New Systems for Asymmetric Electrophilic Heteroatom Transfer

by

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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 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]
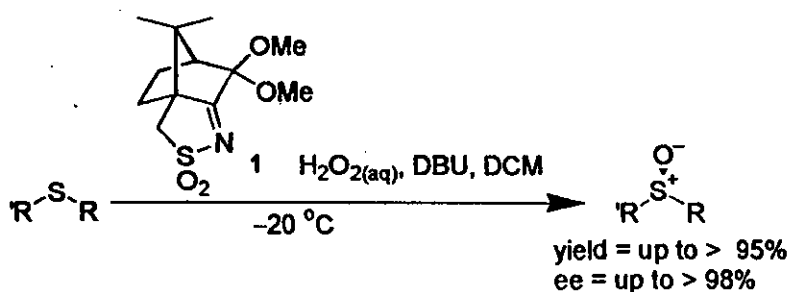
Scheme 1

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.
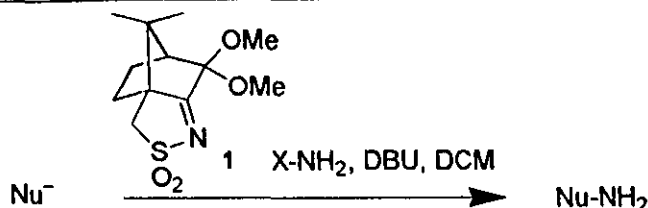
Scheme 2

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.[2] 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,[3] 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).[4]

$$RMgX \xrightarrow[\text{$-15\,^{\circ}C$ to $-10\,^{\circ}C$}]{\text{MeONH$_2$ \textbf{2}, Et$_2$O,}} RNH_2$$

40-90%

X=Cl, Br
R=C_2-C_5 alkyls, Allyl, Bz, cyclo(CH$_2$)$_n$, (n= 5, 6, 10)
Ph, 4-BrC$_6$H$_4$, 2,4,6-(CH$_3$)$_3$C$_6$H$_2$, ^{t}Bu, ^{t}Pentyl, α-naphthyl
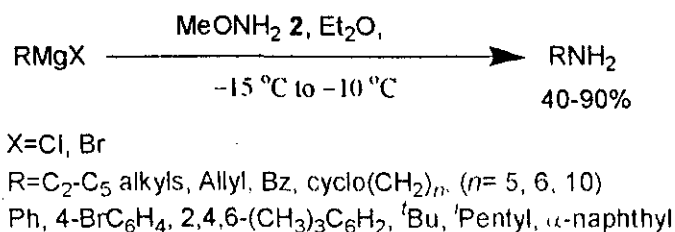
Scheme 3

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 [5]

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,[6] 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 lithiums by the sequential deprotonation of **2** with methyllithium followed by the addition of the intended organolithium nucleophile (Scheme 4).[7]

$$\text{RLi} \xrightarrow[\text{2. "H}^+\text{"}]{\text{1. MeLi-MeONH}_2, \text{ Et}_2\text{O}, -15\,^{\circ}\text{C}} \text{RNH}_2$$

67-97%

R = C_1-C_5 alkyls, Ph, 4-BrC$_6$H$_4$, Bn, 2-CH$_3$C$_6$H$_4$
RLi/MeLi-MeONH$_2$ molar ratio = 1/2

$$\text{RLi} \xrightarrow[\text{2. "H}^+\text{"}]{\text{1. MeLi-MeONHMe, Et}_2\text{O}, -15\,^{\circ}\text{C}} \text{RNHMe}$$

30-67%

R = ^{n}Bu, ^{s}Bu, ^{t}Bu, Ph
RLi/MeLi-MeONHMe molar ratio = 1/1
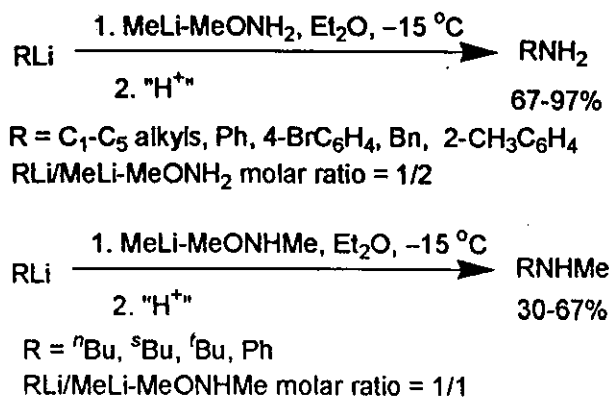
Scheme 4

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-fluorenecarboxylate enolates (Scheme 5).[8]
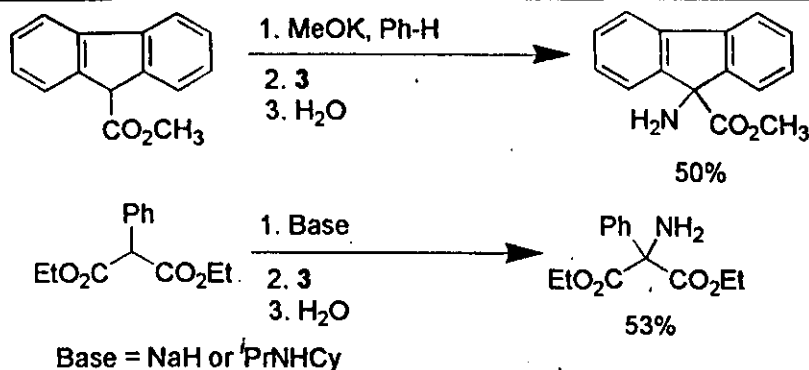
Scheme 5

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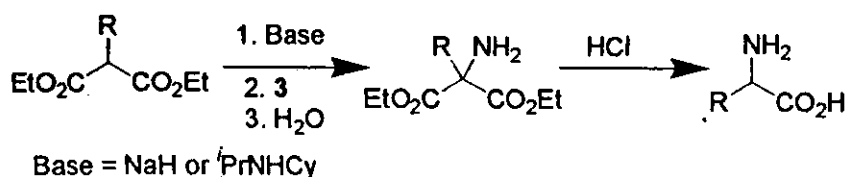
Scheme 6

R	Me	Et	"Bu	Bn	CH_2CO_2Et
Yield Decarboxylated Product (%)	84	74	46-57	73	61

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).
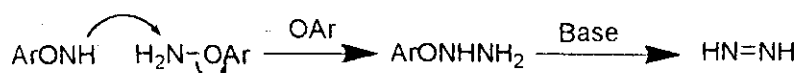
Scheme 7

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

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.[10] 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.[11]

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.[12] 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[13] and some Grignard reagents[14] (Scheme 8).

RMgCl $\xrightarrow[\text{2. "H}^{+}\text{"}]{\text{1.H}_2\text{NCl 4, Et}_2\text{O, 0 °C}}$ RNH$_2$ + NH$_3$

57-85% 4-41%

R = C$_2$-C$_5$ alkyls, PhCH$_2$CH$_2$, Bn

R=H, Me, Et, ^{i}Pr, ^{s}Bu, Ph, Bn

1. NaH, PhH
2. 4, Et$_2$O
3. morpholine

70-92%
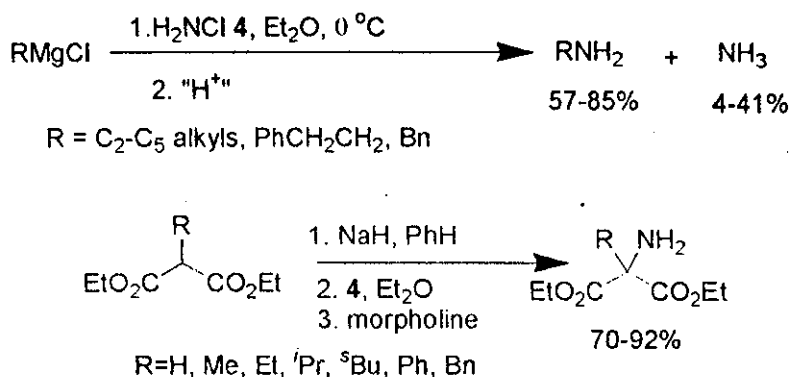
Scheme 8

The reaction of **4** and other *N*-haloamines with simple organozinc, lithium, Grignard 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.[15] For di- and tri- *N*-haloamines, wide product distributions between non-, mono-, di- and tri-alkylated amines are also a problem.[16] In addition there is formation of chlorinated side products.[17] 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.

$$RMgX + H_2NCl \begin{cases} RNH_2 + MgXCl \\ RCl + H_2NMgX \xrightarrow{H_2O} NH_3 \end{cases}$$
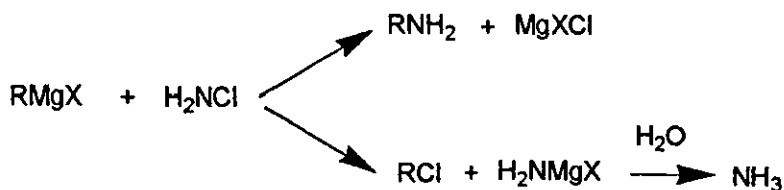
Scheme 9

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 hydrazine[19] or tetrazine[20] derivatives, and tertiary amine derivatives to form 1,1,1-trisubstituted hydrazinium salts[19, 21] (Scheme 10).

$$(^{n}Bu)_2NH \xrightarrow{\textbf{5, KOH, H}_2\textbf{O, 75 °C}} (^{n}Bu)_2NNH_2$$

34%

$$(Me)_3N \xrightarrow[\textbf{2. HI}]{\textbf{1. 5, KOH, H}_2\textbf{O, Reflux}} (Me)_3{}^{+}N-NH_2 \quad I^{-}$$

85%

5, NaOH, H₂O, 60-70 °C

18%
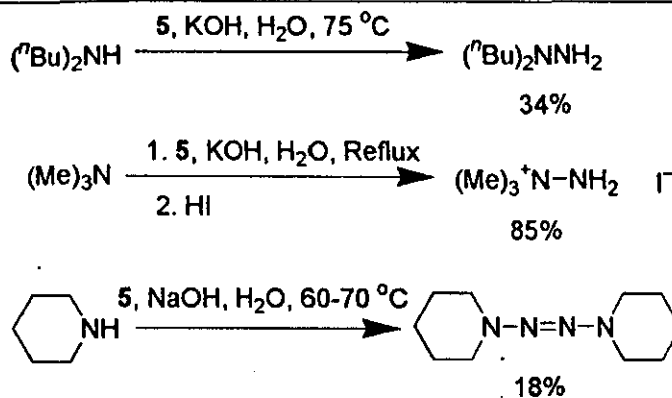
Scheme 10

A range of carbon nucleophiles have also been aminated successfully with **5**, and these include lithium enolates[5a], aromatic C-H compounds,[22] boranes[23] and heterocyclic compounds[24] (Scheme 11).

1.LDA, HMPT, THF-Hexane

2. 5, –15 °C

83%

5, AlCl₃, 95-105 °C

21%

1. NaBH₄, BF₃-Et₂O
diglyme, room temp

2. 5, 100 °C

58%

5, H₂O, 60-65 °C

R = Me, H

50-86%
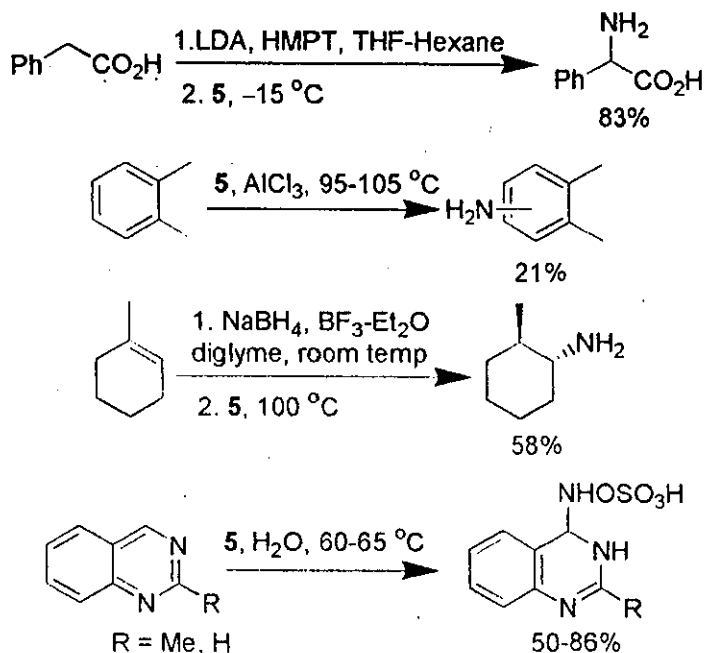
Scheme 11

Other heteroatoms that have been aminated with **5** include numerous types of sulfur nucleophile to give hydrosulfamines[25] and sulfimine[26] products, and triphenylphosphine to give triphenylphosphinium sulfate[27] (Scheme 12).
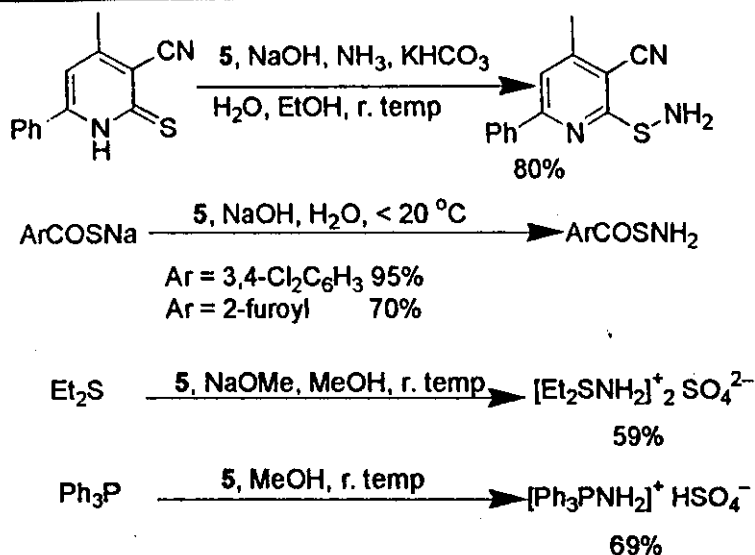
Scheme 12

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).
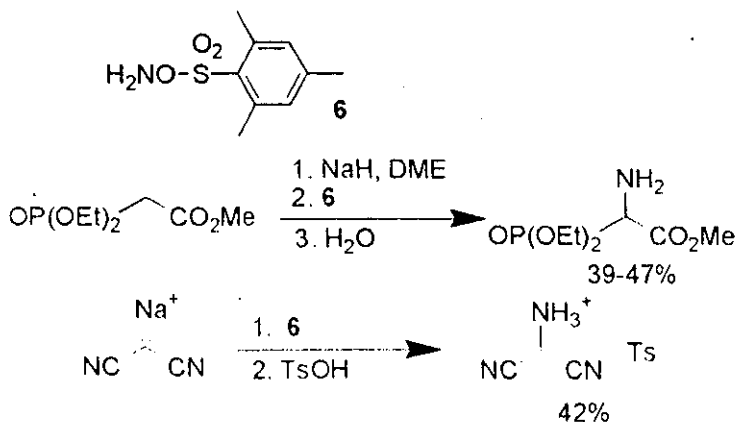
Scheme 13

N,N-Dialkyl *O*-sulfonyl hydroxylamine derivatives have been used for the amination of less stabilised nucleophiles such as organocuprates,[30] Grignard reagents[31] and organolithium reagents[32] (Scheme 14).

$$RLi \xrightarrow[\text{2. } H_2O]{\text{1. 7, THF}} RN(Me)_2 \quad 31\text{-}69\%$$

R = Me, ^{n}Bu, (Z)-MeCH=CH, PhCH=CR^{1}Bn
R^1 = H, Ph, ^{t}Bu,
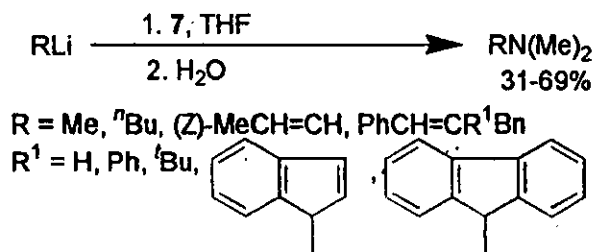
Scheme 14

As well as carbon nucleophiles, compounds such as **6** have been used for amination of sulfur nucleophiles such as sulfides and sulfoxides.[10] This methodology has been used in an attempt at asymmetric induction using a chiral *O*-sulfonyl hydroxylamine (+)-*O*-(α-bromocamphor-π-sulfonyl)-hydroxylamine **8** (Scheme 15).[33]

yield = 100%
ee = 4%
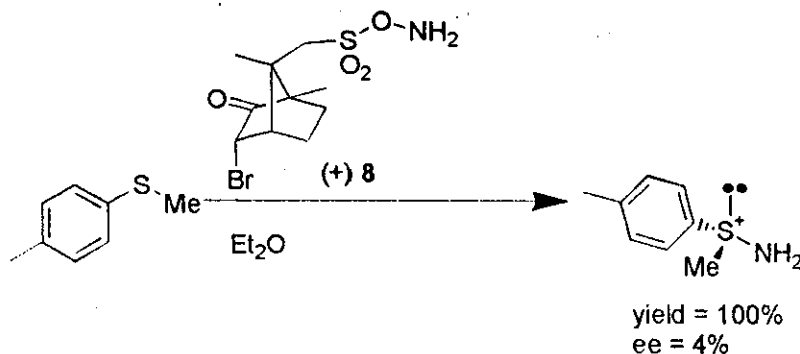
Scheme 15

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

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.[34] 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.
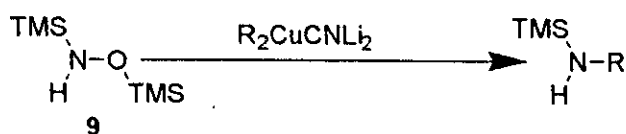
Scheme 16

Cuprate	Product	Yield (%)
$Ph_2CuCNLi_2$	$PhNH_2$	90
$(4\text{-}MeOC_6H_4)_2CuCNLi_2$	$4\text{-}MeOC_6H_4NH_2$	70
		70
		58

Secondly, metallated N-arylsulfonyloxycarbamates **10**, **11** and **12** (Figure 1) have been shown to be useful aminating reagents.[35]

$$R^{O}\underset{O}{\overset{M}{\underset{\|}{\bigvee}}}N\underset{O_2}{\overset{}{\underset{S}{-}}}Ar$$

10 R = ^{t}Bu, Ar = *p*-Tol
11 R = allyl, Ar = *p*-Tol
12 R = allyl, Ar = 2,4,6-(Me)$_3$C$_6$H$_2$ (Mes)
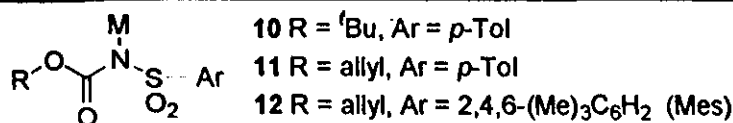
Figure 1

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]

10(+H$^+$), K$_2$CO$_3$, room temp or
10(+H$^+$), 2 equiv RNH$_2$, 80 °C
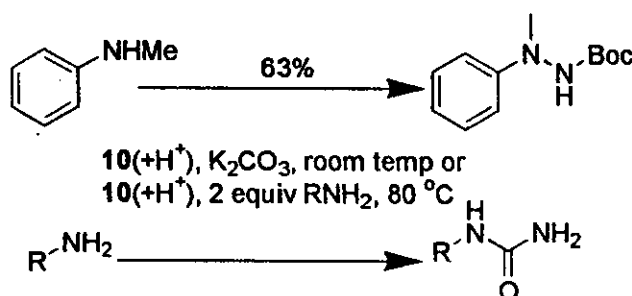
Scheme 17

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]

$$RM \xrightarrow[\text{2. Hydrolysis}]{\text{1. 10}} R-N\overset{H}{\underset{Boc}{\big|}}$$
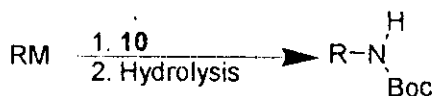
Scheme 18

RM	Metal (on 10)	Yield (%)
^{n}BuLi	Li	71
^{t}BuLi	Li	42
^{t}Bu$_2$CuLi	Li	32
	MgCl	57
$\left(\text{}\right)_2$CuMgCl	Li	66
	MgCl	72

$$\text{ArCu} \xrightarrow[\text{2. Hydrolysis}]{\text{1. 10, 11 or 12}} \text{Ar—N}\overset{\text{H}}{\underset{\text{CO}_2\text{R}}{}}$$
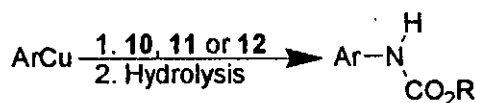
Scheme 19

Ar	Electrophile	Yield (%)
Ph	10, 11, 12	51
2-anisyl	10	73
4-anisyl	11	68
2-pyridyl	10	53
2-thienyl	10	52
1-naphthyl	11	57

Other carbon nucleophiles that have been successfully aminated with these reagents include α-cuprophosphates[35] and boranes[37] (Scheme 20).

$$\text{Me}\diagdown\overset{\overset{\text{O}}{\|}}{\text{P(OEt)}_2} \xrightarrow[\text{2. hydrolysis}]{\text{1. }N\text{-Lithio 10}} \text{Me}\diagup\underset{\text{NHBoc}}{\overset{\overset{\text{O}}{\|}}{\text{P(OEt)}_2}}$$

80%

$$^n\text{Bu}_3\text{B} \xrightarrow[\text{2. hydrolysis}]{\text{1. }N\text{-Lithio 10}} {}^n\text{BuNHBoc}$$

81%
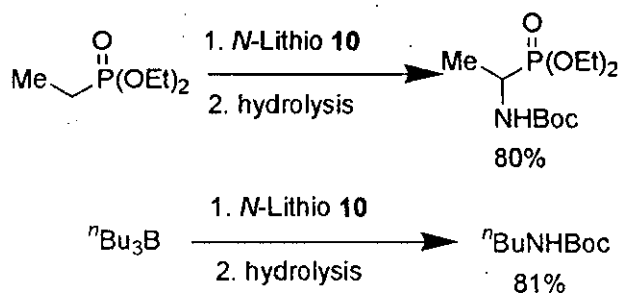
Scheme 20
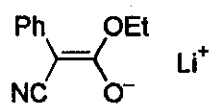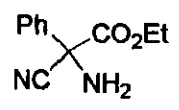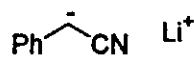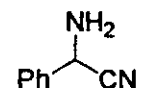
1.2.6 *O*-Phosphinoyl Hydroxylamines and Related Compounds

Another hydroxylamine derivative, which has been used for electrophilic amination, is *O*-(diphenylphosphinoyl)hydroxylamine **13**.[38] 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).

$$\text{R-M} \xrightarrow[\text{-20 °C to r. temp}]{\text{Ph}_2\text{P(O)ONH}_2 \text{ 13, THF,}} \text{RNH}_2$$
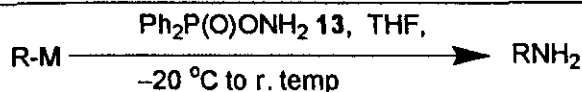
Scheme 21

Nucleophile	Product	Yield (%)
PhMgBr	PhNH$_2$	22
[Ph(CH$_2$)$_2$]$_3$B	Ph(CH$_2$)$_2$NH$_2$	36
(Ph, OEt, NC, O⁻) Li⁺	(Ph, CO$_2$Et, NC, NH$_2$)	>96
PhCH$_2$Li	PhCH$_2$NH$_2$	30
Ph⁻CN Li⁺	(NH$_2$) Ph⁻CN	37

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 (–)-(2*R*,4*S*,5*R*)-2-*O*-(*N,N*-dimethylhydroxylamino)3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidinone **14** as the product (Scheme 22).[39]
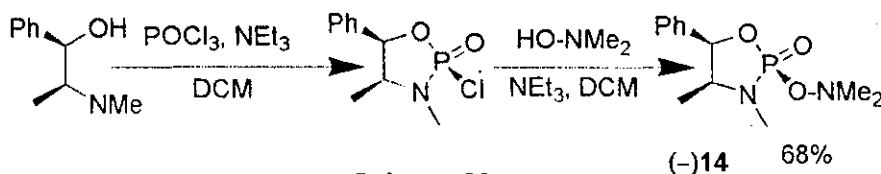
Scheme 22

(–) **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).

$$R^1 \underset{Ph}{\overset{R^2}{\diagdown\!\!\diagup}} M \quad \xrightarrow[\text{$-75\,^{\circ}$C to $-10\,^{\circ}$C}]{\text{$(-)$ 14, THF}} \quad R^1 \underset{Ph}{\overset{R^2}{\diagdown\!\!\diagup}} NH_2$$

Yield = 26.5-63%
ee = 8-44%
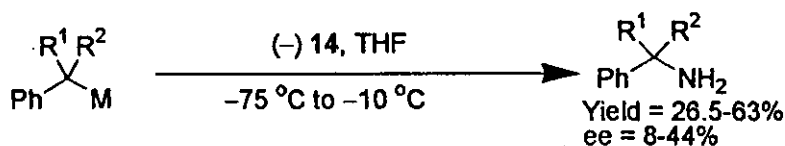
Scheme 23

R-M	Product	Temp (°C)	Yield (%)	ee (%)
Ph⤳MgBr	Ph⤳NH$_2$	-15	63	30
[Ph⤳B]$_3$	Ph⤳NH$_2$	-10	26.5	11
Ph⤳CO$_2$Et Li$^+$	Ph⤳NH$_2$ CO$_2$Et	-15	56	21

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.*[40] A number of acyl substituents were used with good to excellent yields, and good to excellent diastereoselectivities (Scheme 24).
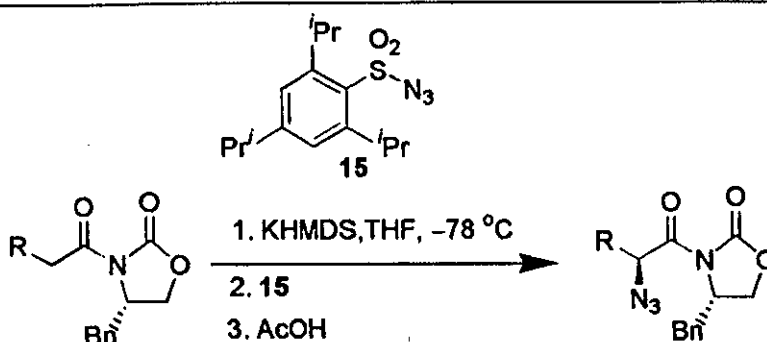
Scheme 24

Imide , R	Kinetic Ratio (2S:2R)[a]	Product Yield[b] (%)
Me	97:3	74
-CH$_2$CH=CH$_2$	97:3	78
-CH$_2$Ph	97:3	91
-Ph	91:9[c]	82
-CHMe$_2$	98:2	77
-CMe$_3$	>99:1	90

(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.[40] 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 phoshorinane[41] and chiral α-alkylphosphonamide[42]-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).

are 1,2-bis-Boc-protected hydrazines that can be deprotected selectively by standard well-known procedures.[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**.[45] All of these studies report good to excellent yields and good to excellent diastereoselectivities (Scheme 27).
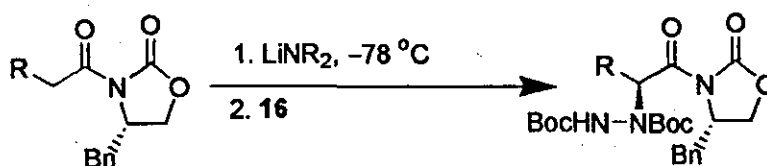
Scheme 27

Imide, R	Product Yield (%)[a]	dr (2*S*:2*R*)
Me	92[b]	98:2
Allyl	94	98:2
Bn	91	97:3
Ph	96	97:3
*i*Pr	95	98:2
*t*Bu	96	>99:1

(a) Values refer to isolated yields of isomerically pure compound (2*S*:2*R* > 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).[46]

yield = 48%
de = >98%
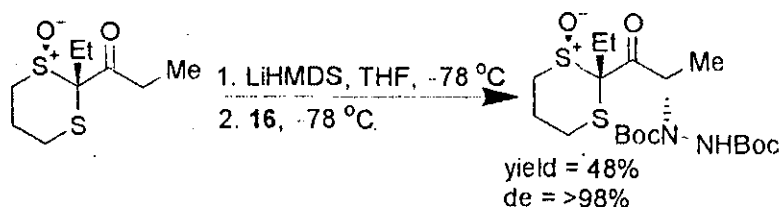
Scheme 28

N,N-Dimethyl hydrazones are further type of ketone derivative that have been aminated with **16** in good yields (Scheme 29).[43]

Scheme 29
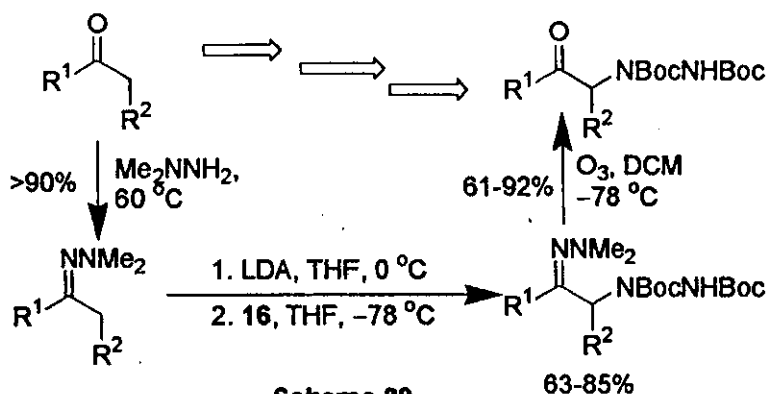
R[1]	R[2]	Yield Hydrazone (%)	Yield Ketone (%)
Et	Me	85	92
[n]Pr	Et	74	85
-(CH$_2$)$_4$-		78	78
Ph	Me	66	65
Bn	Ph	63	61

α-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 α-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 α-amino ketones[48] and

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 (NsONHCO₂Et) **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]

yield = 18%
ee = 77%

yield = 77%
de = 70%
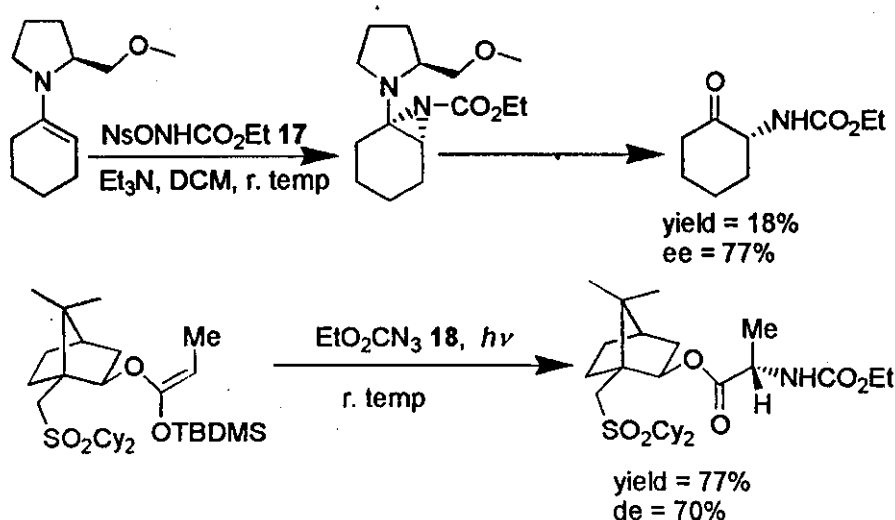
Scheme 30

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 α,β-unsaturated ketones.[52] Photolysis of ethyl azidoformate **18**, the reaction of NsONHCO₂Et **17** and the reaction of ethyl *N*-[(4-methylbenzenesulfonyl)oxy]carbamate (TsONHCO₂Et) **19** were compared for a number of different substrates and reagents **17**, **18** and **19** were shown to give similar results (Scheme 31).
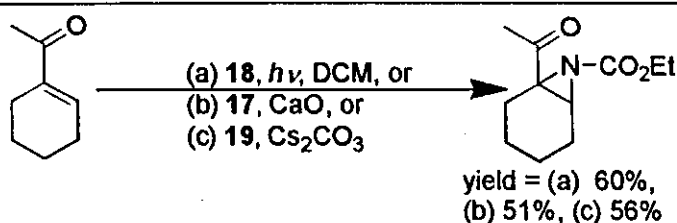
Scheme 31

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).

X = *N,N* disubst amide, alkyl or aryl
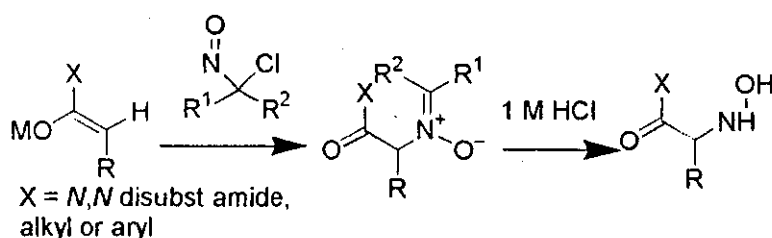
Scheme 32

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).[53]
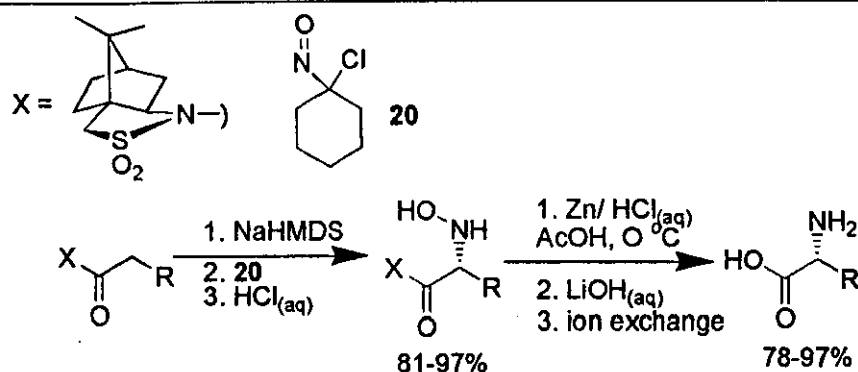
Scheme 33

R	Yield Hydroxylamine (%)	Yield Amino Acid (%)
Me	87	83
Me	88[a]	78[a]
Allyl	88	78
^{i}Pr	82	85
^{t}Bu	97	97
Bn	91	93
Ph	88	95
p-MeOPh		84 (overall)
p-MeOPh	81[a]	90[a]

(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 *N*-acyl camphorsultam were without exception, all found to be 100% within the bounds of accuracy of ^{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

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-hydroxylamino ketones have also been prepared using α-choronitroso compounds derived from camphor sulfonamides.[54] Reagents **21** and **22** were prepared by oximination of the respective camphorsulfonamide followed by α-chlorination with *tert*-butyl hypochlorite in 70-78% yields (Scheme 34).
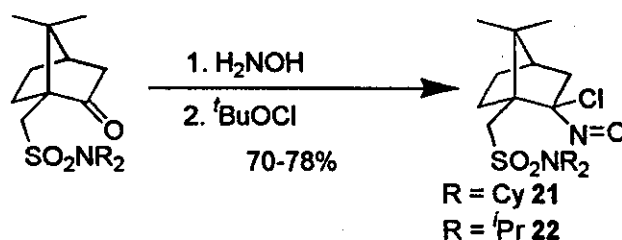
Scheme 34

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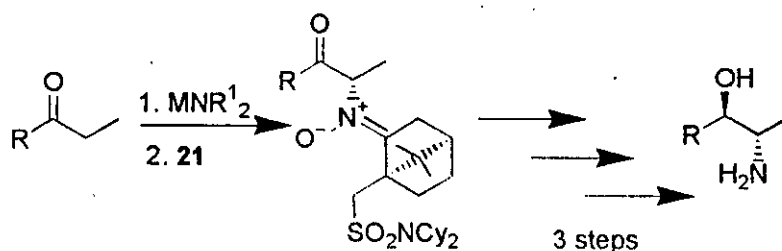
Scheme 35

R	M	dr (nitrone)	Yield (%) (aminol)[a]	Ratio (aminol) *Anti:Syn*	ee (%)[b] (aminol)
Ph	Zn	<1:99	68	95:5	96
2,5-(MeO)$_2$C$_6$H$_3$	Na	<1:99	57	90:10	(>99)
^{t}Bu	Zn	5:95	54	>99.9:<0.1	>99.9
^{i}Pr	Zn	5:95	65	98:2	(>99.9)
Et	Zn	5:95	65	90:10	98.2

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

This methodology forms a useful approach for the synthesis of chiral *anti* α-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 recrystalisation 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 α-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).
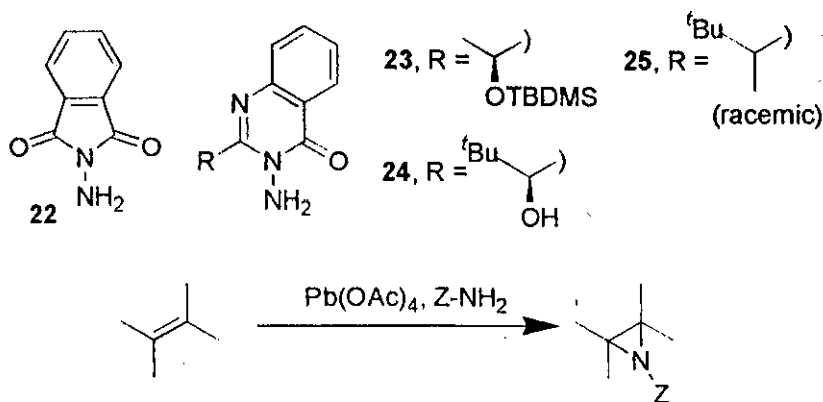
Scheme 36

These reagents have been shown to aziridinate both electron-deficient and electron-rich alkenes in good yields.[57] Substrate-[58] and reagent-[59] controlled diastereoselective reactions with double bonds have been carried out. For example, the reaction of α,β-unsaturated camphorsultam derivative **26** with **22** in the presence of lead tetra-acetate gives the product **27** in over 95% de (Scheme 37).[58a]
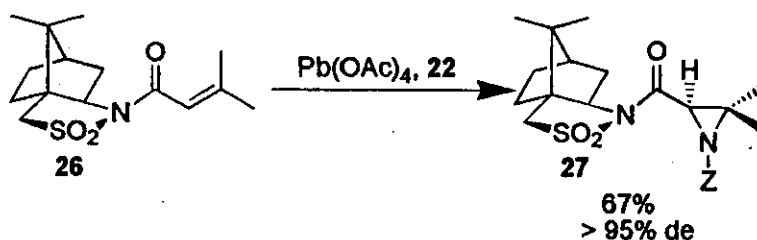
Scheme 37

Originally it was though that the reactive species for this transformation was an *N*-nitrenoid heterocycle,[57a] 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).[57a] This reactive species aziridinates carbon-carbon double bonds in a way that has been likened to the per-acid epoxidation of alkenes (Scheme 38).[57a] 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.
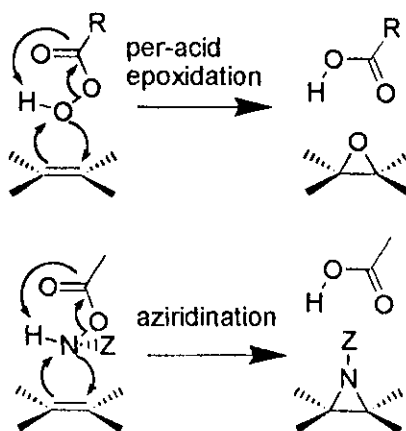
Scheme 38

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 co-ordinate to the aziridinating agent during the transition-state of the reaction.[57a] To this end there have been a number of modifications to the reaction system, and various diastereotopic ZNH_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.[60] Much of the emphasis of research into this system has focused upon the development of diastereoselective reactions. Lactic acid-derived quinazoline **23** (Q^1NH_2) has been shown to be useful as a stereoselective aziridinating reagent for various styrene derivatives (Scheme 39).
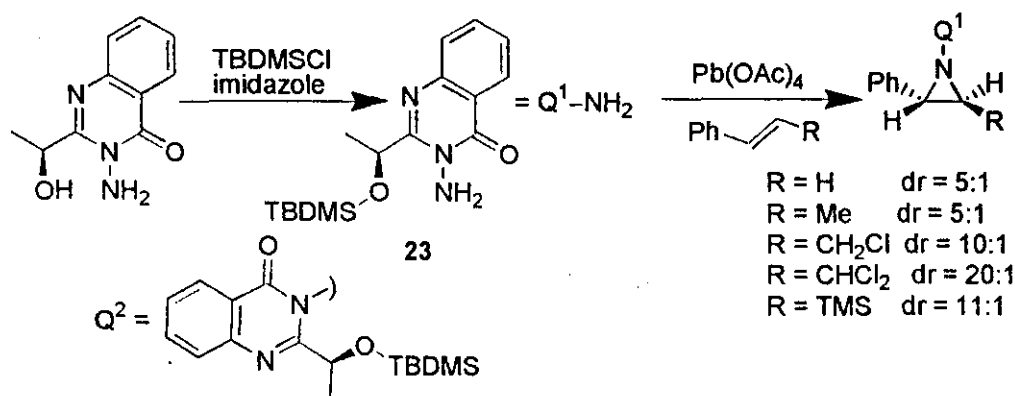
Scheme 39

The use of titanium (IV) *tert*-butoxide for the aziridination of alkenes with quinazoline derivative **24** (Q^2NH_2) was shown to greatly enhance the diastereoselectivity of the reaction.[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).
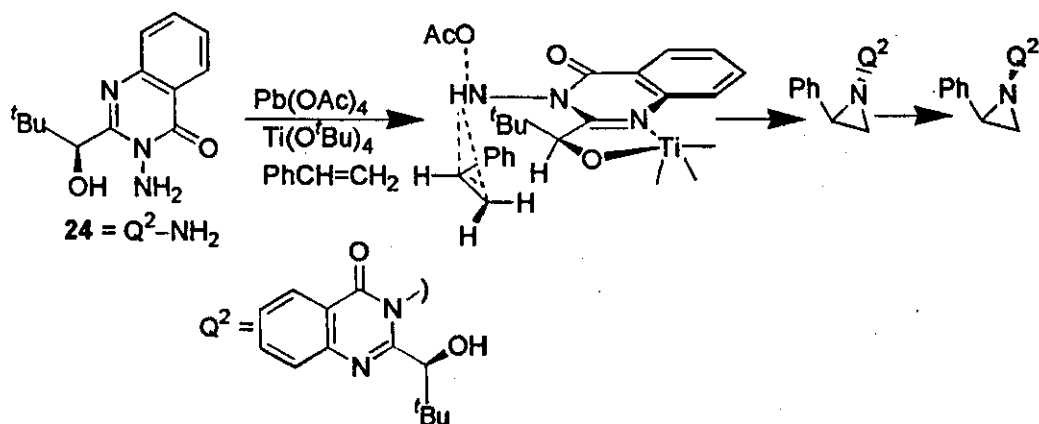
Scheme 40

A number of different types of alkene were aziridinated with this system, all with good diastereoselectivities (Scheme 41).
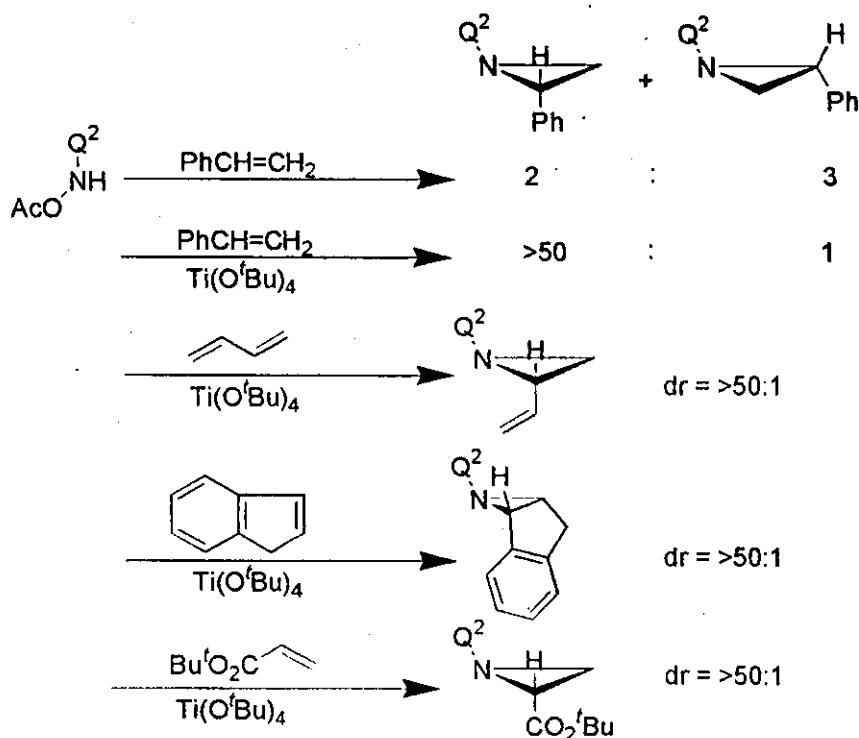
Scheme 41

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

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^3NH_2) (Scheme 42).[57a]
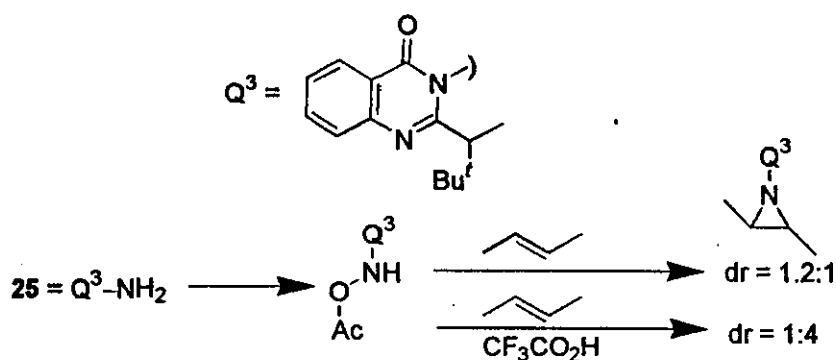
Scheme 42

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).
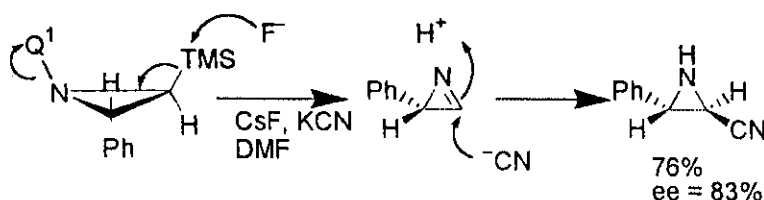
Scheme 43

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

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.[63] *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.[57a] An example of this is the use of styrene aziridinated with **24** to give both enantiomers of a chiral *N*-Boc 1,2-diamine (+) and (−) **28** (Scheme 44).[57a]
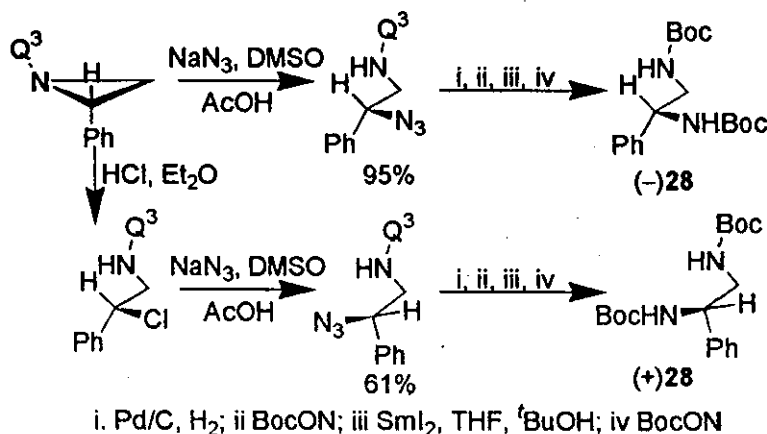

i. Pd/C, H₂; ii BocON; iii SmI₂, THF, ᵗBuOH; iv BocON

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

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*-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).
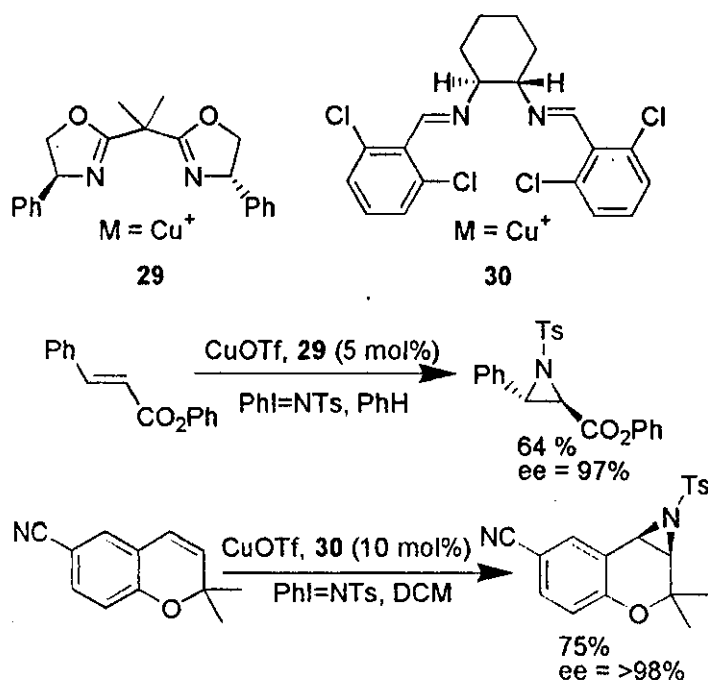
Scheme 45

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

moderate.[65] 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).[66]

31
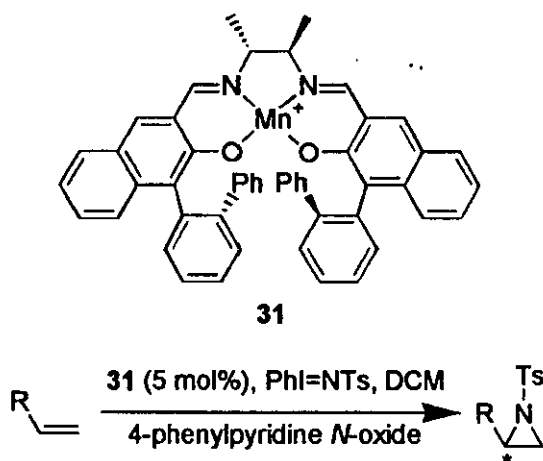
Scheme 46

Substrate	Yield (%)	ee (%)	Configuration
Styrene	76	94	*S*
p-chlorostyrene	70	86	*S*
p-methylstyrene	75	81	*S*
Indene	10	50	*S*

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=NSO$_2$Ar, have been prepared and evaluated for non-enantioselective copper catalysed aziridination of olefins.[67] 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).
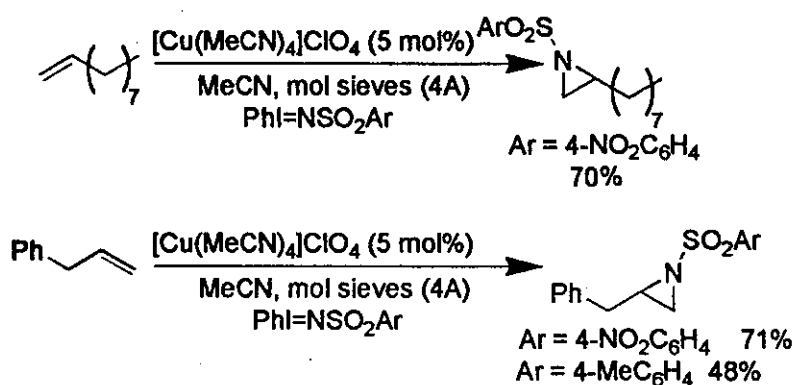
Scheme 47

Another benefit of using this system is that *p*-nitrobenzenesulfonamides are readily cleaved using thiols.[68] Furthermore, only one equivalent of the olefin was used in the reaction together with 1.5 equivalents of nitrene precursor.

Very recently, [*N*-((trimethylsilyl)ethanesulfonyl)imino]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.[69] 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).

Ph⟋⟍ →(10 mol% CuOTf, MeCN / mol sieves / PhI=NSes (1.2 eq.)) → Ph⟋△N–Ses →(F⁻, DMF, r. temp) → Ph⟋△NH

(1 eq.) 68% 62%

$F^- = TASF = (Me_2N)_3S(Me_3SiF_2)$
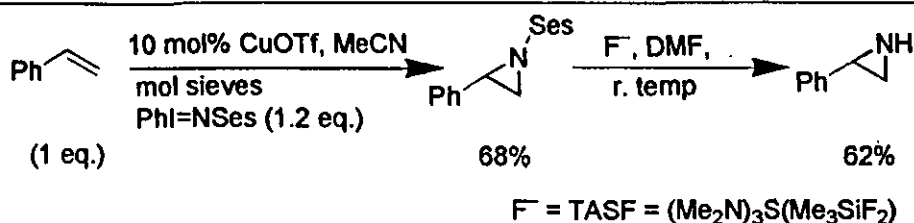
Scheme 48

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,[70] 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.[71] 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.
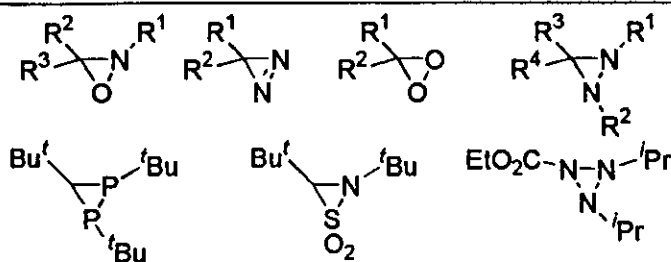
Figure 2

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° 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.[72] . 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.[73]

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.[72]

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.[75] 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.[76] 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).[1c, 77]
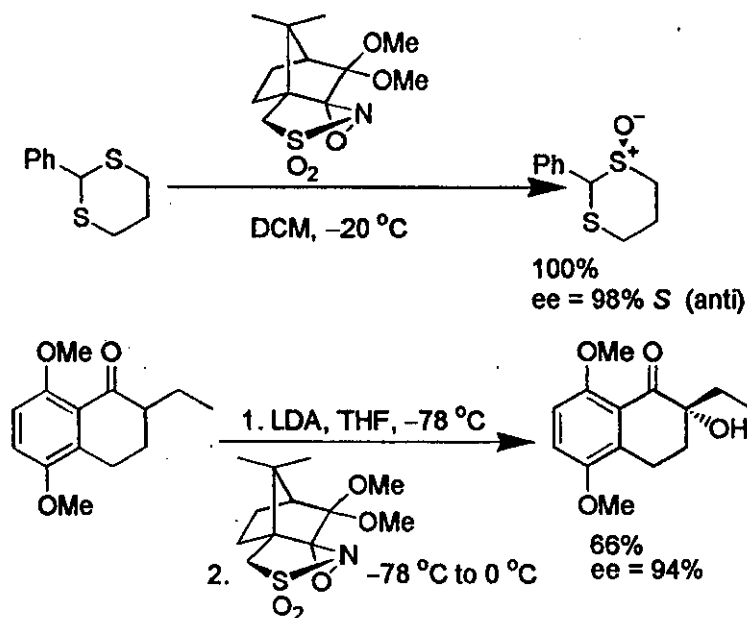
Scheme 49

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 oxone[®] have been shown to epoxidise certain alkenes in excellent yields and enantiomeric excesses (Scheme 50).[80]
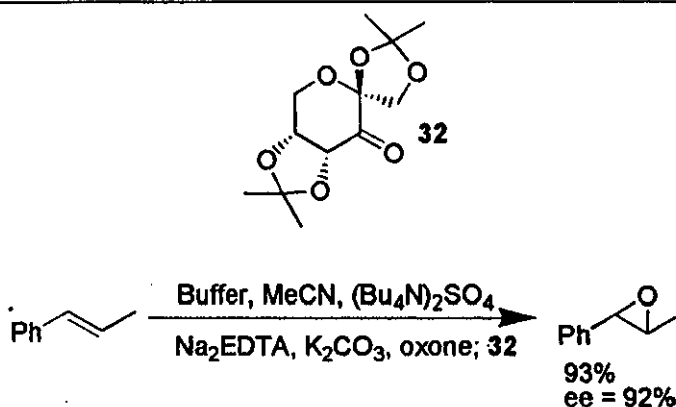
Scheme 50

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 alkene[81]. Although attempts have been made to achieve asymmetric induction using chiral iminium salts,[81,82] 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).[81, 82b]
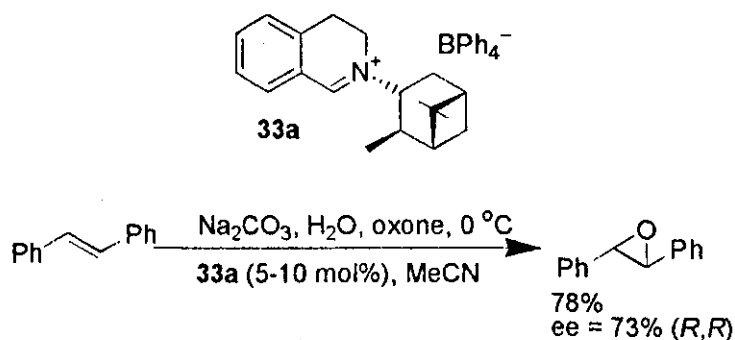
Scheme 51

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[83] and sulfoxidation[84] 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.[71] 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).[85]
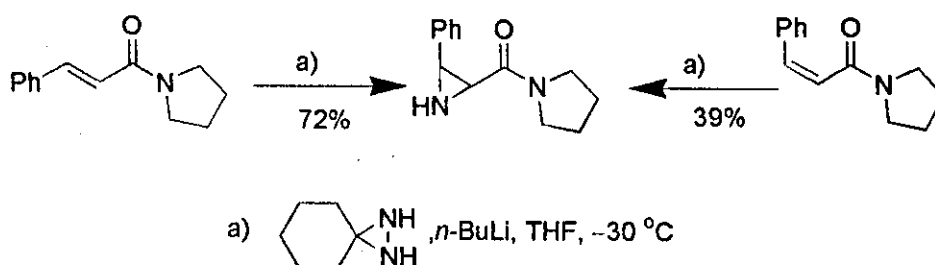
Scheme 52

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).[85]
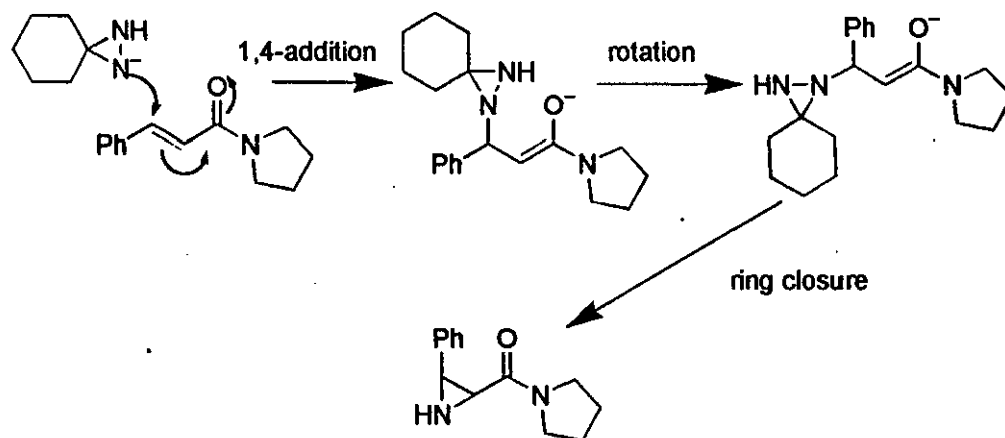
Scheme 53

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]

65-75%
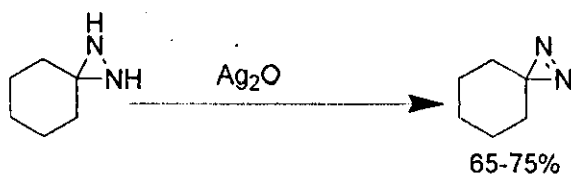
Scheme 54

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

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-alkyldiaziridines in good yields, and this reaction has been used to serve access to hydrazines (Scheme 55).[86]
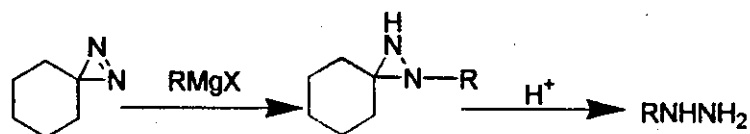
Scheme 55

R	Yield (%)
Cy	86[a]
*n*Pr	88[b]
*i*Pr	95[b]
Bn	85[b]

(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.

(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,[76, 77] and *N*-phosphinoyl oxaziridines are also known to transfer oxygen,[78] the lesser-known *N*-unfunctionalised and *N*-acyl or alkoxycarbonyl oxaziridines are known to transfer an amino or a masked amino functionality to a range of nucleophiles.[87]

N-Unfunctionalised oxaziridines have been shown to aminate nitrogen, oxygen, sulfur and carbon nucleophiles,[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.[87] It is because of this that only one (33b) has ever been isolated as a stable compound in its pure form,[88] and only one (34) has been investigated for functional group transformation on a preparative scale and in any depth,[87] and these compounds are illustrated in Figure 3.

33b   **34**
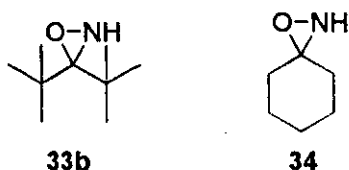
Figure 3

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,[89] or chloramine 4 (prepared *in situ* by the reaction of ammonia with sodium hypochlorite)[90] (Scheme 56).
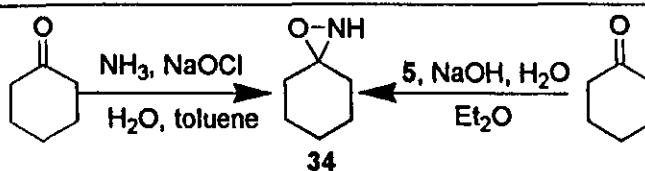
Scheme 56

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.[87] Photolysis of oximes in dilute solution has been reported as another method of preparation of *N*-unfunctionalised oxaziridines.[91] 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).
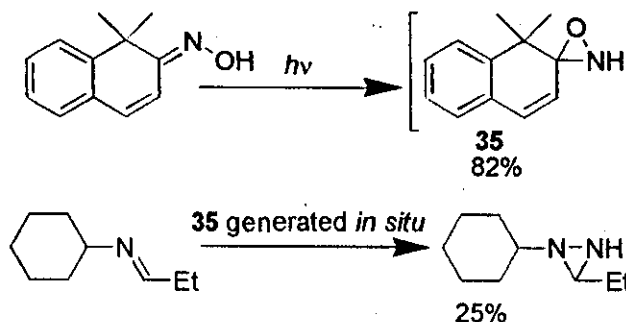
Scheme 57

Other less common methods of synthesis of *NH*-oxaziridines include per-acid oxidation of *NH* imines[88] and ozonolysis of an alkene in the presence of ammonia[92] (Scheme 58).

Scheme 58
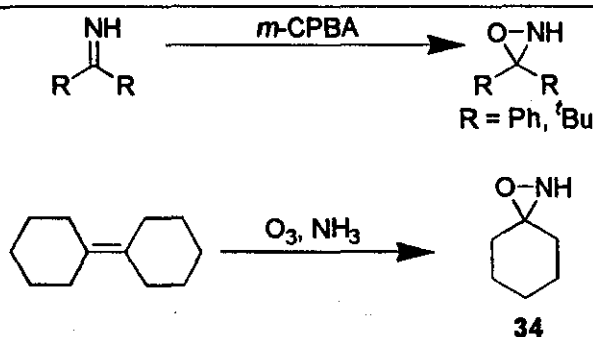
Once prepared, dilute solutions of *NH*-oxaziridines undergo a wide range of chemical reactions with a variety of nucleophiles.

A range of amino compounds have been aminated using oxaziridines to form hydrazino derivatives.[87] Secondary amines **36** 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).[87]

Scheme 59
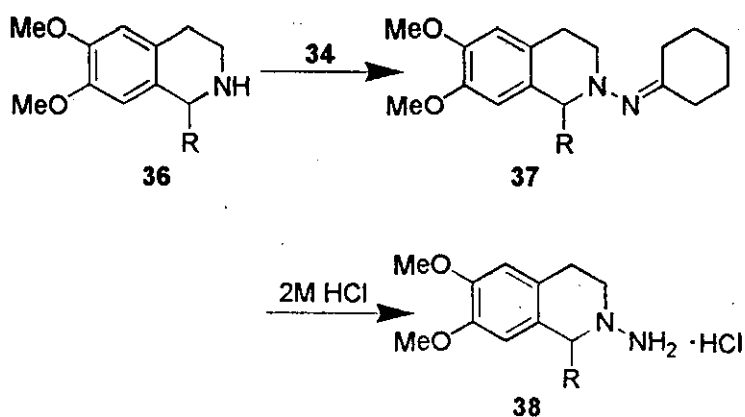
Substituent R	Yield 37 (%)	Yield 38 (%)
H	>80	78
Me	>80	71
CH₂CO₂Et	98	–
3,4(MeO)₂C₆H₃CH₂	59	–

Primary amines tend to give lower yields of hydrazones than secondary amines. Aniline only gives 22% of phenylhydrazine and cyclohexylamine gives 50% cyclohexylhydrazine.[93] 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]
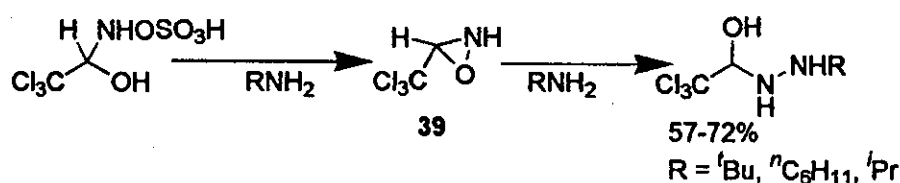
Scheme 60

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]
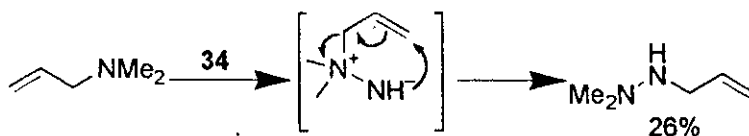
Scheme 61

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]
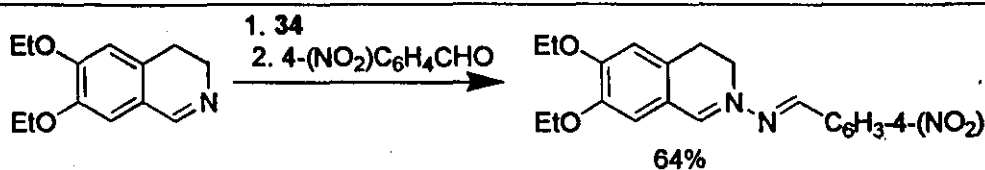
Scheme 62

A number of bivalent sulfur nucleophiles have also been aminated with *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.
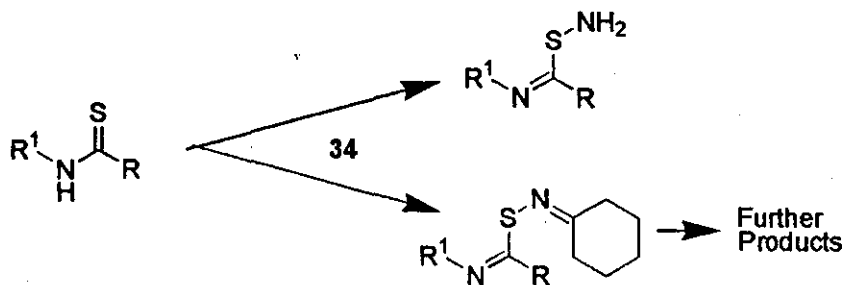
Scheme 63

For example, benzopyrimidine derivatives gave the free sulfenamide in 66% to 97% yields,[87] whereas mercaptobenzazoles gave thiooximes[87] (Scheme 64).

66-97%
R = Bu, Ph, Allyl, 2,6Me$_2$C$_6$H$_3$

68-78%
X = Se, S, NH
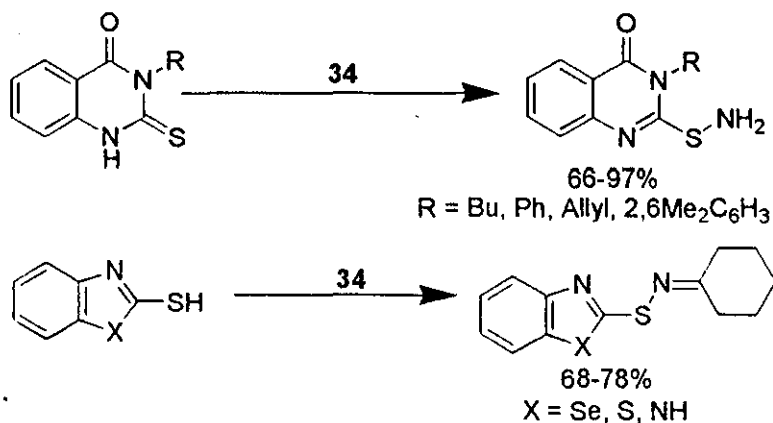
Scheme 64

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]

R = Ph, R^1 = H, 75%   R = Ph, R^1 = Ph, 44%
R = OEt, R^1 = Ph, 68%;   R = Ph, R^1 = 2-MeOC$_6$H$_4$, 42%
R = OEt, R^1 = 2-MeOC$_6$H$_4$, 63%
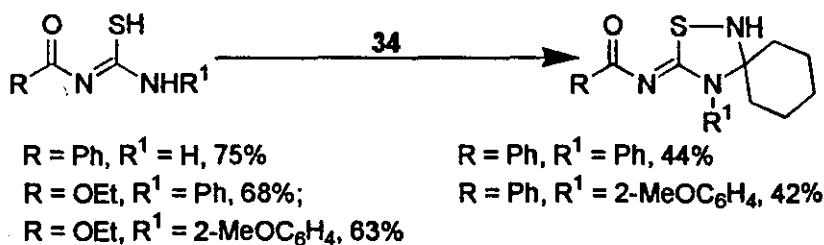
Scheme 65

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]
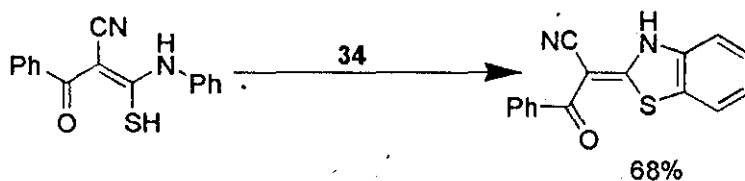
Scheme 66

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]
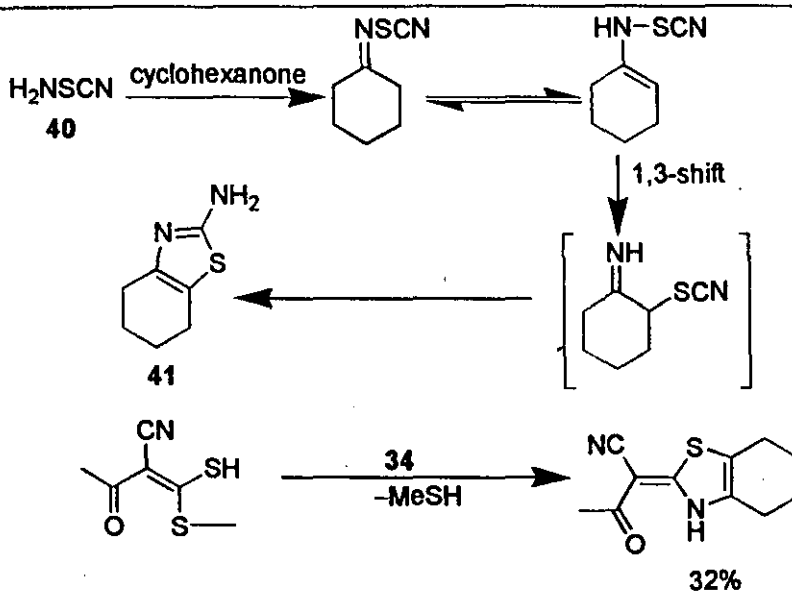
Scheme 67

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).[87]
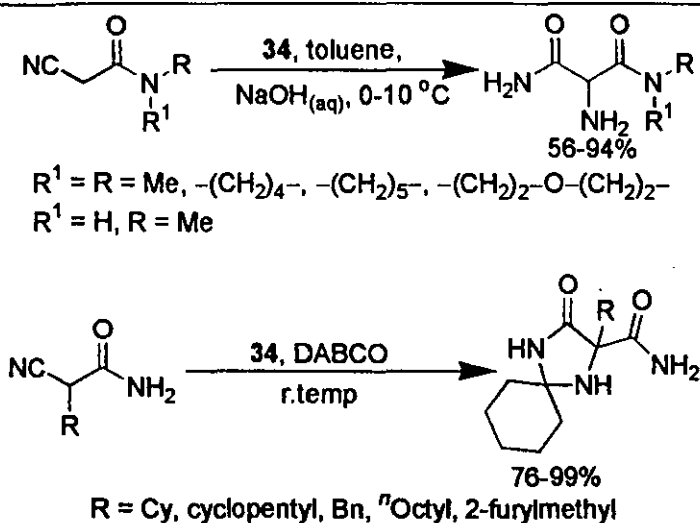
Scheme 68

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).[87] 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).[87]
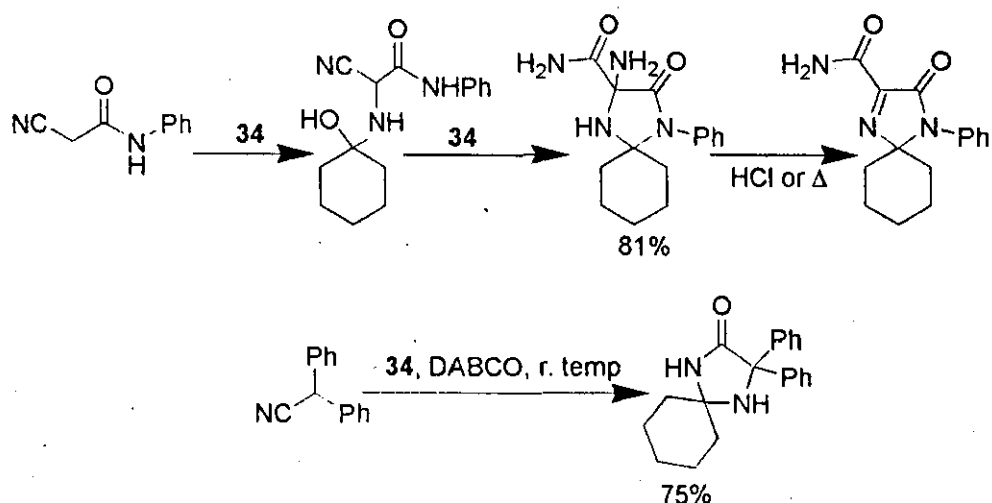
Scheme 69

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

poor to moderate yields (Scheme 70).[96] 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.
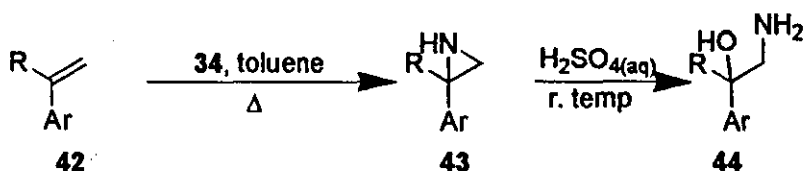
Scheme 70

Ar	R	Yield (%)	
		43	**44**
Ph	H		53
4-MeC$_6$H$_4$	H		45
4-MeOC$_6$H$_4$	H		45
4-ClC$_6$H$_4$	H	58	50
4-NO$_2$C$_6$H$_4$	H	49	
Ph	Me	46	65
Ph	Ph		68

Non-aromatic alkenes were shown to be unreactive towards *NH*-oxaziridines and are only aminated in exceptional cases. For example, norbornene gave the *exo* aziridine in 20% yield, while acrylonitrile was aminated in 41% yield (Scheme 71).[96]
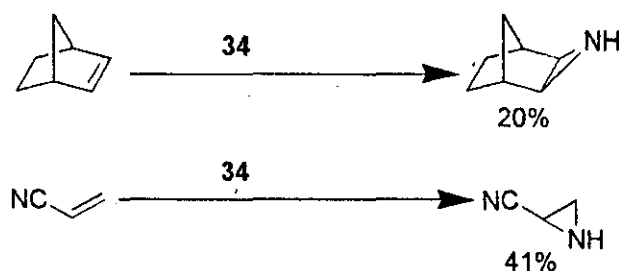
Scheme 71

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.[87, 97] 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).[98]
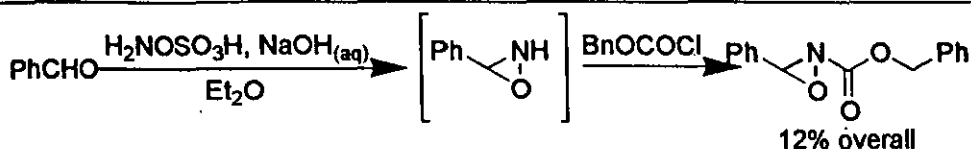
Scheme 72

Yields for these reactions were poor, and these compounds are now generally prepared by oxidation of *N*-protected imines.[97] 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).[97, 99]

P-G = Fmoc, Moc
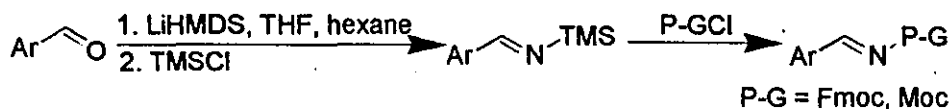
Scheme 73

N-Boc benzaldimines are prepared in only low yields by acylation of *N*-silyl imines with di-*tert*-butyl carbonate (Boc₂O) or *tert*-butyl fluoroformate (Boc-F), and are instead usually prepared by the aza-Wittig reaction between a benzaldehyde and an *N-tert*-butoxycarbonyl iminophosphorane (Scheme 74).[99]
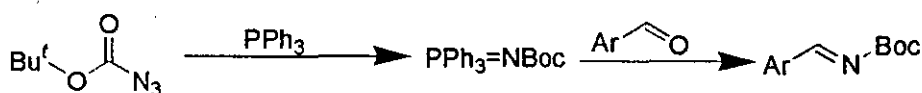
Scheme 74

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).
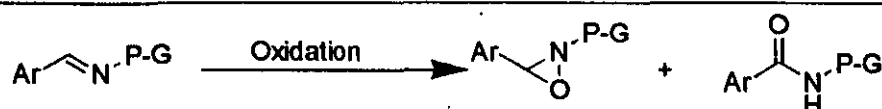
Scheme 75

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).[97]
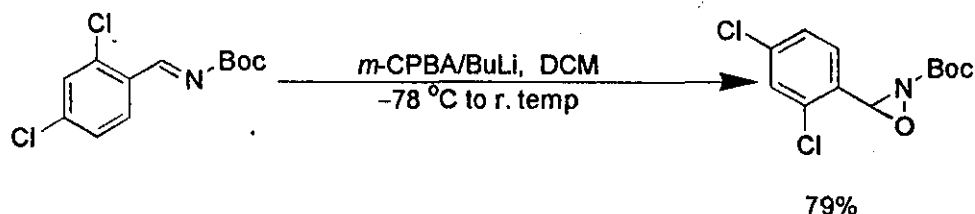
Scheme 76

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).[100]

R = ^{n}Pr, Ph, 4-(ClCH$_2$)C$_6$H$_4$; 2,6-F$_2$C$_6$H$_3$;
2-FC$_6$H$_4$; 3F,4,6Cl$_2$C$_6$H$_2$; (ClCH$_2$)Me$_2$C;
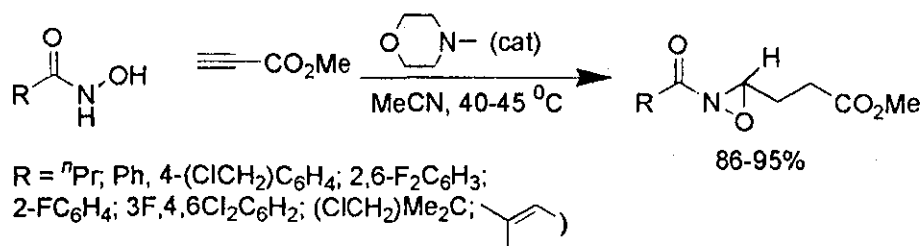
Scheme 77

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.[97] 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 5 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).
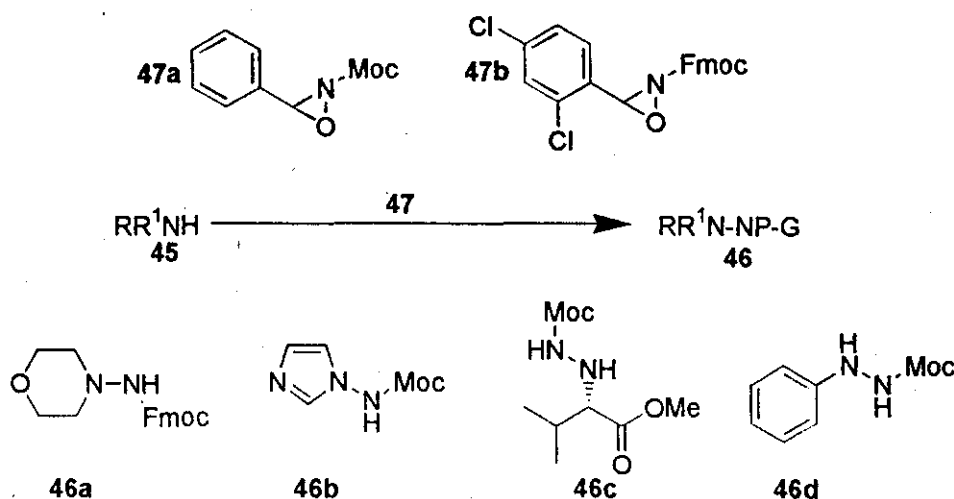
Scheme 78

Product	Oxaziridine	Yield (%)	Reaction Conditions
46a	47b	89	r. temp, 0.5 hours
46b	47a	76	r. temp, 24 hours
46c	47a	57	60 °C, 3 hours
46d	47a	75	r. temp, 1 hour

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

synthesis of hydrazine derivative **46c** from **45c** (Scheme 79) where the imine and hydrazine were isolated in a 70:30 ratio.[97]
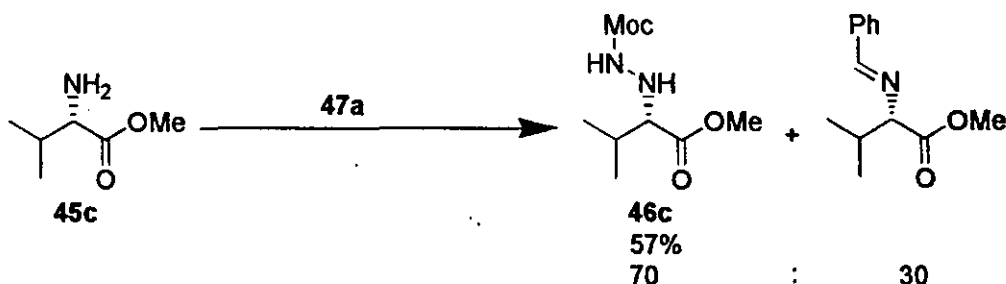
Scheme 79

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 °C, the *N*-oxide/aminimide product-ratio was 70:30 (Scheme 80).

r. temp	5	:	95
−78 °C	30	:	70
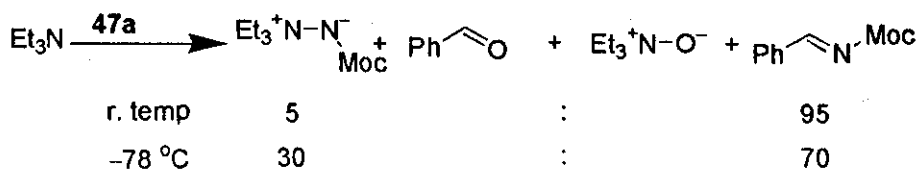
Scheme 80

One of the most synthetically useful of these reactions is the synthesis of α-hydrazino-acid derivatives. A closely related reaction is the amination of free amino-acids to give the corresponding N_β-protected hydrazino acids.[97] These reagents are currently employed in conventional peptide synthesis,[97] which involves carbamate protection of the amino functionality. This synthesis involves the use of either N_α-unfunctionalised or preferably N_α-benzyl protected hydrazino acids that can be prepared from the corresponding *N*-benzyl amino acids.[97] Initial conversion of amino acids or benzyl derivatives into benzyl trimethylammonium or tetrabutyl ammonium

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 °C (Scheme 81).
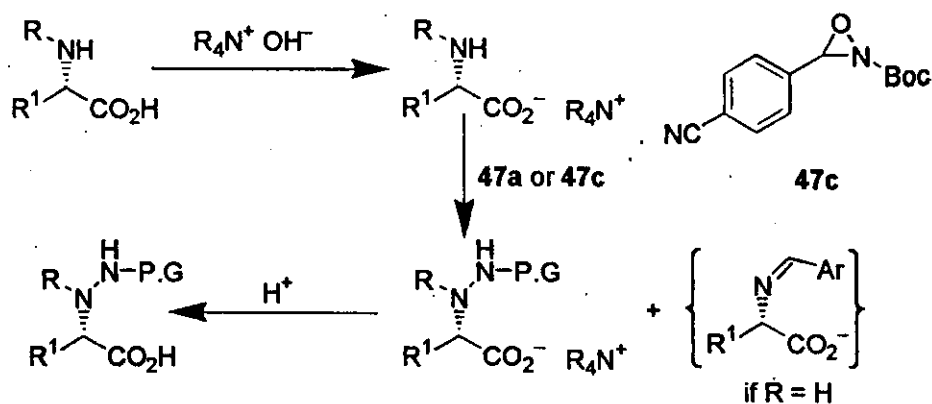
Scheme 81

R	R^1	P-G	Temp (°C)	Yield (%)
	−(CH$_2$)$_4$−	Moc	−15	85
	−(CH$_2$)$_4$−	Boc	−15	95
Bz	Me	Boc	0	88

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 α-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]
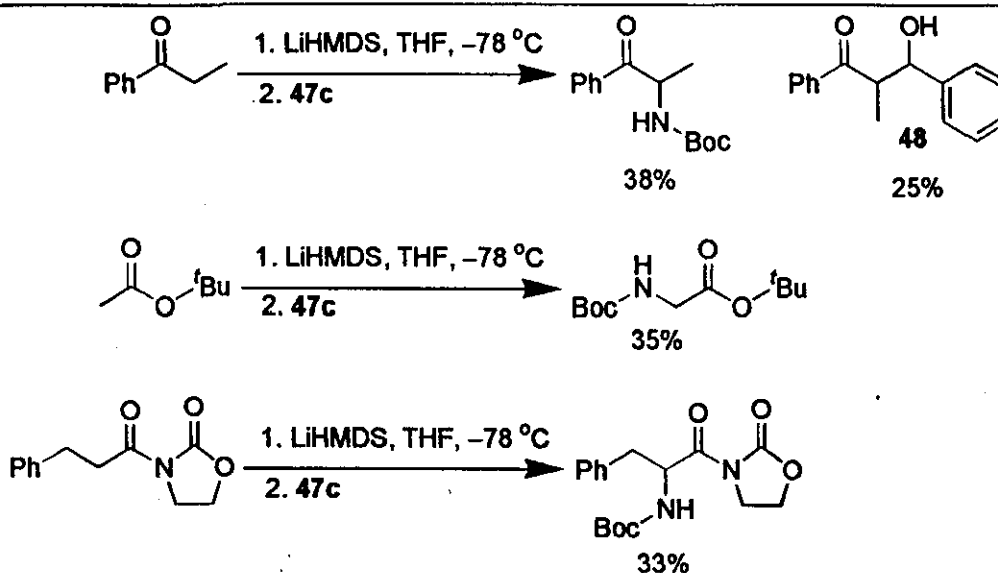
Scheme 82

Attempts have been made to achieve substrate-controlled asymmetric induction for the synthesis of chiral α-amino ketones.[101] 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).
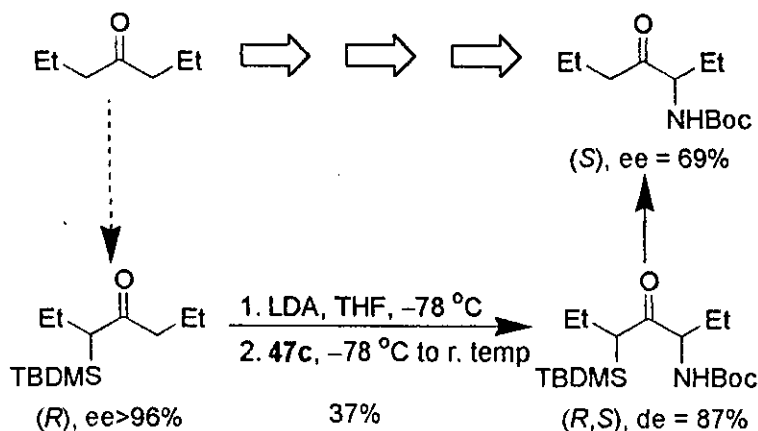
Scheme 83

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

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).[97]
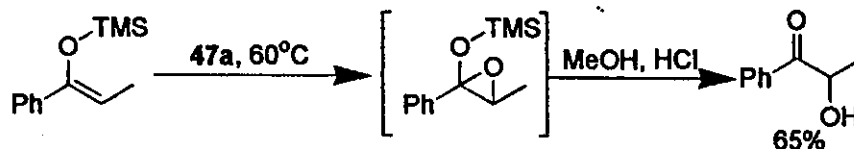
Scheme 84

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**[87] and epoxidised by *N*-sulfonyl oxaziridines[76].

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[97] (Scheme 85).[97]
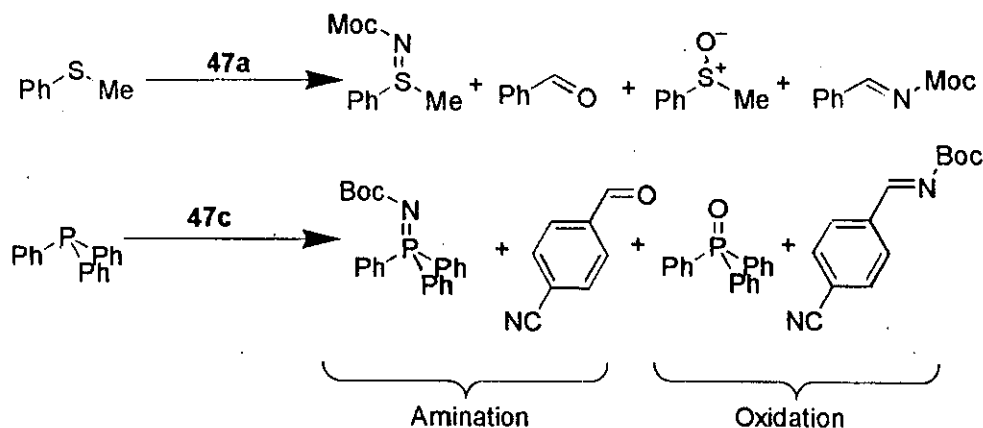
Scheme 85

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 analogues 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 stable[102] 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.

O-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-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 β-diketones gave little or no product. It is difficult to see how we could effectively incorporate chirality into O-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-Acyl hydroxylamines have been reported as aminating agents, but literature on these reagents is sparse due to their instability.

N-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-haloamines are rarely used, and preclude them from further development on this basis.

Hydroxylamine-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-(mesitylsulfonyl)hydroxylamine 6 and similar N,N-dialkylated derivatives such as 7 have been shown to be of some use for amination of a wider range of organometallic

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-protienogenic) amino acids. These unusual amino acid structures are produced in nature mainly by micro-organisms 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[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_2X 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_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).
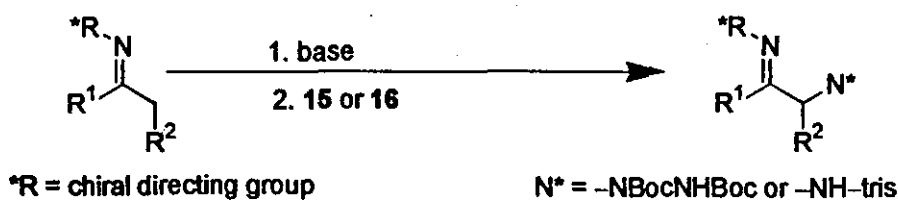
Scheme 86

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

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,[57b] 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 α,β-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

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. While 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

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 (α-hydroxy ketone) and not the amination product (*N*-protected α-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 α-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 α-amino ketone or acid derivatives in that the reaction would be a one-step synthesis of an *N*-protected α-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.

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).
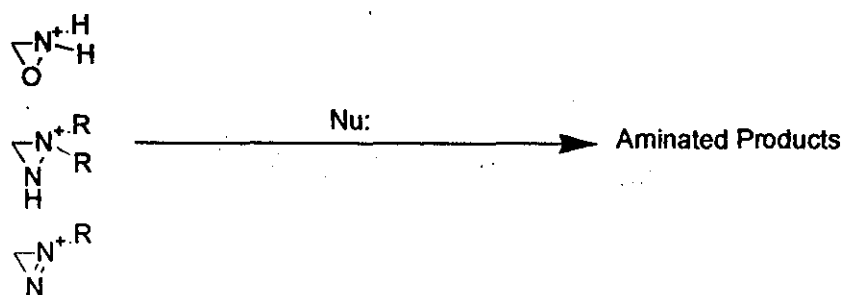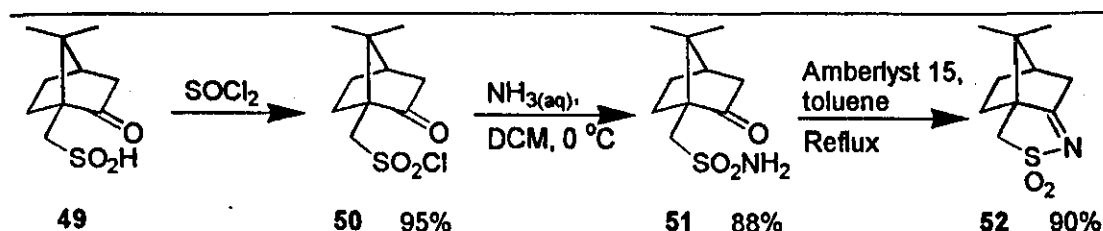

Scheme 87

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,[1] 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*,[77] and **1** was synthesised according to literature procedures. (1*S*)-(+)-Camphorsulfonic acid **49** was first reacted with thionyl chloride to give crude (1*S*)-(+)-camphorsulfonyl chloride **50** in 95% yield,[104] which was then reacted with concentrated ammonia solution to afford crude (1*S*)-(+) camphorsulfonamide **51** in an 88% yield.[105] Cyclisation of **51** to (1*S*)-(−)-camphorsulfonyl imine **52** was effected in 90% yield by reflux of (1*S*)-(+)-camphorsulfonamide in toluene in the presence of amberlyst 15[R] (Scheme 88).[105]

Scheme 88

(1*S*)-(−)-Camphorsulfonyl imine **52** was then oxidised at the 3 position by reaction with selenium dioxide in acetic acid under refluxing conditions to give (1*S*)-(−)-3-oxocamphorsulfonyl imine **53** in a 62% yield.[106] (1*S*)-(−)-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 (1*S*)-(+)-3,3-dimethoxycamphorsulfonyl imine **1** in a 90% yield (Scheme 89).[106]
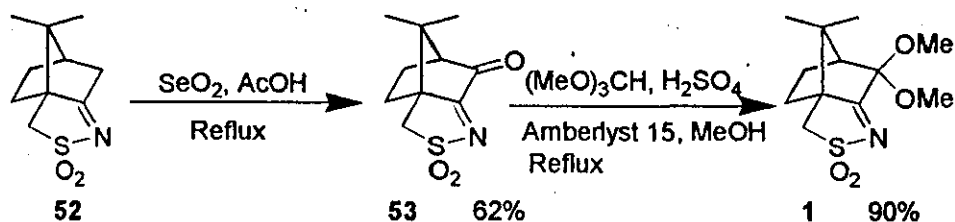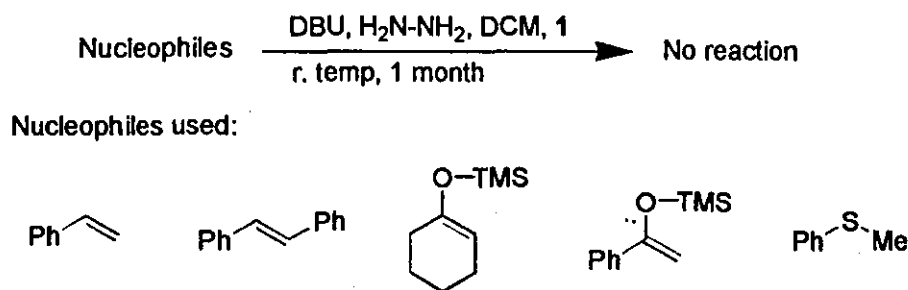

Scheme 89

(1*S*)-(+)-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

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

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

Nucleophiles used:

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).

$\xrightarrow[\text{r. temp, 2 weeks}]{\text{DBU, H}_2\text{N-X, DCM or DCM/MeOH, 1}}$ No reaction

X = TsNH−, HO−
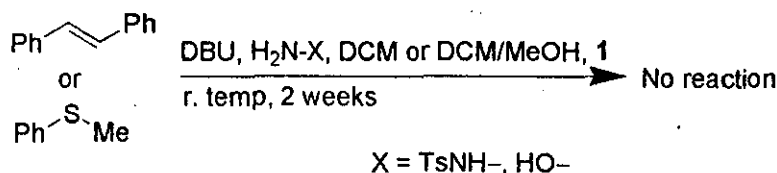
Scheme 91

At this stage, our investigations into this reaction had been completely unsuccessful, and the question arose of whether any adduct between the potential catalyst 1 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 *trans*-imination reactions with these types of potential *N*-transfer reagents.[107] The *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

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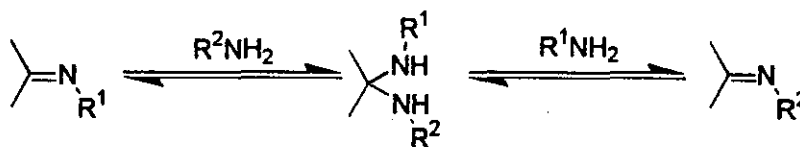
Scheme 92

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).[81]
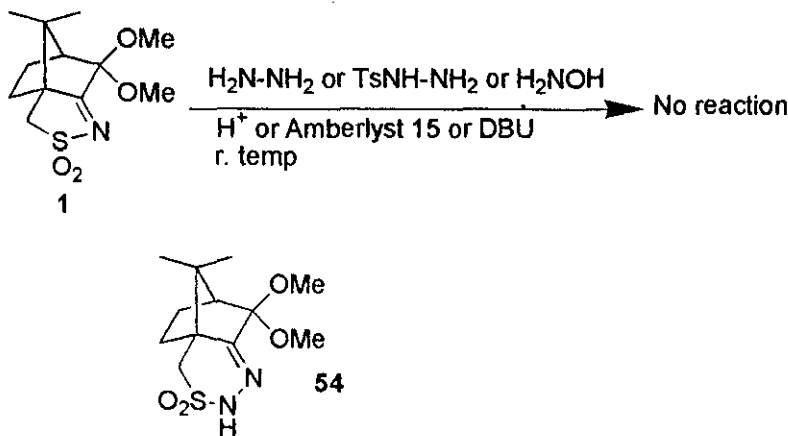
Scheme 93

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 *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 *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. *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

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

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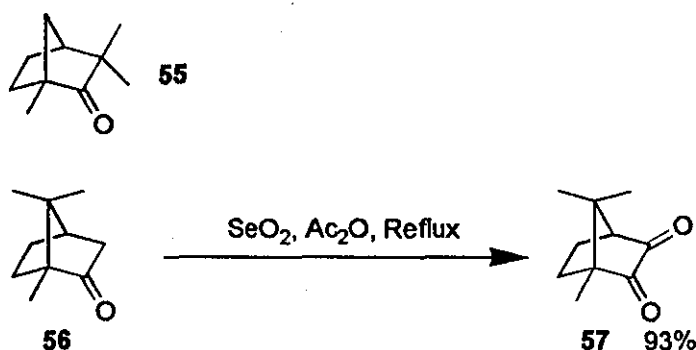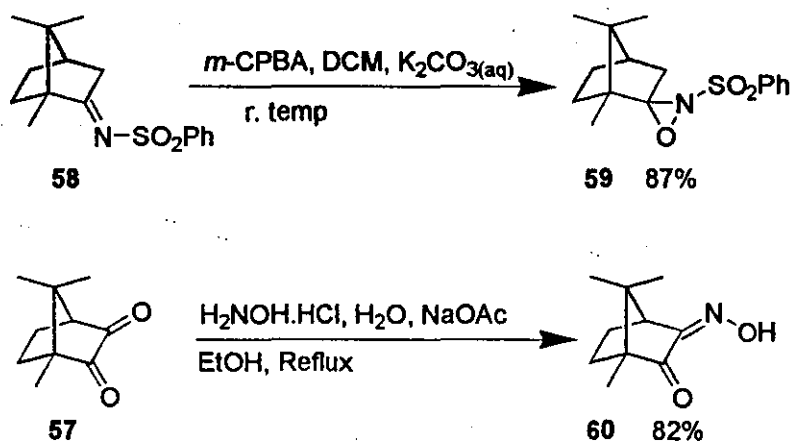

Scheme 94

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 *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 *endo* face of the molecule, and therefore limits the formation of

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 (1*R*)-(–)-*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 (1*R*)-(–)-camphorquinone to form the single mono-oximated product (1*R*)-(+)-camphorquinone monoxime **60** (Scheme 95).[110]

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).
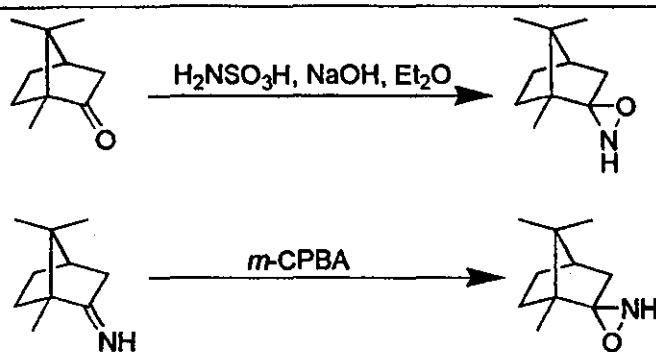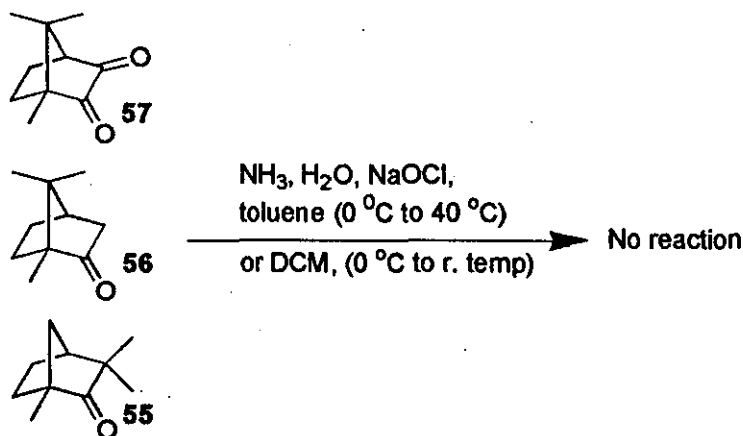
Scheme 96

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

Initially, our attempts were made to prepare chiral oxaziridines directly from (1*R*)-(−)-fenchone **55**, (1*R*)-(+)-camphor **56** and (1*R*)-(−)-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*-oxaziridine for *in situ* acylation (Scheme 56, Scheme 72).[89, 90. 98] 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 °C to 40 °C, 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 °C and room temperature and the concentrations were varied (Scheme 97). Although no new compounds could

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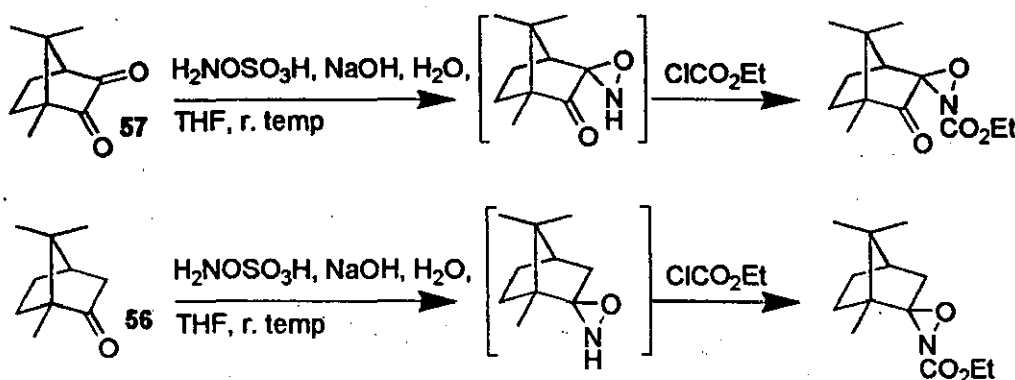

Scheme 97

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).
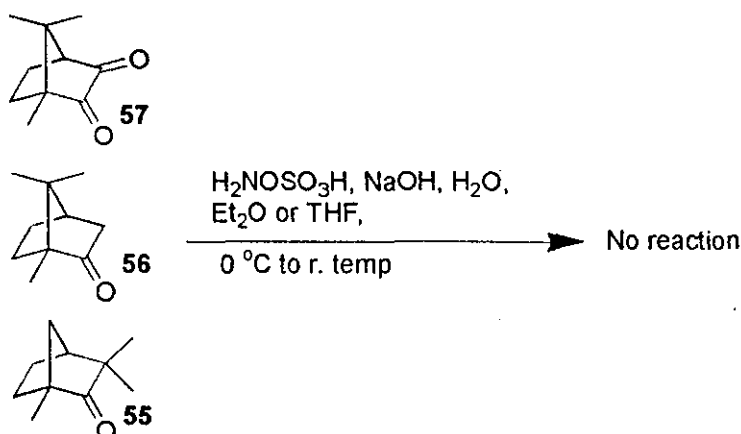
Scheme 98

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.
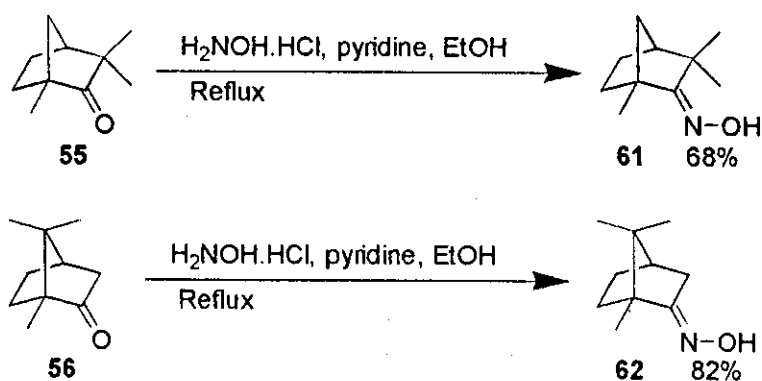

Scheme 99

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,[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-O-sulfonic acid may be due to the slight solubility of hydroxylamine-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 *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 α,α-unsubstituted cyclohexanones or for benzaldehydes.[89, 90, 98]

NH-oxaziridines have also been prepared by photolyses of oximes (See 1.2.13 (b), Scheme 57).[91] Analogously, the photolyses of (1*R*)-(–)-fenchone oxime **61**, (1*R*)-(–)-camphor oxime **62** and (1*R*)-(+)-camphorquinone monoxime **60** were attempted. (1*R*)-(+)-Camphorquinone monoxime was synthesised in 82 % yield by oximation of (1*R*)-(–)-camphorquinone **57** with hydroxylamine hydrochloride in the presence sodium acetate in water and ethanol under refluxing conditions (Scheme 95).[110] (1*R*)-(–)-Fenchone oxime **61**[113] and (1*R*)-(–)-camphor oxime **62**[114] were synthesised from (1*R*)-(–)-fenchone **55** (1*R*)-(+)-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).
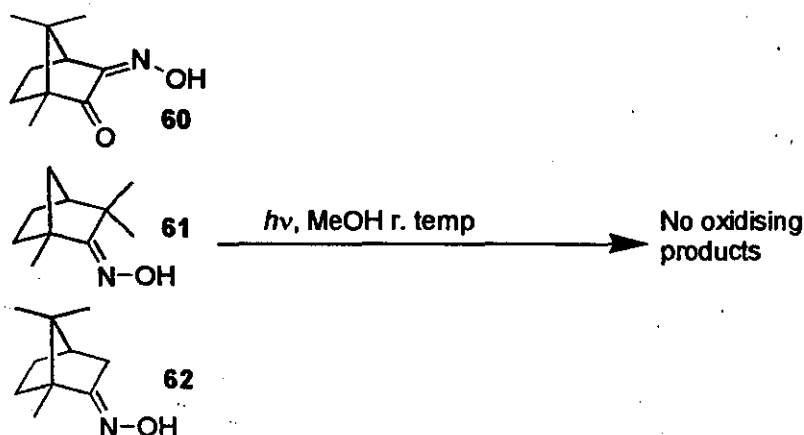

Scheme 100

Oximes **60**, **61** and **62** were then irradiated under the same conditions reported for the synthesis of other *NH*-oxaziridines by photolysis.[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).

Scheme 101

Photolyses of (1*S*)-(+)-fenchone oxime (+)-**61** and (1*S*)-(+)-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 (1*R*)-(−)-camphor oxime **62** in Scheme 102.
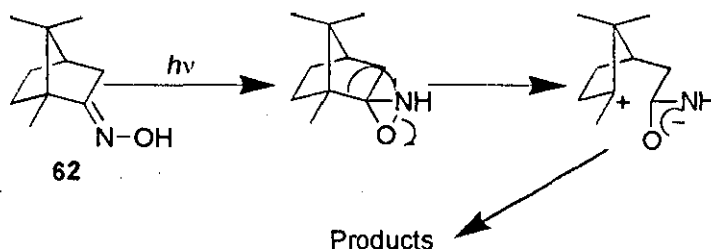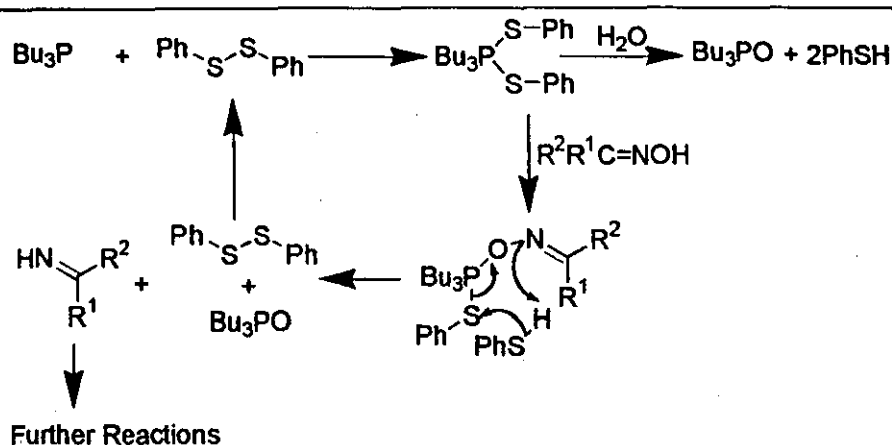

Scheme 102

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),[89] and we thought that chiral *NH*-oxaziridines might perhaps be prepared in this way from *NH*-imines derived from (1*R*)-(–)-fenchone **55** and (1*R*)-(+)-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.[115] One reported method of accomplishing this reaction under anhydrous conditions that prevents hydrolysis of the imine is by carrying out the reduction using tributyl phosphine and diphenyl disulfide.[116] 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).[116a]

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 (1*R*)-(+)-camphor; none of either of the desired *NH*-imine products were recovered for either of these reactions (Scheme 104).
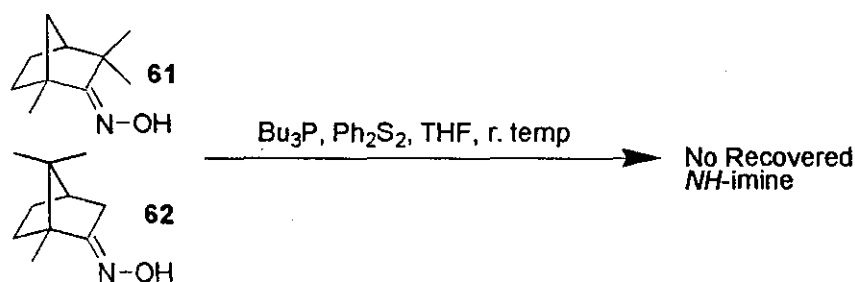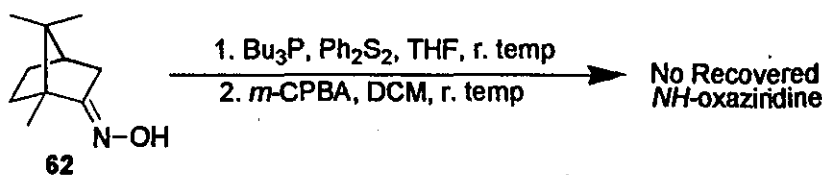

Scheme 104

For (1*R*)-(−)-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

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).

	1. Bu$_3$P, Ph$_2$S$_2$, THF, r. temp	
	2. *m*-CPBA, DCM, r. temp	No Recovered *NH*-oxaziridine

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, (1*R*)-(–)-camphor nitrimine **63** was prepared by nitrosation of (1*R*)-(–)-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).[117] Nitrimine **63** was then converted to (1*R*)-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).[118]


	NaNO$_2$, H$_2$O		NH$_{3(g)}$, THF	
N–OH	AcOH, r. temp	N–NO$_2$	0 °C	NH
62		**63** 54%		**64** ca. 100%
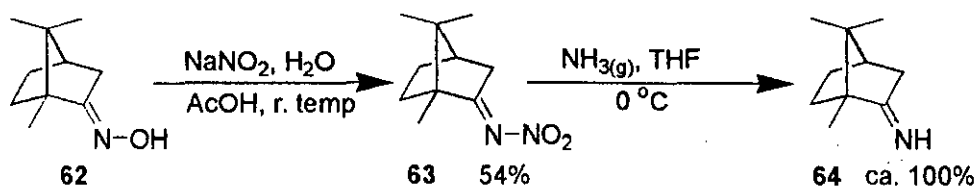
Scheme 106

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[119] *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 furnished (+)-camphoryl oxaziridine **65** as a colourless solid in a yield of 94% (Scheme 107).
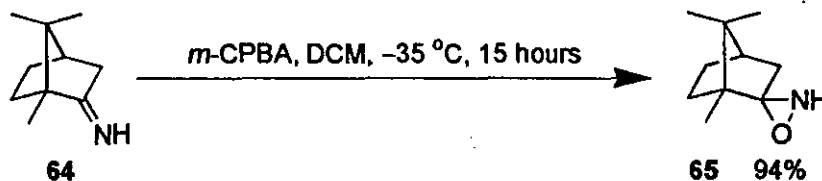
Scheme 107

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 recrystalisation 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

oxaziridine **33** (Figure 3),[88] 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 *exo* or *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).
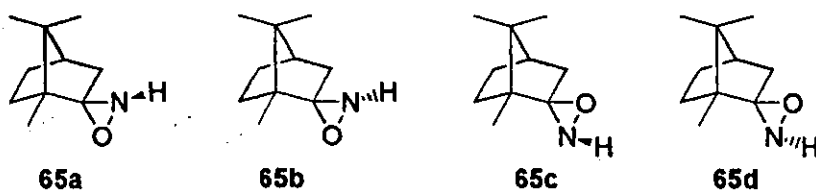

65a　　　　**65b**　　　　**65c**　　　　**65d**

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 *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 *endo* and *exo* attack of the oxidant occurs, then we may expect the *NH*-proton to be in the more sterically favoured position, transposed on the un-congested 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 *exo* attack and *endo* attack of the per-acid occurs to give *exo* and *endo* isomers of the oxaziridine. Rapid nitrogen inversion on the NMR

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*-sulfonyl[122] and *N*-phosphinoyl[123] 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).
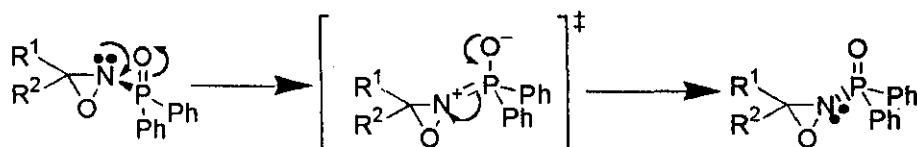
Scheme 108

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**.

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.

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.[109] 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).
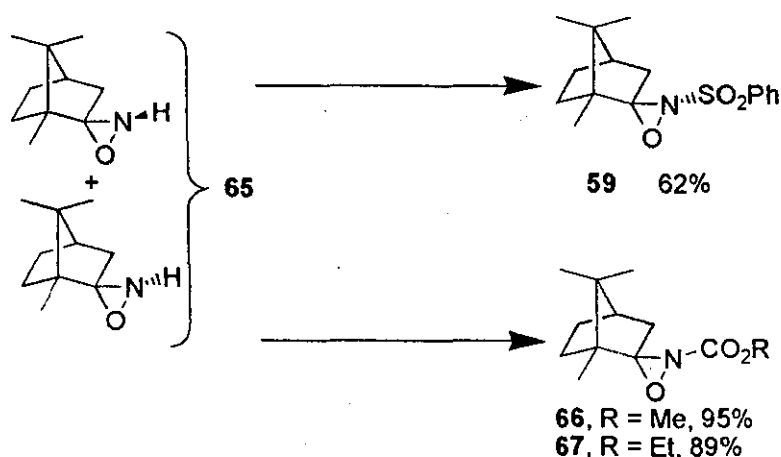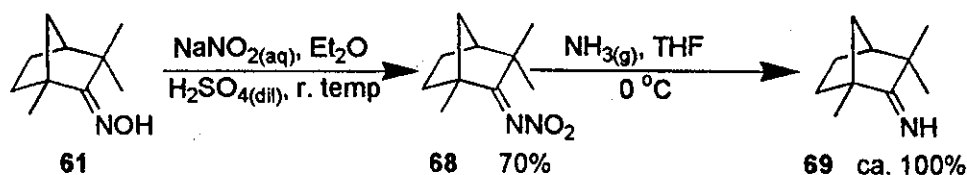

Scheme 109

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

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.[124] We found however, that (1*R*)-(–)-fenchone oxime **61** was only sparingly soluble in acetic acid. (1*R*)-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 (1*R*)-(–)-fenchone oxime **61** and aqueous sodium nitrite (Scheme 110).[125] (1*R*)-fenchone nitrimine **68** was converted into the corresponding (1*R*)-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).[118]

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. (1*R*)-Fenchone imine, **69**, was reacted with one equivalent of pure *m*-CPBA[119] 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).
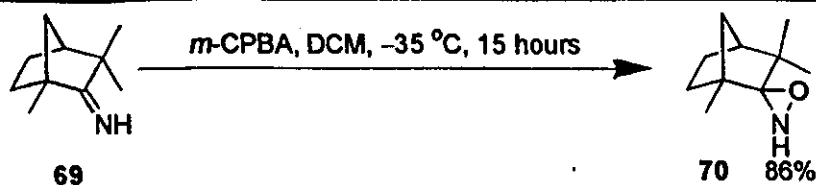
Scheme 111

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 *exo* face. Based upon this factor alone, we have predicted the structure of *NH*-oxaziridine **70** as being *exo*, with an *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 *endo* oxidation will have two invertomers, and similarly, that the product of *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 *endo* and *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

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 (1*R*)-(−)-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.[108] High pressures needed during the reaction, however, were deemed too unsafe for preparation of this imine. As an alternative to this procedure, (1*R*)-(+)-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 (1*R*)-(−)-camphorquinone **57** as the product. (1*R*)-(+)-Camphorquinone mononitrimine **72** was prepared by the reaction of (1*R*)-(+)-camphorquinone monoxime **60** with nitrosyl sulfuric acid in the presence of pyridine in acetonitrile at room temperature in a yield of 30% (Scheme 112).
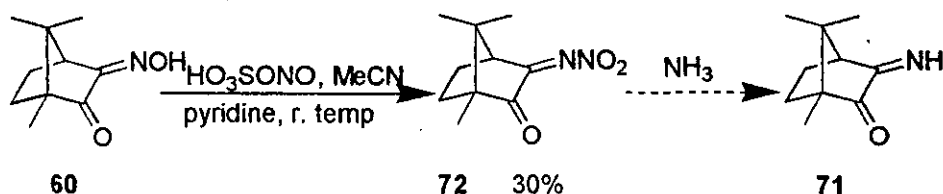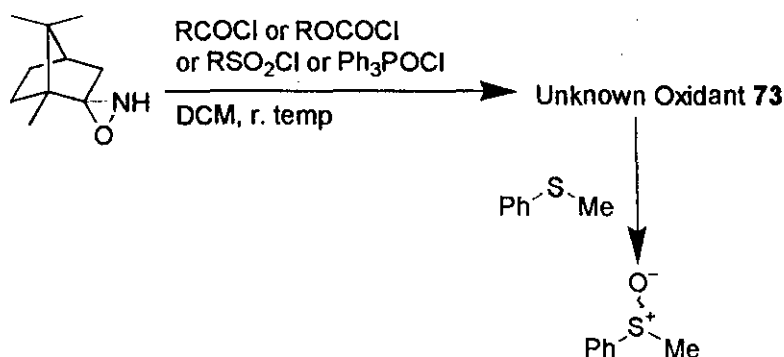

Scheme 112

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).
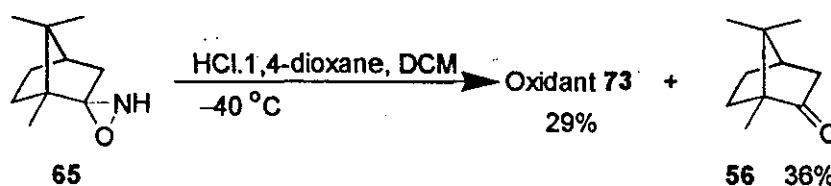

Scheme 113

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 be 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 (1*R*)-(+)-camphor **56** was also isolated from the reaction mixture in a yield of 36% (Scheme 114).

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 recrystalisation 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**).
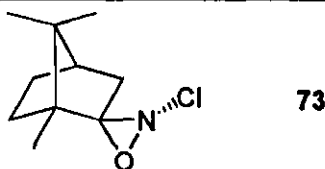
Figure 5

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 (1*R*)-(+)-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 (1*R*)-(+)-camphor **56**, from the product mixture (Scheme 115).
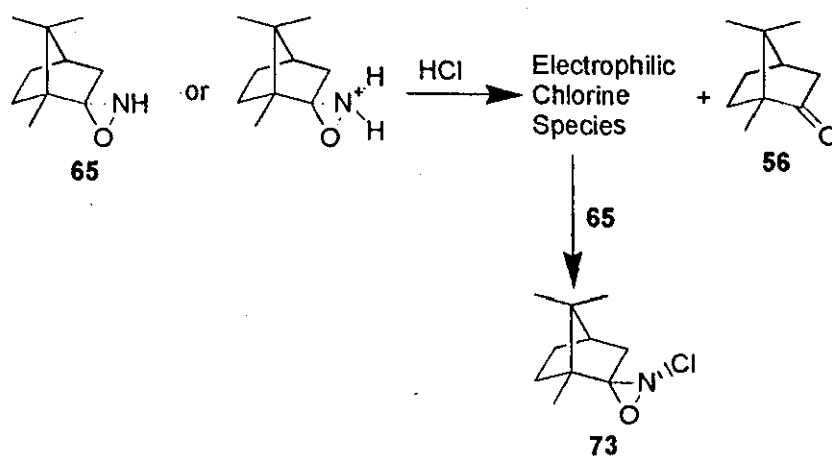
Scheme 115

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

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]
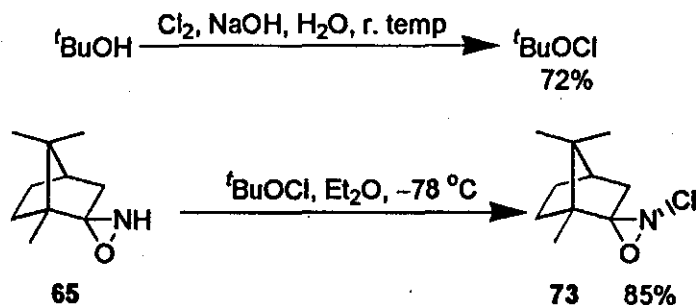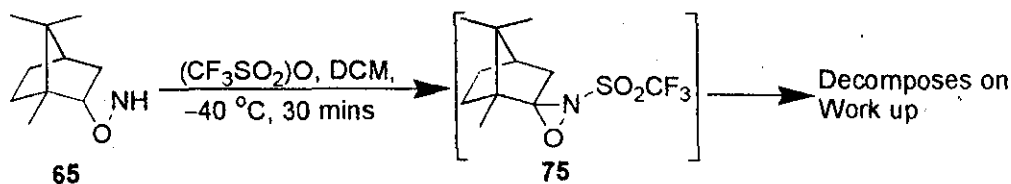

Scheme 116

We thought that it would be useful to synthesise *N*-sulfonyl oxaziridines by *N*-functionalisation of *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 *N*-sulfonyl oxaziridines with known stereochemistries. Secondly, although conventional syntheses of chiral *N*-sulfonyl oxaziridines are generally well developed and high yielding processes, *N*-functionalisation could provide us with a convenient alternative route to the synthesis of other potentially useful *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 (–)-*N*-(phenylsulfonyl)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 (–)-*N*-(methanesulfonyl)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 *N*-methanesulfonyl oxaziridine **74** and *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.
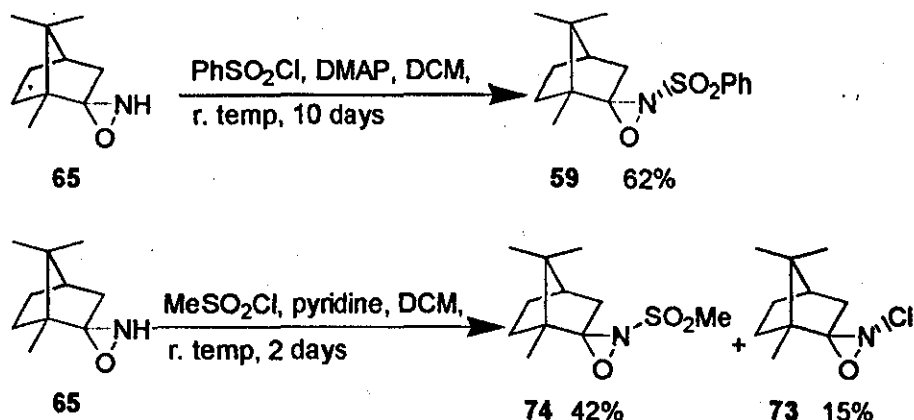
Scheme 117

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 °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.

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

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).
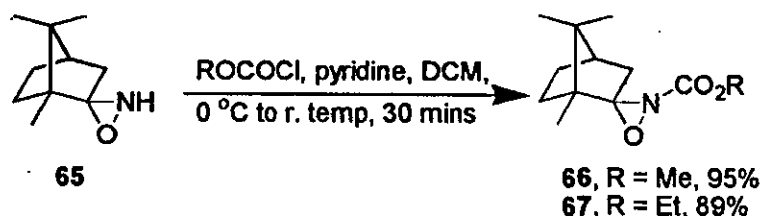
Scheme 119

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).
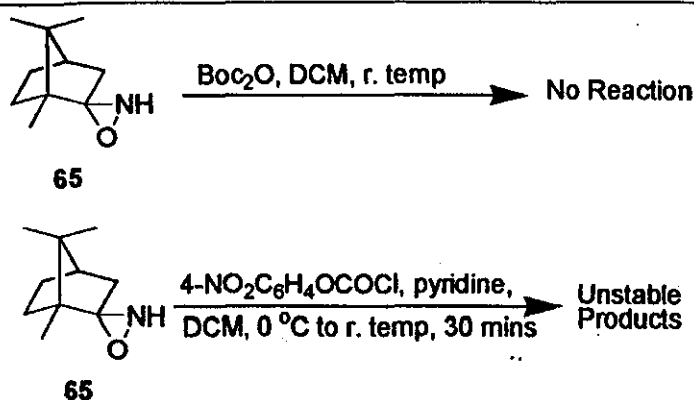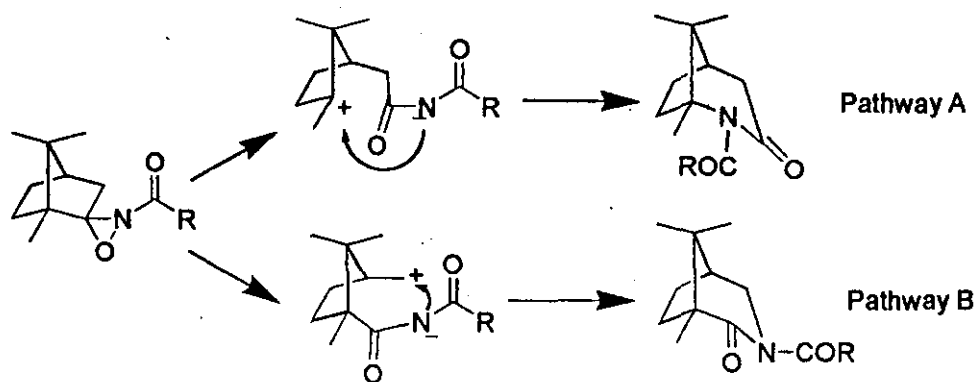
Scheme 120

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).
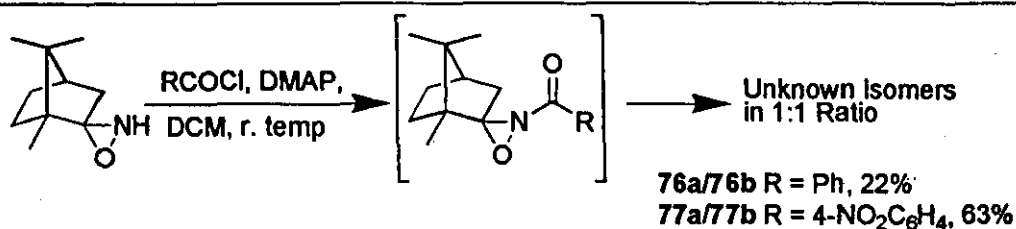
Scheme 121

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.
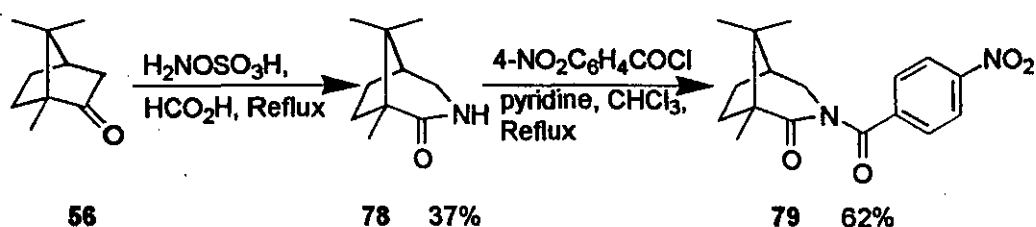

Scheme 122

Firstly, this type of oxaziridine to lactam rearrangement is known to occur.[71, 72] 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.[113]

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 (1*R*)-(+)-camphor **56** with hydroxylamine-*O*-sulfonic acid in formic acid under refluxing conditions to give (–)-α-camphidone **78** in a 37% yield[113, 127] (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).

Scheme 123

An isomer of α-camphidone, lactam **80** ((1*R*)-1,8,8-trimethylbicyclo[3.2.1]octan-3-one), was synthesised by Beckmann rearrangement of (1*R*)-(–)-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).
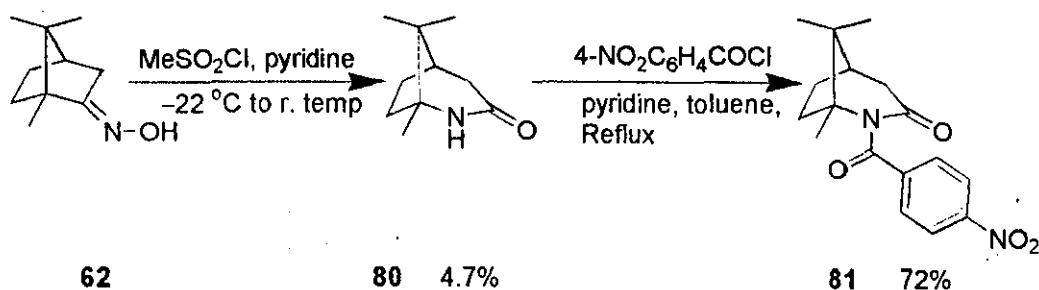
Scheme 124

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).

76a/76b, Ar = Ph, 22%
77a/77b, Ar = 4-NO$_2$C$_6$H$_4$, 63%
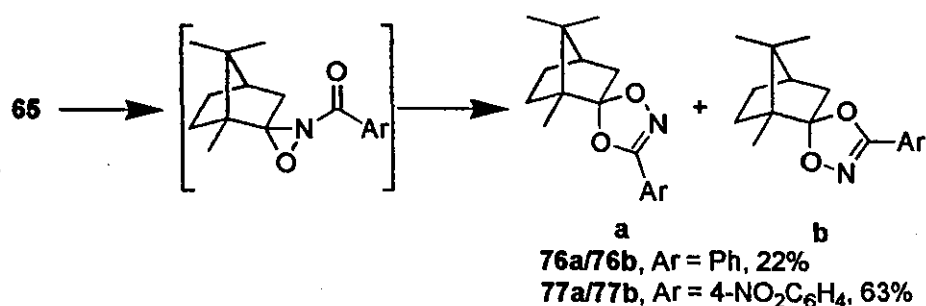
Scheme 125

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 (1*R*)-(+)-camphor **56**. Benzohydroximinoyl chloride was prepared by the reaction of benzaldehyde 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 (1*R*)-(+)-camphor **56**. The reaction mixture was left overnight, and on work up, (1*R*)-(+)-camphor **56** was recovered and no products of cycloaddition to **56** were observed (Scheme 126).
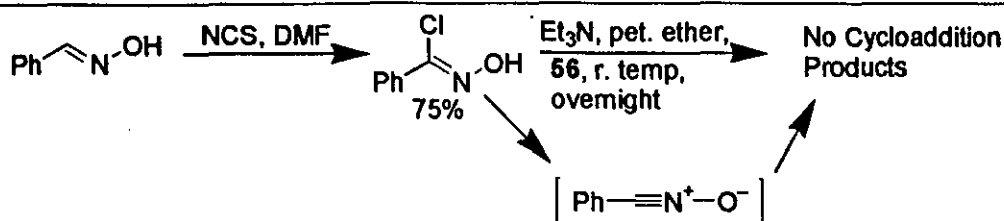
Scheme 126

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.[131] 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/77b**, however, was deprotected to give benzamide in a 47% yield together with (1*R*)-(+)-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).
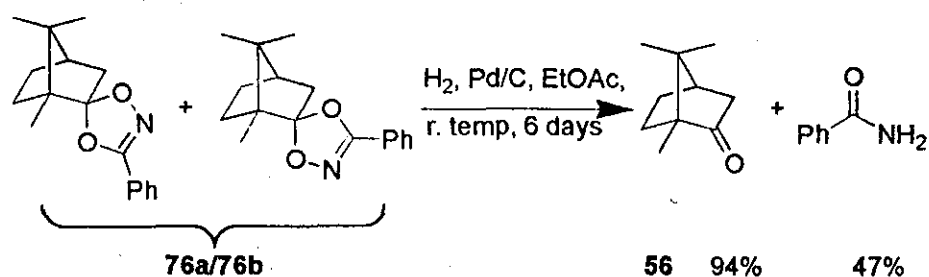
Scheme 127

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

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.


endo attack   *exo* attack
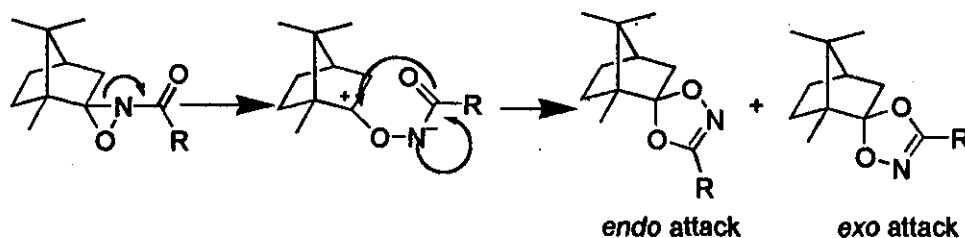
Scheme 128

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.
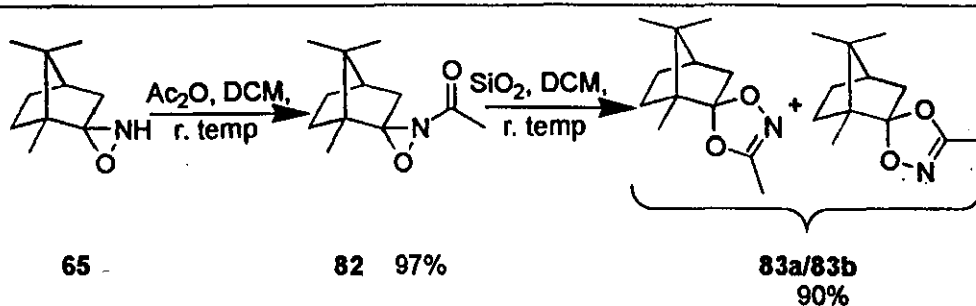
Scheme 129

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).
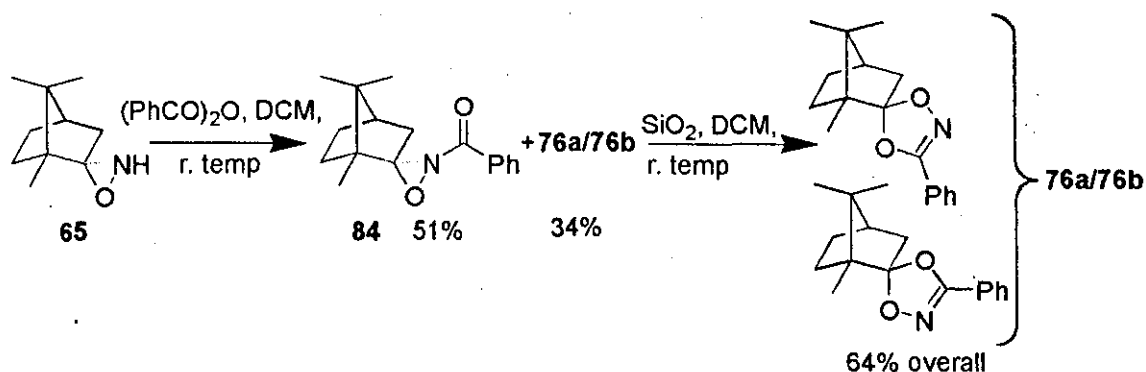
Scheme 130

N-Phosphinoyl oxaziridines are another class of *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,[78a] and an investigation into their potential development as chiral reagents for sulfoxidation reactions has been

reported.[78c] 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.[78c]

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.[132] 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 (Scheme131).[81] 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).


65   **85**   37%
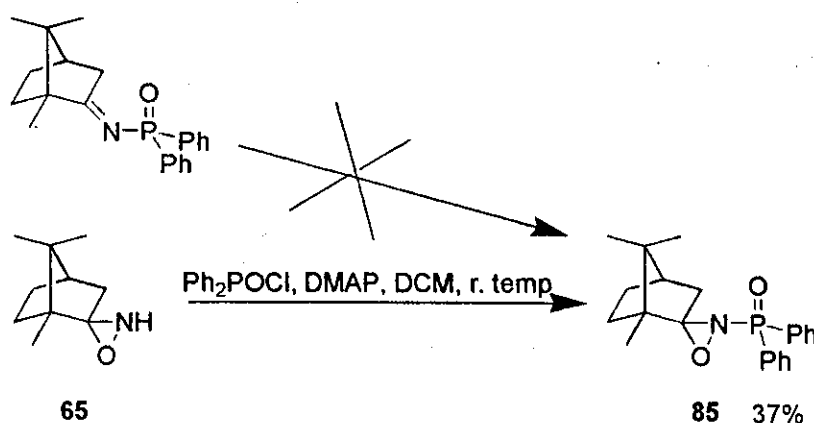
Scheme 131

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).
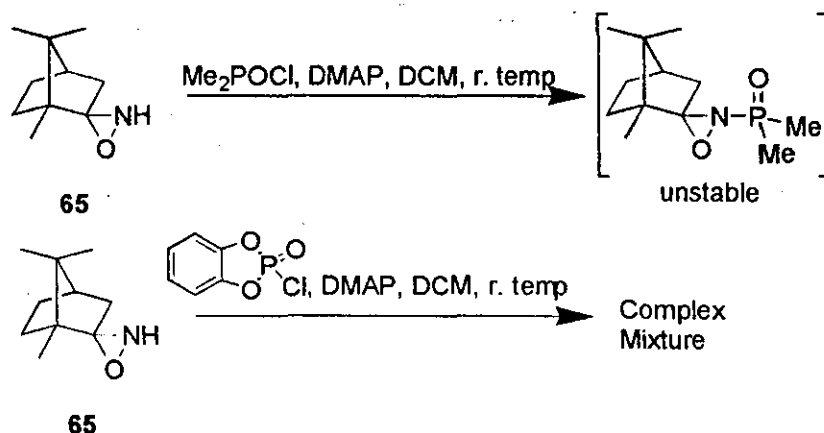
Scheme 132

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 (TMSCl) in DCM at room temperature in the presence of DMAP over a period of one week. The reaction of **65**

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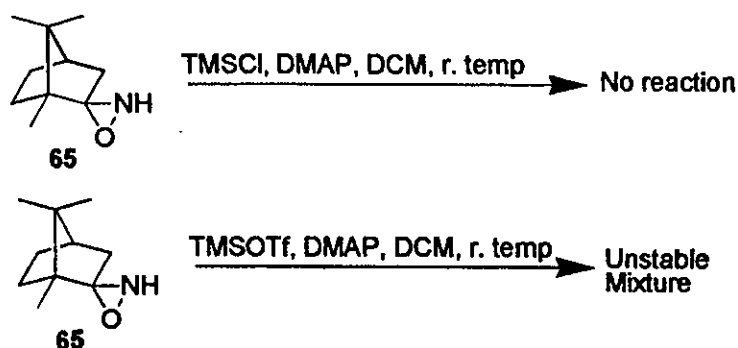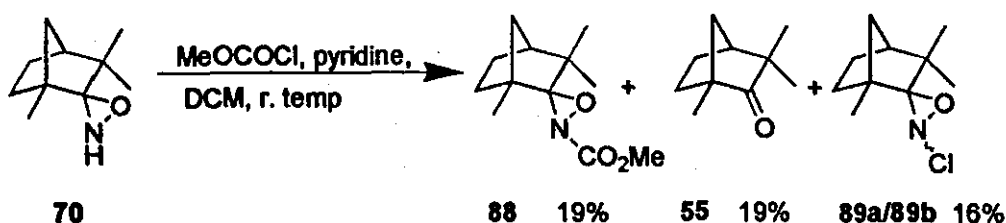

Scheme 133

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*-pentafluorphenyl)camphor thiooxime **86** in a yield of 10%, (1*R*)-(+)-camphor **56** in a yield of 28%, and (−)-*N*-(pentafluorophenylsulfenyl)camphoryl oxaziridine **87** in a yield of 41% (Scheme 134).
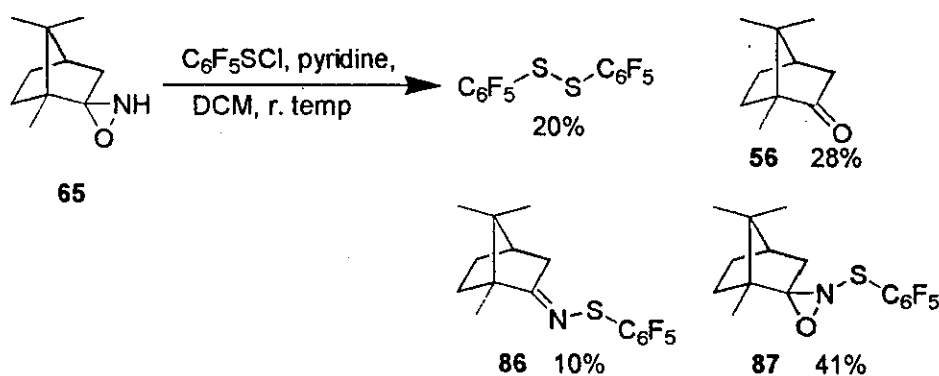
Scheme 134

(−)-*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.

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 (1*R*)-(–)-fenchone 55 (19% yield), together with a mixture of *N*-chlorofenchyl oxaziridines 89a/89b in 16% overall yield (Scheme 135).

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.[133] *N*-Chloro oxaziridines 89a/89b were shown by ^{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 invertomers 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 invertomers 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 α-chloronitroso compounds (Scheme 136).[133a] These α-chloronitroso compounds have a characteristic blue colour as well as a characteristic N=O absorption chromophore in their IR spectrum.
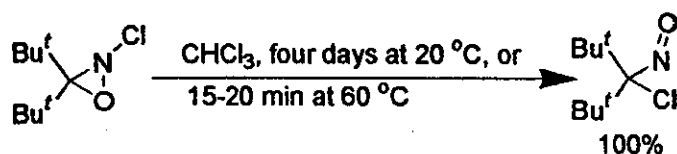
Scheme 136

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 α-chloronitrosyl compound. As well as this, oxaziridines **89a/89b** are blue, and, the ^{1}H 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).
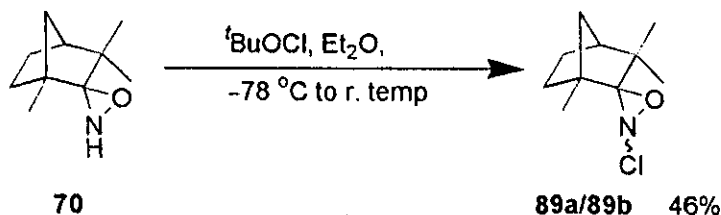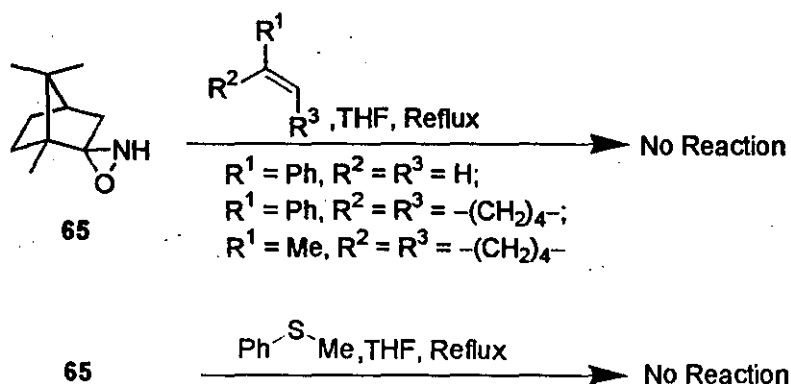

Scheme 137

The product isolated in this reaction was identical to the product isolated during the reaction of **70** with methyl chloroformate.

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).

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).
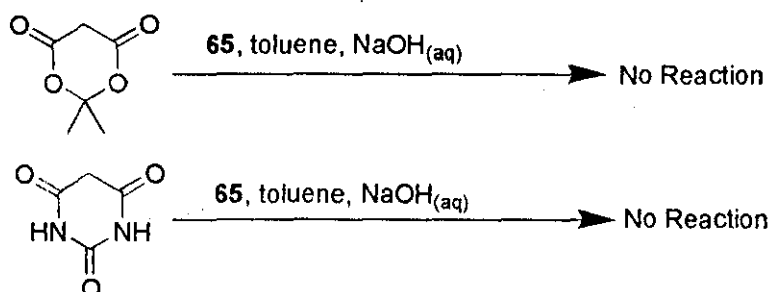
Scheme 139

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).

65

X = CN, COMe
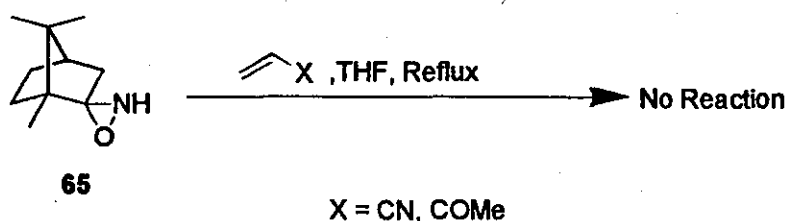
Scheme 140

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).
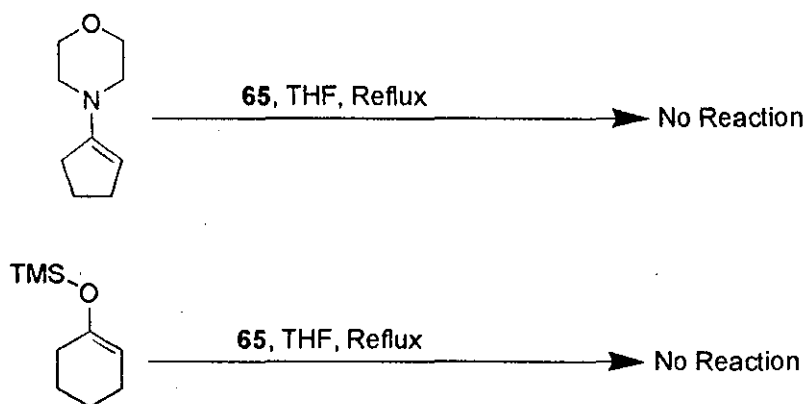
Scheme 141

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

and oxaziridine **65** in DCM at –78 °C. Zinc bromide and zinc chloride brought about decomposition of both 1-cyclohexenyloxytrimethylsilane 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-cyclohexenyloxytrimethylsilane 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).
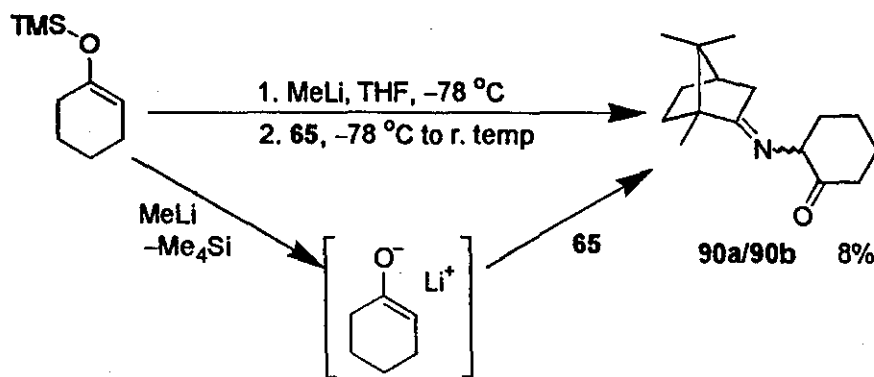
Scheme 142

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.
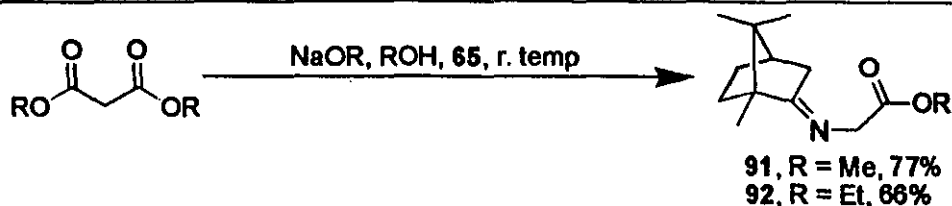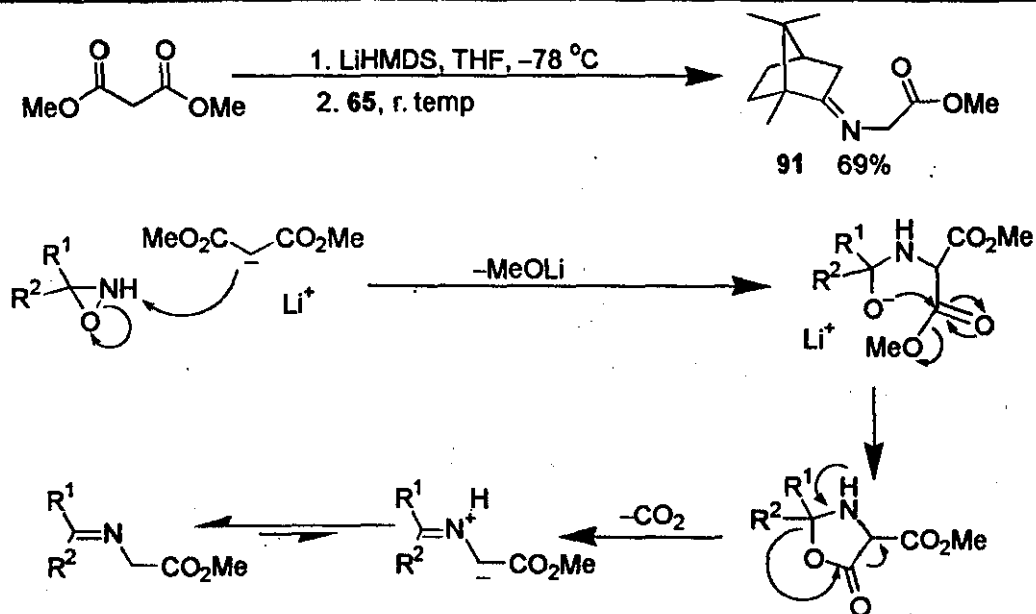
Scheme 143

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).[134]
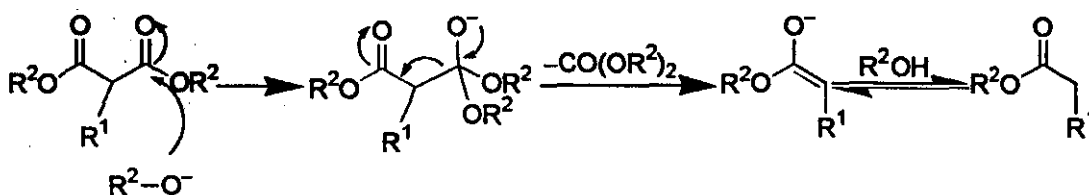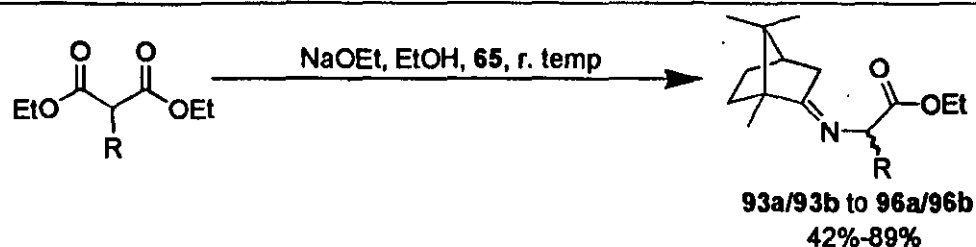

Scheme 144

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 °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

Scheme 145

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).

Scheme 146

| Imine Product	R	Reaction Time (h)	Yield (%)	dr
93a/93b	Me	4	89	1:1
94a/94b	Et	5	77	1:1
95a/95b	Allyl	5	80	1:1
96a/96b	Ph	24	42	1:1

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).

R* = chiral inducting group

Scheme 147
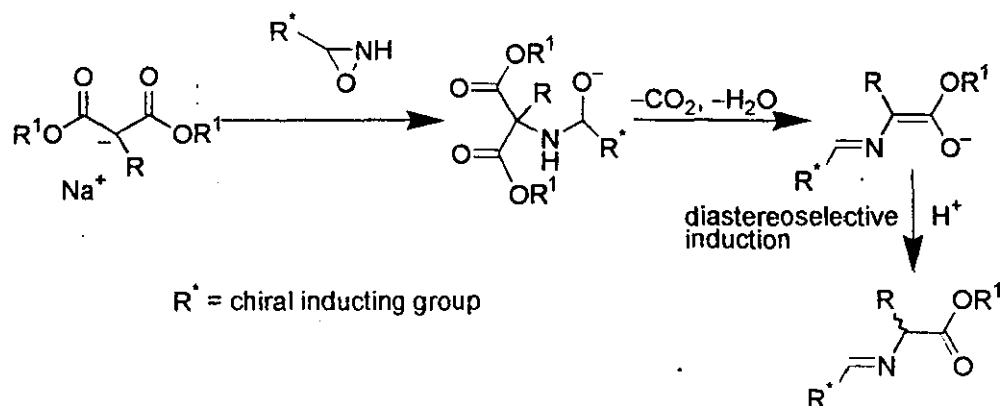
Because some success had been achieved in the amination of enolates of malonates, we examined other bis-activated carbanions as substrates for amination reactions using (+)-camphoryl oxaziridine **65**.

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.
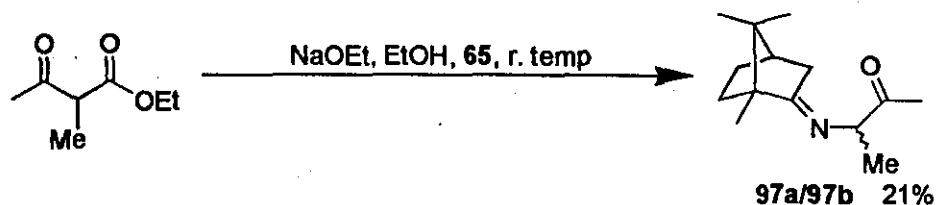
Scheme 148

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).
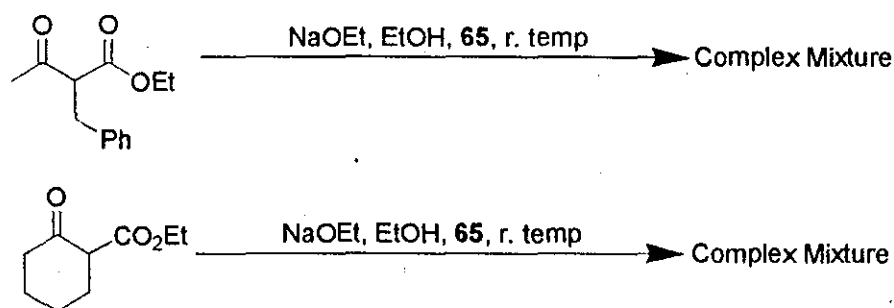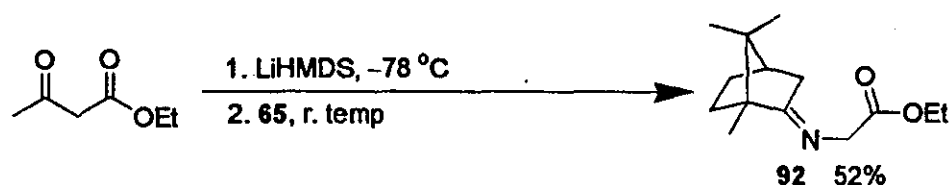
Scheme 149

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

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).

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.[135] 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).[135b]
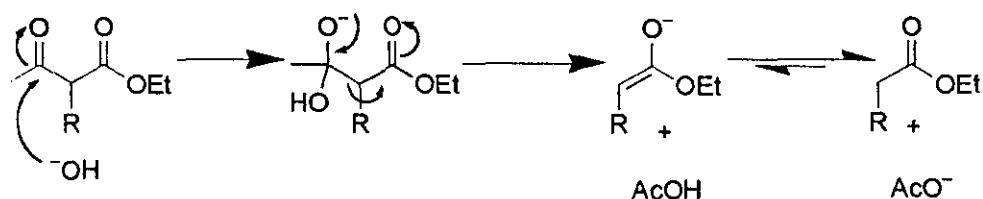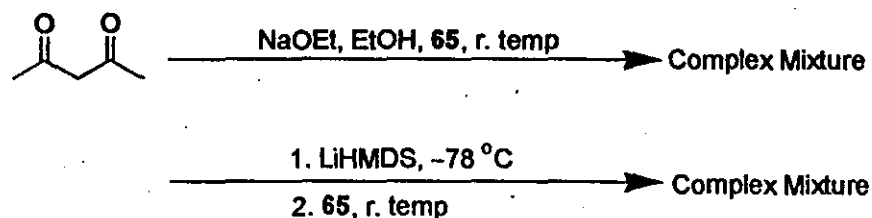

Scheme 151

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).
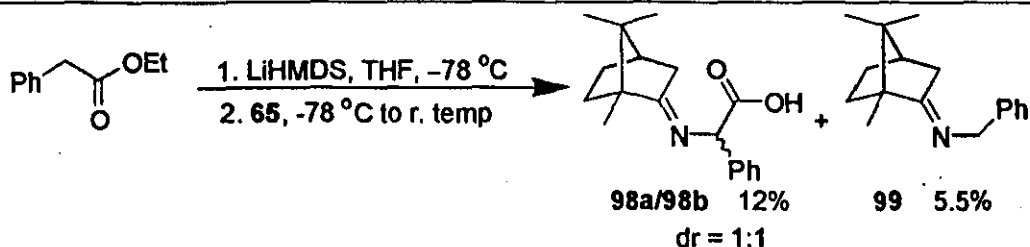

Scheme 152

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 phenylacetate 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**, (1*R*)-*N*-benzyl camphor imine **99** in a yield of 5.5% (Scheme 153).
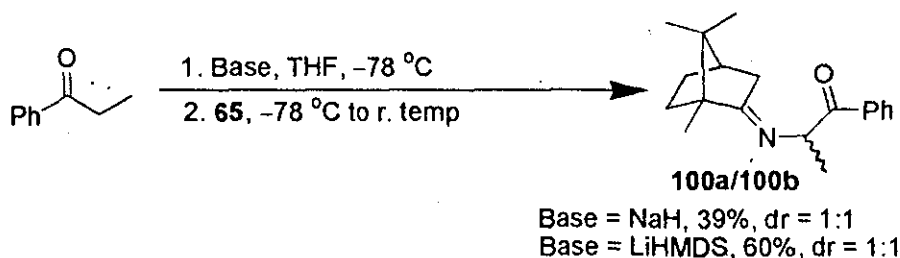
Scheme 153

(1*R*)-Camphor imines of (2*R*)- and (2*S*)-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.
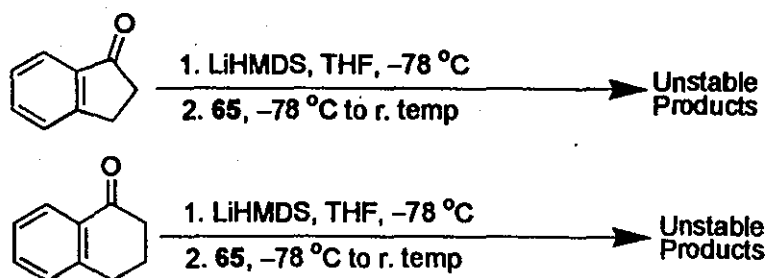
The reaction of (+)-camphoryl oxaziridine **65** with ketones was subsequently investigated. First, the reaction between oxaziridine **65** and propiophenone was attempted under various conditions. It was found that in the presence of triethylamine, under refluxing conditions in THF over three hours, 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).


Base = NaH, 39%, dr = 1:1
Base = LiHMDS, 60%, dr = 1:1

Scheme 154

The electrophilic amination of a number of different ketones using oxaziridine 65 was then attempted. Ketones were deprotonated using LiHMDS in THF at −78 °C and then treated with (+)-camphoryl oxaziridine 65 at between −78 °C and room temperature for between 5 and 20 hours. Both indan-1-one and α-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).

1. LiHMDS, THF, −78 °C
2. 65, −78 °C to r. temp → Unstable Products

1. LiHMDS, THF, −78 °C
2. 65, −78 °C to r. temp → Unstable Products

Scheme 155

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).

1. LiHMDS, THF, −78 °C
2. 65, −78 °C to r. temp

90a/90b   21%
dr = 1:1
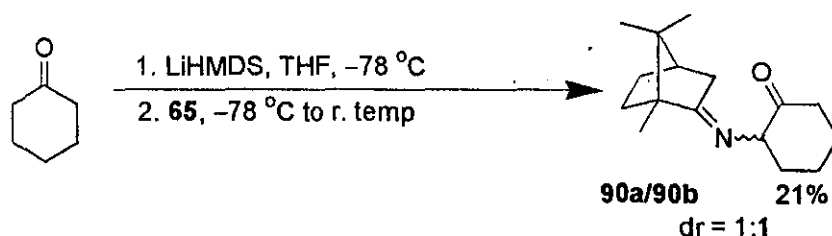
Scheme 156

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

enantiomeric excess of 0%. There is evidence (^{1}H and ^{13}C 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).
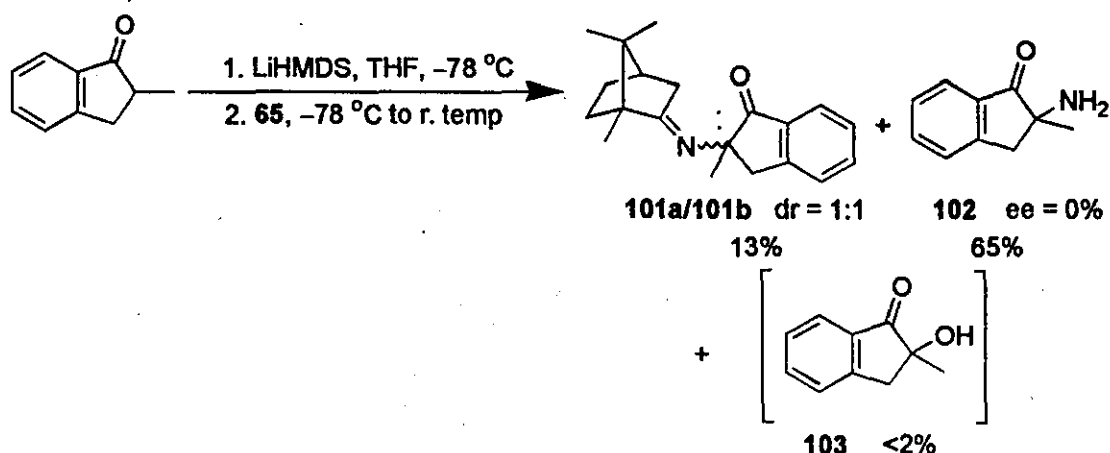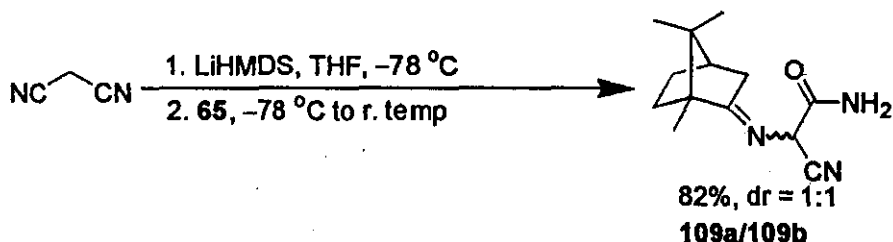

Scheme 157

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).
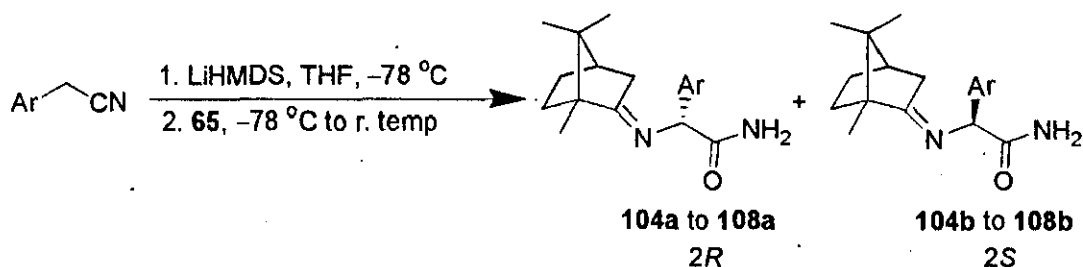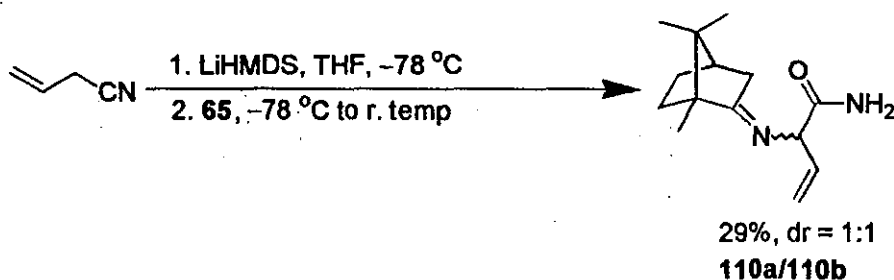

Scheme 158

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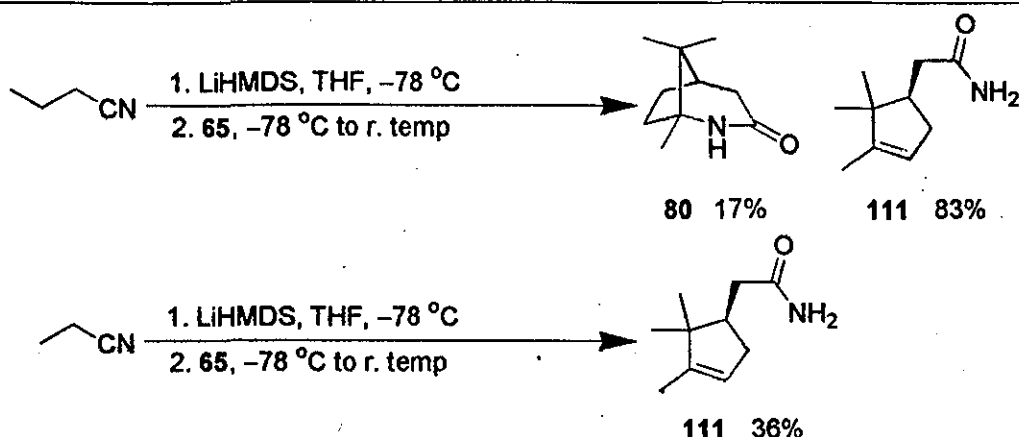

Scheme 160

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).
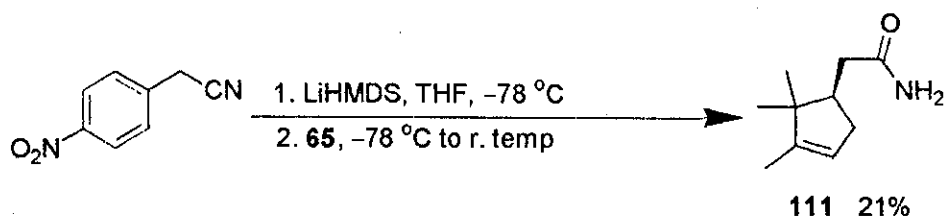

Scheme 161

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).

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).
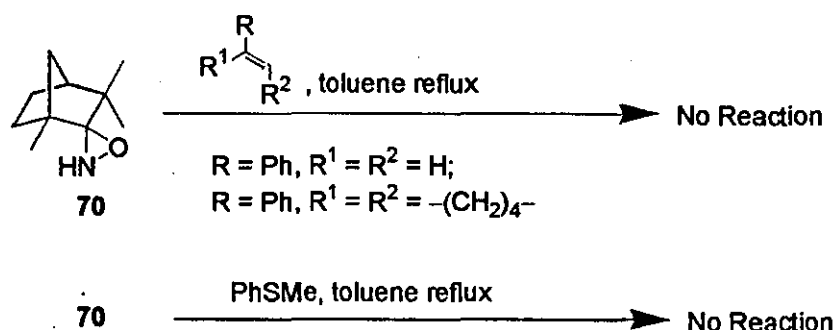

Scheme 163

(−)-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

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).
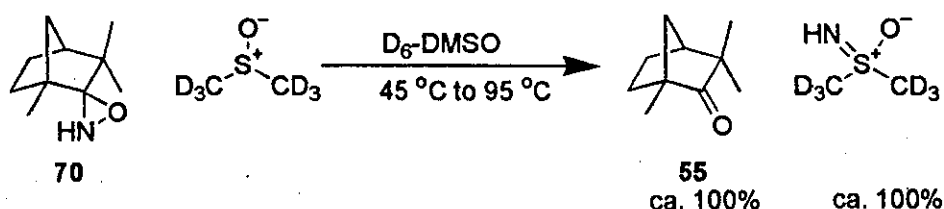

Scheme 164

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).
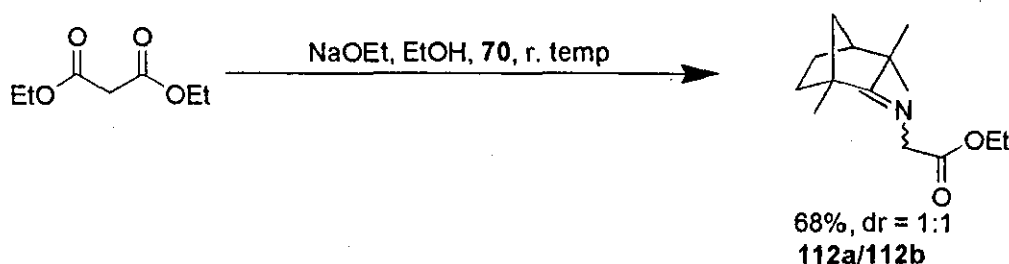
Scheme 165

As discussed previously in section 2.2.1, (–)-fenchyl oxaziridine **70** underwent decomposition during a variable temperature NMR experiment carried out in D_6-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 (1*R*)-(–)-fenchone **55**. Significant decomposition of the *NH*-oxaziridine began at 45 °C, and by 95 °C, conversion was complete. The spectrum of (1*R*)-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 ^{13}C 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 (1*R*)-fenchone **55**, the characteristic CD_3 septet from the D_6-DMSO solvent signal, but also a smaller signal at higher δ from what appears to be another septet possibly originating from another CD_3 signal. These observations can be explained if (–)-fenchyl oxaziridine **70** had reacted with D_6-DMSO to form the corresponding D_6-dimethylsulfoximine and (1*R*)-(–)-fenchone **55** (Scheme 166).

Scheme 166

If so, then this would also explain the presence of a broad singlet in the ^{1}H 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 D_6-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 D_8-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 ^{1}H 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 ^{1}H NMR and ^{13}C NMR spectra of the mixture of products (see appendices).

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.
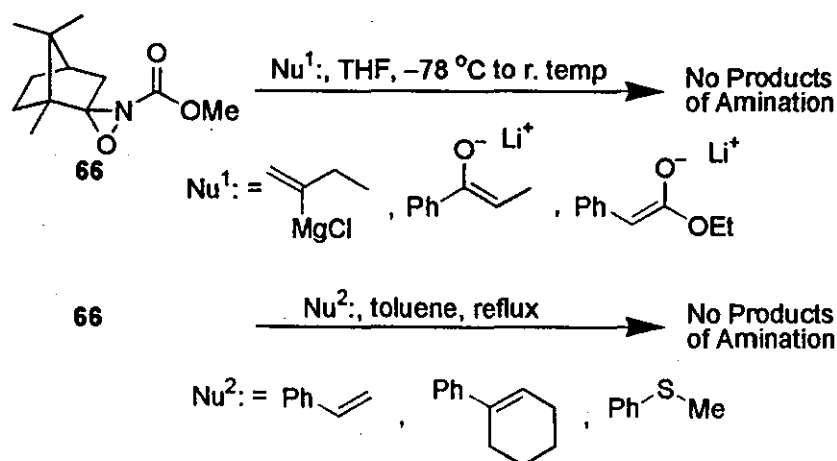
Scheme 167

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),[81, 82b] was investigated in order to see if we could bring about *N*-transfer.[136] If we could generate a diaziridinium salt *in situ* in the presence of

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).
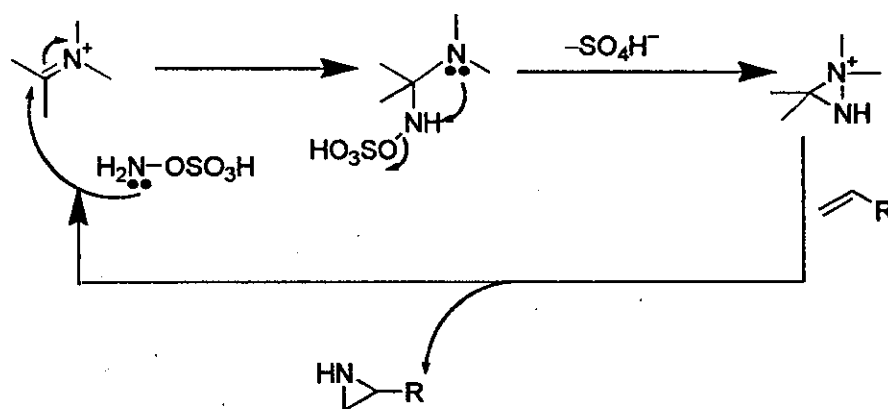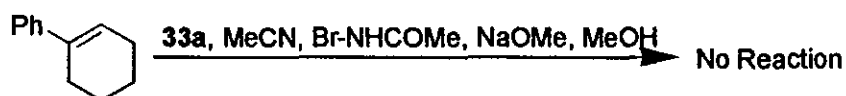

Scheme 168

1-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).

33a
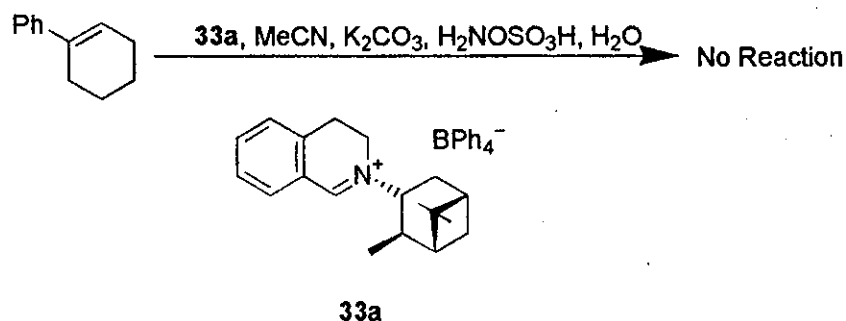
Scheme 169

If *N*-bromoacetamide is deprotonated, then the resulting amide anion can been 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.[137] 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 1-phenylcyclohexene in acetonitrile at −10 °C. It

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 °C, no reaction of the alkene, or destruction of the iminium catalyst was observed by tlc (Scheme 170).
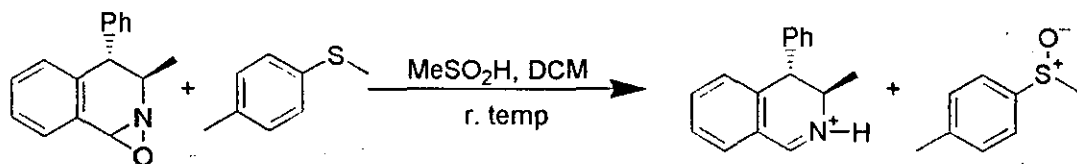

Scheme 170

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]
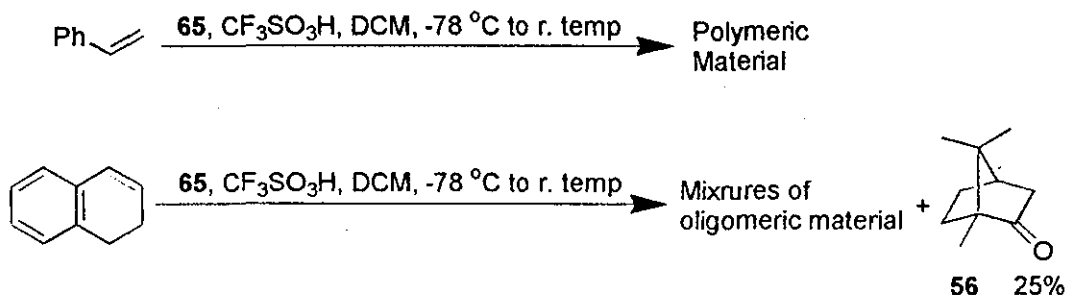

Scheme 171

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 trfluoromethane 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 (1*S*)-(+)-camphor oxime **62** in a yield of 35% was observed (Scheme 172).
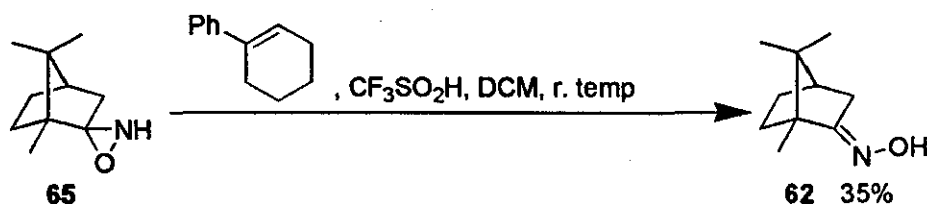
Scheme 172

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. (1*R*)-(+)-camphor **56** was also isolated from this reaction mixture in a yield o 25% (Scheme 173).
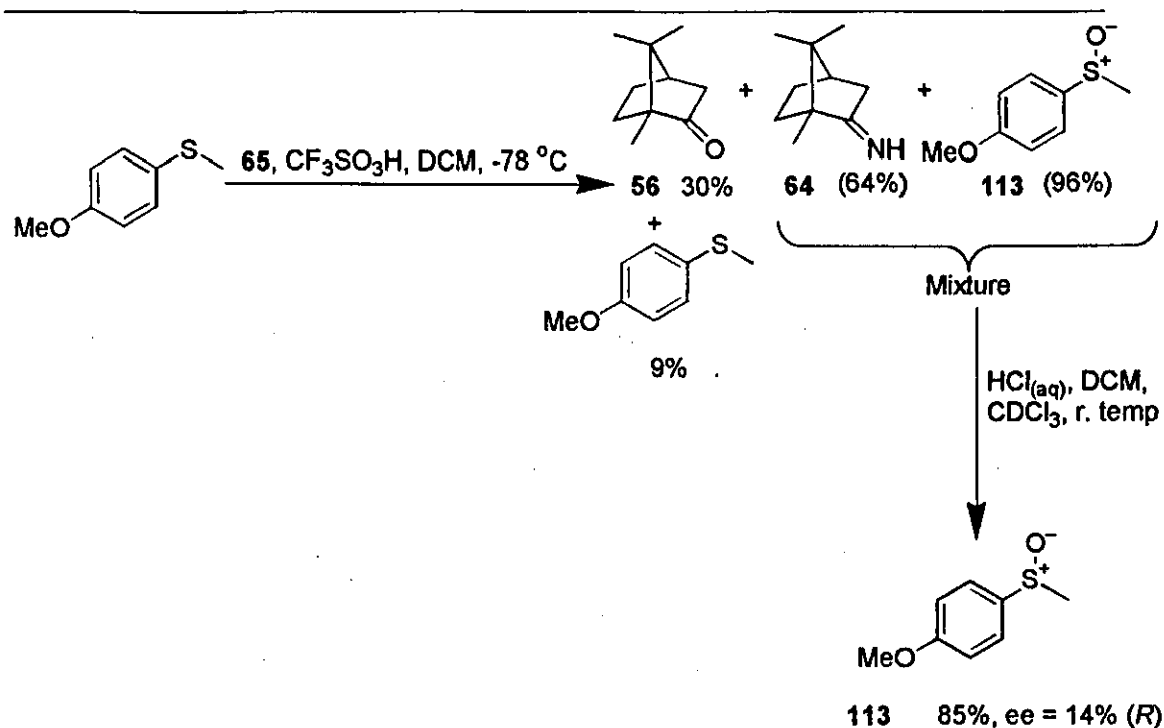

Scheme 173

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 °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%. (1*R*)-(+)-Camphor **56** was isolated in a yield of 30%. (1*R*)-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 ¹H 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).

Scheme 174

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 (1*S*)-(+)-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 that 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,

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

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

The attempted derivatisation of (−)-fenchyl oxaziridine **70** has given only poor yields of unstable N-functionalised products.

The reaction of (+)-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 °C) aryl acetonitriles has been shown to proceed in goods yield in most cases, but with little or no stereocontrol. Malononitrile has also been shown to react with (+)-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 (+)-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 *NH*-oxaziridine.

Investigations into the use of (–)-fenchyl oxaziridine **70** have been limited, however, **70** has been shown to react successful 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 Na_2CO_3) 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:-

δ = chemical shift (in parts per million)

J = coupling constant (in Hz)

s = singlet

d = doublet

tr = triplet

q = quartet

m = multiplet

br = 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

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 λ = 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 °C), refers to the temperature of the cooling medium rather than the internal temperature of the reaction itself.


(1*S*, 4*S*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)-methanesulfonyl Chloride, *(1S)-(+)-Camphorsulfonyl Chloride* 50
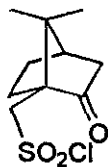
(1*S*)-(+)-Camphorsulfonic acid **49** (86.00 g, 0.370 mol) was heated (neat) to 40 °C in a two-necked round bottomed flask equipped with a reflux condenser and a drying tube (CaCl$_2$). Thionyl chloride (108 mL, 176 g, 1.48 mol) was then added from a dropping funnel over a period of 2 hours with stirring. Vigorous evolution of gas (HCl, SO$_2$) 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 hydrolyse 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: $[\alpha]^{25}_{D}$ = +31.2 (CHCl$_3$); mp 63-65 °C ;δ_{H} (250 MHz; CDCl$_3$) 4.30(1H, d, *J* = 14.6, RCHHSO$_2$Cl), 3.75(1H, d, *J* = 14.6, RCHHSO$_2$Cl), 2.50-2.39(2H, m, CH$_2$ 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]


(1*S*, 4*S*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)-methanesulfonamide, *(+)-*
Camphorsulfonamide **51**
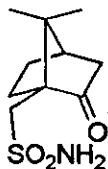
In a 1L three necked round bottomed flask equipped with a mechanical stirrer, a 100 mL addition funnel and a glass plug was placed concentrated ammonia (225 mL). The reaction mixture was cooled to 0 °C in an ice bath and stirred vigorously. A solution of (+)-camphorsulfonyl chloride **50** (25.0 g, 99.7 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 (MgSO$_4$) 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; CDCl$_3$) 5.75(2H, br.s, NH$_2$), 3.55(1H, d, *J* = 15.1, RCHHSO$_2$X), 3.16(1H, d, *J* = 15.1, RCHHSO$_2$X), 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]

(1*S*, 7*S*)-10,10-Dimethyl-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-ene-3,3-dione, *(–)-*
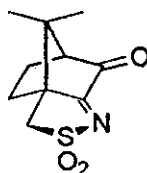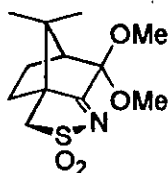*Camphorsulfonyl Imine* **52**
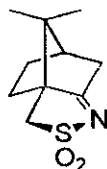
In a 500 mL round-bottomed flask equipped with a magnetic stirrer, Dean-Stark trap and reflux condenser were placed Amberlyst 15^R ion-exchange resin (2.4 g) and

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; δ_H (250 MHz; CDCl$_3$) 3.20(1H, d, J =13.3, RCHHSO$_2$R) 3.00(1H, d, J =13.3, RCHHSO$_2$R), 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-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]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 (MgSO$_4$) 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: $[\alpha]^{25}_D$ = –178.2 (acetone); mp 189-190 °C; Found%: C, 52.74; H, 5.83; N, 6.13 C$_{10}$H$_{13}$NO$_3$S requires%: C, 52.86; H, 5.77; N, 6.16; v_{max} (nujol)/cm^{-1} 1750, 1640, 1330, 1160; δ_H (400 MHz; CDCl$_3$) 3.46(1H, d, J =13.7, RCHHSO$_2$R), 3.24(1H, d, J =13.7, RCHHSO$_2$R), 2.79(1H, d, J =4.8, CH at bridgehead C4), 2.40-2.20(2H, m), 2.10-

1.80(2H, m), 1.17(3H, s, Me), 0.99(3H, s, Me); δ_C (100 MHz; CDCl₃) 18.3(Me), 20.1(Me), 22.2(CH₂), 27.9(CH₂), 44.6(C$_{quat}$), 50.0(CH), 59.0(CH₂, CH₂SO₂NR) 62.7(C$_{quat}$), 183.5(C$_{quat}$, C=N), 197.8(C$_{quat}$, C=O); Found: M⁺, 22706160 C₁₀H₁₃NO₃S requires 227.06161; *m/z* 245(M(NH₄)⁺). This compound showed identical spectral properties to the same compound, which was prepared previously.[106]

(1S, 7S)-10,10-Dimethyl-6,6-di(methoxy)-3λ⁶-thia-4-azatricyclo[5.2.1.0¹˒⁵]dec-4-ene-3,3-dione, *(+)-3,3-Dimethoxycamphorsulfonyl Imine* **1**

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; δ_H (400 MHz; CDCl₃) 3.46(3H, s, MeO), 3.38(3H, s, MeO), 3.16(1H, d, *J* =12.0, RCHHSO₂R), 2.97(1H, d, *J* =12.0, RCHHSO₂R), 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]

(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2,3-dione, *(1R)-(–)-Camphorquinone*
57
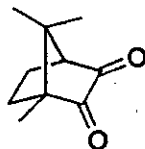
To (1R)-(+)-camphor **56** (100 g, 0.657 mol) in acetic anhydride (80 mL) was added finely powdered selenium dioxide (80.0 g, 0.72 mol) and the reaction mixture was refluxed for 2 hours after which more selenium dioxide (20.0 g, 0.180 mol) was added. The reaction mixture was refluxed for a further 2 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 (MgSO$_4$) 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; δ$_H$ (250 MHz; CDCl$_3$) 2.63(1H, d, J = 5.4), 2.27-2.07(1H, m), 2.01-184(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**
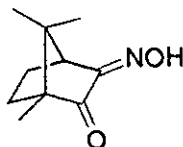
To a solution of hydroxylamine hydrochloride (2.4 g, 34.5 mmol) and sodium acetate (4.2 g, 51.2 mmol) in water (16 mL) was added (1R)-(–)-camphorquinone **57** (1.96 g,

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 (1*R*)-(+)-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; δ_C (63 MHz; CDCl$_3$) 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]

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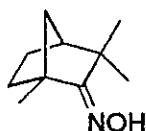

(1*R*)-(−)-Fenchone **55** (106 mL, 100 g, 657 mmol), hydroxylamine hydrochloride (100 g, 1439 mmol) and pyridine (80 mL, 78.2 g, 989 mmol) were heated under reflux in ethanol (1.0 L) for 5 hours. After the reaction vessel had cooled most of the ethanol in the reaction mixture was removed *in vacuo* 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 (1*R*)-(−)-fenchone oxime **61** in a 68% (75.0 g, 449 mmol) yield: mp 169-170 °C; δ_H (250 MHz; CDCl$_3$) 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); δ_C (63 MHz; CDCl$_3$) 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**
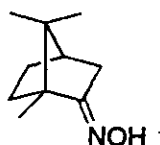
Hydroxylamine hydrochloride (100 g, 1439 mmol), (1R)-(+)-camphor **56** (100 g, 658 mmol) and pyridine (80 mL, 78.2 g, 989 mmol) were heated under reflux in ethanol (1.0 L) for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed *in vacuo*. Water was 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; δ_H (250 MHz; CDCl₃) 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), 1.51-141(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**
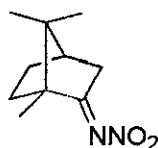

(1R)-(−)-Camphor oxime **62** (30 g, 180 mmol) in glacial acetic acid (900 mL) was treated with 5% aqueous sodium nitrite (450 mL). A bright yellow colour developed and dispersed over 30 minutes. After another 1.5 hours the crude product was precipitated as a white solid by the addition of water and isolated by filtration. After

drying under vacuum, the crude product was recrystallised from 95% ethanol to afford pure (1*R*)-(−)-camphor nitrimine **63** as a white crystalline solid in a 54% (19.0 g, 96.9 mmol) yield: mp 41-42 °C; ν_{max} (neat)/cm^{-1} 1645, 1569; δ_H (250 MHz; CDCl$_3$) 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; CDCl$_3$) 10.7(Me), 19.0(Me), 19.8(Me), 27.1(CH$_2$), 31.9(CH$_2$), 35.5(CH$_2$), 43.8(CH), 49.2(C$_{quat}$), 54.5(C$_{quat}$) 189.8(C$_{quat}$, C=N). This compound displayed identical spectral properties to that prepared previously.[117]

(1*R*, 4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-imine, *(1R)-Camphor Imine* 64
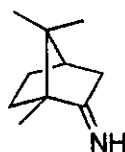
A solution of (1*R*)-(−)-camphor nitrimine **63** (10.0 g, 51.0 mmol) in dry tetrahydrofuran (100 mL) was treated at 0 °C with a slow stream of ammonia gas in the fumehood for 4 hours. The solvent was removed *in vacuo* keeping the water bath below 30 °C to give (1*R*)-camphor imine **64** as a pale yellow solid in a 100% (7.70 g, 51.0 mmol) yield: ν_{max} (DCM)/cm^{-1} 1666; δ_H (250 MHz; CDCl$_3$) 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; CDCl$_3$) 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

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

(1*R*, [1α, 2β(*S), 4α])-1,7,7-Trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], *(+)-Camphoryl Oxaziridine* 65**
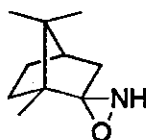

A solution of pure[119] 3-chloroperoxybenzoic acid (17.6 g, 102 mmol) in dry dichloromethane (600 mL) was cooled to between –30 °C and –40 °C causing some of the per-acid to crystallise out of the solution. On addition of a solution of (1*R*)-camphor imine **64** (15.4 g, 102 mmol) in dry dichloromethane (40 mL) to this solution over a period of 4-5minutes, 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 *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 *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 *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 ¹H NMR spectroscopy, however in this state the product decomposes slowly evolving ammonia gas over a few of days. Dissolution of the product in

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 (CHCl$_3$); 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; v_{max} (CDCl$_3$)/cm^{-1} 3202(NH); δ_H (250 MHz; CDCl$_3$) 4.22(1H$_A$, br.s, NH), 3.74(1H$_B$, br.s, NH), 2.33-2.21(1H$_{A+B}$, m, camphoryl *exo* C3), 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); δ_C (100 MHz; CDCl$_3$) 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$_{quat}$, oxaziridine), 89.7(C$_{quat}$, 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.

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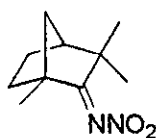

A solution of sodium nitrite (13.8 g, 200 mmol) in water (100 mL) was added to a solution of (1*R*)-(–)-fenchone oxime **61** (20.0 g, 120 mmol) in diethyl ether (320 mL) placed in a separatory funnel. A solution of 0.5 M sulfuric acid (200 mL) was then added with occasional vigorous swirling over 2 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$_2$SO$_4$) and the solvent removed *in vacuo*. The resulting solid was then purified by column chromatography (petroleum ether/ dichloromethane) over silica to give (1*R*)-fenchone nitrimine **68** as

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_{max} (neat)/cm^{-1} 1641(C=N), 1562(=N-NO$_2$); δ_H (250 MHz; CDCl$_3$) 2.03-1.52(6H$_{A+B}$, m), 1.48(1H$_A$, dd, J =10.5, 1.5), 1.37(1H$_B$, dd, J =10.6, 1.5), 1.30(3H$_{A+B}$, s, Me$_A$ and Me$_B$), 1.26(3H$_A$, s, Me), 1.23(3H$_B$, s, Me), 1.20(3H$_A$, s, Me), 1.17(3H$_B$, s, Me); δ_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]

(1*R*, 4*S*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-imine, *(1R)-Fenchone Imine* 69
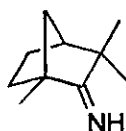
(1*R*)-Fenchone nitrimine (18.9 g, 96.4 mmol) in dry tetrahydrofuran (190 mL) was treated at 0 °C with a slow stream of ammonia gas in the fumehood for 5 hours. The solvent was removed *in vacuo* to give (1*R*)-fenchone imine as a pale yellow liquid in a 100% (14.6 g, 96.4 mmol) yield: v_{max} (neat)/cm^{-1} 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.

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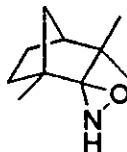

A solution of pure[119] 3-chloroperoxybenzoic acid (16.6 g, 96.2 mmol) in dry dichloromethane (500 mL) was cooled to between –30 °C and –40 °C and this caused some of the per-acid to crystallise out of the solution. On addition of a solution of (1*R*)-fenchone imine **69** (14.5 g, 96.0 mmol) in dry 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 *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 *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, 3x200 mL). The organic solution was dried (MgSO₄) and the solvent removed *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 *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 *endo/exo*

diastereoisomers. $[\alpha]^{25}{}_D$= –4.40 (CHCl₃); ν_{max} (neat)/cm⁻¹ 3199(NH); δ_H (250 MHz; CDCl₃) 3.81(1H$_A$, br.s, NH), 3.69(1H$_B$, br.s, NH), 1.91-1.01(7H$_{A+B}$, m), 0.92(9H, s, 3xMe), 0.90(3H, s, Me), 0.84(6H, s, Me); δ_C (100 MHz; CDCl₃) 13.0(Me), 14.1(Me), 22.4(Me), 22.6(Me), 23.3(Me), 23.4(Me), 25.3(Me), 31.1(CH₂), 31.7(CH₂), 39.8(C$_{quat}$), 41.1(CH₂), 41.8(CH₂), 46.56(C$_{quat}$), 46.60(C$_{quat}$), 47.2(CH), 47.4(CH), 92.9(C$_{quat}$), 93.4(C$_{quat}$) (one CH₂, and two C$_{quat}$ signals obscured presumably by overlap with another signal); Found: M⁺, 167.13090 C₁₂H₁₉NO₂ requires 167.13101; *m/z* 168(MH⁺), 167(M⁺), 152, 138,134, 124, 108, 95, 91, 81, 69, 67, 55.

(1*S*, 4*R*)-1-Oxo-2-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate, *(1R)-(+)-Camphorquinone Mononitrimine* 72
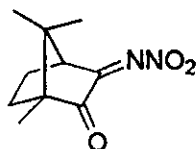
To a mixture of (1*R*)-(+)-camphorquinone monoxime 60 (500 mg, 2.76 mmol) and pyridine (250 μL, 224 mg, 3.09 mmol) in acetonitrile (10 mL) was added nitrosyl sulfuric acid (355 mg, 2.79 mmol) and the reaction mixture stirred for 1 hour at room temperature. When the reaction was complete (tlc), the reaction mixture was added to a solution of brine (40 mL) and extracted with dichloromethane (3x50 mL). The combined organic extracts were dried (MgSO₄) and the solvent removed *in vacuo* to give a yellow solid mixture which was purified by column chromatography to give (1*R*)-(+)-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 (CHCl₃); mp 46-47 °C; Found%: C, 57.24; H, 6.64; N, 13.04 C₁₀H₁₄N₂O₃ requires%: C, 57.13; H, 6.71; N, 13.32; ν_{max} (neat)/cm⁻¹ 1760(C=O), 1652(C=N), 1574(NNO₂); δ_H (250 MHz; CDCl₃) 2.90(1H$_A$, d, *J* =5.0, CH$_A$ at C1), 2.79(1H$_B$, d, *J* =4.7, CH$_B$ at C1), 2.27-2.19(1H$_{A+B}$, m), 1.95-1.64(3H$_{A+B}$, 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); δ_C (63 MHz; CDCl₃) 8.73, 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,

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, 135, 121, 120, 109, 107, 95, 94, 93, 82, 77, 67, 55.

(1R, 2'S, [1α, 2β(S'), 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)
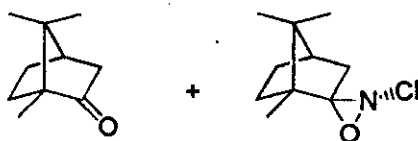

To a stirring cooled (–40 °C) solution of (+)-camphoryl oxaziridine **65** (4.0 g, 24.0 mmol) in dichloromethane (15 mL) was added hydrogen chloride in 1,4-dioxane (6 mL, 4.0 M, 24.0 mmol). A white precipitate appeared over the next 20 seconds and by 5 minutes (tlc) the reaction was complete. The reaction mixture was then diluted with dichloromethane (50 mL) and washed once with distilled water. The organic layer was then dried (MgSO$_4$) 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: $[\alpha]^{25}_{D}$= –160.6 (CHCl$_3$); mp 46-47 °C; Found%: C, 59.70; H, 8.13; N, 6.83 C$_{10}$H$_{16}$NOCl requires%: C, 59.55; H, 8.00; N, 6.83; ν_{max} (neat)/cm^{-1} No NH signal, 1469, 1371, 620(N-Cl); δ_{H} (250 MHz; CDCl$_3$) 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); δ_{C} (100 MHz; CDCl$_3$) 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; δ_{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 has been described previously.[138]

Tert-Butyl Hypochlorite
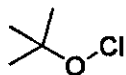
A solution of sodium hydroxide (80 g, 2.0 mol) in water (500 mL) was prepared in a 2 L three-necked round bottomed flask equipped with a gas inlet tube reaching to nearly the bottom of the flask, a gas outlet tube and a mechanical stirrer. The flask was placed in a water bath at 15-20 °C and *tert*-butyl 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 ($CaCl_2$) to give 72% (87 g, 0.72 mol) of crude *tert*-butyl hypochlorite which was subsequently shown by IR to be pure: v_{max} (neat)/cm^{-1} no broad OH signal from ^tBuOH at around 3500, 695(OCl). This compound was shown to exhibit the same spectral properties as the same compound, which was previously reported[126]. The title compound is best stored in a dark coloured bottle in the refrigerator.

(1*R*, 2'*S*, [1α, 2β(*S**), 4α])-2'-Chloro-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], *(−)-N-Chlorocamphoryl Oxaziridine* 73 (synthesis from ^tBuOCl in Et_2O)
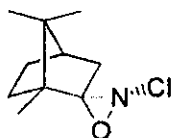
To a stirring cooled (−78 °C) solution of (+)-camphoryl oxaziridine **65** (500 mg, 2.99 mmol) in diethyl ether (23 mL) was added dropwise a solution of *tert*-butyl hypochlorite (340 mg, 3.13 mmol) in diethyl ether (7 mL). After 2 hours the reaction was complete (tlc), and the mixture was allowed to 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 (MgSO$_4$) 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; δ$_H$ (250 MHz; CDCl$_3$) 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.

(1*R*, [1α, 2β(*S), 4α])-2'-(Phenylsulfonyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine],** *(−)-N-(Phenylsulfonyl)camphoryl Oxaziridine* **59**
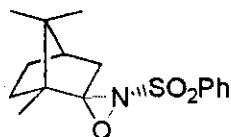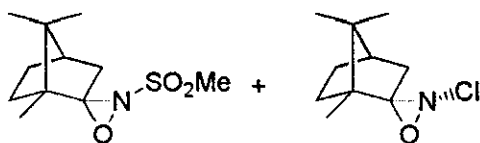

To a mixture of (+)-camphoryl oxaziridine **65** (200 mg, 1.20 mmol) and 4-dimethylamino pyridine (200 mg, 1.64 mmol) in dichloromethane (5 mL) was added benzenesulfonyl chloride (350 µL, 484 mg, 2.74 mmol) and the reaction mixture was stirred at room temperature for 10 days. After this period, the reaction 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 (MgSO$_4$) 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 give (–)-*N*-(phenylsulfonyl)camphoryl oxaziridine **59** in a 62% (227 mg, 0.738 mmol) yield: mp 132-134 °C; δ_H (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) ; δ_C (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]

(1*R*, [1α, 2β(*S**), · 4α])-2'-(Methanesulfonyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine] and (1*R*, 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; δ_H (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 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: $[\alpha]^{25}_D$ = −136.33 (CHCl$_3$); mp 62-64 °C; Found%: C, 54.36; H, 7.81; N, 5.58 C$_{11}$H$_{19}$NSO$_3$ requires%: C, 53.85; H, 7.81; N, 5.71; ν_{max} (neat)/cm^{-1} 1740, 1345(SO$_2$), 1152(SO$_2$); δ_H (250 MHz; CDCl$_3$) 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); δ_C (63 MHz; CDCl$_3$) 9.1, 18.8, 19.4, 26.6, 29.5, 35.2, 40.4, 44.5, 47.4, 50.1, 97.9; Found: M$^+$, 245.10886, C$_{13}$H$_{21}$NO$_3$ 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 (MgSO$_4$) 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.

(1*R*,   [1α,   2β(*S),   4α])-2'-(Methoxycarbonyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine],   *(–)N-(Methoxycarbonyl)camphoryl Oxaziridine* 66**
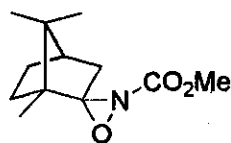
N-Alkoxycarbonyl oxaziridine **66** was synthesised according to the above procedure to give the title compound as a colourless solid in a 95% (1.28g, 5.69mmol) yield: $[\alpha]^{25}_D$ = –93.8 (CHCl₃); mp 78-80 °C; Found%: C, 64.16; H, 8.49; N, 6.13 $C_{12}H_{19}NO_3$ requires%: C, 63.98; H, 8.50; N, 6.22; ν_{max} (nujol)/cm⁻¹ 1764; δ_H (250 MHz; CDCl₃) 3.85(3H, s, MeO), 2.14(1H, ddd, *J* =14.7, 4.7 and 3.1, *exo* at C3), 1.93(1H, t, *J* =4.5, *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); δ_C (63 MHz; CDCl₃) 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⁺, 225.13674, $C_{12}H_{19}NO_3$ requires 225.13649; *m/z* 226(MH⁺), 225(M⁺), 210, 198, 197, 183, 182, 169, 168, 154, 150, 143, 140, 128, 124, 122, 115, 108, 96, 93, 81, 70, 67, 55.

(1*R*,   [1α,   2β(*S),   4α])-2'-(Ethoxycarbonyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine],   *(–)-N-(Ethoxycarbonyl)camphoryl Oxaziridine* 67**
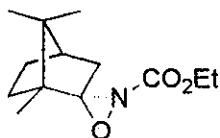

N-Alkoxycarbonyl oxaziridine **67** was synthesised according to the above procedure to give the title compound as a colourless oil in an 89% (1.27 g, 5.33 mmol) yield: $[\alpha]^{25}_D$ = –84.8 (CHCl₃); ν_{max} (neat)/cm⁻¹ 1769, 1736; δ_H (250 MHz; CDCl₃) 4.39-4.15(2H, m, MeCH₂O), 2.15(1H, ddd, *J* =14.6, 4.6 and 3.0, *exo* at C3), 1.93(1H, t, *J*

=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, CH_3CH_2O), 1.01(3H, s, Me), 0.93(3H, s, Me), 0.71(3H, s, Me); δ_C (63 MHz; $CDCl_3$) 8.8, 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, $C_{13}H_{21}NO_3$ requires 239.15214; *m/z* 239(M^+), 222, 211, 194, 182, 167, 152, 135, 124, 108.

(1R, [1α, 2β(S^*) and 2α(R^*), 4α])-3'-Phenyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-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)
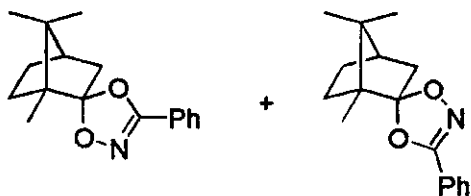
To a stirring solution of (+)-camphoryl oxaziridine **65** (500 mg, 2.99 mmol) and 4-dimethylamino pyridine (440 mg, 3.60 mmol) in dichloromethane (15 mL) was added benzoyl chloride (0.4 mL, 484 mg, 3.45 mmol) and the reaction mixture was stirred at room temperature for 2 hours. More 4-dimethylamino 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 ($MgSO_4$) 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: v_{max} (DCM)/cm^{-1} 1627, 1604; δ_H (250 MHz; $CDCl_3$) 7.82-7.75($2H_{A+B}$, m, Ar-H), 7.51-7.38($3H_{A+B}$, m, Ar-H), 2.43-2.33($1H_{A+B}$, m, *exo* at camphoryl C3) 2.09-1.70($4H_{A+B}$, m), 1.55-1.21($2H_{A+B}$, m)

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); δ_C (100 MHz; CDCl$_3$) 9.0(Me), 9.2(Me), 19.9(Me), 20.1(Me), 26.8(CH$_2$), 26.9(CH$_2$), 28.0(CH$_2$), 28.6(CH$_2$), 44.3(CH$_2$), 44.6(CH$_2$), 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 C$_{17}$H$_{21}$NO$_2$ 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; δ_H (250.13 MHz; CDCl$_3$) 4.22(1H$_A$, br.s, NH), 3.74(1H$_B$, br.s, NH), 2.33-2.21(1H$_{A+B}$, m), 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).

(1*R*, [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)
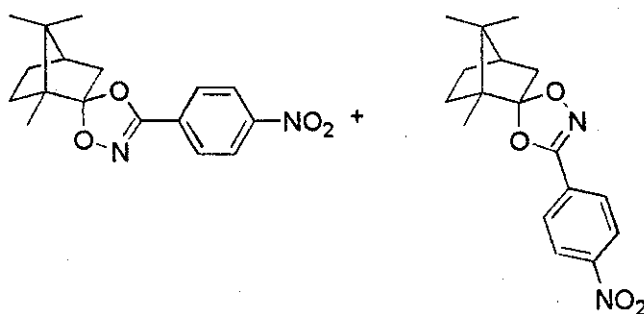

To a stirring solution of (+)-camphoryl oxaziridine **65** (500 mg, 2.99 mmol) and 4-dimethylamino pyridine (440 mg, 3.60 mmol) in dichloromethane (15 mL) was added a solution of 4-nitrobenzoyl chloride (620 mg, 3.34 mmol) in acetonitrile (4 mL). This reaction mixture was stirred at room temperature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

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 (MgSO$_4$) 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; v_{max} (DCM)/cm^{-1} 1626, 1593, 1526, 1347; δ_H (250 MHz; CDCl$_3$) 8.32-8.25 (2H$_{A+B}$, m, Ar-H), 7.99-7.90(2H$_{A+B}$, m, Ar-H), 2.44-2.36(1H$_{A+B}$, m, camphoryl *exo* at C3), 2.07-1.27(6H$_{A+B}$, m), 1.12(3H, s, Me), 1.06(3H, s, Me), 0.92(3H, s, Me), .090(3H, s, Me), 0.88(3H, s, Me), 0.86(3H, s, Me); δ_C (100 MHz; CDCl$_3$) 9.3(Me), 9.5(Me), 20.25(Me), 20.34(Me), 20.38(Me), 20.41(CH$_3$), 27.1(CH$_2$), 27.24(CH$_2$), 28.24(CH$_2$), 29.0(CH$_2$), 44.7(CH$_2$) 44.9(CH$_2$), 45.00(CH), 45.1(CH), 48.7(C$_{quat}$), 48.8(C$_{quat}$), 53.4(C$_{quat}$), 53.7(C$_{quat}$), 124.26(CH, Ar), 124.29(CH, Ar), 126.5(C$_{quat}$), 127.0(C$_{quat}$), 127.7(CH, Ar), 127.8(CH, Ar), 129.75(C$_{quat}$), 129.82(C$_{quat}$), 149.6(C$_{quat}$, Ar, C-NO$_2$), 156.9(C$_{quat}$, C=N on dioxazole ring), 157.3(C$_{quat}$, C=N on dioxazole ring), one aromatic C-NO$_2$ signal obscured presumably due to overlap with other signals; Found: MH$^+$, 317.14920. C$_{17}$H$_{20}$N$_2$O$_4$[H]$^+$ requires 317.15012; *m/z* 317 (MH$^+$), 316(M$^+$), 217, 166, 164, 153, 152, 148, 126, 108, 95, 81, 55.

**(1*R*, 5*S*)-1,8,8-Trimethyl-3-azabicyclo[3.2.1]octan-2-one, *(−)-α-Camphidone* 78**
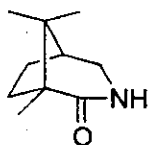
A solution of (1*R*)-(+)-camphor **56** (1.0 g, 6.58 mmol) and hydroxylamine-*O*-sulfonic acid (1.5 g, 13.3 mmol) in formic acid (30 mL) was heated under reflux for 20 hours. The cooled reaction mixture was then added to a solution of brine (30 mL) and the

mixture was extracted with dichloromethane (3x50 mL). The combined organic extracts were then washed with aqueous sodium hydroxide (1.0 M, 2x75 mL), dried (MgSO$_4$) 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; δ$_H$ (250 MHz; CDCl$_3$) 6.25(1H, br.s), 3.42(1H, dd, *J* =11.1 and2.7, *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); δ$_C$ (63 MHz; CDCl$_3$) 13.3(Me), 19.2(Me), 22.9(Me), 27.6(CH$_2$), 37.8(CH$_2$), 42.1(C$_{quat}$), 43.5(CH), 47.0(CH$_2$), 52.1(C$_{quat}$), 178.8(C$_{quat}$, RCONHR). This product showed spectral properties identical to those previously reported for this compound.[113, 127]

**(1*R*, 5*S*)-1,8,8-Trimethyl-3-(4-nitrobenzoyl)-3-azabicyclo[3.2.1]octan-2-one, *(–)N-(4-Nitrobenzoyl)-α-camphidone* 79**
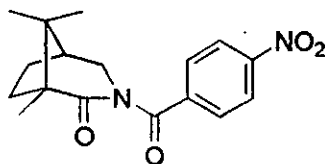
To a mixture of (–)-α-camphidone **78** (100 mg, 0.599 mmol) and pyridine (0.5 mL, 489 mg, 6.18 mmol) in chloroform (4 mL) was added 4-nitrobenzoyl chloride (120 mg, 0.647 mmol), and the reaction mixture was stirred under reflux for eight hours. More 4-nitrobenzoyl chloride (70 mg, 0.377 mmol) was added 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 (MgSO$_4$) 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 (CHCl$_3$); 186-187 °C; ν$_{max}$ (DCM)/cm^{-1} 1700, 1670, 1528, 1350; δ$_H$ (250 MHz; CDCl$_3$) 8.25-8.20(2H, m, Ar-H),

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; CDCl$_3$) 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. C$_{17}$H$_{20}$N$_2$O$_4$ 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.
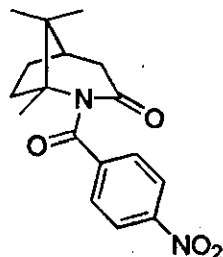
(1*R*, 5*S*)-1,8,8-Trimethyl-2-azabicyclo[3.2.1]octan-3-one, *Isomer of α-Camphidone, Isomeric Lactam* **80**
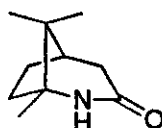
To a cold (–22 °C) solution of (1*R*)-(–)-camphor oxime **62** (5.38 g, 32.2 mmol) in pyridine (25 mL) was added methanesulfonyl chloride (5.0 mL, 4.89 g, 58.1 mmol) and the reaction mixture was stirred for 3 hours. The temperature was then raised and at approximately 10 °C, a strong exothermic reaction 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 (MgSO$_4$) 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 (1*R*, 5*S*)-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; CDCl$_3$) 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]

(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 (MgSO$_4$) 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: $[\alpha]^{25}_D$ = –63.39; mp 124-126 °C; v_{max} (DCM)/cm^{-1} 1707, 1670, 1530, 1349; δ_H (250 MHz; CDCl$_3$) 8.28-8.22(2H, m, Ar-H), 7.92-7.86(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); δ_C (63 MHz; CDCl$_3$) 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$^+$, 316.142112. C$_{17}$H$_{20}$N$_2$O$_4$ 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.

**Benzohydroximinoyl chloride**
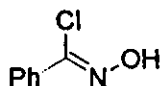
To a stirring solution of benzaldehyde oxime (45.66 g, 0.300 mol) in DMF (250 mL) at 25-30 °C was added about 10-20% of 40.1 g (0.300 mol) *N*-chlorosuccinimide. As the reaction did not self-initiate within the first 10 minutes (as indicated by a slight temperature rise), 20 mL of gas from the head space 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 (CaSO$_4$) and the solvent removed *in vacuo* to give benzohydroximinoyl chloride in a 75% (34.9 g, 0.224 mol) yield: mp 50-52°C; v_{max} (DCM)/cm^{-1} 3320(OH), 1600(C=N). This compound showed identical spectral properties to the same compound, which was previously described.[130]

(1*R*)-*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**)
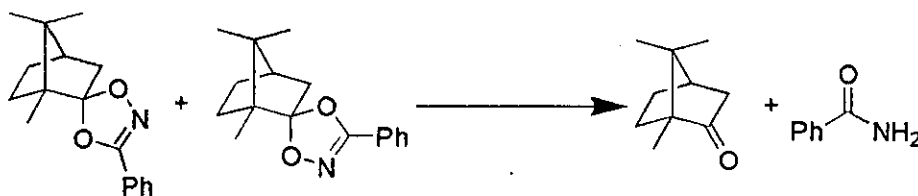
A mixture of isomeric *endo/exo*-5-camphoryl-3-phenyl-1,4,2-dioxazoles **76a/76b** (100 mg, 0.369 mmol) obtained from the reaction of (+) camphoryloxaziridine **65** and benzoyl chloride was dissolved in ethyl acetate (5 mL). Palladium on charcoal was then added to this mixture and the flask was sealed 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; δ_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$_2$); ν_{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; δ_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, [1α, 2β(S^*), 4α])-2'-Acetyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], *(–)-N-Acetylcamphoryl Oxaziridine* **82**
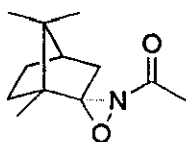
To (+)-camphoryl oxaziridine **65** (250 mg, 1.50 mmol) in dichloromethane (5 mL) at room temperature was added acetic anhydride (450 μL, 487 mg, 4.77 mmol) and the reaction mixture was stirred overnight at room temperature. This mixture was then

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: $[\alpha]^{20}_D$ = −82.21 (CHCl₃); v_{max} (DCM)/cm⁻¹ 1732(C=O); δ_H (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); δ_C (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(C$_{quat}$, oxaziridine C), 188.1(C$_{quat}$, Acetyl C=O); Found: M⁺, 209.1466. C₁₂H₁₉NO₂ requires 209.14157; *m/z* 209 (M⁺), 192, 167, 152, 134, 124, 108, 95, 93, 81, 67, 55.

(1*R*, [1α, 2β(*S**) 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**)
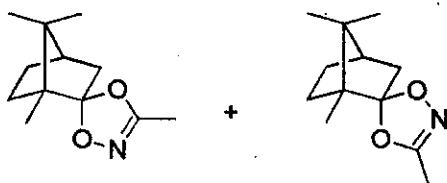

(−)-*N*-Acetylcamphoryl oxaziridine **82** (194 mg, 0.929 mmol) was stirred overnight in dichloromethane (5 mL) with silica gel (3.0 g) at room temperature, after which time the mixture showed no oxidising properties (tlc/KI). The solvent was removed *in vacuo* and to the remaining mixture further solvent 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: δ_H (250 MHz; CDCl₃) 4.27-4.15(1H$_{A+B}$, m),

3.93(3H$_A$, s, Me-dioxazole C3), 3.93(3H$_B$, s, Me-dioxazole C3), 3.80-3.60(4H$_{A+B}$, m), 3.43-3.13(2H$_{A+B}$, 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_C (63 MHz; CDCl$_3$) 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; v_{max} (DCM)/cm^{-1} 1660; Found: M$^+$, 209.1462. C$_{12}$H$_{19}$NO$_2$ requires 209.14157; *m/z* 210(MH$^+$), 209(M$^+$), 153, 152, 138, 126, 108, 95, 83, 68, 55.

(1R, [1α, 2β(S^*), 4α])-2'-Benzoyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine] and (1R, [1α, 2β(S^*) and 2α(R^*), 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)
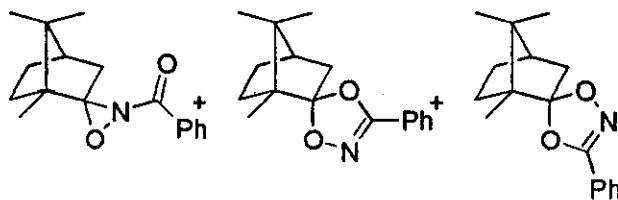

To a stirring solution of (+)-camphoryl oxaziridine **65** (250 mg, 1.50 mmol) in dichloromethane (5.0 mL) at room temperature was added benzoic anhydride (900 μL, 1.08 g, 4.77 mmol) and the reaction mixture was stirred for three days. When the reaction was complete (tlc), the reaction mixture was diluted to 75 mL with dichloromethane, washed with aqueous sodium hydroxide (1.0 M, 4x50 mL), dried (MgSO$_4$) 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 ^{1}H NMR spectroscopy to consist of a mixture of benzoic anhydride, *N*-benzoylcamphoryl 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*-benzoylcamphoryl 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 ^{1}H 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 *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$_{C/D}$, then this signal comes from either C or D: ν_{max} (neat)/cm^{-1} 1786(anhydride C=O), 1726(anhydride C=O and oxaziridine C=O), 1626 and 1599 (dioxazole C=N); δ_H (250 MHz; CDCl$_3$) 8.18-8.13(4H$_A$, m, Ar-H), 8.07-8.02(2H$_B$, m, Ar-H), 7.81-7.74(2H$_{C+D}$, m, Ar-H), 7.71-7.37(6H$_A$ and 3H$_{B+C+D}$, m, Ar-H), 2.43-2.25(1H$_{B+C+D}$, m), 2.16-1.19(6H$_{B+C+D}$, m), 1.12(3H$_{C/D}$, s, Me), 1.06(3H$_{C/D}$, s, Me), 0.91(3H$_{C/D}$, s, Me), 0.90(3H$_B$, s, Me), 0.88(6H$_{C/D}$, s, 2xMe), 0.87(3H$_{C/D}$, s, Me), 0.85(3H$_B$, s, Me), 0.77(3H$_B$, s, Me).

(1*R*, [1α, 2β(*S**) and 2α(*R**), 4α])-3'-Phenyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,5'-[1,4,2]dioxazoles], *endo/exo*-5-*Camphoryl-3-phenyl-1,4,2-dioxazoles* **76a/76b** (isomerisation of *N*-benzoylcamphoryl oxaziridine **84** to phenyl dioxazoles)
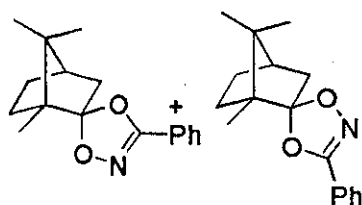

The crude mixture prepared previously containing benzoic anhydride, *endo/exo*-5-camphoryl-3-phenyl-1,4,2-dioxazoles **76a/76** and *N*-benzoylcamphoryl oxaziridine **84** (632 mg) was stirred at room temperature in dichloromethane (10 mL) with silica gel (5.0 g) overnight. When no oxidising products 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

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: v_{max} (neat)/cm^{-1} 1788(anhydride C=O), 1727(anhydride C=O), 1626 and 1600 (dioxazole C=N); δ_H (250 MHz; CDCl$_3$) 8.18-8.11(4H$_A$, m, Ar-H), 7.82-7.75(2H$_{B+C}$, m, Ar-H), 7.72-7.38(6H$_A$ and 3H$_{B+C}$, m, Ar-H), 2.43-2.32(1H$_{B+C}$, m), 2.10-1.64(4H$_{B+C}$, m), 1.55-1.25(2H$_{B+C}$, m), 1.13(3H$_{B/C}$, s, Me), 1.06(3H$_{B/C}$, s, Me), 0.91(3H$_{B/C}$, s, Me), 0.89(6H$_{B+C}$, s, 2xMe), 0.88(3H$_{B+C}$, 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, [1α, 2β(S*), 4α])-2'-(Diphenylphosphinic)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], *(–)N-(Diphenylphosphinic)camphoryl Oxaziridine* **85**
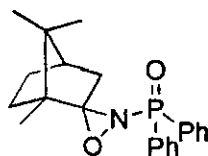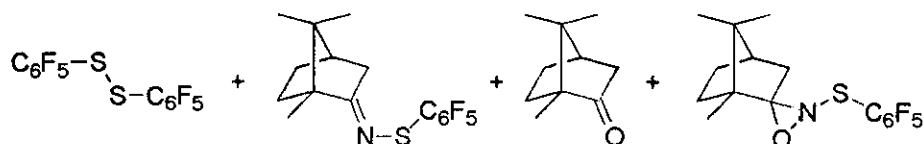

To a solution of (+)-camphoryl oxaziridine **65** (2.00 g, 12.0 mmol) and 4-dimethylaminopyridine (1.60 g, 13.1 mmol) in dichloromethane (25 mL) was added diphenylphosphinic chloride (2.45 mL, 3.04 g, 12.8 mmol), and the reaction mixture was stirred at room temperature overnight. More 4-dimethylaminopyridine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

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 (MgSO$_4$) 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: $[\alpha]^{25}_D$ = –6.649 (CHCl$_3$); ν_{max} (neat)/cm^{-1} 1440(P-Ar), 1215(P=O); δ_H (250 MHz; CDCl$_3$) 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); δ_C (63 MHz; CDCl$_3$) 9.3(Me), 18.4(Me), 19.4(Me), 26.5(CH$_2$), 29.7(CH$_2$), 36.6(CH$_2$), 44.3(CH), 47.1(C$_{quat}$), 49.8(C$_{quat}$), 98.8(C$_{quat}$), 128.4(CH, d, *J* =9.5), 128.6(CH, d, *J* =8.4), 128.8(C$_{quat}$, part of a multiplet which was obscured by the doublets at 128.39 and 128.59), 130.6(C$_{quat}$, 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$^+$, 367.170100 C$_{22}$H$_{26}$NO$_2$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, (1*R*, 4*S*)-*N*1-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-yliden)pentafluorobenzene-1-sulfenamide, (1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one and (1*R*, [1α, 2β(*S**), 4α])-2'-(Pentafluorobenzenesulfenyl)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine], *Dipentafluorophenyl Disulfide, ( )-(S-Pentafluorphenyl)camphor Thiooxime* **86,** *(1R)-( )-Camphor* **56** *and (–)-N-(Pentafluorophenylsulfenyl)camphoryl Oxaziridine* **87**

To a mixture of (+)-camphoryl oxaziridine **65** (250 mg, 1.50 mmol) and dry pyridine (250 μL, 245mg, 3.10 mmol) in dry dichloromethane (5 mL) was added with stirring pentafluorobenzene sulfenyl 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 (MgSO$_4$) 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; v_{max} (DCM)/cm^{-1} 1540, 1503, 1487, 1092, 1023, 978, No C-H signals; δ_H (250 MHz; CDCl$_3$) No signal; δ_C (63 MHz; CDCl$_3$) 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, C$_{13}$H$_{21}$NO$_3$ requires 397.92817; *m/z* 399(MH$^+$), 398(M$^+$), 231, 200, 199, 180, 155, 149, 117, 69; followed by (+)-(*S*-pentafluorphenyl)camphor thiooxime **86** as a light brown liquid 10% (54 mg, 0.156 mmol) yield: $[\alpha]^{25}_D$ = +35.58 (CHCl$_3$); v_{max} (DCM)/cm^{-1} 1637, 1512,1488, 1094, 982; δ_H (250 MHz; CDCl$_3$) 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); δ_C (63 MHz; CDCl$_3$) 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 C$_{16}$H$_{16}$NSF$_5$ requires 349.09257; *m/z* 350(MH$^+$), 348(M$^+$), 334, 306, 293, 200, 199, 155, 150, 133, 123, 109, 94, 81, 69, 67, 55; then (1*R*)-(+)-camphor **56** as a white solid in a 28% (63 mg, 0.414 mmol) yield: mp 178-180 °C; δ_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 described previously,[138] and finally, (−)-*N*-(pentafluorophenylsulfenyl)camphoryl oxaziridine **87** as a colourless oil that

solidified upon standing overnight in a 41% (222 mg, 0.608 mmol) yield: $[\alpha]^{25}_D$ = −3.6 (CHCl₃); mp 85-87 °C; ν_{max} (nujol)/cm^{-1} 1680, 1641, 1377, 1260, 1148, 1084, 761, 747, 720, 695; δ_H (250 MHz; CDCl₃) 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); δ_C (63 MHz; CDCl₃) 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 C₁₆H₁₆NSF₅ 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.

(1*R*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one, (1*R*, [1α, 2α(*S**), 4α])-2'-(Methoxycarbonyl)-1,3,3-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridine] and (1*R*, 2'*R* and 2'*S*, [1α, 2α(*S**), 4α])-2'-Chloro-1,3,3-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridines], *(1R)-(–)-Fenchone* 55, *N-(Methoxycarbonyl)fenchyl Oxaziridine* 88 *and N-Chlorofenchyl Oxaziridines* 89a/89b
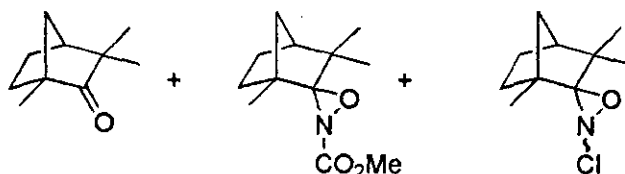

To an ice-cooled stirring solution of dry pyridine (300 μL, 293 mg, 3.71 mmol) in dry dichloromethane was added methyl chloroformate (200 μL, 245 mg, 2.59 mmol) followed by a solution of (–)-fenchyl oxaziridine 70 (250 mg, 1.50 mmol) in dry dichloromethane (1.0 mL). The reaction mixture was then allowed 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

hydroxide (1.0 M, 3x40 mL). The organic solution was dried (MgSO$_4$) 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): ν_{max} (neat)/cm^{-1} 1575(N=O), 666(N-Cl); δ_H (250 MHz; CDCl$_3$) 2.14-1.44(6H$_A$ and 6H$_B$, m), 1.38(1H$_A$, dd, J=10.4, 1.6), corresponding signal from B too small and obscured by methyl signal at 1.26, 1.26(3H$_A$ and 1H$_B$, s), 1.10(3H$_B$, s), 0.89(3H$_A$, s), 0.82(3H$_A$, s), 0.77(3H$_B$, s); δ_C (63 MHz; CDCl$_3$) As this product was unstable it was not possible to obtain a reliable ^{13}C 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 (1*R*)-(−)-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 (1*R*)-(−)-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: ν_{max} (nujol)/cm^{-1} 1767(N-CO$_2$Me), 1740(fenchone C=O); δ_H (250 MHz; CDCl$_3$) 3.74(3H$_A$, s, MeO), 2.08-2.05(1H$_A$, m), 1.86-1.05(6H$_A$ and 7H$_B$, m), 1.06(3H$_A$, s, Me), 0.96(3H$_A$, s, Me), 0.93(3H$_B$, s, Me), 0.89(3H$_A$, s, Me), 0.81(6H$_B$, s, 2xMe); Found: M$^+$, 225.13640 C$_{12}$H$_{19}$NO$_2$ requires 225.13648; *m/z* 226(MH$^+$), 225(M$^+$), 208, 152, 134, 123, 93, 84, 81, 69, 55.

(1*R*, 2'*R* and 2'*S*, [1α, 2α(*S), 4α])-2'-Chloro-1,3,3-trimethylspiro[bicyclo[2.2.1]heptane-2,3'-oxaziridines],** *N-Chlorofenchyl Oxaziridines* **89a/89b**
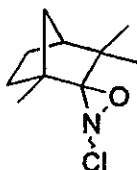
A solution of *tert*-butyl hypochlorite (0.34 g, 3.13 mmol) in diethyl ether (7 mL) was added dropwise to a cooled (–78 °C) stirring solution of fenchone oxaziridine (500 mg, 2.99 mmol) in diethyl ether (25 mL). The solution was allowed to warm to room temperature over a period of 1 hour, and stirred 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_H (250 MHz; CDCl$_3$) 2.14-1.44(6H$_A$ and 6H$_B$, m), 1.38(1H$_A$, dd, J=10.4, 1.6), corresponding signal from isomer B was too small and obscured by methyl signal at 1.26, 1.26(3H$_A$ and 1H$_B$, s), 1.10(3H$_B$, s), 0.89(3H$_A$, s), 0.82(3H$_A$, s), 0.77(3H$_B$, s) This compound showed identical properties to that prepared previously by the action of methyl chloroformate upon fenchone oxaziridine in the presence of pyridine.

(2*R*)- and (2*S*)- 2-{[(1*R*, 4*S*)-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-cyclohexenyloxytrimethylsilane and (+)-camphoryloxaziridine)
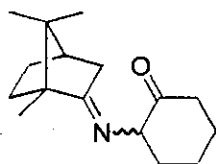
To a stirring cooled (–78 °C) stirring solution of 1-cyclohexenyloxytrimethylsilane (730 µL, 639 mg, 3.75 mmol) in dry THF (10 mL) was added methyllithium (3.75 mL, 1.0 M in THF/cumene (10/90), 3.75 mmol) dropwise. After stirring at –78 °C for 30 minutes, a solution of (+)-camphoryl oxaziridine **65** (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 (1*R*)-camphor imines of (2*R*)- and (2*S*)-aminocyclohexanone **90a/90b** present in a 1:1 ratio and formed in an 8% (74.2 mg, 0.300 mmol) yield; δ_H (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 C3$_{A+B}$ and cyclohexanone C6$_B$), 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

‚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.

(1*R*, 4*S*)-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)
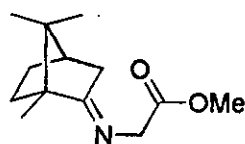
Imine **91** was synthesised according to the above procedure in a 77% (257 mg, 1.16 mmol) yield in a reaction time of 3 hours; v_{max} (neat)/cm⁻¹ 1743, 1674; δ_H (250 MHz; CDCl₃) 4.07(2H, s, RO₂CCH₂NR), 3.70(3H, s, MeO₂CR), 2.31(1H, dt, *J* =16.8 and 3.9, *exo* at C3), 1.99-1.62(4H, m), 1.45-1.35(1H, 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 reported[140].

(1*R*, 4*S*)-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)
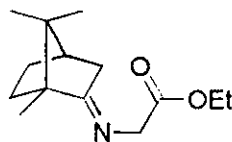
Imine **92** was synthesised according to the above procedure in a 66% (237 mg, 1.00 mmol) yield in a reaction time of 3 hours: ν_{max} (neat)/cm^{-1} 1743 (CO, ester), 1686 (CN, imine): δ_H (250 MHz; CDCl$_3$) 4.18 (2H, q, J = 7.2, MeCH$_2$O); 4.09(2H, s, RO$_2$CCH$_2$NR$_2$), 2.34(1H, dt, J = 17.7 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); δ_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]

(1*R*,   4*S*)-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 LiHMDS as a base)
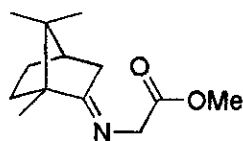

To a stirring cooled (–78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL, 1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added a solution of dimethyl malonate (170 μL, 197 mg, 1.49 mmol) dropwise in dry THF (1 mL). After stirring at –78 °C for 20 minutes a solution of (+)-camphoryl oxaziridine **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 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

(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: v_{max} (neat)/cm^{-1} 1743, 1674; δ_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, *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 reported.[140]

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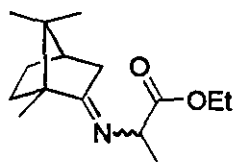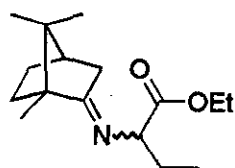

Imines **93a/93b** were synthesised according to the general procedure for the reaction of dialkyl malonates with (+)-camphoryl oxaziridine **65** in the presence of sodium ethoxide. The reaction time was 4 hours. Imines **93a/93b** were formed in an 89% (330 mg, 1.31 mmol) yield, and found by ^{1}H NMR spectroscopy to be present in a 1:1 ratio: v_{max} (neat)/cm^{-1} 1740(C=O), 1683(C=N); δ_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); δ_C (63 MHz; CDCl$_3$) 11.3, 13.9, 14.0, 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(RCO$_2$Et), 172.89(RCO$_2$Et), 184.2(C=N), 184.3(C=N); Found: M$^+$, 251.18836 C$_{15}$H$_{25}$NO$_2$ requires 251.18853; *m/z* 252(MH$^+$), 251(M$^+$), 236, 222, 179, 178, 162, 152, 150, 135, 122, 109, 95, 83, 70, 55.

(2R)- and (2S)-Ethyl 2-{[(1R, 4S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yliden]amino}butanoate, *(1R)-Camphor Imines of Ethyl (2R)- and (2S)-Amino Butyrate* **94a/94b** (reaction between diethyl ethylmalonate 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 ^{1}H NMR spectroscopy to be present in a 1:1 ratio: v_{max} (neat)/cm^{-1} 1740(C=O), 1684(C=N); δ_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$_A$, 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); δ_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.

(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**)
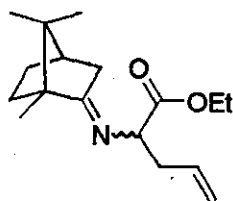
Imines **95a/95b** were synthesised according to the general procedure for the reaction of dialkyl malonates with (+)-camphoryl oxaziridine **65** in the presence of sodium ethoxide. The reaction time was 4 hours. Imines **95a/95b** were formed in 80% (332mg, 1.20mmol) yield, and found by ^{1}H NMR spectroscopy to be present in a 1:1 ratio: ν_{max} (neat)/cm^{-1} 1740(C=O), 1684(C=N); δ_H (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(both 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); δ_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-Pheny2-{[(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**)
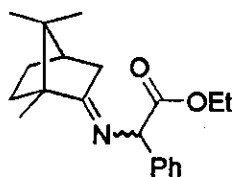
Imines **96a/96b** were synthesised according to the general procedure for the reaction of dialkyl malonates with (+)-camphoryl oxaziridine **65** in the presence of sodium ethoxide. The reaction time was 24 hours. The starting material (diethyl phenylmalonate) was recovered in 32% (112 mg, 0.474 mmol) yield: δ_H (250 MHz; CDCl$_3$) 7.68-7.61(2H, m, Ar-H), 7.42-7.34(3H, m, Ar-H), 4.40-4.20(3H, m, MeCH$_2$-O [keto and enolic forms] and CHPh(CO$_2$Et)$_2$), 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 ^{1}H NMR spectroscopy to be present in a 1:1 ratio: ν_{max} (neat)/cm^{-1} 1742(C=O), 1682(C=N); δ_H (250 MHz; CDCl$_3$) 7.54-7.47(2H and 2H, m, Ar-H), 7.45-7.22(3H and 3H, m, Ar-H), 5.06(1H$_A$, s, =N-CHPhCO$_2$R), 5.05(1H$_B$, s, =N-CHPhCO$_2$R), 4.15(2H$_A$, q, J =7.2, MeCH$_2$OCOR), 4.14(2H$_B$, q, J =7.1, MeCH$_2$OCOR), 2.48-2.36(1H$_A$, m), 2.30-2.18(1H$_B$, 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$_A$, t, J =7.2, CH$_3$CH$_2$OCOR) and 1.19(3H$_B$, t, J =7.1, CH$_3$CH$_2$OCOR), 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); δ_C (63 MHz; CDCl$_3$) 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(RCO$_2$Et), 172.1(RCO$_2$Et), this mixture contained approximately 10% impurities which made the assignment of some of the smaller (eg. CH and C$_{quat}$) ^{13}C NMR signals difficult to do with confidence, as a result of this, eleven ^{13}C 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 C$_{20}$H$_{27}$NO$_2$ requires 313.20418; *m/z*

314(MH⁺), 313(M⁺), 284, 265, 252, 241, 240, 206, 192, 179, 164, 157, 136, 118, 107, 105, 79, 77, 69, 55.

(3*R*)- and (3*S*)-3-{[(1*R*, 4*S*)-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)
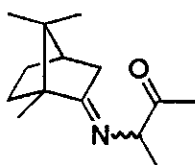

Sodium (100 mg, 4.35 mmol) was added to dry ethanol (6 mL) and the solution was stirred until the effervescence had ceased and all of the sodium had reacted. After allowing the solution to cool down to room temperature, a solution of (+)-camphoryl oxaziridine 65 (300 mg, 1.80 mmol) in ethanol (1 mL) 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 (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 gel to give (1*R*)-camphor imines of (3*R*)- and (3*S*)-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: v_{max} (neat)/cm⁻¹ 1715(C=O), 1681(C=N); δ_H (250 MHz; CDCl₃) 4.09-3.93(1H$_{A+B}$, m), 3.90-3.77(2H, m, impurity), 2.40-2.25(1H$_{A+B}$, 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); δ_C (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)(NR$_2$) signals of the two diastereoisomers; Found: M$^+$, 221.1780 C$_{14}$H$_{23}$NO 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)
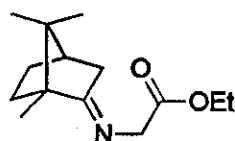
To a stirring cooled (−78 °C) solution of lithium bis(trimethylsilyl)amide (1.55 mL, 1.0 M in THF, 1.55 mmol) in dry THF (5 mL) was added ethyl acetoacetate (190 μL, 194 mg, 1.49 mmol). After stirring at −78 °C for 30 minutes a solution of (+)-camphoryl oxaziridine **65** (270 mg, 1.62 mmol) in dry THF (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 (MgSO$_4$) 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: δ$_H$ (250 MHz; CDCl$_3$) 4.18(2H, q, *J* =7.1, CH$_3$CH$_2$OR), 4.09-4.08(2H, m, =N-CH$_2$CO$_2$R), 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, CH$_3$CH$_2$OR), 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, 164, 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]

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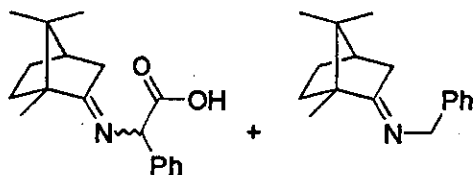

To a cooled (−78 °C) stirring solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.50 mL, 1.50 mmol) in dry diethyl ether was added ethyl phenylacetate (238 µL, 245 mg, 1.49 mmol) in diethyl ether (1 mL). After 30 minutes at −78 °C, a solution of (+)-camphoryl oxaziridine **65** (250 mg, 1.50 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 (MgSO$_4$) 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; δ_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 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; δ_H (250 MHz; CDCl$_3$) 4.22(1H$_A$, br.s, NH), 3.74(1H$_B$, br.s, NH), 2.33-2.21(1H$_{A,B}$, m, camphoryl *exo* C3), 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); 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**.

This compound was followed by the (1*R*)-camphor imine of benzylamine **99** as a pale yellow oil in 5.5% (20 mg, 0.0829 mmol) yield: v_{max} (neat)/cm^{-1} 1685(C=N); δ_H (250 MHz; CDCl$_3$) 7.17-7.34(5H, m, ArH), 4.47(2H, q$_{ab}$, 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); δ_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 (1*R*)-camphor imines of (2*R*)- and (2*S*)-phenylalanine **98a/98b** were isolated as a yellow oil in a yield of 12.0% (51.2 mg, 0.180 mmol). Imines **98a/98b** were subsequently shown by ^{1}H NMR spectroscopy to be present in a ratio of 1:1: v_{max} (neat)/cm^{-1} 3029(Ar), 2958(CO$_2$H), 1771(C=O, from CO$_2$H), 1683(C=N); δ_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 **98a/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 **98a/98b**.

(2*R*)- and (2*S*)-1-Phenyl-2-{[(1*R*, 4*S*)-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 (+)-camphoryl oxaziridine **65** and propiophenone with NaH base)
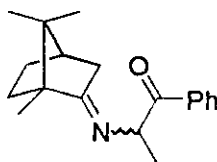
To a stirring cooled (–78 °C) mixture consisting of sodium hydride (60 mg of 60% dispersion in mineral oil, 1.50 mmol) in dry THF (5 mL) was added propiophenone (200 μL, 202 mg, 1.50 mmol) dropwise in dry THF (2 mL). After stirring at –78 °C for 45 minutes, the effervescence had ceased and a solution of (+)-camphoryl

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 (MgSO$_4$) 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 ^{1}H NMR spectroscopy to be an inseparable mixture of (1*R*)-camphor imines of (2*R*)- and (2*S*)-amino propiophenone **100a/100b** present in a 1:1 ratio and in 39% (164 mg, 0.580 mmol) yield: δ$_H$ (250 MHz; CDCl$_3$) 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(NR$_2$)(COAr)), 4.72(1H$_B$, q, *J* =6.8, MeCH(NR$_2$)(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, CH$_3$CH(NR$_2$)(COAr)), 1.47(3H$_B$, d, *J* =6.8, CH$_3$CH(NR$_2$)(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 (+)-camphoryl oxaziridine **65** with propiophenone using LiHMDS as a base.

(2*R*)- and (2*S*)-1-Phenyl2-{[(1*R*, 4*S*)-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 (+)-camphoryl oxaziridine **65** and propiophenone with LiHMDS base)
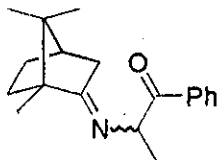

To a stirring cooled (–78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL, 1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added propiophenone (200 µL,

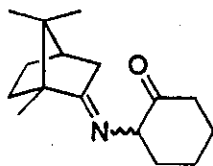202 mg, 1.50 mmol) dropwise in dry THF (1 mL). After stirring at −78 °C for 30 minutes a solution of (+)-camphoryl oxaziridine **65** (250 mg, 1.50 mmol) in dry THF (1 mL) was added, and the reaction mixture was allowed to reach room temperature over a period of 2 hours. The reaction mixture was then 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 (MgSO$_4$). 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 ^{1}H NMR spectroscopy to be an inseparable mixture of (1*R*)-camphor imines of (2*R*)- and (2*S*)-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); δ_H (250 MHz; CDCl$_3$) 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(NR$_2$)(COAr)), 4.72(1H$_B$, q, *J* =6.8, MeCH(NR$_2$)(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, CH$_3$CH(NR$_2$)(COAr)), 1.47(3H$_B$, d, *J* =6.8, CH$_3$CH(NR$_2$)(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); δ_C (63 MHz; CDCl$_3$) 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(CH$_2$), 27.3(CH$_2$), 31.5(CH$_2$), 32.0(CH$_2$), 35.9(CH$_2$), 36.0(CH$_2$), 43.0(C$_{quat}$), 43.2(C$_{quat}$), 43.8(CH), 43.9(CH), 63.6(CH, CHMe(COAr)(NR$_2$)), 63.7(CH, CHMe(COAr)(NR$_2$)), 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(CHRNR$_2$) signals and two camphoryl C$_{quat}$ signals were too small to be identified with any confidence; Found: M$^+$, 283.1933 C$_{19}$H$_{25}$NO requires 283.19360; *m/z* 284(MH$^+$), 283(M$^+$), 220, 178, 172, 148, 122, 105, 95, 77, 69, 55.

(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)-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 (MgSO$_4$) 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 ^{1}H NMR spectroscopy to be present in a 1:1 ratio: v_{max} (neat)/cm^{-1} 1716(C=O), 1686(C=N); δ_H (250 MHz; CDCl$_3$) 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 C3$_{A+B}$ and cyclohexanone C6$_B$), 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); δ_C (63 MHz; CDCl$_3$) 11.25(Me), 11.3(Me), 18.8(Me), 19.0(Me), 19.4(Me), 19,5(Me), 22.7(CH$_2$), 23.1(CH$_2$), 23.1(CH$_2$), 27.2(CH$_2$), 27.2(CH$_2$), 31.5(CH$_2$), 32.18(CH$_2$), 35.22(CH$_2$), 35.3(CH$_2$), 35.8(CH$_2$), 40.8(CH$_2$), 40.9(CH$_2$), 43.76(CH), 43.80(CH), 46.8(C$_{quat}$), 47.3(C$_{quat}$), 53.3(C$_{quat}$), 54.0(C$_{quat}$), 68.9(CH, CHR(COR)(NR$_2$)), 69.2(CH,

CHR(COR)(NR$_2$)), 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 CH$_2$ signal obscured, probably due to overlap; Found: M$^+$, 247.1937 C$_{16}$H$_{25}$NO requires 247.19360; *m/z* 248(MH$^+$), 247(M$^+$), 219, 191, 178, 163, 151, 136, 111, 109, 95, 69, 55.

(2*R*)- and (2*S*)-2-Methyl-2-{[(1*R*, 4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}-2,3-dihydro-1*H*-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)
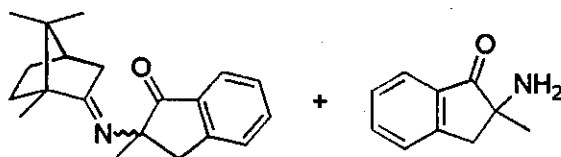

To a stirring cooled (−78 °C) solution of lithium bis(trimethylsilyl)amide (1.50 mL, 1.0 M in THF, 1.50 mmol) in dry THF (5 mL) was added a solution of 2-methyl-1-indanone (206 μL, 219 mg, 1.50 mmol) in dry THF (1 mL). After stirring at −78 °C for 30 minutes, a solution of (+)-camphoryl oxaziridine **65** (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 (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 (methanol/dichloromethane) over silica gel. The first fraction was an inseparable mixture of the (1*R*)-camphor imines of (2*R*)- and (2*S*)-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 (^{1}H NMR spectroscopy) of 1:1: v_{max} (neat)/cm^{-1} 3433(OH), 1718(C=O), 1676(C=N), 1608 (C=O); δ_H (250 MHz; CDCl$_3$) 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$_A$,

ddd, 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$_{A+B}$, m), 1.55(3H$_A$, s, CH$_3$CR(NR$_2$)(COAr)), 1.52(3H$_B$, s, CH3CR(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; δ_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: ν_{max} (neat)/cm^{-1} 3355 and 3304(primary NH$_2$), 1716(C=O), 1608(Ar C=C); δ_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); δ_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.

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.

(2*R*)- and (2*S*)-2-Phenyl-2-{[(1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}ethanamide, *(1R)-Camphor Imine of (2R)- and (2S)-Phenylglycine Amides* **104a/104b** (reaction between benzyl cyanide and (+)-camphoryl oxaziridine **65**).
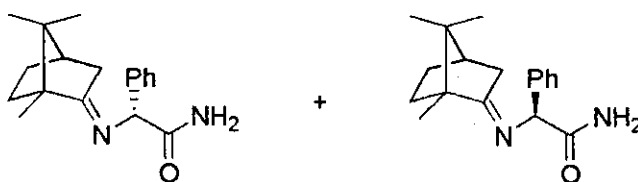
Imino amides **104a/104b** were synthesised according to the above procedure in a overall reaction time of 4.5 hours. The (1*R*)-camphor imine of (2*R*)-phenylglycine amide **104a** was first eluted, to give a colourless solid in a 32% (137 mg, 0.482 mmol) yield: $[\alpha]^{25}_D$ = −87 (CHCl₃); mp 131-133 °C; Found%: C, 76.02; H, 8.48; N, 9.60 C₁₈H₂₄N₂O requires%: C, 76.02; H, 8.51; N, 9.85; ν_{max} (neat)/cm⁻¹ 3438(NH), 3170(NH), 1696(C=O amide), 1651(C=N); δ_H (400 MHz; CDCl₃) 7.48(1H, br s, RCONH₂), 7.20-7.43(m, 5H, ArH), 6.26(1H, br s, RCONH₂), 4.78(1H, s,

PhCH(CONH$_2$)(NR$_2$)), 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); δ$_C$ (100 MHz; CDCl$_3$) 11.6(Me), 19.3(Me), 19.9(Me), 27.5(CH$_2$), 32.1(CH$_2$), 36.3(CH$_2$), 44.2(CH), 47.5(C$_{quat}$), 54.9(C$_{quat}$), 68.3(CH, PhCH(CONH$_2$)(NR$_2$)), 127.6(CH, Ar), 127.8(CH, Ar), 128.7(CH, Ar), 139.9(C$_{quat}$, Ar-alkyl), 176.0(C$_{quat}$, RCONH$_2$)), 185.5(C$_{quat}$, C=N); Found: M$^+$, 284.18987 C$_{18}$H$_{24}$N$_2$O requires 284.18942; *m/z* 285(MH$^+$), 284(M$^+$), 241, 224, 212, 198, 184, 172, 156, 135, 118, 106, 91, 79, 69, 55, 41. The (1*R*)-camphor imine of (2*S*)-phenylglycine amide **104b** was next isolated as a colourless solid in 46% (196 mg, 0.690 mmol) yield: [α]^{25}$_D$ = +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; ν$_{max}$ (neat)/cm^{-1} 3435(NH), 3200(NH), 1700(C=O amide), 1654(C=N); δ$_H$ (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$_2$)), 2.00(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); δ$_C$ (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$_2$)), 127.2(CH, Ar), 127.4(CH, Ar), 128.3(CH, Ar), 139.2(C$_{quat}$, Ar-alkyl), 175.5(C$_{quat}$, RCONH$_2$), 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%.

(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**)
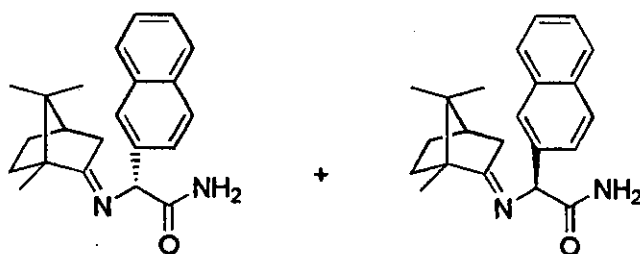

Imino amides **105a/105b** were synthesised according to the above procedure in a overall reaction time of 4.5 hours. The (1R)-camphor imine of (2R)-2'-naphthylglycine amide **105a** was first eluted, to give a colourless solid in a 27% (135 mg, 0.404 mmol) yield: $[\alpha]^{25}_D = -91$ (CHCl$_3$); mp 159-162 °C; v_{max} (neat)/cm^{-1} 3428(NH), 1692(C=O amide), 1652(C=N); δ_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, *exo* at camphor C3), 1.89(1H, t, $J = 4.2$, camphor C4), 1.83-1.61(2H, m), 1.56(1H, d, $J = 17.5$, *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 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: $[\alpha]^{25}_D = +115$ (CHCl$_3$); mp 135-150 °C; ; Found%: C, 79.12; H, 7.85; N, 8.36 C$_{22}$H$_{26}$N$_2$O requires%: C, 79.01; H, 7.84; N, 8.38; v_{max} (neat)/cm^{-1} 3429(NH), 1694(C=O amide), 1651(C=N); δ_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), 5.68(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); δ_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,

19.7, 27.2, 27.4, 31.8, 32.1, 36.1, 36.5, 43.90, 43.94, 47.2, 47.9, 53.5, 54.7, 68.1(CH, ArCH(CONH$_2$)(NR$_2$)), 68.7(CH, ArCH(CONH$_2$)(NR$_2$)), 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(C$_{quat}$, RCONH$_2$), 176.0(C$_{quat}$, RCONH$_2$), 185.7(C$_{quat}$, C=N), 186.1(C$_{quat}$, 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$^+$, 334.20384 C$_{22}$H$_{26}$N$_2$O requires 334.20451; *m/z* 335(MH$^+$), 334(M$^+$), 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%.

(2*R*)- and (2*S*)-2-Naphthalen-1-yl-2-{[(1*R*,4*S*)-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**)
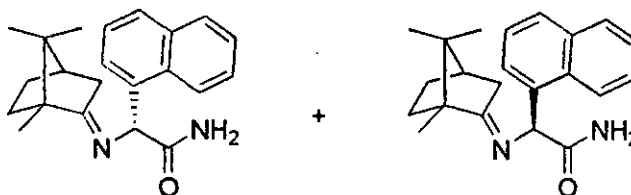

Imino amides **106a/106b** were synthesised according to the above procedure in a overall reaction time of 4.5 hours. The (1*R*)-camphor imine of (2*R*)-1'-naphthylglycine amide **106a** was first eluted, to give a colourless solid in a 31% (154 mg, 0.461 mmol) yield: [α]$^{25}_D$ = –127 (CHCl$_3$); mp 155-158 °C; Found%: C, 78.94; H, 7.89; N, 8.39 C$_{22}$H$_{26}$N$_2$O requires%: C, 79.01; H, 7.84; N, 8.38; ν$_{max}$ (neat)/cm^{-1} 3420(NH), 1696(C=O amide), 1653(C=N); δ$_H$ (250 MHz; CDCl$_3$) 8.42(1H, d, *J* = 8.5, Ar-H), 7.72-7.83 (2H, m, ArH), 7.63(1H, br.s, RCONH$_2$), 7.36-7.56(4H, m, Ar-H), 6.39(1H, br.s, RCONH$_2$), 5.45(1H, s, ArCH(CONH$_2$)(NR$_2$)), 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

signal at 0.77(3H, s, Me); δ_C (63 MHz; CDCl$_3$) 11.4, 18.9, 19.6, 27.0, 31.4, 36.1, 43.9, 47.1, 54.6, 65.2(ArCH(CONH$_2$)(NR$_2$)), 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(C$_{quat}$, Ar), 134.0(C$_{quat}$, Ar), 136.6(C$_{quat}$, Ar), 175.6(RCONH$_2$), 185.3(C=N); Found: M$^+$, 334.20483 C$_{22}$H$_{26}$N$_2$O requires 334.20451; *m/z* 334(M$^+$), 290, 222, 185, 172, 155, 141, 127, 115, 95, 69, 55, 41. The (1*R*)-camphor imine of (2*S*)-1'-naphthylglycine amide **106b** was next eluted, to give a colourless solid in 53% (266 mg, 0.796 mmol) yield: [α]$^{25}_D$ = +133 (CHCl$_3$); mp 190-192 °C; Found%: C, 78.64; H, 7.80; N, 8.40 C$_{22}$H$_{26}$N$_2$O requires%: C, 79.01; H, 7.84; N, 8.38; ν$_{max}$ (neat)/cm^{-1} 3429(NH), 3196(NH), 1697(C=O amide), 1651(C=N); δ_H (250 MHz; CDCl$_3$) 8.41-8.44(1H, m, Ar-H); 7.73-7.84(3H, m, 2xAr-H and 1x RCONH$_2$), 7.36-7.58(4H, m, Ar-H), 6.00(1H, br.s, RCONH$_2$), 5.50(1H, br.s, ArCH(CONH$_2$)(NR$_2$)), 1.99-1.56(3H, m) 1.50-1.18(2H, m), 1.08-0.56(2H, m) this signal overlaps signals at1.07(3H, s, Me) and 0.85(3H, s, Me), 0.28(3H, s, Me); δ_C (63 MHz; CDCl$_3$) 11.5, 19.1, 19.2, 27.3, 32.0, 36.8, 43.9, 48.0, 54.5, 65.7(ArCH(CONH$_2$)(NR$_2$)), 125.0(CH, Ar), 125.3(CH, Ar), 125.4(C$_{quat}$, Ar) 125.7(CH, Ar), 126.0(CH, Ar), 126.2(CH, Ar), 128.3(CH, Ar), 128.7(CH, Ar), 131.6(C$_{quat}$, Ar), 134.0(C$_{quat}$, Ar), 175.4(RCONH$_2$), 186.0(C=N); Found: M$^+$, 334.20420 C$_{22}$H$_{26}$N$_2$O 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%.

(2*R*)- and (2*S*)-2-(4-Chlorophenyl)-2-{[(1*R*,4*S*)-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**)
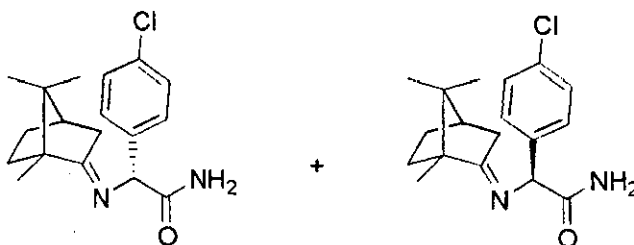
Imino amides **107a/107b** were synthesised according to the above procedure in a overall reaction time of 5 hours. The (1*R*)-camphor imine of (2*R*)-(4-chlorophenyl)glycine amide **107a** was first eluted, to give a pale yellow oil in 35% (165 mg, 0.518 mmol) yield: $[\alpha]^{25}_D$ = −113 (CHCl$_3$); v$_{max}$ (neat)/cm^{-1} 3429(NH), 1694(C=O amide), 1653(C=N); δ_H (250 MHz; CDCl$_3$) 7.46(1H, br.s, RCONH$_2$), 7.37-7.33(2H, m, Ar-H), 7.29-7.25(2H, m, Ar-H), 6.13(1H, br.s, RCONH$_2$), 4.73(1H, s, ArCH(CONH$_2$)(NR$_2$)), 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); δ_C (63 MHz; CDCl$_3$) 11.1, 18.8, 19.4, 27.0, 31.6, 35.9, 43.7, 47.0, 54.5, 67.1(ArCH(CONH$_2$)(NR$_2$)), 128.4(CH, Ar), 128.5(CH, Ar), 133.2(C$_{quat}$, Ar), 137.1(C$_{quat}$, Ar), 174.9(C$_{quat}$, RCONH$_2$), 185.3(C$_{quat}$, C=N). The (1*R*)-camphor imine of (2*S*)-(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 (CHCl$_3$); mp 145-156 °C; Found%: C, 67.86; H, 7.19; N, 8.75 C$_{18}$H$_{23}$N$_2$OCl requires%: C, 67.81; H, 7.27; N, 8.79; v$_{max}$ (neat)/cm^{-1} 3430(NH), 3200(NH), 1694(C=O amide), δ_H (250 MHz; CDCl$_3$) 7.53(1H, br.s, RCONH$_2$), 7.37-7.34(2H, m, Ar-H), 7.29-7.23(2H, m, Ar-H), 5.61(1H, br.s, RCONH$_2$), 4.76(1H, s, ArCH(CONH$_2$)(NR$_2$)), 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); δ_C (63 MHz; CDCl$_3$) 11.3, 18.9, 19.3, 27.2, 31.8, 36.2, 43.7, 47.6, 54.2, 67.7(ArCH(CONH$_2$)(NR$_2$)), 128.4(CH, Ar), 131.2(C$_{quat}$, Ar), 135.9(C$_{quat}$, Ar), 173.2(RCONH$_2$) 185.4(C=N), one aromatic CH signal obscured probably due to overlap with another signal; Found: M$^+$, 318.15068 C$_{18}$H$_{23}$N$_2$OCl requires 318.1497; *m/z* 335(MH$^+$), 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%.

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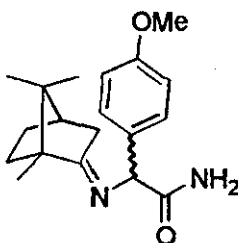

Imino amides **108a/108b** were synthesised according to the above procedure in a overall reaction time of 7 hours. Title imino amides **108a/108b** were isolated as an inseparable mixture of diastereoisomers, and as a pale-yellow oil in 76% (352 mg, 1.12 mmol) overall yield. Imino amides **108a/108b** were subsequently shown by ^{1}H NMR spectroscopy to be present in a 1:1 ratio; v_{max} (neat)/cm^{-1} 3250(NH), 3190(NH), 1693(C=O), 1510(p-disubst benzene ring); δ_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=CR$_2$)), 4.69(1HB, s, ArCH(CONH$_2$)(N=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); δ_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), 46.95(C$_{quat}$), 47.90(C$_{quat}$), 54.03(C$_{quat}$), 54.19(C$_{quat}$), 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$_{quat}$, Ar-C-R), 131.92(C$_{quat}$, Ar-C-R), 158.56(C$_{quat}$, C=N), 158.66(C$_{quat}$, C=N), 176.12(C$_{quat}$, RCONH$_2$), 176.22(C$_{quat}$, 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$_{quat}$ signals for the aromatic C-

OMe position; Found: M$^+$, 314.19907 $C_{17}H_{27}NO_2$ requires 314.19940; *m/z* 315(MH$^+$), 314(M$^+$), 271, 256, 242, 227, 214, 202, 175, 164, 148, 136, 121, 109, 107, 93, 91, 81, 77, 69, 55.

(2R)- and **(2S)-2-Cyano-2-{[(1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}ethanamide,** *(1R)-Camphor Imines of (2R)- and (2S)-2-Cyanoglycine Amides* **109a/109b** (reaction between malononitrile and (+)-camphoryl oxaziridine **65)**

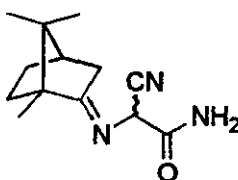2-Cyanoglycine derivatives **109a/109b** were synthesised according to the above procedure in an overall reaction time of 6 hours. Title imino amides **109a/109b** were isolated as an inseparable mixture of diastereoisomers, and as a colourless solid in 82% (288 mg, 1.236 mmol) overall yield. Imino amides **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 $C_{13}H_{19}N_3O$ requires%: C, 66.92; H, 8.21; N, 18.01; v_{max} (neat)/cm^{-1} 3413(NH), 3165(NH), 2254(CN nitrile), 1704(C=O amide), 1675(C=N); δ_H (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* t 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); δ_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 $C_{13}H_{29}N_3O$ requires 233.15281; *m/z* 234(MH$^+$), 233(M$^+$), 218, 207, 189, 175, 162, 150, 133, 121, 108, 95, 77, 69, 55, 41.
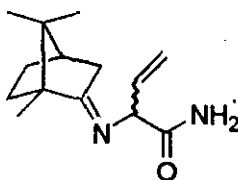
(2*R*)- and (2*S*)-2-Vinyl-2-{[(1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden]amino}ethanamide, *(1R)-Camphor Imines of (2R)- and (2S)-2-Vinylglycine Amides* **110a/110b** (reaction between allyl cyanide and (+)-camphoryl oxaziridine **65**)

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 ^{1}H NMR spectroscopy to be present in a 1:1 ratio: mp 130-133 °C; v_{max} (neat)/cm^{-1} 3530(NH), 3431(NH), 3054(CH=CH$_2$), 1691(C=O); δ_H (250 MHz; CDCl$_3$) 7.24(1H$_{A+B}$, br.s, RCONH$_2$), 6.32(1H$_{A+B}$, br.s, RCONH$_2$), 5.96-5.79(1H$_{A+B}$, m, CH$_2$=CHR), 5.07-5.20(2H$_{A+B}$, m, CH$_2$=CHR), 4.27(1H$_A$, d, J =6.0, R$_2$NCH(CONR$_2$)(CH=CH$_2$)), 4.22(1H$_B$, dt, J =5.5 and 1.6, =NCH(CONR$_2$)(CH=CH$_2$)), 2.33(1H$_A$, ddd, J =17.2, 4.6 and 2.9, *exo* at camphor C3), 2.23(1H$_B$, ddd, J =17.2, 4.3 and 3.1, *exo* at camphor C3), 1.94-1.61(4H$_{A+B}$, m), 1.36-1.03(2H$_{A+B}$, m), 0.97(3H, s, Me), 0.96(3H, s, Me), 0.91(6H, s, 2xMe), 0.70(6H, s, 2xMe); δ_C (63 MHz; CDCl$_3$) 11.1(Me), 11.3(Me), 18.8(Me), 18.9(Me), 19.39(Me), 19.44(Me), 27.1(CH$_2$), 27.2(CH$_2$), 31.9(CH$_2$), 32.0(CH$_2$), 35.3(CH$_2$), 35.6(CH$_2$), 43.6(CH), 43.7(CH), 46.9(C$_{quat}$), 47.7(C$_{quat}$), 54.3(C$_{quat}$), 54.9(C$_{quat}$), 66.7(CH, CH(NR$_2$)(CONH$_2$)(CH=CH$_2$)), 67.9(CH, CH(NR$_2$)(CONH$_2$)(CH=CH$_2$)), 115.9(CH$_2$, CH$_2$=CHR), 116.2(CH$_2$, CH$_2$=CHR), 134.1(CH, RCH=CH$_2$), 134.5(CH, RCH=CH$_2$), 175.0(C$_{quat}$, C=N), 175.1(C$_{quat}$, C=N), 185.3(C$_{quat}$, RCONH$_2$), 185.4(C$_{quat}$ RCONH$_2$); Found: M$^+$, 234.17314 C$_{17}$H$_{27}$NO$_2$ requires 234.17320; *m z* 234(M$^+$), 190, 176, 163, 148, 134, 122, 108, 95, 81, 67, 56.

(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**)
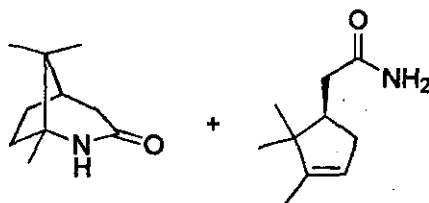
The title compounds were synthesised according to the above procedure with a total reaction time of 4 hours. α-Campholenic amide **111** was isolated as a white solid in 83% (210 mg, 1.257 mmol) yield: mp 130°C; δ_H (250 MHz; CDCl$_3$) 6.20(1H, br.s, RCONH$_2$), 5.78(1H, br.s, RCONH$_2$), 5.23(1H, br.s, C=CH-R), 2.07-2.44(4H, m), 1.86-1.97(1H, m), 1.61(3H, q, J = 1.5 Hz, C=CCH$_3$(R)), 1.01(3H, s, Me), 0.78(3H, s, Me); δ_C (100 MHz; CDCl$_3$) 12.6, 19.9, 25.5, 35.3, 37.0, 46.8, 121.7, 148.0, 176.2(RCONH$_2$). 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; δ_H (250 MHz; CDCl$_3$) 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**)
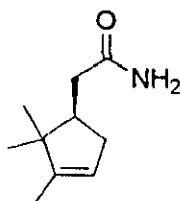
The title compound was synthesised according to the above procedure in a total reaction time of 1.5 hours. α-Campholenic amide **111** was isolated as a white solid in 83% (210 mg, 1.257 mmol) yield: mp 130°C; δ_H (250 MHz; CDCl₃) 6.20(1H, br.s, RCONH₂), 5.78(1H, br.s, RCONH₂), 5.23(1H, br.s, C=CH-R), 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); δ_C (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]

(1*R*)-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; δ_H (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); δ_C (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]

E- and ***Z*-(1*R*, 4*S*)-Ethyl 2-[(1,3,3-Trimethylbicyclo[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)
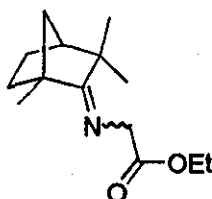
Sodium (100 mg, 4.35 mmol) was added to dry ethanol (5 mL) and the solution was stirred until the effervescence had ceased and all of the sodium had reacted. After allowing the solution to reach room temperature, a solution of (−)-fenchyl oxaziridine **70** (250 mg, 1.50 mmol) in ethanol (1 mL) was added 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 (MgSO$_4$) 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 the product as a pale yellow oil. The product was found to be a mixture of inseparable diastereoisomeric *syn-* and *anti-* (1*R*)-fenchone imines of ethyl glycinate **112a/112b**, present in a ratio of 1:1, and in 68% (213 mg, 0.897 mmol) yield: v_{max} (neat)/cm^{-1} 1750(C=O), 1684(C=N); δ_H (250 MHz; CDCl$_3$) 4.35(2H$_A$, s, CH$_2$(CO$_2$Et)(NR$_2$)), 4.34(2H$_B$, s, CH$_2$(CO$_2$Et)(NR$_2$)), 4.27-4.11(2H$_{A+B}$, m, MeCH$_2$O), 1.87-1.35(7H$_{A+B}$, m) 1.283(3H, t, *J* = 7.5, CH$_3$CH$_2$O), 1.281(3H, t, *J* = 7.2, CH$_3$CH$_2$O), 1.23(6H, s, 2xMe), 1.22(6H, s, 2xMe), 1.19(6H, s, 2xMe); δ_C (63 MHz; CDCl$_3$) 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(CH$_2$(CO$_2$R)(NR$_2$)), 170.8(RCO$_2$Et), 188.2(C=N), 6 signals are obscured and cannot be assigned confidently due to the presence of impurities; Found: M$^+$,

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)
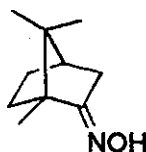
To a stirring mixture of (+)-camphoryl oxaziridine **65** (250 mg, 1.50 mmol) and 1-phenyl cyclohexene (238 μL, 237 mg, 1.50 mmol) in dichloromethane (5 mL) at room temperature was added trifluoromethanesulfonic acid (132 μL, 225 mg, 1.50 mmol). Within 5 minutes, the reaction was complete (tlc), and 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), 1.51-41(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]

(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)
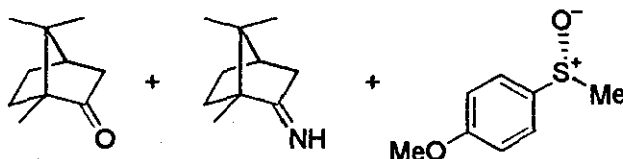
To a stirring cooled (−78 °C) solution of 1-methoxy-4-(methylthio)benzene (294 mg, 1.91 mmol) and (+)-camphoryl oxaziridine **65** (320 mg, 1.92 mmol) in dichloromethane (6 mL) was added pure trifluoromethanesulfonic acid (185 μL, 314 mg, 2.09 mmol). Initially the solution turned dark green, but approximately 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 (2×40 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; δ_H (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; δ_H (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[138]; 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

1.82 mmol) yield of (4-methoxyphenyl)methylsulfoxide **113**; δ_H (250 MHz; CDCl$_3$) 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, MeS(O)Ar), 2.53-2.37(1H, m, *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); ν_{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 ((1*R*)-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 (Mg$_2$SO$_4$) and the solvent removed *in vacuo* to give a colourless oil which was purified by flash chromatography (methanol/dichloromethane) over silica gel to give (+)-(*R*)-(4-methoxyphenyl)methyl sulfoxide **113** in an 85% (277mg, 1.63mmol) yield; $[\alpha]^{25}_D$ = +2.96 (CHCl$_3$) ee = 14%, *R* (worked out using ^{1}H NMR and shift reagent); δ_H (250 MHz; CDCl$_3$) 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); δ_C (63 MHz; CDCl$_3$) 43.8(Me, Me-S(O)Ar), 55.4(Me, Me-OAr), 114.8(CH, Ar), 125.4(CH, Ar), 126.6(C$_{quat}$, Ar), 162.1(C$_{quat}$, Ar); ν_{max} (DCM)/cm^{-1} 3067, 1595, 1304, 1256, 1091, 1027; *m/z* 171(MH$^+$), 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

Amberlyst 15® Ion Exchange Resin

BocON 2-(*Tert*-butoxycarbonyloxyimino)-2-phenylacetonitrole

DABCO 1,4-Diazabycyclo[2.2.2]octane

DBAD Di-*tert*-butylazodicarboxylate

DBU 1,8-Diazabycyclo[5.4.0]undec-7-ene

DCM Dichloromethane

DEAD Diethylazodicarboxylate

Diglyme 2-Methoxyethyl ether

DMAP 4-Dimethylaminopyridine

DME Ethylene glycol dimethyl ether (1,2-Dimethoxyethane)

DMF Dimethylformamide

DMSO Dimethylsulfoxide

HMPT Hexamethylphosphorus triamide

KHMDS Potassium hexamethyldisilazide

LDA Lithium diisopropylamide

LiHMDS Lithium hexamethyldisilazide

m-CPBA 3-Chloroperoxybenzoic acid

NaHMDS Sodium hexamethyldisilazide

NCS *N*-Chlorosuccinimide

Oxone® Potassium peroxymonosulfate

RAMP (*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine

SAMP (*S*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine

TASF Tris(dimethylamino)sulfur (trimethylsilyl)difluoride

TBDMSCl *tert*-Butyldimethylsilyl chloride

Tf$_2$O Trifluoromethanesulfonic anhydride (Triflic anhydride)

THF Tetrahydrofuan

TMSCl Trimethylsilyl chloride

TMSOTf Trimethylsilyl trifluoromethanesulfonate (Trimethylsilyl triflate)

TsCl   4-Toluenesulfonyl chloride   (Tosyl chloride)

TsOH   4-Toluenesulfonic acid

Abbreviations used for the Description of Functional Groups

Ac-   Acetyl-

Ar-   Aryl-

Bn-   Benzyl-

Boc-   *tert*-Butoxycarbonyl-

*i*Bu-   *iso*-Butyl-

*n*Bu-   *n*-Butyl-

*s*Bu-   *sec*-Butyl-

*t*Bu   *tert*-Butyl-

Bz-   Benzoyl-

Cy-   Cyclohexyl-

Et-   Ethyl-

Fmoc-   9-Fluorenylmethyloxycarbonyl-

Me-   Methyl-

Mes-   2,4,6-Trimethylphenyl-   (Mesityl-)

Moc-   Methoxycarbonyl-

Ms-   Methanesulfonyl-   (Mesyl-)

Ns-   4-Nitrophenylsulfonyl-   (Nosyl-)

Ph-   Phenyl-

*i*Pr-   *iso*-Propyl-

*n*Pr-   *n*-Propyl-

Ses-   2-Trimethylsilylethyl-

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-)

Z- Benzyloxycarbonyl-

Other Terms Used

^{13}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

hν   Indicates photolysis

APPENDIX 2: References

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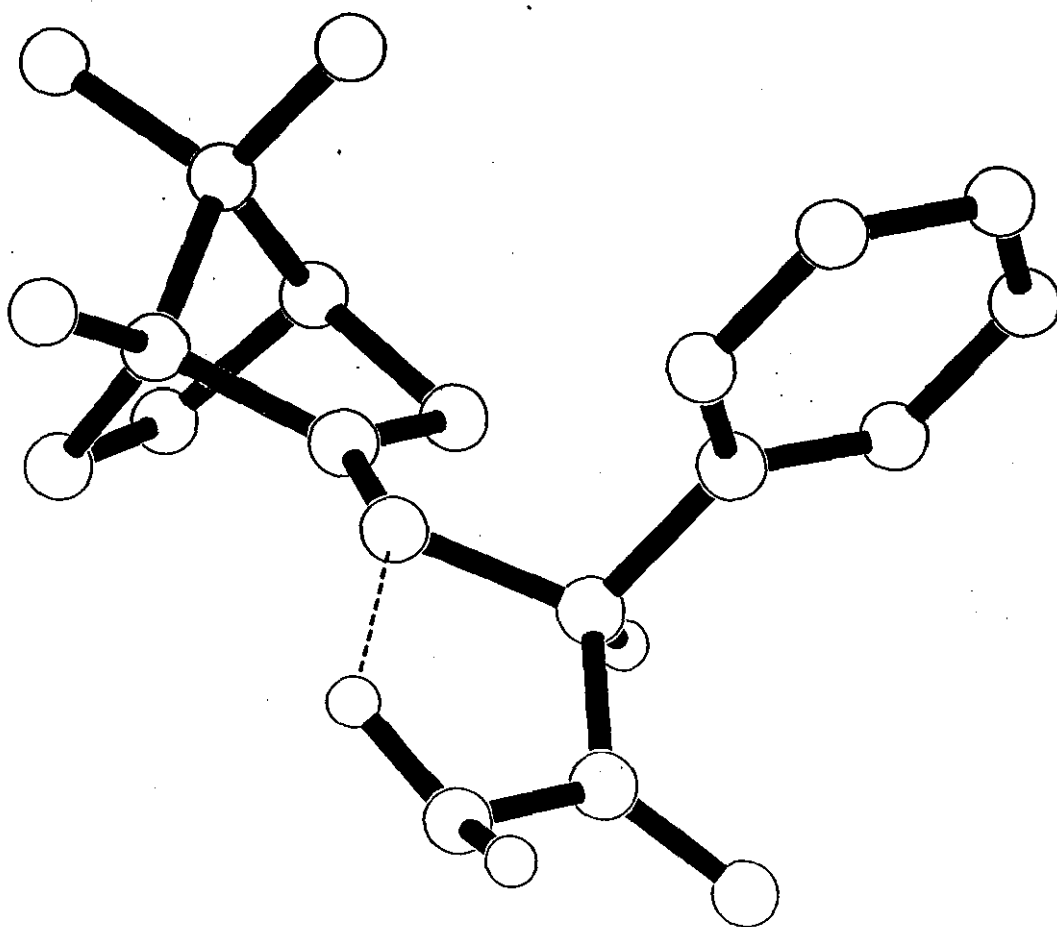
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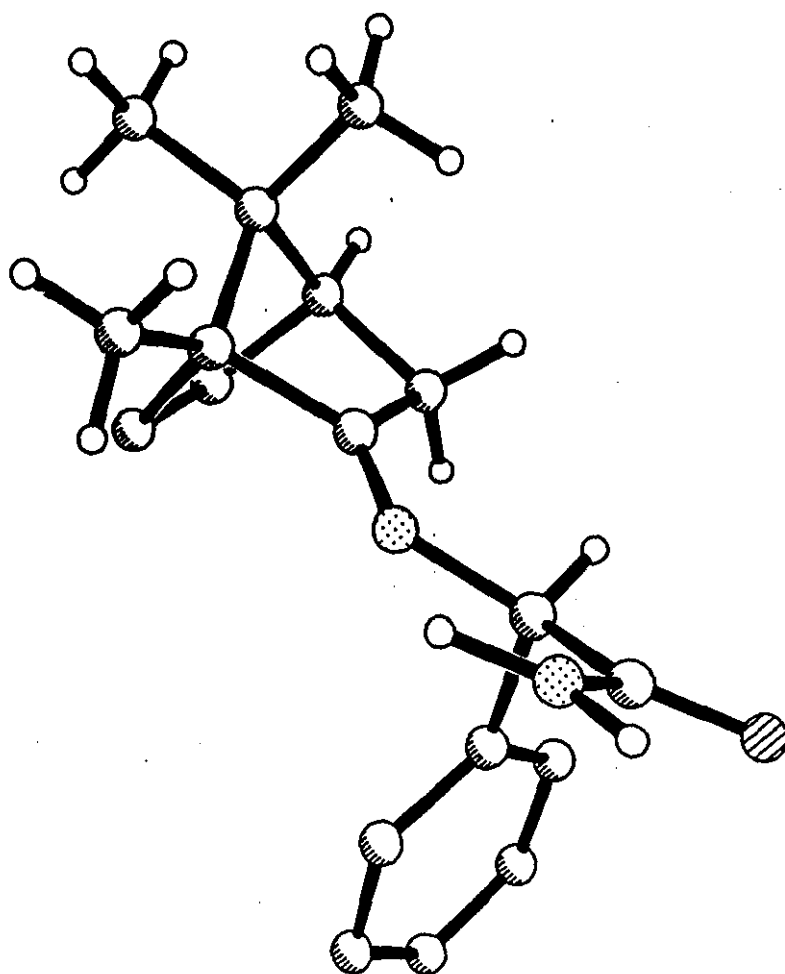
APPENDIX 3: Crystal Structures and NMR Data

All crystal structure analyses were performed by Dr A. Slawin, and NMR experiments were carried out by Dr. T Smith.
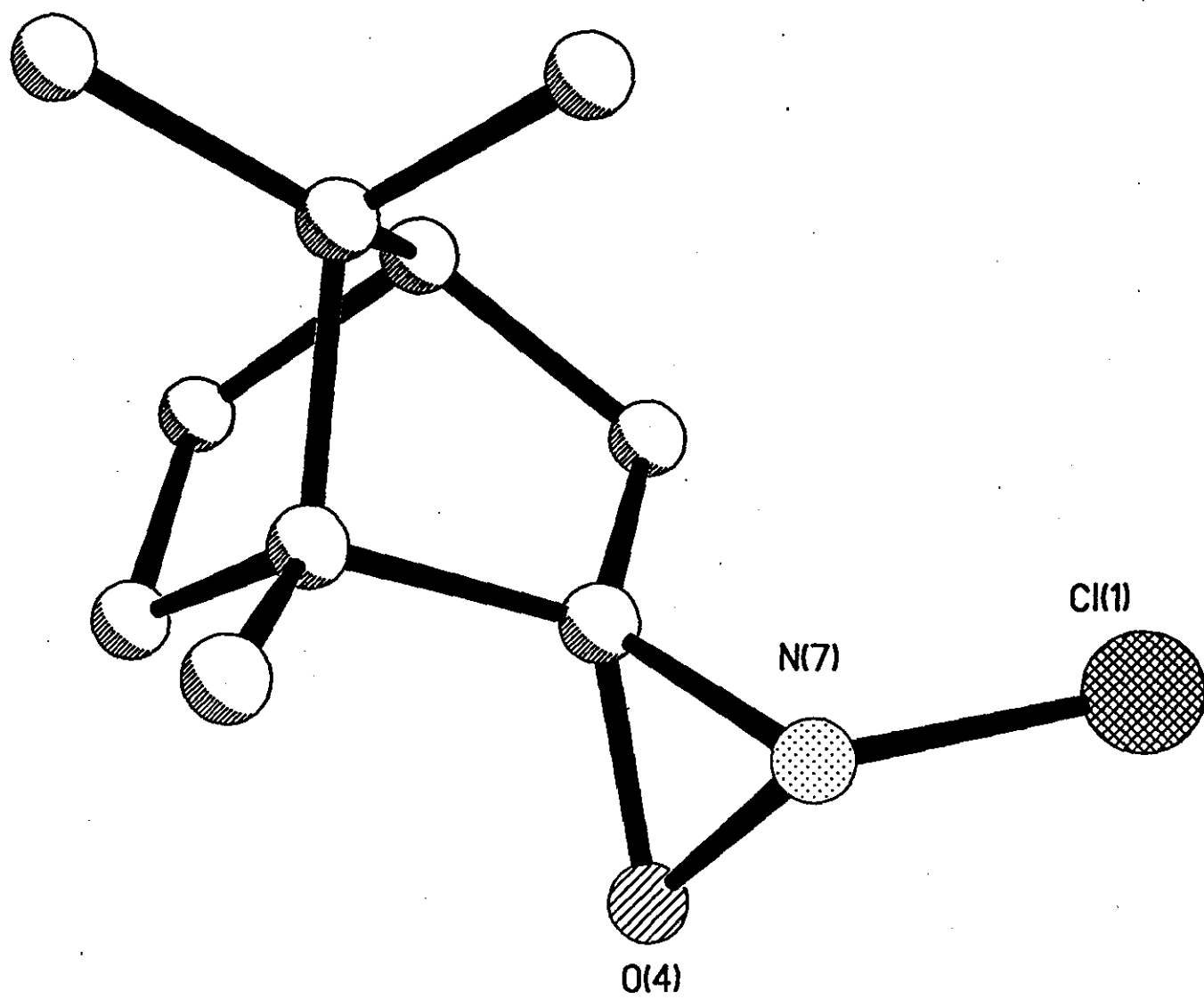
Cl(1)

N(7)

O(4)

Oxaziradine — VT in d6-DMSO at 25C

ppm

Integral

- 0.9139
- 0.9221
- 1.9456
- 0.9956
- 2.9158
- 0.2135
- 1.1209
- 6.0000
- 1.2136

- 5.731
- 5.057
- 4.911
- 3.281
- 1.865
- 1.855
- 1.736
- 1.730
- 1.727
- 1.712
- 1.705
- 1.701
- 1.401
- 1.389
- 1.378
- 1.370
- 1.349
- 1.303
- 1.300
- 1.279
- 1.274
- 1.271
- 1.268
- 0.918
- 0.859
- 0.844
- 0.831
- 0.818
- 0.750

Oxaziradine - VT in d6-DMSO at 95C

25C

35C

45C

55C

65C

75C

85C

95C

105C
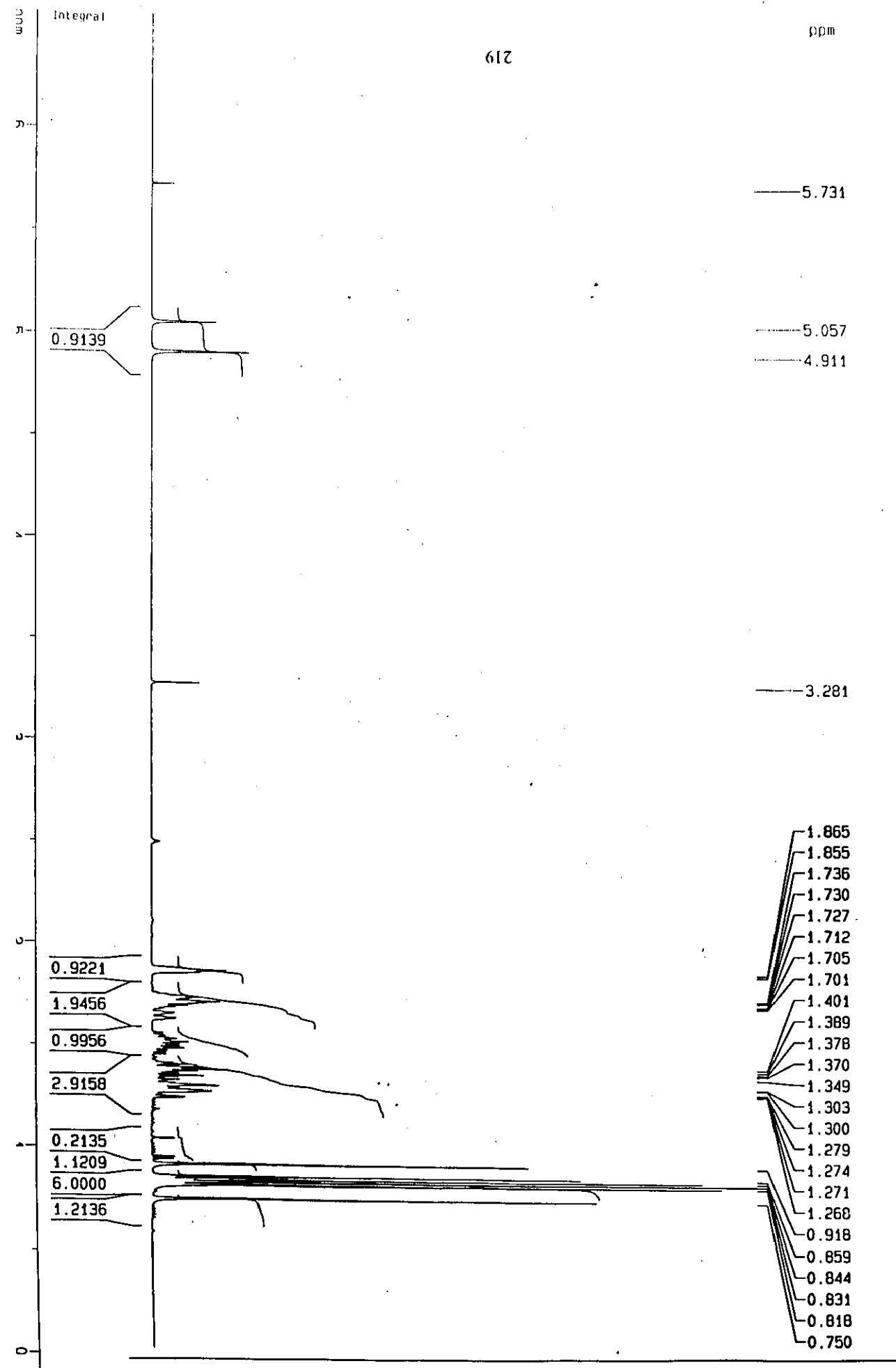
115C
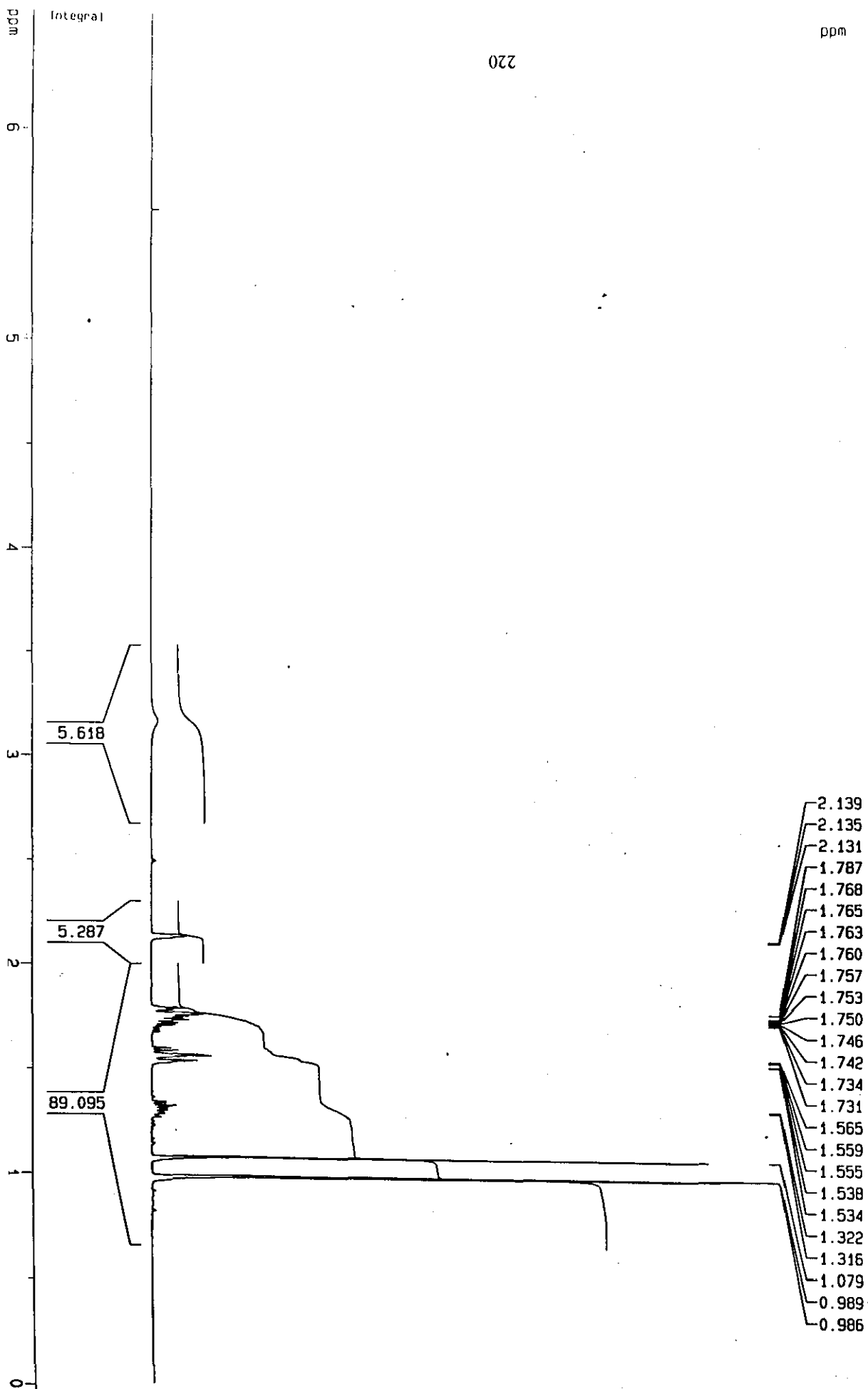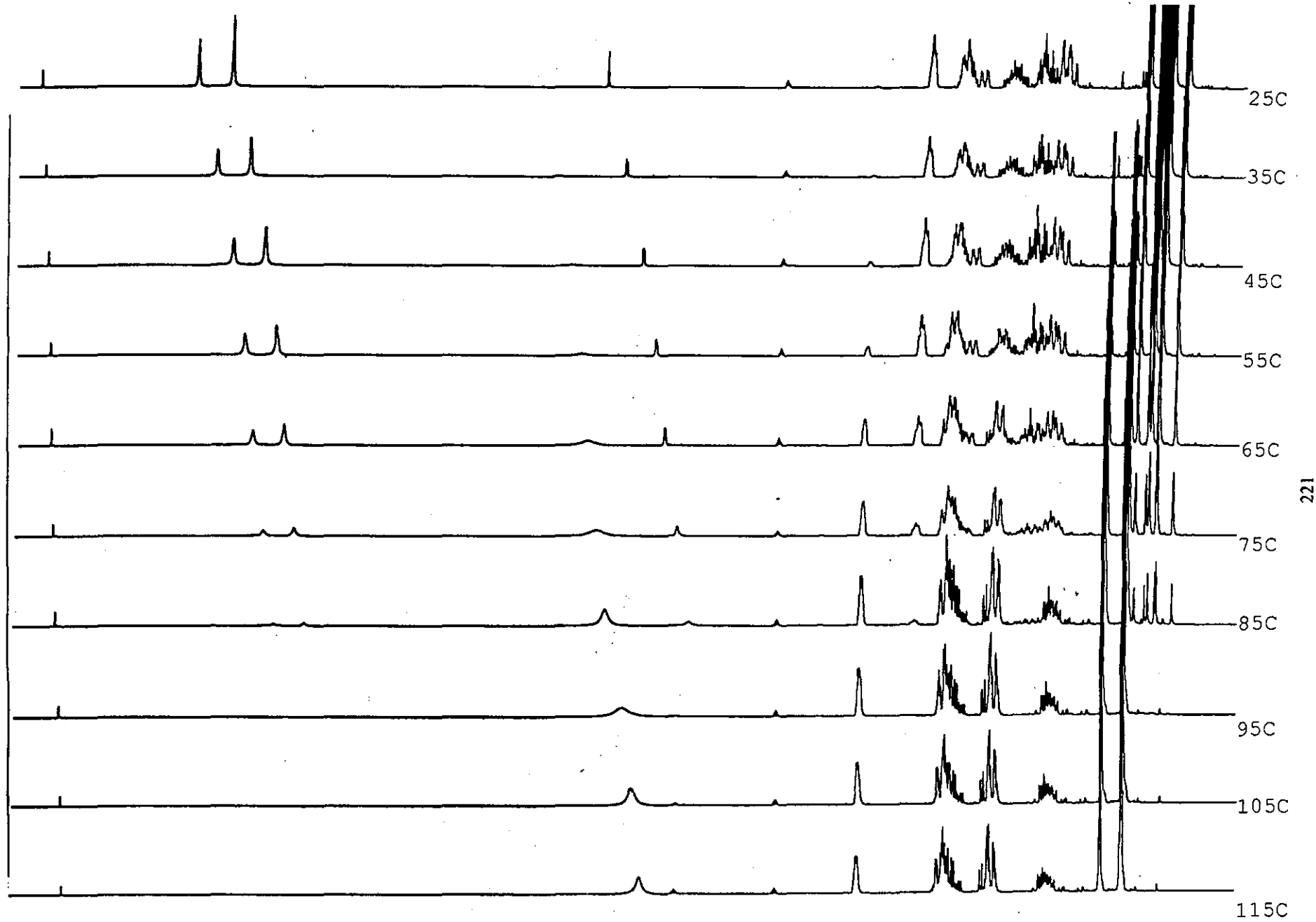
Oxaziridine — VT in d6-DMSO at 25C

ppm

88.022

222

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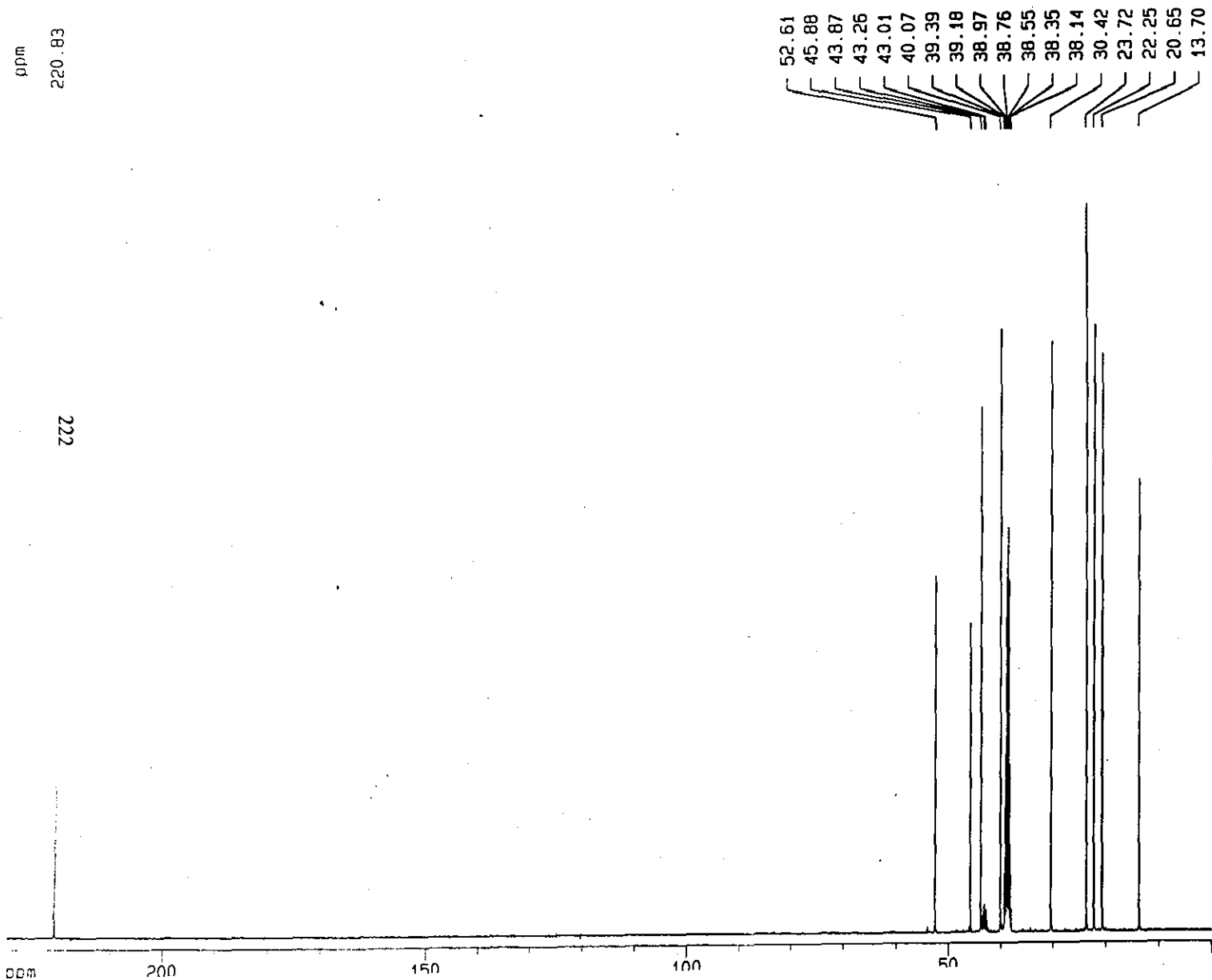
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SWH   31847.133 Hz
FIDRES   0.485949 Hz
AQ   1.0289652 sec
RG   8192
DW   15.700 usec
DE   7.50 usec
TE   300.0 K
d11   0.03000000 sec
d12   0.00002000 sec
PL13   120.00 dB
D1   1.00000000 sec
CPDPRG2   waltz16
PCPD2   100.00 usec
SFO2   400.1316005 MHz
NUC2   1H
PL2   -6.00 dB
PL12   12.00 dB
P1   5.50 usec
SFO1   100.6254358 MHz
NUC1   13C
PL1   -6.00 dB

F2 - Processing parameters
SI   32768
SF   100.6128942 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.40

1D NMR plot parameters
CX   20.00 cm
F1P   230.000 ppm
F1   23140.96 Hz
F2P   0.000 ppm
F2   0.00 Hz
PPMCM   11.50000 ppm/cm

ppm   200   150   100   50

Appendices

APPENDIX 4: Acknowledgements

Firstly, I would like to thank Prof. P. C. B. Page for his help, advice and patience throughout the course of my Ph.D.

I would also like to thank Dr. Dave Laffan for his help and advice over the duration of my research, and his support during my stay at Macclesfield.

I would like to express my gratitude to Dr Tim Smith, Dr Alex Slawin, John Kershaw, Alistair Daley, and all of the other technical staff at the Robert Robinsons laboratories at Liverpool, at Zeneca-PDD in Macclesfield, and at the department of chemistry at Loughborough university.

I would also like to thank the following:

The EPSRC and Zeneca for the provision of a grant and CASE award.

My friends at the universities of Liverpool and Loughborough, both inside and outside of the departments of chemistry, particularly Steve C., Steve H., Damien, Kev, Rob, Dave, Ed, and Abu for friendship and light entertainment.

My friends, Anthony Mullen, Steve Collier, and Steve Hindley for their friendship, help and support throughout the course of my research.

My Father, Mother, Nan and Grandad, for everything that they have done for me while I have been at university.

Andrea, for being a great girlfriend to me and a great mother to my children, Talia and Mica.