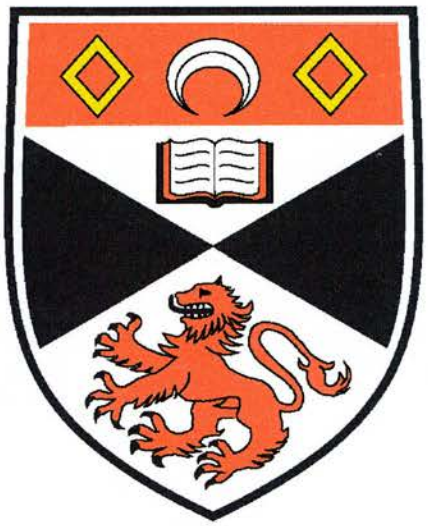
Novel Approach to Asymmetric Synthesis in Organic and Organo-Fluorine Chemistry



A thesis presented for the degree of Doctor of Philosophy to the University of St. Andrews on the 09th April 2004

by Marcello Nicoletti

Declaration

I, Marcello Nicoletti, hereby certify that this thesis, which is approximately 36,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

Signed. Date. 8-4-04.....

I was admitted as a research student in December 2000 and as a candidate for the degree of Ph.D in April 2004; the higher study for which this is a record was carried out in the University of St. Andrews between December 2000 and December 2003.

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Ph.D in the University of St. Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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A special tank to the St. Andrews links Golf to give me the opportunity to learn the fantastic game of Golf, without them I would have had no chance to swing a golf club.

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Ancora una volta mi siete stati vicini nelle mie scelte e spero che questi tre anni spesi all'estero siano serviti ancora una volta a rendervi fieri di me.

Abstract

The Bischler-Napieralski reaction has been used widely and for many years for the preparation of isoquinoline derivatives. The reaction involves the cyclodehydration of phenylethylamides. **Chapter 2** describes the first example of asymmetric Bischler-Napieralski reaction on chiral phenylethylamides. The cyclisation occurs in a highly stereoselective manner to deliver 3,4-dihydroisoquinolines containing two at (C3 - C4) contiguous stereogenic centres with a predominat *trans* geometry between substituents at C(3) and C(4) (ratio between 20:1 and 9:1 depending on the substituents).

Fluorinated organic compounds are objects of studies in many areas such as organic chemistry, biochemistry, medicinal chemistry and material sciences because of their unusual chemical properties. The Fluorine atom is the most electronegative element in the periodic table and this property can influence dramatically the chemical and physical behaviour of the molecules. It is also well known that two consecutive fluorine atoms prefer to assume a *gauche* conformation rather than an anti relationship.

Chapter 4 presents the synthesis of a new class of fluorinated compounds carrying three fluorine atoms in vicinal positions and their properties with particular interest on to the fluorine *gauche effect*. A new route in their synthesis has been established and their use as new materials could be investigated.

In recent years, there has been an increasing demand for 'clean' and environmentally-friendly chemical processes. Perfluorinated solvents satisfy these requirements because they are non-toxic and biologically compatible.

Fluorous solvents are a class of perfluorinated and saturated aliphatic compounds like perfluoroalkanes, perfluoroalkyl ethers and perfluoroalkylamines. The principal characteristic of fluorinated solvents is the thermo-and pressure-controlled miscibility with common organic solvents. **Chapter 5** presents the synthesis of new fluorous amines and their potential applications.

Abbreviations

Å:	angstrom
Ac:	acetyl
AIBN:	2,2'-azobisisobutyronitrile
BINAPHOS:	((*R*)-2-(diphenylphosphino)-1,1'-binaphthalene-2'-yl-{(*S*)-1,1'-binaphthalene-2,2'-diyl}phosphite)
BN:	Bischler-Napieralski
BNR:	Bischler-Napieralski reaction
br:	broad
Bu:	butyl
^{t}Bu:	tertiary butyl
c:	concentration
CI:	chemical ionization
CNS:	central nervous system
conc:	concentrated
d:	doublet
DAST:	(diethylamino)sulfurtrifluoride
DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM:	dichloromethane
de:	diastereomeric excess
DHQ	dihydroquinidine
DIPT:	diisopropyl tartrate
DMAP	dimethylaminopyridine
DME:	1,2-dimethoxy ethane
DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
dTMP:	2'-deoxyuthymidine-5'-monophosphate
dUMP:	2'-deoxyuridine-5'-monoposphate
ee:	enantiomeric excess
EI:	electron ionisation
eq:	equivalent
Et:	ethyl

EtOAc:	ethyl acetate
5'FDA:	5'-fluoro-5'-deoxyadenosine
FBC:	fluorous biphasic catalysis
FBS:	Fluorous Biphase System
FC-72:	perfluorohexane
FdUMP:	5-fluoro-2'-deoxyuridine-5'-phosphate
FLC:	Ferroelectric Liquid Crystal
FPSG:	Fluorous Phase Silica Gel
F-TEDA-BF_4:	selectfluor™
GC:	gas chromatography
GCMS:	Gas Chromatography-Mass Spectrometry
h:	hour
HRMS:	high resolution mass spectroscopy
Hz	hertz
IR:	infrared spectroscopy
J:	coupling constant
KDA:	Potassium diisopropylamide
LCD:	Liquid Crystal Display
M:	molar
MALDI	Matrix Assisted Laser Desorption/Ionization
mCPBA	m-chloro peroxybenzoic acid
Me:	methyl
min:	minute
Mp:	melting point
MS:	mass spectroscopy
MsO:	mesylate
NFOBS:	N-fluoro-o-benzenedisulfonimide
NMO:	N-methylmorpholine N-oxide
NMR $\{^1H\}$:	NMR proton decoupled
NMR $\{^{19}F\}$:	NMR fluorine decoupled
NMR:	nuclear magnetic resonance
NOE:	Nuclear Overhauser Effect
Nu^-	nucleophile
PCC	Pyridinium Chloro Chromate

PFCs:	Perfluorocarbons
Ph:	phenyl
PFMCH:	perfluoromethylcyclohexane
Py:	pyridine
^{i}Pr:	*iso*-propyl
q:	quartet
R_f :	fluorous ponytail
RT:	room temperature
RTN:	EU research training Network
s:	singlet
SAM:	*S*-(5'-adenosyl)-L-methionine-chloride
sat.	saturated solution
scCO_2:	supercritical CO_2
SCF's:	supercritical fluids
SmA	smectic phase A
Sn:	nucleophilic substitution
t:	triplet
TADDOL:	α,α,α,'α'-tetraaryl-1,3-dioxolane-4,5,-dimethanol
TBAF:	tetrabutyl ammonium fluoride
TEA:	triethylamine
TEBA:	triethylbenzylammonium chloride
TEDA:	1,4-diazabicyclo[2.2.1] octane
TEMPO:	2,2,6,6-tetramethylpiperidin-*N*-oxyl radical
TfO:	trifluoro methanesulfonate
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMS:	trimethylsilyl
TsO:	tosylate
UV:	ultra-violet

Index

1 Isoquinolines: Chemistry and reactivity

Part A

1.1 Introduction

Man has used natural products, albeit as crude plant extracts, since the early days. Primitive men found the extracts were a good remedy for the relief of pain or alleviation of the symptoms of diseases, as poisons for hunting or murdering, as narcotics, hallucinogens or to reduce fatigue and hunger in life. Many of our modern drugs now contain the same compounds or synthetic analogues and are typically used for the same general purpose.

The study of natural products is now very much an interdisciplinary area, including the chemistry biology interface. In *vivo,* chemical compounds are made and degraded by a series of reactions, each facilitated by an enzyme. All organisms possess similar metabolic pathways by which they synthesise chemical species considered vital for the organism itself: sugars, amino acids, and fatty acids polymers. These compounds essential for the survival of the cells are known as *primary metabolites.* The rest of the chemical compounds, such as alkaloids, peptides, isoprenoids are usually surplus to metabolic requirements, but enhance the fitness of the organism and are known *as secondary metabolites.*

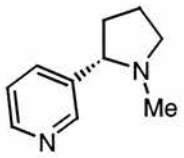
1.2 Alkaloids

The majority of alkaloids occur in flowering plants although, in recent years, an increasing numbers have been found in animals, insects and microrganisms. These are *secondary metabolites* and their amine character produces an alkaline solution in water hence they were originally termed the "vegetable alkalis". There is a wide variety of structural types of alkaloids as shown in **figure 1.1,** which match a broad variety of pharmacological effects.

Nicotine (**1**), the main alkaloid found in tobacco, is probably the most widely used alkaloid by man, and its addictiveness has arguably caused the death of more people in the world than any other compound.

Atropine (**2**) isolated from *Atropa belladonna* plants, is widely used in medicine for its muscle relaxant properties. Thus, it is used as an antispasmotic agent, with one of its effects being the dilation of the pupil by relaxation of the eye muscles. Cocaine (**3**), which comes from the coca plant, has similar properties to atropine. At one time, it was used as a local anaesthetic, however, now it is rarely used medically due to its toxic and addictive effects.

Papaverine (**4**), with antispasmotic properties, and dimorphine (**5**) the most widely used analgesic, are extracted from the opium poppy. One of the most widely used alkaloids in therapy is quinine (**6**), isolated from the bark of the *cinchona* tree. It is used as an antimalarial drug and at low concentrations is used to flavour tonic water.



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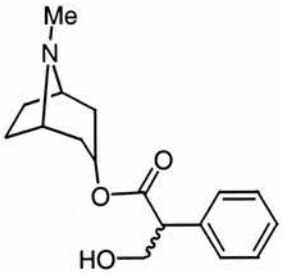

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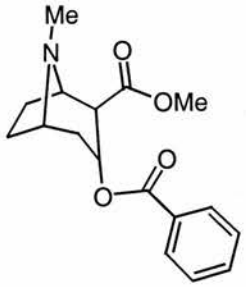

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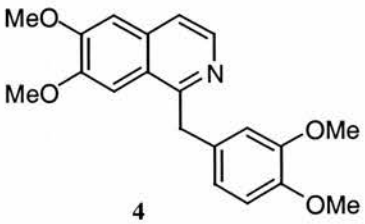

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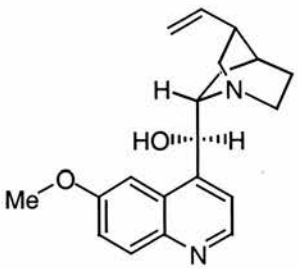

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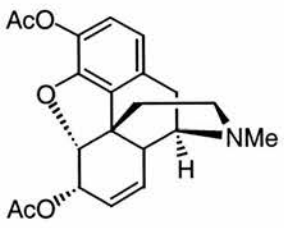

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Figure 1.1. Structure of some alkaloids

1.3 Chemistry and Biosynthesis

If the 19th century represented the glory days for structural studies on the alkaloids, the 20th century has been notable for the large number of elegant total syntheses that have been achieved. Many of these complex syntheses are biomimetic in character; where the synthetic steps imitate Nature.

The first such example was the Robinson's synthesis of tropinol[1] (**7**). At the beginning of the 19th century the tropane ring (**8**) was a most challenging and attractive target. The tropane alkaloids attracted enormous interest mainly due to the folklore surrounding their potent activity. For example hyoscyamine (**9**) was used in the Middle Ages as a hallucinogen while atropine (**2**), which is the racemate of hyoscyamine, was known for its midriatic effect. During the Renaissance, fashionable ladies used the extract as drops to dilate their pupils and to make themselves appear more attractive. Cocaine (**3**) was well known for its local anaesthetic effect and as a stimulant of the CNS. (**Figure 1.2**).

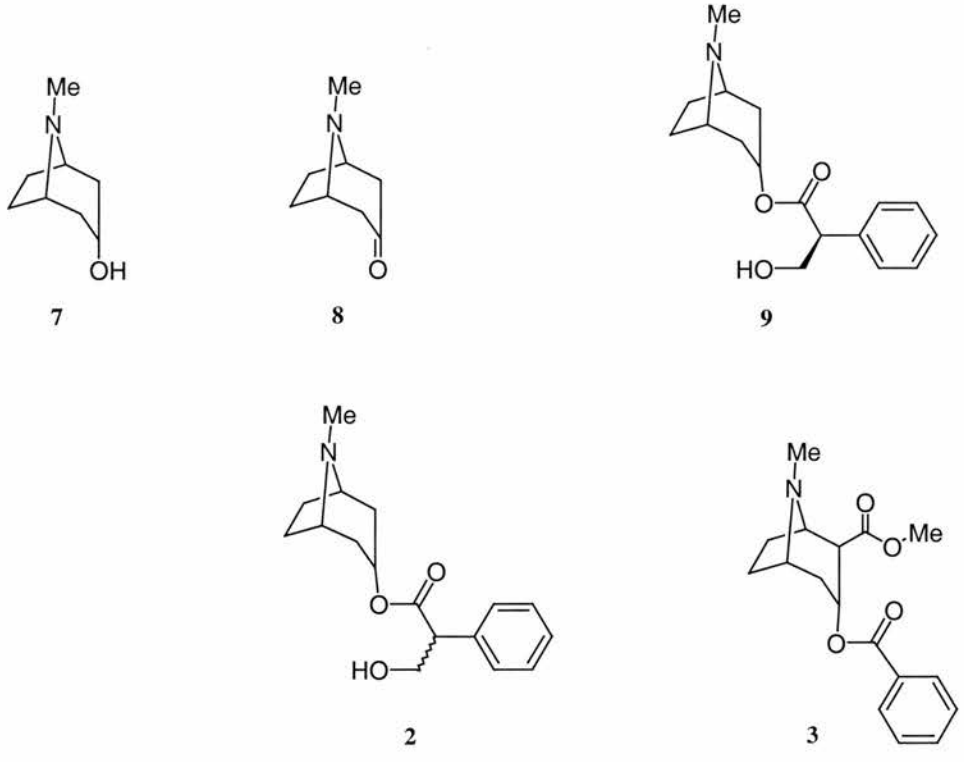
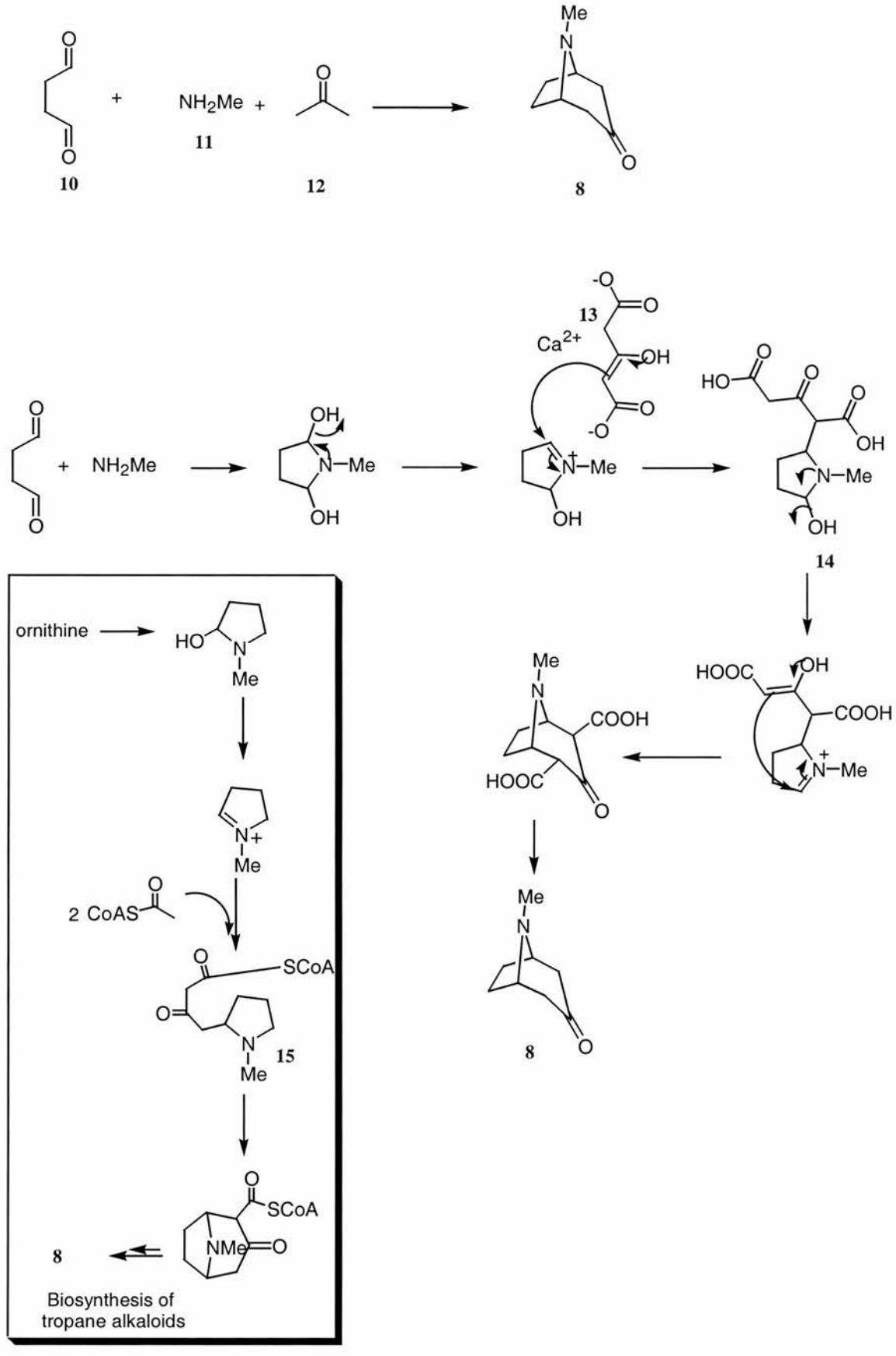


Figure 1.2. Tropane alkaloids

Willstatter's tortuous synthesis[2] of tropine involved 20 steps and was the first synthesis of the tropane ring system. It is also the first example of a total synthesis as it is viewed today. Willstatter's early masterpiece was perhaps buried by the elegant approach of Robinson's synthesis. Sir Robert Robinson published the synthesis of tropinone (**8**) in a "one pot" process by addition of succinaldehyde (**10**) to an aqueous solution of methylamine (**11**) and acetone (**12**) as shown in **scheme 1.1**. The yield improved to 45% when acetone was replaced by the calcium salt of acetonedicarboxylic acid (**13**).

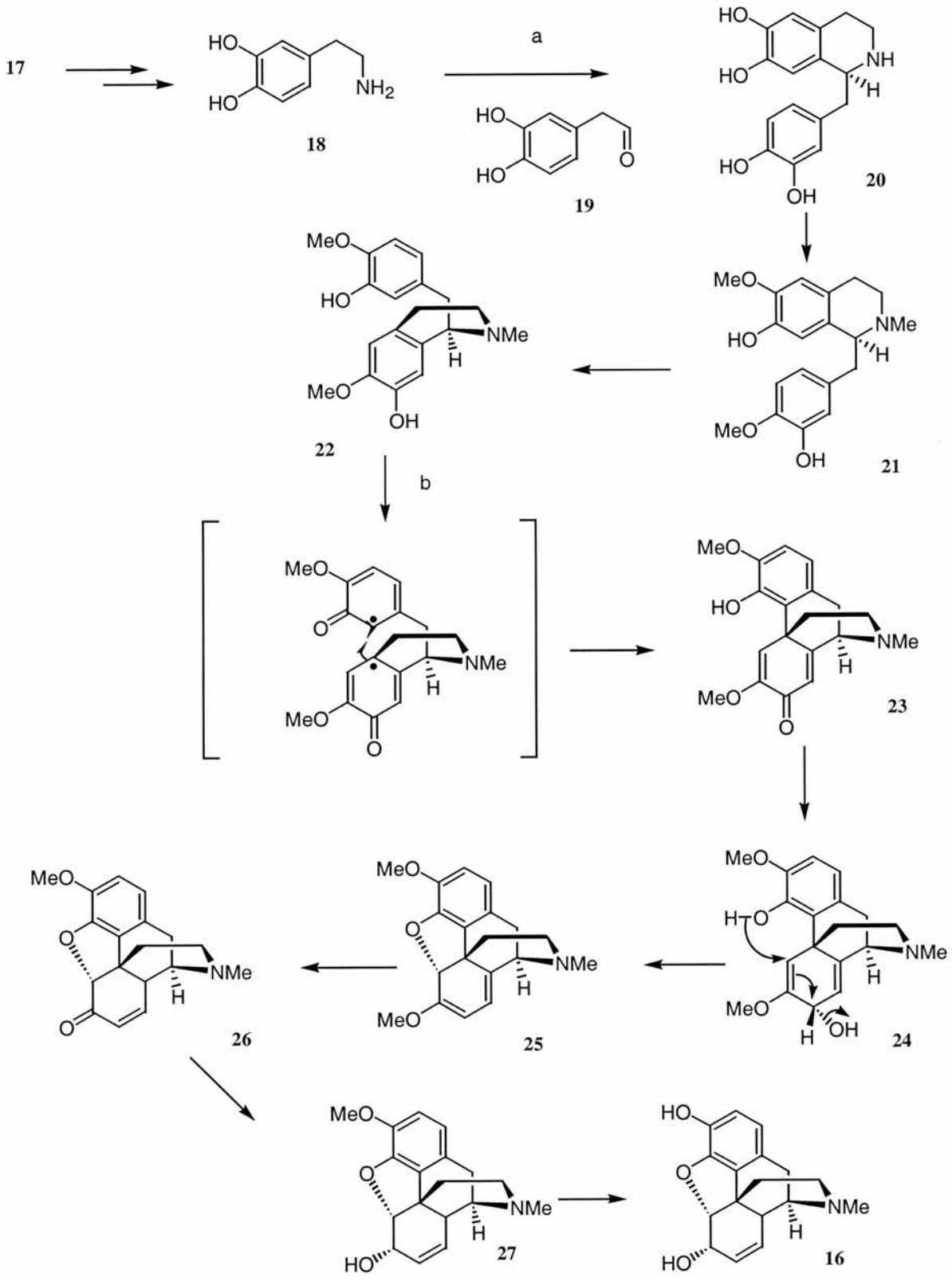
The mechanism of Robinson's synthesis shown in **scheme 1.1** imitates to some extent the biosynthesis of the tropane alkaloids.[3-6] For example the intermediate (**14**) is structurally related to intermediate (**15**) present on the biosynthetic pathway of the tropane alkaloids. Robinson's preparation provided the inspiration for others to consider biosynthetic pathways when planning their synthesis of natural products.



Scheme 1.1. Mechanistic interpretation of Robinson's synthesis and the biosynthesis of tropanone.

The biosynthesis of the opium alkaloids has inspired numerous biomimetic syntheses. Crude opium contains 25% by weight of alkaloids of which 10% is morphine (**16**). The biosynthesis starts[7, 8] with a decarboxylation reaction on the amino acid tyrosine (**17**) to produce tyramine (**18**). Condensation with 4-hydroxyphenylethanal (**19**) generates the benzylisoquinoline alkaloid (*S*)- reticuline (**21**). (*S*)- Reticuline (**21**) is then epimerised to the (*R*) isomer (**22**) prior to its conversion in salutaridine (**23**) by means of oxidative phenolic coupling. After reduction to salutaridinol (**24**) the oxygen bridge is formed, by a S_N2' reaction, to produce thebaine (**25**) which undergoes a demethylation reaction to produce codeinone (**26**). After reduction of the ketone to give codeine (**27**), the molecule undergoes another demethylation reaction to produce morphine (**16**).

Several syntheses were completed before this pathway was delineated. For example, Spath and Burger[9] prepared N-norlaudanosine (**20**) according to step (a) in the biosynthesis (**scheme 1.2**). This condensation and subsequent ring-closure is an example of the Pictet Spengler reaction,[10] a process which has been widely used for preparing this class of alkaloid. The oxidative biosynthetic phenol coupling reaction (b, **scheme 1.2**) has inspired significant synthesis in the laboratory. For example, reticuline (**21**) has been treated with Fe(III) complexes and although the yields were poor, the product of the *ortho/para* coupling was obtained and used as an intermediate for the total synthesis of morphine. More recently tandem biomimetic reactions have been achieved. Tandem reactions combine several transformations in sequence to produce fused ring structures. The biomimetic tandem reaction for the synthesis of progesterone[11] and carpanone,[12, 13]are early examples which have been followed by more complex synthesis achievements such as trichodimerol.[14, 15]



Scheme 1.2. Biosynthesis of the opium alkaloids

Part B

1.4 Isoquinoline

Structure and reactivity

A benzene ring fuses to a pyridine ring to generate either a quinoline (**28**) or an isoquinoline (**29**) (**figure 1.3**).

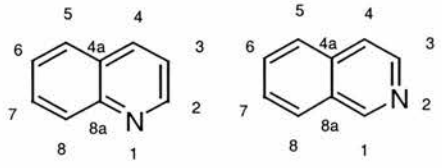


Figure. 1.3. Numbering for quinoline and isoquinoline structures.

Isoquinoline (**29**) was first reported in 1885 by Hoogewerff and Van Dorp[16] who isolated a small amount from the quinoline fraction of coal tar by taking advantage of the greater basicity of isoquinoline (pKa=5.1 vs 4.9 of quinoline). However the largest number of isoquinoline compounds are found in plants as discussed in the previous sections**.** Because of the importance of the isoquinoline alkaloids numerous synthetic methods have been developed to generate the isoquinoline core. Many of them can be considered as a variation of four classsical methods as listed in **table 1.1**.

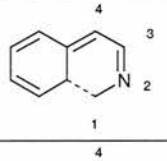
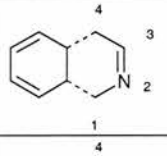
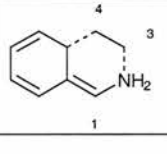
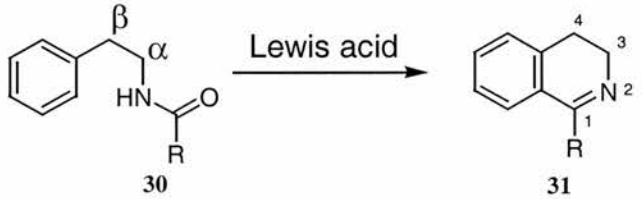
Disconnection approach	Reaction	Product formed
	Bischler Napieralski	3,4-dihydroisoquinoline
	Pictet Spengler	1,2,3,4-Tetrahydroisoquinoline
	Pomeranz Fritsch	Isoquinoline
	Schlitter and Muller	Isoquinoline

Table. 1.1

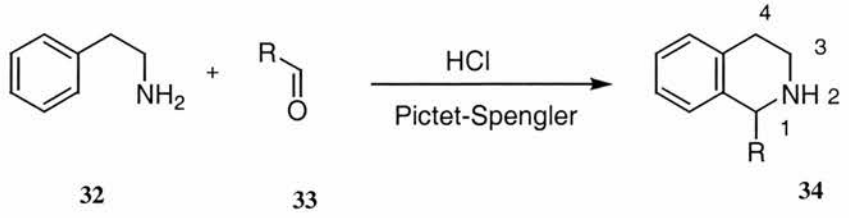
The Bischler-Napieralski reaction (BNR),[17] represented in **figure 1.4,** connects the phenyl ring with C(1) of the resulting isoquinoline structure. It is indeed the most valuable and frequently used method for the synthesis of isoquinoline compounds. The reaction involves the cyclodehydration of an N-acyl derivative of β-phenylethylamine (**30**) to form a 3,4-dihydroisoquinoline (**31**). The reaction requires a Lewis acid and is carried out in a dry inert organic solvent.



30 **31**

Figure 1.4. The Bischler-Napieralski reaction.

The condensation of β-phenylethylamine with a carbonyl compound, usually an aldehyde, in the presence of an acid generates 1,2,3,4-tertahydroisoquinoline (**figure 1.5**). This is the Pictet-Spengler reaction.[10] The resultant bond is formed between the phenyl ring and C(1) of the isoquinoline product, the same mode as illustrated for the BNR. The reaction is carried out in concentrated hydrochloric acid and does not generally require any additional solvent.



32 33 34

Figure 1.5. The Pictet-Spengler cyclisation

During the biosynthesis of the tetrahydroisoquinoline alkaloids a similar enzymatic reaction occurs although it is not acid catalysed. This process has been successfully reproduced in the laboratory under physiological conditions. The reaction was optimised at a pH between 4 and 10 yielding the desired 1,2,3,4-tetrahydroisoquinoline in c.a. 83% yield. [18, 19]

The Pomeranz-Fritsch[20, 21] reaction is also included among the classical methods for the preparation of the isoquinoline ring. Typically the cyclisation (**figure 1.6**) occurs in two stages. Firstly an aromatic aldehyde (**35**) condenses with the acetal of aminoacetaldehyde (**36**) to form the iminoacetal (**37**), which cyclises under acidic condition to give the isoquinoline (**38**).

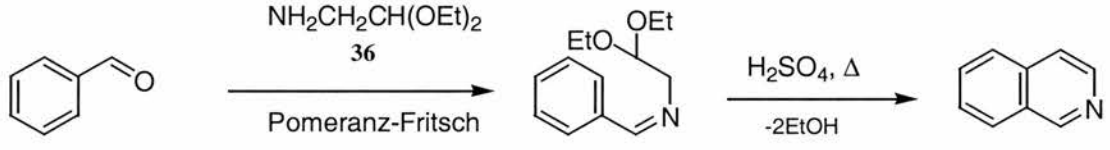


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Figure. 1.6. The Pomeranz-Fritsch cyclisation.

An alternative method reported by Schlittler and Muller[22] is available in the reaction of benzylamine (**39**) with glyoxal semiacetal (**40**). Cyclisation of the product (**41**) obtained with sulphuric acid gives the same isoquinoline achieved *via* the Pomeranz-Fritsch cyclisation (**figure 1.7**). The reaction is useful when the desired isoquinoline posseses a substituent in C(1). For example the synthesis of (**43**) does not progress under the Pomeranz-Fritsch (yield 0.1%) due to the difficulty of reacting a ketone (**42**) with an aminoacetal (**36**). The Schlittler -Muller alternative gives a modest 37% yield when amine (**44**) is reacted with (**45**)[22] as shown in **figure 1.7**.

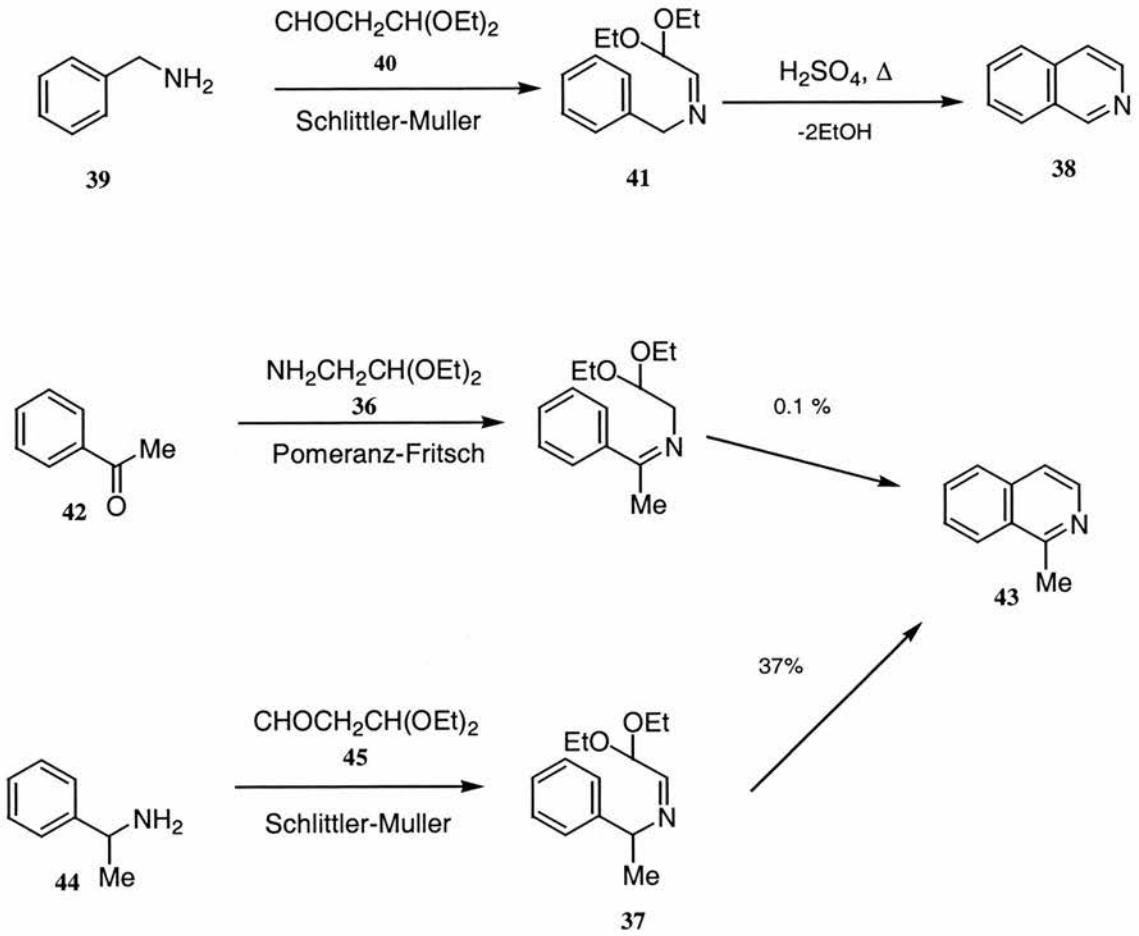
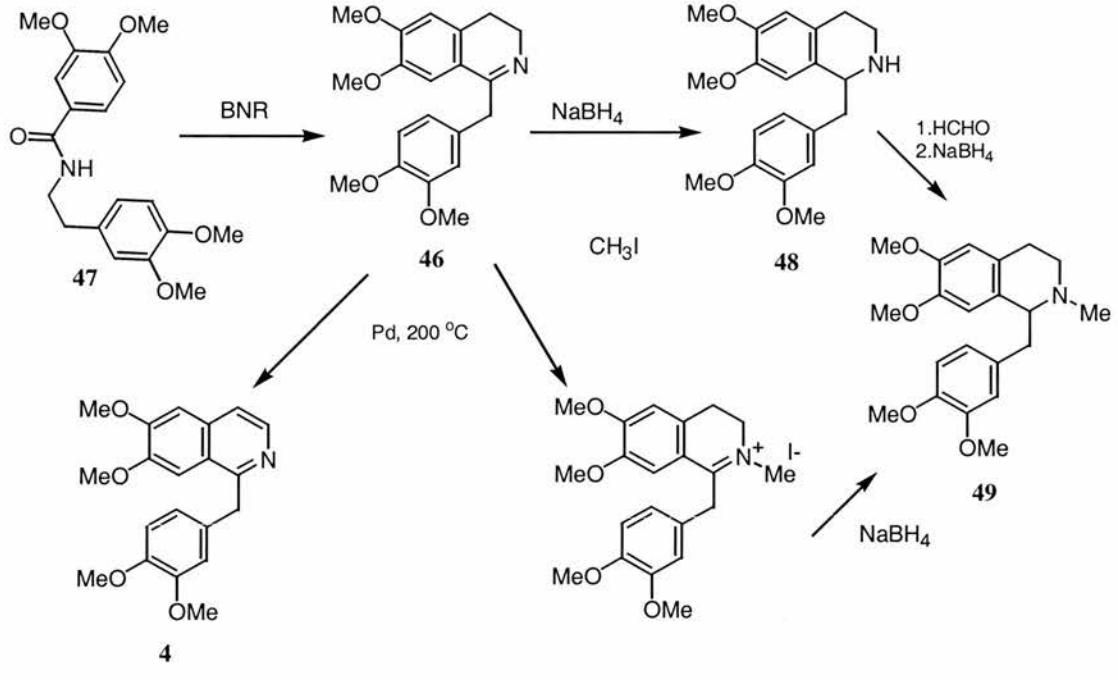


Figure. 1.7. The Pomeranz-Fritsch and Schlittler-Muller cyclisations.

1.5 The Bischler-Napieralski reaction

The Bischler-Napieralski (BN) reaction is somewhat more attractive compared to the other alternatives, as it employs easily accessible starting materials. Additionally, the reaction affords 3,4-dihydroisoquinoline which can be potentially reduced to 1,2,3,4-tetrahydroisoquinoline or oxidised to deliver a fully aromatised product.

Some of these transformations have been successfully applied to the synthesis of natural products or pharmaceuticals. Mild dehydrogenation of 3,4-dihydroisoquinoline (**46**), derived from amide (**47**) under BN conditions, with Pd, yields papaverine (**4**),[9] one of the constituents of the opium alkaloids; alternatively reduction of (**46**), with $NaBH_4$, gives a 1,2,3,4-tetrahydroisoquinoline (**48**) which is N-methylated under Eschweiler-Clarke[23] conditions to give the laudanosine[24] (**49**) (**scheme 1.3**).



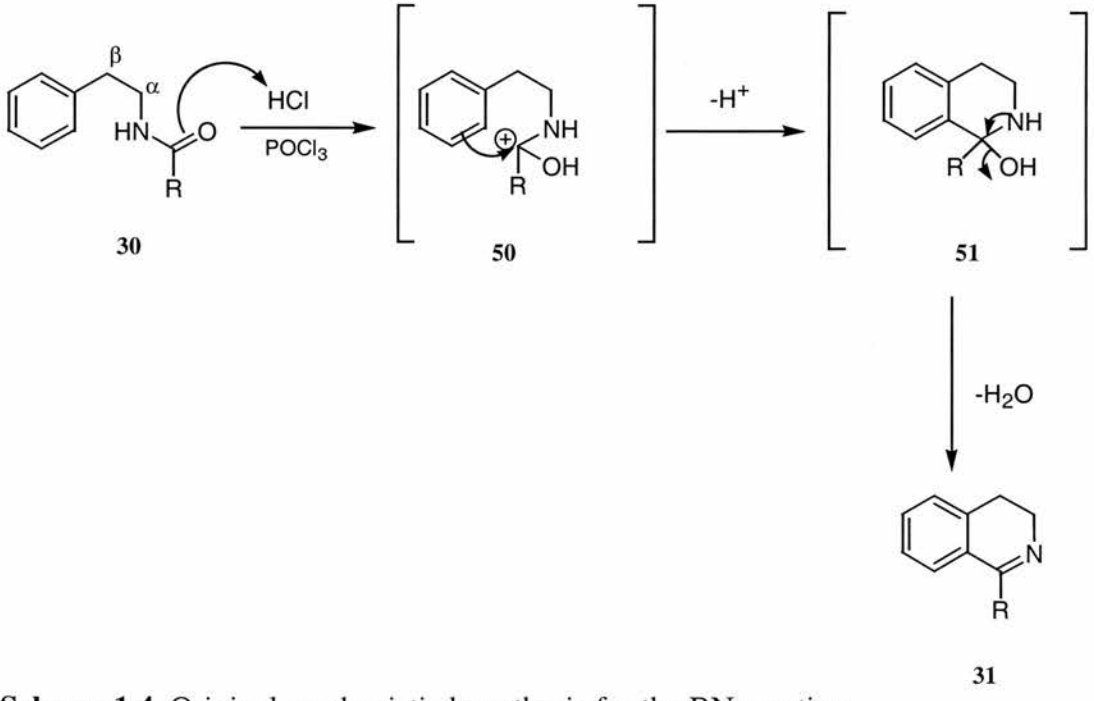
Scheme 1.3. Synthesis of some alkaloids *via* the Bischler-Napieralki reaction.

The reaction is carried out in a dry inert solvent, (eg. chloroform, benzene, toluene, xylene, nitrobenzene, tetralin) and the choice depends on the reflux temperature required for the reaction. The yield of the reaction has been improved when acetonitrile, either at reflux[25] or in a microwave oven,[26] is used as solvent. Recently environmentally friendly preparations of isoquinolines have been achieved at room temperature using ionic liquids as alternative solvents. [27]

Phosphoryl chloride is the most popular dehydrating agent although phosphorous pentoxide, solo or in combination with phosphoryl chloride[28, 29] and phosphorous pentachloride have been widely utilized.

1.5.1 Mechanism

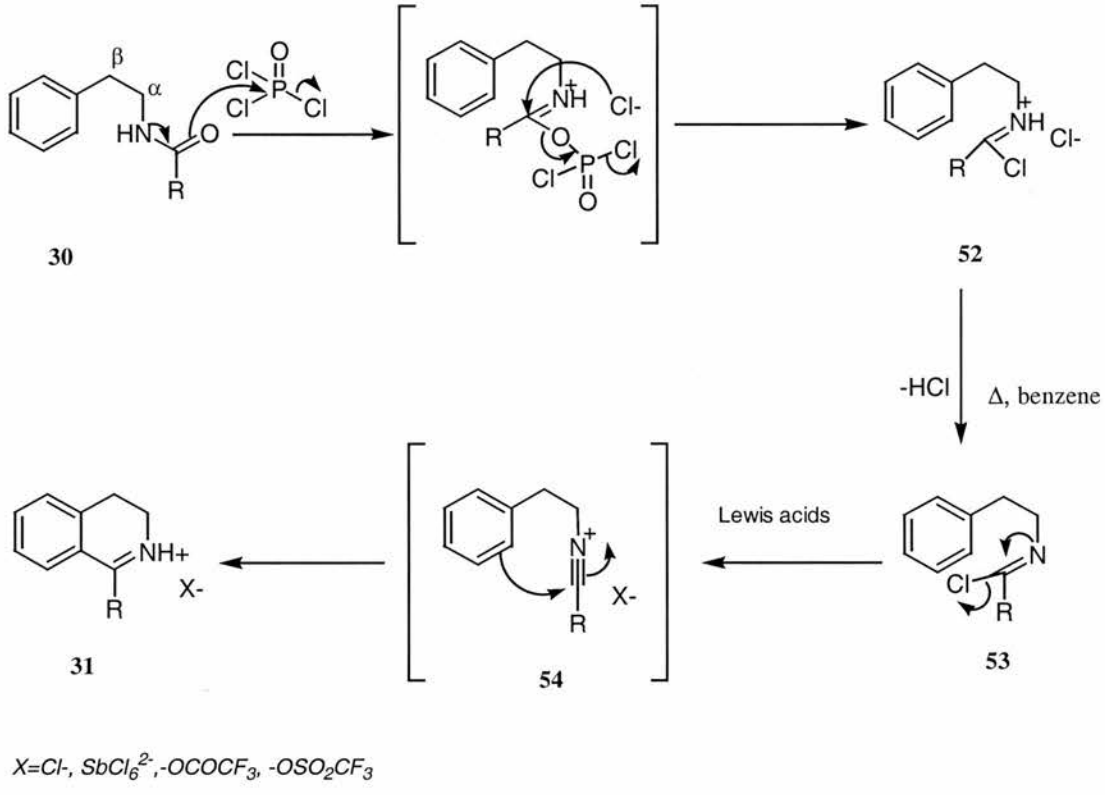
For almost 80 years, the mechanism of the BN reaction was assumed to be as shown in **scheme 1.4.** According to the scheme, traces of HCl associated with phosphoryl chloride mediate the protonation of the amide (**30**) to form the intermediate (**50**), which cyclises to give a second intermediate, 1-hydroxy-tetrahydroisoquinoline (**51**). This ultimately dehydrates to afford the 3,4-dihydroisoquinoline (**31**).



Scheme 1.4. Original mechanistic hypothesis for the BN reaction

This mechanism was later invalidated by the work of Nagubandi and Fodor.[28, 30] They demonstrated that the amide (**30**) in the presence of Lewis acids such as $POCl_3$ or $SOCl_2$, formed an imidoyl chloride (**52**) at room temperature without subsequent cyclisation. Therefore dehydration must precede the ring closure. It was also observed that the hydrochloride salt spontaneously lost HCl upon gentle heating in benzene to

generate imidoyl chloride (**53**), which was purified, characterised and in some cases crystallised. The imidoyl chloride (**53**) was then reacted with a variety of Lewis acids ($FeCl_3$, $SnCl_4$, $ZnCl_4$, $POCl_3$) to give the final product of the Bischler-Napieralski reaction as a salt (**31**). The Lewis acid converts the imidoyl chloride species (**53**) into a nitrilium salt derivative (**54**) which is then attacked by the aromatic ring *via* an electrophilic aromatic substitution. (**scheme 1.5**).



X=Cl-, $SbCl_6^{2-}$,-$OCOCF_3$, -OSO_2CF_3

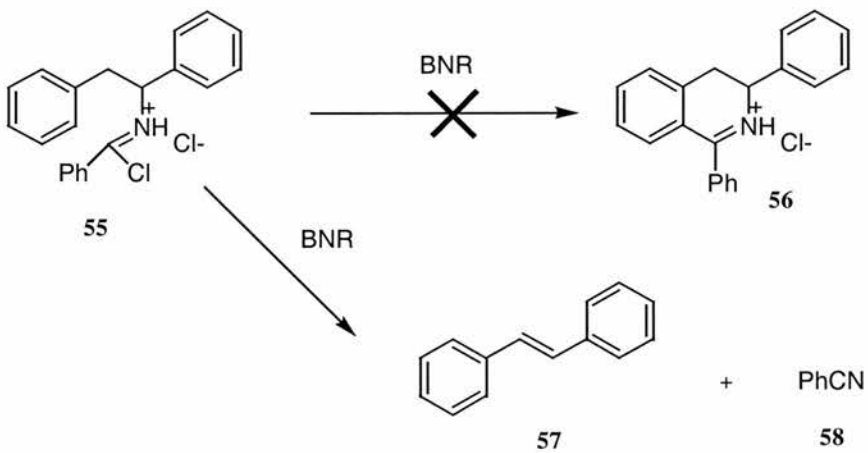
Scheme 1.5. The mechanism of the BN reaction by Nagubandi and Fodor.[28, 30]

The new two steps protocol for the Bischler-Napieralki reaction gave excellent yields, 85-90 % vs 40-60% and above all, clarified the mechanism of the reaction. Furthermore, the existence of a new intermediate (**54**) was demonstrated in the reaction which was in some cases trapped as a stable crystalline salt[31] of SbF_6^-.

As discussed above phosphorous pentoxide is employed alone or together with phosphorous oxychloride for the BN reaction. In the first case, an imidoyl phosphate is formed and in the latter, an imidoyl chloride is obtained, which explains the higher yields obtained with a combination of 1:1. Of course the pyrophosphate group is a better leaving group than the chloride ion.

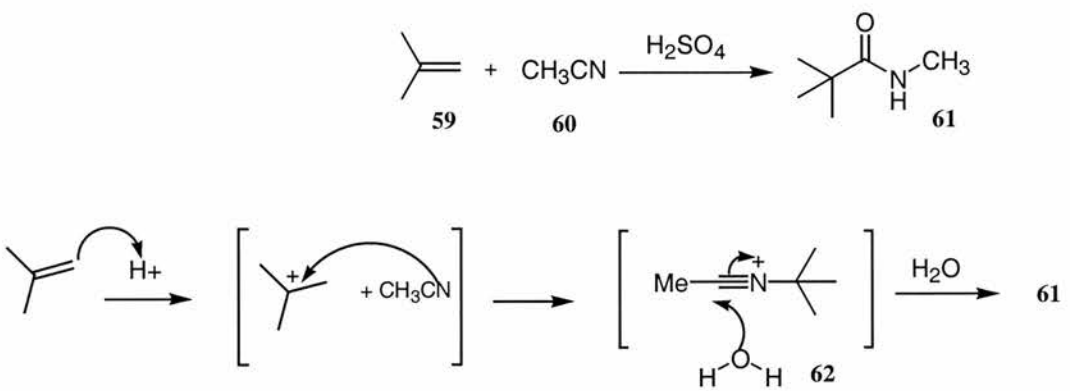
1.5.1.1 Side Reactions

The identification of a nitrilium ion as an intermediate in the BN reaction explains a number of side reactions. For example cyclisation of (**55**) to form (**56**), does not take place under the classical conditions of the BN reaction, the only products detectable are stilbene (**57**) and the benzonitrile (**58**). (**Scheme 1.6**)



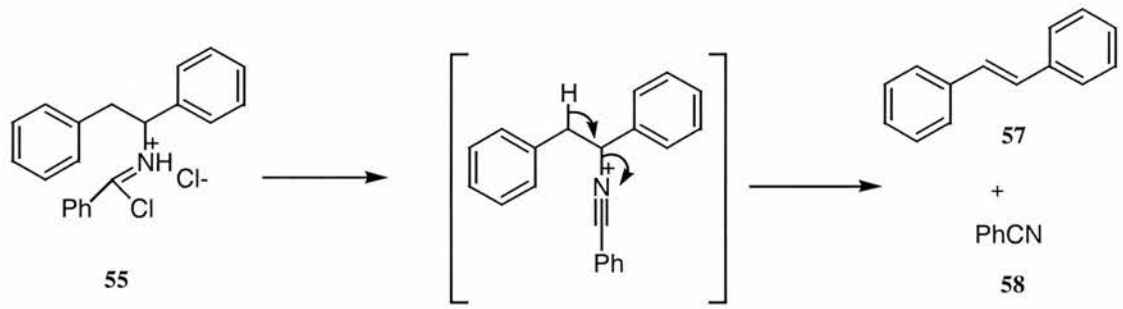
Scheme. 1.6. Side products of BN reaction

Nagubandi and Fodor rationalised[28] this observation by assuming a "retro" Ritter process, competing with the BNR. The Ritter reaction [32] shown in **scheme 1.7** allows the synthesis of an amide (**61**) starting from alkene (**59**) and acetonitrile (**60**) in a strongly acidic medium.



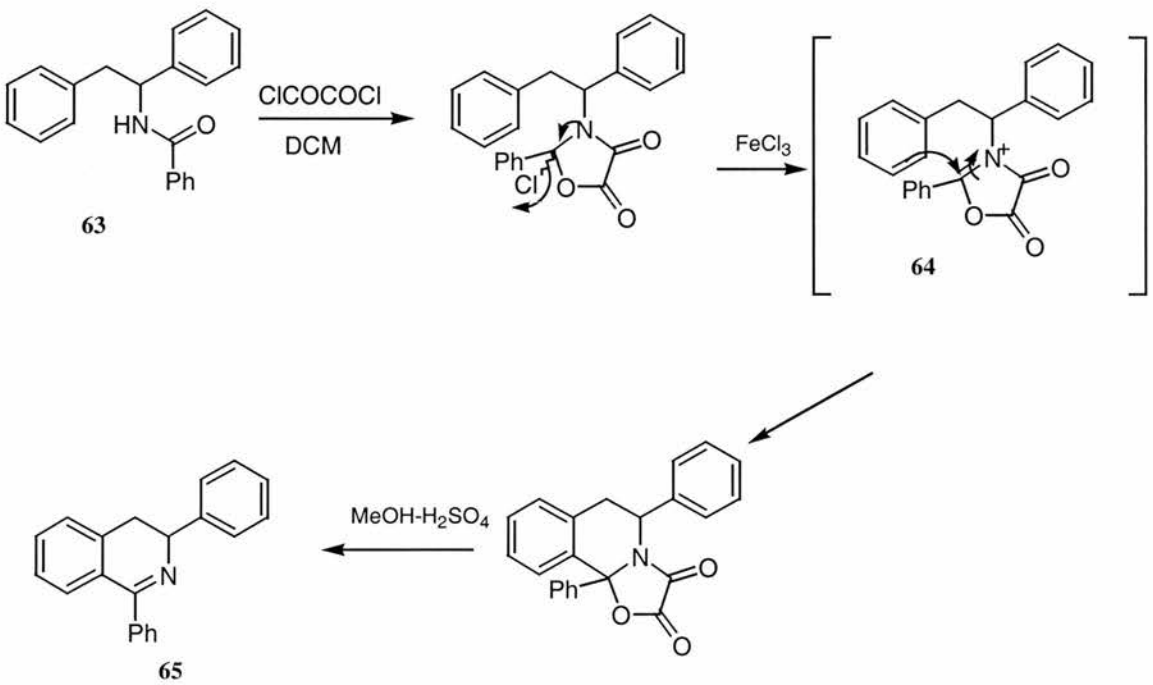
Scheme 1.7. A Ritter reaction

The reaction proceeds through the same nitrilium ion (**62**) intermediate, postulated for the BNR, which after hydrolysis yields amide (**61**). Therefore, compound (**55**) in **scheme 1.8,** forms the corresponding nitrilium ion that loses the RCN fragment to provide the stilbene (**57**) *via* a "retro" Ritter reaction rather than of the expected 3,4-dihydroisoquinoline. The competitive reaction is probably enhanced due to the formation of a fully conjugated product in the resulting *trans* stilbene.



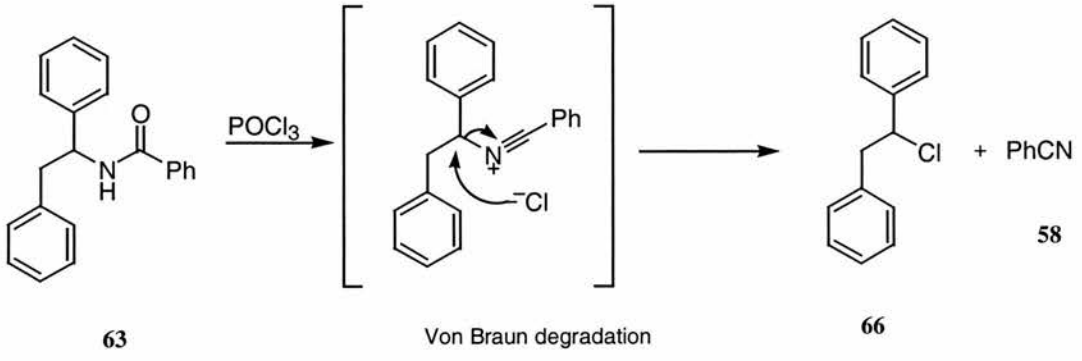
Scheme 1.8. Competitive "retro" Ritter reaction

The competitive reaction can be avoided by conversion of amide (**63**) into the N-acyliminium intermediate (**64**), with a mixture of oxalyl chloride and $FeCl_3$; removal[33] of the oxalyl group in MeOH-H_2SO_4 provides the desired 3,4-dihydroisoquinoline (**65**) in moderate and high yield **Scheme 1.9.**



Scheme 1.9. Modified Bischler-Napieralski reaction for the synthesis of 3-Aryl-3,4-dihydroisoquinoline

The nitrilium ion is also responsible for another competitive reaction. It dissociates into a carbonium ion, which reacts with the counter ion to yield the products of the Von Braun degradation.[34, 35] For instance in the case of amide (**63**), the chloride ion displaces benzylnitrile (**58**) to give a chlorinated Von Braun product (**66**). **Scheme 1.10**.



Scheme 1.10. Competitive Von Braun reaction

1.5.2 Reduction of 3,4-dihydroisoquinoline

The BN reaction affords an imine (C=N) functionality which is amenable to reduction. If the 3,4-dihydroisoquinoline is substituted on C(1), reduction generates a stereogenic centre. An asymmetric process, as illustrated in **figure 1.8**, can be achieved *via* two general routes:

a, reduction *via* an achiral reagent to give 1,2,3,4-tetrahydroisoquinoline followed by conventional enantiomeric resolution techniques;

b, reduction using an asymmetric reducing reagent.

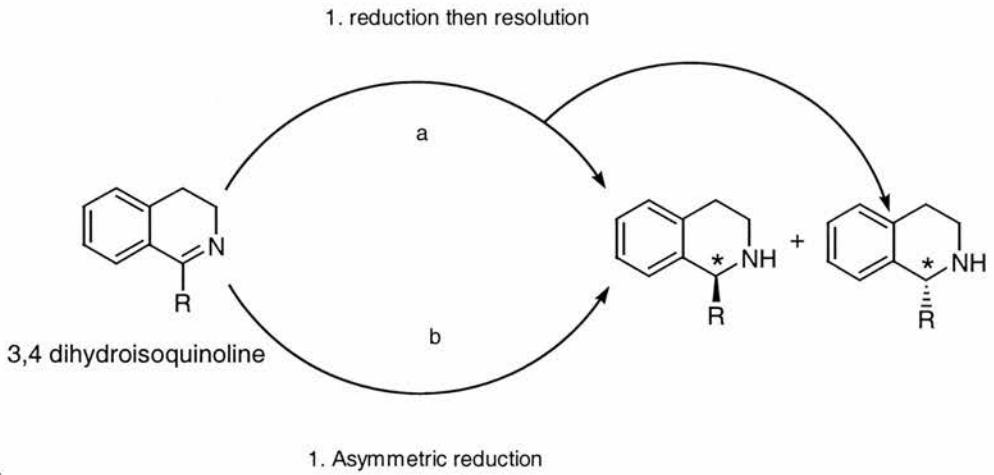


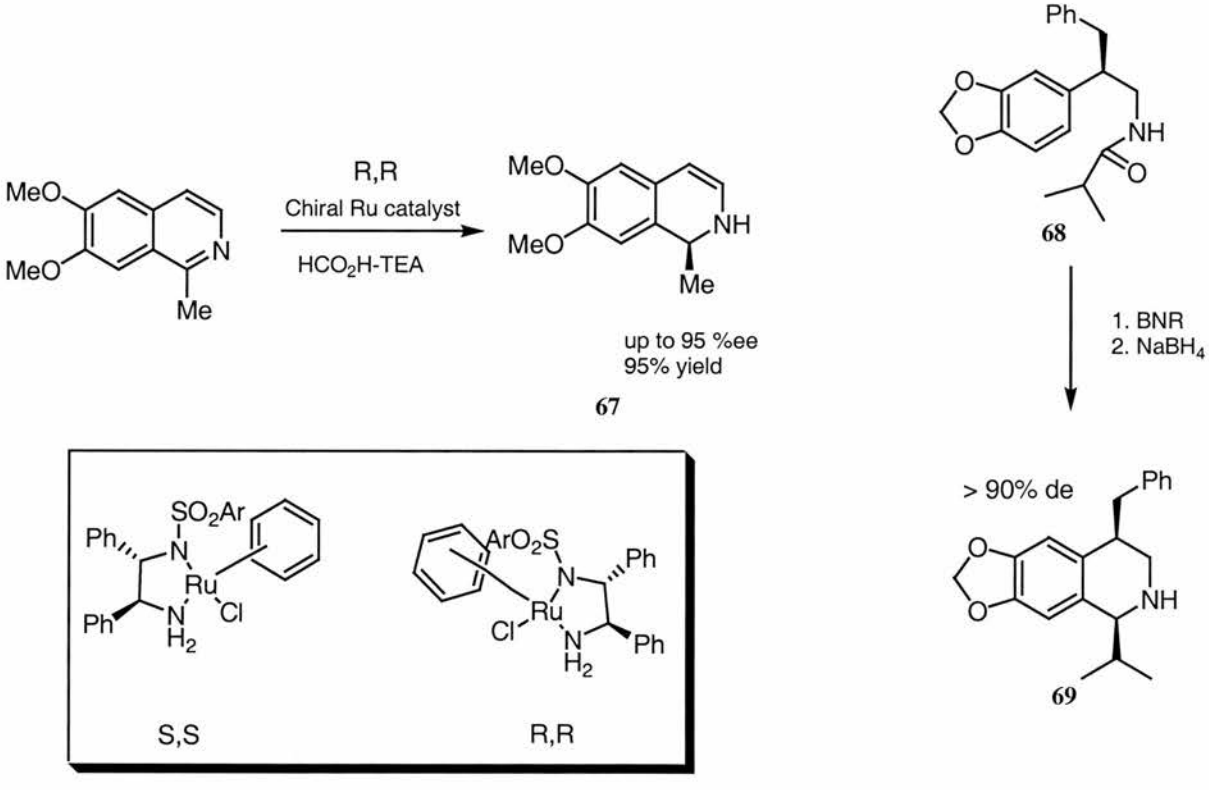
Figure 1.8. Asymmetric reduction of 3,4-dihydroisoquinolines

The imine functionality of the 3,4-dihydroisoquinoline, can readily be reduced by various reagents: $NaCNBH_3$, $LiAlH_4$, $NaBH_4$ and so on. Resultant racemates have been resolved by crystallisation of diastereoisomeric salts, in which a substrate (usually a racemic amine) is treated with one enantiomer of a chiral carboxylic acid. The diastereoisomeric pairs are usually resolved *via* fractional crystallisation. This technique has been extensively used in the resolution of CAPTIQ*, a tertahydroisoquinoline used for the asymmetric protonation of amides.[36-38]

* CAPTIQ:(R)-1-(2-methylamino-5-chloro)-phenyl-1,2,3,4-tetrahydroisoquinoline.

Asymmetric reduction of 3,4-dihydroisoquinoline has also been performed by using chiral reducing agents that posses the ability to attack preferentially only one face of the imine functionality. Noyori[39] and co-workers have developed chiral Ru(II) complexes which catalyse the asymmetric reduction of the imine functionality with a mixture of formic acid and triethylamine under mild condition as shown **scheme 1.11.** The alkaloids salsolidine (**67**) and tetrahydro-β-carbolines[40] have been prepared using this methodology.

Asymmetric 1,2,3,4-tetrahydroisoquinolines, have also been prepared by achiral reduction on an asymmetric substrate[41]. Chiral amide (**68**) undergoes BN cyclisation and the product is reduced *in situ* with $NaBH_4$ to yield a predominant steroisomer (**69**).

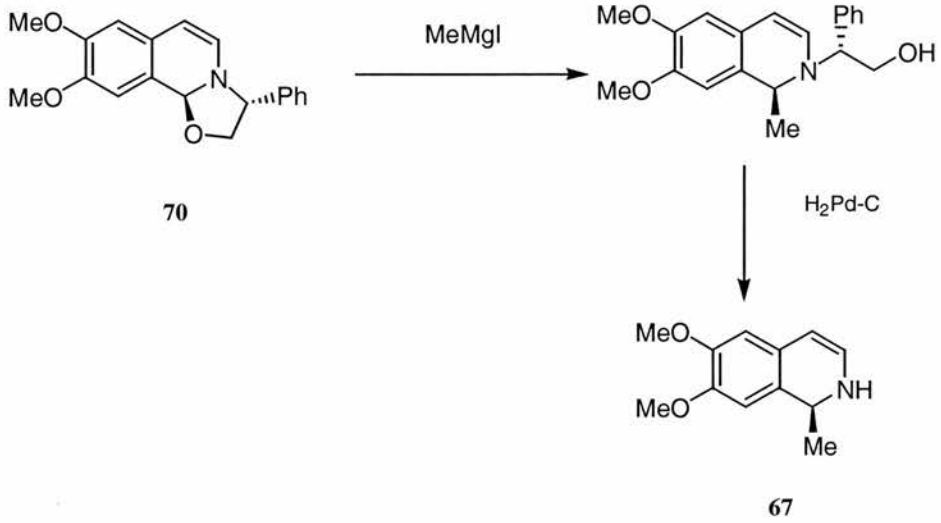


Scheme 1.11. 1). Chiral reduction to salsolidine (**67**) in the presence of asymmetric Ru (II) catalyst. 2). BN reaction on a chiral amide (**68**)

2 The asymmetric BN reaction

2.1 Asymmetric synthesis of tetrahydroisoquinoline containing alkaloids

Several important asymmetric routes have been developed for the stereoselective synthesis of tetrahydroisoquinoline alkaloids. The alkaloid salsolidine (**67**), for instance, has been utilised as a convenient model for developing asymmetric methods to the isoquinolines. For example, asymmetric hydrogenation of the 3,4-dihydroisoquinoline, in the presence of a chiral ligand, has been already discussed section **1.2.3**. Other examples are found in the literature, eg. Yamato[42], reported the synthesis of salsolidine (**67**) *via* a chiral oxazolo [2,3-a]- tetrahydroisoquinoline (**70**) as shown in **scheme 2.1.** This methodology extends to the synthesis of 1-alkyl and 1-aryl tetrahydroisoquinolines.

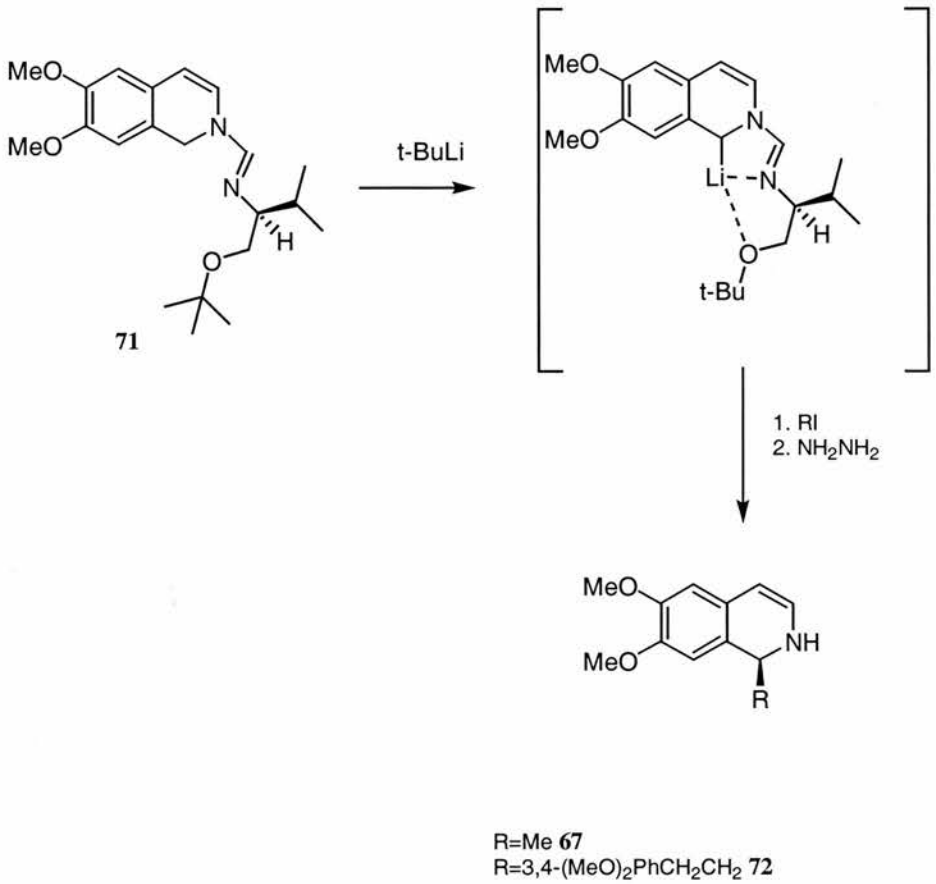


70 **67**

Scheme 2.1. Asymmetric synthesis of alkyl and phenyl 1,2,3,4-tetrahydroisoquinolines

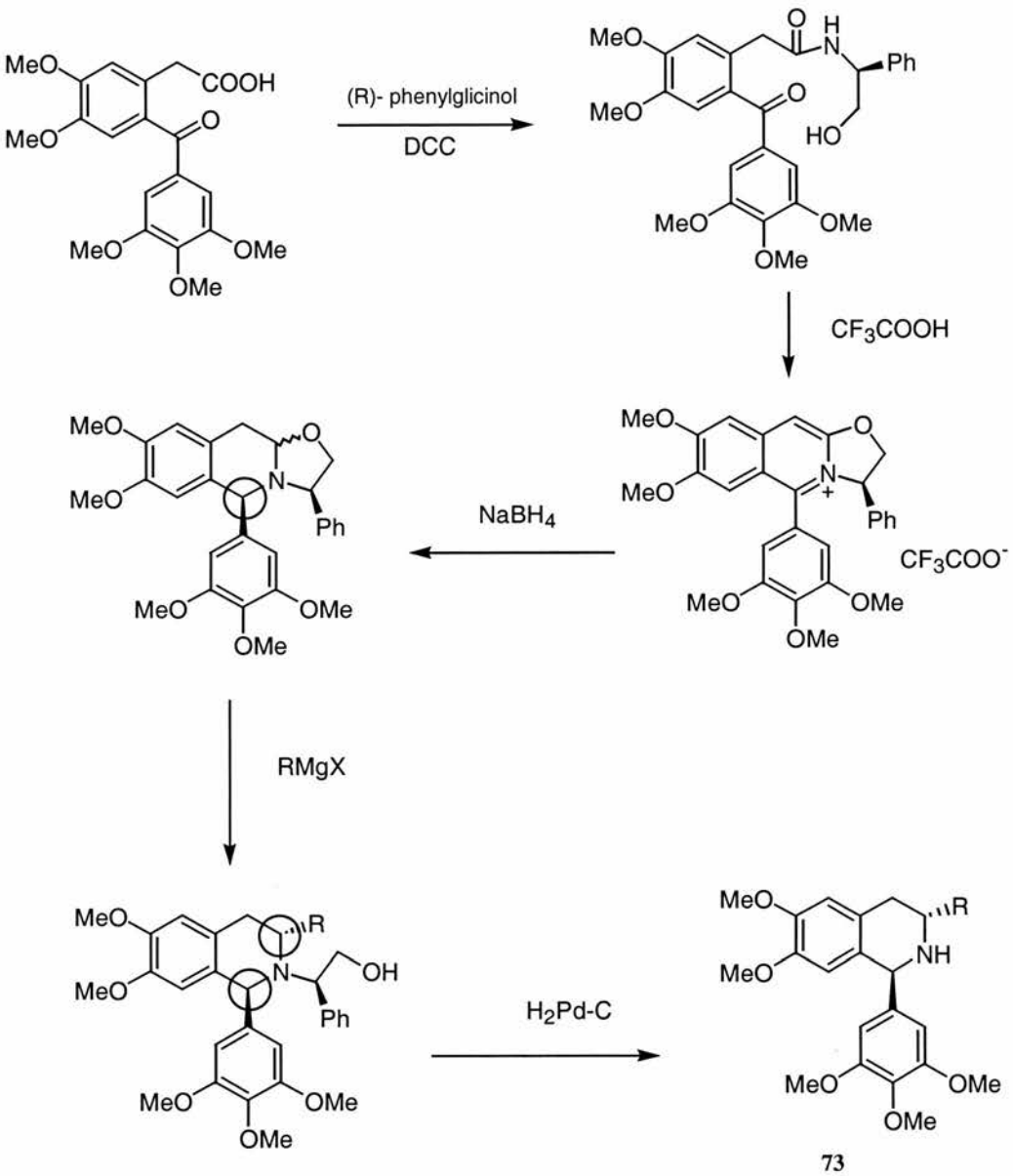
Chiral formamidines have also been used as chiral auxiliaries.[43]For example, (**71**) has been used in the synthesis of alkaloids such as salsolidine (**67**) and homolaudanosine (**72**) as shown in **scheme 2.2**. Treatment of (**71**) with *t*BuLi and MeI, gave only one

stereoisomer. The alkaloids (**67**) and (**72**) were delivered by release of the formamidine group in a hydrazine-acetic acid mixture.



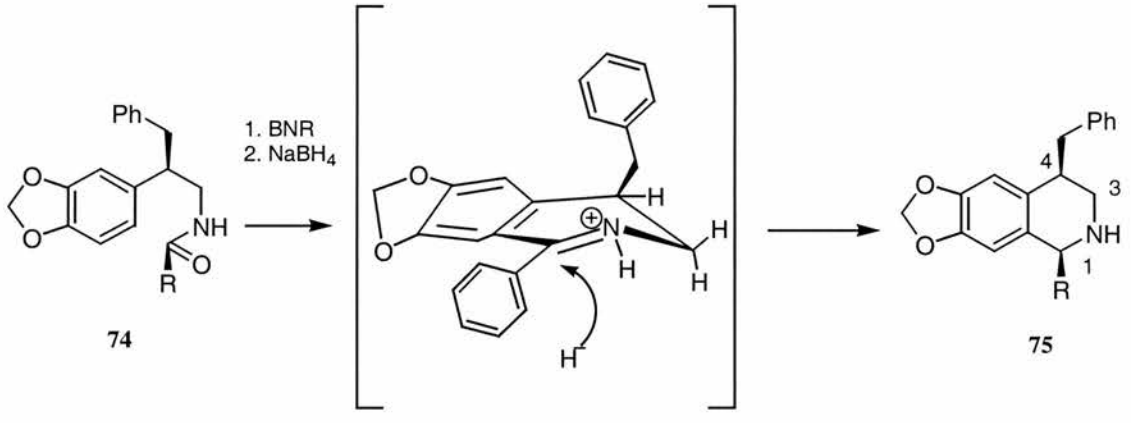
Scheme 2.2. The use of chiral formamidines affixed to tetrahydroisoquinolines to generate an asymmetric C-C bond.

The first example of an asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines was reported as recently as 1996 by Husson.[44] The stereoselectivity was controlled by the appended phenylglycinol, and this was then removed by hydrogenation to yield the 1,2,3,4-tetrahydroisoquinoline (**73**) with two new stereogenic centres at C(1) and C(3), as illustrated in **scheme 2.3** .



Scheme 2.3. Asymmetric synthesis of 1,3-tetrahydroisoquinoline by Husson's methodology.[44]

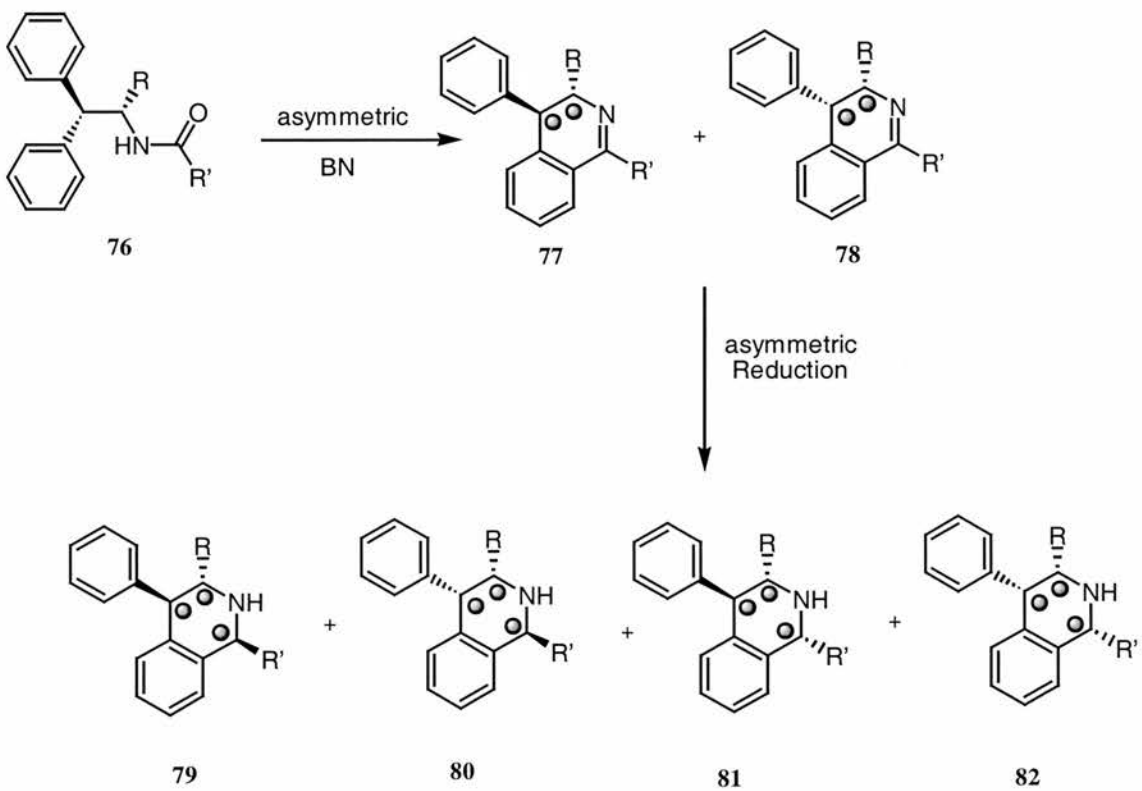
The same research group subsequently reported the first asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines based upon a Bischler-Napieralski reaction of β-substituted phenylethylamines.[41] The Bischler-Napieralski reaction was conducted on chiral amide (**74**) to generate the 3,4-dihydroisoquinoline, which was reduced *in situ* by treatment with $NaBH_4$ to form (**75**). The stereogenic centre at C(4) controlled the stereochemical course of the reduction. In the event, hydride approached C(1) to the opposite face of C(4) as illustrated in **scheme 2.4.**



Scheme 2.4. Asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines by a BN reaction.

2.2 Aims

It was an objective to explore an asymmetric Bischler-Napieralski reaction using substrate (**76**). The amide (**76**) has two diastereotopic aryl groups β to the nitrogen, therefore cyclisation to one or other will generate diastereoisomeric products (**77** and **78**). The ratio of **77:78** is a measure of the stereoselectivity of the BN reaction. Furthermore, asymmetric reduction of the 1,3,4-trisubsituted 3,4-dihydroisoquinolines products, is anticipated to generate 1,2,3,4-tetrahydroisoquinoline carrying three stereogenic centres at C(1), C(3) and C(4) (**79-82**). These reactions were also investigated (**scheme 2.5**).

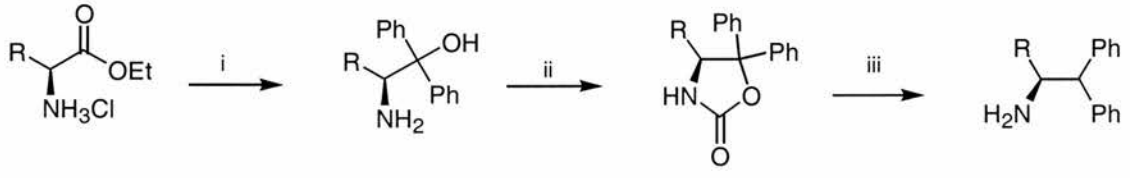


76 77 78 79 80 81 82

Scheme 2.5. Molecule targets which allow to investigate the first asymmetric Bischler-Napieralski reaction

2.3 The asymmetric Bischler-Napieralski reaction

The availability of a series of *(S)*-1-alkyl-2,2-diphenylethylamine, including **(83)** and **(84)** opened up an opportunity to explore the asymmetric BN reaction**.** These amines are available in enantiomerically pure form from their corresponding amino acids (*S*)-alanine and (*S*)-valine [45] as shown in **scheme 2.6.**



R= Me **83**

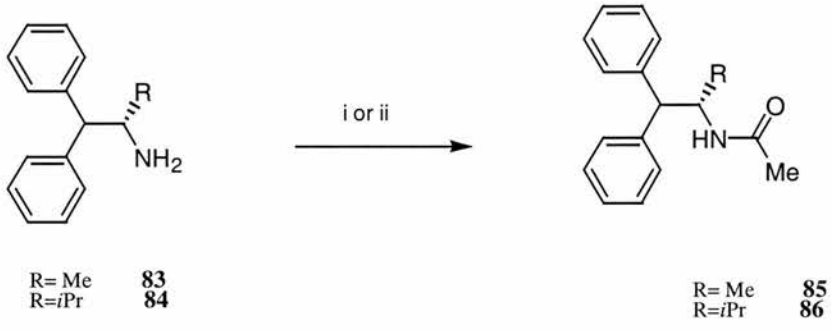
R=*i*Pr **84**

Scheme 2.6. Reagents and conditions. (i). PhMgBr,Et_2O, 40-50%. (ii). Triphosgene, Et_3N, 80-90%, (iii). H_2 Pd-C, 70%.

Amines **(83)** and **(84)**, which are commercially available, were converted into their corresponding acetamides (**85** and **86**) or benzamide (**87**) for use as substrates for the Bischler-Napieralski reaction.

2.3.1 Acetamides synthesis

The acetamides (**85**) and (**86**) were prepared in a straightforward manner[23] by treatment of amines (**83**) or (**84**) with acetyl chloride in presence of triethylamine (**scheme 2.7**).



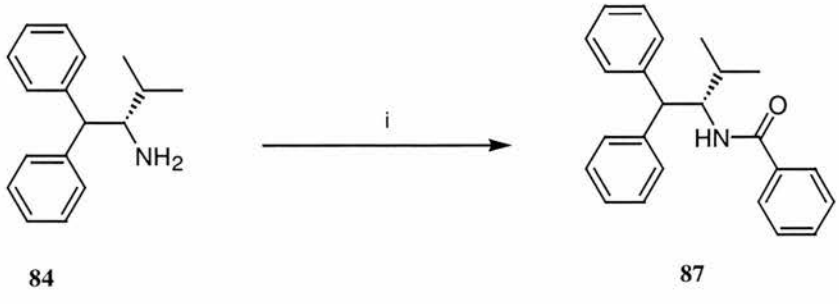
R= Me **83**
R=*i*Pr **84**

R= Me **85**
R=*i*Pr **86**

Scheme 2.7. Reagents and conditions. (i and ii) AcCl, TEA, CH_2Cl_2, 12 h, RT, 94 % for both amides (**85**) and (**86**).

2.3.2 Synthesis of benzamide (**87**)

Benzamide (**87**) was prepared by coupling benzoyl chloride and amine (**84**) in the presence of triethylamine (TEA) as a base. The reaction provided the product as crystalline material and in excellent yield (**scheme 2.8**).

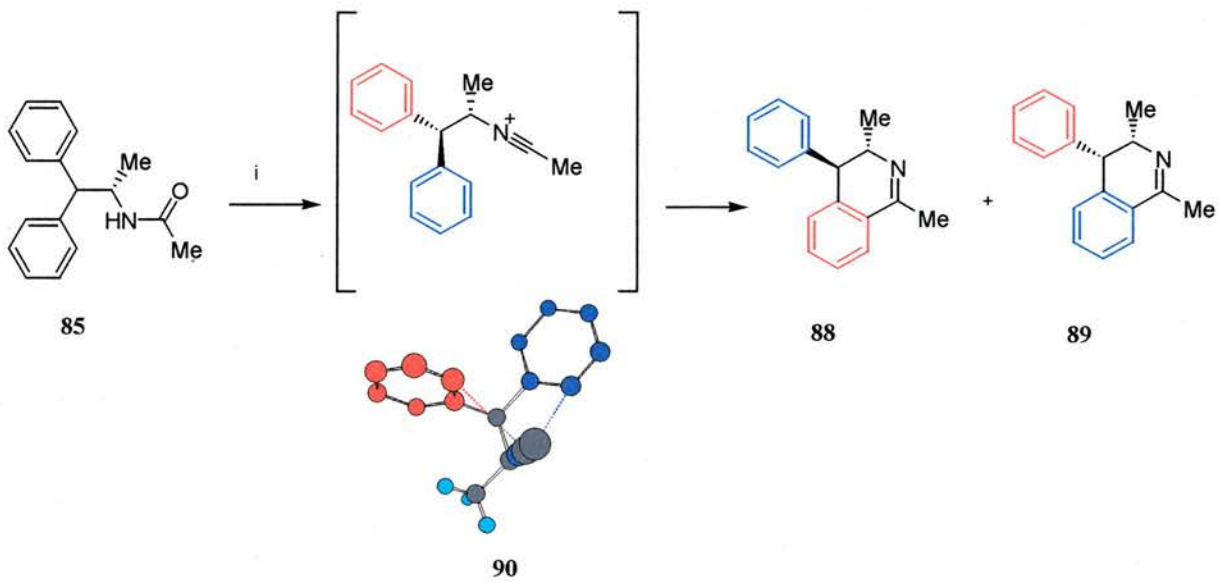


84 **87**

Scheme 2.8. Reagents and conditions. (i) benzoylchloride, TEA, CH_2Cl_2, 12 h, RT, 94 %

2.3.3 Preparation 3,4-dihydroisoquinoline (**88**) and (**89**) via the asymmetric BN reaction

Amide (**85**) was treated with a mixture of $POCl_3$-P_2O_5 (10 eq: 10eq) under classical Bischler-Napieralski conditions[28] in dry toluene. This generated the 3,4-dihydroisoquinoline as a diastereomeric mixture (**88**) and (**89**). **Scheme 2.9** shows clearly the two possible modes of cyclisations. Cyclisation involving the red phenyl group, represented in the image of intermediate (**90**), leads to the formation of (**88**). On the other hand reaction involving the blue phenyl group gives the diasteromeric product (**89**).



Scheme 2.9. Reagents and conditions. (i) $POCl_3$, P_2O_5, toluene at reflux 12 h, 29%.

^{1}H NMR of the crude reaction product indicated the presence of two diastereoisomers (**88**) and (**89**) by two sets of signals for the protons at C(4) and methyl group at C(1), as shown in the spectrum in **figure 2.1**. It was clear that the two 3,4- dihydroisoquinoline (**88** and **89**) were generated in the ratio of 9:1. The coupling constants between the protons at C(3) and C(4) were measured. The major diasteroisomer had the larger vicinal H(3)-H(4) coupling constant (11.0 Hz) and was assigned structure (**88**). The minor isomer had a smaller vicinal coupling constant (6.0 Hz) consistent with structure (**89**). Therefore it was deduced that the preferred reaction route was cyclisation to the red phenyl group which led to the formation of the 3,4-dihydroisoquinolines with Me at C(3) and Ph at C(4) *trans* to each other.

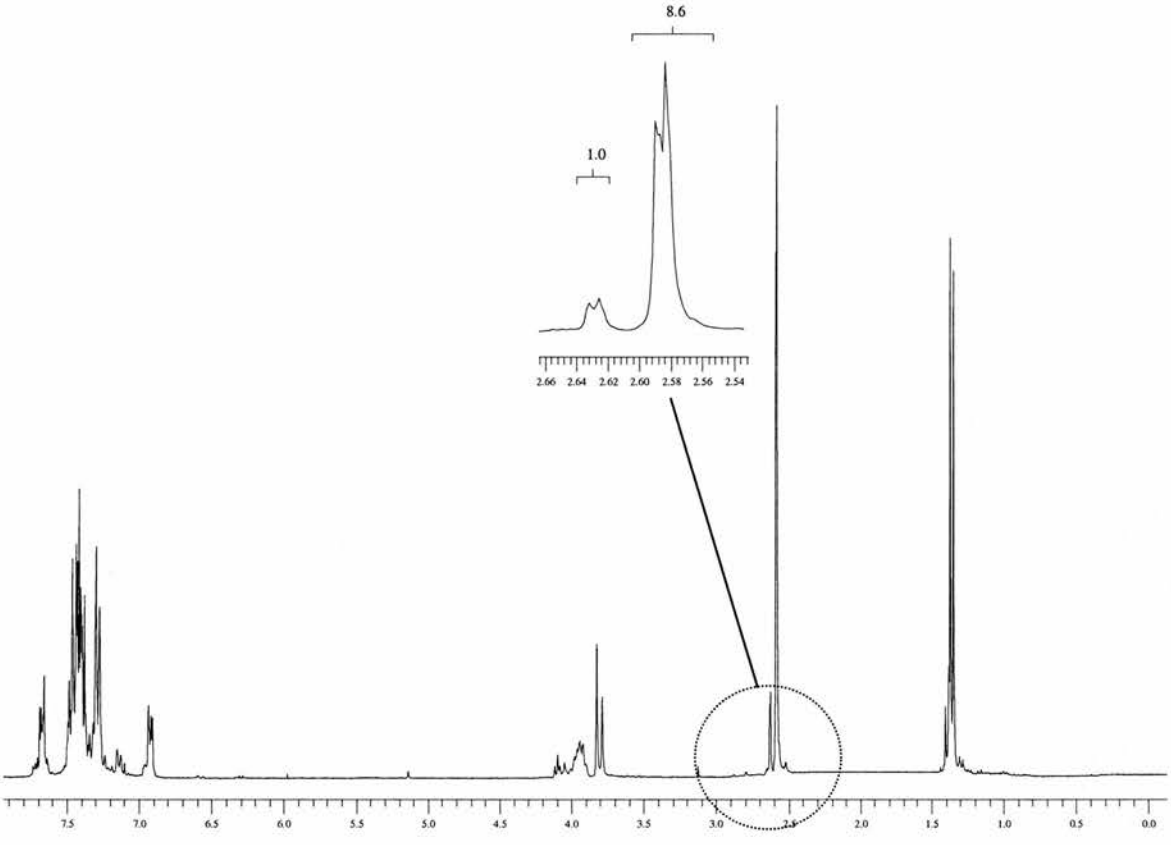
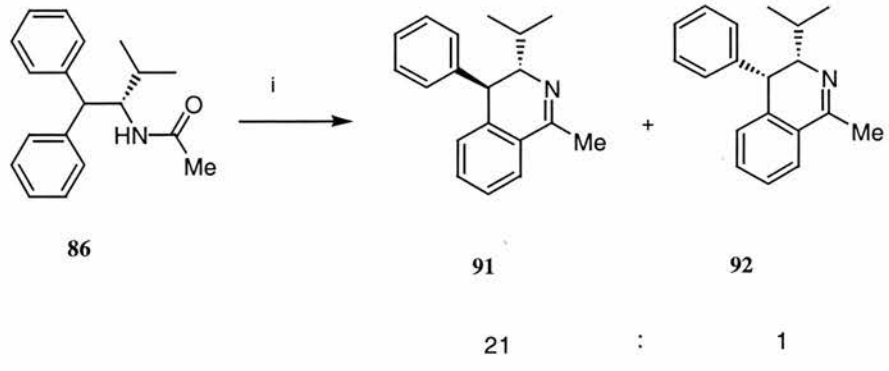


Figure 2.1. ^{1}H NMR of the BN reaction mixture product performed on amide **(85).**

2.3.4 Preparation of 3,4-dihydroisoquinoline (**91**) and (**92**)

Amide (**86**) was also treated under Bischler-Napieralski conditions as shown in **scheme 2.10.** This generated a mixture of two diastereoisomers, which were again analysed by ^{1}H NMR spectroscopy.



Scheme 2.10. Reagents and conditions. (i) $POCl_3$, P_2O_5, toluene at reflux 12 h, 60%.

From this analysis it was deduced that the product ratio was 21:1 **figure 2.2**. The major diastereoisomer was assigned structure **91** based on the value of H (3) H (4) coupling constant (9.7 Hz). The minor isomer had a smaller value (5.6 Hz) consistent with structure **92.** Recrystallisation of the reaction mixture from petrol and acetone afforded crystals of (**91**), suitable for X-ray structure analysis.

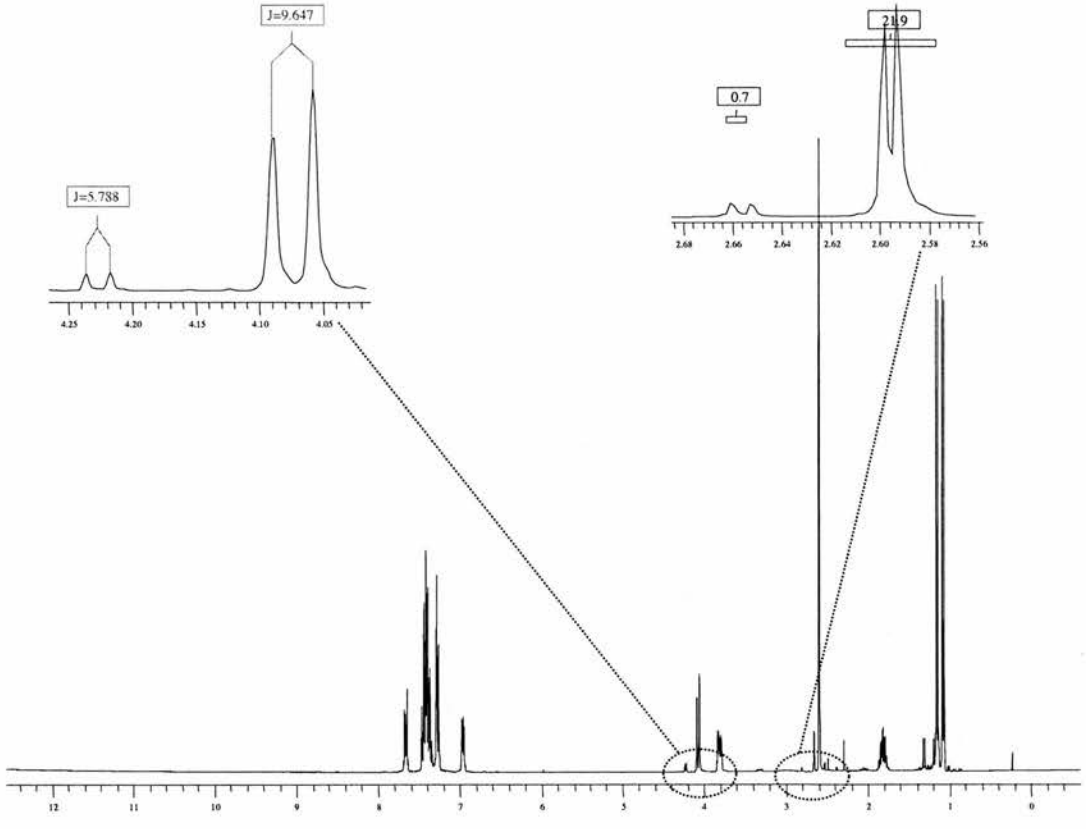


Figure 2.2. ^{1}H NMR of the BN reaction product performed on amide **(86)**

The X-ray derived structure of (**91**) in **Figure 2.3** confirmed the absolute stereochemistry at C(3) and C(4) as *3S* and *4*S. This *trans* relative configuration for the major diastereoisomer is consistent with the larger coupling constant observed by ^{1}H NMR.

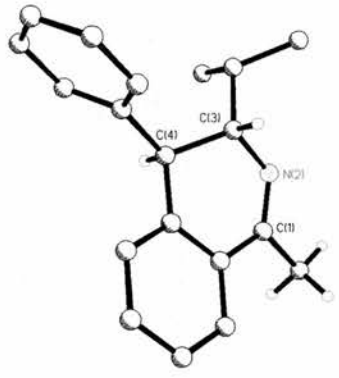
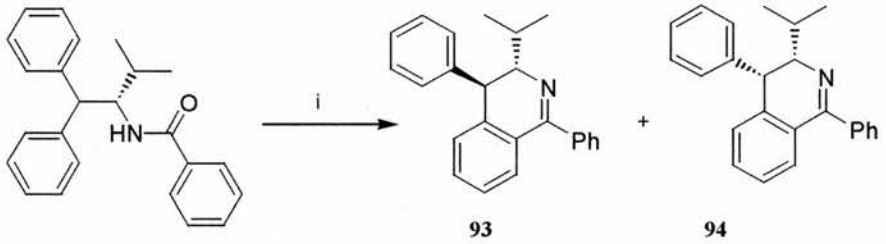


Figure 2.3. Ball and stick drawing of the molecular structure of **91** in the solid state showing the *trans* relative configuration between substituents at C(3) and C(4).

2.3.5 Preparation of 3,4-dihydroisoquinoline (**93**) and (**94**)

Treatment of amide (**87**) with P_2O_5 and $POCl_3$ again gave a mixture of two diastereoisomers as Bischler-Napieralski products (**scheme 2.11**). ^{1}H NMR analysis of the crude reaction product, revealed a diastereomeric ratio of 13:1 as shown in **figure 2.4**. The coupling constants for the two diastereoisomers were also very different (major 8.7 Hz vs minor 5.3 Hz and the major was assigned structure (**93**) consistent with a transoid relationship between the hydrogens in C(3) and C(4).



87 **93** **94**

13 : 1

Scheme 2.11. Reagents and conditions. (i) $POCl_3$, P_2O_5, toluene at reflux 12 h, 32%.

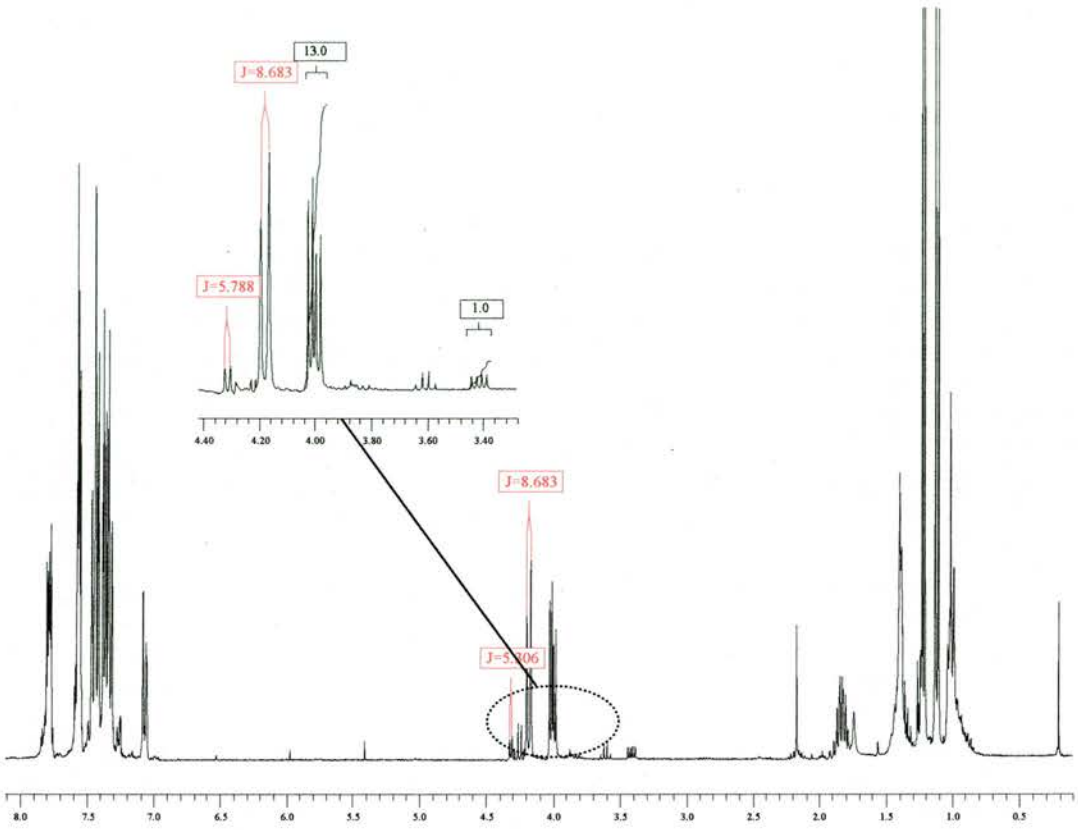


Figure 2.4. ^{1}H NMR of the BN reaction product with diasteroisomers **(93** and **94)**

Recrystallisation from petrol-ethyl acetate provided crystals of **(93)** suitable for X-Ray analysis. Inspection of the X-ray crystal structure **(figure 2.5)** clearly showed the *trans* diaxial relation between H_3 and H_4 reinforcing the assumption made from the ^{1}H NMR coupling constants values.

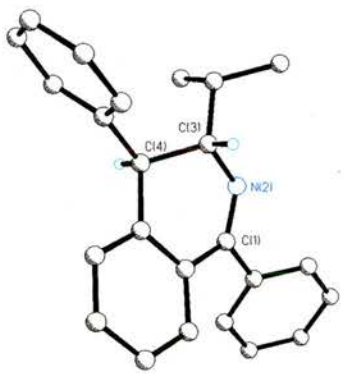
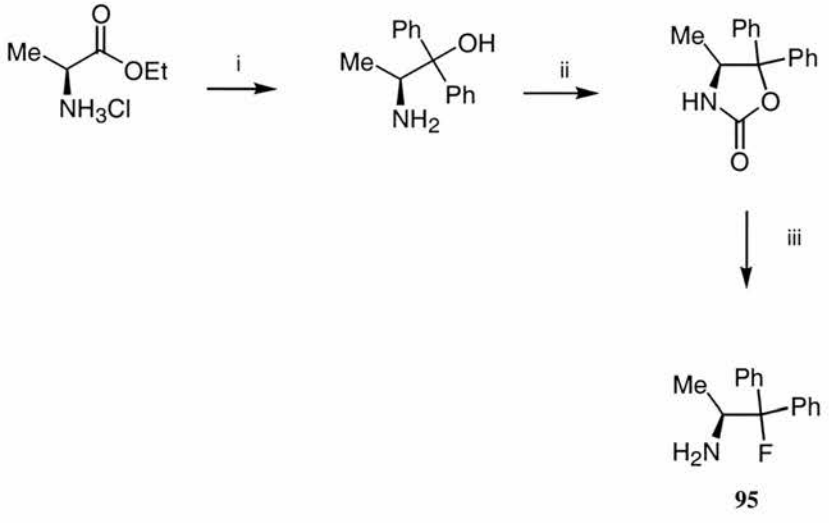


Figure 2.5. Ball and stick drawing of the molecular structure of **93** in the solid state showing the trans relative configuration between substituents at C(3) and C(4).

2.4 Bischler-Napieralski reactions on a β-fluoroamide

There is a desire to develop synthetic methods for the preparation of fluorine containing analogues of amino acids, nucleosides, and sugars. Such building blocks contribute to the arsenal of molecules available for the synthesis of fluorinated drugs and agricultural chemicals.

Recently our research group reported the synthesis of a series of fluorine containing chiral amines. For example, the chiral amine (**95**), shown in **scheme 2.12**, was a potential starting point for exploring a fluorine containing substrate in the asymmetric Bischler-Napieralski reaction.

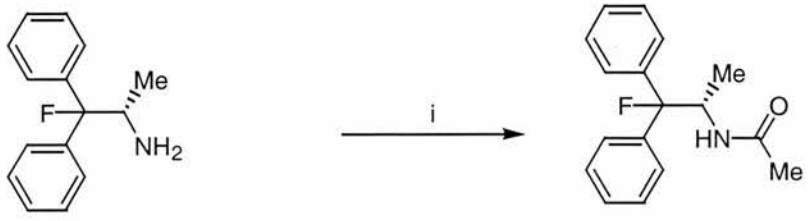


95

Scheme 2.12. Reagents and conditions. (i). PhMgBr, Et_2O, 40-50%. (ii). triphosgene, Et_3N, 80-90%, (iii) HF-pyridine, 77%.[45]

2.4.1 β-Fluoroacetamide (**96**)

The synthesis of the fluorinated acetamide (**96**) follows the general method of amide preparation discussed in the previous section. Therefore, acetyl chloride was added to a solution of the amine (**95**) and TEA and this gave the desired product as a crystalline solid. **(Scheme 2.13).**



95 96

Scheme 2.13. Reagents and conditions. (i). AcCl, TEA, 12 h, 97%.

2.4.2 Attempted synthesis of 4-fluoro-3,4-dihydro-isoquinoline (**97**).

Following the previous BN preparations, amide (**96**) was treated with P_2O_5 and $POCl_3$ in anhydrous toluene. The reaction mixture was stirred at room temperature and aliquots were taken every 5 min. Each aliquot was then analysed by ^{19}F NMR to monitor the progress of the reaction (**figure 2.6**). ^{19}F NMR of the first aliquot showed a doublet at –170 ppm, attributable to the starting material (**96**).

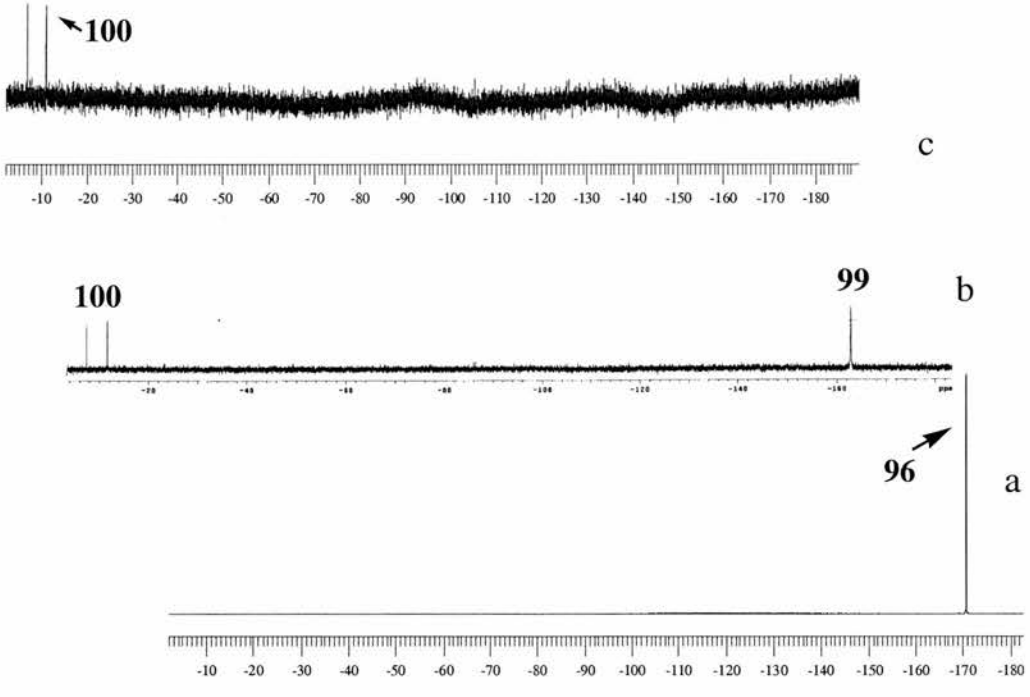
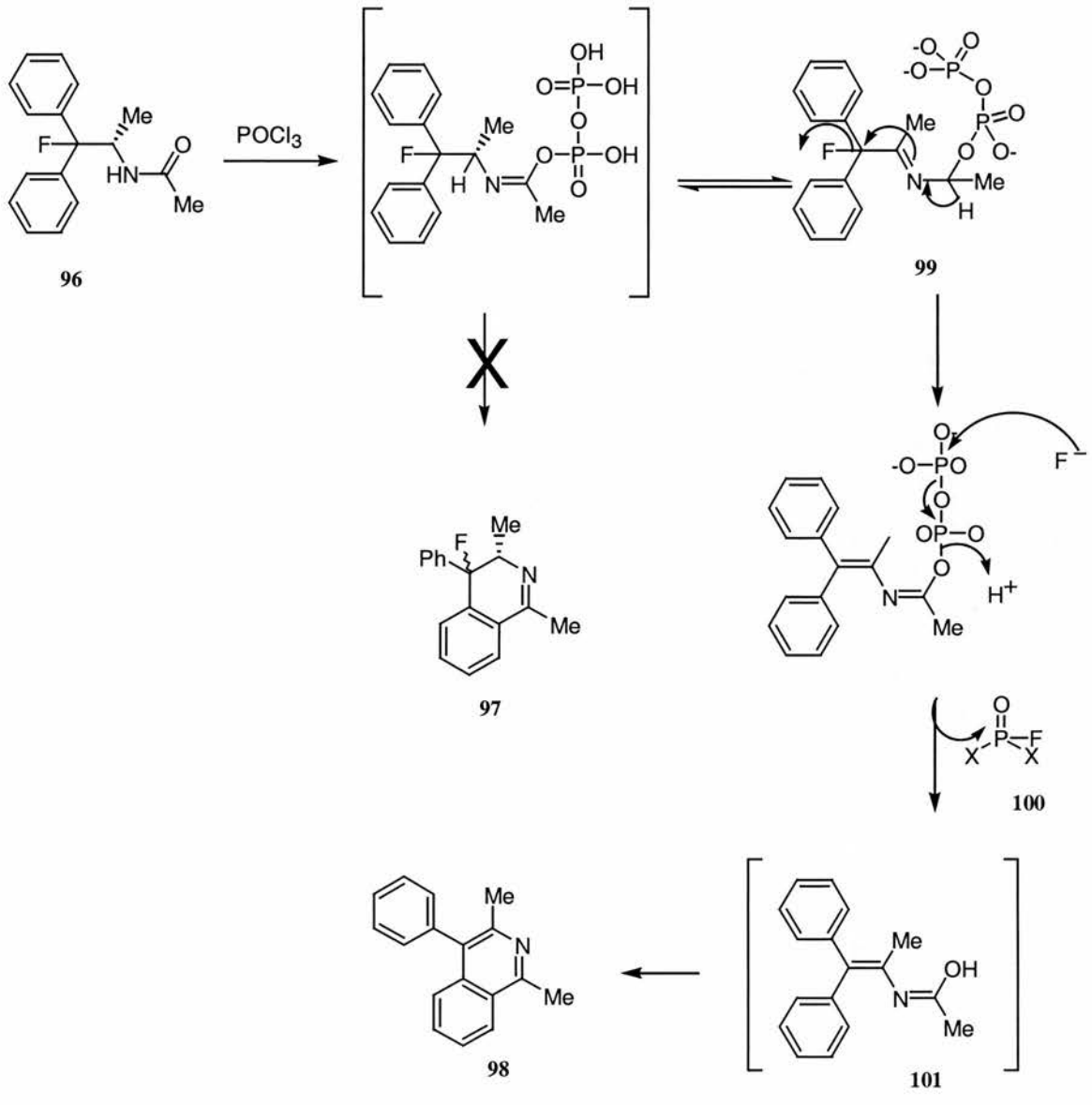


Figure 2.6. ^{19}F NMR spectra of the crude reaction mixture of a BN reaction with (**96**) taken (a) after 5 min, (b) 10 min and (c) 30 min.

After 10 minutes the spectrum showed the presence of two new ^{19}F NMR peaks; a singlet at –160 ppm and a doublet at –10 ppm (J=1190 Hz), which was clearly due to P-F coupling. A third aliquot was taken at 30 minutes and the spectrum showed only the presence of the peak at –10 ppm. The anticipated 4-fluoro-1,3-dimethyl-4-phenyl-3,4-

dihydroisoquinoline (**97**) was not detected. Instead the major product was the fully aromatised isoquinoline (**98**) which was identified in the product mixture. The formation of (**98**) suggested the reaction course shown in (**scheme 2.14**). After 10 min all of the organic fluorine was converted to a new entity, which appeared as a singlet at -160 ppm in the ^{19}F NMR. This is consistent with structure (**99**) or isomeric product of (**99**).[46]Additionally a P-F intermediate was clearly detectable (doublet J=1190 Hz), most likely attributable to a structure (**100**), derived from fluoride elimination and addition to phosporus to generate amide (**101**). In fact (**101**) instantly cyclises to form the fully aromatised structure (**98**). The presence of P-F species in the reaction mixture is consistent with previous reports that HF in the presence of phosphorous pentoxide can generate fluorophosporic acids and anhydrides.[47] Perhaps this is structure (**100**), although the literature chemical shift values ranges between -30 ppm for fluorophospates and fluoropyroposphates[48] and around -70 ppm for fluorophosporic acid.



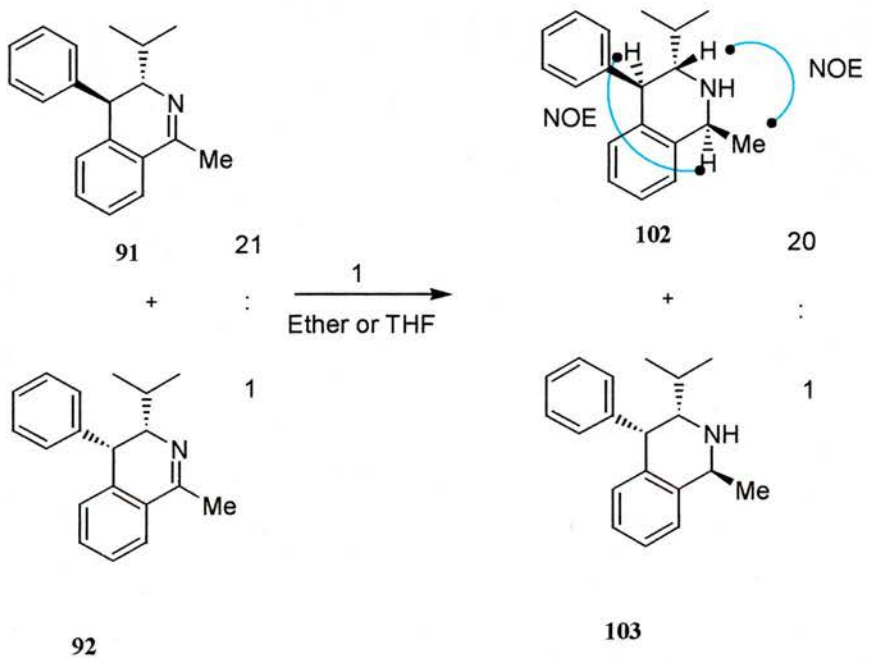
Scheme 2.14. Proposed mechanism for the Bischler-Napieralski reaction on substrate (**96**)

2.5 Asymmetric reduction of the Bischler-Napieralski products

The BN reaction generated a series of novel 3,4-dihydroisoquinoline products. With the 3,4-dihydroisoquinoline products in hand, their reduction with $LiAlH_4$ was explored to assess stereospecificity in the formation of 1,2,3,4- tetrahydroisoquinoline products. In this study the reduction of substrates **91** and **92** and **93** and **94** with $LiAlH_4$[49] in diethyl ether or THF was explored.

2.5.1 Synthesis 1,2,3,4-tetrahydroisoquinoline (**102**) and (**103**)

The 3,4-dihydroisoquinolines (**91** and **92**), which were prepared as 21:1 diastereoisomeric mixtures, were treated with $LiAlH_4$. In the event the reduced product had formed in a similar diastereomeric ratio of (20:1) **scheme 2.15**, consistent with previous literature[41, 50] and suggesting that the reduction was stereospecific on each enantiomer.



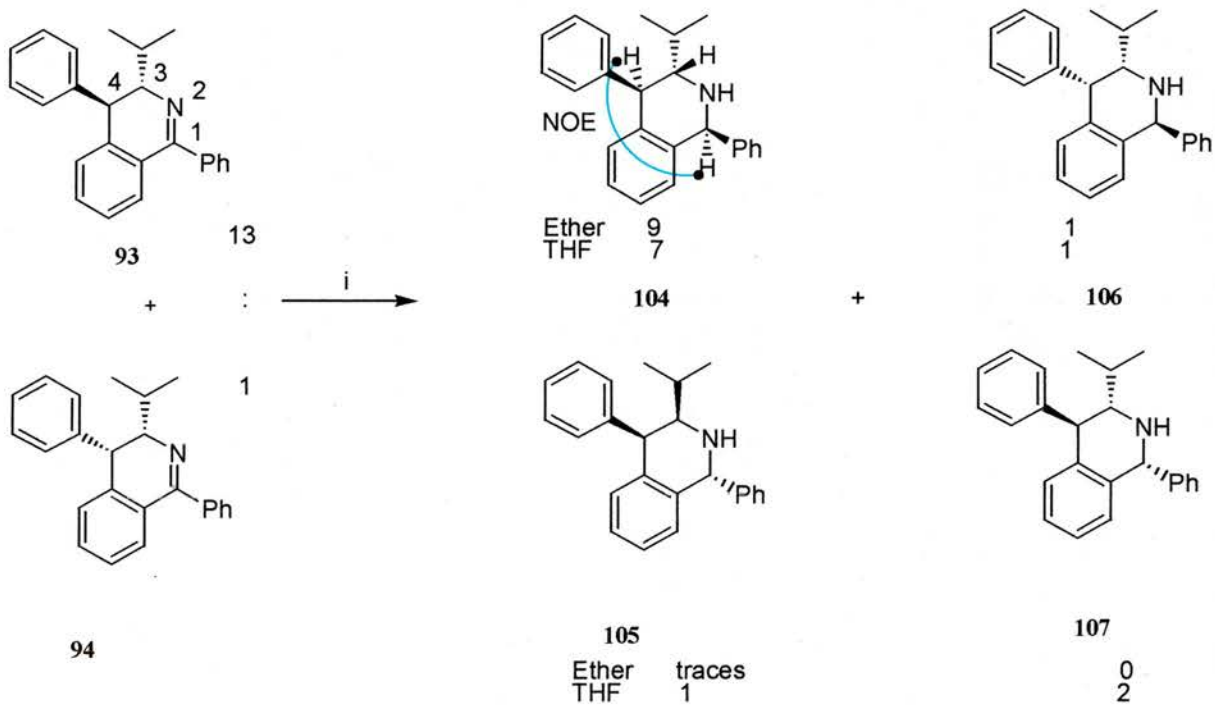
Scheme 2.15. Reagents and conditions. (i) $LiAlH_4$, reflux, 69%.

This outcome suggested that the reduction was highly stereoselective and generated products with a *trans* C(1)-C(3) relative stereochemistry. The major stereoisomer in this reaction was assigned to structure (**102**). It retained the larger coupling constant between H3 and H4 (J=7.1 Hz) relative to that of J=2.4 Hz for the minor product. A ^1H

NMR difference NOE analysis was also carried out to establish the relative stereochemistry at C(1). In particular, there was a strong perturbation at H(3) when the C(1) methyl hydrogen signal was irradiated and *vice versa*. There was also a strong and reciprocated NOE response between H(1) and H(4) indicating that these hydrogens are on the same face of the ring system in accordance with structure (**103**).

2.5.2 Synthesis 1,2,3,4-tetrahydroisoquinolines (**104**), (**105**) and (**106**)

The stereoselective reduction of (**93**) and (**94**) with $LiAlH_4$ was observably solvent dependant (**scheme 2.16**). When the reaction was carried out in ether at reflux the products (**104**) and (**105**) where formed in a 9:1 ratio. Their structures were assigned by calculating the $J_{H3\text{-}H4}$ (7.9 Hz for **104** and 3.5 Hz **105**) coupling constants as shown in **figure 2.7a.**



Scheme 2.16. Reagents and conditions. (i) $LiAlH_4$, ether or THF at reflux 24 h, 65% (THF) or 67% (ether).

It is not clear why this ratio had changed from that found in the staring material (13:1). It is possible that an isomerisation at C(3) has occurred, prior to hydride reduction and thus isomer (**105**), which is the mirror image of **106**, emerged as a minor component in the product mixture. This isomer is clearly not resolvable from its enantiomer **105** by ^1H

NMR (**figure 2.7 a**) and therefore the change in bias from 13:1 to 9:1, may reflect the formation of **106** as a minor component.

When the reduction was carried out in THF under reflux, then a new diastereoisomer was observed by ^{1}H NMR (**figure 2.7 b**) as a significant product in addition to (**104-106**).

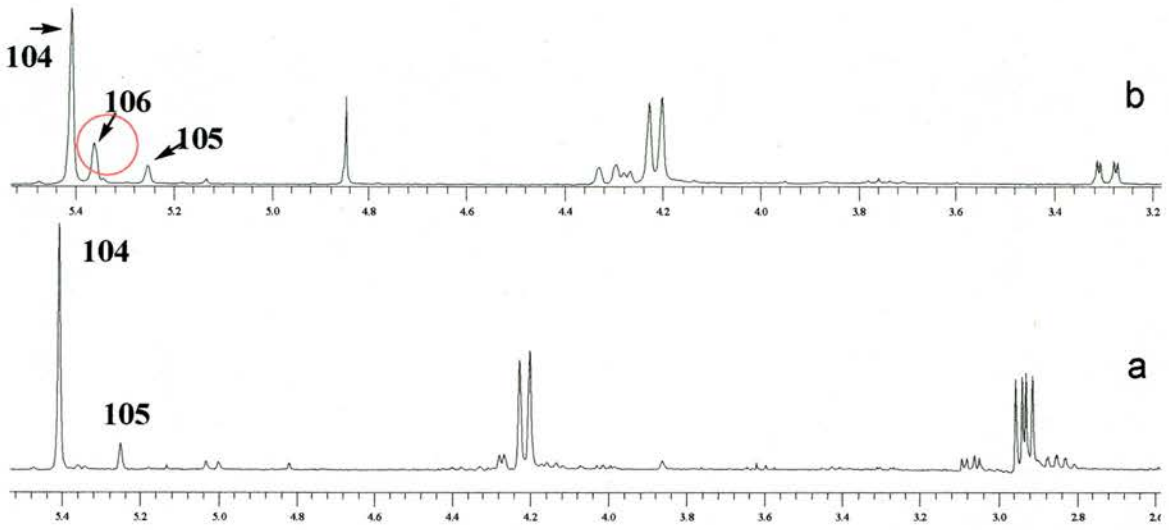


Figure 2.7 a and **b. (a)** ^{1}H NMR of reaction mixture after $LiAlH_4$ reduction in ether. (**b**) ^{1}H NMR of reaction mixture after $LiAlH_4$ reduction in THF. Please note the signals refers to H1 H4 and H3 from left to right.

This new isomer was assigned structure (**107**) on basis of a $J_{H3\text{-}H4}$ coupling constant of 10. 6 Hz and ^{1}H NMR NOE difference analysis. The structure represents hydride delivery to the *Si* face of imine (**92**). The stereochemical outcome of these reactions in ether indicates that hydride exclusively attacks the *Re* face of both imines (**92**) and (**93**) in a pseudoequatorial fashion, suggesting that the stereochemical course of the reduction is controlled by the substituent in C(4). Lithium co-ordinates to the nitrogen in *anti* manner to the C(3) isopropyl group covering the lower *Re* face of the imine. Therefore, hydride is more easily presented the top (*Re*) face of the imine. Perhaps in THF, lithium is sequestered by the solvent, promoting an increased accessibility of the hydride to the *Si* face of (**93**) and thus (**106**) emerges as significant product. (**Figure 2.8**)

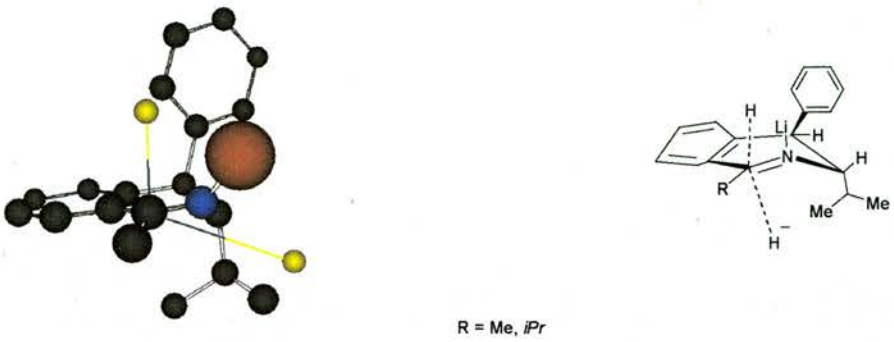
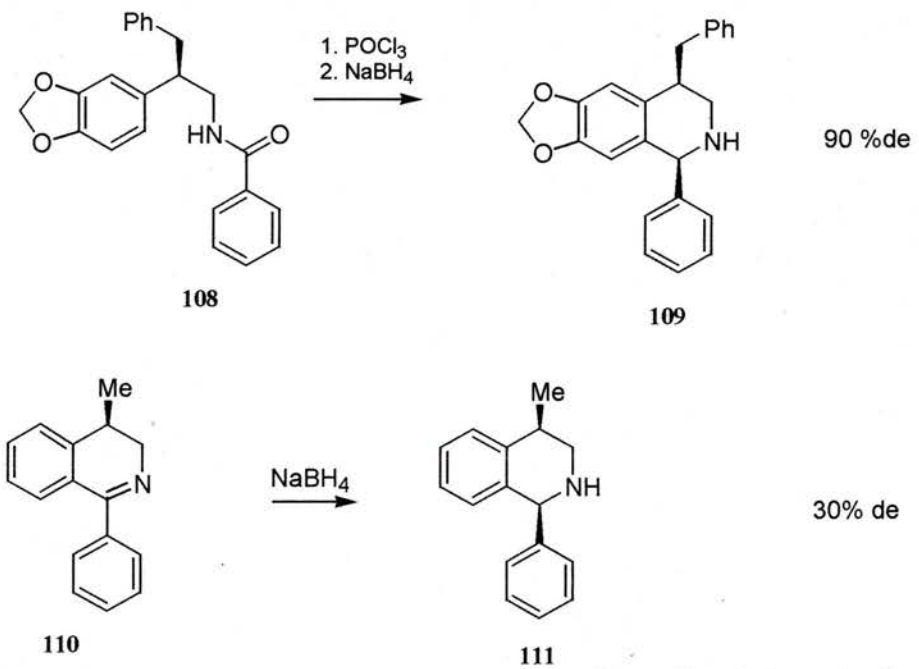


Figure 2.8. Pseudoaxial or pseudoequatorial hydride attacks on **C(1)** atoms of (**92-93**)

Similar results[41, 51] have been obtained with $NaBH_4$ in place of $LiAlH_4$. Julian *et al.* have shown that $NaBH_4$ reduction at C(1) of 4-substituted 3,4 dihydroisoquinolines (**108,**) gave (**109**) with a 90% diastereomeric excess in favour of the isomer carrying the 1, 4 substituents *cis* to each other. **scheme 2.13**. Also Vecchietti *et al.* demonstrated a similar stereochemical course for the transformation of **110** to **111**, although in this case the de was only 30%.



Scheme 2.17. Stereoselective reduction of 4 substituted 3,4-dihydroisoquinolines.

2.6 Summary of Chapter 2

In summary, amides of the amines **83-84** and **95** have been prepared to explore the asymmetric Bischler-Napieralski reaction. The cyclisation of **85-87** occurred in highly stereoselective manner to deliver 3,4-dihydroisoquinoline (**88-89** and **91-94**) (80-91% diastereomeric excess) in favour of the isomers carrying the substituents at C(3) and C(4) in *trans* relationship. The stereochemistry was deduced from the H3-H4 coupling constants in ^{1}H NMR. Additionally recrystallisation of the major diastereoisomer **91** and **93** gave crystals suitable for X-ray analysis which confirmed the stereochemistry deduced by ^{1}H NMR.

The amide (**96**) carrying a fluorine atom in β to the nitrogen was also used as substrate for studying the BN reaction. The cyclisation occurred to deliver the fully aromatised isoquinoline (**98**) instead of the anticipated 3,4-dihydroisoquinoline (**97**). However ^{19}F NMR analysis of the intermediates of the reaction suggested the existence of an imidoyl pyrophosphate (**99**) intermediate, which undergoes rearrangements to produce an α,β amide (**101**). This intermediate cyclises to form the aromatised product.

Reduction of the 3,4-dihydroisoquinolines (**91-94**) BN products, was also investigated. Reduction by $LiAlH_4$ at C(1), was completely stereoselective yielding 1,2,3,4-tetrahydroisoquinolines with a *trans* geometry between the substituent at C(1) and C(3) and a *cis* geometry between C(1) and C(4).

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3 Fluorine in organic chemistry

Part A

3.1 Introduction

Fluorine from the Latin and French words for flow, *fluere*, is the most reactive and electronegative of all the elements. It forms compounds with most other elements, including the noble gases xenon and radon and for this reason, fluorine does not occur free in nature and proved extremely difficult to isolate.

Fluorine occurs principally as fluorospar (CaF_2) and cryolite (Na_2AlF_6), (**figure 3.1**) but it is rather widely distributed in other minerals.

Figure 3.1. Fluorospar or fluorite (CaF_2),on the left and cryolite (Na_2AlF_6), on the right.

The first recorded use of a fluorine compound dates to around 1529 when Georigius Agricola used fluorospar as a flux in metallurgical processes. It was only in 1886, when Ferdinand Frederic Henri Moissan, a French chemist, isolated elemental fluorine as a gas (F_2). He accomplished this by the electrolysis of potassium fluoride (KF) and hydrofluoric acid (HF)[1]. Today, fluorine gas, is still produced by this process as well as by the electrolysis of molten potassium hydrogen fluoride (KHF_2).

Fluorine forms the strongest covalent bond to carbon and fluorocarbon compounds are generally stable. Several fluorocarbon compounds are widely used in everyday products. Freon (CF_2Cl_2) was used universally in home refrigerators and automobile air conditioning systems until their damaging impact on the ozone layer was established. These products have been replaced by hydrofluorocarbons (CHF).

Poly **te**tra**fl**uoro**e**thyle**n**e or Teflon™, is another well known and globally utilised fluorocarbon polymer having the repeat structure of $(CF_2CF_2)n$.

3.2 Chemical and physical properties of Fluorine

3.2.1 Electronic effects

The electronic properties of the fluorine atom relative to hydrogen and chlorine are represented in **Table 3.1.**

	H	F	Cl
Electronic configuration	$1s^1$	$--2s^2 2p^5$	$--3s^2 3p^5 3d^0$
Electronegativity (Pauling)	2.1	4.0	3.0
Ionisation energy (kcal/g atom)[a]	315.0	403.3	300.3
Electron affinity (kcal/g atom)[b]	17.8	83.5	87.3
Bond energies of C-X (kcal/mole)[c]	99.5	116	~78
Bond lengths of C-X (Å)[d]	1.091	1.317	1.766
Preference as a leaving group	H^+	F^-	Cl^-

[a] $X^+ + e^- \longrightarrow X.$
[b] $X + e^- \longrightarrow X^-$
[c] For CX_4.
[d] Covalent radii in CX_4.

Table 3.1[2]**.** Electronic properties of fluorine

The large ionisation energy of fluorine renders the fluoronium ion (F^+) very high in energy and it is very rare. On the other hand the high electron affinity of fluorine makes F^- stable and in organic chemistry is a good leaving group, particularly in elimination reactions.

3.2.2 Fluorine's ability to stabilize charge

Fluorine is the most electronegative element in the periodic table (4.0 in the Pauling scale) and as consequence, when covalently bonded to another atom the bond becomes polarised. For example the C-F bond is the strongest and shortest C-X bond due to a significant ionic character, and the bond can be represented to some extent as C^+ F^-. This explains the resistance of the C-F bond, towards nucleophilic substitution. The strong inductive effect of fluorine (-I) can stabilise carbanions β to the fluorine atom (a) **figure 3.2.** Also the large inductive effect is responsible for its susceptibility to leave as a leaving group in elimination reaction (a).

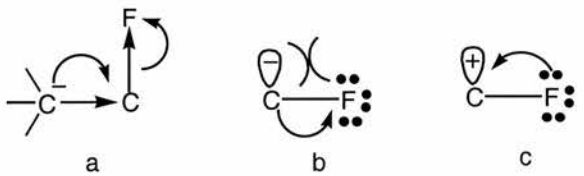


Figure 3.2. Inductive and mesomeric effects of fluorine in C-F bond.

By contrast fluorine destabilises α carbanions by n-π repulsion (b) **figure 3.2**. However fluorine stabilises α carbocations by a n-π conjugation (c).

In summary, fluorine is always electron withdrawing by the inductive effect and electron donating by the mesomeric or resonance effect.

When fluorine is succesively substituted for hydrogen in mono-, di- and trifluoroacetic acid there is an associated reduction in pKa along the series **table 3.2.**

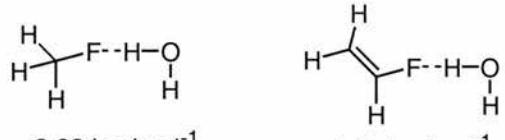
Acetic acids	**ΔPka**
CH_3COOH	0[3]
CH_2FCOOH	-2.2[4]
CHF_2COOH	-3.5[5]
CF_3COOH	-4.6[6]

Table 3.2. Δpk_a of mono di-tri fluorinated acetic acids relative to the parent compounds from Schlosser[7]

The acidity increases regularly as the number of fluorine atoms are substituted at the α C. The strong mesomeric effect is predictable from the σ_r Hammett value of –0.34[8] for fluorine. Consequently it is an *ortho-para* director in the electrophilic aromatic substitution which is consistent with the ability of fluorine to donate electrons by the mesomeric effect (+R).

Although there are still little controversies about the ability of fluorine to act as hydrogen bond acceptor, theoretical calculations estimate[9] the strength of a, F···H-X bond to be between 2 to 3.2 kcal mol,$^{-1}$ compared to 5-10 kcal mol $^{-1}$ of a O···H-X hydrogen bond.[10] This difference in strength reflects the lower polarisability of fluorine over oxygen.

Interestingly, it has been found that the C(sp^3)-F···H interaction is stronger then C(sp^2)-F···H. For example the interaction between water and fluoromethane (**112**) gave a stabilisation energy of –2.38 kcalmol^{-1}and an equilibrium distance of 1.9 Å whereas a value of 1.48 kcal/mol-^{1} was found for the interaction between fluoroethene (**113**) and water [11](**figure 3.3**).

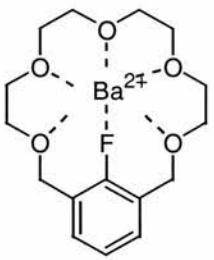


2.38 kcalmol^{-1} 1.48 kcalmol^{-1}

112 **113**

Figure 3.3. Calculated strengths of hydrogen bond for fluoromethane and fluoroethene in water

Organic bound fluorine can coordinate metals. Such interactions have been detected by ^{19}F NMR. For example, fluorinated crown ether derivative (**114** and **115**)[12] shown in **figure 3.4** form 1:1 complexes with alkaline earth metals, and a remarkable chemical shift change was observed, in the ^{19}F NMR when sodium or barium was added. The barium complex was crystallised and showed a clean interaction between Ba^{2+} and the fluorine atom, with a distance of 2.8 Å.



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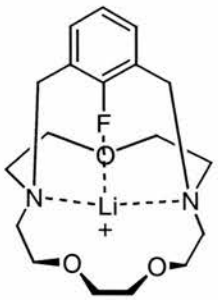

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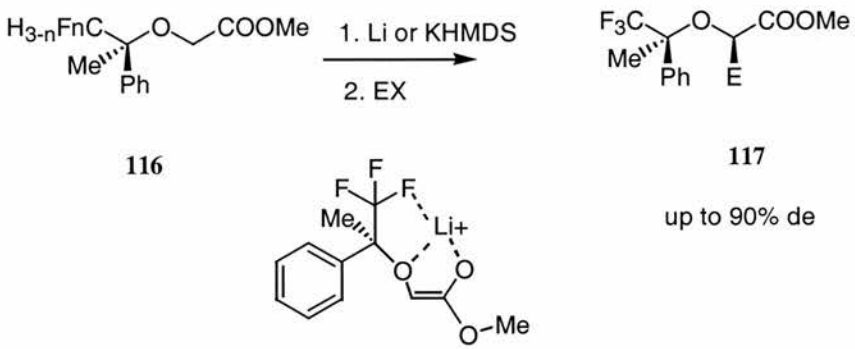
Figure 3.4. Fluorine containing crown ethers

The ability of organic fluorine to participate in C-F···M interaction has been exploited in chiral enolate chemistry. It has been demonstrated,[13] that enolates of the type (**116**) shown in **figure 3.5,** react with various electrophiles to the *Re* face. The high stereoselectivity (90% de) (**117**) was attributed to chelation of the lithium with the α-oxygen and the fluorine atom as illustrated in enolate (**118**).



116

117

up to 90% de

118

Figure 3.5. Reaction involving chelation of lithium to fluorine

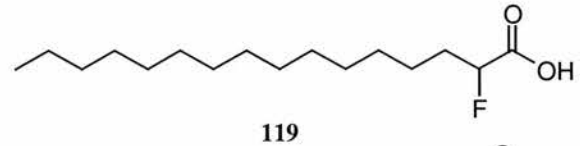
3.2.3 The steric influence of fluorine

Fluorine is the smallest substituent after hydrogen in the periodic table as measured by covalent radius.[14] The Van der Waals radii shown in **table 3.3** suggest that fluorine has a closer isosteric relationship to oxygen rather than hydrogen.

Element	**Van der Waals radii**
H	1.20
F	1.47
Cl	1.80
O	1.52

Table 3.3. Van der waals radii in Å

Despite the larger Van der Waals radius of fluorine over hydrogen, substitution of fluorine for hydrogen generally produces only a minimum steric perturbation. For example monofluorinated analogues of biological substrates often follow the metabolic pathway of their parent compound. The enzymes are deceived by the substitution and cannot make a steric distinction between H and F. For example, very little distortion was observed in the two-dimensional packing of 2-fluorostearic acid (**119**) on a graphite surface compared to the unsubstituted acid (**120**)[15](**figure 3.6**). This study reinforced the similarity in size between fluorine and hydrogen.



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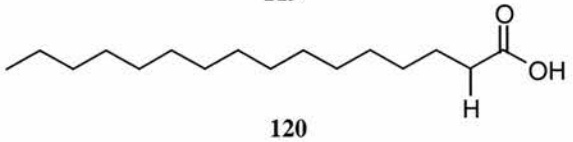

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Figure 3.6. Fluorostearic and stearic acids

The replacement of a methylene (CH_2) group, for a difluoromethylene (CF_2) group is much less compatible. For example, the stability of monolayers on water of the corresponding 12,12-difluoro stearic acid (**121**) was investigated by Langmuir pressure/area isotherms.[16]

The analysis indicated that the monolayer of the difluoromethyl stearic acid, was unstable and vulnerable to collapse and reorganisation, indicative of significant conformational disorder as shown in **figure 3.7**.

The origin of these anomalies in the 12-difluoro series can be related to the differences between the C-CH_2-C and C-CF_2-C bond angles. Crystallographic[17] and theoretical evidence[18, 19] support a widening of the C-CF_2-C angle from the classical 109.5 ^{0} to 115-119.^{0} Therefore the extended *zig-zag* conformation is favoured in a long chain hydrocarbon (**120**) or (**122**) since the *gauche* conformation brings the 1 and 4 hydrogens into close contact. On the other hand, the *gauche* conformations is energetically more favoured for the 12,12-difluoro substituted chain (**121**), as the 1,4 hydrogen interactions are now minimised by the angle widening.

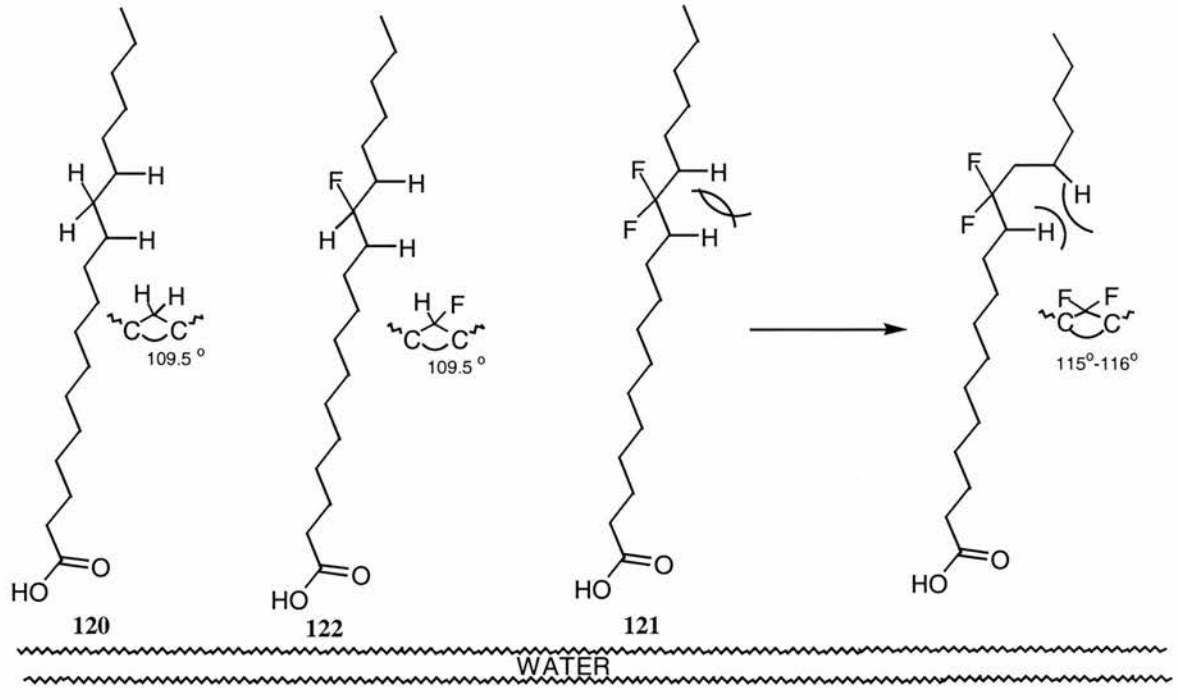


Figure 3.7. Schematic representation of selectively fluorinated stearic acids on the surface of water

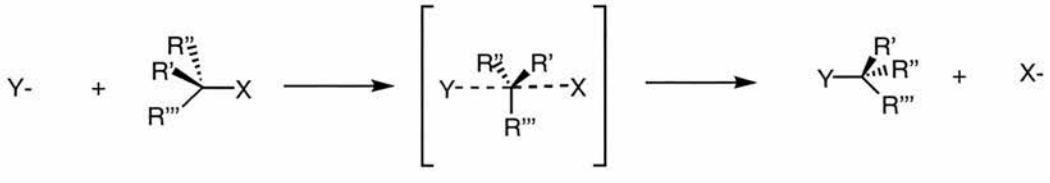
A comparison of the molar volumes* of the trifluoromethyl group with various substituents indicates that the CF_3 is comparable to an isopropyl group [12, 14]rather then a methyl group.

* *The van der Waals volume* is defined as the volume that is impenetrable to thermal collision.

Similar results were obtained by comparison of the van der Walls hemispheres.** Interestingly, the trifluoromethyl group was found to be almost three times larger than the methyl group.[12]

3.2.4 Stereolectronic effects

The reactivity of most organic molecules depends upon stereoelectronic effects.
The concerted displacement of a leaving group by a nucleophile in aliphatic (S_N2 reaction) substitution reactions was one of the first reactions recognised to take place with stereoelectronic control[20]. This S_N2 reaction is a one step process proceeding through a transition state, resulting in an inversion of configuration. The nucleophile (Y^-) must approach the substrate from a 180° angle opposite to the leaving group (X) as shown in **figure 3.8**. The stereochemistry of the resulting transition state is governed by the transition state (**123**) where the central carbon, can be considered to be sp^2 hybridised carbon. The remaining p-orbital, not hybridised, has one lobe overlapping the nucleophile and the other overlapping the leaving group (**124**). Therefore the mechanism of this reaction is controlled by electronic effects which impose a specific stereochemistry at the transition state level.



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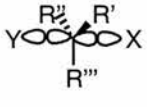


124

Figure 3.8. Stereoelectronic effects in S_N2 reactions.

** *The van der Waals radius* is the distance at which the repulsion between two atoms just balances the attraction forces between the two atoms

3.2.4.1 *Gauche effect*

The most widely described stereoelectronic effect associated with organic fluorine compounds is perhaps the *gauche effect*. The gauche effect was originally described by Wolfe and acknowledges the tendency for a molecule to assume a gauche *conformation* between adjacent electron pairs and/or polar bonds[21].

For butane there are five possible conformers (A, B, C, D, E) at energy maxima or minima, which are represented by the Newman projections in **figure 3.9**. The fully staggered *conformation* or *anti, trans,* (D) is the lower in energy than the two staggered *anticlinal* conformers (B, E). The energy barrier between is about 0.9 kcal mol^{-1} The three potential energy maxima correspond to the *eclipsed* conformers with the highest the fully *eclipsed* or *syn-periplanar* (A) conformers. The methyl-methyl *eclipsed* (A) conformer is about 6.0 kcal mol^{-1} higher in energy than the *anti* conformation (D).

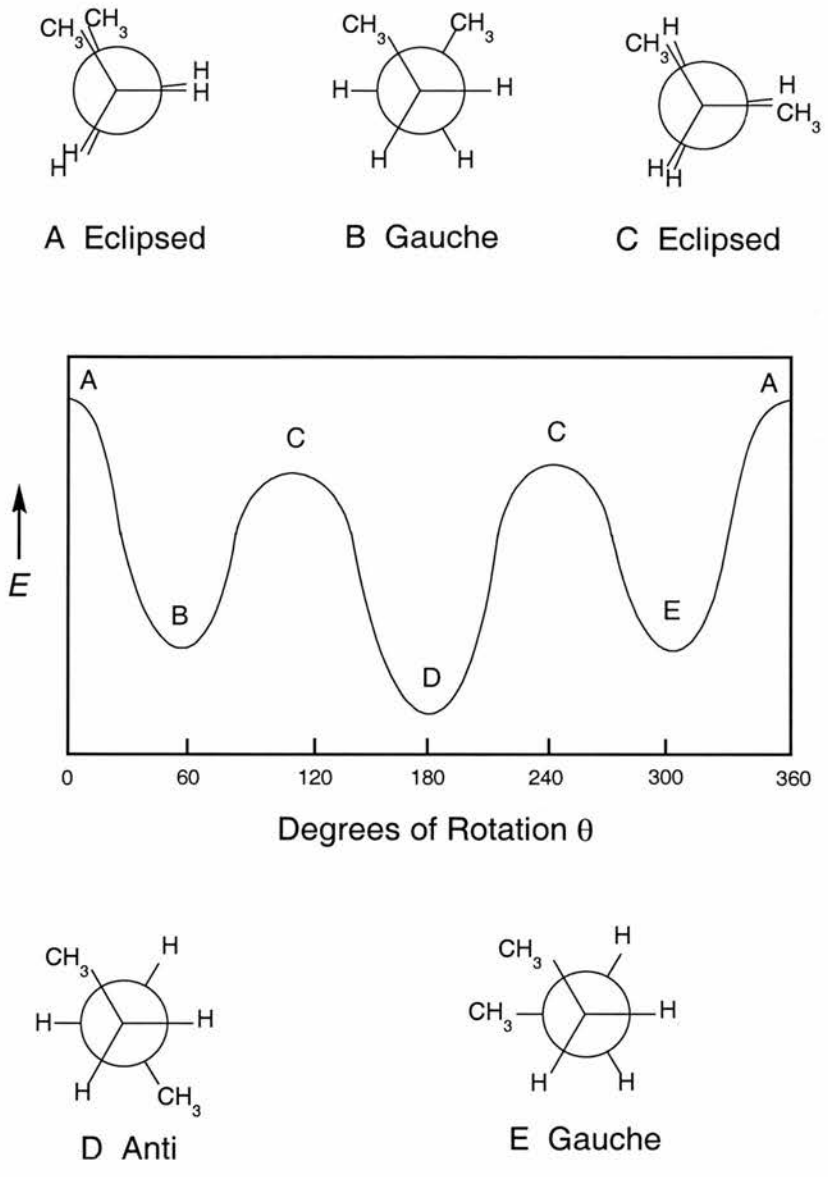


Figure 3.9. Rotational energy diagram for butane showing maximum and minum conformers.

These conformational preferences are fully understood in terms of steric repulsion between bonding orbitals. Therefore these repulsive interactions are largest in the eclipsed and minimised for the staggered conformations. At energies up to about 30 kcal $mol,^{-1}$ enough energy is present to surpass the energetic barriers between the different conformers.

The *gauche effect* recognises that there are some cases in which the *gauche* conformer is lower in energy than the *anti* conformer. For example in certain 1,2-diheterosubstituted

ethanes, where the C-H or C-F bonds are replaced with more electronegative atoms X and Y, the population of *gauche* conformers was found to be larger than the *anti*. This preference is contra intuitive since the dipole repulsion and steric effects are anticipated to favour the *anti* conformers. For example theoretical and experimental evidence demonstrates that 1,2-dimethoxyethane[22] (**125**) and 1,2 dicyanoethane[23] (**126**) in **figure 3.10** prefer to adopt a *gauche* over an *anti* conformer.

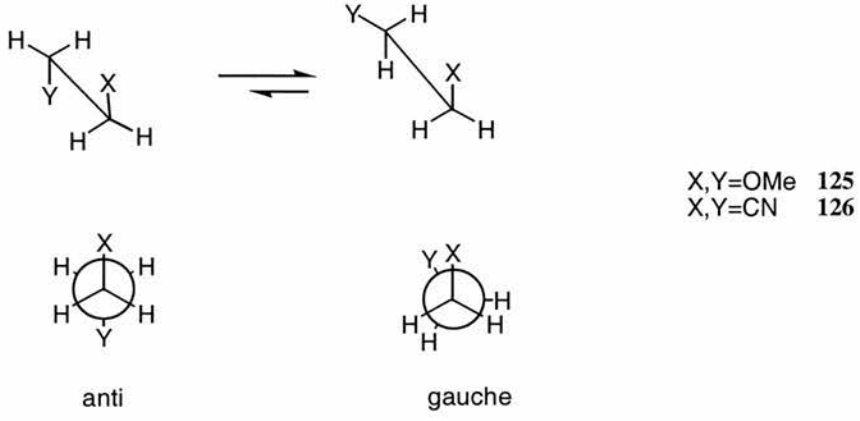


Figure 3.10. *Gauche* and *anti* conformers for 1,2-disubstituted ethanes

An established example of the *gauche effect* is the relationship between the rotamers of 1,2-difluorobutane (**125**) where the *gauche* conformer has an energy 0.5-1 kcal mol^{-1}, lower than the *anti* conformer.[24, 25]

Theoretical and experimental calculations, using ^{19}F NMR and ^{1}H NMR spectroscopy have demonstrated that the fluorine *gauche* effect influences the relative energies of conformations of both (±)-*erythro* (**125a**) and (±)-*threo*-2,3-difluorobutane (**125b**).[26] The two staggered (±) *erythro* conformers (**125a'** and **125a''**) were very similar in energy suggesting that the instability derived by bringing the two methyl group *gauche* to each other is compensated for the energy gained by having the two fluorine atoms also *gauche.* For the (±)-*threo* isomers, the most stable conformer (**125b'**) had the two methyl groups *anti* to each other and the two fluorine atoms *gauche* **(Figure 3.11)**.

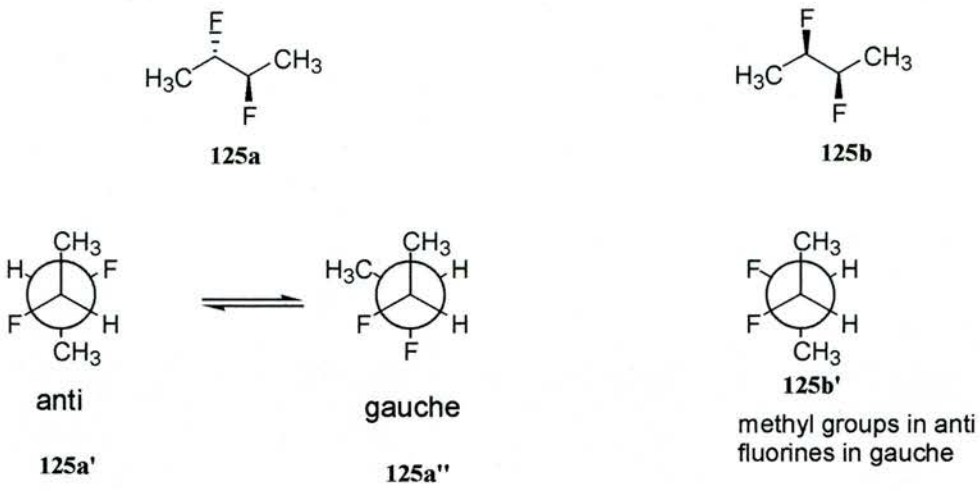


Figure 3.11. The fluorine *gauche* effect in 2,3-difluorobutane

The influence of the fluorine *gauche* effect has been investigated also on the long chain fatty acids (±)-*erythro* and (±)-*threo*-9,10-difluorostearic acids[27] (**126** and **127**) as shown in **figure 3.12**. The extended *zig-zag* conformation for the (±)-*erythro* isomers (**126a**) has the alkyl groups and the two fluorine atoms *anti* to each other. Thus, the system does not benefit from the fluorine *gauche effect.* On the other hand, the (±)-*threo* isomer (**127a**) has the fluorine atoms *gauche* and the two alkyl chains (R' and R'') *anti* to each other and therefore is the most energetically favoured conformer. There is a large difference in melting points between the two series (*erythro*= 67-69 °C against 86-88 ° C for the *threo*) which indicates a significant conformational mobility of the (±) *erythro* series relative to the *threo* series.

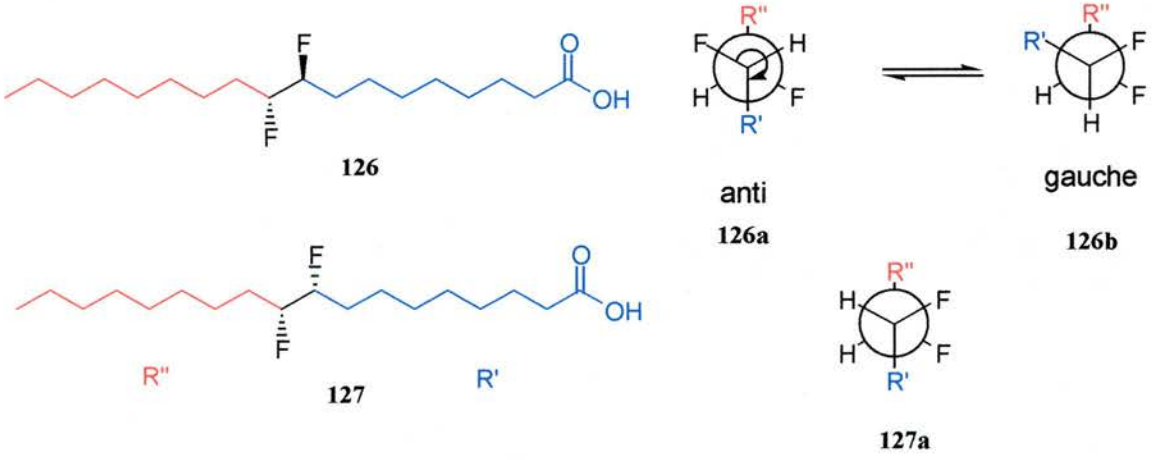


Figure 3.12. Staggered rotamers of (±)-*erythro* and *threo*-9,10- difluorostearic acids

In order to explore the conformational stability in these systems further, each of the isomers (**126**) and (**127**) was deposited on water in a Langmuir trough (**figure 3.13**). The hydrophilic head groups oriented towards the water subphase and the hydrophobic fatty acid chains towards the air. When a few molecules are spread on the water surface they diffuse freely and do not interact with each other (see **I**). However as the barriers are moved together, reducing the area, there is a transition at which the pressure suddenly starts to increase as the molecules touch each other (**II**).

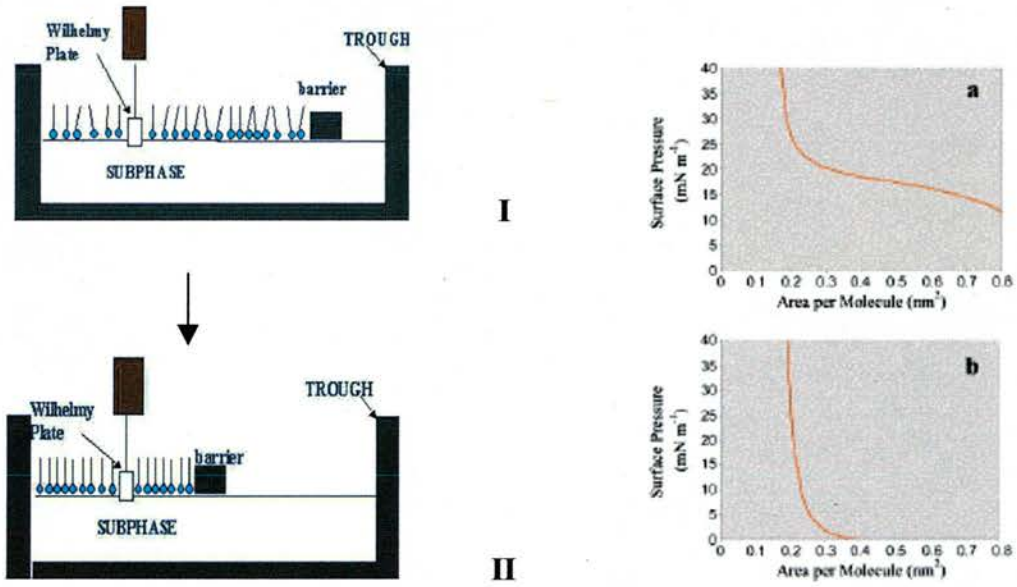


Figure3.13. Representation of Langmuir trough (from http://www.inapg.inra.fr/ens_rech/siab/asteq/elba/lb_tech.htm), and Langmuir isotherm for *threo* **a** and *erythro* **b** (from ref. 31).

The shape of the Langmuir isotherm, for the (±)-*erythro*-9,10-difluorostearic acids (**a**) is extremely expanded indicating a significant level of conformation disorder. On the other hand, the isotherm (**b**) for the *threo* isomer is similar to stearic acid suggesting that the molecules are conformationally more ordered (*zig-zag*). In conformer (**127**) the fluorine *gauche* effect reinforces the classical anti *zig-zag* conformation, stabilising this system relative to (**126**).

3.2.4.2 The fluorine amide *gauche* effect

In 1965 theoretical calculations predicted the *gauche* conformation of N-acetyl-β-fluoroethylamide[28] (**128**) to be 1.8 kcal mol^{-1} lower in energy than the *anti* conformation. This difference was initially attributed to dipolar relaxation between the C=O and C-F bonds. However more recently it has been shown that the C-N bond of an amide is significantly electron withdrawing and aligns *gauche* to a C-F bond.[29, 30](**figure 3.14**).

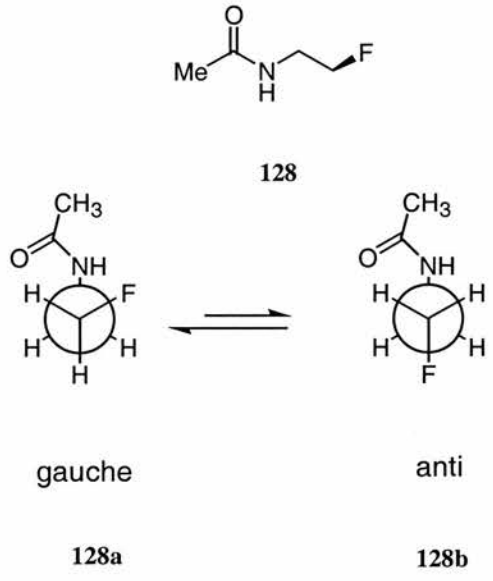


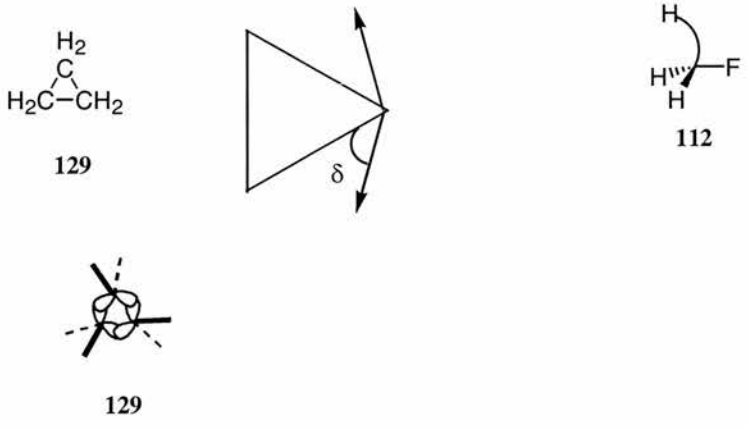
Figure 3.14. The fluorine amide *gauche* effect

3.2.4.3 Explanation of the *gauche effect*

There are currently two accepted and perhaps reinforcing explanations to account for *gauche* effect: These have been attributed to *bent bonds theory* and *σ-hyperconjugation theory*.

3.2.4.3.1 *Bent bonds theory*

The bonds in organic compounds are usually taken as a linear path between the two atomic nuclei. However experimental X- ray data indicated that in most cases the bond path is not collinear with a line between the atoms. The most commonly recognised bent bonds are those found in small ring compounds, such as cyclopropane (**129**) (**figure 3.15**) and cyclobutane derivatives. Theoretical calculations have shown that the electron density in cyclopropanes is directed away from the ring[31, 32] as illustrated in **figure 3.15**. For cyclopropane the δ angle is 21,° and the bonds have an intermediate character between σ and π, and cyclopropanes behave in some respects like double-bonded compounds.[32] Bent bonds are also found in small linear molecules. For example, theoretical calculations have demonstrated that the bond path in methylfluoride (**112**) can be represented (exaggerated) as in **figure 3.15**. [33]



129 **112**

129

Figure 3.15. Bent bonds in cyclopropane (**129**)

Theoretical calculations[34] of the bond paths in 1,2-difluoroethane (**130**) indicated a certain angular deviations (α_1 and α_2) from the conventional linear bond path as shown in **figure 3.16.** This goes some way to explain the fluorine *gauche effect*. In the case of the *anti* conformer (**130a**) the two C-F bonds are bent in opposite directions, whereas in the *gauche* rotamers (**130b**) they are bent in the same direction, providing an increased overlap of the bonding orbitals.

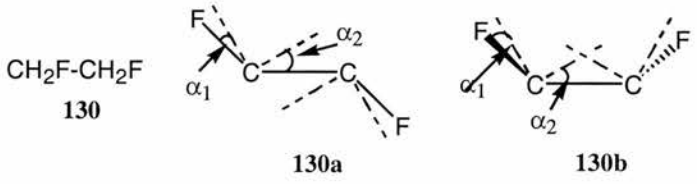


Figure 3.16. Bent bond rationale for the *gauche* preference in1,2-difluoroethane

Another case in which these considerations may apply is in 1,2-difluoroethene where the *cis* (**131a**) isomer is more stable than the *trans*[35] (**131b**) by 1 kcal mol.$^{-1}$

Charge density difference maps were used to explore this and they confirmed a greater overlap of the orbitals in the *cis* isomer than the *trans* isomer. **Figure 3.17** shows that in the case of the *cis,* there is a clear "bent" bond between the fluorine bound carbons promoting overlap of the C-C atoms. For the *trans* isomer the overlap is poor and the density assumes a sigmoidal shape.

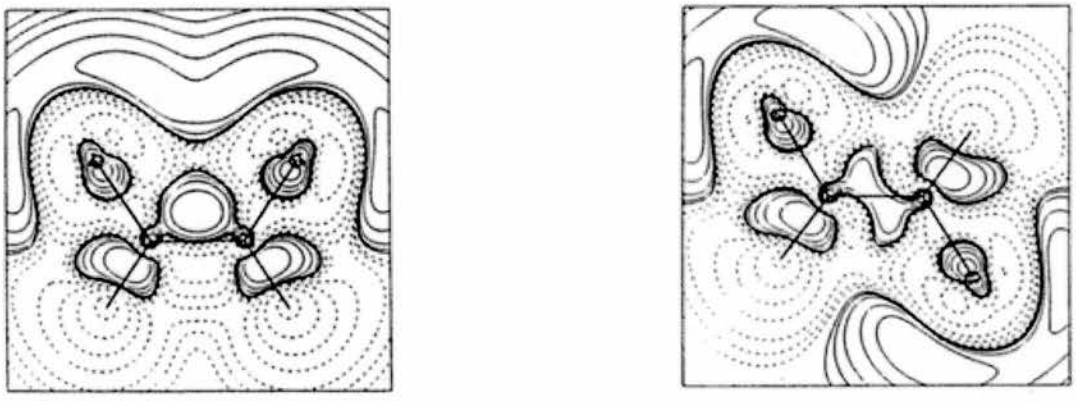
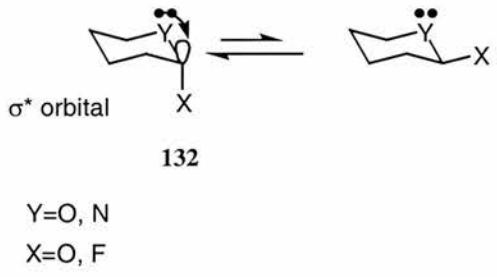


Figure 3.17. Difference between the charge density maps for *trans* 1,2 difluoroethene (left side) (**131a**) and for *cis* 1,2-difluoroethene (right side) (**131b**). [35]

3.2.4.3.2 *σ-Hyperconjugation*

The *anomeric effect*[20, 36] refers to the tendency of an alkoxy group at C(1) of a pyranose ring (**132**) to assume an axial rather than an equatorial orientation despite unfavourable steric interactions. The molecular orbital explanation suggests an n-σ* overlap between a filled non bonding electron pair on oxygen and the vacant σ* orbital of C-O bond[37]. This situation can also be represented graphically as shown in **figure 3.18**.



132

Y=O, N
X=O, F

Figure 3.18. The *anomeric effect*.

The *gauche* effect has also been explained by σ-hyperconjugation, a stabilising interaction arising from the overlap of an occupied σ orbital with an adjacent unoccupied σ* orbital.[38] (**figure 3.19**).

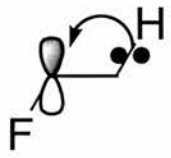


Figure 3.19. Representation of σ hyperconjugation

The hyperconjugative electron donation into C-F σ* plays a dominant role in stabilising conformations of 2-substituted-1-fluoroethanes. For example, the C-F bonds in 1,2 difluoroethane (**130**) are much weaker donors than the C-H bonds. Therefore the C(2)-H σ bond donates more strongly than the C(2)-F σ* C(1)-F.

In the *gauche* conformer (**130b**) the C(2)-H posses the correct geometry (antiperiplanar) in respect of the σ* C-F, whereas in the *anti* conformer (**130a**) only the C(1)-F σ bonds can act as electron donors[39] (**figure 3.20**). Hence, the *gauche* unlike the *anti* conformer of 1,2-difluoroethane benefits from the hyperconjugation.

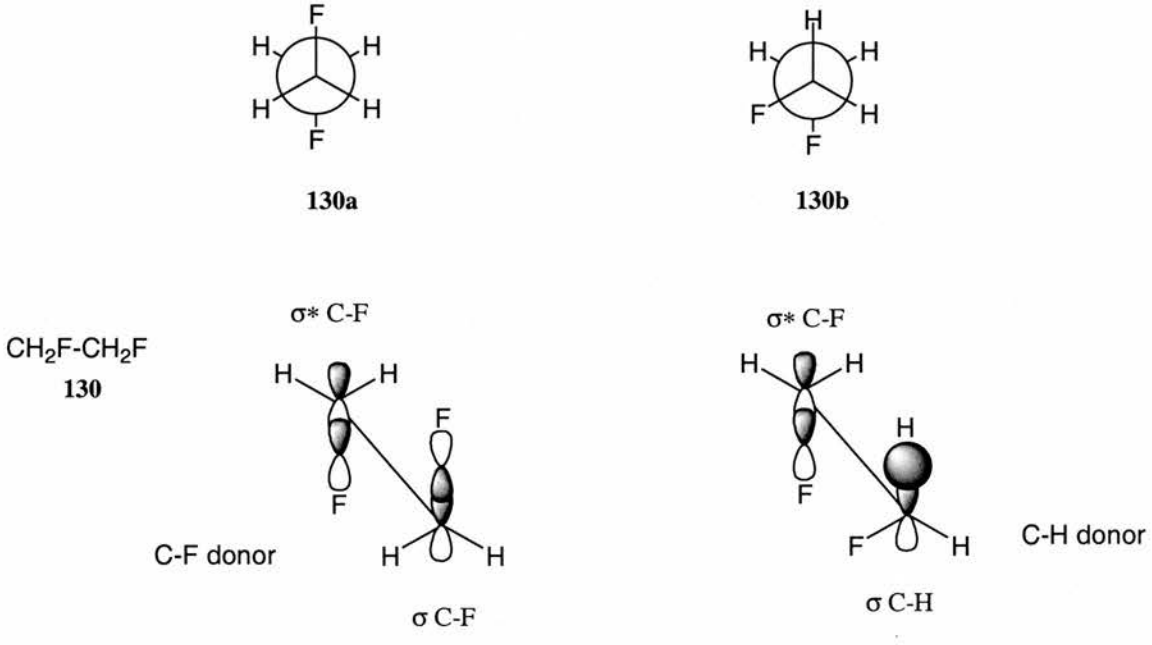


Figure 3.20. σ-Hyperconjugation for 1,2-difluoroethane (**130**)

Part B

3.3 Preparation of Organo-fluorine compounds

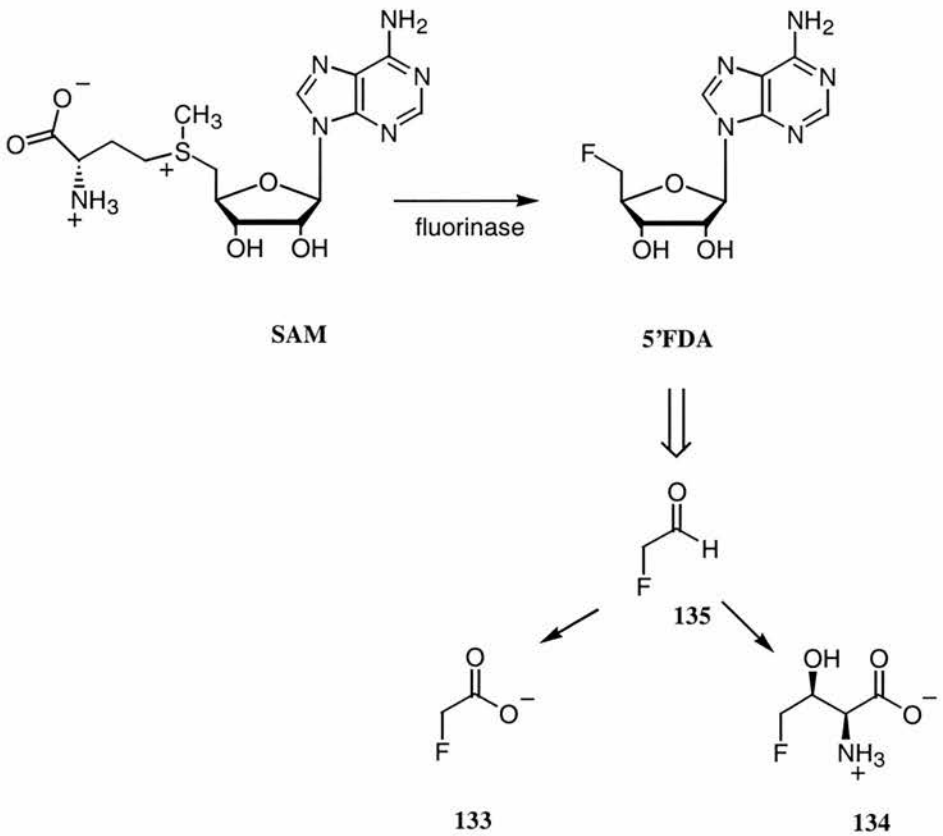
3.3.1 Introduction

There is a wide distribution of fluoride in nature and it is estimated that, among the elements, fluorine is the thirteenth in abundance. However, natural organo-fluorine compounds are very rare because much of the fluorine exists in an insoluble form which is biologically unavailable. The first organo-fluorine natural product to be identified, the extremely toxic compound fluoroacetate (**133**), was isolated in 1943 from the Southern African plant, *Dichapetalum cymosum.* [40]

The synthesis of organo-fluorine compounds commenced between the 19th and the first decades of the 20th century after the pioneering work of the Belgian chemist Frederic Swarts. He prepared a range of aliphatic organo-fluorine compounds using the reaction[40] between alkyl chlorides and SbF_3 and it was on this foundation that Midgley and Henne[41] in 1930 were able to apply fluoromethanes and ethanes as refrigerants.

Since then, the number of methods and compounds has increased dramatically and today we are surrounded by organic fluorine compounds as refrigerants, thermally resistant surface coatings, liquid crystals, agrochemicals, and pharmaceutical products.

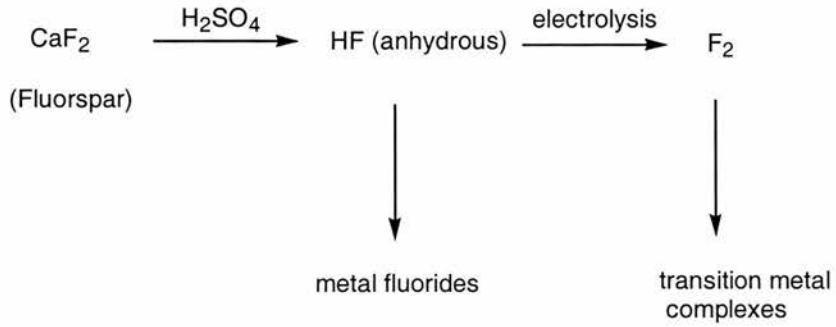
The metabolites, fluoroacetate (**133**) and 4-fluorothreonine (**134**) are produced by the bacterium *Streptomyces cattleya*, and the carbon-fluorine bond formation that occurs in the micro organism was recently found to be catalysed by a *fluorinase* enzyme. [42] The enzyme catalyses the reaction of fluoride ion and S-adenosyl-L-methionine (SAM) to produce into 5'-fluoro-5'-deoxyadenosine (5'FDA). After a number of undefined steps, 5'FDA is converted to fluoroacetaldehyde (**135**), which is the common precursor to both 4-fluorothreonine (**134**) and fluoroacetate (**133**) (**Scheme 3.1**).



Scheme 3.1. The *fluorinase* in *S. cattleya* converts SAM to 5'FDA

The possibility of producing complex organic compounds containing fluorine by using this enzyme is still a long way off and the preparation of organo-fluorine compounds is still dominated by chemical methods.

The ultimate source of fluorine is CaF_2 (fluorspar) from which anhydrous hydrogen fluoride can be made by distilling it from a mixture of the mineral and concentrated sulphuric acid. Hydrogen fluoride can be used directly as a reagent for the synthesis of organic-fluorine compounds or can be converted into elemental fluorine or metallic fluorides which are the most widely employed reagents for the preparation of the C-F bond (**scheme 3.2**).



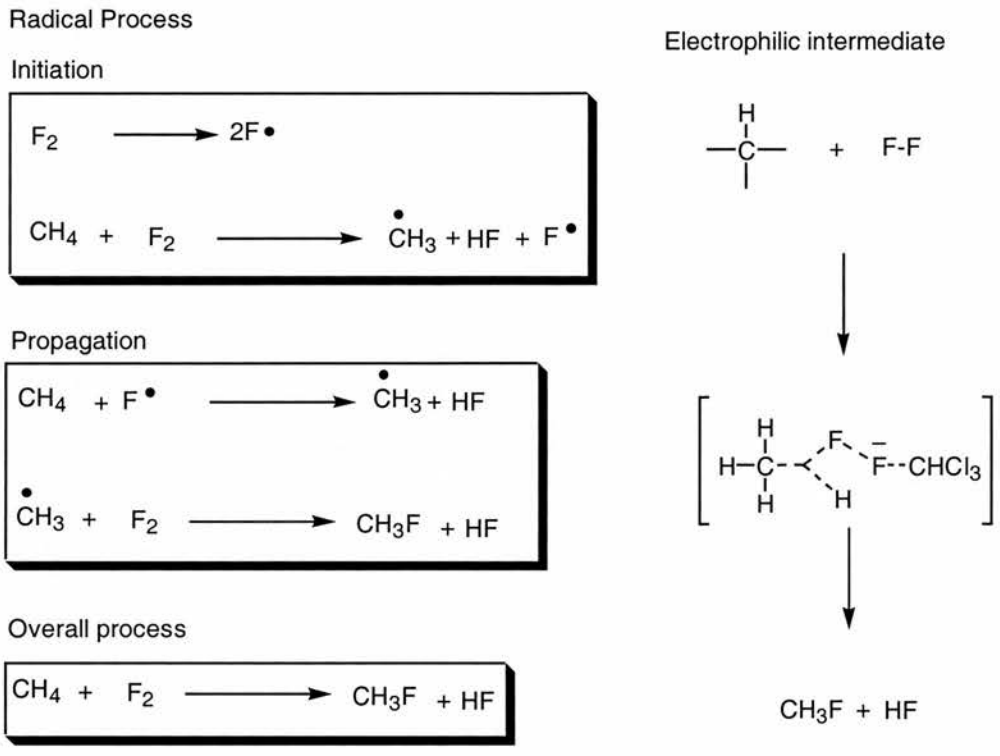
Scheme 3.2. Sources of fluorine and fluorinating reagents

3.3.2 Fluorinating reagents[43]

3.3.2.1 Direct fluorination using elemental F_2

Elemental fluorine is a diatomic molecule existing as a pale yellow gas. It is produced by the electrolysis of solutions of KF in anhydrous HF, as originally demonstrated by Moissan. Fluorine readily reacts with almost all organic and inorganic materials. The transformation of a carbon–hydrogen to a carbon–fluorine bond using fluorine is a very exothermic process[43] (ΔH = –99 kcal mol^{-1}) and there has been much discussion in the literature concerning whether the mechanism follows a free radical[44] or an electrophilic pathway[45] (**scheme 3.3**). Experimental results seems to confirm the latter.[46]

Because of the heat evolved during such reactions, elemental fluorine is generally diluted in an inert gas (N_2). This enables fluorinations of organic substrates to be conducted in a laboratory setting.



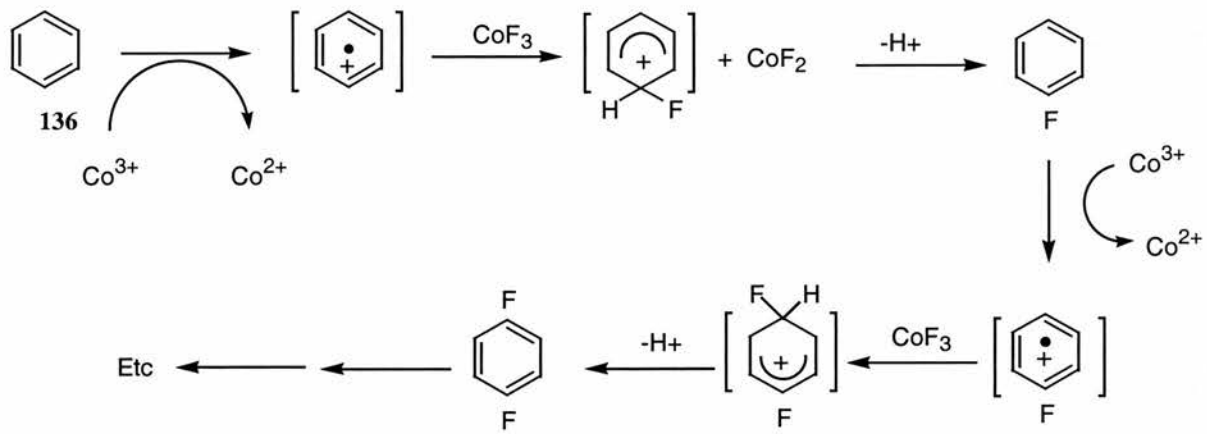
Scheme 3.3. Radical or electrophilic process involved in the fluorination of methane using F_2

3.3.2.2 Fluorination using transition metal fluorides

Fluorination with metal fluorides involves a change of higher valence metal fluorides to lower valence species where the metal acts as a fluorine carrier. The reaction mediates the exchange of fluorine for some other ligand such as a halogen on the metal (see **scheme 3.4.).**

Scheme 3.4. Overall reaction involving fluorination with a transition metal fluoride

The most important member of this group, is cobalt trifluoride, which is prepared by passage of fluorine (F_2) over cobalt difluoride[2]. Fluorination of benzene[2] (**136**) for example is one of the reactions which is accomplished using CoF_3. The mechanism in **scheme 3.5** shows that the Co (III) is reduced to Co (II) transferring the fluorine atom to the organic substrate.

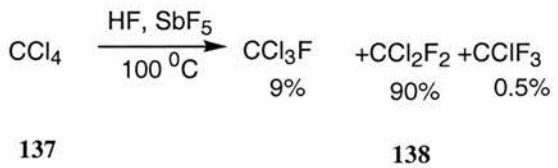


Scheme 3.5. Fluorination of benzene with CoF_3

3.3.2.3 Fluorinations using Hydrogen Fluoride

These reactions generally involve the nucleophilic displacement of a halogen (chlorine) using hydrogen fluoride in combination with a metal fluoride. The metal fluoride acts as a Lewis acid to assist the displacement of the halogen. Antimony fluorides are the most common Lewis acids used in these reactions.

SbF_5 in combination with HF, is widely utilised for industrial purposes. For example, Freon 12 (**137**) is still produced from tetrachloromethane (**138**) using this reaction (**Scheme 3.6**).



Scheme 3.6. Industrial production of Freon

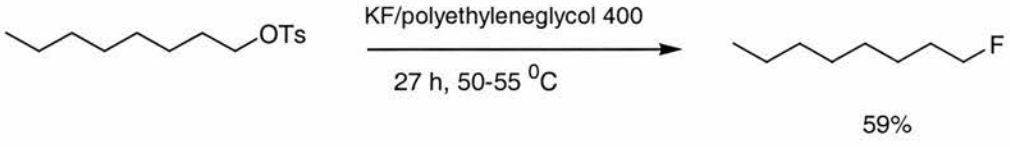
3.3.2.4 Alkali metal fluorides

This group of reactions generally involves the nucleophilic displacement of a halide ion mediated by a fluoride ion as shown in **scheme 3.7**.

Scheme 3.7. Fluorination involving a S_N2 process

Fluoride ion in protic solvents is a poor nucleophile but it is a very strong nucleophile in polar aprotic solvents such as DMF, DMSO, etc. Fluoride ion is a small hard anion and susceptible to hydrogen bonding interactions which mask the charge in protic solvents. In contrast, in aprotic solvents, fluoride becomes a very strong nucleophile, more nucleophilic than the other halide ions.

Potassium fluoride (KF), potassium bifluoride (KHF_2) and cesium fluoride (CsF_2) are the most common fluoride reagents, and the fluorination reactions are carried out in high boiling solvent or anhydrous solvents. Under these conditions the hydrogen bonds between F^- and the solvent are minimised and this encourages the formation of "naked fluoride."[47] Solvation of metal cations using crown ethers or with solvents such as glycols and glymes[48], have also been successfully exploited, for example, in monofluorination reactions with potassium fluoride at modest temperature as shown in **scheme 3.8**.

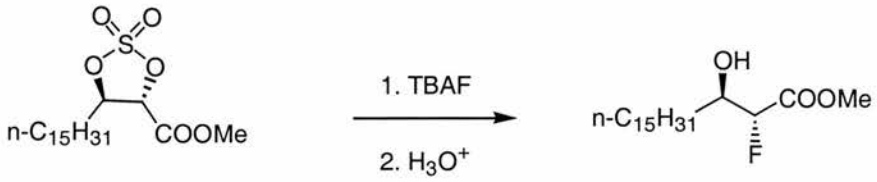


Scheme 3.8. Fluorination using KF and glycols

3.3.2.5 Other sources of fluoride ion

Silver (I) fluoride is a good alternative to the alkali metal reagents, because of its high selectivity and its low basicity which generally gives more selective reactions. It is mainly used in halogen exchange processes. Interestingly, an increase in the yield of AgF reactions has been reported in presence of wet rather then anhydrous solvents.

Tetralkylammoniumfluorides are another class of reagents capable of generating fluoride ions. They were developed to overcome the problems associated with the alkali metal fluorides. The M^+ ion is replaced with a bulky organic cation which reduces the interaction between the solvent and F^- and thus increases its nucleophilicity. Hydrated[49] TBAF (tetrabutylammonium fluoride) is the most widely used of this category and it is particularly effective in displacement of OTs, OMs and OTf groups and in ring opening[50] of cyclic sulphates in a S_N2 manner as illustrated in **scheme 3.9**.



63% yield

Scheme 3.9. Fluorination involving TBAF

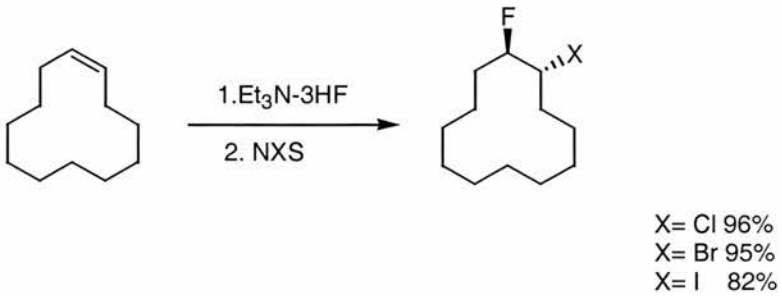
Anhydrous hydrogen fluoride is one of the cheapest fluorinating agents available but due to its corrosive nature it is usually complexed with suitable solvents. For example polypyridinium hydrogen fluoride, known as Olah's reagent,[51] is one of the most common HF reagents, where HF is complexed with pyridine in a 1:9 ratio. The reagent is commercially available as a stable liquid (30% py: 70% HF). It has been used to fluorinate secondary and tertiary alcohols,[52] alkenes,[52]and in ring opening[53] epoxide reactions in a regiospecific manner as shown in **scheme 3.10.** Epoxide (**139**) when treated with Olah's reagent gave the two possible regio isomers in a 9:1 (**140**)/(**141**) ratio depending on the amount of HF complexed with pyridine in the reagent, suggesting that the process occurs in a S_N1-type fashion.

139 **140** **141**

9 1

Scheme 3.10. Epoxide ring opening with HF•pyridine complex

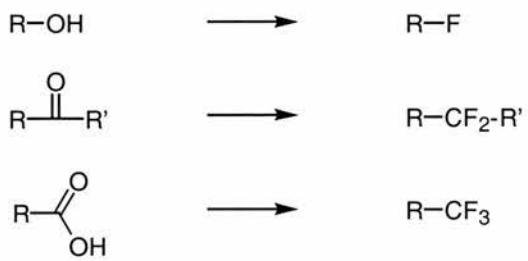
Et_3N•HF originally introduced by Franz,[54] is a popular source of F^- and it is less corrosive than the HF•Py complex. It has been used successfully for the halofluorinations reactions of alkenes[54] as shown in **scheme 3.11**.



Scheme 3.11. Halofluorination with Et_3NH^+3HF

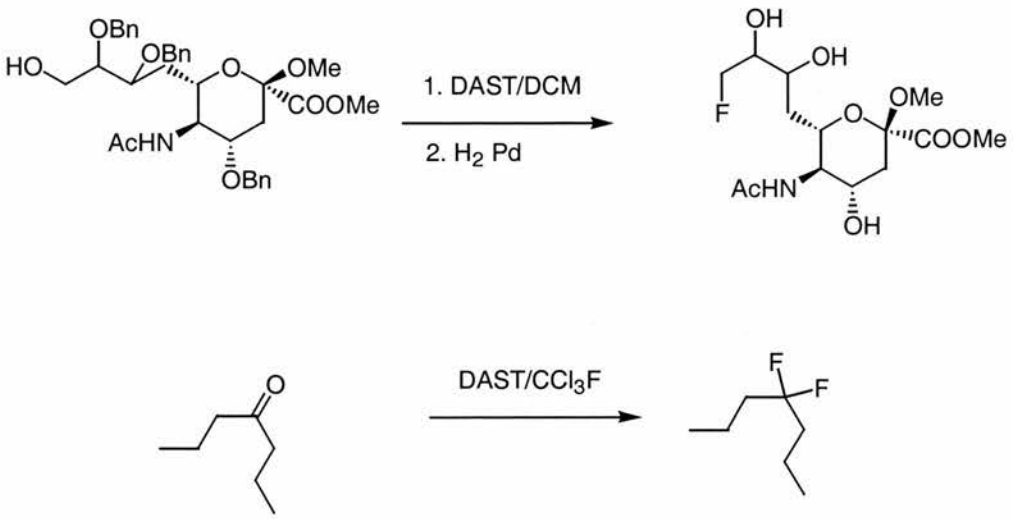
Et_3N•3HF has also been used in the regioselective ring opening of epoxides[55].

Sulfur tetrafluoride (SF_4) is used in combination with HF and is best known for its fluorodeoxygenation ability as shown in **scheme 3.12.** However there are some drawbacks to using this reagent, SF_4 is highly toxic and on exposure to moisture (air, skin) liberates HF, moreover reactions with SF_4 usually require HF•pyridine complex, which precludes the use of glassware.



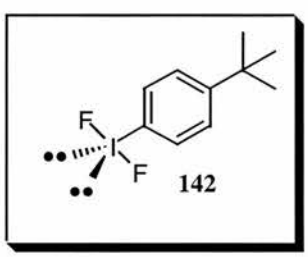
Scheme 3.12. Reactions promoted by SF_4/HF

Recently, DAST (diethylaminosulfur trifluoride) has become one of the more friendlier alternatives to SF_4 in fluorodeoxygenation reactions[56]. DAST is a commercially available liquid which can be stored in plastic bottles, and is stable in dry conditions at room temperature or with refrigeration. DAST is mainly used to fluorinate alcohol and carbonyl groups **Scheme 3.13**.



Scheme 3.13. Example of fluorination reactions using DAST

Other reagents capable of generating F^- are illustrated in **figure 3.21**. For example aromatic hypervalent iodine fluorides (**142**) have been applied to the fluorination of steroids in conjunction with an electron-transfer agent.[57] Bromine trifluoride (**143**) and Mercury (II) fluoride (**144**) have all been used for replacing bromine with fluorine[43] whereas XeF_2 (**143**) is one of the most stable fluorinating agents and it has been used in the fluorination of, a variety of different substrates.[46]



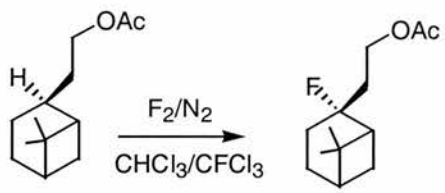
BrF_3	HgF_2	XeF_2
143	**144**	**145**

Figure 3.21. Other sources of fluoride ions

3.3.2.6 Electrophilic sources of fluorine

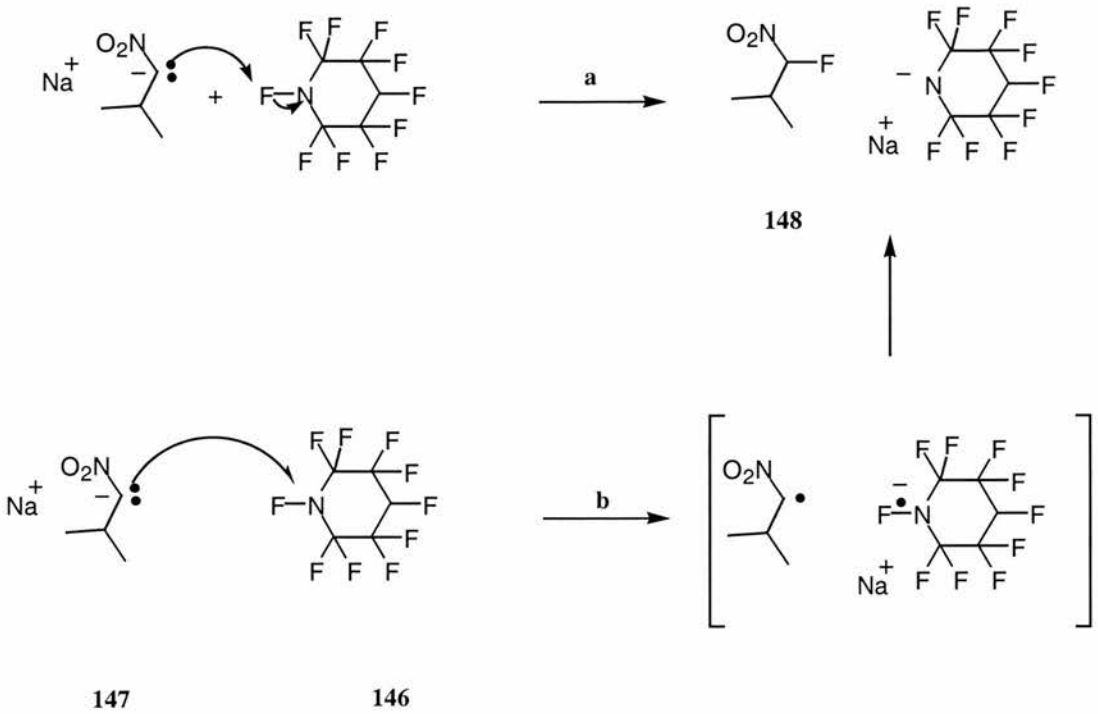
Intuitively, chemists think of using fluorine as F^-, however ingenious ways have been developed for generating fluorine as F^+ for electrophilic fluorinations.

As discussed in section 3.3.2.1, elemental fluorine (F_2) can behave as a free radical source and as an electrophile. This is deduced because substitution of tertiary hydrogens by fluorine proceeds with retention of configuration (**scheme 3.14**) and involves the formation of a carbonium ion intermediate.



Scheme 3.14. Electrophilic fluorination with F_2/N_2

However, the most efficient reagents able to generate $F,^+$ are the N-F reagents.[58, 59] The first fluorination reaction involving a F^+ carrier was reported by Banks and Williamson[60] they discovered that perfluoro-N-fluoropiperidine (**146**) converted the sodium salt of 2-nitropropane (**147**) to the corresponding 2-fluoroderivative (**148**). This conversion was rationalised on the basis of a nucleophilic displacement on the fluorine by the carbanion as shown in **scheme 3.15 (a).** However, a different mechanism, involving an electron-transfer process, was later, proposed[61] **scheme 3.15 (b).**



Scheme 3.15. Fluorination with perfluoro-N-fluoropiperidine: (**a**) nucleophilic mechanism and (**b**) a single electron transfer.

Although perfluoro-N-fluoropiperidine (**146**) was found to be a powerful fluorinating reagent, it has never been widely applied, perhaps as it generally provides low yielding products. In the early 1980's more successful N-F reagents were developed (**figure 3.22**). The first was Purrington's reagent,[62] dihydro-N-fluoro-2-pyridone (**149**), followed by the Barnette's reagent, [63] (**150**), Umemoto's N-fluoropyridinium [64, 65] (**151**), fluoroquiniclidinium salts[66] (**152**) and then the most powerful reagent of this class, the N-fluorobis (trifluoromethylsulfonyl) imide[67] (**153**). The discovery of N-fluoroquinuclidinium fluoride as a fluorinating reagent (**152**) inspired chemists to develop cheaper and more stable alternatives. In fact, the commercial 1,4-diazabicyclo[2.2.1] octane known in the polyurethane industry as TEDA, was used in place of the quinuclidinium ring, but the first bis (NF) salts (**154**) proved difficult to isolate[68]and were found to deliver only one half of the theoretical F^+ available due to self-defluorination reactions. [69] These problems were circumvented by using BF_4^- as a counter ion and by placing an alkyl group on one of the two nitrogens. It emerged that (**155**) (so called F-TEDA-BF_4) which has been commercialised under the name of Selectfluor,™ is one of the most potent electrophilic fluorinating agent.[70]

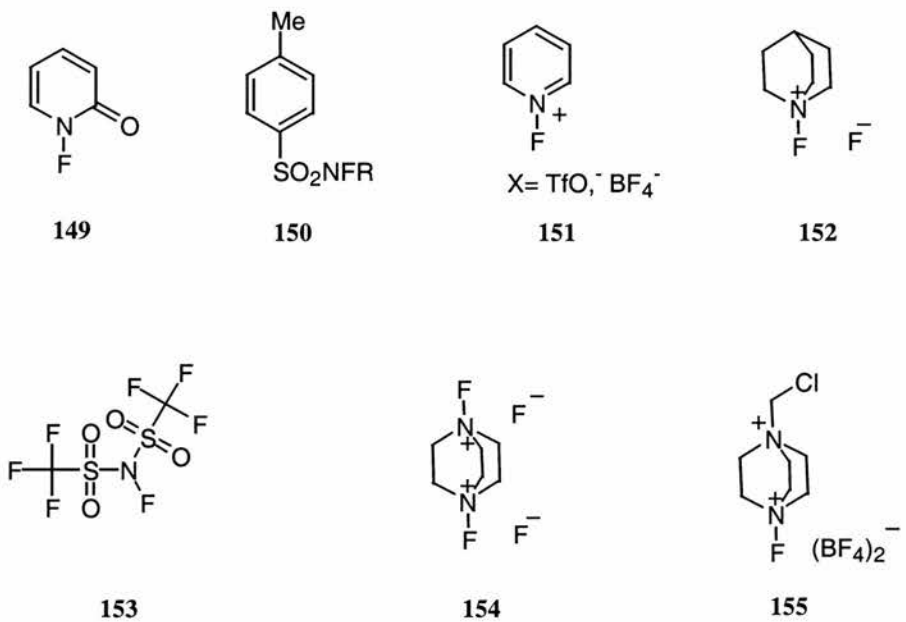
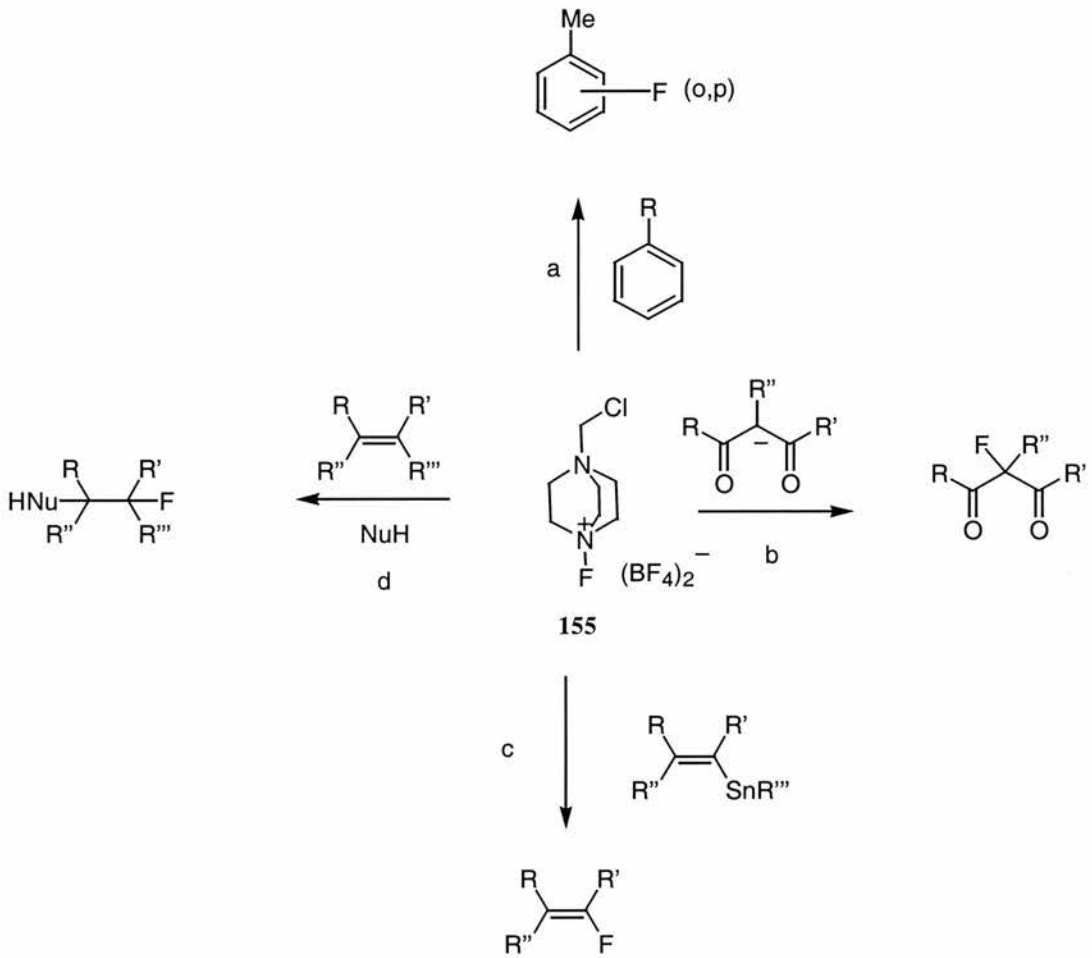


Figure 3.22. Electrophilic N-F fluorinating reagents

F-TEDA-BF_4 (**155**) has been used successfully in the preparation of a variety of different organo-fluorine compounds from a different range of electron-rich substrates. Reactions generally proceed under mild condition and these are summarised in **scheme 3.16**.



Scheme 3.16. Some of the reactions of F-TEDA-BF_4

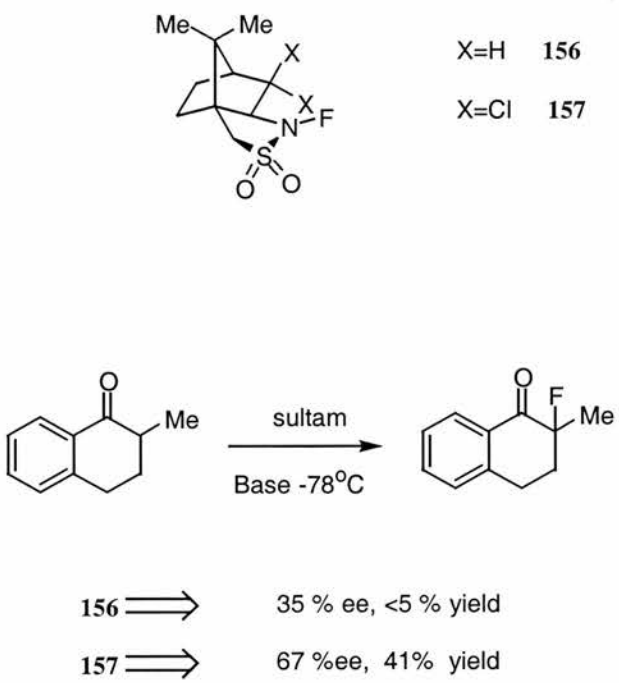
Activated aromatic substrates undergo fluorination and in some cases difluorination[71] (pathway a in **scheme 3.16**). Perhaps the most common reaction employing F-TEDA-BF_4 as a reagent is the fluorination of β-dicarbonyl compounds (*via* b).[70, 72, 73] This involves the reaction of the stabilised carbanion with the reagent. Fluorodemetallation of vinylstannanes[74] and fluorination of alkenes (*via* d) in the presence of nucleophiles[75] are examples of other processes which can be achieved using F-TEDA-BF_4.

3.3.3 Asymmetric fluorination

Many stereoselective syntheses of organo-fluorine compounds have been reported, however they can be classified into four general categories according to the strategy employed to form the stereogenic C-F bond.

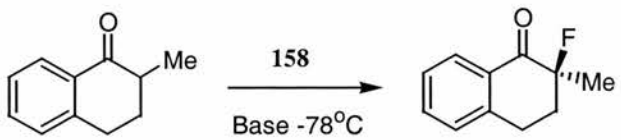
3.3.3.1 Asymmetric fluorination using chiral fluorinating reagents

Asymmetric fluorinations require a chiral reagent capable of delivering the fluorine F atom in a stereoselective manner. N-Fluorocamphorsultams[76, 77](**156** and **157**) were the first examples of these reagents and they have been used for the asymmetric fluorination of metal enolates as shown in **scheme 3.17**. However the yield and the ee's for the asymmetric fluorinations were very poor and this has limited their use.

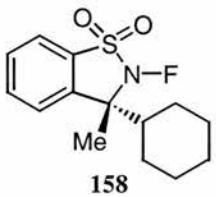


Scheme 3.17. Asymmetric fluorination of metal enolates with chiral camphorsultams

The selectivities were improved later by of Takeuchi and Shibata[78] who were able to prepare N-fluoro sultams (**158**) and successfully applied these to the electrophilic fluorination of enolates as shown in **scheme 3.18**



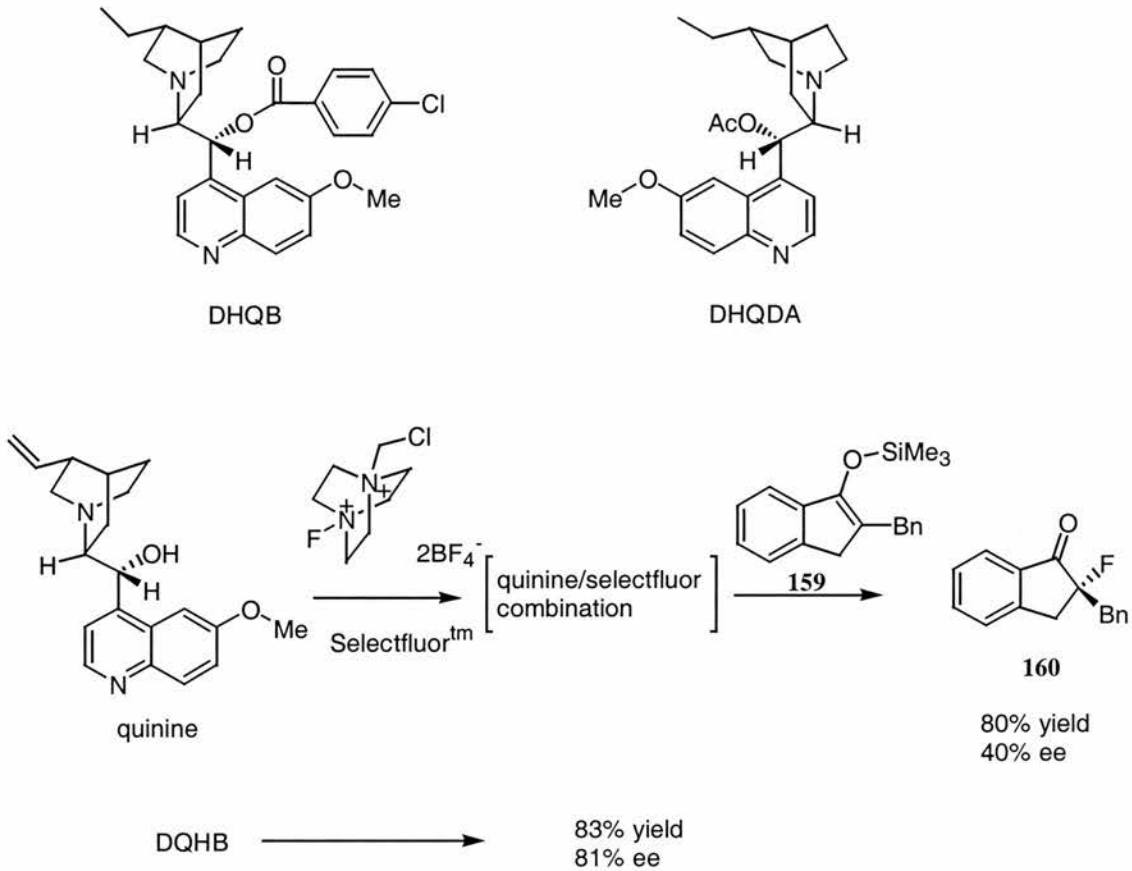
74% ee, 67% yield



158

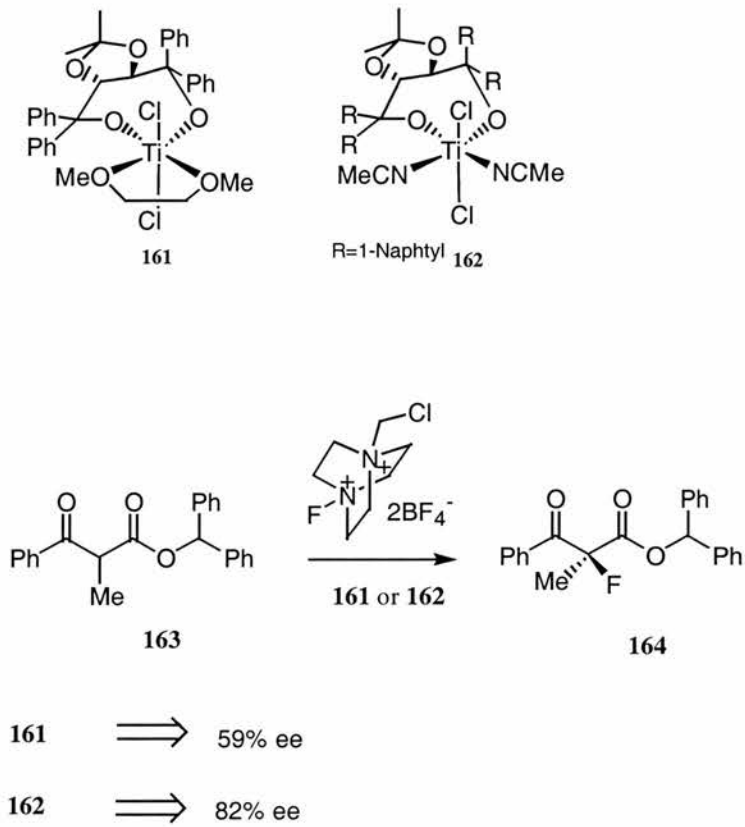
Scheme 3.18. New generation of sultams for asymmetric fluorination reactions.

A significant step forward on asymmetric fluorination methodology was reported simultaneously by Shibata and Cahard.[79, 80] They noticed that a combination of Selectfluor™ and the cinchona alkaloid generates a chiral N-fluoroquinuclidinium species capable of selective F^+ delivery. Furthermore it was observed that the choice of the cinchona alkaloid had a substantial influence on the stereoselectivity of the reaction. Enol silane (**159**) was used as a model for investigating the selectivity of the reaction with different combinations of cinchona alkaloids and Selectfluor. Quinine and Selectfluor gave only a 40% ee in favour in of *R* the enantiomer at C(2) (**160**), whereas with DHQB/Selectfluor improved the stereoselectivity to 81 ee % in favour of the *S* isomer. (**scheme 3.19**). The most effective combinations, including the ones obtained with DHQDA, were used for other aryl enol silanes and in some cases the selectivity (ee) was greater than 85% ee.



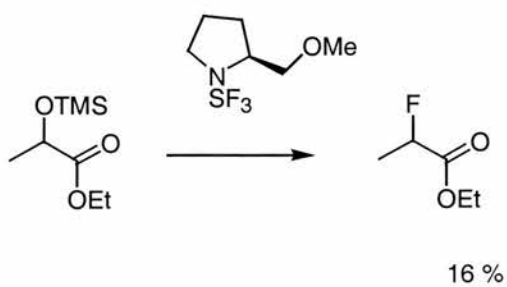
Scheme 3.19. Asymmetric fluorination with Selectfluor/cinchona alkaloids

The asymmetric fluorinations hitherto described require the use of stoichiometric amounts of the chiral reagents. However, the first catalytic fluorination were recently reported by Togni.[81] These use only catalytic amounts of Ti (IV) complexes generated by reactions of [$TiCl_2$(*R*,*R*-TADDOLato)] with DME or acetonitrile to form stable adducts (**161**) and (**162**). These adducts have the ability to catalyze enantioselective fluorination reactions. The reaction presumably proceeds *via* coordination of the Lewis acid (Ti) to the carbonyl oxygen of the β-ketoester (**163**) to form a stable enolate capable of attacking the F^+ reagent to generate the fluorinated product (**164**) see **scheme 3.20**. The reactions were conducted at room temperature with a slight excess of a saturated F-TEDA solution in acetonitrile on different substrates and in all cases the yields ranged between 80 – 95% and the best enantioselectivities were obtained by using catalyst (**162**).



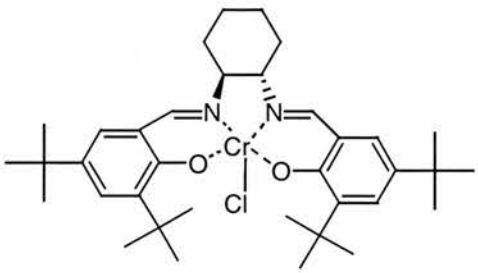
Scheme 3.20. Catalytic enantioselective fluorination using chiral Lewis acids.

The enantioselective introduction of fluorine *via* nucleophilic attack of an asymmetric F^- source remained unexplored. Until recently the only example[82] of such as asymmetric fluoride attack occurred in only 16% ee using a (*S*) proline-based DAST analogue **scheme 3.21**. Although the % ee was low, this strategy relied on a kinetic resolution.

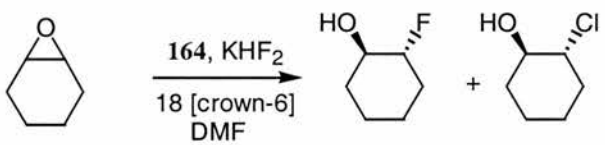


Scheme 3.21. First example of stereoselective nucleophilic fluorination

The most representative example of stereoselective nucleophilic fluorination was reported by Haufe.[83] The reaction involves epoxide ring opening using Cr (salen) complexes. When cyclohexene oxide (**165**) was treated with potassium hydrogen difluoride in the presence of 18 crown-6 and a stoichiometric amount of Jacobsen's chiral chromium salen complex (**166**) the two products (**167**) and (**168**) were generated in an 89:11 ratio and 92% combined yield. The desired fluorohydrin product (**167**) was formed with an 55% ee. (**scheme 3.22**)



166



165 **167** **168**

55% ee

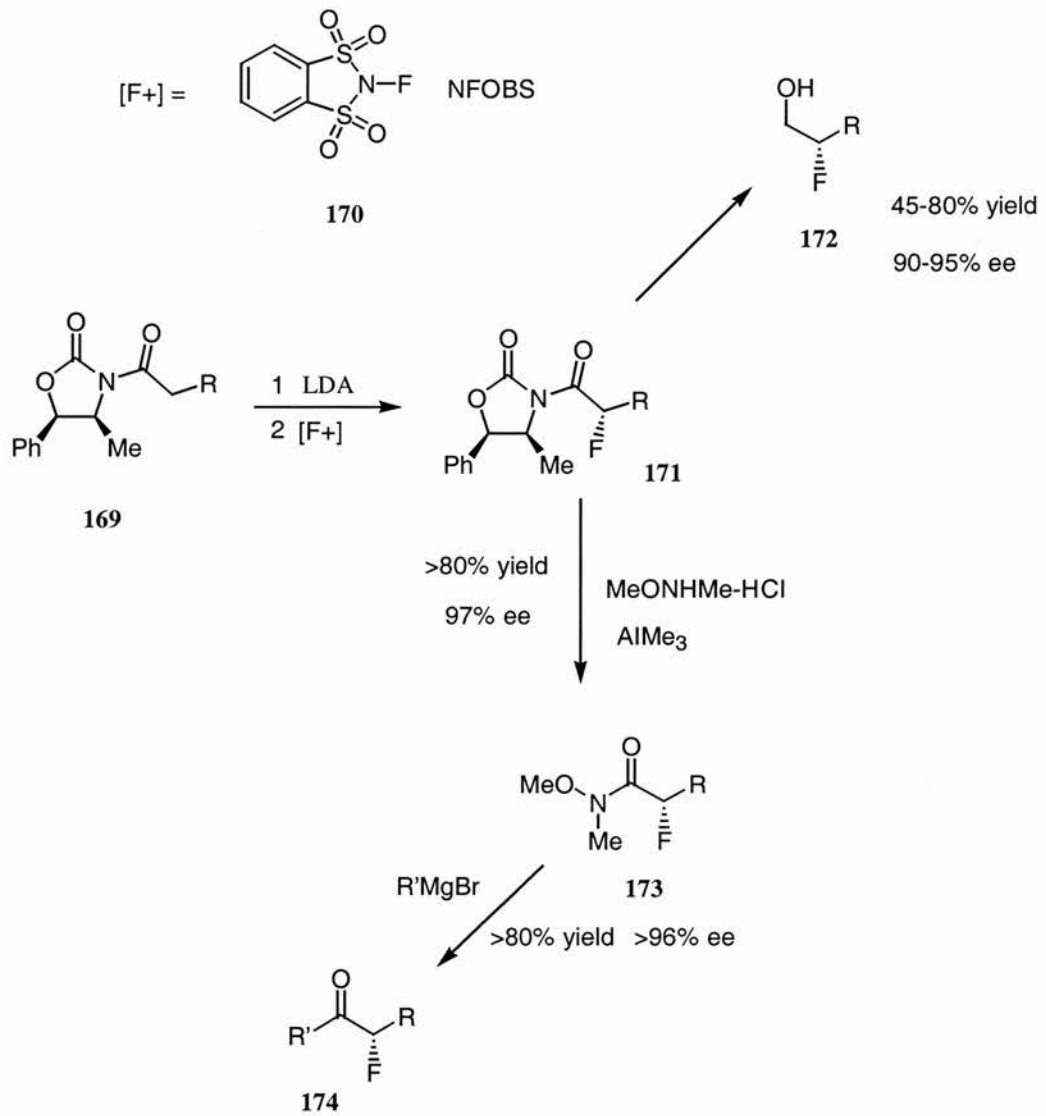
Scheme 3.22. Enantioselective ring opening of a *meso* epoxide

3.3.3.2 Asymmetric fluorination controlled by chiral auxiliaries

An alternative approach to direct stereoselective fluorinations involves the use of covalently linked chiral auxiliaries. Davis *et al.* have used Evans' oxazolidinones as chiral auxiliaries in asymmetric fluorinations.

Fluorination of oxazolidinone (**169**) with the stable fluorinating reagent N-fluoro-o-benzedisulfonimide (**170**, NFOBS)[84, 85] has produced α-fluorocarboxiimides (**171**) in excellent yield (86-95 %) and excellent de (90-99%). The products can then be converted into various functionalities without significant racemization. As shown in **scheme 3.23,** compound (**171**) can be converted into the corresponding alcohols (**172**) by a simple

reduction with $LiBH_4$ Alternatively, conversion into the α-fluoro N-methoxy-N-methylamides (**173**) *via* the transamination procedure developed by Weinreb[86] followed by treatment with the appropriate Grignard reagent (R'MgBr,) afforded ketones (**174**) in high yield and high ee's (**scheme 3.23**).

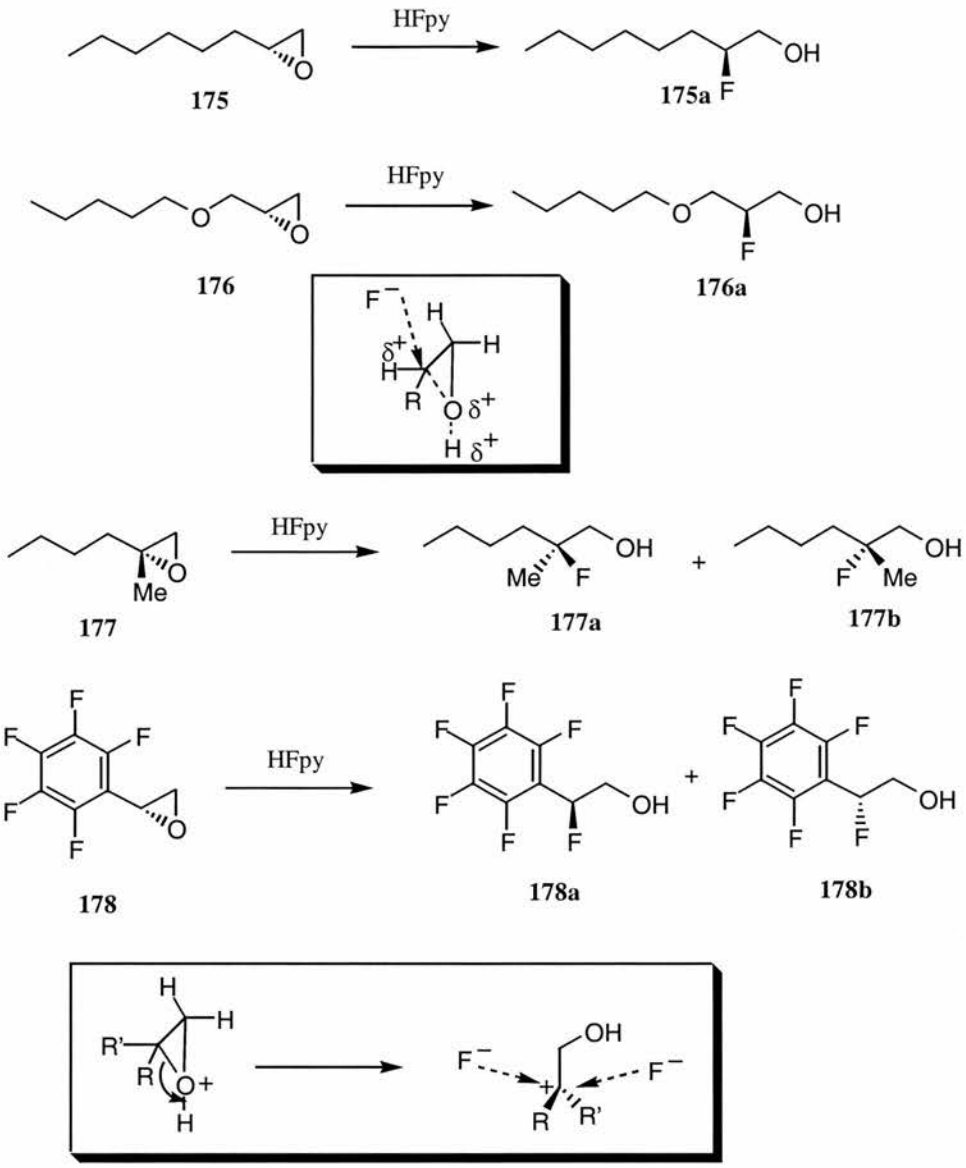


Scheme 3.23. Davis asymmetric fluorination controlled by Evans' oxazolidinones

3.3.3.3 Asymmetric fluorination controlled by substrates

The stereoselectivity for this type of reaction is controlled by the presence of a covalently modified chiral fragment that is retained in the target molecule. One of the most representative examples of this type is the hydrofluorination of optically active terminal epoxides[87]. 1,2-Epoxyoctane (**175**) and glycidyl hexyl ether (**176**) gave the corresponding 2-fluoro-1-alkanol (**175a** and **176a**) derivatives when treated with a HF•amine complex, suggesting a configurational inversion of the asymmetric centre (ee 90%), while during the hydrofluorination of pentafluorostyrene oxide (**177**) and 2-methyl-1,2-epoxyhexane (**178**), partial racemization occurred.

The high stereoselectivity for the first two reactions can be rationalised by assuming the formation of an intermediate state, in which the positive charge is delocalised on three atoms and the fluoride attacks in a S_N2 fashion to the carbon centre leading to the product with inverted stereochemistry. On the other hand, the low selectivity for (**177**) and (**178**) is presumably caused by formation of a stable carbocation (tertiary and benzylic) with two faces exposed to the attack of the fluoride ion **scheme 3.24.**



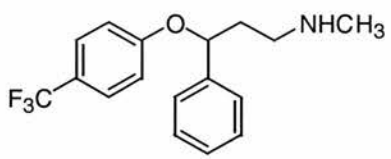
Scheme 3.24. Epoxide ring opening with an HF-amine complex

Part C

3.4 Applications of Organo-fluorine compounds

3.4.1 Fluorine containing drugs

Many fluorinated compounds are currently used in the treatment of disease. These include the antidepressant fluoxetine (**179**), which is the most significant anti-depressant drug by volume and sales.[88] Other major products include the anti-inflammatory agent diflunisal (**180**), the antibacterial ciprofloxacin (**181**) and chemotherapic agents such as 5-fluorouracil (**182**) shown in **figure 3.23**.



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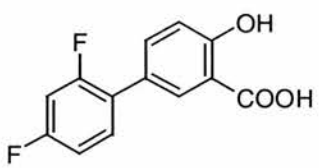

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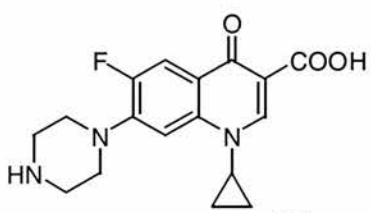

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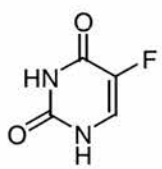


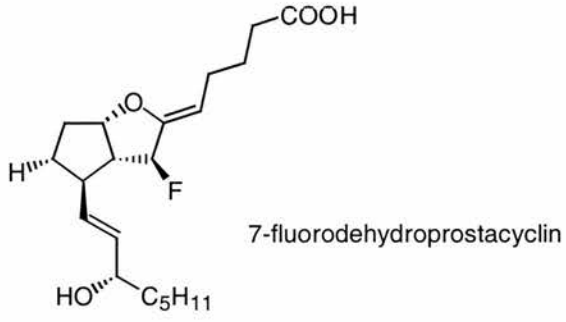
182

Figure 3.23. Example of commercially significant fluorinated drugs

The inclusion of fluorine in a drug, can influence both the metabolism or the interaction of the drug with the target protein. The replacement of an hydroxyl group or a hydrogen atom by fluorine is an important strategy in medicinal chemistry. Although, fluorine is a little bigger in size than hydrogen, it has already been discussed that the substitution of fluorine over hydrogen causes minimal steric effects at receptor sites and it can be considered as an hydrogen mimic.[89] However it also can act as an isostere of the hydroxyl group. F and OH are both hydrogen bond acceptors although the CF····HX bond is weaker than the corresponding CO····HX.[11]

Fluorine generally acts to increase the lipophilicity of an organic molecule and the effect is pronounced with the CF_3 group. This feature has been used in medicinal chemistry as a general strategy to increase the lipophilicity of drugs. Drugs acting on the central nervous system (CNS) must pass through the blood brain barrier and many of these drugs contain either a CF_3 or a fluoro/phenyl group which contributes to the pharmacological activity of the biologically active compound.

Fluorination can also increase the metabolic stability of a pharmaceutical formulation and replacement of different groups with fluorine has been used to increase the biological half-life of endogenous or synthetic compounds. For example, fluorinated analogues of prostacyclin, which is an inhibitor of platelet aggregation, contain an acidic labile enol-ether responsible for its short half-life. A fluorine atom placed alpha to the enol ether as is structure (**183**) reduces the electron density and prevents any acidic hydrolysis[90] **figure 3.24**.



7-fluorodehydroprostacyclin

183

Figure 3.24. Examples of fluorinated analogues of endogenous compound

Fluorinated nucleosides and nucleotides are a very important class of anticancer or anti-AIDS drugs. 5-Fluorouracil (**182**) is one of the major drugs used to treat solid cancers. It is converted into the active metabolite 5-fluoro-2'-deoxyuridine 5'-phosphate (FdUMP) which inhibits thymidylate synthase and its cofactor, a tetrahydrofolate derivative, responsible for the trasformation of dUMP into dTMP (**figure 3.25 A)**. The FdUMP acts as suicide inhibitor, binding covalently to the enzyme co-factor resulting in the inactivation of the enzyme, as shown in **figure 3.25 B,** and interfering with the synthesis of the DNA.[90, 91]

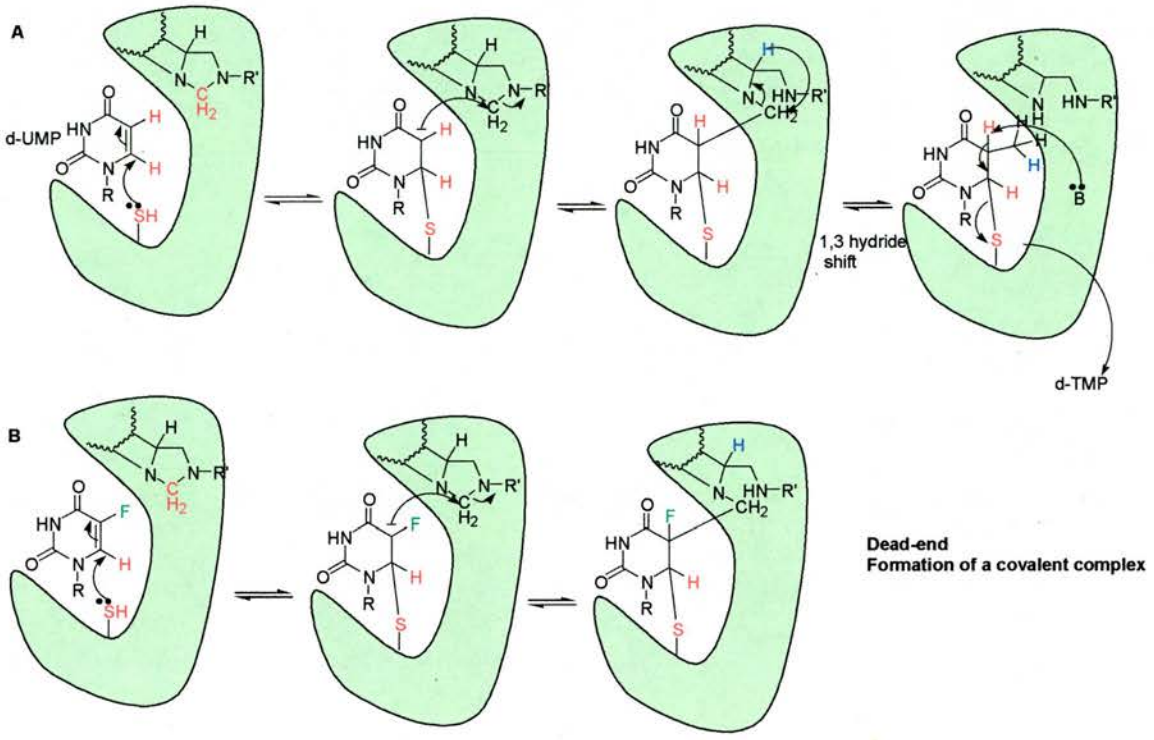


Figure 3.25. Conversion of dUMP to dTMP and its inhibition by FdUMP

3.4.2 Fluorine-containing chiral liquid crystals

Fluorine also has a major role to play in material science. Some solid materials exhibit a long-range order even after they melt giving rise to *liquid crystalline* behaviour where the molecules do not exhibit any positional order, but only a certain degree of orientational order is maintained. Liquid crystals are *anisotropic* materials, where the properties of the material differ depending on the direction they are measured. Liquid crystals behave differently depending on what direction electric or magnetic fields are applied relative to the director and this property forms the basis of their use as data displays in calculators, watches and flat screens.

There are many kinds of liquid crystal. *Nematic* liquid crystals have a tendency to organize themselves in a parallel fashion as shown in **figure 3.26**. In *Smectic* liquid crystal the molecules align themselves in layers **figure 3.26**. In smectic A (SmA) liquid crystals the molecular orientation is perpendicular to the layers, whereas the director is tilted in the SmC phase. Both show no positional order within the layers and therefore are often considered as two-dimensional liquids. The SmC phase of chiral molecules form a helical structure to form the phase known as *smectic SmC**.

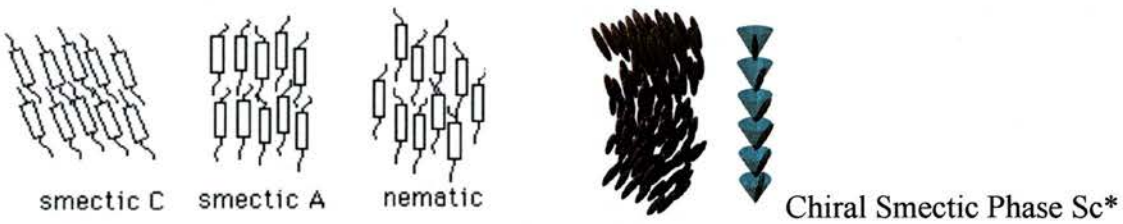
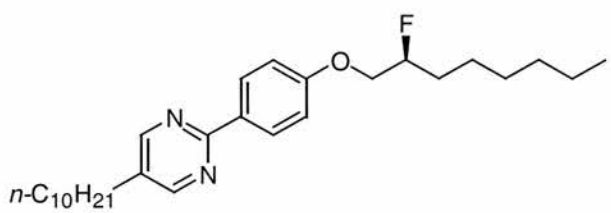


Figure 3.26. Representation of liquid crystal phases

Liquid crystals which contain chiral molecules and show the SC* phase are known as *ferroelectric liquid crystals* (FLC). The (FLCs) posses a spontaneous ferroelectric polarisation (Ps) or macroscopic dipole moment. Appropriate application of an external electric field results in alignment of the chiral molecules by θ degrees from the normal line of the layer. When the sign of the applied field is reversed a realignment or switching of FLC molecules occurs[92]. This response or switching time (τ) falls in the order of a μs. This property of the FLC's can be useful in high-speed, high-resolution electro-optic devices, such as flat panel displays and the research in the field of chiral smectic material has greatly expanded. Ever faster switching speeds are required nowadays and small τ are associated with FLCs which posses high polarisation density (Ps) and low viscosity.

Chiral organo-fluorine molecules are typical examples of *ferroelectric-liquid* crystal. The C-F bond possesses a dipole moment of 1.79 D and since fluorine has a relative small atomic radius it induces an appropriate Ps and generally a low viscosity.

Fluoroalkyl ethers such as the one shown (**184**) in **figure 3.27** are currently used in Canon displays. An additional fluorine atom may induce a larger Ps such as difluoro ethers (**185a** and **185b**) prepared by Walba.[93, 94] The *syn*-isomer **185a** induced a large Ps whereas the *anti*- isomer **185b** showed a smaller value. The difference can be explained in terms of the dipole moment induced by the two fluorine groups. The *syn*-isomer possesses two fluorines in parallel, which increase the Ps, whereas the dipole moments in the *anti*-isomers compensate each other and hence the Ps is minimised.



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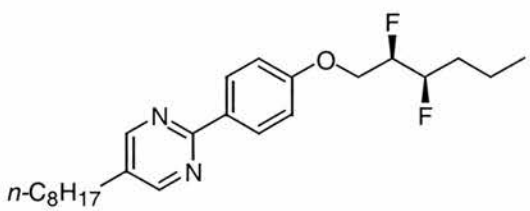
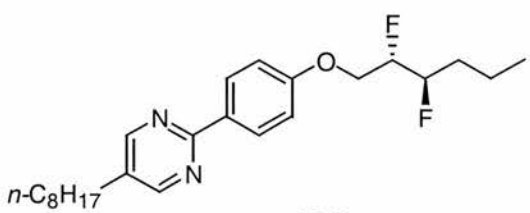


185a



185b

Figure 3.27. Fluorine containing liquid crystals.

4 Vicinal Trifluoro Alkanes: Stereoselective Synthesis of a New Class of Fluorinated Compounds

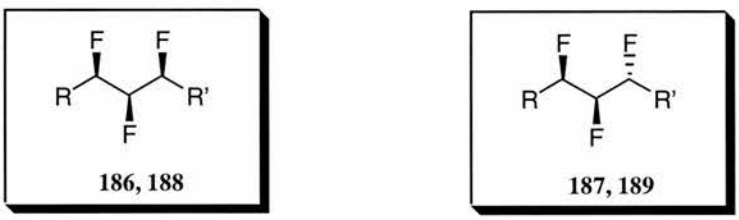
4.1 Aims

There is clear evidence that the C-F bond can be exploited as a tool for influencing the conformation of organic molecules, particularly when it is used as a replacement for hydrogen. This is most easily illustrated by the well known *gauche effect* which recognises that 1,2-difluoroethane prefers a *gauche* over an *anti* conformation. The gauche preference of vicinal fluorines influences the conformation of hydrocarbon chains for example in 2,3-difluorobutane. It extends also to longer chain systems (see difluorostearic acids) as previously discussed in **section 3.2.3.2**. This is attributed to the vicinal C-F bonds preferring to align *gauche* to each other in both systems, the former stabilising and the latter destabilising the classical *anti-zig-zag* conformation of the hydrocarbon chain. With the fluorine *gauche effect* reasonably well understood for vicinal difluorohydrocarbons, it appeared desirable to investigate the behaviour of a hydrocarbon system with a third vicinal fluorine. This chapter explores the synthesis of such vicinal trifluoro systems in a diastereoselective manner.

4.2 Stereoselective synthesis of trifluorononanes

4.2.1 Synthetic strategy for the synthesis of a vicinal trifluoro system

A synthesis of trifluoro derivatives **186- 189 (figure 4.1)** was explored.

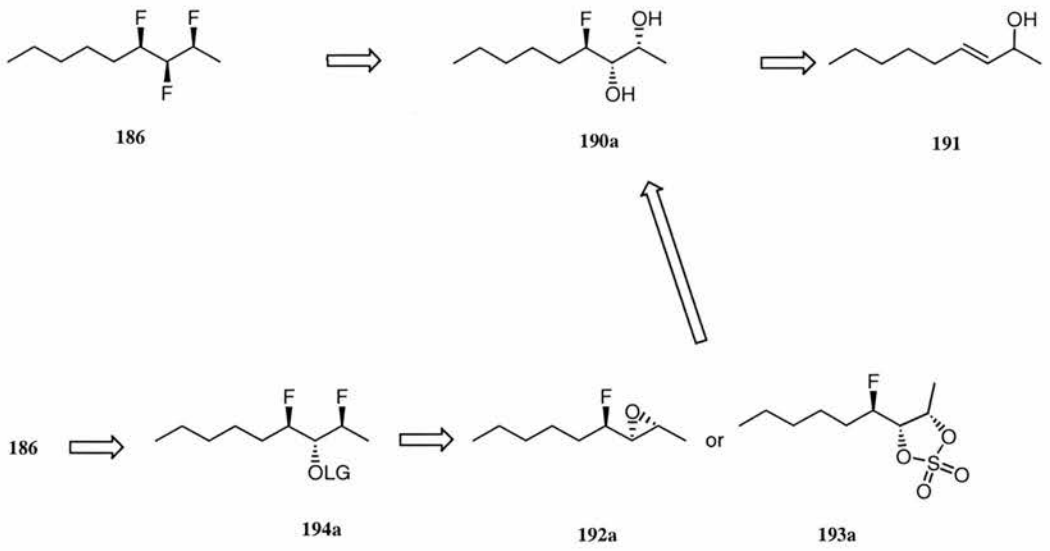


186 and **188** R=$(CH_2)_4$-CH_3, R'=-CH_3

187 and **189** R=$(CH_2)_6$-CH_3, R'=Ph-$(CH_2)_5$

Figure 4.1. Novel structures of trifluoroalkanes

The synthesis of trifluoro derivatives **186** and **187** was explored as illustrated in **scheme 4.1.** Two different approaches (***a, b***) were taken having a common intermediate **190a** (or **190b)** which can be easily synthesised from the allylic alcohol (**191**). Approach ***a,*** requires direct fluorination of substrate (**190a** or **190b**) *via* a nucleophilic replacement of two hydroxy groups with DAST. Alternatively approach ***(b)*** introduces the two remaining fluorine atoms in step wise manner. It was envisaged that the fluorodiols **190a** (or **190b**) could be converted in to either an epoxide (**192a** or **192b**) or into cyclic sulfates (**193a** or **193b**). The sulfates would then be substrates for the second fluorination *via* a HF-pyridine reaction or TBAF respectively. The final fluorine could be placed by simple activation of the remaining OH (**194a**) and then by nucleophilic displacement using fluoride ion source.

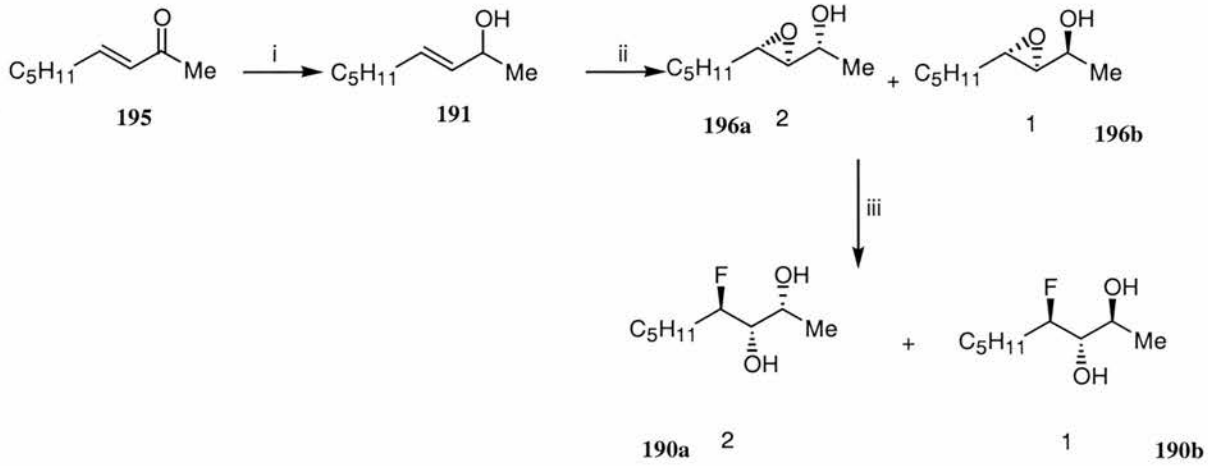


Scheme 4.1. Retrosynthetic analysis for trifluorononanes **186** (or **187**)

4.2.2 Direct fluorination approach (a)

4.2.2.1 Preparation of fluorodiols (**190a**) and (**190b**)

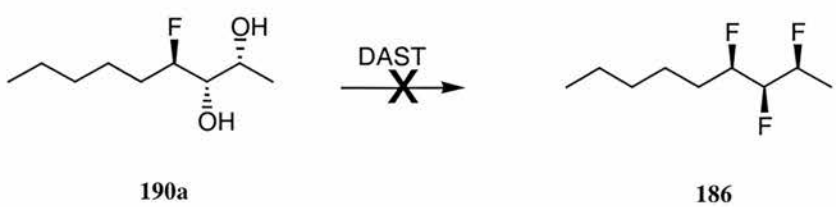
The required fluorodiols **190a** and **190b** were synthesised from the commercially available α,β-*trans*-unsaturated-ketone *via* a three step protocol. The route is illustrated in **scheme 4.2.** The sequence starts with the reduction of enone (**195**) using $NaBH_4$ in the presence of $CeCl_3 \bullet 7H_2O$. This reaction proceeded in almost quantitative yield to give alcohol (**191**). The alcohol was then converted into the two diastereotopic epoxides **196a** and **196b** as a 2:1 mixture. It proved more efficient to separate the diastereomers after the next step following treatment with HF•Pyridine. This reaction resulted in a regio- and stereo-specific ring opening generating the fluorodiols **190a** and **190b** retaining the ratio 2:1. Diastereoisomers **190a** and **190b** were readily separated by silica gel chromatography and they were then used individually for their separate conversion to the diastereomeric trifluoroalkanes.



Scheme 4.2. Reagents and conditions: (i) $NaBH_4$, $CeCl_3 7H_2O$ in MeOH, 0 °C 15 min 90%; (ii) mCPBA in DCM, 0 °C 2 h, 85%; (iii) HF•Pyridine in DCM, -10 °C 4 h, 62%.

4.2.2.2 Attempted to the synthesis of trifluorononane (**185**) *via* the DAST reaction of the fluorodiol (**190a**)

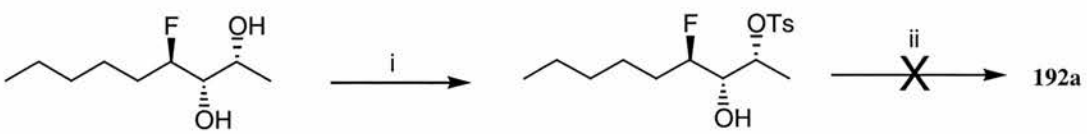
With the fluorodiol **190a** in hand, the direct fluorination approach discussed in the previous section was explored. However simultaneous replacement of the two OH groups by fluorine using classical DAST conditions **scheme 4.3** was unsuccessful. In fact, the reaction which could be followed by TLC, instantly showed the formation of several by-products. Spectroscopic analysis of the reaction mixture after work-up, confirmed the existence of four or five products with proton signals in the olefinic region of the ^1H NMR spectrum (5-6 ppm) and with fluorine signals in the aliphatic region of the ^{19}F NMR spectrum (-180 - -190 ppm). Clearly, a number of elimination reactions competed with the nucleophilic displacement, generating different olefins in place of the desired trifluoroalkane.



Scheme 4.3. Conversion of **190a** to **186** was unsuccessful with DAST.

4.2.2.3 Attempted synthesis of fluoroepoxide (**192a**) from **190a**

The preparation of the desired epoxide (**192a**) required a two step protocol. The first step required the activation of only one OH group of the fluorodiol (**190a**) and this was achieved using one equivalent of tosyl chloride, which generated the tosyl derivative (**197**) in a regioselective manner. It was envisaged that the second step would involve a deprotonation of the remaining OH with a base (DBU).[95] This was unsuccessful, even when LiBr was added, and the expected epoxide was not formed. (**scheme 4.4.**)

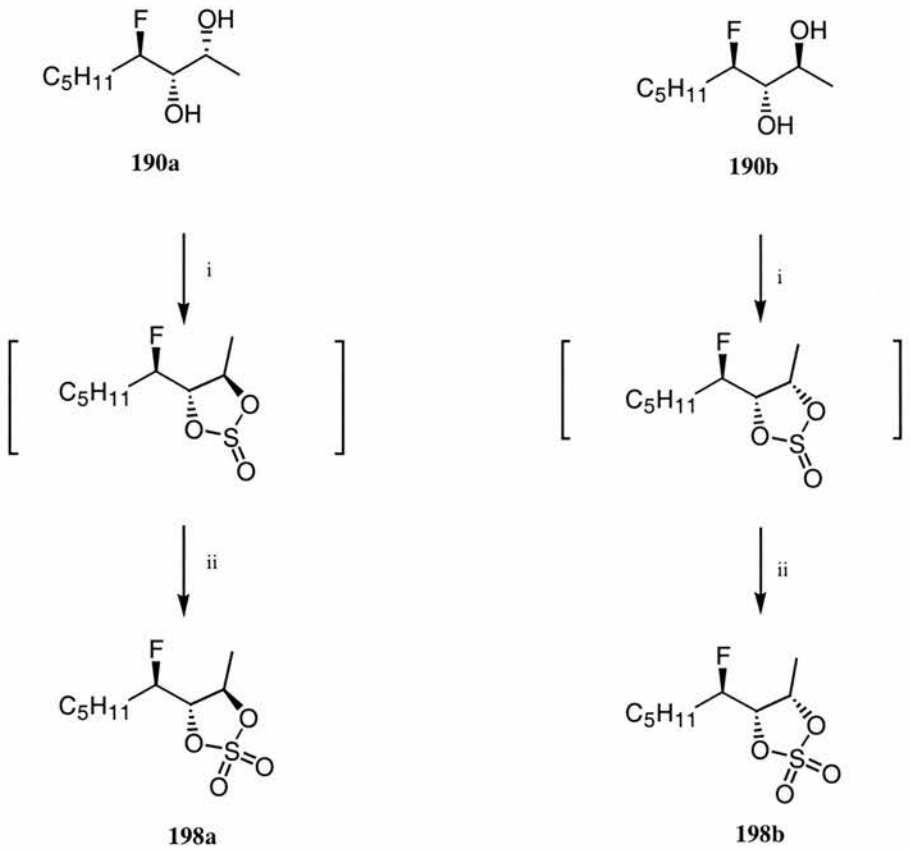


190a **197**

Scheme 4.4. Reagents and conditions: (i) Tosyl chloride, pyridine, DMAP, DCM, rt 24 h, 70%; (ii) DBU, LiBr, THF RT.

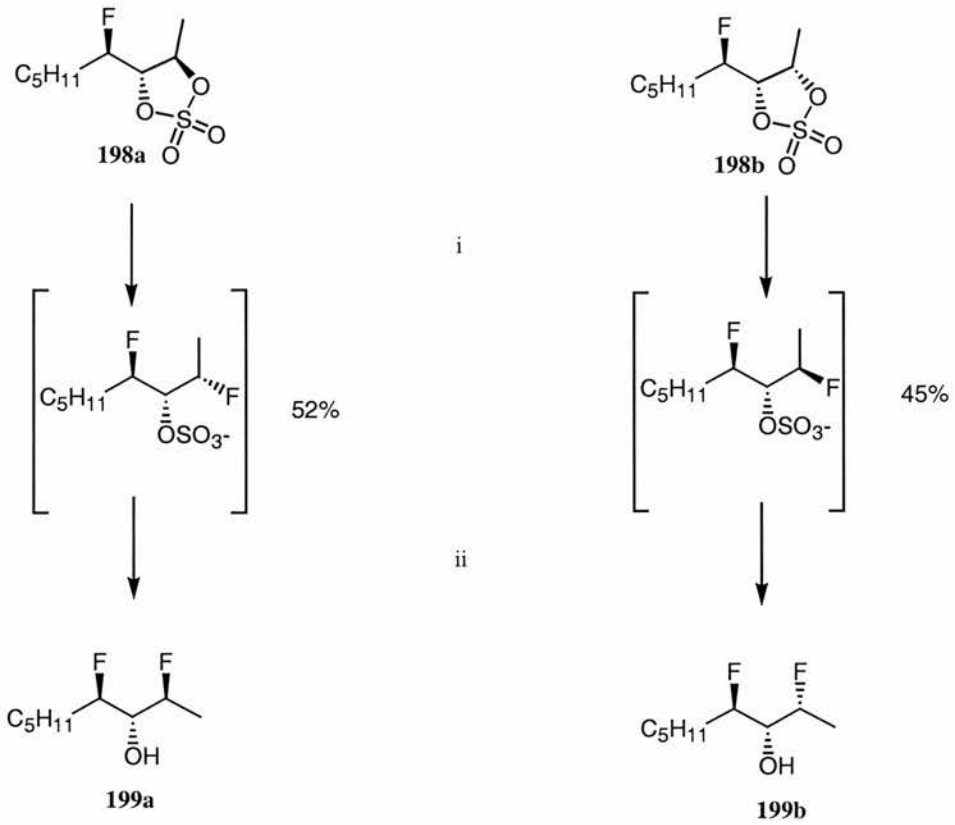
4.2.2.4 Stepwise fluorination by ring opening of a cyclic sulphate

Sharpless has shown that cyclic sulfates can be ring opened with fluoride ion. This strategy was now explored as a method for the stereospecific introduction of fluoride. The vicinal diols of both diastereoisomeric series (**190a** and **190b**) were efficiently converted to their cyclic sulfates **198a** and **198b** using the Sharpless protocol.[96, 97]The reaction was performed with $SOCl_2$ and pyridine generating a cyclic sulfite in less than 1 hour. This intermediate was then oxidised with RuO_4 ($NaIO_4$ and catalytic amount of $RuCl_3$) in MeCN-H_2O to yield the desired cyclic sulphates in 85-90% yield over the two steps (**scheme 4.5**).



Scheme 4.5. Reagents and conditions. (i) Thionyl chloride, pyridine, DCM, 0 °C 45 min. (ii) $NaIO_4$/ $RuCl_3$ in CH_3CN/H_2O, 0 °C.

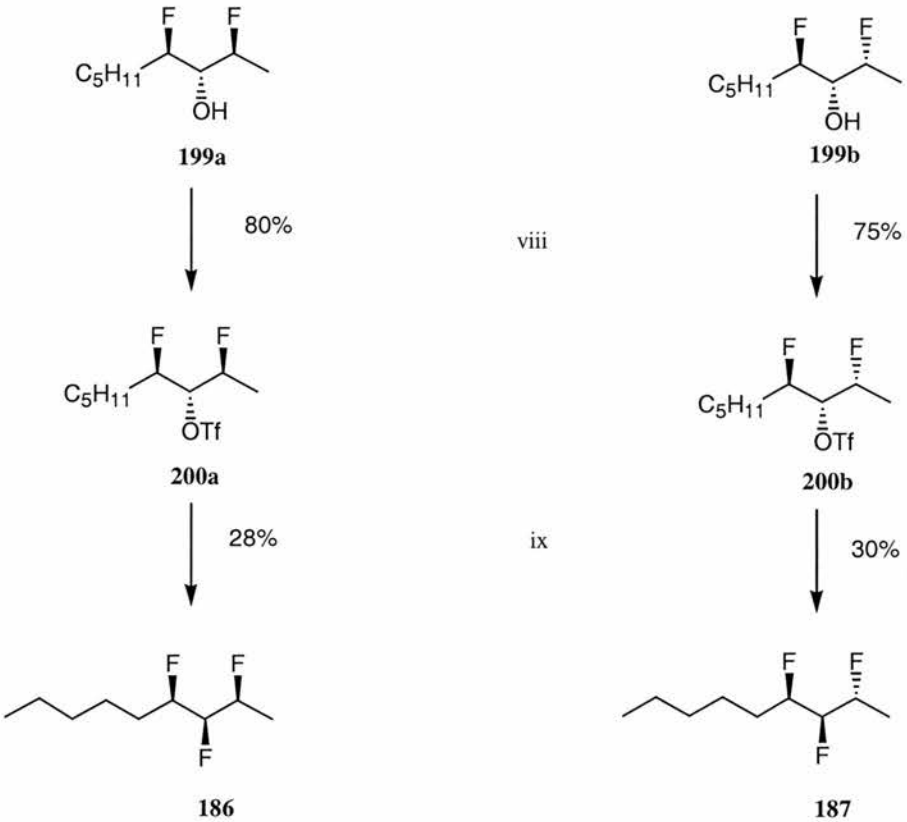
The sulfates (**198a** and **198b**) were subsequently treated with TBAF [98] in acetonitrile and after 30 min all of the starting material was consumed (TLC). The reaction mixture was then hydrolysed *in situ* in a biphasic system (H_2SO_4 20% and ether) at room temperature. Spectroscopic analysis showed that the difluoro alcohols **199a** and **199b** were formed in a highly regio- and stereo- specific manner. Fluoride ion attacked the less hindered position of the sulfate ring in a S_N2 manner generating exclusively a single diastereoisomer of the difluoroalcohols. The structures of these products are shown in **scheme 4.6**.



Scheme 4.6. Reagents and con*ditions*. (i) TBAF in acetone, 0 °C 2 h; (ii) Et_2O/H_2SO_4 20% RT 24 hours.

4.2.2.5 Introduction of the third fluorine

The third fluorine atom was introduced *via* fluorination with TBAF on the triflates **200a** and **200b.** These materials were easily prepared from their corresponding alcohols (**199a** and **199b**) after reaction with triflic anhydride and pyridine in DCM at –40 °C. The nucleophilic displacement of the OTf group led to the desired vicinal trifluoroproducts as shown in **scheme 4.7,** although the desired products were accompanied by elimination products. These fluoroolefins could not be isolated due to their volatility. However the desired products **186** and **187** could be secured in a straightforward manner after chromatography.



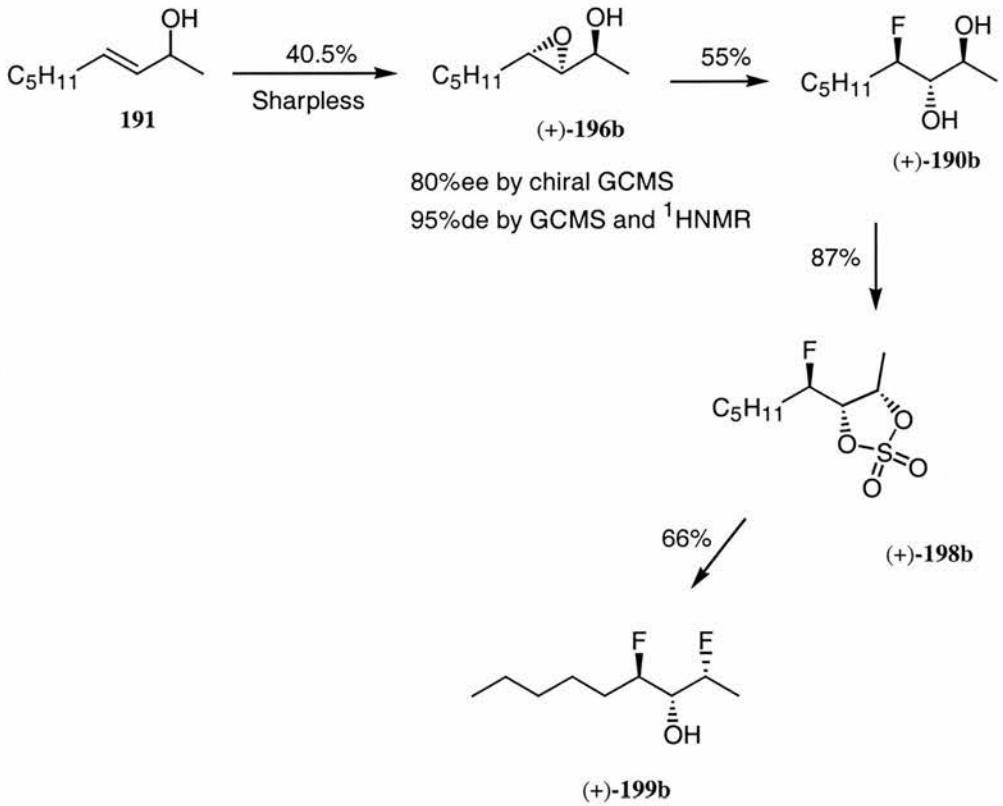
Scheme 4.7. Reagents and conditions. (i) Tf_2O, pyridine in DCM, -40°C 1 h; (ii) TBAF in acetonitrile, 0 °C 30 min.

4.2.3 Synthesis of enantiomerically pure difluoroalcohol (**199b**) *via* a Sharpless epoxidation of allylic alcohol (**191**)

Although all of the vicinal trifluoro products in this study were prepared as racemates, the enantiomerically pure products can be accessed by initiating the synthetic protocol with a Sharpless asymmetric epoxidation/kinetic resolution.[99, 100] This was explored to confirm the stereochemical course of the first two fluorination reactions in **schemes 4.7** and **4.8**. Compound (**196b**) was prepared by the Sharpless kinetic resolution of racemic 3-nonen-2-ol **189** as a substrate using (+)-DIPT and a limiting (0.5 equiv) amount of ^{t}BuOOH. This generated the allylic epoxide **196b**, of known configuration[101] in 95% de and 80% ee. **scheme 4.8.**

With enantiomerically enriched epoxide **196b** in hand it was possible to explore the stereochemical course of the two fluorination reactions. Therefore the sequence described

above was applied again to the synthesis of enantiomerically enriched **198b** as shown in **scheme 4.8.** The difluroro alcohol **(198b)** was a crystalline material and proved suitable for X-ray analysis and structure determination.



191

(+)-**196b**

80%ee by chiral GCMS
95%de by GCMS and ^{1}HNMR

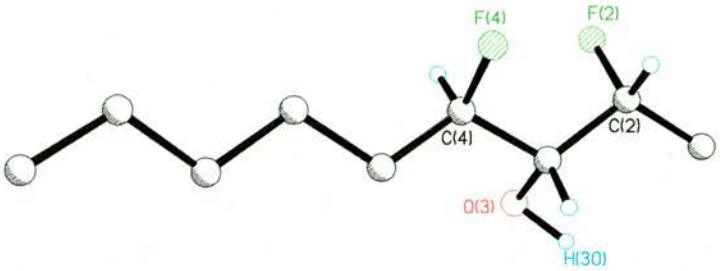
(+)-**190b**

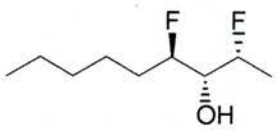
(+)-**198b**

(+)-**199b**

Scheme 4.8. The preparation of enantiomerically pure **199b**

The resultant X-ray structure of **199b** is shown in **figure 4.2.** This revealed a stereochemistry consistent with two configurational inversions at C(4) and at C(2) for each C-F bond forming reactions. The final trifluoro product, which results from fluoride ion displacement of a triflate is assumed to proceed with an inversion of configuration. These trifluoroalkanes were not crystalline materials and were not amenable to crystallisation, however with this latter assumption, the relative (and in this case the absolute) stereochemistry of the method is on a secure footing.





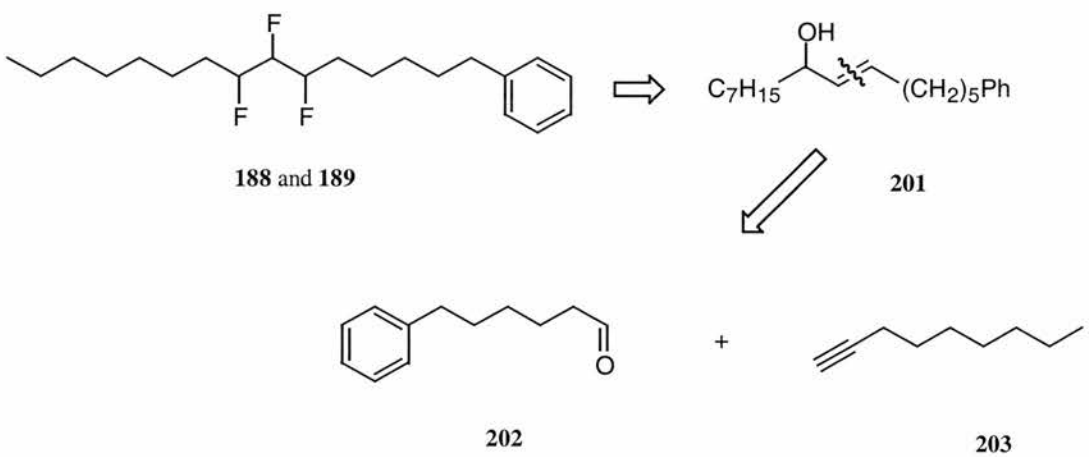
(+)-199b

Figure 4.2. The X-Ray structure of **199b** confirmed the relative stereochemistry after two fluorinations reactions

4.3 Stereoselective synthesis of a second trifluoroalkane series

4.3.1 Retrosynthetic analysis

The methodology developed in the last section for placing three vicinal fluorines along an alkyl chain was then applied to the synthesis of a second system. The aryl alkanes, **188** and **189** as shown in **figure 4.1,** contain a longer chain hydrocarbon system (15 carbons)**.** Retrosynthetic analysis reveals an allylic alcohol as the starting point for the synthesis of these trifluoro alkyl; systems (**188** and **189**). The required allylic alcohol **201** was readily accessible from a condensation of 6-phenyhexanaldehyde **202** and non-1-yne **203** followed by a LAH reduction as illustrated in **scheme 4.9**.

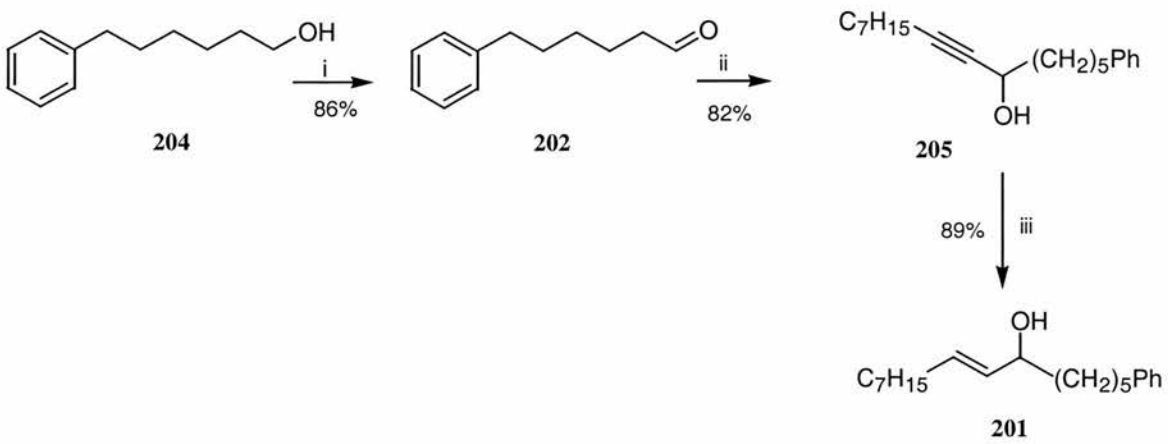


188 and **189** **201** **202** **203**

Scheme 4.9. Retrosynthetic strategy from **188** and **189**

4.3.2 Preparation of allylic alcohol (**201**)

The methodology developed for the synthesis of trifluorononanes (**186** and **187**) required allylic alcohol (**191**) as the starting material. It can be generalised that the synthesis of any such trifluoro derivative by our method requires an allylic alcohol as a starting point. Therefore the synthesis of the desired trifluoro compounds commenced with the allylic alcohol (**201**) as shown in **scheme 4.10.**



Scheme 4.10 Reagents and conditions. (i) PCC, 2 h; DCM. (ii) HC≡C-C_7H_{15} (**203**), BuLi in THF, -78 °C, 3 h. (iii) $LiAlH_4$ in THF, reflux.

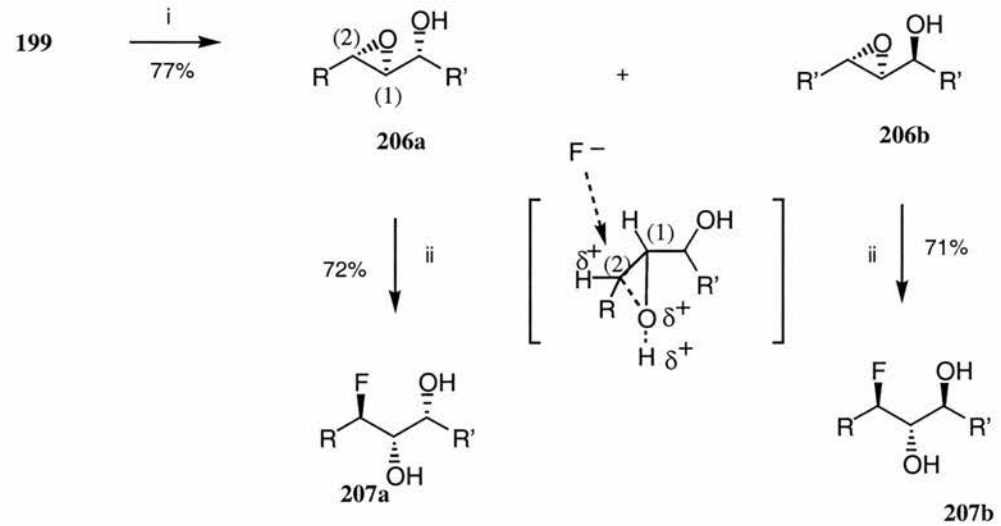
The method started with the oxidation of alcohol (**204**) with PCC in DCM[105] to afford 6-phenylhexaldehyde (**202**) in 86% yield. The acetylide derived from (**203**) was generated *in situ* with BuLi. Treatment of this with aldehyde (**202**)[102] gave propargyl alcohol derivative (**205**) in good yield. Finally, the *trans*-allylic alcohol (**201**) was secured after $LiALH_4$ reduction of **205**.[103]

4.3.3 Synthesis of trifluoro derivatives **188** and **189**

4.3.3.1 HF ring opening of epoxides (**206a** and **206b**)

In the trifluorononane series the first fluorination reaction required the allylic epoxides (**196a** and **196b**) as substrates for HF ring opening. Similarly, epoxides **206a** and **206b** were prepared by transformation of the allylic alcohol (**201**) to their corresponding diastereoisomeric pairs by reaction with mCPBA. The two distereoisomers were again generated as a 2:1 mixture in favour of isomer **206a.** These diastereoisomers could be separated by chromatography and the resulting epoxides were used individually for the subsequent steps. Olah's reagent (HF•py) was then used again for opening of the epoxides of **206a** or **206b** to yield the fluorodiols **207a** or **207b** in a completely regio-and stereo-specific manner **scheme 4.11.** The high stereospecificity suggests that F^- attacks

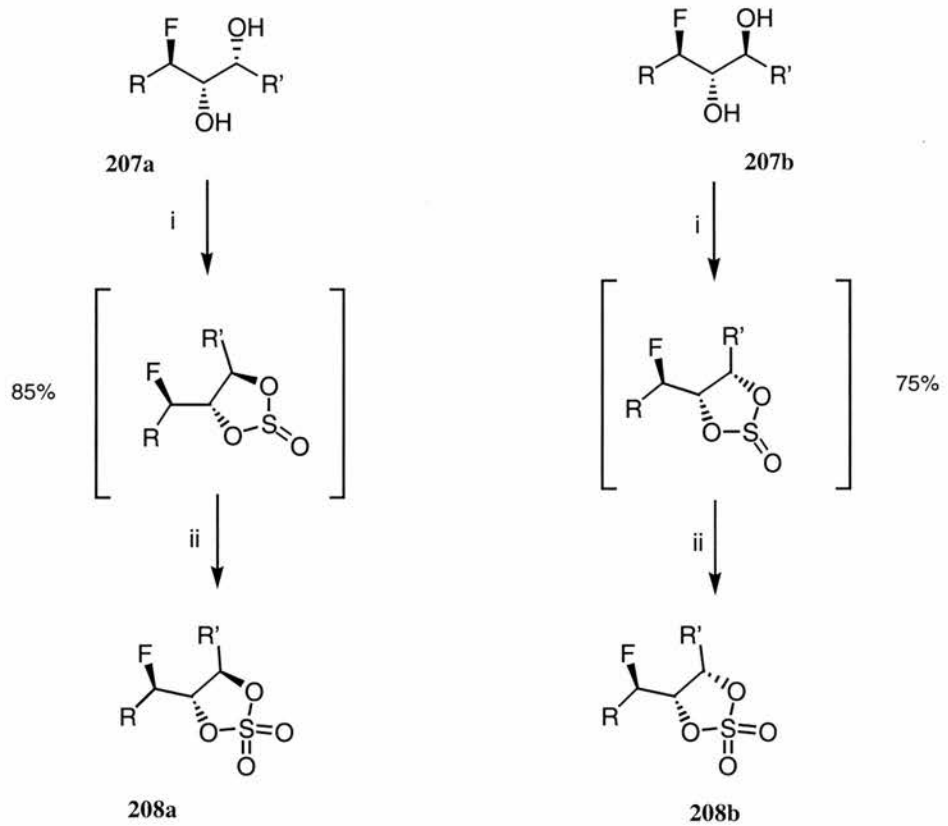
preferentially at C(2) where a developing carbocation is most supported during the substitution reaction.



Scheme 4.11. R=C_7H_{15} and R'=$(CH_2)_5$Ph. Reagents and conditions. (i) mCPBA, DCM, 0 °C, 75%; (ii) HF-Pyridine, 0 °C, DCM.

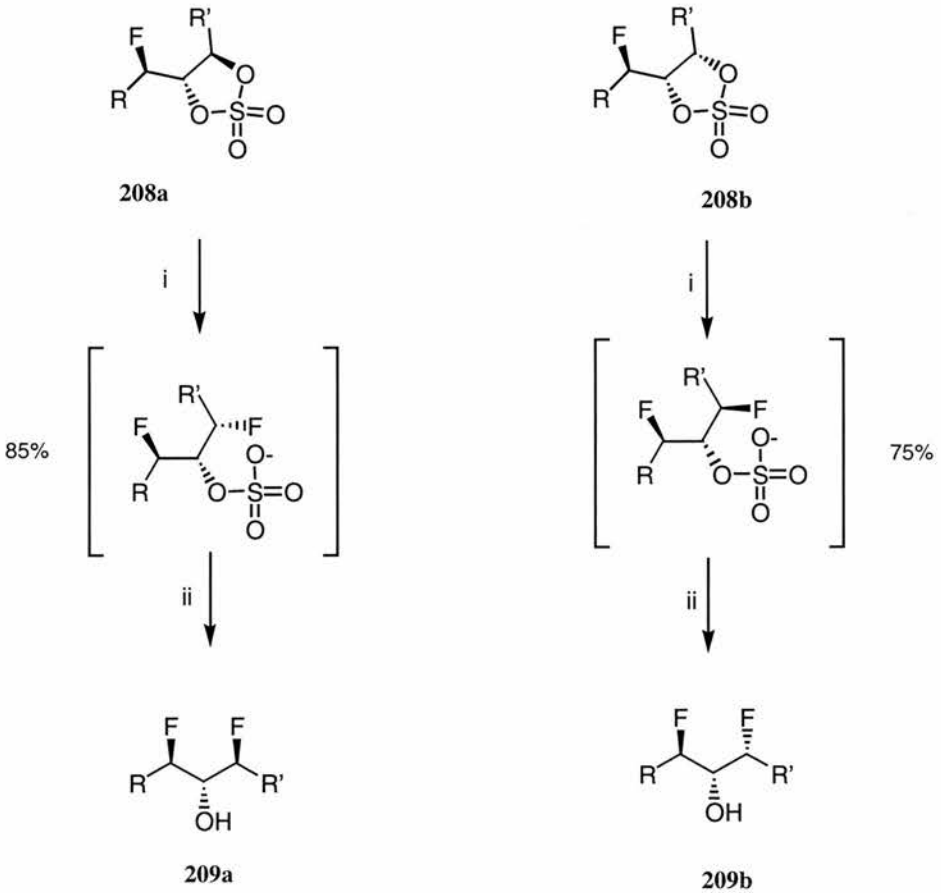
4.3.4 TBAF ring opening of cyclic sufates (**208a** and **208b**)

The second C-F bond was introduced once more *via* reaction of TBAF with the appropriate cyclic sulfate. The cyclic sulfates were prepared *via* the two step procedure discussed in **section 4.2.3.2.** This consists of the initial formation of a cyclic sulfite by treatment of the corresponding vicinal diols (**207a** and **207b**) with thionyl chloride, followed by a straightforward oxidation with RuO_4 **(scheme 4.12)**.



Scheme 4.12. R=C_7H_{15} and R'=$(CH_2)_5Ph$. Reagents and conditions. (i) Thionyl chloride, pyridine in DCM, 0 °C 45 min then $NaIO_4$/ $RuCl_3$ in CH_3CN/H_2O, 0 °C 1 h; (ii) TBAF in acetonitrile, 0 °C 1 h; THF/H_2SO_4 conc RT 2 h.

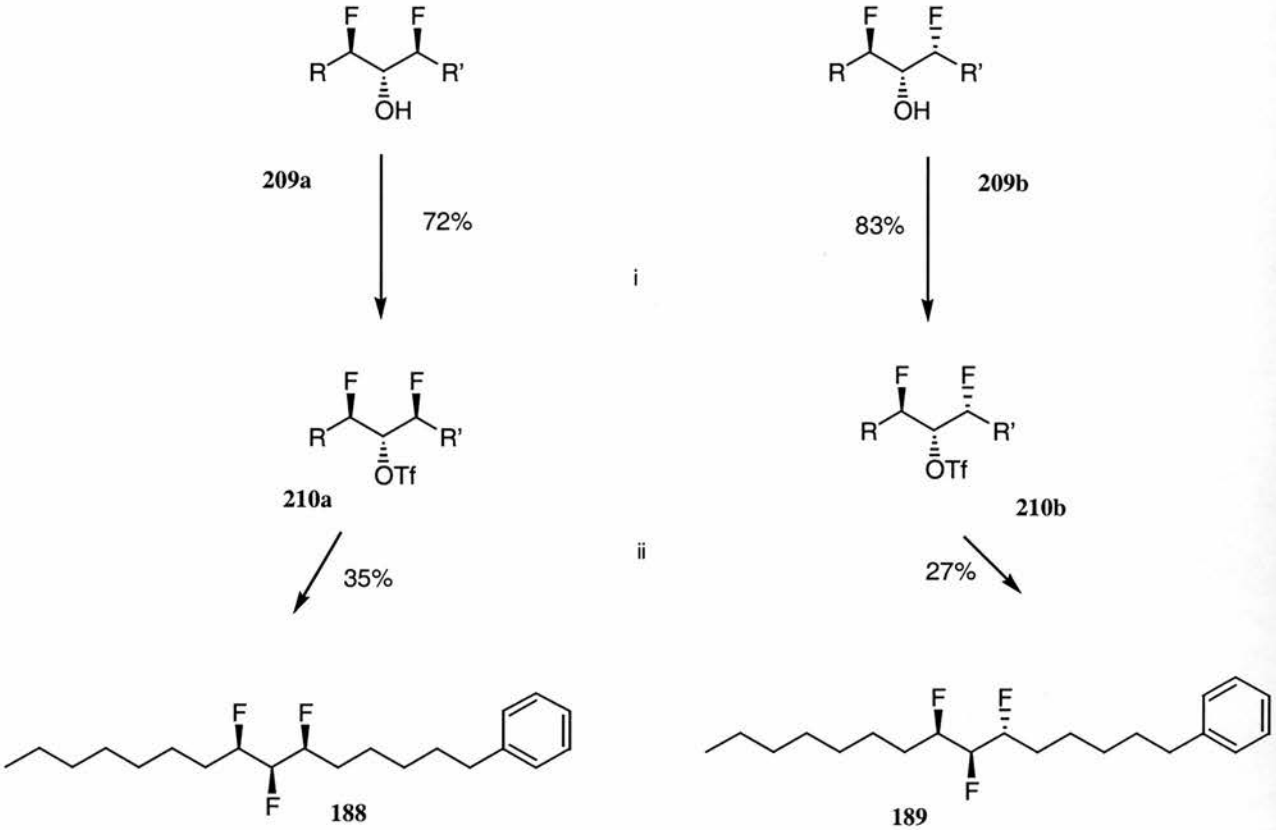
Cyclic sulfates **208a** and **208b** were then reacted with TBAF in acetonitrile and the resultant difluorinated sulfates were obtained. Hydrolysis using conc. H_2SO_4 in THF gave the difluoro alcohols **209a** and **209b** in a good yield. Nucleophilic attack by fluoride ion resulted again in a totally regio- and stereo- specific reaction with the nucleophile attacking exclusively at the C(3) of the cyclic sulfates **(scheme 4.13)**. The high selectivity is perhaps attributed to the preference of fluoride ion to attack the less hindered position of the sulfate ring system, and distant from the electron withdrawing C-F bond.



Scheme 4.13. Reagents and conditions. (i). TBAF in acetonitrile, 0 °C 1 h; (ii). THF/H_2SO_4 conc RT 2 h.

4.3.4.1 Introduction of the third fluorine

The third fluorine atom was introduced again by a fluoride substitution reaction. The remaining OH of **209a** or **209b** was first transformed into a good leaving group and then reacted with a F^- source. As shown in **scheme 4.14,** the alcohol functionality (**209a** or **209b**) was straightforwardly converted to the corresponding triflates (**210a** or **210b**) by treatment with triflic anydride and pyridine at –50 ^{0}C. The displacement of the triflate group was then successfully achieved with 2 equivalents of TBAF to produce the desired trifluoro alkanes (**188** and **189**). This reaction was also accompanied by elimination products visible by spectroscopic methods. However the mixture was found to be difificult to resove by conventional chromatographic methods.



Scheme 4.14. Reagents and conditions. R=C_7H_{15} and R'=$(CH_2)_5Ph$. (i) Tf_2O, DCM –40 °C; (ii) TBAF, acetonitrile, 0°C 15 min.

4.4 ^{19}F NMR analysis of trifluoroalkanes

Both series of the vicinal trifluoroalkanes were analysed by ^{19}F {^{1}H} NMR spectroscopy. The three fluorine atoms displayed very different chemical shifts as shown in **figure 4.3.** The difference is comprehensible for compounds **186** and **187** where each fluorine atom is positioned in a very different chemical environment. Whereas the large difference in chemical shifts of F(1) and F(3) is less understandable for compound **189,** where the two fluorines mentioned above are in a much similar chemical environment. Perhaps such large difference in chemical shifts is derived from the *fluorine gauche effect.*

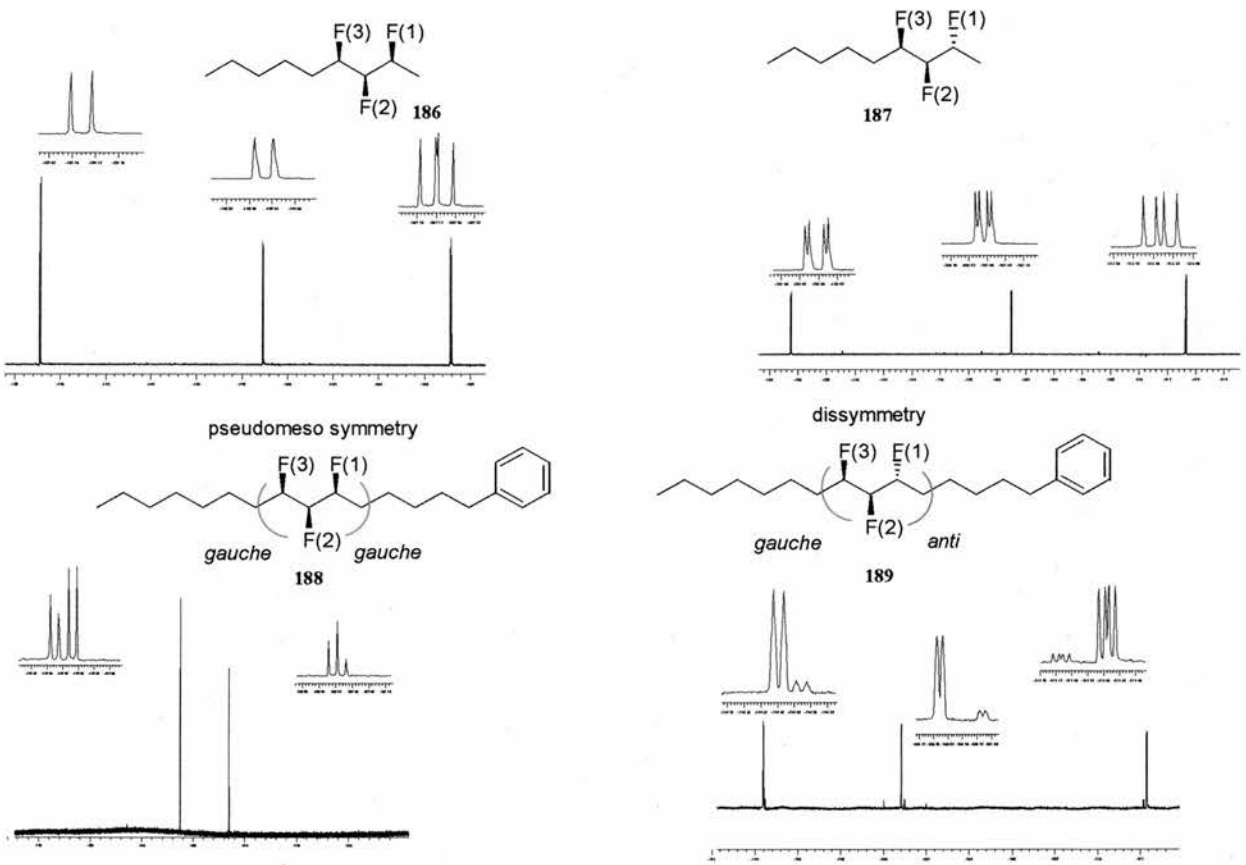
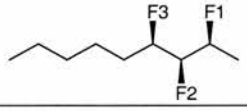
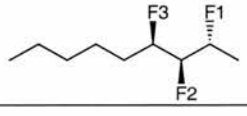
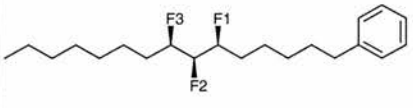
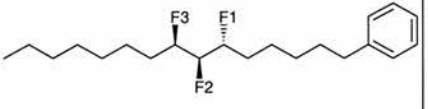


Figure 4.3. ^{19}F {^{1}H} NMR spectra of trifluroalkanes **184-187**

Compound (**188**) possesses a certain symmetry derived from the fact that all the three fluorine atoms are *syn* to each other. On the other hand (**189**) possesses both an *anti* relationship between F(1) and F(2) and a *syn* relationship between F(2) and F(3). Additionally, the two sets of diastereoisomers displayed similar NMR characteristics.

magnitudes of the fluorine-fluorine coupling constants and chemicals shifts are similar within each diastereomeric series and they are clearly characteristic of that stereochemistry, as shown in **Table 4.1**. There is a clear analogy between compounds **186** and **187** and **188** and **189**. The **186** and **188** isomers which have the three fluorine all in *gauche* have both $J_{F1\text{-}F2}$ and $J_{F2\text{-}F3}$ around 12 Hz on the other hand compound **187, 189** have $J_{F1\text{-}F2}$ value around 14 Hz and $J_{F2\text{-}F3}$ around 9 Hz.

Table 4.1

Entry		**Chemical Shift in ppm and multiplicity**			**J_{FF} Coupling constants in hertz**		
		F1	**F2**	**F3**	**$J_{1\text{-}2}$**	**$J_{2\text{-}3}$**	**$J_{1\text{-}3}$**
1 **(186)**		-189 d	-207 dd	-199 d	12.9	11.2	-
2 **(187)**		-185 dd	-213 dd	-201 d	14.4	9.3	3.4
3 **(188)**		-197 d	-207 t	-197 d	12.3	12.3	-
4 **(189)**		-194 d	-212 dd	-200 d	14.9	9.2	-

4.5 Conclusion and Future work

In summary the first synthetic method has been developed for the stereospecific synthesis of vicinal trifluoroalkanes, and provides access to this novel class of molecules. The structural motif of this new class of organo-fluorine compounds hold some future promise in the design of performance materials. For example the synthesis of building block (**211**) could give access to the synthesis of the novel ferroelectric liquid crystal (FLC) (**212**) analogues of the well known FLC's such as (**185**). The potential synthetic route would start from a readily available (**figure 4.4**) starting material and using the chemistry already evaluated in the St. Andrews laboratories and as discussed in this thesis. These compounds are required to be prepared in optically pure forms, a prerequisite of the ferroelectric response. However we have shown that this is achievable using Sharpless asymmetric epoxidations methods.

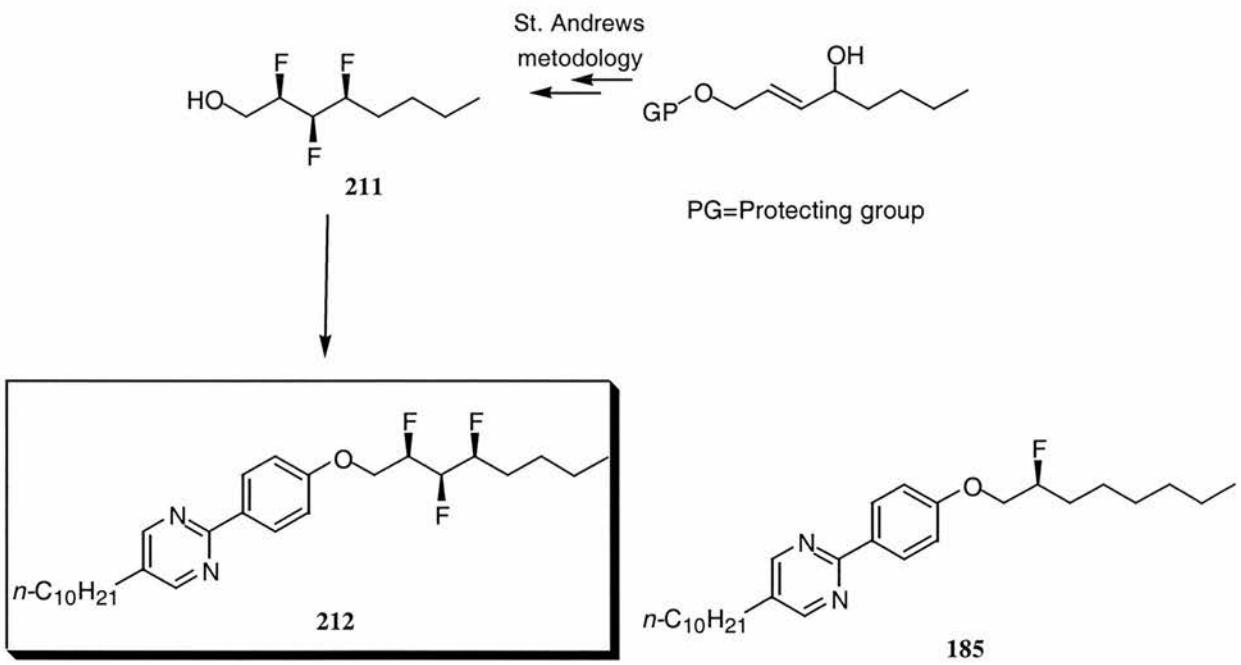


Figure 4.4. Trifluoroderivative compound as potential FLC.

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5 Synthesis of new Fluorous Phase reagents containing Nitrogen

Part A

5.1 Introduction

This Chapter introduces the concept of the *Fluorous Phase,* a new technique and strategy for reaction and separation in organic chemistry. This concept was first proposed in a Ph.D thesis by Vogt[1] in 1991 and later independently brought to the scientific community by the seminal work of Horváth and Rábai,[2] who also coined the term of *Fluorous* for perfluorinated solvents, in analogous way to "aqueous" for water-based system. However, unlike water the miscibility of fluorous molecules with organic solvents is strongly temperature dependent. This characteristic has been crucial for the success of fluorous chemistry and its applications, particularly in catalysis.

5.1.1 Perfluorinated solvents

Perfluorocarbons (PFCs) are defined as those saturated fluids such as alkanes, alkenes, ethers or amines in which all hydrogen atoms have been replaced by fluorine atoms.[3] Perfluorinated solvents are liquids of high density, colourless, non toxic and they are remarkably hydrophobic. Unlike the volatile halofluorocarbons, PFCs are not ozone-depleting compounds although their high stability expressed by their long atmospheric lifetime (>2000 years) makes them potent greenhouse gases. It emerges that PFCs are excellent solvents for gaseous substances, being able to dissolve significant quantities of oxygen (twice as much as the corresponding hydrocarbon[4]), nitrogen and carbon dioxide, but they are poor miscible with organic solvents. The miscibility with the organic media is thermo-and pressure-dependent. The phase diagram in **figure 5.1** shows the miscibility and

the critical temperature (Tc)* of two liquids (benzene and pefluoromethylcyclohexane (PFMCH)). For example equal volumes of benzene and perfluoromethylcyclohexane are completely miscible (forming one phase) at temperatures above 75 °C.

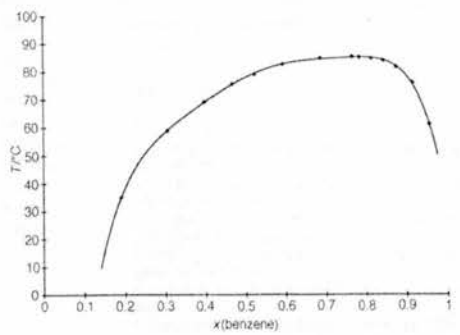
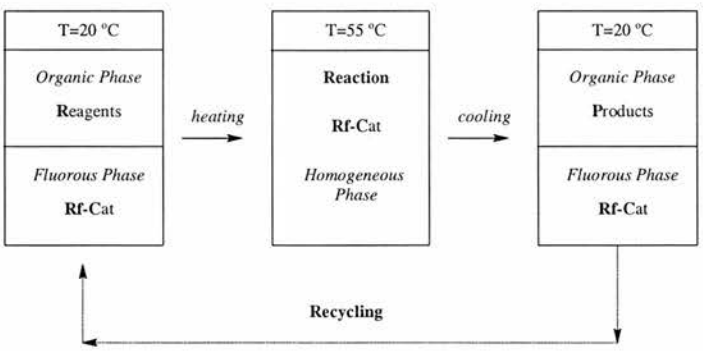


Figure 5.1. Phase diagram of perfluoromethylcyclohexane and benzene; x= mole fraction of benzene (redrawn from data in ref[5])

The thermo controlled miscibility of perfluorocarbons with organic solvents is the basis of a *Fluorous Biphase Chemistry*[6] and its resulting applications particularly in catalysis. A typical *Fluorous Biphase System* consists of a fluorous soluble reagent or catalyst (RF-**C**at) in a fluorous solvent (*e.g.* perfluorodecalin) and a second phase which is generally a typical organic solvent (*e.g.* hexane) containing the organophilic reagents. On warming, the two phases become completely miscible (in our case at ca. 50-55 °C) providing a homogeneous phase which allows catalysis to occur. On cooling, the system returns to a genuine biphasic system, with the fluorous catalyst immobilised in the fluorous solvent (**Scheme 5.1**).



Scheme 5.1. The Fluorous Biphase System (FBS) strategy

Thus, a fluorous biphase system can combine the advantages of homogeneous catalysis with the liquid-liquid separation technique. The availability of fluorous solvents within a wide range of boiling points, ranging from 56°C for perfluorohexane to 220 °C for

* Tc is the temperature above which two liquids are miscible in all ratios.

perfluorotripentylamine, allows a variety of reactions to be performed under various conditions.

5.2 "Fluorophilic" Molecules

A suitable catalyst or reagent for a FBS reaction must partition preferentially in the fluorous phase. This is obtained by attaching appropriate perfluorinated group or "ponytails" to the active site of the molecule as shown in **figure 5.2.** To quantify the extent of the fluorous phase preference for a compound Rabai[7] *et al* have introduced the concept of specific *fluorophilicity* (*fi*) expressed by the **equation 5.1:**

$$fi = \ln Pi = \ln\left[\frac{ci(CF_3C_6F_{11})}{ci(CH_3C_6H_5)}\right], \quad T = 25\ ^0C$$

According to this equation, the fluorophilicity of a generic compound "i," is a function of the partition coefficient (*Pi*) between two solvents (e.*g.* perfluoromethylcyclohexane $CF_3C_6F_{11}$ and toluene $CH_3C_6H_5$) at 25 ^{0}C, and a compound is fluorophilic when the value of *fi* is positive. However the fluororphilicity of a substance can be predicted by some empirical rules derived from experimental data:

- ✓ *Fluorine content*. The total fluorine content of a fluorous compatible molecule should be at least above 60%.
- ✓ *Length of fluorous ponytails*. Generally, longer fluorous ponytails increase the fluorophilicity of a molecule, but in contrast decrease the absolute solubility.
- ✓ *Number of fluorous ponytails*. Usually, increasing the number of perfluoro ponytails results in higher *Pi.*

✓ *The structure.* Functional groups which are responsible of intermolecular interactions have a negative effect on the fluorophilicity and should be limited (e.g. H-bonding interactions).

Therefore, the design of fluorophilic molecule should also consider the strong electron-withdrawing properties of the fluoro ponytails. This can be controlled by the insertion of "spacer" usually two or three[8] CH_2 groups capable of insulating the reactive centre of the molecule as shown in **figure 5.2.**

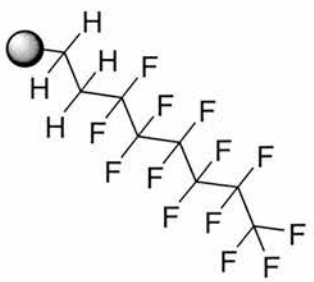
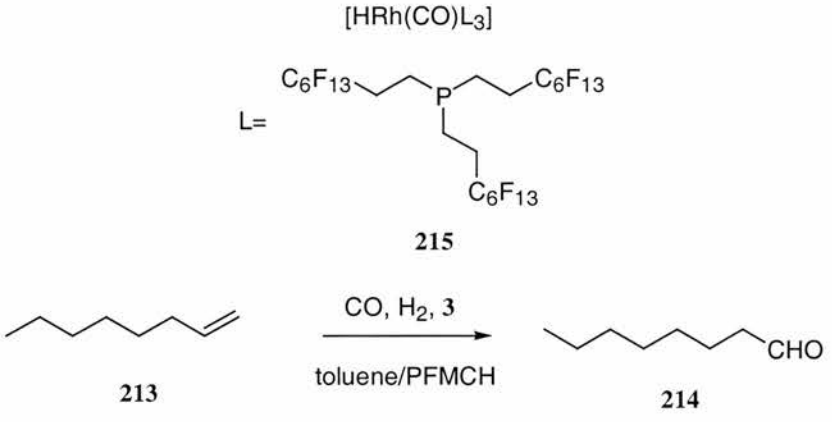


Figure. 5.2 An example of fluorophilic molecule where the reactive centre is represented with the solid sphere and is separated from the fluorous ponytail by two methylenes groups.

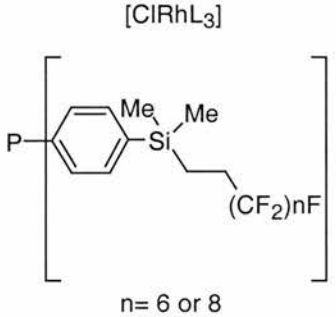
5.2.1 Fluorous Catalysts

The special physical properties of perfluorinated compounds are ideally suited for catalysis and it is not surprising that the main field of application for fluorous phase chemistry is in fluorous biphasic catalysis (FBC). Generally the catalyst is modified with a fluorous tag such that the catalyst can be removed from the product by washing with a perfluorous solvent. The reaction can proceed either in a heterogeneous biphasic fashion or under homogeneous conditions, if the temperature is raised such that the biphasic solvent becomes homogeneous. However in the latter situation, the phases are separated at the end of the process by cooling the system again and the products can be recovered free of catalyst contamination. This avoids purification procedures such as chromatography or distillation. One of the most studied and widely applied methods in FBC has focussed on the development of monodentate florous phosphines as suitable ligands for various metals.

In 1994, Horváth and Rábai first reported the hydroformylation of 1-octene (**213**) in 85% conversion to the corresponding aldehyde (**214**) catalysed by rhodium complex (**215**) at 100°C and 10 atm of syngas[2] **(scheme 5.2)**.



215 **213** **214**



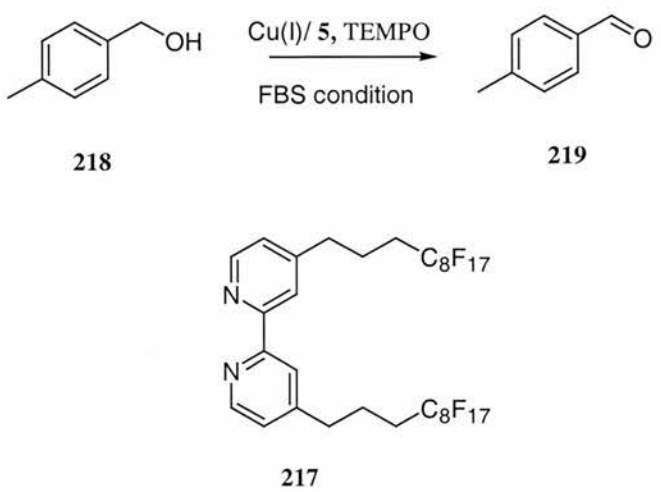
216

Scheme 5.2. Hydroformylation of terminal olefins with an *in situ* generated fluorous rhodium catalyst. ((PFMCH) perfluoromethylcyclohexane)

215 has also been employed in hydroboration[9] and hydrosylation[10, 11] and the analogue of Wilkinson's catalyst (**216**) has been also used as catalyst for hydrogenation[12] in fluorous biphasic systems.

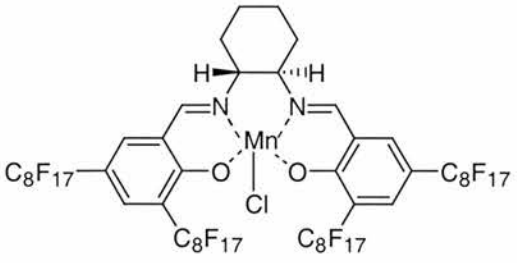
Palladium–catalysed C-C bond forming reactions have been also performed in the fluorous phase system and these have included the Heck[13], Negishi[14], Stille[15], Suzuki[16] and Sonogashira[17] reactions. The fluorous media are especially suitable for oxidation reactions since the solubility of the oxygen is very high in fluorous solvents.[18, 19] For example Betzemeier *et al.* have demonstrated that the catalyst generated *in situ* from the

perfluoroalkylbipyridine **217** together with $CuBr{\cdot}Me_2S$ (2 mol%) and 2,2,6,6-tetramethylpiperidine-N-Oxide (TEMPO) (3.5 mol%) in a fluorous biphasic system is excellent for the aerobic oxidation of alcohol (**218**) to aldehyde (**219**).[20] The catalyst could be recycled and used for eight cycles without loss of activity (**scheme 5.3**).



Scheme 5.3. Oxidation of 4-methyl-benzylalcohol with fluorous bipyridine

There are several examples of epoxidation reactions on olefins performed by fluorous compatible catalysts. The greater challenge has been in developing fluorous compatible asymmetric epoxidation catalysts. For example, Pozzi *et al.* have synthesised the optically active (salen) manganese(III) complexes of **(220)** (Jacobsen-Katsuki type analogue) in **figure 5.3** which catalyses the aerobic epoxidation of alkenes in presence of various oxygen donors in FBS[21]. Surprisingly, many advantages with respect to the classic homogenous system were observed including an increased stability towards bleaching, and the activity of the catalyst remained high after recycling.[22]



220

Figure. 5.3. Chiral Mn(III) complex soluble in Fluorous Phase

The same fluorous-salen ligand (**220**) and closely related analogues were also used by Maillard *et al.* in the iridium catalysed asymmetric reduction of ketones, using an isopropanol/perfluorooctane biphase system. Enantiomeric excesses of up to 60% were observed.[23]

5.2.2 Fluorous Reagents

Fluorous reagents can be used to separate the by-products or excess reagents from the products of a reaction. This can be achieved by extraction with an appropriate fluorous solvent or by filtration over Fluorous Phase Silica Gel (FPSG).

There are examples of fluorocarbon bonded silica gel (fluorous reverse phase silica gel) that can be used to purify fluorous from organic molecules using this solid-liquid process. In such cases a reaction mixture is charged on the column. The silica is eluted first with an organic solvent to remove the organic reagents and then with a fluorophilic solvent to clearly collect the fluorous reagents as shown in **figure 5.4.**

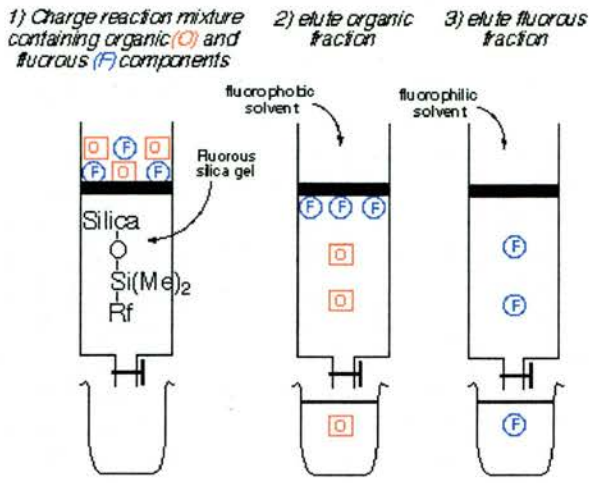
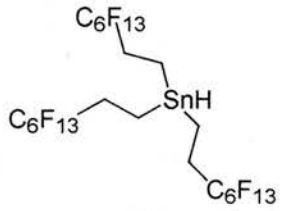


Figure 5.4. Fluorous phase silica gel.

This approach is especially attractive for those reactions which require the use of toxic, expensive or difficult to remove compounds. The toxicity of trialkyl tin reagents and selenium compounds is well known. Notably Curran[24] and co-workers have developed fluorous compatible tin reagents (**221**) as shown in **figure 5.5**.

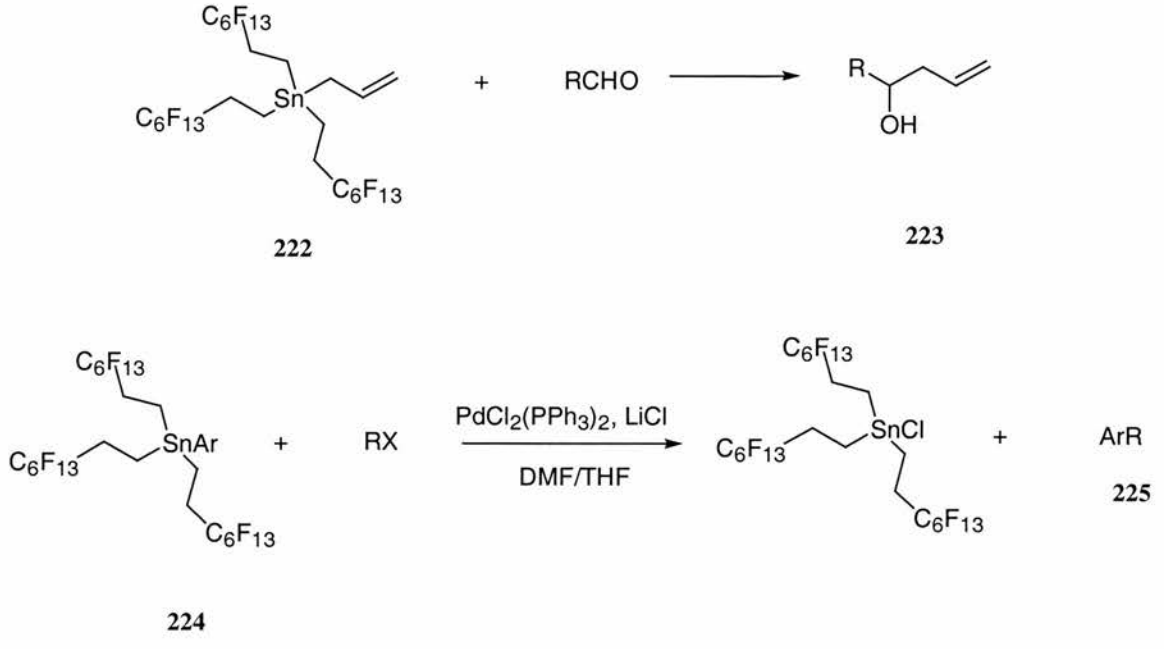


221

Figure 5.5. Perfluorinated analogue of tin hydride

In the presence of AIBN (10%) these catalysts can reduce various functional groups (*e.g.* R-Br). The reactions are carried out in the homogeneous phase and at the end the solvent benzotrifluoride ($C_6H_5CF_3$) is evaporated. The products are isolated by extraction in a biphasic mixture (DCM/PFMCH).[24] Fluorous tin reagents have been used also in the allylation of aldehydes. The allyl stannane (**222**) reacts with the aldehyde in the absence of solvent to generate allylic alcohols (**223**). The reaction mixture is purified by extraction of the tin treagents with a fluorous solvent or by FPSGC[25]. Cross coupling reactions (*e.g.* Stille coupling) have also been performed using fluorous stannanes (**224**) to yield the

corresponding product (**225**) which was isolated from the reaction mixture as described before[26] (**scheme 5.4**).



Scheme 5.4. Fluorous tin reagents

5.3 Recent developments in Fluorous chemistry

Although perfluorocarbon media are believed to play no significant contribution to ozone depletion they are coming under scrutiny because of their difficulty of disposal. Therefore there is an increasing requirement to develop alternative reaction methods which reduce the amount of fluorous media. Recently, several modifications of the classical FBS protocol have been provided. For example, Gladysz *et al.* have used FBS catalysis without any fluorous medium[27]. They noticed that the same factors that give temperature-dependent miscibility between fluorous media and organic media can also be valid for a highly solid fluorous catalyst in organic media. A fluorous catalyst, which normally has a low melting point, when heated at T near the melting point, forms a homogenous phase with the organic media allowing homogeneous catalysis (**figure 5.6**) in the organic medium. At the end of the process, the mixture is cooled and the catalyst separates again from the organic products and can be recycled without the use of any fluorous solvents.

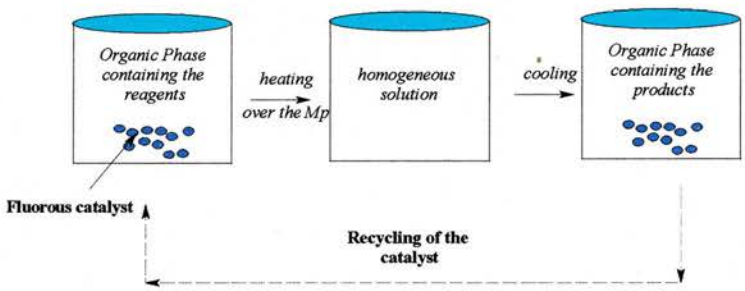
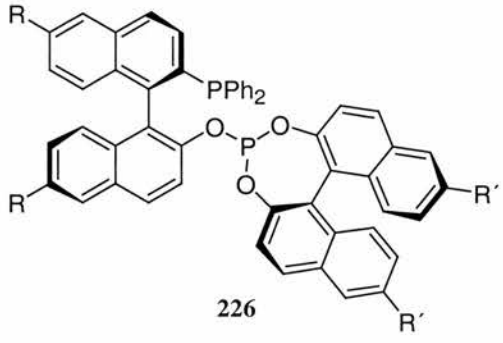


Figure 5.6. Fluorous catalyst recycling based on liquid/solid phase separation

The high affinity of fluorocarbons for gases led to the opportunity of replacing the fluorous media with supercritical fluids (SCFs). The supercritical state is the state in which the distinction between gas and liquids disappears and the physical properties of the SCF are intermediate between those of a liquid and a gas. The critical point represents the highest pressure (p_c) and temperature (T_c) at which the vapour and the liquid of a substance can exist in equilibrium. The properties of the SCFs such as polarity, viscosity and solubility properties vary with the temperature and the pressure. In principle, by adjusting the T and P

of SCF it is possible to change the reaction conditions and selectivity. Another important feature of SCFs is their total miscibility with gases, a characteristic which makes the SFCs an ideal medium for reactions as hydrogenation, hydroformylation and oxidation. Among these are different SCFs, carbon dioxide is the most widely used as it becomes supercritical ($sc CO_2$) at Tc=31.1 °C and pc= 73.8 bar allowing reactions to be performed under mild conditions. $sc CO_2$ is finding many applications as a solvent in clean synthesis because it is non toxic and can be completely removed from the reaction just by releasing the pressure from the reactor. Therefore, $sc CO_2$ is a clean alternative to fluorous media. In fact, Ojima and coworkers[28] have prepared a fluorous BINAPHOS ligand (**226**) in **Figure 5.7** for rhodium-catalysed asymmetric hydroformylation and the catalysis was performed successfully in $sc CO_2$.



226

R, R`= H or $Rf(CH_2)_n$

Figure 5.7. Fluorous catalyst for utilization in supercritical CO_2

Part B

5.4 Synthesis and potential application of fluorinated amine reagents

5.4.1 Aims of the project

This aspect of the project was part of a collaboration between members of a EU Research Training Network (RTN Fluorous Phase) which involves several laboratories throughout Europe (UK, Italy, Hungary, France and Germany). The aim of the Network was to develop new reagents and catalysts for reaction in the Fluorous Phase. The aim of the St. Andrews laboratories was to develop a new class of perfluorinated amines to employ them in catalytic and stoichiometric reactions performed in the fluorous phase.

The amines synthesised are illustrated in **figure 5.8**. Initially, the work has focused on the synthesis of amines such as the morpholine analogue (**227**) in which the nitrogen atom is linked to a long perfluorinated ponytail through one CH_2 spacer. This reagent exhibits basic properties and had the potential to be used in reactions in a fluorous phase which require the use of an organic base. Assuming the successful synthesis of the fluorous amine (**227**), it was anticipated that the corresponding N-oxides (**228**) could also be prepared and used in a variety of applications. For example, the parent, *N*-methylmorpholine *N*-oxide (NMO), is a strong oxidizing agent and is used in organic synthesis to regenerate osmium tetroxide. The reaction of an olefin with osmium tetroxide is the most reliable method for *cis*-dihydroxylation of a double bond, particularly for preparation of *cis*-diols on the least hindered side of the molecule. However, osmium tetroxide is volatile and toxic, resulting in handling problems and catalytic osmylation to regenerate osmium tetroxide avoids some of these problems.[29, 30]

The most challenging aspect of the research programme was the synthesis and use of fluorous chiral amines. Mono branched chiral amines (**229, 230**) were designed, starting from commercially available (*S*)-phenylethylamine, with the intention to apply them in the fluorous phase. Assuming the successful synthesis of the fluorous amines (**229-230**), the

work was aimed at the synthesis of di-branched chiral amines (**230-232**) with the aim to convert them to their quaternary ammonium salts, and employ them as chiral phase transfer catalysts in reactions performed in biphasic fluorous/organic systems. The C_2-symmetric diamines (**233** and **234**) were prepared as potential ligands to chelate metals such as Cu and Ni for catalysis.

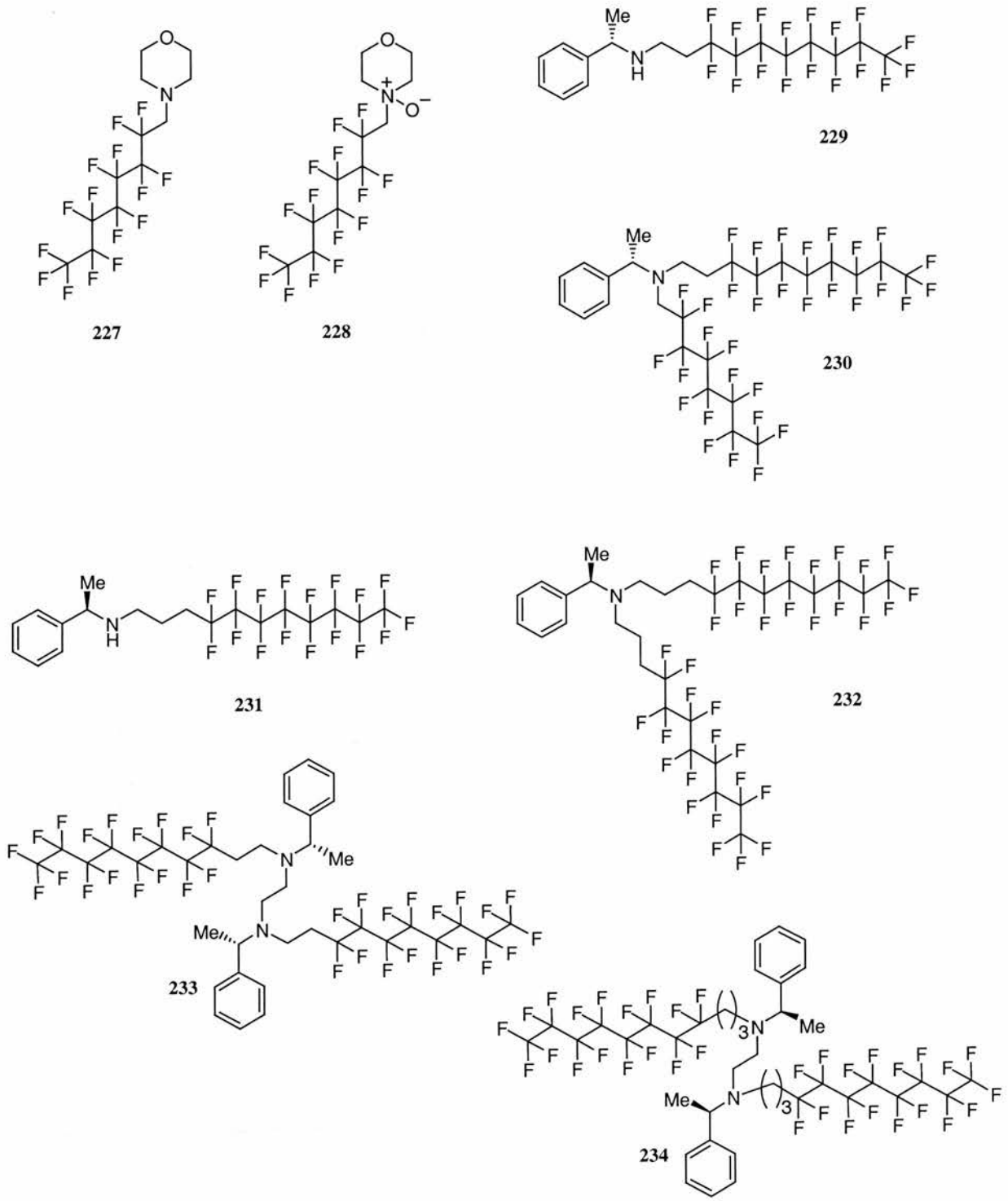
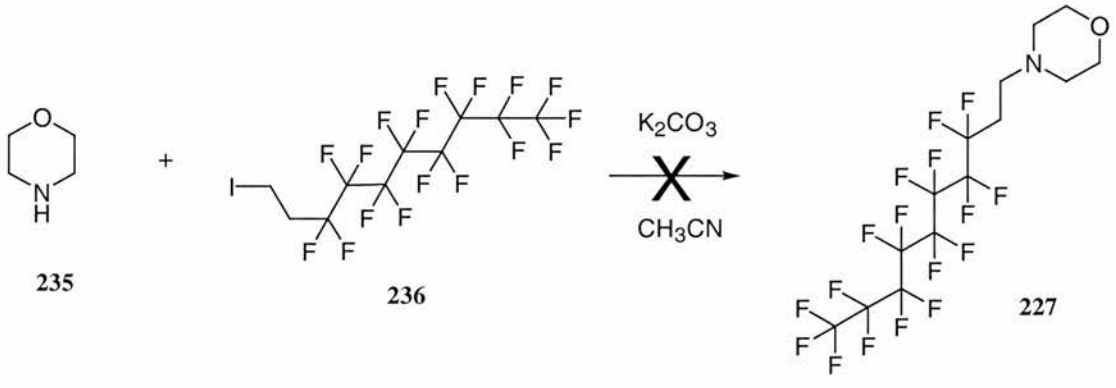


Figure 5.8. Fluorous compatible amines target structures.

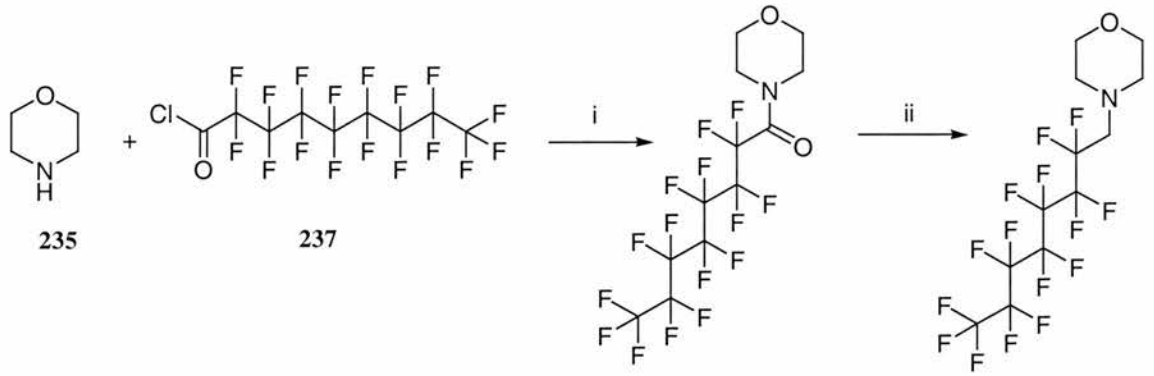
5.4.2 Synthesis of morpholine analogue (**227**)

The alkylation reaction, shown in **scheme 5.5**, was attempted in order to prepare the corresponding fluorous morpholine derivative (**227**).Amine (**227**) is designed with two CH_2 spacers between the N atom and the perfluorinated chain, to insulate the fluorines from nitrogen and retain its basicity.



Scheme 5.5. Attempted synthesis of fluorous morpholine derivative

It is a classical example of N-alkylation[31] in which potassium carbonate is used to neutralize the hydrogen iodide formed during the reaction. Direct alkylation of morpholine (**235**) was attempted, however this proved unsuccessful. This failure is attributed to an elimination reaction that competes with the required nucleophilic substitution reaction. Morpholine is a strong base (pK_b=5.7) and the elimination reaction is much more favoured than the N-alkylation. This is also facilitated by the increased acidity of the proton *alpha* to the perfluorinated chain. Therefore a different approach to the synthesis of the fluorous morpholine derivative was taken and shown in **scheme 5.6.** The commercially available, pentadecafluoro-octanoyl chloride (**237**) was reacted with morpholine (**235**) to generate first the amide (**238**) which was subsequently reduced to fluorous morpholine (**227**). Generally amide formation is carried out using an excess of acyl chloride and TEA as a catalyst in DCM. It was decided however to carry out the reaction with an excess of morpholine (**227**) but in the absence of triethylamine (TEA). The amide (**238**) was obtained in excellent yield and was subsequently reduced using a solution of borane in tetrahydrofuran (THF) according to Brown's protocol[32] to generate the mono branched fluorous morpholine (**227**) carrying one CH_2 spacer between the N and the perfluorinated chain.



Scheme 5.6. Reagents and conditions. (i) CH_2Cl_2, 2h, 25°C, (96%); (ii) BH_3 / THF reflux, 1h (70%).

5.4.3 The synthesis and application of N-oxide derivative (**228**)

Alkyl and aryl tertiary amines are readily converted to their corresponding stable N-oxides under a variety of conditions such as treatment with mCPBA.[33] Some supported polymer-bound amine N-oxides (**239, 240**) (**figure 5.9**) have been synthesised and their use in organometallic cluster chemistry demonstrated [34].

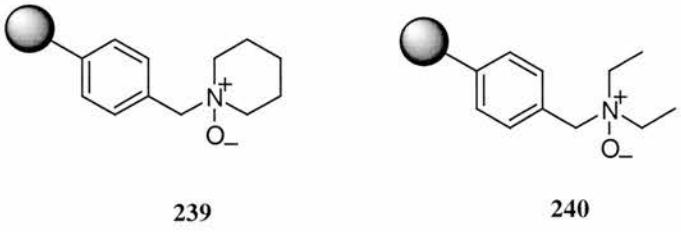
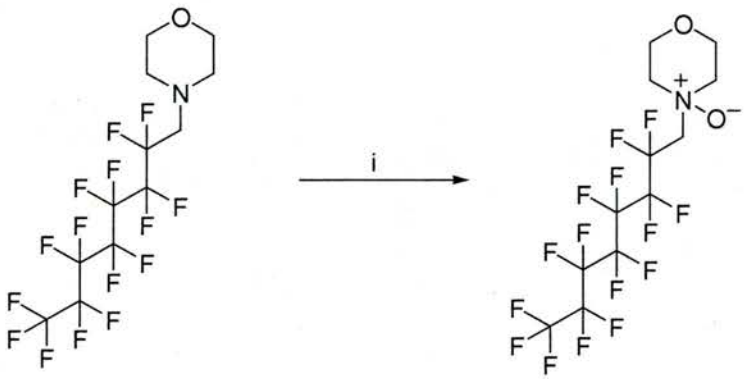


Figure 5.9. Polymer supported N-oxides

It was decided to use fluorous phase technology to the same effect in place of solid phase chemistry. For this reason N-oxide N-perfluorinated morpholine was synthesised as shown in **scheme 5.7**. Morpholine derivative (**227**) was stirred at 0 °C for 12 hours with mCPBA.

This generated the N-oxide derivative as a crystalline material suitable for X-ray structure analysis.



227 228

Scheme 5.7. Reagents and conditions. (i) mCPBA, CH_2Cl_2, 12h, 0°C, (80%).

The resultant structure is shown in **figure 5.10.** The ring is in the chair conformation with the N-O oxygen axial and the long perfluorinated chain lying *zig-zag* and equatorial.

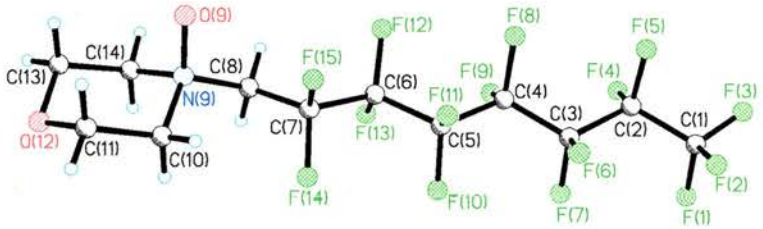
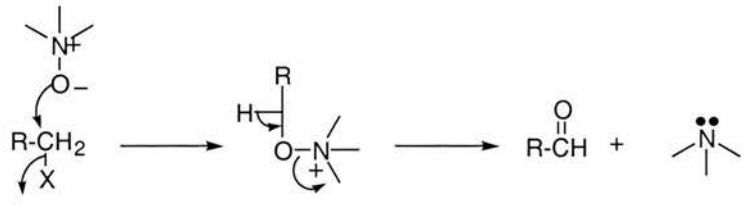


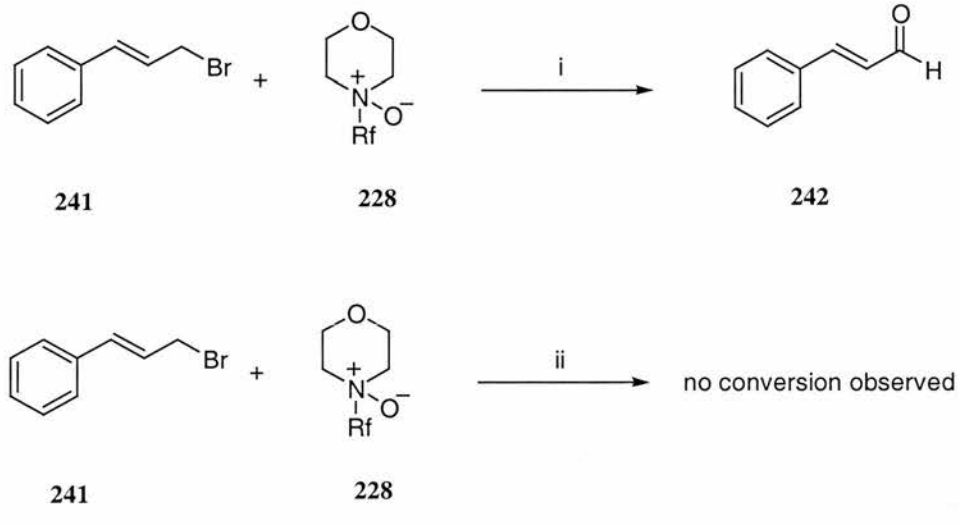
Figure 5.10. X-Ray structure of N-oxide (**228)**

The reactivity of the N-oxide (**228**) was tested in the conversion of primary aliphatic halides into aldehydes.[35-37] The reaction involves nucleophilic displacement of the halide by N-O oxygen, followed by a base-induced elimination *via* cleavage of the heteroatom-heteroatom bond to form the aldehyde (**scheme 5.8).**



Scheme 5.8. Oxidation of halides into aldehydes employing N-Oxides

The reactions were carried following Chandrasekhar's protocol,[37] and cinnamyl bromide (**241**) was stirred together with N-oxide (**2**) in acetonitrile. The formation of cinnamyl aldehyde (**242**) was monitored by ^{1}H NMR and after 30 h reflux the conversion reached 50%. The low conversion is probably due to the poor solubility of the N-oxide reagent in the organic solvent. The same reaction was also carried out under fluorous biphase (hexane:perfluorodecalin), but the reaction was unsuccessful due to the very poor solubility of the N-Oxide (**228**) in both phases (**scheme 5.9**).



241 **228** **242**

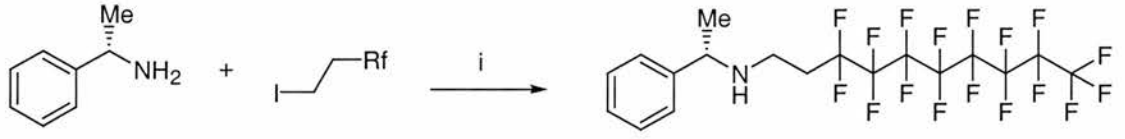
241 **228**

Scheme 5.9. Reagents and conditions. (i) Acetonitrile, 30h, 50 °C, (50%); (ii) perfluorodecalin/hexane 30h, 50 °C.

5.5 Synthesis and application of chiral fluorous amines

The main objective of the fluorous phase RTN project was to develop a new class of chiral amines soluble in fluorous media and to demonstrate their use as reagents or catalyst for straightforward organic reactions performed in fluorous phase.

The first chiral amine designed (**229**) was accessed by reaction of the (*S*)-alpha phenylethylamine (**243**) with the perfluoroalkyl iodide derivative (**236**). The best yields (54%) were achieved using an excess of amine (2.5 equivalent) rather then an excess of the alkyliodide derivative (**scheme 5.10**).

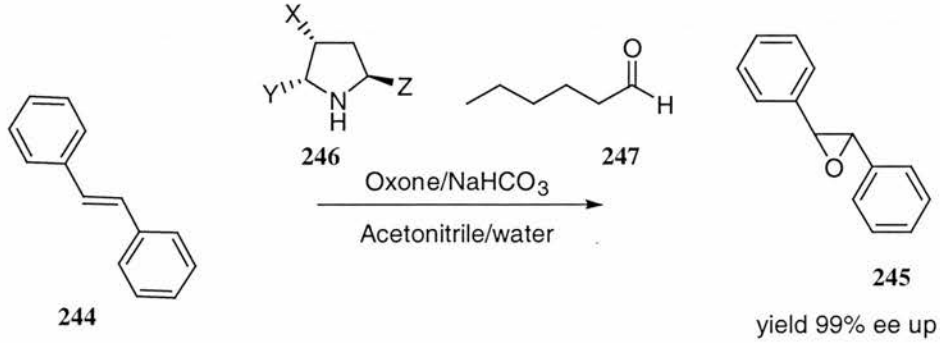


243 **236** **229**

Rf= $CF_3(CF_2)_7$-

Scheme 5.10. Reagents and conditions. (i). Acetonitrile, K_2CO_3, 24h, reflux (54%).

Amine (**229**) was then used as catalyst for the asymmetric epoxidation of olefins. There are a few examples in the literature[38, 39] where chiral oxaziridinium salts catalyse the asymmetric epoxidation of olefins. For example, *trans*-stilbene (**244**) is converted to *trans*-stilbene oxide (**245**) by reaction with amine (**246**) and aldehyde (**247**) and in presence of oxone (**Scheme 5.11**).



246 **247** **244** **245**

yield 99% ee up to 30%

Scheme 5.11. Asymmetric epoxidation of *trans*-stilbene with amine (**246**)

Scheme 5.12 shows a mechanism for the reaction. The iminium salts which can be formed *in situ* is oxidised by oxone to an oxaziridinium species which catalyses the epoxidation of the olefin

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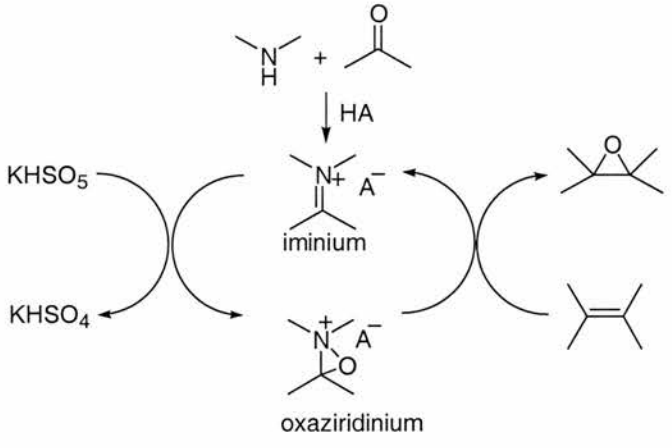
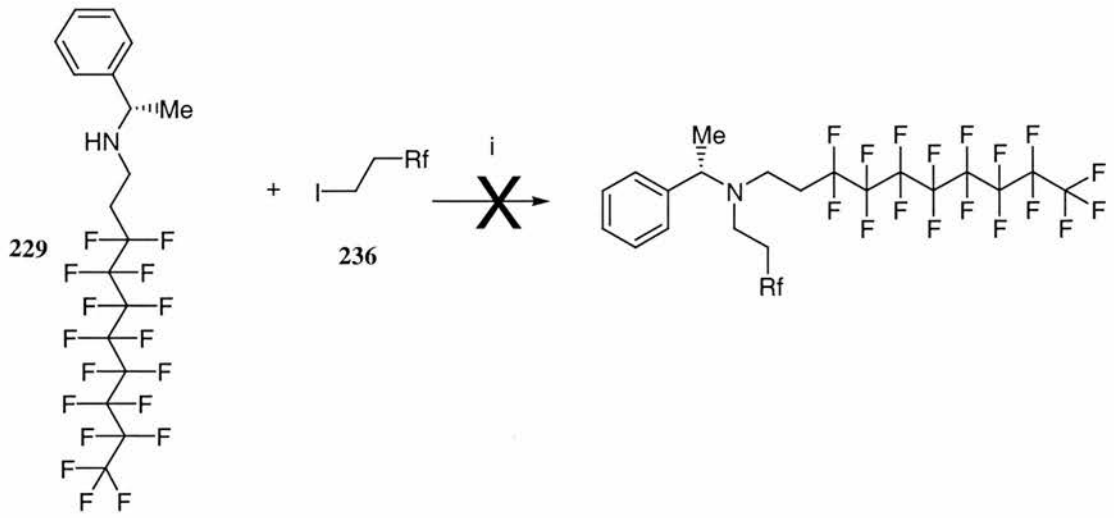


Scheme 5.12. Mechanism of the epoxidation of olefin catalysed by an oxaziridinium species.

The reaction conditions used previously **scheme 5.11** [39] were followed for the chiral amine (**229**) but catalysis was not observed even after 36 hours.

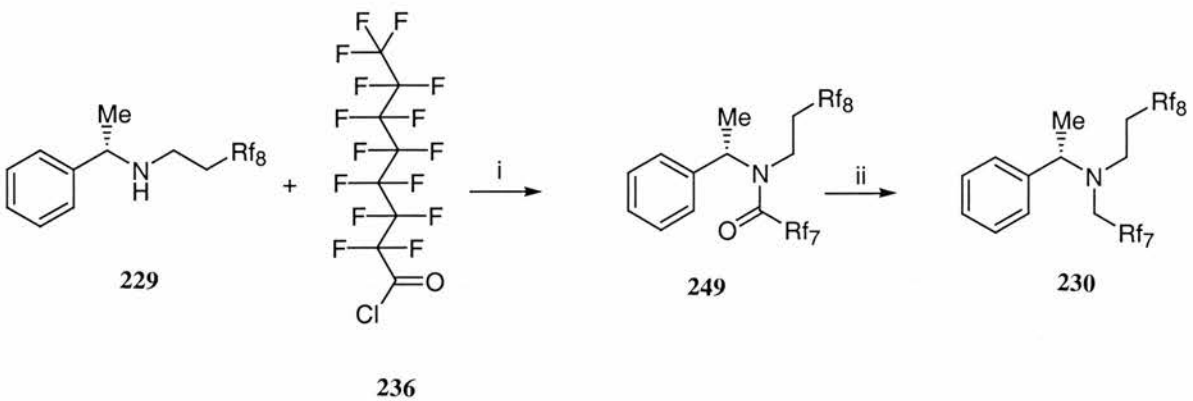
We conclude that the nitrogen atom is a poor nucleophile due to the electron withdrawing property of the perfluorinated chain. Amine (**229**) carrying one perfluorinated tail, had the partition ratio of 37:63 (perfluorodecalin/hexane) and therefore was not suitable for reaction in the fluorous phase. As previously discussed the "fluorophilicity" of a molecule can be increased by adding extra perfluorinated chains. The original plan to introduce an extra perfluorinated branch, involved reaction of amine (**229**) with an excess of (**236**) as illustrated in **scheme 5.13.** However, no reaction was observed after 24 hours reflux in acetonitrile, suggesting that the lone pair on nitrogen was significantly less nucleophilic due to steric effect and perhaps also to the proximity of the CF_2 group.



Rf= $CF_3(CF_2)_7$-

Scheme 5.13. Reagents and conditions. Acetonitrile, K_2CO_3, 24h, reflux.

In order to circumvent this problem a different approach to the synthesis of a di-branched chiral amine was taken and is shown in **scheme 5.14**. The idea was to react the amine (**229**) with a more reactive electrophile, such as the perfluorinated acyl chloride (**236**), to generate amide (**249**), which would be then reduced to tertiary amine (**230**).



Rf_8= CF_3-$(CF_2)_7$-

Rf_7= CF_3-$(CF_2)_6$-

Scheme 5.14. Reagents and conditions. (i). DCM, TEA, 12h, RT. (97%). (ii). THF, BH_3-THF, 24 h RT (55%).

Amine (**229**) was converted in a straightforward manner to tertiary amide (**249**) by treatment with acylchloride (**236**). The reduction of the amide was first attempted with $LiAlH_4$ but no product was observed and only the starting amine (**229**) was recovered. However succesfull reduction was achieved using BH_3-THF as the reducing agent. After 24 hours the amine was recovered in 55% yield.

Amine (**230**) was found to be very "fluorophilic" with a partition ratio of 97:3.This material is clearly attractive for fluorous phase chemistry. Tertiary amines can be converted to their quaternary ammonium salts and these are extensively used in organic chemistry as phase transfer catalysts. Due to the high solubility of **230** in fluorous media the idea was to convert amine (**230**) into the corresponding quaternary ammonium salt (**250**) and this would be explored as a chiral phase transfer catalyst across the fluorous-organic interface as illustrated in **figure 5.11.**

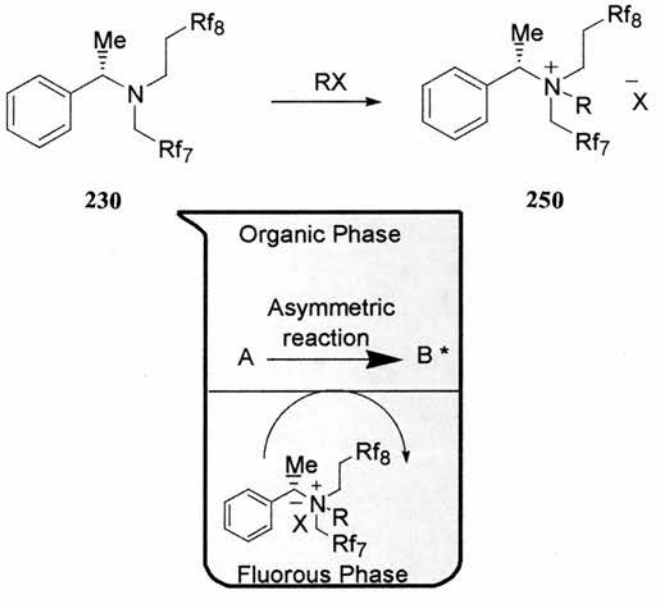
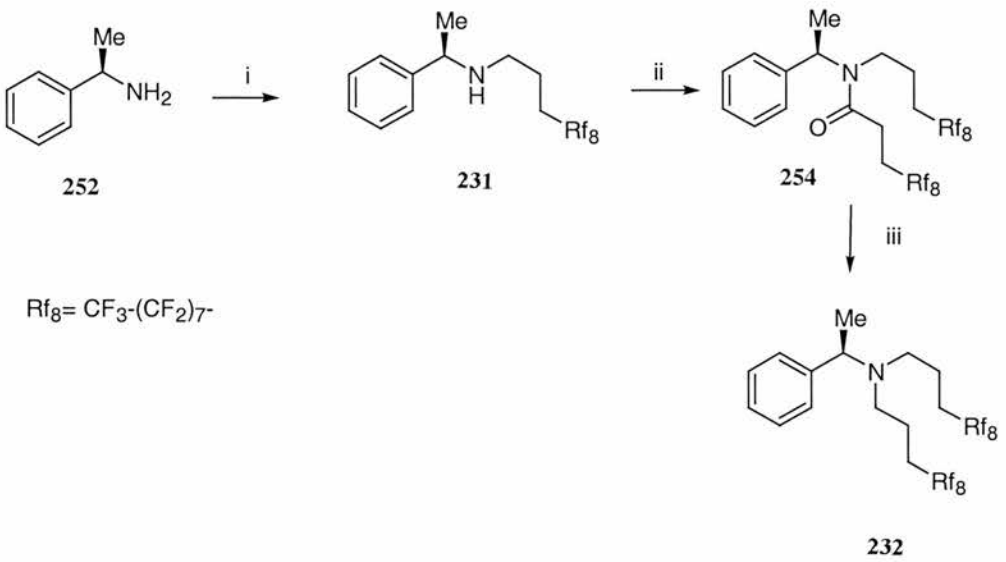


Figure 5.11. Chiral Phase transfer catalyst in Fluorous Phase

In the event the reaction of the tertiary amine (**230**) with HCl-Et_2O to form the hydrochloride salt was unsuccessful. This confirms the poor basicity of this N when attached to the perfluorinated chains. Therefore the idea to generate the quaternary salt of (**230**) was abandoned. A different molecule (**232**) was then designed. The new target carried three spacer CH_2's between the perfluorinated chains and the nitrogen to insulate the lone pair from the strong electron withdrawal fluorine atoms. The synthesis, shown in

scheme 5.15 followed the same protocol seen for the synthesis of **230** with minor modifications in the first step.



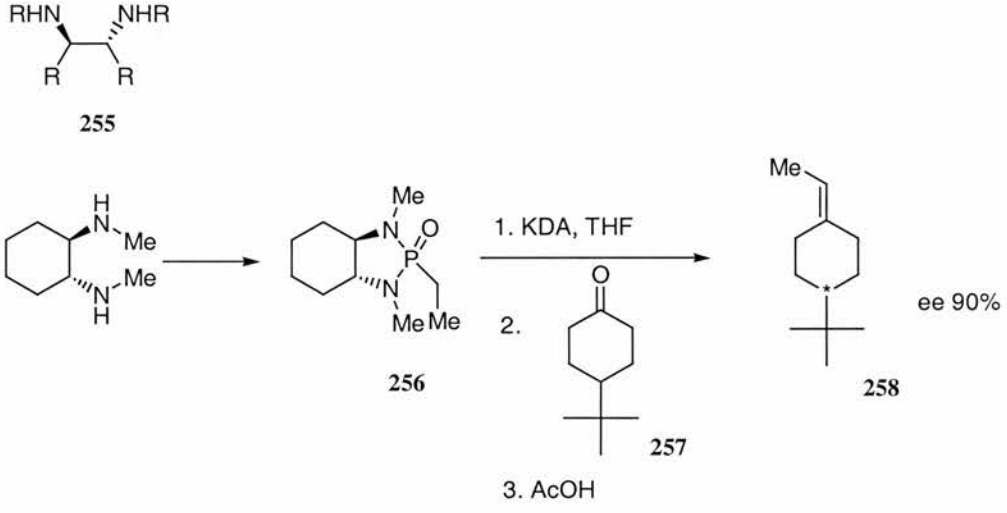
Scheme 5.15 Reagents and conditions. (i). $C_8F_{17}(CH_2)_3I$ (**251**), TEBA, Acetonitrile, K_2CO_3, 24h, reflux (70%). (ii). $Rf_8CH_2CH_2COCl$ (**253**) DCM, TEA, 12h, RT. (84%). (iii). THF, BH_3-THF, 24 h. RT. (51%)

Perfluoroalkyl iodide **251** was reacted with one molar equivalent of (*R*)-1-phenylethylamine (**252**) in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA) and solid K_2CO_3 as a base[40]. Under these conditions, the enantiomerically pure primary amine was *N*-alkylated selectively, affording the chiral secondary amine **231** (yield = 70%) as the only products. HI elimination has little effect on the iodide **251** featuring an extra methylene spacer inserted between the perfluoroalkyl chain and the iodine atom. Indeed, unreacted **251** could be recovered from the mixture at the end of the reaction. Amide formation (**254**) by reaction with acyl chloride (**253**) followed by BH_3 reduction delivered the desired di-branched amine (**232**). Preliminary results confirmed a certain reactivity of the N lone pair towards acids. However the reactivity versus electrophile to generate quaternary ammonium salts has not been explored.

5.6 Synthesis and application of fluorous chiral diamines

5.6.1 Chiral diamines in asymmetric synthesis.

Chiral C_2 symmetrical 1,2-diamines (**255**) have recently emerged as versatile auxiliaries or ligands in many asymmetric reactions. The key features of these 1,2 –diamines is their ability to coordinate metals such as Cu, Ni, Zn to generate metal complexes which are capable of catalysing numerous organic reactions.[41] In particular such chiral 1,2-diamines have been used as ligands employed in asymmetric olefination, 1,2-nucleophilic addition and asymmetric cyclopropanation reactions.

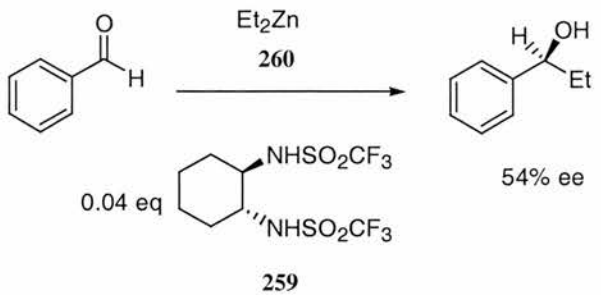


Scheme 5.16. Asymmetric olefination.

Several N, N'-dimethyl and P-alkyl bicyclic phosponamides have been prepared and their reactivity as asymmetric olefination reagents has been evaluated.[42-44] For example, treatment of chiral phosphonamide (**256**) with KDA at low temperature followed by the addition of a symmetrical ketone such as 4-*tert*-butylcyclohexanone (**257**) and gave (**258**) as a single enantiomer (**scheme 5.16**).

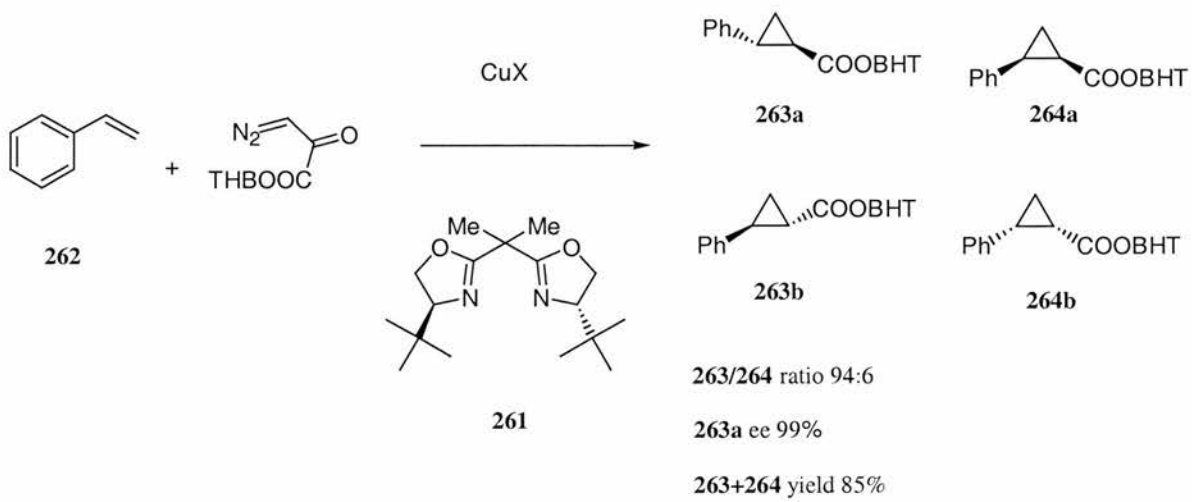
1,2-Nucleophilic addition reactions to aldehydes and ketones are important and well-documented method for functionalising organic molecules. An example of the asymmetric version of this reaction was reported by Kobayashi and co-workers[45] using the chiral diamine (**259**) by addition of the organozinc (**260**) reagent as shown in **scheme 5.17.** The

resultant Lewis acid, derived from the coordination of the zinc metal to the amino group, was found to be very efficient in mediating an asymmetric reaction. The strong electron withdrawing group increases the acidity of the Lewis acid and the reaction gave good yields and high ee's at a low concentration of (**261**).



Scheme 5.17. Asymmetric 1,2-nucleophilic addition.

Enantioselective cyclopropanation has been the focus of much research since the seminal work of Nozaki[46] which represents the first example of the use of chiral metal complexes to catalyse the conversion of a prochiral substrate into a chiral product with an excess of one enantiomer. Presently, highly efficient enantioselective cyclopropanation is obtained using the bisoxazoline copper complex (**261**)[47]. In **scheme 5.18,** styrene (**262**) is converted to the cyclopropane in 99% ee in favour of (*R*) enantiomer (**263a**) and with a **263/264** ratio of 94:6. Chiral binapthyldiimines[48] and bis(ferrocenyll)diamines[49] have been also employed in such reactions again with high *trans:cis* selectivities and high enantiomeric excesses.



Scheme 5.18. Asymmetric cyclopropanation using chiral bisoxazolidines as ligand for Cu(I).

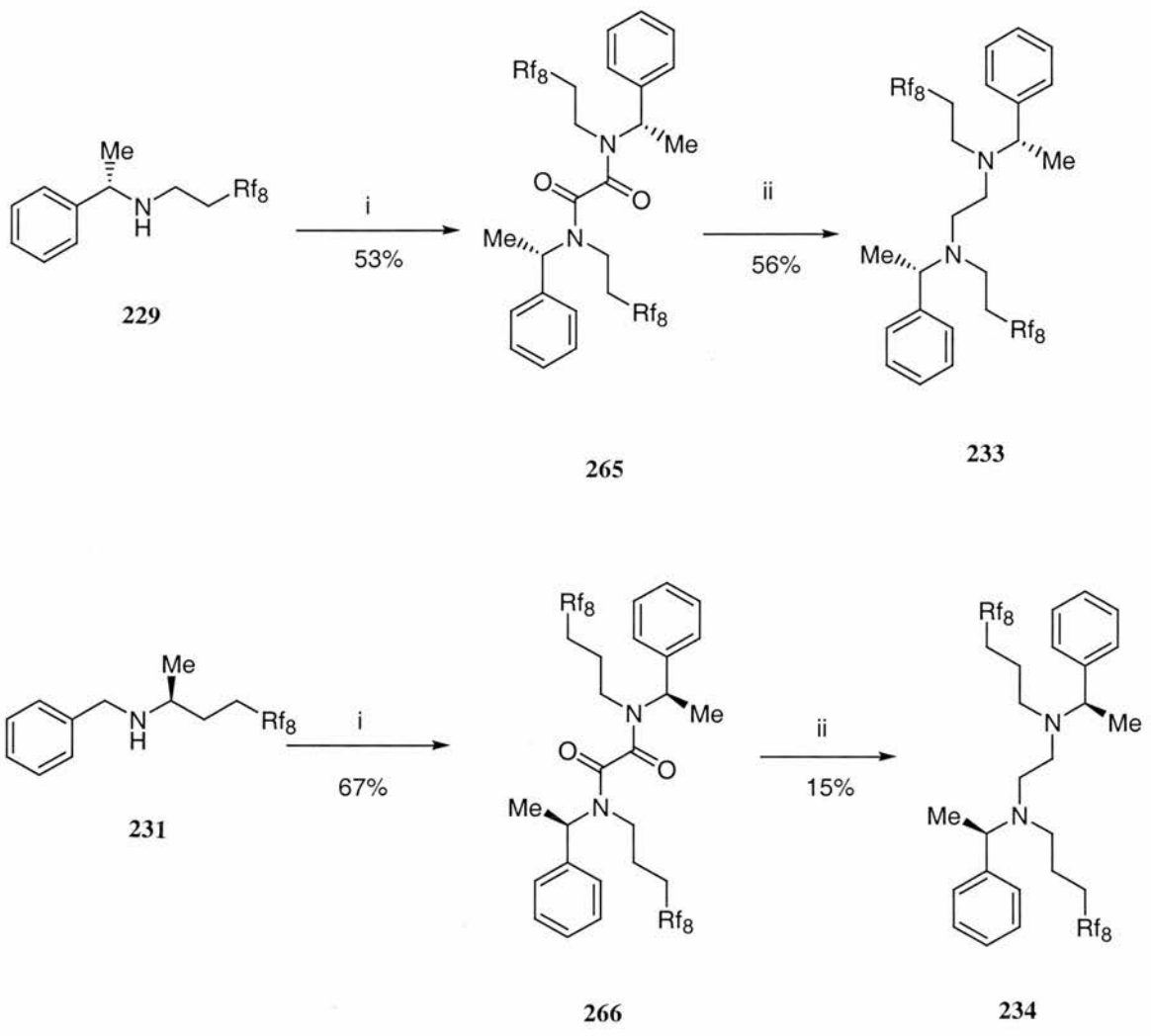
One of the limitations of the complexes discussed above is the difficulty to remove them from the reaction mixture and to reuse them. However, bisoxazolines and other ligand have been linked to inorganic and organic supports to allow filtration and thus recovery of the catalyst. Although the selectivity remains analogous to the "unlinked" system, a drop in activity has been noticed[50]. Chiral bisoxazolidines have been also linked to a soluble support such as PEG. The reaction could be run in a homogeneous phase without loosing the selectivity and the activity of the catalyst.[51]

Clearly another immobilisation strategy could be to link the catalyst to perfluoro ponytails to generate "fluorophilic molecules" soluble in FBS. To this end, fluorous carboxylates have been used with rhodium as a catalyst for achiral cyclopropanations and the complex could be recovered by fluorous liquid/liquid extractions.

Fluorous bisoxazoline have been also prepared and employed in asymmetric cyclopropanation reactions however the recycling of the catalyst was unsuccessful[52].

5.6.2 Synthesis of novel perfluorinated chiral diamines

With perfluorinated amines (**229**) and (**231**) in hand the synthesis of C_2 symmetry chiral amines (**265**) and (**266**). Proved straightforward. Only two synthetic steps synthesis were necessary to prepare perfluorinated diamine (**233**) and (**234**). As shown in **scheme 5.19**, (**229**) or (**231**) were converted first into diamides (**265** or **266**) in a good yield and these diamides were readily reduced to (**233**) or (**234**) by treatment with $LiAlH_4$.

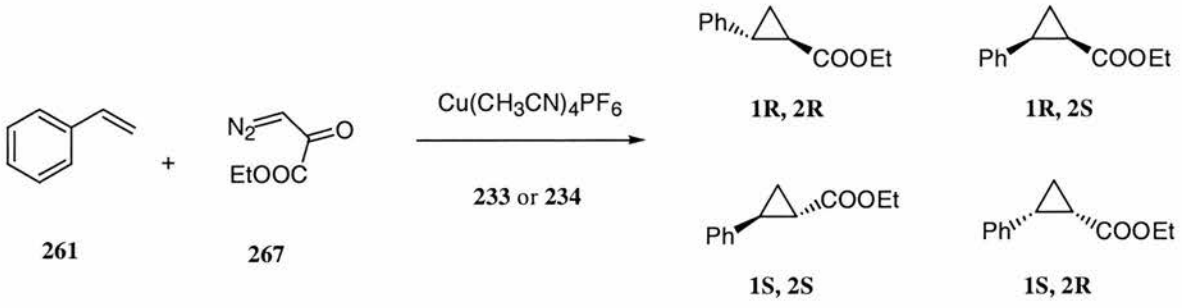


Scheme 5.19. Rf_8= $CF_3(CF_2)_7$-. Reagents and conditions. (i). DCM, oxalyl chloride, TEA, 6h 0 °C-RT. (ii). THF (**233**) or ether (**234**), $LiAlH_4$, 12 h. RT.

Due to their poor solubility of (**233**) and (**234**). in fluorous solvent (P% 50:50) the catalysis (**scheme 5.20**) was performed in DCM using copper acetonitrile hexafluorophospate salt as metal catalyst.

Preliminary results have shown that the diamines (**233** or **234**) are encouraging ligands for asymmetric cyclopropanation. The yield of the conversion is reasonably good (around 60%). However the selectivity and the enantiomeric excess were found to be low. It is interesting to note the different reaction time for the two ligands. The reaction with (**233**) took 24 hours whereas that for (**234**) took only 90 mins. This may be a result of the different conformational flexibility of the two systems. Diamine (**234**) carrying an extra spacer is more flexible than (**233**) therefore the reaction maybe much faster for this reason.

In contrast the flexibility of (**234**) could be responsible of the lower ee (11% against 16% with **233**)



Ligand	Copper source	Solvent	Time	Recovered yield	Trans:cis	ee	Config.
233 (S,S)	$Cu(CH_3CN)_4PF_6$	DCM	24 h	62%	58/42	16%	1R, 2R
234 (R,R)	$Cu(CH_3CN)_4PF_6$	DCM	90 mins	57%	58/42	11%	1S, 2S

Scheme 5.20. Asymmetric cyclopropanation of styrene using **233** or **234** as ligand.

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6 Experimental

6.1 General experimental procedures

This chapter documents the experimental procedures for Chapters: two, four and five. All the work was undertaken at the University of St. Andrews except the work concerning compounds (**231, 232, 234, 254** and **266**) which was undertaken during two weeks at the CNR in Milan under the direction of Dr. Gianluca Pozzi as part of the EU Research training Network.

6.2 Reagents and Solvents

All commercially available materials were purchased from Acros, Avocado, Fluka, Fluorochem or Sigma-Aldrich unless otherwise stated and purified according to literature procedures[1]. The solvents used in reactions were dried, distilled and stored under nitrogen prior to use: Diethyl ether (sodium, benzophenone), dichloromethane (calcium hydride), tetrahydrofuran (sodium, benzophenone), pyridine and triethylamine (potassium hydroxide), perfluorodecalin (phosporous pentoxide, molecular sieves (4Å). Petrol refers to the 40 - 60 °C boiling fraction of petroleum ether and ether refers to diethyl ether, perfluorodecalin was used as a mixture of *cis* and *trans* isomers.

6.3 Reaction conditions

Air- and moisture sensitive reactions were carried out under a positive pressure of nitrogen/ argon in oven-dried (160°C) glassware. Room temperature (RT) refers to 20-25°C. Reaction temperatures of –78 °C were obtained using solid CO_2 pellets and acetone and temperatures of 0 °C were obtained in an ice/water bath. Reaction reflux condition were obtained using an oil bath equipped with a contact thermometer. Solvent evaporations were carried out under reduced pressure on a Büchi rotary evaporator.

6.4 **Chromatography**

Thin layer chromatography (TLC) was performed using Merck, Kieselgel 60 plates and were visualised by the use of a UV lamp or by the use of cerium (IV) sulfate stain.
Liquid chromatograpy was performed using Merck, Kieselgel 60 (230-400) silica and preparative TLC was performed using Merck, Kieselgel 60 plates (1000 μm thickness).
Gas chromatography/mass spectroscopy (GC/MS) analysis of synthetic samples was conducted using an Agilent 5890 plus gas chromatograph equipped with a 5973N mass selective detector (EI mode) and 7683 series injector/autosampler, . Chromatographic separations were performed using a HP-5MS 5% Phenyl methyl siloxane capillary column (30 m x 250 μm with a film thickness of 0.25 μm). Chiral analysis were performed using a supelco 24304 Beta Dex 120 fused silica (30 m x 250 μm with a film thickness of 0.30 μm). The carrier gas was helium, with a flow rate of 1.1 ml $min.^{-1}$ the injection volume was 1μl and the injection port temperature was 250 °C.

6.5 **Instrumentation**

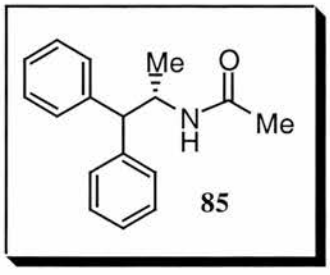
Melting points were measured on a Gallenkamp Griffin MPA350BM2.5, Büchi SMP-20 (Milan) melting point apparatus and are not corrected. Optical rotations were determined with a A-1000 polarimeter (optical polarimeter Ltd.) using a 2 dm cell, Perkin Elmer 241 polarimeter (Milan). Specific rotations are given in units of 10^{-1} $deg.g^{-1}$ cm^2. High-resolution CI and EI mass spectra were performed on a VG AUTOSPEC spectrometer, Bruker APEX II ICR-FTMS. Source: nano ESI at 45° (Milan). Carbon, hydrogen and nitrogen analyses were obtained using a CE Instrument EA 1110 CHNS analyser, Departmental Service of Microanalysis (University of Milano). Infrared spectra were recorded with Perkin Elmer 2000 FT-IR instrument as a thin layer between NaCl disks. Solid materials were prepared with KBr pellets. Values were rounded to 5 cm^{-1} upon manual assignment.
Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions on a Bruker Av-300.06 (7.0T) operating at 299.98 MHz for ^1H, 75.45 MHz for ^{13}C and 282.4 for ^{19}F, and Varian Unity Plus 300 MHz operating at 299.98 MHz for ^1H, 75.43 MHz for ^{13}C and Bruker AC 300 spectrometer operating as above stated (Milan). The assignments of the signals in the ^1H NMR spectra are based on the first-order analysis of the spin systems and when required were confirmed by $^1H\{^1H\}$ decoupling and two-

dimensional (2-D) (^{1}H, ^{1}H) homonuclear chemical shift correlation (COSY) experiments. ^{1}H-NMR NOE experiments was conducted in a Varian Unity Plus 500 MHz (^{1}H at 500.08 MHz) spectrometer. All chemical shifts δ are reported in parts per million (ppm) and quoted relative to the residual proton and/or fluorine peak $CDCl_3$ (δ_H 7.24 or δ_C 77.0 ppm, for ^{1}H and ^{13}C, respectively), $CFCl_3$ (0.0 ppm) for ^{19}F. Proton-proton coupling constants (J) are given in Hertz. Spectral coupling patterns are designated as follows: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad..

6.6 **Partition coefficient measurement**

The partitioni coefficient is reported as P % and measured according to Gladysz[2] procedure. In a typical experiment a vial was charged with the compound in exam (0.03 mmol), perfluorodecalin (0.500 cm^3), and hexane (0.500 cm^3), capped, vigorously shaken (2 min), and immersed (cap-level) in a 55 °C bath. After 2 h, the bath was removed. After 1 h (at RT), 0.010 cm^3 aliquots of each layer were added to stock solutions of 1-hexadecene in hexane (0.0022 M in 2 cm^3 hexane) and from this solution, aliquots of 50 μl were injected in GCMS.

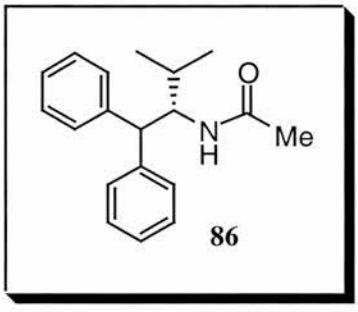
6.7 **Preparation of *(S)-N-(1- methyl- 2,2-diphenyl-ethyl)-acetamide* (85)**



85

Triethylamine (0.34 cm^3, 2.41 mmol) and acetyl chloride (0.13 cm^3, 1.77 mmol) were added drop wise to a solution of amine **83** (0.3 g, 1.61 mmol) in DCM (15 cm^3) at 0^0C. The reaction was stirred at RT for 12 h and was then worked up by washing with water (3 x 20 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by recrystallisation (petrol: acetone 90:10) to give amide **85** (0.3 g, 94%) as a white crystalline salt. Mp= 104 - 106 ^{0}C. $[\alpha]_D^{20}$ = -67.2 (*c*= 0.64, $CHCl_3$). HRMS ($C_{17}H_{20}NO$ requires, 254.1551. Found M+1, 254.1545). IR (Kbr), ν : 3445, 3305, 1640, 1545, 700. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.10 (3H, d, J= 6.4, CHC*H*$_3$), 1.73 (3H, s, COC*H*$_3$), 3.80 (1H, d, J= 9.8, Ph_2C*H*), 4.80 (1H, m, CH_3C*H*NH), 5.18 (1H, d broad, J= 8.3, N*H*, D_2O exchangeable), 7.10-7.22 (10H, m, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 20.4 (s, CH*C*H$_3$), 23.4 (s, C=O, *C*H$_3$), 47.5 (s, Ph_2*C*H), 58.1 (s, *C*HNH), 126.6 (s, aromatic), 128.1 (s, aromatic), 128.2 (s, aromatic), 128.5 (s, aromatic), 128.6 (s, aromatic), 141.7 (s, aromatic), 142.2 (s, aromatic), 168.9 (s, *C*=O). MS m/z (rel. int. %), (CI-isobutane): 254 (M+1, 100), 86 ($C_4H_8NO^+$, 5).

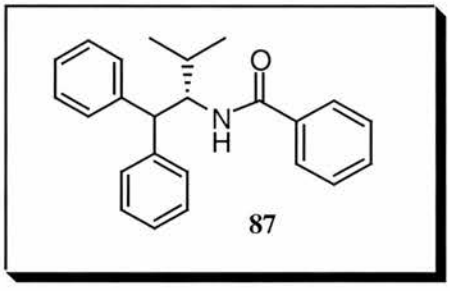
6.8 **Preparation of *(S)-N-(1-benzhydryl-2-methy1-propyl)acetamide* (86)**



86

Triethylamine (0.88 cm^3, 6.27 mmol.) and acetyl chloride (0.30 cm^3, 4.60 mmol) were added dropwise to a solution of amine **84** (1.00 g, 4.18 mmol) in DCM (40 cm^3) at 0 ^0C and the mixture was then heated under reflux for 4h. The reaction was washed with water (3 x 30 cm^3) and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave a white amorphous powder. This material was recrystallised from hexane:EtOAc (85:15) to obtain the title amide **86** as a white crystalline solid (1.10 g, 94%). Mp= 130 - 132 ^0C. $[\alpha]^{20}_D$ = -35.3 (*c*=0.56, $CHCl_3$). HRMS ($C_{19}H_{24}NO$ requires, 282.1850. Found M+1, 282.1858). IR (Kbr), ν : 3405, 2960, 1645, 1555, 1515, 1495, 1450, 755, 705. ^1H NMR (300 MHz, $CDCl_3$), δ : 0.99 (3H, d, J= 6.7, CH_3CHCH_3), 1.10 (3H, d, CH_3CHCH_3), 1.80 (3H+1H, m, CH_3CHCH_3 and $COCH_3$), 4.01 (1H, d, J= 10.6, Ph_2CH), 4.99 (1H, m, $(Ph)_2CHCHNH$), 5.18 (1H, d broad, J= 9.1, NH, D_2O exchangeable), 7.20-7.50 (10H, m, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 15.5 (s, CH_3CHCH_3), 21.2 (s, CH_3CHCH_3), 23.6 (s, $COCH_3$), 29.3 (s, CH_3CHCH_3), 55.6 (s, CHNH), 55.7 (s, Ph_2CH), 126.8 (s, aromatic), 126.9 (s, aromatic), 128.2 (s, aromatic), 128.5 (s, aromatic), 128.8 (s, aromatic), 129.2 (s, aromatic), 142.7 (s, aromatic), 143.0 (s, aromatic), 170.4 (s, C=O). MS m/z (rel. int. %), (CI-isobutane): 282 (M+1, 100), 114 ($C_6H_{12}NO^+$, 20).

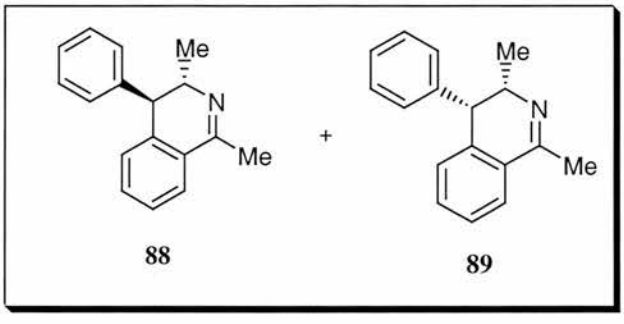
6.9 **Preparation of *(S)-N-(1-Benzhydryl-2-methyl-propyl) benzamide* (87)**



87

Triethylamine (0.4 cm^3, 2.19 mmol) and benzoyl chloride (0.2 cm^3, 1.61 mmol) was added to a solution of amine **84** (0. 350 g, 1.46 mmol) in DCM (20 cm^3) at 0 °C. The reaction was stirred for 12 h at RT. The reaction mixture was washed with water (3 x 20 cm^3) and the organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The product was recrystillised from ethanol:water (80:20) to obtain the title amide **87** (0.410 g, 94%) as a white crystalline solid . Mp= 221 - 223 ^{0}C. $[\alpha]^{20}_D$= -29.5 (*c*= 0.59, $CHCl_3$). HRMS ($C_{24}H_{26}NO$ requires, 344.2014. Found M+1, 344.2009). IR (Kbr), ν : 3340, 2950, 1635, 1530, 1490, 1450, 700. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.00 (3H, d, J= 6.7, CH_3CHCH_3), 1.10 (3H, d, J= 6.7, CH_3CHCH_3), 1.95 (1H, m, CH_3CHCH_3), 4.20 (1H, d, J= 11.1, Ph_2CH), 5.20 (1H, m, $(Ph)_2CHCHNH$), 5.80 (1H, d broad, J= 10.1, NH, D_2O exchangeable), 7.10-7.60 (15H, m, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 15.5 (s, CH_3CHCH_3), 20.9 (s, CH_3CHCH_3), 29.3 (s, CH_3CHCH_3), 55.3 (s, $(Ph)_2CHCHNH$), 55.9 (s, Ph_2CH), 126.5 (s, aromatic), 126.6 (s, aromatic), 127.8 (s, aromatic), 128.0 (s, aromatic), 128.3 (s, aromatic), 128.6 (s, aromatic), 130.9 (s, aromatic), 142.3 (s, aromatic), 142.5 (s, aromatic), 168 (s, C=O). MS m/z (rel. int. %), (CI-isobutane): 344 (M+1, 100), 176 ($C_{11}H_{14}NO^+$, 15), 77 (Ph^+, 26).

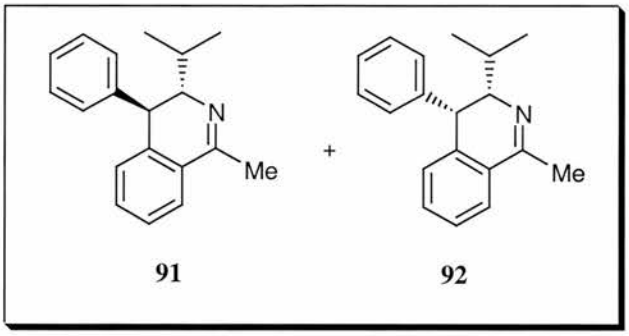
6.10 **Preparation of *(3S, 4S)- 1,3-dimethyl-4-phenyl-3,4-dihydroisoquinoline* (88) and *(3S, 4R)- 1,3-dimethyl-4-phenyl-3,4-dihydroisoquinoline* (89)**



88 **89**

Phosphoryl chloride (1.35 g, 9.40 mmol) was added dropwise to a suspension of phosphorous pentoxide (0.86 cm^3, 9.40 mmol) in a solution of amide **85** (0.200 g, 0.94 mmol) in anhydrous toluene (25 cm^3). After complete addition the reaction mixture was heated under reflux for 12 h. After cooling, crushed ice (25 cm^3) was added. The organic layer was separated and the aqueous residue was made basic with sodium hydroxide (15% w/v) solution and the product was then extracted into chloroform (3 x 25 cm^3). The chloroform extract was dried ($MgSO_4$), evaporated under reduce pressure and the product purified over silica (1:1 hexane: EtOAc) to give **88** and **89** as a mixture in 9:1 ratio of yellow oils (0.047 g, 29%). HRMS ($C_{17}H_{18}N$ requires, 236.1431. Found M+1, 236.1444). IR (neat), ν : 2965, 2925, 2865, 1630, 1570, 1490, 1450, 1140, 765. ^1H NMR (300 MHz, $CDCl_3$), δ : 1.40 (3H, d, J= 6.7, CHC*H*$_3$), 2.59 (3H, d, J= 1.9, N=CC*H*$_3$), 3.80 (1H, d, J= 11.1, PhC*H*), 6.90-6.95 (1H, m, aromatic), 7.20-7.50 (7H, m, aromatics H), 7.60-7.65 (1H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 21.8 (s, CH*C*H$_3$), 23.4 (s, N=C*C*H$_3$), 49.5 (s, Ph*C*H), 57.7 (s, *C*HN); 126.5 (s, aromatic), 125.2 (s, aromatic), 126.8 (s, aromatic), 127.7 (s, aromatic), 128.6 (s, aromatic), 129.0 (s, aromatic) 140.2 (s, aromatic), 141.9 (s, aromatic), 163.3 (s, C=N). MS m/z (rel. int. %), (CI-isobutane): 236 (M+1, 100).

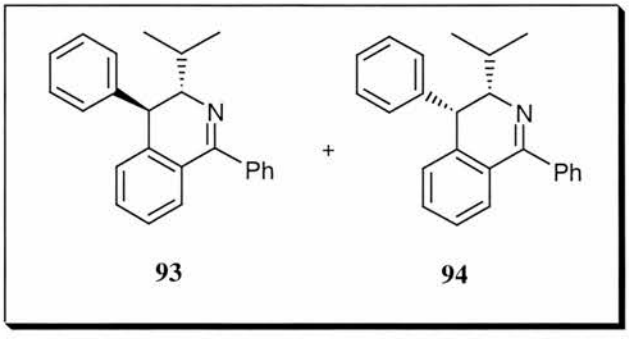
6.11 **Preparation of *(3S, 4S)-3-isopropyl-1-methyl-4-phenyl-3,4-dihydro-isoquinoline* (91) and *(3S, 4R)-isopropyl-1-methyl-4-phenyl-3,4-dihydro-isoquinoline* (92)**



91 **92**

Phosphoryl chloride (3.25 cm^3, 35.00 mmol) was added dropwise to a suspension of phosphorous pentoxide (5.00 g, 35.00 mmol) in a solution of amide **86** (1.00 g, 3.54 mmol) in anhydrous toluene (60 cm^3). After complete addition the reaction mixture was heated under reflux for 12 h. After cooling, crushed ice (60 cm^3) was added. The organic layer was separated, the aqueous residue was washed with basic sodium hydroxide (15% w/v) solution, and the product was then extracted into chloroform (3 x 25 cm^3). The chloroform extract was dried ($MgSO_4$), evaporated under reduce pressure and the product purified over silica gel (2:1 hexane: EtOAc) to give a mixture of **91** and **92** in 21:1 ratio as a white amorphous solid (0.558 g, 60%). The product was recrystallised from (95:5 petrol: acetone) to give **91** (94% de). Mp= 65 - 67 ^{0}C. HRMS ($C_{19}H_{21}N$ requires, 263.1674. Found M, 263.1666). IR (Kbr), ν : 2955, 1625, 1425, 1370, 1295, 770. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.05 (3H, d, J= 6.7, CH_3CHCH_3), 1.20 (3H, d, J= 6.7, CH_3CHCH_3), 1.85 (1H, m , CH_3CHCH_3), 2.60 (3H, d, J= 1.5, N=CCH_3), 4.00 (1H, dd, J= 8.7, J= 4.8, CHN=C), 4.20 (1H, d, J= 9.7, PhCH), 6.85-6.90 (1H, m, aromatic), 7.15-7.35 (7H, m, aromatics H), 7.58-7.60 (1H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 17.8 (s, CH_3CHCH_3), 20.9 (CH_3CHCH_3), 23.8 (N=CCH_3), 30.9 (CH_3CHCH_3), 45.3 (PhCH), 67.8 (CHN=C), 125.2 (s, aromatic), 126.9 (s, aromatic), 127.2 (s, aromatic), 128.4 (s, aromatic), 128.9 (s, aromatic), 129.1 (s, aromatic), 129.5 (s, aromatic), 131.0 (s, aromatic) 140.5 (s, aromatic), 143.2 (s, aromatic), 162.9 (s, C=N). MS m/z (rel. int. %), (EI): 263 (M, 44), 248 (M- Me^+, 100), 220 ($C_{16}H_{14}N^+$, 20).

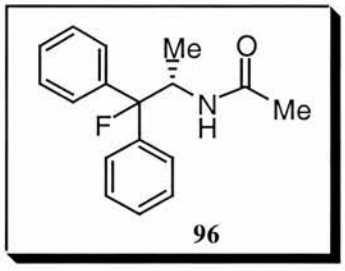
6.12 **Preparation of *(3S, 4S)- 3-isopropyl-1,4-diphenyl-3,4-dihydroisoquinoline* (93) and *(3S, 4R) - 3-isopropyl-1,4-diphenyl-3,4-dihydroisoquinoline* (94)**



93 **94**

Phosphoryl chloride (1.24 g, 8.90 mmol) was added dropwise to a suspension of phosphorus pentoxide (0.80 cm^3, 8.90 mmol) in a solution of amide **87** (0.303 g, 0.88 mmol) in anhydrous toluene (25 cm^3). After complete addition the reaction mixture was heated under reflux for 12 h and was then quenched by the addition of crushed ice (25 cm^3). The aqueous residue was made basic by the addition of sodium hydroxide (15% w/v) solution and the product was then extracted into chloroform (3 x 25 cm^3). The chloroform extract was dried ($MgSO_4$), evaporated under reduced pressure and the product purified over silica (90:10 hexane: ethyl acetate) to give **93** and **94** as a mixture in13:1 ratio and as white crystalline solid (0.091 g, 32%) which was recrystallised from (95:5 petrol: acetone) to give **93** in 88 de%. Mp = 119 - 121 ^{0}C. HRMS ($C_{24}H_{23}N$ requires, 326.1908. Found M+1, 326.1915). IR (Kbr), ν : 3060, 3025, 2955, 2925, 1610, 1540, 1450, 695. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.06 (3H, d, J= 6.7, CH_3CHCH_3), 1.20 (3H, d, J= 6.7, CH_3CHCH_3), 1.82-1.85 (1H, m, CH_3CHCH_3), 3.84 (1H, dd, J= 8.7, J= 4.5, PhCHCHN), 4.00 (1H, d, J= 8.7, PhCH), 6.85 -7.63 (14H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 17.9 (s, CH_3CHCH_3), 20.5 (s, CH_3CHCH_3), 30.2 (s, CH_3CHCH_3), 44.9 (s, PhCH), 67.9 (PhCHCHN), 126.5 (s, aromatic), 128.1 (s, aromatic), 128.2 (s, aromatic), 128.3 (s, aromatic), 128.6 (s, aromatic), 128.7 (s, aromatic), 128.9 (s, aromatic), 128.9 (s, aromatic), 129.1 (s, aromatic), 141.2 (s, aromatic), 142.3 (s, aromatic), 165.4 (s, C=N). MS m/z (rel. int. %), (CI-isobutane): 326 (M+1, 100).

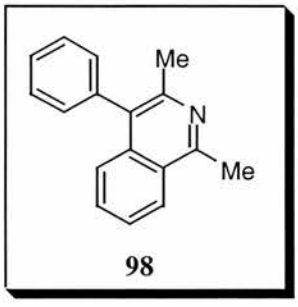
6.13 **Preparation of *(N-(2-fluoro-1-methyl-2,2-diphenyl-ethyl)-acetamide* (96)**



96

Triethylamine (0.18 cm^3, 1.32 mmol) and acetyl chloride (0.062 cm^3, 0.97 mmol) were added dropwise to a solution of amine **95** (0.200 g, 0.88 mmol) in DCM (15 cm^3) at 0^0C. The reaction was stirred at RT for 12 h and was then worked up by washing with water (3 x 20 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by recrystallisation (petrol: acetone 90:10) to give the product amide **96** as white crystalline solid (0.230 g, 97%). Mp= 120 - 122 ^{0}C. $[\alpha]^{20}_D$=-+12.37 (*c*= 0.49, DCM). HRMS ($C_{17}H_{18}FNO$ requires 271.1372. Found M, 271.1367). IR (Kbr), ν : 3290, 1645, 1540. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.10 (d, 3H, J= 6.7, CHC*H*$_3$), 1.89 (s, 3H, COC*H*$_3$), 5.32 (1H, ddq, J= 16.0, J= 9.6, J= 6.7, $(Ph)_2CFCHCH_3$), 6.06 (1H, d broad, J= 9.6, N*H*, D_2O exchangeable), 7.10-7.22 (m, 10H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 15.7 (CH*C*H$_3$), 23.1 (CO*C*H$_3$), 47.5 (d, J= 20.5, FC*C*HNH), 100.1 (d, J= 181.9, F*C*H), 124.1 (s, aromatic), 124.2 (s, aromatic), 124.8 (s, aromatic), 124.9 (s, aromatic), 127.4 (s, aromatic), 127.6 (s, aromatic), 128.2 (s, aromatic), 128.3 (s, aromatic), 141. 3 (d, J= 23.0, aromatic), 141.6 (d, J= 23.0, aromatic), 169.1 (s, *C*=O). ^{19}F NMR (282 MHz, $CDCl_3$), δ : -170.1 (d, J= 16,). MS m/z (rel. int. %), (EI): 271 (M, 5), 213 ($C_{15}H_{14}F^+$, 10), 185 ($C_{13}H_{10}F^+$, 15), 165 (17), 86 ($C_4H_8NO^+$, 90), 44 (C_2HF^+, 100).

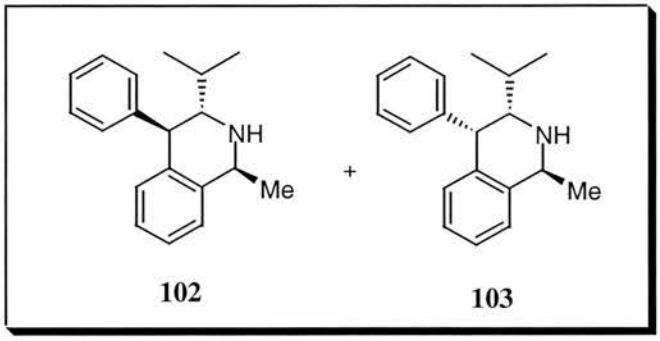
6.14 **Preparation of *1,3-dimethyl-4-phenyl-isoquinoline* (98)**



98

Phosphoryl chloride (0.930 g 6.6 mmol) was added dropwise to a suspension of phosphorous pentoxide (0.60 cm^3, 6.6 mmol) in a solution of amide **96** (0.18 g, 0.66 mmol) in anhydrous toluene (15 cm^3). After complete addition the reaction mixture was heated under reflux for 12 h and was then quenched by the addition of crushed ice (25 cm^3). The aqueous residue was made basic by the addition of sodium hydroxide (15% w/v) solution and the product was then extracted into chloroform (3 x 15 cm^3). The chloroform extract was dried ($MgSO_4$) and evaporated under reduced pressure to give **98** as a orange crystalline solid (0.090 g, 59%). Mp= 106 - 108 ^{0}C. HRMS ($C_{24}H_{23}N$ requires, 234.1283. Found M+1, 234.1293). ^{1}H NMR (300 MHz, $CDCl_3$), δ : 2.57 (3H, s, CH_3), 3.12 (3H, s, CH_3), 7.38-7.61 (8H, m, aromatic), 8.23 (1H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 22.4 (CH_3), 23.0 (CH_3), 125.3 (s, aromatic), 125.4 (s, aromatic), 125.5 (s, aromatic), 125.6 (s, aromatic), 127.3 (s, aromatic), 128.5 (s, aromatic), 129.5 (s, aromatic), 130.2 (s, aromatic), 135.8 (s, aromatic), 137.9 (s, aromatic), 147.4 (s, aromatic), 156.4 (C=N). MS m/z (rel. int. %), (CI-isobutane): 234 (M+1, 100).

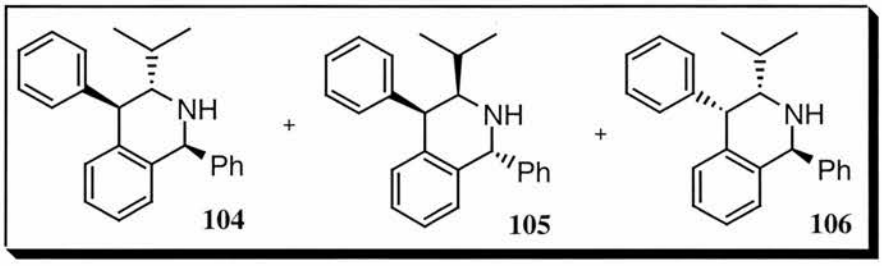
6.15 **Preparation of *(1S, 3S, 4S)-1-methyl-3-isopropyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline* (1025) and *(1S, 3S, 4R)-1-methyl-3-isopropyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline* (103).**



102 **103**

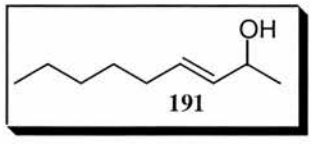
A solution of **91** and **92** (0.350 g, 1.33 mmole) in ether (30 cm^3) was added dropwise to a suspension of $LiAlH_4$ (0.500 g, 13.3 mmole) in ether (10 cm^3) at 0 ^0C and then the reaction was heated under refluxed for 24 h. The reaction was then quenched with 5% HCl solution. The aqueous layer was made basic with 15% NaOH and the products were extracted into ether (3 x 30 cm^3). The organic extract was dried ($MgSO_4$) and evaporated under reduce pressure to give **102** and **103** as colourless oil and in 21:1 ratio (0.242 g, 69%). HRMS ($C_{19}H_{24}N$ requires, 266.1908. Found M+1, 266.1901). ^1H NMR (300 MHz, $CDCl_3$), δ : 0.98 (3H, d, J= 7.1, $CH_3CHC\mathit{H_3}$), 1.01 (3H, d, J= 7.1, $C\mathit{H_3}CHCH_3$), 1.56 (3H, d, J= 6.6, $NHCHC\mathit{H_3}$), 1.70 (1H, m, $(CH_3)_2C\mathit{H}$), 2.97 (1H, t, J= 6.2, $PhCHC\mathit{H}NH$), 4.00 (1H, d, J= 7.1, $PhC\mathit{H}$), 4.30 (1H, q, J= 6.6, $NHC\mathit{H}CH_3$), 6.80-7.30 (9H, m, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 16.7 (CH_3CHCH_3), 20.8 (CH_3CHCH_3), 23.4 ($NHCHCH_3$), 27.7 (CH_3CHCH_3), 47.9 ($PhCH$), 49.4 ($NHCHMe$), 61.1 ($PHCHCHNH$), 125.7 (s, aromatic), 128.2 (s, aromatic), 129.0 (s, aromatic), 130.4 (s, aromatic), 137.3 (s, aromatic), 140.7 (s, aromatic), 145.1 (s, aromatic). MS m/z (rel. int. %), (CI-isobutane): 266 (M+1, 100), 222 (M-$i\mathrm{Pr}^+$, 22).

6.16 **Preparation of *(1S, 3S, 4S)- 3-Isopropyl-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline* (104) and *(1R, 3R, 4S) 3-isopropyl-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline* (105) and *(1S, 3S, 4R) -3-isopropyl-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline* (106)**



A solution of **93** and **94** (0.048 g, 0.147 mmol) in ether (5 cm^3) was added dropwise at 0^0C to a suspension of $LiAlH_4$ (0.056 g, 1.47 mmol) in ether (5 cm^3) and then the reaction was heated under reflux for 24 h. The reaction was then quenched with % HCl. The aqueous layer was made basic with 1% NaOH and the products were extracted into ether (3 x 10 cm^3). The organic extract was dried ($MgSO_4$) and evaporated under reduce pressure to give **104** (and **105** and **106)** as a colourless oil and in 9:0.7:0.3 ratio. (0.025 g, 52%). HRMS ($C_{24}H_{26}N$ requires, 328.2065. Found M+1, 328.2058). ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.80 (3H, d, J= 6.8, CH_3CHCH_3), 1.01 (3H, d, J= 6.8, CH_3CHCH_3), 1.67 (1H, m, CH_3CHCH_3), 2.84 (1H dd, J= 7.9, J= 4.9, PhCHCHNH), 4.10 (1H, d, J= 7.9, PhCHCHNH), 5.30 (1H, s, NHCHPh), 6.90-7.45 (14 H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 16.3 (CH_3CHCH_3), 20.6 (CH_3CHCH_3), 27.7 (CH_3CHCH_3), 47.9 (PhCHCHNH) , 58.9 (NHCHPh), 61.1 (PhCHCHNH), 125.6 (s, aromatic), 126.7 (s, aromatic), 126.9 (s, aromatic), 127.5 (s, aromatic), 127.9 (s, aromatic), 128.2 (s, aromatic), 128.7 (s, aromatic), 129.3 (s, aromatic), 129.8 (s, aromatic), 130.4 (s, aromatic), 130.8 (s, aromatic), 137.2 (s, aromatic), 139.2 (s, aromatic), 144.9 (s, aromatic), 145.2 (s, aromatic). MS m/z (rel. int. %), (CI-isobutane): 328 (M+1, 100).

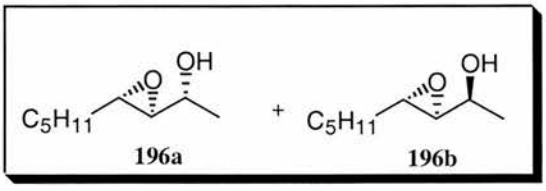
6.17 **Preparation of *(E)-non-3-en-2-ol* (191).**



191

Sodium borohydride (2.7 g, 71.4 mmol) was added to a solution of **195** (10 g, 71.4 mmol) and cerium (III) chloride heptahydrate (27 g, 71.4 mmol) in methanol (100 cm^3) at 0 °C. The resulting suspension was stirred for 15 min. The reaction was concentrated by rotary evaporation and diluted with water (100 cm^3) and a 1 N HCl solution (30 cm^3). The aqueous phase was extracted into ether (3 x 100 cm^3) and the combined organics were washed with brine (100 cm^3), dried over magnesium sulfate, filtered and concentrated to yield **191** (9.0 g, 89%) as clear oil. This material was used without further purification. IR (neat), ν : 3360, 2960, 2930, 2855, 1465, 1370, 1060, 965. ^1H NMR (300 MHz, $CDCl_3$), δ : 0.87 (t, 3H, J= 6.6, CH_3CH_2), 1.21 (d, 3H, J= 6.4, $CHOHCH_3$), 1.24-1.41 (m, 6H), 1.98 (q, 2H, J= 6.6, $CH_2CH{=}CH$), 4.23 (p, 1H, J= 6.4, $CHOHCH_3$), 5.42-5.66 (m, 2H, $CH{=}CH$). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 22.4 (s, CH_3CH_2), 23.3 (s, $CHOHCH_3$), 28.8 (s, $CH_3CH_2CH_2$), 31.3 (s, $CH_2CH_2CH{=}CH$), 32.0 (s, $CH_2CH_2CH{=}CH$), 68.9 (s, *CH*OH), 131.1 (s, *C*H=CHCHOH), 134.0 (s, CH=*C*HCHOH). MS m/z (rel. int. %), (EI): 142 (M, 15), 124 (M- H_2O, 20), 109 (M- H_2O-Me 25), 99 (20), 82 (60).

6.18 **Preparation of *1-(3-pentyl-oxiranyl)-ethanol* (196a) and (196b)**



A solution of **191** (9.4 g, 63.4 mmol) and *m*CPBA (ca. 70% purity, 15.6 g, 63.4 mmol) in DCM (70 cm^3) was stirred at 0 °C for 2 h. The reaction mixture was then stirred at 0°C with 10% aqueous Na_2SO_3, (50 cm^3) and was then washed with sat. $NaHCO_3$ (50 cm^3) and sat. NaCl (75 cm^3), dried over anhydrous $MgSO_4$, and concentrated in *vacuo* to yield a mixture of **196a** and **196b** (2:1 ratio) (8.5 g, 85%) as a colourless oil which was used without further purification.

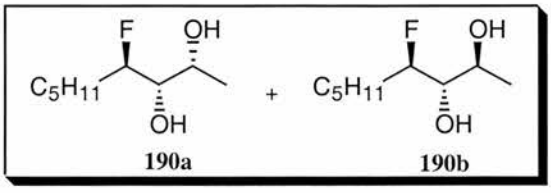
(196a).

IR (neat), ν : 3450, 2960, 2930, 2860, 1460, 1260, 1150, 1090, 940. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.86-0.94 (m, 3H, CH_3CH_2), 1.25 (d, 3H, J= 6.1, $CHOHCH_3$), 1.28-1.64 (m, 8H), 2.76 (dd, 1H, J= 3.0, J= 2.5, CHOCHCHOH), 2.96 (m, 1H, CHOH), 3.91-4.01 (m, 1H, CHOCHCHOH). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 19.6 (s, $CHOHCH_3$), 22.5 (s, CH_3CH_2), 25.5 (s, $CH_3CH_2CH_2$), 31.5 (s, CH_2CH_2CHO), 31.5 (s, CH_2), 55.1 (s, CHOCHCHOH), 62.7 (s, CHOCHCHOH), 64.8 (s, CHOH). MS m/z (rel. int. %), (EI): 125 ($C_9H_{17}^+$, 2), 83 (60), 71 (20).

(196b).

IR (neat), ν : 3450, 2960, 2930, 2860, 1460, 1260, 1150, 1090, 940. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.86-0.94 (m, 3H, CH_3CH_2), 1.25 (d, 3H, J= 6.4, $CHOHCH_3$), 1.28-1.64 (m, 8H), 2.71 (dd, 1H, J= 5.1, J= 2.3, CHOCHCHOH), 2.90 (td, 1H, J= 5.6, 2.3, $CHOHCH_3$), 3.60-3.69 (m, 1H, *OCH*CHOH). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 18.7 (s, $CHOHCH_3$), 22.5 (s, CH_3CH_2), 25.6 (s, $CH_3CH_2CH_2$), 31.4 (s, $OCHCH_2CH_2$), 56.8 (s, CHOCHCHOH), 61.7 (s, CHOCHCHOH), 67.7 (s, CHOH). MS m/z (rel. int. %), (EI): 125 ($C_9H_{17}^+$, 2), 83 (60), 71 (20).

6.19 **Preparation of *4-fluoro-nonane-2,3-diol* (190a) and (190b)**



190a **190b**

A solution of **196a** and **196b** (7.20 g, 36.0 mmol), in DCM (50 cm^3) was treated with pyridine polyhydrogenfluoride (13 cm^3) at -5 °C for 4h. The reaction mixture was poured into 5% aq. $NaHCO_3$ (30 cm^3) and the organic layer was washed with sat. NH_4Cl (20 cm^3), was dried and, was evaporated to yield a mixture of **190a** and **190b** in 2:1 ratio as a white solid (4.0 g, 62%). The diastereoisomers were separated by column chromatography (hexane:EtOAc: 3:1) to obtain **190a** as white solid (2.1 g , Mp= 60 – 62 °C) and **190b** as amorphous solid (0.70 g, Mp= 45 - 47 °C) and a mixture of **190a** and **190b** (1.2 g) not resolvable.

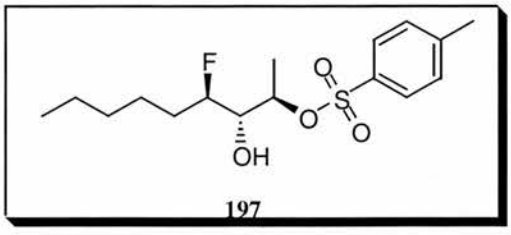
(**190a**).

Anal. Calcd: *C*, 60.65; *H*; 10.74. Found: *C*; 61.28; *H*, 11.15. HRMS ($C_9H_{20}O_2F$ requires, 179.1447. Found M+1, 179.1449). IR (Kbr), ν : 3400, 2925, 2855, 1460, 1380, 1065. ^1H NMR (300 MHz, $CDCl_3$), δ: 0.85-0.92 (m, 3H, CH_3CH_2), 1.26 (d, 3H, J= 6.7, $CHOHCH_3$), 1.28-1.77 (m, 8H), 3.31-3.39 (m 1H, CHFCHOHCHOH), 3.89-3.99 (m, 1H, $CHOHCHOHCH_3$), 4.40 (dq, 1H, J= 48.4, J= 5.9, CHF). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, CH_3CH_2), 19.6 (d, J= 1.1, CH_3), 22.5 (s, CH_3CH_2), 24.6 (s, $CH_3CH_2CH_2$), 31.0 (d, J= 20.4, CH_2CHF), 31.6 (s, CH_2CH_2CHF), 66.2 (d, J= 4.4, $CHOHCH_3$), 75.8 (d, J= 22.7, CHFCHOH), 94.3 (d, J= 169.7, CHF). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-192.2] – [-191.6] (m, CHF). MS m/z (rel. int. %), (CI-isobutane): 179 (M+1, 95), 161 (M+1-H_2O, 100), 141 ($C_9H_{17}O^+$, 40), 123 ($C_9H_{16}^+$, 18).

(190b).

Anal. Calcd: *C*, 60.65; *H*; 10.74. Found: *C*; 61.30; *H*; 11.13. HRMS ($C_9H_{20}O_2F$ requires, 179.1447. Found M+1, 179.1442). IR (Kbr), ν : 3340, 2925, 2855, 1460, 1380, 1065. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.83-0.96 (m, 3H, C*H*$_3$CH$_2$), 1.23 (dd, 3H, J= 6.6, J= 1.0, CHOHC*H*$_3$), 1.27-1.87 (m, 8H), 3.62-3.73 (m, 1H, C*H*OHCHOHCH$_3$), 3.92-4.03 (m, 1H, CHOHC*H*OHCH$_3$), 4.32-4.57 (dm, 1H, J= 48.4, C*H*F). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, *C*H$_3$CH$_2$), 17.2 (d, J= 1.7, CHOH*C*H$_3$), 22.5 (s, CH$_3$*C*H$_2$), 24.6 (d, J= 2.7, CH$_3$CH$_2$*C*H$_2$), 31.3 (d, J= 20.5, *C*H$_2$CHF), 31.6 (s, *C*H$_2$CH$_2$CHF), 67.9 (d, J= 4.4, *C*HOHCH$_3$), 75.3 (d, J= 23.7, *C*HOHCHF), 93.9 (d, J= 168.1, *C*HF). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-194.5] – [-194.0] (m, CH*F*). MS m/z (rel. int. %), (CI-isobutane): 179 (M+1, 85), 161 (M+1-H_2O, 100), 141 ($C_9H_{17}O^+$, 93), 123 ($C_9H_{16}^+$, 45), 114 ($C_7H_{14}O^+$, 10), 96 ($C_7H_{13}^+$, 7), 81($C_6H_{10}^+$, 5).

6.20 **Preparation of *toluene-4-sulfonic acid 3-fluoro-2-hydroxy-1-methyl-octyl ester* (197)**

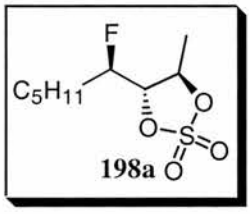


197

To a solution of **190a** (0.178 g, 1.00 mmol), pyridine (0.098 cm^3, 1.2 mmol), and DMAP (2.0 mg, 0.02 mmol) in DCM (20 cm^3) was added TsCl (0.226 g, 1.1 mmol) at RT. After being stirred for 24 h at reflux, the reaction mixture was diluted with DCM, washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane-AcOEt (3 : 1) gave (**197**) (0,232 g, 70%) as a colourless oil. HRMS ($C_{16}H_{26}O_4FS$ requires, 333.1531. Found M+1, 333.1536. ^1H NMR (300 MHz, $CDCl_3$), δ : 0.80-0.91 (m, 3H, CH_3CH_2), 1.17-1.88 (m, 8H + 3H), 2.44 (s, 3H, $TsCH_3$), 4.14 (ddt, 1H, J= 48.1, J= 8.7, J= 2.5, CHF), 4.82-4.92 (dm, 1H, CHOTs), 7.30-7.37 (m, 2H, aromatic), 7.77-7.83 (m, 2H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 17.8 (d, J= 1.1, $CHOTsCH_3$), 21.6 (s, $TsCH_3$), 22.5 (s, CH_3CH_2), 24.2 (d, J= 2.7, $CH_3CH_2CH_2$), 31.1 (d, J= 20.4, CH_2CHF), 31.4 (s, CH_2CH_2CHF), 74.7 (d, J= 26.0, $CHOTsCH_3$), 91.6 (d, J= 173.1, CHF). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-191.6] – [-191.0] (m, CHF). MS m/z (rel. int. %), (CI-isobutane): 333 (M+1, 95), 161 ($C_9H_{18}FO^+$, 100), 141 ($C_9H_{17}O^+$, 12).

6.21 **Two step protocol procedure for the preparation of cyclic sulfates (198a) and (198b)**

6.21.1 Preparation of *4-(1-fluoro-hexyl)-5-methyl-[1,3,2]dioxathiolane 2,2-dioxide* **(198a).**



198a

Cyclic Sulfite.

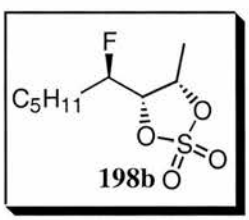
Pyridine (1.26 cm^3, 15.50 mmol) was injected at room temperature to a solution of **190a** (1.80 g, 10.34 mmol) in DCM (50 cm^3). After the mixture was stirred and chilled at 0 °C, $SOCl_2$ (0.91 cm^3, 12.40 mmol) was added. The reaction was stirred at 0 ^0C for 30 min and then sat. $CuSO_4$ (50 cm^3) was added. The organic layer dried with $MgSO_4$, concentrated on a rotary evaporator and used in the subsequent oxidation without isolation.

Cyclic Sulfate.

$NaIO_4$ (5.53 g, 25.85 mmol) was added to a solution of the crude cyclic sulfite in MeCN (20 cm^3) followed by the addition of a catalytic amount of $RuCl_3$-$3H_2O$ (1 mol%) and H_2O (18 cm^3). The heterogeneous mixture was stirred vigorously at 0 ^0C until full consumption of the starting material (30 min). Ether (20 cm^3) was then added and the organic layer was separated, washed with $NaHCO_3$ 5% solution, dried, filtered through a pad of silica gel and concentrated under reduced pressure. The residue was purified over silica gel (elution with hexane:EtOAc 6:1) to obtain **198a** (1.95 g, 78%) as colourless oil.

HRMS ($C_9H_{18}O_4FS$ requires, 241.0909. Found M+1, 241.090). IR (neat), ν : 2960, 2860, 1460, 1390, 1210. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.87-1.00 (m, 3H, CH_3CH_2), 1.29-1.63 (m, 6H), 1.66 (dd, 3H J= 6.4, J= 1.02, SOCHCH_3), 1.69-1.89 (m, 2H) 4.34 (q, 1H, J= 7.1, CHFC*H*OS), 4.71 (dm, 1H, C*H*F), 5.01 (p, 1H, J= 7.1, C*H*OSCH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 18.9 (d, J= 1.6, CH_3), 22.4 (s, CH_3CH_2), 24.0 (d, J= 2.7, $CH_3CH_2CH_2$), 31.2 (s, CH_2CH_2CHF), 31.6 (d, J= 19.9, CH_2CHF), 81.1 (s, SO*C*HCH$_3$), 85.4 (d, J= 30.4, CHF*C*HOS), 91.21 (d, J= 174.1, *C*HF). ^{19}F NMR (275 MHz, $CDCl_3$), δ : [-196.0] – [-195.5] (m, CH*F*). MS m/z (rel. int. %), (CI-isobutane): 241 (M+1, 100), 143 ($C_9H_{16}F^+$, 7), 123 ($C_9H_{15}^+$, 32).

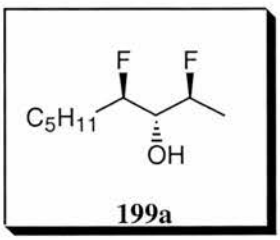
6.21.2 Preparation *of 4-(1-fluoro-hexyl)-5-methyl-[1,3,2]dioxathiolane 2,2-dioxide* (**198b**).



198b

In a similar manner to the method described above, cyclic sulfate **(198b)** was prepared as colourless oil (0.80 g, 3.3 mmol, 85%) starting from **190b** (0.70 g, 3.93 mmol). HRMS ($C_9H_{18}O_4FS$ requires, 241.0894. Found M+1, 241.0901). IR (neat), ν : 2960, 2865, 1460, 1390, 1215. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.87-0.96 (m, 3H, CH_3CH_2), 1.29-1.60 (m, 6H), 1.64 (dd, 3H, J= 6.6, J= 2.5, OSCHCH_3), 1.69-1.89 (m, 2H) 4.66-4.91 (m 2H, CHFC*H*OS and C*H*F), 5.21 (dq, 1H, J= 6.6, J= 5.6, SO*C*HCH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 14.4 (d, J= 3.8, SOCH*C*H$_3$), 22.4 (s, CH_3CH_2), 23.6 (d, J= 2.7, $CH_3CH_2CH_2$), 31.3 (s, CH_2CH_2CHF), 31.9 (d, J= 20.5, CH_2CHF), 81.6 (s, SO*C*HCH$_3$), 82.1 (d, J= 5.5, CHF*C*HOS), 88.5 (d, J= 170.3, *C*HF). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-194.9] – [-194.4] (m, CH*F*). MS m/z (rel. int. %), (CI-isobutane): 241 (M+1, 100), 143 ($C_9H_{16}F^+$, 7), 123 ($C_9H_{15}^+$, 32).

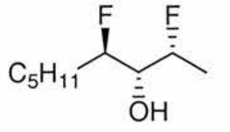
6.22 **Preparation of *2,4-difluoro-nonan-3-ol* (199a).**



199a

To a solution of **198a** (1.80 g, 10.11 mmol) in dry acetone (30 cm^3) was added 1 M TBAF solution in THF (14.8 cm^3, 14.8 mmol). The reaction mixture was stirred at 0^0 C until **198a** was fully consumed (TLC, hexane/EtOAc 4:1, 40 min). Most of the acetone was removed on a rotary evaporator, and the residue was dried by high vacuum for 6-10 min (0.8 Torr). Ether (20 cm^3) and 20% aqueous H_2SO_4 (20 cm^3) were added, and the heterogeneous mixture was stirred vigorously at ambient temperature until hydrolysis was complete (48 h). The two phases were separated and the organic layer was washed with sat. $NaHCO_3$ (25 cm^3), evaporated, dried and the residue was purified over silica gel (7:1 hexane/ethyl acetate) to yield **199a** as a colourless oil (0.70 g, 52%). HRMS ($C_9H_{19}OF_2$ requires, 181.1404. Found M+1, 181.1411). IR (neat), ν : 3440, 2960, 2865, 1460, 1395, 1060, 995. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.84-0.98 (m, 3H, CH_3CH_2), 1.27-1.34 (m, 6H), 1.41 (ddd, 3H, J= 25.3, J= 6.4, J= 0.8, $CHFCH_3$), 1.50-1.82 (m, 2H), 3.83-3.96 (m 1H, $CHFCHOH$), 4.47 (dm, 1H, CH_2CHF, J= 47.4), 4.77 (dm, 1H, J= 46.6, $CHFCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, CH_3CH_2), 15.4 (dd, J= 22.7, J= 1.6, $CHFCH_3$), 22.5 (s, CH_3CH_2), 24.6 (d, J=3.3, $CH_3CH_2CH_2$), 30.6 (dd, J= 20.4, J= 1.1, CH_2CH_2CHF), 31.6 (s, CH_2CH_2CHF), 73.9 (dd, J= 23.7, J= 22.6, $CHFCHOHCHF$), 90.1 (dd, J= 164.4, J= 5.5, CH_2CHF), 93.24 (dd, J= 168.1, J= 6.1, $CHFCH_3$). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-195.6] – [-195.2] (m, CH_2CHF), [-185.7] – [-185.2] (m, $CHFCH_3$). MS m/z (rel. int. %), (CI-isobutane): 181 (M+1, 5), 161 (M+1 – HF, 90), 141 (M+1 – 2HF, 20), 123 ($C_9H_{15}^+$,100).

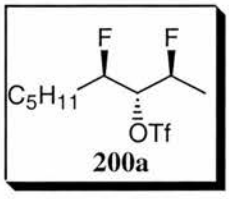
6.23 **Preparation of** 2,4-difluoro-nonan-3-ol **(199b).**



199b

In a similar manner to the method described above **(199b)** was prepared as colourless oil (0.250 g, 45%) from **198b** (0.750 g, 3.12 mmol). HRMS ($C_9H_{20}OF_2$ requires**,** 181.1404. Found M+1, 181.1402). IR (neat), ν : 3405, 2960, 2865, 1460, 1380, 1060, 1000. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.85-0.93 (m, 3H, CH_3CH_2), 1.21-1.37 (m, 6H), 1.41 (ddd, 3H, J= 24.8, J= 6.6, J= 0.7, CHFC*H*$_3$), 1.50-1.82 (m, 2H), 3.83-3.96 (m, 1H, C*H*OH), 4.45 (dm, 1H, J= 47.9, CH_2C*H*F), 4.90 (dm, 1H, J= 47.4, C*H*FCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, *C*H$_3$CH$_2$), 17.1 (dd, J= 22.6, J= 1.1, CHF*C*H$_3$), 22.5 (s, CH$_3$*C*H$_2$), 24.4 (d, J= 2.7, CH$_3$CH$_2$*C*H$_2$), 31.4 (dd, J= 20.4, J= 3.3, CH$_2$*C*H$_2$CHF), 31.6 (s, *C*H$_2$CH$_2$CHF), 73.9 (dd, J= 23.6, J= 22.8, CHF*C*HOHCHF), 88.9 (dd, J= 167.5, J= [illegible] 15), 123 ($C_9H_{15}^+$, 30).

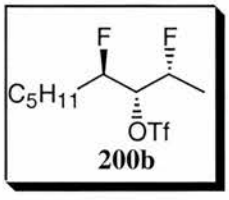
6.24 **Preparation of *trifluoro-methanesulfonic acid 2-fluoro-1-(1-fluoro-ethyl)-heptyl ester* (200a).**



200a

Pyridine (0.22 cm^3, 2.67 mmol) was added to a solution of **199a** (0.3 g, 1.78 mmol) in dry DCM (15 cm^3) at ambient temperature. The solution then was cooled to -40° C and triflic anidride (0.31 cm^3, 1.86 mmol) was added over a period of 5 min. The resulting dark orange solution was stirred for 1 h at – 40 °C and then allowed to warm to ambient temperature. Hexane (10 cm^3) was added and the solution filtered. The filtrate obtained was evaporated, dried and the residue passed over a silica gel pad (eluent 10:1, hexane/ethyl acetate) to afford **200a** (0.41 g, 74%) as a clear oil. HRMS ($C_9H_{17}F_2$ requires, 163.1298. Found [M-SO_3CF_3+1] 163.1295); ($C_9H_{16}F$ requires, 143.1236. Found [M-SO_3CF_3-HF+1], 143.1230); (C_9H_{15} requires, 123.1173. Found [M-SO_3CF_3-2HF+1], 123.1168). IR (neat), ν : 2960, 2870, 1415, 1465, 1245, 1210, 1145, 950, 920. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.82-0.96 (m, 3H, CH_3CH_2), 1.24-1.43 (m, 6H), 1.49 (ddd, 3H, J= 23.6, J= 6.4, J= 1.0, CHFCH_3), 1.57-1.85 (m, 2H), 4.61-4.68 (m 1H, CHFC*H*OTf), 4.76-5.09 (m, 2H,C*H*FCHOTfC*H*F). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.3 (s, CH_3CH_2), 16.4 (dd, J= 22.6, J= 2.8, CHFCH_3), 22.7 (s, CH_3CH_2), 24.9 (d, J= 3.3 $CH_2CH_2CH_3$), 30.8 (dd, = 21.0, J= 1.7, CH_2CH_2CHF), 31.6 (s, CH_2CH_2CHF), 87.3 (dd, J= 173.6, J= 5.5, CH_2CHF) 87.35 (t, J= 23.8, CHF*C*HOTfCHF), 91.3 (dd, J= 176.9, J= 6.1, *C*HFCHOTf*C*HF), 118.9 (q, J= 318.9, CF_3). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-193.3] – [-193.2] (m, CH_2CHF), [-182.4] – [-182.3] (m, $CHFCH_3$), -74.5 (dd, J= 4.8, J= 3.3, CF_3). MS m/z (rel. int. %), (CI-isobutane): 163 (M+1–OTf, 10), 143 ($C_9H_{16}F^+$, 30), 123 ($C_9H_{15}^+$, 100).

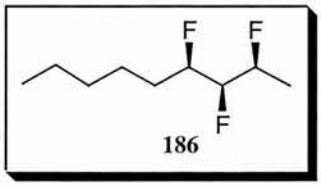
6.25 **Preparation of *trifluoro-methanesulfonic acid 2-fluoro-1-(1-fluoro-ethyl)-heptyl ester* (200b).**



200b

In a similar manner to the method described above, **(200b)** was prepared as colourless oil (0.18 g, 70%) from **199b** (0.60 g, 0.83 mmol). HRMS (C_9H_{15} requires, 123.1173. Found [M-SO_3CF_3-2HF+1], 123.1167). IR (neat), ν : 2960, 2865, 1465, 1415, 1245, 1215, 1145, 950, 920.^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.87-0.99 (m, 3H, CH_3CH_2), 1.26-1.41 (m, 6H), 1.48 (dd, 3H, J= 24.2, J= 6.3, $CHFCH_3$), 1.54-1.94 (m, 2H), 4.60-4.68 (m 1H, CHFCHOTfCHF), 4.76-5.06 (m, 2H, CHFCHOTfCHF). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 17.1 (d, J= 23.0, $CHFCH_3$), 22.4 (s, CH_3CH_2), 24.9 (d, J= 3.3, $CH_3CH_2CH_2$), 30.0 (d, = 20.7, CH_2CH_2CHF), 31.2 (s, CH_2CH_2CHF), 87.3 (dd, J= 177.2, J= 6.9, CH_2CHF) 88.5 (dd, J= 23.0, J= 18.2, CHFCHOTfCHF), 90.4 (dd, J= 170.3, J= 4.6, CHFCHOTFCHF), 114.3 (q, J= 319.1, CF_3). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-189.1] – [-188.2] (m, $CHFCH_2$), [-185.5] – [-184.6] (m, $CHFCH_3$), -74.5 (dd, J= 4.83, J= 3.7, CF_3). MS m/z (rel. int. %), (CI-isobutane): 123 ($C_9H_{15}^+$, 35), 80 (C_6H_8,$^+$100)

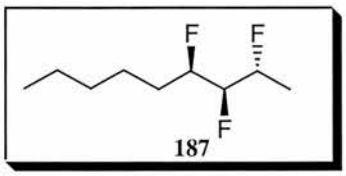
6.26 **Preparation of *2,3,4-trifluoro-nonane (186).***



186

A solution of 1M TBAF in THF (1.2 cm^3, 1.2 mmol) was added to a solution of the triflate **200a** (0.30 g, 0.96 mmol) in dry acetone (10 cm^3). The reaction mixture was stirred at 0 ^0C until the triflate was consumed (TLC, hexane/Ether 9:1, 10 min). The residue was washed with water (10 cm^3) and extracted into hexane (2 x 10 cm^3). The organic layer was evaporated, dried and the residue purified by preparative TLC (elution with hexane/Ether 9:1) to obtain **186** (0.050 g, 28%) as a clear oil. HRMS ($C_9H_{18}F_3$ requires, 183.1361. Found M+1, 183.1356). ^1H NMR (300 MHz, $CDCl_3$), δ : 0.87-0.97 (m, 3H, CH_3CH_2), 1.23-1.37 (m, 6H), 1.44 (ddt, 3H, J= 24.1, J= 6.4, J= 0.8, $CHFCH_3$), 1.50-1.98 (m, 2H), 4.18-5.03 (m, 3H, $CHFCHFCHF$). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 16.3 (dd, J= 23.0, J= 6.9, $CHFCH_3$), 22.4 (d, J= 6.1, CH_3CH_2), 24.4 (d, J= 4.6, $CH_3CH_2CH_2$), 30.1 (dd, = 20.7, J= 4.0, CH_2CH_2CHF), 31.5 (s, CH_2CH_2CHF), 88.2-95.4 (m, $CHFCHFCHF$). ^{19}F NMR (275 MHz, $CDCl_3$), δ : [-207.4] – [-206.9] (m, CHF-$CHFCHF$), [-199.4] – [-198.7] (m, CH_2CHF), [-189.4] – [-188.7] (m, $CHFCH_3$). ^{19}F NMR {^1H} (282 MHz, $CDCl_3$), δ : -207.1 (dd, J= 12.9, J= 11.2, $CHFCHFCHF$), -198.9 (d, J= 11.2, CH_2CHF) -189.1 (d, J= 12.9, $CHFCH_3$). MS m/z (rel. int. %), (CI-isobutane): 183 (M+1, 5), 143 (M+1-2HF, 100), 123 (M+1 -3HF, 20).

6.27 *Preparation of* ***2,3,4-trifluoro-nonane (187).***

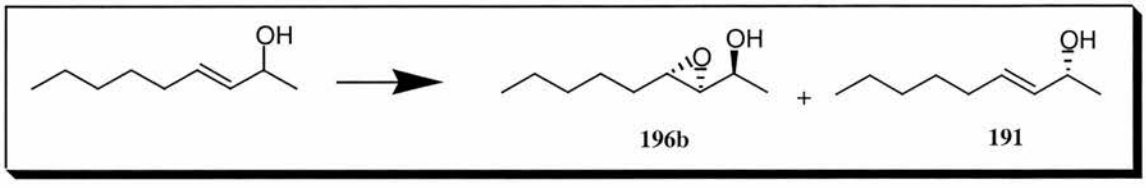


187

A solution of 1M TBAF in THF (1.2 cm^3, 1.2 mmol) was added to a solution of the triflate **200b** (0.150 g, 0.48 mmol) in dry acetone (5 cm^3). The reaction mixture was stirred at 0 ^0C until the triflate was consumed (TLC, hexane/Ether 9:1, 10 min). The residue was washed with water (5 cm^3) and extracted into hexane (2 x 5 cm^3). The organic layers were evaporated, dried and the residue purified by preparative TLC (elution with hexane/Ether 9:1) to obtain **187** (0.021 g, 0.115 mmol, 24%) as colourless oil. ^1H NMR (300 MHz, $CDCl_3$), δ : 0.81-0.96 (m, 3H, CH_3CH_2), 1.22-1.41 (m, 6H), 1.48 (dddd, 3H, J= 25.4, J= 6.1, J= 2.3, J= 0.5, $CHFCH_3$), 1.54-1.99 (m, 2H), 4.29 (dtdd 3H, J= 45.8, J= 26.4, J= 7.4, J= 1.8, $CHFCH_3$), 4.50-4.73 (m, 1H, $CHFCHFCHF$), 4.86 (dm, 1H, J= 48.1, $CHFCHFCHF$).^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.9 (s, CH_3CH_2), 17.1 (dd, J= 20.7, J= 2.1, $CHFCH_3$), 22.4 (s, CH_3CH_2), 24.6 (d, J= 5.1, $CH_2CH_2CH_3$), 27.8 (dd, = 21.7, J= 5.1, CH_2CH_2CHF), 32.5 (s, CH_2CH_2CHF), 86.4 (ddd J= 173.1, 29.3, 5.3, $CHFCHFCHF$), 90.1 (ddd J= 181.1, 29.3, 18.0, $CHFCHFCHF$), 92.9 (ddd J= 180.0, J= 18.4, J= 3.3, $CHFCHFCHF$). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-213.5] – [-213.1] (m, $CHFCHFCHF$), [-201.2] – [-200.7] (m, CH_2CHF), [-185.8] – [-185.2] (m, $CHFCH_3$). ^{19}F NMR {^1H} (282 MHz, $CDCl_3$), δ : 213.3 (dd, J= 14.4, J= 9.3, $CHFCHFCHF$), -201.0 (dd, J= 9.3, J= 3.4, CH_2CHF), -185.5 (dd, J= 14.4, J= 3.4, $CHFCH_3$). MS m/z (rel. int. %), (EI): 134 (2), 113 (5).

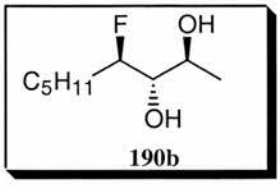
6.28 **Sharpless epoxidation of *(E)-3-nonen-2-ol.***

1.1.1 Preparation of *(1S)-1-[(2S,3S)-3-pentyloxiranyl]ethanol* (**196b**) *and E-(2R,)-3-nonen-2-ol* (**191**)



Molecular sieves (4 Å), DCM (30 cm^3), **191** (1.10 g, 7.8 mmoles) and (L)-(+)-diisopropyl tartrate (0.258 g, 1.11 mmoles), were mixed under nitrogen and the mixture cooled at –23 ^{0}C. Ti(O^iPr) (0.218 g, 0.78 mmoles) was then added *via* syringe and the mixture stirred at –23 ^{0}C for 30 min, before ^{t}BuOOH (1.0 cm^3 of an approximately 5-6 M solution in isooctane, pre-dried for 12 h over molecular sieves 4 Å) was slowly added. After 2 h the reaction was quenched by adding a solution obtained by dissolving $FeSO_4 \cdot 7H_2O$ (3.0 g) and citric acid (1.0 g) in 10 cm^3 of water. The organic layer was recovered and the aqueous solution extracted into DCM (2 x 30 cm^3). The combined organic phases were dried and evaporated. A pre-prepared aqueous solution (0.5 g of NaCl, 3.3 g of NaOH, in 10 cm^3 of H_2O) was then added to the organic residue whereby an emulsion formed. After the emulsion (approx. 30 min) had disappeared the mixture was worked up as described above. After evaporation of the solvent, column chromatography (hexane:EtOAc 2:1) gave **191** (0.300 g $[\alpha]_D^{20}$= +9.20[3], c = 0.555, DCM) and **196b** (0.500 g, 40.5%, $[\alpha]_D^{20}$= -6.87, *c* = 0.495, DCM, 90% de and 80% ee).

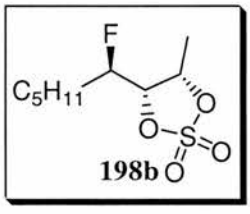
6.29 **Preparation of *(2S,3R,4R)-4-fluoro-2,3-nonanediol* (190b)**



190b

In a similar manner to the method described in section **6.19, (190b)** was prepared as colourless oil (0.226 g, 55%, $[\alpha]_D^{20}$= +19.17, *c*= 0.135, DCM) from **196b** (0.400 g, 2.53 mmol).

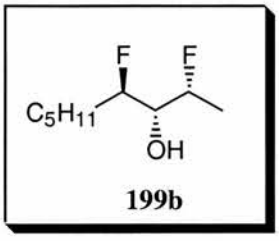
6.30 **Preparation of *(4R,5R)-4-[(1S)-1-fluorohexyl]-5-methyl-1,3,2-dioxathiolane 2,2-dioxide* (198b)**



198b

In a similar manner to the method described in section **6.21, (198b)** was prepared as colourless oil (0.230, 87%, $[\alpha]_D^{20}$= +15.27 *c*= 0.14 in DCM) from **190b** (0.20 g, 1.10 mmol), to afford **198b** (0.230, 87%).

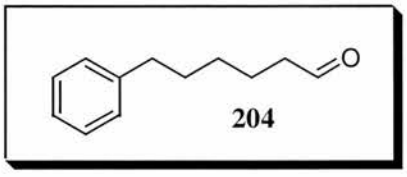
6.31 Preparation of *(2S,3R,4S)-2,4-difluoro-3-nonanol* (**199b**)



199b

In a similar manner to the method described in section **6.22, (199b)** was prepared as a white crystalline solid (0.050 g, 66%, Mp = 41 - 43 °C , $[\alpha]_D^{20}$= +11.99, *c*= 0.18, DCM) from **198b** (0.10 g, 0.42 mmol).

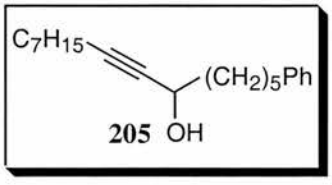
6.32 **Preparation of *6-phenyl-hexanal* (204)**



204

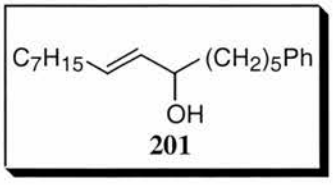
A solution of alcohol **202** (4.1 g, 23.00 mmol) in DCM (20 cm^3) was added to a suspension of PCC (7.4 g, 34.50 mmol) in dry DCM (50 cm^3) in one portion and the mixture was stirred at RT for 2 hours. Dry ether (25 cm^3) was then added and the residue passed through a short pad of silica gel. The organic phase was evaporated to obtain **204** as a yellow oil (3.5 g, 86%). This material was used without further purification. IR (neat), ν : 2930, 2855, 1725, 1495, 1450, 745, 690. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.30-1.44 (m, 2H), 1.58-1.75 (m, 2H, C*H*$_2$), 2.43 (dt, 2H, J= 7.2, J= 1.8, C*H*$_2$C=O), 2.62 (t, 2H, J= 7.7, C*H*$_2$Ph), 7.14-7.32 (m, 5H, aromatics), 9.76 (d, 1H, J= 1.8, C*H*O). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 21.9 (s, *C*H$_2$), 28.7 (s, *C*H$_2$), 31.2 (s, *C*H$_2$), 35.7 (s, *C*H$_2$C=O), 43.8 (s, Ph*C*H$_2$), 125.7 (s, aromatic), 128.3 (s, aromatic), 128.4 (s, aromatic), 142.4 (s, aromatic), 202.8 (*C*=O). MS m/z (rel. int. %), (EI): 176 (M, 10), 130 ($C_{11}H_{14}^+$, 20), 91 ($PhCH_2^+$,100).

6.33 **Preparation of 1-*phenyl-pentadec-7-yn-6-ol* (205)**



A solution of *n*-BuLi (2.5M in hexane, 6.8 cm^3, 17.0 mmol) was added to a THF (30 cm^3) solution of alkyne **203** (2.1 g, 17.0 mmol) at –78°C, and the mixture was stirred for 30 min. A solution of **202** (3.0 g, 17.0 mmol) in THF (30 cm^3) was then added, and the reaction mixture was warmed to 0 °C and stirred for 2 hr. A sat. NH_4Cl (25 cm^3) was then added and the mixture was extracted into ether (2 x 50 cm^3). The organic layer was dried over $MgSO_4$, evaporated and the organic residue purified over silica gel (hexane:EtOAc, 6:1) to afford **205** as colourless oil (4. g, 82%). HRMS ($C_{21}H_{33}O$ requires, 301.2524. Found M+1, 301.2524). IR (neat), ν : 3336, 2931, 2854, 1496, 1454, 1086, 1029, 745, 698. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.67-0.87 (m, 3H, C*H*$_3$), 1.10-1.74 (m, 18H), 2.07 (dt, 2H, J= 6.9, J= 2.0, C*H*$_2$CH$_2$OH), 2.48 (t, 2H, J= 7.6, C*H*$_2$Ph), 4.16-4.26 (m, 1H, C*H*OH) 7.00-7.19 (m, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 18.6 (s, *C*H$_2$CHOH), 22.6 (s, CH$_2$), 25.0 (s, *C*H$_2$), 28.6 (s, *C*H$_2$), 28.8 (s, *C*H$_2$), 28.8 (s, *C*H$_2$), 28.9 (s, *C*H$_2$), 31.4 (s, *C*H$_2$), 35.8 (s, *C*H$_2$Ph), 38.1 (s, *C*H$_2$C≡C), 62.8 (s, *C*HOH), 81.2 (s, *C*≡CCHOH), 85.5 (s, C≡*C*CHOH), 125.7 (s, aromatic), 128.2 (s, aromatic), 128.4 (s, aromatic), 142.7 (s, aromatic). MS m/z (rel. int. %), (CI-isobutane): 301 (M+1, 5), 283 (M+1-H_2O, 100), 193 ($C_{14}H_{25}^+$ 25).

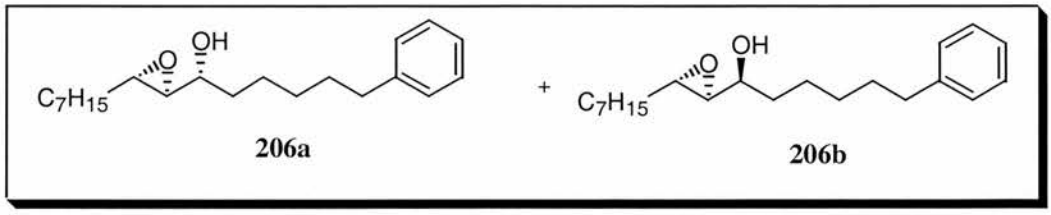
6.34 **Preparation of *1-phenyl-pentadec-7-en-6-ol* (201)**



201

A solution of alkyne **205** (3.0 g, 10.0 mmol) in THF (20 cm^3) was added to a suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (30 cm^3) at 0 °C. The reaction mixture was then stirred under reflux for 12 hours, and the excess of $LiAlH_4$ was quenched by dropwise addition of water (1 cm^3). The mixture was filtered and the white precipitate washed with ether. The combined organic filtrates were dried over $MgSO_4$ and evaporated to afford **201** as colourless oil (2.7 g, 89%). This material was used without further purification. HRMS ($C_{21}H_{35}O$ requires, 303.2680. Found M+1, 303.2688). IR (neat), ν : 3360, 2930, 2850, 1495, 1455, 1020, 970, 910, 730, 695. ^1H NMR (300 MHz, $CDCl_3$), δ : 0.79-0.95 (m, 3H, C*H*$_3$), 1.18-1.75 (m, 18H), 2.01 (q, 2H, J= 6.6, C*H*$_2$CHOH), 2.60 (t, 2H, J= 7.4, C*H*$_2$Ph), 4.02 (q, 1H, J= 6.4, C*H*OH), 5.43 (ddt, 1H, J= 15.3, J= 6.9, J= 1.2, C=C*H*CHOH), 5.62 (dt, 1H, J= 15.3, J= 6.6, C*H*=CHCHOH), 7.19-7.33 (m, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H_3), 22.7 (s, *C*H_2), 25.3 (s, CH_2), 29.0 (s, *C*H_2), 29.1 (s, *C*H_2), 29.1 (s, *C*H_2), 31.4 (s, *C*H_2), 31.8 (s, *C*H_2), 32.1 (s, *C*H_2), 35.8 (s, *C*H_2Ph), 37.1 (s, *C*H_2C=C), 73.1 (s, *C*HOH), 125.5 (s, aromatic), 128.1 (s, aromatic), 128.3 (s, aromatic), 132.2 (s, C=*C*), 132.8 (s, *C*=C), 142.7 (s, aromatic). MS m/z (rel. int. %), (CI-isobutane): 303 (M+1, 2), 285 (M+1-H_2O, 20), 203 ($C_{14}H_{19}O^+$, 20), 189 ($C_{13}H_{17}O^+$, 70) 175 (20).

6.35 **Preparation of *1-(3-heptyl-oxiranyl)-6-phenyl-hexan-1-ol* (206a) and (206b)**



A solution of **201**(1.85 g, 6.12 mmol) and *m*CPBA (ca. 70% purity, 1.51 g, 6.12 mmol) in DCM (40 cm^3) was stirred at 0 °C for 3 h. The reaction mixture was then stirred at 0 °C with 10% aqueous Na_2SO_3, (40 cm^3) and was then washed with sat. $NaHCO_3$ (40 cm^3) and sat. NaCl (50 cm^3), dried over anhydrous $MgSO_4$, and concentrated in *vacuo* to yield a mixture **206a** and **206b** in 2:1 ratio (1.5 g, 77%) which was purified by column chromatography (hexane:EtOAc 4:1) to yield **206a** (0.80 g), **206b** (0.4 g) as a colourless oil and a mixture of **206a** and **206b** (0.2 g) .

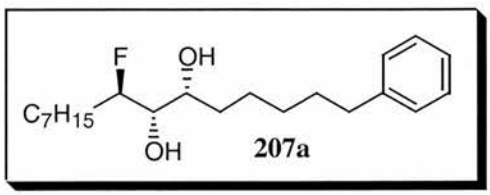
(206a)

HRMS ($C_{21}H_{35}O_2$ requires, 319.2637. Found M+1, 319.2646). IR (neat), ν : 3430, 2930, 2860, 1490, 1455, 1040. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.82-0.92 (m, 3H, C*H*$_3$), 1.18-1.73 (m, 20H), 2.61 (t, 2H, J= 7.7, C*H*$_2$Ph), 2.71 (dd, 1H, J= 5.3, J= 2.3, OC*H*CHOH), 2.89 (td, 1H, J= 5.3, J= 2.6, CH_2C*H*OCH), 3.35-3.48 (m, 1H, C*H*OH), 7.14-7.21 (m, 3H, aromatics), 7.15-7.31 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 25.1 (s, *C*H$_2$), 25.9 (s, *C*H$_2$), 29.2 (s, *C*H$_2$), 29.2 (s, *C*H$_2$), 29.3 (s, *C*H$_2$), 31.3 (s, *C*H$_2$), 31.6 (s, *C*H$_2$), 31.7 (s, *C*H$_2$), 34.2 (s, *C*H$_2$Ph), 35.8 (s, *C*H$_2$CHOCH), 57.0 (s, *C*HOCHCHOH), 61.8 (s, CHO*C*HCHOH), 71.3 (s, *C*HOH), 125.6 (s, aromatic), 128.2 (s, aromatic), 128.4 (s, aromatic), 142.6 (s, aromatic). MS m/z (rel. int. %), (CI-isobutane): 301 (M+1–H_2O, 100), 283 (M+1-2H_2O, 15), 207 (15), 189 (10), 175 (10).

(206b)

HRMS ($C_{21}H_{35}O_2$ requires, 319.2637. Found M+1, 319.2651). IR (neat), ν : 3340, 2930, 2855, 1495, 1455, 1015. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.85-0.95 (m, 3H, C*H*$_3$), 1.21-1.72 (m, 20H), 2.61 (t, 2H, J= 7.4, C*H*$_2$Ph), 2.75 (dd, 1H, J= 2.6, J= 2.3, CHOC*H*CHOH), 2.99 (td, 1H, J= 5.3, J= 2.3, CH$_2$C*H*OCH), 3.75-3.48 (m, 1H, C*H*OH), 7.14-7.21 (m, 3H, aromatics), 7.24-7.31 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 22.5 (s, *C*H$_2$), 25.1 (s, CH$_2$), 26.0 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 29.2 (s, *C*H$_2$), 29.3 (s, *C*H$_2$), 31.3 (s, *C*H$_2$), 31.6 (s, *C*H$_2$), 31.7 (s, *C*H$_2$), 33.4 (s, *C*H$_2$Ph), 35.8 (s, *C*H$_2$CHOCH), 54.8 (s, *C*HOCHCHOH), 60.9 (s, CHO*C*HCHOH), 68.4 (s, *C*HOH), 125.6 (s, aromatic), 128.2 (s, aromatic), 128.3 (s, aromatic), 142.6 (s, aromatic). MS m/z (rel. int. %), (CI-isobutane): 301 (M+1–H_2O ,100), 283 (M+1–2H_2O, 25), 207 (5), 175 (10).

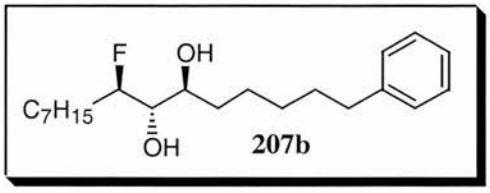
6.36 **Preparation of *8-fluoro-1-phenyl-pentadecane-6,7-diol* (207a)**



207a

A solution of **206a** (0.6 g, 3.12 mmol), in DCM (20 cm^3) was treated with pyridine polyhydrogenfluoride (4 cm^3) at -5 °C for 4h. The reaction mixture was poured into 5% aq. $NaHCO_3$ (20 cm^3) and the organic layer was washed with sat. NH_4Cl (20 cm^3), was dried and, was evaporated to afford a residue which was purified over silica (hexane:EtOAc 80/20) to yield **207a** as a waxy solid (0.460 g, Mp= 87 - 89 °C, 72%). HRMS ($C_{21}H_{36}O_2F$ requires, 339.2699. Found M+1, 339.2684). IR (neat), ν : 3053, 2986, 2930, 2858, 1421, 1262, 835. ^1H NMR (300 MHz, $CDCl_3$), δ : 0.82-0.93 (m, 3H, C*H*$_3$), 1.20-1.79 (m, 20H), 2.61 (t, 2H, J= 7.4, C*H*$_2$Ph), 3.36-3.47 (m, 1H, CHFC*H*OHCHOH), 3.78-3.87 (m, 1H, CHFCHOC*H*OH), 4.48 (dm, 1H, J= 48.13, C*H*F), 7.13-7.21 (m, 3H, aromatics), 7.24-7.31 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 25.0 (s, *C*H$_2$), 25.1 (s, *C*H$_2$), 25.5 (s, *C*H$_2$), 29.1 (d, J= 1.1, *C*H$_2$), 29.4 (s, *C*H$_2$), 31.0 (s, *C*H$_2$), 31.3 (s, *C*H$_2$), 31.8 (s, *C*H$_2$), 33.6 (s, *C*H$_2$Ph), 35.8 (s, *C*H$_2$CHOCH), 69.7 (d, J= 3.8, CHFCHOH*C*HOH), 74.2 (d, J= 23.2, CHF*C*HOHCHOH), 94.3 (d, J= 169.7, *C*HF), 125.6 (s, aromatic), 128.2 (s, aromatic), 128.4 (s, aromatic), 142.6 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-192.4] – [-191.9] (m, CH*F*).). MS m/z (rel. int. %), (CI-isobutane): 339 (40), 321 (M+1 –H_2O, 100), 301 (M+1-HF, 25), 283 ($C_{21}H_{31}^+$, 30), 176 (10).

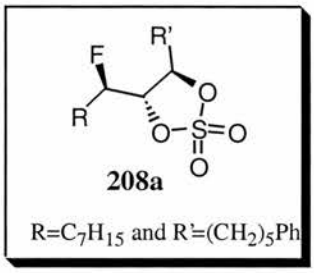
6.37 **Preparation of *8-fluoro-1-phenyl-pentadecane-6,7-diol* (207b)**



207b

In a similar manner to the method described in section **6.36, (207b)** was prepared as waxy solid (0.300 g, Mp= 66 - 68 °C, 71%) from **206b** (0.40 g, 1.25 mmol). HRMS ($C_{21}H_{36}O_2F$ requires, 339.2699. Found M+1, 339.2697). IR (Kbr), ν : 3320, 2930, 2855, 1460, 1060, 700. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.83-0.95 (m, 3H, C*H*$_3$), 1.22-1.80 (m, 20H), 2.61 (t, 2H, J= 7.6, C*H*$_2$Ph), 3.66-3.79 (m, 2H, CHFC*H*OHC*H*OH), 4.55 (dm, 1H, J= 47.8, C*H*F), 7.12-7.21 (m, 3H, aromatics), 7.22-7.32 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 25.0 (s, *C*H$_2$), 25.1 (s, *C*H$_2$), 25.5 (s, *C*H$_2$), 29.2 (d, J= 1.6, *C*H$_2$), 29.4 (s, *C*H$_2$), 30.6 (s, *C*H$_2$), 30.9 (s, *C*H$_2$), 31.4 (s, *C*H$_2$), 31.7 (d, J= 1.6, *C*H$_2$), 35.9 (s, CHOH*C*H$_2$), 72.1 (d, J= 4.4, CHFCHOH*C*HOH), 75.1 (d, J= 23.2, CHF*C*HOHCHOH), 93.9 (d, J= 166.9, *C*HFCHOHCHOH), 125.6 (s, aromatic), 128.2 (s, aromatic), 128.4 (s, aromatic), 142.6 (s, aromatic). ^{19}F NMR (282 MHz), δ : [-193.5] – [-193.0] (m, CH*F*). MS m/z (rel. int. %), (CI-isobutane): 339 (M+1, 55), 321 (M+1 –H_2O, 100), 303 (M+1-HF, 55), 283 ($C_{21}H_{31}^+$, 70), 193 (10).

6.38 **Preparation of *4-(1-fluoro-octyl)-5-(5-phenyl-pentyl)-[1,3,2]dioxathiolane 2,2-dioxide* (208a)**



208a

R=C_7H_{15} and R'=$(CH_2)_5Ph$

Cyclic Sulfite.

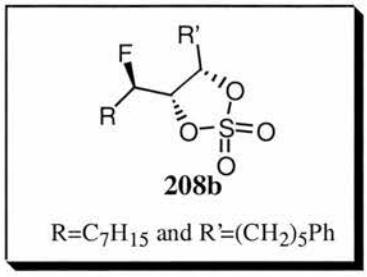
Pyridine (0.120 cm^3, 1.33 mmol) was was injected at room temperature to a solution of **207a** (0.33 g, 0.97 mmol) in DCM (20 cm^3). After the mixture was stirred and chilled at 0 °C, $SOCl_2$ (0.085 cm^3, 1.0 mmol) was added. The reaction was stirred at 0 ^{0}C for 30 min and then sat. $CuSO_4$ (20 cm^3) was added to the organic layer dried with $MgSO_4$, concentrated on a rotary evaporator and used in the subsequent oxidation without isolation.

Cyclic Sulfate.

$NaIO_4$ (0.48 g, 2.25 mmol) was added to a solution of the crude cyclic sulfite in MeCN (7 cm^3) followed by the addition of a catalytic amount of $RuCl_3$-$3H_2O$ (1 mol%) and H_2O (5 cm^3). The heterogeneous mixture was stirred vigorously at 0 ^{0}C until full consumption of the starting material (45 min). Ether (10 cm^3) was added and the organic layer was separated, washed with $NaHCO_3$ 5% solution, dried, filtered through a pad of silica gel and concentrated under reduced pressure. The residue was purified over silica gel (elution with hexane:EtOAc 6:1) to obtain **208a** (0.300 g, 77%) as colourless oil.

HRMS ($C_{21}H_{34}O_4FS$ requires, 401.2162. Found M+1, 401.2156). IR (neat), ν : 2935, 2855, 1395, 1210, 965. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.79-0.93 (m, 3H, C*H*$_3$), 1.17-1.92 (m, 20H), 2.62 (t, 2H, J= 7.4, C*H*$_2$Ph), 4.36-4.46 (m, 1H, CHFC*H*OS), 4.67 (dm, 1H, J= 47.6, C*H*F), 4.80-4.89 (m, 1H, SOC*H*CH$_2$), 7.13-7.22 (m, 3H, aromatics), 7.23-7.30 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, *C*H$_3$), 22.5 (s, *C*H$_2$), 24.3 (s, *C*H$_2$), 24.3 (s, *C*H$_2$), 24.9 (s, *C*H$_2$), 29.2 (d, J= 1.6, *C*H$_2$), 29.4 (s, *C*H$_2$), 30.6 (s, *C*H$_2$), 30.9 (s, *C*H$_2$), 31.4 (s, *C*H$_2$), 31.7 (d, J= 1.6, *C*H$_2$), 35.9 (s, SOCH*C*H$_2$), 72.1 (d, J= 4.4, SO*C*HCH$_2$), 75.1 (d, J= 23.2, CHF*C*HOS), 93.9 (d, J= 166.9, *C*HF), 125.6 (s, aromatic), 128.2 (s, aromatic), 128.4 (s, aromatic), 142.6 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-195.8] – [-195.3] (m, CH*F*). MS m/z (rel. int. %), (CI-isobutane): 401 (M+1, 50), 303 (70), 283 ($C_{21}H_{31}^+$, 100) 131 (65).

6.39 **Preparation of *4-(1-fluoro-octyl)-5-(5-phenyl-pentyl)-[1,3,2]dioxathiolane 2,2-dioxide* (208b)**

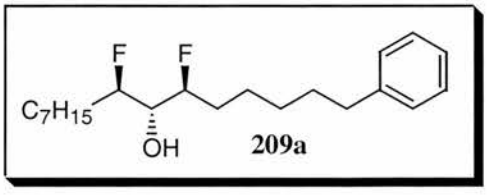


208b

R=C_7H_{15} and R'=$(CH_2)_5Ph$

In a similar manner to the method described in section **6.38, (208b)** was prepared as colourless oil (0.220 g, 75%) starting from **207b** (0.25 g, 0.74 mmol). HRMS ($C_{21}H_{34}O_4FS$ requires, 401.2162. Found M+1, 401.2152). IR (neat), ν : 2929, 2861, 1389, 1209, 992. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.72-0.85 (m, 3H, C*H*$_3$), 1.11-1.99 (m, 20H), 2.55 (t, 2H, J= 7.4, C*H*$_2$Ph), 4.60-4.70 (m, 1H, CHFC*H*OS), 4.67 (dtd, 1H, J= 48.6, J= 8.7, J= 2.8, C*H*F), 4.94 (ddd, 1H, J= 10.1, J= 5.2, J= 3.3, SOC*H*CH$_2$), 7.06-7.15 (m, 3H, aromatics), 7.16-7.25 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 23.9 (s, *C*H$_2$), 24.0 (s, *C*H$_2$), 25.3 (s, *C*H$_2$), 28.1 (d, J= 3.3, *C*H$_2$), 28.5 (s, *C*H$_2$), 29.0 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 31.0 (s, *C*H$_2$), 31.7 (d, J= 1.6, *C*H$_2$), 35.6 (s, *C*H$_2$CHOS), 82.1 (d, J= 34.8, CHFCHOS), 85.9 (s, SO*C*HCH$_2$), 88.4 (d, J= 170.1, CHOHCHOH*C*HF), 125.7 (s, aromatic), 128.3 (s, aromatic), 128.4 (s, aromatic), 142.2 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-193.7] – [-193.2] (m, CH*F*). MS m/z (rel. int. %), (CI-isobutane): 401 (65), 303 (55), 283 ($C_{21}H_{31}^+$, 65) 131 (35).

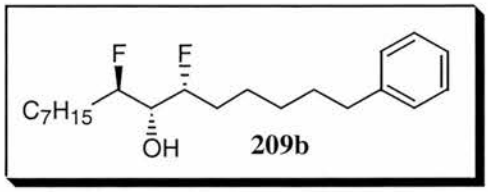
6.40 **Preparation of *6,8-difluoro-1-phenyl-pentadecan-7-ol* (209a)**



209a

To a solution of **208a** (0.3 g, 0.75 mmol) in dry acetonitrile (15 cm^3) was added 1 M TBAF solution in THF (1.5 cm^3, 1.5 mmol). The reaction mixture was stirred at 0^0 C until **208a** fully dissolved (TLC, hexane/EtOAc 4:1, 40 min). Most of the organic solvent was removed on a rotary evaporator, and the residue was dried. THF (10 cm^3) and H_2SO_4 (catalytic amount 1%) were added, and the mixture was stirred vigorously at ambient temperature until hydrolysis was complete (1 h). The organic layer was washed with sat. $NaHCO_3$ (15 cm^3), and extracted into ether (10 x 2), evaporated, dried and the residue was purified over silica gel (hexane:EtOAc 10:1) **209a** as an amorphous solid (0.160 g, 63%, Mp= 59 - 61 °C). HRMS ($C_{21}H_{34}OF_2$ requires, 341.2656. Found M+1, 341.2669). IR (neat), ν : 3450, 2930, 2855, 1495, 1460, 1075, 1035. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.83-0.95 (m, 3H, C*H*$_3$), 1.21-1.82 (m, 20H), 2.62 (t, 2H, J= 7.4, C*H*$_2$Ph), 3.83-3.97 (m, 1H, C*H*OH), 4.53 (dm, 2H, J= 48.4, C*H*FCHOOC*H*F), 7.13-7.21 (m, 3H, aromatics), 7.23-7.31 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 24.9 (s, *C*H$_2$), 29.0 (s, *C*H$_2$), 29.2 (s, *C*H$_2$), 29.4 (s, *C*H$_2$), 30.1 (dd, J= 21.1, J= 1.1, CHF*C*H$_2$), 30.2 (d, J= 21.5, *C*H$_2$CHF), 31.3 (s, *C*H$_2$), 31.7 (s, *C*H$_2$), 35.8 (s, *C*H$_2$), 73.5 (t, J= 23.2, CHF*CH*OHCHF), 93.5 (dt, J= 168.1, J= 5.6 *C*HFCHOH*C*HF), 125.6 (s, aromatic), 128.2 (s, aromatic), 128.4 (s, aromatic), 142.6 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-194.3] – [-193.9] (m, CH*F*CHOHCH*F*). MS m/z (rel. int. %), (CI-isobutane): 341 (M+1, 35), 321 (M+1–HF, 100), 303 (M+1–HF-H_2O, 35), 283 ($C_{21}H_{31}^+$, 65), 131 (35).

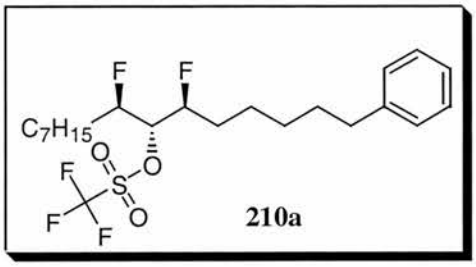
6.41 **Preparation of *6,8-difluoro-1-phenyl-pentadecan-7-ol* (209b)**



209b

In a similar manner to the method described in section **6.40, (209b)** was prepared as a white solid (0.090 g, 59%, Mp= 66 - 68 °C,) starting from **208b** (0.180 g, 0.45 mmol). HRMS ($C_{21}H_{34}OF_2$ requires, 341.2656. Found M+1, 341.2642). IR (Kbr), ν : 3415, 2923, 1466, 1071. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.84-0.93 (m, 3H, C*H*$_3$), 1.21-1.86 (m, 20H), 2.62 (t, 2H, J= 7.4, C*H*$_2$Ph), 3.47 (dt, 1H, J= 24.3, J= 7.9, C*H*OH), 4.45 (dtd, 1H, J= 48.1, J= 8.4, J= 2.6, C*H*FCHOHCHF), 4.70 (dm, 1H, J= 48.1, CHFCHOHC*H*F), 7.10-7.22 (m, 3H, aromatics), 7.23-7.32 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 24.8 (s, *C*H$_2$), 24.8 (s, *C*H$_2$), 28.9 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 29.4 (s, *C*H$_2$), 31.0 (d, J= 21.5, CHF*C*H$_2$), 31.3 (s, *C*H$_2$), 31.5 (d, J= 19.9, *C*H$_2$CHF), 31.8 (s, *C*H$_2$), 35.8 (s, *C*H$_2$), 73.4 (dd, J= 24.8, J= 17.7, *C*HOH), 92.0 (dd, J= 172.0, J= 16.0, CHFCHOH*C*HF), 92.0 (dd, J= 169.7, J= 9.4, CHFCHOH*C*HF), 125.7 (s, aromatic), 128.2 (s, aromatic), 128.3 (s, aromatic), 142.5 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-202.6] – [-202.4] (m, CHFCHOHCH*F*), [-191.3] – [-191.2] (m, CH*F*CHOHCHF). MS m/z (rel. int. %), (CI-isobutane): 341 (M+1, 75), 321 (M+1–HF, 100), 303 (M+1–HF-H_2O, 35), 283 ($C_{21}H_{31}^+$, 45), 171 (10).

6.42 **Preparation of *trifluoro-methanesulfonic acid 2-fluoro-1-(1-fluoro-6-phenyl-hexyl)-nonyl ester* (210a)**

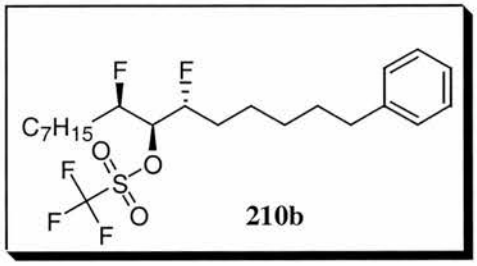


210a

Pyridine (0.048 cm^3, 0.66 mmol) was added to a solution of **209a** (0.15 g, 0.44mmol) in dry DCM (10cm^3) at ambient temperature. The solution then was cooled to -40° C and triflic anhydride (0.030 cm^3, 0.048 mmol) was added over a period of 1 min.

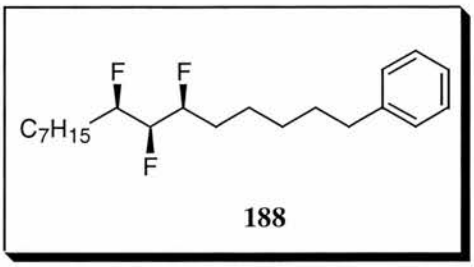
The resulting dark orange solution was stirred for 1 h at – 40 °C and was then allowed to warm to ambient temperature. Hexane (10 cm^3) was added and the solution filtered. The filtrate obtained was evaporated, dried and the residue passed over a silica gel pad (eluent 10:1, hexane/ethyl acetate) to afford **210a** as a clear oil (0.150 g, 72%). HRMS ($C_{27}H_{33}O_4FS$ requires, 472.2084. Found M+1, 472.2078). IR (neat), ν : 2930, 2870, 1470, 1415, 1210, 1140, 1030. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.83-0.93 (m, 3H, C*H*$_3$), 1.20-1.87 (m, 20H), 2.62 (t, 2H, J= 7.7, C*H*$_2$Ph), 4.72 (dm, 2H, J= 45.6, C*H*FOTfC*H*F), 5.00 (tt, 1H, J= 14.6, J= 4.1, C*H*OTf), 7.14-7.22 (m, 3H, aromatics), 7.24-7.33 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.0 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 24.7 (d, J= 2.7,*C*H$_2$) 24.8 (d, J= 3.3, *C*H$_2$), 28.7 (s, *C*H$_2$), 29.0 (s, *C*H$_2$), 29.0 (s, *C*H$_2$), 30.2 (ddd, J= 21.5, J= 10.5, J= 2.2, CHF*C*H$_2$), 31.1 (s, *C*H$_2$), 31.7, (s, *C*H$_2$), 35.8 (s, *C*H$_2$), 87.51 (t, J= 24.3, *C*HOTf), 90.5 (dt, J= 176.9, J= 6.1, *C*HFCHOTf*C*HF), 118.3 (q, J= 318.9), 125.7 (s, aromatic), 128.3 (s, aromatic), 128.4 (s, aromatic), 142.4 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-192.2] – [-191.4] (m, CH*F*CHOTfCH*F*), -74.4 (t, J= 3.9, CHOSOOC*F*$_3$). MS m/z (rel. int. %), (CI-isobutane): 472 (M+1, 20), 304 (M+1-OTf, 70), 283 ($C_{21}H_{31}^+$, 100).

6.43 **Preparation of *trifluoro-methanesulfonic acid 2-fluoro-1-(1-fluoro-6-phenyl-hexyl)-nonyl ester* (210b)**



In a similar manner to the method described in section **6.42, (210b)** was prepared as a clear oil (0.065 g, 69) from **209b** (0.070 g, 020 mmol). HRMS ($C_{27}H_{33}O_4FS$ requires, 472.2084. Found M+1, 472.2074). IR (neat), ν : 2930, 2870, 1470, 1415, 1210, 1145, 1035. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 0.80-0.95 (m, 3H, C*H*$_3$), 1.19-1.87 (m, 20H), 2.62 (t, 2H, J= 7.7, C*H*$_2$Ph), 4.66 (dm, 2H, J= 46.3, C*H*FOTfC*H*F), 4.86-5.03 (m, 1H, C*H*OTf), 7.14-7.22 (m, 3H, aromatics), 7.23-7.33 (m, 2H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 14.1 (s, *C*H$_3$), 22.6 (s, *C*H$_2$), 24.7 (s, *C*H$_2$), 24.7 (s, *C*H$_2$), 28.6 (s, *C*H$_2$), 29.0 (s, *C*H$_2$), 29.2 (s, *C*H$_2$), 29.8 (s, *C*H$_2$), 29.95 (d, J= 20.7, CHF*C*H$_2$), 30.96 (d, J= 20.7, CHF*C*H$_2$), 31.1, (s, *C*H$_2$), 31.7 (s, CH$_2$), 35.75 (s, CH$_2$), 87.51 (dd, J= 23.0, J= 18.4, *C*HOTf), 90.5 (ddd, J= 177.2, J= 46.1, J= 4.6, *C*HFCHOTf*C*HF), 118.3 (q, J= 317.7), 125.7 (s, aromatic), 128.3 (s, aromatic), 128.3 (s, aromatic), 142.3 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-193.9] – [-192.6] (m, CHFCHOTfCH*F*), [-188.4] – [-187.6] (m, CH*F*CHOTfCHF), -74.5 (d, J= 5.1, CHOSOOC*F*$_3$).). MS m/z (rel. int. %), (CI-isobutane): 472 (M+1, 20), 304 (M+1-OTf, 70), 283 ($C_{21}H_{31}^+$, 100).

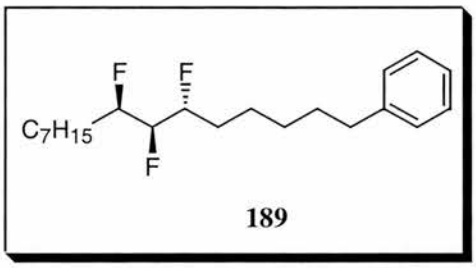
6.44 **Preparation of *(6,7,8-trifluoro-pentadecyl)-benzene* (188)**



188

A solution of 1M TBAF in THF (0.25 cm^3, 0.25 mmol) was added to a solution of the triflate **210a** (0.150 g, 0.48 mmol) in dry acetonitrile (10 cm^3). The reaction mixture was stirred at 0 ^0C until the triflate was consumed (TLC, hexane/Ether 9:1, 10 min). The residue was purified by preparative TLC (elution with hexane/Ether 15:1) to obtain **188** as a white solid (0.025 g, 35%). Mp= 27 - 29 °C. HRMS ($C_{21}H_{34}F_3$ requires, 343.2612. Found M+1, 343.2626. ^1H NMR (500 MHz, $CDCl_3$), δ : 0.84-0.94 (m, 3H, CH_3CH_2), 1.28-1.88 (m, 20H), 2.62 (t, 2H, J= 7.4, CH_2-Ph), 4.35 (dm, 1H, J= 47.6, CHFCHFCHF), 4.65 (dm, 2H, J= 48.9, CHFCHFCHF), 7.14-7.32 (m, 5H, aromatics). ^{13}C NMR (100 MHz, $CDCl_3$), δ : 14.1 (s, CH_3), 22.6 (s, CH_2) 24.6 (d, J= 4.1, CH_2), 24.7 (d, J= 4.1, CH_2), 28.9 (s, CH_2), 29.1 (s, CH_2), 29.2 (s, CH_2), 30.1 (dd, J= 20.7, J= 6.3, CHFCH_2), 31.2 (s, CH_2), 31.7 (s, CH_2), 35.8 (s, CH_2), 91.5 (ddd, J= 174.5, J= 20.7, J= 11.6, CHFCHFCHF), 91.6 (ddd, J= 173.4, J= 20.7, J= 2.0, CHFCHFCHF), 93.2 (tt, J= 183.8, J= 20.8, CHFCHFCHF), 125.8 (s, aromatic), 128.2 (s, aromatic), 128.3 (s, aromatic), 142.5 (s, aromatic). ^{19}F NMR (470 MHz, $CDCl_3$), δ : [-207.6] – [-207.2] (m, CHFCHFCHF), [-198.2] – [-197.6] (m, 2F, CHFCHFCHF). ^{19}F NMR {^1H} (470 MHz, $CDCl_3$), δ : -207.4 (t, J= 12.3, CHFCHFCHF), -197.9 (d, J= 12.4, CHFCHFCHF). MS m/z (rel. int. %), (CI-isobutane): 343 (M+1, 20), 323 (M+1-HF, 70), 303 (M+1-2HF, 25), 283 (M+1-3HF, 30).

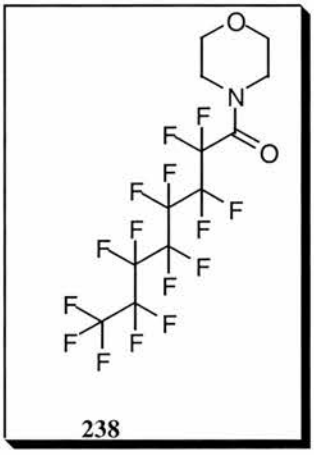
6.45 **Preparation of *(6,7,8-trifluoro-pentadecyl)-benzene* (189)**



189

A solution of 1M TBAF in THF (0.15 cm^3, 0.15 mmol) was added to a solution of the triflate **210b** (0.050 g, 0.11 mmol) in dry acetonitrile (5 cm^3). The reaction mixture was stirred at 0 ^0C until the triflate was consumed (TLC, hexane/Ether 12:1, 10 min). The residue was purified by preparative TLC (elution with hexane/Ether 15:1) to obtain **189** as a clear oil (0.010 g, 27%). HRMS ($C_{21}H_{34}F_3$ requires, 342.2534. Found M, 342.2436). ^1H NMR (500 MHz, $CDCl_3$), δ : 0.83-0.92 (m, 3H, CH_3CH_2), 1.20-1.95 (m, 20H), 2.61 (t, 2H, J= 7.7, CH_2-Ph), 4.28 (dddt, 1H, J= 45.5, J= 26.3, J= 6.4, J= 1.2, CHFCHFCHF), 4.66 (dm, 2H, J= 47.4, CHFCHFCHF), 7.16-7.30 (m, 5H, aromatics). ^{13}C NMR (100 MHz, $CDCl_3$), δ : 14.0 (s, CH_3), 22.6 (s, CH_2) 24.3 (d, J= 2.1, CH_2), 24.9 (d, J= 5.2, CH_2), 28.9 (s, CH_2), 29.1 (s, CH_2), 29.2 (dd, J= 20.7, J= 6.3, CHFCH_2), 29.6 (d, J= 25.8, CH_2), 31.7 (s, CH_2), 35.8 (s, CH_2), 89.3 (ddd, J= 169.2, 29.0, J= 5.1, CHFCHFCHF), 93.4 (ddd, J= 188.9, J= 19.7, J= 13.5, CHFCHFCHF). ^{19}F NMR (470 MHz, $CDCl_3$), δ : [-212.2] – [-212.6] (m, CHFCHFCHF), [-201.1] – [-200.6] (m, CHFCHFCHF), [-194.1] – [-194.5] (m, CHFCHFCHF). ^{19}F NMR {^1H} (470 MHz, $CDCl_3$), δ : -212.3 (dd, J= 14.9, J= 9.2, CHFCHFCHF), -200.8 (d, J= 9.2, CHFCHFCHF), -194.4 (d, J= 14.9, CHFCHFCHF). MS m/z (rel. int. %), (CI-isobutane): 342 (M+1, 75), 303 (M+1-2HF, 25), 283 (M+1-3HF, 35).

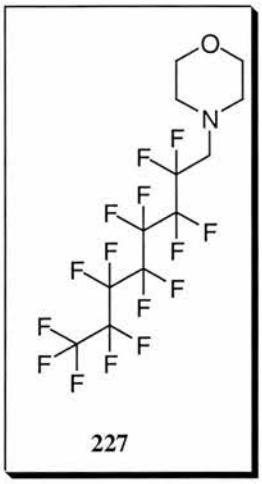
6.46 **Preparation of *2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-1-morpholin-4-yl-octan-1-one* (238)**



238

A solution of the pentadecafluorooctanoyl chloride (**237**) in DCM (0.13 cm^3, 5.2 mmol) was added dropwise to a solution of morpholine (**235**) (0.680 cm^3, 7.8 mmol) in DCM (25 cm^3) at 0 ^{0}C. The reaction was, heated under reflux for 2 h. The organic layer was evaporated under reduced pressure and the residue was washed with ether (3 x 15 cm^3) to give the product amide **238** as a white crystalline solid (2.83 g, 96%). Mp= 47-49 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 3.7 (m, 8H). ^{19}F NMR (282 MHz, $CDCl_3$), δ : -126.3 (br s, 2F, CF_2), -123.0 (br s, 2F, CF_2), -122.2 (br s, 2F, CF_2), -121.2 (br s, 2F, CF_2), -121.0 (br s, 2F, CF_2), -111.2 (t, J= 10, 2F, $COCF_2$), -81.2 (t, J= 10, 3F, CF_3). MS m/z (rel. int. %), (EI): 483 (M, 72), 114 (morpholine, 100).

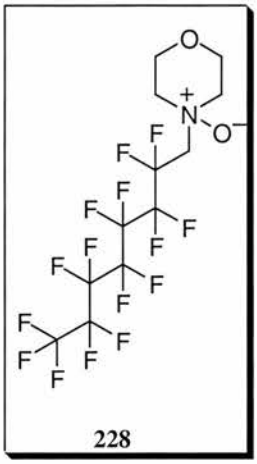
6.47 **Preparation of *4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octyl)-morpholine* (227)**



227

A solution 1.5 M of Borane-THF (7 cm^3, 10.5 mmol) was added dropwise to a solution of **238** (2.7 g, 6.2 mmol) in THF (25 cm^3) at 0^0 C. The mixture was heated under reflux for 1 hour. The excess of borane was quenched using a solution of HCl 5% (2 cm^3), and then ether (5 cm^3) was added. The organic layer was collected and dried with $MgSO_4$. The aqueous layer was basified with 2 N NaOH and extracted into DCM (3 x 10 cm^3). The combined organic layers were evaporated under reduced pressure to give amine **227** as white solid (2.0 g, 70%). Mp= 25 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 2.6 (t, J= 4.8, 4H, CH_2NCH_2), 2.9 (t, J= 16, 2H, CH_2CF_2), 3.69 (t, J= 4.8, 4H, CH_2OCH_2). ^{19}F NMR (282 MHz, $CDCl_3$), δ : -127.3 (br s, 2F, CF_2), -124.2 (br s, 2F, CF_2), -123.8 (br s, 2F, CF_2), -123.0 (br s, 2F, CF_2), -122.8 (br s, 2F, CF_2), -116.3 (br s, 2F, CF_2), -82.1 (t, J =10, 3F, CF_3). MS m/z (rel. int. %), (EI): 469 (M, 46), 451 (M-H_2O, 100).

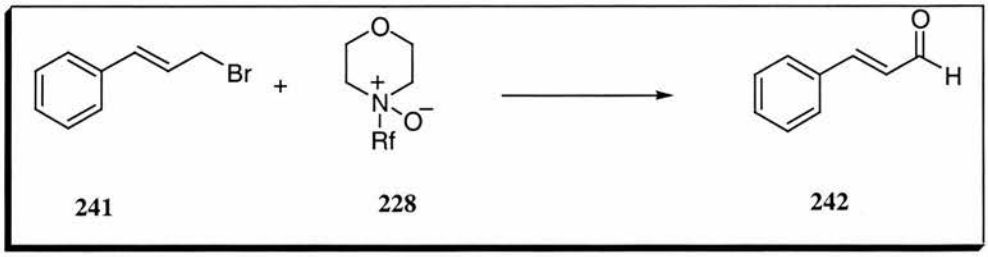
6.48 **Preparation of *4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluoro-octyl)-morpholine 4-oxide* (228)**



228

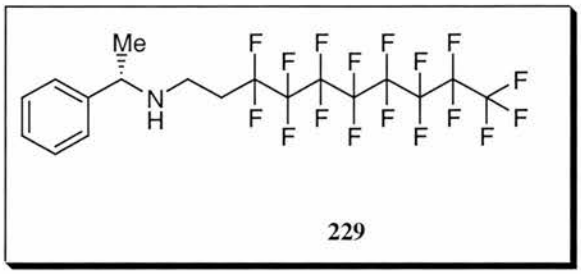
A solution of compound **227** (2.0 g, 4.2 mmol) in DCM (15 cm^3) was added to a suspension of mCPBA (1.0 g, 5.8 mmol) in DCM (20 cm^3) at 0 °C. The mixture was stirred at 4^0 C for 12 hours. An excess of diluite NaOH 1N (5 cm^3) was added to neutralise residual mCPBA. Distilled water (10 cm^3) was added and the product was extracted into DCM (3 x 25 cm^3). The organic layer was filtered and the solvent evaporated under reduced pressure to give a compound **228** as a white crystalline solid (1.63 g, 80%). Mp= 143-145 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 3.20 (d, J= 10, 2H,) 3.60-3.65 (m, 4H), 4.10 (t, J= 16, 2H, CH_2), 4.50 (t, J= 11, 2H, CH_2CF_2). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 61.4 (CH_2OCH_2) 66.1 (CH_2NCH_2), 69.5 (t, J= 19, CH_2CF_2). ^{19}F NMR (282 MHz, $CDCl_3$), δ : -126.4 (br s, 2F, CF_2), -123.3 (br s, 2F, CF_2), -123.0 (br s, 2F, CF_2), -122.2 (br s, 2F, CF_2), -121.6 (br s, 2F, CF_2), -113.1 (br s, 2F, CH_2CF_2), -81.3 (t, J= 10, 3F, CF_3). MS m/z (rel. int. %), (EI): 483 (M, 72), 114 (morpholine, 100).

6.49 **Conversion of *cynnamyl bromide* (241) into *cynnamyl aldehyde* (242)**



Cynnamyl bromide **241** (0:098 g, 0.50 mmol) was added to a solution of N-oxide **228** (0,267 g, 0.55 mmol) in dry acetonitrile (20 cm^3) and the reaction mixture was stirred under reflux. The formation of cinnamyl aldehyde (**242**) was monitored by ^1H NMR and after 30 h reflux the conversion reached 50%.

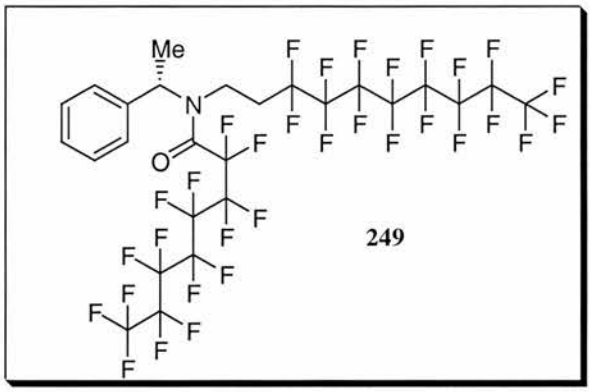
6.50 **Preparation of *3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-N-[(1S)-1-phenylethyl]-1-decanamine* (229).**



229

A mixture of (1*S*)-1-phenylethylamine (**243**) (1.69 g, 13.9 mmol), K_2CO_3 (2.0 g) and perfluorooctyliodide iodide **236** (4.0 g, 6.98 mmol) in dry acetonitrile (30 cm^3) was reacted under reflux for 24 h. After filtration the solvent was evaporated, and the product was purified over silica gel column using hexane: ethylacetate 70/30 as eluent to give **229** (2.1 g, 54%) as a yellow oil. $[\alpha]_D^{20}$ = - 16.2 (*c*= 0.52, DCM). HRMS ($C_{18}H_{15}NF_{17}$ requires, 568.0933. Found M+1, 568.0914). IR (neat), ν : 3065, 3030, 2970, 1450, 1210, 1150, 705. ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.32 (d, 3H, J= 6.6, C*H*$_3$), 1.40 (br, 1H, N*H*), 2.11-2.41 (m, 2H, C*H*$_2$Rf), 2.69-2.90 (m, 2H, C*H*$_2$NH), 3.78 (q, 1H, J= 6.6, C*H*), 7.21-7.38 (m, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 24.3 (s, *C*H$_3$), 31.6 (t, J= 21.5, Rf*C*H$_2$), 39.2 (t, J= 3.8, NH*C*H$_2$), 58.3 (s, *C*H), 107.5-122.3 (m, *C*F$_2$), 126.4 (s, aromatic), 127.1 (s, aromatic), 128.6 (s, aromatic), 145.0 (s, aromatic). ^{19}F NMR (282 MHz, $CDCl_3$), δ : -126.7 (br s, 2F, C*F*$_2$), –124.2 (br s, 2F, C*F*$_2$), -123.7 (br s, 2F, C*F*$_2$), [-122.8] – [-121.7] (m, 6F), -114.2 (br s, 2F, C*F*$_2$), [-81.6] – [-81.2] (m, 3F, C*F*$_3$). MS m/z (rel. int. %), (EI): 552 (M-Me, 30), 490 (M-Ph, 10), 147 (M-Rf, 13), 105 ($C_7H_7N^+$, 11).

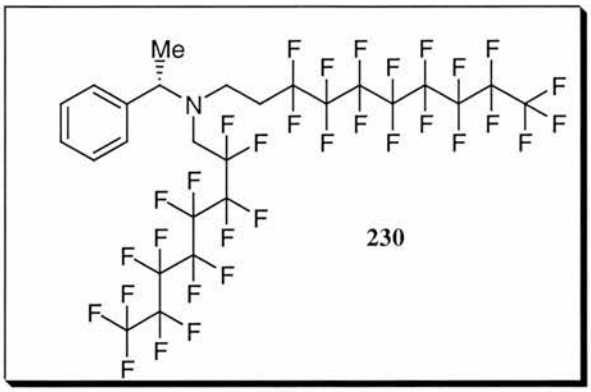
6.51 **Preparation of *3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-N-[(1S)-1-phenylethyl]octanamide* (249).**



249

Pentadecafluorooctanoylchloride **236** (0.96 cm^3, 3.83 mmol) was added to a solution of **229** (2.0 g, 3.53 mmol) and TEA (0.74 cm^3, 5.30 mmol) in DCM (30 cm^3) at 0° C. The reaction mixture was stirred under nitrogen for 12 h. The organic layer was then washed with $NaHCO_3$ 5% solution (30 cm^3), sat. NH_4Cl (30 cm^3) and $CuSO_4$ solution (30 cm^3) and then dried over $MgSO_4$ evaporated to afford **249** as a colourless oil (3.3 g, 97%). This material was used without further purification. $[\alpha]_D^{20}$ = - 17.36 (*c*= 0.70, DCM). MALDI TOF ($C_{26}H_{13}F_{32}NNaO$ requires, 986.0384. Found M+Na 986.0467). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of two rotamers in ratio 5:1 (*M*, *m*), δ : 1.61 (d, 3H, J= 7.2, CH_3 *m*) 1.70 (d, 3H, J= 6.8, CH_3 *M*), 1.99-2.15 (m, 2H, CH_2-Rf *m*), 2.18-2.43 (m, 2H, CH_2-Rf *M*) 3.27-3.56 (m, 2H, CH_2-N *M*), 3.58 –3.74 (m, 2H, CH_2-N *m*) 5.49 (q, 1H, C*H*, J= 6.6 *M*), 5.96 (q, 1H, C*H*, J= 7.2 *m*) 7.30-7.47 (m, 5H, aromatics). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ : 15.7 (s, CH_3, *m*), 17.3 (s, CH_3 *M*), 28.7 (t, J= 24.9, RfCH2), 35.9 (s, NCH_2 *m*), 36.6 (s, NCH_2, *M*), 54.6 (s, *C*H, *m*), 55.2 (s, *C*H, *M*), 108.0-122.3 (m, *C*F), 127.3 (s, aromatic), 128.0 (s, aromatic, *m*), 128.8 (s, aromatic *m*) 129.1 (s, aromatic, *M*) 137.1 (s, aromatic quaternary), 167.2 (*C*=O) ^{19}F NMR (282 MHz, $CDCl_3$), δ : -126.7 (br s, 2F, CF_2), –124.3 (br s, 2F, CF_2), -123.6 (br s, 2F, CF_2), [-123.5] – [-122.1] (m, 12F), -121.4 (br s, 2F, CF_2), -120.5 (br s, 2F, CF_2), -115.4 (br s, 2F, CF_2), -110.4 (br s, 2F, CF_2), [-81.5] – [-81.1] (m, 6F). MS m/z (rel. int. %), (MALDI TOF): 986 (M+23, 100)

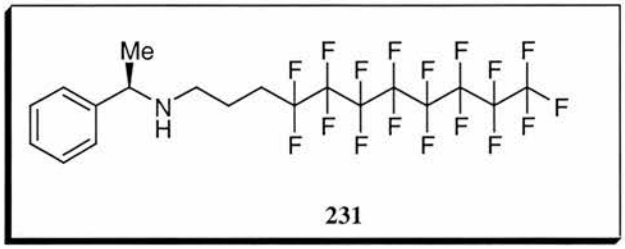
6.52 **Preparation** ***of*** ***3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-N-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl)-N-[(1S)-1-phenylethyl]-1-decanamine*** **(230).**



230

A solution of Borane-THF complex 1.5 M (24 cm^3, 36 mmol) was added dropwise to a solution of **249** (3.3 g, 3.4 mmol) in THF (25 cm^3) at 0^0 C and the mixture was stirred under for 24 hour. The excess borane was destroyed by dropwise addition of water at 0^0 C. Ether (10 cm^3) then was added and the combined organic layers were collected and dried over $MgSO_4$ and evaporated. The resultant residue was purified over silica using hexane:ether 95:5 as the eluent to afford **230** as a clear oil (1.78 g, 55%). $[\alpha]_D^{20}$ = +0.25 (*c*= 2.0, DCM). MALDI TOF ($C_{26}H_{15}F_{32}NNa$ requires, 972.0590. Found M+Na 971.8840). ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.35 (d, 3H, J= 6.8, C*H*$_3$), 1.90-2.30 (m, 2H, C*H*$_2$-Rf), 2.83 (t, 2H, J= 7.8 RfC*H*$_2$N), 2.97-3.33 (m, 2H, C*H*$_2$-N), 3.94 (q, 1H, J= 6.8, C*H*), 7.14-7.34 (m, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 16.1 (s, *C*H_3,), 30.9 (t, J= 19.3, RfCH2), 43.9 (s, N*C*H_2) 51.3 (t, J= 20.5, RfN-*C*H_2-Rf,), 61.2 (s, CH_3*C*H,), 105.0-122.3 (m, CF), 127.5 (s, aromatic), 127.6 (s, aromatic), 128.0 (s, aromatic), 141.6 (s, aromatic quaternary) ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-127.2] – [-126.6] (m, 4F), [-124.5] – [-123.9] (m, 4F), -123.5 (br s, 2F, C*F*$_2$), [-122.9] – [-122.1] (m, 12F), -117.6 (br s, 2F, C*F*$_2$), -115.0 (br s, 2F, C*F*$_2$), [-81.7] – [-81.4] (m, 6F).

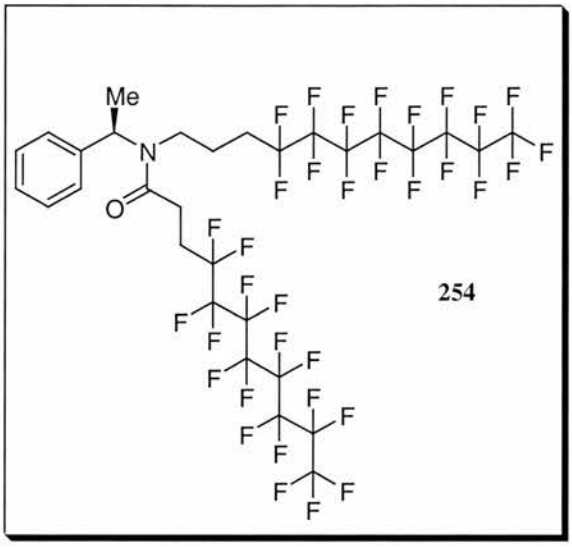
6.53 **Preparation of *4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-N-[(1R)-1-phenylethyl]-1-undecanamine* (231)**



231

A mixture of (1*R*)-1-phenylethylamine (**252**) (0.366 g, 3.0 mmol), K_2CO_3 (1.5 g), TEBA (0.067 g, 0.3 mmol) and perfluorooctyliodide iodide (**251**) (1.78 g, 3.03 mmol) in dry acetonitrile (20 cm^3) was reacted under reflux for 8 h. The suspension was cooled to room temperature and diluted with ether (40 cm^3). After filtration of the inorganic salts, the organic layer was washed with H_2O (2 x 15 cm^3), sat. NH_4Cl (15 cm^3) and dried over $MgSO_4$. The solvent was evaporated, and the product was purified over silica (flash chromatography) using hexane: ethyl acetate 80/20 as the eluent and yielding **231** (1.22 g , 70%) as a pale yellow oil. $[\alpha]_D^{20}$ = +13.2 (*c*= 0.2, Ether). HRMS (ESI) ($C_{19}H_{16}F_{17}N$ requires, 582.10890. Found M+1, 582.11288). ^1H NMR (300 MHz, $CDCl_3$), δ : 1.45 (d, 3H, J= 6.6, C*H*$_3$), 1.43 (br, 1H, N*H*), 1.65-1.76 (m, 2H, RfC*H*$_2$CH$_2$), 1.98-2.20 (m, 2H, RfCH$_2$C*H*$_2$), 2.43-2.63 (m, 2H, C*H*$_2$NH), 3.73 (q, 1H, J= 6.6, C*H*), 7.23-7.35 (m, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 21.0 (s, *C*H$_3$), 24.4 (s, CH$_2$*C*H$_2$CH$_2$), 28.8 (t, J= 21.9, RfCH$_2$), 46.4 (s, NH*C*H$_2$), 58.4 (s, *C*H), 107.5-122.3 (m, Rf), 126.1 (s, aromatic), 127.9 (s, aromatic), 128.6 (s, aromatic), 145.5 (s, aromatic quaternary). ^{19}F NMR (282 MHz, $CDCl_3$), δ : -126.5 (br s, 2F, C*F*$_2$), -123.9 (br s, 2F, C*F*$_2$), [-122.2] – [-122.0] (m, 6F), -114.7 (br s, 2F, C*F*$_2$), [-81.2] – [-81.3] (m, 3F, C*F*$_3$).

6.54 **Preparation of *4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-N-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)-N-[(1R)-1-phenylethyl]undecanamide* (254).**

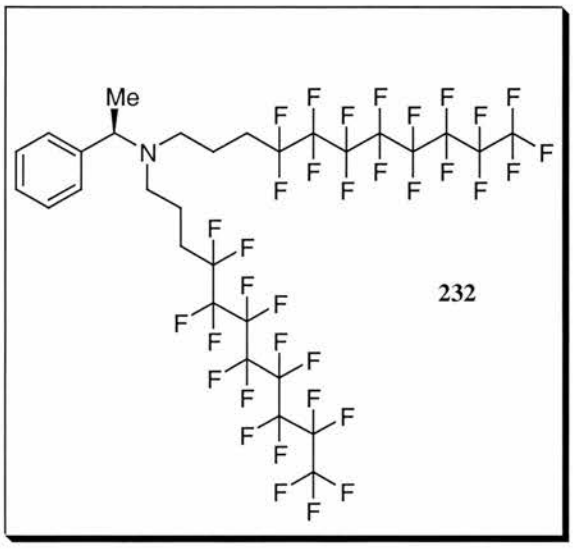


254

Acylchloride (**253**) (0.39 g, 0.76 mmol) was added to a solution of **231** (0.305 g, 0.51 mmol) and TEA (0.14 cm^3, 1.00 mmol) in DCM (10 cm^3) at 0° C. The reaction mixture was stirred at RT for 12 h. The organic layer was then washed with water (10 cm^3), sat. NH_4Cl (10 cm^3) and sat. $CuSO_4$ (10 cm^3) and was then dried over $MgSO_4$ to afford a **254** as a colourless oil (0.45 g, 84%). This material was used without further purification. $[\alpha]_D^{20}$ = + 11.8 (*c*= 0.2, Ether). HRMS (ESI) ($C_{30}H_{19}F_{34}NNaO$ requires, 1078.08204. Found M+Na, 1078.13382). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of two rotamers in ratio 2:1 (*M*, *m*), δ : 1.53 (d, 3H, J= 7.2, C*H*$_3$ *m*) 1.66 (d, 3H, J= 7.0, C*H*$_3$ *M*) 1.70 (d, 3H, J= 6.8, C*H*$_3$ *M*), 2.4-2.7 (m, 4H, C*H*$_2$-Rf), 3.00-3.31 (m, 2H, C*H*$_2$-NH), 5.12 (q, 1H, C*H*, J= 7.2, *M*), 6.01 (q, 1H, C*H*, J= 6.8 *m*) 7.22-7.39 (m, 5H, aromatics).^{13}C NMR (75 MHz, $CDCl_3$), δ : 16.9 (s, $RfCH_2CH_2CH_2$, *m*), 18.7 (s, $RfCH2CH_2CH_2$, *M*), 20.4 (s, $RfCH2CH_2CO$, *M*), 22.1 (s, $RfCH_2CH_2CO$, *m*), 25.1 (s, CH_3, *M* + *m*), 26.9-27.9 (m, $RfCH_2CH_2CO$, *M* + *m*), 29.1 (t, J= 23.5, $RfCH_2CH_2CH_2$, *m* + *M*), 42.9 (s, $RfCH_2CH_2CH_2$, *M*), 43.3 (s, $RfCH_2CH_2CH_2$, *m*), 52.1 (s, CH, *m*), 55.7 (s, CH, *M*), 107.0-119.9 (m, Rf), 127.0 (s, aromatic), 128.0 (s, aromatic), 128.3 (s, aromatic), 128.5 (s, aromatic), 129.1 (s, aromatic), 129.3 (s, aromatic), 140.1 (s, aromatic quaternary, *M*), 140.6 (s, aromatic quaternary, *m*), 170.29 (C=O).^{19}F NMR

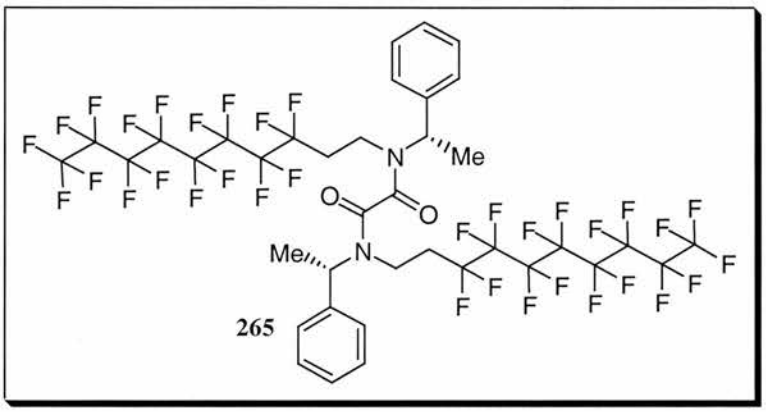
(282 MHz, $CDCl_3$), δ : -126.7 (br s, 4F), -124.0 (br s, 4F), -123.1 (br s, 4F), [-122.9] – [-121.8] (m, 12F), -114.8 (br s, 2F, CF_2), -113.0 (br s, 2F, CF_2), [-81.5] – [-81.8] (m, 6F).

6.55 **Preparation of *4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-N-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)-N-[(1R)-1-phenylethyl]-1-undecanamine* (232)**



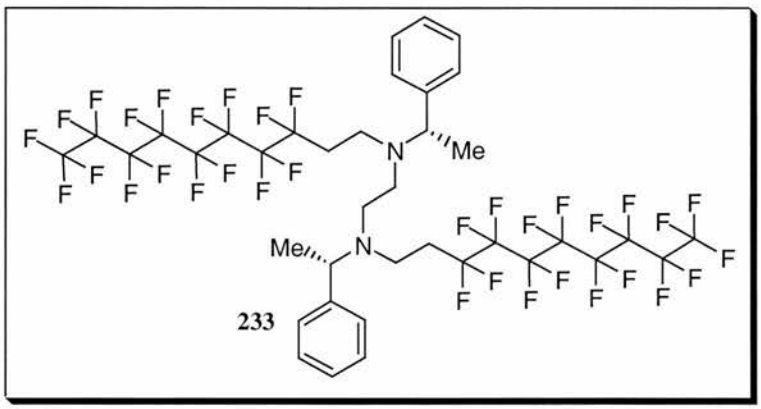
A solution of Borane-THF complex 1.5 M (3.0 cm^3, 4.5 mmol) was added dropwise to a solution of **254** (0.45 g, 0.43 mmol) in THF (15 cm^3) at 0^0 C. The mixture was then stirred under nitrogen for 24 h. The excess borane was destroyed by adding water dropwise at 0^0 C. Ether (15 cm^3) was then added and the combined organic layers were collected and dried over $MgSO_4$ and evaporated. The residue was purified over silica using hexane:ether 95:5 as the eluent to afford compound **232** as a pale yellow oil (0.23 g, 51%). $[\alpha]_D^{20}$ = + 2.0 (*c*= 0.2, Ether). HRMS (ESI) ($C_{30}H_{21}F_{34}N$ requires, 1041.11300. Found M, 1042.13368). ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.35 (d, 3H, J= 6.9, CH_3), 1.64-1.74 (m, 8H, CH_2Rf) 1.76-2.11 (m, 8H, CH_2CH_2Rf), 2.39-2.62 (m, 4H, CH_2NH), 3.89 (q, 2H, J= 6.9, C*H*), 7.22-7.38 (m, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 13.5 (s, CH_3), 18.4 (s, $CH_2CH_2CH_2$), 28.4 (t, J= 21.9, RfCH_2), 48.3 (s, NHCH_2), 57.5 (s, CH), 106.1-123.5 (m, Rf), 126.9 (s, aromatic), 127.7 (s, aromatic), 127.9 (s, aromatic), 142.8 (s, aromatic quaternary).^{19}F NMR (282 MHz, $CDCl_3$), δ : -126.6 (br s, 4F), -123.8 (br s, 4F), 123.1 (br s, 4F), [-122.9] – [-121.8] (m, 12F), -114.9 (br s, 4F), -81.6 (t, J= 10, 6F, CF_3).

6.56 **Preparation of *4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-N-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)-N-[(1R)-1-phenylethyl]-1-undecanamine* (265)**



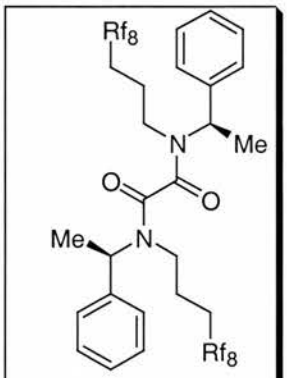
Oxalyl chloride (0.12 cm^3, 1.3 mmol) was added dropwise to a solution of the amine **229** (1.36 g, 2.4 mmol) and TEA (0.5 cm^3, 3.6 mmol) in dry DCM (20 cm^3) at 0^0 C. and the resultant mixture was stirred for 6 hours at RT. The organic layer was then washed with water (20 cm^3) and sat. $CuSO_4$ (20 cm^3) and then dried over $MgSO_4$ and evaporated to give **265** as a white solid (0.74 g, 53%) which was used for the next step without further purification. HRMS (MALDI TOF) ($C_{38}H_{26}F_{34}N_2NaO_2$ requires, 1211.10. Found M+Na, 1210.96). ^{1}H NMR (300 MHz, $CDCl_3$), mixture of four rotamers in ratio 2:2:1:0.5 only the major is reported. δ : 1.74 (d, 6H, J= 7.1, CH_3), 2.35-2.60 (m, 4H, CH_2Rf), 3.27-3.56 (m, 4H, CH_2NH), 5.49 (q, 2H, J= 6.6, *C*H), 7.30-7.47 (m, 10H, aromatics); ^{13}C NMR (75 MHz, $CDCl_3$), δ :17.5 (s, CH_3), 34.4, (t, J= 24.9, RfCH_2), 36.7 (s, NCH_2), 51.9 (s, *C*H), 108.0-120.3 (m, Rf), 127.2 (s, aromatic), 128.5 (s, aromatic), 128.7 (s, aromatic), 128.9 (s, aromatic), 129.0 (s, aromatic), 129.1 (s, aromatic), 138.2 (s, aromatic quaternary), 164.9 (s, *C*=O). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-127.5] – [-126.1] (m, 4F), [–124.9] – [-123.1] (m, 4F), [-123.5] – [-120.9] (m, 16F), [-115.9] – [-114.9] (m, 4F), [-81.8] – [-81.1] (m, 6F).

6.57 **Preparation of N^1,N^2-bis(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-N^1,N^2-bis[(1S)-1-phenylethyl]-1,2-ethanediamine (233).**



A solution of **265** (0.740 g, 0.63 mmol) in dry THF (5 cm^3) was added *via* syringe to a suspension of $LiAlH_4$ (0.12 g, 3.10 mmol) in THF (5 cm^3) at 0^0 C. The reaction mixture was stirred for 12 h at RT. The excess of hydride was then destroyed by dropwise addition of water until formation of a crystalline solid was observed. The suspension was then filtered and the solid washed with ether. The combined organic layers were collected and dried with $MgSO_4$, and evaporated to afford compound **233** as a white solid that was recrystallised from ether/MeOH (0.405 g, 56%). Mp= 71 – 73 °C. $[\alpha]_D^{20}$ = +6.47 (*c*= 0.14, DCM). (MALDI TOF) ($C_{38}H_{28}F_{34}N_2Na$ requires, 1161.1944. Found M+Na, 1161.1932). ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.22 (d, 6H, J= 6.7, CH_3), 1.92-2.13 (m, 4H, CH_2Rf), 2.26-2.45 (m, 4H, CH_2CH_2), 2.55 - 2.83 (m, 4H, J= 7.8 RfCH_2NH), 3.64 (q, 1H, J= 6.7, C*H*), 7.11-7.26 (m, 10H, aromatics); ^{13}C NMR (75.4, $CDCl_3$), δ : 16.9 (s, CH_3,), 29.5 (t, J= 20.4, RfCH_2), 42.4 (s, NHCH_2) 49.6 (s, NHCH_2CH_2NH,), 60.1 (s, CH,) 105.0-122.3 (m, Rf), 127.05 (s, aromatic), 127.5 (s, aromatic,), 128.2 (s, aromatic *m*) 143.5 (s, aromatic quaternary). ^{19}F NMR (282 MHz, $CDCl_3$), δ : [-126.8] – [-126.5] (m, 4F) [–124.2] – [-123.8] (m, 4F).-123.3 (br s, 2F, CF_2), [-122.7] – [-122.1] (m, 12F), [-114.8] – [-114.4] (m, 4F), -81.3 (t, J= 10.3, 6F, CF_3).

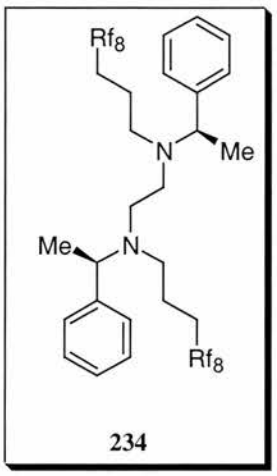
6.58 **Preparation of N^1,N^2-bis(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluorodecyl)-N^1,N^2-bis[(1R)-1-phenylethyl]ethandiamide (266)**



266

Amine (**231**) (1.15 g, 1.97 mmol) and triethylamine (0.39 cm^3, 2.81 mmol) were dissolved in ether (20 cm^3) and the solution was cooled to 0 ^{0}C. A solution of oxalyl chloride (0.082 cm^3, 0.94 mmol) in dry ether was then added dropwise. The solution was stirred at 0 ^{0}C for 1 hour and then was allowed to warm to room temperature and left stirring over night. The reaction was filtered and the filtrate washed with water and brine and dried over sodium sulphate. The ether was removed under vacuum and the crude product purified over silica using 20% ethyl acetate and 80% hexane. The product (**266**) was recovered as colourless oil (0.76 g, 67%). HRMS (ESI) ($C_{30}H_{19}F_{34}NNaO$ requires, 1078.08204. Found M+Na, 1078.13382). ^{1}H NMR (300 MHz, $CDCl_3$), product exists as four rotomers, δ : 2.03- 1.56 (m), 3.31-3.07 (m), 5.04 (q), 5.15 (q), 5.79 (q), 5.92, (q, *J*= 7.2), 7.42-7.27 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 16.9 (s), 17.1 (s), 18.2 (s), 19.9 (s), 18.7 (s), 21.9 (s), 22.2 (s), 28.9 (q, *J*= 91.1), 41.3 (s), 41.6 (s), 44.4 (s), 44.8 (s), 52.0 (s), 52.2 (s), 56.4 (s), 56.6 (s), 125 –102 (m), 127.8 (d, J= 40.2),128.6 (t, *J*= 37.8), 129.2 (s), 139.0 (s), 139.3 (s), 139.9 (s), 165.4 (s), 165.6 (s). ^{19}F (282 MHz, $CDCl_3$), δ : -126.6 (s), -124.0 (s), -123.9 (s), –123.2 (s), -122.4 (s), [-114.8] – [-114.4] (m), -81.2 (m), -81.3 (m).

6.59 **Preparation of N^1,N^2-bis(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluorodecyl)-N^1,N^2-bis[(1R)-1-phenylethyl]ethandiamine (234)**



234

Lithium aluminium hydride (0.035 g, 0.91 mmol) was suspended in dry ether (10 cm^3) and cooled to 0 ^{0}C. A solution of amide (**266**) (0.55 g, 0.45 mmol) in ether (10 cm^3) was added dropwise to the suspension. The reaction was stirred for 30 min at 0 ^{0}C and was then hydrolysed by the dropwise addition of water until a white precipitate formed. The reaction was filtered and the filtrate was dried over sodium sulfate. The solvent was evaporated to leave the crude product which was purified by column chromatography 20% ethyl acetate and 80% hexane. Finally the product **234** was recrystallised from methanol and ether to give the title compound as a white solid (0.080 g, 15%). Mp= 64 - 66 ^{0}C. $[\alpha]^{20}_D$= –1.0 (*c*= 0.2, Ether). Calcd. *C* 40.42, *H* 2.88, *N* 2.36: Found *C* 40.70, *H* 3.11, *N* 2.91. HRMS (ESI) ($C_{30}H_{22}F_{34}N$ requires, 1042.12082. Found M+1, 1042.13368). ^{1}H NMR (300 MHz, $CDCl_3$), δ : 1.27 (d, *J*= 6.7), 1.63- 1.51 (m, 4H), 1.96 (m, 4H), 2.51- 2.27 (m, 8H), 3.74 (q, *J*= 6.7, 2H), 7.30 – 7.18 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$), δ : 16.3 (s), 19.2 (s), 29.0 (t), 49.9 (s), 50.2 (s), 60.0 (s), 127.2 (s), 128.0, (s), 128.4 (s), 144.3 (s).^{19}F (282 MHz, $CDCl_3$), δ : -126.6 (s, 4F), -123.9 (s, 4F), -123.2 (s, 4F), -122.4 (s, 8F), -114.5 (s, 4F), -81.1 (m, 6F).

References for chapter 6

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3 T. Okhuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, T. Yokozawa, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1998, **120**, 13529.

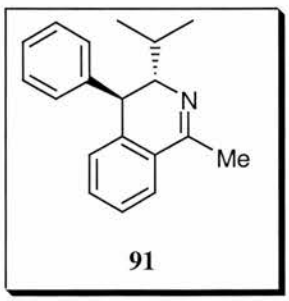
A.1 Appendix one: X-Ray crystallographic data.

A.1.1 General experimental

Data for all compounds were measured on a Bruker SMART diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.7107) using a 0.3° width steps accumulating area detector frames spanning a hemisphere of recripocal space for both structures; the reflections were corrected for Lorentz and polarisation effects. Absorption effects were corrected on the basis of multiple equivalent reflections.
The structures were solved by direct methods and refined by full matrix least squares on F^2 using the program SHELXTL. All hydrogen atoms were included in calculated positions using a riding model. All non - hydrogen atoms were refined as anisotropic

A.1.2 X-Ray data for chapter 2

A.1.2.1 X-Ray data for **91**



91

Table 1. Crystal data and structure refinement for **91**.

Identification code	mndh6	
Empirical formula	C19 H21 N	
Formula weight	263.37	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.9721(3) Å	α= 90°.
	b = 8.5759(4) Å	β= 90°.
	c = 30.5762(9) Å	γ = 90°.
Volume	1565.99(12) $Å^3$	
Z	4	
Density (calculated)	1.117 Mg/m^3	
Absorption coefficient	0.064 mm^{-1}	
F(000)	568	
Crystal size	.1 x .1 x .07 mm^3	
Theta range for data collection	2.47 to 23.23°.	
Index ranges	-5<=h<=6, -9<=k<=9, -33<=l<=32	
Reflections collected	7903	
Independent reflections	2244 [R(int) = 0.0709]	
Completeness to theta = 23.23°	98.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.862945	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2244 / 0 / 182	
Goodness-of-fit on F^2	0.872	
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0647	
R indices (all data)	R1 = 0.0474, wR2 = 0.0678	
Absolute structure parameter	7(4)	
Extinction coefficient	0.055(4)	
Largest diff. peak and hole	0.071 and -0.076 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **91**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)

C(1)	5480(3)	9558(2)	552(1)	51(1)
N(2)	4143(3)	8703(2)	777(1)	54(1)
C(3)	2671(3)	9457(2)	1099(1)	49(1)
C(4)	3808(3)	10844(2)	1328(1)	48(1)
C(5)	4696(3)	11943(2)	979(1)	47(1)
C(6)	5622(3)	11274(2)	605(1)	47(1)
C(7)	6612(3)	12230(2)	290(1)	58(1)
C(8)	6644(3)	13820(2)	345(1)	63(1)
C(9)	5695(3)	14487(2)	709(1)	62(1)
C(10)	4735(3)	13549(2)	1025(1)	57(1)
C(11)	6922(4)	8778(2)	215(1)	68(1)
C(12)	1770(3)	8215(2)	1416(1)	59(1)
C(13)	3629(3)	7428(2)	1674(1)	74(1)
C(14)	339(4)	7020(2)	1180(1)	81(1)
C(15)	2354(3)	11633(2)	1666(1)	50(1)
C(16)	3033(3)	11735(2)	2096(1)	66(1)
C(17)	1714(4)	12497(3)	2404(1)	88(1)
C(18)	-271(4)	13153(3)	2286(1)	86(1)
C(19)	-978(3)	13050(2)	1862(1)	73(1)
C(20)	318(3)	12303(2)	1557(1)	62(1)

Table 3. Bond lengths [Å] and angles [°] for **91**.

C(1)-N(2)	1.283(2)
C(1)-C(6)	1.483(2)
C(1)-C(11)	1.501(2)
N(2)-C(3)	1.471(2)
C(3)-C(12)	1.536(2)
C(3)-C(4)	1.538(2)
C(4)-C(15)	1.510(2)
C(4)-C(5)	1.518(2)
C(5)-C(10)	1.384(2)
C(5)-C(6)	1.394(2)
C(6)-C(7)	1.396(2)
C(7)-C(8)	1.374(2)
C(8)-C(9)	1.374(2)
C(9)-C(10)	1.381(2)
C(12)-C(14)	1.516(3)
C(12)-C(13)	1.520(2)
C(15)-C(16)	1.379(2)

C(15)-C(20)	1.385(2)
C(16)-C(17)	1.390(3)
C(17)-C(18)	1.361(3)
C(18)-C(19)	1.364(3)
C(19)-C(20)	1.372(2)

N(2)-C(1)-C(6)	122.98(16)
N(2)-C(1)-C(11)	118.03(16)
C(6)-C(1)-C(11)	118.97(16)
C(1)-N(2)-C(3)	118.68(14)
N(2)-C(3)-C(12)	109.12(14)
N(2)-C(3)-C(4)	112.35(14)
C(12)-C(3)-C(4)	113.88(12)
C(15)-C(4)-C(5)	113.77(14)
C(15)-C(4)-C(3)	113.78(14)
C(5)-C(4)-C(3)	108.43(12)
C(10)-C(5)-C(6)	119.05(15)
C(10)-C(5)-C(4)	123.55(15)
C(6)-C(5)-C(4)	117.31(15)
C(5)-C(6)-C(7)	119.46(15)
C(5)-C(6)-C(1)	118.38(15)
C(7)-C(6)-C(1)	122.15(15)
C(8)-C(7)-C(6)	120.26(17)
C(7)-C(8)-C(9)	120.49(17)
C(8)-C(9)-C(10)	119.63(16)
C(9)-C(10)-C(5)	121.08(17)
C(14)-C(12)-C(13)	110.96(15)
C(14)-C(12)-C(3)	111.48(14)
C(13)-C(12)-C(3)	112.26(15)
C(16)-C(15)-C(20)	117.47(17)
C(16)-C(15)-C(4)	120.81(17)
C(20)-C(15)-C(4)	121.72(15)
C(15)-C(16)-C(17)	120.61(19)
C(18)-C(17)-C(16)	120.54(19)
C(19)-C(18)-C(17)	119.6(2)
C(18)-C(19)-C(20)	120.16(19)
C(19)-C(20)-C(15)	121.62(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **91**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	57(1)	51(1)	44(1)	1(1)	-1(1)	0(1)
N(2)	64(1)	51(1)	48(1)	-2(1)	2(1)	-5(1)
C(3)	48(1)	48(1)	50(1)	2(1)	2(1)	-2(1)
C(4)	50(1)	50(1)	46(1)	1(1)	-2(1)	-2(1)
C(5)	43(1)	48(1)	48(1)	1(1)	-4(1)	-3(1)
C(6)	47(1)	47(1)	48(1)	-1(1)	0(1)	-3(1)
C(7)	56(1)	59(1)	58(1)	2(1)	10(1)	-1(1)
C(8)	68(1)	53(1)	69(1)	10(1)	11(1)	-9(1)
C(9)	65(1)	47(1)	73(1)	2(1)	7(1)	-5(1)
C(10)	61(1)	55(1)	54(1)	-6(1)	1(1)	-5(1)
C(11)	87(2)	57(1)	61(1)	-4(1)	15(1)	4(1)
C(12)	64(1)	52(1)	60(1)	5(1)	9(1)	-2(1)
C(13)	94(2)	64(1)	62(1)	12(1)	-2(1)	-1(1)
C(14)	81(1)	66(1)	96(1)	12(1)	-2(1)	-23(1)
C(15)	54(1)	48(1)	46(1)	0(1)	2(1)	-6(1)
C(16)	67(1)	80(1)	51(1)	-2(1)	-3(1)	-2(1)
C(17)	95(2)	118(2)	51(1)	-16(1)	5(1)	3(2)
C(18)	88(2)	100(2)	69(1)	-14(1)	26(1)	5(2)
C(19)	64(1)	82(1)	72(1)	-6(1)	10(1)	11(1)
C(20)	60(1)	71(1)	56(1)	-7(1)	0(1)	3(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **91**.

	x	y	z	U(eq)
H(3A)	1382	9873	939	58
H(4A)	5113	10427	1483	58
H(7A)	7253	11790	42	69
H(8A)	7313	14449	135	76
H(9A)	5698	15565	743	74
H(10A)	4104	14003	1272	68
H(11A)	6648	7675	219	103
H(11B)	8470	8973	279	103

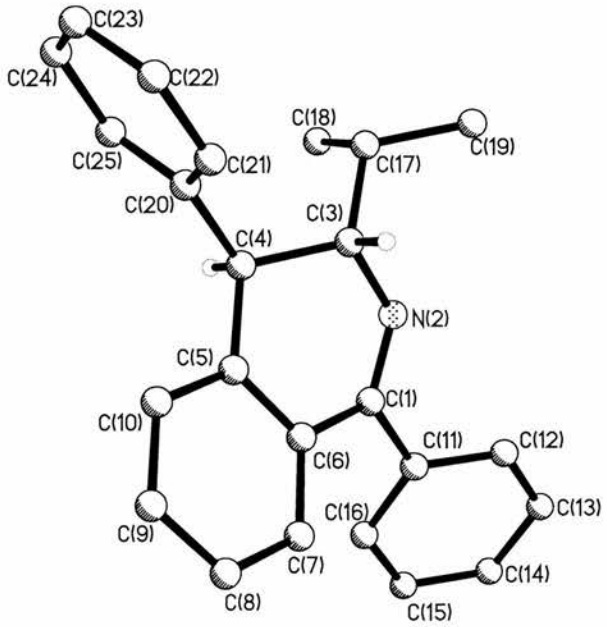
H(11C)	6569	9187	-69	103
H(12A)	802	8750	1627	70
H(13A)	2994	6663	1866	110
H(13B)	4420	8195	1842	110
H(13C)	4647	6928	1475	110
H(14A)	-196	6262	1386	121
H(14B)	1219	6509	960	121
H(14C)	-911	7533	1045	121
H(16A)	4385	11291	2181	79
H(17A)	2192	12558	2693	106
H(18A)	-1140	13670	2493	103
H(19A)	-2340	13487	1781	87
H(20A)	-183	12245	1269	75

Table 6. Torsion angles [°] for **91**.

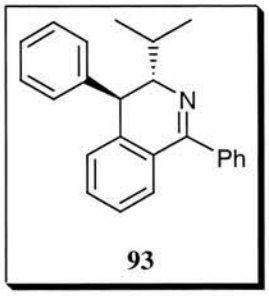
C(6)-C(1)-N(2)-C(3)	0.4(2)
C(11)-C(1)-N(2)-C(3)	-178.18(15)
C(1)-N(2)-C(3)-C(12)	-163.26(15)
C(1)-N(2)-C(3)-C(4)	-36.0(2)
N(2)-C(3)-C(4)-C(15)	-179.24(13)
C(12)-C(3)-C(4)-C(15)	-54.5(2)
N(2)-C(3)-C(4)-C(5)	53.09(18)
C(12)-C(3)-C(4)-C(5)	177.80(15)
C(15)-C(4)-C(5)-C(10)	17.4(2)
C(3)-C(4)-C(5)-C(10)	145.05(17)
C(15)-C(4)-C(5)-C(6)	-166.05(15)
C(3)-C(4)-C(5)-C(6)	-38.4(2)
C(10)-C(5)-C(6)-C(7)	1.5(2)
C(4)-C(5)-C(6)-C(7)	-175.23(16)
C(10)-C(5)-C(6)-C(1)	-177.41(17)
C(4)-C(5)-C(6)-C(1)	5.8(2)
N(2)-C(1)-C(6)-C(5)	16.1(2)
C(11)-C(1)-C(6)-C(5)	-165.34(16)
N(2)-C(1)-C(6)-C(7)	-162.80(16)
C(11)-C(1)-C(6)-C(7)	15.8(3)
C(5)-C(6)-C(7)-C(8)	-1.0(3)
C(1)-C(6)-C(7)-C(8)	177.89(17)
C(6)-C(7)-C(8)-C(9)	-0.3(3)
C(7)-C(8)-C(9)-C(10)	1.1(3)

C(8)-C(9)-C(10)-C(5)	-0.5(3)
C(6)-C(5)-C(10)-C(9)	-0.8(3)
C(4)-C(5)-C(10)-C(9)	175.75(17)
N(2)-C(3)-C(12)-C(14)	-63.0(2)
C(4)-C(3)-C(12)-C(14)	170.55(15)
N(2)-C(3)-C(12)-C(13)	62.18(18)
C(4)-C(3)-C(12)-C(13)	-64.2(2)
C(5)-C(4)-C(15)-C(16)	-114.07(18)
C(3)-C(4)-C(15)-C(16)	121.07(16)
C(5)-C(4)-C(15)-C(20)	64.8(2)
C(3)-C(4)-C(15)-C(20)	-60.1(2)
C(20)-C(15)-C(16)-C(17)	-0.5(3)
C(4)-C(15)-C(16)-C(17)	178.39(18)
C(15)-C(16)-C(17)-C(18)	0.0(3)
C(16)-C(17)-C(18)-C(19)	0.6(4)
C(17)-C(18)-C(19)-C(20)	-0.7(3)
C(18)-C(19)-C(20)-C(15)	0.2(3)
C(16)-C(15)-C(20)-C(19)	0.4(3)
C(4)-C(15)-C(20)-C(19)	-178.51(16)

Symmetry transformations used to generate equivalent atoms:



A.1.2.2 X-Ray data for **93**



93

Table 1. Crystal data and structure refinement for **93**.

Identification code	mndh7	
Empirical formula	C24 H23 N	
Formula weight	325.43	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.4794(3) Å	α= 90°.
	b = 10.2277(3) Å	β= 90°.
	c = 19.5795(4) Å	γ = 90°.
Volume	1898.28(9) $Å^3$	
Z	4	
Density (calculated)	1.139 Mg/m^3	
Absorption coefficient	0.065 mm^{-1}	
F(000)	696	
Crystal size	.1 x .1 x .07 mm^3	
Theta range for data collection	2.08 to 23.28°.	
Index ranges	-10<=h<=10, -11<=k<=10, -19<=l<=21	
Reflections collected	8352	
Independent reflections	2729 [R(int) = 0.1259]	
Completeness to theta = 23.28°	99.7 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.902814	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2729 / 0 / 227	
Goodness-of-fit on F^2	0.957	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.0776	
R indices (all data)	R1 = 0.0742, wR2 = 0.0869	

Absolute structure parameter	1(5)
Extinction coefficient	0.020(2)
Largest diff. peak and hole	0.170 and -0.165 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **93**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1854(2)	8531(2)	1848(1)	47(1)
N(2)	529(2)	8680(2)	1740(1)	52(1)
C(3)	-381(2)	8940(2)	2333(1)	47(1)
C(4)	79(2)	8148(2)	2962(1)	46(1)
C(5)	1632(2)	8423(2)	3096(1)	48(1)
C(6)	2504(2)	8613(2)	2532(1)	48(1)
C(7)	3922(3)	8892(3)	2634(1)	64(1)
C(8)	4488(3)	8925(3)	3284(1)	74(1)
C(9)	3632(3)	8675(3)	3835(2)	73(1)
C(10)	2212(3)	8438(2)	3745(1)	59(1)
C(11)	2744(2)	8260(2)	1230(1)	48(1)
C(12)	2447(3)	8878(2)	621(1)	57(1)
C(13)	3223(3)	8607(2)	38(1)	63(1)
C(14)	4295(3)	7700(3)	59(1)	64(1)
C(15)	4590(3)	7070(3)	658(1)	64(1)
C(16)	3825(3)	7349(2)	1246(1)	59(1)
C(17)	-1919(2)	8732(2)	2124(1)	56(1)
C(18)	-2224(3)	7330(3)	1924(1)	74(1)
C(19)	-2343(3)	9654(3)	1550(1)	84(1)
C(20)	-869(2)	8350(2)	3578(1)	49(1)
C(21)	-981(3)	9558(3)	3889(1)	60(1)
C(22)	-1847(3)	9740(3)	4451(1)	67(1)
C(23)	-2640(3)	8720(3)	4690(1)	74(1)
C(24)	-2554(3)	7526(3)	4389(1)	76(1)
C(25)	-1660(3)	7334(3)	3831(1)	63(1)

Table 3. Bond lengths [Å] and angles [°] for **93**.

C(1)-N(2)	1.283(3)
C(1)-C(6)	1.478(3)
C(1)-C(11)	1.500(3)
N(2)-C(3)	1.470(3)
C(3)-C(17)	1.529(3)
C(3)-C(4)	1.536(3)
C(4)-C(20)	1.518(3)
C(4)-C(5)	1.521(3)
C(5)-C(10)	1.386(3)
C(5)-C(6)	1.393(3)
C(6)-C(7)	1.388(3)
C(7)-C(8)	1.382(3)
C(8)-C(9)	1.374(4)
C(9)-C(10)	1.379(3)
C(11)-C(12)	1.379(3)
C(11)-C(16)	1.385(3)
C(12)-C(13)	1.386(3)
C(13)-C(14)	1.376(3)
C(14)-C(15)	1.368(3)
C(15)-C(16)	1.389(3)
C(17)-C(18)	1.514(4)
C(17)-C(19)	1.522(3)
C(20)-C(25)	1.373(3)
C(20)-C(21)	1.381(3)
C(21)-C(22)	1.385(3)
C(22)-C(23)	1.369(4)
C(23)-C(24)	1.359(4)
C(24)-C(25)	1.397(4)

N(2)-C(1)-C(6)	123.4(2)
N(2)-C(1)-C(11)	116.2(2)
C(6)-C(1)-C(11)	120.4(2)
C(1)-N(2)-C(3)	117.78(19)
N(2)-C(3)-C(17)	108.80(19)
N(2)-C(3)-C(4)	111.76(18)
C(17)-C(3)-C(4)	114.28(18)
C(20)-C(4)-C(5)	114.3(2)
C(20)-C(4)-C(3)	113.37(18)

C(5)-C(4)-C(3)	108.38(18)
C(10)-C(5)-C(6)	119.3(2)
C(10)-C(5)-C(4)	123.0(2)
C(6)-C(5)-C(4)	117.6(2)
C(7)-C(6)-C(5)	119.3(2)
C(7)-C(6)-C(1)	123.1(2)
C(5)-C(6)-C(1)	117.6(2)
C(8)-C(7)-C(6)	120.9(3)
C(9)-C(8)-C(7)	119.3(2)
C(8)-C(9)-C(10)	120.6(3)
C(9)-C(10)-C(5)	120.4(3)
C(12)-C(11)-C(16)	118.6(2)
C(12)-C(11)-C(1)	119.8(2)
C(16)-C(11)-C(1)	121.5(2)
C(11)-C(12)-C(13)	120.8(2)
C(14)-C(13)-C(12)	120.2(3)
C(15)-C(14)-C(13)	119.6(3)
C(14)-C(15)-C(16)	120.5(3)
C(11)-C(16)-C(15)	120.4(2)
C(18)-C(17)-C(19)	110.2(2)
C(18)-C(17)-C(3)	112.6(2)
C(19)-C(17)-C(3)	111.3(2)
C(25)-C(20)-C(21)	118.4(2)
C(25)-C(20)-C(4)	120.5(2)
C(21)-C(20)-C(4)	121.1(2)
C(20)-C(21)-C(22)	121.1(3)
C(23)-C(22)-C(21)	119.7(3)
C(24)-C(23)-C(22)	120.2(3)
C(23)-C(24)-C(25)	120.2(3)
C(20)-C(25)-C(24)	120.5(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **93**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	45(1)	53(2)	43(1)	-1(1)	3(1)	-3(1)
N(2)	50(1)	64(1)	41(1)	3(1)	4(1)	-1(1)
C(3)	48(2)	53(1)	41(1)	-2(1)	3(1)	2(1)
C(4)	50(2)	47(1)	42(1)	-1(1)	4(1)	0(1)
C(5)	49(1)	48(1)	45(2)	-4(1)	-2(1)	4(1)
C(6)	44(1)	57(2)	44(1)	-4(1)	-3(1)	1(1)
C(7)	54(2)	87(2)	50(2)	-11(2)	4(1)	-4(1)
C(8)	51(2)	110(2)	60(2)	-18(2)	-10(2)	-6(2)
C(9)	66(2)	103(2)	51(2)	-15(2)	-12(2)	7(2)
C(10)	56(2)	80(2)	41(2)	-2(1)	2(1)	3(1)
C(11)	45(1)	60(2)	40(1)	-4(1)	2(1)	-4(1)
C(12)	54(2)	65(2)	51(2)	-1(1)	5(1)	0(1)
C(13)	67(2)	79(2)	45(2)	3(2)	6(1)	-1(2)
C(14)	55(2)	85(2)	52(2)	-7(2)	13(1)	-5(2)
C(15)	53(2)	81(2)	59(2)	-9(2)	6(1)	10(1)
C(16)	57(2)	73(2)	46(2)	-1(1)	-2(1)	4(1)
C(17)	47(2)	70(2)	51(2)	1(1)	2(1)	3(1)
C(18)	62(2)	86(2)	73(2)	-2(2)	-14(2)	-11(2)
C(19)	68(2)	100(2)	84(2)	24(2)	-13(2)	15(2)
C(20)	52(2)	54(2)	39(1)	0(1)	1(1)	3(1)
C(21)	61(2)	64(2)	54(2)	-9(2)	8(1)	-2(1)
C(22)	72(2)	74(2)	56(2)	-13(2)	4(2)	8(2)
C(23)	78(2)	94(2)	49(2)	0(2)	18(2)	8(2)
C(24)	92(2)	81(2)	54(2)	6(2)	16(2)	-7(2)
C(25)	84(2)	58(2)	47(2)	2(1)	12(2)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **93**.

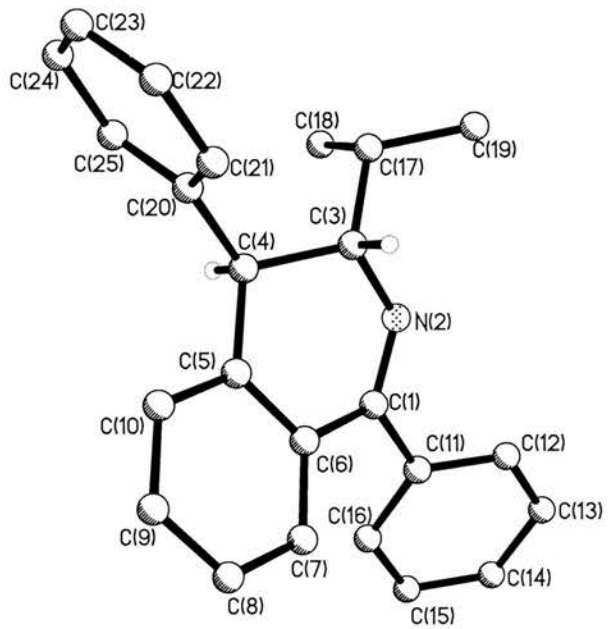
	x	y	z	U(eq)
H(3A)	-273	9867	2448	57
H(4A)	7	7223	2836	56
H(7A)	4499	9059	2260	76
H(8A)	5438	9114	3348	89
H(9A)	4013	8665	4273	88
H(10A)	1640	8287	4123	71
H(12A)	1716	9483	601	68
H(13A)	3020	9040	-368	76
H(14A)	4815	7517	-332	77
H(15A)	5307	6451	673	77
H(16A)	4040	6922	1652	70
H(17A)	-2508	8939	2521	67
H(18A)	-3199	7249	1797	111
H(18B)	-2028	6764	2303	111
H(18C)	-1639	7089	1544	111
H(19A)	-3311	9502	1430	126
H(19B)	-1755	9500	1159	126
H(19C)	-2232	10543	1699	126
H(21A)	-467	10260	3718	72
H(22A)	-1889	10551	4664	81
H(23A)	-3239	8844	5061	89
H(24A)	-3093	6835	4554	91
H(25A)	-1599	6513	3629	75

Table 6. Torsion angles [°] for **93**.

C(6)-C(1)-N(2)-C(3)	-0.2(3)
C(11)-C(1)-N(2)-C(3)	179.7(2)
C(1)-N(2)-C(3)-C(17)	-165.48(19)
C(1)-N(2)-C(3)-C(4)	-38.4(3)
N(2)-C(3)-C(4)-C(20)	-177.7(2)
C(17)-C(3)-C(4)-C(20)	-53.6(3)
N(2)-C(3)-C(4)-C(5)	54.3(2)
C(17)-C(3)-C(4)-C(5)	178.4(2)
C(20)-C(4)-C(5)-C(10)	19.9(3)
C(3)-C(4)-C(5)-C(10)	147.4(2)
C(20)-C(4)-C(5)-C(6)	-162.8(2)
C(3)-C(4)-C(5)-C(6)	-35.3(3)
C(10)-C(5)-C(6)-C(7)	-3.8(4)
C(4)-C(5)-C(6)-C(7)	178.7(2)
C(10)-C(5)-C(6)-C(1)	177.3(2)
C(4)-C(5)-C(6)-C(1)	-0.1(3)
N(2)-C(1)-C(6)-C(7)	-157.6(2)
C(11)-C(1)-C(6)-C(7)	22.5(3)
N(2)-C(1)-C(6)-C(5)	21.2(3)
C(11)-C(1)-C(6)-C(5)	-158.7(2)
C(5)-C(6)-C(7)-C(8)	2.9(4)
C(1)-C(6)-C(7)-C(8)	-178.3(2)
C(6)-C(7)-C(8)-C(9)	0.1(5)
C(7)-C(8)-C(9)-C(10)	-2.2(5)
C(8)-C(9)-C(10)-C(5)	1.3(4)
C(6)-C(5)-C(10)-C(9)	1.8(4)
C(4)-C(5)-C(10)-C(9)	179.1(2)
N(2)-C(1)-C(11)-C(12)	37.8(3)
C(6)-C(1)-C(11)-C(12)	-142.3(2)
N(2)-C(1)-C(11)-C(16)	-139.0(2)
C(6)-C(1)-C(11)-C(16)	40.9(3)
C(16)-C(11)-C(12)-C(13)	-0.8(4)
C(1)-C(11)-C(12)-C(13)	-177.7(2)
C(11)-C(12)-C(13)-C(14)	0.9(4)
C(12)-C(13)-C(14)-C(15)	-0.2(4)
C(13)-C(14)-C(15)-C(16)	-0.6(4)
C(12)-C(11)-C(16)-C(15)	0.1(4)
C(1)-C(11)-C(16)-C(15)	176.9(2)

C(14)-C(15)-C(16)-C(11)	0.6(4)
N(2)-C(3)-C(17)-C(18)	63.7(2)
C(4)-C(3)-C(17)-C(18)	-62.0(3)
N(2)-C(3)-C(17)-C(19)	-60.6(3)
C(4)-C(3)-C(17)-C(19)	173.7(2)
C(5)-C(4)-C(20)-C(25)	-120.3(2)
C(3)-C(4)-C(20)-C(25)	114.8(2)
C(5)-C(4)-C(20)-C(21)	60.9(3)
C(3)-C(4)-C(20)-C(21)	-63.9(3)
C(25)-C(20)-C(21)-C(22)	1.2(4)
C(4)-C(20)-C(21)-C(22)	-180.0(2)
C(20)-C(21)-C(22)-C(23)	-2.0(4)
C(21)-C(22)-C(23)-C(24)	1.5(4)
C(22)-C(23)-C(24)-C(25)	-0.2(4)
C(21)-C(20)-C(25)-C(24)	0.1(4)
C(4)-C(20)-C(25)-C(24)	-178.7(2)
C(23)-C(24)-C(25)-C(20)	-0.6(4)

Symmetry transformations used to generate equivalent atoms:



A.1.2.2 X-Ray data for **96**

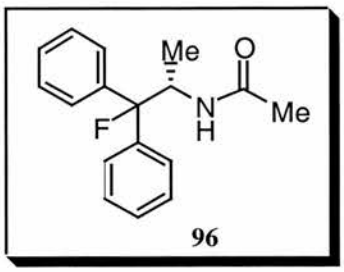


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Table 1. Crystal data and structure refinement for **96**.

Identification code	mndh8	
Empirical formula	C17 H18 F N O	
Formula weight	271.32	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.9943(18) Å	α= 90°.
	b = 17.942(4) Å	β= 90°.
	c = 19.366(4) Å	γ = 90°.
Volume	3125.3(11) $Å^3$	
Z	8	
Density (calculated)	1.153 Mg/m^3	
Absorption coefficient	0.644 mm^{-1}	
F(000)	1152	
Crystal size	0.1000 x 0.2000 x 0.0500 mm^3	
Theta range for data collection	5.19 to 70.18°.	
Index ranges	-10<=h<=4, -21<=k<=21, -18<=l<=23	
Reflections collected	20991	
Independent reflections	5550 [R(int) = 0.0819]	
Completeness to theta = 70.18°	96.6 %	
Absorption correction	MULTISCAN	
Max. and min. transmission	1.0000 and 0.2479	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5550 / 2 / 370	

Goodness-of-fit on F^2	0.992
Final R indices [I>2sigma(I)]	R1 = 0.0649, wR2 = 0.1642
R indices (all data)	R1 = 0.0858, wR2 = 0.1763
Absolute structure parameter	-0.1(2)
Extinction coefficient	0.0041(6)
Largest diff. peak and hole	0.208 and -0.168 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **96**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	6781(2)	3451(1)	8497(1)	65(1)
C(1)	7084(3)	3395(2)	7784(1)	50(1)
C(2)	6568(3)	4138(2)	7469(1)	51(1)
N(3)	7547(3)	4736(1)	7693(1)	51(1)
C(4)	8311(3)	5163(2)	7255(1)	53(1)
O(4)	8277(3)	5082(2)	6627(1)	73(1)
C(5)	9256(5)	5753(2)	7580(2)	81(1)
C(6)	4967(4)	4317(2)	7641(2)	72(1)
C(7)	6226(3)	2727(2)	7512(2)	51(1)
C(8)	5927(6)	2643(3)	6826(2)	99(2)
C(9)	5229(7)	2013(3)	6572(2)	107(2)
C(10)	4803(4)	1464(2)	7002(2)	76(1)
C(11)	5066(5)	1536(2)	7680(2)	87(1)
C(12)	5755(4)	2166(2)	7943(2)	71(1)
C(13)	8717(4)	3246(2)	7712(2)	64(1)
C(14)	9451(5)	3370(3)	7103(3)	106(2)
C(15)	10929(8)	3185(4)	7039(5)	159(3)
C(16)	11707(6)	2874(4)	7557(7)	181(5)
C(17)	11011(7)	2755(4)	8167(6)	161(4)
C(18)	9499(5)	2931(3)	8261(3)	105(2)
F(21)	10299(2)	4844(1)	11053(1)	73(1)
C(21)	10544(3)	4808(2)	10329(1)	60(1)
C(22)	9118(3)	4466(2)	10036(2)	60(1)
N(23)	7835(3)	4924(2)	10198(1)	58(1)
C(24)	6964(4)	5243(2)	9726(1)	56(1)
O(24)	7225(3)	5213(2)	9106(1)	78(1)
C(25)	5642(5)	5640(2)	9991(2)	77(1)
C(26)	8857(4)	3668(2)	10290(2)	81(1)

C(27)	11908(3)	4334(2)	10213(2)	63(1)
C(28)	12229(4)	4055(3)	9567(2)	103(2)
C(29)	13494(5)	3635(3)	9450(2)	106(2)
C(30)	14497(5)	3489(3)	9969(3)	98(1)
C(31)	14200(5)	3788(3)	10610(3)	97(1)
C(32)	12909(4)	4203(2)	10731(2)	76(1)
C(33)	10830(4)	5603(2)	10095(2)	69(1)
C(34)	10740(9)	5809(4)	9432(2)	162(4)
C(35)	11066(10)	6513(4)	9208(3)	173(4)
C(36)	11520(8)	7033(3)	9652(3)	125(2)
C(37)	11741(12)	6839(3)	10309(3)	157(3)
C(38)	11379(8)	6120(3)	10538(2)	123(2)

Table 3. Bond lengths [Å] and angles [°] for **96**.

F(1)-C(1)	1.411(3)
C(1)-C(13)	1.500(5)
C(1)-C(7)	1.520(4)
C(1)-C(2)	1.538(4)
C(2)-N(3)	1.455(4)
C(2)-C(6)	1.512(5)
N(3)-C(4)	1.333(4)
C(4)-O(4)	1.224(3)
C(4)-C(5)	1.498(5)
C(7)-C(8)	1.363(5)
C(7)-C(12)	1.374(4)
C(8)-C(9)	1.382(6)
C(9)-C(10)	1.345(6)
C(10)-C(11)	1.341(6)
C(11)-C(12)	1.385(6)
C(13)-C(14)	1.371(6)
C(13)-C(18)	1.393(6)
C(14)-C(15)	1.376(9)
C(15)-C(16)	1.345(13)
C(16)-C(17)	1.354(13)
C(17)-C(18)	1.409(8)
F(21)-C(21)	1.421(3)
C(21)-C(27)	1.510(5)
C(21)-C(33)	1.518(5)

C(21)-C(22)	1.531(4)
C(22)-N(23)	1.451(4)
C(22)-C(26)	1.532(5)
N(23)-C(24)	1.333(4)
C(24)-O(24)	1.225(3)
C(24)-C(25)	1.477(5)
C(27)-C(32)	1.369(4)
C(27)-C(28)	1.377(5)
C(28)-C(29)	1.383(7)
C(29)-C(30)	1.376(7)
C(30)-C(31)	1.377(7)
C(31)-C(32)	1.400(6)
C(33)-C(34)	1.338(5)
C(33)-C(38)	1.357(6)
C(34)-C(35)	1.369(8)
C(35)-C(36)	1.332(8)
C(36)-C(37)	1.335(7)
C(37)-C(38)	1.401(8)

F(1)-C(1)-C(13)	107.0(2)
F(1)-C(1)-C(7)	107.3(2)
C(13)-C(1)-C(7)	108.9(3)
F(1)-C(1)-C(2)	105.5(2)
C(13)-C(1)-C(2)	114.5(2)
C(7)-C(1)-C(2)	113.2(2)
N(3)-C(2)-C(6)	110.8(3)
N(3)-C(2)-C(1)	109.8(2)
C(6)-C(2)-C(1)	112.6(3)
C(4)-N(3)-C(2)	123.0(2)
O(4)-C(4)-N(3)	123.5(3)
O(4)-C(4)-C(5)	121.0(3)
N(3)-C(4)-C(5)	115.5(2)
C(8)-C(7)-C(12)	116.8(3)
C(8)-C(7)-C(1)	121.7(3)
C(12)-C(7)-C(1)	121.5(3)
C(7)-C(8)-C(9)	121.7(4)
C(10)-C(9)-C(8)	120.5(4)
C(11)-C(10)-C(9)	119.0(4)
C(10)-C(11)-C(12)	121.2(4)
C(7)-C(12)-C(11)	120.8(3)

C(14)-C(13)-C(18)	118.7(4)
C(14)-C(13)-C(1)	121.5(4)
C(18)-C(13)-C(1)	119.7(4)
C(13)-C(14)-C(15)	120.2(7)
C(16)-C(15)-C(14)	122.5(8)
C(17)-C(16)-C(15)	118.4(6)
C(16)-C(17)-C(18)	121.5(8)
C(13)-C(18)-C(17)	118.7(6)
F(21)-C(21)-C(27)	107.4(2)
F(21)-C(21)-C(33)	106.2(3)
C(27)-C(21)-C(33)	110.3(3)
F(21)-C(21)-C(22)	104.7(2)
C(27)-C(21)-C(22)	113.5(3)
C(33)-C(21)-C(22)	114.1(3)
N(23)-C(22)-C(21)	111.0(3)
N(23)-C(22)-C(26)	109.8(3)
C(21)-C(22)-C(26)	112.6(3)
C(24)-N(23)-C(22)	124.2(2)
O(24)-C(24)-N(23)	122.7(3)
O(24)-C(24)-C(25)	121.0(3)
N(23)-C(24)-C(25)	116.3(2)
C(32)-C(27)-C(28)	117.7(3)
C(32)-C(27)-C(21)	121.4(3)
C(28)-C(27)-C(21)	120.7(3)
C(27)-C(28)-C(29)	121.3(4)
C(30)-C(29)-C(28)	121.6(4)
C(31)-C(30)-C(29)	117.1(4)
C(30)-C(31)-C(32)	121.3(4)
C(27)-C(32)-C(31)	120.9(4)
C(34)-C(33)-C(38)	116.1(4)
C(34)-C(33)-C(21)	122.4(4)
C(38)-C(33)-C(21)	121.0(3)
C(33)-C(34)-C(35)	123.1(5)
C(36)-C(35)-C(34)	120.5(5)
C(35)-C(36)-C(37)	118.6(6)
C(36)-C(37)-C(38)	120.4(6)
C(33)-C(38)-C(37)	120.9(4)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **96**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	94(1)	61(1)	41(1)	-3(1)	4(1)	3(1)
C(1)	60(2)	52(2)	39(1)	-4(1)	5(1)	-9(1)
C(2)	61(2)	50(2)	42(1)	-2(1)	-3(1)	-5(1)
N(3)	70(1)	47(2)	36(1)	-5(1)	0(1)	-8(1)
C(4)	63(2)	57(2)	38(1)	4(1)	-4(1)	-5(1)
O(4)	91(2)	91(2)	37(1)	9(1)	-5(1)	-25(1)
C(5)	105(3)	77(3)	61(2)	4(2)	-8(2)	-38(2)
C(6)	70(2)	59(2)	87(2)	0(2)	-2(2)	-1(2)
C(7)	52(1)	48(2)	53(2)	-4(1)	7(1)	-2(1)
C(8)	165(4)	81(3)	50(2)	-8(2)	13(2)	-60(3)
C(9)	175(5)	85(3)	59(2)	-15(2)	11(3)	-61(3)
C(10)	81(2)	62(2)	86(2)	-6(2)	-3(2)	-20(2)
C(11)	103(3)	63(3)	95(3)	19(2)	-6(2)	-27(2)
C(12)	96(2)	61(2)	57(2)	13(2)	-12(2)	-16(2)
C(13)	60(2)	49(2)	82(2)	-18(2)	3(2)	-4(1)
C(14)	82(3)	95(4)	142(4)	-4(3)	40(3)	8(2)
C(15)	107(5)	100(5)	271(10)	-13(5)	107(6)	8(4)
C(16)	51(3)	76(4)	416(15)	-64(6)	37(6)	-12(3)
C(17)	63(3)	113(5)	308(11)	-40(6)	-61(5)	15(3)
C(18)	74(2)	102(4)	137(4)	-16(3)	-39(3)	7(2)
F(21)	77(1)	106(2)	37(1)	7(1)	2(1)	-10(1)
C(21)	63(2)	86(2)	32(1)	7(1)	2(1)	-8(2)
C(22)	57(2)	77(2)	44(1)	6(1)	2(1)	-3(2)
N(23)	57(1)	82(2)	35(1)	6(1)	2(1)	1(1)
C(24)	71(2)	59(2)	37(1)	5(1)	-3(1)	-8(2)
O(24)	104(2)	93(2)	36(1)	0(1)	-6(1)	8(2)
C(25)	97(3)	74(3)	61(2)	4(2)	-3(2)	18(2)
C(26)	66(2)	78(3)	99(3)	14(2)	-4(2)	-5(2)
C(27)	54(2)	81(2)	53(2)	5(2)	-1(1)	-10(2)
C(28)	61(2)	181(5)	65(2)	-12(3)	-1(2)	10(3)
C(29)	63(2)	163(5)	94(3)	-25(3)	14(2)	0(3)
C(30)	61(2)	107(4)	128(4)	-7(3)	-4(2)	-5(2)
C(31)	82(3)	93(3)	115(4)	8(3)	-35(3)	3(2)
C(32)	78(2)	84(3)	65(2)	5(2)	-16(2)	-1(2)
C(33)	69(2)	90(3)	48(2)	6(2)	4(1)	-6(2)

C(34)	252(8)	168(6)	66(3)	52(3)	-53(4)	-148(6)
C(35)	263(9)	170(6)	85(3)	58(4)	-60(4)	-140(7)
C(36)	180(6)	96(4)	99(4)	26(3)	23(4)	-15(4)
C(37)	303(11)	77(4)	90(3)	-17(3)	-2(5)	-7(5)
C(38)	226(7)	76(4)	67(2)	-8(2)	-19(3)	-2(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **96**.

	x	y	z	U(eq)
H(2A)	6650	4097	6966	61
H(3N)	7500(40)	4870(20)	8183(5)	77(10)
H(5A)	9759	6030	7226	121
H(5B)	9975	5525	7879	121
H(5C)	8638	6084	7844	121
H(6A)	4696	4782	7431	108
H(6B)	4854	4354	8132	108
H(6C)	4334	3929	7468	108
H(8A)	6199	3019	6521	118
H(9A)	5053	1969	6101	128
H(10A)	4333	1041	6831	91
H(11A)	4780	1157	7979	105
H(12A)	5900	2210	8416	86
H(14A)	8949	3581	6731	128
H(15A)	11407	3277	6622	191
H(16A)	12700	2745	7498	217
H(17A)	11545	2551	8533	194
H(18A)	9030	2839	8680	125
H(22A)	9217	4449	9532	71
H(23N)	7560(40)	4950(20)	10686(5)	75(10)
H(25A)	5093	5845	9611	116
H(25B)	5951	6034	10293	116
H(25C)	5023	5297	10240	116
H(26A)	7959	3476	10090	121
H(26B)	8770	3667	10784	121
H(26C)	9681	3360	10156	121
H(28A)	11583	4151	9203	123

H(29A)	13671	3447	9011	128
H(30A)	15340	3201	9891	118
H(31A)	14871	3713	10969	116
H(32A)	12729	4393	11170	91
H(34A)	10441	5456	9109	195
H(35A)	10971	6630	8742	207
H(36A)	11680	7520	9507	150
H(37A)	12137	7183	10618	188
H(38A)	11518	5996	11000	148

Table 6. Torsion angles [°] for **96**.

F(1)-C(1)-C(2)-N(3)	69.5(3)
C(13)-C(1)-C(2)-N(3)	-47.9(3)
C(7)-C(1)-C(2)-N(3)	-173.5(2)
F(1)-C(1)-C(2)-C(6)	-54.4(3)
C(13)-C(1)-C(2)-C(6)	-171.8(3)
C(7)-C(1)-C(2)-C(6)	62.6(3)
C(6)-C(2)-N(3)-C(4)	-113.7(3)
C(1)-C(2)-N(3)-C(4)	121.3(3)
C(2)-N(3)-C(4)-O(4)	-1.3(5)
C(2)-N(3)-C(4)-C(5)	179.7(3)
F(1)-C(1)-C(7)-C(8)	160.6(4)
C(13)-C(1)-C(7)-C(8)	-83.8(5)
C(2)-C(1)-C(7)-C(8)	44.7(4)
F(1)-C(1)-C(7)-C(12)	-21.4(4)
C(13)-C(1)-C(7)-C(12)	94.1(4)
C(2)-C(1)-C(7)-C(12)	-137.4(3)
C(12)-C(7)-C(8)-C(9)	-2.2(7)
C(1)-C(7)-C(8)-C(9)	175.9(5)
C(7)-C(8)-C(9)-C(10)	0.9(9)
C(8)-C(9)-C(10)-C(11)	0.0(8)
C(9)-C(10)-C(11)-C(12)	0.4(7)
C(8)-C(7)-C(12)-C(11)	2.6(6)
C(1)-C(7)-C(12)-C(11)	-175.5(4)
C(10)-C(11)-C(12)-C(7)	-1.8(7)
F(1)-C(1)-C(13)-C(14)	-161.0(4)
C(7)-C(1)-C(13)-C(14)	83.3(4)
C(2)-C(1)-C(13)-C(14)	-44.5(4)

F(1)-C(1)-C(13)-C(18)	22.9(4)
C(7)-C(1)-C(13)-C(18)	-92.8(4)
C(2)-C(1)-C(13)-C(18)	139.4(3)
C(18)-C(13)-C(14)-C(15)	0.2(7)
C(1)-C(13)-C(14)-C(15)	-175.9(5)
C(13)-C(14)-C(15)-C(16)	0.4(10)
C(14)-C(15)-C(16)-C(17)	-1.2(11)
C(15)-C(16)-C(17)-C(18)	1.5(10)
C(14)-C(13)-C(18)-C(17)	0.1(7)
C(1)-C(13)-C(18)-C(17)	176.2(4)
C(16)-C(17)-C(18)-C(13)	-0.9(9)
F(21)-C(21)-C(22)-N(23)	59.9(3)
C(27)-C(21)-C(22)-N(23)	176.7(2)
C(33)-C(21)-C(22)-N(23)	-55.8(3)
F(21)-C(21)-C(22)-C(26)	-63.6(4)
C(27)-C(21)-C(22)-C(26)	53.1(3)
C(33)-C(21)-C(22)-C(26)	-179.3(3)
C(21)-C(22)-N(23)-C(24)	118.9(3)
C(26)-C(22)-N(23)-C(24)	-116.0(3)
C(22)-N(23)-C(24)-O(24)	-4.4(5)
C(22)-N(23)-C(24)-C(25)	175.2(3)
F(21)-C(21)-C(27)-C(32)	-19.1(5)
C(33)-C(21)-C(27)-C(32)	96.2(4)
C(22)-C(21)-C(27)-C(32)	-134.3(3)
F(21)-C(21)-C(27)-C(28)	164.9(4)
C(33)-C(21)-C(27)-C(28)	-79.8(4)
C(22)-C(21)-C(27)-C(28)	49.7(5)
C(32)-C(27)-C(28)-C(29)	2.2(7)
C(21)-C(27)-C(28)-C(29)	178.4(5)
C(27)-C(28)-C(29)-C(30)	-1.2(9)
C(28)-C(29)-C(30)-C(31)	-0.9(8)
C(29)-C(30)-C(31)-C(32)	1.9(8)
C(28)-C(27)-C(32)-C(31)	-1.2(6)
C(21)-C(27)-C(32)-C(31)	-177.4(4)
C(30)-C(31)-C(32)-C(27)	-0.9(7)
F(21)-C(21)-C(33)-C(34)	-163.0(5)
C(27)-C(21)-C(33)-C(34)	81.0(6)
C(22)-C(21)-C(33)-C(34)	-48.2(6)
F(21)-C(21)-C(33)-C(38)	25.7(5)
C(27)-C(21)-C(33)-C(38)	-90.4(5)

C(22)-C(21)-C(33)-C(38)	140.5(5)
C(38)-C(33)-C(34)-C(35)	-4.9(11)
C(21)-C(33)-C(34)-C(35)	-176.6(7)
C(33)-C(34)-C(35)-C(36)	1.0(15)
C(34)-C(35)-C(36)-C(37)	4.3(14)
C(35)-C(36)-C(37)-C(38)	-5.4(14)
C(34)-C(33)-C(38)-C(37)	3.6(10)
C(21)-C(33)-C(38)-C(37)	175.5(7)
C(36)-C(37)-C(38)-C(33)	1.4(13)

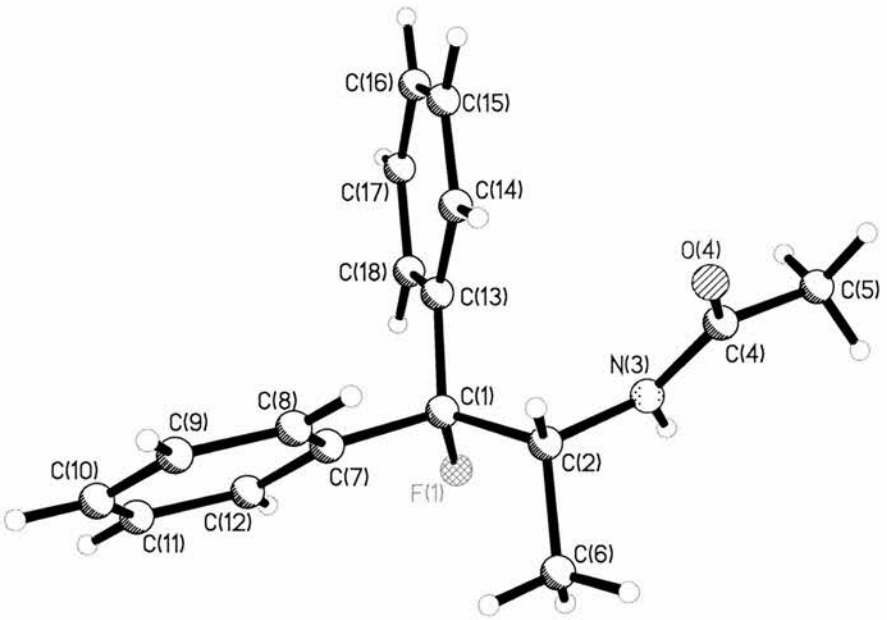
Symmetry transformations used to generate equivalent atoms:

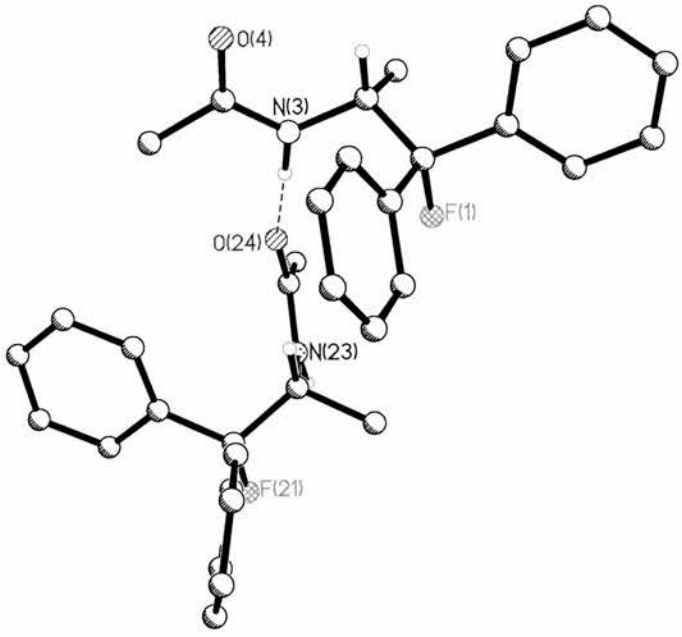
Table 7. Hydrogen bonds for **96** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3N)...O(24)	0.9798(11)	1.906(6)	2.882(3)	173(3)
N(23)-H(23N)...O(4)#1	0.9799(11)	1.971(7)	2.943(3)	171(3)

Symmetry transformations used to generate equivalent atoms:

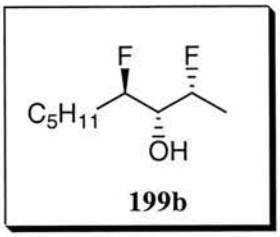
#1 -x+3/2,-y+1,z+1/2




O(4)
N(3)
F(1)
O(24)
N(23)
F(21)

A.1.3 X-Ray data for chapter 4

A.1.3.1 X-ray data for **199b**



199b

Table 1. Crystal data and structure refinement for **199b.**

Identification code	mndh13	
Empirical formula	C9 H18 F2 O	
Formula weight	180.23	
Temperature	125(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 13.519(8) Å	α= 90°.
	b = 5.089(3) Å	β= 106.268(13)°.
	c = 15.551(9) Å	γ = 90°.
Volume	1027.1(11) $Å^3$	
Z	4	
Density (calculated)	1.166 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	392	
Crystal size	.1 x .1 x .02 mm^3	
Theta range for data collection	1.36 to 23.43°.	
Index ranges	-15<=h<=12, -4<=k<=5, -17<=l<=17	
Reflections collected	4431	
Independent reflections	2201 [R(int) = 0.1684]	
Completeness to theta = 23.43°	97.8 %	
Absorption correction	MULTISCAN	
Max. and min. transmission	1.00000 and 0.36976	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2201 / 1 / 218	

Goodness-of-fit on F^2	0.890
Final R indices [I>2sigma(I)]	R1 = 0.1009, wR2 = 0.2209
R indices (all data)	R1 = 0.2271, wR2 = 0.2727
Absolute structure parameter	-9(4)
Extinction coefficient	0.056(5)
Largest diff. peak and hole	0.393 and -0.364 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **199b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-5996(4)	9575(12)	2061(4)	46(2)
C(2)	-6958(4)	8298(12)	1623(3)	32(2)
F(2)	-6925(2)	5655(7)	1853(2)	45(1)
O(3)	-7779(3)	9285(8)	2772(2)	40(1)
C(3)	-7883(4)	9469(12)	1836(3)	30(2)
F(4)	-8962(3)	7855(8)	463(2)	57(1)
C(4)	-8900(4)	8112(13)	1408(3)	43(2)
C(5)	-9862(4)	9400(12)	1461(3)	29(2)
C(6)	-10857(4)	7975(13)	957(4)	40(2)
C(7)	-11845(4)	9331(12)	1021(3)	37(2)
C(8)	-12780(4)	8034(13)	428(3)	42(2)
C(9)	-13768(4)	9355(14)	440(4)	59(2)
C(11)	-5953(4)	14437(12)	5169(3)	44(2)
F(12)	-6889(3)	18354(7)	4789(2)	50(1)
C(12)	-6985(4)	15714(12)	5055(3)	38(2)
O(13)	-7635(3)	14223(8)	3510(2)	36(1)
C(13)	-7893(4)	14481(12)	4352(3)	29(2)
F(14)	-9028(2)	16138(7)	5068(2)	47(1)
C(14)	-8873(4)	15905(13)	4209(3)	32(2)
C(15)	-9816(4)	14452(12)	3621(3)	28(2)
C(16)	-10785(4)	15891(13)	3572(3)	38(2)
C(17)	-11766(4)	14400(12)	2993(3)	34(2)
C(18)	-12747(4)	15607(14)	3063(4)	42(2)
C(19)	-13697(4)	14101(13)	2539(3)	53(2)

Table 3. Bond lengths [Å] and angles [°] for **199b**.

C(1)-C(2)	1.443(7)
C(2)-F(2)	1.389(7)
C(2)-C(3)	1.503(8)
O(3)-C(3)	1.426(5)
C(3)-C(4)	1.516(7)
F(4)-C(4)	1.453(6)
C(4)-C(5)	1.479(8)
C(5)-C(6)	1.536(7)
C(6)-C(7)	1.532(8)
C(7)-C(8)	1.493(7)
C(8)-C(9)	1.500(8)
C(11)-C(12)	1.504(8)
F(12)-C(12)	1.422(7)
C(12)-C(13)	1.530(7)
O(13)-C(13)	1.452(6)
C(13)-C(14)	1.471(8)
F(14)-C(14)	1.415(6)
C(14)-C(15)	1.535(7)
C(15)-C(16)	1.484(8)
C(16)-C(17)	1.573(7)
C(17)-C(18)	1.493(8)
C(18)-C(19)	1.521(8)
F(2)-C(2)-C(1)	110.8(4)
F(2)-C(2)-C(3)	107.2(5)
C(1)-C(2)-C(3)	114.4(5)
O(3)-C(3)-C(2)	110.4(4)
O(3)-C(3)-C(4)	103.7(4)
C(2)-C(3)-C(4)	115.5(5)
F(4)-C(4)-C(5)	107.0(4)
F(4)-C(4)-C(3)	105.9(4)
C(5)-C(4)-C(3)	118.5(5)
C(4)-C(5)-C(6)	114.9(5)
C(7)-C(6)-C(5)	114.2(5)
C(8)-C(7)-C(6)	111.3(5)
C(9)-C(8)-C(7)	113.4(5)
F(12)-C(12)-C(11)	106.6(5)
F(12)-C(12)-C(13)	107.5(4)

C(11)-C(12)-C(13)	116.1(5)
C(14)-C(13)-O(13)	110.0(4)
C(14)-C(13)-C(12)	114.4(5)
O(13)-C(13)-C(12)	109.5(4)
F(14)-C(14)-C(13)	105.3(4)
F(14)-C(14)-C(15)	106.5(4)
C(13)-C(14)-C(15)	114.5(5)
C(16)-C(15)-C(14)	111.5(5)
C(15)-C(16)-C(17)	112.4(5)
C(18)-C(17)-C(16)	112.5(5)
C(17)-C(18)-C(19)	112.8(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **199b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	33(3)	46(4)	58(4)	1(4)	13(3)	-5(3)
C(2)	41(3)	30(4)	22(3)	8(3)	4(2)	-4(3)
F(2)	76(2)	31(2)	30(2)	-8(2)	16(1)	4(2)
O(3)	65(2)	32(3)	25(2)	5(2)	16(2)	4(2)
C(3)	47(3)	29(4)	16(2)	15(3)	12(2)	6(3)
F(4)	80(2)	68(3)	30(2)	-7(2)	31(2)	-2(2)
C(4)	76(4)	41(4)	23(3)	-4(3)	30(3)	-4(4)
C(5)	52(3)	24(3)	11(2)	5(3)	9(2)	16(3)
C(6)	45(4)	41(4)	26(3)	1(3)	-1(3)	-6(3)
C(7)	58(4)	26(4)	19(3)	7(3)	0(3)	-12(4)
C(8)	60(4)	38(4)	26(3)	9(3)	11(3)	14(4)
C(9)	51(4)	82(6)	42(3)	-15(4)	10(3)	11(4)
C(11)	65(4)	28(4)	34(3)	-3(3)	7(3)	15(4)
F(12)	76(2)	41(2)	17(2)	-3(2)	-11(2)	-5(2)
C(12)	74(4)	19(3)	12(3)	4(3)	-3(3)	-11(4)
O(13)	61(2)	39(3)	9(2)	-7(2)	11(2)	-11(2)
C(13)	46(3)	25(3)	14(2)	-1(3)	6(2)	6(3)
F(14)	69(2)	66(3)	5(1)	-11(2)	8(1)	8(2)
C(14)	42(3)	39(4)	18(3)	-3(3)	12(2)	3(3)
C(15)	43(3)	23(3)	19(2)	2(3)	9(2)	-9(3)
C(16)	63(4)	32(4)	16(3)	8(3)	7(3)	-26(3)

C(17)	43(3)	31(4)	22(3)	8(3)	3(2)	6(3)
C(18)	52(4)	36(4)	27(3)	-2(4)	-8(3)	-11(4)
C(19)	57(4)	63(5)	24(3)	14(4)	-14(3)	-2(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **199b**.

	x	y	z	U(eq)
H(1A)	-5434	8716	1884	68
H(1B)	-5867	9448	2712	68
H(1C)	-6032	11429	1885	68
H(2A)	-7067	8422	961	38
H(3O)	-7723	11053	3030	48
H(3A)	-7941	11362	1656	36
H(4A)	-8874	6310	1670	52
H(5A)	-9880	11203	1218	35
H(5B)	-9846	9552	2099	35
H(6A)	-10876	7830	318	48
H(6B)	-10840	6171	1199	48
H(7A)	-11878	9273	1649	44
H(7B)	-11832	11198	846	44
H(8A)	-12725	8025	-193	50
H(8B)	-12799	6184	620	50
H(9A)	-14350	8413	41	88
H(9B)	-13763	11175	235	88
H(9C)	-13835	9340	1051	88
H(11A)	-5430	15364	5635	66
H(11B)	-5771	14519	4603	66
H(11C)	-5986	12597	5345	66
H(12A)	-7143	15724	5645	46
H(13O)	-7428	15938	3332	43
H(13A)	-7996	12671	4562	35
H(14A)	-8817	17687	3956	39
H(15A)	-9740	14244	3010	34
H(15B)	-9853	12676	3870	34
H(16A)	-10753	17650	3309	45
H(16B)	-10849	16143	4185	45

H(17A)	-11760	14410	2358	40
H(17B)	-11737	12547	3192	40
H(18A)	-12790	17435	2838	51
H(18B)	-12738	15674	3702	51
H(19A)	-14317	14961	2613	79
H(19B)	-13663	12295	2764	79
H(19C)	-13723	14079	1903	79

Table 6. Torsion angles [°] for **199b**.

F(2)-C(2)-C(3)-O(3)	62.3(5)
C(1)-C(2)-C(3)-O(3)	-61.0(6)
F(2)-C(2)-C(3)-C(4)	-54.9(5)
C(1)-C(2)-C(3)-C(4)	-178.1(5)
O(3)-C(3)-C(4)-F(4)	-170.8(4)
C(2)-C(3)-C(4)-F(4)	-49.9(6)
O(3)-C(3)-C(4)-C(5)	69.2(6)
C(2)-C(3)-C(4)-C(5)	-169.9(5)
F(4)-C(4)-C(5)-C(6)	56.7(6)
C(3)-C(4)-C(5)-C(6)	176.2(5)
C(4)-C(5)-C(6)-C(7)	179.8(5)
C(5)-C(6)-C(7)-C(8)	173.0(5)
C(6)-C(7)-C(8)-C(9)	-177.8(5)
F(12)-C(12)-C(13)-C(14)	-56.3(6)
C(11)-C(12)-C(13)-C(14)	-175.4(5)
F(12)-C(12)-C(13)-O(13)	67.7(6)
C(11)-C(12)-C(13)-O(13)	-51.4(6)
O(13)-C(13)-C(14)-F(14)	-177.7(4)
C(12)-C(13)-C(14)-F(14)	-54.0(6)
O(13)-C(13)-C(14)-C(15)	65.6(6)
C(12)-C(13)-C(14)-C(15)	-170.7(5)
F(14)-C(14)-C(15)-C(16)	59.0(6)
C(13)-C(14)-C(15)-C(16)	175.0(5)
C(14)-C(15)-C(16)-C(17)	-178.5(4)
C(15)-C(16)-C(17)-C(18)	170.6(5)
C(16)-C(17)-C(18)-C(19)	-177.4(5)

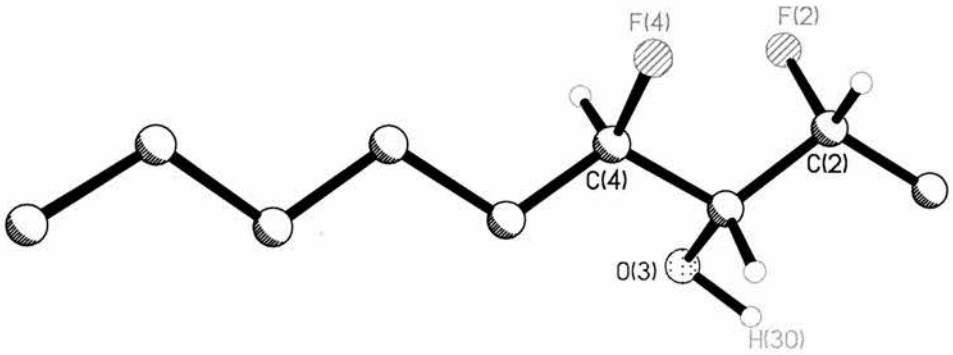
Symmetry transformations used to generate equivalent atoms:

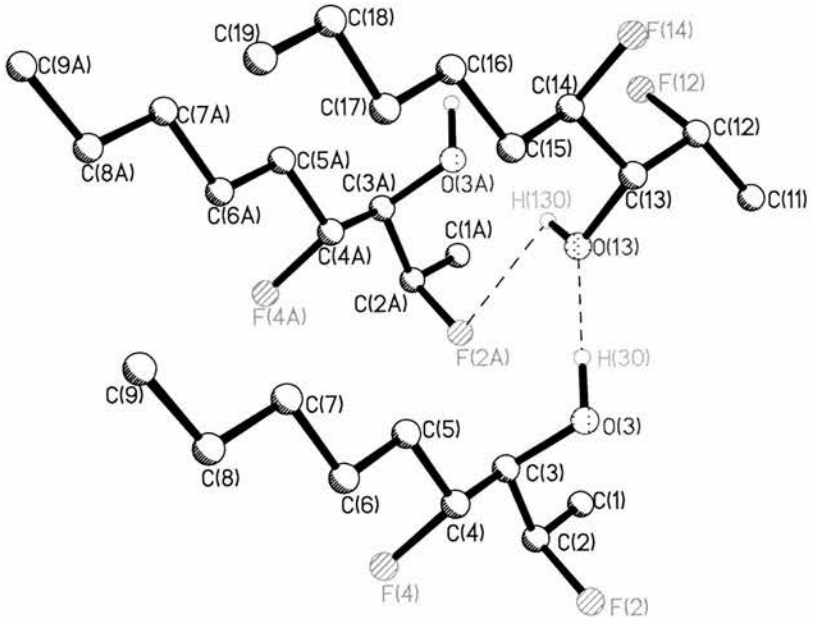
Table 7. Hydrogen bonds for **199b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3O)...O(13)	0.98	1.77	2.747(6)	179.0
O(13)-H(13O)...F(2)#1	0.98	2.58	3.079(5)	111.5

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z





A.1.4 X-Ray data for chapter 5

A.1.4.1 X-Ray data for **228**

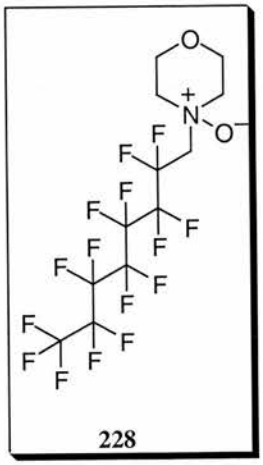


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Table 1. Crystal data and structure refinement for **228**.

Identification code	mndh10
Empirical formula	C12 H10 F15 N O2
Formula weight	485.21
Temperature	293(2) K

Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.2132(6) Å	α= 90°.
	b = 5.0864(3) Å	β= 103.738(2)°.
	c = 23.2981(12) Å	γ = 90°.
Volume	1636.13(15) $Å^3$	
Z	4	
Density (calculated)	1.970 Mg/m^3	
Absorption coefficient	0.245 mm^{-1}	
F(000)	960	
Crystal size	.2 x .1 x .01 mm^3	
Theta range for data collection	1.47 to 23.26°.	
Index ranges	-15<=h<=15, -5<=k<=5, -25<=l<=25	
Reflections collected	7404	
Independent reflections	2309 [R(int) = 0.0476]	
Completeness to theta = 23.26°	97.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.94226	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2309 / 0 / 272	
Goodness-of-fit on F^2	0.933	
Final R indices [I>2sigma(I)]	R1 = 0.0567, wR2 = 0.1333	
R indices (all data)	R1 = 0.1195, wR2 = 0.1609	
Extinction coefficient	0.0017(8)	
Largest diff. peak and hole	0.554 and -0.226 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **228**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	-2314(3)	8366(8)	542(2)	95(1)
F(2)	-2596(2)	4339(8)	713(2)	89(1)
F(3)	-2536(3)	5553(9)	-146(2)	100(1)
C(1)	-2150(4)	5859(15)	407(3)	64(2)
C(2)	-1060(4)	5373(12)	555(3)	54(2)
F(4)	-673(2)	6992(7)	232(1)	66(1)
F(5)	-971(2)	2860(7)	365(2)	80(1)
C(3)	-511(3)	5575(12)	1198(2)	48(1)

F(6)	-862(2)	3859(7)	1527(1)	70(1)
F(7)	-675(2)	8030(7)	1383(2)	82(1)
C(4)	593(4)	5253(11)	1326(2)	46(1)
F(8)	775(2)	2999(7)	1051(2)	74(1)
F(9)	983(2)	7159(7)	1068(1)	75(1)
C(5)	1140(4)	5019(11)	1978(2)	40(1)
F(10)	820(2)	6923(7)	2279(1)	75(1)
F(11)	917(2)	2724(7)	2182(2)	76(1)
C(6)	2253(3)	5260(10)	2102(2)	36(1)
F(12)	2574(2)	3712(6)	1716(1)	53(1)
F(13)	2477(2)	7753(5)	1994(1)	52(1)
C(7)	2840(4)	4507(10)	2728(2)	41(1)
F(14)	2411(2)	5778(6)	3117(1)	56(1)
F(15)	2711(2)	1932(6)	2805(1)	56(1)
C(8)	3895(3)	5324(9)	2833(2)	36(1)
N(9)	4572(3)	3864(7)	3316(2)	33(1)
O(9)	4708(2)	1292(6)	3151(1)	41(1)
C(10)	4244(4)	3885(10)	3888(2)	43(1)
C(11)	5006(4)	2757(11)	4382(2)	52(2)
O(12)	5881(3)	4246(7)	4472(2)	58(1)
C(13)	6237(4)	4139(11)	3954(2)	49(2)
C(14)	5533(3)	5309(10)	3435(2)	40(1)

Table 3. Bond lengths [Å] and angles [°] for **228**.

F(1)-C(1)	1.347(7)
F(2)-C(1)	1.311(7)
F(3)-C(1)	1.285(6)
C(1)-C(2)	1.526(8)
C(2)-F(4)	1.321(6)
C(2)-F(5)	1.368(6)
C(2)-C(3)	1.520(7)
C(3)-F(6)	1.334(6)
C(3)-F(7)	1.359(6)
C(3)-C(4)	1.535(7)
C(4)-F(9)	1.330(5)
C(4)-F(8)	1.368(6)
C(4)-C(5)	1.537(7)
C(5)-F(11)	1.327(5)
C(5)-F(10)	1.338(5)

C(5)-C(6)	1.545(7)
C(6)-F(13)	1.345(5)
C(6)-F(12)	1.353(5)
C(6)-C(7)	1.547(7)
C(7)-F(15)	1.341(5)
C(7)-F(14)	1.370(5)
C(7)-C(8)	1.519(6)
C(8)-N(9)	1.492(6)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
N(9)-O(9)	1.390(5)
N(9)-C(10)	1.514(5)
N(9)-C(14)	1.518(6)
C(10)-C(11)	1.495(7)
C(10)-H(10A)	0.9700
C(10)-H(10B)	0.9700
C(11)-O(12)	1.429(6)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
O(12)-C(13)	1.415(5)
C(13)-C(14)	1.498(7)
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700

F(3)-C(1)-F(2)	109.1(6)
F(3)-C(1)-F(1)	107.0(6)
F(2)-C(1)-F(1)	107.5(5)
F(3)-C(1)-C(2)	112.0(5)
F(2)-C(1)-C(2)	112.2(5)
F(1)-C(1)-C(2)	108.9(5)
F(4)-C(2)-F(5)	108.5(5)
F(4)-C(2)-C(3)	109.5(5)
F(5)-C(2)-C(3)	108.4(5)
F(4)-C(2)-C(1)	108.0(5)
F(5)-C(2)-C(1)	104.2(5)
C(3)-C(2)-C(1)	117.8(5)
F(6)-C(3)-F(7)	107.7(4)
F(6)-C(3)-C(2)	110.3(4)

F(7)-C(3)-C(2)	106.8(4)
F(6)-C(3)-C(4)	108.8(4)
F(7)-C(3)-C(4)	106.3(4)
C(2)-C(3)-C(4)	116.5(4)
F(9)-C(4)-F(8)	104.7(4)
F(9)-C(4)-C(3)	110.6(4)
F(8)-C(4)-C(3)	107.3(4)
F(9)-C(4)-C(5)	109.6(4)
F(8)-C(4)-C(5)	106.8(4)
C(3)-C(4)-C(5)	117.0(4)
F(11)-C(5)-F(10)	108.0(4)
F(11)-C(5)-C(4)	108.3(4)
F(10)-C(5)-C(4)	107.9(4)
F(11)-C(5)-C(6)	108.9(4)
F(10)-C(5)-C(6)	107.8(4)
C(4)-C(5)-C(6)	115.7(4)
F(13)-C(6)-F(12)	107.0(4)
F(13)-C(6)-C(5)	108.5(4)
F(12)-C(6)-C(5)	108.7(4)
F(13)-C(6)-C(7)	108.1(4)
F(12)-C(6)-C(7)	106.9(4)
C(5)-C(6)-C(7)	117.1(4)
F(15)-C(7)-F(14)	105.9(4)
F(15)-C(7)-C(8)	114.0(4)
F(14)-C(7)-C(8)	110.0(4)
F(15)-C(7)-C(6)	108.0(4)
F(14)-C(7)-C(6)	106.4(4)
C(8)-C(7)-C(6)	112.0(4)
N(9)-C(8)-C(7)	114.9(4)
N(9)-C(8)-H(8A)	108.6
C(7)-C(8)-H(8A)	108.6
N(9)-C(8)-H(8B)	108.6
C(7)-C(8)-H(8B)	108.6
H(8A)-C(8)-H(8B)	107.5
O(9)-N(9)-C(8)	111.6(3)
O(9)-N(9)-C(10)	110.0(3)
C(8)-N(9)-C(10)	112.5(3)
O(9)-N(9)-C(14)	109.1(3)
C(8)-N(9)-C(14)	106.7(3)
C(10)-N(9)-C(14)	106.7(4)

C(11)-C(10)-N(9)	111.0(4)
C(11)-C(10)-H(10A)	109.4
N(9)-C(10)-H(10A)	109.4
C(11)-C(10)-H(10B)	109.4
N(9)-C(10)-H(10B)	109.4
H(10A)-C(10)-H(10B)	108.0
O(12)-C(11)-C(10)	110.8(4)
O(12)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11A)	109.5
O(12)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	108.1
C(13)-O(12)-C(11)	109.3(4)
O(12)-C(13)-C(14)	111.5(4)
O(12)-C(13)-H(13A)	109.3
C(14)-C(13)-H(13A)	109.3
O(12)-C(13)-H(13B)	109.3
C(14)-C(13)-H(13B)	109.3
H(13A)-C(13)-H(13B)	108.0
C(13)-C(14)-N(9)	110.8(4)
C(13)-C(14)-H(14A)	109.5
N(9)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
N(9)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	108.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **228**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	66(2)	86(3)	129(4)	-4(3)	15(2)	24(2)
F(2)	50(2)	112(3)	109(3)	21(3)	24(2)	-10(2)
F(3)	69(2)	148(4)	67(3)	-5(3)	-15(2)	-2(3)
C(1)	49(4)	84(5)	55(4)	0(4)	4(3)	-1(4)
C(2)	50(4)	54(4)	55(4)	-1(3)	8(3)	-2(3)
F(4)	61(2)	85(3)	52(2)	15(2)	15(2)	-7(2)
F(5)	78(2)	71(3)	87(3)	-23(2)	12(2)	3(2)

C(3)	38(3)	63(4)	43(3)	-1(3)	8(3)	4(3)
F(6)	55(2)	97(3)	60(2)	27(2)	20(2)	-9(2)
F(7)	81(2)	82(3)	76(3)	-25(2)	8(2)	31(2)
C(4)	52(3)	44(3)	43(3)	2(3)	14(3)	-8(3)
F(8)	60(2)	85(3)	70(2)	-31(2)	1(2)	19(2)
F(9)	52(2)	106(3)	63(2)	34(2)	8(2)	-15(2)
C(5)	43(3)	39(3)	40(3)	1(3)	14(3)	-1(3)
F(10)	54(2)	114(3)	55(2)	-35(2)	9(2)	22(2)
F(11)	52(2)	85(3)	82(2)	40(2)	1(2)	-19(2)
C(6)	41(3)	33(3)	39(3)	-4(2)	16(3)	-4(2)
F(12)	47(2)	63(2)	51(2)	-21(2)	15(2)	8(2)
F(13)	57(2)	36(2)	62(2)	10(2)	10(2)	-7(2)
C(7)	50(3)	32(3)	42(3)	-5(3)	15(3)	-4(2)
F(14)	45(2)	84(2)	41(2)	-9(2)	17(2)	6(2)
F(15)	52(2)	39(2)	70(2)	10(2)	3(2)	-11(1)
C(8)	37(3)	29(3)	43(3)	-1(2)	12(2)	1(2)
N(9)	36(2)	29(2)	36(2)	1(2)	11(2)	1(2)
O(9)	53(2)	23(2)	46(2)	-5(2)	10(2)	4(2)
C(10)	48(3)	47(3)	37(3)	0(3)	17(3)	2(3)
C(11)	64(4)	54(4)	41(3)	1(3)	16(3)	-5(3)
O(12)	62(3)	68(3)	43(2)	-1(2)	10(2)	-2(2)
C(13)	48(3)	56(4)	44(3)	-2(3)	10(3)	-3(3)
C(14)	38(3)	42(3)	42(3)	-3(3)	10(2)	-4(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **228**.

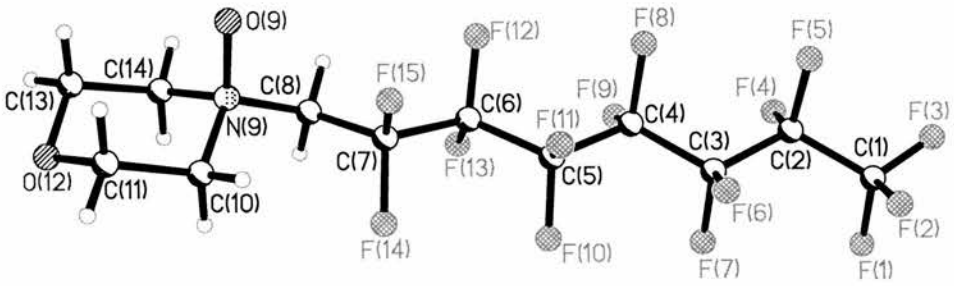
	x	y	z	U(eq)
H(8A)	4104	5078	2469	43
H(8B)	3944	7185	2926	43
H(10A)	4104	5676	3984	51
H(10B)	3653	2866	3840	51
H(11A)	4776	2762	4742	63
H(11B)	5133	949	4291	63
H(13A)	6360	2323	3868	59
H(13B)	6846	5087	4020	59
H(14A)	5798	5210	3089	48
H(14B)	5431	7148	3513	48

Table 6. Torsion angles [°] for **228**.

F(3)-C(1)-C(2)-F(4)	57.3(7)
F(2)-C(1)-C(2)-F(4)	-179.5(5)
F(1)-C(1)-C(2)-F(4)	-60.7(7)
F(3)-C(1)-C(2)-F(5)	-57.9(7)
F(2)-C(1)-C(2)-F(5)	65.3(7)
F(1)-C(1)-C(2)-F(5)	-175.9(5)
F(3)-C(1)-C(2)-C(3)	-178.0(6)
F(2)-C(1)-C(2)-C(3)	-54.9(8)
F(1)-C(1)-C(2)-C(3)	63.9(7)
F(4)-C(2)-C(3)-F(6)	-177.0(4)
F(5)-C(2)-C(3)-F(6)	-58.8(6)
C(1)-C(2)-C(3)-F(6)	59.1(7)
F(4)-C(2)-C(3)-F(7)	66.3(5)
F(5)-C(2)-C(3)-F(7)	-175.5(4)
C(1)-C(2)-C(3)-F(7)	-57.6(7)
F(4)-C(2)-C(3)-C(4)	-52.2(7)
F(5)-C(2)-C(3)-C(4)	65.9(6)
C(1)-C(2)-C(3)-C(4)	-176.2(6)
F(6)-C(3)-C(4)-F(9)	-171.7(4)
F(7)-C(3)-C(4)-F(9)	-56.0(5)
C(2)-C(3)-C(4)-F(9)	62.9(6)
F(6)-C(3)-C(4)-F(8)	74.7(5)
F(7)-C(3)-C(4)-F(8)	-169.6(4)
C(2)-C(3)-C(4)-F(8)	-50.7(6)
F(6)-C(3)-C(4)-C(5)	-45.2(6)
F(7)-C(3)-C(4)-C(5)	70.5(6)
C(2)-C(3)-C(4)-C(5)	-170.7(5)
F(9)-C(4)-C(5)-F(11)	-163.8(4)
F(8)-C(4)-C(5)-F(11)	-50.9(5)
C(3)-C(4)-C(5)-F(11)	69.3(6)
F(9)-C(4)-C(5)-F(10)	79.5(5)
F(8)-C(4)-C(5)-F(10)	-167.6(4)
C(3)-C(4)-C(5)-F(10)	-47.4(6)
F(9)-C(4)-C(5)-C(6)	-41.2(6)
F(8)-C(4)-C(5)-C(6)	71.7(5)
C(3)-C(4)-C(5)-C(6)	-168.2(5)
F(11)-C(5)-C(6)-F(13)	-168.9(4)
F(10)-C(5)-C(6)-F(13)	-52.0(5)

C(4)-C(5)-C(6)-F(13)	68.8(5)
F(11)-C(5)-C(6)-F(12)	75.1(5)
F(10)-C(5)-C(6)-F(12)	-168.0(4)
C(4)-C(5)-C(6)-F(12)	-47.2(6)
F(11)-C(5)-C(6)-C(7)	-46.2(6)
F(10)-C(5)-C(6)-C(7)	70.7(6)
C(4)-C(5)-C(6)-C(7)	-168.5(4)
F(13)-C(6)-C(7)-F(15)	-172.3(3)
F(12)-C(6)-C(7)-F(15)	-57.4(5)
C(5)-C(6)-C(7)-F(15)	64.8(5)
F(13)-C(6)-C(7)-F(14)	74.3(4)
F(12)-C(6)-C(7)-F(14)	-170.8(3)
C(5)-C(6)-C(7)-F(14)	-48.5(6)
F(13)-C(6)-C(7)-C(8)	-45.9(5)
F(12)-C(6)-C(7)-C(8)	69.0(5)
C(5)-C(6)-C(7)-C(8)	-168.8(4)
F(15)-C(7)-C(8)-N(9)	-35.5(6)
F(14)-C(7)-C(8)-N(9)	83.3(5)
C(6)-C(7)-C(8)-N(9)	-158.5(4)
C(7)-C(8)-N(9)-O(9)	72.1(5)
C(7)-C(8)-N(9)-C(10)	-52.1(5)
C(7)-C(8)-N(9)-C(14)	-168.8(4)
O(9)-N(9)-C(10)-C(11)	63.3(5)
C(8)-N(9)-C(10)-C(11)	-171.6(4)
C(14)-N(9)-C(10)-C(11)	-54.9(5)
N(9)-C(10)-C(11)-O(12)	60.1(6)
C(10)-C(11)-O(12)-C(13)	-61.6(5)
C(11)-O(12)-C(13)-C(14)	61.4(5)
O(12)-C(13)-C(14)-N(9)	-59.3(5)
O(9)-N(9)-C(14)-C(13)	-64.6(5)
C(8)-N(9)-C(14)-C(13)	174.6(4)
C(10)-N(9)-C(14)-C(13)	54.2(5)

Symmetry transformations used to generate equivalent atoms:


O(9)
C(14)
C(13)
C(8)
N(9)
O(12)
C(11)
C(10)
F(15)
C(7)
F(14)
F(12)
C(6)
F(13)
F(8)
F(9)
F(11)
C(5)
F(10)
C(4)
C(3)
F(6)
F(7)
F(5)
F(4)
C(2)
C(1)
F(3)
F(2)
F(1)

A.2 Appendix two

A.2.1 List of publications

- M. Nicoletti, D. O'Hagan and A. Slawin, *J Chem. Soc., Perkin Trans 1*, **2002** 116-123 The asymmetric Bischler Napieralski.
- Marcello Nicoletti, David O'Hagan, *Chem. Comm.,* Vicinal Trifluoro Alkanes: Stereoselective Synthesis of a New Class of Fluorinated Compounds **(in preparation).**
- Marcello Nicoletti, David O'Hagan, *J. Fluor. Chem.*, Synthesis of perfluoro amines **(in preparation).**
- Ian Shepperson, Silvio Quici, Gianluca Pozzi, Marcello Nicoletti and David O'Hagan, *Eur. J. Org. Chem.,* Fluorous Diamines and Diimines as Chiral Ligands for Metal-Catalysed Asymmetric Cyclopropanation of Styrene (**in preparation**).

A.2.1 List of Conferences attended

- RSC- Predoctoral BIO-Organic Symposium, University of Warwick 18th December 2000
- Annual meeting RTN European network , Munich 16th March 2000 (**oral presentation**)
- RSC Fluorine Subject Group Postgraduate meeting, University of Leicester 5th September 2001 (**poster presented**)

- RTN TRA (Polymer Materials) Cost (Fluorous Medium as a Tool for Enviromentally Compatible Oxidation Processes) RTN (Development of Fluorous Phase Technology for Oxidation Processes) joint meeting Padova 13th-17th February, 2002 (**poster presented**).
- 8th RSC-SCI joint meeting on heterocyclic chemistry, Edinburgh, 16-19 May 2002 (**poster presented**)
- RSC Fluorine Subject Group Postgraduate meeting, University of Manchester September 2002
- Merck Lecturership Reunion, University of Cambridge 22th- 25th September 2002.
- Annual meeting RTN European network , Budapest, 5th – 8th June 2003 (**oral presentation**)
- 226th ACS National Meeting , September 7-11, 2003 , New York City, NY