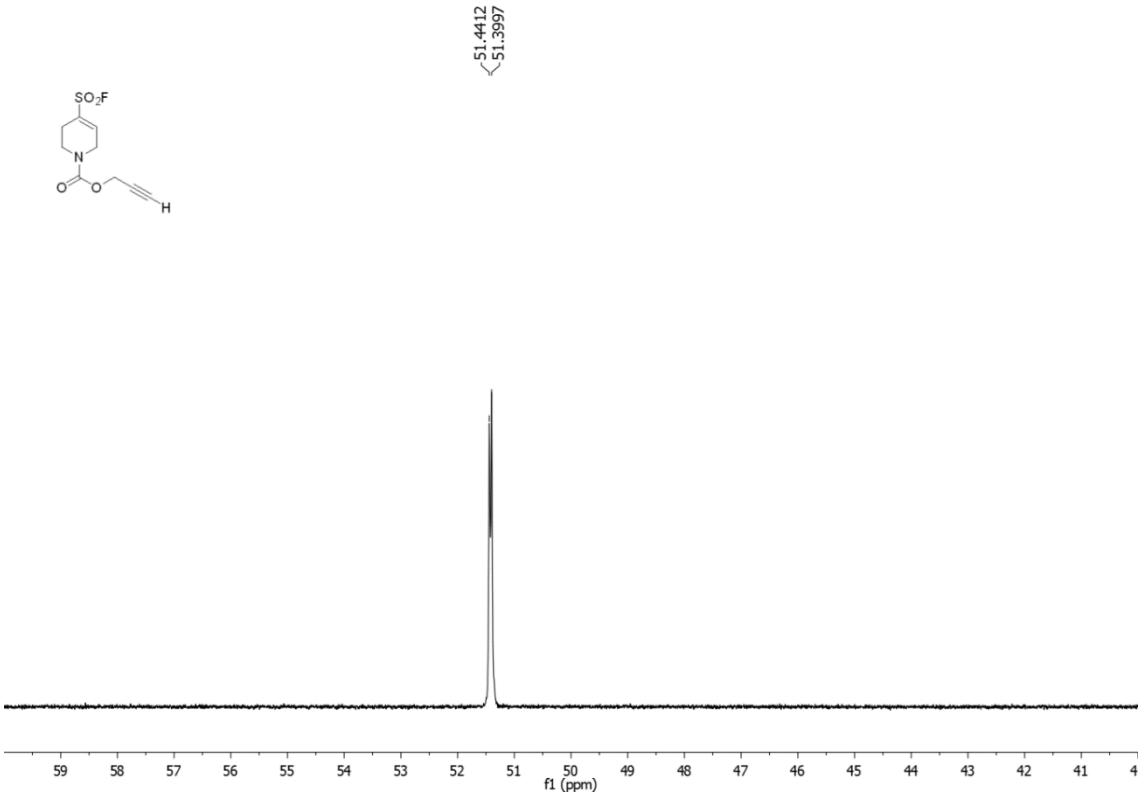
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

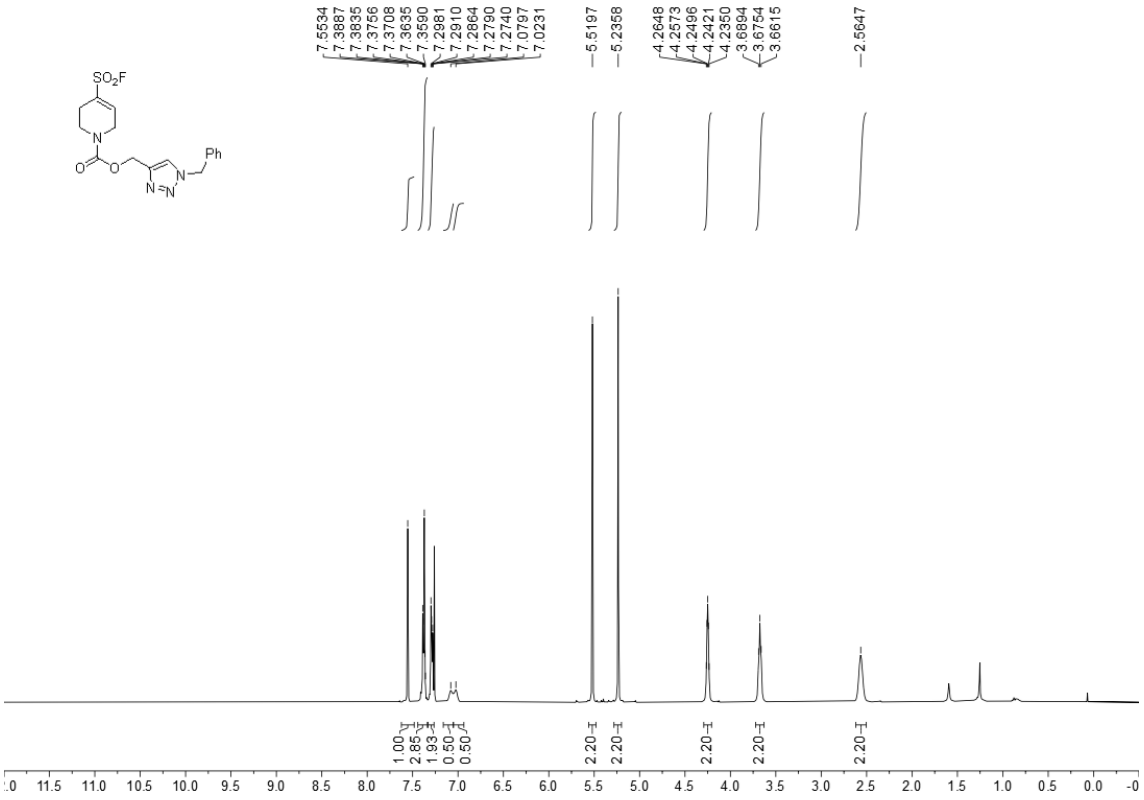


^{19}F-NMR Spectrum:

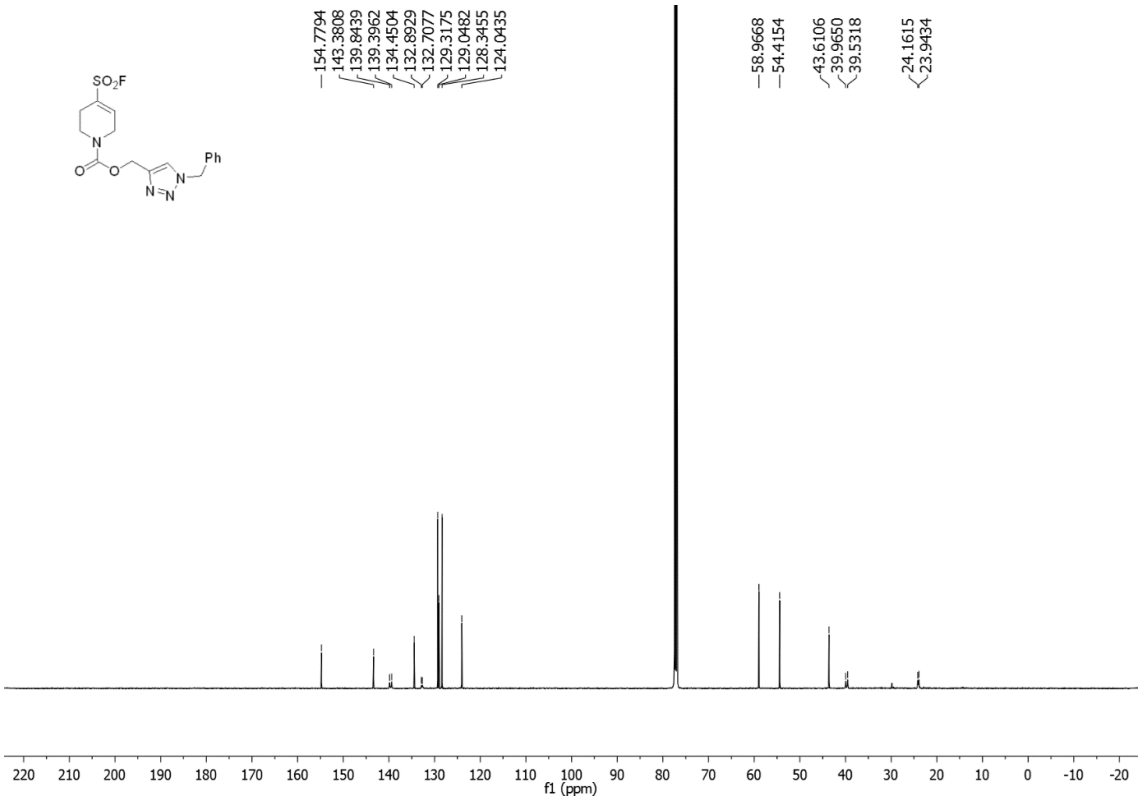


(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl 4-(fluorosulfonyl)-3,6-dihydro-pyridine-1(2*H*)-carboxylate (43)

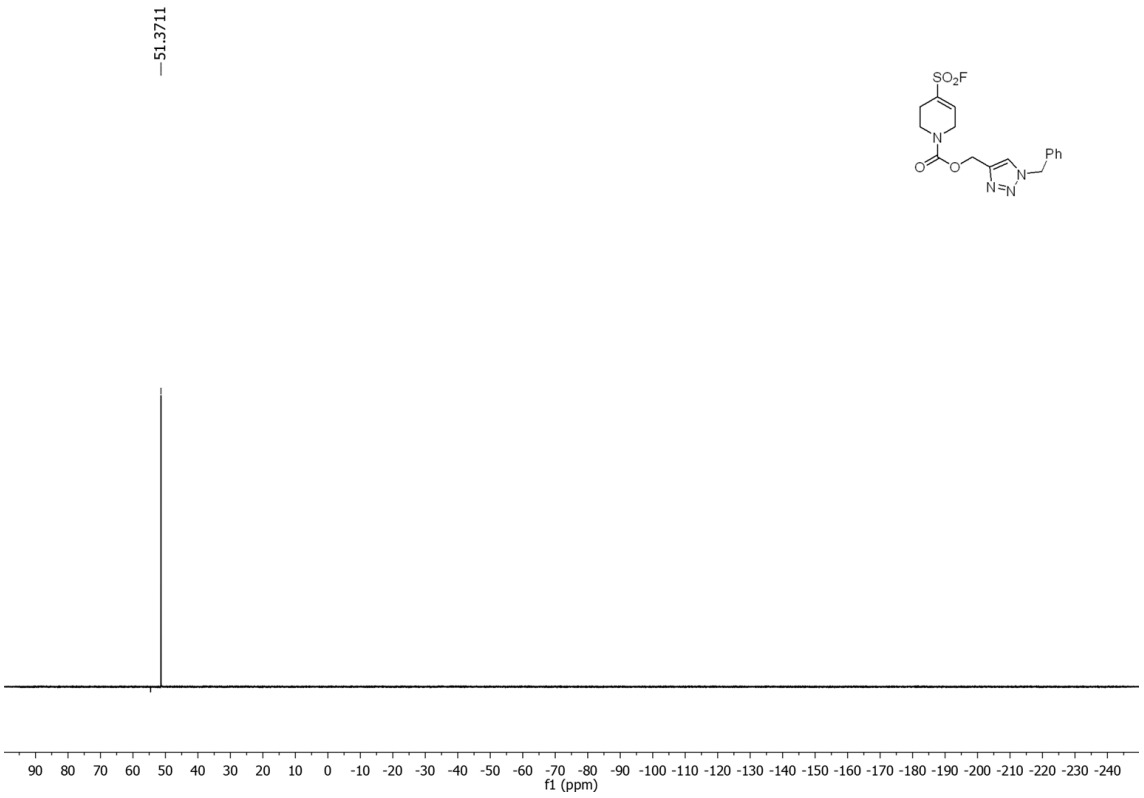
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

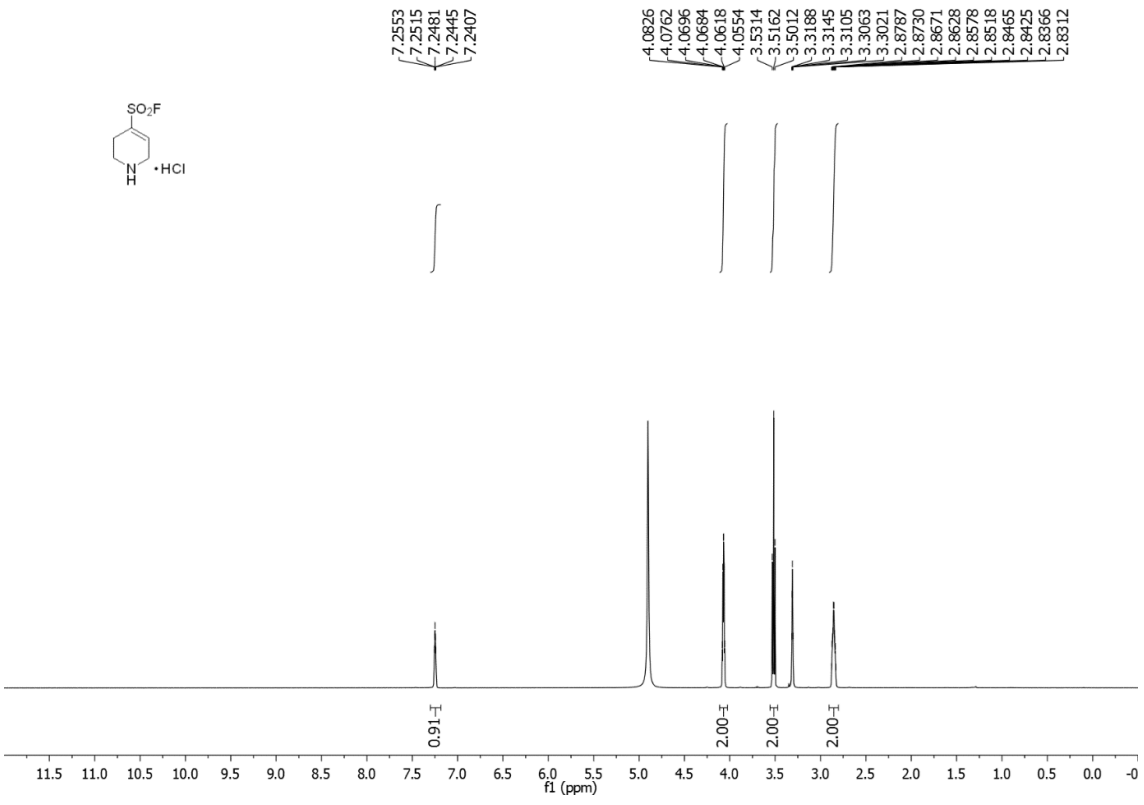


^{19}F-NMR Spectrum:

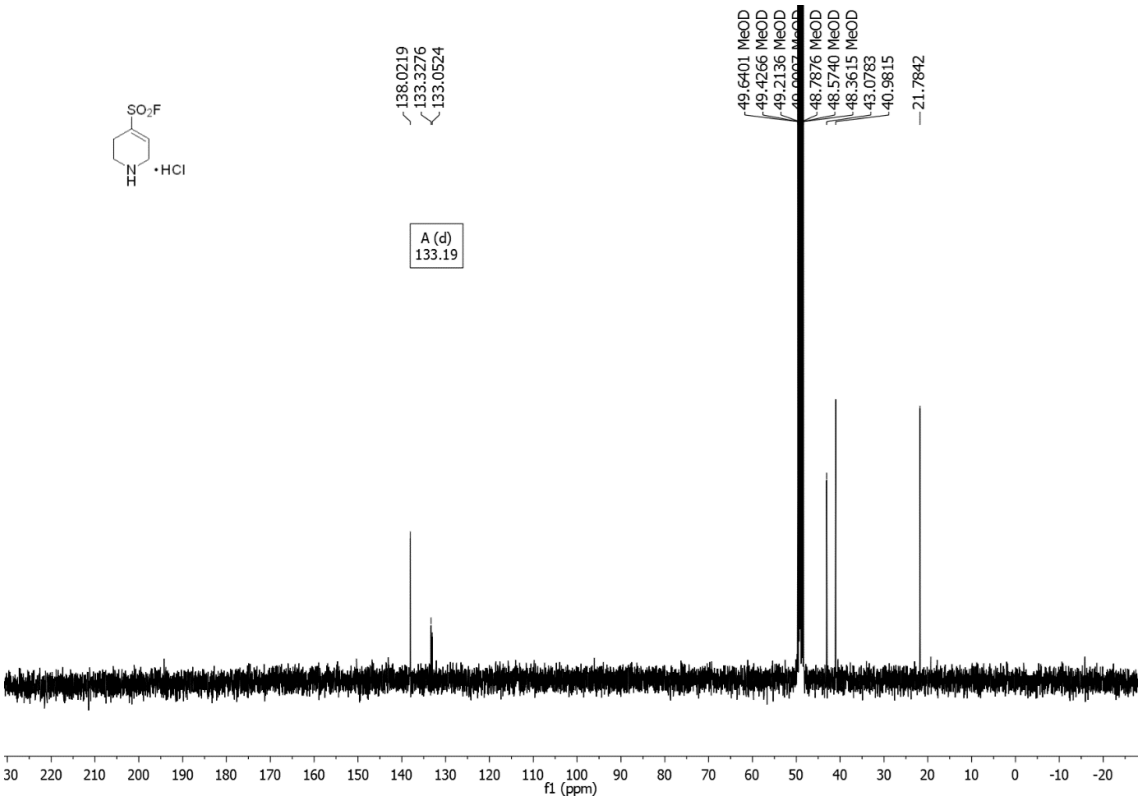


1,2,3,6-Tetrahydropyridine-4-sulfonyl fluoride hydrochloride (44)

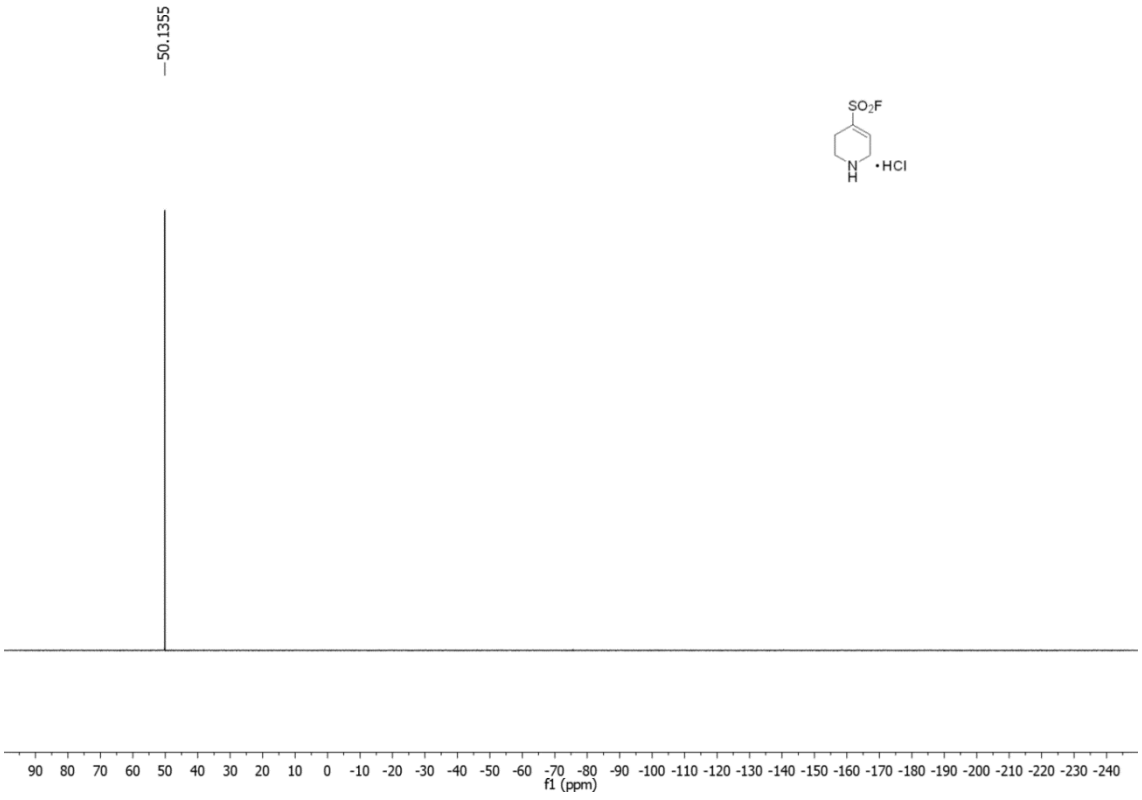
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

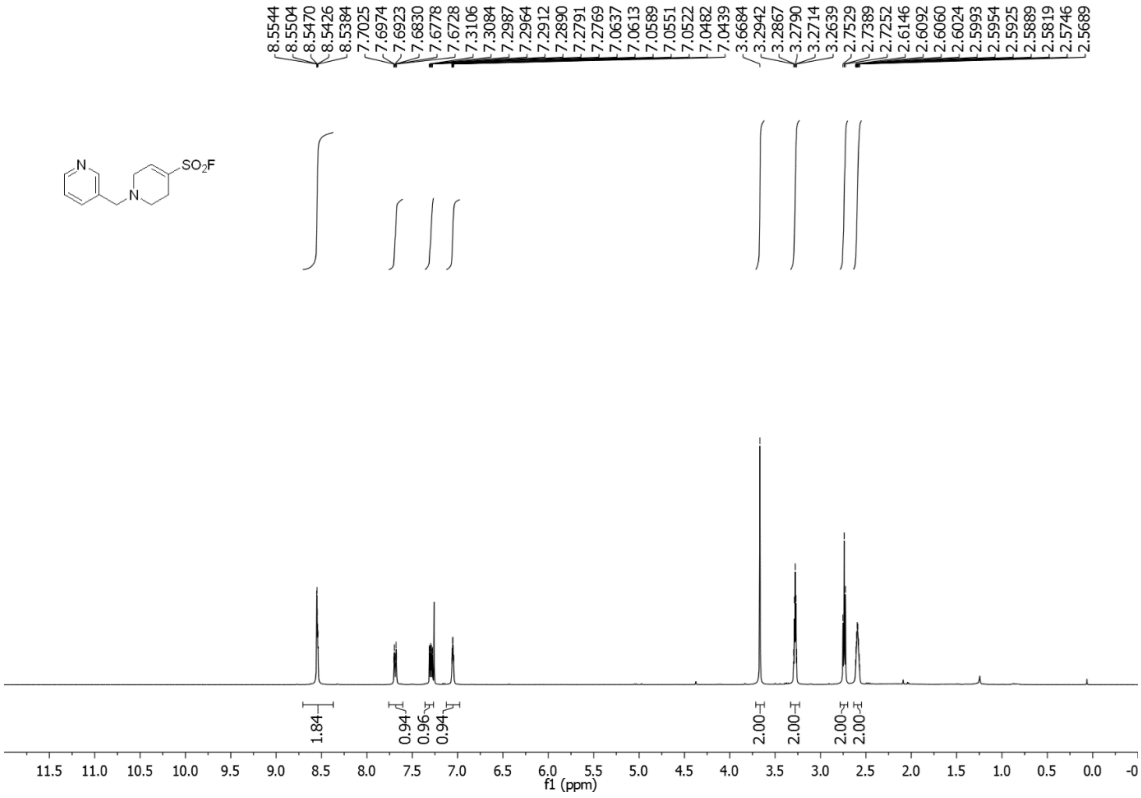


^{19}F-NMR Spectrum:

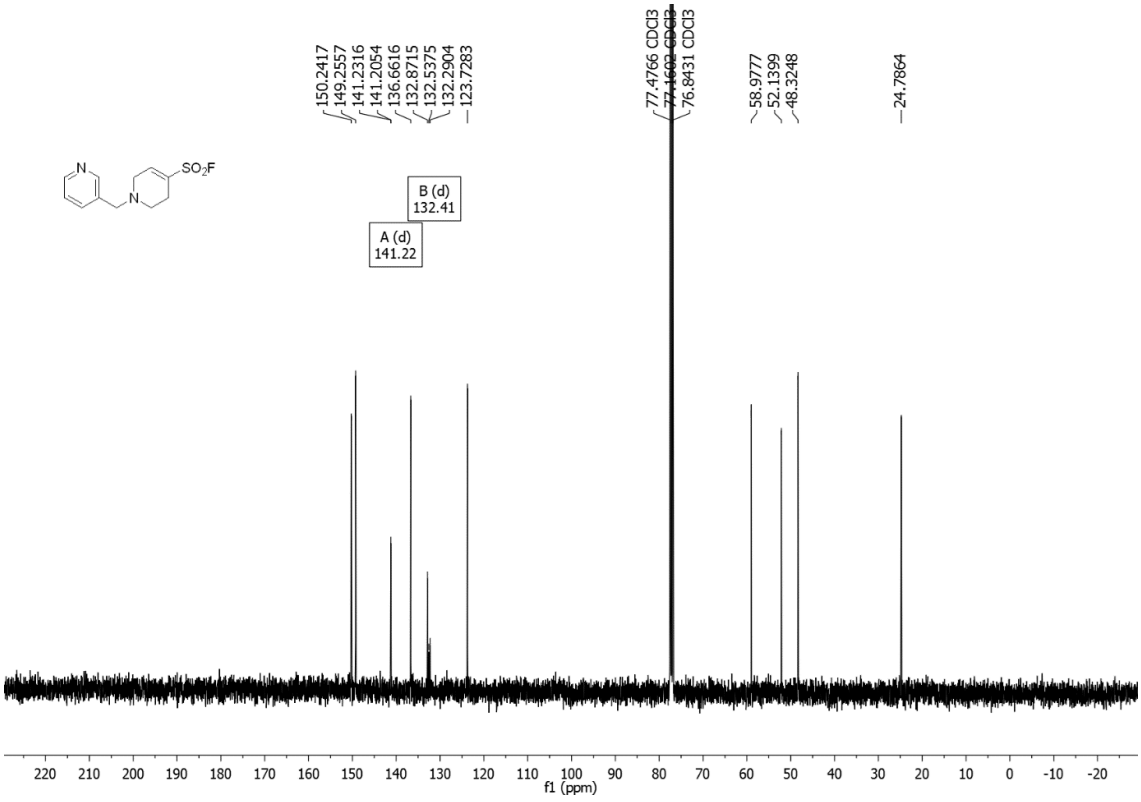


1-(Pyridin-3-ylmethyl)-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (46)

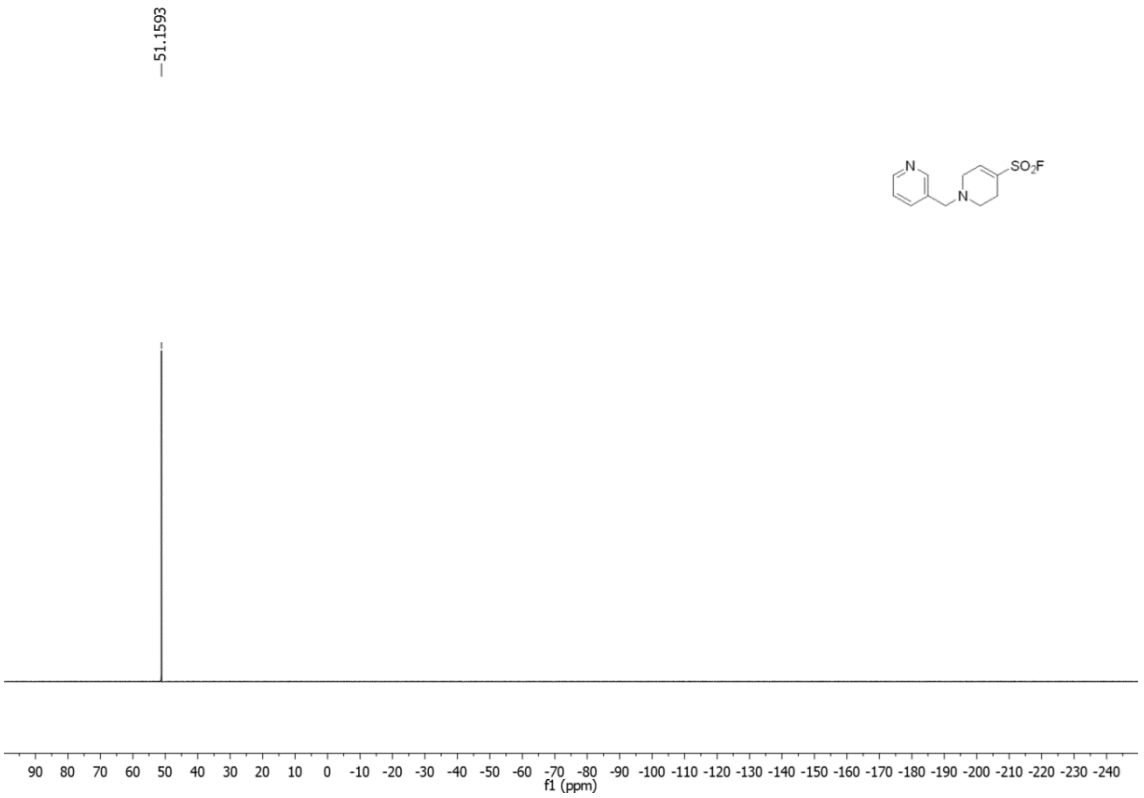
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

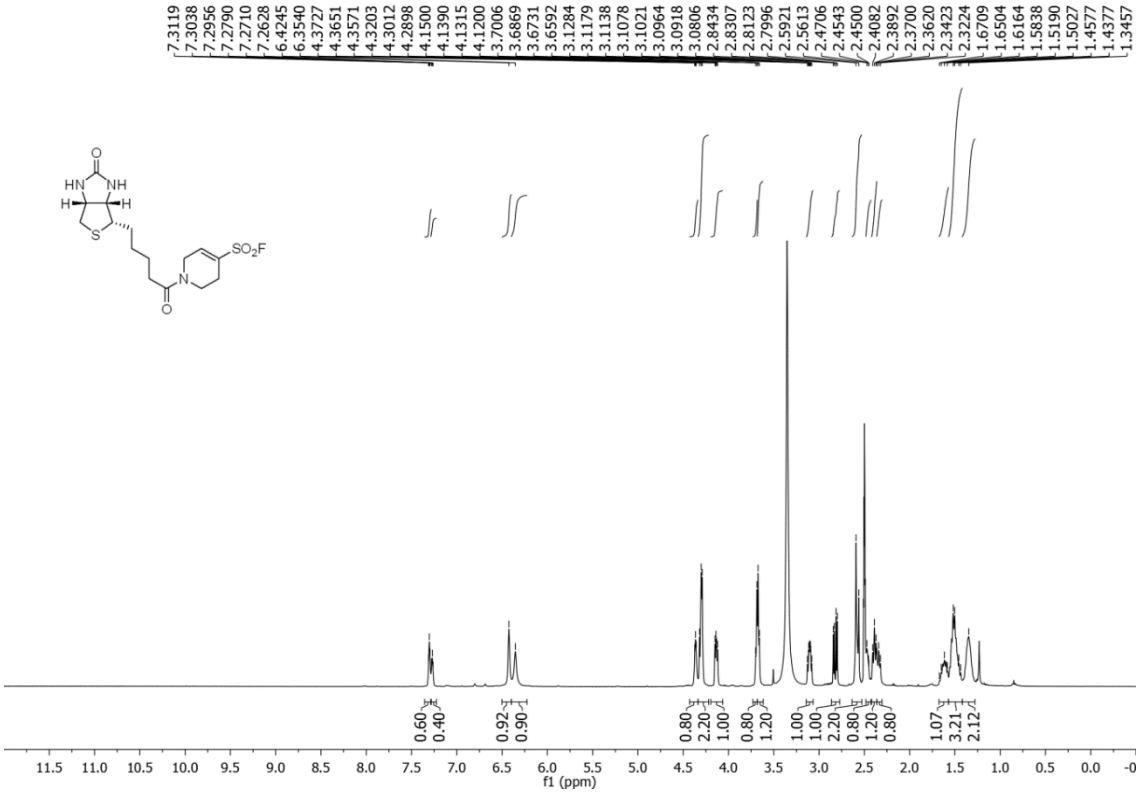


^{19}F-NMR Spectrum:

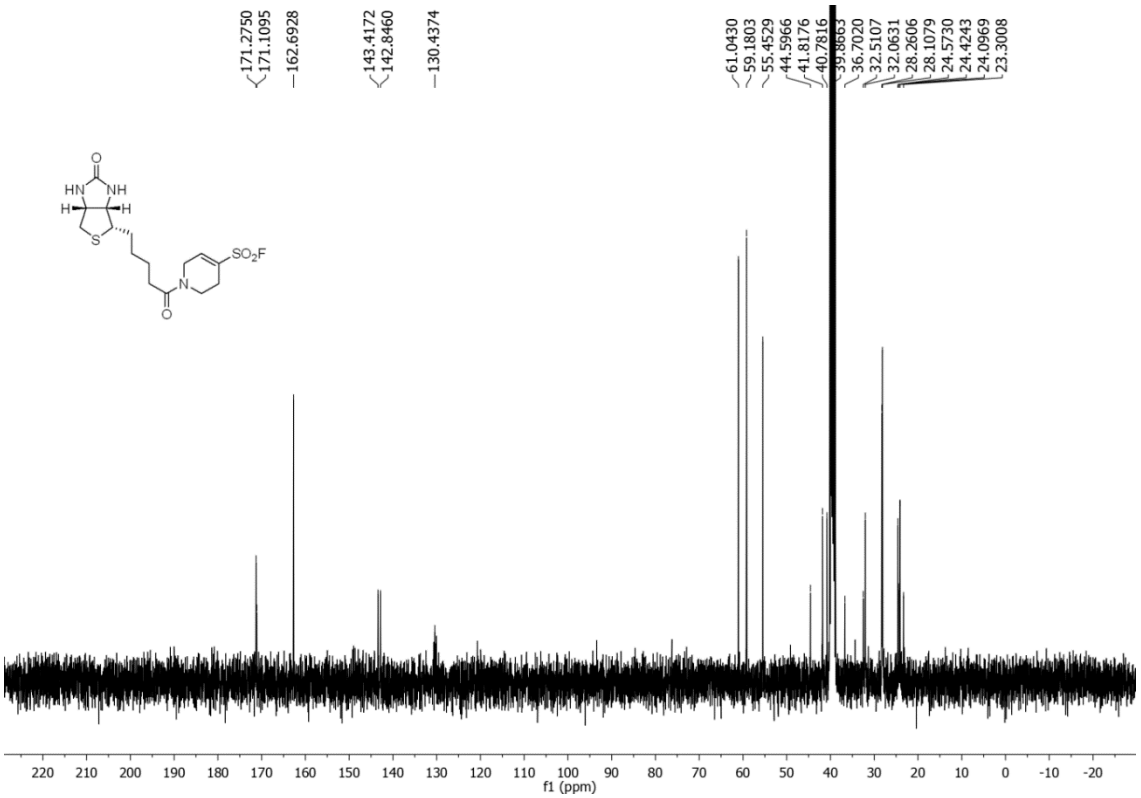


1-(5-((3a*S*,4*S*,6a*R*)-2-Oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoyl)-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (47)

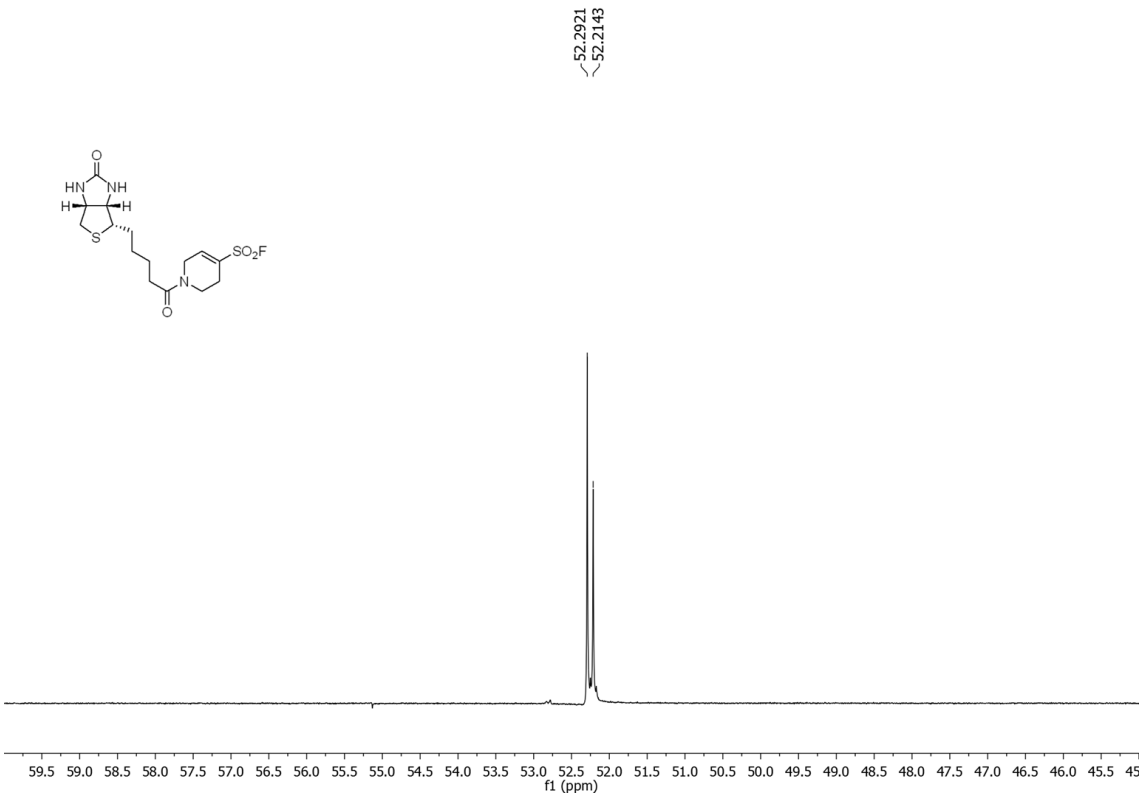
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

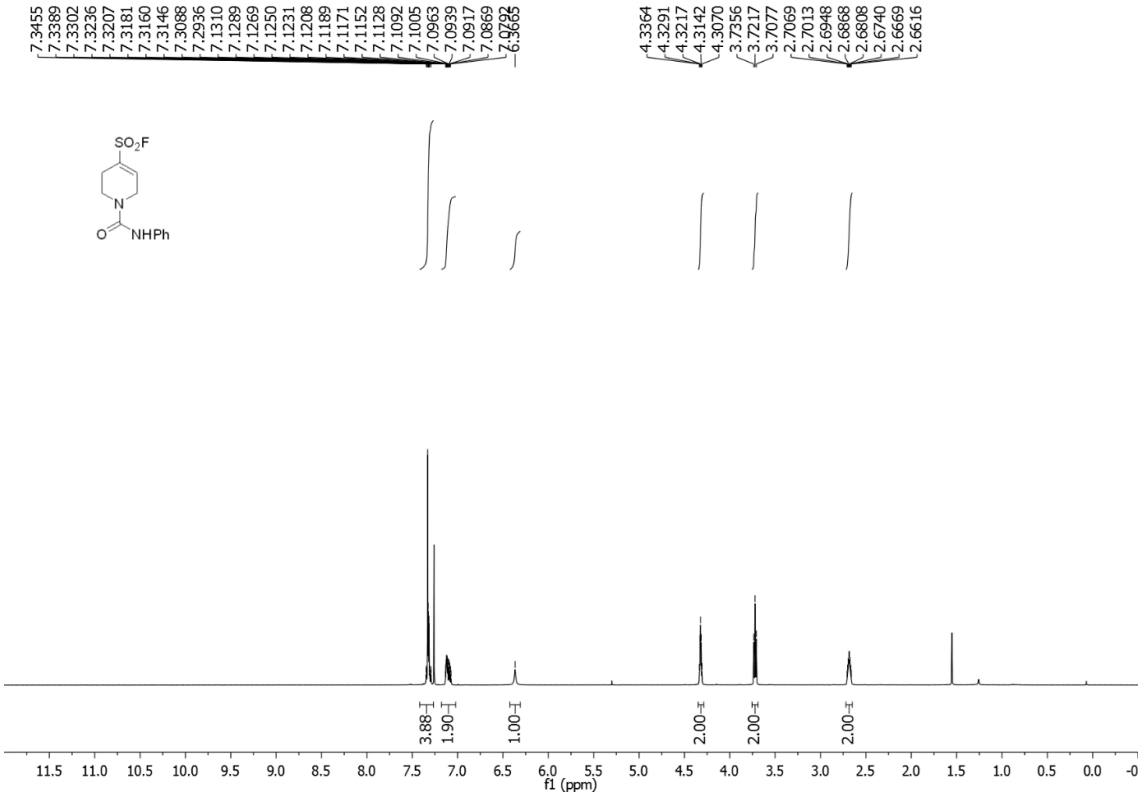


^{19}F-NMR Spectrum:

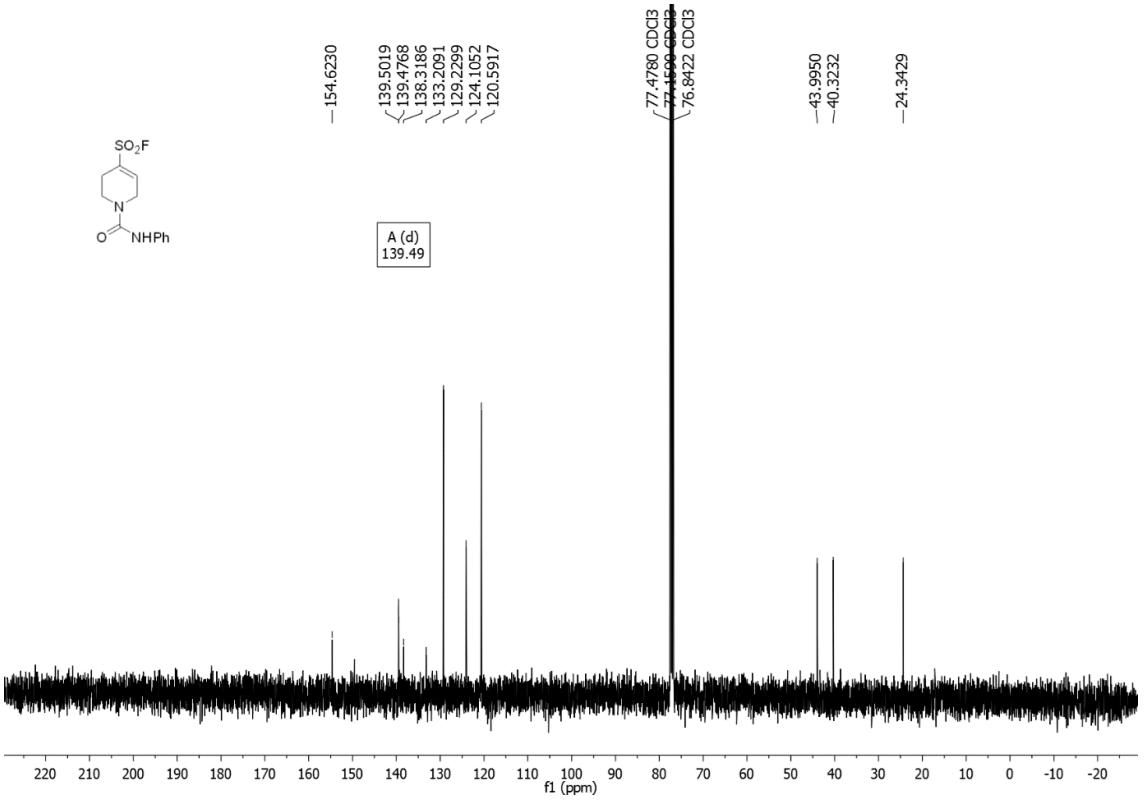


1-(Phenylcarbamoyl)-1,2,3,6-tetrahydro-pyridine-4-sulfonyl fluoride (48)

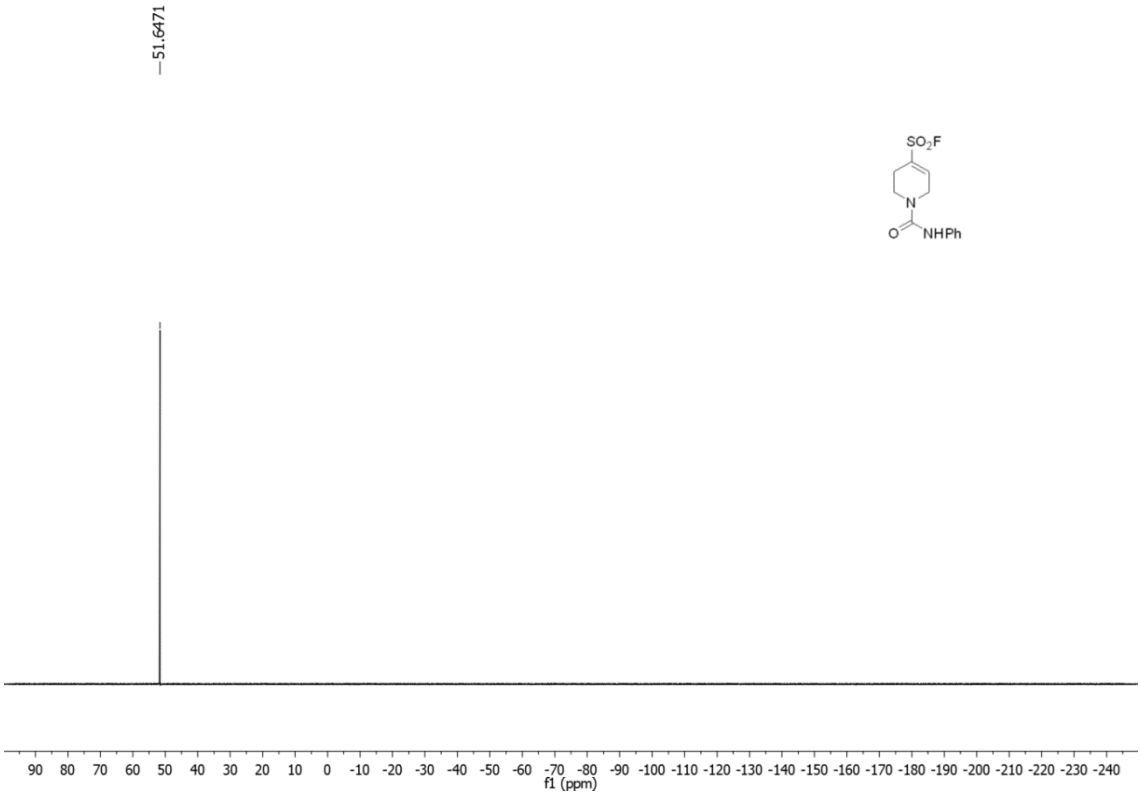
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

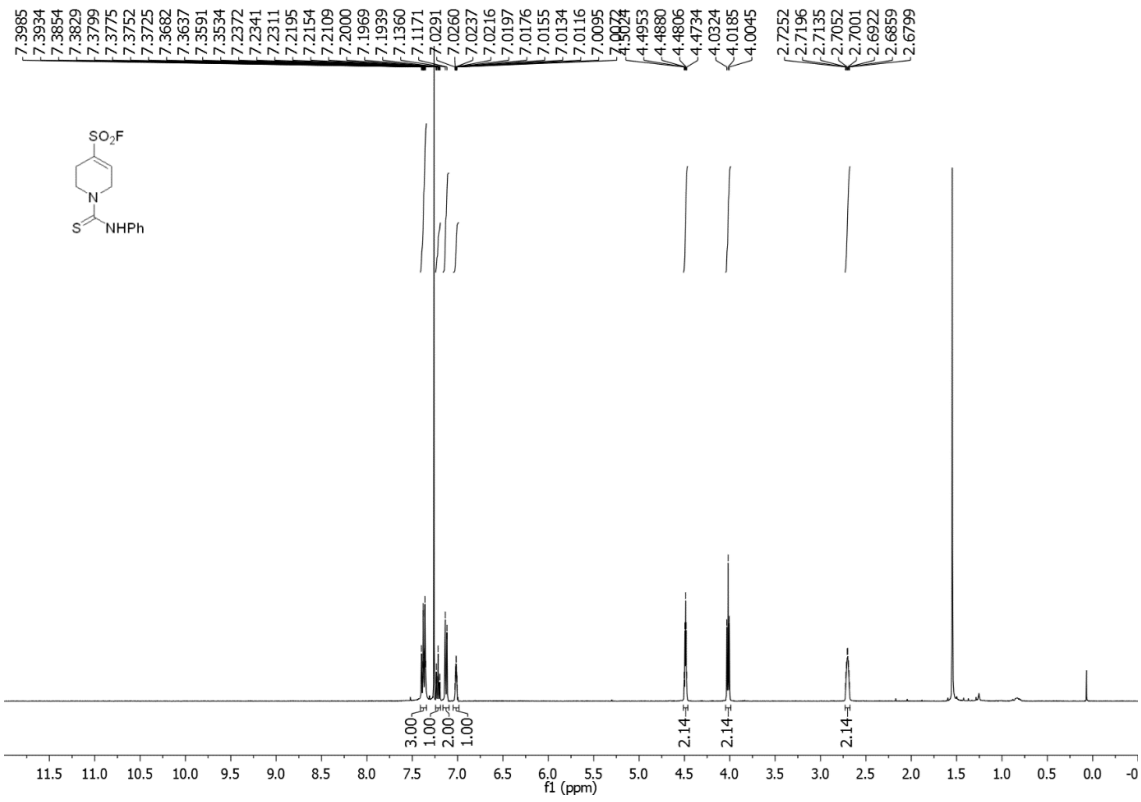


^{19}F-NMR Spectrum:

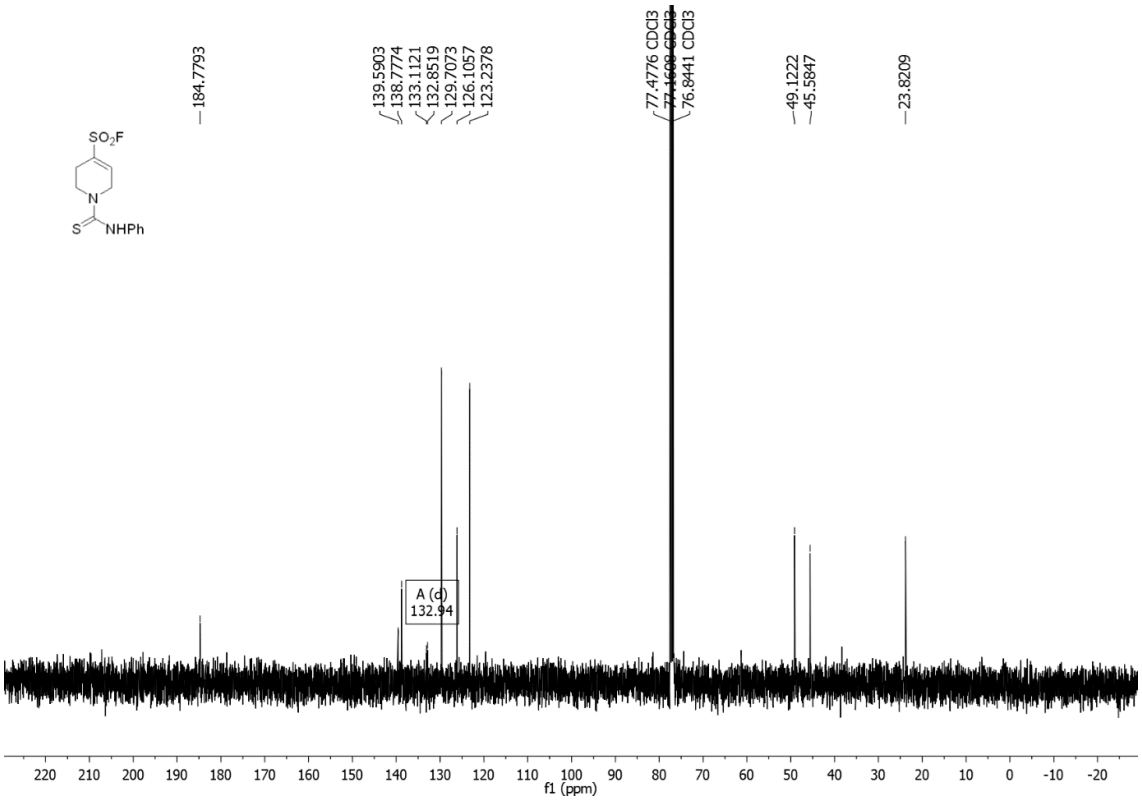


1-(Phenylcarbamothioyl)-1,2,3,6-tetrahydropyridine-4-sulfonyl fluoride (49)

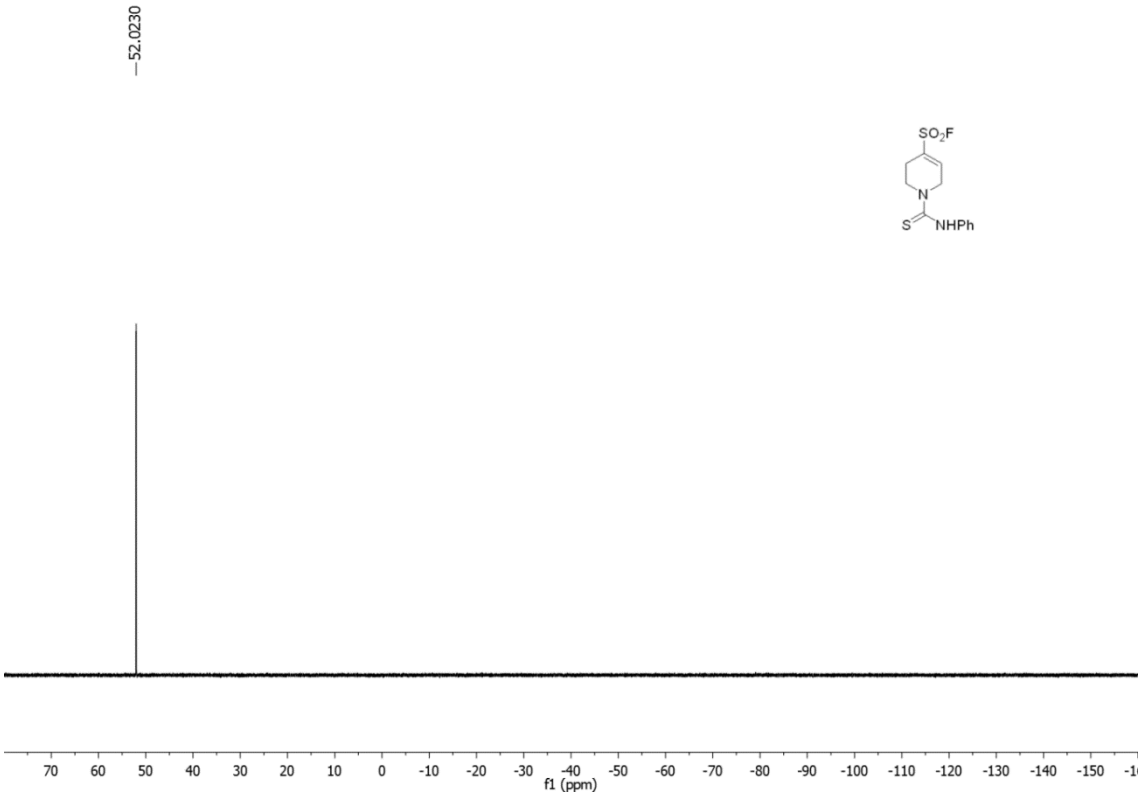
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

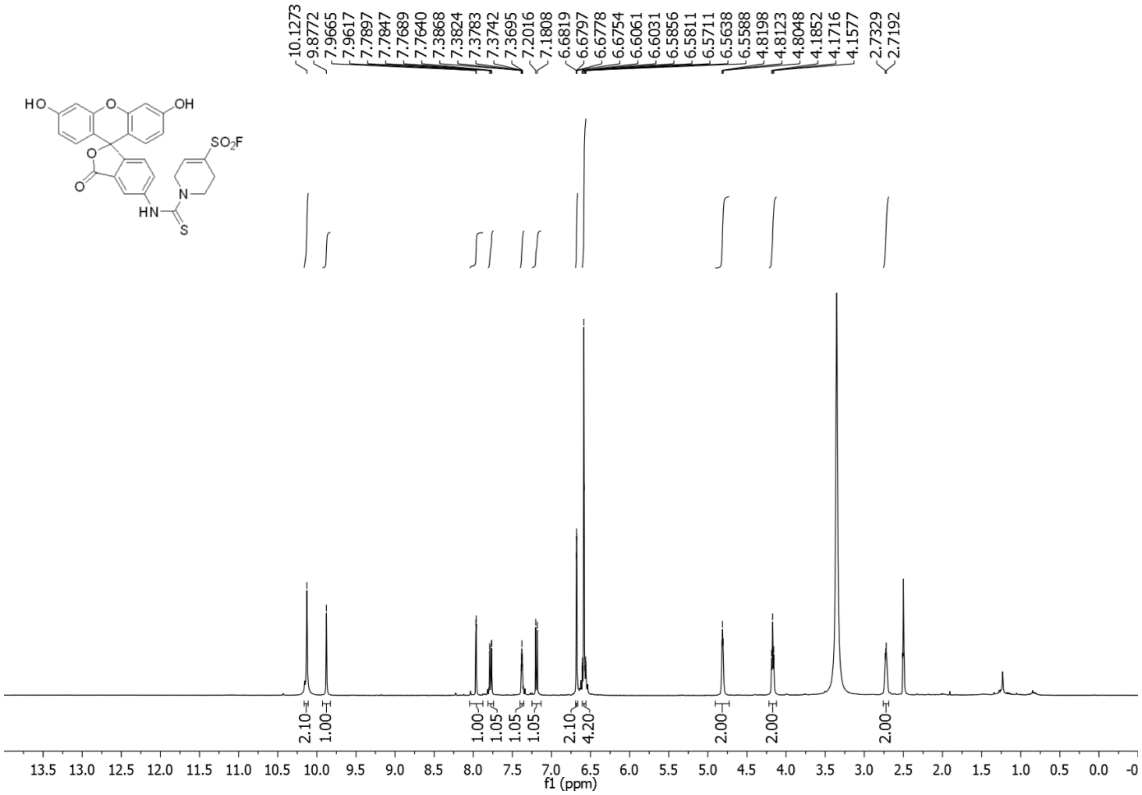


^{19}F-NMR Spectrum:

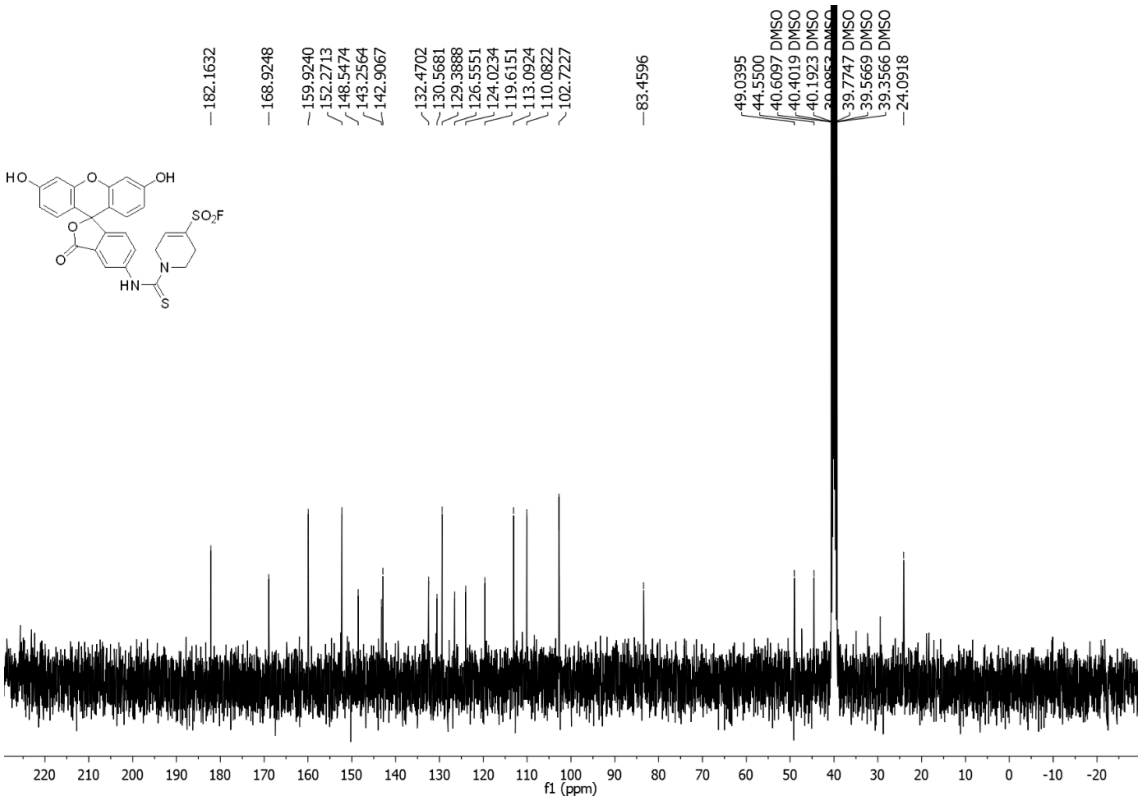


5-(4-(Fluorosulfonyl)-1,2,3,6-tetrahydropyridine-1-carbothioamido)-2-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)benzoic acid (50)

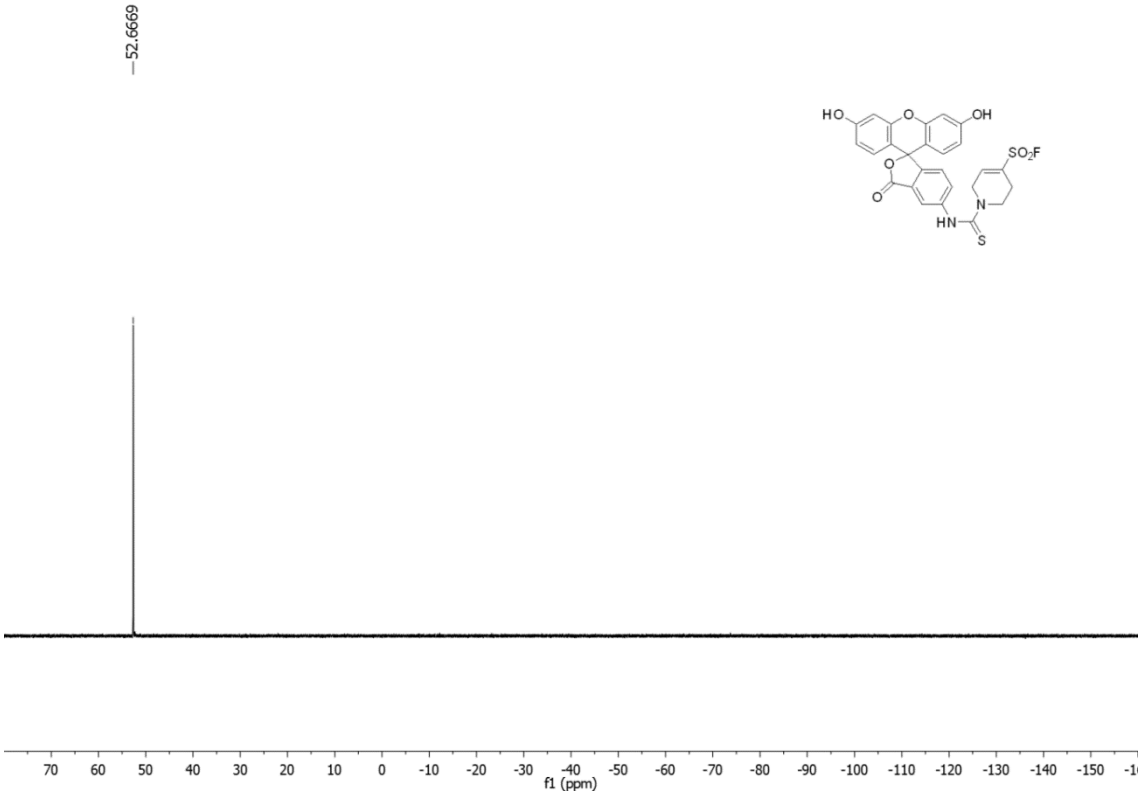
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

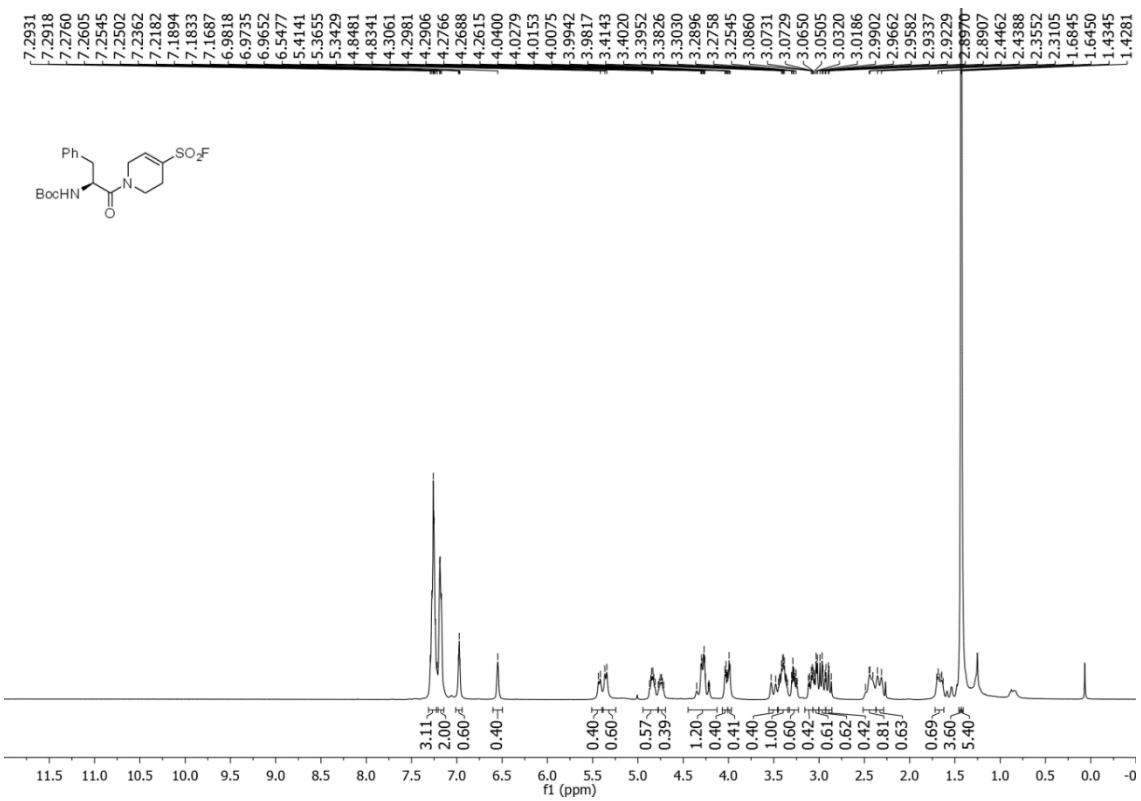


^{19}F-NMR Spectrum:

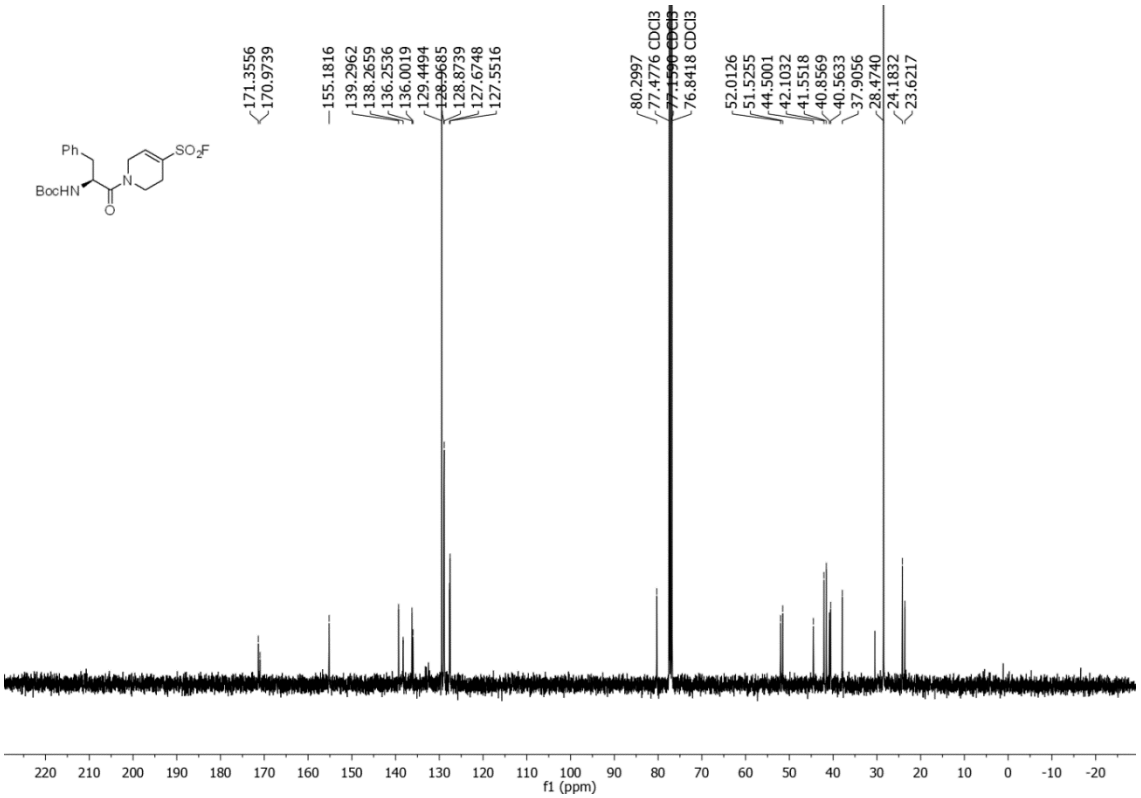


tert-Butyl (_S_)-(1-(4-(fluorosulfonyl)-3,6-dihydropyridin-1(2_H_)-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (51)

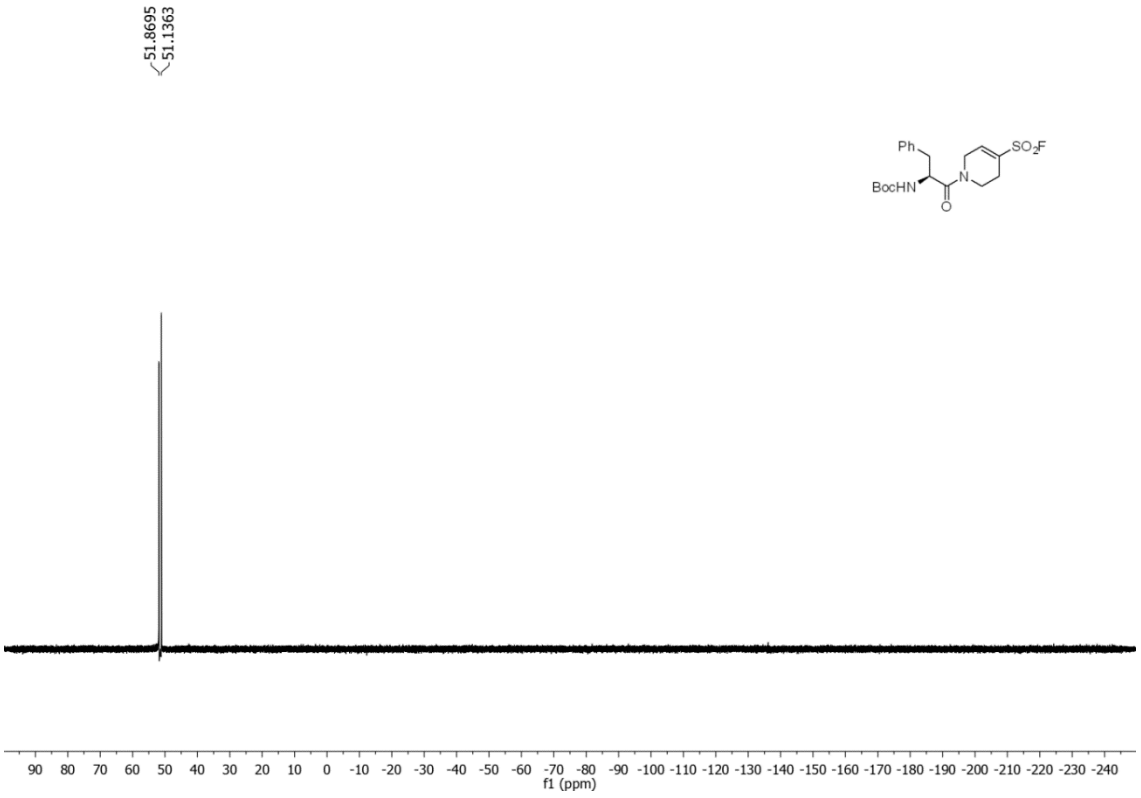
^{1}H-NMR Spectrum:



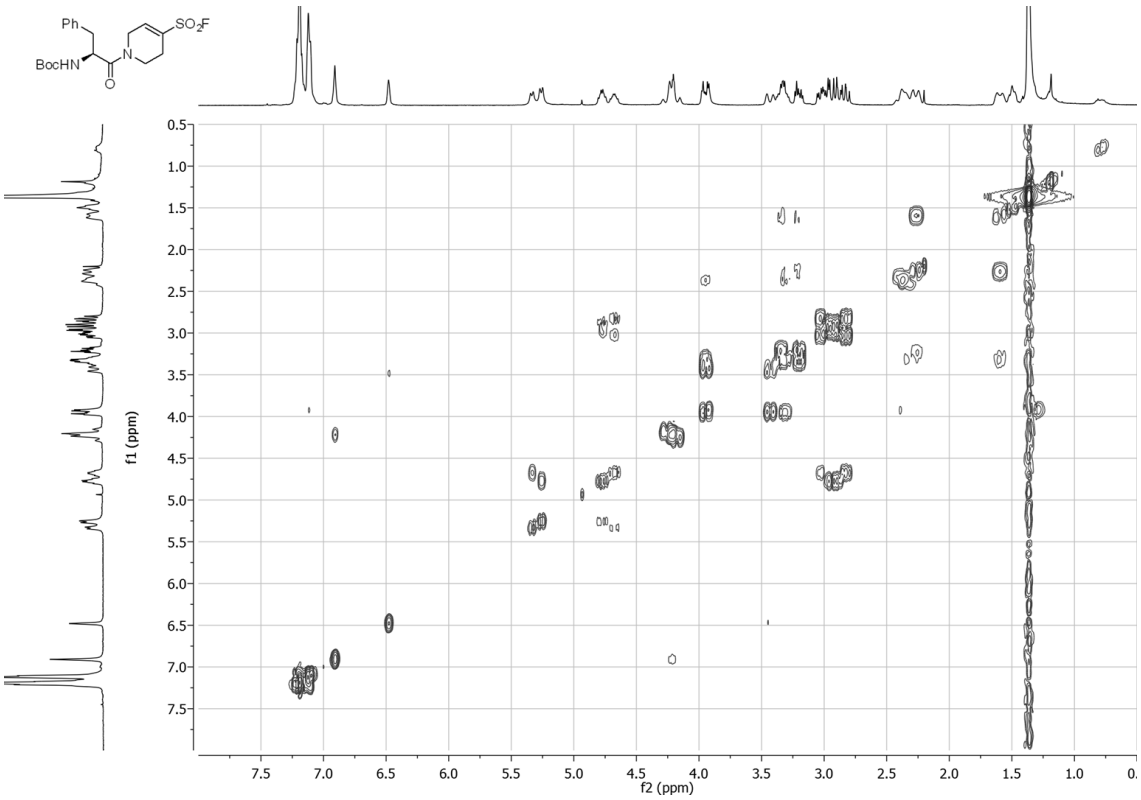
^{13}C-NMR Spectrum:



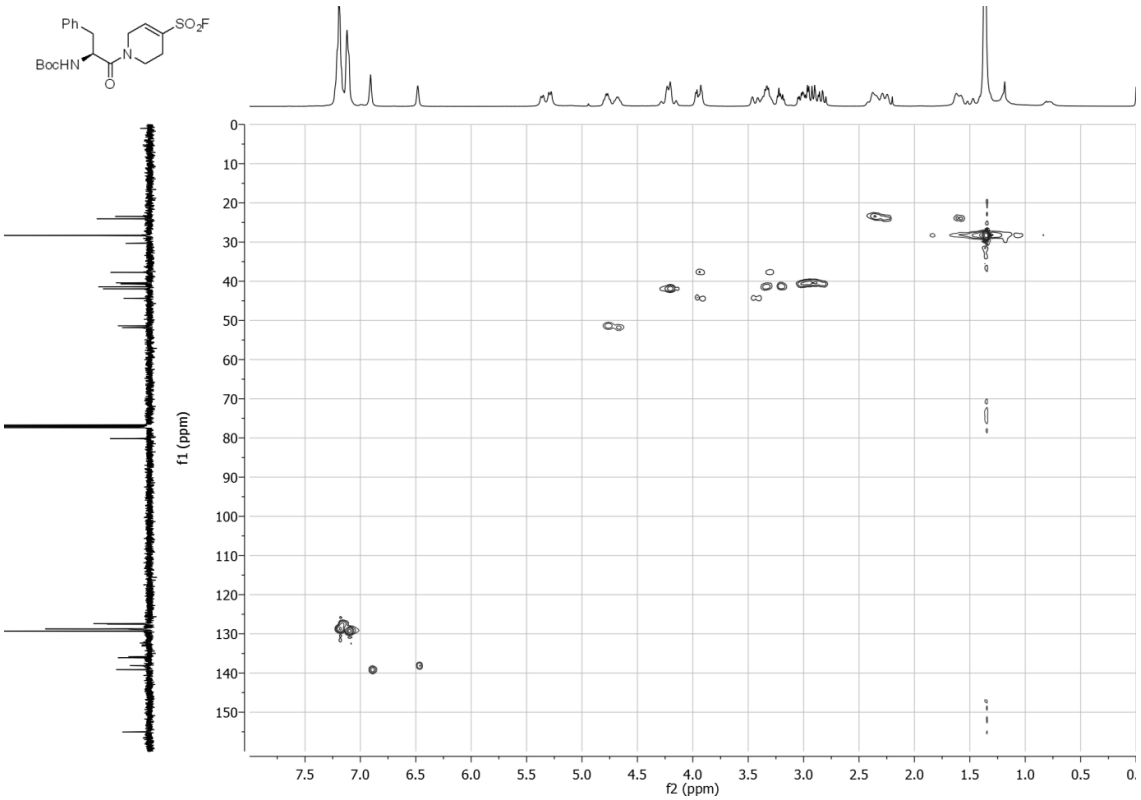
^{19}F-NMR Spectrum:



^{1}H-^{1}H COSY NMR Spectrum:

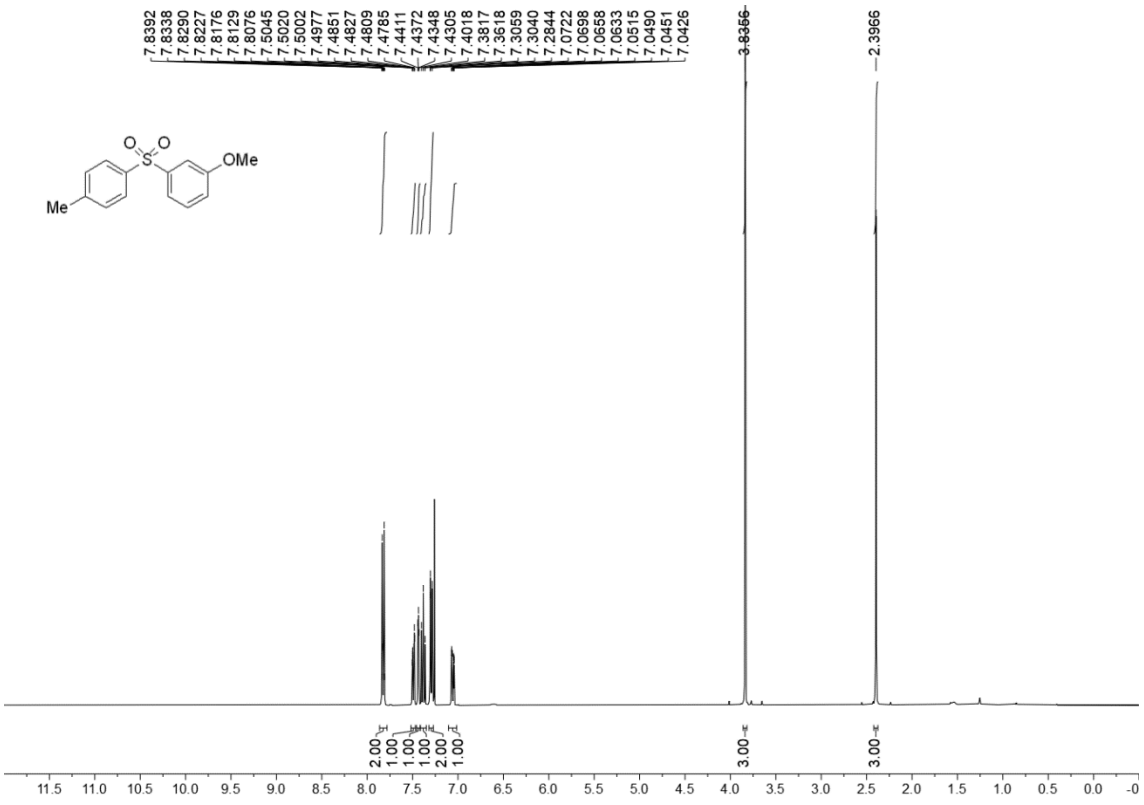


^{1}H-^{13}C HSQC NMR Spectrum:

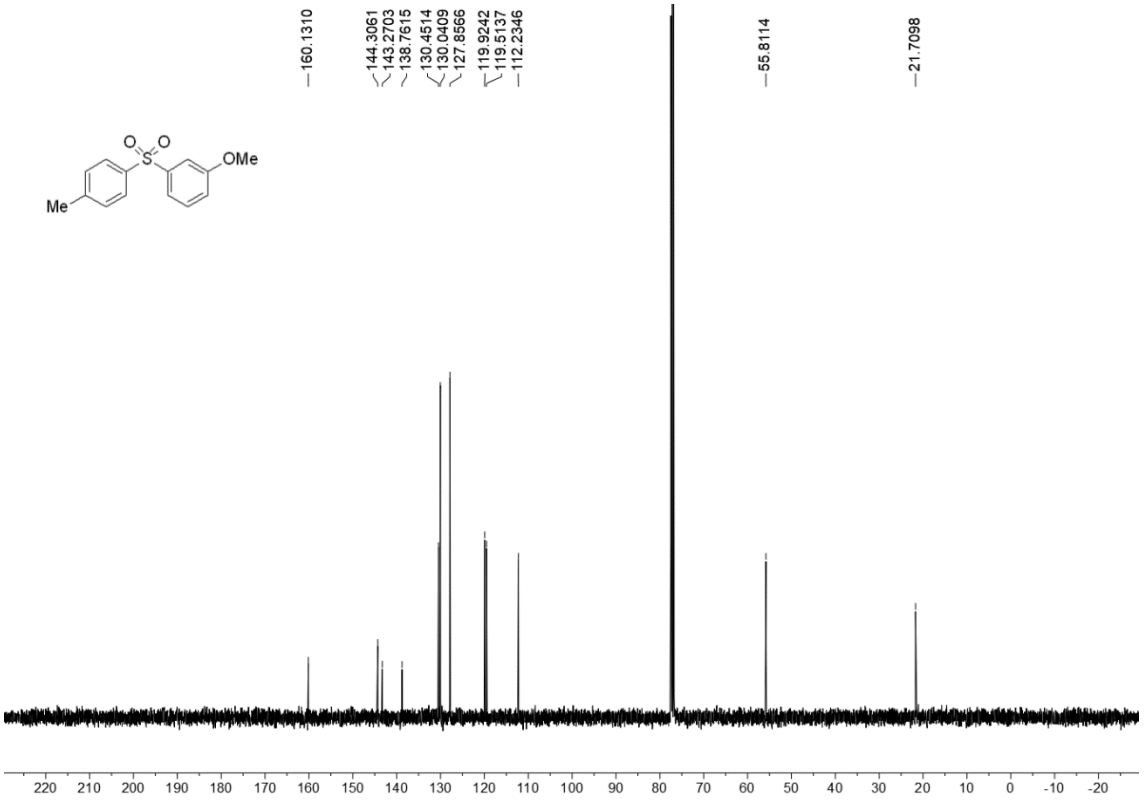


11 NMR Spectra of 1-Methoxy-3-tosylbenzene (58)

^{1}H-NMR Spectrum:



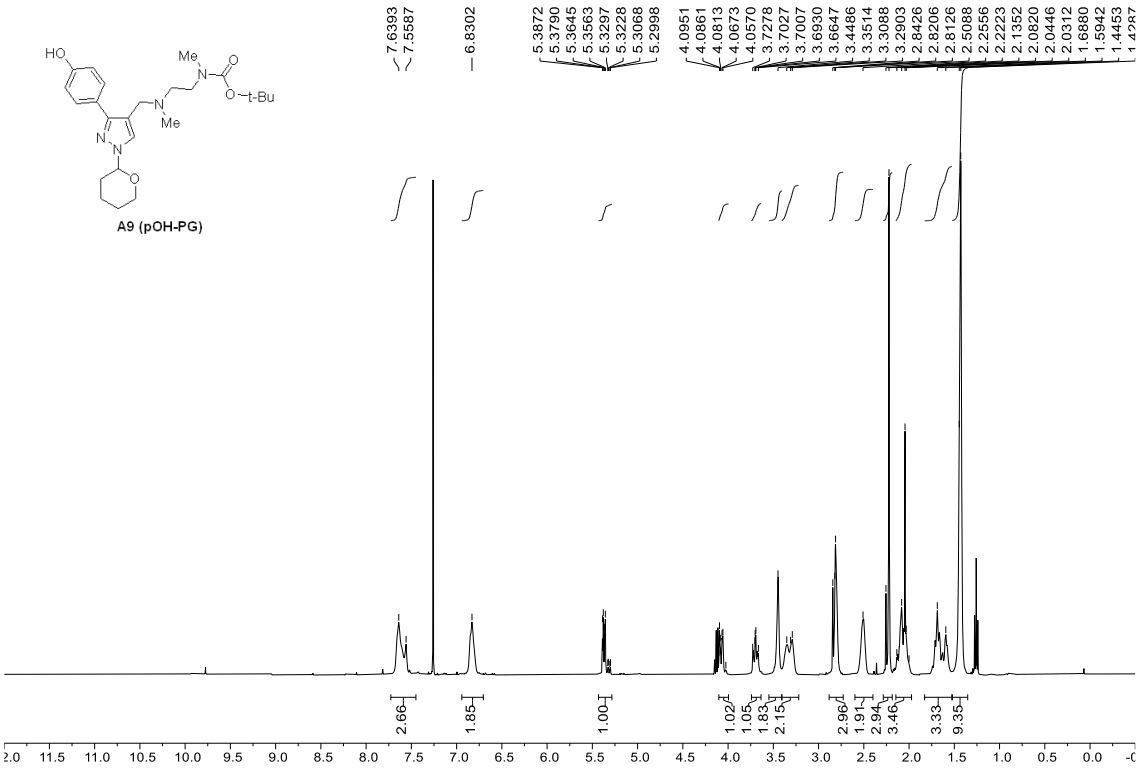
^{13}C-NMR Spectrum:



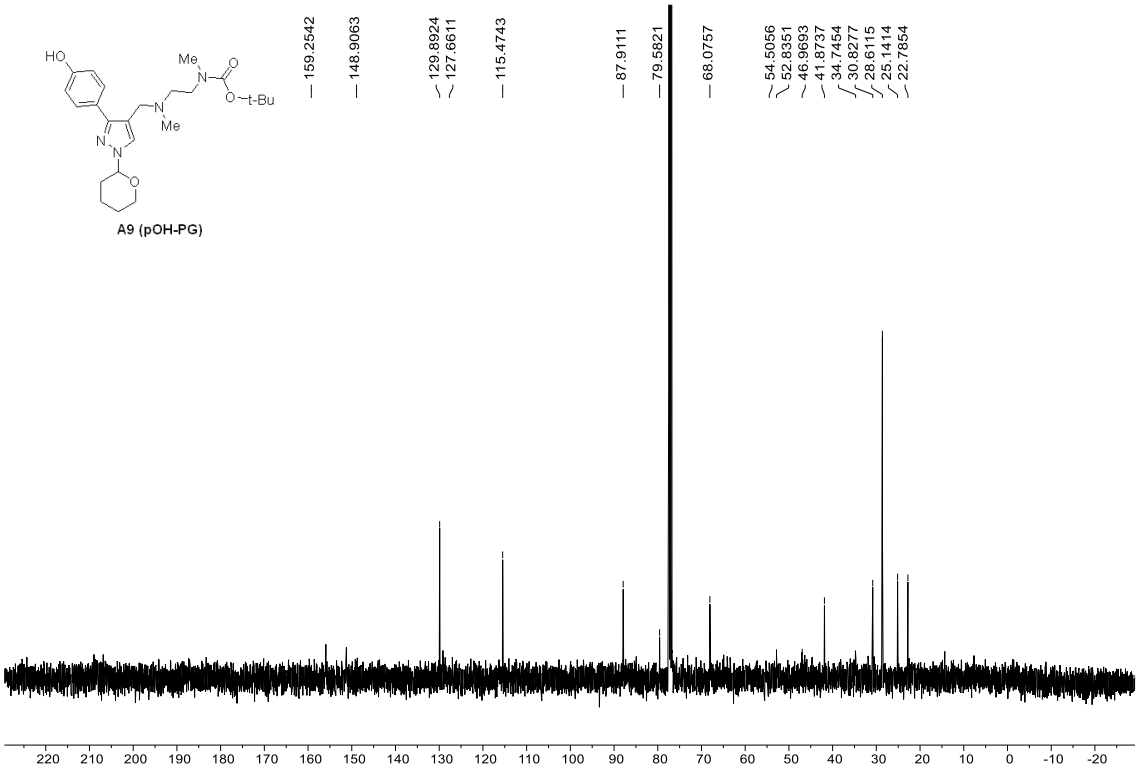
12 NMR Spectra of PRMT1 Inhibitors

tert-Butyl (2-(((3-(4-hydroxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (A9)

^{1}H-NMR Spectrum:

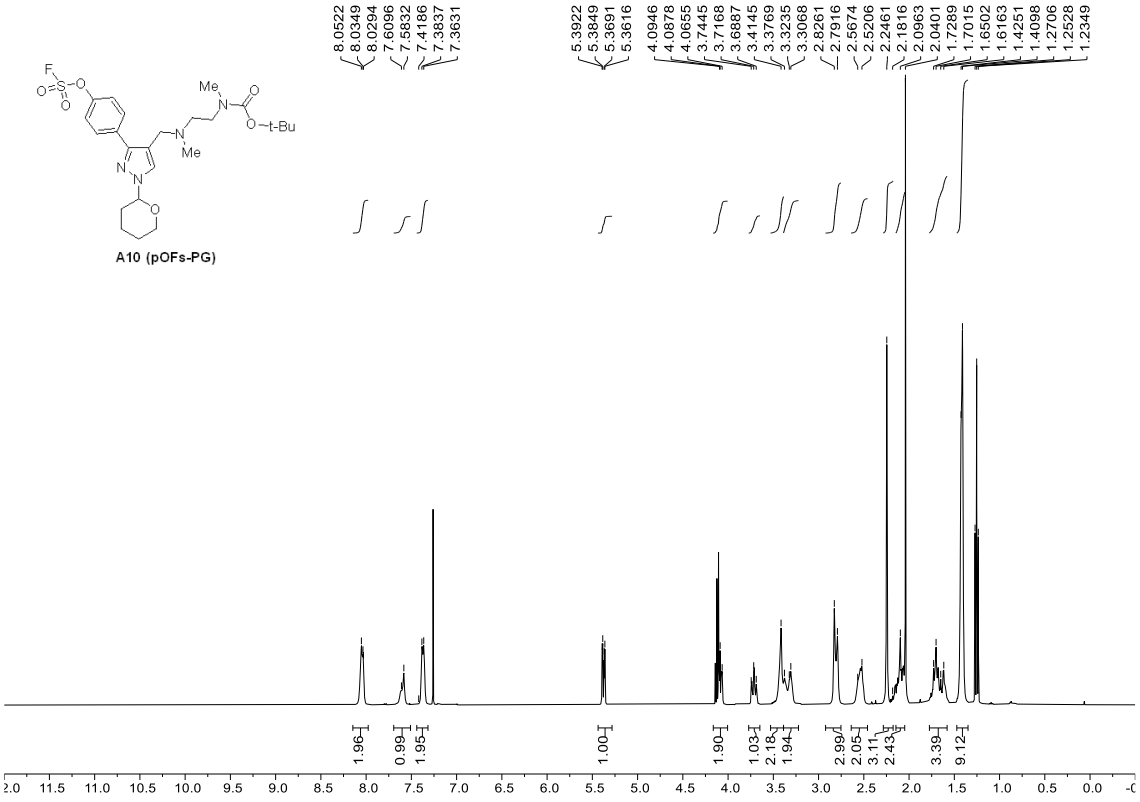


^{13}C-NMR Spectrum:

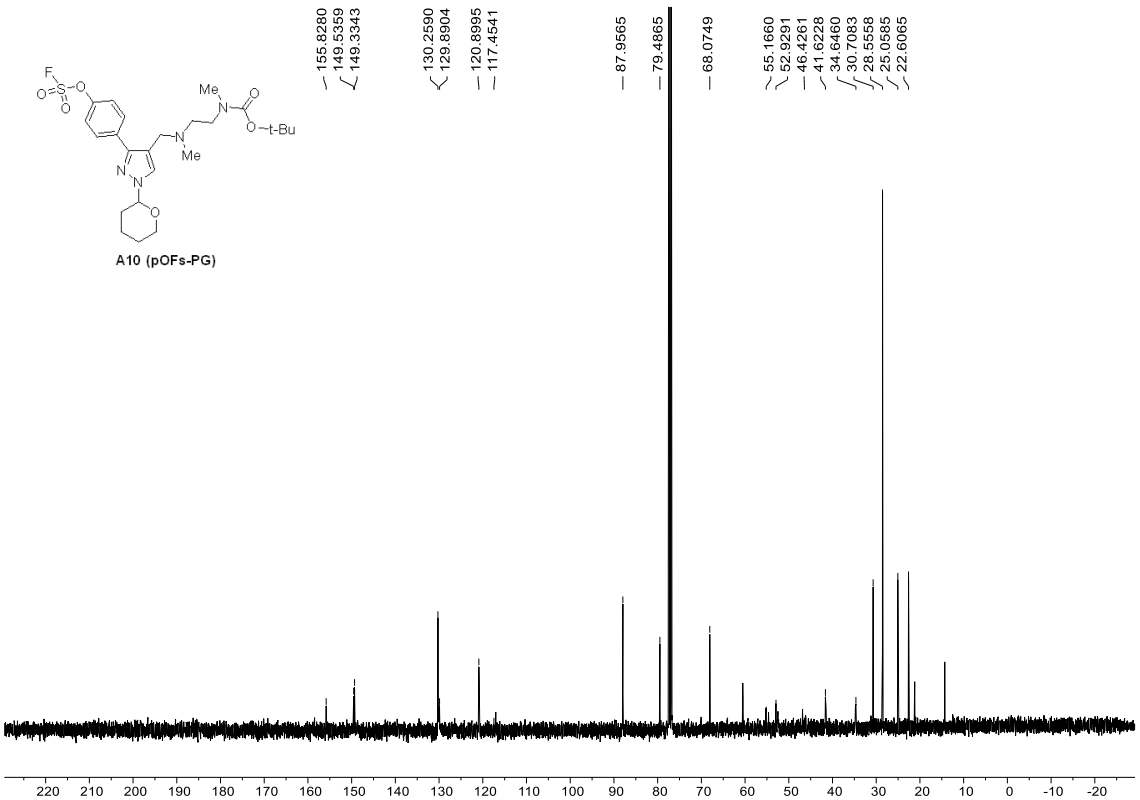


4-(4-(((2-((*tert*-Butoxycarbonyl)(methyl)amino)ethyl)(methyl)-amino)methyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)phenyl sulfurofluoridate (A10)

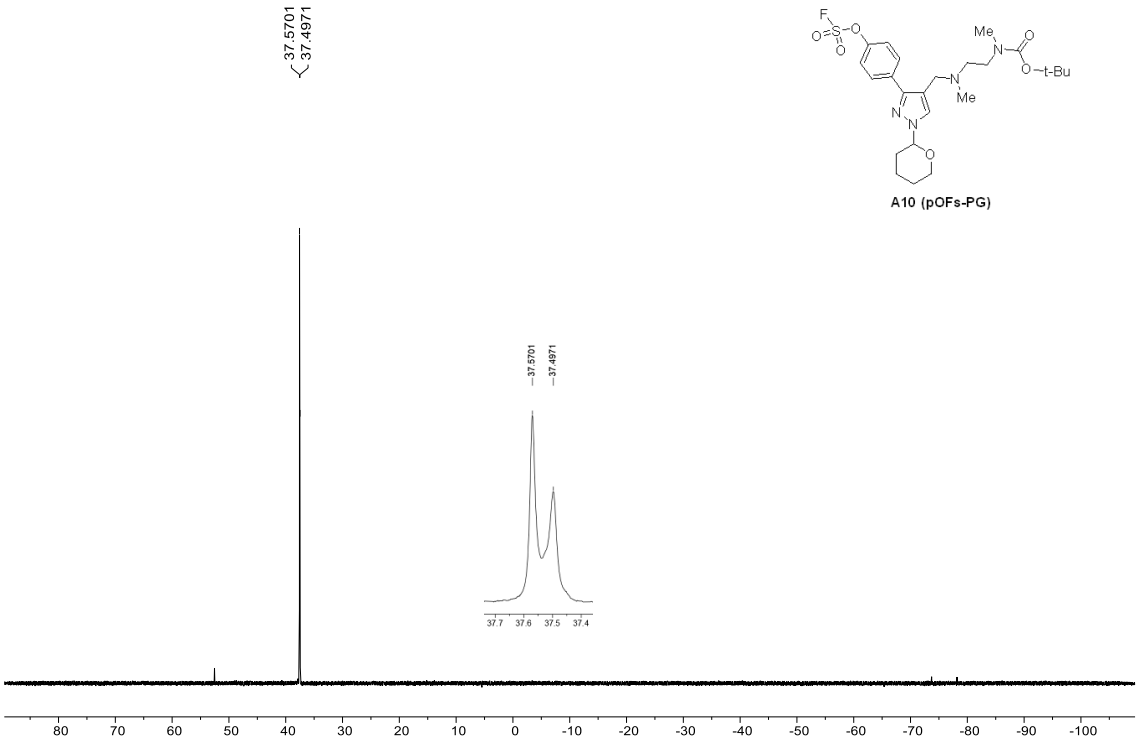
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

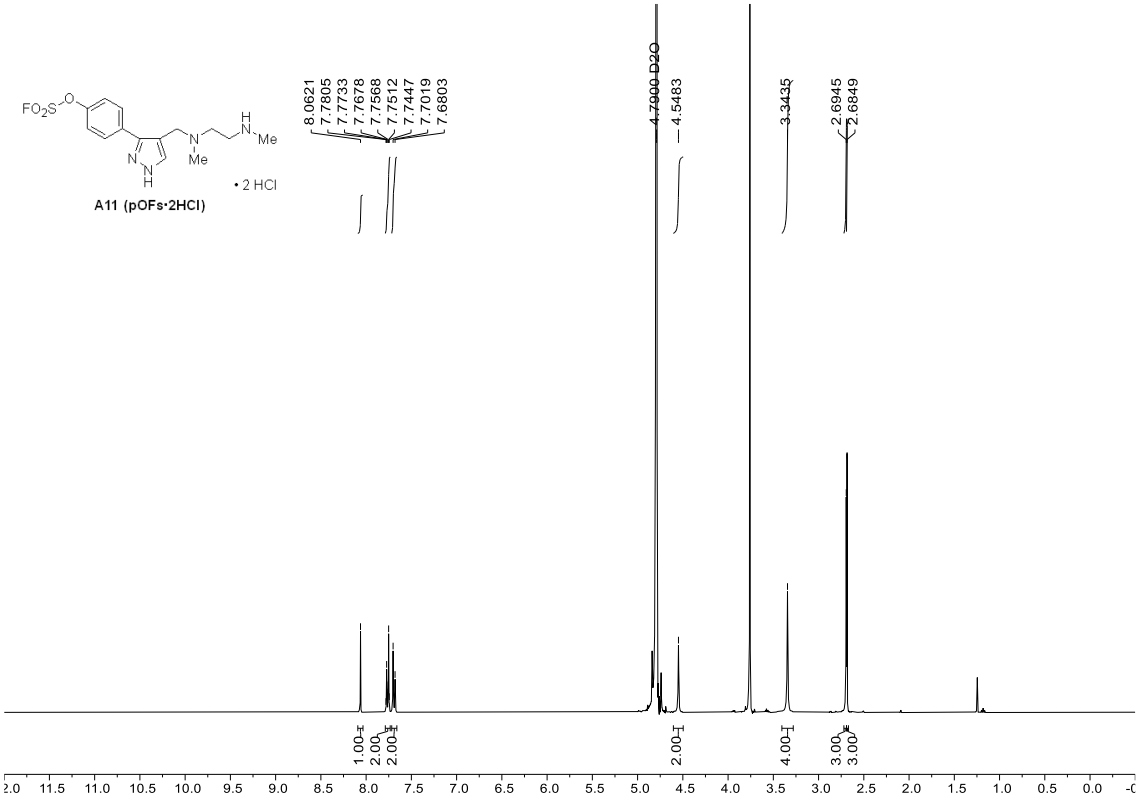


^{19}F-NMR Spectrum:

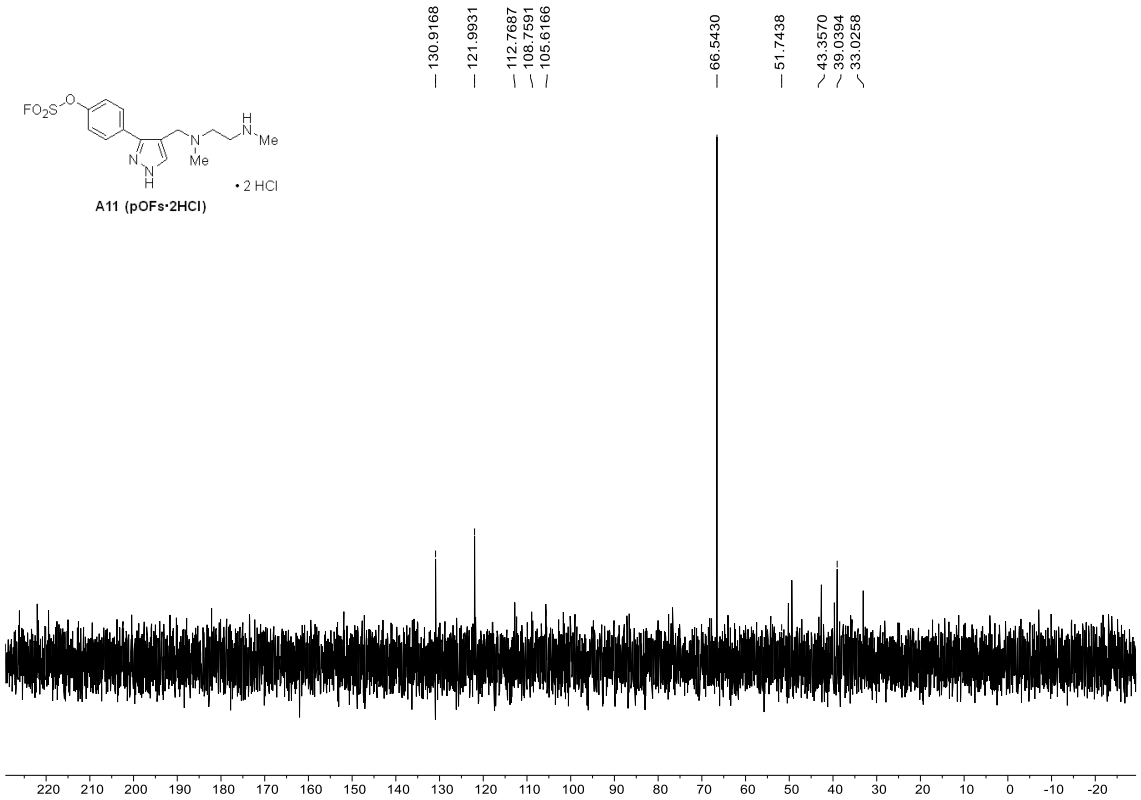


4-(4-((Methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)phenyl sulfurofluoridate dihydrochloride(A11)

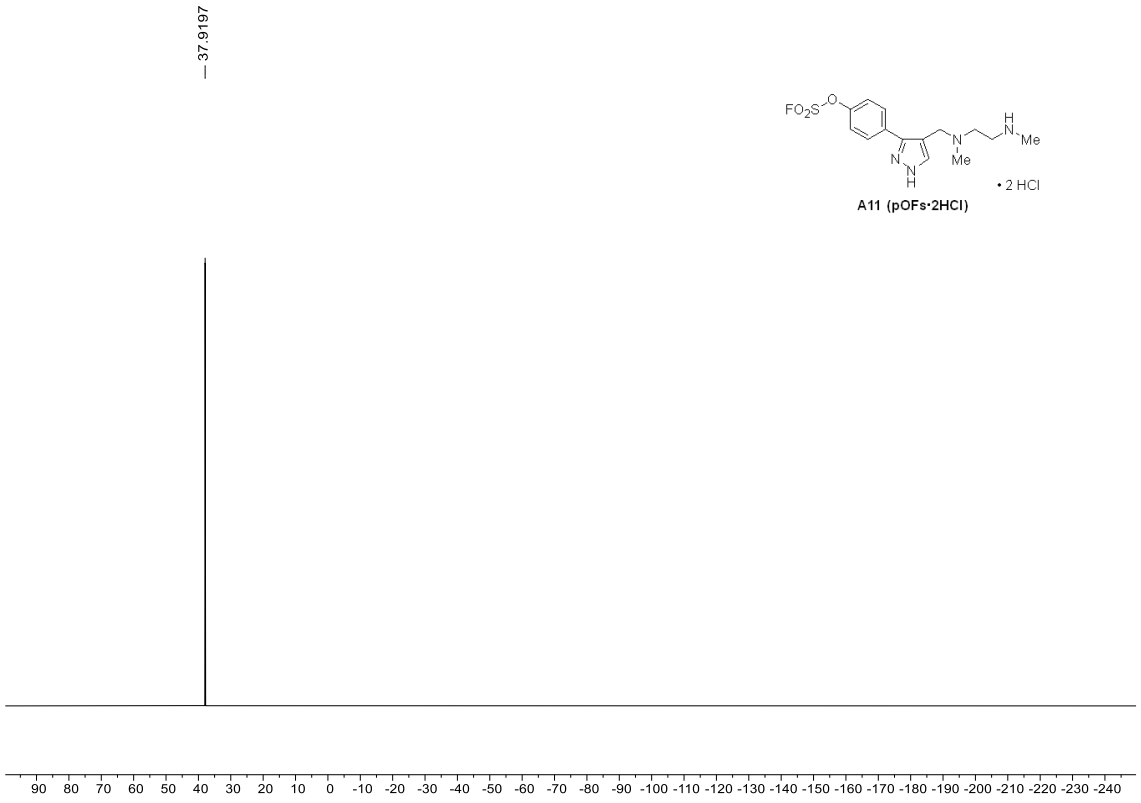
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

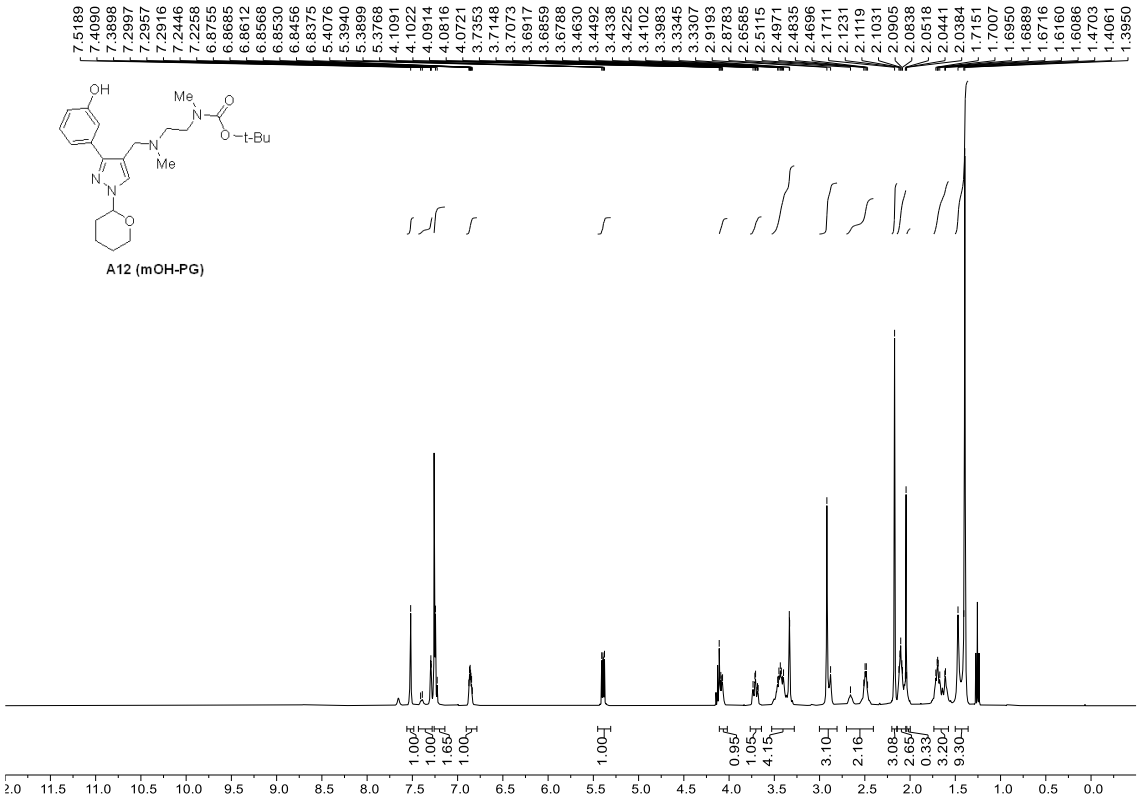


^{19}F-NMR Spectrum:

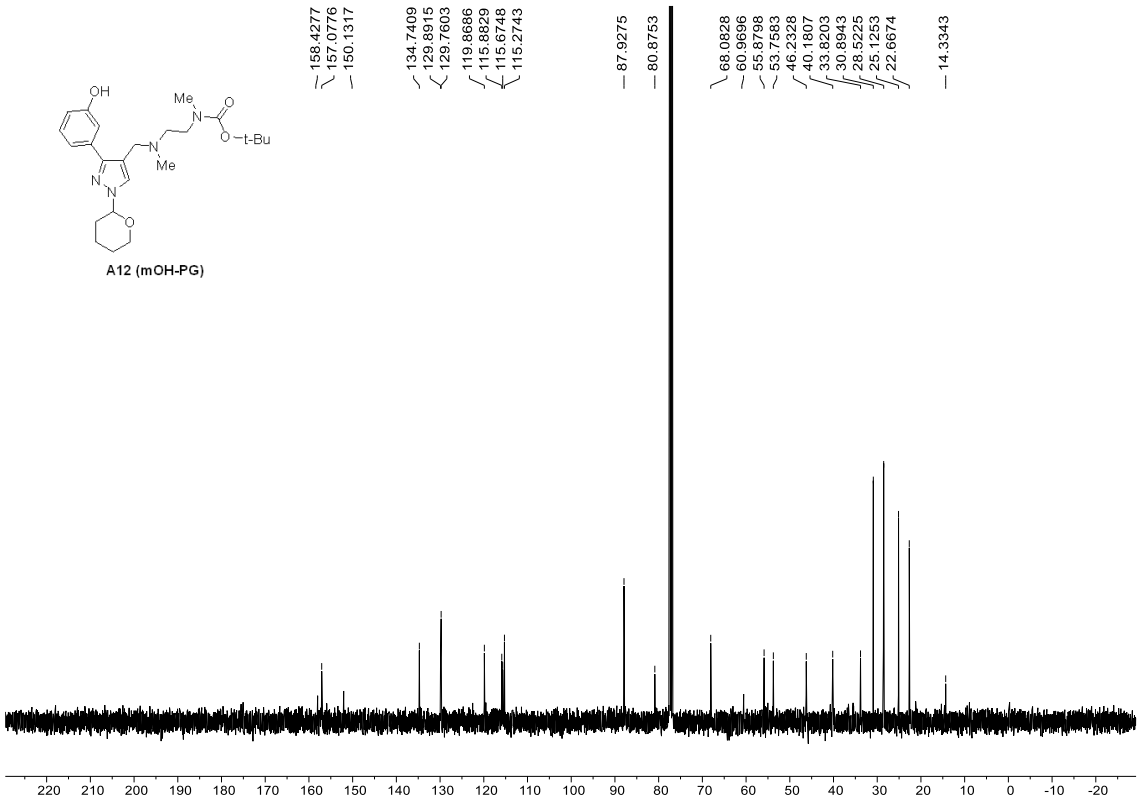


***tert*-Butyl (2-(((3-(3-hydroxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (A12)**

^{1}H-NMR Spectrum:

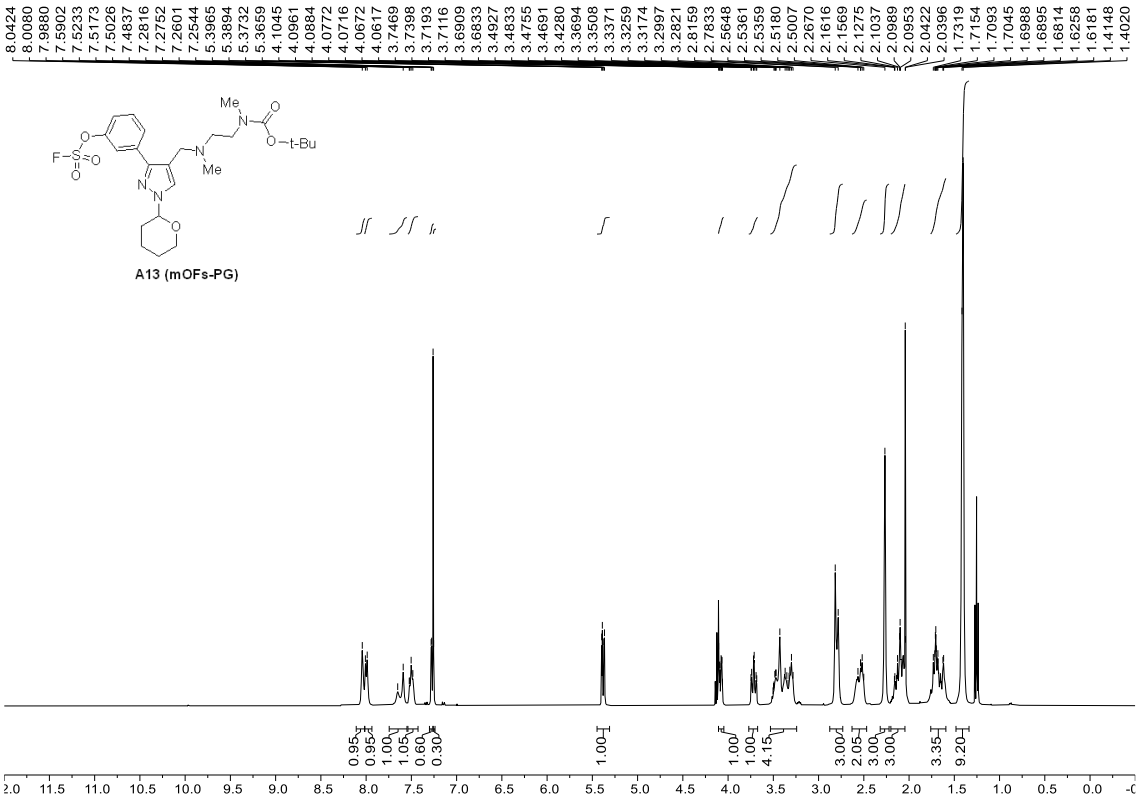


^{13}C-NMR Spectrum:

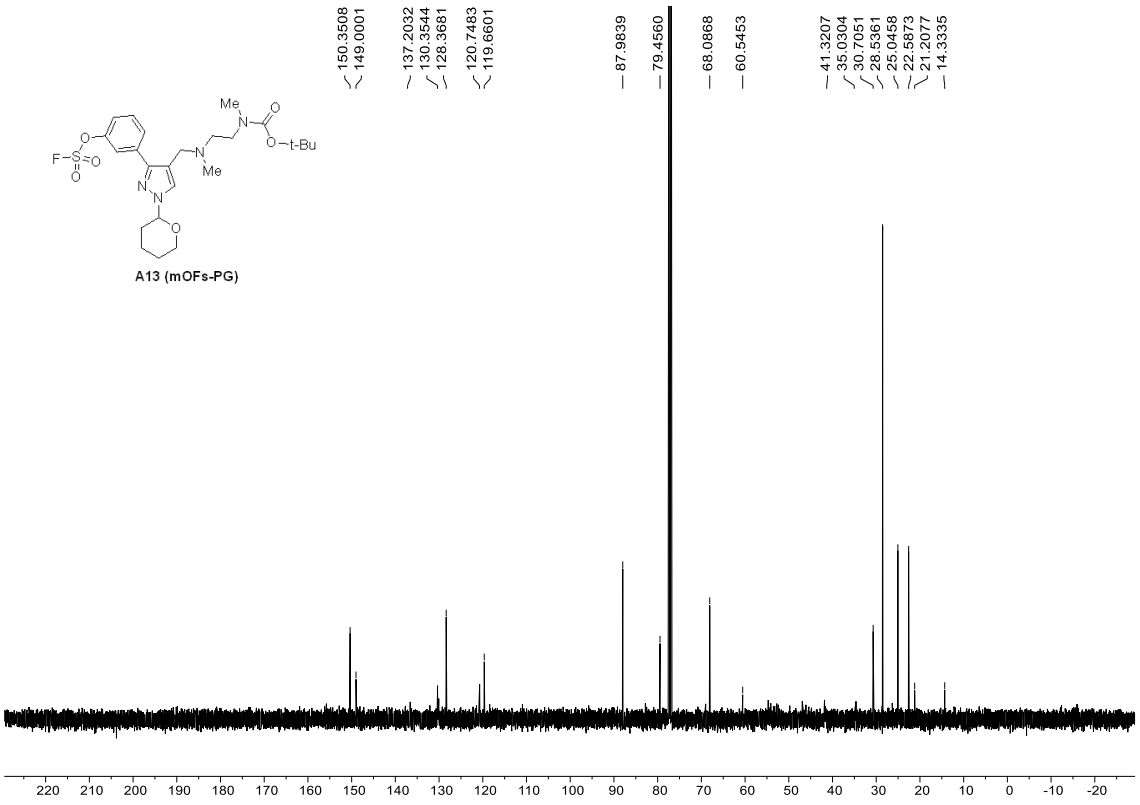


3-(4-(((2-((*tert*-Butoxycarbonyl)(methyl)amino)ethyl)(methyl)-amino)methyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)phenyl sulfurofluoridate (A13)

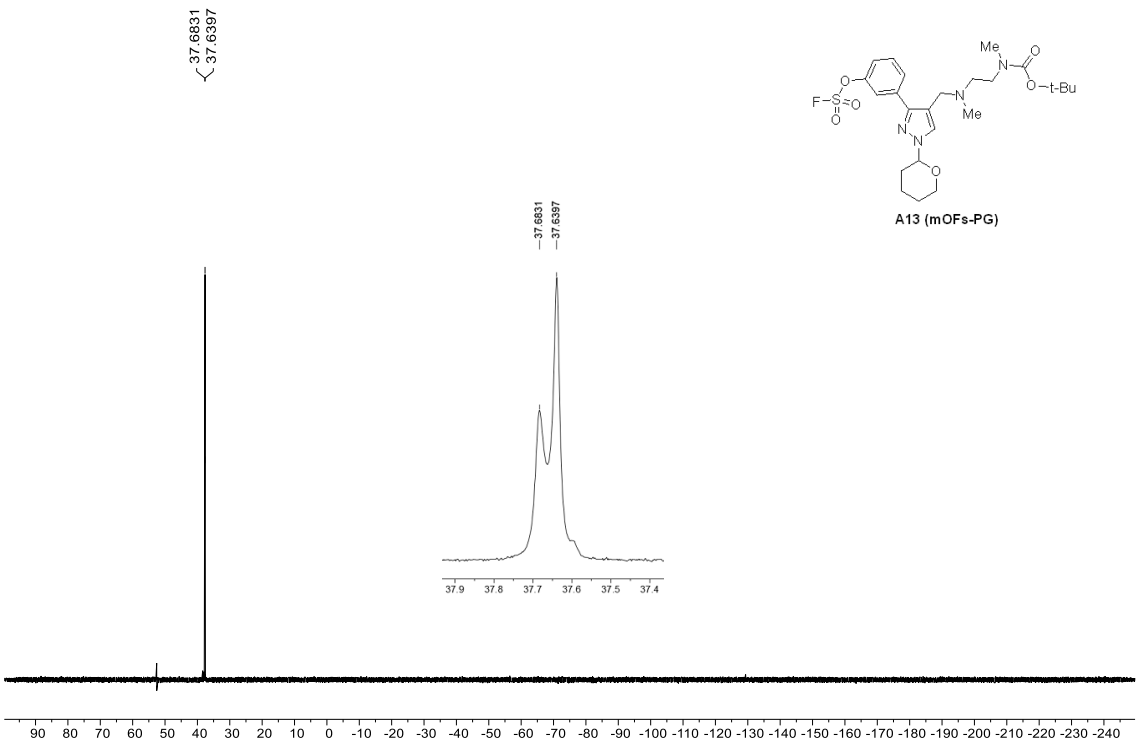
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

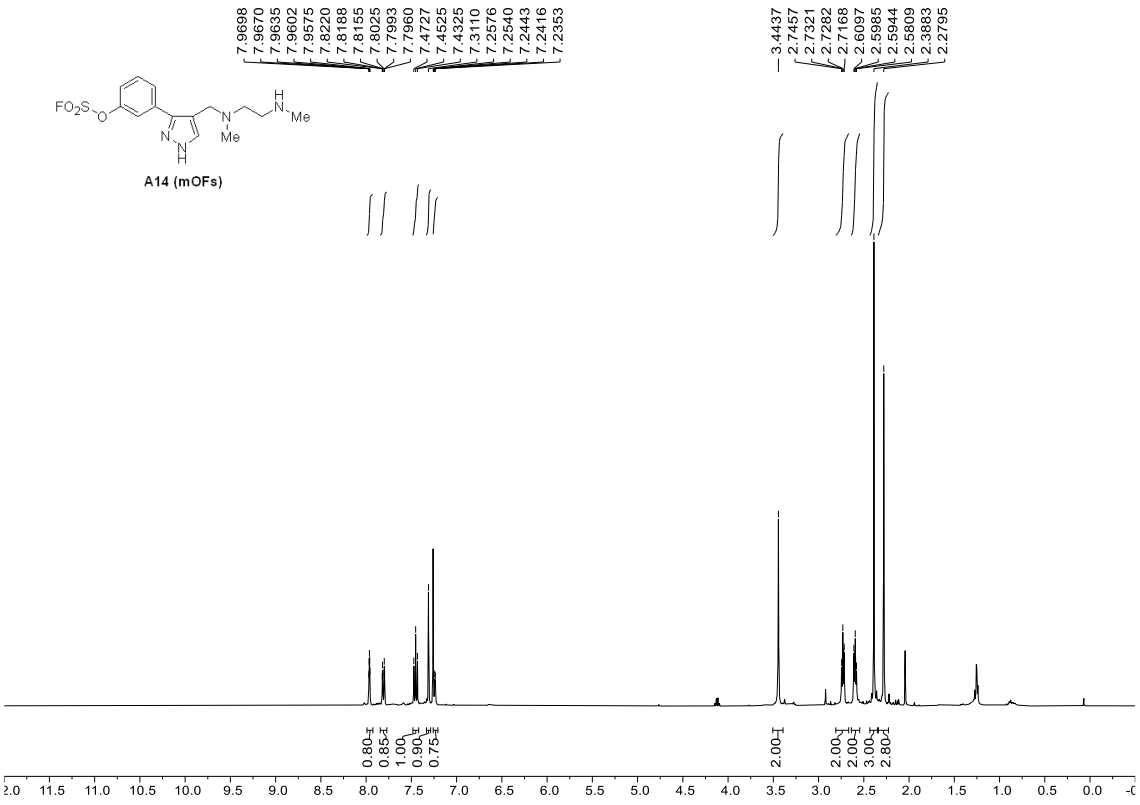


^{19}F-NMR Spectrum:

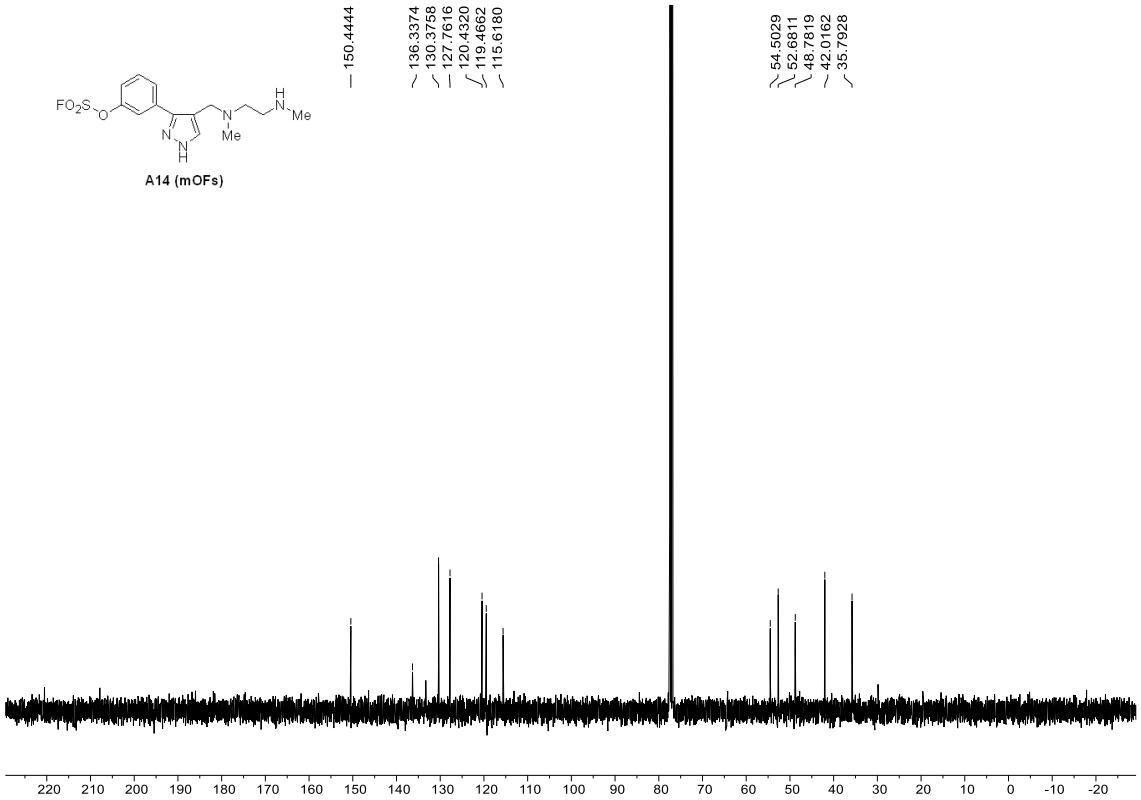


3-(4-((Methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)phenyl sulfurofluoridate (A14)

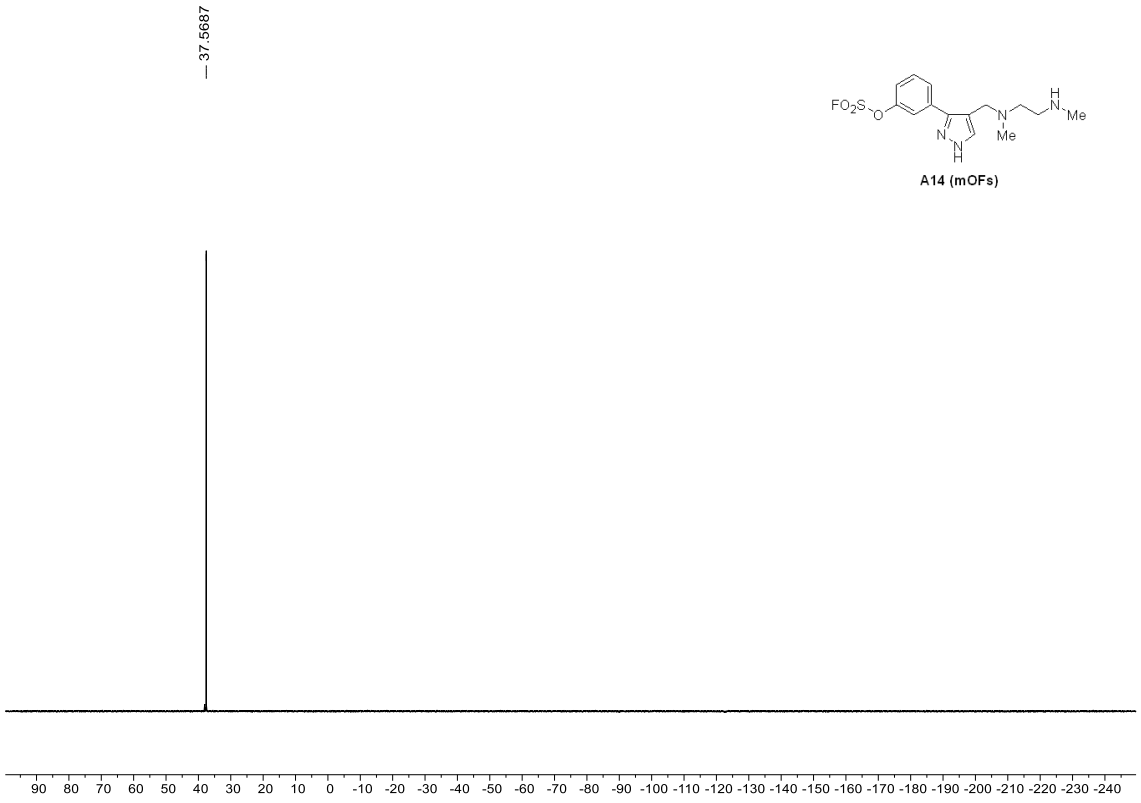
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

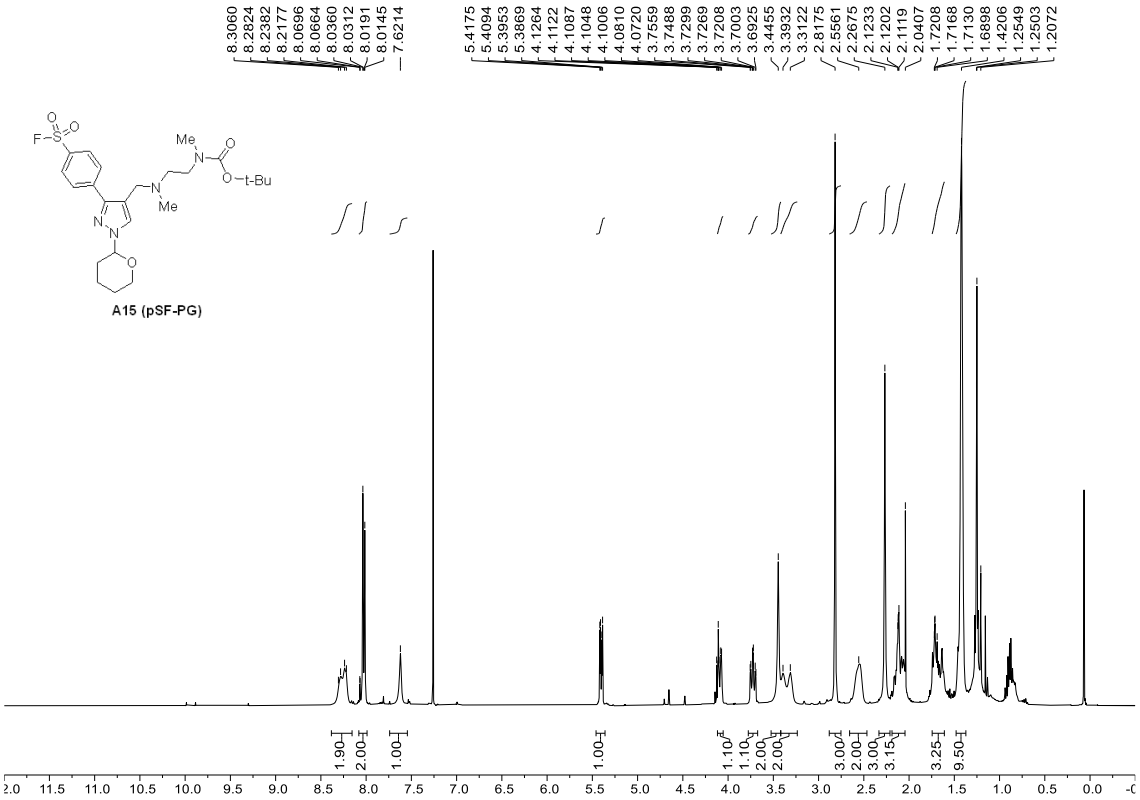


^{19}F-NMR Spectrum:

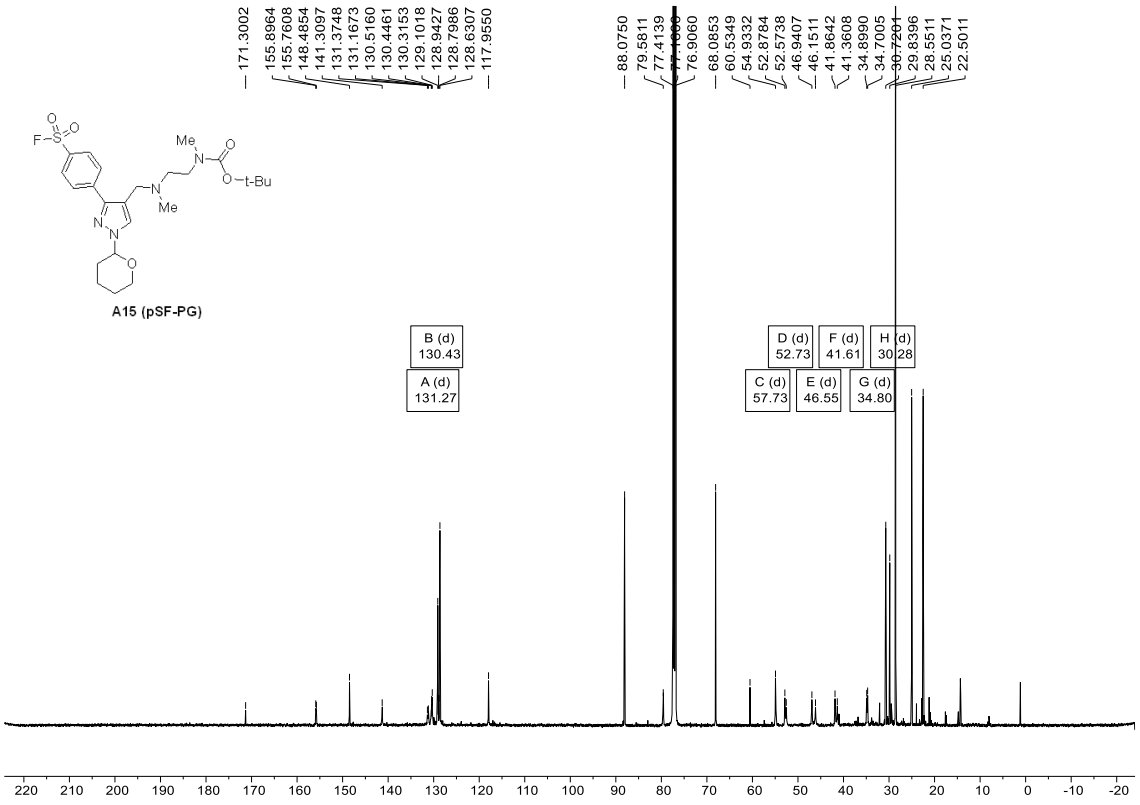


***tert*-Butyl (2-(((3-(4-(Fluorosulfonyl)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (A15)**

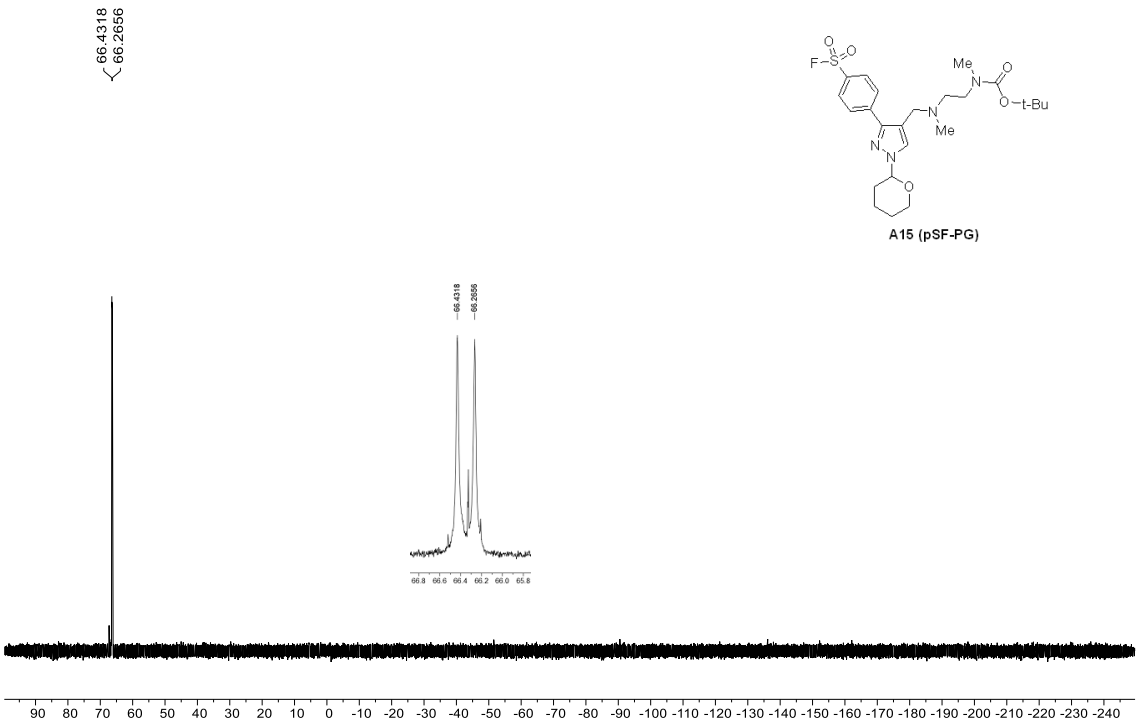
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

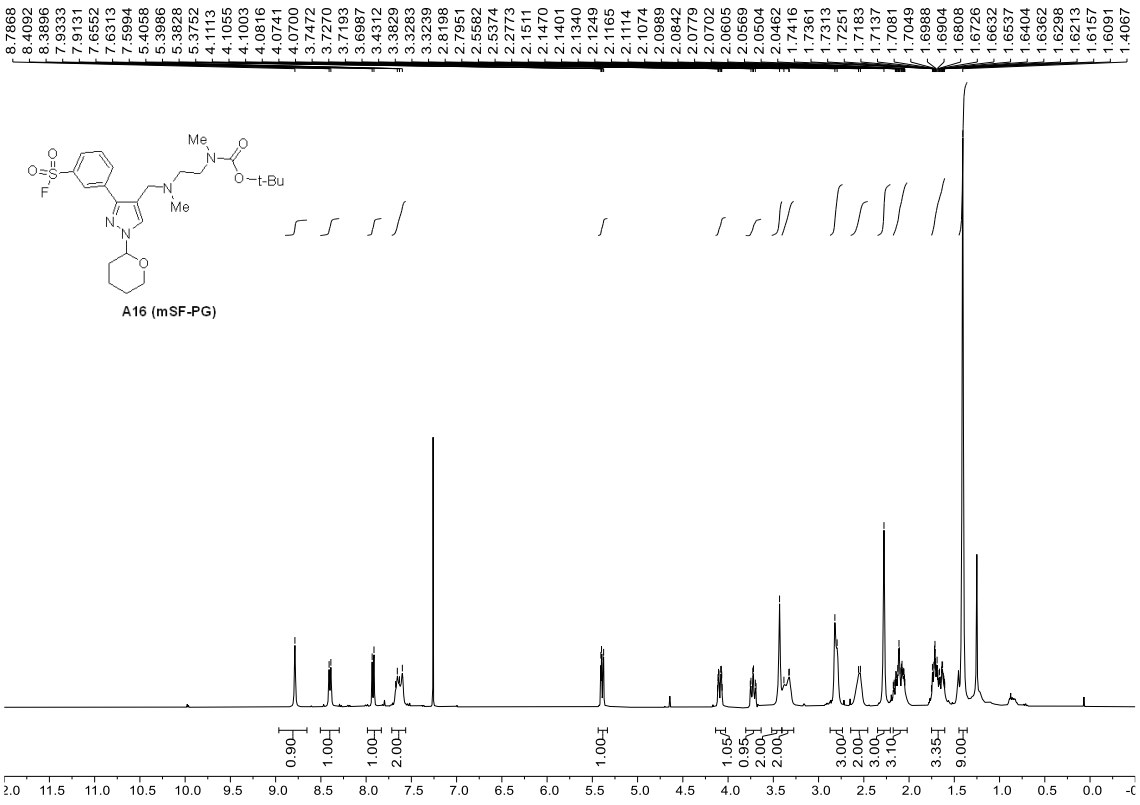


^{19}F-NMR Spectrum:

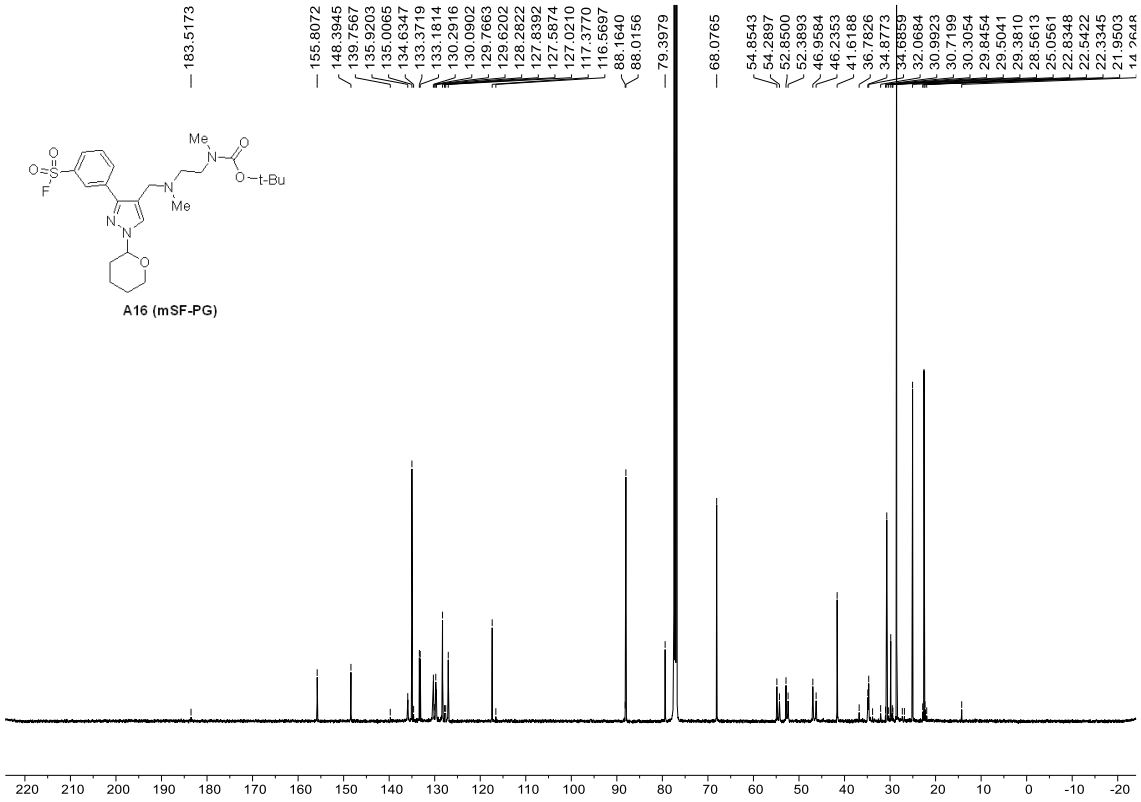


tert-Butyl (2-(((3-(3-(fluorosulfonyl)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate (A16)

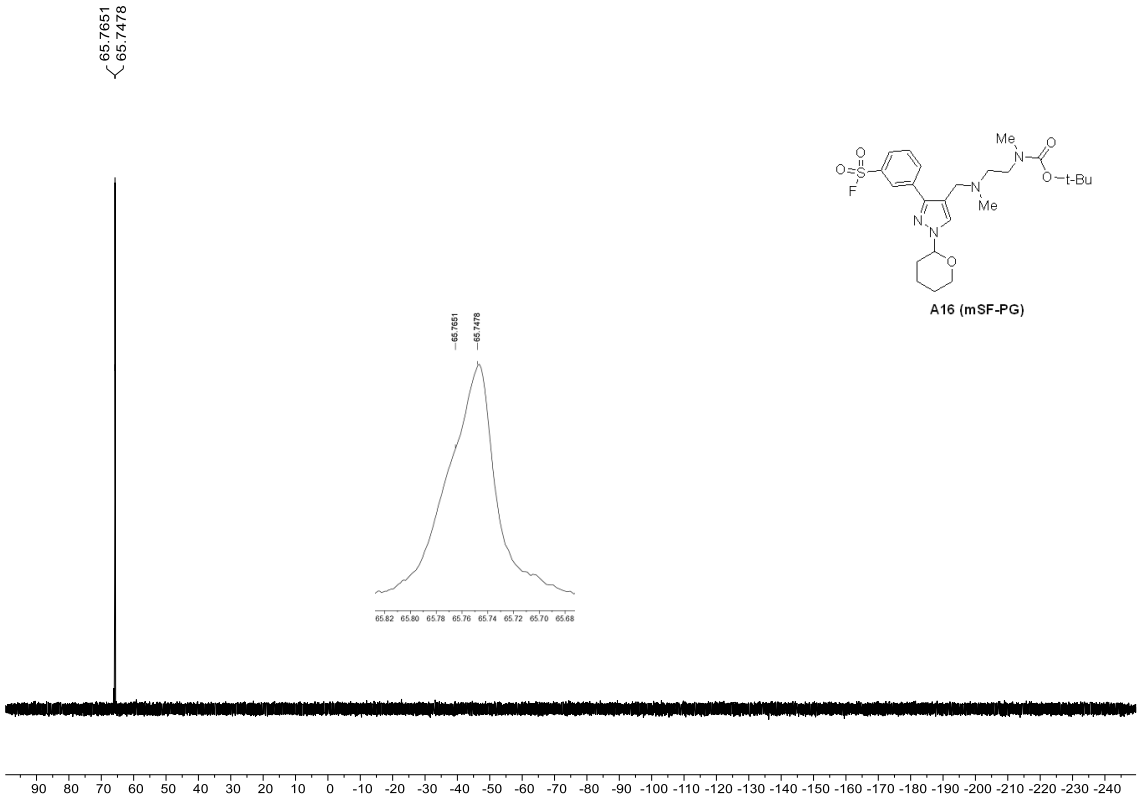
^{1}H-NMR Spectrum:



^{13}C-NMR Spectrum:

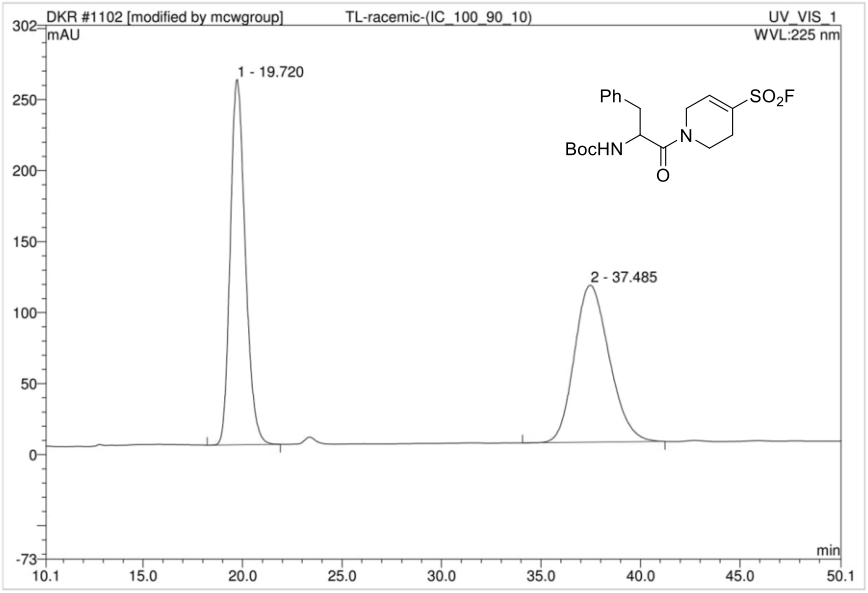


^{19}F-NMR Spectrum:

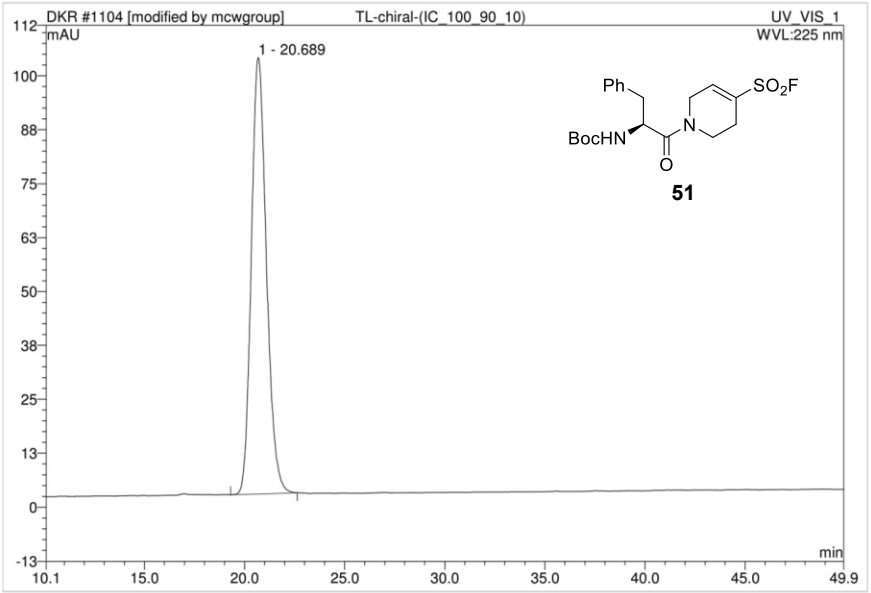


Chiral HPLC Traces

HPLC chromatogram of compound **51**:
(Chiralpak IC column, 4.6×250 mm, 90:10 hexane/*i*-PrOH, 1 mL/min, >99:1 er)



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.72	n.a.	257.229	225.509	50.05	n.a.	BMB*
2	37.49	n.a.	110.571	225.097	49.95	n.a.	BMB*
Total:			367.800	450.606	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.69	n.a.	101.155	88.447	100.00	n.a.	BMB*
Total:			101.155	88.447	100.00	0.000	