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Synthetic Methodologies in Organo (Fluorine) Chemistry Using Chiral Amines



A thesis presented for the degree of Doctor of
Philosophy to the University of St. Andrews on
the 21st June 2004

by

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In memory of my brother

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I was admitted as a research student in April 2001 and as a candidate for the degree of PhD in April 2002; the higher study for which this is a record was carried out in the University of St. Andrews between April 2001 and April 2004.

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To God be the Honour.

Abstract

Synthetic Methodologies in Organo (Fluorine) Chemistry Using Chiral Amines

This thesis describes the development of methodologies for the synthesis of chiral organo (fluorine) compounds using homochiral amines.

Chapter 1 is an introduction, which summarises the importance of incorporating fluorine into molecules of medicinal and biological significance, and describes various methods used to achieve selective organo-fluorination.

Chapter 2 describes stereoselective alkylation/ methylation reactions. In this context the synthesis of organo-fluorine compounds was undertaken to evaluate the stereinduction arising from lithium-fluorine chelation in a pre-designed enolate alkylation system. The lithium chelation capability of H, F and O was examined relative to each other and the results were consistent with the chelation order $O > F > H$. In one study involving a more sterically crowded system, there was no evidence of fluorine chelation.

In **chapter 3**, proline-derived chiral auxiliaries have been used for the stereoselective synthesis of γ -butyrolactones through a sequence of *N*-allyl-/ crotyl- ation, [3,3]-Claisen rearrangement reactions followed by iodolactonisation. Moderate to good diastereoselectivities were observed. In the best cases stereoselectivities of up to 99% de were achieved.

Chapter 4 explores three approaches towards the synthesis of C_2 -symmetrical ethylene diamines. These are direct alkylation with ethane diiodide, dicarbonyl coupling with oxalyl chloride and glyoxal condensations. Glyoxal condensation was the best method and led to the quantitative synthesis of **315**, **317** and **350**. C_2 -symmetrical diamines have become an increasingly important focus in enantioselective organic reactions. Such diamines are widely employed as metal ligands in catalytic asymmetric synthesis, chiral resolving agents and chiral auxiliaries. Thus, novel diamines **325**, **317**, and **350** constitute new entities in this area.

Chapter 5 presents the stereoselective synthesis of Ugi (4-CR) multi-component reactions using chiral amines with a novel fluorodiphenylmethyl motif. In some cases, stereinduction up to 93% de was obtained in the Ugi reactions with the amine, an isonitrile, an aldehyde and a carboxylic acid.

Chapter 6 details the experimental procedures for the compounds synthesised in this thesis.

Abbreviations

| | |
|--------------------------|--------------------------------------|
| Å: | angstrom |
| Ac: | acetyl |
| <i>c</i> : | concentration |
| CI: | chemical ionization |
| CNS: | central nervous system |
| conc: | concentrated |
| DAST: | (diethylamino)sulfurtrifluoride |
| DBU: | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCM: | dichloromethane |
| de: | diastereomeric excess |
| DHQ | dihydroquinidine |
| DMAP | dimethylaminopyridine |
| DMF: | dimethylformamide |
| DMSO: | dimethylsulfoxide |
| ee: | enantiomeric excess |
| EI: | electron ionisation |
| eq: | equivalent |
| F-Ac: | fluoroacetaldehyde |
| 5'FDA: | 5'-fluoro-5'-deoxyadenosine |
| F-FT: | fluorothreonine |
| 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 |
| LDA: | lithium diisopropylamide |
| M: | molar |
| min: | minute |
| mp: | melting point |
| MS: | mass spectroscopy |

| | |
|-------------------------|---|
| NFOBS: | N-fluoro-o-benzedisulfonimide |
| NMR { ¹ H}: | NMR proton decoupled |
| NMR { ¹⁹ F}: | NMR fluorine decoupled |
| NMR: | nuclear magnetic resonance |
| NOE: | Nuclear Overhauser Effect |
| NOESY | Nuclear Overhauser enhancement spectroscopy |
| Nu ⁻ | nucleophile |
| Py: | pyridine |
| rt: | room temperature |
| SAM: | <i>S</i> -(5'-adenosyl)-L-methionine-chloride |
| sat. | saturated solution |
| TEA: | triethylamine |
| THF: | tetrahydrofuran |
| TLC: | thin layer chromatography |
| TMS: | trimethylsilyl |
| UV: | ultra-violet |

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1

INTRODUCTION

SYNOPSIS

Recent years have witnessed major advances in organic-fluoro chemistry. New synthetic methods and novel fluorinating (electrophilic and nucleophilic) reagents have been developed that facilitate the incorporation of fluorine or fluorine-containing units into small building blocks, designer compounds and materials of peculiar properties.

The licensing of fluorine containing drugs is steadily increasing, such that 18% of all drugs in clinical trials at the moment contain fluorine.

1.1. Discovery and Developments in Elemental Fluorine Chemistry

The element fluorine (*L. fluo*, flow) was not prepared until 1886, however, the fluorine-containing mineral fluorspar (CaF_2) had already been described in 1529 by Georg Bauer, the German physician and mineralogist.

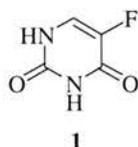
The belated developments and availability of fluorine owe to its high reactivity and toxicity, hence its group VII counterparts were more widely described and readily available even though they were discovered later. Chlorine was discovered by in 1772 by Scheele¹ bromine in 1826 by the French chemist Balard and iodine's discovery is credited to Courtois Bernard^{2,3} in 1811.

In 1771, the Swedish chemist Carl Wilhelm Scheele succeeded in obtaining impure hydrofluoric acid by reaction of fluorspar with sulfuric acid. The recognition that fluorspar was calcium fluoride came when André-Marie Ampère prepared nearly anhydrous hydrofluoric acid in 1809 and in 1811 he suggested that it was a compound

of hydrogen and an unknown element, analogous to chlorine, for which he proposed the name fluorine.

In 1886, Henri Moissan⁴⁻⁶ first isolated elemental fluorine by electrolysis of KHF_2 in HF , an advancement for which he received a Nobel Prize in 1906 a year before his tragic death from fluorine poisoning.

Fluorine is used in the manufacture of uranium hexafluoride (UF_6),^{7, 8} which in turn is used for the gaseous separation by membrane partitioning of uranium isotopes (U-235). Developments of organo-fluorine compounds, polymers and use of fluoride in dental products have made it a much more familiar element over decades. With an increasing awareness of the importance of fluorine chemistry, the prejudice and hazardous perceptions that reactions of elemental fluorine cannot be controlled, had to be overcome. Several researchers have unequivocally demonstrated that such a prejudice should be laid to rest.⁹⁻¹¹ An early practical example of taming elemental fluorine was demonstrated in the industrial scale manufacture of 5-fluorouracil **1**.

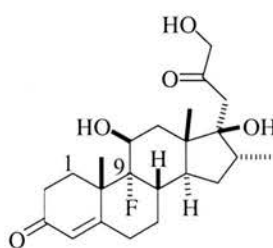


Recent developments from groups such as Chambers at Durham have unlocked the potential of this element in organic synthesis. The selective introduction of fluorine into organic compounds still remains a great synthetic challenge although significant advancements have been reported in this area.¹²

1.1.1. Fluorinated compounds in medicine

A prominent feature in the growth of fluorinated pharmaceuticals is the number of bioactive compounds containing aryl-F and aryl- CF_3 groups. These functional groups are chemically inert and are not readily metabolised *in vivo*, thus they are attractive substituents in drug design and development. Fluorine substitution can alter the chemical properties, disposition, and biological activity of drugs. Currently many fluorinated compounds are being widely used in the treatment of diseases. These

include antidepressants, anti-inflammatory agents, antimalarial drugs, antiviral agents, steroids, and general anaesthetics¹³ in which polar effects of F and CF₃ cause change in biological activity compared to their hydrocarbon counterparts. The chemistry and medicinal chemistry of fluoro-organic compounds and drugs have been reviewed.^{13, 14} The development of new fluorinating agents (section 1.3) has vastly increased the potential for synthesis of novel fluorinated drugs. In addition, the development of sophisticated non-invasive analytical techniques based on ¹⁹F nuclear magnetic resonance (NMR) and positron emission tomography has transformed the study of fluorinated drugs in humans and animals.¹⁵



Dexamethasone 2

Since the discovery by Fried¹⁶ of the increased therapeutic effect conferred by fluorine in 9- α -fluorohydrocortisone acetate, an interest has emerged in the medicinal chemistry of organofluorine compounds. In his original studies, Fried reported the replacement of 9- α -hydrogen atom by a halogen. The main interest in this study was the observation that halo compounds possessed marked glucocorticoid activity, which in the case of chloro-derivatives exceeded by a factor of four that of the parent hormones. The 9- α -fluoro derivatives dexamethasone **2** were prepared, prompted by the finding that the activity was inversely proportional to the size of halogen.

During the past 50 years, several useful advances in organofluorine chemistry have been translated into products of medicinal value.¹⁷ The reason for this profound therapeutic activity has been rationalised mainly on the basis of the physicochemical properties of the fluorine atom in these compounds.¹⁸

Fluorinated compounds have gained broad application in medicine. Paracetamol is one example of the effect of fluorination in analgesics. When non-fluorinated paracetamol is taken in overdose, hepatic necrosis results.^{19, 20}

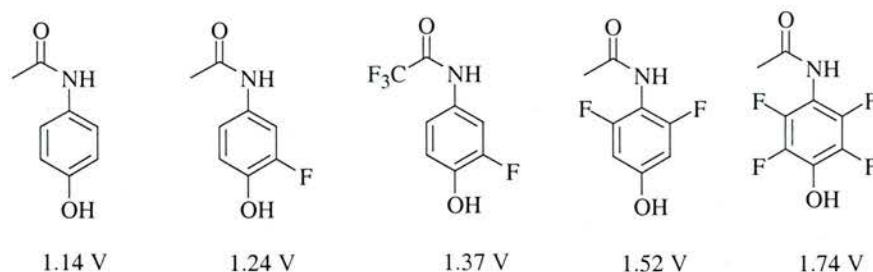


Figure 1.1 Effect of fluorine on the oxidation potential (V) in paracetamol.

The introduction of fluorine into paracetamol changes its oxidation potential (figure 1.1). Both the number of fluorine atoms and the position around the aromatic ring affect the oxidation potential. Thus a reduction in oxidative bioactivation and therefore reduced *in vivo* toxicity of the compound is elicited by judicious placement of the fluorine atoms.²¹

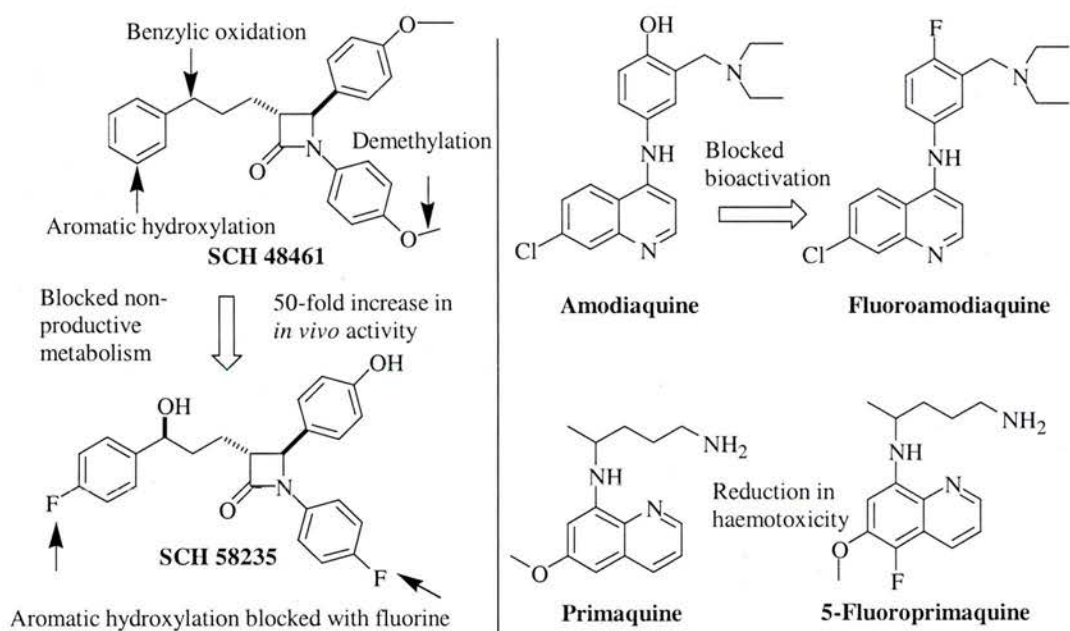


Figure 1.2 Fluorine substitution in drug design.

The strategic value of fluorine substitution in rational drug design is neatly illustrated by the development of the orally active inhibitor of cholesterol absorption SCH58235 from SCH48461²²⁻²⁴ (figure 1.2). Fluorine was introduced to block undesirable metabolic transformations and produce a lead compound with 50-fold greater potency *in vivo*.

1.1.1.1. Fluorinated CNS Drugs

Fluorinated drugs are widely represented in medicine. Good examples can be found in central nervous system drugs (CNS). Prozac (fluoxetine) **4** is the most commercially successful fluorinated drug in pharmaceutical markets in its class for treatment of depression. Other most commonly encountered CNS drugs are fluvoxamine **5**, paroxetine **6**, and citapram **7** (figure 1.3).

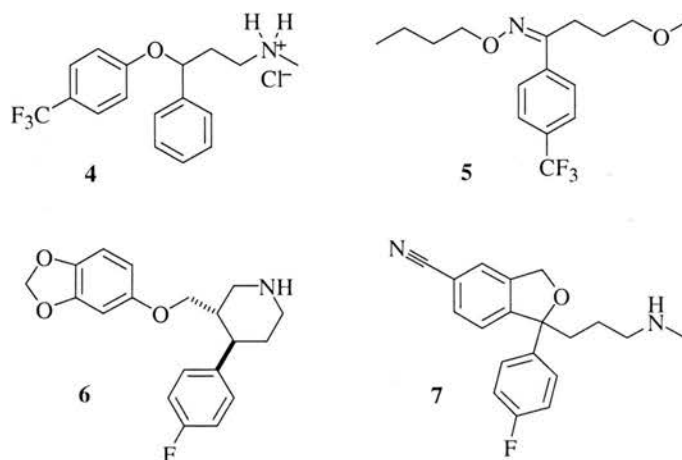


Figure 1.3 Example of leading fluorinated CNS drugs.

Prozac is an antidepressant medication originally approved by the FDA in 1987 and currently available for the treatment of depression, obsessive-compulsive disorder, and bulimia nervosa. It preferentially inhibits the reuptake of serotonin into brain synaptosomes and platelets in rats and humans. Befloxatone²⁵ **8** (figure 1.4) is an oxazolidinone derivative belonging to a new generation of reversible and selective monoamine oxidase-A (MAO-A) inhibitors. Befloxatone belongs to a rare group of fluorinated drugs, which possess fluorine/ CF₃ at a stereogenic centre.

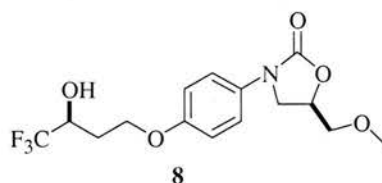


Figure 1.4 MAO-A inhibitor

1.1.1.2. Anti-Cancer

5-Fluorouracil **1** (5-FU) was the first fluorinated pyrimidine to show bioactivity and it is widely used for the treatment of breast and gastrointestinal cancer, and palliation of inoperable malignant neoplasms. Its effect on living cells is limited to those in the proliferative phase. It is a potent mechanism based inhibitor of thymidylate synthase, an enzyme that converts deoxyuridine monophosphate (dUMP) to deoxythymidinemonophosphate.

1.1.1.3. Antibiotics

The penicillins have dominated the antibacterial market since their discovery in the mid 1940's but a multitude of other antibacterial drugs have since been developed. Fluorinated compounds of the 6-fluoroquinolone-core structure have been prepared and widely employed as antibacterial agents (figure 1.5). These were first introduced about two decades ago with norfloxacin **9** and many like daichi **11**, trovafloxacin **12** and ciprofloxacin **10** were since developed. Quinolone antibacterial agents act by inhibition of bacterial DNA synthesis.

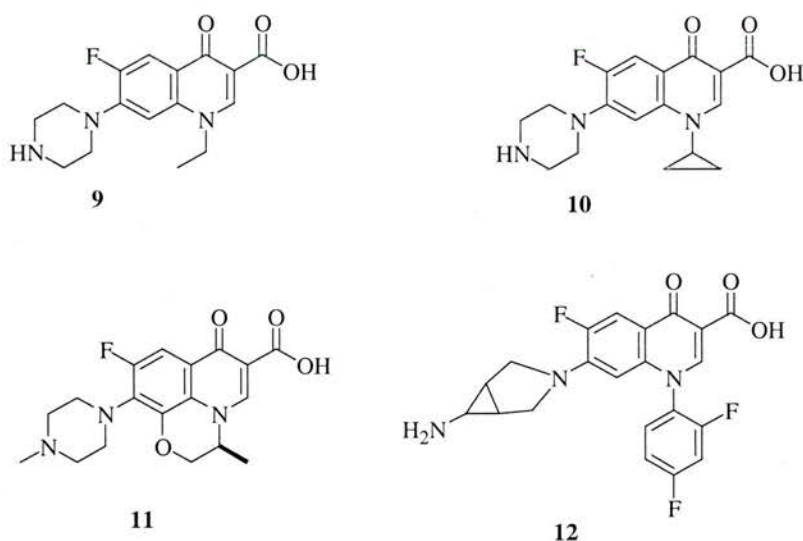


Figure 1.5 6-Fluoroquinolone antibacterial agents

The 6-fluoroquinolones are active against a wide range of gram-positive and gram-negative pathogens. They possess improved oral absorption and systemic distribution,

and therefore have extended clinical applications that include urinary and respiratory tract infections, skin, and soft tissue infections. The structural features, which determine tissue distribution and cellular uptake, are complicated by specific efflux mechanisms.²⁶ Nevertheless, it has been proposed that the 6-fluoro group is important for both cell penetration and gyrase affinity.²⁷ The presence of the fluorine atom is important for activity. Replacement with hydrogen, or other groups such as amino or methyl groups always result in less active compounds.

1.1.1.4. Anti-virals

There has been an intense focus on developing agents against the human immunodeficiency virus (HIV) which leads to AIDS. Zidovudine **13** [3-azidothymidine (AZT)] (figure 1.6) was the first anti-HIV agent to be approved for clinical use, after which the direct fluorinated analogue alovudine **14** [3'-fluorothymidine (FTL)]. FTL was found to exhibit an anti-HIV-7 potency similar to that of AZT but with slightly better sensitivity and higher intracellular active metabolite levels.²⁸ Nucleoside analogues **15** (2',3'-dideoxyadenosine) (ddAdo) and **16** the 3'-fluoro derivative have been indicated to improve the immune system in AIDS patients.

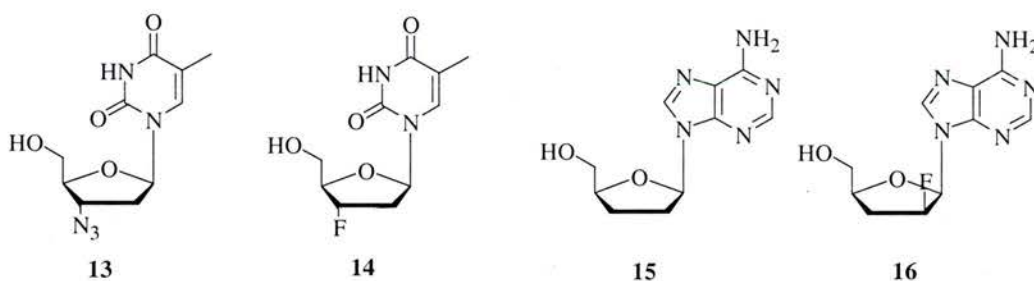


Figure 1.6 Nucleoside HIV-drugs

Non-nucleoside HIV drugs are widely represented one example being efavirine^{29, 30} **17** which is a reverse transcriptase inhibitor that shows high potency against a variety of HIV-1 mutant strains.³¹ It is notable in that it has a CF₃ group directly attached to the chiral centre, rather than, for example on the aryl ring system. It is also among a small group of licensed fluorinated compounds, which contain a CF₃ group at a stereogenic centre. Diflucan/ fluconazole **18** (anti fungal, figure 1.6) works by inhibiting fungal cytochrome P-450 sterol C-14 α -demethylation, thus obstructing the conversion of lanosterol to ergosterol,³² which leads to the inhibition of membrane sterol synthesis and

therefore prevents fungal cell replication. Diflucan appears relatively free from serious side effects or toxicity and it is clearly an exciting new drug in AIDS therapy.

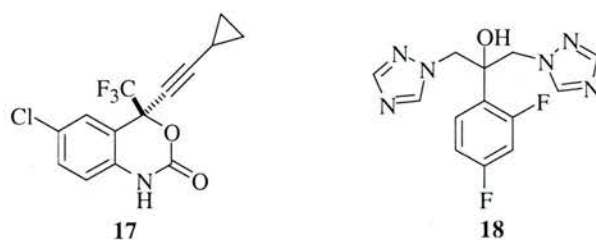


Figure 1.6 Non-nucleoside drugs for HIV treatment.

1.1.1.5. Antimalarial Drugs

Resistance by the malarial strains to many drugs has led to the development of fluorinated drugs for malaria. Traditionally, quinine **19** and quinidine **20** (figure 1.7) are administered for malaria, but however the parasite has developed resistance to these drugs. Thus, mefloquine **21**, which was developed from these cinchona alkaloids, is marketed in racemic form under the trade name lariam.

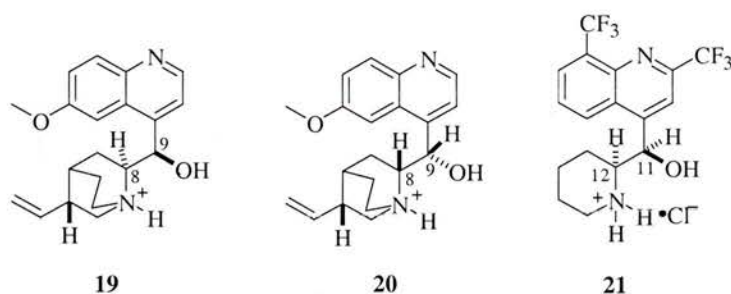


Figure 1.7 Structures of quinine, quinidine and (-)-mefloquine

(-)-Mefloquine **21** has the same stereochemistry at C-11 as quinine **19** at C-9, and (+)-mefloquine has the same stereochemistry C-11 with quinidine **20** at C-9.³³ The latter is the more potent *in vitro* against D6 and W2 strain of *Plasmodium falciparum*. Mefloquine **21** is one of the major antimalarial drugs prescribed in the Third World and has had a world-wide impact on this regard where it is active in regions where the mosquito is resistant to quinine.

The presence of a fluorine atom can influence the lipophilicity of a molecule and affect the partitioning of the drug across membranes, and across the blood/ brain barrier, and also facilitate hydrophobic interactions of the drug molecule with specific binding sites, on either receptors or enzymes. The replacement of a single aromatic hydrogen atom usually results only in a modest increase in lipophilicity, whereas the CF₃ group is among the most lipophilic of all substituents. Thus, fluorine replacement for hydrogen has allowed the design of new compounds with interesting properties and the refinement of chemical reactivity and biological activity.

1.2. Physical and Stereoelectronic effects of fluorine

The replacement of a hydrogen atom (H) or a hydroxyl group (OH) by a fluorine atom (F) is a strategy widely employed in drug development to change biological activity. Although it is generally thought that the fluorine for hydrogen substitution causes minimal steric effects, the actual van der Waals radius of fluorine (1.47 Å) lies between that of oxygen (1.57 Å) and hydrogen (1.2 Å) (Table 1.1). Despite the fact that the size of fluorine is greater than hydrogen, several studies have demonstrated that it is a reasonable hydrogen mimic and exerts only a minor steric demand at receptor sites, in case of monofunctional analogues.¹⁴

| Element | Electro-negativity | Bond length (CH ₂ X, Å) | Van der Waals radius (Å) | Bond energy (kcal/mol) |
|---------|--------------------|------------------------------------|--------------------------|------------------------|
| H | 2.1 | 1.09 | 1.20 | 99 |
| F | 4.0 | 1.39 | 1.35 | 116 |
| O(OH) | 3.5 | 1.43 | 1.40 | 85 |

Table 1.1 Some physiochemical properties of the carbon-fluorine bond

In contrast to their size similarity, hydrogen and fluorine have quite different electronic properties. Fluorine is the most electronegative element in the periodic table, (table 1.1). The replacement of a hydrogen atom for fluorine in a molecule changes the electron distribution. Consequently this alters the pK_a, the dipole moments, and even the chemical reactivity and acid/ base properties of neighbouring functional groups. The magnitude of the change in these electronic properties is often determined by the

bonding between the fluorine atom and the functional group. Thus, the presence of a fluorine atom *ortho* to a phenolic OH is associated with a reduced pK_a of 1.2, whereas *meta* and *para* fluoro substitutions have much less effect. The incorporation of two fluorine atoms at the 2- and 6- positions of phenol causes reduction in the pK_a of 2.7³⁴ (figure 1.8).

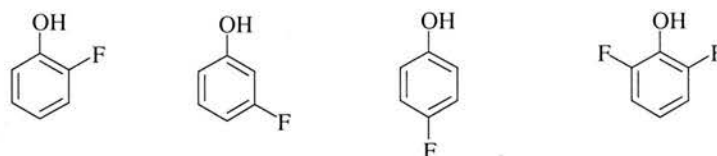


Figure 1.8 Fluorinated phenols

Fluorine forms a strong bond with carbon (bond energy C-F = 116 kcal/mol), which has an increased oxidative and thermal stability compared with the carbon-hydrogen bond (C-H = 99 kcal/mol). In addition to the formation of covalent bonds, a fluorine atom present in a molecule can also form reversible, electrostatic bonds with certain functional groups. The isosteric replacement of the hydroxyl group is a common strategy in medicinal chemistry. This substitution is usually based on the principle that fluorine is a hydrogen bond acceptor similar to oxygen in a hydroxyl group in this respect. However, the higher electronegativity and lower polarizability of fluorine over oxygen has a major influence on the ability of fluorine to mimic a hydroxyl group. Recent calculations have measured the strength of an optimum C-F \cdots H bond (1.9 Å) to be 2.38 kcal/mol in an adduct between fluoromethane and water. Therefore, the F \cdots H bond is clearly much weaker than the corresponding O \cdots H, which is conventionally estimated to be ca 5 kcal/mol.

In contrast to the single replacement of hydrogen for fluorine, replacement of a methylene function with a difluoromethylene function (CH₂ for CF₂) can have a dramatic effect on both conformation and physical properties of a molecule. The difluoromethylene moiety has in fact been used as an electronic mimic of labile oxygen atoms in phosphate esters (R-CF₂-PO₃²⁻ vs. R-OPO₃²⁻) as shown in estrone sulfate analogues **23** and **24**³⁵ (figure 1.9).

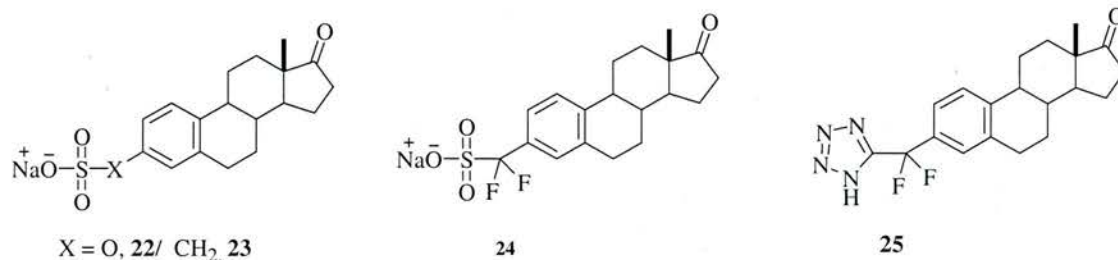


Figure 1.9 Estrone-3-sulfate analogues bearing non-hydrolysable sulfate mimetics.

This functional group has found extensive use in the design of inhibitors of enzymes which hydrolyse or bind phosphate esters.³⁵ The CF_2 group has been proposed as a reasonable isosteric and isopolar replacement for the hydroxyl group because of its size, electron distribution, and ability to act as a hydrogen bond acceptor.³⁶ The CF_2H group is particularly favoured because of its ability to act as a hydrogen donor,³⁷ potentially allowing interaction with solvent and biological molecules. Further introduction of fluorine causes even greater steric restrictions. The frequently used trifluoromethyl group ($-\text{CF}_3$) is judged to be closer in size to an isopropyl group³⁸ (chapter 2). Indeed, several workers have suggested that the CF_3 group can exert an effect comparable to a phenyl ring or even a *tert*-butyl function.³⁹

The replacement of oxygen (O) in phosphates by CH_2 to give hydrolytically stable phosphonates has been known for decades.⁴⁰⁻⁴² This replacement by the CH_2 moiety renders the phosphate resistant to the action of phosphatase hydrolysis. The important feature of this exchange is that it maintains the same spatial distribution of functionality as the substrate and allows similar conformations to be accessed. Such a replacement, however, has some detrimental consequences, due to a mismatch of electronic effects between O and CH_2 group.

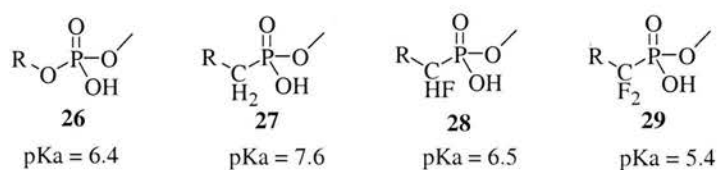


Figure 1.10 pKa values for phosphate, phosphonate and phosphonates fluorinated derivatives.

The pKa (6.4) of the phosphate group **26** is less than the pKa (7.6) of the phosphonate⁴² **27** group (figure 1.10), thus, an oxygen mimic is obviously required to match its electronegativity. The introduction of fluorine atoms into the methylene group **28** increases the acidity of the phosphonate due to the electronegativity of fluorine atom.⁴³ Clearly, a single fluorine atom replacement is a best fit mimic for the pKa (6.5) whereas two fluorines result in a significant increase in pKa (5.4) **29**.

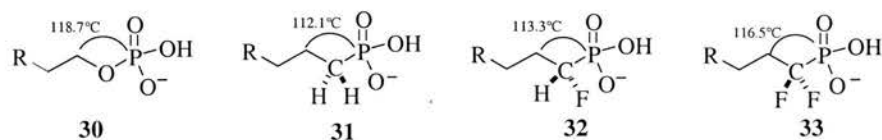


Figure 1.11 The C-X-P angles of the phosphate and phosphonates as determined from X-ray structure data, where (X = O, CH₂, CHF, CF₂).

X-ray analysis of these compounds (**30-33**) revealed another benefit for the replacement of the methylene hydrogens with fluorine. The bond angle in the methylene case **31** is much more deviated (112.1°) compared to the CHF (113.3°) **32** and CF₂ (116.5°) **33** analogues (figure 1.11). Thus, the CF₂ phosphonate group emerges as a good mimic for phosphate since both the pKa and the bond angle closely resemble that found in the phosphate.

1.2.1. The Fluorine *Gauche* Effect

The fluorine *gauche* effect has received special attention in our research group and elsewhere. Although the steric effect between the fluorine and hydrogen atoms is very small, electronic difference between them is profound. The replacement of fluorine for hydrogen in organic compounds can significantly change the properties of a given molecule, especially when a fluorine atom is located close to functional groups.^{44, 45} The *gauche* effect was described by Wolfe⁴⁶ as the tendency of molecules to adopt a structure, with the maximum number of interactions between adjacent electron pairs/ and polar bonds.

It is well established that the lowest energy conformer **34** of 1,2-difluoroethane has the *gauche* arrangement, and that the *anti* conformer **35** is higher in energy by ~1 kcal/mol⁴⁷ (figure 1.12). This is in contrast to 1,2-dichloroethane, which prefers the *anti*

conformation.⁴⁸ The *gauche* effect appears to originate from optimal C-C σ -bond overlap and vicinal hyperconjugation possibilities between the electron rich C-H (HOMO) bond and C-F σ^* -orbital (LUMO).

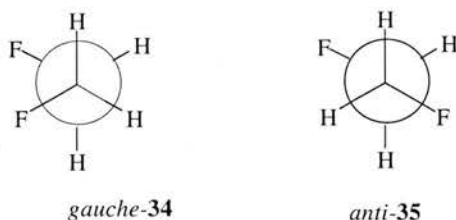


Figure 1.12 Staggered rotamers of 1,2-difluoroethane

The fluorine *gauche* effect has been shown to influence the relative energies of conformers of both *erythro* (*meso*) and (\pm)-*threo*-2,3-difluorobutane **36** and **37** (figure 1.13). In particular the two staggered *erythro* **36a** and **36b** conformers were judged to have the same energy profile and were equally populated in solution, indicating that the two methyl groups *gauche* to each other are compensated for by a favourable fluorine *gauche* effect. The *threo* conformer **37a** with the methyl groups *anti* and the fluorines *gauche* appeared as the lowest energy (~ 0.8 kcal/mol⁻¹) conformers in that series.

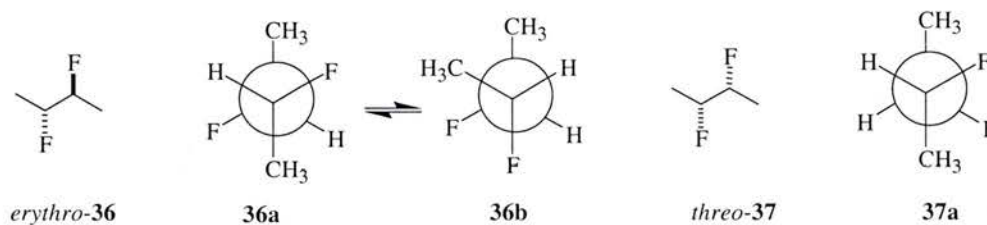


Figure 1.13 Conformations of 2,4-difluorobutane

Recently, a study⁴⁹ on the preferred conformation of the F-C-C(O)-N(H) moiety in α -fluoroamides and β -fluoroammonium systems where the C-F bonds prefer to adopt a conformation *anti* to the carbonyl and *syn* to the N-H⁵⁰⁻⁵² (figure 1.14) has been conducted.

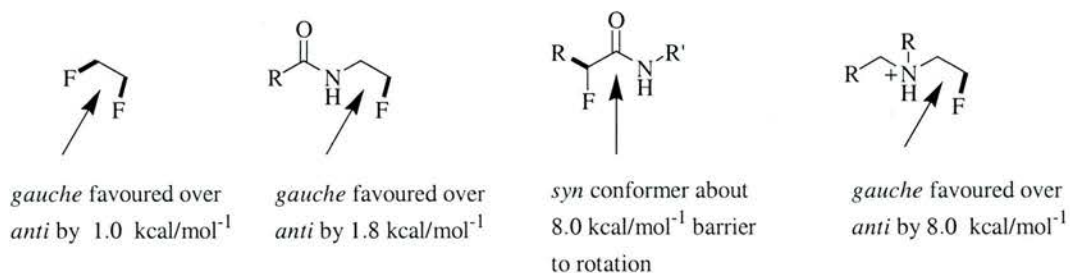


Figure 1.14 *Anti* and *gauche* conformations in fluoroethylenes, R & R' = CH₃

Following the above study, it was anticipated that the preferred conformation around the amide bond could be controlled by the strategic placement of a fluorine atom. In that study amide **38** was prepared (figure 1.15).

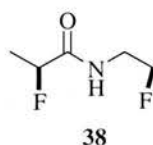


Figure 1.15 Difluoroamide

X-ray diffraction studies revealed that the α -fluoro C-F bond adopts a *gauche* conformation to the C-N-(CO) bonds in N- β -fluoroamide moiety and also the second C-F bond preferred a *syn* conformation to the C-N bond in the α -fluoroamide moiety in the solid state. This observation is in agreement with the prediction on the basis of the previous evaluated influence of the C-F bond in other amide systems.^{50, 51} Related studies by Seebach suggest that the strategic incorporation of the C-F bond into peptides can be used to design and control the conformation of medicinally important compounds.

1.3. Fluorination in organic synthesis.

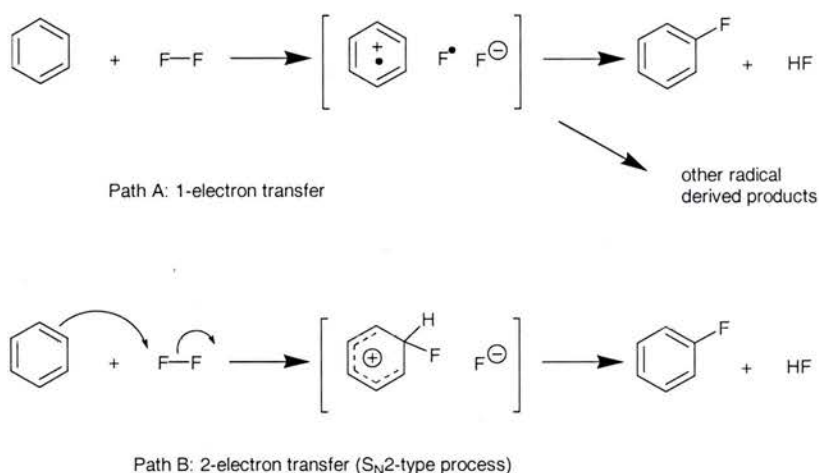
Although the regio-selective introduction of fluorine into organic molecules using F₂ is now well-documented, a number of more robust fluorinating reagents (C-F forming) have been developed for specific transformations in fluoro-organic chemistry. Recent advances in the quest for a broader scope of biotechnological applications have also been made by the discovery of the first native enzyme capable of converting inorganic

fluoride to organic fluorine by means of a specific fluorinase enzyme.⁵³ Fluorinating reagents may be classified⁵⁴ as sources of fluoride ion (F^-), or fluorine radicals (F^\bullet) and as compounds that can deliver electrophilic fluorine (F^+).

1.3.1. Fluorinating reagents in synthesis

1.3.1.1. Elemental Fluorine

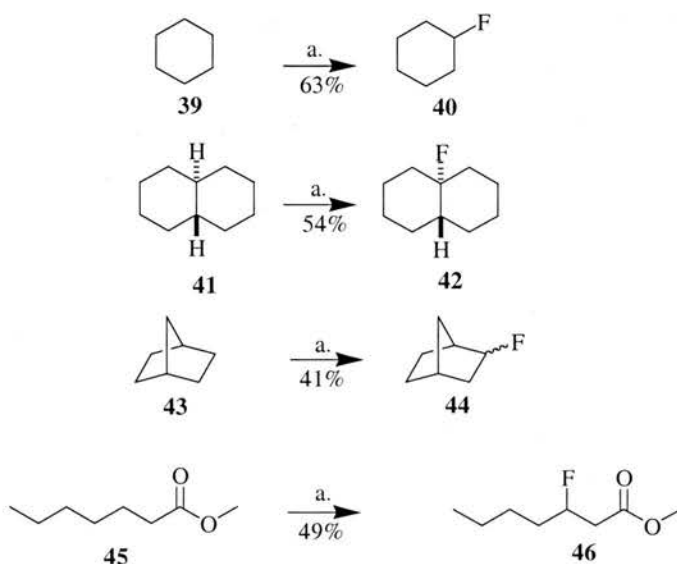
Fluorine, a yellow gas,⁵⁵ is the most electronegative and is the most reactive element. Its high reactivity in certain reactions prevented any widespread uses in the chemical industry for many years. Fluorine reacts with nearly all-organic and inorganic materials; however, it is not particularly reactive towards O_2 and N_2 . Under carefully regulated conditions fluorine can be a useful synthetic reagent.^{9, 56} A site-selective limited introduction of fluorine by direct reaction of F_2 has been demonstrated for many organic substrates, including carbanions,⁵⁷ enolates,⁵⁸ olefins and certain aromatic compounds⁵⁹⁻⁶¹ (scheme 1.1).



Scheme 1.1. Mechanisms of direct fluorination of aromatic compounds using F_2 .

Part A shows a nucleophilic radical (F^\bullet) process, which produces a phenyl radical intermediate to give fluorobenzene. Path B follows an electrophilic aromatic substitution process whereby 2-electrons from benzene react with F_2 to displace fluoride ion (F^-) (scheme 1.1). It appears that the choice of a solvent is critical in achieving successful fluorination facilitated by molecular fluorine with conc. H_2SO_4 and formic acid being commonly employed.

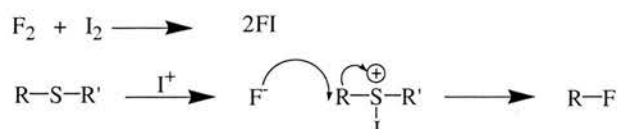
Synthetic procedures for the selective transformation of C-H to C-F bonds offer direct processes for incorporating fluorine atoms into organic compounds. Rozen and co-workers⁵⁶ demonstrated that a tertiary C-H site could be fluorinated using elemental fluorine in a reaction medium of $\text{CHCl}_3/\text{CFCl}_3$ at -78°C . However, limitations of this procedure for scale-up has led to the development of a new procedure by Chambers and co-workers.¹¹ Their procedure involves passing fluorine gas, diluted to 10% (v/v) in nitrogen, through a mixture of substrate and acetonitrile.

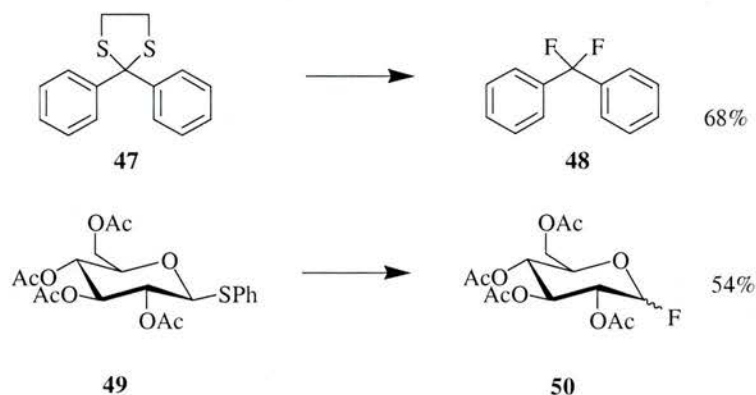


Scheme 1.2 Reagents: (a) F_2 [10%(v/v) mixture in N_2], CH_3CN , 0°C .

This procedure is amenable to both secondary and tertiary C-H sites, eg. cyclohexane **39**, trans-decalin **41** and norbornane **43** give single mono-fluorinated isomers in each case, whereas the linear methyl ester **45** gave a mixture consisting of mono-fluorinated isomers in a ratio of 5.9: 3.9: 3.2: 1 which were identified by NMR studies to be methyl 3-, 4-, 5- and 6-fluoroheptanoate (scheme 1.2).

Prudent manipulation of molecular fluorine by reaction with other halogens has paved a way into the synthesis of difluorinated compounds **48** from their corresponding thiolanes **47** (scheme 1.3). This fluorodesulfuration reaction is achieved upon reaction of FI^{62} with sulfides. The general reaction mechanism is as shown in the equation below.





Scheme 1.3 Fluorodesulfuration using F_2/I_2 .

Thus, elemental fluorine has in recent years experienced a change in achieving new strategic chemical transformations useful in biological and industrial applications.

1.3.2. Nucleophilic Fluorination

Fluorination of organic compounds using nucleophilic fluorination is one of the most widely used methodologies in the field of organo-fluorine chemistry. Development and refinement of several procedures for the selective introduction of fluorine have contributed greatly to the rapid increase in the inventory of fluorinated compounds. Fluoride sources such as HF, KF, CsF, SF_4 , TBAF,⁶³ are generally employed as fluorinating agents to achieve straightforward chemical transformations of carbon-oxygen to carbon-fluorine bonds when the substrate is activated eg. as the mesylate, tosylate, triflate, etc. However, limitations arise when employing the fluoride bases to base sensitive substrates, often leading to elimination reactions. Thus, various complexes of HF with donor bases have been developed to overcome these limitations. THF/HF was the first one to be reported in 1956 by Hirschmann.⁶⁴ Subsequently, stable solutions of HF amines,⁶⁵ amides,⁶⁶ etc. have been reported.

Pyridinium polyfluoride (Olah's reagent⁶⁷), was first prepared by Olah⁶⁸ from a reaction of pyridine and formyl fluoride. This resulted in decarbonylation of the resultant intermediate *N*-formylpyridium fluoride. This reagent is commercially available (HF/Py 70/30%) and is widely used. Solutions of lower concentrations of HF can be prepared by dilution with dry pyridine. Fluorination using HF/pyridine will be discussed in chapter 3 in preparations of α -fluoroacids.

Other common nucleophilic fluorinating reagents include diethylaminosulfur trifluoride (DAST),^{69, 70} triethylamine trihydrofluoride⁷¹ and Deoxo-Fluor.⁷² DAST, the most widely used of this group shows some instability at temperatures above 90 °C, often exploding. Thus a more thermally stable reagent (Deoxo-Fluor) has been developed and occasionally it has better reactivity than DAST.

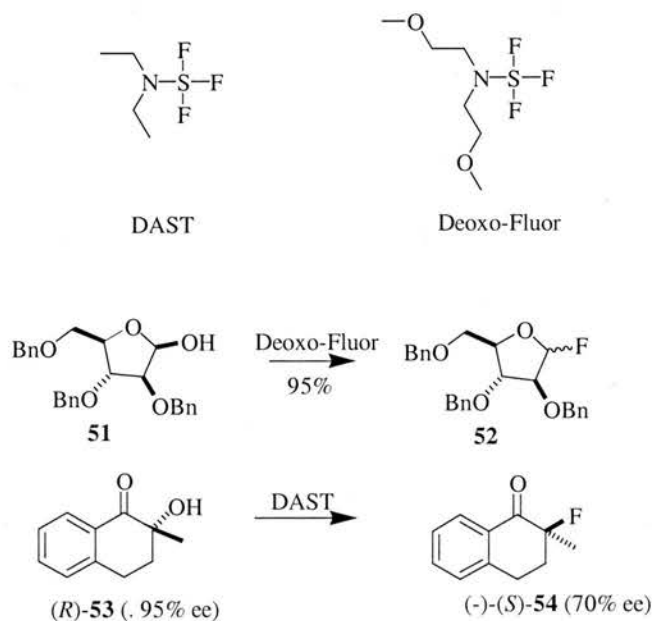
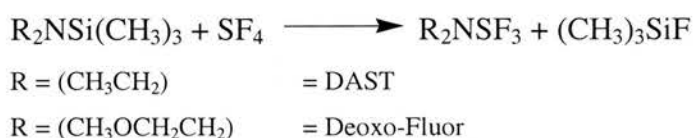


Figure 1.16 Fluorination of alcohols with DAST and Deoxo-Fluor

These reagents are used for the fluorination of alcohols (Figure 1.16), amino alcohols, diols, and the difluorination of aldehydes and ketones. Generally moderate yields are obtained. DAST and Deoxo-Fluor are easily prepared by the reaction of aminosilyl precursors and sulfur tetrafluoride as shown in the equation below.



These reagents have been widely utilised in carbohydrate and nucleoside chemistry and show compatibility with substrates bearing a variety of protecting groups.^{73, 74} These fluorination reagents mediate reactions which are generally reported to proceed smoothly giving high yields.

1.3.3. Electrophilic Fluorination

1.3.3.1. Fluorinating reagents of class N-F

One of the most important developments in the last decade in organo-fluorine chemistry has been the development of a variety of N-F fluorinating agents. A continuing search for regioselective strategies for carbon-fluorine bond formation in organic chemistry has stimulated their development. Conventional electrophilic fluorine sources were identified as F_2 , perchloryl fluoride, $FClO_3$, xenon fluoride, XeF_2 , trichloroacetyl hypofluorite, $Cl_3CC(O)OF$ and various acyl and perfluoroacyl hypofluorides, $RC(O)OF$ and $R_1C(O)OF$, however, their use is limited due to their hazardous nature: explosive, hygroscopic, gaseous, toxic, etc.

Since fluorine is the most electronegative element, the above properties may well be unavoidable in reagents in which fluorine behaves as an electrophile. However, in order to modify molecules such as those of pharmaceutical and agrochemical importance, mild and selective methods for the incorporation of the fluorine atom are required. The recently developed N-F reagents (electrophilic reagents based on compounds with N-F groups) satisfy this requirement and are relatively stable on prolonged storage.^{75, 76}

Electrophilic N-F reagents are now commonplace in organo-fluorine chemistry with the diazoniabicyclo[2.2.2]octane, pyridines and sulfonamides being the most widely encountered motifs.

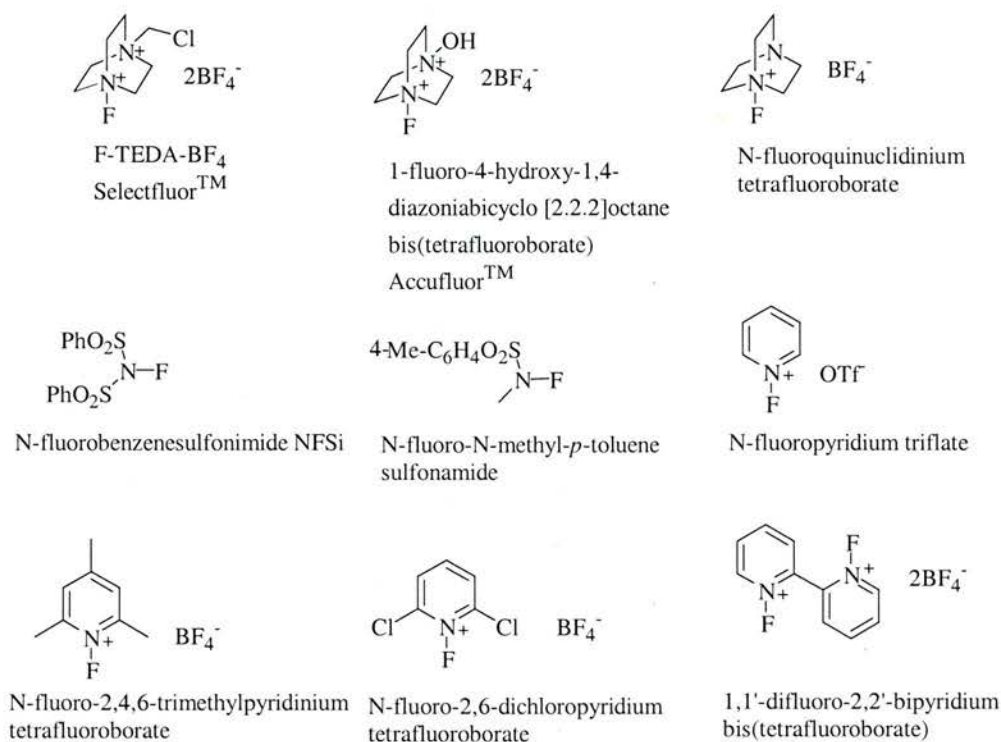


Figure 1.17 Electrophilic fluorinating agents of N-F and [N-F]⁺ classes.

Both N-F and [N-F]⁺ can be prepared by direct fluorination from neat or diluted elemental fluorine and/ or by transfer fluorination.⁶² Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane *bis*(tetrafluoroborate)] is the most commonly used amongst its congeners although it has only been introduced quite recently. It was discovered and developed by researchers from UMIST, Air Products and Chemicals Inc.^{76, 77} This reagent is now produced in multi-ton quantities per year following a protocol fully described in other reports.⁷⁷⁻⁷⁹ The manufacturing process is shown in scheme 1.18. Selectfluor is also used for the preparation α -fluoro acid chlorides in the preparation of fluoroketenes (chapter 3) to provide an alternative fluorination route towards homochiral α -fluoro carbonyls.

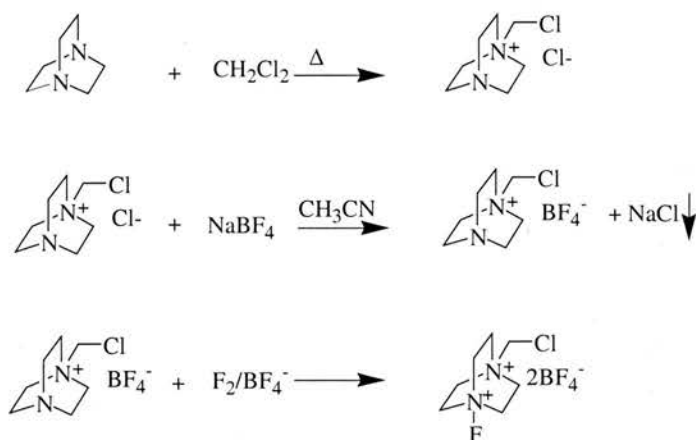


Figure 1.18 A typical Selectfluor industrial manufacturing process

1.3.4. Asymmetric fluorinating reagents in synthesis

The fascinating properties of organo-fluorine molecules together with the desire to control chirality, have led to enormous efforts in the asymmetric synthesis of organo-fluorine compounds.⁸⁰ There is a rapid growth in demand for optically active fluorinated compounds for different applications, e.g. in medicinal chemistry, biochemistry and also in the material sciences. Consequently, there is a need for synthetic procedures to prepare such compounds. A key challenge has been direct asymmetric fluorination.

There are two general methodologies to obtain optically active fluorinated compounds:

- The stereoselective introduction of fluorine at a prochiral center and,
- The chiral auxiliary and enzyme-catalysed resolution of racemates.⁸⁰

Differding and Lang⁵⁸ were the pioneers of asymmetric fluorination of β -ketoester enolates with *N*-fluorocamphorsultam **55** (figure 1.19) which gave ee's up to 70%. The enantioselectivity was later improved up to 75% for the fluorination of 2-methyl-1-tetralone **57** employing *N*-fluoro-3,3-dichlorocamphorsultam **56**.

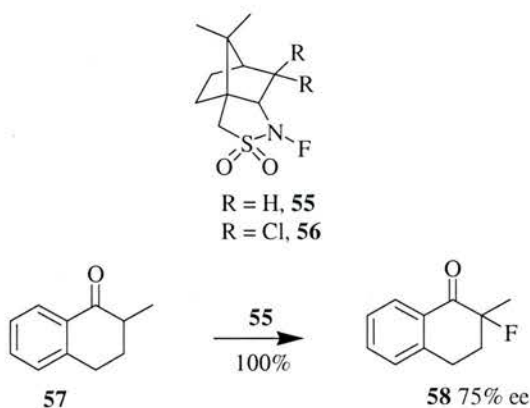


Figure 1.19 Fluorination using camphorsultams

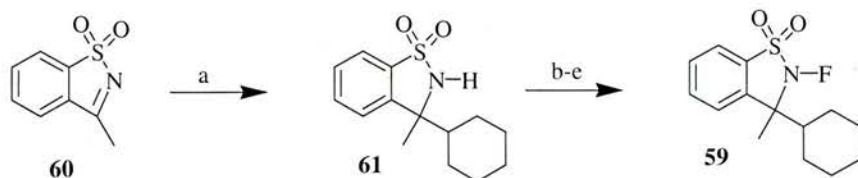
Studies were undertaken by Takeuchi *et al*⁸¹ who employed enantiomeric *N*-fluoro-3-cyclohexyl-3(*R*)-methyl-2,3-dihydrobenz[1,2-*d*]isothiazole 1,1-dioxide (CMIT-F) **59** for fluorination of enolates to furnish optically pure α -fluoroketones, often with high stereoselectivities (88% ee).



Figure 1.20 Saccharin derived N-F fluorinating agent.

The reagent (*R*)-CMIT-F **59** (figure 1.20) has a stable structure, but possesses a reactive N-F bond and has steric factors that favour asymmetric induction. It is believed that the planarity present in the 2,3-dihydrobenzo-isothiazole system is likely to effect the stereochemical course in an ordered transition state.

The reagent (*R*)-CMIT **59** was prepared from saccharin as the starting material and the imine **60** was afforded following Oppolzer's method.⁸² The reaction sequence leading to the compound **59** is outlined in (scheme 1.4).



Scheme 1.4 Reagents: (a) $c\text{-C}_6\text{H}_{11}\text{MgBr}$, THF (70%); (b) (-)-menthyloxyacetyl chloride, NaH, THF, (73%); (c) separation; (d) 2N LiOH, THF_(aq) (93-96%), (e) 15% F₂/He, spray-dried KF, CHCl₃ (51-65%)

The unavailability of these reagents due to the tedious synthetic procedure required for their preparation has led to the development of new a class of enantioselective fluorination agents based on alkaloid derivatives of Selectfluor. Carbanions can be fluorinated enantioselectively with Selectfluor in the presence of dihydroquinine 4-chlorobenzoate (DHQB) or dihydroquinidine acetate (DHQA) (figure 1.21).

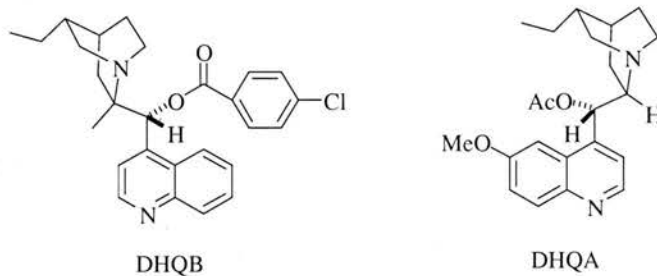
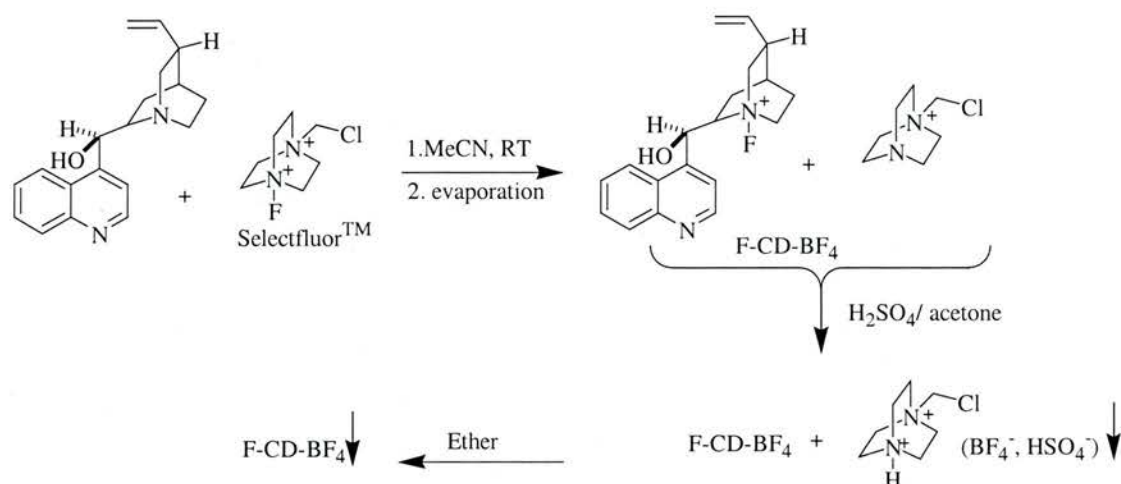


Figure 1.21 Cinchona alkaloids

A typical reagent preparation involves the alkaloid and Selectfluor in acetonitrile at $-20\text{ }^{\circ}\text{C}$ to afford up 91% ee as determined by HPLC. These reagents will fluorinate both cyclic and acyclic carbonyl compounds.⁸³



Scheme 1.5. Preparation and purification of F-CD-BF₄

In order to probe the mechanism of electrophilic fluorination with the cinchona reagents, Cahard *et al.*⁸⁴ have reported the purification and X-ray structure of the first [N-F]⁺ chiral fluorinating agent derived from cinchonidine. X-ray diffraction analysis was carried out on F-CD-BF₄ to reveal N-F bond length of 1.419(7) Å. This is similar to that of fluoroquinuclidinium triflate, 1.407(6) Å and significantly longer than the N-F bond length in Selectfluor, 1.37(2) Å⁸⁵ (figure 1.22).

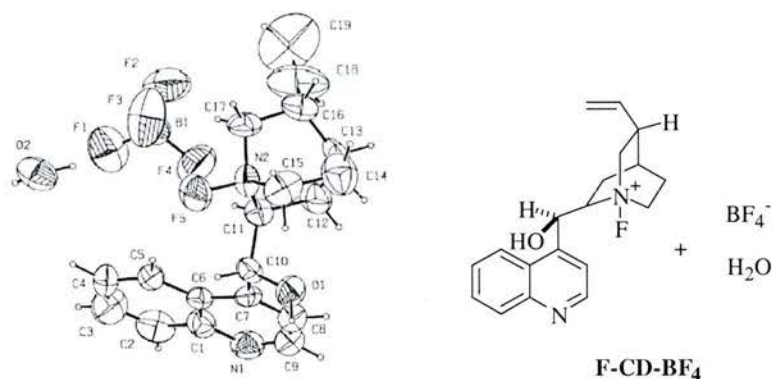
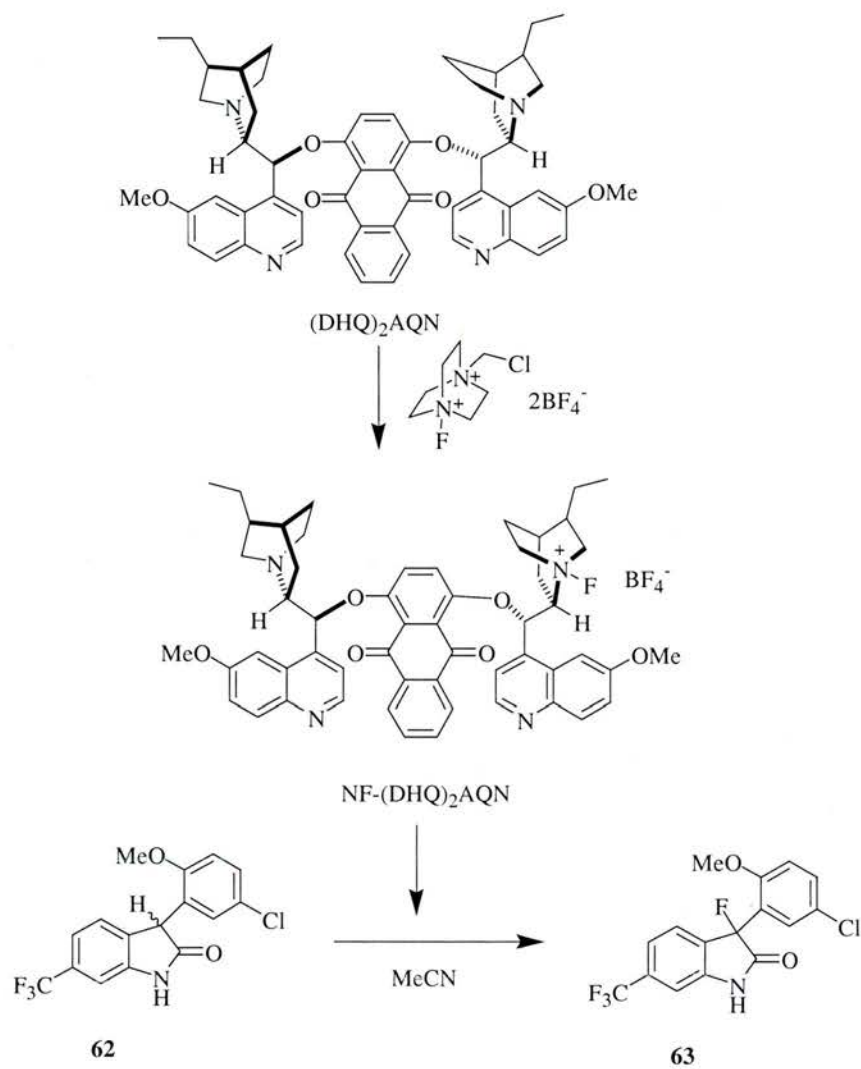


Figure 1.22 N-Fluorocinchonidinium tetrafluoroborate F-CD-BF₄, H₂O drawn using PLATON-98.

Shibata reported the first asymmetric synthesis of fluoro-oxindole (Maxipost) *et al.*⁸⁶ The novel BMS-204352 (Maxipost) **63** is being developed by Bristol-Meyers Squibb Pharmaceutical Research Institute as a potent, effective opener of maxi-K⁺ channels. Worldwide phase III clinical trials of BMS-204352 for treatment of acute ischemic stroke are currently in progress. BMS-204352 is a chiral, nonracemic compound, which

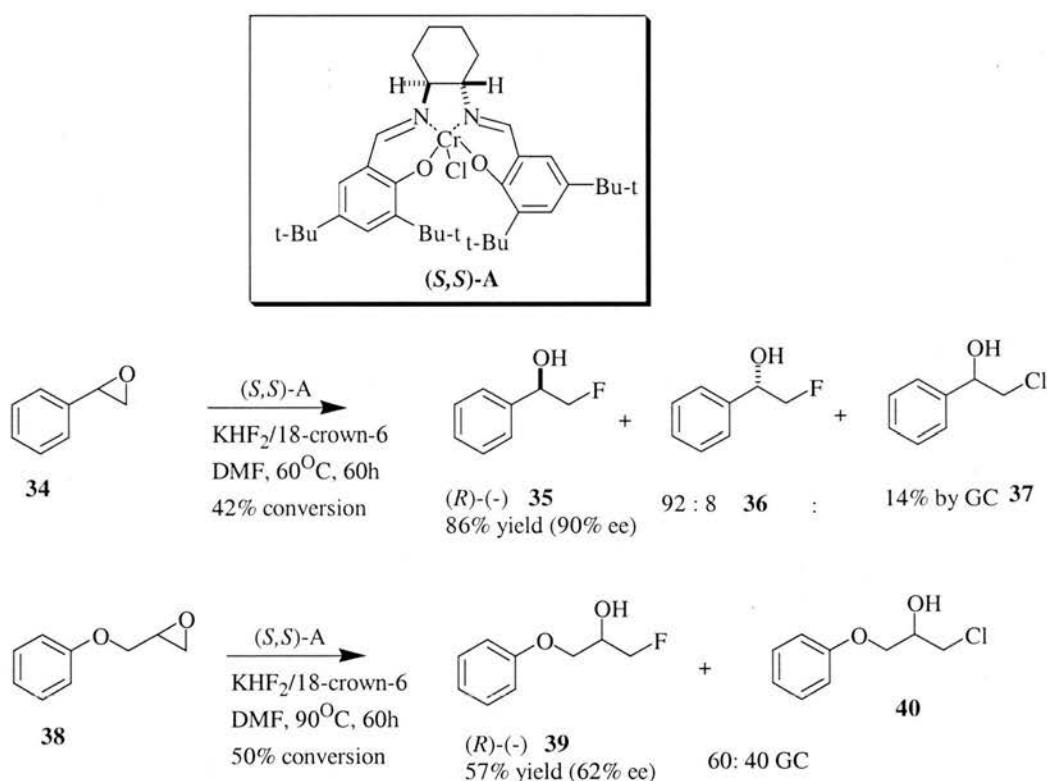
has fluorine at quaternary centre at C-3 of oxindole ring. The (*S*)-enantiomer of this compound has been found to be the most active. Maxipost was successfully prepared from **62** (scheme 1.6) in 99% ee as determined by HPLC after recrystallisation from dichloromethane/ hexane.



Scheme 1.6 Enantioselective fluorination mediated by N-fluoroammonium salts of (DHQ)₂AQN

1.3.5. Synthesis of fluorohydrins by de-racemization

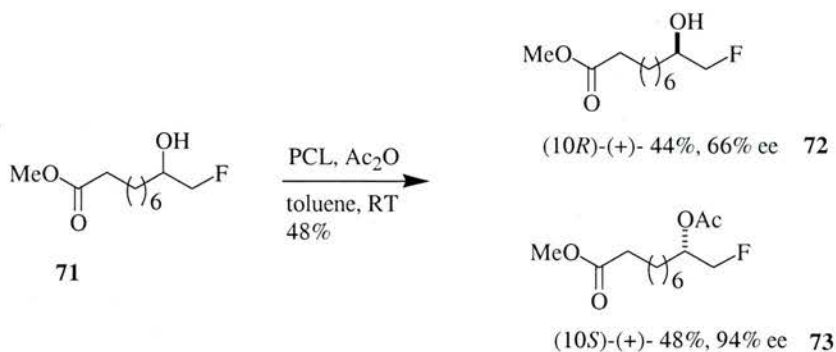
More recently Haufe has demonstrated the asymmetric ring opening of racemic epoxides by a hydrofluorinating reagent mediated by enantiopure (salen) chromium chloride (*S,S*)-**A** (scheme 1.7). Although asymmetric ring opening of epoxides by nucleophiles using enantiopure reagents is a common strategy in asymmetric synthesis, no examples had been reported in organo-fluorine chemistry before Haufe's study.⁸⁷ However there are many examples of diastereo- and regioselective ring opening of epoxides by hydrofluorinating agents.⁸⁸



Scheme 1.7

Haufe employed catalyst (50%) and KHF_2 as optimal conditions for styrene oxide **64** ring opening. This reaction proceeded smoothly to form (*R*)-(-)-2-fluoro-1-phenylethanol **65** in 86% conversion and 90% ee (scheme 1.7).

Another strategy of generating optically active organo-fluorine compounds involves de-racemisation of fluorinated amino acids and fluorinated carboxylic acids. Methyl 10-fluoro-9-hydroxy-decanoate **71** was successfully deracemized by acetylation with acetic anhydride in toluene using *Pseudomonas cepacia* lipase (Lipase Amano PS, LAPS) as a biocatalyst⁸⁹ (scheme 1.8).

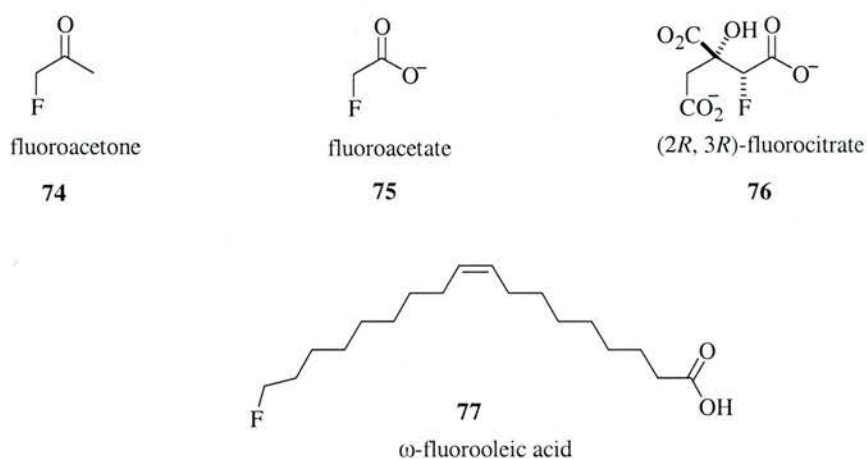


Scheme 1.8 Deracemization of β -fluoro-alcohol

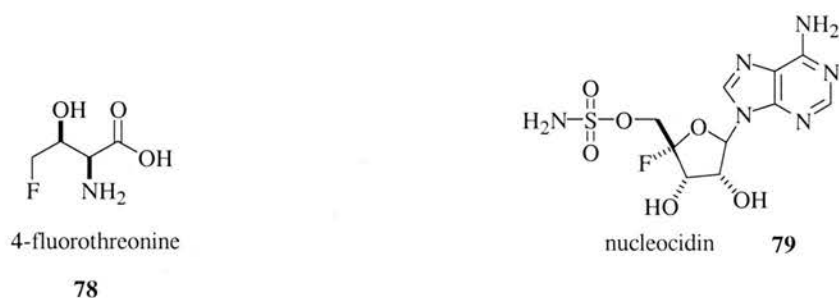
The reaction is typically carried out by stirring a toluene mixture of the enzyme with one equivalent of acetic anhydride and PCL at room temperature over 20 to 26 hours to afford up to 50% conversion and moderate enantiomeric excess (ee). Similarly a deracemisation of 1-fluoro-7-en-2-ol by enzyme an catalysed acetylation using vinyl acetate in an organic solvent and the *Candida antarctica* lipase has also been reported.⁹⁰

1.3.6. Biofluorination

To date there are only a small number of naturally occurring fluorinated molecules known. It seems that although fluorine is the 13th most abundant element in the earth crust⁹¹ it is not bio-available. Nonetheless, around half a dozen different biologically produced organo-fluorine compounds have been identified in different plants and bacteria. The plants are geographically limited to tropical and semitropical regions, but are found in all the major continents (figure 1.23).



plant metabolites



bacterial metabolites

Figure 1.23 Fluorinated products produced by plants and bacteria

Fluorinated natural products produced by micro-organisms have been identified as, fluoroacetone **74**, 4-fluorothreonine **78** and nucleocidin **79**. Nucleocidin **79** was isolated from the bacterium *Streptomyces calvus* in 1957 by Thomas *et al*⁹² and showed a broad spectrum antibiotic activity. Its toxicity however, prevented any clinical application, and further attempts to isolate this compound from cultures of *S. calvus* have been unsuccessful.⁹³

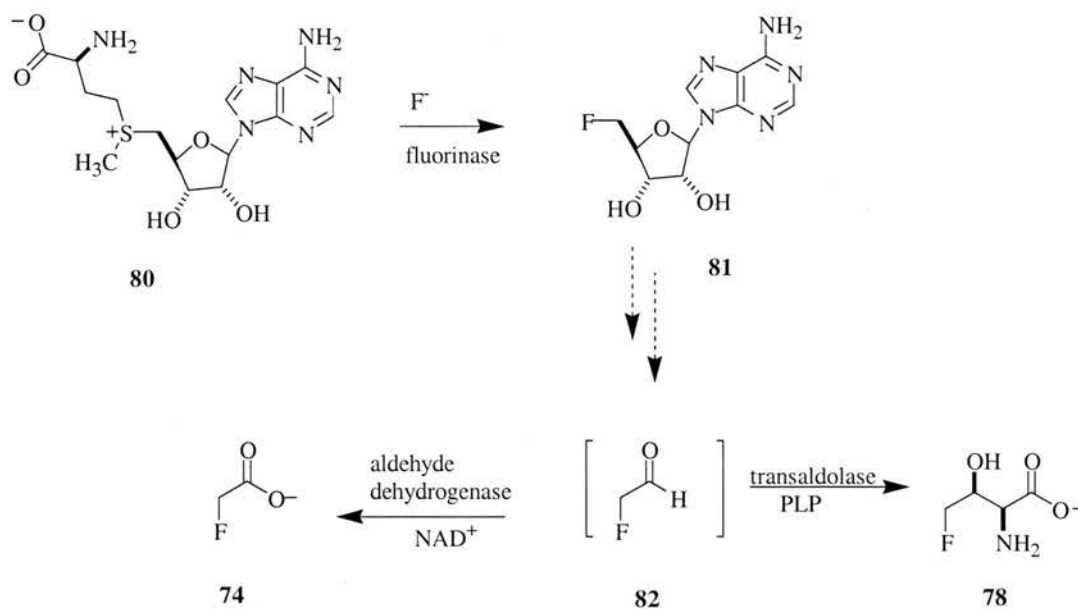
The dearth of naturally produced fluorinated compounds can be attributed to several factors:

- (1) The low bioavailability⁹⁴ of fluoride in comparison to the other halogens. This is mainly attributed to Fluorspar (CaF_2) insolubility hence its concentration in seawater is only 1.3 ppm whereas that of chloride is 19 000 ppm

- (2) Fluoride ion is a poor nucleophile in aqueous medium due to its high heat of hydration therefore, its participation in displacement reactions is significantly compromised.
- (3) Fluoride cannot be incorporated into organic compounds *via* the haloperoxidase reaction⁹⁵ since the redox potential required for the oxidation of fluoride ion is too large to be compensated for by the reduction of hydrogen peroxide.

The most common fluorinated natural product found in plants is fluoroacetate **74**, which was first identified in *Dichapetalum cymosum*, inhabiting the former Transvaal region of South Africa.^{96,97} It has also been found in other *Dichapetalum spp* throughout Africa. One intriguing aspect of these fluorinated metabolites, is the nature of the biosynthesis process.

O'Hagan *et al*⁵³ have recently identified and isolated an enzyme (fluorinase) that is responsible for C-F bond formation in *Streptomyces cattleya*. This enzyme, the first of its class, mediates a reaction between inorganic fluoride ion and (*S*)-adenosyl-L-methionine (SAM) **80** (scheme 1.9) to generate 5'-fluoro-5'-deoxyadenosine **81** (5'-FDA). The metabolite 5'-FDA has been shown to be a precursor to fluoroaldehyde **82**, the common precursor for fluoroacetate **74** and 4-fluorothreonine **78** in the organism. The fluorinase has recently been purified, crystallised and the structure resolved by X-ray diffraction.⁹⁸

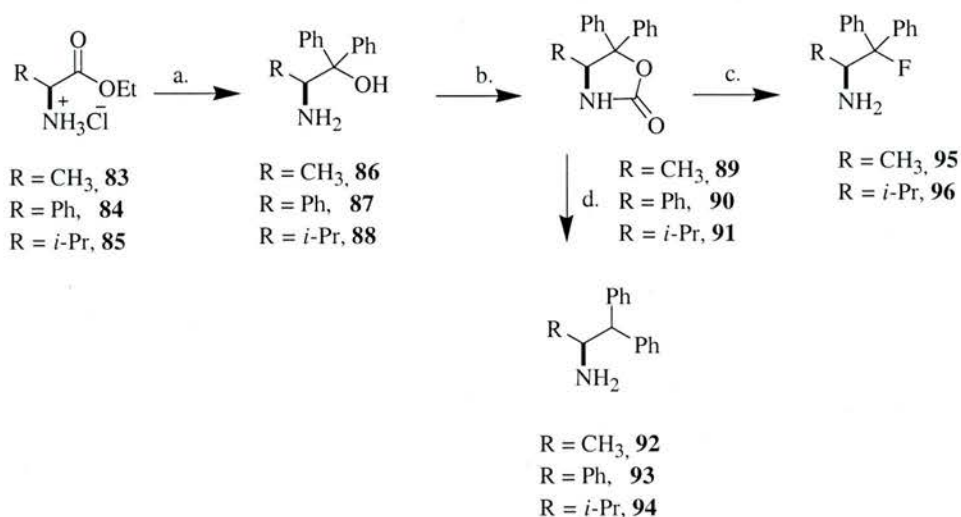


Scheme 1.9 Enzymatic fluorination of SAM by the fluorinase from *S. cattleya* generates 5'-FDA **81** which is then converted to F-Ac **82** and F-FT **78**.

1.4. Onyx Homochiral Amines

Amines are widely used in asymmetric synthesis. They are found as chiral auxiliaries,⁹⁹ ligands,^{100, 101} bases¹⁰² and chiral resolving agents.¹⁰³ This research programme is focused on the application of chiral amines funded by Onyx-Scientific. The main areas addressed are: asymmetric alkylation/ methylation, chiral auxiliaries, synthesis of diamines and methodology development.

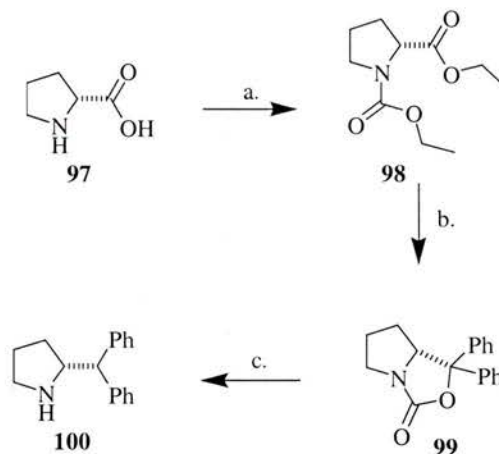
The amines (**92-96** and **100**) employed in this thesis were prepared from their respective amino acid hydrochlorides^{104, 105} (**83-85**). The hydrochloride was treated with phenylmagnesium bromide to generate the amino alcohols **86-88**. Cyclisation of the amino alcohols utilising diposgene gave access the key oxazolidinones intermediates **89-91**. In one study these intermediate was converted directly to amines (**92-94**) through hydrogenolysis using palladium on carbon (10%) under hydrogen atmosphere with release of elements of CO₂.



Scheme 1.10 Reagents: (a) PhMgBr (5 eq), Et₂O, 40-50% (b) triphosgene, Et₃N, 80-90%, (c) HF-pyridine (70/30), 31-85%, (d) Pd(OH)₂/C, H₂ (20%), quant.

O'Hagan *et al.*^{104, 105} have prepared novel fluorinated amines **95** and **96** from a variety of (*S*)-amino esters (scheme 1.10) with HF/Py (70/30%) Olah's reagent.

This resulted in a decarboxylative hydrofluorination reaction to deliver the corresponding fluorinated analogues **95** and **96**.



Scheme 1.11 Reagents: (a) EtCOCl, CH₃OH, K₂CO₃, 100%, (b) PhMgBr, THF, 62%, (c) Pd/C (10%), H₂, 44%.

The pyrrolidine **100** was prepared from the reaction of (*R*)-proline and ethyl chloroformate according to the procedure by Kanth.¹⁰⁶ The oxazolidinone **99** was achieved by treatment of the amido ester **98** with phenylmagnesium bromide. The (*R*)-diphenylmethylpyrrolidine **100** was afforded after hydrogenolysis as described above.

Amines **92-96** and **100** have been patented and licensed to Onyx-Scientific and were generously supplied. This project is thus aimed at exploring their potential in asymmetric synthesis.

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2

The role of fluorine in directing alkylation reactions *via* lithium chelation

Synopsis

Reactions of metal enolates constitute important methods for the design and construction of carbon-carbon bonds. The objective in this study is to evaluate the stereochemical control of alkylation reactions in given model reactions. As part of research directed at utilising organofluorine compounds in organic synthesis, syntheses of organofluorine compounds was undertaken to evaluate the stereoinduction arising from the lithium-fluorine chelation.

Organic bound fluorine was found to display a measurable but moderate to poor chelation effect in a model alkylation system. In one comparative system F is compared with H and with O and the resultant diastereoselectivity is consistent with its intermediate capacity to chelate lithium relative to H and O. It is concluded that there is a potential role for organic bound fluorine to become involved in lithium chelation in well-designed enolate alkylation systems. In this chapter compounds, **101-109** were utilised in this study.

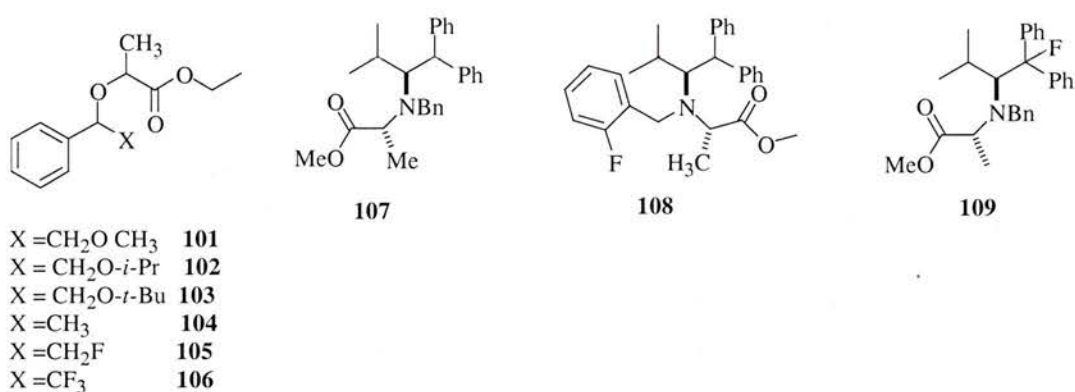
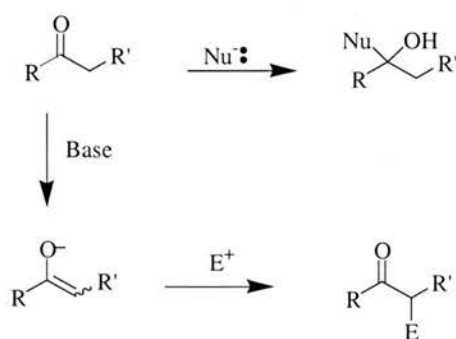


Figure 2.1 Methylation synthetic targets.

2.1. General

The carbon-carbon bond construction is by far the most important chemical reaction in organic synthesis. A plethora of methodologies have been developed to design and rationally execute C-C bond formation to compile an impressive inventory of organic structures. The prime activating function for this bond formation is the carbonyl group.

The carbonyl is an exceptionally versatile group in organic chemistry and functions as either an electrophile or as a nucleophile *via* enolate chemistry (scheme 2.1).



Scheme 2.1

If either R or R', or both, contain an asymmetric centre, the π -faces of the carbonyl and enolate become diastereofacial. Therefore the potential for intramolecular stereoinduction/ diastereoselection exists. This study is focused on manipulation of the geometry of the enolate in a given chiral system. Due to the ubiquity of this class of C-C bond construction, a limited set of chiral enolate systems has been developed to evaluate the significance of fluorine-lithium chelation.

2.1.1. Co-ordination Ability of Organic fluorine to Metals

Interactions of organic bound fluorine and metals was first described by Glusker¹⁻³ and co-workers in 1983. This was made possible by the availability of the Cambridge Crystallographic Data files and associated programmes. The results were deduced from intermolecular interactions by surveying the environment of a given group in a large number of different crystal structures. Although halide ions are common ligands, covalently bonded halogen (C-X, X = halogen) is not normally considered a good donor atom. The effect is weakest for fluorine because of its high electronegativity. However, there is increasing evidence in favour of organic bound fluorine F \cdots M interactions.⁴

The structure determination of alkali metals salts of fluoroacids revealed impressively short M \cdots F distances [Na \cdots F-C in fluoropyruvate = 2.470 (1) Å and Rb \cdots F-C in fluorocitrate = 2.979(5) Å and 3.095(4) Å]. Stalke and Whitmire^{5,6} carried out lithiation of 1,3,5-tris(trifluoromethyl)benzene using *n*-BuLi in ether (figure 2.2). The resultant complex appeared to be a stabilised dimer by Li \cdots F interactions as determined by X-ray diffraction analysis.

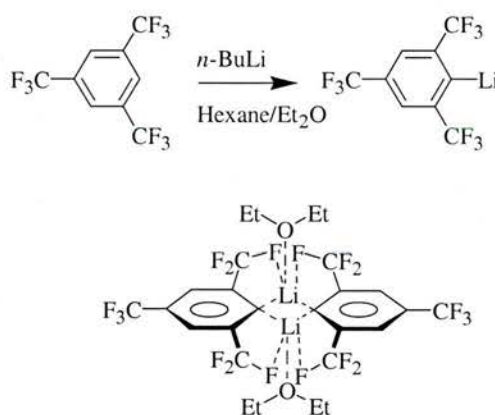


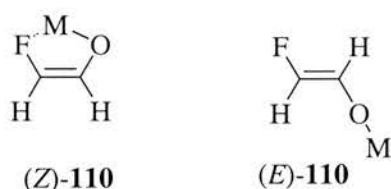
Figure 2.2 Intramolecular F \cdots metal interaction of metallated 1,3,5-tris(trifluoromethyl)benzene.⁵

The co-ordination geometry at lithium was determined to be a distorted trigonal bipyramid. Further analysis of the dimeric structure revealed that each lithium is stabilised by bonding to two carbon atoms, an oxygen of a diethyl ether molecule and two fluorines from the *ortho*-CF₃ groups. The Li \cdots F distance was observed in a range of 2.227 to 2.293 Å.

In order to achieve fluorine co-ordination, the two phenyl rings are spaced with respect to each other making a dihedral angle of 41° . The F-Li-F vector forms an angle of 164° with the C_2LiO plane. The average Li-C bond length is 2.264 \AA which differ little from other relate systems.⁷⁻⁹

Crystallographic analyses by Roesky¹⁰⁻¹² on various types of compounds with intramolecular metal-fluorine interactions revealed a co-ordination distance of $M \cdots F$: $1.816 \sim 2.286 \text{ \AA}$, $Na \cdots F$: $2.15 \sim 2.91 \text{ \AA}$, $Mg \cdots F$: $1.905 \sim 2.026 \text{ \AA}$ and $Al \cdots F$: $1.765 \sim 1.812 \text{ \AA}$ to list a few.

In addition to the crystallographic studies above, Dixon and Smart¹³ have carried out *ab initio* calculations for the metal enolate derived from fluoroacetaldehyde (scheme 2.3).



| M | $E_{(E)} - E_{(Z)}$ (kcal/mol) | $M \cdots F$ (\AA) |
|----|--------------------------------|-------------------------------|
| - | 1.8 | - |
| Li | 13.2 | 1.86 |
| Na | 13.6 | 2.21 |
| K | 10.8 | 2.62 |

Figure 2.3 *Ab initio* calculation of metal enolates of 2-fluoroacetaldehyde.¹³

Their calculations showed a lower ground state energy for (Z)-110 compared to the stereoisomeric (E)-110 by 10 to 14 kcal/mol, at the MP2 level, which was interpreted as a clear indication of an intra- molecular $C-F \cdots M-O$ interaction. Interestingly, relative energies for fluoroacetaldehyde enols revealed a similar pattern, in which the *cis-syn* conformer is more stable than the *cis-anti* conformer (figure 2.4). The $H \cdots F$ bond distance was found to be 2.44 \AA and its strength 3.53 kcal/mol at the MP2 level.¹⁴ Clearly, the $M \cdots F$ in this systems interaction is significantly stronger than the $H \cdots F$ interaction.

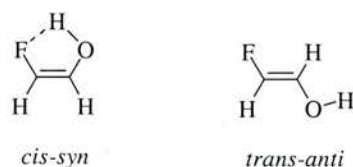


Figure 2.4 The geometries of the 2-fluoroacetaldehyde enols

Fluorine lithium co-ordination was experimentally exemplified by Yamazaki and co-workers¹⁵⁻¹⁷ in the diastereoselective Michael addition of various types of enolate such as **111** to 3-(trifluoromethyl)acrylates **112** (Figure 2.5). They observed that non-fluorinated crotonates were unsuccessful Michael acceptors consistent with a role for the CF₃ group stabilising the intermediate enolate.

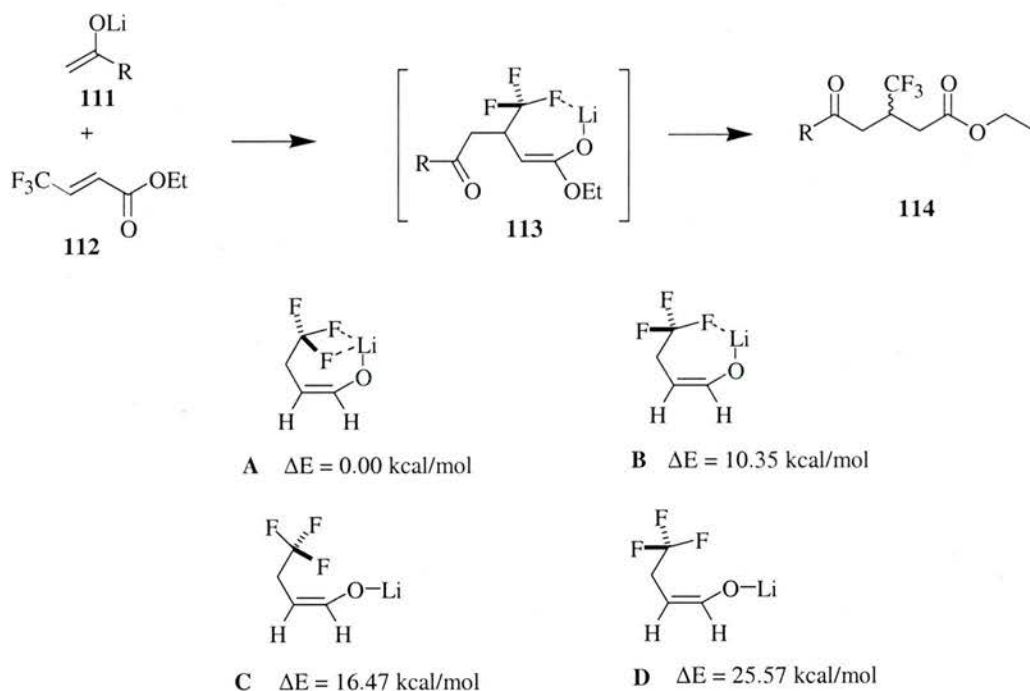
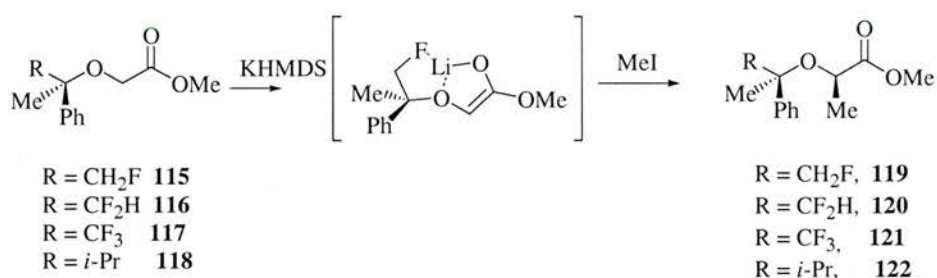


Figure 2.5 *Ab initio* calculations of model conformers of Michael addition intermediates.¹⁸

Verification of F-Li interactions was carried out by *ab initio* calculations of the energies of, **A** to **D**.^{19, 20} **A** was the most stable with co-ordination of the two fluorine atoms to lithium with a distance of 2.015 Å compared to **B** which had a distance of 1.759 Å.

The calculated energy differences indicate that the fluorine-lithium interaction is a strong driving force for smooth conjugate addition, consistent with the experimental reactivity of fluorinated over non-fluorinated enolates in the Michael additions.

The ability of carbon bound oxygen to chelate to lithium is a central tenet in organic chemistry and the strategy has been used widely to design pre-organisation into chemical reactions.²¹⁻²⁶ Of course carbon bound hydrogen is not an obvious candidate for co-ordination to lithium and other metal cations and is not a useful atom for designing pre-organisation into a reaction system. In this study we have explored the ability of organic bound fluorine to influence the stereoselectivity of lithium enolate reactions. In this regard organic fluorine is intermediate between oxygen and hydrogen and there have been some recent reports that it performs very well as a lithium chelator in asymmetric alkylation reactions.^{17, 27-29} Of course organic bound fluorine is not an immediately obvious candidate for lithium chelation particularly as fluorine is a moderate to poor hydrogen bonding acceptor.^{30, 31} Probably the most impressive results have been reported by Yamazaki *et al*³² who have demonstrated convincingly in an experimental system that the fluorine of a fluoromethyl group can induce a diastereoselectivity of 82-90 % de (diastereomeric excess) **119-121** in the methylation reactions illustrated in (scheme 2.2).



Scheme 2.2

The de's were higher for other alkylation reactions involving benzyl bromide and allyl iodide. In the case of **115** it is only the replacement of F for H which can account for this diastereoselectivity, and it was argued that fluorine is chelating lithium in the bicyclo [3.3.0] intermediate enolate as shown in (scheme 2.2). The stereogenic centre in these substrates is a tertiary ether and the steric influence of this tertiary centre is also

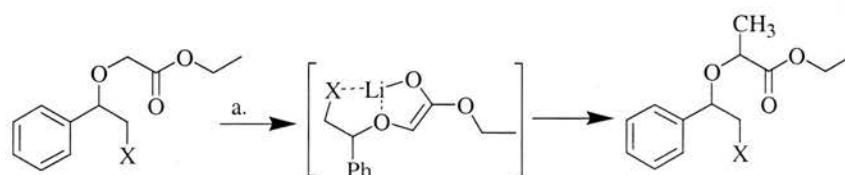
significant and contributes in part to the efficiency of chirality transfer in these reactions.

| R | Isolated yield (%) [% de] | | |
|------------------------------|---------------------------|----------------------|---------|
| | CH ₃ I | PhCH ₂ Br | Allyl-I |
| CH ₂ F 119 | 50 [82] | 41 [84] | 49 [62] |
| CHF ₂ 120 | 58 [88] | 45 [84] | 61 [72] |
| CF ₃ 121 | 67 [90] | 79 [80] | 82 [68] |
| <i>i</i> -Pr 122 | 50 [56] | 31 [48] | 77 [28] |

Table 2.1 Representative reaction results of Yamazaki *et al.*³²

Table 2.1 details the results when esters **115-118** were independently reacted with methyl iodide, benzyl bromide and allyl iodide. A systematic decrease in the number of fluorine atoms resulted in lower alkylation yields. However, the number of fluorine atoms does not significantly influence the % de values of the resultant alkylated product as long as the substrates contained at least one fluorine. On the contrary, the non-fluorinated substrate **118** was found to be both low yielding and less stereochemically discriminating towards alkylation. These studies also show a general trend in %de values in regard to the electrophiles used. Methyl iodide consistently gave higher de values than benzyl bromide, whereas allyl iodide gave the lowest de values.

Prompted by these reports, and by a general focus on evaluating the experimental influence of fluorine in organic chemistry, it appeared appropriate to examine a series of enolates whereby the substrates varied only at a remote site X (scheme 2.3). This remote functionality may (or may not) become involved in lithium chelation with an intermediate [3.3.0] enolate. It was a particular focus of this study to examine the coordination of “H”, “F” and “O” in the series.



Scheme 2.3 Reagents: (a) CH₃I, LDA, THF, 70%

For this purpose the substrate series **123-126** where X = H (**123**), OMe (**124**), O-*i*-Pr (**125**), O-*t*-Bu (**126**), were prepared for alkylation (methylation) reactions. ^1H NMR could readily determine the product diastereoisomer ratios. The substrates varied by changing group X attached to the secondary ether and it was envisaged that the enolate intermediates in these reactions could find stabilisation by co-ordination of X to lithium (scheme 2.3). It is assumed that increased co-ordination ability will lead to higher diastereoisomeric ratios in the product mixture.

2.2. Results and Discussion

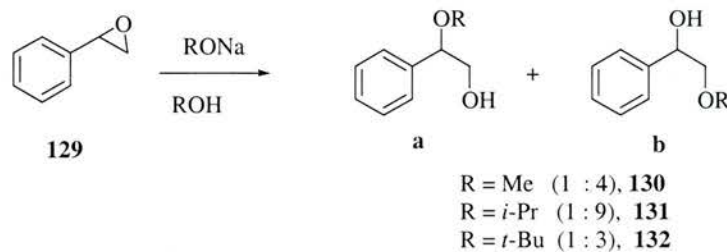
The benzyl ethers **123-126** were selected as they represented substrates which could be readily alkylated/ methylated after treatment with LDA, and as a series they allowed us to explore the relative abilities of oxygen, hydrogen and fluorine (at the X-site) to co-ordinate to lithium in the intermediate enolate. Also these compounds were accessible by straightforward synthetic protocols.



X = H (**123**), OMe (**124**), O-*i*-Pr (**125**), O-*t*-Bu (**126**), F, (**127**) **128**

2.2.1. Synthesis of benzyl ether substrates (123-127)

The substrates for the study were prepared by a straightforward Williamson's ether protocol³³ between the relevant benzyl alcohol and ethyl iodoacetate. For substrates **130-132** the relevant benzyl alcohols were prepared by alkoxide ring opening of styrene oxide **129**.³⁴



Scheme 2.4

| R | Yield | Ratios (a : b) |
|--|-------|----------------|
| CH ₃ 130 | 67 | 1 : 4 |
| CH(CH ₃) ₂ 131 | 90 | 1 : 9 |
| C(CH ₃) ₃ 132 | 68 | 1 : 3 |

Table 2.2 Data for the regioselective styrene oxide ring opening.

Typically the reactions were undertaken in alcohols (ROH) treated with sodium hydride, and allowed to react at 60°C over 5 h. In all cases regioisomers **a** and **b**, as shown in scheme 2.4 were always observed and were readily separated by column chromatography. Regioisomer **b** was identified as the major product and was used further for the purpose of this study.

Attempts at manipulating the regioselectivity in favour of **b** by using polar non-protic solvents such as DMF and the weakly polar THF was explored. This required high temperatures and resulted in very low yields and poor stereoselectivities. These reactions generally proceeded smoothly; surprisingly the tertiary butyl derivative gave the poorest regioselectivity and yield. It appears that a balance between strong nucleophilicity and steric influence is required to achieve optimum regioselectivities. This appeared optimal for the isopropyl product **131**, which was found to have the highest regioselectivity and highest yield.

The corresponding benzyl ethers **124-126** were accessed in a straightforward manner when alcohols **130-132** were treated with ethyl iodoacetate and sodium hydride in THF (scheme 2.6).

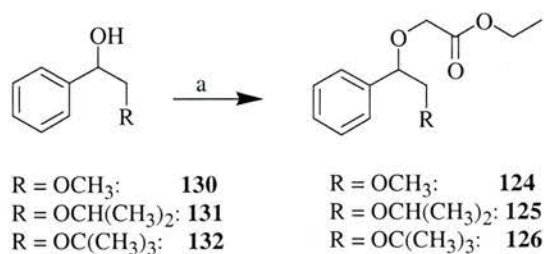
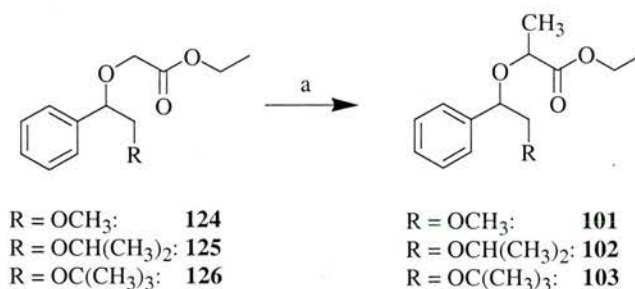


Figure 2.6 *Reagents:* (a) $\text{ICH}_2\text{CO}_2\text{Et}$, NaH (60%), THF, 70-90%.

The benzyl ethers **124-126** were then each methylated using methyl iodide in the presence of LDA (scheme 2.6). In order to determine the diastereoselection of the methylation reaction, the crude products were analysed by $^1\text{H-NMR}$ spectroscopy and GC/MS. The results are shown in Table 2.2 and figure 2.7.



Scheme 2.6 *Reagents:* (a) CH_3I , LDA/ THF, 60-80%

In the event the best results were observed with isopropyl ether **125**, where both electronic effects and steric effects seem to have co-operated. It is concluded that the *tert*-butyl group of **126** exerts such a steric influence as to disallow lithium coordination to the ether oxygen, resulting in a poor stereoinduction. On the contrary, the methyl ether system displayed an intermediate result. It does appear here that $\text{O}^{\ominus}\text{Li}$ coordination enhanced the outcome.

| Substrate | Product | Diastereomeric ratio (dr): (a)NMR/ (b)GC-MS | Diastereomeric excess (% de) |
|-----------|---|---|------------------------------|
| 124 | CH ₂ OCH ₃ 101 | 1:5 (b) | 67 |
| 125 | CH ₂ O- <i>i</i> -Pr 102 | 1:15 (b) | 88 |
| 126 | CH ₂ O- <i>t</i> -Bu 103 | 1:2.6 (a) | 44 |

Table 2.2 Methylation reaction results of **124-126**.

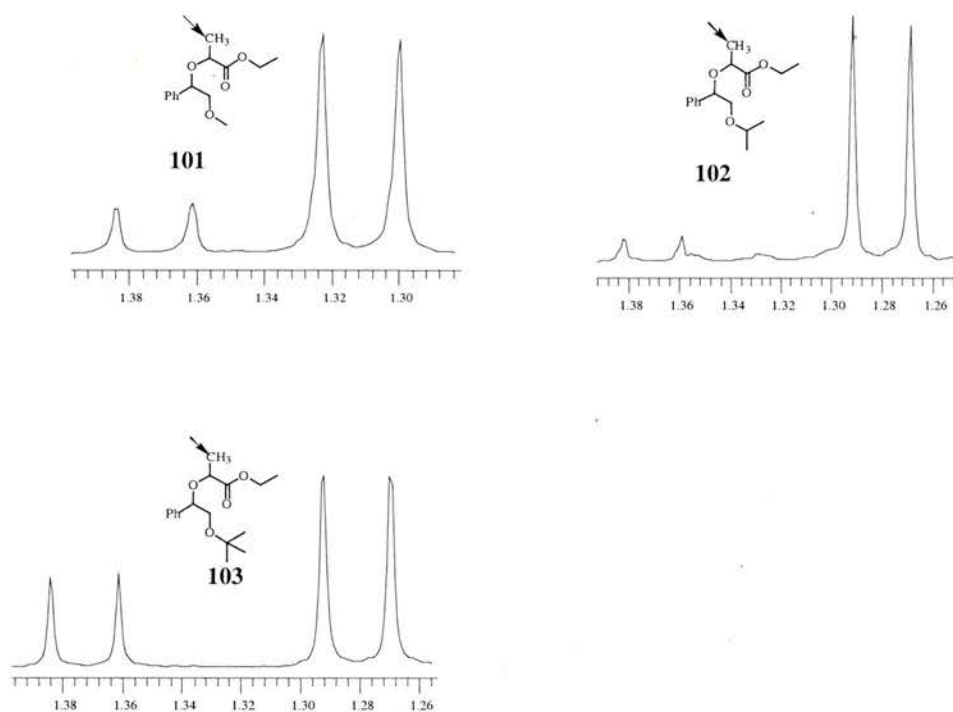
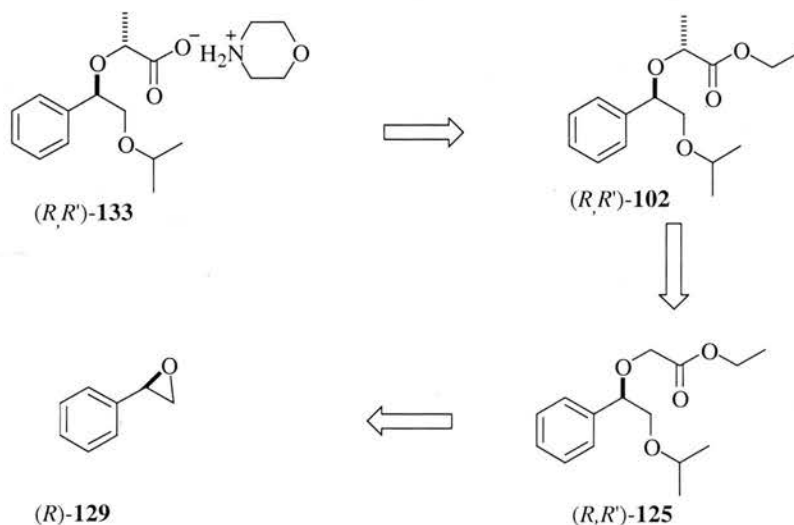


Figure 2.7 Methyl resonances of ¹H-NMR signals of crude reaction mixtures of benzyl ethers **101-104**.

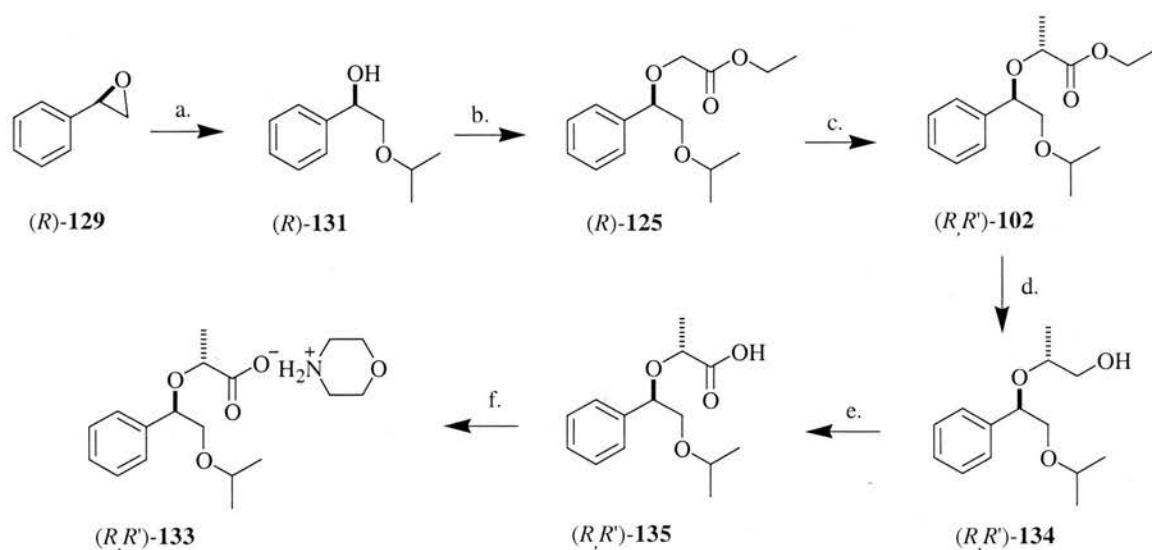
In order to assign the absolute stereochemistry of the methylation products, it was decided to prepare a sample of the benzyl ether (*R,R'*)-**125** in an enantiomerically pure form. Although an enantiomerically pure product was not necessary to establish the relative configuration, it adds value to the method to demonstrate enantiomerically enriched products with the best substrate (*R,R'*)-**125**. Alkylation and conversion to a crystalline derivative would provide access to X-ray analysis for diastereomeric identification. Accordingly, (*R*)-styrene oxide was used as the starting material for the synthesis of (*R,R'*)-**125**. The retrosynthetic analysis identified (*R,R'*)-**133** as a potential

salt for X-ray structure analysis. The acid was easily accessed from the alcohol (*R,R'*)-**134** by Jones oxidation. Further, retrosynthetic analysis of (*R,R'*)-**102** reveals (*R,R'*)-**131** as an intermediate which can also be derived from (*R*)-styrene oxide (scheme 2.7).



Scheme 2.7 Retrosynthetic analysis of (*R,R'*)-**133**

Sequential treatment of styrene oxide (*R*)-**129** with sodium isopropoxide and ethyl iodoacetate furnished the desired compound (*R,R'*)-**125** (scheme 2.8). Alkylation with methyl iodide gave (*R,R'*)-**102** in 88% de. The major diastereoisomer was separated following column chromatography and (*R,R'*)-**102** was then reduced to alcohol (*R,R'*)-**134** by lithium aluminium hydride reduction, followed by Jones oxidation to access carboxylic acid (*R,R'*)-**135**. The acid was combined with morpholine to generate salt (*R,R'*)-**133**. This material was crystalline and a suitable crystal was subjected to X-ray analysis. The structure is shown in figure 2.8. It was clear from this analysis that the alkylation gave rise to the (*R,R'*) diastereoisomer.



Scheme 2.8 Reagents: (a) $(\text{CH}_3)_2\text{CHOH}$, NaH, 92%, (b) $\text{ICH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, THF, 73% , (c) MeI, LDA, THF, 87%, (d) LiAlH_4 , THF, 100%, (e) Jones reagent, 96%, (f) morpholine, hexane, 100%.

Alkylations of the methyl **124** and *t*-butyl **126** ethers were less stereoselective than that of the isopropyl ether substrate **125** and clearly optimal diastereoselectivity resulted due to a balance between steric influence and co-ordination ability of the different ethers.

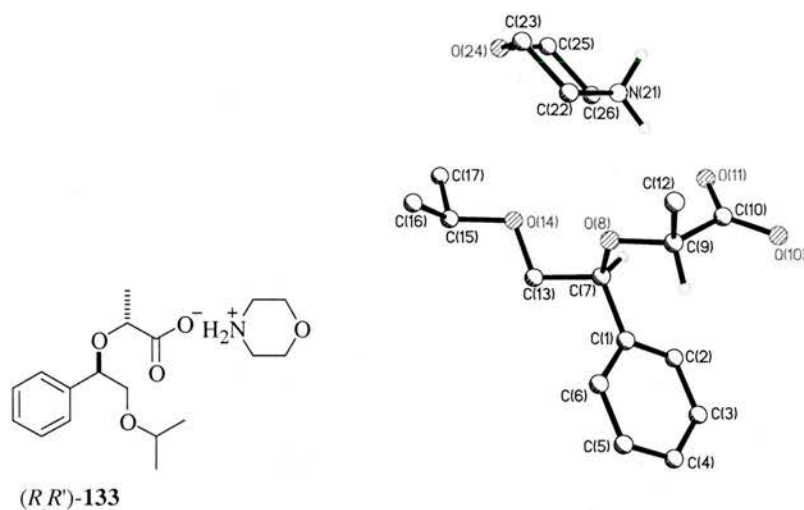
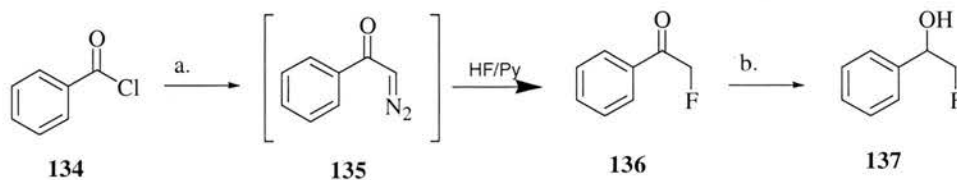


Figure 2.8 Ortep structure of (R,R') -133

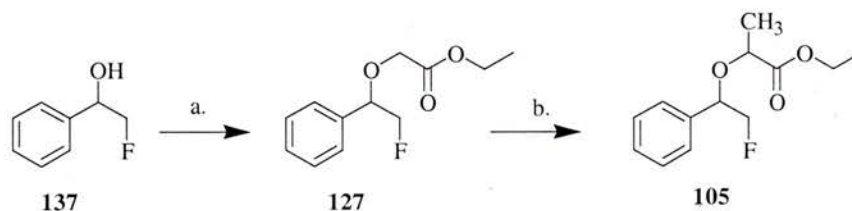
2.2.2. Synthesis of fluorinated benzyl ethers 127-128

Fluorinated benzyl ether **127** and **128** were also investigated as alkylation substrates and the stereochemical outcomes evaluated. For the monofluorinated substrate **127**, the necessary benzyl alcohol **137** was prepared from benzoyl chloride **134** after treatment with diazomethane and then HF-pyridine³⁵ (Olah's reagent).



Scheme 2.9: (a) i. CH_2N_2 , Et_2O ; ii. HF:Py (70/30), 39%; (b) NaBH_4 , CH_3OH , 99%.

The diazo ketone **135** was converted to α -fluoroacetophenone **136** *in situ*. Borohydride reduction of α -fluoroacetophenone **136** afforded **137** in excellent yield (scheme 2.9). Alcohol **137** was then sequentially treated with ethyl iodoacetate to generate substrate **127** which was then methylated using methyl iodide to give **105** (scheme 2.10).



Scheme 2.10 Reagents: (a) $\text{ICH}_2\text{CO}_2\text{Et}$, NaH (60%), THF, 76%, (b) CH_3I , LDA, THF, 58%.

Benzyl ether **123** (where $\text{X} = \text{CH}_3$) was used as a control substrate in these reactions as there was no expectation that hydrogen will chelate the lithium enolate during alkylation. Consistent with this, the resultant product was found to be approximately a 1:1 mixture of diastereoisomers. Accordingly there was no apparent stereo-induction from the stereogenic centre. The diastereoisomeric ratios of all of the alkylation (methylation) reactions are shown in Table 2.3.

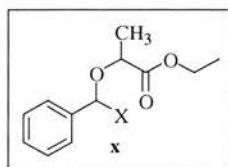
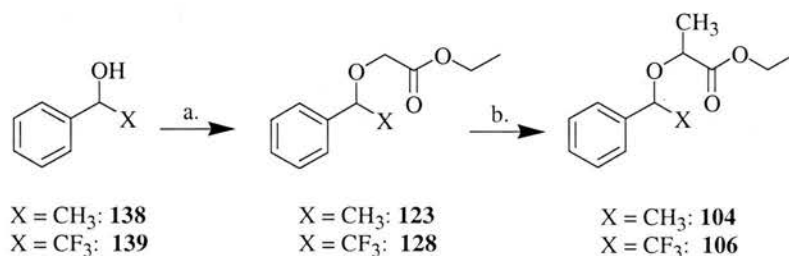


Figure 2.9 Generic structure of the methylated benzyl ethers **101-106**.

| Substrate | Product (X) | Diastereomeric ratio (dr): (a)NMR/ (b)GC-MS | Diastereomeric excess (% de) |
|------------|---|--|---------------------------------|
| 124 | CH ₂ OCH ₃ 101 | 1:5 (b) | 67 |
| 125 | CH ₂ O- <i>i</i> -Pr 102 | 1:15 (b) | 88 |
| 126 | CH ₂ O- <i>t</i> -Bu 103 | 1:2.6 (a) | 44 |
| 127 | CH ₂ F 105 | 1:2 (a) | 33 |
| 123 | CH ₃ 104 | 1:1 (b) | -- |
| 128 | CF ₃ 106 | 1:2 (a) | 33 |

Table 2.3 Diastereoselectivities of methylation reactions with substrates **124-128**. All de values of the methylation products were determined by ¹H-NMR/ GC-MS analyses of crude reaction products.

The trifluoromethyl substrate **128** was readily accessed from trifluoromethyl benzyl alcohol **139**, and the preparation was similar to that previously described for the other benzyl ethers. The difluorinated analogue was not selected for this study, as it was not a readily available compound.



Scheme 2.11 Reagents: (a) ICH₂CO₂Et, NaH (60%), THF, 80-98 (b) CH₃I, LDA, THF, 66-70%

Finally the monofluoro and trifluoro benzyl ethers **127** and **128**³⁶ were examined in methylation reactions and the results are shown in Table 2.3. In both cases the diastereoselectivity was 33% de. This result is very much consistent with the observations of Yamazaki³² where an increasing number of fluorine atoms did not seem

to effect the stereoselectivity.

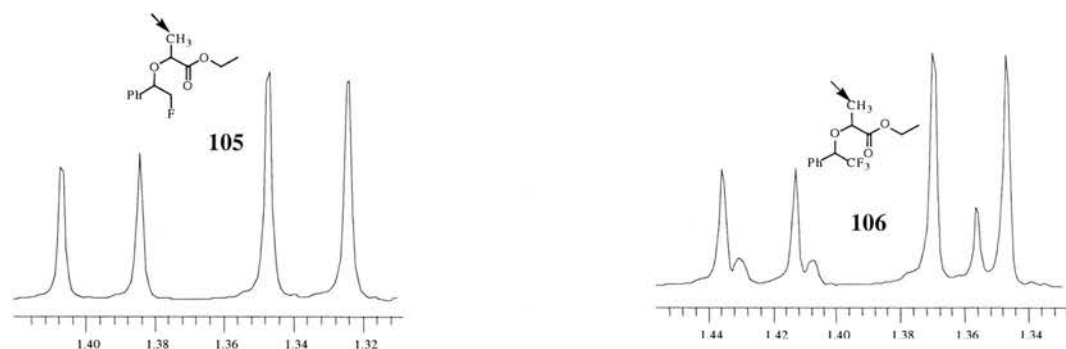
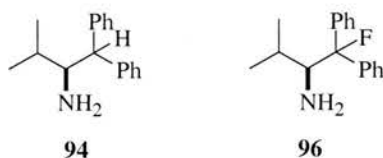


Figure 2.10 Methyl resonances of $^1\text{H-NMR}$ signals of crude reaction products.

A direct comparison of the ratios shown in figures 2.7 and 2.10 indicates the influence of F over H and clearly the incorporation of a single fluorine atom has had a significant and in this case beneficial effect on the diastereoselectivity. However this effect is not as significant as the oxygen series. This is exactly in keeping with the relative donor abilities of oxygen, fluorine and hydrogen. The results for trifluoromethyl substrate **128** indicated no significant benefit in increasing the number of fluorine atoms at the potential co-ordination site. Clearly the Yamazaki³² study benefited from both fluorine co-ordination but also a tertiary stereogenic centre contributing steric induction.

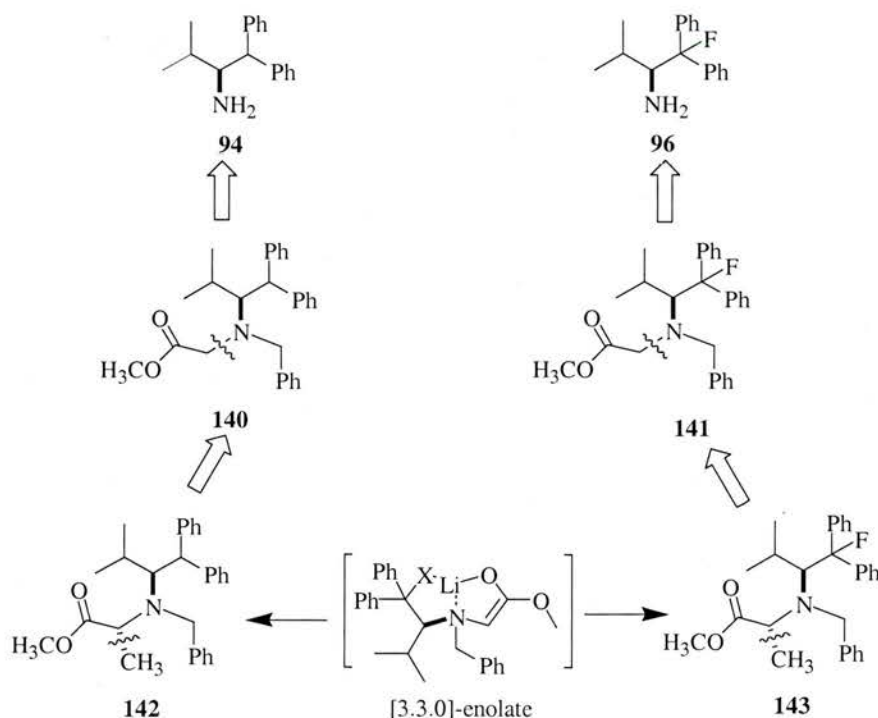
2.3. A More Complex System

In order to explore further the generality of fluorine lithium enolate alkylations a more complex system was investigated. The starting amines **94** and **96** were generously supplied by Onyx-Scientific and their synthesis was reported by O'Hagan and Tavasli^{37, 38} as outlined in chapter 1 (section 1.4) of this thesis. These amines differ only in the replacement of C-H bond for a C-F bond.



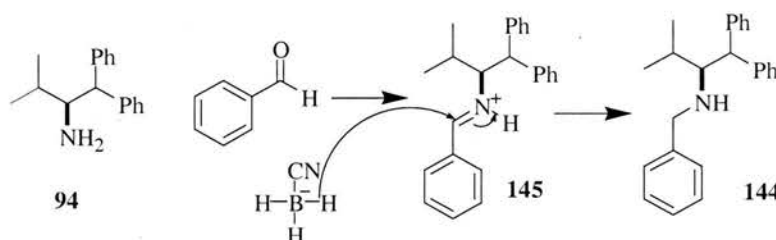
2.3.1. Results and Discussion

Amino esters **140** and **141** became the target compounds such that we could explore methylation to **142** and **143** *via* the [3,3,0] intermediate as shown in scheme 2.12. Both **140** and **141** are clearly accessible from amines **94** and **96** respectively after benzylation and alkylation protocols.



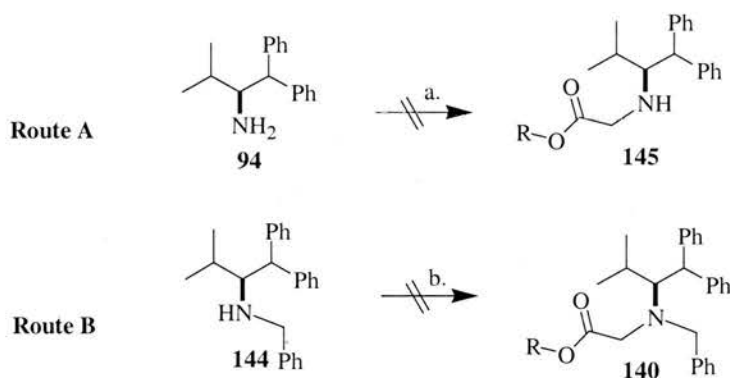
Scheme 2.12 Retrosynthetic analysis of **142** and **143**.

Several syntheses leading to **140** were explored. In the event a number of synthetic challenges were encountered in its preparation and these are discussed below. The benzylamine **144** was successfully synthesised following a reductive amination protocol, from amine **94**, benzaldehyde and NaCNBH₃ in a one-pot reaction (scheme 2.13).



Scheme 2.13 Reduction amination strategy to **144**.

Although this procedure avoided the isolation of the iminium ion **145**, it proceeded only in moderate yield and long reaction times were often required. Thus, for practical purposes a two-step procedure was adopted where the imine was isolated and treated with sodium cyanoborohydride to give **144** in excellent overall yields and shorter reaction times.



Scheme 2.14 Reagents: (a) Mitsunobu conditions, HOCH₂CO₂R, (b) ⁻OH, XCH₂CO₂R.

Several attempts to directly alkylate compounds **94** and **144** to achieve **145** and **140**, respectively, were unsuccessful. To this end a number of bases³⁹⁻⁴¹ were used in routes A and B (scheme 2.14), and different strategies including the Mitsunobu protocol⁴² were employed, but were also unsuccessful.

Given the literature^{43, 44} successes achieved in the chemoselective reduction of amides e.g. **146** and **148** in the presence of ester functional groups (Figure 2.11), it was decided to exploit this selectivity.

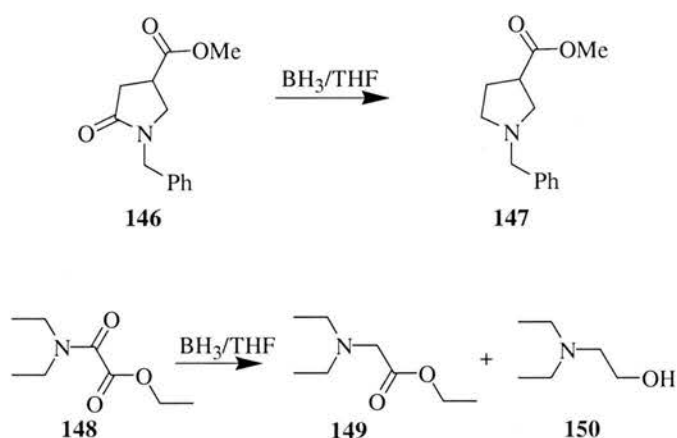
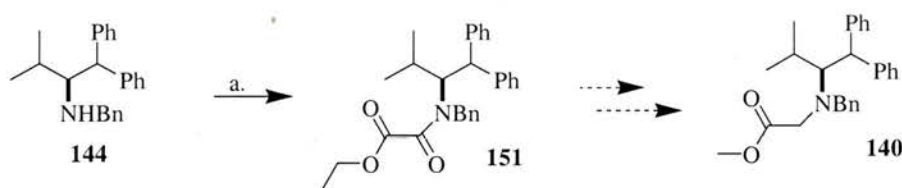


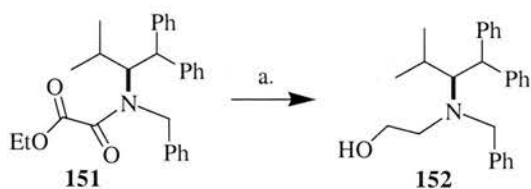
Figure 2.11 Reduction of amido esters using borane.^{43, 44}

This led to an exploration of the more reactive electrophile, ethyl oxalyl chloride. This reagent was reacted with **144** and the reaction proceeded smoothly to give the amido ester **151** in a good yield.



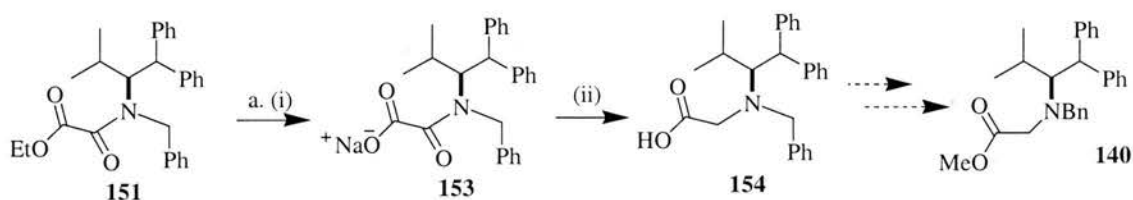
Scheme 2.15: Reagents: (a) $\text{ClCOCO}_2\text{C}_2\text{H}_5$, Et_3N , CH_2Cl_2 , 99%.

Both $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ were consistent with product **151**. The amido ester **151** was then treated with diborane (scheme 2.16) to reduce out the α -carbonyl. This reaction did not proceed when first carried out at low temperatures, however, allowing the reaction mixture to warm to ambient temperature, then brought to reflux, an exhaustive reduction product **152** (amino alcohol) was then isolated. Thus, the selective reduction of **151** proved problematic.



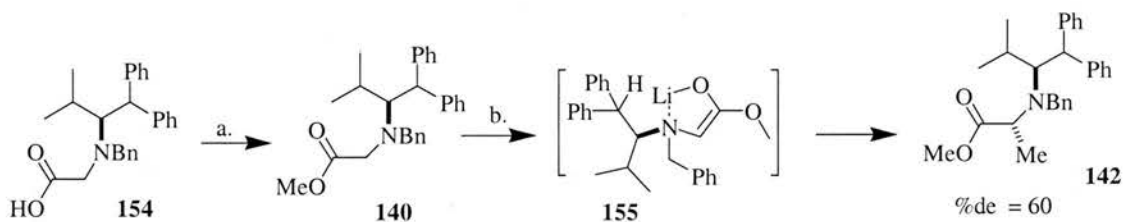
Scheme 2.16 Reagents: (a) BH_3/THF , 70°C , quant.

It was then decided to selectively hydrolyse the ester moiety in **151** to explore the selective reduction of the amide over the carboxylic acid. Treatment of **151** with ethanolic NaOH resulted in sodium salt **153**. This material was then treated with borane in THF at reflux. Happily amino acid **154** was isolated in a moderate yield.



Scheme 2.17 Reagents: (a) (i) NaOH , EtOH , (ii) BH_3 , THF , reflux 65%.

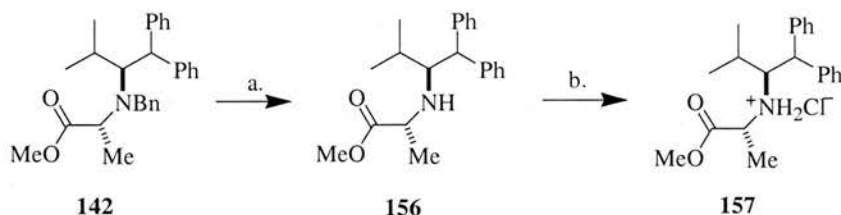
Upon treatment of carboxylic acid **154** with freshly prepared diazomethane, the methyl ester **140** was isolated in quantitative yield. Thus, a convenient route to the key substrate **140** had been established (scheme 2.18).



Scheme 2.18 Reagents: (a) CH_2N_2 , Et_2O , 100%; (b) LDA , CH_3I , THF , 68%

Methyl ester **140** was then treated with lithium diisopropylamide (LDA) in THF to generate enolate **155**, and this was quenched with methyl iodide at low temperature (-78°C). Work-up afforded the methylated product **142** in good yield and as a mixture of diastereoisomers. $^1\text{H-NMR}$ spectroscopy of the crude material revealed a diastereomeric ratio (dr) of 4:1 (expressed herein as a diastereomeric excess, 60%de).

Thin layer chromatography (tlc) allowed successful separation of the diastereoisomers. The products were oils, however, attempts to grow crystalline material by charging the amino ester with anhydrous hydrogen chloride in ether proved unsuccessful. It was then decided to mediate debenzoylation by hydrogenation using Pearlman's catalyst. This provided amine **156**, a candidate for hydrochloride formation and crystallisation.



Scheme 2.19 Reagents: (a) Pd(OH)₂/C (20%)/CH₃OH, 100%. (b) Et₂O-HCl

Treatment of **156** with ethereal hydrochloric acid afforded the hydrochloride salt **157**, which upon addition of hexane and slow removal of ether gave a white crystalline product. A suitable crystal was selected for X-ray structure analysis and the ORTEP picture is shown in (Figure 2.12).

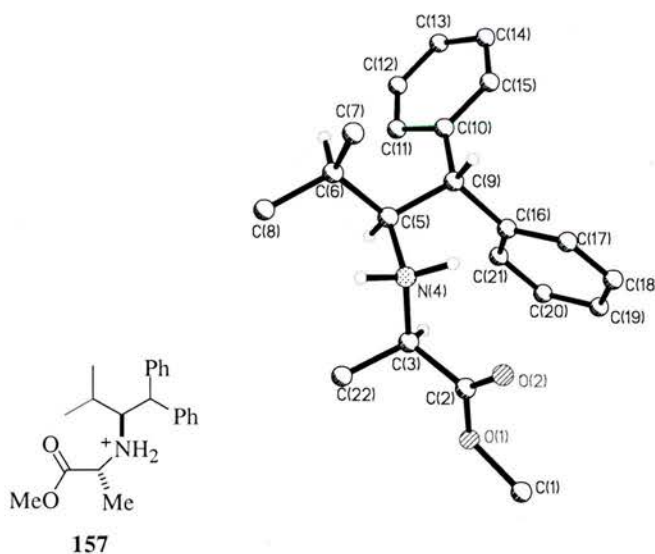
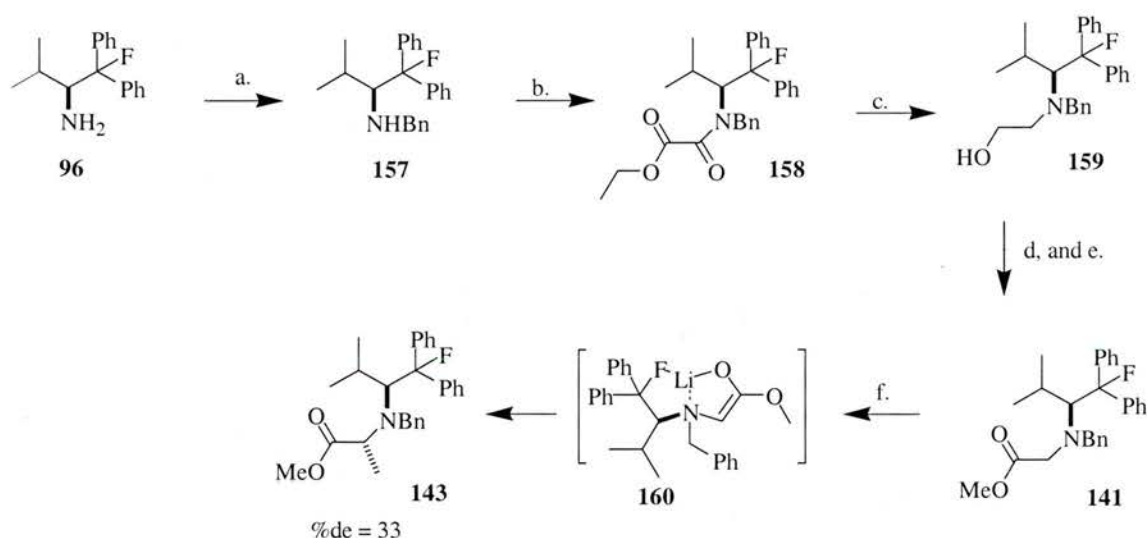


Figure 2.12 Cationic Ortep structure of **157**

The absolute stereochemistry of **157** was deduced from the X-ray structure as the (*R*,*S*) isomer suggesting that the least sterically hindered diastereotopic face of enolate **155** (scheme 2.18) is preferentially methylated.

2.4. Synthesis of the Fluoro Analogues

The substrate **141**, a direct analogue of **140**, with an H for F substitution was now explored. The route to the **143** (scheme 2.20) was similar to the one followed for **142** (scheme 2.18) except for intermediate **159**. In the synthetic route leading to **141**, the previously developed protocol proved unsuccessful. The sensitivity of the fluorinated benzhydryl group rendered it difficult to handle under acidic and basic conditions. Thus, an alternative route to **159** was developed. Amine **96** was benzylated and then acylated to generate **158**. Exhaustive reduction with LiAlH_4 gave alcohol **159** which was then oxidised to the aldehyde under Dess-Martin conditions and further oxidised to the carboxylic acid using sodium chlorite. The acid was then esterified using diazomethane in ether. This gave amine **141** the required substrate for the methylation reaction, and a direct analogue of **140**.

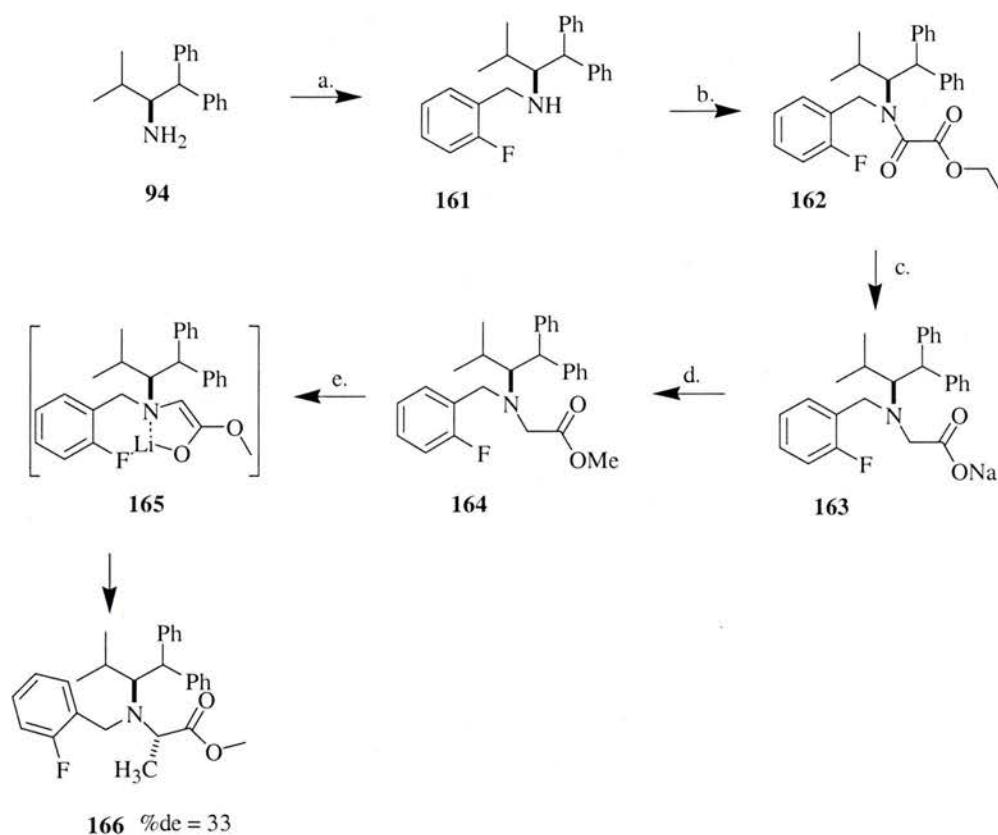


Scheme 2.20 *Reagents:* (a) PhCHO , NaBH_4 , DCM (b) ClCOCO_2Et , Et_3N , DCM (c) $\text{LiAlH}_4/\text{THF}$, Δ , 100%; (d) (i) Dess-Martin periodinane, DCM, 100%, (ii). NaClO_2 , $\text{KH}_2\text{PO}_4/\text{H}_2\text{O}$, $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)_2$, *t*-BuOH, 30%, (e) $\text{CH}_2\text{N}_2/\text{Et}_2\text{O}$, 100%, (f) CH_3I , LDA/THF, 60 %.

It was anticipated that enolate **160** derived from **141** may find additional stabilisation by lithium chelation to fluorine and that this may influence the diastereoselectivity of the methylation reaction. In the event the fluorinated system showed a poorer diastereoselectivity (2:1) when compared with **155** (4:1) the hydrogen analogue already

shown in scheme 2.18. There was no clear advantage in introducing the fluorine atom in this case, presumably because it is in a sterically congested site.

In an opportunistic experiment it was then decided to synthesise **164**. This was to evaluate whether fluorine in the aromatic ring could perhaps participate in co-ordination as depicted in scheme 2.21. It can be observed from this intermediate that there exist possible bicyclic systems arising from a chelation model involving both a five and a six-membered ring.



Scheme 2.21 Reagents: (a) *o*-Fluorobenzaldehyde, NaCNBH₃, DCM, 53%, (b) EtO₂CCOCl, Et₃N, DCM, 92%, (c) i. NaOH, EtOH, ii. BH₃, AcOH, (d) CH₂N₂, Et₂O, quant. (e) LDA, MeI, THF, 35%.

The synthetic procedure followed for **166** was similar to that described for the synthesis for **143** as discussed in section 2.3.1. The methylation showed a decrease relative to **140**, in the diastereomeric excess (33%). Clearly, there is a perturbation resulting from electronic effects induced by fluorine, but whether or not fluorine participates in the hypothesised bicyclic enolate systems is not clear.

2.5. Conclusion

In summary we have shown that there is a clear fluorine effect in an alkylation model involving a fluoromethyl group as a component of a lithium enolate derived from a secondary ether functionality. The effect on the resultant diastereoselectivity is modest relative to oxygen substituents and was also less effective than Yamazaki study involving tertiary ether groups possessing a fluoromethyl group. Perhaps in this latter case a combination of chelation control and steric effects proved synergic in influencing the outcome in a positive way and to a greater extent. When the fluorine atom is placed in a sterically crowded site such as that in **141** or on the aromatic ring in **164** then the evidence for fluorine chelation is poor although there is a perceptible influence which may have its origins in an electronic effect. It is concluded that, with appropriate awareness of the potential for organic bound fluorine to co-ordinate to lithium, such a strategy can improve the design of chiral auxiliaries in certain cases.

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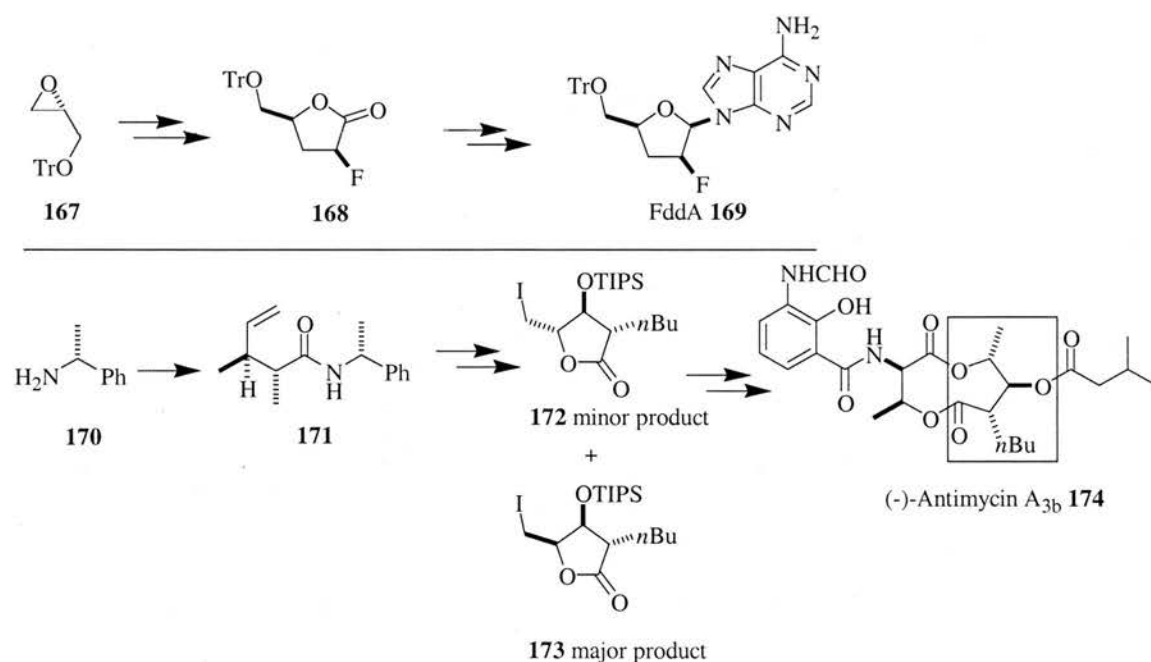
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3

Studies on the asymmetric [3,3]-aza-Claisen rearrangement reactions.

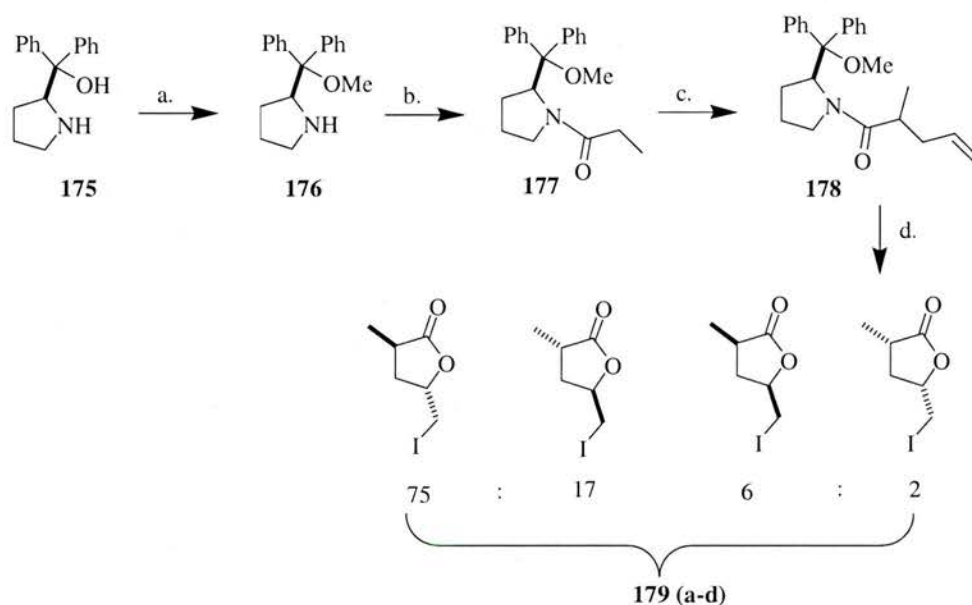
3.1. Introduction

γ -Lactones are important intermediates in synthesis and a common structural motif encountered in the terminus of many natural products such as steroids and terpenoids. They are also useful templates for the synthesis of nucleosides with biological activity. The fluorinated lactone in the synthesis of anti-HIV-active nucleoside β -FddA¹ **169**, for example was accessed starting from a chiral epoxide **167** via a fluorinated γ -lactone **168** in five steps. However, synthetic procedures used to access these key synthetic intermediates involve several steps. Another example of an important synthesis employing γ -lactones is encountered in the synthesis of the antibiotic (-)-Antimycin A_{3b}² **174** using phenylethylamine **170** as a chiral auxiliary to generate **171** followed by an iodolactonisation process to give a mixture **172** and **173** (4.5:1). The minor butyrolactone **172** was incorporated into the core structure of the antibiotic **174**.



Scheme 3.1

Clearly, methodologies that provide substituted γ -lactones in an efficient and straightforward manner and in high enantiopurity are valuable. Studies by Schore³ explored the chirality transfer method using prolinol-based chiral auxiliaries in the synthesis of **178**, the key intermediate in the synthesis of 3,5-disubstituted γ -butyrolactones **179** (scheme 3.2). Following methylation of prolinol **175**, the resultant methyl ether **176** was acylated using propionyl chloride in the presence of DCC to give amide **177**. C-Allylation was achieved by treatment of **177** with allyl iodide in the presence of LDA to afford **178**.^{4, 5} The diastereoselectivity of the α -allylation reaction was observed to be modest (1:4).



Scheme 3.2 Reagents: (a) MeI, NaH, 80%, (b) CH₃CH₂CO₂H, DCC, 71%, DMAP (c) LDA, CH₂=CHCH₂I, d. I₂, THF/H₂O, 42%.

Iodolactonisation of **178** afford a mixture of stereoisomers **179** (a-d) in a ratio of 75:17:6:2 as shown on scheme 3.2. This was explained as a consequence of two independent processes: the enantioselectivity of the alkylation transmitted to the α -carbon of the lactone and the face selectivity of the iodolactonisation, which dictates the *syn* or *anti* disposition of the two substituents in the lactone ring. The yields however were unimpressive, only averaging 42%. Obviously this procedure has a major drawback in that it requires a three-step synthesis to afford the key intermediate **178**.

A highly stereoselective process for the synthesis of homoallyl intermediates **178** remains to be developed. It was decided to examine the stereoselectivity of the aza-Claisen rearrangement reaction to try to progress this aspect.

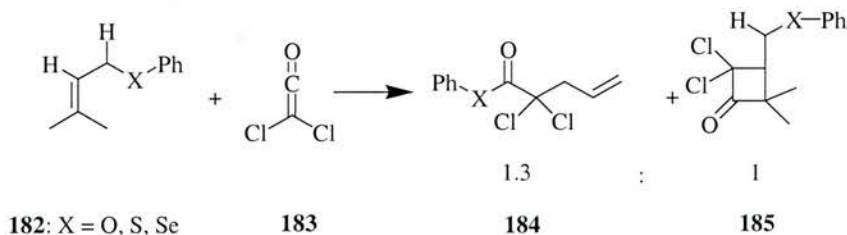
3.2. The [3,3]-Claisen rearrangement

The Claisen rearrangement is an example of sigmatropic rearrangement reaction. Sigmatropic rearrangements are one of the essential sub-classes of the pericyclic reactions first described by Woodward and Hoffman.^{6, 7} These reactions are a one-step process, which proceeds *via* cyclic transition states in which the bonds are made and broken in a concerted manner. A high level of stereoselectivity often accompanies such concertedness. By definition, these reactions involve a simultaneous reorganisation of electrons during which a group linked by a σ -bond migrates to the terminus of an adjacent π -electron system. A typical Claisen rearrangement reaction is a thermally driven process that involves the conversion of an allyl vinyl ether such as **180** (X = O) to a γ -unsaturated aldehyde such as **181**. Variants of the Claisen rearrangement such of those where X = S or N are also well documented. The methodology developed in this chapter is focused on the aza-Claisen rearrangement where X = N.



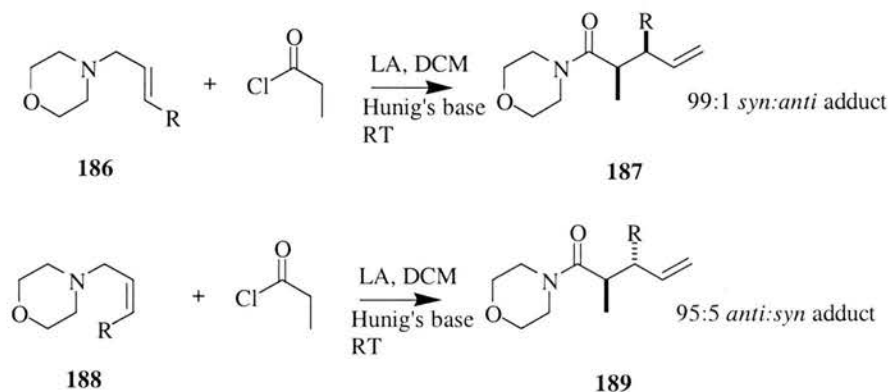
X = O: Claisen rearrangement
 X = S: thia-Claisen rearrangement
 X = N: aza-Claisen rearrangement

Since its discovery in 1912,⁸ the Claisen rearrangement has become one of the most powerful tools for carbon-carbon bond formation in chemical synthesis. Bellus and Malherbe⁹ reported the conceptually novel ketene-Claisen reaction (scheme 3.3) with allyl ethers **182** and dichloroketene **183**. This reaction gave a (1.3: 1) mixture of **184** and **185**.



Scheme 3.3

Based upon the design features derived from Bellus-Claisen reaction^{9, 10} above, MacMillan¹¹ reported an impressive catalytic ketene aza-Claisen reaction utilising Lewis acids, such as Yb(OTf)₃, AlCl₃, TiCl₄ in the presence of *i*Pr₂NEt.

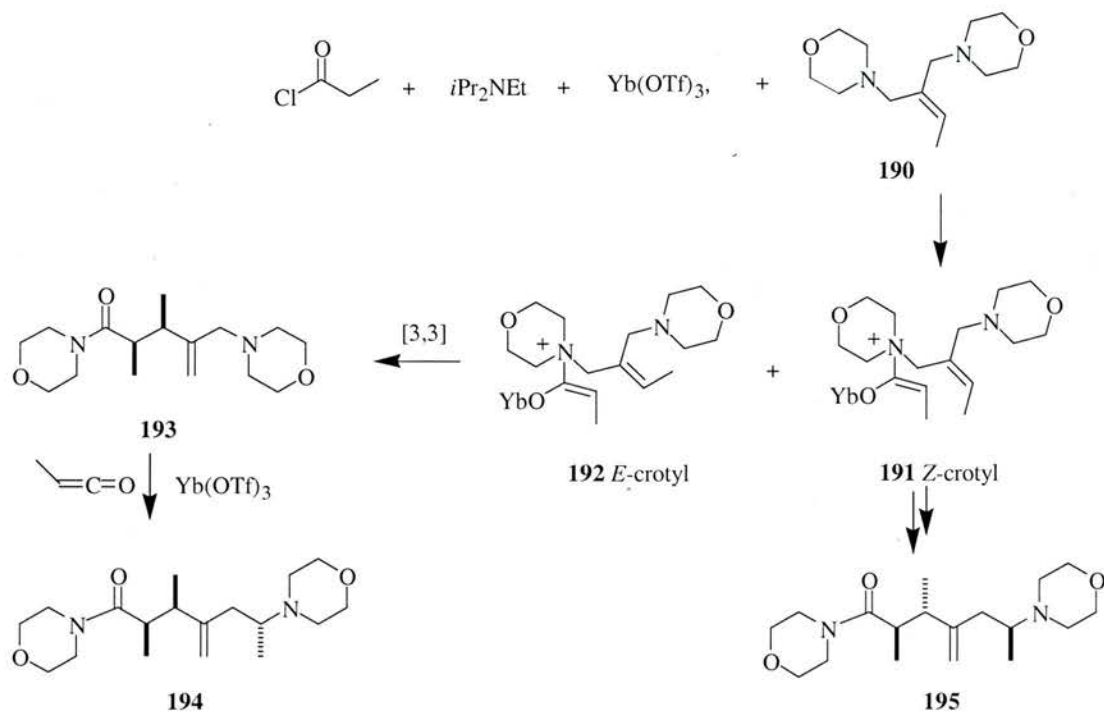


Scheme 3.4

Examples of this reaction are shown in scheme 3.4. For substrate **186**, the reaction is reported to form the 2,3-disubstituted Claisen adduct **187** in high yield (>75%) with excellent levels of stereocontrol (99:1 *syn:anti*). The progress of this reaction in the forward direction was deduced to be contingent upon the action of the Lewis acid. Control experiments without Lewis acids were reported to result in dimerisation of the ketene. Reactions with various allyl morpholine derivatives revealed a common trend in that the *E*-crotyl morpholine **186** furnished *syn*- Claisen adducts **187** whereas the *Z*-crotyl morpholines **188** gave *anti*- Claisen adducts **189** (95:5 *anti:syn*).¹²

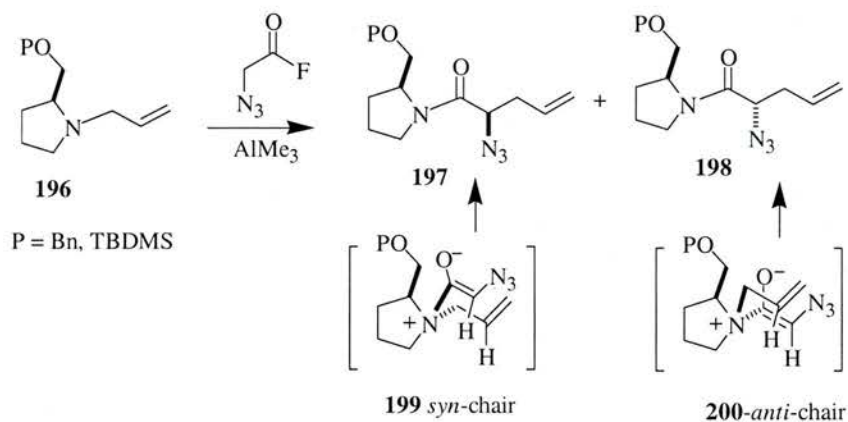
The most impressive results so far are the recent results of MacMillan and Dong¹³ where they have employed allyl dimorpholine **190** as the substrate. Treatment of **190** with propionyl chloride allowed a tandem acyl-Claisen rearrangement resulting in

diastereoselectivities of up to 98:2 (*syn*: *anti*) of the adducts **194** and **195** following a tandem process *via* **193**. Of course the product is racemic in this case.

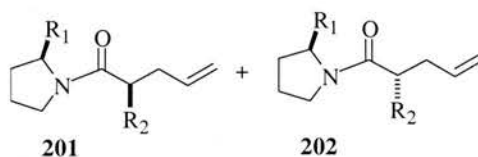


Scheme 3.5

Nubbemeyer¹⁴ has reported related studies using prolinol derivatives proceeding with high yields and excellent levels of enantio- and diastereo-control. The stereochemical control is explained by the reaction proceeding through the six-membered ring transition states **199** and **200** where the enol is set-up in a *syn*-chair in **199** and *anti*-chair in **200** (scheme 3.6). There is no clear role for the trimethyl aluminium in this model other than co-ordination of the oxygen to aluminium.



Scheme 3.6 Mechanistic aspects of the C-allylation



| Entry | R ₁ | R ₂ | Temp °C | 201 : 202 |
|-------|------------------------|--|---------|-----------|
| 1 | CO ₂ Me | N(Boc)CH ₂ CH(OEt) ₂ | 20 | 15:1 |
| 2 | CO ₂ Me | N ₃ | -20 | 9.5:1 |
| 3 | CH ₂ OTBDMS | N(Boc)CH ₂ CH(OEt) ₂ | 0 | 15:1 |
| 4 | CH ₂ OTBDMS | N ₃ | 0 | 15:1 |
| 5 | CH ₂ OBn | N(Boc)CH ₂ CH(OEt) ₂ | 0 | 15:1 |

Table 3.1 Nubbemeyer's aza-Claisen using proline and prolinol auxiliaries.

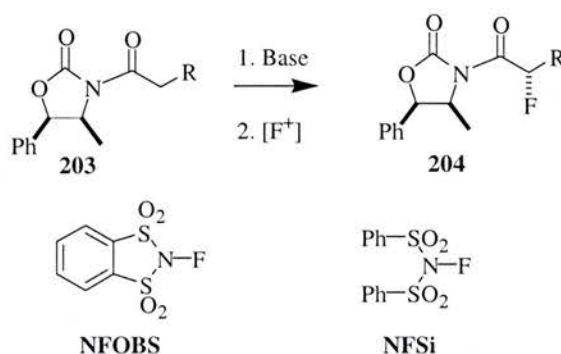
The diastereoselection of the reaction was reported to increase with the sterically more demanding auxiliaries (table 3.1, entry 3 and 4). The configuration of the newly formed stereogenic centre was found to be *R* as determined by nOe studies on the major product **201**. Diastereoisomeric ratios up to 19:1 (*syn*: *anti*) were reported.¹⁵

The seminal contributions of Staudinger to the field of organic synthesis included the landmark discovery of ketene in 1908 and the addition of ketenes to imines to form β-lactams.^{16,17} This was followed by many examples of ketenes in organic synthesis including aza-Claisen rearrangements which are the focus of this project. To our knowledge, there are no examples of aza-Claisen rearrangement involving fluoroketenes

or their equivalents. With the general interest in asymmetric fluorination in organic synthesis, it was decided to explore the synthetic utility of fluoroketenes in aza-Claisen rearrangements.

3.3. Asymmetric α -fluorination in organic synthesis.

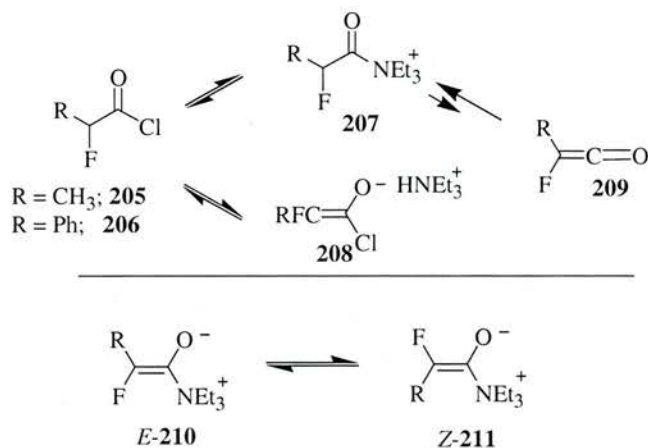
Classically asymmetric α -fluorination is achieved by reaction of electrophilic fluorine to a chiral enolate or inversely by using an asymmetric electrophilic fluorinating reagent on a non-chiral substrate. Thus, Davis^{18, 19} reported a successful fluorination of **203** by using *N*-fluoro-*o*-benzenedisulfonimide (NFOBS) or *N*-fluorobenzenesulfonimide (NFSi) to achieve **204** in 80-90 % and up to 86-99% de.



Scheme 3.7 Selective electrophilic α -fluorination

Alternatively α -fluorination could be accomplished with the C-F already intact. In this regard it was envisaged that fluoroketenes could be used in an aza-Claisen reaction to generate α -fluorination products. The ease of introduction of the chiral auxiliary and its removal thereafter and the predictability of the stereochemical outcome of a Claisen reaction are key and attractive features of this methodology.

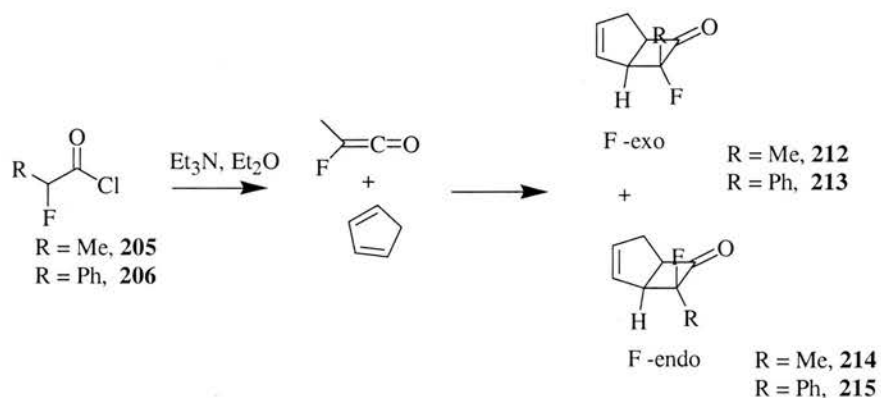
The first evidence of fluoroketenes was convincingly presented by Dolbier²⁰ after treatment of α -fluoro acid chlorides **205** and **206** with triethylamine. It is generally accepted that the mechanism of the reaction of the acid chlorides with amines involves the formation of acyl ammonium salts **207** and enolates **208** before formation of the ketene species²¹ **209**.



Scheme 3.8

Studies of Walborsky involved ketenes that proved difficult to form hence the ammonium acyl salts could be isolated. Brady²² studied ketenes utilising isobutyryl chloride with triethylamine to form dimethylketene and in such cases detected ammonium acyl salts, although no enolate intermediates were observed in that case.

The experiments by Dolbier attempted to detect the fluoroketene **209**, but this resulted in detection (¹⁹F-NMR) only of the *E* and *Z* enolate species (*E*)-**210** and (*Z*)-**211**, even when experiments were carried out at -40 °C. However, when cyclopentadiene was added to the reaction mixture, a [2+2]-cycloaddition occurred, generating adducts **212-215** thereby suggesting the existence of the elusive ketene species (scheme 3.9). The *endo* to *exo* ratios varied depending on the solvent used.



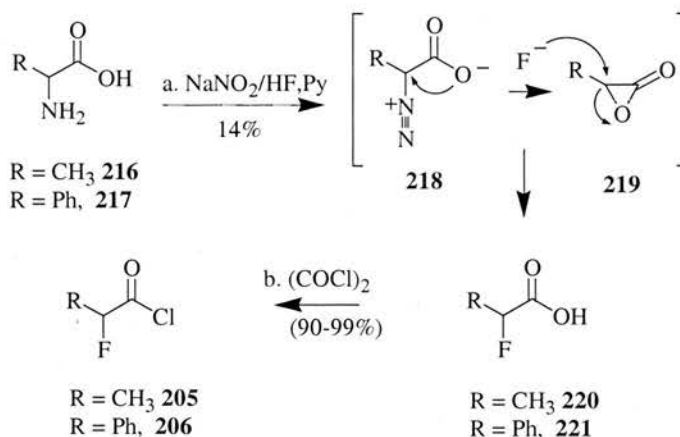
Scheme 3.9

With this background we sought to explore the utility of these fluoroketenes in the aza-Claisen reaction.

3.4. Results and discussion

3.4.1. Synthesis of acid chlorides as ketene precursors

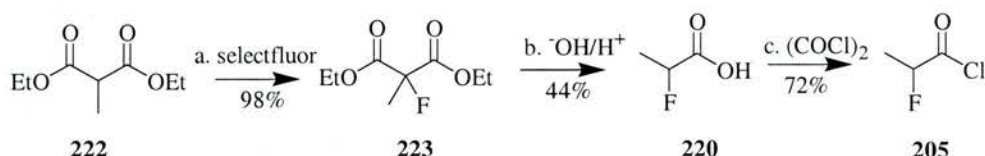
In order to undertake aza-Claisen rearrangement reactions using fluoroketenes, it was necessary to develop an efficient method for the production of the starting reagents, the α -fluoro acid chlorides.²³⁻²⁵ The route reported by Olah employing alanine **216** (R = CH₃, scheme 3.10) involved diazotisation and HF/ pyridine treatment leading to an intramolecular cyclisation to give **219**. The fluoride ion attacks the intermediate α -lactone **219** and results in product **220** with a retention of configuration²⁶ but in extremely poor yield (14%). The low yield could be associated with the high solubility of **220** in water therefore the procedure was abandoned. However, treatment of **220** with oxalyl chloride generated **205** in 90% yield. Similar studies on **217** generated **221** in 70% yield and subsequent treatment with oxalyl chloride with catalytic DMF gave **206** in a quantitative yield.



Scheme 3.10

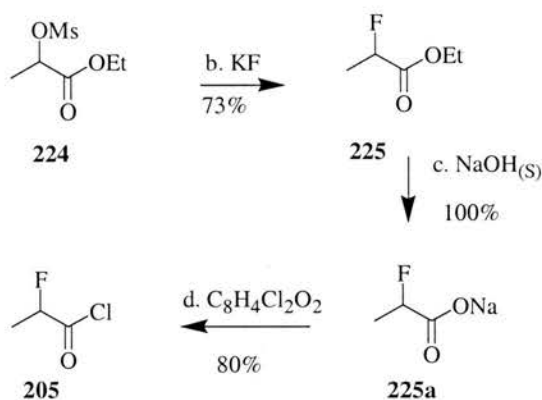
An alternative route to **205** was explored. To this end diethyl methylmalonate **222** was treated with Selectfluor in the presence of sodium hydride to give the fluorinated malonate **223**. Following basic hydrolysis and acid treatment of **220** under thermal

conditions, the 2-fluoropropionic acid **220** was afforded but only in a moderate yield. Acid chloride **205** was generated as previously described.



Scheme 3.11

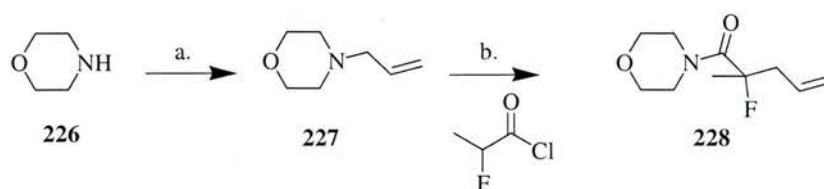
In order to improve the yield of **220**, procedure that does not require aqueous work-up was then explored.²⁵ Nucleophilic fluorination of the mesylate **224** with KF gave **225** in 73%. Saponification afforded **225a** which, was subsequently treated directly with phthaloyl dichloride to furnish **205** after distillation. All the steps in this scheme are highly efficient and this emerged as our route of choice to **205**.



Scheme 3.12

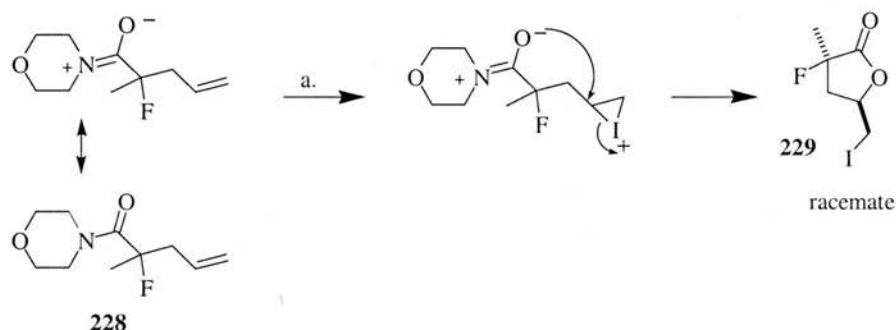
3.4.2. Model studies on aza-Claisen rearrangement using morpholine

In the first instance we sought to explore a [3,3] sigmatropic rearrangement using allyl morpholine **227** and the fluoroketene derived from **205**. Allyl morpholine **227** was easily accessible from a reaction of morpholine and allyl iodide as shown in scheme 3.13. The acyl-Claisen reaction was undertaken following the MacMillan¹³ protocol. The reaction proceeded smoothly and gave **228** in 92% yield.



Scheme 3.13 Reagents: (a) NaH, ICH₂CH=CH₂, THF, 97%, (b) *i*Pr₂EtN, Yb(OTf)₃, DCM, 92%.

The product was analysed by ¹H-NMR spectroscopy revealing a doublet (22.3 Hz, ³J_{HF}) corresponding to the CH₃ group. The amide carbonyl was also observed as a doublet (20.5 Hz, ²J_{CF}) due to fluorine coupling.



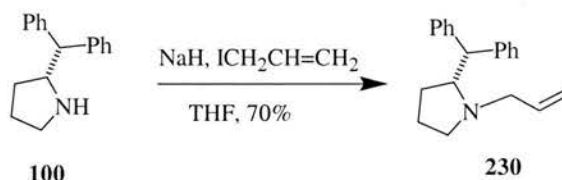
Scheme 3.14 Reagents: (a) I₂, THF/ H₂O, Na₂S₂O₃, 82%.

Iodolactonisation of amide **228** afforded the α -fluoro iodolactone **229** as a 10:1 mixture diastereoisomers following the mechanism shown in scheme 3.14. The morpholine moiety was recovered on work-up as a hydrochloride salt after quenching the reaction mixture with HCl. The iodolactonisation proceeded in accord with Baldwin's rules²⁷ to afford 5-*exo-tet* products exclusively. Based on literature studies,³ the major diastereoisomer was assigned to be *anti* as shown in scheme 3.14 and there was no evidence of any 6-*endo* product.

3.4.3. Exploring an asymmetric aza-Claisen rearrangement.

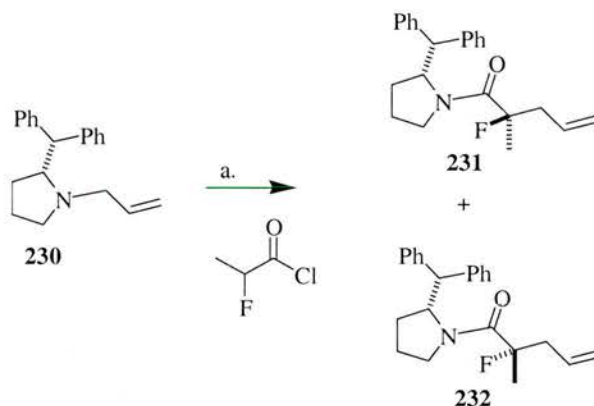
For the chirality transfer in the [3,3]-aza-Claisen rearrangement reaction, introduction of chiral amines was envisaged. In the first instance use of the Onyx chiral amine was explored. Given the success of the aza-Claisen reaction with allyl morpholine, it was

decided to explore a stereoselective process. This was investigated in the first instance by employing amine **100** as a chiral auxiliary. Amine **100** was treated with sodium hydride followed by addition of allyl iodide to generate allylamine **230** in 70% yield after purification (scheme 3.15).



Scheme 3.15 N-allylation of **100**.

The aza-Claisen reaction was undertaken in a similar manner to that described for morpholine and this generated a product, which was a mixture (3:1) of diastereomers **231** and **232**. Significantly, the diastereoisomers could be separated by column chromatography (scheme 3.16).



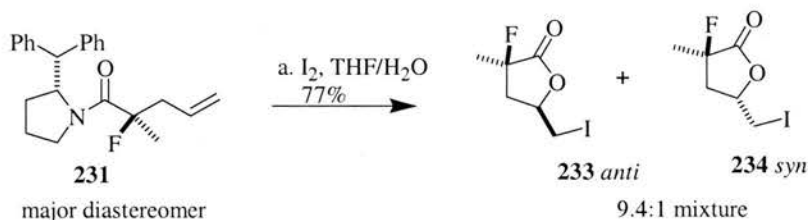
Scheme 3.16 Reagents (a) $i\text{Pr}_2\text{NEt}$, $\text{Yb}(\text{OTf})_3$, CH_2Cl_2 , 68%.

The major diastereoisomer displayed a mixture of rotamers as measured (9:1 ratio) by $^1\text{H-NMR}$ analysed from the $-\text{CHPh}_2$ proton. Similarly, the minor diastereoisomer showed a rotameric mixture (17:1 ratio). It was established however that the two compounds were diastereomerically pure by GC-MS analysis.

The diastereomeric ratio (dr) observed was improved from (3:1) to (6:1) when the reaction was carried out at $-20\text{ }^\circ\text{C}$, but there was no benefit from lowering the

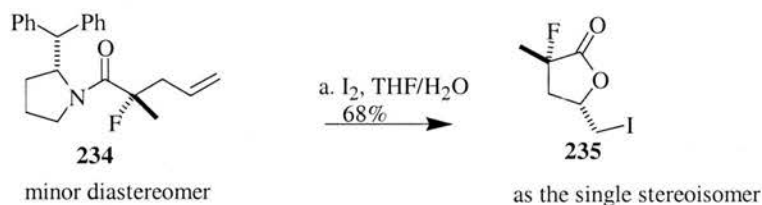
temperature further. Although the selectivities are modest, the ability to separate the diastereoisomers to give optically active compounds, is an attractive feature of this chiral auxiliary.

The major diastereoisomer was then subjected to iodolactonization conditions. Upon aqueous work-up and isolation using standard procedures a 9.4:1 diastereomeric mixture of iodolactones and the chiral auxiliary were recovered from reaction.



Scheme 3.17 Iodolactonization of the diastereoisomer **231**.

A similar procedure was undertaken for the minor diastereoisomer, interestingly, this stereoisomer underwent iodolactonisation with complete *anti* selectivity with no indication of the *syn* isomer. The *anti* stereochemistry was confirmed by nOe negative studies.

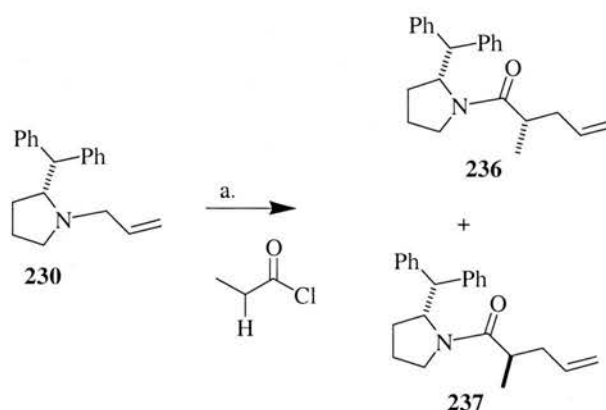


Scheme 3.18 Iodolactonisation of the diastereoisomer **232**.

Given the level of success in this methodology it was decided to further examine the generality of this reaction and extend to a non-fluorinated analogue. The advantage here is that the acid chloride (propionyl chloride) is commercially available, and therefore the reaction can be undertaken without prior preparation of the reagents.

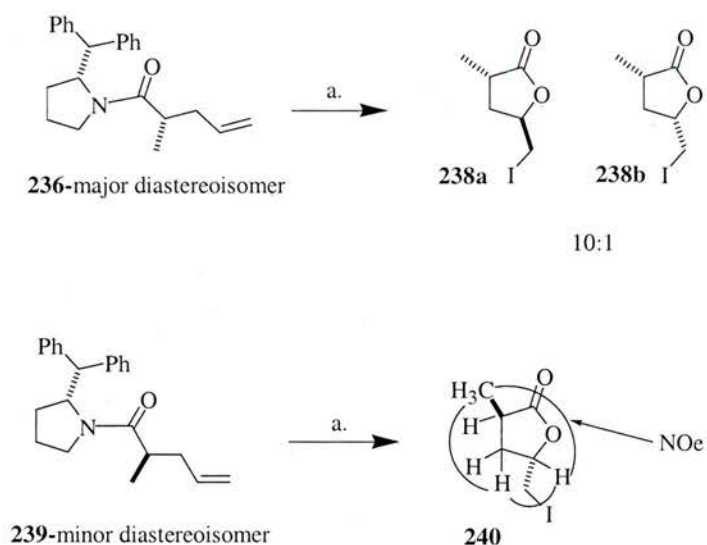
A similar synthetic procedure to that already described was followed as shown in scheme 3.16. The reaction was undertaken at room temperature and afforded a (3:1)

diastereomeric mixture similar to that observed in the fluorinated case. The two diastereoisomers were again readily separated by column chromatography to give diastereomerically pure products **236** and **237**.

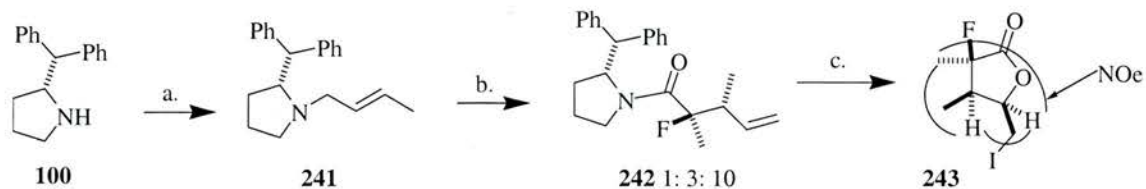


Scheme 3.19 Reagents: (a) $i\text{Pr}_2\text{NEt}$, $\text{Yb}(\text{OTf})_3$, CH_2Cl_2 , 73% (for the mixture).

Iodolactonization furnished the corresponding lactones **238** and **240** successfully (scheme 3.20). As previously observed, iodolactonisation preferentially gave the *anti* stereochemistry again evident from nOe studies.



Scheme 3.20 Reagents: (a) I_2 , THF/ H_2O , $\text{Na}_2\text{S}_2\text{O}_3$.

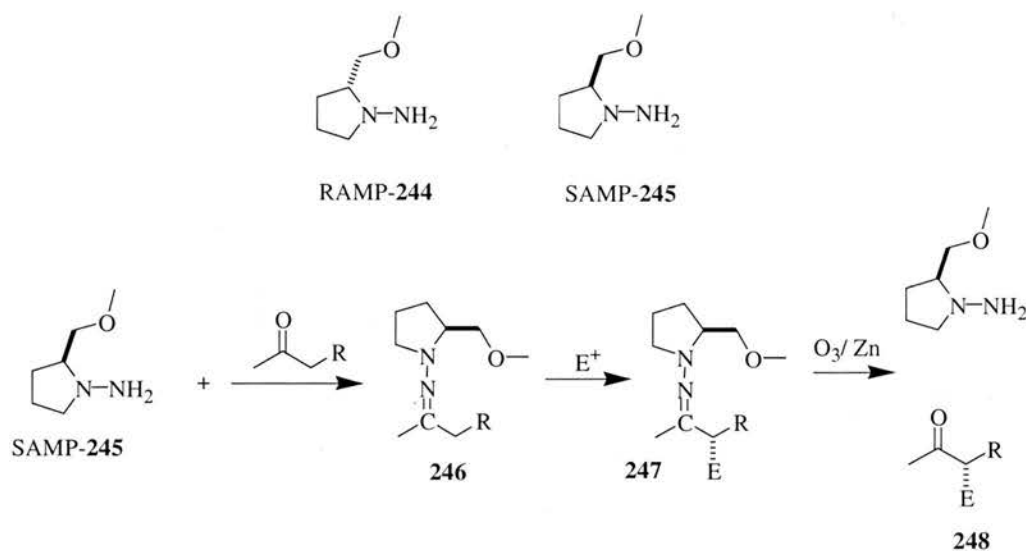


Scheme 3.22 Reagents: (a) NaH, CH₃CH₂=CHCH₂I, TBAI, (b) *i*Pr₂NEt, Yb(OTf)₃, RCHFCl, CH₂Cl₂, (c) I₂, THF/H₂O.

This asymmetric method was explored further by derivatizing pyrrolidine **100** with crotyl bromide to generate **241** as a substrate for the aza-Claisen reaction. The *N*-crotyl amine **241** was then subjected to the aza-Claisen rearrangement as previously described. This gave **242** (10:3:1 diastereoisomeric mixture) with two new stereogenic centres, as shown in scheme 3.22. The diastereoisomers were successfully separated and the major diastereoisomer subjected to iodolactonisation to give **243**. The stereochemistry of **243** was assigned from NOESY experiments. Interestingly, the major iodolactonisation product could be separated from reaction mixture by column chromatography. Thus, diastereomerically pure compounds carrying three contiguous chiral centres can be accessed using this aza-Claisen rearrangement reaction.

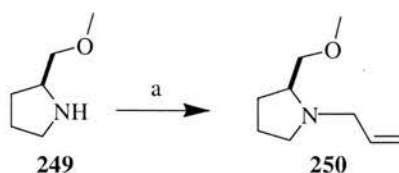
3.4.4. An Improved asymmetric method.

(2*R/S*)-Methoxymethylpyrrolidine is a commonly encountered moiety in the chiral auxiliary arena. The most successful application of this moiety is as the hydrazines RAMP **244** and SAMP **245**²⁸ (scheme 3.23). Conversion of aldehydes and ketones into their corresponding chiral hydrazones **246** has been used as substrates for alkylation in asymmetric synthesis. High levels of stereoselection accompany these reactions. The chiral auxiliaries **244** and **245** are conveniently removed by acid hydrolysis however ozonolysis is often preferred.



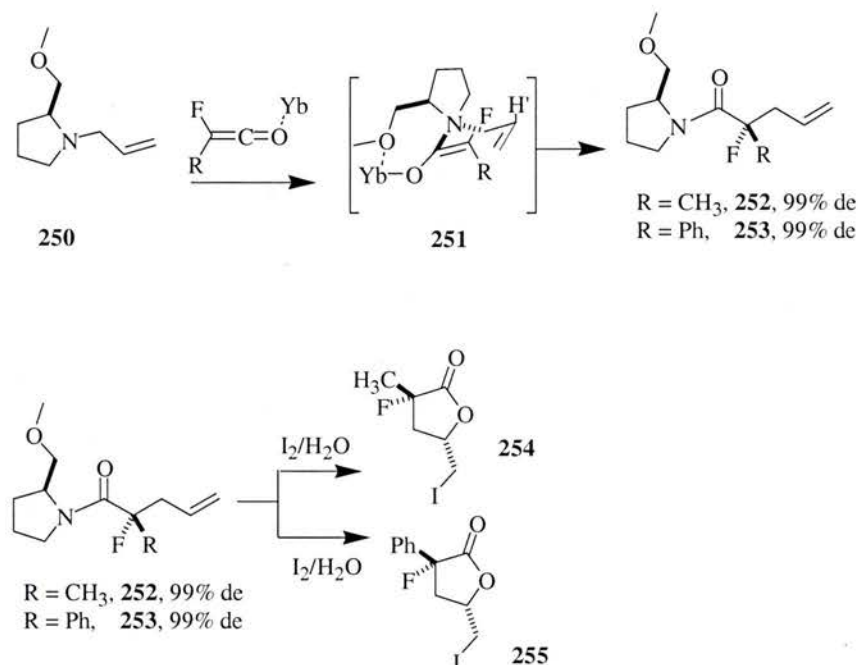
Scheme 3.23

The choice of the (*S*)-methoxymethylpyrrolidine **249** was based on the idea that the OCH₃ oxygen atom would participate in Lewis acid co-ordination and thus improve stereocontrol. To this end, the allyl pyrrolidine **250** (scheme 3.24) was prepared in a straightforward manner following the procedure already described.



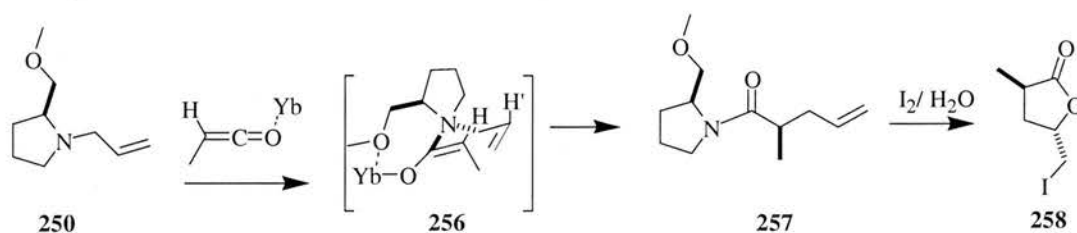
Scheme 3.24 Reagents: (a) NaH, ICH₂CH=CH₂, THF.

The allyl pyrrolidine **250** was then treated with 2-fluoropropionyl chloride in the presence of Hünig's base and $\text{Yb}(\text{OTf})_3$ at room temperature. The reaction was monitored by tlc analysis and the crude reaction mixture analysed by ^{19}F -NMR spectroscopy and GC-MS. This revealed consistently high de (99%) giving a single diastereoisomeric products **252** and **253**. These products gave a notably 3:1 mixture of rotamers. Iodolactonisation afforded **254** and **255** with a diastereomeric ratio of 10:1.



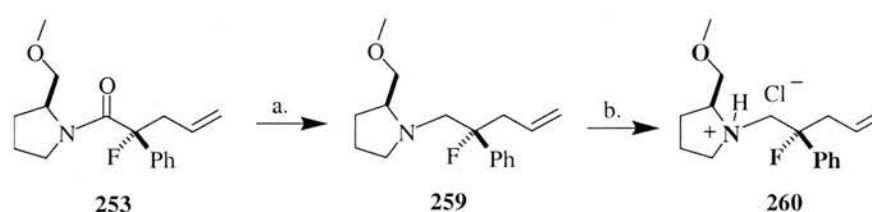
Scheme 3.25

Interestingly, when the reaction was repeated using propionyl chloride (scheme 3.26) under identical reaction conditions, the diastereoselection decreased to 75% de. Thus the fluorine appears to play a role in the high diastereoselectivity observed for the products **252** and **253**. The diastereoisomers (**257**) were then iodolactonised to give **258**.



Scheme 3.26

The high diastereoselection is consistent with the understanding that six-membered transition-states **251** and **256** are favoured which dictates the stereochemical profile of the reaction as depicted in schemes 3.25 and 3.26. Clearly the CH₃ and Ph groups prefer to be equatorial to avoid the 1,3-diaxial interaction with H' in **251** and **256**, whereas the 1,3-interaction with F is much less. It remains unclear why the fluoro products **252** and **253** were produced in higher diastereoselection than **257** (scheme 3.26). The *syn*-chair conformation is clearly set-up for a possible ytterbium co-ordination. Further, the Lewis acid will stabilise the zwitterionic intermediate, until the rearrangement is complete.^{29, 30}



Scheme 3.27 Reagents: (a) LiAlH₄, THF, 100%; (b) HCl-Et₂O.

In order to confirm unambiguously the absolute stereochemistry of the fluorinated aza-Claisen products, it was decided to obtain a crystalline derivative for X-ray analysis. To this end, **253** was treated with LiAlH to give amine **259** which upon HCl-etherate treatment afforded ammonium hydrochloride **260** (scheme 3.27). This material was analysed by X-ray diffraction and the resultant structure revealed the absolute configuration to be (*S,S'*) with the methoxyl methyl and the phenyl groups in **260** *syn* with respect to each other (figure 3.1).

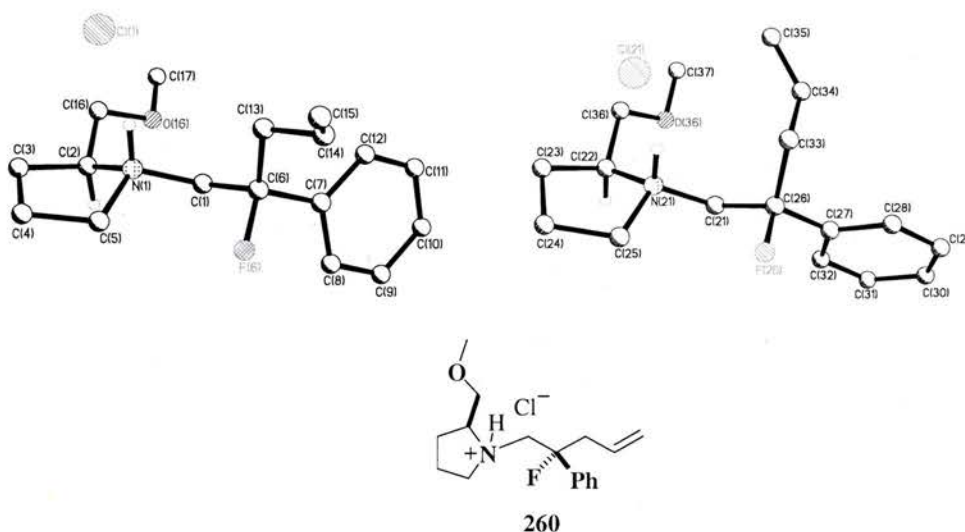


Figure 3.1 ORTEP drawing of **260** showing two crystallographically independent molecules within the unit cell.

Interestingly the X-rays diffraction studies revealed that the C-F bond adopts a *gauche* conformation to the C- N⁺(H) bond in **260**. The N⁺(1)-C(1)-C(6)-F(6) dihedral angle was deduced to be 66.89(17)° and N⁺(21)-C(21)-C(21)-F(6) was 59.44(18)°. This observation is consistent with recent conformational studies reported by Briggs *et al.*³¹ which revealed that a fluorine *gauche* conformation is favoured over an *anti* conformation for fluoroethylammonium systems **261-263** (figure 3.2).

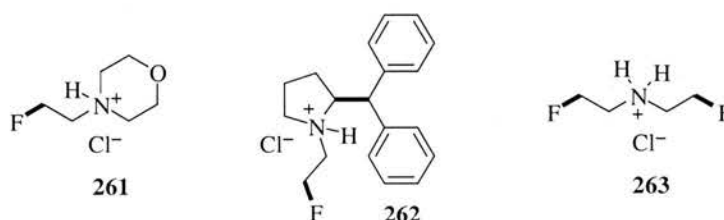
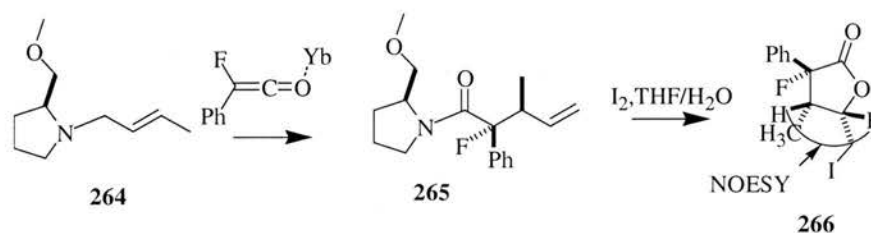


Figure 3.2 Examples of the fluorine *gauche* effect in 2-fluoroethylammonium chlorides **261-263**.

The crotyl amide derivative **264** was investigated as a substrate for the aza-Claisen reaction (scheme 3.28). Surprisingly, this gave only a modest stereoselectivity (77% de).



Scheme 3.28

Happily, the mixture of the diastereoisomers were successfully separated. Following iodolactonisation of **265**, **266** was recovered as a 7.7:1 diastereoisomeric mixture. NOESY studies allowed determination of the relative stereochemistry of the major iodolactonisation product.

3.6. Summary

The asymmetric [3,3]-aza-Claisen rearrangement reaction and its use in organic synthesis of chiral amides have rapidly been accepted for the synthesis of large variety of enantiomerically enriched compounds. Stereoselective introduction of the fluorine atom, which results in a stereogenic centre at the quaternary α -carbon, is a special feature of this reaction.

A range of enantiomerically enriched five-membered lactones have been generated from proline derived amines. The zwitterionic aza-Claisen served as the key step in the diastereoselection process. The most efficient rearrangements in terms of stereocontrol were achieved with allylamine **250**. However, extension of this procedure to crotylamines resulted only in modest des. Iodolactones were generated in high regioselectivity and high yields. NOESY experiments were crucial in determining the relative stereochemistry of the iodolactones. It is notable that the fluorine containing substrates gave highly diastereoselective reactions, and a new method has been developed for the stereoselective synthesis of α -fluorocarbonyl compounds.

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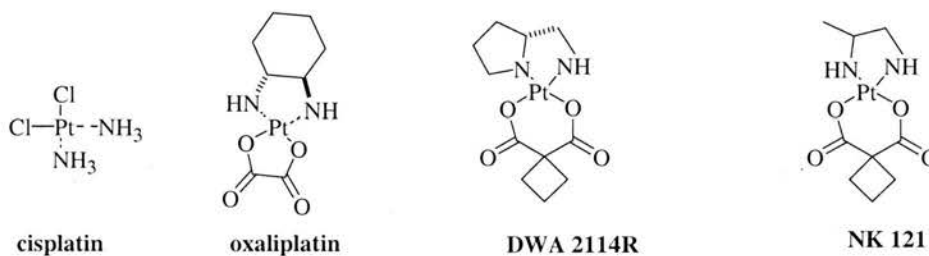
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4

Chemistry of C_2 -Symmetrical Diamines.

4.1. General

Organic compounds with 1,2-diamine functionality have found wide utility in medicinal chemistry and in synthetic methodology. Diamines for example have found application in chemotherapy where various platinum complexes are antitumour agents replacing cisplatin to reduce toxicity and overcome drug resistance. Rozenburg synthesised the antitumor agent cisplatin [*cis*-diaminodichloro platinum(II)] in the 1969.¹ Since its discovery many diamine-platinum-based complexes have been developed in a search for better activity. Such complexes are DWA 2114R, NK 121 and oxaliplatin.²



Enantiomerically pure diamines have found widespread application as versatile chiral bidentate ligands in asymmetric reactions. For example asymmetric dihydroxylation of alkenes by osmium tetroxide has proved very successful using vicinal diamines having C_2 symmetry.³

4.2. Vicinal Diamines in Asymmetric Organic Synthesis

Chiral, optically active vicinal diamines and their derivatives are increasingly used in stereoselective organic synthesis. Such systems are often used as chiral auxiliaries, or as metal ligands in catalytic asymmetric synthesis and as chiral resolving agents. It is these applications that have brought about the development of synthetic procedures for the synthesis of aliphatic 1,2-diamines in diastereomerically and enantiomerically pure forms. Thus, the design of new chiral ligands has increasingly become an important

focus to improve the enantioselectivity of organic reactions. Diamines have been widely used as efficient chiral inductors and they have found applications in many asymmetric processes.

4.2.1. C_2 -Symmetrical Diamines in the Resolution of Racemates.

A vast number of non-chiroptical methods used for the determination of enantiomeric purity of chiral acids are indirect and involve formation of diastereomeric esters or amides prior to NMR⁴ or HPLC analysis. The classical application of chiral amines is their use in the resolution of racemic acids. In solution NMR can use such agents to determine % ee. A suitable chiral solvating agent should possess anisotropic groups such as a phenyl ring, carboxylic acid or localised lone pair that will induce chemical shift non-equivalence. Thus, diamines such as **267**⁵ satisfy these criteria and have been successfully employed for the resolution of several pharmacologically important anti-inflammatory agents (**268-271**). Also α -halo acids (**272-274**) which are susceptible to racemization by other methods of resolution (figure 4.1) have been analysed in this way.

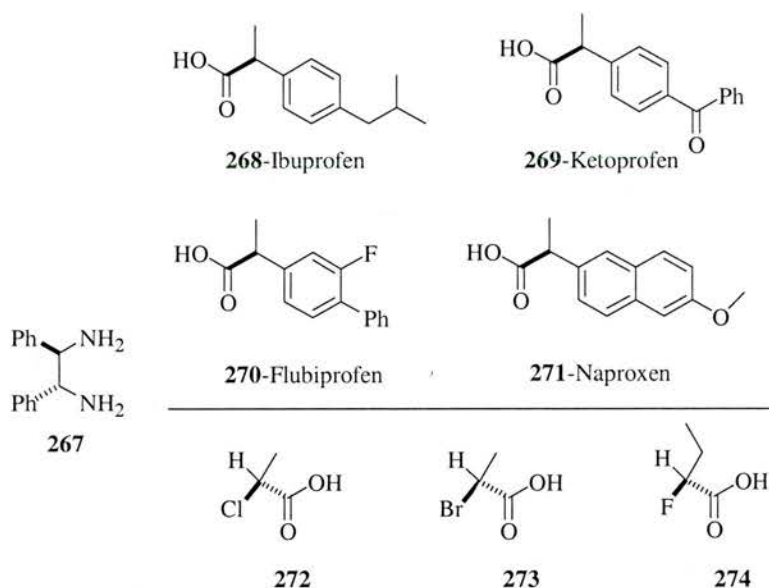


Figure 4.1 Resolution of base-sensitive chiral acids.

Brunner and Schiessling⁶ successfully employed (*R,R*)-1,2-diaminocyclohexane **275** and (*R,R*)-1,2-diphenylethylenediamine **267** to resolve the atropisomeric forms of binaphthols upon column chromatography of the resulting polymeric imines (figure 4.2). Binaphthol (*S*)-**276** forms a 24-membered macrocyclic ring which elutes with

dichloromethane/ toluene whereas (*R*)-**276** forms a polyimine which is left as a residue on the column. Subsequent acid hydrolysis of (*S*)-24-membered macrocycle furnished the enantiomerically pure isomer (*S*)-**278**. (*R,R'*)-1,2-Diphenylethylenediamine **267** has also been widely employed for the chiral resolution of acids and in the determination of enantiomeric purity using NMR spectroscopic analysis.

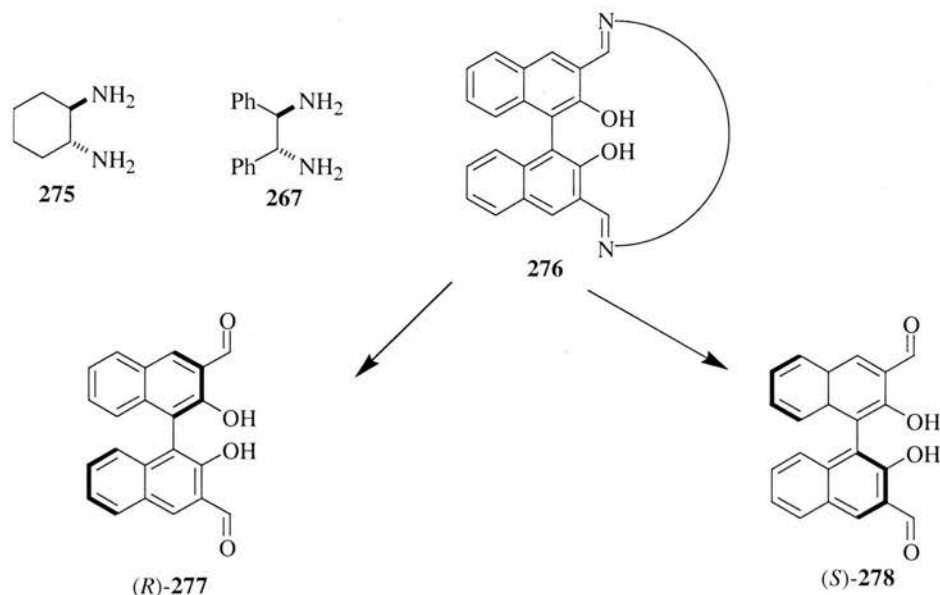


Figure 4.2 Chiral resolution of binaphthol atropisomers.

Mangeny *et al.*⁷ showed that **280** could be used for the resolution of racemic aldehydes **279** through a reaction that proceeds *via* imidazolodines **281** which upon separation and hydrolysis, releases non-racemic aldehyde **282**.

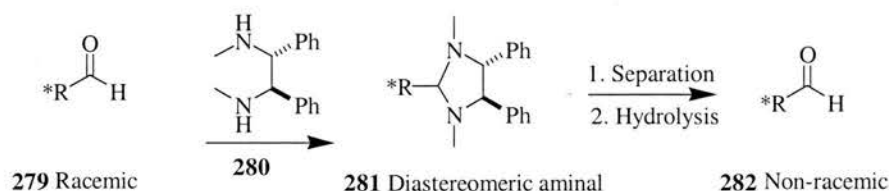
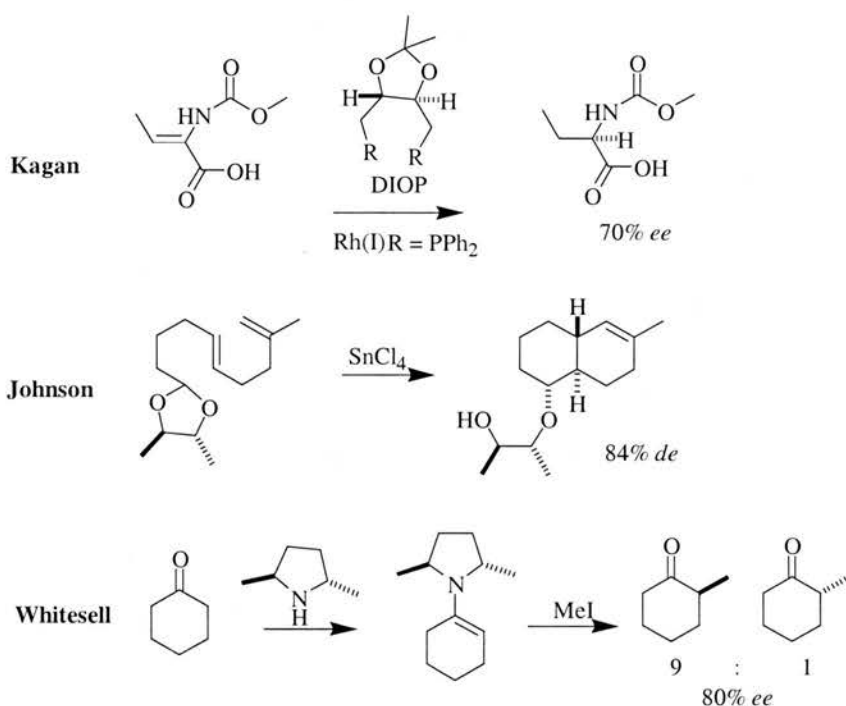


Figure 4.3 Resolution of aldehydes with a chiral vicinal diamine.

Diamines are increasingly used in asymmetric catalysis for reactions as different as carbonyl reductions,⁸ asymmetric dihydroxylation,³ and Diels-Alder reactions,⁹ etc.

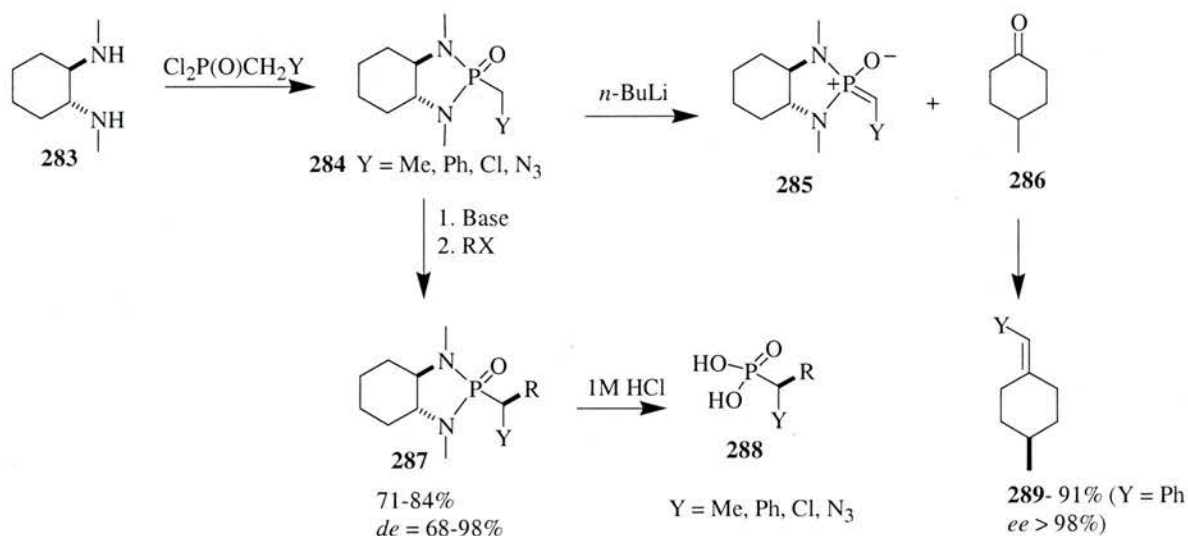
4.2.2. Vicinal diamines as chiral auxiliaries.

There are three seminal contributions in the study of C_2 -symmetrical chiral molecules used in the area of auxiliaries. Kagan introduced Diop^{10, 11} as the first disymmetrical molecule used for reduction reactions (scheme 4.1). Johnson¹² introduced the ketal derived C_2 -symmetrical glycol which has provided a synthetically useful level of stereocontrol in a variety of systems. Whitesell's^{13, 14} 2,5-diaminopyrrolidine was the first monodentate C_2 -Symmetrical auxiliary used for the enamine alkylation reaction.



Scheme 4.1 C_2 -Symmetrical auxiliaries

Caine¹⁵ describes chirality transfer as a process which occurs when achiral substrates are covalently bonded to a chiral agent/ auxiliary. Thus, some chirality transfer reactions require fine-tuning of the chiral auxiliary backbone in order to achieve a successful reaction, whereas in many other cases, only co-ordination through the nitrogen atom to metals is required.¹⁶ Homochiral vicinal diamines have received increased attention during the past decade. They have found enormous application in the area of stereoselective synthesis as chiral auxiliaries. C_2 -symmetrical 1,2-diamines and their derivatives have been widely employed in this field¹⁷ (scheme 4.2).

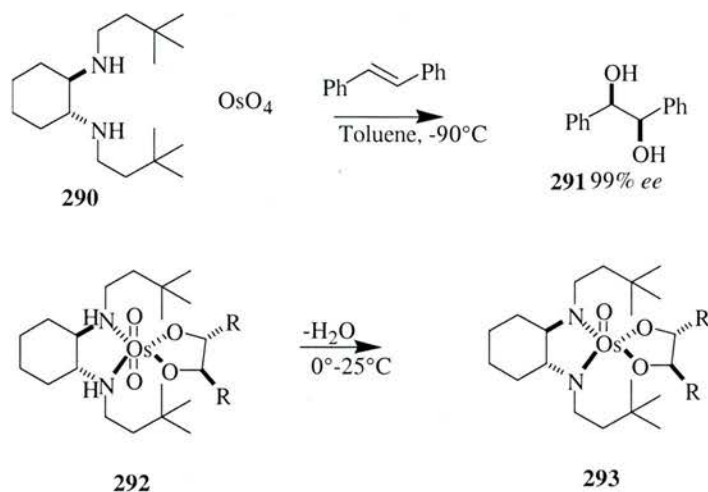


Scheme 4.2 Chiral bicyclic phosphonamide, from vicinal diamines as chiral auxiliaries.

Hanessian¹⁸ developed a chiral bicyclic phosphonamide ylide **285** derived from the *C*₂-symmetrical cyclohexyl diamine **283** (scheme 4.2). The reaction of this diamine with phosphoroyl dichloride provides the phosphonamide **284**, which was deprotonated to afford the ylide **285**. Asymmetric olefination *via* a Wittig reaction on **286** gave access to a single enantiomer of **289**, whereas trapping of the anion with an alkyl halide gave **287** and subsequent acid hydrolysis resulted in α -hydroxyphosphoric acids **288**.

4.2.3. Asymmetric dihydroxylation

The asymmetric dihydroxylation of alkenes using osmium-cinchona alkaloid complexes has received considerable attention since the seminal contributions by Sharpless and co-workers.¹⁹ Over the past two decades the literature has significantly increased for the conversion of *cis* and *trans* alkenes into their corresponding enantiomerically pure or enriched diols e.g. Hanessian²⁰ has prepared diols such as **291** by asymmetric dihydroxylation in the presence of chiral diamine ligands such as **290** (scheme 4.3). Despite the excellent enantioselectivities obtained using a variety of diamines, the reactions are stoichiometric in both OsO₄ and the chiral ligand. This is a direct consequence of the *in situ* formation of the stable chelate complexes **293** between the ligand and osmium(VI) glycolate intermediates, thus hindering recyclisation of the catalytic species (scheme 4.3). Several *C*₂-symmetrical diamines have been successfully employed and they have displayed a wide range of tolerance to a variety of substrates.



Scheme 4.3 Asymmetric dihydroxylation by Hanessian.²⁰

The other most notable chiral ligands for enantioselective oxyosmylation of alkenes are those developed by Synder **275**,²¹ Hirama **294**,^{22, 23} Corey **295**,³ Tomioka **296**²⁴⁻²⁷ and Fuji **297**.²⁸

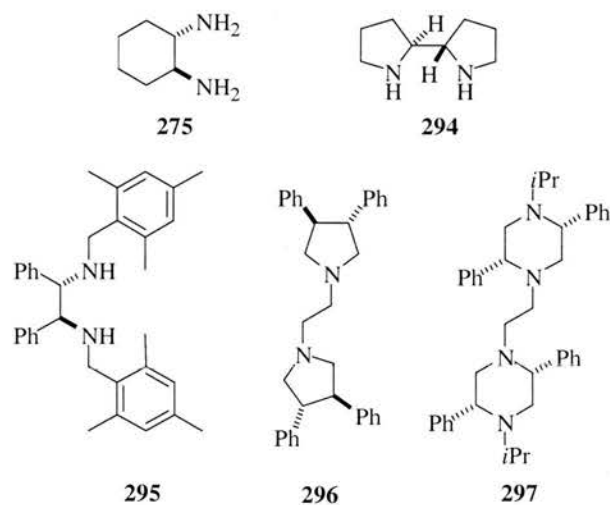


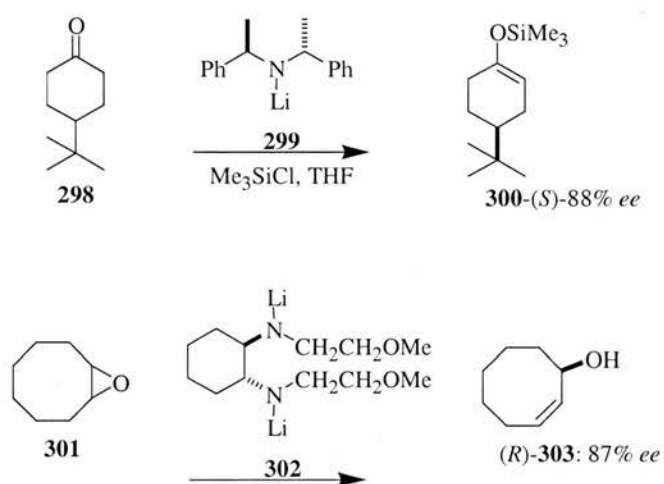
Figure 4.4 Chiral 1,2-diamino ligands for asymmetric dihydroxylation used under stoichiometric conditions.

4.2.4. Diamines as chiral bases

Homochiral lithium amide (HCLA) and diamine bases are important compounds in asymmetric organic reactions (scheme 4.4).^{29, 30} A vast number of chiral amide bases have been developed and employed across a wide spectrum of asymmetric reactions including the following:

1. Deprotonation of conformationally locked prochiral cyclic ketones.^{31, 32}
2. Rearrangement of *meso*-epoxides to enantiomerically enhanced allyl alcohols.^{33, 34}

Despite the wide spread use of HCLA bases in asymmetric chemistry, C_2 -symmetrical diamines are very poorly represented.

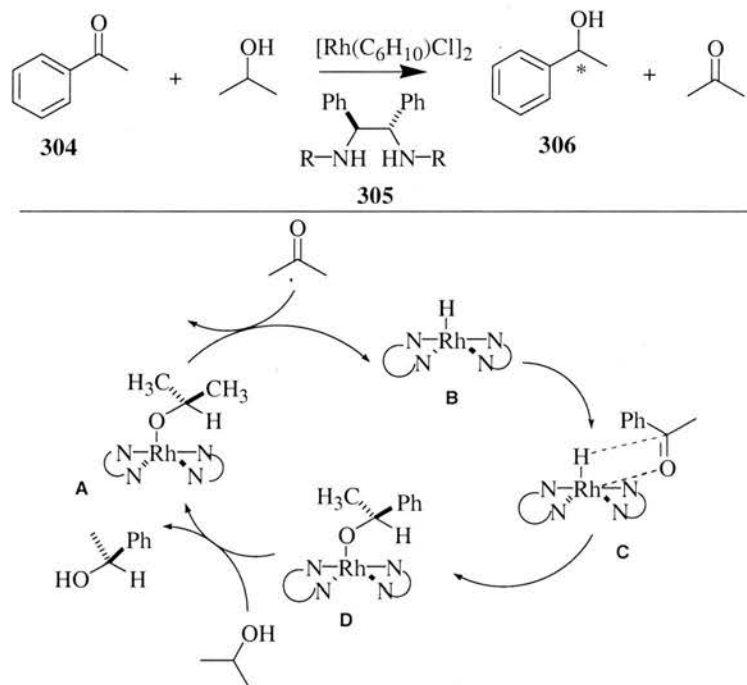


Scheme 4.4 Chiral lithium amide in asymmetric reactions.

Koga³⁵ has reported enantioselectivity in the deprotonation of 4-substituted cyclohexanone **298** with (*R,R'*)-**299** using Corey's³⁶ internal quench method with trimethylsilyl chloride in the presence of HMPA to generate **300** in 88% ee (scheme 4.4). The rearrangement of *meso*-epoxides such as cyclohexene oxide and cyclooctene oxide **301** to their corresponding allyl alcohols (*R*)-**303** has been investigated by Alexakis and co-workers using (*R,R'*)-**302**.

4.2.5. Carbonyl reduction

Chiral diamines have been successfully used as ligands in different asymmetric reduction reactions of carbon-carbon (C=C), carbon-oxygen (C=O) and carbon-nitrogen (C=N) moieties.³⁷⁻³⁹ Enantioselective reduction of unsymmetrical ketones has been reported to proceed with good selectivity in a large number of catalytic methods.⁴⁰

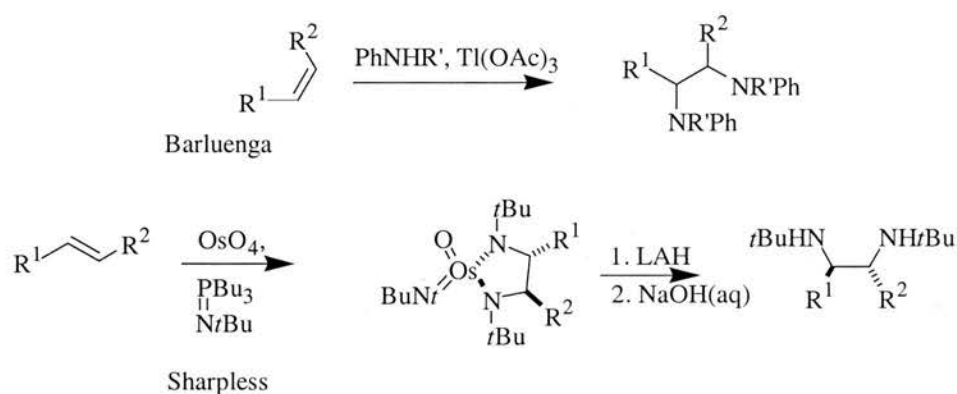


Scheme 4.5 Proposed mechanism of the hydride transfer reduction.⁸

Many of these dissymmetrical diamines **305** used in carbonyl reductions are rhodium complexes, which have many advantages over their phosphorus analogues (accessibility and recovery). An example of such a reduction is the hydrogenation of acetophenone **304** by hydride transfer starting from compound **A**. These reactions show conversions up to 100% and 67% *ees* (scheme 4.5). Hydride **B** is the key intermediate in the process and it is responsible for the stereocontrol. Formation of complex **C** is the rate-determining step at which the hydride adds across the *Re/Si* face of the carbonyl and subsequent addition of isopropanol to **D** releases the required alcohol **306**.

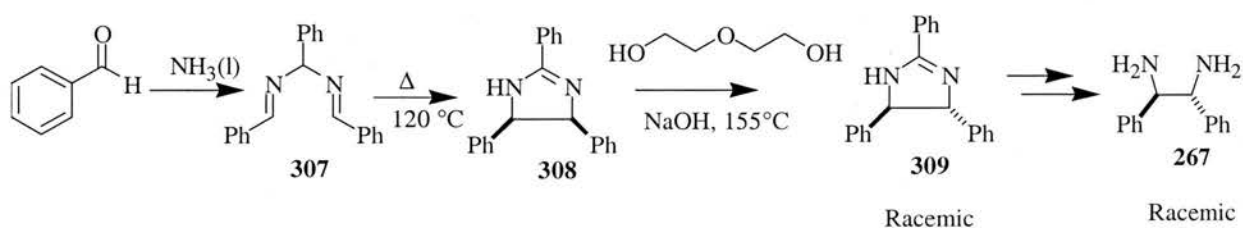
4.3. Methods of preparation for homochiral C₂-symmetrical diamines:

A classical and straightforward method for the generation of the 1,2-diamino unit is by the aminolysis of the corresponding dihalide.⁴¹ Enantiopure 1,2-disubstituted diamines can always be obtained by chiral resolution using homochiral acids however, enantioselective methods are increasingly employed in the synthesis of optically active 1,2-diamines.



Scheme 4.6 Alkene diamination.

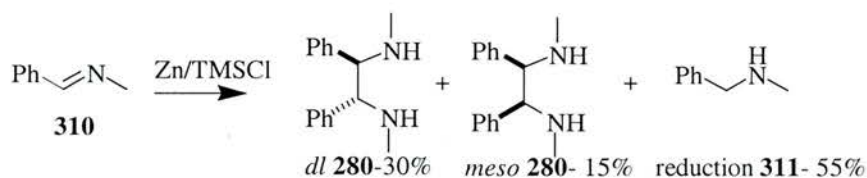
Methods for directed diamination of *Z* and *E* alkenes using organometallic reagents have been developed by Barluenga and Sharpless (scheme 4.6).⁴²⁻⁴⁴ Many other methods involving functional group interconversions have been largely employed e.g. reduction of nitro, azido and cyano compounds.



Scheme 4.7 Synthesis of stilbenediamine.

Recently Corey and Kühnle⁴⁵ re-described the synthesis of 1,2-diphenyl-1,2-diminoethane (stilbenediamine) **267-rac** by amination of benzaldehyde with ammonia to give the hydrobenzamide (amarine) **307** which undergoes cyclization under thermal

conditions to afford **308** (scheme 4.7). Subsequent base treatment results in the desired *trans* isomer **307**, which upon reduction and debenzoylation yields **267**.



Scheme 4.8 Reagents: Zn/Me₃SiCl, H₂O THF, rt.

The pinacol coupling of imines is among the most straightforward methods employed for the synthesis of diamines. Schiff bases undergo inter- or intra- molecular coupling reactions in the presence of metals such as zinc,⁴⁶ samarium/ and ytterbium.⁴⁷ An intermolecular version of this methodology, often results in a mixture of both *dl*-**280** and *meso*-**280** diamines, whereas intra- molecular coupling is prone to *C₁*-symmetry as in Benaglia's studies.⁴⁷ Some of the commonly encountered methods for the preparation of *C₂*-symmetrical diamines are discussed in the next section.

4.4. Results and discussion.

4.4.1. Retrosynthetic analysis of ethylene diamines from the Onyx monoamines.

There is no doubt that *C₂*-symmetrical diamines have received increasing attention during the last decade. Indeed enantiomerically pure diamines and their derivatives have found wide application in stereoselective synthesis. The importance of the vicinal moiety has brought about numerous methods of preparation, however, only a few of them are general. With this background we decided to explore the Onyx amines as precursors for the preparation of *C₂*-symmetrical diamines. In order to establish routes leading to C-C bond formations for the preparation of ethylene diamines, it was decided to employ the retrosynthetic analyses strategies shown in figure 4.5.

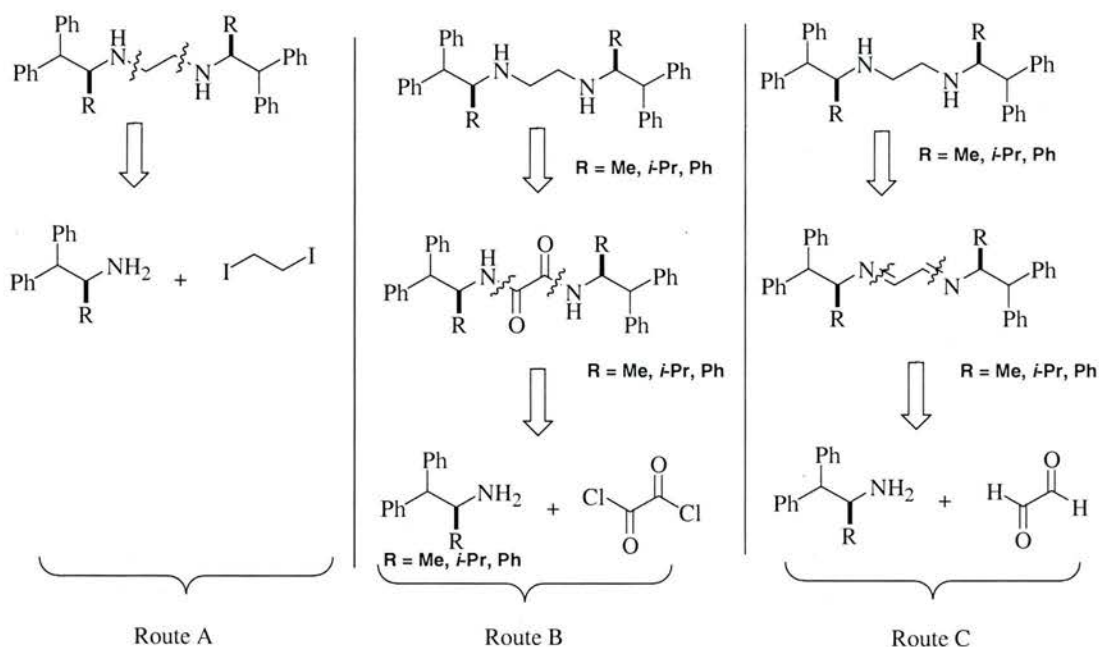


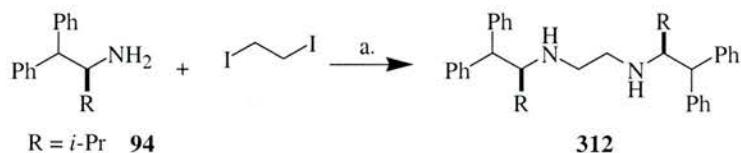
Figure 4.5 Retrosynthetic analyses of diamines

Three routes emerged from the retrosynthetic analysis figure 4.5:

- (1) Route A involves reaction of the monoamines with diiodoethane.
- (2) Route B involves preparation of diamide intermediates *via* a reaction of the monoamines with oxalyl chloride.
- (3) Route C involves preparation of a diimine by reaction of the monoamine with glyoxal.

4.4.2. Synthesis of diamines by direct alkylation.

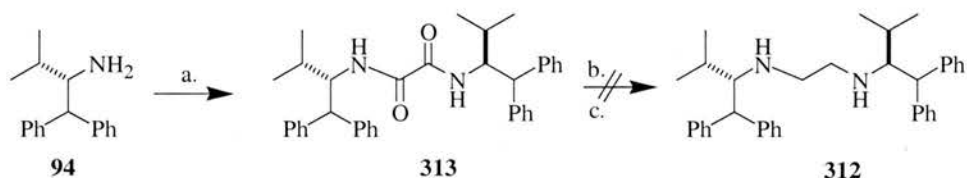
Route A of the retrosynthetic analysis involved a simple single step procedure in order to access diamines **312** (scheme 4.9). Accordingly diiodoethane was reacted with **94** in the presence potassium carbonate. This resulted in diamine **312** but in a rather poor yield (10%). Unreacted starting material could be recovered which offered some advantage, but otherwise the reaction could not be improved. In view of the low yield an alternative procedure (route B) was examined.



Scheme 4.9 Reagents: (a) K₂CO₃, ethanol, Δ, 10%.

4.4.3. Synthesis of diamines by dicarbonyl coupling.

The coupling of amines to bifunctional electrophilic species such as oxalyl chloride provides access to C₂ symmetric diamides such as **313**, generally in high yields.^{24, 25} The reaction of **94** with oxalyl chloride gave product **312** as a white amorphous solid and in good yield.



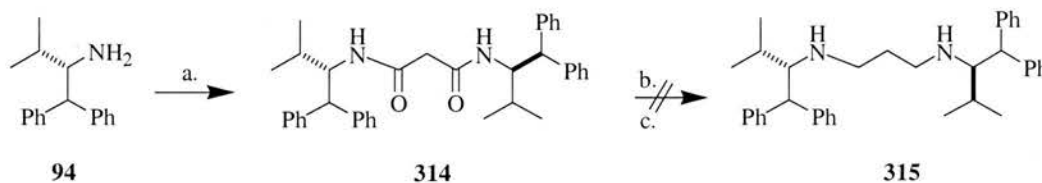
Scheme 4.10 Reagents: (a) (COCl)₂, Et₃N, CH₂Cl₂, 91%, (b) BH₃·THF, Δ, 0%, (c) LiAlH₄, THF, Δ, 0%.

The next step in the synthesis required a reduction of the diamide to generate the diamine. Accordingly compound **313** was then treated with refluxing diborane THF/ for 5 days, however there was no evidence of reduction. Lithium aluminium hydride was then explored as a reducing agent. Following reflux for several days with an excess of LiAlH₄, there was no evidence of the reduction product either. In order to investigate the possible cause of this failure, three structural features were examined:

- (1) Proximity of the carbonyl moieties.
- (2) Steric hindrance around the carbonyl group.
- (3) Presence an amide hydrogen.

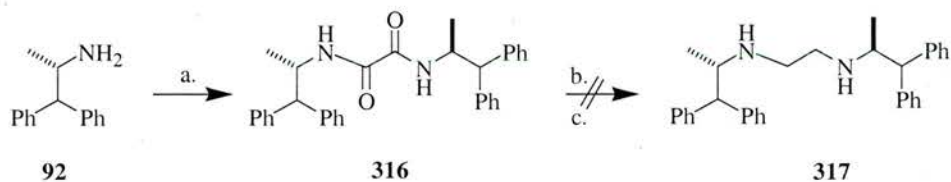
To explore the first factor, the N-C-C-N spacer unit was extended to a 3-carbon unit using malonyl dichloride as the coupling reagent. Following the same procedure described above **313**, this gave the corresponding diamide **314** in 62% yield (scheme 4.12). Diamide **314** was subjected to the similar reducing conditions as discussed earlier

for **313** using both borane and LiAlH_4 . In the event, no reduction occurred, thus it can be tentatively concluded that the proximity of the amide groups in **313** to each other is not interfering with the reduction step (scheme 4.11).



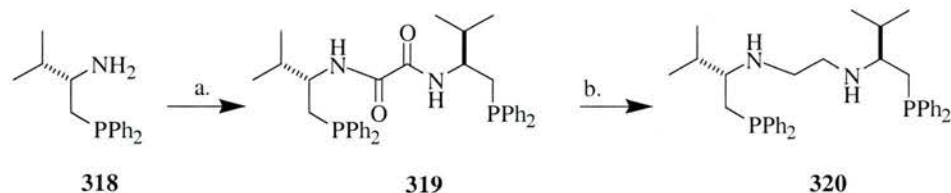
Scheme 4.11 Reagents: (a) $\text{CH}_2(\text{COCl})_2$, Et_3N , CH_2Cl_2 , 62%, (b) $\text{BH}_3 \cdot \text{THF}$, Δ , 0%, (c) LiAlH_4 , THF , Δ , 0%.

The second structural feature examined was the steric hindrance from the isopropyl group inherited from the starting amine **94**. Thus, synthesis of the alanine derived amide **316**, was undertaken. Following treatment of **92** with oxalyl chloride, in triethylamine as shown in scheme 4.12, the ethanediamine was generated in 96% yield and as a crystalline solid. However reduction of product **316** under the previously described conditions was similarly unsuccessful.



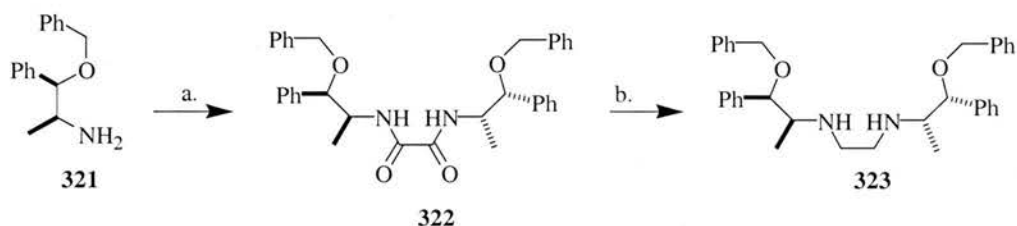
Scheme 4.12 Reagents (a) $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , 96%, (b) $\text{BH}_3 \cdot \text{THF}$, Δ , 0%, (c) LiAlH_4 , THF , Δ , 0%.

This was unexpected, as there are examples of structurally related secondary amide reductions reported in literature, which indicate that such amide reductions can be highly efficient, and robust^{48, 49} and it is not clear why this reaction was so sluggish in our hands.



Scheme 4.13 Reagents: (a) $(\text{COCl})_2$, Et_3N , Et_2O , $-78\text{ }^\circ\text{C}$, 5h, 63%, (b) 6 equiv. LiAlH_4 , THF, Δ , 24 h, 75%.

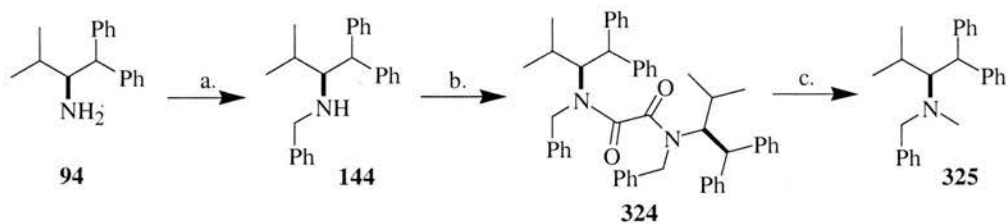
For example the synthesis of **320** from aminophosphine **318** (ValPHOS) was achieved by the reaction of ValPHOS with oxalyl chloride to furnish **319**. This diamide was subsequently treated with LiAlH_4 to give the reduced diamine **320** in an overall yield of 47% based on ValPHOS (scheme 4.13).



Scheme 4.14 Reagents: (a) $(\text{COCl})_2$, CH_2Cl_2 , (b) LiAlH_4 , THF

A similar study by Koga *et al.*⁴⁹ revealed that the secondary diamine **323** could be readily accessed from the corresponding diamide **322** also by the action of lithium aluminium hydride (scheme 4.14).

The third factor evaluated in this study was the influence of the amide hydrogen. To explore this, the strategy required the synthesis of the secondary amine **144** which is accessed by reaction of **94** with benzaldehyde and NaCNBH_3 in methanol as shown in scheme 4.15. The benzyl amine **144** was then coupled to oxalyl chloride as described earlier to afford the tertiary bisamide **324** in 83% yield.



Scheme 4.15 Reagents: (a) PhCHO, NaCNBH₃, CH₃OH, 82% (b) (COCl)₂, CH₂Cl₂, 83% (c) LiAlH₄, THF, 66%.

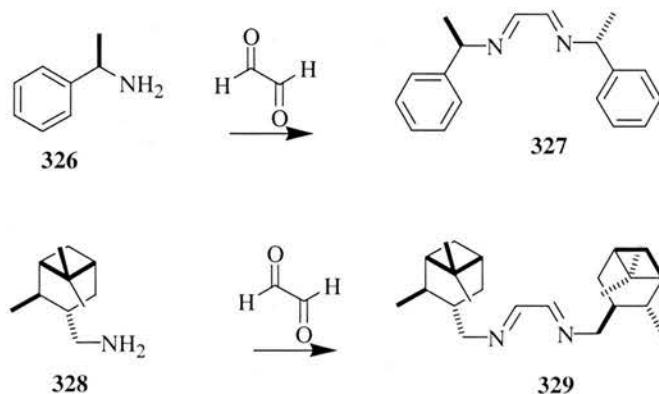
Compound **324** was then treated with LiAlH₄ in THF. Surprisingly, amine **325** was isolated in 66% yield. Although the amide reduction method is widely used, LiAlH₄ reduction gave exclusively this undesired product as a result of scission of the central C-C bond from which it may be concluded that:

- (1) The amide hydrogen in **313**, **314** and **316** interferes in the reduction step.
- (2) The proximity of the two N-C=O amide groups did not interfere in the reduction step, thus, neither the sterics nor the proximity factors are significant.
- (3) These tertiary diamides are highly susceptible to C-C cleavage.

Taken together these consequences led to a change in our synthetic strategy.

4.4.4. Synthesis of imines by glyoxal condensation

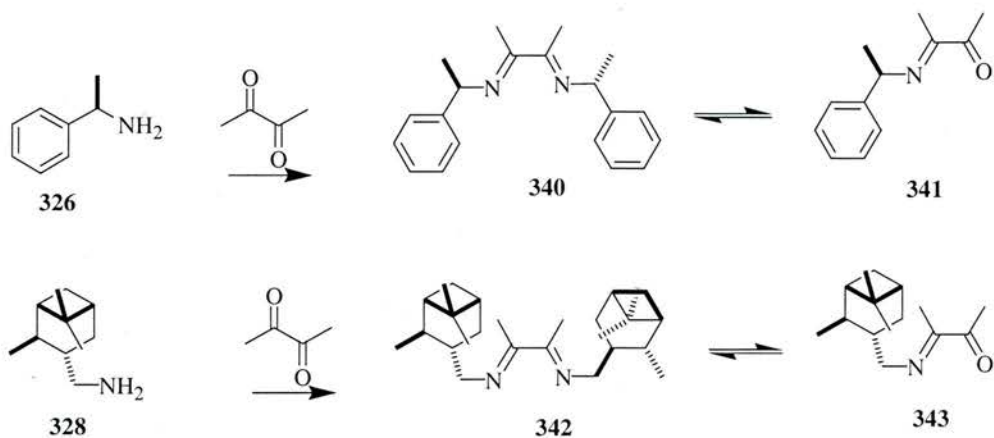
The condensation of glyoxal (as its hydrate) and biacetyl (2,3-butanedione) with primary amines is a reaction that has been used for decades in the preparation of C_2 symmetrical 1,2-diimines⁵⁰ (scheme 4.16). These diimines yield symmetrical diamines upon reduction and this class of compounds has been of great importance in catalytic asymmetric synthesis.



Scheme 4.16 Synthesis of 1,2-diimines from glyoxal.

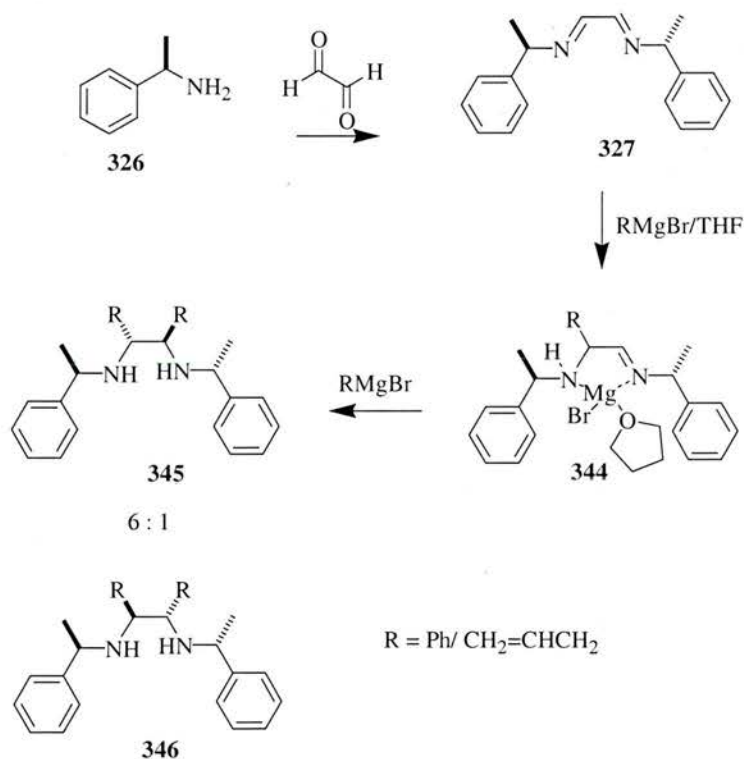
Dieck and Dietrich⁵¹ were successful in condensing glyoxal with the optically pure primary amines (*R*)-1-phenylethylamine **326** and (1*S*, 2*S*, 3*S*, 5*R*)-3-(aminomethyl)pinane **328** to afford their corresponding diimines (**327**, **329**) in excellent yields (scheme 4.16). These reactions were typically carried out in solvents such as methanol, chloroform, dichloromethane and diethyl ether in the presence drying reagents and catalytic amounts of formic acid.

The condensation reaction of (*R*)-1-phenylethylamine **326** with diacetyl is reported to proceed slowly due to steric factors associated with the diacetyl (scheme 4.17). The reaction rate however, increases proportional with temperature increase. The equilibrium between (*R,R'*)-**340** and (*R*)-**341** was found to favour of the oxo-complex (*R*)-**341**. Similar results were obtained when **328** was employed, with the equilibrium also found to favour **343** over **342**.



Scheme 4.17 Condensation of chiral amines with diacetal.

Alternatively, Neumann and co-workers⁵² developed a stereoselective synthesis of 1,2-diamines such as **345** and **346** by a reaction of 1,2-diimine **327** with Grignard reagents.

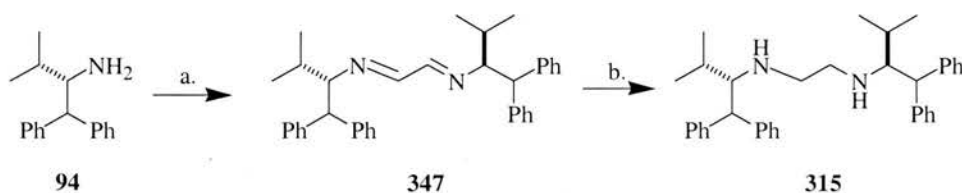


Scheme 4.18 Synthesis of disubstituted diamines *via* diimines.

This was facilitated by nucleophilic addition of allylic and aromatic Grignard reagents⁵³ to generate double functionalised secondary vicinal diamines **345:346** systems in a ratio of 6:1 and in 85% yield (scheme 4.18). Thus, an alternative approach to the synthesis of

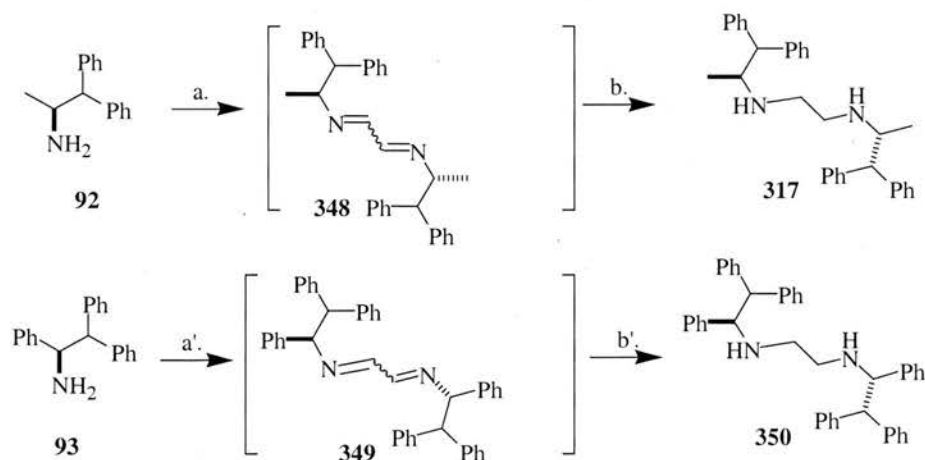
C_2 -symmetrical diamines is achievable, which avoids the difficulty in direct condensation with diketones such as 2,3-butanedione and amines.

It was an objective to explore the glyoxal condensation with the Onyx amines. In the first instance the condensation of glyoxal (as its hydrate) with amine **94** was explored. This gave the stable bisimine **347** in quantitative yield as illustrated in scheme 4.19. $^1\text{H-NMR}$ studies indicated a singlet at 7.35 ppm from the imine hydrogens, whilst the imine carbons resonated in 162.3 ppm in the $^{13}\text{C-NMR}$ spectrum. Reduction of diazadiene **347** with lithium aluminium hydride gave the disymmetrical diamine **315** also in quantitative yield.



Scheme 4.19 Reagents: (a) HCOCHO , HCO_2H , CH_2Cl_2 , MgSO_4 anh, quant., (b) LiAlH_4 , THF, Δ , 100%.

The straightforward nature of this protocol stimulated further investigation of the scope and utility of a series of chiral amines. Thus both the alanine **92** and phenylglycine **93** derived amines were treated with glyoxal as already outlined above to access their corresponding diazadienes **348** and **349** respectively (scheme 4.20).



Scheme 4.20 Reagents: (a), (a') $(\text{CHO})_2$, CH_2Cl_2 , MgSO_4 , (b), (b') LiAlH_4 , THF, quant.

A typical, reaction was undertaken in CH_2Cl_2 at room temperature with magnesium sulfate as a dehydrating agent. Reaction times were in the region of 10-16 h depending on the amine in question. Following filtration and removal of the solvent, the diimines **348** and **349** were treated directly with lithium aluminium hydride to give the corresponding diamines **317** and **350** in good yield. At this moment, these amines remain unexplored as ligands in catalysis however they offer some prospects for future investigations.

4.5. Summary

Three synthetic protocols for the synthesis of C_2 -symmetrical diamines were evaluated. The route employing oxalyl chloride was abandoned due to an inability to mediate a reduction of the intermediate diamide. The diazadienes are versatile intermediates, which were readily transformed to their corresponding diamines under mild conditions. A straightforward single step procedure is possible but it is very low yielding and thus impractical. A practical route to the ethylene diamines derived from Onyx amines was successfully developed, and offers new ligands for exploration in asymmetric chemistry.²⁴

4.6. References

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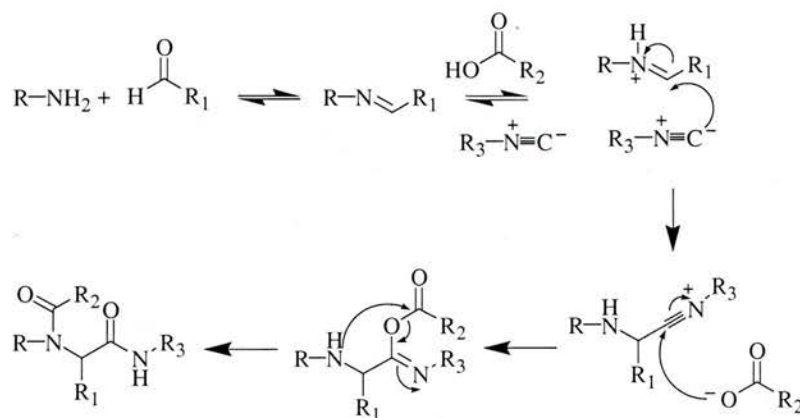
5

Asymmetric Ugi (4-CR) reactions using novel chiral amines.

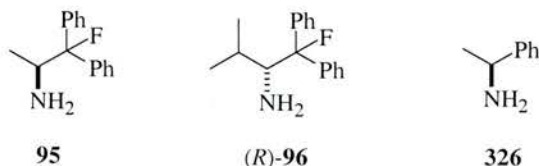
5.1 Introduction

The Ugi four component reaction (U-4CR) is a valuable one-pot synthetic tool used in organic chemistry for the synthesis of α -amino acid derivatives. This reaction is widely used for generating molecular diversity for drug discovery and in natural product syntheses.^{1,2}

A classical 4-multicomponent Ugi reaction (4-MCR) involves mixing an amine, aldehyde, isocyanide and a carboxylic acid to give diamide products.³ Scheme 5.1 shows an example of the Ugi reaction in which an amine reacts with an aldehyde to give an imine, which then undergoes a nucleophilic attack by the isocyanide leading to subsequent attack by the acid. This leads to an intramolecular *N*-acylation and subsequent irreversible product formation. In the course of the reaction two peptide bonds and one carbon-carbon are formed and a new chiral centre is created. Thus, employment of stereoselective methods to these reactions are highly desirable. It has been reported that the asymmetric induction in Ugi reactions is largely dependent on the chiral amine component.⁴



Scheme 5.1 General mechanism of the Ugi 4-CR



Chiral amines **95**, **(R)-96** and **326** were chosen in this project in order to generate libraries of chiral compounds and to evaluate the diastereoselection imposed by these amines, along with acids, aldehydes and isocyanide in figure 5.1.

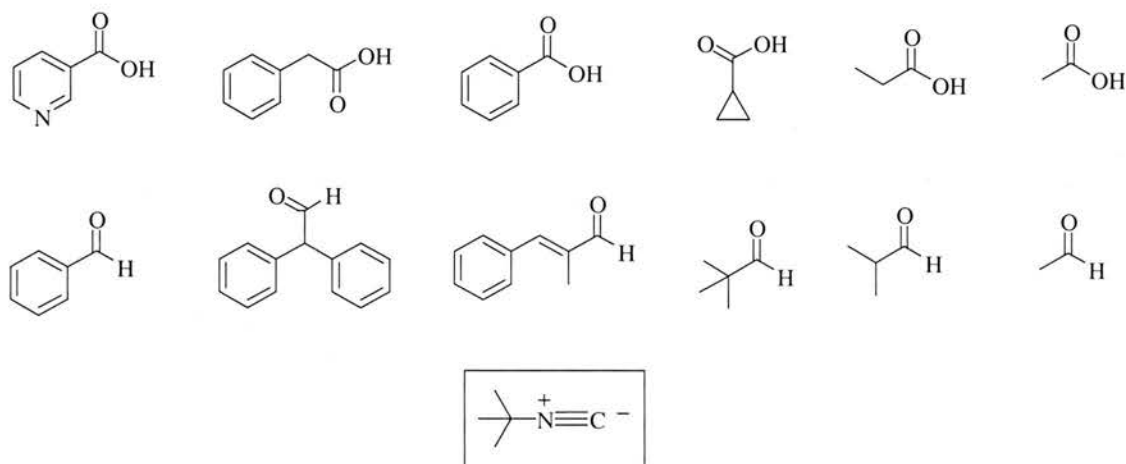
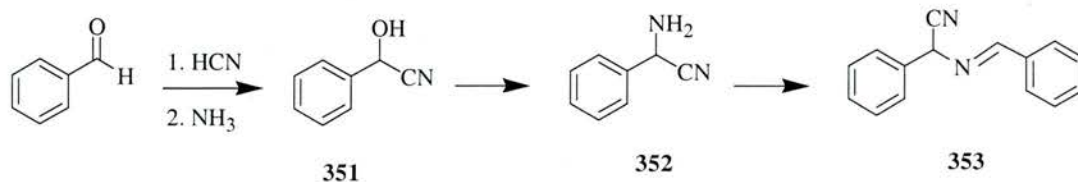


Figure 5.1

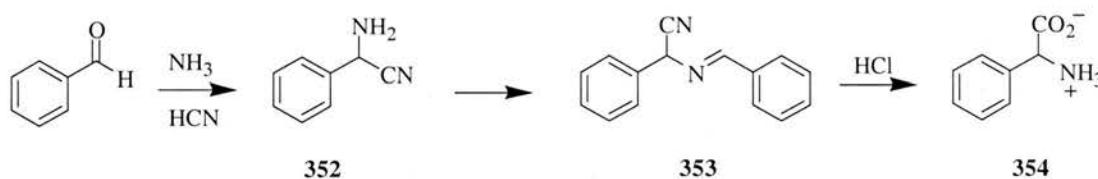
5.2 A brief historical background on the MCRs.

Multi-component reactions were first accomplished in 1838 by Laurent and Gerhardt.⁵ This involved a reaction of bitter almond oil (*via* benzaldehyde) with ammonia and hydrogen cyanide. This reaction proceeds by condensation of benzaldehyde and hydrogen cyanide to give cyanohydrin **351**, which reacts in a Strecker type reaction⁶ with ammonia affording aminobenzyl cyanide **352** whose further reaction with benzaldehyde generates **353**.

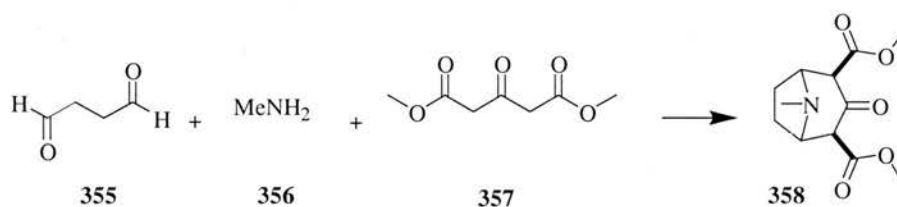


Scheme 5.2

Although this reaction has historical significance, the Strecker⁶ synthesis (scheme 5.3) of α -amino acids is generally considered to be the first MCR accomplished (1850).⁷ The reaction involves condensation of benzaldehyde with ammonia followed by nucleophilic attack on the resultant imine by cyanide to give aminobenzyl cyanide **352** (the reverse order of the Laurent and Gahardt⁵ reaction). Subsequent acid hydrolysis furnishes the amino acid **354**. Robinson⁸ demonstrated a MCR in his synthesis of the alkaloid tropinone **358** in 1917 from succinic dialdehyde **355**, methylamine **356**, and dimethyl acetonedicarboxylate **357**.



Strecker reaction

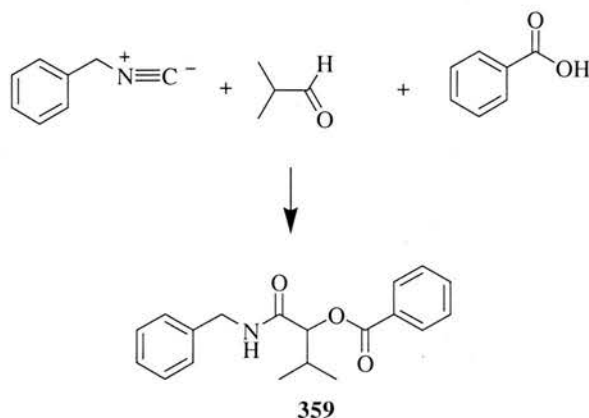


Robinson tropinone

Scheme 5.3

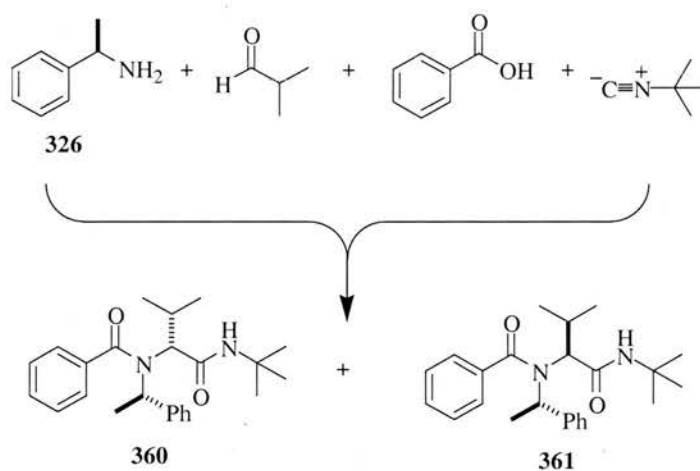
The most prominent of the multi-component reactions (MCRs) are the isocyanide based Passerini⁹ (P-3CR) and Ugi¹⁰ (U-4CR) reactions described in 1921 and 1959 respectively. The Passerini reaction involves an isocyanide, carboxylic acid and an oxo component. The Ugi¹⁰ reaction is the most reputed MCR and involves a variant of the Passerini from a reaction of primary amines, carboxylic acids, an oxo component and isocyanides giving access to α -acyloxycarboxamides in one step. These isocyanide

based MCRs proceed by formation of a new stereogenic centre at the position of the former carbonyl (scheme 5.4).



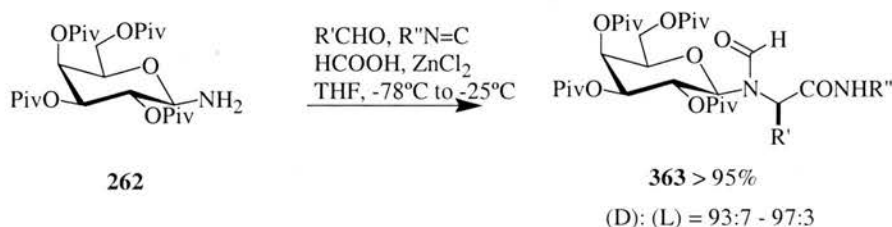
Scheme 5.4 Illustration of the Passerini reaction¹¹ MCR.

In the early stages of development of this chemistry, there was no conclusive way to control the stereochemistry of the products. About a decade later, Ugi¹² utilised the chiral amines, which resulted in high stereoselection of the newly formed stereogenic centre (scheme 5.5). The first chiral amines employed were the chiral phenylethylamines that could be cleaved by hydrogenation under acidic conditions.¹³ The highest diastereoisomeric ratio obtained was 3.8:1 for **360**:**361**.



Scheme 5.5

Diastereoselective studies on MCRs reported by Ugi and others¹⁴⁻¹⁹ achieved different levels of stereo-control, but this still needed further improvement. Thus, the quest for enantiomerically pure peptides led to significant advances in the area of asymmetric Ugi reaction (4-CRs). Until recently α -ferrocenyl alkyamines were the only amine components used that provided high levels stereoselectivity^{20, 21}. In 1988 a new generation of chiral amines was explored, derived from 2,3,4,6-tetra-*O*-pivaloyl- β -D-galactopyranosylamine **362** which underwent 4-CRs with high stereoselectivity to give **363**.²²



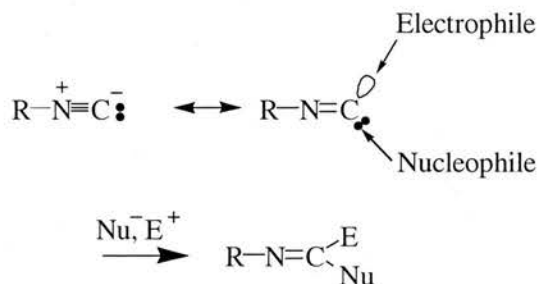
Scheme 5.6

To date the chemistry of the asymmetric Ugi (4-CRs) is still dominated by the glycopyranose derivatives as chiral auxiliaries.²³⁻²⁷

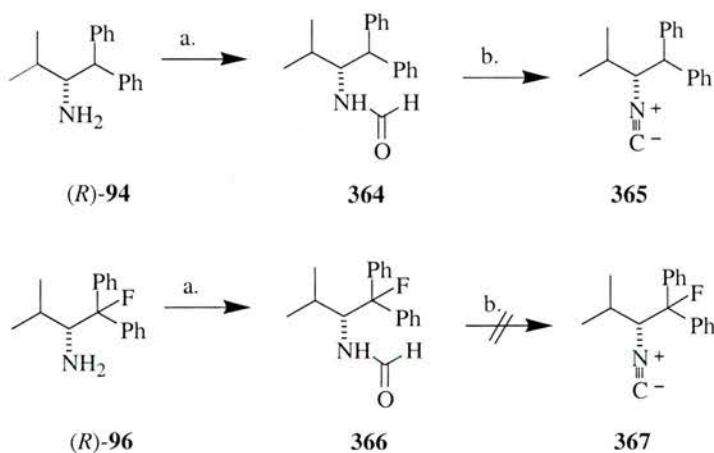
5.3 Results and discussions

5.3.1 Preparation of novel isocyanides

Isocyanides, also known as isonitriles, are compounds of extreme importance with an extraordinary amphiphilic functional group. They are among the most stable organic carbenes (divalent carbon centre). The isocyanide reacts like a carbene by a sequential α -addition of a nucleophile and an electrophile. It is this reactivity of isocyanides that makes them attractive in organic synthesis.



Currently only about 12 to 15 isocyanides are commercially available. To overcome this limitation it was decided to prepare some novel chiral isocyanides from our amines. These have potential as chiral auxiliaries in the synthesis of optically active α -amino acids. Even though many methods for the preparation of isocyanides have been described,²⁸ the reaction of *N*-formamides with phosgene and its derivatives^{29, 30} is still widely used, followed by a convenient dehydration with phosphorus oxychloride.

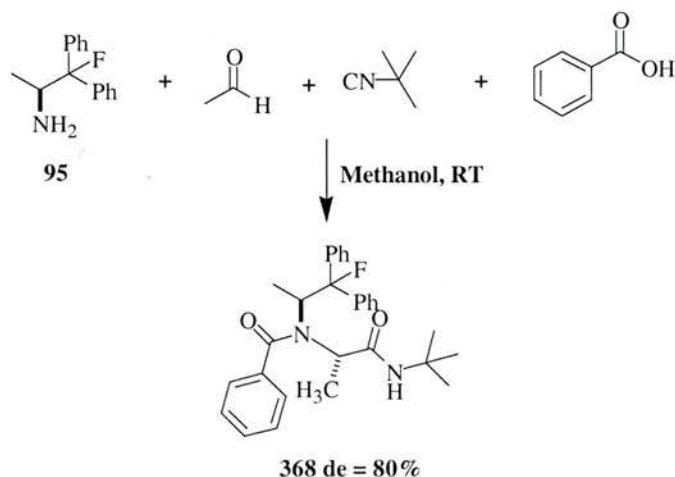


Scheme 5.7 Reagents: (a) HCO_2H , Δ , 100%, (b) $POCl_3$, iPr_2NEt , CH_2Cl_2 , 90%.

The synthesis of isocyanides **365** and **367** was carried out following known literature protocols³¹ by treatment of the primary amines **(R)-94** and **(R)-96** with refluxing formic acid. The resultant formamides **364** and **366** could be purified on extraction into diethyl ether, as they precipitated out of the ethereal solution as a white crystalline material requiring no further purification. The product **364** was then treated with phosphorus oxychloride in the presence of diisopropylethylamine to give the isocyanide **365** as thick colourless oils in good yield. However, treatment of **366** in a similar manner was unsuccessful, resulting only in a number of unidentified compounds and did not give the desired **367**. This may have been due to HF elimination.

5.3.2 Asymmetric Ugi (4-CR) using Onyx amines.

A survey of the substrates **95**, (*R*)-**96** and **326** with aromatic, conjugated and aliphatic aldehydes was undertaken. Combination of amine **95**, acetylaldehyde, *tert*-butylisocyanide and benzoic acid gave product **368**. In this case the stereoinduction was up to 80% de.



Scheme 5.8

Different acids, with aromatic, acyclic and cyclic motifs were also examined. Reactions were typically run in methanol at a concentration of 0.5 M. Good yields were obtained, and optimal conditions involved precondensation of the amine and the aldehyde. In these studies variation was introduced with the acid, aldehyde, and chiral amine moieties whilst the isocyanide was kept unchanged. The diastereoselectivities were found to be dependent on both the structure of the substrate and the aldehyde used, it was not clear whether the acid has a significant role in dictating the stereochemical outcome. Diastereoselectivities were measured by ^{19}F -NMR in all cases.

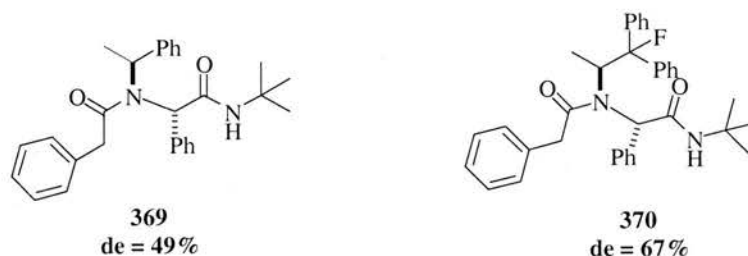


Figure 5.2 Diastereoselectivity studies between **369** and **370**.

A direct comparison of phenylethylamide **369** and alanine derived amide **370**, where both the acid moiety and the aldehyde are kept unchanged, showed a significant difference in diastereoselection. It was clear from these studies that the more bulky substrate has greater influence on the stereo-control. Thus phenylethylamide **369** was afforded in 49% de whereas **370** was recovered in 67% de (figure 5.2).

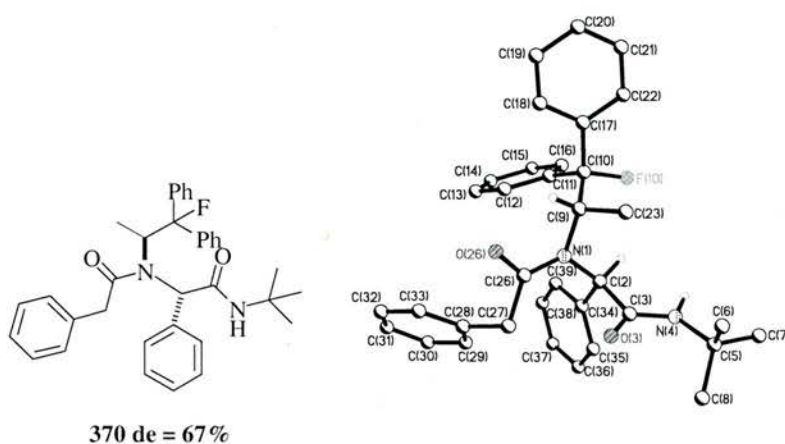


Figure 5.3 X-ray structure and ORTEP drawing of the major diastereoisomer **370**.

The diastereomeric mixture of **370** was successfully separated and the major diastereoisomer analysed by X-ray diffraction to reveal the absolute configuration of the newly formed stereogenic centre as (*S,S'*).

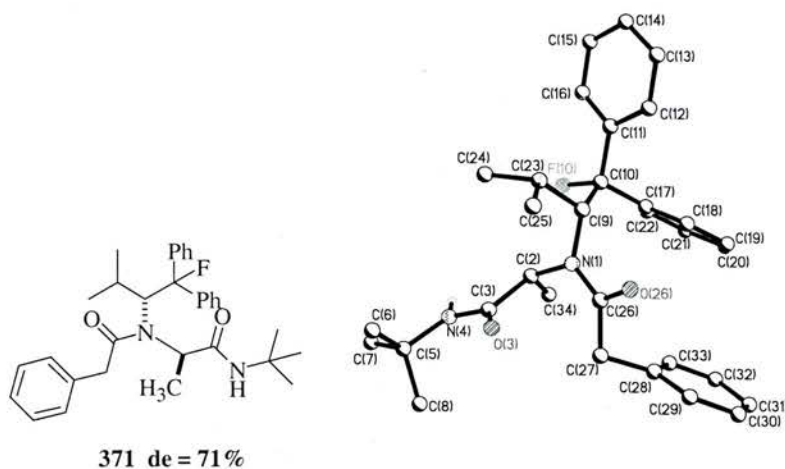


Figure 5.4 X-ray structure and ORTEP drawing of the major diastereoisomer **371**.

From the structure in figure 5.4 it is clear that the reaction proceeds in such a way that the methyl group (from acetaldehyde) is opposite to the isopropyl group from the amine

moiety. The reaction proceeded with a 71% de. The two phenyl rings of the benzhydryl moiety are aligned perpendicular to each other. The absolute configuration of products **371-375** (figure 5.4) was assumed to have the same stereochemistry by analogy.

Crytallographic data on products **370** and **371** (figures 5.3 and 5.4) revealed that the C-F and the C-N(CO) bonds preferred the *gauche* rather than *anti* conformation to each other. The (CO)-N(1)-C(9)-C(10)-F(10) in **370** and **371** indicated a dihedral angle of $-82.5(3)^\circ$ and $62.06(18)^\circ$ respectively. This observation is in agreement with literature reports^{32, 33} which indicate that *N*- β -fluoroethylamides have more stable C-F and C-N(CO) *gauche* rather than the *anti* conformations.

Some more Ugi reactions on valine derived amines were also carried out. Although there are numerous possible permutations in these reactions, by changing the reactants, this study was directed to exemplifying the synthetic utility of the Onyx amines, and particularly the amines that possess the fluorobenzhydryl moieties, as this is a novel motif.

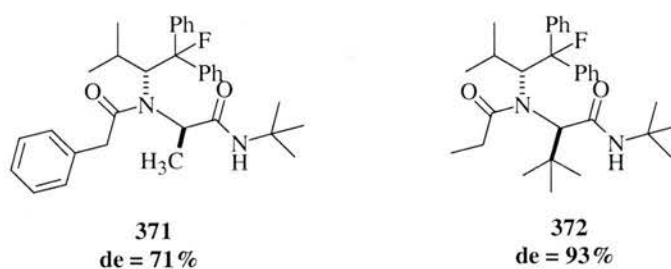
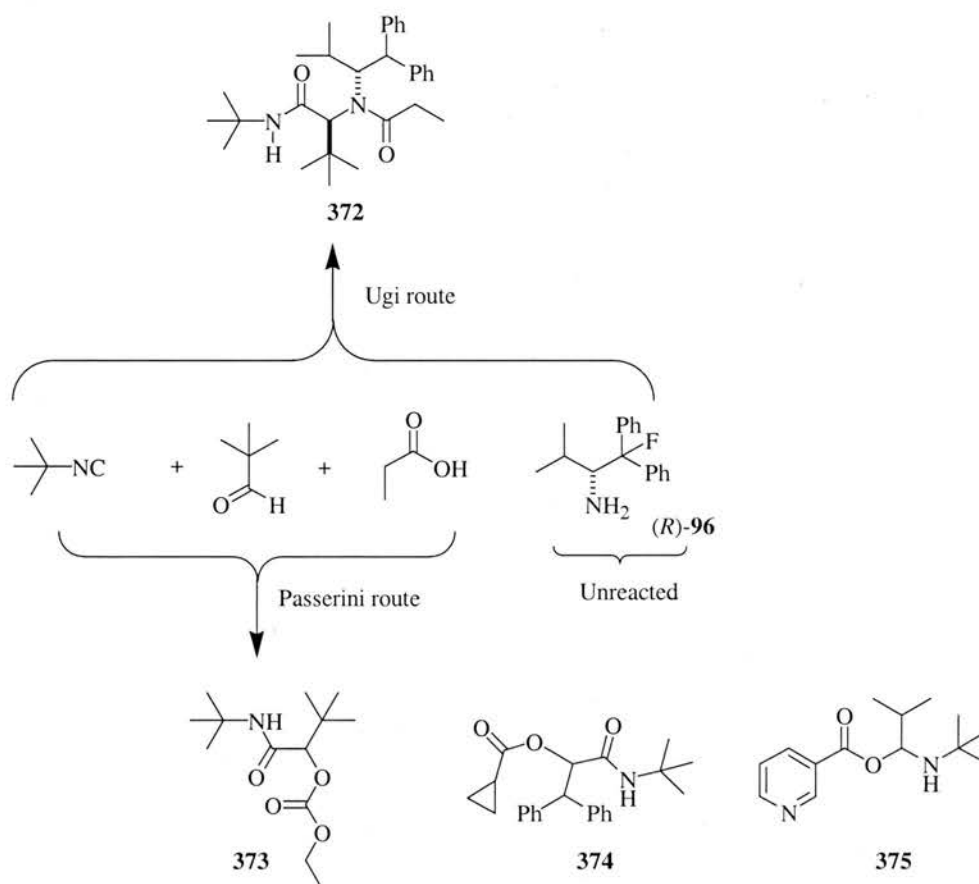


Figure 5.5 Diastereoselectivities on selected Ugi products **371** and **372**.

The stereoselectivity of these reactions were measured by ^{19}F -NMR from the crude product. In some cases, the diastereoisomers were successfully separated by chromatography and the absolute stereochemistry determined by X-ray analysis. The synthesis of **372** which utilised the bulky aldehyde pivaldehyde, gave the highest diastereoselectivity (93% de), but with a low conversion (40% yield). The reaction, however, proceeds more efficiently to form the Passerini product **373** (scheme 5.7) Other bulky aldehydes that were investigated such as diphenylacetaldehyde and isobutyraldehyde also gave the Passerini products **374** and **375** respectively as the predominant products. Precondensation of the amine and aldehyde did not solve this

problem, since these aldehydes react relatively slowly with the amine (*R*)-**96** even when in the presence of a Lewis acid (zinc chloride).



Scheme 5.9

It has been demonstrated that high diastereoselectivities can be obtained with chiral amines (**95**, (*R*)-**96** and **326**) in Ugi MCR's, however, the choice of the aldehyde is critical in achieving high stereoselectivity, since bulky aldehydes tend to favour the Passerini reaction. These were isolated and fully characterised as racemates.

5.4 Summary

In most cases, the Ugi reactions occurred smoothly affording the products with satisfactory yields and with moderate to high diastereo-control. Based on the stereochemical studies, it was clear that the both the structures of the chiral amine and the aldehyde influence stereo-control. It was not immediately clear whether or not the acid and the isonitrile participate in stereoinduction, as these were not investigated as such. In general the Onyx amines explored in this study gave higher %de's than that of the widely used amine, phenylethylamine. Further investigations and optimisation are still necessary and studies with chiral isocyanides derived from Onyx amines remains to be undertaken.

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6 Experimental.

Air- and moisture sensitive reactions were carried out under a positive pressure of nitrogen in oven-dried (200 °C) glassware. Room temperature (rt) refers to 20-25 °C. Evaporations were carried out under reduced pressure on a Büchi rotary evaporator. All reagents were of synthetic grade and were used without further purification. Solvents and reagents were dried according to standard methods prior to use.

Optical rotations were measured using an Optical Activity AA-1000 polarimeter as solutions in dichloromethane (CH₂Cl₂). Specific rotations are given in units of 10⁻¹ deg.cm².g⁻¹. High-resolution mass spectra were recorded on VG AUTOSPEC and VG PLATFORM spectrometers. Carbon, hydrogen and nitrogen analyses were obtained using a CE Instrument EA 1110 CHNS analyser.

Infrared spectra were recorded on a Perkin Elmer 2000 FTIR instrument as a thin layer between NaCl disks. Solid materials were prepared with KBr pellets. Values were rounded to 5 cm⁻¹. Melting points were measured on a Gallenkamp Griffin MPA350.BM2.5 melting point apparatus.

Nuclear magnetic resonance (NMR) spectra were measured in CDCl₃ solutions on a Bruker Av-300.00 (7.0T) operating at 300.00 MHz for ¹H, 75.45 MHz for ¹³C and 282.4 MHz for ¹⁹F, and Varian Unity Plus 300 MHz operating at 300.00 MHz for ¹H, 75.43 MHz for ¹³C. All chemical shifts are reported as δ values down-fielded from (CH)₄Si using CDCl₃ as internal standard (δ_H 7.24 or δ_C 77.00 ppm, for ¹H and ¹³C, respectively) and CFCl₃ (0.00 ppm) for ¹⁹F. All coupling constants (J) are given in Hertz (Hz). Spectral coupling patterns are designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; br: broad signal. 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) (H, ¹H) homonuclear chemical shift correlation (COSY) and NOESY (Nuclear Overhauser Exchange Spectroscopy) experiments. The ¹³C chemical shifts were obtained from proton-

decoupled spectra. Standard Bruker pulse sequence programs were used in these experiments.

Reaction progress was monitored by thin-layer chromatography (TLC) using glass plates coated with silica gel 60 F₂₅₄ (Merck). Plates were visualised under UV light (254 and 366 nm). Column chromatography was performed on Merck silica gel 60 (60-200 μm , 70-230 mesh).

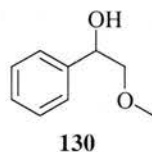
Standard work-up procedure: The reaction mixture was quenched with water and the aqueous layer extracted into diethyl ether (3 x). The organics were dried over MgSO_4 , filtered and concentrated under reduced pressure.

(*): Denotes minor diastereoisomer whenever identifiable.

6.1. Procedures.

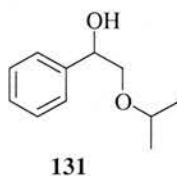
6.1.1. General Procedure A: preparation of 2-methoxy-1-phenylethanol.

6.1.1.1. 2-Methoxy-1-phenylethanol **130**¹



Sodium hydride (60% suspension, 790 mg, 19.9 mmol) after being washed (3x) times with hexane (2.0 cm³) was added portion-wise to a flask containing dry methanol (60 cm³). After hydrogen evolution had ceased, styrene oxide (2.0 g, 16.6 mmol) was added and the reaction mixture heated to 60 °C for 10 h. Methanol was evaporated and the residue partitioned between water (50 cm³) and ether (20 cm³). The ethereal layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product (2.51 g, 99%) was purified over silica gel using EtOAc-hexane (1:4) to achieve the major regioisomer (1.7 g, 67%) as a colourless oil; $\nu_{\max}/\text{cm}^{-1}$ 3425, 2893, 1453, 1195, 1120; δ_{H} 3.22 (1 H, br, OH), 3.23 (3 H, s, OCH₃), 3.35 (1 H, dd, J 8.8, 9.9, CH₂OCH₃), 3.45 (1 H, dd, J 3.3, 9.9, CH₂OCH₃), 4.79 (1 H, dd, J 3.3, 8.8) and 7.19-7.28 (5 H, m, Ph), δ_{C} 59.4 (OCH₃), 73.0 (PhCH), 78.6 (CH₂OCH₃), (126.5, 128.2, 128.9 and 140.7 (aromatic carbons); MS (CI) *m/z* (rel. int.): 152 [M]⁺ (7), 135 (100), 121 (7) and 107 (8).

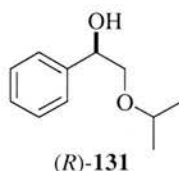
6.1.1.2. 2-Isopropoxy-1-phenylethanol **131**¹



Prepared according to the general procedure A from styrene oxide (1.0 g, 8.33 mmol); sodium hydride (433 mg, 10.8 mmol) and isopropanol (20 cm³) to provide the title compound as colourless oil (1.35 g, 90%); $\nu_{\max}/\text{cm}^{-1}$ 3459, 2973, 1755, 1453, 1199, 1129; δ_{H} 1.21 [3 H, d, J 6.0, OCH(CH₃)₂], 1.22 [3 H, d, J 6.0, OCH(CH₃)₂], 2.99 (1 H, br s, OH), 3.39 [1 H, m, OCH(CH₃)₂], 3.62 [1 H, dd, J 3.1, 9.6, CH₂OCH(CH₃)₂], 3.69,

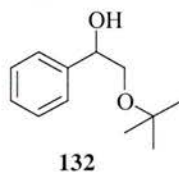
[1 H, dd, J 6.1, 9.6, $\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 4.86 (1 H, dd, J 3.1, J 6.1, PhCH) and 7.27-7.42 (5 H, m, Ph), δ_{C} 21.9 [$\text{OCH}(\text{CH}_3)_2$], 72.1 [$\text{OCH}(\text{CH}_3)_2$], 73.7 (PhCH), 73.8 [$\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 126.0, 127.6, 128.2 and 140.3 (aromatic carbons); MS (CI) m/z (rel. int.): 163 (100) and 121 (30).

6.1.1.3. *2(R)-Isopropoxy-1-phenylethanol (R)-131*



Prepared from (*R*)-styrene oxide (866 mg, 7.22 mmol), NaH (347 mg, 8.66 mmol) and isopropanol (20 cm³) to give the title compound as a colourless oil (1.20g, 92%); $[\alpha]_{\text{D}}^{20} = -71.1$ (*c* 0.65, CH_2Cl_2), IR, NMR and MS same as of **131** above.

6.1.1.4. *2-Tert-Butoxy-1-phenylethanol 132*²

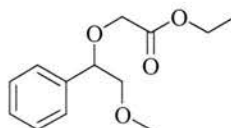


Prepared according to the general procedure A from styrene oxide (966 mg, 8.04 mmol); sodium hydride (418 mg, 10.4 mmol) and *tert*-butanol (20 cm³) to provide the title compound in yield as colourless oil (1.06 g, 68%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3452, 2975, 1453, 1364, 1199; δ_{H} 1.13 [9 H, s, $\text{OC}(\text{CH}_3)_3$], 3.02 (1 H, br s, OH), 3.24 [1 H, dd, J 9.0, 9.2, $\text{CH}_2\text{OC}(\text{CH}_3)_3$], 3.43 [1 H, dd, J 3.1, 9.0, $\text{CH}_2\text{OC}(\text{CH}_3)_3$], 4.71 (1 H, dd, J 3.1, 9.2, PhCH), 7.19-7.33 (5 H, m, Ph), δ_{C} 27.5 [$\text{OC}(\text{CH}_3)_3$], 67.8 [$\text{CH}_2\text{OC}(\text{CH}_3)_3$], 73.1 (PhCH), 73.5 [$\text{OC}(\text{CH}_3)_3$], (126.1, 127.6, 128.2 and 140.5 (aromatic carbons), MS (EI) m/z (rel. int.): 216.8 [$\text{M}+\text{Na}$]⁺ (100).

6.1.2. General Procedure B: Preparation of 2-alkoxy-1-phenylethoxy esters
124-126

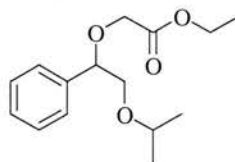
Sodium hydride (1.2 eq) was added to a stirred solution of 2-alkoxy-1-phenylethanol **124-126** (1.0 eq) in THF (20 cm³). After 15 min, ethyl iodoacetate (1.2 eq) was added and the reaction stirred for a further 5 h at rt. The products were isolated following the standard work-up procedure. The residue was purified over silica gel EtOAc-hexane (1:4) to furnish the title compound as colourless oil.

6.1.2.1. Ethyl (2-methoxy-1-phenylethoxy) acetate **124**

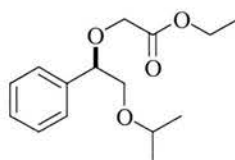


124

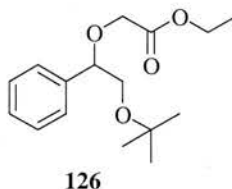
Prepared as above as prescribe in general procedure B from **130** (810 mg, 5.32 mmol), sodium hydride (255 mg, 6.4 mmol) and ethyl iodoacetate (1.37 mg, 6.14 mmol) in THF (20 cm³) to furnish the title compound as a colourless oil (980 mg, 77%); HRMS (CI) Calc. for C₁₃H₁₉O₄: 239.1295, Found 239.1283; $\nu_{\max}/\text{cm}^{-1}$ 2983, 1754, 1453, 1306, 1202 1130; δ_{H} 1.16 (3 H, t, J 7.2, OCH₂CH₃), 3.33 (3 H, s, OCH₃), 3.42 (1 H, dd, J 3.4, 10.7, CH₂OCH₃), 3.65 (1 H, dd, J 7.9, 10.7, CH₂OCH₃), 3.89 (1 H, d, J 16.4, OCH₂CO), 4.02 (1 H, d, J 16.4, OCH₂CO), 4.08 (2 H, m, OCH₂CH₃), 4.62 (1 H, dd, J 3.4, 7.9, PhCH) and 7.26-7.28 (5 H, m, Ph), δ_{C} 14.5 (OCH₂CH₃), 59.5 (OCH₃), 61.1 (OCH₂CH₃), 66.5 (OCH₂CO), 77.5 (CH₂OCH₃), 81.7 (PhCH), 127.5, 128.7, 128.9 and 138.4 (aromatic carbons) and 170.6 (C=O), MS (CI) m/z (rel. int.): 239 [MH]⁺ (8), 207 (20), 207 (25) and 135 (100).

6.1.2.2. Ethyl (2-isopropoxy-1-phenylethoxy)acetate **125****125**

Prepared as described under general procedure B utilising 2-isopropoxy-1-phenylethanol **131** (370 mg, 2.05 mmol); sodium hydride (120 mg, 3.08 mmol) and ethyl iodoacetate (520 mg, 246 mmol) in THF (10 cm³) to afford the title compound (400 mg, 73%) as a colourless oil; HRMS (CI) Calc. for C₁₅H₂₃O₄: Calc. 267.1596, Found 267.1603; $\nu_{\max}/\text{cm}^{-1}$ 2974, 1756, 1453, 1380, 1202, 1130; δ_{H} 1.04 [3 H, d, J 6.1, OCH(CH₃)₂], 1.08 [3 H, d, J 6.0, OCH(CH₃)₂], 1.17 (3 H, t, 7.2, OCH₂CH₃), 3.47 [1 H, dd, J 4.1, 10.6, CH₂OCH(CH₃)₂], 3.68 [1 H, dd, J 7.4, 10.6, CH₂OCH(CH₃)₂], 3.92 (1 H, d, J 16.4, OCH₂CO), 4.06 (1 H, d, J 16.4, OCH₂CO), 4.10 (2 H, q, 7.2, OCH₂CH₃), 4.54 (1 H, dd, J 4.1, 7.4, PhCH) and 7.19-7.29 (5 H, m, Ph); δ_{C} 14.1 (OCH₂CH₃), 21.9 [OCH(CH₃)₂], 22.0 [OCH(CH₃)₂], 60.6 (OCH₂CH₃), 66.5 (OCH₂CO), 72.1 [OCH(CH₃)₂], 72.7 [CH₂OCH(CH₃)₂], 82.0 (PhCH), 127.1, 128.0, 128.3 and 138.6 (aromatic carbons) and 170.3 (C=O); MS (CI) m/z (rel. int.): 267 [MH]⁺ (13), 193 (22), 163 (100) and 121 (45).

6.1.2.3. Ethyl (2*R*-isopropoxy-1-phenylethoxy)acetate (*R*)-**125***(R)*-**125**

The procedure was repeated using (*R*)-**131**, the product was recovered as a colourless oil (700 mg, 90%) [α]_D²⁰ = -48.0 (*c* 0.10, CH₂Cl₂), IR, NMR and MS same as **125** above.

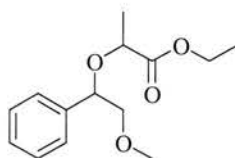
6.1.2.4. Ethyl (2-*tert*-butoxy-1-phenylethoxy)acetate **126**

The product was prepared as described under general procedure B utilising 2-*tert*-butoxy-1-phenylethanol **132** (160 mg, 0.823 mmol); sodium hydride (43 mg, 1.07 mmol) and ethyl iodoacetate (229 mg, 1.07 mmol) in THF (10 cm³) to afford the title compound as colourless oil (168 mg, 73%); HRMS (CI) Calc. for: C₁₆H₂₅O₄: 281.1753, Found 281.1755; $\nu_{\max}/\text{cm}^{-1}$ 2976, 1732, 1307, 1198, 1133; δ_{H} 1.12 [9 H, s, OC(CH₃)₃], 1.24 (3 H, t, J 7.2, OCH₂CH₃), 3.47 [1 H, dd, J 4.6, 9.9, CH₂OC(CH₃)₃], 3.71 [1 H, dd, J 6.9, 9.9, CH₂OC(CH₃)₃], 4.05 (1 H, d, J 16.4, OCH₂CO), 4.17 (1 H, d, J 16.4, OCH₂CO), 4.26, (2 H, q, J 7.2, OCH₂CH₃), 4.54 (1 H, dd, J 4.6, 6.9, PhCH), 7.03-7.36 (5 H, m, Ph); δ_{C} 14.1 (OCH₂CH₃), 27.3 [OC(CH₃)₃], 60.5 (OCH₂CH₃), 66.8 [CH₂OC(CH₃)₃], 67.9 (OCH₂CO), 73.1 [OC(CH₃)₃], 82.3 (PhCH), 127.1, 128.0, 128.2 and 139.0 (aromatic carbons), 170.4 (C=O); MS (CI) *m/z* (rel. int.): 281 [MH]⁺ (23), 259 (100), 255 (66), 207 (10) and 121 (10).

6.1.3. General Procedure C: Preparation of methylated 2-alkoxy-1-phenylethoxy esters **101-103**

LDA (2 M in THF) was slowly added to a solution of ethyl (2-alkoxy-phenylethoxy) acetate **124-126** (1.0 eq) in THF (3.0 cm³) at -78 °C. The solution was stirred for 30 min before methyl iodide (1.2 eq) was introduced. The reaction was allowed to warm-up to rt for 12 h. Isolation of the products followed the standard work-up procedure and subsequent preparative TLC purified the products as colourless oils.

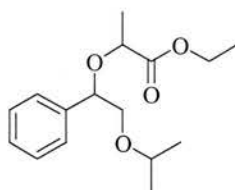
6.1.3.1. Ethyl 2-(2-methoxy-1-phenylethoxy) propanoate **101**



101

The product was prepared according to the general procedure C from LDA (2 M) (49.5 mg, 0.462 mmol), ethyl (2-methoxy-phenylethoxy) acetate **124** (100 mg, 420 mmol) and methyl iodide (72 mg, 0.507 mmol) in THF (3.0 cm³) at -78 °C. The crude product was then purified tlc eluting EtOAc-hexane (1:6). The product was isolated as a colourless oil (75 mg, 68%); HRMS (CI) Calc. for C₁₄H₂₀O₄: 253.3062, Found 253.3059; $\nu_{\max}/\text{cm}^{-1}$ 2974, 1747, 1454, 1368, 1200, 1126, 912; δ_{H} 1.22 (3 H, t, J 7.2, OCH₂CH₃), 1.31 and 1.37* (3 H, d, J 6.9, OCHCH₃), 3.32 (3 H, s, OCH₃), 3.38 (1 H, dd, J 4.1, 10.5, CH₂OCH₃), 3.63 (1 H, dd, J 7.2, 10.5, CH₂OCH₃), 3.81 (1 H, q, J 6.9, OCHCH₃), 4.13 (2 H, t, J 7.2, OCH₂CH₃), 4.58 (1 H, dd, J 4.1, 7.2, PhCH) and 7.26-7.27 (5 H, m, Ph), δ_{C} 14.2 (CH₂CH₃), 18.2* and 19.0 (OCHCH₃), 59.1 (OCH₃), 60.7 (OCH₂CH₃), 72.3 (OCHCH₃), 74.2 (CH₂OCH₃), 80.3 and 80.9* (PhCH), 127.1, 128.2, 128.5 and 138.9 (aromatic carbons) and 172.2 (C=O); MS (CI) m/z (rel. int.): 253 [MH]⁺ (338) and 193 (100).

6.1.3.2. Ethyl 2-(2-isopropoxy-1-phenylethoxy)propanoate **102**

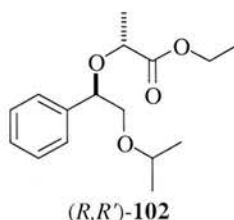


102

The product was prepared according to the general procedure C from **125** (83 mg, .0312 mmol); LDA (2 M) (36.7 mg, 0.343 mmol); methyl iodide (49 mg, 0.343 mmol) in THF (5.0 cm³) to furnish the title compound as a colourless oil (74 mg, 85%); HRMS (CI) Calc. for C₁₆H₂₅O₄: 281.1753, Found 281.1762; $\nu_{\max}/\text{cm}^{-1}$ 2973, 1748, 1454, 1369,

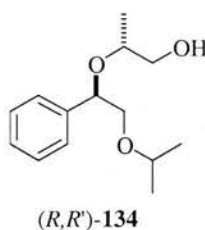
1127; δ_{H} 0.99 [3 H, d, J 6.1, $\text{OCH}(\text{CH}_3)_2$], 1.04 [3 H, d, J 6.1, $\text{OCH}(\text{CH}_3)_2$], 1.21 (3 H, t, J 7.2, OCH_2CH_3), 1.28 and 1.39* (3 H, d, J 6.9, OCHCH_3), 3.41 [1 H, dd, J 5.4, 10.5, $\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 3.46 [1 H, dd, J 5.4, 10.5, $\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 3.50 [1 H, dd, J 6.1, 10.5, $\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 3.84 (1 H, q, J 6.9, OCHCH_3), 4.13 (2 H, q, J 7.2, OCH_2CH_3), 4.48 (1 H, dd, J 5.4, PhCH) and 7.24-7.27 (5 H, m, Ph), δ_{C} 13.6* and 14.2 (OCH_2CH_3), 18.3* and 19.0 (OCHCH_3), 21.9 [$\text{OCH}(\text{CH}_3)_2$], 60.6 (OCH_2CH_3), 72.4 [$\text{OCH}(\text{CH}_3)_2$], 72.5 [$\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 72.5 (OCH_2CH_3), 80.9 and 81.4* (PhCH), 127.1, 127.9, 128.3 and 139.5 (aromatic carbons) and 173.3 ($\text{C}=\text{O}$); de = 88%; MS (CI) m/z (rel. int.): 281 $[\text{MH}]^+$ (5), 207 (10), 163 (75), 121 (22) and 58 (100).

6.1.3.3. Ethyl (2*R*)-2-[(1*R*)-2-isopropoxy-1-phenylethoxy]propanoate (*R,R'*)-**102**



The product was prepared from (*R*)-**125** following general procedure B, to give (*R,R'*)-**102** (215 mg, 87%) as colourless oil; $[\alpha]_{\text{D}}^{20} = -82.8$ (*c* 0.83, CH_2Cl_2), IR, NMR and MS same as **102** above.

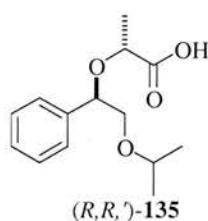
6.1.3.4. (2*R*)-2-[(1*R*)-2-Isopropoxy-1-phenylethoxy]propan-1-ol, (*R,R'*)-**134**



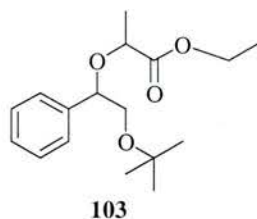
A solution of (*R,R'*)-**102** (180 mg, 0.642 mmol) in THF (5 cm^3) was introduced to a flask containing a suspension of lithium aluminium hydride (24 mg, 0.642 mmol) in THF (10 cm^3). The mixture was refluxed for 16 h before being quenched with ethyl acetate and water. Filtration afforded the product (*R,R'*)-**134** (153 mg, 100%) as a

colourless oil; HRMS (CI) Calc. for $C_{14}H_{23}O_3$: 239.1647, Found 239.1647; $\nu_{\max}/\text{cm}^{-1}$ δ_{H} 1.06 (3 H, d, J 6.1, CH_3), 1.20 [3 H, d, J 6.1, $\text{OCH}(\text{CH}_3)_2$], 1.22 [3 H, d, J 5.9, $\text{OCH}(\text{CH}_3)_2$], 3.46-3.56 (3 H, m, CH_2OH , OCHCH_3), 3.61-3.75 [3 H, m, $\text{OCH}(\text{CH}_3)_2$, $\text{CH}_2\text{OCH}(\text{CH}_3)_2$], 4.72 (1 H, dd, J 3.6, 9.0, PhCH), 7.28-7.38 (5 H, m, Ph); δ_{C} 18.0 (CHCH_3), 21.7 [$\text{OCH}(\text{CH}_3)_2$], 21.9 [$\text{OCH}(\text{CH}_3)_2$], 67.1 (CH_2OH), 72.5 [$\text{OCH}(\text{CH}_3)_2$], 73.6 [$\text{OCH}(\text{CH}_3)_2$], 77.6 (OCHCH_3), 82.3 (PhCH), 126.3, 127.7, 128.3 and 140.0 (aromatic carbons); MS (CI) m/z (rel. int.): 239 (12) and (100).

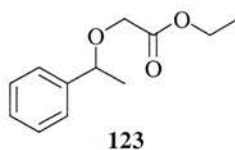
6.1.3.5. (2*R*)-2-[(1*R*)-2-isopropoxy-1-phenylethoxy]propanoic acid (*R,R'*)-**135**



Propanol (*R,R'*)-**134** (130 mg, 0.545 mmol) was treated with Jones reagent [CrO_3 , H_2SO_4 (50%), acetone: water (3:1)] over 5 h. Isopropanol was added to the mixture and the product was isolated following a standard work-up procedure to give (*R,R'*)-**135** (132 mg, 96%) as a colourless oil. Treatment of the product with morpholine (95 μl , 1.09 mmol) in hexane (10 cm^3) afforded (*R,R'*)-**133** as crystalline solid. Analytical data for (*R,R'*)-**135**; HRMS (CI) Calc. for: $C_{14}H_{20}O_4\text{Na}$: Calc. 275.1259, Found 275.1255; $\nu_{\max}/\text{cm}^{-1}$ 3185, 2973, 2933, 1759, 1454, 1371, 1334, 1119, 1064; δ_{H} 1.24 [3 H, d, J 6.1, $\text{OCH}(\text{CH}_3)_2$], 1.27 [3 H, d, J 6.1, $\text{OCH}(\text{CH}_3)_2$], 1.45 (3 H, d, J 6.9, OCHCH_3), 3.50-3.61 (2 H, m, OCH_2CH), 3.79 [1 H, sextet, J 6.1, $\text{OCH}(\text{CH}_3)_2$], 3.99 (OCHCH_3), 4.47 (1 H, dd, J 3.8, 9.2, PhCH), 7.31-7.42 (5 H, m, Ph); δ_{C} 19.4 (OCHCH_3), 21.6 [$\text{OCH}(\text{CH}_3)_2$], 21.7 [$\text{OCH}(\text{CH}_3)_2$], 72.1 [$\text{OCH}_2\text{CH}(\text{CH}_3)_2$], 73.2 [$\text{OCH}(\text{CH}_3)_2$], 75.0 (OCHCH_3), 82.9 (PhCH), 126.4, 128.7 and 136.9 (aromatic carbons), 174.8 ($\text{C}=\text{O}$); MS (LCTOF) m/z (rel. int.): 275 [$\text{MH}+\text{Na}$]⁺ (100).

6.1.3.6. Ethyl 2-(2-tert-butoxy-1-phenylethoxy)propanoate **103**

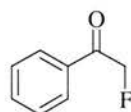
Product **103** was prepared according to the general procedure C from **126** (83 mg, 0.312 mmol); LDA (2 M) (36.7 mg, 0.343 mmol) and methyl iodide (49 mg, 0.343 mmol) in THF (5.0 cm³) to furnish the title compound (74 mg, 85%) as colourless oil; HRMS (CI) Calc. for: C₁₇H₂₇O₄: Calc. 295.1910, Found 295.1919; $\nu_{\max}/\text{cm}^{-1}$ 2974, 1736, 1450, 1377, 1198; δ_{H} 0.99 and 1.07* [9 H, s, OC(CH₃)₃], 1.22 (3 H, t, J 7.2, OCH₂CH₃), 1.28 and 1.36* (3 H, d, J 6.9, OCHCH₃), 3.36 (1 H, dd, J 4.4, 9.5, CH₂OCH₃), 3.65 [1 H, dd, J 7.7, 9.5, CH₂OC(CH₃)₃], 3.87 (1 H, q, J 6.9, OCHCH₃), 4.14 (2 H, q, J 7.2, OCH₂CH₃), 4.45 (1 H, dd, J 4.4, 7.7, PhCH) and 7.24-7.27 (5 H, m, Ph); δ_{C} 13.8* and 14.0 (OCH₂CH₃), 18.2* and 18.8 (OCHCH₃), 27.2* and 27.1 (OC(CH₃)₃), 60.3* and 60.4 (OCH₂CH₃), 66.3 and 67.3* (CH₂OCH₃), 72.5 and 72.9* [OC(CH₃)₃], 74.4* (OCHCH₃), 81.0 and 81.2* (PhCH), 126.7*, 127.0, 127.4*, 127.6, 127.8*, 127.9 and 139.6*, 139.7 (aromatic carbons) and 173.2 (C=O). MS (CI) m/z (rel. int.): 295 [MH]⁺ (48), 239 (91), 207 (46), 177 (57) and 119 (100).

6.1.3.7. Ethyl (1-phenylethoxy)acetate **123**²

Product **123** was prepared following general procedure B from 1-phenylethanol (500 mg, 4.09 mmol); sodium hydride (150 mg, 6.14 mmol) and ethyl iodoacetate (1.14g, 5.33 mmol) in THF (15 cm³) to afford the title compound as a colourless oil (830 mg, 98%); HRMS (EI) Calc. for C₁₂H₁₆O₃ + Na: 231.0997, Found 231.1001; $\nu_{\max}/\text{cm}^{-1}$ 2981, 1754, 1452, 1133, 1119; δ_{H} 1.25 (3 H, t, J 7.2, OCH₂CH₃), 1.52 (3 H, d, J 6.4,

OCHCH₃), 3.87 (1 H, d, J 16.4, OCH₂CO), 3.96 (1 H, d, J 16.4, OCH₂CO), 4.18 (1 H, q, J 7.2, OCH₂CH₃), 4.56 (1 H, q, J 6.4, PhCH) and 7.32-7.35 (5 H, m, Ph), δ_{C} 14.0 (OCH₂CH₃), 23.7 (OCHCH₃), 60.6 (OCH₂CH₃), 65.7 (OCH₂CO), 78.4 (PhCH), 126.3, 127.7, 128.4 and 142.3 (aromatic carbons) and 170.4 (C=O); MS (EI) m/z (rel. int.): 230.8 [M+Na]⁺ (100).

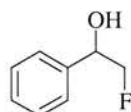
6.1.3.8. 2-Fluoro-1-phenylethanone **136**³



136

A solution of poly(hydrogen fluoride) (70/30) in pyridine (3.0 cm³) was added to an ethereal solution of 2-oxo-2-phenyldiazothane at -15 °C, prepared *in situ* from benzoyl chloride (1.0 g, 7.11 mmol) and diazomethane. The reaction was allowed to warm to rt and was stirred for 4 h. Water (100 cm³) was added and after separation of the two phases, the aqueous layer was extracted into hexane (3x 25 cm³). The organics were treated with anhydrous potassium fluoride until neutral to litmus, dried over MgSO₄ and concentrated under reduced pressure. Purification over silica gel provided α -fluoroacetophenone **136** as a colourless oil (386 mg, 39%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3065, 2938, 1707, 1598, 1451, 1318, 1286, 1234, 1089; δ_{H} 5.54 (2 H, d, J 46.8, CH₂F), 7.46-7.96 (5 H, m, Ph), δ_{C} 83.7 (d, J 182.4, CH₂F), 127.7, 128.8, 128.4 and 134.1 (aromatic carbons) and 193.3 (d, J 15.3, CO), δ_{F} -231.5 (t, J 46.8); MS (EI) m/z (rel. int.): 160.6 [M+Na]⁺ (100).

6.1.3.9. 2-Fluoro-1-phenylethanol **137**⁴

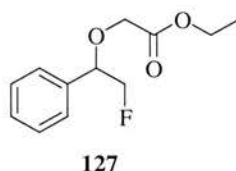


137

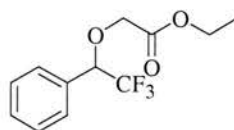
Alcohol **137** was prepared from 2-fluoro-1-phenylethanone **136** (300 mg, 2.14 mmol), and sodium borohydride (240 mg, 6.42 mmol) in CH₃OH (20 cm³) to give the title

compound (301 mg, 99%) as a colourless oil; $\nu_{\max}/\text{cm}^{-1}$ 3406, 2893, 1495, 1454, 1101, 1012; δ_{H} 2.58 (1 H, br s, OH), 4.32 (1 H, ddd, J 8.0, 9.6, 46.7, CH_2F), 4.41 (1 H, ddd, J 3.3, 9.6, 46.7, CH_2F), 4.91 (1 H, ddd, J 3.3, 8.0, 14.3, PhCH) and 7.23-7.30 (5 H, m, Ph); δ_{C} 72.9 (d, J 19.9, PhCH), 87.1 (d, J 174.2, CH_2F), 126.3, 128.3, 128.6 and 138.2 (aromatic carbons); δ_{F} -220.8 (dt, J 14.3, 46.7); MS (EI) m/z (rel. int.): 163.1 $[\text{M}+\text{Na}]^+$ (100).

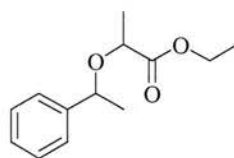
6.1.3.10. Ethyl (2-fluoro-1-phenylethoxy)acetate **127**



Ester **127** was prepared according to general procedure B from 2-fluoro-1-phenylethanol **137** (260 mg, 1.86 mmol); sodium hydride (211 mg, 5.58 mmol) and ethyl iodoacetate (596 mg, 279 mmol) in THF (10 cm^3). The product was recovered as a colourless oil (319 mg, 76%); HRMS (CI) Calc. for $\text{C}_{12}\text{H}_{16}\text{FO}_3$: 227.1083, Found 227.1080; $\nu_{\max}/\text{cm}^{-1}$ 2983, 1755, 1455, 1135; δ_{H} 1.17 (3 H, t, J 7.2, CH_2CH_3), 3.92 (1 H, d, J 16.4, OCH_2CO), 4.05 (1 H, d, J 16.4, OCH_2CO), 4.10 (2 H, q, J 7.2, CH_2CH_3), 4.38 (1 H, ddd, J 3.6, 9.7, 46.9, CH_2F), 4.52 (1 H, ddd, J 7.4, 9.7, 46.9, CH_2F), 4.71 (1 H, ddd, J 3.6, 7.4, 15.1, PhCH) and 7.50-7.31 (5 H, m, Ph); δ_{C} 14.0 (OCH_2CH_3), 60.7 (OCH_2CH_3), 66.1 (OCH_2CO), 80.8 (d, J 19.6, PhCH), 85.5 (d, J 173.5, CH_2F), 127.2, 128.6, 128.7 and 135.7 (aromatic carbons) and 169.9 (C=O); δ_{F} -220.9 (dt, J 15.1, 46.9), MS (CI) m/z (rel. int.): 227 $[\text{MH}]^+$ (82), 206 (16), 123 (63) and 105 (100).

6.1.3.11. Ethyl (2,2,2-trifluoro-1-phenylethoxy)acetate **128**⁵**128**

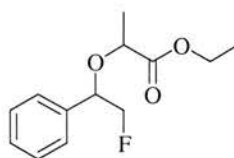
Ester **128** was prepared according to the general procedure B from 2,2,2-trifluoro-1-phenylethanol (200 mg, 1.14 mmol); ethyl iodoacetate (360 mg, 1.71 mmol) and sodium hydride (55 mg, 2.28 mmol) in THF (10 cm³) to provide the ethyl trifluoroacetate (240 mg, 80%) as a colourless oil; HRMS (CI) Calc. for C₁₅H₁₃FO₂: 263.0884, Found 263.0884; $\nu_{\max}/\text{cm}^{-1}$ 2987, 1754, 1381, 1268, 1128; δ_{H} 1.25 (3 H, t, J 7.2, OCH₂CH₃), 4.03 (1 H, d, J 16.4, OCH₂CO), 4.19 (1 H, q, J 7.2, OCH₂CH₃), 4.21 (1 H, d, J 16.4, OCH₂CO), 4.94 (1 H, q, J 6.4, PhCH) and 7.40-7.43 (5 H, m, Ph), δ_{C} 14.0 (OCH₂CH₃), 61.1 (OCH₂CH₃), 66.0 (OCH₂CO), 78.1 (q, J 31.5, PhCH), 127.6 (q, J 281.4, CF₃), 128.4, 128.7, 129.8 and 131.5 (aromatic carbons) and 169.2 (C=O); δ_{F} -76.9 (d, J 6.4, CF₃); MS (CI) m/z (rel. int.): 263 [MH]⁺ (100) and 159 (7).

6.1.3.12. Ethyl 2-(1-phenylethoxy)propanoate **104****104**

Product **104** was prepared as described under general procedure C from ethyl (1-phenylethoxy)acetate **123** (105 mg, 0.504 mmol), LDA (2 M in THF) (64.8 mg, 0.605 mmol) and methyl iodide (79 mg, 0.554 mmol) in THF (3.0 cm³) to provide the ethyl propanoate ester as a colourless oil (78 mg, 70%); HRMS (EI) Calc. for C₁₃H₁₈O₃: 246.2802, Found 246.2715; $\nu_{\max}/\text{cm}^{-1}$ 2983, 1736, 1453, 1377, 1208, 909; δ_{H} 1.09 (3 H, t, J 7.2, OCH₂CH₃), 1.22 and 1.27 (3 H, d, J 6.9, OCHCH₃), 1.42 (3 H, d, J 6.4, PhCHCH₃), 3.92 (1 H, q, J 6.9, OCHCH₃), 4.13 (2 H, q, J 7.2, OCH₂CH₃), 4.82 (1 H, q,

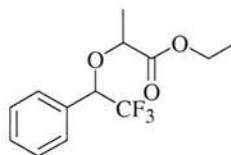
J 6.4, PhCH), 7.18 (5 H, m, Ph); δ_{C} 14.0 and 14.2 (OCH₂CH₃), 18.3 and 18.9 (OCHCH₃), 60.6 and 61.7 (OCH₂CH₃), 71.9 and 72.9 (OCHCH₃), 77.2 and 77.3 (PhCH), 126.2, 127.6, 128.5 and 143.1 (aromatic carbons) 173.7 (C=O); MS (EI) m/z (rel. int.): 246 [M+Na]⁺ (100).

6.1.3.13. Ethyl 2-(2-fluoro-1-phenylethoxy)propanoate **105**

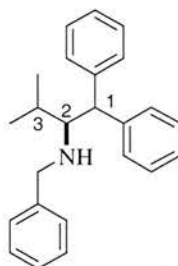


105

Product **105** was prepared according to general procedure C from ethyl (2-fluoro-1-phenylethoxy)acetate **127** (129 mg, 0.570 mmol); LDA (2 M in THF) (67 mg, 0.628 mmol) and methyl iodide (202 mg, 3.56 cm³) in THF (5.0 cm³) to provide the title compound as a colourless oil (79 mg, 58%); HRMS (CI) Calc. for C₁₃H₁₈FO₃: 241.1239, Found 241.1239; $\nu_{\text{max}}/\text{cm}^{-1}$ 2985, 1747, 1455, 1122; δ_{H} 1.13* and 1.29 (3 H, t, J 7.2, OCH₂CH₃), 1.40 and 1.46* (3 H, d, J 6.9, OCHCH₃), 3.92 (1 H, q, J 6.9, OCHCH₃), 4.17* and 4.20 (1 H, q, J 7.2, OCH₂CH₃), 4.44 (1 H, ddd, J 3.8, 9.7, 46.9, CH₂F), 4.57 (1 H, ddd, J 9.7, 10.5, 46.9, CH₂F), 4.74 (1 H, ddd, J 3.8, 10.5, 15.6, PhCH) and 7.32-7.39 (5 H, m, Ph); δ_{C} 14.0* and 14.2 (OCH₂CH₃) 18.2* and 18.9 (CHCH₃); 60.7* and 60.9 (OCH₂CH₃), 72.8 (OCHCH₃), 80.5 (d, J 20.7, PhCH), 85.5 and 86.0* (d, J 177, CH₂F), 127.2, 128.4, 128.7 and 136.6 (aromatic carbons), 172.5* and 172.9 (C=O); δ_{F} -219.1* and -221.6 (dt, J 15.6, 46.9), MS (CI) m/z (rel. int.): 241 [MH]⁺ (82), 220 (12), 123 (57) and 119 (100).

6.1.3.14. Ethyl 2-(2,2,2-trifluoro-1-phenylethoxy)propanoate **106**.**106**

Product **106** was prepared according to the general procedure C from **128** (158 mg, 0.60 mmol), LDA (2 M in THF) (70.9 mg, 0.66 mmol) and methyl iodide (94 mg, 0.66 mmol) in THF (5.0 cm³) to afford the title compound as colourless oil (110 mg, 66%); HRMS (CI) Calc. for C₁₃H₁₆F₃O₃: 277.1052, Found 277.1049; $\nu_{\max}/\text{cm}^{-1}$ 2987, 1754, 1382, 1269, 1127; δ_{H} 1.17 (3 H, t, J 7.2, OCH₂CH₃), 1.36 and 1.42* (3 H, d, J 6.9, OCHCH₃), 3.86 (1 H, q, J 6.9, OCHCH₃), 4.13 (2 H, q, J 7.2, OCH₂CH₃), 4.85 (1 H, q, J_{HF} 6.4, PhCH), 7.18-7.36 (5 H, m, Ph); δ_{C} 13.9 (OCH₂CH₃), 31.0 (OCHCH₃), 61.0 (OCH₂CH₃), 65.9 (OCHCH₃), 79.26 (q, J 31.5, PhCH), 127.1 (q, J 281.4, CF₃), 128.3, 128.4, 128.6 and 131.5 (aromatic carbons), 169.1 (C=O); δ_{F} -76.9 and -78.9 (d, J_{CF} 6.4, CF₃).

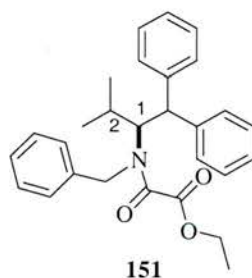
6.1.3.15. (*S*)-*N*-Benzyl-3-methyl-1,1-diphenyl-2-butanamine **144****144**

Methanolic HCl was added to a solution of isopropylamine **94** (204 mg, 0.85 mmol) in CH₃OH (3.0 cm³), so as to adjust the pH to 6.3. Benzaldehyde (115 mg, 1.08 mmol) was then added followed by sodium cyanoborohydride (132 mg, 2.10 mmol). The mixture was allowed to stir for 17 h at rt. The CH₃OH was then removed under reduced pressure, before addition of water (50 cm³) followed by potassium hydroxide (1M) until the solution was strongly alkaline. The aqueous phase was saturated with sodium

chloride before being extracted into ether (3 x 20 cm³). The combined ethereal extracts were washed with 20% ferrous sulfate (aq.) (2x 20 cm³), dried over MgSO₄ and concentrated. The crude product was dissolved in hexane and purified over silica, yielding benzylamine **144** (230 mg, 82%) as a white amorphous solid: mp 114-115 °C; $[\alpha]_D^{20} = +64$ (c 0.62, CH₂Cl₂); HRMS (CI) Calc. for C₂₄H₂₈N: 330.2222, Found 330.2217; $\nu_{\max}/\text{cm}^{-1}$ 3319, 3026, 2952, 1491, 1451, 1360, 1098; δ_{H} 0.76 [3 H, d, J 6.8, CH(CH₃)₂]; 0.93 [3 H, d, J 6.9, CH(CH₃)₂]; 1.69 (1 H, m, H-3), 3.19 (1 H, dd, J 6.1, 10.5, H-2), 3.20 (1 H, d, J 12.3, PhCH₂N), 3.46 (1 H, d, J 12.3, PhCH₂N), 3.70 (1 H, d, J 10.5, H-1), 6.89-7.36 (10 H, m, Ph); δ_{C} 16.1 [CH(CH₃)₂], 21.8 [CH(CH₃)₂], 30.5 (C-3), 56.2 (PhCH₂N), 57.4 (C-1), 66.5 (C-2), 126.6, 126.8, 127.6, 128.5, 128.6, 128.8, 129.1, 142.6, 144.1 (aromatic carbons); MS (CI) m/z (rel. int.): 330 [MH⁺] (100), 240 (6) and 162 (58).

6.1.3.16. Ethyl [N-(1*S*)-1-benzhydryl-2-methylpropyl]-N-benzylamino](oxo) acetate

151

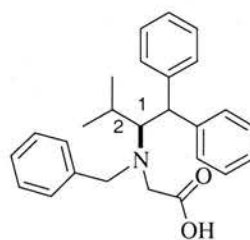


Triethylamine (158 mg, 1.56 mmol) was added to a stirred solution of *N*-benzylamine **144** (174 mg, 0.53 mmol) in CH₂Cl₂ (3.0 cm³) at -78 °C. The reaction was stirred for 15 min and then ethyl oxalyl chloride (110 mg, 0.79 mmol) was added. The mixture was allowed to warm to ambient temperature and was stirred for a further 4 h. Following the standard work-up procedure, the crude product was purified over silica gel to give the title compound (890 mg, 92%) as a white crystalline solid: mp 117-119 °C; $[\alpha]_D^{20} = -9.3$ (c 0.62, CH₂Cl₂); HRMS (CI): Calc. for C₂₈H₃₂NO₃: 430.2382, Found 430.2392; $\nu_{\max}/\text{cm}^{-1}$ 3062, 3025, 2960, 1727, 1631, 1427, 1175; δ_{H} 0.78 (3 H, m, OCH₂CH₃), 0.93 [3 H, d, J 6.9, CH(CH₃)₂], 1.04 [3 H, d, J 6.9, CH(CH₃)₂], 1.79 (1 H, m, H-2), 3.47 (1 H, dq, J 7.5, 10.8, OCH₂CH₃), 3.52 (1 H, dq, J 7.5, 10.8, OCH₂CH₃), 4.23 (1 H, d, J 13.5, NCH₂Ph), 4.32 (1 H, d, J 12.3, CHPh₂), 4.28 (1 H, d, J 13.5, NCH₂Ph), 5.68 (1 H, dd, J 12.3, J 12.6, H-2), 6.54-7.37 (15 H, m, Ph); δ_{C} 13.8 (OCH₂CH₃), 17.8 [CH(CH₃)₂], 20.9

[CH(CH₃)₂], 31.0 (C-2), 49.67 (NCH₂Ph), 53.8 (CHPh₂), 61.9 (C-1), 62.7 (OCH₂CH₃), 127.2, 127.6, 128.1, 128.2, 128.6, 129.2, 129.4, 129.5, 136.7, 142.0, 142.5, 143.1 (aromatic carbons), 163.1 (NCOCO₂Et), 164.8 (NCOCO₂Et; MS (CI) m/z (rel. int.): 430 [MH]⁺ (100) and 75 (76).

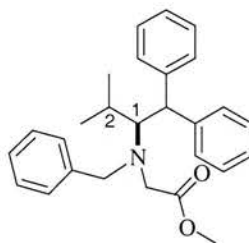
6.1.3.17. *[N-[(S)-1-Benzhydryl-2-methylpropyl]-N-benzylamino]acetic acid*

154



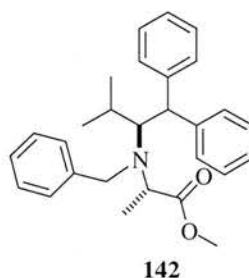
154

Sodium hydroxide (25.0 mg, 0.65 mmol) was added to a solution of amidoester **151** (281 mg, 0.65 mmol) in CH₃CH₂OH/ THF solution (1:3). The reaction was stirred at rt for 15 h, when the solvents were evaporated under reduced pressure, yielding the sodium carboxylate. The salt (164 mg, 0.38 mmol) was dissolved in THF (5.0 cm³), and charged into a flask containing diborane (1.5 M in THF, 0.51 cm³, 0.76 mmol) at 0 °C. The reaction mixture was heated under reflux for 15 h. The mixture was cooled to rt, and subsequently quenched with glacial acetic acid (1.0 cm³). The solvent was removed under reduced pressure and the crude product purified over silica gel to give carboxylic acid **154** (190 mg, 65% as a white amorphous solid mp: 148-150 °C; HRMS (CI) Calc. for C₂₆H₃₀NO₂: 388.2277, Found 388.2283; $\nu_{\max}/\text{cm}^{-1}$ 3430, 3062, 3029, 265, 1770 (C=O), 1638, 1493, 1454, 1337; δ_{H} 0.68 [3 H, d, J 7.2, CH(CH₃)₂], 0.90 [3H, d, J 6.9, CH(CH₃)₂], 2.02 (1 H, m, NCH), 3.35 (2 H, br, NCH₂CO₂H), 3.55 (2 H, br, NCH₂Ph), 3.65 (1 H, dd, J 5.8, 11.7, H-1), 4.15 (1 H, d, J 11.7, CHPh₂), 7.01-7.26 (15 H, m, Ph); δ_{C} 20.4 [CH(CH₃)₂], 28.9 CHPh₂), 54.0 (C-1), 54.7 (NCH₂Ph), 60.7 (NCH₂CO₂H), 127.3, 127.6, 128.6, 128.7, 128.9, 129.1, 129.2, 129.6, 130.4, 136.1, 142.8, 143.1 (aromatic carbons), 171.8 (CH₂CO₂H), MS (CI) m/z (rel. int.): 388 [MH]⁺ (100), 344 (15) and 220 (48).

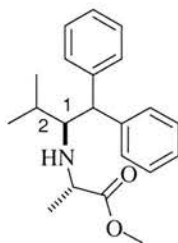
6.1.3.18. *Methyl 2-[N-[(1S)-1-benzhydryl-2-methylpropyl]-N-benzylamino]acetate***140****140**

A solution of diazomethane [prepared from: di(ethylene glycol) ethyl ether (3.5 cm³); ether 2.0 cm³ potassium hydroxide (625 mg); water 1.0 cm³) and a solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (1.25 g) in ether (11.3 cm³)] in ether was added to a solution of carboxylic acid **154** (139 mg, 0.36 mmol) in ether until the yellow diazomethane solution persisted. Glacial acetic acid was then added until the yellow solution turned colourless. The ether solution was evaporated *in vacuo* to obtain the methyl ester **140** (144 mg, 100%) as a yellow oil. $[\alpha]_D^{20} = +4.8$ (*c* 0.78, CH₂Cl₂); HRMS (CI) Calc. for C₂₇H₃₂NO₂: 402.2433; Found 402.2445; $\nu_{\max}/\text{cm}^{-1}$ 2965, 1709, 1494, 1363, 1222; δ_{H} 0.72 [3H, d, *J* 7.2, CH(CH₃)₂]; 0.90 [3H, d, *J* 6.9, CH(CH₃)₂]; 1.77 (1 H, m, NCH); 3.13 (1 H, d, *J* 16.8, NCH₂CO); 3.40 (1 H, d, *J* 16.8, NCH₂CO); 3.41 (3 H, s, OCH₃); 3.56 (1 H, d, *J* 13.2, PhCH₂N); 3.63 (1 H, d, *J* 13.2, PhCH₂N); 3.62 (1 H, dd, *J* 11.40, *J* 12.0, H-1); 4.17 (1 H, d, *J* 11.4, CHPh₂); 6.95-7.99 (15 H, m, Ph); δ_{C} 18.6 [CH(CH₃)₂]; 21.5 [CH(CH₃)₂]; 30.6 (C-2); 51.6 (OCH₃); 54.1 (PhCH₂N); 55.0 (NCH₂CO); 68.5 (CHPh₂); 126.7, 127.2, 128.2, 128.5, 128.7, 128.9, 129.0, 129.3, 130.0, 139.6, 144.5, 144.6 (aromatic carbons); 173.3 (C=O); MS (CI) *m/z* (rel. int.): 402 [MH]⁺ (100).

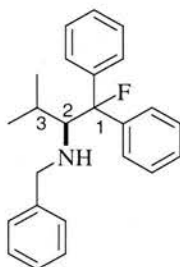
6.1.3.19. Methyl (2R)-[N-[(1S)-1-benzhydryl-2-methylpropyl]-N-benzylamino]propanoate **142**



A solution of methyl ester **140** (119 mg, 0.30 mmol) in THF (15 cm³) was added to an LDA/ THF preparation: [diisopropylamine (33.1 mg, 0.33 mmol) and *n*-BuLi (2.5 M in hexane), 150 μ l, 0.39 mmol at 0 °C) solution at -50 °C]. Methyl iodide (42.2 mg, 0.30 mmol) was added and the reaction was allowed to warm to rt over 1 h and was further stirred at ambient temperature for 8 h. THF was evaporated, ether (10 cm³) added, and the products extracted from water (30 cm³). The combined ethereal layer was evaporated to dryness. The diastereoisomers were separated over silica gel to give a colourless oil (84.3 mg, 68%). Data for the major diastereoisomer [α]_D²⁰ = +21 (*c* 0.81, CH₂Cl₂); HRMS (CI) Calc. for C₂₈H₃₄NO₂: 415.5672, Found 415.5668; ν_{\max} /cm⁻¹ 3062, 3027, 2960, 2929, 1735 (C=O), 1452, 1261, 1147; δ_{H} 0.50 (3 H, d, J 7.2, NCHCH₃), 0.82 [3 H, d, J 7.2, CH(CH₃)₂], 0.89 [3 H, d, J 6.9, CH(CH₃)₂], 2.13 (1 H, m, H-2), 3.50 (1 H, q, J 7.2, NCHCH₃), 3.59 (3 H, s, OCH₃), 3.63 (1 H, m, H-1), 3.89 (1 H, d, J 14.1, PhCH₂N), 3.96 (1 H, d, J 14.1, PhCH₂N), 4.10 1H, (d, J 11.4, CHPh₂), 6.92-7.25 (15 H, m, Ph); δ_{C} 18.5 [CH(CH₃)₂], 19.3 [CH(CH₃)₂], 23.8 (NCHCH₃), 29.3 (C-2), 51.4 (OCH₃), 51.4 (PhCH₂N), 53.9 (C-1), 54.6 (NCH₂CO), 62.5 (CHPh₂), 126.1, 126.7, 127.2, 128.2, 128.3, 128.7, 129.0, 129.1, 130.5, 140.1, 144.4, 144.8 (aromatic carbons), 176.7 (C=O); MS (CI) *m/z* (rel. int.): 417 [MH]⁺ (100).

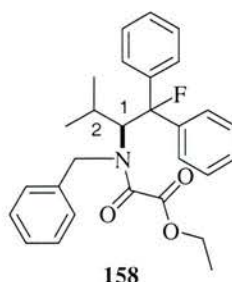
6.1.3.20. Methyl (2*R*)-2-[*N*-(1*S*)-1-Benzhydryl-2-methylpropylamino]propanoate **156****156**

A sample of **142** (100 mg, 0.241 mmol) in methanol (50 cm³) was charged with Pearlman's catalyst (30 mg). The reaction vessel was pressurised with hydrogen (10 bars). After 10 h the pressure was released to afford (77 mg, 99%) of the debenzylated product upon filtration. Treatment of **156** with anhydrous HCl provided **156a** in quantitative yield. Data for **156** $[\alpha]_{\text{D}}^{20} = +62$ (*c* 0.77, CH₂Cl₂); HRMS (CI) Calc. for C₂₁H₂₈NO₂: 326.2120, Found 326.2118; $\nu_{\text{max}}/\text{cm}^{-1}$ 2963, 2947, 1714, 1495, 1451, 1214, 1152; δ_{H} 0.71 [3H, d, *J* 6.9, CH(CH₃)₂], 0.89 [3H, d, *J* 7.2, CH(CH₃)₂], 1.03 (3 H, d, *J* 6.9, NCHCH₃), 1.64-4.73 (1 H, m, H-2), 2.94 (1 H, q, *J* 6.9, NCHCH₃), 3.20 (1 H, dd, *J* 2.3, 10.5, H-1), 3.45 (3 H, s, OCH₃), 3.74 (1 H, d, *J* 10.5, CHPh₂), 7.05-7.32 (10 H, m, Ph), δ_{C} 19.9 [CH(CH₃)₂], 21.2 [CH(CH₃)₂], 29.3 (NCHCH₃), 55.7 (C-1), 57.2 (NCHCH₃), 63.4 (CHPh₂), 63.4 (OCH₃), 126.2, 126.4, 128.2, 128.4, 128.5, 128.6 (aromatic carbons) 142.8, 143.6, (C-1 of Ph), 175.6 (C=O), MS (CI) *m/z* (rel. int.): 326 [MH]⁺ (100), 167 (30).

6.1.3.21. (*S*)-*N*-Benzyl-1-fluoro-3-methyl-1,1-diphenyl-2-butanamine **157****157**

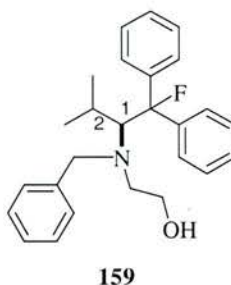
Methanolic HCl was added to a solution of (*S*)- α -diphenylmethyl isopropylamine **96** (1.00 g, 3.86 mmol) in CH₃OH (50 cm³), and the pH adjusted to 6.6. Benzaldehyde (537 mg, 5.06 mmol) was then introduced followed by sodium cyanoborohydride (733 mg, 11.7 mmol). The procedure used in section 6.1.3.15 was followed. Chromatographic purification of the crude mixture yielded secondary amine **157** (686 mg, 50%) as a white solid, mp 90-92 °C; $[\alpha]_D^{20} = -38$ (*c* 0.80, CH₂Cl₂); Elemental analysis Found C, 82.96, H, 7.54, N, 4.03. C₂₄H₂₆FN requires C, 82.98, H, 7.59, N, 4.04; $\nu_{\max}/\text{cm}^{-1}$ 3314, 3026, 2956, 1494, 1449, 1326, 1098, 980, 704; δ_{H} 0.81 [3 H, d, J 6.9, CH(CH₃)₂], 0.92 [3 H, d, J 7.0, CH(CH₃)₂], 1.52 (1 H, br, NH), 1.79 (1 H, m, H-3), 3.45 (1 H, dd, J 2.8, J 31.9, H-2), 4.55 (2 H, s, NCH₂Ph), 7.10-7.41 (15 H, m, Ph); δ_{C} 17.0 [CH(CH₃)₂], 23.1 [CH(CH₃)₂], 29.8 (C-3), 55.2 (NCH₂Ph) 68.1 (d, J 21.0, C-2), 102.9 (d, J 183.0, C-1), 124.96, 125.0, 125.2, 126.7, 127.1, 127.2, 128.0, 128.3, 140.9, 143.1, 143.2, 143.5 (aromatic carbons), δ_{F} -168.2 (d, J 31.9).

6.1.3.22. Ethyl [N-Benzyl[N-(1*S*)-1-[fluoro(diphenyl)methyl]-2-methylpropylamino](oxo)acetate **158**



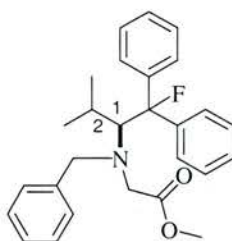
A solution of *N*-benzylamine **157** (471mg, 1.36 mmol) in CH₂Cl₂ (15 cm³) was treated with triethylamine 413 mg, 4.08 mmol) and ethyl oxalylchloride (241 mg, 1.77 mmol) in CH₂Cl₂ (15 cm³) as described under section 6.1.3.16. Purification over silica gel afforded the title compound **158** (586 mg, 96%), as a white amorphous solid: mp 117-120 °C; [α]_D²⁰ = -9.6 (c 0.60, CH₂Cl₂); HRMS (CI) Calc. for C₂₈H₂₉FNO₃: 450.2127, Found 450.2108; ν_{max}/cm⁻¹ 2968, 1734, 1656, 1451, 1311, 1265, 1198; δ_H 0.83 [3 H, d, J 6.9, CH(CH₃)₂], 0.88 [3 H, m, CH(CH₃)₂], 1.25 (3 H, t, J 7.2, OCH₂CH₃), 1.92 (1 H, m, H-1), 4.15 (1 H, dq, J 7.2, 10.2, OCH₂CH₃), 4.23 (1 H, dq, J 7.2, 10.2, OCH₂CH₃), 4.47 (1 H, d, J 7.2, NCH₂Ph), 4.49 (1 H, d, J 7.2, NCH₂Ph), 4.98 (1 H, ddd, J 2.2, 10.6, 35.9, H-1), 7.09-7.47 (15 H, m, Ph); δ_C 14.3 (OCH₂CH₃), 17.3 [CH(CH₃)₂], 21.3 [CH(CH₃)₂], 22.5 [CH(CH₃)₂], 29.2 (C-3), 58.7 (d, J 18.6, C-2), 63.7 (OCH₂CH₃), 67.5 (NCH₂Ph), 102.3 (d, J 183.3, CFPh₂), 124.5, 124.6, 124.8, 125.0, 126.1, 128.1, 128.4, 128.8, 129.1, 129.6, 142.0, 142.3 (aromatic carbons), 157.0 (NCOCO₂Et), 160.69 (NCOCO₂Et), δ_F -168.7 (d, J 35.9); MS (CI) m/z (rel. int.): 449 [MH]⁺ (80), 429 (100) and (16).

6.1.3.23. 2-(*N*-Benzyl[*N*-(1*S*)-1-[fluoro(diphenyl)methyl]-2-methylpropyl]amino)ethanol **159**



A solution of ethyl amido ester **158** (350 mg, 0.78 mmol) in THF (10 cm³) was slowly added to a suspension of lithium aluminium hydride (58 mg, 1.56 mmol) in THF at rt. The reaction was heated under reflux for 30 min. Excess hydride was cautiously quenched by the addition of water. The organics were filtered and the solvent removed under reduced pressure to give alcohol **159** (306 mg, 100%) as a white amorphous solid: mp 90-91°C; $[\alpha]_{\text{D}}^{20} = +5.6$ (*c* 0.69, CH₂Cl₂); Elemental analysis Found C, 79.76, H, 7.72, N, 3.58. C₂₆H₃₀FNO requires C, 79.46, H, 7.99, N, 3.70; $\nu_{\text{max}}/\text{cm}^{-1}$ 3423, 2956, 1599, 1493, 1450, 1047; δ_{H} 0.94 [3 H, d, *J* 7.2, CH(CH₃)₂], 0.96 [3 H, dd, *J*_{HF} 1.5, 7.2, CH(CH₃)₂], 2.27 (1 H, m, H-2), 2.85 (2 H, m, NCH₂CH₂OH), 3.16-3.27 (4 H, m, NCH₂Ph and NCH₂CH₂OH), 3.72 (1 H, dd, *J* 3.3, 36.8, H-1), 7.09-7.36 (15 H, m, Ph); δ_{C} 22.6 [CH(CH₃)₂], 23.3 [CH(CH₂)], 29.8 (C-2), 29.9 (NCH₂CH₂OH), 57.0 (NCH₂CH₂OH), 67.9 (NCH₂Ph), 69.3 (d, *J* 19.3), 104.9 (d, *J* 188.5), 124.2, 124.4, 124.8, 125.0, 126.9, 127.0, 127.1, 128.1, 128.2, 144.3, 144.4, 144.7 (aromatic carbons); δ_{F} -169.3 (d, *J* 36.8).

6.1.3.24. Methyl (N-benzyl[N-(1S)-1-fluoro(diphenyl)methyl-2-methylpropyl]amino)acetate **141**



141

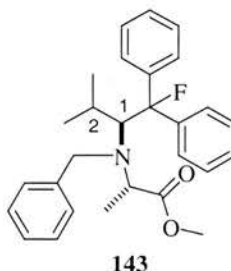
A solution of amino alcohol **159** (95mg, 0.245 mmol) in CH_2Cl_2 (1.0 cm^3) was added to a flask containing Dess-Martin periodinane (103 mg, 0.243 mmol) in CH_2Cl_2 (2.0 cm^3). After 20 min, a saturated solution of sodium bicarbonate was added, the organics were then washed with sodium thiosulfate solution (10%). The combined aqueous extracts were washed with ether ($2 \times 10 \text{ cm}^3$) and then evaporation of the organic solvent under reduced pressure gave the aldehyde (95 mg, 100%) product, which was used directly in the next step.

To a stirred solution of the aldehyde (95 mg, 0.243 mmol) in *t*-butanol (8.0 cm^3) and 2-methyl-2-butene (2.0 cm^3) was added a solution of sodium chlorite (NaClO_2) (250 mg, 2.19 mmol) and NaH_2PO_4 (403 mg, 1.70 mmol) in water (2.5 cm^3). The reaction was allowed to stir at rt for 40 min, whereupon water (10 cm^3) and ethyl acetate (30 cm^3) were added. The phases were separated, and the organic layer washed with saturated NaCl solution (10 cm^3), dried over MgSO_4 , filtered, and concentrated *in vacuo*.

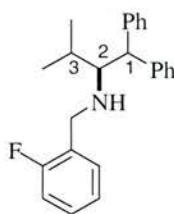
The residue was dissolved in methanol (5.0 cm^3) and treated with TMS-diazomethane (2 M in hexane) (15 cm^3 , 0.292 mmol). Methanol was removed under reduced pressure and the crude product purified over silica gel to give the title compound (31 mg, 30%) as a colourless oil. $[\alpha]_D^{20} = +5.9$ (c 0.63, CH_2Cl_2); HRMS (CI) Calc. for $\text{C}_{27}\text{H}_{31}\text{FNO}_2$: 420.2338, Found 420.2335; $\nu_{\text{max}}/\text{cm}^{-1}$ 2926, 1751, 1449, 1277, 1199, 1169, 1030; δ_{H} 0.73 [3 H, d, J 6.9, $\text{CH}(\text{CH}_3)_2$], 0.97 [3 H, d, J 6.9, $\text{CH}(\text{CH}_3)_2$], 2.10 (1 H, m, H-2), 3.33 (1 H, d, J 17.4, NCH_2CO), 3.44 (3 H, s, OCH_3), 3.48 (1 H, d, J 13.3, NCH_2Ph), 3.60 (1 H, d, J 13.3, NCH_2Ph), 3.72 (1 H, dd, J 3.1, J 37.1, H-1), 3.84 (1 H, d, J 17.4, NCH_2CO), 7.09-7.48 (15 H, m, Ph); δ_{C} 19.2 [$\text{CH}(\text{CH}_3)_2$], 23.0 [$\text{CH}(\text{CH}_3)_2$], 28.9 (C-3), 51.2 (OCH_3), 53.9 (NCH_2Ph), 58.9 (NCH_2CO), 69.3 (d, J 19.4, C-2), 104.5 (d, J 186.9,

C-1), 124.2, 124.4, 125.1, 125.3, 127.0, 127.7, 127.9, 128.0, 128.8, 130.0, 141.3, 144.6 (aromatic carbons), 173.0 (C=O), δ_{F} -168.3 (d, J 37.1); MS (CI) m/z (rel.): 420 [MH]⁺ (100), 400 (8) and 234 (14).

6.1.3.25. *Methyl (2R)-(N-benzyl[N-(1S)-1-[fluoro(diphenyl)methyl]-2-methylpropyl]amino)propanoate* **143**

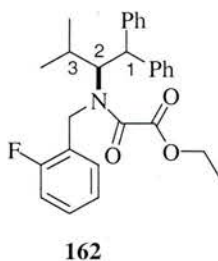


Methylation of amino ester **141** (54 mg, 0.129 mmol) followed the procedure outlined in section 6.1.3.19. The product was purified over silica gel to give a mixture of diastereoisomers 2:1 as colourless oil; HRMS (CI) Calc. for C₂₈H₃₂FNO₂: 434.5576, Found 434.5570; $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 1738 (C=O), 1493, 1384, 1262, 1148, δ_{H} 0.73 [d, J 6.9, CH(CH₃)₂], 0.97 [d, J 6.9, CH(CH₃)₂], 1.28 (d, J 6.7, NCHCH₃), 1.30* (d, J 6.7, NCHCH₃), 2.00 (1 H, m, H-2), 3.45 (3 H, s, OCH₃), 3.48 (1 H, q, J 6.7, NCHCH₃), 3.50 (1 H, d, J 13.6, NCH₂Ph), 3.59 (1 H, d, J 13.6, NCH₂Ph), 3.72 (1 H, dd, J 3.1, 36.7, H-1), 7.01-7.48 (15 H, m, Ph), δ_{C} 18.1 [CH(CH₃)₂], 18.8 [CH(CH₃)₂], 23.4 (NCHCH₃), 28.9 (C-2), 51.0 (OCH₃), 53.9 (NCHCH₃), 65.8 (NCH₂Ph), 69.3 (d, J 19.4, C-1), 105.6 (d, J 186.9, CFPh₂), 124.3, 124.4, 125.1, 125.3, 127.0, 127.8, 128.4, 130.0, 139.7, 144.0, 144.3 (aromatic carbons), 176.3 (C=O), δ_{F} -168.3 (d, J 36.7); MS (CI) m/z (rel. int.): 434 [MH]⁺ (100) and 414 (10).

6.1.3.26. (2*S*)-*N*-(2-Fluorobenzyl)-3-methyl-1,1-diphenyl-2-butamine **161****161**

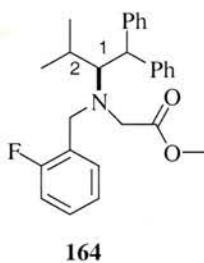
The reductive amination of *o*-fluorobenzaldehyde (674 mg, 5.43 mmol) with isopropylamine **94** (1.00 g, 4.18 mmol) and sodium cyanoborohydride (530 mg, 8.43 mmol) in methanol (50 cm³) was achieved following the procedure outlined in section 6.1.3.15. Chromatographic purification (EtOAc-hexane, 1:4) of the crude product gave the *o*-fluorobenzylamine (769 mg, 53%) as a white crystalline solid, mp 90-92°C; $[\alpha]_D^{20} = +65$ (*c* 0.72, CH₂Cl₂; Exact mass: Calculated for C₂₄H₂₇NF, 348.2128; Observed, 348.2133; $\nu_{\max}/\text{cm}^{-1}$ 3223, 3026, 2950, 1491, 1447; δ_{H} 0.74 (3 H, d, *J* 6.6, H-3); 0.89 (3 H, d, *J* 6.9, CH₃); 1.14 (1 H, br, NH); 1.71 (1 H, m, H-2), 3.19 (dd, H, *J* 7.5, 10.5, H-2), 3.24 (1 H, d, *J* 13.8, CH₂), 3.49 (1 H, d, *J* 13.8, CH₂), 3.79 (1 H, d, *J* 10.5, H-5), 7.04-7.34 (14 H, m, Ph); δ_{C} 16.1 (C-3), 21.5 (CH₃), 30.3 (C-2), 48.8 (d, *J* 2.6), 57.3 (CHPh₂), 66.2 (C-1), 115 (d, *J* 21.0), 124.2, 126.6, 126.8, 128.6, 128.7, 128.8, 128.9, 129.0, 130.9, 131.0 (aromatic carbons), 143.7 (C-1 of Ph), 144.0 (C-1 of Ph), 143.9 (d, *J* 26.1), 161.4 (d, *J* 246.1); δ_{F} -119.7m; MS *m/z* (rel. int. %) (CI) 348 (MH⁺) (100%) and (48%).

6.1.3.27. Ethyl [*N*-[(1*S*)-benzhydryl-2-methylpropyl]-*N*-(2-fluorobenzyl)]aminoacetate **162**



N-Fluorobenzylamine **161** (748 mg, 215 mmol) was converted into amidoester **3a** by reaction with triethylamine (653 mg, 6.45 mmol) and ethyl chlorooxoacetate (441 mg, 3.23 mmol) in CH₂Cl₂ (10 cm³) as described under section 6.1.3.16. Purification was achieved over silica (EtOAc-hexane 1:2) to give the amidoester **162** (890 mg, 92%) as a white amorphous solid, mp 85-87 °C; [α]_D²⁰ = +1.5 (*c* 0.65, CH₂Cl₂), Exact mass: Calculated for C₂₇H₃₁NO₃F, 420.2339; Observed, 420.2354; $\nu_{\max}/\text{cm}^{-1}$ 3406, 1712, 1728, 1450; δ_{H} 0.88 (3 H, m, CH₂CH₃); 1.17 (6 H, m, H-3 & CH₃), 1.81 (1 H, m, H-2), 3.74 (2 H, m, CH₂CH₃), 4.20 (1 H, d, J 12.0, NCH₂Ph), 4.24 (1 H, d, J 12.0, CHPh₂), 4.30 (1 H, d, 2.0, NCH₂Ph), 5.69 (1 H, dd, J 12.0, 12.0, H-1), 6.85-7.36 (14 H, m, Ph); δ_{C} 13.8 (CH₂CH₃), 18.8 (C-3), 20.9 (CH₃), 58.9 (NCH₂Ph), 60.4 (CHPh₂), 62.1 (CH₂CH₃), 66.7 (C-1), 114.9, 124.3, 127.1, 127.9, 128.2, 128.5, 128.6, 128.6, 129.1, 129.4 (aromatic carbons), 143.1 (C-1 of Ph), 158.6 (NCH₂Ph), 161.9 (C=O); δ_{F} -118.6m; MS *m/z* (rel. int. %) (CI) 420 (MH⁺) (64%), 252 (26%) and 57 (100%).

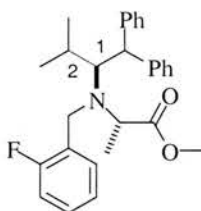
6.1.3.28. Methyl 2-[N-[(1*S*)-1-benzhydryl-2-methylpropyl]-N-(2-fluorobenzyl)amino] propanoate **164**



Sodium hydroxide (27.5 mg, 0.69 mmol) was added to a solution of the amidoester **162** (179 mg, 0.40 mmol) in absolute alcohol/ THF solution (20 cm³, 1:3) and the mixture was stirred for 16 h. The solvents were evaporated and the resulting product was directly converted to the amino acid salt **163** after treatment with borane (0.77 cm³, 1.15 mmol) as outlined above 6.1.3.17.

A solution of diazomethane in ether was introduced to the crude product, followed by addition of glacial acetic (1.0 cm³) to destroy the excess diazomethane. The ether was concentrated *in vacuo* and the residue was purified over silica (EtOAc-hexane, 1:9) to generate the methyl ester **164** as a colourless oil (167 mg, 100%); Exact mass: Calculated for C₂₇H₃₁NO₂F, 420.2338; Observed, 420.2354; $\nu_{\max}/\text{cm}^{-1}$ 3086, 3062, 3027, 2954, 2874, 1750, 1490, 1453, 1197, 1163; δ_{H} 0.70 (3 H, d, J 7.2, H-3), 0.84 (3 H, d, J 6.6, H-CH₃), 1.74 (1 H, m, J 7.2, 6.6, H-2), 3.12 (1 H, d, J 16.5, NCH₂CO), 3.41 (1 H, d, J 16.5, NCH₂CO), 3.43 (3 H, s, OCH₃), 3.54 (1 H, d, J 13.8, NCH₂Ph), 3.65 (1 H, dd, J 11.4, 11.7, H-1), 3.74 (1 H, d, J 13.8, NCH₂Ph), 4.15 (1 H, d, J 11.4, CHPh₂), 6.85-7.30 (14 H, m, Ph); δ_{C} 18.1 (C-3), 21.3 (CH₃), 30.2 (C-2), 51.6 (OCH), 51.9 (NCH₂Ph), 54.3 (NCH₂CO), 55.1 (CHPh₂), 68.95 (C-1), 115.2 (d, J 21.9), 124.0, 126.5, 126.7, 128.5, 128.7, 128.8, 129.1, 129.3, 132.5 (aromatic carbons), 144.3 (d, J 14.87 C-1 of Ph), 161.8 (d, J 246.0), 173.3 (C=O); δ_{F} -120.4 m, MS *m/z* (rel. int. %) (CI) 448 (MH⁺) (86%), 280 (35%) and 75 (100).

6.1.3.29. Methyl 2-[N-[(1*S*)-benzhydryl-2-methylpropyl]-N-(2-fluorobenzyl)amino]propanoate **166**.



166

The alkylation of the methyl ester **164** (43.0 mg, 0.10 mmol) with methyl iodide (14.5 mg, 0.10 mmol), in THF (2.0 cm³), LDA/ THF [prepared from diisopropylamine (15.5 mg, 0.15 mmol) and *n*-BuLi (2.5 M, 70 μ l, 0.18 mmol at 0 °C)] was undertaken following the procedure outlined under section 6.1.3.19. Methyl propanoate **166** (15.0 mg, 35%) was obtained as colourless oil after preparative thin layer chromatography; HRMS (CI) Calc. for C₂₈H₃₂ FNO₂: 434.5576, Found 434.5570; $\nu_{\max}/\text{cm}^{-1}$ 2930, 1738 (C=O), 1493, 1384, 1262, 1148; δ_{H} 0.51 (3 H, d, J 7.2, NCHCH₃), 0.77 (3 H, d, J 7.2, H-3), 0.87 (3 H, d, J 6.6, CH₃), 2.20 (1 H, m, H-2), 3.58 (1 H, m, H-1), 3.60 (3 H, s, OCH₃), 3.91 (1 H, d, J 14.1, NCH₂Ph), 4.06 (1 H, d, J 11.4, CHPh₂); 4.13 (1 H, d, J 14.1, NCH₂Ph), 6.97-7.38 (14 H, m, Ph); δ_{C} 18.2 (CH₃), 19.1 (CH₃), 23.3 (NCHCH₃), 28.8 (C-2), 51.0 (OCH₃), 50.9 (NCH₂Ph), 53.5 (CHPh₂), 54.5 (NCHCO), 63.0 (C-1), 126.9, 127.0, 127.2, 127.3, 127.5, 127.9, 128.7, 129.3, 144.2, (aromatic carbons), 173.3 (C=O); MS (CI) *m/z* (rel. int.): 434 [MH]⁺ (100).

6.1.4. General Procedure D

A solution of an amine in THF was added to a stirred suspension of sodium hydride (60% in mineral oil) in THF. The mixture was stirred for 15 min at rt before allyl iodide was added. After 10 h, the reaction was quenched with isopropanol, followed by sodium thiosulfate (10%). The mixture was extracted into ether (3 x) and the combined extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified over silica (1:3, EtOAc-hexane) to give the title compounds as oils.

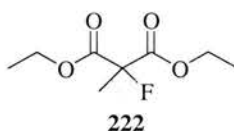
6.1.5. General Procedure E

A flask containing an allyl amine, Yb(OTf)₃ and Hünig's base in CH₂Cl₂ was charged with the acid chloride in CH₂Cl₂ over 3 min. After 5 h, the reaction was diluted with ethyl acetate followed by washing with sodium hydroxide (1 M) and then the organics were washed with HCl (2 M). The aqueous layer was then extracted into ethyl acetate (3 x), and the combined organic layers dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified over silica gel (1:3, EtOAc-hexane) to afford the title compound.

6.1.6. General Procedure F

Iodine was added to a solution of an homoallyl amide in THF/ H₂O (1:1) at rt. The resulting solution was maintained in the absence of light for 24 h, before being quenched with Na₂S₂O₃ (10%). The mixture was then extracted into ether (3 x), dried over MgSO₄, filtered and concentrated to provide the corresponding iodolactone, which was purified on silica gel chromatography (1:3, EtOAc-hexane).

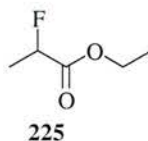
6.1.6.1. Diethyl 2-fluoro-2-methylmalonate **222**⁶



Diethyl methylmalonate (1.00 g, 5.74 mmol) was slowly added to a suspension of sodium hydride (344 mg, 8.61 mmol) in THF at rt. After 15 min, Selectfluor (2.44 g, 6.89 mmol) was added and the reaction allowed to stir for 3 h. Excess NaH was quenched with ethanol (1.0 cm³) and diluted with water (50 cm³). The mixture was extracted into ether (3x 20 cm³). The product was isolated following the standard work-up procedure, to give the title compound as a colourless oil (1.00 g, 98%); HRMS (CI) Calc. for C₈H₁₄FO₄: Calc. 193.0876, Found 193.0874. $\nu_{\max}/\text{cm}^{-1}$ 2988, 2944, 1756, 1448, 1378, 1302, 1127, 1018; δ_{H} 1.29 (6 H, t, J 7.2, CH₂CH₃), 1.76 (3 H, d, J 22.0, CH₃), 4.27 (4 H, q, J 7.2, CH₂CH₃); δ_{C} 13.9 (CH₂CH₃), 20.6 (d, J 23.2, CH₃CF), 62.5

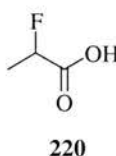
(CH₂CH₃), 90.3 (d, J 194.6, CH₃CF), 166.7 (d, J 25.5, C=O); δ_F -157.9 (q, J 22.0); MS (CI) m/z (rel. int.): 193 [MH]⁺ (80) 165 (100) and 137 (33).

6.1.6.2. Ethyl 2-fluoropropanoate **225**⁷



Ethyl lactate methanesulfonate **224** (25.0 g, 127 mmol) was incrementally added to a heated (60 °C) solution of potassium fluoride (15.0 g, 258 mmol) in formamide (150 cm³) under reduced pressure (20 atm) in a flask fitted with a distillation apparatus. The distillate was collected into a cold trap (-78 °C) to give the product (11.2 g, 73%) as colourless oil; δ_H 1.29 (3 H, t, J 7.2, CH₂CH₃), 1.55 (3 H, dd, J 6.9, 23.8, CH₃CHF), 4.23 (2 H, q, J 7.2, CH₂CH₃), 4.98 (1 H, dq, J 6.9, 48.6, CH₃CHF); δ_C 14.0 (CH₂CH₃), 18.2 (d, J 22.7, CH₃CHF), 61.4 (CH₂CH₃), 85.6 (d, J 181.3, CH₃CHF), 170.6 (d, J 23.2); δ_F -185 (dq, J 23.8, 48.6); MS (CI) m/z (rel. int.): 121 [MH]⁺ (100).

6.1.6.3. 2-Fluoropropanoic acid **220**^{7,8}



Method A

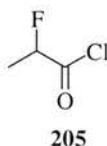
NaNO₂ (5.89 g, 85.3 mmol) was added portion-wise over 20 min to a mixture of DL-alanine (5.00 g, 51.1 mmol) and HF/ pyridine (70/30) (70 cm³) were stirred in a Teflon bottle at -78 °C. The reaction was allowed to reach ambient temperature over 3 h. The reaction was then quenched by adding ice water (80 cm³) and extracted into CH₂Cl₂ (3 x 50 cm³) to give a yellow oil. Following distillation (bp 51-53 °C at 23 mbar, lit.⁹ 50 °C) the title compound was isolated as colourless oil, yield, 658 mg, 14%; ν_{max}/cm^{-1} 1671, 1449, 1125; δ_H 1.63 (3 H, d, J 6.9, 23.6, CH₃), 5.07 (1 H, dq, J 6.9, 48.4, CHF), 10.9 (1

H, br, OH); δ_C 18.1 (d, J 22.1, CH₃), 85.0 (d, J 182.4, CHF), 176.3 (d, J 24.8, C=O); δ_F -185.7 (dq, J 23.6, 48.4); MS (CI) m/z (rel. int.): 93 [MH]⁺ (100).

Method B⁶

Sodium hydroxide (374 mg, 9.35 mmol) was added to a stirred solution of diethyl 2-fluoro-2-methylmalonate **222** (900 mg, 4.68 mmol) in ethanol (20 cm³). After 16 h, the solvent was evaporated under reduced pressure and the residue was treated with 20% HCl (20 cm³) and heated to 100 °C for 3 h. The product was isolated following the standard work-up procedure to give the acid **220** as a colourless oil (190 mg, 44%)

6.1.6.4. 2-Fluoropropionyl chloride **205**^{6, 10, 11}

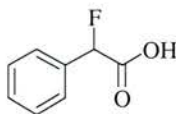


Method 1

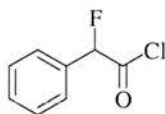
A solution of 2-fluoropropionic acid (500 mg, 5.43 mmol) in CH₂Cl₂ was charged with oxalyl chloride (689 mg, 5.43 mmol) and DMF (1 drop). After 3 h the solvent was removed and the residue distilled to give the title compound as a colourless oil (540 mg, 90%), bp 54-56 °C, lit⁹ 56 °C; $\nu_{\max}/\text{cm}^{-1}$ 2950, 1820, 1421, 1089, 955; δ_H 1.68 (3 H, d, J 6.9, 23.0, CH₃), 5.10 (1 H, dq, J 6.9, 48.6, CHF); δ_C 17.6 (d, J 22.9, CH₃), 90.3 (d, J 184.5, CHF), 172.4 (d, J 27.9, C=O); δ_F -171.5 (dq, J 22.7, 48.5); MS (CI) m/z (rel. int.): 110 [MH]⁺ (100), 75 (30) and 47 (100).

Method 2

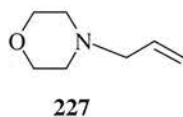
Sodium hydroxide (668 mg, 16.7 mmol) was added into a solution of ethyl 2-fluoropropanoate **225** (2.00 g, 16.7 mmol) in ethanol (10 cm³). The reaction was stirred for 16 h before the solvent was removed. The residue was treated with phthaloyl dichloride (6.76 g, 33.3 mmol) and upon distillation, the title compound was isolated in 80% yield (1.52 g).

6.1.6.5. 2-Fluorophenylacetic acid **221**^{10, 12}**221**

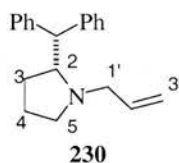
2-Phenylglycine (8.00 g, 52.9 mmol) was added into a Teflon bottle containing HF/pyridine (65-/70) (80 cm³) at -0 °C. Solid NaNO₂ (4.00 g, 79.4 mmol) was added portion-wise at -78 °C with stirring. After 30 min, the reaction was allowed to reach ambient temperature over 2 h. The reaction was then quenched by adding ice water (100 cm³) and extracted into CH₂Cl₂ (3 x 50 cm³) to give the crude product as a yellow solid. Following recrystallization in ethyl acetate and hexane, the title compound was isolated as white solid, (5.90 g, 72%), mp 126-127 °C, (lit.^{10, 12} 129 °C); $\nu_{\max}/\text{cm}^{-1}$ 3069, 2607, 1955, 1760, 1455, 1169, 1047; δ_{H} 5.81 (1 H, d, J 47.8, CHF), 7.40-7.44 (5 H, m, Ph), 10.5 (1 H, br, OH); δ_{C} 89.3 (d, J 186.9, CHF), 127.1, 129.4, 130.7 (aromatic carbons), 131.2 (d, J 20.4, C-1 of Ph), 174.9 (d, J 27.6, C=O); δ_{F} -181.2 (d, J 47.8); MS (CI) m/z (rel. int.): 155 [MH]⁺ (100) and 109 (18).

6.1.6.6. 2-Fluoro-2-phenylacetyl chloride **206**^{8, 12}**206**

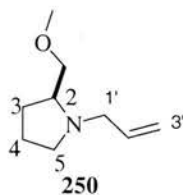
Oxalyl chloride (1.11 g, 8.75 mmol) was added to a solution of acid **221** (1.35 g, 8.75 mmol), DMF (1 drop) in CH₂Cl₂ at rt. After 3 h the reaction was complete as determined by ¹⁹F NMR analysis. Excess oxalyl chloride was removed under reduced pressure to yield the title the acid chloride as colourless oil (1.49 g, 99%); $\nu_{\max}/\text{cm}^{-1}$ 2014, 1852, 1404, 1257, 1071; δ_{H} 5.91 (1 H, d, J 47.7, CHF), 7.48-7.50 (5 H, m, Ph); δ_{C} 85.8 (d, J 187.2, CHF), 127.5, 127.6 (aromatic carbons), 125.7 (d, J 28.0, C-1 of Ph), 127.9, 166.2 (d, J 28.0, C=O); δ_{F} -164.5 (d, J 47.6, CHF); MS (CI) m/z (rel. int.): 173 [MH]⁺ (100).

6.1.6.7. 4-Allylmorpholine **227**¹³

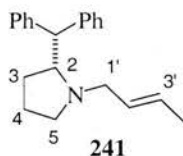
This product was prepared from morpholine (1.00 g, 11.5 mmol), sodium hydride (598 mg, 15 mmol), allyl iodide (2.32 g, 13.8 mmol) following the procedure described under section A to give **227** (1.41 g, 97 %) as a colourless oil; δ_{H} 2.35 (4 H, t, J 4.6, H-3), 2.90 (2 H, dt, J 1.3, 6.6, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.62 (4 H, t, J 4.6, H-2), 5.04-5.09 (2 H, m, $\text{CH}=\text{CH}_2$), 5.13-5.14 (1 H, m, $\text{CH}=\text{CH}_2$); δ_{C} 53.3 (C-3), 61.9 ($\text{CH}_2\text{CH}=\text{CH}_2$), 66.7 (C-2), 118.1 ($\text{CH}=\text{CH}_2$), 134.3 ($\text{CH}=\text{CH}_2$).

6.1.6.8. (2*R*)-1-Allyl-2-Benzhydrylpyrrolidine **230**

Product **230** was prepared according to the general procedure outlined under section D from (*R*)-(diphenylmethyl) pyrrolidine **100** (197 mg, 0.83 mmol), sodium hydride (60% in mineral oil), (50 mg, 1.25 mmol) in THF (5.0 ml) and allyl iodide (280 mg, 1.66 mmol) to give the title compound as light yellow oil (160 mg, 70%); $[\alpha]_{\text{D}}^{20} = -17.8$ (c 0.63, CH_2Cl_2); HRMS (CI) Calc. for $\text{C}_{20}\text{H}_{24}\text{N}$: Calc. 278.1909, Found 278.1902; $\nu_{\text{max}}/\text{cm}^{-1}$ 2966, 2781, 1599, 1494, 1450, 1417, 1352, 1032; δ_{H} 1.41-1.58 (3 H, m, H-3, 2H-2), 1.72-1.87 (1 H, m, H-3), 2.15-2.23 (1 H, m, H-5), 2.49 (1 H, dd, J 7.7, 14.3, NCH_2CH), 2.81 (1 H, ddd, J 1.5, 5.38, 13.7, NCH_2CH), 2.98-3.04 (1 H, m, H-5), 3.22-3.29 (1 H, m, H-2), 3.85 (1 H, d, J 8.19, H-3), 4.86-4.92 (2 H, m, $\text{CH}=\text{CH}_2$), 5.55-5.69 (1 H, dddd, J 5.4, 7.7, 9.5, 13.1, $\text{CH}=\text{CH}_2$), 7.07-7.28 (10 H, m, Ph); δ_{C} 23.4 (C-4), 30.6 (C-3), 54.6 (C-5), 57.7 (CHPh_2), 58.9 (NCH_2CH), 66.8 (C-2), 116.1 ($\text{CH}=\text{CH}_2$), 125.6, 126.1, 128.0, 128.2, 128.7, 128.8 (aromatic carbons), 136.5 ($\text{CH}=\text{CH}_2$), 143.9, 144.0 (C-1 of Ph); MS (CI) m/z (rel. int.): 278 $[\text{MH}]^+$ (100) and 110 (62).

6.1.6.9. (2*S*)-1-Allyl-2-methoxymethylpyrrolidine **250**

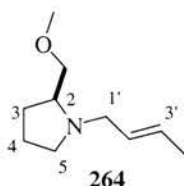
This product was prepared according to the general procedure outlined under section D from (*S*)-(methoxymethyl)pyrrolidine (500 mg, 4.34 mmol), sodium hydride (60% in mineral oil), (226 mg, 5.64 mmol) in THF (10.0 cm³) and allyl iodide (1.09 g, 6.51 mmol) to give the title compound as light yellow oil. Yield, 593 mg, 88%; $[\alpha]_{\text{D}}^{20} = -74.9$ (*c* 0.12, CH₂Cl₂); HRMS (CI) Calc. for C₉H₁₈NO: 156.1388, Found 156.1393, $\nu_{\text{max}}/\text{cm}^{-1}$ 3068, 2874, 1644, 1459, 1349, 1118, 916; δ_{H} 1.53-1.75 (2 H, m, H-4), 1.80-1.91 (2 H, m, H-3), 2.13-2.22 (1 H, m, H-5), 2.52-2.60 (2 H, m, H-2), 2.76 (1 H, dd *J* 7.6, 13.3, CH₂CH=CH₂), 3.00-3.06 (1 H, m, H-5), 3.25 (1 H, dd *J* 6.1, 9.4, CH₂OCH₃), 3.31 (3 H, s, OCH₃), 3.37 (1 H, dd, *J* 5.1, 9.4, CH₂OCH₃), 3.48 (1 H, dd, *J* 5.9, 13.3, CH₂CH=CH₂), 5.10 (2 H, m, CH=CH₂), 5.89 (1 H, dddd, *J* 5.9, 7.6, 13.3, 17.2, CH=CH₂); δ_{C} 22.7 (C-4), 28.4 (C-3), 54.4 (CH₂CH=CH₂), 58.3 (C-5), 59.0 (OCH₃), 62.6 (C-2), 76.0 (CH₂OCH₃), 116.6 (CH=CH₂), 136.2 (CH=CH₂), MS (CI) *m/z* (rel. int.): 156 [MH]⁺ (44) and 110 (7).

6.1.6.10. (2*R*)-2-Benzhydryl-1-[(2*E*)-2-butenyl]pyrrolidine **241**

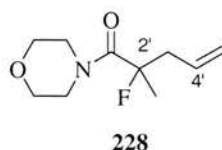
This product was prepared according to the general procedure outlined under section D from (*R*)-(diphenylmethyl) pyrrolidine **100** (207 mg, 0.710 mmol), sodium hydride (60% in mineral oil), (42 mg, 1.05 mmol) in THF (10 cm³) and crotyl bromide (141 mg, 1.05 mmol), TBAI (5% mol eq.) to give the title compound as light yellow oil (139 mg, 55%); $[\alpha]_{\text{D}}^{20} = -70.9$ (*c* 0.61, CH₂Cl₂); HRMS (CI) Calc. for C₂₁H₂₆N: Calc. 292.2065, Found 292.2070; $\nu_{\text{max}}/\text{cm}^{-1}$; δ_{H} 1.60-1.61 (3 H, m, CH₃), 1.52-1.57 (2 H, m, H-4), 1.82-

1.90 (2 H, m, H-3), 2.22-2.30 (1 H, m, H-5), 2.57-2.53 (1 H, m, $\text{CH}_2\text{CH}=\text{CH}$), 2.80-2.86 (1 H, m, $\text{CH}_2\text{CH}=\text{CH}$), 3.06-3.12 (1 H, m, H-5), 2.80-3.60 (2 H, m, H-2), 3.93 (1 H, d, J 8.2, CHPh_2), 5.32-5.36 (2 H, m, $\text{CH}=\text{CH}$), 7.12-7.37 (10 H, m, Ph); δ_{C} 17.8, (CH_3), 23.4 (C-4), 30.7 (C-3), 54.5 ($\text{CH}_2\text{CH}=\text{CH}$), 57.7 (C-2), 58.3 (C-5), 66.8 (CHPh_2), 125.9 ($\text{CH}=\text{CH}$), 126.1, 128.1, 128.2, 128.7, 128.7, 128.8, (aromatic carbons), 144.0 (2C-1 of Ph); MS (CI) m/z (rel. int.): 292 $[\text{MH}]^+$ (100) and 238 (8).

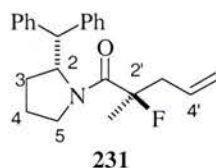
6.1.6.11. (2*R*)-1-[(2*E*)-2-Butenyl]-2-(methoxymethyl)pyrrolidine **264**



Product **264** was prepared according to the general procedure outlined under section D from (*S*)-methoxymethylpyrrolidine **249** (150 mg, 1.30 mmol), sodium hydride (60% in mineral oil), (68 mg, 1.69 mmol) in THF (10 cm³) and crotyl bromide (228 mg, 1.69 mmol), TBAI (5% mol eq.) to give the title compound as light yellow oil (187 mg, 85%); $[\alpha]_{\text{D}}^{20} = -73.8$ (*c* 0.11, CH_2Cl_2); HRMS (CI) Calc. for $\text{C}_{10}\text{H}_{20}\text{NO}$ 170.1545, Found 170.1544; $\nu_{\text{max}}/\text{cm}^{-1}$ 2965, 2875, 1450, 1197, 1115, 968; δ_{H} 1.50-1.68 (2 H, m, H-4), 1.59-1.60 (3 H, m, CH_3), 1.75-1.84 (2 H, m, H-3), 2.09-2.18 (1 H, m, H-5), 2.47-2.56 (1 H, m, $\text{CH}_2\text{CH}=\text{CH}$), 2.77-2.83 (1 H, m, $\text{CH}_2\text{CH}=\text{CH}$), 2.96-3.02 (1 H, m, H-5), 3.18-3.24 (1 H, m, H-1), 3.26 (3 H, s, OCH_3), 3.32-3.39 (2 H, m, CH_2OCH_3), 5.48-5.53 (2 H, m, $\text{CH}=\text{CH}$); δ_{C} 17.6, (CH_3), 22.6 (C-4), 28.3 (C-3), 54.1 ($\text{CH}_2\text{CH}=\text{CH}$), 57.1 (C-5), 58.8 (OCH_3), 62.4 (C-2), 75.8 (CH_2OCH_3), 127.9 ($\text{CH}=\text{CH}$), 128.3 ($\text{CH}=\text{CH}$); MS (CI) m/z (rel. int.): 170 $[\text{M}]^+$ (98), 138 (61) and 124 (100).

6.1.6.12. 4-(2-Fluoro-2-methyl-4-pentenoyl)morpholine **228**

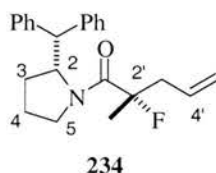
Amide **228** was prepared according to the general procedure described under section E from **227** (261 mg, 2.1 mmol), ytterbium triflate (1.30 g, 2.1 mmol), Hünig's base (814 mg, 6.3 mmol) and 2-fluoropropionyl chloride (464 mg, 4.2 mmol), to give the product as a colourless oil (380 mg, 92%); HRMS (CI) Calc. for $C_{10}H_{17}NO_2F$: Calc. 202.1243, Found 202.1241; $\nu_{\max}/\text{cm}^{-1}$ 2974, 2857, 1645, 1432, 1376, 1270, 1185, 1118, 1033; δ_{H} 1.55 (3 H, d, J 22.0, CH_3), 2.52 (1 H, ddd, J 7.9, 14.3, 22.3, H-3'), 2.75 (1 H, ddd, J 6.7, 14.3, 21.3, H-3'), 3.65-3.78 (8 H, br, H-2, H-3), 5.10-5.11 (1 H, m, H-5'), 5.55-5.56 (1 H, m, H-5'), 5.77 (1 H, dddd, J 6.7, 7.9, 9.5, 16.1, H-4'); δ_{C} 23.9 (d, J 23.8, CH_3), 43.1 (d, J 22.1, C-3'), 46.9* (d, J 18.9, C-3'), 66.9 (C-2, C-3), 98.1 (d, J 187.4, C-2'), 119.5 (C-5'), 131.3 (C-4'), 169.6 (d, J 20.5, C=O); δ_{F} -149.9-150.6m; MS (ES) m/z (rel. int.): 201 $[\text{MH}]^+$ (100) and 183 (11).

6.1.6.13. (2S)-2-Benzhydryl-1-[(2S)-2-fluoro-2-methyl-4-pentenoyl]pyrrolidine **231**

Amide **231** was prepared following the procedure described under section E from (*R*)-1-allyl-2-benzhydrylpyrrolidine **230** (604 mg, 2.18 mmol), ytterbium triflate (2.70 g, 4.36 mmol), Hünig's base (1.13 g, 8.72 mmol) and 2-fluoropropionyl chloride (867 mg, 7.85 mmol), to afford the title compound as a (1:6) mixture of diastereomers. These were successfully separated over silica gel (1:3, EtOAc-hexane). Combined yield (519 mg, 68%); (data for the major diastereoisomer) $[\alpha]_{\text{D}}^{20} = -12.3$ (*c* 0.58, CH_2Cl_2); HRMS calc. for $C_{23}H_{26}NOFNa$: 374.1894, Found: 374.1893; $\nu_{\max}/\text{cm}^{-1}$ 2980, 1746, 1633, 1495, 1452, 1416, 1152, 922; δ_{H} 1.02* (3 H, d, J 21.8, CH_3), 1.48 (3 H, d, J 21.5, CH_3), 1.69-2.00 (4 H, m, H-3, H-4), 2.56 (1 H, ddd, J 6.9, 14.8, 21.3, H-3'), 2.63 (1 H, ddd, J 6.1, 14.6, 22.5, H-3'), 3.40-3.49 (1 H, m, H-5), 3.65-3.78 (1 H, m, H-5), 4.10* (1 H, d, J 8.2,

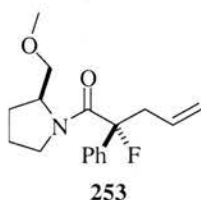
*CHPh*₂) 4.39 (1 H, d, J 8.2, *CHPh*₂), 5.08-5.14 (2 H, m, H-5'), 5.21* (1 H, dt, J 2.8, 7.2, H-2), 5.53 (2 H, m, H-2, H-4'), 5.72* (1 H, m, H-4'), 7.21-7.30 (10 H, m, Ph); δ_C 23.0 (d, J 23.2, CFCH₃), 24.2 (C-4), 26.7 (C-3), 43.1 (d, J 22.7, C-3') 44.5* (d, J 22.7, C-3'), 47.0 (d, J 16.0, C-5), 52.9 (C-2), 54.8* (C-2), 61.0 (*CHPh*₂), 98.6 (d, J 188.5, C-2'), 119.0 (C-5'), 119.2* (C-5'), 126.2, 126.3, 126.6, 127.9, 128.3, 128.5, 128.9, 129.4 (aromatic carbons), 132.0* (C-4'), 132.1 (C-4'), 141.9 (C-1 of Ph), 142.0 (C-1 of Ph), 170.4 (d, J 22.1, C=O); δ_F -151.3*m, -154.4m (*: denotes minor rotamer); MS ES 374 [M+Na]⁺ (100) and 352 (18).

6.1.6.14. (2*S*)-2-Benzhydryl-1-[(2*R*)-2-fluoro-2-methyl-4-pentenoyl]pyrrolidine **234**



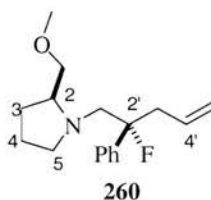
Data for the minor diastereoisomer: $[\alpha]_D^{20} = +3.7$ (c 0.71, CH₂Cl₂); HRMS (CI) Calc. for C₂₃H₂₆NOFNa: 374.1896, Found 374.1891; $\nu_{\max}/\text{cm}^{-1}$ 2980, 1746, 1633, 1495, 1452, 1416, 1152, 922; (minor diastereoisomer) δ_H 1.32 (3 H, d, J 22.3, CH₃), 1.47-1.57 (2 H, m, H-4), 1.70-1.90 (2 H, m, H-3), 2.44 (1 H, ddd, J 7.7, 14.3, 21.0, H-3'), 2.68 (1 H, ddd, J 6.9, 14.3, 21.3, H-3'), 3.40 (1 H, ddd, J 5.1, 8.7, 12.3, H-5), 3.75 (1 H, ddd, J 5.1, 7.7, 12.8, H-5), 4.30* (1 H, d, J 6.1, *CHPh*₂), 4.40 (1 H, d, J 7.2, *CHPh*₂), 5.10-5.22 (3 H, m, H-2, H-5'), 5.78 (1 H, dddd, J 6.9, 7.7, 14.3, 21.3, H-4'), 7.21-7.31 (10 H, m, Ph); δ_C 24.2 (d, J 24.3, CFCH₃), 24.3 (C-4), 26.8 (C-3), 42.6 (d, J 22.1, C-3'), 46.7 (d, J 17.7, C-5), 52.8 (C-2), 55.3 (C-2), 60.9 (*CHPh*₂), 98.0 (d, J 189.1, C-2'), 119.2 (C-5'), 126.1, 126.6, 127.8, 128.1, 128.2, 128.4, 128.9, 129.3, (aromatic carbons), 131.6, 131.7 (C-4'), 141.9, 142.0 (C-1 of Ph), 170.4 (d, J 22.1, C=O); δ_F -152.6*m, -153.7m (*: denotes minor rotamer); MS (ES) m/z (rel. int.): 374 [M+Na]⁺ (100) and 352 (35).

6.1.6.15. (2*S*)-1-[(2*R*)-2-Fluoro-2-phenyl-4-pentenoyl]-2-(methoxymethyl)pyrrolidine
253



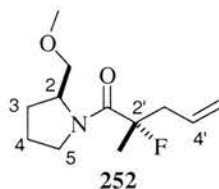
Amide **253** was prepared following the procedure described under section E from (*S,S'*)-1-allyl-2-methoxymethylpyrrolidine **250** (298 mg, 1.92 mmol), ytterbium triflate (595 mg, 0.960 mmol), Hünig's base (744 mg, 5.76 mmol) and 2-fluoro-2-phenylacetyl chloride (662 mg, 3.84 mmol), to afford the title compound as a (397 mg, 72%); $[\alpha]_D^{20} = -89.0$ (*c* 0.60, CH₂Cl₂); HRMS (CI) Calc. for C₁₇H₂₃NO₂F: 292.1713, Found 292.1714; $\nu_{\max}/\text{cm}^{-1}$ 3077, 2979, 2927, 1643, 1450, 1420, 1116, 920; δ_{H} 1.32-1.50 (2 H, m, H-4), 1.64-1.84 (2 H, m, H-3), 2.64-2.80 (1 H, m, H-3'), 3.00-3.12 (1 H, m, H-3'), 3.19* (3 H, s, OCH₃), 3.30 (3 H, s, OCH₃), 3.30 (1 H, dd, *J* 5.6, 9.5, CH₂OCH₃), 3.35 (1 H, dd, *J* 6.9, 9.5, CH₂OCH₃), 4.20-4.27 (1 H, m, H-2), 4.97-4.06 (2 H, m, H-5'), 5.60-5.75 (1 H, m, H-4'), 7.23-7.38 (5 H, m, Ph); δ_{C} 24.6* (C-4), 24.7 (C-4), 44.3* (d, *J* 24.3, C-3'), 44.9 (d, *J* 23.7, C-3'), 47.2 (C-3), 47.3* (C-3), 57.9* (C-2), 59.0 (C-2), 71.0* (CH₂OCH₃), 72.2 (CH₂OCH₃), 98.8 (d, *J* 192.4, C-2'), 99.3* (d, *J* 191.3, C-2'), 119.0 (CH=CH₂), 119.2* (CH=CH₂), 124.0* (d, *J* 8.8), 124.1 (d, *J* 8.3), 127.9* (d, *J* 1.1), 128.0 (d, *J* 1.1), 128.2* (d, *J* 1.7), 128.4 (d, *J* 2.2), 138.4 (d, *J* 21.5, C-1 of Ph), 138.8 (d, *J* 21.1, C-1 of Ph), 167.6* (d, *J* 22.1, C=O), 168.1 (d, *J* 22.1, C=O); δ_{F} -165.7-165.5*m, -164.5-164.3m (*: denotes minor rotamer); MS (ES) *m/z* (rel. int.): 292 [M+H]⁺ (32), 272 (100) and 246 (22).

6.1.6.16. (2*S*)-1-[(2*S*)-2-Fluoro-2-phenyl-4-pentenyl]-2-(methoxymethyl)pyrrolidine
260



A suspension of LiAlH_4 (78.9 mg, 2.08 mmol) in THF (15 cm^3) was charged with homoallyl amide **253** (300 mg, 1.04 mmol). The reaction was heated under reflux for 1 h and was then quenched with ethyl acetate and water. The organics were decanted and concentrated to give the title compound as colourless oil (284 mg, 100%) $[\alpha]_{\text{D}}^{20} = -49.7$ (*c* 0.87 CH_2Cl_2); HRMS (CI) Calc. for $\text{C}_{20}\text{H}_{24}\text{N}$: 278.1909, Found 278.1910; $\nu_{\text{max}}/\text{cm}^{-1}$ 3076, 3030, 2946, 2874, 1448, 1272, 1103, 915; δ_{H} 1.47-1.56 (1 H, m, H-4), 1.68-1.91 (3 H, m, H-3 and H-4), 2.29 (1 H, dd, *J* 9.0, 16.9, H-5), 2.57-2.81 (3 H, m, H-2, H-3' and H-5), 3.05-3.39 (3 H, m, H-3' and CH_2OCH_3), 4.97-5.06 (2 H, m, H-5'), 5.63 (1 H, dddd, *J* 6.9, 10.2, 14.1, 17.2, H-4'), 7.24-7.38 (5 H, m, Ph); δ_{C} 23.8 (C-4), 28.1 (C-3), 41.3 (d, *J* 23.2, C-3'), 56.6 (C-5), 58.9 (OCH_3), 64.0 (C-2), 64.8 (d, *J* 22.1, C-1'), 77.4 (CH_2OCH_3), 99.9 (d, *J* 179.1, C-2'), 118.0 (C-5'), 124.8 (d, *J* 9.9, C-1 of Ph), 127.1 (d, *J* 1.1, C-4 of Ph), 128.0 (d, *J* 1.7, C-3 of Ph), 132.9 (C-4'), 142.3 (d, *J* 21.6, C-1 of Ph); δ_{F} -159.6-160.0 m; MS (CI) *m/z* (rel. int.): 278 $[\text{M}+\text{H}]^+$ (48), 258 (93), 232 (45) and 128 (100).

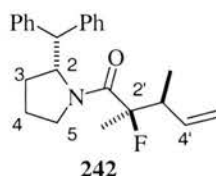
6.1.6.17. (2*S*)-1-[(2*R*)-2-Fluoro-2-methyl-4-pentenyl]-2-(methoxymethyl)pyrrolidine
252



Product **252** was prepared following the procedure described under section E from (*S*)-1-allyl-2-methoxymethylpyrrolidine **250** (400 mg, 2.58 mmol), ytterbium triflate (800 mg, 1.29 mmol), Hünig's base (1.00 g, 7.74 mmol) and 2-fluoropropionyl chloride (428

mg, 3.87 mmol), to afford the title compound as a colourless oil (373 mg, 63%); $[\alpha]_D^{20} = -37.8$ (c 0.84, CH_2Cl_2); HRMS (CI) Calc. for $\text{C}_{12}\text{H}_{20}\text{NO}_2\text{F}$: Calc. 229.1478, Found 229.1471; δ_{H} 1.55 (3 H, d, J 21.8, CH_3), 1.57* (3 H, d, J 22.0, CH_3), 1.83-2.03 (4 H, m, H-3, H-4), 2.45-2.60 (1 H, m, H-3'), 2.64-2.86 (1 H, m, H-3'), 3.36 (1 H, dd, J 7.2, 9.5, CH_2OCH_3), 3.34 (3 H, s, OCH_3), 3.52 (1 H, dd, J 3.3, 9.5, CH_2OCH_3), 3.65-3.71 (1 H, m, H-5), 4.30-4.37 (1 H, m, H-2), 4.44-4.51* (1 H, m, H-2), 5.13-5.19 (1 H, m, H-5'), 5.71-5.89 (1 H, m, H-4'); δ_{C} 20.0* (C-4), 23.4 (d, J 24.3, CH_3), 24.0* (d, J 24.3, CH_3), 24.8 (C-4), 26.2 (C-3), 28.9* (C-3), 42.6* (d, J 22.1, C-3'), 43.3 (d, J 22.7, C-3'), 47.6 (d, J 17.1, C-5), 58.1 (C-2), 58.8 (C-2), 71.9 (CH_2OCH_3), 74.1* (CH_2OCH_3), 97.7 (d, J 188.0, C-2'), 98.7* (d, J 189.6, C-2'), 119.1 (C-5'), 119.3* (C-5'), 131.5* (C-4'), 131.6 (C-4'), 170.1 (d, J 22.1, C=O); δ_{F} (-156.2-155.6)*m, -(154.7-154.2)m (* denotes minor rotamer); MS (CI) m/z (rel. int.): 229 $[\text{MH}]^+$ (11), 197 (7) and 184 (100).

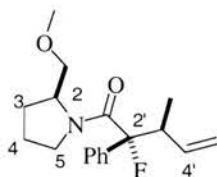
6.1.6.18. (2*S*)-2-Benzhydryl-1-[(2*S*,3*R*)-2-fluoro-2,3-dimethyl-4-pentenoyl]pyrrolidine **242**



Amide **242** was prepared following the procedure described under section E from **241** (207 mg, 0.710 mmol), ytterbium triflate (220 mg, 0.355 mmol), Hünig's base (367 mg, 2.84 mmol) and 2-fluoropropionyl chloride **205** (235 mg, 2.13 mmol), to afford the title compound as a mixture of diastereoisomers (1:6). Combined yield (215 mg, 83%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3027, 2980, 1747, 1634, 1496, 1452, 1416, 1152, 923; δ_{H} 0.73* (3 H, d, J 6.7, CH_3), 0.97 (3 H, d, J 6.9), 1.17-1.33 (2 H, m, H-4), 1.42* (3 H, d, J 21.8, CH_3F), 1.47 (3 H, d, J 22.0, CH_3F), 1.63-1.77 (1 H, m, H-3), 1.82-1.96 (1 H, m, H-3), 2.49-2.66* (1 H, m, H-3'), 2.30-2.87 (1 H, m, H-3'), 3.39-3.51 (1 H, m, H-5), 3.65-3.78 (1 H, m, H-5), 4.36* (1 H, d, J 7.2, CHPh_2), 4.46 (1 H, d, J 5.9, CHPh_2), 4.96-5.12 (2 H, m, H-5'), 5.18-5.24 (1 H, m, H-2), 5.26-5.33* (1 H, m, H-2), 5.61-5.80 (1 H, m, H-4'), 7.09-7.32 (10 H, m, Ph); δ_{C} 13.2 (d, J 4.4, CH_3), 14.9 (d, J 5.0, CH_3), 21.5 (d, J 24.3, CH_3F), 21.9* (d, J 24.3, CH_3F), 24.2* (C-4), 24.3 (C-4), 26.7 (C-3), 26.4* (C-3), 44.5 (d, J 22.1, C-3'), 45.4* (d, J 21.0, C-3'), 52.6 (C-2), 53.2* (C-2), 61.1* (CHPh_2), 61.3 (CHPh_2),

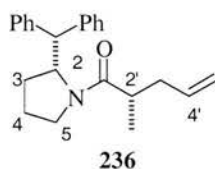
99.5* (d, J 191.3, C-2'), 100.9 (d, J 194.6, C-2'), 116.1 (C-5'), 16.9 (C-5'), 126.2, 126.3*, 126.5, 126.5*, 127.9*, 128.0, 128.2, 128.3*, 128.5*, 128.9, 129.1*, 129.4 (aromatic carbons), 138.7 (d, J 5.0, C-4'), 138.4* (d, J 3.3, C-4'), 142.1, 142.2, (C-1 of Ph), 170.5 (d, J 22.1, C=O).

6.1.6.19. (2*S*)-1-[(2*R*,3*R*)-2-Fluoro-3-methyl-2-phenyl-4-pentenoyl]-2-(methoxymethyl)pyrrolidine **265**

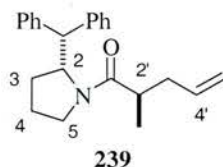


264

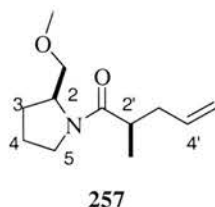
Product **264** was prepared following the procedure described under section E from **264** (300 mg, 1.77 mmol), ytterbium triflate (549 mg, 0.885 mmol), Hünig's base (686 mg, 5.31 mmol) and 2-fluoro-2-phenylacetyl chloride (610 mg, 3.54 mmol) to afford the title compound as a mixture of diastereomers (1:7.5). Combined yield (346 mg, 64%); $[\alpha]_D^{20}$ -75.4 (*c* 0.79, CH₂Cl₂); HRMS (CI) Calc. for C₁₈H₂₅NO₂F: 306.1869, Found 306.1873; $\nu_{\max}/\text{cm}^{-1}$ 3067, 2978, 2927, 1638, 1449, 1116, 920; δ_{H} 0.80* (3 H, d, J 7.2, CH₃), 0.82 (3 H, d, J 6.9, CH₃), 1.52-1.91 (4 H, m, H-3, H-4), 3.36 (3 H, s, OCH₃), 3.39 (1 H, dd, J 6.9, 9.5, CH₂OCH₃), 3.56 (1 H, dd, J 3.3, 9.5, CH₂OCH₃), 3.59-3.65 (2 H, m, H-5), 4.24 (1 H, m, H-2), 5.10-5.23 (2 H, m, H-5'), 5.86-6.10 (1 H, m, H-4'), 7.28-7.53 (5 H, m, Ph); δ_{C} 13.1* (d, J 3.9, CH₃), 13.4 (d, J 3.9, CH₃), 24.3* (C-4), 26.2 (C-3), 44.9* (d, J 22.7, C-3'), 45.7 (d, J 22.1, C-3'), 46.9* (d, J 16.0, C-5), 47.3 (d, J 15.5, C-5), 58.1* (OCH₃), 58.9 (OCH₃), 70.9* (CH₂OCH₃), 72.2 (CH₂OCH₃), 101.1 (C-5'), 124.6 (d, J 10.0), 125.1* (d, J 10.5), 127.8* (d, J 1.1), 127.8 (d, J 1.1), 128.2 (d, J 2.2), 128.3* (d, J 2.2), 137.6 (Aromatic carbons), (d, J 22.1, C-1 of Ph), 138.2 (d, J 3.9, C-4'), 138.5* (2 H, d, J 4.4, C-4'), 168.5 (d, J 22.7, C=O), δ_{F} -179.0-179.1m, -179.0-180.0* , 177.9-178.0m; MS (ES) *m/z* (rel. int.): 306 [MH]⁺ (92) and 286 (100), 260 (43) and 142 (66).

6.1.6.20. (2*R*)-2-Benzhydryl-1-[(2*S*)-2-methyl-4-pentenoyl]pyrrolidine **236**

Amide **236** was prepared following the procedure described under section E from (*R,R'*)-1-allyl-2-benzhydrylpyrrolidine **230** (400 mg, 1.20 mmol), ytterbium triflate (372 mg, 0.60 mmol), Hünig's base (465 mg, 3.60 mmol) and 2-fluoropropionyl chloride (265 mg, 2.40 mmol), to afford the title compound as a mixture of diastereomers (1:3) which were successfully separated over silica gel (1:3, EtOAc-hexane). Combined yield (519 mg, 68%); $[\alpha]_{\text{D}}^{20} = +71.6$ (*c* 0.25, CH₂Cl₂); HRMS (CI) Calc. for C₂₃H₂₈NO: Calc. 334.2161, Found 334.2162; $\nu_{\text{max}}/\text{cm}^{-1}$ 3061, 2933, 2976, 1735, 1625, 1450, 1266, 1032; (major diastereoisomer) δ_{H} 0.94* (3 H, d, *J* 6.9, CH₃), 1.00 (3 H, d, *J* 6.7, CH₃), 1.21-1.36 (2 H, m, CH₂), 1.58-2.10 (6 H, m, CH-2',2,3,4), 2.57-2.37 (2 H, m, H-3'), 3.16 (1 H, ddd, *J* 4.1, 10.0, 14.1, H-5), 3.37-3.47 (1 H, m, H-5), 3.83-3.73* (2 H, m, H-5), 4.08* (1 H, d, *J* 8.7, CHPh₂), 4.58 (1 H, d, *J* 5.9, CHPh₂), 4.90-5.11 (3 H, m, H-2, 5'), 5.36* (1 H, dddd, *J* 5.9, 7.9, 14.1, 23.6, H-4'), 5.75 (1 H, dddd, *J* 6.1, 7.4, 13.8, 24.1, H-4'), 7.12-7.36 (10 H, m, Ph); δ_{C} 16.9* (CH₃), 17.4 (CH₃), 21.3* (C-4), 23.6 (C-4), 27.5 (C-3), 30.0* (C-3), 37.0* (C-3'), 37.1* (C-2'), 37.6 (C-3'), 38.0 (C-2'), 44.8* (C-5), 46.5 (C-5), 52.2 (C-2), 54.3* (C-2), 59.3 (CHPh₂), 61.1* (CHPh₂), 116.5* (C-5'), 116.3 (C-5'), 126.0, 126.5, 127.8, 128.1, 128.5, 128.6, 128.8, 128.8, 129.0, 129.6 (Ph), 136.4 (C-4'), 136.6* (C-4'), 140.8, 141.5, 142.0, 142.1 (C-1 of Ph), 174.7 (C=O), 175.5* (C=O); MS (ES) *m/z* (rel. int.): 334 [M+H]⁺ (100), 286 (38) and 166 (40). (*: denotes minor rotamer).

6.1.6.21. (2R)-2-Benzhydryl-1-[(2R)-2-methyl-4-pentenoyl]pyrrolidine **239**

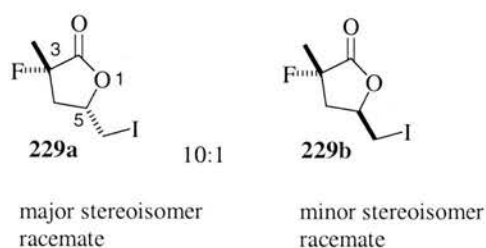
Data for minor diastereoisomer: HRMS calculated for $C_{23}H_{28}NO$: 334.2161, Found: 344.2171; $\nu_{\max}/\text{cm}^{-1}$ 3061, 2933, 2976, 1735, 1625, 1450, 1266, 1032; δ_{H} (minor diastereoisomer) 0.99 (3 H, d, J 6.7, CH_3), 1.18-1.26 (2 H, m, C-4), 1.62-2.10 (8H, m, CH_2S), 2.40-2.51 (1 H, m, C-3'), 2.18-2.27 (1 H, m, H-3'), 3.15 (1 H, ddd, J 4.1, 10.0, 14.1, H-5), 3.29-3.41 (1 H, m H-5), 4.48 (1 H, d, J 5.63, CHPh_2), 4.91-5.05 (3 H, m, H-2, H-5'), 5.58 (1 H, dddd, J 6.40, 7.68, 14.1, 24.3, H-4'), 7.04-7.30 (10 H, m, Ph); δ_{C} 16.4 (CH_3), 16.5* (CH_3), 21.3* (C-4), 23.6 (C-4), 27.5 (C-3), 29.7* (C-3), 37.9 (C2'), 38.1* (C-2'), 38.1 (C-3'), 39.5* (C-3'), 44.7* (C-5), 46.7 (C-5), 52.5 (C-2), 54.4* (C-2), 116.3 (C-5'), 116.6* (C-5'), 126.1, 126.5, 126.8, 126.9, 127.9, 128.1, 128.5, 128.9, 129.0, 129.6, (aromatic carbons) 135.9, 136.5* (C-4'), 141.0, 141.4, 142.1, 142.3 (C-1 of Ph), 174.8 (C=O), 175.3* (C=O); MS (TOF ES) 334 $[\text{M}+\text{Na}]^+$ (100), 286 (38) and 166 (40). (* Denotes minor rotamer).

6.1.6.22. (2S)-2-(Methoxymethyl)-1-[(2R)-2-methyl-4-pentenoyl]pyrrolidine **257**

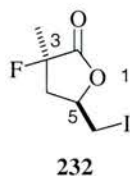
Amide **257** was prepared following the procedure described under section E from (*S*)-1-allyl-2-methoxymethylpyrrolidine **250** (265 mg, 1.71 mmol), ytterbium triflate (530 mg, 855 μmol), Hünig's base (663 mg, 5.13 mmol) and 2-fluoropropionyl chloride (316 mg, 5.13 mmol), to afford the title compound as a colourless oil (241 mg, 67%); HRMS (CI) Calc. for $C_{12}H_{22}NO_2$: Calc. 212.1650, Found 212.1658; δ_{H} 1.07* (3 H, d, J 6.9, CH_3), 1.09 (3 H, d, J 6.9, CH_3), 1.83-1.98 (2 H, m, H-4), 2.00-2.15 (2 H, m, H-3), 2.32-2.48 (2 H, m, H-3'), 2.63-2.50 (2 H, m, H-2'), 3.30 (3 H, s, OCH_3), 3.35 (1 H, dd,

J 7.2, 9.5, CH_2OCH_3), 3.39-3.50 (2 H, m, H-5), 3.50 (1 H, dd, J 3.3, 9.5, CH_2OCH_3), 3.94-4.01* (1 H, m, H-2), 4.18-4.27 (1 H, m, H-2), 4.94-5.07 (2 H, m, H-5'), 5.73 (1 H, dddd, J 6.4, 7.7, 10.2, 17.2, H-4'); δ_{C} 17.2 (CH_3), 17.6* (CH_3), 21.4* (C-4), 24.1 (C-4), 27.3 (C-3), 28.7* (C-3), 37.6* (C-2'), 37.9 (C-2'), 45.6* (C-3'), 47.0 (C-3'), 56.1 (C-5), 56.6* (C-5), 58.9, (C-2), 59.0 (C-2), 72.1 (CH_2OCH_3), 74.3* (CH_2OCH_3), 116.2* (C-5'), 116.3 (C-5'), 136.3 (C-4'), 136.5* (C-4'), 174.9 (C=O), 175.3* (C=O); MS (CI) m/z (rel. int.): 212 $[\text{MH}]^+$ (100) and 166 (8); 75% de.

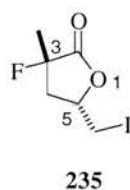
6.1.6.23. 3-Fluoro-5-(iodomethyl)-3-methyltetrahydrofuran-2-one **229**



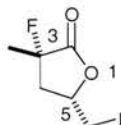
Lactone **229** was prepared from **228** (200 mg, 0.994 mmol), iodine (378 mg, 2.98 mmol), THF/ H_2O (50/50) (2.0 cm^3) to afford **229** (210 mg, 82%) as a mixture of stereoisomers; HRMS (CI) Calc. for $\text{C}_6\text{H}_9\text{FIO}_2$: Calc. 258.9631, Found 258.9629; $\nu_{\text{max}}/\text{cm}^{-1}$ 2989, 2929, 1795, 1752, 1598, 1380, 1225, 1119; δ_{H} 1.66 (3 H, d, J 22.8, CH_3), 2.47 (1 H, ddd, J 6.7, 14.6, 41.0, H-4), 2.63 (1 H, ddd, J 6.7, 14.1, 35.1, H-4), 3.28 (1 H, dd, J 8.4, 10.2, CH_2I), 3.46 (1 H, dd, J 4.9, 10.2, CH_2I), 4.47-4.57 (1 H, m, H-5); δ_{C} 5.36, 6.14* (CH_2I), 20.1* (d, J 25.4, CH_3), 21.3 (d, J 26.5, CH_3), 40.7 (d, J 23.2, C-4), 42.1* (d, J 22.7, C-4), 75.5 (d, J 3.9, C-5), 92.7 (d, J 186.8, C-3), 172.5 (d, J 24.9, C=O); δ_{F} (-148.7-148.3)*m, (-146.7-146.3)m (*: denotes minor stereoisomer); MS (CI) m/z (rel. int.): 258 $[\text{MH}]^+$ (55) and 238 (100).

6.1.6.24. (3*S*,5*R*)-3-Fluoro-5-(iodomethyl)-3-methyltetrahydrofuran-2-one **232**

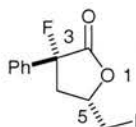
Lactone **232** was prepared following the procedure outlined under section F from **231** (79 mg, 0.22 mmol) and iodine (85 mg, 0.70 mmol) to give the product as a colourless oil (46 mg, 77 %); $[\alpha]_D^{20} = -15.9$ (*c* 0.93, CH₂Cl₂) HRMS (CI) Calc. for C₆H₉FO₂: 258.9631, Found 258.9630; $\nu_{\max}/\text{cm}^{-1}$ 2988, 2932, 1795, 1710, 1438, 1381, 1256, 1226, 1109, 999; (major diastereoisomer) δ_{H} 1.65 (3 H, d, *J* 22.8, CH₃), 2.47 (1 H, ddd, *J* 6.7, 14.6, 41.0, H-4), 2.63 (1 H, ddd, *J* 6.7, 14.1, 35.1, H-4), 3.28 (1 H, dd, *J* 8.4, 10.2, CH₂I), 3.46 (1 H, dd, *J* 4.9, 10.2, CH₂I), 4.47-4.57 (1 H, m, H-5); δ_{C} 5.39 (CH₂I), 21.3 (d, *J* 26.5, CH₃), 40.7 (d, *J* 22.1, C-4), 75.5 (C-5), 92.9 (d, *J* 186.3, C-3), 171.5 (d, *J* 24.9, C=O); δ_{F} (-148.8-148.4)*m, -146.7-146.3m; MS (CI) *m/z* (rel. int.): 258 [MH]⁺ (55) and 238 (100). (*: denotes *syn* diastereoisomer following iodolactonization).

6.1.6.25. (3*S*,5*R*)-3-Fluoro-5-(iodomethyl)-3-methyldihydrofuran-2-one **235**

Lactone **235** was prepared following the procedure outlined under section F from **234** (55 mg, 0.14 mmol) and iodine (54 mg, 0.43 mmol) to give the product as a colourless oil (38 mg, 94 %); $[\alpha]_D^{20} = +16.0$ (*c* 0.92, CH₂Cl₂); HRMS (CI) Calc. for C₆H₉FO₂: 258.9631, Found 258.9631; $\nu_{\max}/\text{cm}^{-1}$ 2916, 2845, 1794, 1588, 1377, 1227, 1112; MS (CI) *m/z* (rel. int.): 258 [MH]⁺ (55) and 238 (100). (Other analytical data of **235** were identical to that of **232**: enantiomeric relationship except that no *syn* isomer was observed in ¹⁹F NMR).

6.1.6.26. (3*R*,5*S*)-3-Fluoro-5-(iodomethyl)-3-methyltetrahydrofuran-2-one **254****254**

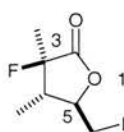
Product **254** was prepared from **253** (105 mg, 0.458 mmol), iodine (232 mg, 1.83 mmol), THF/H₂O (50/50) (2.0 cm³) to afford **254** as a colourless oil (114 mg, 97%); $[\alpha]_{\text{D}}^{20} = +15.1$ (*c* 0.93, CH₂Cl₂); HRMS (CI) Calc. for C₆H₉FIO₂: Calc. 258.9631, Found 258.9623; $\nu_{\text{max}}/\text{cm}^{-1}$ 2988, 2916, 1796, 1438, 1381, 1255, 1227, 1109, 999; δ_{H} 1.66 (3 H, d, *J* 22.3, CH₃), 2.47 (1 H, ddd, *J* 6.4, 14.1, 42.5, H-4), 2.63 (1 H, ddd, *J* 6.7, 14.1, 36.9, H-4), 3.31 (1 H, ddd, *J* 0.8, 8.2, 10.2, CH₂I), 3.48 (1 H, ddd, *J* 1.0, 4.9, 10.2, CH₂I), 4.49-4.59 (1 H, m, H-5); δ_{C} 5.30 (CH₂I), 6.11* (CH₂I) 20.1* (d, *J* 25.4, CH₃), 21.3 (d, *J* 26.5, CH₃) 40.7 (d, *J* 22.1, C-4), 42.1 (d, *J* 22.7, C-4), 75.6 (d, *J* 3.9, C-5), 92.9 (d, *J* 186.3, C-3), 172.7 (d, *J* 24.9, C=O); δ_{F} -146.5 (qdd, *J* 1.0, 23.1, 39.2), -148.5 (qdd, *J* 1.6, 22.6, 35.9)*m (1:9.7 diastereomeric mixture); MS (CI) *m/z* (rel. int.): 258 [MH]⁺ (55) and 238 (100).

6.1.6.27. (3*S*,5*S*)-3-Fluoro-5-(iodomethyl)-3-phenyltetrahydrofuran-2-one **255****255**

Product **255** was prepared from **253** (211 mg, 0.724 mmol), iodine (368 mg, 2.90 mmol), THF/H₂O (50/50) (2.0 cm³) to afford **255** as a colourless oil (220 mg, 95%); $[\alpha]_{\text{D}}^{20} = +3.9$ (*c* 0.80, CH₂Cl₂); HRMS (CI) Calc. for C₈H₁₂FIO₂: Calc. 320.9726, Found 320.9724; $\nu_{\text{max}}/\text{cm}^{-1}$ 3033, 2935, 1790, 1499, 1450, 1269, 1179, 1055; δ_{H} 2.70 (1 H, ddd, *J* 7.9, 14.1 22.0, H-4), 3.11 (1 H, ddd, *J* 6.1, 10.8, 14.1, H-4), 3.38 (1 H, ddd, *J* 0.5, 7.9, 10.5, CH₂I), 3.53 (1 H, ddd, *J* 1.0, 4.9, 10.5, CH₂I), 4.56 (1 H, dddd, *J* 1.5, 4.9, 6.1, 7.9, H-5), 4.74* (1 H, dddd, *J* 4.1, 5.6, 6.9, 8.7, H-5), 7.43-7.50 (5 H, m, Ph); δ_{C}

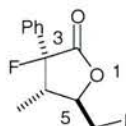
5.21 (CH₂I), 6.10* (CH₂I), 41.9 (d, J 23.2), 43.4* (d, J 23.2), 75.3 (d, J 5.5, C-5), 95.1 (d, J 191.8, CFPh), 125.2 (d, J 6.1, Ph), 125.3* (d, J 7.2, Ph), 128.7*, 129.0, 130.0 (d, J 2.2, Ph), 134.7 (d, J 24.3 C-1 of Ph), 171.3 (d, J 25.4, C=O); δ_F -144.1 (dd, J 10.7, 22.0), -150.8* (dd, J 21.2, 37.1) (diastereomeric mixture 1:17.6); MS (CI) m/z (rel. int.): 320 [MH]⁺ (5), 300 (43) and 174 (100).

6.1.6.28. (3*R*,4*S*,5*S*)-3-Fluoro-5-(iodomethyl)-3,4-dimethyltetrahydro-furan-2-one
243

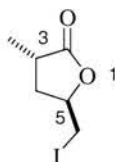


243

Lactone **243** was prepared from **242** (50 mg, 0.137 mmol), iodine (70 mg, 0.548 mmol), THF/H₂O (50/50) (2.0 cm³) to afford **243** (34 mg, 93%) as a mixture of stereoisomers. The stereoisomers were successfully separated over silica; data for major diastereoisomer: $[\alpha]_D^{20} = +6.3$ (*c* 0.59, CH₂Cl₂); HRMS (CI) Calc. for C₇H₁₁FIO₂: Calc. 272.9788, Found 272.9792; $\nu_{\max}/\text{cm}^{-1}$ 2978, 2928, 1792, 1450, 1324, 1190, 1050; δ_H 1.14 (3 H, dd, J 2.3, 7.2, CH₃), 1.62 (3 H, d, J 22.5, CFCH₃), 2.52-5.57 (1 H, m, H-4), 2.73 (1 H, dd, J 6.9, 10.5, CH₂I), 3.36 (1 H, ddd, J 1.8, 7.7, 10.5, CH₂I), 4.69 (1 H, ddd, J 6.9, 7.7, 13.4, H-5); δ_C 6.86 (d, J 9.2, CH₂I), 19.9 (d, J 27.6, CH₃), 29.7 (4-CH₃), 43.0 (d, J 20.7, 3-CH₃), 80.1 (C-5), 93.9 (d, J 188.8, C-3), 172.2 (d, J 25.3, C=O); δ_F -162.0-162.3)m; MS (CI) m/z (rel. int.): 272 [MH]⁺ (30) and 252 (100).

6.1.6.29. (3*S*,5*R*,5*S*)-3-Fluoro-5-(iodomethyl)-4-methyltetrahydrofuran-2-one **266****266**

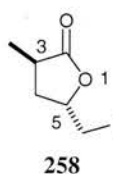
Lactone **266** was prepared from **264** (60 mg, 0.196 mmol), iodine (70 mg, 0.548 mmol), THF/H₂O (50/50) (2.0 cm³) to afford **266** (57 mg, 87%) as a mixture of stereoisomers. HRMS (CI) Calc. for C₁₂H₁₂OFI: Calc. 333.9866, Found 333.9861; $\nu_{\max}/\text{cm}^{-1}$ 3033, 2974, 1792, 1450, 1324, 1190, 1018; δ_{H} 1.15* (3 H, dd, J 1.5, J 6.9, CH₃), 1.21 (3 H, dd, J 2.3, J 7.2, CH₃), 3.00-3.14 (1 H, m, H-4), 3.26 (1 H, dd, J 7.9, 10.5, CH₂I), 3.41-3.47 (1 H, m, CH₂I), 3.70* (1 H, dd, J 3.8, 11.5, CH₂I), 4.14* (1 H, ddd, J 4.1, 7.9, 13.1, H-5), 4.66 (1 H, ddd, J 5.6, 7.4, 13.1, H-5), 7.38-7.49 (5 H, m, Ph), δ_{C} 5.4* (CH₂I), 6.80 (CH₂I), 29.4 (CH₃), 44.1 (d, J 21.6, C-4), 79.3 (C-5), 80.5* (C-5), 97.1 (d, J 196.3, CFPPh), 125.1, 125.3, 1125.7, 125.7, 129.0, 129.3, 129.9 (Aromatic carbons), 143.2 (C-1 of Ph), 171.3 (d, J 25.3, CO), δ_{F} -153.6* (d, J 22.0.), -159.5-(-159.6)m, MS (CI) *m/z* (rel. int.): 233 [MH]⁺ (10), 206 (3).

6.1.6.30. (3*R*,5*S*)-5-(Iodomethyl)-3-methyltetrahydrofuran-2-one **237**¹⁴**237**

Product **237** was prepared from **236** (150 mg, 0.450 mmol), iodine (350 mg, 2.77 mmol), THF/ H₂O (50/50) (2.0 cm³) to afford **237** as a colourless oil (91 mg, 85%); $[\alpha]_{\text{D}}^{20} = -4.3$ (*c* 0.72, CH₂Cl₂); HRMS (CI) Calc. for C₆H₁₀IO: Calc. 240.9726, Found 240.9725; $\nu_{\max}/\text{cm}^{-1}$ 2969, 2927, 1768, 1454, 1377, 1345, 1174, 1004; δ_{H} 1.27 (3 H, d, J 7.2, CH₃), 2.08 (1 H, ddd, J 4.9, 12.8, 13.3, H-4), 2.29 (1 H, ddd, J 4.6, 9.5, 13.3, H-4), 2.72-2.86 (1 H, m, H-3), 3.25 (1 H, dd, J 7.4, CH₂I), 3.35 (1 H, dd, J 7.4, CH₂I), 4.32-

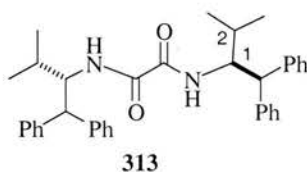
4.41* (1 H, m, H-5), 4.54-4.62 (1 H, m, H-5); δ_{C} 6.8* (CH₂I), 7.1 (CH₂I), 15.1* (CH₃), 16.1 (CH₃), 34.1 (C-3), 25.3 (C-4), 36.2* (C-3), 37.6 (C-4), 76.5 (C-5), 179.1 (C=O); MS (CI) m/z (rel. int.): 240 [MH]⁺ (100) and 113 (20).

6.1.6.31. (3*S*,5*S*)-5-(Iodomethyl)-3-methyltetrahydrofuran-2-one **258**¹⁴



Product **258** was prepared from **257** (147 mg, 0.696 mmol), iodine (353 mg, 2.78 mmol), THF/ H₂O (50/50) (2.0 cm³) to afford **258** as a colourless oil (155 mg, 93%); $[\alpha]_{\text{D}}^{20} = +4.1$ (*c* 0.72, CH₂Cl₂); HRMS (CI) Calc. for C₆H₁₀IO: Calc. 240.9726, Found 240.9725; $\nu_{\text{max}}/\text{cm}^{-1}$ 2969, 2932, 1768, 1454, 1377, 1345, 1174, 1004; δ_{H} 1.27 (3 H, d, J 7.2, CH₃), 2.08 (1 H, ddd, J 4.9, 12.8, 13.3, H-4), 2.29 (1 H, ddd, J 4.6, 9.5, 13.3, H-4), 2.72-2.86 (1 H, m, H-3), 3.25 (1 H, dd, J 7.4, CH₂I), 3.35 (1 H, dd, J 7.4, CH₂I), 4.32-4.41* (1 H, m, H-5), 4.54-4.62 (1 H, m, H-5); δ_{C} 6.8* (CH₂I), 7.1 (CH₂I), 15.1* (CH₃), 16.1 (CH₃), 34.1 (C-3), 25.3 (C-4), 36.2* (C-3), 37.6 (C-4), 76.5 (C-5), 179.1 (C=O); MS (CI) m/z (rel. int.): 240 [MH]⁺ (100) and 113 (20).

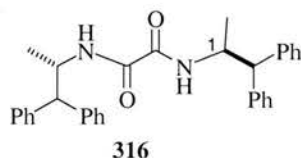
6.1.6.32. *N*¹,*N*²-Bis[(1*S*)-1-benzhydryl-2-methylpropyl]ethanediamide **313**



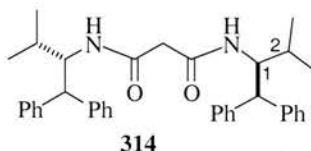
Oxalyl chloride (54.2 mg, 0.42 mmol) was added to a solution of isopropylamine **94** (206 mg, 0.84 mmol) and triethylamine (2.54 mg, 2.51 mmol) in CH₂Cl₂ (2.0 cm³) at -78 °C. The reaction was allowed to reach rt over 1 h. Stirring was continued for a further 3 h, followed by the addition of water (20 cm³). The phases were separated, and the aqueous layer extracted into ether (3 x 5.0 cm³). The combined organic extracts were evaporated and the resulting solid residue was purified over a short silica plug (EtOAc-hexane, 1:1), affording the bisamide **313** (203 mg, 91%), as a white amorphous

solid mp 210-213 °C; $[\alpha]_{\text{D}}^{20} = +3.3$ (*c* 0.35, CH₂Cl₂), Exact mass: Calculated for C₃₆H₄₁N₂O₂, 553.3168; Observed, 553.3176; $\nu_{\text{max}}/\text{cm}^{-1}$ 3375, 1680, 1669; δ_{H} 0.79 (6 H, d, J 6.6, H-3), 0.81 (6 H d, J 6.6, CH₃), 1.69 (2 H, m, H-2), 3.90 (2 H, d, J = 10.5, H-1), 4.54 (2 H, m, CHPh₂), 6.99-7.19 (12 H, m, Ph); δ_{C} 14.1 (C-3), 19.7 (CH₃), 28.1 (C-2), 53.5 (CHPh₂), 55.6 (C-1), 125.3, 125.6, 126.8, 127.4, 127.8, 140.3, 144.1 (aromatic carbons), 158.4 (C=O); MS *m/z* (rel. int. %) (CI) 553 (MH⁺) (100), 365 (70) and 286 (50).

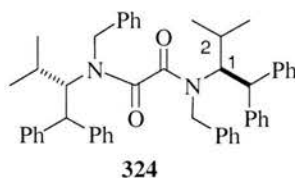
6.1.6.33. *N*¹,*N*²-Bis[(1*S*)-1-Benzhydrylethyl]ethanediamide **316**



Oxalyl chloride (301 mg, 2.37 mmol) was added to a stirred solution of methylamine **92** (1.00 g, 4.73 mmol) and triethylamine (1.44 g, 14.2 mmol) in CH₂Cl₂ (50 cm³) at -78 °C. The mixture was allowed to reach rt in 15 min, and was further stirred for 3 h. Water (40 cm³) was added and the aqueous layer extracted into ether (3 x 10 cm³). The combined ethereal extracts were dried, filtered and evaporated. The crude product was washed with cold hexane, to give ethanediamide **316** (1.09g, 96%) as a crystalline solid, mp 210-212 °C; $[\alpha]_{\text{D}}^{20} = -62$ (*c* 0.80, CH₂Cl₂); Exact mass: Calculated for C₃₂H₃₃N₂O₂, 447.2542; observed, 447.2530; $\nu_{\text{max}}/\text{cm}^{-1}$ 3320, 3031, 3024, 1645, 1505, 1450; δ_{H} 1.05 (6 H, d, J 6.3, CH₃), 3.80 (2 H, d, J 9.9, CHPh₂), 4.65 (2 H, m, H-1), 7.08-7.20 (20 H, m, Ph); δ_{C} 20.3 (CH₃), 48.5 (CHPh₂), 58.2 (C-1), 127.1, 127.2, 128.4, 128.6, 128.9, 129.1, 129.3, 141, 142.2 (aromatic carbons), 159.2 (C=O); MS *m/z* (rel. int. %) (CI) 447 (MH⁺) (30), 163 (100) and 75 (45).

6.1.6.34. *N*¹,*N*²-Bis[(1*S*)-1-benzhydryl-2-methylpropyl]propanediamide **314**

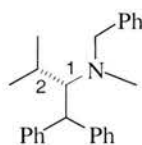
Triethylamine (216 mg, 2.13 mmol) was added to a solution of isopropylamine **94** (200 mg, 0.836 mmol) and malonyl dichloride (58.7 mg, 0.418 mmol) in CH₂Cl₂ (3.0 cm³) following the procedure outlined under section 6.4.1. The product was purified by washing with cold hexane to afford propanediamide **314** (142 mg, 62%), as a white amorphous solid mp (175-178 °C); [α]_D²⁰ = -1.4 (c 0.70, CH₂Cl₂); Exact mass: Calculated for C₃₆H₄₁N₂, 501.3270; Observed, 501.3255; ν_{\max} /cm⁻¹ 3306, 3031, 3024, 2960, 1664, 1450; δ_{H} 0.97 (12 H, m, H-3 & CH₃), 1.85 (2 H, m, H-1), 2.68 (2 H, m, CH₂), 4.051 (2 H, d, J 11.1, CHPh₂), 4.95 (2 H, m, J 11.1, 10.8, H-1), 6.59-7.44 (20 H, m, Ph); δ_{C} 15.2 (C-3), 21.2(CH₃), 29.3 (C-2), 43.2 (CH₂), 55.5 (CHPh₂), 56.2 (C-1), 126.8, 126.9, 128.2, 128.3, 128.8, 129.2, 142.6, 142.7, (aromatic carbons); 167.5 (C=O); MS m/z (rel. int. %) (CI) 501 (MH⁺) (100), 335 (17) and 194 (50).

6.1.6.35. *N*¹,*N*²-Bis[(1*S*)-1-benzhydryl-2-methylpropyl]-*N*¹,*N*²-dibenzylethanediamide **324**

Compound **324** was prepared by coupling of the secondary amine **144** (300 mg, 0.91 mmol) with oxalyl chloride (57.8 mg, 0.46 mmol) and Et₃N (277 mg, 2.73 mmol) in CH₂Cl₂ (5.0 cm³) using the procedure described in section 6.4.1 above. The product was purified over SiO₂ to afford benzylethanediamide **324** (269 mg, 83%) as a white amorphous solid, mp 222-224 °C, [α]_D²⁰ = +6.6 (c 0.65, CH₂Cl₂); ν_{\max} /cm⁻¹ 3031, 3025, 2960, 2953, 1634, 1450; δ_{H} 0.48 (6 H, d, J 7.20, H-3), 0.53 (6 H, d, J 6.90, CH₃), 1.50 (2 H, m, H-2), 3.21 (2 H, d, J 9.0, CH₂), 3.42 (2 H, d, J 9.0, CH₂), 4.06 (2 H, d, J 12.6, CHPh₂), 5.67 (2 H, dd, J 12.6, 12.6, H-1), 6.65-7.61 (24 H, m, Ph); δ_{C} 20.3 (C-3), 22.2

(CH₃), 33.5 (C-2), 55.3 (CH₂), 59.5 (CHPh₂), 67.0 (C-1), 126.6, 126.8, 127.6, 128.5, 128.6, 128.9, 129.1, 130.1, 131.4, 137.7, 143.0, 143.5, 143.9 (aromatic carbons); 169.2 (C=O).

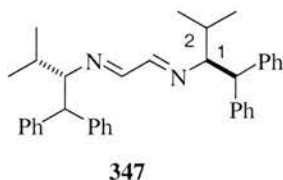
6.1.6.36. *N*-[(1*S*)-1-Benzhydryl-2-methylpropyl]-*N*-benzylmethylamine **325**



325

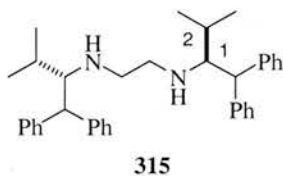
LiAlH₄ (6.10 mg, 0.16 mmol) was added to a solution of bisamide **324** (23.0 mg, 0.03 mmol) in THF (5.0 cm³) and the reaction was stirred for 15 h at reflux. Unreacted LiAlH₄ was quenched with ethyl acetate, and then water (1.0 cm³) added. The mixture was filtered, dried over MgSO₄ and evaporated *in vacuo*. The product was purified over SiO₂ (EtOAc-hexane, 1:9) to give **325** (14.6 mg, 66%) as a white amorphous powder, mp 92-95 °C; [α]_D²⁰ = -0.4 (c 0.60, CH₂Cl₂); Exact mass: Calculated for C₂₅H₃₀N, 344.2378; Observed, 344.2387; δ_H 0.80 (3 H, d, J 7.2, H-3), 1.00 (3 H, d, J 6.9, CH₃), 1.78 (1 H, m, H-2), 2.11 (3 H, s, NCH₃); 3.56 (1 H, dd, J 7.7, J 11.4, H-1), 3.58 (1 H, d, J 14.1, CH₂), 3.68 (1 H, d, J 14.1, CH₂), 4.21 (1 H, d, J 11.4, CHPh₂), 6.84-7.38 (15 H, m, Ph); δ_C 14.6 (C-3), 16.1 (CH₃), 30.8 (C-2), 39.2 (NCH₃), 54.9 (CHPh₂), 61.1 (CH₂), 71.3 (C-1), 126.4, 126.7, 126.9, 28.3, 128.4, 128.6, 128.9, 129.0, 129.1, 141.4 (aromatic carbons), (C-1 of Ph), 144.9 (C-1 of Ph), 145.4 (C-1 of Ph); MS m/z (rel. int. %) (CI) 344 (MH⁺) (45), 176 (23) and 57 (100).

6.1.6.37. (2*S*)-*N*-((*E*,2*E*)-2-[[*E*,1*S*]-1-Benzhydryl-2-methylpropylimino]-ethylidene)-3-methyl-1,1-diphenyl-2-butanamine **347**



Formic acid (90%), (2.05 mg, 0.05 mmol), and isopropylamine **94** (200 mg, 0.84 mmol) were added to a suspension of aq. glyoxal (40%) and freshly dehydrated MgSO₄ (1.00 g) in CH₂Cl₂ (5.0 cm³). The mixture was vigorously stirred for 16 h, filtered and the product concentrated under vacuum. The crude product was purified over a small SiO₂ plug (EtOAc-hexane, 1:9), to give the diazadiene **347** (210 mg, 100%) as a white amorphous solid, mp 115-117 °C; [α]_D²⁰ = +28 (c 0.50, CH₂Cl₂); Exact mass: Calculated for C₂₈H₃₁NO₃F, 448.2288; Observed, 448.2299; ν_{max}/cm⁻¹ 3453, 3319, 3065, 3029, 2960, 2953, 1629, 1594, 1497, 1447, 1360; δ_H 0.73 (6 H, d, J 5.9, H-3), 0.82 (6 H, d, J 6.9, CH₃), 1.78 (2 H, m, H-2), 3.51 (2 H, dd, J 9.3, H-1), 4.22 (2 H, d, J 9.3, CHPh₂), 6.98-7.18 (20 H, m, Ph), 7.35 (2 H, s, CH=CH); δ_C 16.6 (C-3), 21.1 (CH₃), 29.9 (C-2), 55.2 (CHPh₂), 80.2 (C-1), 126.6, 126.7, 128.7, 128.8, 129.0, 142.2 (aromatic carbons), (C-1 of Ph), 142.8 (C-1 of Ph), 162.3 (C=C); MS m/z (rel. int. %) (CI) 501 (MH⁺) (100), 280 (46) and 75 (100).

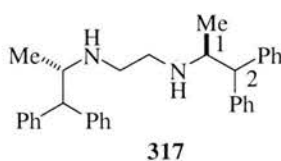
6.1.6.38. *N*¹,*N*²-Bis[(1*S*)-1-benzhydryl-2-methylpropyl]-1,2-ethanediamine **315**.



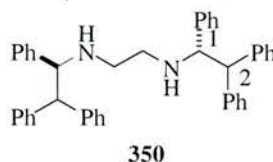
A suspension of LiAlH₄ (45 mg, 1.20 mmol) in THF (10 cm³) was charged with diimine **347** (120 mg, 0.240 mmol). The reaction mixture was heated under reflux for 1 h and was then quenched with ethyl acetate and water. The organics were decanted, concentrated to give a white solid which was recrystallised in ether (121 mg, 100%). Mp 115-117 °C; [α]_D²⁰ = +46 (c 0.50, CH₂Cl₂); Elemental analysis C, 85.66, H, 8.79, N, 5.55. C₃₆H₄₄N₂ requires: C, 85.41, H, 9.14, N, 5.37; ν_{max}/cm⁻¹ 3319, 3060, 3026, 2964,

2928, 1598, 1493, 1450, 1374, 1152, 1031; δ_{H} 0.65 [6 H, d, J 6.9, CH(CH₃)₂], 0.82 [6 H, d, J 6.9, CH(CH₃)₂], 1.57 [2 H, m, CH(CH₃)₂], 1.99 (2 H, m, CH₂), 2.16 (2 H, m, CH₂), 2.92 (1 H, m, H-1), 3.64 (1 H, d, J 10.3, H-2), 7.06-7.26 (20 H, m, Ph); δ_{C} 14.2 (CH₃), 20.0 (CH₃), 28.6 [CH(CH₃)₂], 35.6 (CH₂), 55.6 (C-2), 64.9 (CHPh₂), 124.6, 124.8, 126.8, 127.1, 127.3 (aromatic carbons) 142.6 (C-1 of Ph), 142.6 (C-1 of Ph); MS m/z (rel. int. %) (CI) 505 (MH⁺) (100), 337 (95) and 169 (16).

6.1.6.39. *N*¹,*N*²-Bis[(1*S*)-methyl-2,2-diphenylethyl]-1,2-ethanediamine **317**.



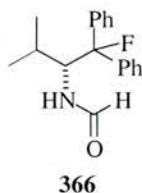
A suspension of aq. glyoxal (40%) (10.3 mg, 0.710 mmol) was added to a solution of ZnCl₂ (2 M in ether) (2 drops) and amine **92** (300 mg, 1.42 mmol) in CH₂Cl₂ (10.0 cm³). The mixture was vigorously stirred for 1 h, following standard work up procedure, the crude product was directly charged with LiAlH₄ (108 mg, 2.85 mmol) in THF (15 cm³). After 1 h of reflux, the reaction was then quenched with ethyl acetate and water. The organics were decanted, concentrated and the title compound was recovered as colourless oil (314 mg, 99%) yield; $[\alpha]_{\text{D}}^{20} = -27$ (c 0.63, CH₂Cl₂); Exact mass: Calculated for C₃₂H₃₆N₂: 446.2957, found: 449.2962; $\nu_{\text{max}}/\text{cm}^{-1}$ 3316, 3084, 3061, 3026, 2954, 2924, 2851, 1598, 1493, 1451, 1374, 1140, 1031; δ 0.85 (3 H, d, J 6.0, CH₃), 1.52 (1 H, br, NH), 2.36 (2 H, m, CH₂), 2.59 (2 H, m, CH₂), 3.28 (2 H, dt, J 9.6, J 6.0, H-1), 3.59 (2 H, d, J 9.6, H-2), 7.05-7.19 (20 H, m, Ph), δ_{C} 19.2 (CH₃), 47.2 (CH₂), 56.2 (C-1), 59.5 (C-2), 126.7, 127.0, 128.7, 128.9, 129.1, 129.3, 143.0 (C-1 of Ph), 143.8 (C-1 of Ph), MS m/z (rel. int. %) (CI) 449 (MH⁺) (100), 281 (26) and 212 (25).

6.1.6.40. *N*¹,*N*²-Bis[(1*S*)-1,2,2-triphenylethyl]-1,2-ethanediamine **350**.

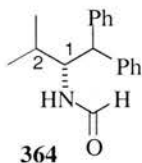
A suspension of aq. glyoxal (40%) (9.79 mg, 0.710 mmol) was added to a solution of ZnCl₂ (2 M in ether) (2 drops) and amine **93** (370 mg, 1.35 mmol) in CH₂Cl₂ (10.0 cm³). The mixture was vigorously stirred for 1 h, following standard work up procedure, the crude product was directly charged with LiAlH₄ (102 mg, 2.70 mmol) in THF (15 cm³). After 1 h under reflux, the reaction was then quenched with ethyl acetate and water. The organics were decanted, concentrated the title compound as colourless oil (385 mg, 99%) yield mp 132-124 °C; [α]_D²⁰ = -66 (c 0.72, CH₂Cl₂); Elemental analysis C, 88.07, H, 7.04, N, 4.89. C₄₂H₄₀N₂ requires: C, 87.76, H, 6.79, N, 4.83; ν_{max}/cm⁻¹ 3318, 3060, 3024, 2909, 2838, 1596, 1490, 1450, 1341, 1136, 1028; δ_H 1.61 (1 H, br, NH), 2.14 (2 H, m, CH₂), 2.22 (2 H, m, CH₂), 3.96 (1 H, d, J 9.90, H-1), 4.12 (1 H, d, J 9.90, H-2), 6.90-7.34 (30 H, m, Ph); δ_C 47.4 (CH₂), 60.1 (C-1), 66.9 (C-2), 126.3, 127.2, 127.2, 128.2, 128.7, 128.9, 129.0, 129.2 (aromatic carbons), 142.4 (C-1 of Ph), 142.8 (C-1 of Ph); MS m/z (rel. int. %) (CI) 573 (MH⁺) (100), and 405 (27).

6.1.7. General Procedure G

An aldehyde (1,2 eq.) was added to a solution of the amine in methanol (0.5 M) at rt. Following addition of and acid (1.2 eq), *tert*-butyl isocyanide (1.5 eq.) was added and the reaction allowed to stir for 3 h at ambient temperature. The reaction was then quenched with a solution of saturated bicarbonate and extracted with ether (3 x), the ethereal layer was dried with MgSO₄, filtered and concentrated *in vacuo*.

6.1.7.1. (1*S*)-1-[Fluoro(diphenyl)methyl]-2-methylpropylformamide **366**

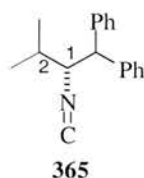
Formic acid (81 mg, 1.71 mmol) was added to a solution of the amine (*R*)-**96** (220 mg, 0.855 mmol) in toluene (20 cm³). The mixture was heated to 100 °C for 6 h saturated bicarbonate (10 cm³) was added. The organics were extracted into ether (3x 10 cm³) upon which the title compound precipitated out as white crystalline solid (239 mg, 98%); mp 118-119 °C; $[\alpha]_D^{20} = -61.8$ (*c* 0.54 CH₂Cl₂); Elemental analysis C, 75.76, H, 7.06, N, 4.91. C₁₈H₂₀FNO requires: C, 75.61, H, 6.93, N, 4.90; $\nu_{\max}/\text{cm}^{-1}$ 3396, 2926, 1677, 1505, 1452, 1391, 1264; δ_{H} 0.90* [3 H, d, J 6.9, CH(CH₃)₂], 0.91 [3 H, d, J 6.7, CH(CH₃)₂], 0.92 [3 H, d, J 6.9, CH(CH₃)₂], 1.87-1.94 [1 H, m, CH(CH₃)₂], 5.17 (1 H, ddd, J 2.0, 10.5, 34.6, NCH), 6.09 (1 H, d, J 10.5, NH), 7.17-7.50 (10 H, m, Ph), 8.04 (1 H, d, J 1.7, HCO); δ_{C} 21.8* [CH(CH₃)₂], 22.0 [CH(CH₃)₂], 27.9* [CH(CH₃)₂], 28.4 [CH(CH₃)₂], 52.3* (d, J 19.9, NCH), 55.6 (d, J 18.2 NCH), 102.9 (d, J 183.0, CFPh₂), 123.8, 123.9, 124.5, 124.6, 127.4, 127.5, 127.6, 128.2, 128.3, 128.5, 128.6 (aromatic carbons), 141.9* (C-1 of Ph), 142.2 (C-1 of Ph), 161.1 (CO), 164.4* (CO); δ_{F} -170.8* (d, J 31.7), -168.9 (d, J 35.6).

6.1.7.2. *N*-(1*S*)-1-Benzhydryl-2-methylpropylformamide **364**

Formic acid (346 mg, 7.52 mmol) was added to a solution of the amine (*R*)-**94** (485 mg, 1.88 mmol) in toluene (30 cm³). The mixture was heated to 100 °C for 6 h saturated bicarbonate (10 cm³) was added. The organics were extracted into ether (3 x 10 cm³) upon which the title compound precipitated out as white crystalline solid (498 mg, 98%); mp 168-170 °C; $[\alpha]_D^{20} = +9.1$ (*c* 0.34 CH₂Cl₂); Elemental analysis Found: C, 80.86, H, 7.92, N, 5.24. C₁₈H₂₁NO requires: C, 80.98, H, 7.66, N, 5.29; $\nu_{\max}/\text{cm}^{-1}$ 3395,

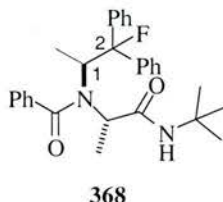
2926, 1676, 1505, 1452, 1390, 1264; δ_{H} 0.84* [3 H, d, J 6.7, $\text{CH}(\text{CH}_3)_2$], 0.86 [3 H, d, J 6.7, $[\text{CH}(\text{CH}_3)_2]$], 0.93 [3 H, d, J 6.9, $[\text{CH}(\text{CH}_3)_2]$], 0.94* [3 H, d, J 6.9, $[\text{CH}(\text{CH}_3)_2]$], 1.69-1.79 [1 H, m, $\text{CH}(\text{CH}_3)_2$], 1.82-1.89* [1 H, m, $\text{CH}(\text{CH}_3)_2$], 3.93 (1 H, d, J 11.3, CHPh_2), 4.99 (1 H, ddd, J 8.2, 11.3, 10.5, C-1), 5.30 (1 H, d, J 10.5, NH), 7.12-7.35 (10 H, m, Ph), 8.00 (1 H, s, HCO); δ_{C} 14.7* $[\text{CH}(\text{CH}_3)_2]$, 14.8 $[\text{CH}(\text{CH}_3)_2]$, 20.7* $[\text{CH}(\text{CH}_3)_2]$, 20.9 $[\text{CH}(\text{CH}_3)_2]$, 28.3* $[\text{CH}(\text{CH}_3)_2]$, 28.7 $[\text{CH}(\text{CH}_3)_2]$, 55.3* (C-1), 54.9 (C-1), 60.8 (CHPh_2), 126.6, 126.7, 126.9, 127.0, 127.7, 127.8, 127.9, 128.1, 128.2, 128.6, 128.8, 128.9 (aromatic carbons), 141.3* (C-1 of Ph), 141.4* (C-1 of Ph), 142.0 (C-1 of Ph), 142.3 (C-1 of Ph), 161.1 (CO), 164.4* (CO) (*: denotes the minor rotamer).

6.1.7.3. (R)-1-Benzhydryl-2-methylpropyl isocyanide **365**



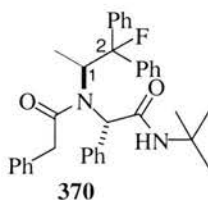
Diisopropylamine (204 mg, 2.02 mmol) was added to a stirring solution of the formamide **364** (200 mg, 0.748 mmol) followed by a slow addition of phosphorus oxychloride at rt. After 4 h K_2CO_3 (5.0 cm^3 , 20%) was added and stirring continued for 45 min after which water (30 cm^3). The organics were extracted into CH_2Cl_2 (3x 10 cm^3) following standard work-up procedure. The product was purified over column chromatography to give the title product as light yellow oil, yield 167 mg, 90%; $[\alpha]_{\text{D}}^{20} = +15.4$ (c 0.63 CH_2Cl_2); HRMS (ES) Calc. For $\text{C}_{18}\text{H}_{19}\text{N}$: 249.1517, Found 249.1515; $\nu_{\text{max}}/\text{cm}^{-1}$ 3089, 3063, 3029, 2968, 2933, 2877, 2138, 1598, 1496, 1452, 1372, 1222, 1082; δ_{H} 1.05 [3 H, d, J 6.9, $\text{CH}(\text{CH}_3)_2$], 0.99 [3 H, d, J 6.7, $\text{CH}(\text{CH}_3)_2$], 1.69-1.80 [1 H, m, $\text{CH}(\text{CH}_3)_2$], 4.08 (1 H, d, J 10.7, CHPh), 4.21 [1 H, dd, J 3.1, 10.7, $\text{CH}(\text{CH}_3)_2$], 7.16-7.39 (10 H, m, Ph); δ_{C} 14.9 $[\text{CH}(\text{CH}_3)_2]$, 20.6 $[\text{CH}(\text{CH}_3)_2]$, 28.1 $[\text{CH}(\text{CH}_3)_2]$, 53.9 (C-1), 64.6 (CHPh_2), 127.1, 127.1, 127.6, 128.0, 128.6, 128.9 (aromatic carbons), 140.0 (C-1 of Ph), 140.6 (C-1 of Ph), 157.3 (NC); MS (CI) m/z (rel. int.): 249 $[\text{M}]^+$ (8) and 167 (100).

6.1.7.4. *N*-[(1*R*)-2-(*Tert*-Butylamino)-1-methyl-2-oxoethyl]-*N*-[(1*S*)-2-fluoro-1-methyl-2,2-diphenylethyl]benzamide **368**



The title compound was prepared according to the general procedure G described above from amine **95** (23 mg, 0.100 mmol), acetaldehyde (7.00 mg, 0.15 mmol), benzoic acid (13 mg, 0.11 mmol) and isocyanide (13 mg, 0.11 mmol) in methanol (0.2 cm³) to give the product as a white amorphous solid, mp 157-159 °C (27 mg, 59%), δ_{H} 1.13 [9 H, s, C(CH₃)₃], 1.38 (3 H, d, J 7.1, CHCH₃), 1.65 (3 H, d, J 6.9, NCHCH₃), 4.30 (1 H, q, J 6.9, NCHCH₃), 5.06 (1 H, dq, J 7.1, CHCFPh₂), 6.88-7.55 (15 H, m, Ph); δ_{C} 14.8 (CH₃), 16.7 (CH₃), 28.3 [C(CH₃)₃], 50.3 [C(CH₃)₃], 58.4 (NCHCH₃), 60.1 (CHCH₃), 97.2 (d, J 183.0), 123.7, 123.9, 125.0, 125.1, 126.7, 127.9, 128.6, 128.7, 130.4, 137.0 (aromatic carbons), 140.1 (C-1 of Ph), 142.0 (C-1 of Ph), 165.1 (NCO), 169.4 (NCO); δ_{F} -171.6 (d, J 29.0).

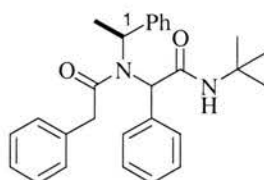
6.1.7.5. *N*-(*Tert*-Butyl)-2-[*N*-[(1*S*)-2-fluoro-1-methyl-2,2-diphenylethyl](phenylacetyl)amino]-2-phenylacetamide **370**



Prepared from amine **95** (49 mg, 0.214 mmol), benzaldehyde (27.3 mg, 0.257 mmol), phenylacetic acid (32 mg), isocyanide (27 mg, 0.321 mmol) and methanol (0.4 cm³) to give (77 mg, 67%) of a diastereomeric mixture mp 164-166 °C; HRMS (CI) Calc. for C₃₅H₃₇FN₂O₂Na: 559.2917, Found 559.2900; ν_{max} /cm⁻¹ 3421, 2924, 2853, 1730, 1692, 1597, 1461, 1377; δ_{H} 1.13 [9 H, s, C(CH₃)₃], 1.38 (3 H, d, J 7.1, CHCH₃), 3.82 (1 H, d, J 15.1, CH₂), 3.92 (1 H, d, J 15.1, CH₂), 5.06 (1 H, dq, J 7.1, CHCFPh₂), 5.26 (1, s, NCHPh), 6.88-7.55 (15 H, m, Ph); δ_{C} 14.8 (CH₃), 16.7 (CH₃), 28.3 [C(CH₃)₃], 42.7

(CH₂), 50.3 (CCH₃), 60.1 (CHCH₃), 97.2 (d, J 183.0), 123.7, 123.9, 125.0, 125.1, 126.7, 127.9, 128.6, 128.7, 130.4, 137.0 (C-1 of Ph), 140.1 (C-1 of Ph), 142.0 (C-1 of Ph), 165.1 (NCO), 169.4 (NCO); δ_F -171.6 (d, J 29.0); MS (ES) m/z (rel. int.): 559 (100) and 357 (8).

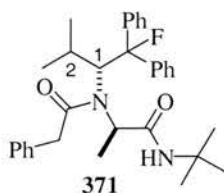
6.1.7.6. *N*-(*Tert*-Butyl)-2-phenyl-2-[(phenylacetyl)[*N*-(1*S*)-1-phenylethyl]amino]acetamide **369**



369

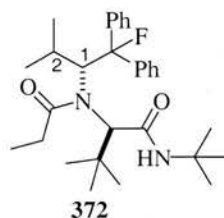
Prepared from (*S*)-phenylethanamine **326** (509 mg, 4.20 mmol), benzaldehyde (363 mg, 8.25 mmol), phenylacetic acid (686 mg, 4.20 mmol) and isocyanide (349, 4.20 mmol) in methanol (5.0 cm³) to afford the product as white amorphous solid (1.20 g, 67%), mp 86-88 °C; $\nu_{\max}/\text{cm}^{-1}$ 3424, 3053, 2926, 2935, 1674, 1642, 1543, 1496, 1454, 1364, 1264; HRMS (CI) Calc. for C₂₈H₃₃N₂O₂: 429.2542, Found 429.2552; δ_H 1.11* [9 H, s, C(CH₃)₃], 1.23 * [9 H, s, C(CH₃)₃], 1.30* (3 H, d, J 6.9, CH₃), 1.59 (3 H, d, J 7.2, CH₃) 3.82 (1 H, d, J 15.1, CH₂), 3.92 (1 H, d, J 15.1, CH₂), 4.39 (1 H, br, NH), 5.26 (1, m, NCHPh), 6.34 (1 H, s, NCHCO), 6.81-7.29 (15 H, m, Ph); δ_C 17.1, 18.3* (CH₃), 28.5, 30.9* (CCH₃), 42.7 (CH₂), 56.8 (NCHCO), 64.6 (PhCH), 127.0, 127.1, 127.3, 127.4, 127.5, 127.5, 127.7, 127.8, 127.9, 128.2, 128.4, 128.7, 128.9 (aromatic carbons), 134.9 (C-1 of Ph), 136.6 (C-1 of Ph), 138.5 (C-1 of Ph), 169.7 (NCO), 169.8 (RCO₂R'); MS (CI) m/z (rel. int.): 429 (100), 356 (32), 325 (30) and 224 (10).

6.1.7.7. (2*R*)-*N*-(*Tert*-Butyl)-2-[*N*-[(1*S*)-1-[fluoro(diphenyl)methyl]-2-methylpropyl](*N*-phenylacetyl)amino]propanamide **371**



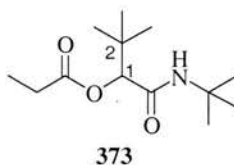
Prepared from amine (*R*)-**96** (50 mg, 0.19 mmol), acetaldehyde (10.0 mg, 0.228 mmol), phenylacetic acid (31 mg, 0.228), isocyanide (24 mg, 0.285 mmol) and methanol (0.4 cm³) to give (74 mg, 77%), mp 105-107 °C, $\nu_{\max}/\text{cm}^{-1}$ 3400, 3053, 2924, 2854, 2305, 1670, 1651, 1456, 1377, 1264; HRMS (CI) Calc. for C₃₂H₄₀FN₂O₂Na: 525.2817, Found 525.2815; δ_{H} 0.79 [3 H, J 6.9, CH(CH₃)₂], 0.90 [C(CH₃)₃], 0.97 [3 H, J 7.1, CH(CH₃)₂], 1.77 (3, d, J 7.1, NCHCH₃), 2.02-2.09 [CH(CH₃)₂], 3.31 (1 H, dd, J 5.9, 21.0, CHCFPh₂), 3.25 (1 H, d, J 15.6, CH₂), 3.70 (1 H, d, J 15.6, CH₂), 4.76 (1 H, q, J 7.1, NCHCH₃), 6.99-7.63 (15 H, m, Ph); δ_{C} 19.1 (CH₃), 20.0 [CH(CH₃)₂], 20.6 [CH(CH₃)₂], 31.5 [CH(CH₃)₂], 27.8 [C(CH₃)₃], 51.1 (CH₂), 59.9 (d, J 21.0, NCHCFPh₂), 65.2 (NCHCH₃), 105.0 (d, J 186.3, CFPh₂), 127.8, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.7, 129.3, 129.4, 129.7 (aromatic carbons), 135.9, 141.8, 143.4 (C-1 of Ph), 170.8 (C=O), 172.8 (C=O); MS (ES) *m/z* (rel. int.): 525 (100) and 503 (10).

6.1.7.8. (2*R*)-*N*-(*Tert*-Butyl)-2-[*N*-[(1*S*)-1-[fluoro(diphenyl)methyl]-2-methylpropyl](*N*-propionyl)amino]-3,3-dimethylbutanamide **372**



Prepared from amine (*R*)-**96** (50 mg, 0.19 mmol), pivalaldehyde (20.0 mg, 0.228 mmol), propionic acid (17 mg, 0.228), isocyanide (24 mg, 0.285 mmol) and methanol (0.4 cm³) to give (37 mg, 40%), $\nu_{\max}/\text{cm}^{-1}$ 3401, 3053, 2925, 2855, 1671, 1651, 1496, 1455, 1376, 1265; δ_{H} 0.77 [3 H, d, J 6.7, CH(CH₃)₂], 0.78 [3 H, d, J 6.9, CH(CH₃)₂], 0.94 (9 H, s, CCH₃), 1.22 (3 H, t, J 7.7, CH₂CH₃), 1.27 (9 H, s, CCH₃), 1.96-2.07 [1 H, m, CH(CH₃)₂], 2.35 (2 H, q, J 7.7, CH₂CH₃), 3.32 (1 H, dd, J 5.9, 21.0, CHCFPh₂), 4.63 (1 H, s, CHCCH₃), 5.54 (1 H, br, NH), 7.12-7.28 (10 H, m, Ph); δ_{C} 9.14 (CH₂CH₃), 15.7 [CH(CH₃)₂], 15.8 [CH(CH₃)₂], 26.2 [C(CH₃)₃], 26.6 [C(CH₃)₃], 27.6 (CH₂CH₃), 29.3 [CH(CH₃)₂], 34.0 [C(CH₃)₃], 51.1 (NCCH₃), 60.9 (d, J 20.5, NCCFPh₂), 83.5 (d, J 24.9, NCHCO), 102.9 (d, J 184.1, (CFPh₂), 124.3, 124.8, 126.0, 126.4, 126.9, 127.6, 127.8, 128.5 (aromatic carbons), 141.1 (C-1 of Ph), 142.9 (C-1 of Ph), 167.6 (NC=O), 172.9 (NC=O); δ_{F} -153.7 (d, J 21.0), -168.7* (d, J 35.5).

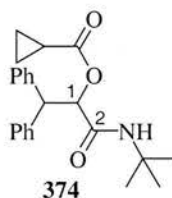
6.1.7.9. 1-[(*Tert*-Butylamino)carbonyl]-2,2-dimethylpropyl propionate **373**



Prepared from amine (*R*)-**96** (50 mg, 0.19 mmol), pivalaldehyde (20.0 mg, 0.228 mmol), propionic acid (17 mg, 0.228), isocyanide (24 mg, 0.285 mmol) and methanol (0.4 cm³) to give (15 mg, 33%), mp 45-47°C, (the Passerini product) HRMS (ES) Calc. For: C₁₃H₂₅NO₃Na: 266.1732, Found 266.1726; $\nu_{\max}/\text{cm}^{-1}$ 3439, 3387, 3055, 2927, 1742, 1684, 1519, 1455 1366, 1265; δ_{H} 1.02 [9 H, s, C(CH₃)₃], 1.20 (3 H, t, J 7.7,

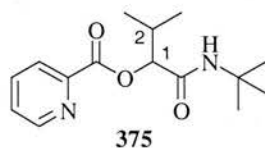
CH_2CH_3), 1.35 [9 H, s, $\text{C}(\text{CH}_3)_3$], 2.43 (2 H, q, J 7.7, CH_2CH_3), 4.71 [1 H, s, $\text{OCHC}(\text{CH}_3)_3$], 5.63 (1 H, s br, NH); ^{13}C NMR: δ 9.1 (CH_2CH_3), 26.2 [$\text{C}(\text{CH}_3)_3$], 27.6 (CH_2CH_3), 28.6 [$\text{C}(\text{CH}_3)_3$], 34.0 [$\text{C}(\text{CH}_3)_3$], 51.1 [$\text{NC}(\text{CH}_3)_3$], 80.7 [$\text{CHC}(\text{CH}_3)_3$], 167.6 (NCO), 172.9 ($\text{RCO}_2\text{R}'$); MS (TOF ES) m/z (rel. int.): 266.1 [$\text{M}+\text{Na}$] $^+$ (100).

6.1.7.10. 1-Benzhydryl-2-(*tert*-butylamino)-2-oxoethyl cyclopropanecarboxylate **374**



Prepared from amine (*R*)-**96** (45 mg, 0.17 mmol), diphenylacetaldehyde (40.0 mg, 0.204 mmol), cyclopropane carboxylic acid (14 mg, 0.204), isocyanide (21 mg, 0.255 mmol) and methanol (0.4 cm^3) to give (53 mg, 85%), mp 128-130°C (the Passerini product), HRMS (ES) Calc. For: $\text{C}_{23}\text{H}_{27}\text{NO}_3\text{Na}$: 388.1891, Found 388.1893; $\nu_{\text{max}}/\text{cm}^{-1}$ 3429, 3054, 2926, 2854, 2305, 1737, 1683, 1523, 1454, 1393, 1265; δ_{H} 0.69-0.75 (2 H, m, CH_2), 0.79-0.85 (2 H, m, CH_2), 0.99 [9 H, s, $\text{C}(\text{CH}_3)_3$], 1.46-1.54 (CHCO_2R), 4.57 (1 H, d, J 7.2, OCHN), 5.27 (1 H, s br, NH), 5.60 (1 H, d, J 7.2, CHPh_2), 7.10-7.26 (10 H, m, Ph), δ_{C} 8.6 (CH_2), 12.9 (CHCO_2R), 28.1 [$\text{C}(\text{CH}_3)_3$], 51.0 [$\text{C}(\text{CH}_3)_3$], 52.3 (OCHN), 75.7 (CHPh_2), 126.8, 128.2, 128.2, 128.4, 128.4, 129.1 (aromatic carbons), 139.6 (C-1 of Ph), 140.0 (C-1 of Ph), 197.2 (NCO), 173.7 ($\text{RCO}_2\text{R}'$), MS (TOF ES) m/z (rel. int.): 388.2 [$\text{M}+\text{Na}$] $^+$ (100), 366.2 [$\text{M}+\text{H}$] $^+$ (8).

6.1.7.11. 1-[(*Tert*-Butylamino)carbonyl]-2-methylpropyl 2-pyridinecarboxylate **375**



Prepared from amine (*R*)-**96** (47 mg, 0.18 mmol), isobutyraldehyde (16.0 mg, 0.216 mmol), nicotinic acid (27 mg, 0.228), isocyanide (22 mg, 0.270 mmol) and methanol (0.4 cm^3) to give (34 mg, 68%) mp 48-50°C (the Passerini product), HRMS (ES) Calc. For: $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$: 301.1528, Found 301.1523; $\nu_{\text{max}}/\text{cm}^{-1}$ 3436, 3054, 2925, 2854,

1745, 1676, 1518, 1495, 1318, 1265; δ_{H} 1.02 (3 H, d, J 6.9, $\text{CH}(\text{CH}_3)_2$), 1.05 (3 H, d, J 6.9, $\text{CH}(\text{CH}_3)_2$), 1.35 [9 H, s, $\text{C}(\text{CH}_3)_3$], 2.37-2.48 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 5.14 (1 H, d, J 4.6, OCHN), 5.73 (1 H, s br, NH), 7.46 (1 H, dd, J 4.9, 7.9, Ph), 8.33-8.37 (1 H, m, Ph), 8.83 (1 H, br, Ph), 9.28 (1 H, s br, Ph); δ_{C} 17.1 (CHCH_2), 18.9 $\text{CH}(\text{CH}_3)_2$, 28.7 [$\text{C}(\text{CH}_3)_3$], 79.4 (OCHN), 123.8 (C-3 of Ph), 137.6 (C-5 of Ph), 150.5 (C-4 of Ph), 153.6 (C-6 of Ph), 164.1 (NCO), 167.8 ($\text{RCO}_2\text{R}'$); MS (TOF ES) m/z (rel. int.): 301.2 [$\text{M}+\text{Na}]^+$ (100), 279.2 [$\text{M}+\text{H}]^+$ (50).

6.2. References

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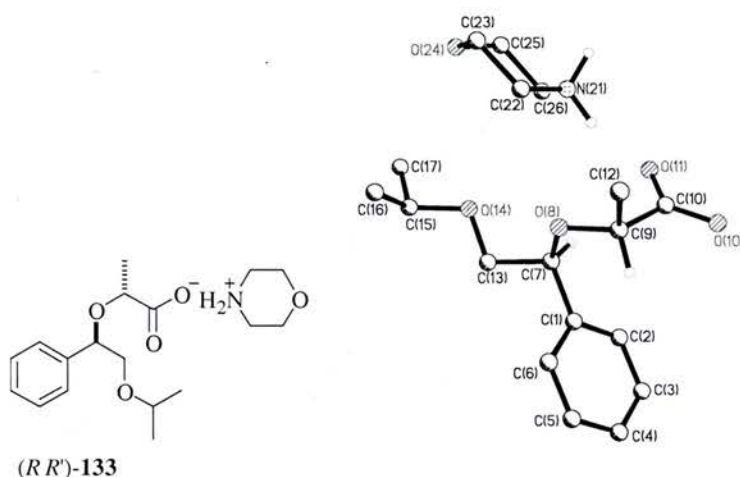
A.1 Appendix one: X-ray crystallographic data

A.1.1 General Experimental

Data for all compounds were measured on a Bruker SMART diffractometer with graphite monochromated Mo-K α radiation ($\lambda = 0.7107$) using a 0.3° width steps accumulating area detector frames spanning a hemisphere of reciprocal 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 (*R,R'*)-133



Crystal data and structure refinement for (*R,R'*)-133.

Crystal data for (*R,R'*)-133

$C_{18}H_{29}NO_5$, $M=339.42$, monoclinic, space group $C2$, $a = 25.418(4)$, $b = 6.5104(9)$, $c = 11.3405(16)$ Å, $\beta = 101.540(2)^\circ$, $V = 1838.7(4)$ Å³, $T = 125(2)$ K, $Z = 4$, μ (Mo-K α) = 0.089 mm⁻¹, colourless block, crystal dimensions, $0.12 \times 0.1 \times 0.02$ mm³. Full matrix least squares based on F^2 gave $R1 = 0.0345$ for 3120 observed ($F > 4\sigma(F)$) and $wR2 = 0.0867$ for all data, $GOF = 1.026$ for 226 parameters.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² $\times 10^3$) for (*R,R'*)-133.

$U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

| | x | y | z | U(eq) |
|------|--------|----------|---------|-------|
| C(1) | 412(1) | -1319(3) | 2705(2) | 22(1) |
| C(2) | 475(1) | -3385(3) | 3014(2) | 27(1) |

| | | | | |
|-------|---------|----------|----------|-------|
| C(3) | 64(1) | -4468(3) | 3373(2) | 35(1) |
| C(4) | -417(1) | -3497(4) | 3418(2) | 36(1) |
| C(5) | -487(1) | -1458(4) | 3100(2) | 30(1) |
| C(6) | -77(1) | -366(3) | 2752(2) | 24(1) |
| C(7) | 871(1) | -103(3) | 2368(2) | 21(1) |
| O(8) | 1071(1) | 1462(2) | 3244(1) | 21(1) |
| C(9) | 1177(1) | 774(3) | 4470(1) | 20(1) |
| O(10) | 1611(1) | -1933(2) | 5670(1) | 25(1) |
| C(10) | 1627(1) | -844(3) | 4765(2) | 19(1) |
| O(11) | 1986(1) | -906(2) | 4153(1) | 23(1) |
| C(12) | 1339(1) | 2665(3) | 5241(2) | 29(1) |
| C(13) | 684(1) | 990(3) | 1176(2) | 24(1) |
| O(14) | 1125(1) | 1876(2) | 767(1) | 25(1) |
| C(15) | 953(1) | 3140(3) | -286(2) | 24(1) |
| C(16) | 850(1) | 5320(4) | 59(2) | 41(1) |
| C(17) | 1386(1) | 3032(4) | -1022(2) | 33(1) |
| N(21) | 2392(1) | 2298(2) | 3090(1) | 21(1) |
| C(22) | 2100(1) | 4297(3) | 2945(2) | 25(1) |
| C(23) | 2387(1) | 5799(3) | 2275(2) | 26(1) |
| O(24) | 2457(1) | 5005(2) | 1146(1) | 29(1) |
| C(25) | 2761(1) | 3155(3) | 1313(2) | 27(1) |
| C(26) | 2481(1) | 1518(3) | 1914(2) | 24(1) |

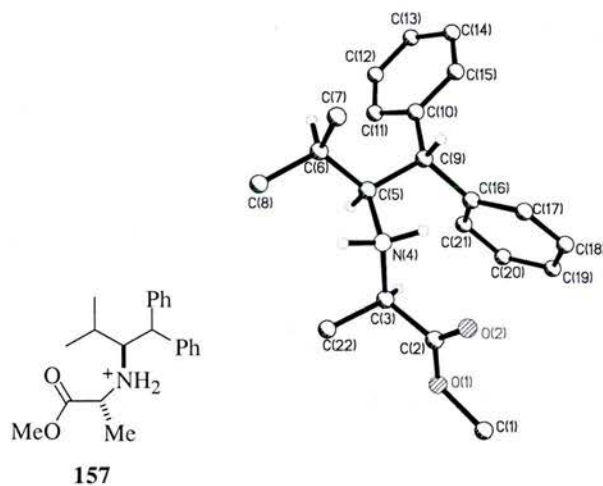
Table 2. Bond lengths [\AA] and angles [$^\circ$] for (*R,R*)-**133**.

| | | | |
|-------------|----------|-----------------|------------|
| C(1)-C(2) | 1.391(3) | C(25)-H(25A) | 0.99 |
| C(1)-C(6) | 1.398(3) | C(25)-H(25B) | 0.99 |
| C(1)-C(7) | 1.522(2) | C(26)-H(26A) | 0.99 |
| C(2)-C(3) | 1.387(3) | C(26)-H(26B) | 0.99 |
| C(2)-H(2A) | 0.95 | C(2)-C(1)-C(6) | 118.56(18) |
| C(3)-C(4) | 1.387(3) | C(2)-C(1)-C(7) | 120.73(17) |
| C(3)-H(3A) | 0.95 | C(6)-C(1)-C(7) | 120.67(16) |
| C(4)-C(5) | 1.378(3) | C(3)-C(2)-C(1) | 120.7(2) |
| C(4)-H(4A) | 0.95 | C(3)-C(2)-H(2A) | 119.7 |
| C(5)-C(6) | 1.384(3) | C(1)-C(2)-H(2A) | 119.7 |
| C(5)-H(5A) | 0.95 | C(4)-C(3)-C(2) | 120.0(2) |
| C(6)-H(6A) | 0.95 | C(4)-C(3)-H(3A) | 120 |
| C(7)-O(8) | 1.443(2) | C(2)-C(3)-H(3A) | 120 |
| C(7)-C(13) | 1.517(2) | C(5)-C(4)-C(3) | 119.88(18) |
| C(7)-H(7A) | 1 | C(5)-C(4)-H(4A) | 120.1 |
| O(8)-C(9) | 1.434(2) | C(3)-C(4)-H(4A) | 120.1 |
| C(9)-C(12) | 1.519(3) | C(4)-C(5)-C(6) | 120.27(19) |
| C(9)-C(10) | 1.541(2) | C(4)-C(5)-H(5A) | 119.9 |
| C(9)-H(9A) | 1 | C(6)-C(5)-H(5A) | 119.9 |
| O(10)-C(10) | 1.255(2) | C(5)-C(6)-C(1) | 120.59(18) |
| C(10)-O(11) | 1.253(2) | C(5)-C(6)-H(6A) | 119.7 |

| | | | |
|---------------------|------------|---------------------|------------|
| C(12)-H(12A) | 0.98 | C(1)-C(6)-H(6A) | 119.7 |
| C(12)-H(12B) | 0.98 | O(8)-C(7)-C(13) | 106.71(15) |
| C(12)-H(12C) | 0.98 | O(8)-C(7)-C(1) | 112.11(13) |
| C(13)-O(14) | 1.419(2) | C(13)-C(7)-C(1) | 110.34(13) |
| C(13)-H(13A) | 0.99 | O(8)-C(7)-H(7A) | 109.2 |
| C(13)-H(13B) | 0.99 | C(13)-C(7)-H(7A) | 109.2 |
| O(14)-C(15) | 1.444(2) | C(1)-C(7)-H(7A) | 109.2 |
| C(15)-C(16) | 1.509(3) | C(9)-O(8)-C(7) | 114.78(14) |
| C(15)-C(17) | 1.510(3) | O(8)-C(9)-C(12) | 106.34(15) |
| C(15)-H(15A) | 1 | O(8)-C(9)-C(10) | 114.27(14) |
| C(16)-H(16A) | 0.98 | C(12)-C(9)-C(10) | 108.96(14) |
| C(16)-H(16B) | 0.98 | O(8)-C(9)-H(9A) | 109 |
| C(16)-H(16C) | 0.98 | C(12)-C(9)-H(9A) | 109 |
| C(17)-H(17A) | 0.98 | C(10)-C(9)-H(9A) | 109 |
| C(17)-H(17B) | 0.98 | O(11)-C(10)-O(10) | 125.57(16) |
| C(17)-H(17C) | 0.98 | O(11)-C(10)-C(9) | 119.51(15) |
| N(21)-C(26) | 1.487(2) | O(10)-C(10)-C(9) | 114.79(15) |
| N(21)-C(22) | 1.491(2) | C(9)-C(12)-H(12A) | 109.5 |
| N(21)-H(21A) | 0.9799(10) | C(9)-C(12)-H(12B) | 109.5 |
| N(21)-H(21B) | 0.9800(10) | H(12A)-C(12)-H(12B) | 109.5 |
| C(22)-C(23) | 1.513(3) | C(9)-C(12)-H(12C) | 109.5 |
| C(22)-H(22A) | 0.99 | H(12A)-C(12)-H(12C) | 109.5 |
| C(22)-H(22B) | 0.99 | H(12B)-C(12)-H(12C) | 109.5 |
| C(23)-O(24) | 1.424(2) | O(14)-C(13)-C(7) | 110.71(13) |
| C(23)-H(23A) | 0.99 | O(14)-C(13)-H(13A) | 109.5 |
| C(23)-H(23B) | 0.99 | C(7)-C(13)-H(13A) | 109.5 |
| O(24)-C(25) | 1.423(2) | O(14)-C(13)-H(13B) | 109.5 |
| C(25)-C(26) | 1.517(3) | C(7)-C(13)-H(13B) | 109.5 |
| H(13A)-C(13)-H(13B) | 108.1 | N(21)-C(22)-H(22A) | 109.7 |
| C(13)-O(14)-C(15) | 111.94(12) | C(23)-C(22)-H(22A) | 109.7 |
| O(14)-C(15)-C(16) | 111.14(15) | N(21)-C(22)-H(22B) | 109.7 |
| O(14)-C(15)-C(17) | 107.28(14) | C(23)-C(22)-H(22B) | 109.7 |
| C(16)-C(15)-C(17) | 111.70(18) | H(22A)-C(22)-H(22B) | 108.2 |
| O(14)-C(15)-H(15A) | 108.9 | O(24)-C(23)-C(22) | 112.11(15) |
| C(16)-C(15)-H(15A) | 108.9 | O(24)-C(23)-H(23A) | 109.2 |
| C(17)-C(15)-H(15A) | 108.9 | C(22)-C(23)-H(23A) | 109.2 |
| C(15)-C(16)-H(16A) | 109.5 | O(24)-C(23)-H(23B) | 109.2 |
| C(15)-C(16)-H(16B) | 109.5 | C(22)-C(23)-H(23B) | 109.2 |
| H(16A)-C(16)-H(16B) | 109.5 | H(23A)-C(23)-H(23B) | 107.9 |
| C(15)-C(16)-H(16C) | 109.5 | C(25)-O(24)-C(23) | 110.45(14) |
| H(16A)-C(16)-H(16C) | 109.5 | O(24)-C(25)-C(26) | 111.29(15) |
| H(16B)-C(16)-H(16C) | 109.5 | O(24)-C(25)-H(25A) | 109.4 |
| C(15)-C(17)-H(17A) | 109.5 | C(26)-C(25)-H(25A) | 109.4 |
| C(15)-C(17)-H(17B) | 109.5 | O(24)-C(25)-H(25B) | 109.4 |
| H(17A)-C(17)-H(17B) | 109.5 | C(26)-C(25)-H(25B) | 109.4 |
| C(15)-C(17)-H(17C) | 109.5 | H(25A)-C(25)-H(25B) | 108 |
| H(17A)-C(17)-H(17C) | 109.5 | N(21)-C(26)-C(25) | 109.43(15) |
| H(17B)-C(17)-H(17C) | 109.5 | N(21)-C(26)-H(26A) | 109.8 |
| C(26)-N(21)-C(22) | 111.22(14) | C(25)-C(26)-H(26A) | 109.8 |
| C(26)-N(21)-H(21A) | 111.5(13) | N(21)-C(26)-H(26B) | 109.8 |
| C(22)-N(21)-H(21A) | 106.7(13) | C(25)-C(26)-H(26B) | 109.8 |
| C(26)-N(21)-H(21B) | 105.4(14) | H(26A)-C(26)-H(26B) | 108.2 |
| C(22)-N(21)-H(21B) | 109.8(16) | | |
| H(21A)-N(21)-H(21B) | 112(2) | | |
| N(21)-C(22)-C(23) | 109.87(15) | | |

Table 3. Torsion angles [°] for (*R,R*)-**133**.

| | | | |
|------------------------|-------------|-------------------------|-------------|
| C(6)-C(1)-C(2)-C(3) | -0.7(3) | C(1)-C(7)-C(13)-O(14) | -171.39(15) |
| C(7)-C(1)-C(2)-C(3) | 177.10(16) | C(7)-C(13)-O(14)-C(15) | -172.82(16) |
| C(1)-C(2)-C(3)-C(4) | 0.5(3) | C(13)-O(14)-C(15)-C(16) | 88.30(19) |
| C(2)-C(3)-C(4)-C(5) | 0.4(3) | C(13)-O(14)-C(15)-C(17) | -149.33(17) |
| C(3)-C(4)-C(5)-C(6) | -0.9(3) | C(26)-N(21)-C(22)-C(23) | -52.88(18) |
| C(4)-C(5)-C(6)-C(1) | 0.7(3) | N(21)-C(22)-C(23)-O(24) | 55.4(2) |
| C(2)-C(1)-C(6)-C(5) | 0.1(3) | C(22)-C(23)-O(24)-C(25) | -59.48(19) |
| C(7)-C(1)-C(6)-C(5) | -177.69(15) | C(23)-O(24)-C(25)-C(26) | 60.55(18) |
| C(2)-C(1)-C(7)-O(8) | -112.90(18) | C(22)-N(21)-C(26)-C(25) | 54.08(18) |
| C(6)-C(1)-C(7)-O(8) | 64.9(2) | O(24)-C(25)-C(26)-N(21) | -57.88(19) |
| C(2)-C(1)-C(7)-C(13) | 128.31(18) | | |
| C(6)-C(1)-C(7)-C(13) | -53.9(2) | | |
| C(13)-C(7)-O(8)-C(9) | 169.23(13) | | |
| C(1)-C(7)-O(8)-C(9) | 48.32(18) | | |
| C(7)-O(8)-C(9)-C(12) | -175.68(13) | | |
| C(7)-O(8)-C(9)-C(10) | 64.08(17) | | |
| O(8)-C(9)-C(10)-O(11) | 25.9(2) | | |
| C(12)-C(9)-C(10)-O(11) | -92.85(18) | | |
| O(8)-C(9)-C(10)-O(10) | -157.87(14) | | |
| C(12)-C(9)-C(10)-O(10) | 83.36(19) | | |
| O(8)-C(7)-C(13)-O(14) | 66.58(18) | | |

A.1.2.2 X-ray data for **157**Crystal data and structure refinement for **157**.*Crystal data for 157*

C₂₁H₂₉ClNO₂, M=370.90, tetragonal, space group *P4* (1), a = 10.1769(15), b = 10.1769(15), c = 40.051(9) Å, V = 4148.0(12) Å³, T = 125 (2) K, Z = 8, μ (Mo-Kα) = 0.200 mm⁻¹, colourless block, crystal dimensions, 0.1 x 0.04 x 0.02 mm³. Full matrix least squares based on F² gave R1 = 0.1021 for 7564 observed (F > 4σ(F)) and wR2 = 0.2803 for all data, GOF = 0.993 for 479 parameters.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **157**.

$U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

| | x | y | z | $U(\text{eq})$ |
|-------|----------|----------|----------|----------------|
| Cl(1) | 2061(1) | -5(2) | 9244(1) | 64(1) |
| C(1) | 5991(10) | 3810(7) | 8825(2) | 159(4) |
| O(1) | 5342(5) | 3608(3) | 9150(1) | 120(2) |
| C(2) | 5146(6) | 2410(5) | 9238(2) | 59(2) |
| O(2) | 5479(3) | 1406(3) | 9089(1) | 53(1) |
| C(3) | 4450(5) | 2422(5) | 9578(1) | 50(2) |
| N(4) | 4307(1) | 1022(1) | 9695(1) | 42(1) |
| C(5) | 4404(5) | 870(5) | 10076(1) | 47(2) |
| C(6) | 3311(5) | -17(6) | 10201(1) | 62(2) |
| C(7) | 3378(6) | -1417(6) | 10079(1) | 72(2) |
| C(8) | 1953(6) | 566(7) | 10141(2) | 81(2) |
| C(9) | 5802(5) | 398(5) | 10163(1) | 42(2) |
| C(10) | 6092(4) | 288(5) | 10540(1) | 40(1) |
| C(11) | 5498(6) | 1043(5) | 10777(1) | 54(2) |
| C(12) | 5923(5) | 943(5) | 11111(1) | 54(2) |
| C(13) | 6843(6) | 124(6) | 11200(1) | 71(2) |
| C(14) | 7433(8) | -664(9) | 10969(2) | 129(3) |
| C(15) | 7072(7) | -532(6) | 10638(2) | 81(2) |
| C(16) | 6883(5) | 1246(5) | 9994(1) | 38(1) |
| C(17) | 7680(5) | 752(5) | 9736(1) | 46(2) |
| C(18) | 8680(5) | 1489(5) | 9607(1) | 56(2) |
| C(19) | 8908(5) | 2796(5) | 9715(1) | 52(2) |
| C(20) | 8123(5) | 3276(6) | 9965(1) | 52(2) |
| C(21) | 7137(5) | 2508(5) | 10101(1) | 50(2) |
| C(22) | 3185(6) | 3142(6) | 9571(2) | 75(2) |
| C(31) | 6081(9) | -3788(8) | 9662(2) | 183(4) |
| O(31) | 5338(6) | -3604(4) | 9346(1) | 113(2) |
| C(32) | 5122(6) | -2407(6) | 9247(2) | 63(2) |
| O(32) | 5476(4) | -1433(3) | 9393(1) | 53(1) |
| C(33) | 4474(5) | -2417(5) | 8908(1) | 47(2) |
| N(34) | 4336(1) | -1030(1) | 8788(1) | 42(1) |
| C(35) | 4390(5) | -892(5) | 8411(1) | 46(2) |
| C(36) | 3297(5) | 22(6) | 8280(1) | 59(2) |

| | | | | |
|--------|---------|----------|----------|--------|
| C(37) | 3397(6) | 1433(6) | 8415(2) | 76(2) |
| C(38) | 1946(6) | -587(7) | 8344(2) | 75(2) |
| C(39) | 5824(5) | -412(5) | 8327(1) | 44(2) |
| C(40) | 6089(5) | -297(5) | 7952(1) | 47(2) |
| C(41) | 5535(5) | -1057(6) | 7712(1) | 53(2) |
| C(42) | 5894(6) | -965(5) | 7376(1) | 55(2) |
| C(43) | 6858(6) | -133(6) | 7282(1) | 68(2) |
| C(44) | 7398(8) | 649(8) | 7526(2) | 108(3) |
| C(45) | 7025(7) | 544(7) | 7859(2) | 96(2) |
| C(46) | 6887(4) | -1243(5) | 8487(1) | 38(1) |
| C(47) | 7695(5) | -773(5) | 8746(1) | 48(2) |
| C(48) | 8683(5) | -1522(6) | 8881(1) | 58(2) |
| C(49) | 8899(5) | -2773(6) | 8776(1) | 57(2) |
| C(50) | 8103(5) | -3276(6) | 8526(1) | 58(2) |
| C(51) | 7119(5) | -2543(5) | 8384(1) | 43(2) |
| C(52) | 3206(6) | -3163(6) | 8911(2) | 76(2) |
| Cl(31) | 4064(1) | 4046(1) | 10492(1) | 74(1) |
| O(61) | 6163(2) | 6207(2) | 10493(1) | 39(1) |

Table 2. Bond lengths [Å] and angles [°] for **157**.

| | | | |
|-------------|-----------|-------------------|----------|
| C(1)-O(1) | 1.472(9) | C(50)-C(51) | 1.374(7) |
| O(1)-C(2) | 1.284(6) | C(2)-O(1)-C(1) | 116.3(5) |
| C(2)-O(2) | 1.231(6) | O(2)-C(2)-O(1) | 127.8(5) |
| C(2)-C(3) | 1.535(8) | O(2)-C(2)-C(3) | 124.2(5) |
| C(3)-C(22) | 1.482(8) | O(1)-C(2)-C(3) | 107.9(5) |
| C(3)-N(4) | 1.507(5) | C(22)-C(3)-N(4) | 112.9(4) |
| N(4)-C(5) | 1.536(5) | C(22)-C(3)-C(2) | 112.9(5) |
| C(5)-C(6) | 1.518(7) | N(4)-C(3)-C(2) | 108.3(4) |
| C(5)-C(9) | 1.542(7) | C(3)-N(4)-C(5) | 113.4(3) |
| C(6)-C(7) | 1.509(8) | C(6)-C(5)-N(4) | 110.0(4) |
| C(6)-C(8) | 1.524(8) | C(6)-C(5)-C(9) | 114.6(4) |
| C(9)-C(10) | 1.542(6) | N(4)-C(5)-C(9) | 108.5(3) |
| C(9)-C(16) | 1.554(7) | C(7)-C(6)-C(5) | 114.9(5) |
| C(10)-C(15) | 1.358(8) | C(7)-C(6)-C(8) | 110.9(5) |
| C(10)-C(11) | 1.363(7) | C(5)-C(6)-C(8) | 112.4(5) |
| C(11)-C(12) | 1.409(7) | C(10)-C(9)-C(5) | 115.0(4) |
| C(12)-C(13) | 1.303(8) | C(10)-C(9)-C(16) | 109.5(4) |
| C(13)-C(14) | 1.365(10) | C(5)-C(9)-C(16) | 112.3(4) |
| C(14)-C(15) | 1.380(9) | C(15)-C(10)-C(11) | 118.1(5) |
| C(16)-C(21) | 1.379(7) | C(15)-C(10)-C(9) | 117.9(4) |
| C(16)-C(17) | 1.406(7) | C(11)-C(10)-C(9) | 123.8(4) |
| C(17)-C(18) | 1.366(7) | C(10)-C(11)-C(12) | 118.9(5) |
| C(18)-C(19) | 1.418(7) | C(13)-C(12)-C(11) | 121.8(5) |
| C(19)-C(20) | 1.370(7) | C(12)-C(13)-C(14) | 120.4(6) |
| C(20)-C(21) | 1.385(7) | C(13)-C(14)-C(15) | 118.5(7) |
| C(31)-O(31) | 1.488(9) | C(10)-C(15)-C(14) | 122.2(6) |

| | | | |
|-------------------|----------|-------------------|----------|
| O(31)-C(32) | 1.300(7) | C(21)-C(16)-C(17) | 117.0(4) |
| C(32)-O(32) | 1.205(6) | C(21)-C(16)-C(9) | 120.8(4) |
| C(32)-C(33) | 1.511(8) | C(17)-C(16)-C(9) | 122.1(4) |
| C(33)-C(52) | 1.497(8) | C(18)-C(17)-C(16) | 120.7(5) |
| C(33)-N(34) | 1.497(5) | C(17)-C(18)-C(19) | 121.5(5) |
| N(34)-C(35) | 1.517(5) | C(20)-C(19)-C(18) | 117.5(5) |
| C(35)-C(36) | 1.542(7) | C(19)-C(20)-C(21) | 120.6(5) |
| C(35)-C(39) | 1.576(7) | C(16)-C(21)-C(20) | 122.5(5) |
| C(36)-C(38) | 1.529(8) | C(32)-O(31)-C(31) | 117.5(5) |
| C(36)-C(37) | 1.538(9) | O(32)-C(32)-O(31) | 125.0(5) |
| C(39)-C(46) | 1.515(7) | O(32)-C(32)-C(33) | 124.9(5) |
| C(39)-C(40) | 1.530(7) | O(31)-C(32)-C(33) | 109.9(5) |
| C(40)-C(45) | 1.333(8) | C(52)-C(33)-N(34) | 113.6(4) |
| C(40)-C(41) | 1.355(7) | C(52)-C(33)-C(32) | 111.9(5) |
| C(41)-C(42) | 1.400(7) | N(34)-C(33)-C(32) | 108.8(4) |
| C(42)-C(43) | 1.350(8) | C(33)-N(34)-C(35) | 113.7(3) |
| C(43)-C(44) | 1.377(9) | N(34)-C(35)-C(36) | 111.7(4) |
| C(44)-C(45) | 1.391(9) | N(34)-C(35)-C(39) | 106.0(3) |
| C(46)-C(51) | 1.405(7) | C(36)-C(35)-C(39) | 114.1(4) |
| C(46)-C(47) | 1.409(7) | C(38)-C(36)-C(37) | 112.3(5) |
| C(47)-C(48) | 1.372(7) | C(38)-C(36)-C(35) | 110.3(5) |
| C(48)-C(49) | 1.358(8) | C(37)-C(36)-C(35) | 113.3(5) |
| C(49)-C(50) | 1.386(8) | C(46)-C(39)-C(40) | 109.3(4) |
| C(46)-C(39)-C(35) | 113.4(4) | C(40)-C(45)-C(44) | 120.8(6) |
| C(40)-C(39)-C(35) | 113.5(4) | C(51)-C(46)-C(47) | 115.9(4) |
| C(45)-C(40)-C(41) | 117.8(5) | C(51)-C(46)-C(39) | 121.5(4) |
| C(45)-C(40)-C(39) | 116.6(5) | C(47)-C(46)-C(39) | 122.6(5) |
| C(41)-C(40)-C(39) | 125.3(5) | C(48)-C(47)-C(46) | 122.0(5) |
| C(40)-C(41)-C(42) | 122.4(5) | C(49)-C(48)-C(47) | 121.2(5) |
| C(43)-C(42)-C(41) | 120.0(5) | C(48)-C(49)-C(50) | 118.4(5) |
| C(42)-C(43)-C(44) | 117.0(5) | C(51)-C(50)-C(49) | 121.7(5) |
| C(43)-C(44)-C(45) | 121.9(7) | C(50)-C(51)-C(46) | 120.8(5) |

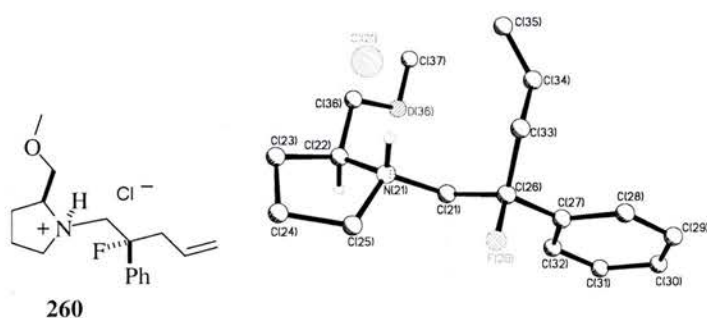
Table 3. Torsion angles [°] for **157**.

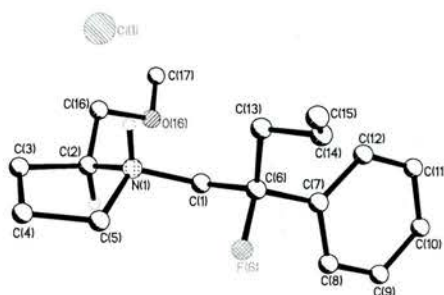
| | | | |
|------------------------|-----------|-------------------------|-----------|
| C(1)-O(1)-C(2)-O(2) | 3.0(10) | C(32)-C(33)-N(34)-C(35) | 149.8(4) |
| C(1)-O(1)-C(2)-C(3) | -179.3(6) | C(33)-N(34)-C(35)-C(36) | 134.5(4) |
| O(2)-C(2)-C(3)-C(22) | -123.7(6) | C(33)-N(34)-C(35)-C(39) | -100.7(4) |
| O(1)-C(2)-C(3)-C(22) | 58.4(6) | N(34)-C(35)-C(36)-C(38) | -65.3(6) |
| O(2)-C(2)-C(3)-N(4) | 2.0(7) | C(39)-C(35)-C(36)-C(38) | 174.5(4) |
| O(1)-C(2)-C(3)-N(4) | -175.8(4) | N(34)-C(35)-C(36)-C(37) | 61.5(6) |
| C(22)-C(3)-N(4)-C(5) | -87.9(5) | C(39)-C(35)-C(36)-C(37) | -58.7(6) |
| C(2)-C(3)-N(4)-C(5) | 146.4(4) | N(34)-C(35)-C(39)-C(46) | 50.9(5) |
| C(3)-N(4)-C(5)-C(6) | 134.1(4) | C(36)-C(35)-C(39)-C(46) | 174.3(4) |
| C(3)-N(4)-C(5)-C(9) | -99.9(4) | N(34)-C(35)-C(39)-C(40) | 176.4(4) |
| N(4)-C(5)-C(6)-C(7) | 64.4(6) | C(36)-C(35)-C(39)-C(40) | -60.2(6) |
| C(9)-C(5)-C(6)-C(7) | -58.1(6) | C(46)-C(39)-C(40)-C(45) | -77.5(6) |
| N(4)-C(5)-C(6)-C(8) | -63.7(5) | C(35)-C(39)-C(40)-C(45) | 154.8(5) |
| C(9)-C(5)-C(6)-C(8) | 173.8(4) | C(46)-C(39)-C(40)-C(41) | 96.4(6) |
| C(6)-C(5)-C(9)-C(10) | -60.8(6) | C(35)-C(39)-C(40)-C(41) | -31.3(7) |
| N(4)-C(5)-C(9)-C(10) | 175.9(4) | C(45)-C(40)-C(41)-C(42) | -1.3(9) |
| C(6)-C(5)-C(9)-C(16) | 173.1(4) | C(39)-C(40)-C(41)-C(42) | -175.2(5) |
| N(4)-C(5)-C(9)-C(16) | 49.9(5) | C(40)-C(41)-C(42)-C(43) | 2.6(9) |
| C(5)-C(9)-C(10)-C(15) | 156.9(5) | C(41)-C(42)-C(43)-C(44) | -3.5(9) |
| C(16)-C(9)-C(10)-C(15) | -75.6(6) | C(42)-C(43)-C(44)-C(45) | 3.4(11) |

| | | | |
|-------------------------|-----------|-------------------------|-----------|
| C(5)-C(9)-C(10)-C(11) | -28.7(7) | C(41)-C(40)-C(45)-C(44) | 1.2(10) |
| C(16)-C(9)-C(10)-C(11) | 98.9(6) | C(39)-C(40)-C(45)-C(44) | 175.5(6) |
| C(15)-C(10)-C(11)-C(12) | 0.1(8) | C(43)-C(44)-C(45)-C(40) | -2.3(12) |
| C(9)-C(10)-C(11)-C(12) | -174.3(5) | C(40)-C(39)-C(46)-C(51) | -58.7(6) |
| C(10)-C(11)-C(12)-C(13) | -1.9(9) | C(35)-C(39)-C(46)-C(51) | 69.1(6) |
| C(11)-C(12)-C(13)-C(14) | 0.4(10) | C(40)-C(39)-C(46)-C(47) | 121.6(5) |
| C(12)-C(13)-C(14)-C(15) | 2.7(12) | C(35)-C(39)-C(46)-C(47) | -110.7(5) |
| C(11)-C(10)-C(15)-C(14) | 3.1(10) | C(51)-C(46)-C(47)-C(48) | 2.5(7) |
| C(9)-C(10)-C(15)-C(14) | 177.8(7) | C(39)-C(46)-C(47)-C(48) | -177.8(5) |
| C(13)-C(14)-C(15)-C(10) | -4.5(12) | C(46)-C(47)-C(48)-C(49) | -2.1(8) |
| C(10)-C(9)-C(16)-C(21) | -56.6(6) | C(47)-C(48)-C(49)-C(50) | 0.6(8) |
| C(5)-C(9)-C(16)-C(21) | 72.4(6) | C(48)-C(49)-C(50)-C(51) | 0.3(8) |
| C(10)-C(9)-C(16)-C(17) | 120.5(5) | C(49)-C(50)-C(51)-C(46) | 0.2(8) |
| C(5)-C(9)-C(16)-C(17) | -110.5(5) | C(47)-C(46)-C(51)-C(50) | -1.5(7) |
| C(21)-C(16)-C(17)-C(18) | 1.7(7) | C(39)-C(46)-C(51)-C(50) | 178.7(5) |
| C(9)-C(16)-C(17)-C(18) | -175.5(5) | | |
| C(16)-C(17)-C(18)-C(19) | -3.2(8) | | |
| C(17)-C(18)-C(19)-C(20) | 2.7(8) | | |
| C(18)-C(19)-C(20)-C(21) | -0.7(8) | | |
| C(17)-C(16)-C(21)-C(20) | 0.3(7) | | |
| C(9)-C(16)-C(21)-C(20) | 177.5(5) | | |
| C(19)-C(20)-C(21)-C(16) | -0.7(8) | | |
| C(31)-O(31)-C(32)-O(32) | -0.1(10) | | |
| C(31)-O(31)-C(32)-C(33) | 174.7(6) | | |
| O(32)-C(32)-C(33)-C(52) | -126.9(6) | | |
| O(31)-C(32)-C(33)-C(52) | 58.3(7) | | |
| O(32)-C(32)-C(33)-N(34) | -0.7(8) | | |
| O(31)-C(32)-C(33)-N(34) | -175.5(5) | | |
| C(52)-C(33)-N(34)-C(35) | -84.9(5) | | |

A.1.3 X-ray data for chapter 3

A.1.3.1 X-ray data for **260**





Crystal data and structure refinement for **260**

Crystal data for **260**

$C_{17}H_{25}NClFNO$, $M=313.83$, monoclinic, space group $P2(1)$, $a = 7.0446(8)$, $b = 23.709(4)$, $c = 9.8268(16)$ Å, $V = 1639.6(4)$ Å³, $T = 125(2)$ K, $Z = 4$, μ (Mo-K α) = 0.242 mm⁻¹, colourless block, crystal dimensions, $0.1 \times 0.1 \times 0.03$ mm³. Full matrix least squares based on F^2 gave $R1 = 0.0256$ for 4572 observed ($F > 4\sigma(F)$) and $wR2 = 0.0652$ for all data, $GOF = 1.032$ for 390 parameters.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² $\times 10^3$) for **260**.

$U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

| | x | y | z | $U(eq)$ |
|-------|---------|---------|----------|---------|
| Cl(1) | -753(1) | 2547(1) | 354(1) | 16(1) |
| C(1) | 4495(2) | 1861(1) | 359(2) | 12(1) |
| N(1) | 3609(2) | 2437(1) | 339(1) | 11(1) |
| C(2) | 4226(2) | 2786(1) | 1587(2) | 13(1) |
| C(3) | 3594(3) | 3377(1) | 1167(2) | 18(1) |
| C(4) | 3885(3) | 3404(1) | -364(2) | 30(1) |
| C(5) | 4139(2) | 2803(1) | -850(2) | 15(1) |
| F(6) | 4820(1) | 1721(1) | -2016(1) | 16(1) |
| C(6) | 4005(2) | 1476(1) | -854(2) | 13(1) |
| C(7) | 5024(2) | 923(1) | -567(2) | 13(1) |
| C(8) | 6970(2) | 889(1) | -758(2) | 21(1) |
| C(9) | 7974(3) | 401(1) | -436(2) | 25(1) |
| C(10) | 7065(3) | -62(1) | 84(2) | 19(1) |
| C(11) | 5127(3) | -37(1) | 279(2) | 16(1) |
| C(12) | 4126(2) | 453(1) | -47(2) | 14(1) |
| C(13) | 1876(2) | 1420(1) | -1213(2) | 14(1) |
| C(14) | 1441(2) | 1054(1) | -2426(2) | 17(1) |

| | | | | |
|--------|----------|---------|----------|-------|
| C(15) | 189(3) | 1177(1) | -3420(2) | 21(1) |
| C(16) | 3374(2) | 2589(1) | 2889(2) | 16(1) |
| O(16) | 4309(2) | 2096(1) | 3388(1) | 19(1) |
| C(17) | 3734(3) | 1945(1) | 4717(2) | 23(1) |
| Cl(21) | 4252(1) | 3487(1) | 5989(1) | 17(1) |
| C(21) | 9622(2) | 4259(1) | 5899(2) | 13(1) |
| N(21) | 8645(2) | 3696(1) | 5887(2) | 12(1) |
| C(22) | 9264(2) | 3323(1) | 4726(2) | 14(1) |
| C(23) | 8591(3) | 2743(1) | 5161(2) | 17(1) |
| C(24) | 8930(3) | 2733(1) | 6711(2) | 26(1) |
| C(25) | 9019(3) | 3347(1) | 7162(2) | 18(1) |
| F(26) | 8685(1) | 4508(1) | 8113(1) | 16(1) |
| C(26) | 8697(2) | 4713(1) | 6739(2) | 13(1) |
| C(27) | 9833(2) | 5259(1) | 6788(2) | 13(1) |
| C(28) | 9024(3) | 5747(1) | 7304(2) | 19(1) |
| C(29) | 10029(3) | 6245(1) | 7433(2) | 20(1) |
| C(30) | 11894(3) | 6272(1) | 7034(2) | 19(1) |
| C(31) | 12713(2) | 5795(1) | 6510(2) | 20(1) |
| C(32) | 11711(2) | 5291(1) | 6394(2) | 17(1) |
| C(33) | 6599(2) | 4803(1) | 6294(2) | 14(1) |
| C(34) | 6316(2) | 5033(1) | 4878(2) | 18(1) |
| C(35) | 5173(3) | 4806(1) | 3917(2) | 22(1) |
| C(36) | 8445(2) | 3505(1) | 3352(2) | 16(1) |
| O(36) | 9462(2) | 3970(1) | 2856(1) | 19(1) |
| C(37) | 8704(3) | 4146(1) | 1558(2) | 25(1) |

Table 2. Bond lengths [Å] and angles [°] for **260**.

| | | | |
|-------------|----------|-------------------|------------|
| C(1)-N(1) | 1.502(2) | C(12)-C(7)-C(6) | 122.91(15) |
| C(1)-C(6) | 1.528(2) | C(8)-C(7)-C(6) | 118.96(16) |
| N(1)-C(5) | 1.514(2) | C(9)-C(8)-C(7) | 120.76(18) |
| N(1)-C(2) | 1.527(2) | C(10)-C(9)-C(8) | 120.55(16) |
| C(2)-C(16) | 1.511(2) | C(9)-C(10)-C(11) | 119.52(18) |
| C(2)-C(3) | 1.521(3) | C(12)-C(11)-C(10) | 119.79(18) |
| C(3)-C(4) | 1.529(3) | C(11)-C(12)-C(7) | 121.35(16) |
| C(4)-C(5) | 1.517(3) | C(14)-C(13)-C(6) | 113.45(14) |
| F(6)-C(6) | 1.424(2) | C(15)-C(14)-C(13) | 124.67(18) |
| C(6)-C(7) | 1.516(2) | O(16)-C(16)-C(2) | 110.55(14) |
| C(6)-C(13) | 1.532(2) | C(16)-O(16)-C(17) | 112.06(14) |
| C(7)-C(12) | 1.391(3) | N(21)-C(21)-C(26) | 115.24(14) |
| C(7)-C(8) | 1.395(2) | C(21)-N(21)-C(25) | 114.66(14) |
| C(8)-C(9) | 1.386(3) | C(21)-N(21)-C(22) | 112.05(13) |
| C(9)-C(10) | 1.380(3) | C(25)-N(21)-C(22) | 104.94(14) |
| C(10)-C(11) | 1.388(3) | C(36)-C(22)-C(23) | 113.46(16) |

| | | | |
|-----------------|------------|-------------------|------------|
| C(11)-C(12) | 1.388(3) | C(36)-C(22)-N(21) | 113.22(14) |
| C(13)-C(14) | 1.495(3) | C(23)-C(22)-N(21) | 102.16(14) |
| C(14)-C(15) | 1.319(3) | C(22)-C(23)-C(24) | 104.91(16) |
| C(16)-O(16) | 1.420(2) | C(25)-C(24)-C(23) | 106.07(16) |
| O(16)-C(17) | 1.430(2) | N(21)-C(25)-C(24) | 106.15(15) |
| C(21)-N(21) | 1.502(2) | F(26)-C(26)-C(21) | 106.95(14) |
| N(1)-C(1)-C(6) | 116.98(14) | F(26)-C(26)-C(27) | 106.43(13) |
| C(1)-N(1)-C(5) | 114.49(13) | C(21)-C(26)-C(27) | 112.48(14) |
| C(1)-N(1)-C(2) | 112.25(13) | F(26)-C(26)-C(33) | 105.60(13) |
| C(5)-N(1)-C(2) | 103.83(14) | C(21)-C(26)-C(33) | 111.97(14) |
| C(16)-C(2)-C(3) | 113.01(15) | C(27)-C(26)-C(33) | 112.83(15) |
| C(16)-C(2)-N(1) | 113.84(14) | C(28)-C(27)-C(32) | 117.58(17) |
| C(3)-C(2)-N(1) | 102.17(14) | C(28)-C(27)-C(26) | 119.67(15) |
| C(2)-C(3)-C(4) | 104.85(16) | C(32)-C(27)-C(26) | 122.68(16) |
| C(5)-C(4)-C(3) | 106.97(16) | C(29)-C(28)-C(27) | 121.82(17) |
| N(1)-C(5)-C(4) | 105.00(15) | C(28)-C(29)-C(30) | 120.05(18) |
| F(6)-C(6)-C(7) | 107.30(13) | C(31)-C(30)-C(29) | 119.04(17) |
| F(6)-C(6)-C(1) | 107.30(14) | C(30)-C(31)-C(32) | 121.04(17) |
| C(7)-C(6)-C(1) | 106.45(14) | C(31)-C(32)-C(27) | 120.47(18) |
| F(6)-C(6)-C(13) | 106.06(13) | C(34)-C(33)-C(26) | 113.65(14) |
| C(7)-C(6)-C(13) | 114.70(14) | C(35)-C(34)-C(33) | 124.33(19) |
| C(1)-C(6)-C(13) | 114.60(14) | O(36)-C(36)-C(22) | 110.59(14) |
| C(12)-C(7)-C(8) | 118.04(17) | C(36)-O(36)-C(37) | 111.22(14) |

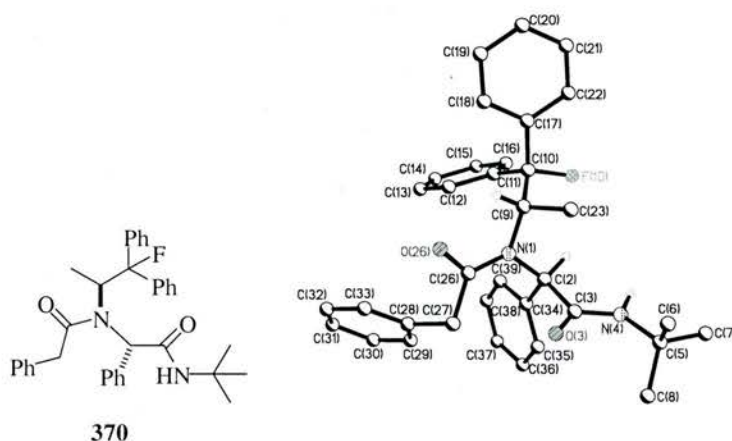
Table 3. Torsion angles [°] for **260**.

| | | | |
|------------------------|-------------|-------------------------|-------------|
| C(6)-C(1)-N(1)-C(5) | -61.01(19) | C(26)-C(21)-N(21)-C(22) | 162.97(14) |
| C(6)-C(1)-N(1)-C(2) | -179.05(14) | C(21)-N(21)-C(22)-C(36) | -73.73(18) |
| C(1)-N(1)-C(2)-C(16) | -71.81(17) | C(25)-N(21)-C(22)-C(36) | 161.25(14) |
| C(5)-N(1)-C(2)-C(16) | 164.00(14) | C(21)-N(21)-C(22)-C(23) | 163.88(13) |
| C(1)-N(1)-C(2)-C(3) | 166.01(13) | C(25)-N(21)-C(22)-C(23) | 38.86(16) |
| C(5)-N(1)-C(2)-C(3) | 41.82(16) | C(36)-C(22)-C(23)-C(24) | -159.34(15) |
| C(16)-C(2)-C(3)-C(4) | -157.55(15) | N(21)-C(22)-C(23)-C(24) | -37.12(17) |
| N(1)-C(2)-C(3)-C(4) | -34.80(18) | C(22)-C(23)-C(24)-C(25) | 21.7(2) |
| C(2)-C(3)-C(4)-C(5) | 15.2(2) | C(21)-N(21)-C(25)-C(24) | -149.13(15) |
| C(1)-N(1)-C(5)-C(4) | -155.30(15) | C(22)-N(21)-C(25)-C(24) | -25.76(18) |
| C(2)-N(1)-C(5)-C(4) | -32.56(17) | C(23)-C(24)-C(25)-N(21) | 2.5(2) |
| C(3)-C(4)-C(5)-N(1) | 10.7(2) | N(21)-C(21)-C(26)-F(26) | 59.44(18) |
| N(1)-C(1)-C(6)-F(6) | 66.89(17) | N(21)-C(21)-C(26)-C(27) | 175.94(14) |
| N(1)-C(1)-C(6)-C(7) | -178.48(13) | N(21)-C(21)-C(26)-C(33) | -55.8(2) |
| N(1)-C(1)-C(6)-C(13) | -50.6(2) | F(26)-C(26)-C(27)-C(28) | -74.68(19) |
| F(6)-C(6)-C(7)-C(12) | -146.20(16) | C(21)-C(26)-C(27)-C(28) | 168.52(16) |
| C(1)-C(6)-C(7)-C(12) | 99.17(19) | C(33)-C(26)-C(27)-C(28) | 40.7(2) |
| C(13)-C(6)-C(7)-C(12) | -28.7(2) | F(26)-C(26)-C(27)-C(32) | 102.28(19) |
| F(6)-C(6)-C(7)-C(8) | 37.5(2) | C(21)-C(26)-C(27)-C(32) | -14.5(2) |
| C(1)-C(6)-C(7)-C(8) | -77.1(2) | C(33)-C(26)-C(27)-C(32) | -142.37(17) |
| C(13)-C(6)-C(7)-C(8) | 155.06(16) | C(32)-C(27)-C(28)-C(29) | -0.4(3) |
| C(12)-C(7)-C(8)-C(9) | 0.0(3) | C(26)-C(27)-C(28)-C(29) | 176.72(17) |
| C(6)-C(7)-C(8)-C(9) | 176.43(18) | C(27)-C(28)-C(29)-C(30) | 0.5(3) |
| C(7)-C(8)-C(9)-C(10) | -0.2(3) | C(28)-C(29)-C(30)-C(31) | 0.2(3) |
| C(8)-C(9)-C(10)-C(11) | 0.3(3) | C(29)-C(30)-C(31)-C(32) | -1.0(3) |
| C(9)-C(10)-C(11)-C(12) | -0.2(3) | C(30)-C(31)-C(32)-C(27) | 1.1(3) |
| C(10)-C(11)-C(12)-C(7) | 0.0(3) | C(28)-C(27)-C(32)-C(31) | -0.4(3) |
| C(8)-C(7)-C(12)-C(11) | 0.1(3) | C(26)-C(27)-C(32)-C(31) | -177.43(17) |
| C(6)-C(7)-C(12)-C(11) | -176.16(16) | F(26)-C(26)-C(33)-C(34) | 178.56(15) |

| | | | |
|-------------------------|-------------|-------------------------|-------------|
| F(6)-C(6)-C(13)-C(14) | 60.20(19) | C(21)-C(26)-C(33)-C(34) | -65.4(2) |
| C(7)-C(6)-C(13)-C(14) | -58.0(2) | C(27)-C(26)-C(33)-C(34) | 62.7(2) |
| C(1)-C(6)-C(13)-C(14) | 178.37(16) | C(26)-C(33)-C(34)-C(35) | 127.8(2) |
| C(6)-C(13)-C(14)-C(15) | -135.72(19) | C(23)-C(22)-C(36)-O(36) | -165.30(15) |
| C(3)-C(2)-C(16)-O(16) | -167.49(14) | N(21)-C(22)-C(36)-O(36) | 78.85(17) |
| N(1)-C(2)-C(16)-O(16) | 76.52(18) | C(22)-C(36)-O(36)-C(37) | 179.95(15) |
| C(2)-C(16)-O(16)-C(17) | 171.41(15) | | |
| C(26)-C(21)-N(21)-C(25) | -77.56(18) | | |

A.1.4 X-ray structure for chapter 5

A.1.4.1 X-ray data for 370



Crystal data and structure refinement for 370

Crystal data for 370

$C_{35}H_{37}FN_2O_2$, $M = 36.67$, orthorhombic, space group $P4(1)2(1)2(1)$, $a = 12.3466(19)$, $b = 12.4688(19)$, $c = 18.968(3)$ Å, $V = 2920.1(82)$ Å³, $T = 125(2)$ K, $Z = 8$, μ (Mo-K α) = 0.080 mm⁻¹, colourless block, crystal dimensions, $0.2 \times 0.05 \times 0.05$ mm³. Full matrix least squares based on F^2 gave $R1 = 0.0555$ for 5294 observed ($F > 4\sigma(F)$) and $wR2 = 0.0987$ for all data, $GOF = 1.046$ for 366 parameters.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² $\times 10^3$) for 370. $U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

| | x | y | z | U(eq) |
|------|---------|---------|----------|-------|
| N(1) | 9580(2) | 7009(2) | -123(1) | 22(1) |
| C(2) | 8629(3) | 7513(2) | -450(2) | 23(1) |
| C(3) | 8946(3) | 8631(2) | -742(2) | 24(1) |
| O(3) | 9833(2) | 8779(2) | -1013(1) | 30(1) |
| N(4) | 8171(2) | 9381(2) | -670(1) | 24(1) |

| | | | | |
|-------|----------|----------|----------|-------|
| C(5) | 8310(3) | 10519(2) | -867(2) | 26(1) |
| C(6) | 9243(3) | 11006(3) | -457(2) | 38(1) |
| C(7) | 7255(3) | 11082(3) | -669(2) | 37(1) |
| C(8) | 8496(4) | 10613(3) | -1656(2) | 47(1) |
| C(9) | 9755(3) | 7232(2) | 638(1) | 22(1) |
| C(10) | 8977(3) | 6659(2) | 1143(2) | 23(1) |
| F(10) | 8008(2) | 7268(1) | 1174(1) | 33(1) |
| C(11) | 8648(3) | 5533(2) | 932(2) | 25(1) |
| C(12) | 9377(3) | 4853(2) | 594(2) | 27(1) |
| C(13) | 9086(3) | 3825(3) | 412(2) | 36(1) |
| C(14) | 8062(4) | 3449(3) | 563(2) | 41(1) |
| C(15) | 7337(3) | 4103(3) | 900(2) | 41(1) |
| C(16) | 7621(3) | 5150(3) | 1090(2) | 32(1) |
| C(17) | 9459(3) | 6655(2) | 1885(2) | 25(1) |
| C(18) | 10326(3) | 5983(3) | 2038(2) | 29(1) |
| C(19) | 10778(3) | 5937(3) | 2704(2) | 36(1) |
| C(20) | 10376(3) | 6583(3) | 3230(2) | 40(1) |
| C(21) | 9532(3) | 7265(3) | 3087(2) | 46(1) |
| C(22) | 9062(3) | 7305(3) | 2418(2) | 37(1) |
| C(23) | 9787(3) | 8437(2) | 779(2) | 31(1) |
| C(26) | 10473(3) | 6639(3) | -481(2) | 24(1) |
| O(26) | 11303(2) | 6349(2) | -165(1) | 31(1) |
| C(27) | 10483(3) | 6529(2) | -1280(2) | 26(1) |
| C(28) | 10542(3) | 5355(2) | -1511(2) | 25(1) |
| C(29) | 9697(3) | 4913(3) | -1896(2) | 33(1) |
| C(30) | 9737(3) | 3847(3) | -2105(2) | 41(1) |
| C(31) | 10611(4) | 3221(3) | -1936(2) | 43(1) |
| C(32) | 11464(3) | 3666(3) | -1568(2) | 42(1) |
| C(33) | 11438(3) | 4728(3) | -1356(2) | 35(1) |
| C(34) | 8022(3) | 6824(2) | -987(2) | 23(1) |
| C(35) | 7707(3) | 7211(3) | -1640(2) | 28(1) |
| C(36) | 7124(3) | 6577(3) | -2106(2) | 31(1) |
| C(37) | 6851(3) | 5538(3) | -1930(2) | 30(1) |
| C(38) | 7140(3) | 5150(3) | -1272(2) | 30(1) |
| C(39) | 7722(3) | 5781(2) | -812(2) | 28(1) |

Table 2. Bond lengths [Å] and angles [°] for **370**.

| | | | |
|------------|----------|--------------|------|
| N(1)-C(26) | 1.375(4) | C(22)-H(22A) | 0.93 |
|------------|----------|--------------|------|

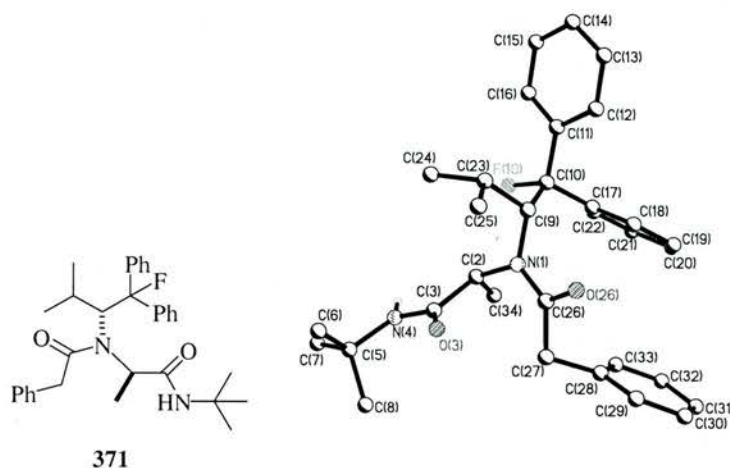
| | | | |
|------------------|------------|--------------------|----------|
| N(1)-C(2) | 1.470(4) | C(23)-H(23A) | 0.96 |
| N(1)-C(9) | 1.484(4) | C(23)-H(23B) | 0.96 |
| C(2)-C(34) | 1.529(4) | C(23)-H(23C) | 0.96 |
| C(2)-C(3) | 1.550(4) | C(26)-O(26) | 1.241(4) |
| C(2)-H(2A) | 0.98 | C(26)-C(27) | 1.522(4) |
| C(3)-O(3) | 1.223(4) | C(27)-C(28) | 1.530(4) |
| C(3)-N(4) | 1.345(4) | C(27)-H(27A) | 0.97 |
| N(4)-C(5) | 1.478(4) | C(27)-H(27B) | 0.97 |
| N(4)-H(4N) | 0.9800(10) | C(28)-C(33) | 1.386(5) |
| C(5)-C(6) | 1.516(5) | C(28)-C(29) | 1.388(5) |
| C(5)-C(8) | 1.518(4) | C(29)-C(30) | 1.388(5) |
| C(5)-C(7) | 1.527(5) | C(29)-H(29A) | 0.93 |
| C(6)-H(6A) | 0.96 | C(30)-C(31) | 1.370(5) |
| C(6)-H(6B) | 0.96 | C(30)-H(30A) | 0.93 |
| C(6)-H(6C) | 0.96 | C(31)-C(32) | 1.381(5) |
| C(7)-H(7A) | 0.96 | C(31)-H(31A) | 0.93 |
| C(7)-H(7B) | 0.96 | C(32)-C(33) | 1.383(5) |
| C(7)-H(7C) | 0.96 | C(32)-H(32A) | 0.93 |
| C(8)-H(8A) | 0.96 | C(33)-H(33A) | 0.93 |
| C(8)-H(8B) | 0.96 | C(34)-C(35) | 1.386(4) |
| C(8)-H(8C) | 0.96 | C(34)-C(39) | 1.392(4) |
| C(9)-C(23) | 1.527(4) | C(35)-C(36) | 1.387(4) |
| C(9)-C(10) | 1.534(4) | C(35)-H(35A) | 0.93 |
| C(9)-H(9A) | 0.98 | C(36)-C(37) | 1.379(5) |
| C(10)-F(10) | 1.418(4) | C(36)-H(36A) | 0.93 |
| C(10)-C(11) | 1.515(4) | C(37)-C(38) | 1.384(4) |
| C(10)-C(17) | 1.528(4) | C(37)-H(37A) | 0.93 |
| C(11)-C(16) | 1.388(4) | C(38)-C(39) | 1.377(4) |
| C(11)-C(12) | 1.393(4) | C(38)-H(38A) | 0.93 |
| C(12)-C(13) | 1.375(5) | C(39)-H(39A) | 0.93 |
| C(12)-H(12A) | 0.93 | C(26)-N(1)-C(2) | 125.1(2) |
| C(13)-C(14) | 1.378(5) | C(26)-N(1)-C(9) | 115.2(2) |
| C(13)-H(13A) | 0.93 | C(2)-N(1)-C(9) | 116.5(2) |
| C(14)-C(15) | 1.370(5) | N(1)-C(2)-C(34) | 115.6(2) |
| C(14)-H(14A) | 0.93 | N(1)-C(2)-C(3) | 109.5(3) |
| C(15)-C(16) | 1.399(5) | C(34)-C(2)-C(3) | 113.0(2) |
| C(15)-H(15A) | 0.93 | N(1)-C(2)-H(2A) | 106 |
| C(16)-H(16A) | 0.93 | C(34)-C(2)-H(2A) | 106 |
| C(17)-C(22) | 1.385(4) | C(3)-C(2)-H(2A) | 106 |
| C(17)-C(18) | 1.390(5) | O(3)-C(3)-N(4) | 125.1(3) |
| C(18)-C(19) | 1.383(4) | O(3)-C(3)-C(2) | 120.8(3) |
| C(18)-H(18A) | 0.93 | N(4)-C(3)-C(2) | 114.1(3) |
| C(19)-C(20) | 1.375(5) | C(3)-N(4)-C(5) | 124.0(3) |
| C(19)-H(19A) | 0.93 | C(3)-N(4)-H(4N) | 117(2) |
| C(20)-C(21) | 1.373(5) | C(5)-N(4)-H(4N) | 118(2) |
| C(20)-H(20A) | 0.93 | N(4)-C(5)-C(6) | 110.1(3) |
| C(21)-C(22) | 1.396(5) | N(4)-C(5)-C(8) | 110.0(3) |
| C(21)-H(21A) | 0.93 | C(6)-C(5)-C(8) | 111.1(3) |
| N(4)-C(5)-C(7) | 106.3(3) | C(22)-C(17)-C(18) | 118.3(3) |
| C(6)-C(5)-C(7) | 109.7(3) | C(22)-C(17)-C(10) | 122.1(3) |
| C(8)-C(5)-C(7) | 109.6(3) | C(18)-C(17)-C(10) | 119.6(3) |
| C(5)-C(6)-H(6A) | 109.5 | C(19)-C(18)-C(17) | 121.8(3) |
| C(5)-C(6)-H(6B) | 109.5 | C(19)-C(18)-H(18A) | 119.1 |
| H(6A)-C(6)-H(6B) | 109.5 | C(17)-C(18)-H(18A) | 119.1 |
| C(5)-C(6)-H(6C) | 109.5 | C(20)-C(19)-C(18) | 119.5(4) |

| | | | |
|--------------------|----------|---------------------|----------|
| H(6A)-C(6)-H(6C) | 109.5 | C(20)-C(19)-H(19A) | 120.2 |
| H(6B)-C(6)-H(6C) | 109.5 | C(18)-C(19)-H(19A) | 120.2 |
| C(5)-C(7)-H(7A) | 109.5 | C(21)-C(20)-C(19) | 119.6(3) |
| C(5)-C(7)-H(7B) | 109.5 | C(21)-C(20)-H(20A) | 120.2 |
| H(7A)-C(7)-H(7B) | 109.5 | C(19)-C(20)-H(20A) | 120.2 |
| C(5)-C(7)-H(7C) | 109.5 | C(20)-C(21)-C(22) | 121.2(3) |
| H(7A)-C(7)-H(7C) | 109.5 | C(20)-C(21)-H(21A) | 119.4 |
| H(7B)-C(7)-H(7C) | 109.5 | C(22)-C(21)-H(21A) | 119.4 |
| C(5)-C(8)-H(8A) | 109.5 | C(17)-C(22)-C(21) | 119.7(3) |
| C(5)-C(8)-H(8B) | 109.5 | C(17)-C(22)-H(22A) | 120.2 |
| H(8A)-C(8)-H(8B) | 109.5 | C(21)-C(22)-H(22A) | 120.2 |
| C(5)-C(8)-H(8C) | 109.5 | C(9)-C(23)-H(23A) | 109.5 |
| H(8A)-C(8)-H(8C) | 109.5 | C(9)-C(23)-H(23B) | 109.5 |
| H(8B)-C(8)-H(8C) | 109.5 | H(23A)-C(23)-H(23B) | 109.5 |
| N(1)-C(9)-C(23) | 111.1(2) | C(9)-C(23)-H(23C) | 109.5 |
| N(1)-C(9)-C(10) | 115.4(2) | H(23A)-C(23)-H(23C) | 109.5 |
| C(23)-C(9)-C(10) | 111.4(3) | H(23B)-C(23)-H(23C) | 109.5 |
| N(1)-C(9)-H(9A) | 106.1 | O(26)-C(26)-N(1) | 121.4(3) |
| C(23)-C(9)-H(9A) | 106.1 | O(26)-C(26)-C(27) | 116.7(3) |
| C(10)-C(9)-H(9A) | 106.1 | N(1)-C(26)-C(27) | 121.9(3) |
| F(10)-C(10)-C(11) | 106.3(2) | C(26)-C(27)-C(28) | 111.8(2) |
| F(10)-C(10)-C(17) | 107.0(2) | C(26)-C(27)-H(27A) | 109.2 |
| C(11)-C(10)-C(17) | 110.2(2) | C(28)-C(27)-H(27A) | 109.3 |
| F(10)-C(10)-C(9) | 107.8(2) | C(26)-C(27)-H(27B) | 109.2 |
| C(11)-C(10)-C(9) | 115.7(3) | C(28)-C(27)-H(27B) | 109.2 |
| C(17)-C(10)-C(9) | 109.5(3) | H(27A)-C(27)-H(27B) | 107.9 |
| C(16)-C(11)-C(12) | 118.7(3) | C(33)-C(28)-C(29) | 119.1(3) |
| C(16)-C(11)-C(10) | 120.4(3) | C(33)-C(28)-C(27) | 121.2(3) |
| C(12)-C(11)-C(10) | 120.9(3) | C(29)-C(28)-C(27) | 119.7(3) |
| C(13)-C(12)-C(11) | 120.9(3) | C(28)-C(29)-C(30) | 120.2(4) |
| C(13)-C(12)-H(12A) | 119.5 | C(28)-C(29)-H(29A) | 119.9 |
| C(11)-C(12)-H(12A) | 119.5 | C(30)-C(29)-H(29A) | 119.9 |
| C(12)-C(13)-C(14) | 120.3(4) | C(31)-C(30)-C(29) | 120.5(4) |
| C(12)-C(13)-H(13A) | 119.8 | C(31)-C(30)-H(30A) | 119.7 |
| C(14)-C(13)-H(13A) | 119.8 | C(29)-C(30)-H(30A) | 119.7 |
| C(15)-C(14)-C(13) | 119.6(3) | C(30)-C(31)-C(32) | 119.3(3) |
| C(15)-C(14)-H(14A) | 120.2 | C(30)-C(31)-H(31A) | 120.3 |
| C(13)-C(14)-H(14A) | 120.2 | C(32)-C(31)-H(31A) | 120.3 |
| C(14)-C(15)-C(16) | 120.8(3) | C(31)-C(32)-C(33) | 120.9(4) |
| C(14)-C(15)-H(15A) | 119.6 | C(31)-C(32)-H(32A) | 119.5 |
| C(16)-C(15)-H(15A) | 119.6 | C(33)-C(32)-H(32A) | 119.5 |
| C(11)-C(16)-C(15) | 119.7(3) | C(32)-C(33)-C(28) | 119.9(4) |
| C(11)-C(16)-H(16A) | 120.2 | C(32)-C(33)-H(33A) | 120.1 |
| C(15)-C(16)-H(16A) | 120.2 | C(28)-C(33)-H(33A) | 120.1 |
| C(35)-C(34)-C(39) | 117.6(3) | C(36)-C(37)-C(38) | 119.0(3) |
| C(35)-C(34)-C(2) | 122.5(3) | C(36)-C(37)-H(37A) | 120.5 |
| C(39)-C(34)-C(2) | 119.8(3) | C(38)-C(37)-H(37A) | 120.5 |
| C(34)-C(35)-C(36) | 121.1(3) | C(39)-C(38)-C(37) | 120.4(3) |
| C(34)-C(35)-H(35A) | 119.4 | C(39)-C(38)-H(38A) | 119.8 |
| C(36)-C(35)-H(35A) | 119.4 | C(37)-C(38)-H(38A) | 119.8 |
| C(37)-C(36)-C(35) | 120.5(3) | C(38)-C(39)-C(34) | 121.4(3) |
| C(37)-C(36)-H(36A) | 119.8 | C(38)-C(39)-H(39A) | 119.3 |
| C(35)-C(36)-H(36A) | 119.8 | C(34)-C(39)-H(39A) | 119.3 |

Table 3. Torsion angles [°] for **370**.

| | | | |
|-------------------------|-----------|-------------------------|-----------|
| C(26)-N(1)-C(2)-C(34) | 59.5(4) | F(10)-C(10)-C(17)-C(18) | 170.2(3) |
| C(9)-N(1)-C(2)-C(34) | -141.4(3) | C(11)-C(10)-C(17)-C(18) | 55.0(4) |
| C(26)-N(1)-C(2)-C(3) | -69.5(3) | C(9)-C(10)-C(17)-C(18) | -73.3(4) |
| C(9)-N(1)-C(2)-C(3) | 89.5(3) | C(22)-C(17)-C(18)-C(19) | 1.3(5) |
| N(1)-C(2)-C(3)-O(3) | 37.3(4) | C(10)-C(17)-C(18)-C(19) | -178.9(3) |
| C(34)-C(2)-C(3)-O(3) | -93.1(3) | C(17)-C(18)-C(19)-C(20) | -1.1(5) |
| N(1)-C(2)-C(3)-N(4) | -142.9(2) | C(18)-C(19)-C(20)-C(21) | 0.0(5) |
| C(34)-C(2)-C(3)-N(4) | 86.6(3) | C(19)-C(20)-C(21)-C(22) | 0.8(6) |
| O(3)-C(3)-N(4)-C(5) | -4.2(5) | C(18)-C(17)-C(22)-C(21) | -0.4(5) |
| C(2)-C(3)-N(4)-C(5) | 176.0(3) | C(10)-C(17)-C(22)-C(21) | 179.8(3) |
| C(3)-N(4)-C(5)-C(6) | -59.0(4) | C(20)-C(21)-C(22)-C(17) | -0.7(6) |
| C(3)-N(4)-C(5)-C(8) | 63.7(4) | C(2)-N(1)-C(26)-O(26) | 170.6(3) |
| C(3)-N(4)-C(5)-C(7) | -177.8(3) | C(9)-N(1)-C(26)-O(26) | 11.4(4) |
| C(26)-N(1)-C(9)-C(23) | 106.7(3) | C(2)-N(1)-C(26)-C(27) | -11.5(5) |
| C(2)-N(1)-C(9)-C(23) | -54.4(3) | C(9)-N(1)-C(26)-C(27) | -170.7(3) |
| C(26)-N(1)-C(9)-C(10) | -125.3(3) | O(26)-C(26)-C(27)-C(28) | 65.3(4) |
| C(2)-N(1)-C(9)-C(10) | 73.6(3) | N(1)-C(26)-C(27)-C(28) | -112.7(3) |
| N(1)-C(9)-C(10)-F(10) | -82.5(3) | C(26)-C(27)-C(28)-C(33) | -64.1(4) |
| C(23)-C(9)-C(10)-F(10) | 45.3(3) | C(26)-C(27)-C(28)-C(29) | 117.2(3) |
| N(1)-C(9)-C(10)-C(11) | 36.3(4) | C(33)-C(28)-C(29)-C(30) | 1.8(5) |
| C(23)-C(9)-C(10)-C(11) | 164.2(3) | C(27)-C(28)-C(29)-C(30) | -179.6(3) |
| N(1)-C(9)-C(10)-C(17) | 161.5(2) | C(28)-C(29)-C(30)-C(31) | -0.2(5) |
| C(23)-C(9)-C(10)-C(17) | -70.7(3) | C(29)-C(30)-C(31)-C(32) | -1.3(5) |
| F(10)-C(10)-C(11)-C(16) | -26.9(4) | C(30)-C(31)-C(32)-C(33) | 1.2(5) |
| C(17)-C(10)-C(11)-C(16) | 88.7(3) | C(31)-C(32)-C(33)-C(28) | 0.4(5) |
| C(9)-C(10)-C(11)-C(16) | -146.5(3) | C(29)-C(28)-C(33)-C(32) | -1.8(5) |
| F(10)-C(10)-C(11)-C(12) | 154.9(3) | C(27)-C(28)-C(33)-C(32) | 179.5(3) |
| C(17)-C(10)-C(11)-C(12) | -89.5(3) | N(1)-C(2)-C(34)-C(35) | -133.0(3) |
| C(9)-C(10)-C(11)-C(12) | 35.3(4) | C(3)-C(2)-C(34)-C(35) | -5.7(4) |
| C(16)-C(11)-C(12)-C(13) | 0.7(4) | N(1)-C(2)-C(34)-C(39) | 50.1(4) |
| C(10)-C(11)-C(12)-C(13) | 178.9(3) | C(3)-C(2)-C(34)-C(39) | 177.4(3) |
| C(11)-C(12)-C(13)-C(14) | 0.1(5) | C(39)-C(34)-C(35)-C(36) | -0.8(5) |
| C(12)-C(13)-C(14)-C(15) | -0.6(5) | C(2)-C(34)-C(35)-C(36) | -177.7(3) |
| C(13)-C(14)-C(15)-C(16) | 0.4(5) | C(34)-C(35)-C(36)-C(37) | -0.4(5) |
| C(12)-C(11)-C(16)-C(15) | -0.8(4) | C(35)-C(36)-C(37)-C(38) | 1.8(5) |
| C(10)-C(11)-C(16)-C(15) | -179.1(3) | C(36)-C(37)-C(38)-C(39) | -2.1(5) |
| C(14)-C(15)-C(16)-C(11) | 0.3(5) | C(37)-C(38)-C(39)-C(34) | 0.9(5) |
| F(10)-C(10)-C(17)-C(22) | -9.9(4) | C(35)-C(34)-C(39)-C(38) | 0.6(5) |
| C(11)-C(10)-C(17)-C(22) | -125.1(3) | C(2)-C(34)-C(39)-C(38) | 177.6(3) |
| C(9)-C(10)-C(17)-C(22) | 106.6(3) | | |

A.1.4.2 X-ray data for 271



Crystal data and structure refinement for **371**.

Crystal data for 371

$C_{32}H_{39}FN_2O_2$, $M=502.65$, orthorhombic, space group $P2(1)2(1)1$, $a = 12.3918(12)$, $b = 18.0983(17)$, $c = 24.794(2)$ Å, $V = 5560.5(9)$ Å³, $T = 125(2)$ K, $Z = 8$, μ (Mo-K α) = 0.079 mm⁻¹, colourless block, crystal dimensions, $0.1 \times 0.1 \times 0.02$ mm³. Full matrix least squares based on F^2 gave $R1 = 0.0383$ for 10133 observed ($F > 4\sigma(F)$) and $wR2 = 0.0907$ for all data, $GOF = 1.020$ for 676 parameters.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² $\times 10^3$) for **371**. $U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

| | x | y | z | U(eq) |
|-------|---------|---------|----------|-------|
| N(1) | 5059(1) | 2580(1) | 526(1) | 23(1) |
| C(2) | 5853(1) | 2557(1) | 78(1) | 24(1) |
| C(3) | 5312(1) | 2745(1) | -468(1) | 23(1) |
| O(3) | 4333(1) | 2839(1) | -504(1) | 29(1) |
| N(4) | 6007(1) | 2809(1) | -877(1) | 27(1) |
| C(5) | 5697(2) | 2969(1) | -1444(1) | 30(1) |
| C(6) | 5096(2) | 3703(1) | -1475(1) | 35(1) |
| C(7) | 6748(2) | 3031(1) | -1768(1) | 42(1) |
| C(8) | 5011(2) | 2335(1) | -1662(1) | 36(1) |
| C(9) | 5200(1) | 3119(1) | 968(1) | 23(1) |
| C(10) | 6225(1) | 2934(1) | 1303(1) | 26(1) |
| F(10) | 7134(1) | 2988(1) | 962(1) | 28(1) |

| | | | | |
|-------|----------|---------|----------|-------|
| C(11) | 6408(2) | 3486(1) | 1758(1) | 28(1) |
| C(12) | 5665(2) | 3560(1) | 2174(1) | 39(1) |
| C(13) | 5821(2) | 4084(1) | 2577(1) | 48(1) |
| C(14) | 6724(2) | 4535(1) | 2571(1) | 47(1) |
| C(15) | 7471(2) | 4448(1) | 2172(1) | 47(1) |
| C(16) | 7323(2) | 3929(1) | 1767(1) | 37(1) |
| C(17) | 6202(2) | 2144(1) | 1521(1) | 27(1) |
| C(18) | 5268(2) | 1833(1) | 1738(1) | 34(1) |
| C(19) | 5281(2) | 1126(1) | 1945(1) | 40(1) |
| C(20) | 6218(2) | 711(1) | 1945(1) | 42(1) |
| C(21) | 7147(2) | 1012(1) | 1721(1) | 43(1) |
| C(22) | 7138(2) | 1721(1) | 1516(1) | 35(1) |
| C(23) | 5032(2) | 3944(1) | 823(1) | 29(1) |
| C(24) | 5817(2) | 4298(1) | 426(1) | 35(1) |
| C(25) | 3873(2) | 4067(1) | 633(1) | 34(1) |
| C(26) | 4120(1) | 2187(1) | 523(1) | 23(1) |
| O(26) | 3381(1) | 2327(1) | 843(1) | 28(1) |
| C(27) | 3975(2) | 1527(1) | 152(1) | 26(1) |
| C(28) | 3798(2) | 826(1) | 476(1) | 26(1) |
| C(29) | 2756(2) | 609(1) | 614(1) | 32(1) |
| C(30) | 2578(2) | -54(1) | 883(1) | 41(1) |
| C(31) | 3428(2) | -497(1) | 1028(1) | 40(1) |
| C(32) | 4462(2) | -278(1) | 910(1) | 42(1) |
| C(33) | 4647(2) | 380(1) | 636(1) | 36(1) |
| C(34) | 6561(2) | 1861(1) | 59(1) | 29(1) |
| N(41) | -712(1) | 8011(1) | 601(1) | 28(1) |
| C(42) | 136(2) | 8348(1) | 260(1) | 30(1) |
| C(43) | -233(2) | 8334(1) | -338(1) | 32(1) |
| O(43) | -1192(1) | 8286(1) | -449(1) | 45(1) |
| N(44) | 550(1) | 8409(1) | -711(1) | 34(1) |
| C(45) | 341(2) | 8436(1) | -1304(1) | 37(1) |
| C(46) | -85(3) | 7690(2) | -1490(1) | 65(1) |
| C(47) | 1412(2) | 8602(2) | -1569(1) | 80(1) |
| C(48) | -471(2) | 9038(1) | -1439(1) | 55(1) |
| C(49) | -1241(2) | 8449(1) | 1031(1) | 30(1) |
| C(50) | -485(2) | 8618(1) | 1507(1) | 30(1) |
| F(50) | 231(1) | 9189(1) | 1348(1) | 38(1) |
| C(51) | 215(2) | 7973(1) | 1690(1) | 29(1) |

| | | | | |
|-------|----------|---------|---------|-------|
| C(52) | 1255(2) | 8106(1) | 1882(1) | 37(1) |
| C(53) | 1880(2) | 7530(2) | 2072(1) | 49(1) |
| C(54) | 1487(2) | 6817(2) | 2074(1) | 51(1) |
| C(55) | 444(2) | 6686(1) | 1895(1) | 46(1) |
| C(56) | -185(2) | 7259(1) | 1704(1) | 34(1) |
| C(57) | -1123(2) | 8903(1) | 1992(1) | 31(1) |
| C(58) | -2018(2) | 8513(1) | 2183(1) | 43(1) |
| C(59) | -2589(2) | 8764(2) | 2629(1) | 48(1) |
| C(60) | -2264(2) | 9390(1) | 2895(1) | 51(1) |
| C(61) | -1367(3) | 9759(1) | 2718(1) | 58(1) |
| C(62) | -801(2) | 9527(1) | 2268(1) | 44(1) |
| C(63) | -1945(2) | 9107(1) | 844(1) | 46(1) |
| C(64) | -2932(2) | 8821(2) | 546(1) | 68(1) |
| C(65) | -1427(2) | 9755(2) | 577(1) | 66(1) |
| C(66) | -1181(2) | 7351(1) | 476(1) | 31(1) |
| O(66) | -2032(1) | 7148(1) | 689(1) | 38(1) |
| C(67) | -615(2) | 6814(1) | 102(1) | 35(1) |
| C(68) | -341(2) | 6108(1) | 407(1) | 42(1) |
| C(69) | -1132(3) | 5581(1) | 502(1) | 55(1) |
| C(70) | -897(4) | 4939(2) | 769(1) | 76(1) |
| C(71) | 113(4) | 4805(2) | 946(1) | 83(1) |
| C(72) | 908(3) | 5309(2) | 869(1) | 73(1) |
| C(73) | 680(2) | 5975(1) | 599(1) | 55(1) |
| C(74) | 1286(2) | 8079(1) | 374(1) | 35(1) |

Table 2. Bond lengths [Å] and angles [°] for **371**.

| | | | |
|-------------|----------|-------------|----------|
| N(1)-C(26) | 1.364(2) | C(45)-C(46) | 1.521(4) |
| N(1)-C(9) | 1.477(2) | C(49)-C(50) | 1.539(3) |
| N(1)-C(2) | 1.483(2) | C(49)-C(63) | 1.548(3) |
| C(2)-C(34) | 1.536(3) | C(50)-F(50) | 1.418(2) |
| C(2)-C(3) | 1.547(2) | C(50)-C(51) | 1.523(3) |
| C(3)-O(3) | 1.230(2) | C(50)-C(57) | 1.527(3) |
| C(3)-N(4) | 1.337(2) | C(51)-C(56) | 1.384(3) |
| N(4)-C(5) | 1.486(2) | C(51)-C(52) | 1.394(3) |
| C(5)-C(6) | 1.525(3) | C(52)-C(53) | 1.382(3) |
| C(5)-C(8) | 1.527(3) | C(53)-C(54) | 1.380(4) |
| C(5)-C(7) | 1.533(3) | C(54)-C(55) | 1.387(4) |
| C(9)-C(23) | 1.551(3) | C(55)-C(56) | 1.382(3) |
| C(9)-C(10) | 1.554(3) | C(57)-C(62) | 1.379(3) |
| C(10)-F(10) | 1.412(2) | C(57)-C(58) | 1.397(3) |
| C(10)-C(11) | 1.525(3) | C(58)-C(59) | 1.390(3) |
| C(10)-C(17) | 1.529(3) | C(59)-C(60) | 1.371(4) |
| C(11)-C(16) | 1.388(3) | C(60)-C(61) | 1.369(4) |

| | | | |
|-------------------|------------|-------------------|------------|
| C(11)-C(12) | 1.389(3) | C(61)-C(62) | 1.384(3) |
| C(12)-C(13) | 1.391(3) | C(63)-C(65) | 1.491(4) |
| C(13)-C(14) | 1.386(4) | C(63)-C(64) | 1.520(4) |
| C(14)-C(15) | 1.364(4) | C(66)-O(66) | 1.234(2) |
| C(15)-C(16) | 1.387(3) | C(66)-C(67) | 1.517(3) |
| C(17)-C(22) | 1.390(3) | C(67)-C(68) | 1.522(3) |
| C(17)-C(18) | 1.394(3) | C(68)-C(73) | 1.374(4) |
| C(18)-C(19) | 1.379(3) | C(68)-C(69) | 1.388(3) |
| C(19)-C(20) | 1.383(3) | C(69)-C(70) | 1.369(4) |
| C(20)-C(21) | 1.389(3) | C(70)-C(71) | 1.348(5) |
| C(21)-C(22) | 1.381(3) | C(71)-C(72) | 1.356(5) |
| C(23)-C(24) | 1.524(3) | C(72)-C(73) | 1.407(4) |
| C(23)-C(25) | 1.526(3) | C(26)-N(1)-C(9) | 116.68(14) |
| C(26)-O(26) | 1.236(2) | C(26)-N(1)-C(2) | 123.15(15) |
| C(26)-C(27) | 1.518(3) | C(9)-N(1)-C(2) | 119.71(14) |
| C(27)-C(28) | 1.518(3) | N(1)-C(2)-C(34) | 115.25(15) |
| C(28)-C(33) | 1.384(3) | N(1)-C(2)-C(3) | 111.15(14) |
| C(28)-C(29) | 1.392(3) | C(34)-C(2)-C(3) | 113.60(15) |
| C(29)-C(30) | 1.389(3) | O(3)-C(3)-N(4) | 124.56(17) |
| C(30)-C(31) | 1.372(3) | O(3)-C(3)-C(2) | 121.50(16) |
| C(31)-C(32) | 1.372(3) | N(4)-C(3)-C(2) | 113.92(14) |
| C(32)-C(33) | 1.390(3) | C(3)-N(4)-C(5) | 124.74(15) |
| N(41)-C(66) | 1.363(2) | N(4)-C(5)-C(6) | 110.06(16) |
| N(41)-C(42) | 1.480(2) | N(4)-C(5)-C(8) | 109.42(16) |
| N(41)-C(49) | 1.481(2) | C(6)-C(5)-C(8) | 111.41(16) |
| C(42)-C(74) | 1.532(3) | N(4)-C(5)-C(7) | 106.86(15) |
| C(42)-C(43) | 1.553(3) | C(6)-C(5)-C(7) | 108.94(17) |
| C(43)-O(43) | 1.223(2) | C(8)-C(5)-C(7) | 110.05(17) |
| C(43)-N(44) | 1.347(3) | N(1)-C(9)-C(23) | 116.57(15) |
| N(44)-C(45) | 1.494(2) | N(1)-C(9)-C(10) | 110.61(14) |
| C(45)-C(47) | 1.512(3) | C(23)-C(9)-C(10) | 116.18(15) |
| C(45)-C(48) | 1.521(3) | F(10)-C(10)-C(11) | 106.24(14) |
| F(10)-C(10)-C(9) | 108.50(13) | F(10)-C(10)-C(17) | 106.96(14) |
| C(11)-C(10)-C(9) | 112.13(15) | C(11)-C(10)-C(17) | 110.69(15) |
| C(17)-C(10)-C(9) | 111.99(15) | C(47)-C(45)-C(48) | 110.0(2) |
| C(16)-C(11)-C(12) | 118.33(19) | N(44)-C(45)-C(46) | 109.34(18) |
| C(16)-C(11)-C(10) | 120.76(17) | C(47)-C(45)-C(46) | 110.4(2) |
| C(12)-C(11)-C(10) | 120.91(17) | C(48)-C(45)-C(46) | 109.8(2) |
| C(11)-C(12)-C(13) | 120.4(2) | N(41)-C(49)-C(50) | 112.91(16) |
| C(14)-C(13)-C(12) | 120.5(2) | N(41)-C(49)-C(63) | 116.53(17) |
| C(15)-C(14)-C(13) | 119.2(2) | C(50)-C(49)-C(63) | 114.80(17) |
| C(14)-C(15)-C(16) | 120.8(2) | F(50)-C(50)-C(51) | 106.57(15) |
| C(15)-C(16)-C(11) | 120.7(2) | F(50)-C(50)-C(57) | 107.28(15) |
| C(22)-C(17)-C(18) | 118.28(18) | C(51)-C(50)-C(57) | 108.62(15) |
| C(22)-C(17)-C(10) | 119.72(17) | F(50)-C(50)-C(49) | 108.15(15) |
| C(18)-C(17)-C(10) | 121.99(17) | C(51)-C(50)-C(49) | 115.05(16) |
| C(19)-C(18)-C(17) | 120.6(2) | C(57)-C(50)-C(49) | 110.81(16) |
| C(18)-C(19)-C(20) | 120.9(2) | C(56)-C(51)-C(52) | 118.91(19) |
| C(19)-C(20)-C(21) | 118.9(2) | C(56)-C(51)-C(50) | 121.23(17) |
| C(22)-C(21)-C(20) | 120.3(2) | C(52)-C(51)-C(50) | 119.72(18) |
| C(21)-C(22)-C(17) | 121.0(2) | C(53)-C(52)-C(51) | 120.3(2) |
| C(24)-C(23)-C(25) | 109.89(17) | C(54)-C(53)-C(52) | 120.6(2) |
| C(24)-C(23)-C(9) | 117.97(16) | C(53)-C(54)-C(55) | 119.2(2) |
| C(25)-C(23)-C(9) | 109.77(16) | C(56)-C(55)-C(54) | 120.4(2) |
| O(26)-C(26)-N(1) | 121.45(16) | C(55)-C(56)-C(51) | 120.5(2) |

| | | | |
|-------------------|------------|-------------------|------------|
| O(26)-C(26)-C(27) | 117.48(15) | C(62)-C(57)-C(58) | 118.3(2) |
| N(1)-C(26)-C(27) | 120.93(15) | C(62)-C(57)-C(50) | 121.13(19) |
| C(28)-C(27)-C(26) | 110.78(14) | C(58)-C(57)-C(50) | 120.48(18) |
| C(33)-C(28)-C(29) | 118.06(18) | C(59)-C(58)-C(57) | 120.6(2) |
| C(33)-C(28)-C(27) | 121.94(17) | C(60)-C(59)-C(58) | 120.2(2) |
| C(29)-C(28)-C(27) | 120.00(17) | C(61)-C(60)-C(59) | 119.2(2) |
| C(30)-C(29)-C(28) | 120.6(2) | C(60)-C(61)-C(62) | 121.4(2) |
| C(31)-C(30)-C(29) | 120.5(2) | C(57)-C(62)-C(61) | 120.2(2) |
| C(30)-C(31)-C(32) | 119.5(2) | C(65)-C(63)-C(64) | 113.5(2) |
| C(31)-C(32)-C(33) | 120.4(2) | C(65)-C(63)-C(49) | 119.7(2) |
| C(28)-C(33)-C(32) | 120.9(2) | C(64)-C(63)-C(49) | 109.6(2) |
| C(66)-N(41)-C(42) | 122.38(16) | O(66)-C(66)-N(41) | 121.92(18) |
| C(66)-N(41)-C(49) | 116.23(16) | O(66)-C(66)-C(67) | 117.75(18) |
| C(42)-N(41)-C(49) | 120.28(15) | N(41)-C(66)-C(67) | 120.14(17) |
| N(41)-C(42)-C(74) | 115.09(16) | C(66)-C(67)-C(68) | 109.72(16) |
| N(41)-C(42)-C(43) | 109.18(15) | C(73)-C(68)-C(69) | 118.1(2) |
| C(74)-C(42)-C(43) | 116.40(16) | C(73)-C(68)-C(67) | 121.6(2) |
| O(43)-C(43)-N(44) | 123.58(18) | C(69)-C(68)-C(67) | 120.2(2) |
| O(43)-C(43)-C(42) | 120.18(18) | C(70)-C(69)-C(68) | 121.0(3) |
| N(44)-C(43)-C(42) | 116.18(17) | C(71)-C(70)-C(69) | 120.5(3) |
| C(43)-N(44)-C(45) | 123.60(18) | C(70)-C(71)-C(72) | 120.5(3) |
| N(44)-C(45)-C(47) | 106.40(18) | C(71)-C(72)-C(73) | 119.8(3) |
| N(44)-C(45)-C(48) | 110.75(18) | C(68)-C(73)-C(72) | 120.0(3) |

Table 3. Torsion angles [°] for **371**.

| | | | |
|-------------------------|-------------|-------------------------|-------------|
| C(26)-N(1)-C(2)-C(34) | -76.8(2) | C(18)-C(17)-C(22)-C(21) | -0.2(3) |
| C(9)-N(1)-C(2)-C(34) | 111.23(18) | C(10)-C(17)-C(22)-C(21) | 178.58(19) |
| C(26)-N(1)-C(2)-C(3) | 54.3(2) | N(1)-C(9)-C(23)-C(24) | -64.9(2) |
| C(9)-N(1)-C(2)-C(3) | -117.69(17) | C(10)-C(9)-C(23)-C(24) | 68.3(2) |
| N(1)-C(2)-C(3)-O(3) | -5.2(2) | N(1)-C(9)-C(23)-C(25) | 62.0(2) |
| C(34)-C(2)-C(3)-O(3) | 126.72(19) | C(10)-C(9)-C(23)-C(25) | -164.85(16) |
| N(1)-C(2)-C(3)-N(4) | 173.23(15) | C(9)-N(1)-C(26)-O(26) | 6.9(2) |
| C(34)-C(2)-C(3)-N(4) | -54.8(2) | C(2)-N(1)-C(26)-O(26) | -165.27(16) |
| O(3)-C(3)-N(4)-C(5) | -3.1(3) | C(9)-N(1)-C(26)-C(27) | -168.74(15) |
| C(2)-C(3)-N(4)-C(5) | 178.47(17) | C(2)-N(1)-C(26)-C(27) | 19.1(2) |
| C(3)-N(4)-C(5)-C(6) | 59.2(2) | O(26)-C(26)-C(27)-C(28) | -58.0(2) |
| C(3)-N(4)-C(5)-C(8) | -63.5(2) | N(1)-C(26)-C(27)-C(28) | 117.82(18) |
| C(3)-N(4)-C(5)-C(7) | 177.36(18) | C(26)-C(27)-C(28)-C(33) | -90.6(2) |
| C(26)-N(1)-C(9)-C(23) | -103.41(18) | C(26)-C(27)-C(28)-C(29) | 90.4(2) |
| C(2)-N(1)-C(9)-C(23) | 69.0(2) | C(33)-C(28)-C(29)-C(30) | -2.7(3) |
| C(26)-N(1)-C(9)-C(10) | 120.95(16) | C(27)-C(28)-C(29)-C(30) | 176.25(18) |
| C(2)-N(1)-C(9)-C(10) | -66.59(19) | C(28)-C(29)-C(30)-C(31) | 1.3(3) |
| N(1)-C(9)-C(10)-F(10) | 62.06(18) | C(29)-C(30)-C(31)-C(32) | 0.7(3) |
| C(23)-C(9)-C(10)-F(10) | -73.77(19) | C(30)-C(31)-C(32)-C(33) | -1.3(3) |
| N(1)-C(9)-C(10)-C(11) | 179.09(15) | C(29)-C(28)-C(33)-C(32) | 2.1(3) |
| C(23)-C(9)-C(10)-C(11) | 43.3(2) | C(27)-C(28)-C(33)-C(32) | -176.84(18) |
| N(1)-C(9)-C(10)-C(17) | -55.77(19) | C(31)-C(32)-C(33)-C(28) | -0.1(3) |
| C(23)-C(9)-C(10)-C(17) | 168.40(15) | C(66)-N(41)-C(42)-C(74) | -84.9(2) |
| F(10)-C(10)-C(11)-C(16) | 1.5(2) | C(49)-N(41)-C(42)-C(74) | 107.6(2) |
| C(17)-C(10)-C(11)-C(16) | 117.3(2) | C(66)-N(41)-C(42)-C(43) | 48.1(2) |
| C(9)-C(10)-C(11)-C(16) | -116.9(2) | C(49)-N(41)-C(42)-C(43) | -119.40(18) |
| F(10)-C(10)-C(11)-C(12) | -178.53(17) | N(41)-C(42)-C(43)-O(43) | 22.1(3) |
| C(17)-C(10)-C(11)-C(12) | -62.8(2) | C(74)-C(42)-C(43)-O(43) | 154.5(2) |
| C(9)-C(10)-C(11)-C(12) | 63.1(2) | N(41)-C(42)-C(43)-N(44) | -160.69(17) |

| | | | |
|-------------------------|-------------|-------------------------|-------------|
| C(16)-C(11)-C(12)-C(13) | 2.3(3) | C(74)-C(42)-C(43)-N(44) | -28.3(3) |
| C(10)-C(11)-C(12)-C(13) | -177.6(2) | O(43)-C(43)-N(44)-C(45) | -0.6(3) |
| C(11)-C(12)-C(13)-C(14) | -0.5(4) | C(42)-C(43)-N(44)-C(45) | -177.72(18) |
| C(12)-C(13)-C(14)-C(15) | -1.5(4) | C(43)-N(44)-C(45)-C(47) | 174.4(2) |
| C(13)-C(14)-C(15)-C(16) | 1.6(4) | C(43)-N(44)-C(45)-C(48) | 54.8(3) |
| C(14)-C(15)-C(16)-C(11) | 0.2(3) | C(43)-N(44)-C(45)-C(46) | -66.4(3) |
| C(12)-C(11)-C(16)-C(15) | -2.2(3) | C(66)-N(41)-C(49)-C(50) | 121.79(18) |
| C(10)-C(11)-C(16)-C(15) | 177.79(19) | C(42)-N(41)-C(49)-C(50) | -69.9(2) |
| F(10)-C(10)-C(17)-C(22) | 20.5(2) | C(66)-N(41)-C(49)-C(63) | -102.2(2) |
| C(11)-C(10)-C(17)-C(22) | -94.8(2) | C(42)-N(41)-C(49)-C(63) | 66.1(2) |
| C(9)-C(10)-C(17)-C(22) | 139.22(17) | N(41)-C(49)-C(50)-F(50) | 76.16(19) |
| F(10)-C(10)-C(17)-C(18) | -160.80(16) | C(63)-C(49)-C(50)-F(50) | -60.7(2) |
| C(11)-C(10)-C(17)-C(18) | 83.9(2) | N(41)-C(49)-C(50)-C(51) | -42.8(2) |
| C(9)-C(10)-C(17)-C(18) | -42.1(2) | C(63)-C(49)-C(50)-C(51) | -179.66(17) |
| C(22)-C(17)-C(18)-C(19) | 0.6(3) | N(41)-C(49)-C(50)-C(57) | -166.51(16) |
| C(10)-C(17)-C(18)-C(19) | -178.16(18) | C(63)-C(49)-C(50)-C(57) | 56.6(2) |
| C(17)-C(18)-C(19)-C(20) | 0.2(3) | F(50)-C(50)-C(51)-C(56) | -158.52(17) |
| C(18)-C(19)-C(20)-C(21) | -1.3(3) | C(57)-C(50)-C(51)-C(56) | 86.2(2) |
| C(19)-C(20)-C(21)-C(22) | 1.7(3) | C(49)-C(50)-C(51)-C(56) | -38.7(2) |
| C(20)-C(21)-C(22)-C(17) | -1.0(3) | F(50)-C(50)-C(51)-C(52) | 25.7(2) |
| C(57)-C(50)-C(51)-C(52) | -89.6(2) | C(50)-C(57)-C(62)-C(61) | -177.4(2) |
| C(49)-C(50)-C(51)-C(52) | 145.58(18) | C(60)-C(61)-C(62)-C(57) | -1.2(4) |
| C(56)-C(51)-C(52)-C(53) | 1.3(3) | N(41)-C(49)-C(63)-C(65) | -66.4(3) |
| C(50)-C(51)-C(52)-C(53) | 177.13(18) | C(50)-C(49)-C(63)-C(65) | 68.8(3) |
| C(51)-C(52)-C(53)-C(54) | 0.1(3) | N(41)-C(49)-C(63)-C(64) | 67.2(3) |
| C(52)-C(53)-C(54)-C(55) | -1.5(4) | C(50)-C(49)-C(63)-C(64) | -157.5(2) |
| C(53)-C(54)-C(55)-C(56) | 1.6(3) | C(42)-N(41)-C(66)-O(66) | -164.20(18) |
| C(54)-C(55)-C(56)-C(51) | -0.3(3) | C(49)-N(41)-C(66)-O(66) | 3.8(3) |
| C(52)-C(51)-C(56)-C(55) | -1.2(3) | C(42)-N(41)-C(66)-C(67) | 20.9(3) |
| C(50)-C(51)-C(56)-C(55) | -176.96(19) | C(49)-N(41)-C(66)-C(67) | -171.13(16) |
| F(50)-C(50)-C(57)-C(62) | -14.2(3) | O(66)-C(66)-C(67)-C(68) | -59.0(2) |
| C(51)-C(50)-C(57)-C(62) | 100.6(2) | N(41)-C(66)-C(67)-C(68) | 116.1(2) |
| C(49)-C(50)-C(57)-C(62) | -132.1(2) | C(66)-C(67)-C(68)-C(73) | -100.7(2) |
| F(50)-C(50)-C(57)-C(58) | 169.26(18) | C(66)-C(67)-C(68)-C(69) | 78.6(2) |
| C(51)-C(50)-C(57)-C(58) | -75.9(2) | C(73)-C(68)-C(69)-C(70) | -1.6(3) |
| C(49)-C(50)-C(57)-C(58) | 51.4(2) | C(67)-C(68)-C(69)-C(70) | 179.1(2) |
| C(62)-C(57)-C(58)-C(59) | 2.3(3) | C(68)-C(69)-C(70)-C(71) | 0.2(4) |
| C(50)-C(57)-C(58)-C(59) | 178.9(2) | C(69)-C(70)-C(71)-C(72) | 0.7(5) |
| C(57)-C(58)-C(59)-C(60) | -1.7(4) | C(70)-C(71)-C(72)-C(73) | -0.2(5) |
| C(58)-C(59)-C(60)-C(61) | -0.4(4) | C(69)-C(68)-C(73)-C(72) | 2.1(4) |
| C(59)-C(60)-C(61)-C(62) | 1.9(4) | C(67)-C(68)-C(73)-C(72) | -178.6(2) |
| C(58)-C(57)-C(62)-C(61) | -0.8(3) | C(71)-C(72)-C(73)-C(68) | -1.3(4) |

A.2 Appendix two

A.2.1 List of publications

- The role of organic fluorine in directing alkylation reactions *via* lithium chelation, K. Tenza, D. O'Hagan, J. S. Northen and A. M. Z. Slawin, *J. Fluorine Chem.*, **2004** (in press)
- K. Tenza, D. O'Hagan, J. S. Northen and A. M. Z. Slawin *Org. Biomol. Chem.*, **2004** (in preparation).

A.2.2 List of Conferences attended

- RSC Fluorine Subject Group Postgraduate Meeting, University of Leicester, 2001
- RSC Scottish Regional Perkin Meeting, Glasgow University, Scotland, 2001
- 8th RSC-SCI Joint Meeting on Heterocyclic Chemistry, Edinburgh, 2002
- RSC Fluorine Subject Group Postgraduate Meeting, University of Manchester, 2002
- Merck Lecturership Reunion, University of Cambridge, 2002
- RSC Fluorine Subject Postgraduate Meeting, University of St-Andrews, 2003
- RSC Organic Division Meeting, University of Edinburgh, 2003
- 1st University of Glasgow/ Organon Symposium on Synthetic Chemistry, 2003
- 14th Scottish Graduate Symposium on Novel Organic Chemistry, Aberdeen, 2003.