Stereocontrol with 2-oxazolines

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STEREOCONTROL WITH 2-OXAZOLINES

by

Justin Fairfield Bower

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of Loughborough University

August 1996

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Abstract

This thesis discusses the stereochemical controlling properties of the 2-oxazoline ring system in several organic transformations.

Chapter 1 reviews the literature, discussing the effective use of 2-oxazolines as ligands for various asymmetric catalytic processes.

Chapter 2 describes the synthesis of sulfoxide-based oxazoline ligands. In this chapter the diastereoselective oxidation of several aryl sulfides tethered to enantiomerically pure 2-oxazolines in the ortho-position is discussed, where the diastereoselectivity achieved is a consequence of the stereochemical controlling properties of the 2-oxazoline moiety.

Chapter 3 discusses the use of novel sulfoxide-based oxazoline compounds (both diastereomerically pure and enantiomerically pure) as effective ligands for an asymmetric palladium catalysed allylic substitution reaction. The use of diastereomerically pure sulfoxide-based oxazoline compounds (of known stereochemistry at both centres) as potential Lewis acid-type catalysts is also discussed.

Chapter 4 describes an asymmetric palladium catalysed allylic substitution reaction which proceeds through an unsymmetrical η3-allylpalladium intermediate, providing complete regiocontrol and excellent enantiocontrol. The chapter then goes on to discuss the manipulation of these substitution products into a range of highly enantiomerically enriched β-amino acids.

Chapter 5 extends the methodology described in Chapter four, towards the synthesis of α-substituted-β-amino acids. Several bulky, substituted nucleophiles are shown to provide high levels of enantiomeric excess for asymmetric palladium catalysed allylic substitution reactions proceeding through both symmetrical and unsymmetrical η3-allylpalladium intermediates. The attempted manipulation of these substitution products into α-substituted-β-amino acids is discussed.
Acknowledgements

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Abbreviations

AcOH  acetic acid
Ac  acetyl
acac  acetylacetonate
Ac₂O  acetic anhydride
BINAP  2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn  benzyl
n-BuLi  n-butyllithium
t-Bu  tert-butyl
Boc  tert-butoxycarbonyl
bipymox  bipyridine, bis(oxazolinyl)
BSA  N, O-bis(trimethylsilyl)acetamide
cat.  catalytic
cod  1,5-cyclooctadiene
dba  trans, trans-dibenzylideneacetone
d.e.  diastereomeric excess
DET  diethyl tartrate
DIOP  2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP  4-dimethylaminopyridine
DMF  N,N-dimethylformamide
DMSO  dimethyl sulfoxide
e.e.  enantiomeric excess
eqv.  equivalent
Et  ethyl
Eu(hfc)₃  tris[3-(heptafluoropropylhydroxy-methylene)camphorato], europium (III)
GC  gas chromatography
HMPA  hexamethylphosphoramide
HPLC  high pressure liquid chromatography
hr  hour
i-Pr  iso-propyl
IR  infra red
LDA  lithium diisopropylamide
mCPBA  meta-chloroperoxybenzoic acid
Mesityl  2,4,6-trimethylphenyl
Me  methyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>min.</td>
<td>minute</td>
</tr>
<tr>
<td>MMPP</td>
<td>magnesium monoperoxyphthalate hexahydrate</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxy methyl</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nuc</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pybox</td>
<td>pyridine, bis(oxazolinyl)</td>
</tr>
<tr>
<td>tr</td>
<td>retention time</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butylhydroperoxide</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N, N', N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>para-tolyl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
</tbody>
</table>
CHAPTER 1

2-OXAZOLINES AS LIGANDS IN CATALYTIC ASYMMETRIC SYNTHESIS
1.1 Introduction

Catalytic asymmetric synthesis is a rapidly growing area of research and has received considerable attention over the last two decades.\(^1\) Most synthetically designed catalysts contain a chiral ligand complexed to a metal centre, and it is this ligand which controls the asymmetry of any given reaction. The molecular design of a chiral ligand is essential for obtaining highly enantiomerically enriched/pure compounds in metal catalysed asymmetric reactions, and there has been considerable effort devoted towards the preparation of efficient ligands.\(^2\) Many chiral ligands are derived from natural products such as terpenes, carbohydrates, alkaloids and amino acids, with oxazolines being ultimately derived from the latter.\(^3\) This short review concentrates on the use of 2-oxazolines as ligands in asymmetric catalysis.

1.2 2-Oxazolines as ligands for asymmetric catalysis

Oxazolines were first used as recoverable ligands some twenty two years ago, facilitating ketone reductions\(^4\) and nucleophilic additions\(^5\) in an asymmetric sense. Treatment of the enantiopure 4-hydroxymethyloxazoline 1 with 0.5 equivalents of lithium aluminium hydride gave the presumed species 2 which mediated the reduction of a variety of ketones giving enantiomeric excesses in the range 4-65\%.\(^4\)

\[
\text{Ph} \quad \text{CH}_2\text{OH} \quad \text{LiAlH}_4 \quad \text{Et}\text{O}\text{N} \\
\text{Et} \quad \text{O} \quad \text{N} \quad \text{Et} \quad \text{CH}_2\text{O} \quad \text{LiAlH}_2\text{Li}
\]

Since this discovery, many applications of 2-oxazolines as ligands in asymmetric catalysis have been reported and the majority of examples involve the use of bis-oxazolines (as \(C_2\)-symmetrical ligands) bound to transition metals.\(^6\) The strong affinity of the oxazoline nitrogen for various metals accounts for the ready formation of bidentate coordination complexes that have been observed for bis-oxazolines.
1.2.1 Hydrosilylation

The hydrosilylation of prochiral ketones, usually catalysed by rhodium species, is an efficient method for the synthesis of highly enantiomerically enriched secondary alcohols.

Brunner and co-workers have developed a series of 2-(2-pyridyl)oxazoline ligands 3 which was found to provide reasonable levels of enantioselectivity (up to 83% e.e.) for the hydrosilylation of acetophenone 4 to the benzyl alcohol 5. The enantioselectivity is strongly dependent on the ligand:metal ratio, as well as on the steric effects due to the reducing silane and to the substituent at the 4-position of the oxazoline ring.

\[
\text{4 mol\% [Rh(cod)Cl]_2, 20 mol\% 3, CCl}_4, 18 \text{ hr, 67-95\%}}
\]

In an attempt to increase this enantioselectivity various substitution patterns were undertaken, providing varying degrees of success. The phenanthroline ligand 6 provided low levels of enantioselectivity, 8-20% e.e. However, manipulation of the 5-position of the oxazoline ring, ligand 7, led to an improvement in enantioselectivity for the hydrosilylation of acetophenone 4, (75-89% e.e.).

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Clinet and co-workers have also reported the hydrosilylation of acetophenone 4 under rhodium catalysis using pyridyl-oxazoline ligands. Using α-naphthylphenylsilane as the silylating reagent and 4 mol% of a catalyst system derived from ligand 8 and [Rh(C₂H₄)₂Cl₂]₂ they were able to achieve enantiomeric excesses of up to 80%.

Nishiyama et al. reported the first C₂-symmetric variants of the pyridyl ligands when they demonstrated that the tridentate ligand "pybox" 9 and the related tetradeutate ligand "bipymox" 10 produced enantiomeric excesses of 90% and over for the asymmetric hydrosilylation of a range of alkyl aryl ketones. They found that after forming a 1:1 complex between the ligand and rhodium trichloride, the addition of a Lewis acid (usually a silver salt) was required in order to generate the "active" hydrosilylation catalyst.
Helmchen and co-workers have also reported significant levels of enantioselectivity for the rhodium catalysed hydrosilylation of acetophenone using the bis-oxazolines 11, 12 and 13. However, they found that only the bis-oxazoline 11, without a carbon linker provided good levels of enantioselectivity (up to 84% e.e.).

Uemura et al. have recently reported an interesting result for the metal (rhodium(I) or iridium(I)) catalysed hydrosilylation of acetophenone using the phosphinoferrocenyl oxazoline ligand 14. The rhodium catalysed reaction produces the secondary alcohol with 91% e.e. with the (R)-stereochemistry predominating, whilst the iridium catalysed reaction provides the secondary alcohol in 96% e.e. with the (S)-stereochemistry predominating.

More recently Williams and Newman have reported the results for the rhodium catalysed asymmetric hydrosilylation of acetophenone, achieving up to 88% e.e. using a catalyst derived from [Rh(cod)Cl]2 and ligand 15.
1.2.2 Transfer hydrogenation

Pfaltz has reported the asymmetric transfer hydrogenation of alkyl aryl ketones using a catalyst system derived from ligand 11 and \([\text{Ir(cod)Cl}]_2\) with enantiomeric excesses reaching 91\%, Scheme 1.16

![Scheme 1](image)

More recently Helmchen has reported a similar transformation, catalysed by 0.1 mol\% of a ruthenium species derived from \([\text{RuCl}_2(\text{PPh}_3)_2]\) and ligand 15. Under reflux in the presence of 2.5 mol\% sodium hydroxide, enantiomeric excesses for the corresponding secondary alcohols of up to 94\% were achieved.17

1.2.3 Cyclopropanation

The catalytic asymmetric cyclopropanation reaction is a very important process and many groups have achieved excellent diastereoselectivity and high enantioselectivity using a variety of chiral ligands. The reaction essentially involves the interaction of a metal-carbene species with an alkene, forming an intermediate metallocyclobutane species which in turn breaks down to form the cyclopropane product and the catalytic metal species. Masamune has demonstrated the cyclopropanation of a number of olefins using 1 mol\% of a chiral copper catalyst derived from \([\text{Cu(CH}_3\text{CN})_4]\text{ClO}_4\) and ligand 16.18a The highest enantioselectivity
and trans selectivity achieved was for the reaction of diazoacetate 18 with 2,5-dimethylhexadiene 17, forming the trans cyclopropane 19.\textsuperscript{18b}

![Chemical Reaction Diagram]

Evans and co-workers have also reported similar results with ligand 13 (R = t-Bu, R' = Me), in a study that corrected earlier stereochemical assignments given by Masamune.\textsuperscript{19}

Evans et al. have recently reported the enantioselective aziridination of a range of alkenes, which in turn led to the synthesis of phenylalanine derivatives and \(\beta\)-hydroxy-\(\alpha\)-amino esters.\textsuperscript{20} Treatment of the cinnamate ester 20 with \(N\)-(p-toluene-sulfonyl)iminophenyliodinane 21 in the presence of 6 mol\% of ligand 13 (R = Ph, R' = Me) and 5 mol\% of copper triflate at room temperature gave the aziridine product, 22 in 64\% yield with an enantiomeric excess of 97\%.

![Chemical Reaction Diagram]

An intramolecular cyclopropanation reaction has recently been reported by Pfaltz and co-workers.\textsuperscript{21} They employed 3 mol\% of a catalyst system derived from copper (I) triflate and bis-oxazoline 13 (R = t-Bu, R' = H) in the conversion of diazo ketone 23 into the bicyclic product 24. The relatively moderate level of enantioselectivity (77\% e.e.) was surprising as ligand 13 is known to be a highly effective ligand for intermolecular cyclopropanations.\textsuperscript{18}
Nishiyama and co-workers have recently developed a highly efficient cyclopropanation catalyst derived from the "pybox" ligand. The complex ruthenium catalyst provided high trans:cis selectivity (up to 98:2) and high enantioselectivity (up to 97% e.e.) for the cyclopropanation of styrene with a range of diazoacetates.

In the search for a new and efficient cyclopropanation catalyst, Corey and co-workers have designed a new ligand which is able to catalyse an intramolecular cyclopropanation reaction. In a simple and highly enantioselective synthesis of the bioactive form of sirenin, they used the cyclopropanation of diazo ester to the bicyclic compound as a key step. The reaction, which was catalysed by 2 mol% of a copper species derived from ligand and copper triflate proceeded in 77% yield and with 90% enantiomeric excess.
Andersson and Bedekar have developed a new class of bis-oxazoline based ligand, where the two oxazoline moieties are separated by a tartrate backbone and thus form a seven membered chelate with the metal during the cyclopropanation reaction. Reasonable trans:cis selectivity (up to 70:30) and good enantioselectivity (up to 80% e.e.) was achieved for the cyclopropanation of styrene with ethyl diazoacetate catalysed by 1 mol% of a copper catalyst derived from copper triflate and ligand 30.
1.2.4 Diels-Alder reaction

Corey et al. have combined ligand 13 with Lewis acid catalysts in a Diels-Alder cycloaddition between cyclopentadiene 31 and the bidentate dienophile 3-acryloyl-1,3-oxazolidin-2-one, 32 to afford adduct 33.26 The choice of FeI₃ as the Lewis acid component led to enantioselectivities of up to 86% (endo:exo = 99:1).26a The use of the hexamethyl bis-oxazoline 34 with MgI₂ as Lewis acid gave slightly better results (91% e.e., endo:exo = 98:2), where the choice of counter-ion was not a critical factor; though solvent selection affected both enantioselectivity and endo selectivity.26b

However, Evans has recently shown that the choice of counter-ion can have a dramatic effect on the selectivity and rate of a Diels-Alder reaction.27 He reported interesting results for the Diels-Alder reaction of α-substituted acroleins with cyclopentadiene, catalysed by the copper(II) complex, 35. Best results were achieved when using $X = \text{SbF}_6^-$ as the counter-ion (98:2, endo:exo selectivity and 96% e.e., whilst for $X = \text{OTf}^-$ as the counter-ion the endo selectivity was 97:3 (87% e.e.), with the reaction taking four times as long to reach completion.
The groups of Davies and Ghosh have independently developed the conformationally constrained indane derived bis-oxazoline ligands, 36 and 37. Both groups concentrated on the Diels-Alder reaction between cyclopentadiene 31 and the bidentate binding dienophile, 32. The Davies group achieved high endo selectivity (130:1) and good enantioselectivity (92% e.e.) for a reaction conducted at -65 °C in the presence of 10 mol% of a catalyst system derived from copper triflate and ligand 36.28 The Ghosh group achieved superior results (>99:1, endo:exo; 97-99% e.e.) using 4 mol% of a catalyst system derived from ligand 37 and copper triflate for the identical reaction conducted at room temperature.29

Jørgensen and Johansen have recently demonstrated a copper(II) catalysed asymmetric hetero Diels-Alder reaction and ene reaction between diene 38 and glyoxylate ester 39 using bis-oxazoline 13 (R = t-Bu, R' = Me) as the chiral source.30 The ratio of the two products 40 and 41 was found to be highly dependent on the chiral ligand, the glyoxylate ester and the reaction temperature. Best results were achieved at -30 °C using 10 mol% of a catalyst system derived from copper(II) triflate and ligand 13 (R = t-Bu, R' = Me), with a 1:0.8 ratio for products 40 and 41 respectively; 40 having an enantioselectivity of 95% and 41 having an enantioselectivity of 94%. 

Page 10
A related process, the catalytic iron-mediated enediene carbocyclisation reaction has recently been reported by Takacs and co-workers. Triene 42 was converted into the bicyclic products 43 and 44 with high diastereoselectivity (>20:1, 42:43) (exclusively (E)-enol ether) in the presence of 20 mol% of a catalyst system derived from Fe(acac)$_3$ and ligand 13 (R = Bn, R' = Me).
1.2.5 Addition reactions

Recently Williams et al. have reported the enantioselective addition of diethylzinc to a range of aromatic aldehydes. In the presence of 6 mol% of a catalyst derived from ligands such as 45 they were able to reduce various aromatic aldehydes 46 to the corresponding secondary benzyl alcohols 47 with moderate levels of enantioselectivity (25-67% e.e.).

Moberg and Macedo have also reported an asymmetric addition of diethylzinc to aromatic aldehydes, 46, with the pyridyl-oxazoline ligand 48 providing up to 88% enantiomeric excess for the corresponding secondary benzyl alcohols, 47.

Corey and Wang have used cyano-bis-oxazoline-magnesium complexes such as 49 for the enantioselective conversion of cyclohexane carboxaldehyde 50 to the TMS protected cyanohydrin 51. The addition of 12 mol% of the bis-oxazoline 13 (R = Ph, R' = H), which acts as a co-catalyst, leads to an increase in enantioselectivity and yield for the reaction (95% yield, 94% e.e.).
Chapter 1: Introduction

Zhou and Pfaltz have recently achieved good levels of enantioselectivity for the copper catalysed enantioselective conjugate addition of iso-propylmagnesium chloride to 2-cycloheptene. Using 10 mol% of the copper catalyst they were able to isolate the addition product, in reasonable yield (55%) and with good enantioselectivity (87% e.e.).

Denmark and co-workers have recently reported the enantioselective addition of organolithium reagents to a range of prochiral imines. In the presence of ligand 13 (R = t-Bu, R' = Et) a range of organolithium species were added to a variety of imines, resulting in formation of the corresponding amines in good yield (81-99%) and with enantiomeric excesses in the range 51-91%.
1.2.6 Allylic oxidation

Pfaltz et al. and Andrus et al. have prepared copper(I) complexes in situ from chiral bis-oxazolines and copper(I) triflate and used them as catalysts for the allylic oxidation of cycloalkenes. Using 5 mol% of a catalyst system derived from copper triflate and ligand 13 (R = i-Pr or t-Bu, R' = Me) and tert-butyl perbenzoate as oxidant, cycloalkenes 57 were converted to the corresponding optically active 2-cycloalkenyl benzoates 58 in moderate to good yield. Best results were achieved for the oxidation of cyclopentene and cycloheptene, with enantiomeric excesses reaching 74% for reactions that were conducted at room temperature and up to 84% e.e. for reactions that were conducted at lower temperatures; whilst cyclohexene derivatives gave somewhat lower selectivities (64-74% e.e.).

Gupta and Singh have developed a modified Nishiyama "pybox" ligand, 59 which they have used to good effect for the allylic oxidation of cyclohexene. They were able to isolate the allylic benzoate product in 58% yield and with 81% e.e. The reaction required 4 Å molecular sieves and the enantioselectivity of the reaction was found to be highly dependent upon the copper source, with the best results being achieved through the use of in situ generated copper(I) triflate.
Chapter 1: Introduction

Not only do bis-oxazolines act as efficient catalysts for allylic oxidation reactions, but tris-oxazolines have also been recently shown to provide good levels of enantioselectivity for this reaction.\(^{39}\) In the presence of a catalytic amount of a copper species derived from copper(II) triflate and tris-oxazoline 60 a number of cycloalkenes were oxidised to the corresponding allylic benzoates in reasonable yield (up to 68%) and good enantioselectivity (up to 88% e.e.).

\[
\begin{array}{c}
\text{N} \\
\text{R}
\end{array}
\]

1.2.7 Allylic alkylation

Another area of application for oxazoline ligands which has received considerable attention recently is the asymmetric palladium catalysed allylic substitution reaction.\(^{40}\) During this reaction an allylic substrate 61 containing a suitable leaving group, such as acetate, is converted into the substitution product, 62 in the presence of catalytic amounts of a palladium(0) source and an appropriate chiral ligand. Excellent levels of enantioselectivity have been achieved for this process (up to 99% e.e.) using oxazoline ligands, and this area will be discussed in more detail in Chapter 3.

\[
\begin{array}{c}
\text{R} \\
\text{OAc}
\end{array}
\]
Pfaltz and co-workers have recently demonstrated a tungsten catalysed allylic substitution reaction using phosphine oxazoline ligand 15. The "active" tungsten catalyst was thought to be 63, being derived from ligand 15 and \([\text{W(CO)}_3(\text{CH}_3\text{CN})_3]\).

\[
\text{Pr} \quad \text{Ph} \quad \text{N}\quad \text{Me} \quad \text{Ph} \quad \text{CO} \\
\text{H}\quad \text{OC} \quad \text{W} \quad \text{N} \quad \text{C} \quad \text{II} \\
\]

63

In a representative example (E)-cinnamyl diethyl phosphate 64 was converted in the presence of sodiodimethyl malonate and catalyst 63 into a mixture of the two regioisomers 65 and 66. In this case, alkylation at the more substituted benzylic position was preferred (the opposite selectivity is favoured for palladium catalysed allylic substitution reactions) affording a 3:1 mixture of 65 and 66, respectively, in 89% yield. The enantiomeric excess of 65 was 96%.

\[
\begin{align*}
\text{Ph} & \quad \text{CH} & \quad \text{CO}_2\text{CH}_3 \quad \text{EtO}_2\text{P} \\
\end{align*}
\]

5 eq. NaCH(CO\(_2\)CH\(_3\))

10 mol% 63

THF, -10 \(^\circ\)C, 71 hr

89%

65 (96% e.e.)

1.2.8 Miscellaneous

Larock and Zenner have recently reported Heck reactions with the functionalised substituted aryl iodide 67 and the allene 68. Under palladium catalysis in the presence of 5 mol% of the bis-oxazoline ligand 13 (R = Bn, R' = Me)
they were able to achieve the cyclised product, 69 with an enantiomeric excess of 82%.

Pfaltz et al. have also demonstrated an enantioselective Heck reaction. Reaction of 2,3-dihydrofuran, 70 with 1-cyclohexenyl triflate 71 in the presence of 3 mol% of a palladium source and 6 mol% of ligand 72, gave the 2,5-dihydrofuran derivative 73 in good yield (92%) and with excellent enantioselectivity (99% e.e.).

Richards and co-workers have developed a series of phosphinoferrocenyl oxazoline ligands that they have used for cross-coupling reactions. Using the diastereomeric ligands 74 and 75, they prepared the corresponding palladium dichloride complexes. Subsequent investigation into their efficiency for Grignard cross-coupling reactions provided low to modest levels of asymmetric induction, Scheme 2.
Chapter 1: Introduction

Uemura has recently reported a novel asymmetric catalytic synthesis of sulfimides.\textsuperscript{45} Using the nitrene transfer reagent \textit{21}, previously reported by Evans for an aziridination reaction, Uemura was able to convert sulfides, \textit{76} into the corresponding sulfimides \textit{77} in good yield (up to 82\%) and with reasonable enantioselectivity (up to 71\% e.e.). The reactions were catalysed by a copper complex derived from copper(I) triflate and the \textit{bis}-oxazoline ligand, \textit{13} (R = Ph, R' = Me or H).

1.3 Conclusions

In conclusion, it has been illustrated that the oxazoline ring system is a very efficient ligand for a number of asymmetric catalytic processes. The majority of asymmetric processes rely upon the C\textsubscript{2}-symmetric \textit{bis}-oxazoline systems for enantiocontrol, however, \textit{mono}-oxazolines tethered to auxiliary donor atoms have also been shown to be capable of providing high levels of enantiocontrol for certain reactions. The success of the oxazoline ring system in asymmetric synthesis is due, in part, to the fact that the stereochemical controlling functionality on the oxazoline
is directed towards the substrate during the metal catalysed reaction. The following chapters provide more examples of the effective use of the oxazoline ring system as a stereochemical controlling group in asymmetric synthesis.
CHAPTER 2

DIASTEREOSELECTIVE OXIDATION OF ARYL SULFIDES
Chapter 2: Diastereoselective oxidations

2.1 Introduction

The use of chiral sulfoxides has established itself over the years as a reliable technique in asymmetric organic synthesis.\textsuperscript{46} There are many examples in the literature where chiral sulfoxides have played a vital role in introducing asymmetry into a variety of reactions, including; Michael addition of nucleophiles to activated $\alpha,\beta$ unsaturated sulfoxides,\textsuperscript{47} Diels-Alder reactions,\textsuperscript{48} Aldol reactions,\textsuperscript{49} and carbonyl reductions.\textsuperscript{50}

Many reagents have been developed for the non-stereoselective oxidation of sulfides to sulfoxides, for example; peroxides (especially $m$CPBA),\textsuperscript{51} periodates (NaI$_4$),\textsuperscript{52} perborates (NaBO$_3$),\textsuperscript{53} magnesium monoperoxy phthalate (MMPP),\textsuperscript{54} and oxone.\textsuperscript{55} However, in order to gain enantiomerically pure/enriched sulfoxides, a chiral source is required. Indeed for sulfoxides to be effective synthetic tools for asymmetric carbon-carbon bond formation, they are in general, required in optically active form. This can be achieved through the use of either reagent control, or substrate control.\textsuperscript{56}

The enantioselective synthesis of sulfoxides can be split into three main categories:
• Chemical synthesis through nucleophilic substitution at sulfur.
• Enantioselective oxidation of prochiral sulfides.
• Kinetic resolution of sulfoxides.

2.1.1 Nucleophilic substitution at sulfur

This approach to sulfoxides of high optical purity was first developed by Andersen in 1964 and is still probably the most important and widespread application used today.\textsuperscript{57} This is based upon the reaction of an organometallic nucleophile, usually a Grignard or organolithium reagent with a resolved menthyl sulfinate ester. The first optically active sulfoxide to be produced by this method was (+)-(R)-ethyl-$p$-tolyl sulfoxide 79, prepared from (-)-(S)-menthyl $p$-toluenesulfinate 78 and ethylmagnesium iodide,\textsuperscript{57} the reaction proceeding with clean inversion of stereochemistry at sulfur.
Chapter 2: Diastereoselective oxidations

However, it is difficult to obtain dialkylsulfoxides using the Andersen methodology, due to the problems of accessing the desired resolved alkyl sulfinate esters.

Several groups have developed strategies in order to combat this problem. Llera and co-workers\textsuperscript{58} used diacetone-D-glucose (DAG), \textsuperscript{80} as their source of chirality. Initial reaction between DAG and alkyl- or arylsulfonyl chlorides will yield, depending upon which tertiary amine base is used, either the (S)- or (R)-alkyl- or arylsulfinate. The corresponding sulfoxides were achieved with inversion of stereochemical integrity at sulfur through nucleophilic displacement by a Grignard reagent. More recently, Fernandez\textsuperscript{58c} has reported the use of "DAG Methodology" in the asymmetric synthesis of a range of optically pure tert-butyl sulfoxides.

Other groups have developed strategies based on a chiral sulfinyl group flanked by two different leaving groups. Kagan and co-workers\textsuperscript{59} outlined their approach using a chiral sulfite, \textsuperscript{83} derived from (S)-ethyl lactate \textsuperscript{81}. Reaction of \textsuperscript{81} with 2 equivalents of phenylmagnesium bromide gave the diphenylpropanediol, \textsuperscript{82} which in turn reacts diastereoselectively (90:10) with thionyl chloride affording the cyclic sulfite, \textsuperscript{83}. Substitution at the heterocycle, \textsuperscript{83} with an organometallic reagent results in the formation of sulfinate \textsuperscript{84}, where control of regiochemistry is largely governed by the size of the nucleophile. Whereas bulky organometallic reagents react regioselectively (95:5) with the sulfite \textsuperscript{83}, affording sulfinate \textsuperscript{84}, small organometallic reagents almost reverse the regioselectivity (10:90). Reaction of \textsuperscript{84}
Chapter 2: Diastereoselective oxidations

with a second organometallic reagent afforded a range of enantiomerically pure dialkyl sulfoxides, 85.

\[
\begin{align*}
\text{H} & \quad \text{2 eq. PhMgBr} \\
\text{HO} & \quad \text{PhMgBr} \\
\text{CO}_2\text{Et} & \quad \text{SOCl}_2/\text{NEt}_3
\end{align*}
\]

These regiochemical problems were overcome by Benson and Snyder,\(^60\) making use of oxathiazolinidine-(S)-oxide 86, derived from ephedrine.

2.1.2 Enantioselective oxidation of prochiral sulfides

A convenient and relatively simple route to chiral sulfoxides is through the asymmetric oxidation of prochiral sulfides using optically active oxidising reagents. Approaches to this goal can be roughly split into two categories:

- Chemical oxidation
- Enzymatic oxidation

Chemical oxidation

Currently, the best methods available for the asymmetric oxidation of prochiral sulfides to sulfoxides are those developed by Kagan\(^61\) and Modena,\(^62\) both based on the Sharpless asymmetric epoxidation system.\(^63\) Kagan's methodology uses a titanium-based Sharpless catalyst, modified by the addition of one equivalent of water, \((\text{Ti(OiPr})_4/\text{DET}/\text{H}_2\text{O}, 1:2:1)\). The observed enantiomeric excesses of the reaction are high (74-96%) for a wide range of alkyl aryl sulfoxides, but lower for
dialkyl sulfoxides (42-71%).\textsuperscript{61b} Recently, it has been found that by using cumene hydroperoxide as the oxidant instead of the previously reported \textit{tert}-butyl hydroperoxide, it is possible to reduce the amount of titanium complex used (0.5 to 0.2 mol eq. from 1.0 eq.) without loss of enantioselectivity. Although under these conditions 4 Å molecular sieves are required in order to control the amount of water in the system. Indeed it has been shown that this modification actually increases enantioselectivities.\textsuperscript{61d} More recently Kagan has achieved up to 96% enantiomeric excess for the oxidation of alkyl aryl sulfides using 10 mol\% of a catalyst system (Ti(O\textit{OiPr})\textsubscript{4}/DET/i-PrOH, 1:4:4: 4 Å MS-1 weight equivalent based on sulfide) devoid of water.\textsuperscript{64} The stereochemistry of this reaction is thought primarily to be due to steric effects, Scheme 3.

\begin{equation}
\text{Ti(O\textit{OiPr})}_4 \quad \text{L-(-)-DET,}
\end{equation}

\begin{equation}
\begin{aligned}
\text{PhC(Me)}_2\text{OOH,} \\
\text{H}_2\text{O, CH}_2\text{Cl}_2}
\end{aligned}
\end{equation}

\begin{equation}
\text{S}^\text{O}^\text{+} \\
\text{(L)}^\text{-} \text{S}^\text{O}^\text{+} \text{(S)}
\end{equation}

\begin{equation}
\text{Ti(O\textit{OiPr})}_4 \quad \text{D-(-)-DET,}
\end{equation}

\begin{equation}
\begin{aligned}
\text{PhC(Me)}_2\text{OOH,} \\
\text{H}_2\text{O, CH}_2\text{Cl}_2}
\end{aligned}
\end{equation}

\begin{equation}
\text{S}^\text{O}^\text{(S)} \\
\text{(L)}^\text{-} \text{S}^\text{(S)}
\end{equation}

\begin{equation}
\text{e.g. (L) = "Large" e.g. aryl, t-Bu}
\end{equation}

\begin{equation}
\text{(S) = "Small" e.g. n-alkyl}
\end{equation}

\textbf{Scheme 3}

If L-(-)-diethyl tartrate is used in the catalyst system oxygen delivery is from the lower face of the prochiral sulfide, and from above if D-(-)-diethyl tartrate is used.

The Modena methodology on the other hand is based on a system lacking water. Using a system based on an excess of diethyl tartrate (Ti(O\textit{OiPr})\textsubscript{4}/DET/TBHP, 1:4:2) he was able to achieve up to 88\% enantiomeric excess for the oxidation of alkyl aryl sulfides.\textsuperscript{62} Modena \textit{et al.} have recently extended this methodology, synthesising \textit{bis}-sulfoxides in up to 99\% enantiomeric excess.\textsuperscript{65}

A related titanium-based oxidation procedure has recently been developed by Uemura \textit{et al.}\textsuperscript{66} This system utilizes a chiral binaphthol ligand rather than a tartrate ester and has the added advantage that commercial 70\% TBHP (aqueous) can be
used as oxidant at room temperature and with just 2.5 mol% catalyst. Using this method enantiomeric excesses of up to 96% have been achieved for the oxidation of alkyl aryl sulfides.\textsuperscript{66b}

The effective use of enantiomerically pure oxaziridines as stoichiometric oxidants for the conversion of prochiral sulfides to sulfoxides was initially reported by Davis and co-workers.\textsuperscript{67} N-sulfamoyl \textsuperscript{67a} and N-sulfonyloxaziridines \textsuperscript{67b} were shown to oxidise prochiral alkyl aryl sulfides in high yields, but with modest enantioselectivity.

\begin{center}
\includegraphics[width=0.8\textwidth]{oxaziridine.png}
\end{center}

More recently Davis\textsuperscript{67c} has reported the use of \textit{N-}-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine \textsuperscript{89}, prepared from (+)-camphor in three steps, as a highly effective reagent for the stoichiometric oxidation of prochiral alkyl aryl sulfides. Enantiomeric excesses of up to 96% have been achieved using this reagent.

\begin{center}
\includegraphics[width=0.5\textwidth]{oxaziridine_89.png}
\end{center}

Although the Davis oxaziridine methodology provides sulfoxides of high enantioselectivity, it seems that the Kagan methodology uses a catalyst system which has significant advantages;

- the sense of asymmetric induction can readily be reversed by simply using the opposite enantiomer of diethyl tartrate (as is the case for the Sharpless epoxidation) and,

- the ease with which the Kagan oxidation (one step) can be carried out, compared to the rather tricky preparation of oxaziridines.

When using the Kagan and Davis methods for the oxidation of prochiral sulfides it is the respective reagents that control the stereochemical outcome of the
reaction. Other groups have also demonstrated the effective use of asymmetric oxidants in the enantioselective oxidation of prochiral sulfides. Jacobsen\textsuperscript{68} has shown the effectiveness of (salen)Mn(III) Cl complexes \textsuperscript{90} as catalysts for the oxidation of sulfides to sulfoxides. An optimal reaction system consisting of unbuffered hydrogen peroxide as the oxidant, acetonitrile as solvent, and 2-3 mol\% of the catalyst, gives aryl sulfoxides in high yield with enantiomeric excesses in the range 34-68\%. Katsuki has recently improved on this.\textsuperscript{69} Using 1 mol\% of catalyst \textsuperscript{91} in the presence of 1 equivalent of iodosylbenzene he was able to achieve up to 90\% e.e. for the oxidation of alkyl aryl sulfides. Iodosobenzene\textsuperscript{70} has also been used, in the presence of iron porphyrin catalysts, to oxidise aryl sulfides, with enantiomeric excesses for the aryl sulfoxides reaching 71\%.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Reaction.png}
\caption{Reaction Diagram}
\end{figure}

**Enzymatic oxidation**

The oxidation of prochiral sulfides using biological techniques has recently been reviewed by Holland.\textsuperscript{71} It should be noted however that, in general, enzymatic methods do not provide a high yielding route to sulfoxides with high enantiomeric excesses. However, with certain substrates excellent results can be achieved. Wong and co-workers\textsuperscript{72} have recently shown that Chloroperoxidase, a haem-containing glycoprotein, from *Caldariomyces fumago*, catalyses the asymmetric oxidation of alkyl aryl sulfides in the presence of hydrogen peroxide. Enantiomeric excesses in the range, 97-100\% were achieved with yields reaching as high as 92\%.

Ohta and co-workers\textsuperscript{73} have shown that enantiopure 2-hydroxyethyl and vinyl sulfoxides can be prepared using *Rhodococcus equi* IFO 3730. Enantiomeric excesses for this process have reached 99\% when using methyl or MOM ethers of the parent sulfide.
Chapter 2: Diastereoselective oxidations

The fungus *Helminthosporium* species has recently been shown by Holland\(^7^4\) to effect oxidation of alkyl aryl sulfides to their corresponding sulfoxides with enantiomeric excesses reaching as high as 95%.

### 2.1.3 Kinetic resolution

It is well known that enantiomers exhibit different reactivity towards chiral reagents and this knowledge has been applied to obtain optically active sulfoxides. The first oxidative kinetic resolutions of sulfoxides were undertaken in the 1960's by Yobe\(^7^5\) and Jarossi.\(^7^6\) Both processes used chiral peracids, affording a mixture of optically active sulfoxide, with an optical purity of 5%, and achiral sulfone. Recently Ohta and co-workers\(^7^7\) have reported that the enzyme mediated hydrolysis of some racemic sulfinyl acetates and propionates using *Carynebacterium equi* IF 3730, returns unreacted sulfoxides having enantiomeric excesses in the range 90-97%. The chemical mediated kinetic resolution of racemic sulfoxides has recently been demonstrated by Uemura and co-workers.\(^7^8\) Using a chiral titanium-binaphthol complex, tert-butyl hydroperoxide as oxidant in water, the unreacted (R)-sulfoxide was recovered with up to >99% enantiomeric excess, although yields were low (~26%) Scheme 4.

![Scheme 4](image)

### 2.2 Diastereoselective oxidation

The enantioselective oxidation of prochiral sulfides has been studied in depth and there are many examples of this process (section 2.1). The diastereoselective oxidation of sulfides to sulfoxides on the other hand, where the stereochemical configuration at sulfur is determined by the asymmetric centre(s) in the substrate, has been studied less.
Several groups have investigated the diastereoselective oxidation of chiral sulfide molecules using achiral oxidants. Ohta and co-workers have reported the diastereoselective oxidation of aryl sulfide 92 to the sulfoxide 93 with up to 78% diastereomeric excess.

\[
\begin{align*}
\text{AcOH, r.t., 15 hr} & \quad \text{NaBO}_3\cdot 4\text{H}_2\text{O} \\
10\% & \quad \text{O},\text{S~NMe}_2
\end{align*}
\]

92 \rightarrow 93 \quad \text{(up to 78\% d.e.)}

Thomas et al. have recently reported the diastereoselective oxidation of racemic sulfanyl-tricarbonyl(\(\eta^5\)-arene)chromium(0) complexes. Using dimethyl dioxirane as oxidant, sulfanyl-chromium complex 94 was oxidised in high diastereoselectivity (up to >96\% d.e.) and excellent yield (up to 92\%) to the corresponding sulfinyl-chromium complex 95.

\[
\begin{align*}
\text{Cr} & \quad \text{O}_2\text{O} \\
\text{CH}_3\text{CO} & \quad \text{S~NMe}_2
\end{align*}
\]

\[
\begin{align*}
R' & \quad \text{S~O} \\
\text{Cr} & \quad \text{O}_2\text{O} \\
\text{S~NMe}_2 & \quad \text{R''}
\end{align*}
\]

\[
\begin{align*}
(\pm) \quad 94 & \quad \text{Cr}(\text{CO})_3 \quad \text{S~O} \\
-78 \text{C-r.t., 1.25 hr} & \quad \text{(}\pm) \quad 95 \quad \text{(up to >96\% d.e.)}
\end{align*}
\]

Glass and co-workers have also demonstrated the effective use of the mild, achiral oxidant, dimethyl dioxirane. Reaction of the chiral disulfide 96 with dimethyl dioxirane in dichloromethane at -78 \text{C} led to the highly diastereomerically enriched (up to 18:1) dithiolane-1-oxide, 97 in reasonable yield.
More recently Otera and Sato have reported the diastereoselective oxidation of a range of \( \alpha \)-methylbenzyl sulfides with \( t \)-BuOCl.\(^{79d} \) \( \alpha \)-Methylbenzyl aryl sulfide, \( 98 \) was oxidised to the corresponding sulfoxide \( 99 \) with excellent diastereoselectivity (>98% d.e.).

\[
\begin{align*}
\text{Ph-S-R} & \quad \text{1) \( t \)-BuOCl, CH}_2\text{Cl}_2, -78 ^\circ \text{C}, 1.5 \text{ hr} \\
& \quad 2) \text{NaHCO}_3 \quad 79\% \\
\rightarrow \text{Ph-S}^+\text{R} \quad 99 \ (>98\% \text{ d.e.})
\end{align*}
\]

We were interested in synthesising ligands through the diastereoselective oxidation of aryl sulfides tethered to enantiomerically pure 4,5-dihydrooxazoles (oxazolines) in the \textit{ortho}-position, Scheme 5. The stereochemical controlling properties of the oxazoline ring system are well known (Chapter 1),\(^{80} \) and it was envisaged that the approach of the incoming oxidant to the sulfur centre would be influenced by the substituent at the 4-position of the oxazoline ring.

Potentially, this process could provide a simple route to bidentate ligands, where both the sulfoxide and oxazoline moieties could act as donor groups; or tridentate binding ligands with the group at the 4-position of the oxazoline ring being an additional donor group. As these potential ligands possess two chirality centres, it would be possible to have \textit{matched} and \textit{mismatched} pairs between the 4\textit{S} centre of the oxazoline ring and the \textit{Ss} and \textit{Rs} isomers of the sulfoxide.

### 2.3 Synthesis of sulfide valinol-derived oxazoline substrates

We initially chose aryl sulfides tethered to oxazolines derived from (S)-valinol, \( 100 \) and \( 101 \) as our substrates.
Chapter 2: Diastereoselective oxidations

The enantiomerically pure sulfide oxazoline ligands 100 and 101 were prepared from the corresponding sulfanyl nitriles, using methodology previously reported by this group.\textsuperscript{81}

2-(Methylsulfanyl)benzonitrile, 102 was commercially available. 2-(Phenylsulfanyl)benzonitrile, 103 and 2-((4-methylphenyl)sulfanyl)benzonitrile, 104 were prepared from ortho-fluorobenzonitrile 105. The appropriate thiol, 106 or 107 was added to a stirred suspension of sodium hydride in dry THF at 0 °C and warmed to room temperature, before the addition of ortho-fluorobenzonitrile 105. After heating to reflux for 24 hr the nitrile products 103 and 104 were isolated in good yield. Infra-red analysis confirmed product formation with the disappearance of the weak S-H band at approximately 2500 cm\(^{-1}\) and the appearance of a band at 2220 cm\(^{-1}\) (103) and 2224 cm\(^{-1}\) (104) respectively, corresponding to the nitrile (CN) stretch.

\[
\begin{align*}
106 \quad R = \text{Ph} \\
107 \quad R = \text{Tol} \\
103 \quad R = \text{Ph} (60\%) \\
104 \quad R = \text{Tol} (75\%)
\end{align*}
\]

The sulfanyl nitrile compounds 102 and 104 were then converted into the corresponding oxazoline compounds 100 and 101 using methodology previously reported by this group.\textsuperscript{81} (S)-Valinol 108 was prepared through in situ generated diborane reduction of the corresponding \(\alpha\)-amino acid, 109.\textsuperscript{82}
Chapter 2: Diastereoselective oxidations

\[
\text{CO}_2\text{H} \quad \xrightarrow{\text{NaBH}_4, \text{I}_2, \text{THF}, \text{reflux, 20 hr}} \quad \text{CH}_2\text{OH}
\]

\[
\begin{array}{c}
\text{H}_2\text{N} \quad \xrightarrow{\text{+}} \quad \text{H}_2\text{N} \\
\text{109} \quad \text{108}
\end{array}
\]

75%

Reaction of the sulfanyl nitrile compounds 102 and 104 with (S)-valinol 108 in the presence of a catalytic amount of dry zinc chloride in a refluxing chlorobenzene solution resulted in, after aqueous work-up and "flash" column chromatography, formation of the corresponding oxazoline compounds 100 and 101 respectively. \(^1\)H NMR analysis of 100 and 101 confirmed product formation with the appearance of the characteristic multiplets at approximately \(\delta\) 4.0 ppm and \(\delta\) 4.4 ppm corresponding to the oxazoline ring protons. Further confirmation of oxazoline ring formation was also obtained through infra-red analysis, revealing a strong band at 1649 cm\(^{-1}\), corresponding to the C=N stretch of the oxazoline ring in both cases (100 and 101).

\[
\begin{array}{c}
\text{CN} \\
\text{R} \\
\text{102} \quad \text{R} = \text{Me} \\
\text{104} \quad \text{R} = \text{Tol}
\end{array}
\quad + \quad \begin{array}{c}
\text{HO} \\
\text{H}_2\text{N} \quad \xrightarrow{\text{cat. ZnCl}_2, \text{C}_6\text{H}_5\text{Cl}, \text{reflux, 48 hr}} \quad \text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{108} \\
100 \quad \text{R} = \text{Me (53%)} \\
101 \quad \text{R} = \text{Tol (60%)}
\end{array}
\]

2.4 Oxidation of sulfide valinol-derived oxazoline substrates

The sulfide oxazoline substrates 100 and 101 were oxidised under a variety of conditions affording the corresponding sulfoxide oxazoline compounds 110a:110b and 111a:111b in variable isolated yield, Table 1.
### Table 1

<table>
<thead>
<tr>
<th>Sulfide</th>
<th>Conditions</th>
<th>Product</th>
<th>Ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>mCPBA, CHCl₃, r.t., 10 min</td>
<td>110a:110b</td>
<td>43:57</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>mCPBA, CHCl₃, 0 °C, 10 min</td>
<td>110a:110b</td>
<td>43:57</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>mCPBA, CHCl₃, -20 °C, 45 min</td>
<td>110a:110b</td>
<td>40:60</td>
<td>95</td>
</tr>
<tr>
<td>100</td>
<td>mCPBA, CHCl₃, -78 °C, 1.25 hr</td>
<td>110a:110b</td>
<td>30:70</td>
<td>94</td>
</tr>
<tr>
<td>100</td>
<td>NaIO₄, MeOH/H₂O (1:1), 0 °C, 1 hr</td>
<td>110a:110b</td>
<td>65:35</td>
<td>91</td>
</tr>
<tr>
<td>100</td>
<td>NaBO₃·4H₂O, AcOH, 20 °C, 16 hr</td>
<td>110a:110b</td>
<td>41:59</td>
<td>94</td>
</tr>
<tr>
<td>100</td>
<td>MMPP, EtOH/H₂O (1:1), 50 °C, 1 hr</td>
<td>110a:110b</td>
<td>38:62</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>PhC(Me)₂OOH, Ti(OiPr)₄, (+)-DET, H₂O, CH₂Cl₂, -20 °C, 24 hr</td>
<td>110a:110b</td>
<td>65:35</td>
<td>42</td>
</tr>
<tr>
<td>100</td>
<td>PhC(Me)₂OOH, Ti(OiPr)₄, (-)-DET, H₂O, CH₂Cl₂, -20 °C, 24 hr</td>
<td>110a:110b</td>
<td>40:60</td>
<td>42</td>
</tr>
<tr>
<td>100</td>
<td>t-BuOOH, Ti(OiPr)₄, CH₂Cl₂, -20 °C, 24 hr</td>
<td>110a:110b</td>
<td>48:52</td>
<td>38</td>
</tr>
<tr>
<td>100</td>
<td>t-BuOOH, Ti(OiPr)₄, (+)-DET, H₂O, CH₂Cl₂, -20 °C, 24 hr</td>
<td>110a:110b</td>
<td>89:11</td>
<td>19</td>
</tr>
<tr>
<td>100</td>
<td>t-BuOOH, Ti(OiPr)₄, (-)-DET, H₂O, CH₂Cl₂, -20 °C, 24 hr</td>
<td>110a:110b</td>
<td>37:63</td>
<td>19</td>
</tr>
<tr>
<td>100</td>
<td>t-BuOOH, VO(acac)₂, CH₂Cl₂, -20 °C, 24 hr</td>
<td>110a:110b</td>
<td>85:15</td>
<td>77</td>
</tr>
<tr>
<td>101</td>
<td>mCPBA, CHCl₃, -78 °C, 1 hr</td>
<td>111a:111b</td>
<td>28:72</td>
<td>55</td>
</tr>
</tbody>
</table>

a) The ratio of the two diastereoisomers, 110a:110b was calculated by capillary GC analysis, (BP1 column (SGE); oven temperature: 200 °C). (tR = 9.46 and 10.42 min.).

b) The ratio of the two diastereoisomers, 111a:111b was calculated by capillary GC analysis, (BP1 column (SGE); oven temperature: 250 °C). (tR = 45.00 and 46.10 min.).

¹H NMR analysis confirmed product formation. For sulfoxides 110a:110b a definite shift of the three proton singlet corresponding to the protons of the methyl group attached to sulfur (from δ 2.4 ppm-sulfide to δ 2.9 ppm-sulfoxide) was seen. For sulfoxides 111a:111b a splitting of the signals corresponding to the protons of the iso-propyl group was seen at δ 0.7 ppm and δ 0.9 ppm (major diastereoisomer) and δ 0.9 ppm and δ 1.1 ppm (minor diastereoisomer). In every case ¹H NMR analysis indicated a mixture of two diastereoisomers.

Results from Table 1 indicate that by using achiral oxidants such as mCPBA, NaIO₄, NaBO₃ and magnesium monoperoxy phthalate (MMPP),...
oxidation was achieved in high yield but with relatively low selectivity. The results gained through the use of mCPBA as oxidant clearly indicate an increase in diastereoselectivity as the temperature of the reaction is lowered (40% d.e. at -78 °C whilst at room temperature only 6% d.e. was achieved). When tert-butylhydroperoxide was used as the oxidant, with titanium tetraisopropoxide or vanadyl acetylacetonate promoters, lower yields were obtained, but in the case of the latter, good levels of selectivity were obtained in the formation of sulfoxide 110a.

The reasonably high level of diastereoselectivity (70% d.e.) achieved through the use of an oxidation system derived from tert-butyl hydroperoxide and vanadyl acetylacetonate is probably due to a pre-coordination of the "active" vanadium peroxide species to the nitrogen of the oxazoline ring, thus favouring nucleophilic attack of the sulfide on the bound vanadium peroxide species from one face. The results indicate that the favoured diastereoisomer is 110a, suggesting that oxygen delivery has occurred from below the plane of the molecule, Figure 1.

For the diagram that represents oxygen delivery from above the plane of the molecule, there seems to be an unfavourable steric interaction between the bulky iso-propyl group of the oxazoline ring and the oxygen which undergoes nucleophilic attack by sulfur. For oxygen delivery from below the plane of the molecule this steric interaction does not exist, as the iso-propyl group is directed away from the vanadium peroxide oxygen. However, this model is based on pure speculation and at present there is no evidence to support these theories.

Under the above oxidation conditions the diastereoselectivity of the whole process is being entirely controlled by the oxazoline moiety (substrate controlled). By introducing the use of an chiral oxidant (reagent control), we should be able to
combine the attributes of reagent and substrate control to increase the
diastereoselectivity of the reaction. Indeed, this was found to be the case, with the
highest diastereoselectivity (78% d.e.) being achieved for the oxidation of sulfide 100
using the so-called Kagan methodology.61

The system uses a Sharpless reagent modified by the addition of one mol eq.
of water. Kagan achieved the best results using the following system, with strict
control of reagent ratio, (Ti(OiPr)4 (0.5 eq.)/diethyl tartrate (1 eq.)/H2O (0.5 eq.)/
cumene hydroperoxide (1 eq.)/sulfide (1 eq.)). In our system however, we found
that the use of tert-butyl hydroperoxide (TBHP) as oxidant gave the highest
diastereoselectivities, (when using TBHP in conjunction with (+)-DET, an 89:11 ratio
of diastereoisomers 110a:110b was achieved; under the same conditions, but using
cumene hydroperoxide as oxidant a 65:35 ratio of diastereoisomers 110a:110b was
achieved). The Kagan method of oxidation of prochiral alkyl aryl sulfides is very
versatile as either enantiomer of sulfoxide can be accessed through appropriate
choice of diethyl tartrate enantiomer. From Table 1, it can be seen that the use of a
titanium reagent modified by (R,R)-(+)-DET affords the product 110a with good
diastereoselectivity with the (R)-stereochemistry at sulfur predominating, whereas
the use of (S,S)-(−)-DET affords the other diastereomer 110b albeit with a lower
selectivity. The pairing of substrate 100 with the (R,R)-(+)-enantiomer of diethyl
tartrate constitutes a matched case, as the two components have the same stereofacial
preference, whereas the pairing of 100 with the (S,S)-(−) enantiomer of diethyl
tartrate constitutes a mismatched case because the two components do not have the
same stereofacial preference.

The mechanism for tartrate promoted oxidation of sulfides is not fully
understood, but was tentatively assigned by Kagan61a and thought to proceed
through either one of two pathways, Scheme 6.
Path A depicts external attack on the sulfur by the chiral titanium hydroperoxide, whilst path B depicts coordination of sulfur to titanium prior to the oxidation. Asymmetric induction would occur at the coordination stage (sulfur becomes chiral) if path B is favoured, whilst in path A, the oxidation process directly creates asymmetry at sulfur. Recently, Jørgensen has reported the results of an in depth study into the mechanism of the oxidation of alkyl aryl prochiral sulfides using the Kagan oxidation conditions. He concluded that sulfide oxidation under these conditions was more likely to occur through interaction with the peroxygen, path A in Scheme 6. However, he also stated that a pre-coordination of the sulfide to the titanium atom of the chiral oxidant could not be excluded.

In order to assign the correct stereochemistry of the sulfoxide oxazoline diastereoisomers, 110a:110b and 111a:111b two diastereomerically pure sulfoxide oxazoline compounds 111a and 111b were synthesised.
Chapter 2: Diastereoselective oxidations

Synthesis of 111a and 111b was achieved from 2-phenyloxazoline, 112 using methodology developed by Andersen et al. in 1964.\textsuperscript{57}

2-Phenyloxazoline, 112 was synthesised using methodology previously reported by this group.\textsuperscript{81}

![Chemical reaction](image)

Reaction of benzonitrile, 113 with (S)-valinol 108 in the presence of a catalytic amount of dry zinc chloride in refluxing chlorobenzene led to, after aqueous work-up and "flash" column chromatography the desired oxazoline, 112 in good yield. \textsuperscript{1}H NMR analysis confirmed product formation with the appearance of the characteristic multiplets at $\delta$ 4.1 ppm and $\delta$ 4.4 ppm, corresponding to the protons of the oxazoline ring. Further confirmation was gained through infra-red analysis with the disappearance of a band at 2200 cm$^{-1}$, corresponding to the nitrile (CN) stretch of 113 and the appearance of a strong band at 1651 cm$^{-1}$, corresponding to the oxazoline C=N stretch of 112.

2-Phenyloxazoline 112 was ortho-lithiated with $n$-BuLi in the presence of TMEDA in THF at -70 $^\circ$C and then quenched with the appropriate sulfinate ester, 114 or 115, resulting in formation of the desired diastereomerically pure (through inversion of stereochemistry at sulfur) sulfoxide oxazoline compounds 111a and 111b respectively, in good yield. \textsuperscript{1}H NMR analysis confirmed product formation with the appearance of a three proton singlet at $\delta$ 2.32 ppm (111a) and $\delta$ 2.31 ppm (111b) respectively, corresponding to the methyl protons of the respective p-tolyl groups. Further confirmation was also gained through infra-red analysis indicating a band at 1650 cm$^{-1}$ for both compounds (111a and 111b), corresponding to the oxazoline C=N stretch.
Chapter 2: Diastereoselective oxidations

X-ray crystallography analysis of 111b clearly indicates the (S)-stereochemistry at sulfur and is consistent with the fact that the reactions proceed with inversion of stereochemistry at sulfur, Figure 2 (see Appendix for more details).

Figure 2
The assignment of stereochemistry for diastereoisomers 110a and 110b was based tentatively on analogy with 111a and 111b. The diastereomers 111a and 111b, gained through mCPBA oxidation of 101 were compared to diastereomerically pure 111a and 111b (derived via the Andersen method), using GC analysis. Assignment was also based on the fact that the Kagan method of oxidation with (R,R)-(+) DET modified titanium reagents generally affords the (R)-stereochemistry of product in the oxidation of alkyl aryl sulfides.\textsuperscript{61}

Diastereomerically pure sulfoxide oxazoline ligands, 111a and 111b (of known configuration at both chiral centres) have also been used as ligands in several asymmetric processes (Chapter 3).

We believe that the moderate degree of diastereoselectivity obtained for the oxidation of sulfides 100 and 101 is due to the lack of organisation in the transition state, and that rotation of the oxazoline group leads to a poorly defined asymmetric environment, \textbf{Figure 3}.

We therefore required a substituent attached to the oxazoline ring that was capable of associating more strongly with the incoming oxidising reagent.

There are many examples in the literature of substrate directed reactions, where certain functional groups have the ability to direct incoming reagents, resulting in high levels of regio- and stereochemical control.\textsuperscript{86} Indeed, directed sulfide oxidation reactions have been studied by several research groups.\textsuperscript{87} In 1972, Kingsbury demonstrated the ability of the hydroxy group in directing the oxidation
Chapter 2: Diastereoselective oxidations

of prochiral sulfides.\textsuperscript{87a} Oxidation of hydroxy sulfide 116 with mCPBA at room temperature in chloroform led to the formation of hydroxy sulfoxide 117 in good yield and high diastereoselectivity (90\% d.e.).

\[
\begin{array}{c}
\text{OH} \\
\text{Ph} \\
\text{H} \\
\text{Ph} \\
\text{S} \\
\text{Ph} \\
\end{array} 
\begin{array}{c}
\text{OH} \\
\text{Ph} \\
\text{H} \\
\text{Ph} \\
\text{S} \\
\text{Ph} \\
\end{array}
\xrightarrow{\text{mCPBA, CHCl}_3, \text{r.t., 1 hr}}
\begin{array}{c}
\text{OH} \\
\text{Ph} \\
\text{H} \\
\text{Ph} \\
\text{S}^- \\
\text{Ph} \\
\end{array}
\]

116 \quad 117 \quad (90\% \text{ d.e.})

Other groups have since demonstrated the effectiveness of hydroxy-directed sulfide oxidations, with diastereomeric excesses reaching 100\%.\textsuperscript{87b-h}

Due to the good literature precedence for such reactions we decided to investigate the directing influence of a hydroxymethyl group tethered to the 4-position of the oxazoline ring.

2.5 Preparation of sulfide-hydroxy oxazoline substrates

A series of sulfide oxazoline substrates 118, 119 and 120 containing an hydroxymethyl tether at the 4-position of the oxazoline ring was prepared.

\[
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{Ph} \\
\text{S}^- \\
\text{N} \\
\text{Ph} \\
\text{R} \\
\end{array} 
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{Ph} \\
\text{S}^- \\
\text{N} \\
\text{Ph} \\
\text{R} \\
\end{array} 
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{Ph} \\
\text{S}^- \\
\text{N} \\
\text{Ph} \\
\text{R} \\
\end{array} 
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{Ph} \\
\text{S}^- \\
\text{N} \\
\text{Ph} \\
\text{R} \\
\end{array}
\]

118 \quad R = \text{Me}  \\
119 \quad R = \text{Ph}  \\
120 \quad R = \text{Tol}

Preparation of sulfide oxazolines 118 and 119 was achieved from the corresponding nitriles 102 and 103 respectively, according to methodology reported by Schumacher \textit{et al.}\textsuperscript{88} Reaction of nitriles 102 and 103 with (1S, 2S)-(+)2-amino-1-phenylpropane-1,3-diol, 121 in the presence of a catalytic amount of potassium carbonate in an ethylene glycol/glycerol mixture at 115 °C gave, after aqueous work-up and "flash" column chromatography the corresponding sulfide oxazolines, 118 and 119 respectively in reasonable yield.
**Chapter 2: Diastereoselective oxidations**

\[
\begin{align*}
\text{R}^2 R &= \text{Me} \\
\text{R}^3 R &= \text{Ph}
\end{align*}
\]

1H NMR analysis of 118 and 119 confirmed product formation with the appearance of a one proton doublet at \( \delta 5.47 \) ppm (118) and \( \delta 5.51 \) ppm (119), corresponding to the oxazoline ring proton at the 5-position. Further confirmation was also acquired through infra-red analysis indicating a strong band at 1644 cm\(^{-1}\) (118) and 1642 cm\(^{-1}\) (119) respectively, corresponding to the oxazoline C=N stretch.

Sulfide oxazoline 120 was prepared in four steps from benzonitrile, 113. Oxazoline 122 was prepared in excellent yield from benzonitrile, 122 using the Schumacher methodology.\(^{88}\) 1H NMR analysis of 122 confirmed product formation with the appearance of a one proton doublet at \( \delta 5.6 \) ppm, corresponding to the oxazoline ring proton at the 5-position. Protection of the primary alcohol of 122 was achieved by reaction with tert-butyldimethylsilyl chloride and triethylamine as base in the presence of a catalytic amount of DMAP\(^{89}\) in dichloromethane at room temperature. Infra-red analysis of 123 confirmed product formation with the disappearance of a broad band at 3440 cm\(^{-1}\), corresponding to the primary hydroxy group of 122. The oxazoline TBDMS ether, 123 was ortho-lithiated using n-BuLi in the presence of TMEDA in THF at -70 °C and then quenched with di-p-tolyl disulfide 124 resulting in, after aqueous work-up and "flash" column chromatography, formation of the desired sulfide compound, 125. 1H NMR analysis confirmed product formation with the appearance of a three proton singlet at \( \delta 2.40 \) ppm, corresponding to the methyl protons of the tolyl group. Deprotection of 125 with tetrabutylammonium fluoride in THF at room temperature resulted in, after aqueous work-up and "flash" column chromatography, formation of the desired sulfide oxazoline, 120. Infra-red analysis of 120 confirmed product formation with the appearance of a broad band at 3530 cm\(^{-1}\) corresponding to the primary OH stretch. 1H NMR analysis also confirmed product formation with the appearance of a one proton doublet at \( \delta 5.53 \) ppm, corresponding to the oxazoline ring proton at the 5-position.
Chapter 2: Diastereoselective oxidations

2.6 Oxidation of 4-hydroxymethyl substituted oxazoline sulfide substrates

As was the case with the valinol derived sulfide oxazolines 100 and 101 several oxidants were used in order to oxidise the 4-hydroxymethyl substituted oxazolines 118, 119 and 120 to their corresponding sulfoxides 126a:126b, 127a:127b and 128a:128b, Table 2.83
Chapter 2: Diastereoselective oxidations

![Diastereoselective oxidations](image)

\[ \text{CH}_2\text{OH} \]

\[ \text{R} = \text{Me} \]

\[ \text{R} = \text{Ph} \]

\[ \text{R} = \text{Tol} \]

\[ \text{CH}_2\text{OH} \]

\[ \text{R} = \text{Me} \]

\[ \text{R} = \text{Ph} \]

\[ \text{R} = \text{Tol} \]

### Table 2

<table>
<thead>
<tr>
<th>Sulfide</th>
<th>Conditions</th>
<th>Product</th>
<th>Ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>( m\text{CPBA, CHCl}_3, -70 ^\circ \text{C, 1 hr} )</td>
<td>126a:126b</td>
<td>87:13(^a)</td>
<td>78</td>
</tr>
<tr>
<td>118</td>
<td>( m\text{CPBA, MeOH, -70 ^\circ \text{C, 1.25 hr} )</td>
<td>126a:126b</td>
<td>57:43</td>
<td>76</td>
</tr>
<tr>
<td>118</td>
<td>( m\text{CPBA, Hex/CHCl}_3 \ (3:1), -70 ^\circ \text{C, 1 hr} )</td>
<td>126a:126b</td>
<td>96:4</td>
<td>76</td>
</tr>
<tr>
<td>118</td>
<td>( \text{NaBO}_3\text{.4H}_2\text{O, AcOH, 20 ^\circ \text{C, 16 hr} )</td>
<td>126a:126b</td>
<td>61:39</td>
<td>76</td>
</tr>
<tr>
<td>118</td>
<td>( \text{PhC(Me)}_2\text{OOH, Ti(OiPr)}_4, (-)-\text{DET, H}_2\text{O, CH}_2\text{Cl}_2, -20 ^\circ \text{C, 24 hr} )</td>
<td>126a:126b</td>
<td>73:27</td>
<td>55</td>
</tr>
<tr>
<td>118</td>
<td>( \text{PhC(Me)}_2\text{OOH, Ti(OiPr)}_4, (+)-\text{DET, H}_2\text{O, CH}_2\text{Cl}_2, -20 ^\circ \text{C, 24 hr} )</td>
<td>126a:126b</td>
<td>86:14</td>
<td>55</td>
</tr>
<tr>
<td>118</td>
<td>( \text{t-BuOOH, VO(acac)}_2, -20 ^\circ \text{C, 3 hr} )</td>
<td>126a:126b</td>
<td>87:13</td>
<td>85</td>
</tr>
<tr>
<td>118</td>
<td>( \text{t-BuOOH, Ti(OiPr)}_4, \text{CH}_2\text{Cl}_2, -20 ^\circ \text{C, 24 hr} )</td>
<td>126a:126b</td>
<td>97:3</td>
<td>41</td>
</tr>
<tr>
<td>118</td>
<td>( \text{t-BuOOH, Ti(OiPr)}_4, \text{CH}_2\text{Cl}_2, -20 ^\circ \text{C, 24 hr} )</td>
<td>126a:126b</td>
<td>99:1</td>
<td>32</td>
</tr>
<tr>
<td>119</td>
<td>( \text{mCPBA, CHCl}_3, -70 ^\circ \text{C, 2 hr} )</td>
<td>127a:127b</td>
<td>83:17(^b)</td>
<td>94</td>
</tr>
<tr>
<td>119</td>
<td>( \text{t-BuOOH, VO(acac)}_2, \text{CH}_2\text{Cl}_2, -20 ^\circ \text{C, 4 hr} )</td>
<td>127a:127b</td>
<td>79:21</td>
<td>15</td>
</tr>
<tr>
<td>120</td>
<td>( \text{mCPBA, CHCl}_3, -20 ^\circ \text{C, 1 hr} )</td>
<td>128a:128b</td>
<td>80:20(^c)</td>
<td>90</td>
</tr>
</tbody>
</table>

\(^a\) The ratio of the two diastereoisomers 126a:126b was determined by reverse phase HPLC (Bondapak C18 column); acetonitrile/water, 2:1, 1 ml/min. (\( t_R=16.5 \) and 17.5 min.).

\(^b\) The ratio of the two diastereoisomers 127a:127b was determined by inspection of the \(^1\)H NMR spectra, (integration of the doublets at \( \delta 5.4 \) ppm and \( \delta 5.5 \) ppm, corresponding to the CHO proton of the oxazoline ring).

\(^c\) The ratio of the two diastereoisomers 128a:128b was determined by reverse phase HPLC (Bondapak C18 column); acetonitrile/water, 2:1, 1 ml/min. (\( t_R=20.5 \) and 21.9 min.).

\(^1\)H NMR analysis confirmed product formation. For sulfoxides 126a:126b a definite shift of the three proton singlet corresponding to the protons of the methyl...
group attached to sulfur (from $\delta$ 2.47 ppm-sulfide to $\delta$ 2.91 ppm-sulfoxide) was seen. For sulfoxides 127a:127b and 128a:128b a splitting of the signal (indicating a mixture of two diastereoisomers) was seen at $\delta$ 5.38 ppm (minor) and $\delta$ 5.44 ppm (major), and $\delta$ 5.35 ppm (minor) and $\delta$ 5.43 ppm (major) respectively corresponding to the proton of the oxazoline ring at the 5-position.

From Table 2 it can clearly be seen that the levels of diastereoselectivity achieved for the oxidation of sulfide substrates containing an hydroxymethyl tether 118, 119 and 120 are far greater than for the corresponding substrates containing an iso-propyl group in the 4-position of the oxazoline ring 100 and 101 (see section 2.4).

For example oxidation of sulfide oxazoline 118 with mCPBA at -70°C resulted in formation of the corresponding sulfoxide oxazoline diastereoisomers 126a:126b in a ratio of 87:13. The analogous reaction undertaken in section 2.4 (Table 1) on sulfide oxazoline 100, resulted in formation of the corresponding sulfoxide diastereoisomers 110a:110b in a ratio of 30:70. It can also be seen that for substrates containing a 4-hydroxymethyl tether 118, 119 and 120, oxygen delivery has preferentially occurred from the same face of the molecule as the 4-hydroxymethyl substituent. This result is entirely consistent with a number of other groups who have demonstrated the directing ability of the hydroxy group in the oxidation of sulfide substrates. It is also noticeable from Table 2 that the diastereoselectivity for the mCPBA oxidation of sulfide oxazoline 118 is highly dependant upon the nature of the solvent. Here, the diastereoselectivity of this oxidation procedure was seen to increase dramatically on changing from a protic solvent (MeOH), (57:43) to an aprotic solvent (CHCl$_3$), (87:13) and to increase still further on reducing the polarity of the solvent (Hex/CHCl$_3$, 3:1), (96:4). This suggests that hydrogen bonding between the hydroxy group and the mCPBA is important for high levels of selectivity.

A simple experiment was undertaken to test this theory. The sulfide oxazoline substrate, 129 containing a 4-methoxymethyl tether was synthesised from sulfide oxazoline 118 as shown.
Treatment of the sodium salt of sulfide oxazoline 118 with methyl iodide resulted in, after aqueous work-up and "flash" column chromatography, formation of the desired methoxy compound 129 in excellent yield. \(^1\)H NMR analysis of 129 confirmed product formation with the appearance of a three proton singlet at \(\delta 3.45\) ppm, corresponding to the protons of the methoxy group.

\(m\)CPBA oxidation of the sulfide methoxy compound, 129 in chloroform at \(-70\) \(^\circ\)C, resulted in the formation of a mixture of two diastereoisomers of the desired sulfoxide compound, 130a:130b. \(^1\)H NMR analysis of 130a:130b confirmed product formation with a definite shift of the three proton singlet corresponding to the protons of the methyl group attached to sulfur (from \(\delta 2.47\) ppm-sulfide to \(\delta 2.90\) ppm-sulfoxide).

Reverse phase HPLC analysis (Bondapak C\(_{18}\)); eluant, acetonitrile/water, 2:1, 1 ml/min., of 130a:130b indicated a diastereoisomeric ratio of 55:45. (t\(_R\) = 25.5 and 28.0 min.).

Such a result achieved when oxidising sulfide oxazoline 129, suggests that the substrate is not able to coordinate effectively with the incoming oxidant, hence the low diastereoselectivity. This also tends to suggest that for high diastereoselectivity to be achieved in these systems hydrogen bonding between the substrate (hydroxy) and the incoming reagent (\(m\)CPBA) is essential.

Table 2 also indicates that for the tert-butylhydroperoxide, vanadyl acetylacetonate promoted reactions no increase in diastereoselectivity was observed for the oxidation of sulfide substrates 118 and 119. If we compare these results with the identical oxidation reactions performed on sulfide substrate 100 (Table 1, section 2.4), where an increase in diastereoselectivity was seen, then we should have observed a similar result for sulfide substrates containing a 4-hydroxymethyl tether, 118 and 119. Assuming that both the hydroxy group and the oxazoline nitrogen are able to coordinate to the vanadium centre, then we would predict a similar model to that proposed for the titanium tetraisopropoxide promoted tert-butylhydroperoxide oxidation reactions (see page 46). The moderate levels of diastereoselectivity...
achieved (74% d.e. (126a:126b) and 58% d.e. (127a:127b)) could be due to coordination problems between the hydroxy group and the vanadium centre, although at this stage we have no evidence to support this theory.

However, the titanium tetraisopropoxide-promoted tert-butylhydroperoxide oxidation of sulfide substrate, 118 was highly diastereoselective (97:3, 126a:126b), and this selectivity could be enhanced still further by the use of an (R,R)-(+)−DET-modified titanium reagent (99:1, 126a:126b). This provides an excellent example of how the attributes of substrate and reagent (matched case) can be combined to provide very high levels of diastereocontrol.

Again, the assignment of stereochemistry for sulfoxide diastereoisomers 126a:126b, 127a:127b and 128a:128b was based tentatively upon analogy to the work done by Kagan ((R,R)-(+)−enantiomer of diethyl tartrate, generally affords the (R)-stereochemistry of product in the oxidation of alkyl aryl sulfides)61 and on HPLC analysis of the corresponding diastereomerically pure sulfoxide oxazoline compound, 128b (compare with the mCPBA oxidation of sulfide 120).

![Chemical structures](image)

Synthesis of 128b was achieved in two steps from the oxazoline TBDMS-ether, 123 using Andersen methodology.57 ortho-Lithiation was achieved with n-BuLi in the presence of TMEDA in THF at -70 °C. The resultant dark red lithium anion was then quenched with the (S)-enantiomer of commercially available...
menthyl sulfinate ester 115, resulting in inversion of stereochemistry at sulfur, giving the diastereomERICally pure TBDMS-protected sulfoxide oxazoline, 131. $^1$H NMR analysis of 131 confirmed product formation with the appearance of a three proton singlet at $\delta$ 2.29 ppm, corresponding to the methyl protons of the tolyl group. Deprotection of 131 with tetrabutylammonium fluoride in THF at room temperature resulted in, after aqueous work-up and "flash" column chromatography, formation of the desired diastereomERICally pure sulfoxide oxazoline compound, 128b in good yield. $^1$H NMR analysis confirmed product formation with the appearance of a one proton doublet at $\delta$ 5.30 ppm, corresponding to the oxazoline ring proton at the 5-position. Infra-red analysis also confirmed product formation with the appearance of a broad band at 3380 cm$^{-1}$, corresponding to the OH stretch.

The stereochemistry at the sulfur centre of 128b was confirmed through X-ray crystallography analysis, clearly showing it to be (S)-, Figure 4 (see Appendix for more details).
We believe that the high levels of 1,6-asymmetric induction that we observe for the oxidation of sulfide substrates 118, 119 and 120 is made possible by the combined effect of the hydroxy group and the oxazoline nitrogen both of which associate with the incoming reagent (mCPBA or Ti), providing more organisation in the transition state than is possible in the absence of the hydroxy group, Figure 5.

In both cases (Figure 5) we assume that the R group attached to sulfur is in the same plane as the aromatic ring (perhaps due to an overlap of the available lone pairs on sulfur with the \( \pi \)-electrons of the aromatic ring). If this is the case, rotation about the sulfur to aromatic ring bond (S-C) should be somewhat restricted, thus resulting in a highly ordered, well defined transition state for both models (Figure 5).

2.7 Conclusions

It has been shown that enantiomerically pure 4,5-dihydrooxazoles (oxazolines) tethered to an phenyl group ortho to a sulfide containing group, are able to direct the oxidation of these sulfides to the corresponding sulfoxides with good diastereoselectivity. Good levels of diastereoselectivity (up to 70% d.e.) were achieved for the oxidation of sulfide oxazolines which contained a 4-substituted iso-propyl group as the stereochemical controlling group. Whereas, when the oxazoline contained a 4-hydroxymethyl tether as the stereochemical controlling group excellent levels of diastereoselectivity could be achieved in the presence of achiral oxidants (up to 94% d.e.) and this could be improved still further (98% d.e.) when using a chiral oxidant (Kagan). All sulfides 100, 101, 118, 119 and 120 provide effective examples of 1,6-asymmetric induction, a process which in the past has been notorious for providing only moderate levels of diastereoselectivity.86
CHAPTER 3

SULFOXIDES AS LIGANDS IN ASYMMETRIC SYNTHESIS
3.1 Introduction

In Chapter 2 the diastereoselective oxidation of a range of aryl sulfides was described, where the diastereoselectivity achieved was a consequence of the stereochemical controlling properties of the 4,5-dihydrooxazole moiety. Although, in some cases high diastereoselectivity (up to 98% d.e.) was achieved, the successful application of sulfoxide-based oxazoline compounds as ligands would require essentially diastereomerically pure compounds of known stereochemistry at both centres (sulfur and the 4-position of the oxazoline ring). As was described in Chapter 2, the use of sulfoxides as stereochemical controlling groups in asymmetric synthesis is well known. In the majority of cases these sulfoxides have been used as chiral auxiliaries, however there are relatively few examples relating to the use of sulfoxides as ligands in asymmetric synthesis. It is known that sulfoxides have the ability to coordinate to metals through either oxygen (O) or sulfur (S) and as such, have been termed ambidentate ligands. We were interested in the possible application of sulfoxides tethered to oxazolines as ligands for asymmetric synthesis. Initially we chose to concentrate our efforts on the asymmetric palladium catalysed allylic substitution reaction, a process well known to this group.

3.2 Sulfoxides as ligands in the asymmetric palladium catalysed allylic substitution reaction

3.2.1 Background

Palladium catalysed reactions are of particular importance in synthetic organic chemistry, examples include Heck reactions, Stille couplings, Suzuki couplings, Wacker oxidation and allylic substitution reactions. Central to all of these catalytic reactions is the ease with which palladium is able to undergo oxidative addition and reductive elimination reactions.

The palladium catalysed allylic substitution reaction is a very reliable process with new developments in its synthetic utility being reported regularly. \( \eta^3 \)-Allyl palladium complexes were initially isolated 34 years ago, being produced by the reaction of palladium(II) salts with dienes. In 1965, Tsuji et al. demonstrated a stoichiometric reaction of \( \pi \)-allylpalladium complexes with a range of nucleophiles effecting an overall allylic substitution. Throughout the early 1970's the process was developed into a catalytic process to the main palladium catalysed allylic substitution reaction that we have today. The basic palladium catalysed allylic
substitution process involves the conversion of a suitable allylic substrate such as an allyl acetate into its substitution product, through reaction with a nucleophile (dimethyl malonate) in the presence of catalytic amounts of phosphine ligand and palladium(0), Scheme 7.

\[
\text{Scheme 7}
\]

3.2.2 Mechanism

The mechanism of the reaction for many nucleophiles is outlined in Scheme 8. Initial association of a palladium(0) catalyst with the alkene, followed by an oxidative addition process affords a \( \pi \)-allylpalladium intermediate (\( \eta^3 \)-allyl complex). In the presence of phosphine, an equilibrium between a neutral and cationic complex results. The cationic complex is favoured by the use of bidentate phosphine ligands. These complexes behave as palladium stabilised allyl cations, which readily undergo reaction with various nucleophiles to afford the palladium(0) complex of product. Dissociation of the palladium(0) liberates the product and regenerates the active palladium catalyst.\textsuperscript{100}
3.2.3 Geometry of allyl complexes

For mono- and di-substituted allyl complexes during formation of the intermediate π-allyl complexes there arises the possibility of forming syn 132 and anti 133 and syn, syn 134 and anti, anti 135 geometries of the allyls respectively. In both cases the anti geometries 133 and 135 are sterically unfavourable, and the isomeric forms are able to equilibrate by a π-σ-π mechanism. However, in certain cases the choice of ligand, L may result in a preference for the anti configuration as a consequence of unusual steric considerations.101

3.2.4 Range of substrates and nucleophiles

Allylic acetates are almost certainly the most commonly employed substrates for palladium catalysed allylic substitution reactions, although a number of other leaving groups will function effectively including, halides,102 carbonates,103 sulfones,104 carbamates, epoxides105 and phosphates.106 The more commonly employed nucleophiles for the palladium catalysed allylic substitution reaction are the "soft" stabilised carbanions such as the enolate of dimethyl malonate but under suitable conditions, nitrogen based nucleophiles,107 sulfur nucleophiles,108 oxygen nucleophiles,109 organometallics,110 and various others96a have all been successfully employed.
3.2.5 Stereochemistry in the palladium catalysed allylic substitution reaction

Studies undertaken by Trost and co-workers have illustrated a net retention of stereochemistry when using stabilised nucleophiles in the palladium catalysed allylic substitution reaction. The results gained were rationalised by two sequential inversion steps. Firstly the palladium displaces the leaving group with inversion and then the nucleophile attacks from the \textit{exo} face with inversion, Scheme 9.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {CO\textsubscript{2}CH\textsubscript{3}};
\node (b) at (1,0) {CO\textsubscript{2}CH\textsubscript{3}};
\node (c) at (2,0) {CO\textsubscript{2}CH\textsubscript{3}};
\node (d) at (-0.5,0) {\text{inversion}};
\node (e) at (0.5,0) {\text{inversion}};
\node (f) at (-1,0) {\text{CHO(CO}_{2}\text{CH}_{3})_{2}};
\node (g) at (-1,-1) {PdL\textsubscript{2}};
\node (hi) at (-1,-2.5) {\text{OAc}};
\draw[->] (a) -- (d) -- (b) -- (e) -- (c) -- (f);
\draw[->] (g) -- (a);
\draw[->] (hi) -- (g);
\end{tikzpicture}
\end{center}

\textit{overall retention}

Scheme 9

However, it has been shown that not all nucleophiles afford overall retention of stereochemistry.

3.2.6 Enantiocontrol of reactions

Trost and Dietsche were the first to show that the use of an enantiopure ligand could produce enantiomerically enriched products. The stoichiometric reaction of an allylpalladium chloride dimer, 136 with the sodium salt of dimethyl malonate and enantiomerically pure phosphine ligand (+)-DIOP resulted in formation of the substitution product 137, in good yield and with 23\% enantiomeric excess.
Chapter 3: Sulfoxides as ligands

The first catalytic asymmetric example of this reaction was reported in 1977 by Trost and Stege, involving the conversion of the racemic allylic acetate 138 into the modestly enantiomerically enriched (46% e.e.) alkylated product, 139.114

Most palladium catalysed allylic substitution processes are based around the formation of an intermediate meso-allylpalladium intermediate 140. In the absence of an enantiopure ligand the allylic substrate 141, which initially forms the meso complex 140, can undergo nucleophilic attack at either terminus of the allyl resulting in the formation of the two enantiomers 142 and 143. In the presence of an enantiopure ligand nucleophilic attack should be preferentially directed towards one terminus of the allyl (path a or b), resulting in the formation of enantiomerically enriched products.

Mechanistically this is difficult to achieve as the stereochemical controlling group of the ligand will be on the opposite face of the allyl to the incoming...
nucleophile. Hence, exploitation of this reaction as an enantioselective process has challenged organic chemists to develop efficient enantiomerically pure ligands.

Trost has recently written a review describing the recent advances in asymmetric metal catalysed allylic substitution reactions and in it, there are many examples of ligands capable of affording high levels of enantioselectivity for this reaction. Basically there are three types of ligand that have been used to control enantioselectivity in palladium catalysed allylic substitution processes:

- those which exert enantiocontrol through secondary interactions of the ligand.

Examples in this class include:

- Example by Hayashi et al.\textsuperscript{115}

- Example by Minami et al.\textsuperscript{116}

- Example by Kumada et al.\textsuperscript{117}

In effect these ligands contain an "arm" which is able to reach around the allyl moiety, thus preferentially directing nucleophilic addition to one of the two termini.
those which exert enantiocontrol through affecting steric distortions upon the allyl moiety.

Examples in this class include:

Due to a steric interaction between one of the groups on the chiral ligand (X) and one of the allylic termini the symmetry of the allyl is perturbed. This results in a distortion of the intermediate meso-\(\eta^3\)-allylpalladium intermediate, thus lengthening one of the palladium-carbon (Pd-C of the allyl) bonds. Therefore, the terminus which has been forced away from the palladium complex will be more electrophilic in nature and hence more likely to undergo nucleophilic addition.
Chapter 3: Sulfoxides as ligands

• those which exert enantiocontrol by achieving an electronic distortion of the allyl moiety.

\[
\begin{align*}
\text{Pd} & \quad L \quad Nuc^- \\
\text{N} & \quad \text{S} \quad \text{R} \\
\end{align*}
\]

\( L = \) Auxiliary donor ligand (e.g. S or P) which is also a good \( \pi\)-acceptor

Examples in this class include:

\[
\begin{align*}
&\text{Williams et al.}^{124} \\
&\text{Williams et al.}^{125} \\
&\text{Pfaltz et al.}^{126} \\
&\text{Helmchen et al.}^{127} \\
&\text{Brown et al.}^{128}
\end{align*}
\]

Due to the presence of two different donor atoms (L and N) these ligands are able to achieve an overall "electronic asymmetry" in the \( \eta^3\)-allyl palladium intermediate. Work originally carried out by Åkermark, Vitagliano and co-workers suggested that if a ligand contained two different donor atoms, it would be able to impart an electronic distortion upon the allyl moiety in an intermediate palladium \( \pi\)-allyl complex, thus controlling the approach of any incoming nucleophile.\(^{129}\) For the above system, L (sulfur or phosphorus) is a much better \( \pi\)-acceptor (i.e. can accept back donation from a full d-orbital on the palladium) than nitrogen, N. Due to the geometry of the d-orbitals on L more electron density is drawn from the carbon (of the allyl moiety) \textit{trans} to the better \( \pi\)-acceptor, L, resulting in a relatively more electrophilic centre at this position. Nucleophilic addition to the allyl moiety will therefore occur \textit{trans} to the better \( \pi\)-acceptor, as this position has more positive charge character.

This group has been concerned with the preparation of ligands that are able to effect an electronic distortion upon the allyl moiety. Initially the mode of action of these ligands was not thoroughly understood, but recent work undertaken independently by the groups of Brown,\(^{128}\) Helmchen\(^{130}\) and Pfaltz\(^{131}\) has shed some
light onto this problem. X-Ray crystallography work undertaken by Helmchen and co-workers\textsuperscript{130} (on phosphine-based oxazoline ligands) indicates that during formation of the diastereomeric \( \eta^3 \)-allylpalladium intermediates, the major and in fact more reactive diastereoisomer at equilibration is when the allyl moiety is fixed into the so-called "W" conformation, Figure 6.

![Figure 6](image)

\textbf{Figure 6} clearly indicates that the R groups of the allyl are pointing in the same direction as the R' group of the ligand. Upon first inspection this would seem to be the least likely scenario as the R' group can be quite large (iso-propyl, tert-butyl or phenyl) and this sort of relationship would create considerable steric crowding. However, it has been suggested that the R' group can "flip" back and away from the complex, which in turn, brings the hydrogen at the same carbon closer to the allyl moiety. Hence, if this is the likely scenario then it would seem that the hydrogen provides a greater stereochemical influence than the R' group, causing the allyl R groups to be placed as far away as possible from the hydrogen atom.

Williams \textit{et al.} have recently demonstrated the effective use of sulfide-based oxazoline compounds as ligands for the asymmetric palladium catalysed allylic substitution reaction.\textsuperscript{124} Using sulfide ligand 144 they were able to achieve an enantiomeric excess of 90\% for the conversion of racemic allylic acetate 145 into its alkylated product 146.
Based on the X-ray crystallography work undertaken by Helmchen and co-workers plus the knowledge that π-acceptor groups (e.g. sulfur) direct nucleophilic addition trans to themselves, then it would seem likely that the more reactive diastereomeric intermediate is when the allyl is again fixed into the "W" conformation, (although it must be noted that there is no real evidence for the bidentate binding behaviour of sulfide-based oxazoline ligands). If this is the case, then for sulfide-based oxazoline ligands such as 144 a new undefined stereocentre is formed at sulfur during formation of the intermediate π-allylpalladium complex. As the sulfide centre possesses two pairs of unpaired electrons there arises the possibility of forming two diastereoisomers, 147 and 148.

Does the sulfur centre play a crucial role in determining the overall stereochemical outcome of this reaction?

We considered the possibility of using sulfoxide-based oxazoline compounds of defined stereochemistry at sulfur, as ligands for the asymmetric palladium catalysed allylic substitution reaction. For sulfoxides there is only one lone pair on sulfur available for complexation, and we assume that the palladium can bind without perturbing stereochemical integrity.
3.3 Synthesis of diastereomerically and enantiomerically pure sulfoxide-based oxazoline ligands

We decided to prepare a series of sulfoxide-based oxazoline compounds that could be used as ligands for the asymmetric palladium catalysed allylic substitution process.

The synthesis of diastereomerically pure sulfoxide oxazolines, 111a, 111b and 128b was achieved using Andersen methodology and is described in Chapter 2.

Two enantiomerically pure sulfoxide-based oxazoline ligands were also synthesised. Synthesis of 149 and 150 was achieved from the corresponding 2-phenyl-substituted oxazolines, 151 and 152 respectively, again using Andersen methodology.

Reaction of the commercially available oxazoline compounds 151 and 152 with n-BuLi in the presence of TMEDA in THF at -70 °C for 4 hr resulted in formation of the corresponding ortho-lithiated oxazoline compounds. The lithium anions were then quenched with the (S)-enantiomer of commercially available menthyl sulfinate ester, 115 resulting in formation of, after aqueous work-up and "flash" column chromatography, the corresponding sulfoxide-based oxazoline compounds 149 and 150 respectively (through an inversion mechanism) in reasonable yield. \(^1\)H NMR analysis confirmed product formation in both cases with the appearance of a three
proton singlet at $\delta$ 2.32 ppm corresponding to the methyl protons of the tolyl group. Infra-red analysis also confirmed product formation with the appearance of a strong band at 1648 cm$^{-1}$ (149) and 1650 cm$^{-1}$ (150) corresponding to the C=N stretch of the oxazoline ring.

With a range of diastereomerically pure 111a, 111b, 128b and enantiomerically pure 149, 150 sulfoxide-based oxazoline ligands in hand we turned our attention towards the asymmetric palladium catalysed allylic substitution reaction.

### 3.4 Asymmetric palladium catalysed allylic substitution

We chose to focus our attention on reactions that proceeded through meso $\eta^3$-allyl intermediates, and by suitable choice of starting allyl acetate the $\eta^3$-allyl moiety will be symmetrical. (E)-1,3-Diphenyl-1-acetoxy-prop-2-ene, 145 was chosen as the allylic substrate. The synthesis of allylic acetate 145 was achieved in two steps from commercially available *trans*-cinnamaldehyde 153, as previously reported by this group.132

![Chemical Reaction](image)

Treatment of *trans*-cinnamaldehyde 153 with a 3.0 M solution of phenylmagnesium bromide in ether at 0 °C resulted in, after aqueous work-up and "flash" column chromatography, formation of the disubstituted allylic alcohol, 154 in excellent yield. $^1$H NMR analysis of 154 confirmed product formation with the appearance of a one proton broad singlet at $\delta$ 2.5 ppm, corresponding to the proton of the hydroxy group. Acetylation of the allylic alcohol 154 was achieved using
acetic anhydride, triethylamine as base in the presence of a catalytic amount of DMAP\(^8\) in dichloromethane at room temperature. \(^1\)H NMR analysis of 145 confirmed product formation with the disappearance of a one proton broad singlet at \(\delta 2.5\) ppm, corresponding to the hydroxy group of 154 and the appearance of a three proton singlet at \(\delta 2.1\) ppm, corresponding to the protons of the acetoxy group.

The enantioselective palladium catalysed allylic substitution reactions were performed as previously reported by this group.\(^1\)

\[
\text{Ph} = \text{CH} = \text{CH} - \text{Ph} + \text{CH}_2(\text{CO}_2\text{CH}_3)_2, \text{BSA,} \\
2.5 \text{ mol\% } [\text{Pd(} \eta^3-\text{C}_3\text{H}_5\text{)}\text{Cl}]_2 \\
10 \text{ mol\% Ligand,} \\
2 \text{ mol\% NaOAc,} \\
\text{CH}_2\text{Cl}_2, 20 ^\circ\text{C, 48 hr} \\
\]

A solution of BSA,\(^2\) dimethyl malonate and sodium acetate in dichloromethane was added to a stirred solution of the allylic acetate 145, ligand (10 mol\%) and allylpalladium chloride dimer (2.5 mol\%) (pre-stirred for 15 min) in dichloromethane at room temperature. After stirring for 48 hr at room temperature the alkylated product 146 was isolated (after aqueous work-up and "flash" column chromatography) in good yield. In every case \(^1\)H NMR analysis confirmed product formation with the disappearance of a three proton singlet at \(\delta 2.1\) ppm, corresponding to the acetoxy group of 145 and the appearance of a one proton doublet at \(\delta 4.3\) ppm corresponding to the methine proton of 146.

In all cases the substitution product 146 was isolated enriched in the (S)-enantiomer, as determined by comparison of the optical rotations with literature values.\(^3\)

The results for the asymmetric palladium catalysed allylic substitution reactions are summarised in Table 3.\(^4\)

### Table 3

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%) (146)</th>
<th>e.e. (%)(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111a</td>
<td>42</td>
<td>55</td>
</tr>
<tr>
<td>111b</td>
<td>96</td>
<td>89</td>
</tr>
<tr>
<td>128b</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>149</td>
<td>92</td>
<td>56</td>
</tr>
<tr>
<td>150</td>
<td>69</td>
<td>50</td>
</tr>
</tbody>
</table>

\(^a\) The enantiomeric excess of 146 was determined by chiral HPLC (Chiralcel OD), hexane/isopropanol, 99:1, 0.7 ml/min. (\(t_R = 13.6\) and 14.6 min.), and by \(^1\)H NMR studies in the presence of 0.5 equivalents of the enantiopure shift reagent Eu(hfc)\(_3\). (Best results were achieved using 2 mg of 146).
Table 3 clearly indicates that both yield and enantioselectivity are dependent upon the choice of sulfoxide ligand. Ligand 111b provides both a much greater yield (96%) and enantioselectivity (89% e.e.) in the palladium catalysed reaction than does the diastereomeric ligand 111a (42% yield and 55% e.e.). Such a result tends to suggest that the stereochemistry of the sulfur centre is indeed important in determining the stereochemical outcome of the reaction. As the sulfoxide hydroxy oxazoline ligand 128b provides a similar yield and enantioselectivity to ligand 19 it is fair to assume that the hydroxy group of 128b does not participate in this process (i.e. does not coordinate to palladium or the incoming nucleophile). Table 3 also indicates that ligand 111b provides similar levels of enantioselectivity to the corresponding sulfide ligand (92% e.e. when there is an iso-propyl group at the 4-position of the oxazoline ring and a p-tolyl group attached to sulfur). Such a result tends to suggest that for the sulfide ligands the stereochemistry at the sulfur centre can switch readily to the preferred configuration upon binding to the palladium (see 147 and 148, section 3.2.6). Ligands 149 and 150 are also able to provide a reactive palladium catalyst system, affording 56% and 50% enantiomeric excess respectively. When using 149 and 150 as ligands there is no stereochemistry in the oxazoline moiety and as such the enantioselectivity of the whole process is being controlled by the enantiomerically pure sulfoxide group. Specifically with the use of sulfoxide ligands we have in theory two centres available for palladium coordination (sulfur and oxygen). Although it is known that in general Pd(II) salts coordinate to sulfoxides through sulfur, coordination through oxygen is known. The sulfone ligand 155 was synthesised through mCPBA oxidation of sulfoxide diastereoisomer 111a.

\[
\text{CHCl}_3, \text{r.t.}, 2 \text{ hr} \rightarrow \text{S=O (sulfoxide, 111a) and the appearance of a band at 1156 cm}^{-1}, \text{ corresponding to the } S=O \text{ stretch of the sulfone group of 155. When used as a ligand for the asymmetric palladium catalysed allylic substitution reaction none of the required alkylated product 146 was observed. This means that the sulfone ligand, 155 which is not able to bind to palladium through sulfur, cannot provide a reactive}
\]
palladium catalyst, suggesting that coordination through the oxygen of the sulfone is unfavourable. Furthermore, this also suggests that the sulfoxide ligands are more likely to bind through the sulfur atom than the oxygen. Infra-red analysis was attempted to ascertain whether palladium coordination was through the sulfur or oxygen of the sulfoxide (coordination of a sulfoxide ligand through oxygen is known to effect a decrease in S=O stretching frequency and an increase if coordination is through sulfur)\(^\text{137}\) but unfortunately the results obtained were not conclusive.

As to why sulfoxide diastereoisomer 111b affords a higher yield and enantioselectivity than the other sulfoxide diastereoisomer, 111a is not entirely clear. Simple modelling however seems to provide a plausible explanation, Figure 7.

![Figure 7](image)

Based on the work undertaken by Helmchen et al.\(^\text{130}\) and if palladium coordination to the sulfoxide is through sulfur it is possible to imagine the two intermediates 156 and 157, where 156 represents palladium coordination to the \((S)\)-sulfoxide and 157 represents palladium coordination to the \((R)\)-sulfoxide. In both intermediates 156 and 157 we have more or less square planar geometry around palladium and such an arrangement places the \(p\)-tolyl group attached to sulfur, the oxygen of the sulfoxide, both phenyl groups of the allyl moiety and the groups at the 4-position of the oxazoline ring out of this plane. For intermediate 156 the \(p\)-tolyl group is above the square plane and as such is placed in very close proximity to one of the phenyl groups of the allyl moiety. With this type of arrangement it is not impossible to imagine a \(\pi\)-interaction (face-edge) between these two aromatic groups, which could lead to a more stable, well-defined transition state than is possible for intermediate 157. For intermediate 157 the \(p\)-tolyl group lies below the square plane and as such is too far away from the phenyl group of the allyl moiety to experience any \(\pi\)-interaction. This however is pure speculation and at present we have no evidence to support this theory.
3.5 Sulfoxide-oxazolines as ligands in other asymmetric processes

3.5.1 Asymmetric addition of diethylzinc to benzaldehyde

The asymmetric addition of dialkylzinc reagents to aldehydes catalysed by enantiomerically pure ligands is a well known and studied process. The resultant enantiomerically enriched alcohols are important synthetic intermediates in the synthesis of a variety of compounds. We were interested to see if the diastereomerically pure sulfoxide-oxazoline ligands 111b and 128b (of known stereochemistry at both centres) could be used as effective catalysts for this process. Indeed, Williams et al. have recently reported the use of enantiomerically pure oxazoline ligands tethered to alcohols as effective catalysts for the addition of diethylzinc to aldehydes, achieving up to 67% enantiomeric excess when using ligand 45.

Carreño and co-workers have demonstrated the use of β-hydroxysulfoxides as chiral catalysts for the asymmetric addition of diethylzinc to benzaldehyde, achieving up to 45% enantiomeric excesses when using ligand 158. They postulated an initial coordination of diethylzinc with the hydroxy group of 158, forming the zinc monoalkoxide and then coordination of this species with the basic sulfinyl oxygen.

With this in mind the asymmetric addition of diethylzinc to benzaldehyde 46 was attempted using catalyst systems derived from ligands 111b and 128b. Here, we were hoping to achieve a catalyst system derived from the ligand (111b or 128b)
and diethylzinc, where zinc coordination would be through the sulfinyl oxygen and the oxazoline nitrogen.

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{Tol} \quad \text{iPr}
\end{array}
\]

\[111b\]

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

\[128b\]

A mixture of benzaldehyde and the appropriate ligand (6 mol%) (111b or 128b) in hexane was stirred at room temperature for 30 min before the addition of diethylzinc. The reaction mixture was stirred for 16 hr before being quenched with 1M HCl. The benzyl alcohol, 47 was isolated in both cases after aqueous work-up and "flash" column chromatography, see Table 4.

Table 4

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%) (47)</th>
<th>e.e. (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111b</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>128b</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) The enantiomeric excess of 47 was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 99:1, 1.0 ml/min. (\(t_R = 17\) and 20 min.).

Table 4 indicates that the use of sulfoxide diastereoisomer 111b as chiral catalyst led to a very poor yield (10%) and very low enantiomeric excess (5%). The use of sulfoxide diastereoisomer 128b on the other hand led to an enhanced yield (50%) and enantioselectivity (60%). These results tend to suggest that catalyst 128b is a successful bidentate binding ligand and 111b is obviously not. Furthermore, this also tends to suggest that for ligand 128b, zinc coordination is almost certainly through the oxazoline nitrogen and the hydroxy group and not the sulfoxide oxygen and oxazoline nitrogen. Two pieces of evidence support this theory:
• Use of sulfoxide diastereoisomer 111b, which does not contain an additional coordinating group (i.e. hydroxy) led to a very poor yield and enantioselectivity, suggesting that zinc coordination to the sulfoxide oxygen has not occurred.

• The work undertaken by Allen and Williams\textsuperscript{32} provided similar levels of enantioselectivity and yield (compare ligand 45, where zinc coordination to the ligand was postulated to have been through the oxazoline nitrogen and the hydroxy group) to sulfoxide diastereoisomer 128b.

Further investigation into these problems was not undertaken due to time restraints, and the fact that there are better ligands available for this process.

3.5.2 Use of sulfoxide oxazolines as ligands for the addition of trimethylsilylcyanide to benzaldehyde

The enantioselective addition of a cyanide source to aldehydes catalysed by chiral titanium-based catalysts, resulting in the formation of cyanohydrins, has recently received considerable attention.\textsuperscript{139} Optically active cyanohydrins are versatile intermediates in the preparation of a variety of important classes of organic compounds, including $\alpha$-hydroxy carboxylic acids.\textsuperscript{140}

Oguni \textit{et al.} have recently reported the enantioselective addition of trimethylsilylcyanide to a range of aldehydes catalysed by a chiral titanium-Schiff base compound. They reported enantiomeric excesses in the range 34–96% when using catalysts derived from Schiff base 159.\textsuperscript{141}

![Diagram](image)

We hoped to achieve similar levels of enantioselectivity by using chiral titanium Lewis acid catalysts derived from the sulfoxide-based oxazoline ligands 111b and 128b. With these ligands initial coordination of titanium with the ligand was expected to be through the sulfinyl oxygen and the oxazoline nitrogen. Ligand
128b, which has an additional coordinating group (hydroxy) should provide a superior asymmetric environment for the coordinated aldehyde molecule, thus encouraging cyanide addition preferentially from one face of the aldehyde double bond, Figure 8.

The addition of trimethylsilylcyanide to benzaldehyde 46 catalysed by titanium species derived from ligands 111b and 128b was undertaken as shown.

Benzaldehyde and TMSCN were added to a stirred solution of the pre-prepared catalyst system (20 mol%), derived from titanium tetraisopropoxide and ligand (111b or 128b) at -70 °C and the solution stirred at this temperature for 10 hr, before being kept in a freezer (-25 °C) for a further 30 hr. The reaction mixture was quenched with 1M HCl and the cyanohydrin, 160 isolated after aqueous work-up and "flash" column chromatography. $^1$H NMR analysis of 160 confirmed product formation with the appearance of a one proton singlet at $\delta$ 5.4 ppm, corresponding
Chapter 3: Sulfoxides as ligands

to the methine proton. Infra-red analysis also confirmed product formation with the appearance of a band at 2249 cm\(^{-1}\) corresponding to the nitrile (CN) stretch.

The yields for the reactions were high; 90\% when using a catalyst system derived from ligand 111b and 95\% when using ligand 128b. However, no enantioselectivity was achieved through the use of either ligand. The enantiomeric excesses were determined through \(^1\)H NMR analysis of the Mosher's ester of 160. \(^1\)H NMR analysis of the Mosher's esters revealed a splitting of the peaks (singlets) due to the methoxy group at \(\delta 3.46\) ppm and \(\delta 3.57\) ppm. Integration of these peaks indicated a racemic mixture of product in both cases (for ligands 111b and 128b). As to why 0\% e.e. was obtained through the use of both ligands 111b and 128b, is not entirely clear. There could be a problem with the initial titanium coordination to the ligand (111b and 128b), see Figure 8 or, if titanium coordination has occurred the ligand may not be providing a suitable "stereochemical environment" for the aldehyde molecule. The development of modified sulfoxide-based oxazoline ligands to see if the "stereochemical environment" could be improved was not undertaken.

3.6 Conclusions

It has been shown that aryl sulfoxides of defined stereochemistry at sulfur tethered through a phenyl group to an oxazoline moiety can act as ligands in asymmetric synthesis. In the case of the asymmetric palladium catalysed allylic substitution reaction (section 3.4) all the sulfoxide-based oxazoline ligands 111a, 111b, 128b, 149 and 150 were able to induce enantioselectivity. The results gained through the use of the diastereomeric ligands 111a (55\% e.e.) and 111b (89\% e.e.) in the palladium catalysed reaction demonstrated the importance of the stereochemistry at sulfur for these reactions. Furthermore, the sulfone ligand 155 did not provide a reactive palladium catalyst suggesting that coordination of palladium to the sulfoxide ligands 111a, 111b, 128b, 149 and 150 is more likely to be through the sulfur atom than the oxygen atom. Enantiomerically pure ligands 149 and 150 provided only reasonable levels of enantioselectivity 56\% e.e. and 50\% e.e. respectively but, here the enantioselectivity of the reaction is being entirely controlled by the stereochemistry of the sulfoxide moiety. Ligands 149 and 150 provide the first examples of the use of sulfoxides as ligands in controlling the enantioselectivity of the palladium catalysed allylic substitution reaction. Whilst the application of diastereomerically pure sulfoxide-based oxazoline ligands 111b and 128b as Lewis acid-type catalysts (diethylzinc addition and titanium induced
cyanide addition to benzaldehyde) did not prove to be successful, manipulation of
the ligand skeleton may lead to an improvement in enantioselectivity for these
processes. Approximately one year was spent on trying to develop the sulfoxide-
based oxazoline compounds into successful ligands, and the work described above
represents the best results achieved for both processes (diethylzinc addition and
cyanide addition).
CHAPTER 4

UNSYMMETRICAL PALLADIUM π-ALLYL COMPLEXES IN THE SYNTHESIS OF β-AMINO ACIDS
4.1 Introduction

Recently, the preparation of enantiomerically pure \( \beta \)-amino acids has received much attention.\(^{142} \) Although much less abundant than their \( \alpha \)-anallogues, \( \beta \)-amino acids do exist in nature and in their "free" form they can show interesting pharmacological effects.\(^{143} \) \( \beta \)-Amino acids also have synthetic utility in the synthesis of \( \beta \)-lactams,\(^{144} \) a well known class of biologically active compounds, as well as therapeutically enhanced peptides.\(^{145} \) Potentially, \( \beta \)-amino acids can be used as intermediates in the synthesis of chiral ligands, chiral building blocks and chiral auxiliaries.

Currently, there are several routes to enantiomerically pure \( \beta \)-amino acids including:

- homologation of \( \alpha \)-amino acids,\(^{146} \)
- from aspartic acid, asparagine and derivatives,\(^{147} \)
- enzymatic resolution,\(^{148} \)
- enantioselective hydrogenation of prochiral 3-amino acrylic acid derivatives,\(^{149} \)
- by addition of carbon nucleophiles to chiral imines\(^{150} \) and by
- Michael addition of amines to acrylate derivatives.\(^{151} \)

We planned to synthesise a range of enantiomerically enriched \( \beta \)-amino acids using the asymmetric palladium catalysed allylic substitution of racemic trisubstituted acetates,\(^{161} \) as a key step, Scheme 10. Racemic trisubstituted allylic acetates,\(^{161} \) were initially shown by Bosnich \textit{et al.} to act as suitable substrates in the asymmetric palladium catalysed allylic substitution reaction.\(^{152} \) More recently, Dawson and Williams extended this methodology towards the synthesis of a range of enantiomerically enriched succinic acids and enantiomerically enriched \( \gamma \)-lactones.\(^{153} \)

\[ \begin{align*}
\text{O}_2\text{C} & \quad \text{R} \\
\text{CH}_2\text{NH}_3^+ & \quad \text{Ph} \\
\text{CH}_2(\text{CO}_2\text{CH}_3)_2 & \quad \text{Ph} \quad \text{CH(}\text{CO}_2\text{CH}_3)_2 \quad \text{Ph} \\
\text{R} & \quad \text{Ph} \quad \text{Ph} \quad \text{OAc} \\
161 & \\
\text{CH}_2(\text{CO}_2\text{CH}_3)_2 & 
\end{align*} \]

Scheme 10

Although the asymmetric palladium catalysed allylic substitution reaction has not been used before as a key step in the synthesis of enantiomerically enriched \( \beta \)-amino acids, there are examples where palladium chemistry has been used as a
key step to assist the formation of protected β-amino acids. Hegedus and Masters reported an palladium(II)-assisted alkylation reaction as a key step towards the synthesis of (-)-5-epi-negamycin, 162. Palladium(II)-assisted alkylation of the optically active N-vinylcarbamate, 163 followed by carbynylative coupling to isobutenyltrimethylstannane afforded the diester, 164 which, after hydrolysis and decarboxylation gave the protected β-amino acid 165, a key compound in the synthesis of 162.

\[
\text{1) PdCl}_2(\text{MeCN})_2 \quad \text{2) NEt}_3 \quad \text{3) NaCH(CO}_2\text{Et})(\text{CO}_2\text{Bu}) \quad \text{1) CO} \quad \text{2) Me}_3\text{SnCH=CM}_2
\]

\[
\text{77%}
\]

\[
\text{163}
\]

\[
\text{164}
\]

\[
\text{165}
\]

\[
\text{Several steps}
\]

\[
\text{162}
\]

**4.2 Unsymmetrical palladium π-allyl systems**

Since its introduction, almost thirty years ago, the palladium catalysed allylic substitution reaction has been studied in great detail by many research groups. Very often the test substrate for such reactions is the racemic diphenyl-substituted allylic acetate, 145. However, although excellent enantioselectivities have been achieved using this substrate 145, it does not have a great deal of synthetic potential.
Variants of 145 which contain identical termini, 61 would perhaps be too problematic to synthesise.

\[
\begin{align*}
145 & \quad & 61
\end{align*}
\]

The synthesis of substrates such as 161, first introduced by Bosnich et al., is on the other hand very easy to achieve. Such substrates have recently been shown by Dawson and Williams to provide enhanced enantioselectivity for asymmetric palladium catalysed allylic substitution reactions in comparison with their counterparts containing identical allylic termini.

\[
161
\]

4.2.1 Preparation of trisubstituted allylic alcohols

A range of trisubstituted allylic alcohols, 167a-d was prepared according to methods previously reported within this group.

\[
\begin{align*}
166 & \quad & 167a-d
\end{align*}
\]

Treatment of commercially available β-phenylcinnamaldehyde 166 with either an organolithium or Grignard reagent at 0 °C resulted in smooth formation of the corresponding allylic alcohols 167a-d, Table 5. Grignard reagents were commercially available, with the organolithium reagent, 1-lithionaphthalene being prepared from the corresponding bromide and n-butyllithium. Analysis of the
infra-red spectra of 9a-d confirmed product formation with the presence of a broad band at 3300-3500 cm\(^{-1}\), corresponding to the OH stretch.

<table>
<thead>
<tr>
<th>R</th>
<th>Alcohol</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>167a</td>
<td>92</td>
</tr>
<tr>
<td>Ph</td>
<td>167b</td>
<td>95</td>
</tr>
<tr>
<td>Naphth</td>
<td>167c</td>
<td>90</td>
</tr>
<tr>
<td>Mesityl</td>
<td>167d</td>
<td>85</td>
</tr>
</tbody>
</table>

### 4.2.2 Preparation of trisubstituted allylic acetates

Acetylation of the allylic alcohols 167a-d was achieved using methodology developed within this group.\(^{153}\)

\[ \text{AcO, NEt}_3, \text{cat. DMAP} \]

\[ \text{CH}_2\text{Cl}_2, \text{r.t.} \]

\[ \text{1 hr} \]

\[ 167a-d \]

\[ 161a-d \]

Treatment of the allylic alcohols 167a-d with acetic anhydride, triethylamine as base in the presence of a catalytic amount of DMAP\(^{89}\) gave, after aqueous work-up and "flash" column chromatography, the corresponding trisubstituted allylic acetates, 161a-d in excellent yield, Table 6. \(^1\)H NMR analysis of 161a-d confirmed product formation with the appearance of a three proton singlet at approximately δ 2.0 ppm, corresponding to the protons of the acetoxy group.

<table>
<thead>
<tr>
<th>R</th>
<th>Acetate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>161a</td>
<td>96</td>
</tr>
<tr>
<td>Ph</td>
<td>161b</td>
<td>98</td>
</tr>
<tr>
<td>Naphth</td>
<td>161c</td>
<td>95</td>
</tr>
<tr>
<td>Mesityl</td>
<td>161d</td>
<td>99</td>
</tr>
</tbody>
</table>
Chapter 4: β-amino acid synthesis

With a range of trisubstituted allylic acetates 161a-d in hand we turned our attention to the asymmetric palladium catalysed allylic substitution reaction.

4.2.3 Asymmetric palladium catalysed allylic substitution

As previously demonstrated by Dawson and Williams only the diphenyl-phosphinophenyl oxazoline ligand, 15 is able to provide a reactive catalyst system when undertaking asymmetric palladium catalysed allylic substitution reactions using racemic trisubstituted allylic acetates as substrates. Consequently, the sulfoxide-based oxazoline ligands (111a, 111b, 128b, 149 and 150) shown in Chapter 3 to be of similar reactivity to the corresponding sulfide-oxazoline ligands are not effective for these trisubstituted allyl systems. We believe this is due to the poorer π-accepting properties of sulfur as compared to phosphorus.

The synthesis of ligand 15 was accomplished according to methods already established within this group. Ortho-fluorobenzonitrile, 105 and (S)-valinol, 108 were heated to reflux in chlorobenzene in the presence of a catalytic amount of dry zinc chloride. Infra-red analysis confirmed formation of 2-(2-fluorophenyl)oxazoline 168 with the disappearance of the nitrile (CN) stretch at 2210 cm\(^{-1}\) and the appearance of the characteristic oxazoline C=N stretch at 1651 cm\(^{-1}\). Reaction of 168 in a refluxing THF solution of potassium diphenylphosphide gave the desired diphenylphosphinophenyl oxazoline ligand, 15 in good yield. \(^1\)H NMR analysis of 15 confirmed product formation with the appearance of the characteristic oxazoline proton multiplets appearing at δ 3.8-4.1 ppm.
The enantioselective palladium catalysed allylic substitution reactions, using trisubstituted allylic acetates, 161a-d were undertaken according to methodology previously reported by this group.\textsuperscript{153}

\[ \text{Ph} \xrightarrow{\text{NaCH(CO_2CH_3)_2}} \text{Ph} \xrightarrow{2 \text{.5 mol\% [Pd(\eta^3-C_3H_5)Cl]_2}, \text{10 mol\% ligand 15}} \text{Ph} \]

Treatment of the trisubstituted allylic acetates 161a-d with a solution of sodiodimethyl malonate in the presence of 2.5 mol\% of allylpalladium chloride dimer and 10 mol\% of ligand 15 afforded, after aqueous work-up and "flash" column chromatography the desired alkylated products 169a-d, Table 7. $^1$H NMR analysis of 169a-d confirmed product formation with the disappearance of a three proton singlet at approximately δ 2.0 ppm corresponding to the protons of the acetoxy
group of 161a-d and the appearance of a one proton doublet at approximately δ 4.0 ppm, corresponding to the proton of the malonate substituent.

Table 7

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>169a</td>
<td>24</td>
<td>95</td>
<td>95&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ph</td>
<td>169b</td>
<td>24</td>
<td>97</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Naphth</td>
<td>169c</td>
<td>36</td>
<td>94</td>
<td>&gt;95&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mesityl</td>
<td>169d</td>
<td>36</td>
<td>86</td>
<td>98&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a) The enantiomeric excess of 169a and 169c was determined from <sup>1</sup>H NMR spectra in the presence of 0.8 equivalents of the enantiopure shift reagent Eu(hfc)<sub>3</sub>. (Best results were achieved using 2 mg of 169a and 169c).
b) The enantiomeric excess of 169b was determined by chiral HPLC (Chiralcel OJ); hexane/isopropanol, 97:3 (containing 3% NHEt<sub>3</sub>), 1 ml/min. (t<sub>R</sub> = 20.5 and 27.6 min.).
c) The enantiomeric excess of 169d was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 99:1, 1 ml/min. (t<sub>R</sub> = 6.4 and 7.2 min.).

The results from Table 7 indicate that a variety of differently substituted racemic allylic acetates, 161a-d can participate in the asymmetric palladium catalysed allylic substitution reaction. In fact, not only are the enantioselectivities excellent (95-99% e.e.), there is also only one regioisomer of alkylated product, 169a-d formed and, as demonstrated by Dawson and Williams<sup>153</sup> these trisubstituted allylic acetates give enhanced enantioselectivities in comparison to their disubstituted counterparts containing identical termini. Such results suggest that the bulky 1,1-diphenyl terminus of racemic acetates 161a-d is able to position the allyl intermediates into one conformation upon reaction with ligand, 15.

4.2.4 Regiochemistry

If we consider an unsymmetrical allylic acetate, then under normal conditions nucleophilic substitution at the allyl will result in a variety of products as a consequence of SN and SN<sup>1</sup> attack.<sup>156</sup> However, if palladium is co-ordinated to the allyl, then the regioselectivity of the nucleophilic reaction will be changed. Previously, Trost has shown that during palladium catalysed allylic substitution the regioselectivity of the reaction can be dependant upon a number of factors, among which are the steric hindrance of the two allyl sites and also the stability of the palladium-olefin bond that is developed during nucleophile attack.<sup>99c</sup> Specifically considering the acetate system, 161a-d it would seem more logical for the nucleophile to attack the allyl unit at the least hindered end; in other words away
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from the bulky 1,1-diphenyl terminus. However, it is unlikely that only steric hindrance plays a role in directing the regiochemical course of the reaction. It is known that palladium(0)-phosphine complexes co-ordinate more strongly with electron deficient olefins than with those that are electron rich.\(^{157}\) As nucleophilic attack on the allyl intermediate results in the simultaneous formation of a palladium(0) species and olefin, then we would expect formation of the more highly conjugated olefin double bond. Hence, control of regiochemistry is more likely to be a consequence of both steric and electronic effects.

4.2.5 Mechanism of enantioselection in unsymmetrical palladium \( \pi \)-allyl systems

It is known that asymmetric palladium catalysed allylic substitution reactions are generally considered to proceed through overall retention of stereochemistry when using stabilised nucleophiles such as sodiodimethyl malonate.\(^{111}\) Thus, on first inspection it would appear that for racemic allylic acetates, \textbf{161} the only possibility is that racemic product \textbf{169} would form, since \textbf{161} affords \textbf{169} and \textbf{ent-161} affords \textbf{ent-169}. However, as has already been described this is not the case and enantiomerically enriched products, \textbf{169a-d} are gained. Other research groups have established that intermediate allylpalladium complexes are able to undergo interconversion through a \( \pi \)-\( \sigma \)-\( \pi \) mechanism.\(^{158}\)
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Therefore, the enantioselectivity of the overall process is achieved by the fact that more of complex 171 is converted into ent-169 than complex 170 being converted into the enantiomeric product 169. There are two possible explanations for this; either there is a higher population of complex 171 with respect to complex 170, or that nucleophilic addition takes place more quickly to complex 171 than to complex 170.

The specific use of a phosphine-containing oxazoline ligand, such as 15 means that during the transition state for the palladium catalysed allylic substitution reaction there are four possible cationic allylpalladium complexes, 172, 173, 174 and 175 that need to be considered. X-Ray crystallography data obtained by Helmchen for an analogous palladium allyl complex (without the additional phenyl group), suggested that the most reactive conformation for the allyl moiety during the reaction was when it was in a "W" conformation. Based on this and the fact that the absolute stereochemistry of alkylated products, 169a-d has already been designated as the (S)-(−)-enantiomer, we can discount two of the cationic complexes, namely 172 and 173, as they would lead to the wrong enantiomer of product upon addition of the malonate nucleophile.
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Of the two remaining cationic complexes it seems likely that the sense of asymmetric induction occurs through complex 175. Complex 174 could indeed lead to the observed enantiomer of product, but for this to be possible nucleophilic addition on the allyl would have to occur cis to phosphorus and \textit{trans} to the oxazoline nitrogen, a process already shown to be unlikely,\textsuperscript{129} also the allyl moiety is in the less reactive "M" conformation.

Based on the results gained by the Helmchen group,\textsuperscript{130} it would seem that complex 175, where the allyl is fixed into the so-called "W" conformation, is the more reactive. Although it is clearly obvious that complex 175 experiences considerable steric crowding due to the proximity of the four phenyl groups, it is assumed that the rate of addition of the malonate nucleophile to complex 175 is greater than for the other complexes. Here, nucleophilic addition to the allyl occurs \textit{trans} to phosphorus, which is favoured for ligands such as 15, affording the observed product.
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Nucleophilic addition to this complex leads to the observed enantiomer of product. Additionally, nucleophilic addition occurs \textit{trans} to the phosphorus, which is advantageous.

From Table 7 it can be seen that reaction times for the asymmetric palladium catalysed allylic substitution process range from 24-36 hr depending on the choice of allylic substrate, 169a-d. For example, the triphenyl-substituted allylic acetate, 169b required a reaction time of 24 hr. Under the exact same conditions, disubstituted allylic acetates such as 145 required reaction times of no longer than 6 hr. The longer reaction time for allylic acetate 169b can be attributed to its lower reactivity. For disubstituted allylic acetate 145, reaction will proceed through an symmetrical \(\eta^3\)-allyl complex. Due to the symmetrical nature of the intermediate allyl, only two cationic diastereomeric complexes will be formed during the reaction (see Chapter 3). However, for reactions proceeding through an unsymmetrical \(\eta^3\)-allyl complex, there are four possible cationic diastereomeric complexes 172, 173, 174 and 175, that can be formed. As nucleophilic addition to the allyl is considered to be the rate determining step of these reactions, then for reactions proceeding through unsymmetrical allyl complexes, the nucleophile has a relatively longer period of time to wait to allow for interconversion of the four cationic complexes, in order to react with the most reactive cationic allyl species.

4.3 Formation of mono-esters

Decarboxylation of the alkylated products, 169a-d was achieved under Krapcho conditions.\(^\text{159}\)
The alkylated compounds, 169a-d were heated in a pressure vessel to 180 °C, in the presence of sodium chloride, water and dimethyl sulfoxide, resulting in, after aqueous work-up and "flash" column chromatography, the desired mono-esters 176a-d in good yield, Table 8. ¹H NMR analysis confirmed product formation with the disappearance of one of the methyl ester signals of 169a-d and the appearance of a two proton double doublet at approximately δ 2.7 ppm, corresponding to the CH₂.

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>176a</td>
<td>81</td>
</tr>
<tr>
<td>Ph</td>
<td>176b</td>
<td>79</td>
</tr>
<tr>
<td>Naphth</td>
<td>176c</td>
<td>80</td>
</tr>
<tr>
<td>Mesityl¹</td>
<td>176d</td>
<td>93</td>
</tr>
</tbody>
</table>

a) The ¹H NMR spectra indicated the presence of a six proton broad "hump" at δ 2.0 ppm and a three proton singlet at δ 2.2 ppm, corresponding to the three methyl groups attached to the phenyl ring (Mesityl), there is also a two proton singlet at δ 6.7 ppm, corresponding to the two aromatic protons of the mesityl ring.

This tends to suggest that there is restricted rotation about the carbon-carbon bond, of 176d, Figure 9.

**Figure 9**

### 4.4 Formation of mono-acids

Hydrolysis of the decarboxylated compounds, 176a-d was achieved as detailed.
Subjection of mono-esters 176a-d to base-assisted hydrolysis in a refluxing methanol/water solution afforded after aqueous work-up and "flash" column chromatography the corresponding mono-acids, 177a-d in excellent yield, Table 9.

Table 9

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>177a</td>
<td>95</td>
</tr>
<tr>
<td>Ph</td>
<td>177b</td>
<td>98</td>
</tr>
<tr>
<td>Naphth</td>
<td>177c</td>
<td>98</td>
</tr>
<tr>
<td>Mesityl</td>
<td>177d</td>
<td>98</td>
</tr>
</tbody>
</table>

a) A similar pattern for the $^1$H NMR of 177d was seen to that of 176d (see section 4.4).

$^1$H NMR analysis of 177a-d confirmed product formation with the disappearance of a three proton singlet at approximately $\delta$ 3.5 ppm, corresponding to the protons of the methyl ester of 176a-d and the appearance of a one proton broad singlet at $\delta$ 10.0 ppm, corresponding to the carboxylic acid group. Infra-red analysis also confirmed product formation with the presence of a broad band at approximately 3000 cm$^{-1}$, corresponding to the $-\text{CO}_2\text{H}$ stretch.

With a range of highly enantiomerically enriched mono-acid compounds, 177a-d in hand we then turned our attention to the introduction of the nitrogen functionality.

4.5 Introduction of nitrogen

It is nearly one hundred years since the introduction of the Curtius rearrangement, which involves the pyrolysis of acyl azides to yield isocyanates.$^{160}$ Under appropriate reaction conditions these isocyanates can be converted to amines, carbamates or acylureas.$^{161}$

We planned the introduction of nitrogen through the use of a modified Curtius reaction, first reported by Yamada in 1972.$^{162}$ The Curtius rearrangement (nucleophilic 1,2-shift) has been studied thoroughly since its introduction and is
known to proceed with overall retention of stereochemical integrity, if the migrating group is chiral.\textsuperscript{163} The modified Curtius reactions of mono-acids 177a-d were carried out as detailed.

\[
\begin{array}{c}
\text{Ph} & \text{R} & \text{CH}_2\text{CO}_2\text{H} \\
\text{Ph} & & \\
\end{array}
\xrightarrow{(\text{PhO})\text{P(O)N}_3, \text{NET}_3, \text{t-BuOH, reflux, 16 hr}}
\begin{array}{c}
\text{Ph} & \text{R} & \text{CH}_2\text{NHCO}_2\text{Bu} \\
\end{array}
\]

177a-d 178a-d

Treatment of the mono-acids, 177a-d under modified Curtius conditions (diphenylphosphoryl azide and triethylamine in refluxing tert-butyl alcohol) led to the formation of the tert-butoxycarbonyl-amino products, 178a-d in reasonable yield, Table 10.

<table>
<thead>
<tr>
<th>R</th>
<th>Product \textsuperscript{a}</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>178a</td>
<td>52</td>
</tr>
<tr>
<td>Ph</td>
<td>178b</td>
<td>61</td>
</tr>
<tr>
<td>Naphth</td>
<td>178c</td>
<td>52</td>
</tr>
<tr>
<td>Mesityl</td>
<td>178d</td>
<td>49</td>
</tr>
</tbody>
</table>

\textsuperscript{a} In every case a slight broadening of the -CH\textsubscript{2} and -CH signals could be seen, which tends to suggest the presence of rotamers, a consequence of the bulky tert-butoxy group.

\textsuperscript{1}H NMR analysis of 178a-d confirmed product formation with the disappearance of a broad one proton singlet at $\delta$ 10.0 ppm, corresponding to the proton of the carboxylic acid group of 177a-d and the appearance of a nine proton singlet at approximately $\delta$ 1.4 ppm, corresponding to the protons of the tert-butoxycarbonyl group. Proof of product formation for carbamate 178a was also achieved through X-ray crystallography analysis (see Appendix for more details), Figure 10.
The $^{1}$H NMR of 178d again indicated that there must be restricted rotation about the carbon-carbon single bond, Figure 11.

Figure 12 shows a series of $^{1}$H NMR spectra for carbamate, 178d obtained at room temperature A, -50 °C, B and +50 °C, C respectively. It can clearly be seen that at room temperature the singlet at $\delta$ 2.2 ppm corresponds to one of the methyl groups of the mesityl ring and the broad "hump" at $\delta$ 2.0 ppm, corresponds to the other two methyl groups of the mesityl ring. Performing the NMR study at -50 °C essentially "freezes" the structure and we see three singlets at $\delta$ 1.6 ppm, $\delta$ 2.2 ppm and $\delta$ 2.5 ppm, corresponding to the three methyl substituents of the mesityl ring. Performing the NMR study at +50 °C allows for rapid rotation about the carbon-carbon single bond and hence we see two singlets (a six proton singlet at $\delta$ 2.0 ppm,
corresponding to the two ortho-methyl substituents and a three proton singlet at δ 2.2 ppm, corresponding to the para-methyl substituent).
A postulated mechanism for the modified Curtius rearrangement of mono-acids 177a-d is represented in Scheme 11.

Initial reaction of the carboxylate anion of 177 with diphenylphosphoryl azide forms, after elimination, the mixed carboxylic phosphoric anhydride species, 179 and the "active" azide nucleophile. The azide nucleophile then attacks the carbonyl group of 179, resulting in formation of the acyl azide, 180. The acyl azide, 180 then undergoes Curtius rearrangement giving the isocyanate, 181 which in-turn reacts with tert-butyl alcohol, producing the tert-butoxycarbonyl amino products, 178a-d with complete retention of stereochemistry.

The yields obtained when conducting this reaction were consistently around 50%, with 61% being the best yield achieved. TLC analysis (petroleum ether/ether, 3:1) indicated the formation of two other compounds. Isolation of the two other compounds by "flash" column chromatography and $^1$H NMR analysis indicated that
one of the unknown compounds was the *tert*-butyl ester, 182 (presence of a nine proton singlet at δ 1.3 ppm, corresponding to the protons of the *tert*-butoxycarbonyl group and a two proton double doublet at δ 2.6 ppm, corresponding to the CH₂-group).

\[
\begin{align*}
\text{Ph} & \quad \text{R} \\
\text{Ph} & \quad \text{CH}_2\text{CO}_2^\text{tBu}
\end{align*}
\]

182

Formation of 182 can be realised from the intermediate carboxylic phosphoric anhydride, 179. During formation of 179 the "active" azide nucleophile is also generated. At the start of the reaction there is a relatively low concentration of "active" azide nucleophile in comparison to a very high concentration of *tert*-butyl alcohol. It is therefore possible to envisage *tert*-butyl alcohol attacking species 179, resulting in formation of the *tert*-butyl ester, 182.

Physical data (¹H NMR and MS) gained for the other unknown compound did not provide any proof as to the true nature of its structure. It is possible however, that during the reaction a small amount of hydrazoic acid (HN₃) was formed. It is known that hydrazoic acid can nucleophilically attack isocyanates, resulting in formation of carbomoyl azides.¹⁶² In our case nucleophilic attack of hydrazoic acid on isocyanate, 181 would result in formation of the carbomoyl azide, 183, Scheme 12.

\[
\begin{align*}
\text{R'} & \quad \text{N} = \text{C} = \text{O} \\
\text{181} & \quad + \\
\text{HN}_3 & \quad \text{N}_3
\end{align*}
\]

\[
\text{N} = \text{C} = \text{OH}^+ \quad \text{N} = \text{C} = \text{OH} \quad \text{N} = \text{C} - \text{OH}
\]

\[
\begin{align*}
\text{N} & \quad \text{N}_3 \\
\equiv & \quad \text{R'} \quad \text{H} \quad \text{N} - \text{C} = \text{O} \\
\text{183} & \quad \text{HN}_3
\end{align*}
\]

Scheme 12

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Indeed, infra-red analysis indicated that 183 may be the unknown compound, with bands appearing at 3432 cm\(^{-1}\), 2149 cm\(^{-1}\) and 1698 cm\(^{-1}\), corresponding to the NH, N\(_3\) and C=O vibrations respectively.

### 4.6 Carbon-carbon double bond oxidation

Having achieved nitrogen introduction through Curtius reaction we then required a method that would allow cleavage of the carbon-carbon double bond. There are many methods available to the organic chemist for double bond cleavage which allow for isolation of the required carboxylic acid functionality.\(^{164}\) However, we chose to concentrate on the ruthenium tetroxide oxidation of carbon-carbon double bonds, using methodology developed by Sharpless in the early eighties.\(^{165}\)

Ruthenium tetroxide was generated \textit{in situ} using a catalytic amount of ruthenium trichloride in the presence of sodium metaperiodate in a critical solvent mixture of acetonitrile, carbon tetrachloride and water in a 2:2:3 ratio. The oxidative cleavage of carbamate compounds 178a-d was undertaken as shown.

![Chemical reaction](image)

Reaction of the carbamates 178a-d with \textit{in situ} generated ruthenium tetroxide resulted in conversion to the corresponding Boc-protected \(\beta\)-amino acids 184a-d in reasonable yield, Table 11.\(^{166}\) \(^1\)H NMR analysis of 184a-d confirmed product formation with the disappearance of a one proton doublet at approximately \(\delta\) 6.5 ppm, corresponding to the carbon-carbon double bond proton of 178a-d and the appearance of a one proton broad singlet at approximately \(\delta\) 10.0 ppm, corresponding to the carboxylic acid proton of 184a-d.
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Table 11

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>184a</td>
<td>60</td>
<td>a</td>
</tr>
<tr>
<td>Ph</td>
<td>184b</td>
<td>65</td>
<td>99b</td>
</tr>
<tr>
<td>Naph</td>
<td>184c</td>
<td>61</td>
<td>99c</td>
</tr>
<tr>
<td>Mesityl</td>
<td>184d</td>
<td>63</td>
<td>98d</td>
</tr>
</tbody>
</table>

a) Compound 184a was converted to the "free" β-amino acid, a rotation taken and this value was then compared with a known value from the literature (see section 4.7).
b) The enantiomeric excess of 184b was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 80:20 (containing 5% TFA), 1 ml/min. (t_R = 6.1 and 7.1 min.).
c) The enantiomeric excess of 184c was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 80:20, 0.9 ml/min. (t_R = 9.1 and 9.9 min.).
d) The enantiomeric excess of 184d was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 80:20, 0.85 ml/min. (t_R = 12.5 and 13.4 min.).

In every case, analysis of the 13C NMR spectra of compounds 184a-d indicated a doubling up of all the peaks, except for those pertaining to the R group. 1H NMR analysis also indicated a broadening of the -CH2 and -CH signals, with the broad singlet corresponding to the NH of the carbamate group seemingly doubled-up in every case. Again, as with compounds 178a-d this tends to suggest the presence of rotamers. The doubling up of the peaks in the 13C NMR could be due to the formation of a hydrogen bond between the carbonyl group of the carbamate functionality and the carboxylic acid functional group.

4.7 Preparation of "free" β-amino acids

Deprotection of the Boc-protected β-amino acids 184a and 184b was achieved as shown using methodology reported by Stahl.167

\[
\begin{align*}
\text{HO}_2\text{C} - \text{R} & \quad \text{1) 4.0M HCl/Dioxane} \\
\text{CH}_2\text{NHCO}_2\text{Bu} & \quad \text{r.t., 4 hr} \\
184\text{a-b} & \quad \text{2) DOWEX} \\
\rightarrow \text{O}_2\text{C} - \text{R} & \quad \text{CH}_2\text{NH}_3^+ \\
185\text{a-b} &
\end{align*}
\]

Reaction of the Boc-protected β-amino acids 184a and 184b with a 4.0M solution of HCl in dioxane at room temperature led to the formation of the hydrochloride salts of 184a and 184b. The hydrochloride salts were then passed down a DOWEX acid ion-exchange column, resulting in isolation of the "free" β-amino acids 185a and 185b in good yield, Table 12.
4.8 Preparation of protected β-amino acids with the asymmetric centre adjacent to nitrogen

In section 4.6 all the enantiomerically enriched Boc-protected β-amino acids, 184a-d synthesised had their asymmetric centre adjacent to the carboxylic acid functional group. We were interested to see if, using the same methodology as outlined in section 4.6, we could synthesise β-amino acids containing an asymmetric centre adjacent to the nitrogen-containing functional group. This was achieved by simply altering the reaction sequence.

Table 12

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>e.e. (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>185a</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>Ph</td>
<td>185b</td>
<td>85</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\) The enantiomeric excess of 185a and 185b was determined by comparing the optical rotations with those already reported in the literature for 185a\(^{168}\) and 185b.\(^{169}\)

\(\text{Ph} \quad \text{Mesityl} \quad \text{CH}_2\text{CO}_2\text{CH}_3\)

\(\text{Ph} \quad \text{CH}_2\text{CO}_2\text{CH}_3\)

\(\text{176d} \quad \text{2.2 mol}\% \text{RuCl}_3(\text{H}_2\text{O})_n, \quad \text{NaIO}_4 \quad \text{HO}_2\text{C} \quad \text{Mesityl} \quad \text{CH}_2\text{CO}_2\text{CH}_3\)

\(\text{CH}_3\text{CN}/\text{CCl}_4/\text{H}_2\text{O} (2:2:3) \quad \text{r.t., 2 hr} \quad 65\%\)

\(\quad \text{(PhO)}\text{P(0)}\text{N}_3, \quad \text{NEt}_3 \quad \text{t-BuOH, reflux,} \quad 16\text{ hr} \quad 50\%\)

\(\text{Bu'O}_2\text{CHN} \quad \text{Mesityl} \quad \text{NaOH, H}_2\text{O}/\text{CH}_3\text{OH} \quad \text{Bu'O}_2\text{CHN} \quad \text{Mesityl}\)

\(\text{CH}_2\text{CO}_2\text{H} \quad \text{reflux, 2 hr} \quad 91\% \quad \text{CH}_2\text{CO}_2\text{CH}_3\)

\(\text{188} \quad (98\% \text{ e.e.}\(^b\)) \quad \text{187}\)

\(^a\) The enantiomeric excess of 188 was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 80:20, 1.0 ml/min. \((t_R = 4.4 \text{ and } 4.8 \text{ min.})\).\(^{166}\)
Chapter 4: \(\beta\)-amino acid synthesis

Cleavage of the carbon-carbon double bond of mono-ester 176d was achieved using the Sharpless methodology. \(^1\text{H}\) NMR analysis of 186 confirmed product formation with the appearance of a one proton double doublet at \(\delta\) 4.70 ppm corresponding to the methine proton. Subsequent Curtius reaction of 186 allowed for the introduction of nitrogen in reasonable yield. Again, \(^1\text{H}\) NMR analysis of 187 confirmed product formation with the appearance of a nine proton singlet at \(\delta\) 1.38 ppm corresponding to the protons of the \(\text{tert}\)-butoxy group. Finally base-assisted hydrolysis of the \(\text{tert}\)-butoxycarbonyl amino compound, 187 led to the isolation of the desired Boc-protected \(\beta\)-amino acid 188 in excellent yield. \(^1\text{H}\) NMR analysis of 188 confirmed product formation, as did \(^{13}\text{C}\) NMR analysis, again revealing a doubling-up of the signals due to the possible presence of rotamers.

4.9 Conclusions

It has been shown that racemic allylic acetates which possess a 1,1-diphenyl moiety can undergo highly enantioselective palladium catalysed allylic substitution reactions when performed in the presence of the 4,5-dihydrooxazole ligand, 15. From the highly enantiomerically enriched alkylated products 169a-d, Boc-protected \(\beta\)-amino acids (with the asymmetric centre adjacent to the carboxylic acid group or the nitrogen-containing functional group) and "free" \(\beta\)-amino acids, 185a and 185b can be synthesised through manipulation of the carbon-carbon double bond and the malonate moiety, without any apparent loss of stereochemical integrity.
CHAPTER 5

STUDIES TOWARDS THE SYNTHESIS OF α-SUBSTITUTED-β-AMINO ACIDS
5.1. Introduction

It was shown in Chapter 4 that the asymmetric palladium catalysed allylic substitution reaction could be used successfully as a key step in the enantioselective synthesis of a range of \( \beta \)-amino acids\(^a\).

Recently, there has been considerable attention directed towards the enantioselective synthesis of \( \alpha \)-substituted-\( \beta \)-amino acids, principally due to the fact that this unit is present in a variety of biologically important compounds\(^b\). Perhaps the most striking and talked about example is that of the \( \beta \)-phenylisoserine side chain found in Taxol, 189. Taxol, a complex natural product isolated from the bark of the Pacific Yew tree, \textit{Taxus brevifolia}, is currently considered to be a promising anticancer agent and the \( \beta \)-phenylisoserine side chain is essential to its antitumour activity\(^c\).

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \\
\text{Ph} & \quad \text{O} \\
\text{AcO} & \quad \text{O} \\
\text{OH} & \quad \text{HO} \\
\text{OAc} & \quad \text{OBz}
\end{align*}
\]

Indeed, there are many important compounds possessing \( \alpha \)-substituted-\( \beta \)-amino acid side chains that show interesting pharmacological properties. For example, \( \alpha \)-hydroxy-\( \beta \)-amino acids are present in various peptidic enzyme inhibitors such as bestatin\(^d\) and pepstatin\(^e\), and also in a variety of protease inhibitors\(^f\). 3-amino-2-methylpentanoic acid is present in the structurally related antifungal depsipeptides, majusculamide C and 57-normajusculamide C\(^g\), and the antitumour agents, aldoostatins 11 and 12\(^h\).

We were interested in developing the asymmetric palladium catalysed allylic substitution methodology towards the synthesis of a range of \( \alpha \)-substituted-\( \beta \)-amino acids. If the synthesis of \( \beta \)-amino acids containing an \( \alpha \)-substituent (\( X \)) such as 190 was to be realised using this methodology, then substituted malonate derived nucleophiles of the type 191 would be required, Scheme 13.
Indeed, Trost et al. have recently demonstrated the use of dimethyl methylmalonate derived nucleophiles in the asymmetric palladium catalysed allylic substitution reaction of (E)-2-acetoxy-3-pentene, 192.\textsuperscript{175} They found that they were able to obtain the alkylated product, 193 with good levels of enantioselectivity (87\% e.e.) using a catalyst system derived from 5 mol\% of ligand 194 and 2.5 mol\% of allylpalladium chloride dimer.

Trost has also reported the use of the sodium salt of dimethyl malonate substituted compounds as nucleophiles for the asymmetric alkylation of allylic gem-dicarboxylates, such as 195.\textsuperscript{176} Using a catalyst system derived from allylpalladium chloride dimer and ligand 196, he was able to achieve products, 197 and 198 with excellent enantioselectivity (>95\% e.e.) where the size of the substituent on the malonate had little effect.
Conversely, Yamaguchi et al. demonstrated that the choice of incoming nucleophile can be of considerable importance in the enantioselectivity of the asymmetric reaction. For example, employing (S)-BINAP as the ligand in the palladium catalysed allylic substitution of (E)-1,3-diphenyl-1-acetoxyprop-2-ene, 145, only a modest enantioselectivity (34% e.e.) of alkylated product 146, was obtained when sodiodimethyl malonate (R = H) was used as the nucleophile. However, by using sodiodimethyl acetamidomalonate (R = NHAc) as the nucleophile the alkylated product, 199 was obtained with a far higher enantioselectivity (95% e.e.).

We chose to concentrate on three stabilised, substituted malonate derived compounds namely, dimethyl methylmalonate, 191a, dimethyl acetoxymalonate, 191b and diethyl acetamidomalonate, 191c. Meaning, that potentially we have the possibility of forming carbon, oxygen and nitrogen α-substituted-β-amino acids.
5.2 Palladium catalysed allylic substitution proceeding through symmetrical cationic π-allyl complexes using substituted malonate derived nucleophiles

Dimethyl methylmalonate, 191a and dimethyl acetamidomalonate, 191c are both commercially available. Dimethyl acetoxymalonate, 191b was prepared from dimethyl bromomalonate, 200. Treatment of the bromo-substituted malonate, 200 with an excess of sodium acetate in DMF at r.t., followed by purification using Kugelrohr distillation, afforded the desired acetoxy-substituted malonate, 191b in good yield. $^1$H NMR analysis of 191b confirmed product formation with the appearance of a three proton singlet at δ 2.2 ppm, corresponding to the protons of the acetoxy group.

With a range of substituted malonate compounds, 191a, 191b and 191c in hand we turned our attention towards a palladium catalysed allylic substitution reaction. The initial choice of allylic substrate was (E)-1,3-diphenyl-1-acetoxyprop-2-ene, 145 and has become known over the years as the general "test" substrate for all new ligands/nucleophiles that have been designed specifically for palladium catalysed allylic substitution reactions. Using this substrate any reaction that takes place will do so through a meso η^3-allyl intermediate. Enantioselective palladium catalysed allylic substitutions, using sodium hydride as base were carried out as detailed.
The reaction of 145 in THF or DMF with the sodium salt of the nucleophile (191a, 191b, 191c) in the presence of 2.5 mol% allyl palladium chloride dimer and 10 mol% of ligand 15 or ligand 111b afforded, after aqueous work-up and "flash" column chromatography, the substitution products 201, 202 and 203, with the results being summarised in Table 13. $^1$H NMR analysis of 201, 202 and 203 confirmed product formation with the disappearance of a three proton singlet at $\delta$ 2.0 ppm corresponding to the protons of the acetoxy group of 145, and the appearance of a one proton doublet at $\delta$ 4.3 ppm (201), $\delta$ 4.2 ppm (202) and $\delta$ 4.8 ppm (203) respectively, corresponding to the methine protons.

The identical reactions were also carried out under standard BSA conditions,\textsuperscript{133} and the results are summarised in Table 14. Again $^1$H NMR analysis confirmed formation of the products 201, 202 and 203.
Chapter 5: Studies towards α-substituted-β-amino acids

\[
\text{CH}(X)(\text{CO}_2\text{R'})_2/\text{BSA}
\]

(191a, 191b, 191c)

\[
\begin{array}{cc}
\text{OAc} & \text{Ph} \\
\text{Ph} & \text{Ph}
\end{array}
\]

145

\[
\begin{array}{ccc}
2.5 \text{ mol\% } [\text{Pd}(\eta^3\text{C}_3\text{H}_5)_2\text{Cl}]_2 \\
10 \text{ mol\% } 15 \text{ or } 111\text{b} \\
\text{NaOAc, CH}_2\text{Cl}_2, \text{ r.t.}
\end{array}
\]

\[
\begin{array}{ccc}
\text{R'O}_2\text{C} & \text{X} & \text{CO}_2\text{R'}
\end{array}
\]

201 (X = R' = CH₃)
202 (X = OAc, R' = CH₃)
203 (X = NHAC, R' = CH₂CH₃)

Table 14

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Ligand</th>
<th>Time (hr)</th>
<th>Yield (%) (Product)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCH₃(CO₂CH₃)₂</td>
<td>15</td>
<td>2</td>
<td>90 (201)</td>
<td>96ᵃ</td>
</tr>
<tr>
<td>(191a)</td>
<td>111b</td>
<td>92</td>
<td>90 (201)</td>
<td>91ᵃ</td>
</tr>
<tr>
<td>CHOAc(CO₂CH₃)₂</td>
<td>15</td>
<td>4</td>
<td>80 (202)</td>
<td>97ᵇ</td>
</tr>
<tr>
<td>(191b)</td>
<td>111b</td>
<td>92</td>
<td>53 (202)</td>
<td>91ᵇ</td>
</tr>
<tr>
<td>CHNHAC(CO₂CH₂-)</td>
<td>15</td>
<td>38</td>
<td>70 (203)</td>
<td>?ᶜ</td>
</tr>
<tr>
<td>CH₃(191c)</td>
<td>111b</td>
<td>120</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a) The enantiomeric excess of 201 was determined from ¹H NMR spectra in the presence of 1.6 equivalents of the enantiopure shift reagent Eu(hfc)₃. (Best results were achieved using 2 mg of 201).
b) The enantiomeric excess of 202 was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 99.75:0.25, 0.5 ml/min. (t_{R} = 44.6 and 46.4 min.).
c) The enantiomeric excess of 203 could not be determined using either NMR, chiral GC or chiral HPLC.

The results from Tables 13 and 14 indicate that all three enolates derived from 191a, 191b and 191c are able to act as efficient nucleophiles for the asymmetric palladium catalysed allylic substitution reaction when using 145 as the allylic substrate. In general it seems that the reactions taking place using the sodium hydride generated nucleophiles of 191a, 191b and 191c, coupled with the use of the diphenylphosphinophenyl oxazoline ligand 15 are far more efficient (80-90% yield) with reaction times varying between 5-25 min.; than the corresponding BSA generated nucleophiles (70-90% yield) with reaction times varying between 2-38 hr. Such a phenomenon is probably due to the slower formation of the active nucleophile in solution when using BSA. This becomes even more evident when using the sulfoxide-based oxazoline ligand 111b. Even nucleophiles generated through the use of sodium hydride resulted in reaction times of 72 hr (90% yield) and 80 hr (90% yield) for nucleophiles 191a and 191b respectively, with nucleophile 191c failing to react with the active cationic π-allyl species. Again nucleophiles generated under BSA conditions required longer reaction times, with the BSA.

Page 95
generated nucleophile of 191b giving a moderate yield (53%). The enantioselectivities gained using both the sodium hydride and BSA procedures were excellent when using ligand 15 and although slightly lower, still good when using ligand 111b. The longer reaction times and slightly lower enantioselectivities produced when using the sulfoxide ligand 111b, can be attributed to the poorer π-accepting properties of sulfur compared to phosphorus, resulting in a lower reactivity of the sulfoxide ligand 111b.

In every case we assume that the nucleophiles (191a, 191b and 191c) preferentially add to the carbon of the intermediate meso η3-cationic allyl species which is trans to the better π-acceptor (sulfur or phosphorus). If this is the case then it is fair to assume a predominance of the (S)-(−) enantiomer of product (see Chapter 3) for 201, 202 and 203.

5.3 Palladium catalysed allylic substitution proceeding through unsymmetrical cationic π-allyl complexes using substituted malonate derived nucleophiles

As has been described in section 5.2 allylic acetate 145 was found to be a successful "test" substrate for the palladium catalysed allylic substitution reaction when using enolates derived from 191a, 191b and 191c as nucleophiles. However, in order for this process to be synthetically useful, trisubstituted allylic acetates such as 161 need to be used, which have already been shown (Chapter 4) to produce higher enantioselectivities than their corresponding disubstituted allylic acetates and also to have greater synthetic potential. We focused our attention on the use of 1,1,3-triphenylprop-2-enyl acetate, 161b as the allylic substrate.

\[
\text{Ph} - \text{Ph} - \text{R}
\]

161

\[
\text{Ph} - \text{Ph} - \text{OAc}
\]

161b

The enantioselective palladium catalysed allylic substitution reactions of substrate 161b with substituted malonate derived nucleophiles were performed as detailed.
Chapter 5: Studies towards α-substituted-β-amino acids

\[
\text{CH(X)(CO_2R')_2/NaH} \quad (191a, 191b, 191c) \quad \xrightarrow{2.5 \text{ mol\% } [\text{Pd}(\text{n}^3\text{C}_3\text{H}_5)\text{Cl})_2, 10 \text{ mol\% of ligand, 15 }] \quad \text{Ph} \quad \xrightarrow{\text{r.t.}} \quad \text{Ph} \quad \xrightarrow{\text{RO}_2\text{C}} \quad \text{Ph} \quad \xrightarrow{\text{CO}_2\text{R'}} \quad 161b \quad \xrightarrow{204 \ (X = R' = \text{CH}_3)} \quad 205 \ (X = \text{OAc}, R' = \text{CH}_3)
\]

The reaction of 161b in THF or DMF with the sodium salt of the nucleophiles 191a, 191b and 191c in the presence of 2.5 mol% allylpalladium chloride dimer and 10 mol% of ligand, 15 afforded, after aqueous work-up and "flash" column chromatography the substitution products 204 and 205. The results are summarised in Table 15. 1H NMR analysis of 204 and 205 confirmed product formation with the disappearance of a three proton singlet at δ 2.0 ppm corresponding to the protons of the acetoxy group of 161b and the appearance of a one proton doublet at δ 4.2 ppm (204) and δ 4.1 ppm (205) respectively, corresponding to the methine protons.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCH_3(CO_2CH_3)_2</td>
<td>THF</td>
<td>48</td>
<td>85 (204)</td>
<td>&gt;99^a</td>
</tr>
<tr>
<td>(191a)</td>
<td>DMF</td>
<td>48</td>
<td>84 (204)</td>
<td>&gt;99^a</td>
</tr>
<tr>
<td>CHOAc(CO_2CH_3)_2</td>
<td>THF</td>
<td>72</td>
<td>80 (205)</td>
<td>&gt;99^b</td>
</tr>
<tr>
<td>(191b)</td>
<td>DMF</td>
<td>72</td>
<td>80 (205)</td>
<td>&gt;99^b</td>
</tr>
<tr>
<td>CHNHAc-(CO_2CH_2CH_3)_2</td>
<td>THF</td>
<td>120</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(191c)</td>
<td>DMF</td>
<td>120</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>DMF 100°C</td>
<td>120</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a) The enantiomeric excess of 204 was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 98:2, 0.7 ml/min. (t_R = 7.8 and 9.1 min.).
b) The enantiomeric excess of 205 was determined by chiral HPLC (Chiralcel OD); hexane/isopropanol, 98.75:1.25, 0.73 ml/min. (t_R = 13.3 and 14.4 min.).

The results from Table 15 suggest that as the size of the nucleophile increases, so the reaction time lengthens. This is aptly demonstrated in the failure of the massive nucleophile, derived from 191c, to react with the cationic π-allyl intermediate even after being heated to 100 °C for 5 days. The longer reaction times (48-72 hr) for these reactions (as compared to reactions proceeding through symmetrical cationic π-allyl intermediates, section 5.2) can be attributed to their
lower reactivity (see Chapter 4). This also explains why only the diphenylphosphinophenyl oxazoline ligand 15 (sulfoxides are not reactive enough) is able to provide a reactive cationic π-allyl intermediate. In both cases, irrespective of solvent, the enantioselectivities were excellent (>99% e.e.), the other enantiomer being undetectable by HPLC.

Again in both cases we assume that the nucleophiles (191a and 191b) preferentially add to the carbon of the intermediate meso η₃-cationic allyl species which is trans to the better π-acceptor (phosphorus). If this is the case then it is fair to assume a predominance of the (S)-(−) enantiomer of product (see Chapter 4) for 204 and 205.

5.4 Carbon-carbon double bond oxidation

Having established an efficient route to highly enantiomerically enriched (>99% e.e.) alkylated products 204 and 205, we then required a method that would allow for cleavage of the carbon-carbon double bond. As already mentioned (Chapter 4) there are many methods available to the organic chemist for carbon-carbon double bond cleavage where the required carboxylic acid functionality can be isolated.¹⁶⁴ We chose to focus our attention on the cleavage of the double bond of alkylated product 204.

![Structural formula of 204 and 206](image)

A number of methods for double bond oxidation were attempted, as shown.

Cleavage of the carbon-carbon double bond of 204 was not easily achieved. Both chromium(VI) oxide oxidation¹⁷⁸ (previously reported by Dawson and Williams¹⁵³b to give good yields (~70%) for the double bond oxidation of similar
substrates) and potassium permanganate assisted oxidation\textsuperscript{164} failed to afford any of the desired product, \textit{206} even after heating for 5 days. Performing the reaction under standard Sharpless oxidation conditions (2.2 mol\% \textit{RuCl}_3(\textit{H}_2\textit{O})\textit{n}, \textit{NaIO}_4 in a solvent mixture of acetonitrile, carbon tetrachloride and water, 2:2:3)\textsuperscript{165} at r.t. for 5 days resulted in re-isolation of the starting material. However, on warming the reaction mixture to 50 °C the desired product, \textit{206} was isolated, after "flash" column chromatography albeit in poor yield (25%). In an attempt to increase the poor yield we turned our attention to a much harsher oxidant, periodic acid. Used in conjunction with a catalytic amount of ruthenium trichloride, periodic acid was reported by Nuñez and Martin to give superior yields to sodium periodate in the oxidative cleavage of phenyl rings.\textsuperscript{179} Under the standard Sharpless conditions (using periodic acid as the stoichiometric oxidant) at 40 °C, a higher yield (40\%) of product, \textit{206} was achieved. The moderate yields obtained (25 and 40\%) are probably due to over oxidation of the phenyl rings which occurs readily at these temperatures (40-50 °C). Steric hindrance of the carbon-carbon double bond could also account for the poor yields and sluggishness of the reaction. \textit{1H NMR} analysis indicated formation of the desired product, \textit{206} as judged by the disappearance of a one proton doublet at \(\delta\) 6.7 ppm, corresponding to the carbon-carbon double bond proton of \textit{204} and the appearance of a one proton singlet at \(\delta\) 4.6 ppm corresponding to the methine proton. X-Ray quality crystals were grown for \textit{169b} and \textit{206}. X-Ray crystallography analysis seems to provide a plausible explanation as to why double bond oxidation of \textit{204} is so difficult to achieve. \textbf{Figure 13} and \textbf{Figure 14} show the X-ray diagrams of \textit{169b} and \textit{204} respectively (see Appendix for more details).
Chapter 5: Studies towards $\alpha$-substituted-$\beta$-amino acids

Figure 13

Figure 14
It can clearly be seen in both diagrams that one face of the double bond is being totally blocked by the malonate derived chain. It is also clear that the methyl substituent in Figure 14 is not directly affecting the double bond (i.e. it is not causing one of the methoxy groups to block the pathway open to the incoming oxidant). However, it can be seen that for 204 (Figure 14) the phenyl ring (3-substituent) is tilted inwards (towards the double bond). With 169b (Figure 13) the same phenyl ring is not tilted towards the double bond to the same degree. It therefore seems that there is, in effect relatively less space for the incoming reagent to oxidatively cleave the double bond in 204 as compared with 169b. However, this is a solid state consideration and we have no evidence to support such a theory in solution.

5.5 Attempted decarboxylations

For formation of α-substituted-β-amino acids of the type 190 to be possible we need to introduce another centre of asymmetry.

![Chemical Structure](image)

Decarboxylation of 206 could in theory introduce the second asymmetric centre and the decarboxylation of malonate derivatives has been well documented.\(^{180}\) Any diastereoselectivity achieved would probably be a consequence of hydrogen-bonding between the carboxylic acid functionality and one of the methyl ester groups of 206, thus "locking" the intermediate enolate resulting in reprotonation (diastereoselective step) from one face of the enolate double bond.

The attempted decarboxylation of 206 to 207 was undertaken as shown.
Several methods of decarboxylation were attempted, including:
- Krapcho decarboxylation (NaCl, H₂O, DMSO, 180 °C),¹⁵⁹
- Propionic acid (141 °C) induced decarboxylation,¹⁸¹
- Acid induced decarboxylation (2M HCl, H₂O, THF, reflux).¹⁸⁰

Under no circumstances was there any detectable signs of product, 207 or starting material, 206 (¹H NMR analysis). This could be due to the decarboxylation of more than one carboxylate group, resulting in degradation.

5.6 Attempted diastereoselective reprotonations

Failure of the decarboxylation chemistry turned our attention towards another route to the desired diastereomerically enriched decarboxylated compound, 207.

Recently Davies et al. have reported the synthesis of cis-pentacin, 208, a naturally occurring antifungal agent.¹⁸² Reaction of tert-butyl-1-cyclopentene-1-carboxylate, 209 with the chiral lithium amide base, 210 affords the cis-aminocyclopentane carboxylate ester, 211 with excellent diastereoselectivity (>98% d.e.).
Chapter 5: Studies towards α-substituted-β-amino acids

Michael addition of the lithium amide base 210 to 209 gave an intermediate enolate which was subsequently quenched with the hindered acid 2,6-di-tert-butylphenol, resulting in high diastereoselectivity.

We felt that this type of methodology could be used to produce compounds such as 212 with high diastereoselectivity, where reprotonation of the enolate double bond (rendered diastereotopic due to the presence of the asymmetric centre) would occur preferentially from one face.

```
Ph    Ph

Ph
H H

H3CO2C CH3

212
```

The double bond of 212 could then easily be cleaved, resulting in formation of the desired diastereomerically enriched acid, 207.

The synthesis of 212 was achieved through Krapcho decarboxylation\textsuperscript{159} of 204, as shown.

```
\[
\begin{array}{c}
\text{Ph} \\
\text{H3CO2C} \\
\text{CH3}
\end{array}
\quad \begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{H}
\end{array}
\to
\begin{array}{c}
\text{Ph} \\
\text{H3CO2C} \\
\text{CH3}
\end{array}
\]
\[
\text{NaCl/H2O/DMSO} \quad 180^\circ C \quad 6.5 \text{ hr} \quad 60\%
\]

204 \to 212 (22\% d.e.)
```

Decarboxylation of 204 under standard Krapcho conditions\textsuperscript{159} led to, after aqueous work-up and "flash" column chromatography, the desired decarboxylated compound, 212. \textsuperscript{1}H NMR analysis of 212 confirmed product formation with the disappearance of one of the methyl ester singlets of 204 at δ 3.5 ppm and the appearance of a one proton multiplet at δ 2.8 ppm, corresponding to the methine proton at the newly formed stereocentre. \textsuperscript{1}H NMR analysis also indicated a mixture of two diastereoisomers and the diastereomeric excess was found to be 22\%, calculated by integration of the methyl doublets at δ 0.9 (major) and δ 1.2 ppm (minor).

The decarboxylated compound, 212 was then taken and subjected to a number of deprotonation-reprotonation experiments as shown, using the hindered base lithium diisopropylamide (LDA) with a number of electrophilic quenches.
The decarboxylated compound, 212 was added under nitrogen to a pre-prepared LDA solution in THF at -78 °C and stirred for 1.5 hr. The appropriate quench was then added at -78 °C and the reaction mixture allowed to warm to r.t. over 16 hr. Aqueous work-up, followed by $^1$H NMR analysis confirmed formation of the desired product, 212. The results are summarised in Table 16.

### Table 16

<table>
<thead>
<tr>
<th>Quench</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>d.e. (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHTa</td>
<td>16</td>
<td>99</td>
<td>22</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>16</td>
<td>99</td>
<td>24</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>16</td>
<td>99</td>
<td>23</td>
</tr>
</tbody>
</table>

a) BHT-Butylated Hydroxy Toluene (2,6-Di-tert-butyl-4-methylphenol)

b) Diastereomeric excesses were determined by $^1$H NMR analysis through integration of the methyl doublets at δ 0.9 (major) and δ 1.2 ppm (minor).

As can be seen from Table 16 none of the chosen electrophilic quenches seemed to provide any significant increase in the diastereomeric excess of compound 212. This could be due to one of two reasons:

- either (i) the LDA did not deprotonate 212, meaning no enolate formation;
- or (ii) an equilibration of the two possible enolates occurred (thermodynamic mixture).

However, due to time restraints this was not investigated any further.

Cleavage of the carbon-carbon double bond of 212 was achieved using the oxidation conditions developed by Sharpless.165
Chapter 5: Studies towards \( \alpha \)-substituted-\( \beta \)-amino acids

Reaction of 212 with *in situ* prepared ruthenium tetroxide at r.t. afforded, after aqueous work-up and "flash" column chromatography, 213 in good yield. \(^1\)H NMR analysis of 213 confirmed product formation with the disappearance of a one proton doublet at \( \delta \) 6.3 ppm, corresponding to the carbon-carbon double bond proton of 212 and the appearance of a one proton doublet at \( \delta \) 3.8 ppm, corresponding to the methine proton (adjacent to the carboxylic acid functionality). \(^1\)H NMR analysis also indicated a mixture of two diastereoisomers and the diastereomeric excess was found to be 22%, (calculated by integration of the methyl doublets at \( \delta \) 1.0 (minor diastereoisomer) and \( \delta \) 1.4 ppm (major diastereoisomer).

5.7 Conclusions

Whilst this work does not complete the synthesis of diastereomerically pure/enriched \( \alpha \)-substituted-\( \beta \)-amino acids, methodology has been described which may enable the synthesis of racemic \( \alpha \)-substituted-\( \beta \)-amino acids from 213. It has been shown that several trisubstituted "bulky" nucleophiles are effective in the asymmetric palladium catalysed allylic substitution reaction. Very high levels of enantioselectivity (up to 97% e.e.) can be achieved when allylic substitution proceeds through the highly reactive symmetrical cationic \( \eta^3 \)-allyl intermediate and excellent levels of enantioselectivity (>99% e.e.) achieved when the reaction proceeds through the less reactive unsymmetrical cationic \( \eta^3 \)-allyl intermediate. Further investigation into either or both the decarboxylation and/or the deprotonation-reprotonation step may enable compounds such as 212 to be achieved with high diastereoselectivity. Curtius rearrangement should then allow easy access into a range of diastereomerically enriched \( \alpha \)-substituted-\( \beta \)-amino acids.
CHAPTER 6

EXPERIMENTAL
Chapter 6: Experimental

6.1 General Information

Commercially available solvents were used throughout without further purification, except for those detailed below which were purified as described. Petroleum ether refers to the fraction of petroleum ether boiling between 40 °C and 60 °C, and was distilled through a 36cm Vigreux column over calcium chloride before use. Diethyl ether was distilled from sodium benzophenone ketyl under nitrogen, prior to use, as was tetrahydrofuran (THF). Dichloromethane was distilled from phosphorous pentoxide. Dimethylformamide (DMF) was dried by stirring over calcium hydride for 15 hr, decanted, and distilled under reduced pressure before storing over 4 Å molecular sieves under nitrogen. Triethylamine was distilled from, and stored over potassium hydroxide.

Analytical thin layer chromatography was carried out using precoated aluminium-backed silica plates (coated with Merck Kieselgel 60 GF254) which were visualised using either ultraviolet light (at 254 nm) or permanganate stain, or by bromocresol green dip. "Flash" column chromatography was carried out using Merck Kieselgel 60 H silica gel. Pressure was applied at the column head with hand bellows. Samples were applied pre-absorbed on silica or as a saturated solution in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600cm⁻¹ using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in dichloromethane or as thin films. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser. ¹H and ¹³C NMR spectra were recorded using a Brucker AC-250 instrument and/or DPX 400. Chemical shifts were expressed in parts per million (ppm) downfield of tetramethylsilane (singlet at 0 ppm, TMS) for proton resonances and referenced to the central peak of the triplet of deuterated chloroform (77 ppm) for ¹³C resonances. The multiplicities of the spectroscopic data are represented as follows; singlet (s), doublet (d), double doublet (dd), triplet (t) and multiplet (m). High and low resolution mass spectra were recorded on a Kratos MS80 instrument. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were measured on an Optical Activity AA 100 polarimeter.
Chapter 6: Experimental

6.2 Chapter 2 experimental
Experimental procedures.

(S)-2-Amino-3-methyl-1-butanol, 108

\[
\begin{align*}
\text{CO}_2\text{H} & \\
\text{H}_2\text{N} & \quad \rightarrow \\
\text{CH}_2\text{OH}
\end{align*}
\]

(S)-Valine 109 (10 g, 85 mmol) and sodium borohydride (7.7 g, 206 mmol) were stirred in dry THF (200 ml) at 0 °C under nitrogen. A solution of iodine (21.6 g, 85 mmol) in dry THF (50 ml) was then added dropwise over 30 min, resulting in vigorous evolution of hydrogen. On complete addition the flask was heated to reflux and stirred for 24 hr. The flask was then cooled to r.t. and methanol added until the mixture became clear. After stirring for 30 min the solvent was removed under vacuum, and the resulting white paste dissolved in 20% potassium hydroxide solution (160 ml) and stirred for 2 hr. The solution was extracted with dichloromethane (5 x 150 ml), and the combined organics collected, dried (MgSO₄), filtered and concentrated in vacuo yielding the title compound (6.6g, 75% yield) as a colourless liquid. B.p. 64-66 °C at 10 mmHg (lit.82 62-65 °C at 10 mmHg).

\[\left[\alpha\right]_{D}^{20} +14.1 \text{ (neat).} \]

\[v_{\text{max}} / \text{cm}^{-1} 3300 (\text{OH}), 1590. \]

\[\delta_{\text{H}} (250 \text{ MHz, CDCl}_3) 0.92 (\text{d, 6H, } J=2.5 \text{ Hz, } 2 \times \text{CH}_3), 1.53-1.66 (\text{m, 1H, CH(CH}_3)_2), 2.51-2.61 (\text{m, 4H, NH}_2 \text{ and OH}), 3.28-3.66 (\text{m, 2H, CH}_2\text{OH}). \]

\[\delta_{\text{C}} (62.5 \text{ MHz, CDCl}_3) 18.2 ((\text{C}_3\text{H}_2)\text{CH}), 19.2 ((\text{CH}_3)_2\text{CH}), 31.2 (\text{CH(CH}_3)_2), 58.3 (\text{CHNH}_2), 64.5 (\text{CH}_2\text{OH}). \]

General procedure for the preparation of nitriles 103 and 104.

A solution of the appropriate aromatic thiol 106 or 107 (36 mmol) in dry THF (15 ml) was added cautiously to a stirred suspension of sodium hydride (45 mmol), in dry...
THF (15 ml) at 0 °C. The resulting white precipitate was warmed to r.t. and ortho-fluorobenzonitrile 105 added (3.86 ml, 36 mmol). The reaction mixture was heated to reflux until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been consumed (24 hr). On completion, the reaction mixture was diluted with diethyl ether (60 ml) and washed with 15% sodium hydroxide solution (3 x 30 ml). The combined organics were dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown tar. Purification by recrystallisation from petroleum ether gave the title compounds as described.

2-(Phenylsulfanyl)benzonitrile, 103. (60%) as a pale yellow solid. M.p. 35-37 °C. (Found: M⁺, 211.0455. C₁₃H₉NS requires M⁺, 211.0455). vₓ̂ /cm⁻¹ 2220 (CN). δₓ̂ (250 MHz, CDCl₃) 7.11-7.65 (m, 9H, ArH). δₓ (62.5 MHz, CDCl₃) 113.2 (CN), 117.0 (ArC), 126.4 (ArCH), 128.9 (ArCH), 129.7 (ArCH), 129.9 (ArCH), 131.1 (ArC), 132.9 (ArCH), 133.5 (ArCH), 133.6 (ArCH), 142.5 (ArC). m/z (El) 211 (M⁺, 100%), 184 (40).

2-(4-Methylphenylsulfanyl)benzonitrile, 104. (75%) as a colourless solid. M.p. 74-76 °C. (Found: M⁺, 225.0612. C₁₄H₁₁NS requires M⁺, 225.0612). vₓ̂ /cm⁻¹ 2224 (CN). δₓ̂ (400 MHz, CDCl₃) 2.37 (s, 3H, ArCH₃), 7.02 (d, 1H, J=8.0 Hz, ArH), 7.17-7.21 (m, 3H, ArH), 7.34-7.40 (m, 3H, ArH), 7.59 (dd, 1H, J=1.5, 7.7 Hz, ArH). δₓ (100 MHz, CDCl₃) 21.1 (ArCH₃), 111.7 (ArC), 116.8 (CN), 125.8 (ArCH), 127.4 (ArCH), 128.7 (ArCH), 130.5 (ArCH), 132.7 (ArCH), 133.3 (ArCH), 134.1 (ArCH), 139.4 (ArC), 143.3 (ArC). m/z (El) 225 (M⁺, 100%), 209 (10), 123 (8), 91 (78).

General procedure for the preparation of 4,5-dihydrooxazoles 112, 100 and 101.

\[
\begin{align*}
\text{CN} & \quad \Rightarrow \\
\text{O} & \quad \text{Pr} \\
\text{X} = \text{H, SMe, STol} \\
\end{align*}
\]

In a 50 ml Schlenck flask, zinc chloride (136 mg, 1mmol) was melted under high vacuum and cooled under nitrogen. After cooling to r.t., chlorobenzene (10 ml) was added followed by the appropriate nitrile (113, 102, 104), (20 mmol) and (S)-valinol 108, (2.90 g, 28 mmol). The mixture was heated under reflux until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been
consumed (24-48 hr). The resulting solution was diluted with dichloromethane (50 ml) and extracted with distilled water (3 x 30 ml). The combined organics were collected, dried (MgSO₄), filtered and concentrated in vacuo yielding a dark-brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 4:1) gave the title compounds as described.

(4R)-4,5-Dihydro-4-isopropyl-2-(2-phenyl)-1,3-oxazole, 112. (75%) as a colourless oil. (Found: M⁺, 189.1154. C₁₂H₁₇NO requires M⁺, 189.1154). [α]D²⁰ -72.0 (c=6.5, CHCl₃). νmax/cm⁻¹ 2950, 1651 (C=N), 1253. δH (250 MHz, CDCl₃) 0.91 (d, 3H, J=6.8 Hz, (CH₃)₂CH), 1.04 (d, 3H, J=6.8 Hz, (CH₃)₂CH), 1.82-1.90 (m, 1H, CH(CH₃)₂), 4.05-4.16 (m, 2H, CH₂O), 4.34-4.45 (m, 1H, CHN), 7.35-7.45 (m, 3H, ArH), 7.93-7.97 (m, 2H, ArH). δC (63 MHz, CDCl₃) 17.9 (CH₃CH), 18.9 (CH₃CH), 32.7 (CH(CH₃)₂), 69.9 (CH₂O), 72.5 (CHN), 128.0 (ArC), 128.1 (ArC), 131.1 (ArC), 163.1 (C=N). m/z (El) 189 (M⁺, 77%), 169 (100).

(4R)-4,5-Dihydro-4-isopropyl-2-((2-methylsulfanyl)phenyl)-1,3-oxazole, 100. (53%) as a colourless solid. M.p. 47-49 ºC. (Found: M⁺, 235.1030. C₁₃H₁₇NOS requires M⁺, 235.1030). (Found: C, 65.97; H, 7.59; N, 5.95. C₁₃H₁₇NOS requires C, 66.35; H, 7.28; N, 5.95). [α]D²⁰ -73.5 (c=0.18, CHCl₃). νmax/cm⁻¹ 3053, 2900, 1649 (C=N),1265. δH (250 MHz, CDCl₃) 0.97 (d, 3H, J=6.7 Hz, (CH₃)₂CH), 1.07 (d, 3H, J=6.7 Hz, (CH₃)₂CH), 1.81-1.95 (m, 1H, CH(CH₃)₂), 2.42 (s, 3H, CH₃S), 4.10 (t, 1H, CHHO), 4.18-4.24 (m, 1H, CHN), 4.33-4.39 (m, 1H, CHHO), 7.10-7.16 (m, 1H, ArH), 7.24 (dd, 1H, J=1.4, 7.7 Hz, ArH), 7.36-7.44 (m, 1H, ArH), 7.79 (dd, 1H, J=1.4, 7.7 Hz, ArH). δC (63 MHz, CDCl₃) 15.8 (CH₃S), 18.2 (CH₃CH), 18.8 (CH₃CH), 32.9 (CH(CH₃)₂), 69.3 (CH₂O), 73.4 (CHN), 123.4 (ArCH), 124.1 (ArCH), 125.1 (ArC), 130.0 (ArCH), 130.6 (ArCH), 140.9 (ArC), 162.3 (C=N). m/z (El) 235 (M⁺, 100%), 220 (90), 192 (66).

(4R)-4,5-Dihydro-4-isopropyl-2-((4-methylphenyl)sulfanyl)-1,3-oxazole, 101. (60%) as a colourless solid. M.p. 76-78 ºC. (Found: M⁺, 311.1344. C₁₉H₂₁NOS requires M⁺, 311.1344). [α]D²⁰ -62.0 (c=0.50, CHCl₃). νmax/cm⁻¹ 2095, 1649 (C=N), 1245. δH (400 MHz, CDCl₃) 0.98 (d, 3H, J=6.7 Hz, CH(CH₃)₂), 1.08 (d, 3H, CH(CH₃)₂), 1.83-1.94 (m, 1H, CH(CH₃)₂), 2.38 (s, 3H, ArCH₃), 4.12 (ap. t, 1H, J=7.8 Hz, CHHO), 4.19-4.25 (m, 1H, CHN), 4.39 (ap. t, 1H, J=7.8 Hz, CHHO), 6.78 (dd, 1H, J=1.0, 8.1 Hz, ArH), 7.08-7.10 (m, 1H, ArH), 7.10-7.25 (m, 1H, ArH), 7.21 (d, 2H, J=8.0 Hz, ArH), 7.44 (d, 2H, J=8.0 Hz, ArH), 7.76 (dd, 1H, J=1.5, 8.1 Hz, ArH). δC (100 MHz, CDCl₃) 21.1 (CH(CH₃)₂), 21.7 (CH(CH₃)₂), 24.0 (ArCH₃), 35.8 (CH(CH₃)₂), 72.5 (CH₂O), 76.2 (CHN), 126.8 (ArCH), 127.7 (ArC), 129.9 (ArCH), 132.4 (ArC), 132.6 (ArCH), 133.1
General procedure for the diastereoselective oxidation of (4S)-4,5-Dihydro-4-isopropyl-2-[2-(methylsulfinyl)phenyl]-1,3- oxazole, 100 and (4S)-4-isopropyl-2-[2-(4-methylphenylsulfinyl)phenyl]-4,5-dihydro-1,3-oxazole, 101 using mCPBA.

A solution of mCPBA (0.43 mmol) in chloroform (3 ml) was added dropwise to a stirred solution of 100 or 101 (0.43 mmol) in chloroform at -70 °C under nitrogen. Stirring was continued until TLC analysis (petroleum ether/ethyl acetate, 4:1) indicated that all of the starting material had been consumed (1.25 hr). The reaction mixture was then diluted with dichloromethane (10 ml) and washed with saturated sodium carbonate solution (2 x 10 ml). The dichloromethane layer was collected, dried (MgSO₄), filtered and concentrated in vacuo yielding a yellow oil. Purification by "flash" column chromatography (eluant, eluant, petroleum ether/ethyl acetate, 1:4) gave the title compounds, a mixture of two diastereoisomers, 110a/110b and 111a/111b, as described.

(4S,Rs/Ss),4,5-Dihydro-4-isopropyl-2-[2-(methylsulfinyl)phenyl]-1,3-oxazole, 110a/110b. (94%) as a colourless oil. (Found: M⁺, 251.0979. C₁₃H₁₇NO₂S requires M⁺, 251.0979). [α]D²⁰ -140.0 (c=0.45, CHCl₃). v_max/cm⁻¹ 3000, 2960, 1651 (C=N), 1356, 1061 (S=O). δ_H (400 MHz, CDCl₃) 0.98 (d, 3H, J=6.7 Hz, (CH₃)₂CH), 1.03 (d, 3H, J=6.7 Hz, (CH₃)₂CH), 1.78-1.84 (m, 1H, CH(CH₃)₂), 2.91 (s, 3H, CH₃S=O), 4.07-4.15 (m, 2H, CH₂O), 4.42-4.46 (m, 1H, CHN), 7.52-7.55 (m, 1H, ArH), 7.72-7.75 (m, 1H, ArH), 7.87 (dd, 1H, J=1.1, 7.7 Hz, ArH), 8.27 (dd, 1H, J=1.1, 7.8 Hz, ArH). δ_C (100 MHz, CDCl₃) (Major diastereoisomer) 18.9 (CH₃CH), 19.1 (CH₃CH), 33.1 (CH(CH₃)₂), 43.9 (CH₃SO), 70.5 (CH₂O), 73.5 (CHN), 123.9 (ArCH), 124.4 (ArC), 129.4 (ArCH), 130.0 (ArCH), 132.0 (ArCH), 148.3 (ArC), 160.6 (C=N). δ_C (100 MHz, CDCl₃) (Minor diastereoisomer) 18.5 (CH₃CH), 18.8 (CH₃CH), 34.0 (CH(CH₃)₂), 44.0 (CH₃SO), 70.6 (CH₂O), 73.5 (CHN), 123.9 (ArCH), 124.6 (ArC), 129.1 (ArCH), 130.0
Chapter 6: Experimental

(ArCH), 131.9 (ArCH), 148.3 (ArC), 160.2 (C=N). m/z (El) 251 (M+, 15%), 236 (100), 203 (50), 136 (52). (110a:110b, 30:70).

All the other mCPBA reactions were conducted under the same conditions, except for temperature.

\[ \alpha \]D \textsuperscript{20} -123.0 (c=0.80, CHCl\textsubscript{3}) (Reaction conducted at r.t.). (110a:110b, 43:57). (95% yield).

\[ \alpha \]D \textsuperscript{20} -123.0 (c=0.50, CHCl\textsubscript{3}) (Reaction conducted at 0 °C). (110a:110b, 43:57). (90% yield).

\[ \alpha \]D \textsuperscript{20} -125.2 (c=0.50, CHCl\textsubscript{3}) (Reaction conducted at -20 °C). (110a:110b, 40:60). (95% yield).

All reactions produced consistent data.

\((4S,R_5/S_3)-4,5\text{-Dihydro}-4\text{-isopropyl-2-[2-(4-methylphenylsulfinyl)phenyl]-1,3-oxazole}, \text{111a/111b.} (57\%) \text{ as a colourless oil.} \) (Found: M+, 327.12929. C\textsubscript{19}H\textsubscript{21}N\textsubscript{1}O\textsubscript{2}S requires M+, 327.1293). \[ \alpha \]D \textsuperscript{20} -110.2 (c=0.71, CHCl\textsubscript{3}). \n
\[ \nu \text{max/cm}^{-1} \] 3058, 2960, 1649 (C=N), 1054 (S=O).

8H (250 MHz, CDCl\textsubscript{3}) (The isopropyl group was split, indicating the presence of two diastereoisomers) (Major diastereoisomer) 0.73 (d, 3H, J=6.7 Hz, \((\text{CH}_3)_2\text{CH})\), 0.89 (d, 3H, J=6.7 Hz, \((\text{CH}_3)_2\text{CH})\), 1.74-1.76 (m, 1H, CH\textsubscript{2}CH), 2.32 (s, 3H, CH\textsubscript{3}Ar), 4.01-4.06 (m, 2H, CH\textsubscript{2}O), 4.31-4.37 (m, 1H, CHN), 7.15 (d, 2H, J=7.9 Hz, ArH), 7.53 (d, 2H, J=7.9 Hz, ArH), 7.54-8.34 (m, 4H, ArH). \n
8C (62.5 MHz, CDCl\textsubscript{3}) (Major diastereoisomer) 17.8 (CH\textsubscript{3}CH), 18.7 (CH\textsubscript{3}CH), 21.2 (CH\textsubscript{3}Ar), 32.4 (CH(CH\textsubscript{3})\textsubscript{2}), 69.8 (CH\textsubscript{2}O), 73.2 (CHN), 125.2 (ArCH), 125.5 (ArC), 126.4 (ArCH), 129.4 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 131.6 (ArCH), 140.7 (ArC), 143.8 (ArC), 146.9 (ArC), 160.6 (C=N). \n
8C (62.5 MHz, CDCl\textsubscript{3}) (Minor diastereoisomer) 18.8 (CH\textsubscript{2}CH), 18.9 (CH\textsubscript{3}CH), 21.2 (CH\textsubscript{3}Ar), 33.1 (CH(CH\textsubscript{3})\textsubscript{2}), 70.4 (CH\textsubscript{2}O), 73.2 (CHN), 125.3 (ArCH), 125.7 (ArC), 126.5 (ArCH), 129.4 (ArCH), 129.9 (ArCH), 130.1 (ArCH), 131.7 (ArCH), 140.9 (ArC), 143.9 (ArC), 147.0 (ArC), 160.7 (C=N). m/z (El) 327 (M+, 100%), 227 (40), 160 (32), 41 (50). (111a:111b, 28:72).

110a:110b.

Sodium metaperiodate (49 mg, 0.23 mmol) was added to an ice-cooled (0 °C) stirred solution of 100, (53 mg, 0.23 mmol) in MeOH/H\textsubscript{2}O, (1:1). After 2 hr the reaction mixture was diluted with dichloromethane (10 ml) and washed with distilled water (3 x 10 ml). The combined organics were dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title compound, (51 mg, 91% yield).
yield), a mixture of two diastereoisomers, as a colourless oil. $[\alpha]_D^{20} +135.5$ (c=0.50, CHCl$_3$). Ratio of diastereoisomers 110a:110b, is 65:35.

All data was consistent with the above.

110a:110b.
A solution of MMPP (60 mg, 0.097 mmol) in distilled water (5 ml) was added to a stirred solution of 100 (41 mg, 0.175 mmol) in ethanol (5 ml) and the mixture stirred at 50 °C for 1.5 hr. The reaction mixture was then diluted with diethyl ether (20 ml) and washed with saturated sodium carbonate solution (3 x 10 ml). The combined organics were dried (MgSO$_4$), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 1:4) gave the title compound, (41 mg, 90% yield), a mixture of two diastereoisomers, as a colourless oil. $[\alpha]_D^{20} -128.0$ (c=0.25, CHCl$_3$). Ratio of diastereoisomers 110a:110b, is 38:62.

All data was consistent with the above.

110a:110b.
To a solution of 100 (30 mg, 0.13 mmol) in glacial acetic acid (2 ml) was added powdered sodium perborate tetrahydrate (20 mg, 0.13 mmol). The reaction mixture was stirred at r.t. for 16 hr, before being poured onto 10% aqueous HCl (10 ml). The resulting aqueous solution was extracted with diethyl ether (3x15 ml), and the combined organics dried (MgSO$_4$), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title compound, (30 mg, 94% yield) a mixture of two diastereoisomers, as a colourless oil. $[\alpha]_D^{20} -127.1$ (c=0.40, CHCl$_3$). Ratio of diastereoisomers 110a:110b is 41:59.

All data was consistent with the above.

110a:110b.
To a stirred solution of 100 (50 mg, 0.21 mmol) and vanadyl acetylacetonate (5.9 mg, 0.021 mmol) in dichloromethane at -20 °C under nitrogen, was added t-butylhydroperoxide (0.055 ml, 0.21 mmol). The reaction mixture was stirred at -20 °C for 1 hr, then kept in a freezer at -20 °C for a further 23 hr. The reaction mixture was diluted with dichloromethane (15 ml) and washed with saturated sodium carbonate solution (2 x 10 ml). The combined organics were dried (MgSO$_4$), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title...
compound (40 mg, 77% yield), a mixture of two diastereoisomers, as a colourless oil. 
\[
\alpha\text{D}_{20}^{20} +171.5 (\text{c}=0.40, \text{CHCl}_3) \quad \text{Ratio of diastereoisomers } 110a:110b \text{ is 85:15.}
\]
All data was consistent with the above.

General procedure for the oxidation of (4S)-4,5-Dihydro-4-isopropyl-2-[2-

methylsulfanyl]phenyl)-1,3-oxazole, 100, using methodology developed by Kagan.

Titanium tetraisopropoxide (0.43 mmol) was added to a stirred solution of diethyl
tartrate (0.86 mmol) in dichloromethane (3 ml) at r.t. under nitrogen. Distilled water
(0.43 mmol) was then added, and the pale yellow solution stirred until it became
homogenous. A solution of 100 (0.43 mmol) in dichloromethane (3 ml) was then
added, before being cooled to -30 °C. The oxidant (0.43 mmol), was added and the
reaction mixture stirred for 1 hr at -30 °C, before being transferred to a freezer, kept
at -20 °C, for 23 hr. 10 mol eq. of distilled water was then added and the reaction
mixture stirred at -20 °C for 1 hr, before warming to room temperature. The
resulting white gel was filtered through celite, and washed with dichloromethane (4
x 20 ml). The filtrate was vigorously stirred in a mixture of 2M sodium hydroxide
solution (40 ml) and saturated aqueous sodium chloride (30 ml). The organic phase
was separated, dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow
oil. Purification by “flash” column chromatography (eluant, petroleum ether/ethyl
acetate, 1:4) gave the title compound, a mixture of two diastereoisomers, as a
colourless oil.

\[
\alpha\text{D}_{20}^{20} +133.0 (\text{c}=0.15, \text{CHCl}_3) \quad \text{(Oxidant was Cumene hydperoxide, using (+)-enantiomer of DET). (110a:110b, 65:35). (42% yield).}
\]

\[
\alpha\text{D}_{20}^{20} +125.0 (\text{c}=0.15, \text{CHCl}_3) \quad \text{(Oxidant was Cumene hydperoxide, using (-)-enantiomer of DET). (110a:110b, 40:60). (42% yield).}
\]

\[
\alpha\text{D}_{20}^{20} +180.3 (\text{c}=0.30, \text{CHCl}_3) \quad \text{(Oxidant was \textit{t}-butyl hydperoxide, using (+)-enantiomer of DET). (110a:110b, 89:11). (19% yield).}
\]

\[
\alpha\text{D}_{20}^{20} +130.2 (\text{c}=0.30, \text{CHCl}_3) \quad \text{(Oxidant was \textit{t}-butyl hydperoxide, using (-)-enantiomer of DET). (110a:110b, 37:63). (19% yield).}
\]
All reactions produced data consistent with the above.
General procedure for the preparation of 4,5-dihydrooxazoles 111a and 111b.

To a stirred solution of 112 (0.32 g, 1.69 mmol) and TMEDA (0.59 g, 5.08 mmol) in THF (4 ml) at -70 °C, under nitrogen was added n-butyllithium (1.16 ml, 1.86 mmol) (1.6M solution in hexane). The resulting red solution was stirred at -70 °C for 4 hr. A solution of p-tolylmenthylsulfinate ester 114 or 115 (0.5 g, 1.69 mmol) in THF (10 ml) was then added to the reaction mixture at -70 °C. The reaction mixture was allowed to warm to r.t. and stirred under nitrogen for 16 hr. The reaction mixture was then diluted with diethyl ether (25 ml) and washed with distilled water (2 x 20 ml) and brine (30 ml). The ether layer was dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compounds as described.

(4S,Rs)-4,5-Dihydro-4-isopropyl-2-[2-(4-methylphenylsulfinyl)phenyl]-1,3-oxazole, 111a. (50%) as a pale yellow oil. (Found: M+, 327.12929. C19H21NO25 requires M+, 327.1293). [α]D20 +156.5 (c=0.25, CHCl3). νmax/cm-1 3053, 2960, 1654 (C=N), 1054 (S=O). δH (250 MHz, CDCl3) 0.97 (d, 3H, J=6.7 Hz, (CH3)CH), 1.06 (d, 3H, J=6.7 Hz, (CH3)2CH), 1.74-1.82 (m, 1H, (CH3)2CH), 2.32 (s, 3H, CH3Ar), 4.00-4.08 (m, 2H, CH2O), 4.28-4.35 (m, 1H, CHN), 7.15 (d, 2H, J=8.3 Hz, ArH), 7.49-7.53 (m, 1H, ArH), 7.62 (d, 2H, J=8.2 Hz, ArH), 7.68-7.74 (m, 1H, ArH), 7.85 (dd, 1H, J=1.2, 7.7 Hz, ArH), 8.37 (dd, 1H, J=1.1, 8.0 Hz, ArH). δC (62.5 MHz, CDCl3) 18.7 (CH3CH), 18.8 (CH3CH), 21.3 (CH(CH3)2), 33.0 (CH3Ar), 70.4 (CH2O), 73.2 (CHN), 124.9 (ArCH), 125.2 (ArC), 126.5 (ArCH), 129.3 (ArCH), 129.4 (ArCH), 129.9 (ArCH), 131.6 (ArCH), 140.8 (ArC), 143.9 (ArC), 146.9 (ArC), 160.6 (C=N). m/z (El) 327 (M+, 100%), 227 (27), 160 (40), 132 (40).
(4S,5S)-4,5-Dihydro-4-isopropyl-2-[2-(4-methylphenylsulfinyl)phenyl]-1,3-oxazole, **111b.** (50%) as a colourless solid. M.p. 105-107 °C. (Found: M⁺, 327.12929. C₁₉H₂₁NO₂S requires M⁺, 327.1293). (Found: C, 69.61; H, 6.25; N, 4.28. C₁₉H₂₁NO₂S requires C, 69.69; H, 6.25; N, 4.28). [α]D²⁰ -251.2 (c=0.66, CHCl₃). v max / cm⁻¹ 3058, 2960, 1649 (C=N), 1054.5 (S=O). δH (250 MHz, CDCl₃) 0.72 (d, 3H, J=6.7 Hz, (CH₃)₂CH), 0.89 (d, 3H, J=6.7 Hz, (CH₃)₂CH), 1.72-1.79 (m, 1H, CH(CH₃)₂), 2.31 (s, 3H, CH₃Ar), 4.00-4.15 (m, 2H, CH₂O), 4.30-4.36 (m, 1H, CHN), 7.15 (d, 2H, J=8.1 Hz, ArH), 7.52 (d, 2H, J=8.1 Hz, ArH), 7.52-7.57 (m, 1H, ArH), 7.67-7.70 (m, 1H, ArH), 7.91 (dd, 1H, J=1.2, 7.7 Hz, ArH), 8.33 (dd, 1H, J=1.1, 7.8 Hz, ArH). δC (62.5 MHz, CDCl₃) 17.8 (CH₃CH), 18.8 (CH₃CH), 21.2 (CH(CH₃)₂), 32.4 (CH₃Ar), 69.8 (CH₂O), 73.2 (CHN), 125.2 (ArCH), 125.6 (ArC), 126.4 (ArCH), 129.4 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 131.7 (ArCH), 140.8 (ArC), 143.6 (ArC), 146.2 (ArC), 160.7 (C=N). m/z (El) 327 (M⁺, 100%), 227 (40), 160 (40), 132 (40).

General procedure for the preparation of hydroxy-oxazolines, 118, 119 and 122.

![Chemical structure](image)

The appropriate nitrile 102, 103 or 112 (10 mmol) was added to a mixture of (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol 121 (9.1 mmol), potassium carbonate (1.8 mmol), ethylene glycol (8 ml) and glycerol (4 ml), at 115 °C and stirred for 18 hr. The reaction mixture was cooled to r.t. and diluted with distilled water (30 ml). The resulting white solution was extracted with dichloromethane (3 x 30 ml), and the combined organics dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 2:1), gave the title compounds as described.

(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole, **118.** (47%) as a colourless solid. M.p. 105-107 °C. (Found: M⁺, 299.0979. C₁₇H₁₇NO₂S requires M⁺, 299.0979). (Found C, 67.74; H, 5.55; N, 4.71. C₁₇H₁₇NO₂S requires C, 68.10; H, 5.72; N, 4.68). [α]D²⁰ +7.41 (c=4.7, CHCl₃). v max / cm⁻¹ 3500 (OH), 3053, 2985, 1644 (C=N), 1265. δH (250 MHz, CDCl₃) 2.37-2.39 (m, 1H, OH).
2.47 (s, 3H, CH$_3$SO), 3.75 (dd, 1H, $J$=7.6, 10.6 Hz, CHHOH), 4.07 (dd, 1H, $J$=4.1, 10.5 Hz, CHHOH), 4.36-4.42 (m, 1H, CHN), 5.47 (d, 1H, $J$=7.3 Hz, CHO), 7.14-7.19 (m, 1H, ArH), 7.20-7.44 (m, 7H, ArH), 7.87 (dd, 1H, $J$=1.5, 7.7 Hz, ArH). $\delta_C$ (62.5 MHz, CDCl$_3$) 15.9 (CH$_3$SO), 63.9 (CH$_2$OH), 77.3 (CHN), 82.2 (CHO), 123.8 (ArCH), 124.6 (ArCH), 124.9 (ArC), 125.7 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 130.1 (ArCH), 130.2 (ArCH), 131.2 (ArCH), 140.6 (ArC), 140.9 (ArC), 163.6 (C=N). $m/z$ (EI) 299 (M$^+$, 23%), 284 (27), 268 (18) 166 (42), 151 (100), 91 (80).

(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[2-(phenylsulfanyl)phenyl]-1,3-oxazole, 119. (19%) as a colourless solid. M.p. 121-123 $^\circ$C. (Found: M$^+$ 361.1136. C$_{22}$H$_{19}$N$_2$O$_2$S requires M$^+$, 361.1136). $[\alpha]D^{20} +30.2$ (c=0.25, CHCl$_3$). $\nu$ max/cm$^{-1}$ 3400 (OH), 3053, 2965, 1642 (C=N), 1263. $\delta_H$ (250 MHz, CDCl$_3$) 2.23-2.25 (m, 1H, OH), 3.80 (dd, 1H, $J$=7.5, 10.5 Hz, CHHOH), 4.12 (dd, 1H, $J$=4.2, 10.5 Hz, CHHOH), 6.91 (dd, 1H, $J$=1.2, 7.9 Hz, ArH), 7.16-7.25 (m, 2H, ArH), 7.37-7.42 (m, 8H, ArH), 7.53-7.56 (m, 2H, ArH), 7.88 (dd, 1H, $J$=1.7, 7.6 Hz, ArH). $\delta_C$ (62.5 MHz, CDCl$_3$) 63.9 (CH$_2$OH), 77.4 (CHN), 82.4 (CHO), 124.8 (ArCH), 125.1 (ArC), 125.8 (ArCH), 128.1 (ArCH), 128.4 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 129.6 (ArCH), 130.0 (ArCH), 131.1 (ArCH), 134.8 (ArCH), 140.5 (ArC), 140.7 (ArC), 163.7 (C=N). $m/z$ (EI) 361 (M$^+$, 100%), 330 (35), 224 (90), 91 (70).

(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-phenyl-1,3-oxazole, 122. (95%) as a colourless solid. M.p. 126-128 $^\circ$C. (Found: M$^+$, 253.1103. C$_{16}$H$_{15}$N$_2$O$_2$ requires M$^+$, 253.1103). $[\alpha]D^{20} -43.5$ (c=1.1, EtOH). $\nu$ max/cm$^{-1}$ 3450, 3000, 1644 (C=N), 1250. $\delta_H$ (250 MHz, CDCl$_3$) 2.8 (s, 1H, OH), 3.79 (dd, 1H, $J$=5.0, 11.8 Hz, CHHOH), 4.06 (dd, 1H, $J$=3.8, 11.7 Hz, CHHOH), 4.20-4.27 (m, 1H, CHN), 5.58 (d, 1H, $J$=7.2 Hz, CHO), 7.29-7.94 (m, 10H, ArH). $\delta_C$ (62.5 MHz, CDCl$_3$) 63.4 (CH$_2$OH), 76.9 (CHN), 82.3 (CHO), 125.7 (ArCH), 126.8 (ArC), 128.3 (ArCH), 128.8 (ArCH), 131.5 (ArCH), 140.4 (ArC), 164.7 (C=N). $m/z$ (FAB) 254 (MH$^+$, 100%), 224 (16), 147 (8), 121 (9), 105 (11).
(4S)-4,5-Dihydro-4-(t-butyldimethylsiloxymethyl)-5-phenyl-2-[2-(4-methylphenylsulfanyl) phenyl]-1,3-oxazole, 123.

A mixture of trans-(4S,5S)-2-phenyl-4-hydroxymethyl-5-phenyl-1,3-oxazoline 122 (1.5 g, 6 mmol), tert-butyldimethylsilyl chloride (0.98 g, 6.5 mmol), triethylamine (0.67 g, 6.6 mmol) and DMAP (2 mol%) in dichloromethane (15 ml) was stirred under nitrogen until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been consumed (16 hr). The reaction material was then diluted with dichloromethane (20 ml) and extracted with water (20 ml). The dichloromethane layer was separated, washed with brine (25 ml), dried (MgSO4), filtered and concentrated in vacuo, yielding a dark yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 4:1) gave the title compound (2.18 g, 99% yield) as a pale yellow oil. (Found: M+, 367.1967. C22H29N02Si requires M+, 367.1967). \([\alpha]_D^{20} +54.29 (c=0.51, CHCl_3).\) \(\nu_{max}/cm^{-1}\) 3065, 2954, 1651 (C=N), 1253, 1120-1063 (Si-O). \(\delta_H (250 MHz, CDCl_3) 0.01 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3), 0.81 (s, 9H, (CH_3)_3CSi), 3.73 (dd, 1H, J=7.6, 10.1 Hz, CHHOSi), 3.94 (dd, 1H, J=4.2, 10.1 Hz, CHHOSi), 4.17-4.25 (m, 1H, CHN), 5.50 (d, 1H, J=7.2 Hz, CHO), 7.18-7.37 (m, 8H, ArH), 7.94 (dd, 2H, J=1.3, 7.8 Hz, ArH). \(\delta_C (62.5 MHz, CDCl_3) 18.2 (C(CH_3)_3), 25.7 (C(CH_3)_3), 65.1 (CH_2OSi), 76.8 (CHN), 83.5 (CHO), 125.4 (ArCH), 125.6 (ArC), 127.8 (ArCH), 128.2 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 131.3 (ArCH), 141.4 (ArC), 163.9 (C=N).\) \(m/z (El) 367 (M^+, 1%), 310 (42), 105 (100).\)
(4S,5S)-4,5-Dihydro-4-(t-butyldimethylsiloxymethyl)-5-phenyl-2-[2-(4-methyl-phenylsulfanyl)-phenyl]-1,3-oxazole, 125.

\[
\text{CH}_2\text{OTBDMS} \quad \longrightarrow \quad \text{CH}_2\text{OTBDMS}
\]

\text{n-BuLi} (0.28 ml, 0.45 mmol) (1.6M solution in hexane) was added to a stirred solution of the TBDMS ether 123 (150 mg, 0.4 mmol) and TMEDA (142 mg, 1.2 mmol) in THF (4 ml) at -70 °C. The resulting brown solution was stirred at -70 °C for 15 min before the addition of a solution of di-p-tolyl disulfide 124 (100 mg, 0.4 mmol) in tetrahydrofuran (3 ml). Upon complete addition the reaction mixture was warmed to r.t. and stirred under nitrogen for 16 hr. The reaction mixture was then diluted with diethyl ether (15 ml) and washed with distilled water (3 x 10 ml). The combined organics were dried (MgSO₄), filtered and concentrated \textit{in vacuo} yielding a dark yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compound (26 mg, 13% yield), as a pale yellow oil. (Found: M⁺, 489.2157. C₂₉H₃₅NO₂SSi requires M⁺, 489.2157). \([\alpha]_{D}^{20} -12.2 (c=0.18, \text{CHCl}_3). v_{\text{max}}/\text{cm}^{-1} 3064, 2953, 1654 (C=N), 1100 (Si-O), 964 (Si-O). \delta_{H} (250 MHz, \text{CDCl}_3) 0.01 (s, 3H, SiCH₃), 0.02 (s, 3H, SiCH₃), 0.81 (s, 9H, (CH₃)₃CSi), 2.29 (s, 3H, ArCH₃), 3.70 (dd, 1H, \(J=7.6, 10.1\) Hz, CHHOSi), 4.01 (dd, 1H, \(J=4.2, 10.1\) Hz, CHHOSi), 4.27-4.35 (m, 1H, CHN), 5.47 (d, 1H, \(J=7.2\) Hz, CHO), 6.64 (d, 1H, \(J=8.1\) Hz, ArH), 7.01-7.37 (m, 11H, ArH), 7.84 (d, 1H, \(J=8.1\) Hz, ArH). \delta_{C} (63 MHz, \text{CDCl}_3) 18.2 (C(CH₃)₃), 21.2 (ArCH₃), 25.8 (C(CH₃)₃), 65.2 (CH₂OSi), 77.5 (CHN), 83.0 (CHO), 124.1 (ArCH), 124.6 (ArC), 125.6 (ArCH), 127.0 (ArCH), 127.8 (ArCH), 128.5 (ArCH), 129.1 (ArC), 130.2 (ArCH), 130.4 (ArCH), 130.8 (ArCH), 135.4 (ArCH), 139.2 (ArC), 141.4 (ArC), 142.9 (ArC), 163.6 (C=N). \textit{m/z} (El) 489 (M⁺, 43%), 433 (15), 247 (80), 227 (100).
(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[2-(4-methylphenylsulfanyll-phenyl]-1,3-oxazole, 120.

\[
\begin{align*}
\text{Tetrabutylammonium fluoride (0.053 ml, 0.053 mmol) (1.0M in THF) was added to a} \\
stirred solution of the TBDMS-protected sulfide 125 (26 mg, 0.053 mmol) in THF (1 ml) at r.t. under nitrogen. The reaction material was stirred until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (2 hr). The reaction material was diluted with ether (10 ml) and extracted with water (2 \times 10 ml). The ether layer was dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 1:1) gave the title compound (12 mg, 60% yield) as a colourless solid. M.p. 112-114 °C. (Found: M+, 375.1293. C\textsubscript{23}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2}S requires M+, 375.1293). [\alpha]D\textsubscript{20} = -17.64 (c=1.7, CHCl\textsubscript{3}). \ \nu_{\text{max}}/\text{cm}^{-1} 3530 (OH), 3053, 1643 (C=\text{N}), 1265. \ \delta_{\text{H}} (250 \text{ MHz, CDCl}_3) 2.40 (s, 3H, CH\textsubscript{3}Ar), 3.79 (dd, 1H, J=7.6, 10.1 Hz, CHOH), 4.12 (dd, 1H, J=4.1, 10.1 Hz, CHOH), 4.41-4.47 (m, 1H, CHN), 5.53 (d, 1H, J=7.4 Hz, CHO), 6.85 (d, 1H, J=8.1 Hz, ArH), 7.14-7.25 (m, 1H, ArH), 7.26-7.38 (m, 3H, ArH), 7.23 (d, 1H, J=8.1 Hz, ArH), 7.39-7.46 (m, 6H, ArH), 7.87 (dd, 1H, J=1.4, 7.8 Hz, ArH). \ \delta_{\text{C}} (62.5 \text{ MHz, CDCl}_3) 21.3 (CH\textsubscript{3}Ar), 63.9 (CH\textsubscript{2}OH), 77.4 (CH\textsubscript{N}), 82.4 (CHO), 124.4 (ArCH), 124.6 (ArC), 125.8 (ArCH), 127.4 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 129.1 (ArCH), 130.0 (ArCH), 130.5 (ArC), 131.1 (ArCH), 135.3 (ArCH), 139.2 (ArC), 140.6 (ArC), 141.6 (ArC), 163.6 (C=\text{N}). \ m/z (El) 375 (M+, 50%), 344 (25), 238 (60), 91 (100).
Chapter 6: Experimental

General procedure for the diastereoselective oxidation of 118, 119 and 120 using mCPBA.

A solution of mCPBA (0.43 mmol) in chloroform (3 ml) was added dropwise to a stirred solution of the appropriate sulfide 118, 119 or 120 (0.43 mmol) in chloroform at -70 °C. The reaction mixture was stirred until TLC analysis (petroleum ether/ethyl acetate, 1:4) indicated that all the starting material had been consumed (1-1.25 hr). The reaction mixture was then diluted with dichloromethane (10 ml) and washed with saturated sodium carbonate solution (2 x 10 ml). The combined organics were collected, dried (MgSO4), filtered and concentrated in vacuo yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title compounds, a mixture of two diastereoisomers, 126a:126b, 127a:127b, and 128a:128b.

Data for diastereoisomers (4S,R,S,S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[2-(methylsulfinyl)phenyl]-1,3-oxazole, 126a:126b. (78%) as a colourless oil. (Found: M+, 315.0929. C17H17NO3S requires M+, 315.0929). [α]D20 +172.2 (c=0.30, CHCl3). νmax / cm⁻¹ 3369 (OH), 3053, 2990, 1649 (C=N), 1062 (S=O). δH (250 MHz, CDCl3) 2.21 (broad s, 1H, OH), 2.91 (s, 3H, CH350), 3.79 (dd, 1H, J=7.1, 11.5 Hz, CHHOH), 4.01 (dd, 1H, J=3.9, 11.5 Hz, CHHOH), 4.31-4.36 (m, 1H, CHN), 5.55 (d, 1H, J=7.6 Hz, CHO), 7.33-7.40 (m, 5H, ArH), 7.54-7.58 (m, 1H, ArH), 7.72-7.75 (m, 1H, ArH), 8.01 (dd, 1H, J=1.1, 7.7 Hz, ArH), 8.27 (dd, 1H, J=0.9, 7.8 Hz, ArH). δC (62.5 MHz, CDCl3) 43.9 (CH3SO), 63.8 (CH2OH), 77.2 (CHN), 82.7 (CHO), 124.1 (ArCH), 125.4 (ArCH), 125.5 (ArC), 128.5 (ArCH), 128.9 (ArCH), 129.5 (ArCH), 130.2 (ArCH), 132.4 (ArCH), 140.2 (ArC), 148.3 (ArC) 161.6 (C=N). m/z (El) 315 (M⁺, 5%), 270 (20), 167 (100), 151 (55). (126a:126b, 87:13).

All the other mCPBA oxidations of sulfide 118 were conducted under the same conditions, except for solvent.

[α]D20 +110.1 (c=0.25, CHCl3) (Reaction conducted in MeOH). (126a:126b, 57:43). (76% yield).
[α]_D^20 +195.3 (c=0.45, CHCl₃) (Reaction conducted in hexane/chloroform, 3:1). (126a:126b, 96:4). (76% yield).

All the reactions produced data consistent with the above.

Data for diastereoisomers (4S,R/S₅)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[2-(phenylsulfinyl)phenyl]-1,3-oxazole, 127a:127b. (94%) as a colourless oil. (Found: M⁺, 377.1086. C₂₂H₁₉N₀₃5 requires M⁺, 377.1086). [α]_D^20 +102.1 (c=0.15, CHCl₃) (Major diastereoisomer) 3.73-3.79 (dd, 1H, J=7.0, 11.4 Hz, CHHOH), 4.01 (dd, 1H, J=3.9, 11.4 Hz, CHHOH), 4.19-4.23 (m, 1H, CHN), 5.44 (d, 1H, J=7.6 Hz, CHO), 7.10-8.49 (m, 14H, ArH). (Minor diastereoisomer) 3.58-3.64 (dd, 1H, J=3.9, 11.5 Hz, CHHOH), 4.01 (dd, 1H, J=3.9, 11.5 Hz, CHHOH), 4.25-4.29 (m, 1H, CHN), 5.38 (d, 1H, J=7.6 Hz, CHO), 7.10-8.49 (m, 14H, ArH). δ_C (100 MHz, CDCl₃) (Major diastereoisomer) 63.9 (CH₂OH), 76.9 (CHN), 82.8 (CHO), 125.5 (ArCH), 126.2 (ArCH), 126.8 (ArCH), 128.5 (ArCH), 129.1 (ArCH), 130.4 (ArCH), 130.9 (ArCH), 132.2 (ArCH), 140.1 (ArC), 146.8 (ArC), 162.0 (C=N). (Minor diastereoisomer) 63.4 (CH₂OH), 76.7 (CHN), 82.6 (CHO), 125.5 (ArCH), 126.1 (ArCH), 126.6 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 129.0 (ArCH), 130.1 (ArCH), 132.1 (ArCH), 140.0 (ArC), 146.2 (ArC), 161.7 (C=N). m/z (EI) 377 (M⁺, 36%), 229 (100), 213 (70), 104 (62). (127a:127b, 83:17).

Data for diastereoisomers (4S,5S, R₅/S₅)-4,5-Dihydro-4-Hydroxymethyl-5-phenyl-2-[2-(4-methylphenylsulfinyl)-phenyl]-1,3-oxazole, 128a:128b. (90%) as a colourless solid. M.p. 137-139 °C. (Found: M⁺, 391.1242. C₂₃H₂₁N₀₃5 requires M⁺, 391.1242). [α]_D^20 +90.0 (c=0.50, CHCl₃) (Major diastereoisomer) 2.35 (s, 3H, CH₃Ar), 3.75 (dd, 1H, J=7.6, 10.1 Hz, CHHOH), 4.15 (dd, 1H, J=4.2, 10.1 Hz, CHHOH), 4.25-4.29 (m, 1H, CHN), 5.43 (d, 1H, J=7.5 Hz, CHO), 7.08-8.26 (m, 13H, ArH). (Minor diastereoisomer) 2.34 (s, 3H, CH₃Ar), 3.75 (dd, 1H, J=7.6, 10.1 Hz, CHHOH), 4.15 (dd, 1H, J=4.2, 10.1 Hz, CHHOH), 4.25-4.29 (m, 1H, CHN), 5.35 (d, 1H, J=7.5 Hz, CHO), 7.08-8.26 (m, 13H, ArH). δ_C (62.5 MHz, CDCl₃) (Major diastereoisomer) 21.3 (CH₃Ar), 63.5 (CH₂O), 76.7 (CHN), 82.7 (CHO), 124.8 (ArC), 125.7 (ArCH), 125.8 (ArCH), 127.0 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 130.4 (ArCH), 132.2 (ArCH), 139.9 (ArC), 141.5 (ArC), 143.7 (ArC), 145.9 (ArC), 161.6 (C=N). (Minor diastereoisomer) 21.6 (CH₃Ar), 63.6 (CH₂OH), 77.0 (CHN), 82.9 (CHO), 124.2 (ArC), 126.0 (ArCH), 126.2 (ArCH), 126.9 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 130.6 (ArCH), 132.3 (ArCH), 139.5 (ArC), 141.3
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(ArC), 143.5 (ArC), 145.7 (ArC), 161.5 (C=N). m/z (El) 391 (M+, 51%), 227 (60), 184 (60), 104 (70), 91 (100). (128a:128b, 80:20).

126a:126b.
To a solution of 118 (50 mg, 0.17 mmol) in glacial acetic acid (2 ml) was added powdered sodium perborate tetrahydrate (27 mg, 0.17 mmol). The reaction mixture was stirred at r.t. for 5.5 hrs, before being poured onto 10% HCl (10 ml). The resulting aqueous solution was extracted with diethyl ether (3 x 15 ml), and the combined organic solvents dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, 80% ethyl acetate/light petroleum) gave the title compound, (40 mg, 76% yield) a mixture of two diastereoisomers, as a colourless oil. [α]D20 +125.2 (c=0.40, CHCl3). Ratio of diastereoisomers 126a:126b is 61:39.

All data was consistent with the above.

126a:126b and 127ab:127b.
To a stirred solution of 118 or 119 (0.1 mmol) and vanadyl acetylacetonate (2.6 mg, 0.01 mmol) in dichloromethane (2 ml) at -20 °C under nitrogen, was added t-butyldihydroperoxide (0.026 ml, 0.1 mmol). The reaction mixture was stirred at -20 °C for 3 hr. On completion the reaction mixture was diluted with dichloromethane (15 ml) and washed with saturated sodium carbonate solution (2 x 10 ml). The combined organic solvents were dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title compounds.

126a:126b (85% yield) a mixture of two diastereoisomers, as a colourless oil. [α]D20 +175.4 (c=0.20, CHCl3). Ratio of diastereoisomers 126a:126b is 87:13.

All data was consistent with the above.

127a:127b (15% yield) a mixture of two diastereoisomers, as a colourless oil. [α]D20 +82.4 (c=0.15, CHCl3). Ratio of diastereoisomers 127a:127b is 79:21.

All data was consistent with the above.
General procedure for the oxidation of 118, using methodology developed by Kagan.

Titanium tetraisopropoxide (0.16 mmol) was added to a stirred solution of diethyl tartrate (0.32 mmol) in dichloromethane (3 ml) at r.t. under nitrogen. Distilled water (0.16 mmol) was then added, and the pale yellow solution stirred until it became homogenous. A solution of 118 (0.32 mmol) in dichloromethane (3 ml) was then added, before being cooled to -20 °C. The oxidant (0.32 mmol) was added and the reaction mixture stirred for 1 hr at -20 °C, before being transferred to a freezer, kept at -20 °C, for 23 hr. After reaction, 10 mol eq. of distilled water was added and the reaction mixture stirred at -20 °C for 1 hr, before warming to room temperature. The resulting white gel was filtered through celite, and washed with dichloromethane (4 x 20 ml). The filtrate was vigorously stirred in a mixture of 2M sodium hydroxide solution (40 ml) and saturated aqueous sodium chloride (30 ml). The organic phase was separated, dried (MgSO₄), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 1:4) gave the title compound, a mixture of two diastereoisomers, as a colourless oil. 

\[ [\alpha]_D^{20} +168.0 \ (c=0.40, \text{CHCl}_3) \] (Oxidant was Cumene hydroperoxide, using (+)-enantiomer of DET). (126a:126b, 86:14). (55% yield).

\[ [\alpha]_D^{20} +145.0 \ (c=0.40, \text{CHCl}_3) \] (Oxidant was Cumene hydroperoxide, using (-)-enantiomer of DET). (126a:126b, 73:27). (55% yield).

\[ [\alpha]_D^{20} +195.1 \ (c=0.50, \text{CHCl}_3) \] (Oxidant was tert-butyl hydroperoxide, using (+)-enantiomer of DET). (126a:126b, 99:1). (32% yield).

\[ [\alpha]_D^{20} +186.2 \ (c=0.50, \text{CHCl}_3) \] (Oxidant was tert-butyl hydroperoxide, with no DET). (126a:126b, 97:3). (41% yield).

All reactions produced data consistent with the above.
A solution of the sulfide hydroxy oxazoline, 118 (50 mg, 0.17 mmol) in THF (2 ml) was added to a stirred suspension of sodium hydride (6.7 mg, 0.17 mmol) (60% dispersion in mineral oil) in THF (1 ml) at room temperature. After 1 hr methyl iodide (28 mg, 0.20 mmol) was added and the reaction mixture stirred until TLC analysis (dichloromethane/ether, 1:1) indicated that all the starting material had been consumed (7 hr). The reaction material was then diluted with ether (20 ml), extracted with water (15 ml) and brine (15 ml). The organic layer was dried (MgSO₄), filtered and concentrated in vacuo yielding a yellow oil. Purification by "flash" column chromatography (eluant, dichloromethane/ether, 1:1) gave the title compound (51 mg, 98% yield) as a colourless oil. (Found: M⁺, 313.1136. C₁₈H₁₉NO₂S requires M⁺, 313.1136). [α]D²⁰ +20.2 (c=0.20, CHCl₃). νmax/cm⁻¹ 2950, 1642 (C= N), 1250. δH (250 MHz, CDCl₃) 2.47 (s, 3H, CH₃), 3.45 (s, 3H, CH₃O), 3.62 (dd, 1H, J=7.1, 9.8 Hz, CHHOCH₃), 3.81 (dd, 1H, J=4.0, 9.8 Hz, CHHOCH₃), 4.40-4.50 (m, 1H, CHN), 5.47 (d, 1H, J=6.6 Hz, CHO), 7.17-7.96 (m, 9H, ArH). δC(62.5 MHz, CDCl₃) 15.8 (CH₃), 59.3 (CH₃O), 74.4 (CH₂OCH₃), 75.5 (CHN), 82.9 (CHO), 123.5 (ArCH), 124.2 (ArCH), 124.7 (ArC), 125.6 (ArCH), 128.0 (ArCH), 128.7 (ArCH), 130.5 (ArCH), 131.1 (ArCH), 140.9 (ArC), 141.2 (ArC), 162.9 (C=N). m/z (EI) 313 (M⁺, 1%), 301 (100), 285 (30), 151 (50).
(4S,R<sub>5</sub>/S<sub>5</sub>)-4,5-Dihydro-4-methoxymethyl-5-phenyl-2-[2-(methylsulfinyl)phenyl]-1,3-oxazole, 130a:130b.

A solution of mCPBA (48 mg, 0.162 mmol) in chloroform (2 ml) was added dropwise to a stirred solution of the methoxy sulfide 129, (51 mg, 0.162 mmol) in chloroform at -70 °C. The reaction mixture was stirred until TLC analysis (petroleum ether/ethyl acetate, 1:4) indicated that all the starting material had been consumed (2 hr). The reaction mixture was then diluted with dichloromethane (10 ml) and washed with saturated sodium carbonate solution (2 x 10 ml). The combined organics were collected, dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title compound (50 mg, 95% yield), a mixture of two diastereoisomers, 130a:130b as a colourless oil. (Found: M<sup>+</sup>, 329.1086. C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>S requires M<sup>+</sup>, 329.1086). [a]_<sub>D</sub>^20 +85.0 (c=0.15, CHCl<sub>3</sub>). ν<sub>max</sub>/cm<sup>-1</sup> 3053, 2990, 1642 (C=N), 1060 (S=O). δ<sub>H</sub> (250 MHz, CDCl<sub>3</sub>) (Major diastereoisomer) 2.89 (s, 3H, CH<sub>3</sub>), (minor diastereoisomer) 2.89 (s, 3H, CH<sub>3</sub>), (major diastereoisomer) 3.42 (s, 3H, CH<sub>3</sub>), (minor diastereoisomer) 3.46 (s, 3H, CH<sub>3</sub>). 3.55 (dd, 1H, J=7.2, 10.0 Hz, C=H), 3.74 (dd, 1H, J=5.0, 10.0 Hz, C=H), 4.34-4.41 (m, 1H, CHN), 5.51 (d, 1H, J=6.9 Hz, CHO), 7.32-7.40 (m, 5H, ArH), 7.73-7.77 (m, 1H, ArH), 8.01 (dd, 1H, J=1.0, 7.6 Hz, ArH), 8.30 (dd, 1H, J=0.8, 7.6 Hz, ArH). δ<sub>C</sub> (62.5 MHz, CDCl<sub>3</sub>) (Major diastereoisomer) 43.5 (CH<sub>2</sub>), 59.2 (CH<sub>3</sub>), 73.6 (CH<sub>2</sub>OCH<sub>3</sub>), 75.2 (CHN), 83.4 (CHO), 124.0 (ArCH), 125.6 (ArC), 128.4 (ArCH), 128.8 (ArCH), 129.7 (ArCH), 130.0 (ArCH), 132.2 (ArCH), 140.1 (ArC), 148.2 (ArC), 161.9 (C=N). (Minor diastereoisomer) 43.9 (CH<sub>2</sub>), 59.4 (CH<sub>3</sub>), 73.6 (CH<sub>2</sub>OCH<sub>3</sub>), 74.1 (CHN), 83.2 (CHO), 124.0 (ArCH), 124.1 (ArCH), 125.2 (ArCH), 130.0 (ArC), 132.2 (ArCH), 140.4 (ArC), 148.3 (ArC), 161.9 (C=N). m/z (EI) 329 (M<sup>+</sup>, 7%), 314 (20), 151 (40), 45 (100).
(4S, S)_5-4,5-Dihydro-4-(t-butyldimethylsiloxymethyl)-5-phenyl-2-[2-(4-methyl-phenylsulfinyl)-phenyl]-1,3-oxazole, 131.

The TBDMS ether 123 was prepared as described earlier in this section. n-Butyllithium (0.75 ml, 1.2 mmol) (1.6M solution in hexane) was added to a stirred solution of the TBDMS ether 123 (400 mg, 1.1 mmol) and TMEDA (380 mg, 3.3 mmol) in THF (10 ml) at -70 °C. The resulting brown solution was stirred at -70 °C for 4 hr before the addition of a solution of (S)-p-tolylmenthyl sulfinate ester 115 (320 mg, 1.1 mmol) in THF (5 ml). Upon complete addition the reaction mixture was allowed to warm to r.t. and stirred under nitrogen for 16 hr. The reaction mixture was then diluted with diethyl ether (15 ml) and washed with distilled water (3 x 10 ml). The combined organics were dried (MgSO4), filtered and concentrated in vacuo yielding a pale yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the TBDMS-protected sulfoxide (102 mg, 20% yield) as a pale yellow oil. (Found: M+ , 505.21068. C_{29}H_{35}NO_3SSi requires M+ , 505.21068). [α]_D^20 -78.09 (c=0.42, CHCl3). v_{max} /cm^{-1} 3059, 2953, 1654 (C=N), 1052 (S=O), 836. δ_H (250 MHz, CDCl3) 0.02 (s, 3H, CH3Si), 0.03 (s, 3H, CH3Si), 0.84 (s, 9H, (CH3)_3C), 2.29 (s, 3H, ArCH3), 3.36 (dd, 1H, J=7.6, 10.1 Hz, CHHOSi), 3.86 (dd, 1H, J=4.2, 10.1 Hz, CHHOSi), 4.24-4.29 (m, 1H, CHN), 5.46 (d, 1H, J=6.3 Hz, CHO), 7.12 (d, 2H, J=8.2 Hz, ArCH), 7.23-7.29 (m, 5H, ArCH), 7.49-7.55 (m, 3H, ArCH), 7.70-7.76 (m, 1H, ArCH), 8.03 (d, 1H, J=1.1, 8.3 Hz, ArCH), 8.40 (d, 1H, J=1.1, 8.3 Hz, ArCH). δ_C (62.5 MHz, CDCl3) 19.1 (C(CH3)_3), 21.2 (ArCH3), 25.7 (C(CH3)_3), 64.6 (CH2OSi), 76.9 (CHN), 83.7 (CHO), 125.4 (ArCH), 125.5 (ArCH), 126.2 (ArC), 126.7 (ArCH), 128.1 (ArCH), 128.6 (ArCH), 129.3 (ArCH), 129.8 (ArCH), 130.2 (ArCH), 132.0 (ArCH), 136.9 (ArC), 141.9 (ArC), 142.2 (ArC), 146.1 (ArC), 161.8 (C=N). m/z (El) 505 (M+ 100%), 448 (70), 219 (30).
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(4S,S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[2-(4-methylphenylsulfinyl)-phenyl]-1,3-oxazole, 128b.

Tetrabutylammonium fluoride (0.16 ml, 0.16 mmol) (1.0M solution in THF) was added to a stirred solution of the TBDMS-protected sulfoxide 131 (81 mg, 0.16 mmol) in THF (3 ml) at r.t. under nitrogen. The reaction material was stirred until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (2 hr). The reaction material was diluted with ether (10 ml) and extracted with water (2 x 10 ml). The ether layer was dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:4) gave the title compound (53 mg, 84% yield) as a colourless solid. M.p. 137-139 °C. (Found: M+, 391.1242. C23H21NO3S requires M+, 391.1242). (Found: C, 70.37; H, 5.31, N, 3.48. C23H21NO3 requires C, 70.63; H, 5.41; N, 3.58). [α]D20 -134 (c=0.61, CHCl3). νmax/cm⁻¹ 3380 (OH), 3053, 2927, 1650 (C=N), 1068 (S=O). δH (250 MHz, CDCl3) 2.25 (s, 3H, CH3Ar), 3.51 (dd, 1H, J=7.6, 10.1 Hz, CHHOH), 3.71 (dd, 1H, J=4.2, 10.1 Hz, CHHOH), 4.17-4.20 (m, 1H, CHN), 5.28 (d, 1H, J=7.7 Hz, CHO), 7.08 (d, 2H, J=8.1 Hz, ArH), 7.17-7.28 (m, 5H, ArH), 7.38 (d, 2H, J=8.1 Hz, ArH), 7.50-7.53 (m, 1H, ArH), 7.69-7.73 (m, 1H, ArH), 7.97 (dd, 1H, J=1.1, 8.0 Hz, ArH), 8.37 (dd, 1H, J=1.1, 8.0 Hz, ArH). δC (62.5 MHz, CDCl3) 21.3 (CH3Ar), 63.3 (CH2OH), 77.2 (CHN), 82.6 (CHO), 124.6 (ArC), 125.7 (ArCH), 125.8 (ArCH), 126.9 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 130.4 (ArCH), 132.1 (ArCH), 139.8 (ArC), 141.4 (ArC), 143.5 (ArC), 145.6 (ArC), 161.5 (C=N). m/z (EI) 391 (M+, 100%), 227 (61), 104 (80).
General procedure for the preparation of sulfoxides, 149 and 150.

\[
\begin{align*}
  & \text{R} = \text{R'} = \text{H} \\
  & \text{R} = \text{R'} = \text{Me}
\end{align*}
\]

\( n \)-Butyllithium (1.2 ml, 1.9 mmol) (1.6M solution in hexane) was added to a stirred solution of oxazoline 151 or 152 (1.7 mmol) and TMEDA (0.59 g, 5.1 mmol) in THF (5 ml) at -70 °C under nitrogen. After stirring at -70 °C for 4 hr, a solution of (S)-\( p \)-tolylmenthylsulfinate (0.5 g, 1.7 mmol) in THF (5 ml) was added. On complete addition the reaction mixture was allowed to warm to r.t. and stirred under nitrogen for 16 hr. The reaction mixture was diluted with diethyl ether (15 ml) and washed with distilled water (3 x 15 ml). The combined organics were dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:3) gave the title compounds as described.

\((S)_5\)-4,5-Dihydro-2-[2-(4-methylphenylsulfinyl)phenyl]-1,3-oxazole, 149. (50%) as a colourless solid. M.p. 146-148 °C. (Found: M+, 285.0823. C\(_{16}\)H\(_{15}\)NO\(_2\)S requires M+, 285.0823). (Found: C, 67.28; H, 4.92; N, 4.84. C\(_{16}\)H\(_{15}\)NO\(_2\)S requires C, 67.37; H, 5.26; N, 4.91). [\( \alpha \)]\(_D\)\(^{20}\) -225.0 (c=0.61, CHCl\(_3\) \( \nu \max /\text{cm}^{-1} \) 3057, 2975, 1648 (C=N), 1054 (S=O). \( \delta \)\(_H\) (250 MHz, CDCl\(_3\)) 2.32 (s, 3H, CH\(_3\)Ar), 3.99-4.14 (m, 2H, CH\(_2\)N), 4.29-4.38 (m, 2H, CH\(_2\)O), 7.17 (d, 2H, J=8.2 Hz, ArH), 7.50-7.58 (m, 1H, ArH), 7.56 (d, 2H, J=8.2 Hz, ArH), 7.70-7.73 (m, 1H, ArH), 7.88 (dd, 1H, J=1.2, 7.7 Hz, ArH), 8.37 (dd, 1H, J=1.1, 7.1 Hz, ArH). \( \delta \)\(_C\) (62.5 MHz, CDCl\(_3\)) 21.3 (CH\(_3\)Ar), 54.8 (CH\(_2\)N), 67.3 (CH\(_2\)O), 124.9 (ArCH), 125.1 (ArC), 126.6 (ArCH), 129.4 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 131.8 (ArCH), 140.9 (ArC), 143.6 (ArC), 146.8 (ArC), 161.8 (C=N). m/z (El) 285 (M+, 60%), 118 (43), 105 (100).
(S)-4,5-Dihydro-4,4-dimethyl-2-[2-(4-methylphenylsulfinyl)phenyl]-1,3-oxazole, 150. (50%) as a colourless solid. M.p. 105-107 °C. (Found: M+, 313.1136. C_{18}H_{19}NO_{2}S requires M+, 313.1136.). (Found: C, 68.89; H, 5.95; N, 4.77. C_{18}H_{19}NO_{2}S requires C, 69.01; H, 6.07; N, 4.47). [α]D^20 -240 (c=1.00, CHCl3). \nu_{\text{max}}/\text{cm}^{-1} 3056, 2969, 1650 (C=N), 1052 (S=O). \delta_H (250 MHz, CDCl3) 1.26 (s, 3H, (CH3-gem)), 1.31 (s, 3H, (CH3-gem)), 2.32 (s, 3H, CH3Ar), 4.00 (s, 2H, CH2O), 7.15 (d, 2H, J=8.1 Hz, ArH), 7.49-7.57 (m, 1H, ArH), 7.59 (d, 2H, J=8.1 Hz, ArH), 7.68-7.74 (m, 1H, ArH), 7.88 (dd, 1H, J=1.2, 7.7 Hz, ArH), 8.36 (dd, 1H, J=1.2, 7.7 Hz, ArH). \delta_C (100 MHz, CDCl3) 21.3 (CH3Ar), 28.1 (CH3-gem), 28.4 (CH3-gem), 68.5 (C(CH3)2), 78.9 (CH2O), 124.9 (ArCH), 125.6 (ArC), 126.9 (ArCH), 129.4 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 131.7 (ArCH), 140.9 (ArC), 143.6 (ArC), 146.4 (ArC), 159.2 (C=N). m/z (El) 313 (M+, 44%), 140 (88), 92 (100).

(4S)-4,5-Dihydro-4-isopropyl-2-[2-(4-methylphenylsulfonyl)phenyl]-1,3-oxazole, 155.

mCPBA (23 mg, 0.067 mmol) was added to a solution of sulfoxide 111a (22 mg, 0.067 mmol) in chloroform (3 ml) at r.t. and the reaction mixture stirred until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been consumed (2 hr). On completion the reaction mixture was diluted with dichloromethane (10 ml), washed with distilled water (3 x 10ml) and brine (25 ml). The combined organics were dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 2:1) gave the title compound (22 mg, 96% yield) as a colourless oil. (Found: M+, 343.1242. C_{19}H_{21}NO_{3}S requires M+, 343.1242). [α]D^20 -62.0 (c=0.5, CHCl3). \nu_{\text{max}}/\text{cm}^{-1} 2960, 1649 (C=N), 1320, 1156 (SO2). \delta_H (250 MHz, CDCl3) 0.96 (d, 3H, J=6.7 Hz, (CH3)2CH), 1.05 (d, 3H, J=6.7 Hz, (CH3)2CH), 1.86-1.94 (m, 1H, (CH3)2CH), 2.38 (s, 3H, CH3Ar), 4.01-4.11 (m, 1H, CHHO), 4.13-4.19 (m, 1H, CHN), 4.45-4.52 (m, 1H, CHHO), 7.26 (d, 2H, J=8.3 Hz, ArH), 7.56-7.63 (m, 3H, ArH), 7.82 (d, 2H, J=8.3 Hz, ArH), 8.09-8.14 (m, 1H, ArH). \delta_C (62.5 MHz, CDCl3) 18.5 (CH3CH), 19.2 (CH3CH), 21.4 (CH3Ar), 32.6 (CH(CH3)2), 71.3 (CHN), 73.2 (CH2O), 121.2 (CH3CH), 124.9 (ArCH), 125.6 (ArC), 126.9 (ArCH), 129.4 (ArCH), 129.6 (ArCH), 130.1 (ArCH), 131.7 (ArCH), 140.9 (ArC), 143.6 (ArC), 146.4 (ArC), 159.2 (C=N). m/z (El) 313 (M+, 44%), 140 (88), 92 (100).
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127.8 (ArCH), 129.3 (ArC), 129.4 (ArCH), 130.1 (ArCH), 130.6 (ArCH), 131.3 (ArCH), 132.8 (ArCH), 139.1 (ArC), 140.2 (ArC), 143.9 (ArC), 162.8 (C=N). m/z (El) 343 (M+, 15%), 300 (28), 278 (100).

(E)-1,3-Diphenyl-2-en-1-ol, 154,132

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\text{Ph} - \text{CHO} \quad \text{Ph} \quad \text{OH}
\]

Phenylmagnesium bromide (27.7 ml, 83.23 mmol) (as a 3.0M solution in ether) was added gradually (over 15 min) to a stirred solution of trans-cinnamaldehyde 153 (10 g, 75.67 mmol) in ether (50 ml) at 0 °C under nitrogen. The reaction mixture was then warmed to r.t, and stirred for 1 hr before being quenched with a saturated solution of ammonium chloride (20 ml). The ether layer was separated extracted with brine (40 ml), dried (MgSO₄), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (petroleum ether/ether, 3:1) gave the title compound (15 g, 94% yield) as a colourless solid. M.p. 75-77 °C. vₓcm⁻¹ 3375 (OH), 3027, 1494, 1217. δₓH (250 MHz, CDCl₃) 2.46 (broad s, 1H, OH), 5.31 (d, 1H, J=6.4 Hz, CHPh), 6.32 (dd, 1H, J=6.4, 15.8 Hz, CH=CHPh), 6.64 (d, 1H, J=15.8 Hz, PhCH=CH), 7.17-7.58 (m, 10H, ArH). δₓC (62.5 MHz, CDCl₃) 75.1 (CHPh), 126.4 (ArCH), 126.8 (ArCH), 127.1 (ArCH), 127.8 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 130.5 (CH=CH), 131.5 (CH=CH), 136.7 (ArC), 143.5 (ArC).

(E)-1,3-Diphenyl-3-acetoxy-1-propene, 145,132

\[
\text{Ph} - \text{OH} \quad \text{Ph} \quad \text{OAc}
\]

A solution of the alcohol 154 (10 g, 47.55 mmol), triethylamine (9.97 ml, 71.33 mmol), acetic anhydride (7.29 g, 71.33 mmol) and DMAP (2 mol%) in dichloromethane was stirred at r.t. under nitrogen until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (2 hr). The reaction material was washed with 2M sodium hydroxide solution (40 ml), water (40 ml), dried (MgSO₄), filtered and concentrated in vacuo, yielding a pale yellow oil. (11.9g, 99% yield). vₓcm⁻¹ 3029, 1736 (C=O), 1236. δₓH (250 MHz, CDCl₃) 2.12 (s, 3H, OCOCH₃), 6.34 (d, 1H, J=6.9 Hz, CHCOCH₃), 6.44 (dd, 1H, J=6.9, 15.6 Hz,
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CH=CHPh), 6.63 (d, 1H, J=15.6 Hz, PhCH=CH), 7.21-7.42 (m, 10H, ArH). δ_C (62.5 MHz, CDCl₃) 21.3 (OCOCH₃), 76.1 (CHPh), 126.7 (ArCH), 127.0 (ArCH), 127.5 (ArCH), 128.0 (ArCH), 128.1 (ArCH), 128.5 (ArCH), 128.6 (CH=CH), 132.5 (CH=CH), 136.1 (ArC), 139.2 (ArC), 169.9 (C=O).

General procedure for the palladium catalysed allylic substitution reaction using ligands 111a, 111b, 128b, 149, 150 and 155.

1,3-Diphenylprop-2-enylmalonate, 146.

A solution of the allylic acetate 145 (0.6 mmol), palladium chloride dimer (0.015 mmol), and the appropriate sulfoxide 111a, 111b, 128b, 149, 150 or sulfone 155 (0.06 mmol) in dichloromethane (2 ml) was stirred for 15 min before the addition of a solution of BSA (1.8 mmol), dimethyl malonate (1.8 mmol) and potassium acetate (2mg) in dichloromethane (2 ml). The reaction material was stirred under nitrogen, at r.t. for 16hrs. On completion the reaction material was washed with distilled water (2 x 10 ml), and the combined organics dried (MgSO₄), filtered and concentrated in vacuo. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 5:1) gave the title compound as a pale yellow solid.

1,3-Diphenylprop-2-enylmalonate, 146:

[α]_D^{20} -17.0 (c=1.10, EtOH) (using ligand 111b),
[α]_D^{20} -13.1 (c=1.10, EtOH) (using ligand 111a),
[α]_D^{20} -13.1 (c=1.10, EtOH) (using ligand 149),
[α]_D^{20} -12.2 (c=1.10, EtOH) (using ligand 150),
[α]_D^{20} -17.1 (c=0.80, EtOH) (using ligand 128b),

(Found: M⁺, 324.1361. C₂₀H₂₀O₄ requires M⁺, 324.1361) ν_max/cm⁻¹ 2995, 1758 (C=O), 1605, 1495, 1453, 1434, 1317, 1258. δ_H (250 MHz, CDCl₃) 3.51 (s, 3H, CH₃CO₂), 3.69 (s, 3H, CH₃CO₂), 3.93 (d, 1H, J=10.9 Hz, CHCO₂Me), 4.26 (dd, 1H, J=8.3, 10.8 Hz, PhH), 6.34 (dd, 1H, J=8.2, 15.5 Hz, HC=CHPh), 6.51 (d, 1H, J=15.8 Hz, HC=CHPh), 7.19-7.33 (m, 10H, ArH). δ_C (62.5 MHz, CDCl₃) 49.1 (CHPh), 52.3 (CH₃CO₂⁻), 52.5 (CH₃CO₂⁻), 57.6 (CH(CO₂Me)₂), 126.3 (ArCH), 127.1 (ArCH), 127.5 (ArCH), 127.8 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 129.1 (ArCH), 131.7 (HC=C-Ar), 136.7 (ArC), 140,12 (ArC), 167.7 (C=O), 168.1 (C=O).
Enantiomeric excesses were measured using 0.5 mol eq. of the homochiral shift reagent Eu(hfc)_3 and by chiral HPLC (Chiralcel OD); hexane/isopropanol, 99:1, 0.75 ml/min. (tR = 13.5 and 14.6 min.).

General procedure for the enantioselective addition of diethylzinc to benzaldehyde, using catalysts 111b and 128b.

A solution of benzaldehyde 46 (100 mg, 0.94 mmol) and ligand 111b or 128b (0.057 mmol) in hexane (2 ml) was stirred under nitrogen at r.t. for 30 min, before the addition of diethylzinc (1.88 ml, 1.88 mmol) (1.0M solution in hexanes). The reaction mixture was stirred at r.t. for 16 hr and quenched with 1M HCl (2 ml) and extracted into dichloromethane (3 x 20 ml). The combined dichloromethane layers were dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, dichloromethane) gave the title compound as a pale yellow oil. (10% yield; 5% enantiomeric excess using ligand 111b). (50% yield; 60% enantiomeric excess using ligand 128b). Enantiomeric excesses were determined using a Diacel (Chiralcel) OD column, hexane/isopropanol, 99:1; 1.0 ml/min. (tR = 17 and 20 min.).

1-Phenylpropan-1-ol, 47, 32 νmax/cm⁻¹ 3363 (OH), 1452. δH (250 MHz, CDCl3) 0.86 (t, 3H, J=7.5 Hz, CH2CH3), 1.65-1.80 (m, 2H, CH2CH3), 2.40 (s, 1H, OH), 4.47-4.52 (m, 1H, CHPh), 7.21-7.31 (m, 5H, ArH). δC (62.5 MHz, CDCl3) 10.1 (CH2CH3), 31.8 (CH2CH3), 75.9 (CHPh), 125.9 (ArCH), 127.4 (ArCH), 128.3 (ArCH), 144.5 (ArC).
General procedure for the addition of trimethylsilyl cyanide to benzaldehyde using ligands 111b and 128b.

A solution of the ligand 111b or 128b (0.46 mmol) and titanium tetraisopropoxide (0.12 ml, 0.42 mmol) in dichloromethane (2 ml) was stirred under nitrogen at r.t. for 1 hr. This catalyst solution was then cooled to -78 °C and benzaldehyde (0.21 ml, 2.05 mmol) added followed by TMSCN (0.61 ml, 4.57 mmol). The reaction mixture was stirred at -78 °C, under nitrogen for 10 hrs, before being kept in a freezer (-25 °C) for 30 hrs. The reaction mixture was then poured onto 1M HCl (20 ml) and extracted with ethyl acetate (2 x 20 ml). The ethyl acetate layers were combined and washed with a saturated solution of sodium bicarbonate (30 ml), followed by brine (30 ml). The organic layer was dried (MgSO4), filtered and concentrated in vacuo, yielding a yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 4:1) gave the title compound as a colourless oil. (90% yield, 0% enantiomeric excess using ligand 111b). (95% yield, 0% enantiomeric excess using ligand 128b). (Enantiomeric excesses were determined through 1H NMR analysis of the Mosher's esters of 160, by integration of the methyl signals of the methoxy group at δ 3.46 ppm and δ 3.57 ppm).

2-Hydroxy-2-phenylacetonitrile 160.141 \(\nu_{\text{max}}/\text{cm}^{-1}\) 3415 (OH), 2249 (CN), 1455. \(\delta_H\) (250 MHz, CDCl3) 3.50 (broad s, 1H, OH), 5.44 (s, 1H, CHPh), 7.34-7.47 (m, 5H, ArH). \(\delta_C\) (62.5 MHz, CDCl3) 63.3 (CHPh), 119.1 (CN), 126.6 (ArCH), 129.1 (ArCH), 129.6 (ArCH), 135.4 (ArC).
In a 50 ml Schlenk flask, zinc chloride (68 mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to r.t. chlorobenzene (30 ml) was added, followed by ortho-fluorobenzonitrile 105 (1.21 g, 10 mmol) and (S)-valinol 108 (1.55 g, 15 mmol) and the reaction mixture refluxed for 48 hr. The reaction mixture was diluted with dichloromethane (50 ml) and extracted with water (50 ml) followed by brine (50 ml). The dichloromethane layer was dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compound (1.24 g, 60% yield) as a colourless oil. [α]D²⁰ -63.0 (c=0.5, CHCl₃). νmax/cm⁻¹ 2960, 1651 (C=N), 1225. δH (250 MHz, CDCl₃) 0.93 (d, 3H, /=6.8 Hz, CH(CH₃)₂), 1.03 (d, 3H, /=6.8 Hz, CH(CH₃)₂), 1.86-1.94 (m, 1H, CH(CH₃)₂), 4.10-4.20 (m, 2H, CH₂O), 4.34-4.45 (m, 1H, CHN), 7.08-7.20 (m, 2H, ArH), 7.38-7.44 (m, 1H, ArH), 7.84-7.91 (m, 1H, ArH). δC (62.5 MHz, CDCl₃) 17.8 (CH(CH₃)₂), 18.8 (CH(CH₃)₂), 32.6 (CH(CH₃)₂), 69.7 (CH₂O), 72.5 (CHN), 116.3 (ArCH), 116.7 (ArCH), 123.8 (ArCH), 131.0 (ArCH), 132.0 (ArC), 132.6 (ArC), 162.8 (C=N).
To a flame dried 50 ml two-necked flask under nitrogen was added potassium diphenylphosphide (16.75 ml, 8.38 mmol) (as a 0.5M solution in THF). The solution was then heated to reflux and a solution of (4S)-4,5-dihydro-4-isopropyl-2-(2-fluorophenyl)-1,3-oxazole 168 (1.24 g, 5.98 mmol) in THF (10 ml) added under nitrogen. The reaction material was heated to reflux for 2 hr, whereupon the red solution of the phosphide fades to pale yellow. The reaction mixture was diluted with ether (40 ml) and extracted with water (30 ml) and brine (30 ml). The ether layer was then dried (MgSO₄), filtered and concentrated in vacuo yielding a dark yellow oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 4:1) gave the title compound (1.69 g, 76% yield) as a colourless solid. M.p. 86-88 °C. [a]D²⁰ -42.0 (c=0.5, CHCl₃). \( \nu_{\max } / \text{cm}^{-1} \) 2995, 1651 (C=N), 1265. \( \delta_H \) (400 MHz, CDCl₃) 0.68 (d, 3H, J =6.7 Hz, CH(CH₃)₂), 0.80 (d, 3H, J =6.7 Hz, CH(CH₃)₂), 1.44-1.52 (m, 1H, CH(CH₃)₂), 3.81-3.89 (m, 2H, CH₂O), 4.09-4.17 (m, 1H, CHN), 6.85-6.88 (m, 1H, ArH), 7.23-7.38 (m, 12H, ArH), 7.89-7.91 (m, 1H, ArH). \( \delta_C \) (100 MHz, CDCl₃) 18.4 (CH(CH₃)₂), 18.9 (CH(CH₃)₂), 32.8 (CH(CH₃)₂), 70.1 (CH₂O), 73.1 (CHN), 127.9 (ArCH), 128.2 (ArCH), 128.3 (ArCH), 128.4 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 129.8 (ArCH), 130.3 (ArC), 133.6 (ArCH), 133.8 (ArCH), 134.2 (ArCH), 138.1 (ArC), 138.3 (ArC), 138.9 (ArC), 162.9 (C=N).

General preparation of allylic alcohols 167a-d.\(^{153}\)

The appropriate organo Grignard or organolithium species (31 mmol) was added gradually, under nitrogen to an ice-cooled stirred solution of β-phenylcinnamaldehyde 166 (14.1 mmol) in ether (40 ml). On complete addition the reaction material was allowed to warm to r.t. and stirred for 1 hr. The reaction was
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quenched with saturated ammonium chloride solution (50 ml) and extracted with ether (2 x 50 ml). The combined ether extracts were washed with brine (100 ml), dried (MgSO₄), filtered and concentrated in vacuo, yielding the crude alcohol. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compounds as described.

Preparation of 1-lithionaphthalene was achieved by the slow addition (over 45 min) of n-BuLi (26.9 ml, 1.6M solution in hexane, 43 mmol) to a stirred solution of 1-bromonaphthalene (8.28 g, 40 mmol) in THF at -40 °C under nitrogen.

4,4-Diphenyl-4-hydroxybut-2-ene, 167a. (92%) as a colourless oil. (Found: M⁺, 224.1201. C₁₆H₁₆O requires M⁺, 224.1201). νmax/cm⁻¹ 3450 (OH), 3056, 1072. δH (250 MHz, CDCl₃) 1.31 (d, 3H, J=6.2 Hz, CHCH₃), 1.79 (s, 1H, OH), 4.34-4.40 (m, 1H, CHCH₃), 6.06 (d, 1H, J=9.1 Hz, CH=C(Ph)₂), 7.15-7.36 (m, 10H, ArH). δC (62.5 MHz, CDCl₃) 23.6 (CHCH₃), 65.6 (CHOH), 127.4 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 129.6 (ArCH), 132.4 (CH=C(Ph)₂), 139.8 ((Ph)₂C=CH), 142.0 (ArC), 142.4 (ArC). m/z (EI) 224 (M⁺, 21%), 167 (100), 103 (70).

1,1,3-Triphenyl-3-hydroxyprop-1-ene, 167b. (95%) as a colourless solid. (Found: M⁺, 286.1357. C₂₁H₁₉O requires M⁺, 286.1357). νmax/cm⁻¹ 3450 (OH), 3056, 1073. δH (250 MHz, CDCl₃) 2.05 (s, 1H, OH), 5.25 (d, 1H, J=9.3 Hz, CHCPh), 6.29 (d, 1H, J=9.3 Hz, CH=C(Ph)₂), 7.21-7.39 (m, 15H, ArH). δC (62.5 MHz, CDCl₃) 71.6 (CHPh), 126.1 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.5 (ArCH), 129.7 (ArCH), 130.1 (CH=C(Ph)₂), 138.2 ((Ph)₂C=CH), 142.1 (ArC), 143.4 (ArC), 143.4 (ArC). m/z (EI) 286 (M⁺, 7%), 268 (10), 167 (40), 105 (100).

3-(1-Naphthyl)-3-hydroxy-1,1-diphenylprop-1-ene, 167c. (90%) as a colourless oil. (Found: M⁺, 336.1514. C₂₅H₂₀O requires M⁺, 336.1514). νmax/cm⁻¹ 3450 (OH), 2964, 1073. δH (250 MHz, CDCl₃) 2.17 (s, 1H, OH), 5.91 (d, 1H, J=9.23 Hz, CHNphth), 6.42 (d, 1H, J=9.3 Hz, CH=C(Ph)₂), 7.09-7.47 (m, 13H, ArH), 7.67-7.81 (m, 4H, ArH). δC (62.5 MHz, CDCl₃) 69.4 (CHNphth), 123.4 (ArCH), 123.8 (ArCH), 125.4 (ArCH), 125.5 (ArCH), 125.9 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 128.7 (CH=C(Ph)₂), 129.9 (ArCH), 133.8 ((Ph)₂C=CH), 138.4 (ArC), 138.6 (ArC), 141.7 (ArC), 144.1 (ArC). m/z (EI) 336 (M⁺, 72%), 167 (35), 155 (100), 128 (50).

3-(2,4,6-Trimethylphenyl)3-hydroxy-1,1-diphenylprop-1-ene, 167d. (85%) as a colourless oil. (Found: M⁺, 328.1827. C₂₄H₂₄O requires M⁺, 328.1827). νmax/cm⁻¹ 3420 (OH), 2964, 1073. δH (400 MHz, CDCl₃) 1.81 (s, 1H, OH), 2.16 (s, 6H, 2 ×
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ArCH₃ 2.19 (s, 3H, ArCH₃), 5.62 (d, 1H, J=8.6 Hz, CHMes), 6.60 (d, 1H, J=8.6 Hz, CH=C(Ph)₂), 6.74 (s, 2H, ArH), 7.15-7.23 (m, 7H, ArH), 7.31-7.33 (m, 3H, ArH).

δC (100 MHz, CDCl₃) 20.3 (2 x ArCH₃), 20.5 (ArCH₃), 69.2 (CHMes), 127.3 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 127.9 (CH=C(Ph)₂), 128.1 (ArCH), 128.3 (ArCH), 129.0 (ArCH), 130.0 (ArCH), 130.1 ((Ph)₂C=CH), 136.4 (ArC), 136.5 (ArC), 139.4 (ArC), 141.8 (ArC), 143.4 (ArC). m/z (EI) 328 (M⁺, 3%), 310 (35), 147 (83), 28 (100).

General preparation of allylic acetates 161a-d.¹⁵³

A solution of the appropriate allylic alcohol 167a-d (10 mmol), triethylamine (15 mmol), acetic anhydride (15 mmol) and DMAP (2 mol%) in dichloromethane (20 ml) was stirred at r.t. under nitrogen until TLC analysis (petroleum ether/ether, 3:1), indicated all of the starting material had been consumed (2 hr). The reaction material was diluted with dichloromethane (30 ml) and washed with 1M sodium hydroxide solution (2 x 40 ml). The dichloromethane layer was then washed with brine (50 ml), dried (MgSO₄), filtered and concentrated in vacuo to give the crude acetate. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 4:1), gave the title compounds as described.

4,4-Diphenylbut-3-enyl acetate, 161a. (96%) as a colourless oil. (Found: M⁺, 266.1308. C₁₈H₁₈O₂ requires M⁺, 266.1306). vmax/cm⁻¹ 3026, 1740 (C=O), 1250. OH (250 MHz, CDCl₃) 1.32 (d, 3H, J=6.2 Hz, CHCH₃), 1.99 (s, 3H, OCOCH₃), 5.34-5.39 (m, 1H, CHCH₃), 6.04 (d, 1H, J=8.9 Hz, CH=CHCH₃), 7.17-7.38 (m, 10H, ArH). δC (62.5 MHz, CDCl₃) 20.9 (CHCH₃), 21.3 (OCOC₂H₅), 69.4 (CHCH₃), 127.3 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 129.4 (CH=C(Ph)₂), 138.4 (Ph)₂C=CH, 141.2 (ArC), 144.6 (ArC), 169.7 (C=O). m/z (EI) 266 (M⁺, 25%), 206 (40), 191 (30), 43 (100).

1,3,3-Triphenylprop-2-enyl acetate, 161b. (98%) as a colourless solid. M.p. 69-71 °C. (Found: M⁺, 328.1463. C₂₃H₂₀O₂ requires M⁺ 328.1463). vmax/cm⁻¹ 3053, 1735 (C=O), 1235. δH (250 MHz, CDCl₃) 2.09 (s, 3H, OCOCH₃), 6.33 (s, 2H, CHPh and CH=C(Ph)₂), 7.22-7.44 (m, 15H, ArH). δC (62.5 MHz, CDCl₃) 21.3 (OCOC₂H₅), 74.1 (CHPh), 126.1 (ArCH), 126.8 (ArCH), 127.4 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 127.8 (ArCH).
127.9 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 129.6 (CH=C(Ph)₂), 138.7 ((Ph)₂C=CH), 139.8 (ArC), 141.3 (ArC), 144.7 (ArC), 169.6 (C=O). m/z (EI), 328 (M⁺, 1%), 286 (7), 268 (100), 191 (50).

3,3-Diphenylprop-2-enyl-1-(1-naphthyl) acetate, 161c. (95%) as a colourless solid M.p. 95-97 °C. (Found: M⁺, 378.1619. C₂₇H₂₂O₂ requires M⁺, 378.1619). νmax/cm⁻¹ 3054, 1746 (C=O), 1229. δH (250 MHz, CDCl₃) 2.05 (s, 3H, OCOCH₃), 6.49 (d, 1H, J=9.1 Hz, CHNphth), 6.98 (d, 1H, J=9.1 Hz, CH=C(Ph)₂), 7.18-7.21 (m, 7H, ArH), 7.34-7.44 (m, 6H, ArH), 7.55 (d, 1H, J=7.1 Hz, ArH), 7.74-7.84 (m, 3H, ArH). δC (62.5 MHz, CDCl₃) 21.2 (OCOCH₃), 71.9 (CHNphth), 123.8 (ArCH), 124.9 ArCH), 125.2 (ArCH), 125.6 (ArCH), 126.0 (ArCH), 126.1 (ArCH), 127.5 (ArCH), 127.8 (ArCH), 128.1 (CH=C(Ph)₂), 128.3 (ArCH), 128.6 (ArCH), 128.7 (ArCH) 129.6 (ArCH), 130.5 ((PhhC=CH), 133.9 (ArC), 136.4 (ArC), 138.7 (ArC), 141.3 (ArC), 145.1 (ArC), 169.4 (C=O). m/z (EI) 378 (M⁺, 4%), 318 (80), 241 (40), 43 (100).

3,3-Diphenylprop-2-enyl-1-(2,4,6-trimethylphenyl)acetate, 161d. (99%) as a colourless oil. (Found: M⁺, 370.1932. C₂₆H₂₆O₂ requires M⁺, 370.1932). νmax/cm⁻¹ 2957, 1738 (C=O), 2957, 1738 (C=O), 1238. δH (400 MHz, CDCl₃) 1.97 (s, 3H, ArCH₃), 2.30 (s, 9H, 2 x ArCH₃ + OCOCH₃), 6.51 (d, 1H, J=8.7 Hz, CHMes), 6.69 (d, 1H, J=8.7 Hz, CH=C(Ph)₂), 6.71 (s, 2H, ArH), 7.14-7.24 (m, 7H, ArH), 7.32-7.57 (m, 3H, ArH). δC (100 MHz, CDCl₃) 19.5 (ArCH₃), 19.5 (ArCH₃), 20.8 (ArCH₃), 20.8 (ArCH₃), 71.6 (CHMes), 71.6 (CHMes), 127.4 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 128.3 (ArCH), 128.4 (CH=C(Ph)₂), 129.5 (ArCH), 129.7 (ArCH), 129.8 (ArCH), 130.0 (ArCH), 130.4 ((Ph)₂C=CH), 133.4 (ArC), 136.8 (ArC), 137.4 (ArC), 138. (ArC), 141.6 (ArC), 145.1 (ArC), 169.6 (C=O). m/z (EI) 370 (M⁺, 1%), 310 (100), 147 (80), 43 (70).

General procedure for palladium catalysed allylic alkylation reactions.¹⁵³

![Diagram](attachment://diagram.png)

The allylic acetate 161a-d (200 mg, 0.55 mmol), [[Pd(η-C₅H₅)Cl]₂] (9 mg, 2.5 mol%) and ligand 15 (20 mg, 10 mol%), were dissolved in THF (2 ml) and stirred at 20 °C for 15 min. The resulting yellow solution was treated with dimethyl sodiomalonate (0.32 mmol/ml in dry THF). The reaction mixture was stirred at room temperature until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been consumed (24-36 hr). The reaction mixture was quenched with
water (40 ml) and dichloromethane added (3 x 20 ml) and extracted. The dichloromethane layers were combined, dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 5:1) gave the title compounds as described.

**Methyl-2-carbomethoxy-3-methyl-5,5-diphenylpent-4-enoate, 169a.** (95%) as a colourless oil. (Found: M⁺, 338.1518. C₂₁H₂₂O₄ requires M⁺, 338.1518). [α]D²⁰ -173.9 (c=0.46, EtOH). νmax/cm⁻¹ 3024, 2970, 1739 (C=O), 1242. δH (250 MHz, CDCl₃) 1.14 (d, 3H, /=6.5 Hz, CHCH₃), 3.12-3.19 (m, 1H, CHCH₃), 3.36 (d, 1H, /=8.7 Hz CH(CO₂Me)), 3.65 (s, 3H, CO₂CH₃), 3.67 (s, 3H, CO₂CH₃), 6.00 (d, 1H, /=10.3 Hz, CH=CPh₂), 7.13-7.37 (m, 10H, ArH). δC (62.5 MHz, CDCl₃) 19.2 (CHCH₃), 34.2 (CHCH₃), 52.2 (CO₂CH₃), 52.2 (CO₂CH₃), 57.5 (CH(CO₂CH₃)₂), 127.2 (ArCH), 127.3 (ArCH), 128.0 (ArCH), 128.2 (ArCH), 129.4 (ArCH), 130.1 (ArCH), 139.5 (ArC), 142.2 (ArC), 142.6 (ArC), 168.5 (C=O). m/z (EI) 338 (M⁺, 20%), 219 (80), 207 (100), 129 (80).

**Methyl 2-carbomethoxy-3,5,5-triphenylpent-4-enoate, 169b.** (97%) as a colourless oil. (Found: MH⁺, 400.1740. C₂₅H₂₅O₄ requires MH⁺, 400.1740). [α]D²⁰ -186.0 (c=0.44, CHCl₃). νmax/cm⁻¹ 3057, 2952, 1735 (C=O), 1265. OH (250 MHz, CDCl₃) 3.47 (s, 3H, CO₂CH₃), 3.70 (s, 3H, CO₂CH₃), 3.90 (d, 1H, /=10.3 Hz, CH(CO₂CH₃)), 4.25 (ap.t, 1H, /=10.0 Hz, CHPh), 6.36 (d, 1H, /=10.3 Hz, CH=CPh₂), 7.10-7.39 (m, 15H, ArH). δC (62.5 MHz, CDCl₃) 45.1 (CHPh), 52.2 (CO₂CH₃), 52.5 (CO₂CH₃), 58.5 (CH(CO₂Me)₂), 126.9 (Ar CH), 127.4 (Ar CH), 127.4 (Ar CH), 127.7 (Ar CH), 128.0 (ArCH), 128.1 (ArCH), 128.6 (ArCH), 129.6 (ArCH), 139.2 (C=CH), 141.2 (ArC), 142.2 (ArC), 143.7 (ArC), 168.0 (C=O). m/z (EI) 400 (M⁺, 3%), 269 (100), 191 (82).

**Methyl 2-carbomethoxy-5,5-diphenyl-3-(1-naphthyl)pent-4-enoate, 169c.** (94%) as a colourless oil. (Found: M⁺, 450.1831. C₃₀H₂₆O₄ requires M⁺, 450.1831). [α]D²⁰ +87.2 (c=1.1, CHCl₃). νmax/cm⁻¹ 3102, 2953, 1750 (C=O), 1248. δH (250 MHz, CDCl₃) 3.30 (s, 3H, CO₂CH₃), 3.68 (s, 3H, CO₂CH₃), 4.06 (d, 1H, /=9.2 Hz, CHCO₂CH₃), 5.13 (ap. t, 1H, /=9.7 Hz, CHCHCO₂CH₃), 6.62 (d, 1H, /=10.2 Hz, CH=CPh₂), 6.95-6.99 (m, 2H, ArH), 7.21-7.77 (m, 15H, ArH). δC (62.5 MHz, CDCl₃) 39.7 (CHNphth), 52.3 (CO₂CH₃), 52.5 (CO₂CH₃), 58.4 (CH(CO₂CH₃)₂), 123.6 (ArCH), 125.4 (ArCH), 125.5 (ArCH), 125.8 (ArCH), 127.4 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 129.9 (ArCH), 130.6 ((Ph)₂C=CH), 134.1 (ArC), 137.6 (ArC), 139.6 (ArC), 142.3 (ArC), 143.8 (ArC), 167.8 (C=O), 168.3 (C=O). m/z (EI) 450 (M⁺, 15%), 319 (100), 283 (58), 241 (65), 191 (72).
Methyl-2-carbomethoxy-5,5-diphenyl-3-mesitylpent-4-enoate, 169d. (86%) as a colourless solid. M.p. 105-107 °C. (Found: M+, 442.2144. C_{29}H_{30}O_{4} requires M+, 442.2144). [α]_{D}^{20} -68.8 (c=1.96, EtOH). ν_{max}/cm^{-1} 3080, 2964, 1758 (C=O), 1247. δ_{H} (400 MHz, CDCl3) 1.47 (s, 3H, ArCH3), 2.17 (s, 3H, ArCH3), 2.52 (s, 3H, ArCH3), 3.29 (s, 3H, CO_{2}CH_{3}), 3.75 (s, 3H, CO_{2}CH_{3}). 4.17 (d, 1H, J=10.8 Hz, CH(CO_{2}CH_{3})), 4.78 (dd, 1H, J=8.9, 10.9 Hz, CHMes), 6.48 (d, 1H, J=8.9 Hz, CH=C(Phh)), 6.55 (s, 1H, ArH), 6.74 (s, 1H, ArH), 7.03-7.05 (m, 2H, ArH), 7.14-7.22 (m, 5H, ArH), 7.22-7.30 (m, 3H, ArH). δ_{C} (100 MHz, CDCl3) 19.9 ArCH3, 20.6 (ArCH3), 22.4 (ArCH3), 40.2 (CHMes), 51.9 (CO_{2}CH_{3}), 52.6 (CO_{2}CH_{3}), 55.9 (CH(CO_{2}CH_{3})_{2}), 126.9 (ArCH), 127.1 (ArCH), 127.8 (ArCH), 128.1 (CH=C(Phh)_{2}) 128.4 (ArCH), 128.6 (ArCH), 129.3 (ArCH), 129.7 (ArCH), 130.5 (ArCH), 134.3 (ArC), 135.8 (ArC), 136.2 (ArC), 137.7 (ArC), 139.6 ArC), 142.3 (ArC), 143.6 ((Phh)_{2}C=CH), 168.0 (C=O), 168.8 (C=O). m/z (El) 442 (M+, 1%), 206 (100), 191 (40), 129 (55).

General procedure for the decarboxylation of substitution products 169a-d.

A degassed solution of the appropriate alkylated product 169a-d (1.0 mmol), NaCl (2.6 mmol) and H_{2}O (2.8 mmol) in DMSO (5 ml) was heated in a sealed tube at 180 °C for 6 hr. After cooling to room temperature the mixture was diluted with dichloromethane (30 ml) and brine (100 ml) added and then extracted followed by two further extraction's with dichloromethane (30 ml). The combined organic extracts were dried (MgSO_{4}), filtered and concentrated in vacuo. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compounds as described.

Methyl-3-methyl-5,5-diphenylpent-4-enoate, 176a. (81%) as a colourless oil. (Found: M+, 280.1463. C_{19}H_{20}O_{2} requires M+, 280.1463). [α]_{D}^{20} -67.2 (c=0.83, CHCl_{3}). ν_{max}/cm^{-1} 3024, 2980, 1738 (C=O), 1433. δ_{H} (400 MHz, CDCl3) 1.47 (s, 3H, J=6.6 Hz, CH_{3}), 2.30-2.38 (m, 2H, CH_{2}CO_{2}CH_{3}), 2.81-2.85 (m, 1H, CHCH_{3}), 3.59 (s, 3H, CO_{2}CH_{3}), 5.88 (d, 1H, J=10.1 Hz, CH=C(Phh)), 7.15-7.24 (m, 6H, ArH), 7.32-7.36 (m, 4H, ArH). δ_{C} (100 MHz, CDCl3) 21.1 (CH_{3}), 31.2 (CHCH_{3}), 41.9 (CH_{2}CO_{2}CH_{3}), 51.6 (CO_{2}CH_{3}), 127.1 (ArCH), 127.3 (ArCH), 127.5 (ArCH) 128.2 (ArCH), 128.4 (ArCH), 130.1 (ArCH), 133.2 (CH=C(Phh)_{2}), 139.9 ((Phh)_{2}C=CH), 141.4 (ArC), 142.4 (ArC), 172.5 (C=O). m/z (El) 280 (M+, 13%), 206 (100), 129 (60).
Methyl-3,5,5-triphenylpent-4-enoate, 176b. (79%) as a colourless solid. M.p. 117-119 °C. (Found: M+, 342.1619. C24H22O2 requires M+, 342.1619). \([\alpha]D^{20} -125.0\) (c=0.96, CHCl₃). \(v_{\text{max}}/\text{cm}^{-1} 3054, 1736 (\text{C}=\text{O}), 1438, 1265.\) \(\delta_H (400 \text{ MHz, CDCl}_3) 2.73 (d, 2H, J=7.6 \text{ Hz, CH}_2\text{CO}_2\text{CH}_3), 3.58 (s, 3H, \text{CO}_2\text{CH}_3), 3.93-3.99 (m, 1H, CHPh), 6.24 (d, 1H, J=10.4 \text{ Hz, CH=C(Ph)}_2), 7.11-7.37 (m, 15H, ArH). \(\delta_C (100 \text{ MHz, CDCl}_3) 44.3 \text{ (CHPh), 44.4 (CH}_2\text{CO}_2\text{CH}_3), 53.9 \text{ (CO}_2\text{CH}_3), 128.9 \text{ (ArCH), 129.5 (ArCH), 129.6 (ArCH), 129.7 (ArCH), 129.8 (ArCH), 130.6 (ArCH), 131.1 (ArCH), 131.6 (ArCH), 132.1 (ArCH), 132.7 (CH=C(Ph)}_2), 142.0 ((\text{Ph})_2\text{C}=\text{CH}, 144.6 \text{ (ArC), 144.8 (ArC), 145.9 (ArC), 174.2 (C}=\text{O). m/z (El) 342 (M+1%), 268 (100), 191 (82).\)

Methyl-5,5-diphenyl-3-(1-naphthyl)pent-4-enoate, 176c. (80%) as a colourless solid. M.p. 107-109 °C. (Found: M+, 392.1776. C28H24O2 requires M+, 392.1776). \([\alpha]D^{20} +110.8\) (c=1.37, CHCl₃). \(v_{\text{max}}/\text{cm}^{-1} 3020, 1734 (\text{C}=\text{O}), 1443, 1216.\) \(\delta_H (250 \text{ MHz, CDCl}_3) 2.77 (dd, 1H, J=8.9, 14.7 \text{ Hz, CHHC}_2\text{CO}_2\text{CH}_3), 2.91 (dd, 1H, J=5.9, 14.7 \text{ Hz, CHHC}_2\text{CO}_2\text{CH}_3), 3.55 (s, 3H, \text{CO}_2\text{CH}_3), 4.76-4.86 (m, 1H, CHNaphth), 6.45 (d, 1H, J=10.0 \text{ Hz, CH=C(Ph)}_2), 7.02-7.06 (m, 1H, ArH), 7.22-7.29 (m, 8H, ArH), 7.38-7.44 (m, 5H, ArH), 7.50-7.75 (m, 3H, ArH). \(\delta_C (62.5 \text{ MHz, CDCl}_3) 37.1 \text{ (CHNaphth), 42.4 (CH}_2\text{CO}_2\text{CH}_3), 51.5 \text{ (CO}_2\text{CH}_3), 123.2 \text{ (ArCH), 124.0 (ArCH), 125.5 (ArCH), 125.9 (ArCH), 127.1 (ArCH), 127.2 (ArCH), 127.3 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 128.1 (ArCH), 128.8 (ArCH), 129.7 (ArCH), 130.3 (CH=C(Ph)}_2), 134.2 ((\text{Ph})_2\text{C}=\text{CH), 139.1 (ArC), 140.0 (ArC), 142.0 (ArC), 142.5 (ArC), 172.1 (C}=\text{O). m/z (El) 392 (M+29%), 319 (100), 241 (80), 191 (90), 165 (60).\)

Methyl-5,5-diphenyl-3-(2,4,6-trimethylphenyl)pent-4-enoate, 176d. (93%) as a colourless solid. M.p. 100-102 °C. (Found: M+, 384.2089. C27H28O2 requires M+, 384.2089). \([\alpha]D^{20} +153.1\) (c=1.9, CHCl₃). \(v_{\text{max}}/\text{cm}^{-1} 3023, 2919, 1738 (\text{C}=\text{O), 1440, 1160. \delta_H (400 \text{ MHz, CDCl}_3) 2.03 (broad s, 6H, 2 x \text{ArCH}_3), 2.19 (s, 3H, \text{ArCH}_3), 2.57 (dd, 1H, J=5.3, 14.7 \text{ Hz, CHHC}_2\text{CO}_2\text{CH}_3), 2.86 (dd, 1H, J=10.2, 14.7 \text{ Hz, CHHC}_2\text{CO}_2\text{CH}_3), 3.62 (s, 3H, \text{CO}_2\text{CH}_3), 4.34-4.39 (m, 1H, CHMes), 6.54 (d, 1H, J=8.6 \text{ Hz, CH=C(Ph)}_2), 6.70 (s, 2H, ArH), 6.93-6.95 (m, 2H, ArH), 7.18-7.25 (m, 8H, ArH). \(\delta_C (100 \text{ MHz, CDCl}_3) 20.6 \text{ (ArCH), 21.2 (2 x \text{ArCH}_3), 37.5 (CHMes), 39.4 (CH}_2\text{CO}_2\text{CH}_3), 51.5 \text{ (CO}_2\text{CH}_3), 126.3 \text{ (ArCH), 126.9 (ArCH), 127.1 (ArCH), 127.4 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 129.5 (ArCH), 130.6 (CH=C(Ph)}_2), 135.4 ((\text{Ph})_2\text{C}=\text{CH), 136.0 (ArC), 137.6 (ArC), 139.9 (ArC), 142.1 (ArC), 142.8 (ArC), 172.5 (C}=\text{O). m/z (El) 384 (M+17%), 311 (100), 191 (45).\)
General procedure for the hydrolysis of mono-esters 176a-d.

A solution of the appropriate mono-ester 176a-d (1 mmol) and sodium hydroxide (5 mmol) in MeOH (5 ml)/H2O (4 ml) was heated to reflux until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (2 hr). The reaction mixture was acidified (1M HCl) and the aqueous extracted with dichloromethane (3 x 30 ml). The organic extracts were combined, dried (MgSO4), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, eluant, petroleum ether/ether, 2:1) gave the title compounds as described.

3-Methyl-5,5-diphenylpent-4-enoic acid, 177a. (95%) as a colourless oil. (Found: M+, 266.1306. C18H18O2 requires M+, 266.1306). [α]D20 -62.4 (c=0.82, CHCl3). νmax/cm-1 3100 (CO2H), 2999, 1708 (C=O), 1444, 1296. δH (400 MHz, CDCl3) 1.09 (d, 3H, J=6.7 Hz, CH3), 2.29-2.41 (m, 2H, CH2CO2H), 2.79-2.87 (m, 1H, CHCH3), 5.89 (d, 1H, J=10.1 Hz, CH=C(Ph2)), 7.13-7.35 (m, 10H, ArH), 8.70-10.0 (broad s, 1H, CO2H). δC (100 MHz, CDCl3) 20.9 (CH3), 30.9 (CHCH3), 41.7 (CH2CO2H), 127.1 (ArCH), 127.3 (ArCH), 127.9 (ArCH), 128.3 (ArCH), 129.6 (ArCH), 132.8 (CH=C(Ph2)), 139.9 ((Ph)2C=CH), 141.7 (ArC), 142.2 (ArC), 178.4 (C=O). m/z (EI) 266 (M+, 18%), 206 (100), 191 (40), 129 (65), 69 (60).

3-Phenyl-5,5-diphenylpent-4-enoic acid, 177b. (98%) as a colourless solid. M.p. 129-131 °C. (Found: M+, 328.1463. C23H20O2 requires M+, 328.1463). [α]D20 -121.8 (c=0.78, CHCl3). νmax/cm-1 3054 (CO2H), 2987, 1709 (C=O), 1265. δH (400 MHz, CDCl3) 2.73 (d, 2H, J=7.2 Hz, CH2CO2H), 3.90-3.96 (m, 1H, CHPh), 6.22 (d, 1H, J=10.4 Hz, CH=C(Ph2)), 7.05-7.33 (m, 15H, ArH), 9.0-10.1 (broad s, 1H, CO2H). δC (100 MHz, CDCl3) 41.6 (CHPh), 41.7 (CH2CO2H), 126.6 (ArCH), 127.2 (Ar CH), 127.3 (ArCH), 127.4 (ArCH), 128.1 (Ar(Ch), 128.3 (Ar(Ch), 128.4 (Ar(Ch), 128.7 (Ar(Ch), 129.7 (Ar(Ch), 130.1 (CH=C(Ph2)), 139.5 ((Ph)2C=CH), 142.0 (ArC), 142.7 (ArC), 143.2 (ArC), 177.2 (C=O). m/z (EI) 328 (M+, 7%), 268 (100), 191 (89).

5,5-Diphenyl-3-(1-naphthyl)pent-4-enoic acid, 177c. (98%) as a colourless solid. M.p. 85-87 °C. (Found: M+, 378.1619. C27H22O2 requires M+, 378.1620). [α]D20 +146.8 (c=0.94, CHCl3). νmax/cm-1 3000 (CO2H), 2592, 1735 (C=O), 1252. δH (400 MHz, CDCl3) 2.79 (dd, 1H, J=8.7, 15.1 Hz, CHHCO2H), 2.91 (dd, 1H, J=5.9, 15.1 Hz, "Chapter 6: Experimental"
5,5-Diphenyl-3-(2,4,6-trimethylphenyl)pent-4-enoic acid, 177d. (98%) as a colourless solid. M.p. 136-138 °C. (Found: M+, 370.1932. C_{26}H_{26}O_2 requires M+, 370.1932). [α]_D^{20} +160.1 (c=0.90, CHCl_3). v \text{max} /cm^{-1} 3058 (CO_2H), 2921, 1768 (C=O), 1265. δ_H (400 MHz, CDCl_3) 2.03 (broad s, 6H, 2 x ArCH_3), 2.19 (s, 3H, ArCH_3), 2.59 (dd, 1H, J=5.1, 15.0 Hz, CHHC02H), 2.88 (dd, 1H, J=10.0, 15 Hz, CHHC02H), 4.33-4.39 (m, 1H, CHMes), 6.55 (d, 1H, J=8.6 Hz, CH=C(Ph)_2), 6.87 (s, 2H, ArH), 6.91-6.93 (m, 2H, ArH), 7.17-7.24 (m, 8H, ArH), 9.0-10.0 (broad s, 1H, CO_2H). δ_C (100 MHz, CDCl_3) 20.6 (ArCH_3), 21.2 (2 x ArCH_3), 37.3 (CHMes), 39.4 (CH_2CO_2H), 126.9 (ArCH), 126.9 (ArCH), 127.1 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 129.5 (ArCH), 129.9 (ArCH), 130.4 (CH=C(Ph)_2), 135.5 ((Ph)_2C=CH), 136.0 (ArC), 137.5 (ArC), 139.7 (ArC), 141.9 (ArC), 143.0 (ArC), 178.2 (C=O). m/z (El) 370 (M+, 35%), 311 (100), 191 (40), 91 (75).

General procedure for the preparation of Boc-protected amines 178a-d.

A solution of the appropriate carboxylic acid 177a-d, (1 mmol), triethylamine (1.1 mmol) and diphenylphosphoryl azide (1.1 mmol) in tert-butyl alcohol (5 ml) was refluxed under nitrogen until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been consumed (16 hr). The reaction mixture was cooled to room temperature and poured onto saturated sodium bicarbonate solution (30 ml). The resulting milky white precipitate was extracted with dichloromethane (3 x 30 ml) and the combined organic extracts washed with brine (50 ml), dried (MgSO_4), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compounds as described.
Chapter 6: Experimental

N-(tert-butoxycarbonyl)-1-amino-2-methyl-4,4-diphenyl-but-3-ene, 178a. (52%) as a colourless solid. M.p. 88-90 °C. (Found: M+, 337.2042. C_{22}H_{27}NO_{2} requires M+, 337.2042). [\alpha]_{D}^{20} -58.3 (c=0.7, CHCl_{3}). \nu_{\text{max}} / \text{cm}^{-1} 3359 (NH), 2965, 1712 (C=O), 1249, 1172. \delta_{H} (400 MHz, CDCl_{3}) 1.01 (d, 3H, J=6.6 Hz, CH_{3}), 1.41 (s, 9H, NHCO_{2}C(CH_{3})_{3}), 2.44-2.49 (m, 1H, CH_{2}C), 2.97-3.03 (m, 1H, CH=CHNHBOc), 3.03-3.15 (m, 1H, CHCHOBoc), 4.45 (broad s, 1H, NHBOc), 5.84 (d, 1H, J=10.2 Hz, CH=C(Ph)_{2}), 7.16-7.38 (m, 10H, ArH). \delta_{C} (100 MHz, CDCl_{3}) 18.5 (CH_{3}), 28.4 (C(CH_{3})_{3}), 35.2 (CHCH_{3}), 46.5 (CH_{2}NBoc), 79.0 (C(CH_{3})_{3}), 127.0 (ArCH), 127.1 (ArCH), 127.2 (ArCH), 128.1 (ArCH), 128.4 (ArCH), 129.7 (ArCH), 132.5 (CH=C(Ph)_{2}), 140.1 ((Ph)_{2}C=CH), 142.1 (ArC), 142.7 (ArC), 155.9 (C=O). m/z (EI) 337 (M+, 0.3%), 281 (20), 207 (100), 129 (45), 57 (90).

N-(tert-butoxycarbonyl)-1-amino-2,4,4-triphenyl-but-3-ene, 178b. (61%) as a colourless solid. M.p. 118-120 °C. (Found: M+, 399.2198. C_{27}H_{29}NO_{2} requires M+, 399.2198). [\alpha]_{D}^{20} -87.2 (c=0.86, CHCl_{3}). \nu_{\text{max}} / \text{cm}^{-1} 3443 (NH), 3054, 2984, 1711 (C=O), 1265, 1170. \delta_{H} (400 MHz, CDCl_{3}) 1.39 (s, 9H, NHCO_{2}(CH_{3})), 3.38-3.48 (m, 2H, CH_{2}NBoc), 3.55-3.59 (m, 1H, CHPh), 4.44 (broad s, 1H, NBOc), 6.25 (d, 1H, J=10.3 Hz, CH=C(Ph)_{2}), 7.12-7.36 (m, 15H, ArH). \delta_{C} (100 MHz, CDCl_{3}) 28.4 (C(CH_{3})_{3}), 46.0 (CH_{2}NBoc), 46.3 (CHPh), 79.2 (C(CH_{3})_{3}), 126.7 (ArCH), 127.2 (ArCH), 127.3 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 129.4 (ArCH), 129.8 (CH=C(Ph)_{2}), 139.8 ((Ph)_{2}C=CH), 142.1 (ArC), 142.1 (ArC), 143.6 (ArC), 155.8 (C=O). m/z (EI) 399 (M+, 10%), 269 (100), 191 (62).

N-(tert-butoxycarbonyl)-1-amino-2-(1-naphthyl)but-3-ene, 178c. (52%) as a colourless oil. (Found: M+, 450.2433. C_{31}H_{31}NO_{2} requires M+, 450.2433). [\alpha]_{D}^{20} +118.2 (c=0.44, CHCl_{3}). \nu_{\text{max}} / \text{cm}^{-1} 3446 (NH), 3054, 2983, 2932, 1710 (C=O), 1265. \delta_{H} (250 MHz, CDCl_{3}) 1.39 (s, 9H, NHCO_{2}C(CH_{3})_{3}), 3.43-3.58 (m, 2H, CH_{2}NBoc), 4.47-4.54 (m, 2H, CHNaphth and NBoc), 6.45 (d, 1H, J=10.1 Hz, CH=C(Ph)_{2}), 7.06-7.23 (m, 2H, ArH), 7.25-7.30 (m, 8H, ArH), 7.36-7.48 (m, 4H, ArH), 7.66-7.85 (m, 3H, ArH). \delta_{C} (62.5 MHz, CDCl_{3}) 28.3 (C(CH_{3})_{3}), 41.0 (CHNaphth), 46.1 (CH_{2}NBoc), 79.1 (C(CH_{3})_{3}), 123.2 (ArCH), 124.4 (ArCH), 125.5 (ArCH), 125.9 (ArCH), 127.2 (ArCH), 127.2 (ArCH), 128.0 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 129.5 (CH=C(Ph)_{2}), 129.8 (ArCH), 134.2 ((Ph)_{2}C=CH), 138.2 (ArC), 138.2 (ArC), 139.3 (ArC), 139.3 (ArC), 153.5 (C=O). m/z (EI) 450 (M+, 0.2%), 393 (12), 319 (100), 241 (40).

N-(tert-butoxycarbonyl)-1-amino-2-(2,4,6-trimethylphenyl)but-3-ene, 178d. (49%) as a colourless oil. (Found: M+, 441.2667. C_{30}H_{35}NO_{2} requires M+, 441.2667). [\alpha]_{D}^{20} +155.1 (c=0.25, CHCl_{3}). \nu_{\text{max}} / \text{cm}^{-1} 3362 (NH), 2975, 1712 (C=O), 1265. \delta_{H}
(400 MHz, CDCl₃) 1.46 (s, 9H, NHC=O₂C(CH₃)₃), 2.07 (broad s, 6H, 2 x ArCH₃), 2.24 (s, 3H, ArCH₃), 3.25-3.29 (m, 1H, CHHNHBoc), 3.48-3.54 (m, 1H, CHHNHBoc), 4.00-4.06 (m, 1H, CH Mes), 4.55 (broad s, 1H, NHBoc), 6.65 (d, 1H, J=10.0 Hz, CH=C(Ph)₂), 6.75 (s, 2H, ArH), 6.95-6.97 (m, 2H, ArH), 7.23-7.29 (m, 8H, ArH). δ_C (100 MHz, CDCl₃) 20.6 (ArCH₃), 21.3 (2 x ArCH₃), 28.4 (C(CH₃)₃), 42.1 (CHMes), 43.6 (CH₂NHBOc), 79.2 (C(CH₃)₃), 126.9 (ArCH), 127.1 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 129.7 (ArCH), 129.8 (ArCH), 129.9 (ArCH), 129.9 (CH=C(Ph)₂), 135.6 ((Ph)₂C=CH), 135.9 (ArC), 136.6 (ArC), 139.8 (ArC), 142.0 (ArC), 143.7 (ArC), 155.9 (C=O). m/z (El) 441 (M⁺, 0.2%), 311 (100), 191 (30), 57 (50).

General procedure for the preparation Boc protected β-amino acids 184a-d.

To a vigorously stirred solution of Boc-protected amine 178a-d (0.5 mmol) and sodium periodate (2.05 mmol) in a solvent mixture of acetonitrile (2 ml), carbon tetrachloride (2 ml) and water (3 ml) was added ruthenium trichloride hydrate (2.2 mol%). The reaction mixture was stirred until TLC analysis (petroleum ether/ether, 3:1; silica plates stained with bromocresol green-yellow coloration develops for carboxylic acid functionality) indicated that all of the starting material had been consumed (2 hr). The reaction mixture was diluted with dichloromethane (25 ml) and washed with H₂O (20 ml). The organic layer was collected, dried (MgSO₄), filtered and concentrated in vacuo, yielding a dark brown oil. Purification by "flash" column chromatography (eluants, petroleum ether/ether, 1:1) gave the title compounds as described.

N-(tert-butoxycarbonyl)-3-amino-2-methylpropanoic acid, 184a. (60%) as a colourless solid. M.p. 81-83 °C. (Found: M⁺, 203.1157. C₉H₁₇NO₄ requires M⁺, 203.1157). [α]D²⁰ +63.1 (c=0.25, CHCl₃). νmax/cm⁻¹ 3343 (NH), 3300-3000 (C=O acid), 2938, 1712 (C=O carbamate), 1698 (C=O carboxylic acid), 1252. δ_H (400 MHz, CDCl₃) 1.20 (d, 3H, J=6.9 Hz, CH₃), 1.44 (s, 9H, NHC=O₂C(CH₃)₃), 2.69 (broad s, 1H, CHCH₃), 3.32 (m, 2H, CH₂NHBOc), 5.07 and 6.35 (broad s, 1H, NHBOc), 9.79 (broad s, 1H, CO₂H). δ_C (100 MHz, CDCl₃) (Some of the peaks are doubled-up, probably due to the presence of rotamers) 14.6 (CH₃), 28.1 and 28.3 (C(CH₃)₃), 40.0 and 40.1 (CHCH₃), 42.8 and 44.2 (CH₂NHBOc), 79.6 and 81.1 (C(CH₃)₃), 156.1 and 157.7 (C=O)
carbamate), 179.5 and 180.6 (C=O acid). m/z (EI) 203 (M⁺, 0.2%), 148 (70), 130 (40), 57 (100).

\textit{N-(tert-butoxycarbonyl)-3-amino-2-phenylpropanoic acid, 184b.} (65%) as a colourless solid. M.p. 144-146 °C (Found: M⁺, 265.1314. C₁₄H₁₉N₀₄ requires M⁺, 265.1314). [α]D²⁰ +88.2 (c=1.25, CHCl₃). νmax/cm⁻¹ 3448 (NH), 3338-3054 (C=O), 2892, 1718 (C=O carbamate), 1708 (C=O acid), 1264.

\textit{N-(tert-butoxycarbonyl)-3-amino-2-(1-naphthyl)propanoic acid, 184c.} (61%) as a colourless solid. M.p. 140-142 °C. (Found: M⁺, 315.1471. C₁₈H₂₁N₀₄ requires M⁺, 315.1470). [α]D²⁰ +130.0 (c=0.5, CHCl₃). νmax/cm⁻¹ 3400 (NH), 3390-3000 (C=O), 2900, 1720 (C=O acid), 1695 (C=O carbamate), 1265. δH (250 MHz, CDCl₃) 3.45-3.60 (m, 2H, CH₂NHBoc), 4.52-4.56 (m, 1H, CHNaphth), 4.70 and 6.50 (broad s, 1H, NHBoc), 7.12-8.21 (m, 7H, ArH), 9.0-10.5 (broad s, 1H, CO₂H). δC (62.5 MHz, CDCl₃) (Some of the peaks are doubled-up, probably due to the presence of rotamers) 27.9 and 28.3 (C(CH₃)₃), 46.1 and 47.5 (CH₂NHBOc), 54.5 and 55.8 (CHNaphth), 79.4 and 80.6 (C(CH₃)₃), 123.1 (ArCH), 125.3 (ArCH), 126.1 (ArCH), 126.3 (ArCH), 127.7 (ArCH), 128.7 (ArCH), 128.9 (ArCH), 129.1 (ArC), 134.0 (ArC), 155.6 and 156.1 (C=O carbamate), 177.2 and 178.1 (C=O acid). m/z (EI) 315 (M⁺, 10%), 297 (50), 200 (55), 57 (100).

\textit{N-(tert-butoxycarbonyl)-3-amino-2-(2,4,6-trimethylphenyl)propanoic acid, 184d.} (63%) as a colourless solid. M.p. 160-162 °C. (Found: M⁺, 307.1784. C₁₇H₂₅N₀₄ requires M⁺, 307.1784). [α]D²⁰ -142.0 (c=0.15, CHCl₃). νmax/cm⁻¹ 3331 (NH), 3400-2976 (CO₂H), 1728 (C=O acid), 1688 (C=O carbamate), 1251. δH (400 MHz, CDCl₃) 2.24 (s, 3H, ArCH₃), 2.32 (broad s, 6H, 2 x ArCH₃), 3.36-3.40 (m, 1H, CHNHBoc), 3.63-3.73 (m, 1H, CHNHBoc), 4.01-4.05 (m, 1H, CHMes), 4.19 and 5.09 (broad s, 1H, NHBoc), 6.85 (s, 2H, ArH), 9.0-10.1 (broad s, 1H, CO₂H). δC (100 MHz, CDCl₃) (Some of the peaks are doubled-up, probably due to the presence of rotamers) 20.5 (ArCH₃), 20.8 (2 x ArCH₃), 28.2 and 28.4 (C(CH₃)₃), 40.5 and 41.3 (CH₂NHBOc), 46.8 and 48.7 (CHMes), 79.6 and 81.3 (C(CH₃)₃), 129.9 (2 x...
ArCH), 130.4 (ArC), 130.7 (ArC), 136.9 (ArC), 137.0 (ArC), 155.9 and 157.7 (C=O carbamate), 177.3 and 178.9 (C=O acid). m/z (EI) 307 (M+, 0.8%), 178 (55), 133 (45), 57 (100).

General procedure for the preparation of "free" β-amino acids, 185a-b.

\[
\text{HO}_2\text{C} \quad \text{R} \quad \text{CH}_2\text{NHCO}_2\text{Bu} \quad \text{R} \quad \text{O}_2\text{C} \quad \text{CH}_2\text{NH}_3^+ \\
\text{CH}_2\text{NHCO}_2 \quad \text{Bu} \quad \text{CH}_2\text{NH}_3^+
\]

The Boc-protected β-amino acid 184a or 184b (0.25 mmol) was dissolved in a 4.0M HCl/Dioxane solution (8 ml) and stirred under nitrogen at r.t. until TLC analysis (petroleum ether/ether, 1:2, stained using ninhydrin) indicated that all of the starting material had been consumed (4 hr). The solvent was removed in vacuo and the resulting colourless solid passed down a DOWEX (200 mesh) acid ion exchange column (eluant, H₂O (1000 ml, containing 10 ml 1 N ammonia)). Removal of the solvent in vacuo gave the title compounds as described.

3-Amino-2-methyl propanoic acid, 185a.168 (90%) as a colourless solid. M.p. 182-184 °C. (Found: M⁺, 103.0633. C₄H₉NO₂ requires M⁺, 103.0633). [α]D²⁰ -13.5 (c=0.5, H₂O), (lit.₁₆⁸ [α]D²⁰ -14.2 (c=0.42, H₂O). νmax/cm⁻¹ 1550 (C=O). δH (400 MHz, D₂O) 1.25 (d, 3H, J=6.0 Hz, CH₃), 2.90 (broad s, 1H, CHCH₃), 3.20 (m, 2H, CH₂NH₃⁺). δC (100 MHz, D₂O) 14.6 (CH₃), 37.4 (CHCH₃), 41.6 (CH₂NH₃⁺), 177.9 (C=O). m/z (EI) 103 (M⁺, 2%), 30 (100).

3-Amino-2-phenyl propanoic acid, 185b.169 (85%) as a colourless solid. M.p. 220-222 °C. (Found: M⁺, 165.0789. C₉H₁₁O₂ requires M⁺, 165.0789). [α]D²⁰ -95.0 (c=0.18, H₂O), (lit.₁₆⁹ [α]D²⁰ -94.0 (c=0.20, H₂O). νmax/cm⁻¹ 1660 (C=O). δH (400 MHz, D₂O) 3.39 (dd, 1H, J=7.1, 13.1 Hz, CHHNH₃⁺), 3.62 (dd, 1H, J=7.7, 13.1 Hz, CHHNH₃⁺), 4.08 (t, 1H, J=7.4 Hz, CHPh), 7.37-7.48 (m, 5H, ArH). δC (100 MHz, D₂O) 43.9 (CH₂NH₃⁺), 51.6 (CHPh), 130.9 (ArCH), 131.5 (ArCH), 132.3 (ArCH), 137.3 (ArC), 177.8 (C=O). m/z (EI) 166 (MH⁺, 30%), 118 (40), 91 (40), 30 (100).

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3-Carboxmethoxy-2-(2,4,6-trimethylphenyl)propanoic acid, 186.

To a vigorously stirred solution of the allylic decarboxylated compound 176d (754 mg, 1.96 mmol) and sodium periodate (1.72 g, 8.04 mmol) in a solvent mixture of acetonitrile (3 ml), carbon tetrachloride (3 ml) and water (4.5 ml) was added ruthenium trichloride hydrate (8.95 mg, 0.043 mmol). The reaction mixture was stirred until TLC analysis (petroleum ether/ether, 3:1; silica plates stained with bromocresol green-yellow coloration develops for carboxylic acid functionality) indicated that all of the starting material had been consumed (2 hr). The reaction mixture was diluted with dichloromethane (25 ml) and washed with H₂O (20 ml). The organic layer was collected, dried (MgSO₄), filtered and concentrated in vacuo, yielding a dark brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 1:1) gave the title compound (319 mg, 65% yield) as a pale yellow oil. (Found: M⁺, 250.1205. C₁₄H₁₈O₄ requires M⁺, 250.1205). [α]D⁺²⁰ +230.3 (c=0.35, CHCl₃). vₘₐₓ/cm⁻¹ 3250-2900 (CO₂H), 2956, 1739 (C=O ester), 1708 (C=O acid), 1167. δH (400 MHz, CDCl₃) 2.27 (s, 3H, ArCH₃), 2.31 (broad s, 6H, 2 x ArCH₃), 2.43 (dd, 1H, J=4.6, 16.7 Hz, CH₂CO₂CH₃), 3.26 (dd, 1H, J=7.8, 16.7 Hz, CHH₂CO₂CH₃), 3.68 (s, 3H, CO₂CH₃), 4.70 (dd, 1H, J=4.5, 9.2Hz, CHMes), 6.85 (s, 2H, ArH). δC (100 MHz, CDCl₃) 20.5 (ArCH₃), 20.8 (2 x ArCH₃), 34.9 (CH₂CO₂CH₃), 41.3 (CO₂CH₃), 52.0 (CHMes), 129.9 (ArCH), 129.9 (ArCH), 132.2 (ArC), 136.4 (ArC), 137.1 (ArC), 172.4 (C=O ester), 179.3 (C=O acid). m/z (EI) 250 (M⁺, 10%), 163 (40), 133 (100), 119 (37).

Methyl-N-(tert-butoxycarbonyl)-3-amino-3-(2,4,6-trimethylphenyl)propanoate, 188.

A solution of the carboxylic acid 186, (176 mg, 0.70 mmol), triethylamine (78 mg, 0.78 mmol) and diphenylphosphoryl azide (213 mg, 0.78 mmol) in tert-butyl alcohol (1.5 ml) was refluxed under nitrogen until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (16 hr). The reaction
mixture was cooled to room temperature and poured onto saturated sodium bicarbonate solution (30 ml). The resulting milky white precipitate was extracted with dichloromethane (3 x 30 ml) and the combined organic extracts washed with brine (50 ml), dried (MgSO4), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 3:1) gave the title compound (113 mg, 50% yield) as a colourless oil. (Found: M+, 321.1939. C18H27N04 requires M+, 321.1940). [α]D20 +115.0 (c=0.25, CHCl3). νmax/cm⁻¹ 3350 (NH), 3071, 1737 (C=O ester), 1711 (C=O carbamate), 1227. δH (250 MHz, CDCl3) 1.38 (s, 9H, NHC02C(CH3)3), 2.22 (broad s, 6H, 2 x ArCH3), 2.27 (s, 3H, ArCH3), 2.75 (dd, 1H, J=4.8, 16.7 Hz, CHHCO2CH3), 2.92 (dd, 1H, J=7.6, 16.7 Hz, CHHCO2CH3), 3.64 (s, 3H, CO2CH3), 4.96 (m, 1H, CHMes), 5.50 (broad s, 1H NHBoc), 6.80 (s, 2H, ArH). δC (62.5 MHz, CDCl3) 20.4 (ArCH3), 20.8 (2 x ArCH3), 28.3 (C(CH3)3), 34.9 (CH2CO2CH3), 41.0 (CO2CH3), 46.0 (CHMes), 129.0 (ArCH), 136.2 (ArC), 137.0 (ArC), 137.5 (ArC), 150.4 (C=O carbamate), 170.2 (C=O ester). m/z (El) 321 (M+, 0.6%), 233 (20), 170 (30), 94 (40), 65 (65).

N-(tert-butoxycarbonyl)-3-amino-3-(2,4,6-trimethylphenyl)propanoic acid, 188.

A solution of the tert-butoxy-amino mono-ester 187 (87 mg, 0.27 mmol) and sodium hydroxide (54 mg, 1.35 mmol) in MeOH (1 ml)/H2O (0.75 ml) was heated to reflux until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (2 hr). The reaction mixture was extracted with dichloromethane (3 x 30 ml). The organic extracts were combined, dried (MgSO4), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 1:1) gave the title compound (76 mg, 91% yield) as a colourless solid. M.p. 158-160 °C. (Found: M+, 307.1783. C17H25NO4 requires M+, 307.1784). [α]D20 +100.5 (c=0.43, CHCl3). νmax/cm⁻¹ 3300 (NH), 3300-2900 (CO2H), 2931, 1700 (C=O acid), 1690 (C=O carbamate), 1252. δH (400 MHz, CDCl3) 1.43 (s, 9H, NHCO2C(CH3)3), 2.24 (s, 3H, ArCH3), 2.34 (broad s, 6H, 2 x ArCH3), 2.65 (dd, 1H, J=5.1, 15.0 Hz, CHHCO2H), 2.92 (dd, 1H, J=10.1, 15.0 Hz, CHHCO2H), 4.39-4.45 (m, 1H, CHMes), 5.0 (broad s, 1H, NHBoc), 6.85 (s, 2H, ArH). δC (100 MHz, CDCl3) 20.5 (ArCH3), 20.8 (2 x ArCH3), 28.2 and 28.4 (C(CH3)3), 40.5 and 41.3 (CH2CO2H), 46.9 and 48.7 (CHMes), 79.6 and 81.3 (C(CH3)3), 129.9 (ArCH), 130.3 (ArCH), 136.8 (ArC), 142.8 (C=O carbamate), 170.2 (C=O ester).
137.0 (ArC), 155.8 and 157.7 (C=O carbamate), 177.3 and 178.9 (C=O acid). \( m/z \) (El) 307 (M+, 2%), 178 (55), 133 (50), 57 (100).

6.5 Chapter 5 experimental

Experimental procedures.

Dimethyl acetoxymalonate, 191b.

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{Br} \quad \text{CO}_2\text{CH}_3 & \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{OAc} \quad \text{CO}_2\text{CH}_3 \\
\end{align*}
\]

Dimethyl bromomalonate 200 (10 g, 47.39 mmol) was added to a stirred suspension of sodium acetate (7.77 g, 94.78 mmol) in DMF (15 ml) under nitrogen and the contents stirred until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (17 hr). The reaction material was diluted with dichloromethane (80 ml), washed with water (2 x 50 ml), brine (60 ml) and the organic layer dried (MgSO₄), filtered and concentrated in vacuo, yielding a yellow liquid. Purification by Kugelrohr bulb-to-bulb distillation gave the title compound (7.13 g, 79% yield) as a colourless liquid. B.p. 150 °C (10 mm Hg). (Found: M+, 190.0477. C₇H₁₀O₆ requires M+, 190.0477). \( \nu_{\text{max}}/\text{cm}^{-1} \) 2961, 1750 (C=O), 1220. \( \delta_\text{H} \) (250 MHz, CDCl₃) 2.22 (s, 3H, OCOCH₃), 3.84 (s, 6H, 2 x CO₂CH₃), 5.56 (s, 1H, CH(OAc)(CO₂CH₃)₂). \( \delta_\text{C} \) (62.5 MHz, CDCl₃) 20.2 (OOCCH₃), 53.2 (2 x CO₂CH₃), 71.4 (CH(OAc)(CO₂CH₃)₂), 164.7 (2 x C=O), 169.3 (C=O). \( m/z \) (El) 190 (M+, 0.1%), 159 (3), 148 (7), 104 (10), 43 (100).
Palladium catalysed allylic alkylation.

\[
\begin{align*}
\text{Ph} - \text{C} - \text{C} - \text{Ph} & \quad \text{Ph} - \text{C} - \text{C} - \text{Ph} \\
\text{OAc} & \quad X
\end{align*}
\]

201 (X = R' = CH₃)
202 (X = OAc, R' = CH₃)
203 (X = NHAc, R' = CH₂CH₃)

**General procedure using NaH**

1,3-Diphenylprop-2-enylacetate 145 (100 mg, 0.40 mmol), allylpalladium chloride dimer (2.5 mol%) and the relevant ligand 15 or 111b (10.0 mol%) were dissolved in THF (2 ml) and stirred under nitrogen for 15 min. The sodium salt of the relevant nucleophile 191a-c (0.39 M solution in THF) was then added and the reaction mixture stirred under nitrogen at r.t until TLC analysis (petroleum ether/ether, 3:1) indicated that all the starting material had been consumed (5 min-72 hr). The reaction mixture was quenched with a saturated solution of ammonium chloride and extracted with ether (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 5:1) gave the title compounds as described.

**Palladium catalysed allylic alkylation (general procedure using BSA)**

1,3-Diphenylprop-2-enylacetate 145 (100 mg, 0.40 mmol), allylpalladium chloride dimer (2.5 mol%) and the relevant ligand 15 or 111b (10.0 mol%) were dissolved in dichloromethane (2 ml) and stirred under nitrogen for 15 min. A solution of BSA (242 mg, 1.19 mmol), sodium acetate (2 mol%) and the relevant nucleophile 191a-c (1.19 mmol) in dichloromethane was then added and the reaction mixture stirred under nitrogen at r.t until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (2 hr-92 hr). The reaction mixture was quenched with a saturated solution of ammonium chloride (10 ml) and extracted with dichloromethane (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 5:1) gave the title compounds as described.
Dimethyl 1,3-diphenylprop-2-enyl-methylmalonate, 201. (90%) as a colourless oil. (Found: M+, 338.1518. C_{21}H_{22}O_{4} requires M+, 338.1518). [\alpha]_{D}^{20} +42.5 (c=1.196, CHCl_{3}). v_{\text{max}}/\text{cm}^{-1} 3027, 1731 (C=O), 1495, 1242. \delta_{H} (400 MHz, CDCl_{3}) 1.48 (s, 3H, CO_{2}CH_{3}), 3.62 (s, 3H, CO_{2}CH_{3}), 3.69 (s, 3H, CO_{2}CH_{3}), 4.29 (d, 1H, J=8.8 Hz, CHPh), 6.45 (d, 1H, J=15.7 Hz, PhCH=CH), 6.67 (dd, 1H, J=8.8, 15.7 Hz, PhCH=CH), 7.18-7.35 (m, 10H, ArH).

Dimethyl 1,3-diphenylprop-2-enyl-acetoxymalonate, 202. (90%) as a colourless solid. M.p. 87-89 °C. (Found: M+, 382.1349. C_{22}H_{22}O_{5} requires M+, 382.1349). [\alpha]_{D}^{20} +18.7 (c=0.6, CHCl_{3}). v_{\text{max}}/\text{cm}^{-1} 3037, 2953, 1775 (C=O), 1750 (C=O), 1252. \delta_{H} (250 MHz, CDCl_{3}) 2.19 (s, 3H, OCOCH_{3}), 3.52 (s, 3H, CO_{2}CH_{3}), 3.68 (s, 3H, CO_{2}CH_{3}), 4.24 (d, 1H, J=9.4 Hz, CHPh), 6.46 (d, 1H, J=15.8 Hz, PhCH=CH), 7.20-7.36 (m, 10H, ArH).

Diethyl 1,3-diphenylprop-2-enyl-acetamidomalonate, 203. (80%) as a colourless solid. M.p. 92-94 °C. (Found: C, 70.11; H, 6.66; N, 3.30. C_{24}H_{27}NO_{5} requires C, 70.39; H, 6.66; N, 3.30). (Found: M+, 409.1889. C_{24}H_{26}NO_{5} requires M+, 409.1811). [\alpha]_{D}^{20} +60.6 (c=0.66, CHCl_{3}). v_{\text{max}}/\text{cm}^{-1} 3398 (NH), 3057, 2984, 1739 (C=O ester), 1686 (C=O amide), 1256. \delta_{H} (400 MHz, CDCl_{3}) 1.16 (t, 3H, J=7.2 Hz, CO_{2}CH_{2}CH_{3}), 1.24 (t, 3H, J=7.2 Hz, CO_{2}CH_{2}CH_{3}), 1.97 (s, 3H, NHCOCCH_{3}), 4.01-4.15 (m, 2H, CO_{2}CH_{2}CH_{3}), 4.25-4.29 (m, 2H, CO_{2}CH_{2}CH_{3}), 4.78 (d, 1H, J=7.2 Hz, CHPh), 6.31 (d, 1H, J=15.8 Hz, PhCH=CH), 6.61 (s, 1H, NHCOCCH_{3}), 6.77 (dd, 1H, J=7.2, 15.8 Hz, PhCH=CH), 7.18-7.32 (m, 10H, ArH). \delta_{C} (100 MHz, CDCl_{3}) 12.0 (CO_{2}CH_{2}CH_{3}), 12.2 (CO_{2}CH_{2}CH_{3}), 21.2 (CHPh), 51.1 (NHCOCCH_{3}), 60.6 (CO_{2}CH_{2}CH_{3}), 60.8 (CO_{2}CH_{2}CH_{3}), 67.1 (C(NHCOCH_{3})(CO_{2}CH_{2}CH_{3})_{2}), 126.7 (ArCH), 127.5 (ArCH), 127.9 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 129.1 (ArCH), 129.8 (CH=CH), 132.7 (CH=CH), 137.9 (ArC), 138.8 (ArC), 167.5 (C=O ester), 167.8 (C=O ester), 169.3 (C=O amide). m/z (EI) 409 (M+, 3%), 350 (20), 194 (45), 115 (100).
Bulky nucleophiles in unsymmetrical systems.
Palladium catalysed allylic alkylation (general procedure using NaH)

1,3,3-Triphenylprop-2-enyl acetate 161a (100 mg, 0.304 mmol), allylpalladium chloride dimer (2.8 mg, 0.0076 mmol) and the diphenyl-phosphinoaryl oxazoline ligand 15 (11.4 mg, 0.030 mmol) were dissolved in THF (2 ml) and stirred under nitrogen for 15 min. The sodium salt of the relevant nucleophile 191a-b (0.39 M solution in THF) was then added and the reaction mixture stirred under nitrogen at r.t until TLC analysis (petroleum ether/ether, 3:1) indicated that all of the starting material had been consumed (48-72 hr). The reaction mixture was quenched with a saturated solution of ammonium chloride (10 ml) and extracted with ether (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried (MgSO₄), filtered and concentrated in vacuo, yielding a brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 5:1) gave the title compounds as described.

2-Methyl-2-carbomethoxy-3,5,5-triphenyl-4-enoate, 204. (85%) as a colourless solid. M.p. 82-84 °C. (Found: C, 78.20; H, 6.39. C₂₇H₂₆O₄ requires C, 78.26; H, 6.28). (Found: M⁺, 414. 1831. C₂₇H₂₆O₄ requires M⁺, 414.1831). [α]D²⁰ -137.3 (c=0.67, CHCl₃). v max /cm⁻¹ 3057, 2952, 1733 (C=O), 1265. δ H (400 MHz, CDCl₃) 1.44 (s, 3H, OCH₃). 3.58 (s, 3H, OCH₃). 3.63 (s, 3H, OCH₃). 4.24 (d, 1H, J=10.8 Hz, CHPh). 6.71 (d, 1H, J=10.8 Hz, CH=C(Ph)₂). 6.95-6.97 (m, 2H, ArH). 7.19-7.30 (m, 13H, ArH). δ C (100 MHz, CDCl₃) 18.8 (C(CH₃)(CO₂CH₃)₂), 49.5 (CHPh), 52.3 (CO₂CH₃), 52.4 (CO₂CH₃), 58.8 (C(CH₃)(CO₂CH₃)₂), 126.8 (ArCH), 126.9 (ArCH), 127.3 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 128.1 (ArCH), 129.8 (ArCH), 129.9 (CH=CH(Ph)₂), 139.5 (Ph)₂C=CH), 140.4 (ArC), 142.8 (ArC), 143.8 (ArC), 171.2 (C=O), 171.5 (C=O). m/z (EI) 414 (M⁺, 5%), 269 (100), 191 (77).

2-Acetoxy-2-carbomethoxy-3,5,5-triphenyl-4-enoate, 205. (80%) as a colourless solid. M.p. 90-92 °C. (Found: C, 72.84; H, 5.61. C₂₈H₂₆O₆ requires C, 73.00; H, 5.71). (Found: M⁺, 458.1729. C₂₈H₂₆O₆ requires M⁺, 458.1729). [α]D²⁰ -145.7 (c=1.7,
2-Phenyl-3-methyl-(3-carbomethoxy)-methyl-butanoic acid, 206.

To a vigorously stirred solution of the allylic alkylated compound 204 (100 mg, 0.24 mmol) and periodic acid (225 mg, 0.99 mmol) in a solvent mixture of acetonitrile (0.6 ml), carbon tetrachloride (0.6 ml) and water (0.9 ml) was added ruthenium trichloride hydrate (1.1 mg, 0.0053 mmol). The reaction mixture was stirred until TLC analysis (petroleum ether/ether, 3:1; silica plates stained with bromocresol green-yellow coloration develops for carboxylic acid functionality) indicated that all the starting material had been consumed (16 hr). The reaction mixture was diluted with dichloromethane (10 ml) and washed with H2O (10 ml). The organic layer was collected, dried (MgSO4), filtered and concentrated in vacuo, yielding a dark brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ether, 1:1) gave the title compound (27 mg, 40% yield) as a colourless solid. M.p. 114-116 °C. (Found: C, 59.63; H, 5.49. C14H16O6 requires C, 59.99; H, 5.75). (Found: M+ 280.0946. C14H16O6 requires M+, 280.0946). [α]D20 +381.3 (c=0.45, CHCl3). vmax/cm⁻¹ 3500-3000 (CO2H), 3020, 1735 (C=O ester), 1700 (C=O acid), 1216. δH (400 MHz, CDCl3) 1.54 (s, 3H, C(CH3)(CO2CH3)), 3.68 (s, 3H, CO2CH3), 3.78 (s, 3H, CO2CH3), 4.63 (s, 1H, CHPh), 7.21-7.32 (m, 5H, ArH), 9.0-10.0 (broad s, 1H, CO2H). δC (100 MHz, CDCl3) 16.8 (CH3), 52.9 (CO2CH3), 53.0 (CO2CH3), 54.4 (CHPh), 57.6 (CH(CH3)(CO2CH3)), 128.3 (ArCH), 128.5 (ArCH), 129.8 (ArCH), 133.4 (ArC), 170.6 (C=O ester), 171.3 (C=O ester), 176.7 (C=O acid). m/z (El) 281 (MH+, 13%), 263 (20), 236 (28), 176 (100), 116 (60).
2-Methyl-3,5,5-triphenylpent-4-enoate, 212.

A degassed solution of the alkylated product 204 (1.3 g, 3.14 mmol), NaCl (477 mg, 8.15 mmol) and H₂O (0.158 ml, 8.78 mmol) in DMSO (5 ml) was heated in a sealed tube at 180 °C for 6 hr. After cooling to room temperature the mixture was diluted with dichloromethane (60 ml) and brine (100 ml) added and then extracted followed by two further extractions with dichloromethane (50 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 6:1) gave the title compound (663 mg, 60% yield) (a mixture of two diastereoisomers) as a colourless solid. M.p. 62-64 °C. (Found: M⁺, 356.1776. C₂₅H₂₄O₂ requires M⁺, 356.1776). [α]D²⁰ -176.0 (c=0.4, CHCl₃). ν max/cm⁻¹ 3026, 2946, 1736 (C=O), 1165. δH (400 MHz, CDCl₃) (Major diastereoisomer) 0.89 (d, 3H, J=6.9 Hz, CH(CH₃)CO₂CH₃), 2.83-2.89 (m, 1H, CH(CH₃)CO₂CH₃), 3.51 (ap. t, 1H, J=10.3 Hz, CHPh), 3.61 (s, 3H, CO₂CH₃), 6.35 (d, 1H, J=10.7 Hz, CH=CH Ph), 7.04-7.35 (m, 15H, ArH). (Minor diastereoisomer) 1.20 (d, 3H, J=6.9 Hz, CH(CH₃)CO₂CH₃), 2.83-2.89 (m, 1H, CH(CH₃)CO₂CH₃), 3.34 (ap. t, 1H, J=10.3 Hz, CHPh), 3.68 (s, 3H, CO₂CH₃), 6.24 (d, 1H, J=10.7 Hz, CH=CH Ph), 7.04-7.35 (m, 15H, ArH). δC (100 MHz, CDCl₃) (Major diastereoisomer) 15.8 (CH(CH₃)CO₂CH₃), 47.2 (CH(CH₃)CO₂CH₃), 49.6 (CO₂CH₃), 51.9 (CHPh), 126.9 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 127.9 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 128.5 (ArCH), 129.1 (ArCH), 130.2 (ArCH), 130.3 (CH=CH Ph), 140.1 (CH₂=CH), 142.8 (ArC), 142.9 (ArC), 143.8 (ArC), 175.7 (C=O). (Minor diastereoisomer) 15.6 (CH(CH₃)CO₂CH₃), 46.8 (CH(CH₃)CO₂CH₃), 48.8 (CO₂CH₃), 51.7 (CHPh), 126.8 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.4 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 128.9 (ArCH), 129.4 (ArCH), 130.3 (CH=CH Ph), 140.1 (CH₂=CH), 142.8 (ArC), 142.9 (ArC), 143.8 (ArC), 175.7 (C=O). m/z (EI) 356 (M⁺, 5%), 269 (100), 191 (60).
4-Methoxy-3-methyl-2-phenylbutanoic acid, 213.

To a vigorously stirred solution of the allylic decarboxylated compound 212 (190 mg, 0.53 mmol) and sodium periodate (467 mg, 2.19 mmol) in a solvent mixture of acetonitrile (1.5 ml), carbon tetrachloride (1.5 ml) and water (2.25 ml) was added ruthenium trichloride hydrate (2.4 mg, 0.012 mmol). The reaction mixture was stirred until TLC analysis (petroleum ether/ether, 3:1; silica plates stained with bromocresol green-yellow colouration develops for carboxylic acid functionality) indicated that all of the starting material had been consumed (2 hr). The reaction mixture was diluted with dichloromethane (20 ml) and washed with H₂O (20 ml). The organic layer was collected, dried (MgSO₄), filtered and concentrated in vacuo, yielding a dark brown oil. Purification by "flash" column chromatography (eluant, petroleum ether/ethyl acetate, 1:1) gave the title compound (84 mg, 71% yield) (a mixture of two diastereoisomers) as a colourless solid. M.p. 54-56 °C. (Found: M⁺, 222.0892. C₁₂H₁₄O₄ requires M⁺, 222.0892). [α]₀⁺²⁰ +85.3 (c=1.47, CHCl₃). νmax/cm⁻¹ 3500-2800 (CO₂H), 2955, 1732 (C=O ester), 1698 (C=O acid), 1291. δH (400 MHz, CDCl₃) (Major diastereoisomer) 1.36 (d, 3H, /=6.8 Hz, CH(CH₃)CO₂CH₃), 3.25-3.30 (m, 1H, CH(CH₃)CO₂CH₃), 3.46 (s, 3H, CO₂CH₃), 3.86 (d, 1H, /=8.2 Hz, CHPh), 7.29-7.39 (m, 5H, ArH), 9.0-10.0 (broad s, 1H, CO₂H). (Minor diastereoisomer) 1.00 (d, 3H, /=6.8 Hz, CH(CH₃)CO₂CH₃), 3.16-3.21 (m, 1H, CH(CH₃)CO₂CH₃), 3.76 (s, 3H, CO₂CH₃), 3.83 (d, 1H, /=8.2 Hz, CHPh), 7.29-7.39 (m, 5H, ArH), 9.0-10.0 (broad s, 1H, CO₂H). δC (100 MHz, CDCl₃) (Major diastereoisomer) 16.8 (CH(CH₃)CO₂CH₃), 43.7 (CH(CH₃)CO₂CH₃), 52.0 (CO₂CH₃), 55.2 (CHPh), 128.3 (ArCH), 128.8 (ArCH), 128.9 (ArCH), 136.6 (ArC), 174.8 (C=O ester), 178.3 (C=O acid). (Minor diastereoisomer) 15.7 (CH(CH₃)CO₂CH₃), 42.4 (CH(CH₃)CO₂CH₃), 52.5 (CO₂CH₃), 54.5 (CHPh), 128.4 (ArCH), 128.8 (ArCH), 129.0 (ArCH), 136.1 (ArC), 176.4 (C=O ester), 178.3 (C=O acid). m/z (EI) 222 (M⁺, 1.5%), 204 (45), 176 (45), 118 (100), 91 (95).
Reprotonation experiments.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{H} \\
\text{H}_3\text{CO}_2\text{C} & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{H} \\
\text{H}_3\text{CO}_2\text{C} & \quad \text{CH}_3
\end{align*}
\]

A solution of the allylic decarboxylated compound 212 (80 mg, 0.22 mmol) in THF (1 ml) was added, under nitrogen to a pre-prepared solution of LDA (0.25M solution in THF) at -78 °C. The resulting yellow solution was stirred at -78 °C for 1.5 hr before the addition of the appropriate quench (1 mmol) (H2O/MeOH or 2,6-di-tert-butyl-4-methylphenol) at -78 °C. On complete addition of the quench the reaction material was allowed to warm to r.t. and stirred under nitrogen for 16 hr. The resulting colourless solution was diluted with ether (15 ml) and washed with saturated ammonium chloride solution (15 ml). The ether layer was dried (MgSO4), filtered and concentrated in vacuo. (Neither the water or methanol quench required further purification.) Purification by "flash" column chromatography (eluant, petroleum ether/ether, 5:1) gave the title compound (79 mg, 99% yield) as a colourless solid. All data was consistent with that already described for (2-methyl-3,5,5-triphenylpent-4-enoate, 212).
REFERENCES
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### EXPERIMENTAL DETAILS

#### A. Crystal Data

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#### B. Intensity Measurements

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#### C. Structure Solution and Refinement

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| p-value                        | 0.001          |
| Anomalous Dispersion            | All non-hydrogen atoms |
| No. Observations (1>3σ(i,i))    | 1414           |
| No. Variables                   | 229            |
| R/factor                       | 0.57           |
| R-factor                       | 0.33 (R-factor) |
| Goodness of Fit Indicator       | 0.36           |
| Max. Shift/Cycle in Final Cycle| 0.62           |
| Maximum peak in Final Diff. Map | 0.59 σ<sub>i</sub> / λ<sup>2</sup> |
| Maximum peak in Final Diff. Map | -0.18 σ<sub>i</sub> / λ<sup>2</sup> |

#### Table 1:Atomic coordinates and β<sub>Uαα</sub>/β<sub>Uαα</sub>

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\[ R_{1s} = \frac{1}{2} (U_{1s} (eV) + U_{2s} (eV) + U_{3s} (eV) + 20/\mu^2 \mu M) \cos \gamma + 20/\mu^2 \mu M \cos \theta + 20/\mu^2 \mu M \cos \phi) \]

Table 2: Bond Lengths (\( \mu m \))

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Table 3: Bond Angles (\( \mu m \))

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Table 4: Bond Angles (\( \mu m \))

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<td>C(16)</td>
<td>1.35(13)</td>
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EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula
C_{11}H_{14}O_{5}

Formula Weight
391.48

Crystal Color, Habit
clear, block

Crystal Dimensions
0.20 x 0.30 x 0.61 mm

Crystal System
monoclinic

Lattice Type
C-centered

No. of Reflections Used for Unit Cell Determination (2θ range)
23 (24.3 - 72.0°)

Omega Scan Peak Width
0.01°

Lattice Parameters
a = 27.98(1) Å
b = 7.90(2) Å
0 = 92.40(2)°

Space Group
C2 (No. 4)

V = 2842.0(8) Å³

Z value
2

D, (CuKα)
1.274 g/cm³

B. Intensity Measurements

Diffractometer
Rigaku AFC7S

Table 1. Atomic coordinates and Biso/Bmax

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<th>z</th>
<th>Biso (Å²)</th>
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C. Structure Solution and Refinement

Structure Solution
Direct Methods (SIR92)

Refinement
Full-matrix least-squares

Function Minimized
Residuals

Least-Square Weights
p-factor

Anomalous Dispersion
All non-hydrogen atoms

No. Observations
1610

No. Variables
234

Reflections/Parameter Ratio

Residuals: R, Rw

Goodness of Fit Indicator

Max. Shift/Error in Final Cycle
0.12

Maximum peak in Final Diff. Map

Maximum peak in Final Diff. Map

-0.23 e/Å³
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<tr>
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<th>Uiso</th>
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<td>H(4)</td>
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Table 2: Bond Length (Å)

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</table>

**Table 1:** Atomic coordinates and Uiso values (continued)

**Table 2:** Bond Distance (Å)

**Table 3:** Bond Distance (Å)
EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula: Cu₅P₂O₁₀

Formula Weight: 537.46

Crystal Color, Habit: clear, block

Crystal Dimensions: 0.23 x 0.21 x 0.43 mm

Crystal System: orthorhombic

Lattice Type: Primitive

No. of Reflections Used for Unit Cell Determination (0-20 angle): 55 (73.3 - 74.9°)

Omega Scan Peak Width at Half-height: 0.21°

Lattice Parameters:

\[ a = 18.281(1) \, \text{Å} \]
\[ b = 21.549(1) \, \text{Å} \]
\[ c = 2.2696(6) \, \text{Å} \]

\[ V = 2056(1) \, \text{Å}³ \]

Space Group: P2₁/a (No. 14)

Z value: 4

\[ \rho_{o} = 1.339 \, \text{g/cm³} \]

\[ Fobs = 778.66 \]

\[ \mu(\text{CuKα}) = 5.35 \text{mm}^{-1} \]

B. Intensity Measurements

Radiation: CuKα (λ = 1.54178 Å)

Detector Aperature: 20° (at 0.37 Å)

No. of Variables: 177

No. of Reflections: (190999)

Reflections/Parameter Ratio: 1.36

Reflections per Parameter: 1.3587 × 10⁻³

Decay: 0.44 °/min

C. Structure Solution and Refinement

Structure Solution: Direct Methods (SIR92)

Refinement: Full-matrix least-squares


Table 1. Atomic coordinates and \( \beta_{	ext{iso}}/\beta_{	ext{eq}} \)

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<thead>
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<th>z</th>
<th>( \beta_{	ext{iso}}/\beta_{	ext{eq}} )</th>
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Table 1. Atomic coordinates and $R_{int} / R_{exp}$ (continued)

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<th>z</th>
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<th>atom</th>
<th>x</th>
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<td>0.0500</td>
<td>13.91(6)</td>
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<td>C(5b)</td>
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<td>0.2194</td>
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<tr>
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Table 2. Bond lengths (Å)

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<td>1.516(4)</td>
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<td>1.372(5)</td>
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EXPERIMENTAL DETAILS

A. Crystal Data

<table>
<thead>
<tr>
<th>Empirical Formula</th>
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<td>Crystal Color, Habit</td>
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</tr>
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<td>Crystal Dimensions</td>
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</tr>
<tr>
<td>Crystal System</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>orthorhombic</td>
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<tr>
<td>No. of Reflections Used for Unit Cell Determination (19 range)</td>
<td>75 (358.0 - 14.0°)</td>
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Omega Scan Peak Width:

at Half Height: 0.2°

Lattice Parameters:
s = 22.359(4) Å
b = 11.408(3) Å
c = 11.105(3) Å
β = 96.76(2)°

V = 2886(1) Å³

Space Group: C2/c (15)

Z Value: 8

Density: 1.239 g/cm³

Fmax: 1648.00

µ(CaO4): 0.22 cm⁻¹

B. Intensity Measurements

Table 1. Atomic coordinates and Biso/σ

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<td>Cr(3)</td>
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<td>-0.043(3)</td>
<td>-0.653(7)</td>
<td>2.1(7)</td>
</tr>
</tbody>
</table>

C. Structure Solution and Refinement

Data Collection (LaO4)

Monochromated Ni-filtered CuKα radiation (λ = 1.5418 Å)

1.8°<2θ<25.0°

Twinning

Refinement

Structure Solution

Direct Methods (SIR92)

Reflections

Full-matrix least-squares

Frac. Minimized

Least Squares Weights

Determination

p-factor

Anomalous Dispersion

All non-hydrogen atoms

No. Observations (I>2σ(I))

1566

Refinement Variables

277

Reflection/Parameter Ratio

2.20

Independent R; Rw

0.067; 0.048

Goodness of Fit Indicator

1.10

Max. Shift/error in final cycle

0.011

R-index/σ (max)

0.22 r.Å²

Min. peak in final difference map

0.20 r.Å²

Decay (1.5% decline)

Secondary Extinction

0.4653_1.0000

SIR92

0.0000

Cryst. Structure

CaLaO4 (1.5418 Å)
Table 1. Atomic coordinates and B_{eq}/B_{eq} (continued)

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... (continued)

Table 2. Bond Lengths (Å)

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Table 4. Bond Lengths (Å)

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EXPERIMENTAL DETAILS

A. Crystal Data

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<td>Lattice Type</td>
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| No. of Reflections Used for Unit Cell Determination (19 range) | 25 (75.6 - 14.6°) |
| Omega Scan Peak Width at Half-Height | 0.75° |

Lattice Parameters

V = 7205.5(5) Å³

Space Group P2₁/a (No. 14)

Z value 4

D₀ = 1.015 g/cm³

Fₘₐₓ = 800.00

μ(CuKα) = 0.47 cm⁻¹

B. Intensity Measurements

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C. Structure Solution and Refinement

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Table 1: Atomic coordinates and Bₘₐₓ/θ₂

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### Table 1: Atomic coordinates and B_{<>/B_{</>} (continued)

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### Table 2: Bond Lengths (Å)

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