Novel enantiopure ligands for asymmetric catalysis

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Novel Enantiopure Ligands For Asymmetric Catalysis

by

Christopher Gregory Frost

A Doctoral Thesis

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

September 1994

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Abstract

The scope of the palladium catalysed allylic substitution reaction is reviewed with particular reference to stereocontrol. The use of enantiopure oxazolines and acetals in asymmetric synthesis is briefly outlined.

The work presented is concerned with the design and construction of enantiopure ligands which are able to impart very high levels of enantioselectivity in the aforementioned palladium catalysed allylic substitution reaction. The ligands exploit the stereochemistry-controlling properties of the oxazoline moiety, whilst incorporating a secondary donor atom. The ligands rely upon an electronic disparity between these two atoms to direct nucleophilic addition.

The performance of the ligands was examined in the reaction of racemic 1,3-diphenyl-3-acetoxy-1-propene with the sodium salt of dimethyl malonate. The yield and enantioselectivity of the process varied depending upon which ligand was employed in the process. By increasing the \( \pi \)-accepting ability of the auxiliary donor, the enantioselectivity of nucleophilic addition is observed to increase.

It was discovered that enantiopure phosphine containing oxazolines were the most effective ligands, the substitution product being obtained in quantitative yield with very high enantioselectivity (>95% ee) and short reaction times. The origin of enantioselectivity using the enantiopure oxazoline ligands is discussed.

The use of enantiopure acetals as ligands examined the incorporation of other heteroatoms into the design of the ligand, whilst generating a similar topology. Again, the enantioselectivity was found to be highly dependent upon the nature of the auxiliary ligand.
friendship, especially Dr. Joshua Howarth, Mark Elliott, Carrie Harrison, Leigh Ferris, Claire Norton and the Williams' group (Jo, Craig, Graham, Roshan, Justin, Chris and Andy). I am further indebted to Dr. Andy Westwell and Jo Allen for the thorough proof reading of this manuscript.

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To my parents and family, I will be eternally grateful for their support and encouragement without which I would not be in the position I am today. I reserve the deepest and most sincere words of gratitude for Mandy, my wife. For her unfailing love and support I dedicate this work.

Christopher Gregory Frost
Loughborough
September 1994
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<td>nBuLi</td>
<td>$n$-Butyllithium</td>
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<tr>
<td>tBu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>BSA</td>
<td>N,O-bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>cat</td>
<td>Catalytic</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
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<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>de</td>
<td>Diastereomeric excess</td>
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<td>DMAP</td>
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<td>Pr</td>
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<td>py</td>
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<td>Tetrahydrofuran</td>
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<td>TLC</td>
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<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethlenediamine</td>
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Chapter One

Scope Of Palladium Catalysed Allylic Substitution
1.1 Introduction

Transition metal based catalysts have found widespread use in many synthetically useful processes, frequently achieving high levels of chemo- and stereoselectivity.\(^1\) Palladium catalysed reactions are of particular importance both in the laboratory and on an industrial scale. Examples of these include Stille couplings\(^2\), Heck reactions\(^3\), Wacker oxidation\(^4\) and allylic substitution reactions\(^5\).

The palladium catalysed nucleophilic substitution of allylic compounds is an established, efficient and reliable process, and has become an important tool for the synthetic organic chemist. The first \(\eta^3\)-allylpalladium complexes were isolated and characterised by Shaw over 30 years ago, synthesised by the reaction of dienes with palladium(II) salts.\(^6\) In 1965, Tsuji et al.\(^7\) reported on the stoichiometric reaction of \(\pi\)-allylpalladium complexes with nucleophiles, effecting an overall allylic substitution. Later, in the early 1970's the groups of Walker\(^8\) and Hata\(^9\) discovered that the allylic displacement of acetate with a variety of nucleophiles required only a catalytic amount of palladium. These findings opened the door to a vast area of further studies and applications. Since the mid-1970's the palladium catalysed allylic substitution reaction has evolved into a very mild, efficient process illustrated by the reaction of allyl acetate 1 with the sodium salt of dimethyl malonate in the presence of catalytic amounts of triphenylphosphine and palladium(0).\(^10\) Such reactions are typically conducted in a polar solvent such as THF to afford the substitution product 2 in good yield and with a high number of turnovers (Scheme 1).

\[
\begin{align*}
\text{OAc} \quad & \quad \text{cat. Pd(0) / PPh}_3 \quad \text{NaCH(CO}_2\text{Me})_2 \\
1 \quad & \quad \text{THF / reflux} \\
\quad & \quad \text{2}
\end{align*}
\]

Scheme 1
1.2 Mechanism of palladium catalysed allylic substitution

The generally accepted mechanism of palladium catalysed substitution involves the initial co-ordination of palladium(0) to the alkene followed by oxidative addition to afford an intermediate $\eta^3$-allyl complex. In the presence of triphenylphosphine, or other $\pi$-accepting ligands, an equilibrium between a neutral and cationic complex results. The use of bidentate ligands favours formation of the cationic complex. Nucleophilic addition to the cationic complex is favoured, and occurs at one of the allylic termini to furnish the palladium(0) complex of the product. Dissociation of the palladium(0) catalyst liberates the product, and regenerates the active palladium catalyst, as shown in Scheme 2.11

![Scheme 2](image)

For a mono-substituted allyl complex, there are two geometrical isomers which may be adopted, the syn isomer 3, and the anti isomer 4. The preferred geometry is syn, 3 for obvious steric reasons. Likewise the disubstituted allyl complexes favour the syn, syn geometry 5.
For more highly substituted allyl complexes, a similar geometrical preference based on the steric requirements of the substituents involved occurs. The isomeric forms are able to equilibrate by a π-σ-π mechanism, and when one terminus of the allyl unit contains two identical groups, this process can occur rapidly. The enantiomeric forms of such a complex are in equilibrium as demonstrated in Scheme 3. The importance of enantioface inversion is that the stereochemistry of the starting substrate is lost during the isomisation process and enantioselection is then determined by the stereochemistry of the palladium complex intermediate, since there is no memory of the original stereochemistry provided by the starting material.

Scheme 3
1.3 Range of substrates and nucleophiles

Whilst allylic acetates remain the most frequently employed substrates for palladium catalysed allylic substitution, a range of other leaving groups will also function perfectly well. These include halides, sulfones, carbonates, epoxides and phosphates. Tsuji and Minami applied the carbonate class of leaving group in 1985. In this process palladium(0) initially co-ordinates to the allylic substrate displacing the carbonate group which loses carbon dioxide generating an alkoxide. The alkoxide is sufficiently basic to deprotonate many of the nucleophile precursors employed in these reactions. The mechanism is outlined in Scheme 4.

\[
\text{Scheme 4}
\]

For the allylic substrate containing both carbonate and acetate functionalities, the carbonate functions as a better leaving group than the acetate, thereby affording the substitution product in good yield (Scheme 5).

\[
\text{Scheme 5}
\]
Although related derivatives of allylic alcohols have frequently been used as substrates, the parent alcohols themselves are generally much less reactive. This apparently stems from the poor capability of a non-activated hydroxyl to serve as a leaving group. Recently Kocovsky et al have developed a method which allows palladium catalysed allylic substitution to occur between allylic alcohols and anionic carbon nucleophiles. The alkoxide is first generated from 9 by means of n-butyllithium in THF and then converted in situ into an activated intermediate 10 by adding triphenylboron. Addition of palladium(0) generates the $\eta^3$-complex 11, nucleophilic addition to which rapidly occurs, as shown in Scheme 6.

The nucleophiles which are most commonly employed for the palladium catalysed allylic substitution reaction are the 'soft' stabilised carbanions such as dimethyl malonate, but under suitable conditions, a variety of other nucleophiles have been used including nitrogen based nucleophiles, sulfur nucleophiles, oxygen nucleophiles, phosphorus nucleophiles, silicon nucleophiles, vinyl boranes, hydrides, tetraphenylborate and organometallics. In the presence of carbon monoxide and suitable nucleophiles, carbonylation reactions have also been achieved, as shown in Scheme 7.

\[ \text{Scheme 6} \]

\[ \text{Scheme 7} \]
1.4 Mechanistic aspects of stereochemistry

As with a number of transition-metal catalysed reactions, palladium catalysed allylic substitution is known to occur via a stepwise process. Two important steps have been identified:

1. The reaction of the palladium catalyst with the substrate to produce the π-allyl intermediate.
2. The displacement of the palladium by a nucleophile to give the product via an intermediate olefin complex.

In the absence of isomerisation processes, the overall stereochemistry of the reaction will be dependent upon the stereochemistry of the individual steps. Trost et al. investigated the stereochemistry of alkylation reactions using substituted cyclic substrates, and soft nucleophiles, which gave rise to diastereomeric products. Reaction of the cis-substituted compound 12 affords the cis-substituted product 14, whereas the trans-substituted compound 13 affords the trans-substituted product 15 (Scheme 8).
Net retention of configuration was demonstrated to be the result of two steps that proceed with inversion of configuration. The palladium displaces the leaving group with inversion, followed by nucleophilic attack from the exo face, again with inversion, as shown in Scheme 9.

In contrast, it was discovered that many nucleophiles do not afford retention of stereochemistry. For example, Trost et al demonstrated that the nucleophile Bu₃SnAlEt₂ furnishes the allylstannane 16 with clean inversion, and Keinan et al have shown on the same system that sodium borodeuteride also affords inversion of stereochemistry, to afford 17 (Scheme 10). Likewise, Negishi et al have shown that other hard nucleophiles undergo the reaction with overall...
inversion\textsuperscript{34} This can be rationalised by assuming the hard nucleophile first attacks the metal centre and then migrates to the allyl ligand\textsuperscript{35}

\[
\text{CO}_2\text{Me} \quad \xrightarrow{\text{Bu}_3\text{SnAlEt}_2} \quad \text{cat.}(\text{Ph}_3\text{P})_4\text{Pd} / \text{Ph}_3\text{P} \quad \text{CO}_2\text{Me}
\]

\[
\text{OAc} \quad \xrightarrow{\text{NaBD}_4} \quad \text{cat.}(\text{Ph}_3\text{P})_4\text{Pd} / \text{Ph}_3\text{P} \quad \text{D}
\]

\textbf{Scheme 10}

A classification of nucleophiles exists based on their ability to substitute sterically hindered allylic acetates,\textsuperscript{36} In such cases, only nucleophiles which attack via prior co-ordination to the metal are effective, since nucleophiles are sterically blocked from approaching the complex from the exo face. As a rough guide, nucleophiles with a pKa > 20 attack via the metal, whereas nucleophiles with a pKa < 20 attack the allyl ligand directly.

\subsection{1.5 Enantiocontrol of reactions}

\textit{(i) Background}

In 1973, Trost and Dietsche showed that the stoichiometric reaction of palladium chloride dimer 18 with NaCH(CO$_2$Me)$_2$ and enantiopure phosphate ligands, such as (+)-DIOP afforded the substitution product 19, achieving an enantiomeric excess of up to 23\% (\textbf{Scheme 11})\textsuperscript{37}
Scheme 11

The first reported example of a catalytic, asymmetric palladium catalysed allylic substitution reaction was the conversion of racemic allyl acetate 20 to the enantiomerically enriched product 21, however only a modest enantioselectivity of up to 46% ee was achieved (Scheme 12)

Scheme 12

(ii) Asymmetric induction via secondary interactions

Most of the reported asymmetric palladium catalysed allylic substitution processes\textsuperscript{38} start from a racemic allylic component 22, which in the absence of enantiopure ligands, forms an intermediate \emph{meso} complex 23 with palladium(0). Since a nucleophile may attack at either terminus of the allylic component, the enantiomers 24 and 25 are formed (Scheme 13) The degree of the enantioselectivity of a reaction depends on the ability of the enantiopure ligand to promote attack of the nucleophile to one terminus of the allylic component in preference to the other
The problem of achieving high levels of asymmetric induction results from the fact that a soft nucleophile attacks complex 23 from the opposite side to the ligand, and as a result, the distance between the reaction centre and the chirality-controlling centre is large. On the basis of this mechanism Hayashi et al. designed ligands to interact with the reacting substrates by means of secondary interactions between functional groups on the enantiopure ligands and substrates.

Phosphine ligands 26 and 27 were examined for stereoselectivity in the palladium catalysed reaction of sodium enolate of 2-acetylcyclohexanone 28 with allyl acetate. The reaction with 26a at −50°C gives the alkylation product 29 in the highest enantiomeric excess of 52% ee for the cases tested (Scheme 14).
The enantioselectivities are remarkable in view of how remote the existing stereocentre is from the newly created stereocentre.

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

\[
\begin{array}{c}
\text{28} \\
Pd(0) \text{ L* NaH}
\end{array}
\]

\[
\text{O} \\
\text{O} \\
\text{29}
\]

Scheme 14

The co-ordinative interaction between the enantiopure functional groups and the sodium enolate has been proposed for the origin of the observed stereoselectivity as illustrated in Figure 1. The low selectivity (15% ee) with 27c which has 1-phenylethyl as the chirality controlling group supports the proposed chelation. The importance of linker chain length is shown by lower selectivity of 27a compared with 26a.

Chirotopic group

\[
\begin{array}{c}
Z^* \\
\text{Na}^+ \\
\text{Pd} \\
\text{P}
\end{array}
\]

Co-ordinative interaction

\[
\begin{array}{c}
\text{Nuc}^-
\end{array}
\]

Figure 1

Hayashi et al. have also devised a family of enantiopure ligands 30-32 with similar side chain modifications, prepared from (R)-1-[(S)-1, 2-bis(diphenylphosphino)ferrocenyl]ethyl acetate. In a similar fashion to above, ligands 30-32 were used in the same palladium catalysed allylic alkylation. The palladium catalyst bearing ferrocenylphosphine 32 which contains one hydroxyl group on the terminal.
position of the pendant chain, is the most catalytically active and stereoselective, giving the alkylation product 29 in 73% yield and in 81% ee at -60°C.

![Chemical structure](image)

It is noteworthy that the catalysts that show the highest levels of stereoselectivity are more catalytically active in general. Hayashi has proposed that a secondary interaction between the enantiopure ferrocenylphosphine ligands and the nucleophile accelerates the alkylation by drawing the nucleophile up to the π-allyl complex. In this case, hydrogen bonding between the hydroxyl group and enolate anion is more probably the secondary interaction involved, rather than coordination to the sodium of the enolate. The evidence for this lies in the fact that replacement of the terminal hydroxyl group with an amino or a methoxy group resulted in the formation of alkylation product with opposite configuration and low enantioselectivity.

A further series of enantiopure ferrocenylphosphine ligands have been recently developed by Ito et al. The incorporation of monoaza or diaza crown ethers of varying ring sizes and linker chain lengths furnishes ligands 33a-c and 34. These ligands were designed to interact with the nucleophile through formation of an inclusion complex with the crown ether.42
The crown ether modified ligands were examined for enantioselectivity and catalytic activity in the asymmetric alkylation of 28 using potassium fluoride as a base with mesitylene as solvent. As expected from the complementarity between hole size of crown ether and ionic radius of a guest cation, ligand 33b with monoaza-18-crown-6 moiety significantly accelerates the alkylation with increased enantioselectivity (60% ee) compared with the ferrocenylphosphine ligand lacking the crown ether moiety (22% ee). Ligands 33a and 33c were found to retard the reaction, giving the alkylation product in low yield with reduced enantioselectivity. The highest enantioselectivity of 75% was obtained at -40°C with 34.

Interestingly, the sense of asymmetric induction achieved by use of the crown ether modified ligands is always opposite to that of Hayashi's hydroxylated ligand 32. This is deemed to originate from the fact that rather than directing nucleophilic attack through non-covalent bonding the sterically bulky crown ether moiety blocks the approach of the enolate to one terminus of the π-allyl moiety, providing a chiral pocket for nucleophilic attack at the other.
The enantiopure hydroxylated ferrocenylphosphines 30-32 previously applied to the asymmetric allylation of β-diketones have also been used to attain asymmetric induction at symmetrically substituted allylic substrates. Hayashi et al. have achieved extremely high enantioselectivities in the palladium catalysed allylic alkylation of 1,3-disubstituted allylic acetates with sodium acetylacetonate and related stabilised carbon nucleophiles (Scheme 15). The enantioselectivity in the reaction of 1,3-diphenyl-3-acetoxy-1-propene 35 with sodium acetylacetonate increases as the number of hydroxyl groups on the pendant side of the enantiopure ligand increases.

\[
\begin{array}{c}
\text{OAc} \\
\text{Ph} \\
\text{CH} \text{(COMe)}_2 \\
\text{NaCH(COMe)}_2 \\
\text{THF} / 40^\circ C \\
\text{[(π-allyl)PdCl]_2} \\
\text{CH(COMe)}_2 \\
\text{Ph} \\
\text{Ph} \\
\text{35}
\end{array}
\]

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<td>NMe</td>
<td>OH</td>
<td>OH</td>
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<td>31</td>
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<td>90% ee</td>
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<td>32</td>
<td>NMe</td>
<td>OH</td>
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<td>86% ee</td>
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Scheme 15

The X-ray crystal structure of the π-allylpalladium complex bearing hydroxylated ligand 32 has been published. The pendant hydroxyl group is shown to reach over to the exo face of the π-allyl group and is located in close proximity to one of the π-allyl carbon atoms. Hayashi proposes a hypothetical transition state model where hydrogen bonding between the hydroxyl group and enolate anion causes preferential attack of the enolate to one terminus of the π-allyl moiety, as illustrated in Figure 2.
Palladium catalysed allylic amination with benzylamine or its derivatives occurs with increased stereoselectivity compared to allylic alkylation using dihydroxylated ligand 31 as shown in Scheme 16.\(^{45}\)

\[
\begin{align*}
\text{R} \quad \text{X} & \quad \text{Pd(0) / 31} & \quad \text{THF 40°C} \\
\text{R=Ph} & \quad \text{X=OCO₂Et} & \quad 96\% \, \text{ee} \\
\text{R=Me} & \quad \text{X=OPOPh₂} & \quad 73\% \, \text{ee} \\
\text{R=iPr} & \quad \text{X=OCO₂Et} & \quad 96\% \, \text{ee}
\end{align*}
\]

Scheme 16

\(^{31}\text{P} NMR of a π-allyl complex bearing 1,3-diphenyl π-allyl group and enantiopure ligand 31 indicates that the complex exists as an equilibrium mixture of two isomeric forms in a ratio of 20:1, which are tentatively assigned to 'W' form and 'M' form, respectively, as shown in Figure 3. An addition of an excess of benzylamine to the equilibrium mixture gave allylic amine product in up to 96% ee.
On the other hand a 2:1 equilibrating mixture of 1,3-diphenyl π-allylpalladium complex bearing an enantiopure ferrocenylphosphine ligand lacking the hydroxyl pendant, gave the amination product of lower enantiomeric purity (62% ee) on treatment with an excess of benzylamine.

Minami et al have synthesized a series of enantiopure monodentate phosphine ligands, which have a carboxylic acid functionality and a cyclobutane or cyclopentane backbone 36 and 37.
The ligands have been applied successfully to the asymmetric alkylation of 1,3-diphenyl-3-acetoxy-1-propene 35 with triethyl sodiophosphonoacetate 39 and dimethyl malonate (Table 1).  

Table 1

<table>
<thead>
<tr>
<th>Nuc</th>
<th>Ligand</th>
<th>% ee</th>
<th>Nuc</th>
<th>Ligand</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>36a</td>
<td>79</td>
<td>CH$_2$(CO$_2$Me)$_2$</td>
<td>36b</td>
<td>85</td>
</tr>
<tr>
<td>39</td>
<td>36b</td>
<td>83</td>
<td>CH$_2$(CO$_2$Me)$_2$</td>
<td>37a</td>
<td>2</td>
</tr>
<tr>
<td>39</td>
<td>37a</td>
<td>2</td>
<td>CH$_2$(CO$_2$Me)$_2$</td>
<td>37b</td>
<td>7</td>
</tr>
<tr>
<td>39</td>
<td>37b</td>
<td>48</td>
<td>CH$_2$(CO$_2$Me)$_2$</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>CH$_2$(CO$_2$Me)$_2$</td>
<td>36a</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although high enantioselectivity of around 80% ee is obtained in the reaction with both nucleophiles in the presence of enantiopure ligands 36b and its cyclobutane analogue 36a, a drastic decrease in the stereoselectivity is caused by the use of enantiopure ligands whose carboxyl group is connected to the cycloalkane backbone via a methylene group 37a and 37b. This indicates that the position of the carboxyl substituent is important for the stereoselective allylic alkylation. The importance of the carboxyl group is further supported by the decrease in enantioselectivity observed for the reaction using ligand 38 which is the ester analogue of 36b. It has been proposed that the high enantioselectivities observed with ligands 36a and 36b is caused by an electronic repulsion between the carboxylate anion on the ligands and the negative charge of the incoming nucleophiles, which directs the nucleophilic attack onto one of the π-allyl carbons, as illustrated in Figure 4.
Novel enantiopure diphosphine ligands bearing hetero-functional groups have been prepared in eleven steps by Achiwa et al. The ligands 40 were designed so that the hetero-functional group would extend over the diphenylphosphine substituents to interact with the incoming nucleophile. The ligands were examined for stereoselectivity in the reaction of 1,3-diphenyl-3-acetoxy-1-propene 35 with the sodium salt of dimethyl malonate in the presence of palladium complexes. Ligand 40a produced only racemic alkylation product whereas ligand 40f possessing a pendant carboxyl group achieved an enantioselectivity of 49% ee. Again this lends support to the idea of secondary interactions occurring between functional group on the ligand and the approaching nucleophile.

In a similar fashion to the enantiopure crown ether modified ferrocenylphosphines 33 and 34, Trost et al. have developed the sterically bulky ligand 41, which is able to sterically block the approach of a nucleophile to one of the allylic termini.
The large ring size formed in the bidentate phosphine-palladium complex forces the 'arms' of the ligand around the allyl moiety and leads to increased enantioselectivity. Reactions proceeding via a meso complex have been achieved with up to 69% ee employing this ligand.

\[
\begin{align*}
\text{Ar} & = \text{TMS} \\
\text{TMS} & = \\
\end{align*}
\]

(iv) Asymmetric induction via steric effects

Many ligands which are able to impart impressive levels of asymmetric induction are not able to reach around to the exo face of the allyl group and direct or block the incoming nucleophile. In these cases it seems that the effect may be caused by an electronic bias in the symmetry of the allyl unit. The steric effects of the ligand could force the allyl group away at one terminus, and thereby presumably generate an enhanced centre for nucleophilic addition, since it should carry more positive charge character, as represented in Figure 5.

\[
\begin{align*}
\text{Nuc} & = \\
\text{R} & = \\
\text{Pd} & = \\
\text{L} & = \\
\end{align*}
\]

Figure 5
Ligands which may be considered in this category include the bis–oxazolines 42–44 and 5-azasemicontrins 45 employed by Pfaltz et al. Initial experiments were performed with palladium complexes of enantiopure ligand 42 in the reaction of racemic 1,3-diphenyl-3-acetoxy-1-propene 35 with the sodium salt of dimethyl malonate. The alkylation product 46 was obtained in good chemical yield with an enantiomeric excess of 77% (Scheme 17)

Replacement of the benzyl groups in 42 by more bulky isopropyl or tert-butyl substituents resulted in loss of catalytic activity. Surprisingly, the bis–oxazoline 42 and the corresponding methylene bis–oxazoline 43 gave essentially identical results, despite their different coordination geometries (5- vs 6-membered chelate ring) and different electronic properties (42 is a better $\pi$-acceptor than 43) (see Table 2). The selectivities and reaction rates were found to be solvent-dependent. The best results were obtained in polar media using a mixture of dimethyl malonate and N,O-bis(trimethylsilyl)acetamide, according to a
procedure described by Trost et al. The catalytic procedure is smoothly initiated by the addition of a catalytic amount of potassium acetate. Under these conditions, in the presence of 1-2 mol% of catalyst the reaction proceeded smoothly at room temperature to give the desired alkylation product 46 in very high enantiomeric purity and essentially quantitative yield. The most effective ligands were found to be the azasemiacorrin 45 and the methylene bisoxazoline 44 which both carry silyloxymethyl groups at the stereogenic centre adjacent to the co-ordination site.

Table 2

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Nucleophile</th>
<th>Solvent</th>
<th>%Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>NaCH(CO₂Me)₂</td>
<td>THF</td>
<td>86</td>
<td>77 (R)</td>
</tr>
<tr>
<td>43</td>
<td>NaCH(CO₂Me)₂</td>
<td>THF</td>
<td>85</td>
<td>76 (R)</td>
</tr>
<tr>
<td>43</td>
<td>CH₂(CO₂Me)₂</td>
<td>CH₂Cl₂</td>
<td>97</td>
<td>88 (R)</td>
</tr>
<tr>
<td>44</td>
<td>CH₂(CO₂Me)₂</td>
<td>CH₂Cl₂</td>
<td>97</td>
<td>97 (R)</td>
</tr>
<tr>
<td>45</td>
<td>CH₂(CO₂Me)₂</td>
<td>CH₂Cl₂</td>
<td>99</td>
<td>95 (S)</td>
</tr>
</tbody>
</table>

Evidence for the concept of regioselective steric activation of one of the Pd-C bonds is provided by the crystal structures of two π-allylpalladium complexes with enantiopure ligand 43. The important features of the two structures are depicted in Figure 6 as reported by Pfaltz.
The complex with the unsubstituted allyl ligand was found to adopt the expected square planar co-ordination geometry of Pd(II) and an almost planar conformation of the methylene bis-oxazoline ligand framework. The structure of the corresponding (1,3-diphenylallyl)Pd complex, which is the actual intermediate in the catalytic reaction, was found to be strikingly different. As a consequence of the steric repulsion between the allylic phenyl group and the adjacent benzyl substituent of the enantiopure ligand, the methylene bis-oxazoline ring system adopts a strongly distorted, non-planar conformation. The repulsive interaction between the enantiopure ligand and one of the allylic termini is also reflected in the bond lengths and angles of the [PdC₃N₂] core. The longer, more strained Pd–C bond carries more positive charge character at carbon. From the absolute configuration of the product it is known that the nucleophile preferentially attacks this terminus, this is a major factor in the enantioselection process.
It should be made clear that other oxazoline containing ligands have been prepared by ourselves, and other groups. These will be discussed in subsequent chapters.

Another ligand which achieves appreciable levels of enantioselectivity presumably by the distortion of the symmetrical allyl unit by steric forces is the naturally occurring alkaloid (-)-sparteine. Despite early reports of only mediocre enantioselectivities, Togni tested palladium complexes of sparteine 47 in the asymmetric alkylation of 48 by stabilised anions and was able to produce the product 49 with up to 85% ee (Scheme 18) \(^5\)

![Scheme 18](image)

This reaction does not proceed via a meso intermediate, but the diastereomeric allyl complexes are in rapid equilibrium. An X-ray crystal structure of the proposed intermediate has been solved, and the observed diastereomer is consistent with the stereochemical outcome of the reaction. Various 2D \(^1\)H NMR techniques indicate that the structure of the complex in solution remains essentially unchanged. More recently Togni et al have successfully applied isosparteine to the asymmetric alkylation reaction.\(^5\)

Koga et al reports the development of a simple diamine ligand 50 for use in palladium catalysed asymmetric alkylation of 1,3-diphenyl-3-acetoxy-1-propene.
The product 46 was obtained in high yields and high enantiomeric excesses. Little solvent effect on enantioselectivity was observed. In diethyl ether, THF, benzene, or 1,2-dichloroethane, the enantioselectivity was almost unchanged (87-88% ee). Interestingly, in polar solvents such as acetonitrile or DMF, the reaction proceeded smoothly without diminishing enantioselectivity (Scheme 19)

The mechanism of enantioselection was investigated by X-ray diffraction and NMR studies. As a result of the analysis, the asymmetric induction was found to be caused by the repulsive interaction between the enantiopure ligand and the substrate, which affected the electronic character of the two allylic termini, in complete agreement with the explanation given by Pfaltz.

In a related approach, Tanner et al. have explored the use of enantiopure aziridines for palladium catalysed allylic substitution. The readily available bis-aziridines 51, effect an enantioselective nucleophilic substitution of allylic acetate 35 furnishing the addition product with >99% ee.
Lately, other enantiopure ligands have been used successfully for asymmetric palladium catalysed alkylations, these include the ferrocenylphosphine 52 synthesised by Togni \textit{et al.} and the monodentate phosphorus-based ligand 53, devised by Wills \textit{et al.}

Recently, Trost \textit{et al.} have reported the nature of the ion pair as nucleophile being critical in determining the enantioselectivity in allylic alkylation of 3-(acyloxy)cycloalkenes. Using tetrahexylammonium as counterion gave the best results, excellent enantioselectivities (up to 98\% ee) have been obtained with both a carbon and a nitrogen nucleophile and with varying ring sizes of the allylic acetate.
Chapter Two

Enantiopure Oxazolines as Ligands
2.1 Introduction

The naturally occurring 2-oxazoline ring system, a simple cyclic imino ester was first identified over a century ago. Since then, the synthetic utility of 2-oxazolines has been demonstrated to provide novel, efficient routes to various organic molecules. A number of reliable synthetic routes towards 2-oxazolines exist, the majority of which have been covered in a number of excellent reviews. One worthy of particular note is a recent, comprehensive report on the chemistry of 2-oxazolines by Meyers.

Since their introduction in 1974 by Meyers, enantiopure 2-oxazolines have been extensively used as valuable auxiliaries in asymmetric synthesis. They can effect efficient chirality transfer from the heterocycle to newly formed bonds, thereby generating new centres of chirality with high asymmetric induction. Oxazolines have been found in many microbial metal chelators such as vibriobactin, mycobactin and parabactin. In these cases they are incorporated into multidentate metal complexes, illustrating the high chelating ability of this moiety. Based on these properties, enantiopure oxazolines have been used as ligands for transition metals in asymmetric catalysis.

The first reported examples of enantiopure oxazolines as ligands facilitating asymmetric synthesis were by the group of Meyers in 1974. It was shown that enantiopure 4-hydroxymethylloxazoline treated with 0.5 equivalents of lithium aluminum hydride was effective in the asymmetric reduction of ketones in up to 65% ee (Scheme 20).
Similarly, oxazolines 55 and 56 after treatment with one equivalent of Grignard reagent would add to various prochiral ketones furnishing enantiomerically enriched alcohols with up to 25% ee.

The same family of enantiopure oxazolines proved to be competent ligands for the Zn(II) catalyzed asymmetric addition of Grignard reagents to \( \alpha,\beta \)-unsaturated ketones. A feature of the asymmetric transformation shown in Scheme 21 using the Zn(II) complex derived from oxazoline 55 was high chemical yield (92%) and high regioselectivity (1,4 versus 1,2 addition gave a ratio of 165:1). The enantioselectivity however was rather modest at 16% ee.
Oxazoline 55 and structurally related oxazolines 57 and 58 have enjoyed further success in the enantioselective addition of diethylzinc to various aromatic aldehydes yielding the enantiomERICALLY enriched benzyl alcohols in up to 67% ee, as recently disclosed by Allen and Williams (Scheme 22) \(^\text{71}\)

\[
\begin{align*}
\text{ArCH}_2\text{CHO} + \text{Et}_2\text{Zn} &\rightarrow \text{ArCH}_2\text{CH(OEt)}_2 \text{OH} \\
\text{enantiopure oxazoline} &\rightarrow \text{Up to 67% ee}
\end{align*}
\]

\[\text{Scheme 22}\]

In 1989, Brunner and Obermann introduced novel, enantiopure 2-(2-pyridinyl)oxazoline 59 which was used together with [Rh(COD)Cl]₂, to form homogeneous \textit{in situ} catalysts for the enantioselective hydrosilylation of prochiral ketones using diphenylsilane \(^\text{72}\). After hydrolysis, 1-phenylethanol 62 is produced in up to 84% ee from acetophenone 61, as illustrated in Scheme 23 (59, \(R=t\text{Bu}\)). Much lower selectivity was obtained using tridentate mono-oxazoline 60.

\[
\begin{align*}
\text{PhCOCH}_2\text{Me} + \text{Ph}_2\text{SiH}_2 &\rightarrow \text{PhCH(OH)CH}_2\text{Me} \\
1. [\text{Rh}] / \text{Ligand} &\rightarrow 2. \text{H}^+ / \text{H}_2\text{O}
\end{align*}
\]

\[\text{Scheme 23}\]
Structurally similar enantiopure 2-(2-pyridyl)oxazolines 63 were prepared by Balavoine and Clinet, for use in the enantioselective hydrosilylation reaction.\textsuperscript{73} The efficiency of these new chelating ligands was tested in the reaction of acetophenone 61 with α-naphthylphenylsilane.

It was discovered that the enantioselectivity was highly dependent on both the steric and electronic properties of the substituent located at the 4-position on the oxazoline ring. When the co-ordinating properties were similar, there was a clear correlation between the enantioselectivity and the size of the 4-substituent. The highest level of enantioselection, (80\% ee), was achieved in quantitative yield with the bulky trityl ether.

Significant advances in the levels of asymmetric induction occurred with the introduction of the C2-symmetric bis-oxazolines by Masamune \textit{et al.}\textsuperscript{74} The catalytic enantioselective cyclopropanation of styrene 64 with ethyl diazoacetate in the presence of copper complexes of 65 as catalysts was found to occur in good yields and with high levels of enantioselectivity (Scheme 24). Two diastereomeric products are formed in a \textit{trans} : \textit{cis} ratio of 2:5:1. The
enantiomeric excess of the two enantiomers is strongly dependent on the substituents R on the ligand. The best results were obtained when the ligand 65 bears bulky substituents such as the tert-butyl group (trans, 90% ee; cis, 77% ee).

\[
\begin{align*}
\text{64} & \quad \xrightarrow{\text{N}_2\text{CHCO}_2\text{R}'} \quad \text{CO}_2\text{R}' \\
\end{align*}
\]

\[\text{trans} \quad \text{cis} \]

Independently, Evans et al. reported that copper complexes of a similar family of \textit{bis}-oxazolines 66 increase the enantioselectivity still further.\textsuperscript{75} The geminal dimethyl groups prevent enolisation of the ligand, which therefore reacts in neutral form with copper (I) triflate to give a catalytically active complex. In this case, the cyclopropanation of mono- and 1,1-disubstituted olefins using achiral diazoesters affords very high optical yields (up to 99% ee for styrene) and excellent \textit{trans} : \textit{cis} ratios (up to 94.6 for styrene). The reaction can be carried out at room temperature and 0.1 to 1 mol% of the complex is sufficient for efficient catalysis. Further to this Evans et al. have also recently revealed that the copper (I) triflate complex of 66 is a highly effective catalyst for aziridination of
olefins affording both azindines and α-amino-β-hydroxy esters in very high enantiomeric excess.

Pfaltz et al. have also investigated the effectiveness of bis-oxazolines 65 in enantioselective catalysis. The results obtained for the asymmetric cyclopropanation of olefins with copper complexes of bis-oxazolines 65 are in agreement with the results described by Masamune and Evans. Further to this, Pfaltz has employed oxazoline 65 in the indium catalysed hydrogenation of ketones, affording excellent levels of enantioselection.

The family of bis-oxazolines have been successfully applied to the enantioselective hydrosilylation of prochiral ketones with diphenylsilane. Helmchen revealed respectable levels of enantioselectivity (up to 84% ee in the reduction of acetophenone 61) using ligand 65 whilst 67 and 68 surprisingly gave poor results.

\[
\begin{align*}
\text{67} & \quad \text{68}
\end{align*}
\]

The enantiopure C₂-symmetric bis-oxazoline 69, a tridentate ligand and the related tetridentate ligand devised by Nishiyama have proved highly successful, giving up to 94% ee in the rhodium catalysed reduction of acetophenone 61. Nishiyama et al. have recently developed a powerful ruthenium catalyst derived from 69 for the efficient asymmetric cyclopropanation of olefins with diazoacetates.
Corey has applied ligand 66 in conjunction with Lewis acidic catalysts to the Diels-Alder cycloaddition between cyclopentadiene and acryloyl oxazolidinone 71, shown in Scheme 25 resulting in formation of the endo cycloaddition product 72 with an enantioselectivity of 86% (endo · exo, 99 · 1) 82.

\[
\begin{align*}
\text{71} & \xrightarrow{10 \text{ mol\% } 66 / \text{FeCl}_2 / \text{I}_2} \text{72} \\
\end{align*}
\]

Scheme 25

The use of bis-oxazolines as enantiopure catalysts for the enantioselective Diels–Alder reaction has also been reported by Evans et al. 83 In an extensive study, Evans expands the scope of utilisable dienophiles and rationalises the sense of asymmetric induction for the cycloaddition process.

A new enantioselective method for the synthesis of enantiomerically enriched cyanoxydrins from aldehydes has recently been reported by Corey and Wang 84. A pair of synergistic enantiopure bis-oxazolines, 65 (R=Ph) and 73 are used, one to activate the aldehyde and the other to provide an equivalent of enantiopure
cyanide ion (Figure 7) High enantioselectivities, up to 95% ee, were obtained for aliphatic, non-conjugated aldehydes.

![Chemical structure](image)

Figure 7

The high affinity of sulfur ligands for copper is exploited by Pfaltz and Zhou in the development of enantiopure heterocuprate complexes for enantioselective copper catalysed conjugate addition. Modified mono-oxazoline 74 proved to be an effective ligand for the catalytic, conjugate addition of Grignard reagents to cyclic α,β-unsaturated ketones, furnishing the addition product in up to 87% ee as illustrated in Scheme 26.
The synthesis of highly isotactic polymers with main chain chirality has been achieved using palladium (II) catalysts based on C₂-symmetric bis-oxazolines.86

2.2 Ligand design

EnantiomERICally pure oxazolines have been shown to be effective ligands for a variety of catalytic, asymmetric reactions. The success of oxazolines as enantiopure ligands can be attributed to the fact that stereochemical information is directed towards the substrate bound to the metal catalyst.

The majority of successful oxazoline catalysts have relied upon a C₂-symmetrical nature to reduce the number of possible stereochemical outcomes within the catalytic cycle, thereby affording high levels of enantiocontrol. Although this strategy has proved very effective in an impressive repertoire of catalytic, asymmetric transformations, a problem has been the enantioselective palladium catalysed allylic substitution reaction.

Our interests lay in the design of enantiopure ligands which exploit the stereochemistry-controlling properties of the oxazoline moiety, whilst incorporating a secondary donor atom, as shown in Figure 8.
The secondary donor atom could be tailored to the catalytic system to provide:

i) Modified binding properties

ii) Different steric environments

iii) Non-equivalent electronic behaviour of the donor atoms

Electronic bias of this nature has been observed by Åkermark *et al* on allyl ligands bound to palladium. Specifically, it was noted that the rates and regioselectivity in the stoichiometric addition of nucleophiles to the $\eta^3$-(3-methylbutenyl)palladium(II) system were proportional to the total and relative charge of the $\eta^3$-allyl unit. Ligands with $\pi$-acceptor properties were found to produce reactive complexes which reacted preferentially at the more substituted $\eta^3$-allyl terminus and display large downfield $^{13}$C NMR shifts for this terminus. On the other hand, ligands not possessing $\pi$-acceptor properties gave less reactive complexes which reacted preferentially at the less substituted terminus. The $^{13}$C downfield shifts for these complexes were found to be small, as is also true for the shift difference between the two $\eta^3$-allyl termini.

This can be seen clearly by considering complexes 75 and 76. The two methyl groups allow for the development of more positive charge on the C$_3$ carbon. For the bidentate phosphorus/nitrogen ligand used in 75 and 76, a dramatic effect was observed.
When the phosphorus is *trans* to the C₃ position, a substantial C₃-C₁ shift difference is observed. However, when the nitrogen is *trans* to the C₃ position, the C₃-C₁ shift difference is dramatically reduced to just 8 ppm. Nucleophilic addition to complex 75 occurs mainly at the C₃ position, despite the steric constraints, due to the electronic properties of the ligand.

Whilst phosphorus and nitrogen both function as good σ-donors, only the phosphorus functioned as a π-acceptor, thereby reducing the electron density on the *trans* carbon atom, rendering it more electrophilic and hence, more susceptible to nucleophilic attack.

It has been shown previously that good levels of stereocontrol are achievable by the use of enantiopure ligands that are able to either interact with the incoming nucleophile or sterically hinder the approach of the nucleophile, directing to one end of the allyl moiety. Alternatively, similarly high levels of stereocontrol have been achieved utilising enantiopure ligands which distort the symmetry of the allyl moiety by steric forces, thus, generating a more electrophilic centre for preferential nucleophilic attack.

The designed enantiopure oxazoline ligands should be able to exert steric and electronic control over the palladium catalysed allylic substitution process, by
creating an asymmetric environment and introducing an electronic bias into the intermediate palladium allyl species via the differing trans effects of the two donor atoms in the ligand

2.3 Preparation of enantiopure thienyl oxazolines

We wished to prepare enantiopure oxazoline ligands which contained a secondary donor atom. One such possibility would be a sulfur donor contained within a thiophene ring, providing a family of bidentate, electronically non-equivalent ligands.

![Thiophene ligand](image)

Thiophenes have only occasionally been employed as ligands, although there are reports of thiophene functioning as either an $\eta^1$ or $\eta^5$ ligand. In order to act as a bidentate ligand, we are assuming that an $\eta^1$ binding mode would be more plausible. In support of this, Maitlis et al. has reported spectroscopic evidence for the complexation of two tetramethylthiophene ligands to a cationic palladium allyl moiety in an $\eta^1$ binding mode, this is illustrated in Figure 9.

![Spectroscopic evidence](image)
In 1974 Witte and Seeliger reported a procedure for the preparation of mono- and bis-oxazolines by direct reaction of nitriles with amino alcohols in the presence of catalytic amounts of metal salts. By a reinvestigation of this procedure, Bolm et al demonstrated that a variety of substituted, optically active bis-oxazoline derivatives could readily be prepared under mild conditions. Using a slightly modified procedure Bolm prepared known mono-oxazolines 59 (R=iPr) and 78, from 2-cyanopyridine and 2-hydroxybenzonitrile respectively, in high yields.

\[
\begin{align*}
59 \ (R=\text{iPr}) \\
78
\end{align*}
\]

We decided to adopt this mode of oxazoline synthesis in preference to other literature methods. Thus, the thienyl oxazolines 77b-f were prepared in one step from commercially available thiophene carbonitrile 79 and enantiopure amino alcohols 80b-f (Scheme 27), which were either commercially available or easily obtained by reduction of the corresponding amino acids.

\[
\begin{align*}
\text{Scheme 27}
\end{align*}
\]

The procedure entails heating a solution of the thiophene carbonitrile with an excess of the appropriate enantiopure amino alcohol in chlorobenzene in the presence of a catalytic amount of zinc dichloride. Aqueous work-up followed by column chromatography furnishes the desired ligands in good yields.
All of the thienyl oxazoline ligands have been satisfactorily characterised by both spectroscopic and analytical techniques. Strong evidence in favour of oxazoline formation can be found in the $^1\text{H}$ NMR spectra where a characteristic splitting pattern associated with the protons of the oxazoline ring is revealed. In the case of ligands 77d and 77e, a $^1\text{H}^\text{13C}$ correlation spectrum was required to distinguish between the CH$_2$-O and CH-N protons of the oxazoline ring. Further confirmation of oxazoline formation can be found in the infra-red spectrum where a C=N stretching band at $\sim$1650 cm$^{-1}$ is observed.

### Table 3

<table>
<thead>
<tr>
<th>Amino alcohol</th>
<th>$R$</th>
<th>$R'$</th>
<th>Oxazoline</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80b</td>
<td>PhCH$_2$</td>
<td>H</td>
<td>77b</td>
<td>73</td>
</tr>
<tr>
<td>80c</td>
<td>iPr</td>
<td>H</td>
<td>77c</td>
<td>88</td>
</tr>
<tr>
<td>80d</td>
<td>Ph</td>
<td>H</td>
<td>77d</td>
<td>79</td>
</tr>
<tr>
<td>80e</td>
<td>Bu</td>
<td>H</td>
<td>77e</td>
<td>74</td>
</tr>
<tr>
<td>80f</td>
<td>Me</td>
<td>Ph</td>
<td>77f</td>
<td>91</td>
</tr>
</tbody>
</table>

A similar strategy was employed in the preparation of ligand 82, from thiophene carbonitrile 79 and the cheap, commercially available enantiopure diol, (1S, 2S)-(+)-1-phenyl-2-amino-1,3-propanediol 81 (Scheme 28). Accompanying the formation of 82 is a small quantity (<10%) of the isomeric oxazoline. This can be conveniently removed by recrystallisation.

![Scheme 28](image-url)
The pendant hydroxyl group in 82 is useful in two ways; firstly, as a ligand 82 could be used to probe the effects of secondary interactions between ligand and nucleophile on enantioselectivity. Also, further elaboration of 82 would provide ligands with different steric properties. Upon treatment with triethylamine and trityl chloride, 82 is converted to the bulky trityl ether 83 (Scheme 29).

The reasonable mechanism of oxazoline formation is illustrated in Scheme 30. The nitrile functionality is able to co-ordinate to the zinc dichloride facilitating the initial nucleophilic addition of the amine. The subsequent intermolecular nucleophilic attack by the hydroxyl group leads to the desired oxazoline with loss of ammonia and regeneration of the zinc dichloride catalyst.
In order to ensure that no racemisation had occurred during the zinc-catalysed ring formation, ligand 77d was hydrolysed under acidic conditions liberating (S)-phenylglycinol, ([α]D25=+32° (c=0 5, CH2Cl2)) (Scheme 31)
Comparison of the optical rotation with an authentic sample of (S)-phenylglycinol confirmed that there had been no loss of stereochemical integrity. Since the 4-phenyl substituted ligand was considered to be the most prone to potential racemisation, it is assumed that all of the other thienyl oxazoline ligands are likewise enantiomerically pure

2.4 Results for palladium catalysed allylic substitution

With all of the enantiopure thienyl oxazoline ligands to hand, an investigation into the suitability of these ligands for asymmetric palladium catalysed allylic substitution began. Thus, the allylic acetate 35 was prepared in two steps shown in Schemes 32 and 33. The initial reaction of cinnamaldehyde with phenylmagnesium bromide in sodium dried ether at room temperature produced after work-up the allylic alcohol 85 as a low melting solid which could be used directly in the next step.

\[
\text{Cinnamaldehyde} \quad \text{PhMgBr} \quad \text{Et}_2\text{O} \quad 83\% \quad \text{PhOH}
\]

Scheme 32

Treatment of 85 with an excess of acetic anhydride and a few crystals of DMAP in pyridine furnishes the desired allylic acetate 35 in excellent yield.

\[
\text{85} \quad \text{Ac}_2\text{O} \quad \text{DMAP} \quad \text{C}_5\text{H}_5\text{N} \quad 96\% \quad \text{35}
\]

Scheme 33
The reaction between allylic acetate 35 and sodiodimethylmalonate catalysed by 2.5 mol% of allyl palladium chloride dimer (equivalent to 5 mol% of palladium) and 10 mol% of one of the ligands 77b-f was studied (Scheme 34). Initially, the catalytic reactions were carried out in dry THF and in all cases oxygen was excluded. The ligand and palladium catalyst were pre-mixed in the reaction solvent for 15 minutes prior to the reaction.

After 48 hours at reflux, the reaction mixtures were quenched with water and were extracted with ether. The product was isolated by means of flash chromatography. The overall yields were modest, but as far as we could ascertain there are no detectable side products.

The isolated product 46 was assayed for enantiomeric excess by employing the enantiopure shift reagent Eu(hfc)₃, in ¹H NMR. The use of enantiopure lanthanide shift reagents is a simple, widely used technique for the determination of enantiomeric purities by NMR spectroscopy. Under normal conditions the equilibrium between the substrate and the enantiopure lanthanide shift reagent is rapid on the NMR time scale.
(S)-substrate $\cdot$ (R)-shift reagent $\rightleftharpoons$ $\frac{K_S}{K_R}$ \[
\begin{cases} 
(R)\text{-substrate} \\
(S)\text{-substrate}
\end{cases} + 2(R)\text{-shift reagent}
\]

Therefore only a single time-averaged spectrum results from the average of complexed and uncomplexed substrate molecules. Rapidly equilibrating complexes are formed by an enantioselective lanthanide shift reagent binding to each of two enantiomers. These complexes are diastereomeric and can have different average chemical shifts. This difference in shifts may have at least two causes. Firstly, the equilibrium constants ($K_R$, $K_S$) may be different for diastereomeric complexes, thereby causing larger shifts for the complex having the larger binding constant. Also, the two diastereomeric complexes formed may differ in their geometry which may cause a difference in the induced shift for corresponding signals in the two complexes.

The shift experiment was carried out by preparing a solution of the substrate 46 in CDCl$_3$. The concentration of the substrate is kept as low as is compatible with having adequate signal strength. Normally the more concentrated the sample, the broader will be the signals and therefore the poorer the resolution. For our purposes, 2 mg of the substrate 46 in 1 ml of solvent gave a perfectly acceptable spectrum. Solid portions of the enantiopure shift reagent were then added incrementally to build up a series of spectra in which the molar ratio of enantiopure shift reagent is varied.
In our case a baseline separation of one of the signals due to a methyl ester was achieved using 0.8 equivalents of enantiopure shift reagent, this can be seen clearly in Figure 10 where the chiral shift spectrum of the racemic mixture is compared with an enantiomerically enriched mixture ((S)-(−)-enantiomer in excess). In each case we obtained the (S)-(−)-enantiomer shown in excess, where the absolute configuration was determined by comparison of the optical rotation with literature values\textsuperscript{95}

Good levels of enantiocontrol were obtained using ligand 77c containing an iso-propyl group, but attempts to improve enantioselectivity by using ligands 77d and
77e with the phenyl and tert-butyl groups afforded no reaction, presumably for steric reasons. A similar lack of reactivity was observed employing ligand 83 containing the sterically cumbersome trityl ether. After being heated under reflux for 120 hours no product was detected by TLC analysis or by examination of the crude NMR spectra (Table 4).

Table 4

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Isolated yield (%)</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77b</td>
<td>68</td>
<td>24</td>
</tr>
<tr>
<td>77c</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>77d</td>
<td>No reaction</td>
<td>–</td>
</tr>
<tr>
<td>77e</td>
<td>No reaction</td>
<td>–</td>
</tr>
<tr>
<td>77f</td>
<td>56</td>
<td>6</td>
</tr>
</tbody>
</table>

Remarkably, there was no observed enantiomeric excess when ligand 82 containing the pendant hydroxy component was used in the alkylation reaction though the product 46 was obtained in a respectable 65% yield. This implies two things. Firstly, the hydroxy group does not impair the ligand’s role in the catalytic cycle. Second, there are no beneficial interactions with the incoming nucleophile that would enhance asymmetric induction.

It should be noted that the observed enantioselectivity was very sensitive to the reaction solvent. Performing the reaction in more co-ordinating solvents dramatically lowered the level of enantioselection. For example, employing ligand 77c in DMF under otherwise identical conditions to those in THF afforded the product 46 in enhanced yield (91%) but with diminished enantioselectivity (12% ee). The reaction in non-co-ordinating solvents gave problems due to the
Insolubility of the nucleophile. However, the use of dimethyl malonate in the presence of bis-trimethylsilylacetamide\(^6\) allowed the reaction to proceed in dichloromethane initiated by the addition of a catalytic amount of potassium acetate as illustrated in Scheme 35, but unfortunately with reduced yield (35%) and reduced enantiomeric excess (30% ee).

![Scheme 35](image)

The role of BSA in palladium catalysed allylic alkylations has not been clearly defined. No reaction occurs when the nucleophile is mixed with BSA in THF-\(d_8\) over 48 hours as judged by the \(^1\)H and \(^{13}\)C NMR spectra, indicating that BSA is not involved in the direct silylation of the nucleophile\(^7\). In addition, the reaction does not take place without added BSA or in the presence of triethylamine or 1,8-bis(dimethylamino)naphthalene. The ability of BSA to promote the reaction may be due to desilylation of BSA by liberated acetate leading to deprotonation of the nucleophile \textit{in situ}. Alkylation may then take place liberating more acetate as illustrated in Scheme 36.
Under the standard conditions in dry THF, increasing the ratio of ligand 77c to palladium was found to increase both the yield and enantioselectivity of the reaction (Table 5). These facts strongly suggest a low affinity between the ligand and the palladium allyl complexes, although association constants have not been determined.

Table 5

<table>
<thead>
<tr>
<th>Palladium : Ligand</th>
<th>Isolated yield</th>
<th>Enantiomeric excess</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>1 : 1</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>1 : 2</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>1 : 4</td>
<td>85</td>
<td>76</td>
</tr>
<tr>
<td>1 : 10</td>
<td>89</td>
<td>81</td>
</tr>
</tbody>
</table>

The fact that the thienyl oxazolines do not bind strongly to palladium is further demonstrated by keeping the ligand 77c to palladium ratio constant at 2:1 and
varying the volume of solvent added to the reaction under otherwise standard conditions. At low concentrations of palladium ligand complex the resulting yields and enantioselectivities were diminished. However, increasing the concentration of enantiopure catalyst led to higher selectivities and increased conversions (Table 6).

<table>
<thead>
<tr>
<th>Volume of added solvent (ml)</th>
<th>Isolated yield (%)</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>2.0</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>20.0</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

**2.5 Summary**

(i) The thienyl oxazolines are easily prepared in one step from commercially available materials.

(ii) The thienyl oxazolines succeed in their aim of controlling enantioselectivity through a combination of steric and electronic factors. The question of increasing the levels of asymmetric induction has to be addressed.

(iii) The thienyl oxazoline ligands do not bind strongly to the palladium allyl complexes. A symptom of this is their low reactivity.
Chapter Three

Sulfur and Phosphorus Containing Oxazolines
3.1 Introduction

We anticipated that the precise nature of the auxiliary donor ligand would have an influence on the electronic and steric environment around the metal. In order to examine such influences which directly relate to the rate of reaction and enantioselectivity, it was decided to synthesise enantiopure oxazoline ligands with auxiliary sulfide and diphenylphosphinophenyl donors, as shown in Figure 11.

![Figure 11](image)

3.2 Preparation of enantiopure aryl sulfide and phosphine containing oxazolines

(i) Preparation of enantiopure aryl sulfide ligands

We wished to prepare enantiopure oxazoline ligands which contained a sulfide donor ligand. Although the possibilities are wide-ranging, we considered two electronically and stenically distinct ligand types 86 and 87.
The family of enantiopure 2-((2-methylthio)phenyl)oxazolines 86a–e, was prepared in one step from the commercially available 2-(methylthio)benzonitrile 88 and enantiopure amino alcohols as depicted in Scheme 37.

\[
\begin{align*}
\text{OH} & \quad \text{NC} \\
\text{R} \text{NH}_2 & \quad \text{MeS} \\
80a–e & \quad 88
\end{align*}
\]

Scheme 37

Thus, 88 was heated under reflux with the appropriate enantiopure amino alcohol 80a–e in the presence of a catalytic amount of anhydrous zinc chloride in chlorobenzene for 48 hours. After aqueous work-up the ligands were readily purified by column chromatography affording the corresponding 2-((2-methylthio)phenyl)oxazolines 86a–e in good yields (Table 7).

<table>
<thead>
<tr>
<th>Amino alcohol</th>
<th>R</th>
<th>Oxazoline</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80a</td>
<td>Me</td>
<td>86a</td>
<td>60</td>
</tr>
<tr>
<td>80b</td>
<td>CH₂Ph</td>
<td>86b</td>
<td>42</td>
</tr>
<tr>
<td>80c</td>
<td>iPr</td>
<td>86c</td>
<td>56</td>
</tr>
<tr>
<td>80d</td>
<td>Ph</td>
<td>86d</td>
<td>58</td>
</tr>
<tr>
<td>80e</td>
<td>iBu</td>
<td>86e</td>
<td>53</td>
</tr>
</tbody>
</table>

The family of 2-((2-methylthio)phenyl)oxazolines 86a–e proved to be air-stable ligands and have all been fully characterised. The formation of the oxazoline is easily demonstrated by £H NMR where the singlet due to the SCH₃ of the 2-(methylthio)benzonitrile at δ 2.53 ppm disappears and is replaced by the
heated under reflux for 24 hours whereupon a clear solution was obtained. Aqueous work-up followed by flash chromatography afforded the desired 2-(phenylthio)benzonitrile 90 as a colourless crystalline solid.100

In an analogous fashion to the 2-((2-methylthio)phenyl)oxazolines, conversion of 2-(phenylthio)benzonitrile 90 to the oxazolines 87c and 87e was achieved by treatment with the corresponding enantiopure amino alcohols 80c and 80e under the standard zinc chloride catalysed conditions, as shown in Scheme 39.

\[
\text{Scheme 39}
\]

(ii) Preparation of enantiopure phosphine ligands

The enantiopure 2-((2-diphenylphosphino)phenyl)oxazolines 91a-e were prepared in collaboration with Graham J. Dawson. The ligands were assembled by a two step process. Initially, 2-fluorobenzonitrile 89 was converted into the corresponding oxazoline 92a-e upon treatment with an enantiopure amino alcohol using the standard catalytic zinc chloride conditions, the reaction mixtures being heated under reflux in chlorobenzene for 24 hours (Scheme 40).

\[
\text{Scheme 40}
\]
After work-up and purification the 2-(2-fluorophenyl)oxazolines 92a-e were obtained in moderate yields (Table 8)

<table>
<thead>
<tr>
<th>Amino alcohol</th>
<th>R</th>
<th>F-oxazoline</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80a</td>
<td>Me</td>
<td>92a</td>
<td>47</td>
</tr>
<tr>
<td>80b</td>
<td>PhCH₂</td>
<td>92b</td>
<td>48</td>
</tr>
<tr>
<td>80c</td>
<td>Pr</td>
<td>92c</td>
<td>46</td>
</tr>
<tr>
<td>80d</td>
<td>Ph</td>
<td>92d</td>
<td>49</td>
</tr>
<tr>
<td>80e</td>
<td>tBu</td>
<td>92e</td>
<td>56</td>
</tr>
</tbody>
</table>

The experimental procedure was optimised for the case of 92c. It became apparent that as the reaction time increased beyond 12 hours the yield of product diminished. It was also noted that decreasing the volume of chlorobenzene added to the reaction mixture enhanced the isolated yield of 92c. The highest yields of 92c were obtained when the 2-fluorobenzonitrile 89 and L-valinol 80c were heated together with 10 mol% of zinc chloride in the absence of any solvent at 160°C for 2 hours. Aqueous work-up and flash chromatography afforded 92c as colourless oil in 85% yield.

We have demonstrated that potassium diphenylphosphide may be employed to displace fluoride from 2-substituted aryl fluorides. Potassium diphenylphosphide may be conveniently purchased as a 0.5M solution in THF (Aldrich). Addition of the 2-substituted aryl fluoride to a solution of the phosphide at reflux affords the corresponding phosphines in good to excellent yields, as illustrated in Scheme 41.
The same methodology could be applied to the synthesis of the 2-((2-diphenylphosphino)phenyl)oxazolines 91a-e. Hence, the addition of a solution of the appropriate 2-(2-fluorophenyl)oxazoline 92a-e in THF to a stirring solution of the diphenylphosphide at reflux afforded, after work-up and flash chromatography the corresponding 2-((2-diphenylphosphino)phenyl)oxazoline 91a-e as shown in Scheme 42.

The potassium diphenylphosphide is a red solution in THF. When the solution is heated to reflux temperature, no loss of colour is observed. Upon the addition of the 2-(2-fluorophenyl)oxazoline as a solution in THF the red solution associated with the diphenylphosphide rapidly fades to orange and then pale yellow. This provides a convenient method of monitoring the progress of the reaction because
when the solution has changed to the yellow colour the transformation is complete. This occurs within one minute for all of the 2-(2-fluorophenyl) oxazolines 92a-e affording the corresponding 2-((2-diphenylphosphino)phenyl) oxazolines 91a-e in excellent yield (Table 9)

### Table 9

<table>
<thead>
<tr>
<th>F-oxazoline</th>
<th>R</th>
<th>P-oxazoline</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>92a</td>
<td>Me</td>
<td>91a</td>
<td>80</td>
</tr>
<tr>
<td>92b</td>
<td>PhCH₂</td>
<td>91b</td>
<td>76</td>
</tr>
<tr>
<td>92c</td>
<td>tPr</td>
<td>91c</td>
<td>76</td>
</tr>
<tr>
<td>92d</td>
<td>Ph</td>
<td>91d</td>
<td>84</td>
</tr>
<tr>
<td>92e</td>
<td>tBu</td>
<td>91e</td>
<td>92</td>
</tr>
</tbody>
</table>

All of the 2-((2-diphenylphosphino)phenyl)oxazolines 91a-e were isolated as air-stable crystalline solids and all have been satisfactorily characterised. Examination of the infra-red spectra and the $^1$H NMR spectra clearly confirmed the presence of an oxazoline. The mass spectra complemented this information in all cases revealing the expected molecular ion. Indisputable evidence for the presence of the phosphine moiety was discovered in the $^{31}$P NMR spectrum. A singlet at $-4.7$ ppm is reported to be characteristic of a trivalent aryl phosphine.$^{102}$ It was discovered that on exposure to air in solution, slow oxidation to the corresponding phosphine oxides occurs over a period of several weeks. This could be seen quite clearly in the infra-red spectrum with the appearance of an absorption band at $\sim1250$ cm$^{-1}$ due to the P=O stretch of the phosphine oxide.
3.3 Results for palladium catalysed allylic substitution

(i) Using enantiopure aryl sulfide ligands

With a facile ligand synthesis in hand, we investigated the suitability of the 2-((2-methylthio)phenyl)oxazoline ligands 86a-e for asymmetric palladium catalysed allylic substitution (Scheme 43).

Hence, the allylic acetate 35 was treated with a slight excess of the sodium salt of dimethyl malonate in THF at reflux in the presence of 2.5 mol% of [Pd(η3-C5H5)Cl]2 and 10 mol% of the ligand 86a-e. After 2 hours the reaction was complete in every case according to TLC analysis. After work-up, the substitution product 46 was isolated by flash chromatography in good yields and with reasonable levels of asymmetric induction (Table 10). In each case we observed the S-(-)-enantiomer predominating.

The rate of the allylic substitution reaction with ligands 86a-e is far greater than for the thienyl oxazoline ligands 77b-f. This rate difference may be attributed to the increased \( \pi \)-acceptor ability of a sulfur as a sulfide compared with a sulfur contained within an electron rich thiophene ring.
Table 10

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Isolated yield (%)</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86a</td>
<td>91</td>
<td>40</td>
</tr>
<tr>
<td>86b</td>
<td>78</td>
<td>50</td>
</tr>
<tr>
<td>86c</td>
<td>93</td>
<td>55</td>
</tr>
<tr>
<td>86d</td>
<td>95</td>
<td>62</td>
</tr>
<tr>
<td>86e</td>
<td>92</td>
<td>68</td>
</tr>
</tbody>
</table>

Encouraged by the increase in reactivity observed with the 2-((2-methylthio)phenyl)oxazolines 86a-e, the substitution reactions were performed at room temperature. It was found that the reactions proceeded to completion within 12 hours, and at the lower temperature the process was more enantioselective (Table 11).

Table 11

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Isolated yield (%)</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86b</td>
<td>90</td>
<td>52</td>
</tr>
<tr>
<td>86c</td>
<td>98</td>
<td>58</td>
</tr>
<tr>
<td>86d</td>
<td>84</td>
<td>66</td>
</tr>
<tr>
<td>86e</td>
<td>86</td>
<td>80</td>
</tr>
</tbody>
</table>

The level of enantioselectivity was observed to decrease when the alkylation reaction was performed under the standard BSA conditions in dichloromethane with ligand 86c. After 24 hours at room temperature the product 46 was obtained in quantitative yield and an enantiomeric excess of 42% was detected.
In comparison with the corresponding 2-((2-methylthio)phenyl)oxazolines 86c and 86e, the 2-((2-phenylthio)phenyl)oxazolines 87c and 87e were employed as ligands for enantioselective palladium catalysed allylic substitution. The allylic acetate 35 was treated with dimethyl malonate and BSA in the presence of 2.5 mol% of the palladium chloride dimer catalyst and 10 mol% of the appropriate ligand as detailed in Scheme 44.

![Scheme 44]

After stirring at room temperature the substitution product 46 was isolated in all cases enriched in the S-(-)-enantiomer as determined by comparison of the optical rotation with literature values. The superior asymmetric induction achieved by changing from a methyl sulfide to a phenyl sulfide can be rationalised in terms of the obvious steric effects or the electronic effects as aromatic sulfides are better $\pi$-acceptors than aliphatic sulfides (Table 12).

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>87c</td>
<td>THF</td>
<td>36</td>
<td>91</td>
<td>78</td>
</tr>
<tr>
<td>87c</td>
<td>CH$_2$Cl$_2$</td>
<td>36</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>87e</td>
<td>THF</td>
<td>36</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>87e</td>
<td>CH$_2$Cl$_2$</td>
<td>48</td>
<td>67</td>
<td>&gt;95</td>
</tr>
<tr>
<td>87e</td>
<td>CH$_2$Cl$_2$</td>
<td>96</td>
<td>92</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>
For those reactions using dichloromethane as solvent, enhanced enantioselectivity was observed. This is likely to be due to the increased binding of the ligands in the non-coordinating solvent. Excellent levels of enantioselectivity are achieved with ligand 87e. However, there is a price to be paid; a feature of the asymmetric substitution involving 87e in dichloromethane was lower reactivity of the catalytic complex.

(ii) Using enantiopure phosphines

The readily accessible 2-((2-diphenylphosphino)phenyl)oxazolines 91a-e were applied to the palladium catalysed allylic substitution reaction of allylic acetate 35 shown in Scheme 45, affording the substitution product 46 with very high levels of enantioselectivity (Table 13).

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{Ph} & \quad \text{Ph} \\
\text{35} & \quad \text{NaCH(CO}_2\text{Me)}_2 \\
\text{2.5 mol%} & \quad [\eta^3\text{-C}_3\text{H}_5\text{PdCl}_2]_2 \\
10 \text{ mol%} & \quad \text{O} \\
\text{R} & \quad \text{Ph}_2\text{P} \\
\text{THF} & \quad \text{Scheme 45}
\end{align*}
\]

All of the ligands 91a-e were seen to provide consistently high enantioselectivities. All the complexes were found to induce the (S)-configuration of product. Surprisingly, there is only a small variation in the enantioselectivity observed when the size of the R group is varied considerably. Another remarkable feature of these ligands is the very short reaction times. In all cases, essentially quantitative yields of the substitution product 46 were obtained in less than one hour.
Table 13

<table>
<thead>
<tr>
<th>Ligand</th>
<th>R</th>
<th>Isolated Yield (%)</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>91a</td>
<td>Me</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>91b</td>
<td>PhCH₂</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>91c</td>
<td>Pr</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>91d</td>
<td>Ph</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>91e</td>
<td>Bu</td>
<td>&gt;99</td>
<td>90</td>
</tr>
</tbody>
</table>

Compared to the other oxazoline ligands 77a-e, 86a-e, 87c and 87e the 2-((2-diphenylphosphino)phenyl)oxazolines 91a-e are less dependent on the choice of solvent and temperature. For example, in the presence of the palladium complex derived from ligand 91a, the allylic acetate 35 is smoothly converted into the substitution product 46 in quantitative yield by treatment with the sodium salt of dimethyl malonate in THF at reflux temperature with no loss of enantioselectivity. When the reactions were run in dichloromethane under the standard BSA conditions employing ligand 91c, conversion was found to be complete within one hour at room temperature affording the expected product 46 in quantitative yield with an enantioselectivity of >95% ee.

From these results the 2-((2-diphenylphosphino)phenyl)oxazolines 91a-e are established as the most effective ligands for asymmetric palladium catalysed allylic substitution. After this work was completed reports appeared in the literature from the laboratories of Pfaltz and Helmchen disclosing the synthesis and application of enantiopure phosphine containing oxazolines. Both groups reported their use in palladium catalysed allylic substitution and achieved equally high enantioselectivities and reactivity (Figure 12).
Very recently, Brown\textsuperscript{106} has reported the use of chelating ligand 93 which contains two distinct donor atoms for asymmetric palladium catalysed allylic substitution.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{ligand_93.png}
\caption{Ligand 93, with 98\% ee with 35}
\end{figure}

3.4 \textit{The effect of pressure}

It has been recognised that an important factor for the decrease in asymmetric induction in the palladium catalysed allylic substitution reaction is the dissociation of ligands from palladium. Therefore, the reaction of allylic acetate 35 with dimethyl malonate was investigated under high pressure conditions (10 Kbar) since it was anticipated that high pressure would enhance the binding of ligands to palladium.\textsuperscript{107} This approach has been reported to be successful in the palladium catalysed coupling of 2,3-dihydrofuran and aryl compounds. At high
pressure an increase in activity of the catalyst and an increase in enantioselectivity compared to normal pressure was observed 108

Oxazolines 86c, 87c and 91c were chosen to participate in this study due to their structural similarity but distinct binding properties. To ensure a valid comparison, the reactions at normal and high pressure were performed on the same stock solution. The components of the reaction mixture were added together at room temperature and pressure, the reaction was then initiated by the addition of a catalytic amount of potassium acetate. The reaction mixture was then divided into two equal portions, one half of which was left standing for the requisite time, the other half was sealed in a teflon tube and subjected to a pressure of 10Kbar for the same amount of time (Scheme 46).

![Scheme 46](image)

After the allotted time, the reaction mixtures were filtered through a pad of silica and then analysed by capillary gas chromatography to compare their extent of conversion to desired product 46. The crude mixtures were further purified by flash chromatography to isolate the product 46. The preferred assay to determine the enantiomeric excess was the use of the enantiopure shift reagent Eu(hfc)3 in 1H NMR.
The experiments were executed with 10 mol% of ligand and a palladium to ligand ratio of 1 to 2. After 4 hours it emerged that for oxazolines 86c and 87c the rate of reaction is significantly increased at higher pressures (Table 14). It was to be expected that no discernible increase in rate would be detected for the phosphine containing oxazoline 91c, which is known from previous studies to reach completion within one hour at normal temperature and pressures. However, in all cases enantioselectivity was diminished at high pressure compared with ambient pressure.

3.5 Summary

(i) Both sulfide and phosphine containing oxazolines are effective in controlling the enantioselectivity of palladium catalysed allylic substitution.

(ii) The observed enantioselectivity was dependent on the nature of the auxiliary ligand and increased in the order (PPh₂ > SPh > SMe)
(iii) The reactivity of the phosphine containing oxazolines are exceptional even in comparison to triphenylphosphine as the supporting ligand.

(iv) For the sulfide containing oxazolines, the observed enantioselectivities were dependent on the steric environment created by the 4-substituent on the oxazoline ring (tBu > Ph > iPr > PhCH₂ > Me). The phosphine containing oxazolines were surprisingly insensitive to these changes.

(v) High pressure (10 Kbar) reduces the observed enantioselectivity but increases the rate of reaction for palladium catalysed allylic substitution.
Chapter Four

Origin Of Enantioselectivity Using Enantiopure Oxazoline Ligands
4.1 Introduction

The enantioselectivities obtained using the enantiopure oxazolines have demonstrated that the strategy we have adopted represents a fresh solution to the problem of asymmetric palladium catalysed allylic substitution. The mechanistic rationale for the observed enantioselectivity is not obvious. With the non-symmetrical enantiopure oxazolines, two diastereomeric allyl complexes are generated with palladium (0). Intuitively, it would be expected that complex 94, the 'M' form would be sterically preferred over 95, the 'W' form, due to the steric interactions between the R and the allyl moiety, and this was the reason for preparing these ligands. In complex 94 this steric interaction appears not to be present, and therefore we assumed that the reaction would proceed via this complex.

\[
\begin{align*}
94 & \quad \text{Sterically favoured} \\
95 & \quad \text{Sterically disfavoured}
\end{align*}
\]

For enantioselection to be achieved the differing \textit{trans} influences of the two donor atoms in the ligand would create an electronic bias in the intermediate palladium allyl species. This would then be expected to direct nucleophilic addition to one terminus of the allyl group in preference to the other.
4.2 Using enantiopure thienyl oxazolines

The thienyl oxazolines were successful in controlling the enantioselectivity of nucleophilic addition. The experimental evidence suggests that the reaction proceeds via one of two possible diastereomeric transition states 96 or 97 in favour of the product with the (S)-configuration (Figure 13).

![Diagram of 96 and 97 complexes](image)

If the reaction proceeds via the sterically favoured complex 96 the nucleophile would have to attack _trans_ to the nitrogen of the oxazoline ring. This would infer that the thiophene ring was not acting as a π-acceptor but was instead behaving more like a π-donating moiety. This might not be unexpected if the thiophene is viewed as a π-excessive aromatic. Thus, electronic information would be relayed via the _trans_ effect to the terminus _trans_ to the sulfur. This terminus would be
expected to possess a greater electron density, rendering the site less susceptible to nucleophilic attack.

On the other hand, the reaction might proceed via the less favoured complex 97. If this was the case, the nucleophile would have to attack the terminus trans to the thiophene ring. This would imply that a sulfur contained within a thiophene ring could act as a $\pi$-acceptor, which as a consequence would render the carbon trans to the sulfur more electrophilic. Whichever is the correct reaction pathway, the stereochemical outcome is being controlled by both the steric and electronic properties of the ligand.

4.3 Using enantiopure sulfide containing oxazolines

All of the enantiopure sulfide containing oxazolines furnished the addition product enriched with the (S)–(–)-enantiomer. This is analogous to the stereochemical outcome observed for the enantiopure thienyl oxazolines. In the case of the thienyl oxazolines it has been discussed that the thienyl group might function as a $\pi$-donor, and hence nucleophilic addition might occur cis to the sulfur. However, for the sulfide containing oxazolines this argument is not valid, the nucleophile is only likely to approach the allyl terminus trans to the auxiliary sulfide ligand. Either the transition state is more distorted than represented here or the two diastereomeric allyl complexes are in rapid equilibrium as represented in Scheme 47. The reaction might then proceed through the less stable, but possibly more reactive, intermediate 99.
The rate at which such an equilibrium occurs would have an effect on the enantioselectivity of the reaction. Since palladium allyl complexes are known to equilibrate in the presence of acetate, it was decided to examine the effect of adding acetate to the reaction. Oxazoline 86c was chosen to participate in this study, since the levels of enantioselectivity achieved with this ligand were modest and therefore either enhancement or reduction of the enantioselectivity would be easily detected (Scheme 48).

The reactions were performed under standard conditions at room temperature in THF. It was found that the addition of excess acetate to the reaction dramatically decreases the observed enantioselectivity of the product 46 (Table 15). This
implies that the rate of equilibration of the two possible diastereomeric intermediates may be significant

Table 15

<table>
<thead>
<tr>
<th>Added acetate</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>58</td>
</tr>
<tr>
<td>1 eq KOAc</td>
<td>48</td>
</tr>
<tr>
<td>10 eq KOAc</td>
<td>30</td>
</tr>
<tr>
<td>10 eq NaOAc</td>
<td>34</td>
</tr>
</tbody>
</table>

During the course of the reaction, the concentration of liberated acetate ion increases (in the absence of added acetate). In accord with the previous observations, the enantioselectivity of the reaction would be expected to decrease as the reaction progresses. This was investigated under the standard reaction conditions in THF at room temperature using ligand 86c. At various time intervals aliquots were removed from the reaction and quenched with water. After work-up the crude mixture was subjected to gas chromatography (SGE BP1 capillary column) to reveal the extent of conversion and analysis of the $^1$H NMR spectrum in the presence of enantopure shift reagent to determine the enantiomeric excess. Remarkably, no significant variation in the level of enantioselectivity was observed in relation to time and the extent of conversion (Table 16)
Table 16

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Conversion (%)</th>
<th>Enantioselectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>48</td>
</tr>
</tbody>
</table>

4.4 Using enantiopure phosphine containing oxazolines

The enantiopure phosphine containing oxazolines have proved to be the most effective ligands for the palladium catalysed allylic substitution reactions studied. In all cases, the reactions reached completion within one hour at room temperature, the enantioselectivities were consistently very high and furnished the product with the (S)-(−)–enantiomer predominating.

Very recently, Helmchen et al have obtained crystal and solution structures of an allylpalladium complex co-ordinated to a phosphine containing oxazoline ligand. The results presented by Helmchen along with our own observations enable conclusions concerning the stereochemical course of allylic substitution to be drawn. The X-ray crystal structure of the allylpalladium complex derived from ligand 91c is shown in Figure 14, the anions and hydrogen atoms have been omitted for clarity. Selected bond lengths and angles are given.
In the side view, the horizontal line (a) marks the co-ordination plane spanned by C1, C3, Pd, P, and N. The vertical line (b) is erected perpendicularly to the co-ordination plane at the P atom. The angle between (a) and (d) is mainly determined by the necessity of bond angles near 90° at Pd and steric effects. Axial disposition of the iso-propyl group is a consequence of steric interactions of this group with ligands at Pd.
Contrary to expectations, the 'W' form corresponding to the sterically disfavoured complex 100 was found in the crystal. The disclosure by Helmchen that the Pd–C bond trans to phosphorus (226 ± 1 pm) is longer than the Pd–C bond trans to nitrogen (214 ± 1 pm) would be anticipated from the allylic complexes of other N–N and P–P chelate ligands. The revelation that 100 is the more stable complex may be remarkable in the light of the previous steric analysis, but there is a notable absence of any steric interactions between the 4–substituent on the oxazoline ring and the allylic phenyl group in the crystal structure (Figure 14).

NMR investigations were carried out by a variety of methods and revealed interesting results. The palladium complex of 91c with allylic acetate 35 displays an 8 : 1 ratio of the two diastereomeric allyl complexes 100 and 101. This ratio was found to increase upon lowering of temperature. The two complexes are able to interconvert via a Pd–C rotation mechanism, this is reported to proceed via the opening of the weaker (longer) Pd–C3 bond, as illustrated in Scheme 49. However, Togni et al have recently disclosed an unusual, η3–η1 allyl isomerisation in allylpalladium complexes involving novel enantiopure chelating diphosphine ligands.

Scheme 49
The level of asymmetric induction achieved with the phosphine containing oxazoline 91c was consistently above 95% ee (> 39 : 1), whilst the equilibrium diastereomer ratio of the two complexes 100 and 101 is only 8 : 1. This would infer that the control of enantioselectivity is a question of which diastereomer is the most reactive. Nucleophilic addition would 'funnel' through the more reactive diastereomer whilst equilibration of the two diastereomers was being maintained.

Nucleophilic addition at the allylic carbon with the weaker (longer) bond to palladium has previously been demonstrated by Pfaltz and co–workers with palladium complexes of C₂–symmetric bis–oxazoline ligands.¹¹³ In line with this reasoning, the observed stereochemical outcome is consistent with complex 102 being the more reactive conformer, nucleophilic addition occuring mainly trans to the π-accepting phosphine ligand to afford principally the (S)–enantiomer of alkylation product 46, as illustrated in Figure 15. It is feasible that nucleophilic attack occurs at the minor diastereomer to a small extent. This would be expected to take place mainly trans to the phosphorus furnishing the (R)–enantiomer of addition product.

A similar conclusion was reached by Bosnich and co–workers in that the major diastereomer of their Pd–allyl complex, as defined by X–ray, was the one involved in the nucleophilic addition step.¹¹⁴ For the phosphine containing
oxazolines the same concept was independently derived by Pfaltz\textsuperscript{115} In a related paper Brown rationalises the sense of asymmetric induction for enantioselective alkylation with palladium complexes of 1-(2-diphenylphosphino-1-naphthyl)isoquinoline 93.\textsuperscript{116}

For the enantiopure oxazolines studied, the enantioselectivity was observed to decrease as the \(\pi\)-accepting capability of the ligand decreased (SMe < SPh < PPh\(_2\)). This could be attributed to increased nucleophilic attack at the allylic terminus cis to the auxiliary ligand in the more reactive diastereomer as the electronic disparity between the two allylic termini decreases. A recent paper by Togni et al/lends support to this theory\textsuperscript{117} For asymmetric allylic alkylation with palladium complexes of novel enantiopure ferrocenyldiphosphines, a decrease in enantioselectivity is observed utilising ligand 103 containing two electronically similar phosphine fragments compared with ligand 52 containing two electronically distinct phosphine groups.

\[
\begin{align*}
52 & \quad 93\% \text{ ee with 35} \\
103 & \quad 66\% \text{ ee with 35}
\end{align*}
\]

4.5 Summary

The recent crystallographic and NMR spectroscopic studies from the Helmchen and Pfaltz laboratories have shed some light on the pathway of asymmetric palladium catalysed allylic substitution with enantiopure P–N chelate ligands. It seems likely that the sulfur containing oxazolines function in a similar fashion. However, as no X-ray or NMR studies have been conducted with the sulfur
containing oxazoline ligands, any analogies with the phosphine analogues are hypothetical

(i) Two diastereomeric allylpalladium complexes are generated in the presence of enantiopure ligand. The 'W' form predominates in the solid state and in solution.

(ii) The ligands rely upon an electronic disparity between the two donor atoms to direct nucleophilic addition.

(iii) The 'W' form is the more reactive of two rapidly equilibrating diastereomers, attack occurs trans to the π-accepting auxiliary ligand to furnish in each case the (S)-(−)-enantiomer of product predominantly.

(iv) By increasing the π-accepting ability of the auxiliary ligand the enantioselectivity of nucleophilic addition is observed to increase.
Chapter Five

Enantiopure Acetals as Ligands
5.1 Introduction

In previous chapters it has been established that enantiopure oxazoline ligands provide high levels of asymmetric induction in palladium catalysed allylic substitution reactions. The oxazolines incorporate an auxiliary donor ligand with distinct electronic properties, whilst providing an asymmetric environment adjacent to the chelated metal. We wished to examine the incorporation of other heteroatoms into the design of the ligand. Enantiopure acetals would allow this whilst generating a similar topology (Figure 16).

![Oxazoline ligands](attachment:oxazoline.png) ![Acetal ligands](attachment:acetal.png)

**Figure 16**

Enantiopure acetals have been successfully employed in diastereoselective reactions for over twenty years. A highly effective method for the synthesis of optically active alcohols was developed using enantiopure acetal protecting groups that are subjected to activation by electrophiles or nucleophiles. Johnson et al report the reaction of enantiopure acetals derived from (R,R)- and (S,S)-pentane-2,4-diol and cyanotrimethylsilane leading to the production of cyanohydrin ethers and derivatives thereof in high optical and chemical yields (Scheme 50).
Yamamoto et al. demonstrate the high efficiency of enantiopure α,β-unsaturated acetics in the asymmetric cyclopropanation reaction\textsuperscript{121}. The process is outlined in Scheme 51, since both \((R,R)\)- and \((S,S)\)-tartaric acid esters are readily available in an enantiomERICally pure form, this method allows the synthesis of both enantiomers of cyclopropanes from α,β-unsaturated aldehydes in a predictable manner.

Alexakis et al. have reported the diastereoselective conjugate addition of achiral organocopper reagents to enantiopure α,β-unsaturated acetics prepared from enantiopure C\(_2\) symmetrical diols\textsuperscript{122} Aryl-, alkenyl- or vinylcopper with
BF₃ Et₂O react with vinyl acetics in an \textit{anti} S_N2 reaction that results in a diastereoselective cleavage of the acetal ring. The resulting enol ethers were easily hydrolysed to furnish enantiomerically enriched β-substituted aldehydes with the recovery of the enantiopure diol. \textbf{(Scheme 52)} Conjugate addition to enantiopure ketals has also been achieved with moderate stereoselectivity \textit{(up to 48% ee)}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme52.png}
\end{center}

\textbf{Scheme 52}

In a related study, Yamamoto \textit{et al} report the diastereoselective, nucleophilic 1,4- or 1,2-addition of trimethylaluminium to enantiopure vinyl acetals derived from α,β-unsaturated aldehydes and (R,R)-(+)–N,N,N′,N′-tetramethyltartaric acid diamide \textsuperscript{123} Excellent levels of asymmetric induction are achieved, thus providing easy access to β-substituted aldehydes or allylic alcohols, as depicted in \textbf{Scheme 53}.
Tartrate derived aryl aldehyde acetals have been used successfully as enantiopure auxiliaries in the asymmetric metalation of chromium tricarbonyl arene complexes. Treatment of complex 104 with nBuLi followed by quenching with various electrophiles afforded products with high levels of diastereoselectivity (Scheme 54).
Whilst enantiopure acetals have played an important role in auxiliary based asymmetric synthesis, their use as chelating ligands for asymmetric catalysis has not been reported. There are however, numerous reported examples of ketal containing enantiopure ligands, for example, derived from tartaric acid or carbohydrates. Electronically similar, but synthetically complex, podand ionophores have also found applications in enantioselective complexation.

5.2 Preparation of enantiopure acetals

The success of acetals as enantiopure auxiliaries has led to the preparation of such compounds being well documented. The acetal ligands 105–108 were prepared by the reaction of the corresponding aldehyde with an enantiopure C₂-symmetric diol by heating in the presence of catalytic amounts of camphorsulfonic acid in toluene with removal of the toluene/water azeotrope. All of the enantiopure acetal ligands have been satisfactorily characterised by both analytical and spectroscopic techniques. The preparation of these ligands is summarised in Table 17. The starting diols employed are (S,S)-1,2-diphenylethanediol, (R,R)-2,3-butanediol and (R,R)-2,4-pentanediol.
### Table 17

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Diol</th>
<th>Yield (%)</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine CHO</td>
<td>HO-Ph</td>
<td>63</td>
<td><img src="image" alt="Ligand 105" /></td>
</tr>
<tr>
<td>1,2-Diphenylethane CHO</td>
<td>HO-Me</td>
<td>77</td>
<td><img src="image" alt="Ligand 106" /></td>
</tr>
<tr>
<td>1,2-Diphenylethane CHO</td>
<td>HO-Me</td>
<td>82</td>
<td><img src="image" alt="Ligand 107" /></td>
</tr>
<tr>
<td>1,2-Diphenylethane CHO</td>
<td>HO-Ph</td>
<td>61</td>
<td><img src="image" alt="Ligand 108" /></td>
</tr>
</tbody>
</table>

Alternatively, the aldehyde was initially converted into the dimethyl acetal upon treatment with trimethyl orthoformate in methanol using cerium trichloride as a catalyst.\textsuperscript{128} Subsequent transacetalisation with the diol in the presence of camphorsulfonic acid with the removal of the toluene/methanol azeotrope affords the desired ligands 112–115, as summarised in Table 18.
<table>
<thead>
<tr>
<th>Acetal</th>
<th>Diol</th>
<th>Yield (%)</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure Image" /></td>
<td><img src="image2" alt="Structure Image" /></td>
<td>92</td>
<td><img src="image3" alt="Structure Image" /></td>
</tr>
<tr>
<td><img src="image4" alt="Structure Image" /></td>
<td><img src="image5" alt="Structure Image" /></td>
<td>77</td>
<td><img src="image6" alt="Structure Image" /></td>
</tr>
<tr>
<td><img src="image7" alt="Structure Image" /></td>
<td><img src="image8" alt="Structure Image" /></td>
<td>52</td>
<td><img src="image9" alt="Structure Image" /></td>
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<tr>
<td><img src="image10" alt="Structure Image" /></td>
<td><img src="image11" alt="Structure Image" /></td>
<td>64</td>
<td><img src="image12" alt="Structure Image" /></td>
</tr>
</tbody>
</table>

Aldehyde 117 is not commercially available, but is easily synthesised by the nucleophilic substitution of 2-fluorobenzaldehyde 116 with sodium benzenethiolate in an analogous procedure to the preparation of 2-(phenylthio)benzonitrile 90, as illustrated in Scheme 55.
5.3 Results for palladium catalysed allylic substitution

The enantiopure acetal ligands were examined for their ability to provide asymmetric induction in palladium catalysed allylic substitution reactions. The reaction of dimethyl malonate with the allylic acetates 35 and 2-acetoxypent-3-ene 118 were examined, in all cases 2.5 mol% of [Pd(η3-C3H5)Cl]2 and 20 mol% of the ligand were used.

Table 19

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Substrate</th>
<th>Time (hr)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>105</td>
<td>35</td>
<td>96</td>
<td>46</td>
<td>70</td>
<td>32</td>
</tr>
<tr>
<td>112</td>
<td>35</td>
<td>48</td>
<td>46</td>
<td>59</td>
<td>&lt;5</td>
</tr>
<tr>
<td>113</td>
<td>35</td>
<td>24</td>
<td>46</td>
<td>79</td>
<td>60</td>
</tr>
<tr>
<td>114</td>
<td>35</td>
<td>48</td>
<td>46</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td>115</td>
<td>35</td>
<td>24</td>
<td>46</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>106</td>
<td>35</td>
<td>24</td>
<td>46</td>
<td>75</td>
<td>68</td>
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<td>107</td>
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<td>46</td>
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<td>88</td>
</tr>
<tr>
<td>108</td>
<td>118</td>
<td>72</td>
<td>19</td>
<td>62</td>
<td>36</td>
</tr>
</tbody>
</table>

The alkylations were initially performed under standard BSA conditions in dichloromethane at room temperature. However, for ligands 105, 112 and 113,
these conditions failed to give any product. In these cases, the alkylation reaction was accomplished with the sodium salt of dimethyl malonate in THF at 60°C. The enantiomeric excess was determined from the ^1H NMR spectrum in the presence of enantiopure shift reagent Eu(hfc)$_3$, and the results are detailed in Table 19. In each case the product 46 was formed with the (S)-(−)-enantiomer predominating, as determined from the sign of the optical rotation. This is surprising, since the absolute configuration of the ligand is opposite for the diphenyl-substituted acetals and the dimethyl-substituted acetals.

It was noted that by increasing the π-accepting capability of the auxiliary ligand, the enantioselectivity of the isolated product 46 was observed to increase. This is in accordance with the findings for the substitution reaction employing the enantiopure oxazoline ligands.

In a similar way to our previous studies with oxazolines, where we have assumed that the incoming nucleophile approaches trans to the better π-acceptor, we assume that the same will be true for the acetal ligands. It is anticipated that the ligands bind in a chelating fashion as other allylpalladium complexes have been reported containing P–O chelating ligands. It is less clear which lone pair of electrons on the acetal (all four are different from each other) is involved in binding to the palladium.

Upon binding to the palladium a new stereocentre is generated at the carbon between the two oxygen atoms of the acetal. For steric reasons, it would be expected that the palladium binds to the lone pair trans to the adjacent Ph group of the acetal, this would then give rise to two possible isomers as illustrated in Figure 17.
When the palladium is bound to the acetal ligand the complex could be considered analogous to a fused bicyclic system. When small rings are involved in such systems, the cis-fused isomer would be expected to be more stable than the corresponding trans-fused isomer. Nucleophilic attack would then be expected to occur trans to the π-accepting auxiliary ligand furnishing the addition product 46 with the observed (S)-conformation, as depicted in Figure 18. The circumstances are more complex for the dimethyl-substituted acetal ligands, consequently an alternative interpretation is required.

The rationale cited for the origin of enantioselectivity is purely conceptual and without the support of X-ray crystal structure data and NMR binding studies, no categorical conclusions can be reached.
5.4 Summary

(i) Enantiopure acetals tethered to auxiliary donor ligands afford good levels of enantioselectivity in palladium catalysed allylic substitution.

(ii) In comparison with enantiopure oxazoline ligands, the acetals exhibit lower levels of reactivity and asymmetric induction.

(iii) The observed enantioselectivity was dependent on the nature of the auxiliary ligand and increased as the π-accepting capability of the ligand increased.
Chapter Six

Experimental Section
6.1 General Information

Solvents and Reagents—Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction of petroleum ether boiling between 40°C and 60°C, and was distilled through a 36cm Viguex column before use. 'Ether' refers to diethyl ether, this was dried by standing over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane was distilled from phosphorus pentoxide. DMF was dried by stirrning over calcium hydride for 15h, decanted, and distilled under reduced pressure before storing over 4Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over, potassium hydroxide pellets.

Chromatographic Procedures—Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 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.

Spectroscopic Techniques—Infra red spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform, thin films or as a nujol mull. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser. \(^1\)H and \(^{13}\)C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments. \(^1\)H NMR spectra are referenced against residual undeuterated solvent, in the case of...
removed in vacuo  The residue was purified by flash chromatography (light petroleum/ether 3:1) to afford a clean product

\((4S,5R)-4,5\text{-Dihydro}-4\text{-methyl-5-phenyl-2-(2-thienyl)-1,3-oxazole 77f}\). (91%) as a viscous, colourless oil  B p  210–211°C at 0.5 mmHg (found MH+, 244 0796  C\textsubscript{14}H\textsubscript{13}NOS requires MH+, 244 0796)  \([\alpha]_D\textsuperscript{25} +553.6 \) (c 0.28, CHCl\textsubscript{3})  \(v_{\text{max}} /\text{cm}^{-1}\)  1651(C=N), 1445, 1093, 1056, 966, 847, 747  \(\delta_H \) (400 MHz, CDCl\textsubscript{3})  0.87 (3H, d, J 7 0, CH\textsubscript{3}), 4.63 (1H, dd, J 7.0, 6.8, CH\textsubscript{2}CH\textsubscript{3}), 5.74 (1H, d, J 9.7, CHO), 7.11 (1H, m, thiophene CH), 7.23–7.37 (5H, m, aromatic CH), 7.49–7.69 (2H, m, thiophene CH)  \(\delta_C \) (100 Hz, CDCl\textsubscript{3})  175.6 (CH\textsubscript{3}), 65.5 (CHN), 84.3 (CHO), 126.0 / 127.5 / 127.8/128.2/129.7 (aromatic CH), 130.3 (aromatic C), 158.7 (C=N)  \(m/z \) (EI) 244(MH+, 100%), 170(14), 137(32), 111(8)

\((4S)-4\text{-benzyl-4,5\text{-Dihydro-2-(2-thienyl)-1,3-oxazole 77b}\). (73%) as a colourless crystalline solid  M p. 42–44°C. (found M\(+, 243.0725.  C\textsubscript{14}H\textsubscript{13}NOS requires M\(+, 243.0718\).  \([\alpha]_D\textsuperscript{25} +26.0 \) (c 0.5, CHCl\textsubscript{3})  \(v_{\text{max}} /\text{cm}^{-1}\)  1651(C=N), 1436, 1057, 709.  \(\delta_H \) (400 MHz, CDCl\textsubscript{3})  2.70 (1H, dd, J 9.1, 13.7, CH\textsuperscript{3}Ph), 3.25 (1H, dd, J 4.8, 13.7, CH\textsuperscript{3}Ph), 4.13 (1H, dd, J 7.3, 8.7, CH\textsuperscript{3}OH), 4.32 (1H, t, J 8.7, CH\textsuperscript{3}OH), 4.52–4.60 (1H, m, CHN), 7.06–7.08 (1H, m, thiophene CH), 7.20–7.32 (5H, m, aromatic CH), 7.44–7.45 (1H, m, thiophene CH), 7.57–7.59 (1H, m, thiophene CH).  \(\delta_C \) (100 MHz, CDCl\textsubscript{3})  41.5 (CH\textsubscript{2}Ph), 67.9 (CHN), 72.1 (CH\textsubscript{2}O), 126.4 / 127.4 / 129.1 / 129.7 / 130.2 (aromatic CH), 137.7 (aromatic C), 159.6 (C=N)  \(m/z \) (EI) 243(M\(+, 5\%), 152(100), 124(14), 97(16), 69(12)

\((4S)-4,5\text{-Dihydro-4-isopropyl-2-(2-thienyl)-1,3-oxazole 77c}\). (82%) as a colourless oil  B p  125–126°C at 0.5 mmHg. (found M\(+, 195.0718.  C\textsubscript{10}H\textsubscript{13}NOS requires M\(+, 195.0718\)  \([\alpha]_D\textsuperscript{25} -89.3 \) (c 0.28, CHCl\textsubscript{3})  \(v_{\text{max}} /\text{cm}^{-1}\)  1651(C=N), 1433, 1060, 1021, 951, 853, 715.  \(\delta_H \) (400 MHz, CDCl\textsubscript{3})  0.90 (3H, d, J 6.8, CH\textsubscript{3}), 1.00 (3H, d, J 6.8, CH\textsubscript{3}), 1.84 (1H, m, CH\textsubscript{3}CH\textsubscript{3}), 4.05–4.15 (2H, m, CH\textsubscript{2}O),

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4.34-4.41 (1 H, m, CHN), 7.05 (1 H, m, thiophene CH), 7.41 (1 H, m, thiophene CH), 7.57 (1 H, m, thiophene CH). δC (100 MHz, CDCl₃) 17.8 (CH₃), 18.8 (CH₃), 32.5 (CH(CH₃)₂), 70.2 (CH₂O), 72.6 (CHN), 127.4/129.4/129.9 (aromatic CH), 130.3 (aromatic C), 158.9 (C=)= m/z (EI) 195(M⁺, 10%), 152(100), 124(47), 111(24), 97(52)

(4S)-4,5-Dihydro-4-phenyl-2-(2-thienyl)-1,3-oxazole 77d. (79%) as a colourless crystalline solid. Mp 78-79°C (Found C, 68.4 H, 4.9, N, 6.1. C₁₃H₁₁NOS requires C, 68.1; H, 4.8; N, 6.1%). [α]₂⁰⁺18.33 (c 0.6, CHCl₃). νmax / cm⁻¹ 1644(C=N), 1434,1464. δH (250 MHz, CDCl₃) 4.26 (1 H, t, J 8.1, CHH'O), 4.77 (1 H, dd, J 8.2, 10.0, CHH'O), 5.36 (1 H, dd, J 8.1, 10.0, CHN), 7.10 (1 H, m, thiophene CH), 7.28 (m, 5H, aromatic CH), 7.47 (1 H, m, thiophene CH), 7.68 (1 H, m, thiophene CH). δC (63 MHz, CDCl₃) 70.3 (CHN), 75.2 (CH₂O), 126.8/127.7/128.8/130.1/130.7 (aromatic CH), 142.1 (aromatic C), 160.2 (C=N) m/z (EI) 229(M⁺, 75%), 199(100), 171(18), 151(19), 111(24), 96(39)

(4S)-4,5-Dihydro-4-tert-butyl-2-(2-thienyl)-1,3-oxazole 77e. (74%) as a colourless crystalline solid. Mp 44-45°C (found M⁺, 209.0868 C₁₁H₁₅NOS requires M⁺, 209.0874) [α]₂⁰⁻76.5 (c 0.34, CHCl₃). νmax / cm⁻¹ 1654(C=N) δH (250 MHz, CDCl₃) 0.95 (9H, s, C(CH₃)₃), 4.03 (1 H, dd, J 7.4, 10.0, CHN), 4.26 (2H, m, CH₂O), 7.06 (1 H, m, thiophene CH), 7.43 (1 H, m, thiophene CH), 7.59 (1 H, m, thiophene CH). δC (63 MHz, CDCl₃) 25.9 (CH₃ x 3), 34.1 (C(CH₃)₃), 69.1 (CH₂O), 76.4 (CHN), 127.5/129.5/130.0 (aromatic CH), 130.2 (aromatic C), 159.1 (C=N). m/z (EI) 209(M⁺, 5%), 152(100), 124(15), 111(15), 97(10).

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\((4S,5S)-4,5\text{-Dihydro-4-hydroxymethyl-5-phenyl-2-(2-thienyl)-1,3-oxazole}\) 82.

In a 50ml Schlenk flask, zinc chloride (68mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by 2-thiophenecarbonitrile (1.1g, 10 mmol) and \((1S,2S)-(+)\)-1-phenyl-2-amino-1,3-propanediol (2.5g, 15 mmol). The mixture was heated under reflux for 48 hours. The solvent was removed in vacuo to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml). The combined organic phases were dried (Na\(_2\)SO\(_4\)), filtered and the solvent removed in vacuo to give a crude solid which could be crystallised by dissolving in ether and cooling to -78°C to give the \textit{title compound} (168g, 65%) as a colourless crystalline solid. M.p. 160-162°C (found C, 65.0; H, 5.0; N, 5.4; C\(_{14}\)H\(_{13}\)NO\(_2\)S requires C, 64.9; H, 5.1; N, 5.4). 

\([\alpha]_D^{25}+50.0\) (c 1.02, CHCl\(_3\)). \(\nu_{\text{max}}\) / cm\(^{-1}\) 1670 (C=N).

\(\delta_H\) (400 MHz, CDCl\(_3\)) 3.75 (1H, dd, J 3.2, 11.9, CH\(_3\)OH), 4.02 (1H, br S, O\(_{\text{H}}\)), 4.11 (1H, dd, J 3.2, 11.9, CH\(_3\)OH), 4.21 (1H, m, CHN), 5.60 (1H, d, J 8.1, CHO), 7.01 (1H, m, thiophene CH), 7.30-7.40 (5H, m, aromatic CH), 7.42-7.57 (1H, m, thio phene CH) \(\delta_C\) (100 MHz, CDCl\(_3\)) 62.9 (CH\(_2\)OH), 76.7 (CHN), 83.0 (CHO), 125.8-130.9 (aromatic CH), 129.4/139.2 (aromatic C), 160.4 (C=\(\text{N}\)) m/z (El) 260(MH\(^+\), 100%), 230(27), 111(9)
(4S,5S)-4,5-Dihydro-5-phenyl-2-(2-thienyl)-4-triphenylmethoxymethyl-1,3-oxazole 83.

To a stirring mixture of (4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-(2-thienyl)-1,3-oxazole 82 (0.50g, 1.9 mmol), triethylamine (0.59g, 5.7 mmol) and DMAP (1-2 crystals) in dichloromethane (20 ml) at room temperature was added trityl chloride (0.58g, 2.0 mmol). The mixture was allowed to stir overnight (12 hours), after which time TLC (light petroleum / ether 3:1) indicated that the starting material had been consumed. The mixture was extracted with dichloromethane (3 x 30 ml) then the organic extracts washed with water (3 x 30 ml). The organic extracts were then dried (Na2SO4), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (light petroleum / ether 3:1) to afford the title compound (0.64g, 67%) as a colourless crystalline solid. M p. 126-127°C (found C, 79.5, H, 5.7, N, 2.8. C33H27N03S requires C, 79.1; H, 5.4; N, 2.8.). [α]D25 +35.7 (c 0.98, CHCl3). vmax / cm⁻¹ 1643(C=N). δH (250 MHz, CDCl3) 3.29 (1H, dd, J 7.3, 9.2, CHH'OTr), 3.55 (1H, dd, J 3.9, 9.2, CHH'OTr), 4.37 (1H, m, CHN), 5.46 (1H, d, J 6.3, CHO), 7.09-7.67 (23H, m, aromatic CH), δC (63 MHz, CDCl3) 65.7 (CH2OTr), 75.2 (CHN), 84.9 (CHO), 86.8 (CPh3), 125.9-130.6 (aromatic CH), 140.8/143.8 (aromatic Q), 159.9 (C=N) m/z (El) 501(M⁺, 5%), 320(10), 244(32), 228(100), 165(56), 111(25).
1,3-diphenylprop-2-en-1-ol 85.

To a stirred solution of phenylmagnesium bromide, prepared from Mg (6.07g, 0.25mol) and bromobenzene (39.3g, 0.25mol) in sodium dried ether (50ml), was added dropwise to a solution of cinnamaldehyde (33g, 0.25mol) in sodium dried ether (50ml) over 15 min. The mixture was allowed to stir for 3 hours at 25°C and then was quenched with saturated ammonium chloride. The aqueous layer was extracted once with ether (30ml) and the combined ether extracts were washed with water (2 x 30ml), with brine (2 x 30ml), and dried (MgSO4). Filtration followed by removal of the ether in vacuo afforded the title compound (43.6g, 83%) as a low melting solid which was used directly in the next step.

\[ \delta_H (250 \text{ MHz, CDCl}_3): 2.39 (1H, s, \text{O}H), 5.25 (1H, d, J 6.8, \text{CH}OH), 6.32 (2H, m, \text{HC} = \text{CH}), 7.22-7.40 (10H, m, \text{aromatic CH}) \]

(E)-1,3-diphenyl-3-acetoxy-1-propene 35.

To a solution of 1,3-diphenylprop-2-en-1-ol 85 (25g, 0.12 mol) in acetic anhydride (12.4ml) and pyridine (50ml) was added DMAP (1-2 crystals). The mixture was then allowed to stir for 24 hours at room temperature. The solvent was removed in vacuo and the residue diluted with water. This was then extracted with ether (3 x 50ml). The combined ether extracts were washed with water (2 x 50ml) and then with brine (50ml) and then dried (Na2SO4). Filtration followed by removal of
To [(n3-C3H3)PdCl]2 (4mg, 2.5mol%) was added a solution of the ligand (10 mol%) in dry dichloromethane (1ml). The solution was allowed to stir for 15 mins at room temperature. The resulting yellow solution was treated successively with a solution of rac-(E)-1,3-diphenyl-3-acetoxy-1-propene (0.4mmol) in dichloromethane (1ml), dimethyl malonate (1.2mmol), N,O-bis(trimethylsilyl) acetamide (1.2mmol), and anhydrous potassium acetate (3mol%). The reaction mixture was stirred at room temperature for 12-96 hours, until conversion was complete according to TLC analysis. The reaction mixture was diluted with ether (25ml), transferred to a separatory funnel and washed with ice-cold saturated aqueous ammonium chloride (2x25ml). The organic phase was dried (MgSO4), filtered then concentrated in vacuo. The residue was purified by flash chromatography (light petroleum/ether 3:1).

**Dimethyl-1,3-diphenylprop-2-enylmalonate 46.** $\nu_{\text{max}} / \text{cm}^{-1}$ 1765, 1740, 1605, 1500, 1460, 1440, 1325, 1265 $\delta_H$ (250 MHz, CDCl3) 3.53 (3H, s, CO$_2$CH$_3$), 3.70 (3H, s, CO$_2$CH$_3$), 3.95 (1H, d, J 11, CH$_2$E$_2$), 4.27 (1H, dd, J 11, 8, PhCHCE$_2$), 6.32 (1H, dd, J 15, 8, H=C=CHPh), 6.48 (1H, d, J 15, H=C=CHPh), 7.15-7.44 (10H, m, aromatic CH) $\delta_C$ (63 MHz, CDCl3) 49.1 (CH), 52.4 (CH$_3$), 52.6 (CH$_3$), 57.6 (CH), 126.3/127.1/127.5/127.8/128.4/128.7/129.1/131.8 (alkene/aromatic CH), 136.8/140.1 (aromatic C), 167.7/168.1 (C=O).

### 6.3 Experimental for Chapter Three

**General procedure for preparation of (4S)-4-substituted-4,5-Dihydro-2-[2-(methylsulfanyl)phenyl]-1,3-oxazoles**

```latex
\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {OH};
  \node (B) at (1,-1) {NH$_2$};
  \node (C) at (2,0) {SMel};
  \node (D) at (3,0) {CN};
  \node (E) at (4,0) \text{MeS};
  \node (F) at (4,-1) \text{MeS};
  \node (G) at (5,0) \text{R};
  \node (H) at (5,-1) \text{R};

  \draw [->] (A) -- (B);
  \draw [->] (B) -- (C);
  \draw [->] (C) -- (D);
  \draw [->] (D) -- (E);
  \draw [->] (E) -- (F);
  \draw [->] (F) -- (G);
  \draw [->] (G) -- (H);
\end{tikzpicture}
\end{center}
```
In a 50ml Schlenk flask, zinc chloride (68mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by (2-methylsulfonyl)benzonitrile (10 mmol) and the amino alcohol (13 mmol). The mixture was heated under reflux for 48 hours. The solvent was removed in vacuo to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml). The combined organic phases were dried (Na$_2$SO$_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (light petroleum/ether 3:1).

(4S)-4,5-Dihydro-4-methyl-2-[2-(methylsulfonyl)phenyl]-1,3-oxazole 86a. (60%) as a colourless oil. B p. 180–185°C (Bath temperature) at 4mmHg (found M$^+$, 207.0718 C$_{11}$H$_{13}$NOS requires M$^+$, 207.0718). [α]$_D^{25}$ -21.4 (c 0.28, CHCl$_3$) $\nu_{max}$/ cm$^{-1}$ 1645(C=N), 1472, 1434, 1354, 1245, 1034. δ$_H$ (400 MHz, CDCl$_3$) 1.38 (3H, d, J 6.4, CH$_3$CH), 2.44 (3H, s, SCH$_3$), 3.91 (1H, m, CHH'O), 4.45 (1H, m, CHH'O), 4.49 (1H, m, CHN), 7.11-7.81 (4H, m, aromatic CH). δ$_C$ (100 MHz, CDCl$_3$) 15.6 (SCH$_3$), 21.5 (QH$_2$CH), 62.6 (QHN), 73.0 (CH$_2$O), 123.4/124.0/130.1/130.7/124.9 (aromatic CH), 140.6 (aromatic C), 162.1 (C=N) m/z (El) 207(M$^+$, 54%), 192(100), 152(31), 135(22), 51(21), 45(21).

(4S)-4-benzyl-4,5-Dihydro-2-[2-(methylsulfonyl)phenyl]-1,3-oxazole 86b. (42%) as a colourless crystalline solid. M p. 68–69°C. (Found: C, 72.4; H, 5.9, N, 4.9 C$_{17}$H$_{17}$NOS requires C, 72.1; H, 6.0, N, 4.9%). [α]$_D^{25}$ 18.75 (c 0.16, CHCl$_3$). $\nu_{max}$/ cm$^{-1}$ 1640(C=N) δ$_H$ (400 MHz, CDCl$_3$) 2.47 (3H, s, SCH$_3$), 2.74 (1H, dd, J 9.1, 13.7, PhCHH'H$^+$), 3.31 (1H, dd, J 5.0, 13.7, PhCHH'H$^+$), 4.10 (1H, dd, J 7.1, 8.4, CHH'O), 4.27 (1H, dd, J 8.4, 9.2, CHH'O), 4.69 (1H, m, CHN), 7.12-7.81 (9H, m, aromatic CH). δ$_C$ (100 MHz, CDCl$_3$) 15.7 (SCH$_3$), 41.7 (PhCH$_2$), 68.6.
(CHN), 70 7 (CH2O), 123 4/ 124 0/ 126 3/ 128 4/ 129.2/ 130.1/ 130 8 / 124 7 (aromatic CH), 137 9/ 140 8 (aromatic Q), 162.7 (C=N) m/z (El) 283(M+, 35%), 268(23), 192(100), 137(24), 117(31), 91(31), 51(20).

(4S)-4,5-Dihydro-4-isopropyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole 86c. (56%) as a colourless oil B p 210°C (Bath temperature) at 2mmHg. (found M+, 235 1030 C13H17NOS requires M+, 235 1030) [α]D25 72 22 (c 0.18, CHCl3) νmax / cm⁻¹ 1649(C=N), 1471, 1436, 1352, 1244 δH (400 MHz, CDCl3) 0.95 (3H, d, J 6 7, CH3CH), 1.06 (3H, d, J 6 7, CH3CH), 1.85 (1H, m, CH(CH3)2), 2.44 (3H, s, SCH3), 4.09 (1H, t, J 7 8, CHH’O), 4.20 (1H, m, CHN), 4.35 (1H, dd, J 7 8, 9 5, CHH’O), 7.11-7.79 (4H, m, aromatic CH) δC (100 MHz, CDCl3) 15 7 (SCH3), 18 1 (CH3CH), 18 8 (CH3CH), 32 8 (CH(CH3)2), 69 3 (CH2O), 73 3 (CHN), 123 3/ 124 0/ 129.9/ 130 6 (aromatic CH), 125 0/ 140 8 (aromatic Q), 162.0 (C=N) m/z (El) 235(M+, 100%), 220(91), 192(73), 152(55), 137(49), 45(45)

(4S)-4,5-Dihydro-4-phenyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole 86d. (58%) as a colourless crystalline solid. M p 72-73°C. (Found: C, 71 5, H, 5 5; N, 5.2 C16H15NOS requires C, 71 4, H, 5 6, N, 5 2%) [α]D25 +100 0 (c 0.12, CHCl3) νmax / cm⁻¹ 1638(C=N), 1471, 1436, 1352, 1244 δH (250 MHz, CDCl3) 2 46 (3H, s, SCH3), 4 20 (1H, t, J 8 2, CHN), 4 75 (1H, dd, J 10 1, 8 2, CHH’O), 5 51 (1H, dd, J 10 1, 8 2, CHH’O), 7 14-7.91 (9H, m, aromatic CH) δC (63 MHz, CDCl3) 15 8 (SCH3), 70.7 (PhCH), 74 0 (CH2O), 123 5/ 124 3/ 124 7/ 126 6/ 127.4/ 128 6/ 130 4/ 131 0 (aromatic CH), 137 0/ 142 0 (aromatic Q), 159 5 (C=N). m/z (El) 269(M+, 50%), 254(58), 151(27), 120(28), 104(43), 51(39)

(4S)-4,5-Dihydro-4-tert-butyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole 86e. (53%) as a colourless crystalline solid M p 67.5-68 5°C. (found M+, 249 1187 C14H19NOS requires M+, 249 1187) [α]D25 -121.05 (c 0 38, CHCl3)
To a stirring mixture of sodium hydride (9 mmol) in THF (5ml) was added a solution of benzenethiol (9mmol) in THF (2ml) To the resulting white precipitate was added a solution of 2-fluorobenzonitrile (8 mmol) in THF (2ml) The mixture was allowed to stir under reflux for 48 hours whereupon the solution became clear. The reaction mixture was poured into dichloromethane (20ml), washed with 15% NaOH (20ml) then H₂O (20ml). The aqueous layers were extracted dichloromethane (2 x 50ml), the organic extracts were then combined, dried (Na₂SO₄), filtered and then concentrated in vacuo. The crude product was purified by flash chromatography (light petroleum/ether 3:1) to afford the title compound (93%) as a colourless crystalline solid. M p. 35-37 °C (lit 39-40 °C)\(^{131}\)

\(v_{\text{max}} / \text{cm}^{-1} 1651(\text{C} = \text{N}) \quad \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) 0.98 (9\text{H}, \text{s, C(CH}_3)_3), 2.44 (3\text{H}, \text{s, SCH}_3), 4.15 (1\text{H, m, CHN}), 4.20 (1\text{H, m, CH}_2\text{O}), 4.26 (1\text{H, dd, J 7.7, 9.4, CH}_2\text{O}), 7.11-7.78 (4\text{H, m, aromatic CH}) \quad \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 15.8 (\text{SCH}_3), 25.7 (\text{CH}_3 \times 3), 33.9 (\text{C(CH}_3)_3), 67.7 (\text{CH}_2\text{O}), 77.0 (\text{CHN}), 123.3/124.0/129.0/130.6 (\text{aromatic CH}), 125.0/141.0 (\text{aromatic C}), 161.9 (\text{C} = \text{N}) \quad m/z (\text{El}) 249(\text{M}^+, 45\%), 234(28), 192(100), 151(30), 137(29), 41(29).

\((2\text{-phenylsulfanyl})\text{benzonitrile 90.}\)
General procedure for preparation of (4S)-4,5-Dihydro-2-[(2-phenylsulfanyl)phenyl]-4-substituted-1,3-oxazoles.

In a 50ml Schlenk flask, zinc chloride (68mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by (2-phenylsulfanyl)benzonitrile 90 (10 mmol) and the amino alcohol (15 mmol). The mixture was heated under reflux for 48 hours. The solvent was removed in vacuo to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml). The combined organic phases were dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (light petroleum/ether 3:1) to afford a clean product (4S)-4,5-dihydro-4-isopropyl-2-[(2-phenylsulfanyl)phenyl]-1,3-oxazole 87c. (73%) as a colourless oil (found M⁺, 297.1187. C₁₈H₁₉NOS requires M⁺, 297.1187). \[\alpha\]D²⁵ -42.5 (c 0 4, CHCl₃). νmax / cm⁻¹ 1650(C=N) δH (250 MHz, CDCl₃) 0.99 (3H, d, J 6.7, CH₃CH), 1.10 (3H, d, J 6.7, CH₃CH), 1.85 (1H, m, CH(CH₃)₂), 4.17 (2H, m, CH₂N and CHH'O), 4.43 (1H, dd, J 8.7, 7.1, CHH'O), 6.87-7.64 (9H, m, aromatic CH). δC (63 MHz, CDCl₃) 18 4 (CH₂CH), 18 9 (CH₂CH), 33.0 (CH(CH₃)₂), 69 8 (CH₂O), 73 4 (CHN), 124.4/126.4/127.6/128 6/128 8/129 9/132.9/133.6/134 9 (aromatic CH), 125 0/141.0/142.9 (aromatic C), 162.2 (C=N) m/z (El) 297(M⁺, 92%), 254(100), 220(53), 197(100), 137(29)
(4S)-4,5-Dihydro-4-tert-butyl-2-[(2-phenylthio)phenyl]-1,3-oxazole 87e. (62%) as a colourless oil (found M+, 311 1344  C_{19}H_{21}NOS requires M+, 311 1344) [α]D\(^{25}\) -37.5 (c 0.24, CHCl\(_3\)) \(v_{\text{max}} / \text{cm}^{-1}\) 1644(C=N) \(\delta_{\text{H}}\) (250 MHz, CDCl\(_3\)) 1.03 (9H, s, C(C\(_3\))\(_3\)), 4.27 (3H, m, CHN and CH\(_2\)O), 6.83-7.81 (9H, m, aromatic CH) \(\delta_{\text{C}}\) (63 MHz, CDCl\(_3\)) 25.9 (CH\(_3\) x 3), 34.0 (C(CH\(_3\))\(_3\)), 68.2 (CH\(_2\)O), 77.4 (CHN), 124.3/126.4/127.5/128.6/129.5/129.7/130.5/135.1 (aromatic C\(_\text{H}\)), 125.0/130.0/141.0 (aromatic C), 162.4 (C=O) m/z (EI) 311(M\(^+\), 41%), 254(100), 197(32), 151(26), 109(19).

General Procedure For Preparation of 4-substituted (4S)-4,5-Dihydro-2-[2-fluorophenyl]-1,3-oxazoles

In a 50ml Schlenk flask, zinc chloride (68mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by 2-fluorobenzonitrile (10 mmol) and the amino alcohol (15 mmol). The mixture was heated under reflux for 72 hours. The solvent was removed \textit{in vacuo} to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml). The combined organic phases were dried (Na\(_2\)SO\(_4\)), filtered and the solvent removed \textit{in vacuo}. The residue was purified by flash chromatography (light petroleum/ether 3:1) to afford a clean product.
(4S)-4,5-Dihydro-4-methyl-2-(2-fluorophenyl)-1,3-oxazole 92a. (47%) as a colourless oil (found M⁺, 179 0749. C₁₀H₁₀FNO requires M⁺, 179 0746). [α]D²⁵ -66° (c 0 8, CHCl₃) νmax / cm⁻¹ 1651 (C=O) δH (400 MHz, CDCl₃) 1.37 (3H, d, J 6 4, CH₃), 3.95 (1H, t, J 7 3, CH₂H'O), 4.41 (2H, m, CHN and CHH'O), 7.10–7.49 (3H, m, aromatic CH), 7.84–7.91 (1H, m, aromatic CH). δC (100 MHz, CDCl₃) 21.3 (CH₃), 62.1 (CH₂O), 73.5 (CH₂), 116.3/116.5/123 6/131 0 (aromatic CH), 132 4/132 5 (aromatic C), 163 2 (C=N) m/z (El) 179 (M⁺, 42%).

(4S)-4-benzyl-4,5-Dihydro-2-(2-fluorophenyl)-1,3-oxazole 92b. (48%) as a colourless oil. (found M⁺, 255 1064. C₁₆H₁₄FNO requires M⁺, 255 1059). [α]D²⁵ +6° (c 0 82, CHCl₃) νmax / cm⁻¹ 1649 (C=O) δH (400 MHz, CDCl₃) 2.74 (1H, dd, J 9 0 4 9, PhCHH'), 3.27 (1H, dd, J 9 0 4 9, PhCHH'), 4.14 (1H, dd, J 7 4, 8 6, CH₂H'O), 4.32 (1H, dd, J 8 6, 9 4, CH₂H'O), 4.62 (1H, m, CHN), 7.11–7.87 (9H, m, aromatic CH). δC (100 MHz, CDCl₃) 41.5 (QH₂Ph), 67.9 (QHN), 71.2 (QH₂D). 116 4/116 6/123 7/123 8/126.3/128 4/129 1/130 9 (aromatic CH), 132 6/132 7/137.6 (aromatic C), 162 4 (C=N). m/z (El) 255 (M⁺, 100%).

(4S)-4,5-Dihydro-4-isopropyl-2-(2-fluorophenyl)-1,3-oxazole 92c. (46%) as a colourless oil (found M⁺, 207 1059. C₁₂H₁₄FNO requires M⁺, 207 1058) [α]D²⁵ -62° (c 0 5, CHCl₃) νmax / cm⁻¹ 1651 (C=O) δH (400 MHz, CDCl₃) 0.91 (3H, d, J 6 8, CH(CH₃)), 1.01 (3H, d, J 6 8, CH(CH₃)), 1.89 (1H, m, CH(CH₃)₂), 4.14 (2H, m, CH₂H'O and CHN), 4.38 (1H, m, CH₂H'O), 7.09–7.88 (4H, m, aromatic CH). δC (100 MHz, CDCl₃) 16.6 (CH₃), 17.4 (CH₃), 31.0 (CH(CH₃)₂), 69.0 (CHN), 71.3 (CH₂), 116 3/116 6/123.7 (aromatic CH), 131.0/132 0 (aromatic C), 163 0 (C=N) m/z (El) 207 (M⁺, 22%).

(4S)-4,5-Dihydro-4-phenyl-2-(2-fluorophenyl)-1,3-oxazole 92d. (49%) as a colourless oil. (found M⁺, 241 0903 C₁₅H₁₂FNO requires M⁺, 241 0903). [α]D²⁵ -30° (c 0 5, CHCl₃) νmax / cm⁻¹ 1647 (C=O) δH (250 MHz, CDCl₃) 4.27 (1H, t,
J 8 4, CHN), 4 35 (1H, dd, J 8 2, 8 4, CHH'O), 4.79 (1H, dd, J 8 2, 8 4, CHH'O), 7 13–8 00 (4H, m, aromatic CH). δC (63 MHz, CDCl3) 70 0 (CHN), 74 5 (CH2O), 123 9/124 0/124 7/126 6/127 6/128 5/128 7/131 3 (aromatic CH), 133 2/133 5/142 0 (aromatic C), 163 3 (C=N). m/z (EI) 241(M⁺, 32%), 211(100), 123(27), 90(49) m/z (EI) 241(M⁺, 75%)

(4S)-4-tert-butyl-4,5-Dihydro-2-(2-fluorophenyl)-1,3-oxazole 92e. (56%) as a colourless oil. (found M⁺, 221.1213 C13H1sFNO requires M⁺, 221.1216) [α]D25 -69.3 (c 1, CHCl3) υmax / cm⁻¹ 1651 (C=N) δH (400 MHz, CDCl3) 0.95 (9H, s, C(CH3)3), 4.06 (1H, dd, J 7.7, 10.2, CHH'O), 4.22 (1H, t, J 7.7 Hz, CHN), 4.33 (1H, dd, J 7.7, 10.2, CHH'O), 7 14–7.86 (4H, m, aromatic CH). δC (100 MHz, CDCl3) 25.6 (C(CH3)3), 33.8 (C(CH3)3), 68.3 (CHN), 76.0 (CH2O), 116.3/116.5/123.6/131.0 (aromatic CH), 132.4/132.5 (aromatic C), 162.9 (C=N). m/z (EI) 221(M⁺, 62%)

**General procedure preparation of 4-substituted (4S)-4,5-Dihydro-2-[2- (diphenylphosphino)phenyl]-1,3-oxazoles**

To a 50ml two-necked flask, was added potassium diphenylphosphide (1mmol) (as a 0.5M solution in THF) via syringe. The solution was then heated to reflux and the 4-substituted (4S)-4,5-Dihydro-2-(2-fluorophenyl)-1,3-oxazole (1mmol) added as a solution in THF (2ml). The mixture was stirred under reflux for 2 hours, whereupon the red solution of the phosphide fades to a pale yellow. The mixture is then cannulated into a separating funnel and portioned between dichloromethane (20ml) and water (20ml). The dichloromethane layer is taken,
dried (Na₂SO₄), filtered then the solvent removed in vacuo. The residue is purified by dry flash chromatography with diethyl ether as eluant, to afford a clean product.

(4S)-4,5-Dihydro-4-methyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole 91a. (80%) as a white solid. M.p. 93–95°C. (found M⁺, 345.1303. C₂₂H₂₀NOP requires M⁺, 345 1282). [α]₀²⁵ +7 5 (c 2.0, CHCl₃) v_max / cm⁻¹ 1650 (C=N) δ_H (400 MHz, CDCl₃) 0.95 (3H, d, J 6 5, CH₃), 3 54 (1H, m, CHN), 4 08–4 21 (2H, m, CH₂O), 6 84 (1H, m, aromatic CH), 7 20–7 70 (13H, m, aromatic CH) δ_C (100 MHz, CDCl₃) 20 6 (CH₃), 61 7 (CHN), 73 4 (CH₂O), 127 7/128 1/128 2/128 3/128 5/128 6/128 7/130 2/130 4/130 6/132 3/133 2/133 6 (aromatic CH), 133 8/133 9/134 0/134 3 (aromatic CH), 163 3 (C=N). δ_p (162 MHz, CDCl₃) -4 7 (PPh₂) m/z (El) 345(M⁺, 17%)

(4S)-4-benzyl-4,5-Dihydro-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole 91b. (76%) as a white solid. M.p. 106–108°C. (found M⁺, 421.1573. C₂₈H₂₄NOP requires M⁺, 421.1595). [α]₀²⁵ +1 4 0 (c 0.5, CHCl₃) v_max / cm⁻¹ 1649 (C=N) δ_H (400 MHz, CDCl₃) 2 12 (1H, dd, J 9 1, 13 8, CHH'Ph), 2 92 (1H, dd, J 5 1, 13 8, CHH'Ph), 3 75 (1H, t, J 8 2, CHH'O), 4 01 (1H, t, J 8 2, CHH'Ph), 4 33 (1H, m, CHN), 6 86 (1H, m, aromatic CH), 7 17–7 34 (17H, m, aromatic CH), 7 85 (1H, m, aromatic CH) δ_C (100 MHz, CDCl₃) 41 0 (CH₂Ph), 67 8 (CHN), 7 3 (CH₂O), 126 3–138 1 (aromatic CH and CH), 163 8 (C=N). δ_p (162 MHz, CDCl₃) -4 9 (PPh₂) m/z (El) 421(M⁺, 12%)

(4S)-4,5-Dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole 91c. (76%) as a white solid. M.p. 84–86°C. (found M⁺, 373 1597. C₂₄H₂₄NOP requires M⁺, 373 1595). [α]₀²⁵ -4 0 0 (c 0 5, CHCl₃) v_max / cm⁻¹ 1651 (C=N) δ_H (400 MHz, CDCl₃) 0 69 (3H, d, J 6 7, CH₃), 0 80 (3H, d, J 6 7, CH₃), 1 52 (1H, m, CH(CH₃)₂), 3 80 (2H, m, CHN and CHH'O), 4 10 (1H, m, CHH'Ph), 6 89 (1H, m,
aromatic CH), 7.20–7.70 (12H, m, aromatic CH), 7.92 (1H, m, aromatic CH), δC (100 MHz, CDCl₃) 18.2 (CH₃), 18.7 (CH₃), 32.7 (CH(CH₃)₂), 69.7 (CH₂O), 72.9 (CHN), 127.9–138.1 (aromatic CH and C), 162.9 (C=O) δP (162 MHz, CDCl₃) −46 (PPh₂) m/z (EI) 373(M⁺, 26%).

(4S)-4,5-Dihydro-4-phenyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole 91d. (84%) as a colourless glassy solid M.p 57–58°C (found M⁺, 407.1439. C₂₇H₂₂NOP requires M⁺, 407 1439). [α]D²⁵ +24 0 (c 0.25, CHCl₃) νmax / cm⁻¹ 1649 (C=N) δH (400 MHz, CDCl₃) 3.92 (1H, t, J 8.4, CHH'O), 4.55 (1H, dd, J 8 4, 9.9, CHH'O), 5.22 (1H, t, J 9 9, CHN), 6.89–8 01 (19H, m, aromatic CH). δC (100 MHz, CDCl₃) 70.0 (CHN), 74.2 (CH₂O) 126 5/127 0/127 9/128 3/128 4/128 6/130 2/130 5/131.4/133 6/133 8 (aromatic CH), 134.1/134.3/134.3/137 7/141.9 (aromatic C). δP (162 MHz, CDCl₃) −47 (PPh₂) m/z (EI) 407(M⁺, 8%).

(4S)-4,5-Dihydro-4-tert-butyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole 91e. (92%) as a white solid. M.p 114–116°C (found M⁺, 387.1741. C₂₅H₂₆NOP requires M⁺, 387.1751). [α]D²⁵ −55 2 (c 0.6, CHCl₃). νmax / cm⁻¹ 1650 (C=N). δH (400 MHz, CDCl₃) 0.72 (9H, s, C(CH₃)₃), 3.99 (1H, t, J 8 3, CHN), 4.10 − 4.21 (2H, m, CH₂O), 6.90 (1H, m, aromatic CH), 7.20–7.80 (12H, m, aromatic CH), 7.94 (1H, m, aromatic CH) δC (100 MHz, CDCl₃) 25.7 (C(CH₃)₃), 33.4 (C(CH₃)₃), 68.1 (CHN), 75.8 (CH₂O), 127.9/128.0/128.1/128.2/128.3/128.4/129.7/130.2/130.6/131.1/131.6/131.7/133.3 (aromatic CH), 133.5/134.0/134.2/138.5 (aromatic C), 162.9 (C=O). δP (162 MHz, CDCl₃) −47 (PPh₂) m/z (EI) 387(M⁺, 11%).

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To a stirring mixture of sodium hydride (9 mmol) in THF (5 ml) was added a solution of benzenethiol (9 mmol) in THF (2 ml). To the resulting white precipitate was added a solution of 2-fluorobenzaldehyde (8 mmol) in THF (2 ml). The mixture was allowed to stir under reflux for 48 hours whereupon the solution became clear. The reaction mixture was poured into dichloromethane (20 ml), washed with 15% NaOH (20 ml) then H₂O (20 ml). The aqueous layers were extracted with dichloromethane (2 x 50 ml), the organic extracts were then combined, dried (Na₂SO₄), filtered then concentrated in vacuo. The crude product was purified by flash chromatography (light petroleum/ether 3:1) to afford the title compound (40%) as a pale yellow oil (found M⁺, 214 0436 C₁₃H₁₀OS requires M⁺, 214 0452) \( \nu_{\text{max}} \text{ cm}^{-1} \) 1699, 1673 \( \delta_{\text{H}} \) (250 MHz, CDCl₃) 7.10–7.91 (9H, m, aromatic CH), 10.40 (1H, s, \text{CHO}) \( \delta_{\text{C}} \) (63 MHz, CDCl₃) 126.3/128.4/129.6/130.3/131.8/131.9/133.0/133.1/134.0 (aromatic CH), 137.1, 137.9 (aromatic C), 191.5 (CHO) \( m/z \) (EI) 214 (M⁺, 85%).
General procedure for the preparation of enantiopure acetal ligands from the aldehyde

A mixture of the aldehyde (1.6 mmol), enantiopure diol (1.6 mmol) and (±)-10-camphorsulfonic acid (10 mol%) in toluene (10 ml) was stirred under reflux for 2 hours. The toluene/water azeotrope was then distilled off. The residue was diluted with diethyl ether (30 ml) and poured into a saturated solution of sodium hydrogen carbonate (50 ml). The organic layer was washed with water (3 x 30 ml), the organic extracts dried (Na₂SO₄), filtered and solvent removed in vacuo. The crude solids were recrystallised from ethyl acetate to give a clean product.

(4S, 5S)-2-(2-pyridyl)-[4,5-Bis(phenyl)]-1,3-dioxolane 105. (63%) as a colourless crystalline solid. M. p. 105-107°C (found M⁺, 303 1259. C₂₀H₁₇NO₂ requires M⁺, 303 1259) \([\alpha]_D^{25} -24\) 8 (c 2.5, CHCl₃) \(v_{\text{max}} / \text{cm}^{-1}\) 1029, 1044, 1074, 1108. δH (250 MHz, CDCl₃) 5 00 (1H, d, J 7.9, CHPh), 5.02 (1H, d, J 7.9, CHPh), 6.44 (1H, s, CHOO), 7.12-7.81 (14H, m, aromatic CH) δC (63 MHz, CDCl₃) 85 4 (CHPh), 87 2 (CHPh), 104 4 (CHOO), 120 8/124 2/126 4/126 9/127 8/128 0/128 3/138.5 (aromatic CH) 137 0/140 5/149 2 (aromatic C) m/z (El) 303(M⁺, 16%)

(4R, 5R)-2-((2-diphenylphosphino)phenyl)-[4,5-Bis(methyl)]-1,3-dioxolane 106. (77%) as a colourless crystalline solid. M. p. 136-137°C (found M⁺, 362 1588 C₂₃H₂₃O₂P requires M⁺, 362.1436) \([\alpha]_D^{25} -10\) 3 (c 3 5, CHCl₃)
υ_{max} / cm^{-1} 1050, 1092, 1105. δ_{H} (250 MHz, CDCl\textsubscript{3}) 1.02 (3H, d, J 5 6, CH\textsubscript{3}) 1 18 (3H, d, J 5 6, CH\textsubscript{3}), 3 60 (2H, m, 2 x CH\textsubscript{2}CH\textsubscript{3}), 6 59 (1H, s, CHOO), 7 17--7.87 (14H, m, aromatic CH) δ_{C} (63 MHz, CDCl\textsubscript{3}) 16 8 (CH\textsubscript{3}), 16 9 (CH\textsubscript{3}), 78 5 (CHMe), 80 0 (CHMe), 98 9 (1C, d, J 5 1, CHOO), 128.1/ 128 2/ 128 3/ 128 4/ 131 6/ 131 8/ 131 9/ 132 1/ 132 2/ 133.1/ 133 3 (aromatic CH) 143 0 (aromatic C) m/z (El) 362 (M\textsuperscript{+}, 28%).

(4R, 6R)-2-((2-diphenylphosphino)phenyl)-[4, 6-Bis(methyl)]-1,3-dioxan 107.

(82%) as a colourless crystalline solid M p 141--142°C (found M\textsuperscript{+}, 376 1603 C\textsubscript{24}H\textsubscript{25}O\textsubscript{2}P requires M\textsuperscript{+}, 376 1592). [α]D\textsuperscript{25} -40 0 (c 0 5, MeOH) υ_{max} / cm^{-1} 1118, 1128, 1186 δ_{H} (250 MHz, CDCl\textsubscript{3}) 0 91 (3H, d, J 6 1, CH\textsubscript{3}), 1 12 (3H, d, J 7 0, CH\textsubscript{3}), 1 82 (2H, m, CH\textsubscript{2}), 3 80 (2H, m, 2 x CH\textsubscript{2}CH\textsubscript{3}), 6 61 (1H, s, CHOO), 7 07--7 69 (14H, m, aromatic CH) δ_{C} (63 MHz, CDCl\textsubscript{3}) 16 8 (CH\textsubscript{3}), 21 4 (CH\textsubscript{3}), 36 8 (CH\textsubscript{2}), 68 0 (CHMe), 69 0 (CHMe), 91 1 (1C, d, J 5 6, CHOO), 127 8/ 128 1/ 128 2/ 128 4/ 131 6/ 131 9/ 132 0/ 132 1/ 132 2/ 132 3/ 133 1 (aromatic CH) 142 9 (aromatic C) m/z (El) 376 (M\textsuperscript{+}, 5%).

(4S, 5S)-2-((2-diphenylphosphino)phenyl)-[4, 5-Bis(phenyl)]-1,3-dioxolane 108. (61%) as a colourless crystalline solid M p 94--95°C (found M\textsuperscript{+} 486 2000. C\textsubscript{33}H\textsubscript{27}O\textsubscript{2}P requires M\textsuperscript{+}, 486 1749) [α]D\textsuperscript{25} +14.0 (c 0 5, CHCl\textsubscript{3}) υ_{max} / cm^{-1} 1026, 1057, 1090, 1101 δ_{H} (250 MHz, CDCl\textsubscript{3}) 4 74 (1H, d, J 7 8, CHPh), 4 76 (1H, d, J 7 8, CHPh), 6 96 (1H, s, CHOO), 7 10--7.71 (24H, m, aromatic CH). δ_{C} (63 MHz, CDCl\textsubscript{3}) 85.1 (CHPh), 87 0 (CHPh), 101.0 (1C, d, J 5.2, CHOO), 125 9/ 126 8/ 127 0/ 127.6/ 127.7/ 127.9/ 128 3/ 128 4/ 128 6/ 128 7/ 128 8/ 131.8/ 132 0/ 132 1/ 132 2/ 132 4/ 133.1/ 133 3 (aromatic CH) 136.7/ 138.7/ 142 4 (aromatic C) m/z (El) 486 (M\textsuperscript{+}, 11%)
Alternative procedure for preparation of enantiopure acetal ligands

Acetalisation

\[ \text{CHO} \xrightarrow{\text{L}} \text{OMe} \]

To a stirring mixture of the aldehyde (50 mmol) and cerium (III) chloride heptahydrate (2.6 mmol) in methanol (30 ml) was added trimethyl orthoformate (75 mmol). The mixture was allowed to stir for 8 hours then concentrated \textit{in vacuo}. The residue was diluted with diethyl ether (30 ml) then poured into sodium hydrogen carbonate solution (50 ml). The aqueous layer is extracted with diethyl ether (2 x 50 ml). The organic extracts are then washed with water (2 x 50 ml), brine (50 ml), dried (Na$_2$SO$_4$), filtered then the solvent is removed \textit{in vacuo}. The residual oil is purified by distillation under reduced pressure to give a clean product.

\textit{2-thiophene carboxaldehyde dimethyl acetal 109.} (86%) as a colourless oil.

(found M$^+$, 158 0390. C$_7$H$_{10}$O$_2$S requires M$^+$, 158 0401). $\nu_{\text{max}}$ / cm$^{-1}$ 1095, 1075, 1054. $\delta_H$ (250 MHz, CDCl$_3$) 3 35 (6H, s, 2 x OCH$_3$), 5 62 (1H, s, CHOMe), 7.03 (3H, m, thiophene CH). $\delta_C$ (63 MHz, CDCl$_3$) 52.4 (2 x CH$_3$), 100 0 (CHOMe), 125 4/ 125 6/ 126 6 (thiophene CH) 141.5 (thiophene C). $m/z$ (El) 158(M$^+$, 100%).

\textit{(2-phenylsulfanyl)benzaldehyde dimethyl acetal 111.} (96%) as a colourless oil

(found M$^+$, 260 0873 C$_{14}$H$_{15}$O$_2$S requires M$^+$, 260 0871). $\nu_{\text{max}}$ / cm$^{-1}$ 1073, 10759. $\delta_H$ (250 MHz, CDCl$_3$) 3 34 (6H, s, 2 x OCH$_3$), 5 72 (1H, s, CHOMe), 7 23–7 29 (9H, m, aromatic CH). $\delta_C$ (63 MHz, CDCl$_3$) 53.8 (2 x CH$_3$), 101.7
A mixture of the acetal (1.6 mmol), enantiopure diol (1.6 mmol) and (±)-10-camphorsulfonic acid (10 mol%) in toluene (10 ml) was stirred under reflux for 2 hours. The toluene/methanol azeotrope was then distilled off. The residue was diluted with diethyl ether (30 ml) and poured into a saturated solution of sodium hydrogen carbonate (50 ml). The organic layer was washed with water (2 x 30 ml), the organic extracts dried (Na₂SO₄), filtered and solvent removed in vacuo. The crude solids were recrystallised from ethyl acetate to give a clean product.

(4R, 5R)-2-(2-thienyl)-[4, 5-Bis(methyl)]-1,3-dioxolane 112. (92%) as a colourless oil. (found M⁺, 184.0566. C₉H₁₂O₂S requires M⁺, 184.0558). [α]D²⁵ -30 0 (c 1, CHCl₃) νmax / cm⁻¹ 1089, 1048, 1039 δH (250 MHz, CDCl₃) 1.31 (3H, d, J 4 0, CH₃), 1 38 (3H, d, J 4 0, CH₃), 3 80 (2H, m, 2 x CHCH₃), 6 23 (1H, s, CHO), 6 99 (1H, dd, J 5 0, 3 4, thiophene CH), 7.16 (1H, m, thiophene CH), 7.32 (1H, m, thiophene CH) δC (63 MHz, CDCl₃) 16 7 (CH₃), 16 8 (CH₃), 78 2 (CHMe), 80.2 (CHMe), 98 9 (CHO), 125 9/126 2/126.5 (thiophene CH) 142 9 (thiophene O). m/z (El) 184 (M⁺, 21%)

(4S, 5S)-2-(2-thienyl)-[4, 5-Bis(phenyl)]-1,3-dioxolane 113. (77%) as a colourless crystalline solid M p 85–86°C. (Found C, 73 7, H, 5 1 C₁₉H₁₆O₂S
requires C, 74.0, H, 5.2%) \[\alpha\]D25 -21.0 (c 1.0, CHCl3) \(v_{\text{max}} / \text{cm}^{-1}\) 2933, 2895, 2830, 1093, 1056 \(\delta_H\) (250 MHz, CDCl3) 4.94 (1H, d, J 8.0, CHPh), 4.96 (1H, d, J 8.0, CHPh), 6.70 (1H, s, CHO0), 7.07 (1H, dd, J 5.0, 3.4, thiophene CH), 7.27-7.44 (12H, m, aromatic CH), \(\delta_C\) (63 MHz, CDCl3) 84.9 (CHPh), 87.1 (CHPh), 101.0 (CHO0) 126.5/126.6/126.7/126.9/128.3/128.5 (aromatic CH), 136.9/137.8/143.0 (aromatic C) m/z (El) 308(M+, 21%), 307(100)

\((4S, 5S)-2-((2\text{-methylsulfanyl})\text{methyl})-4, 5\text{-Bis(phenyl)}\)-1,3-dioxolane 114.
(52%) as a colourless crystalline solid M.p 41-42°C (found M+NH4+, 304 1371 C17H18O2S requires M+NH4+, 304 1371) \[\alpha\]D25 +31.0 (c 1.0, CHCl3) \(v_{\text{max}} / \text{cm}^{-1}\) 1043, 1078, 1035 \(\delta_H\) (250 MHz, CDCl3) 2.30 (3H, s, SCH3), 2.97 (2H, d, J 4.3, CH2SCH3), 4.80 (2H, m, 2 x CHPh), 5.71 (1H, t, J 4.3, CHO0), 7.21-7.36 (10H, m, aromatic CH), \(\delta_C\) (63 MHz, CDCl3) 16.9 (SCH3), 38.3 (CH2SCH3), 85.1 (CHPh), 86.6 (CHPh), 105.3 (CHO0) 126.3/126.8/128.1/128.5 (aromatic CH), 137.2/137.7 (aromatic C) m/z (Cl) 304(M+NH4+, 100%)

\((4S, 5S)-2-((2\text{-phenylsulfanyl})\text{phenyl})-4, 5\text{-Bis(phenyl)}\)-1,3-dioxolane 115.
(64%) as a colourless crystalline solid M.p 70-71°C (found M+, 410.1333. C27H22O2S requires M+, 410 1340). \[\alpha\]D25 +11.9 (c 0.9, CHCl3) \(v_{\text{max}} / \text{cm}^{-1}\) 1074, 1059, 1010. \(\delta_H\) (250 MHz, CDCl3) 5.09 (2H, m, 2 x CHPh), 6.81 (1H, s, CHO0), 7.28-7.36 (19H, m, aromatic CH), \(\delta_C\) (63 MHz, CDCl3) 85.3 (CHPh), 87.4 (CHPh), 102.4 (CHO0) 126.2/126.5/126.9/127.0/127.6/127.8/128.1/128.6/128.7/129.2/129.7/130.1/130.8/133.1/134.9/136.7 (aromatic CH), 138.1/138.6/139.4/139.7 (aromatic C) m/z (El) 410(M+, 22%), 304(100)

Procedure for palladium catalysed allylic alkylation of 2-acetoxypent-3-ene 118.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {OAc};
\node at (1,0) {Me};
\node at (2,0) {Me};
\node at (4,0) {Me};
\node at (5,0) {Me};
\draw [->] (0,0) -- (2,0);
\draw [->] (2,0) -- (4,0);
\draw [->] (4,0) -- (6,0);
\node at (8,0) {CH(CO2Me)2};
\end{tikzpicture}
\end{center}
To the reaction flask was added [(η³-C₃H₅)PdCl]₂ (2.5 mol%) and ligand (10 mol%) in dichloromethane (2 ml), the mixture was allowed to stir for 15 mins. rac-2-acetoxypent-3-ene 118 (0.4 mmol) in dichloromethane (2 ml) was then added and stirring continued for a further 20 mins before adding dimethyl malonate (1.2 mmol), N,O-bis(trimethylsilyl)acetamide (1.2 mmol) in dichloromethane (1 ml) and a catalytic amount of sodium acetate (3 mol%). Stirring was continued until all the starting material had been consumed as shown by TLC (petroleum ether:ether (3:1)). The reaction mixture was diluted with diethyl ether (10 ml) and washed with saturated ammonium chloride solution (10 ml). The separated organic layer was dried (MgSO₄), filtered and concentrated in vacuo to give a yellow oil. Purification by column chromatography yielded 19 as a colourless oil. ¹H (250 MHz, CDCl₃) 1.28 (3H, d, J 6.2, CH₃), 1.68 (3H, d, J 6.8, CH₃), 2.03 (3H, s, OCH₃), 5.27 - 5.32 (1H, m, CH), 5.43 - 5.53 (1H, m, CH), 5.65 - 5.76 (1H, m, CH).
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