Synthesis and Use of New Chiral DABCO Derivatives for Asymmetric Fluorination

John O. Ilupeju

A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Oxford

Wolfson College

Trinity Term 2012

Author's Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory at the University of Oxford and at the Chemistry Fluorine Laboratory at Durham University between Michaelmas Term 2008 and Trinity Term 2012 under the supervision of Professor Véronique Gouverneur and Professor Graham Sandford. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

John O. Ilupeju

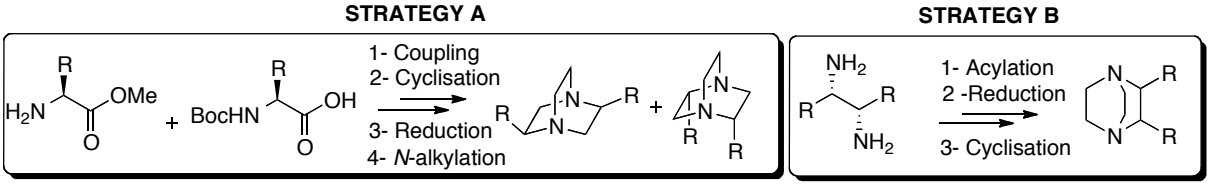
October 2012

Synthesis and Use of New Chiral DABCO Derivatives for Asymmetric Fluorination

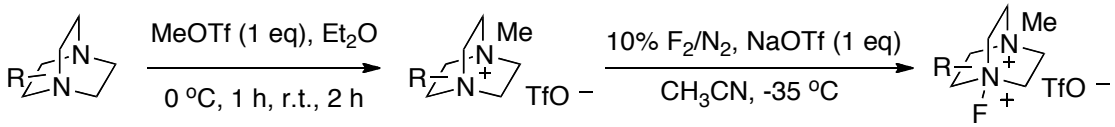
In this thesis, the synthesis, reactivity and enantioselectivity of novel chiral Selectfluor Analogues were investigated.

Chapter 1: Discussed is a general introduction to Selectfluor as an achiral electrophilic fluorinating reagent and its role as an oxidant in a wide variety of transformations and summarises the aims and objectives of the project.

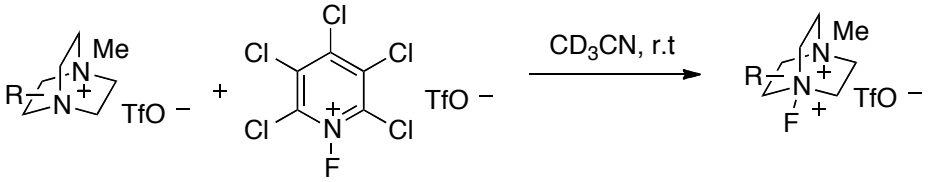
Chapter 2: The synthesis of chiral 2-monosubstituted, 2,3-disusbstituted and 2,5-disubstituted DABCO derivatives is described. We selected two strategies to prepare these chiral analogues of DABCO. Strategy **A** takes advantage of a large range of commercially available natural and unnatural amino acids. 2,3-Disubstituted DABCO motifs were prepared *via* a protocol of Sharpless in strategy **B**. Eleven chiral DABCO systems have been synthesized, six of which are novel compounds.



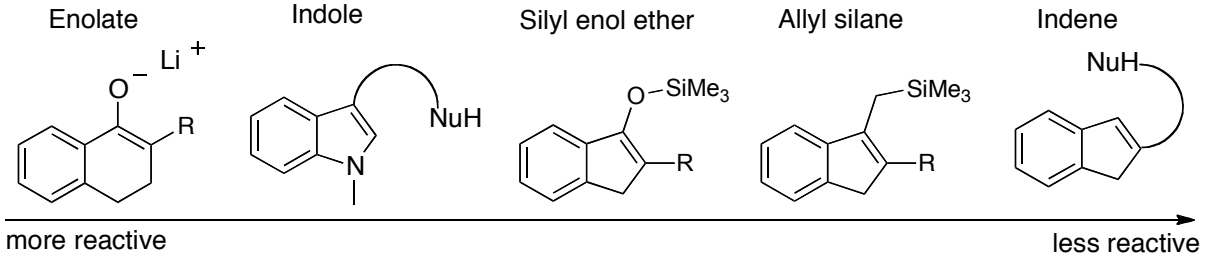
Chapter 3 describes the synthesis of novel chiral non-racemic Selectfluor analogues using F_2. Mono-fluorinated chiral DABCOs were found to be unstable at low temperature, however, quaternized derivatives of these chiral reagents induced stability. The fluorination proved challenging with chiral DABCO derivatives having sterically demanding substituents.



Moreover, we have developed a practical and general process for the synthesis of novel chiral non-racemic Selectfluor using *N*-fluoropentachloropyridinium triflate **221**. This methodology alleviates the need to handle F_2 gas.



In **Chapter 4**: An investigation into how chiral Selectfluor analogues compare to N-F derived cinchona alkaloids in term of reactivity and enantioselectivity. The reactivity of the chiral Selectfluor analogues was challenged with both activated and less activated substrates. The novel chiral Selectfluor analogues showed superior reactivity than the cinchona alkaloids. Moderate to excellent yields of the desired products were obtained for all of the substrates studied.



Acknowledgements

I am very much indebted to Professor Véronique Gouverneur for all her help and strong support during these four years spent working together. Without her enthusiasm, dedication and encouragement, this thesis would never have been possible.

My thanks must go to the people who have directly contributed in some way to the work presented in this thesis. Thank you to Nathalie Wurz for starting the project with me as a Part II student. Special thanks to Dr. Oscar Lozano and Jamie Wolstenhulme for their contribution, highly valuable discussions and suggestions in this project. I would also like to thank Dr. Oscar Lozano and Dr. Matthew Tredwell, for proof reading this thesis and for general advice. Thanks to Dr. Satoshi Mizuta for proof reading the experimental section.

I am also greatly indebted to EPSRC for funding my DPhil and to my co-supervisor Professor Graham Sandford for all his help, expertise advice and suggestions in the use of F_2.

Thank you to Dr. Barbara Odell, Dr. Tim Claridge and the NMR and mass spectrometry services for their assistance with characterisation. Thanks must also go to Guy Giuffredi and Keary Engle for running and analysing all the crystal data presented in this thesis.

I would like to thank all the past and present members of Gouverneur group (the VG World) for making the lab work such an enjoyable experience. A special mention must go to past and present F9 and F12 power, power, power laboratory colleagues: Dr. Oscar Lozano, Lorraine Combette, Nathalie Wurz, Jamie Wolstenhulme, George Blessley, Faye Buckingham, Matthew Johnson and Dr. Enrico Emer for many good times in the lab. I would like to appreciate the friendship, help and advice of various people in the VG group: Dr. Begoña Checa, Dr. Juliana Manso, Oscar Galicia, Dr. Erika Luethi, Elena Benedetto (you can do it), Ida Sofia, Charlotte Hollingworth, Jamie Wolstenhulme, Faye Buckingham, Miriam O Duill.
I am particularly grateful to Dr. Oscar Lozano for being a great friend over the past four years.

I would like to take this opportunity to thank my family and friends for all their encouragement and support in everything I have done. Finally I would like to thank God for his Grace upon my life.

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

T. Hayashi and V. A. Soloshonok, Tetrahedron Asymmetry, 1994, 5, xiii

CONTENTS

Abbreviations and Acronyms

Å	**Ångström (10^{-10} metres)**
Ac	**Acetyl**
aq	**Aqueous**
Ar	**Aryl**
Bn	**Benzyl**
Bu	**Butyl**
Cbz	**Carboxybenzyl**
CI	**Chemical Ionisation**
COSY	**Correlation spectroscopy**
Cy	**Cyclohexyl**
DABCO	**1,4-Diazabicyclo[2.2.2]octane**
DCM	**Dichloromethane**
DIPEA	**Diisopropylethylamine**
DMAP	**4-Dimethylaminopyridine**
DMF	***N*,*N*-Dimethylformamide**
DMSO	**Dimethylsulfoxide**
dppm	**1,1-Bis(diphenylphosphino)methane**
dr	**Diastereoisomeric Ratio**
E^0	**Standard Electrode Potential**
ee	**Enantiomeric Excess**
eq	**Equivalent(s)**

ESI	**Electrospray Ionisation**
Et	**Ethyl**
eV	**Electron Volt(s)**
FI	**Field Ionisation**
g	**Gram(s)**
h	**Hour(s)**
HOESY	**Heteronuclear Overhauser Effect Spectroscopy**
HOMO	**Highest Occupied Molecular Orbital**
HPLC	**High Performance Liquid Chromatography**
HRMS	**High Resolution Mass Spectrometry**
Hz	**Hertz**
i	***Iso***
IPr	**1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene**
IR	**Infrared Spectroscopy**
LRMS	**Low Resolution Mass Spectrometry**
LUMO	**Lowest Unoccupied Molecular Orbital**
M	**Moles per cubic decimetre ($moldm^{-3}$)**
Me	**Methyl**
Mes	**1,3,5-Trimethylphenyl (Mesityl)**
min	**Minute(s)**
mL	**Millilitre(s)**
mol	**Mole(s)**
Mp	**Melting Point**

Ms	**Methanesulfonyl (Mesyl)**
n	**Normal**
NBS	***N*-Bromosuccinimide**
NCS	***N*-Chlorosuccinimide**
NFSI	***N*-Fluorobenzenesulfonimide**
NIS	***N*-Iodosuccinimide**
NOE	**Nuclear Overhauser Effect**
NR	**No Reaction**
$^{n}J_{XY}$	**Scalar coupling constant (in NMR Spectra) between nuclei X and Y through n bonds**
NMR	**Nuclear Magnetic Resonance Spectroscopy**
Pet. Ether	**Petroleum Ether**
Ph	**Phenyl**
ppm	**Parts per Million**
Pr	**Propyl**
R_f	**Retention Factor**
rt	**Room Temperature**
S_EAr	**Electrophilic Aromatic Substitution**
Selectfluor	**1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)**
S_NAr	**Nucleophilic Aromatic Substitution**
t	**Tertiary (*tert*)**
TBAF	**Tetra-*n*-butylammonium fluoride**
TBDPS	***tert*-Butyldiphenylsilyl**

TBDMS	***tert*-Butyldimethylsilyl**
Tf	**Trifluoromethanesulfonyl (Triflyl)**
TFA	**Trifluoroacetic Acid**
THF	**Tetrahydrofuran**
TLC	**Thin Layer Chromatography**
Ts	***para*-Toluenesulfonyl (Tosyl)**
UV	**Ultraviolet**
V	**Volt(s)**
Z	**Atomic Number**
Z_{eff}	**Effective Nuclear Charge**
δ	**Chemical Shift**
µL	**Microlitre(s)**
ºC	**Degrees Celcius**

Chapter 1

Introduction

1.1 Fluorine in Organic Chemistry

Fluorine is the most abundant halogen in the Earth's crust, ranking 13th in abundance of all the elements.[1] Naturally occurring organic molecules largely consist of carbon, hydrogen, nitrogen and oxygen atoms, and all molecules containing carbon frameworks possess many carbon atoms that are attached to hydrogen atoms. Of the countless naturally occurring molecules, only a handful of systems have carbon atoms that are attached to fluorine atoms, and most of these are metabolites in tropical plants found in the Southern Hemisphere.[2] The toxin fluoroacetate is the most widespread fluorinated natural product, occurring in the leaves and seeds of a wide variety of higher plants. Several ω-fluorofatty acids, the most abundant being 18-fluoro-oleic acid, have been identified in the shrub *Dichapetalum toxicarium* (fluoroacetyl-CoA as a starter unit in fatty acid biosynthesis) and traces of fluoroacetone and fluorocitrate have been reported in certain plants. Organofluorine compounds of microbial origin include the antibiotic nucleocidin containing a fluorinated sugar residue, which is formed by *Streptomyces calvus* and the fluorinated amino acid 4-fluorothreonine which is biosynthesized together with fluoroacetate in *Streptomyces cattleya*.[3]

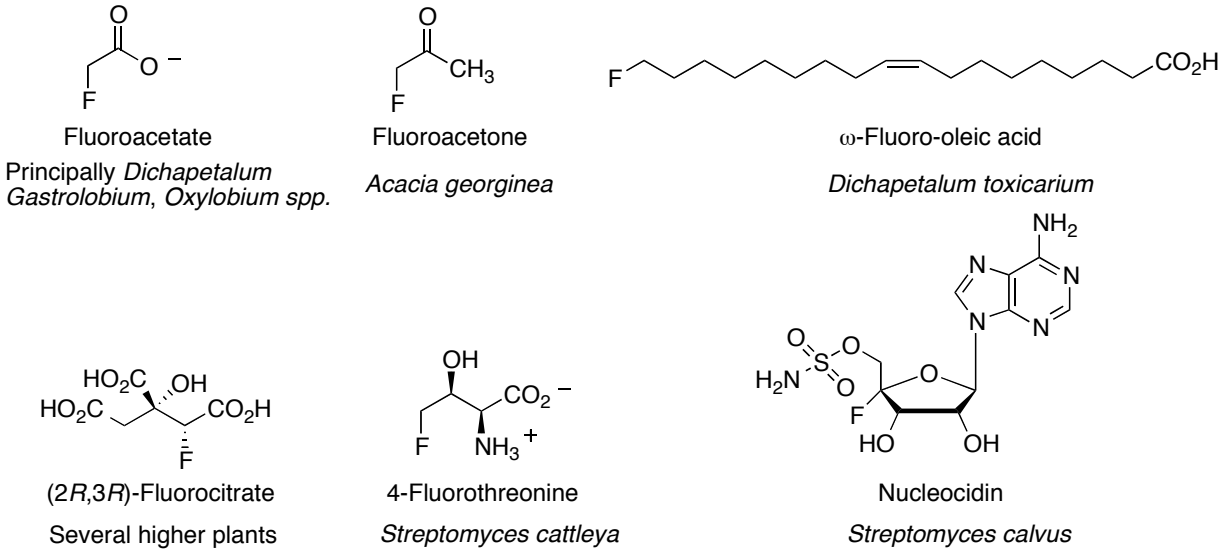


Figure 1.1 Natural products containing fluorine

Fluorine has come a long way from the time Henri Moissan, who first isolated elemental fluorine in 1886, to the present era of organofluorine compounds.[4] The atomic configuration of F [(He)$2s^2p^5$] has an unshielded high nuclear charge that strongly attracts the surrounding electrons. It is the most electronegative of all elements, causing highly polar carbon fluorine bonds. Its strongly localized electrons render very low polarizability and a relatively small size (Table 1.1). The excellent match between the fluorine 2s and 2p orbitals with the corresponding orbitals of carbon are unique. It forms one of the strongest bonds with carbon (105.4 kcal/mol compared to 99.0 kcal/mol for C-H bond).[5] It occupies a van der Waals radii of 1.47 Å, smaller than oxygen (1.52 Å) but larger than hydrogen (1.20 Å).[6, 7] And although fluorine is closer to oxygen in size than to hydrogen, it closely mimics hydrogen with respect to steric requirements at enzyme receptor sites,[8] making it extremely useful in medicinal chemistry.

Elements	Electronegativity (Pauling scale) χ_p	Van der Waals Radii (Å)	Electron Affinity (kcal/mol)Å	Ionization Potential (kcal/mol)	Atom Polarizability ($Å^3$)
H	2.20	1.20	17.7	313.6	0.667
C	2.55	1.70	29.0	240.5	1.76
N	3.04	1.55	-6.2	335.1	1.10
O	3.44	1.52	33.8	314.0	0.82
F	**3.98**	**1.47**	**79.5**	**401.8**	**0.557**
Cl	3.16	1.75	83.3	299.0	2.18
Br	2.96	1.85	72.6	272.4	3.05
I	2.66	1.98	70.6	241.2	4.70

Table 1.1 Atomic parameters of the fluorine atom

1.2 Selective Formation of C-F Bonds

Since very few naturally occurring compounds that possess a carbon–fluorine bond exist, organofluorine compounds must be prepared by synthesis. Many fluorinating agents have been developed over the years with the goal of solving this fundamental problem, with varying degrees of success.[9] Fluorinated organic compounds are prepared by two different approaches: (i) by insertion of a group already containing C-F bonds into an existing molecule (the building-

block approach), or (ii) by creating new C-F bonds by fluorination.[10]

Possibly, the most effective method for the introduction of fluorine atoms into an organic system is the replacement of hydrogen, attached to an sp^2 or sp^3 carbon, by fluorine, using either readily available nucleophilic or electrophilic fluorinating agents. The advantage of such a direct method is that it could enable late-stage fluorination of large molecules, which could be theoretically applied to a range of functional compounds such as drug candidates. Many of the strategies used for selective fluorination rely on the use of stable and easy to handle fluorinating reagents.[11] These reagents can be conveniently split into three classes: nucleophilic sources (F^-), radical sources ($F^\cdot$) and electrophilic sources (F^+) of fluorine.[12]

1.2.1 Achiral N-F Nucleophilic Fluorinating Reagents

Although most commercial fluorine containing chemicals are produced using sources of fluoride ion, the introduction of fluorine using nucleophilic substitution is not straightforward, in part due to the challenges associated with poor solubility and its dual reactivity profile both as a nucleophile and a base.[13] The most atom economic nucleophilic fluorinating agent is hydrogen fluoride, however this reagent is scarcely used in laboratories due to its toxic and corrosive properties and its low reactivity resulting from high bond energy.[14] Recent efforts have seen a surge in the development of nucleophilic fluorinating agents with very interesting properties.[15] Examples of such nucleophilic fluorinating reagents are shown in Figure 1.2.[16]

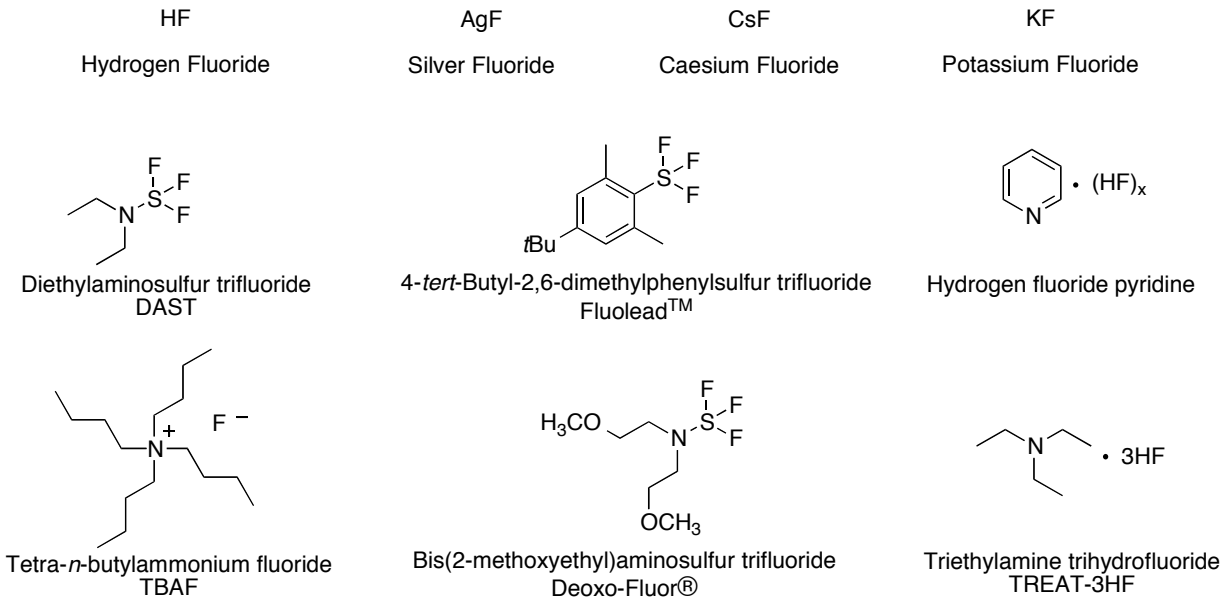
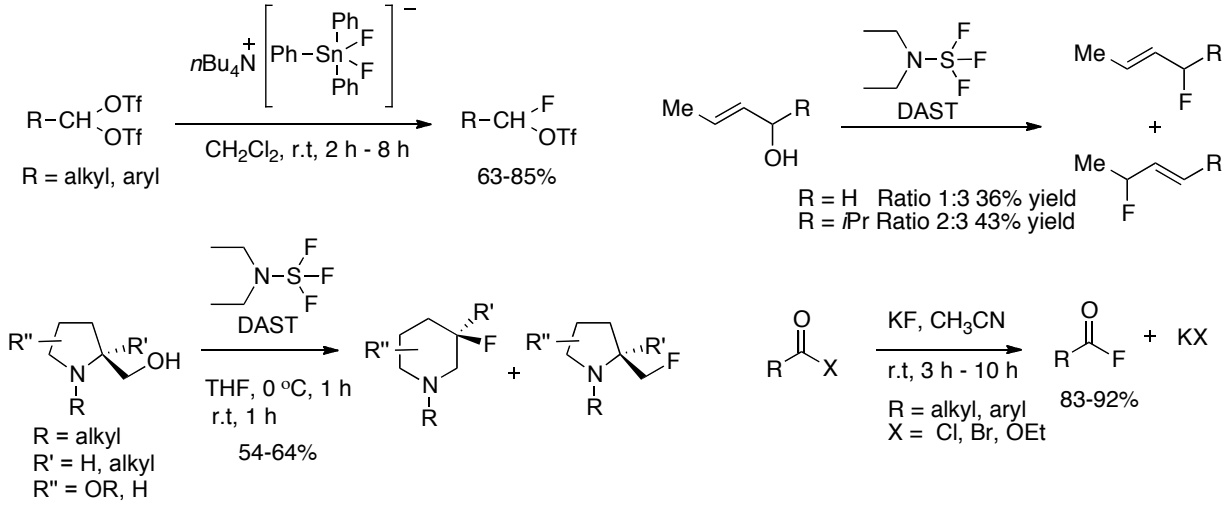


Figure 1.2 Nucleophilic fluorinating reagents.

These reagents are now commonly used in the preparation of both simple and complex fluorinated organic molecules, usually *via* displacement of halide or oxygen based leaving group (Scheme 1.1).[17, 18, 19]



Scheme 1.1 Examples of nucleophilic fluorination.

1.2.2 Achiral N-F Electrophilic Fluorinating Reagents

Elemental fluorine (F_2) is one of the most chemically reactive substances known, due to the weakness of the F-F bond (F-F bond energy is 36.6 kcal/mol resulting from strong repulsion of

lone pair electrons) and the great strength of the bonds fluorine forms to most other elements, including hydrogen, carbon and silicon.[20, 21] Fluorine can behave both as a fluorinating agent and a powerful oxidant. It reacts readily with almost every other element and many common materials, often with near explosive violence. In organic molecules, C-H bonds tend to be attacked indiscriminately by both free-radical and ionic mechanisms. Elemental fluorine has been successfully harnessed, notably by the Chambers' group,[22] using strongly acidic, polar media to promote selective heterolytic fluorination and minimise the non-selective free-radical pathways. However, because of the ease of F^- formation and the extremely dangerous properties of F_2 (highly toxic, strong oxidant with little or no specificity, potential runaway free-radical reactions), many alternative electrophilic fluorinating reagents have been developed over the last 40-50 years with the objective of providing selectivity and ease of handling.[23] The first electrophilic fluorinating reagent, fluoroxytrifluoromethane (CF_3OF), was reported by Barton *et al*.[24] The introduction of other reagents followed, including perchloryl fluoride ($FClO_3$),[25] xenon difluoride (XeF_2),[26] nitrogen oxide fluorides,[27] caesium fluorooxysulfate, ($CsSO_4F$),[28] and several other hypofluorides[29] (Figure 1.3).

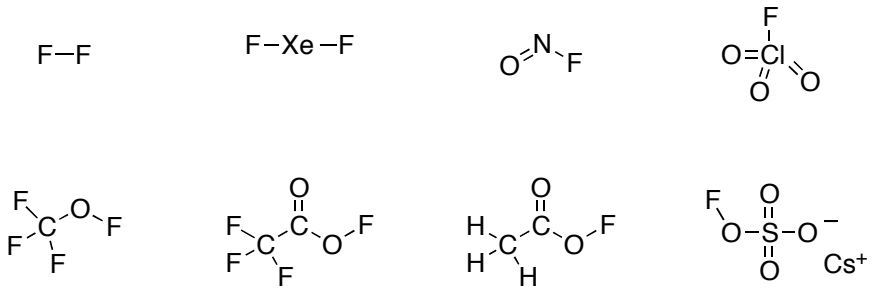


Figure 1.3 Early electrophilic fluorinating reagents

Unremitting interest worldwide in site-selective fluorination of biologically-active molecules has heightened demand for more generally acceptable (less aggressive, non-explosive, less toxic, inexpensive) electrophilic fluorinating agents.[30] Thus, a new class of electrophilic fluorinating reagents with the general structure R_2N-F or R_3N^+-F has been introduced as

alternatives. These reagents are usually more stable, milder and easy to handle than F_2 gas. They are prepared from relatively inexpensive starting materials (usually prepared by reacting the corresponding R_2N-H or R_3N compound with F_2) and a number of these agents are now commercially available. These N-F reagents have transformed the field of electrophilic fluorination and have received the most attention in recent years.[31] The N-F reagents can be conveniently separated into two classes: the neutral reagents [RN(F)R'] and the quaternary reagents [R_3N^+F X^-] where X^- represents a non-nucleophilic counter ion. The most common, commercially available, electrophilic fluorinating reagents are outlined in Figure 1.4.

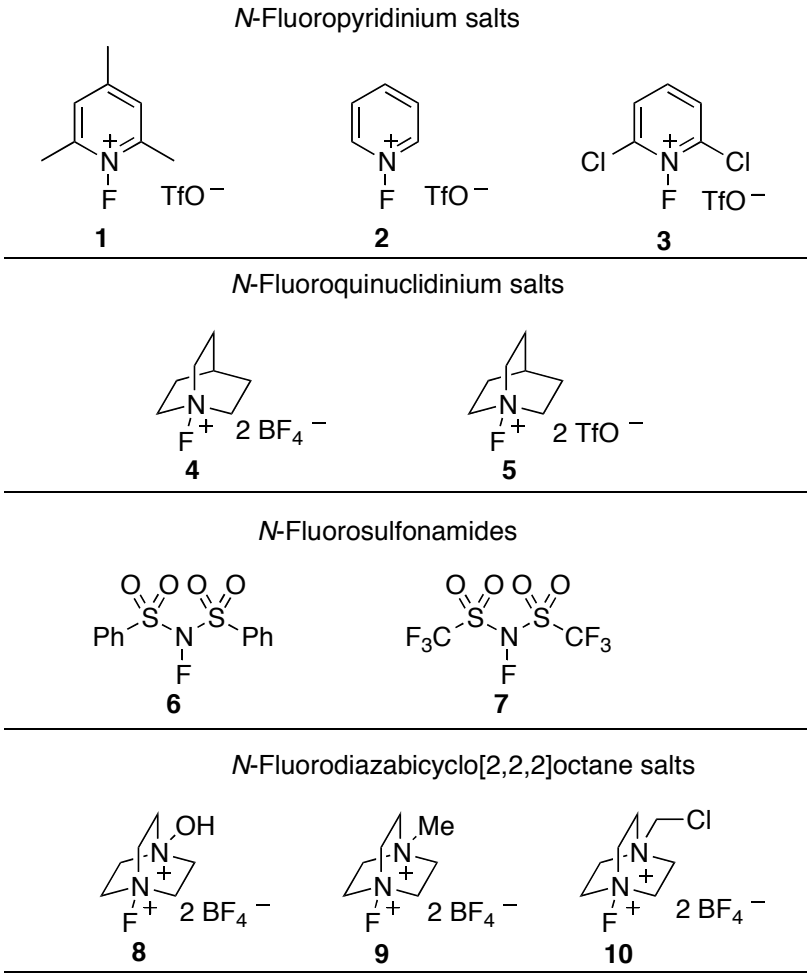


Figure 1.4 Common N-F fluorinating reagents

N-Fluoropyridinium salts were first developed by Umemoto *et al*. as an easy-to-handle crystalline solid and have become an important source of electrophilic fluorine for fluorination.[32] *N*-Fluoropyridinium salts allow the fluorination of a wide range of nucleophilic substrates and their reactivity can be adjusted by substitution of the pyridine core. Electron-withdrawing substituents increase the reactivity of the N-F bond (Figure 1.4).[33]

New classes of fluorinating reagents that are prepared by the treatment of *N*-sulfonamides with dilute elemental fluorine were reported by Barnette in 1984.[34] Subsequently, several research groups reported the synthesis and use of additional fluorinating reagents such as *N*-fluorobenzenesulfonimide (NFSI, **6**) or *N*-fluorobis[(trifluoromethyl)sulfonyl] imide **7** (Figure 1.4). [35 , 36] The development of the reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor or F-TEDA-BF_4, **10**; Figure 1.4) and its derivatives presented a major advance for electrophilic fluorination. Selectfluor was developed by Banks in collaboration with Air Products (the corporate science and technology centre [CSTC]) and is a commercially available, stable and effective source of electrophilic fluorine.[37] As sources of F^+, all the N-F reagents are also oxidizing agents, as indicated by the conversion of aqueous iodide to iodine.

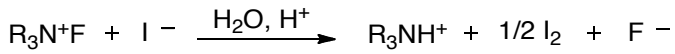


Figure 1.5 Conversion of iodide to iodine

The currently known NF reagents display a wide range of oxidizing and fluorinating power towards nucleophiles.[38] Selectfluor has a reduction potential of -0.04 V versus saturated calomel electrode (SCE), which makes it one of the most powerful oxidants in the N-F compounds series and therefore a convenient reagent for many "other-than-fluorine" functionalizations of organic compounds (Figure 1.6).[38]

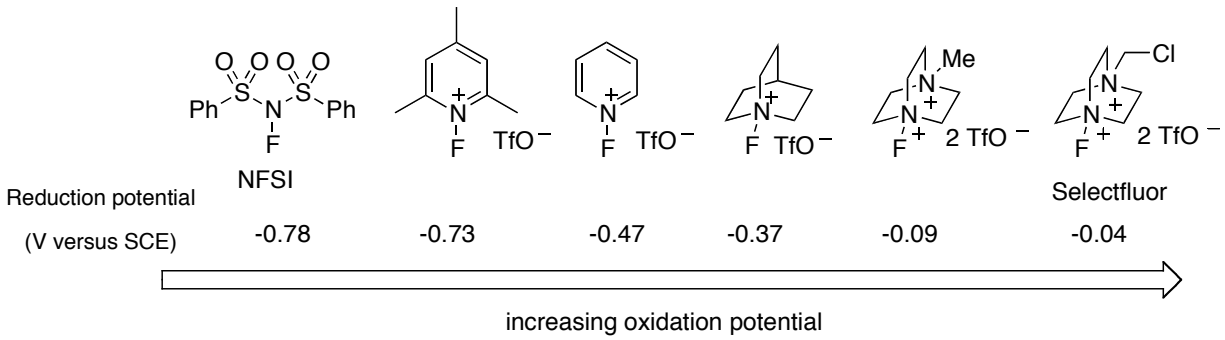


Figure 1.6 Oxidation potential of electrophilic fluorinating reagents

The literature data related to Selectfluor F-TEDA-BF_4 as a fluorinating reagent and its role in other transformations is the subject of the next discussion in this chapter.

1.3 Selectfluor

Selectfluor or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) is the most commonly used NF reagent for electrophilic fluorination reactions.[39,37,40] The fluorinating power can be modulated by variation of the electron withdrawing alkyl side chain as well as the counterion.[41] Although the Selectfluor family represents a variety of compositions, there are currently only three commercially available (Figure 1.7). Selectfluor **10** is a white, free-flowing, virtually non-hydroscopic crystalline solid, which can be handled, safely in ambient air.[42] It incorporates the chloromethyl group as the quaternizing functionality as well as two tetrafluoroborate anions, and it is the combination of these two properties, which impart to this molecule the ideal balance between the N-F bond electrophilicity ("F" strength) and overall thermal stability of the molecule.[43] Finally, the ease of incorporating both the chloromethyl group and the BF_4^- anions made this a good choice to scale up and commercialize.

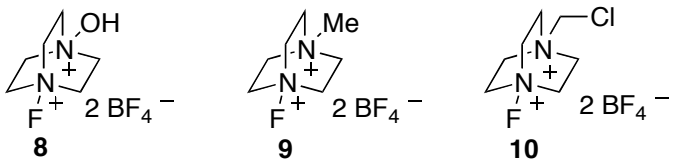
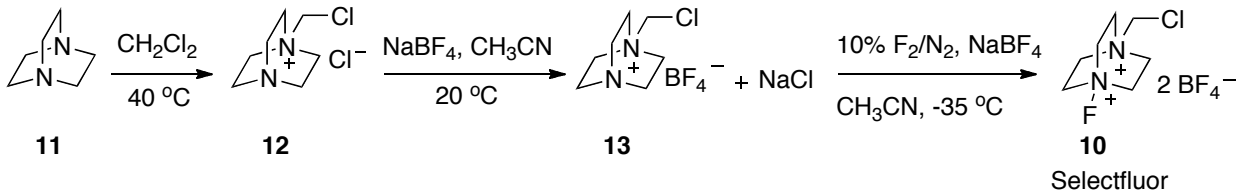


Figure 1.7 Commercially available Selectfluor derivatives

1.3.1 Preparation

Banks *et al*. developed Selectfluor as part of their research on N-F chemistry at the University of Manchester Institute of Science and Technology (UMIST).[30] The preparation of Selectfluor was designed to be simple, flexible, and efficient. The most practical procedure for the production of Selectfluor involves initial alkylation of 1,4-diazabicyclo[2.2.2]octane **11** (DABCO, also known as triethylenediamine (TEDA)) with dichloromethane. After counterion exchange with sodium tetrafluoroborate and subsequent precipitation of sodium chloride from the acetonitrile solution, fluorination with fluorine gas provides Selectfluor **10** (Scheme 1.2).[44]



11 **12** **13** **10** Selectfluor

Scheme 1.2 Preparation of Selectfluor

The fluorinating power can be modulated by variation of the electron withdrawing alkyl side chain. In general, the more electron withdrawing the alkyl substituent, the more electrophilic the fluorine group will be. Thus, the order of reactivity follows the relative electron-withdrawing power of the alkylating organic groups (CF_3CH_2 > CH_2Cl > Me ~ Et), hence the 'tunability' of the series. In addition, a variety of counterion combinations can be selected which impart to these molecules very different solubility characteristics. Some derivatives are shown in Figure 1. 8.[45]

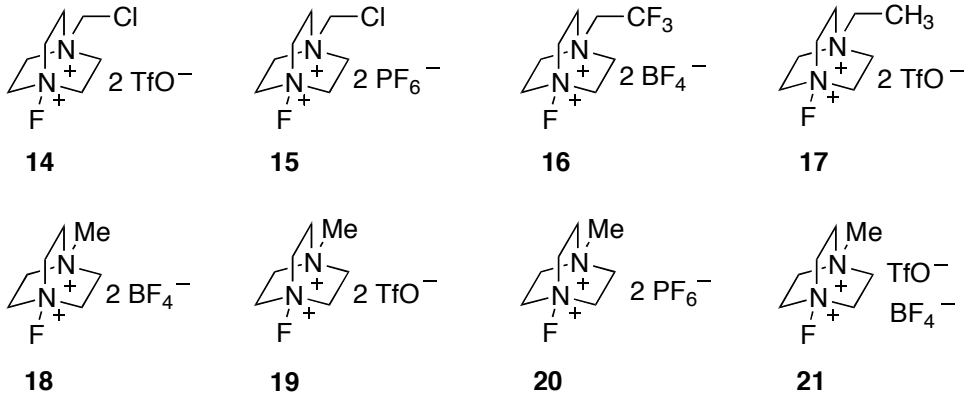
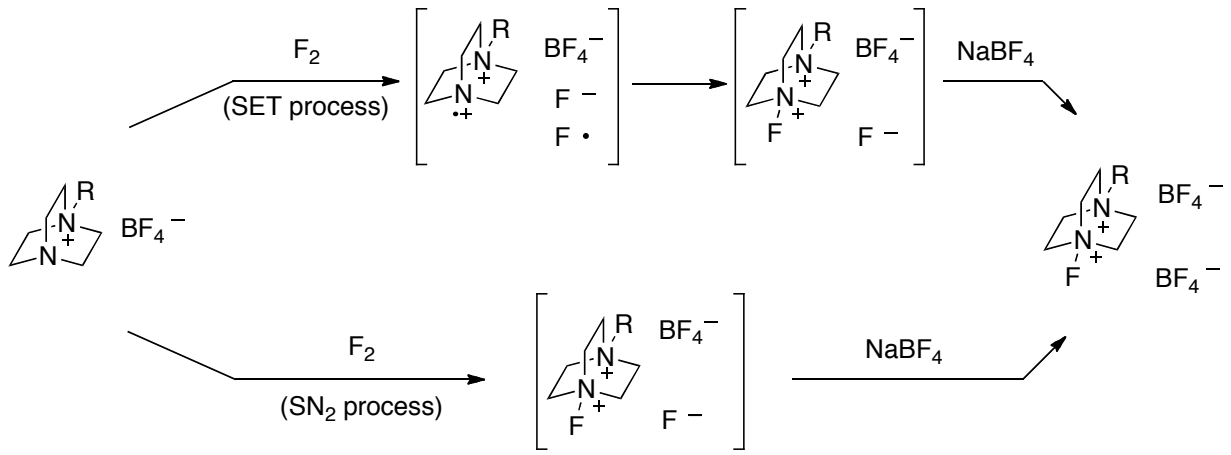


Figure 1.8 Selectfluor derivatives

The counterion employed with Selectfluor can have an impact on both the reactivity and the cost of the final compound. In earlier studies, no obvious effect of the counterion on the reactivity had been observed, leading to the commercialization of the tetrafluoroborate salt.[36] However, recent studies demonstrated that the use of the trifluoromethanesulfonate (triflate) salt **14** for the fluorination of glycals led to decreased side-product formation and higher yields of the desired product than with Selectfluor **10**.[46] This outcome was rationalized by the greater solubility of the triflate salt of Selectfluor in the desired solvent (nitromethane) and the fact that no bisfluorinated by-products were formed, a side reaction that occurs with Selectfluor presumably due to the BF_4^- counterion. Although the F-TEDA family represents a variety of compositions, Selectfluor **10** was an ideal reagent for commercialization from a cost-effectiveness viewpoint and can be synthesized conveniently. Selectfluor derivatives are reactive enough to fluorinate both pyridine and quinuclidine, demonstrating their superior reactivity over *N*-fluoropyridinium and *N*-fluoroquinuclidinium reagents.[38]

The mechanism for the transfer of fluorine from F_2 to the TEDA-X salts is not well defined but it is likely that the reaction proceeds *via* an S_N2 or a single-electron transfer (SET) process as shown in Scheme 1.3.[37]



Scheme 1.3 Proposed mechanisms for the transfer of F_2 to TEDA-X salts

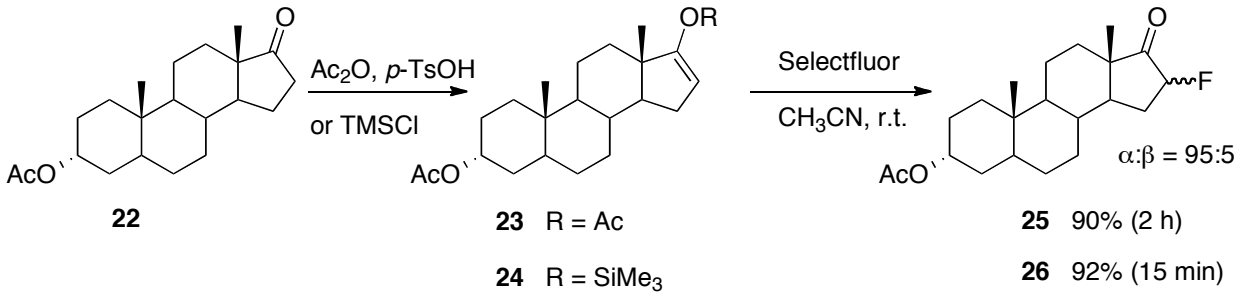
1.3.2 Selectfluor as a Fluorinating Reagent

Selectfluor has become the electrophilic fluorinating agent of choice for a wide variety of applications as described below.

1.3.2.1 Fluorination of Carbonyl Compounds

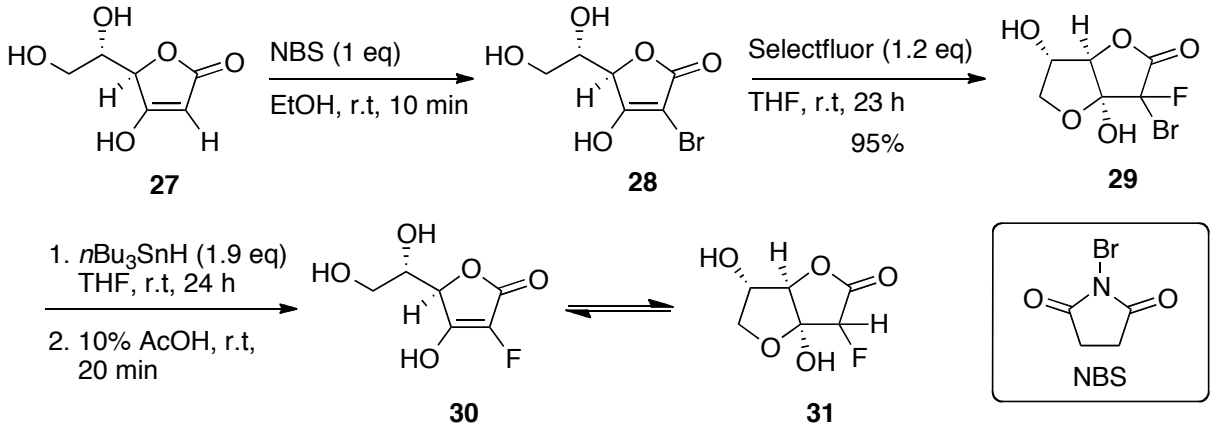
1.3.2.1.1 Metal Free Fluorination

Selectfluor efficiently fluorinates a variety of carbonyl compounds in a highly selective manner to furnish α-fluorocarbonyl compounds. During their work on site-selective fluorination of organic compounds, Lal *et al*. found that Selectfluor was effective for the fluorination of steroidal enol acetates and silyl enol ethers. They first converted the carbonyl functionality of the steroids into an enol ester **23** or a silyl enol ether **24** prior to reaction with Selectfluor (Scheme 1.4).[47]



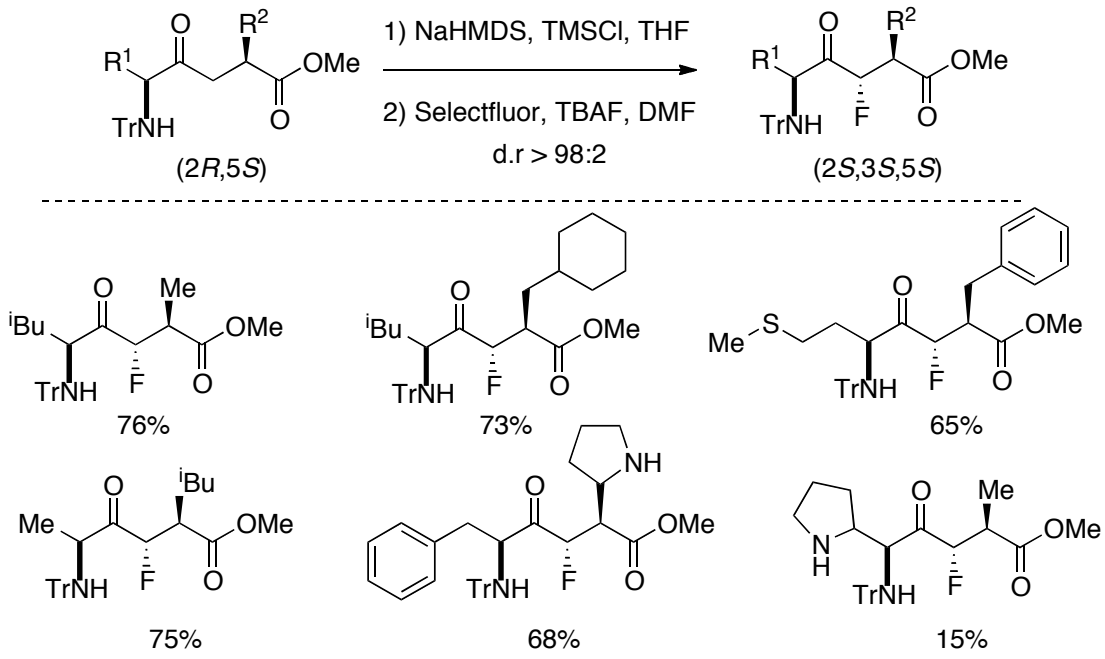
Scheme 1.4 α-Fluorination of ketones *via* an enol ester or a silyl enol ether

In an investigation into the effects of fluorine substituents on the behaviour of bioactive compounds, Ge and Kirk reported the synthesis of fluorinated derivatives of L-ascorbic acid (Scheme 1.5).[48] It was necessary to preactivate the corresponding α-carbon of **27** with *N*-bromosuccinimide (NBS) to form a hemiketal that enolised to give a more reactive enol **28**. Reductive debromination of **29** by tributyltin hydride, followed by treatment with aqueous acid gave 2-deoxy-2-fluoro-L-ascorbic acid **30**. The strong electronegativity of the fluorine atom in **30** led to facile tautomerization between the enol and the hemiketal **31**.



Scheme 1.5 α-Fluorination of derivatives of L-ascorbic acid

Hoffman *et al*. developed a stereocontrolled synthesis of monofluoro ketomethylene dipeptide isosteres. Various trimethylsilyl enol ethers (*Z* isomer), prepared from *syn*-(2*R*,5*S*)-*N*- tritylated ketone dipeptides using sodium hexamethyldisilazide and trimethylsilyl chloride, were subjected to fluorination with Selectfluor in the presence of tetrabutylammonium fluoride (Scheme 1.6).[49] The resulting products were isolated in synthetically useful yields. The cooperative stereocontrol induced by the *N*-tritylamino group and the substituent at C2 led to diastereoselectivities all superior to 98:2. The *anti*-(2*S*,5*S*)-*N*-tritylated ketone dipeptides can be fluorinated but these reactions are not stereoselective (dr ~1:1)



Scheme 1.6 Synthesis of monofluoro ketomethylene dipeptide isosteres

Conformational analysis of the TMS-enol ether **32** provided an explanation for the observed stereoselection (Figure 1.9). According to calculation, the preferred conformation of **32** lies 3 kcal/mol lower than the next lowest energy conformer, minimizing $A_{1,2}$ interactions, and has both the *N*-trityl group at C-5 and the methyl group at C-2 above one face of the enol double bond. Approach of the fluorinating agent from the face opposite these groups led to the observed stereochemistry.

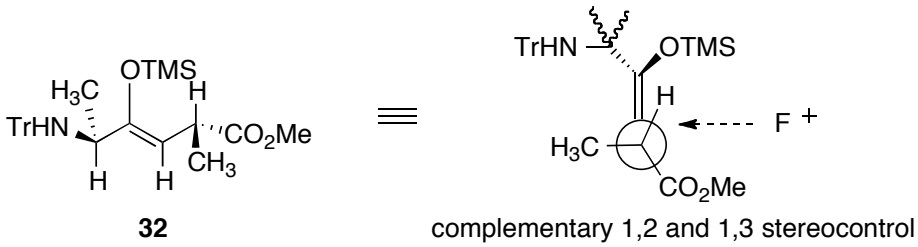
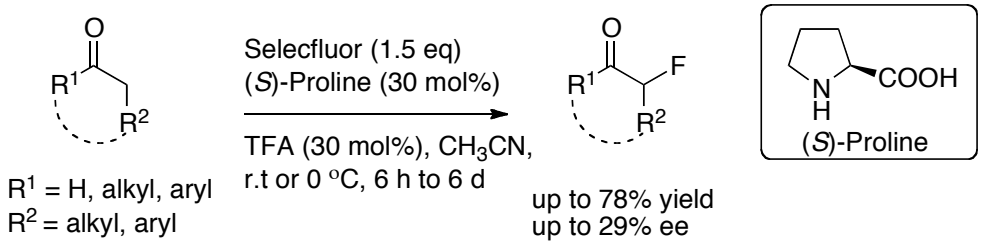


Figure 1.9 Conformational analysis of the TMS-enol ether **32**

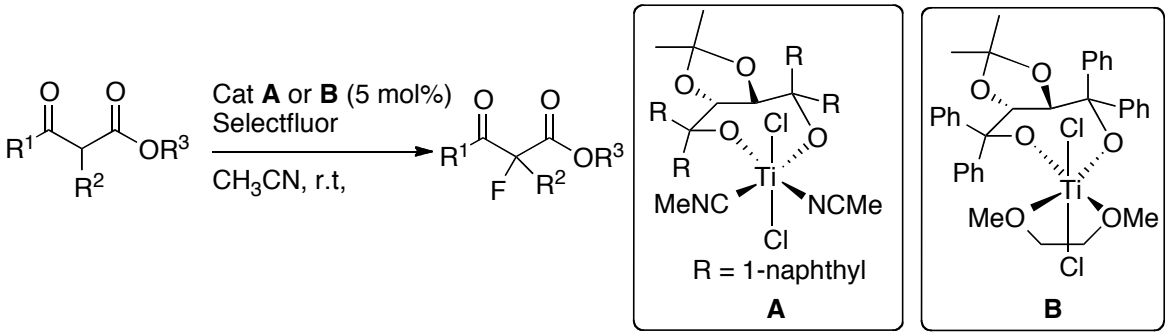
Enders reported in 2005 the first protocol for the direct organocatalytic enantioselective α-fluorination of aldehydes and ketones employing proline as the catalyst and Selectfluor as the electrophilic source of fluorine (Scheme 1.7).[50]



Scheme 1.7 (*S*)-Proline-catalysed α-fluorination of aldehydes and ketones

1.3.2.1.2 Metal Mediated Carbonyl Fluorination

In 2000, Togni *et al.* reported the first catalytic enantioselective fluorination of β-ketoesters using Selectfluor and a catalytic amount of a Lewis acid.[51] Initially, they found that titanium-based Lewis acids such as $TiCl_4$ constituted the most potent catalysts. Following this, they then synthesized and isolated the enantiopure Lewis acidic Ti complexes **A** and **B**. The fluorination of various β-ketoesters using 5 mol% of Ti complexes **A** and **B** with a slight excess of Selectfluor in acetonitrile at room temperature led to products having a quaternary stereogenic center (Table 1.2).



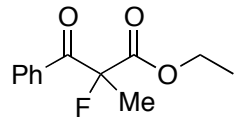
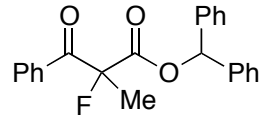
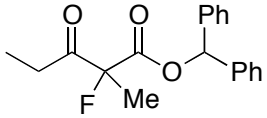
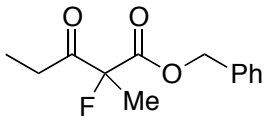
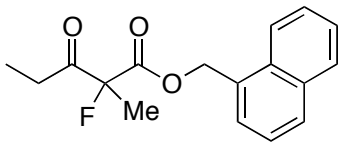
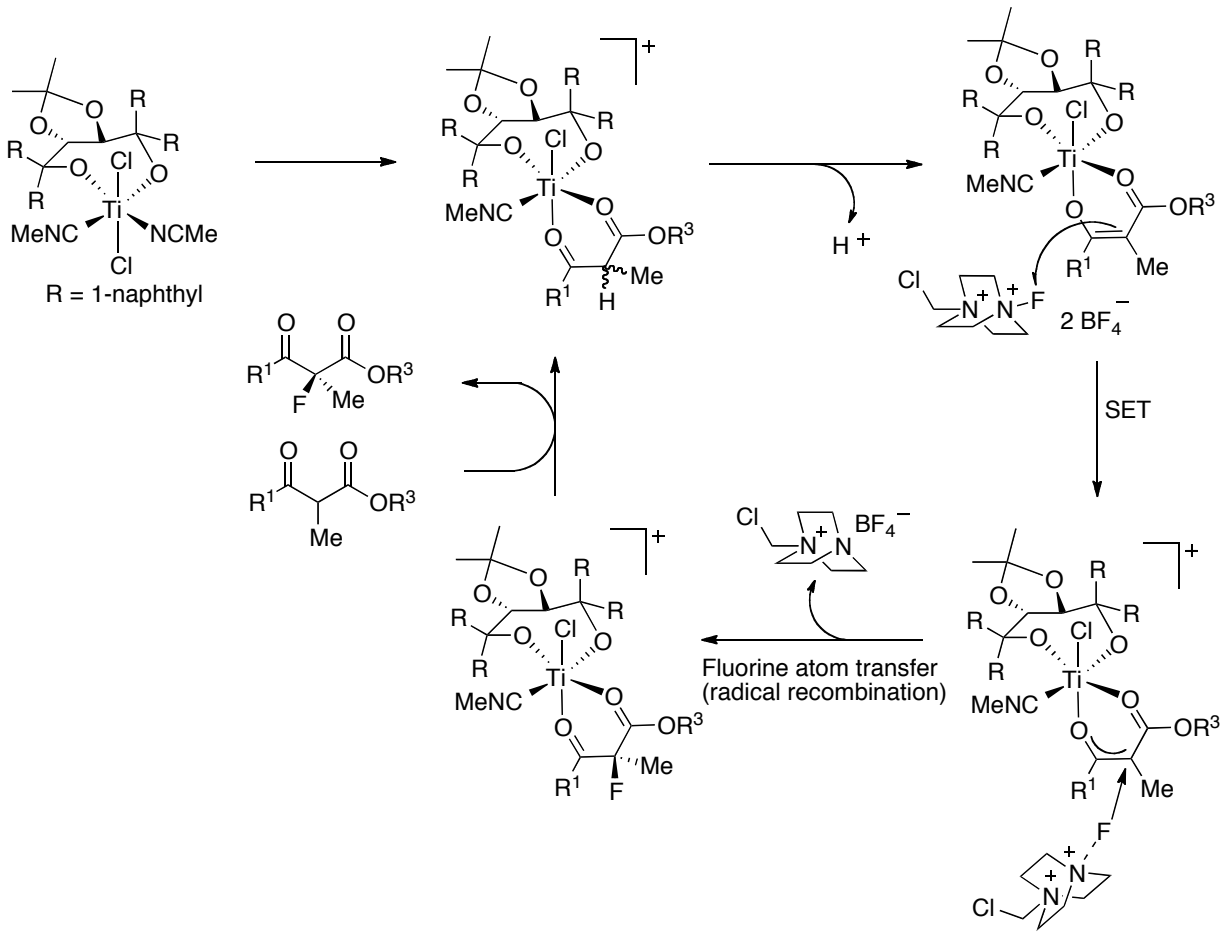
Product	Selectivity (Reaction time) cat **A**	cat **B**
	28% *ee* (4 h)	62% *ee* (40 min)
	59% *ee* (1 d)	82% *ee* (1 d)
	58% *ee* (2 h)	81% *ee* (20 min)
	48% *ee* (15 min)	71% *ee* (< 7 min)
	51% *ee* (< 15 min)	68% *ee* (< 15 min)

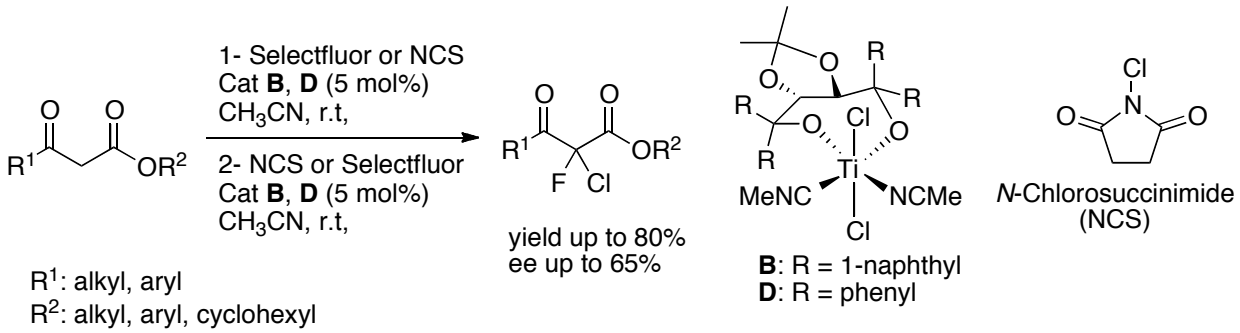
Table 1.2 Catalytic enantioselective fluorination reactions using isolated Ti complexes

Mechanistically, interaction of the β-ketoester with the catalyst facilitates enolization and the coordinated enol or enolate is susceptible to electrophilic attack by Selectfluor. The first step involved the chelation of the substrate to titanium and its deprotonation, followed by the external attack by the electrophile. Subsequent single electron transfer led to the formation of the C-F bond (Scheme 1.8).[52]



Scheme 1.8 Mechanistic scheme for the Ti-catalyzed fluorination of β-keto esters

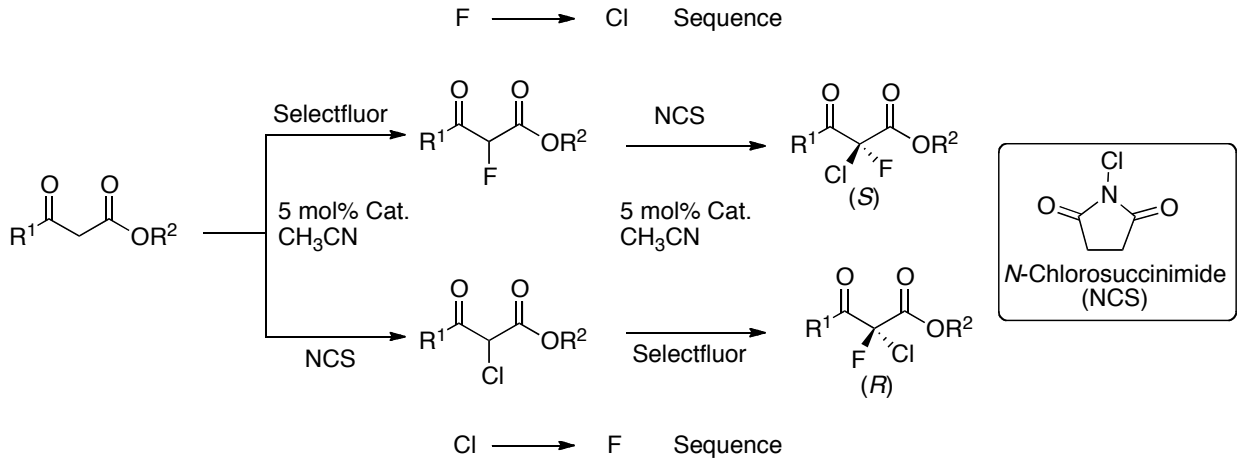
Subsequently, this electrophilic atom transfer reaction was extended to the related chlorination and to a geminal dihalogenation process (Scheme 1.9).



Scheme 1.9 Formation of geminal dihalogenation

The sequence of addition of the halogenating agents determined the sense of chiral induction. Given one enantiomeric form of the catalyst, it is possible to form either enantiomer of the

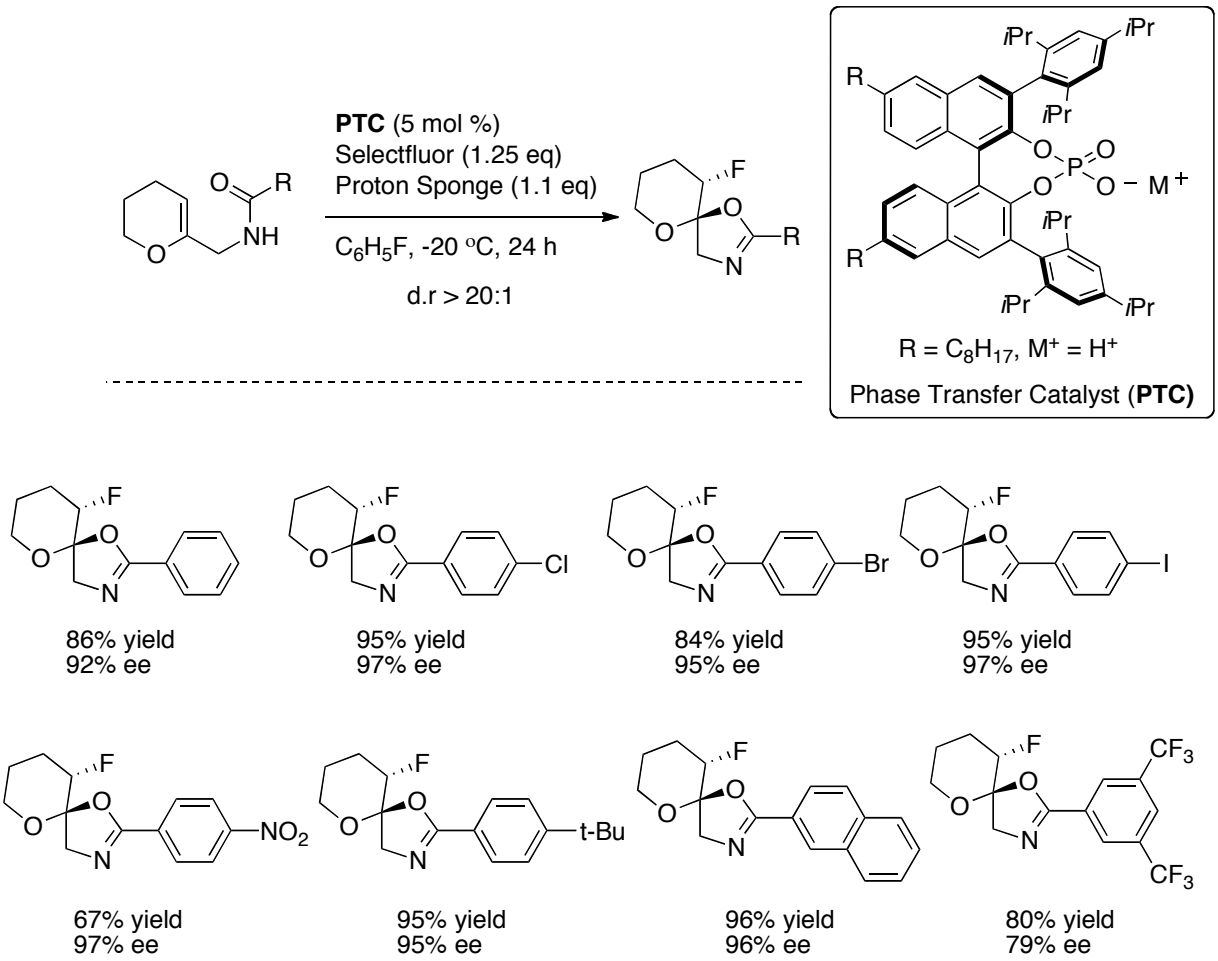
product preferentially by choosing the order of the two halogenation steps in this one-pot tandem process. The first halogen is introduced in a nonstereoselective manner and, overall, the stereochemical outcome is solely determined by the second halogenation step. As the catalysts derived from (*R*,*R*)-TADDOLs the major product enantiomer is formed *via Si*-side attack of the halogenating agent onto the coordinated enolate, Togni assigned the absolute configuration (*S*)- to the preferred enantiomer obtained via the F → Cl sequence (and (*R*)- for the Cl → F sequence) (Scheme 1.10).



Scheme 1.10 Sequence of addition of the Selectfluor and *N*-chlorosuccinimide

1.3.2.2 Fluorination of Enol Ether Functionalities

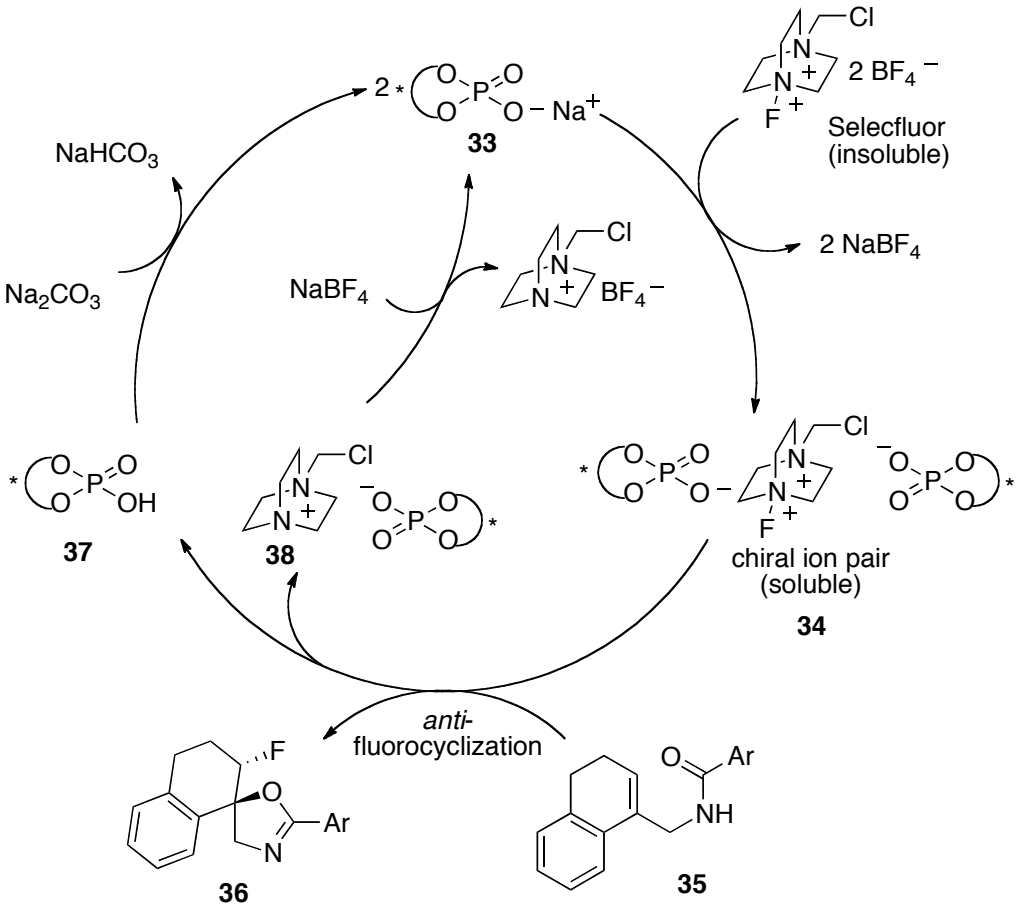
Recently, Toste and co-workers reported an enantioselective fluorocyclization of enol ethers with Selectfluor and a chiral phosphate catalyst. The reactions proceeded in high yield and stereoselectivity (Scheme 1.11).[53] The method generated heterocyclic products with two stereogenic centers, including a carbon-fluorine stereocenter that would be difficult to construct using alternative approaches. Furthermore, the reactivity of their system allowed less electron-rich olefins to be fluorinated relative to previous reports. Moreover, the enhanced reactivity did not affect the stereoselectivity, which compares favorably with other chiral electrophile–based fluorination methods.



Scheme 1.11 Enantioselective fluorocyclization using chiral counter ion

Toste proposed a catalytic mechanism to account for the formation of fluorocyclized products (Scheme 1.12).[53] Two equivalents of phosphate **33** underwent salt metathesis with dicationic Selectfluor, which is insoluble in nonpolar solvents, to generate **34**. Exchange of the tetrafluoroborate anions from the reagent with lipophilic chiral phosphate anions brings the active electrophile into solution as a chiral ion pair **34**. Then, the ion pair **34** efficiently mediated the fluorocyclization of alkene substrate **36**. Upon reaction, one equivalent of phosphoric acid **37** was generated along with one equivalent of the defluorinated monocationic ion pair **38**. The anionic phosphate **33** was regenerated by deprotonation and ion exchange.

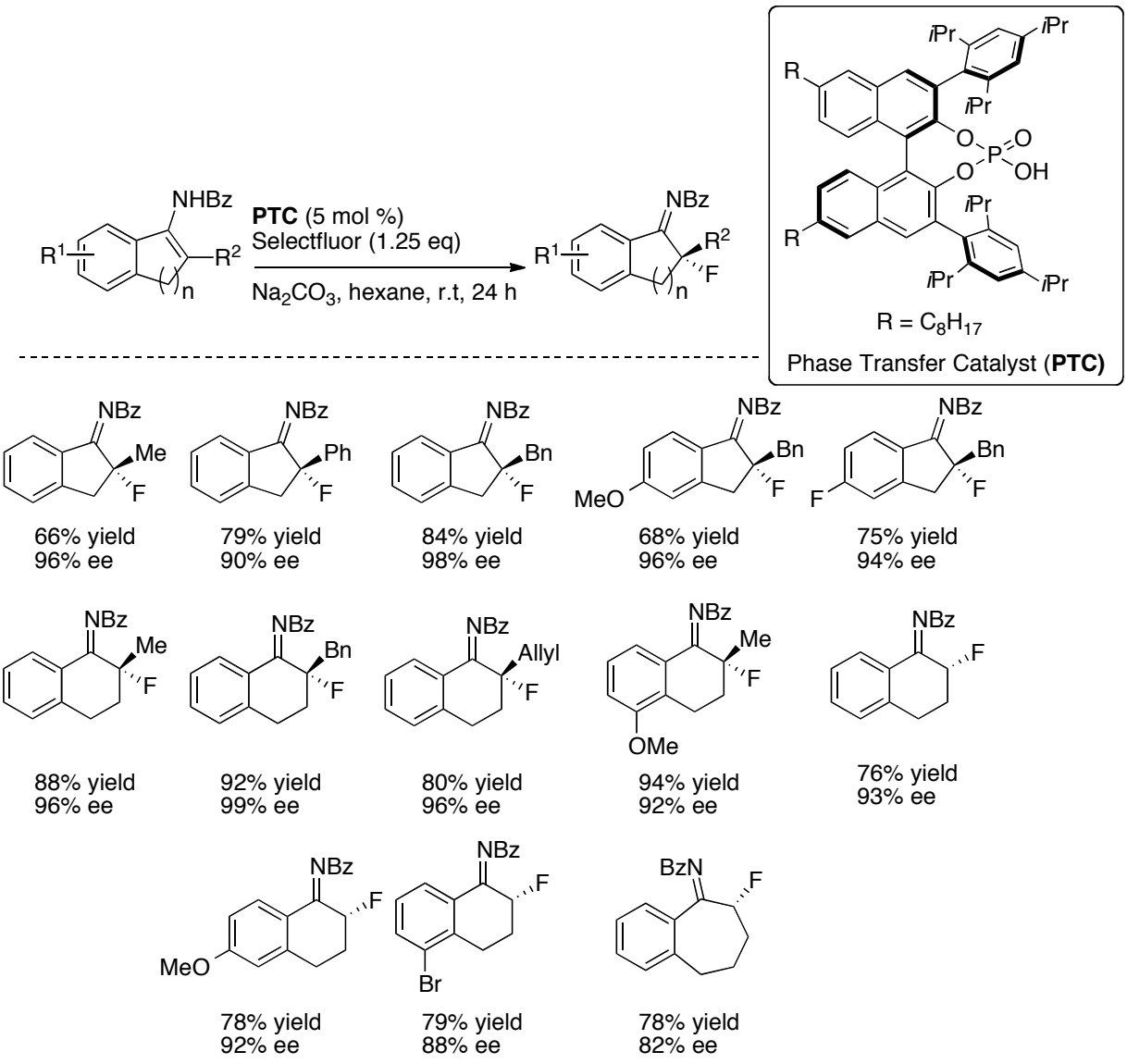
.



Scheme 1.12 Enantioselective fluorocyclization using chiral counter ion

1.3.2.3 Fluorination of Enamines

Toste and co-workers reported in 2012 the enantioselective synthesis of α-fluoroimines.[54] Their protocol allows isolation of the stable *N*-benzoyl imine products. A range of cyclic enamides including five-, six-, and seven-membered rings provided high yields of stable α-(fluoro)benzoylimines with high selectivities (Scheme 1.13).



Scheme 1.13 Asymmetric fluorination of enamides

A suitable model was proposed to account for the absolute stereochemistry observed upon fluorination of the enamides. The phosphate anion forms an ion pair with Selectfluor and simultaneously activates the enamide through hydrogen bonding (Figure 1.10). The enamide would reside in a position as to put the bulk of the tetralone in an 'open' quadrant, with the amide group occupying a 'closed' quadrant. The high tolerance of the reaction towards substitution on the enamide may reflect that these positions point away from the catalyst and thus have no effect on catalyst–substrate binding.

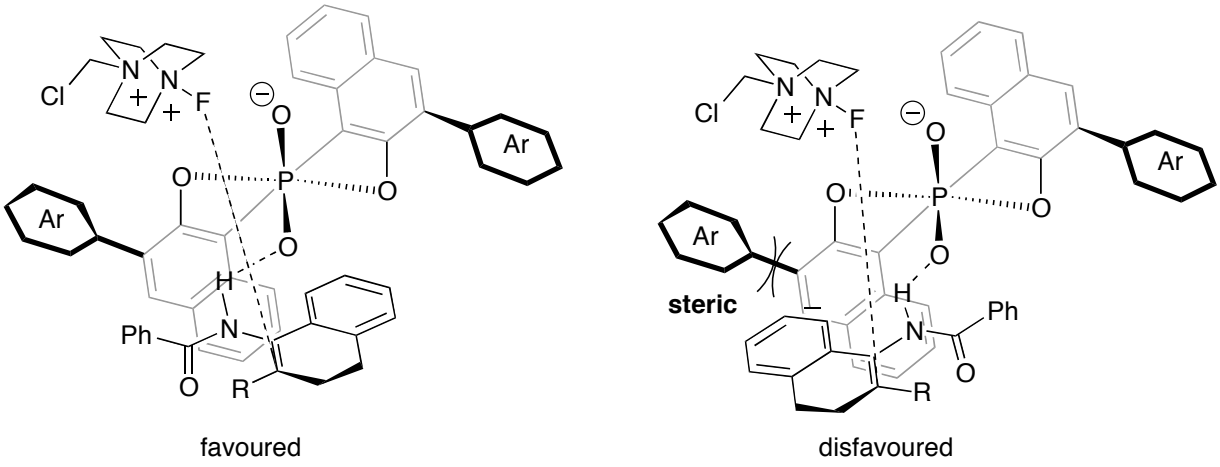
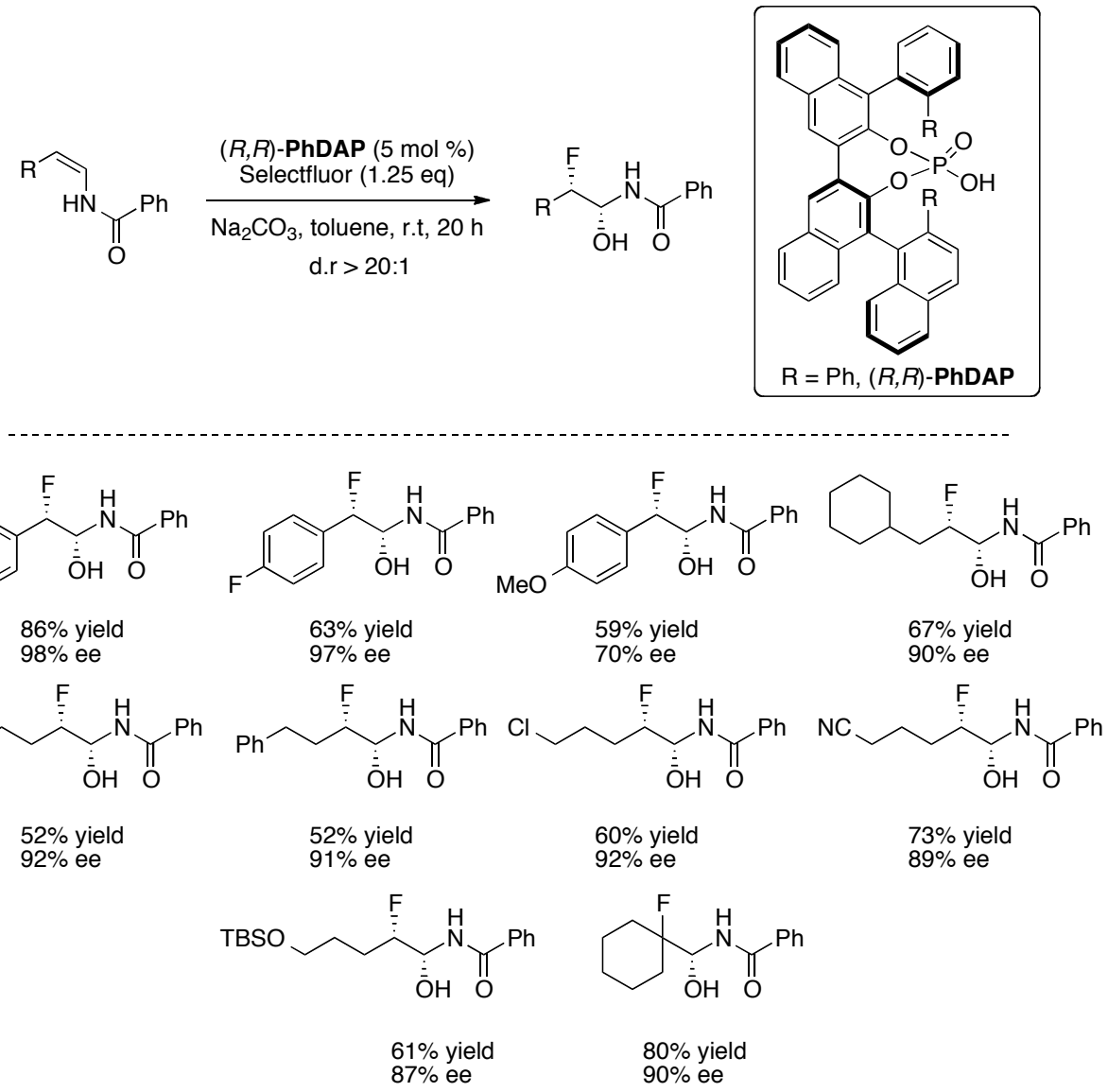


Figure 1.10 Postulated transition state for observed absolute stereochemistry

Recently, Toste developed an enantioselective tandem oxyfluorination of enamides, taking advantage of the ability of a chiral phosphoric acid catalyst to control both fluorination, through a chiral anion phase-transfer strategy, as well as addition to the resulting imine, most likely through a hydrogen-bonding mechanism.[55] In order to access the highest enantioselectivities in this process a catalyst possessing double axial chirality was used (Scheme 1.14).

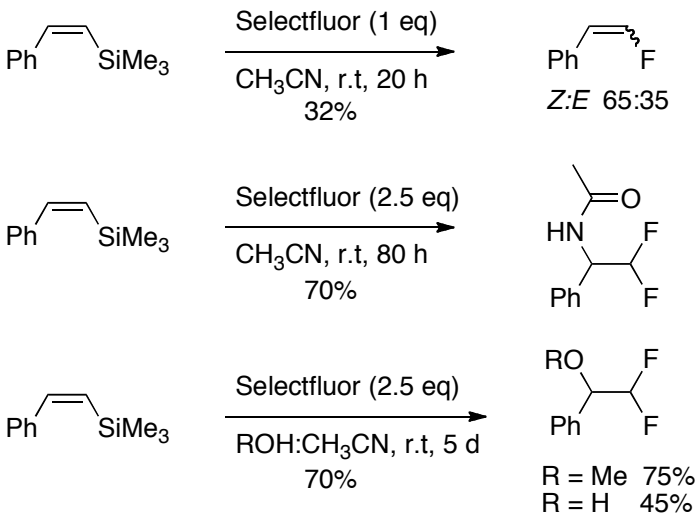


Scheme 1.14 Asymmetric oxyfluorination of enamides

1.3.2.4 Fluorination of Organosilane/Stannane Compounds

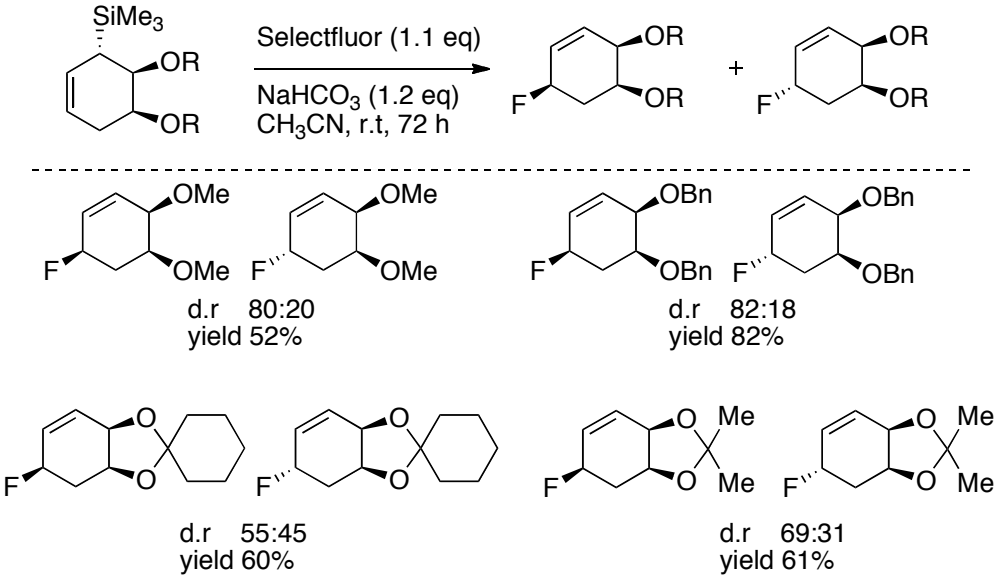
1.3.2.4.1 Organosilanes

Gouverneur *et al.* reported the fluorination of vinyl silanes with Selectfluor (Scheme 1.15).[56] The use of 1 equivalent of Selectfluor led to fluoroalkene products. In the presence of 2.5 equivalents of Selectfluor in acetonitrile, a Ritter-type reaction occurred resulting in the formation of α,α-difluoro-substituted products. Furthermore, the addition of methanol or water to the reaction mixture led to the incorporation of alcohol and ether groups in the products.



Scheme 1.15 Formation of fluoroalkenes and difluoromethyl-substituted amides, alcohols or ethers

Gouverneur and co-workers studied the electrophilic fluorodesilylation of various endocyclic allylsilanes (Scheme 1.16).[57] These reactions afforded fluorinated carbocycles featuring allylic fluorides in moderate to good yields. The fluorinations were regioselective and gave products resulting from transposition of the double bond.



Scheme 1.16 Diastereoselective synthesis of fluorinated cyclitols

Gouverneur suggested that the approach of the fluorinating reagent took place preferentially *anti* to the silyl group as expected for these bimolecular electrophilic substitutions. Assuming

cyclohexene adopts a half-chair conformation **A**, with the silyl group on the pseudo-equatorial position, the preferential stereochemical outcome is the result of an axial addition of Selectfluor taking place *anti* to the silyl group (Figure 1.11). This approach is hampered by an 1,3-diaxial interaction with the methoxy group, leading to erosion of *anti* stereospecificity. If the ring adopts the alternative inverted conformation, which features a pseudo-axial silyl group **B**, with the reagent approaching the double bond axially, the attack is *syn* to the large silyl group with concomitant unfavourable steric interactions. Thus, this approach led to the minor diastereomer.

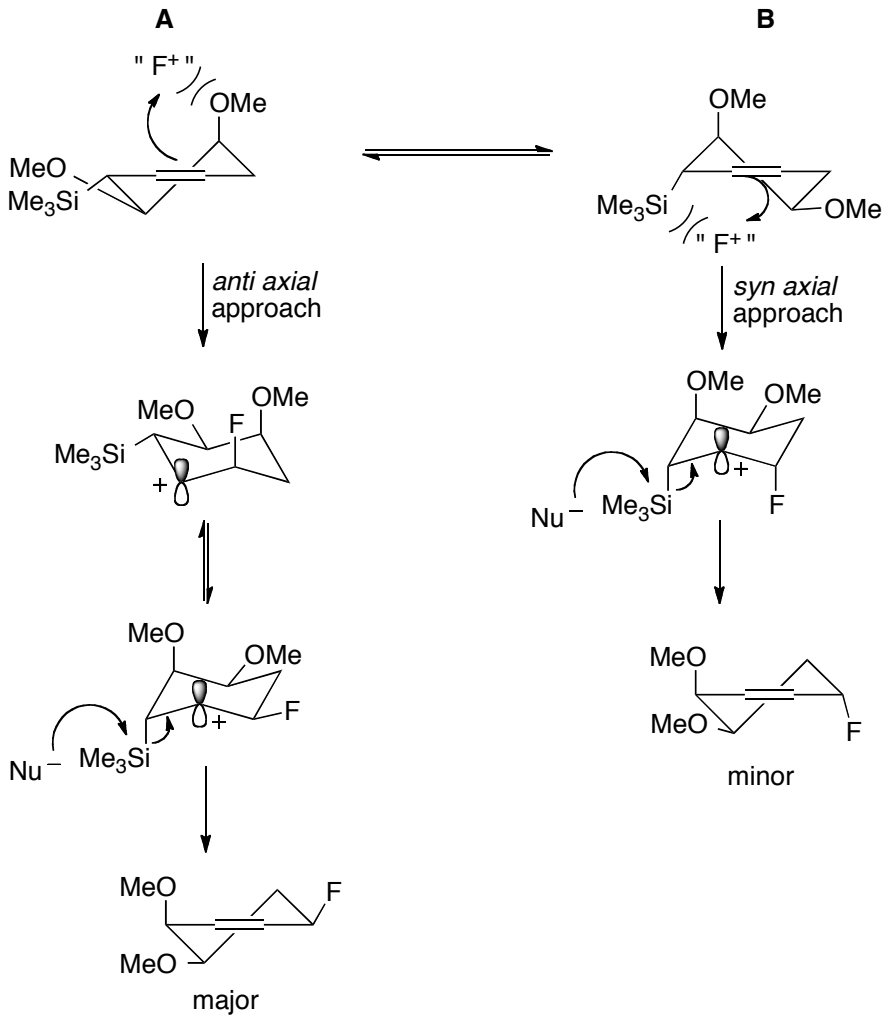
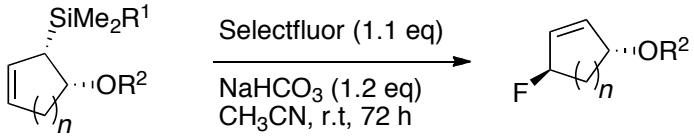


Figure 1.11 Proposed stereochemical pathway

Furthermore, Gouverneur developed an efficient approach to enantioenriched fluorinated carbocycles featuring an endocyclic allylic fluoride functional group, by electrophilic

fluorodesilylation of the corresponding allylsilanes with chemical yields up to 90% (Table 1.3).[58] For the *syn*-allylsilanes under investigation, the chirality transfer upon fluorination was highly efficient and proceeded preferentially *anti* with respect to the silyl group.

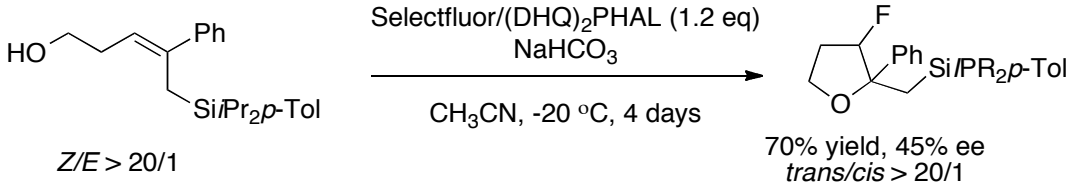


Entry	R^1	R^2	*n*	Yield (%)	dr	ee (%)
1	Me	Bz	1	76	> 98:2	86
2	Ph	Bz	1	56	> 98:2	80
3	Me	Bz	2	75	> 98:2	83
4	Ph	Bz	2	75	> 98:2	77
5	Me	Ac	2	90	92:8	-
6	Ph	Ac	2	69	94:6	-

Table 1.3 Electrophilic fluorination of cyclic *syn*-β-hydroxysilanes

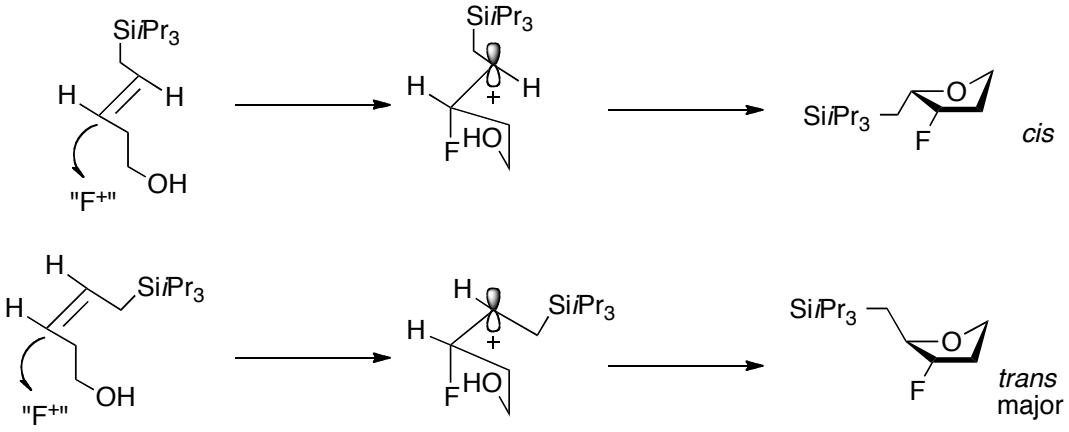
Gouverneur validated a diastereoselective fluorination of silylated 1,2-oxazines to access fluorinated *N*,*O*-heterocycles bearing up to three stereogenic centres, of which one is fluorinated. [59] Gouverneur also reported a general and concise strategy leading to enantioenriched fluorinated carbocycles relying on a catalytic asymmetric Diels–Alder reaction of silylated dienes followed by a highly regio- and stereoselective electrophilic fluorination of the silylated adducts.[60]

In 2009, Gouverneur and co-workers developed the first example of an asymmetric fluorocyclisation that proceeds through a cascade fluorination–ring-closure process (Scheme 1.17).[61]



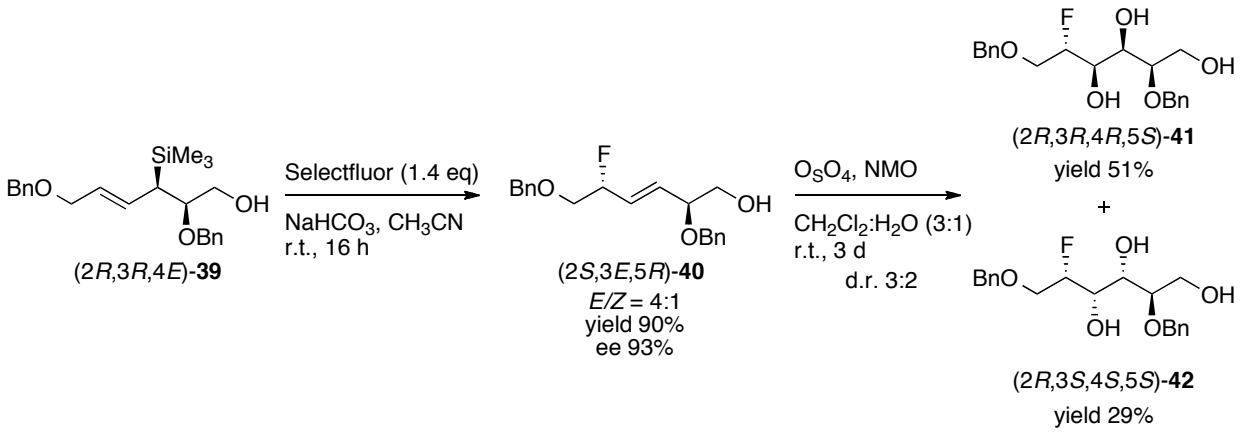
Scheme 1.17 Enantioselective fluorocyclization of allyl silanes

In the reactive conformation of the allyl silanes, the C-Si bond is presumably aligned parallel to the empty *p*-orbital of the carbocation intermediate to enable σ–p hyperconjugative stabilization. Subsequent cyclization through the addition of the alcohol to the β-silyl cation occured preferentially *anti* to the bulky silyl group (Scheme 1.18).



Scheme 1.18 Predominant *syn* addition in the fluorocyclization.

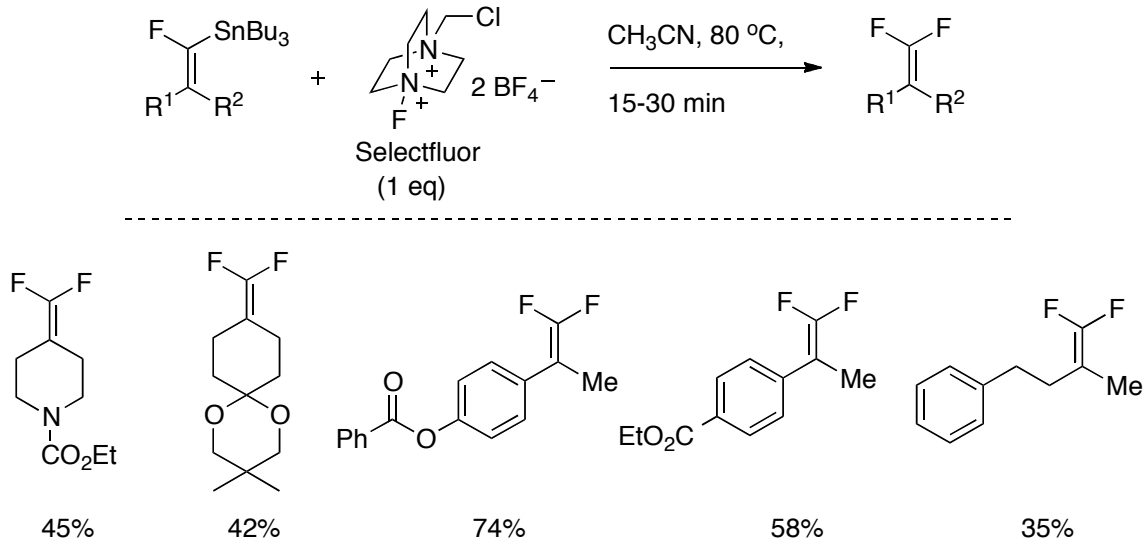
Gouverneur *et al.* recently validated the first asymmetric *de novo* synthesis of three fluorinated carbohydrate analogues starting from functionalised enantioenriched acyclic allylsilanes.[62] They first validated the synthesis of glucitol derivatives using Selectfluor as an electrophilic fluorinating reagent in the fluorodesilylation step and followed by dihydroxylation of the resulting allylic fluorides (Scheme 1.19). The fluorodesilylation step proceeded with the approach of Selectfluor *anti* with respect to the silyl group (*anti*-S_E2' mechanism).



Scheme 1.19 Synthesis of fluorinated carbohydrate analogues **41** and **42**

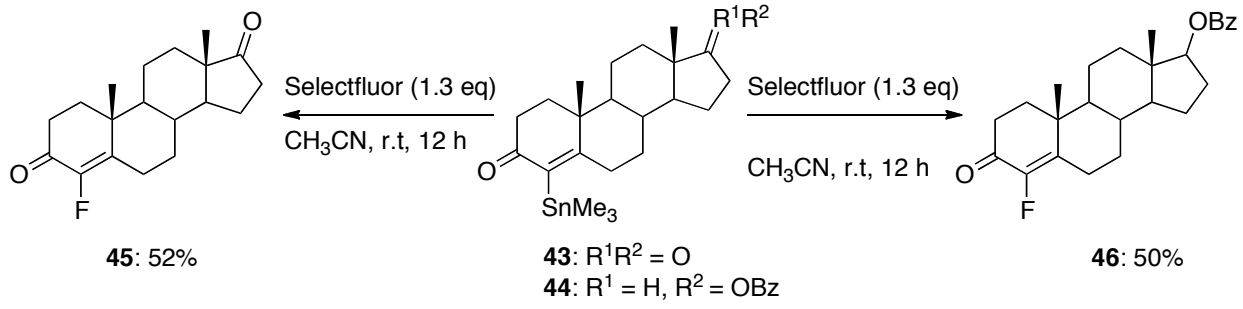
1.3.2.4.2 Organostannanes

McCarthy *et al*. reported the electrophilic fluorination of vinyl stannanes with Selectfluor (Scheme 1.20).[63] The conversion of (fluorovinyl)stannanes to vinyl difluorides in the presence of 1 equivalent of Selectfluor proceeded in acetonitrile at 80 °C in moderate to good yields.



Scheme 1.20 Fluorination of stannanes

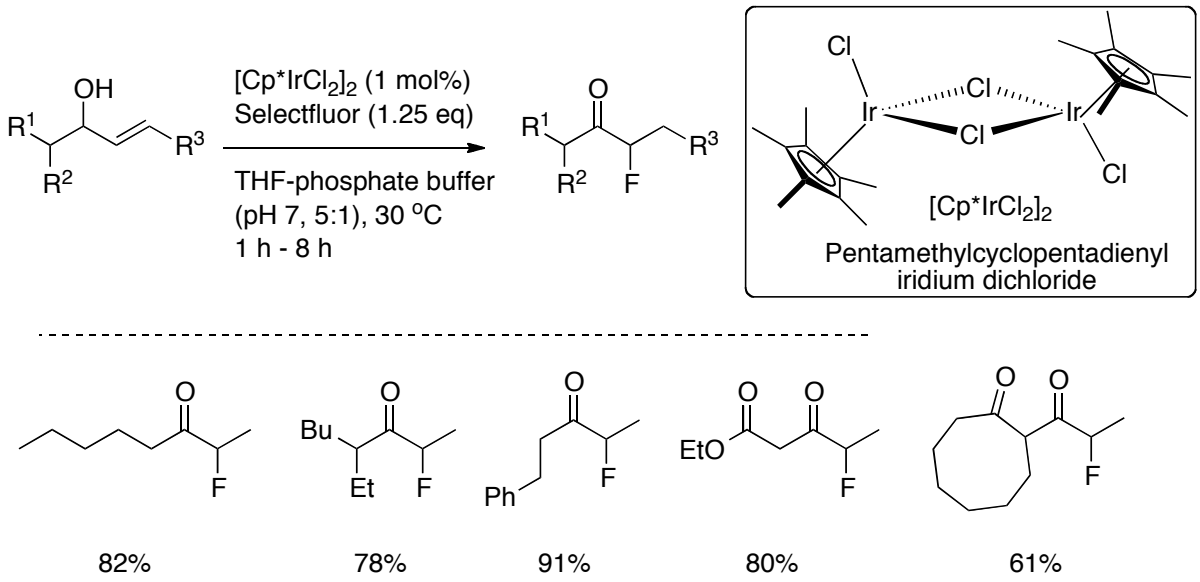
Widdowson *et al*. applied this strategy to steroid derivatives containing vinyl stannane groups to prepare fluorinated steroid products (Scheme 1.21).[64] The fluorination of trimethylstanny-landrostenedione **43** and benzoyltrimethylstannyltestosterone **44** with Selectfluor in acetonitrile at room temperature provided the fluoro derivatives **45** and **46** in 52% and 50% yield.



Scheme 1.21 Conversion of vinyl stannane into fluorides

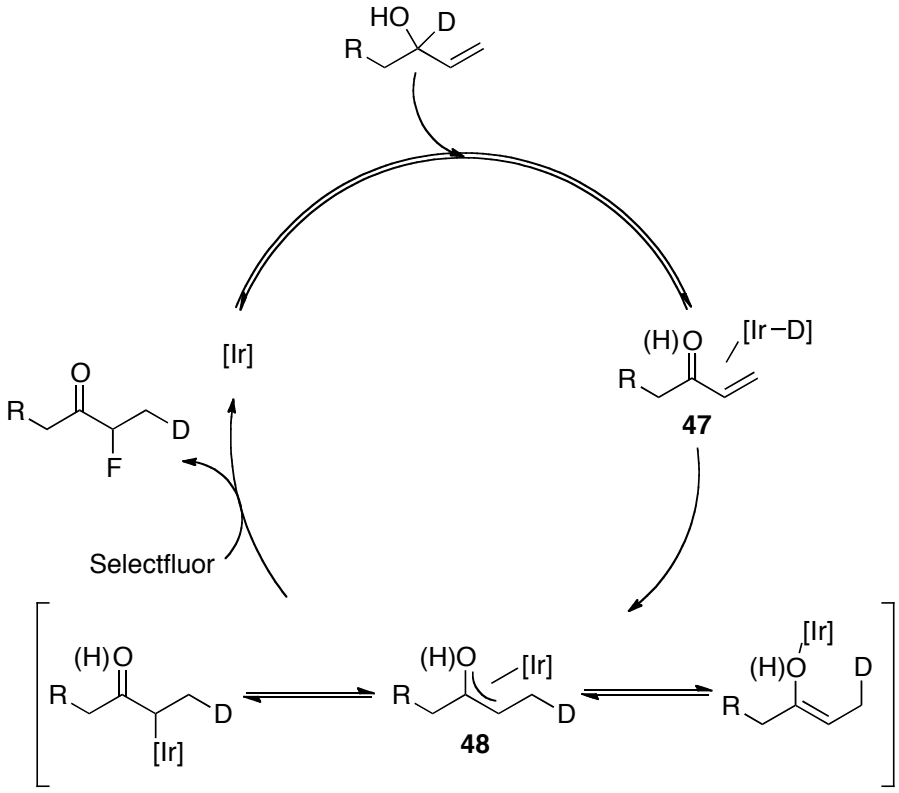
1.3.2.5 Fluorination of Allylic Alcohols

Recently, Martín-Matute *et al*. reported the iridium-catalyzed tandem fluorination reaction of allylic alcohols using Selectfluor.[65] The reaction of various allylic alcohols with Selectfluor in THF in the presence of 1 mol % of $(IrCp^*Cl_2)_2$ (Cp* = 1,2,3,4,5-pentamethylcyclopentadiene) provided two regioisomeric products (Scheme 1.22).



Scheme 1.22 Fluorination of allylic alcohol compounds

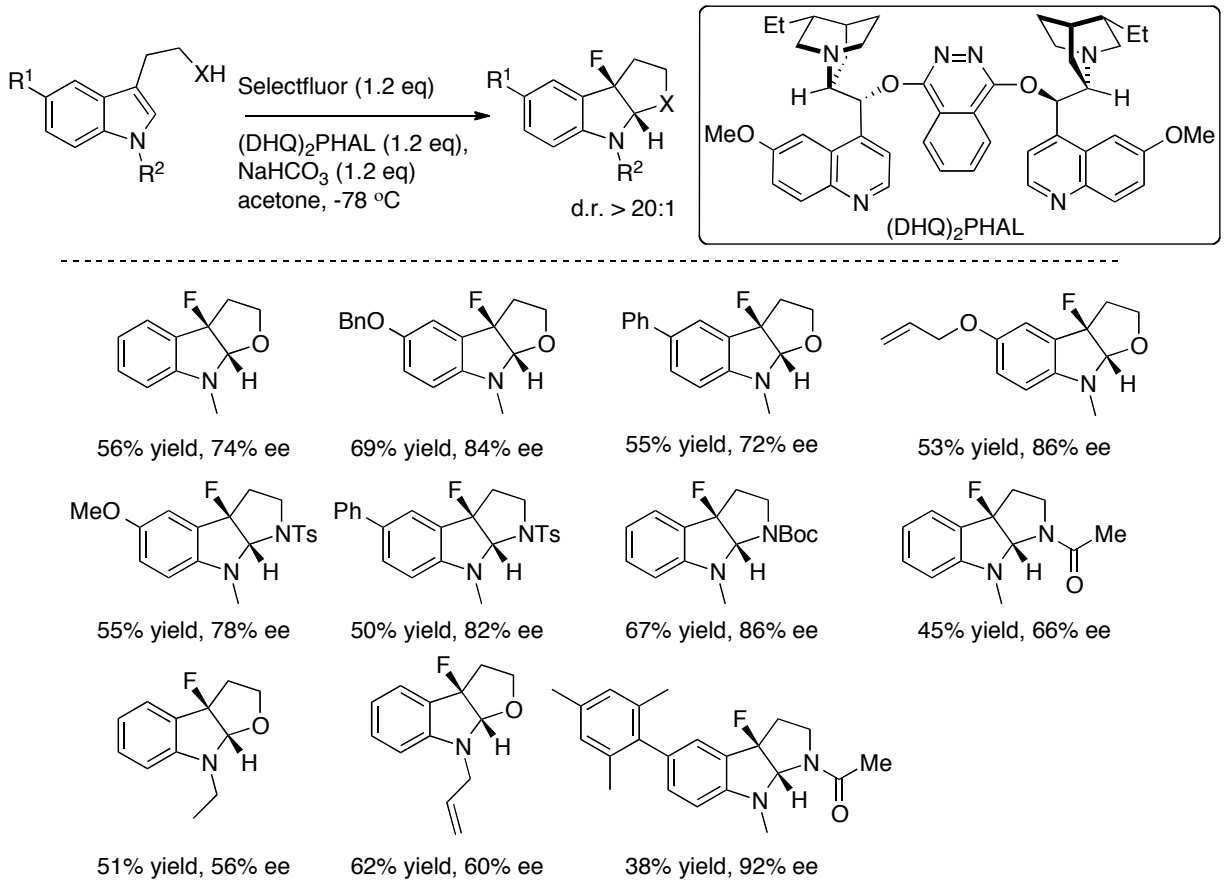
A mechanism based on deuterium labeling studies and cross-over experiments was proposed (Scheme 1.23). The first step involves the oxidation of the allylic alcohol to the corresponding α,β-unsaturated carbonyl compound **47**. An iridium-hydride complex is formed, which forms an enolate intermediate **48**. In the last step, the iridium enolate reacts with Selectfluor to give the α-fluoro ketone.



Scheme 1.23 Proposed mechanism based on deuterium labeling studies

1.3.2.6 Fluorination of Indole Derivatives

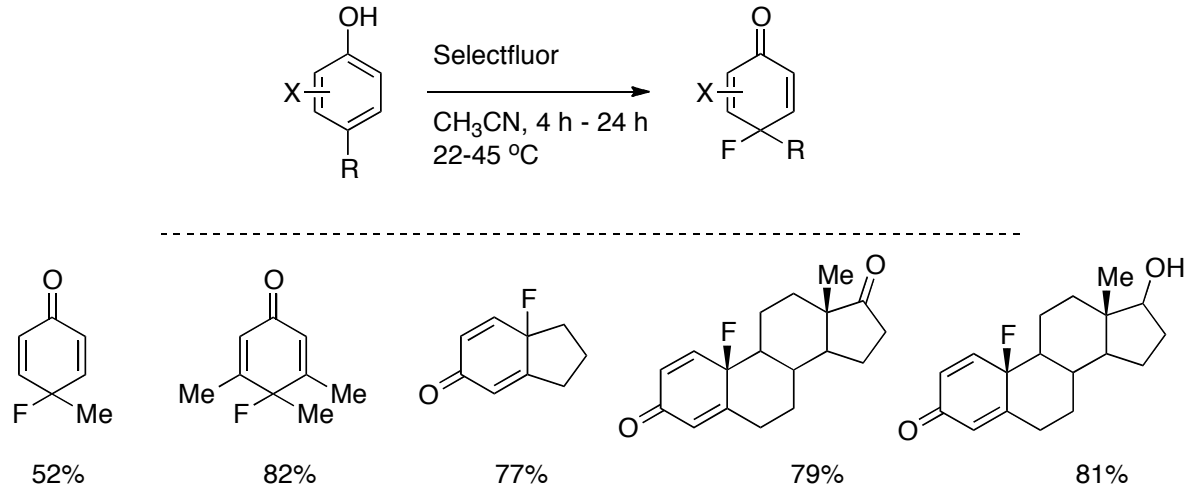
Recently, Gouverneur and co-workers reported the first organocatalytic route to enantioenriched fluorinated heterocycles induced by Selectfluor or *N*-fluorobenzenesulfonimide (NFSI).[66] The process installed the fluorine substituent on a quaternary benzylic stereogenic carbon center and led to new fluorinated analogues of natural products featuring the hexahydropyrrolo[2,3-*b*]indole or the tetrahydro-2*H*-furo-[2,3-*b*]indole skeleton (Scheme 1.24).



Scheme 1.24 Enantioselective fluorocyclization of prochiral indoles

1.3.2.7 Fluorination of Aromatic Compounds

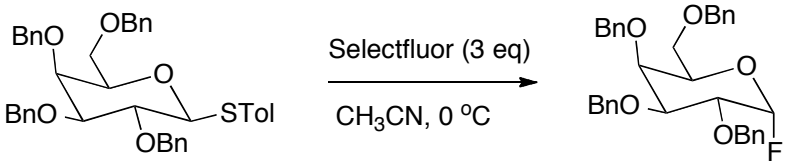
Selectfluor has proven to be a competent reagent for the fluorination of substituted aromatic systems. Although benzene was unreactive towards Selectfluor, aromatic compounds with an electron-donating group in the ring were found to be reactive under appropriate conditions.[45] Stavber has also utilized Selectfluor in the direct synthesis of 4-fluorocyclohexa-2,5-dienone and 10-fluoroestradiene-3-one derivatives (Scheme 1.25).[67]



Scheme 1.25 Fluorination of various substituted aromatic compounds

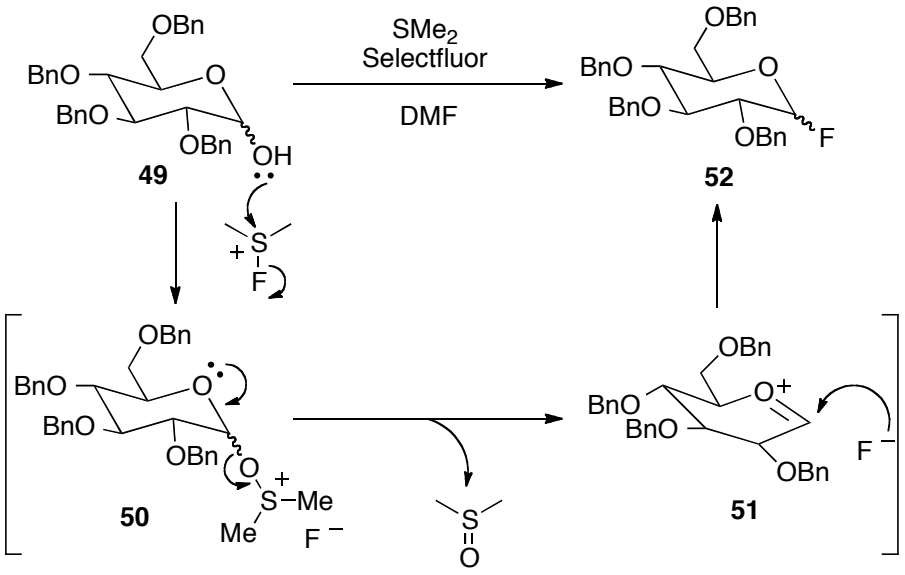
1.3.2.8 Fluorination of Thioglycoside Compounds

Fluorinated carbohydrates are important since the fluorine substituent may affect hydrogen-bonding interactions while maintaining key structural features of the parent compounds. For example glycosyl fluorides are widely used in carbohydrate chemistry and biochemistry.[68] Wong and co-workers have reported one-pot syntheses of 2-deoxy-2-fluoro sugars and their glycosides from glycals using Selectfluor in the presence of nucleophiles.[69] This methodology has been further extended to the synthesis of glycosyl fluorides and glycosides from anomeric hydroxy or thioglycoside derivatives (Scheme 1.26).



Scheme 1.26 Synthesis of glycosyl fluorides

Furthermore, Wong used a one step strategy to access glycosyl fluorides directly from anomeric hemiacetals using the reagent combination of Selectfluor and dimethylsulfide (Scheme 1.27).[46,69] The reaction proceeded through a fluorosulfonium ion which then reacts with the anomeric hydroxy group of the sugar **49** followed by displacement of the sulfoxide by fluoride.



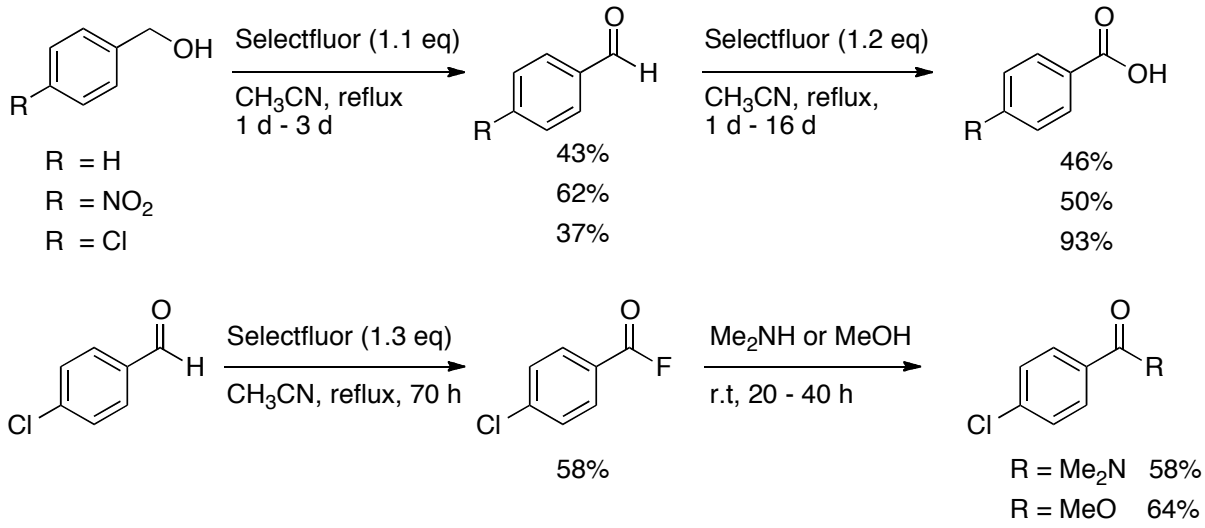
Scheme 1.27 Conversion of 1-hydroxy sugars to glycosyl fluorides

1.3.3 Selectfluor in Reactions other than Fluorination

Selectfluor serves as a strong oxidant, a property that is useful in other reactions in organic chemistry.[70]

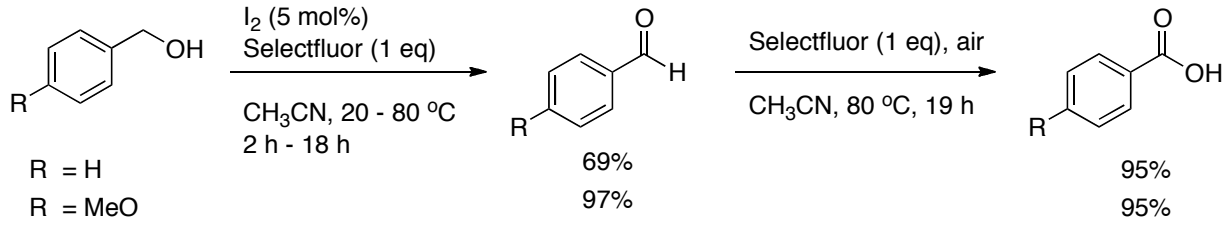
1.3.3.1 Oxidation of Alcohols and Carbonyl Compounds

In the presence of oxidizing agents, hydroxyl or aldehyde functional groups can often be transformed to various kinds of carbonyl functionalities. Banks *et al*. exploited the oxidative properties of Selectfluor for the synthesis of benzaldehyde derivatives from benzylic alcohols in moderate yields (Scheme 1.28).[71] They subsequently oxidized benzaldehyde derivatives to the corresponding benzoic acids in good to excellent yields, a transformation occuring *via* a benzoyl fluoride intermediate (Scheme 1.28). The isolation of the benzoyl fluorides intermediates proved difficult owing to hydrolysis but was achieved in the case of *p*-chlorobenzoyl fluoride then derivatised with dimethylamine or methanol. The reaction most likely proceeds through radical fluorination at the benzylic position initiated by a single-electron transfer (SET), followed by the rapid loss of HF to yield the aldehyde product.



Scheme 1.28 Oxidation of alcohols and aldehydes

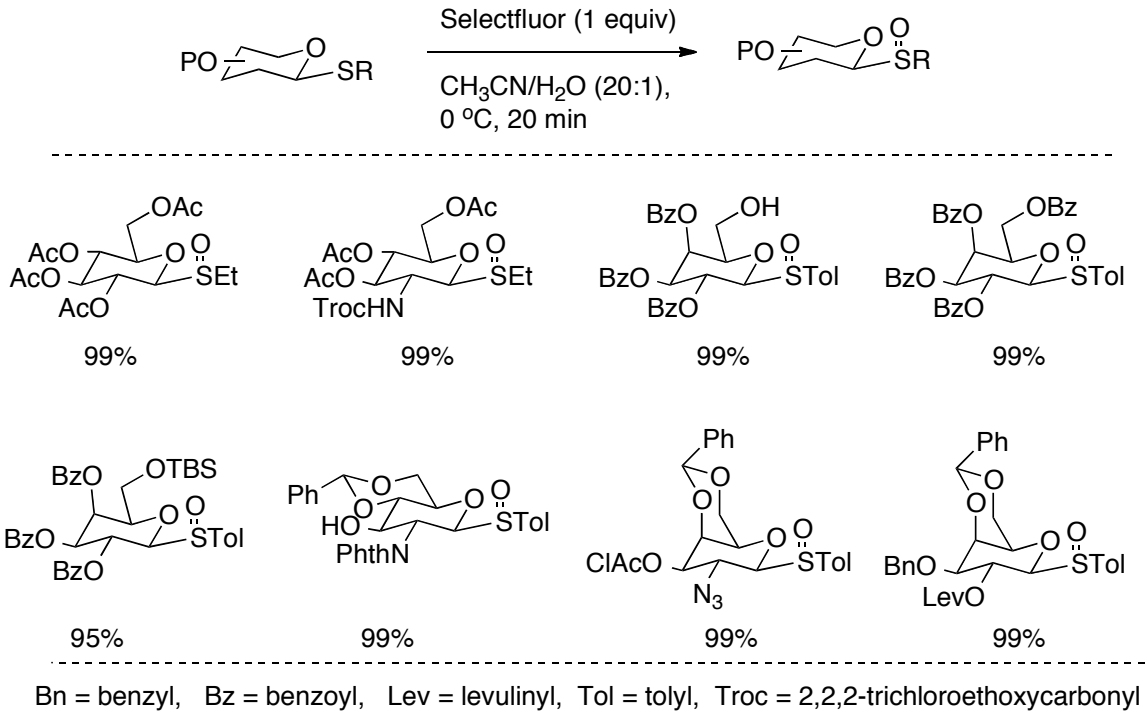
On the other hand, Stavber *et al*. improved considerably this protocol and its efficiency using catalytic amounts of molecular iodine. Thus primary benzylic alcohols and aldehydes were found to be relatively reactive towards Selectfluor in the presence of catalytic amounts of iodine (Scheme 1.29).[72]



Scheme 1.29 Stavber oxidation of alcohols and aldehydes

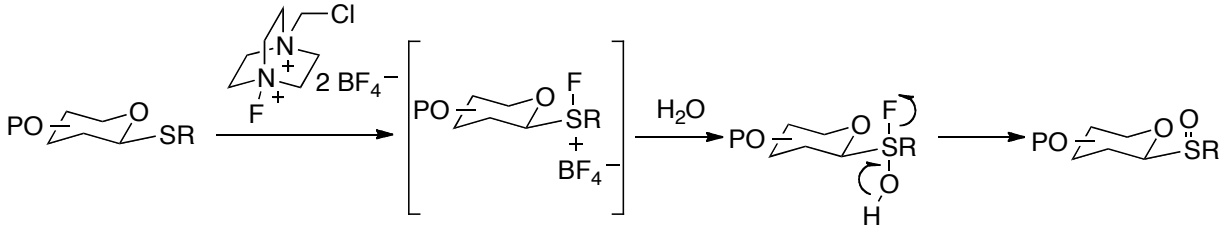
1.3.3.2 Oxidation of Thioethers

Wong and co-workers reported the conversion of thioglycosides into the corresponding sulfoxides. Selectfluor in CH_3CN-H_2O (20:1) could oxidize thioglycosides to the corresponding sulfonyl glycosides. Quantitative yields (> 95%) were observed for all substrates examined (Scheme 1.30).



Scheme 1.30 Oxidation of thioglycoside to sulfoxide

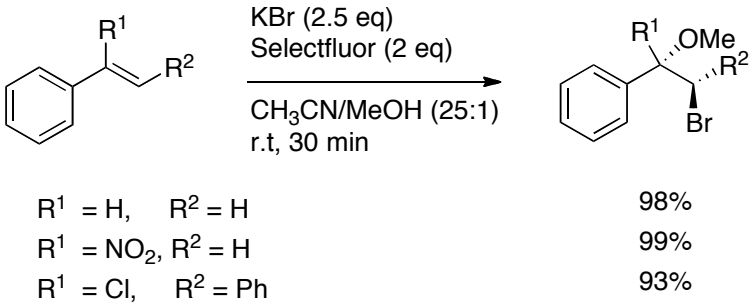
Wong suggested that the reaction proceeded through a fluorosulfonium cation, which reacted with water to give the sulfoxides (Scheme 1.31).



Scheme 1.31 Mechanism of oxidation of thioglycoside to sulfoxide

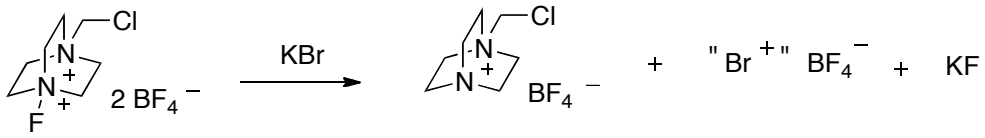
1.3.3.3 Oxidation of Olefins

Shreeve performed various oxidative brominations of different types of olefins using Selectfluor/KBr combination affording addition, monobromo-substituted, or Hunsdiecker-Borodin reaction products in good yields (Scheme 1.32).[73]



Scheme 1.32 Direct bromination of olefins with Selectfluor and potassium bromide

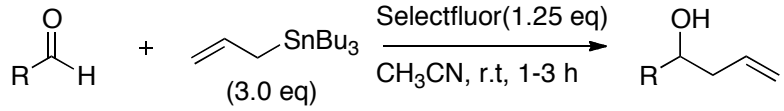
The mechanism pathway below was proposed to account for the oxidative bromination (Scheme 1.33)



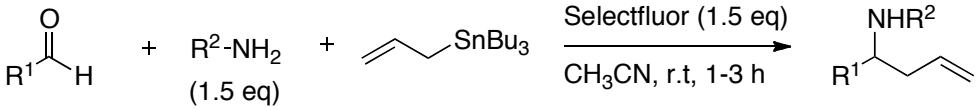
Scheme 1.33 Oxidation of bromine with Selectfluor

1.3.3.4 Selectfluor-Mediated Allylstannation of Aldehydes and Imines

Wong *et al*. reported an application of Selectfluor as a promoter for the allylstannation of aldehydes and imines.[74] Reactions of aldehydes and imines with allyltributyltin, mediated by Selectfluor in acetonitrile, gave homoallylic alcohols and amines respectively in good to excellent yields (Scheme 1.34). The reactions of aldehydes in the presence of tributyl(vinyl)stannane proceeded to completion within hours when a stoichiometric amount of Selectfluor was used. However, using a catalytic amount of Selectfluor (0.05 equivalent) required longer reaction times (24 hours) and yields were lower (~ 60% conversion). In the absence of Selectfluor no product formation was observed. Although the mechanism for this transformation is not well understood, Wong speculated that Selectfluor might act as a Lewis acid to activate the aldehyde for nucleophilic addition. The effective Lewis acid may also be the tri-*n*-butyltin cation, formed in conjunction with allyl fluoride from the reaction between allyl(tri-*n*-butyl)tin and Selectfluor.



R = $PhCH=CH_2$	93%
R = 1-Naphthyl	90%
R = 1-Hydroxy-Ph	86%

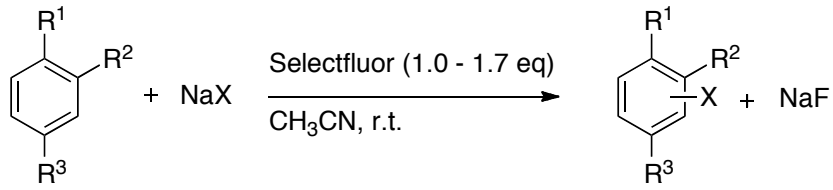


$R^1 = PhCH=CH_2$, $R^2 = p\text{-}NO_2\text{-}C_6H_4$	73%
R^1 = 1-Naphthyl, $R^2 = p\text{-MeO-}C_6H_4$	46%
R^1 = Ph, $R^2 = p\text{-MeO-}C_6H_4$	64%

Scheme 1.34 Allylstannation of aldehydes and imines

1.3.3.5 Selectfluor-Mediated Functionalization of Aromatic Compounds

The inherent electrophilic activity of Selectfluor has been exploited recently for the umpolung of nucleophilic compounds into electrophilic reagents. Stavber *et al*. reported direct iodination reactions of various benzene derivatives under the mediation of Selectfluor.[75,76] Selectfluor also proved useful for the conversion of common anions into electrophilic reagents. Electrophiles such as Cl^+, Br^+, SCN^+, and NO_2^+ can be generated from their respective sodium salts NaCl, NaBr, NaSCN and $NaNO_2$ using Selectfluor in acetonitrile solution at room temperature. These electrophiles subsequently react *in situ* with a variety of aromatic substrates containing one or more substituents, including H, F, Cl, CH_3, COOH, C(O)-CH_3, and NO_2 (Table 1.4).[77]



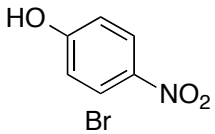
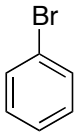
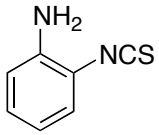
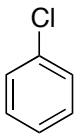
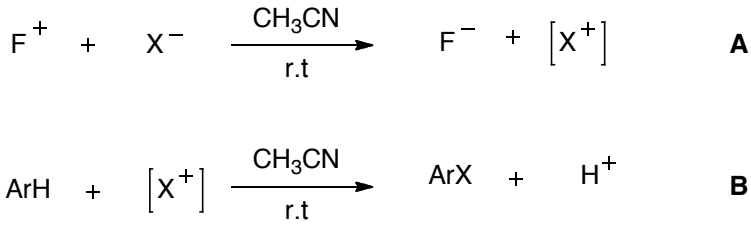
Substrate	NaX	Product	Yield [%]
Phenol	$NaNO_2$		81
Benzene	NaBr		100
Aniline	NaSCN		96
benzene	NaCl		97

Table 1.4 Electrophilic functionalization of activated benzene derivatives

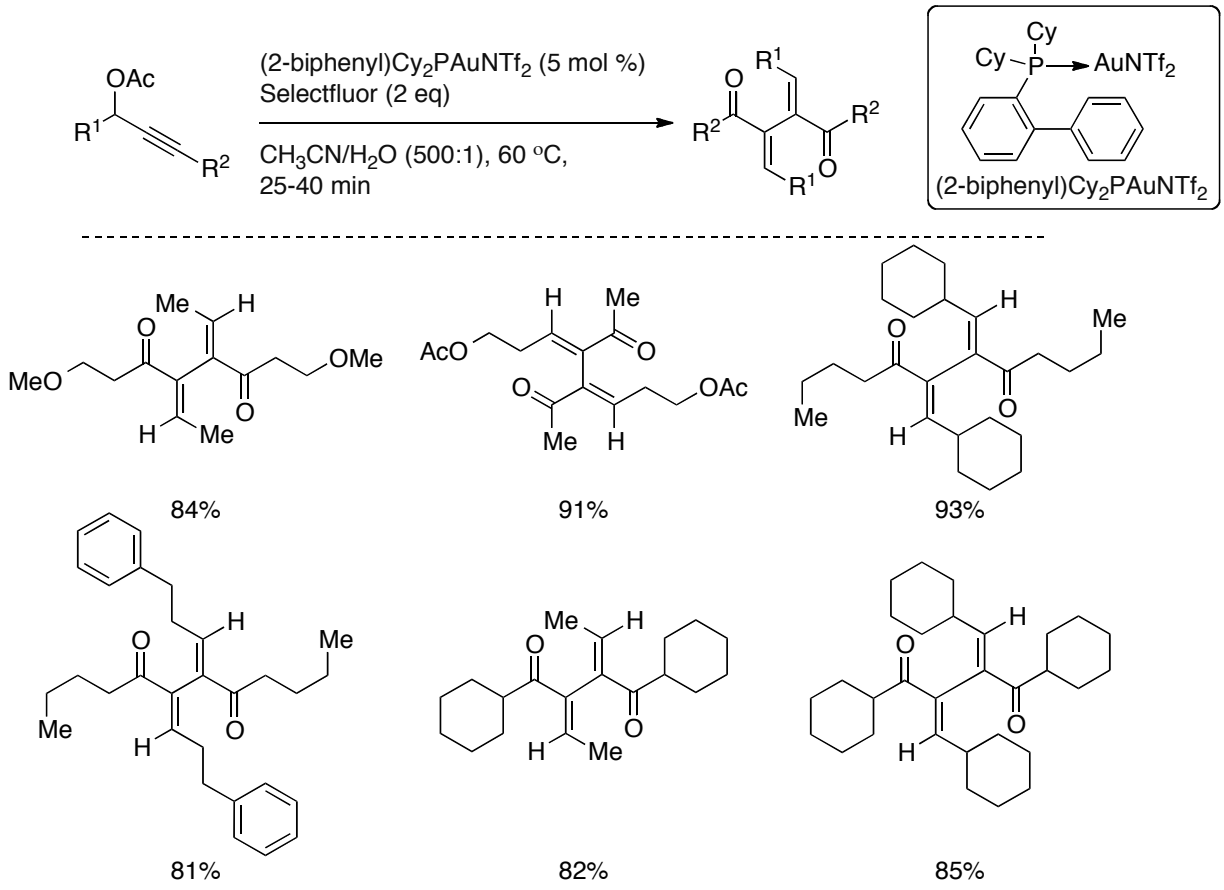
Syvret suggested that the combination of Selectfluor, represented in equation **A** by F^+, and various anions, represented by X^-, in acetonitrile at room temperature produced the equivalent of an X^+ electrophile, such that, in the presence of an aromatic substrate (ArH), electrophilic substitution of X-for-H occurred (equation **B**). [77]



Scheme 1.35 Reaction pathway

1.3.3.6 Selectfluor in Metal Oxidative Coupling Reactions

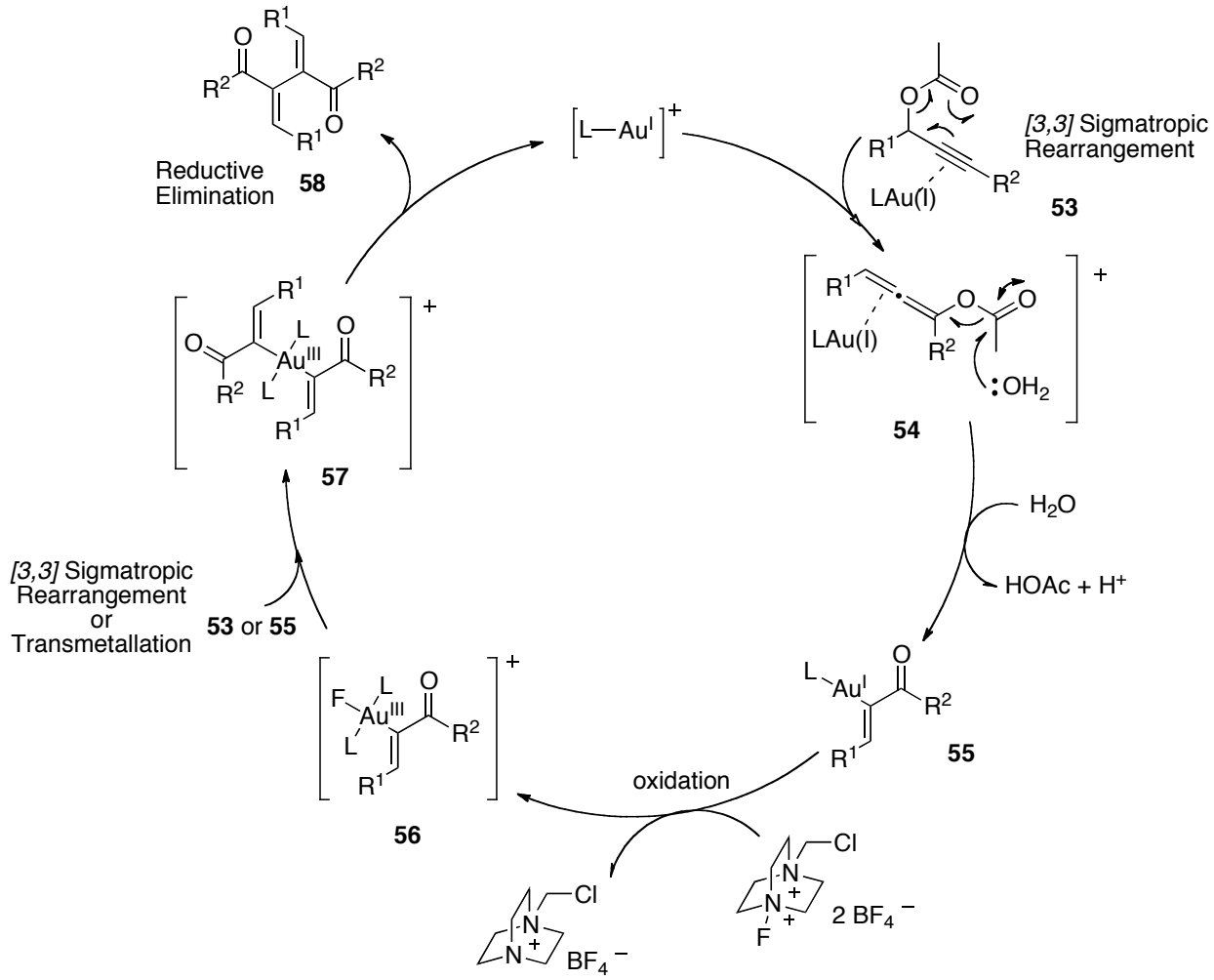
Selectfluor has recently found great utility as bystanding oxidants in the field of homogeneous gold catalysis.[78] In 2009, Zhang *et al*. reported the first gold-catalyzed oxidative cross-coupling reactions using Selectfluor as an oxidant. They successfully demonstrated that propargylic acetates with oxygen-functionalized alkyl chains on either side of the propargyl moiety undergo a Au-catalyzed homogeneous oxidative dimerization, leading to highly efficient formation of enone dimers in excellent yields (Scheme 1.36).[79]



Scheme 1.36 Gold-catalyzed oxidative dimerization of propargyl acetates

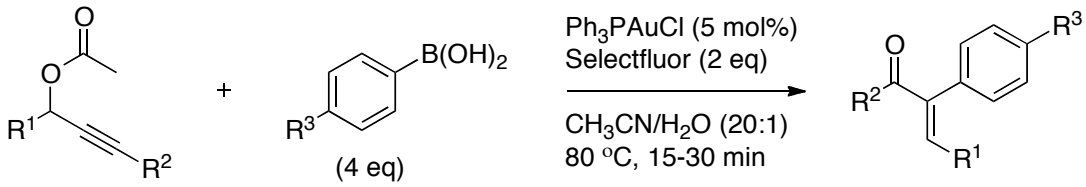
The mechanism of this highly efficient homo-coupling reaction is proposed in Scheme 1.37.[80] The cationic (phosphine)-gold(I) species coordinated to the alkyne followed by a [3,3] sigmatropic rearrangement to give the allenyl acetate intermediate **54**. Hydrolysis of **54** led to the (Z)-vinyl complex **55** upon rearrangement and loss of the acetyl group, which is then oxidized by Selectfluor to give the Au(III) species **56**. Coordination of a second enone unit to

complex **56** either by rearrangement of a second molecule of the propargyl acetate or transmetalation would lead to the diorganogold(III) complex **57**, which could then undergo reductive elimination to give dimer **58** and regenerate the gold(I) catalyst.



Scheme 1.37 Proposed reaction mechanism for the oxidative dimerization of propargyl acetates

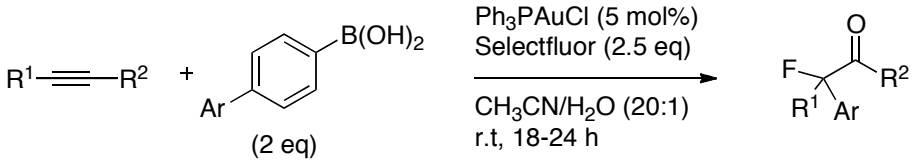
When an alternative coupling partner in the form of an arylboronic acid was added to the reaction mixture, the cascade [3,3] sigmatropic rearrangement–oxidative dimerization of propargyl acetates could be re-routed in favor of C-C cross-coupling (Table 1.5).[81] Reaction of propargylic acetates with 4 equivalents of arylboronic acids in the presence of Ph_3PAuCl (5 mol%) and 2 equivalents of Selectfluor in CH_3CN/H_2O (20:1) at 80 °C delivered (*E*)-α-arylenones as single diastereoisomers in yields up to 70%.



Entry	R^1	R^2	$ArB(OH)_2$	Yield (%)
1	Ph	*n*-butyl	$PhB(OH)_2$	62
2	*i*Ph	*n*-butyl	$PhB(OH)_2$	65
3	Me	Ph	$PhB(OH)_2$	59
4	Me	$MeOCH_2CH_2$	$PhB(OH)_2$	60
5	Ph	*n*-butyl	$PhB(OH)_2$	62
6	cyclohexyl	cyclohexyl	$PhB(OH)_2$	70
7	$PhCH_2CH_2$	*n*-butyl	$PhB(OH)_2$	70
8	cyclohexyl	*n*-butyl	*p*-$MePhB(OH)_2$	72
9	cyclohexyl	*n*-butyl	*p*-$MeO_2PhB(OH)_2$	57
10	cyclohexyl	*n*-butyl	*p*-$ClPhB(OH)_2$	58

Table 1.5 Gold-catalyzed oxidative cross-coupling of arylboronic acids

A similar gold-catalyzed cascade nucleophilic addition-oxidative arylation reaction using arylboronic acids in the presence of Selectfluor was reported by Hammond and Xu.[82] Functionalized and unfunctionalized internal alkynes reacted with aryl boronic acids, giving very good yields of α-substituted ketones, with moderate regioselectivity (Table 1.6).



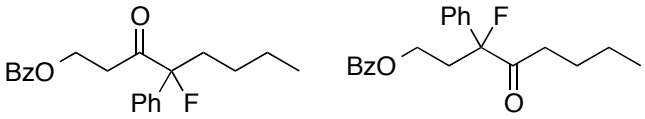
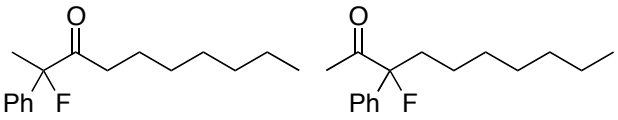
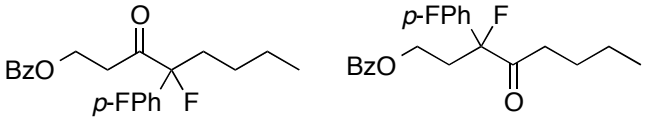
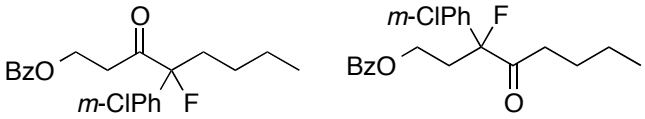
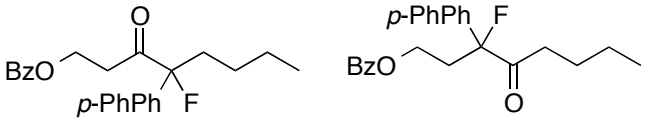
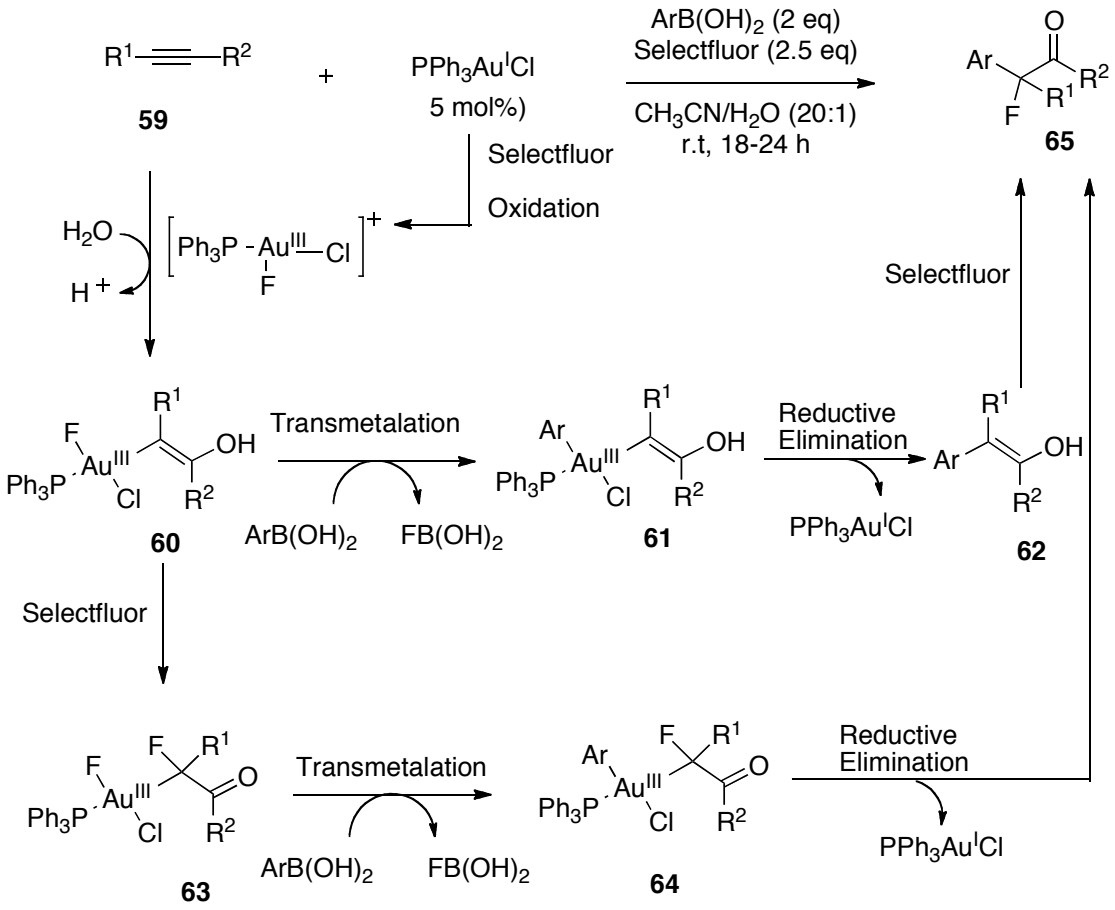
Entry	$ArB(OH)_2$	Products	Yield (ratio)
1	$PhB(OH)_2$		88% (6.7:1)
2	$PhB(OH)_2$		85% (2.2:1)
3	$PhB(OH)_2$		47% (2.1:1)
4	*p*-$FPhB(OH)_2$		88% (5.3:1)
5	*m*-$ClPhB(OH)_2$		71% (3.4:1)
6	*p*-$PhPhB(OH)_2$		90% (5.3:1)

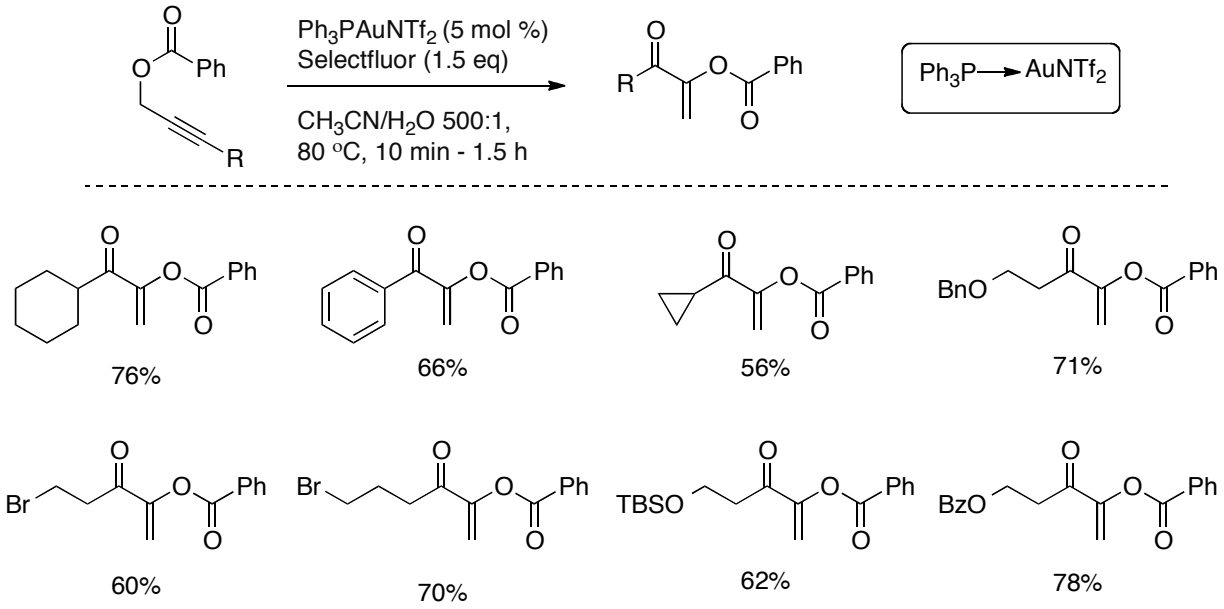
Table 1.6 Gold-catalyzed cascade nucleophilic addition-oxidative arylation.

The suggested mechanism begins with water attacking the gold-activated alkyne to form a vinyl–gold complex **60**; this species then reacts with $ArB(OH)_2$ through a transmetalation process, to give intermediate **61**. Reductive elimination of **61** gave **62**, which was fluorinated by Selectfluor to give the functionalized ketone **65** (Scheme 1.38). Hammond and Xu believed that the strong B-F bond and the weak Au-F bond are the driving forces behind the transmetalation step. Alternatively, it is also possible that intermediate **60** reacted with Selectfluor first to give **63**, and following transmetalation and reductive elimination, gave the final product **65**.



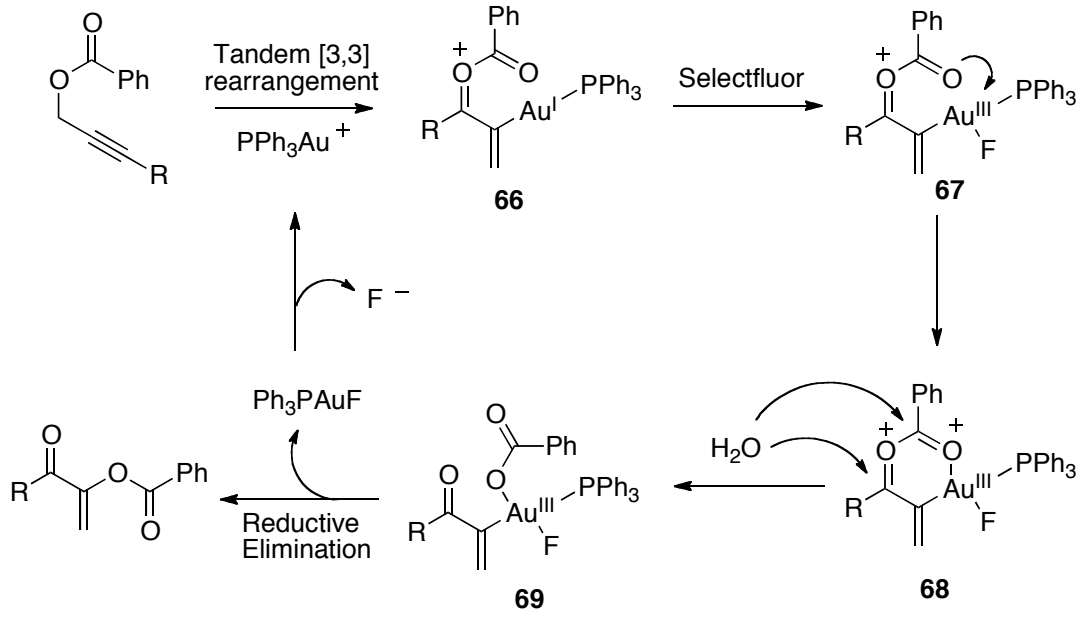
Scheme 1.38 Cascade hydration–oxidative arylation–fluorination of alkynes

Furthermore, Zhang reported a Au-catalyzed homogeneous oxidative C-O bond-forming reaction.[83] The reaction of benzoates with various substituents at the alkyne terminus, such as cyclohexyl, phenyl, cyclopropyl including a range of functional groups including protected OH groups and bromide afforded benzoxyvinyl ketones in moderate to good yields (Scheme 1.39).



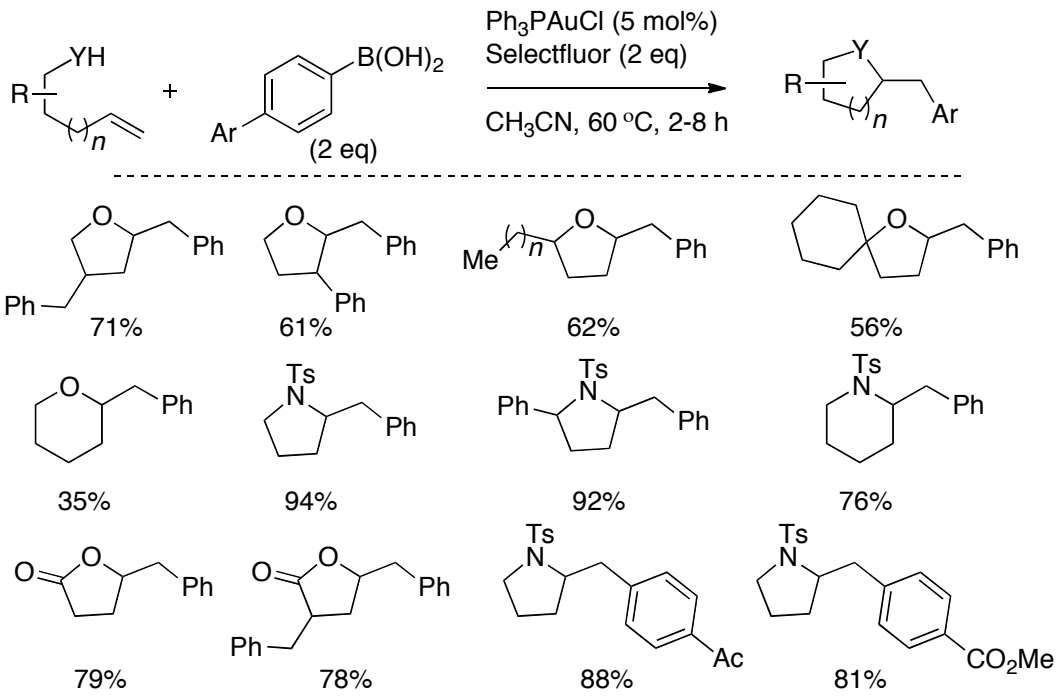
Scheme 1.39 Formation of 1-benzoxyvinyl ketones

The mechanism of this reaction is proposed in Scheme 1.40. The cationic Au(I) complex first catalyzes tandem transformations of propargylic benzoates, leading to the formation of Au-containing oxocarbenium intermediate **66**. The Au(I) complex **66** is oxidized by Selectfluor to afford Au(III) complex **67**. Subsequent cyclization of the benzoxy group in **67** to its cationic Au(III) center forms cyclic Au(III) complex **68** and thus initiates an intramolecular migration of the benzoxy group. Hydrolysis of **68** completes the benzoxy migration and affords intermediate **69**, which undergoes facile reductive elimination to yield 1-benzoxyvinyl ketones.



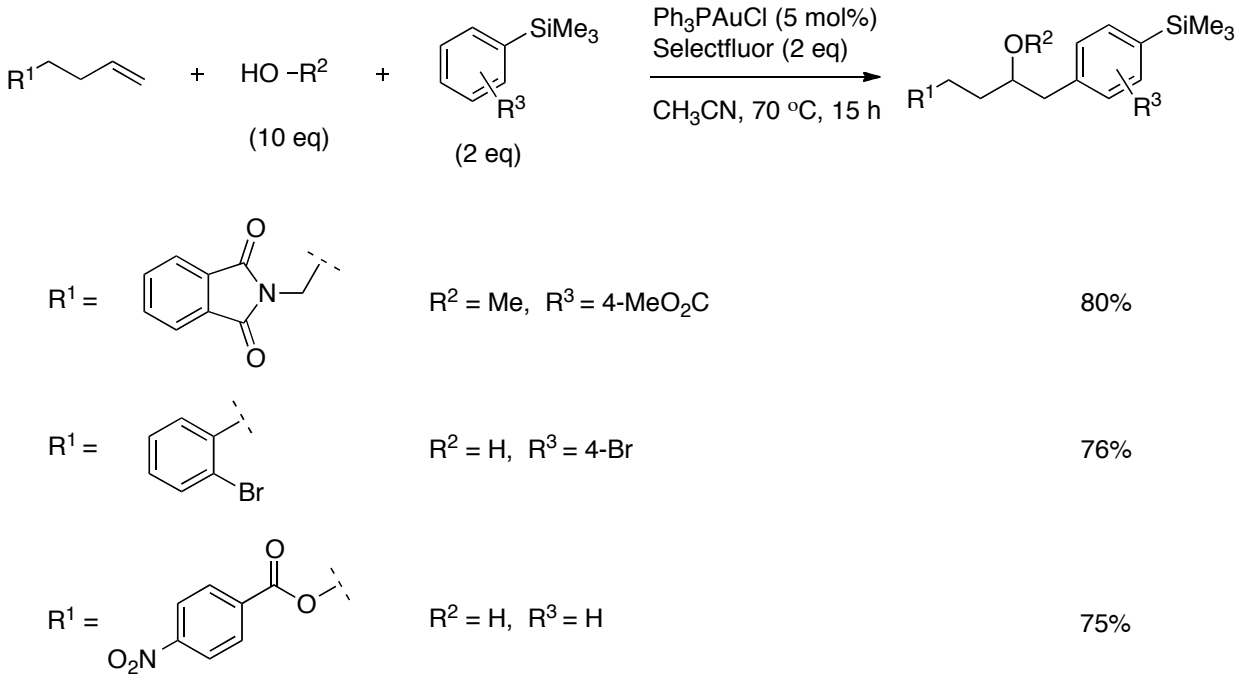
Scheme 1.40 Mechanism of formation of benzoxyvinyl ketones

Zhang also reported an efficient gold-catalyzed oxidative functionalization that follows a nucleophilic addition to alkenes. Substituted pent-4-en-1-ols, including secondary and tertiary alcohols, yielded various tetrahydrofurans (Scheme 1.41).[84] Tosylamides were better substrates and various pyrrolidine products were isolated in excellent yields. This chemistry also provided access to piperidines, γ-lactones and pyrrolidines in moderate to good yields.



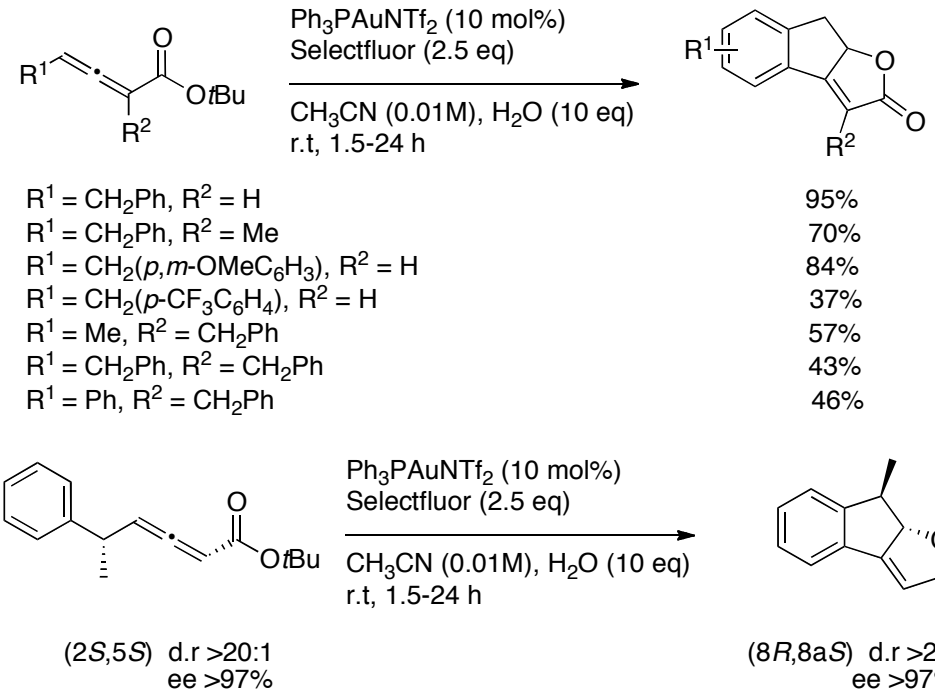
Scheme 1.41 Gold-catalyzed homogeneous oxidative carboheterofunctionalization of alkenes

Russell *et al*. demonstrated that arylsilanes could be employed in gold-catalyzed oxyarylation reactions with Ph_3PAuCl and Selectfluor, affording the products of two- and three-component coupling in generally good to excellent isolated yields.[85] The dual role of Selectfluor as both an oxidant and a source of fluoride not only facilitates entry to the Au(I/III) manifold but also provides a fluoride anion for silane activation, thereby avoiding the need for addition of a stoichiometric base (Scheme 1.42).



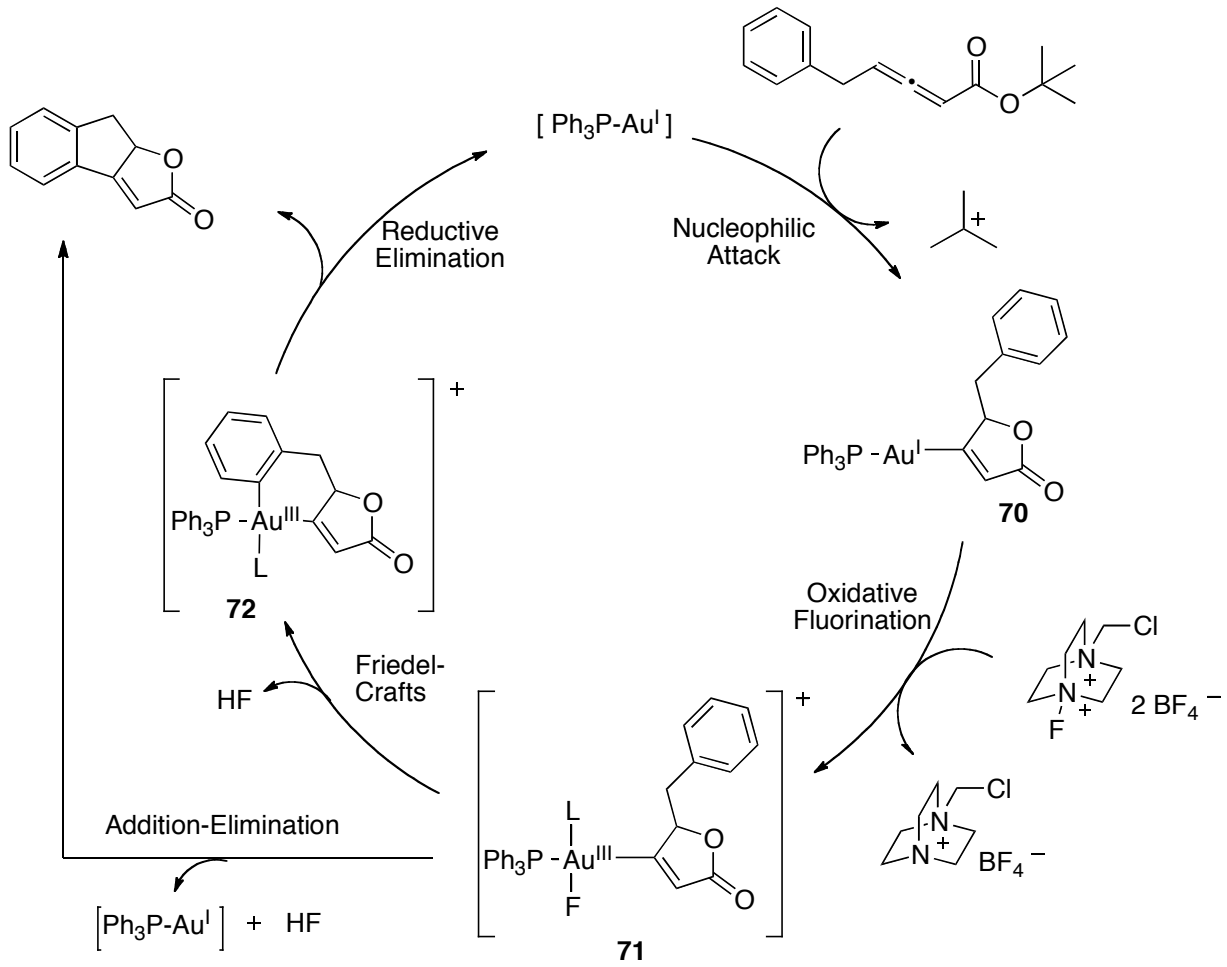
Scheme 1.42 Gold-catalyzed oxyarylation reactions with Ph_3PAuCl and Selectfluor

Recently, Gouverneur *et al.* reported an elegant approach to gold-catalyzed nucleophilic oxidative cross-coupling reactions that do not require preactivated arenes.[86] In these processes, gold selectively delivered both the organic fragments, one through activation of a carbon-carbon multiple bond and the second by $C(sp^2)$-H bond functionalization, prior to mediating the coupling event itself. The cascade cyclization cross-coupling process led to tricyclic dihydroindenofuranone-type products (Scheme 1.43).



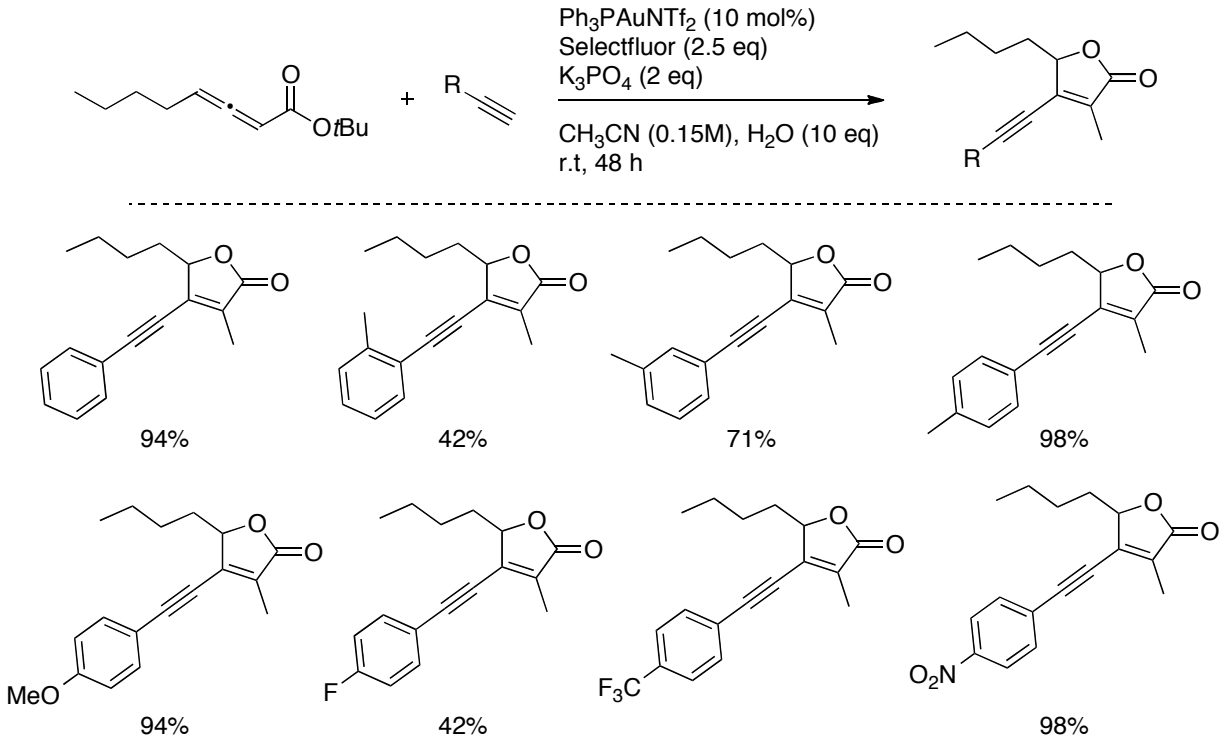
Scheme 1.43 Cascade cyclization-oxidative arylation of *tert*-butyl allenoates

Gouverneur envisaged that initial Au^{I} mediated 5-*endo*-*dig* cyclization of the *tert*-butyl ester with concomitant loss of an isopropene unit would afford intermediate **70**. Oxidation of Au^{I} to Au^{III} by Selectfluor led to species **71** followed by Friedel–Crafts-type arylation with fluoride displacement to give auracyclic species **72**. Reductive elimination of the latter delivered the cross-coupled product. An alternative pathway involving a conjugated Michael-type addition-elimination of the arene onto complex **71** could also lead to the final product (Scheme 1.44).



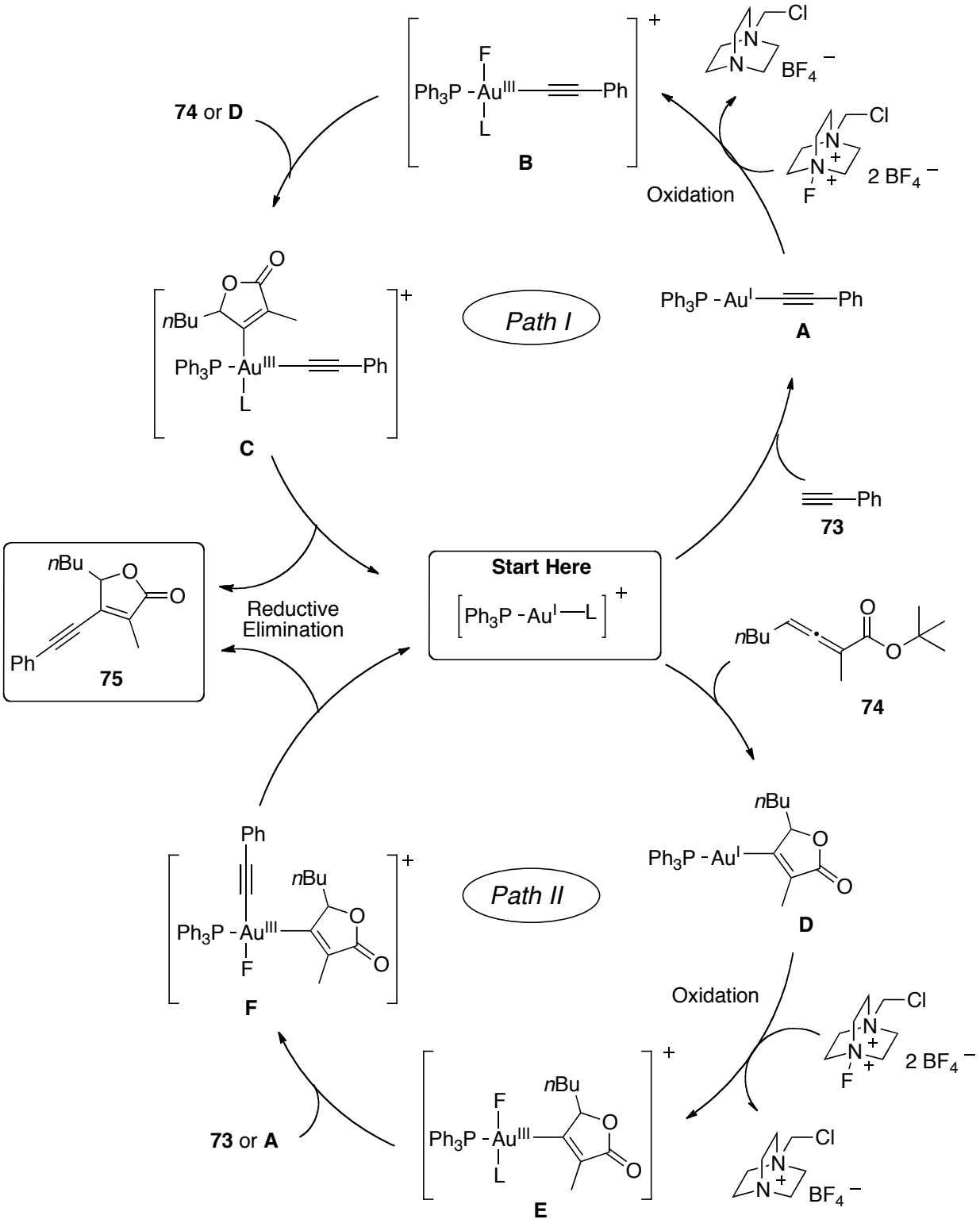
Scheme 1.44 Reaction mechanism of cascade cyclization-oxidative arylation

Gouverneur and co-workers also investigated a gold-catalyzed cascade cyclization-oxidative alkynylation of allenoates.[87] The transformation was compatible with a wide range of arylacetylenes including *para*-, *meta*-, and *ortho*- substituted derivatives (Scheme 1.45).



Scheme 1.45 Oxidative alkynylation of allenoates

Two plausible pathways for the cascade allenoate cyclization-oxidative alkynylation process were envisaged, both involving a Au^{I}/Au^{III} redox cycle (Scheme 1.46). In pathway I, alkyne **73** and Au^{I} initially form the alkynyl-Au^{I} intermediate **A**. Oxidation of gold center by Selectfluor affords cationic intermediate **B**. Coordination of this species to the allene followed by nucleophilic attack of the pendant *tert*-butyl ester led to the Au^{III} complex **C** bearing both butenolide and alkyne substituents. After reductive elimination, this species delivered the cross-coupled product and regenerates the cationic Au^{I} catalyst (Scheme 1.46, path I). Alternatively, the allenoate cyclization may occur prior to the alkyne coordination step. In this case, oxidation of the organo- Au^{I} intermediate **D** by Selectfluor led to complex **E**. Reductive elimination from intermediate **F**, formed after alkynylation, afforded the product and regenerated the catalyst (Scheme 1.46, path II).



Scheme 1.46 Reaction mechanism of alkynylation of allenoates

1.4 Thesis Outline

This thesis is focused on the synthesis and use of a new category of chiral N-F reagents, structurally related to Selectfluor, fluorinating reagents. One of our strategies is to utilize the unique reactivity properties of Selectfluor as a toolbox to solve the reactivity issue encountered in asymmetric electrophilic fluorination. To the best of our knowledge, syntheses of chiral analogues of Selectfluor surprisingly are unknown in the literature. These chiral variants of Selectfluor could be prepared from chiral DABCO precursors **A** to **C** and serve as efficient fluorinating reagents with improved reactivities and selectivities (Figure 1.12). In Chapter 2 the synthesis of chiral 1,4-diazabicyclo[2.2.2]octane (DABCO) **A**, **B** and **C** derivatives is presented, whilst Chapter 3 focused on the quaternization and fluorination on the chiral DABCO cores to access the novel non-racemic Selectfluor **I**, **II** and **III**. Chapter 4 describes how the chiral Selectfluor analogues compare to cinchona alkaloid derivatives in term of reactivity and selectivity.

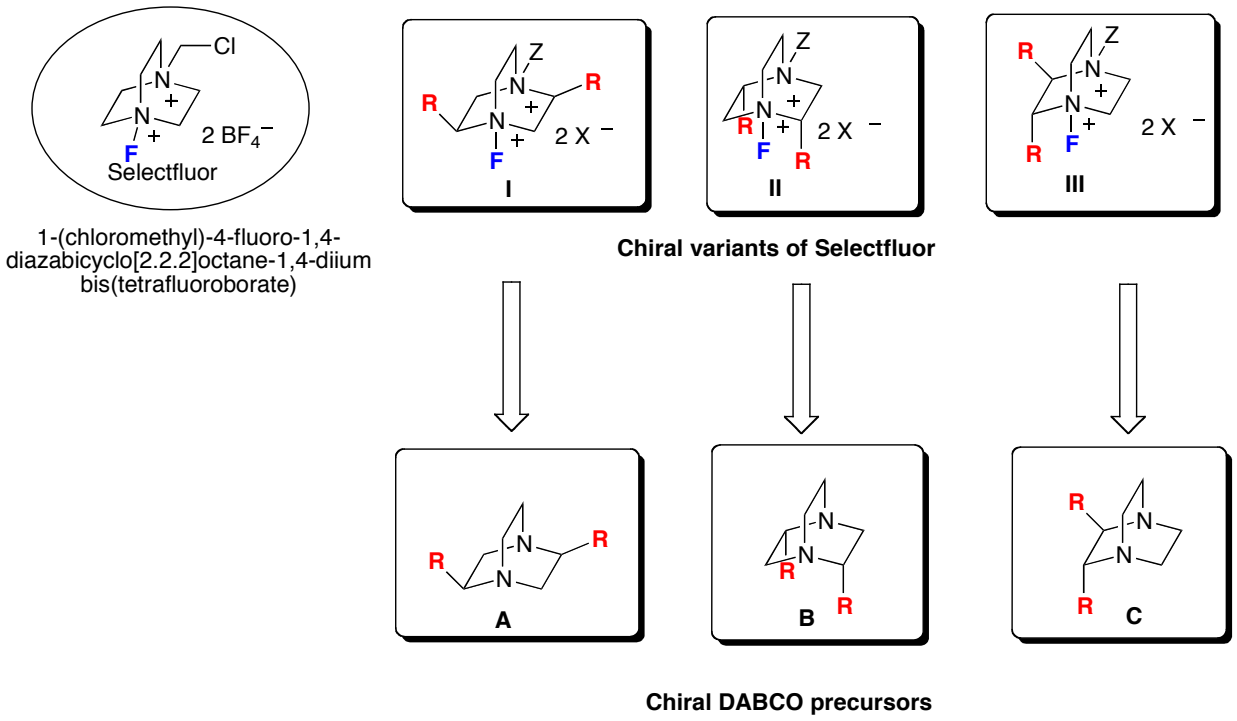


Figure 1.12 Chiral variants of Selectfluor

Chapter 2:

Synthesis of Chiral DABCO Derivatives

2.1 Introduction

2.1.1 Properties of DABCO and Applications

1,4-Diazabicyclo[2.2.2]octane (DABCO) is considered to be a typical globular cage molecule with high symmetry – D_{3h} (Figure 2.1).[88] It forms colourless, transparent crystals that display sharp hexagonal faces, which sublime readily *in vacuo*.[89] DABCO structure is unique with two nitrogen atoms linked to three ethylenic groups. Its has an ammoniacal odour and is a hygroscopic white crystalline solid with a high melting point (158 °C) and boils at 174 °C.[90] It is a weak base (pK_{aH} = 8.8) with two nucleophilic nitrogen atoms at the bridgehead positions, which are responsible for its interesting catalytic properties. [88]

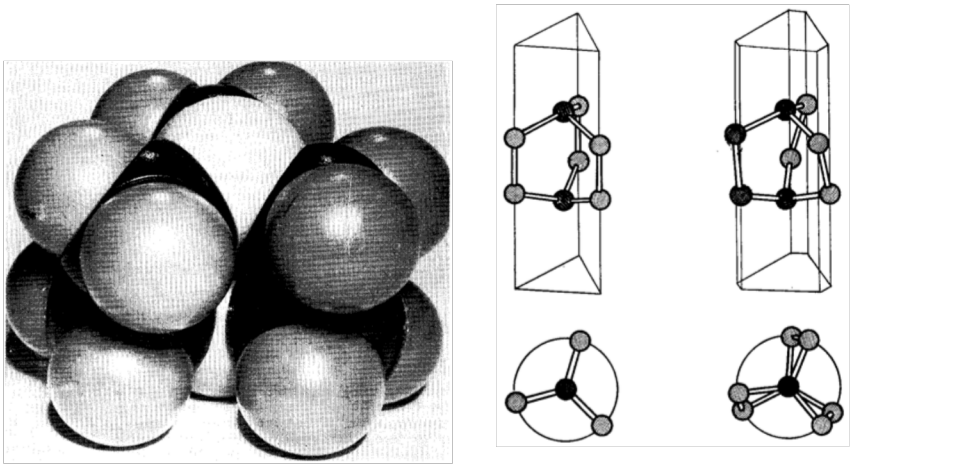


Figure 2.1 Globular structure and molecular conformation of DABCO

DABCO is much more active catalytically than appreciably stronger bases probably due to its compact structure that makes the electron pairs which are located at the nitrogen atoms readily accessible.[91] The symmetry in DABCO is usually lost during compound or complex formation resulting in large entropy increase and providing additional driving force in chemical reactions.[89]

1,4-Diazabicyclo[2.2.2]octane has a great potential to form single and double salts. An aqueous solution of DABCO is weakly basic and its pK_{aH} values were reported to be 2.92 and 8.8 at 25

°C in water.[92] Thus, it is a weaker base than either triethylamine or quinuclidine (Figure 2.2).

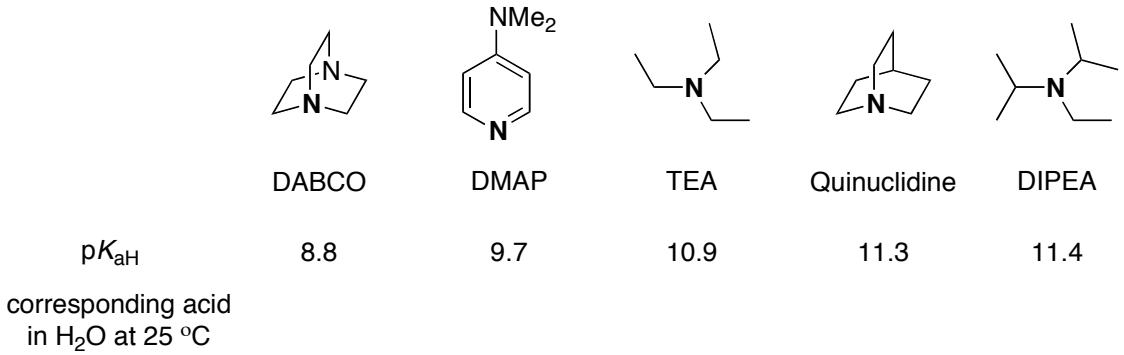


Figure 2.2 pK_{aH} of tertiary amines

The spectroscopic and chemical properties of 1,4-diazabicyclo[2.2.2]octane are consistent with a strong interaction of the in-phase combination of the two occupied sp^3 hybridized lone pairs on the nitrogen atoms which can be described by an interaction diagram shown in Figure 2.3.[93] DABCO has two ionization potentials (7.6 and 9.7 eV) separated by several electron-volts, and is more easily oxidized than tertiary amines such as trimethylamine.[94]

Figure 2.3 Interaction of the non-bonded electron pairs of the nitrogen in DABCO

DABCO has been used as a weak base and ligand in a variety of transformations particularly in C-C and C-heteroatom bond forming reactions (Figure 2.4).[95, 96, 97]

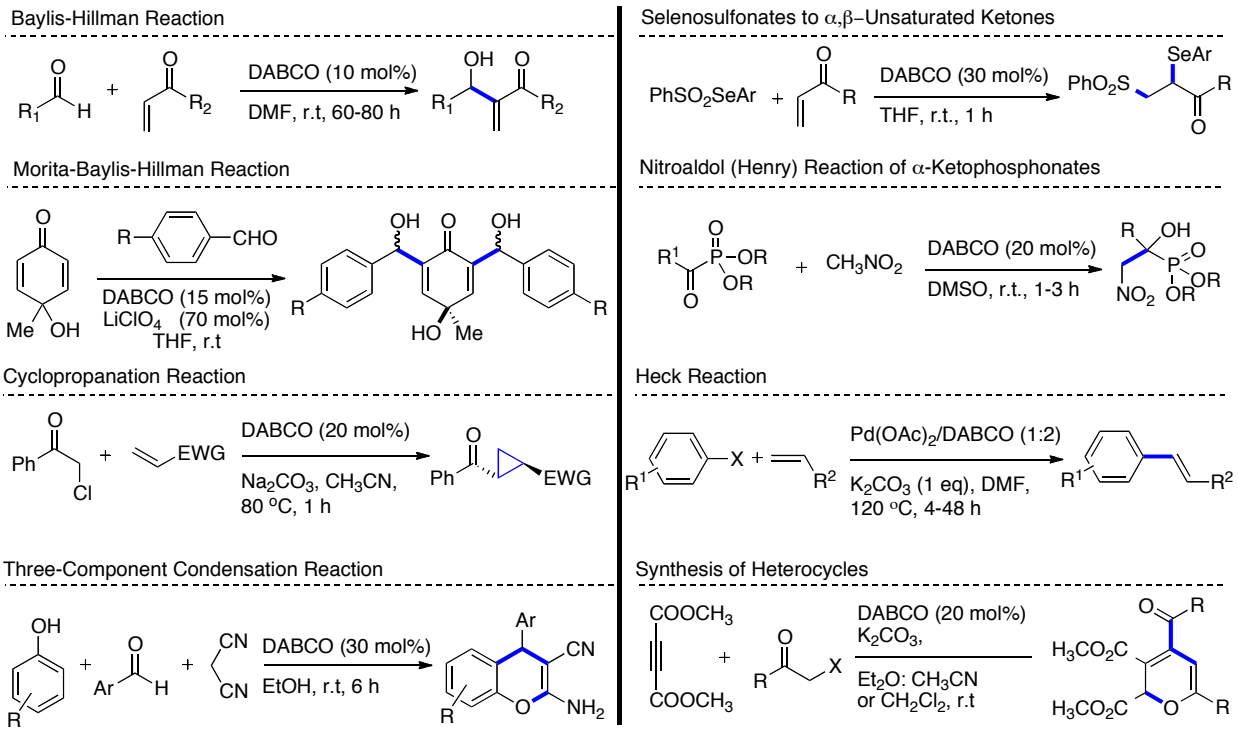


Figure 2.4 DABCO in organic synthesis

Chiral derivatives of DABCO are therefore potential chiral reagents for asymmetric syntheses. According to the above study on the basicity of the tertiary amines, which showed that DABCO is less basic than quinuclidine, we postulate that chiral N-F DABCO salts would be more electrophilic in comparison with their structurally related quinuclidines (Figure 2.5). They would be able to fluorinate less activated substrates such as olefins, which are not responsive to fluorination using chiral quinuclidine derivatives.

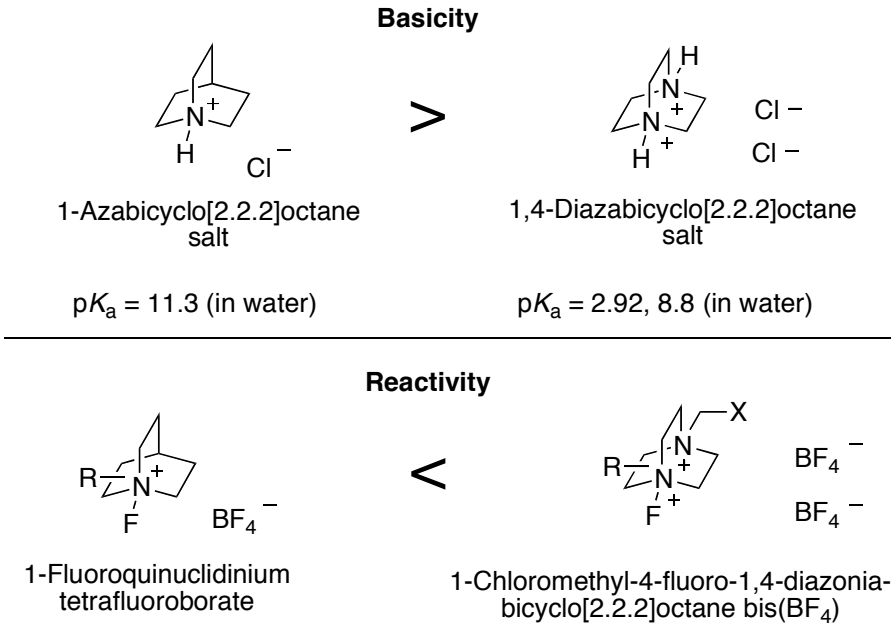


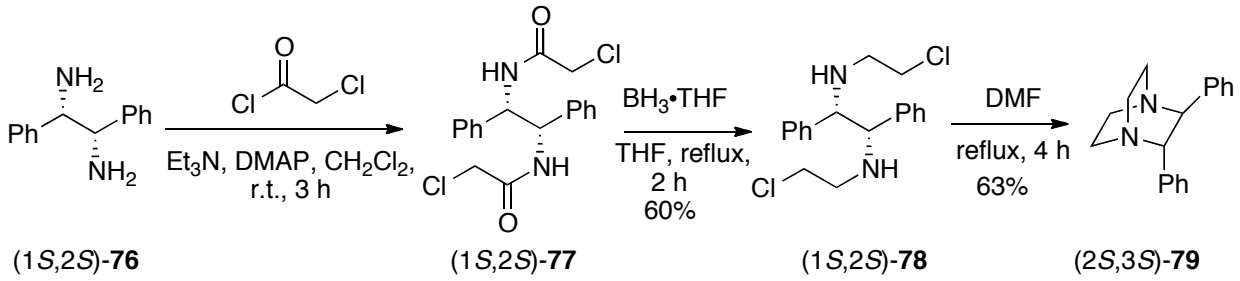
Figure 2.5

These observations encouraged us to investigate the synthesis of chiral DABCO derivatives, their fluorination and the value of the resulting chiral N-F DABCO derivatives in asymmetric fluorination. To date, only a few reports have appeared on the synthesis of enantiopure 2,3-disubstituted and 2,5-disubstituted DABCO derivatives.

2.1.2 Synthesis of 2,3-Disubstituted-DABCO Derivatives

2.1.2.1 Sharpless Synthesis

The first synthesis of enantiomerically active *trans*-2,3-disubstituted-diazabicyclo[2.2.2]octane was reported in 1991 by Sharpless and co-workers.[98] The preparation of (*S,S*)-2,3-diphenyl DABCO **79** was achieved over three steps (Scheme 2.1). The synthesis started with the chloroacetylation of enantiopure (1*S,*2*S*)-stilbene diamine **76** followed by reduction of the resulting diacylated (1*S,*2*S*)-**77**. The acetylated compound (1*S,*2*S*)-**77** generated (*S,S*)-bis(2-chloroethyl)-1,2-diphenylethane-1,2-diamine **78** in 60% yield. Cyclization of (1*S*,2*S*)-**78** in refluxing DMF gave enantiopure (2*S,*3*S*)-2,3-diphenyl DABCO **79** in 63% yield.

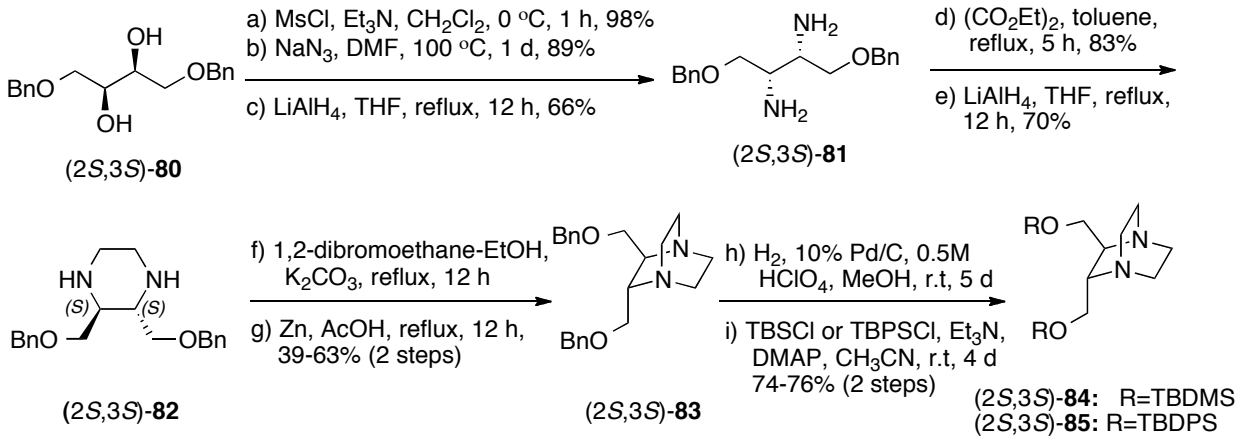


(1*S*,2*S*)-**76** (1*S*,2*S*)-**77** (1*S*,2*S*)-**78** (2*S*,3*S*)-**79**

Scheme 2.1 Synthesis of (2*S*,3*S*)-2,3-diphenyl DABCO **79**

2.1.2.2 Hirama Synthesis

A variety of *trans*-2,3-disubstituted DABCO derivatives were prepared by Hirama et *al.*[99] Enantiomerically pure (*S,S*)-2,3-disubstituted DABCOs **83**, **84** and **85** were synthesized from readily available (*S,S*)-1,4-dibenzyl ether **80** through the piperazine derivative (2*S,*3*S*)-**82** (Scheme 2.2). In the first instance, methanesulfonyl chlorides were used for activating the primary hydroxyl groups of the threitol (*S,S*)-**80** in the presence of triethylamine. The displacement of the mesylate groups with sodium azide proceeded with 89% yield. The azide groups were reduced using lithium aluminium hydride in refluxing tetrahydrofuran to give diamine (2*S,*3*S*)-**81** in 66% yield. Acylation of the diamine (2*S,*3*S*)-**81** with diethyl oxalate in toluene proceeded with 83% yield after 5 hours followed by reduction of the diketopiperazine into piperazine (2*S,*3*S*)-**82**. Chiral DABCO (2*S,*3*S*)-**83** was generated in 39-63% yield from (2*S,*3*S*)-**82** via double *N*-alkylation with dibromoethane and reduction of the quarternary ammonium salt formed with zinc. Hydrogenation of the benzyl ethers in (2*S,*3*S*)-**83** using palladium on carbon, followed by alkylation with either *tert*-butyldimethylsilyl chloride or *tert*-butyldiphenylsilyl chloride delivered chiral DABCO (2*S,*3*S*)-**84** and (2*S,*3*S*)-**85** in 74% and 76% yields respectively.

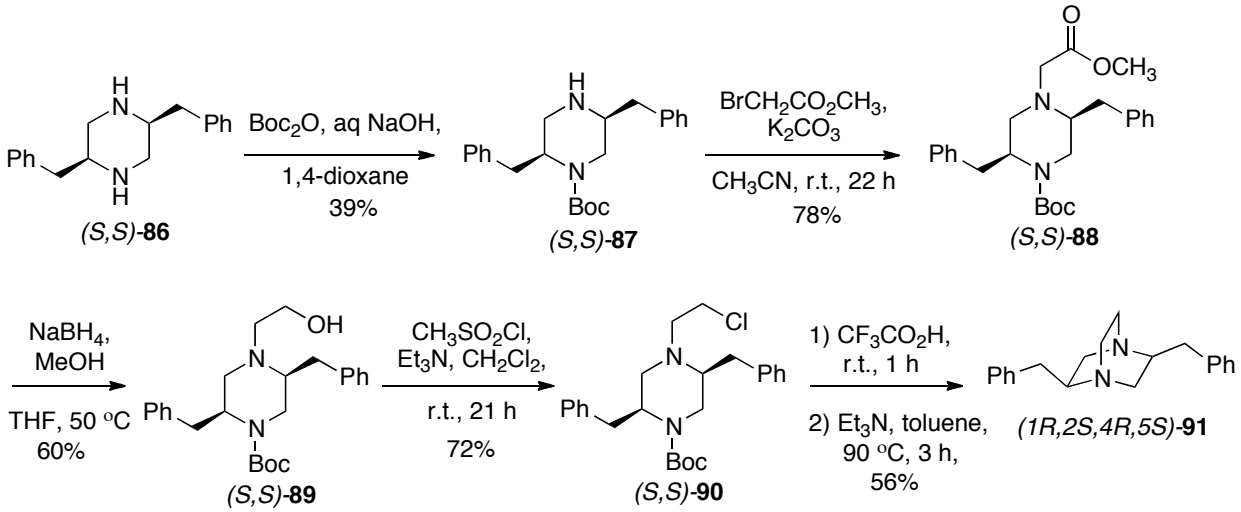


Scheme 2.2 Synthesis of (*S,S*)-2,3-disubstituted DABCOs **83**, **84** and **85**

2.1.3 Synthesis of 2,5-Disubstituted-DABCO Derivatives

2.1.3.1 Soai Synthesis

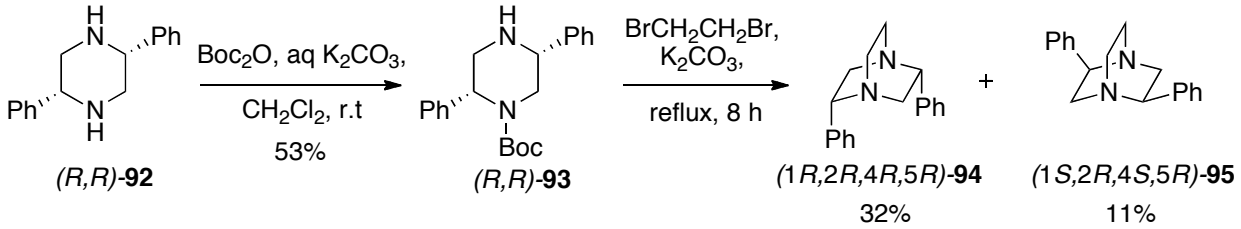
Soai *et al.* reported in 1992 the synthesis of a 2,5-disubstituted optically active DABCO derivative, (1*R,*2*S,*4*R,*5*S*)-2,5-bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane **91**.[100] Reaction of (2*S*,5*S*)-bis (phenylmethyl)piperazine **86**, prepared from (*S*)-phenylalanine, with di-*tert*-butyl dicarbonate (Boc_2O) in aqueous sodium hydroxide and 1,4-dioxane gave the monoprotected piperazine (2*S*,5*S*)-**87** in 39% yield (Scheme 2.3). Treatment of the latter with methyl bromoacetate in acetonitrile in the presence of potassium carbonate afforded (2*S*,5*S*)-**88** in 78% yield. The methyl ester of (2*S*,5*S*)-**88** was chemoselectively reduced with sodium borohydride giving aminoalcohol (2*S*,5*S*)-**89** in 60% yield. The subsequent reaction of (2*S*,5*S*)-**89** with methanesulfonyl chloride and triethylamine in dichloromethane did not afford the corresponding mesylate but gave exclusively the chloride (2*S*,5*S*)-**90** in 72% yield. The steric bulkiness of the phenylmethyl group may be the reason for this conversion, as when the two phenylmethyl substituents were not present, the corresponding mesylate derivative was obtained. Removal of the Boc protecting group with trifluoroacetic acid followed by cyclization in toluene at 90 °C for 3 hours afforded (1*R,*2*S,*4*R,*5*S*)-**91** in 56% yield (Scheme 2.3).



Scheme 2.3 Synthesis of (1*R*,2*S*,4*R*,5*S*)-**91**

2.1.3.2 Fuji Synthesis

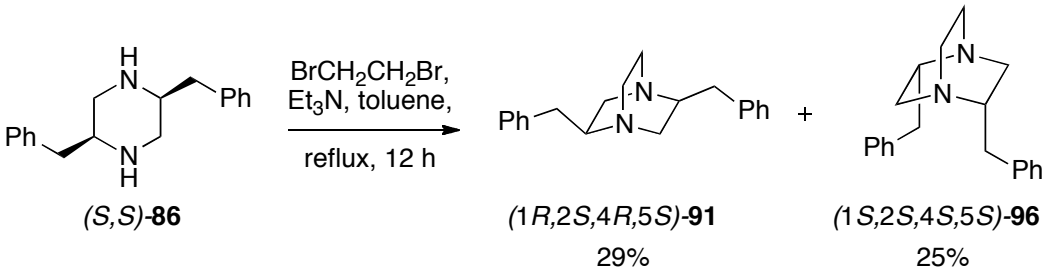
Fuji *et al.*[101] followed the same synthetic strategy as Soai and co-workers but found that the direct alkylation of the intermediate *(2R,5R)*-**93** could give *(1R,2R,4R,5R)*- and *(1S,2R,4S,5R)*-2,5-diphenyl-l,4-diazabicyclo[2.2.2]octanes **94** and **95** in one step. Thus, refluxing enantiomerically pure 1-butoxycarbonyl-*2R,5R*-diphenylpiperazine **93** in 1,2-dibromoethane in the presence of potassium carbonate for 8 hours gave the two separable isomers *(1R,2R,4R,5R)*-**94** and *(1S,2R,4S,5R)*-**95** in 32% and 11% yield respectively after purification by silica gel column chromatography.



Scheme 2.4 Synthesis of *(1R,2R,4R,5R)*-**94** and *(1S,2R,4S,5R)*-**95**

2.1.3.3 Zhang Synthesis

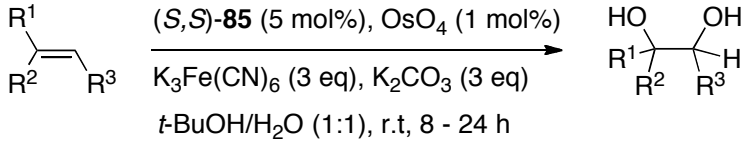
Zhang *et al.*[102] reported in 2003 a similar synthetic approach to Fuji *et al.* for the formation of both (1*R*,2*S*,4*R*,5*S*)- and (1*S*,2*S*,4*S*,5*S*)-2,5-bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane **91** and **96**.[101] In this case, piperazine (2*S*,5*S*)-**86** was treated with 1,2-dibromoethane in the presence of triethylamine to give the two separable stereoisomers (1*R*,2*S*,4*R*,5*S*)-**91** and (1*S*,2*S*,4*S*,5*S*)-**96** in 29% and 25% yield respectively (Scheme 2.5).

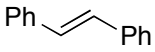
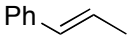
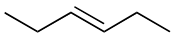
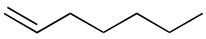
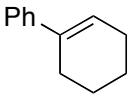


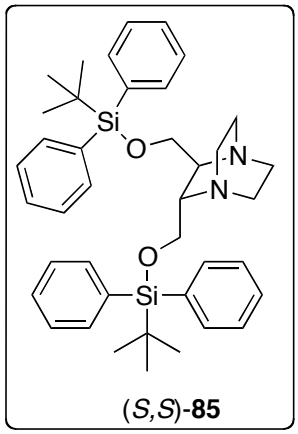
Scheme 2.5 Synthesis of (1*R*,2*S*,4*R*,5*S*)-**91** and (1*S*,2*S*,4*S*,5*S*)-**96**

2.1.4 Use of Chiral 1,4-Diazabicyclo[2.2.2]octane Derivatives

The application of chiral DABCO derivatives has been examined by Hirama and co-workers in catalytic asymmetric dihydroxylation. Hirama examined the osmium tetroxide-catalyzed dihydroxylation of various olefins in the presence of $K_3Fe(CN)_6$ and K_2CO_3 in *t*-BuOH/H_2O (1:1). The reaction proceeded smoothly in 8 to 24 hours at room temperature to give the corresponding products in good yields (up to 95%) and low selectivities (up to 41% ee) (Table 2.1).



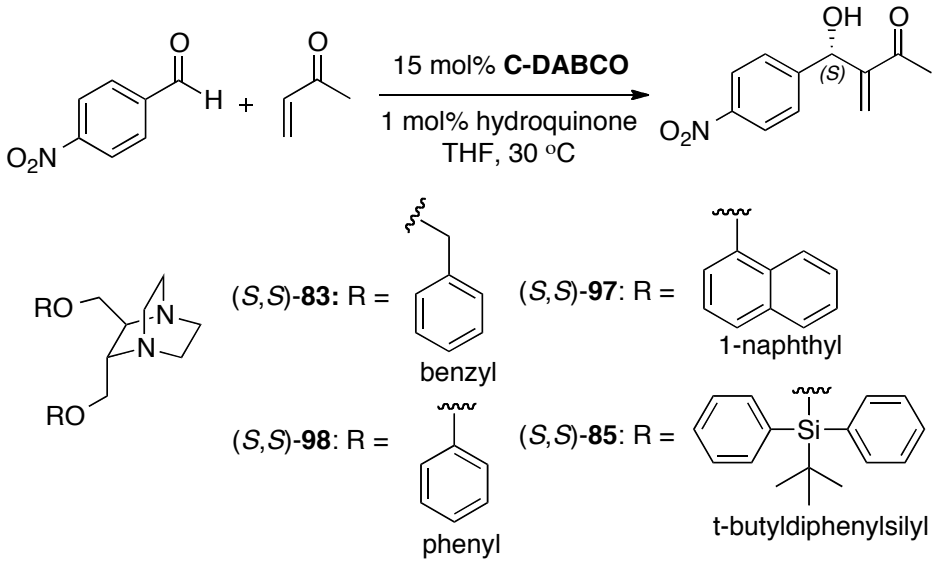
Olefin	Yield (%)	ee (%)	Configuration
	85	40	*SS*
	95	19	*SS*
	80	21	*S*
	83	41	*SS*
	92	27	*S*
	95	18	*SS*



(*S,S*)-**85**

Table 2.1 Catalytic asymmetric dihydroxylation of olefins using (*S,S*)-**85**

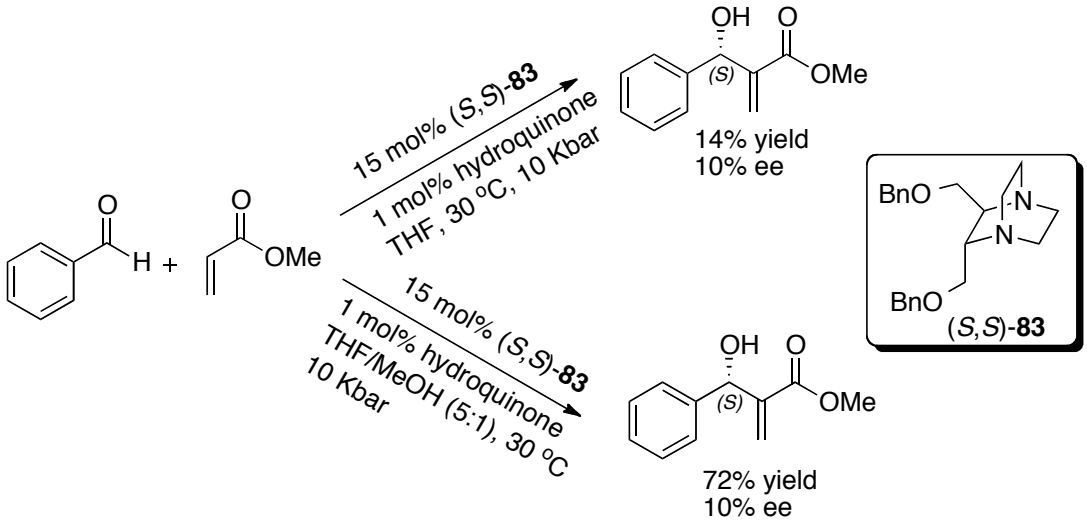
Hirama investigated the use of chiral DABCOs in catalytic asymmetric Baylis-Hillman reactions. They first examined the reaction of 4-nitrobenzaldehyde with methyl vinyl ketone. The condensation was performed under pressure (5 -10 Kbar) using 1 mol% of hydroquinone with chiral DABCO ligands to generate (*S*)-3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (Table 2.2).[103] The necessity of 1 mol% of hydroquinone was not discussed.



Entry	Chiral DABCO	Time (h)	Yield (%)	ee (%)
1	(*S,S*)-**83**	12	45	47
2	(*S,S*)-**97**	16	66	42
3	(*S,S*)-**98**	16	60	35
4	(*S,S*)-**85**	12	23	34

Table 2.2 Condensation of 4-nitrobenzaldehyde and methyl vinyl ketone

Hirama and co-workers also examined the condensation of a less reactive benzaldehyde and methyl acrylate using chiral DABCO (*S,S*)-**83** in THF (Scheme 2.6). The product was obtained in low yield and ee. However, the reaction was accelerated by addition of MeOH to give the product in 72% yield while the enantioselectivity remained unchanged.



Scheme 2.6 Catalytic asymmetric Baylis-Hillman reaction using (*S,S*)-**83**

2.1.5 Chapter Outline

This chapter is focused on the synthesis of three classes of molecules: chiral 2,5-disubstituted-DABCO, chiral 2,3-disubstituted-DABCO and chiral 2-substituted-DABCO derivatives. We selected two strategies, **A** and **B**, to prepare these chiral analogues of DABCO (Figure 2.6). In strategy **A**, we anticipated that chiral DABCOs **99** and **100** could be prepared *via* the protocol of Zhang. We envisaged using this methodology on a variety of amino acids to give the corresponding diketopiperazines **102**, which upon reduction and double *N*-alkylation can afford DABCO derivatives (Figure 2.6). This strategy takes advantage of a wide variety of different commercially available natural and unnatural amino acids. We selected phenylalanine, valine, naphthylalanine and phenylglycine for preliminary investigations.

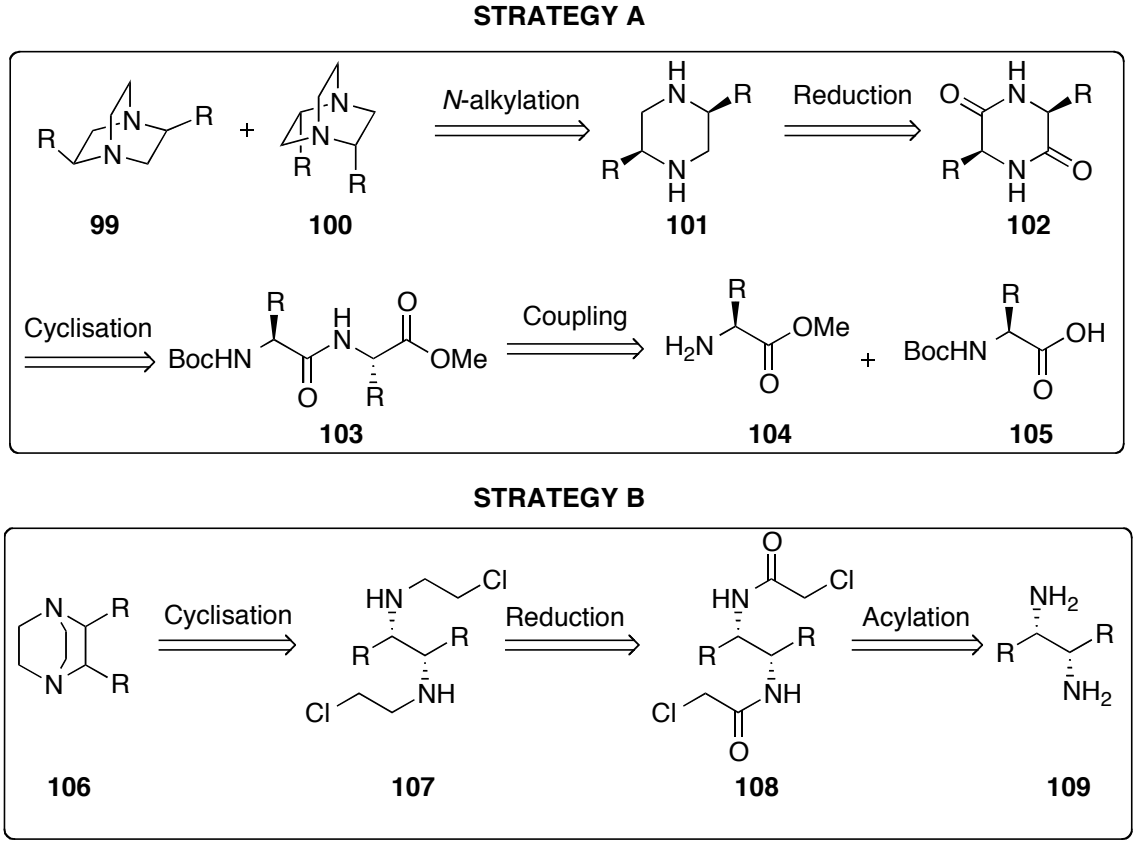


Figure 2.6 Retrosynthesis of chiral DABCO derivatives

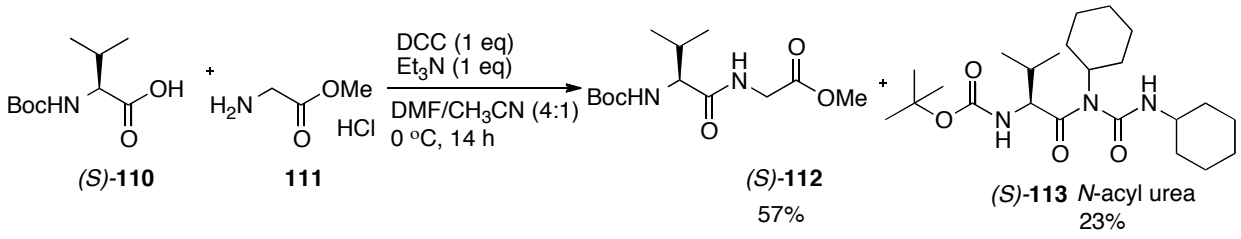
In strategy **B**, we sought to synthesize 2,3-disubstituted DABCO motifs *via* the protocol of Sharpless. Retrosynthetically, the target molecules **106** could be accessed from intramolecular

cyclization of chloroethyl-diamines **107** (Figure 2.6). The requisite chloroethyl-diamines could be prepared by reduction of chloroacetamides **108**. These latter compounds could be synthesized by acylation of the diamine **109**. This strategy would also be applied to the synthesis of chiral 2-substituted DABCO derivatives.

2.2. Synthesis of chiral 2,5-Disubstituted-DABCO Derivatives

2.2.1 Formation of Dipeptides

The first step in the proposed syntheses of the chiral non-racemic DABCO is the formation of required dipeptide derivatives. The choice of the coupling agent is very important for the success of the reaction, since it must efficiently induce coupling while minimizing by-product formation. Initially the formation of the dipeptide (*S*)-**112** was performed with the commonly used *N,N′*-dicyclohexylcarbodiimide (DCC) reagent to validate this procedure.[104, 105] Commercially available glycine methyl ester hydrochloride **111** was condensed with an equimolar amount of (*S*)-*N*-(*tert*-butoxycarbonyl)-valine methyl ester **110** (Scheme 2.7). The condensation was carried out in acetonitrile and dimethylformamide (4:1) with 1 equivalent of DCC in the presence of triethylamine. After 14 hours, the (*S*)-*N*-Boc-dipeptide ester **112** was obtained in 57% yield, after purification by silica gel column chromatography.



Scheme 2.7 Amino acids coupling reaction with DCC.

The yield is diminished by the formation of the unreactive *N*-acyl urea (*S*)-**113** which was identified by mass spectrometric analysis (positive ion $C_{23}H_{14}CN_2NaO_4$ $[M+Na]^+$: 446.5789).

To increase the efficiency of this process, another method for the condensation of amino acids has been explored, in which the formation of side-products could be minimized. McAlpine *et al.* reported the use of *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU), *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HATU) as reagents in a variety of peptide coupling in CH_2Cl_2 (Figure 2.7).[106, 107]

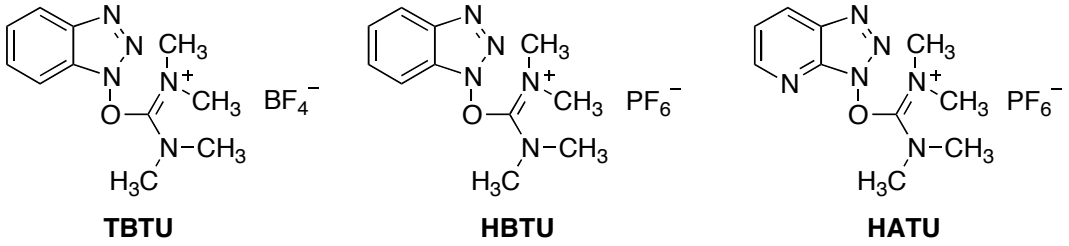
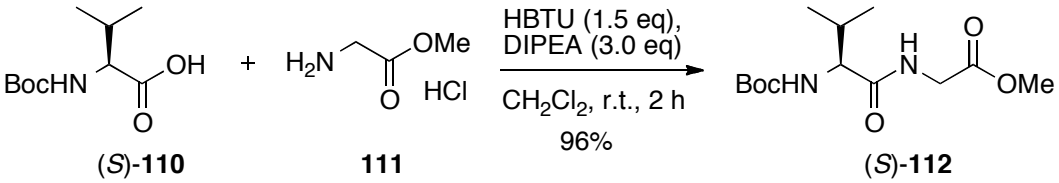


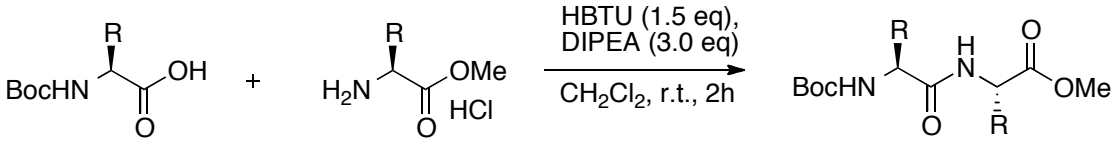
Figure 2.7 Uronium coupling reagents.

This alternative route was attempted by coupling (*S*)-*N*-(*tert*-butoxycarbonyl)-valine methyl ester **110** with 1.2 equivalent of glycine methyl ester hydrochloride **111** and 1.5 equivalent of HBTU in the presence of *N*,*N*-diisopropylethylamine as a base. The reaction was performed in dichloromethane at room temperature for 2 hours furnishing (*S*)-*N*-Boc-dipeptide ester **112** in 96% yield (Scheme 2.8).



Scheme 2.8 Coupling reaction with HBTU.

These optimised conditions have several advantages over the previous ones as they avoid the use of toxic DCC, enable significant shortening of the reaction time and give an improved yield. This strategy was successfully applied to the coupling of selected amino acids giving the desired products (*S*,*S*)-**120**, (*S*,*S*)-**121** and (*S*,*S*)-**122** in good to excellent yields (Scheme 2.9).



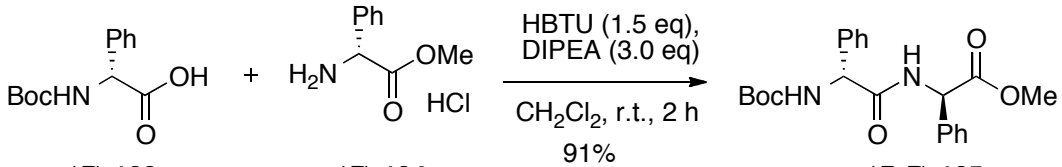
(*S*)-**114**: R = Bn
(*S*)-**115**: R = Isopropyl
(*S*)-**116**: R = 1-Naphthylmethyl

(*S*)-**117**: R = Bn
(*S*)-**118**: R = Isopropyl
(*S*)-**119**: R = 1-Naphthylmethyl

(*S,S*)-**120**: R = Bn (97%)
(*S,S*)-**121**: R = Isopropyl (98%)
(*S,S*)-**122**: R = 1-Naphthylmethyl (88%)

Scheme 2.9 Formation of selected (*S,S*)-dipeptides **120**, **121** and **122**

The specific rotation of dipeptides (*S,S*)-**120** and (*S,S*)-**121** were in agreement with the reported values.[108] Dipeptide (*S,S*)-**122** is a novel compound with a specific rotation of $[\alpha]^{22}$ = -54.7 (*c* 0.64, DMSO). The same conditions were adopted for the formation of the dipeptide (*R,R*)-**125** giving an excellent yield of 91% (Scheme 2.10).

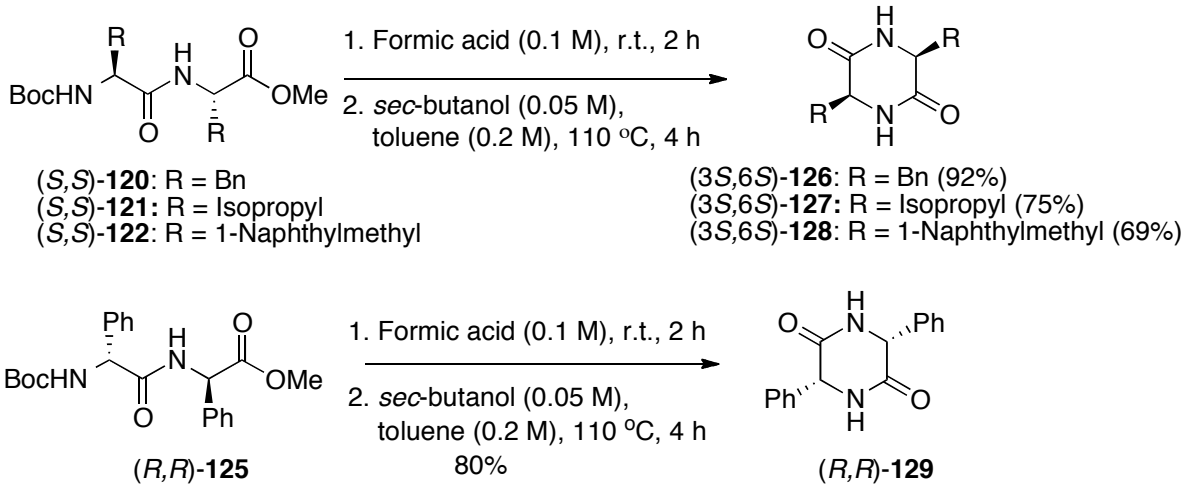


(*R*)-**123** (*R*)-**124** (*R,R*)-**125**

Scheme 2.10 Formation of dipeptide (*R,R*)-**125**

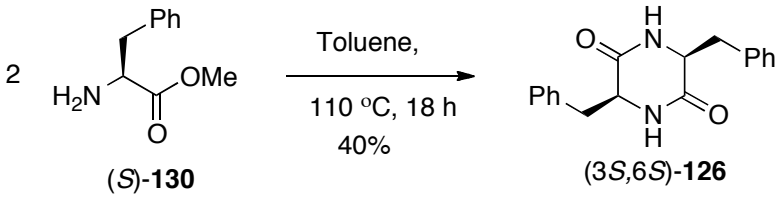
2.2.2 Formation of Chiral 3,6-Disubstituted Diketopiperazines

The synthesis of dipeptides (*S,S*)-**120,** (*S,S*)-**121,** (*S,S*)-**122** and (*R,R*)-**125** allowed for an investigation into the cyclisation step. There are several general methods in the literature for preparing enantiomerically pure 3,6-diketopiperazines starting from dipeptides.[109, 110] The synthesis was attempted using the conditions developed by Nitecki *et al*.[111] Accordingly, the acyclic dipeptides (*S,S*)-**120**, (*S,S*)-**121**, (*S,S*)-**122** and (*R,R*)-**125** were treated with formic acid at room temperature for 2 hours to selectively remove the *tert*-butyloxycarbonyl protecting group. Refluxing in *sec*-butanol favoured intramolecular attack of the amino group on the terminal carboxyl group generating the cyclic diketopiperazines (3*S,*6*S*)-**126**, (3*S,*6*S*)-**127**, (3*S,*6*S*)-**128** and (3*R,*6*R*)-**129** in 92%, 75%, 69% and 80% yield respectively (Scheme 2.11).



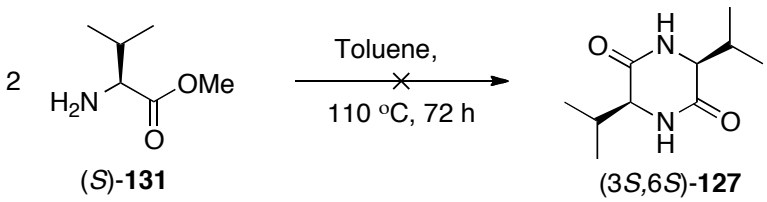
Scheme 2.11. Formation of chiral diketopiperazines

Qiu *et al*. reported a direct route to compound (3*S*,6*S*)-**126** by condensation of amino acids in toluene.[112] Utilising this method, the symmetrical diketopiperazine (3*S*,6*S*)-**126** was generated in a one-pot reaction. To obtain the cross-coupled substrate, treatment of the phenylalanine methyl ester (*S*)-**130** in toluene at elevated temperature was necessary, but the product was obtained in low yield (Scheme 2.12).



Scheme 2.12 Direct cyclisation to afford (3*S*,6*S*)-**126**

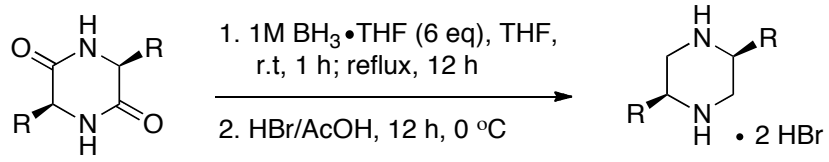
Although this transformation was suitable for this substrate, attempts to employ these conditions to valine methyl ester (*S*)-**131** proved unsuccessful (Scheme 2.13). The ^{1}H and ^{13}C NMR analysis showed only starting material (*S*)-**131**.



Scheme 2.13 Attempted direct cyclisation of valine amino acids.

2.2.3 Formation of Chiral 2,5-Disubstituted Piperazines

The reduction of diketopiperazines to the corresponding piperazines has been examined by various research groups using a variety of reducing agents such as lithium aluminium hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$) and borane-tetrahydrofuran complex (BH_3•THF).[113,114] We sought to investigate the reduction step using the standard borane-tetrahydrofuran complex, which is a potent, yet selective, reducing agent for polar functional groups like amides. Thus, 2,5-diketopiperazines (3*S*,6*S*)-**126,** (3*S*,6*S*)-**127** and (3*S*,6*S*)-**128** were treated with borane in THF and subsequently quenched with a mixture of hydrobromic acid and acetic acid (1:3). The hydrobromide salts formed were recrystallised in a mixture of methanol and ether (1:4) giving the pure piperazine salts (2*S*,5*S*)-**132**, (2*S*,5*S*)-**133** and (2*S*,5*S*)-**134** in 55%, 39% and 43% yield respectively (Scheme 2.14). Although this methodology proved effective for the formation of piperazine salts, attempts to extract neutral 2,5-piperazines upon treatment of the piperazine salts with 3M NaOH proved difficult, giving low yields especially for substrates (2*S*,5*S*)-**132** and (2*S*,5*S*)-**133**.



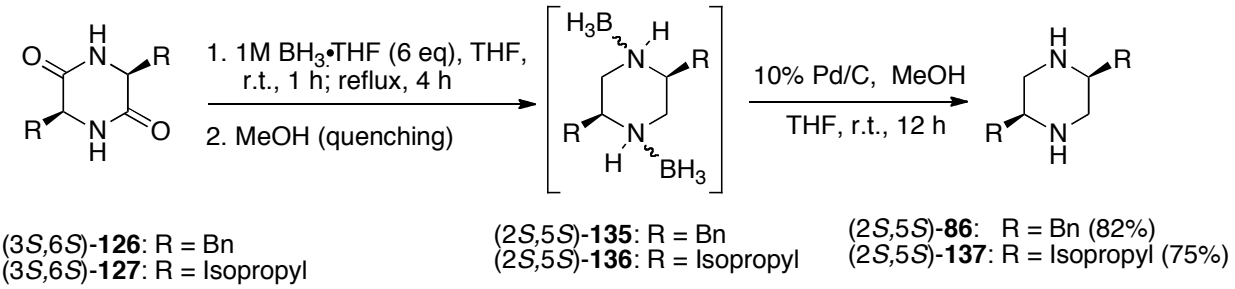
(3*S*,6*S*)-**126**: R = Bn
(3*S*,6*S*)-**127**: R = Isopropyl
(3*S*,6*S*)-**128**: R = 1-Naphthylmethyl

(2*S*,5*S*)-**132**: R = Bn (55%)
(2*S*,5*S*)-**133**: R = Isopropyl (39%)
(2*S*,5*S*)-**134**: R = 1-Naphthylmethyl (43%)

Scheme 2.14 Piperazine hydrobromide salts formation.

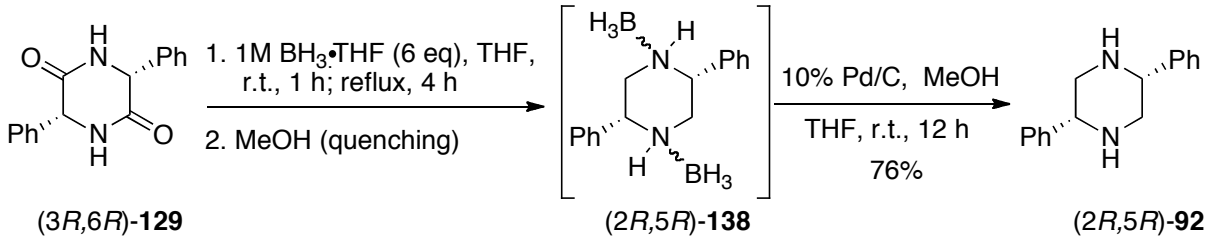
The search for new and more versatile synthetic routes for the reduction of 2,5-diketopiperazines led us to investigate the catalytic cleavage of the borane–amine complex. Couturier *et al*. reported the cleavage of strong borane-amine complex using palladium or Raney nickel catalysts.[115] This approach was examined, as outlined in Scheme 2.15, where (3*S*,6*S*)-**126** and (3*S*,6*S*)-**127** were treated with 6 equivalents of BH_3•THF and quenched with methanol. The

borane-amine complex intermediates (2*S*,5*S*)-**135** and (2*S*,5*S*)-**136** were subjected to 10% palladium on carbon in a mixture of methanol and tetrahydrofuran (5:1), at room temperature for 12 hours, affording piperazines (2*S*,5*S*)-**86** and (2*S*,5*S*)-**137** in 82% and 75 % yield respectively, after purification by silica gel column chromatography.



Scheme 2.15 Catalytic cleavage of borane-amine complexes.

In light of the above results (3*R*,6*R*)-3,6-diphenylpiperazine-2,5-dione **129** was subjected to borane reduction followed by catalytic cleavage of the borane−amine complex with Pd/C. The reduced product (2*R*,5*R*)-**92** was isolated in 76% yield (Scheme 2.16).



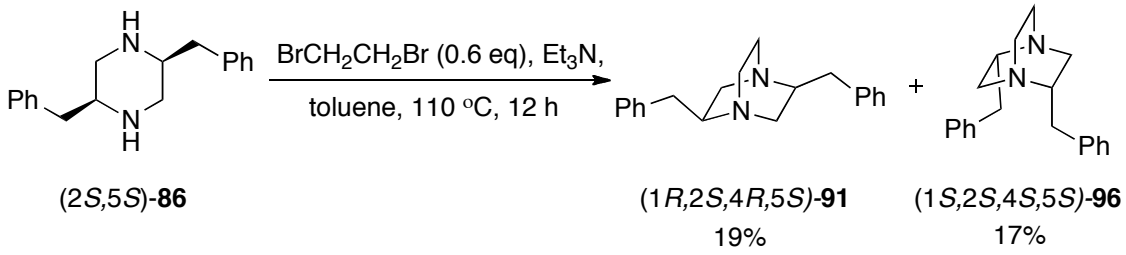
Scheme 2.16 Catalytic cleavage of (2*R*,5*R*)-**138**

The catalytic cleavage strategy gave better results than the hydrobromic acid approach with good to excellent yields.

2.2.4 Synthesis of Chiral 2,5-Disubstituted 1,4-Diazabicyclo[2.2.2]octane

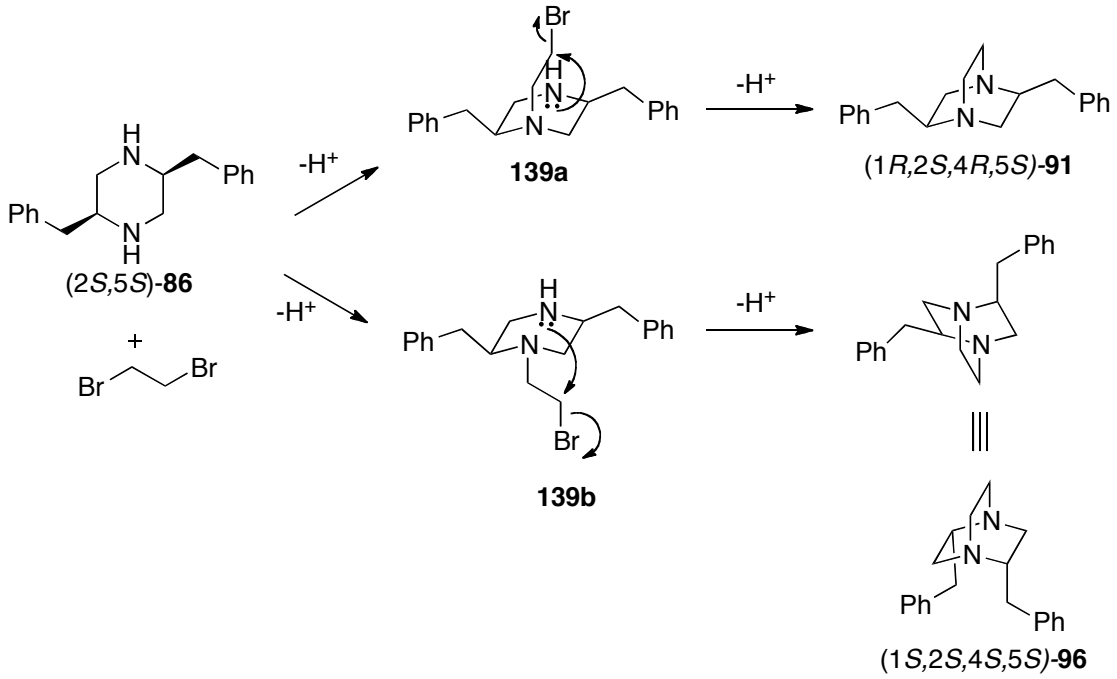
Having formed the desired 2,5 piperazine precursors, we wanted to investigate the direct alkylation with dibromoethane as reported by Zhang and co-workers.[102] In the first instance, the

alkylation was performed by refluxing (2*S*,5*S*)-**86** in toluene in the presence of 1,2-dibromoethane and triethylamine at 110 ^{o}C for 12 hours giving a 1:1 mixture of diastereomers. Chromatographic separation gave pure (1*R*,2*S*,4*R*,5*S*)-**91** and (1*S*,2*S*,4*S*,5*S*)-**96** in 19 % and 17% yield respectively (Scheme 2.17). The low yield obtained is due to the complex reaction mixture obtained and the difficulty encountered in separating the two diastereomers, which have similar polarity. Indeed, the diastereomers were eluting together in most eluents following tlc analysis. Chloroform and methanol (98:2) were found to be the solvents of choice, as the combination of other solvents did not show separation.



Scheme 2.17 Formation of chiral DABCOs **91** and **96**.

The formation of a mixture of diastereomers suggest that upon monoalkylation of the piperazine (2*S*,5*S*)-**86**, intramolecular cyclisation undergoes either on the top face of the intermediate **139a** leading to isomer (1*R*,2*S*,4*R*,5*S*)-**91** or at the bottom face of the intermediate **139b** giving isomer (1*S*,2*S*,4*S*,5*S*)-**96** (Scheme 2.18).



Scheme 2.18 Suggested mechanism for the formation of diastereomers **91** and **96**

The configuration of the bicyclic isomers is of great importance, as the precise arrangement of the benzyl groups in space will have an effect on their reactivity. Isomers (1*R*,2*S*,4*R*,5*S*)-**91** and (1*S*,2*S*,4*S*,5*S*)-**96** have very similar ^{13}C NMR spectra but different ^{1}H NMR which allowed the assignment of the relative configuration. The diagnostic singlet peak at 2.80 ppm observed in the proton NMR, which is characteristic to the CH_2 of the nitrogen bridgehead (4H) were identified as belonging to (1*S*,2*S*,4*S*,5*S*)-**96**. We postulated that the protons of the phenylmethyl at the endo position would not have any interaction with the geminal protons of the nitrogen bridgehead. On the other hand, the CH_2 of the nitrogen bridgehead of (1*R*,2*S*,4*R*,5*S*)-**91** should not show a singlet peak (indeed, we observed a multiplet between 2.64-2.77 ppm corresponding to those CH_2 of the nitrogen bridgehead). Both isomers have opposite relative configuration at the nitrogen atoms. The X-ray analysis of a suitable single crystal of isomer **91** dihydrochloride salt provided unequivocal evidence of the relative configuration assigned by NMR spectra (Figure 2.8).

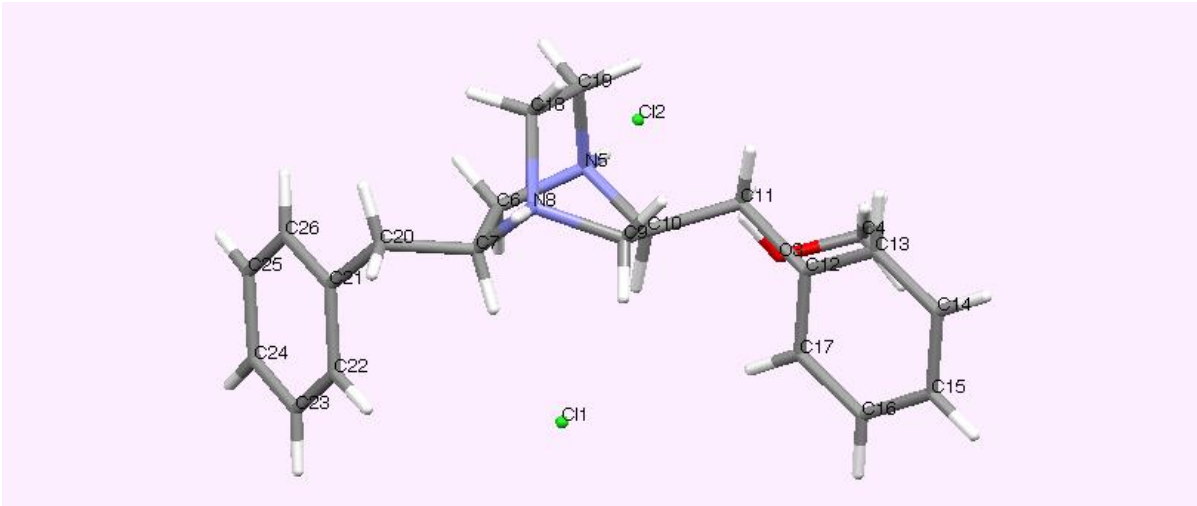
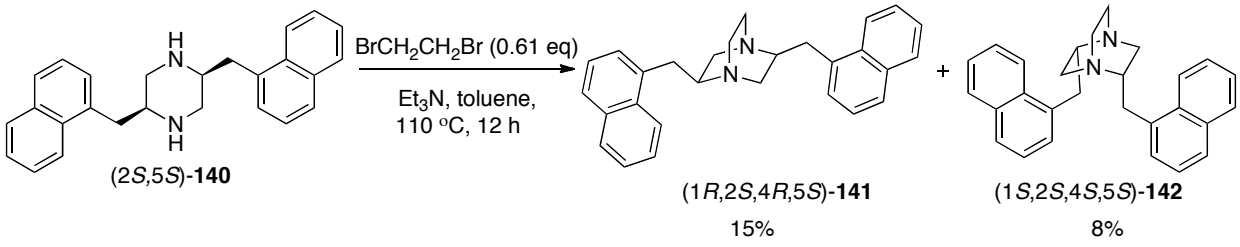


Figure 2.8 X-ray crystal structure of **91** dihydrochloride salt methanol solvate

The crystal contains one molar equivalent of methanol. The non-nucleophilic anion chlorides counterbalance the positive charges on the nitrogen. There are four chiral atoms in the cation, namely C7, C10, with *S* configuration and N5 and N8, with *R* configuration.

Subsequently, the bicyclic systems (1*R*,2*S*,4*R*,5*S*)-**141** and (1*S*,2*S*,4*S*,5*S*)-**142** were obtained upon double *N*-alkylation of piperazine (2*S*,5*S*)-**140** by subjecting it to the same conditions as above (Scheme 2.19). The reaction produced a complex mixture and the separation proved challenging and difficult.



Scheme 2.19 Formation of the chiral DABCOs **141** and **142**

The two resulting diastereomers (1*R*,2*S*,4*R*,5*S*)-**141** and (1*S*,2*S*,4*S*,5*S*)-**142** were purified and separated by silica gel column chromatography with a combined yield of 23%. The original (^{1}H, ^{13}C and HMQC) NMR assignment was confirmed by NOESY analysis of the two isomers. Of

the transient NOEs observed, those were crucial for assignments of stereochemistry are shown in Figure 2.9. For both isomers, correlations between geminal protons (Ha and Ha'; Hb and Hb') and between protons that are close in space (Ha and Hb) were indeed observed as expected for both diastereomers. A diagnostic NOE was observed between Hb and Ha' for compound **141**. For compound **142**, the crucial observation is a transient NOE between Hd and Hb. Moreover, no NOE correlation between any of the benzylic protons Ha/Ha' and the protons assigned to the non-substituted bridge, Hb and Hb' was observed for **142**. Thus, it may be concluded that the naphthyl substituents point away from these protons and therefore away from the ethylene bridge. With this evidence in hand, the two diastereomers were assigned to structures (1*R*,2*S*,4*R*,5*S*)-**141** and (1*S*,2*S*,4*S*,5*S*)-**142**.

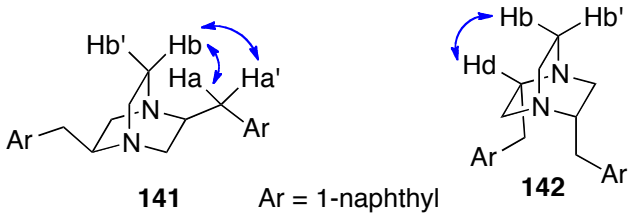
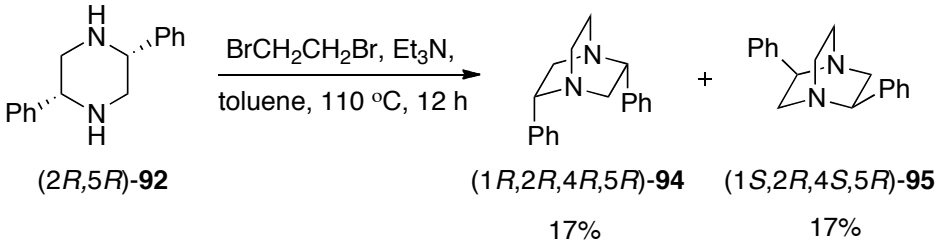


Figure 2.9 Transient NOEs observed that proved crucial for assignment of stereochemistry

Due to the difficulty in accessing the substituted naphthalene DABCO systems, it was concluded not to pursue this system further.

Extending the same strategy to diphenylpiperazine we found that direct alkylation of (2*R*,5*R*)-**92** could give **94** and **95** in one step (Scheme 2.20). Thus, refluxing enantiomerically pure diphenylpiperazine (2*R*,5*R*)-**92** in 1,2-dibromoethane in the presence of triethylamine for 12 hours gave a diastereomeric mixture (ratio 1:1). Silica gel chromatography separation followed by recrystallisation gave pure (1*R*,2*R*,4*R*,5*R*)-**94** and (1*S*,2*R*,4*S*,5*R*)-**95** both in 17% isolated yield. The diagnostic singlet peak at 3.08 ppm observed in the ^{1}H NMR, which is characteristic

to the CH_2 of the nitrogen bridgehead (4H) was identified as belonging to (1*R*,2*R*,4*R*,5*R*)-**94**, according to previous observations.



Scheme 2.20 Formation of chiral DABCOs **94** and **95**

The X-ray structure of (1*R*,2*R*,4*R*,5*R*)-**94** showed the relative configuration corroborating NMR analysis.

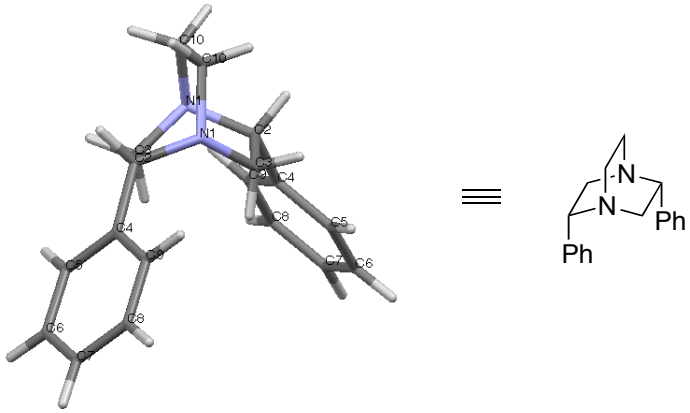
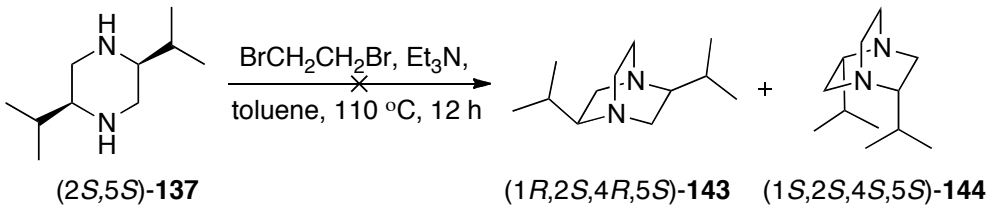


Figure 2.10 X-ray structure of chiral DABCO **94**

Attempts to isolate the bicyclic isomers of the piperazine (2*S*,5*S*)-**137** upon double *N*-alkylation with dibromoethane proved unsuccessful (Scheme 2.21).

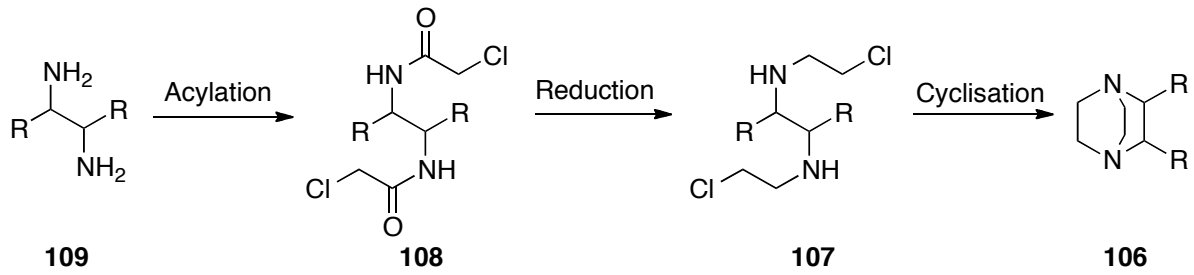


Scheme 2.21 Attempted formation of chiral DABCOs **143** and **144**

In summary, these studies have shown that the synthesis of 2,5-disubstituted chiral DABCO derivatives is feasible. This strategy could give a variety of non-racemic 2,5-disubstituted-DABCOs, since the optically active amino acid starting materials are readily available. The bicyclic systems can be obtained using the direct alkylation of the piperazine precursors with 1,2-dibromoethane. The methodology has the advantage of a short synthetic route, high yields, operationally simple, and cheap starting materials. However, the difficulty in separating diastereomeric mixtures was the limitation of this route.

2.3 Synthesis of 2-Substituted and 2,3-Disubstituted-DABCO Derivatives

The search for new and more versatile synthetic routes to chiral DABCO motifs led to investigation into the vicinal diamines approach (Scheme 2.22).[98]



Scheme 2.22 Synthetic route to 2,3-disubstituted DABCO systems **106**

During the course of this project, only chiral vicinal diamines (1*R*,2*R*)-1,2-bis(2-hydroxyphenyl)ethylenediamine **145** and (1*R*,2*R*)-1,2-diphenylethylenediamine **76** were commercially available (Figure 2.11).

(1*R*,2*R*)-**145** (1*R*,2*R*)-**76**

Figure 2.11 Commercially available vicinal diamines **145** and **76.**

We sought to synthesize a small library of enantiomerically pure diamines that could be used as starting materials for the synthesis of chiral 2-substituted and 2,3-disubstituted DABCO derivatives. Monosubstituted chiral diamines (*R*)-**146** and (*R*)-**147**, and disubstituted chiral diamines (1*R*,2*R*)-**76**, (1*S*,2*S*)-**148**, (1*S*,2*S*)-**149** and (1*S*,2*S*)-**150** were selected as preliminary precursors for this study (Figure 2.11 and Figure 2.12). These diamines were chosen to allow us to examine the effect of unsubstituted aryl groups (1*R*,2*R*)-**76**, (*R*)-**146** and (*R*)-**147**, substituted electron withdrawing groups at the para position (1*S*,2*S*)-**148** and sterically bulky groups (1*S*,2*S*)-**149** and (1*S*,2*S*)-**150** on the chiral DABCO derivatives.

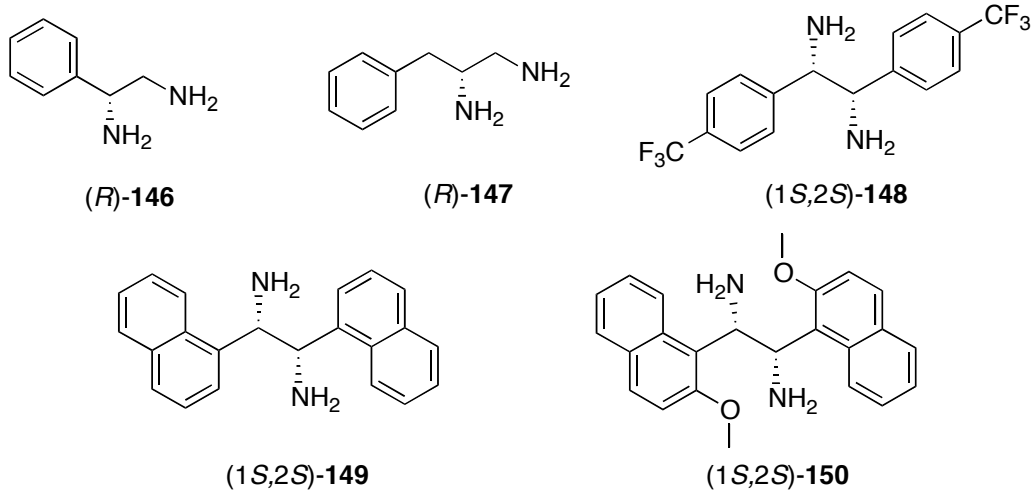
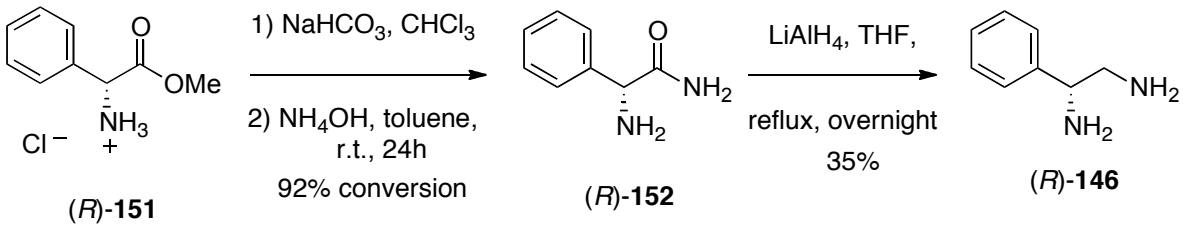


Figure 2.12 Selected diamines for chiral DABCO synthesis

2.3.1 Synthesis of Monosubstituted Vicinal Diamines 146 and 147

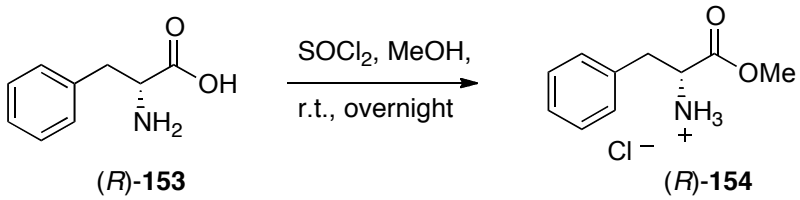
The synthesis of (*R*)-1-phenylethane-1,2-diamine **146** was envisaged over a two-step approach according to a literature procedure (Scheme 2.23).[116] In the first step commercially available amino acid (*R*)-phenylglycine methyl ester hydrochloride **151** was neutralised with saturated aqueous solution of sodium bicarbonate and then treated with saturated ammonium hydroxide solution in toluene at room temperature for 24 hours. This reaction furnished (*R*)-2-amino-2-phenylacetamide **152** in 92% conversion. Reduction of the acetamide (*R*)-**152** with 3 equivalents

of lithium aluminium hydride in tetrahydrofuran delivered the diamine (*R*)-**146** in 35% yield, after distillation.



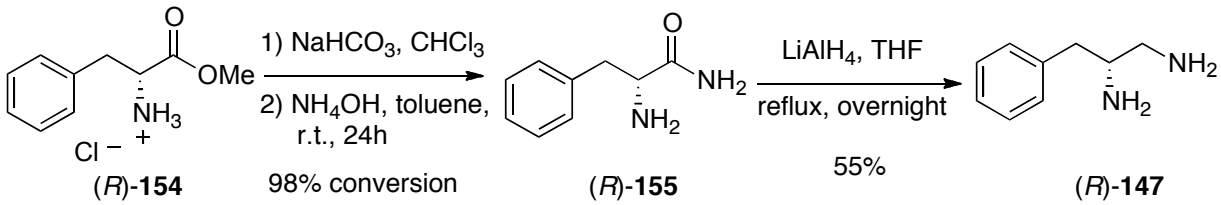
Scheme 2.23 Synthesis of monosubstituted diamine (*R*)-**146**

The synthesis of (*R*)-3-phenylpropane-1,2-diamine **147** was accomplished in a four step procedure. (*R*)-1-Methoxy-1-oxo-3-phenylpropan-2-aminium chloride salt **154** is commercially available, but its high cost led us to prepare it from a cheaper material in one step. Thus, commercially available *L*-phenylalanine **153** was treated with thionyl chloride in methanol at room temperature overnight affording the amino acid methyl ester hydrochloride salt (*R*)-**154** in quantitative yield (Scheme 2.24).



Scheme 2.24 Formation of hydrochloride salt (*R*)-**154**

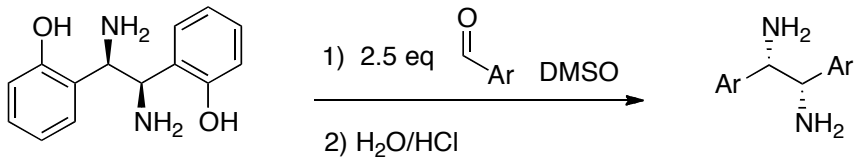
The hydrochloride (*R*)-**154** was neutralised with sodium bicarbonate and then treated with saturated ammonium hydroxide solution in toluene at room temperature for 24 hours to furnish (*R*)-2-amino-3-phenylpropanamide **155** in 98% conversion. Reduction of the acetamide with 3 equivalents of lithium aluminium hydride in refluxing tetrahydrofuran afforded the diamine (*R*)-**147** in 55% yield, after distillation (Scheme 2.25).



Scheme 2.25 Synthesis of monosubstituted diamine (*R*)-**147**

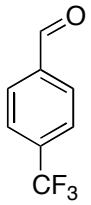
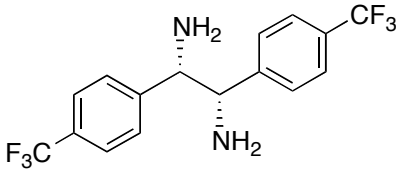
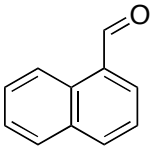
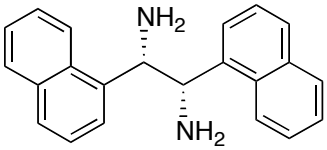
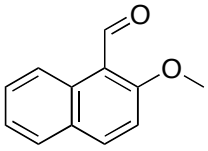
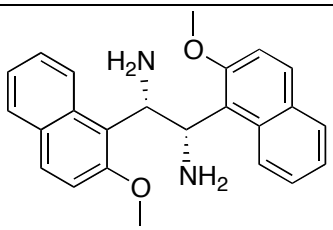
2.3.2 Synthesis of Chiral Disubstituted Vicinal Diamines 148, 149 and 150

We next turned our attention to the preparation of diamines (1*S,*2*S*)-**148**, (1*S,*2*S*)-**149** and (1*S,*2*S*)-**150**, using the protocol of Chin and co-workers.[117] Thus, we studied the reaction of (*R,R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane **145** with selected aryl aldehydes. The diaminoethane (1*R,*2*R*)-**145** was treated with aryl aldehydes **156**, **157** and **158** at room temperature overnight. The resulting imine intermediates were hydrolysed with a hydrochloric acid solution at ambient temperature for 12 hours affording the diamines (1*S,*2*S*)-**148**, (1*S,*2*S*)-**149** and (1*S,*2*S*)-**150** in 72%, 87% and 66% yield respectively, after neutralisation of the dihydrochloride salt with sodium hydroxide solution (Table 2.3).



(1*R*,2*R*)-**145**

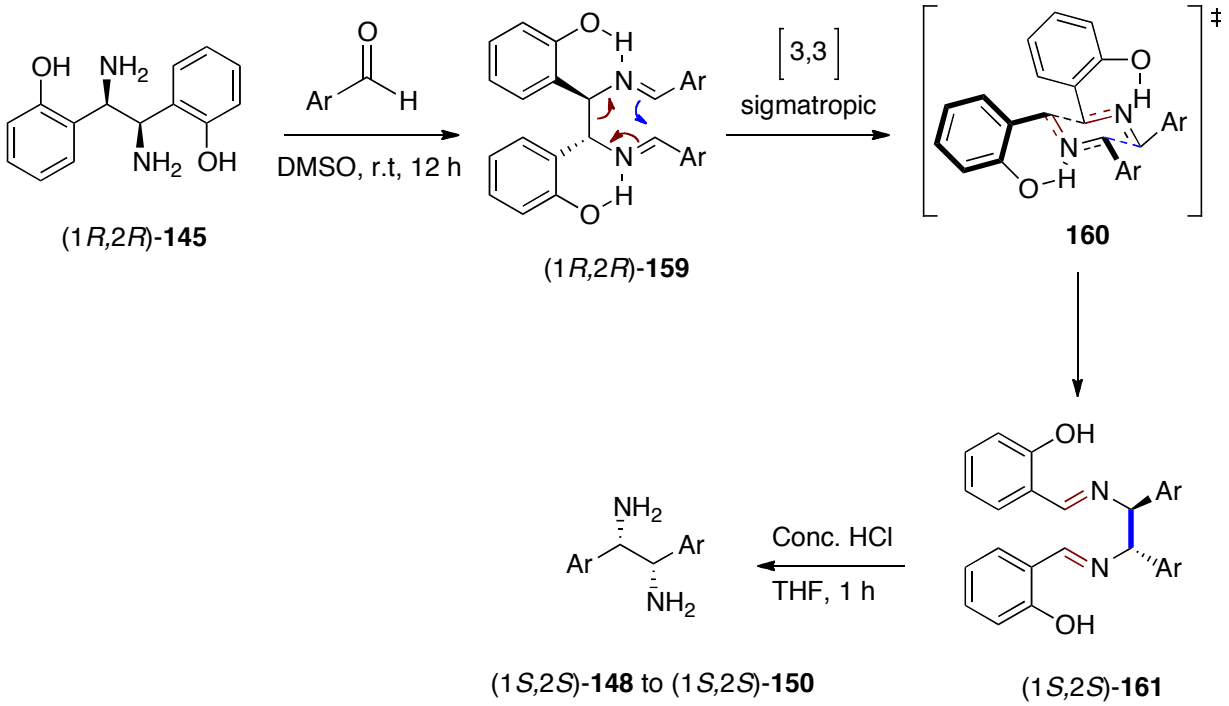
(1*S*,2*S*)-**148** to (1*S*,2*S*)-**150**

Entry	Aldehyde	Product	Yields [%]	Yields [%][a]
1	 **156**	 (1*S*,2*S*)-**148**	72	80
2	 **157**	 (1*S*,2*S*)-**149**	87	78
3	 **158**	 (1*S*,2*S*)-**150**	66	-

[a]literature yield

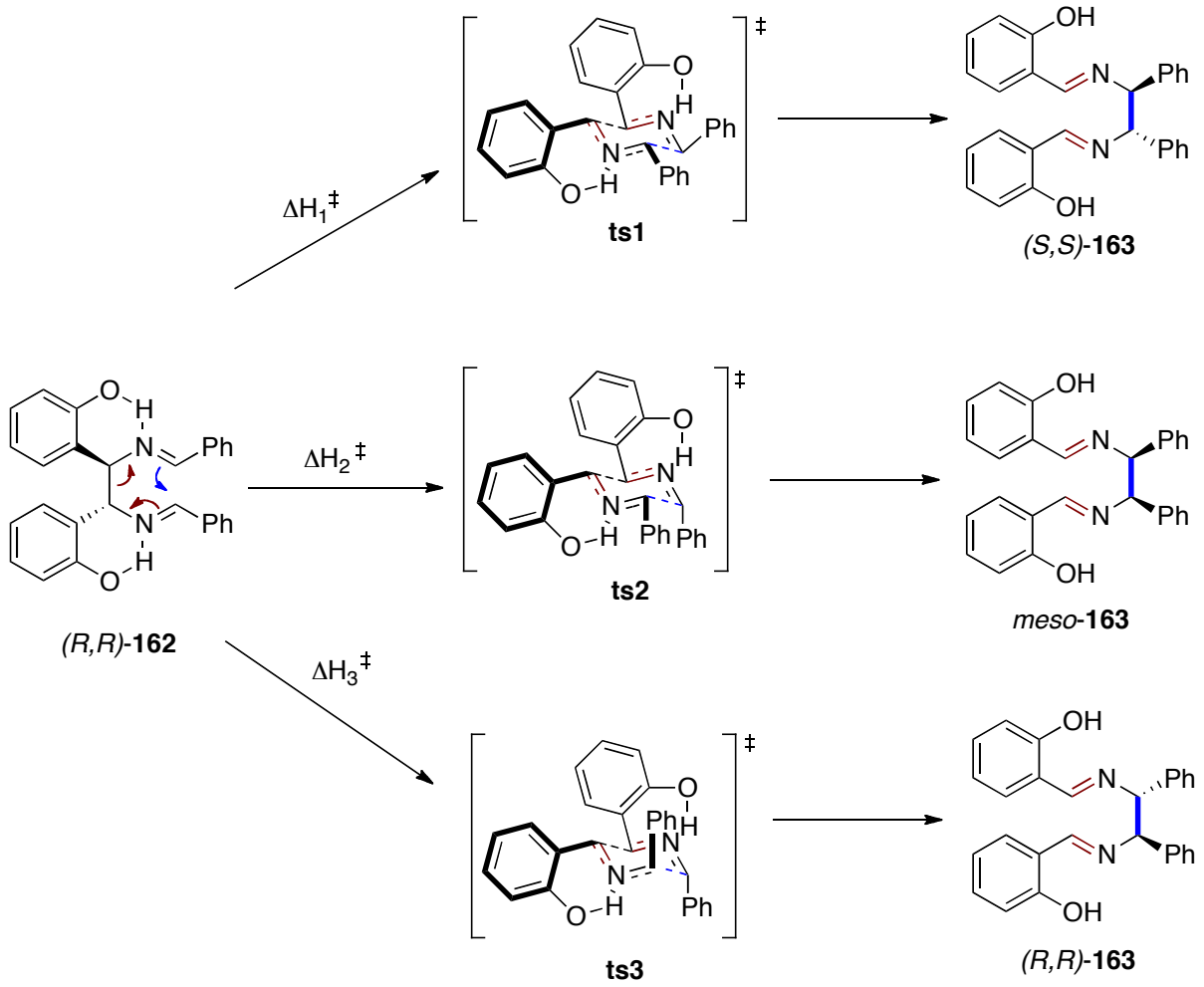
Table 2.3 Synthesis of the targeted disubstituted vicinal diamines

The common chiral diamine (1*R*,2*R*)-**145** reacts with the aldehydes to form the initial diimines (1*R*,2*R*)-**159**. These intermediates undergo a stereospecific diaza-Cope rearrangement that proceeds through a chair-like transition state **160** where all substituents adopt pseudoequatorial positions to form diimines **161**. The stilbene diamine products (1*S*,2*S*)-**148** to (1*S*,2*S*)-**150** are formed after the hydrolysis of diimines (1*S*,2*S*)-**161** (Scheme 2.26).



Scheme 2.26 Vicinal diamines synthesis pathways

Chin and co-workers considered three chairlike transition states for the diaza-Cope rearrangement reaction (Scheme 2.27). Among these structures, transition state 1 (**ts-1**) is expected to be the most stable since all aryl substituents are in pseudoequatorial positions. In fact, density functional theory (DFT) calculations performed by Chin *et al.* showed that **ts-1** is more stable than **ts-2** and **ts-3** by about 7.7 and 15.3 kcal/mol, respectively. Thus one phenyl group in the pseudoaxial position (**ts-2**) should result in about 4×10^{5}-fold decrease in the rate of rearrangement at ambient temperature. Therefore, the reaction of (*R*,*R*)-**162** through **ts-1** is expected to produce (*S*,*S*)-**163**.



	ΔH‡ (Kcal/mol)	ΔH‡- ΔH1‡
ts-1	15.4	–
ts-2	23.1	7.7
ts-3	30.7	15.3

Scheme 2.27 Calculated activation enthalpies for the three possible chairlike transition states [117]

In contrast, reactions of (*R*,*R*)-**162** through **ts-2** or **ts-3** are expected to produce *meso*-**163** or (*R*,*R*)-**163** respectively (Scheme 2.27). Thus, the DFT calculations indicate that the rearrangement should take place exclusively by **ts-1** with apparent inversion in stereochemistry. According to Chin and co-workers, the driving force behind this reaction is the resonance assisted hydrogen bonds (RAHBs) as subtle changes in the strength of H-bonds can have

dramatic effects on the equilibria for diaza-Cope rearrangements. In order to understand the difference in the strength of the H-bonds in (*R*,*R*)-**162** and (*S*,*S*)-**163**, they examined the H-bonds in **A** and **B** (Figure 2.13).[118] Delocalization of the lone pair electrons on the oxygen of **A** resulted in some charge separation. Charged H-bonds are stronger than neutral H-bonds since they are reinforced by favorable electrostatic interactions. Unlike in **A**, resonance-assisted charge separation is not possible in **B**. This explanation provided some intuitive insight into why the H-bond in **A** may be stronger than that in **B**. DFT computation showed that the RAHB in **A** is about 2.7 kcal/mol stronger than regular hydrogen bonds. Thus, the two RAHBs in (*S*,*S*)-**163** are expected to be about 2.7 kcal/mol stronger than the two regular hydrogen bonds in (*R*,*R*)-**162**. If the relative stability of compounds (*R*,*R*)-**162** and (*S*,*S*)-**163** is solely dependent on the strengths of the H-bonds, (*S*,*S*)-**163** should be more stable than (*R*,*R*)-**162** by about 5.4 kcal/mol. DFT computation revealed that (*S*,*S*)-**163** is about 6.8 kcal/mol more stable than (*R*,*R*)-**162**. ^{1}H NMR indeed revealed that (*R*,*R*)-**162** rearranged to (*S*,*S*)-**163** to completion within detection limits. Chin concluded that the equilibrium for the rearrangement of (*R*,*R*)-**162** is largely controlled by the strength of the H-bonds.

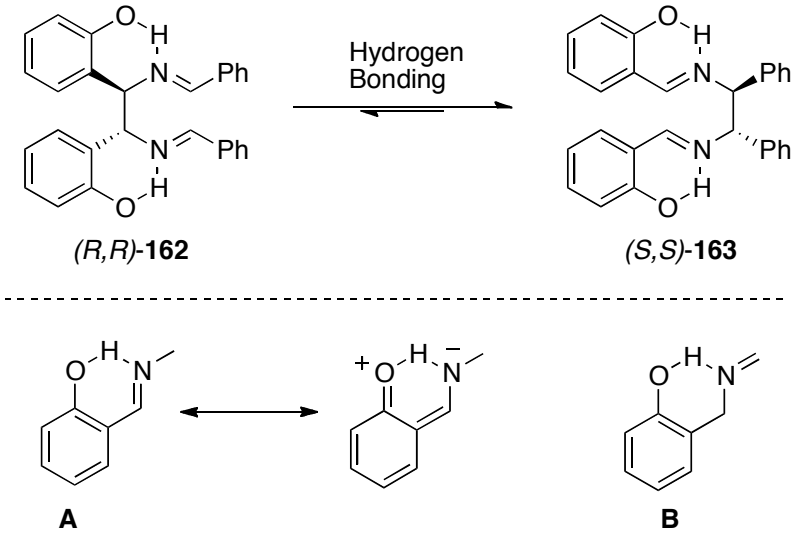
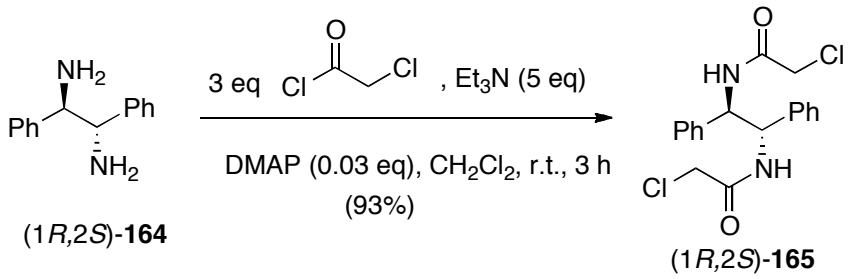


Figure 2.13 Diaza-Cope rearrangement controlled by hydrogen bonding

The specific rotation of the hydrochloride salts of diamines (*S,S*)-**148** and (*S,S*)-**149** were in agreement with the reported values[117] {(*S,S*)-**148** $[\alpha]_{23}^{D}$ = -36 (c 0.5, MeOH); lit. for (*R,R*)-**148** $[\alpha]_{27}^{D}$ = +33 (c 1.0, MeOH) and for (*S,S*)-**149** $[\alpha]_{23}^{D}$ = +266 (c 0.56, H_2O); lit. for (*S,S*)-**149** $[\alpha]_{25}^{D}$ = +235 (c 1.0, H_2O)}. Diamine salt of (*S,S*)-**150** has a specific rotation of $[\alpha]_{25}^{D}$ = -160 (c 0.8, CH_3OH) as it is a novel compound.

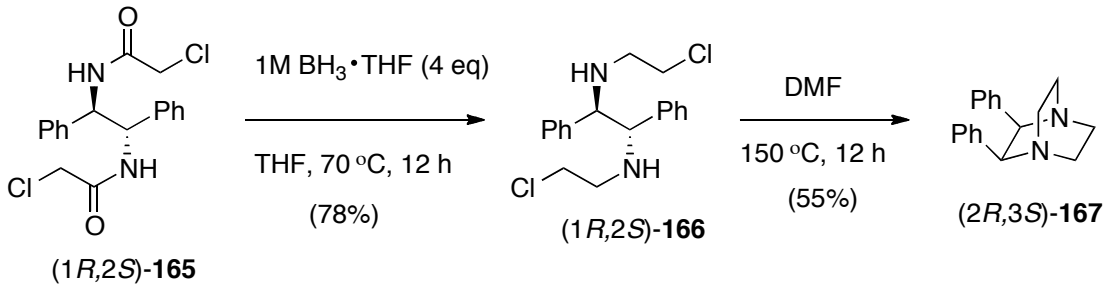
2.3.3 Synthesis of Chiral DABCOs

We began our investigation into the synthesis of the chiral DABCO derivatives using the vicinal diamine approach described by Sharpless and co-workers. Initially, the synthesis focused mainly in the formation of the (*R,S*) and (*R,R*)-2,3-diphenyl-DABCO derivatives. Firstly, the formation of the *meso* diastereoisomer was performed to validate the strategy before applying to the enantiopure chiral diamines. Thus, chloroacetylation of (1*R,*2*S*)-**164** using 3 equivalents of chloroacetyl chloride in the presence of 5 equivalents of triethylamine and a catalytic amount of DMAP gave (1*R,*2*S*)-**165** in 93% yield, after silica gel column chromatography (Scheme 2.28).



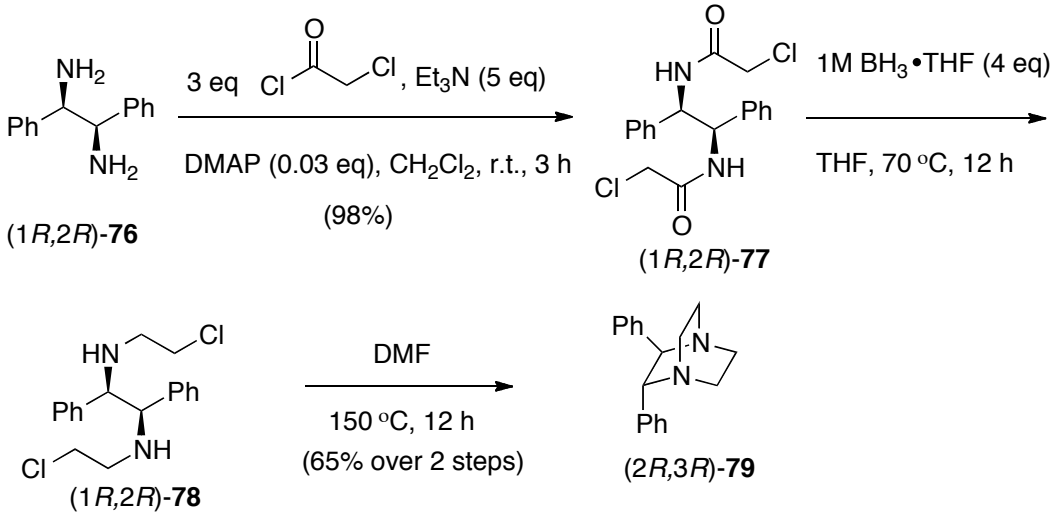
Scheme 2.28 Chloroacetylation of (1*R*,2*S*)-**164**

The reduction of the diacylated compound (1*R,*2*S*)-**165** was performed with borane-tetrahydrofuran complex in refluxing THF for 12 hours and subsequently quenched with 1M hydrochloric acid generating (1*R,*2*S*)-**166** in 78% conversion, after acid-base extraction. Double cyclisation of the reduced diacylated (1*R,*2*S*)-**166** in refluxing dimethylformamide for 12 hours gave the *meso* (*R,S*)-2,3-diphenyl-DABCO **167** in moderate yield (Scheme 2.29).



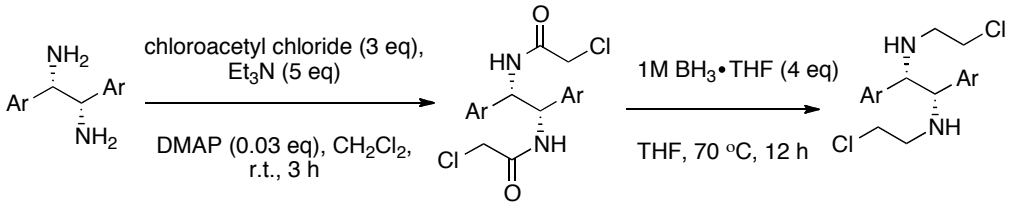
Scheme 2.29 Synthesis of non-chiral DABCO (2*R*,3*S*)-**167**

Pleasingly, this methodology was suitable for the preparation of the (*R,R*)-2,3-diphenyl-DABCO **79** derivative (Scheme 2.30). The diacylated product (1*R,*2*R*)-**77** was obtained in excellent yield, subsequent reduction was performed with BH_3•THF complex. This reduced product (1*R,*2*R*)-**78** was not isolated but subjected directly to the cyclization process to deliver (*R,R*)-2,3-diphenyl-DABCO **79** in 65% yield over two steps, after silica gel column chromatography. The structure of the final product (2*R,*3*R*)-**79** was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis and mass spectrometry. More importantly, the optical rotation was verified by using the other (2*S,*3*S*)-enantiomer reported by Sharpless. {For (2*R,*3*R*)-**79** $[\alpha]_{25}^{D}$= -93.9 (c 0.5, MeOH); lit.[98] for (2*S,*3*S*)-**79** $[\alpha]_{25}^{D}$= +93.1 (c 4.34, MeOH)}.



Scheme 2.30 Synthesis of chiral-DABCO (2*R,*3*R*)-**79**

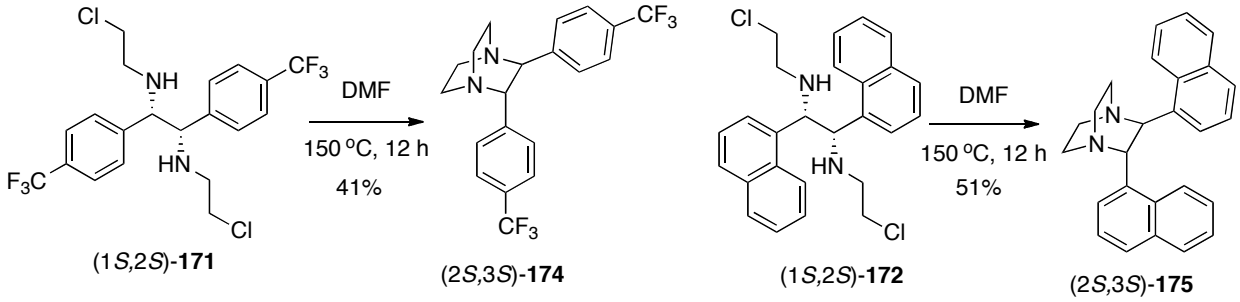
Based on the results obtained with 2,3-diphenyl DABCO derivatives, we investigated the efficiency of the methodology described above on diamines (1*S*,2*S*)-**148**, (1*S*,2*S*)-**149** and (1*S*,2*S*)-**150** (Scheme 2.31). Chloroacetylation was achieved with chloroacetyl chloride giving the isomers (1*S*,2*S*)-**168**, (1*S*,2*S*)-**169** and (1*S*,2*S*)-**170** in moderate to good yields followed by reduction with BH_3•THF complex.



(1*S*,2*S*)-**148:** Ar = $PhCF_3$ (1*S*,2*S*)-**168:** Ar = $PhCF_3$ (34%) (1*S*,2*S*)-**171:** Ar = $PhCF_3$
(1*S*,2*S*)-**149:** Ar = 1-Naphthyl (1*S*,2*S*)-**169:** Ar = 1-Naphthyl (90%) (1*S*,2*S*)-**172:** Ar = 1-Naphthyl
(1*S*,2*S*)-**150:** Ar = 2-methoxynaphthyl (1*S*,2*S*)-**170:** Ar = 2-methoxynaphthyl (25%) (1*S*,2*S*)-**173:** Ar = 2-methoxynaphthyl

Scheme 2.31 Chloroacetylation and reduction of selected diamines

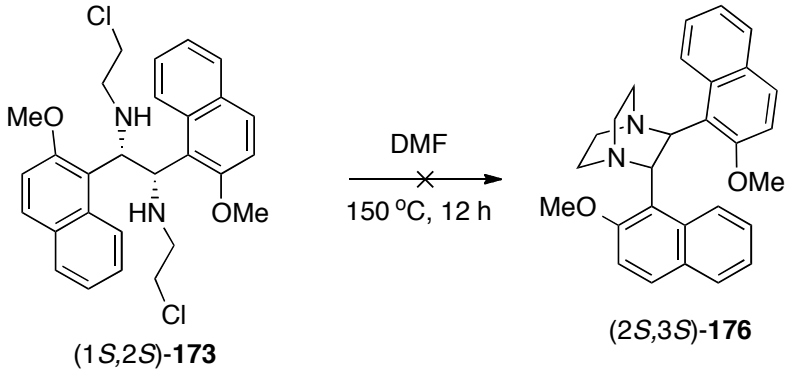
The cyclisation of the intermediates (1*S*,2*S*)-**171** and (1*S*,2*S*)-**172** gave the chiral DABCO (2*S*,3*S*)-**174** and (2*S*,3*S*)-**175** in 41% and 51% yield, over two steps (Scheme 2.32).



(1*S*,2*S*)-**171** (2*S*,3*S*)-**174** (1*S*,2*S*)-**172** (2*S*,3*S*)-**175**

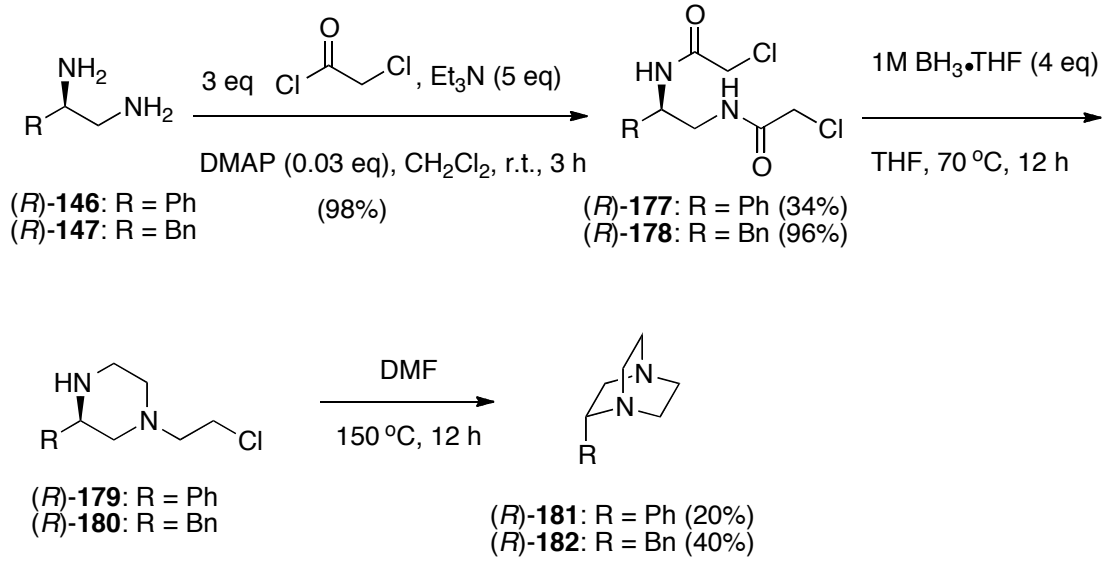
Scheme 2.32 Formation of chiral DABCO (2*S*,3*S*)-**174** and (2*S*,3*S*)-**175**

However, when the same conditions were applied to the isomer (1*S*,2*S*)-**173**, a complex mixture was observed in the ^{1}H NMR and the product could not be isolated (Scheme 2.33).



Scheme 2.33 Attempted formation of chiral DABCO (*S,S*)-**176**

The methodology above was subsequently applied to the preparation of monosubstituted DABCO derivatives (Scheme 2.34). Upon treatment of compounds (*R*)-**177** and (*R*)-**178** with BH_3•THF complex, the expected open chain reduced derivatives were not formed. Instead, the monocyclised products (*R*)-**179** and (*R*)-**180** were obtained as confirmed by mass spectrometry (for (*R*)-**179** a positive ion $C_{12}H_{18}ClN_2$ $[M+H]^+$: 225.7298 and for (*R*)-**180** $C_{13}H_{20}ClN_2$ $[M+H]^+$: 239.1310). The reduced compounds were not isolated but subjected directly to cyclisation conditions giving isomer (*R*)-**181** in 20% yield and isomer (*R*)-**182** in 40% yield.



Scheme 2.34 Formation of mono-chiral DABCO derivatives

2.4 Conclusion

In this chapter, we described the preparation of chiral 2-monosubstituted, 2,3-disubstituted and 2,5-disubstituted DABCO derivatives. In total, eleven chiral DABCO systems have been synthesised, six of which are novel compounds. The synthesis of 2,5-disubstituted DABCO derivatives (Figure 2.14) was achieved starting from commercially available amino acids. These syntheses employ amino acids as the chiral starting materials, a clear advantage due to the large diversity of natural and non-natural amino acid derivatives that could be used for the preparation of structurally tunable N-F reagents. These amino acids were converted into the requisite diketopiperazines, which upon double reduction delivered the enantiopure cyclopiperazines. These latter compounds were functionalised into the desired DABCO motifs.

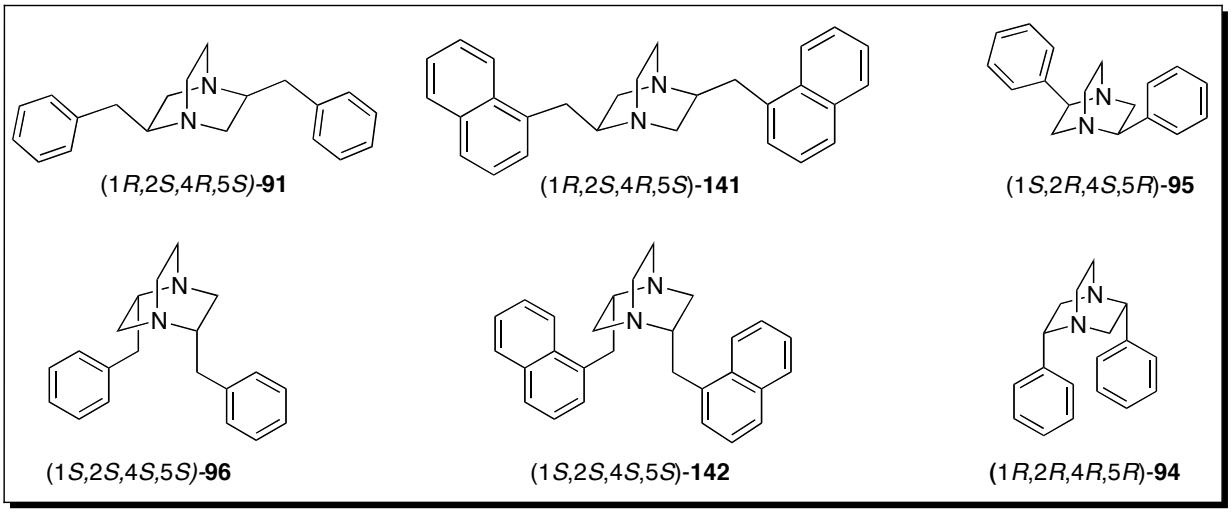


Figure 2.14 Chiral 2,5-disubstituted DABCO derivatives

The strategy of Sharpless was successfully applied in the preparation of the 2-disubstituted and 2,3-disubstituted DABCO derivatives (Figure 2.15). The syntheses relied on chiral vicinal diamines as the starting materials. The chiral diamines were transformed to chloroacetamides. The latter compounds were converted to the requisite chloroethyl diamines, which upon double intramolecular cyclisation gave the targeted DABCO motifs.

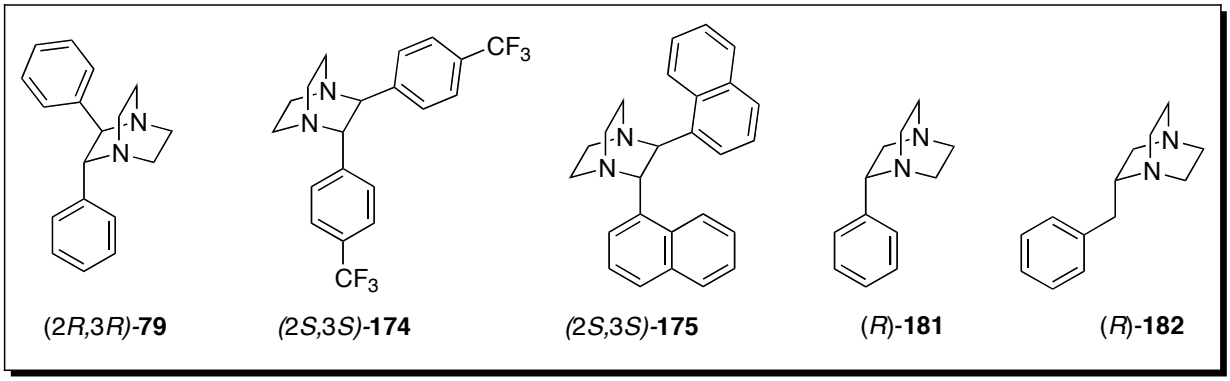


Figure 2.15 Chiral 2-substituted and 2,3-disubstituted DABCO derivatives

Chapter 3

Synthesis of Chiral Selectfluor Analogues

3.1 Introduction

One of the most popular reagents for electrophilic fluorination is 1-chloromethyl-4-fluoro-1,2-diazoniabicyclo[2.2.2]octane, commonly called Selectfluor, an achiral N-F reagent based on the structure of DABCO. In the same way that Selectfluor is prepared from DABCO by alkylation and fluorination, chiral analogues of Selectfluor could be obtained from chiral DABCO-derivatives. Despite their potential as reagents for asymmetric fluorination, chiral derivatives of Selectfluor have not yet been reported. The availability of such reagents could provide a significant advance in the area of asymmetric fluorination especially for poorly activated substrates.

The research carried out in this thesis involved the collaboration of two research laboratories, due to the requirement for special equipment and expertise. This chapter outlines the specific materials and methods used in the handling and manipulation of fluorine gas for the direct fluorination reactions that were performed in the laboratory of Professor Graham Sandford at Durham University. It also describes the synthesis of novel chiral non-racemic Selectfluor derivatives.

3.2 Elemental Fluorine Apparatus

Elemental fluorine is extremely reactive and highly toxic.[119] Fluorine gas reacts spontaneously with atmospheric moisture to give hydrogen fluoride and oxygen or ozone.[120] Consequently, it is necessary to use apparatus, which has been designed specifically to conduct reactions using elemental fluorine in a safe and controllable manner (Figure 3.1). In the Sandford laboratory, elemental fluorine is purchased as a 50% or 20% mixture with nitrogen in high-pressure cylinders (*ca.* 50 L). The fluorine gas is regulated from the primary cylinder at a pressure of 4 bar. This main fluorine cylinder is placed in a vented gas cabinet and is connected to a manifold system *via* a metal-metal connection. It should be pointed out that organic materials, such as

polytetrafluoroethylene (PTFE), are not used in this connection due to the risk of elemental fluorine reacting with such materials because of the relatively high pressure and concentration of fluorine at this stage.

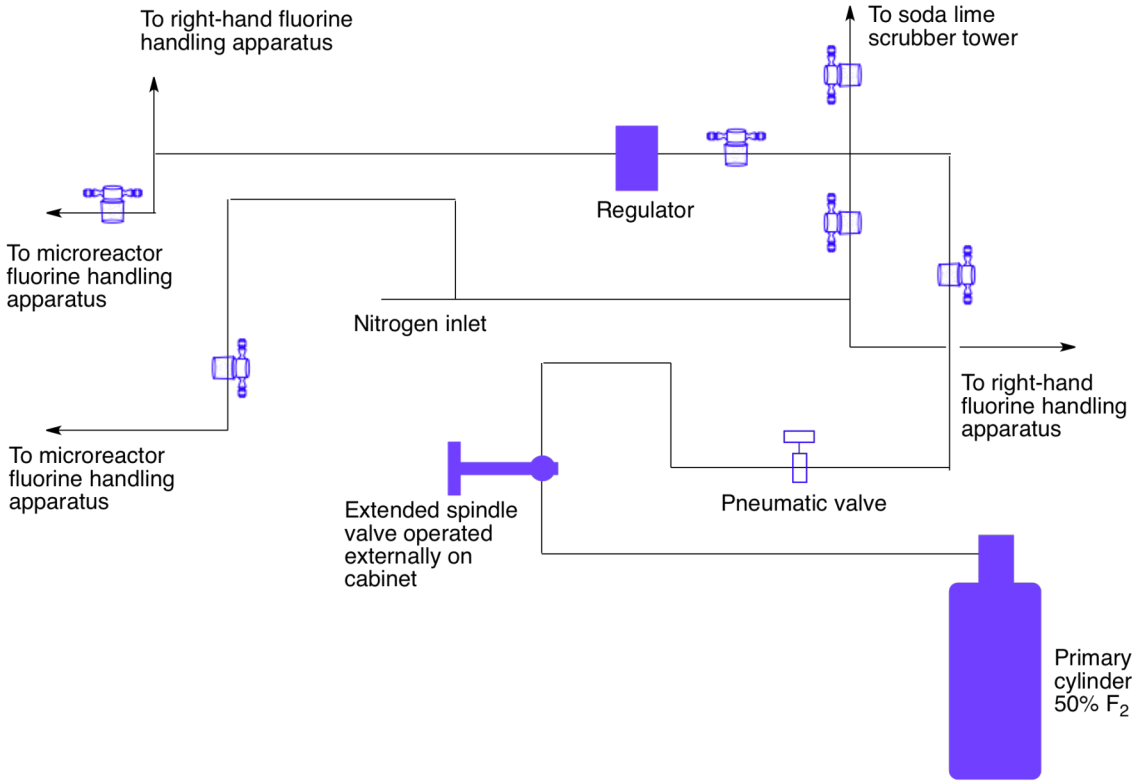


Figure 3.1: Schematic drawing of the laboratory primary rig

The manifold system is equipped with a pneumatic shut-off valve, which can be operated remotely. Fluorine is supplied to two rigs, namely the microreactor rig and the right-hand rig. The right-hand rig (Figure 3.1) is constructed from 1/4" stainless steel tubing, Monel® or stainless steel Swagelok® valves and stainless steel fittings and is housed in a stainless steel fumehood. Using the right hand rig it is possible to fill secondary cylinders (3.7 L) up to a maximum pressure of 5 bar.

These portable cylinders can be detached and installed in other fumehoods, which house small fluorination rigs (Figure 3.2). The small fluorination rig is constructed from stainless steel pipe work and is fitted with Monel® or Swagelok® valves, similar to the right-hand rig. All valves,

tubing, fittings and cylinders, which are used to handle elemental fluorine, are passivated with fluorine before performing fluorination reactions. All reactions described in this chapter were carried out using the small fluorination rig.

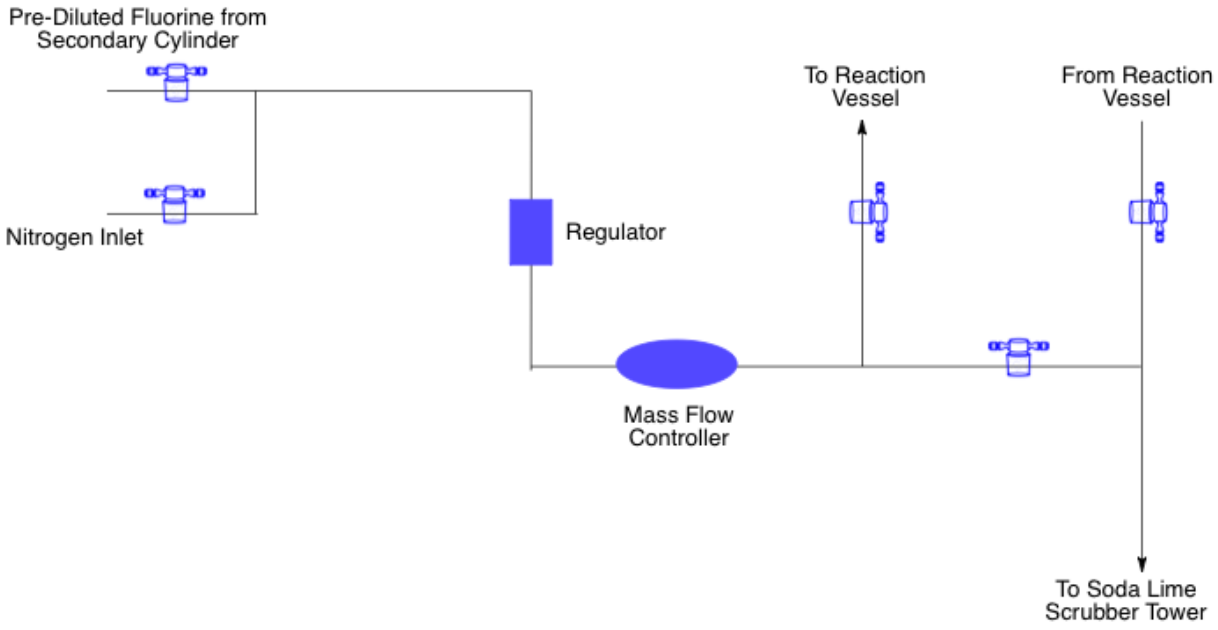


Figure 3.2. Schematic drawing of the laboratory small rig

To perform fluorinations using the small rig, fluorine was run from the secondary cylinder into a PTFE reaction vessel. A mass flow controller was used to control the flow rate of the fluorine. The PTFE reaction vessels were used for direct fluorination reactions under batch conditions. They are equipped with a PTFE pipe, a gas outlet that connects with a scrubber tower (containing potassium iodide) to trap excess fluorine, and a magnetic stirring bar. The rig allowed fluorine gas to be either flushed directly to the soda-lime scrubber tower, or to pass through the reaction mixture.

Fluorine gas is increasingly dangerous at higher concentrations therefore, as a safety precaution, the fluorine used for these experiments was typically 10% (v/v) with N_2. With this diluted source of fluorine, and a specific rate of addition, it is possible to calculate the number of equivalents of fluorine that will be used in a reaction. The amount of fluorine used for each

reaction can only be approximate as fluorine reacts with the regulatory valve diminishing the accuracy addition of fluorine. All reactions were monitored by ^{19}F NMR spectroscopy until complete consumption of the starting materials was observed.

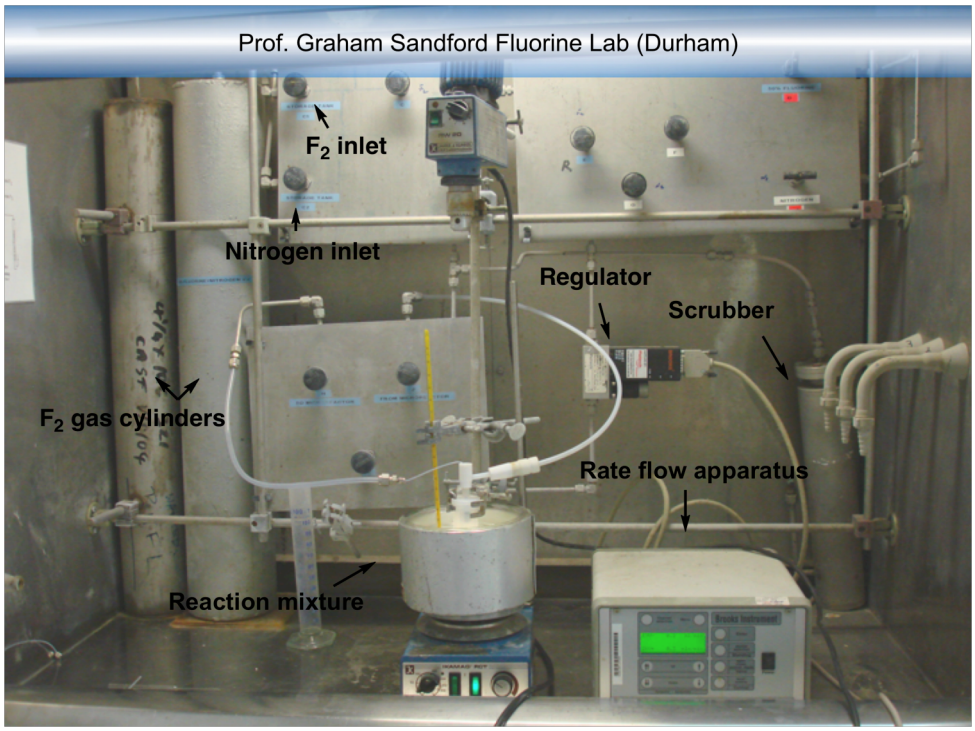
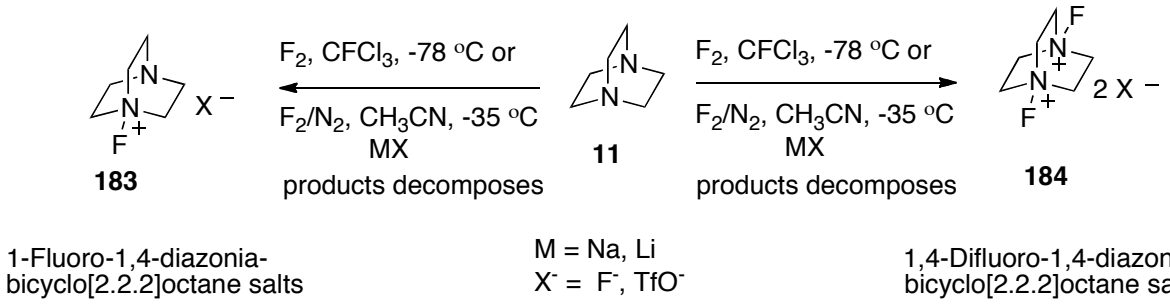


Figure 3.3 Fumehood containing the laboratory small rig.

3.3. Stability of Fluorinated DABCO Compounds

During the conceptual development of Selectfluor, direct fluorination of 1,4-diazabicyclo[2.2.2]octane **11** and its monoquaternary salts were studied with the objective of producing electrophilic fluorinating agents that are stable, easy to handle and safe to use.[121] Banks' attempts to isolate mono-1-fluoro-4-aza-l-azoniabicyclo[2.2.2]octane salts **183** in trichlorofluoromethane at -78 °C or in acetonitrile at -35 °C were unsuccessful (Scheme 3.1).[122] Banks stipulated that if a 'bis-analogue' **184** was prepared, it would be more cost-effective and may provide a more powerful fluorinating agent through the electronic effect induced by the second quaternized nitrogen.[45] However, efforts to prepare 1,4-difluoro-1,4-diazoniabicyclo [2.2.2]octane difluoride **184** using neat fluorine at approximately 20 mmHg or fluorine-nitrogen

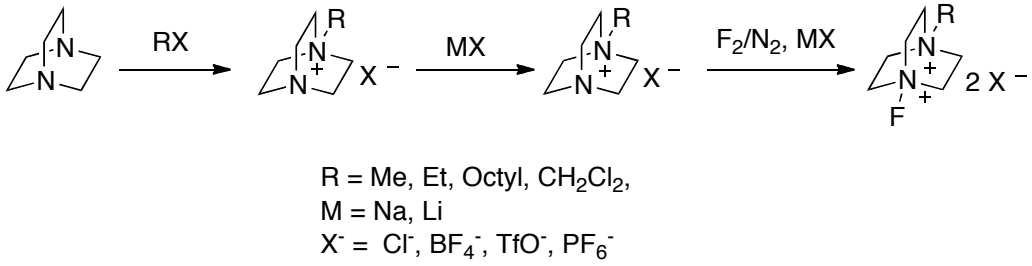
blends at atmospheric pressure, proved unsatisfactory (Scheme 3.1).



Scheme 3.1 Banks' attempts to isolate salts **183** and **184**

Upon synthesis of **183** and **184**, low temperature work-up of the reaction mixtures provided white solids, which readily oxidised iodide to iodine and reacted with phenylmagnesium bromide in diethyl ether to give low yields of fluorobenzene. However, when allowed to warm to room temperature, the newly formed N-F reagents decomposed to red/yellow non-oxidising materials.

This observation led Banks to study the conversion of 1,4-diazabicyclo[2.2.2]octane into quaternary ammonium salts prior to fluorination. The investigation proved successful, as they were able to isolate a variety of stable *N*-fluoroammonium salts (Scheme 3.2).

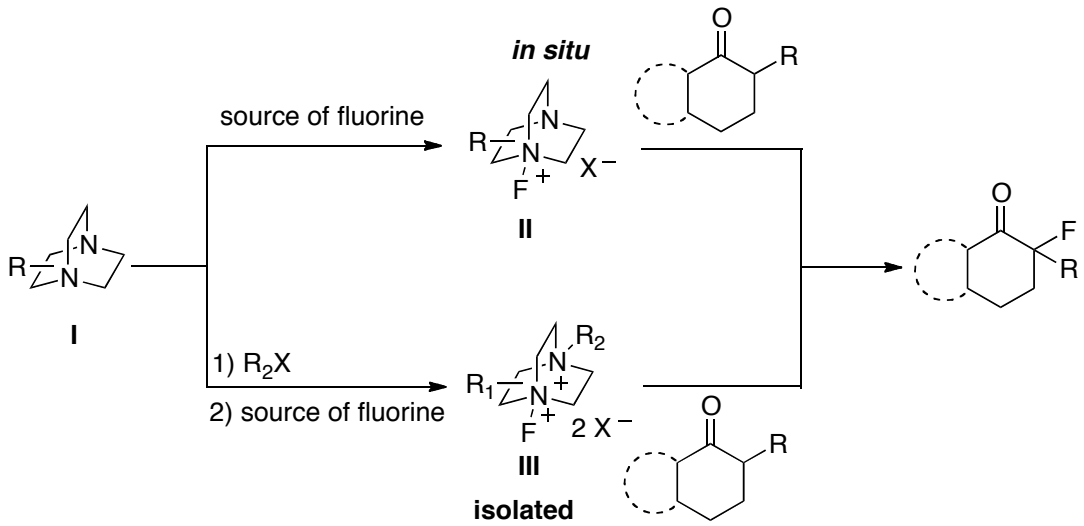


Scheme 3.2 Synthesis of stable fluoroammonium salts.

These observations led us to investigate the synthesis of a series of fluorinated chiral DABCO derivatives at various temperatures and their stability profile.

3.4 Stability Test of Fluorinated Chiral DABCO Precursors

When designing fluorinated chiral DABCO derivatives, our key objectives were to produce reagents of enhanced electrophilicity, thereby allowing high asymmetric induction with the fluorination of a wide range of substrates. It was postulated that the chiral DABCOs could be derivatized and isolated in a similar way to Selectfluor *via* alkylation prior to fluorination. An alternative strategy would be the *in situ* generation of a chiral fluorinating reagent of type **II** that could be tested for the fluorination of prochiral substrates (Scheme 3.3).



Scheme 3.3. Two fluorination strategies

The fluorinations with chiral non racemic fluorinating reagents reported in literature are carried out at low temperature, between 0 °C and -78 °C.[31] Based on Banks' studies on the stability of the mono-fluorinated 1,4-diazabicyclo[2.2.2]octane, it was deemed necessary to assess the stability of mono-fluorinated chiral DABCO analogues **II** produced upon fluorination with Selectfluor at low temperature. Thus, ^{19}F NMR experiments were carried out to probe the stability of any newly formed N-F reagents. Variable temperature (VT) NMR studies were initiated at -80 °C and then warming slowly to room temperature with the aim to monitor the transfer of fluorine from Selectfluor to the chiral DABCO precursor. The two bridgehead

nitrogens on the (*S,S*)-2,3- and (*S,S*)-2,5-disubstituted chiral DABCO systems are equivalent so substitution of either would lead to the same product.

3.4.1 Stability Studies of Chiral N-F 2,5-Disubstituted DABCO Derivatives upon Fluorination with Selectfluor

Initially, the investigation started by recording the ^{19}F NMR spectrum of Selectfluor in acetone-d_6 at -80 °C to use it as a reference. The next step was to follow the fluorine transfer adding (1*S*,2*R*,4*S*,5*R*)-**95** to Selectfluor. The ^{19}F NMR spectrum of Selectfluor in acetone-d_6 at low temperature showed a peak at +45.4 ppm (singlet, Selectfluor N-F). At first instance, 0.5 equivalent of (1*S*,2*R*,4*S*,5*R*)-2,5-diphenyl DABCO **95** was added to the solution of Selectfluor at -80 °C and the spectrum recorded. The spectrum displayed two singlets of equal intensity at +49.2 ppm and +45.4 ppm respectively (Figure 3.4). Upon addition of a further 0.5 equivalent of (1*S*,2*R*,4*S*,5*R*)-**95** at -80 °C almost full transfer from Selectfluor was observed. When the temperature was increased slowly to -60 °C, the signal at +45.4 ppm completely disappeared and only the signal at +49.2 ppm characteristic to N-F (1*R*,2*R*,4*S*,5*R*)-**185** was observed. When the temperature was increased further from -60 °C to -30 °C in 10 °C increments, (1*R*,2*R*,4*S*,5*R*)-**185** started to undergo fragmentation/ decomposition at -40 °C, as two new peaks at -84.1 ppm and -153.7 ppm appeared. At -30 °C the peak at +49.2 ppm in the ^{19}F NMR spectrum had fully vanished (Figure 3.4). This study suggested that the chiral N-F reagent (1*R*,2*R*,4*S*,5*R*)-**185** could be used for *in situ* fluorination at temperatures below -50 °C.

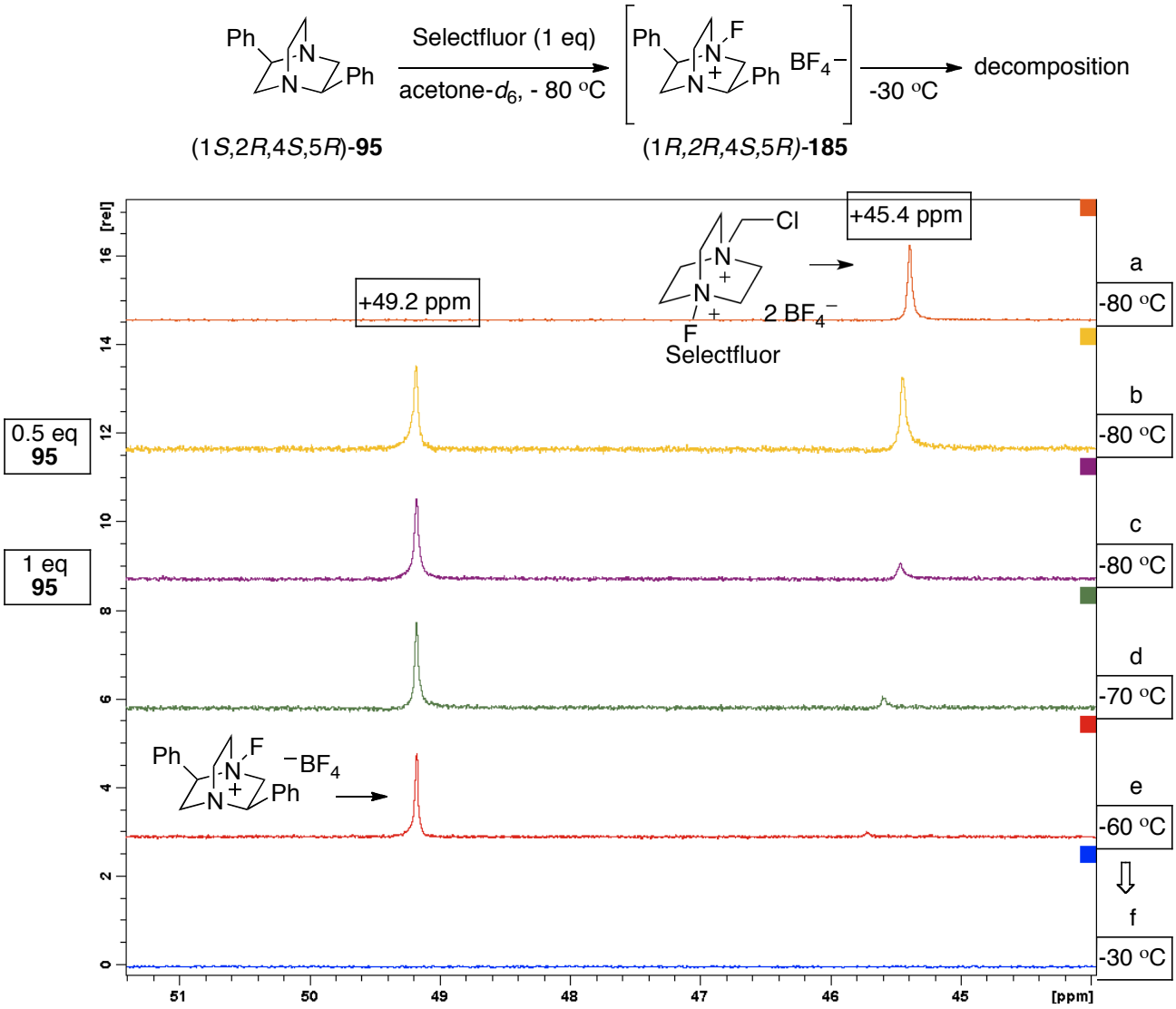


Figure 3.4 ^{19}F NMR spectrum of Selectfluor and the combination with **95** in acetone-d_6. a: Downfield region of the ^{19}F NMR spectrum of Selectfluor in acetone-d_6. b: After addition of 0.5 eq. of **95**. c: After addition of 1.0 eq. of **95**. e: Quantitative formation of **185**. f: Disappearance of **185** peak suggesting decomposition.

The expanded ^{19}F NMR spectrum recorded at -60 °C indicates the formation of (1*R*,2*R*,4*S*,5*R*)-**185** with the N-F signal at +49.2 ppm and the tetrafluoroborate signal at -151 ppm (Figure 3.5). At -30 °C, the signal at +49.2 ppm completely disappeared and additional signals were observed in the negative chemical shift region of the ^{19}F NMR spectrum.

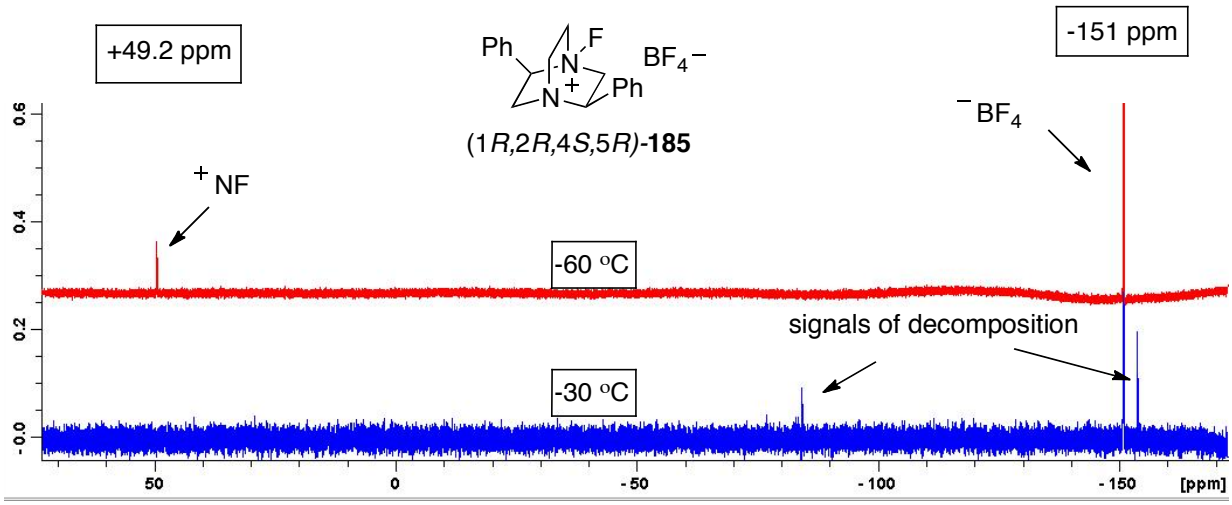
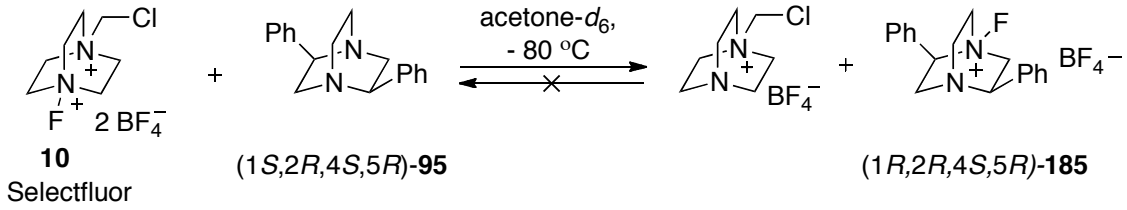


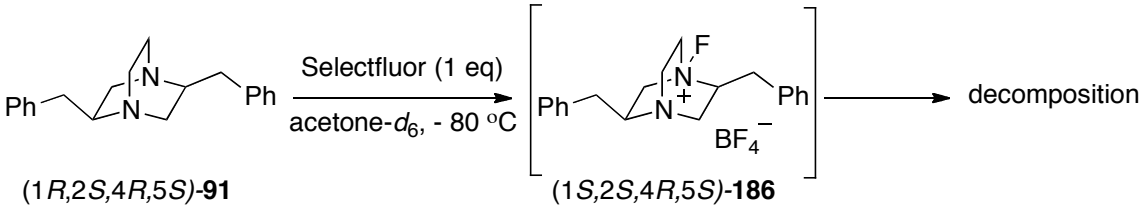
Figure 3.5. ^{19}F NMR spectrum of fluorinated isomer (1*R*,2*R*,4*S*,5*R*)-**185**.

The driving force behind this reaction is that Selectfluor **10**, which is a bis-cationic reagent, is more reactive than the neutral chiral DABCO **95**. Thus transfer of fluorine from Selectfluor to the chiral DABCO (1*S*,2*R*,4*S*,5*R*)-**95** occurred smoothly (Scheme 3.4). The reaction is not reversible as the mono(ammonium) ion (1*R*,2*R*,4*S*,5*R*)-**185** formed is not sufficiently reactive to transfer fluorine back to the quaternary ammonium DABCO.



Scheme 3.4 Fluorination of isomer (1*S*,2*R*,4*S*,5*R*)-**95**

We next investigated the fluorination of (1*R*,2*S*,4*R*,5*S*)-**91** and its stability profile as a function of temperature. Thus, compound (1*R*,2*S*,4*R*,5*S*)-**91** was subjected to fluorination with an equimolar amount of Selectfluor in acetone-d_6 at -80 °C (Scheme 3.5).



Scheme 3.5 Fluorination of isomer (1*R*,2*S*,4*R*,5*S*)-**91**

Upon addition of 1 equivalent of (1*R*,2*S*,4*R*,5*S*)-**91** to Selectfluor, the signal at +45.4 ppm completely disappeared. A signal at +49.3 ppm consistent with $[N\text{-}F]^+$ of (1*S*,2*S*,4*R*,5*S*)-**186** was observed by ^{19}F NMR suggesting successful transfer of fluorine from Selectfluor (Figure 3.6). However, other peaks were observed between -60 ppm and -160 ppm in the ^{19}F NMR spectrum at -80 °C. Warming the sample up to -70 °C resulted in the disappearance of the NF^+ peak suggesting that the fluorinated (1*S*,2*S*,4*R*,5*S*)-2,5-dibenzyl DABCO **186** is instable. This study revealed that unlike N-F (1*R*,2*R*,4*S*,5*R*)-**185**, *in situ* prepared chiral N-F reagent (1*S*,2*S*,4*R*,5*S*)-**186** cannot be used for fluorination at -80 °C.

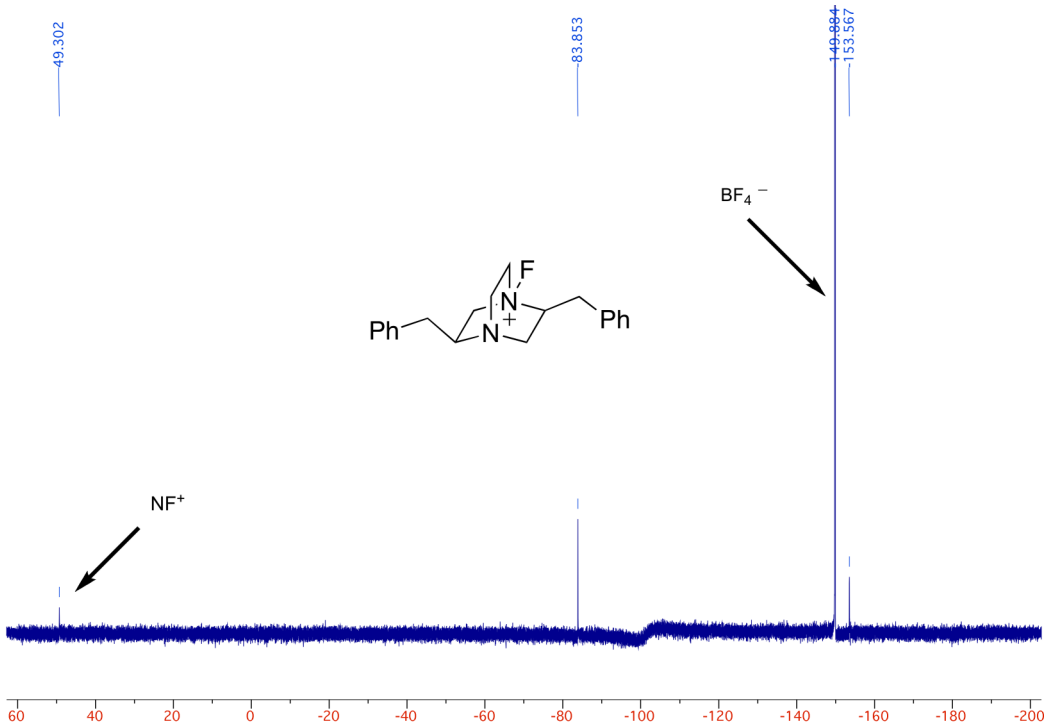
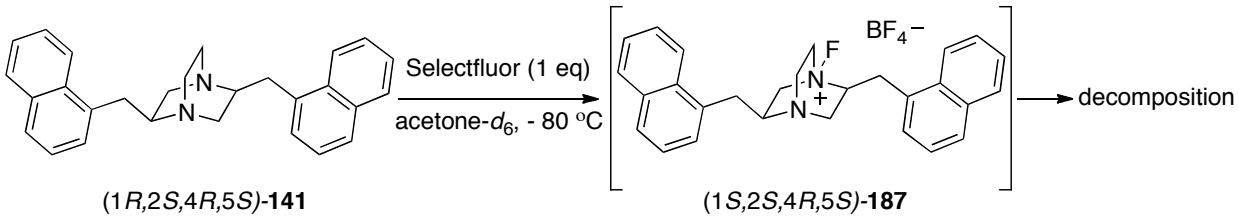


Figure 3.6. ^{19}F NMR of fluorinated isomer (1*S*,2*S*,4*R*,5*S*)-**186** at -80 °C.

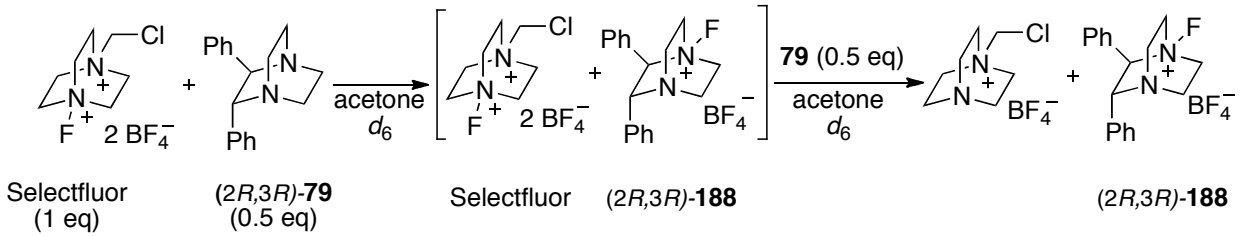
VT NMR experiments were also conducted for the fluorination of (1*R*,2*S*,4*R*,5*S*)-2,5-bis(naphthalen-1-ylmethyl)-1,4-diazabicyclo[2.2.2]octane **141**. When 1 equivalent of (1*R*,2*S*,4*R*,5*S*)-**141** and 1 equivalent of Selectfluor were mixed in acetone-d_6 at -80 °C, a signal at +47.8 ppm in the ^{19}F NMR spectrum suggested the formation of the desired *N*-fluorinated compound, but it was found that (1*S*,2*S*,4*R*,5*S*)-**187** was already unstable at this temperature. Several peaks in the region of -60 to -160 ppm in the ^{19}F NMR spectrum that could not be assigned indicate the presence of products resulting from decomposition of **187** (Scheme 3.6).



Scheme 3.6 Fluorination of (1*R*,2*S*,4*R*,5*S*)-**141**

3.4.2 Stability Studies of Chiral N-F 2,3-Disubstituted DABCO Derivatives upon Fluorination with Selectfluor.

The study started with the fluorination of the (*R,R*)-2,3-diphenyl DABCO derivative **79** at low temperature. As in previous studies, the diagnostic signal corresponding to Selectfluor was recorded at +45.4 ppm in the ^{19}F NMR spectrum at -80°C and served as a reference. Then, addition of 0.5 equivalent of (2*R,*3*R*)-**79** to the solution of Selectfluor showed two singlet peaks at +47.6 ppm and +45.4 ppm in the ^{19}F NMR spectrum corresponding to N-F peaks of 1,2-diphenyl DABCO **188** and Selectfluor respectively (Figure 3.7).



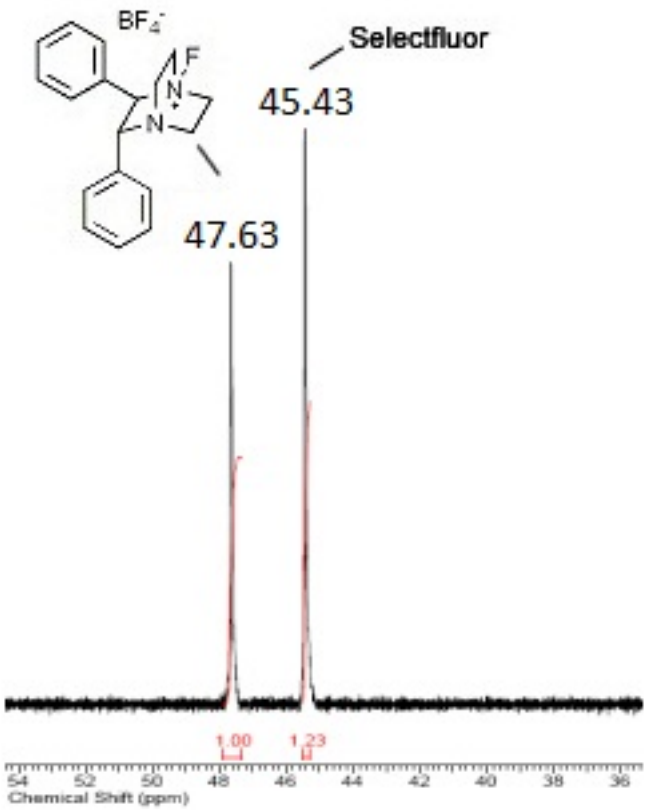
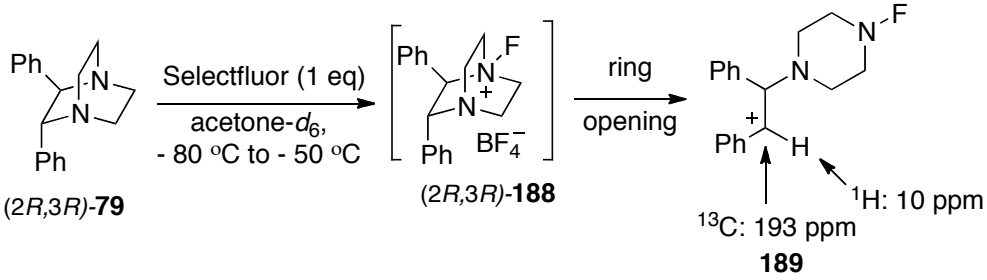


Figure 3.7 ^{19}F NMR of mono-fluorinated (*R,R*)-2,3-diphenyl DABCO **188** and Selectfluor

Addition of another 0.5 eq. of (2*R,*3*R*)-**79** led to disappearance of the peak at +45.4 ppm, and therefore complete transfer of fluorine from Selectfluor has occurred. Pleasingly, only 2 peaks were observed in the ^{19}F NMR spectrum, the characteristic one at -151 ppm corresponding to BF_4^- and a second peak at +47.6 ppm. These observations are consistent with the formation of the desired (2*R,*3*R*)-**188** at -80 °C. When the temperature was increased from -80°C in 10°C increments, (2*R,*3*R*)-**188** started to undergo fragmentation/decomposition at -50°C, as four new peaks at -84 ppm and between – 138 ppm and -153 ppm appeared, in accordance with what had been observed at higher temperature for the other chiral DABCO derivatives. At -30°C the

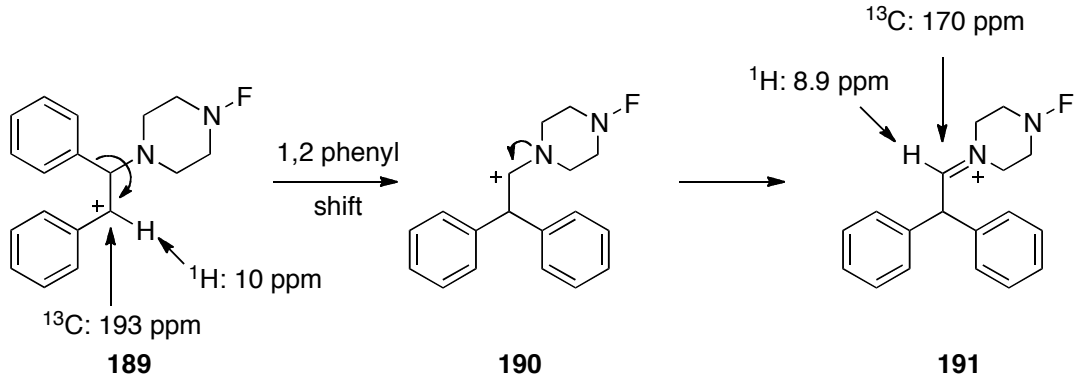
characteristic peak at +47.6 ppm corresponding to the presence of NF (*R,R*)-2,3-diphenyl DABCO **188** had completely vanished.

During the decomposition process, a peak at 10 ppm in the ^{1}H NMR spectrum draws our attention and further analysis of the heteronuclear single quantum coherence (HSQC) revealed that the corresponding proton couples to a carbon at 193 ppm. According to the literature,[123, 124] ^{1}H NMR of secondary benzylic carbocations are observed between 8 to 10 ppm and the corresponding ^{13}C NMR peaks typically appear between 190 to 220 ppm.[125] It is therefore reasonable to assume that the peaks observed in **189** might correspond to the product of E1 elimination of the fluorinated chiral DABCO leading to the stabilised benzylic carbocation **189** (Scheme 3.7).



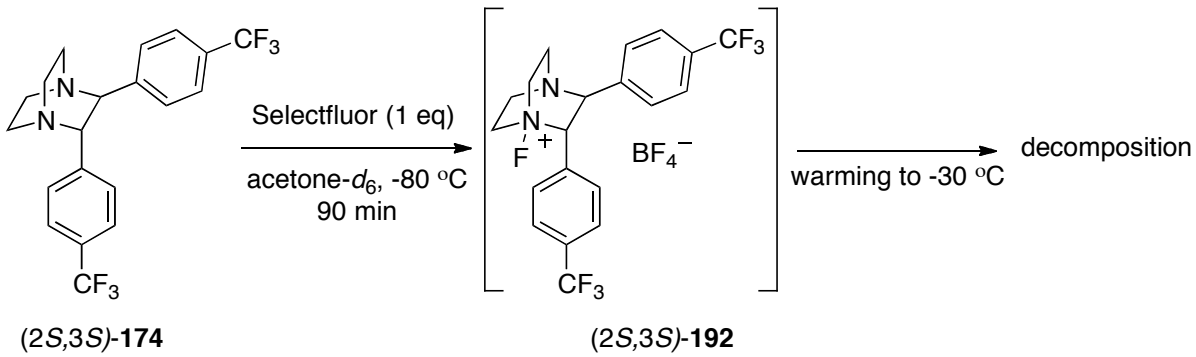
Scheme 3.7 Suggested decomposition pathway of the mono N-F chiral DABCO (2*R,*3*R*)-**188**

Spectroscopic analysis of the decomposed product also revealed signals at 8.9 ppm in the ^{1}H NMR and at 170 ppm in the ^{13}C NMR spectrum. This is consistent with a 1,2-phenyl shift generating an iminium ion (Scheme 3.8). Indeed, the literature chemical shift of iminium compounds is generally observed around 8.5 ppm in ^{1}H NMR and at 168 ppm in the ^{13}C NMR spectrum.[126, 127]



Scheme 3.8 Proposed rearrangement pathway of **189** leading to **191**

In the light of these data, we explored the effect of electron-withdrawing groups at the para-position of the phenyl rings (Scheme 3.9). Thus, Selectfluor and (2*S*,3*S*)-**174** were mixed (1:1 ratio) at -80°C in acetone-d_6. After ten minutes, in addition to the 2 peaks expected in the ^{19}F NMR at -62.2 ppm and -149.7 ppm corresponding to the trifluoromethyl moiety and the counterion BF_4^- respectively, 2 peaks at +47.9 and +45.6 ppm in a ratio of 2.9:1 were observed. The peak at +47.9 ppm was assigned to N-F fluorine of (2*S*,3*S*)-**192** and that the desired *N*-fluorinated adduct has indeed been formed, but that fluorine transfer from Selectfluor had not gone to completion. At -80°C and after forty-five minutes, the ratio of the two peaks had increased to 5.3:1, and full transfer from Selectfluor had occurred after ninety minutes. As under the same conditions transfer of fluorine from Selectfluor to (2*R*,3*R*)-**79** was immediate, we concluded that (2*S*,3*S*)-**174** is less reactive and the bridgehead nitrogen less nucleophilic.



Scheme 3.9 Fluorine transfer from Selectfluor to (2*S*,3*S*)-**174**

On warming the reaction mixture in 10 °C increments, it was found that (2*S*,3*S*)-**192** was stable up to -30°C, at which temperature traces of decomposition begin to be observed, with peaks at -71.5 ppm, -73.0 ppm, and -169.8 ppm increasing in intensity. The peak at +47.9 ppm had fully disappeared at -10°C. Compound (2*S*,3*S*)-**192** could therefore be used for *in situ* fluorination at temperatures below -30 °C. As (2*S*,3*S*)-**192** decomposes at a higher temperature than (2*R*,3*R*)-**188**, the *para*-trifluoromethyl substituents seem to have a beneficial effect on the stability of the chiral N-F adducts. This is consistent with the E1 decomposition pathway, which proceeds via a benzylic cation.

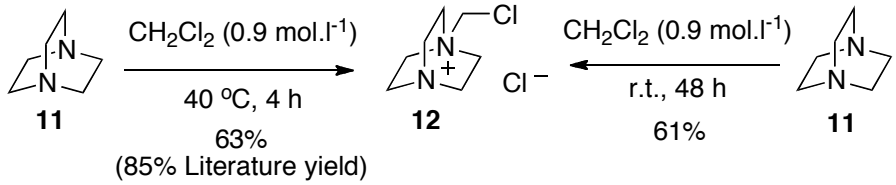
The investigation into the stability of the chiral mono-fluorinated DABCO systems either at low or room temperature corroborates Banks' observation that mono-1-fluoro-4-aza-l-azoniabicyclo[2.2.2]octane salts are unstable at low or room temperature. This study prompted us to explore the conversion of the chiral DABCO motifs into quaternary ammonium salts prior to fluorination.

3.5 Quaternization of the Chiral Diazabicyclic Systems

3.5.1 Quaternization of 1,4-Diazabicylo[2.2.2]octane

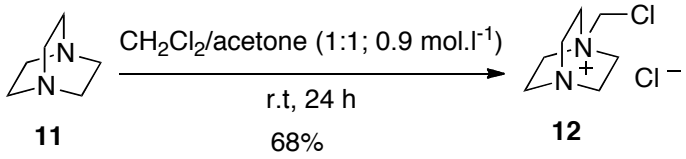
In his pioneering work towards the synthesis of Selectfluor, Banks examined the mono-*N*-alkylation of DABCO **11** under various conditions.[128] The synthesis of Selectfluor involves initial alkylation of **11** with dichloromethane followed by a counterion exchange with sodium tetrafluoroborate and finally fluorination with F_2. We began our investigation by validating Banks' reported protocol. Thus, 1,4-diazabicylo[2.2.2]octane **11** was successfully chloromethylated with CH_2Cl_2 after stirring for 4 hours at 40 ^oC. Subsequent filtration and washing with acetone, led to the desired product in 63% yield (Scheme 3.10). ^1H NMR spectrum showed a distinctive pair of triplets at 3.25 ppm and 3.55 ppm with a coupling

constant of J = 7.6 Hz, reflecting the non-equivalence of the ring protons. This pattern correlates with the monoquaternized structure **12**. This was further validated by mass spectrometry giving the positive ion $C_7H_{14}ClN_2$ $[M]^+$: 161.0841. Furthermore, the purity of the compound was confirmed by elemental analysis (C, H, N) [Anal. Calcd for $C_7H_{14}Cl_2N_2$: C, 42.65; H, 7.16; N, 14.21. Found: C, 42.53; H, 7.22; N, 14.13]. The successful isolation of **12** from refluxing in CH_2Cl_2 led us to investigate the chloromethylation process at room temperature. In this case, **11** was solubilised in CH_2Cl_2 and let stand without stirring for 48 hours at room temperature. To our delight, product **12** was formed in good yield.



Scheme 3.10 Chloromethylation reaction in dichloromethane

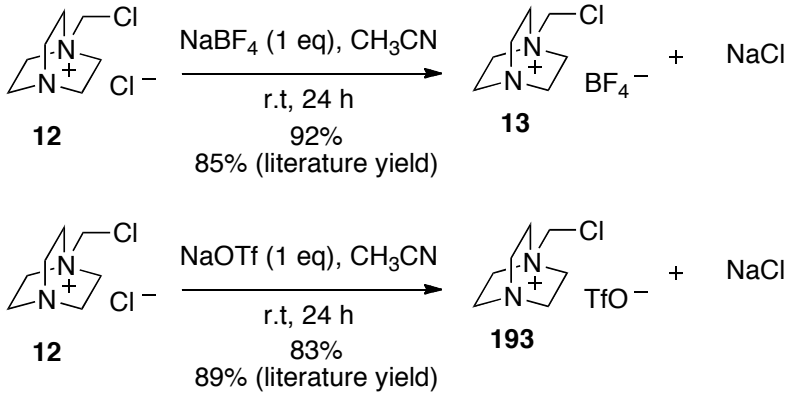
Another chloromethylation strategy was attempted using a mixture of dichloromethane and acetone at room temperature. The choice of this solvent system was based on previous results obtained within the group.[129] Thus, **11** was subject to chloromethylation with CH_2Cl_2 in acetone for 48 hours at room temperature giving **12** in 68% yield (Scheme 3.11). These new conditions gave only slight improved yield in comparison to our previous routes.



Scheme 3.11 Chloromethylation reaction in dichloromethane and acetone

The formation of **12** allowed us to validate the counterion exchange step. This step was achieved by exploiting the difference in solubility of metal salts in various solvents. Thus, the chloride salt **12** was treated with 1 equivalent of sodium tetrafluoroborate in acetonitrile for 24 hours at

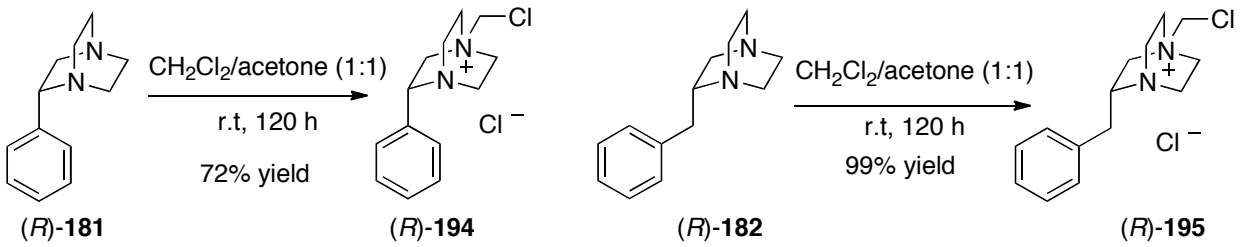
room temperature. As the chloride suspension underwent reaction, the desired tetrafluoroborate salt dissolved in the reaction solvent, while the sodium chloride precipitated out of acetonitrile.[128] The reaction mixture was then filtered to remove the inorganic salt, and concentrated under reduced pressure. Purification by recrystallisation in ($MeOH/Et_2O$) afforded the desired salt **13** in 92% yield (Scheme 3.12). The BF_4^- ion could be observed by ^{19}F NMR with a peak at -151.0 ppm, suggesting that the counterion exchange had taken place. The solubility of the final product also provided convincing evidence for the successful exchange of chloride for tetrafluoroborate, as, unlike the tetrafluoroborate salt, the starting chloride was not soluble in acetonitrile. The purity of the compound was confirmed by elemental analysis (C, H, N) [Anal. Calcd for $C_7H_{14}BClF_4N_2$: C, 33.84; H, 5.68; N, 11.27. Found: C, 33.65; H, 5.52; N, 11.06]. The same procedure was applied for the preparation of triflate salt **193**. The chloride salt **12** was treated with 1 equivalent of sodium triflate in acetonitrile for 24 hours at room temperature. The resulting product was purified by recrystallisation ($EtOH/Et_2O$) to give the desired triflate in 83% yield. The CF_3 group of the triflate could be detected by ^{19}F NMR with a peak at -79.3 ppm, suggesting that counterion exchange had taken place. The purity of the compound was confirmed by elemental analysis (C, H, N) [Anal. Calcd for $C_8H_{14}ClF_3N_2O_3S$: C, 30.92; H, 4.54; N, 9.02. Found: C, 30.65; H, 4.52; N, 8.68].



Scheme 3.12 Counterion exchange

3.5.2 Quaternization of Chiral 2-Diazabicyclic Systems

With the chloromethylation and counter-ion exchange validated on DABCO, we applied the same procedure to mono-substituted chiral DABCO derivatives. 1-(Chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane chlorides (*R*)-**194** and (*R*)-**195** were prepared by treating chiral 1-diazabicyclooctanes (*R*)-**181** and (*R*)-**182** respectively with a mixture of dichloromethane and acetone at room temperature for 120 hours (Scheme 3.13). The structure of (*R*)-**194** was confirmed by ^{1}H and ^{13}C NMR spectroscopy (the diagnostic peaks at 5.53 ppm and 5.60 ppm in the ^{1}H NMR spectrum are characteristic of the CH_2 of the chloromethyl group) and mass spectrometry showing the positive ion $C_{13}H_{18}ClN_2$ $[M]^+$: 237.1157. Furthermore, the purity of the compound was confirmed by elemental analysis (C, H, N) [Anal. Calcd for $C_{13}H_{18}Cl_2N_2$: C, 57.15; H, 6.64; N, 10.25. Found: C, 56.93; H, 6.75; N, 10.14]. Similar analysis was also performed on product (*R*)-**195** with the diagnostic ^{1}H NMR peaks at 5.18 ppm and 5.23 ppm, and mass spectrometry giving the positive ion $C_{14}H_{20}ClN_2$ $[M]^+$: 251.1310.



(*R*)-**181** (*R*)-**194** (*R*)-**182** (*R*)-**195**

Scheme 3.13 Chloromethylation of chiral (*R*)-2-diazabicyclic **181** and **182**

The original NMR assignment concerning the regioselectivity of the quaternization step was confirmed by additional NMR experiments on compound (*R*)-**194**. As it can be observed by the 1D NOESY experiments, when the signal corresponding to the CH_2 of the chlorometyl group at 5.05 ppm was irradiated, some key signals were affected. First of all, a diagnostic transient NOE was observed between protons Ha (CH_2Cl) and one of the protons He. Secondly, no correlation was detected between protons Ha and Hd or any of the aromatic protons proving that the quaternization happened only at the opposite nitrogen away from the phenyl group. Moreover,

transient NOE's were also observed between protons Ha and/or Hb/Hc/He/Hf/Hg (Figure 3.8). As these protons are masked with the rest of the structure, they are not considered as diagnostic.

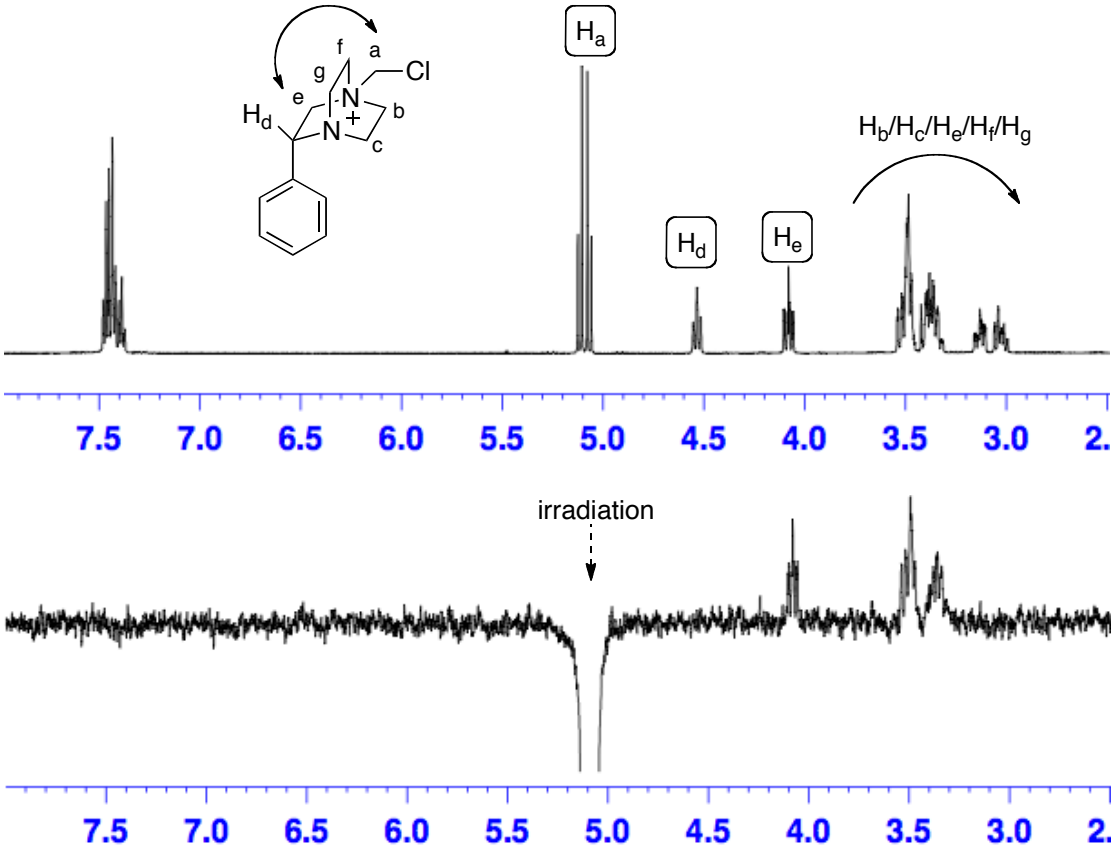


Figure 3.8 Transient NOEs observed crucial for assignment of regioselectivity

The assignment of proton He was made possible by a COSY experiment. Indeed, the COSY spectrum identified the presence of a spin-spin coupling between proton Hd (unambiguously assigned by HSQC) and one of the protons He (Figure 3.9).

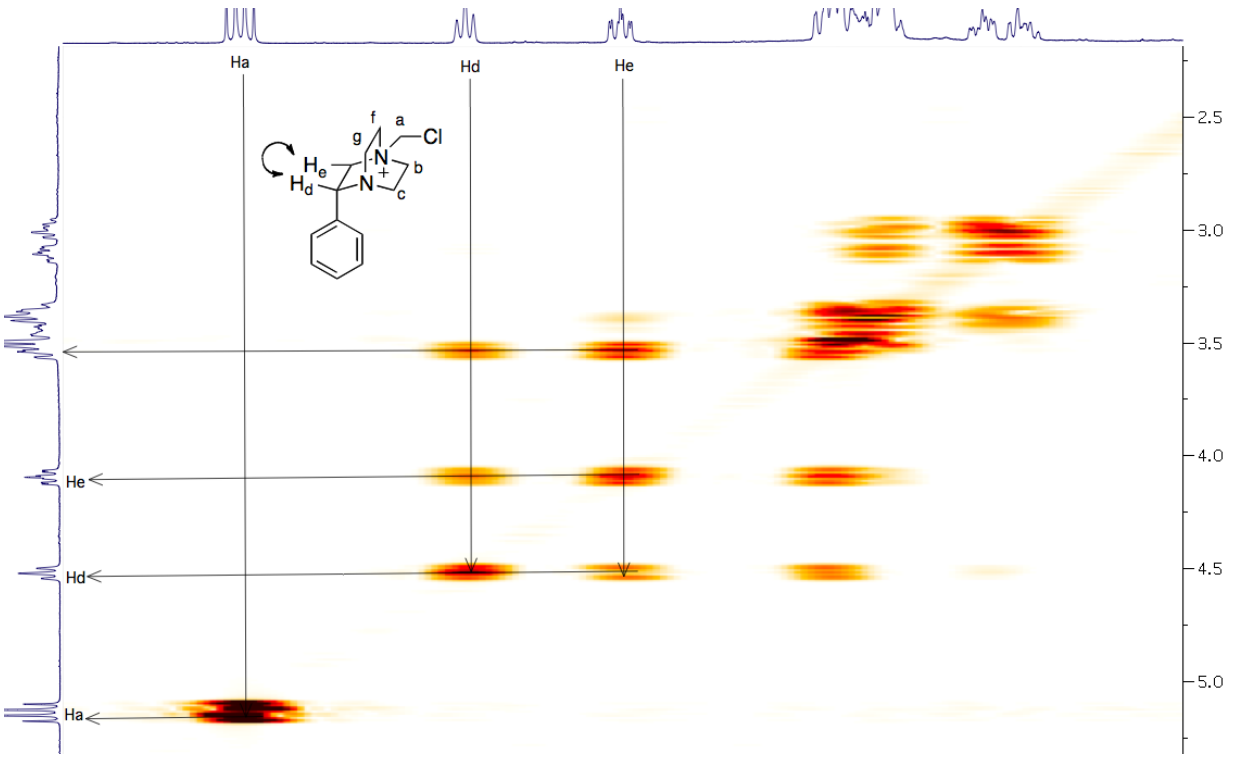
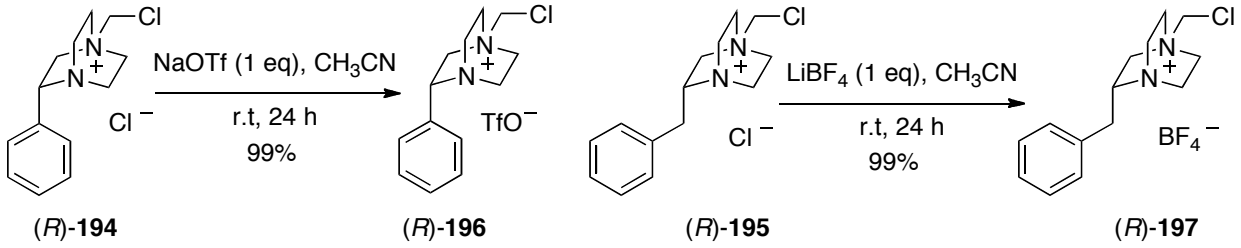


Figure 3.9 Gradiant COSY (^{1}H-^{1}H correlation)

Previous work of Wong and co-workers demonstrated that the use of the trifluoromethanesulfonate salt of Selectfluor for the fluorination of glycals led to decreased side-product formation and higher yields than the corresponding tetrafluoroborate salt.[46] This outcome was rationalized by the greater solubility of the triflate salt of Selectfluor. Therefore, it was decided to explore the use of triflate and tetrafluoroborate as suitable counterions. Compound (*R*)-**194** was reacted with 1 equivalent of sodium triflate in acetonitrile at room temperature for 24 hours to give (*R*)-3-phenyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2] octane trifluoromethanesulfonate (*R*)-**196** upon filtration in excellent yield (Scheme 3.14). The successful counterion exchange was confirmed by ^{19}F NMR analysis where a peak at -79.3 ppm characteristic to the triflate ion was observed. Mass spectrometry confirmed the identity of both ions ($C_{13}H_{18}ClN_2$ $[M]^+$: 237.1150; MS-EI$^-$ *m/z* 148.94 [$^-$OTf]). Addition of lithium tetrafluoroborate to compound (*R*)-**195** in acetonitrile at room temperature produced (*R*)-3-benzyl-1-(chloromethyl)-4-aza-1-azoniabicyclo [2.2.2]octane tetrafluoroborate (*R*)-**197** in 99%

yield. The final product (*R*)-**197** was characterized as above (^{19}F NMR: -153.7 [BF_4^-]; mass spectrometry $C_{14}H_{20}ClN_2$ $[M]^+$: 251.1310).

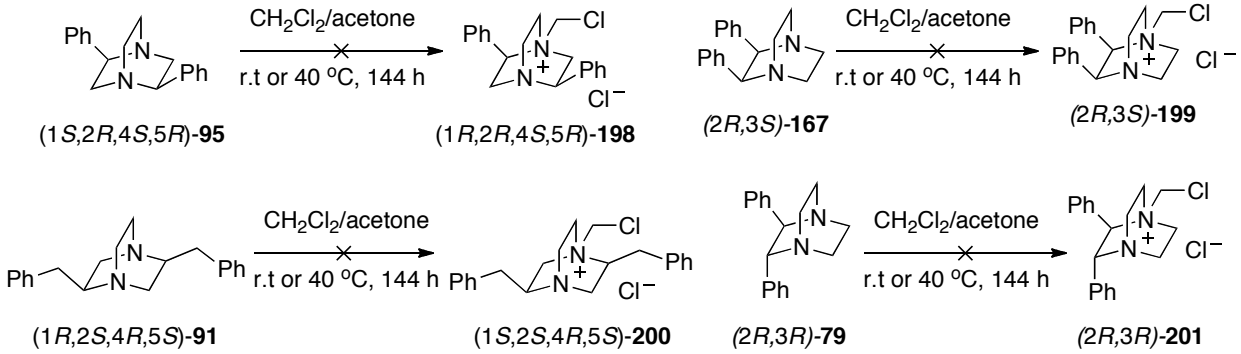


(*R*)-**194** (*R*)-**196** (*R*)-**195** (*R*)-**197**

Scheme 3.14 Counterion exchange of chiral (*R*)-2-azoniabicyclic **194** and **195**.

3.5.3 Quaternization of Chiral 2,3- and 2,5-Disubstituted DABCO Derivatives

The quaternization of the chiral disubstituted DABCOs was first attempted in dichloromethane at room temperature. Although the reaction was stirred for 6 days, no products were formed with NMR spectroscopy showing only the presence of starting materials. The chloromethylation was then attempted using a mixture of dichloromethane/acetone (1:1) at room temperature without stirring. However, no product was formed after 6 days and starting materials were also recovered. Further attempts to isolate either 1-chloromethyl-4-aza-l-azoniabicyclo[2.2.2]octane chloride derivatives (1*R*,2*R*,4*S*,5*R*)-**198**, (2*R*,3*S*)-**199**, (1*S*,2*S*,4*R*,5*S*)-**200** or (2*R*,3*R*)-**201** in dichloromethane at 40 °C for 3 days were unsuccessful (Scheme 3.15).



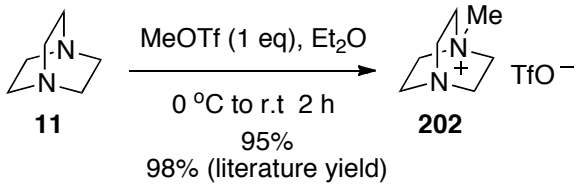
(1*S*,2*R*,4*S*,5*R*)-**95** (1*R*,2*R*,4*S*,5*R*)-**198** (2*R*,3*S*)-**167** (2*R*,3*S*)-**199**

(1*R*,2*S*,4*R*,5*S*)-**91** (1*S*,2*S*,4*R*,5*S*)-**200** (2*R*,3*R*)-**79** (2*R*,3*R*)-**201**

Scheme 3.15 Attempted chloromethylation of chiral disubstituted DABCO derivatives

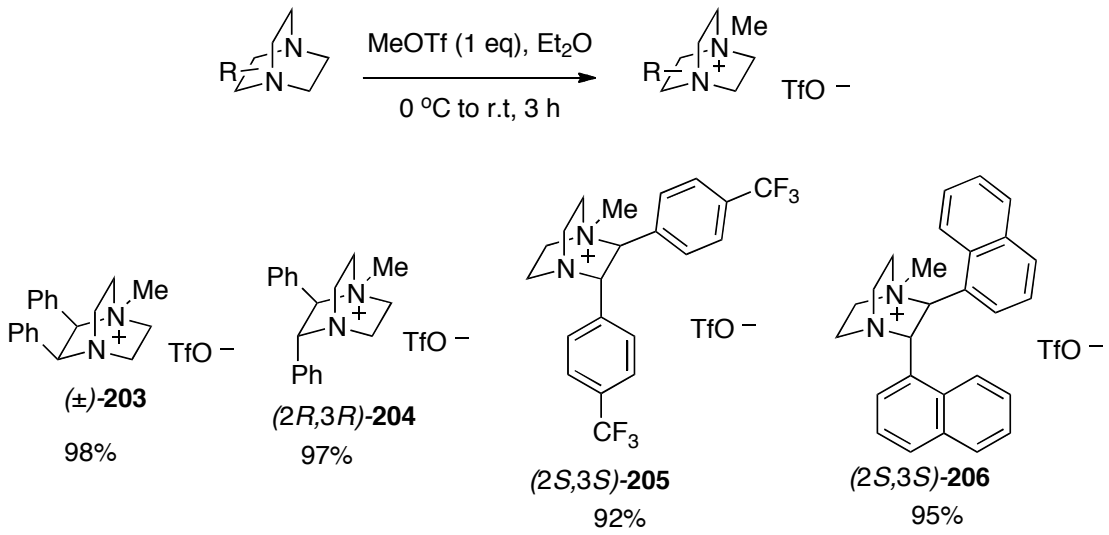
Our efforts then focused on the *N*-methylation of the DABCO systems using methyl trifluoromethane sulfonate. The choice of MeOTf was driven by the fact that is a highly reactive

alkylating agent and would alleviate the need for a counterion exchange. Thus, subjecting compound **11** to quaternization with methyl trifluoromethane sulfonate in diethyl ether for 1 hour at 0 °C and 2 hours at room temperature, followed by recrystallisation of the crude product in MeOH/Et_2O (1:4), we obtained the desired salt product **202** in 99% yield (Scheme 3.16). The resulting white precipitate was characterised by ^{1}H NMR (D_2O) that showed a singlet at 3.03 ppm characteristic to the methyl group and a pair of triplets at 3.19 ppm and 3.38 ppm with a coupling constant of J = 7.6 Hz, as a result of coupling between non-equivalent CH_2 groups.



Scheme 3.16 *N*-Methylation of DABCO with MeOTf

After optimisation of the conditions, the methodology was successfully extended to the chiral 2,3-disubstituted DABCO derivatives, affording (±)-**203**, (2*R*,3*R*)-**204**, (2*S*,3*S*)-**205** and (2*S*,3*S*)-**206** in excellent yields (Scheme 3.17).[121] The structure of the final products was confirmed by NMR spectroscopy, distinctive peaks being a methyl group peak around 2.7 ppm in the ^{1}H NMR and 50.1 ppm in ^{13}C NMR spectra in all the compounds. Moreover, ^{19}F NMR analysis revealed the presence of the triflate peak at -79.3 ppm. In addition, elemental analysis was performed on compound (2*S*,3*S*)-**205** (C, H, N) [Anal. Calcd for $C_{22}H_{21}F_9N_2O_3S$: C, 46.81; H, 3.75; N, 4.96. Found: C, 46.74; H, 3.70; N, 4.61].



Scheme 3.17 *N*-Methylation of chiral 2,3-disubstituted DABCO derivatives with MeOTf

Figure 3.10 illustrates the ^{1}H NMR spectrum of (2*R*,3*R*)-**204** showing the presence of the methyl group.

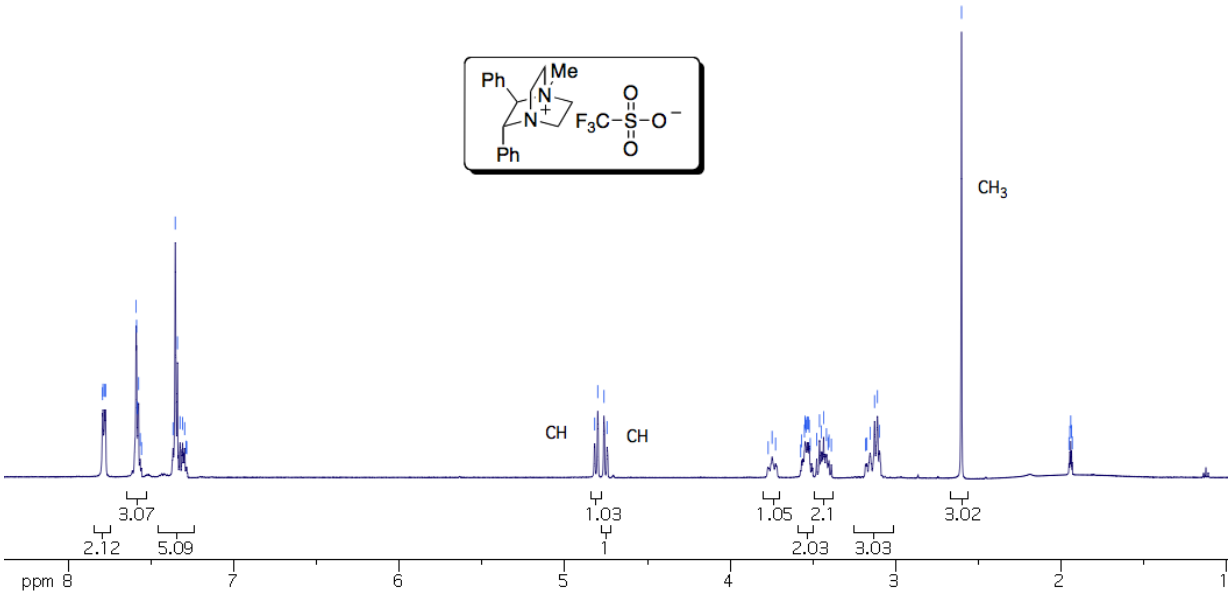


Figure 3.10 ^{1}H NMR spectrum of (2*R*,3*R*)-**204**

The X-ray analysis of a suitable single crystal of (2*R*,3*R*)-**204** confirmed the relative stereochemistry of this quaternized isomer and gave an understanding on the difficulty encountered in the chloromethylation step. When examining the X-ray it is apparent that the phenyl groups shield the *N*-lone pairs.

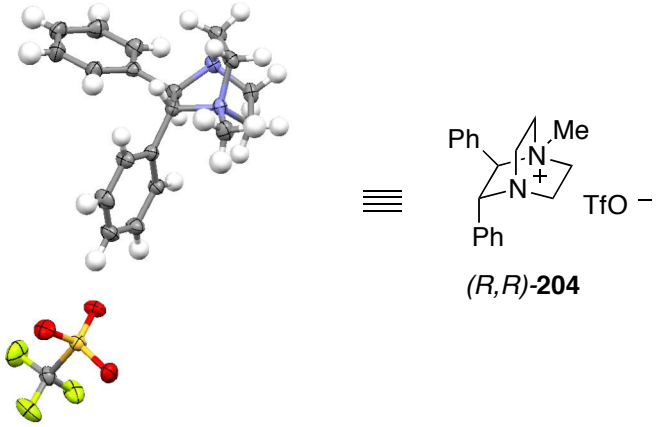
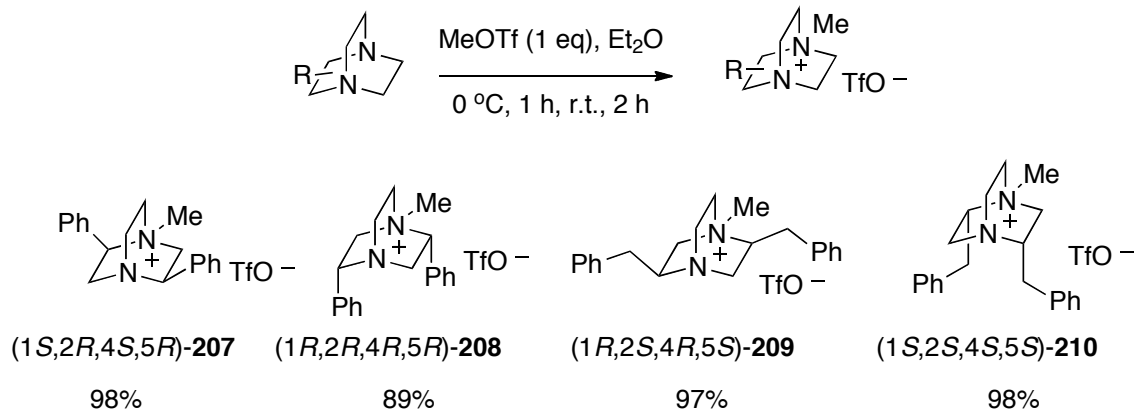


Figure 3.11 X-ray structure of isomer (2*R*,3*R*)-**204**

Pleasingly, the same conditions were successfully adopted for the formation of *N*-alkylated 2,5-substituted chiral DABCO derivatives (1*S*,2*R*,4*S*,5*R*)-**207**, (1*R*,2*R*,4*R*,5*R*)-**208**, (1*R*,2*S*,4*R*,5*S*)-**209** and (1*S*,2*S*,4*S*,5*S*)-**210** giving excellent yields (Scheme 3.18). The characterization of the final products was performed as previously described.



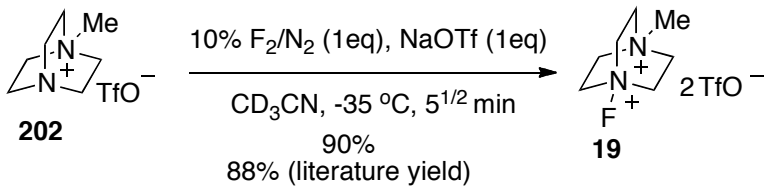
Scheme 3.18 *N*-Methylation of chiral 2,5-disubstituted DABCO derivatives with MeOTf

3.6 Fluorination

3.6.1 Fluorination of DABCO Salts Systems with F_2

The successful synthesis of chiral DABCO quaternary salts enabled us to investigate the key fluorination step. Banks demonstrated that when one nitrogen atom of 1,4-diazabicyclo[2.2.2]octane is quaternized, the resulting product could be *N*-fluorinated with F_2

gas to provide a stable electrophilic fluorinating reagent.[45] An investigation was carried out in order to validate this process (Scheme 3.19). For this preliminary work, reactions were performed in deuterated acetonitrile to facilitate ^{1}H and ^{19}F NMR analyses. Fluorination of the achiral monoquaternary salt **202** in the presence of 1 equivalent of sodium triflate in cold acetonitrile was examined. The solution was purged with N_2 then cooled to -35 ^{o}C before 1 equivalent of elemental fluorine (10% v/v in N_2) was introduced (at a flow rate of 15 mL/min) *via* PTFE tubing. It is important for the PTFE tubing to reach the bottom of the reaction vessel to ensure thorough distribution of fluorine gas throughout the solution. When the reaction was completed, the solution was filtered to remove sodium fluoride, and concentrated under reduced pressure. The corresponding 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(triflate) **19** was obtained in 90% yield after recrystallisation in a mixture of methanol and ether (Scheme 3.19). The structure was confirmed by mass spectrometry analysis $C_7H_{15}FN_2^{+}$ $[M]^{2+}$: 146.1208 and ^{19}F NMR showing an N-F signal at +46.9 ppm and a TfO^{-} signal at -79.3 ppm.

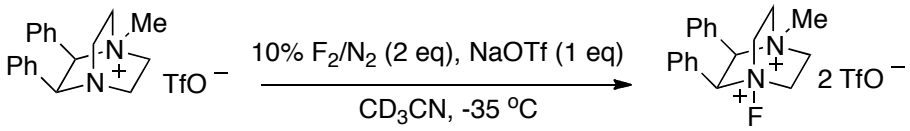


Scheme 3.19 Fluorination of monoquaternary salt **202**

3.6.2 Fluorination of Chiral 2,3-DABCO Salts Systems with F_2

The successful fluorination of **202** with F_2 led us to apply this methodology to the monoquaternary salt (±)-**203** to probe the compatibility of the phenyl groups with molecular fluorine (Table 3.1). Following the addition of 2 equivalents of fluorine gas, the reaction mixture was purged with nitrogen, to unsure any unreacted gas had been transferred to the soda-lime scrubber tower, and allowed to warm to room temperature. The reaction mixture was then filtered to remove sodium fluoride, and concentrated under reduced pressure. Recrystallisation

(MeOH/Et_2O) afforded the desired product in 78% yield, although trace impurities were observed by ^{19}F NMR spectrum (Table 3.1, entry 1). The major product was identified by ^{19}F NMR, with a characteristic signal at +42.6 ppm, which corresponded to the fluorine of the N-F bond, with the triflate ion CF_3 group giving a singlet at -79.3 ppm. Pleasingly upon optimization of the conditions, the additional signals observed in the ^{19}F NMR spectrum were suppressed by decreasing the concentration of the solution (path length between F_2 gas and the substrate) affording the product in 98% yield after recrystallisation (Table 3.1, entry 3).



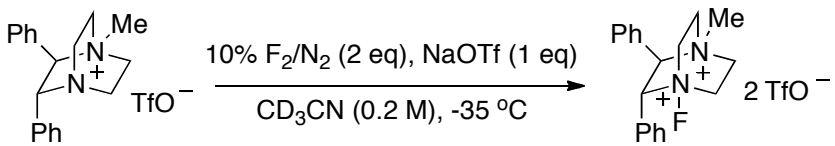
(±)-**203** (±)-**211**

Entry	Amounts (mg)	Concentration (mmol/mL)	Product	Chemical Shift (ppm) NF^+	Chemical Shift (ppm) TfO^-	Yields (%)
1[a]	100	0.066	(±)-**211**	+42.6	-79.3	78
2	100	0.033	(±)-**211**	+42.6	-79.3	94
3	100	0.023	(±)-**211**	+42.6	-79.3	98

[a] extra peaks observed around -151 and -183 ppm in ^{19}F NMR

Table 3.1 Formation of the novel reagent (±)-**211**

Pleasingly, the application of the optimised fluorination of (±)-**203** to the chiral quaternized salt (2*R*,3*R*)-**204** was also successful, providing the novel chiral reagent (2*R*,3*R*)-**212** in 97% yield (Scheme 3.20). The identity of the product was confirmed by ^{19}F NMR, with a characteristic signal corresponding to the N-F bond observed at +35.9 ppm, and the triflate ion CF_3 group observed at -79.3 ppm. The purity of the compound was confirmed by elemental analysis (C, H, N) [Anal. Calcd for $C_{21}H_{23}F_7N_2O_6S_2$: C, 42.28; H, 3.89; N, 4.70. Found: C, 42.38; H, 4.01; N, 4.66].



(2*R*,3*R*)-**204** (2*R*,3*R*)-**212**

Scheme 3.20 Formation of the novel chiral reagent (2*R*,3*R*)-**212**

A representative ^{19}F NMR spectrum of chiral fluorinated DABCO (2*R*,3*R*)-**212** showing the NF^+ and TfO^- peaks is depicted below (Figure 3.12).

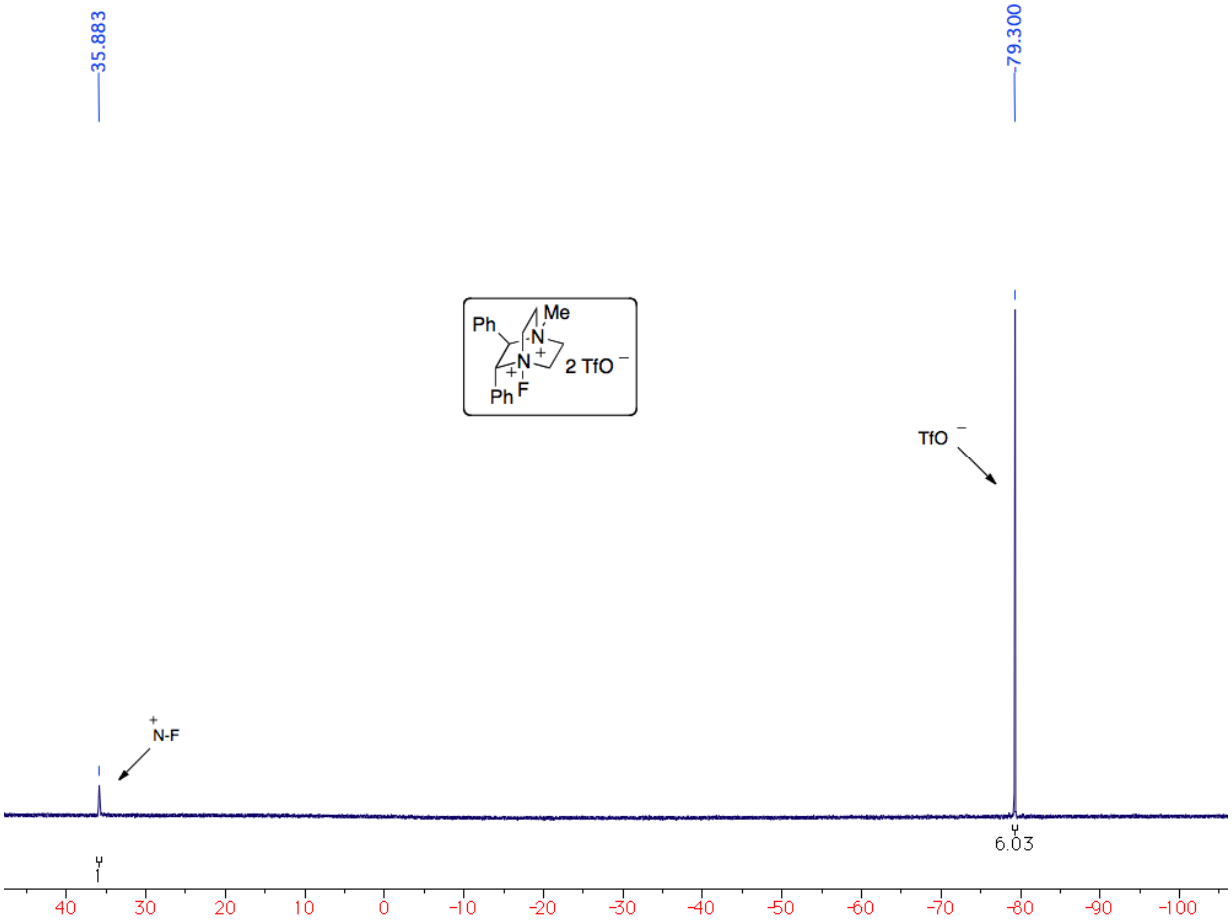


Figure 3.12 ^{19}F NMR spectrum of the fluorinated isomer reagent (2*R*,3*R*)-**212**

The presence of fluorine atom in (2*R*,3*R*)-**212** causes a downfield shift of approximately 0.5-2 ppm in the ^1H NMR spectrum (Figure 3.13). The same pattern was also observed in ^{13}C NMR with a splitting of carbon signals at 77.7 ppm (d, J = 14.3, CH, C2), 59.8 ppm (d, J = 15.4, CH_2, C6/8) and 58.8 ppm (d, J = 14.7, CH_2, C6/8).

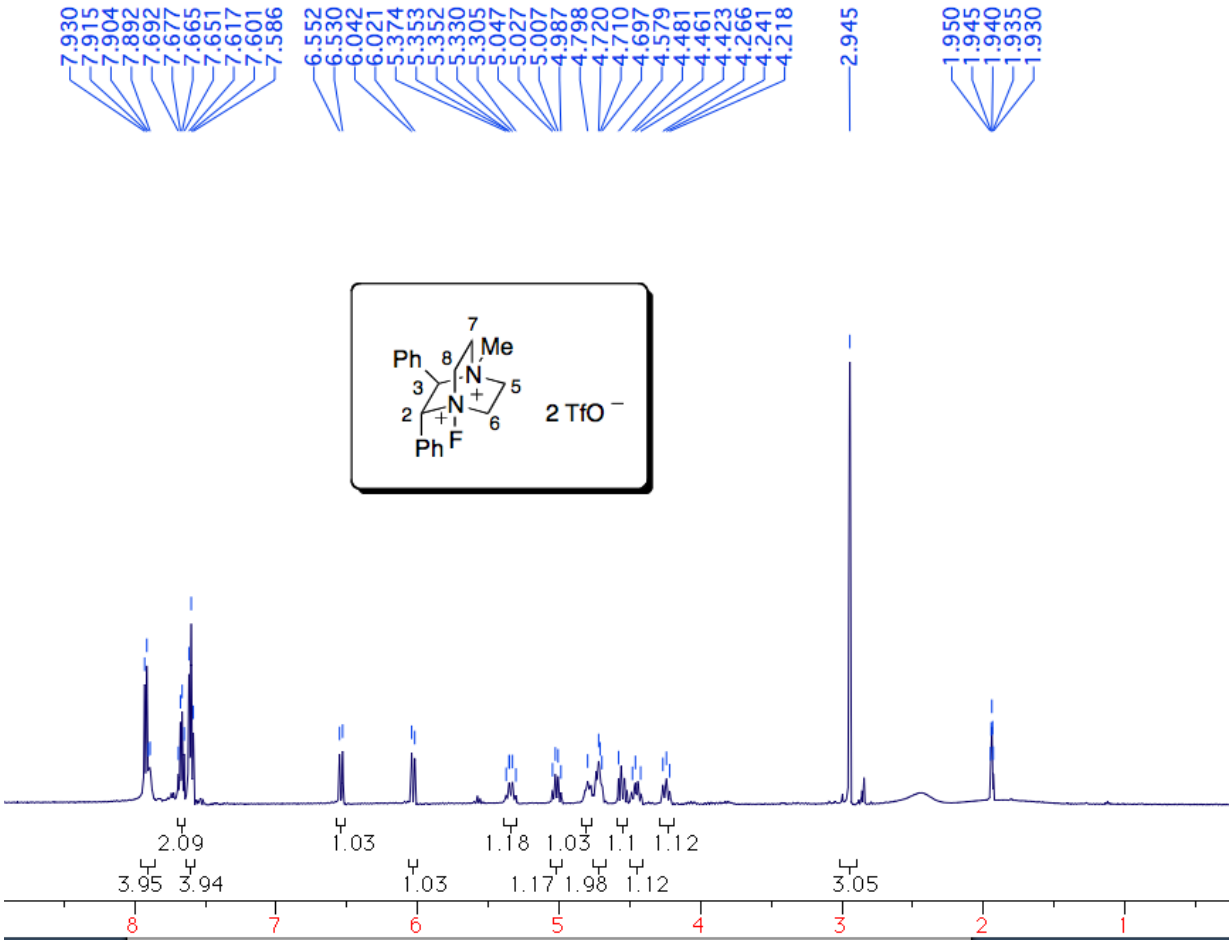
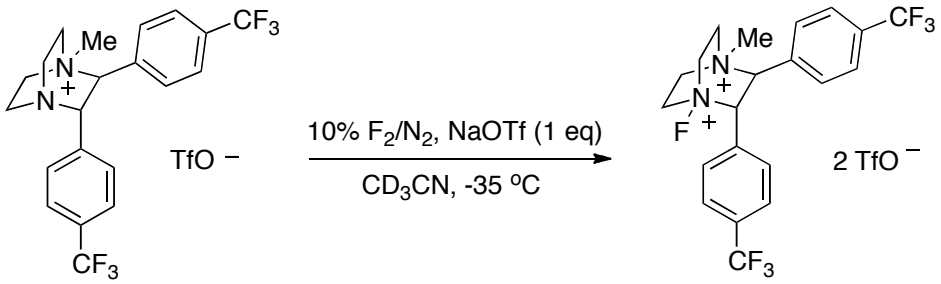


Figure 3.13 ^{1}H NMR spectrum of the fluorinated reagent (2*R*,3*R*)-**212** in CD_3CN

The methodology was extended to the monoquaternary salt (2*S*,3*S*)-**205**, however the use of 2 equivalents of F_2 was not sufficient for full transfer of fluorine to (2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)phenyl)-1-methyl-4-aza-azoniabicyclo[2.2.2]octane triflate **205** (Table 3.2, entry 1). This is likely due to the presence of the electron-withdrawing trifluoromethyl moiety at the *para*-position of the phenyl groups decreasing the nucleophilicity of the nitrogen lone pair. In fact, it has been shown that 4-(trifluoromethyl)phenyl substituents such as benzylamine have a p*K*a around 9 in DMSO.[130] Steric effects of the phenyl ring around the *N*-lone pair could have also influenced the reaction. The addition of 3 equivalents of F_2 to the reaction mixture showed a great improvement in the formation of (2*S*,3*S*)-**213** with up to 83% conversion. The conversion was calculated by comparing the ratio of NF^+ and TfO^- signals in ^{19}F NMR. To our

delight, the use of 4 equivalents of molecular fluorine gave (2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)-phenyl)-1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2] octane bis(triflate) **213** in 97% conversion with no side-products observed in the ^{19}F NMR spectrum (Table 3.2, entry 3). The purity of the compound was confirmed by elemental analysis (C, H, N) [Anal. Calcd for $C_{23}H_{21}F_{13}N_2O_6S_2$: C, 37.71; H, 2.89; N, 3.82. Found: C, 37.43; H, 2.76; N, 3.90].



(2S,3S)-**205** *(2S,3S)*-**213**

Entry	Amounts (mg)	Equivalents of F_2	Product	Chemical Shift (ppm)			Conversion[a] (%)
				NF^+	CF_3	TfO^-	
1	100	2	(2*S*,3*S*)-**213**	+36.6	-64.0	-79.3	72
2	100	3	(2*S*,3*S*)-**213**	+36.6	-64.0	-79.3	83
3	100	4	(2*S*,3*S*)-**213**	+36.6	-64.0	-79.3	97

[a] conversion by ^{19}F NMR (ratio between NF^+ and TfO^- signals)

Table 3.2 Formation of novel fluorinated chiral DABCO (2*S*,3*S*)-**213**

Figure 3.14 shows the ^{19}F NMR spectrum of chiral fluorinated DABCO (2*S*,3*S*)-**213** with the characteristic signals.

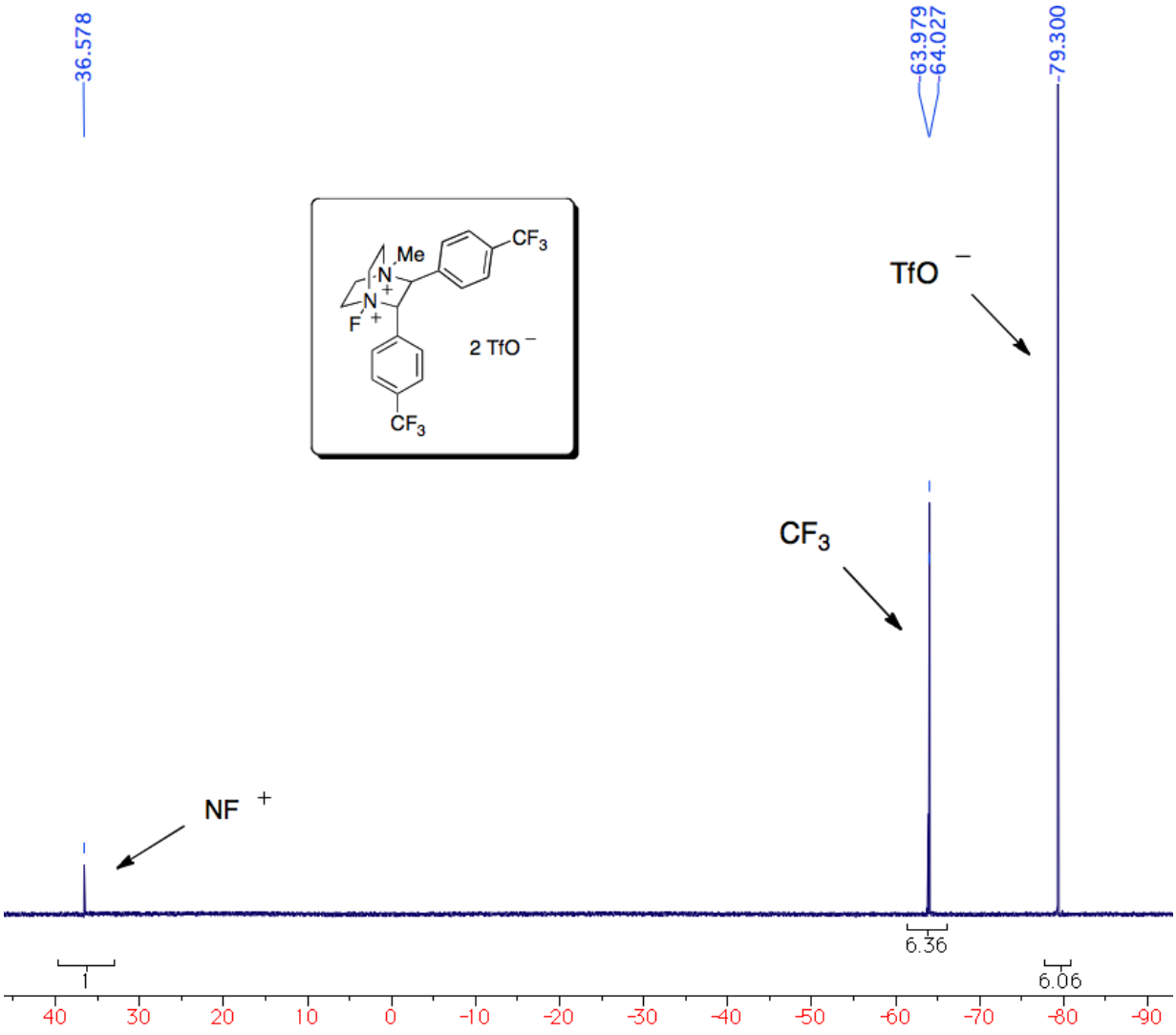
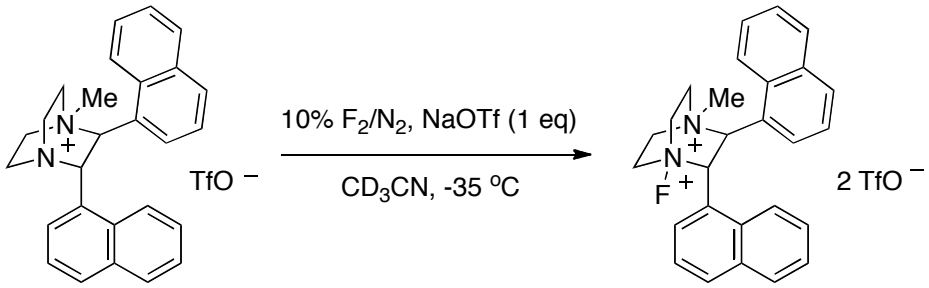


Figure 3.14 ^{19}F NMR spectrum of fluorinated isomer (2*S*,3*S*)-**213**

The fluorination of (2*S*,3*S*)-2,3-di(naphthalen-1-yl)-1-methyl-4-aza-1-azoniabicyclo[2.2.2] octane salt **206** proved challenging compared to other chiral 2,3-disubstituted DABCOs. Reaction of (2*S*,3*S*)-**206** with F_2 in acetonitrile at -35 ^{o}C using 2 equivalents of molecular fluorine gave a very low conversion (<5%) (Table 3.3, entry 1). Addition of 3 to 4 equivalents of F_2 showed an increase in conversion to fluorinated (2*S*,3*S*)-**214**. Although the conversions were still low at that stage (~20%), we were encouraged by the fact that no side-reactions were observed. The use of 5 equivalents of F_2 afforded a 36% conversion of the final product. The overall conversion was improved from 36 to 50% by using 6 equivalents of fluorine gas, however this led to the observation of additional peaks in the ^{19}F

spectrum. The steric hindrance around the free nitrogen by the naphthyl group in (2*S*,3*S*)-**206** may explain the difficulties we encountered to secure full conversion upon transfer of fluorine from F_2 to 2,3-di(naphthalen-1-yl)- 1-methyl-DABCO salt (2*S*,3*S*)-**206**.



(2*S*,3*S*)-**206** (2*S*,3*S*)-**214**

Entry	Amounts (mg)	Equivalents of F_2	Product	Chemical Shift (ppm) NF^+	Chemical Shift (ppm) TfO^-	Conversion[a] (%)
1	100	2	(2*S*,3*S*)-**214**	+35.1	-79.3	4.5
2	100	3	(2*S*,3*S*)-**214**	+35.1	-79.3	10
3	100	4	(2*S*,3*S*)-**214**	+35.1	-79.3	23
5	100	5	(2*S*,3*S*)-**214**	+35.1	-79.3	36
6[b]	100	6	(2*S*,3*S*)-**214**	+35.1	-79.3	50

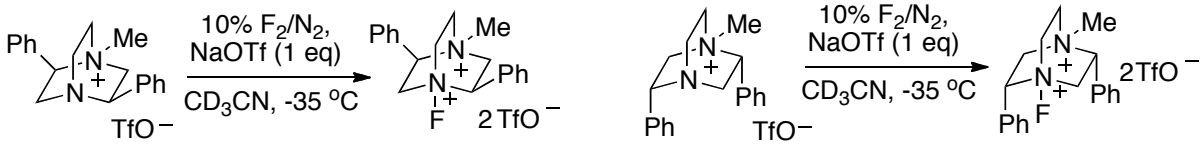
[a] conversion by ^{19}F NMR (ratio between NF^+ and TfO^- signals),
[b] extra peaks observed around -151 ppm and -183 ppm in ^{19}F NMR

Table 3.3 Formation of novel fluorinated chiral DABCO (2*S*,3*S*)-**214**

3.6.3 Fluorination of Chiral 2,5-DABCO Salts Systems with F_2

The fluorination of the chiral 2,5-DABCO (1*S*,2*R*,4*S*,5*R*)-**207** and (1*R*,2*R*,4*R*,5*R*)-**208** cores was examined next. Upon addition of 2 equivalents of F_2 to a solution of **207** and sodium triflate in acetonitrile, diagnostic peaks were observed at -79.3 ppm and +48.9 ppm in the ^{19}F NMR spectrum, corresponding to TfO^- and R_3NF^+ respectively, and the conversion was determined to be 69% (Table 3.4, entry 1). The addition of another equivalent of F_2 to the reaction mixture led to 72% conversion. Increasing the amount of fluorine gas to 4 equivalents did not give further improvement in the conversion (Table 3.4, entry 3). In fact, when 5 equivalents of fluorine gas were used, additional peaks were observed in the ^{19}F NMR spectrum.

We applied the same methodology to (1*R*,2*R*,4*R*,5*R*)-**208** starting with 3 equivalents of F_2. Although fluorination occurred satisfactorily after the addition of 3 equivalents of fluorine gas to (1*R*,2*R*,4*R*,5*R*)-**208**, we observed a similar trend in the conversion to that of (1*S*,2*R*,4*S*,5*R*)-**207** (Table 3.4, entries 4 and 5).



(1*S*,2*R*,4*S*,5*R*)-**207** (1*R*,2*R*,4*S*,5*R*)-**215** (1*R*,2*R*,4*R*,5*R*)-**208** (1*S*,2*R*,4*R*,5*R*)-**216**

Entry	Compounds	Equivalents of F_2	Product	Chemical Shift (ppm)		Conversion[a] (%)
				NF^+	TfO^-	
1	(1*S*,2*R*,4*S*,5*R*)-**207**	2	(1*R*,2*R*,4*S*,5*R*)-**215**	+49.0	-79.3	69
2	(1*S*,2*R*,4*S*,5*R*)-**207**	3	(1*R*,2*R*,4*S*,5*R*)-**215**	+49.0	-79.3	72
3	(1*S*,2*R*,4*S*,5*R*)-**207**	4	(1*R*,2*R*,4*S*,5*R*)-**215**	+49.0	-79.3	76
4	(1*R*,2*R*,4*R*,5*R*)-**208**	3	(1*S*,2*R*,4*R*,5*R*)-**216**	+33.0	-79.3	65
5	(1*R*,2*R*,4*R*,5*R*)-**208**	4	(1*S*,2*R*,4*R*,5*R*)-**216**	+33.0	-79.3	70

[a] conversion by ^{19}F NMR (ratio between NF^+ and TfO^- signals)

Table 3.4 Formation of (1*R*,2*R*,4*S*,5*R*)-**215** and (1*S*,2*R*,4*R*,5*R*)-**216**

The peaks of NF^+ and TfO^- were identified in the ^{19}F NMR spectrum of chiral DABCO (1*R*,2*R*,4*S*,5*R*)-**215** (Figure 3.15).

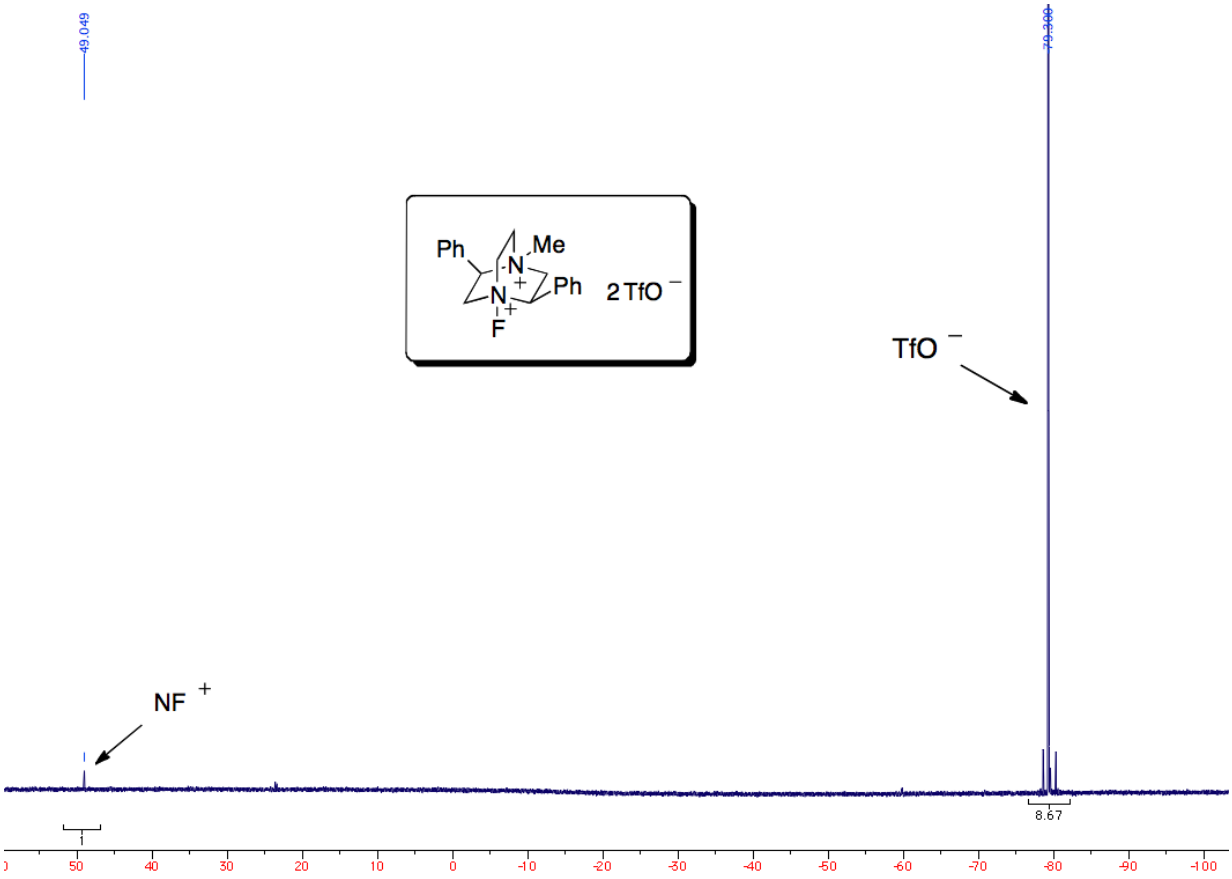
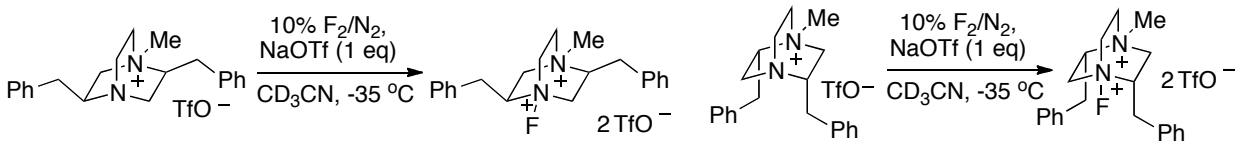


Figure 3.15 ^{19}F NMR spectrum of fluorinated isomer (1*R*,2*R*,4*S*,5*R*)-**215**

The fluorination of the chiral 2,5 dibenzyl salts (1*R*,2*S*,4*R*,5*S*)-**209** and (1*S*,2*S*,4*S*,5*S*)-**210** was next attempted. Firstly, we explored the fluorination of (1*R*,2*S*,4*R*,5*S*)-2,5-dibenzyl-1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate salt **209** with 3 equivalents of F_2, however only a low conversion was obtained (Table 3.5, entry 1). Pleasingly, we observed up to 50% conversion when the amount of fluorine gas was increased. Further addition of F_2 did not lead to significant improvement. The fluorination of (1*S*,2*S*,4*S*,5*S*)-2,5-dibenzyl DABCO salt **210** proved more challenging as the fluorinated product was formed in 38% conversion with 4 equivalents of F_2 (Table 3.5, entry 4). When 5 equivalents of F_2 were used, we observed additional peaks in the fluorine spectrum. The difference in conversion of the members of the 2,5-DABCO family examined could be related to the solubility

profile of these salts in acetonitrile, and to some extent to steric hindrance around the free nitrogen.



(1*R*,2*S*,4*R*,5*S*)-**209** (1*S*,2*S*,4*R*,5*S*)-**217** (1*S*,2*S*,4*S*,5*S*)-**210** (1*R*,2*S*,4*S*,5*S*)-**218**

Entry	Compounds	Equivalent of F_2	Product	Chemical Shift (ppm)		Conversion[a] (%)
				NF^+	TfO^-	
1	(1*R*,2*S*,4*R*,5*S*)-**209**	3	(1*S*,2*S*,4*R*,5*S*)-**217**	+49.1	-79.3	45
2	(1*R*,2*S*,4*R*,5*S*)-**209**	4	(1*S*,2*S*,4*R*,5*S*)-**217**	+49.1	-79.3	50
3	(1*S*,2*S*,4*S*,5*S*)-**210**	3	(1*R*,2*S*,4*S*,5*S*)-**218**	+49.0	-79.3	30
4	(1*S*,2*S*,4*S*,5*S*)-**210**	4	(1*R*,2*S*,4*S*,5*S*)-**218**	+49.0	-79.3	38

[a] conversion by ^{19}F NMR (ratio between NF^+ and TfO^- signals)

Table 3.5. Formation of (1*S*,2*S*,4*R*,5*S*)-**217** and (1*R*,2*S*,4*S*,5*S*)-**218**

Figure 3.16 illustrates the ^{19}F NMR spectrum peaks of (1*R*,2*S*,4*S*,5*S*)-**218** showing the NF^+ and TfO^- peaks.

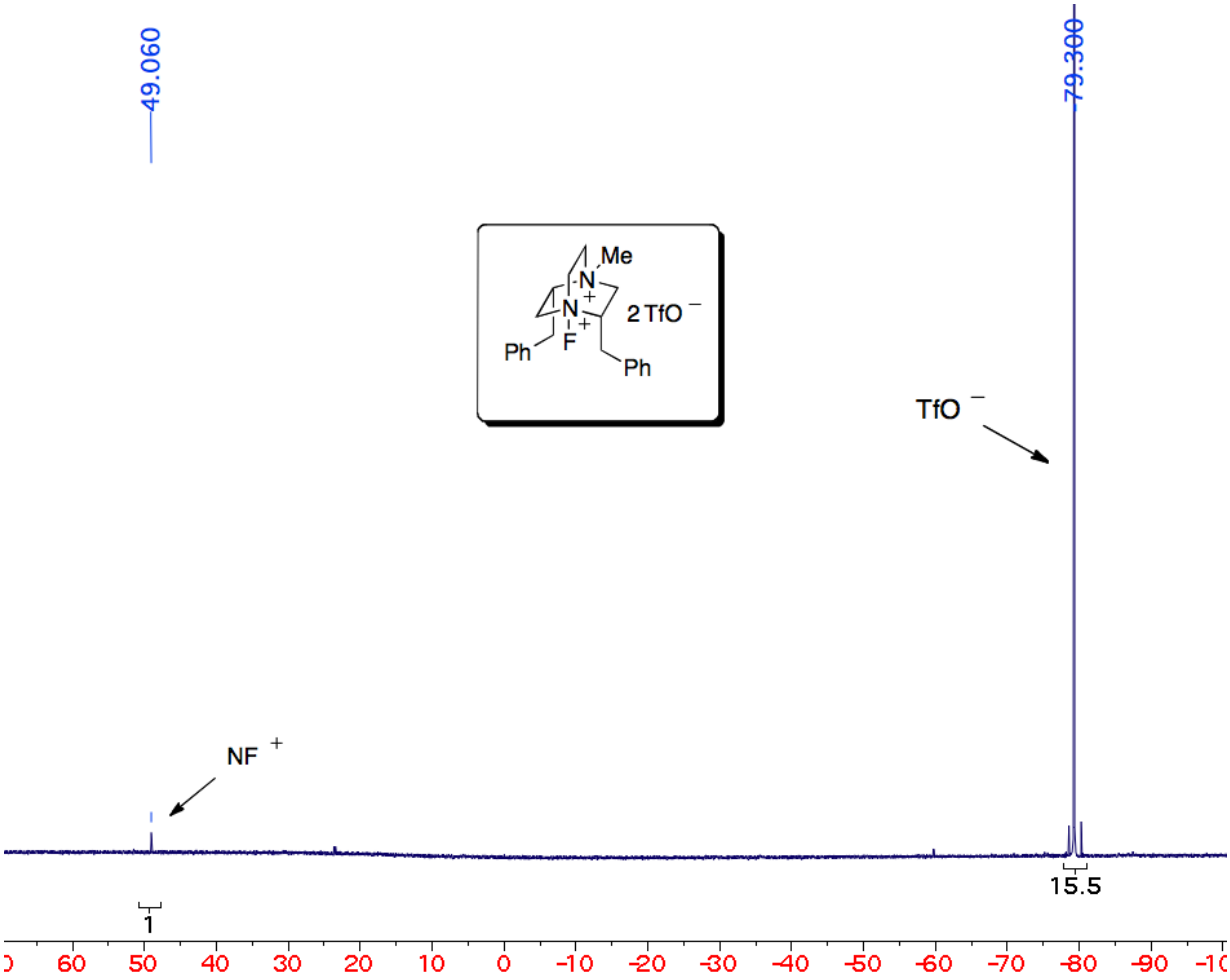
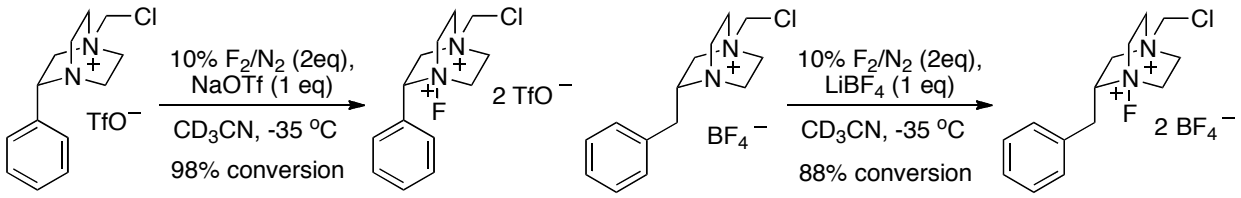


Figure 3.16 ^{19}F NMR spectrum of fluorinated isomer (1*R*,2*S*,4*S*,5*S*)-**218**

3.6.4 Fluorination of the Chiral 2-DABCO Salts Systems with F_2

The fluorination of salts (*R*)-**196** and (*R*)-**197** was achieved using the procedure described above. However in these cases, 2 equivalents of elemental fluorine were sufficient to yield the desired products in 98% and 88% conversion respectively (table 3.6). The product (*R*)-**219** was identified by ^{19}F NMR giving a characteristic signal at +31.0 ppm, which corresponded to the fluorine of the N-F bond, with the triflate ion CF_3 groups giving a singlet at -79.3 ppm (Figure 3.17). The ^{19}F NMR spectrum of (*R*)-**220** revealed the NF^+ peak at +29.5 ppm and the BF_4^- peak at -151.3 ppm.



(*R*)-**196** (*R*)-**219** (*R*)-**197** (*R*)-**220**

Entry	Amounts (mg)	Equivalents of F_2	Product	Chemical Shift (ppm)			Conversion[a] (%)
				NF^+	TfO^-	BF_4^-	
1	100	2	(*R*)-**219**	+31.0	-79.3	-	98
2	100	2	(*R*)-**220**	+29.5	-	-151.3	88

[a] conversion by ^{19}F NMR (ratio between NF^+ and TfO^- or BF_4^- signals)

Table 3.6 Formation of (*R*)-**219** and (*R*)-**220**

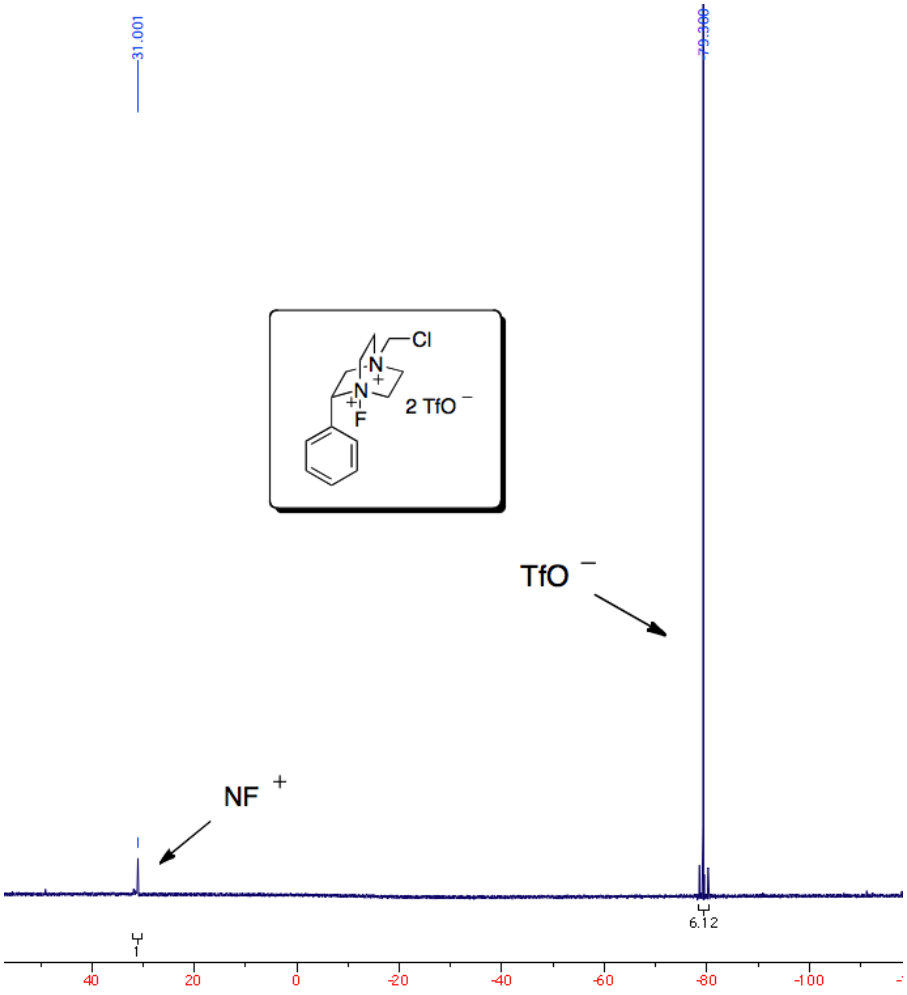


Figure 3.17 ^{19}F NMR spectrum of fluorinated (*R*)-**219**

3.7 Fluorination of Chiral DABCO Systems with N-F Pentachloropyridinium Triflate

3.7.1 Synthesis of N-F Pentachloropyridinium Triflate

Further attempts to synthesise the chiral NF-DABCO reagents and solve the problem of side reactions encountered with F_2 led us to investigate an alternative approach to F_2. It was decided to look for a reagent, which is safer, easier to handle, more selective than F_2 and more powerful than Selectfluor **10** that can be used to transfer fluorine to the quaternized chiral DABCO salts. Few NF reagents are known to display a greater oxidizing and fluorinating power than Selectfluor (Figure 3.18).[131, 132] Selectfluor **10** reacts with toluene at 80 °C in CH_3CN to give 2- and 4-fluorotoluenes.[41] DesMarteau's reagent, *N*-fluoro-trifluoromethanesulfonimide **7**,[36] readily fluorinates benzene at room temperature, but not chlorobenzene.[131] Unfortunately, this reagent is not commercially available due to difficulty in the fluorination step, which requires the reaction with elemental fluorine to be performed under pressure in a stainless steel bomb at -196 °C. Of the quaternary (R_3N^+F A^-) compounds, *N*-fluoropentachloropyridinium triflate **221** is known to be a highly potent fluorinating reagent. It can fluorinate benzene in CH_2Cl_2 at reflux and may be comparable in reactivity to **7**.[33] This reagent is not commercially available, but is easier to access than **7**.

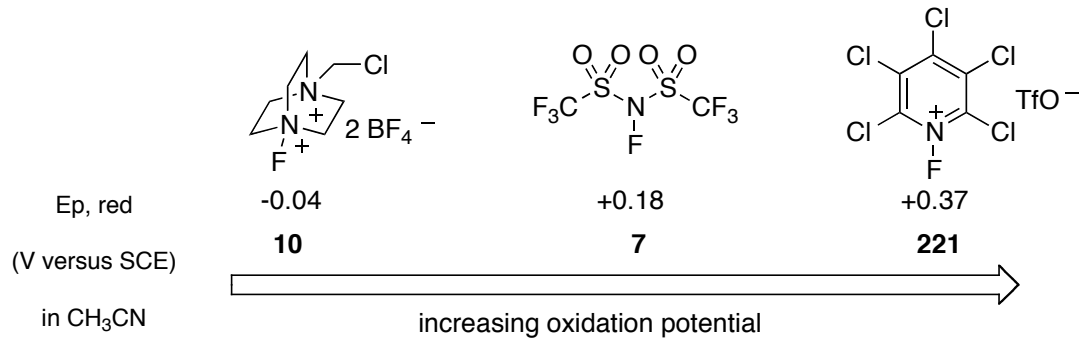


Figure 3.18 N-F fluorinating reagents

The synthesis of *N*-fluoropentachloropyridinim triflate was first reported by Umemoto and co-workers, who prepared a range of N-F fluorinating reagents based on *N*-

fluoropyridinium.[133, 134] They found that by varying the electronic properties on the pyridine ring with electron-donating or electron-withdrawing groups, the fluorinating power of the reagent can be finely tuned (Figure 3.19).[132]

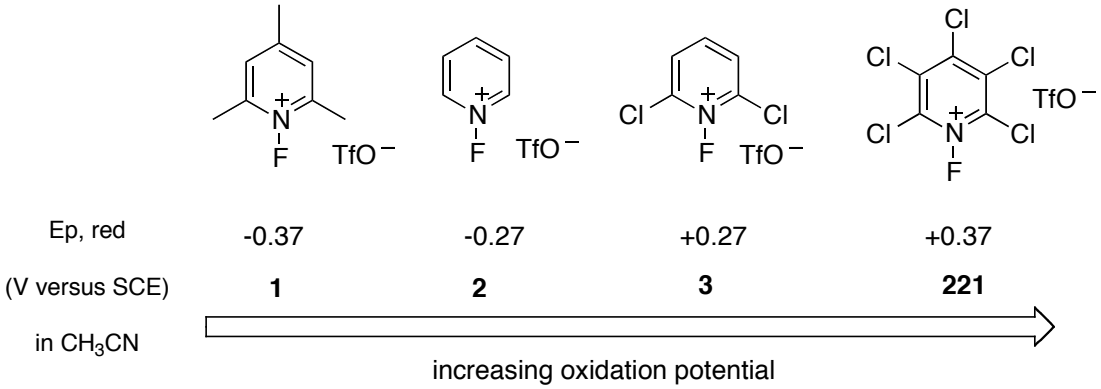
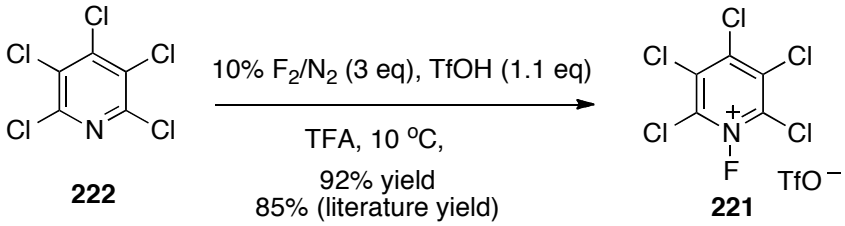


Figure 3.19 N-F pyridinium derivatives **1**, **2**, **3** and **221**

Of the four N-F pyridinium derivatives described above, only **1**, **2** and **3** are commercially available. The most electron-deficient *N*-fluoropentachloropyridinium triflate **221** requires synthesis from F_2.

We opted to synthesise **221** and investigate its reactivity in the fluorination of chiral DABCO salts.[134] Due to its low basicity (p*K*a = -6.02),[135] the fluorination of pentachloropyridine **222** was most efficiently carried out at 10 °C in trifluoroacetic acid. Thus, 2,3,4,5,6-pentachloropyridine **222** and 1.1 equivalents of triflic acid were mixed in trifluoroacetic acid, and the solution was purged with nitrogen for 20 minutes. The reaction was then cooled in ice water before introducing molecular fluorine (as a 10% (v/v) mixture in N_2 at a rate of 15 mL/min at 10 °C) (Scheme 3.21). Following the addition of 3 equivalents of fluorine gas, the mixture was purged with nitrogen for 30 minutes, and the solvent was removed under reduced pressure. Diethyl ether was slowly added to the oily residue and the resulting white precipitate formed was collected by filtration and washed with dry ether to give pure crystals of **221** in 92% yield. The

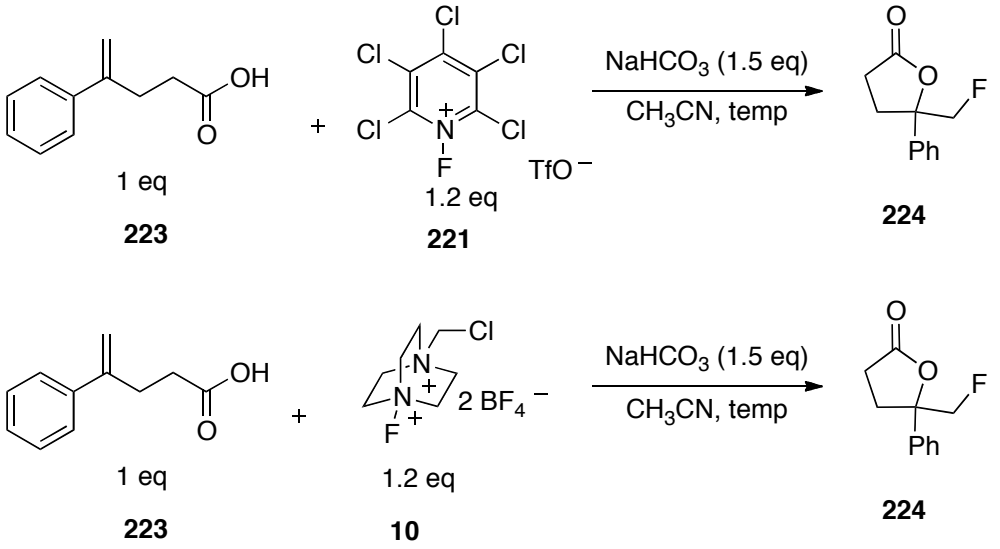
product was readily identified by ^{19}F NMR, with the diagnostic NF^+ peak at +46.5 ppm and the triflate peak at -79.3 ppm. Mass spectrometry also gave the required positive ion $C_5Cl_5FN^+$ [M]+: 270.0113 and negative ion, $CF_3O_3S^-$: -148.9525. The purity of the compound was confirmed by elemental analysis (C, N) [Anal. Calcd for $C_6Cl_5F_4NO_3S$: C, 17.18; N, 3.34. Found: C, 17.07; N, 3.41].



Scheme 3.21 Synthesis of *N*-fluoropentachloropyridinium triflate **221**

There is not a direct comparison of reactivity between Selectfluor **10** and N-F pentachloropyridinium triflate **221** reported in the literature; we therefore evaluated their relative reactivity. Substrate **223** was chosen to carry out this investigation as an example of fluorolactonization has been described in literature using this substrate with *N*-fluoropyridinium derivatives.[136] Initially, fluoro-lactonization of 4-phenyl-4-pentenoic acid **223** was conducted using N-F pentachloropyridinium triflate **221** (Table 3.7). The reaction proceeds smoothly at room temperature in CH_3CN in the presence of 1.5 equivalents of $NaHCO_3$ to give fluorolactone **224** in 66% yield. To probe the reactivity further, the temperature was lowered to -40 °C and the reaction still proceeds after 18 hours giving 38% yield (Table 3.7, entry 2). When the same conditions (25 °C) were applied with Selectfluor **10**, no fluorolactonization occured at room temperature after 48 hours. When the reaction was left for a longer period of time at the same temperature, no fluorinated product was observed by TLC or NMR analysis (Table 3.7, entries 3 and 4). However, the reaction proceeded when the temperature was raised to 80 °C for 2 hours giving the product in 54%

yield, after silica gel column chromatography (Table 3.7, entry 5). The structure of **224** was determined by ^{1}H, ^{13}C and ^{19}F NMR analysis as described in the literature.



Entry	N-F reagents	Temperature	Time (h)	Yield (%)
1	**221**	25 °C	1	66 (69)[b]
2	**221**	-40 °C	18	38
3	**10**	25	48	-[a]
4	**10**	25	144	-[a]
5	**10**	80	2	54

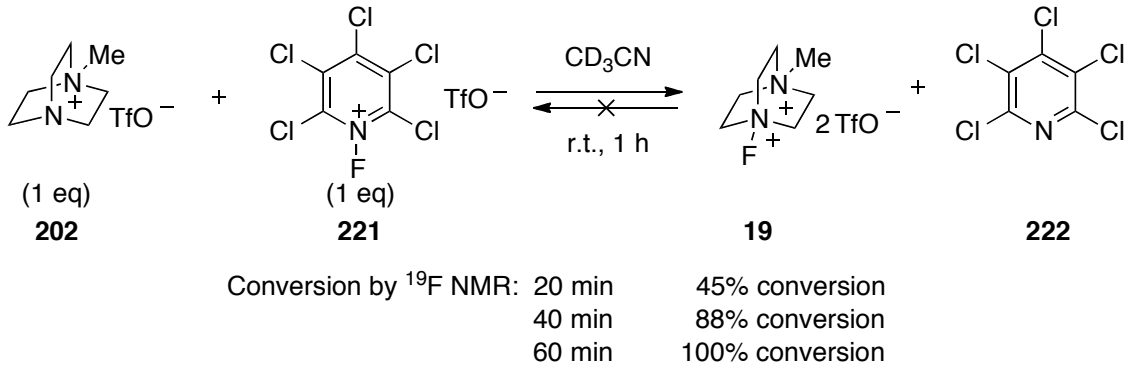
[a] starting material recovered, [b] literature yield

Table 3.7 Fluorolactonization reaction

3.7.2 Fluorination of DABCO Salts with N-F Pentachloropyridinium Triflate

These previous results demonstrate that *N*-fluoropentachloropyridinium triflate **221** is a more reactive NF reagent for the promotion of fluorolactonization than Selectfluor **10**, in line with their redox potentials. It was stipulated that fluorination using **221** to afford the fluorinated chiral DABCOs could be met with greater success. We began our study by investigating the reactivity of **221** on the achiral 1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane **202**. The reaction was performed in deuterated acetonitrile to facilitate analysis of the fluorination process. Accordingly, salt **202** was added to a solution of *N*-fluoropentachloropyridinium triflate **221** in acetonitrile, and the reaction mixture was

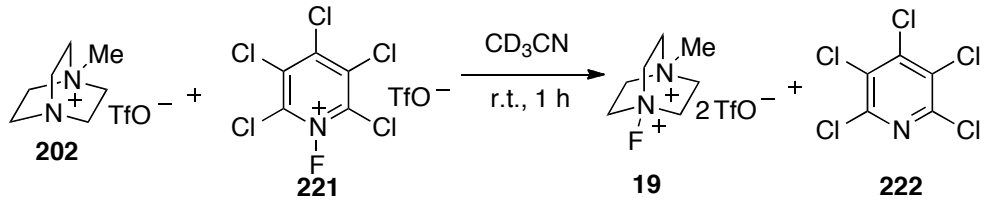
stirred at room temperature and monitored by ^{19}F NMR spectroscopy (Scheme 3.22). After 20 minutes, a 45% conversion of the 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) **19** was estimated by ^{19}F NMR. When the reaction was left for 40 minutes, an improved conversion was recorded and pleasingly, after 60 minutes full transfer of fluorine took place (Scheme 3.22). The NF peak specific to *N*-fluoropentachloropyridinim triflate **221** had totally disappeared in the ^{19}F NMR spectrum. The structure of the product was confirmed by ^{19}F NMR showing an N-F signal at +46.9 ppm and TfO^- signal at -79.3 ppm and mass spectrometry analysis $C_7H_{15}FN_2^+$ $[M]^{2+}$: 146.1208.



Scheme 3.22 Fluorination of **202** with *N*-fluoropentachloropyridinim triflate **221**

One of the challenges we faced during the course of this investigation was to define a suitable protocol to separate the newly formed N-F reagent from the pentachloropyridine by-product. This was achieved by exploiting the difference in solubility of ionic salts in various solvents. Scheme 3.23 shows the solubility profile of all compounds involved in the reaction and can be used as an approximate guide for the isolation of the desired fluorinated DABCOs. Since the methylated DABCO salt **202**, the pyridinium triflate salt **221** and the newly formed NF-DABCO triflate salt **19** were found to be all soluble in acetonitrile and methanol, it is therefore important to use an equimolar amount of starting materials. An excess of any of the starting reagents **202** and **221** would prove difficult to separate from the

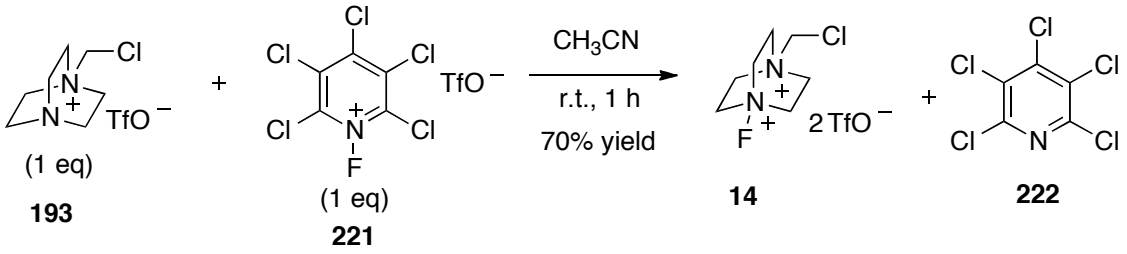
final product, especially **221**, which can be detrimental in the case of chiral DABCO systems. Utilising the solubility pattern described in Scheme 3.23, the purification of **19** was achieved by trituration with dichloromethane, followed by recrystallisation (Et_2O/MeOH) affording the fluorinated DABCO salt **19** in 74% yield.



Solvent	202	221	19	222
Acetonitrile	soluble	soluble	soluble	insoluble
Diethyl ether	insoluble	insoluble	insoluble	soluble
Dichloromethane	insoluble	insoluble	insoluble	soluble
Methanol	soluble	soluble	soluble	insoluble

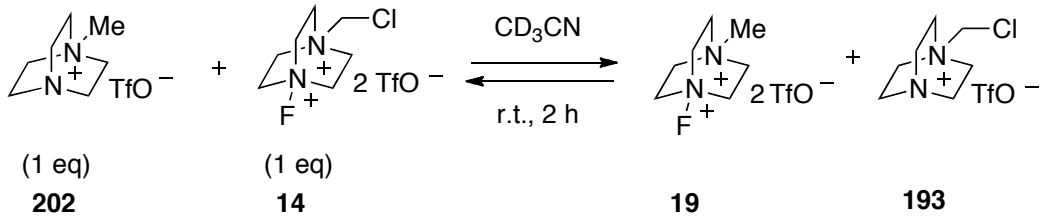
Scheme 3.23 Solubility in CH_3CN, Et_2O, CH_2Cl_2 and MeOH

The same methodology was applied for the fluorination of the chloromethylated DABCO **193**. Thus, treatment of salt **193** with 1 equivalent of *N*-fluoropentachloropyridinium triflate **221** in acetonitrile at room temperature for 1 hour formed 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) **14** in 70% yield after purification. The identity of the product was confirmed by ^{19}F NMR, with a characteristic signal corresponding to the N-F peak observed at +48.5 ppm, and the triflate ion peak observed at -79.3 ppm.



Scheme 3.24 Fluorination of salt **193** with NF-pentachloropyridinium triflate **221** as OTf salt

We also investigated the reactivity of Selectfluor triflate on the achiral 1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane **202**. Thus, 1 equivalent of **202** was added to 1 equivalent of Selectfluor triflate **14** in acetonitrile, and the reaction mixture was stirred at room temperature and monitored by ^{19}F NMR (Scheme 3. 25).



Scheme 3.25 Rapid fluorine exchange between DABCO molecules

After 30 minutes, two peaks were observed in the ^{19}F NMR spectrum at +48.0 ppm and +46.9 ppm with a relative intensity of 1:1.5 and assigned to the fluorine of Selectfluor triflate **14** and **19** respectively (Figure 3.20). When the reaction was left for 1 to 2 hours no improvement in the ratio was observed. The fluorination is reversible under these conditions with rapid exchange of fluorine between the DABCO salts.

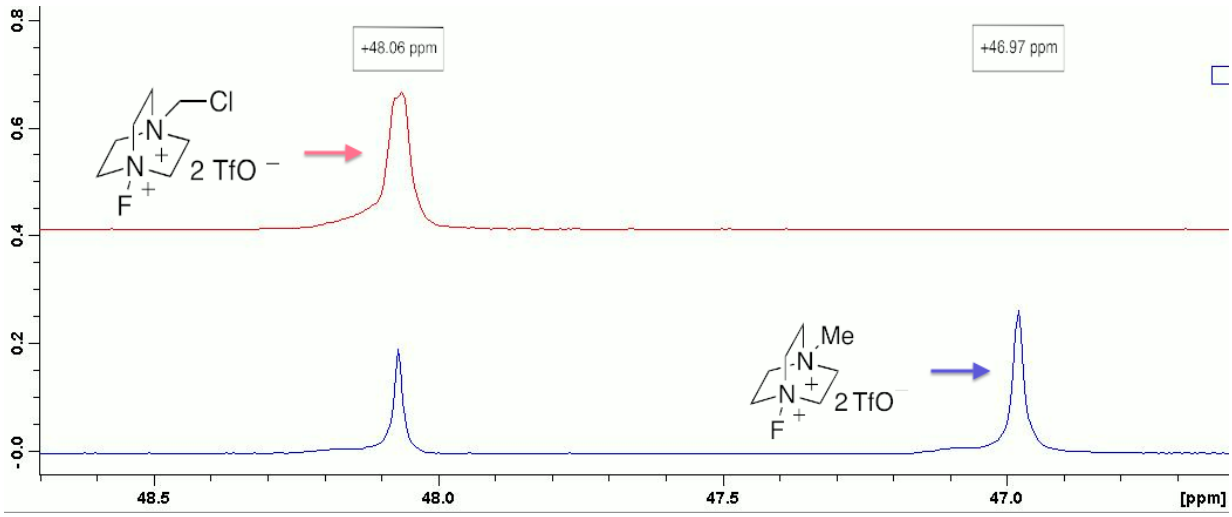
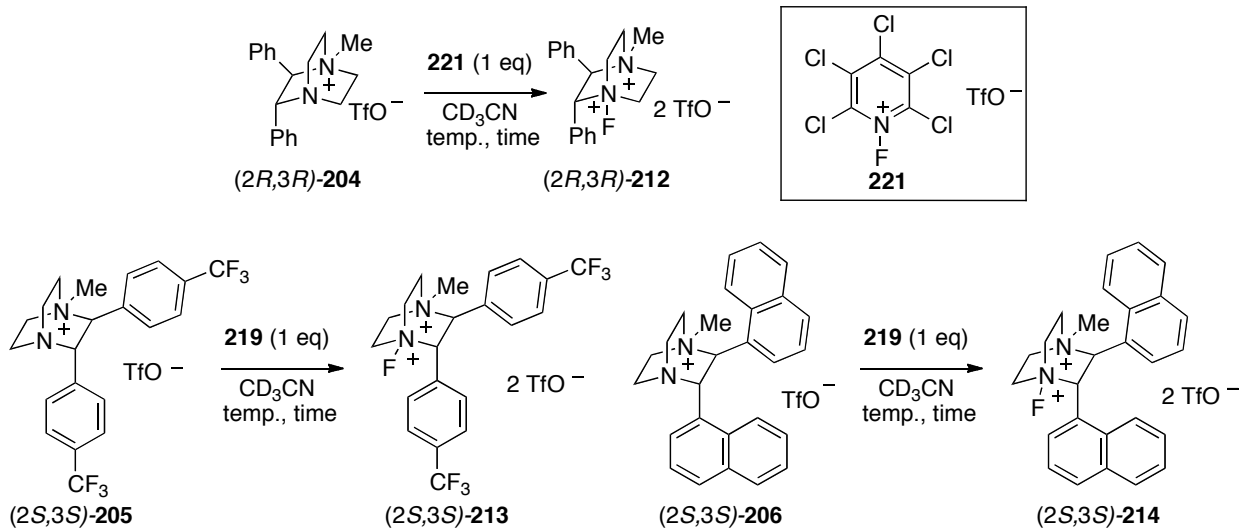


Figure 3.20 ^{19}F NMR spectrum of Selectfluor triflate **14** and fluorinated DABCO **19**

3.7.3 Fluorination of Chiral DABCO Salts with N-F Pentachloropyridinium Triflate

Having established the feasibility and efficiency of the fluorination of the achiral DABCO salts **202** and **193** using *N*-fluoropentachloropyridinium triflate **221**, the fluorination of the chiral 2,3-DABCO (2*R*,3*R*)-**204**, (2*S*,3*S*)-**205** and (2*S*,3*S*)-**206** was next studied. Thus, (2*R*,3*R*)-2,3-diphenyl-1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate salt **204** was reacted with **221** in CD_3CN at room temperature. The reaction was followed by ^{19}F NMR spectroscopy and appeared to have proceeded to completion after approximately 2 hours giving the desired product (2*R*,3*R*)-**212** in 82% conversion (Table 3.8, entry 1). The electron-deficient salt (2*S*,3*S*)-**205** was also successfully fluorinated by **221** but a longer time was required. The ^{1}H NMR spectrum recorded after 4 hours revealed the presence of starting material. Leaving the reaction for 8 hours proved satisfactory and product (2*S*,3*S*)-**213** was obtained in 70% conversion. On the other hand, the fluorination of (2*S*,3*S*)-**206** proved challenging as we did not observe any conversion at room temperature after 2 hours. Although the reaction time was prolonged for 24 hours, only 50% conversion was observed by ^{19}F NMR spectroscopy. Heating the reaction at 50 $^{\circ}C$ for 1 hour, delivered fluorinated isomer (2*S*,3*S*)-**214** in 80% conversion, however, impurities were observed in a region consistent with an aryl fluoride (Table 3.8). The conversions obtained using F_2 are higher than the ones obtained using N-F pentachloropyridinium triflate for chiral N-F DABCOs **212** and **213** and similar for reagent **214**.

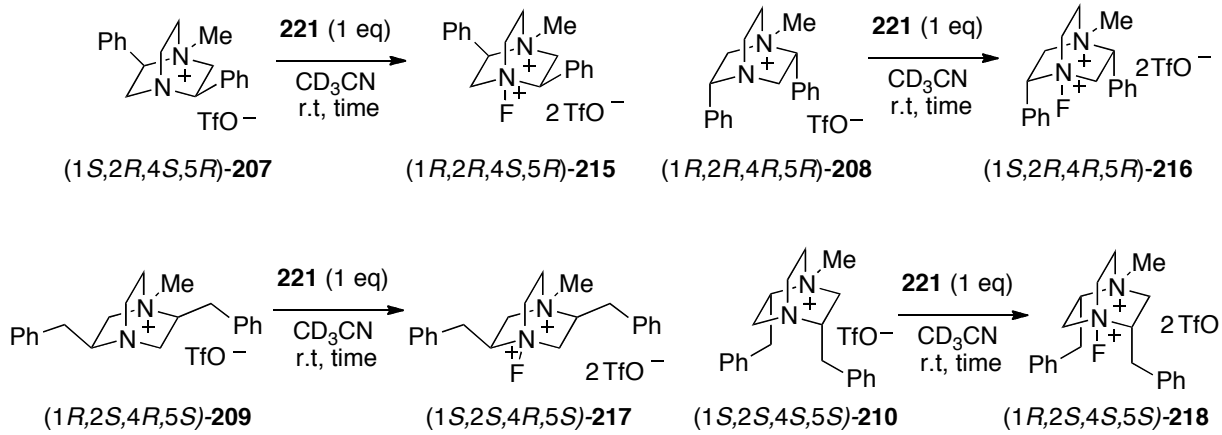


Entry	Compound	Temperature (°C)	Time (h)	Product	Conversion[a] (%)	Conversion Using F_2 (%)
1	(2*R*,3*R*)-**204**	25	2	(2*S*,3*S*)-**212**	82	99
2	(2*S*,3*S*)-**205**	25	8	(2*S*,3*S*)-**213**	70	97
3	(2*S*,3*S*)-**206**	25	2	(2*S*,3*S*)-**214**	-	-
4	(2*S*,3*S*)-**206**	25	8	(2*S*,3*S*)-**214**	15	-
5	(2*S*,3*S*)-**206**	25	24	(2*S*,3*S*)-**214**	50	50
6	(2*S*,3*S*)-**206**	50	1	(2*S*,3*S*)-**214**	80[b]	-

[a] Conversion by ^{19}F NMR, [b] additional peaks observed in ^{19}F NMR spectrum.

Table 3.8 Fluorination of chiral 2,3-disubstituted DABCO using **221**

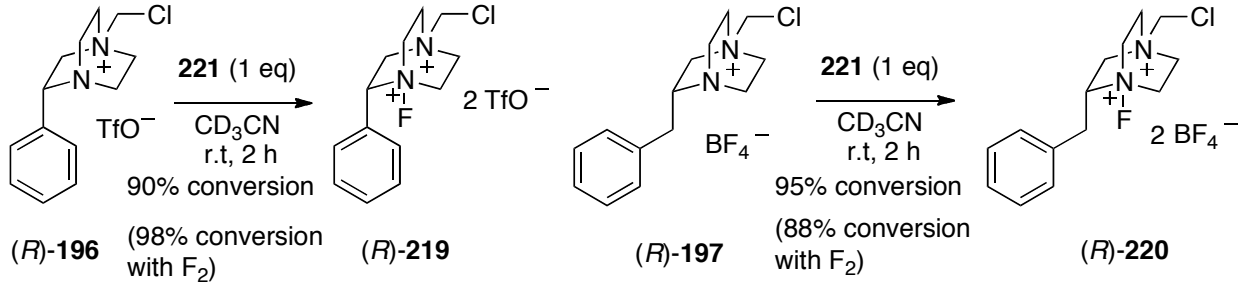
The methodology was further applied to the fluorination of chiral 2,5-disubstituted DABCO salts (1*S*,2*R*,4*S*,5*R*)-**207**, (1*R*,2*R*,4*R*,5*R*)-**208**, (1*R*,2*S*,4*R*,5*S*)-**209** and (*1S,2S,4S,5S)*-**210** and this proved effective for the production of fluorinated chiral 2,5-disubstituted-DABCO salts (1*R*,2*R*,4*S*,5*R*)-**215**, (1*S*,2*R*,4*R*,5*R*)-**216**, (1*S,*2*S,*4*R,*5*S)*-**217** and (1*R,*2*S,*4*S,*5*S)*-**218** in moderate conversions (Table 3.9). The conversions obtained using F_2 are similar to the ones obtained using N-F pentachloropyridinium triflate.



Entry	Compounds	Time (h)	Product	Conversion (%)	Conversion Using F_2 (%)
1	(1*S*,2*R*,4*S*,5*R*)-**207**	4	(1*R*,2*R*,4*S*,5*R*)-**215**	70	76
2	(1*R*,2*R*,4*R*,5*R*)-**208**	6	(1*S*,2*R*,4*R*,5*R*)-**216**	65	70
3	(1*R*,2*S*,4*R*,5*S*)-**209**	5	(*1S,2S,4R,5S)*-**217**	60	60
4	(1*S*,2*S*,4*S*,5*S)*-**210**	9	(1*R*,2*S*,4*S*,5*S)*-**218**	50	38

Table 3.9 Fluorination of chiral 2,5-disubstituted-DABCOs using **221**

Extending this strategy, 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane salts (*R*)-**196** and (*R*)-**197** were subjected to fluorination at room temperature for 2 hours. The desired mono-substituted NF-DABCO salts (*R*)-**219** and (*R*)-**220** were obtained in 90% and 95% conversion respectively.



Scheme 3.26 Fluorination of chiral 2-substituted-DABCO systems using **221**

In summary, we have shown in this investigation that chiral Selectfluor analogues could be synthesised *via* alkylation of chiral DABCO precursors followed by fluorination using either F_2 or *N*-fluoropentachloropyridinium triflate. The study also showed that mono-fluorinated chiral DABCO derivatives are unstable at room temperature and could only be used at low

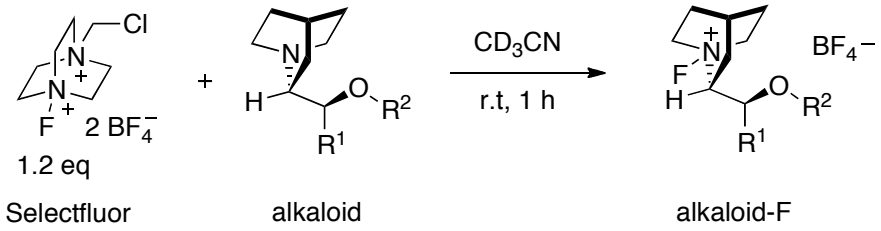
temperature. A library of substituted chiral DABCO cores is likely to be required to evaluate their efficacy for asymmetric fluorination. Thus altering the substituents on the chiral diamine matching complex cinchona alkaloids is planned. Since the key step towards the synthesis of these novel chiral reagents will be the formation of the N-F bond, preliminary work was performed with the aim of defining the compatibility of various functional groups with electrophilic fluorinating reagents.

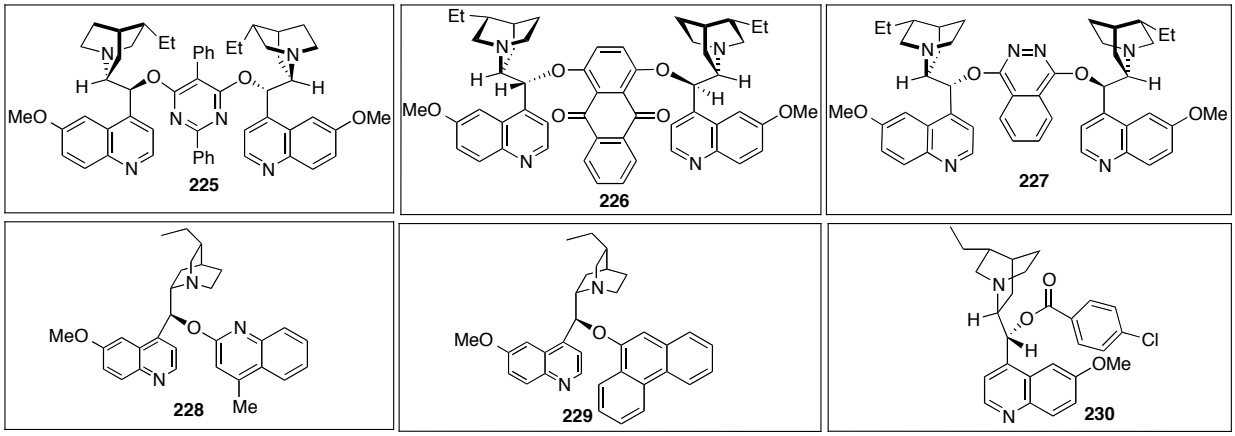
3.8 Fluorination of Cinchona Alkaloids

Selected cinchona alkaloids were fluorinated with three different fluorinating reagents: Selectfluor, F_2 and N-F pentachloropyridinium triflate. The alkaloids used were chosen for fluorination studies due to their ready-availability and their uses in asymmetric fluorination.

3.8.1 Fluorination of Alkaloids with Selectfluor

To begin our investigation, we reproduced literature procedures and fluorinated the selected cinchona alkaloids with Selectfluor in order to validate the conversion of a tertiary amine to a fluorinated quaternary amine.[137] The fluorination data obtained with this method will allow direct comparison with the F_2 and N-F pentachloropyridinium triflate systems. Thus, the alkaloids were treated with Selectfluor in CD_3CN at room temperature for 1 hour giving the fluoroalkaloids in good to excellent conversions. The fluorinated products were identified by mass spectrometry and ^{19}F NMR (Table 3.10).





Entry	Alkaloids	Products	Chemical shifts[a] (ppm)		Conversion[b] (%)
			NF^+	BF_4^-	
1	-	**Selectfluor**	+49.0	-151.0	-
2	**225**	**225F**	+43.6	-151.0	70
3	**226**	**226F**	+43.4	-151.0	92
4	**227**	**227F**	+44.1	-151.0	80
5	**228**	**228F**	+43.3	-151.0	95
6	**229**	**229F**	+37.2	-151.0	93
7	**230**	**230F**	+42.5	-151.0	95

[a] ^{19}F NMR recorded in CD_3CN, [b] conversion by ^{19}F NMR (ratio between NF^+ and BF_4^- signals)

Table 3.10 ^{19}F NMR chemical shifts of selected fluorinated cinchona alkaloids with Selectfluor

For illustration, the ^{19}F NMR spectrum of alkaloid **230F** shows that the transfer of fluorine from Selectfluor to the alkaloids was a clean reaction with no fluorinated side products could be observed in the final compound (Figure 3.21).

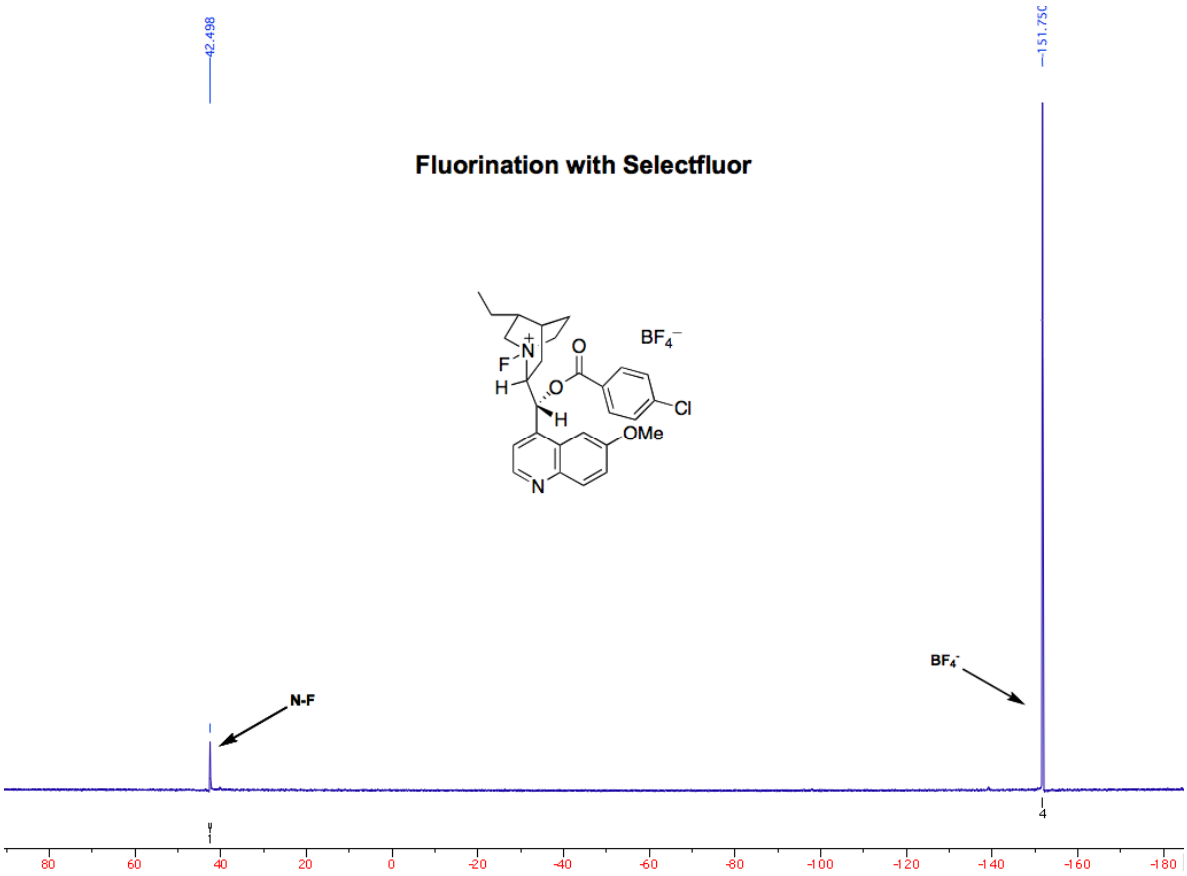
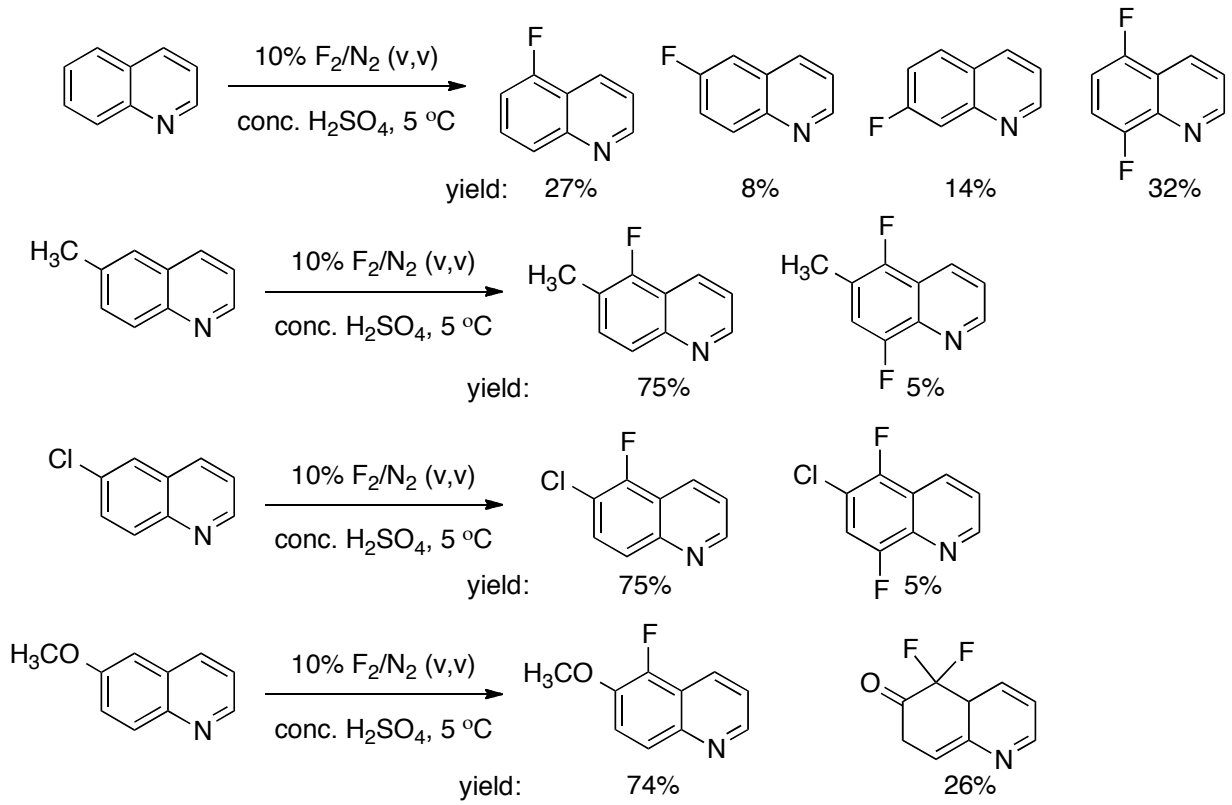


Figure 3.21 ^{19}F NMR spectrum of **230F** in CD_3CN using Selectfluor as fluorine source

3.8.2 Fluorination of Cinchona Alkaloids with F_2

Next, we investigated the fluorination of cinchona alkaloids with F_2 at the laboratory of Prof. Graham Sandford at Durham University.[138] There is no precedent in the literature for the fluorination of alkaloids with F_2. However, Chambers and co-workers reported the fluorination of various quinoline derivatives, which are common structural motifs present in alkaloids, with elemental fluorine (Scheme 3.27).[139] In all cases, fluorination occurred on the benzenoid ring rather than at the nitrogen and this was attributed to the deactivation of the heterocyclic ring towards electrophilic attack by the protonation of the heteroatom in the strongly acidic reaction medium. In contrast, in neutral medium, such as acetonitrile, the fluorination of quinoline gave many products and a significant amount of tarry material.

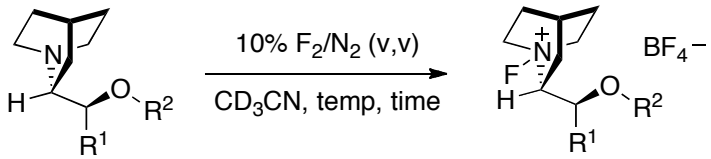


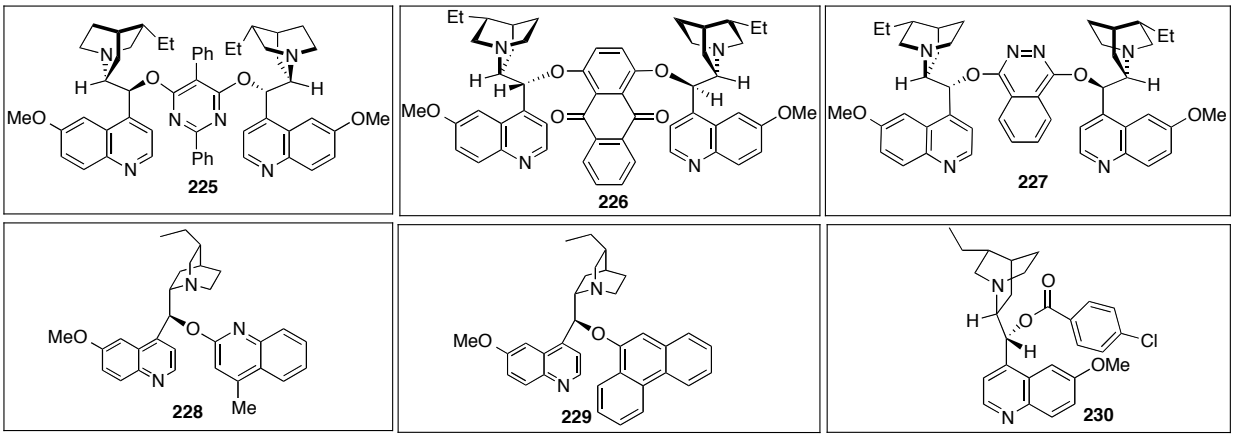
Scheme 3.27 Fluorination of quinoline derivatives

Direct fluorination of various pyridine, quinoline, quinoxaline derivatives at sites adjacent to the heteroatom and aromatic systems have been reported.[140, 141] The C-F peaks on those systems are generally found between -60 ppm and -150 ppm in the ^{19}F NMR spectrum.[142, 143]

Thus, our investigation started by treating the alkaloids with a mixture of fluorine in nitrogen (as a 10% (v/v) mixture in N_2) in the presence of 1 equivalent of sodium tetrafluoroborate in CD_3CN at room temperature (Table 3.11). In most cases, the reactions did not go to completion, although ^{19}F NMR was consistent with the formation of the desired fluoroalkaloids; varying amounts of side-products were detected. Signals observed in the region between -60 ppm and -180 ppm in the spectrum suggests that the aromatic rings and quinoline motifs of the cinchona alkaloids were fluorinated in all cases. Other peaks in the spectrum could not be fully assigned. When the temperature was lowered to -10 ^oC and 1 equivalent of F_2 was used in the case of

mono-alkaloid **230** (Table 3.11, entry 8), the reaction did not go to completion and side-reactions were still observed. Addition of 4 equivalents of fluorine to **230** at -10 °C gave an improved conversion but varying amount of side-products were observed consistently.





Entry	Alkaloids	Conditions	Products	Chemical shifts[a] (ppm) NF^+	Chemical shifts[a] (ppm) BF_4^-	Conversion[b] (%)
1	**225**	$NaBF_4$, 1 eq F_2/N_2, CH_3CN, 4 min, r.t	**225F**	+42.6	-151.0	14
2	**226**	$NaBF_4$, 1 eq F_2/N_2, CH_3CN, 4 min, r.t	**226F**	+43.2	-151.0	16
3	**227**	$NaBF_4$, 2 eq F_2/N_2, CH_3CN, 4 min, r.t	**227F**	+43.3	-151.0	<5
4	**228**	$NaBF_4$, 2eq F_2/N_2, CH_3CN, 8 min, r.t	**228F**	+43.3	-151.0	34
5	**229**	$NaBF_4$, 2 eq F_2/N_2, CH_3CN, 8 min, r.t	**229F**	+34.1	-151.0	10
6	**230**	$NaBF_4$, 1 eq F_2/N_2, CH_3CN, 4 min, rt	**230F**	+43.0	-151.0	15
7	**230**	$NaBF_4$, 2 eq F_2/N_2, CH_3CN, 8 min, r.t	**230F**	+43.0	-151.0	67
8	**230**	$NaBF_4$, 1 eq F_2/N_2, CH_3CN, 4 min, -10 °C	**230F**	+43.0	-151.0	5
9	**230**	$NaBF_4$, 4 eq F_2/N_2, CH_3CN, 16 min, -10 °C	**230F**	+43.0	-151.0	32

[a]varying amount of signals observed in the ^{19}F NMR spectrum, [b] conversion by ^{19}F NMR

Table 3.11 ^{19}F NMR chemical shifts of selected fluorinated cinchona alkaloids with F_2

Figure 3.22 illustrate ^{19}F NMR spectrum of alkaloid **230F** showing the NF^+ and BF_4^- peaks, and additional signals.

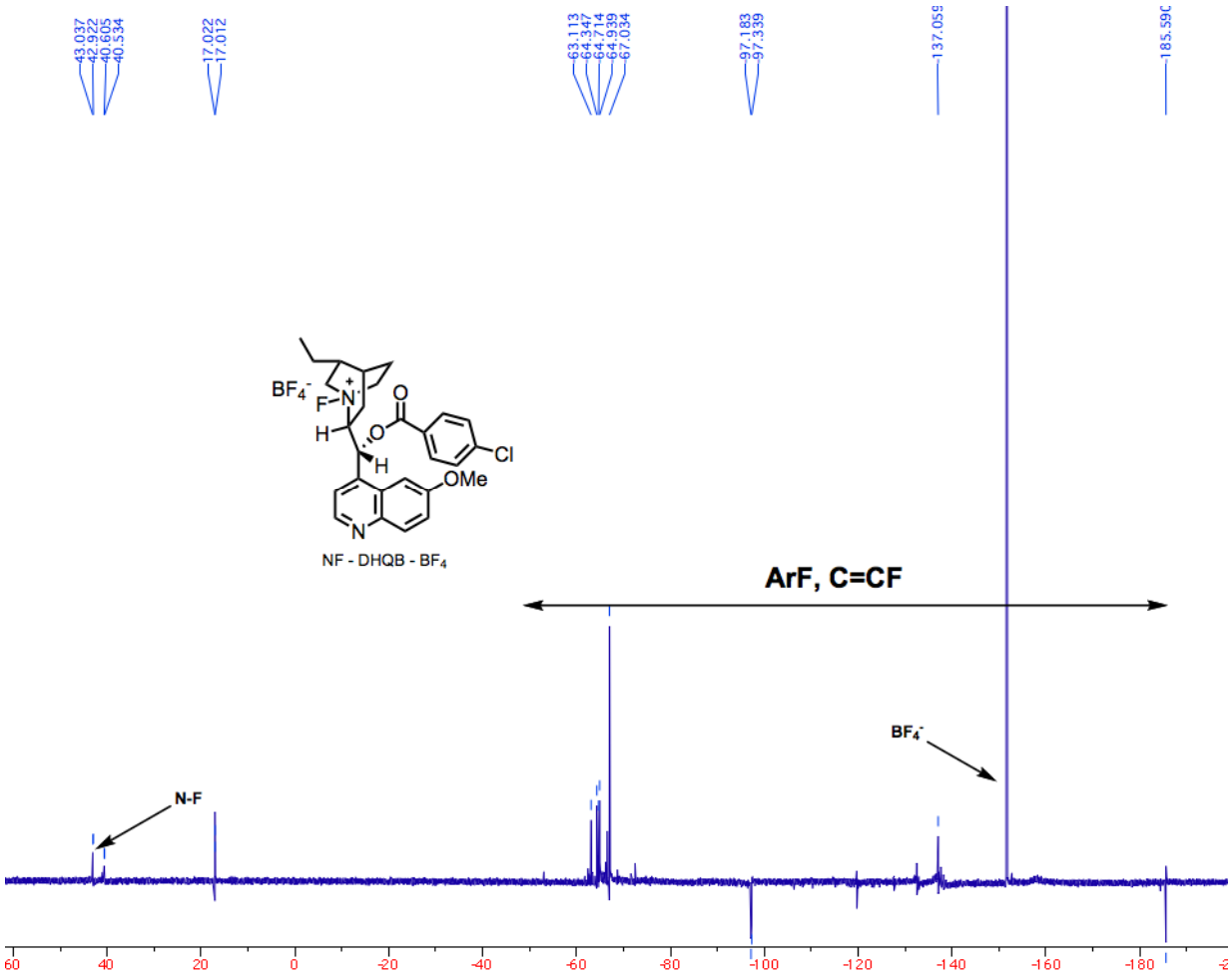
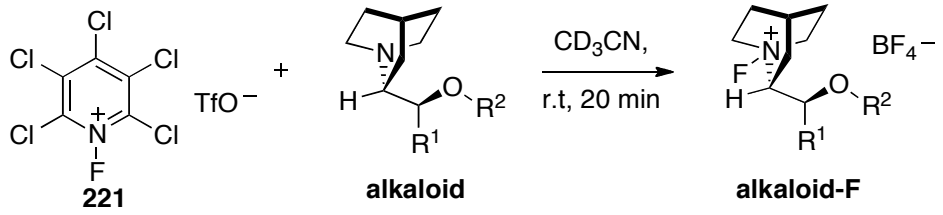


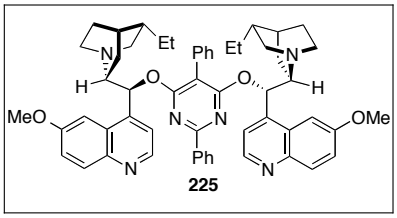
Figure 3.22 ^{19}F NMR spectrum of **230F** using F_2 as fluorine source at -10 ^oC

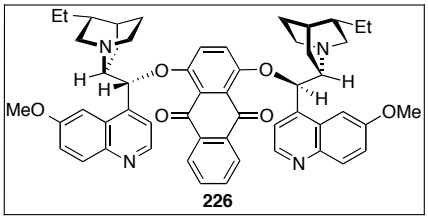
3.8.3 Fluorination of Cinchona Alkaloids with N-F Pentachloropyridinium Triflate

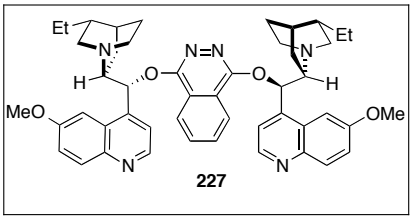
The fluorination and compatibility of functional groups on the cinchona alkaloids with *N*-fluoropentachloropyridinium triflate **221** was also examined. Thus, 1 equivalent of *N*-fluoropentachloropyridinium triflate **221** was added to a solution of the selected alkaloids in CD_3CN at room temperature. The reaction was stirred for 20 minutes and the fluoroalkaloids were obtained in good conversions (Table 3.12). No additional signals were observed in the ^{19}F NMR spectrum. This result is encouraging and it demonstrated that

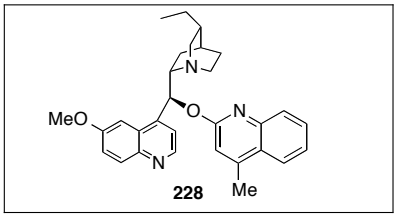
various functional groups are compatible with *N*-fluoropentachloropyridinium triflate **221**. The conversions obtained using Selectfluor are higher than the ones generated using N-F pentachloropyridinium triflate. However, N-F pentachloropyridinium triflate is able to fluorinate DABCO salts, which is not possible with Selectfluor.

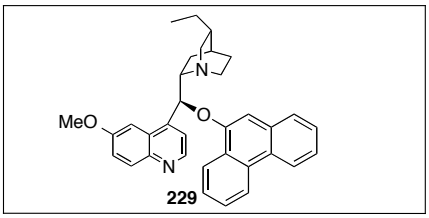


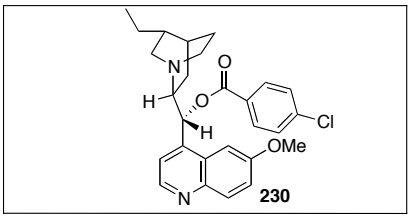












Entry	Alkaloids	Products	Chemical shifts[a] (ppm) NF^+	TfO^-	Conversion[b] (%)	Conversion with Selectfluor (%)
1	-	**NF-Pentachloropyridinium triflate**	+46.6	-79.3	-	-
2	**225**	**225F**	+42.6	-79.3	76	70
3	**226**	**226F**	+43.2	-79.3	75	92
4	**227**	**227F**	+43.4	-79.3	75	80
5	**228**	**228F**	+43.1	-79.3	78	95
6	**229**	**229F**	+37.3	-79.3	80	93
7	**230**	**230F**	+43.0	-79.3	85	95

[a] ^{19}F NMR recorded in CD_3CN, [b] conversion by ^{19}F NMR (ratio between NF^+ and BF_4^- signals)

Table 3.12 ^{19}F NMR chemical shifts of selected fluorinated cinchona alkaloids with NF-pentachloropyridinium triflate

3.9 Conclusions and Future Work

In conclusion, we have synthesised nine novel chiral analogues of Selectfluor for asymmetric fluorination of prochiral substrates. All of the neutral chiral 1,4-diazabicyclo[2.2.2]octanes studied were found to undergo fluorination in the presence of Selectfluor in acetone at low temperature to afford mono-fluoro chiral DABCO reagents. Mono-fluorinated chiral DABCOs were found to be unstable at low temperature, however, subsequent quaternization of these chiral reagents induced stability. The successful synthesis of chiral DABCO quaternary salts has led to fluorination with F_2 yielding chiral non racemic Selectfluor analogues in moderate to good conversion. However, the fluorination with F_2 proved challenging in some cases as by-products were observed by ^{19}F NMR analysis.

We have developed a practical and general process for the synthesis of 1-fluoro-4-alkyl-azoniabicyclo[2.2.2]octane salts using *N*-fluoropentachloropyridinium triflate. We have demonstrated that this reagent solves the problem of selectivity encountered with F_2 and that the reaction can be performed at room temperature, importantly this reagent can be handled easily and safely used in a laboratory environment. The fluorination of chiral DABCO salts using *N*-fluoropentachloropyridinium triflate produced chiral selectfluor analogues in moderate to good conversions. No side-products were detected in the ^{19}F NMR spectra as observed using F_2. The simplicity of this approach should allow the fluorination of more complex DABCO systems.

The study of functional group tolerance towards molecular fluorine has been performed using cinchona alkaloids. The results of this investigation validated the fact that molecular fluorine could be used to transfer fluorine to complex reagents. However, the quinoline and aromatic rings, which are common structural motifs in alkaloids, were fluorinated during the initial studies. Nevertheless, we demonstrated that the used of either Selectfluor or *N*-

fluoropentachloropyridinium triflate gave the desired fluoroalkaloids in excellent conversion with no side-product observed in ^{19}F NMR.

Chapter 4: Asymmetric Fluorination

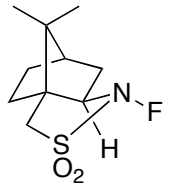
4.1 Introduction

There has been considerable interest in organic fluorinated compounds, which often confer unique biological and physical properties.[144] Because of the importance of chirality in drug design, the enantioselective incorporation of fluorine into organic molecules has been extensively investigated by research groups worldwide and has been frequently reviewed.[145] Enantioselective electrophilic fluorination is a challenging asymmetric process, and the discovery of efficient methods is a fascinating aspect of modern organofluorine chemistry.[146] Among the various approaches explored, an enantioselective fluorination strategy using electrophilic N-F reagents is one of the most popular.[147] To this end, a variety of chiral nonracemic N-F fluorinating agents were developed for the enantioselective fluorination of substrates containing acidic C-H bonds.[148]

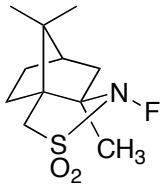
4.2 First-Generation Chiral Fluorinating Reagents: Uncharged N-F Reagents

4.2.1 Differding's Reagents

The pioneering work of Differding and Lang in 1988 led to the development of the *N*-fluoro-camphor-sultams **231** and **232** as the first enantioselective fluorinating agents (Figure 4.1).[149]



(-)-**231**



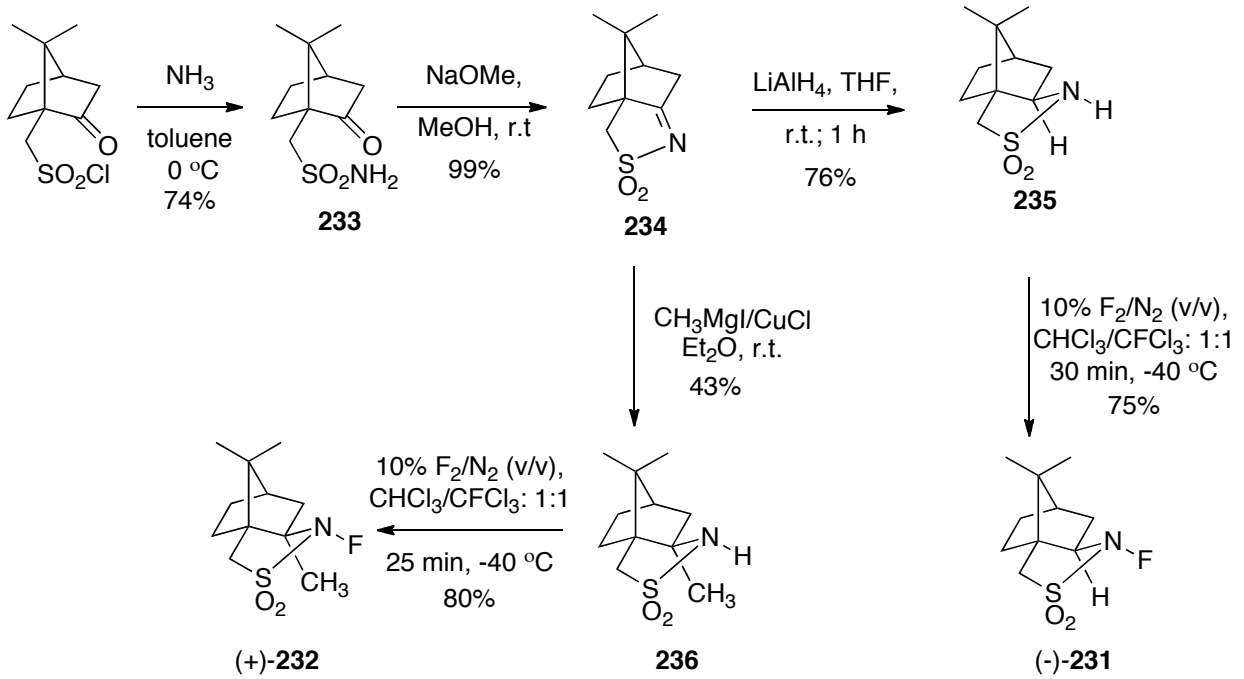
(+)-**232**

Figure 4.1 *N*-fluorocamphor-sultams **231** and **232**

4.2.1.1 Synthesis

Amidation of camphor-10-sulfonyl chloride with NH_3 followed by base catalysed cyclisation led to the formation of compound **234** in 99% yield. Reduction with lithium aluminium hydride furnished sultam **235.** Alternatively, when **234** was methylated using CH_3MgI in the presence of 1 equivalent of CuCl, sultam **236** was obtained (Scheme 4.1).[149] These reactions are proposed to

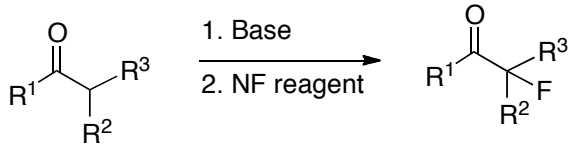
occur *via* attack of the nucleophile from the less hindered face of sultam **234**. Direct fluorination of **235** or **236** in $CHCl_3/CFCl_3$ at -40 °C with 10% F_2/N_2 (v/v) generated (-)-*N*-fluoro-camphorsultam **231** or (+)-*N*-fluoro-camphorsultam **232** in 75% and 80% yield respectively.[150]

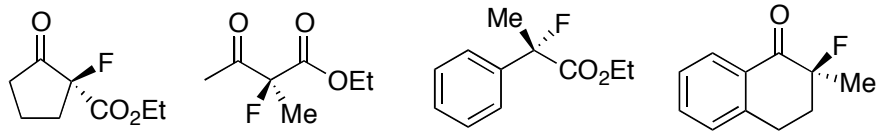


Scheme 4.1 Differding's reagents **231** and **232**

4.2.1.2 Applications

Preliminary fluorination experiments using the optically active *N*-fluoro compounds **231** and **232** were successful with various metal enolates generated under standard reaction conditions (alkali metal hydrides in Et_2O or toluene/THF at room temperature or LDA in THF at -78 °C) to give α-fluoro carbonyl compounds. Enantiomeric excesses were found to be substrate dependent, with reagent (-)-**231** leading to higher ee's (Table 4.1).[149] The highest ee obtained was a respectable 70%; other substrates produced lower enantiomeric excess. These results demonstrated the feasibility of reagent controlled asymmetric fluorination by reaction with an electrophilic source of fluorine.





(*S*)-**237F** (*S*)-**238F** (*S*)-**239F** (*S*)-**240F**

Entry	N-F Reagents	Conditions	Products	Yield (%)	ee (%)
1	(-)-**231**	NaH, Et_2O, 0 °C to r.t	(*S*)-**237F**	63	70
2	(+)-**232**	KH, PhMe/THF, 0 °C to r.t	(*S*)-**237F**	<5	<10
3	(-)-**231**	LiH, Et_2O, r.t	(*S*)-**238F**	31	<10
4	(-)-**231**	LDA, THF, -78 °C to r.t	(*S*)-**239F**	27	35
5	(+)-**232**	LDA, THF, -78 °C to r.t	(*S*)-**239F**	34	<10
6	(-)-**231**	LDA, THF, -78 °C to r.t	(*S*)-**240F**	<5	35

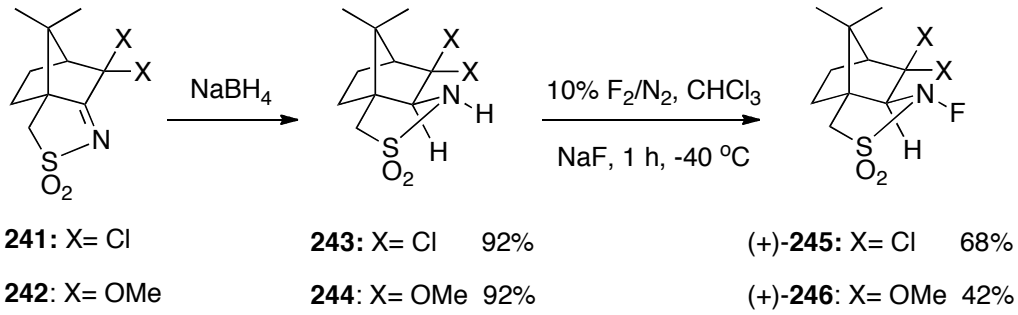
Table 4.1 Enantioselective fluorination of carbonylcompounds with *N*-fluorocamphorsultams (-)-**231** and (+)-**232**

4.2.2 Davis' Reagents

Davis *et al*. carried out further modifications on *N*-fluorocamphorsultam reagents with the introduction of gem-dichloro substitution or methoxy groups with the aim to generate more electrophilic fluorinating reagents and subsequently investigate the fluorination of various enolate derivatives.[148]

4.2.2.1 Synthesis

Reduction of compounds **241** and **242** with $NaBH_4$ yielded dichlorocamphorsultams **243** and **244**. These compounds were subjected to direct fluorination with 10% F_2/N_2 in $CHCl_3$ for 1 hour at -40 °C in the presence of powdered NaF to furnish (+)-*N*-fluoro-camphorsultams **245** and **246** in 68% and 42% yield respectively (Scheme 4.2).[151, 152]



241: X= Cl

242: X= OMe

243: X= Cl 92%

244: X= OMe 92%

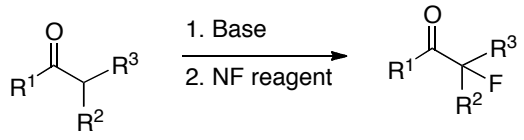
(+)-**245:** X= Cl 68%

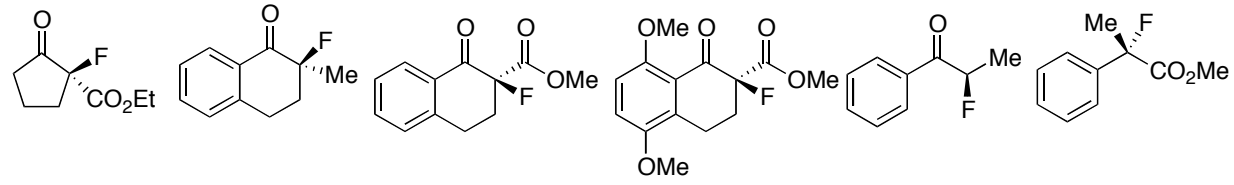
(+)-**246**: X= OMe 42%

Scheme 4.2 Davis' reagents

4.2.2.2 Applications

These modified reagents were more electrophilic than the parent sultams, which meant lower temperatures could be used for the fluorination. In general the fluorination of tertiary enolates afforded quaternary α-fluoro carbonyl compounds in modest yields and enantiomeric excesses (Table 4.2).[153, 154] Propiophenone **249** gave racemic **249F** presumably due to facile base-catalyzed racemisation post-fluorination. The enantioinduction for enolate fluorinations by reagents (+)-**245** and (+)-**246** was found to be substrate dependent as observed with Differding's reagents with (+)-**245** giving higher levels of asymmetric induction. Unfortunately, structural modifications of these sultams to produce more efficient reagents with respect to chemical and optical yields are difficult to accomplish since they originate from natural products.[151]





(*S*)-**237F** (*S*)-**240F** (*S*)-**247F** (*S*)-**248F** (*R*)-**249F** (*S*)-**250F**

Entry	N-F Reagents	Conditions	Products	Yield (%)	ee (%)
1	(+)-**245**	NaH, Et_2O, -78 °C to r.t	(*S*)-**237F**	59	34
2	(+)-**246**	NaH, Et_2O, -78 °C	(*S*)-**237F**	57	<5
3	(+)-**245**	NaHMDS, -78 °C	(*S*)-**240F**	53	76
4	(+)-**246**	NaHMDS, -78 °C to r.t	(*S*)-**240F**	61	<5
5	(+)-**245**	KHMDS, THF, -78 °C	(*S*)-**247F**	90	41
6	(+)-**245**	NaH, Et_2O, 0 °C to -78 °C	(*S*)-**248F**	95	46
7	(+)-**246**	NaHMDS, -78 °C	(*S*)-**248F**	53	14
8	(+)-**245**	NaHMDS, -78 °C to rt	(*R*)-**249F**	61	0
9	(+)-**245**	NaHMDS, -78 °C	(*S*)-**250F**	54	33

Table 4.2 Enantioselective fluorination of enolates with *N*-fluorocamphorsultams (+)-**245** and (+)-**246**

Davis proposed that the enolate attacked the N-F bond of the fluorinating reagent in an S_N2 type mechanism (Figure 4.2). In this regard, **TS-1** and **TS-2** are favoured because (+)-**245** gave (*S*)-**240F** with good enantioselectivity. Furthermore, in **TS-2** there is the possibility of a stabilizing metal enolate chelation with the sulfonyl oxygens. This model is similar to that proposed for enolate hydroxylation with (camphorylsulfonyl)oxaziridine.[148, 155]

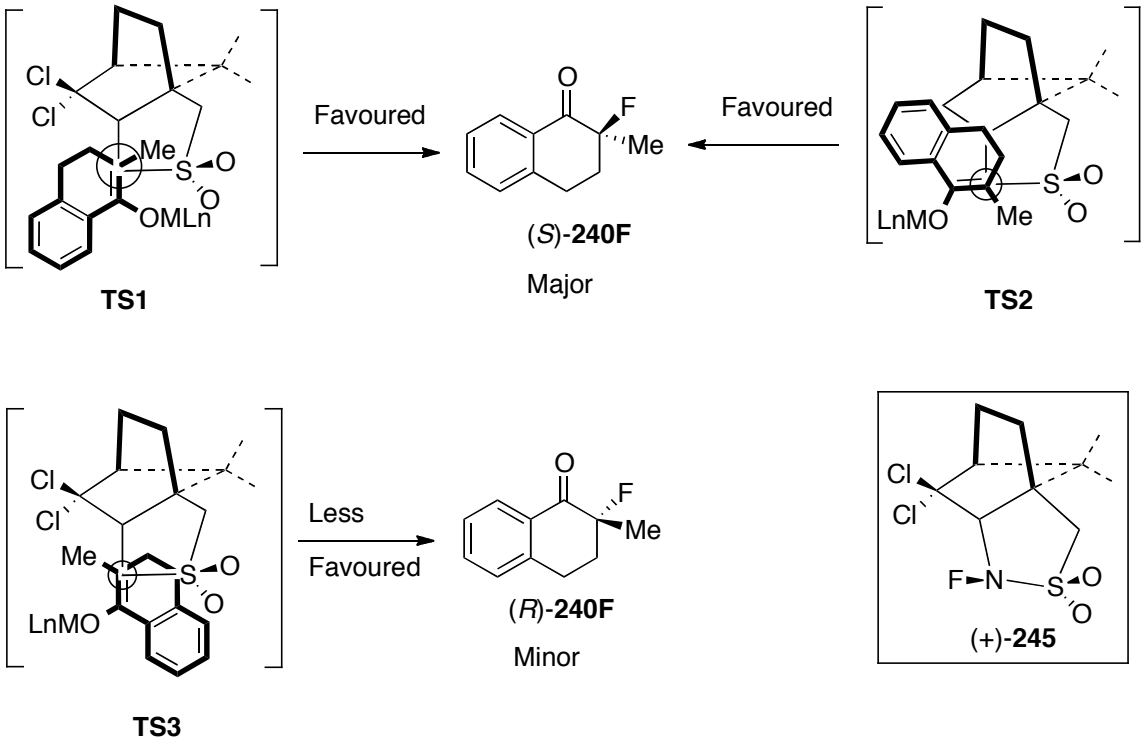
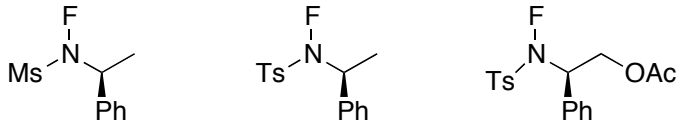


Figure 4.2 Possible transition state leading to (*S*)-**240F**

4.2.3 Takeuchi's Reagents: Synthesis and Applications

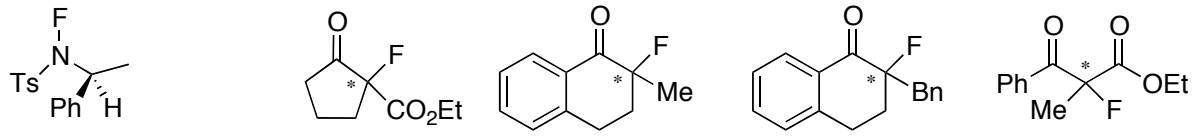
A limitation to the camphor-derived sultams is the difficulty associated with structural modifications to produce more reactive and selective reagents. To develop novel chiral electrophilic fluorinating reagents, Takeuchi and co-workers exploited phenylglycine and α-phenethylamine as chiral starting materials, which would be amenable to structural modifications. These reagents were fluorinated with either perchloryl fluoride ($FClO_3$) or diluted F_2 to produce reagents (*S*)-**251,** (*S*)-**252** and (*R*)-**253** (Figure 4.3).[156]



(*S*)-**251** (*S*)-**252** (*R*)-**253**

Figure 4.3 Takeuchi's reagents

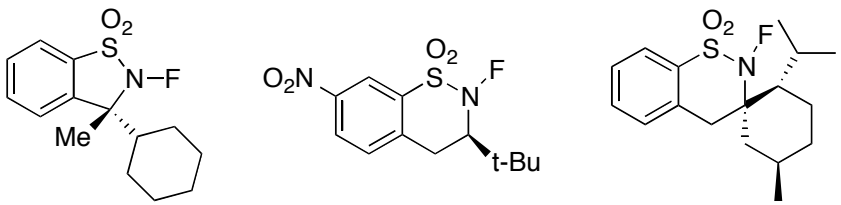
Four model substrates were fluorinated *via in situ* generation of metal enolates. For all substrates, the best results were obtained using reagent (*S*)-**252** (Figure 4.4).[15,16] The absolute configuration of the products was not determined. The low chemical yields in the fluorinations presumably reflected the lower reactivity profile of these *N*-fluoro reagents in comparison to the rigid sultam systems discussed previously.



	(*S*)-**252**	**237F**	**240F**	**254F**	**255F**
Yield (%)		26	46	48	18
ee (%)		54	46	53	21

Figure 4.4 Model substrates fluorinated.

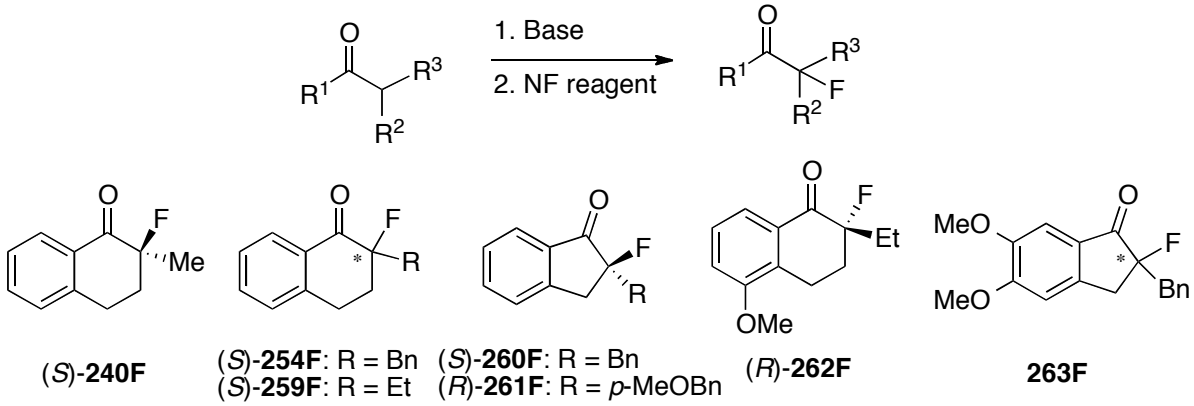
Takeuchi subsequently designed the three new conformationally-locked chiral N-F sulfonamides (*R*)-**256**, (*R*)-**257**, and (*S*)-**258 (**Figure 4.5).[157, 158]



(*R*)-**256** (*R*)-**257** (*S*)-**258**

Figure 4.5 Chiral *N*-F sulfonamides.

These reagents were generally more efficient than the structurally related acyclic derivatives (*S*)-**251,** (*S*)-**252** and (*R*)-**253**. The fluorination of tertiary enolates afforded quaternary α-fluoro carbonyl compounds in good yields and ee, particularly when using reagent (*R*)-**256**. This represents a significant advance in reagent-controlled asymmetric fluorination (Table 4.3).[159]



Entry	N-F Reagents	Conditions	Products	Yield (%)	ee (%)
1	(*R*)-**256**	LDA, THF, -50 °C	**240F**	67	74
2	(*R*)-**256**	LDA, THF, -50 °C	**254F**	79	88
3	(*R*)-**256**	LDA, THF, -50 °C	**259F**	70	72
4	(*R*)-**257**	LiHMDS, THF, -40 °C	**260F**	59	54
5	(*S*)-**258**	LiHMDS, THF, -50 °C	**261F**	70	69
6	(*S*)-**258**	LiHMDS, THF, -50 °C	**262F**	59	60
7	(*S*)-**258**	LiHMDS, THF, -50 °C	**263F**	56	60

Table 4.3 Enantioselective fluorination with reagents (*R*)-**256**, (*R*)-**257** and (*S*)-**258**

Takeuchi and co-workers proposed a model to account for the (*S*)-selectivity observed upon fluorination of **240** with (*R*)-**256** (Figure 4.6).

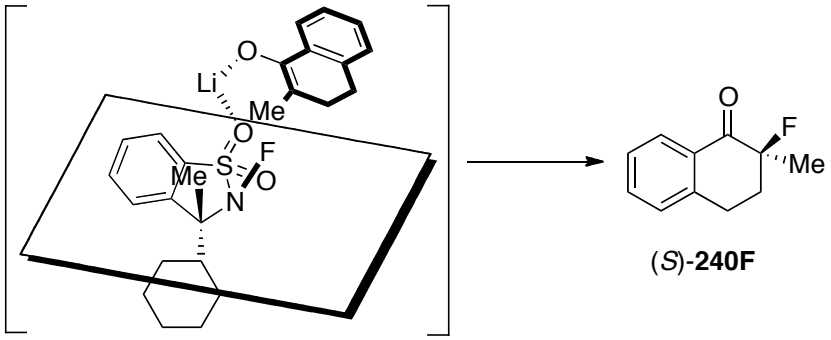


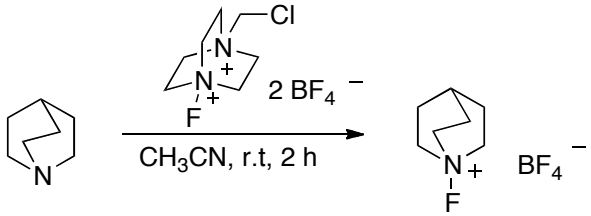
Figure 4.6 Transition-state model for the fluorination of the lithium enolate of **240** with (*R*)-**256**

In summary, the development of the chiral sulfonamide type fluorinating reagents demonstrated the possibility of reagent-controlled asymmetric fluorination. However, the low chemical yield and optical purity of the fluorinated products are the major limitations of these reagents.

Furthermore, the reagents are not commercially available and their preparation requires tedious and multistep procedures.

4.3 Second-Generation Chiral Fluorinating Reagents: Charged N-F Reagents

Rapid advances in electrophilic enantioselective fluorinations led to significant improvements over the past few years.[3] A variety of chiral nonracemic N–F fluorinating reagents, in particular the $[N–F]^+$ reagents, derived from naturally occurring cinchona alkaloids where the fluorine is bound to the quinuclidine nitrogen. These fluorinating agents were developed simultaneously and independently in 2000 by Cahard *et al.*[160] and Shibata *et al.*[137] as a new generation of reagents for direct enantioselective fluorination of C–H acidic substrates. The major breakthrough of N-F cinchona alkaloids is that these reagents do not require the use of F_2. Banks and co-workers first demonstrated transfer fluorination of quinuclidine using Selectfluor.[161] Its fluorination proceeded smoothly and efficiently in acetonitrile at room temperature (Scheme 4.3).



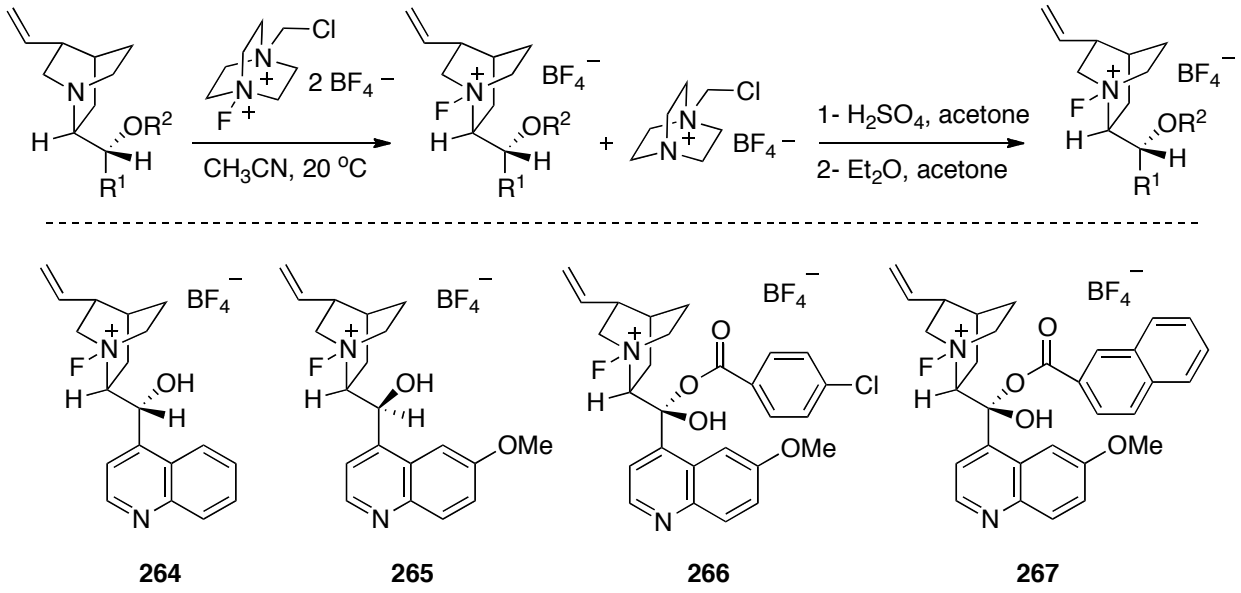
Scheme 4.3 Fluorine transfer from Selectfluor to quinuclidine.

Both Cahard and Shibata employed this methodology for the fluorination of cinchona alkaloids to obtain a large collection of chiral *N*-fluoroammonium salts.

4.3.1 Cahard's Reagents: Synthesis and Applications

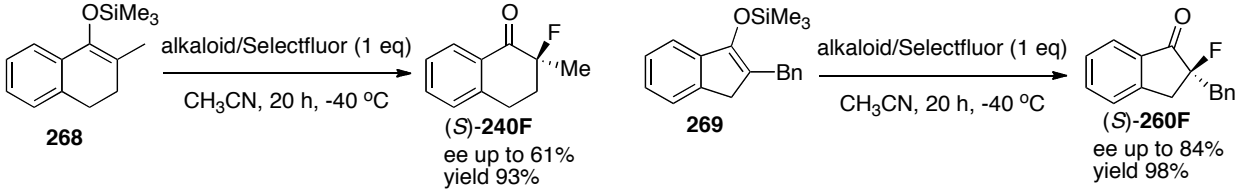
Cahard *et al.* synthesised and isolated the fluorinated alkaloids as pure products using an equimolar mixture of alkaloids and Selectfluor in acetonitrile. A double precipitation procedure yielded N-F alkaloid salts: addition of a solution of H_2SO_4 in acetone caused the formation of 1-chloromethyl-4-hydro-1,4-diazoniabicyclo[2.2.2]octane hydrogen sulfate tetrafluoroborate that

is recovered by filtration; followed by addition of diethyl ether to the filtrate caused the precipitation of the *N*-fluoro cinchonidinium salts (Scheme 4.4).[162, 163, 164]



Scheme 4.4 Cahard's $[NF]^+$ enantiopure reagents

Fluorination of enolates, silyl enol ethers of various ketones and α-fluoro-α-phenylglycine demonstrated the ability of these reagents to promote enantioselective fluorination. Good to excellent enantioselectivities were observed, particularly on trimethylsilyl enol ethers (Scheme 4.5).[165, 166]



Scheme 4.5 Fluorination of trimethylsilyl enol ether derivatives

4.3.2 Shibata's Method: Applications

Rather than isolating the fluorinated alkaloids, Shibata *et al.* generated the reagent *in situ* from a combination of alkaloid and Selectfluor. Once fluorine transfer is completed typically within an hour, the substrate is added to the mixture. Some of the alkaloids used in enantioselective fluorination reactions are shown in Figure 4.7.[167, 168]

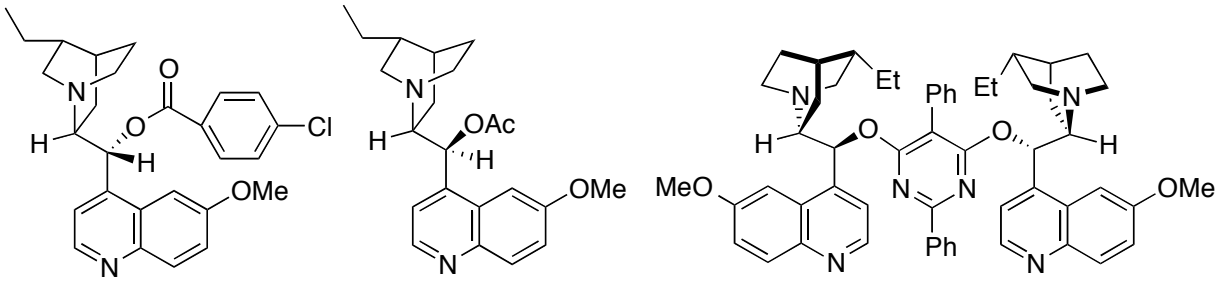
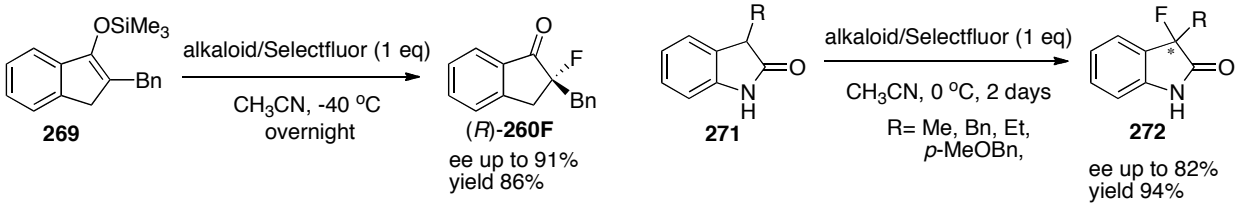


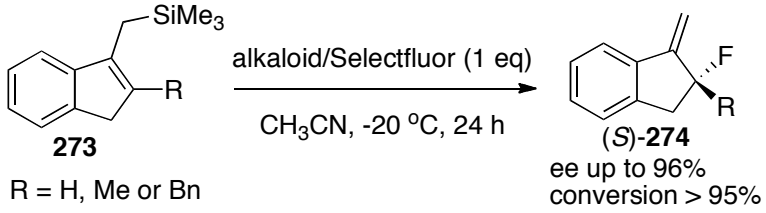
Figure 4.7 Selected alkaloids used by Shibata

Shibata examined the fluorination of silyl enol ethers, β-keto esters and β-cyano esters as well as oxindoles. Results showed that the asymmetric-induction was influenced by the nature of the substrates and reaction conditions. Enantioselectivities up to 91% were observed (Scheme 4.6).[169]



Scheme 4.6 Fluorination of selected substrates.

Gouverneur *et al.* developed a regio- and enantioselective synthesis of allylic fluorides by electrophilic fluorodesilylation of prochiral allylsilanes.[170] The *in situ* generation of the fluorinated cinchona alkaloids was preferred in this reaction, leading to allylic fluorides with excellent enantioselectivities and high conversions (Scheme 4.7).[171]



Scheme 4.7 Gouverneur's enantioselective fluorodesilylation reaction

In 2008, Shibata *et al.* validated a catalytic version of this enantioselective fluorodesilylation reaction.[172]

In summary, the second generation of chiral fluorinating reagents (Selectfluor/cinchona alkaloid combinations) was a breakthrough development in enantioselective fluorination. However, this chemistry remains limited in scope as it is applicable only to highly activated substrates and the reactions are more often requiring several days to reach completion.

The development of a third generation of chiral fluorinating reagents (chiral analogues of Selectfluor) was envisaged as a solution to the pending problem of reactivity encountered with the methodologies known to date for asymmetric electrophilic fluorination. This solution might allow for a much wider diversity of substrates to be fluorinated with the aim of attaining the enantiomeric excesses observed with the alkaloids, with an easier to handle and potential commercial reagent.

4.4 Aims

The aim of this part of the project is to investigate how chiral Selectfluor analogues compare to cinchona alkaloids in terms of reactivity and asymmetric induction. The reactivity of the chiral Selectfluor analogues will be challenged with both activated and unactivated substrates. We anticipated that these chiral N-F DABCOs would match the reactivity observed with Selectfluor, although the insertion of substitutents on the DABCO cores may result in these chiral N-F reagents being less reactive than Selectfluor.

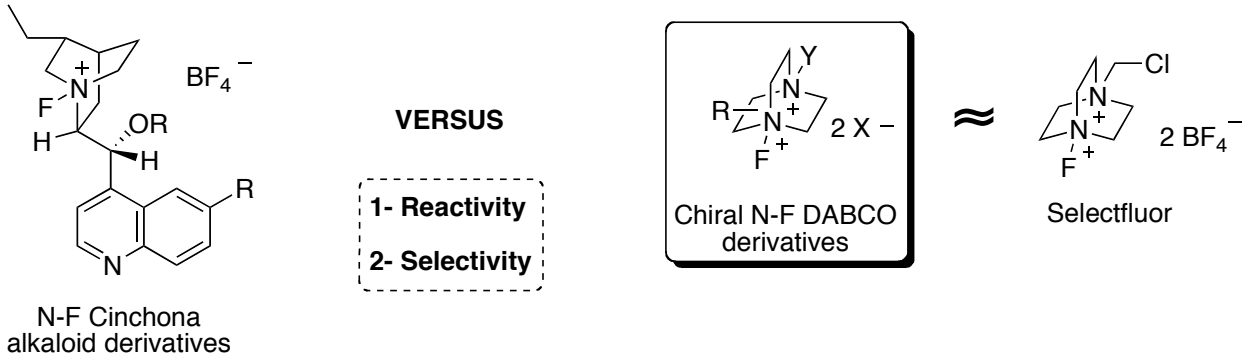


Figure 4.8 Schematic comparison

To calibrate the reactivity and enantioselectivity of the chiral N-F DABCO, a representation of nucleophilic substrates were chosen from the more reactive enolates to the less reactive indenes (Figure 4.9).

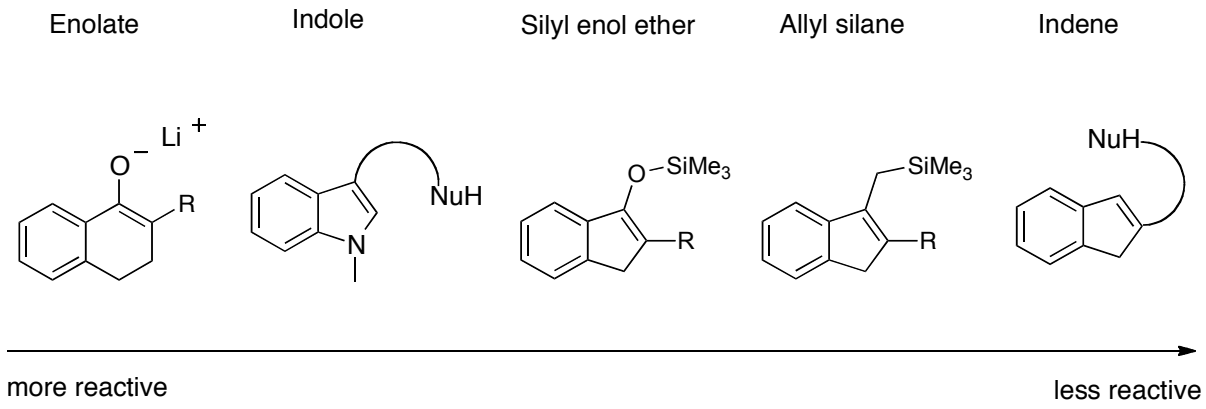


Figure 4.9 Decreasing reactivity of various substrates.

For this study, we selected (2*R*,3*R*)-1-fluoro-4-methyl-2,3-diphenyl-1,4-diazoniabicyclo[2.2.2] octane ditriflate **212** as this novel chiral N-F reagent was accessible in much larger quantities compared to other chiral Selectfluor analogues.

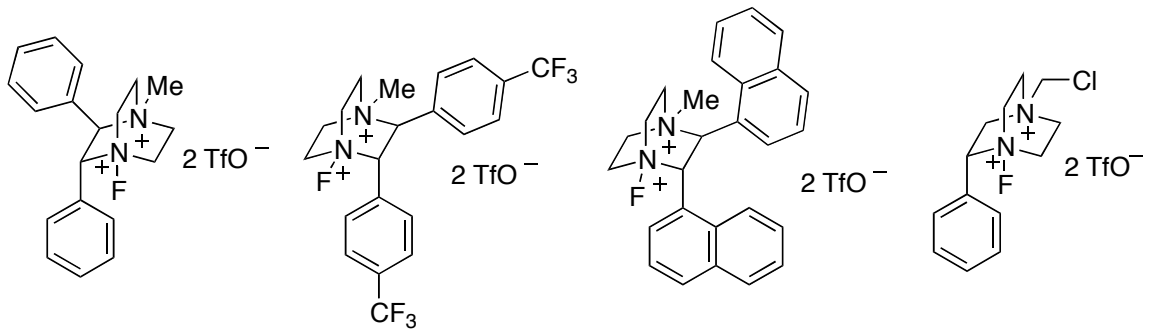


Figure 4.10 Chiral non racemic Selectfluor.

4.5 Asymmetric Electrophilic Fluorination

4.5.1 Choice of Substrates

Three model carbonyl substrates were selected for this preliminary work (Figure 4.11). The methyl-substituted tetralone **240** was initially chosen due to the fact that it is commercially available and all previously reported reagents for enantioselective fluorination have been tested on the enolate of 2-methyl-1-tetralone **240** as model substrate. Our preliminary study was expanded to include another substituted tetralone based substrate **254** and a substituted indanone **275**.

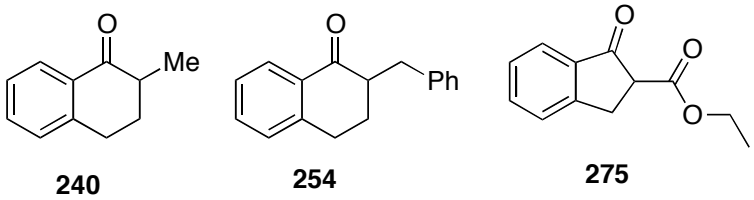
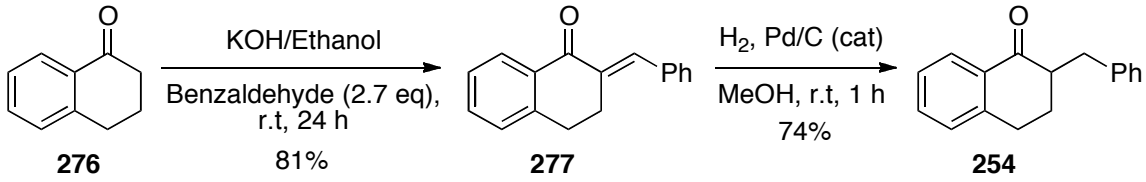


Figure 4.11 First generation model substrates selected for fluorination.

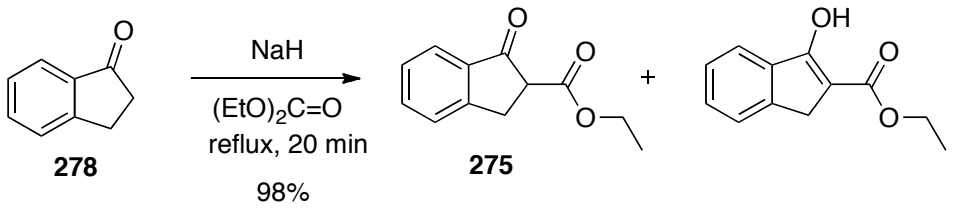
4.5.2 Synthesis of Substrates

2-Methyl-1-tetralone **240** was purchased from a commercial source, while benzyl tetralone **254** was prepared by aldol condensation of tetralone **276** with benzaldehyde followed by catalytic hydrogenation of the α,β-unsaturated ketone **277** (Scheme 4.8).[173]



Scheme 4.8 Preparation of benzyl tetralone **254**

2-Ethoxycarbonyl-1-indanone **275** was obtained in good yield from indanone **278** with diethyl carbonate and sodium hydride (Scheme 4.9).[174, 175] The product observed was predominantly the ketone tautomer according to ^{1}H NMR of crude material in $CDCl_3$ (enol : ketone 1 : 10).



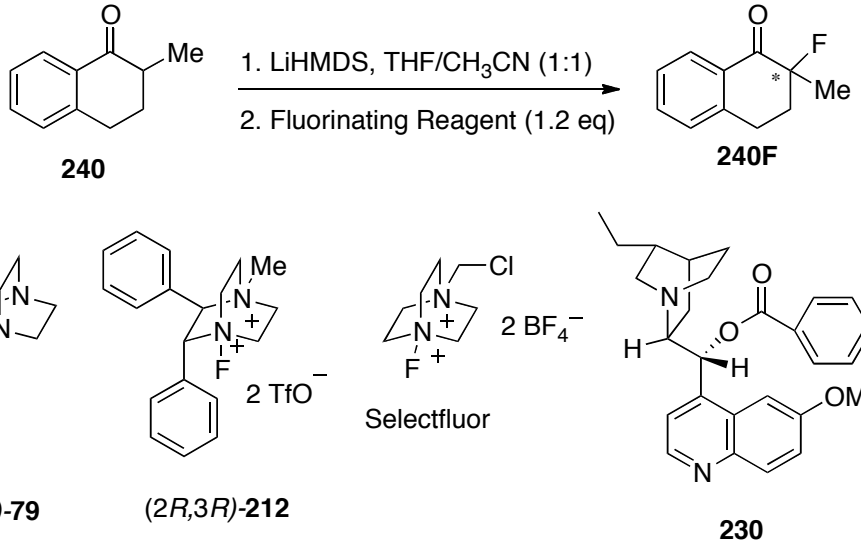
Scheme 4.9 Preparation of indanone **275**

4.5.3 Fluorination of Carbonyl Compounds

Initially we began by fluorinating our model substrates using the fluorinated alkaloids to set a benchmark for comparison. It was decided to probe the asymmetric induction of (2*R*,3*R*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane **79**/Selectfluor combination, the chiral NF DABCO (2*R*,3*R*)-**212** and the alkaloid **230**/Selectfluor combination. Based on the results of the NMR studies at low temperature described in Chapter 3, the fluorinations using a premixed DABCO derivative (2*R*,3*R*)-**79** and Selectfluor were carried out at temperatures below -50 °C to prevent the decomposition of the fluorinating reagent.

We initiated our studies with the fluorination of 2-methyl tetralone **240** under the conditions used by Takeuchi/Shibata.[159] The fluorination of **240** was first carried out with 1.2 equivalents of Selectfluor in a mixture of THF/CH_3CN (1:1) at -60 °C. After stirring the reaction mixture for 2 hours, fluorination occurred to give the desired α-fluoro ketone **240F** in 89% yield, after silica

gel column chromatography purification (Table 4.4, entry 1). This provided a racemic reference sample of ketone **240F** to aid chiral HPLC analysis of enantioenriched samples. In the first instance, the asymmetric fluorination of **240** was investigated using the cinchona alkaloid **230**/Selectfluor combination in THF/CH_3CN at -60 °C. It was found that under these conditions, the fluorination of **240** did proceed after 12 hours to give fluoro ketone **240F** in 46% yield and 13% ee (Table 4.4, entry 2). Lowering the temperature further to -80 °C did not give any improvement in enantioselectivity, however at -70 °C a yield of 70% and 16% ee was obtained (Table 4.4, entry 8). Having established the reactivity and selectivity of alkaloid **230**, we examined the reaction of **240** with the novel chiral fluorinated DABCOs. When tetralone **240** was subjected to fluorination at -60 °C using the isolated chiral N-F DABCO (2*R*,3*R*)-**212**, the α-fluoro ketone **240F** was obtained in 4 hours in excellent conversion of 99% but with a low enantiomeric excess of 8% (Table 4.4, entry 3). Lowering the temperature to -65 °C delivered the desired product in 11% ee (Table 4.4, entry 6). Although the selectivities obtained with (2*R*,3*R*)-**212** were comparable to **230**, chiral N-F DABCO (2*R*,3*R*)-**212** demonstrated superior reactivity. Next, we studied the fluorination using chiral DABCO (2*R*,3*R*)-**79**/Selectfluor combination at various temperatures. To our delight, enantioselectivities of up to 56% ee were obtained when reacting the *in situ* prepared fluorinating reagent with the corresponding enolates of the substrate **240** at a temperature of -70 °C (Table 4.4, entry 7). The low enantiomeric excesses observed with N-F chiral DABCO (2*R*,3*R*)-**212** compared to the *in situ* strategy using (2*R*,3*R*)-**79**/Selectfluor combination is likely due to the higher reactivity of the bis-cationic species.

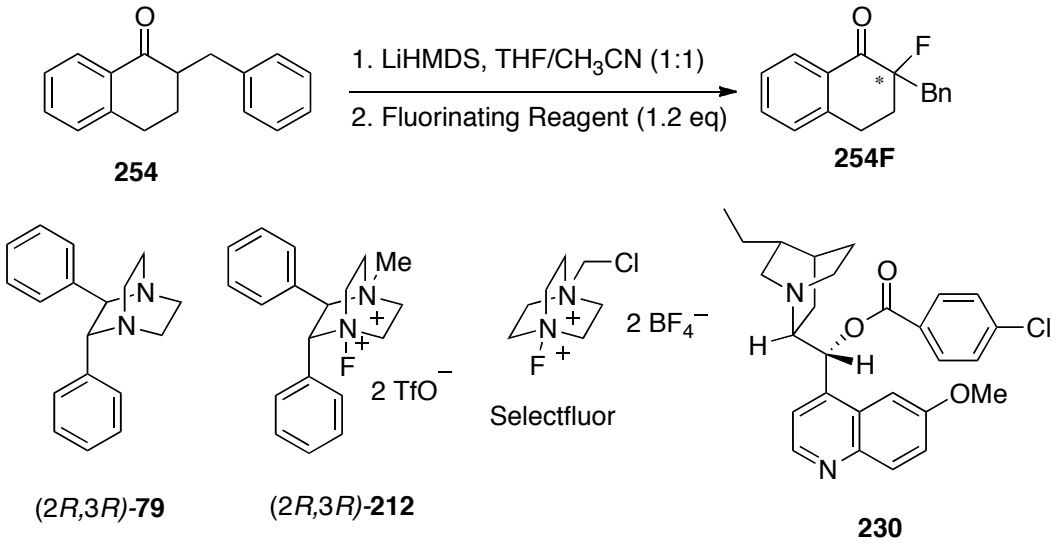


Entry	Fluorinating Reagent	Conditions	Yield [%]	ee [%][b]	Major enantiomer [c]
1	Selectfluor	-60 °C, 2 h	89	-	-
2	**230**/Selectfluor	-60 °C, 12 h	46	13	*S*
3	(2*R*,3*R*)-**212**	-60 °C, 4 h	99[a]	8	*R*
4	(2*R*,3*R*)-**79**/Selectfluor	-65 °C, 12 h	99[a]	54	*R*
5	**230**/Selectfluor	-65 °C, 12 h	60	0	-
6	(2*R*,3*R*)-**212**	-65 °C, 6 h	99[a]	11	*R*
7	(2*R*,3*R*)-**79**/Selectfluor	-70 °C, 13 h	64	56	*R*
8	**230**/Selectfluor	-70 °C, 13 h	70	16	*S*
9	(2*R*,3*R*)-**79**/Selectfluor	-75 °C, 14 h	66	40	*R*
10	**230**/Selectfluor	-75 °C, 14 h	40	0	-
11	(2*R*,3*R*)-**79**/Selectfluor	-80 °C, 14 h	73	14	*R*
12	**230**/Selectfluor	-80 °C, 14 h	63	4	*S*

[a] conversion by ^{1}H NMR, [b] ee value determined by HPLC on a chiral stationary phase, [c] the absolute configuration was assigned on the basis of the HPLC analysis compared with retention times reported in literature.

Table 4.4 Fluorination of methyl tetralone **240**

The fluorination of benzyl tetralone **254** was also performed with the selected NF reagents. The fluorination using Selectfluor proceeded smoothly in a mixture of THF/CH_3CN (1:1) at -60 °C (Table 4.5, entry1). The asymmetric fluorination of **254** using **230**/Selectfluor combination showed similar selectivities to those obtained with methyl tetralone **240** (Table 4.4, entries 2 and 5). We obtained 22% ee using chiral N-F DABCO (2*R*,3*R*)-**212** indicating that the benzyl group has an effect on the enantioselectivity. The fluorination of **254** using chiral DABCO (2*R*,3*R*)-**79**/ Selectfluor combination delivered similar selectivity to **240** (Table 4.5, entry 3).

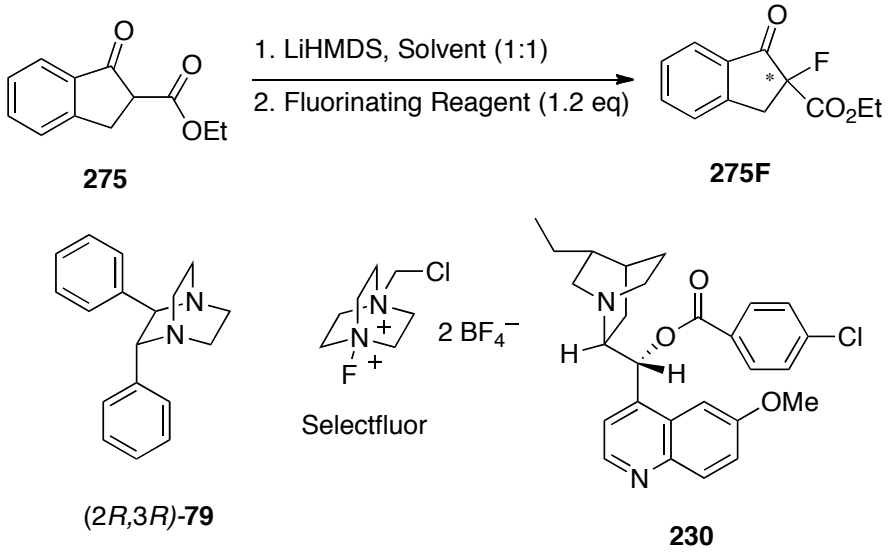


Entry	Fluorinating Reagent	Conditions	Yield [%]	ee [%][b]
1	Selectfluor	-60 °C, 3 h	93[a]	-
2	**230**/Selectfluor	-60 °C, 12 h	42	10
3	(2*R*,3*R*)-**79**/Selectfluor	-60 °C, 12 h	99[a]	50
4	(2*R*,3*R*)-**212**	-60 °C, 5 h	50	22
5	**230**/Selectfluor	-70 °C, 12 h	47	10

[a] conversion by ^{1}H NMR, [b] ee value determined by HPLC on a chiral stationary phase

Table 4.5 Fluorination of benzyl tetralone **254**

On the other hand, fluorination of 2-ethoxy-1-indanone **275** with **230**/Selectfluor generated the fluorinated α-fluoroketo ester **275F** in CH_2Cl_2/CH_3CN at -60°C with 99% conversion and 53% ee (Table 4.6, entry 2). When the chiral DABCO (2*R*,3*R*)-**79**/Selectfluor combination fluorinating reagent was employed in CH_2Cl_2/CH_3CN, the target compound was not formed. On changing the solvent to THF/CH_3CN the fluorinated keto ester **275F** was generated in excellent conversion and low selectivity (Table 4.6, entry 5).



Entry	Fluorinating Reagent	Solvent	Conditions	Conversion [%]	ee [%][b]
1	Selectfluor	CH_2Cl_2/CH_3CN	-60 °C, 3 h	>95	-
2	**230**/Selectfluor	CH_2Cl_2/CH_3CN	-60 °C, 12 h	>95	53
3	(2*R*,3*R*)-**79**/Selectfluor	CH_2Cl_2/CH_3CN	-60 °C, 12 h	-[a]	-
4	(2*R*,3*R*)-**79**/Selectfluor	THF/CH_3CN	-60 °C, 12 h	>95	6
5	(2*R*,3*R*)-**79**/Selectfluor	THF/CH_3CN	-78 °C, 12 h	>95	20

[a] no product observed, [b] ee value determined by HPLC on a chiral stationary phase

Table 4.6 Fluorination of indanone **275**

4.6. Asymmetric Electrophilic Fluorodesilylation

4.6.1 Choice of Substrates

Research within the Gouverneur group reported on the fluorodesilylation of various allyl silanes.[171] In order to explore the potential of the (2*R*,3*R*)-1-fluoro-4-methyl-2,3-diphenyl-DABCO triflate salt **212**, two model substrates were selected: ((2-benzyl-1*H*-inden-3-yl)methyl)trimethylsilane **279** and ((2-benzyl-1*H*-inden-3-yl)oxy)trimethyl- silane **269**.

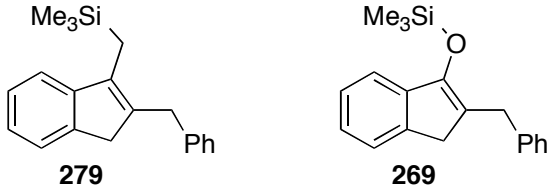
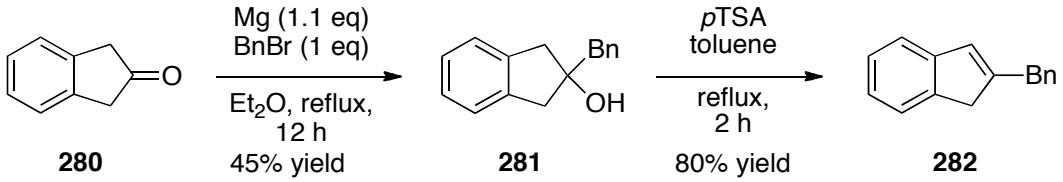


Figure 4.12 Silane substrates.

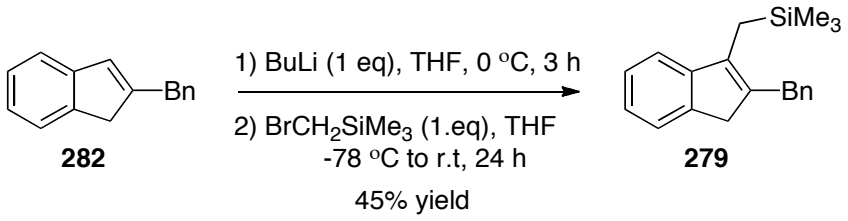
4.6.2 Synthesis of Substrates

Allylsilane **279** was synthesized from 2-indanone **280** according to literature procedures.[171] Treatment of indanone **280** with 1 equivalent of benzyl magnesium bromide in ether, at reflux, generated alcohol **281** in 45% yield, after purification by silica gel column chromatography. Subsequent elimination of water under acidic conditions led to the formation of 2-benzyl-1*H*-indene **282** in 80% yield.



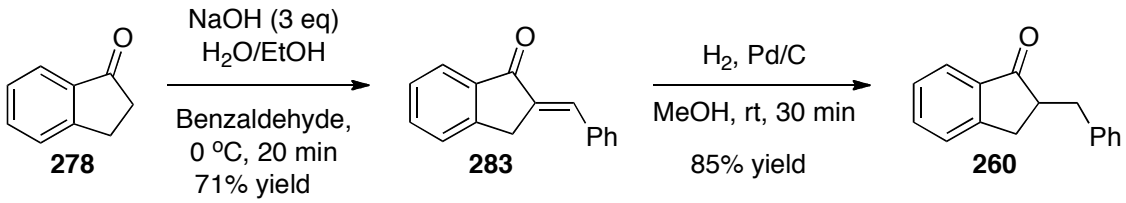
Scheme 4.10 Formation of 2-benzyl-1*H*-indene **282**.

The allylsilane functionality was introduced by deprotonation of 2-benzyl-1*H*-indene **282** using *n*-BuLi in THF at 0 °C for 3 hours followed by addition of bromomethyl trimethylsilane in THF, the reaction was then left at room temperature for 24 hours. Purification by silica gel column chromatography gave the desired silane in 45% yield (Scheme 4.11).



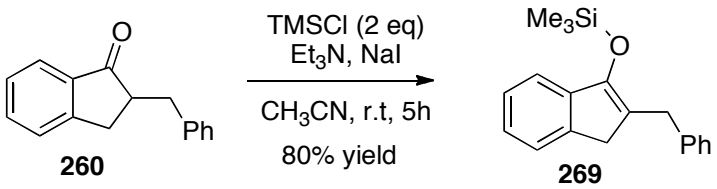
Scheme 4.11 Synthesis of allylsilane **279**

Silyl enol ether **269** was also prepared following a literature procedure. Aldol condensation of 1-indanone **278** and benzaldehyde employing an ethanolic solution of NaOH at 0 °C for 20 minutes, gave the resulting α,β-unsaturated ketone **283**. Reduction by catalytic hydrogenation over palladium on carbon, in methanol at room temperature, gave benzyl indanone **260** in 85% yield after purification by silica gel column chromatography (Scheme 4.12).



Scheme 4.12 Synthesis of 2-benzyl-2,3-dihydro-1*H*-inden-1-one **260**

The silyl enol ether **269** was prepared in 80% yield by reaction of ketone **260** with chlorotrimethylsilane in acetonitrile in the presence of triethylamine and sodium iodide at room temperature for 5 hours.

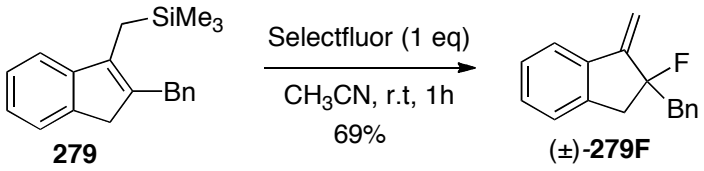


Scheme 4.13 Synthesis of silyl enol **269**

4.6.3 Fluorodesilylation of Allylsilane 279 and Silyl Enol Ether 269

Research within the Gouverneur group has shown that fluorodesilylation of allysilane **279** using *N*-fluorocinchona alkaloids gave the best results in acetonitrile at -20 °C.[171] We therefore explored the efficiency of our isolated (2*R*,3*R*)-1-fluoro-4-methyl-2,3-diphenyl-DABCO triflate salt **212** under the same conditions. Initially, we carried out a preliminary fluorodesilylation reaction with the model allyl silane **279** using Selectfluor in order to access the allylic fluoride **279F** for a racemic reference compound for HPLC analysis of enantioenriched samples. Thus, the fluorodesilylation of **279** with 1 equivalent of Selectfluor proceeded smoothly in acetonitrile at room temperature. The reaction was monitored by TLC, and after 1 hour, analysis showed consumption of the starting material and formation of the product. Purification by silica gel column chromatography delivered racemic allylic fluoride **279F** in 69% yield (Scheme 4.14).

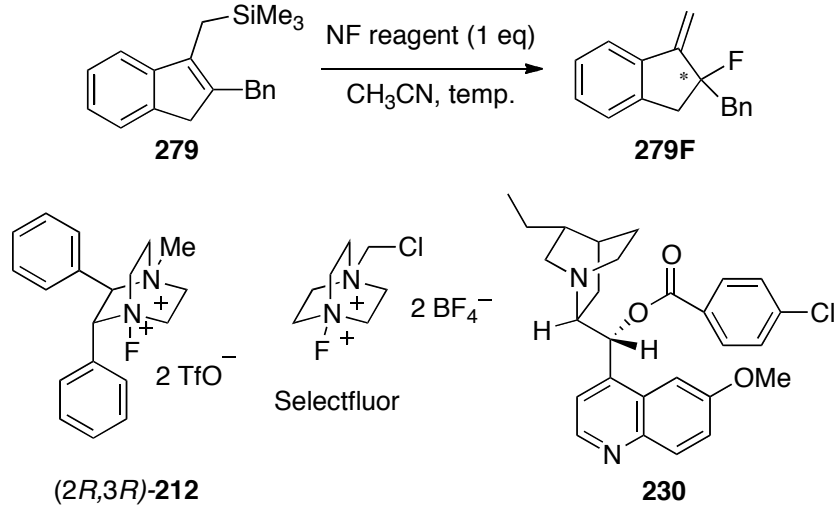
The structure of **279F** was confirmed by ^{19}F NMR spectroscopy with the appearance of a signal at -137.9 ppm (corresponding to CF peak) and the disappearance of the trimethylsilyl group around 0.13 ppm in the ^{1}H NMR spectrum.



Scheme 4.14 Fluorodesilylation of **279** using Selectfluor

In the first instance, the asymmetric fluorodesilylation of **279** was investigated using the mono-cinchona alkaloid **230** prepared using the *in situ* methodology of Shibata.[137] The fluorination of allyl silane **279** using **230**/Selectfluor combination was therefore carried out in acetonitrile at -20 °C by dropwise addition of a solution of **279** in CH_3CN at -20 °C to the **230**/Selectfluor combination. The reaction was monitored by TLC, and the consumption of starting material was observed after 24 hours. The product was obtained in moderate yield after purification by silica gel column chromatography. The enantiomeric excess of 60% was determined by stationary phase HPLC analysis of purified **279F** using a chiral OJ-H column, eluting with hexane/^{i}PrOH=99/1 at a flow rate of 0.5 ml/min. The retention time was shown to be consistent with the racemic reference and the configuration of **279F** was determined to be *R* by comparing the optical rotation and HPLC data with the literature values. Applying the conditions above, the fluorodesilylation of **279** using chiral NF DABCO (2*R*,3*R*)-**212** gave the allylic fluoride **279F** in 67% yield and 24% ee (Table 4.7, entry 2). Chiral NF DABCO (2*R*,3*R*)-**212** showed greater reactivity than the **230**/ Selectfluor combination as the reaction occurred only after 3 hours. However, the high reactivity observed with NF chiral DABCO (2*R*,3*R*)-**212** had a detrimental

effect on enantioselectivity. Lowering the temperature of the reaction to -40 °C did not significantly improve the ee (Table 4.7, entry 3).



Entry	Fluorinating Reagent	Time (h)	Temperature (°C)	Yield (%)	ee [a] (%)	Major enantiomer
1	**230**/Selectfluor	24	-20	48	60	**(+)-279F**
2	(2*R*,3*R*)-**212**	3	-20	67	24	**(-)-279F**
3	(2*R*,3*R*)-**212**	6	-40	65	29	**(-)-279F**

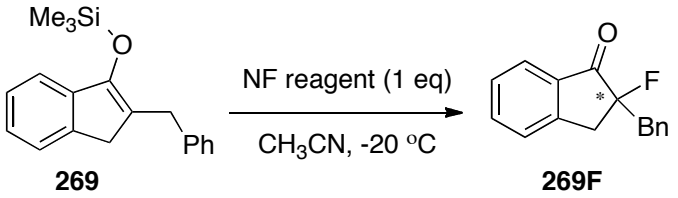
[a] ee value determined by HPLC on a chiral stationary phase

Table 4.7 Asymmetric fluorodesilylation of **279** using **230** and chiral NF (2*R*,3*R*)-**212**

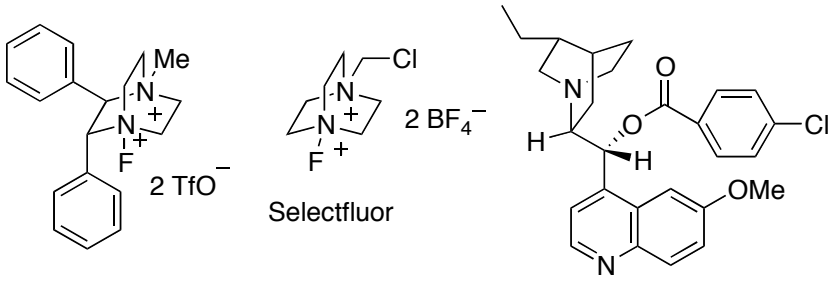
We next investigated the effectiveness of our system for the fluorination of silyl enol ether **269**. It is well known that silyl enol ethers react at a much faster rate than the corresponding allyl silanes.[176] The reaction was first carried out using 1 equivalent of Selectfluor at -20 ^{o}C for 1 hour. The corresponding fluorinated compound with a quaternary carbon-fluorine center was obtained in 95% yield after purification. (Table 4.8, entry 1). The structure of **269F** was determined by NMR analysis as described in the literature.

Silyl enol ether **269** undergoes efficient enantioselective fluorodesilylation with 1 equivalent of **230**/Selectfluor combination. The reaction was completed after 12 hours giving the desired fluoroketone **269F** in 89% yield and 78% ee (Table 4.9, entry 2). The methodology was

effectively extended to chiral DABCO (2*R*,3*R*)-**212** yielding the fluorinated product in 90% yield and 30% ee after only 2 hours reaction.



269 **269F**



(2*R*,3*R*)-**212** **230**

Entry	Fluorinating Reagent	Time (h)	Yield (%)	ee [a] (%)	Major enantiomer
1	Selectfluor	1	95	-	-
2	**230**/Selectfluor	12	89	78	**(-)-269F**
3	(2*R*,3*R*)-**212**	2	90	30	**(-)-269F**

[a] ee value determined by HPLC on a chiral stationary phase.

Table 4.8 Asymmetric fluorodesilylation of **269** using **230** and (2*R*,3*R*)-**212**

4.7 Asymmetric Electrophilic Fluorocyclization

Despite recent advances in asymmetric fluorocyclisation, fundamental key problems of reactivity combined to enantioselectivity need to be addressed.[66] Thus, there is a need to develop a stereocontrolled enantioselective electrophilic fluorocyclisation reaction of alkenes using novel chiral fluorinating reagents.

4.7.1 Choice of Substrates

To probe the feasibility and scope of an asymmetric fluorocyclisation reaction with our chiral non-racemic Selectfluor, we sought to investigate a range of substrates depicted in Figure 4.13. Based on literature precedent, prochiral indole **284** with a pendant heteronucleophile tethered at

C3 was chosen. In addition, the related structure, **285** and **286**, with phenyl groups at position 5 and 4 respectively, were selected to probe the effect of substitution on reactivity and selectivity. Moreover, the less activated cyclic indenes **287**, **288** and **289** were chosen to assess what impact the indole and indene systems would have on reactivity and enantioselectivity.

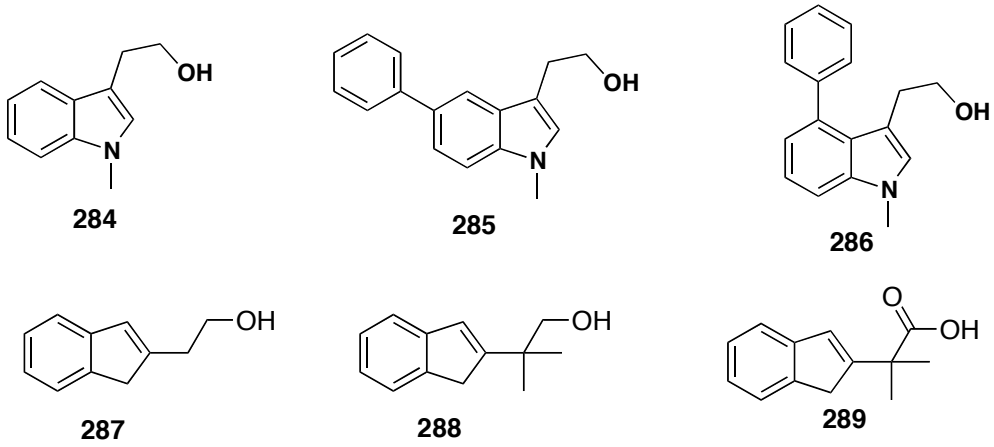
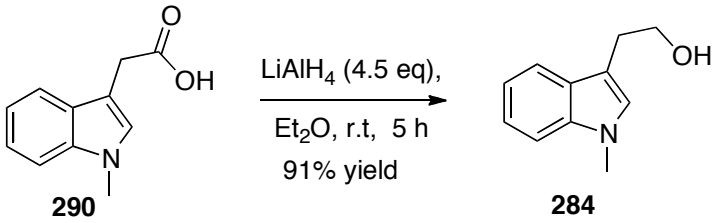


Figure 4.13 Substrates for asymmetric flurocyclisation.

4.7.2 Synthesis of Substrates

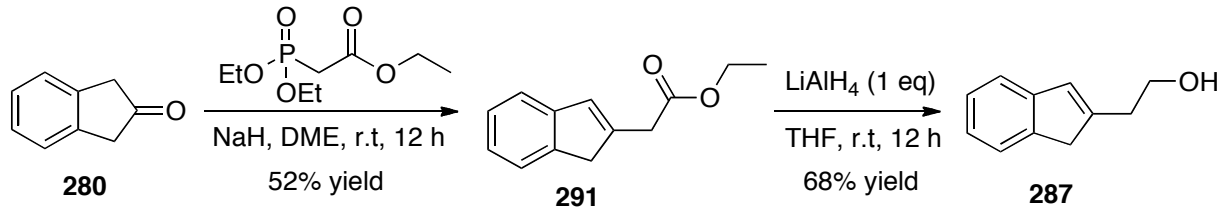
Indoles **285** and **286** were readily available in the group[66] while indole **284** was prepared in 91% yield by the reduction of 2-(1-methyl-1*H*-indol-3-yl)acetic acid **290** with lithium aluminium hydride in diethyl ether at room temperature for 5 hours (Scheme 4.15).[177]



Scheme 4.15 Formation of prochiral indole **284**

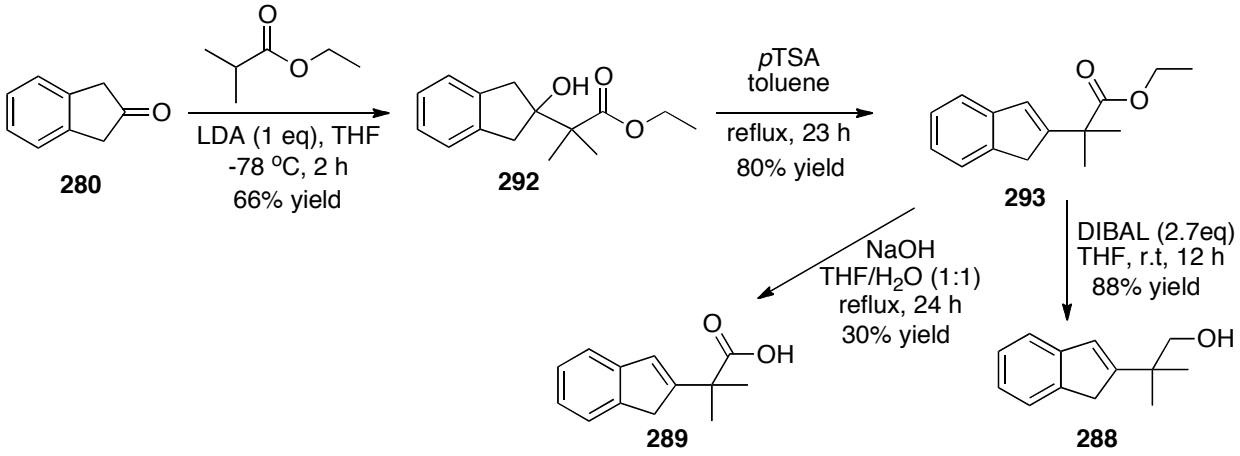
Indene **287** containing a homoallylic alcohol was prepared according to literature procedures.[178, 179] The synthesis of **287** began with a Horner-Wadsworth-Emmons of 2-indanone **280, t**he

reaction proceeded smoothly under mild conditions to give the corresponding indene **291** with the ester functionality in moderate yield of 52%. Subsequent reduction of the ester by treatment with 1 equivalent of lithium aluminium hydride gave the desired alcohol **287** in 68% yield (Scheme 4.16).



Scheme 4.16 Synthesis of homoallylic alcohol **287**

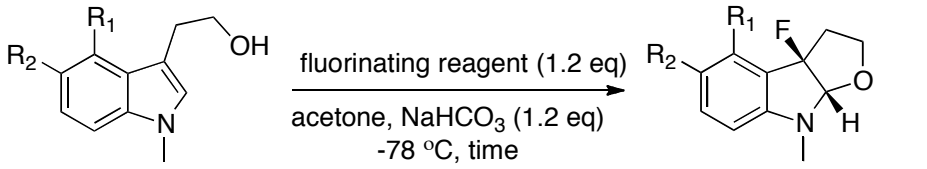
For the synthesis of **288** and **289**, the ester functionality was first introduced by aldol reaction of indanone **280** with isobutyrate. Subsequent elimination of water under acidic conditions led to the formation of ester **293** in 80% yield. The desired alcohol **288** was obtained in 88% yield by reduction of the ester with diisobutylaluminium hydride. Hydrolysis of **293** with NaOH in THF/H_2O (1:1) at reflux gave acid **289** (Scheme 4.17).



Scheme 4.17 Synthesis of homoallylic alcohol **288** and carboxylic acid **289**

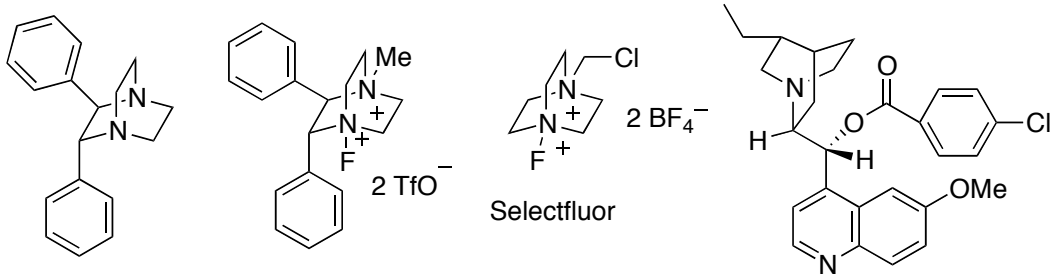
4.7.3 Asymmetric Fluorocyclisation

With the required substrates in hand, the studies commenced with the fluorocyclization of indole **284**. Using the optimised conditions reported by Gouverneur,[66] exposure of indole **284** to 1.2 equivalents of Selectfluor in acetone in the presence of 1.2 equivalent of $NaHCO_3$ at -78 °C gave the fluorocyclised product **284F** as a single *cis* diastereomer (cis:trans, d.r.>20:1) in 65% yield. Premixing cinchona alkaloid **230** with Selectfluor at room temperature followed by the addition of indole **284** at -78 °C led to the formation of **284F** with 30% yield and 30% ee after 14 hours. Both chiral DABCO (2*R*,3*R*)-**79** and (2*R*,3*R*)-**212** induced fluorocyclization at -78 °C to afford the tetrahydrofuroindole **284F** with 20% and 63% yields respectively (Table 9, entries 3 and 4). The products were formed with no enantiomeric excess. The fluorocyclisation process was also investigated on a variety of indoles containing substituents on the aromatic ring. Substitution on the 5-position by a phenyl group (**285F**) gave a moderate yield of 71% with low enantiomeric excess of 5% (Table 4.9, entry 6). However, substitution on the 4-position (**286F**) increased the ee to 27% with an excellent yield of 97% (Table 4.9, entry 8).

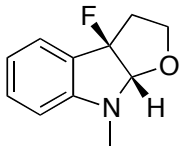
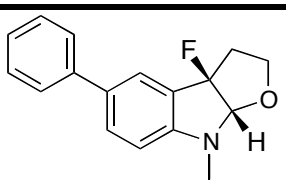
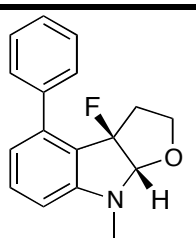


284: $R_1 = R_2 = H$
285: $R_1 = H$, $R_2 = Ph$
286: $R_1 = Ph$, $R_2 = H$

284F: $R_1 = R_2 = H$
285F: $R_1 = H$, $R_2 = Ph$
286F: $R_1 = Ph$, $R_2 = H$



(2*R*,3*R*)-**79** (2*R*,3*R*)-**212** **230**

Entry	N-F reagents	Fluorocyclised product	Time (h)	Yield (%)	ee (%)[c]
1	Selectfluor	 **284F**	2	65	-
2	**230**/Selectfluor		14	30	30
3	(2*R*,3*R*)-**79**/Selectfluor		14	20	0
4	(2*R*,3*R*)-**212**		5	63	0
5	Selectfluor	 **285F**	3	76	-
6	(2*R*,3*R*)-**212**		5	71	5
7	Selectfluor	 **286F**	3	98	-
8	(2*R*,3*R*)-**212**		5	97	27

[a] ee value determined by HPLC on a chiral stationary phase.

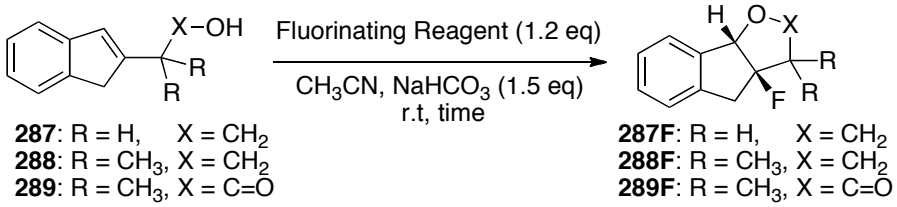
Table 4.9 Asymmetric fluorocyclisation of indole systems.

Investigation into the less reactive substrates started with the fluorocyclisation of the prototypical indene **287**. Initially the reaction was performed at low temperature with Selectfluor. Exposure of the indenyl homoallylic alcohol **287** to 1 equivalent of Selectfluor in the presence of $NaHCO_3$ in acetonitrile at -20 °C did not proceed after 48 hours. As anticipated,

the indene system was less reactive towards selectfluor at low temperature. The reaction was then attempted at room temperature with **287** and **288** to give the fluorocyclised products **287F** in 42% yield **288F** in 60% yield, after 12 and 20 hours respectively. An initial observation was that the reaction times were significantly longer than for the corresponding indole derivatives, which can be attributed to low reactivity of the indene systems. The asymmetric fluorocyclisation was attempted starting with the alkaloid **230**/Selectfluor combination. Thus, indene **287** and **288** were subjected to fluorination using **230**/Selectfluor combination at room temperature and monitored by TLC. After 72 hours starting material was observed by TLC with no product detectable in the crude ^{1}H NMR. Next, we investigated the fluorocyclisation with chiral DABCO (2*R*,3*R*)-**212** using the standard conditions. The fluorocyclised products **287F** and **288F** were obtained after 18 and 24 hours, respectively. Product **287F** was obtained in 4% ee and **288F** in 9% ee (table 4.10, entries 4 and 7).

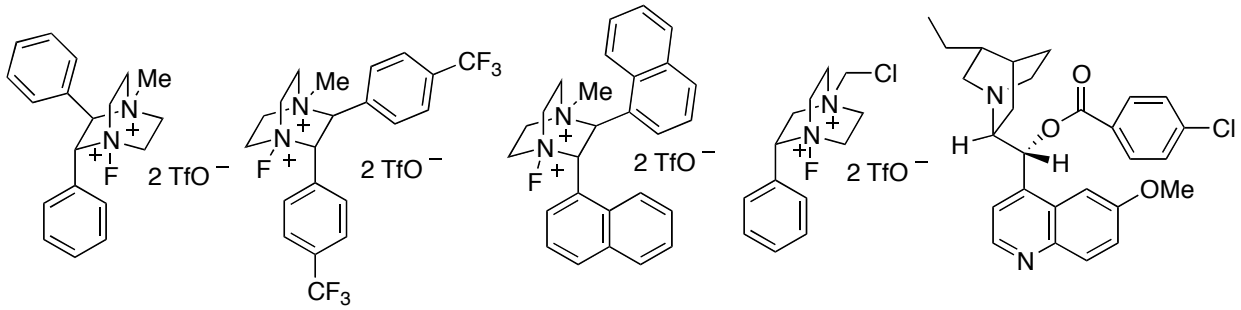
The fluorocyclisation of carboxylic acid **289** showed a similar reactivity pattern to the alcohol derivatives. Reaction with Selectfluor produced the fluorocyclised **289F** in 65% while **230**/Selectfluor combination showed no reactivity after 3 days. The reaction proceeds smoothly with all chiral NF DABCOs investigated ((2*R*,3*R*)-**212**, (2*S*,3*S*)-**213**, (2*S*,3*S*)-**214**, (*R*)-**219** in moderate yields of 60%, 53%, 35% and 52% respectively, and low enantiomeric excesses of 16%, 16%, 17% and 11% respectively (Table 4.10, entry 10-13).

The observations during this investigation suggest that chiral NF DABCO derivatives are more reactive than alkaloids. Whilst the level of enantioselectivity was low, it does provide precedent that chiral Selectfluor analogues mediate fluorocyclisation.

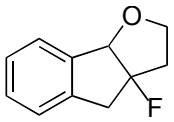
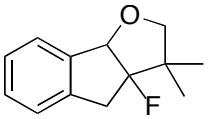
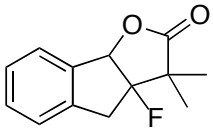


287: R = H, X = CH_2
288: R = CH_3, X = CH_2
289: R = CH_3, X = C=O

287F: R = H, X = CH_2
288F: R = CH_3, X = CH_2
289F: R = CH_3, X = C=O



(2*R*,3*R*)-**212** (2*S*,3*S*)-**213** (2*S*,3*S*)-**214** (*R*)-**219** **230**

Entry	N-F reagents	Fluorocyclised product	Time (h)	Yield (%)	ee (%)[c]
1[a]	Selectfluor	 **287F**	48	-[b]	-
2	Selectfluor		12	42	-
3	**230**/Selectfluor		72	-[b]	-
4	(2*R*,3*R*)-**212**		18	31	4
5	Selectfluor	 **288F**	20	60	-
6	**230**/Selectfluor		72	-[b]	-
7	(2*R*,3*R*)-**212**		24	54	9
8	Selectfluor	 **289F**	20	65	-
9	**230**/Selectfluor		72	-[b]	-
10	(2*R*,3*R*)-**212**		24	60	16
11	(2*S*,3*S*)-**213**		21	53	16
12	(2*S*,3*S*)-**214**		28	35	17
13	(*R*)-**219**		22	52	11

[a] reaction performed at -20 °C, [b] crude product recovered , [c] ee value determined by HPLC on a chiral stationary phase

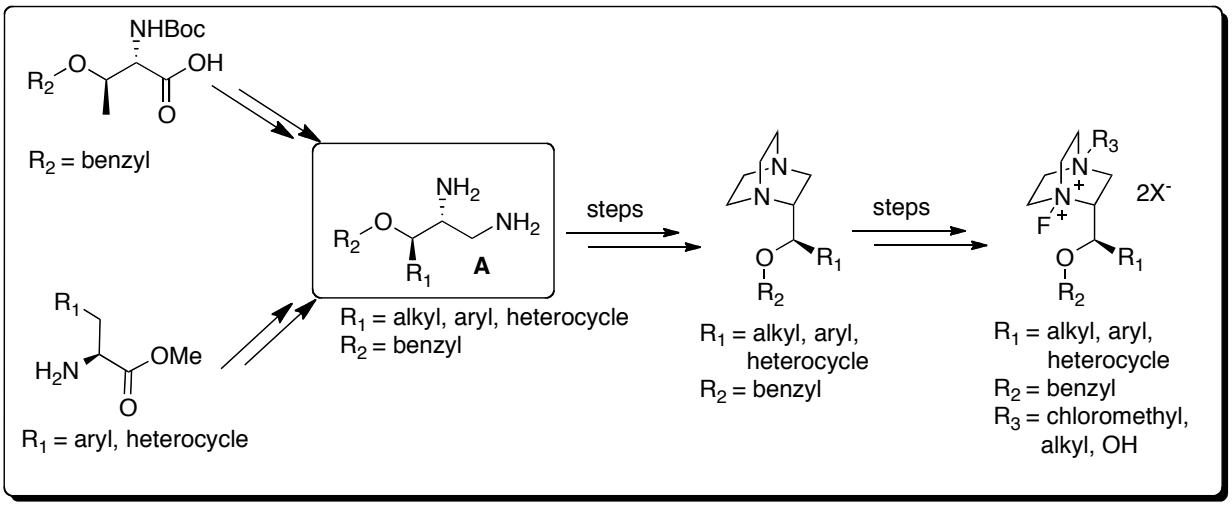
Table 4.10 Asymmetric fluorocyclisation reactions of indene systems.

4.8 Conclusions and Further Work

This study presents the first examples of an asymmetric fluorination, fluorodesilylation and fluorocyclisation reactions of various substrates using chiral non-racemic Selectfluor derivatives. In general, the novel chiral Selectfluor analogues showed superior reactivity than the cinchona alkaloids, owing to their bis-cationic nature compared to known N-F reagents. Moderate to excellent yields of the desired products were obtained for all of the substrates studied using chiral Selectfluor analogues. In some cases, particularly when cyclic indenes are employed, the alkaloids showed no reactivity after over three days while chiral DABCO derivatives mediated fluorocyclisation over a few hours. However, a low to moderate degree of asymmetric induction has been attained using the novel chiral reagents. The low enantiomeric excesses observed with these novel N-F chiral DABCOs may be explained by the substituents on the DABCO cores not having key functionalities such as hydroxyl groups, which have been proposed to be beneficial in the case of cinchona alkaloids by hydrogen bonding to substrates. Despite the modest asymmetric induction observed in the fluorination of various substrates, the N-F chiral DABCOs offer a solution to the pending problem of reactivity encountered with the methodologies known to date for asymmetric electrophilic fluorination. This solution might allow for a much wider diversity of substrates to be fluorinated.

Further work involves altering the substituents on the diamine precursors to provide some functionality similar to cinchona alkaloids that will favour hydrogen bonding, steric and π-π stacking. In addition, syntheses of various reagents are also envisaged to create a library of chiral-DABCO N-F reagents. Thus, we are planning to prepare more complex structures featuring additional chiral centres that will broaden the substitution pattern that can be introduced. As previously reported by Sharpless, the key intermediate in all the synthesis will be a chiral diamine containing two chiral centres (Scheme 4.18). In order to prepare compound **A**

two different routes can be envisaged depending on the substitution pattern (alkyl or aryl). This chiral diamine will then be transformed after several steps in the new chiral DABCO derivatives with a completely new substitution pattern. Furthermore, one of the main advantages of this synthesis is that the groups on the oxygen atom (R_2) can be cleaved at a later stage under mild conditions and sequentially derivatized with other appropriate moieties.



Scheme 4.18 General approach of new chiral DABCO derivatives

CHAPTER 5: EXPERIMENTAL DATA

5.1 General Experimental

^{1}H NMR spectra were recorded in deuterated solvents using Bruker DPX 200, DQX 400, AVC 500 and AVB 500 spectrometers, calibrated using residual undeuterated solvent as an internal reference. ^{13}C NMR spectra were recorded in deuterated solvents using Bruker DPX 200, DQX 400, AVC 500 spectrometers. ^{19}F NMR spectra were recorded on Bruker DQX 400, AVC 500 and AVB 500 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to describe multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet.

Low resolution mass spectra (*m/z*) were recorded on a Micromass LCT Premier XE spectrometer; high resolution mass spectra were recorded on a Bruker micrOTOF spectrometer. IR spectra were recorded as KBr discs on a Bruker Tensor 27 FT-IR spectrometer or as thin films on NaCl. Absorptions are measured in wavenumbers and only peaks of interest are reported. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were recorded on a Philip Harris apparatus and are uncorrected.

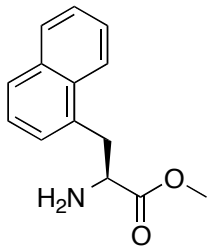
All reactions requiring anhydrous conditions were conducted in dried apparatus under an inert atmosphere of argon. Solvents were dried and purified before use according to standard procedures. Reactions were monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates. Visualisation of the reaction components was achieved using UV fluorescence (254 nm), $KMnO_4$ or ninhydrin stain. Organic layers were dried over Na_2SO_4. Column chromatography was carried out over Merck silica gel C60 (40-60 μm).

High performance liquid chromatography (HPLC) was performed on Waters system (626 Pump, 600S Controller, 996 Photodiode Array Detector, Millenium software) fitted with a chiral column. Gas chromatography was performed on a Thermoquest TraceGC fitted with a Cydex-β chiral column.

Elemental fluorine is purchased as a 50% or 20% mixture with nitrogen in high pressure cylinders (ca. 50 L). The fluorine is regulated from the primary cylinder to 4 bar. The rig is constructed from ¼ inch stainless steel tubing, Monel® or stainless steel Swagelok® valves and stainless steel fittings and is housed in a stainless steel fumehood. Secondary cylinders (3.7 L) up to a maximum pressure of 5 bar. These portable cylinders can be detached and installed in other fumehoods, which house small fluorination rigs. The small rig is constructed of stainless steel pipework which is fitted with Monel® or Swagelok® valves. All valves, tubing, fittings and cylinders, which are used to handle elemental fluorine, are passivated using fluorine before they are used to perform fluorination reactions. All fluorination reactions described in this project were carried out using the small fluorination rig. The flow rate of the fluorine is controlled by a Brooks 5850S mass flow controller. PTFE reaction vessels were used for direct fluorination under batch conditions.

5.2 Experimental data for Chapter 2

(*S*)-1-Naphthylalanine methyl ester (119)



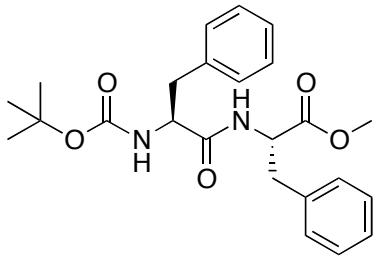
To a solution of (*S*)-*N*-Boc-1-naphthylalanine (800 mg, 2.54 mmol) in MeOH (8 mL) was added trimethylsilyl chloride (1.28 mL, 12.68 mmol) dropwise. The solution was stirred for 38 h at room temperature. After the reaction was completed, the solvent was concentrated under reduced pressure. Anhydrous Et_2O (20 mL) was added, and the resulting slurry was stirred for 15 min and filtered. The precipitate was rinsed with Et_2O and dried to give **119** as a white solid (610 mg, 88%); IR (ν, KBr/cm^{-1}): 3300 (NH), 1744 (C=O); ^{1}H NMR (400 MHz, CD_3OD) δ 3.52 (dd, 1H, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 8.3 Hz, NH_2CHCH_2), 3.70 (s, 3H, OCH_3), 3.80 (dd, 1H, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 6.6 Hz, NH_2CHCH_2), 4.37 (t, 1H, $^3J_{HH}$ = 7.3 Hz, NH_2CHCH_2), 7.42-7.65 (m, 4H, Ar*H*), 7.88-7.96 (m, 2H, Ar*H*), 8.06 (d, 1H, $^3J_{HH}$ = 8.3 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, CD_3OD) δ 34.0 (NH_2CHCH_2), 52.8 (OCH_3), 53.7 (NH_2CHCH_2), 122.9 (*C*H), 125.7 (*C*H), 126.2 (*C*H), 127.0 (*C*H), 128.3 (*C*H), 129.0 (*C*H), 129.3 (*C*H), 130.4 (*C*), 131.9 (*C*), 134.6 (*C*), 169.6 (*C*=O); $[\alpha]^{25}_D$ = +32.9 (c 0.12, MeOH); HRMS (ESI): *m/z* calcd for $C_{14}H_{15}NO_2$ $[M+H]^+$ 230.1167, found 230.1160.

General Procedure 1: Formation of Dipeptides

To a solution of (*S*)-*N*-*tert*-butoxycarbonyl amino acid (1 eq) and (*S*)-amino acid methyl ester hydrochloride (1.2 eq) in CH_2Cl_2 (0.1 M) at 0 °C was added HBTU (1.5 eq) and DIPEA (3 eq). The mixture was stirred for 2 hours at room temperature. The solution was quenched with

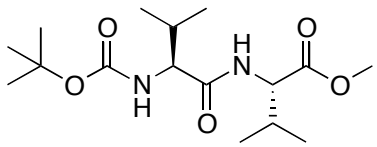
saturated aq. NH_4Cl (1 × volume) and the aqueous layer was extracted with CH_2Cl_2 (2 × volume). The combined organic extracts were combined, dried, filtered over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc 70:30) to give the corresponding dipeptides.

(*S*)-Methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanamido)-3-phenylpropanoate (120)



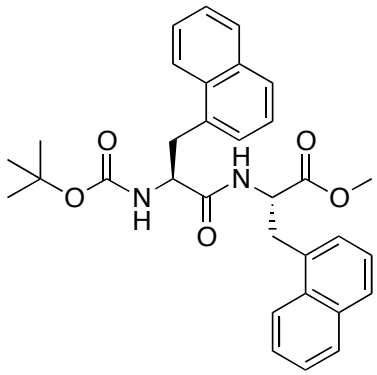
Dipeptide **120** was synthesised from (*S*)-*N*-Boc-1-phenylalanine (5.00 g, 18.9 mmol) and (*S*)-1-phenylalanine methyl ester hydrochloride (4.87 g, 22.6 mmol) according to general procedure GP1. Purification of the crude product by silica gel column chromatography afforded **120** as a white solid (7.81 g, 97%); IR (ν, KBr/cm^{-1}): 1744 (C=O), 1696 (NC=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H, C(CH_3)$_3$), 3.00-3.10 (m, 4H, ArCH_2), 3.67 (s, 3H, OCH_3), 4.35 (d, 1H, $^3J_{HH}$ = 6.3 Hz, NHC*H*), 4.79 (q, 1H, $^3J_{HH}$ = 6.2 Hz, NHC*H*), 4.97 (br d, 1H, $^3J_{HH}$ = 5.5 Hz, N*H*), 6.31 (br d, 1H, $^3J_{HH}$ = 7.0 Hz, N*H*), 6.97-7.00 (m, 2H, Ar*H*), 7.23-7.30 (m, 8H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 28.2 (C(*C*H$_3$)$_3$), 37.9 (Ar*C*H$_2$), 38.2 (Ar*C*H$_2$), 52.3 (OCH$_3$), 53.2 (NH*C*H), 55.7 (NH*C*H), 80.2 (*C*(CH$_3$)$_3$), 126.9 (*C*H), 127.1 (*C*H), 128.5 (2 × *C*H), 128.7 (2 × *C*H), 129.2 (2 × *C*H), 129.3 (2 × *C*H), 135.6 (*C*), 136.5 (*C*), 155.2 (NH*C*OCH), 170.7 (*C*O), 171.3 (*C*O); mp 116-117 ^{o}C; $[\alpha]^{22}_D$ -12.5 (*c* 1, MeOH); HRMS (ESI): *m/z* calcd for $C_{24}H_{30}N_2O_5$ $[M+Na]^+$ 449.2043, found 449.2027.

(*S*)-Methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanamido)-3- methylbutanoate (121)



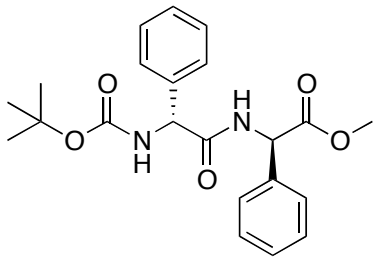
Dipeptide **121** was prepared from (*S*)-*N*-Boc-1-valine (5.00 g, 23.0 mmol) and (*S*)-1-valine methyl ester hydrochloride (4.63 g, 27.6 mmol) according to general procedure GP1. Purification of the crude product by silica gel column chromatography afforded **121** as a white solid (7.36 g, 98%); IR (ν, KBr/cm^{-1}): 1784 (C=O), 1676 (NC=O), 1635 (NC=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, 3H, $^{3}J_{HH}$ = 6.9 Hz, [CH(CH_3)$_2$]$_2$), 0.93 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz, [CH(CH_3)$_2$]$_2$), 0.96 (d, 3H, $^{3}J_{HH}$ = 6.9 Hz, [CH(CH_3)$_2$]$_2$), 1.45 (s, 9H, C(CH_3)$_3$), 2.15-2.19 (m, 2H, [C*H*(CH$_3$)$_2$]$_2$), 3.74 (s, 3H, OCH_3), 3.91 (dd, 1H, $^{3}J_{HH}$ = 8.5 Hz, 6.6 Hz, NHC*H*), 4.53 (dd, 1H, $^{3}J_{HH}$ = 8.7 Hz, $^{3}J_{HH}$ = 4.9 Hz, NHC*H*), 5.05 (d, 1H, $^{3}J_{HH}$ = 7.2 Hz, N*H*), 6.36 (d, 1H, $^{3}J_{HH}$ = 7.0, N*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.7 (CH*C*H$_3$), 17.9 (CH*C*H$_3$), 18.9 (CH*C*H$_3$), 19.3 (CH*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 30.6 (*C*H(CH$_3$)$_2$), 31.2 (*C*H(CH$_3$)$_2$), 52.1 (OCH_3), 57.0 (NH*C*H), 60.2 (NH*C*H), 79.9 (*C*(CH$_3$)$_3$), 156.8 (NH*C*OCH), 171.5 (*C*O), 172.1 (*C*O); mp 145-147 ^{o}C; $[\alpha]^{22}_{D}$ = -27.0 (*c* 1, MeOH**);** HRMS (ESI): *m/z* calcd for $C_{16}H_{30}N_2O_5$ $[M+Na]^+$ 353.1847, found 353.1837.

(*S*)-Methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(naphthalen-1-yl)propanamido)-3-(naphthalen-1-yl)propanoate (122)



Dipeptide **122** was prepared from (*S*)-*N*-Boc-1-naphthylalanine (250 mg, 0.79 mmol) and (*S*)-1-naphthylalanine methyl ester (200 mg, 0.87 mmol) according to general procedure GP1 Purification of the crude product by silica gel column chromatography afforded **122** as a white solid (368 mg, 88%); IR (ν, KBr/cm^{-1}): 1742 (C=O), 1665 (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, C(C*H*$_3$)$_3$), 3.40-3.47 (m, 7H, ArC*H*$_2$, OC*H*$_3$), 4.43 (br s, 1H, NHC*H*),), 4.78 (br s, 1H, NHC*H*), 5.08 (br s, 1H, N*H*), 5.99 (br s, 1H, N*H*), 6.98-7.01 (m, 1H, Ar*H*), 7.25-7.39 (m, 3H, Ar*H*), 7.46-7.58 (m, 4H, Ar*H*), 7.71-7.77 (m, 2H, Ar*H*), 7.82-7.87 (m, 2H, Ar*H*), 8.00-8.14 (m, 2H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.2 (C(*C*H$_3$)$_3$), 35.4 ($ArCH_2$), 36.0 ($ArCH_2$), 52.1 (NHCH), 53.3 (OCH_3), 55.5 (NHCH), 80.1 (*C*(CH$_3$)$_3$) 123.5 (CH), 123.6 (CH), 125.2 (CH), 125.4 (CH), 125.8 (2 × CH), 126.3 (CH), 126.5 (2 × CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.8 (CH), 128.9 (CH), 131.8 (C), 132.1 (C), 132.8 (C), 133.0 (C), 133.8 (C), 133.9 (C), 156.2 (NH*C*OCH), 170.8 (CO), 171.2 (CO); mp = 129-132°C; $[\alpha]^{23}_{D}$= -54.7 (c 0.64, DMSO); HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_2O_5$ $[M+Na]^+$ 549.2360, found 549.2363.

(*R*)-Methyl 2-((*R*)-2-(*tert*-butoxycarbonylamino)-2-phenylacetamido)-2-phenylacetate (125)



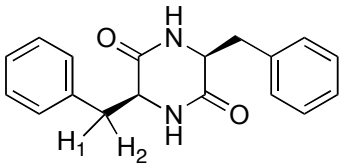
Dipeptide **125** was prepared from (*R*)-*N*-Boc-1-phenylglycine (8.00 g, 31.8 mmol) and (*R*)-1-phenylglycine methyl ester hydrochloride (7.70 g, 38.2 mmol) according to general procedure GP1. Purification of the crude product by silica gel column chromatography afforded **125** as a white solid (11.5 g, 91%); IR (ν, KBr/cm^{-1}): 1736 (C=O), 1638 (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H, C(C*H*$_3$)$_3$), 3.67 (s, 3H, OC*H*$_3$), 5.21 (br s, 1H, N*H*), 5.50 (d, 1H, $^{3}J_{HH}$ = 6.8 Hz, NHC*H*), 5.72 (br s, 1H, N*H*), 6.83 (d, 1H, $^{3}J_{HH}$ = 6.6 Hz, NHC*H*), 7.34-7.39 (m, 10H,

Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.2 (C(CH_3)$_3$), 52.38 (OCH_3), 56.7 (NHCH), 58.5 (NHCH), 80.1 ($C(CH_3)_3$), 127.3 (2 × Ph*C*), 128.4 (2 × Ph*C*), 128.6 (2 × Ph*C*), 128.9 (2 × Ph*C*), 130.0 (2 × Ph*C*), 136.0 (C), 137.8 (C), 154.3 (NH*C*OCH), 169.5 (CO), 170.7 (CO); mp 89-91 ^{o}C; $[\alpha]^{22}_{D}$ +144.5 (*c* 1, MeOH); HRMS (ESI): *m/z* calcd for $C_{22}H_{26}N_2O_5$ $[M+Na]^+$ 421.1731, found 421.1734

General Procedure 2: Formation of Diketopiperazines

A solution of (*S*)-methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-dipeptide (1 eq) in formic acid (0.1 M) was stirred for 2 hours at room temperature. The solution was concentrated under reduced pressure and the residue was dissolved in *sec*-butanol (0.2 M) and toluene (0.1 M), and then refluxed for 4 hours. The resulting precipitate was filtered, and then recrystallised from methanol/ether.

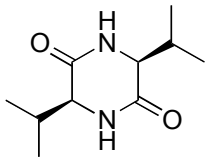
(3*S*,6*S*)-3,6- Bis(phenylmethyl)piperazine-2,5-dione (126)



Diketopiperazine **126** was prepared from (*S*)-methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenyl- propanamido)-3-phenylpropanoate **120** (6.80 g, 15.9 mmol) according to general procedure GP2. After completion, work-up and purification afforded **120** as a white solid (4.30 g, 92%); IR (ν, KBr/cm^{-1}): 1669 (NC=O); ^{1}H NMR (500 MHz, CF_3CO_2D) δ 2.32 (dd, 2H, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 7.6 Hz, H_1), 3.08 (dd, 2H, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 3.7 Hz, H_2), 4.58 (dd, 2H, $^3J_{HH}$ = 7.0, $^3J_{HH}$ = 4.0 Hz, NHC*H*), 7.13 (d, 4H, $^3J_{HH}$ = 7.5 Hz, Ar*H*), 7.34-7.42 (m, 6H, Ar*H*); ^{13}C NMR (125.8 MHz, CF_3CO_2D) δ 39.6 (2 × ArCH_2), 56.6 (2 × NH*C*H), 128.5 (2 × *C*H), 129.4 (4 × CH), 129.9 (4 × CH), 133.6 (2 × C), 170.9 (2 × NHCO); mp 308-310 °C; $[\alpha]^{22}_{D}$ = -99.0 (*c* 0.2,

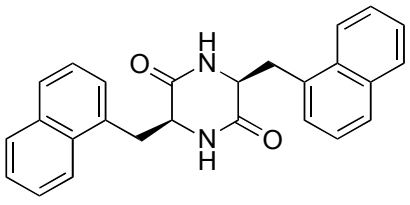
AcOH); HRMS (FI)$^+$: *m/z* calcd for $C_{18}H_{18}N_2O_2$ $[M]^+$ 294.1368, found 294.1355.

(3*S*,6*S*)-3,6-Bis(isopropyl)piperazine-2,5-dione (127)



Diketopiperazine **127** was prepared from (*S*)-methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-methyl-butanamido)-3-methylbutanoate **121** (7.30 g, 22.0 mmol) according to general procedure GP2. After completion, work-up and purification afforded **127** as a white solid (3.30 g, 75%); IR (ν, KBr/cm^{-1}): 1661 (NC=O), 1660 (NC=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.84 (d, 6H, $^3J_{HH}$ = 6.8 Hz, CH(CH_3)$_2$), 0.96 (d, 6H, $^3J_{HH}$ = 7.1 Hz, CH(CH_3)$_2$), 2.08-2.21 (m, 2H, CH(CH$_3$)$_2$), 3.69 (t, 2H, $^4J_{HH}$ = 2.3 Hz, NHCH), 7.94 (br s, 2H, NH); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 17.3 (CH(*C*H$_3$)$_2$), 18.7 (CH(*C*H$_3$)$_2$), 30.7 (*C*H(CH$_3$)$_2$), 31.0 (*C*H(CH$_3$)$_2$) 59.1 (2 × NH*C*H), 167.4 (2 × NH*C*O); mp 272-273 °C; $[\alpha]^{22}_D$ = -61.0 (*c* 0.48, AcOH); HRMS (FI): *m/z* calcd for $C_{10}H_{18}N_2O_2$ $[M]^+$ 198.1447, found 198.1440.

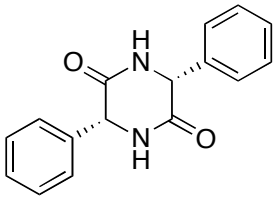
(3*S*,6*S*)-3,6-Bis(naphthalen-1-ylmethyl)piperazine-2,5-dione (128)



Diketopiperazine **128** was prepared from (*S*)-Methyl 2-((*S*)-2-(tert-butoxycarbonylamino)-3-(naphthalen-1-yl)propanamido)-3-(naphthalen-1-yl)propanoate **122** (668 mg, 1.57 mmol) according to general procedure GP2. After completion, work-up and purification afforded **128** as a white solid

(430 mg, 69%); IR (ν, KBr/cm^{-1}): 1672 (NCO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (dd, 2H, $^{2}J_{HH}$ = 14.0 Hz, $^{3}J_{HH}$ = 6.4 Hz, NHCHCH_2), 2.94 (dd, 2H, $^{2}J_{HH}$ = 14.0 Hz, $^{3}J_{HH}$ = 4.8 Hz, NHCHCH_2), 3.98-4.01 (m, 2H, NHCHCH$_2$), 6.70-6.80 (m, 2H, ArH), 7.34-7.38 (m, 2H, ArH), 7.50-7.55 (m, 4H, ArH), 7.77 (d, 2H, $^{3}J_{HH}$ = 8.1 Hz, ArH), 7.87-7.90 (m, 2H, ArH), 7.97-8.00 (m, 2H, ArH), 8.10 (br s, 2H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 37.8 (NHCHCH$_2$), 56.2 (NHCHCH$_2$), 124.7 (CH), 126.2 (CH), 126.4 (CH), 127.0 (CH), 128.2 (CH), 128. 4 (C), 128.7 (C), 128.9 (C), 129.4 (CH), 129.5 (CH), 132.6 (C), 133.4 (C), 134.4 (C), 167.1 (C=O); mp 273-275 °C; $[\alpha]^{22}_{D}$ = -70.3 (c 0.55, CH_3COOH), HRMS (ESI): *m/z* calcd for $C_{26}H_{22}N_2O_2$ $[M+Na]^+$: 417.1573; found 417.1571.

(3*R*,6*R*)-3,6- Bis(phenyl)piperazine-2,5-dione (129)

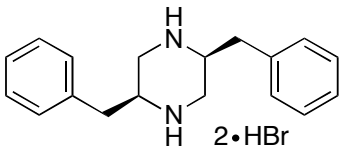


Diketopiperazine **129** was prepared from (*R*)-methyl 2-((*R*)-2-(*tert*-butoxycarbonylamino)-2-phenylacetamido)-2-phenylacetate **125** (6.50 g, 16.3 mmol) according to general procedure GP2. After completion, work-up and purification afforded **129** as a white solid (3.49 g, 80%); IR (ν, KBr/cm^{-1}): 3080 (C-H), 1678 (C=O), 1665 (C=O), 1448 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.08 (s, 2H, NHCH), 7.23-7.30 (m, 10H, ArH), 8.68 (d, 2H, $^{3}J_{HH}$ = 2.7 Hz, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 58.3 (2 × NHCH), 126.8 (2 × PhC), 127.8 (4 × PhC), 128.1 (4 × PhC), 138.4 (2 × C), 165.9 (2 × NHCO); mp 280-282 °C; $[\alpha]^{22}_{D}$ +68.6 (*c* 1, DMSO); HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N_2O_2$ $[M+Na]^+$ 289.0944, found 289.0947

General Procedure 3: Formation of Piperazine Salts

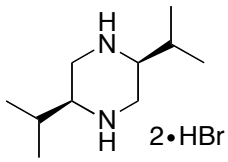
To a vigorously stirred suspension of (3*S*,6*S*)-3,6-disubstituted-piperazine-2,5-dione (1 eq) in THF (0.2 M) was added dropwise BH_3•THF (1M solution in THF) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, then refluxed for 12 hours. The solution was filtered, and the filtrate was cooled to 0 °C. HBr/AcOH (12%) was slowly added to the solution and the reaction mixture was stirred at room temperature. After 2 hours, dry hexane was added and the solution was left to stand overnight in the freezer. The resulting dihydrobromide precipitates were collected by filtration, and then recrystallised from methanol/ether.

(2*S*,5*S*)-2,5-Bis(phenylmethyl)piperazine dihydrobromide (132)



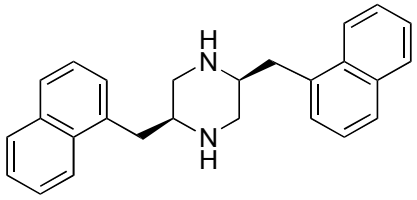
Piperazine dihydrobromide **132** was prepared from (3*S*,6*S*)-3,6-bis-(phenylmethyl)-piperazine-2,5-dione **126** (1.20 g, 5.10 mmol) according to general procedure GP3. After completion, work-up and purification afforded **132** as a white solid (1.20 g, 55%). IR (ν, KBr/cm^{-1}): 3424, 2911, 2777, 1455, 1070, 970, 740, 608; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.22-3.32 (overlap m, 8H, ArCH_2, NHCH_2), 3.89 (dq, 2H, $^3J_{H\text{-}H}$ = 9.9, $^3J_{H\text{-}H}$ = 5.0 Hz, NHC*H*), 7.30-7.43 (m, 10H, Ar*H*), 9.40 (br s, 4H, N*H*); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 33.8 (2 × PhCH_2), 40.7 (2 × NHCH*C*H_2), 51.9 (2 × NH*C*HCH$_2$), 127.4 (2 × Ph*C*), 128.9 (4 × Ph*C*) 129.4 (4 × Ph*C*), 135.3 (2 × C); mp 226-228 °C; $[\alpha]^{22}_D$ -13.4 (*c* 2, H_2O); HRMS (FI): *m/z* calcd for $C_{18}H_{24}Br_2N_2$ $[M]^+$ 426.0306, found 426.0286

(2*S*,5*S*)-2,5-Bis(isopropyl)piperazine dihydrobromide (133)



Piperazine dihydrobromide **133** was prepared from (3*S*,6*S*)-3,6-bis-(isopropyl)-piperazine-2,5-dione **127** (1.70 g, 8.60 mmol) according to general procedure GP3. After completion, work-up and purification afforded **133** as a white solid (1.10 g, 39%); IR (ν, KBr/cm^{-1}): 3425, 3029, 2915, 1470, 970; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.97 (d, 6H, $^{3}J_{H\text{-}H}$ = 6.6 Hz, [CH(CH_3)$_2$]$_2$), 1.02 (d, 6H, $^{3}J_{H\text{-}H}$ = 6.6 Hz, [CH(CH_3)$_2$]$_2$), 2.10-2.18 (m, 2H, [CH(CH$_3$)$_2$]$_2$), 2.49-2.51 (m, 2H, [NHCH]$_2$), 3.28-3.37 (m, 4H, [NHCH_2]$_2$), 8.86 (br s, 2H, NH_2Br), 9.48 (br s, 2H, NH_2Br); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 19.6 [CH(*C*H$_3$)$_2$]$_2$), 27.2 [*C*H(CH$_3$)$_2$]$_2$), 40.8 ([NHCH$_2$]$_2$), 56.3 (NHCH); mp 265-267 °C; [α]$^{22}_{D}$ -22.1 (*c* 1, H$_2$O); HRMS (FI): *m/z* calcd for $C_{10}H_{24}Br_2N_2$ [M]$^+$ 330.0306, found 330.0286

(2*S*,5*S*)-2,5-Bis(naphthalen-1-ylmethyl)piperazine (134)



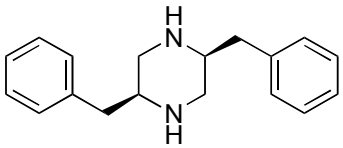
Piperazine **134** was prepared from (3*S*,6*S*)-3,6-bis(naphthalen-1-ylmethyl)piperazine-2,5-dione **126** (180 mg, 0.46 mmol) according to general procedure GP3. After completion, work-up and purification gave **134** as a white solid (225 mg, 93%). After neutralisation: IR (ν, KBr/cm^{-1}): 2917 (NH), 2726 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (dd, 2H, $^{2}J_{H\text{-}H}$ = 11.9, $^{3}J_{H\text{-}H}$ = 3.3 Hz, NHCH_2CH), 3.03 (dd, 2H, $^{2}J_{H\text{-}H}$ = 11.9, $^{3}J_{H\text{-}H}$ = 5.8 Hz, NHCH_2CH), 3.26 (m, 2H, NHCH$_2$CH), 3.35 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.4, $^{3}J_{H\text{-}H}$ = 7.8 Hz, ArCH_2CH), 3.47 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.4, $^{3}J_{H\text{-}H}$ = 6.1 Hz, ArCH_2CH), 7.41-7.44 (m, 4H, ArH), 7.47-7.55 (m, 4H, ArH), 7.75-7.78 (m, 2H, ArH), 7.86-

7.88 (m, 2H, Ar*H*), 8.13 (d, 2H, $^{3}J_{H\text{-}H}$ = 8.1 Hz, Ar*H*), ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 35.5 (CH_2 Ar*C*H_2CH), 47.9 (NH*C*H_2CH), 54.6 (ArCH_2*C*H), 124.0 (Ar*C*), 125.4 (Ar*C*), 125.6 (Ar*C*), 126.0 (Ar*C*), 127.2 (Ar*C*), 127.4 (Ar*C*), 128.8 (Ar*C*), 132.2 (C), 134.0 (C), 135.2 (C); mp 172-174 °C; $[\alpha]^{22}_{D}$ = +19.7 (c 0.4, DCM), HRMS (FI)$^{+}$: *m/z* calcd for $C_{26}H_{26}N_2$ $[M+H]^{+}$ 367.2169, found 367.2164.

General Procedure 4: Formation of Piperazines

To a vigorously stirred suspension of (3*S*,6*S*)-3,6-piperazine-2,5-dione (1 eq) in THF (0.2 M), BH_3•THF (1M solution in THF) was added dropwise at 0 °C. The mixture was stirred for 1 hour, warming to room temperature, and then heated to reflux for 2 hours. The solution was filtered, cooled at 0 °C, carefully quenched with methanol (20 mL), and then concentrated under reduced pressure. The residual crystalline material was dissolved in methanol/THF (1:2), and then a suspension of 10% palladium on carbon (0.1 eq, 50% wet) in methanol (1 M) was added. The mixture was stirred at room temperature for 12 hours. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (chloroform:methanol 95:5) afforded the desired products.

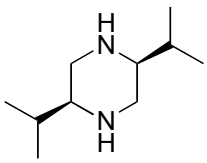
(2*S*,5*S*)-2,5-Bis(phenylmethyl)piperazine (86)



Piperazine **86** was prepared from (3*S*,6*S*)-3,6-bis(phenylmethyl)- piperazine-2,5-dione **126** (4.30 g, 14.6 mmol) according to general procedure GP4. After completion, work-up and purification gave **86** as colourless oil (3.20 g, 82%); R_f 0.51; IR (ν, neat/cm^{-1}): 3320 (NH), 3020 (C-H), 2700 (C-H), 1455 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 (br s, 2H, N*H*), 2.79-3.03 (overlap m,

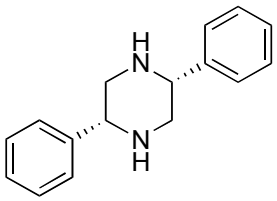
10H, ArCH_2, NHCH_2, NHC*H*), 7.21-7.35 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 38.1 (2 × Ar*C*H_2), 47.5 (2 × NH*C*H_2), 55.2 (2 × NH*C*H), 125.7 (2 × Ph*C*) 128.0 (4 × Ph*C*), 128.7 (4 × Ph*C*), 138.9 (2 × C); HRMS (FI): *m/z* calcd for $C_{18}H_{22}N_2$ $[M]^+$ 266.1775, found 266.1783.

(2*S*,5*S*)-2,5-Bis(isopropyl)piperazine (137)



Piperazine **137** was prepared from (3*S*,6*S*)-3,6-bis(isopropyl)piperazine-2,5-dione **127** (4.56 g, 23.1 mmol) according to general procedure GP4. After completion, work-up and purification gave **137** as colourless oil (3.20 g, 75%); IR (ν, neat/cm^{-1}): 3425 (NH), 3029 (C-H), 2915 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, 6H, $^3J_{H\text{-}H}$ = 6.7 Hz, CH(CH_3)$_2$), 0.88 (d, 6H, $^3J_{H\text{-}H}$ = 6.7 Hz, CH(CH_3)$_2$), 1.73 (br s, 2H, N*H*), 1.80-1.89 (m, 2H, [C*H*(CH_3)$_2$]$_2$), 2.23 (dt, 2H, $^3J_{H\text{-}H}$ = 8.8, $^3J_{H\text{-}H}$ = 4.5 Hz, [NHC*H*]$_2$), 2.76 (d, 4H, [NHCH_2]$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 19.2 (CH(*C*H_3)$_2$), 19.6 (CH(*C*H_3)$_2$), 27.7 (*C*H(CH$_3$)$_2$), 45.8 ([NHCH_2]$_2$), 60.2 (NHCH); $[\alpha]^{22}_D$ -22.5 (*c* 1, H_2O); HRMS (ESI): *m/z* calcd for $C_{10}H_{22}N_2$ $[M+H]^+$ 171.1783, found 171.1651

(2*R*,5*R*)-2,5-Bis(phenylpiperazine) (92)



Piperazine **92** was prepared from (3*R*,6*R*)-3,6-bis(phenyl)piperazine-2,5-dione **129** (1.00 g, 3.76 mmol) according to general procedure GP4. After completion, work-up and purification gave **92** as colourless oil (0.68 g, 76%); IR (ν, neat/cm^{-1}): 3320 (NH), 3020 (C-H), 2700 (C-H), 1455

(C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (br s, 2H, N*H*), 3.14 (dd, 2H, $^{2}J_{H\text{-}H}$ = 12.1 Hz, $^{3}J_{H\text{-}H}$ = 3.6 Hz, NHCH_2), 3.27 (dd, 2H, $^{2}J_{H\text{-}H}$ = 12.1 Hz, $^{3}J_{H\text{-}H}$ = 6.0 Hz, NHCH_2), 4.00 (dd, 2H, $^{3}J_{H\text{-}H}$ = 5.9, $^{3}J_{H\text{-}H}$ = 3.7 Hz, NHC*H*), 7.27 (t, 2H, $^{3}J_{H\text{-}H}$ = 7.3 Hz, Ar*H*), 7.36 (t, 2H, $^{3}J_{H\text{-}H}$ = 7.7 Hz, ArC*H*), 7.57-7.59 (m, 4H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 49.0 (2 × NH*C*H_2), 57.7 (2 × NH*C*H), 126.9 (2 × Ph*C*) 127.6 (4 × Ph*C*), 128.2 (4 × Ph*C*), 142.8 (2 × C); HRMS (ESI): *m/z* calcd for $C_{16}H_{18}N_2$ $[M]^+$ 238.1470, found 238.1474

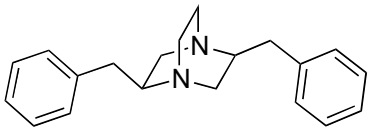
General Procedure 5: Formation of bicyclic systems

To a solution of 2,5-bis-piperazine (1.2 eq) in toluene (0.3 M), 1,2-dibromoethane (1.0 eq) and triethylamine (1.2 M) were added and the solution was heated to reflux for 12 h. The reaction mixture was then cooled to room temperature and brought to pH 9–10 with 1M aq. NaOH. The organic phase was separated and the aqueous phase was extracted with chloroform (3 × solvent). The combined organic phases were dried, filtered and concentrated under reduced pressure. Purification by silica gel flash column chromatography (chloroform:methanol 98:2) gave two diastereomer products.

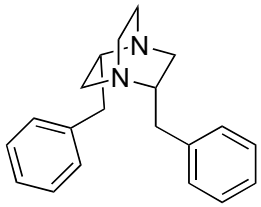
(1*R*,2*S*,4*R*,5*S*)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane (91)

(1*S*,2*S*,4*S*,5*S*)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo [2.2.2]octane (96)

Diazabicyclo-octane **91** and **96** were prepared from (2*S*,5*S*)-2,5-bis(phenylmethyl)piperazine (1.00 g, 3.75 mmol) according to GP5. After 12 hours, work-up and purification gave isolated products **91** and **96** as brown oils respectively.



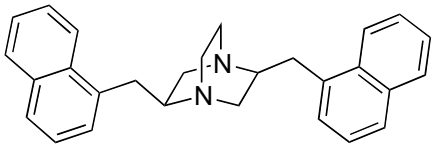
(1*R*,2*S*,4*R*,5*S*)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane, **91** (0.21 g, 19%); IR (ν, neat/cm^{-1}): 3060 (C-H), 2965 (C-H), 2809, 1460 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51-2.58 (m, 2H, NC*H*$_2$CH), 2.64-2.77 (m, 4H), 2.90-2.97 (m, 6H), 3.07 (td, 2H, $^{2}J_{H\text{-}H}$ = 9.5, $^{3}J_{H\text{-}H}$ = 3.5 Hz, ArC*H*$_2$) 7.20 (m, 6H, Ar*H*), 7.27-7.31 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 39.2 (2 × CH_2), 41.2 (2 × CH_2), 55.6 (2 × NCH), 56.4 (2 × Ar*C*H$_2$), 126.2 (2 × Ar*C*) 128.4 (4 × Ar*C*), 128.8 (4 × Ar*C*), 139.0 (2 × C); $[\alpha]^{22}_{D}$ +104.3 (*c* 0.5, MeOH); HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_2$ $[M+H]^+$ 293.1973, found 293.1939



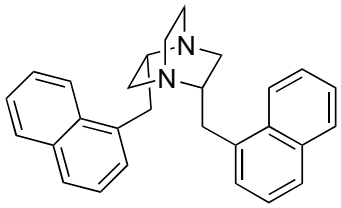
(1*S*,2*S*,4*S*,5*S*)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane **96** (0.19 g, 17%); IR (ν, neat/cm^{-1}): 3055 (C-H), 2960 (C-H), 2812 (C-H), 1465 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67-2.80 (m, 10H), 2.96 (dd, 4H, $^{2}J_{H\text{-}H}$ = 15.9, $^{3}J_{H\text{-}H}$ = 6.6 Hz, ArC*H*$_2$), 7.18-7.33 (m, 10H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 39.1 (2 × Ar*C*H$_2$), 47.5 (2 × NCH_2), 49.0 (2 × N*C*H$_2$CH), 56.4 (2 × N*C*H), 126.4 (2 × Ar*C*) 128.6 (4 × Ar*C*), 129.1 (4 × Ar*C*), 139.0 (2 × C); $[\alpha]^{22}_{D}$ +133.8 (*c* 0.3, MeOH); HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_2$ $[M+H]^+$ 293.1961, found 293.1939

(1*R*,2*S*,4*R*,5*S*)-2,5-Bis(naphthalen-1-ylmethyl)-1,4-diazabicyclo[2.2.2]octane (141)
(1*S*,2*S*,4*S*,5*S*)-2,5-Bis(naphthalen-1-ylmethyl)-1,4-diazabicyclo[2.2.2]octane (142)

Diazabicyclo-octane **141** and **142** were prepared from (2*S*,5*S*)-2,5-bis(naphthalen-1-ylmethyl)piperazine **140** (207 mg, 0.57 mmol) according to general procedure. After 12 hours, work-up and gave **141** and **142** as brown oils.



(1*R*,2*S*,4*R*,5*S*)-2,5-Bis(naphthalene-1-ylmethyl)-1,4-diazabicyclo[2.2.2]octane, **141** (34.0 mg, 15%); IR (ν, cm^{-1}): 3054 (C-H), 2986 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (dd, 2H, ^{2}J = 13.3 Hz, $^{3}J_{H\text{-}H}$ = 7.7 Hz, NCH_2CH), 2.81-2.86 (m, 2H, NCH_2), 2.90 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.3 Hz, $^{3}J_{H\text{-}H}$ = 8.2 Hz, NCH_2CH), 3.05-3.10 (m, 2H, NCH_2CH), 3.14 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.2 Hz, $^{3}J_{H\text{-}H}$ = 8.8 Hz, ArCH_2), 3.21-3.28 (m, 2H, NCH_2), 3.46 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.2 Hz, $^{3}J_{H\text{-}H}$ = 5.3 Hz, ArCH_2), 7.33 (d, 2H, $^{3}J_{H\text{-}H}$ = 6.3 Hz, ArH), 7.36-7.39 (m, 2H, ArH), 7.41-7.49 (m, 4H, ArH), 7.71-7.72 (d, 2H, $^{3}J_{H\text{-}H}$ = 8.2 Hz, ArH), 7.82-7.84 (dd, 2H, $^{3}J_{H\text{-}H}$ = 6.9 Hz, $^{4}J_{H\text{-}H}$ = 1.9 Hz, ArH), 7.99 (d, 2H, $^{3}J_{H\text{-}H}$ = 7.9 Hz, ArH), ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 36.5 (ArCH_2), 41.3 (NCH_2), 54.2 (NCH), 56.4 (NCH_2CH), 123.5 (CH), 125.4 (CH), 125.5 (CH), 126.0 (CH), 126.7 (CH), 127.2 (CH), 128.9 (CH), 131.8 (C), 134.0 (C), 134.5 (C); $[\alpha]^{25}_{D}$ = +70.4 (c 0.42, DCM). HRMS (ESI): *m/z* calcd for $C_{28}H_{28}N_2$ ($[M+H]^+$): 393.2325, found 393.2328.



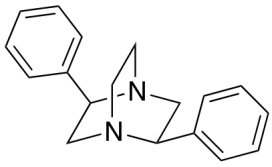
(1*S*,2*S*,4*S*,5*S*)-2,5-Bis(naphthalene-1-ylmethyl)-1,4-diazabicyclo[2.2.2]octane, **142** (18.0 mg, 8%); IR (ν, cm^{-1}): 3055 (C-H), 2987 (C-H), 2306; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.6 Hz, $^{3}J_{H\text{-}H}$ = 8.8 Hz, NCH_2CH), 2.78-2.784 (m, 4H, NCH_2), 3.03 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.6 Hz, $^{3}J_{H\text{-}H}$ = 8.2 Hz, NCH_2CH), 3.11-3.17 (m, 2H, NCH_2CH), 3.28 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.9 Hz, $^{3}J_{H\text{-}H}$ = 8.6 Hz, ArCH_2), 3.55 (dd, 2H, $^{2}J_{H\text{-}H}$ = 13.9 Hz, $^{3}J_{H\text{-}H}$ = 5.7 Hz, ArCH_2), 7.43-7.47 (m, 4H, ArH), 7.52 (dt, 2H, $^{3}J_{H\text{-}H}$ = 7.9, $^{4}J_{H\text{-}H}$ = 1.0 Hz, ArH), 7.58 (dt, 2H, $^{3}J_{H\text{-}H}$ = 6.6, $^{4}J_{H\text{-}H}$ = 1.6 Hz, ArH), 7.79 (dd, 2H, $^{3}J_{H\text{-}H}$ = 7.8, $^{4}J_{H\text{-}H}$ = 1.6 Hz, ArH), 7.91 (d, 2H, $^{3}J_{H\text{-}H}$ = 7.8 Hz, ArH), 8.13 (d, 2H, $^{3}J_{H\text{-}H}$ = 8.5 Hz, ArH), ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 36.5 (ArCH_2), 47.6

(N*C*H_2CH), 48.9 (N*C*H_2), 55.0 (NCH_2*C*H), 123.6 (CH), 125.5 (CH), 125.6 (CH), 126.1 (CH), 126.8 (CH), 134.6 (C), 127.3 (CH), 129.0 (CH), 132.0 (C), 134.0 (C); $[\alpha]^{25}_{D}$= +60.6 (c 0.09, DCM); HRMS (ESI): *m/z* calcd for $C_{28}H_{28}N_2$ ($[M+H]^+$): 393.2325, found 393.2324.

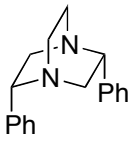
***(1R,2R,4R,5R)*-2,5-diphenyi-l,4-diazabicyclo[2.2.2]octane (94)**

***(1S,2R,4S,5R)*-2,5-diphenyi-l,4-diazabicyclo[2.2.2]octane (95)**

Diazabicyclo-octanes **94** and **95** were prepared from (2*R*,5*R*)-2,5-diphenylpiperazine **92** (300 mg, 1.25 mmol) according to general procedure. After 12 hours, work-up and purification gave **94** and **95** as a solid.



(1S,2R,4S,5R)-2,5-diphenyi-l,4-diazabicyclo[2.2.2]octane **95** (55.2 mg, 17%); IR (ν, cm^{-1}): 2930, 1495, 1445, 1060, 800, 745, 735, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57-2.60 (m, 2H, CH_2), 2.81-2.83 (m, 2H, CH_2), 3.15 (dd, 2H, $^2J_{H\text{-}H}$ = 13.0, $^3J_{H\text{-}H}$ = 8.5 Hz, CH_2), 3.71 (dd, 2H, $^2J_{H\text{-}H}$ = 13.0, $^3J_{H\text{-}H}$ = 8.8 Hz, CH_2), 4.09 (t, 2H, $^3J_{H\text{-}H}$ = 8.8 Hz, NCH), 7.25-7.36 (m, 2H, ArH), 7.38-7.45 (m, 8H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 41.3 (CH_2), 55.1 (CH_2), 56.9 (CH), 126.5 (2 × ArC), 126.7 (4 × ArC),128.2 (4 × ArC), 141.3 (2 × C); mp 153-154 °C, $[\alpha]^{22}_{D}$ = -76.8 (c 0.49, $CHC1_3$); HRMS (ESI): *m/z* calcd for $C_{18}H_{20}N_2$ ($[M+H]^+$): 265.1705, found 265.1708.



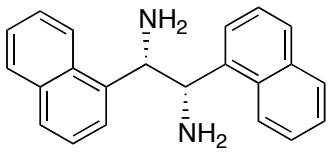
(1R,2R,4R,5R)-2,5-diphenyi-l,4-diazabicyclo[2.2.2]octane **94** (189 mg, 17%): IR (ν, cm^{-1}): 2880, 1600, 1490, 1175, 810, 725, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (dd, 2H, $^2J_{H\text{-}H}$ =

13.4, $^{3}J_{H\text{-}H}$ = 9.0 Hz, CH_2), 3.11 (s, 4H, NCH_2), 3.25 (ddd, 2H, $^{2}J_{H\text{-}H}$ = 13.4, $^{3}J_{H\text{-}H}$ = 9.0, $^{3}J_{H\text{-}H}$ = 1.5 Hz, CH_2), 3.92 (t, 2H, $^{2}J_{H\text{-}H}$ = 9.0 Hz, NCH), 7.12-7.31 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 47.5 (CH_2), 48.8 (CH_2), 56.4 (CH), 126.7 (2 × ArC), 126.9 (4 × ArC), 128.4 (4 × ArC), 141.3 (2 × C); mp 208-208.5 °C, $[\alpha]^{22}_{D}$ = -140.2 (c 0.52, $CHC1_3$), HRMS (ESI): *m/z* calcd for $C_{18}H_{20}N_2$ ($[M+H]^+$): 265.1705, found 265.1710.

General Procedure 6: Vicinal Diamines formation

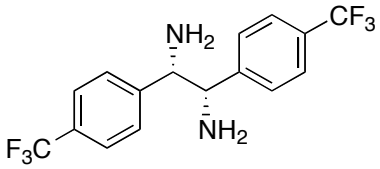
To a clear solution of 2.2 g (10 mmol) of 1,2- bis(2-hydroxylphenyl)-1,2-diaminoethane in 50 mL of DMSO was added 24 mmol of aryl aldehyde. The resulting mixture was stirred overnight at room temperature, and then the mixture was poured into 150 mL of distilled water. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed with distilled water, and dried over sodium sulfate. After evaporation of the solvent, the residue was dried in vacuum to give a diimine. To a clear solution of the intermediate diimine (10 mmol) in 100 mL of THF was added 3.0 mL of 37% HCl solution. Stirring the reaction mixture at ambient temperature for 3 hours afforded the product as a white precipitate. The solid was filtered and washed with THF to afford analytically pure dihydrochloride salt. To the salt was added ethyl acetate, saturated aqueous $NaHCO_3$ solution and some NaOH (3M) and the two layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried, filtered and concentrated under recduced pressure.

(1*S*,2*S*)-1,2-Di(naphthalen-1-yl)ethane-1,2-diamine (149)



1,2-Di(naphthalen-1-yl)ethane-1,2-diamine **149** was obtained according to general procedure 6 (2.34 g, 87%), IR (neat) (ν, cm^{-1}) 2869, 1454, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (br s, 4H, NH_2), 5.14 (s, 2H, NH_2CH), 7.48-7.55 (m, 4H, Ar*H*), 7.60 (td, 2H, $^3J_{H-H}$ = 7.0 Hz, $^4J_{H-H}$ = 1.2 Hz, Ar*H*), 7.80 (dd, 4H, $^3J_{H-H}$ = 8.0, 7.1 Hz, Ar*H*), 7.89 (d, 2H, $^3J_{H-H}$ = 7.8 Hz, Ar*H*), 8.33 (d, 2H, $^3J_{H-H}$ = 8.3 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.3 (NH*C*H), 122.8 (Ar*C*), 124.1 (Ar*C*), 125.4 (Ar*C*), 125.4 (Ar*C*), 125.9 (Ar*C*), 127.6 (Ar*C*), 129.1 (Ar*C*), 130.8 (*C*), 133.9 (*C*), 139.6 (*C*); $[\alpha]^{22}_D$ value of dihydrochloride salt is +266 (*c* 0.56, H_2O); Anal. Calcd for dihydrochloride salt $C_{22}H_{22}Cl_2N_2$: C, 68.57; H, 5.75; N, 7.27; found: C, 68.58; H, 5.77; N, 7.34.

(1*S*,2*S*)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diamine (148)



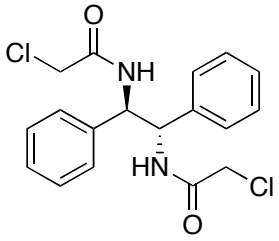
(1*S*,2*S*)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diamine **148** was obtained according to general procedure 6 (495 mg, 97% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (br s, 4H, N*H*$_2$), 4.17 (s, 2H, NH_2CH), 7.39 (d, 4H, $^3J_{H-H}$ = 8.1 Hz, Ar*H*), 7.56 (d, 4H, $^3J_{H-H}$ = 8.1 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 61.6 (NH_2CH), 147.1 (C), 121.9 (q, $^1J_{C-F}$ = 271.8 Hz, CF_3), 125.3 (q, $^3J_{C-F}$ = 3.2 Hz, Ar*C*), 127.3 (Ar*C*), 129.5 (q, $^2J_{C-F}$ = 32.4 Hz, C), ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -61.3 (CF_3) $[\alpha]_{25}^D$= -34.5 (c 0.06, MeOH); MS-EI *m/z* 349.1 (75, $[M+H]^+$), 350.1 (85), 427.1 (100).

General Procedure 7: Chloroacetylation

To a solution of diamine (1 eq), DMAP (3 mol%) and Et_3N (5 eq) in CH_2Cl_2 (40 mL) chloroacetyl chloride (5 eq) was added dropwise at 5 °C and the mixture stirred at room temperature for 3 hours. The solution was quenched with H_2O (15 mL) and the aq. layer made acidic using 1M HCl. The product was extracted with CH_2Cl_2 (3 × 20 mL) and the organic

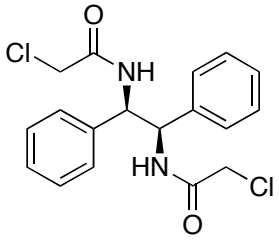
layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure.

_N,N′_-((1_R_,2_S_)-1,2-Diphenylethane-1,2-diyl)bis(2-chloroacetamide) (165)



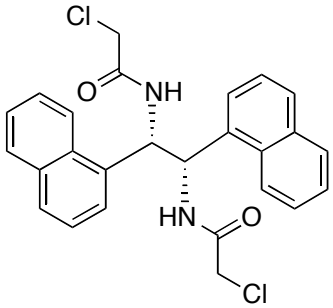
_N,N′_-((1_R_,2_S_)-1,2-Diphenylethane-1,2-diyl)bis(2-chloroacetamide) **165** was obtained according to general procedure 7 (1.60 g, 93%); IR (ν, KBr/cm^{-1}): 3329, 3062, 1651; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.75 (d, 2H, $^2J_{H\text{-}H}$ = 13.1 Hz, CH_2Cl), 3.83 (d, 2H, $^2J_{H\text{-}H}$ = 13.1 Hz, CH_2Cl), 5.25 (dd, 2H, $^3J_{H\text{-}H}$ = 6.3, $^3J_{H\text{-}H}$ = 2.8 Hz, ArCH), 7.25-7.43 (m, 10H, ArH), 8.81 (br s, 2H, NH); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 46.3 (2 × CH_2Cl), 56.8 (2 × NHCH), 128.2 (2 × ArC), 128.5 (4 × ArC), 128.9 (4 × ArC), 140.9 (2 × C), 165.5 (2 × CO); HRMS (ESI): *m/z* calcd for $C_{18}H_{18}Cl_2N_2O_2$ $[M+Na]^+$ 387.0638, found 387.0630.

_N,N′_-((1_R_,2_R_)-1,2-Diphenylethane-1,2-diyl)bis(2-chloroacetamide) (77)



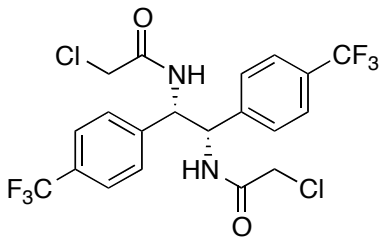
_N,N′_-((1_R_,2_R_)-1,2-Diphenylethane-1,2-diyl)bis(2chloroacetamide) **77** was obtained according to general procedure 7 (1.69 g, 98%); IR (ν, KBr/cm^{-1}): 3291, 1959, 1887; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.06 (s, 4H, (CH_2Cl)$_2$), 5.17-5.19 (m, 2H, ArCH), 7.14-7.20 (m, 10H, ArH), 9.01-9.03 (m, 2H, NH); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 46.4 (2 × CH_2Cl), 58.3 (2 × NHCH), 128.0 (2 × ArC), 128.3 (4 × ArC), 128.8 (4 × ArC), 140.5 (2 × C), 166.4 (2 × CO); (MS-EI) *m/z* 283.1 (7), 336.1 (10), 363.1 (M^-, 90). The compound was used without further purification.

_N_,_N_'-((1_S_,2_S_)-1,2-di(naphthalen-1-yl)ethane-1,2-diyl)bis(2-chloroacetamide) (169)



N,*N*'-((1*S*,2*S*)-1,2-di(naphthalen-1-yl)ethane-1,2-diyl)bis(2-chloroacetamide) **169** was obtained according to general procedure 7 (3.15 g, 90%); IR (ν, KBr/cm^{-1}): 3268, 3065, 1654, 1541, 776; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (d, 4H, $^2J_{H\text{-}H}$ = 16.1, CH_2Cl), 6.73 (br s, 2H, NH), 7.22 (t, 2H, $^3J_{H\text{-}H}$ = 6.0 Hz, Ar*H*), 7.45-7.54 (m, 6H, Ar*H*), 7.65 (d, 2H, $^3J_{H\text{-}H}$ = 6.5 Hz, Ar*H*), 7.76 (d, 2H, $^3J_{H\text{-}H}$ = 6.5 Hz, Ar*H*), 8.23 (br s, 2H, Ar*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 42.4 (CH_2Cl), 122.8 (2 × ArC), 125.1 (2 × ArC), 125.9 (2 × ArC), 126.9 (2 × ArC), 128.9 (2 × ArC), 129.1 (2 × ArC), 131.0 (2 × C), 133.4 (2 × C), 133.9 (2 × C), 166.6 (CO); IR (neat) (ν, cm^{-1}) 3272, 1656, 1545; $[\alpha]^{22}_D$ +367 (*c* 0.28, MeOH); mp 164-166 ºC; HRMS (ESI): *m/z* calcd for $C_{26}H_{22}Cl_2N_2O_2$ $[M+Na]^+$ 487.0951, found 487.0959;

_N,N_'-((1_S_,2_S_)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) (168)



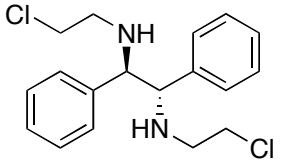
(*N*,*N*'-((1*S*,2*S*)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) **168** was obtained according to general procedure 7 (420 mg, 34%); IR (ν, cm^{-1}): 3302 (NH), 3060 (NH), 1650 (NCO); ^{1}H NMR (400 MHz, DMSO) δ 4.08 (s, 4H, CH_2Cl), 5.40 (d, 2H, $^3J_{H\text{-}H}$ = 7.1 Hz, NHCH), 7.56 (d, 4H, $^3J_{H\text{-}H}$ = 8.1 Hz, ArH), 7.63 (d, 4H, $^2J_{H\text{-}H}$ = 8.1 Hz, ArH), 9.35 (d,

2H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, NH); ^{13}C NMR (100.6 MHz, DMSO) δ 46.4 (CH_2Cl), 57.5 (NCH), 125.0 (q, $^{1}J_{H\text{-}H}$ = 271.6 Hz, CF_3), 125.8 (q, $^{3}J_{C\text{-}F}$ = 4.0 Hz, ArC), 128.7 (d, $^{2}J_{C\text{-}F}$ = 32.0 Hz, C), 129.0 (ArC), 145.0 (C), 166.7 (ArC); ^{19}F {^{1}H} NMR (376 MHz, DMSO) δ -60.9; mp 274-278° C, HRMS (ESI): *m/z* calcd for $C_{20}H_{16}Cl_2F_6N_2O_2$ ($[M+Na]^+$) 523.0385, found 523.0391. The optical rotation could not be determined due to problems with solubility.

General Procedure 8: Reduction and Cyclisation

To a solution of bis(2-chloroacetamide) (1eq) in THF (0.1 M), BH_3•THF (1M solution in THF, 4 eq) was added dropwise at 0 °C and the mixture was heated to reflux for 12 hours. The solution was quenched at 0 °C with MeOH (20 mL) and the reaction mixture was concentrated under reduced pressure. 5% aq. HCl (15 mL) and CH_2Cl_2 (15 mL) were added, and the organic layer was discarded. The aq. layer was made basic with 3M aq. NaOH and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. This intermediate was dissolved in DMF (0.2 M) and refluxed for 5 hours followed by solvent removal under reduced pressure. The crude product was dissolved in H_2O and the solution brought to pH 10 using 3M aq. NaOH. The product was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (chloroform: methanol 97:3).

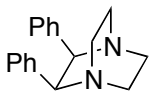
***N,N'*-(1*R*,2*S*)-bis(2-chloroethyl)-1,2-diphenylethane-1,2-diamine (166)**



N,N'-(1*R*,2*S*)-bis(2-chloroethyl)-1,2-diphenylethane-1,2-diamine **166** was obtained according to

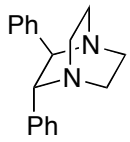
the first part of procedure 8 (1.14 g, 78%); IR (ν, neat/cm^{-1}): 3312, 3025; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57-2.70 (m, 4H), 3.38-3.51 (m, 4H), 3.79 (s, 2H, ArC*H*), 7.27-7.36 (m, 10H, ArH); ^{13}C NMR (125.8MHz, $CDCl_3$) δ 44.6 (CH_2), 48.2 (CH_2), 67.6 (2 × NCH), 127.9 (2 × ArC), 128.3 (4 × ArC), 128.5 (4 × ArC), 140.1 (2 × C); HRMS (ESI): *m/z* calcd for $C_{18}H_{22}Cl_2N_2$ $[M+Na]^+$ 359.1052, found 359.1056. The chiral diastereomer was not fully isolated at this stage.

(2*R*,3*S*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (167)



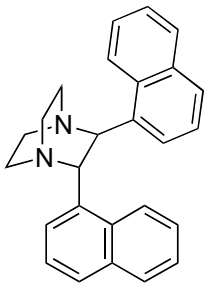
(2*R*,3*S*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane **167** was obtained according to procedure 8 (1.23 g, 55%); IR (ν, neat/cm^{-1}): 2950, 2887, 1887,1460; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68-2.74 (m, 2H), 3.01-3.07 (m, 2H), 3.11-3.19 (m, 4H), 4.63 (s, 2H), 6.99-7.02 (m, 4H, ArH), 7.11-7.15 (m, 6H, ArH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 41.1 (2 × CH_2), 50.0 (2 × CH_2), 62.6 (2 × NCH), 126.2 (2 × ArC), 127.6 (4 × ArC), 129.3 (4 × ArC), 138.6 (2 × C); HRMS $(ESI)^+$: *m/z* calcd for $C_{18}H_{20}N_2$ $[M+H]^+$: 265.1699, found 265.1705.

(2*R*.3*R*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (79)



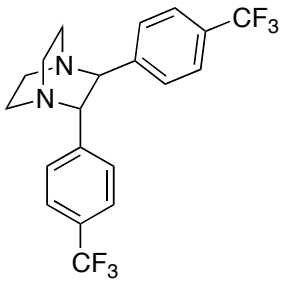
(2*R*,3*R*)-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane **79** was obtained according to procedure 8 (1.45 g, 65%); IR (ν, neat/cm^{-1}): 2950, 2930, 2895, 2880, 1887, 1450; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59-2.64 (m, 2H), 2.76-2.83 (m, 2H), 2.99-3.04 (m, 4H), 4.18 (s, 2H), 7.27-7.48 (m, 10H, ArH), ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 41.1 (2 × CH_2), 49.5 (2 × CH_2), 62.4 (2 × NCH), 127.1 (2 × ArC), 127.7 (4 × ArC), 128.4 (4 × ArC), 141.2 (2 × C); $[\alpha]^{22}_D$ -93.9 (*c* 0.5, MeOH); HRMS $(ESI)^+$: *m/z* calcd for $C_{18}H_{20}N_2$ $[M+H]^+$: 265.1690, found 265.1708

(2*S*,3*S*)-2,3-Di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octane (175)



(2*S*,3*S*)-2,3-di(naphthalen-1-yl)-1,4-diazabicyclo[2.2.2]octane **175** was obtained according to procedure 8 (683 mg, 51%); IR (ν, neat/cm^{-1}): 2932, 2868, 2360, 2341, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69-2.75 (m, 2H, CH_2), 2.92-3.09 (m, 4H, CH_2), 3.54 (td, 2H, $^{3}J_{H-H}$ = 9.4, $^{3}J_{H-H}$ = 2.5 Hz, CH_2), 5.37 (s, 2H, CH), 7.29 (t, 2H, $^{3}J_{H-H}$ = 7.8 Hz, Ar*H*), 7.47 (d, 2H, $^{3}J_{H-H}$ = 7.3 Hz, Ar*H*), 7.54 (t, 2H, $^{3}J_{H-H}$ = 7.3 Hz, Ar*H*), 7.68 (t, 2H, $^{3}J_{H-H}$ = 7.3 Hz, Ar*H*), 7.76 (d, 2H, $^{3}J_{H-H}$ = 8.3 Hz, Ar*H*), 7.88 (d, 2H, $^{3}J_{H-H}$ = 8.1 Hz, Ar*H*), 8.53 (d, 2H, $^{3}J_{H-H}$ = 8.6 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 41.4 (CH_2), 49.3 (CH_2), 55.6 (CH), 123.1 (ArC), 124.6 (ArC), 124.6 (ArC), 125.6 (ArC), 126.5 (ArC), 128.6 (ArC), 128.9 (ArC), 133.3 (C), 134.4 (C), 134.5 (C); mp 105-107 °C, $[\alpha]^{22}_{D}$ +64 (*c* 0.5, MeOH); HRMS (ESI): *m/z* calcd for $C_{26}H_{24}N_2$ $[M+H]^+$: 365.2012, found 365.2008

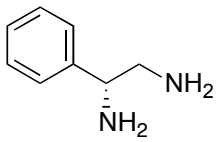
2,3-Bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane (174)



2,3-Bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane **174** was obtained according to procedure (176 mg, 41%). IR (ν, cm^{-1}): 3695, 3584, 3055; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61-2.73 (m, 4H, CH_2), 2.98-3.02 (m, 4H, CH_2), 4.14 (s, 2H, NCH), 7.57 (d, 4H, $^{3}J_{H-H}$ = 8.4 Hz,

ArH), 7.63 (d, 4H, $^{3}J_{H-H}$ = 8.4 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 41.2 (CH_2), 49.4 (CH_2 CH_2), 62.1 (CH), 124.1 (q, $^{1}J_{C-F}$ = 272.4 Hz, CF_3), 125.3 (q, $^{3}J_{C-F}$ = 4.0 Hz, ArC), 128.0 (ArC), 129.6 (q, $^{2}J_{C-F}$ = 32.6 Hz, C), 145.0 (C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -62.5 (CF_3). $[\alpha]^{23}_{D}$ +25.0 (c 0.26, DCM); HRMS (ESI): *m/z* calcd for $C_{20}H_{18}F_6N_2$ $[M+H]^+$ 401.1447, found 401.1448.

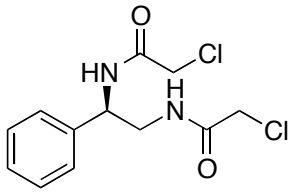
(*R*)-1-Phenylethane-1,2-diamine (146)



(*R*)-1-phenylethane-1,2-diamine was prepared following a 2 step procedure. To a solution of (*R*)-(-)-2-phenylglycine methyl ester hydrochloride (8.5 g, 51.52 mmol) in toluene (100 mL) was added an aqueous solution of NH_4OH (28% in water, 50 mL) and the mixture was stirred at room temperature for 24 hour. The solvent was evaporated and the solid obtained was dried affording 7.09 g (92% conversion) of (*R*)-2-amino-2-phenylacetamide.

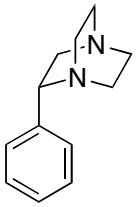
To a suspension of lithium aluminium hydride ($LiAlH_4$) (5.4 g, 141.80 mmol) in tetrahydrofuran (150 mL) at 0 ºC was added portionwise (*R*)-2-amino-2-phenylacetamide (7.09 g, 47.26 mmol). The reaction was stirred at 0 ºC for 10 minutes and then heated at reflux overnight. The mixture was cooled to 0 ºC and then quenched by the careful addition of water and NaOH (1M). The mixture was stirred for 10 minutes until a white precipitate was observed, filtered through celite and evaporated. The residue was purified by distillation affording (*R*)-1-phenylethane-1,2-diamine (2.02 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (br s, 4H, NH_2), 2.73 (dd, 1H, $^{2}J_{H-H}$ = 12.6, $^{3}J_{H-H}$ = 5.3 Hz, CH_2), 2.83 (dd, 1H, $^{2}J_{H-H}$ = 12.6, $^{3}J_{H-H}$ = 5.3 Hz, CH_2), 3.82 (dd, 1H, $^{3}J_{H-H}$ = 6.8, $^{3}J_{H-H}$ = 5.5 Hz, NCH), 7.19-7.23 (m, 1H, ArH), 7.27-7.31 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 49.7 (NCH_2), 58.0 (NCH), 126.2 (Ar*C*), 126.2 (Ar*C*), 128.2 (Ar*C*), 128.2 (Ar*C*), 128.2 (Ar*C*), 143.9 (C); $[\alpha]^{22}_{D}$ -28.5 (*c* 0.5, MeOH).

(*R*)-*N*,*N*'-(1-Phenylethane-1,2-diyl)bis(2-chloroacetamide) (177)



(*R*)-1-Phenylethane-1,2-diamine **146** (3.10 g, 22.79 mmol) was dissolved in dichloromethane (120 mL) and 4-dimethylaminopyridine (95 mg, 0.775 mmol), triethylamine (16 mL, 114 mmol) and chloroacetyl chloride (5.4 mL, 68.40 mmol) were added sequentially at 0 ºC. The solution was stirred at room temperature overnight. Water and HCl (1M) were added, and the mixture stirred for 15 minutes then extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexane:ethyl acetate, from 1:1 to 3:7) affording **177** (2.96 g, 34%) of (*R*)-*N,N*'-(1-phenylethane-1,2-diyl)bis(2-chloroacetamide). ^{1}H NMR (400 MHz, MeOD) δ 3.58 (dd, 2H, $^3J_{H\text{-}H}$ = 8.3, $^3J_{H\text{-}H}$ = 6.0 Hz, CH_2), 4.02 (s, 2H, CH_2Cl), 4.06 (s, 2H, CH_2Cl), 5.13 (dd, 1H, $^3J_{H\text{-}H}$ = 8.1, $^3J_{H\text{-}H}$ = 6.2 Hz, CH), 7.26-7.31 (m, 1H), 7.34-7.37 (m, 4H); ^{13}C NMR (100.6 MHz, MeOD) δ 43.2, 43.4, 45.5, 55.3, 127.9, 127.9, 129.0, 129.9, 129.9, 140.6, 169.2, 170.1 (C); IR (neat) (ν, cm^{-1}) 3312, 1642, 1533, 1262; Anal. Calcd for $C_{12}H_{14}Cl_2N_2O_2$: C, 49.84; H, 4.88; N, 9.69. Found: C, 49.76; H, 4.87; N, 9.62; mp 112-113 ºC; $[\alpha]^{22}_D$ -50 (*c* 0.53, MeOH);. HRMS (ESI): *m/z* calcd for $C_{12}H_{14}Cl_2N_2O_2$ $[M+Na]^+$ 311.0325, found 311.0326;

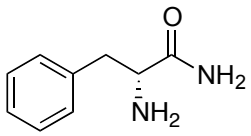
(*R*)-2-Phenyl-1,4-diazabicyclo[2.2.2]octane (181)



To a solution of (*R*)-*N,N*'-(1-phenylethane-1,2-diyl)bis(2-chloroacetamide) **177** (500 mg, 1.73 mmol) in THF (22 mL) at 0 ºC was added dropwise $BH_3 \cdot THF$ (1M in THF, 7 mL, 6.95 mmol)

and the reaction was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and MeOH was added dropwise and stirred for 12 hours at room temperature. Then the solvent was concentrated, HCl (2M) was added and the mixture was stirred at the same temperature for 12 more hours. NaOH (3M) was added to bring the reaction mixture to pH 14 and was extracted with dichloromethane. The combined organic extracts were dried, filtered and evaporated to give 411 mg of a crude, which was used in the next step with no further purification. The crude product (411 mg) was dissolved in dimethylformamide (25 mL) and heated at 150 ºC for 12 hours. The solvent was concentrated under reduced pressure; water and NaOH 3M were added until reach pH 14 and extracted with dichloromethane. The combined organic extracts were dried, filtered and evaporated and the residue was purified by silica gel flash column chromatography (chloroform:methanol 95:5) affording **181** (65 mg, 20% over 2 steps). IR (neat) (ν, cm^{-1}) 2869, 1454, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48-2.54 (m, 1H, CH_2), 2.60 (t, 2H, $^3J_{H-H}$ = 7.0 Hz, CH_2), 2.67-2.74 (m, 3H), 2.85-2.97 (m, 3H), 3.29 (dd, 1H, $^3J_{H-H}$ = 9.6, $^3J_{H-H}$ = 9.6 Hz, CH_2), 3.83 (t, 1H, $^3J_{H-H}$ = 8.6 Hz, CH), 7.13-7.17 (m, 1H), 7.23-7.28 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 40.9, 46.4, 47.1, 49.2, 52.9, 56.4, 126.5, 126.8, 126.8, 128.1, 128.1, 141.2; mp 64-65 ºC; $[\alpha]^{22}_D$ -82 (*c* 0.11, MeOH); HRMS (ESI): *m/z* calcd for $C_{12}H_{17}N_2$ ($[M+H]^+$): 189.1386, found 189.1390.

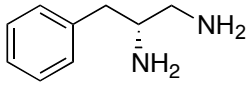
(*R*)-2-Amino-3-phenylpropanamide (155)



To a solution of *L*-Phenylalanine methyl ester hydrochloride **154** (26.1 g, 121 mmol) in chloroform (200 ml) was added saturated $NaHCO_3$ solution until pH paper indicated the solution to be basic. The free amine was extracted with chloroform (2 x 200 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting L-Phenylalanine methyl ester was

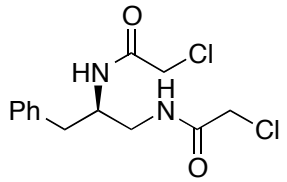
dissolved in toluene (300 ml) and to this solution was added saturated ammonium hydroxide solution (150 ml). The reaction was stirred at room temperature for 24 hours before being evaporated to dryness under reduced pressure. The crude product did not require further purification (19.5 g, 119 mmol, 98 %). ^{1}H NMR (400 MHz, DMSO) δ 1.90 (br s, 2H, NH_2), 2.59 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.4 Hz, $^{3}J_{H\text{-}H}$ = 8.3 Hz, CH_2), 2.92 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.4 Hz, $^{3}J_{H\text{-}H}$ = 5.1 Hz, CH_2), 3.34 (dd, $^{3}J_{H\text{-}H}$ = 8.3 Hz, $^{3}J_{H\text{-}H}$ = 5.1 Hz, NCH), 6.96 (br s, 1H), 7.16-7.30 (m, 5H), 7.32 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 42.0, 57.1, 126.9, 128.9, 130.2, 139.8, 177.6.

(*R*)-2-Phenylpropane-1,2-diamine (147)



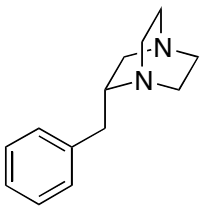
To a solution of $LiAlH_4$ (13.9 g, 365 mmol) in THF (250 ml) at 0 ^{o}C in a 1L flask was carefully added (*R*)-2-amino-3-phenylpropanamide (17.7 g, 108 mmol) and the reaction was heated at reflux for 8 hours before being cooled to 0 ^{o}C and quenched with 1 % KOH (dropwise addition). The reaction mixture was then filtered through a pad of celite and washed with THF. The solvent was evaporated under reduced pressure and the product purified by vacuum distillation (0.25 mmHg, 86-88 ^{o}C) to afford **147** as a colourless liquid (10.0 g, 55%). ^{1}H NMR (400 MHz, DMSO) δ 1.32 (br s, 4H, NH_2), 2.50 (ddd, 2H, $^{2}J_{H\text{-}H}$ = 19.7 Hz, $^{3}J_{H\text{-}H}$ = 8.3 Hz, $^{3}J_{H\text{-}H}$ = 7.7 Hz), 2.77 (ddd, 2H, $^{2}J_{H\text{-}H}$ = 12.6 Hz, $^{3}J_{H\text{-}H}$ = 6.7 Hz, $^{3}J_{H\text{-}H}$ = 4.2 Hz), 2.90-2.97 (m, 1H), 7.15-7.22 (m, 1H), 7.28 (tt, 2H, $^{3}J_{H\text{-}H}$ = 7.3 Hz, $^{4}J_{H\text{-}H}$ = 1.1 Hz, ArH), 7.28 (tt, 2H, $^{3}J_{H\text{-}H}$ = 7.3 Hz, $^{4}J_{H\text{-}H}$ = 1.1 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 42.3 (CH_2), 48.2 (CH_2), 55.1 (CH), 126.2 (ArC), 128.5 (ArC), 129.2 (ArC), 139.2 (C).

(*R*)-*N*,*N*'-(3-Phenylpropane-1,2-diyl)bis(2-chloroacetamide (178)



To a solution of (*R*)-2-Phenylpropane-1,2-diamine **147** (1.00 g, 6.67 mmol) in DCM (100 ml) at 0 °C was added triethylamine (4.65 ml, 33.4 mmol), DMAP (41 mg) and chloroacetal chloride (1.59 ml, 20.0 mmol) dropwise. The reaction was warmed to room temperature and stirred for 3 hours before quenching with $NaHCO_3$ (100 ml), stirred for 1 hour, extracted into DCM (2 x 100 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was redissolved in DCM (200 ml), washed with 2M HCl (2 x 100 ml), then water (100 ml), dried over $MgSO_4$ and evaporated under reduced pressure to afford the title compound as a brown solid (1.93 g, 6.40 mmol, 96 % yield). IR (v, cm^{-1}): 3055 (NH), 2987 (NH), 1673 (NC=O). ^1H NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, 1H, $^2J_{H-H}$ = 13.8 Hz, $^3J_{H-H}$ = 7.5 Hz, $PhCH_2$), 2.98 (dd, 1H, $^3J_{H-H}$ = 6.3 Hz, $PhCH_2$), 3.39-3.50 (m, 2H, $NHCH_2CH$), 4.01 (d, 2H, $^3J_{H-H}$ = 3.1 Hz, CH_2Cl), 4.05 (d, 2H, $^3J_{H-H}$ = 1.3 Hz, CH_2Cl), 4.27-4.35 (m, 1H, NCH), 6.98 (br s, 1H, NH), 7.00 (br s, 1H, NH), 7.22 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, ArH), 7.26 (t, 1H, $^3J_{H-H}$ = 7.2 Hz), 7.33 (t, 2H, $^3J_{H-H}$ = 7.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 38.4 (CH_2), 42.4 (CH_2Cl), 42.5 (CH_2), 43.3 (CH_2), 51.7 (CH), 127.1 (ArC), 128.9 (ArC), 129.1 (ArC), 136.4 (C), 166.7 (CO), 167.2 (CO); mp 144 °C; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}Cl_2N_2O_2$ $[M+Na]^+$ 325.0481, found 325.0474.

(*2R*)-2-Benzyl-1,4-diazabicyclo[2.2.2]octane (182)



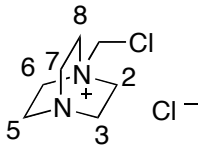
To a solution of (R)-*N*,*N*'-(3-phenylpropane-1,2-diyl)bis(2-chloroacetamide) **178** (200 mg, 0.66

mmol) in THF (5 ml) at 0 ^{o}C was added BH_3.THF (1M, 2.64 ml, 2.64 mmol). The reaction was heated at reflux overnight before being cooled to room temperature and quenched with methanol. After 30 minutes the solution was concentrated *in vacuo*. This intermediate (100 mg, 0.42 mmol) was heated to reflux in DMF (5 ml) and stirred overnight before being cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in 1M NaOH (5 ml), extracted into chloroform (3 x 15 ml), dried over $MgSO_4$ and evaporated. Purification by flash chromatography (SiO_2, 1:9 MeOH/$CHCl_3$) afforded product **182** as a yellow oil (34 mg, 0.17 mmol, 36 % yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (ddd, 1H, $^{2}J_{H-H}$ = 13.1 Hz, $^{3}J_{H-H}$ = 6.7 Hz, $^{3}J_{H-H}$ = 1.9 Hz), 2.64-2.81 (m, 6H), 2.81-2.86 (m, 1H), 2.86 (dd, 1H, $^{3}J_{H-H}$ = 8.9 Hz, $^{3}J_{H-H}$ = 1.9 Hz), 2.90 (td, 1H, $^{3}J_{H-H}$ = 9.2 Hz, $^{3}J_{H-H}$ = 1.8 Hz), 2.92-2.98 (m, 1H), 2.98-3.04 (m, 1H), 3.07-3.14 (m, 1H), 7.19-7.23 (m, 3H, ArH), 7.27-7.32 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.8, 40.9, 46.1, 47.3, 49.8, 53.8, 56.3, 126.3 (ArC), 128.5 (4 × ArC), 128.9 (4 × ArC), 138.8 (C); HRMS (ESI): *m/z* calcd for $C_{13}H_{19}N_2$ $[M+H]^+$ 203.1544, found 203.1543.

5.3 Experimental data for Chapter 3

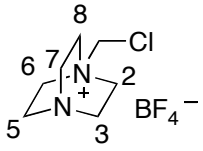
5.3.1 Quaternization Reaction

1-Chloromethyl-4-aza-1-azoniabicylo[2.2.2]octane chloride (12)



1,4-Diazabicyclo[2.2.2]octane **11** (0.50 g, 4.46 mmol) was solubilised in CH_2Cl_2 and acetone (5 mL, 1:1) and the mixture was left to stand, without stirring under an atmosphere of argon for 48 hours at room temperature. The resulting white precipitate formed was filtered and washed with acetone (2 × 10 mL) to afford **12** as a white solid (0.60 g, 68%); IR (ν, KBr/cm^{-1}): 1107, 723; ^{1}H NMR (500 MHz, D_2O) δ: 3.25 (t, 6H, $^3J_{H\text{-}H}$ = 7.6 Hz, H3, H5, H7), 3.55 (t, 6H, $^3J_{H\text{-}H}$ = 7.6 Hz, H2, H6, H8), 5.12 (s, 2H, CH_2Cl); ^{13}C NMR (125.8 MHz, D_2O) δ 44.3 (C3, C5, C7), 51.6 (C2, C6, C8), 68.6 (CH_2Cl); mp 145-147 °C; Anal. Calcd for $C_7H_{14}Cl_2N_2$: C, 42.65; H, 7.16; N, 14.21. Found: C, 42.53; H, 7.22; N, 14.13; HRMS (FI): *m/z* calcd for $C_7H_{14}Cl_2N_2$ $[M]^+$ 197.1108, found 197.1109.

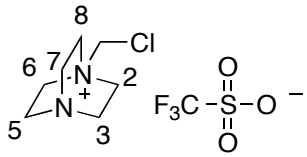
1-Chloromethyl-4-aza-1-azoniabicylo[2.2.2]octane tetrafluoroborate (13)



To a solution of 1-chloromethyl-4-aza-1-azoniabicylo[2.2.2]octane chloride **12** (0.55 g, 2.79 mmol) in anhydrous CH_3CN (5 mL), sodium tetrafluoroborate (0.31 g, 2.79 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature and filtered to remove sodium chloride formed. The precipitate was washed with anhydrous acetonitrile (3 × 10 mL). The combined filtrates were concentrated under reduced pressure to afford **13** as a white solid (0.64 g, 92%). IR (ν, KBr/cm^{-1}): 1115, 1023, 805; ^{1}H NMR (500 MHz, D_2O) δ 3.28 (t, 6H, $^3J_{H\text{-}H}$

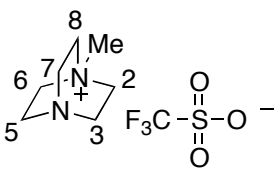
= 7.6 Hz, H3, H5, H7), 3.57 (t, 6H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, H2, H6, H8), 5.13 (s, 2H, CH_2Cl); ^{13}C NMR (125.8 MHz, D_2O) δ 44.3 (C3, C5, C7), 51.6 (C2, C6, C8), 68.6 (CH_2Cl); ^{19}F{^{1}H} NMR (470.4 MHz, D_2O) δ -151.0 (s, BF_4); mp 131-133 °C; Anal. Calcd for $C_7H_{14}BClF_4N_2$: C, 33.84; H, 5.68; N, 11.27. Found: C, 33.65; H, 5.52; N, 11.06; HRMS (FI): *m/z* calcd for $C_7H_{14}BClF_4N_2$ $[M]^+$ 248.4571, found 248.4576

1-Chloromethyl-4-aza-1-azoniabicylo[2.2.2]octane triflate (193)



To a solution of 1-chloromethyl-4-aza-1-azoniabicylo[2.2.2]octane chloride (0.55 g, 2.79 mmol) in anhydrous CH_3CN (5 mL), sodium triflate (0.48 g, 2.79 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature and filtered to remove sodium chloride formed. The precipitate was washed with anhydrous acetonitrile (3 × 10 mL). The combined filtrates were concentrated under reduced pressure to afford **193** as a white solid (0.73 g, 83%). IR (ν, KBr/cm^{-1}): 1470, 1288, 1152, 688; ^{1}H NMR (500 MHz, CD_3CN) δ 3.15 (t, 6H, $^{3}J_{H\text{-}H}$ = 7.5 Hz, H3, H5, H7), 3.35 (t, 6H, $^{3}J_{H\text{-}H}$ = 7.5 Hz, H2, H6, H8), 4.96 (s, 2H, CH_2Cl); ^{13}C NMR (125.8 MHz, CD_3CN) δ 45.4 (C3, C5, C7), 52.3 (C2, C6, C8), 69.2 (CH_2Cl), 122.1 (q, $^{1}J_{C\text{-}F}$ = 321.2, CF_3); ^{19}F{^{1}H} NMR (470.4 MHz, CD_3CN) δ -79.3 (s, $SO_3CF_3^-$); mp 155-156 °C; Anal. Calcd for $C_8H_{14}ClF_3N_2O_3S$: C, 30.92; H, 4.54; N, 9.02. Found: C, 30.65; H, 4.52; N, 8.68.

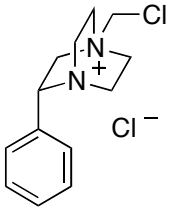
1-Methyl-4-aza-1-azoniabicylo[2.2.2]octane trifluoromethanesulfonate (202)



To a solution of 1,4-diazabicyclo[2.2.2]octane **11** (0.57 g, 5.08 mmol) in Et_2O (67 mL), methyl trifluoromethanesulfonate (0.73 g, 4.42 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C, then for 2 hours at room temperature and the resulting white

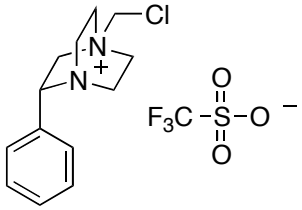
precipitate was filtered and washed with acetone (2 × 10 mL) to afford **202** as a white solid (1.34 g, 95%); IR (ν, KBr/cm^{-1}): 1469, 1315, 1272, 1153, 1030, 911; ^{1}H NMR (500 MHz, D_2O) δ 3.03 (s, 3H, CH_3), 3.19 (t, 6H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, H3, H5, H7), 3.38 (t, 6H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, H2, H6, H8); ^{13}C NMR (125.8 MHz, D_2O) δ: 44.6 (OCH_3), 51.9 (C3, C5, C7), 54.3 (C2, C6, C8), 122.2 (q, $^{1}J_{C\text{-}F}$ = 321.2, CF_3); ^{19}F {^{1}H}NMR (470.4 MHz, D_2O) δ: -79.3(s, $SO_3CF_3^-$); mp 214-216 °C; HRMS (FI): *m/z* calcd for $C_8H_{15}F_3N_2O_3S$ $[M]^+$ 276.0765, found 276.0755.

(3*R*)-1-(Chloromethyl)-3-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (194)



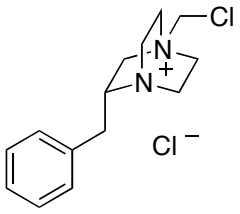
(*R*)-2-Phenyl-1,4-diazabicyclo[2.2.2]octane **181** (60 mg, 0.32 mmol) was dissolved in DCM (0.7 ml) and acetone (0.7 mL) and stirred under argon for 120 hours. The precipitate was filtered and washed with cold dichloromethane and diethyl ether affording (3*R*)-1-(chloromethyl)-3-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride **194** (62 mg, 72%). IR (neat) (ν, cm^{-1}) 2957, 1658, 1097; ^{1}H NMR (500 MHz, CD_3CN) δ 2.94-3.01 (m, 1H, CH_2), 3.04-3.09 (m, 1H, CH_2), 3.35 (dt, 1H, $^{2}J_{H\text{-}H}$ = 13.5, $^{3}J_{H\text{-}H}$ = 8.8 Hz, CH_2), 3.43-3.55 (m, 2H, CH_2), 3.62-3.67 (m, 3H, CH_2), 3.87 (t, 1H, $^{3}J_{H\text{-}H}$ = 10.4 Hz, NCH_2CH(Ph)), 4.20 (ddd, 1H, $^{2}J_{H\text{-}H}$ = 12.3, $^{3}J_{H\text{-}H}$ = 9.5, $^{3}J_{H\text{-}H}$ = 3.0 Hz, 1H, NCH_2CH(Ph)), 4.51 (t, 1H, $^{3}J_{H\text{-}H}$ = 9.0 Hz, NCH_2CH(Ph)), 5.53 (d, 1H, $^{2}J_{H\text{-}H}$ = 9.6 Hz, CH_2Cl), 5.60 (d, 1H, $^{2}J_{H\text{-}H}$ = 9.6 Hz, CH_2Cl), 7.35 (t, 1H, $^{3}J_{H\text{-}H}$ = 7.3 Hz, ArH), 7.41-7.47 (m, 4H, ArH); ^{13}C NMR (125.8 MHz, CD_3CN) δ 40.6 (CH_2), 46.8 (CH_2), 51.7 (CH_2), 52.6 (CH_2), 56.4 (NCH_2CH(Ph)), 56.7 (NCH_2CH(Ph)), 68.9 (CH_2Cl), 127.9 (Ar*C*), 127.9 (Ar*C*), 129.0 (Ar*C*), 129.7 (Ar*C*), 129.7 (Ar*C*), 138.8 (C); mp 147-148 ºC; $[\alpha]^{22}_{D}$ -17 (*c* 0.57, MeOH); Anal. Calcd for $C_{13}H_{18}Cl_2N_2$: C, 57.15; H, 6.64; N, 10.25. Found: C, 56.93; H, 6.75; N, 10.14; HRMS (FI): *m/z* calcd for $C_{13}H_{18}ClN_2$ ($[M]^+$): 237.1153, found 237.1157.

(3*R*)-1-(Chloromethyl)-3-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (196)



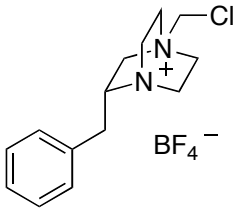
A solution of (3*R*)-1-(chloromethyl)-3-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride **194** (200 mg, 0.84 mmol) and sodium trifluoromethanesulfonate (145 mg, 0.84 mmol) in acetonitrile (12 mL) was stirred for 46 hours at room temperature. The solvent was concentrated under reduced pressure, 3 mL of dry acetonitrile was added and the suspension was filtered. The solid was rinsed twice with acetonitrile (2 x 5 mL) and the filtrate was concentrated under reduced pressure to afford **196** as a solid (282 mg, 99%). IR (neat) (ν, cm^{-1}) 1249, 1156, 1028; ^{1}H NMR (400 MHz, CD_3CN) δ 2.95-3.04 (m, 1H, CH_2), 3.07-3.14 (m, 1H, CH_2), 3.27-3.39 (m, 3H, CH_2), 3.40-3.51 (m, 4H, CH_2), 4.05 (ddd, 1H, $^{2}J_{H-H}$ = 12.1, $^{3}J_{H-H}$ = 9.5, $^{3}J_{H-H}$ = 2.7 Hz, NCH_2CH(Ph)), 4.50 (t, 1H, $^{3}J_{H-H}$ = 9.0 Hz, NCH_2CH(Ph)), 5.03 (d, 1H, $^{2}J_{H-H}$ = 10.0 Hz, CH_2Cl), 5.07 (d, 1H, $^{2}J_{H-H}$ = 10.0 Hz, CH_2Cl), 7.34-7.46 (m, 5H); ^{13}C NMR (125.8 MHz, CD_3CN) δ 40.6 (CH_2), 46.7 (CH_2), 52.1 (CH_2), 53.1 (CH_2), 56.4 (NCH_2CH(Ph)), 57.1 (NCH_2CH(Ph)), 69.3 (CH_2Cl), 121.5 (q, $^{1}J_{C-F}$ = 320, CF_3), 127.6 (Ar*C*), 127.6 (Ar*C*), 129.1 (Ar*C*), 129.8 (Ar*C*), 129.8 (Ar*C*), 138.6 (C); ^{19}F {^{1}H} NMR (376.6 MHz, CD_3CN) δ -79.3 (s, $SO_3CF_3^-$); mp 60-63 ºC; $[\alpha]^{22}_{D}$ -11 (*c* 0.94, MeOH); HRMS (FI): *m/z* calcd for $C_{13}H_{18}ClN_2$ ($[M]^+$): 237.1153, found 237.1150; MS-EI$^-$ *m/z* 148.94 (OTf).

(*R*)-3-Benzyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane chloride (195)



(*R*)-2-Benzyl-1,4-diazabicyclo[2.2.2]octane **182** (300 mg, 1.48 mmol) was dissolved in DCM (5 ml) and left under argon, without stirring, for 120 hours. Removal of the solvent under reduced pressure afforded the product as a solid (426 mg, 99%). ^{1}H NMR (400 MHz, MeOD) δ 2.91 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.8 Hz, 7.8 Hz), 3.03 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.8 Hz, $^{3}J_{H\text{-}H}$ = 7.1 Hz), 3.15-3.22 (m, 2H), 3.29 (t, 2H, $^{3}J_{H\text{-}H}$ = 7.8 Hz), 3.40-3.66 (m, 7H), 5.18 (d, 1H, $^{2}J_{H\text{-}H}$ = 9.9 Hz, CH_2Cl), 5.23 (d, 1H, $^{2}J_{H\text{-}H}$ = 9.9 Hz, CH_2Cl), 7.22-7.28 (m, 1H, ArH), 7.29-7.35 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.6 (CH_2), 39.3 (CH_2), 46.6 (CH_2), 50.9 (CH_2), 51.9 (CH_2), 55.6 (CH), 56.9 (CH_2), 68.1 (CH_2Cl), 126.9 (ArC), 128.7 (2 × ArC), 129.2 (2 × ArC), 137.1 (C); HRMS (ESI): *m/z* calcd for $[C_{14}H_{20}ClN_2]^+$ $(M)^+$: 251.1306, found 251.1310.

(*R*)-3-Benzyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate (197)



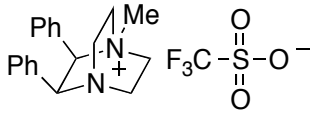
To a solution of (*R*)-3-benzyl-1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane chloride **195** (200 mg, 0.70 mmol) in acetonitrile (5 ml) at room temperature was added lithium tetrafluoroborate (65 mg, 0.70 mmol) and the reaction was stirred for 24 hours before filtering and concentrating in vacuo. Recrystallising twice from methanol/ether afforded the title compound as a grey solid (237 mg, 0.70 mmol, 99 % yield). ^{1}H NMR (400 MHz, MeOD) δ 2.90 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.9 Hz, $^{3}J_{H\text{-}H}$ = 7.9 Hz), 3.02 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.9 Hz, $^{3}J_{H\text{-}H}$ = 7.2 Hz), 3.13-3.21 (m, 2H), 3.28 (t, 2H, $^{3}J_{H\text{-}H}$ = 7.6 Hz), 3.39-3.65 (m, 7H), 4.86 (s, 2H), 5.12 (d, 1H, $^{2}J_{H\text{-}}$

$_H$ = 9.9 Hz), 5.17 (d, 1H, $^2J_{H\text{-}H}$ = 9.9 Hz), 7.21-7.27 (m, 1H, ArH), 7.28-7.34 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.6, 39.3, 46.6, 50.8, 51.9, 55.5, 56.9, 68.0, 126.9, 128.7, 129.2, 137.1; ^{19}F {^{1}H} NMR (376.6 MHz, $CDCl_3$) δ -153.7 (BF_4^-); mp 250 °C, $[\alpha]^{22}_D$ +53.9 (*c* 0.55, MeOH) HRMS (ESI): *m/z* calcd for $C_{14}H_{20}ClN_2$ $(M)^+$: 251.1306, found 251.1310.

General Procedure 1.1: *N*-Methylation of Chiral Disubstituted DABCO Derivatives

To a solution of disubstituted-1,4-diazabicyclo[2.2.2]octane (1 eq) in Et_2O (0.02 M), methyl trifluoromethanesulfonate (1 eq) was added dropwise at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C. The resulting white precipitate was filtered and washed with acetone (2 × 10 mL) to afford a white solid.

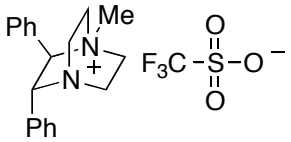
(±)-1-Methyl-2,3-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (203)



(±)-1-Methyl-2,3-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoro methanesulfonate **203** was obtained according to procedure 1.1 (150 mg, 98%); IR (ν, KBr/cm^{-1}): 1469, 1272, 1153, 1030, 992; ^{1}H NMR (500 MHz, CD_3CN) δ 2.72 (s, 3H, C*H*$_3$), 3.16-3.24 (m, 2H, C*H*$_2$), 3.37-3.51 (m, 3H, C*H*$_2$), 3.60 (ddd, 1H, $^2J_{H\text{-}H}$ = 12.4 Hz, $^3J_{H\text{-}H}$ = 9.4 Hz, $^3J_{H\text{-}H}$ = 3.2 Hz, C*H*$_2$), 3.67-3.79 (m, 2H, C*H*$_2$), 5.08 (d, 1H, $^3J_{H\text{-}H}$ = 10.6 Hz, C*H*), 5.21 (d, 1H, $^3J_{H\text{-}H}$ = 10.6 Hz, C*H*), 6.70 (d, 1H, $^3J_{H\text{-}H}$ = 7.5 Hz, ArH), 6.96 (t, 2H, $^3J_{H\text{-}H}$ = 7.3 Hz, ArH), 7.04 (t, 1H, $^3J_{H\text{-}H}$ = 7.3 Hz, ArH), 7.08-7.12 (m, 3H), 7.36 (t, 1H, $^3J_{H\text{-}H}$ = 7.4 Hz, ArH), 7.46 (t, 1H, $^3J_{H\text{-}H}$ = 7.0 Hz, ArH), 7.54 (d, 1H, $^3J_{H\text{-}H}$ = 6.7 Hz, ArH); ^{13}C NMR (125.8 MHz, CD_3CN) δ: 42.6 (CH_2), 48.3 (CH_2), 49.3 (CH_2), 51.2 (CH_3), 58.3 (CH_2), 60.7 (CH), 74.4 (CH), 120.8 (q, $^1J_{C\text{-}F}$ = 320 Hz, CF_3), 127.4 (ArC), 128.2 (ArC), 128.6 (ArC), 129.0 (ArH), 129.3 (ArC), 130.2 (ArC), 131.0 (C), 131.2 (ArC),

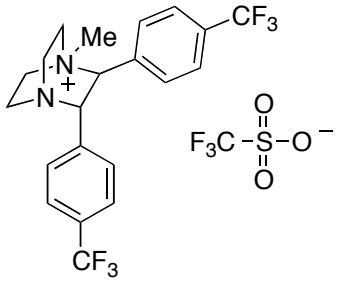
136.8 (ArC), 137.6 (C); mp 178-180 °C; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3 (TfO); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_2$ $[M]^+$ 279.1856, found 279.1855.

(2*R*,3*R*)-1-Methyl-2,3-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (204)



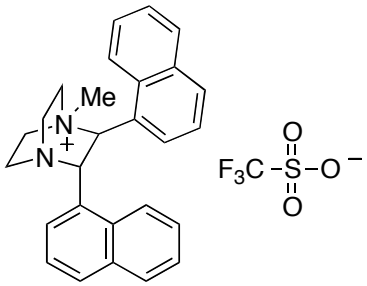
(2*R*,3*R*)-1-Methyl-2,3-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoro methanesulfonate **204** was obtained according to procedure 1.1 (800 mg, 97%); IR (ν, KBr/cm^{-1}): 1469, 1272, 1153, 1030, 992, 708; ^{1}H NMR (500 MHz, CD_3CN) δ: 2.60 (s, 3H, C*H*$_3$), 3.10-3.18 (m, 3H, C*H*$_2$), 3.39-3.48 (m, 2H, C*H*$_2$), 3.52-3.57 (m, 2H, C*H*$_2$), 3.75 (t, 1H, $^{2}J_{H\text{-}H}$ = 11.3 Hz, C*H*$_2$), 4.75 (d, 1H, $^{3}J_{H\text{-}H}$ = 9.6 Hz, NC*H*), 4.81 (d, 1H, $^{3}J_{H\text{-}H}$ = 9.6 Hz, NC*H*), 7.29-7.37 (m, 5H, ArH), 7.56-7.59 (m, 3H, ArH), 7.78 (dd, 2H, $^{3}J_{H\text{-}H}$ = 7.4 Hz, $^{4}J_{H\text{-}H}$ = 1.8 Hz, ArH); ^{13}C NMR (125.8 MHz, CD_3CN) δ 40.8 (CH_2), 47.1 (CH_2), 50.0 (CH_3), 50.7 (CH_2), 58.4 (CH_2), 63.4 (CH), 72.6 (CH), 120.8 (q, $^{1}J_{C\text{-}F}$ = 320 Hz, CF_3), 128.1 (ArC), 129.2 (ArC), 129.7 (ArC), 130.9 (ArC), 131.4 (C), 132.3 (ArC), 137. 8 (C); mp 197-199 °C; $[\alpha]^{22}_D$ -85.7 (*c* 0.27, MeOH); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3 (TfO). HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_2$ $[M]^+$ 279.1856, found 279.1853.

(2*S*,3*S*)-2,3-Bis(4-(trifluoromethyl)phenyl)-1-methyl-4-aza-azoniabicyclo[2.2.2]octane triflate (205)



(2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)phenyl)-1-methyl-4-aza-azoniabicyclo[2.2.2]octane triflate **205** was obtained according to procedure 1.1 (143 mg, 92%). IR (ν, cm^{-1}): 3095, 2955; ^{1}H NMR (400 MHz, CD_3CN) δ 2.92 (s, 3H, CH_3), 3.94-3.99 (m, 2H, CH_2), 4.14-416 (m, 2H, CH_2), 4.23-4.25 (m, 2H, CH_2) 4.54-4.59 (m, 2H, CH_2), 5.75 (s, 2H, CH), 7.84 (d, 4H, $^{3}J_{H-H}$ = 8.1 Hz, ArH), 8.03 (d, 4H, $^{3}J_{H-H}$ = 8.1 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 49.6 (CH), 50.4 (CH_3), 56.0 (CH_2), 121.3 (q, $^{1}J_{C-F}$ = 341.4 Hz, CF_3), 124.6 (ArC), 127.2 (q, $^{3}J_{C-F}$ = 3.6 Hz, C), 129.3 (ArC), 133.7 (q, $^{2}J_{C-F}$ = 33.1, C), 140.4 (C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -62.5 (CF_3), -79.3 (TfO); $[\alpha]^{22}_{D}$ +48.6; mp 182-83 °C; Anal. Calcd for $C_{22}H_{21}F_9N_2O_3S$: C, 46.81; H, 3.75; N, 4.96. Found: C, 46.74; H, 3.70; N, 4.61.

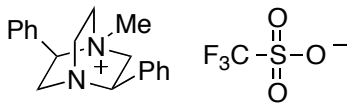
(2*S*,3*S*)-2,3-Di(naphthalen-1-yl)-1-methyl-4-aza-1-azoniabicyclo[2.2.2] octane (206)



(2*S*,3*S*)-2,3-di(naphthalen-1-yl)-1-methyl-4-aza-1-azoniabicyclo[2.2.2] octane salt **206** was obtained according to procedure 1.1 (150 mg, 95%); IR (ν, cm^{-1}): 2932, 2868, 2360; ^{1}H NMR (400 MHz, CD_3CN) δ 2.84 (s, 3H, CH_3), 3.90-3.94 (m, 2H, CH_2), 4.03-4.09 (m, 2H, CH_2), 4.13-4.16 (m, 1H, CH_2), 4.36-4.38 (m, 1H, CH_2), 4.53-4.58 (m, 1H, CH_2), 4.85 (t, 1H, $^{2}J_{H-H}$ = 11.5 Hz, CH_2) 6.30 (d, 2H, $^{3}J_{H-H}$ = 10.3 Hz, CH), 7.93 (d, 2H, $^{3}J_{H-H}$ = 8.3 Hz, Ar*H*) 8.02-80.7 (m,

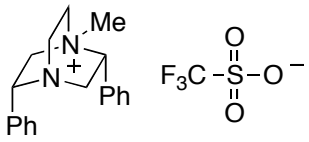
2H), 8.29-8.31 (m, 2H, Ar*H*), 8.34-8.36 (m, 2H, Ar*H*), 8.42-8.54 (m, 2H, ArH), 8.57-8.59 (m, 2H, Ar*H*), 8.78 (d, 2H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 50.2 (CH_3), 56.9 (CH_2), 61.4 (CH_2), 66.6 (CH), 122.1 (q, $^{1}J_{C\text{-}F}$ = 320.1 Hz, CF_3), 125.8 (ArC), 127.7 (ArC), 128.4 (ArC), 128.7 (ArC), 129.5 (ArC), 130.2 (ArC), 133.0 (C), 134.2 (C), 134.5 (C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3 (TfO); mp 210-212 °C; $[\alpha]^{22}_{D}$ = +303.6 (c 0.52, MeOH); HRMS (ESI): *m/z* calcd for $C_{27}H_{27}N_2$ $[M]^+$: 379.2169, found 379.2165

(1*S*,2*R*,4*S*,5*R*)-1-Methyl-2,5-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (207)



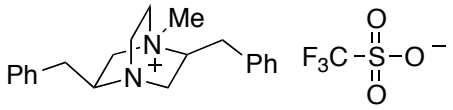
(1*S*,2*R*,4*S*,5*R*)-1-methyl-2,5-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate **207** was obtained according to procedure 1.1 (139 mg, 98%); IR (ν, cm^{-1}): 2930, 1495, 1445, 1060, 800, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H, CH_3), 3.29 (dd, 1H, $^{2}J_{H\text{-}H}$ = 14.6, $^{3}J_{H\text{-}H}$ = 9.3 Hz, CH_2), 3.40-3.46 (m, 2H, CH_2), 3.52-3.54 (m, 3H, CH_2), 3.58-3.67 (m, 1H, CH_2), 3.74-3.79 (m, 1H). 4.55-4.59 (m, 2H, NCH), 7.23-7.31 (m, 2H, ArH), 7.40-7.42 (m, 2H, ArH), 7.45-7.49 (m, 2H), 7.50-7.58 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 46.8 (CH_2), 47.6 (CH_2), 49.8 (CH_3), 56.0 (CH), 57.9 (CH_2), 68.7 (CH_2), 123.0 (q, $^{1}J_{C\text{-}F}$ = 320.1 Hz, CF_3), 127.1 (2 × ArC), 129.0 (4 × ArC), 130.3 (4 × ArC), 132.1 (2 × C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3 (TfO); mp 105-107 °C; $[\alpha]^{22}_{D}$ = -55.2 (c 0.55, MeOH); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_2$ $[M]^+$: 279.1856, found 279.1853.

(1*R*,2*R*,4*R*,5*R*)-1-Methyl-2,5-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (208)



(1*S*,2*R*,4*S*,5*R*)-1-methyl-2,5-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate **208** was obtained according to procedure 1.1 (98 mg, 89%): IR (ν, cm^{-1}): 2880, 1600, 1490, 1175, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 3H, CH_3), 4.04 (s, 4H, CH_2), 4.47 (d, 4H, $^{3}J_{H\text{-}H}$ = 9.9 Hz, CH_2), 5.44 (t, 2H, $^{3}J_{H\text{-}H}$ = 9.6 Hz, CH_2), 7.65-7.69 (m, 4H, ArH), 7.71-7.75 (m, 2H), 7.82 (d, 4H, $^{3}J_{H\text{-}H}$ = 9.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 49.9 (CH_2), 50.6 (CH_3), 60.4 (CH_2), 67.5 (CH), 123.0 (q, $^{1}J_{C\text{-}F}$ = 320.1 Hz, CF_3), 126.8 (2 × ArC), 131.1 (4 × ArC), 132.5 (4 × ArC), 133.7 (2 × C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3 (TfO); mp 109-110 °C; $[\alpha]^{22}_{D}$ = -39.7 (c 0.50, MeOH); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_2$ $[M]^+$: 279.1856, found 279.1858.

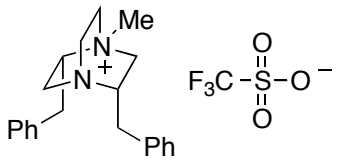
(1*R*,2*S*,4*R*,5*S*)-2,5-Dibenzyl-1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate (209)



(1*R*,2*S*,4*R*,5*S*)-2,5-dibenzyl-1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate salt **209** was obtained according to procedure 1.1 (57 mg, 97%); IR (ν, neat/cm^{-1}): 3060 (C-H), 2965 (C-H), 2809, 1460 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01-3.04 (m, 2H, CH_2), 3.16 (s, 3H, CH_3), 3.43-3.47 (m, 2H), 3.51-3.56 (m, 2H), 3.72-3.84 (m, 4H, CH_2), 4.07-4.11 (m, 2H), 4.36 (d, 2H, *J* = 9.3 Hz), 7.34-7.39 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 32.5 (2 × CH_2), 50.1 (2 × CH_2), 50. 6 (CH_3), 61.1 (2 × CH_2), 63.0 (CH), 122.0 (q, $^{1}J_{C\text{-}F}$ = 320.1 Hz, CF_3), 129.1 (2 × Ar*C*), 130.2 (4 × Ar*C*) 130.5 (4 × Ar*C*), 132.5 (2 × *C*); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3

(TfO); $[\alpha]^{22}_D$ = +57.2 (c 0.55 MeOH); HRMS (ESI): *m/z* calcd for $C_{21}H_{27}N_2$ $[M]^+$ 307.2169, found 307.2165.

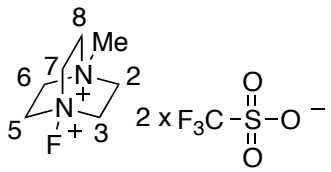
(1*S*,2*S*,4*S*,5*S*)-2,5-Dibenzyl-1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate (210)



(1*S*,2*S*,4*S*,5*S*)-2,5-dibenzyl-1-methyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate **210** was obtained according to procedure 1.1 (52 mg, 98%); IR (ν, neat/cm^{-1}): 3055 (C-H), 2960 (C-H), 2812 (C-H), 1465 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.15 (s, CH_3), 3.45-2.49 (m, 5H), 3.63-3.68 (m, 3H), 3.96 (s, 4H), 4.39-4.43 (m, 2H), 7.38-7.48 (m, 10H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.7 (2 × *C*H_2), 49.8 (CH_3), 54.8 (2 × CH_2), 55.3 (2 × *C*H_2), 63.8 (2 × N*C*H), 123.0 (q, $^1J_{C\text{-}F}$ = 320.1 Hz, CF_3), 128.6 (2 × Ar*C*) 129.6 (4 × Ar*C*), 130.0 (4 × Ar*C*), 132.1 (2 × C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -79.3 (TfO); mp 69-65 °C; $[\alpha]^{22}_D$ = +91.2 (c 0.56, MeOH); HRMS (ESI): *m/z* calcd for $C_{21}H_{27}N_2$ $[M]^+$ 307.2169, found 307.2165.

5.3.2 Fluorination

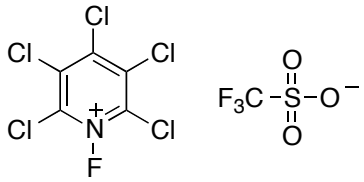
1-Fluoro-4-methyl-1,4-diazoniabicylo[2.2.2]octane bis(trifluoromethanesulfonate) (19)



To a solution of 1-methyl-4-aza-1-azoniabicylo[2.2.2]octane trifluoro- methanesulfonate (0.10 g, 0.36 mmol) and sodium trifluoromethane- sulfonate (0.06 g, 0.36 mmol) in acetonitrile (6 mL), a homogeneous 1:9 (v/v) mixture of F_2 (0.013 g, 0.36 mmol) and N_2 was passed at a rate of 15 mL/min at -35 ^{o}C for 5½ minutes. The solution was filtered to remove sodium fluoride and concentrated under reduced pressure. The crude product was recrystallised in a mixture of

ether/methanol (4:1) to afford **19** as a white solid (0.15 g, 90%), IR (ν, KBr/cm^{-1}): 1524, 1264, 1170, 1035, 914, 639; ^{1}H NMR (500 MHz, CD_3CN) δ 3.34 (s, 3H, OCH_3), 4.26 (t, J = 7.4 Hz, 6H, H2, H6, H8), 4.71 (q, J = 7.5 Hz, 6H, H3, H5, H7); ^{13}C NMR (125.8 MHz, CD_3CN) δ 53.3 (OCH_3), 57.5 (C2, C6, C8), 54.3 (C3, C5, C7), 120.3 (q, $^{1}J_{C\text{-}F}$ = 321 Hz, CF_3); ^{19}F {^{1}H} NMR (470.4 MHz, CD_3CN) δ +46.5 (s, ^{+}NF), -79.7 (s, $CF_3SO_3^-$); HRMS: *m/z* calcd for $C_7H_{15}FN_2$ $[M]^+$ 146.1208, found 146.1205.

N-F Pentachloropyridinium Triflate (221)



Pentachloropyridine (10 g, 39.79 mmol) and triflic acid (5.0 mL, 56.90 mmol) were mixed in trifluoroacetic acid (160 mL). The mixture was purge with nitrogen for 20 min and cooled in ice water. 10% F_2/N_2 (3 eq) was pass through the mixture at a rate of 30 mL/min at 5 ^{o}C for 15 hours. After the reaction, the mixture was purged with nitrogen for 30 min, and the solvent was removed under reduced pressure. 50 mL of dry diethyl ether (Et_2O) was slowly added to the oily residue. The resulting white precipitate formed was collected by filtration and washed with dry ethyl acetate (15 mL) to afford N-F pentachloropyridinium triflate **221**,^{13}C NMR (125.8 MHz, CD_3CN) δ 135.4 (C), 142.0 (C), 156 (C), ^{19}F {^{1}H} NMR (376.6 MHz, CD_3CN) δ +46.5 (^{+}NF), -79.3 ($SO_3CF_3^-$); mp 123-124 °C; Anal. Calcd for $C_6Cl_5F_4NO_3S$: C, 17.18; N, 3.34. Found: C, 17.07; N, 3.41.

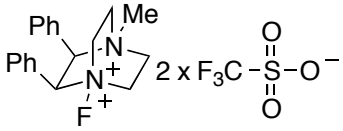
General Procedure 1.2: Formation of N-F reagents Using F_2 gas

A solution of substituted-4-aza-1-azoniabicylo[2.2.2]octane salt (1 eq) and sodium trifluoromethanesulfonate (1 eq) in acetonitrile (0.02 M) was placed in a small PTFE reactor. The mixture was purged with N_2 and cooled to -35 °C. Elemental F_2 as a homogeneous 1:9 (v/v) mixture with N_2 was introduced at a flow rate of 15 mL/min into the rapidly stirred mixture via PTFE tubing at -35 ^{o}C. The reaction was monitored by ^{19}F NMR. The mixture was allowed to warm to room temperature, before filtration to remove sodium fluoride, and the solution was concentrated under reduced pressure. Purification by recrsytallisation (Et_2O/MeOH 4:1) afforded the desired product.

General Procedure 1.3: Formation of N-F reagents Using N-F Pentachloropyridinium Triflate

To a solution of N-F pentachloropyridinium triflate **221** (1 eq) in acetonitrile (0.02 M) was added substituted-4-aza-1-azoniabicylo[2.2.2]octane salt (1 eq) at room temperature. The reaction was monitored by ^{19}F NMR. After completion, the solution was concentrated under reduced pressure. Purification by trituration with dichloromethane followed by recrystallisation (Et_2O/MeOH 4:1) afforded the desired product.

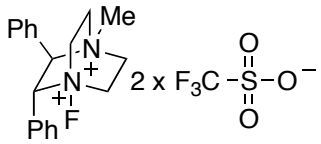
(±)-1-Fluoro-4-methyl-2,3-diphenyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) (211)



(±)-1-Fluoro-4-methyl-2,3-diphenyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) **211** (145 mg, 98%), IR (ν, KBr/cm^{-1}): 1421, 1256, 1140, 1030, 756; 623; ^{1}H NMR (500 MHz, CD_3CN) δ 3.14 (s, 3H, C*H*$_3$), 4.50-4.72 (m, 4H, C*H*$_2$), 5.09-5.13

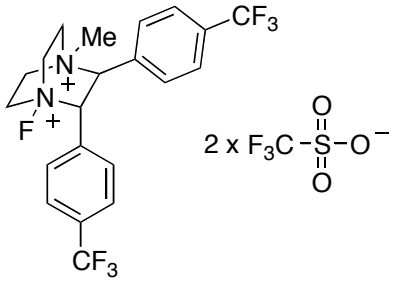
(m, 3H, CH_2), 3.72-3.75 (m, 1H, CH_2), 6.13 (d, J = 11.1 Hz, 1H, ArCH), 6.77 (d, J = 11.1 Hz, 1H, ArCH); 7.34-7.44 (m, 10H, ArH); ^{13}C NMR (125.8 MHz, CD_3CN) δ 52.4 (CH_3), 54.3 (CH_2), 56.1 (CH_2), 59.8 (CH_2), 61.8 (CH_2), 76.9 (CH), 77.3 (CH), 120.6 (q, $^1J_{C\text{-}F}$ = 320 Hz, CF_3), 130.2 (CH), 130.4 (CH), 130.7 (2 × CH), 132.0 (CH), 132.8 (C); mp 140-143 °C; ^{19}F{^{1}H} NMR (470.4 MHz, CD_3CN) δ +42.2 (s, $^+$NF), -79.7 (s, $CF_3SO_3^-$); HRMS: *m/z* calcd for $C_{19}H_{22}FN_2$ $[M]^+$ 297.1761 found 297.176.

(2*R*,3*R*)-1-Fluoro-4-methyl-2,3-diphenyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) (212)



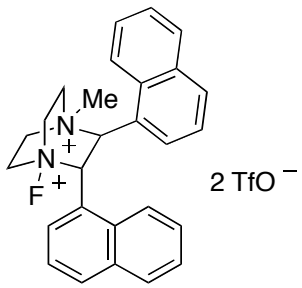
(2*R*,3*R*)-1-Fluoro-4-methyl-2,3-diphenyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) **212** (140 mg, 97%), IR (ν, KBr/cm^{-1}) 1469, 1279, 1153, 1032, 756, 640; ^{1}H NMR (500 MHz, CD_3CN) δ: 2.95 (s, 3H, CH_3), 4.24 (t, 1H, J = 11.9 Hz, CH_2), 4.42-4.49 (m, 1H, CH_2), 4.55 (dt, 1H, J = 11.8, 8.9 Hz, CH_2), 4.70-4.82 (m, 3H, CH_2), 5.02 (q, 1H, J = 9.9 Hz, CH_2), 5.30-5.37 (m, 1H, CH_2), 6.03 (d, 1H, J = 10.9 Hz, CH), 6.54 (d, 1H, J = 10.9 Hz, CH), 7.58-7.61 (m, 4H, ArH), 7.65-7.69 (m, 2H, ArH), 7.89-7.93 (m, 4H, ArH); ^{13}C NMR (125.8 MHz, CD_3CN) δ 50.9 (CH_3), 53.5 (CH_2), 53.6 (CH_2), 58.8 (CH_2), 59.9 (CH_2), 74.5 (CH), 77.8 (CH), 120.7 (q, $^1J_{C\text{-}F}$ = 320 Hz, CF_3), 131.4 (CH), 131.6 (CH), 132.8 (CH), 134.5 (CH), 134.8 (C); mp 174-176 °C; $[\alpha]^{22}_D$ -21.7 (*c* 1, MeOH); ^{19}F{^{1}H} NMR (470.4 MHz, CD_3CN) δ: +35.4 (s, NF^+), -79.7 (s, $CF_3SO_3^-$); Anal. Calcd for $C_{21}H_{23}F_7N_2O_6S_2$: C, 42.28; H, 3.89; N, 4.70. Found: C, 42.38; H, 4.01; N, 4.66; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}FN_2$ $[M]^+$ 297.1761 found 297.1762.

(2*S*,3*S*)-2,3-Bis(4-(trifluoromethyl)-phenyl)-1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2] octane bis(triflate) (213)



(2*S*,3*S*)-2,3-Bis(4-(trifluoromethyl)-phenyl)-1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2] octane bis(triflate) **213** (115 mg, 97%) IR (ν, cm^{-1}): 3095, 2955; ^{1}H NMR (400 MHz, CD_3CN) δ 3.03 (s, 3H, CH_3), 4.30-4.36 (m, 1H), 4.51 (d, 1H, J = 21.8 Hz), 4.61 (dd, 1H, J = 19.8 Hz, J = 10.3 Hz), 4.76-4.86 (m, 3H) 5.09 (q, 1H, J = 10.0 Hz), 5.41 (q, 1H, J = 11.4 Hz), 6.22 (d, 1H, J = 10.5 Hz), 6.71 (d, 1H, J = 10.7 Hz) 7.90 (m, 4H), 8.09-8.20 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 51.2 (CH), 54.02 (CH_3), 59.2 (d, J = 5.2 Hz), 60.2 (d, J = 15.3 Hz), 121.3 (q, $^{1}J_{C\text{-}F}$ = 341.4 Hz, CF_3), 124.6 (ArC), 127.2 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, C), 129.3 (ArC), 133.7 (q, $^{2}J_{C\text{-}F}$ = 33.1, C), 140.4 (C); ^{19}F $\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ +36.6 (NF), -62.5 (CF_3), -79.3 (TfO); mp 147-150 °C, $[\alpha]^{22}_{D}$ +74.5 (*c* 0.53, MeOH), Anal. Calcd for $C_{23}H_{21}F_{13}N_2O_6S_2$: C, 37.71; H, 2.89; N, 3.82. Found: C, 37.43; H, 2.76; N, 3.90.

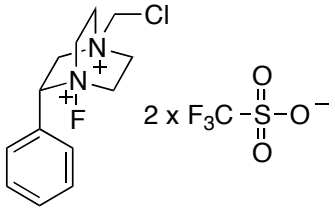
1-Fluoro-4-methyl-2,3-di(naphthalen-1-yl)-1,4-diazoniabicyclo[2.2.2] octane bis(triflate) (214)



1-Fluoro-4-methyl-2,3-di(naphthalen-1-yl)-1,4-diazoniabicyclo[2.2.2] octane bis(triflate) **214** was obtained according to procedure 1.1 (50 mg, 45%); IR (ν, cm^{-1}): 2932, 2868, 2360; ^{1}H NMR (400 MHz, CD_3CN) δ 2.94 (s, 3H, CH_3), 4.10-4.04 (m, 2H), 4.03-4.09 (m, 2H), 4.33-41 (m, 1H), 4.69-4-75 (m, 1H), 4.83-4.92 (m, 1H), 5.08-5.24 (m, 1H) 6.88 (d, 1H, $^{3}J_{H\text{-}H}$ = 11.0,

CH), 7.30 (d, 1H, $^{3}J_{H\text{-}H}$ = 11.0, CH), 7.93 (d, 2H, $^{3}J_{H\text{-}H}$ = 8.3 Hz, Ar*H*), 8.02-80.7 (m, 2H), 8.29-8.31 (m, 2H, Ar*H*), 8.34-8.36 (m, 2H, Ar*H*), 8.42-8.54 (m, 2H, ArH), 8.57-8.59 (m, 2H, Ar*H*), 8.78 (d, 2H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 55.1 (CH_3), 58.4 (CH_2), 63.4 (CH_2), 68.2 (CH), 122.1 (q, $^{1}J_{C\text{-}F}$ = 320.1 Hz, CF_3), 126.3 (ArC), 128.1 (ArC), 129.1 (ArC), 129.8 (ArC), 132.2 (ArC), 132.6 (ArC), 133.4 (C), 134.9 (C), 135.1 (C); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ +35.1 ($^{+}$NF), -79.3 (TfO^{-}); mp 210-212 °C; $[\alpha]^{22}_{D}$ = +303.6 (c 0.52, MeOH); HRMS (ESI): *m/z* calcd for $C_{27}H_{27}N_2$ $[M]^{+}$: 379.2169, found 379.2165

(3*R*)-4-(Chloromethyl)-1-fluoro-2-phenyl-4-aza-1-azoniabicyclo[2.2.2]octane bistrifluoromethanesulfonate (219)



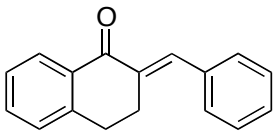
IR (neat) (ν, cm^{-1}) 1636, 1247, 1165, 1028; ^{1}H NMR (400 MHz, CD_3CN) δ 4.42-4.64 (m, 6H, CH_2), 4.66-4.76 (m, 2H, NC*H*$_2$CH(Ph)), 4.89-4.97 (m, 1H, CH_2), 5.07 (dd, 1H, $^{2}J_{H\text{-}H}$ = 10.9, $^{3}J_{H\text{-}H}$ = 10.6 Hz, CH_2), 5.46 (d, 1H, $^{2}J_{H\text{-}H}$ = 10.4 Hz, CH_2Cl), 5.51 (d, 1H, $^{2}J_{H\text{-}H}$ = 10.0 Hz, CH_2Cl), 6.22 (t, 1H, $^{3}J_{H\text{-}H}$ = 9.1 Hz, NCH$_2$C*H*(Ph)), 7.68 (t, 2H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, ArH), 7.76 (t, 1H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, ArH), 7.86 (d, 2H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, ArH); ^{13}C NMR (125.8 MHz, CD_3CN) δ 53.0 (d, $^{2}J_{C\text{-}F}$ = 15.3 Hz, CH_2), 54.5 (CH_2), 55.3 (CH_2), 58.1 (N*C*H$_2$CH(Ph)), 59.1 (d, $^{2}J_{H\text{-}H}$ = 16.2 Hz, CH_2), 70.3, 73.9 (d, $^{2}J_{C\text{-}F}$ = 16.1 Hz, NCH$_2$*C*H(Ph)), 121.50 (q, $^{1}J_{C\text{-}F}$ = 320 Hz, CF_3), 123.4 (Ar*C*), 131.2 (Ar*C*), 131.2 (Ar*C*), 133.1 (Ar*C*), 133.1 (Ar*C*), 134.6 (C); ^{19}F {^{1}H} NMR (376.6 MHz, CD_3CN) δ +30.9 ($^{+}$NF), -79.3 ($SO_3CF_3^{-}$); mp 116-118 ºC; $[\alpha]^{22}_{D}$ -12.0 (c 0.79, MeOH); HRMS (ESI): *m/z* calcd for for $C_{13}H_{17}ClFN_2$ $[M\text{-}H]^{+}$ 255.1059, found 255.1050; MS-EI^{-} *m/z* 148.94 (OTf).

5.4 Experimental data for Chapter 4

5.4.1 Experimental data for Electrophilic Fluorination

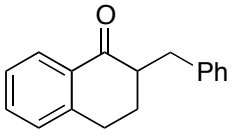
5.4.1.1 Synthesis of Substrates

2-Benzylidene-1-tetralone (277)[180]



1-Tetralone (3.0 mL, 22.6 mmol) and benzaldehyde (2.3 mL, 22.6 mmol) were added to a solution of KOH (2.5 g, 45.1 mmol) in ethanol at room temperature. The solution was stirred at the same temperature for 24 hours before addition of water (100 mL). The mixture was extracted with ether (3 × 50 mL). The organic extracts were combined, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel affording **277** as a green solid (4.3 g, 81%). R_f 0.28 (hexane:ether 4:1); IR (ν, KBr/cm^{-1}): 3059 (C-H), 2939 (C-H), 2842 (C-H), 1657 (C=O), 1590 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (t, 2H, $^3J_{H\text{-}H}$ = 6.5 Hz, ArC*H*$_2$CH$_2$C), 3.15 (td, 2H, $^3J_{H\text{-}H}$ = 6.5 Hz, $^4J_{H\text{-}H}$ = 1.8 Hz, ArCH$_2$C*H*$_2$C), 7.26-7.28 (m, 1H, Ar*H*), 7.36-7.52 (m, 7H, Ar*H*), 7.90 (t, 1H, ^4J = 1.8 Hz, C=C*H*Ph), 8.15-8.17 (m, 1H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 27.1 (ArCH$_2$*C*H$_2$C), 28.8 (Ar*C*H$_2$CH$_2$C), 126.9 (Ar*C*), 128.1 (Ph*C*), 128.1 (Ar*C*), 128.3 (Ph*C*), 128.4 (Ar*C*), 129.8 (Ph*C*), 133.4 (Ar*C*), 135.4 (Ph*C*), 135.7 (Ar*C*), 136.6 (C=*C*HPh), 143.1 (C(O)*C*(CH$_2$)=CHPh), 187.8 (CO); mp 106-107 °C; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O$ $[M+H]^+$ 235.1123, found 235.1134

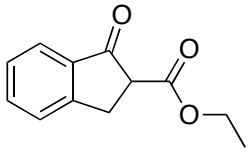
2-Benzyl-1-tetralone (254)[181]



2-Benzylidene-1-tetralone **277** (2.0 g, 8.5 mmol) was added to a suspension of 10% palladium on carbon (184 mg) in anhydrous methanol. The mixture was stirred under a hydrogen

atmosphere at room temperature for 1 hour. After the reaction was completed, the palladium catalyst was removed by filtration through celite and washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel to give **254** as a white solid (1.5 g, 74%). R_f 0.24 (hexane:ether 4:1); IR (ν, KBr/cm^{-1}): 3026 (C-H), 2942 (C-H), 2855 (C-H), 1677 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (dddd, 1H, $^2J_{H\text{-}H}$ = 13.3 Hz, $^3J_{H\text{-}H}$ = 11.5 Hz, $^3J_{H\text{-}H}$ = 10.4 Hz, $^3J_{H\text{-}H}$ = 5.8 Hz $ArCH_2CH_2CH$), 2.13 (dddd, 1H, , $^2J_{H\text{-}H}$ = 13.3 Hz, $^3J_{H\text{-}H}$ = 4.4 Hz, $^3J_{H\text{-}H}$ = 4.4 Hz, $^3J_{H\text{-}H}$ = 4.4 Hz $ArCH_2CH_2CH$), 2.67 (dd, 1H, $^2J_{H\text{-}H}$ = 13.7 Hz, $^3J_{H\text{-}H}$ = 9.6 Hz, CH_2Ph), 2.74-2.81 (m, 1H, $COCH(CH_2Ph)(CH_2)$), 2.89-3.01 (m, 2H, $ArCH_2CH_2CH$), 3.52 (dd, 1H, $^2J_{H\text{-}H}$ = 13.7 Hz, $^3J_{H\text{-}H}$ = 3.8 Hz, CH_2Ph), 7.23-7.35 (m, 7H, Ar*H*), 7.46-7.50 (m, 1H, Ar*H*), 8.09-8.11 (m, 1H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.7 ($ArCH_2CH_2CH$), 28.4 ($ArCH_2CH_2CH$), 35.7 (CH_2Ph), 49.4 ($COCH(CH_2Ph)(CH_2)$), 126.1 (Ar*C*), 126.6 (Ar*C*), 127.5 (Ar*C*), 128.4 (Ph*C*), 128.7 (Ph*C*), 129.3 (Ph*C*), 132.5 (Ar*C*), 133.3 (Ar*C*), 140.0 (Ph*C*), 144.0 (Ar*C*), 199.3 (CO); mp 53-54 °C; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O$ $[M+H]^+$ 237.1279, found 237.1243

2-Ethoxycarbonyl-1-indanone (275)[174]



A solution of 1-indanone (200 mg, 1.51 mmol, 1 eq.) in diethyl carbonate (5.5 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 73 mg, 1.82 mmol) in diethyl carbonate (5.5 mL). The suspension was heated to reflux for 20 min, and a green solid formed. The suspension was left to cool to room temperature, the solid was dissolved in 2M aq. HCl (50 mL) and the aqueous layer extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried, filtered, and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography over silica gel (hexane:EtOAc 4:1) to give a yellow

oil (220 mg, 98%) consisting predominantly of the ketone tautomer (by ^{1}H NMR: enol:ketone 1:10): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, ^{3}J = 7.1 Hz, CH_3CH$_2$), 3.35-3.41 (m, 1H, ArCH_2CH), 3.52-3.60 (m, 1H, COCH(COOEt)CH$_2$), 3.70-3.73 (m, 1H, ArCH_2CH), 4.25 (q, 2H, ^{3}J = 7.1 Hz, CH$_3$CH_2), 7.38-7.42 (m, 1H, ArH), 7.51 (d, 1H, ^{3}J =7.6 Hz, ArH), 7.62-7.65 (m, 1H, ArH), 7.78 (d, 1H, ^{3}J =7.6 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (*C*H$_3$CH$_2$), 30.3 (Ar*C*H$_2$CH), 53.3 (ArCH$_2$*C*H), 61.7 (CH$_3$*C*H$_2$) 124.7 (ArC), 124.7 (C), 126.5 (ArC), 127.8 (ArC), 135.3 (C), 135.4 (ArC), 169.1 (COCH(*C*OOEt)CH$_2$), 199.6 (*C*OCH(COOEt)CH$_2$); MS-EI *m/z* 203.1 (60, [M]$^{-}$) 204.1 (20), 429.1 (30).

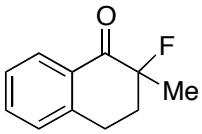
5.4.1.2 Electrophilic Fluorination Reactions

I) Fluorination in Racemic Series

General Procedure 1: Fluorination with Selectfluor

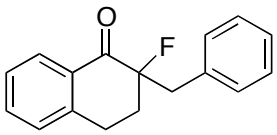
To a solution of the starting material (1 eq) in THF (0.1 M) at -78 °C, LiHMDS (1 M solution in THF, 1.5 eq.) was added. The resulting solution was stirred for 5 minutes, then warmed to room temperature and stirred for 45 minutes. The solution was cooled down to -78 °C and added to a solution of Selectfluor (1.2 eq) in CH_3CN (0.1 M). The reaction mixture was brought to -60 °C and then stirred for 2 to 3 hours. The reaction was quenched with saturated aq. NH_4Cl (3 mL) and warmed to room temperature. The aq. layer was extracted 3 times with Et_2O and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/ether eluent).

(±)-2-Fluoro-2-methyl-1-tetralone (240F)[160]



Compound **240F** was synthesised from 2-methyl-1-tetralone **240** (21 mg, 0.13 mmol) according to general procedure 1. Purification of the crude product by silica gel column chromatography afforded the product as a colourless oil (21 mg, 89%). R_f 0.26 (hexane:ether 4:1); IR (ν, neat/ cm^{-1}): 3023 (C-H), 2986 (C-H), 2940 (C-H), 1699 (C=O), 1602 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, 3H, ^3J = 22.2 Hz, CFC*H*$_3$), 2.21-2.30 (m, 1H, ArCH$_2$C*H*$_2$CF), 2.40-2.49 (m, 1H, ArCH$_2$C*H*$_2$CF), 2.94-3.02 (m, 1H, ArC*H*$_2$CH$_2$CF), 3.09-3.15 (m, 1H, ArC*H*$_2$CH$_2$CF), 7.27 (d, 1H, ^3J = 8.3 Hz, Ar*H*), 7.36 (t, 1H, ^3J = 7.6 Hz, Ar*H*), 7.53 (dt, 1H, ^3J = 7.6 Hz, ^3J = 1.3 Hz, Ar*H*), 8.08 (d, 1H, ^3J = 7.8 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.9 (d, $^2J_{C\text{-}F}$ = 25.8 Hz, CF*C*H$_3$), 26.2 (d, $^3J_{C\text{-}F}$ = 9.5 Hz, Ar*C*H$_2$CH$_2$CF), 35.0 (d, ^2J = 22.9 Hz, ArCH$_2$*C*H$_2$CF), 93.8 (d, J = 179.3 Hz, ArCH$_2$CH$_2$*C*F), 127.1 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 130.7 (C), 134.0 (Ar*C*), 142.7 (C), 194.2 (d, ^2J = 18.1 Hz, C=O); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -152.4; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}FO$ ($[M+NH_4]^+$): 196.1135, found 196.1135.

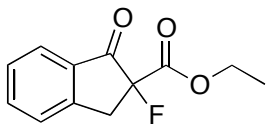
(±)-2-Benzyl-2-fluoro-1-tetralone (254F)[160]



Compound **254F** was synthesised from 2-benzyl-1-tetralone **254** (21 mg, 0.09 mmol) according to general procedure 1. Purification of the crude product by silica gel column chromatography afforded the product as a colourless oil (20 mg, 87%). R_f 0.18 (hexane:ether 9:1); IR (ν, neat/ cm^{-1}): 3029 (C-H), 2950 (C-H), 2868 (C-H), 1684 (C=O), 1600 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10-2.20 (m, 1H, ArCH$_2$C*H*$_2$CF), 2.27-2.36 (m, 1H, ArCH$_2$C*H*$_2$CF), 3.01-3.12 (m,

3H, ArC*H*$_2$CH$_2$CF and CFC*H*$_2$Ph), 3.34 (dd, 1H, ^2J = 17.2 Hz and ^3J = 14.9 Hz, CFC*H*$_2$Ph), 7.27-7.40 (m, 7H, Ar*H*), 7.55 (t, 1H, ^3J = 7.3 Hz, Ar*H*), 8.11 (d, 1H, ^3J = 7.8 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.4 (d, $^3J_{C\text{-}F}$ = 9.6 Hz, ArC*H*$_2$CH$_2$CF), 31.4 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, ArCH$_2$C*H*$_2$CF), 39.4 (d, $^2J_{C\text{-}F}$ = 23.2 Hz, CF*C*H$_2$Ph), 95.2 (d, $J_{C\text{-}F}$ = 185.3 Hz, (CO)*C*F(CH$_2$Ph), 127.1 (Ar*C*), 127.2 (Ar*C*), 128.4 (Ar*C*), 128.8 (ArC), 130.5 (d, $^3J_{C\text{-}F}$ = 1.6 Hz, Ar*C*), 130.9 (Ar*C*), 134.2 (Ar*C*), 134.5 (d, $^3J_{C\text{-}F}$ = 1.6 Hz, Ar*C*), 142.7 (Ar*C*), 194.1 (d, ^2J = 17.9 Hz, C=O); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -152.4; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}FO$ ([M+H]$^+$): 255.1185, found 255.1183.

1*H*-Indene-2-carboxylic acid, 2-fluoro-2,3-dihydro-1-oxo, ethyl ester (275F)[167]



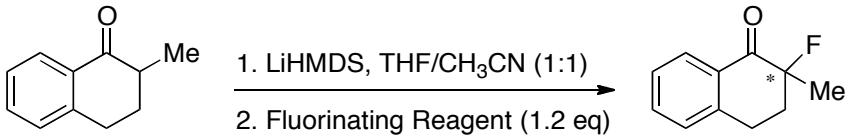
Compound **275F** was synthesised from 2-ethoxycarbonyl-1-indanone **275** (21 mg, 0.10 mmol) according to general procedure 1. Purification of the crude product by silica gel column chromatography afforded the product as a colourless oil (18 mg, 81%). R_f 0.23 (hexane:ether 4:1); IR (ν, neat/ cm^{-1}): 3052 (C-H), 2965 (C-H), 2870 (C-H), 1690 (C=O), 1615 (C=C), 1580 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, ^3J = 7.3 Hz, CH$_2$C*H*$_3$), 3.44 (dd, 1H, $^2J_{H\text{-}H}$ = 17.7 Hz, $^3J_{H\text{-}F}$ = 23.3 Hz, ArC*H*$_2$CF), 3.80 (dd, 1H, $^2J_{H\text{-}H}$ = 17.7 Hz, $^3J_{H\text{-}F}$ = 11.7 Hz, ArC*H*$_2$CF), 4.29 (q, 2H, ^3J = 7.3 Hz, C*H*$_2$CH$_3$), 7.49-7.53 (m, 2H, Ar*H*), 7.69-7.73 (m, 1H, Ar*H*), 7.84-7.86 (m, 1H, Ar*H*); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 14.1 (CH$_2$*C*H$_3$), 38.3 (d, $^2J_{C\text{-}F}$ = 23.9 Hz, ArCH$_2$CF), 62.6 (*C*H$_2$CH$_3$), 94.5 (d, J = 202.2 Hz, ((CO)*C*F(COOEt)), 125.6 (Ar*C*), 126.6 (Ar*C*), 128.6 (Ar*C*), 133.3 (C), 136.7 (Ar*C*), 150.9 (C), 167.3 (d, ^2J = 27.7 Hz, ((CO)CF(*C*OOEt)), 195.2 (d, ^2J = 18.1 Hz, ((*C*O)CF(COOEt)); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -164.4; MS-EI *m/z* 245.1 ([M+Na]$^+$, 50), 281.2 (100), 467.1 (65).

II) Asymmetric Fluorination Reactions

Generalities on fluorination reactions

For fluorinations with the **230**/Selectfluor combination, the cinchona alkaloid and Selectfluor were mixed in a 1:1 ratio at room temperature and left stirring in the respective solvent for 1 hour before being cooled down to the temperature of interest. For fluorinations with (2*R*,3*R*)-**79**/Selectfluor combination, the chiral DABCO **79** and Selectfluor were mixed in a 2:1 ratio. The latter fluorinating reagent was prepared by adding a solution of Selectfluor to a solution of (2*R*,3*R*)-**79** at -80 °C; the resulting solution was left to stir at this temperature for 30 minutes.

General Procedure 2: Fluorination of 2-methyl-1-tetralone using 230/Selectfluor combination, (2*R*,3*R*)-79/Selectfluor combination and (2*R*,3*R*)-212



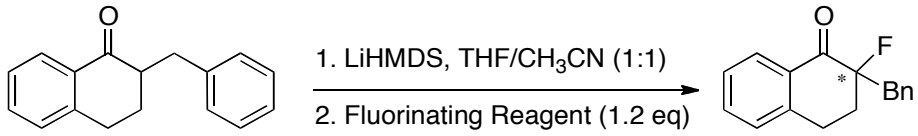
To a solution of the starting material (1 eq.) in THF (0.1 M) at -78 °C LiHMDS (1 M solution in THF, 1.5 eq.) was added. The resulting solution was stirred for 5 minutes, then warmed to room temperature and stirred for 45 minutes. The solution was cooled down to temperature of interest and added to a solution of **230**/Selectfluor combination or (2*R*,3*R*)-**79**/Selectfluor combination (1.2 eq.) in CH_3CN (0.1 M). The reaction mixture was brought to the temperature of interest and left stirring until completion. The reaction was quenched with saturated aq. NH_4Cl (3 mL) and warmed to room temperature. The aq. layer was extracted 3 times with Et_2O and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/ether eluent). The product was subjected to chiral HPLC (Chiralcel OB, hexane/*i*PrOH

90:10, 1 mL/min, retention time: (*R*) 10.8 min and (*S*) 15.5 min) and the enantiomeric excesses determined by comparison to a racemic reference.

Entry	Fluorinating Reagent	Conditions	Yield [%]	ee [%]	Major enantiomer
1	**230**/Selectfluor	-60 °C, 12 h	46	13	*S*
2	(2*R*,3*R*)-**212**	-60 °C, 4 h	99	8	*R*
3	(2*R*,3*R*)-**79**/Selectfluor	-65 °C, 12 h	99	54	*R*
4	**230**/Selectfluor	-65 °C, 12 h	60	0	-
5	(2*R*,3*R*)-**212**	-65 °C, 6 h	99	11	*R*
6	(2*R*,3*R*)-**79**/Selectfluor	-70 °C, 13 h	64	56	*R*
7	**230**/Selectfluor	-70 °C, 13 h	70	16	*S*
8	(2*R*,3*R*)-**79**/Selectfluor	-75 °C, 14 h	66	40	*R*
9	**230**/Selectfluor	-75 °C, 14 h	40	0	-
10	(2*R*,3*R*)-**79**/Selectfluor	-80 °C, 14 h	73	14	*R*
11	**230**/Selectfluor	-80 °C, 14 h	63	4	*S*

Table 5.1 Asymmetric fluorination of methyl tetralone

Asymmetric fluorination of 2-benzyl-1-tetralone using 230/Selectfluor combination, (2*R*,3*R*)-79/Selectfluor combination and (2*R*,3*R*)-212

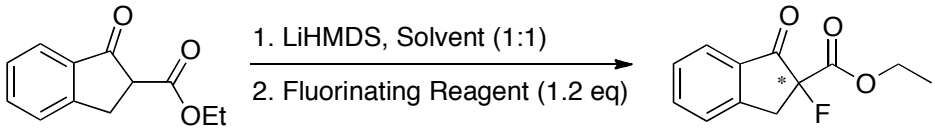


Employing general procedure 2, fluorination of 2-benzyl-1-tetralone gave the desired product with characterisation data identical to that for the racemic compound. Enantiomers were separated by chiral HPLC (Chiralcel OJ, hexane/*i*PrOH 99:1, 1 mL/min, retention time: 21.8 min and 29.3 min)

Entry	Fluorinating Reagent	Conditions	Yield [%]	ee [%]
1	**230**/Selectfluor	-60 °C, 12 h	42	10
2	(2*R*,3*R*)-**79**/Selectfluor	-60 °C, 12 h	99	50
3	(2*R*,3*R*)-**212**	-60 °C, 5 h	50	22
4	**230**/Selectfluor	-70 °C, 12 h	47	10

Table 5.2 Asymmetric fluorination of benzyl tetralone

Asymmetric fluorination of 2-ethoxycarbonyl-1-indanone using 230/Selectfluor combination and (2*R*,3*R*)-79/Selectfluor combination



Employing general procedure 2, fluorination of 2-ethoxycarbonyl-1-indanone gave the desired product with characterisation data identical to that for the racemic compound. Enantiomers were separated by chiral HPLC (Chiralcel OJ-H, hexane/*i*PrOH 90:10, 1 mL/min, retention time: 22.0 min and 36.0 min)

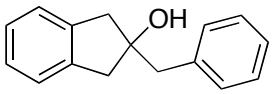
Entry	Fluorinating Reagent	Solvent	Conditions	Conversion [%]	ee [%]
1	**230**/Selectfluor	CH_2Cl_2/CH_3CN	-60 °C, 12 h	>95	53
2	(2*R*,3*R*)-**79**/Selectfluor	CH_2Cl_2/CH_3CN	-60 °C, 12 h	-	-
3	(2*R*,3*R*)-**79**/Selectfluor	THF/CH_3CN	-60 °C, 12 h	>95	6
4	(2*R*,3*R*)-**79**/Selectfluor	THF/CH_3CN	-78 °C, 12 h	>95	20

Table 5.3 Asymmetric fluorination of 2-ethoxycarbonyl-1-indanone

5.4.2 Experimental data for Electrophilic Fluorodesilylation

5.4.2.1 Synthesis of Substrates

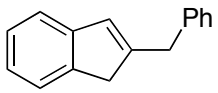
2-Benzylindan-2-ol (281)



Magnesium turnings (300 mg, 12.5 mmol) in diether ether (25 mL) were brought to reflux and treated with benzyl bromide (1.35 mL, 11.4 mmol). After the addition was completed, the solution of Grignard reagent was allowed to cool to room temperature and a solution of 2-indanone (1.5 g, 11.4 mmol) in diethyl ether (25 mL) was added over a period of 10 hours. The resulting solution was then heated for 2 hours. After cooling, the reaction was quenched by careful addition of water (10 mL) followed by 2M HCl solution (20 mL). The phases were separated and the aqueous phase extracted with ether (2 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solution was concentrated under reduced

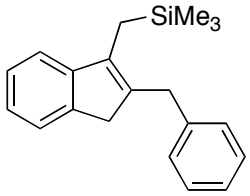
pressure. The crude product was purified by silica gel flash column chromatography (hexane:ether 2:3) to give product **281** as white crystals (1.15 g, 45%); IR (ν, KBr/cm^{-1}): 3338 (OH), 3025 (C-H), 2991 (C-H), 2824 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 1H, OH), 2.89 (d, 2H, $^{2}J_{H\text{-}H}$ = 16.2 Hz, $ArCH_AH_BC(CH_2Ph)(OH)CH_AH_BAr$), 3.07 (s, 2H, $PhCH_2$), 3.19 (d, 2H, $^{2}J_{H\text{-}H}$ = 16.2 Hz, $ArCH_AH_BC(CH_2Ph)(OH)CH_AH_BAr$), 7.18-7.24 (m, 4H, Ar*H*), 7.27-7.40 (m, 5H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 43.6 ($PhCH_2$), 46.5 ($ArCH_AH_BC(CH_2Ph)(OH)CH_AH_BAr$), 82.2 ($ArCH_AH_BC(CH_2Ph)(OH)CH_AH_BAr$), 125.0 (Ar*C*), 126.6 (Ar*C*), 126.7 (Ph*C*), 128.4 (Ph*C*), 130.3 (Ph*C*), 137.7 (Ph*C*), 141.2 (Ar*C*); mp 79-80 °C; MS (CI, *m/z*) 206.1 (100%), 242.2 ($[M+NH_4]^+$, 38%).

2-Benzyl-1*H*-indene (282)[182]



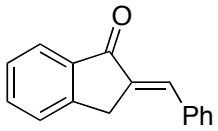
2-Benzylindan-2-ol **281** (1.00 g, 4.50 mmol) was dissolved in toluene (20 mL), *p*-toluenesulfonic acid (150 mg, 0.79 mmol) was added and the solution refluxed for 2 hours. After cooling, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and the product was extracted into ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane, R_f = 0.64) to give product **282** as a yellow oil (750 mg, 80%); IR (ν, KBr/cm^{-1}): 3059 (C-H), 3021 (C-H), 2936 (C-H), 1597 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 2H, $ArCH_2C(CH_2Ph)=CH$), 3.86 (s, 2H, $PhCH_2$), 6.56 (s, 1H, $ArCH=C(CH_2Ph)CH_2$), 7.13-7.17 (m, 1H, Ar*H*), 7.25-7.40 (m, 8H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 38.0 ($PhCH_2$), 40.8 ($ArCH_2C(CH_2Ph)=CH$), 120.2 (Ar*C*), 123.5 (Ar*C*), 123.9 (Ph*C*), 126.2 ($ArCHC(CH_2Ph)CH_2$), 126.3 (Ar*C*), 127.8 (Ph*C*), 128.9 (Ph*C*), 140.0 (Ph*C*), 143.5 (Ar*C*), 149.3 ($ArCH=C(CH_2Ph)CH_2$); mp 46 °C; HRMS (FI): *m/z* calcd for $C_{16}H_{14}$ $[M]^+$ 206.1096, found 206.1096.

(2-Benzyl-3*H*-inden-1-ylmethyl)trimethylsilane (279)



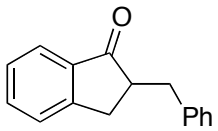
To a solution of 2-benzyl-1*H*-indene **282** (171 mg, 0.80 mmol) in THF (1 mL) at 0 °C was added dropwise *n*BuLi (2M in hexane, 0.33 mL). The reaction was allowed to warm to room temperature and stirred for 3 hours. The anion solution mixture was then added dropwise to a solution of (trimethylsilyl)methyl bromide (0.12 mL, 0.8 mmol) in THF (0.5 mL) at -78 °C. After addition was completed, the reaction mixture was warmed to room temperature and stirred for 20 hours. The red/brown mixture was then evaporated to dryness, and the residue was dissolved in dichloromethane. After filtration through celite, removal of the solvent under reduced pressure afforded the crude allyl silane. Purification by silica gel flash column chromatography (hexane: ether 19:1) gave the desired product **279** as a colourless oil (106 mg, 45%); IR (ν, KBr/cm^{-1}): 3061 (C-H), 3025 (C-H), 2953 (C-H), 1606 (C=C), 1249 ($SiMe_3$), 844 ($SiMe_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9H, Si(C*H*$_3$)$_3$), 2.18 (s, 2H, C*H*$_2$SiMe$_3$), 3.24 (s, 2H, ArC*H*$_2$C(CH$_2$Ph)), 3.83 (s, 2H, PhC*H*$_2$), 7.13-7.39 (m, 9H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -0.8 (Si(*C*H$_3$)$_3$), 15.8 (*C*H$_2$SiMe$_3$), 35.2 (Ph*C*H$_2$), 40.1 (Ar*C*H$_2$C), 119.1 (Ar*C*), 123.1 (Ar*C*), 123.8 (Ar*C*), 126.0 (Ar*C*), 128.4 (Ph*C*), 128.7 (Ph*C*), 129.1 (Ph*C*), 135.8 ((Ar)(CH$_2$SiMe$_3$)*C*=C), 137.5 (C=*C*(CH$_2$Ph)(CH$_2$)), 140.8 (Ph*C*), 143.0 (Ar*C*), 147.0 (Ar*C*); HRMS (CI): *m/z* calcd for $C_{20}H_{25}Si$ $[M+H]^+$ 293.1726, found 293.1723.

2-Benzylidene-indan-1-one (283)[183]



A solution of NaOH (2.3 g, 57.5 mmol) in water (3 mL) and ethanol (92 mL) at 0 °C was treated with 1-indanone (2.5 g, 18.9 mmol) followed by benzaldehyde (1.92 mL, 18.9 mmol). The mixture was stirred vigorously for 15 minutes and the formed precipitate was collected by filtration. The precipitate was washed with water (3 × 30 mL) and dried under vacuum. The resulting solid was recrystallised from ethanol to afford 283 as pale yellow crystals (2.95 g, 71%); IR (ν, KBr/cm^{-1}): 3047 (C-H), 1692 (C=O), 1623 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (d, 2H, $^{4}J_{H\text{-}H}$ = 1.4 Hz ArCH_2C), 7.38-7.69 (m, 9H, Ar*H* and C=C*H*Ph), 7.92 (d, 1H, $^{3}J_{H\text{-}H}$ = 7.9 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 32.4 (Ar*C*H_2C), 124.4 (Ar*C*), 126.1 (Ar*C*), 127.6 (Ar*C*), 128.9 (Ph*C*), 129.6 (Ph*C*), 130.7 (Ph*C*), 133.9 (C=*C*HPh), 134.6 (Ar*C*), 134.7 (Ph*C*), 135.4 (Ar*C*), 138.0 (Ar*C*), 149.6 (C(O)*C*(=CHPh)(CH_2)), 194.3 (C=O); MS (CI+, *m/z*) 221.1 ([M+H]$^{+}$, 100%).

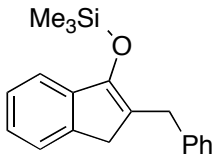
2-Benzylindan-1-one (260)[184]



A solution of 2-benzylidene-indan-1-one **283** (1.00 g, 4.55 mmol) in methanol (20 mL) was treated with 10% palladium on carbon (100 mg). A balloon containing hydrogen was fitted to the reaction flask and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After approximately 30 minutes, TLC indicated the disappearance of the starting material. The palladium catalyst was removed by filtration and the solvent removed by evaporation under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane:ether 4:1, R_f = 0.22) to give **260** as a yellow liquid

(860 mg, 85%); IR (ν, KBr/cm^{-1}): 3061 (C-H), 3028 (C-H), 2922 (C-H), 1709 (C=O), 1623 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (ddd, 1H, $^{2}J_{H\text{-}H}$ = 14.0 Hz, $^{3}J_{H\text{-}H}$ = 10.4 Hz, $^{4}J_{H\text{-}H}$ = 4.4 Hz, CHCH_2Ph), 2.87 (ddd, 1H, $^{2}J_{H\text{-}H}$ = 17.1 Hz, $^{3}J_{H\text{-}H}$ = 8.0 Hz, $^{3}J_{H\text{-}H}$ = 4.0 Hz, ArCH_2CH), 2.98-3.04 (m, 1H, C(O)CH(CH_2Ph)(CH_2)), 3.17 (ddd, 1H, $^{2}J_{H\text{-}H}$ = 17.1 Hz, $^{3}J_{H\text{-}H}$ = 8.0 Hz, $^{3}J_{H\text{-}H}$ = 4.0 Hz, ArCH_2CH), 3.42 (ddd, 1H, $^{2}J_{H\text{-}H}$ = 14.0 Hz, , $^{3}J_{H\text{-}H}$ = 10.4 Hz, $^{4}J_{H\text{-}H}$ = 4.4 Hz, CHCH_2Ph), 7.21-7.42 (m, 7H, ArH), 7.80 (d, 1H, $^{3}J_{H\text{-}H}$ = 7.9 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 32.2 (ArCH$_2$CH), 37.0 (CHCH$_2$Ph), 48.9 (C(O)CH(CH_2Ph)(CH_2)), 124.0 (ArC), 126.3 (PhC), 126.6 (ArC), 127.4 (ArC), 128.5 (PhC), 128.9 (PhC), 134.8 (ArC), 136.5 (ArC), 139.6 (PhC), 153.6 (ArC), 207.7 (C=O); MS (CI, *m/z*) 223.1 ([M+H]$^{+}$, 100%).

(2-Benzyl-3*H*-inden-1-yloxy)trimethylsilane (269)



A solution of 2-benzylindan-1-one **260** (2.08 g, 9.36 mmol) in acetonitrile (20 mL) at room temperature was treated with triethylamine (5.33 mL, 37.44 mmol) and chlorotrimethylsilane (3.56 mL, 28.08 mmol). A solution of NaI (1.40 g, 9.36 mmol) in acetonitrile (10 mL) was then added and the resulting solution stirred for 5 hours. The reaction mixture was poured into a separating funnel containing saturated aqueous $NaHCO_3$ (50 mL) and ice (10 g). The product was then extracted into Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography over silica gel (hexane, R_f = 0.10) afforded product **269** as a colourless oil (2.20 g, 80%); IR (ν, KBr/cm^{-1}): 3059 (C-H), 3025 (C-H), 2956 (C-H), 1630 (C=C), 1249 ($SiMe_3$), 841 ($SiMe_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 9H, Si(CH_3)$_3$), 3.12 (s, 2H, CCH_2Ph), 3.77 (s, 2H, ArCH_2C), 7.13-7.32 (m, 9H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.8 (Si(CH$_3$)$_3$), 33.0 (ArCH$_2$C), 36.0 (CCH$_2$Ph), 117.1

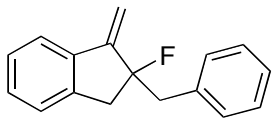
(C=*C*(CH_2Ph)(CH_2)), 123.0 (Ar*C*), 123.6 (Ar*C*), 124.4 (Ar*C*), 125.9 (Ar*C*), 126.0 (Ph*C*), 128.4 (Ph*C*), 128.7 (Ph*C*), 140.7 (Ar*C*), 141.3 (Ph*C*), 142.3 (Ar*C*), 148.2 ((Ar)*C*($OSiMe_3$)(=C); MS (CI+, *m/z*) 294.2 ($[M]^+$, 19%), 295.1 ($[M+H]^+$, 100%).

5.4.2.2 Electrophilic Fluorodesilylation Reaction

I) Fluorodesilylation in Racemic Series

1) Fluorodesilylation of allysilane 279 with Selectfluor

(±)-2-Benzyl-2-fluoro-1-methylene-indan ((±)-279F)

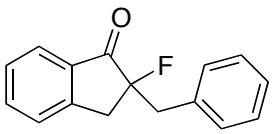


A solution of (2-benzyl-3*H*-inden-1-ylmethyl)trimethylsilane **279** (20 mg, 0.07 mmol) in dry acetonitrile (4 mL) was treated with Selectfluor **10** (24.2 mg, 0.07 mmol) and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was poured into a separating funnel containing saturated aqueous $NaHCO_3$ (30 mL) and the product extracted into Et_2O (3 × 20 mL). The combined organic extracts were washed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether 4:1, R_f = 0.51) to give product **279F** as a pale yellow solid (110 mg, 69%); IR (ν, neat/cm^{-1}): 3063 (C-H), 3029 (C-H), 1655 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95-3.39 (m, 4H, ArCH_2CF(CH_2Ph) and ArCH_2CF(CH_2Ph)), 5.30 (d, 1H, $^4J_{H\text{-}F}$ = 3.9 Hz , C=C$H_A$$H_b$), 5.72 (d, 1H, $^4J_{H\text{-}F}$ = 4.3 Hz, C=C$H_A$$H_b$), 7.21-7.39 (m, 8H, Ar*H*), 7.49-7.54 (m, 1H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 41.9 (d, $^2J_{C\text{-}F}$ = 24.3 Hz, CF*C*H_2Ph), 44.3 (d, $^2J_{C\text{-}F}$ = 26.7 Hz, Ar*C*H_2CF), 101.8 (d, $^1J_{C\text{-}F}$ = 184.0 Hz, C*C*F(CH_2Ph)(CH_2)), 107.1 (d, $^3J_{C\text{-}F}$ = 5.7 Hz, C=*C*H_2), 121.1 (Ar*C*), 125.2 (d, $^3J_{C\text{-}F}$ = 1.8 Hz, Ph*C*), 126.8 (Ar*C*), 127.2 (d, $^4J_{C\text{-}F}$ = 0.8 Hz, Ar*C*), 128.1 (Ar*C*), 128.5 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, Ar*C*), 129.3 (Ar*C*), 130.6 (d, $^4J_{C\text{-}F}$ = 1.6 Hz,

Ph*C*), 136.0 (d, $^{4}J_{C\text{-}F}$ = 1.0 Hz, Ph*C*), 140.9 (d, ^{3}J = 3.4 Hz, Ph*C*), 151.1 (d, $^{2}J_{C\text{-}F}$ = 17.7 Hz, Ar*C*(=CH_2)(CF)); ^{19}F {^{1}H} NMR (376.6 MHz, $CDCl_3$) δ -138.3; mp 36-37 °C; HRMS (CI): *m/z* calcd for $C_{17}H_{15}F$ $[M]^+$ 238.1158, found 238.1148.

2) Fluorodesilylation of Silyl Enol Ether 269 with Selectfluor

(±)-2-Benzyl-2-fluoroindan-1-one ((±)-269F)

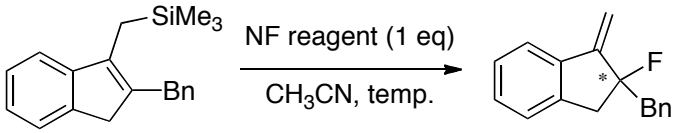


A solution of (2-benzyl-3*H*-inden-1-yloxy)trimethylsilane **269** (20.1 mg, 0.07 mmol) in dry acetonitrile (4 mL) at -20 °C was treated with Selectfluor **10** (24.1 mg, 0.07 mmol) and the reaction mixture stirred at -20 °C for 1 hour. The reaction mixture was poured into a separating funnel containing saturated aqueous $NaHCO_3$ (30 mL) and the product extracted into Et_2O (3 × 20 mL). The combined organic extracts were washed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether 4:1, R_f = 0.24) to give product **269F** as a colourless oil (15.5 mg, 95%); IR (ν, neat/cm^{-1}): 3063 (C-H), 3030 (C-H), 1725 (C=O), 1607 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (dd, 1H, $^{2}J_{H\text{-}H}$ = 30.4 Hz, $^{3}J_{H\text{-}F}$ = 14.1 Hz, ArCH_2CF), 3.15 (dd, 1H, $^{2}J_{H\text{-}H}$ = 22.8 Hz, $^{3}J_{H\text{-}F}$ = 17.8 Hz, CFCH_2Ph), 3.37-3.46 (m, 2H, ArCH_2CF and CFCH_2Ph), 7.23-7.42 (m, 7H, Ar*H* and Ph*H*), 7.60-7.64 (m, 1H, Ar*H*), 7.81 (d, 1H, $^{3}J_{H\text{-}H}$ = 7.8 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 37.3 (d, $^{2}J_{C\text{-}F}$ = 25.2 Hz, CF*C*H_2Ph), 40.2 (d, $^{2}J_{C\text{-}F}$ = 24.4 Hz, Ar*C*H_2CF), 97.5 (d, $^{1}J_{C\text{-}F}$ = 189.0 Hz, (CO)*C*F(CH_2Ph)(CH_2)), 125.1 (Ar*C*), 126.6 (d, $^{3}J_{C\text{-}F}$ = 1.6 Hz, Ph*C*), 127.2 (Ar*C*), 128.2 (Ar*C*), 128.4 (Ar*C*), 130.3 (Ar*C*), 133.9 (d, $^{4}J_{C\text{-}F}$ = 1.6 Hz, Ph*C*), 134.6 (d, $^{3}J_{C\text{-}F}$ = 4.1 Hz, Ph*C*), 136.3 (Ar*C*), 150.4 (d, $^{3}J_{C\text{-}F}$ = 4.1 Hz, Ph*C*), 200.9 (d, ^{2}J = 17.9 Hz, CO); ^{19}F {^{1}H} NMR (376.6 MHz, $CDCl_3$) δ -154.0; HRMS (CI): *m/z* calcd for $C_{16}H_{17}NOF$ $[M+NH_4]^+$

258.1294, found 258.1293.

II) Asymmetric Fluorodesilylation

General Procedure 3: Fluorodesilylation of Allylsilane 279 with 230/Selectfluor combination and (2*R*,3*R*)-212

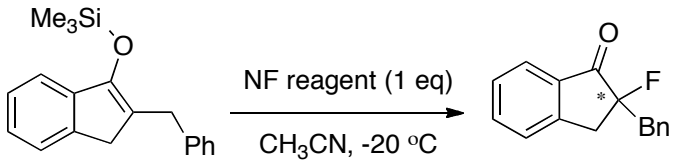


A solution of (2-benzyl-3*H*-inden-1-ylmethyl)trimethylsilane **279** (1 eq) in dry acetonitrile (4 mL) was treated with NF reagent (1 eq) and the reaction mixture stirred at a temperature of interest until completion . The reaction mixture was poured into a separating funnel containing saturated aqueous $NaHCO_3$ (30 mL) and the product extracted into Et_2O (3 × 20 mL). The combined organic extracts were washed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (hexane:ether 4:1, R_f = 0.51) to give product **279F** as a pale yellow solid. The product was subjected to chiral HPLC (Chiralcel OJ-H, hexane/*i*PrOH 99:1, 1mL/min, and retention time: 13.2 min and 16.9 min).

Entry	Fluorinating Reagent	Time (h)	Temperature (°C)	Yield (%)	ee (%)	Major enantiomer
1	**230**/Selecfluor	24	-20	48	60	**(+)-279F**
2	(2*R*,3*R*)-**212**	3	-20	67	24	**(-)-279F**
3	(2*R*,3*R*)-**212**	6	-40	65	29	**(-)-279F**

Table 5.4 Asymmetric fluorodesilylation of **279** using **230**/Selectfluor and chiral NF (2*R*,3*R*)-**212**

General Procedure 4: Fluorodesilylation of Silyl Enol Ether 269 with 230/Selectfluor combination and (2*R*,3*R*)-212



A solution of (2-benzyl-3*H*-inden-1-yloxy)trimethylsilane **269** (1 eq) in dry acetonitrile (4 mL) at -20 °C was treated with NF reagent (1 eq) and the reaction mixture stirred at -20 °C until completion. The reaction mixture was poured into a separating funnel containing saturated aqueous $NaHCO_3$ (30 mL) and the product extracted into Et_2O (3 × 20 mL). The combined organic extracts were washed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether 4:1, R_f = 0.24) to give product **269F** as a colourless oil. The product was subjected to chiral HPLC (Chiralcel OD, hexane/*i*PrOH 99:1, 1mL/min, and retention time: 9.3 min and 10.3 min).

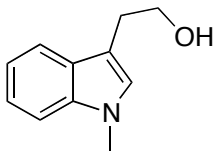
Entry	Fluorinating Reagent	Time (h)	Yield (%)	ee (%)	Major enantiomer
1	**230**/Selecfluor	12	89	78	**(-)-269F**
2	(2*R*,3*R*)-**212**	2	90	30	**(-)-269F**

Table 5.5 Asymmetric fluorodesilylation of **269** using **230**/Selectfluor and (2*R*,3*R*)-**212**

5.4.3 Experimental data for Electrophilic Fluorocyclisation

5.4.3.1 Synthesis of Substrates

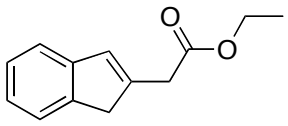
2-(1-Methyl-1*H*-indol-3-yl)ethanol (284)[177]



$LiAlH_4$ (361 mg, 9.51 mmol) was added to diethyl ether (50 mL) and the solution cooled to 0 °C. A solution of 2-(1*H*-Indol-3-yl)acetic acid (400 mg, 2.11 mmol) in Et_2O (4 mL) was added

dropwise and the resulting suspension stirred at room temperature for 5 hours. The reaction process was monitored by TLC (hexane:EtOAc 1:1). The reaction was quenched by the slow addition of water (5 mL) at 0 °C; the suspension was stirred for a further 15 minutes and filtered through celite. The filtrate solution was concentrated under reduced pressure and the crude product was purified by silica gel flash column chromatography (hexane:EtOAc 1:1) to give product **284** as an orange oil (337 mg, 91%). IR (ν, neat/cm^{-1}): 3306 (OH), 3185 (C-H), 2971 (C-H), 2724 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (t, 2H, ^{3}J = 6.3 Hz, NCH=C(CH_2CH$_2$OH)), 3.78 (s, 3H, NCH_3), 3.92 (t, 2H, ^{3}J = 6.3 Hz, NCH=C(CH$_2$CH_2OH)), 6.96 (s, 1H, NC*H*=C), 7.16 (td, 1H, ^{3}J = 6.8, ^{4}J = 1.0 Hz, Ar*H*), 7.28 (td, 1H, ^{3}J = 6.8, ^{4}J = 1.0 Hz, Ar*H*), 7.34 (d, 1H, ^{3}J = 8.3 Hz, Ar*H*), 7.65 (d, 1H, ^{3}J = 7.8 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.7 (NCH=C(*C*H$_2$CH$_2$OH)), 32.7 (N*C*H$_3$), 62.8 (NCH=C(CH$_2$*C*H$_2$OH)), 109.3 (N*C*H=C), 110.7 (NCH=*C*), 118.9 (Ar*C*), 119.0 (Ar*C*), 121.8 (Ar*C*), 127.3 (Ar*C*), 127.9 (C), 137.2(C); HRMS (FI): *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.0996.

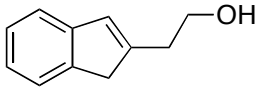
Ethyl 1*H*-inden-2-ylacetate (291)



To a stirred suspension of hexane-rinsed NaH (396 mg, 9.9 mmol) in dimethoxyethane (14 mL) at 0 °C was added triethylphosphonoacetate (2.0 mL, 9.9 mmol) in dimethoxyethane (2.8 mL) dropwise. The mixture was stirred for 2 hours at room temperature. The reaction was then cooled to 15 °C and treated with 2-indanone (1 g, 7.6 mL, 7.6 mmol) in dimethoxyethane (1.4 mL) dropwise and stirred at room temperature overnight. After which time the reaction was cooled to 0 °C and quenched slowly with acetic acid, water was added and the layers separated. The aqueous layer was extracted with cyclohexane. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and the solvent was concentrated under reduced pressure.

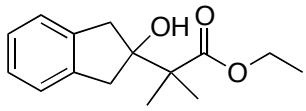
Purification by silica gel column chromatography (Hexane:Et_2O 95:5) gave product **291** as a colourless oil (886 mg, 58% yield). IR (ν, neat/cm^{-1}): 2982 (C-H), 1733 (C=O), 1462 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, 3H, ^3J = 7.2 Hz, CH_2CH_3), 3.47 (s, 2H, CCH_2CO), 3.53 (s, 2H, $ArCH_2C$), 4.19 (d, 2H, ^3J = 7.1 Hz, CH_2CH_3), 6.71 (s, 1H, ArCHC), 7.12-7.44 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (OCH_2CH_3), 37.1 (CH_2CO), 41.3 ($ArCH_2C$), 60.8 (OCH_2CH_3), 120.5 (ArC), 123.4 (ArC), 124.3 (ArC), 126.2 (ArC), 129.9 (ArCHC), 141.1 (ArC), 143.4 (ArC), 144.7 (ArCHC), 170.9 (CH_2COOEt); MS-ESI *m/z* 203.12 ($[M+H]^+$).

2-(1*H*-inden-2-yl)ethanol (287)



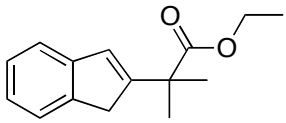
To a stirred suspension of $LiAlH_4$ (29 mL of a 1 M solution in THF, 29 mmol) at 0 °C was added dropwise a solution of ester **291** (5.8 g, 29 mmol) in THF (29 mL) and the mixture was stirred at room temperature for 2 hours. Subsequently water was added dropwise followed by 10% aqueous H_2SO_4. The aqueous phase was extracted with ethyl acetate, washed with brine and dried over anhydrous $MgSO_4$, filtered and the solvent concentrated under reduced pressure. Purification by silica gel column chromatography gave product **287** as a colourless oil (3.6 g, 78%). IR (ν, neat/cm^{-1}): 3357 (OH), 1462 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (t, 2H, ^3J = 6.6 Hz, CH_2CH_2OH), 3.21 (br s, 1H, OH), 3.40 (s, 2H, $ArCH_2C$), 3.89 (t, 2H, ^3J = 6.7 Hz, CH_2OH), 6.68 (s, 1H, ArCHC), 7.25-7.29 (m, 1H, ArH), 7.36-7.43 (m, 2H, ArH), 7.51 (d, 1H, ^3J = 7.3 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 34.5 (CH_2CH_2OH), 41.3 ($ArCH_2C$), 61.7 (CH_2OH), 120.3 (ArC), 123.6 (ArC), 124.1 (ArC), 126.5 (ArC), 128.1 (ArCHC), 143.3 (ArC), 145.5 (ArC), 146.8 (ArCHC); HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O$ ($[M]^+$): 160.0888, found 160.0887.

Ethyl 2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate (292)[179]



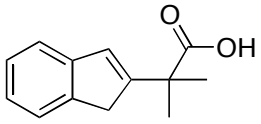
To a solution of diisopropylamine (5.72 mL, 40.8 mmol) in THF (80 mL) at 0 °C, was added *n*BuLi (2.5 M in hexane, 16.4 mL, 40.8 mmol) and the reaction was stirred for 15 minutes before being cooled to -78 °C. Ethyl isobutyrate (5.36 mL, 40.0 mmol) was then added and the reaction was stirred for 20 minutes before the addition of 2-indanone (5.28 g, 40.0 mmol) in THF (20 mL). The reaction was stirred for 2 hours before being warmed to 0 °C and quenched slowly with 1M HCl (50 mL). The product was then extracted into ether, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by silica gel column chromatography (Hexane :Et_2O 80:20) afforded the title compound **292** as an orange oil (6.60 g, 66%). IR (ν, neat/cm^{-1}): 3200 (OH), 2700 (C-H), 1534 (C=O), 1455 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, ^3J = 7.1 Hz, CH_2CH_3), 1.33 (s, 6H, $C(CH_3)_2$), 2.95 (d, 2H, ^2J = 16.6 Hz, $ArCH_2C$), 3.28 (d, 2H, ^2J = 16.6 Hz, $ArCH_2C$), 3.56 (br s, 1H, OH), 4.23 (q, 2H, ^3J = 7.1 Hz, CH_2CH_3), 7.15-7.22 (m, 4H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 22.0 (2 × $C(CH_3)_2$), 43.3 (2 × $ArCH_2C$), 48.8 ($C(CH_3)_2$), 61.0 (CH_2CH_3), 85.2 (CH_2COH), 124.8 (2 × Ar*C*), 126.5 (2 × Ar*C*), 141.0 (2 × *C*), 178.0 (*C*OOEt); HRMS (FI): *m/z* calcd for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412, found 248.3175.

Ethyl 2-(1*H*-inden-2-yl)-2-methylpropanoate (293)[179]



To a solution of ethyl 2-(2-hydroxy-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropanoate **292** (2.13 g, 8.60 mmol, 1.0 eq) in toluene (30 mL) was added *p*-toluenesulfonic acid (325 mg, 0.20 mmol) and the reaction was reflux for 23 hours. The reaction was then cooled to room temperature and the mixture was poured onto saturated $NaHCO_3$. The aqueous phase was then extracted with ether (3 × 15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane eluent) to afford product **293** as a colourless oil (1.57 g, 6.82 mmol, 80% yield). IR (ν, neat/cm^{-1}): 2700 (C-H), 1534 (C=O), 1455 (C=C), 1305 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, 3H, ^3J = 7.1 Hz, CH_2CH_3), 1.53 (s, 6H, $C(CH_3)_2$), 3.43 (s, 2H, $ArCH_2C$), 4.13 (q, 2H, ^3J = 7.1 Hz, CH_2CH_3), 6.69 (s, 1H, ArC*H*C), 7.15 (td, 1H, ^3J = 7.3 Hz, ^4J = 1.2 Hz, Ar*H*), 7.24 (d, 1H, ^3J = 7.4 Hz, Ar*H*), 7.32 (d, 1H, ^3J = 7.4 Hz, Ar*H*), 7.40 (d, 1H, ^3J = 7.4 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 25.7 ($C(CH_3)_2$), 38.7 ($ArCH_2C$), 44.7 ($C(CH_3)_2$), 60.8 (CH_2CH_3), 120.6 (Ar*C*), 123.5 (Ar*C*), 124.3 (Ar*C*), 126.3 (Ar*C*), 126.6 (Ar*C*H), 143.1 ($ArCH_2C$), 144.6 (*C*), 152.5 (*C*), 176.0 (*C*OOEt); HRMS (FI): *m/z* calcd for $C_{15}H_{18}O_2$ $[M]^+$ 230.1307, found 230.3022.

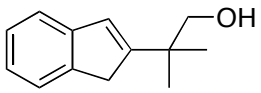
2-(1*H*-inden-2-yl)-2-methylpropanoic acid (289)



To a solution of ethyl 2-(1*H*-inden-2-yl)-2-methylpropanoate **293** (1.57 g, 6.82 mmol) in THF:H_2O (1:1, 4 mL) was added sodium hydroxide (464 mg, 11.59 mmol) and the reaction was reflux for 24 hours. The reaction was then cooled to room temperature and acidified with HCl

(3M, pH = 2). The aqueous phase was then extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (chloroform: methanol 19:1) to afford product **289** as a solid (420 mg, 30%); IR (ν, KBr/cm^{-1}): 3200 (OH), 2700 (C-H), 1643 (C=O), 1455 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 6H, C(C*H*$_3$)$_2$), 3.49 (s, 2H, ArC*H*$_2$C), 6.76 (s, 1H, ArC*H*C), 7.16 (td, 1H, ^3J = 7.3 Hz, ^4J =1.2 Hz, Ar*H*), 7.25 (d, 1H, ^3J = 7.4 Hz, Ar*H*), 7.34 (d, 1H, ^3J = 7.4 Hz, Ar*H*), 7.41 (d, 1H, ^3J = 7.4 Hz, Ar*H*), 11.42 (br. s, 1H, COO*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.4 (C(*C*H$_3$)$_2$), 38.7 (Ar*C*H$_2$C), 44.5 (*C*(CH$_3$)$_2$), 120.8 (Ar*C*), 123.5 (Ar*C*), 124.5 (Ar*C*), 126.3 (Ar*C*), 127.4 (Ar*C*H), 143.1 (ArCH*C*), 144.3 (*C*), 151.4 (*C*), 176.0 (CO); IR (ν, neat/cm^{-1}): HRMS (FI): *m/z* calcd for $C_{15}H_{18}O_2$ $[M]^+$ 202.0994, found 202.1003.

2-(1*H*-inden-2-yl)-2-methylpropan-1-ol (288)



Ethyl 2-(1*H*-inden-2-yl)-2-methylpropanoate **293** (3.56 g, 15 mmol) was dissolved in dry Et_2O (75 mL) and the solution was cooled to -78°C. A solution of DIBAL (1 M in hexane, 42 mL, 42 mmol) was slowly added and the resulting mixture was stirred for 1 hour at -78 °C. The solution was warmed to room temperature and stirred overnight, after which time the reaction was quenched with aqueous NaOH (3 M, 50 mL). The mixture was extracted ether (3 × 30 mL), the aqueous layer was then acidified with 3 M HCl and extracted once more with ether. The combined organic fractions were dried over $MgSO_4$, filtered and the solvent concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (chloroform: methanol 19:1) to give product **288** (2.6 g, 92%). IR (ν, neat/cm^{-1}): 3406 (OH), 2965 (C-H), 1462 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 6H, C(C*H*$_3$)$_2$), 3.41 (s, 2H, ArC*H*$_2$C), 3.57 (s, 2H, C*H*$_2$OH), 6.67 (s, 1H, ArC*H*C), 7.15 (td, 1H, ^3J = 7.3 Hz, ^4J = 1.3 Hz,

Ar*H*), 7.26 (t, 1H, ^{3}J = 7.5 Hz, Ar*H*), 7.33 (d, 1H, ^{3}J = 7.5 Hz, Ar*H*), 7.42 (dd, 1H, ^{3}J = 7.6 Hz, 1H, ^{4}J = 0.9 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.8 (C(*C*H$_3$)$_2$), 38.2 (Ar*C*H$_2$C), 71.7 (*C*H$_2$OH), 120.3 (Ar*C*), 123.5 (Ar*C*), 124.1 (Ar*C*), 126.4 (Ar*C*), 127.0 (Ar*C*HC), 143.1 (Ar*C*), 144.8 (Ar*C*), 152.1 (ArCH*C*); HRMS (FI): *m/z* calcd for $C_{15}H_{18}O_2$ $[M]^+$ 188.1201, found 188.1222.

5.4.3.2 Electrophilic Fluorocyclization Reactions

I) Fluorocyclization in Racemic Series

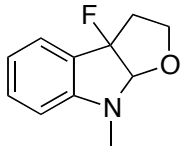
General Procedure 5: Fluorocyclization of Indole Derivatives with Selectfluor

To a solution of Selectfluor (1.2 eq) and $NaHCO_3$ (1.2 eq) in acetone (1.5 mL for 20 mg of indole starting material), a pre-cooled (at –78 °C) solution of the indole derivative material (1 eq) in acetone (0.5 mL for 20 mg of indole starting material) was added dropwise at –78 °C and the reaction was stirred at the same temperature for the time indicated. The solvent was evaporated and the residue was purified through neutral alumina to give the fluorocyclized product.

General Procedure 6: Fluorocyclization of Indenes with Selectfluor

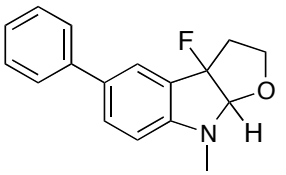
To a solution of indene derivative (1 eq) and $NaHCO_3$ (1.5 eq) in acetonitrile (0.1 M) was added Selectfluor (1.2 eq) at room temperature. The reaction mixture was then stirred for 12-20 hours at room temperature, after which time the solvent was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and saturated $NaHCO_3$ solution was added. The aqueous phase was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane ether eluent).

3a-Fluoro-8-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (284F)[66]



Compound **284F** was synthesized from 2-(1-methyl-1*H*-indol-3-yl)ethanol **284** (20 mg, 0.11 mmol) according to general procedure 5. Purification of the crude product by neutral alumina column chromatography afforded the product as a colourless oil (14 mg, 65%). IR (ν, neat/cm^{-1}): 2926 (C-H), 1615 (C=C), 1494; ^{1}H NMR (400 MHz, C_6D_6) δ 2.37-2.44 (m, 1H, OCH_2CH_2CF), 2.61-2.71 (m, 1H, OCH_2CH_2CF), 2.94 (s, 3H, NCH_3), 3.78-3.68 (m, 1H, OCH_2CH_2CF), 4.17-4.12 (m, 1H, OCH_2CH_2CF), 5.43 (d, 1H, $^{3}J_{H\text{-}F}$ = 18.4 Hz, $NCHOCH_2$), 6.49 (d, 1H, ^{3}J = 7.8 Hz, Ar*H*), 6.77 (t, 1H, ^{3}J = 7.5 Hz, ArH), 7.24-7.33 (m, 2H, Ar*H*); ^{13}C NMR (125.5 MHz, C_6D_6) δ 31.2 (NCH_3), 39.8 (d, $^{2}J_{C\text{-}F}$ = 29.6 Hz, OCH_2CH_2CF), 67.2 (OCH_2CH_2CF), 103.5 (d, $^{2}J_{C\text{-}F}$ = 29.6 Hz, $NCHOCH_2$), 106.7 (Ar*C*), 108.0 (d, ^{1}J = 195.5 Hz, OCH_2CH_2CF), 118.3 (Ar*C*), 124.8 (Ar*C*), 126.2 (C), 131.5 (Ar*C*), 152.0 (C); ^{19}F {^{1}H} NMR (376 MHz, C_6D_6) δ -145.5; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}FNO$ ($[M+H]^+$ 194.0981, found 194.0977.

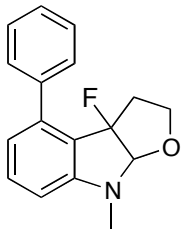
3a-Fluoro-8-methyl-5-phenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (285F)[66]



Compound **285F** was synthesized from 2-(1-methyl-5-phenyl-1*H*-indol-3-yl)ethanol **285** (20 mg, 0.08 mmol) according to general procedure 5. Purification of the crude product neutral alumina column chromatography afforded the product as a colourless oil (16.5 mg, 76%). IR (ν, neat/cm^{-1}): 2930 (C-H), 1620 (C=C), 1485 (C=); ^{1}H NMR (400 MHz, C_6D_6) δ 1.96-2.01 (m, 1H, OCH_2CH_2CF), 2.34-2.45 (m, 1H, OCH_2CH_2CF), 2.47 (s, 3H, NCH_3), 3.40 (m, 1H, OCH_2CH_2CF), 3.72-3.77 (m, 1H, OCH_2CH_2CF), 5.40 (d, 1H, $^{3}J_{H\text{-}F}$ = 17.9 Hz, $NCHOCH_2$), 6.20

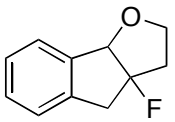
(d, 1H, ^{3}J = 8.3 Hz, Ar*H*), 7.25 (t, 2H, ^{3}J = 7.3 Hz, Ar*H*), 7.45 (dd, 4H, ^{3}J = 7.8, 7.0 Hz, Ar*H*), 7.59 (s, 1H, Ar*H*); ^{13}C NMR (125.8 MHz, C_6D_6) δ 31.5 (NCH_3), 40.2 (d, $^{2}J_{C\text{-}F}$ = 29.0 Hz, OCH_2CH_2CF), 67.6 (OCH_2CH_2CF), 104.0 (d, $^{2}J_{C\text{-}F}$ = 29.0 Hz, $NCHOCH_2$), 107.3 (Ar*C*), 108.3 (d, ^{1}J = 196 Hz, OCH_2CH_2CF), 124.1 (Ar*C*), 126.9 (Ar*C*), 127.2 (Ar*C*), 127.2 (Ar*C*), 127.4 (Ar*C*), 129.4 (Ar*C*), 129.4 (Ar*C*), 130.9 (Ar*C*), 132.3 (Ar*C*), 142.1 (Ar*C*), 151.7 (d, *J* = 4.0 Hz, C); ^{19}F {^{1}H} NMR (376.5 MHz, C_6D_6) δ -145.8; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}FNO$ $[M+H]^+$ 270.1289, found 270.1291.

3a-Fluoro-8-methyl-4-phenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (286F)



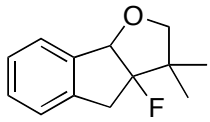
Compound **286F** was synthesized from 2-(1-methyl-4-phenyl-1*H*-indol-3-yl)ethanol **286** (20 mg, 0.08 mmol) according to general procedure 5. Purification of the crude product by neutral alumina column chromatography afforded the product as a colourless oil (21 mg, 98%). IR (ν, neat/cm^{-1}): 2926 (C-H), 1615 (C=C), 1494 (C=C); ^{1}H NMR (400 MHz, C_6D_6) δ 1.92-1.99 (m, 1H, OCH_2CH_2CF), 2.11-2.28 (m, 1H, OCH_2CH_2CF), 2.65 (s, 3H, NCH_3), 3.39 (m, 1H, OCH_2CH_2CF), 3.67 (m, 1H, OCH_2CH_2CF), 5.43 (d, $^{3}J_{H\text{-}F}$ = 18.7 Hz, 1H, $NCHOCH_2$), 6.30 (d, 1H, $^{3}J_{H\text{-}H}$ = 8.1 Hz, Ar*H*), 6.87 (d, 1H, $^{3}J_{H\text{-}H}$ = 7.6 Hz, Ar*H*), 7.18-7.30 (m, 3H, Ar*H*), 7.30-7.39 (m, 2H, Ar*H*), 7.78 (d, 1H, $^{3}J_{H\text{-}H}$ = 7.1 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, C_6D_6) δ 31.4 (NCH_3), 38.5 (d, $^{2}J_{C\text{-}F}$ = 29 Hz, OCH_2CH_2CF), 67.4 (OCH_2CH_2CF), 102.9 (d, $^{2}J_{C\text{-}F}$ = 29 Hz, $NCHOCH_2$), 105.8 (Ar*C*), 109.3 (d, $^{1}J_{C\text{-}F}$ = 196 Hz, OCH_2CH_2CF), 124.1 (Ar*C*), 126.9 (Ar*C*), 127.2 (Ar*C*), 127.2 (Ar*C*), 127.4 (Ar*C*), 129.4 (Ar*C*), 129.6 (Ar*C*), 130.9 (Ar*C*), 131.8 (Ar*C*), 140.5 (Ar*C*), 151.7 (d, $J_{C\text{-}F}$ = 4.0 Hz, C); ^{19}F {^{1}H} NMR (376 MHz, C_6D_6) δ -133.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}FNO$ $[M+H]^+$ 270.1289, found 270.1290.

3a-fluoro-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan (287F)



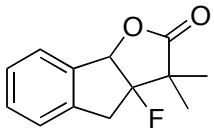
Compoud **287F** was prepared from 2-(1*H*-inden-2-yl)ethanol **287** (20 mg, 012 mmol) according to general procedure general procedure 6. Purification of the crude product by silica gel column chromatography afforded the product **287F** as a colourless oil (9.2 mg, 42%). IR (ν, neat/cm^{-1}): 2700 (C-H), 1455 (C=C), 1305, 1190, 990; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (ddt, 1H, $^{3}J_{H\text{-}F}$ = 25.7 Hz, $^{2}J_{H\text{-}H}$ = 13.6 Hz, $^{3}J_{H\text{-}H}$ = 8.1 Hz, C*H*$_2$CH$_2$O), 2.50 (dddd, 1H, $^{3}J_{H\text{-}F}$ = 23.8 Hz, $^{2}J_{H\text{-}H}$ = 13.5 Hz, $^{3}J_{H\text{-}H}$ = 6.2 Hz, $^{3}J_{H\text{-}H}$ = 4.4 Hz, C*H*$_2$CH$_2$O), 3.38 (dd, 1H, $^{3}J_{H\text{-}F}$ = 20.7 Hz, $^{2}J_{H\text{-}H}$ = 16.7 Hz, ArC*H*$_2$CF), 3.43 (dd, 1H, $^{3}J_{H\text{-}F}$ = 20.8 Hz, $^{2}J_{H\text{-}H}$ = 16.7 Hz, ArC*H*$_2$CF), 3.87 (td, 1H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, $^{3}J_{H\text{-}H}$ = 4.5 Hz, CH$_2$C*H*$_2$O), 4.10 (td, 1H, $^{3}J_{H\text{-}H}$ = 8.6 Hz, $^{3}J_{H\text{-}H}$ = 6.3 Hz, CH$_2$C*H*$_2$O), 5.45 (d, 1H, $^{3}J_{H\text{-}F}$ = 20.3 Hz, ArC*H*OCH$_2$), 7.18 (d, 1H, $^{3}J_{H\text{-}H}$ = 7.2 Hz, Ar*H*), 7.28-7.31 (m, 2H, Ar*H*), 7.38 (t, 1H, $^{3}J_{H\text{-}H}$ = 4.3 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 39.5 (d, $^{2}J_{C\text{-}F}$ = 24.1 Hz, *C*H$_2$CH$_2$O), 41.4 (d, $^{2}J_{C\text{-}F}$ = 27.2 Hz, ArCH$_2$CF), 68.2 (CH$_2$*C*H$_2$O), 90.8 (d, $^{2}J_{C\text{-}F}$ = 27.2 Hz, Ar*C*HOCH$_2$), 113.3 (d, $^{1}J_{C\text{-}F}$ = 192.4 Hz, ArCH$_2$*C*F), 121.2 (Ar*C*), 125.0 (Ar*C*) 125.6 (Ar*C*), 127.7 (Ar*C*), 129.1 (Ar*C*), 139.5 (d, $^{3}J_{C\text{-}F}$ = 27.0 Hz, *C*); ^{19}F {^{1}H} NMR (376.6 MHz, $CDCl_3$) δ -151.3; HRMS (FI): *m/z* calcd for $C_{11}H_{11}FO$ $[M]^+$ 178.0794, found 178.0790.

3a-fluoro-3,3-dimethyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan (288F)



Compoud **288F** was prepared from 2-(1*H*-inden-2-yl)-2-methylpropan-1-ol **288** (20 mg, 0.11 mmol) according to general procedure 6. Purification of the crude product by silica gel column chromatography afforded the product **288F** as a colourless oil (13.5 mg, 60%); IR (ν, neat/cm^{-1}): 2970 (C-H), 1455 (C=C), 1090, 990; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H, C(C*H*$_3$)$_2$), 1.22 (d, 3H, $^{4}J_{H\text{-}F}$ = 3.6 Hz , C(C*H*$_3$)$_2$), 3.14 (dd, 1H, $^{3}J_{H\text{-}F}$ = 26.0 Hz, $^{2}J_{H\text{-}H}$ = 17.5 Hz, ArC*H*$_2$CF), 3.40 (dd, 1H, $^{2}J_{H\text{-}H}$ = 17.4 Hz, $^{3}J_{H\text{-}F}$ = 10.7 Hz, ArC*H*$_2$CF), 3.63 (d, 1H, $^{4}J_{H\text{-}F}$ = 8.4 Hz, OC*H*$_2$), 3.86 (dd, 1H, $^{4}J_{H\text{-}H}$ = 8.4 Hz, $^{4}J_{H\text{-}H}$ = 1.7 Hz, OC*H*$_2$), 5.48 (d, 1H, $^{3}J_{H\text{-}F}$ = 22.2 Hz, ArC*H*OCH$_2$), 7.18 (dd, 1H, $^{3}J_{H\text{-}H}$ = 6.5 Hz, $^{3}J_{H\text{-}H}$ = 1.1 Hz, Ar*H*), 7.27-7.32 (m, 2H, Ar*H*), 7.40 (dd, 1H, $^{3}J_{H\text{-}H}$ = 6.5 Hz, $^{3}J_{H\text{-}H}$ = 2.0 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (d, $^{3}J_{C\text{-}F}$ = 12.1 Hz, C(*C*H$_3$)$_2$), 21.7 (d, $^{3}J_{C\text{-}F}$ = 3.2 Hz, C(*C*H$_3$)$_2$), 37.4 (d, $^{2}J_{C\text{-}F}$ = 30.0 Hz, Ar*C*H$_2$CF), 44.6 (d, $^{2}J_{C\text{-}F}$ = 20.8 Hz, *C*(CH$_3$)$_2$), 80.3 (O*C*H$_2$), 91.2 (d, $^{2}J_{C\text{-}F}$ = 27.2 Hz, Ar*C*HOCH$_2$), 112.4 (d, ^{1}J = 195.8 Hz, ArCH$_2$*C*F), 124.4 (Ar*C*), 125.2 (Ar*C*), 127.5 (Ar*C*), 129.1 (Ar*C*), 140.1 (d, ^{3}J = 8.1 Hz, Ar*C*), 141.0 (d, ^{3}J = 8.1 Hz, Ar*C*); ^{19}F {^{1}H} NMR (376.6 MHz, $CDCl_3$) δ -158.9; HRMS (FI): *m/z* calcd for $C_{13}H_{15}FO$ $[M]^+$ 206.1105, found 206.1107.

3a-fluoro-3,3-dimethyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (289F)



Compoud **289F** was prepared from 2-(1*H*-inden-2-yl)-2-methylpropanoic acid **289** (15 mg, 0.07 mmol) according to general procedure 6. Purification of the crude product by silica gel column chromatography afforded the product **289F** as a colourless oil (11 mg, 65%)**.** IR (ν, neat/cm^{-1}): 2930 (C-H), 1675 (C=O), 1455 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H, C(C*H*$_3$)$_2$),

1.42 (d, 3H, $^{4}J_{H\text{-}F}$ = 4.1 Hz , C(CH_3)$_2$), 3.30 (dd, 1H, $^{3}J_{H\text{-}F}$ = 26.0 Hz, $^{2}J_{H\text{-}H}$ = 17.4 Hz, ArCH_2CF), 3.41 (dd, 1H, $^{2}J_{H\text{-}H}$ = 17.4 Hz, ^{4}J = 10.6 Hz, ArCH_2CF), 5.74 (d, 1H, $^{3}J_{H\text{-}F}$ = 16.0 Hz, 1H, ArC*H*O), 7.18 (s, 1H, Ar*H*), 7.32 (t, 2H, $^{3}J_{H\text{-}H}$ = 7.4, Ar*H*), 7.39 (t, 1H, $^{3}J_{H\text{-}H}$ = 7.4 Hz, Ar*H*), 7.49 (t, 1H, $^{3}J_{H\text{-}H}$ = 7.5 Hz, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.2 (d, $^{3}J_{C\text{-}F}$ = 12.9 Hz, C(*C*H$_3$)$_2$), 21.7 (C(*C*H$_3$)$_2$), 38.5 (d, $^{2}J_{C\text{-}F}$ = 28.6 Hz, Ar*C*H$_2$CF), 45.6 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz, *C*(CH$_3$)$_2$), 87.0 (d, $^{2}J_{C\text{-}F}$ = 28.3 Hz, Ar*C*HO), 112.4 (d, ^{1}J = 195.8 Hz, ArCH$_2$*C*F), 124.9 (Ar*C*), 126.5 (Ar*C*), 128.0 (Ar*C*), 130.6 (Ar*C*), 140.2 (d, ^{3}J = 8.1 Hz, Ar*C*), 141.3 (d, ^{3}J = 8.1 Hz, Ar*C*), 179.1 (CO); ^{19}F {^{1}H} NMR (376.6 MHz, $CDCl_3$) δ -163.9, HRMS (FI): *m/z* calcd for $C_{13}H_{13}FONa$ $[M+Na]^+$ 243.0792, found 243.0780.

II) Asymmetric Fluorocyclisation

General Procedure 7: Fluorocyclization of Indole with 230/Selectfluor combination or (2*R*,3*R*)-79/Selectfluor combination

A solution of the corresponding **230** or (2*R*,3*R*)-**79** (1.2 eq) and $NaHCO_3$ (1.2 eq) in acetone (1 mL) was treated with Selectfluor (1.2 eq) and the resulting mixture was stirred at required temperature for 1 hour, after which time the reaction was cooled to –78 °C. A pre-cooled (at –78 °C) solution of the indole derivative material (1 eq) in acetone (0.5 mL for 20 mg of indole starting material) was added dropwise and the reaction was stirred at the same temperature for the time indicated. The solvent was then evaporated and the residue was purified through neutral alumina to give the fluorocyclized product.

General Procedure 8: Fluorocyclization of Indene with 230/Selectfluor combination

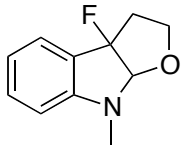
A solution of the corresponding **230** or (2*R*,3*R*)-**79** (1.2 eq) and $NaHCO_3$ (1.2 eq) in required solvent was treated with Selectfluor (1.2 eq) and the resulting mixture was stirred at required temperature for 1 hour, after which time the reaction was cooled to –78 °C. A pre-cooled (at –78 °C) solution of the indole derivative material (1 eq) in acetone (0.5 mL for 20 mg of indole

starting material) was added dropwise and the reaction was stirred at the same temperature for the time indicated. The solvent was then evaporated and the residue was purified through neutral alumina to give the fluorocyclized product.

General Procedure 9: Fluorocyclization of Indole/Indene with chiral N-F DABCO derivatives

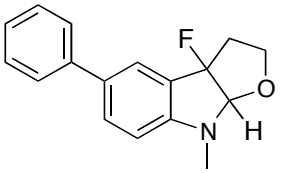
To a solution of indene (1 eq) and $NaHCO_3$ (1.5 eq) in acetone/acetonitrile (0.1 M) was added chiral N-F DABCO (2*R*,3*R*)-**212** (1.2 eq) at the indicated temperature. The reaction mixture was then stirred for 12-20 hours at room temperature, after which time the solvent was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and saturated $NaHCO_3$ solution was added. The aqueous phase was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane ether eluent). For the indoles, the residue was purified through neutral alumina.

3a-Fluoro-8-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (284F)



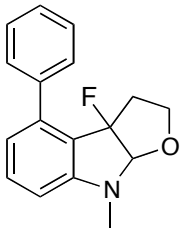
An orange oil was obtained. The enantiomeric mixtures were subjected to chiral HPLC (Chiralcel OJ-H, hexane/*i*PrOH 95:5, 1 mL/min): retention times 8.0 and 9.3 min.

3a-Fluoro-8-methyl-5-phenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (285F)



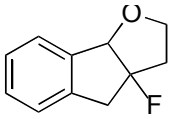
HPLC: (OJ-H, Hexane/ *i*-PrOH= 95/5, 1.0 mL/ min, 254 nm) t_R (minor-isomer) = 14.9 min, t_R (major-isomer) = 25.1 min

3a-Fluoro-8-methyl-4-phenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-b]indole (286F)



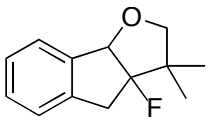
A colourless oil was obtained. The enantiomeric mixtures were subjected to chiral HPLC (Chiralcel OJ-H, hexane/*i*PrOH 90:10, 1 mL/min): retention times 8.1 and 14.0 min.

3a-fluoro-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan (287F)



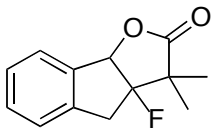
A colourless oil was obtained. The enantiomeric mixtures were subjected to chiral HPLC (Chiralcel OJ-H, hexane/*i*PrOH 99:1, 1 mL/min): retention times 7.1 and 18.1 min.

3a-fluoro-3,3-dimethyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan (288F)



A colourless oil was obtained. The enantiomeric mixtures were subjected to chiral HPLC (Chiralcel OJ, hexane/*i*PrOH 90:10, 1 mL/min): retention times 5.2 and 10.0 min.

3a-fluoro-3,3-dimethyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (289F)



A colourless oil was obtained. The enantiomeric mixtures were subjected to chiral HPLC (Chiralcel OD, hexane/*i*PrOH 95:5, 1 mL/min): retention times 7.4 and 9.7 min.

Chapter 6: References

[1] D. B. Harper and D. O'Hagan, *Nat. Prod. Rep*., 1994, **11**, 123–133.
[2] G. Sandford, *Phil. Trans. R. Soc. Lond*., A 2000, **358**, 455–471.
[3] D. O'Hagan and D. B. Harper, *J. Fluorine Chem.,* 1999, **100**, 127–133.
[4] R. J. H. Gregory, *Chem. Rev.,* 1999, **99**, 3649–3682.
[5] R. J. Abraham, S. L. R. Ellison, P. Schonholzer and W. A. Thomas, *Tetrahedron*, 1986, **42**, 2101–2110.
[6] L. Pauling, *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*; Cornell University Press: Ithaca, NY, 1939.
[7] A. Bondi, *J. Phys. Chem*., 1964, **68**, 441–451.
[8] R. Filler and R. Saha, *Future. Med. Chem*., 2009, **1**, 777–791.
[9] M. Shimizu and T. Hiyama, *Angew. Chem. Int. Ed*., 2005, **44**, 214–231.
[10] C. Ni, L. Zhang and J. Hu, *J. Org. Chem.* 2008, **73**, 5699–5713.
[11] D. O'Hagan and G. Sandford, *Chem. Br*. 2001, **37**, 32–35.
[12] V. Murtagh and R. E. Banks, Electrophilic Fluorination: An Introduction. *Performance Chemicals*, (Aug/Sept), 1991, 36.
[13] J. H. Clark, *Chem Rev*., 1980, **80**, 429–452.
[14] V.Grakauskas, *Intra-Sci. Chem. Rep*., 1971, **5**, 85–104.
[15] H. Zhao and F. P. Gabbaï, *Org. Lett*., 2011, **13**, 1444–1446.
[16] C. Hollingworth and V. Gouverneur, *Chem. Commun*., 2012, **48**, 2929–2942.
[17] A. G. Martinez, J. O. Barcina, A. Z. Rys and L. R. Subramanian, *Tetrahedron Lett.,* 1992, **33**, 7787–7788.
[18] M. C. Pacheco, S. Purser and V. Gouverneur, *Chem. Rev*. 2008**, 108**, 1943–1981.
[19] I. Déchamps, D. G. Pardo and J. Cossy, *Eur. J. Org. Chem*. 2007, **25**, 4224–4234.
[20] J. Emsley, *The Elements*, 3rd ed., Oxford University Press, Oxford, 1998.
[21] H. Rossotti, *Diverse Atoms*, Oxford University Press, Oxford, 1998.
[22] R.D. Chambers, *The fascination of fluorine*, *Chim. Ind. Milan,* 1997, **79**, 325.
[23] S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron,* 1999*,* **55**, 12431–12477.
[24] D. H. R. Barton, L. S. Godinho, R. H. Hesse and M. M. Pechet, *Chem. Commun*., 1968, **14**, 804–806.
[25] D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo and M. M. Pechet, *Chem. Commun*., 1968, **14**, 806–808.
[26] M. A. Tius, *Tetrahedron,* 1995, **51**, 6605–6634.
[27] R. Schmutzler, *Angew. Chem. Int. Ed*., 1968, **80**, 440–455.
[28] S. Rozen, *Chem. Rev.,* 1996, **96***,* 1717–1736.
[29] W. Navarrini, V. Tortelli, A. Russo and S. Corti, *J. Fluorine Chem*., 1999, **95**, 27–39.
[30] R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, L. Sharifa and R. G. Syvret. *J. Chem. Soc., Chem. Commun*., 1992, **8**, 595–596.
[31] J. A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119–6146.
[32] V.A. Brunet and D. O'Hagan, *Angew Chem Int Ed.,* 2008, **47**, 1179–1182.
[33] T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada and K. Tomital, *J. Am. Chem.* Soc., 1990. **112**, 8567–8575.
[34] W. E. Barnette, *J. Am. Chem. Soc.,* 1984, **106**, 452–454.
[35] E. Differding and H. Ofner, *Synlett* 1991, **109**, 187–189.
[36] S. Singh, D. D. DesMarteau, S. S. Zuberi, M. Witz and H. N. Huang, *J. Am. Chem. Soc.,* 1987, **109**, 7194–7196.
[37] R. E. Banks, *J. Fluorine Chem.,* 1998, **87**, 1–17.
[38] T. Furuya, C. A Kuttruff and T. Ritter, *Curr. Opin. Drug Discov. Devel.*, 2008, **11**, 803–819.
[39] P. Kirsch (Ed.), Modern Fluoroorganic Chemistry, Synthesis, Reactivity, Applications, Wiley, Weinheim, 2004.
[40] R. P. Singh and J. M. Shreeve, *Acc. Chem. Res*. 2004, **37**, 31–44.

[41] A. G. Gilicinski, G. P. Pez, R. G. Syvret, G. S. Lal, *J. Fluorine Chem.*, 1992, **59**, 157–162.
[42] R.E Bank, Air Products and Chemicals, Inc.; US Patent no 5,086, 178; 1992
[43] J.J. Hart, R.G. Syvret, *J. Fluorine Chem.,* 1999, **100**, 157–161.
[44] P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C. Wong, *Angew. Chem. Int. Ed*., 2005, **44**, 192–212.
[45] R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf and I Sharif, *J. Chem.* Soc. *Perkin Trans. I.,* 1996, 2069 –2076.
[46] S. P. Vincent, M. D. Burkart, C-Y. Tsai, Z. Zhang, C-H. Wong, *J. Org. Chem*. 1999, **64**, 5264–5279.
[47] G. S. Lal, *J. Org. Chem*., 1993, **58**, 2791–2796.
[48] P. Ge, K. L. Kirk, *J. Org. Chem*., 1997, **62**, 3340–3343.
[49] R. V. Hoffman and J. Tao, *J. Org. Chem*., 1999, **64**, 126–132.
[50] D. Enders and M. R. M. Hüttl, *Synlett* 2005, **6**, 991–993.
[51] L. Hintermann and A. Togni, *Angew. Chem. Int. Ed.*, 2000, **39**, 4359–4362.
[52] M. Perseghini, M. Massaccesi, Y. Liu and A. Togni, *Tetrahedron* 2006, **62**, 7180–7190.
[53] V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, *Science* 2011, **334**, 1681–1684.
[54] R. J. Phipps, K. Hiramatsu and F. D. Toste, *J. Am. Chem. Soc*., 2012, **134**, 8376**–**8379.
[55] T. Honjo, R. J. Phipps, V. Rauniyar and F. D. Toste, *Angew. Chem. Int. Ed*., 2012, **51**, 1–6.
[56] B. Greedy and V. Gouverneur, *Chem. Commun*. 2001, **3**, 233–234.
[57] S. Purser, B. Odell, T. D. W. Claridge, P. R. Moore and V. Gouverneur, *Chem. Eur. J*., 2006, **12**, 9176–9185.
[58] S. Purser, C. Wilson, P. R. Moore and V. Gouverneur, *Synlett* 2007, **7**, 1166–1168.
[59] Y-H Lam, M. N. Hopkinson, S. J. Stanway, V. Gouverneur, *Synlett* 2007, **19**, 3022–3026.
[60] Y-H. Lam, C. Bobbio, I.R. Cooper and V. Gouverneur, *Angew. Chem. Int. Ed*., 2007, **46**, 5106–5110.
[61] S. C. Wilkinson, O. Lozano, M. Schuler, M. C. Pacheco, R. Salmon, and V. Gouverneur, *Angew. Chem. Int. Ed*., 2009, **48**, 7083 –7086
[62] G. T. Giuffredi, S. Purser, M. Sawicki, A. L. Thompson, V. Gouverneur, *Tetrahedron Asymmetry* 2009, **20**, 910–920
[63] D. P. Matthews, S. C. Miller, E. T. Jarvi, J. S. Sabol and J. R. McCarthy, *Tetrahedron Lett*., 1993, **34**, 3057–3060.
[64] H. F. Hodson, D. J. Madge and D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1*., 1995, 2965–2970.
[65] N. Ahlsten, A. Bartoszewicz, S. Agrawal and B. Martín-Matute, *Synthesis* 2011, **16**, 2600–2608.
[66] O. Lozano, G. Blessley, T. Martinez-del-Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, and V. Gouverneur, *Angew. Chem. Int. Ed*., 2011, **50**, 8105–8109.
[67] S. Stavber, M. Jereb, M. Zupan, *Synlett* 1999, **9**, 1375–1378.
[68] S. Dedola, D. L. Hughes and R. A. Field, *Acta Cryst*., 2010, **C66**, o124–o127
[69] M. D. Burkart, Z. Zhang, S.-C. Hung and C.-H. Wong, *J. Am. Chem. Soc.* 1997, **119**, 11743–11746.
[70] S. Stavber, *Molecules* 2011, **16**, 6432–6464.
[71] R. E. Banks, N. J. Lawrence, A. L. Popplewell, *Synlett* 1994, **10**, 831–832.
[72] J. Pavlinac, M. Zupan, S. Stavber, *J. Org. Chem.,* 2006, **71**, 1027–1032.
[73] C. Ye, J. M. Shreeve, *J. Org. Chem*., 2004, **69**, 8561–8563.
[74] J. Liu, C.-H. Wong, *Tetrahedron Lett*., 2002, **43**, 3915–3917.
[75] S. Stavber, P. Kralj, M. Zupan, *Synlett* 2002, 598–600.
[76] S. Stavber, P. Kralj, M. Zupan, *Synthesis* 2002, 1513–1517.
[77] R. G. Syvret, K. M. Butt, T. P. Nguyen, V. L. Bulleck, R. D.Rieth, *J. Org. Chem*., 2002, **67**, 4487–4493.

[78] K. M. Engle, T.-S. Mei, X. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed*., 2011, **50**, 1478–1491.
[79] L. Cui, G. Zhang, L. Zhang, *Bioorg. Med. Chem. Lett*. 2009, **19**, 3884–3887.
[80] M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. Eur. J*., 2011, **17**, 8248–8262.
[81] G. Zhang, Y. Peng, L. Cui, L. Zhang, *Angew. Chem. Int. Ed*., 2009, **48**, 3112–3115.
[82] W. Wang, J. Jasinski, G. B. Hammond, B. Xu, *Angew. Chem. Int. Ed*., 2010, **49**, 7247–7252.
[83] Y. Peng, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc*. 2009, **131**, 5062–5063.
[84] G. Zhang, L. Cui, Y. Wang and L Zhang, *J. Am. Chem. Soc*., 2010, **132**, 1474–1475.
[85] L. T. Ball, M. Green, G. C. Lloyd-Jones, C. A. Russell, *Org. Lett*., 2010, **12**, 4724–4727.
[86] M. N. Hopkinson, A. Tessier, A. Salisbury, G. T. Giuffredi, L. E. Combettes, A.D. Gee, V. Gouverneur, *Chem. Eur. J*. 2010, **16**, 4739–4743.
[87] M. N. Hopkinson, J. E. Ross, G. T. Giuffredi, A. D. Gee, V. Gouverneur, *Org. Lett*., 2010, **12**, 4904–4907.
[88] T Wada, E. Kishida, Y. Tomiie, H. Suga, S. Seki and I. Nitta, *Bull. Chem. Soc. Japan*, 1960, **33**, 1317–1318.
[89] G. S. Weiss, A. S. Parkes, E. R. Nixon and R. E. Hughes, *J. Chem. Phys*. 1964, **41**, 3759–3767.
[90] A. Farkas, G. A. Mills, W. E. Erner and J. B. Maerker, *J. Chem. Eng. Data* 1959, **4**, 334–335.
[91] A. Farkas, G. A. Mills, W. E. Erner and J. B. Maerker, *Ind. Eng. Chem.* 1959, **51**, 1299–1300.
[92] C. Faltin, E. M. Fleming and S. J. Connon, *J. Org. Chem*. 2004, **69**, 6496–6499.
[93] E. Honegger, Z. Z Yang, and E. Heilbronner, *J. Elect. Spectrosc. Rel. Phenom*, 1985, **36**, 297–304.
[94] A. Rauk, *Orbital Interaction Theory of Organic Chemistry*, 2nd Ed. Wiley-Interscience Publication, NY, 2001.
[95] A. G. Doyle and E. N. Jacobsen, *Chem. Rev*. 2007, **107**, 5713−5743.
[96] V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev,* 2009, **109**, 1–48.
[97] B. Baghernejad, *Eur. J. Chem.,* 2010, **1**, 54−60.
[98] R. Oi and K. B. Sharpless, *Tetrahedron Lett.*, 1991, **32**, 4853–4854.
[99] T. Oishi and M. Hirama, *Tetrahedron Lett*., 1992, **33**, 639–642.
[100] Hideharu K. Soai, A. Oshio and H. Yoneyama, *Tetrahedron: Asymmetry* 1992, **3**, 359–360.
[101] K. Fuji, K. Tanaka and K. Takasu, *Tetrahedron: Asymmetry* 1996, **7**, 1749–1751.
[102] Q. Li-Hun, S. Zong-Xuan, C. Wu-Hong, Z. Yong and Z. Ya-Wen, *Chin. J. Chem*., 2003, **21**, 10098–1100.
[103] T. Oishi, H. Oguri and M. Hirama, *Tetrahedron Asymmetry* 1995, **6**, 1241–1244.
[104] S. Jeedigunta, J. M. Krenisky and R. G. Kerr, *Tetrahedron* 2000, **56**, 3303–3307.
[105] K. H. Park, M. M. Olmstead and M. J. Kurth, *Synlett* 2003, 1267–1270.
[106] R. A. Rodriguez, P. S. Pan, C. M. Pan, S. Ravula, S. Lapera, E. K. Singh, T. J. Styers, J. D. Brown, J. Cajica, E. Parry, K. Otrubova and S. R. McAlpine, *J. Org. Chem.*, 2007, **72**, 1980–2002.
[107] K. Otrubova, G. Lushington, D. V. Velde, K. L. McGuire and S. R. McAlpine, *J. Med. Chem.*, 2008, **51**, 530–544.
[108] D. K. Mohapatra and A. Datta, *J. Org. Chem.*, 1999, **64**, 6879–6880.
[109] I. O. Donkor and M. L. Sanders, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2647–2649.
[110] A. Y. Khimiuk, A. V. Korennykh, L. M. van Langen, F. van Rantwijk, R. A. Sheldon and V. K. Svedas, *Tetrahedron: Asymmetry* 2003, **14**, 3123–3128.
[111] D. E. Nitecki, B. Halpern and J. W. Westley, *J. Org. Chem.*, 1968, **33**, 864–866.
[112] L. H. Qiu, Z. X. Shen, W. H. Chen, Y. Zhang and Y. W. Zhang, *Chin. J. Chem.*, 2003, **21**, 1098–1100.
[113] M. E. Jung and J. C. Rohloff, *J. Org. Chem.*, 1985, **50**, 4909–4913.

[114] K. Soai, H. Hayashi, A. Shinozaki, H. Umebayashi and Y. Yamada, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3450–3452.
[115] M. Couturier, J. L. Tucker, B. M. Andresen, P. Dube and J. T. Negri, *Org. Lett.*, 2001, **3**, 465–467.
[116] Y. N. Belokon, L. K. Pritula, V. I. Tararov, V. I. Bakhmutov, Y. T. Struchkov, T. V. Timofeeva and V. M. Belikov, *J. Chem. Soc., Dalton Trans.*, 1990, 1867–1872.
[117] H. Kim, Y. Nguyen, C. P. H. Yen, L. Chagal, A. J. Lough, B. M. Kim and J. Chin, *J. Am. Chem. Soc*. 2008, **130**, 12184–12191.
[118] S. M. So, L. Mui, H. Kim and J. Chin, *Acc. Chem. Res*., 2012, **45**, 1345–1355.
[119] K. L. Kirk, *Org. Proc. Res. Develop.* **2008**, 12, 305–321.
[120] T. Hiyama, *Organofluorine Compound: Chemistry and Applications*, Springer-Verlag Berlin, 2000.
[121] R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf and I. Sharif, *J. Fluorine Chem*., 1996, 7**8**, 43–50.
[122] R. E. Banks and M. K. Besheesh, *J. Fluorine Chem.*, 1995, **74**, 165–166.
[123] C. A. Cupas, M. B. Comisarow and G. A. Olah, *J. Am. Chem. Soc.,* 1966, **88**, 361–362.
[124] G. A. Olah, R. D. Porter and D. P. Kelly, *J. Am. Chem. Soc.,* 1971, **93**, 464–466.
[125] D. Stadler, A. Goeppert, G. Rasul, G. A. Olah, G. K. S. Prakash and T. Bach, *J. Org. Chem.,* 2009, **74**, 312–318.
[126] T. Rosenau, A. Potthast and P. Kosma, *Tetrahedron*, 2004, **60**, 301–306.
[127] W. Schroth and U. J. D. Strohl, *Chem. Ber.*, 1994, **127**, 2013–2022.
[128] R. E. Banks, S. N. Mohialdinkhaffaf, G. S. Lal, I. Sharif and R. G. Syvret, *J. Chem. Soc., Chem. Commun.*, 1992, 595–596.
[129] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra and V. Gouverneur, *Angew. Chem. Int. Ed*. 2010, **49**, 6821–6824.
[130] K. Bowden and S. J. Hirani, *J. Chem. Soc. Perkin Trans.2*. 1990, 1889–1891.
[131] G. S. Lal, G. P. Pez and R. G. Syvret, *Chem. Rev*. 1996, **96**, 1737–1755.
[132] Umemoto, US patent no: 5,573,868
[133] T. Umemoto, K. Kawada and K. Tomita, *Tetrahedron Lett.* 1986, **27**, 4465–4468.
[134] T. Umemoto, K Harasawa, G. Tomizawa, K. Kawada and K. Tomita, *Bull. Chem. Soc. Jpn*. 1991, **64**, 1081–1092.
[135] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell and N. Shakir, *Tetrahedron* 1965, **21**, I055–1059.
[136] M. Okada, Y. Nakamura, H. Horikawa, T. Inoue and T. Taguchi, *J. Fluorine Chem*., 1997, **82**, 157–161.
[137] N. Shibata, E. Suzuki and Y. Takeuchi, *J. Am. Chem. Soc.*, 2000, **122**, 10728–10729.
[138] G. Sandford, Fluorine laboratory, *Chemistry Department*, University of Durham.
[139] R. D. Chambers, D. Holling, G. Sandford, H. Puschmann and J. A.K. Howard, *J. Fluorine Chem*. 2002, **117**, 99–101.
[140] R.D. Chambers, M. Parsons, G. Sandford, C.J. Skinner, M.J.Atherton and J.S. Moilliet, *J. Chem. Soc. Perkin Trans 1*. 1999, 803–810.
[141] R.D.Chambers, J.Hutchinson, M.E.Sparrowhawk, G. Sandford, J.S. Moilliet and J. Thomson, *J. Fluorine Chem.,* 2000, **102**, 169–173.
[142] G. Sandford, *J. Fluorine Chem.*, 2007, **128**, 90–104.
[143] R. S. Matthews, *J. Fluorine Chem.*, 1991, **55**, 163–167.
[144] S. Purser, P. R. MoorGue, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
[145] V. A. Brunet and D. O'Hagan, *Angew. Chem. Int. Ed.*, 2008, **47**, 1179–1182. P. M. Pihko, *Angew. Chem*. 2006, **118**, 558 – 561; *Angew. Chem. Int. Ed*. 2006, **45**, 544 – 547. G. K. S.

Prakash, P. Beier, *Angew.Chem*.2006, **118**, 2228–2230; *Angew. Chem. Int. Ed*. 2006, **45**, 2172 – 2174. J.-A. Ma, D. Cahard, *Chem. Rev*. 2004, **104**, 6119–6146.
[146] K. Muniz, *Angew. Chem. Int. Ed.*, 2001, **40**, 1653–1656.
[147] S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron* 1999, **55**, 12431–12477.
[148] F. A. Davis, M. C. Weismiller, C. K. Murphy, R. T. Reddy and B. C. Chen, *J. Org. Chem.*, 1992, **57**, 7274–7285.
[149] E. Differding and R. W. Lang, *Tetrahedron Lett.*, 1988, **29**, 6087–6090.
[150] E. Differding and R. W. Lang, *Helv. Chimi. Acta*, 1989, **72**, 1248–1252.
[151] F. A. Davis, P. Zhou and C. K. Murphy, *Tetrahedron Lett.*, 1993, **34**, 3971–3974.
[152] F. A. Davis, P. Zhou and B. C. Chen, *Phosphorus Sulfur Silicon Relat. Elem.* 1996, 115, 85–91.
[153] F. A. Davis, W. Han and C. K. Murphy, *J. Org. Chem.*, 1995, **60**, 4730–4737.
[154] F. A. Davis, P. Zhou, C. K. Murphy, G. Sundarababu, H. Y. Qi, W. Han, R. M. Przeslawski, B. C. Chen and P. J. Carroll, *J. Org. Chem.*, 1998, **63**, 2273–2280.
[155] R. D. Bach, J. L. Andres and F. A. Davis, *J. Org. Chem*. 1992, **57**, 613–618.
[156] Y. Takeuchi, A. Satoh, T. Suzuki, A. Kameda, M. Dohrin, T. Satoh, T. Koizumi and K. L. Kirk, *Chem. Pharm. Bull.*, 1997, **45**, 1085–1088.
[157] Y. Takeuchi, T. Suzuki, A. Satoh, T. Shiragami and N. Shibata, *J. Org. Chem.*, 1999, **64**, 5708–5711.
[158] N. Shibata, Z. P. Liu and Y. Takeuchi, *Chem. Pharm. Bull.*, 2000, **48**, 1954–1958.
[159] Z. P. Liu, N. Shibata and Y. Takeuchi, *J. Org. Chem.*, 2000, **65**, 7583–7587.
[160] D. Cahard, C. Audouard, J. C. Plaquevent and N. Roques, *Org. Lett.*, 2000, **2**, 3699–3701.
[161] M. Abdul-Ghani, R. E. Banks, M. K. Besheesh, I. Sharif and R. G. Syvret, *J. Fluorine Chem*. 1995, **73**, 255–257.
[162] D. Cahard, C. Audouard, J. C. Plaquevent, L. Toupet and N. Roques, *Tetrahedron Lett.*, 2001, **42**, 1867–1869.
[163] B. Mohar, M. Baudoux, J. C. Plaquevent and D. Cahard, *Angew. Chem. Int. Ed.*, 2001, **40**, 4214–4216.
[164] B.Thierry, C. Audouard, J-C. Plaquevent and D. Cahard, *Synlett* 2004, **5**, 856–860.
[165] C. Baudequin, J. F. Loubassou, J. C. Plaquevent and D. Cahard, *J. Fluorine Chem.*, 2003, **122**, 189–193.
[166] J-A Ma and D. Cahard, *J. Fluorine Chem.*, 2004, **125**, 1357–1361.
[167] N. Shibata, E. Suzuki, T. Asahi and M. Shiro, *J. Am. Chem. Soc.*, 2001, **123**, 7001–7009.
[168] N. Shibata, T. Ishimaru, E. Suzuki and K. L. Kirk, *J. Org. Chem.*, 2003, **68**, 2494–2497.
[169] N. Shibata, T. Ishimaru, S. Nakamura and T. Toru, *J. Fluorine Chem.*, 2007, **128**, 469–483.
[170] V. Gouverneur and B. Greedy, *Chem. Eur. J.*, 2002, **8**, 767–771.
[171] B. Greedy, J. M. Paris, T. Vidal and V. Gouverneur, *Angew. Chem. Int. Ed.*, 2003, **42**, 3291–3294.
[172] T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem. Int. Ed*. 2008, **47**, 4157 –4161.
[173] Z. Horii, T. –F. Momose and Y. Tamura, *Chem. Pharm. Bull*., 1962, **10**, 946–951.
[174] D. S. Brown, B. A. Marples, P. Smith, L. Walton, *Tetrahedron* 1995, **51**, 3587–3606.
[175] M. Pažický, V. Semak, B. Gášpár, A. Bílešová, M. Sališová and A. Bohác, *ARKIVOC* 2008, **8**, 225–241.
[176] J. Burfeindt, M. Patz, M. Müller, and H. Mayr, *J. Am. Chem. Soc.* 1998, **120***,* 3629–3634.
[177] S. J. Garden, R. B. da Silva and A. C. Pinto, *Tetrahedron* 2002*,* **58**, 8399–8412.
[178] M. P. Wentiand, D. M. Bailey, E. J. Alexander, M. J. Castaldi, R. A. Ferrari, D. R. Haubrich, D. A. Luttinger, and M. H. Perrone, *J. Med. Chem.* 1987, **30***,* 1482–1489.

[179] D. A. Broyles and B. K. Carpenter, *Org. Biomol. Chem*., 2005, **3**, 1757–1767.
[180] D. W. Emerson, R. L. Titus and M. D. Jones, *J. Heterocyclic Chem*., 1998, **35**, 611–617.
[181] G. Cerichelli, S. Cerritelli, M. Chiarini, P. D. Maria, A. Fontana, *Chem. Eur J*., 2002, **8**, 5204–5210.
[182] E.H. Licht, H. G. Alt and M. M. Karim, *J. Organomet. Chem*., 2000, **599**, 275–287.
[183] S. Titouani, W. M. Soufiaoui, L. Toupet and R. Carrie, *Tetrahedron* 1990, **46**, 3869–3878.
[184] D. Basavaiah and R. M. Reddy, *Tetrahedron Lett*., 2001, **42**, 3025–3028.

Appendix

A1 X-Ray Crystollagraphic Data

A typical single crystal was chosen and was mounted on a hair using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems Cryostream N_2 open flow-cooling device. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoKα radiation, λ = 0.71073 Å) to a maximum resolution of 0.77 Å. Intensity data were processed using the DENZO-SMN package and were corrected for absorption and other effects using SCALEPACK. The systematic absences in the intensity data were examined to determine the space group (P212121). The structures were solved using the direct-methods program SIR92, which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite to refine coordinates and anisotropic thermal parameters of all non-hydrogen atoms. Hydrogen atoms were located in the difference map and refined before being added to the model using a riding constraint.

A summary of crystallography data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters, bond lengths and angles not concerning H atoms.

(1*R*,2*S*,4*R*,5*S*)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane dihydrochloride (91)

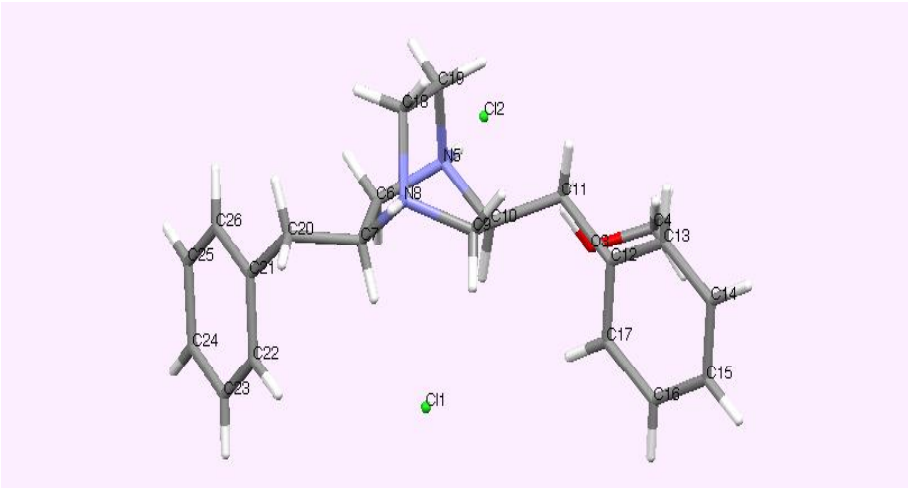


Figure A1 X-ray crystal structure of (1*R*,2*S*,4*R*,5*S*)-**91** dihydrochloride salt methanol solvate

(1*R*,2*S*,4*R*,5*S*)-2,5-bis(phenylmethyl)-1,4-diazabicyclo-[2.2.2]octane dihydrochloride (50 mg) was dissolved in methanol (5 ml). After standing for a week, suitable crystals formed gradually.

Table 1: Crystal data and refinement details

Crystal identification	062JI01
Chemical formula (sum)	$C_{21}H_{30}Cl_2N_2O$
Chemical formula (moiety)	$C_{20}H_{26}N_2$, CH_4O, 2(Cl)
Formula weight	397.39
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group name	P 21 21 21
Space group hall	P 2ac 2ab
a (Å)	7.03660(10)

b (Å)	12.3790(2)
c (Å)	24.9326(5)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å^3)	2171.78(6)
Z	4
Calculated density (Mg/m^3)	1.215
Absorption coefficient (mm^{-1})	0.311
F000	848
Crystal size (mm)	0.06 × 0.08 × 0.20
Description of crystal	Colourless plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min, max)	0.94, 0.98
θ range for data collection (°)	5.176 ≤ θ ≤ 27.487 (0.990)
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 16, -32 ≤ l ≤ 32
Reflections measured/number	19686
Unique reflections	4936
Observed reflections (I > -3σ(I))	4936
Computed reflections (I > 2σ(I))	3973
Refinement method	Full-matrix least-squares on F
Parameters refined	236
Weighting scheme	Auto-statistical

Goodness of fit	0.9441
R (observed)	0.0592
R (computed)	0.0384
wR (observed)	0.0462
wR (computed)	0.0385
Residual electron density (min, max) ($eÅ^{-3}$)	-0.42, 0.40

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	Symbol	x	y	z	U^{equiv}
Cl1	Cl	0.19537(7)	0.33212(4)	0.48498(2)	0.0269
Cl2	Cl	0.26787(9)	0.73203(4)	0.42186(2)	0.0333
O3	O	0.0155(3)	0.5944(2)	0.34458(8)	0.0912
C4	C	0.0693(4)	0.5959(3)	0.29129(12)	0.0649
N5	N	0.5736(2)	0.57408(13)	0.45249(7)	0.0195
C6	C	0.5351(3)	0.54156(17)	0.50935(8)	0.0194
C7	C	0.6614(3)	0.44426(17)	0.52262(8)	0.0205
N8	N	0.8216(2)	0.44540(12)	0.48266(7)	0.0196
C9	C	0.7471(3)	0.41027(14)	0.42903(8)	0.0213
C10	C	0.5671(3)	0.47558(16)	0.41694(9)	0.0201
C11	C	0.5473(3)	0.50757(18)	0.35771(8)	0.0237
C12	C	0.5081(3)	0.41265(18)	0.32163(8)	0.0228
C13	C	0.6158(3)	0.3967(2)	0.27544(9)	0.0308
C14	C	0.5745(4)	0.3134(2)	0.24030(10)	0.037
C15	C	0.4263(4)	0.2442(2)	0.25052(10)	0.0371
C16	C	0.3182(3)	0.25770(19)	0.29643(9)	0.0346
C17	C	0.3587(3)	0.34212(19)	0.33157(9)	0.0306
C18	C	0.9073(3)	0.55566(17)	0.47767(10)	0.024
C19	C	0.7627(3)	0.62939(14)	0.44992(8)	0.0224
C20	C	0.7298(3)	0.44434(15)	0.58082(8)	0.0244
C21	C	0.5570(3)	0.44862(18)	0.61664(8)	0.0237
C22	C	0.4363(4)	0.35960(19)	0.62009(9)	0.0295
C23	C	0.2675(4)	0.36644(19)	0.64825(9)	0.0382
C24	C	0.2145(4)	0.4615(2)	0.67290(9)	0.0432
C25	C	0.3360(4)	0.5498(2)	0.67013(10)	0.0484
C26	C	0.5047(4)	0.5431(2)	0.64263(10)	0.0377

Table 3: Atomic coordinates and equivalent isotropic thermal parameters (Å^2) of hydrogen atoms

Atom	Symbol	x	y	z	U^{equiv}
H62	H	0.5716	0.6038	0.5305	0.0216
H61	H	0.4049	0.5233	0.513	0.0235
H71	H	0.5913	0.3789	0.5161	0.0252
H91	H	0.8444	0.4269	0.4023	0.0254
H92	H	0.7202	0.3345	0.4325	0.0255
H101	H	0.449	0.4343	0.4281	0.0235
H111	H	0.6618	0.5453	0.3477	0.0282
H112	H	0.4423	0.5604	0.3531	0.0271
H131	H	0.7225	0.4415	0.2689	0.0362
H141	H	0.6433	0.3061	0.2089	0.0454
H151	H	0.4012	0.1867	0.2271	0.0457
H161	H	0.2152	0.208	0.3035	0.0413
H171	H	0.2881	0.3492	0.3634	0.0376
H182	H	0.9326	0.5835	0.5129	0.03
H181	H	1.0242	0.5513	0.4576	0.029
H192	H	0.7525	0.6984	0.4689	0.0278
H191	H	0.8	0.6427	0.4124	0.0256
H202	H	0.81	0.5034	0.587	0.0288
H201	H	0.8019	0.3801	0.5863	0.0289
H221	H	0.4727	0.2924	0.6012	0.0338
H231	H	0.1872	0.3045	0.6517	0.0457
H241	H	0.099	0.4667	0.6907	0.0518
H251	H	0.2983	0.618	0.6861	0.0581
H261	H	0.5826	0.6049	0.6395	0.0436
H43	H	0.2084	0.5897	0.2866	0.0973
H42	H	0.0026	0.5389	0.2709	0.0982
H81	H	0.9189	0.4021	0.4921	0.0301
H41	H	0.0208	0.6631	0.2776	0.0987
H31	H	0.096	0.6294	0.3633	0.1365
H51	H	0.4786	0.6209	0.4412	0.0297

Table 4: Anisotropic thermal parameters (Å^2)

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	0.0186(2)	0.0221(3)	0.0400(3)	0.0023(3)	-0.0003(3)	0.0000(2)
Cl2	0.0367(4)	0.0264(3)	0.0367(3)	-0.0037(3)	-0.0056(3)	0.0119(3)
O3	0.0656(15)	0.157(3)	0.0511(14)	-0.0441(16)	0.0325(13)	-0.0636(16)
C4	0.0419(18)	0.110(3)	0.0426(18)	-	0.0002(15)	-0.015(2)

				0.0045(19)		
N5	0.0193(9)	0.0155(9)	0.0237(10)	-0.0002(8)	0.0015(8)	0.0007(8)
C6	0.0190(10)	0.0185(11)	0.0206(12)	-0.0006(9)	0.0024(10)	-0.0004(9)
C7	0.0186(11)	0.0208(10)	0.0222(11)	-0.0011(10)	0.0039(9)	0.0005(8)
N8	0.0169(8)	0.0185(8)	0.0234(9)	0.0001(8)	0.0003(8)	0.0022(7)
C9	0.0244(11)	0.0200(9)	0.0194(10)	-0.0027(9)	0.0005(10)	0.0027(9)
C10	0.0204(11)	0.0180(10)	0.0220(11)	-0.0045(9)	-0.0003(10)	0.0020(9)
C11	0.0269(13)	0.0232(12)	0.0211(12)	0.0011(10)	0.0011(10)	0.0016(10)
C12	0.0239(12)	0.0239(12)	0.0206(12)	0.0000(10)	-0.0038(10)	0.0035(10)
C13	0.0326(14)	0.0313(13)	0.0285(13)	-0.0003(12)	0.0059(11)	0.0000(11)
C14	0.0441(16)	0.0399(15)	0.0268(14)	-0.0057(12)	0.0066(12)	0.0060(14)
C15	0.0532(17)	0.0297(14)	0.0284(13)	-0.0086(11)	-0.0090(12)	0.0025(13)
C16	0.0365(14)	0.0344(13)	0.0330(12)	-0.0034(11)	-0.0077(12)	-0.0074(12)
C17	0.0332(13)	0.0348(14)	0.0238(12)	-0.0026(11)	-0.0008(10)	-0.0002(11)
C18	0.0193(11)	0.0240(11)	0.0286(13)	0.0010(11)	0.0021(10)	-0.0032(9)
C19	0.0243(12)	0.0185(10)	0.0245(11)	0.0011(8)	0.0012(10)	-0.0056(9)
C20	0.0255(12)	0.0259(10)	0.0218(10)	-0.0014(10)	-0.0041(11)	-0.0041(10)
C21	0.0284(13)	0.0235(12)	0.0193(11)	-0.0034(10)	-0.0021(10)	-0.0033(10)
C22	0.0356(14)	0.0279(13)	0.0250(12)	-0.0022(10)	0.0016(11)	-0.0045(11)
C23	0.0381(15)	0.0405(14)	0.0358(14)	0.0005(11)	-0.0087(13)	-0.0122(13)
C24	0.0466(17)	0.0522(17)	0.0310(14)	-0.0048(12)	0.0181(14)	-0.0036(15)
C25	0.070(2)	0.0365(15)	0.0391(16)	-0.0099(13)	0.0232(15)	-0.0008(15)
C26	0.0515(17)	0.0290(14)	0.0325(14)	-0.0046(12)	0.0088(13)	-0.0097(13)

Table 5: Bond lengths (Å)

O3-C4	1.382(3)	N5-C6	1.498(2)
N5-C10	1.508(2)	N5-C19	1.498(2)
C6-C7	1.533(3)	C7-N8	1.505(2)
C7-C20	1.529(3)	N8-C9	1.501(2)
N8-C18	1.497(2)	C9-C10	1.532(3)
C10-C11	1.535(3)	C11-C12	1.505(3)
C12-C13	1.393(3)	C12-C17	1.389(3)

C13-C14	1.384(3)	C14-C15	1.374(3)
C15-C16	1.384(3)	C16-C17	1.393(3)
C18-C19	1.532(3)	C20-C21	1.510(3)
C21-C22	1.394(3)	C21-C26	1.387(3)
C22-C23	1.383(3)	C23-C24	1.378(3)
C24-C25	1.390(3)	C25-C26	1.374(3)

Table 6: Bond angles (Å)

C6-N5-C10	109.47(15)	C6-N5-C19	108.89(16)
C10-N5-C19	111.77(15)	N5-C6-C7	108.10(16)
C6-C7-N8	106.50(16)	C6-C7-C20	112.77(17)
N8-C7-C20	113.10(16)	C7-N8-C9	108.99(15)
C7-N8-C18	111.41(15)	C9-N8-C18	109.33(16)
N8-C9-C10	108.13(15)	C9-C10-N5	106.63(17)
C9-C10-C11	113.61(18)	N5-C10-C11	111.07(16)
C10-C11-C12	112.96(18)	C11-C12-C13	120.3(2)
C11-C12-C17	121.5(2)	C13-C12-C17	118.0(2)
C12-C13-C14	121.0(2)	C13-C14-C15	120.4(2)
C14-C15-C16	119.7(2)	C15-C16-C17	119.9(2)
C16-C17-C12	120.9(2)	N8-C18-C19	108.27(15)
C18-C19-N5	107.35(15)	C7-C20-C21	107.93(17)
C20-C21-C22	120.0(2)	C20-C21-C26	121.3(2)
C22-C21-C26	118.4(2)	C21-C22-C23	120.4(2)
C22-C23-C24	120.7(2)	C23-C24-C25	118.9(2)
C24-C25-C26	120.6(2)	C21-C26-C25	120.9(2)

***(1R,2R,4R,5R)*-2,5-Diphenyi-l,4-diazabicyclo[2.2.2]octane (94)**

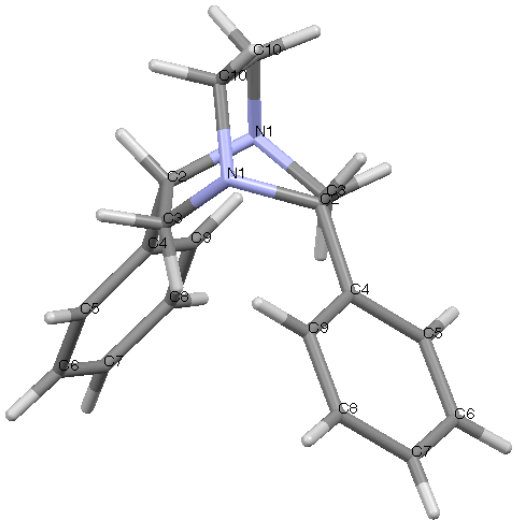


Figure A2 X-ray structure of chiral DABCO (1*R*,2*R*,4*R*,5*R*)-**94**

Crystal Data

a =	10.7033(8) Å	α =	90°
b =	6.3969(6) Å	β =	112.169(4)°
c =	10.7880(9) Å	γ =	90°

Volume	684.03(10) Å³	Crystal Class	monoclinic
Space group	C 1 2 1	Z =	2
Formula	C_{18} H_{20} N_2	M_r	264.37
Cell determined from	809 reflections	Cell θ range =	5 - 27°
Temperature	150K		
Shape	plate		
Colour	colourless	Size	0.14 × 0.38 × 0.40 mm
D_x	1.28 Mg m^{-3}	F000	284.000
μ	0.076 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.97	T_{max}	0.99

Data Collection

Diffractometer	multi-scan
Scan type	ω scans
Reflections measured	4329
Independent reflections	842
Rint	0.0194
θ_{max}	27.4367
h =	-13 → 13
k =	-8 → 7
l =	-13 → 13

Refinement

$\Delta\rho_{min}$ =	-0.17 e Å^{-3}
$\Delta\rho_{max}$ =	0.27 e Å^{-3}
Reflections used	842
Cutoff: I >	-3.00σ(I)
Parameters refined	91
S =	0.93
R-factor	0.041
weighted R-factor	0.098
Δ/σ_{max}	0.0001
Refinement on	F²
w =	$w' \times [1 - (\Delta F_{obs} / 6 \times \Delta F_{est})^2]^2$
w′ =	$[P_0T_0'(x) + P_1T_1'(x) + ...P_{n-1}T_{n-1}'(x)]^{-1}$, where P_i are the coefficients of a Chebychev series in $t_i(x)$, and x = $F_{calc}^2/F_{calc}^2{}_{max}$.
P_0 - P_{n-1} =	115. 192. 120. 52.1 13.1

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
N1	0.12805(14)	0.2154(3)	0.07289(14)	0.0219	1.0000
C2	0.04971(16)	0.3006(3)	0.14893(17)	0.0218	1.0000
C3	0.09789(17)	0.3411(3)	0.04978(17)	0.0238	1.0000
C4	0.11584(17)	0.4879(3)	0.23356(16)	0.0228	1.0000
C5	0.04083(19)	0.6192(3)	0.28324(18)	0.0259	1.0000

C6	0.1022(2)	0.7853(3)	0.36694(18)	0.0296	1.0000
C7	0.2394(2)	0.8255(3)	0.40153(18)	0.0297	1.0000
C8	0.31382(19)	0.6967(3)	0.35202(17)	0.0286	1.0000
C9	0.25309(18)	0.5282(3)	0.26968(17)	0.0254	1.0000
C10	0.07840(17)	0.0006(3)	0.03167(18)	0.0245	1.0000
H21	0.04813(16)	0.1885(3)	0.21111(17)	0.0257	1.0000
H31	0.11035(17)	0.4875(3)	0.02625(17)	0.0276	1.0000
H32	0.16188(17)	0.2975(3)	0.09179(17)	0.0286	1.0000
H51	0.05240(19)	0.5939(3)	0.25888(18)	0.0310	1.0000
H61	0.0505(2)	0.8710(3)	0.40157(18)	0.0344	1.0000
H71	0.2797(2)	0.9404(3)	0.45863(18)	0.0354	1.0000
H81	0.40758(19)	0.7232(3)	0.37403(17)	0.0333	1.0000
H91	0.30586(18)	0.4396(3)	0.23817(17)	0.0309	1.0000
H101	0.11535(17)	-0.0474(3)	0.03417(18)	0.0293	1.0000
H102	0.11079(17)	-0.0891(3)	0.10878(18)	0.0291	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	0.0211(6)	0.0196(7)	0.0253(7)	-0.0012(6)	0.0089(5)	0.0003(6)
C2	0.0212(8)	0.0197(8)	0.0244(8)	0.0005(7)	0.0086(6)	0.0011(6)
C3	0.0204(7)	0.0238(8)	0.0267(8)	0.0006(7)	0.0083(6)	0.0029(7)
C4	0.0251(8)	0.0208(9)	0.0209(8)	0.0020(7)	0.0069(6)	0.0026(7)
C5	0.0260(9)	0.0250(10)	0.0261(9)	-0.0002(7)	0.0091(7)	0.0016(7)
C6	0.0367(10)	0.0253(9)	0.0273(9)	-0.0018(8)	0.0126(7)	0.0044(8)
C7	0.0370(10)	0.0235(10)	0.0245(8)	-0.0026(7)	0.0070(7)	-0.0025(8)
C8	0.0275(8)	0.0285(10)	0.0262(8)	-0.0003(8)	0.0061(7)	-0.0020(8)
C9	0.0264(8)	0.0233(9)	0.0260(8)	-0.0007(8)	0.0093(6)	0.0006(7)
C10	0.0232(9)	0.0207(8)	0.0288(8)	-0.0017(8)	0.0090(6)	0.0002(7)

Distances

N1	C2	1.481(2)Å		N1	C3 3_555	1.476(2)Å
N1	C10	1.480(2)Å		C2	C3	1.559(2)Å
C2	C4	1.510(2)Å		C2	H21	0.987Å
C3	H31	0.967Å		C3	H32	0.993Å
C4	C5	1.401(3)Å		C4	C9	1.394(2)Å
C5	C6	1.388(3)Å		C5	H51	0.945Å
C6	C7	1.396(3)Å		C6	H61	0.950Å

C7	C8	1.386(3)Å		C7	H71	0.952Å
C8	C9	1.392(3)Å		C8	H81	0.955Å
C9	H91	0.949Å		C10	C10 3_555	1.555(3)Å
C10	H101	0.984Å		C10	H102	0.961Å

Angles

C2	N1	C3 3_555	108.53(14)°		C2	N1	C10	107.12(14)°
C3 3_555	N1	C10	107.71(13)°		N1	C2	C3	108.67(13)°
N1	C2	C4	113.13(13)°		C3	C2	C4	113.92(14)°
N1	C2	H21	105.511°		C3	C2	H21	108.311°
C4	C2	H21	106.847°		N1 3_555	C3	C2	110.29(14)°
N1 3_555	C3	H31	109.314°		C2	C3	H31	110.163°
N1 3_555	C3	H32	107.498°		C2	C3	H32	109.573°
H31	C3	H32	109.965°		C2	C4	C5	120.09(15)°
C2	C4	C9	121.30(15)°		C5	C4	C9	118.52(17)°
C4	C5	C6	120.61(17)°		C4	C5	H51	119.210°
C6	C5	H51	120.182°		C5	C6	C7	120.43(18)°
C5	C6	H61	119.657°		C7	C6	H61	119.906°
C6	C7	C8	119.18(18)°		C6	C7	H71	119.317°
C8	C7	H71	121.506°		C7	C8	C9	120.55(18)°
C7	C8	H81	120.127°		C9	C8	H81	119.321°
C4	C9	C8	120.69(17)°		C4	C9	H91	119.745°
C8	C9	H91	119.560°		N1	C10	C10 3_555	109.74(9)°
N1	C10	H101	108.068°		C10 3_555	C10	H101	110.128°
N1	C10	H102	108.823°		C10 3_555	C10	H102	110.945°
H101	C10	H102	109.077°					

(2*R*,3*R*)-1-Methyl-2,3-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromethanesulfonate (204)

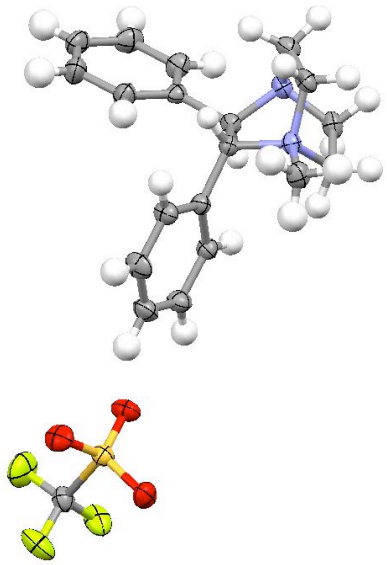


Figure A3 X-ray crystal structure of (2*R*,3*R*)-**204**

(2*R*,3*R*)-1-methyl-2,3-diphenyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoro-methanesulfonate (30 mg) was dissolved in methanol (3 ml). After standing for 24 h, suitable crystals formed gradually.

Table 1: Crystal data and refinement details

Crystal identification	027JOI01
Chemical formula (sum)	$C_{20}H_{23}F_3N_2O_3S$
Chemical formula (moiety)	$C_{19}H_{23}N_2$, CF_3O_3S
Formula weight	428.47
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group name	P 21 21 21
Space group hall	P 2ac 2ab

a (Å)	8.1290(2)
b (Å)	15.2413(3)
c (Å)	16.1054(4)
α (^{o})	90
β (^{o})	90
γ (^{o})	90
Cell volume (Å^{3})	1995.40(8)
Z	4
Calculated density (Mg/m^{3})	1.426
Absorption coefficient (mm^{-1})	0.214
F000	896
Crystal size (mm)	0.12 × 0.20 × 0.27
Description of crystal	Colourless plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min, max)	0.95, 0.97
θ range for data collection (^{o})	$5.174 \leq \theta \leq 27.469$ (0.991)
Index ranges	$-10 \leq h \leq 10$, $-19 \leq k \leq 19$, $-20 \leq l \leq 20$
Reflections measured/number	19262
Unique reflections	4534
Observed reflections ($I > -3\sigma(I)$)	4535
Computed reflections ($I > 2\sigma(I)$)	3870
Refinement method	Full-matrix least-squares on F
Parameters refined	264

Weighting scheme	Auto-statistical
Goodness of fit	0.9536
R (observed)	0.0466
R (computed)	0.0350
wR (observed)	0.0788
wR (computed)	0.0734
Residual electron density (min, max) ($eÅ^{-3}$)	-0.30, 0.28
Flack	-0.01(6)

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	Symbol	x	y	z	U^{equiv}
S1	S	0.71035(5)	0.42792(3)	0.39417(3)	0.0276
O2	O	0.62914(17)	0.44059(10)	0.31549(8)	0.0377
O3	O	0.64840(17)	0.35572(9)	0.44253(8)	0.0368
O4	O	0.74510(19)	0.50730(9)	0.43917(9)	0.0425
C5	C	0.9130(2)	0.38899(13)	0.36341(12)	0.0336
F6	F	0.90354(15)	0.31549(8)	0.31912(8)	0.0468
F7	F	0.99242(15)	0.44796(8)	0.31714(9)	0.053
F8	F	1.00718(17)	0.37173(11)	0.42856(9)	0.0635
N9	N	-0.17790(17)	0.36738(10)	0.68706(9)	0.0262
C10	C	-0.0003(2)	0.37477(11)	0.72249(10)	0.0223
C11	C	0.1212(2)	0.41360(12)	0.66166(10)	0.0244
C12	C	0.2029(2)	0.36302(11)	0.60230(10)	0.0275
C13	C	0.3160(2)	0.40202(13)	0.54888(12)	0.0345
C14	C	0.3483(2)	0.49082(14)	0.55357(13)	0.0371
C15	C	0.2684(3)	0.54150(13)	0.61268(13)	0.0391
C16	C	0.1559(2)	0.50339(12)	0.66679(12)	0.0309
C17	C	0.0437(2)	0.28242(12)	0.75520(10)	0.0239
N18	N	-0.10740(18)	0.23219(10)	0.77408(9)	0.0274
C19	C	-0.1813(2)	0.20596(12)	0.69456(12)	0.0325
C20	C	-0.1940(2)	0.28489(12)	0.63557(11)	0.0313
C21	C	-0.2235(2)	0.28895(12)	0.81875(11)	0.0321
C22	C	-0.2923(2)	0.35930(12)	0.76051(11)	0.0305
C23	C	0.1628(2)	0.28233(12)	0.82814(10)	0.0249
C24	C	0.2522(2)	0.35490(14)	0.85353(12)	0.0368
C25	C	0.3675(3)	0.34826(16)	0.91726(13)	0.0451

C26	C	0.3937(3)	0.26915(16)	0.95641(12)	0.0431
C27	C	0.3052(3)	0.19595(14)	0.93200(12)	0.0407
C28	C	0.1913(2)	0.20249(13)	0.86797(11)	0.0343
C29	C	-0.2242(2)	0.44613(12)	0.63710(12)	0.0349

Table 3: Atomic coordinates and equivalent isotropic thermal parameters (Å^2) of hydrogen atoms

Atom	Symbol	x	y	z	U^{equiv}
H101	H	-0.0106	0.4157	0.7699	0.0288
H121	H	0.1794	0.3014	0.5995	0.0366
H131	H	0.3719	0.3654	0.5082	0.043
H141	H	0.4265	0.5172	0.5161	0.0465
H151	H	0.293	0.6039	0.6164	0.0469
H161	H	0.1026	0.5384	0.7074	0.0373
H171	H	0.0978	0.2491	0.7089	0.0293
H191	H	-0.2944	0.1831	0.7079	0.0384
H192	H	-0.1128	0.1596	0.6682	0.0383
H201	H	-0.3014	0.2869	0.6093	0.0386
H202	H	-0.1033	0.2848	0.5946	0.0384
H211	H	-0.1643	0.3192	0.8649	0.0388
H212	H	-0.3172	0.2526	0.8403	0.038
H221	H	-0.2974	0.4176	0.79	0.0371
H222	H	-0.4011	0.3413	0.7396	0.0371
H241	H	0.2338	0.4101	0.8277	0.0478
H251	H	0.4299	0.3992	0.934	0.0548
H261	H	0.4714	0.2652	1.0005	0.0537
H271	H	0.3213	0.1407	0.9588	0.0496
H281	H	0.1325	0.152	0.8505	0.0423
H291	H	-0.3394	0.4403	0.6213	0.0543
H292	H	-0.2065	0.4978	0.671	0.053
H293	H	-0.1564	0.4478	0.5869	0.0543

Table 4: Anisotropic thermal parameters (Å^2)

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	0.0263(2)	0.0267(2)	0.0297(2)	-0.00075(18)	0.00262(19)	0.00234(18)
O2	0.0313(7)	0.0440(9)	0.0377(7)	0.0067(7)	-0.0079(6)	0.0028(6)
O3	0.0408(8)	0.0312(7)	0.0384(7)	0.0049(6)	0.0119(6)	0.0002(6)
O4	0.0540(9)	0.0302(7)	0.0434(8)	-0.0117(6)	0.0069(7)	-0.0006(6)
C5	0.0255(9)	0.0363(11)	0.0390(10)	-0.0015(9)	-0.0012(9)	0.0008(8)
F6	0.0349(6)	0.0395(7)	0.0661(8)	-0.0183(6)	0.0105(6)	0.0035(5)

F7	0.0371(7)	0.0418(7)	0.0801(9)	0.0095(7)	0.0231(7)	-0.0003(6)
F8	0.0403(7)	0.0925(11)	0.0577(8)	-0.0005(8)	-0.0187(7)	0.0190(8)
N9	0.0225(7)	0.0253(8)	0.0308(7)	0.0003(6)	-0.0019(6)	0.0013(6)
C10	0.0220(8)	0.0221(9)	0.0229(8)	-0.0013(7)	-0.0013(7)	0.0005(7)
C11	0.0223(8)	0.0261(9)	0.0248(8)	0.0016(7)	-0.0004(7)	0.0015(7)
C12	0.0277(8)	0.0264(8)	0.0285(8)	-0.0013(7)	0.0009(8)	-0.0002(8)
C13	0.0300(10)	0.0421(11)	0.0315(9)	0.0009(8)	0.0061(8)	0.0016(8)
C14	0.0334(10)	0.0403(11)	0.0376(11)	0.0068(9)	0.0068(9)	-0.0047(9)
C15	0.0430(11)	0.0254(9)	0.0488(12)	0.0024(8)	0.0064(10)	-0.0059(8)
C16	0.0338(10)	0.0253(9)	0.0337(10)	-0.0011(7)	0.0045(8)	0.0001(8)
C17	0.0227(8)	0.0237(9)	0.0254(8)	0.0007(7)	0.0005(7)	0.0000(7)
N18	0.0226(7)	0.0259(8)	0.0338(8)	0.0012(7)	0.0006(6)	-0.0020(6)
C19	0.0260(9)	0.0289(10)	0.0425(10)	-0.0031(8)	-0.0038(8)	-0.0033(8)
C20	0.0285(9)	0.0317(10)	0.0336(9)	-0.0059(8)	-0.0063(8)	-0.0026(8)
C21	0.0263(9)	0.0356(10)	0.0344(9)	0.0033(8)	0.0067(8)	-0.0007(8)
C22	0.0230(8)	0.0303(9)	0.0381(10)	0.0001(8)	0.0047(8)	0.0005(8)
C23	0.0235(8)	0.0287(9)	0.0225(8)	-0.0006(7)	0.0016(7)	0.0029(7)
C24	0.0406(12)	0.0362(11)	0.0337(10)	0.0039(8)	-0.0087(8)	-0.0065(9)
C25	0.0429(12)	0.0550(14)	0.0375(11)	-0.0006(10)	-0.0097(10)	-0.0144(10)
C26	0.0331(11)	0.0669(16)	0.0292(9)	0.0044(10)	-0.0064(9)	0.0019(11)
C27	0.0426(11)	0.0457(12)	0.0339(10)	-0.0097(9)	-0.0028(10)	0.0108(10)
C28	0.0369(10)	0.0317(10)	0.0343(9)	0.0002(8)	-0.0038(9)	0.0029(9)
C29	0.0311(9)	0.0334(10)	0.0402(10)	0.0076(8)	-0.0067(9)	0.0038(8)

Table 5: Bond lengths (Å)

S1-O2	1.4418(13)	S1-O3	1.4391(14)
S1-O4	1.4383(14)	S1-C5	1.819(2)
C5-F6	1.330(2)	C5-F7	1.334(2)
C5-F8	1.325(2)	N9-C10	1.556(2)
N9-C20	1.512(2)	N9-C22	1.510(2)
N9-C29	1.493(2)	C10-C11	1.512(2)
C10-C17	1.545(2)	C11-C12	1.396(2)

C11-C16	1.400(3)	C12-C13	1.392(3)
C13-C14	1.381(3)	C14-C15	1.387(3)
C15-C16	1.390(3)	C17-N18	1.479(2)
C17-C23	1.522(2)	N18-C19	1.479(2)
N18-C21	1.469(2)	C19-C20	1.536(3)
C21-C22	1.530(3)	C23-C24	1.385(3)
C23-C28	1.395(3)	C24-C25	1.393(3)
C25-C26	1.377(3)	C26-C27	1.384(3)
C27-C28	1.389(3)		

Table 6: Bond angles (Å)

O2-S1-O3	114.70(8)	O2-S1-O4	114.84(9)
O3-S1-O4	116.05(8)	O2-S1-C5	102.64(8)
O3-S1-C5	102.41(9)	O4-S1-C5	103.52(9)
S1-C5-F6	111.63(13)	S1-C5-F7	111.75(14)
F6-C5-F7	107.20(15)	S1-C5-F8	111.86(13)
F6-C5-F8	106.89(16)	F7-C5-F8	107.22(16)
C10-N9-C20	109.98(13)	C10-N9-C22	106.86(12)
C20-N9-C22	107.97(13)	C10-N9-C29	111.91(13)
C20-N9-C29	110.56(13)	C22-N9-C29	109.42(14)
N9-C10-C11	113.36(13)	N9-C10-C17	105.88(13)
C11-C10-C17	115.25(14)	C10-C11-C12	122.58(16)
C10-C11-C16	118.43(15)	C12-C11-C16	118.96(16)
C11-C12-C13	120.11(17)	C12-C13-C14	120.68(18)
C13-C14-C15	119.62(18)	C14-C15-C16	120.37(18)
C11-C16-C15	120.26(18)	C10-C17-N18	110.47(13)
C10-C17-C23	114.27(14)	N18-C17-C23	111.66(13)
C17-N18-C19	107.53(13)	C17-N18-C21	109.24(14)
C19-N18-C21	108.91(14)	N18-C19-C20	110.68(14)
C19-C20-N9	107.83(13)	N18-C21-C22	110.33(14)
C21-C22-N9	108.20(14)	C17-C23-C24	124.11(16)
C17-C23-C28	117.47(16)	C24-C23-C28	118.26(16)
C23-C24-C25	120.81(19)	C24-C25-C26	120.3(2)
C25-C26-C27	119.66(18)	C26-C27-C28	119.95(19)
C23-C28-C27	120.98(18)		