New systems for asymmetric electrophilic heteroatom transfer

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New Systems for Asymmetric Electrophilic Heteroatom Transfer

by

Victor Leon Murrell

Thesis submitted in accordance with the requirements of the University of Loughborough for the degree of Doctor in Philosophy.

September 1999
## Contents

1.0 Introduction ........................................... 1  
1.1 Background to this Project .......................... 1  
1.2 New Systems for Electrophilic Amination ................. 2  
1.2.1 Hydrogen Peroxide Analogues .................... 2  
1.2.2 Simple O-derivatised Hydroxylamines ................. 3  
1.2.3 N-Haloamines .................................. 6  
1.2.4 Hydroxylamine-O-sulfonic Acid and Related Compounds ..... 7  
1.2.5 “New” Hydroxylamine Derivatives .................. 11  
1.2.6 O-Phosphinoyl Hydroxylamines and Related Compounds .... 13  
1.2.7 Diastereomeric Azidation of Oxazolidinone Derivatives .... 15  
1.2.8 Amination with Azodicarboxylates ................. 17  
1.2.9 Amination by Nitrenes .......................... 19  
1.2.10 α-Chloronitroso Compounds ..................... 21  
1.2.11 Aziridination of Alkenes by Oxidative Addition of \[N\text{-Aminoheterocycles}\] .................................. 24  
1.2.12 Metal Catalysed Aziridination of Olefins .......... 30  
1.2.13 Three Membered Heterocycles with Two or More Heteroatoms: ........................................ 
   (a) A General Overview .................................. 33  
   (b) \[N\text{-Unsubstituted Oxaziridines as Reagents for Electrophilic Amination}\] ................. 40  
   (c) \[N\text{-Acyl and N-Alkoxy carbonyl Oxaziridines as Reagents for Electrophilic Amination}\] ...... 49  
1.3 Summary of Systems for Electrophilic Amination ........ 57  
2.0 Results and Discussion ................................ 67  
2.1 Hydrogen Peroxide Analogues .......................... 67  
2.2 Oxaziridines as Electrophilic Aminating Agents .......... 71  
2.2.1 Synthesis of Chiral Oxaziridines ..................... 71  
2.2.2 \[N\text{-Functionalisation of Oxaziridines}\] .............. 90  
2.2.3 Electrophilic Amination with Oxaziridines ............. 108  
2.3 Other Potential Systems for Heteroatom Transfer ........ 125
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 General Experimental Details</td>
<td>134</td>
</tr>
<tr>
<td>Appendices 1: Terms Used in this Thesis</td>
<td>204</td>
</tr>
<tr>
<td>Appendices 2: References</td>
<td>207</td>
</tr>
<tr>
<td>Appendices 3: Crystal Structures and NMR Data</td>
<td>216</td>
</tr>
<tr>
<td>Appendices 4: Acknowledgements</td>
<td>223</td>
</tr>
</tbody>
</table>
1.0 INTRODUCTION

1.1 Background to this Project

The imino analogue of the Payne oxidation system has been shown by our group to be successful for asymmetric catalytic oxidation of sulfides to sulfoxides in good yields and with high enantioselectivities (Scheme 1).¹

![Scheme 1](image)

The development of this system presented some new ideas for further research. Firstly there were unanswered questions relating to the nature of the oxidising species in this system. Evidence suggested the intermediacy of a hydroperoxyamine species as the oxidising agent as opposed to the known sulfonyl oxaziridine. Secondly, despite the positive aspects of this system there was room for improvements. For example, the need to use hydrogen peroxide as a source of oxidant makes this version of the system inappropriate for large-scale industrial syntheses. Also, the modification of the present system or creation of new more reactive systems for catalytic asymmetric epoxidation of unfunctionalised alkenes would be an attractive goal. Another aim for further research would be to develop a system that would transfer other heteroatoms, in particular nitrogen, to nucleophiles in an asymmetric manner. It is this oxidative heteroatom transfer in an asymmetric manner, with particular emphasis upon nitrogen transfer that has been the main goal of this project.
Introduction

The nucleophilic species described in this system could be for example a stabilised carbanion, to give a chiral amino functionality α to the stabilising group. The nucleophile might also be an alkene, to form an aziridine product, or even a sulfide to form a chiral sulfimine product. There is no literature precedent for this reaction and so it is unclear what nucleophiles would react or under what conditions the reaction would be successful.

1.2.2 Simple O-Derivatised Hydroxylamines

A number of systems for electrophilic amination utilise an electrophilic amino or masked amino functionality attached to a suitable leaving group. One group of reagents that work in this way are O-alkyl hydroxylamines. A number of hydroxylamine derivatives alkylated at both N- and O-positions have been studied, but by far the most widely employed of these reagents is O-methyl hydroxylamine 2.

O-Methyl hydroxylamine 2 has been shown by various groups to react with a number of alkyl and aryl Grignard reagents in moderate to good yields (Scheme 3).

\[
\text{RMgX} \quad \xrightarrow{\text{MeONH}_2 2, \text{Et}_2\text{O}, \ -15 ^\circ\text{C to } -10 ^\circ\text{C}} \quad \text{RNH}_2 \quad \text{40-90%}
\]

X=Cl, Br
R=C_2-C_5 alkyls, Allyl, Bz, cyclo(CH_2)_n, (n=5, 6, 10)
Ph, 4-BrC_6H_4, 2,4,6-(CH_3)_2C_6H_2, tBu, Pentyl, 2-naphthyl

Scheme 3

Attempted uses of lithium carboxylic acid, amide and ester enolate with 2 however were shown to furnish poor yields of α-amino acid, amide or ester.
Other problems which emanate from this system using both Grignard and lithiated organic compounds include the fact that reported reactions of 2 all must employ between two and three equivalents of organometallic reagent. The reasons for this have been investigated, and it is thought that these organometallic reagents act firstly as a base, forming a lithium alkoxyamide intermediate by deprotonation of the hydroxylamine derivative. This problem of deprotonation of 2 and other derivatives has been addressed for the reactions of aryl and alkyl lithiurns by the sequential deprotonation of 2 with methyl lithium followed by the addition of the intended organolithium nucleophile (Scheme 4).7

\[
\begin{align*}
\text{RLi} & \quad 1. \text{MeLi-MeONH}_2, \text{Et}_2\text{O}, -15^\circ\text{C} \quad \rightarrow \quad \text{RNH}_2 \\
\text{H}^+ & \quad 67-97\% \\
\text{RLi/MeLi-MeONH}_2 \text{ molar ratio} & \quad 1/2 \\
\text{R} & \quad \text{C}_1-\text{C}_6 \text{ alkyls, Ph, 4-BrC}_6\text{H}_4, \text{Bn, 2-CH}_3\text{C}_6\text{H}_4 \\
\text{RLi-MeONHMe molar ratio} & \quad 1/1 \\
\text{Scheme 4}
\end{align*}
\]

Another group of reagents that work in a similar manner is \(O\)-aryl hydroxylamines. Of this class of compound, the most commonly used reagent is the commercially available \(O\)-(2,4-dinitrophenyl)-hydroxylamine 3, which has been shown to react well with more stabilised carbanions such as malonate and 9-fluorene carboxylate enolates (Scheme 5).8
Introduction

The products of the malonate aminations can then be hydrolysed and decarboxylated to give amino acids (Scheme 6).9

<table>
<thead>
<tr>
<th>R</th>
<th>Me</th>
<th>Et</th>
<th>&quot;Bu</th>
<th>Bn</th>
<th>CH$_2$CO$_2$Et</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield Decarboxylated (%)</td>
<td>84</td>
<td>74</td>
<td>46-57</td>
<td>73</td>
<td>61</td>
</tr>
</tbody>
</table>

Less-stabilised carbanions such as enolates of simple esters or nitriles were shown to give lower yields of aminated products.9,5b The reason for this is that it has been reported that more basic enolates facilitate the decomposition of 3 to diimide, and a mechanism has been suggested (Scheme 7).

The reaction of 3 with other substrates such as β-diketone or carboxylic acid enolates has also been reported to yield little or no product,5b and it appears that
**Introduction**

Synthetically useful reactions of 3 and similar compounds are limited to malonates and other enolates of similar basicity.

*O*-Acyl hydroxylamines are related compounds that have also been used as aminating reagents for certain nucleophiles. The literature reports of these compounds are limited, and in general these compounds are too unstable for use as reagents although some have been reported as being stable at room temperature.

1.2.3 *N*-Haloamines

Various mono-, di- and tri-halogenated *N*-unsubstituted and *N*-alkyl *N*-haloamines have been employed for electrophilic amination reactions with a range of organometallic reagents. The most successful and most studied of these reagents is chloramine 4.

Reactions of 4 have in some circumstances been shown to furnish good yields of primary amine products with certain organometallics such as deprotonated malonates and some Grignard reagents (Scheme 8).

The reaction of 4 and other *N*-haloamines with simple organozinc, lithium, Cirignard reagents and simple enolates have in the main presented problems such as low yields and the need for more than one equivalent of organometallic reagent.

For di- and tri-*N*-haloamines, wide product distributions between non-, mono-, di- and tri-alkylated amines are also a problem. In addition there is formation of chlorinated side products. This problem has been explained as resulting from the
ambident nature of NH$_2$ (Scheme 9), whereby NH$_2^+$ can act as either an electrophile with a halide leaving group, or NH$_2^-$ can serve as a leaving group, reacting with an electrophilic halogen atom.

\[ \text{RMgX} + \text{H}_2\text{NCl} \rightsquigarrow \text{RCI} + \text{H}_2\text{NMgX} \xrightarrow{\text{H}_2\text{O}} \text{NH}_3 \]

Scheme 9

A combination of these factors as well as the facts that 4 is not easily prepared, yields are not reproducible and 4 is unstable and cannot be stored, mean that N-haloamines are not much used in organic syntheses.²

1.2.4 Hydroxylamine-O-sulfonic Acid and Related Compounds

As illustrated by reagents such as 3, one way of increasing the reactivity of O-substituted hydroxylamine aminating reagents is to make a derivative that has a better leaving group than hydroxide or alkoxide. One of the simplest ways of accomplishing this is to convert the hydroxyl group of hydroxylamine into a sulfonic acid or sulfonate ester derivative.

The most common of these reagents is the commercially available hydroxylamine-O-sulfonic acid 5. Compound 5 is a relatively stable solid, which is commercially available, and its uses have been reviewed.¹⁸ Hydroxylamine-O-sulfonic acid 5 has been used for a number of chemical transformations including amination, reductive de-amination, reduction, hydroxymethylation, heterocycle formation and other functional group transformations.¹⁸ Nucleophiles which have been aminated with 5 include amine nucleophiles, to form hydrazine¹⁹ or tetrazine²⁰ derivatives, and tertiary amine derivatives to form 1,1,1-trisubstituted hydrazinium salts¹⁹,²¹ (Scheme 10).
**Introduction**

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Bu)\textsubscript{2}NH</td>
<td>5, KOH, H\textsubscript{2}O, 75°C</td>
<td>34%</td>
</tr>
<tr>
<td>(Me)\textsubscript{3}N</td>
<td>1. 5, KOH, H\textsubscript{2}O, Reflux 2. HI</td>
<td>(Me)\textsubscript{3}N-NH\textsubscript{2} I\textsuperscript{−} 85%</td>
</tr>
<tr>
<td>NH</td>
<td>5, NaOH, H\textsubscript{2}O, 60-70°C</td>
<td>N-N=N-N 18%</td>
</tr>
</tbody>
</table>

Scheme 10

A range of carbon nucleophiles have also been aminated successfully with 5, and these include lithium enolates\textsuperscript{18}, aromatic C-H compounds,\textsuperscript{22} boranes\textsuperscript{23} and heterocyclic compounds\textsuperscript{24} (Scheme 11).

Other heteroatoms that have been aminated with 5 include numerous types of sulfur nucleophile to give hydrosulfamines\textsuperscript{25} and sulfinimine\textsuperscript{26} products, and triphenylphosphine to give triphenylphosphinium sulfate\textsuperscript{27} (Scheme 12).
Hydroxylamine-O-sulfonic acid has been shown to be a versatile aminating reagent and is commercially available, however its complete insolubility in almost all non-aqueous solvents means that 5 is restricted to aminations in aqueous solutions.

A number of \(N\)-unsubstituted and \(N\)-derivatised hydroxylamine-O-sulfonate esters related to 5 have also been investigated for their reactivity with nucleophiles. Most of the literature which surrounds aminations using reagents of this type describes aminations using \(O\)-(mesitylsulfonyl)hydroxylamine 6 and \(N,N\)-dialkyl-\(O\)-(mesitylsulfonyl)hydroxylamines such as the \(N,N\) dimethyl derivative 7.\(^{10}\) Compound 6 has been used for amination of C-H acidic compounds such as malonodinitrile\(^{28}\) and methyl diethylphosphonoacetate\(^{29}\) (Scheme 13).
**Introduction**

*N,N*-Dialkyl *O*-sulfonyl hydroxylamine derivatives have been used for the amination of less stabilised nucleophiles such as organocuprates, Grignard reagents and organolithium reagents (Scheme 14).

\[
\begin{align*}
&\text{RLi} \quad \text{1. 7. THF} \\
&\quad \text{2. H}_2\text{O} \\
&\quad \text{RN(Me)}_2
\end{align*}
\]

As well as carbon nucleophiles, compounds such as 6 have been used for amination of sulfur nucleophiles such as sulfides and sulfoxides. This methodology has been used in an attempt at asymmetric induction using a chiral *O*-sulfonyl hydroxylamine (+)-*O*-(α-bromocamphor-7-t-sulfonyl)-hydroxylamine 8 (Scheme 15).  

\[
\begin{align*}
\text{S Me} \quad \text{Br} \quad (+) 8 \\
\quad \text{Et}_2\text{O} \\
\quad \text{yield} = 100\% \quad \text{ee} = 4\%
\end{align*}
\]

It is not surprising that the ee of the sulfimine product from the reaction (Scheme 15) was low, as any chirality in 8 is comparatively remote from the reacting nitrogen centre. The facts that any chiral groups would have to be at least four atoms away from the reacting nitrogen centre and that all of these four atoms separating the chirality from the reacting centre are free to rotate means that it is unlikely that reagents such as 8 will be successful in asymmetric induction.

Compounds such as 6 are limited in their use for a number of reasons. Firstly, 6 must be prepared by protecting group chemistry. Also, 6 presents problems of
Introduction

stability, there have been reports of 6 exploding, and it has been recommended that 6 be prepared immediately prior to use and not be stored.\(^2\)

1.2.5 “New” Hydroxylamine Derivatives

Over the past ten years other hydroxylamine derivatives related to 5 have been investigated for electrophilic amination reactions. Of these, two types have been shown to be of synthetic importance.

Firstly, \(N,O\)-bis(trimethylsilyl)hydroxylamine 9 has been examined.\(^3\) Amination reactions of simple aliphatic saturated organocuprates form primary amine derivatives along with some organocuprate-derived alcohol. Compound 9 has been shown to be an especially good aminating reagent for higher order cuprates (Scheme 16), which are aminated in high yields with none of the alcohol by-products being observed. This is useful synthetically, and, with a few exceptions, organocuprates have been neglected as nucleophiles for electrophilic amination reactions despite their synthetic importance.

![Scheme 16](image)

<table>
<thead>
<tr>
<th>Cuprate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Ph}_2\text{CuCNLi}_2)</td>
<td>(\text{PhNH}_2)</td>
<td>90</td>
</tr>
<tr>
<td>((4\text{-MeOC}_6\text{H}_4)_2\text{CuCNLi}_2)</td>
<td>(4\text{-MeOC}_6\text{H}_4\text{NH}_2)</td>
<td>70</td>
</tr>
<tr>
<td>(\left(\text{Ph}_2\text{O}\right)_2\text{CuCNLi}_2)</td>
<td>(\text{PhNH}_2)</td>
<td>70</td>
</tr>
<tr>
<td>(\left(\text{Py}\right)_2\text{CuCNLi}_2)</td>
<td>(\text{NH}_2)</td>
<td>58</td>
</tr>
</tbody>
</table>

Secondly, metallated \(N\)-aryl sulfonyloxycarbamates 10, 11 and 12 (Figure 1) have been shown to be useful aminating reagents.\(^4\)
Introduction

Nitrogen nucleophiles have been aminated by the non-metallated (N-H) analogue of 10 to give either N-Boc-β-protected hydrazines from anilines or N-tert-butoxyureas from basic amines through Lössen rearrangement (Scheme 17).\(^{35}\)

\[ \text{Scheme 17} \]

A number of different carbon nucleophiles have also been aminated by these reagents. Studies have shown that various alkyl organocuprate and organolithium reagents were aminated by 10 successfully (Scheme 18).\(^{35}\) Other reports have shown that aryl copper reagents are aminated in respectable yields under mild conditions with 10, 11 and 12 (Scheme 19).\(^{36}\)

\[ \text{Scheme 18} \]

<table>
<thead>
<tr>
<th>RM</th>
<th>Metal (on 10)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'BuLi</td>
<td>Li</td>
<td>71</td>
</tr>
<tr>
<td>'BuLi</td>
<td>Li</td>
<td>42</td>
</tr>
<tr>
<td>'Bu2CuLi</td>
<td>Li</td>
<td>32</td>
</tr>
<tr>
<td>([\text{Mes}])2CuMgCl</td>
<td>MgCl</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Li</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>MgCl</td>
<td>72</td>
</tr>
</tbody>
</table>
Introduction

\[ \text{ArCu} \xrightarrow{1. 10, 11 \text{ or } 12} \xrightarrow{2. \text{Hydrolysis}} \text{Ar-N} \text{CO}_2R \]

**Scheme 19**

<table>
<thead>
<tr>
<th>Ar</th>
<th>Electrophile</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>10, 11, 12</td>
<td>51</td>
</tr>
<tr>
<td>2-anisyl</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>4-anisyl</td>
<td>11</td>
<td>68</td>
</tr>
<tr>
<td>2-pyridyl</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>2-thienyl</td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>11</td>
<td>57</td>
</tr>
</tbody>
</table>

Other carbon nucleophiles that have been successfully aminated with these reagents include α-cuprophosphates and boranes (Scheme 20).

1.2.6 O-Phosphinoyl Hydroxylamines and Related Compounds

Another hydroxylamine derivative, which has been used for electrophilic amination, is O-(diphenylphosphinoyl)hydroxylamine. A number of nucleophiles have been reported to have been aminated with this compound, including metal amides, alkyl and aryl Grignard reagents and lithiums, boranes and cuprates, enolates and doubly activated enolate compounds (Scheme 21).
**Introduction**

\[
\text{Ph}_2\text{P(O)ONH}_2 13, \text{THF,} \quad \text{R-M} \quad \begin{array}{c} \text{259x742} \text{RNH}_2 \end{array} \quad \begin{array}{c} \text{-20 °C to r. temp} \end{array} \quad \text{Scheme 21}
\]

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhMgBr</td>
<td>PhNH₂</td>
<td>22</td>
</tr>
<tr>
<td>[Ph(CH₂)₂]₃B</td>
<td>Ph(CH₂)₂NH₂</td>
<td>36</td>
</tr>
<tr>
<td>PhCH₂Li</td>
<td>PhCH₂NH₂</td>
<td>30</td>
</tr>
<tr>
<td>PhCN Li⁺</td>
<td>PhCN NH₂</td>
<td>37</td>
</tr>
</tbody>
</table>

Due to the ability of the phosphorus atom of this type of molecule to be bound to two alkyl substituents, there is potential for the phosphorus atom to be constrained as part of a chiral ring system. As well as this, the inherent enantiotopicity of the phosphorus atom itself means that O-(phosphinoyl)-hydroxylamines may have more potential as chiral aminating reagents than chiral O-sulfonyl hydroxylamines. Indeed a similar reagent derived from (-)-ephedrine has been investigated as a potential reagent for asymmetric amination. (-)-Ephedrine was reacted with phosphorus oxychloride followed by N,N-dimethylhydroxylamine hydrochloride, to give (-)-\((2R,4S,5R)-2-O-(N,N\text{-dimethylhydroxylamino})3,4\text{-dimethyl-5-phenyl-1,3,2-oxazaphospholidinone 14 as the product (Scheme 22)}^{39}

\[
\begin{array}{c}
\text{Ph} \quad \text{NMe} \\
\text{P} \quad \text{O} \\
\text{O} \quad \text{P} \\
\text{NMe} \quad \text{Et₃} \\
\text{DCM} \\
\end{array}
\quad \text{Scheme 22}
\quad \begin{array}{c}
\text{Ph} \quad \text{P} \quad \text{P} \\
\text{O} \quad \text{O} \\
\text{NMe} \quad \text{Et₃} \\
\text{DCM} \\
\end{array}
\quad \text{(-)14 68%}
\]

(-) 14 was then reacted with a variety of Grignard, borane and enolate nucleophiles to form aminated products in poor to moderate yield and in poor to moderate ees (Scheme 23).
Introduction

![Scheme 23](image)

Although the enantioselectivities induced in these reactions were not of synthetic use they were encouraging. Since these results were published in 1982 however there has been relatively little if any work on this type of chiral reagent.

1.2.7 Diastereoisomeric Electrophilic Azide Transfer to Oxazolidinone Derivatives

The diastereoisomeric electrophilic azide transfer to enolates of N-acyl oxazolidinones with trisyl azide 15 to give a masked amino acid derivative was introduced by Evans et al. A number of acyl substituents were used with good to excellent yields, and good to excellent diastereoselectivities (Scheme 24).
**Introduction**

![Chemical structure](image)

Scheme 24

<table>
<thead>
<tr>
<th>Imide, R</th>
<th>Kinetic Ratio (2S:2R)</th>
<th>Product Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>97:3</td>
<td>74</td>
</tr>
<tr>
<td>-CH₂CH=CH₂</td>
<td>97:3</td>
<td>78</td>
</tr>
<tr>
<td>-CH₃Ph</td>
<td>97:3</td>
<td>91</td>
</tr>
<tr>
<td>-Ph</td>
<td>91:9c</td>
<td>82</td>
</tr>
<tr>
<td>-CHMe₂</td>
<td>98:2</td>
<td>77</td>
</tr>
<tr>
<td>-CMe₃</td>
<td>&gt;99:1</td>
<td>90</td>
</tr>
</tbody>
</table>

(a) Diastereoisomeric ratios determined by HPLC. (b) Values refer to diastereoisomerically pure (2R:2S > 200:1) product isolated by chromatography. (c) Ratio determined by $^1$H NMR spectroscopy.

This methodology has been shown to provide access to a wide range of masked chiral α-amino acid derivatives efficiently and selectively and has been applied to the synthesis of more complicated molecules. Deprotection with lithium hydroxide or hydrogen peroxide proved to be a facile process and was shown to occur without any racemization of the azido ester.

There have also been other reports of chiral phospholine and chiral α-alkylphosphonamide-stabilised carbanion electrophilic azide transfer reactions using 15 to give the α-azido compounds in average to excellent yield, and with poor to excellent diastereoselectivities (Scheme 25).
**Introduction**

are 1,2-bis-Boc-protected hydrazines that can be deprotected selectively by standard well-known procedures.\(^\text{44}\)

There have been various reports of chiral auxiliaries such as \(E\)-silyl ketene acetals derived from \(N\)-methyl ephedrine and Evans type oxazolidinones, used for Lewis acid mediated and base mediated reactions with \(16.\)\(^\text{45}\) All of these studies report good to excellent yields and good to excellent diastereoselectivities (Scheme 27).

---

**Scheme 27**

<table>
<thead>
<tr>
<th>Imide, R</th>
<th>Product Yield (%)</th>
<th>dr (2S:2R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>92(^b)</td>
<td>98:2</td>
</tr>
<tr>
<td>Allyl</td>
<td>94</td>
<td>98:2</td>
</tr>
<tr>
<td>Bn</td>
<td>91</td>
<td>97:3</td>
</tr>
<tr>
<td>Ph</td>
<td>96</td>
<td>97:3</td>
</tr>
<tr>
<td>'Pr</td>
<td>95</td>
<td>98:2</td>
</tr>
<tr>
<td>'Bu</td>
<td>96</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

(a) Values refer to isolated yields of isomerically pure compound (2S:2R > 300:1) (b) Isolated yield of the diastereoisomeric mixture.

Ketone enolates in 2-substituted 2-acyl-1,3-dithiane 1-oxides have also been shown to give high diastereoselectivities in some instances (Scheme 28).\(^\text{46}\)

---

**Scheme 28**
**Introduction**

\(N,N\)-Dimethyl hydrazones are further type of ketone derivative that have been aminated with 16 in good yields (Scheme 29).\(^{43}\)

\[
\begin{align*}
R^1 & \quad R^2 & \quad \text{Yield Hydrazone (%)} & \quad \text{Yield Ketone (%)} \\
Et & \quad Me & \quad 85 & \quad 92 \\
\text{"Pr} & \quad Et & \quad 74 & \quad 85 \\
-(CH_2)_4- & \quad (CH_2)_4- & \quad 78 & \quad 78 \\
Ph & \quad Me & \quad 66 & \quad 65 \\
Bn & \quad Ph & \quad 63 & \quad 61 \\
\end{align*}
\]

\(\alpha\)-Amino ketones are important for a number of different reasons,\(^{43}\) and it would therefore be interesting to see if one could induce asymmetry into reactions such as this by using chiral hydrazones such as RAMP or SAMP. The fact that these \(\alpha\)-amino ketones are isolated from the hydrazones in good yield without the use of acid or base is encouraging.

Dialkyl azodicarboxylates have been shown to aminate alkenes through ene reactions to give allylic 1,2-di-protected hydrazines,\(^{47}\) however this type of reaction is beyond the scope of this discussion.

1.2.9 **Amination by Nitrenes.**

Direct amination of enamines, silyl enol ethers and ketene acetals by their reaction with nitrene precursors has been reported as a route to \(\alpha\)-amino ketones\(^{48}\) and
**Introduction**

α-amino esters\(^{49}\) respectively. Chiral auxiliaries have been utilised in the synthesis of both of these types of amines. The reaction of (S)-proline derived optically active enamines with \(N\)-[(4-nitrobenzenesulfonyl)oxy]carbamate (NsONHCO\(_2\)Et) \(^{17}\) has led to the preparation of (R)-2-(ethoxycarbonylamino)cyclohexanone in high enantiomeric excess (Scheme 30).\(^{50}\) The reaction of chiral silyl ketene acetals with ethyl azidofomate \(^{18}\) has also been studied in the preparation of both enantiomers of alanine (Scheme 30).\(^{51}\)

![Scheme 30](image)

There are two main problems associated with this system. Firstly, the substrates for these diastereoselective reactions are limited. This may be because the success of these reactions is highly substrate dependent, and so these reactions are of limited scope, or simply because other substrates have not been investigated. The other problem is the fact that these photolytic reactions may be difficult to accomplish on an industrially useful scale and may be restricted to laboratory scale syntheses.

Nitrene precursors have also been used in aziridination reactions of \(\alpha,\beta\)-unsaturated ketones.\(^{52}\) Photolysis of ethyl azidoformate \(^{18}\), the reaction of NsONHCO\(_2\)Et \(^{17}\) and the reaction of ethyl \(N\)-[(4-methylbenzenesulfonyl)oxy]carbamate (TsONHCO\(_2\)Et) \(^{19}\) were compared for a number of different substrates and reagents \(^{17},\) \(^{18}\) and \(^{19}\) were shown to give similar results (Scheme 31).
Photolysis reactions (a) have the same limitations as enolate derivative aminations (Scheme 30) in that reactions are substrate dependent and may not be easy to accomplish on large scale, whereas vast excesses of 18 and 19 are required for methods (b) and (c).

1.2.10 α-Chloronitroso Compounds

One method that has been adapted to stereoselective amination of ketone and amide enolate amination reactions involves the use of α-chloro-α-nitroso compounds. Attack of the enolate anion on the nitrogen atom forms a nitrone intermediate that can be hydrolysed in situ to give a hydroxylamine derivative which can then undergo various conversions, including reduction to an amine if desired (Scheme 32).

Chiral α-amino acids have been prepared using this system by substrate-controlled reaction of 1-chloro-1-nitrosocyclohexane 20 with enolates of N-acyl camphorsultams (Scheme 33).

---

Scheme 31

Scheme 32

Scheme 33
Introduction

\[
X = \begin{array}{c}
\text{S-O} \\
\text{N-} \\
\text{N} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \\
\end{array}
\]

\[
1. \text{NaHMDS} \\
2. 20 \\
3. \text{HCl(aq)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{HO} \\
\text{NH} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Zn/ HCl(aq)} \\
\text{AcOH, O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{HO} \\
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_2 \\
\end{array}
\]

Scheme 33

<table>
<thead>
<tr>
<th>R</th>
<th>Yield Hydroxylamine (%)</th>
<th>Yield Amino Acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Me</td>
<td>88\textsuperscript{a}</td>
<td>78\textsuperscript{a}</td>
</tr>
<tr>
<td>Allyl</td>
<td>88</td>
<td>78</td>
</tr>
<tr>
<td>'Pr</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>'Bu</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Bn</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Ph</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>\textit{p-MeOPh}</td>
<td>\textsuperscript{81\textsuperscript{a}}</td>
<td>\textsuperscript{84 (overall)}</td>
</tr>
<tr>
<td>\textit{p-MeOPh}</td>
<td>\textsuperscript{81\textsuperscript{a}}</td>
<td>\textsuperscript{90\textsuperscript{a}}</td>
</tr>
</tbody>
</table>

(a) opposite enantiomer to the one shown in Scheme 32 due to use of the opposite enantiomer of camphorsultam.

Diastereoselectivities for the hydroxylamination of the \textit{N}-acyl camphorsultam were without exception, all found to be 100\% within the bounds of accuracy of \textsuperscript{1}H NMR analysis, and deprotection to the amino acid was shown to cause no epimerisation adjacent to the carbonyl group. This methodology appears to be powerful for both lab syntheses, and also possibly for industrial purposes, for a number of reasons. Firstly, the reactions were shown to be diastereoisomerically specific and enantiospecific for the hydroxylaminated products and the amino acid products respectively, irrespective of the substituent R, and no epimerisation occurred en route to amino acids. Secondly, products were all formed in excellent yields. Thirdly, purification of all hydroxylamino and amino sultams was readily effected by recrystalisation. Also, both enantiomers of camphorsultam are available commercially.
**Introduction**

on a multi-kilogram scale. Finally, the camphorsultam chiral auxiliary can be recovered after deprotection by a simple dichloromethane extraction in a yield of 91%.

Chiral α-hydroxlamino ketones have also been prepared using α-choronitroso compounds derived from camphor sulfonamides. Reagents 21 and 22 were prepared by oximation of the respective camphorsulfonamide followed by α-chlorination with tert-butyl hypochlorite in 70-78% yields (Scheme 34).

![Scheme 34](image)

Compounds 21 and 22 were used in an approach to enantioselective synthesis of anti α-amino alcohols (Scheme 35).

![Scheme 35](image)

<table>
<thead>
<tr>
<th>R</th>
<th>M</th>
<th>dr (nitrone)</th>
<th>Yield (%)</th>
<th>Ratio (aminol)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Zn</td>
<td>&lt;1:99</td>
<td>68</td>
<td>95:5</td>
<td>96</td>
</tr>
<tr>
<td>2,5-(MeOH)C(=H)</td>
<td>Na</td>
<td>&lt;1:99</td>
<td>57</td>
<td>90:10</td>
<td>(&gt;99)</td>
</tr>
<tr>
<td>'Bu</td>
<td>Zn</td>
<td>5:95</td>
<td>54</td>
<td>&gt;99.9;&lt;0.1</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>'Pr</td>
<td>Zn</td>
<td>5:95</td>
<td>65</td>
<td>98:2</td>
<td>(&gt;99.9)</td>
</tr>
<tr>
<td>Et</td>
<td>Zn</td>
<td>5:95</td>
<td>65</td>
<td>90:10</td>
<td>98.2</td>
</tr>
</tbody>
</table>

(a) Yield from ketone starting material. (b) values in parentheses correspond to recrystallised products.
Introduction

This methodology forms a useful approach for the synthesis of chiral anti \(\alpha\)-amino alcohols for several reasons. Again, as in the use of 20 with sultam derived enolates, both enantiomers of 21 and 22 can be synthesised on a kilogram scale from both enantiomers of readily available camphor sulfonyl chloride. Stereoselectivities are high for hydroxylamination reactions. The amino alcohol product can in all cases be purified to \(>99.9\%\) diastereoisomeric excess by simple recrystallisation without appreciable losses in yield. The overall yield of amino alcohol is high given the fact that their syntheses involve four steps.

Organolithiums and Grignard reagents have been reacted with \(\alpha\)-chloronitroso compounds to give only trace amounts of \(N\)-substituted nitrone from attack on the nitrogen atom.\(^{55}\)

1.2.11 Aziridination of Alkenes by Oxidative Addition of \(N\)-Aminoheterocycles

The ability of aziridines to undergo highly regio- and stereoselective ring opening reactions renders them of great value in organic synthesis,\(^{56}\) and there are numerous different approaches to the synthesis of these compounds. A number of these approaches involve the aziridination of olefins. One method for accomplishing this that has generated a large amount of interest is the oxidative addition of \(N\)-amino heterocycles such as compounds 22 to 25 (Z-NH\(_2\)) to alkenes,\(^{57}\) and various reagents have been developed for this transformation (Scheme 36).

![Scheme 36](image-url)
These reagents have been shown to aziridinate both electron-deficient and electron-rich alkenes in good yields. Substrate- and reagent-controlled diastereoselective reactions with double bonds have been carried out. For example, the reaction of \( \alpha,\beta \)-unsaturated camphorsultam derivative 26 with 22 in the presence of lead tetra-acetate gives the product 27 in over 95% de (Scheme 37).58a

![Scheme 37](image)

Originally it was though that the reactive species for this transformation was an \( N \)-nitrenoid heterocycle, however a number of subsequent observations have been made which suggest that the reactive species involved in this mechanism is an \( N \)-(N-acetoxyamino)heterocycle (Z-NHOAc). This reactive species aziridinates carbon-carbon double bonds in a way that has been likened to the per-acid epoxidation of alkenes (Scheme 38). The fact that the Z group is attached directly to the reactive nitrogen atom however means that diastereoselectivity should be easier to induce in this reaction than in per-acid epoxidation of olefins.

![Scheme 38](image)
The identification of Z-NHOAc as the reactive species has given an understanding of how best to take advantage the mechanisms involved in these processes. Another advantage is that it has enabled investigators to undertake a rationalised approach to the development of molecules for reagent-controlled diastereoselective aziridination reactions by consideration of how the alkene must coordinate to the aziridinating agent during the transition-state of the reaction.\textsuperscript{57a} To this end there have been a number of modifications to the reaction system, and various diastereotopic ZNH\textsubscript{2} derivatives have been synthesised.

The yields for aziridinations of certain specific unreactive alkenes (such as hex-1-ene) were low, and this was thought to be because of the competing decomposition of ZNHOAc by acetic acid formed during the reaction. Addition of hexamethyldisilazane as a base in the reaction mixture was shown to increase the reactivity of the system.\textsuperscript{60} Much of the emphasis of research into this system has focused upon the development of diastereoselective reactions. Lactic acid-derived quinazoline 23 (Q\textsuperscript{1}NH\textsubscript{2}) has been shown to be useful as a stereoselective aziridinating reagent for various styrene derivatives (Scheme 39).

![Scheme 39](image)

The use of titanium (IV) tert-butoxide for the aziridination of alkenes with quinazoline derivative 24 (Q\textsuperscript{2}NH\textsubscript{2}) was shown to greatly enhance the diastereoselectivity of the reaction.\textsuperscript{61} Chelation of titanium to the hydroxyl group and N-1 of the quinazoline ring fixes the quinazoline side chain so that no rotation can take place (Scheme 40).
A number of different types of alkene were aziridinated with this system, all with good diastereoselectivities (Scheme 41).

Another modification to the system has been addition of 3 equivalents of trifluoroacetic acid. This has been shown to have a beneficial effect in that yields of
**Introduction**

products and diastereoselectivities are increased.\(^{62}\) This appears to contradict the idea that when acetic acid was removed from the reaction mixture by the addition of a base, the yields were raised. However, evidence exists that the reacting species is a diprotonated molecule that brings about a change in the transition state geometry, and in some cases the opposite diastereoisomer is formed to that formed in the absence of the acid. This can be illustrated by the reaction of but-2-ene with quinazoline derivative \(25 (Q^3{\text{NH}_2})\) (Scheme 42).\(^{57a}\)

\[
25 = Q^3{-NH}_2 \xrightarrow{\text{O,NH}} \xrightarrow{\text{Ac}} \xrightarrow{\text{CF}_3\text{CO}_2\text{H}} \text{dr} = 1.2:1 \quad \text{dr} = 1:4
\]

Scheme 42

Once the aziridine ring has been formed, there are various subsequent transformations that can be performed. One of the problems associated with this system is the fact that the \(N\)-substituent (Z) is difficult to remove. One method for doing this that is particular to 2-trialkylsilyl aziridines is by conversion of the aziridine to the corresponding azirine (Scheme 43).

\[
\text{Q}^1 \xrightarrow{\text{TMS}} \xrightarrow{\text{CSF, KCN. DMF}} \text{Ph} \xrightarrow{\text{H}^+} \text{PhH} \quad \text{76\% ee = 83\%}
\]

Scheme 43

Nucleophilic addition to this azirine then furnishes an \(N\)-unsubstituted aziridine.\(^{60a}\)

Removal of the \(N\)-Z substituent without cleavage of the aziridine ring is
Introduction
difficult for other products of this reaction, so this step is generally carried out after
ring cleavage, and is then generally effected in good yield by the reaction with
samarium (II) iodide in tert-butyl alcohol/THF. N-Z-substituted aziridines have
been shown in general to undergo similar ring opening reactions as do other aziridines
with respect to Lewis acid or nucleophilic mediated ring opening, and in some
circumstances the Z group has been shown to effect regiocontrol over these ring
opening reactions. There have been a number of examples of the conversions of
products of these reactions into useful products. An example of this is the use of
styrene aziridinated with 24 to give both enantiomers of a chiral N-Boc 1,2-diamine
(+1 and (-) 28 (Scheme 44).

\[\text{Scheme 44}\]

In summary, the use of this system for the asymmetric electrophilic amination
of olefins is attractive in several ways. Firstly, the chiral reagents such as 23 and 24
can be derived from the readily available chiral synthons lactic acid and tert-leucine
respectively in relatively few steps, in high yields and without the need for
chromatography at any stage. Secondly, the system has some generality and a wide
range of both electron deficient and electron rich alkenes can be aziridinated with
high stereoselectivities. The products of these reactions are versatile and can be
stereospecifically converted into a number of different ring opened products often
with some directing control from the heterocyclic Z group, and this Z group is easily
removed by reaction with samarium (II) iodide in excellent yields. Disadvantages
associated with this system include the facts that the system is not catalytic and so
Introduction

could prove to be expensive to carry out on a large scale. A further disadvantage is that the yields for these reactions tend to be moderate, being typically in the region of 40-70%. In addition to this, products of aziridinations must be deprotected and this deprotection step is difficult to achieve without aziridine ring opening.

1.2.12 Metal Catalysed Aziridination of Olefins

Manganese or copper nitrenoid addition to olefins using \([N-(p\text{-toluenesulfonyl})imino]phenyliodinane\) (PhI=NTs) is one of the most studied one-step approaches to the synthesis of aziridines to date and there are a number variants. Copper (I) bis(oxazolines) such as 29 developed by Evans et al.\(^63\) and copper (I) diimines such as 30 developed by Jacobsen et al.\(^64\) are amongst the most successful chiral reagents for these transformations. Results from these experiments show that yields for aziridinations of styrene derivatives and other aryl olefins can be good and enantioselectivities can be high (Scheme 45).

![Scheme 45](image)

Manganese (III) salen complexes developed by Katsuki et al. have been employed for these reactions, but initially yields were low and enantioselectivities
Introduction

More recently however, new manganese (III) salen complexes such as 31 have been prepared, which show that styrene derivatives previously aziridinated with poor selectivities can now be aziridinated in high chemical yield and with good to excellent enantioselectivities (Scheme 46).

![Scheme 46](image)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene</td>
<td>76</td>
<td>94</td>
<td>S</td>
</tr>
<tr>
<td>p-chlorostyrene</td>
<td>70</td>
<td>86</td>
<td>S</td>
</tr>
<tr>
<td>p-methylstyrene</td>
<td>75</td>
<td>81</td>
<td>S</td>
</tr>
<tr>
<td>Indene</td>
<td>10</td>
<td>50</td>
<td>S</td>
</tr>
</tbody>
</table>

The yields and the fact that this system is catalytic make this system most attractive. There are however drawbacks to this approach. For example, useful yields and high levels of enantioselection are restricted to a small set of styrene derivatives. Also, in some circumstances, up to five equivalents of olefin are used, and so the nitrene precursor is the stoichiometrically-limiting component of the reaction. Another failing is the fact that while some reactions are high-yielding and highly enantioselective, stereoselectivity is sometimes poor, and cis-alkenes have been shown to form products with substituents trans-disposed on the aziridine ring. A further disadvantage is the fact that deprotection of $N$-tosyl substituents generally
requires fairly harsh conditions, and aziridine ring opening is therefore generally carried out prior to deprotection.

Recently, a range of nitrene precursors of the type PhI=NSO₂Ar, have been prepared and evaluated for non-enantioselective copper catalysed aziridination of olefins. The results from these experiments showed that where the aromatic substituent is 4-nitrophenyl or 4-methoxyphenyl, then the reactivity of the system is enhanced and alkenes which reacted in low yields with PhI=NTs could be aziridinated in high yields (Scheme 47).

Another benefit of using this system is that p-nitrobenzenesulfonamides are readily cleaved using thiols. Furthermore, only one equivalent of the olefin was used in the reaction together with 1.5 equivalents of nitrene precursor.

Very recently, [N-((trimethylsilyl)ethanesulfonylimino)phenyliodinane (PhI=NSes) has been investigated as a nitrene source for the copper catalysed aziridination of alkenes, and has been shown to react to form aziridines in moderate to good yields. The main advantage of the use of this reagent over other reagents is that the N-(Ses)-aziridine product formed by this reaction may easily be deprotected under very mild conditions using a fluoride source (Scheme 48).
Although there are drawbacks to the use of this system at present, research into this approach is something that is likely to generate interest for some time both because of its catalytic activity and because it has been far from exhaustively investigated.

1.2.13 Three Membered Heterocycles with Two or More Heteroatoms:

(a) A General Overview

The first three-membered rings containing two heteroatoms were oxaziridines and diaziridines. These were first synthesised in the late 1950's, and their reactions were studied simultaneously. Since then there have been many more reports of different types of three membered di- and tri-heterocyclic compounds. These compounds exist in numerous states of oxidation and of saturation, and contain heteroatoms such as oxygen, nitrogen, sulfur and phosphorus. Some of these reagents have been shown to undergo useful transformations and are encountered frequently in organic synthesis. The most common of these reagents are oxaziridines, diaziridines, diazirines and dioxiranes, and these are shown along with examples of some of the less common heterocycles in Figure 2.
Since they were first discovered, oxaziridines have generated interest for a number of reasons. Oxaziridines are interesting from a stereochemical perspective because the inversion that occurs at the nitrogen centre occurs at a much slower rate than would be expected, and this is due to a combination of factors. Firstly, placing a nitrogen atom in a three-membered ring causes ring-strain, and thereby destabilises the $120^\circ$ angle of the $sp^2$ like transition-state, and secondly, attaching the nitrogen to an electron withdrawing oxygen atom opposes the increased $s$ orbital character of the nitrogen during inversion. Due to this phenomenon certain oxaziridines are configurationally stable and this has led to chiral oxaziridines being prepared that possess no chiral centres other than at the non-inverting nitrogen atom.

Another area of chemistry associated with oxaziridines is rearrangement chemistry. Ring expansion reactions of $N$-alkyl oxaziridines for the synthesis of chiral lactams have been developed which exploit the configurational stability of the nitrogen atom as a controlling feature of stereoselectivity. Also, more recently, interest has arisen in the use of oxaziridines as precursors for nitrogen- and carbon-centred radicals.

One feature of oxaziridines that has been exploited to a large extent is their ability to transfer a heteroatom to nucleophilic species. As with $N$-halo amines, oxaziridines are ambident in their nature, but unlike $N$-halo amines the ability to transfer exclusively either a nitrogen or oxygen heteroatom if desired, can be achieved by changing the $N$-substituent, and this has been attributed to the stereoelectronic effects. Perhaps the most famous of these types of reagents are the $N$-sulfonyl oxaziridines developed by Davis and others for transfer of oxygen to sulfur and enolised carbon nucleophiles. A number of $N$-sulfonyl oxaziridines have
been developed which give high yields of enantiomerically rich chiral sulfoxides and α-hydroxy carbonyl compounds (Scheme 49).14,77

---

As well as N-sulfonyl oxaziridines, which have achieved a great deal of success and some of which are now commercially available, N-phosphinoyl oxaziridines have also been looked at as potential asymmetric oxygen transfer reagents with limited success.78 As indicated above, either the oxygen or the nitrogen atom of oxaziridines can be transferred to nucleophiles depending upon the nature of the N-substituent. To this end, various reagents have been developed for the synthesis of aminated products, and this is discussed in more detail in part 1.2.13 (b).

Dioxiranes, structurally analogous to oxaziridines, have been investigated over recent years as oxidising agents, capable of alkene epoxidation, amine oxidation and sulfoxidation,79 and to date, various reagents have been developed. Chiral dioxiranes such as the one prepared from the reaction of chiral fructose-derived ketone 32 (employed in catalytic quantities) with oxone8 have been shown to epoxidise certain alkenes in excellent yields and enantiomeric excesses (Scheme 50).80
The use of cheap sources of chirality together with the catalytic activity of this system makes this type of system attractive for further investigation.

Another class of reagent that is closely related to oxaziridines is the oxaziridinium salt. Oxaziridinium salts tend to exist as transient species and have been shown to transfer their oxygen heteroatom to nucleophiles such as sulfides and alkenes. Many reported systems employ aqueous oxone with an iminium salt, to form what is presumed to be an oxaziridinium species in situ, which then goes on to react with the nucleophile in an organic solvent. This type of system is interesting because it is highly catalytic with respect to the iminium salt catalyst, and low quantities of iminium salt have been shown to give high yields of epoxides from alkenes. Although attempts have been made to achieve asymmetric induction using chiral iminium salts, to date enantioselectivities for such reactions remain low, being typically in the range of 20-40%, although ees of up to 73% have been reported recently by our group for the epoxidation of certain alkenes (Scheme 51).
Introduction

There are a number of difficulties encountered in investigating this sort of system. Firstly, oxidation of the iminium salt can take place at either face of the imine, giving rise to the possibility of two diastereoisomeric oxaziridinium salts being formed. Secondly, the need to use a bi-phasic system means that the low temperatures that may be required to increase selectivities for both formation of the oxaziridinium salt and oxidation of the nucleophile by the oxaziridinium salt are impractical. Studies have been carried out into the stoichiometric epoxidation and sulfoxidation reactions using oxaziridinium compounds of known stereochemistries prepared from the corresponding oxaziridine either by N-protonation or by N-alkylation.

Diaziridines, structurally analogous to dioxiranes, were discovered shortly after oxaziridines, and their chemistry has been well documented. Diaziridines have been shown to be somewhat more stable than dioxiranes, oxaziridinium salts or oxaziridines, but surprisingly have not been shown to undergo the same type of heteroatom transfer reactions. Recently, however, N-lithiated diaziridines have been shown to aziridinate both cis- and trans-α,β-unsaturated amides to form cis-aziridines in yields of between 39% and 82% (Scheme 52).

![Scheme 52](image)

The reason for the formation of a cis-aziridine from both cis- and trans-alkenes has been rationalised by the fact that the process is non-concerted, and probably involves 1,4-addition of the N-lithiated aziridine to the α-β-unsaturated amide, followed by free-rotation of the now $sp^3$ β-carbon atom of the enolate intermediate to the most sterically favoured conformation. Subsequent ring-closure of this conformer to form the aziridine product requires the appropriate arrangement.
of enolate and aziridine moieties for stereoelectronic reasons, and occurs stereoselectively with the formation of the cis-aziridine (Scheme 53).  

\[
\begin{array}{c}
\text{Ph} \quad \text{NH} \\
\text{Ph} \quad \text{O} \\
\text{NH} \quad \text{CO} \\
\text{NH} \quad \text{CO} \\
\end{array}
\]

Scheme 53

Because of the fact that in general diaziridines are more stable than oxaziridines, \(N\)-functionalisation is one type of reaction that has been better explored for diaziridines. It is because of this that a wider range of \(N\)-substituted diaziridines have been prepared, and, \(N\)-alkylations, silylations, acylations, sulfonylations and phosphorylations are all documented reactions of diaziridines. \(^{71}\) Diaziridines are also known to undergo various reactions and rearrangements upon heating or in the presence of acid, but probably one of the best known and most well used reactions of diaziridines is the conversion diaziridines to diazirines by oxidation. This is generally carried out by treating with silver (I) oxide (Scheme 54). \(^{71a}\)

\[
\begin{array}{c}
\text{NH} \\
\text{Ag}_2\text{O} \\
\text{NN} \\
\end{array}
\]

Scheme 54

In comparison with other three-membered di- and tri-heterocyclic compounds, diazirines are surprisingly inert. The diazirine ring is inert to many strong oxidants including ozone, dichromate and chlorine, and is only decomposed by strong
Introduction

concentrated acid. Diazirines have been shown to undergo a number of interesting reactions including complexation to metals and various rearrangements. The most common use for diazirines in organic synthesis is the thermal or photolytic extrusion of nitrogen to form a carbene intermediate.\(^{71}\) Although under-reported, diazirines have been shown to undergo reactions with Grignard reagents and alkyl lithiums to give 1-alkyl diaziridines in good yields, and this reaction has been used to serve access to hydrazines (Scheme 55).\(^{86}\)

![Scheme 55](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy</td>
<td>86(^a)</td>
</tr>
<tr>
<td>&quot;Pr</td>
<td>88(^b)</td>
</tr>
<tr>
<td>'Pr</td>
<td>95(^b)</td>
</tr>
<tr>
<td>Bn</td>
<td>85(^b)</td>
</tr>
</tbody>
</table>

(a) Yield of 1-alkyl diaziridine (b) Yield of hydrazine

In general, while many of these three-membered heterocycles with more than one heteroatom may seem structurally analogous, their reactivities vary significantly, and these heterocycles enjoy a mixed variety of different chemistries. In many circumstances the reactivity of one or more of the heteroatoms in the ring is sufficient to effect a heteroatom transfer to nucleophiles. This has been developed with some success for oxygen transfer reagents such as \(N\)-sulfonyl oxaziridines, oxaziridinium salts and dioxiranes, and research into these systems is still intense. To date however, only \(N\)-unsubstituted and \(N\)-acyl or alkoxycarbonyl oxaziridines have been developed for the oxidative transfer of an amino functionality.
Introduction

(b) N-Unsubstituted Oxaziridines as Reagents for Electrophilic Amination

While N-sulfonyl oxaziridines are well-known as commercially available stoichiometric reagents for asymmetric oxidation of sulfides and carbanions,\textsuperscript{76,77} and N-phosphinoyl oxaziridines are also known to transfer oxygen,\textsuperscript{78} the lesser-known N-unfunctionalised and N-acyl or alkoxy carbonyl oxaziridines are known to transfer an amino or a masked amino functionality to a range of nucleophiles.\textsuperscript{87}

N-Unfunctionalised oxaziridines have been shown to aminate nitrogen, oxygen, sulfur and carbon nucleophiles,\textsuperscript{87} however to date only a handful of these compounds have been prepared, and there have been no reports of enantiomerically pure N-unsubstituted oxaziridines prepared for use in enantioselective synthesis. The lack of knowledge of these oxaziridines is perhaps due to their instability. In general, NH-oxaziridines must be prepared and reacted in dilute solution or they decompose.\textsuperscript{87} It is because of this that only one (33b) has ever been isolated as a stable compound in its pure form,\textsuperscript{88} and only one (34) has been investigated for functional group transformation on a preparative scale and in any depth,\textsuperscript{87} and these compounds are illustrated in Figure 3.

\[
\begin{align*}
\text{O-NH} & \quad \text{O-NH} \\
33b & \quad 34
\end{align*}
\]

Figure 3

N-Unsubstituted oxaziridines are prepared by a number of different methods. The most common method of preparing these reagents involves treating a ketone with an electrophilic aminating reagent such as hydroxylamine-O-sulfonic acid 5,\textsuperscript{89} or chloramine 4 (prepared \textit{in situ} by the reaction of ammonia with sodium hypochlorite)\textsuperscript{90} (Scheme 56).
Both of these methods of preparation of oxaziridines are convenient as they are quick— they take no longer than a couple of minutes and simple separation of the phases affords 34 as a dilute solution which can then be used to react with nucleophiles without any further purification. As long as 34 is kept in a dilute solution it is stable and it can be refluxed for three hours in toluene without any noticeable decomposition. Photolysis of oximes in dilute solution has been reported as another method of preparation of \(N\)-unfunctionalised oxaziridines. Oxaziridine 35 was formed as a dilute solution in methanol and partly characterised by its ability to aminate an imine to form a diaziridine product (Scheme 57).

Other less common methods of synthesis of \(NH\)-oxaziridines include per-acid oxidation of \(NH\) imines and ozonolysis of an alkene in the presence of ammonia (Scheme 58).
Once prepared, dilute solutions of NH-oxaziridines undergo a wide range of chemical reactions with a variety of nucleophiles.

A range of amino compounds have been aminated using oxaziridines to form hydrazino derivatives. Secondary amines react with 34 within a few minutes to form $N,N$-dialkyl hydrazones 37 which can then be cleaved to form hydrazine hydrochlorides 38 (Scheme 59).
Primary amines tend to give lower yields of hydrazones than secondary amines. Aniline only gives 22% of phenylhydrazine and cyclohexylamine gives 50% cyclohexylhydrazine.\(^9\) Amino acid esters, less basic than simple amines, react much slower with oxaziridine 34. Temperatures of around 100 °C are needed for any reaction to occur, and yields of hydrazino acid are low to average (32-69%).\(^{94}\) Better yields of product have been obtained by the reaction of oxaziridine 39, prepared from the adduct of hydroxylamine-O-sulfonic acid and chloral (Scheme 60).\(^{87}\)

\[
\begin{align*}
\text{H} & \quad \text{NHOSO}_3\text{H} \\
\text{Cl}_3\text{C} & \quad \text{OH} \\
\end{align*}
\begin{align*}
\text{R} & \quad \text{NH} \\
\text{Cl}_3\text{C} & \quad \text{O} \\
\text{R} & \quad \text{NH}_2 \\
\end{align*}
\begin{align*}
\text{OH} & \quad \text{NHR} \\
\text{57-72\%} & \\
R & = \text{\text{^t}Bu, \text{^n}C_6\text{H}_{11, \text{^t}Pr}} \\
39 & \\
\end{align*}

Scheme 60

In general, oxaziridines do not react with tertiary amines. For example, the product of amination is not detected when 34 is treated with triethylamine even though triethylamine forms 1,1,1-triethyl-hydrazinium chloride with chloramine.\(^{87}\) Amination has, however, been shown to occur on reaction of 34 with allyl(dimethyl)amine to form an intermediate, which subsequently undergoes a Sommelet rearrangement to form 1,1-dimethyl-2-allylhydrazine (Scheme 61).\(^{87}\)

\[
\begin{align*}
\text{NMe}_2 & \quad 34 \\
\end{align*}
\begin{align*}
\text{N} & \quad \text{NH} \\
\text{Me}_2\text{N} & \\
\end{align*}
\begin{align*}
\text{Me}_2\text{N} & \quad \text{26\%} \\
\end{align*}

Scheme 61

With Schiff's bases two alternate reactions can occur. Reaction can occur either at the C=N double bond to form a diaziridine as in Scheme 57, or exclusively at the N-atom to form an imidium amide compound (Scheme 62).\(^{95}\)
Introduction

A number of bivalent sulfur nucleophiles have also been aminated with \( \text{NH-oxaziridines} \). Many of the aminations of sulfur-containing compounds are of thioamides and thioureas to form thiooxime or sulfenamide derivatives (Scheme 63). The outcome of this reaction is not easy to predict, and may be followed by further transformations in certain cases.

For example, benzopyrimidine derivatives gave the free sulfenamide in 66% to 97% yields,\(^8\) whereas mercaptobenzazoles gave thiooximes\(^8\) (Scheme 64).

\( \text{Scheme 62} \)

\( \text{Scheme 63} \)

\( \text{Scheme 64} \)
Introduction

Thiooxime derivatives often also undergo subsequent reactions. Ring closure is a stabilising reaction that takes place in some instances leading to a formal insertion of a cyclohexylamine unit. For example, certain acyl isothioureas are aminated to give 1,2,4-thiadiazolidines (Scheme 65).96

![Scheme 65]

There are numerous rearrangements that can occur after amination of sulfur compounds with 34 depending upon the substrate.87 An example of this is the intramolecular sulfenylation of the aromatic ring of the product as shown in Scheme 66.87

![Scheme 66]

The cyclohexylidene moiety of the thiooxime intermediates obtained in many cases takes part in subsequent rearrangements resulting in cleavage of the S-N bond. There are many of examples of this type of rearrangement of thiooximes. One of the simplest examples that provides a good illustration is the reaction between rhodanamine 40 and cyclohexanone to give aminothiazole 41. The crucial step of the proposed mechanism is a 1,3-shift in the enamine-type structure (Scheme 67). An example where this occurs as a result of amination with 34 is shown in Scheme 67.87
While many different types of sulfur nucleophile have been reported to undergo amination reactions with NH-oxaziridines such as 34, there is little or no precedent for the amination of bivalent sulfides to give sulfimines with a formal change of oxidation state of sulfur from S(II) to S(IV).

C-Nucleophiles have also been investigated for their reaction with NH-oxaziridines. Many different types of CH-acidic compound have been aminated with 34. An example of this is the amination of α-cyano carboxamides, which are aminated smoothly with nitrile hydrolysis to give α-aminomalonamides or malonamide derivatives protected by the cyclohexanone moiety (Scheme 68).
Cyanoamides have also been shown to give bis-aminated products when reacted with two equivalents of 34, forming either hemi-aminal type species or imino compounds (via collapse of the hemi-aminal) (Scheme 69). In another reaction, diphenyl acetonitrile was aminated with 34 using catalytic amounts of an organic amine base with nitrile hydrolysis to give an α-amino amide derivative in a 75% yield (Scheme 69).

As well as anionic C-nucleophiles, 34 has been shown to react with carbon-carbon double bonds to form aziridines. Aryl alkenes have been aminated with 34 in
Introduction

Poor to moderate yields (Scheme 70). Temperatures of over 100 °C are needed to bring about amination of alkenes 42 within a couple of hours to give aziridines 43, or, when these are not isolated directly, aminoalcohols 44 are isolated by hydrolysis with aqueous dilute sulfuric acid.

\[
\begin{align*}
\text{R} & \quad \text{34, toluene} \quad \Delta \quad \text{H} \quad \text{H} \\
\text{Ar} & \quad \text{R} \quad \text{Ar} \\
\text{42} & \quad \text{43} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_{2}\text{SO}_{4}(\text{aq}) \quad \text{r. temp} \\
\text{R} & \quad \text{HO} \quad \text{NH}_{2} \\
\text{Ar} & \quad \text{Ar} \\
\text{43} & \quad \text{44} \\
\end{align*}
\]

\textbf{Scheme 70}

<table>
<thead>
<tr>
<th>Ar</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>53</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>H</td>
<td>45</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>H</td>
<td>45</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>H</td>
<td>58</td>
</tr>
<tr>
<td>4-NO₂C₆H₄</td>
<td>H</td>
<td>49</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>46</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>68</td>
</tr>
</tbody>
</table>

Non-aromatic alkenes were shown to be unreactive towards NH-oxaziridines and are only aminated in exceptional cases. For example, norbornene gave the \textit{exo} aziridine in 20% yield, while acrylonitrile was aminated in 41% yield (Scheme 71).
In general, NH-oxaziridines have until now been shown only to be useful in certain circumstances. Oxaziridines unsubstituted at nitrogen are capable of the amination of carbon nucleophiles such as activated carbanions in the presence of catalytic amounts of organic bases and of the aziridination of alkenes. They have also been shown to be reactive towards many sulfur nucleophiles and nitrogen nucleophiles. The reactions of NH-oxaziridines are however under-represented and there is certainly scope for further development. For example, there have been no reports of chiral NH oxaziridines prepared to date for enantioselective reactions. Such reagents, if successful, could find use in synthesis of chiral amines. There are no reports of oxidative aminations of bivalent sulfides to give sulfimines. These reagents are useful in organic synthesis and enantioselection in aminations of sulfides could also prove fascinating. The instability of NH-oxaziridines is, however, a drawback and is the most likely reason as to the lack of knowledge of these compounds.

(c) N-Acyl and N-Alkoxycarbonyl Oxaziridines as Reagents for Electrophilic Amination

N-Acyl or N-alkoxycarbonyl oxaziridines have been shown to react with N, C, S and P nucleophiles. By comparison with NH compounds, N-acyl or N-alkoxycarbonyl oxaziridines tend to be more stable; they can be kept refrigerated in their pure form for a number of months and can be purified by column chromatography, and so are easier to handle. Like NH-oxaziridines, only a small range of different types of compounds have been studied. With few exceptions, N-acyl or N-alkoxycarbonyl oxaziridines are exclusively based upon N-protected imines of benzaldehydes, and there have been no reports of any chiral reagents for use in enantioselective synthesis.

There are two main methods by which these compounds are prepared. These compounds were originally synthesised by acylation of the corresponding NH-oxaziridines (Scheme 72).
Yields for these reactions were poor, and these compounds are now generally prepared by oxidation of \( N \)-protected imines.\(^9\) In turn, these \( N \)-protected imines are prepared by different methods depending upon the \( N \)-substituent.

\( N \)-Moc and \( N \)-Fmoc benzaldimines can be prepared by the acylation of \( N \)-trimethylsilyl benzaldimines with methyl chloroformate and Fmoc chloroformate respectively. These \( N \)-trimethylsilyl imines can in turn be prepared from benzaldehydes by their reaction with lithium hexamethyldisilazide, followed by trimethylsilyl chloride (Scheme 73).\(^9\,9\)9

\( N \)-Boc benzaldimines are prepared in only low yields by acylation of \( N \)-silyl imines with di-\textit{tert}-butyl carbonate (BOC\(_2\)O) or \textit{tert}-butyl fluoroformate (Boe-F), and are instead usually prepared by the aza-Wittig reaction between a benzaldehyde and an \textit{N-tert}-butoxycarbonyl iminophosphorane (Scheme 74).\(^9\)9

The next step in the synthesis of these oxaziridines is imine oxidation. This reaction has proved to be difficult due to the fact that oxaziridine formation competes with formation of the isomeric \( N \)-alkoxycarbonyl amides (Scheme 75).
Introduction

![Scheme 75]

Competing amide formation is best restricted by the use of one of three methods of imine oxidation. The most suitable of these methods is dependent upon imino and aryl substitution pattern. Basic buffered aqueous oxone and N-alkoxycarbonyl imine in chloroform at 0-4 °C are bi-phasic conditions that have been used for the synthesis of 3-aryl N-Moc oxaziridines. 1,1-Diphenyl N-Moc oxaziridine has been prepared by the reaction of the corresponding imine with m-CPBA in chloroform and aqueous potassium carbonate, again under bi-phasic conditions at room temperature. More recently, a better system of imine oxidation has been developed, from which N-Boc, N-Fmoc and N-Z protected oxaziridines can be prepared in high yields. This system involves the reaction of the corresponding imine with the anhydrous m-CPBA lithium salt at −78 °C to room temperature (Scheme 76).

![Scheme 76]

N-Acyl oxaziridines have been prepared by the reaction of hydroxamic acids with methyl propiolate in high yields in the presence of catalytic N-methyl morpholine in acetonitrile solution (Scheme 77).

![Scheme 77]
**Introduction**

There is only one report of this type of reaction and none of the oxaziridines prepared in this way have yet been investigated as potential aminating agents.

Once prepared, these N-protected oxaziridines have been shown to be reactive with a range of different N, S, C, and even P nucleophiles and some of their reactions have been shown to be synthetically useful.

A large proportion of the literature surrounding amination reactions of these N-protected oxaziridines describes N-amination in the synthesis of hydrazine derivatives. It appears that N-protected oxaziridines are highly competitive reagents for this type of transformation, when compared with other reagents that have been used (such as hydroxylamine-O-sulfonic acid or chloramine 4). They have been shown to aminate a number of differently substituted primary and secondary amines in good to excellent yields (Scheme 78).

![Scheme 78](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>Oxaziridine</th>
<th>Yield (%)</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>46a</td>
<td>47b</td>
<td>89</td>
<td>r. temp, 0.5 hours</td>
</tr>
<tr>
<td>46b</td>
<td>47a</td>
<td>76</td>
<td>r. temp, 24 hours</td>
</tr>
<tr>
<td>46c</td>
<td>47a</td>
<td>57</td>
<td>60 °C, 3 hours</td>
</tr>
<tr>
<td>46d</td>
<td>47a</td>
<td>75</td>
<td>r. temp, 1 hour</td>
</tr>
</tbody>
</table>

Problems arise with this reaction when primary amines are aminated, as the formation of benzaldimines is a competing reaction. This can be illustrated by the
Introduction

synthesis of hydrazine derivative 46c from 45c (Scheme 79) where the imine and hydrazine were isolated in a 70:30 ratio.

\[\text{45c} + \text{47a} \rightarrow \text{46c} \text{ (57\%)} + \text{30\%} \]

Scheme 79

The reaction of 47a with triethylamine was anomalous with respect to other reactions of N-protected oxaziridines because of the fact that O-transfer was the main process. At room temperature, the amine oxide was the main product together with a small amount of aminimide (95:5, amine oxide:aminimide). This distribution changed with reaction temperature, and at \(-78^\circ\text{C}\), the N-oxide/aminimide product-ratio was 70:30 (Scheme 80).

\[\text{Et}_3\text{N} + \text{47a} \rightarrow \text{Et}_3\text{N}^+\text{N}^-_{\text{Moc}} + \text{Ph} = \text{O} + \text{Et}_3\text{N}^+\text{O}^- + \text{Ph} \equiv \text{N}^-_{\text{Moc}} \]

Scheme 80

One of the most synthetically useful of these reactions is the synthesis of \(\alpha\)-hydrazino-acid derivatives. A closely related reaction is the amination of free aminoacids to give the corresponding \(N_p\)-protected hydrazino acids. These reagents are currently employed in conventional peptide synthesis, which involves carbamate protection of the amino functionality. This synthesis involves the use of either \(N_p\)-unfunctionalised or preferably \(N_p\)-benzyl protected hydrazino acids that can be prepared from the corresponding \(N\)-benzyl amino acids. Initial conversion of amino acids or benzyl derivatives into benzyl trimethylammonium or tetrabutyl ammonium
Introduction

Salts makes them soluble in dichloromethane. Also, formation of the carboxylate anion increases the basicity and nucleophilicity of the amino functionality, and hence its reactivity and reaction is complete within one hour at $-30$ to $0 \, ^\circ\text{C}$ (Scheme 81).

\[ R_2NH \overset{R_4NH^+ OH^-}{\longrightarrow} R_2NH \overset{R_4NH^+ CO_2^-}{\longrightarrow} R_2NH \]

\[ \text{Scheme 81} \]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>P-G</th>
<th>Temp ($^\circ\text{C}$)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-(\text{CH}_2)_4-$</td>
<td></td>
<td>Moc</td>
<td>-15</td>
<td>85</td>
</tr>
<tr>
<td>$-(\text{CH}_2)_4-$</td>
<td></td>
<td>Boc</td>
<td>-15</td>
<td>95</td>
</tr>
<tr>
<td>Bz</td>
<td>Me</td>
<td>Boc</td>
<td>0</td>
<td>88</td>
</tr>
</tbody>
</table>

In general, with few exceptions, reactions of $N$-alkoxycarbonyl or $N$-acyl oxaziridines with $C$-nucleophiles are restricted to the amination of enolates. $N$-Protected oxaziridines have been reported to react with simple ketone, amide and ester enolates to form the corresponding $N$-protected $\alpha$-amino compounds.\(^97\) These $C$-aminations are all of low yield due to a competing aldol reaction between the enolate and the benzaldehyde product formed during the reaction. For the reaction of propiophenone with oxaziridine 47c, the side product 48 was isolated in a 25% yield (Scheme 82).\(^97\)
Attempts have been made to achieve substrate-controlled asymmetric induction for the synthesis of chiral α-amino ketones. Chiral α-silyl ketones prepared by RAMP/SAMP hydrazone methods were aminated in 19-37% yields with up to 87% de using 47c. Subsequent desilylation using standard procedures enabled the synthesis of chiral α-amino ketones in between 13% and 67% ee (Scheme 83).

Problems of low yields arise here from competing side reactions that include not only aldol reactions, but also α-hydroxylation of the ketone.
Introduction

The reaction of propiophenone silyl enol ether with 47a was anomalous in that oxygen transfer and not amination was observed. The reaction of oxaziridine 47a with this silyl enol ether proceeded at 60 °C with exclusive oxygen transfer to give an unstable epoxide, which then rearranged to give an α-hydroxyketone in 65% yield (Scheme 84).

Scheme 84

Cyclohexene did not react at all with 47a over a number of hours at 60 °C, in contrast to the fact that cyclohexene is aminated by NH-oxaziridine 34 and epoxidised by N-sulfonyl oxaziridines.

Phosphine and sulfide nucleophiles have also been reported to react with N-protected oxaziridines to give a mixture of N-transfer and O-transfer products. As in the reaction of triethylamine, lower temperatures were shown to favour aminated products (Scheme 85).

Scheme 85

In conclusion, N-protected oxaziridines have been shown to be useful reagents for several transformations. Their reactions with amino nucleophiles remains one of the best single step methods available for the preparation of N-protected hydrazines.
from corresponding amines and this methodology has been usefully applied to
hydrazino peptide synthesis. These compounds, however, are not reactive enough to
aminate unfunctionalised alkenes, and reaction with silyl enol ethers gives the α-
oxidation product and not the desired α-amination product. Reactions between
enolates and N-protected oxaziridines seem to be hindered by the formation of side-
products (mainly aldol products of enolates reacting with benzaldehydes formed from
the amination reaction) and yields for these reactions are low. N-Protected
oxaziridines do not share the rich sulfur chemistry that their N-unsubstituted
anallogues such as 34 do. Further, the only examples of N-alkoxycarbonyl oxaziridine
reactions with sulfides and phosphines that have been described involve the formation
of mixtures of amination and oxidation products.97 Like N-unsubstituted
oxaziridines, the range of these N-protected oxaziridines shows little structural
variation. This is most likely to be due to the fact that virtually all of these
oxaziridines are synthesised by either acylation of an N-unsubstituted oxaziridine or
by oxidation of an N-acyl or alkoxycarbonyl imine. The fact that NH-oxaziridines are
unstable coupled with the fact that only non-enolisable N-acyl imines or those with α-
electron withdrawing groups are stable102 is thus the main reason for this lack of
knowledge.

1.3 Summary of Systems for Electrophilic Amination

In general, there are a variety of different approaches to the electrophilic
amination of nucleophiles. While there have been some successes to these
approaches for the amination of certain nucleophiles there have also been many
failures, and it is fair to say that there are no general methods of amination available
to the organic chemist. If we are to attempt to develop new enantioselective
approaches to electrophilic amination based upon one or more of these systems then
first we must take account of existing pros and cons associated with using these
systems.

Some simple aminating reagents based upon N-haloamines or derivatives of
hydroxylamine that have an amino functionality directly attached to a leaving group
have achieved some success in the electrophilic amination of certain nucleophiles.
Introduction

\[ O\text{-Alkyl hydroxylamines have been shown to be effective reagents for the amination of Grignard and organolithium reagents. They are limited, however, to these substrates, as other carbanions (e.g. enolates) have been shown to give poor yields of aminated products. Although this is one obvious limitation to their use, development of asymmetric variants of these amination reagents could be very useful in the light of the fact that there are no useful enantioselective aminations of Grignard or organolithium reagents available.} \]

\[ O\text{-Aryl hydroxylamines have been shown to be useful for the amination of malonate enolates, but these reagents are limited to malonates as substrates. Reactions of less-stabilised carbanions such as simple enolates were shown to furnish low yields of desired products due to side reactions such as the formation of diimide, and reactions of other enolates such as } \beta \text{-diketones gave little or no product. It is difficult to see how we could effectively incorporate chirality into } O\text{-aryl hydroxylamine reagents, as the nearest possible chiral centre would have to be very remote from the reacting nitrogen centre. Both of these factors discouraged us from investigation of this system further for asymmetric synthesis.} \]

\[ O\text{-Acyl hydroxylamines have been reported as aminating agents, but literature on these reagents is sparse due to their instability.} \]

\[ N\text{-Haloamines, such as chloramine 4, have been shown to react with organometallic reagents to form aminated products in high yields under certain circumstances. However there are many problems associated with their use including the need for more than one equivalent of organometallic reagent and the fact that these reagents cannot be stored. These compounds are, in general, unstable and yields from their reactions are not easily reproducible. Also, reagents such as 4 will chlorinate as well as aminate nucleophiles to give chlorinated by-products. All of these factors mean that } N\text{-haloamines are rarely used, and preclude them from further development on this basis.} \]

\[ Hydroxylamine-\text{-O-sulfonic acid 5 has been used for many transformations, including aminations, which are quite often high-yielding. The main limitation to its use is the fact that it is insoluble in almost all organic media, and so aminations with 5 are limited to aqueous reactions. A related reagent, } O\text{-} (\text{mesitylsulfonyl})\text{hydroxylamine 6 and similar } N,N\text{-dialkylated derivatives such as 7 have been shown to be of some use for amination of a wider range of organometallic} \]
Introduction

reagents, albeit in moderate yields. Problems with the use of 6 include the fact that 6 must be prepared using protecting group chemistry and is explosive in its pure form. Reactions of O-sulfonyl hydroxylamines such as 5, 6, or 7 may form products in respectable yields. The problem with their development for enantioselective synthesis is that their reacting centre would have to be fairly remote from any chirality that we could incorporate into any of these molecules. Enantioselective amination of a sulfide to form a sulfimine using O-sulfonyl hydroxylamine (+) 8 has been reported and was very high yielding but gave very poor asymmetric induction.

More recently, other hydroxylamine derivatives have been developed. \( N,O\)-Bis(trimethylsilyl)hydroxylamine 9 is one such reagent that has been developed and has been shown to be useful for the amination of higher order cuprates. Deprotonated \( N \)-arylsulfonyloxycarbamates 10, 11 and 12 have been shown to be of use for the transfer of \( N \)-protected amines to a number of nucleophiles including amine nucleophiles, organolithiums, organocopper reagents, stabilised carbanions and boranes. As with some of the other compounds discussed previously, it is difficult to see where we could incorporate any chirality into molecules related to 9, 10, 11 or 12 in a way that would invoke enantioselectivity in any of their reactions.

\( O \)-(Diphenylphosphinoyl)hydroxylamine 13 is another hydroxylamine-derived reagent that has been employed with different nucleophiles including organolithiums, Grignard reagents, boranes and various enolates. With a few exceptions, the yields reported for aminations with this reagent are low. Chiral \((-)\)-ephedrine-derived \( O \)-phosphinoyl hydroxylamine derivative \((-)\)-14 was employed with similar nucleophiles as was 13, and was reported to give low to average yields for aminated products and poor to moderate enantioselectivities. We may expect the enantioselectivities for reactions of \( O \)-phosphinoyl hydroxylamines such as \((-)\)-14 to be higher than those of O-sulfonyl reagents such as (+)-8 because the reacting nitrogen centre can be placed in closer proximity to any influencing chiral groups present within the molecule. While the enantioselectivities for reactions of \((-)\)-14 are encouraging, yields from these reactions remain low.

Compounds of the type \( NR_2X \) where \( X \) is a leaving group and \( R \) is alkyl or hydrogen were among the first reagents studied for the amination of nucleophiles. Many of these compounds are unstable and for many of the amination reactions that
employ these compounds, yields of product are low and excesses of organometallic reagent are required. For many of these classes of reagent, asymmetric induction by development of chiral aminating compounds would appear to be difficult as the reacting N-centre would have to be located in a remote position to any chirality within the molecule.

One significant group of target compounds for organic chemists are chiral α-amino carboxyl derivatives, which as well as being useful synthetic intermediates could be used to prepare of chiral unusual (i.e. non-proteinogenic) amino acids. These unusual amino acid structures are produced in nature mainly by microorganisms and some have evolved to interfere in biochemical pathways of other organisms. Analogously, a large number of human-designed unusual amino acids have pharmaceutical applications or are used to control plant growth and plant disease\textsuperscript{101}. It is for this reason that attention has focused upon amination of enolates of carboxylic acid derivatives. Other reagents that transfer a masked amino functionality have been shown to be more successful than reagents of the type NR\textsubscript{2}X for this type of transformation.

Substrate-controlled electrophilic diastereoisomeric azide transfer to enolates of chiral N-acyl oxazolidinones by Evans et al has been achieved in good to excellent yields and with good to excellent diastereoselectivities using trisyl azide 15 (1.2.7). Other activated carbanions have also undergone azide transfer with poor to excellent diastereoselectivities and in moderate to excellent yields. Reaction of 15 with a range of hydrazone enolates with subsequent loss of N\textsubscript{2} to form racemic N-trisyl α-amino ketones has been performed successfully in good yield.

Aminations with azodicarboxylates, such as DBAD 16 have also been shown to be very successful in substrate controlled diastereoselective amination of carboxyl derivatives to form amino acid derivatives in high yields and with excellent diastereoselectivities. As well as this, azodicarboxylates have been shown to be successful in certain diastereoselective amination reactions of other stabilised carbanions. Enolates of hydrazones have been shown to give high yields of 1,2-diprotected hydrazone product on reaction with azodicarboxylates to form products that can be deprotected to give α-hydrazino ketones by ozonolysis.
Asymmetric transfer of amine equivalents to various nucleophiles employing reagents such as 15 or 16 has been shown to be very successful, especially in the synthesis of chiral α-amino acids. There may, however, still be areas of chemistry within this field that have not been fully exploited. For example, it may be possible to react carbanions stabilised by chiral imines or chiral hydrazones derived from compounds such as RAMP or SAMP with reagents 15 or 16 to form α-N-trisyl ketones or diprotected α-hydrazino ketone derivatives respectively (Scheme 86).

![Scheme 86]

Problems associated with enantioselective systems that employ reagents such as 15 or 16 include the fact that the reactions are substrate-controlled, and as such, chiral auxiliaries, which may be expensive, must be employed. Also, these approaches to amination must involve a number of additional steps. As well as addition and removal of the chiral auxiliary, the amine equivalent (azide, trisyl amine or hydrazine) must also be deprotected before the amine is recovered.

Amination with nitrenes generated by a number of different methods has been studied. The number and variety of different substrates that are successful limit this approach to amination. Also, many of the examples of aminations with nitrene precursors report low yields of products and this may be due to the fact that nitrenes are in general highly reactive and unselective species that can undergo numerous reactions that compete with addition to a carbon-carbon double bond.

α-Chloronitroso compounds have been shown to be highly selective reagents for reactant-controlled and substrate-controlled diastereoselective syntheses of α-amino ketone and α-amino acid derivatives respectively. This approach to amination has been shown to have several advantages over other approaches with respect to the synthesis of α-amino acid and α-amino ketone derivatives, in that yields of products are high, reactions are often stereospecific, and it is possible to accomplish these
**Introduction**

reactions on a large scale. Also, for reagent controlled stereoselective syntheses, there is no need for additional steps to add and remove chiral auxiliaries. Other substrates such as Grignard reagents and organolithium compounds have, however, failed to yield appreciable amounts of amination products with these compounds.

Chiral aziridines are another important target for synthesis, both due to their importance as synthetic intermediates and because of their biological activity. There are many different routes for preparing these compounds, and aziridination of alkenes is one approach that has generated much interest.

Oxidative addition of N-amino heterocycles to carbon-carbon double bonds is one route to aziridines that has been shown to have a number of advantages over other approaches. The main advantage is that it is possible to effect aziridinations of a range of both electron-rich and electron-deficient alkenes with high diastereoselectivities. Drawbacks associated with this system include the fact that many of these reactions only occur in moderate yields. Another is the fact that aziridines formed from this reaction are bonded at nitrogen to a heterocyclic species that is difficult to remove without rupture of the aziridine ring system. The fact that these reagents are stoichiometrically employed is another failing of this system.

The enantioselective manganese- or copper-catalysed reaction of PhI=NTs with alkenes has been shown to give high yields of N-tosyl aziridine products with high enantiomeric excesses in certain circumstances. The main problem with this system however is the fact that useful yields and enantioselectivities for this reaction are limited to aziridinations of a small set of styrene derivatives. As well as this, there are problems of stereoselectivity, whereby cis-alkenes form aziridines with their substituents trans-disposed on the aziridines ring. A further problem with this system is the fact that the olefin is often employed in excess, and sometimes up to five equivalents are used. This becomes more of a problem where the olefin that we are attempting to aziridinate is precious. Also, the N-tosyl aziridine products of the reaction are difficult to deprotect without rupture of the aziridine ring. While this type of system has a number of failings at present, there are many more variants of this reaction to explore and it is likely that this approach to the synthesis of aziridines will continue to generate interest.
Another very recent approach that has been reported for the synthesis of aziridines is the reaction of $\alpha,\beta$-unsaturated amides with $N$-lithio diaziridines. Although as yet, this type of reaction has only been reported once, yields are high. Furthermore, the products of these reactions, cis-aziridines, are difficult to obtain in useful yields using other existing methods, and these cis-aziridines can be prepared from either cis- or trans-alkenes (although higher yields of cis-aziridines are obtained from trans-alkenes). Further development of this system may prove useful for the substrate- or reagent-controlled asymmetric synthesis of chiral aziridines.

One method of electrophilic amination that may show potential for further development for asymmetric synthesis is the reaction between Grignard reagents or unstabilised organolithium reagents (e.g. alkyl lithiums) with diazirines to form diaziridines that can then be hydrolysed with acid to give hydrazines. This reaction is documented and could be useful due to the fact that there are no successful asymmetric variants for electrophilic amination reactions of unactivated organolithium reagents or Grignard reagents.

$N$-unsubstituted oxaziridines have been shown to aminate a number of different nucleophiles. These compounds are in general unstable, and only a handful have ever been prepared. It is probably because of this that virtually all of the reports of amination reactions with these compounds employ cyclohexanone derived oxaziridine 34 and there have been no reports of chiral NH-oxaziridines synthesised for asymmetric amination reactions.

Many reported reactions of 34 describe amination of amines to give hydrazines or hydrazones. The development of stereoselective compounds for the synthesis of hydrazines or hydrazones from amines would be futile because the amino nitrogen is configurationally unstable, and thus, achiral in all but a few special circumstances.

There are also many reports of 34 reacting with bivalent sulfur nucleophiles, but all of these reactions involve bivalent sulfur (thiols, or thiocarboxyl derivatives) as the starting material and also as the product (sulfenamides or thiooximes) and again there is little scope for chiral induction in these reactions (see Schemes 63 to 67). However, if we could aminate sulfides to give sulfimines with a formal change...
Introduction

of oxidation state of sulfur from S(II) to S(IV), then there would be scope for asymmetric induction.

There is, however, much more scope for asymmetric induction in reactions of NH-oxaziridines with C-nucleophiles to form primary amine derivatives. There are at present no reports of amination reactions using 34 of moderately to very basic nucleophiles such as enolates of simple ketones, enolates of carboxyl derivatives, Grignard reagents or organolithium reagents. Reports of aminations of more delocalised carbanions such as enolates of barbituric acid or Meldrum’s acid derivatives or of α-cyanoamides or α-aryl amides using 34 describe high yielding reactions that give crystalline products without the need for column chromatography. As mentioned, numerous approaches have been developed with the aim of incorporating enantioselectivity into amination reactions of carbanions such as enolates of simple ketones or carboxyl derivatives, currently, there are no generally useful methods available for enantioselective amination of these more delocalised carbanions. This is one obvious area where chiral NH-oxaziridines could be useful. There are also reports of aziridinations of alkenes with 34. The yields for these reactions are low to moderate, and the alkenes aziridinated with 34 are, with a few exceptions, α-aryl alkenes. Although these are obvious limitations to this approach to the aziridination of alkenes, there is scope for the development of potentially new oxaziridines as aziridinating agents that may be more reactive than 34 and may deliver the nitrogen of the aziridine moiety enantioselectively. The reactivity of NH-oxaziridines therefore makes the incorporation of chirality into these reagents an attractive possibility and worthy of investigation.

N-Acyl or alkoxycarbonyl oxaziridines have also been shown to aminate a range of nucleophiles. Virtually all of the reports of amination reactions with these compounds describe amination reactions using benzaldehyde-derived oxaziridines such as 47a, 47b, or 47c and, like NH-oxaziridines, there are no reports of chiral N-alkoxycarbonyl or N-acyl oxaziridines being prepared for asymmetric amination of nucleophiles. This is probably because although N-alkoxycarbonyl or N-acyl oxaziridines are themselves more stable than NH-oxaziridines, their precursors (NH-oxaziridines or N-acyl or alkoxycarbonyl imines) are unstable. Most of the literature reports of aminations with these compounds involve aminations of amine
Introduction

nucleophiles to give N-protected hydrazine derivatives, and there is little scope for asymmetric induction in these reactions. There is only one report of reaction with a sulfur compound, and this report describes the reaction of a sulfide to give a mixture of oxidation and amination products. The reaction of N-protected oxaziridines with C-nucleophiles has also been studied. In general, these reagents are not as reactive as NH-oxaziridines and will not aziridinate alkenes. In the one report where an electron-rich alkene (propiophenone silyl enol ether) is reacted with an N-protected oxaziridine (47a), the product of the reaction is the oxidation product (\(\alpha\)-hydroxy ketone) and not the amination product (N-protected \(\alpha\)-amino ketone). N-Protected oxaziridines have been shown to aminate enolates of simple carboxyl derivatives and enolates. Yields for these reactions are low due to competing side reactions. These include the formation of \(\alpha\)-hydroxy ketone or carboxyl derivatives due to transfer of oxygen, and also the aldol reaction whereby the remaining enolate reacts with the newly-formed benzaldehyde. Although the achiral reactions of C-nucleophiles with N-protected oxaziridines are not very successful, there is scope for further investigation. For example, if chiral reagents were prepared from ketones more hindered than benzaldehyde, then, as well as inducing asymmetry into this process, this should retard the competing aldol reaction. A successful asymmetric version of this reaction would have some advantages over previous methods of asymmetric syntheses of \(\alpha\)-amino ketone or acid derivatives in that the reaction would be a one-step synthesis of an N-protected \(\alpha\)-amino carboxylate or ketone. It is because of these factors that asymmetric variants of these reagents are worthy of investigation.

While there are a number of literature reports on electrophilic amination reactions that show potential for further development, there may also be other systems that are potentially useful, but that have not been previously described or reported.

Because of the success that had been achieved, by members of our group, in catalytic asymmetric sulfoxidation mediated by \(N\)-sulfonyl imines,\(^1\) we were intrigued by the possibility that a nitrogen analogue of hydrogen peroxide could be used in a similar way to transfer an amino functionality to nucleophilic species. There is no precedent for this sort of reaction, but there are a number of different possible hydrogen peroxide analogues such as hydrazine, hydroxylamine and other derivatives.
Introduction

Finally, other possibilities for the development of new systems for electrophilic amination reactions may involve the use of three-membered heterocyclic species with two heteroatoms. For instance it may be possible transfer an amino functionality from a diaziridinium species to a nucleophile in an analogous fashion to the transfer of oxygen from an oxaziridinium species (Scheme 87). Alternatively, while steric factors have been reported as the main influence in whether nucleophiles abstract oxygen or nitrogen from oxaziridines, we may find that a similar effect is present in oxaziridinium compounds, whereby if we reduce the steric bulk surrounding the nitrogen atom then we may observe some nucleophilic attack of the nitrogen atom (Scheme 87). Another possibility is that a diazirine ring either protonated or alkylated to give a diazirinium species may deliver nitrogen to a nucleophile (Scheme 87).

\[
\begin{align*}
\text{O} & \quad \text{N}^+ \quad \text{H} \\
\text{N}^+ \quad \text{R} & \quad \text{H} \\
\text{N}^+ \quad \text{R} & \quad \text{H} \\
\text{N}^+ \quad \text{R} & \quad \text{H} \\
\text{Nu:} & \\
\text{Aminated Products}
\end{align*}
\]

Scheme 87
Results and Discussion

2.0 RESULTS AND DISCUSSION

2.1 Hydrogen Peroxide Analogues

Due to the success that members of our group had achieved with the catalytic asymmetric imino variant of the Payne oxidation system, we were at first fascinated with the idea that we might replace hydrogen peroxide with a nitrogen transfer analogue in this system in order to achieve asymmetric catalytic amination of nucleophiles. There is no literature precedence for this system and therefore we do not know the types of nucleophiles that would be reactive in this system, or the conditions that we would need to use to effect such a reaction. There is a range of different imine derivatives that we could test in such a system. For example, the sulfoxidation reaction was shown to be catalysed by a number of different N-sulfonyl imines and oximes in the new variant of the Payne oxidation system. Because of the number of different variations of conditions and catalysts that could be considered when investigating a new system such as this, we decided that investigation should begin using the most successful conditions that had been found for the sulfoxidation reaction. It is because of this that the first potential catalyst investigated was 3,3-dimethoxycamphorsulfonyl imine 1.

A number of N-sulfonyl imines, such as 1, derived from camphor have been synthesised as precursors to N-sulfonyl oxaziridines by Davis et al., and 1 was synthesised according to literature procedures. (1S)-(+) Camphorsulfonic acid 49 was first reacted with thionyl chloride to give crude (1S)-(+) camphorsulfon chloride 50 in 95% yield, which was then reacted with concentrated ammonia solution to afford crude (1S)-(+) camphorsulfonamide 51 in an 88% yield. Cyclisation of 51 to (1S)-(−) camphorsulfon imine 52 was effected in 90% yield by reflux of (1S)-(−) camphorsulfon imide in toluene in the presence of amberlyst 15 (Scheme 88).
Results and Discussion

(1S)-(−)-Camphorsulfonyl imine 52 was then oxidised at the 3 position by reaction with selenium dioxide in acetic acid under refluxing conditions to give (1S)-(−)-3-oxocamphorsulfonyl imine 53 in a 62% yield. (1S)-(−)-3-Oxocamphorsulfonyl imine 53 was then treated with trimethyl orthoformate in the presence of amberlyst 15 and concentrated sulfuric acid in methanol under refluxing conditions to give the 3,3-dimethoxy acetal (1S)-(+)—3,3-dimethoxycamphorsulfonyl imine 1 in a 90% yield (Scheme 89).

(1S)-(+)—3,3-Dimethoxycamphorsulfonyl imine 1 was then investigated as a potential catalyst for nitrogen transfer with nucleophiles. Nucleophiles that were initially investigated for nitrogen transfer, using hydrazine as the N-transfer agent, included styrene and trans-stilbene. Silyl enol ethers of cyclohexanone and acetophenone were also employed in order to investigate the reaction with more electron-rich alkenes, and thioanisole was used in order to see if we could achieve transfer of nitrogen to a sulfur nucleophile. These substrates were stirred at room temperature with one equivalent of the catalyst 1, four equivalents of hydrazine hydrate and four equivalents of DBU in dichloromethane, and the reactions were followed by tlc. After one month at room temperature, no reaction had occurred, and

Scheme 88

Scheme 89
Results and Discussion

the catalyst, thioanisole, the alkenes and the hydrolysed silyl enol ethers were recovered quantitatively (Scheme 90).

\[
\text{Nucleophiles} \quad \text{DBU, H}_2\text{N-NH}_2, \text{DCM, 1} \quad \text{r. temp, 1 month} \quad \text{No reaction}
\]

\[
\text{Nucleophiles used:}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{S}^{-}\text{Me}
\end{align*}
\]

Scheme 90

The potential N-transfer agents hydroxylamine and tosyl hydrazine were then employed in a similar system using trans-stilbene and thioanisole as potential substrates to see if these could effect a reaction, but after two weeks at room temperature, no reaction had occurred (Scheme 91).

\[
\begin{align*}
\text{Nucleophiles} & \quad \text{DBU, H}_2\text{N-X, DCM or DCM/MeOH, 1} \\
& \quad \text{r. temp, 2 weeks} \\
\text{No reaction}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{S}^{-}\text{Me}
\end{align*}
\]

\[
x = \text{TsNH}^{-}, \text{HO}^{-}
\]

Scheme 91

At this stage, our investigations into this reaction had been completely unsuccessful, and the question arose of whether any adduct between the potential catalyst \( t \) and the potential \( N \)-transfer agent is formed at all under these conditions. It appears that there is very little if anything in the literature about reactions of \( N \)-sulfonyl imines in general, or \( N \)-sulfonyl imines that are part of an isoxathiazole moiety, with these potential nitrogen transfer reagents. It is known, however, that imines in general undergo \( \text{trans} \)-imination reactions with these types of potential \( N \)-transfer reagents.\(^{107} \) The \( \text{trans} \)-imination of imines by amines is an equilibrium process, and it appears that under refluxing conditions, the driving force for such reactions is the evaporation of the lower boiling point amine from the system, or
Results and Discussion

Alternatively a more basic amine will displace a less basic amine from the imine (Scheme 92).

\[
\begin{align*}
\text{N} & \quad \text{R}^1 \quad \text{R}^2 \text{NH}_2 \\
\text{NH} & \quad \text{NH} \quad \text{R}^1 \quad \text{R}^2 \text{NH}_2 \\
\text{N} & \quad \text{R}^1 \quad \text{R}^2
\end{align*}
\]

Scheme 92

If such a reaction could occur in our system, then it would be favoured by the facts that all of the potential N-transfer agents are stronger bases than the sulfonamide that would be liberated, and all of the potential N-transfer agents are α-nucleophiles and are thus more reactive nucleophiles than simple amines. This reaction would be disfavoured however by the fact that displacement of the sulfonamide moiety would involve the rupture of a stable five-membered ring system.

The reaction of potential catalyst 1 with potential nitrogen transfer reagents in the absence of any substrate was therefore monitored by tlc. No reaction of the catalyst 1 at all was observed under basic or acidic conditions, in the presence of hydrazine, hydroxylamine or tosyl hydrazine, at room temperature over a period of two weeks (Scheme 93). An adduct formed between 1 and hydrazine to give cyclic hydrazone 54 has however been observed when the reaction is carried out under reflux (Scheme 93).
Results and Discussion

Due to the lack of success in our investigations of this type of system in bringing about any amination at all, other techniques were investigated. This system, however, is far from being investigated exhaustively. There is a great number of other potential catalysts available to try out in this system as well as many other reaction conditions. Further, there are many more potential \( N \)-transfer reagents that could be used, including aminating reagents such as hydroxylamine-\( O \)-sulfonic acid, \( O \)-acyl hydroxylamines, or other reagents.

2.2 Oxaziridines as Electrophilic Aminating Agents

2.2.1 Synthesis of Chiral Oxaziridines

Oxaziridines are one type of a class of three-membered heterocycle with two heteroatoms, with properties and reactivity that are discussed in more detail in section 1.2.13. As indicated in section 1.2.13, to date there have been no chiral \( \text{NH} \)-oxaziridines or \( N \)-alkoxycarbonyl or \( N \)-acyl oxaziridines prepared for use in asymmetric synthesis. If an attempt is to be made to develop new chiral oxaziridines for possible use as enantioselective aminating reagents, then a number of factors must be considered. If \( \text{NH} \)-oxaziridines or \( N \)-protected oxaziridines for use as enantioselective amination reactions are to be employed as stoichiometric reagents, and as such, it is important that they can be prepared from cheap chiral starting materials. Ideally this should be in high yields, in as few steps as possible and using methodology that can be performed inexpensively on a large scale. \( \text{NH} \)-oxaziridines and \( N \)-acyl or \( N \)-alkoxycarbonyl oxaziridines are synthesised either directly or indirectly from ketones or aldehydes (with the exception of the single report of ozonolysis of an alkene in the presence of ammonia\(^{92} \) or the reported reaction of hydroxamic acids with methyl propiolate\(^{100} \)). It would therefore seem appropriate to use chiral ketones or aldehydes as a basis for the development of such new chiral reagents for asymmetric amination reactions. There are few chiral aldehydes that are readily available to the organic chemist. There are, however, a large number of terpenes and their derivatives that provide chemists with a rich source of chiral enantiopure, and often cheap ketones. It is because of this that we initially attempted
Results and Discussion

to prepare chiral oxaziridines based upon the commercially available ketones (1R)-
(-)-fenchone 55, (1R)-(+)camphor 56 and (1R)-(−)-camphorquinone 57.

(1R)-(−)-Camphorquinone 57 is commercially available, but was prepared by
treating (1R)-(+)camphor 56 with selenium dioxide under reflux in acetic anhydride
over a period of eight hours (Scheme 94).\textsuperscript{108} This procedure is virtually quantitative
and can be carried out on a 100 g scale.

![Scheme 94](image)

Another point that should be considered is that, if we are to synthesise
oxaziridines from chiral ketones, then the 3-position of the oxaziridine ring becomes a
new stereocentre and so two possible diastereoisomers may be formed from one
chiral ketone starting material. A similar problem is encountered in the formation of
oxaziridinium salts during asymmetric epoxidation reactions (see 1.2.13 (a)). These
oxaziridinium salts are for the main part transient species that are formed \textit{in situ} and
deliver their oxygen atom to the substrate without characterisation. It is difficult
under these circumstances, therefore, to know the ratio of the two diastereoisomers
formed and which isomer of the oxaziridinium salt is responsible for bringing about
any enantioselectivity into these reactions, and to some extent, this has hindered their
development as asymmetric oxidising reagents. The preparation of chiral
oxaziridines from camphor-derived compounds has the advantage that it is more
likely to prevent the problem of diastereoisomeric mixtures of product being formed.
This is because the attack of reagents upon the carbonyl or imino functionality of
camphor, camphorquinone, or reagents derived from these compounds, often occurs
exclusively from the \textit{endo} face of the molecule, and therefore limits the formation of
Results and Discussion

diastereoisomeric mixtures of products. This phenomenon is caused by steric hindrance due to the two bridgehead methyl groups attached to C-7 of the camphor skeleton. For example, the per-acid oxidation of camphor-derived N-phenylsulfonyl imine 58 to the corresponding (1R)-(−)-N-(phenylsulfonyl)camphoryl oxaziridine 59 occurs exclusively with per-acid attack from the endo-face to form a single diastereoisomer of product (Scheme 95).\(^{109}\) Also, while camphorquinone has two available carbonyl groups, in general, reactions are selective and only occur at the less hindered C-3 carbonyl group; this can be illustrated by the oximation of (1R)-(−)-camphorquinone to form the single mono-oximated product (1R)-(+)camphorquinone monoxime 60 (Scheme 95).\(^{110}\)

\[\text{N-SO}_2\text{Ph} \xrightarrow{m\text{-CPBA, DCM, K}_2\text{CO}_3\text{(aq)}} \text{N-SO}_2\text{Ph} \]

\[\text{58} \quad \text{59} \quad 87\%\]

\[\text{H}_2\text{NOH.HCl, H}_2\text{O, NaOAc} \xrightarrow{\text{EtOH, Reflux}} \text{N-OH} \]

\[\text{57} \quad \text{60} \quad 82\%\]

Scheme 95

NH-oxaziridines can either be prepared by amination of a carbon-oxygen double bond using an electrophilic aminating reagent, or by oxidation of a carbon-nitrogen double bond with a per-acid. Because of the high levels of selectivity for additions to carbonyl groups or imino groups of camphor derived compounds, this in theory could allow access to both endo and exo diastereoisomers of camphoryl NH-oxaziridine (Scheme 96).
Results and Discussion

\[
\begin{array}{c}
\text{Scheme 96}
\end{array}
\]

\[N\text{-Alkoxy carbonyl or } N\text{-acyl oxaziridines are all prepared either by the oxidation of } N\text{-protected imines, or by the acylation of } NH\text{-oxaziridines (with the exception of the reaction of hydroxamic acids with methyl propiolate). The fact that only } N\text{-acyl imines of non-enolisable keto functionalities (such as those derived from benzaldehydes), and those with } \alpha\text{-electron withdrawing groups, are stable limits their potential as precursors for aminating agents. It may be viewed, therefore, that acylation of } NH\text{-oxaziridines (either } in \text{ situ } \text{ or after isolation) is the preferred route for the syntheses of these chiral } N\text{-protected oxaziridines.}
\]

Initially, our attempts were made to prepare chiral oxaziridines directly from (1R)-(−)-fenchone 55, (1R)-(−)-camphor 56 and (1R)-(−)-camphorquinone 57, using methods developed by Schmitz et al for the synthesis of cyclohexanone-derived oxaziridine 34, and for the synthesis of the benzaldehyde-derived } NH\text{-oxaziridine for } in \text{ situ } \text{ acylation (Scheme 56, Scheme 72)89,90. Ketones 55, 56 and 57, dissolved in toluene, were employed in bi-phasic systems with chloramine precursors, aqueous ammonia and sodium hypochlorite. These reactions were monitored by tlc, and the organic phases were tested periodically by shaking small amounts with potassium iodide solution to observe any oxidising compounds were being formed.111 The temperature was varied from } 0 \, ^\circ C \text{ to } 40 \, ^\circ C, \text{ and for all of the three ketones, after stirring overnight, the reactions appeared to be completely unsuccessful, although a slightly orange colour was observed on testing with potassium iodide. These reactions were then repeated in dichloromethane, as we thought that a more polar solvent might give a better interaction between the two phases and so enhance reactivity. The reaction temperature was varied between } 0 \, ^\circ C \text{ and room temperature and the concentrations were varied (Scheme 97). Although no new compounds could}
Results and Discussion

be seen by tlc, a slight orange colour was again observed on testing with potassium iodide.

Ketones 55, 56, and 57 were then dissolved in diethyl ether, and these organic phases were employed in bi-phasic systems with an aqueous solution containing sodium hydroxide and hydroxylamine-O-sulfonic acid. The mixtures were stirred vigorously between 0 °C and room temperature and followed by tlc and potassium iodide analysis. No reaction was observed, and the process was repeated, using THF as the organic solvent, as we thought that a more water-soluble organic solvent might increase the interaction between the two phases. Again, no reaction was observed by tlc, but a slight orange colour was observed on shaking a small amount of the organic solutions with potassium iodide (Scheme 98).
Results and Discussion

One possibility was that a small amount of oxaziridine was being formed during these reactions, and that this was the reason for the orange colour observed on testing with potassium iodide. The ability of the organic phase to oxidise potassium iodide slightly was something that disappeared with time, on removal of the solvent and heating to about 40 °C, and we therefore thought that this could be due to the presence of an unstable oxaziridine. The attempted reaction of ketone 56 and diketone 57 was repeated in THF, and after the reaction, ethyl chloroformate was added to the organic phase in an attempt to acylate any unstable oxaziridine that was being formed before it could decompose, as proposed in Scheme 99.

\[ \text{H}_2\text{NOSO}_3\text{H}, \text{NaOH, H}_2\text{O}, \text{THF, r. temp} \rightarrow \begin{array}{c} \text{ClCO}_2\text{Et} \\ \text{H}_2\text{NOSO}_3\text{H}, \text{NaOH, H}_2\text{O}, \text{THF, r. temp} \rightarrow \end{array} \]

Scheme 99

This system was unsuccessful, no N-protected oxaziridine was recovered, and ketones 57 and 56 were recovered quantitatively. On repeating the attempted preparation of an oxaziridine from 56 in DCM using the ammonia/sodium hypochlorite method, it was noticed that the slightly oxidising organic phase formed a white precipitate on standing. This precipitate was filtered, and was found to completely insoluble in all organic solvents, but soluble in water to form an aqueous solution that gave a white precipitate upon addition of a solution of silver (I) nitrate. We may infer from this that one possible reason for the presence of an unstable oxidising agent in the organic solution which decomposes upon attempted isolation or on heating above 40 °C may be due to the presence of hypochlorous acid and not an oxaziridine. Hypochlorous acid is unstable and weakly acidic and may dissolve to some extent in the organic solvent as a result of the need to neutralise the sodium hypochlorite prior to its reaction. This acid disproportionates to give perchloric acid.
and hydrogen chloride,\textsuperscript{112} and this may be the reason for the formation of this precipitate. Also, the reason for the presence of an oxidising organic solution in some cases when attempting to prepare oxaziridines by reaction of a ketone with hydroxylamine-\textit{O}-sulfonic acid may be due to the slight solubility of hydroxylamine-\textit{O}-sulfonic acid in some organic solvents. Because these methods were unsuccessful for the synthesis of any of the desired oxaziridines, other methods of their preparation were attempted. The fact that these classical methods of preparation of \textit{NH}-oxaziridines did not work for ketones 55, 56 and 57 may not be surprising given the fact that these are hindered ketones and that this reaction is only documented for \textit{\alpha,\alpha}-unsubstituted cyclohexanones or for benzaldehydes.\textsuperscript{89,90,98}

\textit{NH}-oxaziridines have also been prepared by photolyses of oximes (See 1.2.13 (b), Scheme 57).\textsuperscript{91} Analogously, the photolyses of (1\textit{R})-(\textit{\textendash})-fenchone oxime 61, (1\textit{R})-(-)-camphor oxime 62 and (1\textit{R})-(\textit{+})-camphorquinone monoxide 60 were attempted. (1\textit{R})-(\textit{+})-Camphorquinone monoxide was synthesised in 82 \% yield by oximation of (1\textit{R})-(\textit{\textendash})-camphorquinone 57 with hydroxylamine hydrochloride in the presence sodium acetate in water and ethanol under refluxing conditions (Scheme 95).\textsuperscript{110} (1\textit{R})-(\textit{\textendash})-Fenchone oxime \textit{61}\textsuperscript{113} and (1\textit{R})-(\textit{\textendash})-camphor oxime \textit{62}\textsuperscript{114} were synthesised from (1\textit{R})-(\textit{\textendash})-fenchone 55 (1\textit{R})-(\textit{+})-camphor 56 respectively and in yields of 68\% and 82\% respectively by their reaction with hydroxylamine hydrochloride in the presence of pyridine under refluxing conditions in ethanol (Scheme 100).

Oximes 60, 61 and 62 were then irradiated under the same conditions reported for the synthesis of other \textit{NH}-oxaziridines by photolysis.\textsuperscript{91} This was carried out in
methanol at room temperature in a Rayonet® reactor with high pressure 254 nm Hg arc lamps, and, due to the apparent instability of NH-oxaziridines in all but dilute solutions, the concentration of the oxime was kept below 0.001 moles per litre.91 The reaction was monitored by tlc and with starch/potassium iodide paper to observe if any new oxidising agents were being formed by the reaction. After 4 hours, no oxidising products had been formed and it appeared that, by tlc, all of the starting material had been consumed (Scheme 101).

Photolyses of (1S)-(+) fenchone oxime (+)-61 and (1S)-(+) camphor oxime (+)-62 have previously been studied, and gave a range of products, mainly nitriles and lactams, originating from Beckmann type cleavages and rearrangements respectively.113 An oxaziridine is in fact proposed as an intermediate in the reaction, which then undergoes cleavage to form an array of products. This is illustrated for the photolysis of (1R)-(−) camphor oxime 62 in Scheme 102.
Results and Discussion

The fact that no stable oxaziridine is formed during the reaction may either be an indication of the complete instability of such oxaziridines, or this may be due to the fact that the oxaziridine is formed in an excited state that readily decomposes under the reaction conditions. It is interesting to note that all of the oxaziridines previously reported to have been prepared by photolytic methods are prepared by photolyses of oxime groups that are conjugated with a phenyl ring, and this may contribute in some way to the stability of these α-aryl oxaziridines under these conditions.

There is a report of oxaziridines being prepared by oxidation of NH-imines with m-CPBA (Scheme 58), and we thought that chiral NH-oxaziridines might perhaps be prepared in this way from NH-imines derived from (1R)-(−)-fenchone 55 and (1R)-(+) camphor 56. The difficulty arises here with the synthesis of these imines, because, unlike imines derived from sterically un-congested ketones, it is impossible to prepare these imines of more hindered ketones by simple condensation of the ketone with ammonia. Other methods, therefore, were sought for their synthesis.

Reduction of oximes is one method by which NH-imines are prepared. In general the reaction is carried out under conditions that cause rapid hydrolysis of the NH-imine to give the ketone, and this reaction is frequently used as a route to ketones from oximes that have been prepared by methods other than ketone oximation. One reported method of accomplishing this reaction under anhydrous conditions that prevents hydrolysis of the imine is by carrying out the reduction using tributyl phosphate and diphenyl disulfide. These NH-imines, prepared in situ, were then reacted further to give a number of other compounds including enamides, pyrroles and pyrrolin-2-ones. This system is anhydrous and self-drying, as the excess of the reducing mixture reacts irreversibly with any water present in the reaction mixture, and a mechanism for this transformation, based upon the evidence, has been proposed (Scheme 103).
Results and Discussion

Further Reactions

Scheme 103

Fenchone- and camphor-derived oximes, 61 and 62 respectively, were treated with tributyl phosphine and diphenyl disulfide in THF at room temperature in an analogous system to that described in Scheme 103. After 2 hours, it appeared in both of the reactions that, by tlc, all of the starting materials had been consumed. The reactions were then worked up by removal of the solvent followed by column chromatography over silica. The only compounds that were recovered from this reaction were tributyl phosphine, tributyl phosphine oxide and a small amount of (IR)-(+)-camphor; none of either of the desired NH-imine products were recovered for either of these reactions (Scheme 104).

Scheme 104

For (1R)-(−)-camphor oxime 62, as an alternative to attempted isolation of the purported NH-imine from the reaction mixture, the product mixture was reacted with m-CPBA in the presence of all of the other reagents. This required around 10 equivalents of the per-acid in order to oxidise all of the tributyl phosphine to the
Results and Discussion

Phosphine oxide and all of the disulfide to the disulfone as well as any of the suspected NH-imine to the oxaziridine. No oxaziridine was however recovered from this reaction (Scheme 105).

\[
\begin{align*}
\text{N-OH} & \quad \text{Bu}_3\text{P, Ph}_2\text{S}_2, \text{THF, r. temp} \\
& \quad \text{m-CPBA, DCM, r. temp} \\
\text{No Recovered} & \quad \text{NH-oxaziridine}
\end{align*}
\]

Scheme 105

Because this method was found to be unsuitable for either isolation of camphor- or fenchone-derived imines, or their oxidation in situ, other methods for the synthesis of these NH-imines were attempted.

The NH-imines derived from camphor and fenchone have been previously reported. These imines are prepared by ammonolysis of nitrimines, which are in turn prepared from the corresponding oximes by nitrosation. Using literature procedures, (1R)-(−)-camphor nitrimine 63 was prepared by nitrosation of (1R)-(−)-camphor oxime 62 with (5%) aqueous sodium nitrite solution in glacial acetic acid at room temperature over a period of two and a half hours and in 54% yield (Scheme 106). Nitrimine 63 was then converted to (1R)-camphor imine 64 by dissolution of 63 in dry THF, and bubbling ammonia gas through the solution at 0 °C for a period of 4 hours. The reaction was worked up by removal of the solvent to furnish the imine 64 quantitatively (Scheme 106).

\[
\begin{align*}
\text{N-OH} & \quad \text{NaNO}_2, \text{H}_2\text{O, AcOH, r. temp} \\
& \quad \text{NH}_3(\text{g}), \text{THF, 0 °C} \\
\text{N-NO}_2 & \quad \text{ca. 100%}
\end{align*}
\]

Scheme 106

Imine 64 is an unstable solid that decomposes if heated above 35 °C or is kept overnight in the freezer, and it was therefore used straightaway in the next stage of the synthesis. Imine 64 was reacted with one equivalent of pure m-CPBA at −35 °C in dry DCM overnight. Removal of solvent, dissolving in petroleum ether,
Results and Discussion

washing with 1M aqueous sodium hydroxide, and removal of the solvent furnished (+)-camphoryl oxaziridine 65 as a colourless solid in a yield of 94% (Scheme 107).

![Scheme 107]

Initially, 65 decomposed when left overnight, liberating ammonia. Subsequently, we found that if the NH-oxaziridine 65 is dissolved in dichloromethane and filtered through an equal mass of silica (1 g silica for 1 g of oxaziridine) then the product does not decompose and is stable in the refrigerator for more than six months.

Although this synthesis of oxaziridine 65 required more steps to accomplish than was originally desired, all of the steps can be carried out without the need for column chromatography, and the synthesis of (+)-camphoryl oxaziridine 65 was accomplished on a greater than 20 g scale. With the exception of the synthesis of nitrimine 63, all of the steps required to prepare 65 are high yielding. Also, for the nitrosation step of camphor oxime 62 to give nitrimine 63, the yield of crude nitrimine is high (80%) and the purity of the crude nitrimine appears to be of around 95% by $^1$H NMR spectroscopy. Most of the reduction of yield in this step is due to the fact that some of the nitrimine is lost during recrystallisation of the crude product. Optimisation of this step, or the use of crude nitrimine 63 to form crude oxaziridine 65 could, therefore, enhance the yield of the product.

Unlike other NH-oxaziridines that have been prepared, (+)-camphoryl oxaziridine is surprisingly stable. It can be kept in its pure form for more than six months and can be heated under reflux in THF for more than five hours without any noticeable decomposition, but decomposes upon reflux in toluene, as this solvent boils at a higher temperature. The reason for this stability is unknown, as, too few NH-oxaziridines have been prepared to be able to relate stability of these compounds to any of their structural features. However, considering the fact that the only other NH-oxaziridine that has been found to be stable in its pure form is 3,3-di-tert-butyl
Results and Discussion

oxaziridine 33 (Figure 3), then the fact that oxaziridine 65 is also stable in its pure form may be related to the fact that it has also been prepared from a hindered ketone.

Oxaziridine 65 was found to be a mixture of two diastereoisomers by $^1$H and $^{13}$C NMR spectroscopy, present in a ratio of approximately 60:40.

One feature of oxaziridine ring formation that has already been discussed is that it is possible to form two isomers depending upon whether the direction of attack of the oxidant is \textit{exo} or \textit{endo}. Another feature of the oxaziridine ring that has already been discussed is that, due to a number of different reasons, the barrier to inversion of the nitrogen atom of oxaziridines is relatively high, leading in some cases to configurational stability of nitrogen at room temperature. It is possible therefore that the oxidation of imine 64 could give rise to four different possible diastereoisomers of oxaziridine 65 (65a, 65b, 65c and 65d) (Figure 4).

There are three possibilities to consider when postulating the structures of the two isomers in our sample of 65 that are observed by NMR spectroscopy. Firstly the two bridgehead methyl groups of 64 may induce exclusive \textit{endo}-attack of the per-acid from underneath the six-membered ring, and nitrogen inversion may be slow on an NMR time scale. This would mean that the two isomers observed by NMR spectroscopy are 65a and 65b. A second possibility is that if nitrogen inversion is slow, and both \textit{endo} and \textit{exo} attack of the oxidant occurs, then we may expect the NH-proton to be in the more sterically favoured position, transposed on the uncongested face of the oxaziridine ring directed away from the quaternary carbon centre at camphor C-1. This would mean that the two isomers of oxaziridine 65 observed by NMR spectroscopy would be 65b and 65d. The third possibility that could be considered is that both \textit{exo} attack and \textit{endo} attack of the per-acid occurs to give \textit{exo} and \textit{endo} isomers of the oxaziridine. Rapid nitrogen inversion on the NMR
Results and Discussion

time-scale would mean that the signals from isomer 65a and 65b would coalesce, as would signals from isomers 65c and 65d, to give the appearance of only two isomers of oxaziridine by NMR spectroscopy, although four are present.

Although there have been no reported studies concerning inversion at nitrogen atoms of NH-oxaziridines, nitrogen inversion in N-alkyl,73,120 N-acyl,121 N-sulfonyl122 and N-phosphinoyl123 oxaziridines have been investigated. It has been shown that nitrogen inversion of N-alkyl oxaziridines is very slow on an NMR time-scale and certain N-alkyl oxaziridines are sufficiently configurationally stable that invertomers can be directly isolated and characterised. N-Sulfonyl oxaziridines also undergo slow nitrogen inversion on an NMR time-scale, and at ambient temperatures, both invertomers of an oxaziridine may be observed by NMR spectroscopy. N-Acyl and N-phosphinoyl oxaziridines undergo more rapid nitrogen inversion, and coalescence of signals from invertomers of these oxaziridines occurs at a temperature below room temperature. This enhanced rate of nitrogen inversion for oxaziridines with electron withdrawing N-substituents may be rationalised as resulting from stabilisation of the transition state by delocalisation of the nitrogen lone pair of electrons about the N-substituent. This is illustrated for inversion of an N-phosphinoyl oxaziridine (Scheme 108).

\[
\begin{array}{c}
\text{Scheme 108}
\end{array}
\]

Because it is not possible for the NH-proton of NH-oxaziridines to stabilise the corresponding transition state in this way, then we may expect NH-oxaziridines to have a higher barrier to inversion than N-phosphinoyl, N-acyl or N-sulfonyl oxaziridines and to invert at a rate more closely related to that of N-alkyl oxaziridines. It is for this reason that the observation of two isomers of NH-oxaziridine due to rapid inter-conversion between 65a and 65b, and, 65c and 65d seems unlikely. There are however a number of ways of investigating the structure of oxaziridine 65.
Results and Discussion

One method of proving the stereochemistry is by single crystal X-ray analysis. All our attempts at growing crystals, however, yielded crystals that were of undefined shape, and although attempts were made at X-ray crystallography using these crystals, no data was obtained that could tell us anything about the structure of 65.

If our sample of 65 consists of 65a and 65b, then we may expect that if we raised the temperature, we would increase the frequency of N-inversion enough on an NMR time scale for the signals from the two diastereoisomers to coalesce. When the temperature was raised to 50 °C in deuteriochloroform, however, no change of the spectrum at all was observed indicating that we may expect to have to raise the temperature considerably if we are to see merging of the two signals. This may be possible if the experiment is conducted in a suitably high boiling point deuterated solvent.

Another potential method of proving the structure of 65 is by functionalisation of the nitrogen atom. If this reaction could be effected in greater than 70% yield to form a product that exists as a single diastereoisomer, then this would demonstrate that both observed isomers of NH-oxaziridine 65 (present in about 60:40 ratio) formed the same oxaziridine product, and this would prove that the isomers observed in our sample of NH-oxaziridine 65 were invertomers, and not endo/exo diastereoisomers. Further, if NH-oxaziridine 65 could be functionalised at nitrogen to form a known oxaziridine with a known stereochemistry, then this reaction could prove the stereochemistry of NH-oxaziridine 65.

If we are to functionalise the nitrogen atom of NH-oxaziridine 65 for this purpose, then the N-substituent on the nitrogen atom is important, as it influences the configuration of the nitrogen atom of the 65-derived oxaziridine, and there are two different types of N-substituent that may be useful. Firstly, assuming that the nitrogen can invert, if the N-substituent is bulky enough to favour an exclusively trans stereochemistry with the N-substituent on the opposite face of the oxaziridine ring to the quaternary carbon atom at camphor C-1, then we may expect just one invertomer of the oxaziridine to be formed. Alternatively, certain types of N-substituent could lower the barrier to nitrogen inversion enough for NMR signals from invertomers of the oxaziridine to coalesce.
Results and Discussion

Camphor-derived N-sulfonyl oxaziridine 59 has been prepared previously as a single exo N-phenylsulfonyl diastereoisomer, and although N-sulfonyl oxaziridines are known to readily invert, oxaziridine 59 exists as a single invertomer due to steric effects. Oxaziridine 59 was prepared in 62% yield from 65 as a single diastereoisomer (Scheme 109). This result is encouraging in that it indicates that oxaziridine 65 is a mixture of invertomers 65a/65b (only oxaziridine with exo nitrogen was isolated), but the yield is not high enough to say for certain whether both isomers of 65 observed by NMR spectroscopy are converted into a single isomeric product. It could therefore be argued that oxaziridine 65 is present as a mixture of endo and exo isomers, but that the endo N-phenylsulfonyl derivative is either not formed or decomposes, and therefore not observed whereas there is a high yield of the exo N-phenylsulfonyl derivative.

Functionalisation of NH-oxaziridine 65 with methyl and ethyl chloroformates to give oxaziridine products 66 and 67 respectively as single diastereoisomers in yields of 95% and 89% respectively proved that the mixture of isomers of NH-oxaziridine 65 observed by NMR spectroscopy were invertomers, and not endo/exo diastereoisomers, whereas the formation of N-phenylsulfonyl oxaziridine 59 proved that both of these invertomers of 65 had an oxaziridine nitrogen atom in the exo position (Scheme 109).

\[
\text{Scheme 109}
\]

\[\text{N-Methoxycarbonyl oxaziridine 66 is a crystalline solid at room temperature, but we were unable to obtain a crystal structure for this compound due to the fact that} \]

86
Results and Discussion

it is prone to X-ray damage and the crystal decomposes before sufficient X-ray data can be obtained. These N-functionalisation reactions along with other N-functionalisation reactions of 65 are discussed in more detail in section 2.2.2.

Fenchone nitrimine has been reported to have been prepared under exactly the same conditions as those used to prepare camphor nitrimine. We found however, that (1R)-(−)-fenchone oxime 61 was only sparingly soluble in acetic acid. (1R)-Fenchone nitrimine 68 was prepared in 70% yield, according to another literature procedure, by addition of a dilute solution of sulfuric acid to a bi-phasic mixture consisting of etheral (1R)-(−)-fenchone oxime 61 and aqueous sodium nitrite (Scheme 110). (1R)-fenchone nitrimine 68 was converted into the corresponding (1R)-fenchone imine 69 by dissolution of 68 in dry THF, and bubbling ammonia gas through the solution at 0 °C for a period of 4 hours. The reaction was worked up by removal of the solvent to furnish the imine 69 quantitatively (Scheme 110).

Like 64, imine 69 is an unstable liquid that decomposes if heated above 35 °C or is kept overnight in the freezer, and imine 69 was therefore used straight away in the next stage of the synthesis. (1R)-Fenchone imine, 69, was reacted with one equivalent of pure m-CPBA at −35 °C in dry DCM overnight. Removal of solvent, dissolving in petroleum ether, washing with 1M aqueous sodium hydroxide, and removal of the solvent, followed by flash chromatography on silica gel furnished (−)-fenchyl oxaziridine 70 as a colourless liquid in a yield of 86% (Scheme 111).
Results and Discussion

\[ \text{Scheme 111} \]

Although we have yet to prove the structure of \( NH \)-oxaziridine 70, attack of reagents upon the C-2 atom of norbornyl systems generally occurs upon the \textit{exo} face. Based upon this factor alone, we have predicted the structure of \( NH \)-oxaziridine 70 as being \textit{exo}, with an \textit{endo} N-H moiety.

Like camphor-derived oxaziridine 65, \((-\)-fenchyl oxaziridine 70 is stable for more than six months in the refrigerator. It appears that oxaziridine 70 is more stable than \((+\)-camphoryl oxaziridine 65 as it can endure refluxing conditions in toluene for more than 5 hours without any noticeable decomposition. The synthesis of 70 was carried out on a 20 g scale, and all of the steps required to prepare 70 are high yielding.

Oxaziridine 70 was shown by NMR spectroscopy to consist of two diastereoisomers, present in a ratio of about 60:40. There are four possible diastereoisomers that could be formed from this reaction if we consider that the product of \textit{endo} oxidation will have two invertomers, and similarly, that the product of \textit{exo} oxidation will also have two invertomers. Given the fact that both invertomers of 65 are observed by NMR, then the fact that only two isomers of 70 are observed points to oxaziridine 70 also being a mixture of invertomers and not a mixture of \textit{endo} and \textit{exo} oxidation products. There is as yet no proof of this proposed structure of 70.

Attempted functionalisation of the nitrogen atom of 70 with various derivatising agents has failed to give any products in greater than 70% yield. Also, a high temperature NMR experiment has been performed on 70 in deuterated DMSO (\( D_6 \)-DMSO). Oxaziridine 70 was shown to undergo a reaction with the solvent that began at between 45 °C and ended at 95 °C, when all of the oxaziridine had been consumed, and no coalescence of the signals from the two isomers was observed up to 95 °C (this reaction is further discussed in section 2.2.3). Additional evidence about the structure of \( NH \)-oxaziridine 70 was sought by performing a variable temperature
Results and Discussion

NMR experiment between room temperature and 100 °C in deuterated toluene, but no coalescence of signals was observed. Alternatively, evidence may be found by functionalising the nitrogen atom of 70 to give a single diastereoisomer of product in a yield of greater than 70% to give a product that is suitable for X-ray crystal structure analysis.

The synthesis of a chiral oxaziridine based upon (1R)-(−)-camphorquinone 57 was attempted. Camphorquinone has been successfully condensed with ammonia by heating in a sealed tube to selectively form the 3-imino product 71 (Scheme 112) in-situ, prior to further reactions. High pressures needed during the reaction, however, were deemed too unsafe for preparation of this imine. As an alternative to this procedure, (1R)-(+) -camphorquinone monoxime 60, was converted into the nitrimine. Attempted conversions using procedures that had been used previously for the preparation of more hindered nitrimines 63 and 68 resulted in hydrolysis and formation of (1R)-(−)-camphorquinone 57 as the product. (1R)-(+) -Camphorquinone mononitrimine 72 was prepared by the reaction of (1R)-(+) -camphorquinone monoxime 60 with nitrosyl sulfuric acid in the presence of pyridine in acetonitrile at room temperature in a yield of 30% (Scheme 112).

Because of the fact that the product was formed in low yield, and that purification of the product required column chromatography, and also due to time constraints, this was not seen as a viable route to the synthesis of a new oxaziridine, and nitrimine 72 was not converted into oxaziridine precursor, imine 71.
2.2.2 N-Functionalisation of Oxaziridines

After the synthesis of NH-oxaziridines 65 and 70, they were reacted with derivatising agents with the intention of forming N-functionalised oxaziridine products. There are a number of reasons for these attempts. First, as described in section 2.2.1, this could provide us with a method of proving the structures of mixtures of diastereoisomers that are formed in the synthesis of 65 and 70 respectively. Secondly, whereas N-phosphinoyl imines are known to be unstable and prone to hydrolysis, and N-acyl imines are known to be even more unstable, then, if NH-oxaziridines can be prepared easily and on a large scale, N-functionalisation may in some circumstances provide a better route for the synthesis of N-substituted oxaziridines than does oxidation of the respective N-substituted imine. Finally, N-functionalisation with a wider variety of derivatising agents could possibly provide as yet unknown classes of oxaziridines that may have interesting properties and uses.

Initially, the functionalisation of (+)-camphoryl oxaziridine 65 was attempted by reacting 65 with acyl chlorides, chloroformates, sulfonyl chlorides and diphenylphosphinic chloride, in dichloromethane at room temperature. This approach was unsuccessful, and in all cases none of the expected N-functionalised products were formed. Instead, another oxidant, 73 was formed in every case that would oxidise aqueous potassium iodide solution instantly, and convert thioanisole into its sulfoxide over a period of two weeks at room temperature (Scheme 113).
Results and Discussion

Oxidant 73 was a colourless crystalline solid that was a single isomer by NMR spectroscopy, appeared to be an isomer of (+)-camphoryl oxaziridine 65 with a molecular ion (M⁺) of 167 (EI), and did not appear to have any NH-protons (IR, NMR). In all cases, 73 was only isolated in less than 10% yield, however we were interested in what this oxidant was and how it was formed.

We thought that this product may have been formed by the reaction of some residual hydrochloric acid, present in these derivatising agents, with (+)-camphoryl oxaziridine 65. In order to test this hypothesis, oxaziridine 65 in DCM was reacted with a solution of anhydrous 1M hydrogen chloride in 1,4 dioxane at -40 °C. A fast reaction ensued that was indicated by the immediate formation of a small amount of white inorganic precipitate, and the reaction had reacted to completion within five minutes (tlc). As expected, oxidant 73 was formed in a yield of 29%, but (1R)-(+) camphor 56 was also isolated from the reaction mixture in a yield of 36% (Scheme 114).

\[
\text{Oxaziridine 65 + HCl, 1,4-dioxane, DCM \rightarrow Oxidant 73 + (1R)-(+) Camphor 56}
\]

Scheme 114

It therefore appeared that the formation of 73 was due to the presence of acid in the reaction mixture, and so therefore, for all subsequent attempted N-functionalisation reactions, a stoichiometric amount of base was employed.

After many attempts at recrystallisation of 73, the structure of oxidant 73 was finally elucidated by X-ray crystallography, and was shown to be (-)-N-chlorocamphoryl oxaziridine (see Figure 5 for representation of the structure of 73 and see appendices for the X-ray data generated structure of 73).
The formation of (-)-N-chlorocamphoryl oxaziridine 73 by the reaction of oxaziridine 65 with hydrogen chloride raise the question of how 73 is formed, as hydrogen chloride does not generally act as an electrophilic chlorinating agent. Is therefore possible that the first step in this reaction is the formation of a chlorinating agent (such as hypochlorous acid) by oxidation of hydrogen chloride. The oxidising agent for this step could either be (+)-camphoryl oxaziridine 65 itself, or 65 that has been N-protonated by hydrogen chloride to form a highly reactive oxaziridinium salt, and the product of this oxidation would either be (1R)-(+)­camphor 56, or a material that could be readily hydrolysed to 56, such as an unfunctionalised iminium salt. The chlorinating species formed by this reaction could then react with further 65 to form N-chlorocamphoryl oxaziridine 73. This type of mechanism would account for the isolation of an approximately 1:1 ratio of N-chloro oxaziridine 73 to (1R)-(+)­camphor 56, from the product mixture (Scheme 115).

$\text{NH}$

\[ \begin{array}{c}
65 \\
\text{O}
\end{array} \]

or

$\text{CH}_2$ \hspace{1cm} $\text{Cl}$

\[ \begin{array}{c}
N^+ \text{H} \text{H} \\
\text{O}
\end{array} \]

$\text{HCl}$ \hspace{1cm} $\text{Electrophilic}$ \hspace{1cm} $\text{Chlorine}$ \hspace{1cm} $\text{Species}$

$\text{NH}$

\[ \begin{array}{c}
65 \\
\text{O}
\end{array} \]

\[ \begin{array}{c}
\text{NH}$

$\text{H}$

\[ \begin{array}{c}
\text{O}
\end{array} \]

$\text{Cl}$

\[ \begin{array}{c}
\text{O}
\end{array} \]

Scheme 115

N-Chloro oxaziridine 73 was also prepared by the reaction of tert-butyl hypochlorite with (+)-camphoryl oxaziridine 65 in diethyl ether at -78 °C in a yield
Results and Discussion

of 85% (Scheme 116). Tert-butyl hypochlorite is not commercially available, and must be prepared by the reaction of tert-butyl alcohol with chlorine in an aqueous solution of sodium hydroxide (Scheme 116).126

\[
\text{tBuOH} \xrightarrow{\text{Cl}_2, \text{NaOH}, \text{H}_2\text{O}, \text{r. temp}} \text{tBuOCl} \quad 72\%
\]

\[
\text{65} \xrightarrow{\text{tBuOCl, Et}_2\text{O}, -78^\circ\text{C}} \text{73} \quad 85\%
\]

Scheme 116

We thought that it would be useful to synthesise \textit{N}-sulfonyl oxaziridines by \textit{N}-functionalisation of \textit{N}-unsubstituted oxaziridines. First, as described in section 2.2.1, this derivatisation could provide a method of proving the structure of 65 by the alternative preparation of known \textit{N}-sulfonyl oxaziridines with known stereochemistries. Secondly, although conventional syntheses of chiral \textit{N}-sulfonyl oxaziridines are generally well developed and high yielding processes, \textit{N}-functionalisation could provide us with a convenient alternative route to the synthesis of other potentially useful \textit{N}-sulfonyl oxaziridines.

We further thought that derivatisation of 65 with phenylsulfonyl chloride would be very useful in proving the stereochemistry of 65, as the expected product \((-\text{)}-\textit{N}-(\text{phenylsulfonyl})\text{camphoryl oxaziridine} 59\) is a known compound that has been well characterised.109 Reaction of 65 with phenylsulfonyl chloride was investigated, and best yields of 59 were formed when DMAP was employed as a stoichiometric base. This reaction was at best sluggish, and at room temperature after a period of ten days in DCM, 59 was formed as a single isomer in a yield of 62% (Scheme 117). The functionalisation of 65 to give \((-\text{)}-\textit{N}-(\text{methanesulfonyl})\text{camphoryl oxaziridine} 74\) was also attempted. Methanesulfonyl chloride was reacted with oxaziridine 65 in the presence of a stoichiometric amount of dry pyridine in DCM over a period of 2 days at room temperature to give a mixture of \textit{N}-methanesulfonyl oxaziridine 74 and \textit{N}-chloro oxaziridine 73 in yields of 42% and 15% respectively (Scheme 117). Like 59, 74 was shown to be a single isomeric product by NMR spectroscopy.
Results and Discussion

\[
\begin{align*}
\text{PhSO}_2\text{Cl}, \text{ DMAP, DCM,} & \quad r. \text{ temp, 10 days} \\
 \text{65} & \rightarrow \text{59} \quad 62\%
\end{align*}
\]

\[
\begin{align*}
\text{MeSO}_2\text{Cl, pyridine, DCM,} & \quad r. \text{ temp, 2 days} \\
 \text{65} & \rightarrow \text{74} \quad 42\% + \text{73} \quad 15\%
\end{align*}
\]

Scheme 117

The derivatisation of 65 with triflic anhydride was then attempted. We felt that \(N\)-(trifluoromethanesulfonyl)camphoryl oxaziridine 75 would be more electrophilic, and therefore more reactive than other \(N\)-sulfonyl oxaziridines that have been prepared because of the strongly electron withdrawing group attached to the oxaziridine nitrogen atom. This could therefore be potentially useful for oxidation of less reactive nucleophiles such as alkenes. Reaction of 65 with triflic anhydride at \(-40^\circ\)C in dichloromethane gave complete conversion of 65 to a new compound that was visualised by tlc, and by analysis with potassium iodide solution appeared to be an oxidant (Scheme 118). On work up followed by attempted purification by chromatography, however, this new compound was not recovered. It is likely therefore, that oxaziridine 75 was produced, but decomposes either under reaction conditions, or during the work-up.

\[
\begin{align*}
\text{65} & \rightarrow \text{75} \quad \text{Decomposes on Work up}
\end{align*}
\]

Scheme 118

The synthesis of chiral \(N\)-alkoxycarbonyl and \(N\)-acyl oxaziridines was thought to be of potential value due to the success of these types of reagents in electrophilic
Results and Discussion

amination reactions (discussed in section 1.2.13, part (c)). Because of the instability of N-acyl imines, N-functionalisation was deemed to be the best route to the syntheses of these compounds.

A number of different conditions and potential derivatising agents were investigated in the attempted syntheses of N-alkoxycarbonyl camphor-derived oxaziridines. The functionalisation of oxaziridine 65 with methyl and ethyl chloroformates in the presence of dry pyridine in dry dichloromethane at between 0 °C and room temperature gave (−)-N-(methoxycarbonyl)camphoryl oxaziridine 66 and (−)-N-(ethoxycarbonyl)camphoryl oxaziridine 67 respectively in yields of 95% and 89% respectively (Scheme 119).

![Scheme 119](image)

The synthesis of 66 and 67 was important for two reasons. Firstly, the fact that 66 and 67 were formed as single diastereoisomers in such high yields proves that NH-oxaziridine 65 exists as a pair of invertomers, as both isomers in the mixture of our sample of 65 react to form the same product (see section 2.2.1). Secondly, 66 and 67 are the first reported examples of chiral N-alkoxycarbonyl oxaziridines that have been prepared in an enantiomerically pure form. The synthesis of N-Boc protected 65 was attempted using di-tert-butyl dicarbonate in dichloromethane at room temperature, however, 65 appeared to be completely inert under these conditions (Scheme 120). Oxaziridine 65 was also reacted with 4-nitrophenyl chloroformate under the same conditions as those used for the preparation of 66 and 67, but all of the products of this reaction appeared to be unstable (Scheme 120).
Results and Discussion

The preparation of N-acyl derivatives of 65 was also attempted. Oxaziridine 65 was treated with acyl chlorides in the presence of DMAP in DCM at room temperature (Scheme 121). In all cases, it was found that all of the oxaziridine starting material was converted into a new material, which by tlc and potassium iodide analysis appeared to be a new oxidant (presumably the N-acyl oxaziridine). This new oxidant, however, was also accompanied by trace amounts of a side product, and, on attempted isolation of the main (oxidant) product by chromatography on both silica gel and basic alumina, all that was isolated was the side product, although in much larger quantities than expected. It appeared, therefore, that the side product formed during this reaction was a decomposition product of the N-acyl oxaziridine, and that these N-acyl oxaziridines were unstable towards chromatography. This finding seems to be contrary to literature reports, which claim that N-acyl oxaziridines previously prepared are more stable than analogous NH-compounds.87,97

The decomposition products isolated from these reactions appeared to be, in all cases, isomers of the corresponding N-acyl oxaziridine, and from each reaction, two inseparable isomers (76a/76b and 77a/77b) were recovered, present in a 1:1 ratio (Scheme 121).
Results and Discussion

\[ \text{Scheme 121} \]

Initially the two compounds observed were thought to be formed as a result of rearrangement of the camphor ring system (Scheme 122), and there are two reasons for this.

\[ \text{Scheme 122} \]

Firstly, this type of oxaziridine to lactam rearrangement is known to occur. Secondly, similar intermediates to the ones shown in Scheme 122 have been proposed for the decomposition of what was thought to be an oxaziridine intermediate during the photolysis of camphor oxime, a reaction which then went on to form the same N-unfunctionalised lactams as those shown in Scheme 122.

We attempted to prove the structures of products 76a/76b and 77a/77b in a number of ways. First, we assumed that we had synthesised N-acyl lactams as proposed in Scheme 122, and we attempted deprotection of their acyl functionalities. Attempted deprotection of 76a/76b and 77a/77b with aqueous acid failed to give anything other than starting material, and attempted deprotection with aqueous sodium hydroxide gave complex mixtures of products.
We also attempted the synthesis of both of the isomers of what we thought were 77a and 77b by alternative methods. Firstly, (-)-α-camphidone 78 was synthesised by the reaction of (1R)-(+) -camphor 56 with hydroxylamine-O-sulfonic acid in formic acid under refluxing conditions to give (-)-α-camphidone 78 in a 37% yield\(^{113}\) (Scheme 123). (-)-α-Camphidone 78 was then acylated with 4-nitrobenzoyl chloride in the presence of pyridine under refluxing conditions in chloroform over 24 hours to give (-)N-(4-nitrobenzoyl)-α-camphidone 79 in a yield of 62% (Scheme 123).

\[\text{Scheme 123}\]

An isomer of α-camphidone, lactam 80 ((1R)-1,8,8-trimethylbicyclo[3.2.1]octan-3-one), was synthesised by Beckmann rearrangement of (1R)-(−)-camphor oxime 62 using methanesulfonyl chloride in pyridine at between -22 °C and room temperature, and in a yield of 4.7% (Scheme 124).\(^{113,128}\) Isomeric lactam 80 was then acylated with 4-nitrobenzoyl chloride in the presence of pyridine under refluxing conditions in toluene overnight to give N-acyl lactam (−)-81 in a yield of 72% (Scheme 124).

\[\text{Scheme 124}\]
Results and Discussion

*N-Acyl lactams, \((-\)-81 and \((-\)-79 were compared with the mixture of products 77a/77b formed by attempted 4-nitrobenzoylation of oxaziridine 65, and neither 81 nor 79 were shown to be a component of this mixture of compounds.*

*N-Acyl oxaziridines have been shown to decompose in a number of different ways.\(^{129}\) One is by ring expansion of the oxaziridine ring to form five-membered 1,4,2-dioxazole compounds.\(^{129a}\) Although this type of rearrangement generally requires heating in pyridine, we felt that mixtures of compounds 76a/76b and 77a/77b could be products of this type of rearrangement (Scheme 125).

![Scheme 125](image)

\[65 \rightarrow \begin{array}{c}
\text{Scheme 125}
\end{array}\]

In order to test this hypothesis, we attempted to synthesise either isomer of 1,4,2-dioxazole 76a/76b independently by addition of benzonitrile oxide to \((1R)-(+)\)-camphor 56. Benzohydroximinoyl chloride was prepared by the reaction of benzoaldehyde oxime with *N*-chlorosuccinimide (NCS) in DMF at below 40 °C in a yield of 75% (Scheme 126).\(^{130}\) Benzohydroximinoyl chloride was then treated with triethylamine in petroleum ether at room temperature to form benzonitrile oxide *in situ* in the presence of \((1R)-(+)\)-camphor 56. The reaction mixture was left overnight, and on work up, \((1R)-(+)\)-camphor 56 was recovered and no products of cycloaddition to 56 were observed (Scheme 126).
Results and Discussion

1,4,2-Dioxazoles such as 76a/76b and 77a/77b have been shown to undergo deprotection to give the parent ketone and an amide by hydrogenolysis in the presence of metal catalysts. Accordingly, mixtures 76a/76b and 77a/77b were treated with hydrogen at ambient pressure and at room temperature in ethyl acetate in the presence of palladium on carbon over a period of six days. Deprotection of the N-4-nitrobenzoyl oxaziridine decomposition product 77a/77b under these conditions failed, the reaction perhaps affected by the nitro substituent on the phenyl ring. The N-benzoyl oxaziridine decomposition product 76a/76b, however, was deprotected to give benzamide in a 47% yield together with (1R)-(+)-camphor 56 in a yield of 94%, and this leads us to conclude therefore, that the structures of components of mixture 76a/76b are the proposed 1,4,2-dioxazoles (Scheme 127).

It is possible that the decomposition process to give 76a/76b and 77a/77b is analogous to the carbocyclic vinyl cyclopropane rearrangement. If so, we would expect a single isomer of 65-derived N-acyl oxaziridine to decompose to give a singe isomer of 1,4,2-dioxazole if this process is concerted. This is because we would expect oxo-attack from the carbonyl moiety of the N-acyl substituent on the oxaziridine ring to cause oxaziridine C-N bond fission to occur from one face. The
Results and Discussion

The fact that two isomers of decomposition product are observed from a single isomer of N-acyl oxaziridine suggests that this process involves some sort of intermediate and is not concerted (Scheme 128). The intermediates for this decomposition are shown as products of heterolytic bond cleavage, there is, however, nothing to suggest that these intermediates are not radical species.

Scheme 128

One observation made about this decomposition was that it appeared to be accelerated by silica gel. We therefore endeavoured to devise methods of preparation of N-acyl oxaziridines derived from 65 that did not require column chromatography. All methods that involved derivatisation of NH-oxaziridine 65 with an acid chloride in the presence of a base yielded impure products that after simple work up required further purification by chromatography. We then attempted acylation of 65 using acid anhydrides. It was found that acylation of 65 with acetic anhydride at room temperature in DCM overnight in the absence of a base could be achieved in 97% yield without the need for chromatography, to give (-)-N-acetylcamphoryl oxaziridine 82 as a semi-stable oil that could be kept for up to three days in the refrigerator without noticeable decomposition (Scheme 129). (-)-N-acetylcamphoryl oxaziridine 82 was then isomerised to a 1:1 mixture of endo and exo-5-camphoryl-3-methyl-1,4,2-dioxazoles 83a/83b in a yield of 90%, by stirring overnight with silica gel in DCM at room temperature (Scheme 129). Oxaziridine 82 is the first reported example of a chiral N-acyl oxaziridine that has been prepared in its enantiomerically pure form.
This experiment was repeated using benzoic anhydride. (+)-Camphoryl oxaziridine 65 was reacted with benzoic anhydride in DCM at room temperature, and the reaction took three days to react to completion. After work-up of the reaction, the products were isolated as a mixture of three compounds. The components of this mixture included both endo and exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b that had been prepared and characterised previously, and another compound that we suspected to be N-benzoylcamphoryl oxaziridine 84, present in yields of 34% and 51% respectively. This mixture was then treated with silica gel in DCM at room temperature overnight to give 1,4,2-dioxazoles 76a/76b in a 1:1 ratio, and in an overall yield of 64% from (+)-camphoryl oxaziridine 65 (Scheme 130).

\textit{N}-Phosphinoyl oxaziridines are another class of \textit{N}-functionalised oxaziridine that may be of potential use as electrophilic oxidising agents. It has been claimed that these reagents are capable of epoxidation of alkenes,\textsuperscript{78a} and an investigation into their potential development as chiral reagents for sulfoxidation reactions has been
Results and Discussion

reported. There have been only two examples of chiral $N$-phosphinoyl oxaziridines reported in the literature, and both of these reagents contain just one chiral centre at the phosphorus atom of the molecule. Attempted asymmetric induction with both of these reagents gave poor to moderate enantioselectivities, and the yields for these reactions are not reported.

The synthesis of $N$-(diphenylphosphinoyl)camphor imine has been reported in an article that describes the synthesis of both $N$-phosphinoyl and $N$-sulfonyl imines as precursors for oxidation to $N$-phosphinoyl and $N$-sulfonyl oxaziridines respectively. It appears however, that the oxaziridine that would be derived from oxidation of this camphor-derived imine, $N$-(diphenylphosphinic)camphoryl oxaziridine 85, has not been reported either in this paper or elsewhere in the literature. Attempted oxidation of $N$-(diphenylphosphinoyl)camphor imine by members of our group using a variety of different methods failed yield any oxaziridine at all (Scheme 131). This may suggest that this imine is too hindered for reaction with conventional oxidising reagents. We were able to synthesise (−)-$N$-(diphenylphosphinic)camphoryl oxaziridine 85 by functionalisation of (+)-camphoryl oxaziridine 65 with diphenylphosphinic chloride in the presence of DMAP in DCM overnight in a yield of 37% (Scheme 131).

We then investigated the reactivity of oxaziridine 85 with several different nucleophiles. Oxaziridine 85 would not epoxidise alkenes under refluxing conditions overnight in toluene. When oxaziridine 85 was employed with a number of prochiral...
aromatic sulfides at room temperature in DCM over 1 week, only trace amounts of product with certain sulfides appeared to have been formed by tlc. It appears therefore that (-)-N-(diphenylphosphinic)camphoryl oxaziridine 85 is much less reactive than other previously reported N-phosphinoyl oxaziridines, perhaps because oxaziridine 85 is much more hindered.

Because of the lack of reactivity of 85, the syntheses of other less hindered N-phosphinoyl oxaziridines were attempted. (+)-Camphoryl oxaziridine 65 was treated with dimethylphosphinic chloride in the presence of DMAP in DCM at room temperature for two hours to give a product thought to be N-(dimethylphosphinic)camphoryl oxaziridine. The product of this reaction, however, was unstable and decomposed before we could obtain any data (Scheme 132). The reaction of NH-oxaziridine 65 with 1,2-phenylene-phosphorochloridate was attempted in DCM in the presence of DMAP at room temperature in an attempt to form a new type of oxaziridine, however this reaction was very slow, and over four days gave a complex mixture of products (Scheme 132).

Because we believed that N-functionalisation could provide a route to new classes of oxaziridine with as yet unknown and potentially useful properties, we attempted to synthesise N-(trimethylsilyl)camphoryl oxaziridine. (+)-Camphoryl oxaziridine 65 was inert to chlorotrimethylsilane (TMSCI) in DCM at room temperature in the presence of DMAP over a period of one week. The reaction of 65

\[ \text{Scheme 132} \]
Results and Discussion

with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of DMAP over four days yielded a mixture of unstable products (Scheme 133).

The reaction of (+)-camphoryl oxaziridine 65 with pentafluorobenzenesulfenyl chloride in the presence of pyridine at room temperature over 1 hour gave a number of different products. From this reaction mixture, dipentafluorophenyl disulfide was isolated in a yield of 20%, (+)-(S)-pentafluorophenylcamphor thiooxime 86 in a yield of 10%, (1R)-(+)camphor 56 in a yield of 28%, and (-)-N-(pentafluorophenylsulfenyl)camphoryl oxaziridine 87 in a yield of 41% (Scheme 134).

(-)-N-(Pentafluorophenylsulfenyl)camphoryl oxaziridine 87 is a semi-stable solid that can be kept in the refrigerator for up to two weeks without decomposition, and is the first reported example of an N-sulfenyl oxaziridine.
Results and Discussion

We also attempted the preparation of a derivatives of (-)-fenchyl oxaziridine 70. Attempted conversion of 70 to N-sulfonyl oxaziridines using tosyl chloride or methanesulfonyl chloride in the presence of DMAP failed to yield any oxaziridine at all. The reaction of (-)-fenchyl oxaziridine 70 with methyl chloroformate in dry DCM in the presence of dry pyridine gave a mixture of N-(methoxycarbonyl)fenchyl oxaziridine 88 (19\% yield) and (1R)-(−)-fenchone 55 (19\% yield), together with a mixture of N-chlorofenchyl oxaziridines 89a/89b in 16\% overall yield (Scheme 135).

\[
\begin{align*}
\text{MeOCOCI, pyridine, DCM, r. temp} & \quad \text{N, 0} \\
\begin{array}{c}
\text{70} \\
\text{DCM, r. temp} \\
\text{MeOCOCI, pyridine, DCM, r. temp} \\
\end{array} & \quad \begin{array}{c}
\text{88 19\%} \\
\text{55 19\%} \\
\text{89a/89b 16\%} \\
\end{array}
\end{align*}
\]

Scheme 135

Oxaziridine 88 was formed as a single diastereoisomer. This implies the fact that NH-oxaziridine 70 exists as diastereoisomers due to inversion of the nitrogen atom, and not because of endo and exo isomerism. There is as yet no conclusive proof of this fact however, because our sample of (-)-fenchyl oxaziridine was a mixture of diastereoisomers, present in a ratio of about 60:40, and the yield of the N-Moc oxaziridine 88 was too low to say that both isomers of starting material reacted to form the same product.

In general, N-chloro oxaziridines are known to be configurationally stable.\textsuperscript{133} N-Chloro oxaziridines 89a/89b were shown by \textsuperscript{1}H NMR spectroscopy to be a mixture of two diastereoisomers present in a ratio of 4:1. This is significant, because the carbon atoms of the oxaziridine rings of 89a and 89b are adjacent to two quaternary carbon centres. This means that the configurationally stable N-chloro substituents of oxaziridines 89a and 89b will have similar steric interactions if transposed upon either face of the oxaziridine ring, and so because of this, unlike N-chloro oxaziridine 73, we may expect both inverteromers of the N-chloro oxaziridines 89a/89b to be formed. We may expect, therefore, that if both endo and exo NH-oxaziridines are converted to their N-chloro analogues, that four diastereoisomers would be formed by this reaction (two inverteromers formed from each endo and exo isomers), and therefore
the fact that only two isomers were formed implies that the diastereoisomerism observed in the starting material ((-)-fenchyl oxaziridine 70) is due to nitrogen inversion and not the presence of endo and exo isomers of the oxaziridine.

One observation that was made was that oxaziridines 89a/89b are unstable, and upon isolation immediately appear to begin to decompose (by tlc). The most common decomposition reaction of N-chloro oxaziridines that has been reported is their decomposition to alpha-chloronitroso compounds (Scheme 136). These alpha-chloronitroso compounds have a characteristic blue colour as well as a characteristic N=O absorption chromophore in their IR spectrum.

The IR spectrum from this isolated mixture of N-chloro oxaziridines 89a/89b immediately upon isolation also displayed a weak, but, characteristic N=O absorption peak that we would expect from an alpha-chloronitrosyl compound. As well as this, oxaziridines 89a/89b are blue, and, the 1H NMR spectrum of 89a/89b showed some evidence of trace amounts of decomposition products immediately upon isolation.

N-Chloro oxaziridines 89a/89b were also prepared by reaction of (-)-fenchyl oxaziridine 70 with tert-butyl hypochlorite at between -78 °C and room temperature in diethyl ether over a period of 5 hours and in a yield of 46% (Scheme 137).
Results and Discussion

2.2.3 Electrophilic Amination with Oxaziridines

(+)Camphoryl oxaziridine 65 was initially tested for reactivity with nucleophiles that were known to be successful in amination reactions using cyclohexanone-derived oxaziridine 34. Unlike oxaziridine 34, (+)-camphoryl oxaziridine 65 is completely unreactive towards aryl and alkyl alkenes under refluxing conditions in THF over a period of 12 hours (Scheme 138). Attempted reaction by reflux in higher boiling point solvents brought about decomposition of 65. (+)-Camphoryl oxaziridine 65 was also found to be unreactive towards thioanisole under refluxing conditions in THF over 12 hours (Scheme 138).

\[
\begin{align*}
\text{R}^1 &= \text{Ph, R}^2 = \text{R}^3 = \text{H;} \\
\text{R}^1 &= \text{Ph, R}^2 = \text{R}^3 = -\text{(CH}_2\text{)}_4-; \\
\text{R}^1 &= \text{Me, R}^2 = \text{R}^3 = -\text{(CH}_2\text{)}_4-
\end{align*}
\]

Scheme 138

It was found that camphor derived oxaziridine 65 would not react under the same conditions with the same stabilised carbanions (such as Meldrum's acid or barbituric acid) as does cyclohexanone-derived oxaziridine 34 (Scheme 139).

\[
\begin{align*}
\text{65, toluene, NaOH}_{\text{(aq)}} & \rightarrow \text{No Reaction} \\
\text{65, toluene, NaOH}_{\text{(aq)}} & \rightarrow \text{No Reaction}
\end{align*}
\]

Scheme 139
Results and Discussion

Due to the apparent lack of reactivity of 65, a number of different nucleophiles were then investigated in order to see what types of nucleophiles would react with 65.

Oxaziridine 65 was investigated for reactivity with electron deficient alkenes. Acrylonitrile and methyl vinyl ketone were each heated under reflux with 65 in THF for 15 hours, and oxaziridine 65 was found to be unreactive with these alkenes under these conditions (Scheme 140).

Reactions of (+)-camphoryl oxaziridine 65 with electron rich alkenes were also investigated. Both 4(1-cyclopenten-1-yl)morpholine and 1-cyclohexenyloxytrimethylsilane were heated under reflux in THF in the presence of oxaziridine 65 overnight without any reaction products being detected (Scheme 141).

We further investigated the reactivity of 1-cyclohexenyloxytrimethylsilane, and attempted to increase the reactivity of the system by adding a Lewis acid. Titanium (IV) chloride brought about rapid decomposition of both the silyl enol ether
Results and Discussion

and oxaziridine 65 in DCM at -78 °C. Zinc bromide and zinc chloride brought about decomposition of both 1-cyclohexenylmethytrimethylsilane and oxaziridine 65 within two days at room temperature in DCM to give complex mixtures of products. In another experiment, methyl lithium was reacted with 1-cyclohexenylmethytrimethylsilane at -78 °C in THF to form the lithium enolate of cyclohexanone, (+)-camphoryl oxaziridine 65 was introduced, and the reaction mixture allowed to reach room temperature over a period of two hours. Imines 90a/90b (the condensation products of 2(R)- and 2(S)-aminocyclohexanones and camphor) were isolated in an overall yield of 8%, as a mixture of two inseparable diastereoisomers, present in a ratio of 1:1. (Scheme 142).

The reaction between (+)-camphoryl oxaziridine 65 and malonate esters was next investigated. Dimethyl malonate was reacted with (+)-camphoryl oxaziridine 65 in the presence of an excess of sodium methoxide in methanol at room temperature over a period of 2 hours. The product of this reaction, imine 91 (the condensation product of glycine methyl ester and camphor), had undergone decarboxylation and was formed in a yield of 77% (Scheme 143). Similarly, diethyl malonate was reacted with oxaziridine 65 in the presence of sodium ethoxide in ethanol at room temperature over a period of two hours to form imine 92 (the condensation product of glycine ethyl ester and camphor) in a yield of 66% (Scheme 143). Again, the product of this reaction had undergone decarboxylation.
We were interested in the process by which the products of these amination reactions had undergone decarboxylation. Although decarboxylation of malonates is generally associated with decarboxylation of the free acid under acidic conditions, malonate esters have been known to decarboxylate under basic conditions in the presence of alkoxide base (Scheme 144).\textsuperscript{134}

In order to investigate whether this decarboxylation process is due to the presence of an excess of sodium alkoxide base, dimethyl malonate was deprotonated under kinetic conditions using one equivalent of LiHMDS at \(-78\,^{\circ}\text{C}\) in THF over 20 minutes, and this lithium enolate was then reacted at room temperature with (+)-camphoryl oxaziridine 65 overnight. We reasoned that this reaction would generate one equivalent of lithium hydroxide in THF at room temperature, which would be unlikely to bring about decarboxylation in the product of this amination reaction. The decarboxylated amination product 91 was isolated from this reaction in a yield of 69\% (Scheme 145) and no non-decarboxylated products of amination were observed. This indicates that decarboxylation of the amination product may not be caused by the presence of base, and may occur by an alternative mechanism such as the one proposed in Scheme 145, involving a cyclic intermediate.
Results and Discussion

The attempted amination of dimethyl malonate at room temperature in THF using triethylamine as a base, and then under refluxing conditions overnight, was found to be unsuccessful. Given that deprotonation of the malonate using a sodium alkoxide base in alcohol, and reaction of this enolate at room temperature with oxaziridine 65, had been established as the best reaction conditions so far for the amination of malonates, the amination of various diethyl substituted malonates was attempted under the same conditions. As the products of these reactions would be imines of α-amino esters, we hoped that the camphor moiety might induce some chirality into these reactions.

Diethyl substituted malonates were reacted with (+)-camphoryl oxaziridine 65 in the presence of an excess of sodium ethoxide in ethanol at room temperature for between 4 and 24 hours. All of these malonates were found to be reactive except for diethyl tert-butyl malonate which was found to be completely unreactive under these conditions over several days at room temperature. The products of these reactions, camphor imines of α-substituted ethyl glycinates 93a/93b to 96a/96b, were formed in yields of between 42% and 89% (Scheme 146).
Results and Discussion

Scheme 146

<table>
<thead>
<tr>
<th>Imine Product</th>
<th>R</th>
<th>Reaction Time (h)</th>
<th>Yield (%)</th>
<th>dr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>93a/93b</td>
<td>Me</td>
<td>4</td>
<td>89</td>
<td>1:1</td>
</tr>
<tr>
<td>94a/94b</td>
<td>Et</td>
<td>5</td>
<td>77</td>
<td>1:1</td>
</tr>
<tr>
<td>95a/95b</td>
<td>Allyl</td>
<td>5</td>
<td>80</td>
<td>1:1</td>
</tr>
<tr>
<td>96a/96b</td>
<td>Ph</td>
<td>24</td>
<td>42</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Disappointingly, the diastereoisomeric ratios of all of the imino products were all 1:1, and no stereocontrol at all was achieved in these reactions. As expected, all of the products of amination had undergone decarboxylation. Because the product of decarboxylation is initially an enolate, then any diastereoisomeric excesses seen in the product would be brought about in this subsequent reaction as a result of diastereoselective reprotonation of this enolate, and not by initial enantioselective amination of the nucleophile (Scheme 147).
Results and Discussion

Because some success had been achieved in the amination of enolates of malonates, we examined other bis-activated carbanions as substrates for amination reactions using (+)-camphoryl oxaziridine 65.

3-Ketoesters were investigated for their reactivity with (+)-camphoryl oxaziridine 65. Ethyl-2-methyl acetoacetate was reacted with oxaziridine 65 in the presence of sodium ethoxide in ethanol at room temperature over a period of 5 hours to form the camphor imines of 3(R)- and 3(S)-amino-butan-2-one 97a/97b in an overall yield of 21%. The product was shown to be a mixture of inseparable diastereoisomers present in a ratio of 1:1 (Scheme 148), and also appeared to contain other impurities.

![Scheme 148]

When ethyl-2-benzylacetoacetate and ethyl-2-cyclohexanonecarboxylate were reacted with oxaziridine 65 under the same conditions, however, complex mixtures of inseparable products were isolated from the reaction mixture (Scheme 149).

![Scheme 149]

In order to simplify our investigation into these reactions, the reaction of (+)-camphoryl oxaziridine 65 was investigated with ethyl acetoacetate. Ethyl...
Results and Discussion

Acetoacetate in the presence of a triethylamine base under refluxing conditions in THF over three hours did not react with 65. In ethanol at room temperature using sodium ethoxide as a base, ethyl acetoacetate did react with (+)-camphoryl oxaziridine 65 to form a complex mixture of products. However, when ethyl acetoacetate was deprotonated using LiHMDS in THF at -78 °C, and (+)-camphoryl oxaziridine 65 was added to the reaction mixture, and the mixture stirred at room temperature overnight, the camphor imine of ethyl glycinate 92 was isolated in a yield of 52% (Scheme 150).

\[
\text{O} \quad \text{O} \quad \text{OEt} \quad \text{1. LiHMDS, -78 °C} \quad \text{O} \quad \text{O} \quad \text{OEt}
\]

\[
\text{2. 65, r. temp} \quad \text{92 52%}
\]

Scheme 150

It appears that under kinetic conditions, the product of the reaction exclusively undergoes scission to lose an acetate anion to form 92, and does not undergo decarboxylation as was expected.

3-Ketoesters have been shown to undergo scission under a variety of different conditions to form either decarboxylated products, products of retro-Claisen type reactions, or mixtures of both types of product. In general, decarboxylation of acetoacetate derivatives has been shown to be the predominant product of scission for the free acid under acidic conditions, whereas, under basic conditions, this type of retro-Claisen product or mixtures of products are formed (Scheme 151).
Results and Discussion

This retro-Claisen scission process and decarboxylation may both occur during amination reactions of 3-keto esters, and this may in part contribute to the observation that complex mixtures of products were observed in many cases.

Pentane-1,3-dione, another similar bis-activated carbon nucleophile, was investigated for reaction with oxaziridine 65. The reaction of pentane-1,3-dione with (+)-camphoryl oxaziridine 65 in the presence of sodium methoxide in methanol gave a complex mixture of products. When pentane-1,3-dione was deprotonated using LiHMDS at −78 °C in THF, and oxaziridine 65 was added to the reaction mixture, a similar complex mixture of products was formed (Scheme 152).

The reaction of oxaziridine 65 was investigated with simple esters. This reagent was completely unsuccessful in the amination of all ester enolates apart from one. Ethyl phenyl acetate was deprotonated using LiHMDS at −78 °C in THF, and the enolate reacted with (+)-camphoryl oxaziridine 65 at between −78 °C and room temperature over a period of eight hours to give what we suspect are imino compounds 98a and 98b as a mixture of inseparable diastereoisomers in a 1:1 ratio in an overall yield of 12%. These products were accompanied by the decarboxylation product of 98a and 98b, (1R)-N-benzyl camphor imine 99 in a yield of 5.5% (Scheme 153).
Results and Discussion

(1R)-Camphor imines of (2R)- and (2S)-phenylglycine 98a/98b were found to be unstable, and decomposed, even at −20 °C, to give imine 99 over a number of hours. It is because of this that we were unable to obtain sufficient data for 98 to be able to confirm this structure confidently.

The reaction of (+)-camphoryl oxaziridine 65 with ketones was subsequently investigated. First, the reaction between oxaziridine 65 and propiophenone was attempted under various conditions. It was found that in the presence of triethylamine, under refluxing conditions in THF over three hours, propiophenone did not react with oxaziridine 65. Propiophenone also did not react with oxaziridine 65 in methanol in the presence of sodium methoxide at room temperature overnight. When propiophenone was deprotonated using sodium hydride in THF at −78 °C, and (+)-camphoryl oxaziridine 65 was added, and the reaction mixture was stirred at between −78 °C and room temperature over 5 hours, the camphor imines of 2(R)- and 2(S)-amino propiophenone 100a/100b were isolated in an overall yield of 39% as a mixture of inseparable diastereoisomers in a 1:1 ratio (Scheme 154). When the reaction was repeated using LiHMDS as a base instead of sodium hydride, the same diastereoisomeric products 100a/100b were obtained in a diastereoisomeric ratio of 1:1 and in a yield of 60% (Scheme 154).
Results and Discussion

The electrophilic amination of a number of different ketones using oxaziridine 65 was then attempted. Ketones were deprotonated using LiHMDS in THF at \(-78^\circ C\) and then treated with (+)-camphoryl oxaziridine 65 at between \(-78^\circ C\) and room temperature for between 5 and 20 hours. Both indan-1-one and \(\alpha\)-tetralone appeared to have reacted within five hours to form a single product by tlc. These products, however, decomposed before they could be isolated, and are unstable (Scheme 155).

\[
\begin{align*}
\text{Scheme 155}
\end{align*}
\]

The reaction of cyclohexanone under the same conditions over 5 hours gave the camphor imines of 2(R)- and 2(S)-aminocyclohexan-1-one 90a and 90b as an inseparable mixture in an overall yield of 21\%, and in a diastereoisomeric ratio of 1:1 (Scheme 156).

\[
\begin{align*}
\text{Scheme 156}
\end{align*}
\]

The lithium enolate of 1-methylindan-1-one was reacted with oxaziridine 65 overnight under these conditions to form an inseparable mixture of diastereoisomeric imines of camphor and 2(R)- and 2(S)-amino-2-methylindan-1-one 101a/101b in a diastereoisomeric ratio of 1:1 and in an over all yield of 13\%. Also, the free amine, 2-amino-2-methylindan-1-one 102 was isolated in a yield of 65\% with an
Results and Discussion

Enantiomeric excess of 0%. There is evidence (1H and 13C NMR, IR), that the mixture of isomeric imines 101a/101b contains a small amount of the O-transfer product, 2-methylindan-2-ol-1-one 103, and, if this is the case, then this is the first time that oxygen transfer has been observed from an NH-oxaziridine (Scheme 157).

Scheme 157

Nitrile stabilised carbanions were also investigated for their reaction with (+)-camphoryl oxaziridine 65 under the same conditions as those used for the amination of ketone enolates. A number of aryl acetonitriles were aminated successfully in good yield, but with poor diastereoselectivities. Deprotonation of the nitrile using LiHMDS at -78 °C, and subsequent reaction of this carbanion with (+)-camphoryl oxaziridine 65 at between -78 °C and room temperature, afforded diastereoisomeric mixtures of camphor imines of aryl glycine amides (products 104a and 104b to 108a and 108b) in yields of between 73% and 80% (Scheme 158).

Scheme 158
Results and Discussion

formed in a ratio of 1:1 (Scheme 160). This result supports the intermediacy of a cyclic species in the reaction mechanism.

![Scheme 160](image)

Allyl cyanide was also aminated under these conditions over a period of 2 hours to form a mixture of inseparable diastereoisomeric imines 110a and 110b in a yield of 29% and in a diastereoisomeric ratio of 1:1 (Scheme 161).

![Scheme 161](image)

The attempted amination of other less stabilised nitrile enolates under these conditions was found to cause decomposition of oxaziridine 65. An isomer of α-camphidone, lactam 80 (Scheme 124) was isolated in a yield of 17% together with α-campholenic amide 111 in a yield of 83%, from the reaction mixture when the amination of butyronitrile was attempted, and α-campholenic amide 111 was isolated in a yield of 36% from the attempted amination of propionitrile (Scheme 162).
Results and Discussion

Scheme 162

One possible explanation for the formation of these two compounds during these reactions is that the nitrile-stabilised carbanion is not further delocalised and is therefore more basic that aryl/nitrile, allyl/nitrile or bis-nitrile stabilised carbanions. Under these conditions therefore, the carbanion acts as a base rather than a nucleophile causing decomposition of (+)-camphoryl oxaziridine 65.

Surprisingly, 4-nitrophenyl acetonitrile was also not aminated with oxaziridine 65 at between -78 °C and room temperature after deprotonation with LiHMDS in THF. Instead, α-campholenic amide 111 was isolated from this reaction in a yield of 21% (Scheme 163).

Scheme 163

(-)-Fenchyl oxaziridine 70 has been investigated to some extent for its reactivity with nucleophiles. It could be suggested that oxaziridine 70 would not be as reactive as (+)-camphoryl oxaziridine 65 due to the fact that the ketone moiety from which oxaziridine 70 is prepared is adjacent to two quaternary carbon centres, so making oxaziridine 70 more hindered. However, (-)-fenchyl oxaziridine has the
Results and Discussion

advantage of being more stable than (+)-camphoryl oxaziridine 65, and it can be reacted at higher temperatures (for example under refluxing conditions in toluene).

The attempted reaction of (-)-fenchyl oxaziridine 70 with styrene or 1-phenyl cyclohexene under refluxing conditions in toluene overnight however failed to yield any products at all, as did the attempted reaction of oxaziridine 70 with thioanisole under the same conditions (Scheme 164).

![Scheme 164]

Oxaziridine 70 was shown to react successfully with diethyl malonate in the presence of sodium ethoxide in ethanol at room temperature over a period of 4 hours to give imines 112a/112b as an inseparable mixture of syn and anti diastereoisomers in a ratio of 1:1 and in a yield of 68% (Scheme 165).

![Scheme 165]

As discussed previously in section 2.2.1, (-)-fenchyl oxaziridine 70 underwent decomposition during a variable temperature NMR experiment carried out in D6-DMSO, and we suspect that NH-oxaziridine 70 reacted with the solvent. As the temperature was raised during this experiment, both isomers of (-)-fenchyl
oxaziridine 70 appeared to undergo quantitative conversion to (1R)-(−)-fenchone 55. Significant decomposition of the NH-oxaziridine began at 45 °C, and by 95 °C, conversion was complete. The spectrum of (1R)-fenchone 55 was accompanied by a single broad singlet at 3.09 ppm, and this spectrum did not change when the sample was allowed to reach room temperature. The 13C NMR spectra taken from the sample at both 115 °C, and when the sample had been allowed to reach 25 °C, again showed the spectrum of (1R)-fenchone 55, the characteristic CD3 septet from the D6-DMSO solvent signal, but also a smaller signal at higher δ from what appears to be another septet possibly originating from another CD3 signal. These observations can be explained if (−)-fenchyl oxaziridine 70 had reacted with D6-DMSO to form the corresponding D6-dimethylsulfoximine and (1R)-(−)-fenchone 55 (Scheme 166).

If so, then this would also explain the presence of a broad singlet in the 1H NMR spectrum of the products of the reaction due to the presence if the sulfoximine N-H moiety. Further evidence to suggest that oxaziridine 70 had reacted with the D6-DMSO solvent during this experiment comes from the fact that (−)-fenchyl oxaziridine 70 did not noticeably decompose at all during another variable temperature NMR experiment that was carried out at temperatures of up to 100 °C in D8-toluene. If the reaction depicted in Scheme 166 did occur during the variable temperature NMR experiment, then it appears to be quantitative. The sulfoximine and fenchone products of the reaction are formed in a ratio of 1:1 (as determined by 1H NMR spectroscopy), and there appear to be no traces of any side-products. This reaction (Scheme 166) however, was not investigated further, nor were any of the suspected products of this reaction isolated or characterised using anything other than the 1H NMR and 13C NMR spectra of the mixture of products (see appendices).
Results and Discussion

While NH-oxaziridines were shown to act as electrophilic aminating reagents, preliminary investigations into the reactivity of N-Moc camphoryl oxaziridine 66 with nucleophiles have failed to yield any products of amination at all. These nucleophiles include Grignard reagents, ester and ketone enolates, sulfides and alkenes, and the lack of reactivity of 66 with these nucleophiles suggests that this type of N-protected oxaziridine is not useful for amination reactions (Scheme 167). This may be due to steric hindrance surrounding the nitrogen atom of this molecule.

![Chemical structure](image)

Scheme 167

The investigation and development of oxaziridines as chiral electrophilic aminating reagents is something that is ongoing within our group, and is likely to generate interest both within our group and with others for some time.

2.3 Other Potential Systems For Heteroatom Transfer

During the study of oxaziridines as potential asymmetric amination reagents, other systems were investigated that may also potentially be of use for heteroatom transfer.

A chiral iminium salt 33a that has been shown by members of our group to catalyse enantioselective epoxidation reactions, presumably via an oxaziridinium intermediate (Scheme 51), was investigated in order to see if we could bring about N-transfer. If we could generate a diaziridinium salt in situ in the presence of

135
an alkene, then we were interested to discover if this diaziridinium salt would transfer a nitrogen atom to an alkene enantioselectively to form an aziridine (Scheme 168).

![Scheme 168](image)

I-Phenylcyclohexene was employed with iminium salt 33a in acetonitrile in a bi-phasic system together with an aqueous solution of potassium carbonate and hydroxylamine-O-sulfonic acid, but after 2 days at room temperature, no reaction at all had taken place (Scheme 169).

![Scheme 169](image)

If N-bromoacetamide is deprotonated, then the resulting amide anion can be used for further reactions over a period of 20 or more hours, and Hofmann rearrangement can be suppressed by cooling the reaction mixture to below 4 °C. In another attempt at a similar type of reaction process to that shown in Scheme 168, N-bromoacetamide was deprotonated using sodium methoxide in methanol, in the presence of iminium salt 33a and I-phenylcyclohexene in acetonitrile at -10 °C. It
Results and Discussion

was hoped that the \( N \)-bromoacetamide anion would add to the iminium salt, and if the intermediate species then eliminated a bromide anion in a similar way to that proposed for hydroxylamine-\( O \)-sulfonic acid (Scheme 168), then the product of this reaction, an \( N \)-acyl diaziridinium species, might react with an alkene to form an aziridine. However, after two days at \(-10^\circ C\), no reaction of the alkene, or destruction of the iminium catalyst was observed by tlc (Scheme 170).

![Scheme 170](image)

Oxaziridines have been shown to transfer both oxygen and nitrogen to different nucleophiles, depending upon their \( N \)-substituent. The factors governing whether oxygen or nitrogen is transferred have been investigated experimentally, and, have been attributed mainly to steric effects.\(^{75}\)

There has been no similar study carried out with oxaziridinium compounds. In general, these compounds are prepared by the reaction of an oxidising agent with an iminium salt, which is generated and reacted in situ. Because of this, most oxaziridinium salts that have been prepared contain a highly hindered quaternised nitrogen atom. We therefore considered that if an oxaziridinium salt was prepared that was unsubstituted at nitrogen, then, nitrogen transfer to nucleophiles might be observed.

Sulfoxidation has been effected by protonation of an \( N \)-alkyl oxaziridine (Scheme 171).\(^{84}\)
Results and Discussion

We therefore proposed that if (+)-camphoryl oxaziridine 65 could be protonated to give an N-unsubstituted oxaziridinium salt, then it may transfer nitrogen as opposed to oxygen to a nucleophilic substrate. When oxaziridine 65 was reacted with trifluoromethane sulfonic acid at room temperature, in the presence of 1-phenyl cyclohexene in DCM, no nitrogen or oxygen transfer was observed at all. Instead, only decomposition of the oxaziridine to (1S)-(+)camphor oxime 62 in a yield of 35% was observed (Scheme 172).

\[
\begin{align*}
\text{Ph} & \quad 65, \text{CF}_3\text{SO}_3\text{H}, \text{DCM}, \text{r. temp} \\
\rightarrow & \quad \text{N-OH} \\
62 & \quad 35\%
\end{align*}
\]

Scheme 172

The reaction of (+)-camphoryl oxaziridine 65 with trifluoromethane sulfonic acid in the presence of styrene in DCM at between -78 °C and room temperature over a period of 2 hours gave a complex mixture of products and complete conversion of styrene into what appears to be polymeric material (Scheme 173). The reaction of 1,2-dihydronaphthalene under similar conditions gave complete conversion of the alkene to uncharacterised products that appear to be mixtures of oligomeric material. (1R)-(+)camphor 56 was also isolated from this reaction mixture in a yield of 25% (Scheme 173).

\[
\begin{align*}
\text{Ph} & \quad 65, \text{CF}_3\text{SO}_3\text{H}, \text{DCM}, -78 \, ^\circ\text{C} \text{ to r. temp} \\
\rightarrow & \quad \text{Polymeric Material}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad 65, \text{CF}_3\text{SO}_3\text{H}, \text{DCM}, -78 \, ^\circ\text{C} \text{ to r. temp} \\
\rightarrow & \quad \text{Mixtures of oligomeric material} + 56, 25\%
\end{align*}
\]

Scheme 173
It is likely that alkenes are unsuitable for this type of reaction, either due to the fact that both the alkene starting material, and the expected epoxide are liable to polymerise under these conditions, or because of the poor nucleophilicity of the starting material.

Sulfides have been shown to be suitable substrates for oxidation using oxaziridinium salts generated by the protonation of oxaziridines (Scheme 171).\(^{84}\) (+)-Camphoryl oxaziridine 65 was thus treated with 1-methoxy-4-(methylthio)benzene in the presence of trifluoromethane sulfonic acid in DCM at \(-78\, ^\circ\text{C}\) over a period of 10 minutes. Although the reaction was rapid, the reaction did not reach completion, and the starting material was isolated from the reaction mixture in a yield of 9%. (1R)-(+)-Camphor 56 was isolated in a yield of 30%. (1R)-Camphor imine 64 and (4-methoxyphenyl)methyl sulfoxide 113 were isolated as a mixture in yields of 64% and 96% respectively (as determined within the bounds of accuracy for this type of determination using \(^1\text{H}\) NMR spectroscopy (+/- 5 to 10%)). This mixture was dissolved in DCM and residual deuteriochloroform from the NMR experiment, and then treated with aqueous dilute hydrochloric acid at room temperature over a period of 2 hours in order to hydrolyse NH-imine 64. From this reaction mixture, (R)-(4-methoxyphenyl)methyl sulfoxide 113 was isolated in a yield of 85% with an enantiomeric excess of 14% (Scheme 174).
Results and Discussion

This reaction is evidence that a lack of steric hindrance about the nitrogen atom of an oxaziridinium species is unlikely to bring about $N$-transfer as opposed to $O$-transfer.

2.3 Conclusions

A number of different approaches have been taken to the attempted development of new methodology for the asymmetric electrophilic amination of nucleophiles.

The use of other hydroxylamine or hydrazine derived reagents as hydrogen peroxide analogues in a nitrogen-transferring derivative of the imino analogue of the Payne oxidation system was attempted. This system was unreactive using oxidation catalyst (1S)-(+)3,3-dimethoxycamphorsulfonyl imine 1 together with various hydrazine and hydroxylamine derivatives in the presence of a range of non-ionic nucleophiles under the conditions described. However, although this system was unsuccessful in bringing about nitrogen transfer to any of the nucleophiles that were tested in this system, there may be other hydrogen peroxide analogues, other catalysts...
or other conditions that have not been used that may be able to bring about amination of nucleophiles.

Chiral oxaziridines have been investigated as reagents for their potential use as asymmetric electrophilic aminating reagents. We have succeeded in the synthesis of the first chiral enantiomerically pure NH-oxaziridine, (+)-camphoryl oxaziridine 65. This compound exists as two diastereoisomers, and we have proven, by functionalisation of the oxaziridine nitrogen atom, that these observed isomers are invertomers and are present due to the enhanced configurational stability of the nitrogen atom in oxaziridines.

Similarly, (-)-fenchyl oxaziridine 70 has been synthesised. NH-oxaziridine 70 also exists as two diastereoisomers. However, we have not been able to prove conclusively whether the presence of these two compounds is due to the slowly inverting nature of the oxaziridine nitrogen, or due to endo/exo diastereoisomerism. Also, if it is the case that these two isomers are invertomers, then we do not know whether they are endo or exo.

The derivatisation of the nitrogen atom of 65 has been investigated. (-)-N-chlorocamphoryl oxaziridine 73 has been synthesised, both by the action of non-aqueous hydrochloric acid upon (+)-camphoryl oxaziridine, and also by the reaction of 65 with tert-butyl hypochlorite.

We have been successful in the synthesis of known N-sulfonyl oxaziridine 59 by functionalisation of the nitrogen atom. Also, we have been successful in the synthesis of the first chiral enantiomerically pure N-alkoxycarbonyl oxaziridines (66 and 67), as well as the synthesis of the first chiral enantiomerically pure N-phosphinoyl oxaziridine ((-)-N-(diphenylphosphinic)camphoryl oxaziridine 85) where the phosphorus atom is not the sole chiral centre within the molecule.

N-Acyl oxaziridines synthesised by acylation of oxaziridine 65 have been investigated, and it has been found that unlike other reported N-acyl oxaziridines, 65-derived N-acyl oxaziridines are less stable than the corresponding N-H compounds. We have been able to show that these N-acyl oxaziridines undergo decomposition to give diastereoisomeric mixtures of 1,4,2-dioxazoles. We have also been able to prepare the first chiral enantiomerically pure N-acyl oxaziridine ((-)-N-acetylcamphoryl oxaziridine 82), which is stable for up to 3 days in the refrigerator,
Results and Discussion

and have demonstrated that the decomposition of 82 to a mixture of diastereoisomeric 1,4,2-dioxazoles is facilitated by silica gel.

\((-\text{-}(S\text{-Pentafluorophenylsulfenyl})\text{camphoryl oxaziridine 87 has been synthesised, and this is the first reported example of an } N\text{-sulfenyl oxaziridine.}

The attempted derivatisation of \((-\text{-}fenchyl oxaziridine 70 has given only poor yields of unstable } N\text{-functionalised products.}

The reaction of \((+\text{-})\text{camphoryl oxaziridine 65 with nucleophiles has been investigated, and it has been established that 65 is unreactive towards a range of alkenes, and also to sulfides. Oxaziridine 65 has been shown to react poorly with simple mono-activated enolates such as simple ester, ketone and nitrile enolates.}

The reaction of oxaziridine 65 with less-hindered mono-substituted dialkyl malonates has been shown to proceed exclusively with decarboxylation despite the conditions of the reaction, to give camphor imines of alkyl, glycine esters in high yields. These glycinate imines are formed as diastereoisomeric mixtures with little or no diastereoselective control. When more-hindered dialkyl monosubstituted malonates are used in the reaction (e.g. diethyl tert-butyl malonate), the yields are low, or the reaction does not proceed.

The reaction of 65 with kinetically deprotonated (LiHMDS, \(-78 ^\circ\text{C} \)) aryl acetonitriles has been shown to proceed in good yield in most cases, but with little or no stereocontrol. Malononitrile has also been shown to react with \((+\text{-})\text{camphoryl oxaziridine 65 in good yield with conversion of one of the nitrile functionalities to an amide, and, in doing so forming a new chiral centre by desymmetrisation.}

Simple enolates of esters or nitriles have been shown to react poorly with oxaziridine 65, and give little or no aminated products.

Ketone enolates have been shown to react with \((+\text{-})\text{camphoryl oxaziridine 65 with varying results. Some of these ketones gave products that were unstable, whereas others gave poor yields of products. When 2-methyl indan-1-one was reacted with oxaziridine 65, the free amine was isolated from the reaction mixture as well as the camphor imine. There is some evidence that oxygen transfer also occurred during this reaction, and while this must be further investigated, if this it is to be confirmed, then this would be the first example of oxygen transfer from an } N\text{-oxaziridine.}
Results and Discussion

Investigations into the use of (−)-fenchyl oxaziridine 70 have been limited, however, 70 has been shown to react successfully with diethyl malonate.

(−)-N-(Methoxycarbonyl)camphoryl oxaziridine 66 has been investigated for its reaction with a range of nucleophiles, and no products of amination have yet been detected.

Other systems have been investigated that may bring about N-transfer to nucleophiles. The attempted synthesis of diaziridinium salts in the presence of alkenes failed to yield any products at all. It is likely that no diaziridinium compounds are being formed under the conditions described, as no decomposition products of the iminium salt were detected.

The reaction of an N-unsubstituted oxaziridinium salt with an alkene failed to yield any identifiable products of either amination or oxidation, and this is possibly due to the fact that either the alkene itself or the product of this reaction is unstable to the reaction conditions. The reaction of the same oxaziridinium salt with a sulfide was shown to give exclusively O-transfer, and the sulfoxide product was isolated in high yield.
3.0 GENERAL EXPERIMENTAL DETAILS

Purification of Reagents

Commercially available reagents were used as supplied without further purification unless otherwise stated. Air and moisture sensitive regents were stored under an inert atmosphere in a desiccator over self-indicating silica pellets. Temperature sensitive reagents were stored in a refrigerator or freezer as instructed by the manufacturer.

Petroleum ether (b.p. 40-60 °C) and ethyl acetate were distilled over anhydrous calcium chloride prior to use. Dichloromethane was distilled over anhydrous phosphorous pentoxide prior to use and if anhydrous dichloromethane was required, then this was used immediately after distillation. Tetrahydrofuran and diethyl ether were freshly distilled under an atmosphere of nitrogen from the sodium benzophenone ketyl radical immediately prior to use. Triethylamine was distilled from calcium hydride under an inert atmosphere and stored over potassium hydroxide pellets.

Purification of Products

Thin layer chromatography (tlc) was carried out on aluminium or glass backed plates coated with a 0.25 mm layer of silica gel or neutral alumina. UV inactive compounds were visualised by exposure to iodine mixed with silica gel, or spraying with potassium permanganate solution (10 g in 1 litre of water containing 5 g Na₂CO₃) followed by heating. Compounds with oxidising properties were visualised by spraying with alkaline potassium iodide solution (3 g in 10 mL of water containing 0.5 g of sodium hydroxide) followed by heating.

Flash and gravity column chromatography was performed using Merck 9385 Kieselgel 60-45 (230-400 mesh) silica gel. An airline or bellows were used to supply the necessary pressure to the column.
Preparation of Glassware

Air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240 °C and were allowed to cool under a nitrogen atmosphere over self-indicating silica pellets. The reactions were carried out under a slightly positive static pressure of nitrogen.

Spectroscopy

Proton Nuclear Magnetic Resonance (\(^1\)H NMR) spectra were recorded on a Bruker AC 250 MHz or a Bruker DPX 400 instrument operating at 250.13 and 400.13 MHz respectively. Carbon-13 Nuclear Magnetic Resonance (\(^{13}\)C NMR) spectra were recorded on a Bruker AC 250 MHz or a Bruker DPX 400 instrument operating at 62.86 and 100.62 MHz respectively. All spectra were recorded using tetramethylsilane (MeTMS) or deuteriochloroform (CDCl\(_3\)) as the internal reference.

The following symbols have been used in the description of the spectra obtained:-

\[ \delta = \text{chemical shift (in parts per million)} \]
\[ J = \text{coupling constant (in Hz)} \]
\[ s = \text{singlet} \]
\[ d = \text{doublet} \]
\[ tr = \text{triplet} \]
\[ q = \text{quartet} \]
\[ m = \text{multiplet} \]
\[ br = \text{broad} \]

In the description of \(^1\)H NMR spectra of mixtures of compounds, the terms \(H_A, H_B\) and \(H_C, \) etc are given arbitrarily to differentiate (where possible) signals which come from protons with similar chemical shift but which are obviously from different compounds/diastereoisomers. They are not, however used for the assignation of particular signals with particular compounds or diastereoisomers (unless otherwise stated). This means that a signal described by the term \(H_A\) may not be from the same diastereoisomer as another signal denoted by \(H_A\) in the same spectrum if there is a significant difference in chemical shift between the two signals (and vice versa). Where it is not possible to differentiate between signals of the two compounds or
Experimental Details

isomers due to unreadable overlap of signals they are denoted together as in $H_{A+B+C}$. The magnitude of these signals is then described as a combination of their intensities (i.e. $1H_{A+B}$ denotes a single proton from molecule A and a single proton from molecule B). Where it is not possible to tell whether a particular signal comes from a different molecule or not then this signal is simply denoted by the term H.

Infrared spectra were recorded in the range 4000 to 600 cm$^{-1}$ using a Perkin-Elmer FT-IR spectrometer Paragon 2001. Solid samples were run as Nujol mulls or evaporated films of solutions in chlorinated solvents as indicated, and liquid samples were recorded neat.

Mass spectra were recorded on Cratos MS-80 or Jeol-SX102 using electron impact (EI) ionisation technique. In the description of mass spectra $MH^+$, $M(NH_4)^+$ and $M^+$ refer to the molecular ion peak obtained by ionisation.

Other Data

Microanalyses were performed in the University of Liverpool Department of Chemistry microanalytical laboratory on a Carlo Erba Elemental Analyser or in Loughborough University on a Perkin Elmer Analyser 2400 CHN.

Melting points (mp) were determined using an Electrothermal-IA 9100 and are uncorrected.

Optical rotations were measured using as Optical Activity-polAAar 2001 instrument operating at $\lambda = 589$ nm corresponding to the sodium line (D) at the temperature indicated. The solvents used as indicated for these measurements were of spectrophotometric grade.

The temperature reported for certain reactions (e.g., $-78 ^\circ C$), refers to the temperature of the cooling medium rather than the internal temperature of the reaction itself.
Experimental Details

(1S, 4S)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)-methanesulfonyl Chloride, (1S)-(+)Camphorsulfonyl Chloride 50

(1S)-(+)Camphorsulfonic acid 49 (86.00 g, 0.370 mol) was heated (neat) to 40 °C in a two-necked round bottomed flask equipped with a reflux condenser and a drying tube (CaCl₂). Thionyl chloride (108 mL, 176 g, 1.48 mol) was then added from a dropping funnel over a period of 2 hours with stirring. Vigorous evolution of gas (HCl, SO₂) was observed as the reaction proceeded. When the evolution of gas had ceased, the reaction mixture was allowed to cool to room temperature and was stirred overnight. The resulting yellow-orange liquid was then poured onto iced water (500 mL) to hydrolyze the excess thionyl chloride. Upon gentle stirring of this mixture the sulfonyl chloride precipitated out of the aqueous phase, it was quickly filtered and then washed with more ice cold water. Most of the water was then removed by suction filtration, then the product was dissolved in dichloromethane and dried over magnesium sulfate. Finally, filtration followed by removal of the solvent in vacuo afforded crude (+)-camphorsulfonyl chloride 50 in a 95% (88.2 g, 0.351 mol) yield: [α]₂⁵° = +31.2 (CHCl₃); mp 63-65 °C; δ (250 MHz; CDCl₃) 4.30 (1H, d, J = 14.6, RCHHSO₂Cl), 3.75 (1H, d, J = 14.6, RCHHSO₂Cl), 2.50-2.39 (2H, m, CH₂ at camphor C3), 2.07-2.19 (2H, m), 1.99 (1H, d, J = 18.6, CH at C4), 1.74-1.82 (1H, m), 1.46-1.54 (1H, m), 1.14 (3H, s, Me), 0.93 (3H, s, Me). This product showed identical properties to the same compound, which had been reported previously.¹⁰⁴
Experimental Details

(1S, 4S)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)-methanesulphonamide, (+)-Camphorsulphonamide 51

In a 1L three necked round bottomed flask equipped with a mechanical stirrer, a 100 mL addition funnel and a glass plug was placed concentrated ammonia (225 mL). The reaction mixture was cooled to 0 °C in an ice bath and stirred vigorously. A solution of (+)-camphorsulfonyl chloride 50 (25.0 g, 99.7 mmol) in dichloromethane (225 mL) was then added dropwise in two portions over 30 mins. The reaction mixture was then stirred for a further 2 hours at 0 °C, then the lower dichloromethane layer was separated and the aqueous ammonia layer was washed with dichloromethane (2x50 mL). The combined organic solution and extracts were dried (MgSO₄) and the solvent removed in vacuo to give crude (+)-camphorsulfonamide 51 as a white solid in an 88% (20.2 g, 87.3 mmol) yield: mp 126-130 °C; δ_H (250 MHz; CDCl₃) 5.75(2H, br.s, NH₂), 3.55(1H, d, J = 15.1, RCHHSO₂X), 3.16(1H, d, J = 15.1, RCHHSO₂X), 2.72-1.47(7H, m), 1.08(3H, s, Me), 0.92(3H, s, Me). This compound was shown to have identical spectral properties to the same compound, which has been previously reported.¹⁰⁵

(1S, 7S)-10,10-Dimethyl-3α-thia-4-azatricyclo[5.2.1.0¹⁺⁵]dec-4-ene-3,3-dione, (-)-Camphorsulfonyl Imine 52

In a 500 mL round-bottomed flask equipped with a magnetic stirrer, Dean-Stark trap and reflux condenser were placed Amberlyst 15⁺ ion-exchange resin (2.4 g) and
**Experimental Details**

Crude (+)-camphorsulfonamide 51 (20.0 g, 86.4 mmol) in toluene (250 mL). The reaction mixture was heated to reflux for 4 hours and then the heat was removed. Whilst the reaction mixture was still warm dichloromethane (100 mL) was added to dissolve the solid imine that forms and the warm solution was filtered and the flask and funnel washed with an additional dichloromethane (50 mL). The solvent was then removed *in vacuo* and the crude product recrystallised from absolute ethanol to give (−)-camphorsulfonyl imine 52 as a white solid in a 90% (16.5 g, 77.4 mmol) yield: mp 224-226 °C; δH (250 MHz; CDCl3) 3.20 (1H, d, J = 13.3, RCHHSO2R) 3.00 (1H, d, J = 13.3, RCHHSO2R), 2.82–1.43 (7H, m), 1.10 (3H, s, Me), 0.89 (3H, s, Me). This compound was shown to have identical spectral properties to the same compound, which has been previously reported.105

(1S, 7S)-10,10-Dimethyl-3λ6-thia-4-azatricyclo[5.2.1.01,5]dec-4-ene-3,3,6-trione, (−)-3-Oxocamphorsulfonyl Imine 53

To a solution of (−)-camphorsulfonyl imine 52 (12.0 g, 56.3 mmol) in acetic acid (430 mL) was added selenium dioxide (15.0 g). The reaction mixture was heated at reflux for 20 hours, the solution was filtered to remove the precipitate selenium and distilled water (500 mL) and dichloromethane (250 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2x250 mL). The combined organic extracts were dried (MgSO4) and the solvent removed *in vacuo* to give the crude product which was recrystallised from methanol to give pure (−)-3-oxocamphorsulfonyl imine 53 in a 62% (7.93 g, 34.9 mmol) yield: [α]D25 = -178.2 (acetone); mp 189-190 °C; Found%: C, 52.74; H, 5.83; N, 6.13 C10H12NO3S requires%: C, 52.86; H, 5.77; N, 6.16; νmax (nujol)/cm−1 1750, 1640, 1330, 1160; δH (400 MHz; CDCl3) 3.46 (1H, d, J = 13.7, RCHHSO2R), 3.24 (1H, d, J = 13.7, RCHHSO2R), 2.79 (1H, d, J = 4.8, CH at bridgehead C4), 2.40–2.20 (2H, m), 2.10-
Experimental Details

1.80(2H, m), 1.17(3H, s, Me), 0.99(3H, s, Me); \( \delta_c \) (100 MHz; CDCl3) 18.3(Me), 20.1(Me), 22.2(CH2), 27.9(CH2), 44.6(C\text{quat}), 50.0(CH), 59.0(CH2, CH\text{OSO2NR}) 62.7(C\text{quat}), 183.5(C\text{quat}, C=N), 197.8(C\text{quat}, C=O); Found: M+, 22706160 C10H13N03S requires 227.06161; \( m/z \) 245(M(NH4)+). This compound showed identical spectral properties to the same compound, which was prepared previously.\(^{106}\)

(IS, 7S)-10,10-Dimethyl-6,6-di(methoxy)-3\(,6\)-thia-4-azatricyclo[5.2.1.0\^{15}]dec-4-ene-3,3-dione, (+)-3,3-Dimethoxycamphorsulfonyl Imine 1

\[
\begin{align*}
&\text{OMe} \\
&\text{N} \\
&\text{OMe} \\
&\text{O}_2
\end{align*}
\]

A mixture of (-)-3-oxocamphorsulfonyl imine 53 (2.27 g, 10.0 mmol), trimethyl orthoformate (25 mL), methanol (5 mL), concentrated sulfuric acid (0.5 mL) and Amberlyst 15® ion-exchange resin (0.5 g) were stirred and refluxed overnight. The room temperature solution was filtered, distilled water (20 mL) was added and the mixture was extracted with dichloromethane (3x30 mL). The combined extracts were washed with distilled water (30 mL), dried (MgSO4), and the solvent removed in vacuo to give the crude product which was recrystallised from absolute ethanol to give pure (+)-3,3-dimethoxycamphorsulfonyl imine 1 in a 90% (2.46 g, 9.01 mmol) yield: mp 185-187 °C; \( \delta_h \) (400 MHz; CDCl3) 3.46(3H, s, MeO), 3.38(3H, s, MeO), 3.16(1H, d, \( J = 12.0 \), RCH\text{OSO2R}), 2.97(1H, d, \( J = 12.0 \), RCH\text{OSO2R}), 2.38-1.80(5H, m), 1.10(3H, s, Me), 1.00(3H, s, Me). This compound was shown to have identical spectral properties to the same compound, which has been previously reported.\(^{106}\)
Experimental Details

(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2,3-dione, (1R)-(−)-Camphorquinone 57

To (1R)-(+)camphor 56 (100 g, 0.657 mol) in acetic anhydride (80 mL) was added finely powdered selenium dioxide (80.0 g, 0.72 mol) and the reaction mixture was refluxed for 2 hours after which more selenium dioxide (20.0 g, 0.180 mol) was added. The reaction mixture was refluxed for a further 2 hours after which more selenium dioxide (20.0 g, 0.180 mol) was added and the reaction mixture refluxed for a further four hours. The mixture was cooled to room temperature and then basified with aqueous sodium hydroxide (2.0 M) and the dichloromethane was added (250 mL). The reaction mass was then filtered to remove any solids present and the filtrate was extracted with dichloromethane (3x200 mL). The combined organic extracts were dried (MgSO4) and the solvent removed in vacuo to give the crude product which was recrystallised from 96% ethanol to give pure (1R)-(−)-camphorquinone 57 in a 93% (101 g, 0.609 mol) yield: mp 199-202 °C; δH (250 MHz; CDCl3) 2.63(1H, d, J = 5.4), 2.27-2.07(1H, m), 2.01-1.84(1H, m), 1.70-1.58(2H, m), 1.11(3H, s, Me), 1.07(3H, s, Me), 0.94(3H, s, Me). This compound displayed identical spectral properties to those previously reported for the same compound.108

(1R,4S)-3-Hydroximino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, (1R)-(−)-Camphorquinone Monoxime 60

To a solution of hydroxylamine hydrochloride (2.4 g, 34.5 mmol) and sodium acetate (4.2 g, 51.2 mmol) in water (16 mL) was added (1R)-(−)-camphorquinone 57 (1.96 g,
Experimental Details

11.8 mmol) in absolute ethanol (16 mL). The solution was refluxed gently for 10 minutes after which time all of the starting material had disappeared (tlc). The solution was cooled and ethanol was removed in vacuo. Distilled water (10 mL) was then added to the remaining aqueous slurry. The slurry was cooled on an ice bath for 20 minutes and the solid that precipitated was collected by suction filtration and then dried under high vacuum to give the product (1R)-(+)camphorquinone monoxime 60 as an off white crystalline solid which required no further purification in an 82% (1.75 g, 9.66 mmol) yield: mp 143-146 °C; δC (63 MHz; CDCl₃) mixture of anti and syn oximes δ (major isomer) 8.8, 17.5, 20.6, 23.7, 30.6, 44.8, 46.5, 58.4, 159.4(C=N), 204.5(C=O) δ (minor isomer) 8.4, 17.9, 20.5, 24.9, 29.8, 46.4, 49.5, 59.5, 156.1(C=N), 204.5(C=O). This compound was shown to have identical spectral properties to the same compound that was previously reported.¹¹⁰

(1R, 4S)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one Oxime, (1R)-(−)-Fenchone Oxime 61

(1R)-(−)-Fenchone 55 (106 mL, 100 g, 657 mmol), hydroxylamine hydrochloride (100 g, 1439 mmol) and pyridine (80 mL, 78.2 g, 989 mmol) were heated under reflux in ethanol (1.0 L) for 5 hours. After the reaction vessel had cooled most of the ethanol in the reaction mixture was removed in vacuo and water was added crude fenchone oxime crashed out of the solution as white crystals which were isolated by filtration and washed with distilled water. This product was dried under vacuum and then recrystallised from ethanol to afford pure crystalline (1R)-(−)-fenchone oxime 61 in a 68% (75.0 g, 449 mmol) yield: mp 169-170 °C; δH (250 MHz; CDCl₃) 8.57(1H, br.s, NOH), 1.86-1.69(3H, m), 1.64-1.40(3H, m), 1.30-1.36(1H, m), 1.33(3H, s, Me), 1.30(3H, s, Me), 1.22(3H, s, Me); δC (63 MHz; CDCl₃) 17.0, 22.1, 22.9, 25.2, 34.1, 43.2, 44.1, 48.5, 50.0, 172.2(C=N). This product showed spectral properties identical to those previously reported for this compound.¹¹³
(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one Oxime, (1R)-(−)-Camphor Oxime 62

Hydroxylamine hydrochloride (100 g, 1439 mmol), (1R)-(+) -camphor 56 (100 g, 658 mmol) and pyridine (80 mL, 78.2 g, 989 mmol) were heated under reflux in ethanol (1.0 L) for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed in vacuo. Water was then added and the crude oxime crashed out of the solution as white crystals, which were isolated by filtration and washed with distilled water. The product was then dried under vacuum and then recrystallised from absolute ethanol to afford pure (1R)-(−)-camphor oxime 62 as white crystals in an 82% (90.3 g, 541 mmol) yield: mp 119-121 °C; $\delta_H$ (250 MHz; CDCl$_3$) 6.19(1H, br.s, OH), 2.56(1H, dt, $J=$17.9 and 3.9, exo at C3), 2.06(1H, d, $J=$17.9, endo at C3), 1.94-1.66(3H, m), 1.51-1.41(1H, m), 1.29-1.20(1H, m), 1.03(3H, s, Me), 0.92(3H, s, Me), 0.81(3H, s, Me). This compound showed identical spectral properties to the same compound that was previously reported.$^{114}$

(1R, 4S)-1-Oxo-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate, (1R)-(−)-Camphor Nitrimine 63

(IR)-(−)-Camphor oxime 62 (30 g, 180 mmol) in glacial acetic acid (900 mL) was treated with 5% aqueous sodium nitrite (450 mL). A bright yellow colour developed and dispersed over 30 minutes. After another 1.5 hours the crude product was precipitated as a white solid by the addition of water and isolated by filtration. After
Experimental Details

drying under vacuum, the crude product was recrystallised from 95% ethanol to afford pure (1R)-(−)-camphor nitrimine 63 as a white crystalline solid in a 54% (19.0 g, 96.9 mmol) yield: mp 41-42 °C; v_max (neat)/cm⁻¹ 1645, 1569; δ_H (250 MHz; CDCl₃) 2.69(1H, ddd, J = 18.6, 4.75 and 2.2, exo at C3) 2.13(1H, d, J = 18.6, endo at C3), 2.05-1.79(3H, m), 1.65-1.51(1H, m) 1.37-1.28(1H, m) 1.04(3H, s, Me), 0.98(3H, s, Me), 0.88(3H, s, Me); δ_C (63 MHz; CDCl₃) 10.7(Me), 19.0(Me), 19.8(Me), 27.1(CH₂), 31.9(CH₂), 35.5(CH₂), 43.8(CH), 49.2(C quat), 54.5(C quat) 189.8(Cquat, C=N). This compound displayed identical spectral properties to that prepared previously.¹¹⁷

(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-imine, (1R)-Camphor Imine 64

A solution of (1R)-(−)-camphor nitrimine 63 (10.0 g, 51.0 mmol) in dry tetrahydrofuran (100 mL) was treated at 0 °C with a slow stream of ammonia gas in the fumehood for 4 hours. The solvent was removed in vacuo keeping the water bath below 30 °C to give (1R)-camphor imine 64 as a pale yellow solid in a 100% (7.70 g, 51.0 mmol) yield: v_max (DCM)/cm⁻¹ 1666; δ_H (250 MHz; CDCl₃) 2.53-2.37(1H, m), 2.03-1.22(6H, m), 0.94(3H, s, Me), 0.93(3H, s, Me), 0.71(3H, s, Me); δ_C (63 MHz; CDCl₃) 10.2, 18.8, 19.4, 27.1, 32.0, 40.3, 43.5, 47.1, 54.6, 193.7. This product showed spectral properties identical to those previously reported for this compound.¹¹⁸

Procedure for Purification of 3-Chloroperoxybenzoic Acid

Commercially available (supplied by Aldrich chemical co.) 3-chloroperoxybenzoic acid (57-86%, 25-30 g) was dissolved in the minimum amount of dichloromethane needed to obtain a homogeneous solution (c. 500 mL). This solution was then washed with an aqueous solution of phosphate buffered saline (pH 7.5, 8-10x200
**Experimental Details**

mL). The organic solution was then separated, dried (MgSO₄) and the solvent removed \textit{in vacuo} to give 3-chloroperoxybenzoic acid which was subsequently shown by iodimetric titration to be of greater than 98% purity.¹¹⁹

\((1R, \, [1\alpha, \, 2\beta(S'),\, \alpha\alpha)]-1,7,7\text{-Trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine]}, \,(+)-Camphoryl Oxaziridine 65\)

A solution of pure¹¹⁹ 3-chloroperoxybenzoic acid (17.6 g, 102 mmol) in dry dichloromethane (600 mL) was cooled to between -30 °C and -40 °C causing some of the per-acid to crystallise out of the solution. On addition of a solution of \((1R)\)-camphor imine 64 (15.4 g, 102 mmol) in dry dichloromethane (40 mL) to this solution over a period of 4-5 minutes, this solution became homogeneous again. This reaction mixture was then allowed to stir overnight at -30 °C to -40 °C and then allowed to warm back up to room temperature. The reaction mixture was then stirred at room temperature for a further 2 hours until all of the per-acid had reacted (tlc) by which time much of the 3-chlorobenzoic acid by-product had crystallised out of the solution. The solvent was then removed \textit{in vacuo} until approximately 25% of the original volume remained. Petroleum ether (500 mL) was then added to the mixture and the solvent was again removed \textit{in vacuo} until approximately 25% of the original volume remained. This process was repeated once more and then more petroleum ether (600 mL) was added to the mixture. The 3-chlorobenzoic acid by-product which had been precipitated out by this process was then removed by filtration, and the rest of this by-product was washed out of the resultant solution by washing it with aqueous sodium hydroxide (1.0 M, 3x200 mL). The organic solution was dried (MgSO₄) and the solvent removed \textit{in vacuo} to give (+)-camphoryl oxaziridine 65 as a colourless solid in a 94% (16.0 g, 95.8 mmol) yield. This product was shown to be pure by \(^1\)H NMR spectroscopy, however in this state the product decomposes slowly evolving ammonia gas over a few of days. Dissolution of the product in
Experimental Details

dichloromethane (40 mL) followed by filtration through silica gel (15 g) and then washing the residual oxaziridine through the silica gel with more dichloromethane followed by subsequent removal of the solvent *in vacuo* was found to increase the stability of the oxaziridine product. Subsequently, the oxaziridine 65 could then be stored in the refrigerator, for a period of more than 6 months, without any noticeable decomposition. No reduction in the yield is observed by using this process. The product (+)-camphoryl oxaziridine 65 was found to exist as a pair of diastereoisomers at N-H in a 60:40 ratio: \([\alpha]^{25}_D = +5.79\) (CHCl₃); mp 153-155 °C; Found%: C, 71.31; H, 10.13; N, 8.11 C\(_{10}\)H\(_{17}\)NO requires%: C, 71.81; H, 10.24; N, 8.37; \(\nu_{\text{max}}\) (CDCl₃)/cm\(^{-1}\) 3202(NH); \(\delta_H\) (250 MHz; CDCl₃) 4.22(1H\(_A\), br.s, NH), 3.74(1H\(_B\), br.s, NH), 2.33-2.21(1H\(_{A+B}\), m, camphoryl exo C\(_3\)), 1.87-1.26(6H\(_{A+B}\), m), 0.93(3H, s, Me), 0.91(3H, s, Me), 0.88(6H, s, 2xMe), 0.63(3H, s, Me), 0.62(3H, s, Me); \(\delta_C\) (100 MHz; CDCl₃) 8.4, 8.6, 19.3, 19.3, 19.5, 19.6, 27.0, 27.3, 29.5, 30.3, 36.5, 37.7, 44.5, 44.3, 47.5, 47.7, 47.8, 48.1, 89.4(C\(_{\text{quat, oxaziridine}}\)), 89.7(C\(_{\text{quat, oxaziridine}}\)); Found: M\(^+\), 167.13120 C\(_{10}\)H\(_{17}\)NO requires 167.13100; m/z 168(MH\(^+\)), 167(M\(^+\)), 152, 149, 135, 124, 123, 109, 108, 95, 93, 83, 81, 79, 69, 67, 55.

(1R, 4S)-1-Oxo-2-(1,3,3-trimethylbicyclo[2.2.1]hepty-2-yliden)hydrazinium-1-olate, (1R)-Fenchone Nitrimine 68

A solution of sodium nitrite (13.8 g, 200 mmol) in water (100 mL) was added to a solution of (1R)-(--)-fenchone oxime 61 (20.0 g, 120 mmol) in diethyl ether (320 mL) placed in a separatory funnel. A solution of 0.5 M sulfuric acid (200 mL) was then added with occasional vigorous swirling over 2 hours. The mixture was then allowed to stand for 3 hours, and then the ether layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2x100 mL), dried (Na\(_2\)SO₄) and the solvent removed *in vacuo*. The resulting solid was then purified by column chromatography (petroleum ether/ dichloromethane) over silica to give (1R)-fenchone nitrimine 68 as
Experimental Details

a colourless solid in a 70% (16.5 g, 84.2 mmol) yield. The product was shown by NMR spectroscopy to be a mixture of syn and anti diastereoisomers of the nitrimine (A and B) present in an approximately 2:1 ratio (although it is not known which isomer (syn or anti) is present in the larger ratio, the major isomer is represented by A): mp 63-65 °C; \( v_{\text{max}} \) (neat)/cm\(^{-1}\) 1641(C=N), 1562(=N-NO\(_2\)); \( \delta_h \) (250 MHz; CDCl\(_3\)) 2.03-1.52(6HA+B, m), 1.48(1HA, dd, \( J =10.5, 1.5 \)), 1.37(1HB, dd, \( J =10.6, 1.5 \)), 1.30(3HA+3HB, s, Me\(_A\) and Me\(_B\)), 1.26(3HA, s, Me), 1.23(3HB, s, Me), 1.20(3HA, s, Me), 1.17(3HB, s, Me); \( \delta_c \) (63 MHz; CDCl\(_3\)) 15.1, 16.2, 22.6, 23.7, 24.5, 24.7, 25.1, 26.0, 33.7, 34.0, 42.1, 45.1, 45.6, 46.8, 47.4, 49.8, 52.4, 53.7, 189.9, 185.9. This product showed spectral properties identical to those previously reported for this compound.\(^{118,124,125}\)

\[(1R, 4S)-1,3,3-\text{Trimethylbicyclo}[2.2.1]\text{heptan-2-imine}, (1R)-\text{Fenchone Imine 69}\]

(\(1R\))-Fenchone nitrimine (18.9 g, 96.4 mmol) in dry tetrahydrofuran (190 mL) was treated at 0 °C with a slow stream of ammonia gas in the fumehood for 5 hours. The solvent was removed in vacuo to give (\(1R\))-fenchone imine as a pale yellow liquid in a 100% (14.6 g, 96.4 mmol) yield: \( v_{\text{max}} \) (neat)/cm\(^{-1}\) 3455(NH), 1664(C=N). This product showed spectral properties similar to those previously reported for this compound.\(^{118}\) This compound was then taken on to the next step immediately without further characterisation.
Experimental Details

(1R, 1α, 2α (S*), 4α)-1,3,3-Trimethylspiro[bicyclo[2.2.1]heptane-2,3'-
oxaziridine], (-)-Fenchyl Oxaziridine 70

A solution of pure\textsuperscript{119} 3-chloroperoxybenzoic acid (16.6 g, 96.2 mmol) in dry dichloromethane (500 mL) was cooled to between −30 °C and −40 °C and this caused some of the per-acid to crystallise out of the solution. On addition of a solution of (1R)-fenchone imine 69 (14.5 g, 96.0 mmol) in dry dichloromethane (40 mL) to this solution over a period of 4-5 minutes the solution became homogeneous again. This reaction mixture was then allowed to stir overnight at −30 °C to −40 °C and then allowed to warm back up to room temperature. The reaction mixture was then stirred at room temperature for a further 2 hours until all of the per-acid had reacted (tlc) by which time much of the 3-chlorobenzoic acid by-product had crystallised out of the solution. The solvent was then removed \textit{in vacuo} until approximately 25% of the original volume remained. Petroleum ether (500 mL) was then added to the mixture and the solvent was again removed \textit{in vacuo} until approximately 25% of the original volume remained. This process was repeated once more and then more petroleum ether (600 mL) was added to the mixture. The 3-chlorobenzoic acid by-product, which had been precipitated out by this process, was then removed by filtration, and the rest of this by-product was washed out of the resultant solution by washing with aqueous sodium hydroxide (1.0 M, 3×200 mL). The organic solution was dried (MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo} to give crude (−)-fenchyl oxaziridine 70 as a pale yellow oil. This was then dissolved in dichloromethane, filtered through silica (15 g) and then washed through with more dichloromethane until no more oxaziridine remained in the silica (tlc). The solvent was then removed \textit{in vacuo} to give (−)-fenchyl oxaziridine 70 as a colourless oil in an 86% (13.9 g, 83.2 mmol) yield. The product (−)-fenchyl oxaziridine 70 was found to exist as a pair of diastereoisomers in a 60:40 ratio, and we are still unsure of whether this diastereoisomerism is due 70 existing as a pair of invertomers, or, a pair of \textit{endo}\textit{exo}
Experimental Details
diastereoisomers. $[\alpha]^{25}_D = -4.40$ (CHCl$_3$); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3199(NH); $\delta_H$ (250 MHz; CDCl$_3$) 3.81($\text{HA}$, br.s, NH), 3.69($\text{HB}$, br.s, NH), 1.91-1.01($\text{H}_{\text{A}+\text{B}}$, m), 0.92(9H, s, 3xMe), 0.90(3H, s, Me), 0.84(6H, s, Me); $\delta_C$ (100 MHz; CDCl$_3$) 13.0(Me), 14.1(Me), 22.4(Me), 22.6(Me), 23.3(Me), 23.4(Me), 25.3(Me), 31.1(CH$_2$), 31.7(CH$_2$), 39.8(C$_{\text{quat}}$), 41.1(CH$_2$), 41.8(CH$_2$), 46.56(C$_{\text{quat}}$), 46.60(C$_{\text{quat}}$), 47.2(CH), 47.4(CH), 92.9(C$_{\text{quat}}$), 93.4(C$_{\text{quat}}$) (one CH$_2$, and two C$_{\text{quat}}$ signals obscured presumably by overlap with another signal); Found: M$^+$, 167.13050 C$_{12}$H$_{19}$N$_2$O$_2$ requires 167.13101; m/z 168(MH$^+$), 167(M$^+$), 152, 138,134, 124, 108, 95, 91, 81, 69, 67, 55.

(1S, 4R)-1-Oxo-2-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate, (IR)-(+)-Camphorquinone Mononitrimine 72

![Image of the nitrimine structure]

To a mixture of (1R)-(+)camphorquinone monoxide 60 (500 mg, 2.76 mmol) and pyridine (250 µL, 224 mg, 3.09 mmol) in acetonitrile (10 mL) was added nitrosyl sulfuric acid (355 mg, 2.79 mmol) and the reaction mixture stirred for 1 hour at room temperature. When the reaction was complete (tlc), the reaction mixture was added to a solution of brine (40 mL) and extracted with dichloromethane (3x50 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed in vacuo to give a yellow solid mixture which was purified by column chromatography to give (1R)-(+)camphorquinone mononitrimine 72 as a yellow solid in a 30% (174 mg, 0.830 mmol) yield. The product was shown to consist of a mixture of syn and anti diastereoisomers of the nitrimine present in a 1:1 mixture: $[\alpha]^{25}_D = +104.95$ (CHCl$_3$); mp 46-47 °C; Found%: C, 57.24; H, 6.64; N, 13.04 C$_{10}$H$_{14}$N$_2$O$_3$ requires%: C, 57.13; H, 6.71; N, 13.32; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 1760(C=O), 1652(C=N), 1574(NNO$_2$); $\delta_H$ (250 MHz; CDCl$_3$) 2.90($\text{HA}$, d, $J = 5.0$, CH$_A$ at C1), 2.79($\text{HB}$, d, $J = 4.7$, CH$_B$ at C1), 2.27-2.19($\text{H}_{\text{A}+\text{B}}$, m), 1.95-1.64($\text{H}_{\text{A}+\text{B}}$, m), 1.09(3H, s, Me), 1.07(3H, s, Me), 1.04(6H, s, 2xMe), 0.98(3H, s, Me), 0.95(3H, s, Me); $\delta_C$ (63 MHz; CDCl$_3$) 87.3, 8.84, 16.9, 17.4, 20.8, 21.1, 23.7, 23.9, 29.5, 29.7, 44.4, 44.7, 50.6, 51.6, 58.2, 59.1, 173.1,
Experimental Details

173.2, C=N signal is obscured, and is too small to read; m/z No MH' or M' ion found
other peaks at 152, 149, 137, 136, 121, 120, 109, 107, 95, 94, 93, 82, 77, 67, 55.

(1R, 2'S, [1α, 2β(5)], 4α)-2'-Chloro-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-
2,3'-oxaziridine) and (1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one, (1R)-(+)-
Camphor 56, and (--)N-Chlorocamphoryl Oxaziridine 73, (synthesis from HCl in
1,4-dioxane)

\[
\begin{align*}
\text{(1R, 2'S, [1α, 2β(5)], 4α)-2'-Chloro-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-}
\text{2,3'-oxaziridine) and (1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one, (1R)-(+) -}
\text{Camphor 56, and (--)N-Chlorocamphoryl Oxaziridine 73, (synthesis from HCl in}
\text{1,4-dioxane)}
\end{align*}
\]

To a stirring cooled (-40 °C) solution of (+)-camphoryl oxaziridine 65 (4.0 g, 24.0 mmol) in dichloromethane (15 mL) was added hydrogen chloride in 1,4-dioxane (6 mL, 4.0 M, 24.0 mmol). A white precipitate appeared over the next 20 seconds and by 5 minutes (tlc) the reaction was complete. The reaction mixture was then diluted with dichloromethane (50 mL) and washed once with distilled water. The organic layer was then dried (MgSO₄) and the solvent removed in vacuo to give a waxy white mixture. This was purified by column chromatography (petroleum ether, then petroleum ether/dichloromethane) over silica gel to afford (--)N-chlorocamphoryl oxaziridine 73 in a 29% (1.431 g, 7.10 mmol) yield: [α]²⁵D = -160.6 (CHCl₃); mp 46-
47 °C; Found%: C, 59.70; H, 8.13; N, 6.83 C₁₀H₁₆NOCl requires%: C, 59.55; H, 8.00;
N, 6.83; νmax (neat)/cm⁻¹ No NH signal, 1469, 1371, 620(N-CI); δH (250 MHz;
CDCl₃) 2.77(1H, ddd, J =15.3, 4.9, 3.1), 2.01(1H, t, J =4.5), 1.93-1.79(1H, m), 1.60-
1.48(3H, m), 1.41-1.31(1H, m), 0.92(6H, s), 0.58(3H, s); δC (100 MHz; CDCl₃) 8.2,
18.9, 19.4, 26.7, 29.0, 34.9, 44.4, 47.3, 50.4, 96.1; m/z 167 (MH' – Cl'), 166(M' – Cl'),
152, 149, 135, 124, 108, 95, 81, 69, 55; (for crystal structure of 73 see appendices);
and (1R)-(+) -camphor 56 in a 36% (1.32g, 8.68mmol) yield: mp 178-180 °C; δH (250
MHz; CDCl₃) 2.34(1H, ddd, J = 18.3, 4.4 and 3.4, exo at C3), 2.08(1H, t, J = 4.4, CH
at bridgehead C4), 1.99-1.88(1H, m), 1.83(1H, d, J = 18.3, endo at C3), 1.73-1.59(1H,
m), 1.45-1.24(2H, m), 0.95(3H, s, Me), 0.90(3H, s, Me), 0.82(3H, s, Me). This
Experimental Details

compound showed identical spectral properties to the same compound, which has been described previously.\textsuperscript{138}

\textit{Tert-Butyl Hypochlorite}

\begin{center}
\includegraphics[width=1cm]{o-Cl.png}
\end{center}

A solution of sodium hydroxide (80 g, 2.0 mol) in water (500 mL) was prepared in a 2 L three-necked round bottomed flask equipped with a gas inlet tube reaching to nearly the bottom of the flask, a gas outlet tube and a mechanical stirrer. The flask was placed in a water bath at 15-20 °C and \textit{tert}-butyl alcohol (96 mL, 74 g, 1.0 mol) was added together with enough water to form a homogeneous solution (about 500 mL). With constant stirring, chlorine gas was then passed through the mixture for 30 minutes at a rate of approximately 1 L per minute and then for an additional 30 minutes at approximately 0.5-0.6 L per minute. The upper oily layer was then separated and was washed with sodium carbonate solution (10% w/v, 50 mL portions) until the washings were no longer acidic (pH paper). The organic layer was finally washed with distilled water (4x50 mL) and dried (CaCl\textsubscript{2}) to give 72% (87 g, 0.72 mol) of crude \textit{tert}-butyl hypochlorite which was subsequently shown by IR to be pure: \textit{v}_{\text{max}} \text{(neat)}/\text{cm}^{-1} \text{ no broad OH signal from 'BuOH at around 3500, 695(OCI).}

This compound was shown to exhibit the same spectral properties as the same compound, which was previously reported\textsuperscript{126}. The title compound is best stored in a dark coloured bottle in the refrigerator.

(1\textit{R}, 2'S, [1α, 2β(S'), 4α]-2'-Chloro-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], \textit{(-)-N-Chlorocamphoryl Oxaziridine} \textsuperscript{73} (synthesis from 'BuOCl in \textit{Et}_2\text{O})

\begin{center}
\includegraphics[width=1cm]{n-cl.png}
\end{center}
Experimental Details

To a stirring cooled (−78 °C) solution of (+)-camphoryl oxaziridine 65 (500 mg, 2.99 mmol) in diethyl ether (23 mL) was added dropwise a solution of tert-butyl hypochlorite (340 mg, 3.13 mmol) in diethyl ether (7 mL). After 2 hours the reaction was complete (tlc), and the mixture was allowed to warm to room temperature. The mixture was then diluted with more diethyl ether (50 mL) and then washed with brine (2x40 mL). The resulting solution was then dried (MgSO₄) and the solvent removed in vacuo to give a colourless oily mixture. This mixture was then purified by column chromatography (petroleum ether) over silica gel to give (−)-N-chlorocamphoryl oxaziridine 73 in an 85% (513 mg, 2.55 mmol) yield: mp 46-47 °C; δH (250 MHz; CDCl₃) 2.77(1H, ddd, J =15.3, 4.9, 3.1), 2.01(1H, t, J =4.5), 1.93-1.79(1H, m), 1.60-1.48(3H, m), 1.41-1.31(1H, m), 0.92(6H, s), 0.58(3H, s). This product was shown to have identical spectral properties to that described previously which was prepared by action of non-aqueous hydrogen chloride upon (+)-camphoryl oxaziridine.

(1R, 1α, 2β(3′), 4α)-2′-(Phenylsulfonyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3′-oxaziridine),

(Phenylsulfonyl)camphoryl Oxaziridine 59

To a mixture of (+)-camphoryl oxaziridine 65 (200 mg, 1.20 mmol) and 4-dimethylamino pyridine (200 mg, 1.64 mmol) in dichloromethane (5 mL) was added benzenesulfonyl chloride (350 μL, 484 mg, 2.74 mmol) and the reaction mixture was stirred at room temperature for 10 days. After this period, the reaction mixture was diluted to with dichloromethane (30 mL) and the organic mixture was washed with aqueous hydrochloric acid (1.0 M, 3x20 mL). The solvent was then removed in vacuo and the oily residue stirred with aqueous sodium hydroxide (1.0 M, 40 mL) for 3 hours. The mixture was then extracted with dichloromethane (3x30 mL) and the combined organic extracts washed with aqueous sodium hydroxide (1.0 M, 3x30 mL). The resulting organic solution was then dried (MgSO₄) and the solvent
Experimental Details

removed in vacuo to give a colourless oily mixture. This mixture was then purified by column chromatography (petroleum ether/dichloromethane) over silica gel to give (−)-N-(phenylsulfonyl)camphoryl oxaziridine 59 in a 62% (227 mg, 0.738 mmol) yield: mp 132-134 °C; δH (400 MHz; CDCl3) 7.98(2H, d, J =8.2), 7.70-7.66(1H, m), 7.59(2H, t, J =8.2), 2.97(1H, ddd, J =15.8, 4.8, 3.2), 2.02-1.48(6H, m), 1.12(3H, s), 0.94(3H, s), 0.63(3H, s); δC (100 MHz; CDCl3) 7.1, 16.9, 17.5, 24.6, 27.6, 33.6, 42.6, 45.5, 48.4, 96.5, 126.4, 127.2, 132.2, 135.6. This product showed spectral properties identical to those previously reported for this compound. 109

(1R, 1α, 2β(S'), 4α)-2'-{(Methanesulfonyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine} and (1R, 2'S, 1α, 2β(S'), 4α)-2'-Chloro-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine}, (−)-N-(Methanesulfonyl)camphoryl Oxaziridine 74 and (−)-N-Chlorocamphoryl Oxaziridine 73

To a mixture of (+)-camphoryl oxaziridine 65 (500 mg, 2.99 mmol) and pyridine (250 μL, 245 mg, 3.09 mmol) in dichloromethane (10 mL) was added methanesulfonyl chloride (250 μL, 370 mg, 3.23 mmol), and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was then diluted with dichloromethane (35 mL) and washed with aqueous hydrochloric acid (1.0 M, 3x50 mL), and then stirred for 2 hours with aqueous sodium hydroxide (0.5 M, 50 mL). The mixture was then separated and the aqueous layer extracted with dichloromethane (2x50 mL). The combined organic extracts were then washed with aqueous sodium hydroxide (0.5 M, 3x50 mL), and the resulting organic solution was dried (MgSO4) and the solvent removed in vacuo to give a colourless oily mixture. This was then purified by column chromatography (petroleum ether, then petroleum ether/dichloromethane) over silica to give (−)-N-chlorocamphoryl oxaziridine 73 in a 15% (89 mg, 4.42 mmol) yield: 46-47 °C; δH (250 MHz; CDCl3) 2.77(1H, ddd, J =15.3, 4.9, 3.1),
Experimental Details

2.01(1H, t, J = 4.5), 1.93-1.79(1H, m), 1.60-1.48(3H, m), 1.41-1.31(1H, m), 0.92(6H, s), 0.58(3H, s) (this product was shown to have identical properties to that described previously which was prepared by action of non-aqueous hydrogen chloride upon (+)-camphoryloxaziridine); together with (−)-N-(methanesulfonyl)camphoryl oxaziridine 74 in a 42% (335 mg, 1.25 mmol) yield: [α]D = −136.33 (CHCl₃); mp 62-64 °C; Found%: C, 54.36; H, 7.81; N, 5.58 C₁₁H₁₉NSO₃ requires%: C, 53.85; H, 7.81; N, 5.71; νmax (neat)/cm⁻¹ 1740, 1345(SO₂), 1152(SO₂); δH (250 MHz; CDCl₃) 3.13(3H, s), 2.81(1H, ddd, J = 15.6, 4.6, 3.0), 1.96-1.78(3H, m), 1.58-1.35(3H, m), 1.05(3H, s), 0.92(3H, s), 0.67(3H, s); δc (63 MHz; CDCl₃) 9.1, 18.8, 19.4, 26.6, 29.5, 35.2, 40.4, 44.5, 47.4, 50.1, 97.9; Found: M⁺, 245.10868, C₁₃H₂₁NO₃ requires 245.10857; m/z 246(MH⁺), 245(M⁺), 231, 230, 203, 189, , 176, 167, 166, 138, 137, 124, 123, 121, 110, 109, 107, 98, 96, 95, 82, 81, 79, 69, 67, 55.

General Procedure for the Synthesis of N-(Alkoxycarbonyl)camphoryl Oxaziridines from (+)-Camphoryl Oxaziridine 65

To an ice cooled solution of dry pyridine (1.0 mL, 0.978 g, 12.4 mmol) in dry dichloromethane (15 mL) was added the alkyl chloroformate (10.4 mmol). This caused a reaction characterised by some effervescence and the formation of a white precipitate. Immediately after this, a solution of (+)-camphoryloxaziridine (1.0 g, 5.99 mmol) in dry dichloromethane (2 mL) was added and the reaction mixture was allowed to warm to room temperature. After 10 minutes at room temperature, more dry pyridine (0.25 mL, 0.245 g, 3.09 mmol) was added, followed by methyl chloroformate (0.2 mL, 0.245 g, 2.59 mmol), and the reaction mixture was stirred at room temperature for a further 30 minutes until the reaction was complete (tlc). The reaction mixture was then added to a separating funnel, diluted with dichloromethane (75 mL), and the organic solution was washed with aqueous hydrochloric acid (1.0 M, 3x40 mL) followed by aqueous sodium hydroxide (1.0 M, 2x40 mL). The organic extract was then dried (MgSO₄) and the solvent removed in vacuo to give a colourless oily mixture. This mixture was then purified by column chromatography (petroleum ether/dichloromethane) over silica gel to afford the title compounds.
Experimental Details

(1R, 1α, 2β(5'), 4α)-2'-(-Methoxycarbonyl)-1,7,7-
trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine),

(-)-N-
(Methoxycarbonyl)camphoryl Oxaziridine 66

\[
\text{\(N\)-Alkoxycarbonyl oxaziridine 66 was synthesised according to the above procedure to give the title compound as a colourless solid in a 95\% (1.28 g, 5.69 mmol) yield:} \\
[\alpha]_{25}^D = -93.8 \text{ (CHCl\textsubscript{3}); mp 78-80 °C; Found\%: C, 64.16; H, 8.49; N, 6.13} \\
\text{C\textsubscript{12}H\textsubscript{19}N\textsubscript{0} requires\%: C, 63.98; H, 8.50; N, 6.22; \nu_{\text{max}} \text{ (nujol)/cm\textsuperscript{-1}} 1764; \delta_{\text{H}} \text{ (250 MHz; CDCl\textsubscript{3}) 3.85(3H, s, MeO), 2.14(1H, ddd, \(J = 14.7, 4.7 \text{ and } 3.1, \text{ exo at C3),} \\
1.93(1H, t, \(J = 4.5, \text{ endo at C3),} 1.89-1.79(1H, m), 1.65-1.48(3H, m), 1.40-1.30(1H, m), 1.01(3H, s, Me), 0.93(3H, s, Me), 0.71(3H, s, Me); \delta_{\text{C}} \text{ (63 MHz; CDCl\textsubscript{3}) 8.8,} \\
18.8, 19.4, 26.8, 29.1, 33.6, 44.3, 47.6, 49.0, 54.3, 96.7, 162.1; Found: M\textsuperscript{+}, \\
225.13674, \text{C\textsubscript{12}H\textsubscript{19}N\textsubscript{0} requires 225.13649; m/z 226(M\textsuperscript{+}), 225(M\textsuperscript{+}), 210, 198, 197,} \\
183, 182, 169, 168, 154, 150, 143, 140, 128, 124, 122, 115, 108, 96, 93, 81, 70, 67, 55.}
\]

(1R, 1α, 2β(5'), 4α)-2'-(-Ethoxycarbonyl)-1,7,7-
trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine),

(-)-N-
(Ethoxycarbonyl)camphoryl Oxaziridine 67

\[
\text{\(N\)-Alkoxycarbonyl oxaziridine 67 was synthesised according to the above procedure to give the title compound as a colourless oil in an 89\% (1.27 g, 5.33 mmol) yield:} \\
[\alpha]_{25}^D = -84.8 \text{ (CHCl\textsubscript{3}); \nu_{\text{max}} \text{ (neat)/cm\textsuperscript{-1}} 1769, 1736; \delta_{\text{H}} \text{ (250 MHz; CDCl\textsubscript{3}) 4.39-} \\
4.15(2H, m, MeCH\textsubscript{2}O), 2.15(1H, ddd, \(J = 14.6, 4.6 \text{ and } 3.0, \text{ exo at C3),} 1.93(1H, t, \(J}
\]
Experimental Details

=4.5, endo at C3), 1.89-1.78(1H, m), 1.66-1.47(3H, m), 1.41-1.26(1H, m), 1.33(3H, t, J = 7.2, CH₃CH₂O), 1.01(3H, s, Me), 0.93(3H, s, Me), 0.71(3H, s, Me); δC (63 MHz; CDCl₃) 88.8, 14.2, 18.8, 19.4, 26.8, 29.1, 33.5, 44.3, 47.6, 49.0, 63.8, 96.5, 161.5; Found: MH⁺, 239.15180, C₁₃H₂₁N⁰₃ requires 239.15214; m/z 239(M⁺), 222, 211, 194, 182, 167, 152, 135, 124, 108.

(1R, 1α, 2β(5') and 2α(R'), 4α)-3'-Phenyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptan-2,5'-[1,4,2]dioxazoles], endo/exo-5-Camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b, (reaction of (+)-camphoryl oxaziridine 65 with benzoyl chloride)

To a stirring solution of (+)-camphoryl oxaziridine 65 (500 mg, 2.99 mmol) and 4-dimethylamino pyridine (440 mg, 3.60 mmol) in dichloromethane (15 mL) was added benzoyl chloride (0.4 mL, 484 mg, 3.45 mmol) and the reaction mixture was stirred at room temperature for 2 hours. More 4-dimethylamino pyridine (200 mg, 1.64 mmol) was introduced into the mixture followed by benzoyl chloride (0.3 mL, 363 mg, 2.58 mmol) and the mixture was stirred at room temperature for another 2 hours. The solvent was then removed in vacuo and the residue stirred for 4 hours with aqueous sodium hydroxide (1.0 M, 25 mL). The mixture was then extracted with dichloromethane (3x50 mL) and the combined organic layers washed with aqueous hydrochloric acid (1.0 M, 3x75 mL). The organic layer was then dried (MgSO₄) and the solvent removed in vacuo to give a colourless oil. This oil was purified by column chromatography to give the products endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b as two inseparable diastereoisomers present in a 1:1 ratio as a colourless oil in a 22% (180 mg, 0.664 mmol) yield: νmax (DCM)/cm⁻¹ 1627, 1604; δH (250 MHz; CDCl₃) 7.82-7.75(2Hα⁺β, m, Ar-H), 7.51-7.38(3Hα⁺β, m, Ar-H), 2.43-2.33(1Hα⁺β, m, exo at camphoryl C3) 2.09-1.70(4Hα⁺β, m), 1.55-1.21(2Hα⁺β, m)
Experimental Details

1.13(3H, s, Me), 1.06(3H, s, Me), 0.91(3H, s, Me), 0.89(6H, s, 2xMe), 0.88(3H, s, Me); δc (100 MHz; CDCl₃) 9.0(Me), 9.2(Me), 19.9(Me), 20.1(Me), 26.8(CH₂), 26.9(CH₂), 28.0(CH₂), 28.6(CH₂), 44.3(CH₂), 44.6(CH₂), 44.66(CH), 44.74(CH), 48.2(C quat), 48.4(C quat), 52.9(C quat), 53.1(C quat), 123.5(C quat), 123.6(C quat), 124.46(C quat), 124.50(C quat), 126.58(CH, Ar) 126.63(CH, Ar), 128.59(CH, Ar), 128.61(CH, Ar), 131.2(CH, Ar), 157.9(C quat, C=N on dioxazole ring), 158.0(C quat, C=N, dioxazole ring), (two methyls and one CH aromatic signal were obscured either by being too small or by overlap with other signals); found: M⁺ 271.15701

C₁₇H₂₁N₀₂ requires 271.15722; m/z 272(MH⁺), 271(M⁺), 153, 152, 126, 119, 108, 95, 91, 81, 77, 67, 55; together with the starting material (+)-camphoryl oxaziridine 65 in a 46% (231mg, 1.38mmol) yield: mp 153-155 °C; δH (250.13 MHz; CDCl₃) 4.22(1HA, br.s, NH), 3.74(1HB, br.s, NH), 2.33-2.21(1HA+B, m), 1.87-1.26(6HA+B, m), 0.93(3H, s, Me), 0.91(3H, s, Me), 0.88(6H, s, 2xMe), 0.63(3H, s, Me), 0.62(3H, s, Me).

(1R, [1α, 2β(S') and 2α(R')] , 4α]-3'- (4-Nitrophenyl)-1,7,7-
trimethylspiro[bicyclo[2.2.1]heptane-2,5'-[1,4,2]dioxazoles], endo/exo-5-
Camphoryl-3-(4-nitrophenyl)-1,4,2-dioxazoles 77a/77b, (reaction of (+)-camphoryl
oxaziridine 65 with 4-nitrobenzoyl chloride)

To a stirring solution of (+)-camphoryl oxaziridine 65 (500 mg, 2.99 mmol) and 4-
dimethylamino pyridine (440 mg, 3.60 mmol) in dichloromethane (15 mL) was added
a solution of 4-nitrobenzoyl chloride (620 mg, 3.34 mmol) in acetonitrile (4 mL).
This reaction mixture was stirred at room temperature for 4 hours. More 4-
dimethylamino pyridine (150 mg, 1.23 mmol) was then added followed by 4-
Experimental Details

Nitrobenzoyl chloride (250 mg, 1.35 mmol), and the reaction mixture stirred at room temperature for a further 4 hours. When the reaction was complete (tlc) the reaction mixture was diluted to 50 mL with dichloromethane and this organic solution was washed, firstly with aqueous hydrochloric acid (1.0 M, 3x50 mL) and then with aqueous sodium hydroxide (1.0 M, 3x50 mL). The organic solution was then dried (MgSO₄) and the solvent removed in vacuo. The resulting solid was then purified by column chromatography (petroleum ether/dichloromethane) over silica gel to give the products *endo/exo*-5-camphoryl-3-(4-nitrophenyl)-1,4,2-dioxazoles 77a/77b as an inseparable mixture of diastereoisomers present in a 1:1 ratio as an off-white powder in a 63% (596 mg, 1.89 mmol) yield: mp 140-143 °C; ν<sub>max</sub> (DCM)/cm⁻¹: 1626, 1593, 1526, 1347; δ<sub>H</sub> (250 MHz; CDCl₃) 8.32-8.25 (2H<sub>A</sub>+<sub>B</sub>, m, Ar-H), 7.99-7.90(2H<sub>A</sub>+<sub>B</sub>, m, Ar-H), 2.44-2.36(1H<sub>A</sub>+<sub>B</sub>, m, camphoryl exo at C3), 2.07-1.27(6H<sub>A</sub>+<sub>B</sub>, m, Me), 1.06(3H, s, Me), 0.92(3H, s, Me), 0.88(3H, s, Me), 0.86(3H, s, Me); δ<sub>C</sub> (100 MHz; CDCl₃) 124.26(CH, Ar), 124.29(CH, Ar), 126.5(C<sub>quat</sub>), 127.0(C<sub>quat</sub>), 127.7(CH, Ar), 127.8(CH, Ar), 129.75(C<sub>quat</sub>), 129.82(C<sub>quat</sub>), 149.6(C<sub>quat</sub>, Ar, C-NO₂), 156.9(C<sub>quat</sub>, C=N on dioxazole ring), 157.3(C<sub>quat</sub>, C=N on dioxazole ring), one aromatic C-NO₂ signal obscured presumably due to overlap with other signals; Found: MH⁺, 317.14920. C₁₇H₂₀N₂O₄[H⁺] requires 317.15012; m/z 317 (MH⁺), 316(M⁺), 217, 166, 164, 153, 152, 148, 126, 108, 95, 81, 55.

(1R, 5S)-1,8,8-Trimethyl-3-azabicyclo[3.2.1]octan-2-one, (−)-α-Camphidone 78

A solution of (1R)-(−)-camphor 56 (1.0 g, 6.58 mmol) and hydroxylamine-O-sulfonic acid (1.5 g, 13.3 mmol) in formic acid (30 mL) was heated under reflux for 20 hours. The cooled reaction mixture was then added to a solution of brine (30 mL) and the
mixture was extracted with dichloromethane (3x50 mL). The combined organic extracts were then washed with aqueous sodium hydroxide (1.0 M, 2x75 mL), dried (MgSO₄) and the solvent removed in vacuo to give a white solid residue. This residue was then purified by column chromatography (methanol/dichloromethane) over silica gel to give (−)-α-camphidone 78 as a white crystalline solid in a 37% (410 mg, 2.46 mmol) yield: mp 228-230 °C; δH (250 MHz; CDCl₃) 6.25 (1H, br.s), 3.42 (1H, dd, J = 11.1 and 2.7, exo at C4), 2.96 (1H, d, J = 11.2, endo at C4), 2.15-1.43 (5H, m), 1.04 (3H, s), 0.99 (3H, s), 0.89 (3H, s); δC (63 MHz; CDCl₃) 13.3 (Me), 19.2 (Me), 22.9 (Me), 27.6 (CH₂), 37.8 (CH₂), 42.1 (C quat), 43.5 (CH), 47.0 (CH₂), 52.1 (C quat), 178.8 (C quat, RCONHR). This product showed spectral properties identical to those previously reported for this compound.¹¹³,¹²⁷

(1R, 5S)-1,8,8-Trimethyl-3-(4-nitrobenzoyl)-3-azabicyclo[3.2.1]octan-2-one, (−)N-(4-Nitrobenzoyl)-α-camphidone 79

To a mixture of (−)-α-camphidone 78 (100 mg, 0.599 mmol) and pyridine (0.5 mL, 489 mg, 6.18 mmol) in chloroform (4 mL) was added 4-nitrobenzoyl chloride (120 mg, 0.647 mmol), and the reaction mixture was stirred under reflux for eight hours. More 4-nitrobenzoyl chloride (70 mg, 0.377 mmol) was added and the reaction mixture left to reflux for a further sixteen hours. The reaction mixture was allowed to cool and was then diluted with dichloromethane (20 mL). This solution was washed with aqueous sodium hydroxide (1.0 M, 3x20 mL) and then dried (MgSO₄) and the solvent removed in vacuo to give a pale brown solid residue. This residue was then purified by column chromatography (petroleum ether/dichloromethane) over silica gel to give (−)-N-(4-nitrobenzoyl)-α-camphidone 79 as a pale yellow crystalline solid in a 62% (118 mg, 0.373 mmol) yield: mp [α]²⁵_D = −15.5 (CHCl₃); 186-187 °C; ν max (DCM)/cm⁻¹ 1700, 1670, 1528, 1350; δH (250 MHz; CDCl₃) 8.25-8.20 (2H, m, Ar-H),
Experimental Details

7.58-7.52 (2H, m, Ar-H), 3.92 (1H, ddd, J = 12.6, 3.1 and 1.6, exo at C4), 3.54 (1H, dd, J = 12.5 and 2.0, endo at C4), 2.33-2.10 (3H, m), 1.98-1.68 (2H, m) 1.02 (3H, s, Me), 1.01 (3H, s, Me), 1.00 (3H, s, Me); δ_c (63 MHz; CDCl₃) 13.7, 19.6, 23.1, 27.3, 35.8, 43.65, 43.76, 51.5, 54.4, 123.5, 127.3, 143.1, 148.9, 172.6, 178.9; Found: M⁺, 316.141811. C₁₇H₂₀N₂O₄ requires 316.142307; m/z 317 (MH⁺), 316 (M⁺), 288, 273, 205, 167, 166, 152, 151, 150, 134, 120, 109, 104, 95, 92, 81, 76, 69, 67, 55.

(1R, 5S)-1,8,8-Trimethyl-2-azabicyclo[3.2.1]octan-3-one, Isomer of α-Camphidone, Isomeric Lactam 80

To a cold (-22 °C) solution of (1R)-(−)-camphor oxime 62 (5.38 g, 32.2 mmol) in pyridine (25 mL) was added methanesulfonyl chloride (5.0 mL, 4.89 g, 58.1 mmol) and the reaction mixture was stirred for 3 hours. The temperature was then raised and at approximately 10 °C, a strong exothermic reaction took place and the mixture became dark yellow. After an additional 2 hours stirring at room temperature the mixture was poured onto iced water and extracted with dichloromethane. The organic layer was washed with sodium bicarbonate and brine, dried (MgSO₄) and the solvent removed in vacuo. The mixture was then separated by column chromatography on silica gel (petroleum ether/dichloromethane) to remove the non-polar products of "abnormal" Beckmann fragmentation (mixture of nitriles, 84%) and the more polar product was eluted with dichloromethane/methanol to give (1R, 5S)-1,8,8-trimethyl-2-azabicyclo[3.2.1]octan-3-one (isomeric lactam 80) in a 4.7% (251 mg, 1.50 mmol) yield: mp 195-197 °C; δ_H (250 MHz; CDCl₃) 6.84 (1H, br.s), 2.54 (1H, ddd, J = 18.0, 4.7 and 2.7, exo at C4), 2.10 (1H, dd, J = 18.0 and 1.6, endo at C4), 2.04-1.78 (4H, m), 1.49-1.39 (1H, m), 1.07 (3H, s, Me), 0.96 (3H, s, Me), 0.91 (3H, s, Me). This product showed spectral properties identical to those previously reported for this compound.¹¹³,¹²⁸
Experimental Details

(1R, 5S)-1,8,8-Trimethyl-2-(4-nitrobenzoyl)-2-azabicyclo[3.2.1]octan-3-one, Isomeric Lactam; 4-Nitrobenzoyl Derivative 81

To a stirring solution of (1R, 5S)-1,8,8-trimethyl-2-azabicyclo[3.2.1]octan-3-one (isomeric lactam 80, 100 mg, 0.599 mmol) in toluene (5 mL) was added pyridine (0.5 mL, 489 mg, 6.18 mmol) followed by 4-nitrobenzoyl chloride (290 mg, 1.56 mmol) and the reaction mixture refluxed overnight. When the reaction was complete (tlc), the reaction mixture was allowed to cool to room temperature and diluted with diethyl ether (25 mL). This mixture was then washed with aqueous sodium hydroxide (1.0 M, 3x20 mL) and then aqueous hydrochloric acid (1.0 M, 3x20 mL) and the organic layer was dried (MgSO4) and the solvent removed in vacuo. The resulting light brown solid residue was purified by column chromatography (petroleum ether/dichloromethane) over silica gel to give (1R, 5S)-1,8,8-trimethyl-2-[(4-nitrophenyl)carbonyl]-2-azabicyclo[3.2.1]octan-3-one (isomeric lactam-4-nitrobenzoyl derivative 81) as a pale yellow crystalline solid in a 72% (136 mg, 0.431 mmol) yield: [α]D25 = -63.39; mp 124-126 ºC; νmax (DCM)/cm-1 1707, 1670, 1530, 1349; δH (250 MHz; CDCl3) 8.28-8.22(2H., m, Ar-H), 7.92-7.56(2H., m, Ar-H), 2.87(1H, ddd, J =18.2, 4.7, 2.5, exo at C4), 2.71-2.61(1H, m), 2.29(1H, dd J =18.2, 1.7, endo at C4), 2.23-1.93(3H, m), 1.70-1.52(1H, m), 1.32(3H, s, Me), 1.26(3H, s, Me), 1.09(3H, s, Me); δC (63 MHz; CDCl3) 16.4, 18.5, 24.6, 27.9, 37.5, 40.3, 42.2, 45.0, 71.4, 123.8, 129.4, 142.1, 159.5, 173.9, 174.9; Found: M+, 316.14212. C17H20N2O4 requires 316.142307; m/z 317 (MH+), 316(M+), 288, 273, 234, 219, 206, 205, 167, 166, 151, 150, 134, 124, 120, 109, 108, 104, 92, 76, 69, 67, 55.
Experimental Details

Benzohydroximinoyl chloride

To a stirring solution of benzaldehyde oxime (45.66 g, 0.300 mol) in DMF (250 mL) at 25-30 °C was added about 10-20% of 40.1 g (0.300 mol) N-chlorosuccinimide. As the reaction did not self-initiate within the first 10 minutes (as indicated by a slight temperature rise), 20 mL of gas from the head space of a concentrated hydrochloric acid reagent bottle was collected in a syringe and bubbled through the DMF solution. The reaction was then initiated within the next 10-15 minutes. Once the reaction had begun, the reaction mixture was kept below 40 °C by both the rate of addition of the rest of the N-chlorosuccinimide and also cooling in the water bath. Completion of the reaction was indicated by the cessation of the exothermic reaction and by the formation of no (or a very weak) dark coloured ring upon the application of a small drop of the reaction mixture to starch-iodide paper previously moistened with distilled water. The solution was then poured into iced water (1 L) and extracted with diethyl ether (2x300 mL). The combined extracts were washed with water (3x200 mL), dried (CaSO₄) and the solvent removed in vacuo to give benzohydroximinoyl chloride in a 75% (34.9 g, 0.224 mol) yield: mp 50-52°C; νmax (DCM)/cm⁻¹ 3320(OH), 1600(C=N). This compound showed identical spectral properties to the same compound, which was previously described.¹³⁰

(1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one and Benzamide, (1R)-(+) Camphor 56 and Benzamide (deprotection of isomeric endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b)
Experimental Details

A mixture of isomeric endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b (100 mg, 0.369 mmol) obtained from the reaction of (+) camphoryloxaziridine 65 and benzoyl chloride was dissolved in ethyl acetate (5 mL). Palladium on charcoal was then added to this mixture and the flask was sealed with a septum. The flask was then purged of residual air with hydrogen, and the reaction mixture was then hydrogenated at room temperature under residual balloon pressure for six days. The palladium catalyst was then removed by filtration and the solvent removed in vacuo to give a white solid. This solid was dissolved in dichloromethane (5 mL) and then petroleum ether (25 mL) was added to the mixture upon which a white precipitate was formed. The precipitate was isolated by filtration and was and dried to give the product benzamide as a white solid in a 47% (21 mg, 0.174 mmol) yield: mp 127-129 °C; \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.85-7.79(2H, m, Ar-H), 7.57-7.42(3H, m, Ar-H), 6.05(2H, br.s, 2H, amide NH\(_2\)); \( \nu_{max} \) (CDCl\(_3\))/cm\(^{-1}\) 3532(NH), 3414(NH), 1676(amide C=O); This product was identical to that previously reported. 139 The filtrate was then evaporated in vacuo and the remaining residue purified by column chromatography (petroleum ether/dichloromethane) over silica gel to give (1R)-(+)‐camphor 56 as a white solid in a 94% (53 mg, 0.349 mmol) yield: mp 178-180 °C; \( \delta_H \) (250 MHz; CDCl\(_3\)) 2.34(1H, ddd, \( J = 18.3, 4.4 \) and 3.4, exo at C3), 2.08(1H, t, \( J = 4.4, \) CH at bridgehead C4), 1.99-1.88(1H, m), 1.83(1H, d, \( J = 18.3, \) endo at C3), 1.73-1.59(1H, m), 1.45-1.24(2H, m), 0.95(3H, s, Me), 0.90(3H, s, Me), 0.82(3H, s, Me). This compound showed identical spectral properties to the same compound, which was reported previously. 138

\((1R, 1\alpha, 2\beta(S'), 4\alpha)-2'-Acetyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], (-)-N-Acetylcamphoryl Oxaziridine 82\)

To (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) in dichloromethane (5 mL) at room temperature was added acetic anhydride (450 \( \mu \)L, 487 mg, 4.77 mmol) and the reaction mixture was stirred overnight at room temperature. This mixture was then
Experimental Details
diluted with diethyl ether (25 mL) and the organic solution washed with 0.5 M aqueous sodium hydroxide (3x25 mL). The organic layer was then dried (MgSO₄) and the solvent removed in vacuo to give crude (-)-N-acetylcamphoryl oxaziridine 82 as a colourless oil in a 97% (1.46 mmol, 305 mg) yield: [α]²⁰D = -82.21 (CHCl₃); νmax (DCM)/cm⁻¹ 1732(C=O); δH (250 MHz; CDCl₃) 2.19(1H, ddd, J =14.6, 4.7 and 3.0, exo at C3), 2.10(3H, s, CH₃CONR₂), 1.90-1.75(2H, m), 1.57-1.25(4H, m), 0.98(3H, s, Me), 0.88(3H, m, Me), 0.66(3H, m, Me); δC (63 MHz; CDCl₃) 9.3, 19.4, 19.9, 23.4, 27.3, 29.6, 34.0, 44.9, 48.2, 49.5, 98.1(Cquat, oxaziridine C), 188.1(Cquat, Acetyl C=O); Found: M⁺, 209.1466. C₁₂H₁₉NΟ₂ requires 209.14157; m/z 209 (M⁺), 192, 167, 152, 134, 124, 108, 95, 93, 81, 67, 55.

(1R, [1α, 2β(5')] and 2α(R'), 4α)-3'-Methyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,5'-[1,4,2]dioxazoles], endo/exo-5-Camphoryl-3-methyl-1,4,2-dioxazoles 83a/83b (isomerisation of N-acetylcamphoryl oxaziridine 82)

(-)-N-Acetylcamphoryl oxaziridine 82 (194 mg, 0.929 mmol) was stirred overnight in dichloromethane (5 mL) with silica gel (3.0 g) at room temperature, after which time the mixture showed no oxidising properties (tlc/KI). The solvent was removed in vacuo and to the remaining mixture further solvent was added (10 mL, 2:1 petroleum ether:dichloromethane). This mixture was then filtered through silica gel (5 g) and then the solids washed with more solvent (45 mL of 2:1 petroleum ether:dichloromethane). The filtrate and combined washings were placed in a round bottomed flask and the solvent removed in vacuo to give an inseparable mixture of endo/exo-5-camphoryl-3-methyl-1,4,2-dioxazoles 83a/83b as a colourless oil in a 90% (174mg, 0.833mmol) yield. 1,4,2-Dioxazoles 83a/83b were shown (¹H NMR spectroscopy) to be present in a 1:1 ratio: δH (250 MHz; CDCl₃) 4.27-4.15(1H A-B, m), 164
Experimental Details

3.93(3H<sub>a</sub>, s, Me-dioxazole C3), 3.93(3H<sub>b</sub>, s, Me-dioxazole C3), 3.80-3.60(4H<sub>A,B</sub>, m), 3.43-3.13(2H<sub>A,B</sub>, m), 2.95(3H, s, Me), 2.94(3H, s, Me), 2.83(3H, s, Me), 2.82(3H, s, Me), 2.80(3H, s, Me), 2.79(3H, s, Me); δ<sub>c</sub> (63 MHz; CDCl<sub>3</sub>) 8.8, 9.05, 9.09, 9.2, 19.7, 19.8, 19.9, 20.0, 26.6, 26.7, 27.9, 28.4, 43.8, 44.3, 44.5, 44.6, 48.0, 48.1, 52.5, 52.8, 123.2, 123.9, 156.8, 157.5; ν<sub>max</sub> (DCM)/cm<sup>-1</sup> 1660; Found: M<sup>+</sup> 209.1462. C<sub>12</sub>H<sub>19</sub>N<sub>2</sub>O requires 209.14157; m/z 210(MH<sup>+</sup>), 209(M<sup>+</sup>), 153, 152, 138, 126, 108, 95, 83, 68, 55.

(1R, [1α, 2β(S)<sup>′</sup>, 4α])-2'-Benzoyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine] and (1R, [1α, 2β(S)<sup>′</sup> and 2α(R)<sup>′</sup>, 4α)-3'-Phenyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,5'-[1,4,2]dioxazoles], N-Benzoylcamphoryl Oxaziridine 84, and endo/exo-5-Camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b (reaction between (+)-camphoryl oxaziridine 65 and benzoic anhydride)

To a stirring solution of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) in dichloromethane (5.0 mL) at room temperature was added benzoic anhydride (900 μL, 1.08 g, 4.77 mmol) and the reaction mixture was stirred for three days. When the reaction was complete (tlc), the reaction mixture was diluted to 75 mL with dichloromethane, washed with aqueous sodium hydroxide (1.0 M, 4x50 mL), dried (MgSO<sub>4</sub>) and the solvent removed in vacuo to give the crude product as a colourless oil in a 632 mg yield. This crude product was found by <sup>1</sup>H NMR spectroscopy to consist of a mixture of benzoic anhydride, N-benzoylecamphoryl oxaziridine 84, and endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b in a ratio of 5:3:1:1. This gives an approximate yield of N-benzoylecamphoryl oxaziridine 84 as 51% (207 mg, 0.77 mmol), and a yield of the endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76b as 17% (69 mg, 0.26 mmol) each, together with 288 mg (1.27 mmol) of unreacted benzoic anhydride. Further attempts to purify the crude product by
removal of excess benzoic anhydride from this mixture were deemed unnecessary at this stage as the partial isomerisation of \( N \)-benzoylcamphoryl oxaziridine 84 to dioxazoles \( 76a/76b \) was already significant, and, any crude \( N \)-benzoylcamphoryl oxaziridine 84 which could be prepared by this method would have to have a purity of less than 60%. For the \( ^1H \) NMR spectrum of this mixture, signals from benzoic anhydride are denoted by the subscript \( A \), signals from \( N \)-benzoylcamphoryl oxaziridine 84 are denoted by the subscript \( B \), and signals from \( \text{endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles} \ 76a/76b \) are denoted by the subscripts \( C \) and \( D \).

Where signals are described by \( H_{CD} \), then this signal comes from either \( C \) or \( D \): \( \nu_{\text{max}} \) (neat)/cm\(^{-1} \) 1786 (anhydride \( C=O \)), 1726 (anhydride \( C=O \) and oxaziridine \( C=O \)), 1626 and 1599 (dioxazole \( C=N \)); \( \delta_H \) (250 MHz; CDCl\(_3\) ) 8.18-8.13 (4\( H_A \), m, Ar-H), 8.07-8.02 (2\( H_B \), m, Ar-H), 7.81-7.74 (2\( H_C+D \), m, Ar-H), 7.71-7.37 (6\( H_A \) and 3\( H_B+C+D \), m, Ar-H), 2.43-2.25 (1\( H_B+C+D \), m), 2.16-1.19 (6\( H_B+C+D \), m), 1.12 (3\( H_C+D \), s, Me), 1.06 (3\( H_C+D \), s, Me), 0.91 (3\( H_C+D \), s, Me), 0.90 (3\( H_B \), s, Me), 0.88 (6\( H_C+D \), s, 2xMe), 0.87 (3\( H_C+D \), s, Me), 0.85 (3\( H_B \), s, Me), 0.77 (3\( H_B \), s, Me).

(1\( R \), [1\( \alpha \), 2\( \beta \)\((S')\) and 2\( \alpha \)(\( R' \)), 4\( \alpha \))3'-Phenyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,5'-[1,4,2]dioxazoles], \( \text{endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles} \ 76a/76b \) (isomerisation of \( \text{N-benzoylcamphoryl oxaziridine} \ 84 \) to phenyl dioxazoles)

The crude mixture prepared previously containing benzoic anhydride, \( \text{endo/exo-5-camphoryl-3-phenyl-1,4,2-dioxazoles} \ 76a/76b \) and \( \text{N-benzoylcamphoryl oxaziridine} \ 84 \) (632 mg) was stirred at room temperature in dichloromethane (10 mL) with silica gel (5.0 g) overnight. When no oxidising products were left in the mixture (tlc/KI), the mixture was diluted with a mixture of petroleum ether/dichloromethane (1:1, 50 mL), and the solution was filtered. The silica gel residue was washed with more of this
**Experimental Details**

organic solvent (150 mL) under pressure. The combined organic solution and washings were then placed into a round-bottomed flask and the solvent was removed *in vacuo* to give the crude product as a colourless oil in a yield of 366 mg. The product was shown by \(^1\)H NMR to be a mixture of benzoic anhydride and *endo/exo*-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76 in a ratio of approximately 1:1:1 respectively. This gives approximate overall yields of *endo/exo*-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76 from (+)-camphoryl oxaziridine 65 to be 32% (129 mg, 0.476 mmol) each together with 108 mg (0.478 mmol) of unreacted benzoic anhydride. For the \(^1\)H NMR spectrum of this mixture, signals from benzoic anhydride have the subscript A and *endo/exo*-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76 have the subscript B and C: \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 1788 (anhydride C=O), 1727 (anhydride C=O), 1626 and 1600 (dioxazole C=N); \(\delta\)\(^{(\text{H})}\) (250 MHz; CDCl\(_3\)) 8.18-8.11 (4H\(_A\), m, Ar-H), 7.82-7.75 (2H\(_{BC}\), m, Ar-H), 7.72-7.38 (6H\(_A\) and 3H\(_{BC}\), m, Ar-H), 2.43-2.32 (1H\(_{BC}\), m), 2.10-1.64 (4H\(_{BC}\), m), 1.55-1.25 (2H\(_{BC}\), m), 1.13 (3H\(_{BC}\), s, Me), 1.06 (3H\(_{BC}\), s, Me), 0.91 (3H\(_{BC}\), s, Me), 0.89 (6H\(_{BC}\), s, 2xMe), 0.88 (3H\(_{BC}\), s, Me); \(m/z\) 272 (MH\(^+\)), 271 (M\(^+\)), 153, 152, 126, 119, 108, 95, 91, 81, 77, 67, 55. The products (*endo/exo*-5-camphoryl-3-phenyl-1,4,2-dioxazoles 76a/76) were shown to have identical spectral properties to the same products that were prepared by the reaction of benzoyl chloride with (+)-camphoryl oxaziridine 65.

\((1R, 1\alpha, 2\beta(\gamma'), 4\alpha))\)-2'-(Diphenylphosphinic)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], (-)N-(Diphenylphosphinic)camphoryl Oxaziridine 85

To a solution of (+)-camphoryl oxaziridine 65 (2.00 g, 12.0 mmol) and 4-dimethylaminopyridine (1.60 g, 13.1 mmol) in dichloromethane (25 mL) was added diphenylphosphinic chloride (2.45 mL, 3.04 g, 12.8 mmol), and the reaction mixture was stirred at room temperature overnight. More 4-dimethylaminopyridine (0.800 g,
Experimental Details

6.55 mmol) was then added followed by diphenylphosphinic chloride (1.22 mL, 1.51 g, 6.39 mmol), and the reaction mixture was then stirred again at room temperature for a further 8 hours. When the reaction was complete (tlc) the reaction mixture was diluted with dichloromethane (100 mL) and the organic mixture was washed with aqueous hydrochloric acid (1.0 M, 3x100 mL) and then with aqueous sodium hydroxide (2.0 M, 3x100 mL). The organic solution was dried (MgSO4) and the solvent removed in vacuo to give a yellow liquid mixture which was purified by column chromatography (dichloromethane/methanol) over silica gel to give (-)-N-(diphenylphosphinic)camphoryl oxaziridine 85 as a pale yellow oil in a 37% (1.65 g, 4.4 mmol) yield: [α]D25 = -6.649 (CHCl3); νmax (neat)/cm⁻¹ 1440(P=O), 1215(P=O); δH (250 MHz; CDCl3) 8.00-7.92(4H, m, Ar-H), 7.54-7.39(6H, m, Ar-H), 2.75(1H, dt, J =15.6 and 3.0, exo at C3), 1.91(1H, d, J =15.6, endo at C3), 1.77-1.21(5H, m), 0.78(3H, s, Me), 0.70(3H, s, Me), 0.36(3H, s, Me); δC (63 MHz; CDCl3) 18.4(Me), 19.4(Me), 26.5(CH2), 29.7(CH2), 36.6(CH2), 44.3(CH), 47.1(Cquat), 49.8(Cquat), 98.8(Cquat), 128.4(CH, d, J =9.5), 128.6(CH, d, J =8.4), 128.8(Cquat, part of a multiplet which was obscured by the doublets at 128.39 and 128.59), 130.6(Cquat, d, J =22.6), 131.7(CH, d, J =11.5), 132.0(CH, d, J =10.2), 132.1(CH, d, J =3.5), 132.6(CH, d, J =3.2); Found: M⁺, 367.17010 C_{22}H_{26}NO_{15}P requires 367.170105; m/z 368(MH⁺), 367(M⁺), 352, 298, 260, 259, 244, 220, 219, 202, 201, 199, 183, 166, 152, 142, 141, 107, 93, 91, 79, 77, 67, 55.

Dipentafluorophenyl Disulfide, (1R, 4S)-N1-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-yliden)pentafluorobenzene-1-sulfenamide, (1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one and (1R, 1\alpha, 2\beta(5'), 4\alpha)-2'-(Pentafluorobenzenesulfenyl)-1,7,7-trimethylspirop[bicyclo[2.2.1]heptane-2,3'-oxaziridine], Dipentafluorophenyl Disulfide, (+)-(S-Pentafluorophenyl)camphor Thiooxime 86, (1R)-(·)-Camphor 56 and (-)-N-(Pentafluorophenylsulfenyl)camphoryl Oxaziridine 87
Experimental Details

To a mixture of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) and dry pyridine (250 µL, 245 mg, 3.10 mmol) in dry dichloromethane (5 mL) was added with stirring pentafluorobenzene sulfonyl chloride (400 mg, 1.71 mmol), and the reaction mixture was stirred at room temperature for 1 hour. After the reaction was complete (1 hour, tlc), the reaction mixture was diluted with dichloromethane 25 mL and then washed firstly with aqueous hydrochloric acid (1.0 M, 3x20 mL) and then with aqueous sodium hydroxide (0.5 M, 3x20 mL). The resultant organic solution was then dried (MgSO4) and the solvent removed in vacuo to give a waxy white mixture. This mixture was then purified by column chromatography (petroleum ether/dichloromethane and then methanol/dichloromethane) to give dipentafluorophenyl disulfide as a pale yellow solid in a yield of 20% (117 mg, 0.294 mmol): mp 52-53 °C; νmax (DCM)/cm⁻¹ 1540, 1503, 1487, 1092, 1023, 978, No C-H signals; δH (250 MHz; CDCl3) No signal; δC (63 MHz; CDCl3) Aromatic C-F multiplets - (149.10-148.96(m), 146.61-146.47 (m), 144.96-144.82(m), 142.38(s), 139.37-139.19(m), 137.00-136.69(m)), Aromatic C-S; 110.66; Found: M⁺, 397.92853, C13H21NO3 requires 397.92817; mlz 399(MH⁺), 398(M⁺), 231, 200, 199, 180, 155, 149, 117, 69; followed by (+)-(S-pentafluorophenyl)camphor thiooxime 86 as a light brown liquid 10% (54 mg, 0.156 mmol) yield: [α]D25 = +35.58 (CHCl3); νmax (DCM)/cm⁻¹ 1637, 1512,1488, 1094, 982, δH (250 MHz; CDCl3) 2.60-2.49(1H, m, exo at C3), 2.04((1H, t, J = 4.5, CH at C4), 1.98-1.83(2H, m), 1.94(1H, d, J = 20.6, endo at C3), 1.74-1.58(1H, m), 1.45-1.23(2H, m), 0.92(3H, s, Me), 0.91(3H, s, Me), 0.78(3H, s, Me); δC (63 MHz; CDCl3) 11.1, 19.3, 19.8, 27.7, 32.3, 39.3, 44.9, 49.0, 57.2, 112.5(Aromatic C-S), Aromatic C-F multiplets(136.8, 139.3, 141.1, 145.6, 145.6, 147.9), 184.5; Found: M⁺, 349.09240 C16H16NSF5 requires 349.09257; mlz 350(MH⁺), 348(M⁺), 334, 306, 293, 200, 199, 155, 150, 133, 123, 109, 94, 81, 69, 67, 55; then (1R)-(−)-camphor 56 as a white solid in a 28% (63 mg, 0.414 mmol) yield: mp 178-180 °C; δH (250 MHz; CDCl3) 2.34(1H, ddd, J = 18.3, 4.4 and 3.4, exo at C3), 2.08((1H, t, J = 4.4, CH at bridgehead C4), 1.99-1.88(1H, m), 1.83(1H, d, J = 18.3, endo at C3), 1.73-1.59(1H, m), 1.45-1.24(2H, m), 0.95(3H, s, Me), 0.90(3H, s, Me), 0.82(3H, s, Me). This compound showed identical spectral properties to the same compound which was described previously,13 and finally, (−)-N-(pentafluorophenylsulfonyl)camphoryl oxaziridine 87 as a colourless oil that
Experimental Details

solidified upon standing overnight in a 41% (222 mg, 0.608 mmol) yield: $[\alpha]^{25}_D = -3.6$ (CHCl$_3$); mp 85-87 °C; $\nu_{\text{max}}$ (nujol)/cm$^{-1}$ 1680, 1641, 1377, 1260, 1148, 1084, 761, 747, 720, 695; $\delta^H$ (250 MHz; CDCl$_3$) 2.81(1H, ddd, $J = 18.3$, 4.9, 2.4, exo at C3), 2.38(1H, dd, $J = 18.3$, 1.5, endo at C3), 2.13-1.76(3H, m), 1.57-1.37(2H, m), 1.45(3H, s, Me), 0.99(3H, s), 0.92(3H, s); $\delta^C$ (63 MHz; CDCl$_3$) 19.0, 20.0, 26.7, 29.3, 39.4, 41.8, 43.4, 46.9, 64.9, 77.3, Aromatic Multiplets due to C-F splitting (C-S;113.2-113.4(m), C-F; 137.4-137.7(m), 139.9-140.2(m), 141.5(s), 143.9-144.1(m), 145.7-145.9(m), 148.3-148.4(m)); Found: M$^+$, 365.08752 C$_{18}$H$_{16}$NSF$_3$ requires 365.08727; m/z 366(MH$^+$), 365(M$^+$), 350, 309, 308, 200, 199, 167, 166, 155, 149, 124, 121, 109, 108, 107, 95, 93, 83, 81, 69, 67, 55.

(1R)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one, (1R, $[\alpha$, 2$c$(S$'$), 4$c$])-2'- (Methoxycarbonyl)-1,3,3-trimethylspirobicyclo[2.2.1]heptane-2,3'-oxaziridine
and (1R, 2$^\alpha$R and 2$^\alpha$S, $[\alpha$, 2$c$(S$'$), 4$c$])-2'-Chloro-1,3,3-trimethylspirobicyclo[2.2.1]heptane-2,3'-oxaziridines, (1R)-(--)-Fenchone 55, N-(Methoxycarbonyl)fenchyl Oxaziridine 88 and N-Chlorofenchyl Oxaziridines 89a/89b

To an ice-cooled stirring solution of dry pyridine (300 µL, 293 mg, 3.71 mmol) in dry dichloromethane was added methyl chloroformate (200 µL, 245 mg, 2.59 mmol) followed by a solution of (--)-fenchyl oxaziridine 70 (250 mg, 1.50 mmol) in dry dichloromethane (1.0 mL). The reaction mixture was then allowed to reach room temperature and stirred for two hours at room temperature. More dry pyridine (300 µL, 293 mg, 3.71 mmol) was then added followed by more methyl chloroformate (200 µL, 245 mg, 2.59 mmol) and the reaction mixture was stirred for a further 4 hours by which time the reaction was complete (tlc). The reaction mixture was then diluted to 50 mL with dichloromethane and this organic mixture was washed firstly with aqueous hydrochloric acid (1.0 M, 3x40 mL) and then with aqueous sodium
Experimental Details

tydroxide (1.0 M, 3x40 mL). The organic solution was dried (MgSO₄) and the solvent removed in vacuo to give a pale blue liquid which was purified by column chromatography (petroleum ether then petroleum ether/dichloromethane) over silica gel to give N-chlorofenchyl oxaziridines 89a/89b as an oxidising (tlc/KI) unstable pale blue liquid in a 16% (24 mg, 0.236 mmol) yield. This product appeared to be present as two isomers in a 4:1 ratio (Isomer A:Isomer B): νₘₐₓ (neat)/cm⁻¹ 1575(N=O), 666(N-Cl); δₓ (250 MHz; CDCl₃) 2.14-1.44(6Hₓ and 6Hᵧ, m), 1.38(1Hₓ, dd, J=10.4, 1.6), corresponding signal from B too small and obscured by methyl signal at 1.26, 1.26(3Hₓ and 1Hᵧ, s), 1.10(3Hᵧ, s), 0.89(3Hₓ, s), 0.82(3Hₓ, s), 0.77(3Hᵧ, s); δᵧ (63 MHz; CDCl₃) As this product was unstable it was not possible to obtain a reliable ¹³C NMR spectrum as it was difficult to distinguish the signals from this product from those of its products of decomposition. The characteristic signal from the oxaziridine C atom was however present at 97.3ppm. N-(Methoxycarbonyl)fenchyl oxaziridine 88 and (1R)-(−)-fenchone 55 were isolated as a colourless liquid, present as an inseparable mixture in a 1:1 ratio, and in 205 mg yield. This ratio indicates that yields of N-(methoxycarbonyl)fenchyl oxaziridine 88 and (1R)-(−)-fenchone 55 were 19% (65.6 mg, 0.291 mmol) and 19% (45.4 mg, 0.291mmol) respectively. For spectral interpretations, oxaziridine 88 has the subscript A, whereas (−)-fenchone 55 has the subscript B: νₘₐₓ (nujol)/cm⁻¹ 1767(N-CO₂Me), 1740(fenchone C=O); δₓ (250 MHz; CDCl₃) 3.74(3Hₓ, s, MeO), 2.08-2.05(1Hₓ, m), 1.86-1.05(6Hₓ and 7Hᵧ, m), 1.06(3Hᵧ, s, Me), 0.96(3Hₓ, s, Me), 0.93(3Hᵧ, s, Me), 0.89(3Hₓ, s, Me), 0.81(6Hᵧ, s, 2xMe); Found: M⁺, 225.13640 C₁₂H₁₅NO₂ requires 225.13648; m/z 226(MH⁺), 225(M⁺), 208, 152, 134, 123, 93, 84, 81, 69, 55.
Experimental Details

(1R, 2'R and 2'S, [1α, 2α(5'), 4α])-2'-Chloro-1,3,3-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridines], N-Chlorofenchyl Oxaziridines 89a/89b

A solution of tert-butyl hypochlorite (0.34 g, 3.13 mmol) in diethyl ether (7 mL) was added dropwise to a cooled (−78 °C) stirring solution of fenchone oxaziridine (500 mg, 2.99 mmol) in diethyl ether (25 mL). The solution was allowed to warm to room temperature over a period of 1 hour, and stirred at this temperature for a further 4 hours. The solvent was then removed in vacuo and the product purified by column chromatography (petroleum ether) over silica gel to give N-chlorofenchyl oxaziridines 89a/89b as an unstable pale blue oil in a 46% (275 mg, 1.37 mmol) yield. This product appeared to be present as two isomers in a 4:1 ratio (Isomer A: Isomer B): ν_{max} (neat)/cm\(^{-1}\) 1575(N=O), 666(N-Cl); δ_{II} (250 MHz; CDCl\(_3\)) 2.14-1.44(6HA and 6HB, m), 1.38(1HA, dd, \(J =10.4, 1.6\), corresponding signal from isomer B was too small and obscured by methyl signal at 1.26, 1.26(3HA and 1HB, s), 1.10(3HB, s), 0.89(3HA, s), 0.82(3HA, s), 0.77(3HB, s) This compound showed identical properties to that prepared previously by the action of methyl chloroformate upon fenchone oxaziridine in the presence of pyridine.

(2R)- and (2S)- 2-{{[1R, 4S]-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yliden|amino)cyclohexan-1-one, (1R)-Camphor imines of (2R)- and (2S)-Aminocyclohexanone 90a/90b (reaction between 1-cyclohexenyloxytrimethylsилane and (+)-camphorlyloxaziridine)
To a stirring cooled (-78 °C) stirring solution of 1-cyclohexenyloxytrimethylsilane (730 μL, 639 mg, 3.75 mmol) in dry THF (10 mL) was added methyllithium (3.75 mL, 1.0 M in THF/cumene (10/90), 3.75 mmol) dropwise. After stirring at -78 °C for 30 minutes, a solution of (+)-camphoryl oxaziridine 65 (630 mg, 3.77 mmol) in dry THF (3 mL) was added, and the reaction mixture was allowed to warm to room temperature over a period of 2 hours. The reaction mixture was then allowed to stir at room temperature for a further 3 hours and when the reaction was complete (tlc) the reaction was quenched by adding the mixture to a saturated aqueous solution of ammonium sulfate (25 mL). The mixture was then extracted with dichloromethane (3x20 mL) and the combined organic extracts were dried (MgSO4) and the solvent removed in vacuo to give a yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give the product as a pale yellow oil. The product was found by 1H NMR to be a mixture of inseparable diastereoisomeric (1R)-camphor imines of (2R)- and (2S)-aminocyclohexanone 90a/90b present in a 1:1 ratio and formed in an 8% (74.2 mg, 0.300 mmol) yield; δH (250 MHz; CDCl3) 3.86-3.77 (1H A+B, m, cyclohexanone C2), 2.89-2.82 (1H A, m, cyclohexanone C6), 2.64-2.50 (1H A+B and 1H B, m, exo at camphoryl C3A+B and cyclohexanone C6B), 2.29-1.10 (13H A+B, m), 0.99 (3H, s, Me), 0.97 (3H, s, Me), 0.90 (6H, s, 2xMe), 0.82 (3H, s, Me), 0.71 (3H, s, Me); m/z 248(MH+), 247(M+), 219, 191, 178, 163, 151, 136, 111, 109, 95, 69, 55. This product showed identical spectral properties to the same mixture of compounds, which were prepared by the reaction between oxaziridine 65 and cyclohexanone.

General Procedure for the Amination of Diethyl or Dimethyl Malonates with (+)-Camphoryl Oxaziridine 65 in the Presence of Sodium Ethoxide or Methoxide Base

Sodium (100 mg, 4.35 mmol) was added to dry ethanol or methanol (5 mL) and the solution was stirred until the effervescence had ceased and all of the sodium had reacted. After allowing the solution to cool to room temperature, a solution of (+)-camphoryl oxaziridine 65 (270 mg, 1.62 mmol) in ethanol or methanol (1 mL) was added followed by the diethyl or dimethyl malonate (1.50 mmol) and the reaction
Experimental Details

mixture was stirred at room temperature. When the reaction was complete (tlc), the reaction mixture was added to a saturated aqueous solution of ammonium sulfate (40 mL). The mixture was then extracted with dichloromethane (3x40 mL) and the combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo to give a pale yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica to give the products as pale yellow oils.

(1R, 4S)-Methyl 2-[(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene)amino]ethanoate, (1R)-Camphor Imine of Methyl Glycinate 91 (reaction between (+)-camphoryl oxaziridine 65 and dimethyl malonate using NaOMe as a base)

$$\text{\begin{array}{|c|c|c|}
\hline
\text{N} & \text{C} & \text{O} \\
\hline
\text{\begin{array}{|c|c|c|}
\hline
\text{Me} & \text{Me} & \text{Me} \\
\hline
\end{array}}
\end{array}}$$

Imine 91 was synthesised according to the above procedure in a 77% (257 mg, 1.16 mmol) yield in a reaction time of 3 hours; $\nu_{\text{max}}$ (neat)/cm⁻¹ 1743, 1674; $\delta_{\text{H}}$ (250 MHz; CDCl₃) 4.07(2H, s, RO₂CCH₂NR), 3.70(3H, s, MeO₂CR), 2.31(1H, dt, J =16.8 and 3.9, exo at C3), 1.99-1.62(4H, m), 1.45-1.35(1H, m), 1.24-1.14(1H, m), 0.99(3H, s, Me), 0.92(3H, s, Me), 0.77(3H, s, Me); m/z 223(M⁺), 208, 194, 180, 164, 152, 140, 134, 122, 115, 108, 95, 83, 67, 55, 41. This compound was shown to have identical spectral properties to the same compound, which has been previously reported¹⁴⁰.

(1R, 4S)-Ethyl 2-[(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene)amino]ethanoate, (1R)-Camphor Imine of Ethyl Glycinate 92 (reaction between (+)-camphoryl oxaziridine 65 and diethyl malonate using NaOEt as a base)

$$\text{\begin{array}{|c|c|c|}
\hline
\text{N} & \text{C} & \text{O} \\
\hline
\text{\begin{array}{|c|c|c|}
\hline
\text{Me} & \text{Me} & \text{Me} \\
\hline
\end{array}}
\end{array}}$$

174
Experimental Details

Imine 92 was synthesised according to the above procedure in a 66% (237 mg, 1.00 mmol) yield in a reaction time of 3 hours: $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 1743 (CO, ester), 1686 (CN, imine): $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 4.18 (2H, q, $J$ = 7.2, MeCH$_2$O); 4.09(2H, s, RO$_2$CCH$_2$NR$_2$), 2.34(1H, dt, $J$ = 17.7 and 4.0, exo at camphor C3) 1.97(1H, t, $J$ = 4.3, CH at camphor C4), 1.79-1.64(3H, m) 1.48-1.38(1H, m), 1.27(3H, t, $J$ = 7.2, CH$_3$CH$_2$O), 1.17-1.23(1H, m), 1.03(3H, s, Me), 0.94(3H, s, Me), 0.81(3H, s, Me); $\delta_{\text{C}}$ (63 MHz; CDCl$_3$) 9.3, 11.2, 18.9, 19.6, 27.4, 32.0, 35.8, 43.8, 47.4, 53.9, 54.4, 60.8, 170.3 (CO$_2$R), 188.0 (C=N); $m/z$ 238 (MH$^+$), 237 (M$^+$), 222, 208, 194, 180, 164, 150, 135, 129, 122, 108, 99, 95, 83, 75, 67, 59, 56, 41. This compound was shown to have identical spectral properties to the same compound, which has been previously reported.$^{140}

(1R, 4S)-Methyl 2-[(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene)amino]ethanoate, (1R)-Camphor Imine of Methyl Glycinate 91 (reaction between (+)-camphor oxaziridine 65 and dimethyl malonate using LiHMDS as a base)

To a stirring cooled (−78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL, 1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added a solution of dimethyl malonate (170 µL, 197 mg, 1.49 mmol) dropwise in dry THF (1 mL). After stirring at −78 °C for 20 minutes a solution of (+)-camphor oxaziridine 65 (250 mg, 1.50 mmol) in dry THF (1 mL) was added, and the reaction mixture was allowed to reach room temperature over a period of 2 hours. The reaction mixture was then allowed to stir at room temperature overnight and when the reaction was complete (tlc), the reaction mixture was added to a saturated aqueous solution of ammonium sulfate (25 mL). The mixture was then extracted with dichloromethane (3x20 mL) and the combined organic extracts were dried (MgSO$_4$) and the solvent removed in vacuo to give a yellow oil which was purified by column chromatography.
Experimental Details

(methanol/dichloromethane) over silica gel. This gave the (1R)-camphor imine of methyl glycinate \(91\) as a pale yellow oil in a 69% (229mg, 1.03mmol) yield: \(\nu_{\text{max}}\) (neat)/\(\text{cm}^{-1}\) 1743, 1674; \(\delta_H\) (250 MHz; CDCl\(_3\)) 4.07(2H, s, RO\(_2\)CCH\(_2\)NR), 3.70(3H, s, MeO\(_2\)CR), 2.31(1H, dt, \(J = 16.8\) and 3.9, \textit{exo} at C3), 1.99-1.62(4H, m), 1.45-1.35(1H, m), 1.24-1.14(1H, m), 0.99(3H, s, Me), 0.92(3H, s, Me), 0.77(3H, s, Me): \(m/z\) 223(M\(_\text{+}\)), 208, 194, 180, 164, 152, 140, 134, 122, 115, 108, 95, 83, 67, 55, 41. This compound was shown to have identical spectral properties to the same compound, which has been previously reported.\(^{140}\)

\((2R)-\) and \((2S)-\text{Ethyl 2-}([1R, \ 4S]-1,7,7-\text{Trimethylbicyclo}[2.2.1]hept-2-yliden]amino)propanoate, (1R)-Camphor Imines of (2R)- and (2S)-Ethyl Alaninate \(93a/93b\) (reaction between (+)-camphoryloxaziridine 65 and diethyl methylmalonate)

Imines \(93a/93b\) were synthesised according to the general procedure for the reaction of dialkyl malonates with (+)-camphoryloxaziridine 65 in the presence of sodium ethoxide. The reaction time was 4 hours. Imines \(93a/93b\) were formed in an 89% (330 mg, 1.31 mmol) yield, and found by \(^1\text{H}\) NMR spectroscopy to be present in a 1:1 ratio: \(\nu_{\text{max}}\) (neat)/\(\text{cm}^{-1}\) 1740(C=O), 1683(C=N); \(\delta_H\) (250 MHz; CDCl\(_3\)) 4.27-3.99(2H\(_{A+B}\), m, O-CH\(_2\)Me), 4.04(1H\(_A\), q, \(J = 6.8\), (RO\(_2\)C)(NR\(_2\))CH-Me), 4.03(1H\(_B\), q, \(J = 6.8\), (RO\(_2\)C)(NR\(_2\))CH-Me), 2.47-2.29(1H\(_{A+B}\), m), 1.97-1.15(9H\(_{A+B}\), m), 1.41(3H\(_A\), d, \(J = 6.6\), CH\(_3\)-CH(RO\(_2\)C)(NR\(_2\))), 1.40(3H\(_B\), d, \(J = 6.8\), CH\(_3\)-CH(RO\(_2\)C)(NR\(_2\))), 1.00(6H, s, 2xMe), 0.93(6H, s, 2xMe), 0.81(3H, s, Me), 0.76(3H, s, Me); \(\delta_C\) (63 MHz; CDCl\(_3\)) 11.3, 13.9, 14.0, 18.4, 18.4, 18.5, 18.6, 18.8, 18.9, 19.4, 27.2, 27.3, 27.4, 31.7, 31.8, 31.9, 35.2, 35.3, 35.5, 35.6, 43.7, 46.8, 47.2, 53.8, 59.3, 59.3, 60.6, 172.86(RO\(_2\)Et), 172.89(RO\(_2\)Et), 184.2(C=N), 184.3(C=N); Found: M\(^+\), 251.18836 C\(_{13}\)H\(_{25}\)N\(_2\)O\(_2\) requires 251.18853; \(m/z\) 252(MH\(^+\)), 251(M\(^+\)), 236, 222, 179, 178, 162, 152, 150, 135, 122, 109, 95, 83, 70, 55.
Experimental Details

(2R)- and (2S)-Ethyl 2-[[1R, 4S]-1,7,7-Trimehtylbicyclo[2.2.1]hept-2-yliden]amino]butanoate, (1R)-Camphor Imines of Ethyl (2R)- and (2S)-Amino Butyrate 94a/94b (reaction between diethyl ethyl malonate and (+) camphoryl oxaziridine 65)

Imines 94a/94b were synthesised according to the general procedure for the reaction of dialkyl malonates with (+)-camphoryl oxaziridine 65 in the presence of sodium ethoxide. The reaction time was 5 hours. Imines 94a/94b were formed in 77% (305mg, 1.15mmol) yield, and found by ¹H NMR spectroscopy to be present in a 1:1 ratio:

- $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 1740(C=O), 1684(C=N);
- $\delta_H$ (250 MHz; CDCl$_3$): 4.31-4.06(2H$_A$+B, m, OCH$_2$-Me), 3.88-3.74(1H$_A$+B, m, =NCH(CO$_2$R)Et), 2.47-2.29(1H$_A$+B, m), 2.11-1.62(6H$_A$+B, m), 1.47-1.15(5H$_A$+B, m), 1.25(3H$_A$, t, J = 7.2, CH$_3$CH$_2$O-) and 1.23(3H$_B$, t, J = 7.1, CH$_3$CH$_2$O-), 1.01(6H, s, 2xMe), 0.94(3H, s, Me), 0.93(3H, s, Me), 0.87(3H, t, J = 7.4, CH$_3$CH$_2$CH), 0.8651(3H$_B$, t, J = 7.4, CH$_3$CH$_2$CH), 0.80(3H, s, Me), 0.76(3H, s, Me); $\delta_C$ (63 MHz; CDCl$_3$): 10.5, 10.7, 11.3, 11.4, 14.0, 14.1, 18.8, 18.9, 19.4, 19.5, 26.06, 26.14, 27.3, 27.4, 28.6, 31.8, 32.3, 35.8, 36.1, 43.77, 43.80, 46.9, 47.1, 54.0, 60.5, 62.0, 65.1 65.8, 172.1(RCO$_2$Et), 172.2(RCO$_2$Et), 184.95(C=N), 185.03(C=N); Found: M', 265.20418 C$_{16}$H$_{27}$NO$_2$ requires 265.20438; m/z 265(M'), 237, 236, 222, 208, 193, 192, 179, 178, 164, 157, 136, 123, 109, 95, 81, 69, 55.
Experimental Details

(2R)- and (2S)-Ethyl 2-[[[(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-
yliden]amino]pent-4-enoate, (1R)-Camphor Imines of Ethyl (2R)- and (2S)-
Allylglycinate 95a/95b (reaction between diethyl allylmalonate and (+)-camphoryl
oxaziridine 65)

Imines 95a/95b were synthesised according to the general procedure for the reaction
of dialkyl malonates with (+)-camphoryl oxaziridine 65 in the presence of sodium
ethoxide. The reaction time was 4 hours. Imines 95a/95b were formed in 80%
(332mg, 1.20mmol) yield, and found by $^1$H NMR spectroscopy to be present in a 1:1
ratio: $\nu_{max}$ (neat)/cm$^{-1}$ 1740(C=O), 1684(C=N); $\delta_{II}$ (250 MHz; CDCl$_3$) 5.82-
5.65(1H$_{A+B}$, m, CH$_2$:CHCH$_2$R) 5.23-4.97(2H$_{A+B}$, m, CH$_2$:CHCH$_2$R), 4.27-
4.10(2H$_A$, m, CH$_3$:CH$_2$:OR), 4.14(2H$_B$, q, $J =$6.9 CH$_3$:CH$_2$:OR), 3.96(1H$_A$, t, $J =$9.2,
=N-CH(CH$_2$:R)(CO$_2$:R)), 3.96(1H$_B$, dd, $J =$8.8, 0.9, =N-CH(CH$_2$:R)(CO$_2$:R)), 2.77-
2.37(2H$_{A+B}$ and 1H$_A$, m, CH$_2$:CHCH$_2$:CHR(bright isomers) and 1 camphoryl exo at
C3), 2.30(1H$_B$, ddd, $J =$17.1, 4.6, 3.2 exo at C3), 1.95-1.62(4H$_{A+B}$, m), 1.45-
1.15(2H$_{A+B}$, m), 1.25(3H$_A$, t, $J =$6.9, CH$_3$:CH$_2$:OR), 1.23(3H$_B$, t, $J =$6.9, CH$_3$:CH$_2$:OR),
1.00(3H, s, Me), 0.99(3H, s, Me), 0.92(6H, s, 2xMe), 0.79(3H, s, Me), 0.76(3H, s,
Me); $\delta_C$ (63 MHz; CDCl$_3$) 11.1, 11.2, 13.9, 14.0, 18.7, 18.8, 19.2, 19.4, 27.2, 27.3,
31.7, 32.2, 35.79, 35.81, 36.0, 37.1, 37.23 43.7, 46.4, 47.0, 53.9, 60.4, 63.90, 63.92,
64.20, 64.23, 117.0(CH$_2$:CHR), 117.1(CH$_2$:CHR), 134.4(RCH=CH$_2$), 134.6(RCH=CH$_2$),
171.9(RCO$_2$:Et), 172.1(RCO$_2$:Et), 185.0(C=N), 185.1(C=N);
Found: M$^+$, 277.20458 C$_{17}$H$_{27}$NO$_2$ requires 277.20418; m/z 278(MH$^+$), 277(M$^+$),236,
222, 204, 162, 135, 116, 95, 81, 79, 67, 55.
(2R)- and (2S)-Ethyl 2-Pheny|2-[(1R, 4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino|ethanoate, (1R)-Camphor Imines of Ethyl (2R)- and (2S)-Aminophenylacetate 96a/96b (reaction between diethyl phenylmalonate and (+)-camphoryl oxaziridine 65)

![Chemical Structure](image)

Imines 96a/96b were synthesised according to the general procedure for the reaction of dialkyl malonates with (+)-camphoryl oxaziridine 65 in the presence of sodium ethoxide. The reaction time was 24 hours. The starting material (diethyl phenylmalonate) was recovered in 32% (112 mg, 0.474 mmol) yield: δH (250 MHz; CDCl₃) 7.68-7.61(2H, m, Ar-H), 7.42-7.34(3H, m, Ar-H), 4.40-4.20(3H, m, MeCH₂-O [keto and enolic forms] and CHPh(CO₂Et)₂), 1.29(3H, t, J = 7.2); this data is the same as that from the spectrum taken from the starting material. 141 Imines 95a/95b were formed in 42% (195mg, 0.623mmol) yield, and found by ¹H NMR spectroscopy to be present in a 1:1 ratio: ν max (neat)/cm⁻¹ 1742(C=O), 1682(C=N); δH (250 MHz; CDCl₃) 7.54-7.47(2H and 2H, m, Ar-H), 7.45-7.22(3H and 3H, m, Ar-H), 5.06(1H, s, =N-CHPhCO₂R), 5.05(1H, s, =N-CHPhCO₂R), 4.15(2H, q, J = 7.2, MeCH₂OCOR), 4.14(2H, q, J = 7.1, MeCH₂OCOR), 2.48-2.36(1H, m), 2.30-2.18(1H, m), 2.04-1.43(4H and 4H, m), 1.37-1.13(5H and 5H, m) this signal overlaps signals at 1.21(3H, t, J = 7.2, CH₃CH₂OCOR) and 1.19(3H, t, J = 7.1, CH₃CH₂OCOR), 1.08(3H, s, Me), 1.07(3H, s, Me), 0.94(3H, s, Me), 0.91(3H, s, Me), 0.82(3H, s, Me), 0.60(3H, s, Me); δC (63 MHz; CDCl₃) 11.29, 11.33, 13.9, 14.0, 18.9, 19.0, 31.8, 31.9, 36.0, 36.1, 43.8, 43.9, 47.2, 47.4, 61.0, 62.1, 62.9, 68.0, 72.8, 126.5, 126.6, 127.6, 127.7, 128.47, 128.50, 138.4, 138.6, 172.0(RCO₂Et), 172.1(RCO₂Et), this mixture contained approximately 10% impurities which made the assignment of some of the smaller (eg. CH and C₆H₅C₆) ¹³C NMR signals difficult to do with confidence, as a result of this, eleven ¹³C NMR signals were obscured either because they were too small to see or because they were too small to distinguish from large signals from impurities; Found: M⁺, 313.20455 C₂₀H₂₇NO₂ requires 313.20418; m/z
**Experimental Details**


(3R)- and (3S)-3-[(1R, 4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino]butan-2-one, (1R)-Camphor Imines of (3R)- and (3S)-Aminobutan-2-one 97a/97b (reaction between ethyl-2-methylacetoacetate and (+)-camphoryl oxaziridine 65)

Sodium (100 mg, 4.35 mmol) was added to dry ethanol (6 mL) and the solution was stirred until the effervescence had ceased and all of the sodium had reacted. After allowing the solution to cool down to room temperature, a solution of (+)-camphoryl oxaziridine 65 (300 mg, 1.80 mmol) in ethanol (1 mL) was added followed by ethyl 2-methylacetoacetate (250 μL, 245 mg, 1.70 mmol) and the reaction mixture was stirred at room temperature for 5 hours. When the reaction was complete (tlc), the reaction mixture was added to a saturated aqueous solution of ammonium sulfate (40 mL). The mixture was then extracted with dichloromethane (3×40 mL) and the combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo to give a pale yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give (1R)-camphor imines of (3R)- and (3S)-aminobutan-2-one 97a/97b as a pale yellow oil in a 21% (80 mg, 0.363 mmol) yield. Imines 97a/97b were found by 1H NMR spectroscopy to be present in a 1:1 ratio: νmax (neat)/cm⁻¹ 1715(C=O), 1681(C=N); δ₁H (250 MHz; CDCl₃) 4.09-3.93(1H, m), 3.90-3.77(2H, m, impurity), 2.40-2.25(1H, m), 2.15(3H, s), 2.14(3H, s), 2.08-1.56(4H and 4H, m), 1.50-1.09(7H and 7H, m), 1.24(Me, d, J=6.8), 1.235(Me, d, J=6.8), 0.97(3H, s), 0.93(3H, s), 0.91(3H, s), 0.892(3H, s), 0.886(3H, s), 0.73(3H, s); δC (63 MHz CDCl₃) Concentration of impurities in the sample too high to distinguish their signals from signals of title compounds. C quat signals from C=O and C=N are too small to be identified with any confidence. Strong
characteristic C-H peaks were found at 66.6 and 67.0 which correspond to the HCMe(COMe)(NR₂) signals of the two diastereoisomers; Found: M⁺, 221.1780 C₁₄H₂₃NO requires 221.17795; m/z 221(M⁺), 220, 219, 179, 178, 151, 150, 109, 94, 81, 69, 68, 55.

(1R, 4S)-Ethyl 2-[(1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene)amino]ethanoate, (1R)-Camphor Imine of Ethyl Glycinate 92 (reaction between ethyl acetoacetate and (+)-camphoryloxaziridine)

To a stirring cooled (−78 °C) solution of lithium bis(trimethylsilyl)amide (1.55 mL, 1.0 M in THF, 1.55 mmol) in dry THF (5 mL) was added ethyl acetoacetate (190 μL, 194 mg, 1.49 mmol). After stirring at −78 °C for 30 minutes a solution of (+)-camphoryloxaziridine 65 (270 mg, 1.62 mmol) in dry THF (1 mL) was added, and the reaction was then allowed to warm up to room temperature over a period of 2 hours. The reaction mixture was then stirred at room temperature overnight. When the reaction was complete (tlc), the reaction mixture was added to a saturated aqueous solution of ammonium sulfate (20 mL). The mixture was then extracted with dichloromethane (3x20 mL) and the combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo to give a yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give the (1R)-camphor imine of ethyl glycinate 92 as a pale yellow oil in a 52% (184 mg, 0.778 mmol) yield: δ₁H (250 MHz; CDCl₃) 4.18(2H, q, J =7.1, CH₃CH₂OR), 4.09-4.08(2H, m, =N-CH₂CO₂R), 2.38-2.28(1H, m), 1.98-1.64(4H, m), 1.52-1.17(2H, m), 1.21(3H, t, J =7.1, CH₃CH₂OR), 1.02(3H, s, Me), 0.94(3H, s, Me), 0.81(3H, s, Me); m/z 238(MH⁺), 237(M⁺), 222, 208, 194, 180, 166, 165, 154, 150, 129, 108, 95, 93, 83, 82, 79, 67, 55. This product showed spectral properties identical to those previously reported for this compound.¹⁴⁰
Experimental Details

(2R)- and (2S)-2-Phenyl-2-{[(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yldien]amino}ethanoic acid and N-[(1R,4S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yldien]phenylmethanamide, (1R)-Camphor Imine of (2R)- and (2S)-Phenylalanine 98a/98b and (1R)-Camphor Imine of Benzylamine 99 (reaction between (+)-camphoryl oxaziridine 65 and ethyl phenylacetate)

To a cooled (−78 °C) stirring solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.50 mL, 1.50 mmol) in dry diethyl ether was added ethyl phenylacetate (238 μL, 245 mg, 1.49 mmol) in diethyl ether (1 mL). After 30 minutes at −78 °C, a solution of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) in diethyl ether (1 mL) was introduced. The reaction vessel was then transferred to a cold bath (0 °C) for 8 hours. When the reaction was complete (tlc) the reaction mixture was quenched with an aqueous solution of ammonium sulfate (20 mL), and this mixture was then extracted with dichloromethane (3x35 mL). The resulting organic solution was then dried (MgSO4) and the solvent removed in vacuo to give a colourless oily mixture. This mixture was then purified by column chromatography (dichloromethane/methanol) over silica gel to give (1R)-(−)-camphor 56 in 8.3% (18.8 mg, 0.124 mmol) yield: mp 178-180 °C; δH (250 MHz; CDCl3) 2.34(1H, ddd, J = 18.3, 4.4 and 3.4, exo at C3), 2.08(1H, t, J = 4.4, CH at bridgehead C4), 1.99-1.88(1H, m), 1.83(1H, d, J = 18.3, endo at C3), 1.73-1.59(1H, m), 1.45-1.24(2H, m), 0.95(3H, s, Me), 0.90(3H, s, Me), 0.82(3H, s, Me); this compound showed identical spectral properties to the same compound, which has been described previously.138

This was followed by (+)-camphoryl oxaziridine 65 in a 12.0% (30.0 mg, 0.180 mmol) yield: mp 153-155 °C; δH (250 MHz; CDCl3) 4.22(1H, br.s, NH), 3.74(1H, br.s, NH), 2.33-2.21(1H, m, camphoryl exo C3), 1.87-1.26(6H, m), 0.93(3H, s, Me), 0.91(3H, s, Me), 0.88(6H, s, 2xMe), 0.63(3H, s, Me), 0.62(3H, s, Me); this compound displayed the same spectral properties to the same compound that was prepared by the reaction of 3-chloroperoxybenzoic acid with (1R)-camphor imine 64.
Experimental Details

This compound was followed by the (1R)-camphor imine of benzylamine 99 as a pale yellow oil in 5.5% (20 mg, 0.0829 mmol) yield: \( \nu_{\max} \) (neat)/cm\(^{-1}\) 1685(C=N); \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.17-7.34(5H, m, ArH), 4.47(2H, qab, \( J_{ab} = 15.0 \), PhCH\(_2\)NR\(_2\)) 2.41(1H, dt, \( J = 16.9 \) and 4.2, \( exo \) at camphor C3), 1.96-1.70(4H, m), 1.46-1.16(2H, m), 1.04(3H, s, Me), 0.95(3H, s, Me), 0.77(3H, s, Me); \( \delta_C \) (63 MHz CDCl\(_3\)) 11.4, 18.9, 19.6, 27.4, 32.2, 35.7, 43.8, 47.1, 53.9, 55.5, 126.3(Ar, CH), 127.3(Ar, CH), 128.2(Ar, CH), 140.4(Ar, C\(_{quat}\)), 184.0(C=N); this compound showed identical spectral properties to the same compound that has been previously reported.\(^{142}\) Next, the (1R)-camphor imines of (2R)- and (2S)-phenylalanine 98\(a/98b\) were isolated as a yellow oil in a yield of 12.0% (51.2 mg, 0.180 mmol). Imines 98\(a/98b\) were subsequently shown by \(^1\)H NMR spectroscopy to be present in a ratio of 1:1: \( \nu_{\max} \) (neat)/cm\(^{-1}\) 3029(Ar), 2958(CO\(_2\)H), 1771(C=O, from CO\(_2\)H), 1683(C=N); \( \delta_H \) (250 MHz; CDCl\(_3\)) 8.27(1H\(_{A+B}\), br.s, NH), 7.36-7.21(5H\(_{A+B}\), m, Ar-H), 4.89(1H, s, PhCH(CO\(_2\)R)NHR), 4.86(1H, s), 2.48-2.36(1H and 1H, m) 2.30-1.16(6H and 6H, m), 1.06(3H, s), 1.05(3H, s), 0.92(3H, s), 0.88(3H, s), 0.74(3H, s), 0.483(3H, s). Imines 98\(a/98b\) were unstable and decomposed to imine 99 during the overnight C-13 spectrum run. It is because of this that there is no more data to confirm the structures of 98\(a/98b\).

\((2R)-\) and \((2S)-1-\text{Phenyl}-2-\{[(1R, 4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}\)propan-1-one, \((1R)-\text{Camphor Imines of (2R)- and (2S)-Amino Propiophenone} 100\(a/100b\) (reaction between (+)-camphoryl oxaziridine 65 and propiophenone with NaH base)

![Diagram](image_url)

To a stirring cooled (−78 °C) mixture consisting of sodium hydride (60 mg of 60% dispersion in mineral oil, 1.50 mmol) in dry THF (5 mL) was added propiophenone (200 \( \mu \)L, 202 mg, 1.50 mmol) dropwise in dry THF (2 mL). After stirring at −78 °C for 45 minutes, the effervescence had ceased and a solution of (+)-camphoryl
**Experimental Details**

oxaziridine 65 (250 mg, 1.50 mmol) in dry THF (1 mL) was introduced. The reaction mixture was allowed to reach room temperature over a period of 2 hours, and was then allowed to stir at room temperature for a further 3 hours. After completion (tlc), the reaction was quenched by addition of a saturated aqueous solution of ammonium sulfate (25 mL). The mixture was then extracted with dichloromethane (3x20 mL) and the combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo to give a yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give the product as a pale yellow oil. The product was found by 1H NMR spectroscopy to be an inseparable mixture of (1R)-camphor imines of (2R)- and (2S)-amino propiophenone **100a/100b** present in a 1:1 ratio and in 39% (164 mg, 0.580 mmol) yield:

δ_H (250 MHz, CDCl₃) 8.05-7.99 (2Hₓ+B, m, Ar-H), 7.55-7.38 (3Hₓ+B, m, Ar-H), 4.73 (1Hₓ, q, J =6.8, MeCH(NR₂)(COAr)), 4.72 (1Hₓ, q, J =6.8, MeCH(NR₂)(COAr)), 2.45-2.27 (1Hₓ+B, m, exo at camphor C3), 1.97-1.06 (6Hₓ+B, m), 1.49 (3Hₓ, d, J =6.8, CH₃CH(NR₂)(COAr)), 1.47 (3Hₓ, d, J =6.8, CH₃CH(NR₂)(COAr)), 0.98 (3H, s, Me), 0.96 (3H, s, Me), 0.92 (3H, s, Me), 0.90 (3H, s, Me), 0.75 (3H, s, Me), 0.61 (3H, s, Me); m/z 284 (MH⁺), 283 (M⁺), 220, 178, 172, 148, 122, 105, 95, 77, 69, 55. This product showed identical spectral properties to the same mixture of compounds, prepared by the reaction of (+)-camphor oxaziridine 65 with propiophenone using LiHMDS as a base.

((2R)- and (2S)-1-Phenyl-2-[[1R, 4S]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino]propan-1-one, (1R)-Camphor Imines of (2R)- and (2S)-Amino Propiophenone **100a/100b** (reaction between (+)-camphor oxaziridine 65 and propiophenone with LiHMDS base)

![Diagram](image)

To a stirring cooled (-78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL, 1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added propiophenone (200 μL,
Experimental Details

202 mg, 1.50 mmol) dropwise in dry THF (1 mL). After stirring at -78 °C for 30 minutes a solution of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) in dry THF (1 mL) was added, and the reaction mixture was allowed to reach room temperature over a period of 2 hours. The reaction mixture was then allowed to stir at room temperature for a further 3 hours and when the reaction was complete (tlc) the reaction was quenched by adding the mixture to a saturated aqueous solution of ammonium sulfate (25 mL). The mixture was then extracted with dichloromethane (3x20 mL) and the combined organic extracts were dried (MgSO4). The solvent was removed in vacuo to give a yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give the product as a pale yellow oil. The product was found by 1H NMR spectroscopy to be an inseparable mixture of (1R)-camphor imines of (2R) and (2S)-amino propiophenone 100a/100b present in a 1:1 ratio and in a 60% (256 mg, 0.905 mmol) yield: v_max (neat)/cm⁻¹ 1691(C=O), 1678(C=N); δH (250 MHz; CDCl3) 8.05-7.99(2H_A+B, m, Ar-H), 7.55-7.38(3H_A+B, m, Ar-H), 4.73(1H_A, q, J =6.8, MeCH(NR₂)(COAr)), 4.72(1H_B, q, J =6.8, MeCH(NR₂)(COAr)), 2.45-2.27(1H_A+B, m, exo at camphoryl C3), 1.97-1.06(6H_A+B, m), 1.49(3H_A, d, J =6.8, CH₃CH(NR₂)(COAr)), 1.47(3H_B, d, J =6.8, CH₃CH(NR₂)(COAr)), 0.98(3H, s, Me), 0.96(3H, s, Me), 0.92(3H, s, Me), 0.90(3H, s, Me), 0.75(3H, s, Me), 0.61(3H, s, Me); δC (63 MHz; CDCl₃) 11.2(Me), 11.3(Me), 18.5(Me), 18.77(Me), 18.83(Me), 18.9(Me), 19.3(Me), 19.4(Me), 27.0(CH₂), 27.3(CH₂), 31.5(CH₂), 32.0(CH₂), 35.9(CH₂), 36.0(CH₂), 43.0(C_quat), 43.2(C_quat), 43.8(CH), 43.9(CH), 63.6(CH, CHMe(COAr)(NR₂)), 63.7(CH, CHMe(COAr)(NR₂)), 127.2(CH, Ar), 127.6(CH, Ar), 128.8(CH, Ar), 129.1(CH, Ar), 129.8(CH, Ar), 132.6(CH, Ar), 134.0(C_quat, Ar), 141.3(C_quat, Ar), 183.9(C_quat, C=N), 184.8(C_quat, C=N), both COAr(CHRNR₂) signals and two camphoryl C_quat signals were too small to be identified with any confidence; Found: M⁺, 283.1933 C₁₀H₂₅NO requires 283.19360; m/z 284(MH⁺), 283(M⁺), 220, 178, 172, 148, 122, 105, 95, 77, 69, 55.
Experimental Details

(2R)- and (2S)-2-[(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylden]amino)cyclohexan-1-one, (1R)-Camphor Imines of (2R)- and (2S)-Amino Cyclohexanone 90a/90b (reaction between (+)-camphoryl oxaziridine 65 and cyclohexanone)

To a stirring cooled (−78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL, 1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added cyclohexanone (155 μL, 147 mg, 1.50 mmol) dropwise in dry THF (1 mL). After stirring at −78 °C for 30 minutes, a solution of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) in dry THF (1 mL) was added, and the reaction mixture was allowed to reach room temperature over a period of 2 hours. The reaction mixture was then allowed to stir at room temperature for a further 3 hours and when the reaction was complete (tlc) the reaction was quenched by adding the mixture to a saturated aqueous solution of ammonium sulfate (25 mL). The mixture was then extracted with dichloromethane (3x20 mL), the combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo to give a yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give the (1R)-camphor imines of (2R)- and (2S)-amino cyclohexanone 90a/90b as a pale yellow oil in 21% (76.3 mg, 0.309 mmol) yield. Imines 90a/90b were isolated as an inseparable mixture, and shown by 1H NMR spectroscopy to be present in a 1:1 ratio: ν max (neat)/cm⁻¹ 1716(C=O), 1686(C=N); δH (250 MHz; CDCl₃) 3.86-3.77(1H-A-B, m, cyclohexanone C2), 2.89-2.82(1H-A, m, cyclohexanone C6), 2.64-2.50(1H-A-B and 1H-B, m, exo camphoryl C3A-B and cyclohexanone C6B), 2.29-1.10(13H-A-B, m), 0.99(3H, s, Me), 0.97(3H, s, Me), 0.90(6H, s, 2xMe), 0.82(3H, s, Me), 0.71(3H, s, Me); δC (63 MHz; CDCl₃) 11.25(Me), 11.3(Me), 18.8(Me), 19.0(Me), 19.4(Me), 19.5(Me), 22.7(CH₂), 23.1(CH₂), 23.1(CH₂), 27.2(CH₂), 27.2(CH₂), 31.5(CH₂), 32.18(CH₂), 35.22(CH₂), 35.3(CH₂), 35.8(CH₂), 40.8(CH₂), 40.9(CH₂), 43.76(CH), 43.80(CH), 46.8(Cquat), 47.3(Cquat), 53.3(Cquat), 54.0(Cquat), 68.9(CH, CHR(COR)(NR₂)), 69.2(CH,
Experimental Details

CHR(COR)(NR2), 184.5(C quat, C=N), 184.7(C quat, C=N), 207.9(C quat, C=O),
208.6(C quat, C=O), one CH2 signal obscured, probably due to overlap; Found: M+,
247.1937 C16H2SNO requires 247.1936; m/z 248(MH+), 247(M+), 219, 191, 178,
163, 151, 136, 111, 109, 95, 69, 55.

(2R)- and (2S)-2-Methyl-2-[(1R, 4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-
yliden]amino]-2,3-dihydro-1H-inden-1-one and 2-Amino-2-methylindan-1-one,
(1R)-Camphor Imines of (2R)- and (2S)-2-Amino-2-methylindan-1-one 101a/101b
and 2-Amino-2-methylindan-1-one 102 (reaction between (+)-camphoryl oxaziridine
65 and 2-methyl-1-indanone)

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To a stirring cooled (−78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL,
1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added a solution of 2-methyl-1-
indanone (206 µL, 219 mg, 1.50 mmol) in dry THF (1 mL). After stirring at −78 °C
for 30 minutes, a solution of (+)-camphoryl oxaziridine 65 (270 mg, 1.62 mmol) in
dry THF (1 mL) was added and the reaction mixture was allowed to reach room
temperature over a period of 2 hours. The reaction mixture was then allowed to stir at
room temperature overnight and when the reaction was complete (tLC) the reaction
was quenched by adding the mixture to a saturated aqueous solution of ammonium
sulfate (25 mL). The mixture was then extracted with dichloromethane (3×20 mL)
and the combined organic extracts were dried (MgSO4) and the solvent removed in
vacuo to give a yellow oil which was purified by column chromatography
(methanol/dichloromethane) over silica gel. The first fraction was an inseparable
mixture of the (1R)-camphor imines of (2R)- and (2S)-2-amino-2-methylindan-1-one
101a/101b as a pale yellow oil in 13% (56.1 mg, 0.190 mmol) yield and in a ratio (1H
NMR spectroscopy) of 1:1: νmax (neat)/cm⁻¹ 3433(OH), 1718(C=O), 1676(C=N),
1608(C=O); δH (250 MHz; CDCl3) 7.80-7.74(1H_A-B, m, Ar-H), 7.67-7.56(1H_A-B, m,
Ar-H), 7.46-7.35(2H_A-B, m, Ar-H), 3.33-3.06(2H_A-B, m, indan-1-one C3), 2.14(1H,
**Experimental Details**

$J = 17.1, 4.2$ and $3.7$, *exo* at camphoryl C3), $2.00(1H_b, dt, J = 16.5, 3.7, *exo* at camphoryl C3), 1.79-0.82(6H$_A$-H, m), 1.55(3H$_A$, s, CH$_3$CR(NR$_2$)(COAr)), 1.52(3H$_b$, s, CH$_3$CR(NR$_2$)(COAr)), 0.98(3H, s, Me), 0.95(3H, s, Me), 0.88(3H, s, Me), 0.87(3H, s, Me), 0.79(3H, s, Me), 0.72(3H, s, Me), impurity at 1.44 also, aromatic and indan-1-one CH$_2$ signals are disproportionately high this is likely to be due to the presence of some 2-methylindan-2-ol-1-one impurity; $\delta$C (63 MHz; CDCl$_3$) 11.5(Me), 11.6(Me), 19.0(Me), 19.1(Me), 19.5(Me), 19.7(Me), 25.6(Me), 26.3(Me), 27.0(Me), 27.2(CH$_2$), 27.5(CH$_2$), 31.9(CH$_2$), 32.1(CH$_2$), 35.8(C$_{quat}$), 37.9(CH$_2$), 38.5(CH$_2$), 42.2(CH$_2$), 43.4(CH$_2$), 43.7(CH$_2$), 44.3(CH), 44.6(CH), 46.7(C$_{quat}$), 62.0(C$_{quat}$), 68.3(C$_{quat}$), 124.2(Ar, CH), 124.3(Ar, C$_{quat}$), 124.8(Ar, CH), 125.8(Ar, CH), 126,28(Ar, CH), 126,31(Ar, CH), 126,7(Ar, CH), 127.6(Ar, CH), 127.7(Ar, CH), 127.8(Ar, CH), 127.9(Ar, C$_{quat}$), 133.8(Ar, C$_{quat}$), 134.9(Ar, CH), 135.0(Ar, CH), 135.7(Ar, CH), 151.7(C$_{quat}$), 151.7(C$_{quat}$), one extra CH$_3$ signal, one extra CH$_2$ signal and three extra aromatic signals are present at the correct positions indicate the presence of 2-methylindan-2-ol-1-one as an impurity. Given that this is the case, one C$_{quat}$, 3 aromatic C$_{quat}$ signals and three C=O signals are obscured either by overlap or by being too small; Found: M$^+$, 295.1937 C$_{20}$H$_{25}$NO requires 295.19360; m/z 296(MH$^+$), 295(M$^-$), 280, 266, 252, 238, 224, 198, 176, 160, 145, 132, 115, 95, 91, 77, 67, 55. The next fraction isolated was 2-amino-2-methylindan-1-one 102 in a yield of 65% (157 mg, 0.975 mmol) which was then shown by chiral HPLC to be completely racemic: $v_{max}$ (neat)/cm$^{-1}$ 3355 and 3304(primary NH$_2$), 1716(C=O), 1608(Ar C=C), $\delta$H (250 MHz; CDCl$_3$) 7.76-7.71(1H, m, Ar-H), 7.63-7.55(1H, m, Ar-H), 7.42-7.32(2H, m, Ar-H), 3.17(1H$_A$, dd(ABX), $J_{AB} = 17.1, J_{AX} = 0.6$, indanone C3) 3.02(1H, d, $J = 17.1$, indanone C3), 1.93(2H, br.s, NH), 1.30(3H, s, Me); $\delta$C (63 MHz; CDCl$_3$) 25.9(CH$_3$), 43.0(CH$_2$), 60.2(C$_{quat}$, indanone C2), 124.7(CH, Ar), 126.6(CH, Ar), 127.7(CH, Ar), 133.8(C$_{quat}$, Ar), 135.3(CH, Ar), 151.0(C$_{quat}$, Ar), 209.9(C$_{quat}$, C=O); Found: M$^-$, 161.0841 C$_{10}$H$_{11}$NO requires 161.08406; m/z 162(MH$^-$), 161(M$^-$), 144, 133, 115, 92, 77, 65, 51.
Experimental Details

General Procedure for the Reaction of Aryl Acetonitriles with (+)-Camphoryl Oxaziridine 65

To a cooled (−78 °C) stirring solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.58 mL, 1.58 mmol) in 5 mL of dry THF was added aryl acetonitrile (1.50 mmol) in THF (1 mL) dropwise. After 1 hour at −78 °C, a solution of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) in dry THF (1 mL) was added, and the reaction was allowed to reach room temperature over a period of 2 hours. The reaction mixture was then stirred at room temperature until the reaction was complete (tlc). The reaction mixture was quenched with an aqueous solution of ammonium chloride (20 mL) and then extracted with dichloromethane (3x35 mL). The resulting organic solution was then dried (MgSO₄) and the solvent removed in vacuo to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate/light petroleum) to afford the title compounds.

(2R)- and (2S)-2-Phenyl-2-{{[(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene]amino}ethanamide, (1R)-Camphor Imine of (2R)- and (2S)-Phenylglycine Amides 104a/104b (reaction between benzyl cyanide and (+)-camphoryl oxaziridine 65).

\[ \text{Imino amides 104a/104b were synthesised according to the above procedure in a overall reaction time of 4.5 hours. The (1R)-camphor imine of (2R)-phenylglycine amide 104a was first eluted, to give a colourless solid in a 32% (137 mg, 0.482 mmol) yield: } [\alpha]^{25}_D = -87 \text{ (CHCl}_3); \text{ mp 131-133 °C; Found} \%: \text{ C, 76.02; H, 8.48; N, 9.60 C}_{18}\text{H}_{24}\text{N}_{2}\text{O requires} \%: \text{ C, 76.02; H, 8.51; N, 9.85; } v_{\text{max}} \text{ (neat)/cm}^{-1} 3438(\text{NH}), 3170(\text{NH}), 1696(\text{C=O amide}), 1651(\text{C=N}); \delta_{\text{H}} (400 \text{ MHZ; CDCl}_3) 7.48(1\text{H, br s, } \text{RCONH}_2), 7.20-7.43(\text{m, 5H, ArH}), 6.26(1\text{H, br s, } \text{RCONH}_2), 4.78(1\text{H, s,}} \]
**Experimental Details**

PhCH(CONH$_2$)(NR$_2$)$_2$, 2.47-2.37(1H, m, exo at camphor C3), 1.91(1H, t, $J$ = 4.4, camphor C4), 1.80-1.50(3H, m), 1.27-1.18(1H, m), 1.04 (3H, s, Me), 0.97-0.87(1H, m) this signal overlaps the signal at 0.93(3H, s, Me), 0.77(3H, s, Me); $\delta_C$ (100 MHz; CDCl$_3$) 11.6(Me), 19.3(Me), 19.9(Me), 27.5(CH$_2$), 32.1(CH$_3$), 36.3(CH$_2$), 44.2(CH), 47.5(C$_{quat}$), 54.9(C$_{quat}$), 68.3(CH, PhCH(CONH$_2$)(NR$_2$)$_2$), 127.6(CH, Ar), 127.8(CH, Ar), 128.7(CH, Ar), 139.9(C$_{quat}$, Ar-alkyl), 176.0(C$_{quat}$, RCONH$_2$)$_2$, 185.5(C$_{quat}$, C=N); Found: M$^+$, 284.1897 C$_{18}$H$_{24}$N$_2$O requires 284.1894; m/z 285(MH$^+$), 284(M$^+$), 241, 224, 212, 198, 184, 172, 156, 135, 118, 106, 91, 79, 69, 55, 41. The (1R)-camphor imine of (2S)-phenylglycine amide 104b was next isolated as a colourless solid in 46% (196 mg, 0.690 mmol) yield: $[\alpha]^2_D$ = +111 (CHCl$_3$); mp 173-177 °C; Found%: C, 75.71; H, 8.45; N, 9.72 C$_{18}$H$_{24}$N$_2$O requires%: C, 76.02; H, 8.51; N, 9.85; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3435(NH), 3200(NH), 1700(C=O amide), 1654(C=N); $\delta_H$ (400 MHz; CDCl$_3$) 7.53(1H, br s, RCONH$_2$), 7.43-7.37(2H, m, ArH), 7.30-7.18(3H, m, ArH), 6.30(1H, br s, RCONH$_2$), 4.79(1H, s, PhCH(CONH$_2$)(NR$_2$)$_2$), 2.00(1H, dt, $J$ = 17.4 and 3.4, exo at camphor C3), 1.95-1.62(4H, m), 1.38-1.32(1H, m), 1.27-1.17(1H, m), 1.04(3H, s, Me), 0.90(3H, s, Me), 0.50(3H, s, Me); $\delta_C$ (100. MHz; CDCl$_3$) 11.3(Me), 18.9(Me), 19.2(Me), 27.2(CH$_2$), 31.9(CH$_2$), 36.2(CH$_2$), 43.7(CH), 47.7(C$_{quat}$), 54.3(C$_{quat}$), 68.5(CH, PhCH(CONH$_2$)(NR$_2$)$_2$), 127.2(CH, Ar), 127.4(CH, Ar), 128.3(CH, Ar), 139.2(C$_{quat}$, Ar-alkyl), 175.5(C$_{quat}$, RCONH$_2$)$_2$, 185.4(C$_{quat}$, C=N); Found: M$^+$, 284.18917 C$_{18}$H$_{24}$N$_2$O requires 284.18942; m/z 285(MH$^+$), 284(M$^+$), 266, 241, 224, 211, 198, 184, 172, 135, 118, 106, 91, 79, 69, 55, 41; (for crystal structures of 104a/104b see appendices. This reaction gave an overall yield of 78% (333 mg, 1.173 mmol) for imines 104a/104b, and a diastereoisomeric excess of 104b of 20%.)
Experimental Details

(2R)- and (2S)-2-Naphthalen-2-yl-2-\{[(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino\}ethanamide, (1R)-Camphor Imines of (2R)- and (2S)-2'-Naphthylglycine Gmides 105a/105b (reaction between 2-naphthylacetonitrile and (+)-camphoryl oxaziridine 65)

Imino amides 105a/105b were synthesised according to the above procedure in an overall reaction time of 4.5 hours. The (1R)-camphor imine of (2R)-2'-naphthylglycine amide 105a was first eluted, to give a colourless solid in a 27% (135 mg, 0.404 mmol) yield: \([\alpha]_{D}^{23} = -91\) (CHCl\(_3\)); mp 159-162 °C; \(\nu_{max}\) (neat)/cm\(^{-1}\) 3428(NH), 1692(C=O amide), 1652(C=N); \(\delta_{H}\) (250 MHz; CDCl\(_3\)) 7.76-7.83(4H, m, Ar-H), 7.54-7.58(2H, m, Ar-H and RCONH\(_2\)), 7.42-7.45(2H, m, Ar-H), 6.18(1H, br.s, RCONH\(_2\)), 4.93(1H, s, ArCH(CONH\(_2\))(NR\(_2\))), 2.53-2.41(1H, m, \(J = 4.2\), camphor C3), 1.89(1H, t, \(J = 17.5\), endo at camphor C3), 1.29-1.19(1H, m), 1.07(3H, s, Me), 0.97-0.84(1H, m) this signal overlaps the signal at 0.92(3H, s, Me), 0.77 (3H, s, Me); Found: M\(^+\), 334.20367 C\(_{22}\)H\(_{26}\)N\(_2\)O requires M\(^+\) 334.20451; \(m/z\) 334(M\(^+\)), 305, 291, 290, 265, 222, 199, 185, 172, 155, 141, 127, 108, 95, 81, 69, 55, 43. The (1R)-camphor imine of (2S)-2'-naphthylglycine amide 105b was next eluted, to give a colourless solid in 47% (234 mg, 0.701 mmol) yield: \([\alpha]_{D}^{23} = +115\) (CHCl\(_3\)); mp 135-150 °C; \(\delta_{H}\) (250 MHz; CDCl\(_3\)) 7.84-7.75(4H, m, Ar), 7.62(1H, br.s, RCONH\(_2\)), 7.59-7.54(1H, m, Ar), 7.48-7.40(2H, m, Ar), 6.18(1H, br.s, RCONH\(_2\)), 4.96(1H, s, ArCH(CONH\(_2\))(NR\(_2\))), 1.65-2.04(5H, m), 1.34-1.43(1H, m), 1.21-1.29(1H, m), 1.09 (3H, s, Me), 0.90(3H, s, Me), 0.47(3H, s, Me); \(\delta_{C}\) (100 MHz; CDCl\(_3\)) Imines 105a/105b epimerised in CDCl\(_3\) during the overnight \(^{13}\)C NMR run to give a mixture of imines 105a/105b in a 1:1 ratio, 11.4, 11.6, 19.0, 19.1, 19.4, 19.9.
Experimental Details

19.7, 27.2, 27.4, 31.8, 36.1, 36.5, 43.90, 43.94, 47.2, 47.9, 53.5, 54.7, 68.1(CH, ArCH(CONH2)(NR2)), 68.7(CH, ArCH(CONH2)(NR2)), 125.1, 125.2, 126.0, 126.1, 126.3, 126.4, 127.7, 128.1, 128.27, 128.33, 133.0, 133.3, 133.4, 136.5, 136.9, 175.9(Cquat, RCONH2), 176.0(Cquat, RCONH2), 185.7(Cquat, C=N), 186.1(Cquat, C=N)), 5 aromatic carbons obscured either because of overlap with other signals, or because they were too small to distinguish from any impurities present; Found: M\textsuperscript{+}, 334.20384 C\textsubscript{22}H\textsubscript{26}N\textsubscript{2}O requires 334.20451; m/z 335(MH\textsuperscript{+}), 334(M\textsuperscript{+}), 291, 274, 261, 246, 234, 222, 206, 193, 185, 168, 156, 141, 128, 109, 95, 81, 69, 55, 41. This reaction gave an overall yield of 73% (369 mg, 1.105 mmol) for imines 105a/105b, and a diastereoisomeric excess of 104b of 33%.

(2R)- and (2S)-2-Naphthalen-1-yl-2-{{(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}ethanamide, (1R)-Camphor Imines of (2R)- and (2S)-1'-Naphthylglycine Amides 106a/106b (reaction between 1-naphthylacetonitrile and (+)-camphoryl oxaziridine 65)

Imino amides 106a/106b were synthesised according to the above procedure in an overall reaction time of 4.5 hours. The (1R)-camphor imine of (2R)-1'-naphthylglycine amide 106a was first eluted, to give a colourless solid in a 31% (154 mg, 0.461 mmol) yield: [α]\textsubscript{D}\textsuperscript{25} = -127 (CHCl\textsubscript{3}); mp 155-158 °C; Found\%: C, 78.94; H, 7.89; N, 8.39 C\textsubscript{22}H\textsubscript{26}N\textsubscript{2}O requires\%: C, 79.01; H, 7.84; N, 8.38; \nu_{\text{max}} (neat)/cm\textsuperscript{-1} 3420(NH), 1696(C=O amide), 1653(C=N); 6\textsubscript{11} (250 MHz, CDCl\textsubscript{3}) 8.42(1H, d, J = 8.5, Ar-H), 7.72-7.83 (2H, m, ArH), 7.63(1H, br.s, RCONH\textsubscript{2}), 7.36-7.56(4H, m, Ar-H), 6.39(1H, br.s, RCONH\textsubscript{2}), 5.45(1H, s, ArCH(CONH2)(NR2)), 2.42(1H, ddd, J = 17.2, 4.8 and 2.2, exo at camphor C3), 1.81(1H, t, J = 4.3, camphor C4), 1.75-1.49(2H, m), 1.33(1H, d, J = 17.3, endo at camphor C3), 1.13-1.02(1H, m) this signal overlaps with signal at 1.05(3H, s, Me), 0.89(3H, s, Me), 0.84-0.71(1H, m) this signal overlaps with
Experimental Details

signal at 0.77(3H, s, Me); δC (63 MHz; CDCl₃) 11.4, 18.9, 19.6, 27.0, 31.4, 36.1, 43.9, 47.1, 54.6, 65.2(ArCH(CONH₂)(NR₂)), 124.9(CH, Ar), 125.3(CH, Ar), 125.6(CH, Ar), 126.2(CH, Ar), 126.3(CH, Ar), 128.1(CH, Ar), 128.7(CH, Ar), 131.8(Cquat, Ar), 134.0(Cquat, Ar), 136.6(Cquat, Ar), 175.6(RCONH₂), 185.3(C=N); Found: M⁺, 334.20483 C₂₂H₂₆N₂O requires 334.20451; m/z 334(M⁺), 290, 222, 185, 172, 155, 141, 127, 115, 95, 69, 55, 41. The (1R)-camphor imine of (2S)-1'-naphthylglycine amide 106b was next eluted, to give a colourless solid in 53% (266 mg, 0.796 mmol) yield: [α]₂⁵ D = +133 (CHCl₃); mp 190-192 °C; Found%: C, 78.64; H, 7.80; N, 8.40 C₂₂H₂₆N₂O requires%: C, 79.01; H, 7.84; N, 8.38;νmax(neat)/cm⁻¹ 3429(NH), 3196(NH), 1697(C=O amide), 1651(C=N); δH (250 MHz; CDCl₃) 8.41-8.44(1H, m, Ar-H); 7.73-7.84(3H, m, 2xA r-H and 1x RCONH₂), 7.36-7.58(4H, m, Ar-H), 6.00(1H, br.s, RCONH₂), 5.50(1H, br.s, ArCH(CONH₂)(NR₂)), 1.99-1.56(3H, m) 1.50-1.18(2H, m), 1.08-0.56(2H, m) this signal overlaps signals at 1.07(3H, s, Me) and 0.85(3H, s, Me), 0.28(3H, s, Me); δC (63 MHz; CDCl₃) 11.5, 19.1, 19.2, 27.3, 32.0, 36.8, 43.9, 48.0, 54.5, 65.7(ArCH(CONH₂)(NR₂)), 125.0(CH, Ar), 125.3(CH, Ar), 125.4(Cquat, Ar) 125.7(CH, Ar), 126.0(CH, Ar), 126.2(CH, Ar), 128.3(CH, Ar), 128.7(CH, Ar), 131.6(Cquat, Ar), 134.0(Cquat, Ar), 175.4(RCONH₂), 186.0(C=N); Found: M⁺, 334.20420 C₂₂H₂₆N₂O requires 334.20451; m/z 335(MH⁺), 334(M⁺), 291, 262, 234, 222, 206, 185, 168, 156, 141, 129, 109, 95, 81, 69, 55, 41. This reaction gave an overall yield of 80% (420 mg, 1.257 mmol) for imines 106a/106b, and a diastereoisomeric excess of 106b of 33%.

(2R)- and (2S)-2-(4-Chlorophenyl)-2-{{(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}ethanamide, (1R)-Camphor Imines of (2R)- and (2S)-(4-Chlorophenyl)glycine Amides 107a/107b (reaction between 4-chlorobenzyl cyanide and (+)-camphoryl oxaziridine 65)
Experimental Details

Imino amides 107a/107b were synthesised according to the above procedure in an overall reaction time of 5 hours. The (1R)-camphor imine of (2R)-(4-chlorophenyl)glycine amide 107a was first eluted, to give a pale yellow oil in 35% (165 mg, 0.518 mmol) yield: \([\alpha]^{24}_{D} = -113\) (CHCl₃); \(v_{\text{max}}\) (neat)/cm⁻¹ 3429(NH), 1694(C=O amide), 1653(C=N); \(\delta_{H}\) (250 MHz; CDCl₃) 7.46(1H, br.s, RCONH₂), 7.37-7.33(2H, m, Ar-H), 7.29-7.25(2H, m, Ar-H), 6.13(1H, br.s, RCONH₂), 4.73(1H, s, ArCH(CONH₂)(NR₂)), 2.41(1H, ddd, \(J = 17.1, 4.5\) and 2.6, \(exo\) at camphor C3), 1.92(1H, t, \(J = 4.3\), camphor C4), 1.87-1.62(2H, m), 1.52(d, 1H, \(J = 17.2\), \(endo\) at camphor C3), 1.30-1.14(1H, m), 1.04(3H, s, Me), 0.95-0.80(1H, m) this signal overlaps signal at 0.93(3H, s, Me), 0.75(3H, s, Me); \(\delta_{C}\) (63 MHz; CDCl₃) 11.1, 18.8, 19.4, 27.0, 31.6, 35.9, 43.7, 47.0, 54.5, 67.1(ArCH(CONH₂)(NR₂)), 128.4(CH, Ar), 128.5(CH, Ar), 133.2(C₂, Ar), 137.1(C₂, Ar), 174.9(C₂, RCONH₂), 185.3(C₂, C=N). The (1R)-camphor imine of (2S)-(4-chlorophenyl)glycine amide 107b was next eluted, to give a colourless solid in 46% (218 mg, 0.684 mmol) yield: \([\alpha]^{25}_{D} = +146\) (CHCl₃); mp 145-156 °C; Found%: C, 67.86; H, 7.19; N, 8.75 C₁₈H₂₃N₂OCl requires%: C, 67.81; H, 7.27; N, 8.79; \(v_{\text{max}}\) (neat)/cm⁻¹ 3430(NH), 3200(NH), 1694(C=O amide), 7.53(1H, br.s, RCONH₂), 7.37-7.34(2H, m, Ar-H), 7.29-7.23(2H, m, Ar-H), 5.61(1H, br.s, RCONH₂), 4.76(1H, s, ArCH(CONH₂)(NR₂)), 2.00-1.65(3H, m), 1.45-1.13(3H, m), 1.04(3H, s, Me), 0.95-0.83(1H, m) this signal overlaps the signal at 0.91(3H, s, Me), 0.51(3H, s, Me); \(\delta_{C}\) (63 MHz; CDCl₃) 11.3, 18.9, 19.3, 27.2, 31.8, 36.2, 43.7, 47.6, 54.2, 67.7(2H, m, Ar-H), 128.4(CH, Ar), 131.2(C₂, Ar), 135.9(C₂, Ar), 173.2(RCONH₂) 185.4(C=N), one aromatic CH signal obscured probably due to overlap with another signal; Found: M⁺, 318.15068 C₁₈H₂₃N₂OCl requires 318.1497; \(m/z\) 335(M⁺), 318(M⁺), 303, 277, 260, 239, 232, 218, 206, 192, 171, 169, 152, 140, 133, 125, 109, 95, 89, 83, 77, 69, 55, 43, 41; This reaction gave an overall yield of 80% (383 mg, 1.203 mmol) for imines 107a/107b, and a diastereoisomeric excess of 107b of 20%.
Experimental Details

(2R)- and (2S)-2-(4-Methoxyphenyl)-2-\{(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene|amino|ethanamide, (1R)-Camphor Imines of (2R)- and (2S)-(4-Methoxyphenyl)glycine Amides 108a/108b (reaction between 4-methoxybenzyl cyanide and (+)-camphoryl oxaziridine 65)

Imino amides 108a/108b were synthesised according to the above procedure in an overall reaction time of 7 hours. Title imino amides 108a/108b were isolated as an inseparable mixture of diastereoisomers, and as a pale-yellow oil in 76% (352 mg, 1.12 mmol) overall yield. Imino amides 108a/108b were subsequently shown by $^1$H NMR spectroscopy to be present in a 1:1 ratio; $\nu_{\max }$ (neat)/cm$^{-1}$ 3250(NH), 3190(NH), 1693(C=O), 1510($p$-disubst benzene ring); $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 7.52(1H$_A$, br.s, amide NH), 7.48(1H$_B$, br.s, amide NH), 7.35-7.26(2H$_{A+B}$, m, Ar-H), 6.86-6.77(2H$_{A+B}$, m, Ar-H), 6.39(1H$_A$, d(br.s), $J$ =5.0, amide NH), 6.34(1H$_B$, d(br.s), $J$ =4.3, amide NH), 4.71(1H$_A$, s, ArCH(CONH$_2$)(N=C=CR$_2$)), 4.69(1H$_B$, s, ArCH(CONH$_2$)(N=C=CR$_2$)), 3.76(3H$_A$, s, MeO), 3.75(3H$_B$, s, MeO), 2.45-2.35(1H$_A$, m, exo at C3), 2.06-1.95(1H$_B$, m, exo at C3), 1.92-1.59(4H$_{A+B}$, m), 1.38-1.14(2H$_{A+B}$, m), 1.02(3H, s, Me), 1.01(3H, s, Me), 0.92(3H, s, Me), 0.88(3H, s, Me), 0.74(3H, s, Me), 0.48(3H, s, Me); $\delta_{\text{C}}$ (63 MHz; CDCl$_3$) 11.18(Me), 11.36(Me), 18.81(Me), 18.94(Me), 19.27(Me), 19.45(Me), 27.05(CH$_2$), 27.20(CH$_2$), 31.60(CH$_2$), 31.84(CH$_2$), 35.73(CH$_2$), 36.15(CH$_2$), 43.70(CH$_2$), 46.95(C$_{\text{quat}}$), 47.90(C$_{\text{quat}}$), 54.03(C$_{\text{quat}}$), 54.19(C$_{\text{quat}}$), 55.13(MeO), 55.18(MeO), 67.20(CH, ArCH(CONH$_2$)(NR$_2$)), 67.82(CH, ArCH(CONH$_2$)(NR$_2$)), 113.65(CH, Ar), 113.74(CH, Ar), 128.05(CH, Ar), 128.13(CH, Ar), 131.42(C$_{\text{quat}}$, Ar-C-R), 131.92(C$_{\text{quat}}$, Ar-C-R), 158.56(C$_{\text{quat}}$, C=N), 158.66(C$_{\text{quat}}$, C=N), 176.12(C$_{\text{quat}}$, RCONH$_2$), 176.22(C$_{\text{quat}}$, RCONH$_2$), three signals are obscured either by being too small or by overlap with other signals, these include one CH from the camphoryl C4 position and both C$_{\text{quat}}$ signals for the aromatic C-
2-Cyanoglycine derivatives 109a/109b were synthesised according to the above procedure in an overall reaction time of 6 hours. Title imino amides 109a/109b were isolated as an inseparable mixture of diastereoisomers, and as a colourless solid in 82% (288 mg, 1.236 mmol) overall yield. Imino amides 109a/109b were subsequently shown by $^1$H NMR spectroscopy to be present in a 1:1 ratio; mp 139-140 °C; Found%: C, 66.91; H, 8.13; N, 17.82 C$_{13}$H$_{19}$N$_3$O requires%: C, 66.92; H, 8.21; N, 18.01; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3413(NH), 3165(NH), 2254(CN nitrile), 1704(C=O amide), 1675(C=N); $\delta_{11}$ (250 MHz; CDCl$_3$) 7.50(1H$_{A+B}$, br.s, RCONH$_2$), 6.11(1H$_{A+B}$, br.s, RCONH$_2$), 4.65(1H$_A$, s, CH(CN)(NR$_2$)(CONH$_2$)), 4.63(1H$_B$, s, CH(CN)(NR$_2$)(CONH$_2$)), 2.83-2.69(1H$_A$, m, exo at camphor C3), 2.41(1H$_B$, ddd, $J = 17.7$, 4.7 and 2.7 exo at camphor C3), 2.20-2.07(1H$_{A+B}$, m)1.99-1.69(3H$_{A+B}$, m), 1.47-1.21(4H$_{A+B}$, m), 1.01(6H, s, 2xMe), 0.98(6H, s, 2xMe), 0.82(3H, s, Me), 0.74(3H, s, Me); $\delta_C$ (63 MHz; CDCl$_3$) 11.0, 11.2, 18.9, 19.0, 19.5, 19.6, 27.1, 31.4, 31.9, 36.5, 37.1, 44.0, 47.6, 48.8, 53.7(CH(CN)(NR$_2$)(CONH$_2$)), 53.8(CH(CN)(NR$_2$)(CONH$_2$)), 55.6, 55.7, 114.6(nitrile), 115.1(nitrile), 167.2(RCONH$_2$), 193.1(C=quat, C=N), 193.5(C=quat, C=N), one amide signal and one camphor signal is obscured probably due to over lap of signals; Found: M', 233.15326 C$_{13}$H$_{29}$N$_3$O requires 233.15281; m/z 234(MH'), 233(M'), 218, 207, 189, 175, 162, 150, 133, 121, 108, 95, 77, 69, 55, 41.
Experimental Details

(2R)- and (2S)-2-Vinyl-2-[[1R,4S]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino]ethanamide, (1R)-Camphor Imines of (2R)- and (2S)-2-Vinylglycine Amides 110a/110b (reaction between allyl cyanide and (+)-camphoryl oxaziridine 65)

Imino amides 110a/110b were synthesised according to the above procedure in an overall reaction time of 3 hours. Title imino amides 110a/110b were isolated as an inseparable mixture of diastereoisomers, and as a yellow solid in 29% (102 mg, 0.437 mmol) overall yield. Imino amides 110a/110b were subsequently shown by 1H NMR spectroscopy to be present in a 1:1 ratio: mp 130-133 °C; νmax (neat)/cm⁻¹ 3530(NH), 3431(NH), 3054(CH=CH₂), 1691(C=O); δH (250 MHz; CDCl₃) 7.24(1Hₐ+B, br.s, RCONH₂), 6.32(1Hₐ+B, br.s, RCONH₂), 5.96-5.79(1Hₐ+B, m, CH₂=CHR), 5.07-5.20(2Hₐ+B, m, CH₂=CHR), 4.27(1Hₐ, d, J =6.0, R₂NCH(CONR₂)(CH=CH₂)), 4.22(1Hₐ, dt, J =5.5 and 1.6, =NCH(CONR₂)(CH=CH₂)), 2.33(1Hₐ, ddd, J =17.2, 4.6 and 2.9, exo at camphor C3), 2.23(1Hₐ, ddd, J =17.2, 4.3 and 3.1, exo at camphor C3), 1.94-1.61(4Hₐ+B, m), 1.36-1.03(2Hₐ+B, m), 0.97(3H, s, Me), 0.96(3H, s, Me), 0.91(6H, s, 2xMe), 0.70(6H, s, 2xMe); δC (63 MHz; CDCl₃) 11.1(Me), 11.3(Me), 18.8(Me), 18.9(Me), 19.39(Me), 19.44(Me), 27.1(CH₂), 27.2(CH₂), 31.9(CH₂), 32.0(CH₂), 35.3(CH₂), 35.6(CH₂), 43.6(CH), 43.7(CH), 46.9(Cₐt), 47.7(Cₐt), 54.3(Cₐt), 54.9(Cₐt), 66.7(CH, CH(NR₂)(CONH₂)(CH=CH₂)), 67.9(CH, CH(NR₂)(CONH₂)(CH=CH₂)), 115.9(CH₂, CH₂=CHR), 116.2(CH₂, CH₂=CHR), 134.1(CH, RCH=CH₂), 134.5(CH, RCH=CH₂), 175.0(Cₐt, C=N), 175.1(Cₐt, C=N), 185.3(Cₐt, RCONH₂), 185.4(Cₐt, RCONH₂); Found: M⁺, 234.17314 C₁₇H₂₇NO₂ requires 234.17320; m/z 234(M⁺), 190, 176, 163, 148, 134, 122, 108, 95, 81, 67, 56.
Experimental Details

(1R)-2-(2,2,3-Trimethylcyclopent-3-enyl)ethanamide and (1R, 5S)-1,8,8-trimethyl-2-azabicyclo[3.2.1]octan-3-one, α-Campholenic Amide 111 and the Isomer of α-Camphidone 80 (reaction between butyronitrile and (+)-camphoryl oxaziridine 65)

The title compounds were synthesised according to the above procedure with a total reaction time of 4 hours. α-Campholenic amide 111 was isolated as a white solid in 83% (210 mg, 1.257 mmol) yield: mp 130°C; δH (250 MHz, CDCl3) 6.20(1H, br.s, RCONH2), 5.78(1H, br.s, RCONH2), 5.23(1H, br.s, C=CH-R), 2.07-2.44(4H, m), 1.86-1.97(1H, m), 1.61(3H, q, J = 1.5 Hz, C=CCH3(R)), 1.01(3H, s, Me), 0.78(3H, s, Me); δC (100 MHz; CDCl3) 12.6, 19.9, 25.5, 35.3, 37.0, 46.8, 121.7, 148.0, 176.2(RCONH2). This compound displayed identical properties to those reported for the same compound.113, 143 The isomer of α-camphidone, lactam 80 was isolated in 17% (43 mg, 0.257 mmol) yield: mp 195-197 °C; δH (250 MHz; CDCl3) 6.84(1H, br.s), 2.54(1H, ddd, J =18.0, 4.7 and2.7, exo at C4), 2.10(1H, dd, J =18.0 and1.6, endo at C4), 2.04-1.78(4H, m), 1.49-1.39(1H, m), 1.07(3H, s, Me), 0.96(3H, s, Me), 0.91(3H, s, Me). This product showed spectral properties identical to those previously reported for this compound.113, 128

(1R)-2-(2,2,3-Trimethylcyclopent-3-enyl)ethanamide, α-Campholenic Amide 111 (reaction between propionitrile and (+)-camphoryl oxaziridine 65)
Experimental Details

The title compound was synthesised according to the above procedure in a total reaction time of 1.5 hours. α-Campholenic amide 111 was isolated as a white solid in 83% (210 mg, 1.257 mmol) yield: mp 130°C; δH (250 MHz; CDCl₃) 6.20(1H, br.s, RCONH₂), 5.78(1H, br.s, RCONH₂), 5.23(1H, br.s, C=CH-R), 2.07-2.44(4H, m), 1.86-1.97(1H, m), 1.61(3H, q, J = 1.5 Hz, C=CCH₃(R)), 1.01(3H, s, Me), 0.78(3H, s, Me); δC (100 MHz; CDCl₃) 12.6, 19.9, 25.5, 35.3, 37.0, 46.8, 121.7, 148.0, 176.2(RCONH₂). This compound displayed identical properties to those reported for the same compound.¹¹₃,¹⁴₃

(1R)-2-(2,2,3-Trimethylcyclopent-3-enyl)ethanamide, α-Campholenic Amide 111
(reaction between 4-nitrophenylacetonitrile and (+)-camphoryl oxaziridine 65)

The title compound was synthesised according to the above procedure in a total reaction time of 3 hours. α-Campholenic amide 111 was isolated as a white solid in 83% (210 mg, 1.257 mmol) yield: mp 130°C; δH (250 MHz; CDCl₃) 6.20(1H, br.s, RCONH₂), 5.78(1H, br.s, RCONH₂), 5.23(1H, br.s, C=CH-R), 2.07-2.44(4H, m), 1.86-1.97(1H, m), 1.61(3H, q, J = 1.5 Hz, C=CCH₃(R)), 1.01(3H, s, Me), 0.78(3H, s, Me); δC (100 MHz; CDCl₃) 12.6, 19.9, 25.5, 35.3, 37.0, 46.8, 121.7, 148.0, 176.2(RCONH₂). This compound displayed identical properties to those reported for the same compound.¹¹₃,¹⁴₃
Experimental Details

E- and Z-(1R, 4S)-Ethyl 2-[(1,3,3-Trtrimethylbicyclo[2.2.1]hept-2-ylidene)amino]ethanoate, Syn- and Anti- (1R)-Fenchone Imines of Ethyl Glycinate 112a/112b (the reaction of diethyl malonate with (-)-fenchyl oxaziridine 70 using sodium ethoxide as a base)

\[
\begin{align*}
\text{N} & \quad \text{Et} \\
\end{align*}
\]

Sodium (100 mg, 4.35 mmol) was added to dry ethanol (5 mL) and the solution was stirred until the effervescence had ceased and all of the sodium had reacted. After allowing the solution to reach room temperature, a solution of (-)-fenchyl oxaziridine 70 (250 mg, 1.50 mmol) in ethanol (1 mL) was added followed by diethyl malonate (200 µL, 211 mg, 1.31 mmol) and the reaction mixture was stirred at room temperature for 4 hours. When the reaction was complete (tlc) the reaction mixture was added to a saturated aqueous solution of ammonium sulfate (40 mL). The mixture was then extracted with dichloromethane (3x40 mL) and the combined organic extracts were dried (MgSO₄) and the solvent removed \textit{in vacuo} to give a pale yellow oil which was purified by column chromatography (methanol/dichloromethane) over silica gel to give the product as a pale yellow oil. The product was found to be a mixture of inseparable diastereoisomeric \textit{syn-} and \textit{anti-} (1R)-fenchone imines of ethyl glycinate 112a/112b, present in a ratio of 1:1, and in 68% (213 mg, 0.897 mmol) yield: \(\nu_{\text{max}}\) (neat)/cm⁻¹ 1750(C=O), 1684(C=N); \(\delta_H\) (250 MHz; CDCl₃) 4.35(2H₃, s, CH₂(CO₂Et)(NR₂)), 4.34(2H₃s, s, CH₂(CO₂Et)(NR₂)), 4.27-4.11(2H₃A-B, m, MeCH₂O), 1.87-1.35(7H₃A-B, m) 1.283(3H, t, \(J = 7.5\), CH₃CH₂O), 1.281(3H, t, \(J = 7.2\), CH₃CH₂O), 1.23(6H, s, 2xMe), 1.22(6H, s, 2xMe), 1.19(6H, s, 2xMe); \(\delta_C\) (63 MHz; CDCl₃) 14.1, 17.4, 20.0, 23.7, 24.2, 24.4, 25.1, 25.2, 26.3, 33.6, 33.6, 42.1, 44.3, 45.7, 46.9, 49.8, 51.8, 52.6, 52.7, 60.5(CH₂(CO₂R)(NR₂)), 170.8(RCO₂Et), 188.2(C=N), 6 signals are obscured and cannot be assigned confidently due to the presence of impurities; Found: M⁺,
Experimental Details

237.17249 C_{14}H_{23}NO_2 requires 237.17288; m/z 238(MH^+), 237(M^+), 222, 208, 194, 177, 164, 157, 149, 121, 104, 93, 84, 81, 76, 69, 65, 55.

(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one Oxime, (1R)-(−)-Camphor Oxime 62 (reaction between (+)-camphoryl oxaziridine 65 and triflic acid at room temperature in the presence of 1-phenyl cyclohexene)

To a stirring mixture of (+)-camphoryl oxaziridine 65 (250 mg, 1.50 mmol) and 1-phenyl cyclohexene (238 µL, 237 mg, 1.50 mmol) in dichloromethane (5 mL) at room temperature was added trifluoromethanesulfonic acid (132 µL, 225 mg, 1.50 mmol). Within 5 minutes, the reaction was complete (tLC), and the reaction mixture was added to a saturated aqueous solution of ammonium sulfate (40 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic extracts were dried (MgSO_4), and the solvent was removed in vacuo to give a pale solid that was purified by column chromatography (dichloromethane/methanol) over silica gel, to afford (1R)-(−)-camphor oxime 62 as a white solid in a 35% (87.5 mg, 0.524 mmol) yield: mp 119-121 °C; δ_H (250 MHz; CDCl_3) 6.19(1H, br.s, OH), 2.56(1H, dt, J = 17.9 and 3.9, exo at C3), 2.06(1H, d, J = 17.9, endo at C3), 1.94-1.66(3H, m), 1.51-1.41(1H, m), 1.29-1.20(1H, m), 1.03(3H, s, Me), 0.92(3H, s, Me), 0.81(3H, s, Me); m/z 168(MH^+), 167(M^+), 152, 150, 138, 134, 124, 110, 108, 94, 93, 79, 69, 67, 55. This compound showed identical spectral properties to the same compound that was previously reported.114
Experimental Details

(1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one, (1R, 4S)-1,7,7-
Trimethylbicyclo[2.2.1]heptan-2-imine and (R)-(4-Methoxyphenyl)methyl
Sulfoxide, (1R)-Camphor 56, (1R)-Camphor imine 64 and (+)-(R)-(4-
Methoxyphenyl)methyl Sulfoxide 113 (reaction between (+)-camphoryl oxaziridine 65
and 1-methoxy-4-(methylthio)benzene)

![Chemical Structure](image)

To a stirring cooled (−78 °C) solution of 1-methoxy-4-(methylthio)benzene (294 mg,
1.91 mmol) and (+)-camphoryl oxaziridine 65 (320 mg, 1.92 mmol) in
dichloromethane (6 mL) was added pure trifluoromethanesulfonic acid (185 μL, 314
mg, 2.09 mmol). Initially the solution turned dark green, but approximately five
seconds later, turned back into a colourless clear solution. After 10 minutes the
reaction was complete (tlc) and the reaction mixture was added to an aqueous solution
of sodium hydroxide (40 mL, 1.0 M). This mixture was then extracted with
dichloromethane (2x40 mL), and the combined organic extracts were dried (MgSO₄)
and the solvent removed in vacuo to give a colourless oil which was purified by
column chromatography (methanol/dichloromethane) over silica gel to give the
starting material 1-methoxy-4-(methylthio)benzene in a 9% (26 mg, 0.169 mmol)
yield; mp 20-23 °C; δH (250 MHz; CDCl₃) 7.30-7.24(2H, m, Ar-H), 6.89-6.81(H, m,
Ar-H), 3.78(3H, s, MeO), 2.44(3H, s, MeS); this data is the same as that taken from
an original sample of 1-methoxy-4-(methylthio)benzene, and as that reported for this
compound;¹⁴⁴ (1R)-camphor 56 in 30% (87 mg, 0.0572 mmol) yield; mp 178-180 °C;
δH (250 MHz; CDCl₃) 2.34(1H, ddd, J = 18.3, 4.4 and 3.4, exo at C3), 2.08(1H, t, J =
4.4, CH at bridgehead C4), 1.99-1.88(1H, m), 1.83(1H, d, J = 18.3, endo at C3), 1.73-
1.59(1H, m), 1.45-1.24(2H, m), 0.95(3H, s, Me), 0.90(3H, s, Me), 0.82(3H, s, Me);
this compound showed identical spectral properties to the same compound which was
described previously¹³⁸; and a 485 mg of a mixture of (1R)-camphor imine 64 and (4-
methoxyphenyl)methyl sulfoxide 113 present in a 1:1.5 ratio, therefore giving
approximately 64% (185 mg 1.23 mmol) yield of camphor imine and a 96% (310 mg
Experimental Details

1.82 mmol yield of (4-methoxyphenyl)methylsulfoxide 113; \( \delta^1H \) (250 MHz; CDCl₃) 7.59-7.52(2H, m, Ar-H), 7.02-6.96(2H, m, Ar-H), 3.77(3H, s, MeOAr), 2.62(3H, s, \( \text{MeS(O)Ar} \)), 2.53-2.37(1H, m, \( \text{exo} \) at camphoryl C₃), 2.03-1.22(6H, m), 0.94(3H, s, Me), 0.93(3H, s, Me), 0.71(3H, s, Me); \( \nu_{\text{max}} \) (DCM)/cm⁻¹ 3447(NH), 1669(C=N). Although the product mixture was not inseparable by chromatography a chemical and more convenient method of purification was accomplished by the following procedure. The mixture \(((1R)\text{-camphor imine 64 and (4-methoxyphenyl)methyl sulfoxide 113})\) was dissolved in dichloromethane (5 mL) and residual deuteriochloroform from the NMR sample (1 mL). This solution was then stirred vigorously with aqueous hydrochloric acid (0.5 M, 25 mL) at room temperature for 2 hours. This reaction mixture was then extracted with dichloromethane (5x20 mL) and the combined organic extracts were dried (MgSO₄) and the solvent removed \( \text{in vacuo} \) to give a colourless oil which was purified by flash chromatography (methanol/dichloromethane) over silica gel to give \((+)-(R)-(4\text{-methoxyphenyl)methyl sulfoxide 113}\) in an 85% (277mg, 1.63mmol) yield; \([\alpha]^{25}_D = +2.96 \text{(CHCl₃)}\) ee = 14%, \( R \) (worked out using \(^1\text{H} \text{NMR and shift reagent); \( \delta^1H \) (250 MHz; CDCl₃) 7.59-7.52(2H, m, Ar-H), 7.02-6.96(2H, m, Ar-H), 3.77(3H, s, MeO), 2.62(3H, s, MeS); \( \delta^13C \) (63 MHz; CDCl₃) 43.8(Me, \( \text{MeS(O)Ar} \)), 55.4(Me, MeOAr), 114.8(CH, Ar), 125.4(CH, Ar), 126.6(C quat, Ar), 162.1(C quat, Ar); \( \nu_{\text{max}} \) (DCM)/cm⁻¹ 3067, 1595, 1304, 1256, 1091, 1027; \( m/z \) 171(M⁺), 170(M⁺), 155, 139, 127, 123, 92, 77, 63, 51. This compound was shown to have identical spectral properties to the same compound, which has been previously reported.\(^{145}\)
Appendices

APPENDIX 1: Terms Used in this Thesis

Alternative Names and Abbreviations for Compounds

<table>
<thead>
<tr>
<th>Alternative Name</th>
<th>Abbreviation</th>
</tr>
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<tbody>
<tr>
<td>Amberlyst 15*</td>
<td>Ion Exchange Resin</td>
</tr>
<tr>
<td>BocON 2-(Tert-butoxycarbonyloxyimino)-2-phenylacetonitrole</td>
<td>DABCO 1,4-Diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBAD Di-tert-butylazodicarboxylate</td>
<td>DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM Dichloromethane</td>
<td>DMAP 4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DEAD Diethylazodicarboxylate</td>
<td>DME Ethylene glycol dimethyl ether (1,2-Dimethoxyethane)</td>
</tr>
<tr>
<td>Diglyme 2-Methoxyethyl ether</td>
<td>DMF Dimethylformamide</td>
</tr>
<tr>
<td>DMAP 4-Dimethylaminopyridine</td>
<td>DMSO Dimethylsulfoxide</td>
</tr>
<tr>
<td>HMPT Hexamethylphosphorus triamide</td>
<td>DCM Dichloromethane</td>
</tr>
<tr>
<td>KHMDS Potassium hexamethyldisilazide</td>
<td>LDA Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS Lithium hexamethyldisilazide</td>
<td>LiHMDS Lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>m-CPBA 3-Chloroperoxybenzoic acid</td>
<td>NaHMDS Sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NaHMDS Sodium hexamethyldisilazide</td>
<td>NCS N-Chlorosuccinimide</td>
</tr>
<tr>
<td>Oxone Potassium peroxymonosulfate</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>RAMP (R)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>SAMP (S)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>TASF Tris(dimethylamino)sulfur (trimethylsilyl)difluoride</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>TBDMSCI tert-Butyldimethylsilyl chloride</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>Tf₂O Trifluoromethanesulfonic anhydride (Triflic anhydride)</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>THF Tetrahydrofuran</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>TMSCI Trimethylsilyl chloride</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>TMSOTf Trimethylsilyl trifluoromethanesulfonate (Trimethylsilyl triflate)</td>
<td>Oxone Potassium peroxymonosulfate</td>
</tr>
</tbody>
</table>
Appendices

TsCl 4-Toluenesulfonyl chloride (Tosyl chloride)
TsOH 4-Toluene sulfonic acid

Abbreviations used for the Description of Functional Groups

Ac- Acetyl-
Ar- Aryl-
Bn- Benzyl-
Boc- tert-Butyloxycarbonyl-
'Bu- iso-Butyl-
"Bu- n-Butyl-
'SBu- sec-Butyl-
'Bu tert-Butyl-
Bz- Benzoyl-
Cy- Cyclohexyl-
Et- Ethyl-
Fmoc- 9-Fluorenylmethyloxycarbonyl-
Me- Methyl-
Mes- 2,4,6-Trimethylphenyl- (Mesityl-)
Moc- Methoxy carbonyl-
Ms- Methanesulfonyl- (Mesyl-)
Ns- 4-Nitrophenylsulfonyl- (Nosyl-)
Ph- Phenyl-
'Pr- iso-Propyl-
"Pr- n-Propyl-
Ses- 2-Trimethylsilyl ethyl-
TBDMS- tert-Butyldimethylsilyl-
Tf- Trifluoromethanesulfonyl- (Triflic-)
TMS- Trimethylsilyl-
p-Tol- 4-Methylphenyl- (para-Tolyl-)
tris- 2,4,6-(Triisopropylphenyl)sulfonyl- (Trisyl-)
Ts- 4-Toluenesulfonyl- (Tosyl-)

205
Appendices

Z- Benzzyloxycarbonyl-

Other Terms Used

$^1$C NMR  Carbon-13 Nuclear Magnetic Resonance
$^1$H NMR  Proton Nuclear Magnetic Resonance
HPLC  High Performance Liquid Chromatography
tlc  Thin Layer Chromatography
de  Diastereoisomeric excess
dr  Diastereoisomeric ratio
ee  Enantiomeric excess
$X_{(aq)}$  Indicates that $X$ is present in aqueous solution
$hv$  Indicates photolysis
APPENDIX 2: References


Appendices

(24) Kasuga, K.; Hirobe, M.; Okamoto, T. Yakugaku Zasshi, 1974, 94, p945 (see ref. 18).
Appendices


Appendices


(57) For a review on this subject as well as an overall overview of other methods for generating aziridines see: (a) Atkinson, R. S. Tetrahedron, 1999, 55, p1519. (b) Osborn, H. M. I.; Sweeney, J. Tetrahedron Asym., 1997, 8, p1693.


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(74) See reference 72.


Appendices

(96) Schmitz, E.; Jahnisch, K. J. Geterozikl. Soedin., 1974, 12, p1629 (see ref. 87).
(103) For a review on the synthesis of α-amino acids see: Duthaler, R. O. Tetrahedron, 1994, 50, p1539.
(111) The presence of NH-oxaziridines has been determined quantitatively and qualitatively by iodimetry. See references 70 and 85 for further information about the oxidation of iodides to iodine to test the presence of NH-oxaziridines.
Appendices


Appendices


(136) Iminium salt 33 was donated by Dr G. Rassias, therefore, experimental details for the synthesis of 33 do not appear in this thesis.


(138) For the melting point of (1R)-(+) -camphor, see the catalogue for Aldrich Chemical Co. Ltd, and for the $^1$H NMR spectrum, see: Pouchert, C. J. The Aldrich Library of NMR Spectra, Edition II, vol. 2.

(139) The $^1$H NMR spectrum obtained for this compound was identical to a spectrum obtained from benzamide that had been obtained from Aldrich Chemical Co. Ltd. For a $^1$H NMR spectrum of this compound, see: Pouchert, C. J. The Aldrich Library of NMR Spectra, Edition II, vol. 2.
Appendices

*Spectra*, Edition II, vol. 2, for the melting point of this compound, see the catalogue for Aldrich Chemical Co. Ltd.


(141) The spectrum for this compound was the same as the spectrum obtained for an authentic sample of diethyl phenyl malonate that was purchased from Aldrich Chemical Co.


(144) See the catalogue for Aldrich Chemical Co. Ltd.

APPENDIX 3: Crystal Structures and NMR Data

All crystal structure analyses were performed by Dr. A. Slawin, and NMR experiments were carried out by Dr. T. Smith.
Oxaziridine - VT in d6-DMSO at 25C
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