Asymmetric catalysis using titanium and palladium

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Asymmetric Catalysis
Using Titanium and Palladium

by

Simon J. Sesay

A Doctoral Thesis
submitted in partial fulfilment
of the requirements for the award

DOCTOR OF PHILOSOPHY

of

Loughborough University

March 1998

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Abstract

This thesis describes, in detail, the synthesis of novel heterobidentate ligands. These ligands were subsequently used in palladium catalysed allylic substitution reactions to synthesise enantiomerically enriched alkylated products. The thesis also describes novel approaches to asymmetric catalysis, in particular asymmetric epoxidation derived from Katsuki-Sharpless methodology.

Chapter 1 - This chapter reviews the literature, discussing the significant synthetic advancements in asymmetric catalysis in the past 10-15 years.

Chapter 2 - This chapter describes in detail the synthesis of new heterobidentate ligands containing nitrogen and phosphorus ligating atoms. These ligands are based on imines containing enantiomerically pure asymmetric centres in an alpha position to the nitrogen moiety. Other ligands that were synthesised were derived from C₂-symmetric diamines, also containing an asymmetric centre alpha position to the nitrogen, that produce ligands with the nitrogen functionality contained in a ring.

Chapter 3 - This chapter describes the use of the novel ligands synthesised in Chapter 2 in palladium catalysed allylic substitution reactions. The racemic substrate, 1,3-diphenyl-3-acetoxy-1-propene, was alkylated to produce an enantiomeric enriched alkylated product. The alkylated product was obtained with up to 77% enantiomeric excess. The reaction was conducted with a palladium catalyst in the presence of a novel ligand using dimethyl malonate as a nucleophile. The development and optimisation of these ligands within this reaction is discussed.

Chapter 4 - This chapter discusses some novel approaches to asymmetric epoxidation. The epoxidation is based on methodology developed by Katsuki and Sharpless. This epoxidation relies on the substrate containing an αβ-unsaturated alcohol. The chapter discusses the use of a reversible nucleophile in the form of cyanide. The nucleophile is designed to react with a substrate to provide an αβ-unsaturated cyanohydrin, suitable to undergo a Katsuki-Sharpless epoxidation. Once
the asymmetric epoxidation is complete, the nucleophile would be removed. This chapter describes the attempts to develop the principle further. An improvement to the system would be to provide an environment capable of sustaining a dynamic kinetic resolution.

Chapter 5 - This chapter contains the experimental which provides the exact details of the reactions reported in the thesis.

Keywords

palladium asymmetric catalysis nucleophile
kinetic resolution epoxidation ligand enantiomeric excess
Acknowledgements

All our knowledge brings us nearer to our ignorance,
All our ignorance brings us nearer to death.....
Where is the life we have lost in living?
Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?

T. S. Elliot- "The Rock"

Firstly I would like to thank Jonathan Williams for his support, encouragement and enthusiasm during my Ph.D. studies. I am indebted to him for giving me this opportunity. I would also like to acknowledge the support and encouragement provided by Robin Attrill, Smithkline Beecham, throughout my studies. I am also grateful to Russ Bowman for the support he has provided during my final year of my studies at Loughborough.

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-BuLi</td>
<td>tert-butylithium</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>BSA</td>
<td>N,N,N',N'-bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>18-crown-6</td>
<td>1,4,7,10,13,16-hexaoxacyclooctadecane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>DIOP</td>
<td>2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>hr</td>
<td>hour</td>
</tr>
<tr>
<td>IR</td>
<td>infra red</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>r.t</td>
<td>room temperature</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethyl silyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>pTSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
</tbody>
</table>
Chapter 1

Catalytic Asymmetric Synthesis

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1.1. Asymmetric Hydrogenation  2
1.2  Asymmetric Aldol Reactions  11
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1.0 Introduction
The introduction of an enantiomerically pure centre into organic molecules is becoming increasingly important in organic synthesis. Many of the biologically active molecules synthesised contain enantiomerically pure centres. As biological systems contain many enantiomerically pure molecules the effectiveness of biological molecules can depend on the enantiomeric purity. The synthesis of the inactive or poorly active enantiomer is inefficient.

Over the past 15 years there have been several important advances in catalytic asymmetric synthesis. This chapter provides a brief overview of these significant advances in asymmetric synthesis. Topics that are discussed include asymmetric oxidation, reduction, dihydroxylation and several addition reactions.

1.1 Asymmetric Hydrogenation
Asymmetric hydrogenation has been studied for a relatively long time.¹ The usual form of this hydrogenation involves the addition of hydrogen to a double bond in the presence of a transition metal catalyst containing an enantiomerically pure ligand. Generally the catalysts found to give the best enantiomeric excesses contain rhodium(I) or ruthenium(II) in conjunction with an enantiopure bidentate diphosphine ligand. Ligands 1 and 2 were amongst the first examples involved in rhodium(I) catalysed hydrogenation of α-acylamino acrylic acids resulting in products with high enantiomeric excesses (over 90 %).²,³

![Images of ligands 1 and 2]

One of the areas of most interest is the hydrogenation of substituted α-acylamino acrylic acids, as the products obtained from these reactions are protected α-amino acids. Kagan reported the first enantioselective hydrogenation of (cis) α-acetamidocinnamic acid using DIOP-Rh complex to give N-acetylphenylalanine.² The first commercial use of catalytic asymmetric hydrogenation was reported by Knowles et al from the Monsanto group.⁴ This hydrogenation played a key role in the
enantioselective synthesis of the natural occurring $\alpha$-amino acid, L-DOPA. The L-DOPA was produced with an enantiomeric excess of 95%.

\[
\begin{array}{c}
\text{3} \quad \text{CO}_2\text{H} \\
\text{NHAc} \\
\text{H}_2 \quad \text{Rh}^+ \\
\text{4} \quad \text{CO}_2\text{H} \\
\text{NHAc} \\
\end{array}
\]

\[
\begin{array}{c}
\text{AcO} \\
\text{OMe} \\
\end{array}
\begin{array}{c}
\text{AcO} \\
\text{OMe} \\
\end{array}
\]

\[
\begin{array}{c}
\text{AcO} \\
\text{OMe} \\
\end{array}
\begin{array}{c}
\text{AcO} \\
\text{OMe} \\
\end{array}
\]

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

\[
\begin{array}{c}
\text{L - DOPA}
\end{array}
\]

**Scheme 1**

The cis isomers of $\alpha$-acylamino acrylic acids, in contrast to the trans isomers, have been shown to undergo hydrogenation reaction more slowly and lead to products with lower enantiomeric excess.5

A wide range of substrates and chiral phosphine ligands has been used in a study of the factors important in the asymmetric hydrogenation of alkenes in high enantiomeric excess. In general, there are two structural features that should be present to increase the enantiomeric excess:

- electron withdrawing groups on the $\alpha$ carbon, such as CO$_2$R, Ph, CN
- basic carbonyl group $\beta$ to alkene bond

![Figure 1](image)

When the substrates 7 to 10 were subjected to the asymmetric hydrogenation the reduced products were produced with high enantiomeric excess (up to 90%). When the substrate 11 was hydrogenated it resulted in a lower enantiomeric excess of 50%, due to the absence of an electron withdrawing group on the $\alpha$ carbon.6
Tetrasubstituted alkenes are generally poor substrates for asymmetric hydrogenation. However, a rhodium(I) complex of the ferrocenyldiphosphine 12 has been found to catalyse the cis hydrogenation of 13 with an excellent enantiomeric excess\textsuperscript{7} (Scheme 2).

\begin{align*}
\text{Me} & \quad \text{R} \\
\text{HO}_2\text{C} & \quad \text{Ph} \\
13 & \\
\text{a R=} & \text{Ph} \\
\text{b R=} & \text{4-Cl-C}_6\text{H}_4 \\
\text{c R=} & \text{4-MeO-C}_6\text{H}_4 \\
\text{d R=} & \text{2-naphthyl} \\
\end{align*}

\begin{align*}
50 \text{ atm H}_2, \text{ Rh-12 (0.5 mol\%)} & \rightarrow \\
\text{Me} & \quad \text{H} \\
\text{R} & \quad \text{HO}_2\text{C} \\
14 & \quad \text{Ph} \\
\end{align*}

\[92-98\% \text{ e.e.}\]

\[\text{NR}_2 = \begin{array}{c}
\text{NEt}_2 \\
\text{NBu}_2
\end{array}\]

\textbf{Scheme 2}

Enamides can be asymmetrically hydrogenated using ruthenium catalysts. Enamide hydrogenation is very selective; only the \textit{Z} isomers of enamides are reduced whilst the \textit{E} isomers are inert. These reduced products provide key intermediates in the synthesis of isoquinoline alkaloids. One example is shown, the hydrogenation of an enamide 15 providing a key step in the synthesis of Laudanosine 18.
Scheme 3

The catalyst R-BINAP, or its enantiomer S-BINAP, can be used with a ruthenium acetate catalyst to efficiently hydrogenate \( \alpha,\beta \)-unsaturated carboxylic acids. These substrates are reduced with high enantioselectively. This is unusual as the substrates do not contain an acylamino group which suggests that these substrates react in a different way compared with previous examples. A possible mechanism involves the alkene reacting with a ruthenium hydride intermediate as opposed to the oxidative addition of molecular hydrogen. Ruthenium acetate and BINAP have been used to prepare the anti-inflammatory agent (S)-Naproxen 20 in excellent yield and enantiomeric excess.\(^8\)

\[
\text{[ent-16]Ru(OAc)}_2 (0.004 \text{ mol%}) \xrightarrow{135 \text{ atm H}_2} 100 \% \text{ conv.} \xrightarrow{20} 97 \% \text{ e.e.} (S)-\text{naproxen}
\]

Scheme 5

Allylic alcohols have been asymmetrically reduced using BINAP-ruthenium(II) catalysts to provide the reduced product in high enantioselectivities. These catalysts are highly efficient and chemoselective. In substrates with multiple double bonds,
only the allylic double bond is reduced. This is exemplified in the reaction of the geometrical isomers Geraniol 21 and Nerol 23.\(^9\)

![Chemical structures and reactions](image)

**Scheme 6**

The BINAP-ruthenium catalyst has also been used in the kinetic resolution of racemic allylic alcohols as shown in Scheme 7.\(^10\)

![Chemical structures and reactions](image)

**Scheme 7**

*Asymmetric reduction using boranes*

Catalytic enantioselective reduction of double bonds is possible using boranes, one method being known as the CBS (Corey, Bakashi, Shibata) reduction.\(^11\) Ketones can be reduced enantioselectively in the presence of an enantiomerically pure oxazaborolidine with borane itself. Several boranes were developed from enantiomerically pure amino acids.
These boranes have produced high enantioselectivities in the reduction of prochiral ketones.  

\[
\begin{align*}
\text{Br} & \quad \text{BH}_3 (0.6 \text{ equiv.}) \\
\text{28} & \quad \text{BH}_3 (0.1 \text{ equiv.}) \\
\text{34} & \quad \text{35} \quad 91 \text{% e.e.}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{BH}_3 (0.6 \text{ equiv.}) \\
\text{28} & \quad \text{BH}_3 (0.1 \text{ equiv.}) \\
\text{38} & \quad \text{39} \quad 97 \text{% e.e.}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{BH}_3 (0.6 \text{ equiv.}) \\
\text{28} & \quad \text{BH}_3 (0.1 \text{ equiv.}) \\
\text{36} & \quad \text{37} \quad 97.6 \text{% e.e.}
\end{align*}
\]

These CBS reductions are also chemoselective and will reduce a ketone in the presence of lactone and ester functionality.  

\[
\begin{align*}
\text{C}_9\text{H}_{11} & \quad \text{BH}_3 (0.6 \text{ equiv.}) \\
\text{28} & \quad \text{28} (0.1 \text{ equiv.}) \\
\text{40} & \quad \text{41} \quad 82 \text{% d.e.}
\end{align*}
\]
Catecholborane has been used in the place of borane and leads to cleaner products.\textsuperscript{13} \(\alpha\)-Hydroxy acids can be synthesised in an enantioselective manner using catecholborane.

\[
\text{Scheme 9}
\]

The reduction of ketones is not restricted to catalysts based on boranes. Ketones can be reduced using BINAP-ruthenium(II) catalysts. High enantiomeric excesses and reactivities have been achieved with substrates that contain a co-ordinating group in a position either \(\alpha\) or \(\beta\) to the carbonyl group.\textsuperscript{14}

\[
\text{Scheme 10}
\]

<table>
<thead>
<tr>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Ligand</th>
<th>E. e. % (S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>(\text{CH}_2\text{NMe})</td>
<td>ent 16</td>
<td>96 (S)</td>
</tr>
<tr>
<td>Ph</td>
<td>(\text{CH}_2\text{NMe})</td>
<td>ent 16</td>
<td>95 (S)</td>
</tr>
<tr>
<td>Me</td>
<td>(\text{CH}_2\text{OH})</td>
<td>16</td>
<td>92 (R)</td>
</tr>
<tr>
<td>Me</td>
<td>(\text{CH}_2\text{CH}_2\text{OH})</td>
<td>16</td>
<td>98 (R)</td>
</tr>
</tbody>
</table>

In the reduction of \(\alpha\)- or \(\beta\)-diketones, high enantioselectivity and diastereoselectivities are possible using the ruthenium BINAP catalysts.\textsuperscript{14}
Enantioselective hydrogenation on substrates without additional functionality to coordinate to is difficult. Transfer hydrogenation is the reduction of a substrate using another molecule as a hydrogen source. Using transfer hydrogenation it is possible to reduce simple ketones in the presence of a bis-oxazoline catalyst and propanol. The enantiomeric excesses obtained of the reduced products are up to 91%. There are very few reports of enantioselective hydrogenation of simple ketones.

![Chemical structures](image)

**Scheme 11**

**Hydrogenation of C=N Functionality**

There are a small number of examples for the enantioselective reduction of imines and related structures. Burk and Feaster reported the catalytic hydrogenation of several substrates with C=N functionalities. (Scheme 12)
Willoughby and Buchwald have published a titanium catalysed hydrogenation of imines with excellent enantiomeric excesses.\(^{17}\) (Scheme 13)

\[
\text{Scheme 12}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R</th>
<th>R</th>
<th>E.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p\text{-EtO}_2\text{CC}_6\text{H}_4)</td>
<td>Me</td>
<td>Ph</td>
<td>96</td>
</tr>
<tr>
<td>(p\text{-NO}_2\text{CC}_6\text{H}_4)</td>
<td>Me</td>
<td>Ph</td>
<td>97</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>Me</td>
<td>Ph</td>
<td>95</td>
</tr>
</tbody>
</table>

\[
\text{Scheme 13}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \begin{array}{c}
\text{\text{55}}
\end{array} \\
\text{H}_3\text{C} & \begin{array}{c}
\text{\text{56}}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{X} & = 1,1'-\text{binaphthyl-2,2'-dilotate}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \begin{array}{c}
\text{\text{57}}
\end{array} \\
\text{H}_3\text{C} & \begin{array}{c}
\text{\text{58}}
\end{array}
\end{align*}
\]
1.2 Asymmetric Aldol Reactions

The addition of an enolate to a ketone or aldehyde to form a β-hydroxy carbonyl compound is often referred to as an aldol reaction. A general scheme of an aldol reaction is shown below.

\[
\text{R} - \text{CH} = \text{R'} \xrightarrow{\text{Base}} \text{R} - \text{CH}_2 \text{R'} + \text{X} - \text{Y} \xrightarrow{\text{OH}} \text{R} - \text{CH} = \text{O} - \text{R'}
\]

The reaction consists of a carbon-carbon bond formation, thus creating two new chiral centres in a highly functionalised product. A particularly convenient method for the formation of the enolate involves the use of a dialkyl boron triflate (R_2B-OSO_2CF_3) and a weak hindered base. The formation is believed to follow the pathway shown in Scheme 14.

\[
\text{R} - \text{CH} = \text{R'} \xrightarrow{\text{Bu}_2\text{BOTf}} \text{Bu}_2\text{B} - \text{R} = \text{O} \xrightarrow{\text{TfO}^-} \text{Bu}_2\text{B} - \text{O}^+ \xrightarrow{\{(\text{Pr})_2\text{NET}} \text{Me}
\]

(\text{Z})-boron enolate

\text{Scheme 14}

One method to achieve an enantioselective product from an aldol reaction is to use a boron enolate with a chiral auxiliary. An excellent example of the use of a chiral auxiliary with the boron enolate was reported by Evans and co-workers (Scheme 15).\textsuperscript{18}
The chiral auxiliary developed by Evans has been applied to many substrates. There are a number of other chiral auxiliaries that have been developed.\textsuperscript{204} The main drawback with the use of chiral auxiliaries is they require a step to attach them to the substrate and a step, at the end, to recover the auxiliary.

**Catalytic Aldol Reactions**

Previous examples have shown the use of chiral auxiliaries in the aldol reaction. When the reaction is catalytic, the auxiliary is not needed which makes the use of the reaction in organic synthesis more attractive. In the example shown in Scheme 16, the complex formed between the tartaric acid derivative and borane provides a good catalyst for various substrates in the aldol reaction.\textsuperscript{19} In this reaction the relative and absolute stereochemistry of the product are independent of the geometry of the precursor silyl enol diethyl ether.
A catalyst based on the natural amino acid tryptophan has shown very good enantioselectivity in the aldol reaction with simple silyl enol ethers.²⁰
On reaction of benzaldehyde with the allylic silyl enol ether 62, the product afforded from the aldol reaction could be reacted further to produce the dihydropyranone 63.

Scheme 18

Catalytic aldol reactions conducted in the presence of gold(I) complexes and ligand 64 have given high levels of stereoselectivity in the coupling reaction of methyl isocyanatoacetate and various aldehydes. The resulting products from these aldol reactions are trans-substituted oxazolines which are useful as intermediates in the synthesis of β-hydroxy α-amino acids.

Scheme 19

<table>
<thead>
<tr>
<th>R</th>
<th>trans : cis</th>
<th>E.e. (%) 65</th>
<th>Yield (%) 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>95:5</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>p-CIC₅H₄</td>
<td>94:6</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>tBu</td>
<td>100:0</td>
<td>97</td>
<td>94</td>
</tr>
</tbody>
</table>
Aldol reactions have been conducted using a Lewis acid, as a catalyst, for the reaction. Mukaiyama reported high enantiomeric excess with the aldol reaction of silyl enol ethers of thioesters with aldehydes in the presence of a chiral promoter and tin triflate.\(^{22}\)

\[
\begin{align*}
R^1\text{CHO} + & \overset{\text{Sn(OTf}_2\text{(20 mol\%)}}{\overset{66\text{ or 67 (20 mol\%)}}{\overset{\text{EtCN}}{67\text{C}}}}} \\
& \overset{\text{-78 °C}}{\overset{\text{Syn / anti}}{\text{E.e. of syn}}} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Syn / Anti</th>
<th>E.e. of Syn (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>66</td>
<td>77</td>
<td>93:7</td>
<td>90</td>
</tr>
<tr>
<td>C_{7}H_{15}</td>
<td>Me</td>
<td>66</td>
<td>80</td>
<td>100:0</td>
<td>98</td>
</tr>
<tr>
<td>C_{6}H_{4}</td>
<td>Me</td>
<td>66</td>
<td>71</td>
<td>100:0</td>
<td>98</td>
</tr>
<tr>
<td>C_{6}H_{4}</td>
<td>H</td>
<td>67</td>
<td>81</td>
<td>100:0</td>
<td>92</td>
</tr>
<tr>
<td>C_{7}H_{15}</td>
<td>H</td>
<td>67</td>
<td>79</td>
<td></td>
<td>93</td>
</tr>
</tbody>
</table>

Mukaiyama also reported the catalytic asymmetric aldol reaction of silyl ketene acetals promoted by chiral zinc complexes. These complexes were prepared in situ from diethylzinc and a sulfonamide ligand derived from optically active amino acids.\(^{23}\) These ligands gave a lower enantioselectivity with benzaldehyde.
Masamune reported the asymmetric aldol reactions with a silyl ketone acetal 70. The catalysts used were boron complexes derived from an α,α-disubstituted glycine tosylamide.  

\[ R^1\text{CHO} + \text{acetal 70} \rightarrow \text{TBMSO} - \text{active catalyst formed in situ} \]

<table>
<thead>
<tr>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>Ligand</th>
<th>Yield(%)</th>
<th>E.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Et</td>
<td>68</td>
<td>79</td>
<td>60</td>
</tr>
<tr>
<td>CCl(_3)</td>
<td>Bn</td>
<td>69</td>
<td>61</td>
<td>88</td>
</tr>
<tr>
<td>CBr(_3)</td>
<td>Bn</td>
<td>69</td>
<td>66</td>
<td>93</td>
</tr>
</tbody>
</table>

Chapter 1 Catalytic Asymmetric Synthesis
Carriera \textit{et al} reported the use of a titanium centred catalyst that provided excellent enantiomeric excesses in aldol reactions.\textsuperscript{25} The reactions coupled various aldehydes with either O-ethyl or O-methyl silyl ketone acetals using a low concentration of the catalyst 75.

\[
\begin{align*}
R'\text{CHO} + \text{OR} & \xrightarrow{1. \ 75 (2-5 \text{ mol }\%)} \xrightarrow{-10 ^\circ \text{C}, \text{Et}_2\text{O}, 4\text{hr}} \text{OH} \\
R = \text{Me, Et} & \xrightarrow{2. \ \text{Bu}_4\text{NF}, \text{THF}} \text{OR}
\end{align*}
\]

Carriera extended the use of the ligand 75, by using the ligand in the addition of diene 76 to various aldehydes.\textsuperscript{26}

\[
\begin{align*}
R'\text{CHO} + \text{O} & \xrightarrow{1. \ 75 (1-3 \text{ mol }\%)} \xrightarrow{\text{Et}_2\text{O}} \text{OH} \\
& \xrightarrow{2. \ \text{TFA}, \text{THF}} \text{OR}
\end{align*}
\]
Carriera and Singer recently reported an extension to the earlier work on aldol reactions. Previously the catalyst 75 required the azeotropic removal of isopropanol prior to its addition to the reaction. Using a new method the catalyst could be prepared in situ.\(^{27}\)

\[
\begin{align*}
R^1\text{CHO} + & \text{OSiMe}_3 \quad \xrightarrow{\text{R} = \text{Me, Bn}} \quad \text{OH} \quad \text{OR} \\
\text{R} = \text{Me}, \text{Bn}
\end{align*}
\]

\[
\begin{align*}
1. & \text{75 (2 mol\%)} \quad \text{-20 °C, Et}_2\text{O}, \text{4-6 hr} \quad \text{TMSCl, Et}_3\text{N} \quad \xrightarrow{\text{2. TFA, THF}} \\
& \text{(R = Me)} \quad \text{(R = Bn)}
\end{align*}
\]

The research group of Shibasaki has recently reported direct catalytic asymmetric aldol reactions on aldehydes and unmodified ketones.\(^{28}\) The catalyst is based on a lanthanide. This procedure has been performed on several substrates and the enantiomeric excesses range from very good to excellent, shown in Table 1.

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>E.e. (%)</th>
<th>Yield (%)</th>
<th>E.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-CHO</td>
<td>95</td>
<td>98</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Ph-CHO</td>
<td>89</td>
<td>97</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>PhCHO</td>
<td>94</td>
<td>96</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

Chapter J Catalytic Asymmetric Synthesis 18
<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield(%)</th>
<th>E.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Bu</td>
<td>Ph</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>'Bu</td>
<td>1-naphthyl</td>
<td>55</td>
<td>76</td>
</tr>
<tr>
<td>PhCH₂(CH₃)₂</td>
<td>CH₃</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>PhCH₂(CH₃)₂</td>
<td>Et</td>
<td>71</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 1

1.3 Catalytic Asymmetric Dihydroxylation

The formation of cis diols through dihydroxylation provides a powerful methodology for alkene functionality. The overall transformation is shown below.

\[
\text{R} \quad \overset{1. \text{OsO}_4}{\longrightarrow} \quad \overset{2. \text{H}_2\text{O}}{\longrightarrow} \quad \text{R}^* \quad \text{R}^*
\]

The transformation has only quite recently become a catalytic process. The osmium is reduced during the dihydroxylation reaction and in order for the reaction to be conducted catalytically, the osmium must be re-oxidised. Several oxidants have been used for the oxidation of the osmium including hydrogen peroxide and sodium/potassium perchlorate. Alternative oxidants have been developed, Sharpless and Akashi introduced alkaline tert-butyl hydroperoxide, VanRheenen, Kelly, and Cha suggested the use of N-methylmorpholine N-oxide and in 1990, Yamamoto et al. introduced potassium ferricyanide.

The first asymmetric dihydroxylation was reported by Hentges and Sharpless. The dihydroxylation of several alkenes in the presence of dihydroquinidine acetate and dihydroquinine acetate under stoichiometric conditions produced cis-diols in 24-94 % e.e. The example shown is with stilbene 80.

\[
\text{Ph} \quad \overset{1. \text{OsO}_4}{\longrightarrow} \quad \overset{2. \text{H}_2\text{O}}{\longrightarrow} \quad \text{Ph}
\]

Chapter 1 Catalytic Asymmetric Synthesis
The ligands 81 and 82 produce opposite enantioselectivity in the dihydroxylation of substrates. These ligands are not enantiomers but are diastereoisomers of each other and are often referred to as pseudo-enantiomers. Sharpless and co-workers reported the first catalysed asymmetric dihydroxylation using N-methylmorpholine N-oxide as the co-oxidant. The dihydroxylation of stilbene was described using a catalytic quantity of osmium and enantiopure ligand in the presence of N-methyl morpholine oxide to provide R,R-(+)-dihydrobenzoin in enantiomeric excess of 88%.\textsuperscript{34}
The osmium tetroxide reacts with the alkene and ligand to form the intermediate 84. This intermediate is oxidised by the N-methyl morpholine and the intermediate 85 is formed. The intermediate 85 dissociates to afford the dihydroxylated alkene and the osmium in a suitable oxidation state to perform further catalytic turnovers, as shown in Scheme 20. N-Methyl morpholine oxide is used in the reaction to oxidise the osmium back to its original oxidation state. The enantiomerically pure ligand is used to provide an asymmetric environment, this environment producing an enantiomerically enriched product.

The dihydroxylation has been applied to many substrates. Substrates with a trans configuration alkene tend to afford higher enantioselectivities. The use of the dimers dihydroquinidine-PHAL [(DHQD)₂-PHAL] and dihydroquinine-PHAL [(DHQ)₂-PHAL] have been shown to give good enantiomeric excesses with a number of substrates.³⁵
These dimers are commercially available as AD-mix-α and AD-mix-β which also contain the osmium and oxidants.

\[ \text{(DHQD)}_2\text{-PHAL} \]

The dihydroxylation reaction has been applied to various types of alkenes as shown in the Table 2.  

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>E.e. (%) 87</th>
<th>E.e. (%) 88</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBu</td>
<td>Me</td>
<td>Me</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>nBu</td>
<td>H</td>
<td>nBu</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>C₅H₁₁</td>
<td>H</td>
<td>CO₂Et</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Ph</td>
<td>-(CH₂)₄⁻</td>
<td></td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>

Table 2
The dihydroxylation reactions can be regio and chemoselective and this methodology has been used as a key step in the synthesis of (-)-Muricatacin.\textsuperscript{36}

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \longrightarrow \quad \text{(DHD)}_2\text{-PHAL} \\
& \quad \text{dihydroxlation} \\
\text{EtO}_2\text{C} & \quad \longrightarrow \quad \text{(DHQD)}_2\text{-PHAL} \\
& \quad \text{dihydroxlation}
\end{align*}
\]

95\% e.e.\hspace{1cm} 96\% e.e.

(-)-Muricatacin

The dihydroxylated products can be converted into epoxides, and this provides a synthetic pathway to obtain enantiomerically enriched epoxides from simple allylic substrates. The pathway forms two different intermediates 89 and 90, both of which form the same final product. This methodology has been successfully applied in the short enantioselective synthesis of leukotriene antagonist SKF 104353 as shown in Scheme 21.\textsuperscript{37}

\[
\begin{align*}
\text{MeC(OMe)}_3 & \quad \longrightarrow \quad \text{Me}_2\text{SiX} \\
& \quad \text{cat.PPTS} \\
\text{K}_2\text{CO}_3 & \quad \longrightarrow \quad \text{MeOH}
\end{align*}
\]

PPTS- Pyridinium p-toluenesulfonate
TMS- Trimethylsilane

89 X = Cl, Br, I 90
Scheme 21 shows the epoxide ring being opened by a nucleophile producing an enantiomerically enriched product. The 1,2-diols can be used to provide other substituted products by formation of a cyclic sulfite. When the cyclic sulfite is oxidised to a sulfate, a nucleophile can displace the sulfate in an $S_N2$ manner. A variety of nucleophiles has been introduced including hydride, azide, nitrates and primary amines. The sulfate ester 91 can be hydrolysed with aqueous acid to afford an alcohol.

This methodology has been applied to the synthesis of enantiomerically pure diamines. The reaction of the $(R,R)$-stilbenediol cyclic sulfate 91 and the benzamidine 92 produces the imidazoline 93 and this can be converted into $S,S$-stilbene diamine.
94. This methodology has been used to produce the enantiomerically pure \(\text{trans-2,3-diphenyl-DABCO}\) (trans-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane).  

\[
\begin{align*}
\text{O=S=O} & \quad \text{Ph} & \quad \text{H}_2\text{N} & \quad \text{92} \quad \text{NH} \\
\text{Ph} & \quad \text{91} & \quad \text{Ph} & \quad \text{92} \quad \text{NH} \\
& \quad \text{Ph} & \quad \text{H}_2\text{N} & \quad \text{NH} \\
& \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{AcOH-H Br} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
& \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
1. \text{Cl} & \quad \text{O} & \quad \text{Cl} & \quad \text{95} \\
2. \text{BH}_3/\text{THF} & \quad \text{3.} & \quad \Delta & \quad \text{94} \\
& \quad \text{NH}_2 & \quad \text{Ph} & \quad \text{Ph} \\
& \quad \text{NH}_2 & \quad \text{Ph} & \quad \text{Ph}
\end{align*}
\]

1.4 Catalytic Asymmetric Epoxidation of Allylic Alcohols  
The catalytic epoxidation of allylic alcohols is one of the major recent advancements in organic chemistry. One of the first examples of asymmetric induction in the epoxidation of alkenes was reported by Henbest in 1965. The enantioselectivity obtained was 8\% using a camphoric acid derivative.  

The real breakthrough in this area was reported by Sharpless and Katsuki in 1980.  

The use of a titanium (IV) alkoxide, an enantiomerically pure tartrate ester and \textit{tert}-butyl hydroperoxide was shown to epoxidise a wide variety of allylic alcohols with enantiomeric excesses exceeding 90\%. In 1987, it was reported that in the presence of molecular sieves, the epoxidation could be conducted with a catalytic quantity of titanium (IV) alkoxide and enantiomerically pure tartrate ester. The epoxidation required only 5-10 mol\% of the catalyst and the allylic alcohols were epoxidised with similar enantiomeric excesses as those obtained when stoichiometric quantities were used.  

The epoxidation is highly predictable in the enantiomer that will be produced, it is general for allylic alcohols, and it often gives high enantioselectivity. The reaction is chemoselective, only the double bond adjacent to a hydroxyl bearing carbon will be epoxidised.
Fundamental to the success of the enantiomeric epoxidation reaction is the alcohol functionality. This accelerates the reaction and is required in order for the reaction to take place enantioselectively. This dependence does provide a limitation to the reaction. The outcome of the epoxidation can be predicted using a simple model. When looking at the model in Scheme 22, delivery of the oxygen is either from the top face when using D-(-)-diethyl tartrate or from the lower face when using L-(+)-diethyl tartrate. The diethyl tartrate, titanium isopropoxide and the tert-butyl hydroperoxide are commercially available and inexpensive.

Scheme 22

The epoxidation reaction is compatible with most functional groups; notable exceptions include carboxylic acids, mercaptans, phosphines and most phenols. When the allylic alcohol is in a cis configuration and R$^3$ is the bulky alkyl group, the reaction is slower but the enantiomeric excesses obtained are similar to those obtained with alcohols in the trans configuration. Several hundred substrates have been used in the Sharpless-Katsuki epoxidation reaction. Examples shown in Table 3 illustrate the range of different substrates that can be used.$^{45}$
<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>Tartrate</th>
<th>E.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>(-)-DET</td>
<td>95</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>H</td>
<td>H</td>
<td>(+)-DET</td>
<td>95</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>(+)-DIPT</td>
<td>92</td>
</tr>
<tr>
<td>H</td>
<td>$\text{CH}_2=\text{CH}$</td>
<td>H</td>
<td>(+)-DIPT</td>
<td>91</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>(+)-DIPT</td>
<td>92</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>(+)-DET</td>
<td>94</td>
</tr>
<tr>
<td>H</td>
<td>Me$\text{CH}=\text{CH}_2$</td>
<td>Me</td>
<td>(+)-DET</td>
<td>95</td>
</tr>
<tr>
<td>H</td>
<td>TBSOCH$_2$CH$_2$</td>
<td>Me</td>
<td>(-)-DET</td>
<td>95</td>
</tr>
<tr>
<td>-(CH$_2$)$_4$&quot;</td>
<td>H</td>
<td>(+)-DET</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>-(CH$<em>2$)$</em>{10}$&quot;</td>
<td>Me</td>
<td>(+)-DIPT</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3**

Catalytic epoxidation reactions are important for the synthesis of water-soluble epoxides and their isolation. Catalytic conditions made the isolation easier and allowed *in situ* derivatisation.\(^{46}\)

The Sharpless epoxidation has been used to kinetically resolve allylic alcohols. If a substrate contains two different substituents on the alcohol-bearing carbon, then the substrate contains chirality. Providing that the two enantiomers have sufficiently different rates of epoxidation and the epoxidation is terminated at 50% conversion, a kinetic resolution will occur. One enantiomer of the alcohol is epoxidised more quickly leaving the other enantiomer intact.
Some examples of kinetic resolution are shown below, the maximum theoretical yield is 50 \%\textsuperscript{47}.

<table>
<thead>
<tr>
<th>R</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>Yield</th>
<th>E.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}</td>
<td>H</td>
<td>CH\textsubscript{2}CH=CH\textsubscript{2}</td>
<td>H</td>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>cC\textsubscript{6}H\textsubscript{11}</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>32</td>
<td>98</td>
</tr>
<tr>
<td>nC\textsubscript{4}H\textsubscript{9}</td>
<td>H</td>
<td>CH=CH\textsubscript{2}</td>
<td>H</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>nC\textsubscript{12}H\textsubscript{25}</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
<td>H</td>
<td>44</td>
<td>97</td>
</tr>
</tbody>
</table>

The enantiomeric excess of the epoxidised product and that of the unreacted allylic alcohols depends on the relative rates of epoxidation, extent of conversion and the structure of the substrate.

Enantiomerically pure epoxides are valued highly in organic synthesis, the epoxide can be selectively opened with a nucleophile. The opening of the epoxide is usually via an S\textsubscript{N}2 pathway, therefore, electron withdrawing groups adjacent to the carbon undergoing substitution cause a decrease in the rate. The electron withdrawing ability of the C-1 hydroxyl group retards attack of a nucleophile at C-2, therefore ring opening at C-3 is electronically more favoured. When considering which carbon is...
more susceptible to nucleophile attack the bulkiness of the substituent at C-3 must be taken into account.\(^{48}\)

![Chemical structure diagram](Image)

\[\text{R} \quad \text{C-3:C-2} \]

\[\begin{align*}
\text{C}_7\text{H}_{15} & \quad 3.5:1 \\
\text{Cyclohexyl} & \quad 1.7:1 \\
\text{BnOCH}_2 & \quad 1:1 \\
\text{tBu} & \quad \text{C-2 only}
\end{align*}\]

If the reaction conditions allow titanium isopropoxide can be added to enhance nucleophilic attack at C-3. The enhancement is thought to be due to the formation of a five-membered ring titanium chelate \(^{96}\). This pathway is only suitable with nucleophiles that are unreactive with titanium isopropoxide.

![Chemical structure diagram](Image)

\[\text{Nuc-H} = (\text{allyl})_2\text{NH}, \text{tPrOH, PhCO}_2\text{H, all 100:1}}\]
\[\text{Nuc-CN} = \text{Me}_3\text{SiCN 14:1; Nuc-N}_3 = \text{MeSiN}_3, 100:1}\]
\[\text{Nuc-H} = \text{R-NH}_2 88:12-94:6\]

**Payne Rearrangement**

Under certain conditions, 2,3-epoxy alcohols can undergo a Payne rearrangement. The Payne rearrangement is an unfavoured process and is in equilibrium with the original substrate. The alcohol moiety displaces one of the epoxide bonds, in an SN2 manner, to form an epoxy alcohol with the epoxide formed in the 1,2 position. The relative stereochemistry of the newly formed epoxide is inverted in comparison to the
original epoxide. The Payne rearrangement allows the attack of a nucleophile at the C-1 position to afford a diol.\(^{50}\)

\[
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{3} \\
\text{2} \\
\text{1} \\
\text{O} \quad \text{OH}^{-} \\
\xrightarrow{\text{Payne rearrangement}} \\
\text{R} \\
\text{2} \\
\text{1} \\
\text{O} \quad \text{Nuc} \quad \text{H} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{OBn} \\
\text{OH} \\
\end{array}
\xrightarrow{\text{NaOH, } \text{'BuSH}}
\begin{array}{c}
\text{OBn} \\
\text{S'Bu} \\
\end{array}
\]

\[
\begin{array}{c}
\text{C}_7\text{H}_{15} \quad \text{O} \\
\text{OH} \\
\end{array}
\xrightarrow{\text{KOH, Et}_2\text{NH}}
\begin{array}{c}
\text{C}_7\text{H}_{15} \\
\text{NEt}_2 \\
\end{array}
\]

The Payne rearranged product can be isolated exclusively using the following synthetic pathway.\(^{48}\)

\[
\begin{array}{c}
\text{O} \\
\text{OBn} \\
\text{OH} \\
\end{array}
\xrightarrow{\text{NaOH, } \text{'BuSH}}
\begin{array}{c}
\text{OBn} \\
\text{OH} \\
\text{S'Bu} \\
\end{array}
\xrightarrow{\text{Me}_3\text{OBF}_4}
\begin{array}{c}
\text{OBn} \\
\text{OH} \\
\end{array}
\xrightarrow{\text{NaH}}
\begin{array}{c}
\text{OBn} \\
\text{O} \\
\end{array}
\xrightarrow{\text{Nuc}}
\begin{array}{c}
\text{OBn} \\
\text{OH} \\
\text{Nuc} \\
\end{array}
\]

\[
\text{Nuc} = \text{'N}_3, \text{'H}, \text{'Me}
\]

### 1.5 Asymmetric Catalytic Epoxidation of Unfunctionalised Alkenes

Enantioselective alkene epoxidation is an appealing strategy for the synthesis of optically active organic compounds. The Sharpless epoxidation has become widely used in research and industry. The Sharpless epoxidation relies implicitly on the presence of an alcohol functionality. A method to catalytically epoxidise unfunctionalised alkenes would be very useful and desirable. This type of reaction would rely on non-bonding interactions to accomplish this. The inspiration for the development of porphyrin type ligands came from a report by Groves.\(^{51}\) Groves
discovered that Fe(III) porphyrin complexes were models for cytochrome P-450, the cytochrome complex is a molecule capable of oxygen transfer. The first example of asymmetric epoxidation of simple alkenes catalysed by enantiomerically pure porphyrin complexes was reported by Groves and Meyer in 1983. Epoxidation reactions of styrene derivatives were reported using the catalyst 97 in the presence of iodosylmesitylene (as a stoichiometric oxidant). The substrate that gave the highest enantiomeric excess was p-chloro styrene, 51 %.

These porphyrin catalysts worked well with alkenes in a cis configuration but were relatively poor with the trans alkenes. This erosion of enantioselectivity was attributed to the angle of approach of the alkene.

The angle of approach was believed to favour cis above the trans alkenes due to the steric interactions with the porphyrin ring. More recently Naruta reported the use of porphyrin 98 in the epoxidation of o-nitrostyrene, the enantiomeric excess of the epoxidised product was 89 %.
Metal Salen Complexes

Chiral salen complexes have similar structural and chemical features to those found in porphyrins. Salen complexes, like porphyrins, are able to catalyse the epoxidation of unfunctionalised alkenes. Salens differ to porphyrins in that they contain asymmetric centres in closer proximity to the central metal and are simpler to synthesise. Several different salen ligands have been developed using different metals and different asymmetric scaffoldings. The most successful is ligand 99 using a manganese metal. This ligand has been applied many substrates, a few examples are shown in Table 4.
Table 4

The epoxidation reaction using salen molecules can be conducted using household bleach (NaOCl). The proposed model to explain the enantioselectivity is shown in Figure 2, however Katsuki disagrees with this model.\(^{205}\)
This catalyst 99 has been applied in the synthesis of the hypertensive agent Cromakalim and the related compound EMD-52,692.\textsuperscript{57}

![Manganese complex](image)

Figure 2

One noteworthy example of asymmetric epoxidation of trans alkenes was reported by Gilheany \textit{et al.}\textsuperscript{56} In the stoichiometric epoxidation of the alkene 101 the trans epoxide
102 was synthesised with an enantiomeric excess of 83% and with 77% e.e. when the reaction was conducted using catalytic conditions.

![Reaction diagram](image)

Epoxidation catalysts based on salen molecules have been applied to the practical synthesis of important enantiomerically enriched compounds. This methodology has enormous potential but a challenge still lies ahead. The discovery of more efficient catalysts for the epoxidation of trans alkenes and simple mono alkyl-substituted alkenes is required and doubtless research in the future will be directed in this direction.

### 1.6 Dialkylzinc Additions To Carbonyl Compounds

The asymmetric addition of dialkylzinc reagents to aldehydes catalysed by enantiomerically pure ligands is a convenient method for the preparation of enantiomerically enriched secondary alcohols. The alcohols are important intermediates for various functionalities such as halides, amines and ethers. Asymmetric alkylation of aldehydes, as well as resulting in enantiomerically enriched secondary alcohols, also provides a method for carbon-carbon bond formation. This methodology is a powerful tool for asymmetric synthesis.

Stoichiometric amounts of enantiopure ligand were required initially to achieve high levels of asymmetric induction. More recently this process has been developed to utilise a catalytic quantity of the enantiomerically pure ligand. The development of a catalytic process provided a challenge to organic chemists. The dialkylzinc would
have to be relatively unreactive towards carbonyl compound when there was no catalyst and reactive when it was (ligand acceleration). Ligands have been developed that are successful in the addition of dialkylzinc to aldehydes, this is shown with the example of \((-\text{DAIB}) = (\text{-}-\text{exo-}(\text{dimethylamino})\text{isoborneol})^{60,61}\)

\[
\text{RCHO} + \text{R'}_2\text{Zn} \rightarrow \text{(-)-DAIB (2 mol%)}
\]

\[
\begin{array}{c|c|c}
\text{R} & \text{Nuc} & \text{E.e. (\%)} \\
\hline
\text{Ph} & \text{Me} & 91 \\
\text{Ph} & \text{Et} & 99 \\
\text{Ph} & \text{nBu} & 98 \\
\text{pClC}_6\text{H}_4 & \text{Et} & 93 \\
\text{pMeOC}_6\text{H}_4 & \text{Et} & 93 \\
\text{2-Furyl} & \text{nC}_5\text{H}_11 & 95 \\
\text{(E)-C}_6\text{H}_5\text{CH}=\text{CH} & \text{Et} & 96 \\
\text{(E)-(nBu)}_3\text{SnCH}=\text{CH} & \text{C}_5\text{H}_11 & 85 \\
\text{PhCH}_2\text{CH}_2 & \text{Et} & 90 \\
\end{array}
\]

As would be expected, (+)-DAIB provides the opposite alcohol enantiomer. The transition state of the alkylation is thought to resemble that shown in Figure 3.

\[
\text{Figure 3}
\]

It is believed that two dialkylzinc molecules are involved in the alkylation, both being co-ordinated to the catalyst. One zinc atom is co-ordinated with the hydroxyl group of the catalyst only, whilst the other zinc atom is co-ordinated with the oxygen and

Chapter 1 Catalytic Asymmetric Synthesis

36
nitrogen of the catalyst as well as the oxygen of substrate. Due to steric reasons, the bulky R group of the aldehyde is orientated away from the catalyst and nucleophile. The alkyl nucleophile is co-ordinated to both zinc atoms as well as the aldehyde. There many enantiomerically pure β-amino alcohols, and related structures, that have given good selectivity in the nucleophilic addition of a dialkylzinc to benzaldehyde. The ligands 104, 105, 106, 107, 108, 109, 110, 111, 112 have been used successfully in the addition of diethylzinc to benzaldehyde.

\[
\begin{align*}
\text{PhCHO} & \xrightarrow{\text{Et}_2\text{Zn, catalyst}} \text{PhOEt} \\
\text{(R) or (S)} & \text{depending on catalyst}
\end{align*}
\]

\[
\begin{align*}
\text{98 % e.e. (R)} & \quad \text{104} \\
\text{81 % e.e. (R)} & \quad \text{105} \\
\text{91 % e.e. (S)} & \quad \text{106} \\
\text{92 % e.e. (R)} & \quad \text{107} \\
\text{95 % e.e. (R)} & \quad \text{108} \\
\text{99 % e.e. (S)} & \quad \text{109} \\
\text{94 % e.e. (S)} & \quad \text{110} \\
\text{90 % e.e. (R)} & \quad \text{111} \\
\text{87 % e.e. (S)} & \quad \text{112}
\end{align*}
\]

This methodology has been applied in the key step of short synthesis of R-Muscone. The reaction utilises an intramolecular cyclisation using 1 mol% of (+)-DAIB.
An interesting discovery was made whilst investigating the use of DAIB in the dialkylzinc additions to aldehydes. The enantiomeric purity of the ligand DAIB was not required to be particularly high in order to achieve high enantiomeric excess in the alkylated product. An enantiomeric excess above 90 % was obtainable using the ligand (-)-DAIB with an enantiomeric purity of just 25 %.\(^6\)

This observation is known as 'chiral amplification', it is due to the way DAIB reacts with dialkylzinc. The DAIB exists either as a monomer or dimer, however, the dimer does not catalyse the alkyl addition.

When using optical pure (-)-DAIB (100 % e.e.) then only one dimer species is possible, (-,-)-115. This dimer is not stable and dissociates to provide the two monomers. When using (-)-DAIB which is not enantiomerically pure (<100 % e.e.)
then there are three possible dimer species possible, (-,-)-**115**, (+)-DAIB/(+)-DAIB **116** and (-,+-)**114**. Of these dimer species the most stable is **114**, this is the *meso* dimer which is formed irreversibly under these conditions. The consequence of this is, the minor enantiomer becomes irreversibly bound to the major enantiomer, leaving only the major enantiomer to catalyse the reaction. Using an example with (-)-DAIB in 50% enantiomeric excess.

\[
\begin{align*}
(-)\text{DAIB} & \quad + \quad (+)\text{DAIB} \\
75\% & \quad 25\%
\end{align*}
\]

\[
\xrightarrow{\text{Et}_2\text{Zn}}
\]

\[
\begin{align*}
\text{(-)DAIB/(-)DAIB} & \quad \text{(+)-DAIB/(+)-DAIB} & \quad \text{(-)DAIB/(+)-DAIB} \\
\text{115} & \quad \text{116} & \quad \text{114} \\
\text{reversible} & \quad \text{reversible} & \quad \text{irreversibly bound} \\
50\% & \quad 0\% & \quad 50\%
\end{align*}
\]

\[
\xrightarrow{}
\]

\[
\begin{align*}
\text{(- DAIB monomer} & \quad 50\%
\end{align*}
\]

Chiral amplification is particularly useful if the catalyst is difficult to obtain in an enantiomerically pure form. The phenomenon means that resolution processes of the ligand or the alcohol product may not be required to be completely efficient.

**1.7 Conclusion**

This Chapter provides a brief overview of catalytic asymmetric synthesis during the last 15 years. The application of these powerful methodologies has proved useful for the asymmetric synthesis of synthetic target molecules.
# Chapter 2

Asymmetric Catalysis
Using Heterobidentate Ligands

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2.0 Introduction

Enantiomerically pure bidentate ligands, where the two donor atoms are different from one another, have been relatively neglected in comparison to the development and utilisation of homobidentate ligands. In recent years there has been an increased interest in the development of enantiomerically pure bidentate ligands. There are several examples of reactions where these ligands have been successful. A large proportion of these ligands has been applied to the palladium catalysed allylic substitution reaction, which is discussed in detail in Chapter 3.

2.1 Nitrogen - Sulfur Ligands

Copper(I) thiolate complexes, developed from enantiomerically pure mercaptophenyl-oxazoline 117, were found to catalyse enantioselectively the 1,4-additions of Grignard reagents to \( \alpha,\beta \)-unsaturated ketones, as reported by Pfaltz and Zhou.\(^67\)

\[
\begin{align*}
\text{PrMgCl} & \quad 5-10 \text{ mol\% } 117 \text{ (Li salt)} \\
\text{Cul} & \quad (5 \text{ mol\%}) \\
\text{THF, HMPA} & \\
\rightarrow & \\
\text{yield} & \quad 43 \% \text{ for } n=2 \\
& \quad 71 \% \text{ for } n=3 \\
& \quad 55 \% \text{ for } n=4
\end{align*}
\]

The lithium ion of 117 provides a neutral and charged donor ligand in which the sulfur has a greater affinity for the copper than for the magnesium. The enantioselectivites were found to increase with ring size, from a low selectivity of 37 \% e.e. with cyclopentenone, to a maximum of 87 \% e.e. with cycloheptenone.

2.2 Nitrogen - Oxygen

Falorni and co-workers prepared the heterobidentate ligand 120 which was utilised in an enantioselective addition of diethylzinc to benzaldehyde.\(^68\) The reaction of
benzaldehyde with two equivalents of diethylzinc, in the presence of ligand 120, gave the alkylated product 121 in near quantitative yield and 100 % e.e.

\[
\begin{align*}
\text{Et}_2\text{Zn (2 equiv)} & \rightarrow \text{Et}_2\text{O} \\
\text{Et}_2\text{O} & \rightarrow 99 \% \text{ conv.} \\
\end{align*}
\]

Wills and co-workers have recently reported the use of the commercially available amino alcohol \((1R,2S)-(+)\)-cis-1-amino-2-indanol 122, in the asymmetric transfer hydrogenation of ketones. Acetophenone 123 was reduced in the presence of amino alcohol 122, a ruthenium catalyst and propan-2-ol (hydrogen source) to afford the alcohol 124 in 91 % e.e.

\[
\begin{align*}
\text{0.25 mol}\% \, \text{[RuCl}_2(\pi\text{-cymene})_2 & \rightarrow \text{OH} \\
1 \text{ mol}\% 122 & \rightarrow \text{OH} \\
2.5 \text{ mol}\% \text{KOH in propan-2-ol} & \rightarrow \text{OH} \\
\text{r.t. 1.5 hr} & \rightarrow \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{70 \%} & \rightarrow \text{OH} \\
\text{91 \% e.e.} & \rightarrow \text{OH} \\
\end{align*}
\]
2.3 Nitrogen - Phosphorus

The research group of Kumada developed ferrocene derived chiral ligands in the early 1980's. These were found to give a good enantioselectivity in nickel catalysed Grignard cross coupling reactions.\(^7\)

Kumada reported the asymmetric coupling of Grignard reagent 130 with vinyl bromide 131 in the presence of NiCl\(_2\) (0.5 mol%) using the ligands 127, 128 and 129 (1:1 mixture), to afford 3-phenyl-but-1-ene 132. Using the ferrocene ligand 127 the enantiomeric purity of the terminal alkene was 61%. Using the opposite enantiomer of the ferrocene ligand 128 afforded a slightly lower enantiomeric excess of 54% and ligand 129 provided an enantiomeric excess of 65%. The relatively high enantiomeric excess obtained from the use of ligand 129 strongly suggests that the methyl group plays a minor part in the enantiomeric outcome of the reaction. It suggests the majority of the enantiomeric enrichment comes from the planar chirality of the ferrocene framework.

Richards and co-workers, inspired by these results, developed alternative ferrocene based ligands.\(^7\) Richards used palladium bound complexes of ligands 135 and 136. The ligands were stirred with PdCl\(_2\)(NCMe)\(_2\), and the complex was crystallised using hexane. The palladium bound complexes were used to catalyse the coupling of Grignard reagent 130 and β-bromostyrene 133 to afford the product 134.
When using palladium-bound ligand 135 the level of asymmetric induction was found to give a modest 45 % e.e. However, when ligand 136 was used the enantiomeric excess was a poor 8 %. This suggests that ligand 136 contained some non-cooperating elements of chirality. Ligand 135 held no significant advantage over the ligands originally designed by Kumada et al.

The research group of Weissensteiner has also developed a ferrocene derived ligand 137 to be used in a palladium catalysed cross coupling reaction. Vinyl bromide 131 was coupled with phenylmagnesium chloride 130 to provide the coupled product 132 in excellent yield and with a good enantiomeric excess of 79 %.

Faraone and co-workers prepared and developed an enantiopure phosphite ligand 138 to be used in an enantioselective hydroformylation reaction. The ligand was complexed with rhodium, to afford the catalyst, \{(\text{Rh(CO)})(\text{PPh}_3)[138]\}\text{ClO}_4. The
hydroformylation of methyl acrylate proceeded smoothly in the presence of the rhodium catalyst, carbon monoxide and hydrogen gas to provide the branched aldehyde $\text{139}$ in a high enantiomeric excess of 92 % with a 95 % conversion.

$$\text{CHO} \quad \begin{array}{c} \text{Rh/138} \\ \text{CO/H}_2 (1:1) \end{array} \quad \begin{array}{c} \text{16h, 60 atm, 60 °C} \\ \text{95 % conv.} \end{array} \quad \text{139}$$

92 % e.e.

Wimmer and Widhalm have described the preparation of ligands $\text{140}$ and $\text{141}$ and their subsequent successful application in two different reactions. The ligands achieved the optimum enantioselectivity in the palladium catalysed allylic substitution reaction. The acetate $\text{142}$ was smoothly converted into the alkylated product $\text{143}$ in the presence of a palladium catalyst, ligand $\text{140}$ or $\text{141}$ and the sodium anion of dimethyl malonate. Ligand $\text{140}$ afforded the highest enantiomeric excess (96 %) and chemical yield (95 %). Ligand $\text{141}$ gave a lower enantiomeric excess of 79 % and 93 % yield.

$$\text{OAc} \quad \begin{array}{c} \text{Ph=Ph} \\ \text{1 mol% Pd} \\ \text{2 mol% ligand 140 or 141} \end{array} \quad \text{Dimethyl malonate} \quad \begin{array}{c} \text{r.t, THF} \\ \text{using 140 95 %} \quad \text{using 141 93 %} \end{array} \quad \begin{array}{c} \text{CH(CO}_2\text{Me})_2 \\ \text{Ph=Ph} \end{array}$$

with $\text{140}$ 96 % e.e. with $\text{141}$ 79 % e.e.

\[ \text{140} \quad \text{141} \]
Ligand 141 was also applied to the hydrogenation of trans-acetamido cinnamic acid 144. The active catalyst was prepared by combination of Rh(COD)ClO₄ with ligand 141. The newly formed chiral centre in the hydrogenated product 145 has the S configuration.

In recent years, the research group of Yamagushi has developed the ligand 146 for the enantioselective hydrogenation of acrylic acid derivatives. The hydrogenation proceeds smoothly in the presence of a rhodium catalyst derived from ligand 146, at a hydrogen pressure of 40 atm in 86 hours. The alkene 147 was reduced to afford the carboxylic acid 148 in a 92 % enantiomeric excess.

In 1993, Brown and co-workers reported the preparation and use of 1-(2-diphenylphosphino-1-napthyl)isoquinoline 149 in rhodium catalysed hydroboration reactions. The secondary alcohols were isolated after hydrogen peroxide oxidation in enantiomeric excesses of up to 94 %.
Brown and co-workers reported an extension of the hydroboration methodology to the synthesis of enantiomerically enriched secondary amines. The initial step was the formation of the catecholboranate ester 153, as seen previously. The subsequent step is the conversion of the boronate ester 153 into a trialkyl borane 154 by the addition of methylmagnesium chloride. The enantiomerically enriched amine is obtained via use of the aminating agent, H$_2$NOSO$_3$H, to displace the alkylborane, thus affording the enantiomerically enriched amine.

This methodology provides a synthetic route to enantiomerically enriched amines in moderate yield with a number of alkenes.
1. [Rh(COD)(acac)]-CF₃SO₃SiMe₃, 149 (1 mol%)
2. catecholborane
3. MeMgCl in THF
4. H₂NOSO₃H

51-61%

The research group of Togni has recently reported the preparation and use of ferrocenyl derived ligands in the hydroboration of styrene. Togni used 19 different ligands in the conversion of styrene 159 to the branched alcohol 160. Two examples are shown using ligands 162 and 163, they give excellent enantioselectivities.

Ph

1. catecholborane
1 mol% Rh-Ligand complex
2. NaOH/H₂O₂

with 162 91% with 163 68% using 162 95% e.e. (160) using 163 98.5% e.e. (160)


(S, R) 162 R=Ph
(R, S) 163 R=3,5 (CF₃)₂Ph

active catalyst

2.4 Synthesis of Novel Heterobidentate Ligands

The project originally set out to design and synthesise novel enantiomerically pure ligands to be utilised in a platinum catalysed epoxidation reaction (discussed in Section 2.11). Within the research group, there is a large amount of experience in the use of oxazolines as ligands. Previous experience had shown that phosphorus and nitrogen ligating atoms provide one of the better combinations for a bidentate ligand. Heterobidentate ligands provide different electronic effects on the metal, particularly if one of the ligating atoms is charged. As well as electronic effects, these types of ligands also provide different steric environments to the molecule tethered to the metal, as in Figure 4.
When phosphorus is bound through a metal to an allyl moiety, the phosphorus is known to impart a trans-effect on the allyl molecule. This effect causes an electronic disparity between the two termini of the allyl functionality; hence electronic density at either end of the allyl functionality is different. The consequences of this disparity are discussed later in Chapter 3. The template chosen for the design of novel heterobidentate chiral ligands was the highly successful 2-diphenylphosphino phenyloxazoline 164.\textsuperscript{79}

Key features of the oxazoline 164

The oxazoline 164 had been shown to give excellent enantioselectivities when used in the palladium catalysed allylic substitution reaction.\textsuperscript{79}

The significant characteristics of the oxazoline 164 are;

- the asymmetric centre is close to the nitrogen atom
- the bidentate character through the nitrogen and phosphorus atoms
- it is accessible via a short and simple synthesis from commercially available starting materials

The asymmetric induction shown by ligand 164 in the palladium catalysed allylic substitution reaction, is known to come from the orientation of the isopropyl moiety. This is discussed in greater depth in Chapter 3.
Synthesis of ligand 164

The synthesis of oxazoline 164 is shown in Scheme 23. 2-Fluorobenzonitrile 165 reacts with (S)-valinol 166 in the presence of a catalytic quantity of zinc chloride to afford the 2-aryl oxazoline 167. The oxazoline 167 reacts further with potassium diphenylphosphine at reflux, with displacement of the fluorine atom to afford the oxazoline 164.

\[
\begin{align*}
\text{F} & \text{CN} \\
\text{H}_2\text{N} & \text{HO} \\
\text{ZnCl}_2, 160^\circ\text{C} & \text{THF, reflux} \\
\text{76\%} & \text{76\%}
\end{align*}
\]

Scheme 23

2.5 Ligand Design

We chose to design the novel ligands using the key feature of the oxazoline 164. The attributes that would be incorporated into the novel ligands were:

- nitrogen and phosphorus ligating atoms
- the number of spacer units between the nitrogen and phosphorus atoms
- positioning of the enantiomerically pure centre next to the nitrogen functionality
- short and simple synthesis

The nitrogen and phosphorus functionality were chosen as they are known to be one of the better bidentate combinations. The spacer units between nitrogen and phosphorus, the 'bite angle', were thought to be important. The bite angle would be maintained to keep the successful stereochemical topology. The oxazoline 164 had been shown to be good at binding metals such as palladium. The enantiomerically pure centre next to the nitrogen was thought to be very important. Chiral induction, imparted from the ligand, would come from the enantiopure centre next to the ligating site.
2.6 Ligands

2.6.1 Aldehyde Derived Ligands

The above criteria for the novel ligand design stipulated a nitrogen ligating site. As an alternative to the oxazoline ring (found in 164) an imine was chosen. The imine would keep the nitrogen double bond character whilst providing the necessary nitrogen binding site, as in the oxazoline ring, and would have an \( \alpha \)-asymmetric centre which would satisfy the criteria regarding the positioning of the enantiopure centre. The synthetic pathway chosen was the coupling of 2-diphenylphosphino benzaldehyde 168 with commercially available amines containing an \( \alpha \)-asymmetric centre.

Synthesis of 2-DiphenylphosphinoBenzaldehyde

The aldehyde was synthesised in three steps from 1-bromobenzaldehyde 169. This pathway could be used to synthesise the aldehyde in multi-gram quantities. \( \text{ortho-} \)Bromo benzaldehyde was protected as an acetal using trimethyl orthoformate. An acetal peak at \( \delta \) 3.4 ppm replaced the aldehyde peak at \( \delta \) 10.5 ppm. This acetal, 170, was sufficiently pure to be used in the next stage without purification. Addition of the diphenylphosphino moiety was achieved by forming the Grignard reagent and quenching with chlorodiphenylphosphine. This intermediate 171 was not purified at this stage. Aldehyde 168 was obtained after de-protection of the acetal 171 in acetone and a catalytic amount of acid, confirmation of the aldehyde product is the aldehyde peak at \( \delta \) 10.5 ppm.\(^8\) The aldehyde 168 was purified using flash silica chromatography to afford a crystalline product in a 40\% yield, shown in Scheme 24.

\[\text{Scheme 24}\]
It had been expected that the lone pairs of the oxygen and the phosphorus would electrostatically repel one another, therefore the oxygen atom would orientate itself away from the phosphorus. This was found not to be the case in the solid state. The crystal structure of 168 (in the appendix) shows the distance between the oxygen and phosphorus to be 2.83 Å (±SD). This short distance suggests the oxygen is actually orientating itself towards the phosphorus, this phenomena was also seen in the crystal structure of 2-diphenylphosphino acetophenone (Section 2.8).

The Amines
To simplify the synthesis of the novel ligands commercially available amines were used. The amines were (S)-methylbenzylamine 174 and the naphthyl derivative (1S)-(1-naphthyl)ethylamine)175.

The Coupling of Aldehyde and Amine
The imines 172 and 173 were readily synthesised by stirring the aldehyde 168 and the requisite free amine 174 or 175 in dichloromethane. The imines were isolated as brown oils and purified using activated basic alumina to give 172 and 173 in 35 % and 45 % yield respectively. Attempts at purification using silica chromatography resulted in the imine hydrolysis. The imine formation was confirmed by the disappearance of the aldehyde proton and a new peak, corresponding to the imine, appeared at δ 8.9 ppm for ligand 172 and δ 9.0 ppm in the case of 173. Brunner et al. have previously reported the preparation of the imine 172.81

\[
\begin{align*}
  & H & H \\
  & \text{PPh}_2 & \text{Me} \\
 168 & & \\
 174 \text{ R = Ph} & 175 \text{ R =1-naphthyl} \\
\end{align*}
\]

2.6.2 Ketone Derived Ligands
Ketone derived ligands, ketimines, were prepared concurrently with the aldehyde versions.
Preparation of Ketone 176

The ketone 2-diphenylphosphino acetophenone 176 was prepared in one step from commercially available 2-fluoroacetophenone 177.82

\[
\begin{align*}
\text{Ketone 176} & \\
\text{2-diphenylphosphino acetophenone} & \\
\text{Preparation:} & \text{KPH}_2, \text{THF} \\
\text{177} & \xrightarrow{\text{KPH}_2, \text{THF}} \text{176} \\
\end{align*}
\]

The ketone 176 is crystalline, the crystal structure shows the distance between the oxygen and phosphorus to be 2.73 Å(±SD). This suggests that the oxygen was orientating itself over the phosphorus, as had been observed with 2-diphenylphosphino benzaldehyde 168.

Coupling of Amines and Ketone

The preparation of the analogous ketimines required more forcing conditions than the aldimines. The method used to synthesise the aldimines from aldehyde 168 proved unsuccessful with the ketone. The ketimines were synthesised by heating the free amines with the ketone 176, at reflux, in the presence of a strong Lewis acid (titanium tetrachloride).

\[
\begin{align*}
\text{Ketone 176} & \\
\text{176} & \xrightarrow{\text{TiCl}_4, \text{Et}_3\text{N}, \text{DCM, reflux}} \text{178, 179} \\
\text{174 Ar = Ph} & \\
\text{175 Ar = naphthyl} & \\
\text{178 Ar = Ph} & \\
\text{179 Ar = naphthyl} \\
\end{align*}
\]

The ketimines 178 and 179 were isolated as brown oils and were purified using flash silica chromatography. These brown oils contained two geometrical isomers 180 and 181 as well as the free amine. The two geometric forms could not be separated from each other or the free amine. $^{13}\text{C}$ and $^1\text{H}$ NMR showed two sets of signals corresponding to the two geometric isomers and a third set for the free amine. Confirmation of the synthesis of imine 178 in the $^1\text{H}$ NMR spectrum was the absence of the acetophenone methyl signal at δ 2.6 ppm. The acetophenone signal was
replaced with two new signals at δ 2.2 and 2.3 ppm (two geometrical isomers) pertaining to the methyl group next to C=N. Further confirmation of the synthesis of imine 178 was obtained using IR spectroscopy. The characteristic stretch of C=N was observed at 1644 cm⁻¹. The synthesis of ketimine 179 was confirmed by ¹H NMR, two new signals at δ 2.3 and 2.5 ppm and the absence of the peak at δ 2.58. Further evidence from IR spectroscopy showed the C=N stretch to be 1646 cm⁻¹.

The Two Geometrical Isomers

![Geometrical Isomers](image)

The geometrical isomer 180 is the only isomer that appears available for bidentate binding. The other isomer is thought to be in the wrong configuration to act as a bidentate ligand (i.e. it is bidentate challenged).

2.7 SAMP Derived Ligand

SAMP (S-(-)-1-amino-2-(methoxymethyl)pyrrolidine) 183 was used as a free amine to synthesise a novel enantiopure hydrazone. The hydrazone 182 was synthesised in an identical manner to ligands 178 and 179.

![Synthesis](image)

The hydrazone was formed as a brown oil which was purified using flash silica chromatography. The hydrazone did not contain the two geometrical isomers previously observed with 178 and 179. The ¹H NMR spectrum provided confirmation of the synthesis of hydrazone 182. The absence of the acetophenone methyl signal at δ 2.6 ppm and the emergence of a new peak at δ 2.3 ppm. The ligand 182
provided new characteristics that were slightly different to previously synthesised ligands;

- It contained an extra spacer unit between the binding nitrogen and enantiopure centre
- the SAMP moiety contained an oxygen which could interfere in binding or with incoming molecules

2.8 Diamine Derived Ligands

Whilst developing imine based ligands, progress was being made on other ligands incorporating the nitrogen within a ring (similar to the oxazoline). Alexakis developed various diamines which have been used to determine the enantiomeric purity of aldehydes. We have used one of these diamines 184 to afford the ligand 185.

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \quad \text{Ph} \\
\text{Ph} & \quad \text{Me} \quad \text{N} \quad \text{H} \\
\text{Ph} & \quad \text{Me} \quad \text{N} \quad \text{H} \\
\text{Ph} & \quad \text{Me} \quad \text{N} \quad \text{H} \\
\end{align*}
\]

Synthesis of ligand 185 proceeded smoothly; the diamine 184 and the aldehyde 168 were heated at reflux for 16 hours to afford the product 185 in good yield. The synthesis was confirmed by \(^1\)H NMR, the aldehyde peak (previously at \(\delta\) 10.5 ppm) was replaced with a peak at \(\delta\) 5.7 ppm corresponding to the proton \(H^a\).

Alexakis also developed the diamine 186 which provided a useful starting material for the preparation of the imidazoline 188. The synthetic pathway employed was the initial formation of the imidazoline ring 187. The imidazoline was subsequently \(o\)-lithiated and quenched with chlorodiphenylphosphine to provide the diphenylphosphino moiety.
The synthesis from the commercially available benzimidate ion progressed smoothly. The benzimidate ion 189 was heated at reflux in ethanol, in the presence of diamine 186, to provide the imidazoline 187. The imidazoline 187 was o-lithiated and then quenched with chlorodiphenylphosphine. The imidazoline 188 was purified using flash silica chromatography. Confirmation of the formation of the imidazoline 188 was provided by IR spectroscopy and $^{13}$C NMR. The peak associated with the C=N stretch was found at 1622 cm$^{-1}$. The signal in the $^{13}$C NMR which correlates to a quaternary carbon with a double bond to nitrogen (in a ring) was found at $\delta$ 163 ppm (similar to the oxazoline).

Attempted preparation of imidazoline 190 using the same synthetic pathway as ligand 188 was unsuccessful. The problematic step was the o-lithiation of substrate 191.

2.9 Application Of The Novel Ligands

During the preparation of these ligands our interest turned to the enantioselective epoxidation reactions. Strukul et al.\(^8\)\(^4\) had shown that terminal alkenes in the presence of platinum could be epoxidised enantioselectively.

\[ R \rightarrow Pt \text{catalyst} \rightarrow \begin{array}{c} \text{H}_2\text{O}_2 \\ \rightarrow \end{array} \begin{array}{c} R \\ \text{O} \\ \end{array} \]

**Scheme 25**

Strukul reported the use of the ligands chiraphos 192 and prophos 193, bound to a platinum catalyst, epoxidised propene with an enantiomeric excess of 41% and 35% respectively. The active platinum catalyst used was $P_2^*Pt(CF_3)(OH)$ where $P_2^*$ denotes the enantiomerically pure bidentate phosphorus ligand.
The enantiomeric excesses obtained with chiraphos and prophos were fairly low. We reasoned the asymmetric centres of prophos and chiraphos were not in close proximity to the substrate, when bound to platinum. If this were the case, then the asymmetric induction of the enantiopure centre would not be very significant. The design of the new novel ligands synthesised in this Chapter, would have their asymmetric centre closer to the substrate. The asymmetric centres being closer to the substrate would hopefully lead to an increased asymmetric induction and thus a higher enantiomeric excess.

Despite contacting Strukul on numerous occasions and despite many attempts to prepare the platinum catalyst, it was never synthesised in a satisfactorily pure form. The second step of the synthesis to produce \((\text{PPh}_3)_2\text{Pt(CF}_3\text{)Br}\) proved very problematic. Unfortunately this reaction afforded side products of \((\text{PPh}_3)_2\text{PtBr}_2\) in both the cis and trans isomers. These impurities were inseparable by various purification techniques. Furthermore, experiments carried out by M. Clarke have shown the displacement of triphenylphosphine with nitrogen and phosphorus bidentate ligands to be very difficult.\(^{85}\)

Due to the problematic synthesis of the platinum catalyst our attention turned to the use of these novel ligands in other metal catalysed reactions. Within the group there is a large amount of experience with palladium catalysed allylic substitution reactions. The application and results of these novel ligands are documented in Chapter 3.
Chapter 3

Palladium Catalysed Allylic Substitution Reaction

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3.0 Introduction

Palladium catalysed reactions have found widespread use in a number of important chemical processes, including Stille coupling, Heck reactions, Wacker oxidations and allylic substitution reactions. This chapter examines the enantioselective palladium catalysed allylic substitution reaction.

Basic Process of the Palladium Catalysed Allylic Substitution Reaction

The essence of the transformation which has been applied to many systems, is the conversion of an allylic substrate, such as \( \text{194} \), into the substituted product \( \text{195} \), using palladium and a nucleophile.

\[
\text{194} \xrightarrow{\text{Nuc}^-} \text{195}
\]

Scheme 26

The Mechanism of the Palladium Catalysed Allylic Substitution Reaction

The mechanism that is generally accepted when using soft nucleophiles is illustrated in Scheme 27.

\[
\text{195} \xrightarrow{\text{Dissociation}} \text{Pd(0)L}_n \xrightarrow{\text{Association}} \text{194} \xrightarrow{\text{Oxidative Addition}} \text{196} \xrightarrow{\text{Reductive Elimination}} \text{198} \xrightarrow{\text{199}} \text{Nuc} \xrightarrow{\text{Pd catalyst}} \text{195}
\]

Scheme 27

Initially, the palladium(0) associates with the alkene followed by oxidative addition to afford the \( \eta^3 \) allyl intermediate \( \text{197} \). The leaving group migrates onto the palladium and an equilibrium between the intermediates \( \text{197} \) and \( \text{198} \) occurs. Bidentate ligands push the equilibrium towards the formation of the cationic intermediate \( \text{198} \). The cationic intermediate \( \text{198} \) is believed to be more susceptible to nucleophilic attack.
which affords the alkene complex 199. The dissociation of palladium from 199 liberates the substituted product 195 and the regenerated active palladium species.

The Geometry of the Allyl Complexes
In the case of a di-substituted allyl complex, two geometrical isomers are possible; 200 and 201. The preferred isomer is 200 this provides the minimal steric interactions between the ligand and the R groups and therefore is preferred.

3.1 The Range of Substrates
The palladium catalysed allylic substitution reaction has been applied to many different substrates, the most common substrate being an allylic acetate. Other substrates that have been used include halides, carbonates, phosphates, sulfones, amines and ammonium salts. Alcohols have been used but require activation. Tsuji developed the use of carbonates in the palladium catalysed allylic substitution reaction. During the reaction the carbonate is displaced and an alkoxide anion is generated through the loss of carbon dioxide. This basic alkoxide ion is capable of deprotonating many of the nucleophiles used in these reactions, the mechanism of which is shown in Scheme 28.

\[
\text{Scheme 28}
\]
3.1.1 The Range of Nucleophiles

The type of nucleophile most commonly used in palladium catalysed allylic substitution reactions are 'soft' nucleophiles. The most common nucleophiles are enolates derived from β-dicarbonyl compounds, such as dimethyl malonate. Other carbon nucleophiles that have been employed include cyanide, simple enolates, as well as harder nucleophiles. There are a number of nucleophiles that have been used which are not based on carbon. Examples include sulfur, nitrogen, oxygen, silicon, tin, and hydride nucleophiles.

3.2 Stereochemical Aspects

3.2.1 Soft Nucleophiles

Several research groups have conducted experimental studies to determine the basic stereochemical outcome of the palladium catalysed process. Trost reported that the use of soft nucleophiles, pKa < 20, led to an overall retention of stereochemistry. Trost attributed the retention of the stereochemistry to the reaction proceeding via two sequential stereochemical inversions. The first inversion is from the addition of the palladium to the substrate, the second from the nucleophile attacking from the exo face of intermediate 202.

3.2.2 Hard Nucleophiles

In the case of hard nucleophiles, pKa > 20, the palladium catalysed allylic substitution reaction generally leads to an overall inversion of stereochemistry. Whilst the allyl palladium complex is formed in an identical manner to that seen with soft nucleophiles, the nucleophile adds to the palladium to form the complex 203. The nucleophile is then delivered to the allyl intermediate 203 from the same face as the palladium, which results in the product 204. The consequence of the addition of the...
nucleophile to the palladium, prior to the attack of the allyl moiety, is that there is a net inversion of stereochemistry.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{PhZnCl} \\
\text{OAc} & \quad \text{Pd cat} \\
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{Ph} \\
\text{Pd} & \quad [\text{Pd}] \\
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{Ph} \\
\end{align*}
\]

**Scheme 30**

**Stereochemical Integrity**

It would be reasonable to expect that an enantiomerically pure substrate should be converted to an enantiomerically pure product and this is sometimes the case. The substrate 205 was converted into the alkylated product 206 with complete transfer of chirality.\(^{110}\)

\[
\begin{align*}
\text{OAc} & \quad \text{NaCH(CO}_2\text{Me)}_2 \\
\text{OH} & \quad \text{Pd(OAc)}_2, \text{PPh}_3, \text{THF} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH(CO}_2\text{Me)}_2 & \quad \text{OH} \\
\end{align*}
\]

However, there are examples in which the stereochemistry has not been preserved which has important implications on the design of palladium catalysed allylic substitution reactions. If the stereochemistry was always preserved, it would be essential to have an enantiomerically pure substrate to afford enantiomerically pure product. Fortunately, enantiomerically pure products can be prepared from racemic substrates.

Tsuji and co-workers conducted the cyclisation of 207 to afford the product 208 using different reaction conditions.\(^{111}\) One reaction was conducted with the nucleophile preformed resulting in the formation of the product 208 with an overall retention of stereochemistry. When the nucleophile was generated in the absence of hydride base, the inherent stereochemistry was lost and the product 208 was produced as a racemic mixture. When the nucleophile is generated in the presence of hydride base,
the slower attack of the nucleophile allows the allyl intermediate to equilibrate, and therefore racemise, via a $\pi$-$\sigma$-$\pi$ mechanism.

![Scheme 31](image)

\[ \text{Scheme 31} \]

$\pi$-$\sigma$-$\pi$ Rearangement

The isomerisation of $\eta^3$-allyl complexes is well known. The complex is believed to change between the isomeric forms by a $\pi$-$\sigma$-$\pi$ mechanism, shown in Scheme 32. The complex exists as an equilibrium of two enantiomeric forms. Bosnich investigated the general characteristics of allyl-Pd(II) intermediates capable of undergoing racemisation in this way. $^{112}$ The racemisation results in the loss of inherent stereochemistry from the allyl precursor. Consequently, the stereochemistry of the product is determined by the palladium complex intermediate.

![Scheme 32](image)

\[ \text{Scheme 32} \]
3.3 Regioselectivity

If the substrate undergoing a palladium catalysed allylic substitution reaction is symmetrical, then the regioselectivity of the incoming nucleophile determines the enantiomeric excess, as the products are enantiomers of each other. When the substrate is unsymmetrical the regioselective addition of the nucleophile, to either end of the allyl intermediate, leads to different products. Studies from Keinan and Sahai have shown when using the substrate 209 in the presence of palladium and a soft nucleophile, a high selectivity of the product 210 is obtained.\textsuperscript{113} The morpholine attacks the allyl intermediate at the least sterically demanding carbon. However, when a hard nucleophile is used the regioselectivity is inverted to give the opposite regioisomer. This change in selectivity is rationalised by the nucleophile proceeding through a different mechanism; the hard nucleophile adds to the palladium species prior to attacking the allyl carbon terminus, as shown with the intermediate 213.

![Chemical structures and schemes](image)

3.4 Enantiocontrol

Trost and Dietsche reported the first example of asymmetric induction in the allylic substitution reaction.\textsuperscript{114} Trost and Stege later reported the first asymmetric catalytic example of the allylic substitution reaction in 1977.\textsuperscript{115} The transformation converted the racemic acetate 214 into the enantiomerically enriched alkylated product 215.
3.4.1 Enantioselective Reactions via a Meso Intermediate

The enantioselective palladium catalysed allylic substitution reaction has predominately been investigated using examples in which the reaction proceeds through a symmetrical allyl intermediate 216, as shown in Figure 4. Trost and Van Vranken have recently reviewed the use of enantiomerically pure ligands in palladium catalysed allylic substitution reactions. The enantioselectivity of the reaction is determined wholly by the regioselective attack of the incoming nucleophile on the allyl moiety; formation of the symmetrical allyl intermediate causes all inherent stereochemistry to be lost. The nucleophilic attack is remote to the metal centre and associated ligand. Hence, exploitation of this reaction as an enantioselective process has challenged organic chemists to develop efficient enantiomerically pure ligands.
The synthesis of an enantiomerically enriched product from a racemic substrate, via the symmetrical allyl intermediate, can be achieved in several ways. There are several strategies used to overcome the problem of remote attack by the nucleophile:

- exerting enantiocontrol through secondary interactions from the ligand
- exerting enantiocontrol using steric interactions on the allyl moiety
- exerting enantiocontrol by achieving electronic distortion of the allyl moiety

3.4.2 Enantiocontrol Through Secondary Interactions From the Ligand

Hayashi et al. reported the use of ligands 218 and 219 which were designed to 'reach around' and direct the attack of the nucleophile onto the allyl moiety as shown in Figure 5.\(^\text{117}\)

\[\text{Figure 5}\]

Nucleophilic attack is remote from the ligands

Ligands using this strategy include:

\[\text{Figure 5}\]

When the ligand 218 was used in the reaction shown in Scheme 34 the product 220 was isolated with 96 % enantiomeric excess.\(^\text{118}\) Ligand 221 was designed using the same principle and achieved an enantiomeric excess of 36 % in the palladium catalysed allylic substitution reaction detailed in Scheme 35.\(^\text{115}\) Other examples of this type of ligand are 222 and 223.\(^\text{117}\)
Exactly how the ligands 222 and 223 provide such high enantioselectivities is unknown. The selectivity is possibly due to the electronic repulsion between the carboxylate and incoming nucleophile. Alternatively the carboxylate could add to the allyl moiety and be displaced by the nucleophile in an SN2 manner. Another possibility is that the carboxylate group could bind to the palladium and function as a bidentate ligand.

3.4.3 Enantiocontrol Using Steric Interactions On the Allyl Moiety
Ligands have been designed to sterically interact with the allyl moiety and therefore influence the enantiomeric outcome of the alkylation reaction. The ligand can achieve this by blocking the approach of the incoming nucleophile or perturbing the symmetry of the allyl moiety. The interaction between the ligand and the allyl moiety can force one of the carbon termini away from the palladium, and as a result of this, the allyl unit becomes electronically unsymmetrical. The terminus being forced away contains more positive charge character and consequently, becomes more susceptible to
nucleophilic attack, this is illustrated in Figure 6. It is thought that C$_2$-symmetric ligands induce asymmetry in this way.

![Diagram](image)

The ligand bound to Palladium perturbing the symmetry of the allyl moiety by steric effects

**Figure 6**

Examples of these types of ligands include the bidentate ligands 224, 225, 226, 227. The enantiomeric excesses given are the results obtained for the alkylated product 143 in Scheme 35, unless the nucleophile is shown.

![Structures](image)

These ligands provide high enantioselectivities in the palladium catalysed allylic substitution reaction shown in Scheme 35. Other examples are based on nitrogen.
and include 228, 229, 230, 231, 184, 233. The enantiomeric excesses given are the results obtained for the alkylated product 143 in Scheme 35.

There are a number of ligands which are non-C₂-symmetric, 234, 235, 236, 237, 238. The ligands 236-8 are unusual as they are monodentate ligands. The enantiomeric excesses given are the results obtained for the alkylated product 143 in Scheme 35.
3.4.4 Enantiocontrol Through Electronic Interactions on the Allyl Moiety
As an alternative to steric interactions a ligand containing two different atoms at the
ligation sites can be used to electronically perturb the allyl moiety. Due to the trans
effect, the better π-acceptor of the two ligating atoms weakens the Pd-C bond in the
trans position. This weakening leads to the carbon terminus, opposite to the better π-
acceptor, to become more susceptible to nucleophilic addition. Åkermark, Vitagaliano
and co-workers demonstrated this concept using N,P donor ligands.133 Figure 7
illustrates the addition of the nucleophile in a trans position to the phosphorus, the
better π-acceptor in this case. The allyl moiety has two possible diastereomeric
intermediates, known as M and W. These intermediates afford opposite enantiomers
in the alkylated product. In a heterobidentate ligand the better π-acceptor will
nominate a carbon terminus for nucleophilic attack via the trans effect. The
scaffolding of the ligand dictates which of the diastereomeric intermediates
predominates. If the ligand can combine these two attributes successfully then an
enantiomerically enriched product will be realised.

Several groups have prepared and used ligands based on oxazolines with two
different donor atoms in palladium catalysed allylic substitution reactions as illustrated
in Scheme 35. The oxazolines that have been developed and used in the alkylation
reaction include 239134, 240135 241 136 242, 137 243. 138 The enantiomeric excesses
shown are the results obtained for the alkylated product 143 in Scheme 35.
NMR and X-ray crystallographic studies of the allyl intermediate have been conducted by the groups of Helmchen and Pfaltz using the oxazoline ligand 239. The predicted major intermediate was the M diastereomer 245, in which the iso-propyl group is positioned away from the phenyl group of the allyl moiety, shown in Figure 8. This M diastereomer leads to the alkylated product 244 which is not the major product in the alkylation reaction. From NMR studies, the diastereomeric intermediates are in very rapid equilibrium and the rate of the nucleophilic attack actually determines the enantioselectivity. The observed selectivity is rationalised by the iso-propyl group being positioned in a pseudoaxial position which forces the hydrogen into the pseudo-equatorial position. The twist in the ligand backbone, as a consequence of the iso-propyl group being pseudoaxial, means the phenyl rings on the phosphorus present an asymmetric environment to the allyl moiety.
There are many examples of ligands containing two different donor atoms. A selection is shown here with nitrogen and phosphorus, 252, 247, 248, 249, 250, 144, 140, 145, 251. The enantiomeric excesses given are the results obtained for the alkylated product 143 in Scheme 35.
There are examples which do not use the nitrogen and phosphorus combination 253, 254, 255, 256, 257. The enantiomeric excesses given are the results obtained for the alkylated product 143 in Scheme 35.

3.5 Cyclic Substrates

Cyclic allylic acetate substrates can also undergo palladium catalysed allylic substitution reactions. The cyclic acetate substitutions proceed through a meso intermediate. The cyclic acetate 258 will undergo palladium catalysed allylic substitution reaction to afford the products 259 and ent 259 via the intermediate 260, as shown in Scheme 36.
Scheme 36
A large proportion of the ligands tested in the alkylations of cyclic substrates have previously been used with the 1,3-diphenylpropenyl substrate 142. There are relatively few examples that perform with good enantiomeric excess in both systems. Trost and Murphy\textsuperscript{151} reported the first example to give a good enantioselectivity. The racemic bicyclic substrate 261 was converted into the product 262 with an enantiomeric excess of 69\%.

In more recent years the research group of Helmchen has reported the use of the oxazoline 264 in the conversion of 265 into the alkylated product 266.\textsuperscript{152} The conversion gave an enantiomeric excess of 50\% using optimised conditions; higher selectivities were reported with larger ring sizes. The research group also reported the use of the ligand 267 which afforded the alkylated product in 98\% e.e.\textsuperscript{153} Kang and co-workers reported the use of sparteine 228 within the same reaction giving the product in a 62\% e.e.\textsuperscript{123} This ligand is unusual in the fact that it performs well in both
cyclic and acyclic alkylations. Trost reported that the ligand 268, which has been widely applied to a number of cyclic substrates, in the conversion of 265 into the alkylated product 266 it gave 96% enantiomeric excess. This ligand played a vital role in the synthesis of the (S)-2-aminopimelic acid derivative 269 from the acetate 270.

![Chemical structures and reactions involving ligands 264, 265, 266, 267, 268, 270, and 271, along with the transformation of 265 to 266 and 270 to 271.]

Scheme 37

3.6 Conclusion

The palladium catalysed allylic substitution reaction is a powerful tool for asymmetric synthesis. The transformation affords the product with a new carbon-carbon bond with excellent selectivity. The reaction is facile and affords the product in high yield. The ligands designed for this reaction can be applied to other reactions. Different nucleophiles provide new products that could be difficult to synthesise using other synthetic routes.
3.7 The Application of novel N,P-Ligands

As described in Chapter 2, novel ligands were synthesised to be used in a platinum catalysed epoxidation reaction. Due to synthetic problems encountered with the platinum catalyst, our attention turned to the use of these ligands in palladium catalysed allylic substitution reactions.

The Substrate

The allyl acetate *trans* 3-acetoxy-1,3-diphenylprop-1-ene 142 was chosen as the substrate to be subjected to the allylic substitution reaction. The synthesis of the acetate 142 was achieved smoothly in two steps from commercially available chalcone 272.

![Scheme 38](image)

Treatment of chalcone 272 in methanol with sodium borohydride in the presence of cerium chloride heptahydrate at 0 °C resulted, after aqueous work up, in the crude alcohol 273. The crude alcohol product required no purification to proceed to the next stage. $^1$H NMR analysis of 273 confirmed the product formation with the appearance of a proton doublet at δ 5.4 ppm, corresponding to hydrogen in the α position to the alcohol. Acetylation of the allylic alcohol 273 was achieved using acetic acid, pyridine as a base and solvent in the presence of a catalytic amount of DMAP. $^1$H NMR analysis of 142 confirmed product formation by the shift of the signal at δ 5.4 ppm seen in 273 to δ 6.4 ppm and the emergence of a three proton singlet at δ 2.1 ppm corresponding to the acetoxy group.
Typical Palladium Catalysed Allylic Substitution Reaction

The enantioselective palladium catalysed allylic substitution reactions were performed as previously reported by this group.\textsuperscript{155}

\[
\begin{align*}
\text{CH}_2(\text{CO}_2\text{Me})_2, \text{BSA (3 equiv)}, \\
2.5 \text{ mol}\% \,[\text{Pd}(\pi-\text{C}_3\text{H}_5)\text{Cl}]_2 \\
10-15 \text{ mol}\% \text{ Ligand} \\
1 \text{ mol}\% \text{ KOAc} \\
\text{CH}_2\text{Cl}_2 \text{ r.t.}
\end{align*}
\]

BSA = \text{N,O-bis(trimethylsilyl)acetamide}

Scheme 39

In a typical allylic substitution reaction, allylpalladium chloride dimer (2.5 mol\%) was stirred with an enantiomerically pure ligand (10-15 mol\%) in dichloromethane for 15 minutes to pre-form the palladium catalyst. After pre-mixing, the dimethyl malonate, BSA, potassium acetate and 1,3-diphenylpropenyl acetate 142 were added sequentially. After stirring for 24 hours at room temperature the alkylated product 143 was afforded in modest to good yield. In every case \(^1\text{H} \text{NMR analysis confirmed the product formation with the disappearance of the three proton singlet at } \delta 2.1 \text{ ppm, corresponding to the acetoxy group of } 142 \text{ and the appearance of an one proton doublet at } \delta 4.2 \text{ ppm corresponding to the methine proton of the dimethyl malonate moiety in product } 143.\)

In all cases the absolute configuration and enantiomeric excess were determined by HPLC analysis and confirmed with NMR shift experiments. When the product was stored for more than three months, a small portion of the oil crystallised to give a racemic crystalline solid and an enantiomerically enriched oil.

3.8 Testing the Aldehyde Derived Imines

The imine 172 was the first ligand to be subjected to the palladium catalysed allylic substitution reaction. This imine had been produced from the coupling of (S)-methyl benzylamine and 2-diphenylphosphine benzaldehyde.
The ligand 172 was subjected to the alkylation reaction detailed in Scheme 39, using dimethyl malonate and BSA to provide the nucleophile. The alkylated product 143 was afforded with a low enantiomeric excess of 20% and a modest chemical yield of 49%. This initial result was disappointing. The imine 172 had been based on the highly successful oxazoline 164 which had achieved an enantiomeric excess of 99% in the identical alkylation reaction. The characteristics of the oxazoline 164 appeared to be similar to those of the imine 172, in particular, the positioning of the C=N bond and the asymmetric centre. One of the fundamental differences between the two ligands was the nitrogen was no longer constrained in a ring. Perhaps this freedom of movement had contributed to the reduced control of the enantioselectivity in the alkylation reaction.

The naphthyl analogue 173, of imine 172, was also used in the palladium catalysed allylic substitution reaction. The naphthyl group provided a larger and more sterically demanding ligand compared to imine 172. It was hoped, this increased steric bulk would sculpt an asymmetric environment that would afford the alkylated product 143 with an increased enantiomeric excess.

The Imine 173 was used as a ligand in the alkylation reaction detailed in Scheme 39. The alkylated product 143 was obtained with an enantiomeric excess of 7% and chemical yield of 52%. This result strongly suggested the naphthyl group had provided a non-contributory effect to the enantiomeric outcome of the alkylation. The steric bulk of the naphthyl group appeared to be inhibiting the proximity of the
asymmetric centre to the allylic substrate. The effect of steric bulk reducing the enantioselectivity had been observed previously. When the oxazoline 274 had been used in the alkylation reaction detailed in Scheme 39, a lower enantiomeric excess of 90 % was recorded. The absolute configuration of the alkylation product 143 was R, using the imines 172 and 173, as shown in Table 5.

**Conclusion**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield %</th>
<th>E. e. %</th>
<th>Configuration S/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>49</td>
<td>20</td>
<td>R</td>
</tr>
<tr>
<td>173</td>
<td>52</td>
<td>7</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 5

Pregosin and co-workers reported the use of the imine 172 and 173 in the identical alkylation reaction, as shown in Table 6. Pregosin’s results were very similar to those reported here but there were slight variations in the absolute configuration of the alkylation product.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>E. e. %</th>
<th>Configuration S/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>10</td>
<td>R</td>
</tr>
<tr>
<td>173</td>
<td>17</td>
<td>S</td>
</tr>
</tbody>
</table>

Table 6

The results presented by Pregosin were interesting, the configuration of the asymmetric centre in both of the ligands was S, but the alkylation product 143 was afforded with opposing configurations. From our own results, and those reported by Pregosin, the use of the imines 172 and 173 as ligands in palladium catalysed allylic substitution reactions were not particularly effective.

Brunner reported the utilisation of several imines in a palladium catalysed allylic substitution reaction. The alkylation of 1,5-dimethylbarbituric acid with allyl acetate, in the presence of DBU and an enantiomerically pure imine ligand, proceeded to give the product 276 in good yield.
The ligands used in the alkylation reaction, detailed in Scheme 40, were imines 277-9, the results of which are documented in Table 7.

### Scheme 40

The maximum enantiomeric excess attained using the imines 277-9 was 13 %. From our own results, and those obtained by Brunner and Pregosin, it appeared that aldehyde derived imines were not particularly efficient as ligands in these asymmetric palladium catalysed allylic substitution reactions.

### Table 7

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield %</th>
<th>E. e.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>277</td>
<td>69</td>
<td>10</td>
</tr>
<tr>
<td>278</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>279</td>
<td>68</td>
<td>13</td>
</tr>
</tbody>
</table>

3.9 Testing the Ketone Derived Imines

The results obtained whilst using the aldehyde derived imines in the alkylation reactions were disappointing. The structural design of the imines was reappraised, in particular, the confirmation of the chiral amine due to the possibility of bond rotation. There was a distinct possibility that the asymmetric centre was no longer in a fixed position during the alkylation reaction. It was reasoned that an enantiomerically pure centre in a fixed position would provide the alkylated product 143 with modest enantiomeric excess. Thus, if the asymmetric centre was able to rotate, there would
be an erosion in the enantiomeric excess of the alkylated product 143. It was proposed the 1,3-allylic strain provided by the hydrogen (H^α) in the aldehyde derived imines, would not be sufficient to hinder the rotation of the enantiomerically pure centre. Thus, the asymmetric centre would rotate and the alkylated product would be afforded with a low enantiomeric excess.

It was also proposed that increasing the 1,3-allylic strain in the ligand and hindering the rotation of the enantiopure centre would lead to the alkylated product 143 being produced with an increased enantiomeric excess. This could be accomplished by replacing the hydrogen H^α with a methyl group. The methyl group would increase the steric interaction and provide a more conformationally stable ligand.

As described in Chapter 2, the analogous ketone versions of imines 172 and 173 were synthesised. The ketone derived imines 178 and 179, contain a mixture of geometries which could not be separated. The imine 179 was used as a ligand in the palladium catalysed allylic substitution reaction detailed in Scheme 39. The alkylated product 143 was afforded with an enantiomeric excess of 20%. This provided a modest increase from the analogous aldmine 173 which had produced the alkylated product 143 with an enantiomeric excess of just 7%. Interestingly, imine 179 afforded the alkylated product 143 with the opposite conformation to that obtained using the aldmine 173.
The imine 178 was used in the alkylation reaction detailed in Scheme 39, using dimethyl malonate and BSA. The alkylated product 143 was produced smoothly with an enantiomeric excess of 67 % and a 94 % chemical yield. Due to this encouraging result, the imine 178 was further optimised.

Optimisation of the Imine 178 in the Palladium Catalysed Allylic Substitution Reaction

The imine 178 contained a major and minor conformation. When an excess of the imine was used as a ligand, there was no increase in the enantiomeric excess in the alkylation product 143. This suggested that only one conformation was active and that the minor conformation did not bind to the palladium. The presence of the minor conformation apparently did not interfere with enantiomeric excess of the alkylation product 143.

Solvent effects

Decreased polarity - The imine 178 was tested with several solvents with different polarities. The original alkylation reaction had been conducted with dichloromethane as a solvent. Optimisation began by decreasing the polarity of the solvent system used in the alkylation reactions. Being less polar, hexane would provide less competition for the binding sites around the palladium catalyst. The alkylation reaction was repeated using a 1:1 dichloromethane:hexane solvent system; the alkylated product 143 was afforded with an enantiomeric excess of 65 %, the chemical yield was reduced to 47 %. The enantiomeric excess obtained, using the 1:1 dichloromethane/hexane solvent system, was comparable to that obtained with dichloromethane alone (67 %). The hexane content was not increased due to possible insolubility problems with the imine or palladium catalyst.

Increased polarity - The use of a more polar solvent was investigated, acetonitrile would provide increased competition for ligation around the palladium catalyst. When
the alkylation reaction was conducted with imine 178 in acetonitrile, the alkylated product 143 was produced with an enantiomeric excess of 64 % and a chemical yield of 46 %. Again, the enantiomeric excess is comparable with the result obtained with dichloromethane alone and provided no enhancement.

Electronic effects - Further optimisation of this reaction resulted in the use of 1,2-dichloroethane. This solvent has very similar chemical properties to dichloromethane, but slightly different electronic properties (dielectric constants). When 1,2-dichloroethane was used as a solvent, in the palladium catalysed allylic substitution reaction, the product 143 was produced with an enantiomeric excess of 65 %. The chemical yield of the product 143 in the alkylation was 38 %.

The experiments conducted using the different solvent systems proved there was very little difference, within experimental error, in the enantiomeric outcome of the alkylated product. The conclusion from these experiments was that the enantiomeric excess of the alkylated product was not enhanced by varying the solvent system.

Pre-mixing step - In the typical palladium alkylation reaction described in Scheme 39, the ligand and palladium are stirred together prior to the addition of the other reagents. The significance of this pre-mixing step was evaluated using the imine 178. An experiment was conducted in which all the reagents were added simultaneously. As a consequence of this, the palladium and ligand could not form the enantioselective catalyst prior to the addition of the other reagents. The alkylated product 143 was produced with a lower enantiomeric excess of just 32 % and a chemical yield of 99 %. This result strongly suggested that the pre-mix step is imperative to obtain higher enantiomeric excesses. Experiments conducted using increased pre-mixing times did not facilitate higher enantiomeric excesses.

Temperature effect
As the pre-mixing step was shown to be important, an experiment was conducted in which the reaction time was prolonged. The alkylation reaction was normally conducted at room temperature. An experiment was conducted at a lower temperature in the hope that this would lead to increased selectivity in the nucleophilic attack of the allylic moiety. The reaction vessel was immersed in a propanol bath.
regulated at -20 °C. The reaction was monitored by TLC, the reaction proceeded at a slower rate. The enantiomeric excess of the alkylated product 143 obtained was slightly reduced at 55%. There appeared to be no enhancement of enantioselectivity by prolonging the reaction rate.

Type of nucleophilic species
In a typical reaction the dimethyl malonate nucleophile was generated by BSA and potassium acetate. An alternative method of generating the dimethyl malonate nucleophile is to de-protonate dimethyl malonate with sodium hydride in THF. This method provides the nucleophile as a sodium salt of dimethyl malonate and therefore BSA or potassium acetate are absent from the reaction.

![Scheme 41](image)

The allylpalladium dimer and imine 178 were pre-mixed, prior to the addition of other reagents, as usual. The nucleophile was prepared in a separate flask by the addition of dimethyl malonate to sodium hydride suspended in THF. After the imine and palladium had been mixed for 15 minutes, the sodium ion of dimethyl malonate and the substrate acetate 142 were added sequentially. Using this method for the generation of the dimethyl malonate nucleophile the alkylated product was afforded with a lower enantiomeric excess of 25%. The conclusion from this experiment was the time taken to generate the nucleophile, using the BSA and potassium acetate, contributed to the enantioselectivity of the product 143.

The palladium catalysed allylic substitution reaction was further optimised, the significance of the two molar excess of dimethyl malonate and BSA was evaluated. The alkylation reaction was conducted using the typical reaction conditions with a lower concentration (1.2 equivalents) of dimethyl malonate and BSA. In this reaction the alkylated product 143 was produced with a reduced enantiomeric excess of 21%. The conclusion from this experiment was that the excess dimethyl malonate and BSA play a contributory role to the enantiomeric excess of the product 143.
Conclusion

Despite the modifications to the alkylation reaction, the optimum result was that obtained using dichloromethane as solvent at room temperature, as documented in Table 8. Experiments conducted with different solvent system proved the enantiomeric excess of the alkylated product was independent of the solvent used. Lowering the temperature and prolonging the reaction time, had little impact on the enantiomeric excess of the alkylated product. The enantiomeric excess was noticeably affected by the use of the sodium anion of dimethyl malonate. The enantiomeric excess was also reduced by the removal of the pre-mixing step and a reduction in the concentration of the dimethyl malonate and BSA.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield %</th>
<th>E.e. %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>179</td>
<td>DCM (2 ml)</td>
<td>48</td>
<td>21 (S)</td>
</tr>
<tr>
<td>178</td>
<td>DCM (2 ml)</td>
<td>94</td>
<td>67 (S)</td>
</tr>
<tr>
<td>178</td>
<td>DCM/Hexane</td>
<td>67</td>
<td>65 (S)</td>
</tr>
<tr>
<td>178</td>
<td>Acetonitrile/DCM</td>
<td>46</td>
<td>64 (S)</td>
</tr>
<tr>
<td>178</td>
<td>DCE</td>
<td>38</td>
<td>65 (S)</td>
</tr>
<tr>
<td>178(b)</td>
<td>DCM (1.5 ml)</td>
<td>100</td>
<td>32 (S)</td>
</tr>
<tr>
<td>178(c)</td>
<td>DCM (1.5 ml)</td>
<td>56</td>
<td>55(S)</td>
</tr>
<tr>
<td>178(d)</td>
<td>THF</td>
<td>87</td>
<td>25 (S)</td>
</tr>
<tr>
<td>178(e)</td>
<td>DCM</td>
<td>57</td>
<td>21(S)</td>
</tr>
</tbody>
</table>

Table 8

a - Enantiomeric excess determined using HPLC (Chiralcel OD column, hexane/isopropanol 99/1)
b - no pre-mixing of the Pd and ligand
c - experiment conducted at -20°C
d - Sodium ion of dimethyl malonate
e - 1.2 equiv. of BSA and dimethyl malonate
DCE - 1,2 Dichloroethane

With the results of the imine ligands in hand, our attention turned to the use of the hydrazone 182 in the palladium catalysed allylic substitution reaction. The hydrazone 182 contained several new properties that were absent in our previous ligands. For example, the asymmetric centre was now in the β position to the ligating nitrogen.
Also, the hydrazone contained an ether moiety capable of interfering with the attack of a nucleophile, when tethered to the allyl intermediate.

![Chemical structure of hydrazone 182](image)

Hayashi and co-workers have reported the use of ligands with 'free' alcohol moieties, such as 218, in the palladium catalysed allylic substitution reaction. The alcohol tether directs the incoming nucleophile into the allyl moiety to provide alkylated products with high enantioselectivity.

The hydrazone 182 was synthesised using the ketone, 2-diphenylphosphine acetophenone. Previous experience had shown that the aldehyde versions of the ligands provided the alkylated product 143 with a reduced enantiomeric excess. It was very unfortunate that these prejudices were held, the aldehyde derived ligand was later synthesised and published by the research group of Yamashita. Yamashita and co-workers have recently reported the alkylated product 143 was afforded with 92 % e.e., using the hydrazone 280.

![Chemical structure of hydrazone 280](image)

Unfortunately the results we obtained using the ketone derived hydrazone 182 were not as spectacular as those reported by Yamashita. The alkylation reaction was conducted using standard conditions. The alkylated product 143 was afforded with an enantiomeric excess of 43 %. When the reaction was repeated using a solvent mixture of hexane/dichloromethane, the alkylated product 143 was produced
racemically with a chemical yield of 67%. As the hexane would be expected to provide less competition for co-ordination around the palladium, it would suggest that the ether functionality made the imine sparingly soluble in hexane. With these results in hand, documented in Table 9, we progressed with the use of ligands with constrained rings.

**Conclusion**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield %</th>
<th>E.e. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>182</td>
<td>DCM (2 ml)</td>
<td>36</td>
<td>43 (R)</td>
</tr>
<tr>
<td>182</td>
<td>DCM/Hexane</td>
<td>67</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 9

**3.10 Imidazoline based Ligands**

From the results of the imine and hydrazone ligands, it became apparent that the ligating nitrogen would have to be constrained in a ring to obtain increased enantioselectivities. Our efforts turned to the use of imidazoline based ligands, such as ligand 188. These ligands are structurally very similar to the oxazoline 164 but contain two nitrogens in the constrained ring.

![164](image1.png) ![188](image2.png)

The anticipated effect of the imidazoline ring was that the ligand would be bound more closely to palladium. The non-ligating nitrogen (NH) would provide an increased electron density into the C-N bond and through the inductive effect the ligating atom would have an increased electron density. The consequence of this increased electron density, on the ligating nitrogen, was the nitrogen-palladium bond would become shorter. The shorter bond would lead to a closer proximity between the ligand and the palladium, and therefore the allyl moiety. In theory, this closer proximity would mean the asymmetric centre would be able to exert a greater effect on the enantiomeric outcome of the reaction. When the ligand 188 was used in the
palladium catalysed allylic substitution reaction, using standard conditions the alkylated product 143 was produced with an enantiomeric excess of 76 % and a chemical yield of 57 %.

Attempts to synthesise the imidazoline 281 were unsuccessful, problems were encountered when attempting to add the diphenylphosphine group. By synthesising this ligand, it was hoped, a greater electron density would be available to the ligating nitrogen, through the inductive effect. The use of ligand 282 has been reported recently, it is structurally very similar to ligand 188. This ligand 282 was developed by Morimoto and co-workers and contains a methyl group to donate electron density onto the non-ligating nitrogen. 159

When the ligand 282 was used in the alkylation shown in Scheme 42 it gave the alkylated product 143 with 96 % enantiomeric excess.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{Me} \\
\text{PhS} & \quad \text{Ph} \\
\text{OPiv} & \quad \text{OPiv}
\end{align*}
\]

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

**Scheme 42**

Another imidazoline based ligand was synthesised from the coupling of the diamine \((2S,3S)-N,N'-\text{dimethyl}-1,2\)-diphenylethylene and 2-diphenylphosphine benzaldehyde. The imidazoline 185 differed from previous ligands as the ligating nitrogen does not have a iminyl bond. Also, the nitrogen atoms of the imidazoline have methyl groups to provide increased electron density to the ligating atom. The cyclopentyl ring in which the nitrogens are held is \(C_2\)-symmetric. As a consequence of this the chiral environment around the allyl intermediate is not dependant on which nitrogen binds to the palladium.
It was anticipated the methyl and phenyl groups would orientate themselves around the allyl intermediate, forcing the nucleophile to preferentially attack one carbon terminus of the allyl moiety. The methyl groups are known to protrude in the opposite direction to the phenyl groups. When the palladium is bound to ligand 185 and the allyl moiety, the lower face is blocked by the methyl group and the upper face by the phenyl group. Using the ligand 185 in the alkylation reaction afforded the alkylated product 143 with an enantiomeric excess of 66 % and a chemical yield of 49 %.

3.11 Extension of the Use of Ligand 185 to a Cyclic Substrate

The alkylation of cyclic acetates was also investigated using the ligand 185. There are relatively fewer examples of ligands that have been used successfully in both the cyclic and 1,3-diphenylpropenyl alkylation. Ligands that are successful in the diphenyl case usually require modification to become successful in the cyclic case.

The Substrate

The cyclic acetate 265 was produced using a similar synthetic pathway to that of the 1,3-diphenylpropenyl example. The commercially available alcohol 25 was stirred in acetic acid in the presence of DMAP and pyridine. Confirmation of the acetate product was the emergence of a three proton singlet at δ 1.9 ppm corresponding to the acetate peak. Further confirmation was obtained using IR spectroscopy; the peak associated with carbonyl was present at 1700 cm⁻¹.
The acetate was purified using flash chromatography. The palladium catalysed allylic substitution reaction was conducted under normal conditions, using three equivalents of dimethyl malonate and BSA and a catalytic quantity of sodium acetate, as detailed in Scheme 44.

\[
\text{OAc} \xrightarrow{\text{Pd catalyst}} \text{CH}_2(\text{CO}_2\text{Me})_2 \\
\text{Ligand 185} \\
\text{BSA, KOAc} \\
\text{265} \xrightarrow{} \text{CH}(\text{CO}_2\text{Me})_2 \xrightarrow{} \text{266}
\]

**Scheme 44**

The alkylation of the acetate 265 was confirmed by \(^1\)H NMR. The disappearance of the three proton singlet at \(\delta\) 1.9 ppm, corresponding to the acetate peak, and the emergence of one proton doublet at \(\delta\) 3.7 ppm corresponding to the methine proton in 266. It was anticipated that the ligand 185 would perform fairly well in the alkylation of cyclic acetates. It was hoped, the ability of the cyclopentyl ring to mould itself around the palladium would provide the alkylated product 266 in good enantiomeric excess. The actual asymmetric induction on the product 266 was 50 % e.e. with a chemical yield of 46 %. This was a good result as there are several examples in which ligands had performed well in one system but poorly in others. The ligand 185 worked well in both the cyclic and 1,3-diphenylpropenyl alkylation due to the malleability of the cyclopentyl ring. The alkylation was attempted using the sodium anion of the dimethyl malonate on several occasions, the palladium became insoluble and provided no alkylated product.

### 3.12 Conclusion

New ligands have been designed and synthesised based on the oxazoline 164. These ligands, as oxazoline 164, are easy to prepare in two steps and are air stable. The ligands have been tested in the palladium catalysed allylic substitution reaction and proved to give fairly good selectivity. Imine 178, in particular, has been optimised for the conditions. The ligands give a range of results from a disappointingly low 7 % up to a good enantiomeric excess of 77 %. The ligands have been shown to give a good selectivity in one reaction and have potential to be applied to other asymmetric reactions.
# Chapter 4

Approaches to Kinetic and Dynamic Resolutions

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*Chapter 4 Approaches to Kinetic and Dynamic Resolutions*
4.0 Introduction
The introduction of an enantiomerically pure centre into organic molecules is becoming increasingly more important. There are two general methods for the preparation of enantiomerically enriched organic molecules. The first method involves a stereodiscriminating reactive intermediate. This can be achieved by using an enantiomerically pure substrate, chiral auxiliary, or through the use of an enantiomerically pure reagent (chemical/enzyme). The second method involves a resolution; in this case asymmetric induction is not required. There are many methods of resolution, both chemical and physical. One form of resolution is kinetic resolution, this resolves two enantiomers using their different rates of reaction. The disadvantage of using the kinetic resolution method is that the maximum yield is limited to 50%. This limit can be overcome by transforming the resolution into a dynamic kinetic resolution, discussed later.160

4.1 Kinetic Resolution
The asymmetric reduction of allylic alcohols can be conducted using kinetic resolution conditions.10 The asymmetric hydrogenation of the alcohol 25 using BINAP-Ru(II) catalyst system in the presence of hydrogen gas provides the α,β unsaturated alcohol 26 in above 95% e.e., at 51% conversion.

\[
\begin{align*}
\text{OH} & \quad \text{100 atm H}_2 \\
25 \quad \text{[16]Ru(OAc)}_2 & \quad (>0.001 \text{ mol%}) \quad \text{OH} \\
\quad \text{R} = \text{H, Me} & \quad \text{R} = \text{H, Me} \\
\end{align*}
\]

R=H, Me  
e.e. >95%  at 51-52 % conv.

In 1993, Faller and Tokunaga developed an extension of this methodology.161 Enantiomerically pure BINAP is usually produced by classical methods, hence the separations are time consuming and this results in a high cost for the pure enantiomer. Faller et al. developed an asymmetric reduction capable of using racemic BINAP with an additive. The additive 'poisons' one enantiomer of the racemic BINAP catalyst, leaving the other enantiomer to reduce the substrate. The additive was enantiomerically pure ephedrine, which is significantly cheaper to produce than enantiomerically pure BINAP.
Fu *et al.* reported the kinetic resolution of various racemic secondary alcohols using catalyst 285.\(^{162}\) The racemic secondary alcohols were kinetically resolved to afford enantiomerically enriched alcohols, in the presence of acetic anhydride and a catalytic quantity of compound 285. One enantiomer of the secondary alcohol reacts faster and is converted into the acetate 284. The substrates contain an unsaturated group and an alkyl group.

The Sharpless epoxidation has been used to kinetically resolve racemic allylic alcohols to afford enantiomerically enriched allylic alcohols.\(^{163}\) A wide range of substrates have been used with various groups in the C1 position.
A few examples are shown in the Table 10.\textsuperscript{164}

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
<th>Conversion %</th>
<th>% E.e. of the alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$<em>6$H$</em>{13}$</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>55</td>
<td>96</td>
</tr>
<tr>
<td>C$_4$H$_9$</td>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>55</td>
<td>96</td>
</tr>
<tr>
<td>cC$<em>6$H$</em>{11}$</td>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>55</td>
<td>96</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>CH$_3$</td>
<td>55</td>
<td>91</td>
</tr>
</tbody>
</table>

Table 10

The efficiency of the kinetic resolution is enhanced by the substrate containing a silyl or iodo substituent in the $R^2$ position of the allylic alcohol, Figure 9.\textsuperscript{165} Studies have shown that the relative rates of each enantiomer are dramatically increased with a silyl group present. The overall rate of epoxidation was approximately one-sixth that of the similar carbon analogue, this effect has been assigned to the different electronic composition. The results, given in the Table 11, show excellent selectivity for both the allylic alcohol and epoxidised alcohol.\textsuperscript{166}

![Figure 9](image_url)

Table 11

The kinetic resolution of allylic alcohols also extends to substrates with the allylic moiety as part of a conformationally restricted ring. Kinetic resolution of the
appropriate racemic alcohol provided 2-cyclohexen-1-ol 286 and 2-cycloheptan-1-ol 287 with 30 % and 80 % e.e. respectively.\textsuperscript{163}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{alcohol_structures.png}
\caption{Structures of 2-cyclohexen-1-ol (286) and 2-cycloheptan-1-ol (287).}
\end{figure}

The kinetic resolution of the alcohol 288 provides a remarkable example. In this example both double bonds are susceptible to epoxidation, the more nucleophilic double bond reacts and the epoxide 289 is formed in high enantiomeric excess.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{epoxidation_reaction.png}
\caption{Epoxidation reaction with (-)DIPT Ti(\textsuperscript{OPr})\textsubscript{2}BuOOH.}
\end{figure}

There are eight possible allylic faces that could be epoxidised, four for each enantiomer, yet only one enantiomer is formed.

\section*{4.2 The Catalyst and Mechanism of the Sharpless Epoxidation}

Due to the enormous value of the Sharpless epoxidation methodology investigations have been conducted to ascertain the nature of the catalyst and mechanism of the reaction. It is believed that the key to the reaction is the rapid ligand exchange of the titanium alkoxides with other alcohols.\textsuperscript{167}

\[
\text{Ti(OR)_4 + tartrate} \quad \xrightarrow{\text{(-)DIPT Ti(\textsuperscript{OPr})\textsubscript{2}BuOOH}} \quad \text{Ti(tartrate)(OR)_2 + 2 ROH}
\]

The last two alkoxides are exchanged with the allylic alcohol and the tert-butyl hydroperoxide. After the final two alkoxides are displaced, the catalyst 290 is 'fully loaded' and epoxidation takes place.
The active catalyst is thought to be a dimeric species. The allylic alcohol and the 1-butyl hydroperoxide are bound to the same titanium species, as shown in Figure 10.

4.3 Dynamic Kinetic Resolution
The simplest form of dynamic kinetic resolution is illustrated with the enzyme acylation of racemic cyanohydrin. When the reaction is conducted in the presence of basic anion exchange resin, a rapid equilibrium occurs between the R and S cyanohydrin.\textsuperscript{168} This racemisation, in conjunction with enantioselective acylation, leads to a high yield of an enantiomerically enriched acetylated product. When benzaldehyde was used as the substrate, the acetylated product 291 was afforded with 96 % yield and an
enantiomeric excess of 84 %. The enzyme used in the acetylation reaction was lipase from *Pseudomonas Sp.*

Dynamic kinetic resolution has been used to convert oxazolin-5(4H)-ones, such as 293, into enantiomerically enriched amino acid derivatives. The acidity associated with the 4-hydrogen is enhanced by the carbonyl and iminyl functionalities. This acidity has been exploited in the transformation of racemic azalactones into enantiomerically enriched amino acid derivatives. In the presence of a suitable lipase enzyme, the *trans* acyl ring is opened by a nucleophile to afford the enantiomerically enriched product with *in situ* racemisation of the azalactone.

This methodology has been applied to the synthesis of L-(S)-tert leucine by Turner *et al.* The treatment of rac-2-phenyl-4-tert butyloxazolin-5(4H)-one 294 with butanol in the presence of the immobilised lipozyme (*Mucon miechii*) afforded S-N-benzoyl tert-leucine butyl ester 295 in excellent yield and enantiomeric excess. The product 295 was manipulated further to afford L-(S)-tert leucine.
nBuOH (2.0 equiv) Lipozyme Et3N (25 mol %) Toluene

294  

295

94% 99.5% e.e.

L-S-\textit{i-ert}-leucine

D-Amino acids have been synthesised from racemic amino acid hydantoins, D-citrulline 296 was obtained in 79 % yield and 92 % enantiomeric excess from the racemic hydantoin 297.\textsuperscript{171}

As described in Chapter 3, the palladium catalysed allylic substitution reactions of a racemic substrate can be used to afford an enantiomerically enriched product via allyl intermediates. In these reactions, the stereochemistry of the substrate is lost by the formation of a common intermediate by the two enantiomers of the allyl acetate, prior to the attack by the nucleophile. The enantiomeric excess is dependant wholly on the regioselectivity of the nucleophilic attack.
This methodology has been successfully combined with an enzymatic kinetic resolution to produce an enantiomerically enriched alcohol from a racemic acetate. Williams and Allen reported the use of an enzymic kinetic resolution in the presence of a palladium catalyst. The palladium racemised the substrate by catalysing a 1,3 sigmatropic acetate shift. The acetate 299 was hydrolysed, using P. fluorescens lipase (PFL), into the alcohol 298 with 81% yield and 96% enantiomeric excess.

![Chemical Structure](image)

**4.3.1 Configurationally Labile Alkyl Halides**

Alkyl halides which have a halogen at the asymmetric centre are generally configurationally stable. Racemisation can be induced in certain cases by the addition of additives such as polar solvents, base or halide sources. Ward et al. reported the dynamic kinetic resolution of a bromopropanoic acid derivative, using Oppolzer's chiral camphor sultam. Using the diastereoisomeric mixture of 300 and heating to 60 °C with dibenzylamine in acetonitrile, or DMSO, produced 2R-301 in excellent yield and diastereomeric excess.

![Chemical Structure](image)

Durst reported that the treatment of the diastereomeric mixture of 302 (1:1 S,R: R,R) with benzylamine and THF resulted in the proline 303 being formed in a 7:1 diastereomeric ratio, in which the S,R diastereomer predominated. Durst proposed the R,R diastereomer reacted significantly faster than the S,R diastereomer and rapid
racemisation of the $S,R$ diastereomer occurred. The liberated halide was thought to catalyse the racemisation of the slower reacting $S,R$ diastereomer to the faster reacting diastereomer $R,R$.

Nunami et al.\textsuperscript{175} have reported the use of tert-butyl-(4S)-1-methyl-2-oxoimidazolidin-4-carboxylate 304 as an effective chiral auxiliary. The substrate 305 containing the racemic bromide was subjected to nucleophilic substitution with a number of different nucleophiles, under base catalysed racemisation conditions. The nucleophiles used were benzylamine, sodium dimethyl malonate\textsuperscript{176} and potassium phthalamide.\textsuperscript{177} When benzylamine was used as a nucleophile, the major product was 2($R$)-306 (96 %, 88 % d.e.), and with dimethyl malonate the product was 2($R$)-307 (92 % and 76 % d.e.). The nucleophilic addition of potassium phthalamide afforded the product 308 with 2($S$) as the major configuration (90 %, 94 % d.e.). The benzylamine nucleophile provided an unusual substitution pattern, the nucleophile attacks from the more hindered face.
Scheme 45

<table>
<thead>
<tr>
<th>Nuc</th>
<th>2 (R) 306 major</th>
<th>2 (S) 306</th>
<th>2 (S) 307</th>
<th>2 (R) 307 major</th>
<th>2 (S) 308 major</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH$_2$NH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MeO$_2$)C$_2$CH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phthalamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This unusual selectivity shown by the nucleophilic addition of benzylamine nucleophile in Scheme 45 was also reported when the chiral auxiliary 309 was used.$^{178}$
The enantioselective preparation of 2-aryloxyacryclic acids using dynamic kinetic resolution methodology has been reported by Devine et al.\textsuperscript{179} The substrate 313 reacted with the preformed sodium/lithium aryloxide, in THF, to afford 314 in good yield and excellent selectivity.

![Chemical structure of 313 and 314]

Matterson and Man reported the dynamic kinetic resolution of racemic boronic esters with enantiomerically pure N-acyloxazolidinone enolates and catalytic iodide racemisation to afford the boronic ester 315.\textsuperscript{180} The racemic boronic ester 316 reacted with the lithium enolate of (S)-4-(1-methylethyl)-3-propanoyloxazolidin-2-one 317 to afford the product 315 in 100 % conversion and 97 % d.e. and 94 % e.e.
4.3.2 Dynamic Kinetic Resolution Using Temporary Oxidation

The racemisation of a secondary alcohol has been reported recently by Williams et al. Williams reported the racemisation of S-phenethyl alcohol using various metal catalysts.

The racemisation of the alcohol proceeded via a temporary oxidation of the alcohol to the ketone and then back to the alcohol, shown in Figure 11. The reduction of the alcohol was conducted in the presence of a transfer hydrogenation catalyst.

Figure 11
The kinetic resolution of racemic phenethyl alcohol to produce S-phenethyl alcohol and the ester 318 in the R configuration was known.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{Me} & \quad \xrightarrow{PFL} & \quad \text{Ph} & \quad \text{OH} & + & \quad \text{Ph} & \quad \text{OAc} \\
\text{Me} & \quad \text{Me} & \quad & & & & & & 318 \\
\end{align*}
\]

40°C

91% e.e.
45% yield
98% e.e.
47% yield

The racemisation and kinetic resolution of the alcohol were combined successfully to provide the ester 318 in high yield and with a high enantiomeric excess from the racemic alcohol.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Enzyme</th>
<th>Time (hr)</th>
<th>Temp (°C)</th>
<th>Conversion (%)</th>
<th>E.e. 318 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{a}[\text{Rh}(\text{Cod})\text{Cl}]_2)</td>
<td>PFL</td>
<td>144</td>
<td>50</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td>(\text{b}[\text{Rh}_2(\text{OAc})_4])</td>
<td>PFL</td>
<td>72</td>
<td>20</td>
<td>60</td>
<td>98</td>
</tr>
</tbody>
</table>

a 3 mol%
b 2 mol%

Bäckvall et al. reported similar results using the identical substrate and a ruthenium based catalyst 319. Bäckvall reported the production of side products during the acetylation reaction, these products could be eliminated by the use of other acetylation reagents.

\[
\text{Ph} & \quad \text{OH} & \quad \text{Me} & \quad \xrightarrow{\text{Novozym 435}} & \quad \text{Ph} & \quad \text{OAc} \\
\text{Me} & \quad \text{Me} & \quad & & & & + & \quad \text{Ph} & \quad \text{O} \\
(\pm)-\text{Phenethyl alcohol} & & & & & & & & 320 \\
\]

92% conv.
99.5% e.e.

Novozym 435 = Candida antartica component B lipase
The isolated yield of the acetate 318 was 92%. Bäckvall extended the work to 1-indanol 321. The indanol acetate 322 was produced with an 81% conversion and an excellent enantiomeric excess of 99.5%.

\[
\text{OH} \
\text{CO} \
(\pm) - 321 \\
(2 \text{ mol}\%)
\text{Novozym 435} \\
\text{I-indanone (1 equiv)} \\
\text{'BuOH} \\
\rho-\text{Cl-PhOAc (3 equiv)} \\
70^\circ\text{C} \\
\rightarrow \\
\text{R - 322} \\
81\% \text{ conv.} \\
99.5\% \text{ e.e.}
\]

4.4 The Use of Catalytic Reversible Nucleophilic Addition in Organic Synthesis

4.4.1 Cyanide
Corey et al. reported the use of reversible nucleophiles in the oxidation of allylic aldehydes.\textsuperscript{183} When allylic primary alcohols are oxidised with manganese dioxide, a small quantity of carboxylic acid is produced. However, in the presence of a cyanide ion a primary alcohol can be oxidised to the corresponding carboxylic acid in high yield. Corey et al. reported the oxidation of cinnamaldehyde in methanol to methyl cinnamate in the presence of hydrogen cyanide. Other aldehydes that were oxidised include benzaldehyde, furfural, geranial and farnesal. Using this methodology there was no observed isomerisation of the \(\alpha-\beta\) double bond which can be a problem when using silver oxide. The reaction mechanism is thought to proceed through the formation of a cyanohydrin, as shown in Scheme 46. The cyanide is displaced by the alcohol after oxidation and can be used catalytically.
4.4.2 Tributyltin cyanide

Fu et al. reported using tributyltin cyanide as a reversible nucleophile in the synthesis of acetylated cyanohydrins from various aldehydes. This methodology was based on two separate observations. The first observation was that tributyltin cyanide could be added to aldehydes. The second observation was that tributyltin isopropoxide reacts with acetyl cyanide to afford tributyltin cyanide. Fu proposed that using catalytic quantities of tributyltin cyanide, the two reactions would proceed smoothly to provide an acetylated cyanohydrin 323 from an aldehyde 324. Several different aldehydes were used as substrates, the acetylated cyanohydrins were afforded with excellent yields.

<table>
<thead>
<tr>
<th>R</th>
<th>323 Yield % Y=OMe (Y=Me)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nC₆H₁₃</td>
<td>92 (98)</td>
</tr>
<tr>
<td>Ph</td>
<td>92 (89)</td>
</tr>
</tbody>
</table>
4.4.3 Thiazolium salts

Breslow reported the use of thiazolium salts to catalyse the formation of acyloins from aldehydes in the presence of mild base. The reaction scheme generally accepted was proposed by Breslow and is shown in Scheme 47.

Scheme 47

The benzoin condensation can also be catalysed by cyanide ions. However, in asymmetric synthesis there are two advantages of using thiazolium salts as opposed to cyanide. Firstly, the reaction proceeds under less basic conditions, therefore enolisable aldehydes may be used. Secondly, thiazolium salts contain available sites for asymmetric functionality unlike the cyanide ion. Several enantiomerically pure thiazolium salts have been synthesised by Leeper et al.

In the benzoin condensation of benzaldehyde, the thiazolium salt 327 gave the optimum enantiomeric excess of 21 % and 50 % chemical yield. In the coupling of butyraldehyde, the thiazolium salt 325 provided the highest enantiomeric excess of 33 % with 75 % chemical yield. The proposed transition state is shown in Scheme 48.
4.5 Conclusion
Dynamic kinetic resolution has been very successfully applied in the synthesis of enantiomerically enriched products. This technique is particularly useful as the enantiomerically enriched product is produced from a racemic substrate. Several examples of organic synthesis have included the use of reversible nucleophiles. However, the use of reversible nucleophiles using dynamic kinetic resolution conditions has not been successfully combined to produce an enantiomerically enriched product.

4.6 Approaches to Asymmetric Epoxidation with Reversible Nucleophiles and Kinetic Resolution Conditions

Concept
Our interests lay in the synthesis of an asymmetric epoxide from a prochiral aldehyde using a reversible nucleophile. The nucleophile would add to the aldehyde to form an alcohol which would be asymmetrically epoxidised using the Sharpless epoxidation reaction. Sharpless epoxidation conditions can be used to kinetically resolve enantiomeric alcohols. If the alcohol could be synthesised enantioselectively then the resulting epoxide would be produced with a high enantiomeric excess. Using the reversible nucleophile, three possible synthetic routes to the asymmetric epoxide were envisaged.
In this synthetic route the nucleophile would attack the aldehyde and provide a temporary chiral centre. The addition of the nucleophile would be asymmetric producing predominately one enantiomer of the alcohol 328. The Sharpless epoxidation can kinetically resolve one alcohol enantiomer preferentially to afford the resultant epoxide 329 with a high enantiomeric excess. After epoxidation the nucleophile would be detached and possibly recycled. With the asymmetric formation of allylic alcohol and the Sharpless epoxidation kinetically resolving the enantiomeric alcohols, the epoxide is afforded with a high enantiomeric excess due to the double differentiation.
This synthetic approach uses a chiral auxiliary to provide a single diastereomer of the alcohol. The epoxidation reaction would be directed by the chiral auxiliary. The enantiomeric excess of the final epoxide would depend on the efficiency of the chiral auxiliary to produce one enantiomer of the alcohol and its ability to direct the epoxidation reaction. This pathway has disadvantages as it requires two additional steps; the installation of the auxiliary prior to epoxidation and the removal post epoxidation.

**Kinetic Resolution**

This synthetic pathway uses a dynamic kinetic resolution and does not require the enantioselective addition of the nucleophile. This approach provides the allylic alcohol in dynamic equilibrium with the initial substrate 330. The nucleophile adds to the substrate 330 to provide both enantiomers of the allylic alcohol. Due to the kinetic resolution in the epoxidation step, one enantiomer of the allylic alcohol reacts preferentially leaving the other unreacted. The dynamic equilibrium continually provides racemic allylic alcohol and eventually all the substrate will be epoxidised enantioselectively. The final step is the loss of the nucleophile to produce the epoxidised aldehyde enantioselectively.

**Theory**

As previously mentioned, the epoxidation route chosen was the Sharpless epoxidation. All of the synthetic routes suggested would provide an alcohol suitable for epoxidation using the Sharpless methodology, with the possible exception of the...
diastereoselective route. The Sharpless epoxidation is known to be highly selective with allylic alcohols and unreactive with allylic aldehydes. The Sharpless epoxidation is known to kinetically resolve racemic allylic alcohols. The reversible nucleophile chosen was cyanide, cyanide is known to add to carbonyls and could provide the alcohol tether required for the Sharpless epoxidation reaction. The idea was to produce the cyanohydrin enantioselectively and then subject the cyanohydrin to Sharpless epoxidation conditions. Literature precedent for the production of enantioselective cyanohydrins was known using titanium isopropoxide and diisopropyl tartrate (DIPT). The precedent for the synthesis of enantiomerically enriched cyanohydrin had been applied to benzaldehyde but had not been extended to allylic alcohols. The kinetic resolution of allylic alcohols is well known, the kinetic resolution of allylic alcohols with nitrile functionalities, however, is less well known. The allylic alcohols 334 and 335 were successfully epoxidised using kinetic resolution conditions. The nitrile functionality remained intact throughout the epoxidation reactions.

![Scheme 49]

The cyanohydrin formation and epoxidation reaction would take place in the same reaction vessel. Furthermore, if the cyanide detached after the epoxidation then the reversible nucleophile could be used catalytically. Several problems were envisaged with the use of the cyanohydrin in the epoxidation reaction:

- compatibility of the cyanohydrin with the other reagents in the epoxidation reaction
- breakdown of the cyanohydrin under the conditions used for epoxidation
- possibility of the nitrile being oxidised to the N-oxide
- toxicity of the cyanohydrin/cyanide
The Substrate

To ascertain whether the cyanohydrin would undergo kinetic resolution, the racemic cyanohydrin was initially synthesised. The cyanohydrin of mesityl oxide was chosen as a substrate. To suppress 1,4 additions of the cyanide ion, the substrate 336 contained an isopropyl group at the end of the allylic bond. The cyanohydrin of the aldehyde 337 was prepared using acetone cyanohydrin and a Lewis acid.

![Chemical Reaction Diagram]

The Lewis acid used was titanium isopropoxide, to provide future compatibility with the Sharpless epoxidation reaction. Three equivalents of acetone cyanohydrin were required to drive the cyanohydrin production to completion. Unfortunately the acetone cyanohydrin could not be isolated from the cyanohydrin product 336 and when the cyanohydrin 336 was subjected to Sharpless epoxidation conditions no epoxide was formed. The compatibility of the acetone cyanohydrin with the epoxidation reagents was a problem. Whilst assessing this problem, the absence of an aryl group or allylic functionality in the epoxidised product became a concern. In order for the product to be detected more easily using HPLC analysis, it was desirable that the product contain an aryl functionality. The substrate chosen in preference to mesityl oxide was α-methyl trans-cinnamaldehyde 338.

![Chemical Structures]

The cyanohydrin 339 was initially synthesised using acetone cyanohydrin, attempts to epoxidise the cyanohydrin using mCPBA were unsuccessful. As seen previously, the residual quantity of acetone cyanohydrin was suppressing the epoxide formation. Encouragingly, the nitrile moiety of the cyanohydrin was intact and was not oxidised. An alternative synthetic route to the cyanohydrin 339 was proposed using trimethylsilyl cyanide. Trimethylsilyl cyanide initially provides the silyl protected
cyanohydrin, this protection can be removed by stirring in hydrochloric acid. This synthetic route was very similar to that used earlier by Hayashi. \(^{189}\)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{CH}_3 & \quad \text{H} \\
\rightarrow & \quad \text{Lewis acid} \\
\text{Ph} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CN}
\end{align*}
\]

The silyl protected cyanohydrin was produced in 72 hours using zinc iodide, deprotection took a further 48 hours of vigorous stirring with hydrochloric acid. The product \(339\) was confirmed by \(^1\)H NMR and IR analysis. The conversion from aldehyde to cyanohydrin, resulted in the upfield shift of the aldehyde signal at \(\delta 9.6\) ppm to \(5.0\) ppm corresponding to the \(\alpha\)-hydrogen of the alcohol. IR analysis confirmed the presence of a nitrile peak at 2248 cm\(^{-1}\). Interestingly, the unpurified cyanohydrin afforded no epoxide when subjected to Sharpless epoxidation conditions. Furthermore, during the synthesis of the cyanohydrin, an aliquot of the silyl protected cyanohydrin was removed prior to the addition of the hydrochloric acid. This aliquot was then subjected to Sharpless epoxidation conditions. The silyl protected cyanohydrin produced no epoxide which strongly suggests that the trimethylsilyl group inhibited the epoxidation reaction.

The cyanohydrin \(339\) was purified using flash column chromatography. Unfortunately, the silica gel in the column was not sufficiently acidic and the cyanohydrin was degraded, a significant quantity of the cyanohydrin was converted back to the aldehyde \(338\). In order to counteract the degradation of the cyanohydrin, 3 % of acetic acid was added to the eluent. However, trace quantities of acetic acid also inhibited the epoxidation process, therefore all traces of acetic acid had to be removed prior to the epoxidation reaction. This finally produced a pure racemic cyanohydrin suitable for the Sharpless epoxidation.

With the racemic cyanohydrin \(339\) in hand, the substrate was subjected to a testbed epoxidation using \(m\)CPBA. This epoxidation would provide both diastereomers of the epoxidised cyanohydrin and the knowledge of the upfield shift of the hydrogens in \(^1\)H NMR. The diastereomers would be racemic and provide a useful sample for HPLC analysis.
This epoxidation using mCPBA actually provided two products: the epoxidised cyanohydrin 340 and the aldehyde 338. The epoxidation was confirmed by the upfield shift of the benzyl hydrogen from δ 6.8 to 4.6 ppm and the α-hydrogen of the alcohol shifting upfield from δ 5.0 to 4.3 ppm.

Our attention then turned to asymmetric epoxidation using Sharpless conditions. The cyanohydrin could be epoxidised using 0.5 equivalents of L-diethyl tartrate, 0.55 equivalents of titanium isopropoxide in the presence of 2 equivalents of t-butyl hydroperoxide and molecular sieves. Initial attempts using lower concentrations of diethyl tartrate were unsuccessful. The reaction was conducted at -20°C and after 4 hours the epoxidation reaction was terminated with the addition of water. The t-butyl hydroperoxide was removed by azeotroping the reaction mixture with toluene. The diethyl tartrate was removed using flash column chromatography. The expected product, the epoxy alcohol 340 was not isolated from the reaction. The reaction products consisted of the epoxidised aldehyde 341 (47 %) and the aldehyde 338 (53 %).

The epoxidised aldehyde 341 had previously been synthesised by Hayashi et al. using a different synthetic pathway. The 1H NMR of the epoxidised aldehyde 341 obtained by us compared favourably with that reported by the Hayashi group. In particular, the singlet signal corresponding to the aldehyde hydrogen for the aldehyde 338 was at δ 9.6 ppm, whilst in the epoxidised aldehyde 341 the singlet signal was at 9.1 ppm. The singlet corresponding to the methyl signal was also characteristic. In the aldehyde 338 the methyl signal was at δ 2.0 ppm and in the epoxidised aldehyde 341 it was at 1.2 ppm. Hayashi synthesised the epoxidised aldehyde with 98 %
enantiomeric excess, determined by optical rotation. Due to the presence of the unepoxidised aldehyde in our product, we were very reluctant to use this method for the determination of the enantiomeric excess. However, with no HPLC method in place at that time, the optical rotation was used to give an indication of any optical activity. The value obtained from the optical rotation suggested the epoxide had been formed with an enantiomeric excess of 55%. The fact there was optical activity suggested that the enantioselective epoxidation of cyanohydrin was a viable route. If the enantiomeric excess was as high as indicated, then a 55% enantiomeric excess would also suggest a kinetic resolution.

To confirm the enantiomeric excess, the aldehyde was derivatised using a diamine. Alexakis had developed several enantiomerically pure diamines that could be used for the determination of enantiomeric excess of aldehydes. The enantiomeric excess would be determined by measuring the diastereomeric excess of the methyl singlets in the $^1$H NMR.

![Chemical structures](image)

Only the epoxidised aldehyde 341 reacted with the diamine 184 to provide the epoxide 342, the unsaturated aldehyde 338 did not react. The enantiomeric excess of the epoxide was provided by $^1$H NMR analysis. The diastereomeric excess of the methyl signals indicated the enantiomeric excess of the epoxide. This provided a more reliable determination of the enantiomeric excess than optical rotation. Subsequently, a GC method was developed for the determination of the epoxy aldehyde 341.

**Optimisation of the Kinetic Resolution**

With the epoxidation reaction producing the epoxide smoothly, our attention turned to the optimisation of the reaction. Once the epoxidation reaction was complete, the diethyl tartrate was removed using column chromatography or by washing with 10% sodium hydroxide in saturated brine to afford the epoxidised product. Sharpless had described experiments in which dimethyl tartrate had been substituted for diethyl...
Dimethyl tartrate is water soluble and therefore would lead to a facile isolation of the resultant epoxide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp</th>
<th>DET</th>
<th>Time (hours)</th>
<th>Epoxide %</th>
<th>E.e. %</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-20-&gt;0</td>
<td>0.5</td>
<td>4</td>
<td>47</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-20-&gt;0</td>
<td>0.75</td>
<td>4</td>
<td>70</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-20</td>
<td>0.75</td>
<td>7</td>
<td>45</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-30</td>
<td>0.75</td>
<td>7</td>
<td>41</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-40</td>
<td>0.75</td>
<td>7</td>
<td>45</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-20</td>
<td>1.0</td>
<td>7</td>
<td>74</td>
<td>62</td>
<td>increased tartrate</td>
</tr>
<tr>
<td>7</td>
<td>-30</td>
<td>0.75</td>
<td>22</td>
<td>70</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-30</td>
<td>0.75</td>
<td>48</td>
<td>96</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

* Enantiomeric excess was determined by GC

The experiments conducted with dimethyl tartrate led to a significant drop in the yield of the epoxide product. Sharpless also suggested that the optimal ratio of diethyl tartrate:titanium isopropoxide was 1.2:1.0. To optimise any kinetic resolution conditions, this ratio was used in all subsequent reactions.

**Temperature Control**

An experiment was conducted using two different temperatures, -20 °C was maintained for 2 hours, then the temperature was increased to 0 °C for a further 2 hours. The cyanohydrin 339 was epoxidised in 70 % conversion and with an enantiomeric excess of 40 %. The slight increase in the temperature and the ratio of diethyl tartrate:titanium isopropoxide led to a faster epoxidation reaction, in comparison to entry 1.

It was thought that slowing the reaction rate of the epoxidation, by lowering the temperature, would lead to an epoxide with a higher enantiomeric excess. The epoxidation was conducted at three different temperatures, -20, -30 and -40 °C. The reaction conducted at -20 °C for 7 hours afforded the epoxide 341 with a 45 % conversion with an enantiomeric excess of 88 %. At -30 °C the conversion to the epoxide was 41 % with an enantiomeric excess of 83 %. The epoxidation reaction was also conducted at -40 °C, the epoxide conversion was 45 % and the enantiomeric
excess was 83 %. These results suggested a kinetic resolution of the two enantiomers was occurring. The effect of the temperature between this range was minimal.

To ascertain the effect of an increased ratio of diethyl tartrate:titanium isopropoxide an epoxidation was conducted with 1.0 equivalent of diethyl tartrate (0.5 equivalents of titanium isopropoxide). The reaction was conducted at -20 °C for 7 hours. The conversion into the epoxidised aldehyde 341 was 74 % with an enantiomeric excess of 62 %. The result of this reaction was very encouraging, the expected enantiomeric excess at 74 % conversion would be much lower. The increased ratio of diethyl tartrate:titanium isopropoxide had accelerated the rate of the epoxidation.

This result inspired us to drive the epoxidation reaction to completion and to determine the enantiomeric excess obtained. The diethyl tartrate ratio was lowered to 0.75 equivalents, to slow the initial kinetic resolution in comparison to the 1.0 equivalent. The conversion from cyanohydrin 339 into the epoxidised aldehyde 341 after 22 hours was 70 %. The enantiomeric excess of the epoxide was 58 %. In order to drive the reaction to completion the reaction time was extended to 48 hours. After 48 hours the epoxidised alcohol 341 was produced with a 96 % conversion and enantiomeric excess of 55 %.

The conversion quoted in these reactions refers only to the percentage component of the products, the actual yield from these reactions was typically 75 %. At 96 % conversion and 75 % yield, the enantiomeric excess expected would be very low (approx. 4 % based on conversion or 33 % based on yield). The actual enantiomeric excess obtained was 55 % suggesting that a kinetic resolution was not solely responsible.

Two hypotheses were proposed for the observed results:
1. A dynamic kinetic resolution had been created during the epoxidation.
2. A kinetic resolution had converted one enantiomer of the cyanohydrin into one enantiomer of the epoxide preferentially. The second enantiomer of the cyanohydrin, instead of being converted to the opposite enantiomer, had been converted into both enantiomers of the epoxide.
Approaches To Dynamic Kinetic Resolution

Several reactions were designed to investigate which of the hypotheses was correct. The first reaction conducted was the attempted epoxidation of the aldehyde 338, this would prove the cyanohydrin was not decomposing to the aldehyde and subsequently being epoxidised. As expected no epoxide was produced in this reaction.

The next set of reactions was designed to nurture a dynamic kinetic resolution. Oda et al. had reported the conversion of an aldehyde into an enantiomerically enriched cyanohydrin acetate utilising a dynamic kinetic resolution. The aldehyde was initially converted into a cyanohydrin using dynamic kinetic resolution conditions. Subsequently, one enantiomer of the cyanohydrin was further converted into the cyanohydrin acetate using an enzyme. The conversion from aldehyde to cyanohydrin acetate occurred in one reaction vessel, as shown in Scheme 50.

The dynamic kinetic resolution between the aldehyde and cyanohydrin was promoted by the addition of amberlyst resin in the presence of acetone cyanohydrin. The addition of the resin provided an in situ racemisation of the cyanohydrin. The idea of adding amberlyst to create a dynamic kinetic resolution was adopted by us. An epoxidation reaction was conducted using acetone cyanohydrin and amberlyst to
promote a dynamic kinetic resolution. The amberlyst was washed with sodium hydroxide to promote the deprotonation of the cyanohydrin, acetone cyanohydrin was added as a cyanide source to convert the aldehyde back to the cyanohydrin. The effect of these two transformations would hopefully lead to the formation of a dynamic kinetic resolution, as in Scheme 51.

\[
\text{Scheme 51}
\]

The epoxidation reaction with the amberlyst resin and acetone cyanohydrin present led to the reduced conversion of 29 % and the enantiomeric excess of the epoxide 341 was 43 %.

The reduced conversion to the epoxide was due to the addition of the acetone cyanohydrin. An experiment conducted with amberlyst resin and without acetone cyanohydrin produced an increased conversion of 64 % in 26 hours with a 72 % e.e. Previous experiments had shown a kinetic resolution was taking place and after 7 hours the reaction was approximately 50 % complete. An experiment was conducted in which the amberlyst was added after 7 hours and then stirred for a further 41 hours. The only difference from previous experiments was the addition of the amberlyst after 7 hours. The epoxide 341 was produced with an 82 % conversion and an enantiomeric excess of 58 %. A reaction conducted in parallel, without amberlyst, afforded the epoxide 341 with an 80 % conversion and enantiomeric excess of 66 %. These results suggested the amberlyst was not promoting a dynamic kinetic resolution and having very little effect on the epoxidation reaction. The use of
amberlyst with or without acetone cyanohydrin did not enhance the epoxidation reaction.

The idea of the dynamic kinetic resolution was still viable. The final product of the epoxidation reaction was an epoxided aldehyde. If, after epoxidation, the cyanide became detached then it could be responsible for the racemisation of the remaining unepoxided cyanohydrin. To test this hypothesis, an experiment was conducted using the cyanohydrin 339 and the aldehyde 338. If the reaction proceeded beyond 50 % conversion, then the cyanide must be attacking the unsaturated aldehyde 338 to form a cyanohydrin. Previous experiments had shown the aldehyde did not epoxidise.

After 48 hours the conversion to the epoxide was 30 % with an enantiomeric excess of 56 %. When the same reaction was conducted with a reaction time of 168 hours the conversion was 49 % with an enantiomeric excess of 43 %. The conclusion from these results was that the cyanide did not detach itself and racemise the remaining cyanohydrin after epoxidation.

From experience we knew that silica gel would degrade the cyanohydrin. A reaction was conducted using 15 mg of silica gel under normal epoxidation conditions. The silica gel is known to convert the cyanohydrin into the aldehyde 338. Presuming the cyanide ion was present in solution, it was proposed that it could re-form the cyanohydrin, thereby creating a dynamic kinetic resolution. The addition of silica gel led to a reduced conversion of 49 % and epoxide enantiomeric excess of 75 %.
Cyanohydrin Formation in Situ

Our previous efforts to create a dynamic kinetic resolution were unsuccessful, our attention then turned to the in situ formation of the cyanohydrin from the allylic aldehyde.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 \\
\overset{\text{C}}{\text{C}} & \quad \overset{\text{O}}{\text{O}} \\
\overset{\text{H}}{\text{H}} & \quad \overset{\text{CN}}{\text{CN}} \\
\text{Ph} & \quad \text{CH}_3 \\
\end{align*}
\]

The epoxidation of the racemic cyanohydrin was known to proceed under kinetic resolution conditions. We were interested in investigating whether the intermediate 343 could be kinetically resolved. If the intermediate 343 was produced in a dynamic equilibrium, and was kinetically resolved, then only a catalytic quantity of the cyanide ion would be required to epoxidise the aldehyde 338.

The first approach used potassium cyanide with 18-crown-6 and Sharpless epoxidation conditions. After 48 hours, all the starting material was recovered with no epoxide formation. The next attempt used potassium cyanide, 18-crown-6 and a catalytic quantity of camphor sulfonic acid. The catalytic acid would protonate the naked negatively charged oxygen, thus providing the cyanohydrin 339 that had successfully been kinetically resolved previously. After 48 hours, all the starting material was recovered with no epoxide formed. To provide enough time for the cyanohydrin formation the reaction was repeated using a longer reaction time of 166 hours, the reaction recovered starting material only. Finally, thinking the potassium cyanide with 18-crown-6 was not soluble in dichloromethane, a phase transfer cyanide source was used; tri-butylammonium cyanide. This reaction also failed to produce any epoxide or any cyanohydrin. In conclusion there is no evidence to suggest that cyanide is functioning catalytically, and so a full dynamic kinetic resolution does not appear to have been successful.

Further Investigations into the Mechanism of Epoxidation

With the possibility of a dynamic kinetic resolution of the cyanohydrin proved incorrect, our investigations turned towards the second hypothesis. The fact that the racemic cyanohydrin 339 could be epoxidised to afford the epoxy aldehyde 341 in 96
% conversion (55 % e.e.), meant that a simple kinetic resolution could not explain this result. Previous experiments had shown that a dynamic kinetic resolution was very unlikely. The second hypothesis proposed the matched and mismatched epoxidation reaction, described earlier. To prove this hypothesis it was necessary to produce the cyanohydrin enantioselectively. There were two ways to prove this theory; one enantiomer of the cyanohydrin could be synthesised and epoxidised using the D and L enantiomers of diethyl tartrate. On the other hand, both enantiomers of the cyanohydrin could be synthesised separately. The S enantiomer of the cyanohydrin would be epoxidised using L-diethyl tartrate and separately, the R enantiomer would also be epoxidised using L-diethyl tartrate. It was expected, that in the matched case, a quick epoxidation would occur with a high enantiomeric excess. In the mismatched case, the epoxidation rate would be much slower and the enantiomeric excess would be reduced.

The enantiomeric excess of the cyanohydrin 339 was determined by derivatisation of the cyanohydrin using Mosher’s ester.

The enantiomeric excess was determined by \(^1\)H NMR analysis of 344, there are distinct peaks for the methoxy and methyl groups at δ 3.5, 3.6 and 2.0, 2.1 ppm respectively.

One possible route towards the enantiomerically enriched cyanohydrin was described earlier by Hayashi, in Scheme 49. This route used diisopropyl tartrate (or diethyl tartrate) and titanium isopropoxide in the presence of trimethylsilyl cyanide to produce an enantiomerically enriched cyanohydrin. There were no examples using \(\alpha\)-methyl cinnamaldehyde.
When this method was applied to α-methyl cinnamaldehyde, the cyanohydrin produced was impure and could not be purified. Other routes towards the synthesis of the cyanohydrin were sought. The synthesis of various cyanohydrins using enzymes has been reviewed. Unfortunately the synthesis of a cyanohydrin from α-methyl cinnamaldehyde is unknown.

Our attention turned to the kinetic resolution of the racemic cyanohydrins using enzymes. Attempts were made to adapt a kinetic resolution reaction described by Effenberger. The enzyme, using kinetic resolution, transforms one enantiomer of the cyanohydrin into the cyanohydrin acetate leaving the other enantiomer unreacted.

\[
\begin{align*}
\text{OH} & \quad \text{PFL} \\
\text{R-} & \quad \text{DCM} \\
\text{CN} & \quad \text{OAc}
\end{align*}
\]

When the reaction was attempted using the racemic cyanohydrin 339 two products were formed; the aldehyde 338 and the starting material 339. The cyanohydrin 339 formed was found to be racemic. The literature reference suggested the use of dichloromethane as a solvent. Enzymes tend to perform more efficiently in hexane or aqueous solvents, the reaction was repeated using hexane as the solvent. The solvent change led to an increased conversion to the aldehyde 338 and as a consequence reduced production of the racemic cyanohydrin. Due to the enzyme PFL being unsuccessful a number of other enzymes were tested.

Twelve different enzymes were tested;

- Lipases from *Pencillium rosqueforti*, *Muscor javanicus*, *Pseudomonas fluorescens*, *Hog pancreas*, *Candida cylindracea*, *Geotrichum candid*, *Alicaligens Sp*, *Rhizopus niveus*, *Candida lipolytica* and *Candida antarctica* were all used. Other enzymes used include esterase from *Thermoanaerobium brocki* and esterase immobilised on *Eupegit* from hog liver. The twelve enzymes were screened at 40 °C, the reaction vessels contained vinyl acetate, the enzyme and the cyanohydrin 339. In all cases the enzymes afforded the unwanted aldehyde 338 to some degree. In every case the residual cyanohydrin was found to be racemic.

Another synthetic pathway was proposed, the idea was to derivatise the cyanohydrin using an enantiomerically pure carboxylic acid. The carboxylic acid to be used was S-phenyl propanoic acid. Once the cyanohydrin was coupled, the two esters formed
would be diastereomers and would hopefully be separable by column chromatography. Once separated, the individual esters could be hydrolysed back to the cyanohydrin, thus providing the enantiomerically pure cyanohydrins. The carboxylic acid coupling to the cyanohydrin proceeded smoothly in the presence of DCC. The yield obtained of the ester was 68 %. Unfortunately the separation of the esters did not proceed smoothly, the esters were not separable using column chromatography.

Our attempts to generate the cyanohydrin enantioselectively using derivatisation and kinetic resolution were unsuccessful, and so further studies on the matched and mismatched pairs were not preformed.

4.6.1 Conclusion
The epoxidation of the racemic cyanohydrin 339 occurs enantioselectively using Sharpless epoxidation conditions. The cyanide is lost after epoxidation which fulfils our criteria of a reversible nucleophile. Below 50 % conversion, the two enantiomers of 339 are kinetic resolved. Beyond 50 % conversion, it would be expected that the enantiomeric excess of the epoxide formed 341, would decrease sharply. This was not observed; at 96 % conversion and 75 % yield the enantiomeric excess was 55 %.
The expected enantiomeric excess would be much lower, hence two hypotheses were
proposed. The first hypothesis suggested that there was a dynamic kinetic resolution. The evidence presented here strongly suggests that dynamic kinetic resolution is not occurring. Attempts to enhance the dynamic kinetic resolution, by the addition of the amberlyst, or the use of the "naked" cyanide ion, had detrimental effects. The second hypothesis requires the enantioselective production of the cyanohydrin. Despite many efforts to afford the cyanohydrin enantioselectively this has not been achieved. If the cyanohydrin had been synthesised enantioselectively the resulting epoxide would be produced with a very high enantiomeric excess, due to the chiral multiplication effect from the epoxidation reaction.

Future work
The synthesis of the enantiomerically pure cyanohydrin would be top priority, this would prove one of the hypotheses and lead to epoxide being formed with a very high enantioselectivity.

4.7 Approaches to Dynamic Kinetic Resolution
Objective
We were interested in producing an enantiomerically enriched 2,3-epoxy alcohol from a racemic allylic secondary alcohol. Using conventional kinetic resolution conditions the yield of the 2,3-epoxy alcohol would be limited to 50%. However, dynamic kinetic resolution conditions, would provide the epoxy alcohol with a high enantiomeric excess and a high yield. The challenge lay in accomplishing an in situ racemisation whilst kinetically resolving one of the alcohol enantiomers. The epoxidation reaction would be conducted using Sharpless conditions to kinetically resolve one of the alcohol enantiomers.

The Substrate
The alcohol substrate used in the epoxidation reaction was the trans-4-phenyl-3-buten-2-ol 348, referred to as the racemic alcohol. This was synthesised smoothly from the commercially available ketone 347 in the presence of sodium borohydride.
The substrate 348 contained an alcohol tether essential for the Sharpless epoxidation, the phenyl group would be useful for detection using HPLC analysis. The synthesis of the alcohol was confirmed by $^1$H NMR, the singlet peak corresponding to the methyl group at $\delta$ 2.4 ppm was converted into a doublet at 1.4 ppm. A new peak emerged at $\delta$ 4.5 ppm, corresponding to the hydrogen in the $\alpha$-position to the alcohol functionality.

The Epoxidation Reaction

With the substrate in hand, the epoxidation reaction was considered. The pre-mixing of the titanium isopropoxide and diethyl tartrate with t-butyl hydroperoxide prior to the addition of the alcohol substrate was vital to obtain high enantiomeric excesses. The substrate was added after a pre-mixing time of 30 mins, unless otherwise stated. In all cases L-diethyl tartrate was used and the reaction time was 96 hours. After 96 hours the reaction mixture was quenched with water and filtered through Celite and the filtrate evaporated to dryness. The tert-butyl hydroperoxide was removed by azeotroping the reaction mixture with toluene. The diethyl tartrate was removed by column chromatography or by washing the reaction mixture with 10 % sodium hydroxide in saturated brine.

Payne Rearrangement

The work up procedure initially employed for the removal of diethyl tartrate was washing of the reaction mixture with 10 % sodium hydroxide in saturated brine. This technique was executed quickly to counteract the Payne rearrangement in the product. Prolonged exposure to sodium hydroxide solution resulted in new peaks appearing in the $^1$H NMR, these peaks were associated with Payne rearranged products. Later the epoxides were purified using column chromatography to minimise the Payne rearranged products.
The epoxidation of the racemic alcohol 348 produces up to two diastereomers (both racemic). The epoxidation was confirmed by $^1$H NMR, the associated peaks of $H^a$, $H^b$ and $H^c$ all shifted upfield in the epoxide. The doublet peak at $\delta$ 6.6 ppm corresponding to $H^a$ in the substrate shifted upfield to $\delta$ 3.8 and 3.9 ppm in the product 349. The double doublet peak at $\delta$ 6.2 ppm, which corresponds to $H^b$ in the substrate, shifted upfield to $\delta$ 3.0 and 3.1 ppm in the product 349. The double quartet peak at $\delta$ 4.5 ppm, which corresponds to $H^c$ in the substrate, shifted upfield to $\delta$ 4.1 and 3.8 ppm in the product 349. The diastereomeric ratio of the epoxidised product 349 was determined by $^1$H NMR.

In Scheme 52, the catalyst derived from L-diethyl tartrate delivers the 'oxygen' to the lower face of the substrates, the diastereomers 352 and 354 would be expected to be formed much faster than those of 351 and 353. A higher proportion of the diastereomer 352 would be expected, the methyl moiety in the S-enantiomer of 348 is orientated away from the incoming oxygen thereby providing reduced steric hindrance to the incoming oxygen. This steric hindrance provides the basis of the kinetic resolution of this substrate. When using L-diethyl tartrate, the less favoured diastereomer to be synthesised is 351, as the oxygen delivery is expected to be from the lower face and delivery from the top face encounters steric hindrance from the methyl group.
Results From the Epoxidation Reactions

The initial epoxidation reaction was conducted using catalytic quantities of diethyl tartrate and titanium isopropoxide, 0.75 and 0.55 equivalents respectively. The epoxidation reaction proceeded to 90% completion and the epoxide 349 was afforded with a diastereomeric ratio of 2:1. The major diastereomer was 2S, 3S, 4S. The epoxidation reaction was repeated using stoichiometric quantities of diethyl tartrate and titanium isopropoxide. The epoxidation produced the epoxide with a higher diastereomeric ratio of 6:1. These results suggested a kinetic resolution had occurred and the diastereomeric ratio was dependant on the quantity of diethyl tartrate and titanium isopropoxide. Further experiments were conducted using different quantities of diethyl tartrate and titanium isopropoxide.

A reaction was conducted using no diethyl tartrate, it was expected that both diastereomers of the epoxide 349 would be produced racemically. The epoxidised product 349 was afforded with good diastereomeric ratio of 10:1. In an attempt to
produce both diastereomers (racemically) in equal quantities the substrate 348 was epoxidised using mCPBA. The reaction afforded the product 349 with a 2:1 diastereomer ratio.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of L-DET</th>
<th>Diastereomer ratio</th>
<th>Conversion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.75</td>
<td>2:1</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>6:1</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>10:1</td>
<td>90</td>
<td>CY 80 %</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>10:1</td>
<td>95</td>
<td>CY 80 %</td>
</tr>
<tr>
<td>5</td>
<td>none</td>
<td>10:1</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>mCPBA</td>
<td>2:1</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

The high diastereomeric ratios obtained were not indicative of an enantioselective epoxidation. Initially, optical rotation was used to provide an indication of whether the epoxidation had proceeded enantioselectively. The epoxidation using mCPBA had afforded a product with a diastereomeric ratio of 2:1, however as expected the product had no optical activity. The other epoxidations did show optical activity.

**Determination of Enantiomeric Excess**

The diastereomer ratios of the epoxidised product 349 was evaluated using $^1$H NMR. It was intended that the enantiomeric excess and diastereomeric excess would be determined more accurately using HPLC or GC analysis. Despite extensive testing and the use of several different HPLC columns (Chiralcel OD, OJ, OB, Chiralpak AD), no satisfactory method could be found, no satisfactory method was obtained using GC analysis either. In order to find a suitable method for HPLC or GC analysis, the epoxidised alcohol was derivatised. The epoxidised alcohol was derivatised to the benzoate using benzoyl chloride and triethylamine in the presence of a catalytic quantity of DMAP. The reaction proceeded smoothly to provide the necessary benzoate which was purified using column chromatography.
The benzoate 350 was confirmed by the downfield shift of the quartet signal, corresponding to the α-hydrogen of the alcohol, from δ 4.1 ppm to 5.2 ppm in the benzoylated product. Attempts to provide a suitable HPLC or GC analysis using the benzoate 350 were unsuccessful.

Attempts to form the acetate of the epoxidised alcohol 349 using acetic anhydride with acetic acid did not provide the required acetate. The derivatisation of the epoxide 349 using dansyl chloride was attempted but the ester was not formed. Derivatisation using 3,5-dinitrobenzoic acid did afford the required ester, however the ester was not stable to purification. Despite efforts to generate a suitable method for the determination of the enantiomeric excess of the epoxy alcohol 349 and the benzoylated derivative 350, no HPLC or GC method was produced.

An HPLC analytical method for the alcohol 348 was developed whilst testing the epoxide 349. If a dynamic kinetic resolution had been achieved, the important feature of the epoxy alcohol 349 would be the enantiomeric excess of the alcohol. All the reactions had proceeded with chemical yields beyond 50%. In order to obtain a high enantiomeric excess and high diastereomeric ratio in the epoxide 349, with a chemical yield above 50%, then a dynamic kinetic resolution must have occurred.

Due to the problems obtaining a suitable HPLC method for the epoxy alcohol 349, the deoxygenation of the epoxide 349 was attempted to determine the enantiomeric excess of the alcohol.

There are a number of synthetic methods for the deoxygenation of epoxides. It was important that the alcohol was not racemised during the deoxygenation process and the conformation of the double bond remained intact. Initial experiments conducted with iodide, sodium iodide in the presence of trimethylsilyl chloride or trifluoroacetic acid, were unsuccessful in providing the deoxygenated product 348. Sodium iodide in
the presence of 18-crown-6 was also unsuccessful, all the attempts with sodium iodide afforded an intractable black tar. The alcohol 348 was successfully produced from the epoxy alcohol 349 using potassium selenocyanide. The epoxy alcohol 349 was refluxed in methanol for 3 days, in the presence of potassium selenocyanide to provide the alcohol 348 with 70 % yield. The mechanism of this reaction is shown in Scheme 53.

![Scheme 53]

This determination of the enantiomeric excess of the alcohol functionality in the epoxidised product 349, was not ideal. However, the method did provide important information as to whether the alcohol had been racemised. A racemic epoxy alcohol 349 was initially subjected to the deoxygenation reaction and the alcohol 348 was produced smoothly. The alcohol was analysed by HPLC and confirmed as racemic. An optically active epoxy alcohol was then subjected to the deoxygenation reaction, the enantiomeric excess of the resulting allylic alcohol was 33 %, by HPLC. This suggested that the two enantiomers of 348 reacted at different rates and a kinetic resolution was occurring.

**Racemisation**

Our efforts then turned to the *in situ* racemisation of the alcohol 348. The proposed racemisation route was to use temporary oxidation, similar to that shown earlier with Williams' work. The alcohol would be temporarily oxidised to the ketone and then reduced back to the alcohol, this oxidation/reduction process would racemise the alcohol.
It was envisaged the temporary oxidation of the alcohol could be carried out using a Lewis acid such as aluminium isopropoxide, as illustrated in Scheme 54. The aluminium would have the potential to reduce the ketone back to the alcohol. The dynamic resolution would depend on the concentration of the acetone/isopropanol.

The alcohol 348 was refluxed in acetone and isopropanol in the presence of one equivalent of aluminium isopropoxide. This reaction would ascertain whether the aluminium was capable of oxidising the alcohol. After 36 hours of refluxing, 10 % of the alcohol had been oxidised to the ketone. The reaction was repeated using titanium isopropoxide, it was suspected that this Lewis acid would not be capable of oxidising the alcohol. Several experiments conducted using various concentrations of acetone, titanium isopropoxide and isopropanol produced no ketone. Due to the modest oxidation observed with aluminium, an experiment was conducted using 10 mol% of aluminium isopropoxide. The oxidation of the alcohol 348 to ketone 347 had occurred at refluxing temperatures. As the epoxidation reaction would be conducted at sub-zero temperature, we were unsure whether the alcohol would be oxidised. The epoxidation reaction was found to be inhibited by the addition of the aluminium isopropoxide, the conversion to the epoxy alcohol 349 was 63 %. Significantly, 15 % of the alcohol 348 had been converted to the ketone 347. The production of the ketone 347 was encouraging, the fact the aluminium appeared to be inhibiting the reaction suggested that it should be replaced. Our attention turned to the use of other transfer hydrogenation catalysts. Williams et al. had shown that these could be used to provide in situ racemisation of alcohols in the presence of enzymes.181

Due to time restrictions only one catalyst was evaluated, iridium chloride dimer. It was anticipated that potassium hydroxide would need to be added to promote
racemisation. When potassium hydroxide was added to the epoxidation reaction without iridium, the conversion to the epoxide was reduced to 50%. This effect was attributed to the hygroscopic nature of the potassium hydroxide. When iridium and potassium hydroxide were added together in an epoxidation reaction a higher proportion of the ketone 347 was produced, 33%, in conjunction with the epoxy alcohol 349. The epoxy alcohol 349 was produced as a single diastereomer.

\[
\begin{align*}
\text{348} & \quad \text{Sharpless Epoxidation} \\
\text{[Ir(COD)Cl}_2 (5 \text{ mol\%}) & \quad \text{KOH (20 mol\%)} \\
\text{348} & \quad 66\% \\
\text{349} & \quad 347 & \quad 33\% 
\end{align*}
\]

4.7.1 Conclusion
The epoxidation of the substrate 348 occurs diastereoselectively to afford the product 349 with a high diastereomeric ratio, when using Sharpless epoxidation conditions. There is a kinetic resolution of the enantiomers of 348 when epoxidised under Sharpless conditions, this has been proven through the deoxygenation step with potassium selenocyanide. The original idea was to conduct the epoxidation using dynamic kinetic resolution conditions. The iridium catalyst oxidised the alcohol 348 to the ketone 347, however the desired temporary oxidation has not been achieved. The final step, to provide the dynamic kinetic resolution conditions, would be the reduction of the ketone 347 back to the alcohol 348.

The viability of this route has been proven, the alcohol substrate 348 is oxidised using kinetic resolution conditions and the conversion from alcohol to ketone 347 does occur.

Further Work
Our primary objective would be to develop an HPLC/GC method for the determination of the enantiomeric excess and diastereomeric excess of the epoxidised alcohol 349. With enantiomeric excess determination in hand, the screening of other transfer hydrogenation catalysts could proceed to develop a system that would provide a dynamic kinetic resolution. Once a dynamic kinetic resolution was obtained, the methodology would be extended to other substrates.
Chapter 5

Experimental

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5.1 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 between 40 °C and 60 °C. Light petroleum and ethyl acetate were distilled from anhydrous calcium chloride through a 36 cm vigreux column before use. Dichloromethane was distilled from phosphorus pentoxide and methanol was distilled from magnesium turnings and iodine.

**Chromatographic Procedures** - Analytical thin layer chromatography was carried out using plastic backed plates coated in Merck Kieselgel 60 F₂₅₄. Plates were visualised by UV light (at 254 and/or 360 nm) or by exposure to an appropriate staining agent. Flash chromatography was carried out using Merck silica gel 60. Pressure was applied at the head of the column with hand bellows. Samples were applied pre-absorbed on silica or as a concentrated 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 thin films or as Nujol mull. ¹H and ¹³C NMR were recorded using Bruker AC-250 and Bruker DPX-400 instruments. ¹H NMR spectra are referenced against residual undeuterated solvent, in the case of deuterochloroform this is 7.260 ppm. Signals are described as singlets (s), doublets (d), double doublet (dd) etc. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (EPSRC mass spectroscopy service, Swansea).

**Other Data and Instrumentation** - Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were measured using a PolAAr 2001 instrument.

All of the following experimental reactions were carried out under an atmosphere of nitrogen except where it was obviously unnecessary. All coupling constants (J values) are quoted in Hertz.
5.2 Experimental for Chapter 2

1-Bromo-2-(dimethoxymethyl)benzene 170

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{H} & \\ \\
169 & \\
\text{CeCl}_3 \cdot 7\text{H}_2\text{O} & \quad \text{(MeO)}_2\text{CH} \\
\text{MeOH} & \quad \text{H} \quad \text{Br} \\
170 &
\end{align*}
\]

2-Bromobenzaldehyde (2.0 g, 10.8 mmol), trimethylorthoformate (1.7 g, 16.1 mmol) and cerium(III) chloride heptahydrate (0.2 g, 0.6 mmol) were suspended in methanol (7 ml) and stirred overnight at room temperature. The solvent was removed \textit{in vacuo} and the resulting residue dissolved in ether (30 ml) and washed with saturated sodium hydrogen carbonate (aq) and water. The organic layer was dried (magnesium sulfate), filtered and the solvent removed under reduced pressure to afford the crude \textit{title compound} which was taken through as a mixture to the next step (2.0 g, 80%).

Crude NMR data

\[
\begin{align*}
\delta_H(250 \text{ MHz, CDCl}_3) & \quad 3.38 (6\text{H, s, OCH}_3), \quad 5.56 (1\text{H, s, CH(OCH}_3)_2) \\
& \quad 7.19-7.58 (4\text{H, m, ar-H}).
\end{align*}
\]

[2-(Dimethoxymethyl)phenyl](diphenyl)phosphine 171

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{Br} & \quad \text{H} \quad \text{PPh}_2 \\
170 & \\
\text{ClPPh}_2 & \\
\text{Mg, THF} & \quad \text{H} \quad \text{PPh}_2 \\
171 &
\end{align*}
\]

In a flame-dried 50 ml flask, magnesium (0.5 g, 20.8 mmol) was suspended in THF (5.0 ml) with a drop of 1,2-dibromoethane. A portion of the bromoacetal 170 and a crystal of iodine were added and the mixture heated. Once initiated, the remaining bromoacetal (5.0 g, 0.02 mol) was added at a rate such that the mixture continued to reflux. After refluxing for 30 minutes, the mixture was cooled to 0°C, chlorodiphenylphosphine (4.8 g, 0.02 mol) in THF (5 ml) was added and the whole
mixture refluxed overnight. On cooling, the solvent was removed under reduced pressure, the residue dissolved in dichloromethane and washed with aqueous ammonium chloride and brine. The organic layer was dried (sodium sulfate) and the solvent removed under reduced pressure to afford the title compound (5.8 g, 87%) which was taken through to the next stage.

Crude NMR data

\[ \delta_{\text{H}}(250 \text{ MHz, CDCl}_3) 3.15 (6\text{H, s, 2 } \times \text{ OCH}_3), 5.97 (1\text{H, d, } J_{\text{p-H}} 5.3, \text{ CH(OCH}_3)_2) 6.95-7.12 (2\text{H, m, ar-H}), 7.22-7.81 (12\text{H, m, ar-H}). \]

2-Diphenylphosphinebenzaldehyde 168
2-(1,1-diphenylphosphino)benzaldehyde

[2-(Dimethoxymethyl)phenyl] diphenylphosphine (1.8 g, 5.4 mmol) was dissolved in acetone (35 ml) and p-toluenesulfonic acid was added. The solution was refluxed overnight, water added (whilst still warm) and the solution partially concentrated in vacuo. The product was filtered from the solution. The residue was purified using flash silica chromatography (light petroleum / ether, 3:1) to give the product as a yellow crystalline solid (0.6 g, 40%), m.p. 117-118 °C, lit 118-119 °C. \(^{80}\)

Spectroscopic data comparable with that found in literature. \(^{80}\)

\[ \delta_{\text{H}}(250 \text{ MHz, CDCl}_3) 6.95-6.97 (2\text{H, m, ar-CH}), 7.24-7.49 (10\text{H, m, ar-CH}), 7.94-7.97 (2\text{H, m, ar-CH}), 10.49 (1\text{H, d, } J_{\text{p-H}} 5.4, \text{ CH=O}); \]

\[ \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 128.6, 128.7, 128.8, 128.9, 129.1, 130.5, 130.6, 131.8, 131.9, 132.5, 132.4, 133.6, 133.8, 134.1, (14 \times \text{ ar-CH}), 136.6, 136.9, 138.6, 139.0 (\text{C, 4 } \times \text{ ar-C}), 191.5 (\text{CH, } J_{\text{p-C}} 19.1 \text{ CH}=\text{O}). \]
2-Diphenylphosphine benzaldehyde (0.5 g, 1.7 mmol) and (S)-methylbenzylamine 174 (0.3 g, 1.7 mmol) were stirred in dichloromethane (10 ml) over molecular sieves under a nitrogen atmosphere for twelve hours. The molecular sieves were filtered from the reaction, the solvent was removed to give the crude product (dark yellow) which was purified using activated basic alumina flash chromatography (dichloromethane eluent) to afford the title compound as a pale brown oil (0.2 g, 35 %).

Spectroscopic data comparable with that found in literature.81

\[ \text{Found MH}^+, 394.1725. \text{C}_{27}H_{25}NP \text{ requires MH}^+, 394.1725; \nu_{\text{max}}/\text{cm}^{-1} (\text{thin film}) 3054, 2969, 1637 (\text{C=N}); \delta_{\text{H}} (250 \text{ MHz, CDCl}_3) 1.32 (3\text{H, d, } J 6.6, \text{PhC(CH}_3\text{)H}), 4.36 (1\text{H, q, } J 6.6, \text{PhC(CH}_3\text{)H}), 6.84-6.97 (1\text{H, m, ar-H}), 7.16-7.38 (17\text{H, m, ar-H}), 7.96-7.98 (1\text{H, m, ar-H}), 8.91 (1\text{H, d, } J_{p,H} 4.8, \text{RC(=N)H}); \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) 24.5 (\text{CH}_3, \text{C(H)(CH}_3\text{)-Ph}) 69.7 (\text{CH, C(H)(CH}_3\text{-Ph}) 126.6, 128.1, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.1, 130.2, 130.5, 133.2, 133.7, 133.9, 134.0, 134.0, 134.2, 134.3 (19 x ar-CH) 139.3, 139.6, 144.7, 157.9, 158.2 (5 x ar-CH), 158.3 (\text{CH, J}_{p,c} 32, \text{CH=N}); m/z (\text{Cl}) 349 (\text{MH}^+, 100 \%), 288 (10); [\alpha]_{D}^{25} - 38.62 (c 0.25, \text{CHCl}_3). \]

\[
\begin{align*}
\text{(S)-2-diphenylphosphanyl-benzylidene)-(1-naphthyl ethyl) amine 173} \\
\text{N-[(E)-1-[2-(1,1-Diphenylphosphino)phenyl)methylidene]-N-[(1S)-(2-naphthyl)ethyl]amine}
\end{align*}
\]

2-Diphenylphosphine benzaldehyde (0.5 g, 1.7 mmol) and (S)-naphthylethylamine 175 (1.7 mmol) were stirred in dichloromethane (10 ml) over molecular sieves under a nitrogen atmosphere for twelve hours. The molecular sieves were filtered from the
reaction, the solvent was removed to give the crude product (dark yellow) which was purified using activated basic alumina flash chromatography (dichloromethane eluent) to afford the *title compound* as a pale brown oil (0.3 g, 45 %).

(Found MH⁺, 444.1881. C₃₁H₂₇NP requires MH⁺, 444.1881); νmax/cm⁻¹ (thin film) 3052, 2971, 1637 (C=N), 1434; δH (250 MHz, CDCl₃) 1.43 (3H, d, J 6.6, naphthC(CH₃)H), 5.18 (1H, q, J 6.6, naphthC(CH₃)H), 6.86-8.08 (m, 21 x ar-H) 8.98 (1H, d, Jp.H 4.8, RC(H)=N); δC (100 MHz, CDCl₃) 24.3 (CH₃, C(H)(CH₃)-naphth) 69.7 (CH, C(H)(CH₃)-naphth) 123.5, 123.8, 124.0, 125.2, 125.6, 125.7, 127.7, 127.2, 127.2, 128.3, 128.3, 128.5, 128.6, 128.7, 128.8, 128.8, 130.2, 131.8, 131.9, 133.3, (21 ar-CH), 137.0, 137.3, 137.8, 138.9, 140.2, (5 x ar-C) 158.6 (CH, Jp.C 30, CH=N); m/z (Cl) 444 (MH⁺, 100 %), 288 (15), 187 (15), 172 (15); [α]D²+69.28 (c 0.61, CHCl₃).

2-(2-Diphenylphosphanyl phenyl)-1,3-dimethyl-(4S,5S)-diphenylimidazolidine 185

(4S,5S)-2-[2-(1,1-Diphenylphosphino)phenyl]-1,3-dimethyl-4,5-diphenyltetrahydro-1H-imidazoline

2-Diphenylphosphine benzaldehyde (117 mg, 0.4 mmol) was added to (2S, 3S)-N,N-dimethyl-1,2-diphenylethane diamine (97 mg, 0.4 mmol) in dichloromethane (5 ml) and refluxed. The reaction was followed by using TLC analysis until starting material was consumed (approx. 24 hours), and with the emergence of a new spot. The solvent was removed under reduced pressure and the resulting residue was purified using flash chromatography (light petroleum/ethyl acetate 5:1) to afford the *title compound* as a pale brown solid (161 mg, 77 %), m.p. 72-74° C.
(Found MH⁺, 513.246. C₃₅H₃₄N₂P requires MH⁺, 513.246); (Found: C, 81.66; H, 6.43; N, 5.31 %. C₃₅H₃₄N₂P requires C, 82.00; H, 6.49; N, 5.46 %); v_{max}/cm⁻¹ (CHCl₃) 3057, 3028, 2940, 2842, 1435; δ_H (250 MHz, CDCl₃) 1.86 (3H, s, CH₃), 1.90 (3H, s, CH₃), 3.48 (1H, d, J 8.3, C(Ph)H), 3.93 (1H, d, J 8.3, C(Ph)H), 5.71 (1H, d, J_p=H 7.0, C(N)(N)H), 7.01-7.47 (23H, m, ar-H), 7.96-8.02 (1H, m, ar-H); δ_C (62.5 MHz CDCl₃) 36.7, 37.6 (CH₃, 2 x N-CH₃), 77.6, 87.6 (CH, 2 x C(Ph)H), 116.2 (CH, C(N)(N)H), 121.2, 124.6, 127.6, 127.8, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.3, 130.1, 130.3, 130.3, 134.2, 134.5, 134.8, 134.9, 137.4, 137.8, 137.9, 138.0 (24 x ar-CH), 138.0, 138.3, 140.1, 140.8, 145.1, 145.5 (C, 6 x ar-C); m/z (Cl) 513 (MH⁺, 100 %), 320 (30), 187 (40); [α]_{D}^{23}=-72.96 (c 0.47, CHCl₃).

2-(2-Diphenylphosphany/ phenyl)-(4S, 5S)-diphenyl-2-imidazoline 188

(4S, 5S)-2-[2-(1,1-Diphenylphosphino)phenyl]-4,5-diphenyl-4,5dihydro-1H-imidazoline

A solution of (2S,3S)-1,2-diphenylethylene diamine (50 mg, 0.3 mmol) and methyl benzimidate hydrochloride (45 mg, 0.3 mmol) in anhydrous ethanol (5 ml) was stirred at room temperature for 1 hour. The solution was then refluxed for 4 hours after which the solvent was removed in vacuo, the residue dissolved in dichloromethane (30 ml) and washed with 5 % sodium carbonate solution. The organic phase was dried (magnesium sulfate), filtered and the solvent was removed under reduced pressure to afford the crude imidazoline. The product was used without further purification.

Crude NMR data
δ_H (250 MHz, CDCl₃) 4.76 (2H, s, CH(Ph)), 7.10-7.46 (14H, m, ar-H), 7.87-7.90 (2H, m, ar-H).
The imidazoline 187 (100 mg, 0.3 mmol) was added to flask containing TMEDA (77 mg, 0.8 mmol). The flask was then immersed in a bath at -78°C. tert-Butyl lithium in pentane (1.5M) (0.5 ml, 0.7 mmol) was slowly added and a change in colour was observed (from pale yellow to dark red). The anion was quenched after 15 minutes with a solution of chlorodiphenylphosphine (90 mg, 0.4 mmol) in ether (0.5 ml). The solution changed colour to dark beige within a minute and after 20 minutes the reaction was allowed to warm to room temperature. The solvent was removed in vacuo, the residue dissolved in dichloromethane (45 ml) and washed with water (2 x 30 ml) followed by brine (40 ml). The dichloromethane layer was dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure. The residue was purified using flash chromatography (light petroleum/ethyl acetate, 5:1) to afford the title compound as a pale brown oil (128 mg, 80%).

(Found MH⁺ of oxide, 499.1939. C₃₃H₂₆N₂PO requires MH⁺ of oxide, 499.1939); νmax/cm⁻¹ (CHCl₃) 3057, 3020, 3011, 1622, 1602, 1452; δH (250 MHz, CDCl₃) 2.24 (1H, s, NH), 4.87 (2H, s, CH(Ph)), 7.00-7.80 (22H, m, ar-H), 7.91-7.95 (2H, m, ar-H); δC (100 MHz, CDCl₃) 45.68 (CH(Ph)), 57.3 (CH(Ph)), 115.6 (C, ar-C), 125.8, 126.2, 126.6, 126.9, 127, 127.6, 127.6, 128, 128.0, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.5, 129.6, 128.0 (18 x ar-CH), 129.8, 130.8 (C, 2 x ar-C), 130.6, 131.1 (2 x ar-CH), 131.2, 131.6 (C, 2 x ar-C), 131.3, 131.5, 131.8, 132.5, 134.4 (C, ar-C), 163.2 (C, C=N); m/z (Cl) 499 (MH⁺ of oxide, 20%), 419 (10), 387 (100), 341 (50) 299 (100) 106 (60); [α]D²⁰ -38.43 (c 0.36, CHCl₃).
2-Diphenylphosphineacetophenone 176

1-[2-{(1,1-Diphenylphosphino)phenyl]-1-ethanone

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{F} \\
\text{PPh}_2
\end{array}
\]

The reaction was carried out under an inert atmosphere. To a flame-dried 50 ml two-necked flask, was added potassium diphenylphosphide (2.0 ml, 1 mmol) (as a 0.5 M solution in THF) via a syringe. The solution was then heated to reflux and then 2-fluoroacetophenone (140 mg, 1 mmol) was added as a solution in THF (2.0 ml). The mixture was then stirred under reflux for 10 minutes, where upon the red solution of the phosphide faded to a dark yellow. The mixture was transferred to a separating funnel and partitioned between dichloromethane (30 ml) and water (30 ml). The dichloromethane layer was separated, dried (magnesium sulfate), filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (light petroleum/ether, 3:1) to afford the title compound as a yellow solid (260 mg, 95%).

Spectroscopic data comparable with that found in literature.  

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{CHCl}_3) \ 3300, \ 1730 (\text{C}=\text{O}), \ 1669; \ \delta_H (250\text{MHz, CDCl}_3) \ 2.58 (3\text{H, d, } J_{\text{P-H}} \ 7, \ \text{COCH}_3), \ 7.02-7.03 (1\text{H, m, ar-H}), \ 7.20-7.47 (12\text{H, m, ar-CH}), \ 7.93-7.95 (1\text{H, m, ar-H}). \]
N-(3Diphenylphosphanylbenzilydene-α-methyl)-S-1-phenylethyl amine 178
N-{(E)-1-[2-(1,1-Diphenylphosphino)phenyl]ethylidene}-N-[1S)-phenylethyl] amine

Titanium chloride (57 mg, 0.2 mmol) was added into an ice-cold solution of dry dichloromethane containing triethylamine (364 mg, 3.6 mmol) and (S)-methylbenzyl amine 174 (87 mg 0.7 mmol). The solution was heated to reflux and 2-diphenylphosphine acetophenone (200 mg, 0.66 mmol) was added over a minute. After 12 hours of reflux, the solution was cooled to room temperature, dichloromethane (75 ml) was added and the solution filtered through Celite. The filtrate was washed with 10 % sodium carbonate solution, dried (sodium sulfate) and the solvent removed under reduced pressure to afford the title compound as a pale brown oil (150 mg, 57 %).

Formation of the ketone imines produced three species; cis, trans and trapped free amine. The major product is most likely to be the trans, the minor product cis, and the amine was denoted as free. Ratio of major:minor:free is 5:2:1.

(Found MH+, 408.1881. C_{28}H_{26}NP requires MH+, 408.1803); ν_{max}/cm^{-1} (thin film) 3053, 2969, 1644 (C=N); δ_{H} (250 MHz, CDCl3) [Minor 1.11 (3H, d, J 6.5, PhC(CH_{3})H), 2.28 (3H, d, J_{p-H} 1.6, C(=N)CH_{3}), 4.21 (1H, q, J 6.4 PhC(CH_{3})H)]. [Free 1.33 (3H, d, J 6.5, PhC(CH_{3})H), 1.6 (2H, br, NH_{2}), 4.07 (1H, q, J 6.4 PhC(CH_{3})H)]. [Major 1.36 (3H, d, J 6.5, PhC(CH_{3})H), 2.23 (3H, d, J_{p-H} 1.6, C(=N)CH_{3}), 4.65 (1H, q, J 6.4, PhC(CH_{3})H)], 6.71-6.72 (1H, m, ar-H), 6.96-7.44 (18H, m, ar-H); δ_{C} (100 MHz, CDCl3) [ Minor 23.8 (CH_{3}, C(H)(CH_{3})), 29.6 (CH_{3}, C(=N)CH_{3}), 60.9 (CH, C(H)(CH_{3})-Ph), [Free 18.8 (CH_{3}), 60.8 (CH, C(H)(CH_{3})-Ph)], [Major 24.7 (CH_{3}, d, C(H)(CH_{3})-Ph) 29.8 (CH_{3}, C(=N)CH_{3}), 61.7 (CH, C(H)(CH_{3})-Ph)] 126.1, 126.2, 126.3, 126.4, 126.5, 126.6, 126.8, 127.3, 127.4, 127.9, 127.9, 128.1, 128.1, 128.1, 128.2, 128.2, 128.3,
N-(3-Diphenylphosphanylbenzylimidene-α-methyl)-S-1-naphthyl-ethyl amine 179
N-{(E)-1-[2-(1,1-Diphenylphosphino)phenyl]ethylidene}-N-[(1S)-(2-naphthyl)ethyl] amine

Titanium chloride (57 mg, 0.2 mmol) was added into an ice cold solution of dry dichloromethane containing triethylamine (364 mg, 3.6 mmol) and (S)-naphthylethylamine 175 (0.7 mmol). The solution was then heated to reflux and 2-diphenylphosphine acetophenone (200 mg, 0.7 mmol) was added over a minute. After 12 hours of reflux, the solution was cooled to room temperature dichloromethane (75 ml) was added and the solution filtered through Celite. The filtrate was washed with 10% sodium carbonate solution, then dried (sodium sulfate), filtered and the solvent removed under reduced pressure to afford the title compound as a pale brown oil (170 mg, 59%).

Formation of the ketone imines produced three species; cis, trans and trapped free amine. The major product is most likely to be the trans, the minor cis, and the amine was denoted as free. Ratio of major:minor:free is 5:2:1.

(Found MH+, 457.1959. C₃₂H₂₆NP requires MH+, 457.1959); νmax/cm⁻¹ (thin film) 3066, 2966, 1646 (C=N), 1433; δH (250 MHz, CDCl₃) [Minor 1.1 (3H, d, J 6.0, PhC(CH₃)H), 2.48 (3H, s, C(=N)CH₃), 4.74 (1H, q, J 6.0, C(=N)(CH₃)-naphth), [Free 1.53 (3H, d, J 6.0 PhC(CH₃)H), 4.95 (1H, q, J 6.0, naphthC(CH₃)H)], [Major 1.58 (3H, d, J 6.0 PhC(CH₃)H), 2.23 (3H, d, J 6.0, C(=N)CH₃), 5.43 (1H, q, J 6.0, naphthC(CH₃)H)], 6.43-8.2 (24 x ar-H); δC (100 MHz, CDCl₃) [Minor 24.9 (CH₃, C(H)(CH₃)-naphth) 29.6 (CH₃, C(=N)CH₃), 57.1 (CH, C(H)(CH₃)-naphth)], [Free 19.1 (CH₃, C(H)(CH₃)-naphth) 57.0 (CH, C(H)(CH₃)-naphth)], [Major 24.1 (CH₃, C(H)(CH₃)-naphth) 29.8 (CH₃, C(=N)CH₃), 58.1 (CH, C(H)(CH₃)-naphth)], 123.0, 123.2, 123.7, 123.9, 124.3, 124.4, 124.6, 124.9, 125.0, 125.1, 125.1, 125.6, 125.7, 125.8, 126.2, 126.5, 126.5, 126.6, 127.4, 127.5. 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3,
Titanium chloride (57 mg, 0.2 mmol) was added into an ice cold solution of dry dichloromethane containing triethylamine (364 mg, 3.6 mmol) and S-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) 183 (94 mg, 0.7 mmol). The solution was then heated to reflux and 2-diphenylphosphine acetophenone (200 mg, 0.7 mmol) was added over a minute. After 12 hours of reflux, the solution was cooled to room temperature dichloromethane (75 ml) was added and the solution filtered through Celite. The filtrate was washed with 10 % sodium carbonate solution, dried (sodium sulfate) and the solvent removed under reduced pressure to afford the title compound as a pale brown oil (200 mg, 72 %).

(Found MH⁺, 417.2096. C₂₆H₃₀N₂O₂P requires MH⁺, 417.2096 ); νmax/cm⁻¹ (thin film)
3066 ,2971, 1585, 1098; δH (250 MHz, CDCl₃) 1.53-1.83 (6H, m, CH₂ of SAMP), 2.28 (3H, d, Jp-H 1.0, C(=N)CH₃), 2.53-2.56 (1H, m,), 3.05-3.08 (2H, m, CH₂O), 3.22 (3H, s, OCH₃), 3.33-3.37 (1H, m, CH), 6.91-6.96 (1H, m, ar-H), 7.18-7.31 (m, 14 x ar-H); 7.49-7.51 (1H, m, ar-H); δC (100 MHz, CDCl₃) 19.9 (CH₃, d, Jp-C 4), 22.9 (CH₂), 28.6 (CH₂), 55.1 (CH₂), 58.9 (OCH₃), 65.9 (CH), 75.1 (CH₂), 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.5, 133.5, 133.6, 133.8, 133.9, 134.8 (14 x ar-CH), 139.2 (C, C=N); m/z (Cl) 417(100 %, MH⁺), 302 (10); [α]D²⁵ +394.5 (c 0.25, CHCl₃).
To a stirred solution of chalcone (5.0 g, 24.0 mmol) and cerium chloride hepta hydrate (9.9 g, 26.6 mmol) containing methanol (50 ml), at 0°C, was added sodium borohydride (1.0 g, 26.6 mmol). The reaction mixture was stirred for 3 hours and concentrated in vacuo. Water (15 ml) was added carefully and product extracted with dichloromethane (3 x 30 ml). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated in vacuo to yield the title compound as a yellow oil (4.8 g, 95 %) which was not purified at this stage. Spectroscopic data comparable with that found in literature.\(^{196}\)

\(\nu_{\text{max}} / \text{cm}^{-1} \) (thin film) 3441 (OH); \(\delta_1 \) (250 MHz, CDCl\(_3\)) 5.39 (1H, d, \(J = 6.4\), CHO\(\text{OH}\)), 6.39 (1H, dd, \(J = 6.4\) and 15.8 =CH), 6.70 (1H, d, \(J = 15.8\), PhCH), 7.23-7.45 (10H, m, 10 x ar-H).

**Chapter 5 Experimental**

\((E)-1,3\text{-Diphenyl-3-acetoxy-1-propene 142}\)

A solution of the alcohol 273 (4.8 g, 22.9 mmol) in acetic anhydride (2.8 g, 45.8 mmol) with pyridine (10 ml) and DMAP (2 crystals) was stirred at room temperature overnight until completion indicated by TLC analysis of the reaction. The reaction was diluted with diethyl ether and washed with copper (II) sulfate solution (4 x 30 ml) and a saturated solution of sodium hydrogen carbonate (20 ml ). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated in vacuo to yield the title compound as a colourless oil (4.9 g, 85 %).
Spectroscopic data comparable with that found in literature.\(^ {196} \)

\( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 1738 (C=O); \( \delta_{\text{H}} (250 \text{ MHz, CDCl}_3) \) 2.13 (3H, s, C(=O)CH\(_3\)), 6.31-6.46 (2H, m, CH\(_2\)), 6.63 (CH, d, J 15.5, PhCH\(_3\)), 7.18-7.38 (10H, m, 10 x ar-H); \( \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) \) 21.31 (CH\(_3\)), 76.16 (CH, CHOCH\(_3\)), 126.8, 127.1, 127.6, 127.9, 128.1, 128.2, 128.5, 128.6, 132.6, (10 x ar-CH), 136.2, 139.3 (2 x ar-C), 170.0 (C=O).

General procedure for the alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene 143

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{Pd}^0 & \\
\text{CH}_2(\text{CO}_2\text{Me})_2 & \\
\text{Ph} & \quad \text{CH(}\text{CO}_2\text{Me})_2
\end{align*}
\]

The palladium catalyst was prepared \textit{in situ} by stirring allylpalladium chloride dimer (3.6 mg, 0.01 mmol, 5 mol\%) with an enantiomerically pure ligand (0.08 mmol, 20 mol\%) in dichloromethane (1 ml) for 15 minutes. The acetate 142 (100 mg, 0.4 mmol) in dichloromethane (0.5 ml) was added followed by dimethyl malonate (157 mg, 1.2 mmol) and BSA (242 mg, 1.2 mmol) and a catalytic amount of sodium acetate (1-2 mg). The reaction was stirred at room temperature until all the starting material was consumed, as shown by TLC analysis (light petroleum/diethyl ether, 3:1). The reaction was extracted into diethyl ether (10 ml) and washed with saturated solution of ammonium chloride (10 ml). The separated organic layer was dried (magnesium sulfate) and concentrated to a yellow oil. Purification by flash chromatography (light petroleum/diethyl ether, 3:1) which yielded the \textit{title compound} as a colourless oil.

Spectroscopic data comparable with that found in literature.\(^ {155} \)

\( \delta_{\text{H}} (250 \text{ MHz, CDCl}_3) \) 3.51 (3H, s, CO\(_2\)CH\(_3\)) 3.70 (3H, s, CO\(_2\)CH\(_3\)) 3.92 (1H, d, J 11 CH(\text{CO}_2\text{Me})_2), 4.22 (1H, dd, J 8 and 11, PhCHCH(\text{CO}_2\text{Me})_2), 6.27 (1H, dd, J 8 and 15, PhCH=CH), 6.44 (1H, d, J 15, PhCH=CH), 7.19-7.33 (10H, m, ar-H); \( \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) \) 21.31 (CH\(_3\)), 76.16 (CH, CHOCH\(_3\)), 126.8, 127.1, 127.6, 127.9, 128.1, 128.2, 128.5, 128.6, 132.6, (10 x ar-CH), 136.2, 139.3 (2 x ar-C), 170.0 (C=O).
MHz, CDCl₃) 48.8 (CH), 52.0, 52.2, (CH₃), 57.3 (CH), 126.0-132.2 (8 x ar-CH and 2 =CH), 136.5, 139.8, (ar-C), 167.8 (2 x C=O).

2-Cyclohexenyl-1-yl acetate 265

![Chemical structure](image)

A solution of the alcohol (1.0 g, 10.3 mmol) in acetic anhydride (2.8 g, 45.8 mmol) and pyridine (20 ml) and DMAP (2 crystals) was stirred at room temperature overnight until completion indicated by TLC analysis of the reaction. The reaction was then diluted with diethyl ether and washed with copper(II) sulfate solution (4 x 30 ml), a saturated solution of sodium hydrogen carbonate (20 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to yield the title compound as a colourless oil. The product was purified by flash column chromatography (dichloromethane) (0.9 g, 67%).

Spectroscopic data comparable with that found in literature.¹⁹⁷

\[
\nu_{\text{max}}/\text{cm}^{-1} \text{ (thin film)} \quad 1700 \text{ (C=O)}; \quad \delta \text{H} \text{ (250 MHz, CDCl₃)} \quad 1.66-2.00 \text{ (6H, m, CH₂)}, \quad 1.95 \text{ (3H, s, COCH₃)}, \quad 5.24-5.26 \text{ (1H, m)}, \quad 5.67-5.71 \text{ (1H, m)}, \quad 5.93-5.97 \text{ (1H, m)}.
\]

General procedure for alkylation of 2-Cyclohexenyl-1-yl acetate 265

![Chemical structure](image)

The palladium catalyst was prepared in situ by stirring allylpalladium chloride dimer (7.3 mg, 0.02 mmol, 5 mol%) with an enantiomerically pure ligand (0.01 mmol, 10 mol%) in dichloromethane (1 ml) for 15 minutes. 2-Cyclohexenyl-1-yl acetate (139 mg, 1.0 mmol) in dichloromethane (0.5 ml) was added followed by dimethyl malonate.
(314 mg, 2.4 mmol, 3 equiv.) and BSA (480 mg, 2.4 mmol, 3 equiv.) and a catalytic amount of sodium acetate (1-2 mg). The reaction was stirred at room temperature until the starting material was consumed, as shown by TLC analysis (light petroleum / diethyl ether, 3:1). The reaction was extracted into diethyl ether (10 ml) and washed with saturated solution of ammonium chloride (10 ml). The separated organic layer was dried (MgSO₄) and concentrated to a yellow oil. Purification by flash chromatography (light petroleum/diethyl ether, 3:1) yielded the title compound as a colourless oil (98 mg, 46%). Spectroscopic data comparable with that found in literature.¹²³ᵇ

δₜₕ (250 MHz, CDCl₃) 1.30-1.41 (1H, m), 1.50-1.65 (1H, m) 1.67-1.83 (2H, m), 1.94-2.10 (2H, m), 2.83-2.99 (1H, m) 3.27 (1H, d, J 9, CH(COOCH₃)₂), 3.74 (3H, s, CO₂CH₃), 3.75 (3H, s, CO₂CH₃), 5.47-5.51 (1H, m, HC=CH), 5.72-5.84 (1H, m, HC=CH).

5.4 Experimental for Chapter 4

(E)-1-Hydroxy-2-methyl-3-phenyl-2-propenyl cyanide 339
(E)-1-Hydroxy-3-methyl-4-phenyl-3-butenenitrile

Procedure ¹ʾ⁹⁸

A solution of diethyl tartrate (113 mg, 0.6 mmol) in dichloromethane (5 ml) in a flame dried flask was cooled to 0 °C. Titanium isopropoxide (0.15 ml, 0.5 mmol) was then added slowly by syringe. After 1hour of stirring at room temperature, dichloromethane (25 ml) was added and the reaction cooled to 0 °C. Trimethylsilyl cyanide (0.75 ml, 5.6 mmol) and α-methyl trans-cinnamaaldehyde (359 mg, 2.5 mmol) were added and the reaction mixture and stirred at 0 °C for 3 days. Hydrochloric acid (1M, 40 ml) (aq) was added to the reaction and the reaction was stirred for a further 48 hours. The organic phase was extracted from the aqueous and dried (magnesium sulfate), filtered and the organic phase was concentrated in vacuo to give the crude title
product. The crude product was purified using flash silica chromatography (light petroleum/ethyl acetate, 9:1 containing 3 % acetic acid). The product fractions were concentrated in vacuo, redissolved in dichloromethane and washed with water (to remove acetic acid). The organic phase was concentrated in vacuo to afford the title compound as a brown oil (170 mg, 40 %).

Procedure 2

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{H} \\
\text{338} & \\
\text{1. TMS-CN, ZnI}_2 & \\
\text{2. HCl} & \\
\text{Ph} & \quad \text{CN} \\
\text{OH} & \quad \text{339}
\end{align*}
\]

To a solution of α-methyl trans-cinnamaldehyde (0.9 g, 6 mmol) in dichloromethane (75 ml), was added trimethylsilyl cyanide (0.9 ml, 6.6 mmol) with a few crystals of zinc iodide (catalytic). The reaction was stirred for 72 hours at room temperature. Hydrochloric acid (1 M, 40 ml) (aq) was then added and the reaction mixture was stirred for a further 24 hours. The organic phase was extracted from the aqueous, dried (magnesium sulfate), filtered and then concentrated in vacuo to give the title compound as a brown oil (0.9 g, 87 %).

Procedure 3

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{H} \\
\text{338} & \\
\text{Acetone cyanohydrin} & \\
\text{Ti(O'Pr)}_4 & \\
\text{Ph} & \quad \text{CN} \\
\text{OH} & \quad \text{339}
\end{align*}
\]

α-Methyl trans-cinnamaldehyde (132 mg, 1 mmol) was added to a flask containing acetone cyanohydrin (0.27 ml, 3 mmol) and titanium isopropoxide (0.32 ml, 0.33 g, 1.17 mmol) was added under an inert atmosphere and stirred for 24 hours at room temperature. The reaction was washed with hydrochloric acid (2M, 15 ml) (aq) and extracted with dichloromethane (2 x 10 ml). The organic phase was dried (magnesium sulfate), filtered and concentrated in vacuo to afford the title compound which contained acetone cyanohydrin (100 mg, 63 %).
(Found M$^+$, 173.0841. C$_{11}$H$_{11}$NO requires M$^+$, 173.08406); \( \nu_{\text{max}} \text{cm}^{-1} \) (thin film) 3424 (OH), 2249 (CN); \( \delta_H \) (250 MHz, CDCl$_3$) 1.99 (3H, s, C=C(CH$_3$)), 4.99 (1H, s, CH(OH) CN), 6.76 (1H, s, PhCH=C), 7.22-7.35 (5H, m, ar-CH); \( \delta_C \) (100 MHz, CDCl$_3$) 14.1 (CH$_3$, C=C(CH$_3$)), 66.9 (CH, CH(OH)CN), 118.6 (C, C=CCH$_3$), 127.6, 128.4, 129.0, 130.1 (CH, ar-CH), 131.7 (C, ar-C), 135.8 (C, CN); \( m/z \) (El) 173 (M$^+$, 100 %), 91 (100).

\( (E)-2\text{-Methyl-3-phenyl-2-propen-1-ol 351} \)

\[
\begin{array}{c}
\text{Ph} \\
\text{338} \\
\end{array}
\xrightarrow{\text{CeCl}_3\cdot7\text{H}_2\text{O, NaBH}_4} 
\begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{351} \\
\end{array}
\]

Cerium (III) chloride heptahydrate (1.4 g, 3.8 mmol) was dissolved in methanol (15 ml) to which \( \alpha\)-methyl trans-cinnamaldehyde (0.50 g, 3.4 mmol) was added. Sodium borohydride was then added slowly to the reaction solution. The reaction was followed by TLC and the reduction took place within an hour. The methanol was removed in vacuo and the reaction quenched with water (50 ml). The product was extracted with dichloromethane (2 x 50 ml) and the combined organic phases were dried (magnesium sulfate) and concentrated in vacuo to give the title compound as a yellow oil (0.4 g, 75 %).

Spectroscopic data comparable with that found in literature.$^{44}$

\( \nu_{\text{max}} \text{cm}^{-1} \) (thin film) 3333 (OH), 1664 (C=C), 1444; \( \delta_H \) (250 Mhz, CDCl$_3$) 1.54 (1H, br, OH), 1.91 (3H, s, CH$_3$), 4.19 (2H, s, CH$_2$(OH)), 6.53 (1H, s, PhCH), 7.22-7.37 (5H, m, ar-CH).
The alcohol 351 (148 mg, 1.0 mmol) was dissolved in dichloromethane (15 ml) and the resulting solution cooled to 0 °C. Meta-chloroperbenzoic acid (189 mg, 1.0 mmol) was added carefully and the reaction was left stirring at room temperature for 3 hours before being quenched with water (30 ml). The organic layer was extracted and washed with sodium hydrogen carbonate solution (30 ml) and sodium thiosulfate (30 ml). The organic phase was dried (magnesium sulfate), filtered and concentrated in vacuo to give the title product as a yellow oil (120 mg, 71 %).

Spectroscopic data comparable with that found in literature.

\( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3424, 2929, 1497, 1070 (C-O); \( \delta H \) (250 MHz, CDCl\(_3\)) 1.09 (3H, s, CH\(_3\)), 1.91 (1H, d br, \( J \) 1,OH), 3.73-3.88 (2H, m, CH\(_2\)(OH)), 4.21 (1H, s, PhCH), 7.24-7.55 (5H, m, ar-H).

**2-Methyl-3-phenyl-2-oxiranecarbaldehyde 341**

Typical experiment

Diethyl tartrate (103 mg, 0.5 mmol) was added to a flame-dried flask containing dichloromethane (1.0 ml) and lowered into a cold bath (-20 °C). Titanium isopropoxide (156 mg, 0.55 mmol) was added to the reaction mixture along with 4 mol. sieves followed by the syringe addition of a solution of tert-butyl hydroperoxide in pentane (3M) (0.67 ml, 2.0 mmol). The reaction was stirred at -20 °C for 30 minutes.
before the addition of (E)-1-hydroxy-2-methyl-3-phenyl-2-propenyl cyanide (173 mg, 1.0 mmol). After 4-48 hours of stirring, at -20 °C, water (1 ml) was added followed by ethyl acetate (1 ml) after 10 mins. Magnesium sulfate (100 mg) and Celite (100 mg) were added and the reaction mixture was stirred for a further 5 mins. The reaction mixture was then filtered through a Celite pad, eluted with ethyl acetate (100 ml) and dichloromethane (60 ml). The organic phase was concentrated in vacuo, the resulting residue was dissolved in toluene (2 x 75 ml) and concentrated in vacuo (to azeotrope tert-butyl hydroperoxide into the receiving flask). The toluene/tert-butyl hydroperoxide mixture was quenched with sodium sulfite. The product was washed with a 10 % sodium hydroxide in saturated brine solution and extracted with dichloromethane. The organic phase was dried (magnesium sulfate), filtered and concentrated to afford the title compound as a pale brown oil (121 mg, 75 %).

Spectroscopic data comparable with that found in literature.191,199

Epoxidised aldehyde
\[ \nu_{\text{max}}/\text{cm}^{-1} \] (thin film) 1730 (C=O), 890, 850 (epoxide). \[ \delta_{\text{H}}(250 \text{ MHz, CDCl}_3) \] 1.20 (3H, s, CH₃), 4.31 (1H, s, CH), 7.25-7.55 (m, ar-H), 9.09 (1H, s, CHO).

Un-epoxidised aldehyde (side product)
\[ \delta_{\text{H}}(250 \text{ MHz, CDCl}_3) \] 2.00 (3H, s, CH₃), 7.25-7.55 (m, ar-H), 9.59 (1H, s, CHO).

(E)-1-Cyano-2-methyl-3-phenyl-2-propenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 345

(\(E\))-1-Hydroxy-2-methyl-3-phenyl-2-propenyl cyanide (10 mg, 0.06 mmol) was dissolved in dichloromethane (0.3 ml) and added to a flame-dried flask. Pyridine (0.2 ml), DMAP (0.5 mg) and \(S\)-(+)\-\(\alpha\)-methoxy-\(\alpha\)-trifluoromethyl-phenylacetyl chloride (25 mg, 10 mmol) were added sequentially. The reaction was stirred overnight under an
inert atmosphere at room temperature. The resulting solution was filtered through a
silica pad. The filtrate was washed with saturated sodium hydrogen carbonate
solution and extracted with dichloromethane (2 x 15 ml). The organic phase was
further washed with water (2 x 5 ml), dried (magnesium sulfate), filtered and
concentrated in vacuo to afford the title compound as a pale brown oil (10 mg, 63 %).
The ratio of the two diastereoisomers was 1:1.

(Found M+NH+, 323.1760. C_{20}H_{19}NO_{2} requires M+NH+, 323.17594); \nu_{\text{max}}/\text{cm}^{-1} (\text{thin film}) 2952, 1760 (C=O), 1681, 1013 (C-O); \delta_{H} (250 \text{ MHz, CDCl}_3) 1.86, 2.00 (2 x 3H, s, C=C(CH}_3)), 3.55, 3.61 (2 x 3H, s, OCH}_3), 6.10, 6.13 (2 x 1H, s, CH(OR)CN), 6.83, 6.88 (2 x 1H, s, PhCH), 7.22-7.50 (10H, m, 10 x ar-H); \delta_{C} (100 \text{ MHz, CDCl}_3) 14.1, 14.3 (CH}_3, =C(CH}_3), 55.6, 55.8 (CH}_3, OCH}_3), 67.9, 68.2 (CH, CH(OR)CN), 114.4, 114.6 (C, 2 x C, =C(CH}_3), 121.5, 121.6 (C, 2 x ar-C), 124.4, 124.4 (C, 2 x ar-C), 127.1, 127.2 (C, 2 x ar-C), 127.1, 127.3 (2 x CH, ar-C), 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.7, 128.7, 128.7, 128.9, 129.0, 129.0, 129.0, 129.1 (CH, 20 x ar-CH), 130.1, 130.1 (CH, ar-C), 131.1, 131.4 (C, 2 x ar-C) 134.1, 134.4 (CH, ar-CH), 135.0 (C, C=O), 165.2, 165.3 (C, C=O), m/z (Cl) 323 (M+NH+, 55 %), 175 (100), 168 (90), 52 (50).

2-Hydroxy-2-(2-methyl-3-phenyl-2-oxiranyl)acetonitrile 340
Hydroxy(2-methyl-3-phenyl-2-oxiranyl)methyl cyanide

(E)-1-Hydroxy-2-methyl-3-phenyl-2-propenyl cyanide (100 mg, 0.6 mmol) was
dissolved in dichloromethane (5 ml) and the reaction cooled to 0°C. Meta-
chloroperbenzoic acid (130 mg, 0.75 mmol) was added carefully and the reaction was
left stirring at room temperature for 3 hours before the reaction was quenched with
water (30 ml). The organic layer was separated and washed with sodium hydrogen
carbonate solution (30 ml) and sodium thiosulfate (30 ml), then was dried
(magnesium sulfate), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (light petroleum/ethyl acetate, 5:1) to afford the title compound as a colourless oil (50 mg, 44 %).

(Found M⁺, 189.0790. C₁₁H₁₁NO requires M⁺, 189.07897); νmax/cm⁻¹ (thin film) 3424, 2246 (CN), 1063; δH (400 MHz, CDCl₃) 1.27, 1.29 (2 x 3H, s, C=C(CH₃)), 3.92 (1H, br, OH) 4.30, 4.33 (2 x 1H, s, CH(OH)), 4.60 4.63 (2 x 1H, s, PhCH), 7.28-7.46 (5H, m, ar-CH); δC (100 MHz, CDCl₃) 12.4, 12.5 (CH₃, C=C(CH₃)), 60.2, 61.2 (CH, CH) (OH)), 64.8, 65.0 (CH, PhCH), 117.2, 117.3 (C, ar-C), 126.4, 126.5 (CH, ar-CH), 128.3, 128.4, 128.4, 128.4 (CH, ar-CH) 133.5, 133.6 (C, CN) 151.2 (CH, ar-CH); m/z (El) 189 (M⁺, 1 %), 162 (30), 105 (30), 91(100).

(E)-1-Cyano-2-methyl-3-phenyl-2-propenyl acetate 353

Procedure 1

(E)-1-Hydroxy-2-methyl-3-phenyl-2-propenyl cyanide (90 mg, 0.5 mmol) was dissolved dichloromethane (5 ml). DMAP (2 mg), acetic acid (80 mg, 1.3 mmol) and acetic anhydride (80 mg, 1.0 mmol) were then added sequentially. The reaction was stirred at room temperature for 4 days. The solution was then washed with water (30 ml) and extracted with dichloromethane (2 x 30 ml). The organic layer was concentrated in vacuo to afford the title compound as pale brown oil (95 mg, 85 %).
Procedure 2

(E)-1-Hydroxy-2-methyl-3-phenyl-2-propenyl cyanide (90 mg, 0.5 mmol) was dissolved dichloromethane (5 ml). DMAP (2 mg), pyridine (79 mg, 1.0 mmol) and acetic anhydride (80 mg, 1.0 mmol) were then added sequentially. The reaction was stirred at room temperature for 4 days. The solution was then washed with water (30 ml) and extracted with dichloromethane (2 x 30 ml). The organic phase was concentrated in vacuo to afford the title compound as a pale brown oil (77 mg, 72%).

(Found M+NH4+, 233.12899. C13H13N02 requires M+NH4+, 233.1290); $\nu_{\text{max}}$/cm$^{-1}$ (thin film) 2360 (CN); $\delta_{H}$ (250 MHz, CDCl$_3$) 1.99 (3H, s, C=C(CH$_3$)), 2.16 (3H, s, C(=O)CH$_3$), 5.91 (1H, s, CH(OH)), 6.79 (1H, s, PhCH=C), 7.25-7.40 (5H, m, ar-CH); $\delta_{C}$ (100 MHz, CDCl$_3$) 14.2 (CH$_3$, C=C(CH$_3$)), 20.5 (CH$_3$, C(=O)CH$_3$), 66.6 (CH, CH(OH)CN), 115.7 (C, C=CH$_2$), 128.0, 128.3, 128.4, 129.0 (CH, 5 x ar-CH), 133.0 (C, CN), 169.0 (C, C(=O)CH$_3$); m/z (El) 233 (M+NH$_4^+$, 90 %), 175 (100), 77 (35).

1-(3-phenyl-2-oxiranyl)ethyl benzoate 350

Triethylamine (241 mg, 1.8 mmol) was added to a solution of alcohol 349 (240 mg, 1.5 mmol) and DMAP (10 mg) in dichloromethane (5 ml) and the reaction was stirred overnight. More triethylamine (82 mg, 0.6 mmol) was added and the reaction was
stirred for a further day. The reaction mixture was evaporated to dryness, dissolved in dichloromethane (50 ml) and washed with sat. sodium hydrogen carbonate solution (2 x 20 ml) and water (2 x 30 ml). The residue was purified using flash column chromatography (light petroleum/ethyl acetate, 9:1) (212 mg, 54 %).

(Found MH+, 269.1177. \( \text{C}_{17}\text{H}_{16}\text{O}_3 \) requires MH+ 269.11776); \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3063, 1719 (C=O), 1270 (CO). \( \delta_{\text{H}} \) (250 MHz, CDCl\(_3\)), 1.48, 1.50 (2 x 3H, s, CH\(_3\)), 3.15 (minor), 3.25 (major) (1H, dd, J 2.1 and 5, (O)CHCOR), 3.85 (minor), 3.96 (major) (1H, d, J 2.1, arCH(O), 5.17 (1H, dq, J 6, CHCH\(_3\))), 7.23-7.5 (5H, m, ar-H), 8.03-8.10 (5H, m, COar-H); \( \delta_{\text{C}} \) (62.5 MHz, CDCl\(_3\)) 16.3, 16.7 (2 x CH\(_3\), CH\(_3\)), 56.1, 57.1 (2 x CH, (O)CHCOR), 63.1, 63.6 (2 x CH, arCH(O)), 70.1, 70.5 (2 x CH, CHOR) 125.5, 125.6, 128.3, 128.4, 128.5, 128.6, 129.6, 129.7, 130.1 (10 x ar-CH), 133.1, 136.4 (C, 2 x ar-CH), 165.7 (C, C(=O)Ar); \( m/z \) (Cl) 269 (MH+, 100%), 131(95).

**Attempted Asymmetric Epoxidation of \( \alpha \)-Methyl trans-cinnamaldehyde**

![Chemical structure](image)

Diethyl tartrate (155 mg, 0.8 mmol) was added to a flame-dried flask containing dichloromethane (1.0 ml), titanium isopropoxide (155 mg, 0.6 mmol) and 4Å mol. sieves. A solution of tert-butyl hydroperoxide in pentane (3M) (0.7 ml, 2.0 mmol) was added slowly by syringe. Potassium cyanide (65 mg, 1 mmol), 18-crown-6 (264 mg, 1.0 mmol) and \( \alpha \)-methyl trans-cinnamaldehyde (148 mg, 1.0 mmol) were sequentially added. The reaction was stirred at room temperature for 18-48 hours. After which the mixture was washed with sodium hydrogen carbonate (20 ml) and extracted with dichloromethane (50 ml). The organic phase was dried (MgSO\(_4\)), filtered and concentrated in vacuo. NMR analysis of the crude product showed only the starting material.

*Chapter 5 Experimental*
Procedure 2

Diethyl tartrate (155 mg, 0.8 mmol) was added to a flame-dried flask with dichloromethane (1.0 ml), titanium isopropoxide (155 mg, 0.6 mmol) and 4Å mol. sieves. A solution of tert-butyl hydroperoxide in pentane (3M) (0.7 ml, 2.0 mmol) was added slowly by syringe. t-Butyl ammonium cyanide (65 mg, 1.0 mmol) and α-methyl trans-cinnamaldehyde (148 mg, 1.0 mmol) were sequentially added and the reaction was stirred at room temperature for 18-48 hours. The procedure was conducted with and without camphorsulfonic acid being present. The reaction mixture was then washed with sodium hydrogencarbonate (20 ml) and extracted with dichloromethane (50 ml). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo. NMR analysis of the crude product showed only the starting material.

(E)-cyano-2-methyl-3-phenyl-2-propenyl hydratropate

![Diagram](image)

S-Phenylpropanoic acid (250 mg, 1.7 mmol) was added to a stirring solution of alcohol 339 (243 mg, 1.7 mmol) in dichloromethane (3 ml). DMAP (20 mg, 0.17 mmol) and N,N-dicyclohexylcarbodiimide (343 mg, 1.7 mmol) were also sequentially added to this solution. A white precipitate immediately formed and the reaction was left to stir overnight, after which the precipitate was removed by filtration. The product was eluted with dichloromethane (10 ml) to give a pale brown oil (60 mg, 68%). Attempts to separate the diastereoisomers using flash column chromatography proved unsuccessful.

(Found M+NH₄⁺, 323.1760. C₂₀H₁₉NO₂ requires M+NH₄⁺, 323.17594); νmax/cm⁻¹ (thin film) 3029, 1750(C=O). δH (250 MHz, CDCl₃) 1.51, 1.53 (2 x 3H, s, C=C(CH₃), 1.74, 1.92 (2 x 3H, d, J 1.4, PhC(CH₃)H), 3.80 (2 x 1H, q, J 1.5, PhCH(CH₃)), 5.90, 5.92 (1H, s, C(CN)H), 6.64, 6.75 (1H, s, PHCH=C), 7.16-7.36 (10H, m, 10 x ar-H); δC (100 MHz, CDCl₃) 127.19 (PhCH=CH), 133.29, 134.47 (10 x ar-C), 137.02, 138.82 (2 × 3H, s, C(CN)H), 144.09, 144.32 (1H, s, C(CH₃)₃).
MHz, CDCl₃) 14.0, 14.2 (CH₃, C=C(CH₃)), 18.1, 18.3 (CH₃, PhC(CH₃)H), 45.2, 45.2 (CH, PhC(CH₃)H) 66.4, 66.8 (CH, CH(OH)CN), 115.4, 115.6 (C, =C(CH₃)), 127.4, 127.5, 127.6, 127.6, 127.8, 127.9, (CH, 6 x ar-CH), 128.2, 128.3, (C, ar-C), 128.4, 128.9, 128.9, 129.0, 132.3, 132.8 (CH, 8 x ar-CH), 135.8 (C, CN), 139.4, 139.5 (C, ar-C), 172.5, 172.5 (C, C=O); m/z (El) (M+NH₄⁺, 323, 100%), 175(30), 52(35).

(E)-4-Phenylbut-3-ene-2-ol 348

![Chemical Structure](image)

Sodium borohydride (0.3 g, 7.2 mmol) was added in small portions to stirred solution of (E)-4-phenylbut-3-ene-2-one (1 g, 6.8 mmol) in methanol (30 ml). The solution was stirred for 3 hours then evaporated to dryness. The residue was then redissolved in ethyl acetate (75 ml). The organic solution was washed with water (2 x 50 ml), dried and evaporated to dryness to afford the alcohol as a pale yellow oil (0.9 g, 90%). Spectroscopic data comparable with that found in literature.²⁰⁰

δH (250 MHz, CDCl₃), 1.25 (3H, d, J 6, CH₃), 1.66 (1H, br s, OH), 4.51 (1H, q, J 6, CHOH), 6.24 (1H, dd, J 16 and 6, =CHCH(OH)) 6.62 (1H, d, J 16, PhCH=), 7.20-7.4 (5H, m, ar-H).

3,4-Epoxy-4-phenylbutan-2-ol 349

![Chemical Structure](image)

m-Chloroperbenzoic acid was slowly added to a stirred solution of the alcohol 348 (150 mg, 1 mmol) in dichloromethane (15 ml) and the mixture was stirred for 12 hours. The reaction mixture was evaporated to dryness, dissolved in dichloromethane and washed with sat. sodium hydrogen carbonate solution (20 ml) and sodium thiosulfate (30 ml). The organic solution was dried and evaporated to dryness to afford a colourless oil (130 mg, 80%).

Chapter 5 Experimental

159
**Typical Sharpless Epoxidation Experiment**

Diethyl tartrate (516 mg, 2.5 mmol) was added to a flame dried flask containing dichloromethane (2.0 ml) and lowered into a cold bath (-20 °C). Titanium isopropoxide (710 mg, 2.5 mmol) was added to the reaction mixture along with 4 Å mol. sieves followed by the syringe addition of a solution of tert-butyl hydroperoxide in pentane (6M) (0.6 ml, 4 mmol). The reaction was stirred at -20 °C for 30 minutes before the addition of (E)-4-phenylbut-3-ene-2-ol (292 mg, 1.0 mmol). After 120 hours of stirring at -20 °C, water (2 ml) was added followed by ethyl acetate (2 ml) after 10 mins. Magnesium sulfate (200 mg) and Celite (200 mg) were added and the reaction mixture stirred for a further 5 minutes. The reaction mixture was then filtered through a Celite pad, eluted with ethyl acetate (100 ml) and dichloromethane (60 ml). The organic phase was concentrated *in vacuo* and the resulting residue dissolved in toluene (2 x 75 ml) and concentrated *in vacuo* (to azeotrope tert-butyl hydroperoxide into the receiving flask). The toluene/tert-butyl hydroperoxide mixture was quenched with sodium sulfite. The product was washed with a 10 % sodium hydroxide in saturated brine solution and extracted with dichloromethane. The organic phase was dried (magnesium sulfate), filtered and concentrated to afford the *title compound* as a pale brown oil (120 g, 75 %).

Spectroscopic data comparable with that found in literature.

$$\delta^1H (250 \text{ MHz}, \text{CDCl}_3), 1.31 \text{ (minor)}, 1.34 \text{ (major)} \ (3H, 2 \times d, J 6, \text{CH}_3), 2.1 \text{ (1H, br s, OH)}, 3.03 \text{ (major)}, 3.07 \text{ (minor)} \ (1H, dd, J 2 \text{ and } 6 \ (O)\text{CH}CO\text{H}), 3.80 \text{ (minor)}, 4.08 \text{ (major)} \ (1H, dq, J 6 \text{ and } 2, \text{CH}OH), 3.85 \text{ (minor)} \ (1H, d, J 2, \text{PhCH}), 3.96 \text{ (major)} \ (1H, d, J 2.1, \text{PhCH}), 7.30-7.39 \ (5H, m, \text{ar-H}).$$
Attempted enantioselective synthesis of (E)-1-hydroxy-2-methyl-3-phenyl-2-propenyl cyanide

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Ph} & \quad \text{H} \\
\text{CN} & \quad \text{H}
\end{align*}
\]

Literature ref. 194

Lipase from \textit{Pseudomonas fluorescens} (20 mg, 800 units) was added to a stirring solution of racemic cyanohydrin 339 (83 mg, 0.5 mmol) in dichloromethane (5 ml). Vinyl acetate (20 mg, 0.25 mmol) and acetate buffer were then added sequentially. The reaction was then stirred overnight, filtered through Celite and eluted with dichloromethane. The product was concentrated \textit{in vacuo} to give \(\alpha\)-methyl cinnamaldehyde and the cyanohydrin. The cyanohydrin was found to be racemic. The reaction was also repeated using hexane as the solvent. The cyanohydrin produced was again racemic.

\textit{Deoxygenation of alcohol 349}

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Ph} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Procedure 1 201

To a flame-dried flask containing anhydrous acetonitrile (5 ml), was added alcohol 349 (164 mg, 1.0 mmol) and sodium iodide (585 mg, 3.9 mmol). Trimethylsilyl chloride (300 mg, 1.9 mmol) was then added dropwise and the reaction was stirred at room temperature for 16 hours. The reaction gave an intractable black tar.

Procedure 2 202

To a flame-dried flask containing anhydrous acetonitrile (0.5 ml), dry THF (0.5 ml) and sodium iodide (585 mg, 3.9 mmol) and trifluoroacetic acid (0.07 ml, 1.0 mmol) were
added. After 5 minutes the alcohol 349 (164 mg, 1.0 mmol) was added and the reaction stirred at room temperature for 16 hours. No recognisable product was formed.

Procedure 3\textsuperscript{203}
Potassium iodide (832 mg, 5.0 mmol) and 18-crown-6 in acetonitrile(1 ml) were sequentially added to the alcohol 349 (80 mg, 0.5 mmol) in acetonitrile (2 ml). Tri-fluoroboroetherate (0.03 ml, 0.2 mmol) was then added and the reaction was left to stir for 48 hours. An unrecognisable product was recovered.

Procedure 4\textsuperscript{195}
To a stirred solution of the methanol (10 ml) was added the epoxide 349 (123 mg, 0.8 mmol) and potassium selenocyanide (74 mg, ) the reaction was heated at reflux for 72 hours. The reaction was cooled and the solvent evaporated. The residue was dissolved in dichloromethane (25 ml) and washed with water (2 x 20 ml). The organic phase was dried (magnesium sulfate), filtered and concentrated. The residue was purified using flash column chromatography (light petroleum/ethyl acetate, 9:1) the title compound as a colourless oil (75 mg, 68 %). Spectroscopic data comparable with literature.\textsuperscript{200}
Chapter 6

References
85. M. Clarke, unpublished results, University of Bath.


Chapter 7

Crystal Structure Data
EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula  
C₁₅H₁₅OP

Formula Weight  
290.30

Crystal Color, Habit  
yellow, block

Crystal Dimensions  
0.10 X 0.32 X 0.38 mm

Crystal System  
triclinic

Lattice Type  
Primitive

No. of Reflections Used for Unit Cell Determination (2θ range)  
25 (73.6 - 74.9°)

Omega Scan Peak Width
at Half-height  
0.43°

Lattice Parameters
  
a = 10.122(2) Å
  b = 11.050(3) Å
  c = 8.577(3) Å
  α = 103.29(3)°
  β = 107.85(3)°
  γ = 113.14(2)°

V = 769.6(5) Å³

Space Group  
P1 (#2)

Z value  
2

D_{calc}  
1.253 g/cm³

F₀₀₀  
304.00

μ(CuKα)  
15.27 cm⁻¹

B. Intensity Measurements
Diffractometer: Rigaku AFC7S
Radiation: CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator: Ni foil (factor = 9.42)
Take-off Angle: 6.0°
Detector Aperture: 9.0 mm horizontal
                13.0 mm vertical
Crystal to Detector Distance: 400 mm
Temperature: 20.0°C
Scan Type: ω
Scan Rate: 16.0°/min (in ω) (up to 4 scans)
Scan Width: (1.26 + 0.35 tan θ)°
2θ_max: 120.2°
No. of Reflections Measured: Total: 2444
                            Unique: 2292 (R_max = 0.050)
Corrections: Lorentz-polarization Absorption
             (trans. factors: 0.8420 - 1.0000)
             Decay (0.46% decline)
             Secondary Extinction
             (coefficient: 9.67393e-06)

C. Structure Solution and Refinement

Structure Solution: Direct Methods (SIR92)
Refinement: Full-matrix least-squares
Function Minimized: \( \Sigma \omega(|F_o| - |F_c|)^2 \)
Least Squares Weights: \( \frac{1}{\sigma^2(F_o)} = \frac{A_F^2}{\sigma^2(F_c)} \)
p-factor: 0.0030
Anomalous Dispersion: All non-hydrogen atoms
No. Observations (I>3.00σ(I)): 1925
No. Variables: 191
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<td>0.038 ; 0.033</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>3.92</td>
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Table 1. Atomic coordinates and $B_{iso}/B_{eq}$

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$B_{eq} = \frac{8}{3} \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha$
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The general temperature factor expression:

$$\exp(-2\pi^2(a^2U_{11}h^2 + b^2U_{22}k^2 + c^2U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

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Table 3. Bond Lengths (Å)

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Table 4. Bond Lengths (Å)

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Chapter 7 Crystal Structure Data
Table 5. Bond Angles(°)

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<td>C(11)</td>
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<td>C(13)</td>
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<td>C(13)</td>
<td>C(12)</td>
<td>121.3(3)</td>
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<td>C(15)</td>
<td>124.8(2)</td>
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<td>C(14)</td>
<td>C(19)</td>
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<td>C(14)</td>
<td>C(15)</td>
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</tr>
<tr>
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<td>C(16)</td>
<td>C(17)</td>
<td>120.1(3)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>C(18)</td>
<td>120.3(3)</td>
</tr>
<tr>
<td>C(17)</td>
<td>C(18)</td>
<td>C(19)</td>
<td>119.6(3)</td>
<td>C(14)</td>
<td>C(19)</td>
<td>C(18)</td>
<td>120.8(2)</td>
</tr>
</tbody>
</table>

*Chapter 7 Crystal Structure Data*
## Table 6. Bond Angles (°)

<table>
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<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
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<td>H(3)</td>
<td>119.3</td>
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<td>C(4)</td>
<td>H(4)</td>
<td>119.8</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>121.0</td>
</tr>
<tr>
<td>C(1)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>119.3</td>
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<tr>
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<td>C(7)</td>
<td>H(7)</td>
<td>116.4</td>
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<td>C(9)</td>
<td>H(9)</td>
<td>119.4</td>
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<td>120.3</td>
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<td>H(11)</td>
<td>120.6</td>
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<td>C(12)</td>
<td>H(12)</td>
<td>119.8</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>H(13)</td>
<td>119.5</td>
</tr>
<tr>
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<td>C(14)</td>
<td>H(15)</td>
<td>119.4</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(15)</td>
<td>H(16)</td>
<td>120.1</td>
</tr>
<tr>
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<td>C(16)</td>
<td>H(17)</td>
<td>120.0</td>
</tr>
<tr>
<td>C(16)</td>
<td>C(17)</td>
<td>H(18)</td>
<td>120.1</td>
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<tr>
<td>C(17)</td>
<td>C(18)</td>
<td>H(19)</td>
<td>119.5</td>
</tr>
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</table>

## Table 7. Non-bonded Contacts out to 3.60 Å

<table>
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<tr>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(7)</td>
<td>C(12)</td>
<td>3.481(4)</td>
<td>65502</td>
</tr>
<tr>
<td>C(7)</td>
<td>C(7)</td>
<td>3.408(7)</td>
<td>65602</td>
</tr>
</tbody>
</table>

Chapter 7 Crystal Structure Data
The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (e.g. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) \(x, \ y, \ z\)  \hspace{1cm}  (2) \(-x, \ -y, \ -z\)
Chapter 7 Crystal Structure Data
EXPERIMENTAL DETAILS

A. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C₂₀H₁₇OP</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>304.33</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>pale, needle</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.20 X 0.20 X 0.33 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>No. of Reflections Used for Unit</td>
<td></td>
</tr>
<tr>
<td>Cell Determination (2θ range)</td>
<td>25 (73.7 - 74.9°)</td>
</tr>
<tr>
<td>Omega Scan Peak Width</td>
<td></td>
</tr>
<tr>
<td>at Half-height</td>
<td>0.32°</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>9.731(4) Å</td>
</tr>
<tr>
<td>b</td>
<td>16.088(3) Å</td>
</tr>
<tr>
<td>c</td>
<td>11.089(3) Å</td>
</tr>
<tr>
<td>β</td>
<td>109.56(3)°</td>
</tr>
<tr>
<td>V</td>
<td>1635.9(9) Åb</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2₁/a (#14)</td>
</tr>
<tr>
<td>Z value</td>
<td>4</td>
</tr>
<tr>
<td>D&lt;sub&gt;calc&lt;/sub&gt;</td>
<td>1.236 g/cm³</td>
</tr>
<tr>
<td>F₀₀₀</td>
<td>640.00</td>
</tr>
<tr>
<td>μ(CuKα)</td>
<td>14.58 cm⁻¹</td>
</tr>
</tbody>
</table>

B. Intensity Measurements

| Diffractometer                  | Rigaku AFC7S                               |
Radiation

CuKα (λ = 1.54178 Å)
graphite monochromated

Attenuator

Ni foil (factor = 9.42)

Take-off Angle

6.0°

Detector Aperture

9.0 mm horizontal
13.0 mm vertical

Crystal to Detector Distance

400 mm

Temperature

20.0°C

Scan Type

ω

Scan Rate

16.0°/min (in ω) (up to 4 scans)

Scan Width

(1.05 + 0.35 tan θ)°

2θ_{max}

120.3°

No. of Reflections Measured

Total: 2710
Unique: 2546 (R_{int} = 0.018)

Corrections

Lorentz-polarization
Absorption
(trans. factors: 0.6462 - 1.0000)
Decay (0.56% decline)
Secondary Extinction
(coefficient: 1.73264e-05)

C. Structure Solution and Refinement

Structure Solution

Direct Methods (SIR92)

Refinement

Full-matrix least-squares

Function Minimized

\[ \sum w(|F_o| - |F_c|)^2 \]

Least Squares Weights

\[ \frac{1}{\sigma^2(F_o)} = \frac{4f^2}{\sigma^2(F_o)} \]

p-factor

0.0060

Anomalous Dispersion

All non-hydrogen atoms

No. Observations (I>3.00σ(I))

1958

No. Variables

200

Reflection/Parameter Ratio

9.79
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<th>Parameter</th>
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</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>3.02</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>$0.13 , \text{e}^{-}/\AA^{3}$</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>$-0.15 , \text{e}^{-}/\AA^{3}$</td>
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</table>
Table 1. Atomic coordinates and $B_{iso}/B_{eq}$

<table>
<thead>
<tr>
<th>atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$B_{eq}$</th>
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</thead>
<tbody>
<tr>
<td>P(2)</td>
<td>0.86174(6)</td>
<td>0.01502(4)</td>
<td>0.65053(6)</td>
<td>4.69(1)</td>
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<tr>
<td>O(7)</td>
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<td>0.1573(1)</td>
<td>0.5627(2)</td>
<td>6.66(5)</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.9487(3)</td>
<td>0.1836(1)</td>
<td>0.7073(2)</td>
<td>5.15(6)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.9809(2)</td>
<td>0.0994(1)</td>
<td>0.7398(2)</td>
<td>4.60(5)</td>
</tr>
<tr>
<td>C(3)</td>
<td>1.1112(3)</td>
<td>0.0819(1)</td>
<td>0.8360(2)</td>
<td>5.40(6)</td>
</tr>
<tr>
<td>C(4)</td>
<td>1.2078(3)</td>
<td>0.1435(2)</td>
<td>0.8988(2)</td>
<td>6.28(7)</td>
</tr>
<tr>
<td>C(5)</td>
<td>1.1752(3)</td>
<td>0.2251(2)</td>
<td>0.8645(3)</td>
<td>6.89(8)</td>
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<tr>
<td>C(6)</td>
<td>1.0472(3)</td>
<td>0.2444(1)</td>
<td>0.7702(3)</td>
<td>6.28(7)</td>
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<tr>
<td>C(7)</td>
<td>0.8094(3)</td>
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<td>0.5587(3)</td>
<td>8.54(9)</td>
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<tr>
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<td>6.78(8)</td>
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<tr>
<td>C(12)</td>
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<tr>
<td>H(3)</td>
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</tr>
<tr>
<td>H(4)</td>
<td>1.2963</td>
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<td>0.9652</td>
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Table 1. Atomic coordinates and $B_{eq}$ (continued)

<table>
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<th>atom</th>
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<th>y</th>
<th>z</th>
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</thead>
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<tr>
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<tr>
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<tr>
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<td>7.2272</td>
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<tr>
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<tr>
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<tr>
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<td>H(20)</td>
<td>1.0925</td>
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<td>6.6736</td>
</tr>
</tbody>
</table>

$B_{eq} = \frac{8}{3} \pi^2 (U_{11} (aa^*)^2 + U_{22} (bb^*)^2 + U_{33} (cc^*)^2 + 2U_{12} aa^* bb^* \cos \gamma + 2U_{13} aa^* cc^* \cos \beta + 2U_{23} bb^* cc^* \cos \alpha)$
Table 2. Anisotropic Displacement Parameters

<table>
<thead>
<tr>
<th>atom</th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{12}$</th>
<th>$U_{13}$</th>
<th>$U_{23}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(2)</td>
<td>0.0629(4)</td>
<td>0.0517(4)</td>
<td>0.0678(4)</td>
<td>-0.0010(3)</td>
<td>0.0277(3)</td>
<td>0.0022(3)</td>
</tr>
<tr>
<td>O(7)</td>
<td>0.082(1)</td>
<td>0.069(1)</td>
<td>0.094(1)</td>
<td>0.0037(9)</td>
<td>0.019(1)</td>
<td>0.0107(10)</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.074(2)</td>
<td>0.051(1)</td>
<td>0.078(2)</td>
<td>-0.002(1)</td>
<td>0.034(1)</td>
<td>0.005(1)</td>
</tr>
<tr>
<td>C(2)</td>
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<td>0.052(1)</td>
<td>0.067(1)</td>
<td>-0.002(1)</td>
<td>0.028(1)</td>
<td>0.003(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>0.069(2)</td>
<td>0.056(1)</td>
<td>0.082(2)</td>
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<td>0.027(1)</td>
<td>0.001(1)</td>
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<tr>
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<td>0.021(1)</td>
<td>-0.006(1)</td>
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<td>0.107(2)</td>
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<td>0.026(2)</td>
<td>-0.068(2)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.094(2)</td>
<td>0.053(1)</td>
<td>0.093(2)</td>
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<td>0.003(1)</td>
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<tr>
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<td>0.092(2)</td>
<td>0.056(2)</td>
<td>0.079(2)</td>
<td>0.010(1)</td>
<td>0.038(2)</td>
<td>0.009(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.140(3)</td>
<td>0.063(2)</td>
<td>0.108(2)</td>
<td>0.015(2)</td>
<td>0.024(2)</td>
<td>0.021(2)</td>
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<tr>
<td>C(9)</td>
<td>0.057(1)</td>
<td>0.051(1)</td>
<td>0.071(1)</td>
<td>0.005(1)</td>
<td>0.027(1)</td>
<td>0.008(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.080(2)</td>
<td>0.060(1)</td>
<td>0.081(2)</td>
<td>0.004(1)</td>
<td>0.038(1)</td>
<td>0.004(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.105(2)</td>
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The general temperature factor expression:

$$\exp(-2\pi^2(a^2U_{11}h^2 + b^2U_{22}k^2 + c^2U_{33}l^2 + 2ab^*U_{12}hl + 2ac^*U_{13}kl + 2bc^*U_{23}kl))$$
Table 3. Bond Lengths (Å)

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### Table 7. Non-bonded Contacts out to 3.60 Å

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The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a-axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) \(X, \ Y, \ Z\)  \hspace{1cm} (2) \(1/2-X, \ 1/2+Y, \ -Z\)
(3) \(-X, \ -Y, \ -Z\)  \hspace{1cm} (4) \(1/2+X, \ 1/2-Y, \ Z\)