Catalytic And Selective Transition Metal Mediated Isomerisations Of Allylic Alkoxides To Enolates

A Thesis Presented By

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In Partial Fulfilment of The Requirements
For The Award of The Degree of

Doctor of Philosophy
of the
University of London

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December 1997
Abstract

The thesis is split into three chapters. The first chapter, the introduction, presents a broad review on enantioselective transfer hydrogenation reactions of organic compounds catalysed by transition metals, and their application in the asymmetric reduction of ketones, imines and activated carbon-carbon double bonds. Emphasis will be placed on mechanistic aspects, in addition to the effect of substrate and ligand architecture on the stereochemical outcome of the reaction. The second chapter will discuss a series of investigations into the application of transition metals in the catalysis of allylic alkoxides to metal enolates in a stereo, regio and enantioselective manner. This catalytic process represents a novel preparation of metal enolates which differs from the traditional approach utilising carbonyl compounds. The third and final chapter will involve a formal description of the experimental procedures that make up the results presented in chapter two.

Several nickel based catalyst systems were investigated which had the potential for use as asymmetric catalysts, by simple replacement of the pre-existing ligands with chiral ligands. The Ni(COD)$_2$/Ligand catalyst system demonstrated a greater activity than the NiCl$_2$(Ligand) based catalyst system, and was therefore studied in greater depth. Excellent stereocontrolled enolate formation was demonstrated when using either benzene as solvent, or using pyridine as ligand, particularly when using a primary allylic alkoxide as substrate. These conditions, however, did not lead to significant improvements in stereoselectivity in tetrasubstituted enolate formation, although there was an exception with the alkoxide of (E)-2-methyl-1-phenyl-2-buten-1-ol, in which an (Z) : (E) enolate ratio of 5 : 1 was obtained. It was also found that both the Ni(COD)$_2$/Ligand and NiCl$_2$(Ligand) catalyst systems demonstrated poor regiocontrol, where enolate regioisomers were possible.

A range of prochiral allylic alkoxide substrates was tested using Ni(COD)$_2$ in combination with a chiral ligand, but enantiomeric excesses in the isomerised products were not detected by chiral shift $^1$H-NMR, or by chiral GC. This lack of asymmetric induction is attributed to a number of possible factors, discussed here in detail. An investigation using deuterium isotopic labelling was also conducted in order to elucidate the possible mechanistic pathways in operation with the nickel catalyst.

Rhodium as a catalyst was also investigated, and interesting results were obtained following an attempt to repeat a reported procedure in which an allylic alcohol was isomerised enantioselectively using a chiral rhodium catalyst. Modification of this catalyst by the addition of n-BuLi, afforded the first rhodium catalyst which was able to perform an isomerisation on the alkoxide of geraniol, in good yield. No enantiomeric excess in the product was detected, and discussions will be presented to account for this observation.
Contents

Abstract i
Contents ii
Abbreviations iv
Stereochemical Notation vi
Acknowledgements vii

Chapter One: Asymmetric Transfer Hydrogenation Reactions Promoted by Chiral Homogeneous Ruthenium, Iridium and Rhodium Complexes

Introduction 2
Transfer hydrogenation 2
Chiral ruthenium catalysis 7
Chiral iridium catalysis 19
Chiral rhodium catalysis 25
Mechanistic studies 32
Conclusions 42

Chapter Two: Results and Discussion

Enolate formation 45
Isomerisation of allylic alcohols 46
New approach to enolate chemistry 52
Mechanistic overview 53
Aims of the project 59
Isomerisations with non-chiral Ni(II) complexes
  introduction 61
  Initial studies 68
  Studies on regiocontrol 71
  Attempted isomerisations of prochiral allylic alkoxides 75
Isomerisations with chiral Ni(0) complexes
  Introduction 81
  Use of chiral phosphine ligands 84
  Chiral nitrogen ligands 85
  Enantioselective isomerisations of other allylic alkoxides 100
Modifications of the isomerisation reaction
  Introduction 111
  Solvent effects 111
  Counter cations 114
  Co-catalysis 117
Isomerisations with non-chiral Ni(0) complexes

Introduction 123
Isomerisation of primary allylic alkoxides 123
Isomerisation of secondary allylic alkoxides 127
Potential synthetic applications 135
Isomerisation of allylic amines 137
Studies on regiocontrol 138

Mechanistic studies

Introduction 141
Isomerisation of simple deuterated substrates 142
Isomerisation of deuterated prochiral substrates 144

Isomerisations with chiral Ni(II) complexes

Introduction 153
Use of pyridine as ligand 153
Use of bis(oxazoline) as ligand 154

Isomerisations with Rh(I) complexes

Introduction 157
Isomerisations with chiral BINAP ligands 157
Isomerisations with bis(oxazoline) as ligand 168

Conclusions and Perspectives

Conclusions and perspectives 173

Chapter Three: Experimental Section

General procedures 177
Standard procedure for degassing 179
Standard procedures for quench and work-up 179
Preparation of the catalyst solutions 180
Standard procedure for the isomerisation reaction 180
Substrate preparation 181
Ligand preparation 205
Isomerisations using NiCl₂(DIPHOS)/PrMgCl 219
Isomerisations using NiCl₂(DIPHOS)/LiBEt₃H or NiCl₂(DIPHOS)/KBEt₃H 220
Isomerisations using Ni(COD)₂ 227
Isomerisations using NiCl₂(Ligands) 258
Isomerisations using [Rh(COD)BINAP]*ClO₄⁻ 262
Isomerisations using [Rh(Ligands)]⁺ 265

References 271
Abbreviations

A = Hydrogen acceptor molecule; e.g. acetophenone
Ac = Acetyl
acac = Acetylacetonate (2,4-Pentane dione anion)
AH₂ = Reduced hydrogen acceptor molecule; e.g. using acetophenone as A, then AH₂ is 1-phenylethanol
AIBN = Azaisobutyronitrile
Ar = Undefined aromatic group
BBN = 9-Borabicyclo[3.3.1]non-9-yl
BDPOP = 2,4-Bis[(diphenylphosphino)oxo]pentane
BHT = 2,6-Di(t-butyl)-4-methylphenyl
BINAP = (R or S)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bis(oxazoline) = 2,2'-Bis[(4S)-4-(alkyl or aryl)-1,3-oxazoline-2-yl]-propane or 4,4'-di(alkyl or aryl)-2,2'-bis(oxazoline)
BMPP = Benzylmethylphenylphosphine
Bn = Benzyl
BPDODP = [(Diphenylphosphino)oxy]-1,3-diphenylpropane
BPPFA = N,N-Dimethyl[1-(2-[diphenylphosphino]ferroceny1)ethyl]amine
BPPP = N-(Butoxycarbony1)-4-[(diphenylphosphino)methyl]pyrrolidine
br = Broad
Bu = Butyl
CHIRAPHOS = (R or S)-2,3-Bis(diphenylphosphino)butane
COD = Cyclooctadiene
COE = Cyclooctene
Cy = Cyclohexyl
D = Deuterium
d = Doublet
D = Oxidised donor molecule; using propan-2-ol as DH₂, then D is acetone
DCM = Dichloromethane
DH₂ = Hydrogen donor molecule; e.g. propan-2-ol
DIBAL = Diisobutylaluminium hydride
DIOP = (R or S) 1,2-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPHOS = 1,2-Bis(diphenylphosphino)ethane
DME = 1,2-Dimethoxyethane
DMF = N,N-Dimethylformamide
DMPP = Dimethylphenylphosphine
DMSO = Dimethylsulfoxide
E° = Redox potential
ee = Enantiomeric excess
equiv = Molar equivalents
Et = Ethyl
FOD = 6,6,7,7,8,8,8-Heptfluoro-2,2-dimethoctane-3,5-dione anion
GC = Gas Chromatography
GCMS = Gas Chromatography Mass spectroscopy
h = Hour(s)
H = Hydrogen
HD = 1,5-Hexadiene
HMPA = Hexamethylphosphoramide
HPLC = High Performance Liquid Chromatography
HRMS = High Resolution Mass Spectroscopy
\( l \) = Iso
IR = Infra-red Spectroscopy
k = Rate constant
L = Any ligand; (L-L is specifically a bidentate ligand)
LDA = Lithium Diisopropylamine
lit. = Literature value
LRMS = Low Resolution Mass Spectroscopy
m = Multiplet
M = Undefined metallic element
m.p. = Melting point
MDPP = Menthyldiphenylphosphine
Me = Methyl
mesityl = 2,4,6-trimethylphenyl
n = Neo
n = Number of ligands
NAD = Nicotinamide adenine dinucleotide
NADH = Reduced form of nicotinamide adenine dinucleotide
NBD = Norbornadiene
NMDPP = Neomenthyldiphenylphosphine
NMR = Nuclear Magnetic Resonance Spectroscopy
NORPHOS = 2(Exo),3(endo)-bis(diphenylphosphino)-bicyclo[2.2.1]heptene
p = Prochiral
PCC = Pyridinium chlorochromate
Ph = Phenyl
Pr = Propyl
PROPHOS = (R or S) 1,2-Bis(diphenylphosphino)propane
pTSA = para-Toluenesulfonyl chloride (4-methylbenzenesulfonyl chloride)
py = Pyridine
r = Racemic
R = Undefined alkyl group
s = Singlet
t = Tert
t = Triplet
t' = Triplet of peaks in the ratio 1:1:1
TBDMS = t-Butyldimethylsilyl
TDA = Tris[2-(2-methoxyethoxy)ethyl]aniline
TEAF = Triethylammonium formate
Tf = Trifluoromethanesulfonyl
Tfc = (+)-Trifluoroacetylcamphorate
THF = Tetrahydrofuran
TLC = Thin layer chromatography
TMS = Trimethylsilyl
Stereochemical Notation

The stereochemistry of compounds is illustrated graphically following the conventions of Maehr.\(^1\) Thus bold type is used to represent bonds towards the observer relative to the page, and dashed bonds to represent bonds away from the observer. Diastereomeric compounds are represented using bold and dashed lines when racemic, and bold and dashed wedges when homochiral.

![Racemic and Homochiral Structures](image-url)
Acknowledgements

I would like to especially thank: my supervisor, Professor Willie Motherwell for his continued support, encouragement and friendship over the last three years; Cathy, Diyan, Kamal, Kit, Matt, Mike and Tilly for their time to proof read this thesis; and to the technical staff at the Christopher Ingold Laboratories for their services, especially Gill Maxwell (NMR), Mike Cocksedge (Mass Spec. at the School of Pharmacy) and John Hill (GCMS).

Special thanks also to all the people, past and present, who have made working on the 4th floor a sheer delight, especially Adrian, Alvin, Ashley, Caroline, Cathy, Diyan, Donogh, Ellen, Eric B., Eric F., Jean-Marc, Kamal, Kit, Letitia, Lewis, Man-Tat, Maria, Marta, Martin, Matt, Mike, Mila, Najeeb, Nicola, Pete, Phill, Pierre, Richard, Rima, Robyn, Rodney, Sheena, Sylvan, Tilly, Tim, Yui-Fai and Zena, to name but a few...

A big hearty thanks also goes to the members of Side-Show-Bob, for introducing me to the delights of numerous pubs in the London area, especially around Camden. And the GC, what can I say? I hope that my successor will be able to continue to manage this very lively operation in the same way that I was able to.

And finally, I'd like to offer my sincerest thanks to my family and close friends who have always been there when I have needed them.
Chapter 1

Asymmetric Transfer Hydrogenation Reactions Promoted by Chiral Homogeneous Ruthenium, Iridium and Rhodium Complexes
Introduction

The work described in this thesis involves the development of a novel approach to the preparation of enolate anions in a regio-, stereo- and enantio-controlled fashion, brought about by the transition metal-mediated isomerisation of allylic alkoxide substrates. The mechanism through which this transformation is believed to proceed bears a close resemblance to an area of chemistry referred to as transfer hydrogenation, whereby an organic substrate is oxidised in order to reduce a different organic compound. Thus, the isomerisation of an allylic alcohol can be formally viewed as an intramolecular transfer hydrogenation process.

There have been many reports in recent years in which high levels of asymmetric induction have been achieved for the transfer hydrogenation reaction of activated double bonds, such as carbonyls, α,β-unsaturated carbonyls and acids. The following survey provides a review of the most significant results obtained so far in this field of study.

Transfer hydrogenation

A technique which has received increasing attention in recent years is the use of transition metals to catalyse the reduction of organic compounds via transfer hydrogenation. Transfer hydrogenation differs from conventional hydrogenation techniques in that the source of the hydrogen is from another organic molecule, rather than molecular hydrogen. The hydrogen source, or H-donor ($DH_2$), is oxidised as the hydrogen is delivered to reduce the substrate molecule, or H-acceptor (Figure 1).

\[
\begin{align*}
R_1 & \quad + \quad DH_2 \\
\text{Hydrogen Acceptor} & \quad \xrightarrow{\text{Catalyst}} \quad R_2 \\
X = \text{CR}_2, \text{O}, \text{NR}_2 \\
\text{Hydrogen Donor} & \\
\text{H} & \\
\end{align*}
\]

Figure 1

In an industrial environment, biological hydrogen sources, such as the reduced form of nicotinamide adenine dinucleotide, or NADH, are impractical, thus other sources of hydrogen have been developed for this purpose. For example, unsaturated hydrocarbons such as cyclohexene or cyclohexadiene, primary and secondary alcohols such as methanol, benzyl alcohol, or propan-2-ol, and formic acid and its salts have all been used as sources of hydrogen. Inorganic reagents, such as hydrazine, have been used less frequently, and will not be discussed any further (Figure 2).
The Meerwein-Ponndorf-Verley reduction of carbonyl compounds by means of Al(O\text{Pr})\text{\textsubscript{3}} and propan-2-ol as a hydrogen source is a classic example of transfer hydrogenation in operation (Figure 3).

In comparison with catalytic reductions using molecular hydrogen, there are advantages using transfer hydrogenation as a method of reduction. The former requires the use of a gas that is highly inflammable and therefore hazardous, particularly on a large scale. The use of H-donors
obviates these difficulties in that gas containment is not necessary and simple mechanical stirring of solutions is usually all that is required. With a catalyst and molecular hydrogen, changes in catalyst, solvent, pressure and temperature are variables in the reaction, but with H-donors, an additional variable is introduced in the choice of H-donor which can affect the rate and specificity of the reduction.

The most popular H-donors are alcohols. According to their relative oxidation potentials, secondary alcohols are better H-donors than primary ones, however both have been successfully employed in the reduction of ketones. Among the secondary alcohols, propan-2-ol is the reagent of choice because it has an appropriate boiling point and solubility properties, and upon dehydrogenation affords acetone, a low boiling liquid which can be easily removed from the reaction mixture. The use of propan-2-ol, however, does have some inherent chemical problems.

Formic acid and its salts, such as triethylammonium formate (TEAF), have proved to be useful sources of hydrogen as dehydrogenation is an irreversible and exothermic process, which usually overwhelms the energetic requirements of the reduction process.

There are several ways to effect an enantioselective hydrogen transfer and, according to a classification scheme introduced several years ago, the following basic types can be distinguished (*Figure 4a and b*).

\[
\begin{align*}
\text{DH}_2 + \text{A(p)} & \xrightarrow{\text{Chiral catalyst}} \text{D} + \text{AH}_2^* \\
\text{DH}_2^* + \text{A(p)} & \xrightarrow{\text{Catalyst}} \text{D(p)} + \text{AH}_2^* \\
\text{DH}_2^* + \text{A(p)} & \xrightarrow{\text{Chiral catalyst}} \text{D(p)} + \text{AH}_2^*
\end{align*}
\]

*Figure 4a*

The most common way to accomplish an asymmetric hydrogen transfer is through enantiofacial discrimination. The chiral information may reside on the metal catalyst (*Equation 2*), the H-donor (*Equation 3*) or on both (*Equation 4*). The majority of the reactions detailed in this review fall within these three reaction types.
Enantiomeric enrichment of racemic H-donors, i.e. kinetic resolution, can take place in the presence of chiral catalysts (Figure 4b, Equation 5) and this has been observed in several instances.\textsuperscript{6}

\[ \text{Chiral Catalyst} \quad \begin{array}{c}
2 \text{DH}_2(r) + A \\
\rightarrow \text{DH}_2^* + D(p) + \text{AH}_2^* \end{array} \quad (5)
\]

\[ \text{Chiral Catalyst} \quad \begin{array}{c}
\text{DH}_2 + 2A(r) \\
\rightarrow D + \text{AH}_2^* + A^* \end{array} \quad (6)
\]

\[ \text{Chiral Catalyst} \quad \begin{array}{c}
2 \text{DH}_2(r) + A(p) \\
\rightarrow \text{DH}_2^* + D + \text{AH}_2^* \end{array} \quad (7)
\]

These reactions are particularly interesting since, when the appropriate experimental conditions are met, kinetic resolution and enantioselective reduction may occur simultaneously, producing two different optically active compounds in a single reaction, i.e. chiral H-donor and the chirally reduced alcohol product. There are two ways to achieve this goal in the presence of a chiral catalyst: either by reducing racemic H-acceptor, \( A(r) \), with a deficit of H-donor (Equation 6), or by reacting an excess of racemic H-donor, \( D(r) \), with a prochiral H-acceptor (Equation 7).

From a mechanistic point of view, two general reaction paths can be envisaged for hydrogen transfer to occur: either via a concerted process referred to as \textit{Direct hydrogen transfer} (Figure 5a), or via a stepwise process, referred to as the \textit{Hydridic route} (Figure 5a).

\[ \text{HO} \quad \begin{array}{c}
+ \text{LnM} \\
\rightarrow \text{H-LnM} \quad + \\n\rightarrow \text{LnM} \quad - \text{H}^+ \end{array} \quad \text{Figure 5a} : \text{Direct Hydrogen Transfer. A = hydride acceptor, e.g. ketone, etc.} \]

\[ \text{O} \quad \begin{array}{c}
+ \text{AH}_2 \quad \} \\
\rightarrow \text{H-LnM} \quad - \\n\rightarrow \text{LnM-A} \quad + \text{H}^+ \end{array} \]
The Direct Hydride Transfer route implies that hydrogen is transferred from the H-donor to the H-acceptor, A, in a concerted process where both the H-donor and H-acceptor are held in close proximity to each other, involving a cyclic transition state similar to that proposed during the Meerwein-Ponndorf-Verley reduction. The Hydridic Route involves the intermediate formation of a metal hydride derivative by interaction of the catalyst with the H-donor, followed by hydride delivery from the metal to substrate A.

If a Hydridic Route is in operation, then enantiofacial discriminating reactions of the type in Equation 4 should be only marginally affected by chiral H-donors. Reactions of the type shown in Equation 3 should in principle yield chiral products. In contrast, enantiomer discriminating reactions of the type shown in Equation 5-7 should always lead to optically active products, irrespective of the reaction mechanism.

The most efficient and economical method to perform an asymmetric hydrogen transfer is by means of an enantiomerically pure catalyst. Transition metals such as cobalt\(^7,8\) and palladium\(^9,10\) have been used to catalyse the transfer hydrogenation reduction of activated unsaturated centres, however much of the effort in achieving this transformation asymmetrically, employed the use of ruthenium(II), iridium(I) and rhodium(I) complexes chelated with chiral phosphorus and nitrogen based ligands. High levels of asymmetric induction using these systems have been obtained, and it is these achievements that will form the basis for the rest of this introduction.
Introduction

Chiral Ruthenium Catalysis

Reduction of Prochiral Ketones

The potential for the asymmetric reduction of prochiral ketones via transfer hydrogenation has been of great interest since this process was first reported in 1980. Very low optical yields were obtained using [H₄Ru₄(CO)₈((−)-DIOP)₂] as a preformed catalyst with propan-2-ol or benzyl alcohol as the source of hydrogen. Aryl-alkyl ketones gave consistently better enantiomeric excesses than dialkyl ketones, with the best result obtained using PhCO(i-Pr) (10% ee) (Figure 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (hours)</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCOMe</td>
<td>111</td>
<td>35%</td>
<td>4% (S)</td>
</tr>
<tr>
<td>2</td>
<td>PhCOEt</td>
<td>139</td>
<td>44%</td>
<td>5% (S)</td>
</tr>
<tr>
<td>3</td>
<td>PhCO(i-Pr)</td>
<td>86</td>
<td>37%</td>
<td>10% (S)</td>
</tr>
<tr>
<td>4</td>
<td>PhCO(t-Bu)</td>
<td>283</td>
<td>36%</td>
<td>7% (S)</td>
</tr>
<tr>
<td>5</td>
<td>MeCOPr</td>
<td>408</td>
<td>27%</td>
<td>&lt;1% (R)</td>
</tr>
<tr>
<td>6</td>
<td>MeCO(t-Bu)</td>
<td>476</td>
<td>22%</td>
<td>2% (S)</td>
</tr>
</tbody>
</table>

In 1991 Backvall and Chowdhury showed that 0.1 mol% of the complex (Ph₃P)₃RuCl₂ was an effective catalyst for the hydrogen transfer reduction of ketones. This discovery has led to the development of several asymmetric processes which use this ruthenium catalyst modified with chiral ligands, a variety of which will be discussed.

In recent years, the design of so-called hemilabile ligands containing one functional group strongly bound to a late transitional metal and another coordinatively labile one has been of considerable interest and developed by several groups. The weakly bound functional group plays the role of an intramolecular solvent molecule assuring the stability of the complex and possibly improving its catalytic activity. This concept was applied by Mathieu and co-workers to tridentate ligands which were expected to exert more stereocontrol around the coordination sphere of the metal than bidentate ligands. The ligand 1-(diphenylphosphino)-2-ethoxy-1-(pyrid-2-yl)ethane was prepared and treated with one equivalent of (Ph₃P)₃RuCl₂ to form the complex (1) (Figure 7). This complex was found to be an efficient catalyst for the asymmetric
transfer hydrogenation reduction of acetophenone, affording \((R)-1\)-phenylethanol in up to 60% ee. Complex (2) offered at most only 12% ee.

![Figure 7](image)

The use of the \(C_2\)-symmetric tridentate ligand, \((1R,1'R)-2,6\)-bis\([1\)-(diphenylphosphino)ethyl\]pyridine (3) was found to be effective in the asymmetric reduction of a variety of ketones in the presence of the catalyst, \([\text{RuCl}_2(\text{C}_6\text{H}_6)]_2\), with 74% as the highest enantiomeric excess obtained (Figure 8).\(^{17}\)

![Figure 8](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Base</th>
<th>Time</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCOMe</td>
<td>NaOMe</td>
<td>24 hours</td>
<td>67%</td>
<td>48% ((R))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NaH</td>
<td>24 hours</td>
<td>93%</td>
<td>40% ((R))</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>NaOMe</td>
<td>24 hours</td>
<td>33%</td>
<td>74% ((R))</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>NaOMe</td>
<td>24 hours</td>
<td>92%</td>
<td>42% ((R))</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>NaOMe</td>
<td>24 hours</td>
<td>98%</td>
<td>30% ((R))</td>
</tr>
</tbody>
</table>
Reports by Noyori and co-workers (see later) postulated that the NH moiety in some ligands, e.g. ligand (4) (Figure 9) played a pivotal role in controlling the reaction selectivity and activity, by hydrogen bonding with the oxygen atom in ketone substrates. The NH functionality was considered to help stabilise the cyclic transition state during the step where the stereochemistry was established.

Promoted by these reports, Zhang and co-workers designed ligands (5), (6) and (7) for use in the transfer hydrogenation on a variety of aryl alkyl and dialkyl ketones. A maximum of 80% ee was achieved for the quantitative reduction of PhCO(f-Bu) in propan-2-ol catalysed by [RuCl₂(C₆H₆)]₂ in the presence of the ligand (7) (n=2). Interestingly, the reduction of pinacolone, MeCO(f-Bu), was achieved in 92% yield and in 49% ee using the ligand (5). The optical yield was found to increase by 12% by repeating the reaction in the presence of 0.1M PhCH(OH)CH₃ with 12% ee (R). The increase was speculated to be attributed to the lower redox potential of acetophenone compared to pinacolone, hence the complex was catalysing the dehydrogenation of 1-phenylethanol more efficiently than that of the chiral MeCH(OH)(f-Bu) product. As a result, erosion of the enantiomeric excess due to the reverse process of hydrogen transfer from the product was reduced, thus affording the transfer hydrogenated product with a higher optical yield.

Knochel recently reported the use of new C₂-symmetrical diaminoferrocenyl derivatives (8) and 2-amino(sulfonamido)cyclohexanes (9) as highly active ligands for the ruthenium catalysed asymmetric transfer hydrogenation of ketones (Figure 10).
Contrary to many existing catalyst systems, the ligands (8) were found to exhibit high activity at 25°C and operate even at -30°C, with up to 90% ee. Ligands (9) were found to offer quantitative conversions and up to 96% ee using triethylammonium formate at 30°C.

Ligand (10) (Figure 11), developed by Sammakia and Stangeland, was also found to be an effective catalyst and was able to reduce a variety of ketones with optical yields generally over 90% ee.$^{21}$

Several experiments were conducted that were designed to elucidate the structure of the active catalytic species in the reaction. A phosphine free catalyst was prepared by the addition of the ferrocenyl ligand to RuCl$_3$·3H$_2$O, the precursor in the literature preparation of (Ph$_3$P)$_3$RuCl$_2$. This catalyst was found to be much less active than the (Ph$_3$P)$_3$RuCl$_2$/(10) catalyst, affording 1-phenylethanol in only 9% ee. Interestingly, the selectivity could be largely restored by the addition of Ph$_3$P, as illustrated below (Figure 12).

Reduction of acetophenone with the phosphine free catalyst afforded the (S) enantiomer of 1-phenylethanol, the opposite to what was observed with the (Ph$_3$P)$_3$RuCl$_2$/(10) catalyst. On
adding Ph₃P and p-methyacetophenone, the p-methyacetophenone was reduced to the \((R)\) enantiomer of the carbinol in 80% ee, indicating that the Ph₃P is bound to the metal in the stereochemistry determining step.

Similar levels of asymmetric induction were achieved using chiral thiourea ligands, developed by Lemaire and co-workers. Using two equivalents of ligand (11) in the presence of \([\text{RuCl}_2(\text{C}_6\text{H}_6)]_2\), up to 94% ee was achieved in the asymmetric reduction of 2-methyl-1-phenyl-propan-1-one (Figure 13).

The excellent catalytic performances of amine-based transition metal complexes as well as the effectiveness of certain \(C_2\)-symmetrical ligands prompted Noyori and co-workers to develop new chiral Ru(II) complexes with well shaped \(C_2\)-chiral ligands, in addition to developing non-phosphine-based chiral ruthenium catalysts due to the greater number of structural permutations (Figure 14).
These new catalyst systems were found to be very effective in the reduction of a variety of aryl-substituted acetophenones, some of which are listed below (Figure 15).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>Hydrogen Donor and Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Propan-2-ol + (12)²²</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>93% (R, 93%)</td>
</tr>
<tr>
<td></td>
<td>Et</td>
<td>78% (R, 96%)</td>
</tr>
<tr>
<td></td>
<td>i-Pr</td>
<td>93% (S, 5%)</td>
</tr>
<tr>
<td></td>
<td>t-Bu</td>
<td>-</td>
</tr>
<tr>
<td>o-Cl</td>
<td>99% (R, 94%)</td>
<td>99% (S, 89%)</td>
</tr>
<tr>
<td>m-Cl</td>
<td>95% (S, 94%)</td>
<td>-</td>
</tr>
<tr>
<td>p-Cl</td>
<td>-</td>
<td>22% (R, 40%)</td>
</tr>
<tr>
<td>p-OMe</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CH₂</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(CH₂)₂</td>
<td>-</td>
<td>62% (S, 94%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>93% (S, 98%)</td>
</tr>
</tbody>
</table>

Figure 15: Product yield (configuration, ee)

The catalytic reduction of acetophenone derivatives proceeds at room temperature using 0.5 mol% of catalyst and 0.5 mol% of Me₂CHOK as co-catalyst. The rate and enantioselectivities were found to be sensitive to steric crowding of the substrates as well as the electronic properties of the ring substituents. The use of ethanolamine as a ligand led to a marked increase in the reaction rate. Chiral ligands based on this structure were therefore developed and catalyst systems such as (13) and (15) were found to offer consistently higher enantiomeric excesses.

The overall efficiency of the transfer hydrogenation reaction is strongly affected by the structures of the ketone, substrates and the properties of the H-donors as well as the reaction conditions. The reversibility of the process results in the formation of an equilibrium between the starting ketone and the reduced alcohol product, the point of which is determined by the redox potentials of the H-donors and H-acceptors present in the reaction mixture. Therefore p-methoxyacetophenone and 2,3-benzo-2-cycloalkenones which have low oxidation potentials remain difficult to reduce with a high yield and satisfactory enantioselection. In order to minimise the reverse reaction it is necessary to dilute the substrate concentration as low as 0.1M, as the calculated 1-phenylethanol : acetophenone equilibrium ratio in a 0.1, 1.0, 2.0 and 10M propan-2-ol solution decrease from 98:2 to 80:20, 70:30 and 37:63 respectively. The equilibrium point
could be shifted by the continuous removal of acetone, however this was found to be technically
difficult.

Despite the reaction reversibility being the greatest flaw in the reduction using propan-2-ol as the 
H-donor, this tendency has however been utilised for the kinetic resolution of secondary alcohols 
by dehydrogenative oxidation. Thus racemic 1-phenylethanol was found to be enriched by up to 
11% enantiomeric excess when heated at 165°C with 1,3-diphenyl-2-propen-1-one as the H-
acceptor, in the presence of chiral Ru(II)/chiral phosphine complexes (Figure 16).^2^8

Far superior enantiomeric excesses of 1-phenylethanol were obtained with the chiral 
Ru(II)-diamine complexes by Noyori and co-workers. Thus, when a 2.0M solution of a racemic 
alcohol in acetone containing 0.2 mol% of the complex (16) was allowed to stand at 28°C for 36 
hours, the \((S)\) enantiomer was consumed preferentially to recover the \((R)\) enriched enantiomer 
(17) in approximately 50% yield and up to 99% enantiomeric excess (Figure 17).^2^9
This ruthenium catalysed asymmetric reaction using acetone as the hydrogen acceptor provides a chemical analogue to the biological oxidation of alcohols using the enzyme alcohol dehydrogenase and NAD$^+$.

The use of formic acid, which can be viewed as an adduct of H$_2$ and CO$_2$, involves an irreversible decomposition which would effect the transfer hydrogenation reaction with complete enantioselectivity and, in principle, 100% conversion, overcoming some of the reversibility problems encountered with propan-2-ol. Its use in asymmetric ketone reduction however has remained elusive due to the lack of suitable transition metal catalysts, however Noyori and co-workers screened several catalysts and ligands and revealed that the chiral ruthenium complex (12) (Figure 15, column 6) offered very high chemical and optical yields.

When compared with alcohols, formic acid is favoured as sterically congested ketones were readily reduced in greater yield and enantiomeric excess. Even low oxidation potential compounds, such as p-methoxyacetophenone, were reduced to chiral alcohols in 97-99% ee. The sulfur containing ketones (18) (Figure 18) were reduced in 98-99% ee to the corresponding chiral alcohols, alcohols which serve as key intermediates for the synthesis of inhibitors for the enzyme carbonic anhydrase. Reduction of ketone (19) afforded the alcohol (20) in 92% ee.
Other examples also demonstrate the chemoselectivity of the reaction, which was found to proceed without affecting an olefinic linkage, ester, sulfide, sulfone, a nitro group, aryl chloride and cyanide, and furan, thiophene, and quinoline rings. It was also noted that the enantiomeric integrity of the product alcohol remained intact under the conditions of the reaction, hence confirming the irreversibility of the process.

Reduction of Imines

The asymmetric transfer hydrogenation of imines has remained largely undeveloped, however Noyori and co-workers found that their chiral Ru(II) catalysts of the type (13) (Figure 14) could achieve the chiral reduction to amines efficiently using TEAF as the hydrogen source (Figure 19, Equation 1).

\[ 	ext{Chiral Ru catalyst} \overset{\text{HCO}_2H \text{ Et}_3H}{\longrightarrow} \]

\[
\begin{align*}
X = S & \quad 82\%, 83\% \text{ ee.} \\
X = \text{SO}_2 & \quad 90\%, 95\% \text{ ee.} \\
& \quad 72\%, 77\% \text{ ee.}
\end{align*}
\]

This method was also applicable to the synthesis of optically active indoles. Chiral amines were accessible from imines, as illustrated (Figure 19, Equation 2). The functional group selectivity of the catalyst system is noteworthy. A competitive experiment using a mixture of the imine (21) (Equation 3) and the structurally similar ketone (22) revealed that the imine (21) is >1000 times more reactive than the ketone (22). \(\alpha\)-Methylstyrene (23) was found to be inactive under the standard condition of the reaction.
Reduction of Activated olefins

The asymmetric transfer hydrogenation of $\alpha,\beta$-unsaturated acids was accomplished for the first time using benzyl alcohol as the H-donor and chiral Ru(I)/phosphine catalysts. The most significant results are summarised, with 16% as the highest optical yield obtained using the catalyst, $[\text{Ru}_2\text{Cl}_4(\text{(-)-DIOP})_3]$ at 180°C (Figure 20).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction time</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_2=\text{CHCO}_2\text{H}$</td>
<td>6 hours</td>
<td>10%</td>
<td>16% (R)</td>
</tr>
<tr>
<td>$\text{PhCHO}$</td>
<td>6 hours</td>
<td>36%</td>
<td>16% (R)</td>
</tr>
<tr>
<td>$\text{CO}_2\text{H}$</td>
<td>6 hours</td>
<td>31%</td>
<td>5% (S)</td>
</tr>
<tr>
<td>$\text{HO}_2\text{C}=\text{CHCO}_2\text{H}$</td>
<td>9 hours</td>
<td>9%</td>
<td>3% (S)</td>
</tr>
</tbody>
</table>

Figure 20

Much better results were obtained later by Brunner and co-workers in the same process using TEAF as the hydrogen source. Preformed catalysts of the general formula $[\text{Ru(acac-F}_6)(\eta^3-$ $\text{C}_3\text{H}_5)(\text{P-P})]$, where P-P are chiral bidentate phosphine ligands, namely (-)-DIOP, (-)-BPPM, (-)-BINAP and BPPFA (Figure 21), were employed, with the best results obtained with the BINAP containing complex, in which itaconic acid was reduced in 94% ee.

Figure 21
Substitution of the BINAP with other phosphine ligands resulted in a decrease of both the yield and the enantioselectivity of the reaction.

Higher selectivities were reported by Ogasawara and co-workers. Itaconic acid was converted into (R)-methylsuccinic acid in 92-97% ee by transfer hydrogenation from propan-2-ol in the presence of \([\text{RuH}((-)-\text{BINAP})_2]\)PF_6 or \([\text{RuH}_2((-)-\text{BINAP})_2]\) as preformed catalysts. These optical yields are certainly higher than the value recorded using molecular hydrogen with related Ru/BINAP catalysts. Ethanol as well as benzyl alcohol could be used instead of propan-2-ol with no detrimental effect, while with methanol both the rate and enantioselectivity were significantly lower.

The enantiofacial discriminating hydrogen transfer reduction of conjugated carbon-carbon double bonds has been accomplished by means of optically active H-donors and in the presence of both achiral or chiral ruthenium catalysts. Optically active glucides were employed with fair success in the reduction of \(\alpha,\beta\)-unsaturated ketones to saturated ketones in the presence of either \((\text{Ph}_3\text{P})_2\text{RuCl}_2\) or \((\text{Ph}_3\text{P})_4\text{RuH}_2\). Good product yields were obtained using non-prochiral substrates using the sugar as a source of hydrogen (Figure 22).

![Figure 22](image)

<table>
<thead>
<tr>
<th>Sugar derivative</th>
<th>Catalyst</th>
<th>Duration</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>20 hours</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>20 hours</td>
<td>6%</td>
</tr>
<tr>
<td>HO</td>
<td>A</td>
<td>4 hours</td>
<td>100%</td>
</tr>
<tr>
<td>HO</td>
<td>B</td>
<td>20 hours</td>
<td>26%</td>
</tr>
<tr>
<td>HO</td>
<td>A</td>
<td>4 hours</td>
<td>100%</td>
</tr>
</tbody>
</table>

Using a variety of prochiral \(\alpha,\beta\)-unsaturated ketones, however, then the reduction was achieved with up to 34% enantiomeric excess, using the sugar derivative (24) (Figure 23).
Enantioselectivities up to 9% ee were reported by Ohkubo and co-workers a few years later in the reduction of tiglic acid with the \((\text{Ph}_3\text{P})_3\text{RuCl}_2\) catalyst and similar optically active H-donors.\(^{39,40}\) Higher optical yields (up to 23% ee) were obtained by the same author when the reaction was carried out in the presence of the chiral \(\text{Ru}_2\text{Cl}_4(\text{(-)-DIOP})_3\) complex (Figure 24).

<table>
<thead>
<tr>
<th>Sugar derivative</th>
<th>Catalyst</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-\text{-DIOP})</td>
<td>((\text{Ph}_3\text{P})_3\text{RuCl}_2)</td>
<td>9% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4(\text{(-)-DIOP})_3)</td>
<td>23% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4((+)-DIOP})_3)</td>
<td>4% (R)</td>
</tr>
<tr>
<td>(-\text{-DIOP})</td>
<td>((\text{Ph}_3\text{P})_3\text{RuCl}_2)</td>
<td>7% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4(\text{(-)-DIOP})_3)</td>
<td>13% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4((+)-DIOP})_3)</td>
<td>6% (R)</td>
</tr>
<tr>
<td>(-\text{-DIOP})</td>
<td>((\text{Ph}_3\text{P})_3\text{RuCl}_2)</td>
<td>3% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4(\text{(-)-DIOP})_3)</td>
<td>7% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4((+)-DIOP})_3)</td>
<td>1% (R)</td>
</tr>
<tr>
<td>(-\text{-DIOP})</td>
<td>((\text{Ph}_3\text{P})_3\text{RuCl}_2)</td>
<td>&lt;1% (R)</td>
</tr>
<tr>
<td></td>
<td>(\text{Ru}_2\text{Cl}_4(\text{(-)-DIOP})_3)</td>
<td>2% (R)</td>
</tr>
</tbody>
</table>

In summary, the discovery of these reactive chiral ruthenium complex catalysts has resulted in highly efficient asymmetric transfer hydrogenations of a variety of prochiral substrates. Enantioselective catalysis in this way provides a viable tool in asymmetric organic synthesis competing well with other processes such as hydrogenation\(^ {41}\) and stoichiometric and catalytic metal hydride reduction.\(^ {42}\)
Chiral Iridium Catalysis

Chiral iridium phosphine catalysts have been successfully used only in the transfer hydrogenation reduction of ketones with propan-2-ol as the hydrogen donor.\textsuperscript{43,44,45}

Selected results obtained in the reduction of acetophenone in boiling propan-2-ol with chiral Ir(II) catalysts, prepared \textit{in situ} from [Ir(COD)Cl]$_2$\textsuperscript{43,44} or [Ir(acac)Cl]$_2$\textsuperscript{45} with the chiral monodentate phosphines NMDPP, MDPP and DMPP, are given below (Figure 25). Using acetophenone, the optical yield increased from 18\% ee\textsuperscript{44} to 48\% ee\textsuperscript{45} upon changing ligands, from NMDPP to MDPP and lowering the reaction temperature from 82°C to 25°C. DMPP affords comparable stereoselectivity, but with opposite enantioselectivity.

\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
Substrate & Ligand & Time & Yield & ee \\
\hline
PhCOEt & (+)-PROPHOS & - & - & 66\% (S) \\
PhCO(n-Pr) & (+)-PROPHOS & - & - & 56\% (S) \\
PhCO(i-Pr) & (+)-PROPHOS & - & - & 51\% (S) \\
PhCO(hexyl) & (+)-PROPHOS & - & - & 17\% (S) \\
\hline
\end{tabular}
\end{center}
Complexes of iridium containing chiral bidentate phophine ligands such as DIOP, etc. displayed good activity in the hydrogen transfer reaction of ketones. The enantioselectivity was strongly dependant on the phosphine ligand employed, with the highest value of 66% ee achieved using PROPHOS. Lower values were obtained using CHIRAPHOS. The bidentate phosphorated ligands such a BDPOP and BPDODP offered poorer enantioselectivities.

Chiral nitrogen ligands have been used in asymmetric transfer hydrogenation more frequently and with greater success than in hydrogenation reactions, reflecting the compatibility of nitrogen donor atoms with the mechanistic peculiarities of the reaction. The active catalyst prepared by the addition of chiral (S)-s-butylphenanthroline (25) to [Ir(COE)Cl]_2 achieved excellent reaction rates and conversions for the reduction of acetophenone, however only 9% enantiomeric excess was obtained (Figure 26). Pfaltz and co-workers, using a series of bis(oxazoline) ligands (26) in combination with the [Ir(COD)Cl]_2 precursor, noted good activity in the hydrogen transfer reduction in propan-2-ol heated to reflux in the presence of KOH. Alkyl aryl ketones were readily reduced, yielding the corresponding carbinol in 47-91% ee, whereas dialkyl ketones were less reactive and gave low yields and racemic products (Figure 26).

<table>
<thead>
<tr>
<th>Ligand</th>
<th>R</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(25)</td>
<td>PhCOMe</td>
<td>0.05 mol%</td>
<td>91%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.025 mol%</td>
<td>90%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.013 mol%</td>
<td>87%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.008 mol%</td>
<td>87%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>(26)</td>
<td>Bn</td>
<td>PhCOMe</td>
<td>1 mol%</td>
<td>89%</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td>t-Pr</td>
<td>PhCOMe</td>
<td>1 mol%</td>
<td>89%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>t-Bu</td>
<td>PhCOMe</td>
<td>1 mol%</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t-Pr</td>
<td>PhCO(t-Pr)</td>
<td>1 mol%</td>
<td>70%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>t-Pr</td>
<td>p-MeOC_6H_4COMe</td>
<td>1 mol%</td>
<td>71%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>t-Pr</td>
<td>2-naphthylCOMe</td>
<td>1 mol%</td>
<td>94%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Figure 26

The size of the chelate ring of the bis(oxazoline) was found to be critical in this process since six-membered Ir(l) complexes derived from neutral (27) or anionic bis(oxazolines) (28) did not show any significant activity (Figure 27).
A set of preformed tetra- and penta-coordinated Ir(I) complexes with pyridine based chiral ligands were prepared and tested for the reduction of a variety of ketones, using propan-2-ol as the H-donor (Figure 28).[^1]

Complexes such as (29) offered conversions greater than 90% within a few hours using only 0.1 mol% of catalyst. The activity and enantioselectivity were found to be strongly dependant on the structure of the ligand. Using the ligand $(R_1=Bn, R_2=Ph)$, then the reduction of acetophenone was achieved with 41% ee.

The Ir(I) complexes containing chiral bidentate 2-pyridinylimethylamine ligands (31) were tested with butyrophenone, $\text{PhCO}(\text{-Pr})$, in propan-2-ol using 0.1 mol% catalyst at 60°C, to afford the carbinol with optical yields ranging from 13% to 65% ee (Figure 29).[^2] A significant improvement of the optical yield, from 19% to 54% and a 10-fold increase of the reaction rate was obtained when a methyl group was introduced onto the 6-position on the pyridine ring. A further increase, up to 65%, is observed upon changing the substituents at the stereogenic carbon, e.g. a methyl by a benzyl, or a phenyl by an ortho-naphthyl group.

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R$</th>
<th>Reaction time</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>H</td>
<td>17 hours</td>
<td>32%</td>
<td>13% (R)</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>20 hours</td>
<td>72%</td>
<td>19% (R)</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>3 hours</td>
<td>92%</td>
<td>54% (S)</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>Bn</td>
<td>Me</td>
<td>12 hours</td>
<td>91%</td>
<td>60% (R)</td>
</tr>
<tr>
<td>H</td>
<td>1-Np</td>
<td>Me</td>
<td>Me</td>
<td>17 hours</td>
<td>33%</td>
<td>65% (R)</td>
</tr>
</tbody>
</table>

[^1]: Figure 28
[^2]: Figure 29
It was noted that introduction of a phenyl group at the end of the alkyl chain, i.e. PhCOCH$_2$CH$_2$CH$_2$Ph increased the enantioselectivity to greater than 90% ee, although a much longer reaction time was required. It was therefore apparent that a slower reaction rate allowed for greater enantioselectivity in this system.

A significant improvement in the stereoselectivity of the hydrogen transfer reduction was obtained using pentacoordinated neutral complexes, such as complex (30) (Figure 28). X-ray crystallography has shown the structure to have a distorted square pyramidal geometry, with the iodine atom in the apical position and with absolute (S) configuration about the iridium centre. This complex could reduce t-butyl phenyl ketone to the carbinol in 80% ee. This was improved to 84% ee when the reduction was carried out in the presence of NaI.

Complexes (32) and (33) achieved moderate levels of product yield and enantioselectivity in the transfer hydrogenation of butyrophenone (Figure 30). Unlike the previous case, introduction of a methyl group to the 6-position on the pyridine ring in complex (33) led to a reduction in the enantioselectivity (66% to 24% ee), which was more pronounced for complex (32), with R = Me on the imino carbon (64% to 3% ee).^{3}

<table>
<thead>
<tr>
<th>Complex</th>
<th>R</th>
<th>R$_1$</th>
<th>Reaction time</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(32)</td>
<td>H</td>
<td>Ph</td>
<td>25 hours</td>
<td>68%</td>
<td>64% (S)</td>
</tr>
<tr>
<td>(32)</td>
<td>Me</td>
<td>Ph</td>
<td>25 hours</td>
<td>26%</td>
<td>3% (S)</td>
</tr>
<tr>
<td>(33)</td>
<td>H</td>
<td>Ph</td>
<td>24 hours</td>
<td>33%</td>
<td>66% (S)</td>
</tr>
<tr>
<td>(33)</td>
<td>Me</td>
<td>Ph</td>
<td>24 hours</td>
<td>13%</td>
<td>24% (S)</td>
</tr>
<tr>
<td>(33)</td>
<td>H</td>
<td>4-styryl</td>
<td>20 hours</td>
<td>19%</td>
<td>68% (S)</td>
</tr>
</tbody>
</table>

Figure 30
The behaviour of these catalysts results from a compromise of two contrasting parameters that determine the basic reactivity of the substrates, namely the steric hindrance and the electrophilicity of the carbonyl group. The latter is related to the redox potential ($E^\circ$) of the ketone/alcohol couple and increases with increasing $E^\circ$. As a general trend, an increase in the bulkiness of the alkyl group on the aryl alkyl ketone substrate is associated with an increase in the $E^\circ$ of the carbonyl group. The reactivity of the carbonyl group in hydrogen transfer reductions is thus dictated by the steric hindrance of the alkyl group when sterically demanding catalysts are used. For less hindered catalysts, this effect is not as prominent, hence the reactivity is mainly dependant on the electrophilicity of the ketone.

Two styryl complexes were synthesised for use either as homogeneous catalysis (34) and (35) or, after immobilisation, as heterogeneous catalysts (36) and (37) (Figure 31).\textsuperscript{50}

![Figure 31](image)

Immobilisation was accomplished through co-polymerisation with 2-ethyl/hexylmethacrylate in the presence of $(Z,Z)$-1,4-di-(2-buten-2-yl)-benzene as the cross-linking agent resulting in a more active catalyst (Figure 32). Sharp differences in stereoselectivities were observed on changing from the homogeneous to the heterogenised system; the optical yields increase from 47% to 84% and from 52% to 84% with the methyl (36) and benzyl (37) substituted ligands respectively.
Polymer parameters are also important and definite improvements in enantioselectivity were achieved by changing the ester moiety of the methacrylate monomer. The heterogeneous catalyst derived from l-butyl methacrylate promotes the hydrogen transfer reduction of butyrophenone in up to 95% ee at 20% conversion. Unlike previous cases, the optical purity of the product is affected by the reaction time and decreases with increasing conversions (90% ee at 65% conversion).

The catalyst generated in situ from [lr(COE)₂Cl]₂ and the potentially tetradentate ligand PDPBI (38) frequently displayed high activity, but poor enantioselectivity in the hydrogen transfer reduction of acetophenone in propan-2-ol. However optical yields of up to 67% were achieved in the chemoselective reduction of 4-phenyl-3-buten-2-one (39) to the allylic alcohol using the same catalyst system (Figure 33). Higher optical yields (82%) could be obtained if the reaction was stopped at lower conversions.^^

Lemaire and co-workers, using the chiral thiourea ligands with the [lr(COD)Cl]₂ precatalyst, achieved only 36% ee in the reduction of acetophenone, and 57% ee in the reduction of propiophenone. These optical yields fall short of the enantiomeric excess obtained with the [RuCl₂(C₆H₅)]₂ precatalyst achieving 87% ee and 91% ee respectively. The reduction of acetophenone, in the presence of chiral iridium 1,2-bis-amine complexes, was found to give the highest optical yield (92% ee) so far obtained for the transfer hydrogenation reduction of this substrate (Figure 34).^8
The results reported above indicate that, although Ir(1) catalysts with chiral nitrogen ligands cannot compete with the most efficient reagents that have been developed for the enantioselective reduction of ketones, the rather high enantioselectivities induced by some of these ligands look very promising for further advances in the future.

### Chiral Rhodium Catalysis

The basic processes that have been investigated, using rhodium to mediate the transfer hydrogenation reactions, are the reduction of ketones with alcohols, and of \( \alpha,\beta \)-unsaturated acids, esters, ketones, and olefins with formic acid or triethylammonium formate (TEAF).

### Chiral Phosphine Ligands

Selected results obtained in the enantioselective transfer hydrogenation of several ketones in boiling propan-2-ol, in the presence of \([\text{Rh}(L-L)(P-P)]\text{PF}_6\) complexes \([L-L = \text{NBD, COD or HD}; P-P = (+)-\text{PROPHOS, (-)-CHIRAPHOS, or (+)-DIOP}]\) are given (Figure 35).
<table>
<thead>
<tr>
<th>Substrate</th>
<th>(P-P)</th>
<th>Reaction time</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCOMe</td>
<td>(-)-CHIRAPHOS</td>
<td>4 hours</td>
<td>46%</td>
<td>7% (R)</td>
</tr>
<tr>
<td></td>
<td>(+)-PROPHOS</td>
<td>3 hours</td>
<td>60%</td>
<td>9% (R)</td>
</tr>
<tr>
<td></td>
<td>(+)-DIOP</td>
<td>5 hours</td>
<td>61%</td>
<td>2% (S)</td>
</tr>
<tr>
<td>PhCOEt</td>
<td>(-)-CHIRAPHOS</td>
<td>4 hours</td>
<td>59%</td>
<td>34% (R)</td>
</tr>
<tr>
<td></td>
<td>(+)-PROPHOS</td>
<td>4 hours</td>
<td>54%</td>
<td>12% (R)</td>
</tr>
<tr>
<td>PhCOPr</td>
<td>(-)-CHIRAPHOS</td>
<td>5.5 hours</td>
<td>53%</td>
<td>7% (R)</td>
</tr>
<tr>
<td>MeCOEt</td>
<td>(-)-CHIRAPHOS</td>
<td>4 hours</td>
<td>70%</td>
<td>3% (S)</td>
</tr>
<tr>
<td></td>
<td>(+)-PROPHOS</td>
<td>1 hour</td>
<td>80%</td>
<td>1% (R)</td>
</tr>
<tr>
<td>MeCO(n-hex)</td>
<td>(-)-CHIRAPHOS</td>
<td>3 hours</td>
<td>41%</td>
<td>9% (R)</td>
</tr>
<tr>
<td></td>
<td>(+)-PROPHOS</td>
<td>3 hours</td>
<td>87%</td>
<td>5% (R)</td>
</tr>
<tr>
<td>MeCO(t-Pr)</td>
<td>(-)-CHIRAPHOS</td>
<td>3 hours</td>
<td>60%</td>
<td>5% (S)</td>
</tr>
<tr>
<td>MeCO(t-Bu)</td>
<td>(-)-CHIRAPHOS</td>
<td>8 hours</td>
<td>41%</td>
<td>9% (R)</td>
</tr>
</tbody>
</table>

The presence of a strong base and an appropriate activation procedure are required to achieve a high catalytic activity and allowing a substrate to metal ratio as high as 1000 (i.e. 0.1 mol% catalyst). The enantioselectivity generally increases from DIOP to PROPHOS to CHIRAPHOS, but remains low, with the best ee not exceeding 34%. Interestingly, dialkyl ketones are smoothly reduced, affording chemical and optical yields comparable to the aryl alkyl derivatives.

Aqueous formic acid (80% solution) was used as a H-donor achieving up to 19% ee in the hydrogen transfer reduction of (Z)-acetamidocinnamic acid (42) to N-acetylphenylalanine using the preformed catalyst [Rh(COD)(+)-NORPHOS]BF₄ (Figure 36). The optical yield increased to 30% ee upon addition of sodium formate, however 67% ee was obtained using the in situ catalyst [Rh(COD)Cl]₂ / NORPHOS. The enantioselectivity was strongly dependant on the structure of the phosphine ligand and decreased in the order NORPHOS > PROPHOS > BPPFA > DIOP.
The use of TEAF instead of aqueous formic acid resulted in a substantial increase in the reaction rate, thereby allowing the reactions to be conducted at temperatures as low as 25°C to 40°C. Increased enantioselectivities were observed, presumably due to the milder conditions of the reaction. (Z)-acetamidocinnamic acid (42) was reduced in 72% ee, while itaconic acid (See Figure 20) was reduced in 84% ee using BPPM as the chiral ligand and DMSO as solvent.

The rate and enantioselectivity of the hydrogen transfer reduction of itaconic acid was found to be dependent on the structure of both the amine and of the rhodium catalyst precursor (Figure 37). A improvement was noticed using [Rh₂(ac)₄]·xH₂O instead of [Rh(COD)Cl]₂. A double enantioselective hydrogen transfer was accomplished by substituting triethylamine with (R) or (S)-phenylethylamine. (S)-methylsuccinic acid was thus prepared in 97% ee, which exceeded the best optical yield obtained in the asymmetric hydrogenation of itaconic acid with the related Rh(I)/(S,S) BPPM catalyst.

![Figure 37](image)

Taken together with the ruthenium-BINAP catalysts, this result is another example where transfer hydrogenation affords excellent enantioselectivities, which are even greater than the optical yields obtained with molecular hydrogen in conventional hydrogenation reductions.
Chiral Nitrogen Ligands

Work in this field has mainly been concerned with optically active ligands containing pyridine derived ring systems. Optically active alkyl-2,2'-bipyridines and alkyl-1,10-phenanthrolines (Figure 38) have been shown to be efficient chiral auxiliaries in Rh(I) catalysed enantioselective transfer hydrogenations, with the first set of results indicating the reduction of acetophenone to (S)-1-phenylethanol in up to 26% ee.\(^3\)

The active catalysts were generated *in situ* by the addition of excess ligand to Rh(COD)Cl\(_2\) in propan-2-ol, after which KOH was then added. In the absence of ligands the rhodium precatalyst was devoid of any catalytic activity since, upon heating in alkaline propan-2-ol, they were readily and quantitatively reduced to metallic rhodium.

The results obtained with ligand (44) (R = (S)-3-s-Bu) are of particular interest for three reasons. Firstly, the s-Bu substituent is usually poorly efficient in chiral transfer processes\(^67\) and secondly, because the stereogenic centre of the alkyl group is four bonds away from the reactive site. Finally in the phenanthroline series the proximity effect does not seem to hold, since 3-substituted derivatives are more efficient than the corresponding 2-substituted.

The enantioselectivity is significantly increased to 63% ee without any detrimental effect on the reaction rate when the (S)-3-s-Bu is substituted with the bulkier (S)-(1,2,2-trimethylpropyl group). This is in contrast to the C\(_2\)-symmetric 3,8-di-(S)-s-Bu-phenanthroline which generated a catalytic system of poor activity and devoid of enantiodifferentiating ability.\(^57\)

Lemaire and co-workers demonstrated the use of their chiral 1,2-bis-amine (See Figure 34),\(^6\) thiourea (11)\(^7\) and diurea (45) (Figure 39)\(^57\) based ligands, using rhodium as the transition metal catalyst and acetophenone as the test substrate. Chiral 1-phenylethanol was prepared with optical yields up to 60%, 66% and 80% ee respectively, for each class of ligand (Figure 39).
A recent report by Uemura and co-workers found that the Rh(I) catalysed hydrosilylation of unfunctionalised alkyl aryl ketones in methanol proceeded to give a chiral alcohol directly, rather than the hydrosilylated alcohol product as was observed when THF was employed as the solvent. Closer examination of the system revealed that the reaction proceeded via a transfer hydrogenation pathway under very mild and neutral conditions, and not via hydrogenation by evolved hydrogen or hydrosilylation by the silane species. A variety of ketones were reduced with enantiomeric excesses ranging from 22% to 95% ee, in the presence of Rh(I) and chiral substituted dichalcogenides (Figure 40).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Yield (days)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-bis-amine</td>
<td>[Rh(COD)Cl]_2 / (40)</td>
<td>5% (6)</td>
<td>22% (R)</td>
</tr>
<tr>
<td></td>
<td>[Rh(COD)Cl]_2 / (41)</td>
<td>29% (6)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>[Rh(COD)Cl]_2 / (4)</td>
<td>4% (1)</td>
<td>60% (S)</td>
</tr>
<tr>
<td>thiourea</td>
<td>[Rh(COD)Cl]_2 / 1 x (11)</td>
<td>98% (1)</td>
<td>15% (S)</td>
</tr>
<tr>
<td></td>
<td>[Rh(COD)Cl]_2 / 2 x (11)</td>
<td>90% (1)</td>
<td>44% (S)</td>
</tr>
<tr>
<td></td>
<td>[Rh(COD)Cl]_2 / 3 x (11)</td>
<td>97% (2)</td>
<td>63% (S)</td>
</tr>
<tr>
<td></td>
<td>[Rh(HD)Cl]_2 / 1 x (11)</td>
<td>94% (6)</td>
<td>17% (S)</td>
</tr>
<tr>
<td></td>
<td>[Rh(HD)Cl]_2 / 2 x (11)</td>
<td>96% (6)</td>
<td>64% (S)</td>
</tr>
<tr>
<td></td>
<td>[Rh(HD)Cl]_2 / 3 x (11)</td>
<td>98% (1)</td>
<td>66% (S)</td>
</tr>
<tr>
<td>diurea</td>
<td>PhCOMe</td>
<td>[Rh(COD)Cl]_2 / (45)</td>
<td>97% (7)</td>
</tr>
<tr>
<td></td>
<td>PhCOEt</td>
<td>[Rh(COD)Cl]_2 / (45)</td>
<td>87% (7)</td>
</tr>
<tr>
<td></td>
<td>PhCO(/-Pr)</td>
<td>[Rh(COD)Cl]_2 / (45)</td>
<td>93% (11)</td>
</tr>
<tr>
<td></td>
<td>PhCO(f-Bu)</td>
<td>[Rh(COD)Cl]_2 / (45)</td>
<td>100% (4)</td>
</tr>
</tbody>
</table>

**Figure 39**

**Figure 40**

[Image of chemical structures and reaction pathway]
From the above table it was apparent that increasing the steric bulk around the ketone moiety resulted in lower conversions: Me (46%) to t-Bu (11%). It was also observed that when the chalcogenide was substituted with a diphenylphosphine group, transfer hydrogenation did not occur; further, the use of \([\text{Ir(COD)Cl}]_2\) or \([\text{Ru(COD)Cl}_2]_n\) as precatalysts failed to generate an active catalyst.

A new catalytic asymmetric transfer hydrogenation system was thus proposed. Ph\_2SiH\_2 and methanol was previously known only to give hydrogen under the conditions employed\(^{58}\) as indicated by the evolution of hydrogen in the reduction of alkenes and alkynes using Ph\_2SiH\_2 and methanol in the presence of a Pd catalyst\(^{59}\).

A mechanism was postulated, which was believed to proceed by an initial ligand exchange of the COD with the dichalcogenide ligand. The resulting complex catalysed the reaction of Ph\_2SiH\_2 with methanol to generate hydrogen and Ph\_2SiH(OMe). It is known that Rh(I) complexes can catalyse such reactions:\(^{60}\)

$$\text{Ph}_2\text{SiH}_2 + \text{MeOH} \xrightarrow{\text{cat. Rh}} \text{Ph}_2\text{SiH}(\text{OMe}) + \text{H}_2$$

The Rh(I) complex then transfers hydrogen from the Ph\_2SiH(OMe) and/or methanol to the carbonyl enantioselectively:

$$\text{ArCOR} + \text{Ph}_2\text{SiH}(\text{OMe}) \xrightarrow{\text{cat. Rh}} \text{ArCH(OH)R} + \text{Ph}_2\text{Si(OMe)}_2$$

The reaction did not proceed under an atmosphere of hydrogen in place of the Ph\_2SiH\_2, even in the presence of the dichalcogenide ligand. The absence of hydroxsilylated material and the formation of Ph\_2SiH(OMe) were both confirmed. When acetophenone was treated in deuterated
methanol (MeOD), almost equal amounts of deuterated and non-deuterated 1-phenylethanol were obtained, indicating that the hydrogen introduced in this reduction came from both methanol and the \( \text{Ph}_2\text{SiH}_2 \). Further, it was found that \( \text{Ph}_2\text{SiD(OMe)} \) was not formed. It was evident that these observations excluded the intervention of a hydrosilylation pathway. The following mechanism was proposed, however there is no direct evidence to support the presence of the intermediary species involved (Figure 41).

The mechanism illustrated above accounts for the formation of the deuterated products when performing the reaction in MeOD. A detailed mechanism for the formation of A from the species having an Rh-O bond B, \( \text{Ph}_2\text{SiH(OMe)} \) and methanol is not yet known.

From these reports it is clear that rhodium behaves as viable catalyst in the transfer hydrogenation of activated unsaturated centres. Although the enantiomeric excesses were high, with up to 95% ee in one case, the results are not as consistently high as the optical yields reported for certain chiral ruthenium catalysts. It is clear, however, that such remarkable results are dependant on the nature of the chelating ligand, and it is very likely that with further development in this area, equally high enantiomeric excesses may be obtained.
Mechanistic Studies

Ruthenium

Sasson and Blum noted in 1975 that the \((\text{Ph}_3\text{P})_2\text{RuCl}_2\) catalyst was selective in the reduction of the olefin moiety in \(\alpha,\beta\)-unsaturated ketones over a range of temperatures up to 180°C. A wide variety of alcohols were used to demonstrate the scope and potential synthetic applications of this catalytic process, as well as structure and electronic effects of the H-donors on the reaction kinetics. The catalysis was inferred to proceed via a *Direct Hydride Transfer* mechanism, whereby dissociation of the \((\text{Ph}_3\text{P})_2\text{RuCl}_2\) with release of \(\text{Ph}_3\text{P}\) (*Step 1*) is followed by coordination of the \(\alpha,\beta\)-unsaturated ketone to the metal (*Step 2*). The alcohol, by loss of a proton, forms an alkoxide and coordinates with the metal (*Step 3*). Hydrogen transfer from the alkoxyl ligand to the coordinated ketone (*Step 4*) is then followed by release of product (*Step 5*) (Figure 42).

\[
\text{(Ph}_3\text{P})_2\text{RuCl}_2 \xrightarrow{\text{Step 1}} \text{(Ph}_3\text{P})_2\text{Ru} - \text{Cl} \quad \text{Cl}
\]

\[
\begin{align*}
\text{R}_1 &+ \text{R}_2 &\xrightarrow{\text{Step 2}} &\text{H} &\xrightarrow{\text{Step 3}} &\text{R}_1 &\xrightarrow{\text{Step 4}} &\text{R}_2
\end{align*}
\]

\[\text{Figure 42}\]

It was clear from these investigations that the mechanistic steps associated with the transfer hydrogenation reaction depends to a great extent, not only on the structure of the catalyst, but also on the donor-acceptor couple under study.
Investigations on the use of propan-2-ol as the H-donor have added some refinement to the above hypothesis. Formation of an intermediate ruthenium hydride has been suggested to occur through attack of alkoxide anion on the metal (Figure 43, Pathway 1) followed by β-hydride elimination. Protonation of the resulting anionic ruthenium complex would then afford the ruthenium dihydride which may then reduce the ketonic substrate or H-acceptor.

In propan-2-ol / NaOH solutions the presence of alkoxide anions in sufficient quantity to achieve a satisfactory reaction rate is questionable. Zassinovich and Mestroni therefore suggested that deprotonation of the alcohol occurred whilst coordinated to the ruthenium, and not beforehand, to form the alkoxy-ruthenium intermediate (Pathway 2).^1

**Iridium**

In the case of transfer hydrogenation with Ir(I) catalysts containing nitrogen ligands, in particular when preformed complexes (29) and (30) are used, a pentacoordinate Ir(I) species containing one chelate chiral ligand has been assumed as the key intermediate in the catalytic cycle.\textsuperscript{63,64,57,49} The sharp variations observed in catalytic activity by changing the counter anion, \textit{i.e.} iodide or BF\textsubscript{4}, indicates its presence in the coordination sphere of the metal. Thus three coordination sites on the metal are occupied by the supporting ligands, the remainder being taken up by the H-donor and acceptor. A mechanism has been suggested, and is illustrated below (Figure 44).
A direct hydrogen transfer from a coordinated 2-propoxy group to the O-coordinated ketone has been suggested as the rate-determining and stereodetermining step of the process. The observation that the reaction depends on both the nature of the H-donor and H-acceptor, supports the proposed mechanism. Such a mechanism warrants further investigation since the nature of the active catalytic species remains unclear.

**Rhodium.**

In 1974, Imai and co-workers performed a systematic study of the relative catalytic activity of a variety of transition metal complexes reported to catalyse transfer hydrogenation. It was noted that (Ph₃P)₄RhH offered the highest activity in the order (Ph₃P)₄RhH > (Ph₃P)₃RhCl > (Ph₃P)₃RuCl₂ > (Ph₃P)₂Rh(CO)Cl > (Ph₃P)₂PtCl₂ > (Ph₃P)₂PtCl₂-SnCl₂, whereas Fe(II), Ni(II), Co(II), Pd(II) and (Ph₃P)₃Rh(CO)H complexes offered little or no activity.
Following kinetic studies performed on the reduction of cycloheptene by propan-2-ol in the presence of \((\text{Ph}_3\text{P})_4\text{RhH}\), a mechanism operating via a *Hydridic Route* was suggested. The transfer hydrogenation process was divided into several steps. Formation of uncoordinated sites on the rhodium by release of two triphenylphosphine ligands (*Step 1*), is followed by coordination of propan-2-ol (*Step 2*). Transfer hydrogenation from the alcohol to the metal occurred with oxidative addition to form a polyhydride rhodium(III) complex (*Step 3*). Replacement of the acetone thus formed with the cycloheptene substrate (*Step 4*) is then followed by sequential delivery of two hydrogens to reduce the olefin (*Step 5*) (*Figure 45*).

*Figure 45*

Over the next 10 years many results have appeared pertaining to the kinetic and mechanistic study of the catalytic aspects of some rhodium, ruthenium and iridium complexes in hydrogen transfer reactions. Many of these reports have been cited by Bauer, in collaboration with Beaupére, Nadjo and Uzan, in their contributions in this area of study. The high reaction temperatures required to conduct these reactions, together with slow kinetics and often long reaction times led Bauer and co-workers to modify the transfer hydrogenation reaction in order to develop milder reaction conditions. The catalyst of choice to achieve this objective was \((\text{Ph}_3\text{P})_4\text{RhH}\), supporting earlier observations by Imai. Initial experiments found that with suitable \(\alpha,\beta\)-unsaturated ketones, satisfactory yields and kinetics were possible even at room temperature (*Figure 46*).
Evidence for the mechanism of transfer hydrogenation was obtained following a systematic study by the same workers on the catalytic effect of \( \text{(Ph}_3\text{P})_4\text{RhH} \) in the reduction of \( \alpha,\beta \)-unsaturated ketones by alcohols. It was found that the mixing order of reactants affected the rate of reaction, a hitherto unobserved phenomenon. Adding the H-acceptor a mixture of the catalyst and H-donor, or adding the catalyst to a mixture of the H-donor and H-acceptor, was found to increase the initial reaction rate. This was not observed if the H-donor was added to a mixture of catalyst and H-acceptor. It was deduced from these results that two types of complexes were formed in solution, i.e. a [catalyst-(H-donor)] complex and a [catalyst-(H-acceptor)] complex. The latter was believed to impede the activity of the catalyst.

IR studies also indicated that the absorption band of \( \nu_{\text{OH}} \) in 1-phenylethanol in benzene at \( 3588\text{cm}^{-1} \), upon addition of \( \text{(Ph}_3\text{P})_4\text{RhH} \), had decreased in intensity, with the concomitant appearance of a large band at \( 3355\text{cm}^{-1} \) and the slow build up of concentration of acetophenone, as indicated by the characteristic C=O band at \( 1688\text{cm}^{-1} \). The \( ^1\text{H-NMR} \) spectrum of \( \text{(Ph}_3\text{P})_4\text{RhH} \) in \( \text{d}_6\text{-benzene} \) is characterised by a doublet at -8.16 ppm (ref. TMS). Upon addition of the alcohol, a strong shift of the OH group was observed, with no observable change in the doublet of the catalyst. These results support the formation of the complex \( (49) \) (Figure 47), invalidating both the hypotheses for the formation of a trihydride intermediate, proposed by Imai, and a previously proposed mechanism whereby the rhodium was believed to insert into the O-H bond of the alcohol.
The addition of Ph₃P was found to increase the rate of transfer hydrogenation. However from previous literature reports, the influence of Ph₃P was variable as a consequence of using different catalysts, H-donors and acceptors, thus precluding any efficient comparisons. It is confirmed however that dissociation of Ph₃P ligands do occur, and with (Ph₃P)₄RhH, the equilibrium is shifted completely to the right:\[ (\text{Ph}₃\text{P})₄\text{RhH} \rightleftharpoons (\text{Ph}₃\text{P})₃\text{RhH} + \text{Ph}₃\text{P} \]

The addition of Ph₃P to the medium does not shift the equilibrium to the left to a large extent. If the H-donor and acceptors are good ligands for the catalyst, then only the basic character of Ph₃P is responsible for the increase in the rate of transfer hydrogenation. Strong bases, such as KOH or NaOH or sodium alkoxides are frequently added as “promoters” in hydrogen transfer reactions since they often exert a beneficial effect on reaction rates.

Further studies used \(^1\text{H-NMR}\) spectroscopy and isotope effects to elucidate mechanistic details for the transfer hydrogenation of \(\alpha,\beta\)-unsaturated ketones by alcohols in the presence of the (Ph₃P)₄RhH catalyst. Using either PhCD(OH)CH₃ or PhCD(OD)CH₃ as the H-donor, and one equivalent of (Ph₃P)₄RhH the following results were obtained at the beginning of the reaction (Figure 48).

The saturated ketone was formed at the beginning of the reaction in a yield corresponding to 20% of the concentration of the ketone with no deuterium incorporation. This result proved unambiguously that the source of the reducing hydride was from the catalyst alone, and not the alcohol.

The doublet observed for the (Ph₃P)₄RhH complex was found to disappear within 3 minutes of commencing the transfer hydrogenation reaction. However, upon completion of the reaction the initial form of the catalyst was obtained following the addition of an excess of the starting alcohol. Regeneration of (Ph₃P)₄RhH was confirmed by the reappearance of the characteristic doublet by \(^1\text{H-NMR}\). In the absence of any alcohol, one equivalent of cyclohexanone was added to the
catalyst, which had the effect of removing the hydride on the \((\text{Ph}_3\text{P})_4\text{RhH}\) complex by reduction of the ketone to the alcohol. The catalyst was treated with a variety of deuterated alcohols, and the resulting rhodium complexes analysed by \(^1\text{H}\)-NMR for the presence or absence of the Rh-H doublet corresponding to \((\text{Ph}_3\text{P})_4\text{RhH}\) and \((\text{Ph}_3\text{P})_4\text{RhD}\) respectively (Figure 49).

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Regenerated Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Phenylethanol</td>
<td>((\text{Ph}_3\text{P})_4\text{RhH})</td>
</tr>
<tr>
<td>PhCD(OD)Me</td>
<td>((\text{Ph}_3\text{P})_4\text{RhD})</td>
</tr>
<tr>
<td>PhCD(OH)Me</td>
<td>((\text{Ph}_3\text{P})_4\text{RhH})</td>
</tr>
<tr>
<td>\text{CH}_3\text{CH}_2\text{OH}</td>
<td>((\text{Ph}_3\text{P})_4\text{RhH})</td>
</tr>
<tr>
<td>\text{CH}_3\text{CH}_2\text{OD}</td>
<td>((\text{Ph}_3\text{P})_4\text{RhD})</td>
</tr>
</tbody>
</table>

After removal of the pre-existing hydride on the \((\text{Ph}_3\text{P})_4\text{RhH}\) complex using cyclohexanone, it was evident from these results that the source of hydride, causing the regeneration of the catalyst, had come from the hydrogen located on the hydroxyl group.

The regioselectivity of the transfer hydrogenation reaction was demonstrated using catalytic quantities of catalyst and a variety of deuterated alcohols (Figure 50). Such specificity had previously been suggested, but not demonstrated.\(^{61}\)
The results clearly show that the carbinolic H (or D atom) on the H-donor had been transferred to the β-position on the α,β-unsaturated ketone, and that this transfer had occurred entirely regiospecifically. Kinetic studies also demonstrated that the rate determining step was cleavage of the O-H (or O-D) bond on the alcohol.

From these findings it was apparent that three steps could be distinguished in the reaction mechanism. Firstly, loss of a Ph₃P group and delivery of the hydride to the H-acceptor (A). Complexation by the H-donor (D) or H-acceptor with the rhodium gives rise to the [(Ph₃P)₃Rh(H-donor)] and [(Ph₃P)₃Rh(H-acceptor)] complexes respectively. The second and third steps are representative of the cycle whereby the hydrogen transfer can occur (Figure 51).

Recent studies by Brown, in collaboration with Brunner and Leitner, employed deuterated substrates to elucidate the mechanistic operation of hydrogen transfer from formic acid. An isotope effect was found to operate in the reduction of itaconic acid using DCO₂D/Et₃N as the source of hydrogen (Figure 52).
isotope effect was found to operate in the reduction of itaconic acid using DCO2D/Et3N as the source of hydrogen (Figure 52).73

Several pathways were proposed to explain these results, including the following:

- Rhodium catalyses the decomposition of the formate to give H2 in situ which is scavenged by the rhodium to reduce the unsaturated centre by conventional hydrogenation.
- Activation of HCO2H so that the proton is transferred first to protonate the substrate, followed by collapse of the alkyl-formate-metal complex to give reduced product and CO2.
- Activation of the HCO2H to give CO2 and a rhodium dihydride which subsequently traps and reduces the unsaturated centre on the H-acceptor.

Using DCO2D to reduce the unsaturated acid (50), it was found that the two deuteriums were transferred to the substrate with syn-specificity to afford a single diastereoisomer (Figure 53). The same product was obtained following the hydrogenation of (50) with D2 gas. Homogeneous hydrogenation is known to operate via stereospecific syn-addition, therefore with the formation of a common product, the mechanisms of these two processes are invariably linked.

Further studies were conducted in order to ascertain where the two hydrogens in the formic acid end up in the product (Figure 54).
From these results it was apparent that the H and D sites in formic acid are scrambled during the catalytic cycle and cannot be distinguished in the product. This suggests the formation of a rhodium dihydride with the two Rh-H sites becoming equivalent before any transfer to the olefin occurs. The results also indicate a competing process whereby the hydrogens are scrambled intermolecularly, hence the formation of products containing zero or two deuteriums.

These remarkable features of the transfer hydrogenation mechanism undoubtedly demonstrate the value of isotopic labelling studies in deciphering the mechanistic aspects of this transformation. The mechanism of transfer hydrogenation and asymmetric hydrogenation of substrates such as itaconic acid by means of Rh(I) / chiral diphosphine catalysis are probably similar, relying on the intermediacy of a Rh(III) dihydride. This common intermediate is formed in the hydrogenation process by oxidative addition of molecular hydrogen in the rate-determining step. In transfer hydrogenation, its formation may occur by oxidative addition of formic acid to give the complex (51), followed by rate limiting decarboxylation of the formate ligand.
The starting complex is then regenerated by the same pathway as the hydrogenation.\(^74\) This insertion into the O-H bond on the formic acid is in contrast to the observations made by Uzan and co-workers\(^66,67\) which invalidated the hypothesis of O-H insertion by the (Ph\(_3\)P\(_4\))RhH catalyst on propan-2-ol.

Conclusions

The reduction of prochiral centres on ketones and \(\alpha,\beta\)-unsaturated carbonyl compounds in an enantioselective manner has been demonstrated with varying degrees of success in a number of catalyst systems.

The use of chiral iridium and rhodium based catalyst systems offered good levels of asymmetric induction, with a few examples exceeding 90% ee. However, more significant advances have been made with non-phosphine based chiral ruthenium complexes, in which chemical and optical yields in excess of 95% have been obtained using TEAF as the hydrogen source. The same catalyst system achieved a remarkable yield of nearly 50% yield and >97% ee for the kinetic resolution of racemic alcohols.

The use of sugars as a chiral source of hydride is of immense interest, despite the moderate levels of enantioselectivity achieved. Sugars have been used as chiral templates in many asymmetric reactions due to desirable facets such as their ready availability, structural diversity and ease of handling. Efforts in this area will no doubt continue to develop.

It is clear from the investigations performed to elucidate the various mechanistic aspects of this unique transformation, that the reaction mechanism is dependant on a number of factors such as catalyst, H-donor, H-acceptor, ligands, etc. The various efforts that have been made to unravel the mysteries of the processes involved, which make up the overall transformation, often take several years of carefully designed experiments, combining NMR investigations, isotope effects and kinetic studies.

Several of the ruthenium and rhodium complexes, which were able to catalyse transfer hydrogenation reactions, have also been shown to be effective catalysts for the isomerisation of allylic alcohols to carbonyl compounds.\(^75,76\) There are similarities in the mechanisms in operation by the transfer hydrogenation and isomerisation reactions, in that the latter can be viewed as an intramolecular transfer hydrogenation reaction: \(i.e.\) hydride abstraction from the allylic alcohol (H-donor) by the metal catalyst will generate an enone (H-acceptor) and a metal hydride. The latter may then reduce the enone by hydride transfer to afford the enol product (B = H), which may then tautomerise to the carbonyl compound.
Although there are many examples in the literature where allylic alcohols have been isomerised
to carbonyl compounds, there are surprisingly very few reports in which this transformation has
been achieved enantioselectively.

This transformation is of greater interest if an allylic alkoxide is used (i.e. $B = Li$, $K$, etc.) instead
of an allylic alcohol ($B = H$), as the product would be an enolate, a synthetically more useful
moiety than the enol. Such a transformation therefore presents a novel method for the
preparation of enolate anions. Indeed, initial studies in this area have already been reported by
our group.$^{77,78}$ It is likely therefore that with the advent of new chiral catalyst systems, bearing
increasing levels of enantiocontrol in the transfer hydrogenation reactions, that these systems
could be applied to isomerise of allylic alkoxides (or alcohols) with greater enantioselectivity.
Investigations into this unique area of asymmetric transition metal catalysis have been largely
unexplored. Thus, by judicious choice of metal catalyst, chiral ligands and appropriate reaction
conditions, such a transformation could be achieved.
Chapter 2

Results and Discussion
Enolate formation

In carbonyl containing compounds, the polarising carbonyl group has an acidifying effect on the adjacent α-hydrogen atoms, allowing the tautomeric formation of enols under acid conditions and the corresponding enolate anions by basic deprotonation. These electron rich species can be subjected to electrophilic attack by protons, alkylating agents, halogens and the positively polarised carbon of other carbonyl compounds. The plethora of bond forming reactions that are available via enolate anion chemistry has ensured a rich development of methodology for the regio-, stereo- and enantiocontrolled formation and reactivity of these intermediates. For example, seven out of the sixteen stereocentres in the ionophore antibiotic Ferensimycin B (52) were constructed using chiral enolate chemistry (Figure 55).

![Figure 55](image)

However, in spite of the attention which enolates have received, their generation is still exclusively dependent on the chemistry of the carbonyl group. The general procedure for the formation of enolate anions is via deprotonation at the α-position to a carbonyl group using a suitable base. By careful choice of base and reaction conditions, an enolate of the required regiochemistry may be obtained (Figure 56). A strong, highly hindered base (and hence a poor nucleophile) will abstract the most accessible proton thus favouring the formation of essentially one regioisomer. In contrast, methods for the formation of thermodynamic silyl enol ethers rely on this reversibility phenomenon.

![Figure 56](image)

Unsymmetrical ketones which differ little in substitution at the α-position render this method of basic enolate generation ineffective, unless the waste in starting material can be accepted.
Enolates prepared in this way may be trapped as the silyl enol ether. Purification, and then regeneration of the required enolate by treatment with methyl lithium\(^3\) may solve the problem of regiochemistry, but, this technique is far from satisfactory. Accordingly, other methods have been devised to obtain regiochemically pure enolates (Figure 57).\(^4\)

\[
\begin{align*}
\text{O} & \quad \text{Cu}/\text{Li} \\
\text{Me$_2$CuLi} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Cu}/\text{Li} \\
\text{Me$_2$CuLi} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Li}/\text{NH}_3(\ell)/\text{ROH} \\
\text{Li} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Li} \\
\text{Li}/\text{NH}_3(\ell)/\text{ROH} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Sml$_2$} \\
\text{2 Sml$_2$} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Sml$_2$} \\
\text{2 Sml$_2$} & \quad \rightarrow \\
\end{align*}
\]

\[\text{Figure 57}\]

The conjugate addition of organocuprates to \(\alpha,\beta\)-unsaturated compounds is particularly useful\(^5\), provided that there is a need for \(\beta\)-substitution in the target molecule (Figure 57, Equation 1). The reduction of \(\alpha\)-cyclopropyl\(^6\) or \(\alpha,\beta\)-unsaturated carbonyl\(^7\) compounds with lithium/liquid ammonia/alcohol has also been useful, provided that the compound can withstand the harsh reaction conditions (Equation 2). Zinc and samarium diiodide\(^8\) have also been employed in the preparation of enolates by the reduction of \(\alpha\)-halo carbonyls (Equation 2). However difficulties arise in the regioselective formation (and purification) of these halogenated compounds. Moreover, any particular restriction in the choice of the enolate counter-cation will in turn alter the reactivity of the enolate itself towards electrophiles.

**Isomerisation of allylic alcohols**

A technique which has received a varying amount of attention over the years is the transition metal mediated catalytic isomerisation of allylic alcohols. An intermediate in such a process would be the enol, tautomerisation of which would yield a carbonyl compound. Sabatier and Senderens\(^9\) reported as long ago as 1903 the conversion of 2-propen-1-ol to propanal over a copper catalyst heated to 180\(^\circ\)C. This reaction was subsequently postulated to proceed via

\[
\begin{align*}
\text{O} & \quad \text{Cu}/\text{Li} \\
\text{Me$_2$CuLi} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Cu}/\text{Li} \\
\text{Me$_2$CuLi} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Li}/\text{NH}_3(\ell)/\text{ROH} \\
\text{Li} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Li} \\
\text{Li}/\text{NH}_3(\ell)/\text{ROH} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Sml$_2$} \\
\text{2 Sml$_2$} & \quad \rightarrow \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Sml$_2$} \\
\text{2 Sml$_2$} & \quad \rightarrow \\
\end{align*}
\]

\[\text{Figure 57}\]
dehydrogenation to the $\alpha,\beta$ unsaturated carbonyl compound followed by intermolecular hydrogen transfer from another molecule of allyl alcohol.\textsuperscript{101} In 1972, Kraus performed one of the earliest systematic structure vs. reactivity studies on a range of allylic alcohols and noted a limitation to the process, namely a decrease in reactivity upon increasing substitution around the allylic double bond (Figure 58).\textsuperscript{102}

\begin{center}
\begin{tabular}{lll}
$\text{OHH} \quad 95\%$ & $\rightarrow$ & $\text{C}=$O \\
$\text{OHH} \quad 35\%$ & $\rightarrow$ & $\text{C}=$O \\
$\text{OHH} \quad 90\%$ & $\rightarrow$ & $\text{C}=$O \\
$\text{OHH} \quad 85\%$ & $\rightarrow$ & $\text{C}=$O \\
$\text{OHH} \quad 40\%$ & $\rightarrow$ & $\text{C}=$O \\
\end{tabular}
\end{center}

Reagents : H$_2$, Pd/C, 180°C

* Denotes modified polymer-supported catalyst

\textit{Figure 58}

Since that time, the isomerisation of a multitude of allylic alcohols has been effected with a variety of transition metals, such as iron,\textsuperscript{103,104} cobalt,\textsuperscript{105} palladium,\textsuperscript{102,106} osmium,\textsuperscript{107} nickel,\textsuperscript{108} ruthenium,\textsuperscript{76} iridium\textsuperscript{109,110,111} and molybdenum.\textsuperscript{112}

The stereochemical outcome of the isomerisation, \textit{i.e.} the ratio of the (E) and (Z) enol stereoisomers, prior to tautomeration to the carbonyl product, were recently investigated. Sufficiently mild catalyst systems were developed in order to prepare solutions of simple enols that were kinetically stable to persist long enough for the stereochemical ratio to be determined by $^1$H-NMR studies.

Chin, and co-workers, first reported the preparation of remarkably persistent enols from allylic alcohols in $d_6$-acetone using the cationic rhodium complex $\{(\text{Ph}_3\text{P})_3\text{Rh(CO)}\}^+\text{ClO}_4^-$. (Figure 59).\textsuperscript{113,114} Further examples were given in a full paper, also using the iridium complex $\{(\text{Ph}_3\text{P})_3\text{Ir(COD)(PhCN)}\}^+\text{ClO}_4^-$.\textsuperscript{115}
The stereochemistry of the enol (53) could not be assigned by $^1$H-NMR, however the major isomer was found to predominate in a ratio up to 9:1. At the start of the isomerisation of allyl alcohol (54), the (Z)-enol (55) was formed initially as the major (kinetic) product, however, during the course of the reaction, it was found to interconvert to the (E) stereoisomer, to give a mixture of (E) and (Z) stereoisomers (no ratios given). Preference for the thermodynamically more favourable (E) stereoisomer was believed to be due to the reversible formation of the $\pi$-allyl intermediate (56), where the hydroxyl group is aligned away from the steric bulk of the ligands on the metal catalyst (Figure 60).

Interconversion of the $\pi$-allyl intermediates to generate a mixture of the (E) and (Z) enols is possible via the well known process referred to as ‘$\pi$-$\sigma$-$\pi$’ fluxionality of transition metal allyl complexes (Figure 61).\(^{116}\) The usually favoured $\eta^3$ form may be in equilibrium with the $\eta^1$ form thus allowing bond rotation and scrambling of the stereochemistry.

Bergens and Bosnich were able to measure the kinetic $(E)/(Z)$ ratio for a range of enols using the cationic rhodium complex $[\text{Rh(DIPHOS)(solvent)}_2]^+\text{ClO}_4^-$ (Figure 62).\(^{117}\)
The divergence of the initial and final (E) and (Z) enol ratios was believed to be due to the difference in their rate of ketonisation under the conditions of the reaction. This effect was somewhat striking for cinnamyl alcohol (58), in which a reversal of the enolic ratio was observed. Efforts were made to suppress the ketonisation process by the addition of MeCN, CO or DIPHOS, however these attempts were not entirely successful. The glass surface of the reaction vessel or the presence of minute amounts of adventitious impurities were both likely to cause ketonisation, thus highlighting the sensitivity of these enol molecules to tautomeration.
[Rh(P-P)(solvent)$_2$]$_2$ClO$_4^-$ complexes (P-P = DIPHOS, BINAP, etc.) are usually prepared from the less reactive [Rh(P-P)(L-L)]$_2$ClO$_4^-$ complexes (L-L = COD, NBD, etc.). The latter is more stable and hence easier to prepare. The L-L ligands are removed by treatment with H$_2$ under atmospheric pressure, with the solvent occupying the vacant coordination sites that are formed on the metal. The solvent is then replaced by the substrate upon addition of the catalyst solution to the substrate. The ClO$_4^-$ counter anion is typically selected as it plays no part in the isomerisation process. Since it is assumed that solvent will occupy all the uncoordinated sites on the metal catalyst, the [Rh(P-P)(solvent)$_2$]$_2$ClO$_4^-$ complex is usually referred to as [Rh(P-P)]$^{+}$. The latter description will therefore be used for the rest of this thesis to describe this active rhodium species.

The potential for asymmetric catalysis was recognized in 1976 by Botteghi and Giacomelli,$^{118}$ who were able to isomerise several prochiral allylic alcohols using the (Ph$_3$P)$_3$RhH(CO) complex in the presence of a chiral bidentate phosphine ligand, (-)-DIOP (Figure 63). Although (E)-3-methyl-2-butan-1-ol (59) is not prochiral at the β-position, the isomerisation proceeded to give the ketone (60) in 4% ee. This asymmetric induction is noteworthy as it implies involvement of the metal complex in the ketonisation of the enol. Despite the low enantiomeric excesses obtained the challenge was nevertheless set to find a catalytic system that would achieve catalytic enantioselective isomerisation.

Since that time very few examples of enantioselective isomerisations of allylic alcohols have been reported. A notable exception is the active cationic rhodium catalyst [Rh(R)-(−)-BINAP]$^+$ (prepared from [Rh(COD)(R)-(−)-BINAP]ClO$_4^-$ by hydrogenation) which could convert the natural product (E)-3,7-dimethyl-2,6-octadien-1-ol, or geraniol (61) to the corresponding aldehyde (62) in 37% ee (Figure 64).$^{119}$ Slightly better results were obtained with (E)-3-phenyl-2-buten-1-ol (63), giving the aldehyde in 53% ee. In both examples, the chiral bidentate ligand (R)-(−)-(BINAP) (10) was used.
In 1984, the challenge of achieving a highly enantioselective isomerisation of allylic amines was conquered by the Otsuka and Noyori groups.\textsuperscript{120} After several years of research, they were able to isomerise N,N-diethylgeranylamine (64) to the corresponding enamine in 96% yield, and greater than 95% ee using the [Rh(S)-(BINAP)]\textsuperscript{+} catalyst (Figure 65).

Remarkably, the optical yield in the isomerisation of N,N-diethylgeranylamine (64) remained constant in the temperature range 0-80°C, and although a number of other chiral phosphine ligands were screened, BINAP proved to be the most successful. It was also noted that the (E) stereoisomer was generated each time using a variety of allylic amines, irrespective of the starting geometry of the starting materials. There was an intriguing dependence, however, of the geometry of the starting amine on the absolute configuration of the enamine product (Figure 66).
It is a striking tribute to the power of enantioselective homogeneous transition metal catalysis that menthol, made in this way, currently accounts for about 25% of the world's menthol production, approximately seven tons a year by the Tagasako Perfumery Ltd. in Japan. In addition, the aldehyde, citronellal (62), is prepared in optically pure form during this process, as compared with only 80% ee from natural sources.

**New approach to enolate chemistry**

The reaction of an allylic alcohol with a catalytic quantity of a suitable transition metal catalyst, results in the formation of an enol which tautomerises to the carbonyl. Although this tautomerisation process has been found to be slow process in some cases, nevertheless, the synthetic utility of enols remains low. Within our own group, however, we believe that using an allylic alkoxide as the starting material, then the product of such an isomerisation would be a metal enolate. Hence, enolate anion chemistry can be accessed via allylic alcohols and not via the traditional ketone precursors (*Figure 67*).
The choice of base is important as the formed conjugate acid must not interfere with either the enolate product or the catalyst. Traditional methods to prepare enolates from carbonyl compounds using metal amide bases for irreversible deprotonation gives rise to amines which can affect the outcome of the reaction of the formed enolate with electrophiles. For example, following the addition of an alkylating reagent to the enolate, rapid protic exchange between unreacted enolate and alkylated material may lead to several unwanted by-products, such as polyalkylated material as well as aldol products.\textsuperscript{121} \textit{n-BuLi} was selected due to its ready availability, ease of handling and manipulation, and its conjugate acid, butane, would not affect the catalyst, nor the outcome of the isomerisation. Moreover, lithium enolates are more commonly used by organic chemists, and are of proven synthetic utility.

**Mechanistic overview**

\textit{Via Metal hydride addition and elimination}

The mechanism by which a transition metal promotes the isomerisation of an allylic alcohol or an allylic alkoxide is largely dependent upon the catalyst used. A metal containing a hydride ligand is likely to isomerise \textit{via} metal-hydride addition and elimination, whereby a metal hydride hydrometallates an olefin which is then followed by \(\beta\)-hydride elimination to form the enolate whilst regenerating the metal hydride (Figure 68).

\begin{equation}
\text{Enolate}
\end{equation}

\textit{Figure 68:} (\(B = \text{H or Li}\))

Such a sequence was inferred by Kraus who found that his Pd/C system was inactive in the absence of hydrogen, indicating the formation of a palladium hydrido species.\textsuperscript{102} A hydride catalyst may be either pre-formed, as is for example, the air sensitive iridium catalyst, \(\text{IrH}_3(\text{P} \text{Pr}_3\text{P})_2\),\textsuperscript{122} or generated \textit{in situ}, as was the case for the hydrido-nickel complex \((\text{Tol}_3\text{P})_2\text{NiHCl}\), prepared by the oxidative addition of hydrogen chloride to \((\text{Tol}_3\text{P})_2\text{Ni}(\text{CH}_2=\text{CH}_2)\).\textsuperscript{103}

The metal hydride may add in one of two ways across the olefin, such that subsequent elimination gives rise to mixture of regioisomeric and stereoisomeric products (Figure 69). The reversibility of the process eventually leads to an accumulation of the lower energy enol/enolate product (65). Such scrambling of stereo and regio isomers can be minimised if the carbinolic hydride is activated and thus more readily abstracted.
For β-Hydride transfer to occur on the alkyl metal intermediate (67), a cis-coplanar relationship is required between the metal -carbon bond and the carbon-hydrogen bond. \(^{123}\) Once hydrometallation has occurred, then elimination of the metal hydride is stereospecific, hence removal of hydrogens numbered 1, 2 and 3 will generate compounds (65), (66) and (68) respectively.

Via \(\pi\)-allyl and enone mechanisms

In the absence of a metal hydride, a second mechanism which is believed to operate occurs via a \(\pi\)-allyl-hydride intermediate (Figure 70). \(^{124-126}\) Coordination of the olefin to the transition metal is followed hydride abstraction of the carbinolic hydrogen. The positive charge developing at the carbinolic site may be stabilised by orbital overlap by the adjacent olefin to generate the \(\pi\)-allyl species with \(\pi^3\)-coordination, or via electron donation by the oxygen to form an enone intermediate.
The hydride is then delivered back to the other terminus of the allylic moiety or added Michael fashion to afford the enol, or enolate product.\footnote{100}

Formation of the enone intermediate was postulated by Sabatier and Senderens in which the isomerisation of allyl alcohol proceeded to give the product propanal via the intermediate propenal (\textit{See Figure 58}).\footnote{100} Other evidence for the formation of enone intermediates may be obtained by analysis of the minor products that are often formed during the isomerisation process. Sasson and Rempel examined a range of ruthenium phosphine complexes as potential allylic isomerisation catalysts, such as $(\text{Ph}_3\text{P})_3\text{RuCl}_2$, $(\text{Ph}_3\text{P})_3\text{RuH}_2$ and found that products of transfer hydrogenation were isolated in all of the reactions performed (\textit{Figure 71}).\footnote{75}

Consideration of the transfer hydrogenation processes, then in the same way that acetone is generated following hydrogen transfer from propan-2-ol, an enone could be generated following hydride transfer from an allylic alkoxide (\textit{See Figure 70}). The intermediary metal hydride that is produced may then reduce the formed enone Michael fashion to the enolate. Metal hydride reduction of enone is common and well documented.\footnote{127} Although no mechanistic studies were carried out, the formation of compound (69) indicates the possible involvement of the enone in the isomerisation process, using these ruthenium phosphine ligands.\footnote{100}

Both mechanisms operate overall via a 1,3-hydrogen shift, and evidence for this process was obtained by Von Rosenberg and co-workers,\footnote{124} who isomerised 1,1-di-[\textsuperscript{2}H]-2-propen-1-ol (70) to afford 1,3 di-[\textsuperscript{2}H]-propanal (71) as the only product (\textit{Figure 72}).

The equal distribution of the deuterium atoms at the 1 and 3 site in the product (71) implies that the first step in the mechanism, the formation of the \pi-allyl or enone intermediate is irreversible. If this was not the case, then it would be expected to observe an unequal distribution of the deuterium atoms between the 1 and 3-position and the appearance of scrambling of the labels in the substrate during catalysis. This was not observed using the Fe(CO)$_5$ catalyst. Although
similar results were obtained by Bergens and Bosnich, following the isomerisation of the same substrate using their [Rh(DIPHOS)]^+ catalyst, nevertheless a reversible mechanism involving a \( \pi \)-allyl intermediate was proposed to account for the (unobserved) scrambling (Figure 73).

![Figure 73](image)

Fiaud, and co-workers, studied the stereoelectronics of \( \pi \)-allyl formation. A mixture of the allylic alcohols (72) and (73), in the ratio 2 : 3, were isomerised in the presence of the Mo(N\(_2\))\(_2\)(DIPHOS)\(_2\) complex. It was noted that only the alcohol had (73) reacted, indicating a coplanar relationship between the C-H bond and the olefinic \( \pi \)-orbitals prior to hydride abstraction has taken place (Figure 74).

![Figure 74](image)

Detailed studies were carried by Noyori and co-workers in order to elucidate the mechanism and the steric course of the asymmetric isomerisation of \( N,N \)-diethylgeranylamine (64) (See Figure 65) using \(^1\)H and \(^31\)P-NMR techniques, kinetic studies and deuterium labelling experiments. Although \( \pi \)-allyl and metal-hydride addition and elimination mechanisms were known a new nitrogen-triggered mechanism was nevertheless proposed (Figure 75).
The complex (76) was initially considered to be generated from complex (75) by \( \beta \)-hydride elimination, however calculations suggested a preference for the cyclometallated complex (77) via oxidative addition of the C-H bond\(^{130} \). This step is the enantiodifferentiating step and is followed by reductive elimination to form the enamine complex (74). Release of the enamine from the rhodium catalyst was found to be the rate determining step. Indeed, complex (74) could be isolated and characterised by NMR spectra despite its thermal instability (above \(-35^\circ \text{C}\)) and extreme air sensitivity.

Isotope labelling studies confirmed that delivery of the hydride was an intramolecular process by isomerising the allylic amine (78) in the presence of the di-deuterated analogue (79). The enamine products were identified as shown, with the absence of the monodeuterated product (80), which could only be formed by an intermolecular process (Figure 76).

The result also confirmed the absence of a metal-hydride addition and elimination mechanism which would have led to the incorporation of deuterium at the 2-position on the enamine product due to the reversible nature of this mechanism.
The enantioselective step was determined also by deuterium labelling studies. It was found that that the chiral rhodium complex could differentiate between the enantiotopic C(1) hydrogens on the diethylgeranylamine substrate (Figure 77, Equation 1). A transoid conformation was suggested to rationalise the (E) selectivity in the formation of the enamine, as a cisoid arrangement was considered unfavourable due to the steric influence of the bulky BINAP ligand. Delivery of the hydride then proceed in a suprafacial manner (Equations 2,3). Thus the enantioselective step was the first step involving hydride abstraction.

![Diagrams](image)

Figure 77

A fourth mechanism was proposed by Davies in 1964 to account for his observations in the isomerisation of oct-1-ene to oct-2-ene in the presence of the sodium chloropalladate catalyst, Na₂[Pd₂Cl₆]. Using deuterium labelled oct-1-ene, the mechanism was believed to operate via a '1,2-hydrogen migration' and an alkylidene intermediate (Figure 78).

![Diagram](image)

Figure 78

Deuterium labelling studies confirmed a π-allyl mechanism was not in operation due to distribution of the deuterium atoms along the carbon chain. It was noted that 2-methyl-1-octene
failed to isomerise indicating the operation of a '1,2-hydrogen migration' due to the absence of a hydrogen at the 2-position. Unfortunately, there was little other conclusive evidence, and since then, the mechanism has received little attention.

**Aims of the project**

Some of the problems associated with the formation of metal enolates using traditional methods, such as basic deprotonation of carbonyl compounds, highlighted a need for a new method for enolate preparation. Controlling the regio and stereochemistry of the enolate, using these techniques, is a problematic area, and it was envisaged that many of these difficulties could be overcome if enolates could be prepared using an allylic alkoxide as the starting material. Isomerisation of this substrate, catalysed by suitable transition metal complexes, would then afford the metal enolate. Catalysis is a powerful method for exerting control in product formation, therefore the potential for this new methodology for regio-, stereo- and enantiocontrolled enolate formation was recognised, and therefore make up the overall aims of this project.

- The most fundamental goal is that of regiocontrol and it was envisaged that a regio-pure enolate could be prepared from a regiochemically defined starting material, *i.e.* the position of the double bond in the enolate is pre-determined by the position of the double bond in the allylic alcohol precursor.

  *i.e.* Whereas basic deprotonation can lead to a mixture of regioisomers, the isomerisation of suitable allylic alkoxide precursors, both regioisomers are accessible individually pure.

- Stereocontrol could in principle arise as a consequence of differences in the activation energy for either isomer, hence a variation in the catalyst and/or the reaction conditions might enable either the *(E)* or the *(Z)* enolate isomer to be obtained.

- Finally, and perhaps our most ambitious goal as implied in *Figure 67*, enantioselectivity could be achieved through the selection of a suitable chiral ligand around the transition metal, and this in turn would create a new chiral centre at the β-carbon on the enolate.
Isomerisations with Non-Chiral Ni(II) Complexes
Introduction

The diversity of transition metal catalysts that have the ability to isomerise allylic alcohols to carbonyl compounds provided a starting point in the search for suitable catalysts, using metal allylic alkoxides as substrates. The catalyst initially investigated within the group was the complex [Rh(DIPHOS)]+, which had also been used by Bergens and Bosnich to analyse the stereochemical formation of persistent enols from allylic alcohols. The results obtained by Bergens and Bosnich therefore served as a guide as to whether or not the isomerisation of allylic alcohols would proceed with the same degree of stereoselectivity as the allylic alcohols.

As the course of the project developed, other catalysts were investigated, such as (Ph₃P)₂RhCl (Wilkinson’s catalyst) and (Cy₃P)₂NiCl₂/n-BuLi. A range of mono-, bi-, tri- and tetra-substituted metal allylic alkoxides were synthesised and isomerised, and the relative reactivities of these catalysts compared in order to elucidate mechanistic details and their scope in terms of regio and stereocontrolled enolate formation.

The use of nickel complexes as isomerisation catalysts was realised following reports that dichloronickel(ll)bis(tricyclohexylphosphine) (81) could be reduced by lithium alkoxides via carbinolic hydride abstraction, generating chlorohydridonickel(ll)bis(tricyclohexylphosphine) (82) and the corresponding carbonyl compound (Figure 79). It was envisaged that by selecting an allylic alkoxide, then the hydride could be returned to the substrate giving rise to an enolate, thus constituting an isomerisation. This complex has since been shown to be an effective catalyst in this chemistry.

![Figure 79](image)

The stereochemical outcome of the isomerisation of allylic alkoxides, i.e. enolate geometry, was initially investigated by treatment of the reaction mixture with benzaldehyde, under kinetically controlled conditions (Figure 80).
Results and Discussion

Figure 80: (i) n-BuLi; (ii) [Rh(DIPHOS)]* (2 mol%), 60°C, 7 h; (iii) PhCHO, -78°C; then NH₄Cl(aq) after 5 seconds.

The ratio of aldol products could be rationalised in terms of the Zimmerman-Traxler transition state model (Figure 81), whereby the bulky phenyl substituent on the aldehyde preferentially lies in an equatorial position in the 6-membered transition state, thus minimising 1,3 diaxial interactions. As a consequence (E) enolates favour the formation of anti aldol products, and (Z) enolates favour the formation of syn aldol products.

Direct enolate ratios were obtained at a later stage by the addition of acetic anhydride to the crude reaction mixture at -78°C, and subsequent analysis of the isolated enol acetates by NMR and gas chromatography (GC). It was also noted that primary allylic alkoxides gave predominantly anti aldol products, thereby derived from (E) enolates, while secondary allylic alkoxides gave predominantly the syn aldol products from the corresponding (Z) enolates.

The preference for the (E) and (Z) enolates, originating from primary and secondary allylic alkoxides respectively, could be rationalised for all three of the proposed mechanisms:
\(\pi\)-Allyl mechanism

Chin and co-workers argued that the preference for the formation of the thermodynamically more stable \((E)\) enol, following the isomerisation of primary allylic alcohols with their cationic rhodium-phosphine complex, was due to the hydroxyl group aligning itself away from the steric bulk of the ligands on the metal in the \(\pi\)-allyl intermediate \((56)\) (Figure 60).\(^{113,114}\)

For allylic alkoxides, an additional factor must be taken into consideration, which is the increased bulk around the oxygen due to lithium aggregation.\(^{140,141,142}\) With this in mind, the same argument still holds true for primary allylic alkoxides where the aggregated lithium-oxygen bond is preferentially aligned away from the steric bulk of the ligands on the metal. Thus complex \((83)\) will proceed to generate an \((E)\) enolate as product (Figure 82).

![Figure 82: Ligands on metal not shown for clarity](image)

For secondary allylic alkoxides, \((Z)\) enolates formation is favoured. This would require the \(R\) group to be aligned away from the metal catalyst. It is likely that the bulk of the ligands on the catalyst imposes a greater steric influence on the \(R\) group than on the labile structure of the O-Li aggregate, hence the preferential formation of the \(\pi\)-allyl complex \((85)\), rather than \((84)\). As a result, the \((Z)\) enolate is formed in preference to the \((E)\) enolate on steric grounds. Interconversion between complexes \((84)\) and \((85)\) is possible either by a reversal in the formation of the \(\pi\)-allyl complex, or by '\(\pi\)-\(\sigma\)-\(\pi\)' fluxionality (See figure 61).

Metal-hydride addition and elimination

Stereoselectivity may depend upon the facial selectivity of the hydrometallation step on the olefinic centre (Figure 83), i.e. if \(k_1 > k_2\) then an accumulation of the \((Z)\) enolate will occur.
Results and Discussion

If the rate of $\beta$-hydride elimination were different, i.e. if $k_3 > k_4$, then stereoselectivity may arise this way too. If elimination to the $(E)$ enolate was sufficiently slow for reversion to the starting material to compete then the selectivity for the $(Z)$ enolate would be further enhanced.

Following hydrometallation, alignment of the $\beta$-hydrogen with the metal must occur before $\beta$-hydride, or metal-hydride elimination can occur. The rate of formation of the complexes (86) and (87) may be influenced by steric interactions between the substituents on the alkyl moiety (Figure 84).

For secondary allylic alkoxides ($R \neq H$), then complex (87) is disfavoured due to steric interactions between the eclipsed $R$ and methyl groups. Interactions between the methyl and the labile structure of the O-Li aggregate is less, thus resulting in the preferred formation of the $(Z)$ enolate. For primary allylic alkoxides, complex ($R = H$) is now favoured as the two groups present which may impose steric effects, i.e. the O-Li aggregate and the methyl, are not eclipsed and are trans to one another. Consequently, the $(E)$ enolate will be preferentially formed.

Although these arguments only apply to kinetic product ratios, the enolate products themselves may undergo metal-hydride addition and elimination, such that the ratio of the $(E)$ and $(Z)$ enolates at the end of the reaction will be thermodynamically controlled.113,114,115
Enone mechanism

A mechanism operating via an enone intermediate, can produce the (Z) and (E) enolates via cisoid and transoid intermediates, as illustrated below (Figure 85).

Formation of the oxo-cyclobutadiene (B) intermediate is unlikely as loss of a ligand is necessary in order to maintain an 18e⁻ configuration. Therefore the cisoid and transoid π-complexes (A) and (C) will result in the formation of the (E) and (Z) enolates respectively. Interconversion of (A) and (C) may be achieved via bond rotation. If R = H, then the olefin may prefer to align away from the bulk of the O-Li aggregates, hence the preference for (E) enolate formation. When R ≠ H, then the R group will be aligned away from the steric bulk of the ligands situated on the metal catalyst, resulting in the formation of the (Z) enolate. Delivery of the hydride to the 3-position on the enone or enal requires an intimate association with the hydrido metal and it is possible that the steric influence (if any) imposed by the R will determine the stereochemical outcome of the isomerisation (Figure 86).

Although these arguments present a simple picture of steric interactions to explain the preference for the formation of the (E) and (Z) enolates from primary and secondary allylic alkoxides
respectively, the potential reversibility of the process means that the initial enolate ratio, \textit{i.e.} kinetic ratio may be different to the enolate ratio at the end of the reaction, as was observed by Bergens and Bosnich in the isomerisation of allylic alcohols to persistent enols.\textsuperscript{117} A kinetic study would therefore need to be conducted in order to fully assess the factors governing the stereocontrolled formation of enolates.

Catalysis is a very powerful and economical method for the introduction of asymmetry into an achiral molecule. The potential for our system to achieve enantioselective isomerisations is considerable, as these phosphine ligands can be replaced, in principle, by one of the vast number of readily available chiral mono and bidentate phosphine ligands.\textsuperscript{143} Chiral monodentate phosphine ligands however have a low metal phosphine bond rotational energy barrier, which generally means that these ligands do not provide a sufficiently rigid chiral environment around the metal centre. As a result, differentiation between diastereotopic intermediates could be inefficient, and indeed, asymmetric induction using these ligands is generally found to be low.\textsuperscript{143} Thus, it was considered not to be a viable option to replace the phosphine ligands in the \((R_3P)_2NiCl_2/n\text{-BuLi}\) catalyst system with chiral monodentate phosphine ligands for use in our asymmetric studies using prochiral allylic alkoxides.

Systems bearing chiral bidentate \(C_2\)-symmetric ligands however enforce single conformations and therefore offer a greater degree of enantiocontrol. Such ligands include CHIRAPHOS, Me-DUPHOS,\textsuperscript{144} DIOP, BDPP and BINAP\textsuperscript{145} (\textit{Figure 87}).

\[
\text{(R,R)-CHIRAPHOS} \quad \text{(R,R)-BDPP} \quad \text{(S,S)-DIOP} \\
\text{(R,R)-Me-DUPHOS} \quad \text{(R)-BINAP}
\]

\textit{Figure 87} : Chiral bidentate phosphine ligands

In the first instance, the complex \(\text{NiCl}_2(\text{DIPHOS})\) was selected as a suitable pre-catalyst since it was envisaged that the achiral DIPHOS ligand could be replaced with a chiral analogue such as CHIRAPHOS, and serve as a suitable catalysts in our asymmetric studies. Activation of the
NiCl$_2$(DIPHOS) complex would be achieved using n-BuLi, in the same way as had been achieved for the NiCl$_2$(Ph$_3$P)$_2$ and NiCl$_2$(Cy$_3$P)$_2$ complexes. Activation of NiCl$_2$(DIPHOS) with n-BuLi, however, failed to give an active catalyst, and attempts to isomerise 1-phenyl-2-propen-1-ol (88) met with little or no success.\\(^{133}\)

At this particular moment in our studies, we were particularly intrigued to note that an Italian group reported the use of an active nickel-(DIPHOS) isomerisation catalyst, which was prepared by the addition of a Grignard reagent, 'PrMgBr, to the NiCl$_2$(DIPHOS) complex.\\(^{145}\)

Thus, the NiCl$_2$(DIPHOS)/'PrMgBr catalyst system was able to isomerise 1,4-but-2-ene diol derivatives to 1,4-but-1-ene diol derivatives in less than one minute, and under very mild conditions. This stands in contrast to the previous isomerisation of allylic ethers to vinyl ethers, which generally require high temperatures and extended periods reaction time.\\(^{106,147-151}\) In a typical experiment, the group treated one molar equivalent of allylic ether and 0.02 molar equivalents of NiCl$_2$(DIPHOS) in THF at 0°C with 0.04 molar equivalents of 'PrMgBr. After the formation of a reddish solution, 0.01 molar equivalents of trimethylsilyl chloride was added at room temperature. Following work-up, the products were isolated virtually free of any impurities. Some of their results are illustrated below (Figure 88).

![Diagram of isomerisation reactions](image)

**Figure 88**: Isomerisation of 1,4-but-2-ene diol derivatives to 1,4-but-1-ene diol derivatives.

(i) NiCl$_2$(DIPHOS) in THF; (ii) 'PrMgCl, 0°C; (iii) TMSCl, RT.

The same group also obtained comparable results using a similar catalytic system prepared by the addition of one equivalent of LiBE$_3$H (or Super-Hydride) to a suspension of NiCl$_2$(DIPHOS) in THF. The resulting complex prepared using this reducing reagent has been shown to be a Ni-H species.\\(^{152,153}\)
Initial Studies

The ease with which this catalyst system could isomerise allylic ethers led us to investigate whether or not this system could isomerise allylic alkoxides under the same conditions, as all previous isomerisations of allylic alkoxides required several hours of reaction time in THF heated to reflux (ca. 65°C).

In the first instance, we were delighted to confirm these results by repeating the isomerisations of 1,4-dimethoxybut-2-ene (89) and 1,4-dibenzyloxybut-2-ene (90), which gave the corresponding enol ethers in virtually quantitative yield (Figure 89). It should be noted however that the addition of the trimethylsilyl chloride was not necessary, as in each case, the isomerisations were complete before its addition.

\[
\begin{align*}
\text{(89)} & \quad \begin{array}{c}
\text{OMe} \quad \text{OMe} \\
\text{OMe} \quad \text{OMe}
\end{array} \\
\text{96%} & \quad \begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{OMe}
\end{array} + \begin{array}{c}
\text{OMe} \\
\text{OMe}
\end{array} \\
& \quad 3.6:1
\end{align*}
\]

\[
\begin{align*}
\text{(90)} & \quad \begin{array}{c}
\text{O} \quad \text{O} \\
\text{Ph} \quad \text{Ph}
\end{array} \\
\text{95%} & \quad \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \\
& \quad 8:1
\end{align*}
\]

Figure 89: (i) NiCl₂(DIPHOS) in THF; (ii) PrMgCl, 0°C.

With this potentially new enantioselective catalytic system in hand, it was decided to attempt the isomerisation using lithium allylic alkoxides. 1-Phenyl-2-propen-1-ol (88) was initially chosen as the isomerisation would bring the olefin into conjugation with the aromatic ring, thus improving reaction rates and yields. This alcohol was prepared in 82% by the addition on vinyl magnesium bromide to benzaldehyde.

Several experiments were conducted using the NiCl₂(DIPHOS)/PrMgCl catalyst using the alkoxide of (88) instead as substrate. The conditions of the reaction were identical to conditions employed for the isomerisation of the 1,4-but-2-ene diol ethers.

In all instances no compounds, other than the starting material, were detected by GC and it was clear that at room temperature there was insufficient energy to drive the isomerisation process (Figure 90, Equation 1). As a consequence it was necessary to modify the reaction conditions. Therefore, a solution of the alkoxide and NiCl₂(DIPHOS) complex was heated to reflux, at which
point the Grignard reagent was added. Using this new procedure we were delighted to obtain reasonable yields of propiophenone (91), following treatment of the formed lithium enolate with saturated NH₄Cl solution (Equation 2).

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

\[(88) \xrightarrow{(i), (ii), (iii), (v)} \text{No Isomerisation} \quad (1)\]

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

\[(88) \xrightarrow{(i), (ii), (iv), (v)} \quad 41\% \quad \text{Ph} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\]

\[(91) \quad \text{(2)}\]

**Figure 90**: (i) n-BuLi; (ii) NiCl₂(DIPPHOS); (iii) 'PrMgCl, 0°C; (iv) 'PrMgCl, reflux; (v) NH₄Cl(aq).

In terms of consistency though, it was noted that a varying response in the colour of the refluxing solution, upon the addition of the Grignard reagent, indicated the capriciousness of the technique, and hence an unsatisfactory catalyst system. However, a more reliable catalyst system was obtained using KBEt₃H as the activating agent instead of 'PrMgCl. Adding KBEt₃H to the NiCl₂(DIPPHOS) complex at -78°C, and allowing the solution to slowly warm to room temperature, an active NiCl₂(DIPPHOS)/KBEt₃H catalyst was able to smoothly isomerise a variety of simple allylic alkoxides giving consistent results each time (Figure 91). Identical results were obtained using either KBEt₃H or LiBEt₃H.

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

\[(88) \xrightarrow{(i), (ii), (iii), (iv)} \quad 81\% \quad \text{Ph} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\]

\[(91) \quad \text{(2)}\]

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

\[(88) \xrightarrow{(i), (ii), (iii), (v)} \quad 73\% \quad \text{Ph} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\]

\[(92) + \quad (93) \quad 96 : 4 \quad \text{Ph} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\]

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

\[(94) \xrightarrow{(i), (ii), (iii), (vii)} \quad 73\% \quad \text{Ph} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\]

\[(95) + \quad (96) \quad 4 : 1 \quad \text{Ph} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\]

**Figure 91**: (i) n-BuLi in THF; (ii) NiCl₂(DIPPHOS)/LiBEt₃H; (iii) reflux, 3 hours; (iv) NH₄Cl; (v) Ac₂O; (vi) reflux, 6 hours; (vii) PhCHO, -78°C.
The enolate products were reacted with acetic anhydride or benzaldehyde. The yields and ratios of the enol acetates, and the syn-anti aldol products compared favourably with the results obtained with the [Rh(DIPHOS)]⁺ and (Cy3P)2NiCl2/n-BuLi catalyst systems from earlier work within the group.133,134

The need to adjust the initial reaction conditions from 0°C to refluxing THF was of little surprise considering the difference in properties between an allylic ether and an allylic alkoxide. It therefore seemed worthwhile to lower the ionic nature of the oxygen anion by methylation with the intention of returning to the conditions originally employed with this catalyst.146

The corresponding methyl ether (97) was prepared and isomerised using the NiCl2(DIPHOS)/1PrMgCl catalyst (Figure 92, Equation 1). In spite of the success with the 1,4-but-2-ene diol derivatives, no isomerised products were detected. However selection of the NiCl2(DIPHOS)/LiBEt3H catalyst combination in THF heated to reflux did lead to isomerisation products, albeit in very low yield and selectivity (Equation 2). The reason for the loss of stereoselectivity is not very clear.

![Figure 92](image-url)

Following on from this success in the isomerisation of these monosubstituted allylic alcohols, it was decided to attempt the isomerisation on more substituted allylic alkoxides. The decrease in reactivity of catalytic systems towards isomerisation as olefinic substitution increases is still an area of difficulty that remains to be resolved.102
Studies On Regiocontrol

One of the objectives of our study was to control the regiochemistry of the enolate. In principle this could be achieved by pre-selection of the allylic alcohol. The area was initially probed using 3-penten-2-ol (100), a commercially available di-substituted allylic alcohol. The alkoxide was isomerised using the NiCl$_2$(DIPHOS)/LiBEt$_3$H catalyst system in THF heated to reflux. After 6.5 hours, TLC analysis of reaction indicated good conversion to the corresponding ketone, however, following reaction of the enolate with benzaldehyde, analysis of the mixture by NMR revealed a complex mixture of products (Figure 93, Equation 1). Identical results were obtained with all the isomerisations conducted on this particular substrate. Replacement of the vinylic methyl group by a phenyl group, as in (101), did not improve the outcome of the isomerisation, as similar results were obtained (Equation 2). GCMS analysis indicated the presence of significant quantities of polymeric, or oligomeric material.

![Complex mixture of aldol products](image1)

**Figure 93**: (i) n-BuLi, THF; (ii) NiCl$_2$(DIPHOS)/LiBEt$_3$H, then reflux for 6.5 hours; (iii) PhCHO, -78°C, then NH$_4$Cl(aq) 5 seconds later

This lack of regioselectivity exerted by the NiCl$_2$(DIPHOS)/LiBEt$_3$H catalyst system was further demonstrated by the isomerisation of 1-phenyl-4-penten-3-ol (102), prepared by the addition of vinyl magnesium bromide to 3-phenylpropanal (103). TLC analysis of the crude reaction mixture, after isomerisation in THF heated to reflux for 90 minutes, indicated that little starting material was present. Benzaldehyde was then added at -78°C, prior to a protic quench five seconds later. Purification of the residue afforded the ketone (104) in 14% yield and an inseparable mixture of all four possible regio and stereoisomers in 59% yield (Figure 94).
Results and Discussion

Figure 94: Regiochemical ratio: i.e. \{(105) + (106)\} : \{(107) + (108)\} = 1 : 1.36

(1) \((\text{CH}_2\text{CH})\text{MgBr}, \text{THF}, 0^\circ\text{C}\); (ii) \(n\text{-BuLi, THF}\); (iii) \(\text{NiCl}_2\text{(DIPHOS)}\text{/LiBEt}_3\text{H}\), then reflux for 6.5 hours; (iv) \(\text{PhCHO}, -78^\circ\text{C}\), then \(\text{NH}_4\text{Cl(aq)}\) 5 seconds later

The problem of regioselectivity has been encountered, especially with this substrate, in previous work. Using the \((\text{Ph}_3\text{P})\text{RhCl}\) and \([\text{Rh(DIPHOS)}]^+\) catalysts, a similar mixture of regioisomers were obtained. This was in contrast however to the \((\text{Cy}_3\text{P})\text{NiCl}_2\)/\(n\text{-BuLi}\) catalyst which only gave the desired regioisomers (105) and (106) in 92% yield, and in the ratio 6 : 1.

There appear to be two possible mechanisms which could lead to this apparent equilibration of enolate regioisomers: either by adventitious protic exchange or by a further transition metal mediated isomerisation of the first formed lithium enolate (Figure 95).

Figure 95: Possible intermediates during enolate equilibrium resulting in loss of regiochemistry.

The proton exchange mechanism requires only a very small quantity of some proton source. Incomplete deprotonation of the starting alcohol was considered as a likely source of protons, however a minimum excess of \(n\text{-BuLi}\) was used each time, which was indicated by the trace
formation of coloured dianions from the benzylic alcohol substrates. Much of the excess \(n\)-BuLi is decomposed by the THF solvent, by a known reaction, to afford ethylene and the lithium enolate of ethanal (Figure 96).^154

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

Figure 96

It was therefore unlikely that incomplete deprotonation was causing the equilibration of the lithium enolates. It was considered that material was being generated during the course of the reaction, which could serve as a proton source to effect the equilibration process, and at the same time, protonate the enolate product to afford the parent ketone (104).

Previous studies, using the same substrate in the presence of the \((\text{Ph}_3\text{P})_3\text{RhCl}\) catalyst, found that conducting the experiment in excess \(n\)-BuLi (up to 50% w.r.t starting material) suppressed the equilibration process to the extent that the ratio of the desired (109) to undesired regioisomers (110) had increased from about 1 : 1.2 up to nearly 10 : 1 respectively (Figure 97).

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

Figure 97

A lower yield of product was obtained using the excess of \(n\)-BuLi, presumably due to inactivation of the \((\text{Ph}_3\text{P})_3\text{RhCl}\) catalyst by the base. Reactive organometallic reagents are commonly used for the reduction of transition metal complexes (See Figure 79) and it is conceivable that a rhodium hydride species was generated following the reaction between \((\text{Ph}_3\text{P})_3\text{RhCl}\) and \(n\)-BuLi. Metal hydride complexes are likely to operate via a metal-hydride addition and elimination mechanism, and such a mechanism is likely to cause equilibration of the enolates. The nature of the \((\text{Ph}_3\text{P})_3\text{RhCl}/n\)-BuLi species was therefore uncertain.

It is known that reduction of dichloronickel complexes with LiBEt\(_3\)H generates nickel hydride species,\(^152,153\) therefore it is likely that the \(\text{NiCl}_2(\text{DIPHOS})/\text{LiBEt}_3\text{H}\) catalyst system operates via metal-hydride addition and elimination mechanism.
A study by Jonas and Wilke\(^{155}\) isolated a dimeric Ni-H species \((111)\) following the reduction of \(\text{NiCl}_2(\text{Cy}_2\text{PCH}_2\text{CH}_2\text{PCy}_2)\) with two equivalents of \(\text{NaBEt}_3\text{H}\), a reaction not too dissimilar to the addition of \(\text{LiBEt}_3\text{H}\) to \(\text{NiCl}_2(\text{DIPHOS})\). The formed complex \((111)\) comprises of two paramagnetic Ni units, \(\text{NiH(Cy}_2\text{PCH}_2\text{CH}_2\text{PCy}_2)\), but is diamagnetic, as evidenced by NMR. It is presumed there is Ni-Ni bonding, however the possibility of two Ni(0) units with a \(\text{H}_2\) molecule cannot be ruled out (Figure 98).

![Figure 98](image)

Complex \((111)\) was found to be very thermally stable, however decomposed in mesitylene solution, with evolution of \(\text{H}_2\) only at the boiling temperature. \(\text{H}_2\) was even replaced at room temperature by \(\text{Ph}_3\text{P}\), olefins such as ethylene, propylene and \(\text{cis}\)-butene as well as by \(\text{MeCN}\); in each case calculated amounts of \(\text{H}_2\) and Ni(0) were formed. In addition, complex \((111)\) reacted with the starting material to give \(\text{NiCl(Cy}_2\text{PCH}_2\text{CH}_2\text{PCy}_2)\) and \(\text{H}_2\).\(^{155}\) It is very likely that a similar array of compounds are formed by the addition of \(\text{LiBEt}_3\text{H}\) to \(\text{NiCl}_2(\text{DIPHOS})\) in our catalyst system.

This lack of regioselectivity demonstrated by the \((\text{Ph}_3\text{P})\text{RhCl}, [\text{Rh(DIPHOS)]}^+\) and \(\text{NiCl}_2(\text{DIPHOS})/\text{LiBEt}_3\text{H}\) catalyst systems was not observed by Bergens and Bosnich during their studies on enol formation (Figure 62),\(^{117}\) even though the same \([\text{Rh(DIPHOS)]}^+\) catalyst was used and the availability of protons from the allylic alcohol substrate themselves. It is likely therefore that the equilibration of the enolate regioisomers is due to a second isomerisation process, competing with the first.

Although a metal-hydride elimination mechanism has been implied to be responsible for the enolate equilibration, previous mechanistic studies have shown that the \([\text{Rh(DIPHOS)]}^+\) catalyst operates via a \(\pi\)-allyl mechanism whereas the \((\text{Cy}_3\text{P})_2\text{NiCl}_2/n\text{-BuLi}\) catalyst operates via metal-hydride elimination. Only the latter catalyst offered high levels of regiocontrolled enolate formation, implying that equilibration does not proceed via metal-hydride addition and elimination. From these observations, it is not apparent how the equilibration of the lithium enolates is mediated.

It was considered that the initial isomerisation step could be accelerated with respect to the enolate scrambling step by making the oxygen lone pairs more available for donation to the C-H bond (Figure 70, Equation 2). This could be achieved by breaking up the lithium aggregates,
which would otherwise tie up the lone pairs, by the addition of chelating agents such as TDA-1, TMEDA, HMPA, DMPU and 18-crown-6. It was envisaged that the outcome of such experiments would be an improvement on reaction rates and regioselectivity. In the event, however, only rate enhancement was observed, implying that lithium aggregation plays an insignificant part in the formation of the enolate regioisomers.

The lack of regiocontrol exerted by our catalytic system was unexpected, especially considering the fact that the apparently closely related (Cy3P)2NiCl2/n-BuLi catalyst achieved an excellent degree of regiocontrol. In spite of this setback in one of our objectives, some effort was made to apply this catalytic system for asymmetric isomerisation.

**Attempted Isomerisations of Prochiral Allylic Alkoxides**

Geraniol (61) possesses the asymmetrical terminal disubstitution required for the creation of a new chiral centre upon isomerisation (*Figure 99*), as well as a second double bond in addition to the allylic moiety. A successful isomerisation of the trisubstituted allylic alcohol moiety on geraniol (61) would therefore be a step closer to achieving asymmetric catalysis.

![Asymmetric isomerisation of geraniol (61), creating a new chiral centre (*).](image)

The isomerisation of the alkoxide was conducted using a variety of different solvents, i.e. refluxing THF, benzene and toluene heated to 60°C. In each case analysis by GC of aliquots taken from the reaction mixture during the course of the isomerisation indicated the formation of the isomerised product citronellal (62). However as the reaction progressed, TLC and GCMS indicated the formation of the transfer hydrogenation product, citronellol, in addition to several other unidentifiable products. Although isolation of the products was not attempted, GC analysis of the crude reaction mixture indicated a trace amount of citronellal (62) using 0.05 molar equivalent of the NiCl2(DIPHOS)/LiBET3H catalyst, and approximately 22% of citronellal (62) using 0.20 molar equivalent of the catalyst (*Figure 100*).
The results were slightly disappointing as geraniol had previously been isomerised to the corresponding enol acetates in 69% yield using 10 mol% of the (Cy3P)2NiCl2/n-BuLi catalytic system. Our attention then turned to a different prochiral allylic alcohol, namely (E)-3-phenyl-2-buten-1-ol (63). This alcohol may be prepared in two steps following literature procedures and involve an initial a Reformatskii reaction between acetophenone and ethyl bromoacetate, followed by the reduction of the ester (113) to the allylic alcohol (63) using diisobutylaluminium hydride (Figure 101).

Prior to using this prochiral alcohol in our catalytic system we attempted the isomerisation on the structurally analogous compound, (E)-3-phenyl-2-propen-1-ol, or cinnamyl alcohol (58) (Figure 102, Equation 1). However, despite numerous attempts on this substrate, no reaction took place. It was therefore no surprise to find that the isomerisation of the (E)-3-phenyl-2-buten-1-ol (63) failed to proceed either (Equation 2).
From a thermodynamic standpoint, the formation of the enolate does not apparently compensate for deconjugation of the styrene chromophore.

During the isomerisations of secondary allylic alkoxides, a dark brown-black solution or suspension was observed, which was maintained throughout the period of reflux. This was in contrast to observations made during the isomerisation of primary allylic alcohols in which a gradual loss of colour finally gave rise to a yellow solution containing a white sediment. It is evident that during the isomerisation of these substrates, deactivation of the catalyst is occurring. This could be achieved via decarbonylation of the alkoxide-catalyst complex giving rise to an inactive Ni-CO species. Such a process has been reported by Y-Lin and X-Lu, who were able to isolate the compound cis-Mo(CO)$_2$(DIPHOS)$_2$ following the isomerisation of primary alcohols with the catalyst Mo(N$_2$)$_2$(DIPHOS)$_2$. Such a deactivation is not in fact uncommon.

The problems encountered with the NiCl$_2$(DIPHOS)/LiBEt$_3$H catalyst, and in particular its decomposition with primary allylic alkoxides, meant that its potential for evolution as an asymmetric catalyst was in some doubt. The use of reducing agents, such as n-BuLi or LiBEt$_3$H also made it difficult to predict what the actual active species was, be it a nickel(0) or a nickel(I) species, or perhaps a combination of the two. Attempts to rationalise the events occurring during this ‘activation’ are made more formidable as n-BuLi can activate NiCl$_2$(Cy$_3$P)$_2$, but not NiCl$_2$(DIPHOS), whereas PrMgBr and LiBEt$_3$H can.

It was considered that treatment of NiCl$_2$(Cy$_3$P)$_2$ (81) with 1 equivalent of n-BuLi might have given a chlorohydridonickel(II)bis(tricyclohexylphosphine) species (82) via β-hydride elimination of the formed α-alkynickel complex (114) (Figure 103).
Results and Discussion

Such a process has been shown by Wilke to occur upon treatment of α-allylnickel bromide with ethyllithium. However, the presence of a β-hydrogen on the alkyllithium reagent is not a prerequisite for the formation of an active isomerisation catalysts, as demonstrated by the addition of MeLi, which does not possess a β-hydrogen, to NiCl₂(Cy₃P)₂ which furnished an active catalyst able to isomerise 1-phenyl-4-penten-3-ol (102) in 63% yield. The picture is further complicated by Otsuka's observation that the alkyl metal complex, NiBr(n-C₆H₁₃)(Ph₃P)₂, decomposes to the nickel(I) complex NiBr(Ph₃P)₃ upon heating.

It is known that the addition of two equivalents of methyllithium to dichloronickel(II)bis(phosphine) complexes in the presence of an arene leads to a (α-arene)nickel(0)bis(phosphine) species, following the reductive elimination of ethane from the bis(alkyl)Ni(II) intermediate (Figure 104).

Therefore the alkyllithium reagents may generate an active isomerisation species in two ways, either by the formation of a chlorohydridonickel(II) intermediate as depicted in Figure 103, or by reductive elimination of an alkane from bis(alkyl)Ni(II) intermediate to form a Ni(0) species, as depicted in Figure 104.

The procedure to prepare this Ni(0) species using MeLi was only applicable to monodentate phosphine ligands, and not to bidentate ligands, such as 1,2-bis(diethylphosphino)ethane. The lack of reactivity exhibited by these nickel-bis(phosphine) complexes to alkyllithium reagents was also observed following the addition of n-BuLi to the NiCl₂(DIPHOS) complex, which failed to isomerise the alkoxide of 1-phenyl-2-propen-1-ol (88), compared with near quantitative conversions using the (Cy₃P)₂NiCl₂/n-BuLi, [Rh(DIPHOS)]⁺ and NiCl₂(DIPHOS)/LiBEt₃H catalyst systems.
It is not clear either whether the Grignard reagent $\text{P}^7\text{rMgBr}$ is behaving in the same way as $\text{n-BuLi}$ to generate an intermediary Ni(II)HCl species, or forms a dialkynickel(II) species, which then reductively eliminates to form a Ni(0) complex.

We therefore decided to attempt to resolve the question of whether or not a Ni(0) species was functioning as the active isomerisation catalyst by selecting the complex Ni(COD)$_2$. The loosely bound COD ligands have been shown to undergo ready ligand exchange with phosphines to generate Ni(0)phosphine complexes. Therefore, Ni(COD)$_2$ presented itself as a suitable entry into Ni(0) chemistry whereby any ligand might be employed, particularly ligands possessing C$_2$-symmetry, with the intention of employing these chiral Ni(0) catalysts in our asymmetric isomerisation studies.
Isomerisations with Chiral Ni(0) Complexes
Introduction

It was reasoned that the addition of two equivalents of phosphine, such as Cy$_3$P, to Ni(COD)$_2$ would furnish a (Cy$_3$P)$_2$Ni(0) species, an intermediary species possibly formed following the addition of n-BuLi to NiCl$_2$(Cy$_3$P)$_2$.$^{133}$ Initial studies found the Ni(COD)$_2$/Cy$_3$P catalyst system could efficiently isomerise the alkoxide of geraniol in 70% yield, requiring only 2 hours of reaction time. Geraniol (61) is a tri-substituted allylic alcohol, and a demanding substrate due to increased hindrance about the allylic centre. There are several reported attempts to isomerise the allylic alcohol with varying degrees of success, though most are unsuccessful. The Ni(COD)$_2$/Ligand catalyst system compares very favourably with these reported attempts (Figure 105).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst System</th>
<th>Yield of (62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 $^{160,161}$</td>
<td>Cp(Ph$_3$P)$_2$RuCl (5%), Et$_3$N$\cdot$HCl</td>
<td>0</td>
</tr>
<tr>
<td>2 $^{109}$</td>
<td>[Ir(COD)(Ph$_2$PMe)$_2$]$^+PF_6$</td>
<td>14</td>
</tr>
<tr>
<td>3 $^{119}$</td>
<td>[Rh(BINAP)]$^+$</td>
<td>70% (24 hours)</td>
</tr>
<tr>
<td>4 $^{133}$</td>
<td>NiCl$_2$(Cy$_3$P)$_2$/n-BuLi$^*$</td>
<td>60% (6 hours)</td>
</tr>
<tr>
<td>5 $^{133}$</td>
<td>Ni(COD)$_2$/2Cy$_3$P$^*$</td>
<td>70% (2 hours)</td>
</tr>
</tbody>
</table>

Figure 105: (* isomerisation of the alkoxide)

Ni(COD)$_2$ was prepared following a procedure published by Krysan and MacKenzie.$^{162,163}$ The reduction of Ni(acac)$_2$ with diisobutylaluminium hydride in the presence of the COD ligands generates a stable product which requires storage at -40°C under an inert atmosphere. A fully equipped glove-box is used to manipulate the complex into the Schlenk reaction vessel, thus minimising decomposition into elemental nickel. The Ni(COD)$_2$/Ligand complex was prepared by adding a degassed solution of the ligand to the solid Ni(COD)$_2$ at -78°C and allowing to warm to room temperatures. In doing so, ligand exchange may occur at the lowest possible temperature, again to minimise decomposition. Initial studies subjected the Ni(COD)$_2$/Cy$_3$P solution to a positive pressure of H$_2$ in order to remove the COD ligands, thereby creating a vacant coordination site on the metal, in analogous fashion to the protocol used to generate the active [Rh(DIPHOS)]$^+$ catalyst from the [Rh(COD)(DIPHOS)]$^+$ClO$_4$· complex (Figure 106).
Results and Discussion

82

Figure 106: Previous studies using Ni(COD)$_2$.

It was evident from entry 3 that pre-hydrogenation was not necessarily beneficial to the performance of the catalyst, and so this step was abandoned for all subsequent experiments. In view of the large cone angle of the Cy$_3$P ligand, estimated to be nearly 180°, it was speculated that ligand dissociation may occur. However, conducting the isomerisation with only one equivalent of Cy$_3$P generated a less active catalyst (Entry 4). Surprisingly, Ni(COD)$_2$ in the absence of any ligand (Entry 5) was able to isomerise the allylic alcohol in 75% yield. It is apparent however that a higher degree of stereoselectivity is obtained in the presence of two Cy$_3$P ligands.

From these studies it was clear that the Ni(0) catalysis was a significant improvement in the rate of isomerisation, compared with the other catalyst systems. In addition the combination of Ni(COD)$_2$ and ligands was of particular interest to us, as any ligand could in theory be employed to prepare the Ni(0)Ligand isomerisation catalyst in situ. Unlike the NiCl$_2$(Ligand) catalysts, prior reduction, with its attendant structural uncertainty, is not necessary. Studies were therefore conducted in order to investigate the applicability of the Ni(COD)$_2$/Ligand catalyst system for enantiocontrolled isomerisations of allylic alkoxides.

Nickel (0) is a neutral d$^0$ species which may accept four ligands to give an electronically saturated eighteen electron NiL$_4$ complex. Such complexes typically exhibit a tetrahedral arrangement, with π-acidic ligands strongly favoured due to the electron rich nature of the metal centre. For the Ni(O) species, Ni(COD)$_2$, the eighteen electron configuration requires that
Ligand exchange occurs via a dissociative or a concerted process. Addition of the ligands, followed by the substrate generates complex (117). Dissociation of the monodentate COD ligand gives a sixteen electron intermediate (118), which may chelate with a solvent molecule to form complex (119), thus temporarily blocking the isomerisation process, or may coordinate to the oxygen moiety on the substrate to form complex (120) (Figure 107).

![Figure 107](image)

Isomerisation of complexes (118) and (120) will generate the π-allyl complex (122) and the π-complex (123) respectively. This π-allyl complex is assumed to be square pyramidal as this geometry is the most common for complexes of the type (η³-allyl)NiL₂X. Coordinated coordination with the enone may occur, i.e. complex (124), however loss of one of the chelating ligands (L) is necessary in order to maintain a stable eighteen electron configuration. Formation of this complex is unlikely to occur.

The scheme above indicates the possible order of events leading to the formation of the π-allyl and enone intermediates in the isomerisation mechanism. It is not clear at this stage by which mechanism the catalyst was believed to operate, as substitution of the enone with the starting allylic alkoxide in the nickel hydride complexes (123) and (124) allows for the possibility of a mechanism operating via metal-hydride addition and elimination.
Use of Chiral Phosphine Ligands

With the success of using Cy3P on the alkoxide of geraniol (61), efforts were then directed towards using bidentate ligands, particularly DIPHOS and a variety of chiral ligands such as (R,R)-CHIRAPHOS, (R)-BINAP, etc. with the intention of enantioselectively isomerising the alkoxide of geraniol (61). Thus, in a typical experiment, treatment of Ni(COD)2 with a ligand generated a solution of the Ni(0)bis(phosphine) complex, which was then transferred to the alkoxide solution. The results are presented below (Figure 108).

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Reflux (Hours)</th>
<th>Yield of (115) + (116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIPHOS</td>
<td>10</td>
<td>ca. 20 %</td>
</tr>
<tr>
<td>2</td>
<td>CHIRAPHOS*</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DUPHOS*</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>BDPP*</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DIOP*</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>BINAP*</td>
<td>87</td>
<td>-</td>
</tr>
</tbody>
</table>

*Figure 108: Previous attempt at enantioselective isomerisation. (* indicates chiral ligand)*

Disappointingly, the results with these chiral bidentate phosphine ligands afforded little, or no product. The DIPHOS ligand furnished our highest yield of enol acetate. However, despite extensive chromatography isolation and purification proved to be very difficult in this instance.

Clearly these ligands are poor in comparison to using Cy3P in this chemistry. DIPHOS has far less steric bulk than Cy3P, and as a bidentate ligand, will adopt a cis arrangement about the nickel centre. It is therefore probable that either a trans arrangement is a prerequisite for catalytic activity, or, more likely, that ligand dissociation is necessary in order to give a further coordination site if required. If this were the case, then due to the strong chelating effect exhibited by these bidentate ligands, then ligand dissociation would be unfavourable and as a result, catalytic activity would be severely impaired.
Chiral Nitrogen ligands

Nitrogen ligands in homogeneous catalysis have received increasing attention in recent years. In particular, the use of optically active, chelating, nitrogen-containing ligands has made many significant contributions to the field of asymmetric catalysis. Asymmetric hydrogenation reactions, catalysed by rhodium complexes containing chiral chelating diphosphanes, have been very successful and constitute classical examples of well established methodologies. For this reason, nitrogen ligands have been rather neglected. However mixed N,P ligands have been shown to give enantioselectivities as high as 84% (Figure 109). In recent years, Pfaltz and co-workers have developed chiral chelating semicorrin ligands and used them for several asymmetric homogeneous catalysed reactions. Such mono-anionic ligands are easily prepared from pyroglutamic acid and form six-membered conjugate chelate rings with C₂-symmetry. By way of example, up to 94% ee too has been achieved using these ligands in the CoCl₂ catalysed reduction of α,β-unsaturated esters with NaBH₄ (Figure 110). In a similar fashion, Brunner and co-workers have demonstrated that chelating nitrogen ligands containing a stereogenic fragment in a peripheral region of the molecule are superior to conventional C₂-symmetric chiral diphosphines in the Rh-catalysed hydrosilylation of ketones. Thus the reaction of acetophenone with diphenylsilane affords (R)-1-phenylethanol with a maximum ee. of 86% (Figure 111).
Chiral Lewis acids effectively catalyse [4+2] cycloaddition reactions of various dienes and dienophiles. In recent years several boron and aluminium catalysts bearing optically active nitrogen ligands have been shown to impart very high enantioselectivities to Diels-Alder reactions. Whereas the vast majority of the successful catalysts contain chelating oxygen ligands, recent developments have shown that optically active nitrogen ligands can give superior results. Corey and co-workers demonstrated an effective catalyst for the cycloaddition of cyclopentadiene derivatives to activated dienophiles (Figure 112).

Chiral complexes of Fe, Mg and Cu have also been successfully employed as catalysts for the Diels-Alder reaction, affording enantiomeric excesses greater than 98% (Figure 113).
Other notable asymmetric reactions include borane reduction, cyclopropanations, transfer hydrogenations, aldol condensations, alkylation of aldehydes, conjugate addition reactions, Grignard cross coupling reactions, allylic alkylations, oxidations, olefin epoxidations, and dihydroxylation of olein.\textsuperscript{16}

A class of nitrogen based ligands which presented a viable route to enantioselective isomerisations were those based on the oxazoliny moiety, in particular bis(oxazolines), which contain two oxazoliny moieties without a bridging methylene unit (Figure 114). The advantages of using such ligands are that they can be prepared from commercially available amino acids in optically pure form. In addition, they are stable, and are not prone to air oxidation, unlike the ligands based on phosphine. The bis(oxazolines) class of ligands has been the topic of a recent review\textsuperscript{169}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure114.png}
\caption{Oxazoline and Bis(oxazoline) class of ligands}
\end{figure}
Under the basic conditions of the isomerisation, bis(oxazoline) (125) would be subject to deprotonation on the methylene bridge due to the acidifying effect of the adjacent of the imidoester functionality. This effect is remedied by alkylation at this site, hence the development of ligands such as (126), (128) and (134). Ligand (129) could be further developed to create the bis(oxazoline) (130), however this ligand would not be suitable for asymmetric catalysis due to the possibility of two available propeller orientations of the phenyl groups on the phosphine, which would confer conformational ambiguity on the ligand. This would not be the case for ligand (131), which contributed to a series of ruthenium catalysed transfer hydrogenation of prochiral ketones, affording the corresponding alcohols in 14-92% ee. The bis(oxazoline) (132) offers the potential for highly effective enantiocontrol, due to the presence of an axially chiral BINAP skeleton.

Although the first synthesis of oxazoline was reported in 1884, their high significance has only emerged recently in organic chemistry. The simplest and most inexpensive method is the condensation of an amino alcohol and a carboxylic acid. The reaction proceeds with elimination of water at temperatures between 160°C and 220°C; however the reaction is sluggish and chemical yields are generally low. Nitriles may be used instead of carboxylic acids, proceeding at high temperatures with elimination of ammonia in the presence of a Lewis acid catalyst. Other synthetic approaches use starting materials such as imino esters, amides, epoxides and cyanoallene. Other synthetic strategies have employed microwave irradiation as a convenient source of energy to rapidly heat starting materials, thus reducing reaction times.

The N,P-bidentate ligand (129) (R = ¹Pr) has been shown by Pfaltz to induce excellent enantioselective control in the substitution of allylic moieties with carbon based nucleophiles. It was decided to prepare the ligand, following a highly practical procedure published by Williams, in a two step synthesis from 2-fluorobenzonitrile (Figure 115). The oxazoline (135) was obtained in 45% yield by refluxing 2-fluorobenzonitrile and the amino alcohol, L-valinol, in chlorobenzene for 48 hours with a catalytic quantity of dry ZnCl₂. The product (135) was then added to a refluxing solution of potassium diphenylphosphide in THF to afford the ligand (129) in 50% yield.

![Figure 115](image)

*Figure 115:* (i) (S)-(+)-2-amino-3-methyl-1-butanol (L-valinol), ZnCl₂, PhCl, reflux 48hr; (ii) KPPh₂, THF, reflux 1-2 hours.
The hemilabile ligand (133) can be synthesised in similar fashion, but using a chiral amino-diol instead of an amino alcohol. The imino ester hydrochloride of 2-fluorobenzonitrile was prepared by purging a solution of the nitrile and two equivalents of MeOH with HCl gas. A precipitate of the imidoester salt (136) was isolated in 30% yield, which was then stirred with the chiral amino diol in DCM for 48 hours. The oxazoline product (137) was then isolated by crystallisation in 82% yield. The oxazoline (137) was also isolated in 25% yield by condensation between the amino diol and 2-fluorobenzonitrile in refluxing chlorobenzene with catalytic quantities of dry ZnCl₂. The alcohol on compound (137) was methylated using sodium hydride and methyl iodide, to give the oxazalinyl methyl ether (138), which was then treated with potassium diphenylphosphide to afford the ligand (133) (Figure 116).

\[
\begin{align*}
(136) & \quad \text{(i) } \text{HCl} \quad \text{HCl, Dioxan, 2 hours; (ii) } (1S, 2S)-2\text{-amino-1-phenyl-1,3-propandiol, DCM, 48 hours; (iii) } (1S, 2S)-2\text{-amino-1-phenyl-1,3-propandiol, chlorobenzene, } \text{ZnCl}_2(\text{cat.}), 48 \text{ hours; (iv) NaH, THF, MeI; (v) KPPh}_2, \text{THF, reflux 1-2 hours.}
\end{align*}
\]

The gem-dimethyl bridging bis-oxazoline (127) (R = iPr) has been used as a ligand in a variety of asymmetric catalytic reactions, such as aziridination, cyclopropanation and the Diels-Alder cyclisation. The ligand was synthesised from dimethyl malonitrile (139), which had previously been prepared from malonitrile using sodium hydride and methyl iodide (Figure 117). Initial attempts to prepare the ligand concentrated on pre-activation of the nitrile (139), with the intention of improving the efficiency of the cyclisation reaction, thereby increasing yields. Oxazolines can be prepared from the imino ester hydrochloride by stirring the salt with an amino alcohol at ambient temperatures, however attempts to make this activated salt from the nitrile...
(139) were unsuccessful. Elemental analysis showed that the precipitate obtained from the reaction between the nitrile (139) and ethanol in a 4.0M solution of hydrogen chloride in dioxan was a mixture of the mono and bis imino ester hydrochlorides. Finally the bis(oxazoline) (127) was prepared in one of the ways which has already been described for the diphenylphosphine ligand (129).

Attempts to purify the product ligand (127) by column chromatography proved to be difficulty as nearly all of the staining reagents available for TLC analysis were ineffective. Analysis of the collected column fractions using GC was necessary, although the method still did not lead to a particularly pure product. Further purification by HPLC, using a refractometer as a method of detection did yield product, but was not effective, as the product was still contaminated. The presence of an inseparable impurity may lead to deactivation of the catalyst.

Previous attempts to prepare this ligand used cadmium acetate as the active catalyst, but it was found to be no more effective than the zinc chloride. However, at this time a series of bis(oxazoline) ligands were available from commercial sources, R = 'Bu (128), Ph (140), thus precluding the necessity for their syntheses.

The syntheses of ligands such as the bis(oxazoline) (126) had previously been prepared, adopting a route reported by Butula and Karlovic, Chiral amino alcohols may be obtained commercially, or by reduction of an amino acid using, for example I₂ and LiBH₄, a method reported by McKennon and Meyers. The amino alcohol was then heated with a diester of oxalic acid in toluene for several hours to afford the N,N'-bis(1-alkyl-2-hydroxyethyl)oxamide (141). Replacement of the hydroxyl group with chloride using thionyl chloride afforded N,N'-bis(1-alkyl-2-chloroethyl)oxamide (142), which cyclises on treatment with base giving the desired bis(oxazoline) ligand (126). The bis(oxazoline) ligands (R = Me, 'Pr, 'Bu) were all prepared using this route, with the benzyl analogue prepared by a colleague (Figure 118).
With a variety of bis(oxazoline) ligands in hand it was then decided to employ these ligands in the Ni(COD)$_2$/Ligand catalyst system, using geraniol (61) as the prochiral substrate. Following each isomerisation, the enolate product was then treated with excess acetic anhydride to afford an inseparable mixture of the (E) and (Z) enol acetates, thereby allowing the stereochemical outcome of the reaction to be assessed, in addition to the level of asymmetric induction for each stereoisomer (Figure 119).

It was necessary to obtain the enantiomeric excesses for each of the four possible enol acetates as it was considered that the reaction pathway to the (E) isomer could proceed to give a higher enantiomeric excess than the pathway to the (Z) isomer. A number of techniques were investigated. Despite the numerous chiral columns tested by GC and HPLC, the best resolution was obtained using a Chiradex α-cyclodextrin dipentylated chiral column. Although this achieved only partial resolution of the minor (Z) enol acetate it was sufficient to determine whether the stereoisomer was racemic or not (Figure 120).
Noyori and co-workers assess the level of asymmetric induction following their enantioselective isomerisation of diethylgeranylamine by transformation of the product into menthol (Figure 65). For our purposes this technique was not feasible as we wanted to know the relative ratio of all four possible enol acetate products. Hydrolysis of the formed enolates to the aldehyde was not practical either since the optical rotation of the aldehyde, citronellal, is much too small for accurate measurements.

Finally, the chiral shift $^1$H-NMR technique offered the best method for enantiomeric excess determination. Using 2.5 equivalents of $\text{tris(trifluoroacetylcamphorate)europium(III)}$, or Eu(tfc)$_3$, the C[3'] methyl doublet was resolved to give a double doublet with only a 1 Hz separation. This separation was increased to 10 Hz using one equivalent each of enol acetate, Eu(tfc)$_3$ and the silver(I) salt, $(6,6,7,7,8,8,8$-heptafluoro-2,2-dimethyl-3,5-octanedionato)silver(I), or Ag(FOD)

(Figure 121).

It was necessary to prepare authentic chiral enol acetate in order to validate the chiral NMR technique. This was achieved by treating (S)-citronellal with potassium hydride in dimethoxyethane at -10°C, followed by excess acetic anhydride to give the (S) enol acetate.
Subsequent analysis by chiral NMR revealed the C(3') methyl only as a doublet, which had not been further split into two doublets as observed using racemic material (Figure 122). Although the NMR peaks corresponding to the minor (Z) enol acetate were partially obscured by those of the (E) enol acetates, this technique, in conjunction with the partial resolution of the Z enol acetates by chiral GC, offered the best technique to ascertain the relative quantities of the 4 possible stereoisomeric products (See Figure 119).
The catalyst solutions were prepared using the chiral oxazoline ligands, and transferred to the alkoxide of geraniol (61). After heating to reflux for 1.5 to 2 hours, the enolate products were acetylated with excess acetic anhydride then purified by chromatography. GC and NMR analyses were used to ascertain the (E) and (Z) stereochemical ratios, and the enantiomeric excesses of all 4 possible stereoisomers. The results of the isomerisation experiments are tabulated below (Figure 123).

Figure 123: Isomerisations using chiral ligands. (a) Results from previous isomerisation.154
(b) Ligands commercially available

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R</th>
<th>Yield</th>
<th>(115) : (116) ratio</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td><img src="image1" alt="Ligand 1" /></td>
<td>Me</td>
<td>41%</td>
<td>5.0 : 1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Ligand 1" /></td>
<td>i-Pr</td>
<td>75%</td>
<td>4.8 : 1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Ligand 1" /></td>
<td>i-Bu</td>
<td>59%</td>
<td>5.3 : 1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Ligand 1" /></td>
<td>Bn</td>
<td>56%</td>
<td>5.4 : 1</td>
<td>0%</td>
</tr>
<tr>
<td>2&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td><img src="image2" alt="Ligand 2" /></td>
<td>i-Bu (128)</td>
<td>70%</td>
<td>4.1 : 1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td><img src="image2" alt="Ligand 2" /></td>
<td>Ph (140)</td>
<td>69%</td>
<td>4.4 : 1</td>
<td>0%</td>
</tr>
<tr>
<td>3&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td><img src="image3" alt="Ligand 3" /></td>
<td>(143)</td>
<td>72%</td>
<td>4.4 : 1</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Ligand 4" /></td>
<td>(129)</td>
<td>33%</td>
<td>3.7 : 1</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Ligand 5" /></td>
<td>(133)</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
The enantiomeric excesses were ascertained as previously described. Although in some cases line broadening confined the two observed C(3') doublets of the \((E)\) enol acetate to a broad triplet, it was quite apparent from NMR and Chiral GC that no asymmetric induction had occurred.

Despite the lack of enantiomeric excesses and the comparatively narrow range of stereoselectivities obtained (3.7 to 5.4 : 1) there are some notable results:

- The range of yields vary considerably from 0 to 75%, suggesting a strong influence by the ligand on the outcome of the reaction. Bidentate phosphine ligands such as BINAP afford little or no enolate product, whereas the \(\text{bis(oxazoline)}\) ligands furnish the enol acetates in high yield. It is not surprising therefore that a N,P-ligand such as (129) should give the enol acetates in an intermediate yield of 33%. The failure of the catalyst containing ligand (133) suggests the limitations of the catalyst system imposed by bulky and sterically demanding ligands.

- Ligand (143) offered one of the highest yielding reaction despite its tri-dentate configuration. Nickel(0) is a neutral \(\text{d}^0\) species, with a tendency to accept 4 ligands in order to achieve an 18 electron saturated \(\text{NIL}_4\) complex. Such complexes generally exhibit tetrahedral geometry. Ligand (143) cannot coordinate to the metal with all three nitrogens simultaneously without losing planarity, therefore coordination is likely with two, as with the other \(\text{bis(oxazoline)}\) ligands.

The isomerisation was repeated with ligand (128), but with 5 equivalents instead of just one. The reaction proceeded very sluggishly, and after approximately 2 hours, work up with acetic anhydride afforded the enol acetates in 18% yield \((\langle E\rangle:Z = 5.0 : 1)\). The result suggests a significant influence imposed by the ligands on the isomerisation process, and that a "back-seat" role is not adopted by the ligands. Saturation of the coordination sites on the nickel centre by the ligand is evident, and that ready displacement of the ligands by the alkoxide, or the solvent is not as apparent as was originally considered.

The possibility of colloidal nickel being the active species was investigated. Colloids are large aggregates of elemental nickel which in the absence of coordinating chiral ligands cannot achieve asymmetric induction. The mechanism of transition metal catalysed hydrosilylation reactions, both the generation of the active catalytic species and the hydrosilylation itself, have been subjected to detailed scrutiny. The traditionally accepted mechanism was first described by Chalk and Harrod involving a homogeneous mononuclear catalyst. Lewis and co-workers, however, have presented compelling evidence that many platinum catalysed hydrosilylation reactions thought to involve homogeneous catalysis in fact involve heterogeneous platinum colloids as the active catalytic species, providing also mechanistic interpretations. The use
of elemental mercury to selectively amalgamate or physiabsorb heterogeneous metal colloids, with consequent attenuation of catalytic activity, has been described previously as a method of investigating the mechanisms of transition metal catalysed processes.\textsuperscript{211, 212,213} In contrast, exposure to mercury generally has little effect on soluble molecular catalysts.

Thus the isomerisation with ligand (128) was repeated, with the addition of mercury prior to the mixture being heated to reflux. The grey, opaque reaction mixture was then quenched with acetic anhydride after 2 hours reaction time, and following chromatographic separation, the enol acetates were isolated in 65% yield (Figure 124).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure124.png}
\caption{Figure 124}
\end{figure}

It was apparent from this result that the isomerisation process was not operating via colloidal catalysis, as the addition of mercury to the isomerisation mixture had little effect on the outcome of the reaction. Reassured by this result, a number of other chiral ligands were prepared for use with the Ni(COD)\textsubscript{2}/Ligand catalyst system (Figure 125).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure125.png}
\caption{Figure 125}
\end{figure}
Ligand (144) was readily prepared in two steps from α-D-glucose. Protection of the 1, 2, 5 and 6 hydroxy functionalities in α-D-glucose with isopropylidene units afforded the protected sugar (151), treatment of which with chlorodiphenylphosphine gave the 1,2:5,6-Di-0-isopropylidene-3-O-diphenylphosphino-α-D-glucofuranose ligand (144), in 46% yield for the 2 steps (Figure 126).

![Figure 126](image)

The optically active pyridine derivatives (145), (146) and (147) were prepared by Bolm and co-workers for their transition metal catalysed enantioselective alkylation of aldehydes with diethyl zinc, and the nickel catalysed asymmetric conjugate addition of organozinc compounds to enones. In contrast to the great number of structural investigations of 2,2′-bipyridyl metal complexes, the syntheses and use of complexes of chiral 2,2′-bipyridyl derivatives have been neglected, despite the use of these 2,2′-bipyridyl ligands in ketone hydrogenations and epoxidations. Only a few optically active compounds of this class have been described and tested in asymmetric catalysis with moderate degrees of success.

Prior to the syntheses of these chiral pyridine based ligands, it was necessary to test whether pyridine and bipyridyl would be suitable as ligands in the Ni(COD)$_2$/Ligand catalyst system. Isomerisations were therefore conducted as previously described, the results of which are given below (Figure 127).

![Figure 127](image)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield</th>
<th>(115) : (116) ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine (2 equiv.)</td>
<td>66 %</td>
<td>&gt; 25 : 1</td>
</tr>
<tr>
<td>Bipyridyl</td>
<td>46 %</td>
<td>4.5 : 1</td>
</tr>
</tbody>
</table>
Both pyridine and bipyridyl were clearly suitable ligands for the isomerisation process, particularly pyridine due its high stereoselectivity in the formation of the enolate product. The reason for this dramatic increase in stereoselectivity was not very clear, however it was hoped that chiral based pyridines, such as ligands (147) and (149) would offer at least some degree of enantiocontrol.

Monolithiation of commercially available 2,6-dibromopyridine with n-BuLi in ether at -78°C followed by trapping with N,N-dimethylacetamide or benzonitrile afforded the corresponding pyridyl ketones, (152) and (153), in excellent yield. Following the asymmetric reduction of ketone (152) with (+)-chlorodiisopinocampheylborane, or (+) DIP-Chloride, the optical purity of the alcohol (154) was determined by derivatisation with (+)-menthylchloroformate, affording compound (155) as essentially one diastereoisomer (Figure 128). The t-Butyl ketone (156) proved to difficult to reduce, affording little product despite several days of reaction time.

![Figure 128](image)

**Figure 128**: (i) n-BuLi, -78°C; (ii) Me₂NCOMe or PhCN; (iii) (+)-DIP Cl, -20°C to RT; (iv) (+)-menthylchloroformate, pyridine, DCM.

The chiral alcohols (154) and (157) were methylated, then subjected to nickel(0) mediated homocoupling to afford the chiral bipyridyls (145) and (146) in good overall yield (Figure 129).

![Figure 129](image)

**Figure 129**: (i) NaH, MeI, THF; (ii) NiCl₂, 6H₂O, Ph₃P, Zn, DMF; (iii) AIBN, ⁵Bu₃SnH, PhMe, 100°C
Replacement of the bromine atom with hydrogen using tin hydride methodology furnished the alcohol (160) in good yield, however the compound could not be isolated pure despite numerous attempts at purification. The bromine can be replaced by other substituents, e.g. phenyl via cross coupling of the bromopyridine with phenylboronic under Suzuki conditions, giving rise to a series of chiral pyridine based ligands.

Catalyst solutions were prepared using the chiral ligands, and transferred to the alkoxide solution of geraniol (61). After heating to reflux for 1.5 to 2 hours, the enolate products were acetylated with excess acetic anhydride and purified by chromatography. GC and NMR was used to ascertain (E) and (Z) stereochemical ratios, and the enantiomeric excesses of all 4 possible stereoisomers. The results of the isomerisation experiments are tabulated below (Figure 130).

\[
\begin{align*}
\text{(61)} & \quad \text{(115)} + \text{(116)} \\
\text{(i) } n\text{-BuLi} & \quad \text{(ii) } \text{Ni(COD)} / \text{Ligand} & \quad \text{(iii) } \text{Ac}_2\text{O}, -78^\circ\text{C}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield</th>
<th>(115) : (116) ratio</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Ligand 144" /></td>
<td>35%</td>
<td>4.7 : 1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(1 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Ligand 144" /></td>
<td>49%</td>
<td>4.8 : 1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(2 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Ligand 145" /></td>
<td>59%</td>
<td>5.7 : 1</td>
<td>0%</td>
</tr>
<tr>
<td>3(a)</td>
<td><img src="image4.png" alt="Ligand 148" /></td>
<td>27%</td>
<td>8.2 : 1</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table continued
Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield</th>
<th>(115) : (116) ratio</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>4&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td><img src="image" alt="Ligand 149" /></td>
<td>51%</td>
<td>5.3 : 1</td>
<td>0%</td>
</tr>
<tr>
<td>5&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td><img src="image" alt="Ligand 150" /></td>
<td>-</td>
<td>No Isomerisation products</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figure 130**: Isomerisations using chiral ligands. (a) Ligands commercially available

The enantiomeric excesses were ascertained as previously described. Although in some cases line broadening confined the two observed C{3'} doublets of the (E) enol acetate to a broad triplet, it was quite apparent from the NMR and chiral GC that no asymmetric induction had occurred.

The involvement of the ligands in the isomerisation process is apparent as the reaction yield improved from using 1 to 2 equivalents of ligand (144). Ligand (150) failed to give any trace of enolate product, however the transfer hydrogenated product, citronellol (112), was obtained in 14% yield as the only major product, other than starting material. Although ligand (150) is comparable in design to N,P-oxazoline ligand (133), the acidic nature of the methyl protons in (150) renders this ligand unsuitable under the basic conditions of the reaction, as previously noted with ligand (125) (Figure 114). The presence of protons in the reaction mixture is certainly detrimental to catalyst activity, as evidenced by the failure of the Ni(COD)<sub>2</sub>/bis(oxazoline) catalyst to isomerise geraniol (61), as the free alcohol and not as the alkoxide.

**Enantioselective Isomerisations of other prochiral allylic alkoxides**

Although efforts to isomerise the alkoxide of geraniol (61) did not achieve any degree of asymmetric induction, it was necessary to attempt the isomerisation on a variety of prochiral allylic alkoxides. (E)-3-phenyl-2-buten-1-ol (63) was a suitable substrate since it had previously been isomerised by Noyori with his [Rh(BINAP)]<sup>+</sup> catalyst in 54% yield, and 34% ee.<sup>119</sup> Two secondary prochiral allylic alkoxides were also attempted, namely 3-phenyl-2-cyclohexen-1-ol (161) and 3,5,5-trimethyl-2-cyclohexen-1-ol (162), or isophorol. (E)-3-phenyl-2-buten-1-ol
(63)\textsuperscript{156,158} (Figure 101) and 3-phenyl-2-cyclohexen-1-ol (161)\textsuperscript{220,221} (Figure 131) were synthesised using published procedures, whereas isophorol was available commercially.

\[
\text{PhCO} \varepsilon \text{COEt} + \text{CH}_2=\text{CHCOCH}_3 \xrightarrow{\text{BnMe}_2\text{NBr,} \text{tBuOH}} \text{Ph} \text{C}=\text{CPh} \quad \text{(163)}
\]

\[
\text{(161)} \rightarrow \xrightarrow{\text{KOH (5%,aq), 12 hours, reflux}} \text{Ph} \text{C}=\text{CPh} \quad \text{(164)}
\]

\[\text{Figure 131: Preparation of (161)}\]

Thus treatment of methyl vinyl ketone with ethylbenzoyl acetate in butanol with benzyltrimethylammonium bromide, or Triton-B, furnished the ester (163) as a brown oily solid. Subsequent de-carboxylation of the ester moiety by heating to reflux in 5% aqueous potassium hydroxide for 10 hours gave the \(\alpha,\beta\)-unsaturated ketone (164). Reduction of the ketone (164) afforded the desired allylic alcohol (161) in an overall 40% yield.

Compounds (162) and (161) are both 2° allylic alcohols and racemic. There are two points during the isomerisation process in which asymmetric induction can occur, either during hydride abstraction, or during hydride delivery; both of which will be discussed.

Mechanistic studies by Cowherd and Rosenberg using \(\text{Fe(CO)}_5\) as catalyst, demonstrated that the carbinolic hydride is abstracted and returned to the intermediate in a suprafacial manner (Figure 132).\textsuperscript{125} Only the alcohol (165) could isomerise to the corresponding ketone (166), whereas compound (167) could not, due to the inaccessibility of the carbinolic hydrogen on the endo face by steric shielding.
Results and Discussion

If an isomerisation proceeds with **suprafacial** hydride transfer, then the **chirality** at the carbinol site will transfer to the β-position in the enolate product. In other words, one enantiomer of substrate is transformed into a single enantiomer of product, with the other substrate enantiomer generating the other product enantiomer (**Figure 133**).

Using **racemic** 3-phenyl-2-cyclohexen-1-ol (161) as substrate, then in an asymmetric environment interactions between catalyst and the two enantiomers of (161) would be different, *i.e.* diastereodifferentiation would occur. Differences in activation energy would then result in the catalyst isomerising one substrate enantiomer faster than the other (*i.e.* rate $k_1 > k_2$, **Figure 133**). The result would be a kinetic resolution, leading to enrichment of one product enantiomer over the other, up to theoretical 100% ee. at 50% conversion of substrate. To test whether this is the case, then the isomerisation of racemic 3-phenyl-2-cyclohexen-1-ol (161) will lead to racemic 3-phenyl-1-cyclohexanone (168) after complete conversion of substrate, however **chiral** 3-phenyl-2-cyclohexen-1-ol (161), will lead to the corresponding **chiral** product.

The second way in which asymmetric induction can occur is during hydride delivery. Following hydride abstraction by the transition metal, the resulting intermediate is a π-allyl or an enone.
Both of these species are essentially planar due to the extended conjugation into the aromatic ring. If the chiral catalyst can enantiofacially differentiate between the two sides of this plane (*i.e.*, if rate $k_1 > k_2$, (Figure 134), then enantioselective hydride delivery would occur, leading to enrichment of one product enantiomer over the other.

To test whether this is the case, then the isomerisation of racemic 3-phenyl-2-cyclohexen-1-ol (161) would lead to chiral 3-phenyl-1-cyclohexanone (168).

The asymmetric isomerisations were conducted using the Ni(COD)$_2$/Bu-bis(oxazoline) catalytic system (*as illustrated below*) using the three aforementioned substrates. In each case, the reaction was quenched with either acetic anhydride or saturated NH$_4$Cl solution after 2 hours reaction time (Figure 135).
The low yield of the enol acetate following the isomerisation of the alkoxide of \((E)-3\text{-phenyl-2-butene-1-ol}\) \(63\), and its difficulty in purification due to co-running impurities by column chromatography made enantiomeric excess determination by chiral NMR impractical.

The tri-substituted allylic alcohols \(63\) and \(161\) are structurally similar, and differ only by a bridging \(\text{CH}_2\text{CH}_2\) unit. Compound \(161\), a cyclic and therefore a conformationally restrained allylic alcohol, surprisingly gave one of the highest isomerisation yields, considering an olefin is moved out of conjugation with an aromatic benzene ring, which is in contrast to compound \(63\), which isomerised sluggishly, affording the enol acetates \(169\) and \(170\) in only 18\% yield. The low yielding reaction by the compound \(63\) could be a consequence of catalyst deactivation by carbonylation, a process previously encountered with \(\text{NiCl}_2\text{(DIPHOS)}/\text{LiBEt}_3\text{H}\), and other catalyst systems whilst attempting to isomerise primary allylic alkoxides. This process, however, is not observed using the alkoxide of geraniol as substrate.

Interestingly, the alkoxide of \(161\) required only 2 hours of reaction time to afford 83\% isomerised product, whereas the \((\text{Cy}_3\text{P})_2\text{NiCl}_2/\text{n-BuLi}\) catalyst required over 24 hours to isomerise the alkoxide of 2-cyclohexen-1-ol in only 64\% yield. The latter catalyst is believed to operate via a metal-hydride addition and elimination mechanism, therefore the result implies that the \(\text{Ni(COD)}_2/\text{Ligand}\) catalyst system operates via a different mechanism, i.e. \(\pi\text{-allyl}\) or enone mechanism.

Consideration of the enone mechanism, then complexation between the alkoxide and the nickel catalyst will result in a complex in which hydride abstraction forms the \textit{transoid} enone intermediate \((174)\) (Figure 136). Structural restriction prevents the formation of a \textit{cisoid} arrangement \((175)\).

A \textit{transoid} arrangement was also proposed by Noyori and co-workers as an intermediate for the isomerisation of \(N,N\text{-diethylgeranylamine}\) \(64\) by the chiral rhodium catalyst, \([\text{Rh(BINAP)}]^+\) (See Figure 77). Further, the same catalyst was able to isomerise \(N,N\text{-diethyl-2-cyclohexamine}\) (in 90\% \textit{ee}), which can only occur via the formation of a \textit{transoid} intermediate, therefore indicating the similarity in mechanisms between this and the \(\text{Ni(COD)}_2/\text{Ligand}\) catalyst.
Consideration of the \( \pi \)-allyl mechanism, then to satisfy Fiaud's stereoelectronic prerequisites for \( \pi \)-allyl formation\(^2\) a coplanar relationship must exist between the olefinic \( \pi \)-orbitals and the C-H bond undergoing oxidative addition. As a consequence, only complex (176) may undergo hydride abstraction to form the \( \pi \)-allyl intermediate (Figure 137).

The cyclohexanone based compounds (171) and (168) were derivativised by reaction with a \( C_2 \)-symmetric chiral diol\(^3\) in this case with dimethyl-L-tartrate, to form the compound (172) and (173) respectively.\(^4\) The ratio of diastereoisomers were then ascertained by NMR and by GC. Unfortunately, in both cases, zero enantiomeric excesses were established.

The lack of asymmetric induction using the cyclohexanone based compounds (171) and (168) indicates that enantiofacial differentiation between the two sides of the plane of the intermediates does not occur. On the other hand, it is possible that the chiral nickel catalyst can differentiate between the enantiomers of the cyclic allylic alkoxide substrate, \( i.e. \) one enantiomer is isomerised by the catalyst faster than the other enantiomer, hence kinetic resolution. Since, however, complete conversion of the substrate was observed, then no level of asymmetric induction would be expected.

To test whether the mechanism is operating via enantiomer differentiation, followed by suprafacial hydride transfer, then chiral 3-substituted-2-cyclohexen-1-ol would have to be prepared and isomerised under the same conditions.

The chiral preparation of 3-phenyl-2-cyclohexen-2-ol (161) and 3,5,5-trimethyl-2-cyclohexen-1-ol (162) were attempted using a variety of chiral reducing agents on the corresponding enones. The enantiomeric excess of the formed allylic alcohol was ascertained by derivatisation with (+)-menthylchloroformate, with the diastereomeric ratios determined by NMR (Figure 138).
Reducing agents such as oxazaborolidines,\textsuperscript{224,225} Brown's chiral boron reducing reagent (+) DIPS Chloride\textsuperscript{226-231} and LiAlH$_4$, partially decomposed with (-)-N-methyllephidrine and 2-ethylaminopyridine (179),\textsuperscript{232,233} generated the alcohol in good yield but with little or no ee. Alternative techniques relied upon resolution, either enzymatically,\textsuperscript{234-236} or by chemical means, such as resolution by chiral rhodium hydrogenation,\textsuperscript{237} or by the Sharpless di-hydroxylation or epoxidation methods.\textsuperscript{238} An optical resolution offered a more practical approach and was therefore adopted (Figure 139).\textsuperscript{239}

During the preparation of the chiral 3-substituted-2-cyclohexen-1-ols, experiments were conducted in order to establish if racemisation at the β-position of the enolate could be occurring under the conditions of the isomerisation, \textit{i.e.} any chirality that is created during an asymmetric isomerisation, is promptly destroyed.
(S)-Citronellal was therefore selected as an appropriate model and an authentic chiral lithium enolate was prepared by deprotonation of (S)-citronellal using potassium hydride in DME at -5°C to afford the potassium enolate, treatment of which with TMS-chloride and triethylamine gave the silyl enol ether. The lithium enolate was then generated by the addition of one equivalent of methylolithium. The isomerisation was performed soon after formation of the silyl enol ether in order to minimise hydrolysis to the aldehyde. The chiral lithium enolate was then treated with the Ni(COD)$_2$/bis(oxazoline) catalyst system under the standard isomerisation conditions then quenched after 2 hours reaction time by the addition of excess acetic anhydride at -78°C (Figure 140). Chiral NMR studies indicated that racemisation had occurred at the β-position in the enolate during the isomerisation.

Although the result went some way to answering the question as to why we are not observing any enantiomeric excesses, why racemisation should occur in such an asymmetric environment was not clear. If the chiral ligands were taking a "back seat" role during the course of the isomerisation, i.e. not becoming actively involved, then one would expect unvarying yields for a range of chiral ligands. This is not the case, as the yields ranged from 0% through to 83%. Using pyridine as ligand excellent stereocontrol was obtained, however chirally substituted pyridines such as N-methyl nicotinate, or bipyridyl did not achieve such stereo- nor enantiocontrol.

From a mechanistic point of view, racemisation at the β-position on the chiral lithium enolate may arise due to a loss of enantiocontrol during any of the three possible mechanistic pathways:

**Metal-hydride addition and elimination**

If the isomerisation was operating via metal-hydride addition and elimination, then the enantioselective step would be the first step in which the metal-hydride adds across the prochiral olefin in the allylic moiety. The second step would be elimination of the metal-hydride to generate the enolate product. The disadvantage of this method is the reversibility of the process as the metal-hydride may add and then eliminate several times on the same substrate molecule during the course of the reaction. The overall result is a decrease in the enantioselective capability of the chiral nickel catalyst.
Enone mechanism

The formation of an enone involves hydride abstraction from the carbinol site on the allylic alkoxide substrate. Such a process bears a resemblance to the first step of hydride abstraction be the chiral rhodium catalysts, [Rh(BINAP)]^+, on allylic amines (See Figure 77). Thus in the same way, abstraction of the hydride by the chiral nickel would then be followed by suprafacial hydride delivery to generate the chiral lithium enolate (Figure 141).

\[ \text{Figure 141: Ligands not drawn on Ni for clarity} \]

A loss of enantiocontrol could result if dissociation between the enone and the metal hydride intermediates occurs, such that hydride delivery may occur on either face of the enone upon re-complexation.

If hydride abstraction was not the enantioselective step, then chirality could only be achieved if the hydride was delivered back onto the enone enantiofacially. Hydride abstraction from the allylic alkoxide may occur using either of the two carbinol hydrogens, resulting in the formation of complexes (A) and (B) (Figure 142).

\[ \text{Figure 142: Ligands not drawn on Ni for clarity} \]

For enantiofacial hydride delivery to occur, then the metal hydride must be on the correct face of the enone. Thus, decomplexation of the enone from complex (A) followed by re-complexation to generate complex (B). Complex (B) may then proceed to generate the chiral enolate product by hydride transfer in an enantiofacial manner.
A lack of enantiocontrol in the hydride delivery would occur if either complex (A) or (B) can generate the enolate product. Alternatively, if the reverse process could occur, i.e. regeneration of the enone from the enolate product, then this reversible step is likely to occur several times on the same substrate molecule during the course of the reaction. The result is a decrease in the enantioselective capability of the chiral nickel catalyst.

\[ \pi \text{-Allyl mechanism} \]

Loss of chirality by \'\pi-\sigma-\pi\' fluxionality by the \( \pi \)-allyl intermediate was not considered to be acceptable as this process would have led to an increase in the quantity of the \((Z)\) stereoisomer \((\text{Figure 143})\). This was not observed. Indeed, the relative quantity of the \((E)\) stereoisomer was found to have increased at the end of the 2 hour reaction time \((\text{See Figure 142})\). This means that if the mechanism is operating via a \( \pi \)-allyl intermediate, then a second mechanism must be in operation to account for the observed racemisation.

\[ \text{Figure 143 : Ligands not drawn on Ni for clarity} \]

It was not clear at this stage by which mechanism the \( \text{Ni(COD)}_2/\text{Ligand} \) complex catalysed the isomerisation of allylic alkoxides. It was therefore hoped that deuterium studies using suitable deuterated analogues would shed some light onto the mechanistic aspects of this intriguing transformation \((\text{See Mechanistic Studies})\).
Modifications of the Isomerisation Reaction
Introduction

Although our efforts to achieve asymmetric induction in the isomerisation of prochiral allylic alkoxides obtained from alcohols such as geraniol (61), 3-phenyl-2-buten-1-ol (63) and 3-phenyl-2-cyclohexen-1-ol (161) were not successful, it was nevertheless necessary to modify some of the variables of the reaction such as solvent, counter cations and reaction temperature to obtain conditions which might favour asymmetric induction, by providing a lower activation energy ($\Delta E_1$) for the formation of the enolate from the allylic alkoxide (Figure 144). This type of course is based on the idea that the isomerisation of the enolate to allylic alkoxide will require a higher activation energy ($\Delta E_2$).

Solvent effects

Solvent plays an important role during transition metal catalysis as vacant coordination sites on the metal are invariably occupied by the solvent. Modifying the properties of the solvent would effect the progress and possibly the outcome of the reaction. THF solvates the formed allylic alkoxide following basic deprotonation of the corresponding alcohol, and it is known that lithium alkoxides form aggregates in solution,\textsuperscript{141} thus rendering the oxygen lone pairs on the alkoxide less available for donation.

THF was also considered to be a possible source of hydride or protons, which may be vital, or progressively detrimental to the isomerisation process. The hydrogen on the $\alpha$-carbon in THF
could be abstracted as a hydride by the catalyst in the same way as the hydride from the substrate during isomerisation (Scheme 145). Solvents such as benzene, toluene, and 2,2,5,5-tetramethyl-tetrahydrofuran were accordingly considered as each did not possess a possible source of hydride or protons.

2,2,5,5-Tetramethyl-tetrahydrofuran was impractical as a solvent as it failed to dissolve any of the starting materials. However, the choice of benzene as solvent offered some unexpected results (Figure 146). Although the lithium alkoxide did not appear to dissolve in the solvent, the corresponding enol acetates were nevertheless isolated in 46% yield, with an (E):(Z) ratio of >20:1. Conducting the same experiment at room temperature gave the enol acetate in a lower 17% yield, but still with an (E):(Z) ratio of >20:1. Disappointingly, no asymmetric induction was detected in either case by chiral ^1H-NMR.

The use of benzene as solvent was clearly a desirable facet in terms of stereocontrolled enolate formation, and it was of some consternation that the enantiomeric excess did not reflect this result, even when the reaction was performed at room temperature. In addition, significant quantities of oligomeric material was also formed during the reaction, contaminating the enol acetate despite purification by column chromatography. Nevertheless, the stereochemical outcome of the reaction, even at room temperature, was considerably greater than the stereoselectivities obtained with previous catalyst systems.
The poor solubility of the alkoxide in benzene suggested the formation of extensive aggregates by the alkoxide in solution, and therefore the unlikely formation of a "monomeric" alkoxide species. Previous studies in which an attempt to break up this aggregation in order to form "monomeric" alkoxides by the addition of complexing agents such as TMEDA, DMPU, TDA, LiCl and 12-crown-4 had been carried out within our group. Decreased reaction rates were noted, but without significant influence to the stereochemical outcome of the isomerisations. In an attempt to enforce an asymmetric environment for an enantioselective isomerisation to occur, we considered using chiral lithium chelating agents as an alternative to using chiral ligands. An abundance of such chelating agents are readily available from carbohydrates by simple alkylation of the hydroxyl functionalities. The wealth of knowledge and methodology that has accumulated with respect to the application of carbohydrates as chiral templates for asymmetric induction is quite extensive, thus it seemed appropriate to exploit these polyalkylated carbohydrates for our own purposes.

Two derivatives of D-mannitol (182) were investigated, namely 1,2:5,6-di-O-isopropylidene-3,4-di-O-methyl-D-mannitol (183) and 1,2,3,4,5,6-hexa-O-methyl-D-mannitol (184). Both were prepared in excellent yield by the Purdie methylation on 1,2:5,6-di-O-isopropylidene-D-mannitol (185) and D-mannitol (182) respectively, using silver(I)oxide and methyl iodide (Figure 147).

In a typical experiment one equivalent of the poly-alkylated carbohydrate was added to a solution of the alkoxide in THF. The resulting mixture was then added via cannula to the catalyst solution. Results using the alkoxide of geraniol (61) and 1,2,3,4,5,6-hexa-O-methyl-D-mannitol (184) are given below (Figure 148).
The NiCl₂(PPh₃)₂/n-BuLi catalyst was able to isomerise the alkoxide of geraniol (61) in 65%, but in the presence of the sugar, it was noted that the catalyst had deactivated very shortly after mixing the alkoxide/sugar and catalyst solutions. This was possibly due to thermodynamic reasons, whereby the coordinating ability by the hexadentate sugar being superior to that achieved by the two monodentate tricyclohexylphosphine ligands. Ligands with a greater capacity to bind to the metal were attempted, and using the bipyridyl ligand with Ni(COD)₂, 46% yield of the enol acetates were isolated. Although, no enantiomeric excess were detected by chiral shift ¹H-NMR, nevertheless the reaction proceeded in good yield in the presence of the chiral lithium chelating agent. Clearly, a system based on this method of asymmetric induction, perhaps in combination with a suitable metal chelating ligand, has potential and therefore warrants further investigation.

**Counter Cations**

In the case of preparing enolates from allylic alkoxides, our system had the versatility of preparing an enolate with potentially any counter cation, provided that the corresponding metal allylic alkoxide can be prepared: e.g. lithium enolates are derived from the corresponding allylic alcohol and n-BuLi, magnesium enolates from one of the many Grignard reagents commercially available, sodium enolates using sodium hydride, etc. An area of enolate chemistry that has received increased attention is the use of tetraalkylammonium as the counter cation. Such enolates are difficult to generate due to their high reactivity, and are often prepared in situ by the addition of tetraalkylammonium fluorides to silyl enol ethers.²⁴⁵,²⁴⁶ It was envisaged that our system could be adapted in order to prepare these tetraalkylammonium enolates.

A solution of the tetraalkylammonium halide and the sodium alkoxide of geraniol (61) was treated with the Ni(COD)₂/DIPHOS catalyst system. DIPHOS was selected as the standard ligand as this catalyst system since it had previously been shown to react very poorly with the lithium alkoxide.
of the same substrate. It was hoped that the choice of a tetraalkylammonium counter cation for the allylic alkoxide would result in improved reaction rates and yields, thereby allowing replacement of DIPHOS with chiral phosphine ligands, such as BINAP, DIOP, etc. The results using DIPHOS are given (Figure 149).

\[
\text{Ni(COD)\textsubscript{2}/DIPHOS, \(\text{R}_\text{N}X\)}
\]

<table>
<thead>
<tr>
<th>Ammonium Salt</th>
<th>Yield (62)</th>
<th>Yield (61)</th>
</tr>
</thead>
</table>
| \((\text{t-Bu})_4\text{NBr}\)
  (1 equiv. w.r.t. geraniol)     | 11%        | 39%        |
| \((\text{n-Hex})_4\text{NBr}\)
  (1 equiv. w.r.t. geraniol)     | 31%        | 23%        |

*Figure 149*

Following work-up with acetic anhydride, it was noted that the products (62) and (61) were not acylated. Under the basic conditions of the isomerisation, it was likely that the quaternary ammonium salt had undergone Hoffmann elimination, thus providing a protic source to protonate the alkoxide and enolate to the alcohol (61) and aldehyde (62) respectively. Despite the modest yields of aldehyde attained, both reactions formed significant quantities of unidentifiable material, presumably oligomers.

Alkoxyborinates, ROBR\textsubscript{2}, are covalent in character and therefore form monomeric species in solution. It was envisaged that these alkoxyborinates would isomerise more efficiently than the corresponding lithium alkoxides. Following the preparation of the lithium alkoxide, 9-borabicyclo[3.3.1]nonane-B-triflate, or 9-BBN Tf, was added to the alkoxide solution. The cloudy precipitate, presumably lithium triflate, was removed by transfer of the supernatant solution to a clean reaction vessel via filter-tipped cannula. Isomerisations were then conducted using 1 and 1.2 equivalents of 9-BBN Tf with respect to the alkoxide (Figure 150).
In the event however, using either lithium or sodium allylic alkoxides prior to addition of the 9-BBN-Tf, no improvement in reaction was observed with the starting material, geraniol (61), generally isolated as the predominant compound.

Substitution of the lithium cation with a silyl group would eliminate the speculated problems of aggregation encountered with the lithium alkoxide. The t-butyldimethylsilyl group (TBDMS) was the moiety of choice as it offered a less hydrolytically labile silyl enol ether product compared with the smaller trimethylsilyl (TMS) group. The isomerisation of silyl allylic ethers has previously been reported by Suzuki using the (Ph₃P)₄RuH₄ catalyst at 150°C. Using primary allylic ethers, (Z) enol ethers were formed as the major product, which is in contrast to the isomerisation of primary allylic alcohols and alkoxides which favoured the formation of the (E) stereoisomer (Figure 151).

![Figure 151](image)

The TBDMS derivative of geraniol was prepared, in addition to the TBDMS enol ether of citronellal (186), the isomerised product, in order to determine relevant GC parameters (i.e. retention times) and be able to monitor the progress of the reaction by GC (Figure 152).
In the event, the starting material (187) remained unreacted under the conditions of the isomerisation. It is probable that the steric influence imposed by the adjacent TBDMS group obstructed the isomerisation process. A higher reaction temperature is likely to incur some reaction, however, even in refluxing THF at 65°C, no reaction was observed, and it is likely that at elevated temperatures substrate decomposition could predominate in a similar fashion to that was observed using the Rh(l) catalyst (See Figure, Isomerisations with Rhodium Complexes).

Co-catalysis

One of the possible intermediates following hydride abstraction by the transition metal may be considered as an enone or an enal. The formed metal-hydride can then deliver the hydride back onto the enone via a 1,4-addition, or Michael fashion, to generate the enolate product (Figure 70). Perusal of the literature identified several transition metal hydrides, or precursors, which could achieve this regioselective reduction of the α,β-unsaturated aldehyde or ketone, some of which are illustrated below (Figure 153).
Of these systems, the deep red coloured hexameric phosphine copper hydride complex, \([\text{Ph}_3\text{PCuH}]_6\),\(^{253}\) was of particular interest due to its ability to reduce geranial (188) to citronellal (62) smoothly in 90% yield in THF, over 22 hours at room temperature.\(^{248}\) Notably, isolated double bonds remained intact.

Consideration of the enone mechanism, then following hydride abstraction form the alkoxide of geraniol (61), the enone intermediate that is formed is geranial (188). It was therefore envisaged that the addition of \([\text{Ph}_3\text{PCuH}]_6\) to the isomerisation mixture might facilitate the formation of the enolate product, thereby enabling previously unsuccessful catalyst systems such as \(\text{Ni(COD)}_2/\text{DIPHOS}\) to isomerise the alkoxide of geraniol.

The \([\text{Ph}_3\text{PCuH}]_6\) complex is prepared by reduction of \(\text{Ph}_3\text{PCuCl}\) with \(\text{NaBH(O\text{Me})}_3\) in DMF. It was conceivable that following the addition of \(\text{Ph}_3\text{PCuCl}\) to the isomerisation reaction, the \([\text{Ph}_3\text{PCuH}]_6\) complex could be generated \textit{in situ} by hydride transfer from the hydrido nickel...
intermediate, \([\text{Ni-H}^-]\) (Figure 154). The \([\text{Ph}_3\text{PCuH}]_6\) complex would then add to the enone to afford the enolate product.

Accordingly, the isomerisation mixture for geraniol (61) was prepared in the usual way and, prior to heating to reflux, the \(\text{Ph}_3\text{PCuCl}\) was added in one portion. At reflux, the colour of the reaction mixture turned to a dark red colour, indicating the possible formation of the \([\text{Ph}_3\text{PCuH}]_6\) complex. However, GC analysis of the reaction mixture indicated slow decomposition of the starting material, with no trace of products from the enolate (Figure 155).

The formation of a dark red coloured solution was an encouraging sign, however degradation of the catalyst was apparent due to the formation of black deposits, possibly elemental nickel.
Formation of the initial hydrido nickel species, [Ni-H]⁺ and subsequent delivery of the hydride to the Ph₃PCuCl will generate the [Ph₃PCuH]₆ complex and reform the initial Ni(0) species. However the Ni(O) may aggregate to form colloidal nickel, which in turn will then precipitate as elemental nickel.

The difference in the electrode potentials between the Ni and Cu species could result in oxidation/reduction reactions resulting in the observed degradation of catalytic activity. Clearly, as Entries 1 and 2 indicate, the [Ph₃PCuH]₆ is not compatible under the existing isomerisation conditions. Without Ph₃PCuCl, the alkoxide of geraniol is isomerised to give the enol acetate product in 65% yield.

Other additives were considered, which could potentially act in the same way as the [Ph₃PCuH]₆ complex. Trialkylboron compounds were considered for this reason. In addition, “boronate” complexes are likely to form between the allylic lithium alkoxide and the trialkylboron and indeed, in earlier rhodium studies such substrates were shown to isomerise in good yield (Figure 156).¹³²

\[
\begin{align*}
\text{HO} & \quad \text{KH, BE₃H} \\
\text{Ph} & \quad \text{or KBE₃, BE₃} \\
\text{(88)} & \quad \text{OBET₃K} \\
\text{Ph} & \quad \text{(189)} \\
\text{Ph} & \quad \text{[Rh(DPHOS)]⁺} \\
\text{OBET₃K} & \quad \text{Allyl bromide} \\
\text{Ph} & \quad \text{(91)} \quad + \quad \text{Ph} \\
\text{O} & \quad \text{(190)} \quad + \quad \text{O} \quad \text{CH₂} \quad \text{CH} \\
\text{Ph} & \quad \text{(91)} \quad + \quad \text{Ph} \quad \text{O} \quad \text{CH₂} \quad \text{CH} \\
\end{align*}
\]

*Figure 156*

Depending on the degree of “boronate” complex formation, the addition of Et₃B into the nickel system could facilitate the formation of the enolate product via the formation of a borohydride species, and subsequent reduction of the enone or enal intermediate. The reactions were monitored by GC and the results given below (Figure 157). The quantity of Et₃B initially used was 20 mol%, but due to the likelihood that the lithium alkoxide (and product enolate) would form a “boronate” complex, then 120 mol% was also employed.
The results show clearly that Et₂B has no direct improvement on the isomerisation process, giving rise to mainly reduced product in the form of citronellol (112). It was noted that following the isomerisations of the "boronate" complex (189) using [Rh(DIPHOS)]⁺, an unacceptable quantity of the ketone (91) was also isolated (Figure 156), despite the use of excess alkylating agent on the formed "boronate" enolate (190). Returning to the above isomerisation of geraniol (61), if a protic source was available during the isomerisation process, then protonation of the enolate would occur, resulting in the formation of the aldehyde (62) in situ. Reduction of the aldehyde to the alcohol (112) could then be achieved by the hydrido nickel intermediate, or by a borohydride species. Possible sources of protons will be discussed in a later section (See Mechanistic Studies).
Isomerisations with Non-Chiral Ni(0) Complexes
Introduction

Following the successful isomerisation of the alkoxide of geraniol (61) with the Ni(COD)$_2$/pyridine catalyst system, affording the corresponding enol acetates with a ratio of the (E) and (Z) stereoisomers of greater than 25 : 1 (Figure 127). It was decided to investigate the scope of this catalyst system in terms of regio- and stereocontrolled enolate formation with a variety of other allylic alkoxides.

Isomerisation of Primary Allylic alkoxides

The isomerisation of primary allylic alkoxides will afford an enolate, protonation of which will give an aldehyde. The conversion of an aldehyde to its enolate is not straightforward, as treatment with LDA affords the alcohol as the major product (Figure 158, Equation 1).$^{254}$ There are however several multistep sequences in the literature which overcome some of the difficulties encountered with this simple transformation (Equation 2,$^{255}$ 3$^{256,257}$ and 4$^{258}$).

\[ R \text{CHO} \rightarrow \left[ \begin{array}{c} \text{H} \\ \text{N} \\ \text{R} \end{array} \right] \rightarrow \text{R} \text{OH} + \text{N} \text{R} \]

\[ \text{EtMgBr} \rightarrow \text{n-C}_3\text{H}_7 \text{Br}, \text{then HCl} \rightarrow \text{n-C}_3\text{H}_7 \text{CHO} \]

\[ \text{RX, then NaIO}_4 \]

\[ \text{PhCO}_2\text{H, Toluene} \rightarrow \text{R} \text{O} \text{O} \text{O} \text{R} \text{n-Bu} + \text{R} \text{O} \text{O} \text{O} \text{n-Bu} \]

Figure 158
Deprotonation can be achieved using potassium hydride, however reaction of the enolate with alkylating reagents then gives rise to a mixture of both mono and bis-alkylated products, in addition to aldols by self condensation\textsuperscript{259,260}. Treatment of silyl enol ethers\textsuperscript{138} or enol acetates\textsuperscript{259} with MeLi affords the lithium enolate, although a stoichiometric quantity of lithium \( t \)-butoxide is also generated when using the enol acetate as the enolate precursor.

A variety of other primary allylic alkoxides were attempted with the Ni(COD)$_2$/pyridine catalyst, such that comparisons could be made with results previously obtained using the NiCl$_2$(Cy$_3$P)$_2$/\( t \)-BuLi catalyst system (Figure 159).\textsuperscript{133}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure159.png}
\caption{Figure 159}
\end{figure}

Thus, the alkoxides of (58) and (63) had previously been attempted with the NiCl$_2$(DIPHOS)/LiBEt$_3$H catalyst, but with little or no success (Figure 102). However, the alkoxide of alcohol (63) was converted through to the corresponding enol acetates in a modest 18\% yield using Ni(COD)$_2$/bis(oxazoline) (Figure 135). The syntheses of 4-Benzoxoybut-2-en-1-ol (191) and (E)-2-Dodecen-1-ol (192) are given (Figure 160).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure160.png}
\caption{Figure 160}
\end{figure}
The isomerisations of compounds (58), (63), (191) and (192) are illustrated below (Figure 161).

\[
\begin{align*}
\text{(58)} & \quad \text{(i), (ii), (iii)} \quad \text{No Reaction} \quad (1) \\
\text{(192)} & \quad \text{(i), (ii), (iii)} \quad \text{No Isomerisation} \quad (2) \\
\text{(191)} & \quad \text{(i), (ii), (iii)} \quad 21\% \quad (191) \quad (193) \\
\text{(63)} & \quad \text{(i), (ii), (iii)} \quad 53\% \quad (169) \quad 15:1 \quad (170)
\end{align*}
\]

*Figure 161*: (i) n-BuLi; (ii) Ni(COD)₂/pyridine, reflux 2 hours; (iii) ACO₂H, -78°C

Alcohol (58) (*Equation 1*) presumably did not isomerise for the same reason as with the NiCl₂(DIPhos)/LiBE₃H catalyst, i.e. deactivation of the catalyst by carbonylation. Alcohol (192) (*Equation 2*) offered no trace of the enolate product after 3 hours reflux, which was not the case for the NiCl₂(Cy₃P)₂/n-BuLi and [Rh(DIPhos)]⁺ catalyst systems (*Figure 162*).
Substrate (192) was considered a difficult alcohol to isomerise due to the long lipophillic chain folding back on itself and sterically hindering the coordination between the allyl moiety and the metal catalyst. Other possible difficulties may arise with the formation of micelle structures in solution, further impeding the isomerisation process.

The isomerisation \((Z)-4\text{-Benzyloxybut-2-en-1-ol} (191)\) (Equation 3) gave no enolate product, which was in contrast to the isomerisation of \((Z)-1,4\text{-dibenzyloxy-2-butene} (90)\) with \(\text{NiCl}_2(\text{DIPHOS})/\text{PrMgCl}\), which gave the corresponding isomerised product in high yield (Figure 89).\(^{146}\) It is apparent therefore that the \(cis\) arrangement of the diol ether in (90) forms an integral part in the isomerisation process, as the isomerisation is complete within a minute of reaction time. In accordance with the desirable facets offered by this \(cis\)-oxy arrangement in compound (90), the alkoxide of the mono ether \((Z)-4\text{-Benzyloxybut-2-en-1-ol} (191)\) was attempted with the \(\text{Ni(COD)}_2/\text{pyridine}\) catalyst. Analysis of the reaction mixture following acetic anhydride work-up, revealed predominantly starting material (191) and benzyl acetate (193) (Figure 161).

Allyl phenyl ether (196) has been shown to react in different ways with Ni(0) and Ni(II) species. With \(\text{Ni(COD)}_2\), oxidative addition by the nickel into the C-OPh bond generates a \(\pi\)-allyl nickel(II)phenoxide species (197) (Figure 163, Equation 1),\(^{261}\) whereas with the chlorohydridonickel(II) complex (Tol3P)2NiHCl, transformation to Z-phenylpropenyl ether (198) occurs (Equation 2).\(^{108}\)

![Figure 163](image-url)
Using (Z)-4-benzyloxybut-2-en-1-ol (191) as substrate, Ni(0) insertion into the C-OBn had presumably occurred affording a π-allyl nickel(II)benzyloxo complex, which upon work-up with excess of acetic anhydride had led to nickel(II)acetate, and benzyl acetate (193) which was isolated in approximately the same proportion as the quantity of catalyst initially used. Compared with the NiCl₂(DIPHOS)/PrMgCl catalyst, no such oxidative addition was observed using (Z)-1,4-dibenzyloxy-2-butene (90) as substrate. This would indicate that the NiCl₂(DIPHOS) catalyst is transformed into a chlorohydridonickel(II) intermediate upon treatment with PrMgCl, and that the Ni(COD)₂/pyridine catalyst system is likely operate by way of the π-allyl or enone mechanism (See Figure 70).

However, the isomerisation of the alkoxide of (E)-3-phenyl-2-buten-1-ol (63) (Equation 4) proceeded in good yield and with excellent stereocontrol, reflecting the result obtained with the alkoxide of geraniol (61) (Figure 127).

It is not clear why the use of pyridine as a ligand leads to a greater degree of stereocontrol when compared with the stereoselectivities observed by the much larger and bulkier tri-substituted phosphine ligands, such as Ph₃P or Cy₃P.

**Isomerisations of Secondary Allylic alkoxides**

Previous studies with in the group¹³³,¹³⁴ had established that the isomerisation of the lithium alkoxide of 1-phenyl-2-propen-1-ol (88) could be achieved with a variety of catalyst systems, namely [Rh(DIPHOS)]⁺, NiCl₂(R₃P)₂/n-BuLi, (Ph₃P)₃RhCl and NiCl₂(DIPHOS)/LiBEt₃H affording each time the corresponding (Z) enolate stereochemically pure and in high yield (Figure 80 and 91). It was therefore envisaged that similar results would be obtained with the Ni(COD)₂/pyridine catalyst system. Increased substitution about the double bond afford substrates such as (E)-1-phenyl-2-buten-1-ol (199), which was prepared by the Grignard addition of phenyl magnesium bromide to (E)-2-butenal in 68% yield, and (E)-2,2-dimethyl-4-hexen-3-ol (200), prepared by the addition of t-BuLi to the same aldehyde in 55% (Figure 164).

![Figure 164](image-url)
These two allylic alcohols were converted to the alkoxide, treated with the Ni(COD)$_2$/pyridine catalyst and then heated in THF to reflux for 2 hours prior to quenching the reaction with excess acetic anhydride. The results are presented below (Figure 165).

(i) n-BuLi
(ii) Ni(COD)$_2$/pyridine
(iii) Ac$_2$O, -78°C

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{HO} & \quad \text{Ph} \\
\text{(199)} & \\
\text{(200)} & \\
\end{align*}
\]

These two reactions were conducted as follows:

- **(199)**
  - (i) $\text{n-BuLi}$
  - (ii) Ni(COD)$_2$/pyridine
  - (iii) Ac$_2$O, -78°C
  - Result: $\text{Ph}$\text{O}CPh \quad + \quad \text{Ph}O\text{C} \quad 20:1 \quad 21%$

- **(200)**
  - (i) $\text{n-BuLi}$
  - (ii) Ni(COD)$_2$/pyridine
  - (iii) Ac$_2$O, -78°C
  - Result: $\text{Ph}$\text{O}C \quad + \quad \text{Ph}O\text{C} \quad 33%$

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{C} \\
\text{Ph} \quad \text{O} & \quad \text{C} \\
\text{(201)} & \quad + \quad \text{(202)} \\
\text{Ph} & \quad \text{O} \quad \text{C} \\
\text{Ph} \quad \text{O} & \quad \text{C} \\
\text{(203)} & \quad + \quad \text{(204)} \\
\end{align*}
\]

**Figure 165**

Comparable stereochemical ratios of enol acetate were obtained using the [Rh(DIPHOS)]$^+$ and NiCl$_2$(Cy$_3$P)$_2$/n-BuLi catalyst systems on substrates (199) and (200). The formation of significant quantities of ketone (203) despite the addition of 10 equivalents of acetic anhydride was unexpected. Although the problem of ketone formation had previously been encountered, the possibility of incomplete acylation of the enolate cannot be ruled out. Since the Ni(COD)$_2$/Ligand catalyst was not able to isomerise geraniol (61) itself, *i.e.* as the alcohol, and not the alkoxide, then a prominent proton source is likely not to be present during the isomerisation of the alkoxide of (199), otherwise the reaction product yield would be significantly lower.
The acetic anhydride itself was stirred with excess P$_2$O$_5$ to remove all traces of acetic acid prior to distillation and transfer to the reaction mixture. The question of ketone formation remains unresolved. However it is likely that partial hydrolysis of the enol acetate is occurring during work-up, where the reaction mixture is stirred with saturated NaHCO$_3$ solution to remove excess acetic anhydride prior to purification by column chromatography.

The addition of a further methyl group to the olefin, generates the tri-substituted allylic alcohol (207) (Figure 166). Compared with 3-phenyl-2-cyclohexen-1-ol (161), a similarly substituted allylic alcohol, it would be anticipated that the alkoxide of (207) would isomerise much more readily as the olefin is brought into conjugation with the aromatic benzene ring, whereas with (161), the olefin is taken out of conjugation. In the event, however, the alkoxide of (207) was found to be inert to all the nickel and rhodium catalyst systems, even after prolonged reaction times. As we have already seen, this was not the case for (161) as the isomerised products were isolated in 83% yield (Figure 135).

![Figure 166]

The allylic alcohol (208) was of particular interest since isomerisation will result in the formation of a tetrasubstituted enolate. This entry into stereocontrolled tetrasubstituted enolate formation constitutes a major potential application for the transitional metal mediated isomerisation process. Deprotonation of α-substituted ketones invariably gives rise to a mixture of enolates, as evidenced by the action of LDA on the ketone (209), the isomerised product of compound (208), followed by acylation (Figure 167).
At the present time the control of tetrasubstituted enolate stereochemistry is generally not possible, and there still exists a need for a more general method for their preparation. Some of the approaches to this problem are illustrated below (Figure 168).

\[
\begin{align*}
\text{(1)} & \quad \text{(i) BuLi} \\
& \quad \text{(ii) } \text{TMS-Cl} \\
& \quad 50\% \\
\end{align*}
\]

\[
\begin{align*}
\text{(2)} & \quad \text{(i) } n\text{-BuLi} \\
& \quad \text{(ii) MeLi} \\
& \quad \text{(iii) TMS-Cl} \\
& \quad \begin{array}{c}
\text{OTMS} \\
\text{7:1} \\
\end{array}
\]

\[
\begin{align*}
\text{(3)} & \quad \text{(i) } \text{Me}_2\text{CuLi, THF} \\
& \quad \text{(ii) TMS-Cl, HMPA} \\
& \quad \begin{array}{c}
\text{OTMS} \\
\text{2.6:1} \\
\end{array}
\]

**Figure 168**

Thus n-BuLi has been found to attack ketenes from the least hindered face, generating the silyl enol ether as the sole product (Figure 168, Equation 1).^263^ Similarly, the action of MeLi on ketenes, generated *in situ* by the reaction of n-BuLi with 2,6-di(t-butyl)-4-methylphenyl (BHT) ester enolates, generates the enolate with good stereocontrol (Equation 2).^264^ Problems arise however due to the formation of the BHT alkoxide, and it was noted that alkyl halides were unable to react with enolates prepared in this manner. Organocuprates offer only moderate levels of control in enolate geometry, within acyclic systems, as exemplified by work performed by Nakamura and co-workers (Equation 3).^262^

The allylic alcohol \((E)\)-2-methyl-1-phenyl-2-buten-1-ol (208), and its regioisomer, 2-ethyl-1-phenyl-2-propen-1-ol (210), were prepared by the Grignard addition of phenyl magnesium bromide to the aldehydes \((E)\)-2-methylbuten-1-al (211) and 2-ethylpropenal (212) respectively (Figure 169).
Figure 169

The isomerisation of the alkoxide of either (208) or (210) would give rise to the same enolate product. It was originally supposed that the structural architecture of the starting alkoxide influenced the stereochemical outcome of the reaction, i.e. the allylic alkoxide from one alcohol would give the enolate product in the exact but opposite stereochemical sense to that from the other allylic alcohol. Thus, consideration of the π-allyl mechanism, then if O-Li aggregation is large, then steric factors could play a part in controlling the stereochemistry of the enolate product. The O-Li bond will therefore be aligned away from the steric bulk of the ligands situated on the metal catalyst (Figure 170).

In the event, however, both allylic alkoxides were isomerised smoothly to give predominantly the (Z) enolate (Figure 171). A notable degree of stereocontrol was achieved using the alkoxide of (208), which gave a (Z) : (E) enolate ratio of 5 : 1. This result compares very favourably with those obtained with the other catalyst systems, although similar results were obtained with the alkoxide of the other allylic alcohol (210).
The Ni(COD)$_2$/pyridine catalysts offered a greater rate of conversion for the alkoxide of alcohol (208), affording 56% of material in only 1.5 hours. The NiCl$_2$(Cy$_3$P)$_2$/n-BuLi catalyst system reacted slowly over 24 hours, but nevertheless the corresponding enol acetates were obtained in a higher yield.$^{133}$ Furthermore, in the isomerisation study of the alkoxide of (210) with NiCl$_2$(Cy$_3$P)$_2$/n-BuLi, it was noted by $^1$H-NMR analysis of the recovered starting material that traces of the alcohol (208) were detected.$^{133}$ Such an equilibration could be achieved via metal-hydride addition and elimination mechanism. This equilibration process was not observed with either the Ni(COD)$_2$/Pyridine or the [Rh(DIPHOS)]$^+$ catalysts, indicating the absence of a metal-hydride addition and elimination mechanism. Indeed, the [Rh(DIPHOS)]$^+$ catalyst has previously been shown to operate via the enone or $\pi$-allyl mechanism,$^{117,133}$ thus indicating the similarity in the mechanism between the rhodium and the Ni(COD)$_2$/Pyridine catalyst systems.

As illustrated above in Figure 170, the alkoxide of the alcohol (208) predictably afforded the (Z) enolate. The alkoxide of alcohol (210), however, also gave the (Z) enolate and not the predicted formation of an (E) enolate. Although these results do not confirm the mechanistic argument presented in Figure 170, nevertheless, control of the enolate stereochemistry by the structure of the starting material could still be occurring. It is likely that equilibration of the enolates formed in the first instance, by $\pi$-$\sigma$-$\pi$ fluxionality, has occurred, leading to an accumulation of the
thermodynamically preferred (Z) enolate, under the conditions of the reaction. It should be noted that both starting materials are secondary alcohols, and that the isomerisation of the secondary allylic alkoxides have always been observed to afford predominantly the (Z) enolate.

Returning to the two reactions above, then if the (Z) enolate is formed preferentially under thermodynamic control, then similar enolate ratios would be observed at the end of the reaction. This was not the case, as the (Z) : (E) enolate ratio for the alkoxides of (208) and (210) were 5 : 1 and 2.5 : 1 respectively. It is likely that if the reaction was allowed to proceed for longer, then a lower (Z) : (E) ratio would be expected. Needless to say therefore that the (Z) : (E) enolate ratio generate in the first instance, i.e. at the start of the reaction, could very well be much higher than the final ratio of 5 : 1. Mixing of the product stereochemistry was observed by Bergens and Bosnich following the isomerisation of allylic alcohols to persistent enols using the [Rh(DIPHOS)]^+ catalyst. It follows that similar events are occurring during the isomerisation of allylic alkoxides, and further studies to obtain enolate ratios generated at the start of the reaction would need to be conducted in order to resolve this issue.

Using the Ni(COD)$_2$ catalyst system with the alkoxide of geraniol (61) it was noted that using either benzene as solvent (Figure 146) or pyridine as ligands (Figure 127), then the isomerisation proceeded to give the corresponding enolates with a high level of stereocontrol. Typically, the ratio of the formed (E) and (Z) enol acetates were greater than 20 : 1, far higher than has previously been observed with this substrate.\textsuperscript{133,134} It was possible that enolate mixing, or interconversion, by '\(\pi-\sigma-\pi\)' fluxionality was suppressed under these conditions.

It was therefore envisaged that the combination of these two desirable facets for stereocontrolled enolate formation, i.e. benzene as solvent and pyridine as ligand, could be employed together to enhance the selectivities for the preparation of tetrasubstituted enolates. The isomerisations were therefore repeated with the results indicated below (Figure 172).

![Figure 172]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>(213) : (214) Ratio</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(208)</td>
<td>2.4 : 1</td>
<td>54 %</td>
</tr>
<tr>
<td>(210)</td>
<td>2.4 : 1</td>
<td>52 %</td>
</tr>
</tbody>
</table>
The result was disappointing in that poor stereocontrol was exhibited under the modified conditions of the reaction mixture. It is not clear why this is so, only that in this case, THF favours a greater degree of stereocontrol.

Further work in the area of tetrasubstituted enolate preparation was conducted using the alkoxides of 2,2-dimethyl-4-ethyl-4-penten-3-ol (215) and (E)-2,2,4-trimethyl-4-hexen-3-ol (216), prepared as an inseparable mixture by the addition of t-BuLi to 2-ethylpropanal (212) at -78°C (Figure 173).

A quantity of the alcohol (216) was also formed during the reaction, presumably by deprotonation at the less hindered 5-position on the alkoxide of the alcohol (215). Migration of the carbon-carbon double-bond into the carbon chain would result in a more conjugated olefin, and hence formation of the alkoxide of (216) during the reaction.

It was speculated that the steric hindrance imposed by the adjacent t-butyl group would provide a means to probe the limitations of the Ni(COD)$_2$/pyridine catalyst. The alcohols were deprotonated using n-BuLi and the isomerisations attempted. The reaction was quenched with saturated NH$_4$Cl solution after 2.5 hours reaction in order that comparisons might be made with the other substrates (Figure 174).
The isomerised product (217) was also isolated, in 18% and the recovered starting materials (215) and (216) in 57% yield, in the ratio 1.9 : 1. Although the change in the ratio of these alcohols suggests that a reversibility in the π-allyl mechanism is occurring, or the possible involvement of a metal-hydride addition and elimination mechanism, it is likely that migration of the olefin bond had occurred under the basic conditions of the isomerisation. Direct interconversion of the alkoxide substrates by the formation of the non-conjugated π-allyl hydride (218) appears unlikely on energetic grounds (Figure 175). This mixing of bond geometry was also encountered with the [Rh(DiPHOS)]* and NiCl₂(Cy₃P)₂/n-BuLi catalyst systems, presumably for the same reason.

\[ \text{OLi} \quad \text{Ni(0)} \quad \text{OLi} \]

\[ (218) \]

Figure 175

It is clear that despite a variety of successful transformations using the Ni(COD)₂/pyridine catalyst system, the susceptibility of this, and other catalyst systems, to steric hindrance is an area of difficulty that still remains to be resolved.

**Potential Synthetic Applications**

The isomerisation of the alkoxide of geraniol (61) clearly demonstrates that the Ni(COD)₂/pyridine catalyst system can isomerise allylic alkoxides in a chemoselective manner, *i.e.* the second olefinic centre in geraniol (61) remains intact under the conditions of the isomerisation. The trisubstituted nature of this second olefin may account for the lack of reactivity, therefore it was necessary to employ a substrate containing a more exposed second olefinic site, such that the true chemoselective nature of catalyst Ni(COD)₂/pyridine system could be probed. A suitable substrate was 1,6-heptadien-3-ol (219), as it had previously been shown to isomerise chemoselectively with the catalyst cis-Mo(N₂)₂(DiPHOS), to give the corresponding ketone (220) in high yield (Figure 176). \(^{112}\)

\[ \text{219} \quad \xrightarrow{\text{cis-Mo(N₂)₂(DiPHOS)}} \quad \text{220} \]

98-100%  

\[ \text{Figure 176} \]
Under the isomerisation conditions of this particular substrate, it is possible for the alkoxide of alcohol (219) to undergo intramolecular cyclisation, in similar fashion to that noted for 1,6-heptadiene (221), which was found to cyclise to the substituted cyclopentane (222) in the presence of either nickel(I)\(^{265}\) or rhodium(I)\(^{266}\) (Figure 177). The outcome of such an isomerisation/cyclisation reaction using the alkoxide of (219) and the Ni(COD)\(_2\)/pyridine catalyst was therefore of great interest as it might provide some insight into the nature of the catalytic species.

![Figure 177](image)

1,6-heptadien-3-ol (219) was accordingly prepared in two steps by Swern oxidation of 4-penten-1-ol, and subsequent reaction of the aldehyde with vinyl magnesium bromide to give the alcohol (219), in 22% overall yield.\(^{133}\) The lithium alkoxide of (219) was then heated to reflux in THF for 3 hours in the presence of the Ni(COD)\(_2\)/pyridine catalyst (Figure 178).

![Figure 178](image)

The isomerisation reaction was quenched by the addition of saturated NH\(_4\)Cl solution in order to simplify \(^1\)H-NMR analysis. Ketone (220) was the only identifiable compound, with no evidence for any cyclisation observed.\(^{267,268}\) The same isomerisation, but conducted with the [Rh(DIPHOS)]\(^+\) catalyst, required 13 hours of reaction time, and it was noted that significant isomerisation of the terminal olefin had occurred.\(^{133}\) The NiCl\(_2\)(Cy\(_3\)P)\(_2\)/n-BuLi catalyst systems again required lengthy reaction times, but with a lesser degree of terminal olefinic isomerisation.\(^{133}\) No cyclisation product were noted in either case.

Although the result indicates a chemoselective transformation, the formation of several unidentifiable by-products indicates an involvement of the terminal olefin in the isomerisation process. Despite the absence of any cyclised product, it is believed that further investigation is warranted in this area, such that this transformation may be developed into a synthetically viable process.
Isomerisation of Allylic Amines

As reported by Noyori and co-workers the rhodium catalysed isomerisation of N,N-diethylgeranylamine (64) proceeds to give the corresponding enamine in 96% yield, and greater than 95% enantiomeric excess (Figure 65).\textsuperscript{120} This is far higher than that which has been achieved for allylic alcohols, even with the same chiral catalyst (Figure 64).\textsuperscript{119} It therefore seemed appropriate to use this substrate with the Ni(COD)$_2$/pyridine catalyst system. N,N-Diethylgeranylamine (64) was prepared in one step by the addition of diethylamine to myrcene (223) in the presence of $n$-BuLi (Figure 179).\textsuperscript{269} N,N-Diethylneranylamine (224) can be prepared in similar fashion from isoprene (225).\textsuperscript{270}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure179}
\caption{Figure 179}
\end{figure}

Isomerisations were conducted using a variety of ligands, namely with pyridine, DIPHOS and bipyridyl, however in each case, analysis of the isomerisation reaction by GC indicated only starting material, despite prolonged reaction times. It is possible that the allylic amine is coordinating to the nickel catalyst, displacing the original ligand to form a hexaamine complex, not too dissimilar to the [Ni(NH$_3$)$_6$]$^{2+}$ complex formed by the addition of ammoniacal solution to aqueous nickel(II)chloride.

Although this substrate has been shown not to be suitable substrate with the Ni(COD)$_2$/ligand catalyst systems, nevertheless it was curious as to why rhodium could isomerise this substrate, whereas the nickel could not.
Studies On Regiocontrol

Earlier studies on regiocontrolled enolate formation found that the \((\text{Cy}_3\text{P})_2\text{NiCl}_2/\text{n-BuLi}\) catalyst could isomerise the alkoxide of 1-phenyl-4-penten-3-ol (102) regioselectively in 92% yield. Problems were encountered however using the \([\text{Rh(DIPHOS)}]^{133}\) and the \(\text{NiCl}_2(\text{DIPHOS})/\text{LiBEt}_3\text{H}\) catalyst systems in which a mixture of regioisomers were obtained (Figure 94).

It was envisaged that using the highly stereoselective \(\text{Ni(COD)}_2/\text{pyridine}\) catalyst system that similar degrees of regiocontrol would also be exerted. The alkoxide of 1-phenyl-4-penten-3-ol (102) was therefore treated with the catalyst system in THF heated to reflux for 2 hours, then quenched with acetic anhydride. Purification of the reaction mixture afforded the ketone (226) in 17% yield, the enol acetate products as a mixture of regioisomers in 26% yield (Figure 180) and the starting material as in 21% yield.

\[
\begin{align*}
\text{OH} & \quad \text{Ph} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\((102) \quad \xrightarrow{(\text{i}), (\text{ii}), (\text{iii})} \quad \begin{align*}
\text{OAc} & \quad \text{Ph} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\((226) \quad 17\% \]

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\((227) \quad 8.2:1 \quad 12\% \]

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\((228) \quad 2.3:1 \quad 14\% \]

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\((229) \quad (230) \]

\[
\text{Regiochemical ratio: i.e. } \frac{[(227)+(228)]:[(229)+(230)]}{1:1.16} \]

\((\text{i}) \text{n-BuLi, THF; (ii) Ni(COD)}_2/\text{pyridine, then reflux for 2 hours; (iii) } \text{Ac}_2\text{O, } -78^\circ\text{C} \]

3-phenyl-2-cyclohexen-1-ol (161) had previously been shown to isomerise well using the \(\text{Ni(COD)}_2/\text{bis(oxazoline)}\) catalyst, affording the corresponding 3-phenyl-1-cyclohexanone in 83% yield, one of the highest yields obtained so far. It was necessary to probe this reaction further by trapping the enolate out with acetic anhydride and investigating the regiochemical outcome of the reaction. Pyridine and triphenylphosphine were used as ligands (Figure 181).
Results and Discussion

Using either pyridine or triphenylphosphine as ligand offered the same relative quantities of ketone and enolate product, with a combined yield of 77% and 66% respectively. The formation of significant quantities of ketone despite the addition of 10 equivalents of acetic anhydride was surprising. Although the problem of ketone formation has previously been encountered, the possibility of incomplete acetylation of the enolate cannot be ruled out.

The lack of regio control exhibited by the Ni(COD)$_2$/pyridine catalyst, but not with the NiCl$_2$(Cy$_3$P)$_2$/n-BuLi catalyst, clearly indicates that these two catalysts operate via different mechanisms. Deuterium labelling techniques have been employed as mechanistic probes to determine whether or not the isomerisation mechanism is operating via metal-hydride addition and elimination (See Mechanistic Studies).

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (168)</th>
<th>Yield (231) + (232)</th>
<th>(231) : (232) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>48%</td>
<td>29%</td>
<td>2.0 : 1</td>
</tr>
<tr>
<td>Ph$_3$P</td>
<td>44%</td>
<td>22%</td>
<td>2.1 : 1</td>
</tr>
</tbody>
</table>
Mechanistic Studies
Introduction

Attempts to introduce asymmetry into the product of an isomerisation by the use of chiral transition metal catalysis had failed, despite the range of chiral ligands employed. Following the result whereby optically pure lithium enolate had racemised under the conditions of the isomerisation, it was clear that enantioselective isomerisation would not be possible, under the existing conditions.

It is notable that the isomerisation of $N,N$-diethyleranyiamine using the chiral rhodium catalyst, $[\text{Rh}(S)\text{-BINAP}]^+$ can proceed over a range of temperatures, from 0 to 80°C, and still achieve high levels of enantioselectivity. It was of some concern that the observed racemisation with the Ni(COD)$_2$/ligand catalysts was due to the relatively high reaction temperature (ca. 65°C). However, attempts to isomerise the alkoxide of geraniol (61) at room temperature met with little or no success, neither using benzene as solvent at room temperature which gave the enolate product with high stereocontrol, but with no enantiomeric excess. Repeating the same reaction at 60°C produced similar results, but the greater yield of enolate implies a need for activation energy for the isomerisation process.

Although the racemisation experiment offered no explanation for the absence of any enantiocontrol the reason why racemisation should occur at all, regardless of the chiral environment imposed by the ligands on the nickel metal centre, was not very clear.

A possible clue to the problem could rest with elucidating the mechanism through which the isomerisation process is thought to proceed (Figure 68, 69). If the isomerisation was operating via metal-hydride addition and elimination, then the enantioselective step would be the first step when the metal-hydride adds across the prochiral olefin in the allylic moiety. The second step would be elimination to reform the metal-hydride and to generate the enolate product. The reversible nature of this mechanistic pathway is such that the metal-hydride may add and then eliminate several times on the same substrate molecule during the course of the reaction. The result is a decrease in the enantioselective capability of the chiral nickel catalyst. $\pi$-Allyl and enone mechanisms (See Figures 142 and 143) are more likely to offer asymmetric induction due to the greater binding and rigidity of the substrate-catalyst intermediates during these two processes.

Deuterium labelling experiments have been shown in the past as mechanistic probes, specifically to differentiate between the metal-hydride addition and elimination mechanism, and the $\pi$-allyl and enone mechanisms. Replacement of the carbinol hydrogen with deuterium allows the fate of the abstracted deuteride to be determined. A mechanism operating via metal-hydride addition and elimination is likely to distribute the deuterium within the vicinity of the allyl moiety, whereas via a $\pi$-allyl or enone mechanism the deuterium will be delivered only to the $\beta$-position in the enolate product (Figure 182).
Results and Discussion

This technique of deuteration and analysis of the deuterium distribution in the isomerised product has been employed by several groups. Both Fe(CO)$_5^{124}$ and [Rh(DIPHOS)]$^+$ on alcohols (70) and (233) respectively, were shown to operate via 1,3 deuterium migration, and hence via a π-allyl or enone mechanism, which is in contrast to the hydridoplatinum catalyst, HPt(Ph$_3$P)$_2$(acetone), which isomerised the deuterated allyl methyl ether (234) with significant distribution of the deuterium, indicative of metal-hydride addition and elimination (Figure 183).$^{151}$

Isomérisation of simple deuterated substrates

The deuterated alcohol (233) was therefore prepared from 1-phenyl-2-propen-1-ol (88) in two steps. Oxidation of the alcohol (88) to 1-phenyl-2-propen-1-one (236) was accomplished using

\[ \text{Fe(CO)}_5 \quad \text{(70)} \]
\[ \text{[Rh(DIPHOS)]}^+ \quad \text{(233)} \]
\[ \text{HPt(Ph}_3\text{P)}_2\text{(acetone)} \quad \text{(234)} \]
manganese(IV) oxide, which was then reduced to the deuterated allylic alcohol (233) using lithium aluminium deuteride (Figure 184).

![Chemical structure](image)

**Figure 184**

In the preparation of the deuterated alcohol (233), the formation of the β-deuterated ketone (235), arising via competitive conjugate addition, was noted. The α-deuterated ketone (237) was prepared by quenching the lithium enolate of propiophenone with D$_2$O. Ketones (235) and (237) constitute the two possible deuterated products following an isomerisation of the alkoxide of alcohol (233). The results using the Ni(COD)$_2$/ligand are presented, together with results from previous work within the group (Figure 185).$^{133,134}$

![Chemical structure](image)

**Figure 185**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst System</th>
<th>Yield (235)</th>
<th>Yield (237)</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(COD)$_2$/Cy$_3$P</td>
<td>40%</td>
<td>0%</td>
<td>4.5 hours</td>
</tr>
<tr>
<td>2</td>
<td>Ni(COD)$_2$/bis(oxazoline) (128)</td>
<td>40%</td>
<td>0%</td>
<td>4.5 hours</td>
</tr>
<tr>
<td>3$^{133}$</td>
<td>[Rh(DIPHOS)]$^+$</td>
<td>67%</td>
<td>0%</td>
<td>4 hours</td>
</tr>
<tr>
<td>4$^{133}$</td>
<td>NiCl$_2$(Cy$_3$P)$_2$/n-BuLi</td>
<td>26%</td>
<td>4%</td>
<td>5 hours</td>
</tr>
<tr>
<td>5$^{134}$</td>
<td>(Ph$_3$P)$_3$RhCl</td>
<td>66%</td>
<td>trace</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

It is relatively clear that the mechanism inferred by the results in Entries 1, 2, 3 and 5 is operating via π-allyl or enone intermediates. The absence of compound (237) by $^1$H-NMR indicates that the hydride is delivered only to the β-position of the enolate product, and that a metal-hydride addition and elimination mechanism does not play a detectable role in the
isomerisation process. This is not the case in Entry 4, for the NiCl₂(Cy₃P)₂/n-BuLi catalyst system, where significant quantities of the α-deuterated ketone (237) were detected, indicating the involvement of a metal-hydride addition and elimination mechanism during the isomerisation process.

Although these results indicate that the Ni(COD)₂/ligand and NiCl₂(Cy₃P)₂/n-BuLi catalyst operate via different mechanisms, the question of enantioselectivity still remains unanswered, as a mechanism of metal-hydride addition and elimination for the Ni(COD)₂/ligand catalyst might have gone some way to providing an answer. It is possible, however, that the isomerisation mechanism could vary from one substrate to another, depending on the ease or difficulty of their transformation.

Isomerisation of deuterated prochiral substrates

The deuterated analogues of (E)-3-phenyl-2-buten-1-ol (63) and geraniol (61), namely (E)-1,1-di-[²H]-3-Phenyl-2-buten-1-ol (238) and (E)-1,1-di-[²H]-3,7-dimethyl-2,6-octadien-1-ol (239), were prepared as mechanistic probes for the Ni(COD)₂/ligand catalysts system (Figure 186).

The alkoxides of the alcohols (238) and (239) were isomerised using the Ni(COD)₂/ligand catalyst system, with the results presented below (Figure 187).
Results and Discussion

All of the above isomerisations were worked-up with saturated NH₄Cl solution in order to simplify analysis of the reaction mixture. It was quite apparent by \(^1\)H-NMR analysis that deuterium could not be detected anywhere else other than on carbons 1 and 3 in compounds \(241\) and \(243\), implying that metal-hydride addition and elimination is not occurring at a detectable level during the course of the reaction. This was true for both the Ni(COD)₂/ligand and NiCl₂(Cy₃P)₂/n-BuLi
catalysts systems, although the latter failed to give any isomerised product with the alkoxide of (238). In all instances, the starting materials (238) and (239) were recovered intact, with the carbinol deuterium content unchanged.

The deuterium studies indicate a π-allyl or enone mechanism is operating with the Ni(COD)$_2$/ligand catalyst system, which unfortunately does not resolve the continuing problem of enantioselectivity. In addition, the transfer hydrogenation products, (242) and (244), were both formed containing three deuterium atoms, which was unexpected considering that each starting material contains only two. Formation of these saturated alcohols can occur by metal-deuteride reduction of the corresponding aldehyde, the source of which is by protonation of the enolate product itself. The source of these protons is not clear, however, two processes were considered to account for this observation. Both of which will be discussed.

**By deprotonation**

It was envisaged that deprotonation at the γ-position on the intermediate α,β-unsaturated aldehyde complex (245), the intermediate proposed by the 'enone' mechanism, could occur to afford the complex (246), under the conditions of the isomerisation (Figure 188).
Deprotonation of (245) is likely to occur by reaction with the allylic alkoxide, which can of course function as a base. The pKₐ values of an alcohol (ca. 16) and the γ-proton in an enone (ca. 17.6)²⁷¹ are comparable and therefore is likely that under the basic conditions of the reaction such a deprotonation process could occur. The “available” protons may then protonate the enolate (247) to form the aldehyde (248). Reduction of this aldehyde with the deuterido nickel intermediate will then furnish the alcohol (249) bearing three deuterium atoms.

By pre-equilibration

A recent observation by Blackmond and co-workers noted a striking inversion of enantioselectivity in the hydrogenation of geraniol (61) with [RuCl₂(S)-(di-p-tolylphosphino-1,1'-binaphthyl)]₂NEt₃ to (R) and (S)-citronellol (112).²⁷² It was rationalised that the internal olefin in geraniol had isomerised to the terminal isomer γ-geraniol (250) during the period of catalysts dissolution in the solvent-substrate mixture prior to the addition of hydrogen. These two isomeric olefins underwent hydrogenation with respectively high enantioselectivities to chiral citronellol (112) with opposite absolute stereochemistry (Figure 189).

![Diagram of chemical reactions](image)

**Figure 189**

Compound (250) was confirmed by comparative ¹H and ¹³C-NMR studies of an authentic sample of (250). Temperature dependant studies on the isomerisation reaction in the absence of hydrogen indicated an equilibration concentration of about 22% of (250) at 45°C, and 18% at 20°C. Although treatment of the catalyst with hydrogen prior to addition to the alcohol minimised the interconversion,²⁷³ nevertheless, it was apparent that the isomerisation was effectively competing with the hydrogenation even under reaction conditions.
It was unusual that the chiral ruthenium catalyst offered a ‘wrong-way’ isomerisation as there is a literature precedent for complexes of ruthenium and several other transition metals to isomerise allylic alcohols to the corresponding carbonyl compounds.

Returning to the isomerisation of allylic alkoxides, the possibility of isomeric mixing was considered to account for the formation of the transfer hydrogenated product, citronellol (112) (Figure 190).

![Diagram](image)

*Figure 190*: Ligands not shown on nickel for clarity

Proton exchange between the isomerised product (247) and compound (251) results in the formation of the aldehyde (248), which may be reduced to the alcohol. Work-up with saturated NH₄Cl solution affords the ketone (248) and the alcohol (249).

It was hoped that evidence for either of these processes could be obtained by the isomerisation of compound (252), prepared in two steps from deuterated acetophenone (Figure 191).

![Diagram](image)

*Figure 191*
It was envisaged that if deprotonation was to occur then the deuterium atoms would be expected to be distributed between the \(\alpha\)- and \(\gamma\)-carbons in the isomerised product (254) and (255). Deuterium incorporation at the \(\alpha\)-carbon can occur with deuteration of complex (256), or with (257) which results in the formation of species (258) which may then proceed to form the deuterated product (255). Formation of the transfer hydrogenated product (259) would be accompanied by deuteration at the carbinolic and \(\alpha\)-carbons (Figure 192).

![Figure 192: Ligands not shown on nickel for clarity](image)

If pre-equilibration, or isomeric mixing was occurring then the deuterium atoms would be expected to be distributed between the \(\alpha\)- and \(\gamma\)-carbons to afford the product (255) and (260) (Figure 193).

![Figure 193](image)
Isomerisation of the allylic alkoxide of (252) resulted in the formation of the deuterated enolate product (254) with no detectable loss of deuterium content at the γ-position (Figure 194).

This result implies one of the following

- that deprotonation or pre-equilibration is not occurring and that the deuterated transfer hydrogenated product is formed by some other means; or

- that deprotonation or pre-equilibration is occurring, but not at a detectable level. The strength of the C-D bond is much more than that of the C-H bond. As a consequence, the rate of deprotonation would be significantly slower due to this isotope effect, such that the rate of formation of the deuterated ketone (255) is negligible. In other words, although ketone (255) was not detected using the deuterated allylic alcohol (252) as substrate, the observed result neither proves nor disproves the existence of this deprotonation process using the non-deuterated allylic alkoxide as a substrate.

It is conceivable that if deprotonation or pre-equilibration is occurring, then the flexibility of the intermediary structures, such as (245) and (246) (Figure 188), is such that a rigid transition state required for asymmetric induction to occur is not likely to form. Thus attempts to conduct an isomerisation within a chiral environment will only result in the formation of racemic material, which has been the case with all the chiral ligands and prochiral substrates employed.

In summary, these deuterium studies indicates that a π-allyl or enone mechanism is operating with the Ni(COD)$_2$/ligand catalyst system. Both of these mechanisms could result in racemic products if the isomerisation process was reversible. The results confirm that the enolate product can react with the metal catalyst to regenerate the π-allyl or the enone intermediate, hence the observed racemisation of authentic chiral enolate at the β-position. It is not clear from these results if these intermediates could be transformed back into the starting allylic alkoxide. Further labelling studies using substrates such as (261) (Figure 195) would confirm if such a process was occurring.
Isomerisations with Chiral Ni(II) Complexes
Introduction

The deuterium studies unfortunately did not furnish conclusive answers to the problem of enantioselectivity. The results did however indicate that the [Rh(DIPhos)]⁺ and Ni(COD)₂/ligand catalyst systems operate via a different mechanism to the NiCl₂(Cy₃P)₂/n-BuLi catalyst system. It was suggested that the NiCl₂(Cy₃P)₂/n-BuLi and NiCl₂(DIPhos)/LiBEt₃H operate via similar mechanisms due to the formation of an intermediate Ni(I)H, or a Ni(II)Cl₂ species, and it was therefore envisaged that if nitrogen ligands could be chelated to the Ni(II)Cl₂ precursors instead of the phosphine based ligands, then the resulting pre-catalyst would have the potential for asymmetric catalysis, particularly if the bis(oxazoline) class of ligands were employed.

Use of pyridine as ligand

Following the successful isomerisations of primary allylic alkoxides with the Ni(COD)₂/pyridine catalyst, generating enolates with (E) : (Z) ratios typically greater than 15 : 1, it was hoped that using pyridine could be used instead of the Cy₃P ligand in the NiCl₂(Cy₃P)₂/n-BuLi catalysts system. The NiCl₂Py₂ complex is known, and therefore it was envisaged that an active catalyst could be prepared by the addition of either n-BuLi or LiBEt₃H to this NiCl₂Py₂, in the same way as for the NiCl₂(Cy₃P)₂/n-BuLi catalyst system.

NiCl₂Py₂ was prepared as a powdery yellow green solid from the brown coloured anhydrous NiCl₂ and two equivalents of pyridine in hot ethanol. The nickel salt was dried by heating to reflux in thionyl chloride for several hours, although this was found not to be necessary and NiCl₂Py₂ could be prepared directly from NiCl₂.6H₂O. Isomerisations were attempted with NiCl₂Py₂ using n-BuLi or LiBEt₃H as the activating agents (Figure 197).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reducing Agent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(88)</td>
<td>n-BuLi</td>
<td>33 %</td>
</tr>
<tr>
<td></td>
<td>LiBEt₃H</td>
<td>17 %</td>
</tr>
<tr>
<td>(61)</td>
<td>n-BuLi</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>LiBEt₃H</td>
<td>-</td>
</tr>
</tbody>
</table>

*Figure 197*
The addition of the activating agents to the NiCl\(_2\)Py\(_2\) catalyst at -78°C gave a very dark lilac coloured solution on warming to room temperature. This darkening effect is also observed with the NiCl\(_2\)(Cy\(_3\)P)\(_2\)/n-BuLi catalyst system; the dark colour of the mixture indicative of an active catalyst. It was unexpected therefore to find that NiCl\(_2\)Py\(_2\), activated with either n-BuLi or LiBEt\(_3\)H, achieved only 17-30% yield of isomerised product (91) following the isomerisation of the alkoxide of (88). This is in contrast to the quantitative yields given by the NiCl\(_2\)(Cy\(_3\)P)\(_2\)/n-BuLi catalyst system over the same length in reaction time. The alkoxide of geraniol (61) failed to react.

NiCl\(_2\)Py\(_2\) and adopts a distorted octahedral structure, forming long chains linked by chloride bridges. It is likely that a chlorohydridonickel(II) intermediate is being formed following the addition of the activating agent, however, the adoption of a similar chain-like architecture would severely impede its catalytic ability. NiBr\(_2\)Py\(_2\) is pale green and structurally identical to NiCl\(_2\)Py\(_2\), however NiBr\(_2\)Py\(_2\) is dark green in colour, adopting a tetrahedral arrangement.\(^{275}\) 2-Methyl pyridine has been shown to complex with NiCl\(_2\), generating a dark blue powdery solid which also adopts a tetrahedral structure. It is clear from these observations that tetrahedral structures of NiCl\(_2\)(Ligands) are intensely coloured, whereas octahedral structures are generally pale in colour. Efforts in this area were discontinued in favour of attempting to chelate chiral nitrogen based ligands to NiCl\(_2\).

**Use of bis(oxazoline) as ligand**

The purple coloured complex NiCl\(_2\)bis(oxazoline) (264), indicating tetrahedral geometry, was prepared in 93% yield by heating a mixture of the bis(oxazoline) ligand (128) and anhydrous NiCl\(_2\) in THF for 30 minutes.\(^{276}\) Preparation in ethanol afford a brown solid following removal of the solvent, which slowly turned purple under high vacuum. \(^{1}H\)-NMR and TLC analysis indicated that the bis(oxazoline) had not decomposed during the preparation of the complex. Isomerisations were repeated on the same alkoxide substrates used previously (Figure 198).
### Table 1

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reducing Agent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Reaction" /></td>
<td><em>n</em>-BuLi</td>
<td>11%</td>
</tr>
<tr>
<td><img src="image" alt="Reaction" /></td>
<td>LiBEt₃H</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figure 198**

The addition of *n*-BuLi to the NiCl₂·bis(oxazoline) complex at -78°C afforded a dark solution once again, indicative of an active catalyst. However, on treatment of this solution with the alkoxide of either (88) or (61), little or no isomerised product was detected by GC, with significant decomposition of the starting material occurring.

Although both the NiCl₂·Py₂ and NiCl₂·bis(oxazoline) catalysts failed to isomerise the alkoxide substrates to the same level offered by the other nickel and rhodium based systems, nevertheless, the formation of a nickel complex incorporating a chiral bis(oxazoline) ligand which exhibited moderate levels of catalytic activity was of some interest, and further investigation into this area is warranted.
Isomerisations with Rh(I) Complexes
Introduction

Bergens and Bosnich had previously used the \([\text{Rh(DIPHO S})]^{\circ}\) catalyst to analyse the stereochemical formation of persistent enols from allylic alcohols. However the eventual conversion of the enol product to the corresponding carbonyl moiety ultimately destroys the stereochemical information imposed onto the enol product by the catalyst during the transformation.

The isomerisation of an allylic alkoxide generates an enolate, which is a synthetically more viable building block in organic chemistry than the enol. The potential for the stereo, regio and enantiocontrolled formation of enolates was recognised and the use of transition metal complexes to catalyse the isomerisation of allylic alkoxides has been subjected to extensive study within the group, utilising complexes such as Wilkinson’s catalyst, (\(\text{Ph}_3\text{P})_3\text{RhCl}\) and \([\text{Rh(DIPHOS})]^{\circ}\) to probe this novel transformation.\(^{133,134}\)

In spite of our efforts in the field of chiral nickel chemistry, the problem of enantiocontrolled enolate formation needed to be re-addressed. Modification of the reaction by changing solvent or the counter cation failed to improve the catalytic process, and therefore it was decided to substitute the nickel itself for a different transition metal. The metal of choice was rhodium.

The isomerisation of allylic alcohols is not new as the first publication in this field of study was in 1903.\(^{109}\) Despite the variety of transition metals that have successfully isomerised allylic alcohols to carbonyl compounds, the highest enantiomeric excess achieved in an asymmetric isomerisation is 46%, achieved by the chiral rhodium catalyst, \([\text{Rh}(R)-(\text{BINAP})])^{\circ}\) \((\text{See Figure 65})^{119}\). The same catalyst was reported in 1984 to isomerise \(N,N\)-diethylgeranylamine to the corresponding enamine in high yield and over 95% enantiomeric excess, and of course forms the basis for the Tagasako process for the production of menthol.\(^{120}\)

Although some of our objectives were to control the stereo and regioselective formation of enolates from allylic alkoxides, the main goal of this project was to achieve this transformation in an enantioselective manner, aiming for levels of asymmetric induction comparable to that observed with the chiral rhodium catalyst for the isomerisation of allylic alcohols and amines.

Isomerisations with BINAP ligands

Throughout our entire study, we were always drawn to the success story of the Noyori \([\text{Rh(BINAP})])^{\circ}\) catalyst for the isomerisation of \(N,N\)-diethylgeranylamine and to the fact that the same catalyst was reported by Tani to achieve the conversion of geraniol to citronellal in 70%
yield, with an encouraging 37% enantiomeric excess (See Figure 65).\textsuperscript{119} We therefore decided to attempt to use the rhodium catalyst with geraniol, and its alkoxide. The \( \text{[Rh(COD)/(R)-BINAP]}^+\text{ClO}_4^- \) precursor catalyst complex was obtained from commercial sources,\textsuperscript{277} and treated with hydrogen prior to addition to the substrate. The reaction was then quenched with saturated NH\textsubscript{4}Cl solution after 24 hours of reaction time (\textit{Figure 199}).

\[
\begin{align*}
\text{(61)} & \quad \xrightarrow{(i) \text{[Rh(COD)/(R)-BINAP]}^+\text{ClO}_4^-} \quad \text{THF, reflux, 21 hours} \\
\text{(61)} & \quad \xrightarrow{(ii) \text{NH}_4\text{Cl}} \\
\text{(61)} & \quad + \\
\text{(265)} & \quad \text{(112)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield (61)</th>
<th>Yield (265)</th>
<th>Yield (266)</th>
<th>Yield (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\text{n-BuLi}</td>
<td>49%</td>
<td>-</td>
<td>-</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>43%</td>
<td>12%</td>
<td>15%</td>
<td>1%</td>
</tr>
</tbody>
</table>

\textit{Figure 199}

In all of our attempts to isomerise either the alcohol or alkoxide, only trace quantities of the isomerised product, citronellal (62), was detected each time by GC analysis of aliquots taken from the reaction mixture during the course of the reaction. The reaction of the alkoxide (\textit{Entry 1}) afforded predominantly the starting alcohol and citronellol (112) after work-up. The alcohol however (\textit{Entry 2}) unexpectedly gave a mixture of several products, including starting material and citronellol, two of which were identified by GC as limonene (265) and iso-pulegol (266).

It was not clear at this point why Tani was able to obtain the aldehyde in high yield, whereas a mixture of compounds were obtained in our hands. The presence of impurities in the catalyst was considered as a possible reason for this disagreement between our results, therefore we decided to test the catalyst with \( N,N\)-diethylgeranylamine (64). This substrate is isomerised quantitatively and in high enantiomeric excess with this catalyst on an industrial scale every year in the Tagasako Process (See Figure 65). The isomerisation was therefore conducted by us using the same reaction conditions. After 24 hours of reaction time, the reaction was quenched with saturated NH\textsubscript{4}Cl solution. GC analysis of the reaction mixture indicated predominantly the starting material, with approximately 2% of citronellal, following hydrolysis of the enamine product (\textit{Figure 200}).
The absence of any significant activity with the commercially obtained [Rh(COD)/(R)-BINAP]$^+$ClO$_4^-$ complex prompted us to prepare our own sample following a literature procedure.$^{278}$ (S)-BINAP was at hand, and was therefore employed as the chiral ligand. Although the [Rh(BINAP)]$^+$ complex was shown by Noyori to offer a higher catalytic activity than the [Rh(COD)(BINAP)]$^+$ClO$_4^-$ precursor, nevertheless, the isomerisation reactions were conducted by us using [Rh(COD)/(S)-BINAP]$^+$ClO$_4^-$ without pre-treatment with hydrogen. The quality of the hydrogen could not be guaranteed without adequate facilities to remove all traces of contamination, such as moisture or other volatile substances, which might otherwise deactivate the catalyst.

It was clear after 24 hours of reaction temperature that the [Rh(COD)/(S)-BINAP]$^+$ClO$_4^-$ complex had functioned as a very efficient catalyst, as analysis of the crude reaction mixture by GC after work-up with saturated NH$_4$Cl solution indicated only the aldehyde (62), which was subsequently isolated in 67% yield.

Following the success of the isomerisation of the allylic amine, we then turned our attention back to geraniol. The isomerisations were repeated with our catalyst to afford a mixture of products which were similar to those found using the commercially obtained catalyst (Figure 201).
Analysis of the reaction mixture (Entry 2) by chiral GC indicated the presence of chiral material. Due to the complexity of the sample mixture and a lack of chiral reference materials, only the following information about compound (266) could be deduced (Figure 202).

From this results, there are a number of notable observations:

- Only trace amounts of the isomerised product, citronellal, was detected by GC following the reaction in spite of adhering to the same reaction conditions employed by Noyori and co-workers, who obtained the aldehyde in 70% and in 37% ee.
- Both Iso-pulegol and iso-iso-Pulegol were prepared in nearly 50% enantiomeric excess, which is an increase to the optical yield obtained by Noyori for the aldehyde citronellal (37% ee.)
- The configuration at the 5-position for the major enantiomer of Iso-pulegol is (R) (Indicated above in Figure 218). This is in agreement with the configuration of the chiral aldehyde obtained by Noyori and co-workers for the same reaction.
- Iso-pulegol is formed from citronellal by an ene cyclisation reaction, catalysed by the Lewis acid ZnBr$_2$, in benzene at 0-5°C. This step forms part of the Tagasako process in the industrial synthesis of menthol (See Figure 65).

There are numerous examples in the literature which may achieve this ene cyclisation to generate iso-pulegol from citronellal (62). There are, however, no examples to the best of our knowledge for the transformation of geraniol (61) to iso-pulegol in one synthetic step.

From these observations it is apparent that the aldehyde product, following the isomerisation of geraniol, is being consumed by the catalyst to generate the iso-pulegol stereoisomers via an ene cyclisation. From the enantiomeric excesses estimated for the iso-pulegol stereoisomers by
The formation of (-)-iso-pulegol can be considered to occur via a 6-membered boat transition state from (R)-citronellal (Figure 203).

Another interesting outcome from the reaction was the formation of the hydrocarbon (265), or limonene. Unlike iso-pulegol, limonene can be prepared in one step from geraniol. Reported attempts have used formic acid, charcoal at 200°C, P₂O₅, Et₄NClO₄ and trifluoroacetic anhydride to effect the transformation.

From a mechanistic point of view, the reactions involving formic acid, P₂O₅ and the trifluoroacetic acid are likely to proceed via an intramolecular allylic displacement mechanism, prior to the cyclisation reaction. For example, using acetic acid (Figure 204):
Conversion of geraniol (61) to limonene (265) under the conditions of the reaction may be mediated by the Lewis nature of the cationic rhodium species, via the tertiary alcohol, linalool (267) (Figure 205).

\[
\begin{align*}
\text{Conversion of geraniol (61) to linalool (267) as been achieved successfully with numerous Lewis acid catalysts, such as glacial acetic acid and HBr,}^\text{284} (\text{TMSO})_2\text{ and VO(acac)}_2,^\text{285} \text{ Zr(SO}_4)_2\text{ and Fe(SO}_4)_2.^\text{286} \text{ Studies using the (TMSO)}_2\text{ and VO(acac)}_2\text{ catalyst system found that the migration of the hydroxyl proceeded suprafacially, implying that a “free” allylic cation (i.e. dissociated from the vanadium catalyst) does not from. The implication is that the hydroxyl group is ligated to the metal. Formation of the analogous (\pi-allyl)Rh(OH) complex is therefore possible. Alper and Hachem found that the addition of NaOH to [Rh(COD)Cl]_2 in the presence of BnMe_2NCl generated an active catalyst which could isomerise allylic alcohols to the carbonyl, presumably via a similar hydroxyrhodium intermediate.}
\end{align*}
\]

Conversion of geraniol (61) to linalool (267) as been achieved successfully with numerous Lewis acid catalysts, such as glacial acetic acid and HBr,\textsuperscript{284} (TMSO)_2 and VO(acac)_2,\textsuperscript{285} Zr(SO_4)_2 and Fe(SO_4)_2.\textsuperscript{286} Studies using the (TMSO)_2 and VO(acac)_2 catalyst system found that the migration of the hydroxyl proceeded suprafacially, implying that a “free” allylic cation (i.e. dissociated from the vanadium catalyst) does not from. The implication is that the hydroxyl group is ligated to the metal. Formation of the analogous (\pi-allyl)Rh(OH) complex is therefore possible. Alper and Hachem found that the addition of NaOH to [Rh(COD)Cl]_2 in the presence of BnMe_2NCl generated an active catalyst which could isomerise allylic alcohols to the carbonyl, presumably via a similar hydroxyrhodium intermediate.

It is of interest to examine the direction of this allylic isomerisation.\textsuperscript{287} Allylic primary acetates are produced by treating its tertiary esters (or alcohols) with acetic anhydride,\textsuperscript{288} or alternatively with Pd(II) complexes.\textsuperscript{289,290} Rearrangements from primary to tertiary alcohols are encountered in solvolysis reactions, which are made more complicated by accompanying elimination, cyclisation and skeletal rearrangement reactions, which is presumable why only trace amounts the tertiary alcohol (267) was observed. Dehydrocyclisation of linalool (267) to limonene (265) has also been achieved using Lewis acid catalysts, such as formic acid,\textsuperscript{291} Al_2O_3\textsuperscript{292} and tf_2O.\textsuperscript{293} It is likely that the rhodium species may catalyse this transformation via a similar pathway (See Figure 204).

Although the outcome of the isomerisations of geraniol did not afford the aldehyde, nevertheless, the formation of the chiral iso-pulegol compounds, albeit in low yield, certainly broadens the potential scope of this isomerisation reaction. These products are likely to be formed via an isomerisation, followed by an ene cyclisation reaction. The Tagasako process involves a similar overall transformation sequence, but requires three synthetic steps; viz isomerisation, hydrolysis then cyclisation (See Figure 65).
The isomerisation of the alkoxide of geraniol in the presence of the [Rh(COD)(S)-BINAP]ClO₄ complex offered little or no enolate product, as evidenced by an absence of citronellal following work-up with saturated NH₄Cl solution (Entry 1, Figure 201). In spite of this inactivity, it was noted that the addition of excess n-BuLi to geraniol (61) (i.e. 1.07 equivalents instead of only 1 equivalent) had a dramatic effect on the isomerisation reaction.

Upon addition of the alkoxide and n-BuLi solution to a solution of the [Rh(COD)(S)-BINAP]ClO₄ catalyst, an immediate darkening of the catalyst solution was observed. In all other previous reactions, the orange colour of the catalyst solution remained largely unchanged following the addition of the alkoxide solution. However, in this instance, the catalysts solution turned to a deep purple colour containing a very fine white suspension. It was apparent that the additional n-BuLi in the alkoxide solution had reacted with the rhodium. It is likely that a hydridorhodium(I) species had been generated, in the same way a hydride nickel is generated following the addition of n-BuLi to the NiCl₂(C₃P)₂ complex.

A variety of hydridorhodium(I) species have been shown to isomerise allylic alcohols, for example (Ph₃P)₄RhH was able to catalyse the isomerisation of 1-hexen-3-ol to 3-hexanone in 32% yield. Lower yields were obtained, however, on increasing substitution about the allylic centre.⁷⁶

The isomerisation reaction was conducted at room temperature and allowed to run for 20 hours. Following quench of the isomerised products with acetic anhydride, the corresponding enol acetates were isolated in 69% yield and with an (E) : (Z) ratio of 4.3 : 1 (Figure 206).

![Figure 206](image)

This was the first time that a rhodium based catalyst system had successfully isomerised the alkoxide of geraniol cleanly and in high yield.¹³³,¹³⁴ This reaction was also of great interest as the isomerisation of the allylic amine and the alcohol had proceeded enantioselectively using the same catalyst system. The enol acetate mixture was therefore analysed by chiral ¹H-NMR to determine the optical yield.

It was somewhat disappointing to find that no asymmetric induction had been achieved, as ¹H-NMR indicated only racemic material. It is possible that the addition of n-BuLi to the
[\text{Rh(COD)}(S)-\text{BINAP}]^+\text{ClO}_4^- \text{ complex has generated a new active rhodium hydride species. On the other hand, the addition of } n-\text{BuLi to the rhodium may have generated the same rhodium hydride species that is formed during the isomerisation, but in greater concentration.}

It should be noted that in the isomerisation reaction of allylic amine, the enantioselective step is the formation of the rhodium hydride intermediate. The hydride is then delivered \textit{suprafacially} to produce the chiral enamine product. This enantioselective step cannot occur if the rhodium hydride intermediate is generated by the addition of \textit{n-}BuLi, neither can the suprafacial hydride delivery, as the substrate and the rhodium are not intimate upon formation of the rhodium hydride.

It is likely therefore that the active [\text{Rh(COD)}(S)-\text{BINAP}]^+\text{ClO}_4^-/n-\text{BuLi catalyst operates via a different mechanism to the original [\text{Rh(S)-BINAP}]^+ catalyst used by Noyori. The formation of a rhodium hydride suggests a metal-hydride addition and elimination mechanistic pathway, in which case the reversibility of this process will not lead to significant levels of asymmetric induction. Alternatively, the mechanism may operate via a } \pi\text{-allyl or an enone intermediate, in which case enantiocntrolled enolate formation is still viable. Isotope labelling studies will need to be conducted in order to resolve this mechanistic issue.}

Another consideration is the presence of the COD, as pre-hydrogenation to remove this ligand was not attempted. \textit{n-}BuLi is a strong enough base to deprotonate the COD ligand at the allylic position to form a } \pi\text{-allyl anion, which may then coordinate to the rhodium, with } \eta^3\text{-coordination (Figure 207).}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure207.png}
\caption{Formation of such a complex is certainly intriguing, and further studies would need to be conducted in order to confirm the presence of the chelating } \pi\text{-allyl ligand, either by analysis of the active species by } ^1\text{H-NMR, or by adding the } n-\text{BuLi to a solution of rhodium catalyst, in which the COD ligand has been removed by treatment with hydrogen, to see if the same catalyst, in colour and activity of isomerisation, is generated. If a } \pi\text{-allyl complex is formed, then a similar complex may form by the addition } n-\text{BuLi to the Ni(COD)}_2/Ligand catalyst system. A slight excess of } n-\text{BuLi is added each time to the allylic alcohol to ensure complete deprotonation, therefore...}
"adventitious" traces of base may still be present in solution to generate the π-allyl nickel complex.

The persistence of the COD ligand in reaction medium throughout the isomerisation period, means that re-complexation by the COD with the nickel catalyst is likely during. Under the conditions of the reaction oxidative addition may then follow, by the nickel with the C-H bond situated at the allylic position on the COD ligand, to generate the π-allyl hydrido nickel complex A, or complex D from C (Figure 208).

Complexes A, B, C and D may all function as active isomerisation catalysts. Complexes A and B would be expected to offer asymmetric induction due to chelation with a chiral ligand (L-L), whereas C and D would not due to its absence. Isotope labelling studies had shown that the nickel catalyst does not operate via a metal-hydride addition and elimination mechanism, and since complex A, a metal hydride, may only operate via this mechanism, then this complex is unlikely to predominate in the reaction medium.

Strongly chelating ligands, such the bidentate phosphine ligands, DIPHOS and BINAP, will not be readily displaced by the weaker binding allylic alkoxide or COD ligands. Therefore complexes A and B are more likely to predominate in the reaction medium than complexes C and D. Further, the steric influence imposed by the bulky chiral ligand (L-L) may reduce the catalytic activity of complexes A and B, thus affording little or no isomerised product. This was observed for most of the bidentate phosphines used as ligands, and to an extent, the mixed N,P ligand. Lesser coordinating ligands, such as bis(oxazoline), would mean that ligand displacement is more likely, leading to greater quantities of C and D in solution. Consequently, the chiral (A, B) and the
achiral complexes (C, D) are all competing to isomerise the same allylic alkoxide substrate. The level of chiral product that is generated by the chiral complexes A and B catalysing the isomerisation would therefore be low. In addition, the reversibility of the isomerisation reaction, together with the possibility of complexes C and D catalysing the isomerisation faster than A or B, due to the absence of the bulky chiral ligands, then the level of asymmetric induction would be even lower. This may account for the absence of any enantiomeric excess in the isomerised product, and the observed racemisation of authentic chiral enolate.

Although the involvement of the COD is entirely speculative, its persistence in the reaction medium suggests that intermediates such as A, C and D can nevertheless be formed. A lack of time has prevented a detailed study into the effect of using ligands other than COD (for example NBD), however the result of these investigations would surely provide an intriguing insight into the nature of the active species formed during the Ni(COD)\_2/Ligand catalyst system.

Returning to chiral rhodium catalysis, the question which now remains is how can the a chiral rhodium catalyst isomerise an allylic alcohol or amine enantioselectively, but not an allylic alkoxide?

It is likely that the chiral enol product that is formed following an asymmetric isomerisation of a prochiral allylic alcohol can tautomerise to generate the chiral carbonyl compound. This has the effect of preserving the chirality at the $\beta$-position in the carbonyl product. Studies by Bergens and Bosnich indicated that the ketonisation step was irreversible and catalysed by the metal catalyst. This is clearly demonstrated by conversion of achiral enol to the ketone in 18% ee, involving in this case an intimate association of the enol with the chiral catalyst (Figure 209).

\[
\begin{align*}
\text{Ph} & \text{Ph} & \text{Ph} & \text{OH} & \xrightarrow{\text{[Rh(S)-BINAP]}^+} & \text{Ph} & \text{Ph} & \text{OH} & \xrightarrow{\text{[Rh(S)-BINAP]}^+} & \text{Ph} & \text{Ph} & \text{O}
\end{align*}
\]

**Figure 209**

The isomerisation of an allylic alkoxide forms an enolate, which cannot be converted to the carbonyl under the conditions of the reaction due to the absence of available protons. The enolate will therefore persist in solution until the end of the reaction time. As has been shown with the Ni(COD)\_2/Ligand catalyst system (See Figure 140), authentic chiral enolate was found to racemise under the conditions of the reaction. It is likely that the same result would occur using the [Rh(COD)(S)-BINAP]\(^{+}\)ClO\(_4\)\(^{-}\) catalyst, modified with $n$-BuLi (referred to as [Rh(COD)(S)-BINAP]\(^{+}\)ClO\(_4\)\(^{-}\)/$n$-BuLi).

Such a racemisation process is not evident for the isomerisation of allylic amines, as the enamine product has been obtained in very high enantiomeric excess. The enantioselective step
is the hydride abstraction step, in that the chiral rhodium catalyst can differentiate between the two enantiotopic hydrogens on the substrate (See Figure 77). The step involves suprafacial 1,3-hydride transfer. This step must proceed before ‘π-σ-π’ fluxionality can occur on the π-allyl intermediate, a process which has been suggested as a reason for the loss in enantioselectivity in π-allyl based mechanisms (See Figure 143). If ‘π-σ-π’ fluxionality does not occur, then even if the enamine can revert back to the π-allyl intermediate, the abstracted hydride will be returned in a suprafacial manner, thus preserving the chiral integrity of the enamine product (Figure 210).

For allylic alkoxides, this is not the case as racemic product is generated using the [Rh(COD)(S)-BINAP][ClO₄]⁻/n-BuLi or chiral Ni(COD)₂/Ligand catalyst systems. If a π-allyl mechanism is in operation, then ‘π-σ-π’ fluxionality is likely to occur to generate racemic enolate product. If an enone mechanism was in operation, then dissociation and re-complexation of the enone with the metal catalyst will also result in racemic product.

An additional consideration to note is that coordination between the rhodium and the oxygen on the allylic alkoxide will be affected by the large O-Li aggregates that form in solution, thereby decreasing the availability of the oxygen lone pairs for donation to the metal catalyst. Access of the catalyst to the allylic moiety is also restricted by the bulk of the aggregation. The overall result is presumably a weaker complexation between the substrate and the catalyst, compared with that achieved using an allylic alcohol or allylic amines as the substrate. Dissociation of the intermediates during the isomerisation of allylic alkoxides is therefore more likely, resulting in a decrease in the enatioselective capability of the chiral catalyst.

In support of this argument, then breaking up the O-Li aggregation would therefore be expected to increase the rate of reaction. Indeed this was observed following the addition of reagents such as TDA-1, TMEDA, HMPA, DMPU and 18-crown-6 to the isomerisation reaction. Further investigations into this field using chiral chelating agents, such as the poly-alkylated sugars (See Modifications of The Isomerisation Reaction), would certainly prove to be an interesting method in the preparation of chiral lithium enolates.
Isomerisation with bis(oxazoline) as ligand

Rhodium catalysts containing bidentate phosphine ligands, such as [Rh(DIPHOS)]⁺, may be prepared by the addition of the phosphine ligand to a solution of the Rh(I) cation in acetone. Attempts, however, to prepare similar complexes using a bis(oxazoline) as the ligand were not successful as oily residues were obtained, which failed to crystallise. It was therefore decided to modify the synthetic procedure so that the Rh(I)(ligand) catalysts could be prepared in situ, in the same way as for the Ni(COD)₂/Ligand catalysts system. It was envisaged that an active catalyst system could be prepared by the addition of chiral bis(oxazoline) ligands to the [Rh(COD)Cl₂] complex, such that the isomerisation of allylic alcohols (and alcohols) can proceed with the same degree of enantioselectivity as the BINAP ligand for the asymmetric isomerisation of allylic alcohols.

Consequently, a solution of [Rh(COD)Cl₂] in degassed THF was treated with anhydrous silver(I) perchlorate, followed by the ligand 15 minutes later. After a further 15 minutes, the mixture was purged with dry hydrogen for 5 minutes, then dry nitrogen for 10 minutes. The supernatant solution was then transferred to the alkoxide solution via filter tipped cannulae. Two isomerisation were conducted with the alkoxide of (88) using pre-prepared, [Rh(DIPHOS)]⁺, and material prepared in situ from [Rh(COD)Cl₂] (Figure 211).

\[
\begin{align*}
\text{OH} & \quad \text{(88)} \\
\text{OH} & \quad \text{(91)} \\
\text{OH} & \quad \text{(88)} \\
\text{OH} & \quad \text{(91)} \\
\end{align*}
\]

Figure 211

The isomerised product (91) was formed quantitatively from the alkoxide of (88) using either catalyst system. It was therefore decided to pursue the method for the preparation of [Rh(ligand)]⁺ complexes in situ, as any ligand could be employed without the necessity, or expense, of catalysts pre-preparation.

A variety of ligand were attempted with the [Rh(COD)Cl₂] based catalyst system, all of which were found to smoothly isomerise the alkoxide of (88) to the corresponding ketone (91) in high yield (Figure 212).

\[
\begin{align*}
\text{OH} & \quad \text{(88)} \\
\text{OH} & \quad \text{(91)} \\
\text{OH} & \quad \text{(88)} \\
\text{OH} & \quad \text{(91)} \\
\end{align*}
\]
Using the modified pyridine ligand, DMAP, a higher rate of conversion to the ketone (91) was noted compared with the other ligands. It is likely that electron donation into the aromatic ring by the dimethylamino group is responsible for this rate enhancement, however the influence of the dimethylamino group on the lithium alkoxide, possibly by drawing the substrate closer to the rhodium via chelation, cannot be ruled out. Nevertheless, this ligand, in addition to the bis(oxazoline) ligand (128) was attempted on a more demanding substrate, in this case geraniol (61), either on the alkoxide, or on the alcohol itself (Figure 213).

It was clear from these results that the rhodium catalyst was having difficulty isomerising the hindered, tri-substituted substrate. GC analysis of the isomerisation mixture using the
bis(oxazoline) ligand (128) revealed that the ligand had remained intact during the course of the reaction and had not decomposed as was initially considered to account for the poor transformation. The absence of any reaction using geraniol (61) was unexpected considering the chiral [Rh(BINAP)]⁺ catalysts was able to isomerise the same alcohol in 70% yield under the same reaction conditions.¹²⁰

It was hoped that replacement of the THF with a higher boiling solvent, such as benzene or toluene, would induce some reaction with the alcohol (61). The isomerisations were therefore repeated with the [Rh(DIPHOS)]⁺ catalyst, using these solvents as the reaction medium (Figure 214).

![Diagram showing the reaction of geraniol (61) with [Rh(COD)BINAP]+ in THF, reflux, 21 hours, followed by treatment with NH₄Cl to give a mixture of diastereoisomers (61) and (266).]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Yield (112)</th>
<th>Yield (266)</th>
<th>Yield (265)</th>
<th>Recovered (61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>n-BuLi</td>
<td>19 %</td>
<td>-</td>
<td>-</td>
<td>16 %</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>-</td>
<td>8 %</td>
<td>16 %</td>
<td>70 %</td>
</tr>
<tr>
<td>Toluene</td>
<td>n-BuLi</td>
<td>16 %</td>
<td>-</td>
<td>32 %</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>-</td>
<td>20 %</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 214

Compounds (266) and (265) were identified by GCMS by mass fragmentation correlation. It was unfortunate that the formation of compounds (266) and (265) were accompanied by several other unidentifiable compounds.

As a final consideration in this methodology, attempts were made to modify the reaction by substitution of the lithium cation with a silyl group. The TBDMS group was selected as the silyl enol ether product following an isomerisation would be less hydrolytically labile then the TMS group. Thus, TBDMS protected geraniol was prepared by the addition of i-butyldimethylsilyl chloride to geraniol (61) in the presence of imidazole and catalytic amounts of DMAP. Isomerisation of this substrate by the [Rh(DIPHOS)]⁺ catalyst afforded little or no isomerised product, the silyl enol ether (Figure 215).
It was noted that significant decomposition of the starting material had occurred, to afford a variety of products, most of which were identified by GCMS by mass fragmentation correlation. Compound (270), carene, is likely to have been formed via a rhodium carbenoid intermediate, as the involvement of rhodium in carbenoid chemistry is quite extensive.\textsuperscript{294} Thus, rendering substrates such as (187) unsuitable in this type of transition metal chemistry.

In summary, although the $\text{[Rh(COD)Cl]}_2/bis(\text{oxazoline})$ and $\text{[Rh(COD)\text{(S)-BINAP}]ClO}_4/n$-$\text{BuLi}$ catalyst systems did not achieve any asymmetric induction using the alkoxide of geraniol as substrate, it is possible that enantioselectivity may be achieved by modifications of the reaction conditions. Further investigation in this area is necessary in order that the issue of enantiocontrolled enolate formation may be resolved.
Conclusions and Perspectives
Conclusions and Perspectives

This work has demonstrated the applicability of nickel based catalyst systems in the generation of metal enolates from allylic alkoxides.

Much of the work has used the Ni(COD)$_2$ complex in combination with a ligand. Although good levels of stereocontrol were achieved using trialkyl- or triaryl-phosphine ligands, the use of pyridine as ligand offered the highest stereoselectivity, particularly for primary allylic alkoxides in which (E) : (Z) enolate ratios greater than 15 : 1 were observed.

Mixing, or equilibration, of the enolate regioisomers was observed for both the Ni(COD)$_2$/Ligand and NiCl$_2$(DIPPHOS)/LiBEt$_3$H catalyst systems. Similar observations were noted with the previous rhodium catalysts but not, surprisingly, with the (Cy$_3$P)NiCl$_2$/n-BuLi catalyst system. The equilibration process is likely to operate via a transition metal mediated process, however the reason for the high regioselectivity exclusively with the (Cy$_3$P)NiCl$_2$/n-BuLi nickel catalyst is not clear.

The formation of tetrasubstituted enolates using this methodology was moderately successful with the best (E) : (Z) enolate ratio obtained approximately 5 : 1. This compares well against the highest (E) : (Z) ratios obtained with the other catalyst systems used within the group.

Chiral bidentate phosphine ligands were previously shown to be ineffective as ligands in the Ni(COD)$_2$ catalyst system, in that the alkoxide of the prochiral allylic alcohol, geraniol, failed to isomerise. Nitrogen based ligands were therefore employed, such as the chiral bis(oxazoline) or chiral bipyridyl ligands. Although these ligands have been used to great effect in several other asymmetric catalytic systems, no enantiomeric excesses were detected in the isomerised products either by chiral shift $^1$H-NMR, or by chiral GC.

The influence of the ligand on the outcome of the isomerisation reaction was noted in two ways. First, the use of excess ligand led to a reduction in the rate of the reaction. Second, the varying yields of isomerised product, from 0% to 83%, indicated a significant influence by the ligand on the outcome of the isomerisation reaction. Colloidal nickel, which is an aggregate of Ni(0), was shown not to play a significant part in the isomerisation process, thereby confirming that the active species is homogeneous, possibly Ni(0)(Ligand).

Although modification to the reaction mixture, such as using benzene instead of THF as solvent, led to a dramatic increase in the stereoselectivity of the reaction, even at room temperature, no asymmetric induction was achieved. The use of polyalkylated sugars, however, to provide an asymmetric environment about the O-Li aggregate was an intriguing method in which to achieve enantioselectivity, although initial experiments offered no asymmetric induction. Nevertheless,
sugars are commonly used as chiral templates in a range of asymmetric and catalytic reactions, and therefore further attempts to incorporate this chemistry into our methodology could lead to some encouraging results.

Isotope labelling studies demonstrated that the isomerisation reaction operates via a 1,3-hydride shift, and not via a metal-hydride addition and elimination mechanism, which was originally considered to account for the absence in enantioselectivity. Further studies will attempt to confirm that the 1,3-hydride shift mechanism operates via an intramolecular process. If this is not the case, then dissociation of the intermediates during the isomerisation process is likely, which would lead to a decrease in the enantioselective capability of the catalyst system.

Authentic chiral enolate, under the standard conditions of the isomerisation reaction, was found to racemise, affording racemic enol acetate following reaction of the enolate with acetic anhydride. Several suggestions have been made which may account for the racemisation of the chiral enolate product, depending on whether a \( \pi \)-allyl or enone mechanism was in operation. The possible involvement of the COD ligand itself in the isomerisation process would also need to be investigated, as the formation of achiral complexes is possible, which may function as better catalysts than the chiral complexes, thus reducing the level of asymmetric induction. Alternative ligands, such as NBD, may therefore provide a fascinating insight into this nature of the active catalytic species.

Noyori and co-workers have reported the asymmetric isomerisation of geraniol, in the presence of the chiral \([\text{Rh(BINAP)}]^+\) catalyst, to the aldehyde, citronellal, in 70% yield and 37% ee. No other products were reported. When we repeated the same reaction, however we detected only trace amounts of the aldehyde amongst the plethora of products that were also produced. Analysis of the reaction mixture by chiral GC detected iso-pulegol with an optical yield of nearly 50%, and iso-iso-pulegol, detected in 48% ee. Iso-pulegol may be synthesised from citronellal by a Lewis acid catalysed ene cyclisation reaction, and it was apparent that some of the isomerised product, citronellal, had cyclised to iso-pulegol. The same catalyst was able to isomerise \( \text{N,N-diethylgeranylamine} \) in good yield, thereby confirming the activity of our prepared rhodium catalyst. It is uncertain why the aldehyde was not isolated in the same proportion as that reported by Noyori and co-workers, but nevertheless, the formation of iso- and iso-iso-pulegol, albeit in low yield (ca. 13%), was of great interest as its preparation forms one of the key steps in the Tagasako process for the industrial synthesis of menthol. Further investigations will be conducted in this area in order to increase the chemical and optical yields of these compounds. The addition of catalytic quantities of base is commonly employed in order to increase the rate of transfer hydrogenation reactions, therefore, it will be interesting to see what effect the addition of base, for example potassium tert-butoxide, will have on the outcome of the isomerisation reaction of geraniol.
It was also unexpected that the same rhodium catalyst was able to isomerise the alkoxide of geraniol, as all previous attempts to isomerise this substrate using other rhodium catalysts had failed. It was realised that the addition of a slight excess of n-BuLi had contributed to this activity, with the possible formation of a hydridorhodium species. Although hydridorhodium species such as (Ph₃P)₄RhH have been shown to isomerise allylic alcohols, yields are generally low for substituted substrates, and it should be noted that the alkoxide of geraniol, a hindered and tri-substituted allylic alcohol, was isomerised in 69% yield. It is not clear whether a new catalytic species has been generated, or if it is the same intermediary species that is formed following hydride abstraction from the alkoxide, but in greater concentration.

Ligand architecture certainly has an influence on the outcome of the reaction, and it is likely that ligands specifically tailored to meet the needs of the isomerisation will be required in order to enforce a rigid and an extensive chiral environment about the transition metal centre for an enantioselective isomerisation to occur. Ligands such as (271) combine the use of steric bulk to create such an environment, in addition to coordination sites for the alkoxide counter cation to chelate, thus drawing the substrate into closer proximity to the catalytic centre, and increasing the prospect for enantioselectivity.

\[
\text{(271)}
\]

In summary, this work demonstrates the applicability of using transition metals to mediate the isomerisation of allylic alkoxides to prepare enolates in a regio- and stereoselective manner. The reasons for the lack of enantioselectivity exhibited by both the nickel and rhodium catalyst systems using an allylic alkoxide as substrate remains unclear, nevertheless, such a transformation, albeit ambitious, is not impossible and it is likely that in time such a goal can be achieved.
Chapter 3

Experimental Section
1H NMR spectra were recorded at 400 MHz on a Varian VXR-400 instrument or, unless stated, at 200 MHz on a Varian XL-200 instrument. 13C NMR spectra were recorded at 100.6 MHz on a Varian VXR-400 instrument. Residual protic solvent was taken as internal standard, with CDCl3 as solvent unless otherwise stated, stored over 4Å molecular sieves and filtered through a pad of basic alumina prior to use. Infrared were recorded as thin films on sodium chloride plates or as potassium chloride disks on a Perkin-Elmer FT-IR 1605 instrument. All peaks quoted are medium, unless otherwise stated. Mass spectra measurements were recorded by electron impact (EI) studies with an Autospec Q, VG 7070 or VG 7070B instrument, unless fast atom bombardment (FAB) is stated, in which case a ZAB-SE instrument was used. Analytical gas chromatography was performed on a Hewlett Packard HP5890 machine fitted with a SGE BPX5 capillary (50m x 0.32mm i.d., polyimide coated fused silica column) and flame ionisation detector. Split injection was used with hydrogen as the carrier gas. Melting points were taken on a Reichert hot stage and are uncorrected. Optical rotations were taken with a 'POLAAR 2000' instrument by Optical Activity Ltd. and are given in the units 10^1 deg.cm^2.g^-1.

Petrol refers to light petroleum boiling in the range 40-60°C which was distilled prior to use as a chromatography eluent. Ether refers to diethyl ether, used as received for this purpose, as were ethyl acetate, methanol and DCM. For use as reaction solvents ether, tetrahydrofuran and benzene were freshly re-distilled under dry nitrogen from sodium benzophenone-ketyl and toluene from molten sodium. Dichloromethane was freshly re-distilled from phosphorous (V) oxide. Chlorobenzene and 1,2-dichloroethane were re-distilled from phosphorous (V) oxide and stored over 4Å molecular sieves. Methanol was distilled from magnesium turnings and stored over 4Å molecular sieves. Unless otherwise stated ‘ethanol’ refers to absolute ethanol (>99.7%) and was used as received. Dimethyl sulfoxide and (E)-N,N-diethylgeranylamine were distilled under reduced pressure and stored over 4Å molecular sieves. Trimethylsilyl chloride was freshly re-distilled from calcium hydride. Triethylamine, diisopropylamine and pyridine were distilled from and stored over potassium hydroxide. Acetic anhydride was distilled under reduced pressure from magnesium powder and flushed through phosphorous (V) oxide prior to use. Commercially available allylic alcohols were treated with potassium carbonate and distilled onto 4Å molecular sieves before use as substrates. Benzaldehyde and methyl iodide were purified by accepted procedures prior to distillation.

Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F25,) and visualised with ultraviolet light (254nm), iodine, potassium permanganate [add 62.5g Na2CO3 in water (1.25 litre) to 12.5g KMnO4 in water (1.25 litre)], acidic ammonium molybdate (IV) [conc. H2SO4 (250ml), ammonium molybdate tetrahydrate, water (250ml)], or vanillin [vanillin (2.4g), conc. H2SO4 (2.5ml), ethanol (100ml), stored in the dark] as appropriate. Preparative column chromatography was performed at low positive pressure on Merck Kieselgel...
HPLC was carried out on a Gilson M303 instrument with a 25cm x 5mm normal phase Lichrosorb silica gel column, using a Bischoff RI 8110 refractive detector. Solvents used were HPLC grade and were degassed prior to use.

All isomerisations reactions were performed using Schlenk-line techniques and glassware (oven or flame dried).\textsuperscript{206,207} Solutions were prepared using standard air-sensitive handling procedures and twice degassed prior to mixing. 'Degassed' refers to one freeze-thaw cycle as described below. The Schlenk-line was served by a two stage rotary oil pump and an on-line vacuum maintained at between 0.01 and 0.05 mbar. Argon was dried and deoxygenated by passage through a column of chromium (II) on activated silica:

To a mechanically stirred solution of chromium (VI) oxide (60g) in distilled water (2 l) was slowly added silica gel (1.5kg, ca. 100 mesh). The resulting bright orange slurry was recovered by Büchner filtration and dried first at the pump (12 hours) and then on several large crystallisation dishes in an oven at 100°C (48 hours). The orange powder was placed in a large sintered glass chromatography column, in a cylindrical furnace, and dehydrated in a stream of oxygen at 250°C (3-4 hours). After heating at 500°C (1 hour), and in a stream of dry nitrogen (30 minutes), a supply of carbon monoxide was attached and slow passage of the gas continued at >400°C until the transition through green to blue had run the length of the column (1-2 hours). A flow of nitrogen was then maintained for several hours until the column had cooled to room temperature.

Absorption of oxygen was characterised by a gradual change in colour to orange-brown moving in a distinct front in the direction of argon flow. The column was sufficient for several cylinders of gas and may be regenerated by the above procedure.

'Commercially obtained solutions of n-BuLi were regularly quantified by the 'double-quench and titration' procedure - subtraction of background base (hydroxide by reaction with 1,2-dichloroethane and then water) from total base (n-BuLi and hydroxide by reaction with water); or by direct titration with N-pivaloyl-O-toluidene - the end point being reached when the colourless solution turns yellow.\textsuperscript{208}

The catalysts NiCl\textsubscript{2}(DIPHOS),\textsuperscript{299} NiCl\textsubscript{2}(Cy\textsubscript{3}P)\textsubscript{2},\textsuperscript{135} NiCl\textsubscript{2}(Ph\textsubscript{3}P)\textsubscript{2},\textsuperscript{300} NiCl\textsubscript{2}Py\textsubscript{2},\textsuperscript{301} [Rh(COD)DIPHOS]Cl\textsubscript{4},\textsuperscript{120} [Rh(COD)/(S)-(S)-BINAP]Cl\textsubscript{4} and Ph\textsubscript{3}PCuCl\textsuperscript{253} were prepared by published procedures and stored under argon in air-tight bottles. Ni(COD)\textsubscript{2}\textsuperscript{162} was also prepared by published procedure and was stored at -40°C under argon in a fully equipped glove box. [Rh(COD)/(R)-(R)-BINAP]Cl\textsubscript{4} and [Rh(COD)Cl]\textsubscript{2} were purchased from Aldrich and were stored under argon in air-tight bottles. Note that [Rh(COD)Cl]\textsubscript{2} was used to prepare [Rh(COD)/(S)-(S)-BINAP]Cl\textsubscript{4}.
**Standard Procedure For Degassing**

Solutions of catalyst or alkoxide in THF were degassed via the Freeze-Thaw technique: The Schlenk flask is sealed and the solution frozen in a bath of liquid nitrogen. The vessel is evacuated by opening to high vacuum for a few minutes. The flask is then sealed and the solid allowed to thaw. The flask is then purged with argon. The cycle is then repeated. Freezing of solutions is begun from the bottom and melting from the top. The Freeze-Thaw techniques could not be applied when using either benzene or toluene as solvent. These solvents were degassed by purging with argon for several minutes prior to addition to the alcohol or catalyst.

**Standard Procedures For Quench And Work-Up**

**Aldol reaction**

The reaction was cooled to -78°C and 1.1 equivalents of benzaldehyde added in one portion, via syringe and as quickly as possible. The mixture was stirred for exactly 5 seconds before excess saturated NH₄Cl solution was added in a similar manner. After allowing to warm to room temperature, water was added to dissolve any precipitated NH₄Cl. The phases were separated and the aqueous phase extracted with ether (ca. 3 x 20 ml). The combined organic phases were washed with brine, dried (MgSO₄) and the solvent removed under reduced pressure. The residue was then chromatographed to afford the aldol products.

**Acetylation**

The reaction was cooled to -78°C and 10 equivalents of acetic anhydride was added in one portion, via syringe and as quickly as possible. The mixture was stirred for 30-45 minutes at -78°C before excess saturated NaHCO₃ solution was added. After allowing to warm to room temperature, the mixture was stirred for a further 30 minutes before separating the phases. The aqueous phase was extracted with ether and then the combined organic phases washed with brine, dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed to afford the enol acetate product.

**Protic Quench**

The reaction was cooled to room temperature before excess saturated NH₄Cl solution was added. The mixture was stirred for 30 minutes before separating the phases. The aqueous phase was extracted with ether and the combined organic phases, washed with brine, dried (MgSO₄) and the solvent removed under reduced pressure. The residue was then chromatographed to afford the aldehyde or ketone products.
Preparation of the Catalyst Solutions

**NiCl$_2$(Ligand)$_2$ / n$^\gamma$BuLi, using Cy$_3$P, Ph$_3$P or pyridine as ligands**

A solution of n$^\gamma$BuLi was added dropwise to a doubly degassed stirred suspension of the NiCl$_2$(Ligand)$_2$ catalyst in THF at room temperature. The mixture was allowed to stir for approximately 15 minutes at room temperature.

**NiCl$_2$(Ligand)$_{1.2}$ / MBEt$_3$H, using DIPHOS and pyridine as ligands, and Li or K as M**

A solution of lithium or potassium triethylborohydride was added dropwise to a doubly degassed stirred suspension of the NiCl$_2$(Ligand)$_{1.2}$ catalyst in THF at -78°C. The mixture was allowed to warm to room temperature.

**Ni(COD)$_2$ / Ligand**

In a fully equipped glove box Ni(COD)$_2$ was weighed into a Schlenk flask. A small amount of extra Ni(COD)$_2$ (ca. 5mg) was added to the flask to compensate for loss of material during manipulation. The flask was then sealed under a slight positive pressure of argon and immediately cooled to -78°C. In a second Schlenk flask was weighed the required quantity of ligand. The flask was then flushed with argon and THF added. The ligand solution was degassed twice and then transferred, via teflon cannulae to the solid Ni(COD)$_2$ at -78°C. When using pyridine as ligand, doubly degassed THF was added to the solid Ni(COD)$_2$ followed by the pyridine. The Ni(COD)$_2$ / Ligand mixture was then allowed to warm slowly to room temperature.

**[Rh(COD)Ligand]$^+$ClO$_4^{-}$**

If pre-hydrogenation is required then dry hydrogen gas is bubbled through the stirred catalyst solution for 5 minutes, followed by dry argon gas for 10 minutes. The catalyst solution is then transferred via cannulae to the alcohol or alkoxide solution. Pre-hydrogenation was not used unless otherwise stated.

**Standard procedure for the Isomerisation reaction**

The required quantity of allylic alcohol substrate was weighed into a Schlenk flask. The flask was then flushed with argon and THF added. If a solution of the alkoxide was required, then the solution was cooled to 0°C and 1.00-1.05 equivalents of n$^\gamma$BuLi was added dropwise. The mixture was then stirred at room temperature for 15 minutes. The alkoxide, or alcohol, solution was then degassed twice before receiving the catalyst solution via teflon cannulae. The flask is then fitted with a condenser and the mixture heated to reflux for a number of hours before quenching with benzaldehyde, acetic anhydride or saturated NH$_4$Cl solution.
Substrate Preparation

1,4-Dimethoxybut-2-ene

\[
\text{MeO} - \text{C=C} - \text{CH}_2 - \text{CH}_3 \quad (89)
\]

A solution of 1,4-but-2-ene diol (1.00 ml, 1.07 g, 12.1 mmol) in THF (20 ml) was added dropwise to a stirred suspension of sodium hydride (1.06 g, 60% wt disp. in oil, 25.5 mmol) in THF (20 ml) at 0°C. After 20 min methyl iodide (1.9 ml, 4.33 g, 30.5 mmol) was added followed by potassium iodide (20 mg) and the mixture stirred at ambient temperatures for 16 hours, poured into saturated NH₄Cl solution (30 ml) and extracted with ether (3 × 30 ml). The extract was washed with water (20 ml) and with brine (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 50% ether in petrol) to afford the title compound (89) (842 mg, 7.39 mmol, 61%) as a clear colourless oil; \( R_f \) (50% ether in petrol) 0.41

\[ ^1\text{H-NMR} \delta_h: 5.70 (2H, t, J=4.3, 2 \times \text{C=CHCH}_2), 3.99 (4H, d, J=4.3, 2 \times \text{C=CHCH}_2), 3.32 (6H, s, 2 \times \text{CH}_3) \]

\[ ^13\text{C-NMR} \delta_C: 129.4 (2 \times \text{C=C}), 68.1 (2 \times \text{CH}_2), 58.0 (\text{OCH}_3) \]

\[ \text{IR (film)} \nu_{max}: 2984, 2937, 2892, 2818, 1452, 1195, 1114, 956, 912 \]

\[ \text{LRMS (El)} m/z: 115 \text{ (M}^+\text{+H, 100%)}, 113 \text{ (43)}, 101 \text{ (49)}, 99 \text{ (70)}, 87 \text{ (29)}, 85 \text{ (73)}, 83 \text{ (48)} \]

1,4-Dibenzyloxybut-2-ene

\[
\text{Ph} - \text{O} - \text{C=C} - \text{Ph} \quad (90)
\]

A solution of 1,4-but-2-ene diol (570 µl, 610 mg, 6.92 mmol) in THF (5 ml) was added dropwise to a stirred suspension of sodium hydride (581 mg, 60% wt disp. in oil, 14.5 mmol) in THF (15 ml) at 0°C. After 20 min benzyl bromide (2.05 ml, 2.95 g, 17.2 mmol) was added followed by potassium iodide (10 mg) and the mixture stirred at ambient temperatures for 16 hours, poured into saturated NH₄Cl solution (15 ml) and extracted with ether (3 × 15 ml). The extract was washed with water (20 ml) and with brine (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 50-75% ether in petrol) to afford the title compound (90) (1.32 g, 4.93 mmol, 71%) as a clear colourless oil; \( R_f \) (ether) 0.72


1H-NMR δH: 7.34-7.24 (10H, m, 2 x PhH), 5.79 (2H, m, 2 x C=CHCH₂), 4.48 (4H, s, 2 x C=CHCH₂), 4.05 (4H, m, 2 x CH₂OBn)

13C-NMR δC: 138.1, 128.4, 127.8, 127.6, 129.5, 72.2, 65.7

IR (film) νmax: 3032, 2861, 1455, 1386, 1071, 1025, 979, 607

LRMS (EI) m/z: 269 (M⁺+H, 14%), 107 (35), 92 (26), 91 (100), 69 (35), 52 (20)

1-Phenyl-2-propen-1-ol

A solution of benzaldehyde (4.8 ml, 5.01 g, 47.2 mmol) in THF (20 ml) was added dropwise over 10 min to a solution of vinyl magnesium bromide (40 ml, 40 mmol, 1M in THF) in THF (20 ml) at 0°C. After 2 hours at ambient temperatures, the mixture was poured into saturated NH₄Cl solution (20 ml) and water (40 ml), and extracted with ether (4 x 40 ml). The extract was washed with brine (50 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 25% ether in petrol) to afford the title compound (88) (4.38 g, 32.7 mmol, 82%) as a clear colourless oil. Rf (20% ether in petrol) 0.22

1H-NMR δH: 7.27-7.41 (5H, m, Ph), 6.07 (1H, ddd, J 17.1, 10.4 and 6.3, C=CH₂), 5.37 (1H, d, J 17.1, C=CHHtrans), 5.19-5.24 (2H, m, CHOH and C=CHHcis), 1.92 (1H, d, J 3.8, OH)

13C-NMR δC: 142.6, 140.2, 128.6, 127.8, 126.4, 115.2, 75.4

IR (film) νmax: 3605 (OH), 2981, 1642 (w), 1454, 1112, 1022, 990

LRMS (EI) m/z: 117 (M⁺-OH, 100%), 107(32), 95 (16), 77(23), 69 (32), 44(44)

1-Methoxy-1-phenyl-2-propene

A solution of 1-phenyl-2-propen-1-ol (88) (400 mg, 2.98 mmol) in THF (5 ml) was added dropwise to a stirred suspension of sodium hydride (130 mg, 60% wt disp. in oil, 3.25 mmol) in THF (5 ml) at 0°C. After 20 min methyl iodide (1.9 ml, 4.33 g, 30.5 mmol) was added dropwise and the mixture stirred at ambient temperatures for 2 hours, poured into saturated NH₄Cl solution (10 ml) and extracted with ether (4 x 10 ml). The extract was washed with water (15 ml) and brine (15 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was
chromatographed (SiO₂, 25% ether in petrol) to afford the title compound (97) (400 mg, 2.72 mmol, 91%) as a clear colourless oil; Rf (25% ether in petrol) 0.64

**^1H-NMR** δH: 7.27-7.38 (5H, m, PhH), 5.94 (1H, ddd, J 17.1, 10.3, and 6.8, CH=CH₂), 5.29 (1H, d, J 17.1, C=CHH₅ᵗₐₙ), 5.21 (1H, d, J 10.3, C=CHH₅α), 4.63 (1H, d, J 6.8, CHOMCH₃), 3.34 (3H, s, Me)

**^13C-NMR** δC: 140.8, 138.7, 128.4, 127.7, 126.8, 116.4, 84.7, 56.4

**IR** (film) νₘₓ: 3078, 2978, 2933, 2823, 1639 (w), 1450, 1311, 1176, 1094, 983, 922

**LRMS (El) m/z:** 148 (Mⁿ⁻H, 20%), 147 (36, M¹), 121 (100), 117 (39), 109 (35), 105 (85), 91 (91)

**\( (E)\)-1-Phenyl-1-buten-3-ol**

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

(101)

A solution of methyl lithium (15 ml, 15 mmol, 1.0M in THF) was added dropwise to a solution of (E)-3-phenyl-2-propenal (2.00 g, 15 mmol) at 0°C. After 1 hour at ambient temperatures the mixture was quenched with water, acidified (pH 1-3), and extracted with ether (3 x 30 ml). The extract was washed with brine (30 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 60% ether in petrol) to afford the title compound (101) (1.77 g, 12.0 mmol, 80%) as a clear colourless oil; Rf (50% ether in petrol) 0.27

**^1H-NMR** δH: 7.23-7.41 (5H, m, PhH), 6.58 (1H, d, J 15.9, PhCH=CH), 6.27 (1H, dd, J 15.9 and 6.4, PhCH=CH), 4.51 (1H, q, J 6.4, CH(OH)CH₃), 1.66 (1H, s, CH(OH)CH₃), 1.39 (3H, d, J 6.4, CH(OH)CH₃)

**^13C-NMR** δC: 136.6, 133.5, 129.4, 28.6, 127.6, 126.4, 68.9, 23.4

**IR** (film) νₘₓ: 3346 (OH), 3026, 2972, 1598, 1494, 1489, 1368, 1141, 1059, 967, 942, 748, 693

**1-Phenyl-4-penten-3-ol**

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

(102)

A solution of 3-phenylpropanal (2.0 ml, 2.04 g, 15.2 mmol) in THF (18 ml) was added dropwise over 10 min to a solution of vinyl magnesium bromide (16 ml, 16 mmol, 1M in THF) in THF (10 ml) at 0°C. After 2 hours at ambient temperatures, the mixture was poured into saturated NH₄Cl solution (50 ml) and extracted with ether (3 x 25 ml). The extract was washed with brine (40 ml),
dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 40% ether in petrol) to afford the title compound (102) (1.95 g, 12.0 mmol, 75%) as a clear colourless oil; Rₚ (50% ether in petrol) 0.40

^H-NMR δₚ: 7.29-7.15 (5H, m, PhH), 5.89 (1H, ddd, J 17.2, 10.4, 6.2, CH=CH₂), 5.23 (1H, d, J 17.2, CH=CHH₃ₙₙₙₙ), 5.12 (1H, d, J 10.4, CH=CHH₉ₙₙₙₙ), 4.11 (1H, m, CHOH), 2.69 (2H, m, PhCH₂CH₃), 1.85 (2H, m, PhCH₂CH₂), 1.55 (1H, m, OH)

^C-NMR δₜ: 141.8, 141.0, 128.4, 128.3, 125.8, 114.9, 72.5, 38.5, 31.6

IR (film) νₘₐₓ: 3356 (s, OH), 3027, 2927, 1603, 1496, 1454, 1041, 991, 923, 748, 699

LRMS (El) m/z: 162 (M⁺, 14%), 145 (79%, [M-OH⁺]), 129 (13), 105 (22), 91 (100)

(E)-Ethyl-3-phenyl-2-butoxenate

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{CH₂CH₂CH₂CH₂O} & \quad (113)
\end{align*}
\]

A solution of ethylbromoacetate (2.7 ml, 4.06 g, 24.4 mmol) in benzene (6 ml) was added dropwise over 12 hours to a mixture of zinc dust (3.4 g, 52.0 mmol) and acetophenone (4.0 ml, 34.3 mmol) in refluxing benzene (15 ml). After a further 6 hours at reflux, the mixture was cooled to ambient temperatures and poured into an aqueous solution of HCl (20 ml, 6M). The organic phase was collected, washed with water (20 ml) and heated to reflux in apparatus fitted with a water separator. After 2 hours, phosphoryl chloride (ca. 100-150µl) was added and the mixture heated to reflux for a further 2 hours. The solution was washed with brine (15 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 5% ether in petrol) to afford the title compound (113) (1.62 g, 8.53 mmol, 35%) as a clear colourless oil; Rₚ (10% ether in petrol) 0.32

^H-NMR δₕ: 7.32-7.50 (5H, m, PhH), 6.12 (1H, q, J 1.2, C(CH₃)=CH), 4.20 (2H, q, J 7.2, CH₂CH), 2.56 (3H, d, J 1.2, C(CH₃)=CH), 1.3 (3H, t, J 7.2, CH₃CH₃)

^C-NMR δₜ: 166.9, 155.5, 142.2, 128.9, 128.4, 126.3, 117.2, 59.8, 17.9, 14.9

IR (film) νₘₐₓ: 3059, 2980, 1720 (C=O), 1633 (C=C), 1578, 1447, 1377, 1344, 1273, 1164, 1096, 1045

LRMS (El) m/z: 190 (M⁺, 17%), 161 (M⁺-Et, 30%), 145 (M⁺-OEt, 40), 144 (42), 118 (42), 117 (35), 115 (40), 91 (19)
**Experimental**

**(E)-3-Phenyl-2-buten-1iol**

\[ \text{Ph} \text{CH} = \text{CHCH}_2\text{OH} \]  
(63)

A solution of diisobutylaluminium hydride (8 ml, 12 mmol, 1.5M in toluene) was added dropwise to a solution of (E)-ethyl-3-phenyl-2-butenoate (113) (913 mg, 4.80 mmol) in toluene (15 ml) at -78°C. After 1 hour, water (2 ml) was added dropwise, followed by EtOAc (15 ml) and solid Na$_2$SO$_4$. The mixture was filtered and the solid extracted with EtOAc. The filtrates were combined and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 60% ether in petrol) to afford the title compound (63)\(^{307,157}\) (680 mg, 4.59 mmol, 96%) as a clear colourless oil; $R_t$ (60% ether in petrol) 0.51

$^1$H-NMR $\delta_H$: 7.17-7.44 (5H, m, PhH), 5.99 (1H, tq, $J$ 6.5 and 1.4, C=CH$_2$OH), 4.38 (2H, d, $J$ 6.5, C=CH$_2$OH), 2.10 (3H, d, $J$ 1.4, CH$_3$)

$^{13}$C-NMR $\delta_C$: 142.8, 137.8, 128.2, 127.3, 126.4, 125.7, 59.9, 16.0

IR (film) $\nu_{max}$: 3330 (OH), 3057, 3030, 2923, 2860, 1647 (w, C=C), 1494, 1445, 1380, 1320, 1002

LRMS (EI) m/z: 148 (M+, 26%), 131 (M+-OH, 100%)

**4-(Ethoxycarbonyl)-3-phenyl-2-cyclohexen-1-one**

\[ \text{EtO}_2\text{C} \text{C} = \text{CHCH}_2\text{OH} \]  
(163)

Benzyltrimethylammonium hydroxide (Triton B, 40% in MeOH) was added dropwise to a solution of 3-buten-2-one (6.95 g, 99.1 mmol) and ethyl benzoyl acetate (18.9 g, 98.5 mmol) in butanol (25 ml) at 0°C. The mixture was warmed to room temperature, stirred for 5 hours, diluted with EtOAc (150 ml). The mixture was washed with water (4 x 80 ml), brine (80 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The oily-solid residue was used without further purification for the preparation of 3-phenyl-2-cyclohexen-1-one (164), however trituration with ether and subsequent recrystallisation from MeOH afforded the title compound (163)\(^{200,221}\) as white platelets (m.p. 125-127°C; lit. 125-127°C and 128-130°C).

$^1$H-NMR $\delta_H$: 7.46-7.31 (5H, m, PhH), 7.28-7.21 (1H, m, C=CH), 4.03-3.95 (2H, m, CH$_3$CH$_2$O), 3.44 (1H, dd, $J$ 11.9, 4.1, CHCO$_2$Et), 2.64-2.25 (4H, m, CH$_2$CH$_2$C=O), 1.02 (3H, t, $J$ 7.1, CH$_3$CH$_2$O)
A mixture of crude 4-(ethoxycarbonyl)-3-phenyl-2-cyclohexen-1-one (163) (ca. 21.0 g) and 8% w/w KOH (150 ml) was heated to reflux for 16 hours. The mixture was diluted with ether and the aqueous phase extracted with ether (2 x 150 ml). The organic phases were combined, washed with water (2 x 75 ml), brine (100 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was recrystallised from 4 : 1 hexane: ether to afford the title compound (164) $^{200,221}$ (5.79 g, 33.6 mmol, 34% over 2 steps) as pale yellow needles (m.p. 64-66°C; lit. $^{63-66°C}$Cu $^{6}$$^{6}$H$_{17}$O$_{3}$ (M$^{+}$+H), 245.1170; Required 245.1178

3-Phenyl-2-cyclohexen-1-one

\[
\begin{array}{c}
\text{Ph} \\
\text{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{\underline{
pad rinsed through with EtOAc (3 x 20 ml). The organic phases were combined, washed with brine (40 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 45% ether in petrol) to afford the title compound (161)⁹⁸ (921 mg, 5.29 mmol, 91%) as a viscous oil, which solidified on standing; Rₘ(60% ether in petrol) 0.51 (m.p. 58.5-60.0°C; lit. 59-61°C

<sup>1</sup>H-NMR δ<sub>H</sub>: 7.41-7.23 (5H, m, PhH), 6.11 (1H, m, CH₂C=CH), 4.38 (1H, m, CH₂CHOH), 2.50-2.31 (2H, m, CH₂C=CH), 1.97-1.85 (2H, m, CH₂CHOH), 1.78-1.64 (2H, m, CH₂CH₂CH₂), 1.55 (1H, br s, OH)

<sup>13</sup>C-NMR δ<sub>C</sub>: 141.2, 140.2, 128.2, 127.3, 126.4, 125.2, 66.2 (CH₂CHOH), 31.6, 27.4, 19.3

IR (film) ν<sub>max</sub>: 3598 (s, OH), 3050 m, 2942 (s), 2866, 1642 (w), 1598 (w), 1494, 1445, 1380, 1226, 1155, 1069, 1043 (s), 966 (s), 905, 850 (w)

LRMS (El) m/z: 174 (M⁺, 16%), 173 (22), 157 (M⁺-H₂O, 100%), 141 (15), 128 (35), 115 (62), 107 (5), 103 (16)

HRMS (El) m/z: Found for C₁₃H₁₃O (M⁺-H), 173.0980; Required 173.0966

**3,3,5-Trimethyl-1-cyclohexanone, dimethyl-L-tartrate ketal**

![Structure](image)

A solution of 3,3,5-trimethylcyclohexanone (171) (64.9 mg, 462 μmol), dimethyl-L-tartrate (210 mg, 1.18 mmol) and pTSA monohydrate (19 mg, 100 μmol) in benzene (15 ml in flask) was heated to reflux for 16 hours in apparatus fitted with Dean-Stark apparatus. The solvent was removed under reduced pressure and the residue chromatographed (SiO₂, 25% ether in petrol) to afford the title compound (272)⁹³ (56.5 mg, 188 μmol, 41%) as a clear colourless oil; Rₘ(25% ether in petrol) 0.23

<sup>1</sup>H-NMR δ<sub>H</sub>: 4.84-4.73 (4H, m, 4 x CHCO₂CH₃), 3.84 (12H, t, J 2, 4 x CH₃O), 1.96-1.86 (14H, m, 2 x CH₂C(CH₃)₂CH₂CH(CH₃)CH₂), 1.03 (3H, d, J 6.7, CH₃CH), 0.95 (12H, s, 2 x C(CH₃)₂), 0.92 (3H, d, J 6.7, CH₃CH)

<sup>13</sup>C-NMR δ<sub>C</sub>: 170.1 (4 x C=O), 115.5 and 115.3 (2 x O-C-O), 77.4, 77.2, 77.1 and 75.5 (4 x OCH₂CO₂CH₃), 52.6, 52.5, 47.5, 47.4, 46.5, 46.4, 44.1, 43.5, 33.4, 33.4, 32.1, 32.0, 26.6, 26.2, 26.0, 26.0, 25.9, 22.0

IR (film) ν<sub>max</sub>: 2953, 2869, 2840, 1764 (s, C=O), 1457, 1438, 1388, 1354, 1278 (s), 1203 (s), 1124 (9 s), 1016, 9970, 954, 857, 749 (w)
**LRMS (El) m/z:** 323 (M⁺+Na, 15%), 301 (M⁺, 100%), 243 (50%)

**HRMS (El) m/z:** Found for C₁₅H₂₂O₆ (M⁺+H), 301.1640; Required 301.1651

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### 3-Phenyl-1-cyclohexanone, dimethyl-L-tartrate ketal

![](https://via.placeholder.com/150)

A solution of 3-phenylcyclohexanone (168) (102 mg, 585 μmol), dimethyl-L-tartrate (208 mg, 1.17 mmol) and pTSA monohydrate (10 mg, 52.5 μmol) in benzene (15ml in flask) was heated to reflux for 16 hours in apparatus fitted with Dean-Stark apparatus. The solvent was removed under reduced pressure and the residue chromatographed (SiO₂, 40% ether in petrol) to afford the title compound (173) (130 mg, 389 μmol, 66%) as a clear colourless oil; R(50% ether in petrol) 0.39

**¹H-NMR δH:** 7.32-7.18 (10H, m, 2 x PhH), 4.86 (4H, m, 4 x CHCO₂CH₃), 3.84, 3.83, 3.80 and 3.79 (12H, 4 x s, 4 x CH₃O), 2.98-2.89 (2H, m, 2 x CHPh), 2.04-1.35 (16H, m, 2 x CH₂CH₂CH₂CH₂CHPhCH₂)

**¹³C-NMR δC:** 170.3, 170.2, 170.2 and 170.1 (4 x C=O), 145.7, 145.6, 128.4, 126.8, 126.7, 126.2, 126.1 (Overlapping Ph signals), 114.9 and 114.8 (2 x O=C-O), 77.0, 76.9, 76.7 and 76.6 (4 x C-OC(=O)CH₃), 52.8, 42.7, 42.7, 41.6, 41.4, 35.4, 35.1, 33.6, 33.2, 32.6, 23.4, 23.4

**IR (film) v max:** 3003 (w), 2952, 2854, 1760 (s, 0 = 0), 1602 (w), 1495, 1438, 1358, 1285, 1226 (s), 1152 (s), 1119 (s), 1061, 923, 843 (w), 759, 702

**LRMS (El) m/z:** 334 (M⁺, 15%), 291 (100%), 275 (M⁺-CO₂Me, 7%), 215 (26), 131 (42), 91 (PhCH₃⁺, 30), 77 (7)

**HRMS (El) m/z:** Found for C₁₈H₂₆O₆ (M⁺), 334.1416; Required 334.1410

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### 1-(+)-(Menthyloxyacarboxy)-3-phenyl-2-cyclohexene

![](https://via.placeholder.com/150)

(+)-Menthylchloroformate (80.0 μl, 373 μmol) was added in one portion to a solution of 3-phenyl-2-cyclohexen-1-ol (161) (50.0 mg, 290 μmol) and pyridine (100 μl, 1.24 mmol) in DCM (1 ml).
The solution was stirred for 2 hours at room temperature then added to water (1 ml). The aqueous phase was extracted with ether (2 ml), then the organic phases combined, washed with brine (2 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 4% ether in petrol) to afford the title compound (177) (101 mg, 283 μmol, 98%) as a clear colourless oil; $R_f$ (4% ether in petrol) 0.19.

$^1$H-NMR δ: 7.40-7.24 (10H, m, 2 x PhH), 6.11 (2H, m, 2 x C=CHCHOR), 5.29 (2H, m, 2 x C=CHCHOR), 4.53 (2H, m, 2 x menthyl CHOR), 2.55-1.05 (30H, m, 12 x CH$_2$ and 6 x CH), 0.91 (3H, d, J 2.2, CH$_3$CH), 0.89 (3H, d, J 2.1, CH$_3$CH), 0.88 (3H, d, J 4.4, CH$_3$CH), 0.87 (3H, d, J 4.5, CH$_3$CH), 0.79 (3H, d, J 3.2, CH$_3$CH), 0.77 (3H, d, J 3.1, CH$_3$CH)

$^{13}$C-NMR δ: 154.7 (2 x C=O), 142.7, 141.1, 128.3, 127.7, 125.5 and 121.7 (2 x C=C and 2 x PhH), 78.1 (2 x C=CHCHRO), 72.3 (2 x menthyl CHRO), 47.0, 40.8, 40.8, 34.1, 31.4, 27.9, 27.4, 26.1, 25.9, 23.2, 21.9, 20.8, 19.1, 19.1, 16.2, 16.2

IR (film) νmax: 3033 (w), 2954 (s), 2869 (s), 1945 (s), 1599 (w), 1578 (w), 1495, 1456, 1369, 1252 (s), 1203, 1182, 1162, 1098, 1077, 1061, 1035, 1008, 965, 943, 906, 830 (w), 792, 750, 696

LRMS (FAB) m/z: 355 (M*, 5%), 157 (M*-menthyl, 24%), 157 (M*-menthylOCO$_2$, 100%)

HRMS (EI) m/z: Found for C$_{23}$H$_{31}$O$_3$ (M*), 355.2260; Required 355.2273

1-(-)-(Menthyloxyacarboxy)-3,3,5-trimethyl-2-cyclohexene

(+)-Menthyloxyacarboxamidate (80.0 μl, 373 μmol) was added in one portion to a solution of 3,3,5-trimethyl-2-cyclohexen-1-ol (40.7 mg, 290 μmol) and pyridine (100 μl, 1.24 mmol) in DCM (1 ml). The solution was stirred for 2 hours at room temperature then added to water (1 ml). The aqueous phase was extracted with ether (2 ml), then the organic phases combined, washed with brine (2 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 4% ether in petrol) to afford the title compound (178) (90.0 mg, 279 μmol, 96%) as a clear colourless oil; $R_f$ (50% ether in petrol) 0.82

$^1$H-NMR δ: 5.36 (2H, m, 2 x C=CHCHOR), 5.05 (2H, m, 2 x C=CHCHOR), 4.40 (2H, td, J 10.9, 6.5, 2 x menthyl CHOR), 1.99-0.89 (26H, m, 10 x CH$_2$ and 6 x CH), 1.58 (6H, s, 2 x CH$_3$),
0.89 (6H, s, 2 × CH₃), 0.82 (6H, s, 2 × CH₃), 0.80 (6H, d, J 8.2, 2 × CH₃CH), 0.78 (6H, d, J 7.2, 2 × CH₃CH), 0.68 (3H, d, J 7.0, CH₃CH), 0.67 (3H, d, J 7.0, CH₃CH)

$^{13}$C-NMR δC: 154.8, 138.6, 118.8, 77.9, 73.6, 65.8, 46.9, 46.9, 43.9, 40.8, 40.6, 40.5, 34.1, 34.1, 31.4, 30.8, 30.7, 30.6, 30.5, 26.8, 26.1, 25.9, 23.6, 23.4, 23.3, 21.9, 21.7, 16.3, 16.2, 16.2

IR (film) νmax: 2955 (s), 2870 (s), 2827, 2730 (w), 1732 (s), 1676 (w), 1578 (w), 1456, 1369, 1328, 1256 (s), 1202, 1180, 1007, 964, 945, 916, 848, 821, 794

LRMS (FAB) m/z: 323 (M⁺, 37%), 277 (16), 199 ([menthylOC=O]⁺, 100%), 183 ([menthylOCO₂]⁺, 77%)

HRMS (El) m/z: Found for C₂₀H₃₅O₃ (M⁺+H), 323.2586; Required 323.2600

2-Ethylamino pyridine

\[
\begin{align*}
\text{A solution of 2-aminopyridine (2.00 g, 21.3 mmol) in THF (10 ml) was added dropwise to a stirred suspension of sodium hydride (950 mg, 60% wt disp. in oil, 23.8 mmol) in THF (15 ml) at 0°C. After 20 minutes ethyl bromide (1.60 ml, 23.5 mmol) was added. The mixture was stirred at room temperature for 2 hours, then added to water (15 ml). The aqueous phase was extracted with EtOAc (2 x 30 ml), then the organic phases combined, washed with brine (40 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 50% ether in petrol) to afford the title compound (179)\textsuperscript{232,233} (1.43 g, 11.7 mmol, 55%) as a clear colourless oil; Rf (50% ether in petrol) 0.28
\end{align*}
\]

$^1$H-NMR δH: 7.98 (1H, m, PhH), 7.33-7.27 (1H, m, PhH), 6.44 (1H, m, PhH), 6.25 (1H, m, PhH), 4.49 (1H, br s, NH), 3.18 (2H, dq, J 8.7 7.2, NCH₂CH₃), 1.14 (3H, t, J 7.2, NCH₂CH₃)

$^{13}$C-NMR δC: 158.8, 148.2, 137.4, 112.7, 106.3, 36.9 (NCH₂CH₃), 14.8 (NCH₂CH₃)

IR (film) νmax: 3418, 3264 (s, NH), 3089,3020, 2971, 2930, 2871, 1734 (w), 1602 (w), 1571 (s), 1514 (s), 1446 (s), 1418, 1382, 1328, 1286, 1247, 1154, 1105, 1090, 1064, 984, 850, 771 (s), 736, 628 (w)

LRMS (FAB) m/z: 123 (M⁺+H, 100%), 115 (8%), 107 (23), 105 (11)

HRMS (El) m/z: Found for C₇H₁₇N₂ (M⁺+H), 123.0930; Required 123.0922
Iodine (4.98 g, 19.6 mmol) was added in one portion to a solution of triphenylphosphine (5.12 g, 19.5 mmol) in acetonitrile (150 ml). Triethylamine (2.70 ml, 19.2 mmol) was then added followed by 1,3-cyclohexyldione (2.00 g, 17.8 mmol), and the mixture stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the residue triturated with ether (100 ml). The filtrate was filtered through a short pad of silica, with the pad flushed with more ether (2 x 50 ml). The solvent was removed under reduced pressure and the residue distilled (21 mm Hg) to afford the title compound (180)\(^{239}\) (3.07 g, 13.8 mmol, 78%; Collected at 125-130°C) as a clear colourless oil.

\(^1\)H-NMR \(\delta\) H: 6.85 (1H, t, \(J\) 1.7, C=CH), 2.92 (2H, td, \(J\) 6.1 1.7, CH\(_2\)CH\(_2\)CH\(_2\)CO), 2.44 (2H, m, CH\(_2\)CH\(_2\)CH\(_2\)CO), 2.04 (2H, tt, \(J\) 6.7 6.1, CH\(_2\)CH\(_2\)CH\(_2\)CO)

\(^{13}\)C-NMR \(\delta\) c: 195.2, 140.7, 126.9, 40.6, 36.6, 24.0

IR (film) \(\nu\) max: 2949, 2883, 2821, 1672 (s, \(\nu\) = \(\nu\) ), 1593 (s), 1562, 1422, 1324 (s), 1278 (s), 1233 (s), 1180 (s), 1133, 1055 (w), 966 (w), 882, 826, 780 (w), 728, 616 (w), 504

LRMS (El) m/z: 222 (M\(^+\), 100%), 95 (M\(^-\)I, 98%)

HRMS (El) m/z: Found for C\(_9\)H\(_{16}\)IO (M\(^+\)), 221.9550; Required 221.9542

3-Iodo-2-cyclohexen-1-one

A solution of 3-Iodo-2-cyclohexene-1-one (180) (1.01 g, 4.56 mmol) in ether (5 ml) was added dropwise to a stirred suspension of LiAlH\(_4\) (375 mg, 9.88 mmol) in ether (10 ml) at -5°C. After 2 hours at this temperature, saturated Na\(_2\)SO\(_4\) solution (3.0 ml) added dropwise and the mixture stirred for 1 hour. The mixture was filtered through a pad of celite, then the pad rinsed through with ether (3 x 10 ml) and then DCM (3 x 10 ml). The organic phases were combined, washed with brine (40 ml), dried (MgSO\(_4\)) and the solvent removed under reduced pressure to afford the title compound (181)\(^{239}\) (1.06 mg, 4.71 mmol, 97%), which was used without further purification.
1H-NMR δH: 6.45 (1H, m, C=CHCHOH), 4.17 (1H, m, C=CHCHOH), 2.56-2.48 (2H, m, CH₂CH₂CH₂C=CH), 2.01-1.75 (2H, m, CH₂CH₂CH₂C=CH), 1.74-1.61 (2H, m, CH₂CH₂CH₂C=CH).

13C-NMR δC: 139.9, 101.1, 67.9, 39.4, 30.5, 21.6

IR (film) νmax: 3330 (OH), 2940, 2861, 2361 (w), 1633 (C=C), 1447, 1427, 1321, 1194 (w), 1056 (s), 955 (s), 903, 829, 718, 625, 568 (w)

LRMS (El) m/z: 224 (M⁺, 7%), 206 (M⁺-H₂O, 3%), 201 (14), 183 (13), 128 (23), 97 (M⁺-I, 100%), 79 (21), 55 (22), 41 (67)

(E) and (Z) (3S)-1-Trimethylsilyloxy-3,7-dimethyl-2,6-octadiene

(S)-Citronellal (300 mg, 1.94 mmol) in DME (5 ml) was added dropwise to a stirred suspension of potassium hydride (310 mg, 35% wt disp. in oil, 2.70 mmol) in DME (10 ml) at -5°C. The mixture was stirred for 30 minutes at this temperature. Triethylamine (100 µl, 717 µmol) was added to a stirred solution of trimethylsilyl chloride in DME (5 ml). The stirring was stopped and the supernatant solution transferred to the potassium enolate solution, via filter tipped cannulae. After warming to room temperature and stirring for 30 minutes, the mixture was then diluted with petrol (15 ml), washed with saturated NaHCO₃ solution (15 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure to afford an inseparable mixture of the (E) and (Z) silyl enol ethers, (273) and (274) respectively (400 mg, 1.77 mmol, 91%; (E): (Z) ratio 1.7 : 1) and starting material (26.9 mg, 0.17 mmol, 9%)

1H-NMR δH: (273) 6.17 (1H, d, J 11.9, CH=CHOTMS), 5.09 (1H, m, Me₂C=CH), 4.85 (1H, dd, J 11.9, 8.9, CH=CHOTMS), 2.05-1.89 (3H, m, C=CH₂CH₂CH₂Me), 1.69 (3H, s, CH₃), 1.60 (3H, s, CH₃), 1.07 (3H, d, J 7.6, CHCH₃), 0.19 (9H, s, Si(CH₃)₃); (274) 6.12 (1H, d, J 5.9, CH=CHOTMS), 5.11 (1H, m, Me₂C=CH), 4.30 (1H, dd, J 9.3, 5.9, CH=CHOTMS), 2.05-1.89 (3H, m, C=CH₂CH₂CH₂Me), 1.69 (3H, s, CH₃), 1.60 (3H, s, CH₃), 1.05 (3H, d, J 6.4, CHCH₃), 0.18 (9H, s, Si(CH₃)₃).
1,2:5,6-Di-O-isopropylidene-3,4-di-O-methyl-D-mannitol (183)

A solution of 1,2:5,6-di-O-isopropylidene-D-mannitol (185) (272 mg, 1.04 mmol) in methyl iodide (3 ml) was added to a suspension of silver (I) oxide (481 mg, 2.08 mmol) in acetonitrile (3 ml). After 24 hours in darkness, the mixture was filtered through a pad of celite, then the pad rinsed through with DCM. The solvent was removed under reduced pressure, and the residue chromatographed (SiO₂, 40% ether in petrol) to afford the title compound (183) (278 mg, 0.96 mmol, 92%) as a clear colourless oil; Rₖ(50% ether in petrol) 0.33

¹H-NMR δ: 4.17 (2H, ddd, J₆.8, 6.1 and 5.9, C[2,5]-H), 4.11 (2H, dd, J 8.3 and 6.1, C[1,6]-H), 3.95 (2H, dd, J 8.3 and 5.9, C[1,6]-H), 3.51 (6H, s, 2 x OCH₃), 3.44 (2H, d, J 6.8, C[3,4]-H), 1.42 (6H, s, 2 x CH₃), 1.36 (6H, s, 2 x CH₃)

¹³C-NMR δ: 108.7 (CMe₂), 81.5 (C[3,4]), 75.6 (C[2,5]), 66.9 (C[1,6]), 61.0 (2MeO), 26.8, 25.5 (2Me)

MS (FAB) m/z: 291 (M⁺+H, 14%), 275 (M⁺-CH₃, 11%), 233 (15), 145 (17), 101 (100), 87 (38), 71 (30)

IR (film) ν max: 2988, 2936, 2832, 1455, 1370, 1251, 1162, 1094, 968, 944, 856

1,2,3,4,5,6-Hexa-O-methyl-D-mannitol

A solution of D-mannitol (182) (500 mg, 2.74 mmol) in methyl iodide (10 ml) was added to a suspension of silver (I) oxide (4.00 mg, 17.3 mmol) in acetonitrile (10 ml) and stirred for 24 hours in darkness and at ambient temperatures. The mixture was filterated through a pad of celite and then the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 40% ether in petrol) to afford the title compound (184) (583 mg, 2.19 mmol, 80%) as a clear colourless oil; Rₖ (ether) 0.33

¹H-NMR δ: 3.74 (2H, dd, J 10.7 and 2.4, 2 x C[1]-H), 3.54 (2H, d, J 7.5, 2 x C[3]-H), 3.49 (2H, dd, J 10.7 and 3.9, 2 x C[1]-H), 3.43 (6H, s, 2 x CH₂O), 3.40 (6H, s, 2 x CH₂O), 3.39 (2H, ddd, J 7.5, 3.9 and 2.4, 2 x C[2]-H), 3.38 (6H, s, 2 x 2 x CH₂O)
**Experimental**

\( ^{13}C-NMR \) \( \delta_c: 79.6, 78.9, 70.0, 60.4, 59.0, 56.9 \)

**IR** (film) \( \nu_{max}: 2930, 2828, 1460, 1338, 1241, 1186, 1107, 1022, 956, 855 \)

**LRMS (EI) m/z:** 267 (M\(^+\)+H, 84%), 265 (50), 235 (91), 177 (37), 171 (44), 145 (86), 133 (56), 115 (40), 101 (100), 89 (98), 75 (34), 71 (39), 59 (31)

\((E)\) 1-\(t\)-Butyldimethylsilyloxy-3,7-dimethyl-2,6-octadiene

\[
\text{\(t\)-Butyldimethylsilylchloride (645 mg, 4.28 mmol) was added in one portion to a solution of geraniol (61) (600 mg, 3.89 mmol) and imidazole (291 mg, 4.28 mmol) in DCM (15 ml), followed by DMAP (40 mg, 32.7 \(\mu\)mol) in one portion. After stirring at room temperature for 2 hours, the solution was washed with water (2 x 10 ml), brine (10 ml), dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (SiO\(_2\), 2.5% ether in petrol) to afford the title compound (187)\(^{312}\) (814 mg, 3.03 mmol, 78%) as a clear colourless oil; \(R_f\) (25% ether in petrol) 0.78}

**\(^1H-NMR\)** \( \delta_h: 5.33 \) (1H, m, C=CH\(_2\)O), 5.12 (1H, m, C=CH\(_2\)CH\(_2\)O), 4.22 (2H, d, \(J\) 6.4, C=CH\(_2\)H\(_2\)O), 2.18-2.03 (4H, m, C=CH\(_2\)CH\(_2\)H\(_2\)), 1.70 (3H, s, CH\(_3\)), 1.64 (3H, s, CH\(_3\)), 1.62 (3H, s, CH\(_3\)), 0.92 (9H, s, OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.09 (6H, s, OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\))

\( ^{13}C-NMR \) \( \delta_c: 136.9, 131.6, 124.4, 124.1, 124.1, 60.4, 39.5, 26.4, 26.0, 25.7, 18.4, 17.7, 16.3, 0.0 \)

**IR** (film) \( \nu_{max}: 2956, 2928, 2856, 2174 \) (w), 1726 (w), 1666, 1462, 1444, 1382, 1360, 1254, 1105, 1066 (s), 1006, 939 (w), 836 (w), 775, 665, 588 (w)

**LRMS (FAB) m/z:** 267 (M\(^+\), 100%), 211 (23), 173 (23)

**HRMS (FAB) m/z:** Found for C\(_{16}\)H\(_{31}\)SiO (M\(^+\)-H), 267.2130; Required 267.2144

\((E)-1\)-Trimethylsilyloxy-3,7-dimethyl-1,6-octadiene

\[
\text{Citronellal (62) (100 mg, 648 \(\mu\)mol) in DME (5 ml) was added dropwise to a stirred suspension of potassium hydride (82.0 mg, 35% wt disp. in oil, 715 \(\mu\)mol) in DME (5 ml) at -5°C. The mixture was stirred for 15 minutes at this temperature. Triethylamine (36.0 \(\mu\)l, 258 \(\mu\)mol) was added to a stirred solution of \(t\)-butyldimethylsilyl chloride in DME (5 ml), which was then added dropwise to}
\]
the potassium enolate solution. After warming to room temperature and stirring for 30 minutes, 
the mixture was then diluted with hexane (15 ml), washed with saturated NaHCO₃ solution (15 
ml), dried (Na₂SO₄) and the solvent removed under reduced pressure to afford a mixture 
containing the title compound (186)³¹³,²⁴⁹ (85% by GC; (E): (Z) ratio 3.4 : 1); (GC: 75°C for 2 
minutes, then 10°C/minute to 250°C; (Z): 8.89, (E): 9.52 minutes).

**LRMS (EI) m/z:** 268 (M⁺, 17%), 254 (18), 226 (18), 212 (20), 187 (12), 76 (100), 74 (73)

### 4-Benzylxybut-2-en-1-ol

![Structure of 4-Benzylxybut-2-en-1-ol](191)

A solution of 1,4-but-2-ene diol (1.00 g, 11.4 mmol) in THF (20 ml) was added dropwise to a 
stirred suspension of sodium hydride (908 mg, 60% wt disp. in oil, 22.7 mmol) in THF (20 ml) at 
0°C. After 30 minutes, a solution of benzylbromide (1.35 ml, 1.94 g, 11.4 mmol) in DMF (20 ml) 
was added dropwise followed by potassium iodide (10 mg) and the mixture stirred at room 
temperature for 16 hours. The mixture diluted with ether (50 ml), washed with water (4 x 40 ml), 
brine (40 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was 
chromatographed (SiO₂, 50% ether in petrol) to afford the title compound (191)³¹⁴ (1.29 g, 7.24 
mmol, 64%) as a clear colourless oil; Rₓ (ether) 0.20

**¹H-NMR δ (ppm):** 7.40-7.27 (5H, m, PhH), 5.87-5.72 (2H, m, CH=CH₂), 4.54 (2H, s, PhCHO), 4.19 (2H, m, CH₂OH), 4.11 (2H, d, J 6.5, BnOCH₂), 1.87 (1H, m, OH)

**¹³C-NMR δ (ppm):** 137.8, 132.3, 128.5, 128.3, 127.8, 127.8, 72.5, 65.7, 58.8

**IR (film) νmax (cm⁻¹):** 3446 (s, OH), 3089 (w), 3032 (s), 2933 (s), 2865 (s), 1604, 1496, 1455 (s), 1418, 1386, 1365, 1249 (w), 1205, 1071 (s), 1024 (s), 979 (s), 941 (s), 819 (s), 607

**LRMS (EI) m/z:** 179 (M⁺+H, 17%), 161 (M⁺-OH, 42%), 107 (2), 91 (PhCH₂⁺, 100%), 77 (Ph⁺, 7%)

**HRMS (EI) m/z:** Found for C₁₁H₁₆O₂ (M⁺+H), 179.1080; Required 179.1072

### (E)-2-Dodecen-1-ol

![Structure of (E)-2-Dodecen-1-ol](192)

A solution of diisobutylaluminium hydride (21.0 ml, 32.0 mmol, 1.5M in toluene) was added 
dropwise over 30 minutes to a solution of (E)-ethyl 2-dodecenoate (3.00 g, 13.0 mmol) in toluene 
(40 ml) at -78°C, and the mixture stirred at -78°C for 1 hour. Water (5 ml) was added cautiously, 
followed by ethyl acetate (80 ml) and the mixture warmed to room temperature. Excess 
anhydrous Na₂SO₄ was added and the resulting solid mass filtered through a glass sinter,
washing the solid through with ethyl acetate (3 x 50 ml). The solvent was removed under reduced pressure and then the residue chromatographed (SiO₂, 20-50% ether in petrol) to afford the title compound (192)₃¹⁵ (2.20 g, 12.0 mmol, 92%) as a clear, colourless and viscous oil.

¹H-NMR δₜ: 5.04 (2H, m, CH₂CH=CHCH₂OH), 4.01 (2H, m, CH₂CH=CHCH₂OH), 2.02 (2H, q, J 6.7, CH₂CH=CHCH₂OH), 1.3 (14H, 7 x CH₂-envelope), 0.87 (3H, t, J 6.7, CH₃)

¹³C-NMR δₜ: 133.5, 128.7, 63.7, 32.1, 31.8, 29.4, 29.4, 29.2, 29.1, 29.0, 22.6, 14.0

IR (film) νmax: 3328 (s, OH), 2925, 2855, 1630, 1466, 1090, 1004, 970

LRMS (El) m/z: 184 (M⁺), 166, 138, 123

(E)-1-Phenyi-2-buten-1-ol

\[ (199) \]

A solution bromobenzene (5.30 ml, 50.0 mmol) in THF (20 ml) was added dropwise, over 30 minutes, to a flask containing magnesium turnings (1.46 g, 61.0 mmol) and iodine (ca. 40 mg) in THF (40 ml). The mixture was heated to reflux for 30 minutes, then cooled to 0°C. A solution of trans 2-methyl-2-butenal (4.15 ml, 50 mmol) in THF (20 ml) was added dropwise over 30 minutes. The mixture was warmed to room temperature, stirred for 2 hours and then added to saturated NH₄Cl solution (50 ml). The aqueous phase was extracted with ether (2 x 30 ml) and then the organic phases combined, washed with brine (30 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 20% ether in petrol) to afford the title compound (199)₃¹⁶ (5.00 g, 33.8 mmol, 68%) as a clear colourless oil; Rf (20% ether in petrol) 0.20

¹H-NMR δₜ: 7.39-7.28 (5H, m, PhH), 5.75 (2H, m, CH=CHCH₃), 5.19 (1H, d, J 6.0, CHOH), 1.91 (1H, br s, OH), 1.74 (3H, d, J 5.6, CH=CHCH₃)

¹³C-NMR δₜ: 143.3, 133.5, 128.5, 128.4, 127.4, 126.1, 126.0, 75.1 (COH), 17.6 (CH₃)

IR (film) νmax: 3321 (br s, OH), 3028, 2967, 2856, 1949 (w), 1881 (w), 1811 (w), 1672 (w), 1602 (w), 1492, 1451 (s), 1378, 1302, 1228, 1194, 1116, 1069, 1005, 965 (s), 912

LRMS (FAB) m/z: 131 (M⁺-OH, 100%), 105 (23%)

HRMS (FAB) m/z: Found for C₁₀H₁₁ (M⁺-OH), 131.0855; Required 131.0861
\textbf{(E)-2,2-Dimethyl-4-hexen-3-ol}

\begin{center}
\begin{tikzpicture}[scale=0.5]
    \node at (0,0) {\textcolor{red}{\textbullet}};
    \node at (0,0.5) {OH};
    \node at (-0.5,1) {\textcolor{red}{\textbullet}};
    \node at (-0.5,1.5) {\textcolor{red}{\textbullet}};
    \node at (-0.5,2) {\textcolor{red}{\textbullet}};
    \node at (0,2) {\textcolor{red}{\textbullet}};
    \node at (0,2.5) {\textcolor{red}{\textbullet}};
    \node at (0.5,1) {\textcolor{red}{\textbullet}};
    \node at (0.5,1.5) {\textcolor{red}{\textbullet}};
    \node at (0.5,2) {\textcolor{red}{\textbullet}};
    \node at (0.5,2.5) {\textcolor{red}{\textbullet}};
    \node at (1,1) {\textcolor{red}{\textbullet}};
    \node at (1,1.5) {\textcolor{red}{\textbullet}};
    \node at (1,2) {\textcolor{red}{\textbullet}};
    \node at (1,2.5) {\textcolor{red}{\textbullet}};
    \draw[thick,red] (0,0) -- (0,2);
    \draw[thick,red] (0,0) -- (0.5,1);
    \draw[thick,red] (0,0) -- (0.5,2);
    \draw[thick,red] (0,0) -- (1,1);
    \draw[thick,red] (0,0) -- (1,2);
    \draw[thick,red] (0,0) -- (-0.5,1);
    \draw[thick,red] (0,0) -- (-0.5,2);
    \draw[thick,red] (0,0) -- (-0.5,1.5);
    \draw[thick,red] (0,0) -- (-0.5,2.5);
\end{tikzpicture}
\end{center}

$\text{(200)}$

$t$-BuLi (15.0 ml, 25.5 mmol, 1.70M in hexanes) was added dropwise, over a 15 minute period, to a solution of 2-butenal (1.70 ml, 17.4 mmol) in ether (20 ml) at -78°C. The mixture was warmed to room temperature, stirred for 1 hour then added to water (10 ml). The aqueous phase was extracted with ether (2 x 20 ml), then the organic phases combined, washed with brine (30 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 9% ether in petrol) to afford the title compound (200)$^{317}$ (1.36 g, 9.57 mmol, 55%) as a clear colourless oil; $R_f$ (10% ether in petrol) 0.23

$^1$H-NMR $\delta$: 5.68 (1H, dq, $J_{15.3}$ 6.0, CH=CHCH$_3$), 5.58 (1H, dd, J 15.3 7.3, CH=CHCH$_3$), 3.70 (1H, d, J 7.3, CHO), 1.73 (3H, d, J 6.0, CH=CHCH$_3$), 0.92 (9H, s, C(CH$_3$)$_3$)

$^{13}$C-NMR $\delta$: 131.0 (CH=CHCH$_3$), 128.4 (CH=CHCH$_3$), 81.2 (COH), 34.7 (C(CH$_3$)$_3$), 25.7 (C(CH$_3$)$_3$), 17.9 (CH=CHCH$_3$)

IR (film) $\nu_{max}$: 3418 (br s, OH), 2954 (s), 2869, 1672 (w), 1479, 1363, 1300 (w), 1240, 1180, 1120

LRMS (FAB) m/z: 111 (M$^+$-OH, 14%), 73 (53), 69 (36), 57 (100)

HRMS (FAB) m/z: Found for C$_8$H$_{15}$ (M$^+$-OH), 111.1180; Required 111.1174

\textbf{(E)-2-Methyl-1-phenyl-2-buten-1-ol}

\begin{center}
\begin{tikzpicture}[scale=0.5]
    \node at (0,0) {\textcolor{red}{\textbullet}};
    \node at (0,0.5) {OH};
    \node at (-0.5,1) {\textcolor{red}{\textbullet}};
    \node at (-0.5,1.5) {\textcolor{red}{\textbullet}};
    \node at (-0.5,2) {\textcolor{red}{\textbullet}};
    \node at (0,2) {\textcolor{red}{\textbullet}};
    \node at (0,2.5) {\textcolor{red}{\textbullet}};
    \node at (0.5,1) {\textcolor{red}{\textbullet}};
    \node at (0.5,1.5) {\textcolor{red}{\textbullet}};
    \node at (0.5,2) {\textcolor{red}{\textbullet}};
    \node at (0.5,2.5) {\textcolor{red}{\textbullet}};
    \node at (1,1) {\textcolor{red}{\textbullet}};
    \node at (1,1.5) {\textcolor{red}{\textbullet}};
    \node at (1,2) {\textcolor{red}{\textbullet}};
    \node at (1,2.5) {\textcolor{red}{\textbullet}};
    \node at (1.5,0) {Pr};
    \draw[thick,red] (0,0) -- (0,2);
    \draw[thick,red] (0,0) -- (0.5,1);
    \draw[thick,red] (0,0) -- (0.5,2);
    \draw[thick,red] (0,0) -- (1,1);
    \draw[thick,red] (0,0) -- (1,2);
    \draw[thick,red] (0,0) -- (-0.5,1);
    \draw[thick,red] (0,0) -- (-0.5,2);
    \draw[thick,red] (0,0) -- (-0.5,1.5);
    \draw[thick,red] (0,0) -- (-0.5,2.5);
\end{tikzpicture}
\end{center}

$\text{(208)}$

A solution of bromobenzene (3.95 g, 25.2 mmol) in THF (10 ml) was added dropwise, over 30 minutes, to a flask containing magnesium turnings (740 mg, 30.4 mmol) and iodine (ca. 10-20 mg) in THF (20 ml). The mixture was heated to reflux for 30 minutes, then cooled to 0°C. A solution of trans 2-methyl-2-butenal (2.09 g, 24.8 mmol) in THF (10 ml) was added dropwise over 30 minutes. The mixture was warmed to room temperature, stirred for 2 hours and then added to saturated NH$_4$Cl solution (40 ml). The aqueous phase was extracted with ether (2 x 30 ml) and then the organic phases combined, washed with brine (40 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 20% ether in petrol) to afford the title compound (208)$^{333}$ (3.44 g, 21.2 mmol, 86%) as a clear colourless oil which crystallised on standing, m.p. 40-42°C; $R_f$ (20% ether in petrol) 0.24
A solution of bromobenzene (3.95 g, 25.2 mmol) in THF (10 ml) was added dropwise, over 30 minutes, to a flask containing magnesium turnings (740 mg, 30.4 mmol) and iodine (ca. 10-20 mg) in THF (20 ml). The mixture was heated to reflux for 30 minutes, then cooled to 0°C. A solution of 2-ethylpropenal (2.10 g, 85% technical grade, 21.2 mmol) in THF (10 ml) was added dropwise over 30 minutes. The mixture was warmed to room temperature, stirred for 2 hours and then added to saturated NH$_4$Cl solution (40 ml). The aqueous phase was extracted with ether (2 x 30 ml) and then the organic phases combined, washed with brine (40 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 15% ether in petrol) to afford the title compound (210) as a clear colourless oil; $R_f$ (15% ether in petrol) 0.18

**2-Ethyl-1-phenyl-2-propen-1-ol**

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

(210)

A solution of bromobenzene (3.95 g, 25.2 mmol) in THF (10 ml) was added dropwise, over 30 minutes, to a flask containing magnesium turnings (740 mg, 30.4 mmol) and iodine (ca. 10-20 mg) in THF (20 ml). The mixture was heated to reflux for 30 minutes, then cooled to 0°C. A solution of 2-ethylpropenal (2.10 g, 85% technical grade, 21.2 mmol) in THF (10 ml) was added dropwise over 30 minutes. The mixture was warmed to room temperature, stirred for 2 hours and then added to saturated NH$_4$Cl solution (40 ml). The aqueous phase was extracted with ether (2 x 30 ml) and then the organic phases combined, washed with brine (40 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 15% ether in petrol) to afford the title compound (210) as a clear colourless oil; $R_f$ (15% ether in petrol) 0.18

$^1$H-NMR $\delta$: 7.35-7.24 (5H, m, PhH), 5.71 (1H, q, $J$ 6.8, C(CH$_3$)=CHCH$_3$), 5.13 (1H, d, $J$ 3.2, CHO), 1.82 (1H, d, $J$ 3.2, OH), 1.65 (3H, d, $J$ 6.8, C(CH$_3$)=CHCH$_3$), 1.48 (3H, s, C(CH$_3$)=CHCH$_3$)

$^{13}$C-NMR $\delta$: 152.6, 142.2, 128.4, 127.6, 126.6, 108.7, 65.9, 24.4, 12.0

IR (film) $\nu_{\text{max}}$: 3590 (s), 3086, 3031, 2970 (s), 2878 (s), 1955 (w), 1817 (w), 1648, 1604 (w), 1493, 1454, 1375, 1274 (s), 1255, 1184, 1113, 1071, 1034 (s), 939 (w), 908 (s), 844

LRMS (El) m/z: 162 (M$^+$, 6%), 145 (M$^+$OH, 100%), 117 (12), 105 (14)

HRMS (El) m/z: Found for C$_{11}$H$_{14}$O (M$^+$), 162.1040; Required 162.1045
2,2-Dimethyl-4-ethyl-4-penten-3-ol (215) and (Z)-2,2,4-Trimethyl-4-hexen-3-ol (216)

A solution of t-BuLi (15.0 ml, 25.5 mmol, 1.70 M in pentane) was added dropwise to a solution of 2-ethylpropenal (1.70 ml, 17.4 mmol) in ether (20 ml) at -78°C. The mixture was warmed to room temperature, stirred for 2 hours and then added to saturated NH₄Cl solution (20 ml). The aqueous phase was extracted with ether (2 x 15 ml) and then the organic phases combined, washed with brine (30 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 9% ether in petrol) to afford an inseparable mixture of the title compounds, (215) and (216) respectively, (1.36 g, 9.59 mmol, 55%; 2.2 : 1) as a clear colourless oil; R₁ (15% ether in petrol) 0.19

¹H-NMR δₚ: (215) 4.99 (1H, m, C=CH₂), 4.96 (1H, s, C=CH₂), 3.80 (1H, s, CHO), 2.05 (2H, m, CH₂CH₃), 1.47 (1H, s, OH), 1.06 (3H, t, J₇.3, CH₃CH₂), 0.93 (9H, s, t-Bu); (216) 5.43 (1H, q, J₆.7, C(CH₃)=CHCH₃), 3.70 (1H, m, C=OH), 1.63 (3H, s, C(CH₃)=CHCH₃), 1.60 (3H, d, J₆.7, C(CH₃)=CHCH₃), 1.43 (1H, br s, OH), 0.87 (9H, s, t-Bu)

¹³C-NMR δₚ: (215) 153.2, 110.8, 82.6, 35.3, 27.2, 26.3, 12.8; (216) 136.8, 122.5, 85.1, 32.8, 26.7, 15.3, 11.3

IR (film) νₘₐₓ: Mixture of (215) and (216): 3452 (s, OH), 3083, 2957, 1641, 1463, 1362, 1211, 1177, 1075, 1003, 906

LRMS (FAB) m/z: 267 ([2M-OH]+, 43%), 123 (71), 109 (50)

HRMS (El) m/z: Found for C₁₈H₃₅O ([2M-OH]+), 267.2670; Required 267.2688

(E) 1-Diethylamino-3,7-dimethyl-2,6-octadiene

n-BuLi (6.22 ml, 10.7 mmol, 1.72M in hexanes) was added dropwise to a mixture of diethylamine (10.4 ml, 101 mmol) and myrcene (8.08 g, 59.3 mmol) at 0°C. The flask was sealed and heated to 50°C for 5 hours, then at room temperature for 16 hours. The mixture was diluted with ether (50 ml) then added to water (30 ml). The aqueous phase was extracted with ether (2 x 15 ml), then the organic phases combined, washed with brine (30 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was distilled (5mm Hg) to afford the title compound (64)²⁶⁹ (8.04 g, 38.4 mmol, 65%; Collected at 100°C, fore-run discarded) as a clear colourless oil.
**1-Phenyl-2-propen-1-one**

![Structure](image)

Manganese (IV) oxide (5 g) was added portion-wise to a rapidly stirred solution of 1-phenyl-2-propen-1-ol (88) (800 mg, 5.96 mmol) in ether (40 ml). The mixture was stirred for 6 hours then filtered through a pad of celite, then the pad rinsed through with ether. The solvent was removed under reduced pressure, and the residue chromatographed (SiO₂, 15% ether in petrol) to afford the title compound (236) (243 mg, 1.84 mmol, 31%) as a clear colourless oil; *Rₚ* (20% ether in petrol) 0.35.

**¹H-NMR** δ: 8.00-7.96 (2H, m, PhH), 7.63-7.48 (3H, m, PhH), 7.19 (1H, m, dd, J 17.1 and 10.5, CH=CHH), 6.47 (1H, dd, J 17.1 and 1.7, CH=CHHₜₐₙₑ), 5.96 (1H, dd, J 10.5 and 1.7, CH=CHH₂)

**¹³C-NMR** δ: 191.1, 137.3, 133.0, 132.4, 130.2, 128.7, 128.6

**IR (film)** νₘₐₓ: 3062, 1672, 1597, 1578, 1448, 1404, 1234, 993, 728, 688

**LRMS (El) m/z:** 132 (M⁺, 33%), 105 (100), 77 (66), 55 (12), 51 (24)

1-[²H]-1-Phenyl-2-propen-1-ol and 3-[²H]-1-phenyl-1-propanone

A solution of 1-phenyl-1-butanone (203) (243 mg, 1.84 mmol) in ether (8 ml) was added dropwise to a stirred suspension of LiAlD₄ (100 mg, 2.38 mmol) in ether (10 ml) at -5°C. After 60 minutes as this temperature, water (1 ml) was carefully added dropwise, followed by 2M H₂SO₄ (10 ml). The organic phase was collected and aqueous phase was extracted with ether (2 x 10 ml). The organic phases were combined, washed with brine (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 10-30% ether in
petrol) to afford 3-[\textsuperscript{3}H]-1-phenyl-1-propanone (235)\textsuperscript{133,134} (26.7 mg, 202 \mu\text{mol}, 11\%) and 1-[\textsuperscript{3}H]-1-phenyl-2-propen-1-ol (233)\textsuperscript{139} (151 mg, 1.12 mmol, 61\%) as a clear colourless oils.

\[^{1}H\text{-NMR}\] \(\delta_{H}: (233) 7.45-7.21 (5H, m, PhH), 6.06 (1H, dd, J 17.2, 10.3, \text{CH-CHH})
\]\(, 5.36 (1H, dd, J 17.2 and 1.4, \text{CH=CHH}_{\text{trans}}), 5.21 (1H, dd, J 10.3 and 1.4, \text{CH=CHH}_{\text{cis}}); (235) 7.96 (2H, m, PhH), 7.52-7.44 (4H, m, PhH), 2.98 (2H, tt*, J 7.1 and 1.0, \text{CH}_{2}\text{CH}_{2}\text{D}), 1.20 (2H, tt*, J 7.1 and 1.0, \text{CH}_{2}\text{CH}_{2}\text{D})\).

\[\text{IR (film) } \nu_{\text{max}}: (233) 3363 (s, \text{OH}), 3060, 3027, 1640, 1602, 1494, 1449, 1064, 1015, 991, 926; (235) 3063, 2977, 2942, 1965, 1904, 1819, 1687, 1598, 1582, 1450, 1360, 1277, 1217, 1180, 1014, 951, 746, 720, 691\]

\[\text{LRMS (El) } m/z: (233) 135 (M+, 66\%), 134 (100), 118 (52), 105 (73), 91 (61), 80 (80), 77 (71), 51 (30); (235) 135 (M+, 31\%), 120 (5), 105 (100), 91 (12), 77 (100), 57 (7), 51 (38)\]

\[\text{HRMS (El) } m/z: \text{Found for C}_{9}\text{H}_{9}\text{OD (M+), 135.0791; Required 135.0794}\]

\textbf{2-[\textsuperscript{3}H]-1-Phenyl-1-propanone}

\[
\begin{center}
\text{Ph} \quad \text{O} \\
\text{D}
\end{center}
\]

n-Butyllithium (1.00 ml, 1.49 mmol, 1.49M in hexanes) was added dropwise to a solution of diisopropylamine (209 \mu l, 1.49 mmol) in THF (10 ml) at -78°C and the mixture stirred for 30 minutes. A solution of 1-phenyl-1-propanone (91) (190 mg, 1.42 mmol) was added dropwise, and the mixture then stirred at -78°C for a further 30 minutes, before dropwise transfer over 10 minutes to a solution of D\textsubscript{2}O (3 ml) in THF (7 ml) at 0°C. Ether (15 ml) was added and the phases separated. The organic phase was dried (MgSO\textsubscript{4}) and the solvent removed under reduced pressure. The residue was short-path distilled to afford the title compound (237)\textsuperscript{134,320,321} (157 mg, 82\%, ca. 60\% deuterium incorporation) as a clear colourless oil.

\[^{1}H\text{-NMR}\] \(\delta_{H}: 7.54-7.41 (5H, m, PhH), 2.98 (1H, qt*, J 7.3 and 2.7, \text{CHDCH}_{3}), 1.21 (3H, dt*, J 7.3 and 1.5, \text{CHDCH}_{3})\)

\[\text{IR (film) } \nu_{\text{max}}: 3063, 2978, 2939, 1966, 1910, 1818, 1688, 1598, 1583, 1450, 1333, 1267, 1221, 1181, 1076, 1002, 952, 746, 724, 691\]

\[\text{LRMS (El) } m/z: 135 (M+, 16\%), 134 (12), 119 (2), 105 (100), 91 (3), 77 (43), 57 (5), 51 (15)\]

\[\text{HRMS (El) } m/z: \text{Found for C}_{9}\text{H}_{9}\text{OD (M+), 135.0796; Required 135.0794}\]
(E)-1,1-Di-[\(^2\)H]-3-phenyl-2-buten-1-ol

A solution of (E)-ethyl-3-phenyl-2-butenoate (113) (597 mg, 3.14 mmol) in ether (5 ml) was added dropwise to a stirred suspension of LiAlH\(_4\) (260 mg, 6.19 mmol) in ether (10 ml) at -7°C. After 2 hours at this temperature, water (2.0 ml) was carefully added dropwise, followed by 2M H\(_2\)SO\(_4\) (15 ml). The organic phase was collected and aqueous phase was extracted with ether (4 x 30 ml). The organic phases were combined, washed with brine (40 ml), dried (Na\(_2\)SO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (SiO\(_2\), 40% ether in petrol) to afford the title compound (238)\(^{307,157,322}\) (440 mg, 2.93 mmol, 93%) as a clear colourless oil; \(R_f\) (60% ether in petrol) 0.51

\(^1\)H-NMR \(\delta_c\): 7.41-7.23 (5H, m, Ph\(\text{H}\)), 5.96 (1H, s, C=CH), 2.07 (3H, s, CH\(_3\)), 1.43 (1H, s, OH)

\(^13\)C-NMR \(\delta_c\): 142.8, 137.9, 128.3, 127.3, 126.3, 125.8, 16.0

IR (film) \(v_{\text{max}}\): 3333 (OH), 3082, 3030, 2984, 2862, 2182 (w), 1948 (w), 1645 (w), 1599 (w), 1576 (w), 1494, 1445, 1380, 1150, 1091 (s), 1038 (w), 1004 (s), 956 (s), 891, 759 (s), 696 (s), 551 (s)

LRMS (EI) m/z: 150 (M\(^+\), 27%), 133 (M\(^+-\)OH, 100%), 92 (PhCH\(_2\)\(^+\), 9%)

HRMS (EI) m/z: Found for C\(_{10}\)H\(_{10}\)D\(_2\)O (M\(^+\)), 150.1010; Required 150.1014

(E)-Methyl-3,7-dimethyl-2,6-octadienoate

Triethylphosphonoacetate (7.50 ml, 46.3 mmol) was added to a stirred suspension of sodium hydride (1.85 g, 60% wt disp. in oil, 46.3 mmol) in THF (50 ml) and DMF (50 ml) at 0°C. After 1 hour, a solution of 6-methyl-4-hepten-2-one (3.00 ml, 23.7 mmol) in THF (20 ml) was added and the mixture stirred at room temperature for 16 hours. The mixture was diluted with ether (80 ml) and washed with NH\(_4\)Cl(aq) (80 ml), water (4 x 80 ml) and brine (60 ml), then dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (SiO\(_2\), 5% ether in petrol) to afford the title compound (240)\(^{323}\) (3.07 g, 2.19 mmol, 71%) as a clear colourless oil; \(R_f\) (5% ether in petrol) 0.24

\(^1\)H-NMR \(\delta_c\): 5.69 (1H, s, C=CHCO\(_2\)), 5.09 (1H, m, Me\(_2\)C=CH\(_2\)), 3.70 (3H, s, CH\(_3\)O), 2.16 (7H, m, CH\(_2\)CH\(_2\)C\(_2\)H\(_5\)), 1.71 (3H, s, CH\(_3\)), 1.63 (3H, s, CH\(_3\))

\(^13\)C-NMR \(\delta_c\): 166.7, 160.5, 132.2, 123.6, 115.8, 50.7, 33.6, 33.5, 26.8, 25.6, 25.3, 17.6
IR (film) \( \nu_{\text{max}} \): 2917, 2857, 2360 (w), 1722 (s, C=O), 1435, 1384, 1357, 1325, 1279, 1224 (s), 1146 (s), 1108, 1061, 1029, 922 (w), 865, 819 (w), 734 (w)

LRMS (El) m/z: 182 (M^+, 3%), 151 (M^-OMe, 6%), 69 (Me_2C=CHCH_2^+, 100)

HRMS (El) m/z: Found for C_{11}H_{18}O_2 (M^+), 182.1300; Required 182.1307

\[ \text{(E)-1,1-Di-[\text{^2}H]-3,7-dimethyl-2,6-octadien-1-ol} \]

A solution of (E)-methyl 3,7-dimethyl-2,6-octadienoate (240) (800 mg, 4.39 mmol) in ether (8 ml) was added dropwise to a stirred suspension of LiAlH_4 (370 mg, 8.81 mmol) in ether (17 ml) at -5°C. After 2 hours at this temperature, water (2.5 ml) was carefully added dropwise, followed by 2M H_2SO_4 (20 ml). The organic phase was collected and aqueous phase was extracted with ether (4 x 40 ml). The organic phases were combined, washed with brine (50 ml), dried (MgSO_4) and the solvent removed under reduced pressure. The residue was chromatographed (SiO_2, 40% ether in petrol) to afford the title compound (239)\(^\text{107,157,322}\) (649 mg, 4.15 mmol, 95%) as a clear colourless oil; \( R_f \) (30% ether in petrol) 0.13

\(^1H\)-NMR \( \delta \): 5.42 (1H, s, C=CHCD_2), 5.10 (1H, m, Me_2C=CH), 2.15-2.10 (4H, m, C=CCH_2CH_2), 1.69 (6H, s, [CH_3]_2C=C), 1.61 (3H, s, CH_3), 1.18 (1H, s, br, OH)

\(^13C\)-NMR \( \delta \): 139.8, 131.8, 129.9, 123.2, 39.5, 26.4, 25.7, 17.7, 16.3

IR (film) \( \nu_{\text{max}} \): 3330 (s, OH), 2968, 2918, 2856, 2196, 2088, 1665, 1446, 1377, 1198 (w), 1138, 1081 (s), 1049, 954 (s), 888, 826

LRMS (El) m/z: 156 (M^+, 2%), 69 (Me_2C=CHCH_2^+, 100)

HRMS (El) m/z: Found for C_{10}H_{18}O_2 (M^+), 156.1490; Required 156.1483

\[ \text{(E)-4,4,4-Tri-[\text{^3}H]-ethyl-3-phenyl-2-butenoate} \]

A solution of triethylphosphonoacetate (2.74 ml, 12.2 mmol) in THF (8 ml) was added to a stirred suspension of sodium hydride (1.85 g, 60% wt disp. in oil, 46.3 mmol) in THF (20 ml) at 0°C. After 1 hour, a solution of 1,1,1 tri-[\text{^3}H]-methylphenyl ketone (990 mg, 8.04 mmol) in THF (8 ml) was added and the mixture stirred at room temperature for 16 hours. The mixture was diluted
with ether (40 ml) and washed with NH₄Cl (40 ml), water (40 ml) and brine (30 ml), then dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 5% ether in petrol) to afford the title compound (253) (1.33 g, 6.87 mmol, 85%; 87% deuterium incorporation) as a clear colourless oil; Rₙ (10% ether in petrol) 0.43

**H-NMR** δ: 7.52-7.38 (5H, m, PhH), 6.16 (1H, s, C=CH), 4.24 (2H, q, J 7.2, OCH₂), 2.61-2.54 (H/D, m, CH/D₃), 1.34 (3H, t, J 7.2, CH₃)

**C-NMR** δC: 165.6 (C=O), 154.9, 142.1, 127.8, 127.6, 127.6, 117.7, 59.6 (CH₂CH₂O), 13.9 (CH₃CH₂O)

**IR** (film) νmax: 3082, 3058, 2981, 2937, 2904, 1713 (s, C=O), 1622 (s, C=C), 1677, 1493, 1446, 1369, 1352, 1270 (s), 1237, 1171 (s), 1102, 1040, 948 (w), 918, 873, 766, 733, 695, 560 (w), 529 (w)

(253)

A solution of (E)-4,4,4-tri-[H]-ethyl-3-phenyl-2-butenoate (253) (805 mg, 4.17 mmol) in ether (5 ml) was added dropwise to a stirred suspension of LiAlH₄ (331 mg, 8.29 mmol) in ether (10 ml) at -5°C. After 2 hours at this temperature, water (2.0 ml) was carefully added dropwise, followed by 2M H₂SO₄ (15 ml). The organic phase was collected and aqueous phase was extracted with ether (4 x 30 ml). The organic phases were combined, washed with brine (40 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 40% ether in petrol) to afford the title compound (252) (569 mg, 3.76 mmol, 90%) as a clear colourless oil; Rₙ (60% ether in petrol) 0.51

**H-NMR** δ: 7.44-7.25 (5H, m, PhH), 6.00 (1H, t, J 6.7, C=CH), 4.38 (2H, m, CH₂OH), 2.07 (H/D, m, CH/D₃), 1.49 (1H, s, OH)

**C-NMR** δC: 142.8, 139.0, 128.3, 127.3, 126.5, 125.8, 60.0 (CH₂OH), 16.0 (weak, CH/D)

**IR** (film) νmax: 3312 (OH), 3084, 3030, 3875, 2239 (w), 2068 (w), 1948 (w), 1751 (w), 1639 (w), 1493 (s), 1445, 1420, 1368, 1272, 1119, 1036 (s), 1013 (s), 914 (w), 860, 806 (w), 750 (s), 696 (s)
(2,2-Bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nicket(II)chloride

A suspension of NiCl₂·6H₂O (500 mg, 2.10 mmol) in thionyl chloride (10 ml) was heated to reflux for 16 hours, during which time the green solid went yellow then brown in colour. The thionyl chloride was carefully removed under reduced pressure and the remaining solid washed with dry THF, removing the solvent using a filter-tipped cannulae. The pale brown anhydrous nickel(II)chloride was stored under vacuum until use.

A mixture of anhydrous nickel(II)chloride (22.0 mg, 170 µmol) and 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (50.0 mg, 170 µmol) in THF (4 ml) was heated to reflux for 30 minutes. The purple coloured solution was cooled to room temperature and filtered using a filter-tipped cannulae. The solvent was removed under reduced pressure to afford the title compound (264) as a purple coloured powder (66.7 mg, 157 µmol, 93%).

IR (film) νmax: 2966 (s), 2365 (w), 1654 (s), 1475, 1391, 1371, 1241, 1136 (s), 981, 953, 754 (w), 602, 546

Ligand Preparation

(4S)-2-(2-fluorophenyl)-4-(1-methylethyl)-1,3-oxazoline

In a 100ml Schlenk flask, zinc chloride (340 mg, 2.49 mmol) was melted under high vacuum, then cooled to room temperature. 2-Fluorocyanobenzene (1.88 ml, 2.10 g, 17.3 mmol), (S)-(−)-2-amino-3-methyl-1-butanol (2.00 ml, 2.15 g, 20.82 mmol) and chlorobenzene (50 ml) were added to the flask and the mixture heated to reflux for 48 hours. The solvent was removed under reduced pressure and the oily residue dissolved in DCM (40 ml). The solution was washed with water (3 x 30 ml) and the combined aqueous washings were extracted with DCM (40 ml).
combined organic phase was dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 5-25% ether in petrol) to afford the title compound (135)\(^{179}\) (1.68 g, 8.10 mmol, 47%) as a clear colourless oil; R$_f$(25% ether in petrol) 0.24; [α]$_D$ -70.4° (c=0.5, CHCl$_3$); Lit: [α]$_D$ -62°, c=0.5, CHCl$_3$)

$^1$H-NMR δH: 7.89-7.10 (4H, m, PhH), 4.39 (1H, m, OCH$_2$CHN), 4.15 (2H, m, OCH$_2$CHN), 1.90 (1H, m, CH(CH$_3$)$_2$), 1.05 (3H, d, J 6.7, CH$_3$), 0.95 (3H, d, J 6.7, CH$_3$)

$^{13}$C-NMR δC: 162.3 (C=N), 132.7, 132.6, 131.1, 131.0, 123.9, 123.8, 116.6, 116.4 (Ph, with C-F coupling), 72.6 (CH$_2$O), 69.7 (CHN), 32.6 (CHMe$_2$), 18.8, 17.9 (CH$_3$)

IR (film) ν$_{max}$: 3005, 1651 (C=N), 1497, 1358, 1196, 1112, 1061, 1030, 965

LRMS (FAB) m/z: 208 (72%, [M+H$^+$]), 164 (25), 123 (100), 41 (53), 122 (29), 39 (43)

(4S)-2-(2-Diphenylphosphinophenyl)-4-(1-methylethyl)-1,3-oxazoline

A solution of (4S)-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazoline (135) (300 mg, 1.45 mmol) in THF (3 ml) was added dropwise to a refluxing solution of potassium diphenylphosphide (2.90 ml, 1.45 mmol, 0.5M in THF). After 2 hours the mixture was transferred via cannulae into a separating funnel and partitioned between DCM (20 ml) and water (20 ml). The organic phase was removed, dried (MgSO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 5-25% ether in petrol) to afford the title compound (268 mg, 0.72 mmol, 50%) as a clear colourless oil, which slowly solidified (129)\(^{179}\) (m.p. 87-89°C; lit. 84-86°C); R$_f$(25% ether in petrol) 0.36; [α]$_D$ -37.7° (c=0.55, CHCl$_3$); Lit. [α]$_D$ -40°, c=0.50, CHCl$_3$)

$^1$H-NMR δH: 7.91-7.87 (1H, m, PhH), 7.24-7.35 (12H, m, PhH), 6.84-6.87 (1H, m, PhH), 4.10-4.15 (1H, m, CHN), 3.80-3.88 (2H, m, CH$_2$O), 1.45-1.50 (1H, m, CHMe$_2$), 0.81 (3H, d, J 6.7, CH$_3$), 0.69 (3H, d, J 6.7, CH$_3$)

$^{13}$C-NMR δC: 162.9 (C=N), 127.9, 128.2, 128.3, 128.4, 128.5, 129.8, 130.3, 131.8, 132.0, 133.6, 133.7, 134.2, 134.4, 138.0, 138.2, 138.3, 138.7, 73.1 (CHN), 70.0 (CH$_2$O), 32.7, 18.9, 18.3

IR (film) ν$_{max}$: 2963, 1732, 1652 (C=N), 1478, 1434, 1352, 1090, 1047, 964

LRMS (FAB) m/z: 374 (M$^+$+H, 86%), 330 (36), 302 (100), 296 (49), 288 (41), 282 (74), 240 (20), 183 (31)
(4S,5S)-2-(2-Fluorophenyl)-4-(hydroxymethyl)-5-phenyl-1,3-oxazoline

Method 1
Dry HCl gas was bubbled through a stirred solution of 2-fluorobenzonitrile (2.00 ml, 18.4 mmol) and methanol (1.50 ml, 37.0 mmol) in dioxan (20 ml) for 2 hours. The solvent was removed under reduced pressure and the residue triturated with dry ether to afford a white powdery solid of the imino ester hydrochloride (136) (1.04 g, 5.51 mmol, 30%). Elemental analysis (CHN): Found C 50.39%, H 4.75%, N 7.28%; Required C 50.67%, H 4.78%, N 7.38%. A mixture of imino ester hydrochloride (136) (170 mg, 897 pmol) and (1S, 2S)-2-amino-1-phenyl-1,3-propandiol (150 mg, 897 µmol) in DCM (5 ml) was rapidly stirred for 48 hours, or until completion of the reaction. The solvent was removed under reduced pressure, the residue dissolved in EtOAc and passed through a plug of silica, washing the silica through with EtOAc. The solvent was removed under reduced pressure to afford the title compound as a clear, colourless viscous oil (137) (200 mg, 740 µmol, 82%), which was used without further purification.

Method 2
Zinc chloride (250 mg, 1.83 mmol) was melted under high vacuum and then cooled to ambient temperatures. 2-Fluorocyanobenzene (1.00 ml, 9.21 mmol), (1S, 2S)-2-amino-1-phenyl-1,3-propandiol (1.47 g, 8.79 mmol) and chlorobenzene (50 ml) were added and the mixture then heated to reflux for 48 hours using apparatus fitted with water separator. The solvent was removed under reduced pressure and the residue chromatographed (SiO₂, 50% ethyl acetate in petrol) to afford the title compound (585 mg, 2.16 mmol, 25%) as a clear, colourless, viscous oil (137); IR (film) ν max: 3630 (s, OH), 3030, 2926, 1647 (C=N), 1228, 1222, 1020

¹H-NMR δ H: 7.95-7.91 (1H, m, PhH), 7.51-7.14 (8H, m, PhH), 5.53 (1H, d, J 7.8, PhCH CH₂OH), 4.32 (1H, dt, J 7.8 and 3.8, PhCH CH₂OH), 4.11 (1H, dd, J 11.7 and 3.8, PhOHCHCHHOH), 3.81 (1H, dd, J 11.7 and 3.8, PhOHCHCHAOH), 2.62 (1H, br s, PhCH CH₂OH)

¹³C-NMR δ c: 162.6, 160.0, 140.3, 133.3, 131.2, 128.9, 128.4, 125.7, 124.0, 116.8, 116.6, 82.4, 76.7, 63.7

IR (film) ν max: 3630 (s, OH), 3030, 2926, 1647 (C=N), 1228, 1222, 1020

LRMS (EI) m/z: 272 (M⁺+H, 31%), 168 (74), 140 (100), 123 (41)

HRMS (EI) m/z: Found for C₁₉H₁₉NO₅F (M⁺+H), 272.1080; Required 272.1087
(4S,5S)-2-(2-Fluorophenyl)-4-(methoxymethyl)-5-phenyl-1,3-oxazoline

A solution of (4S, 5S) 2-(2-Fluorophenyl)-4-(hydroxymethyl)-5-phenyl-1,3-oxazoline (137) (191 mg, 704 µmol) in THF (10 ml) was added dropwise to a stirred suspension of sodium hydride (86.0 mg, 60% wt disp. in oil, 2.15 mmol) in DMF (5 ml) at 0°C. After 45 minutes, methyl iodide (2 ml) was added. The mixture was stirred at room temperature for 3 hours, then added to water (10 ml). The layers were separated and the aqueous phase was extracted with ether (3 x 10 ml). The organic phases were combined, washed with brine (20 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 10-25% ether in petrol) to afford the title compound (138) (190 mg, 666 µmol, 95%) as a clear colourless oil; Rᵢ (25% ether in petrol) 0.16.

**¹H-NMR** δ: 7.98-7.93 (1H, m, PhH), 7.49-7.13 (8H, m, PhH), 5.49 (1H, d, J 6.7, PhCHCH₂OCH₃), 4.35 (1H, ddd, J 6.7, 6.6 and 4.2, PhCHCH₂OCH₃), 3.75 (1H, dd, J 9.7 and 4.2, PhCHCH₂OCH₃), 3.63 (1H, dd, J 9.7 and 6.6, PhCHCH₂OCH₃), 3.43 (3H, s, PhCHCH₂OCH₃)

**¹³C-NMR** δ: 162.6 (C=N), 160.0, 140.7, 133.1, 131.3, 128.7, 128.1, 125.5, 123.9, 116.8, 116.6, 83.2, 75.1, 74.2, 59.4

**LRMS (FAB) m/z:** 286 (M⁺H, 65%), 149 (79%), 123 (100)

**HRMS (El) m/z:** Found for C₁₇H₁₇NO₂F (M⁺H), 286.1250; Required 286.1243

(4S,5S)-2-(2-Diphenylphosphinophenyl)-4-(methoxymethyl)-5-phenyl-1,3-oxazoline

A solution of (4S, 5S) 2-(2-Fluorophenyl)-4-(methoxymethyl)-5-phenyl-1,3-oxazoline (138) (54.0 mg, 189 µmol) in THF (2 ml) was added dropwise to a refluxing solution of potassium diphenylphosphide (380 µl, 190 µmol, 0.5M in THF) in THF (3 ml). After 1 hour, the mixture was
partitioned between DCM (10 ml) and water (10 ml). The phases were separated and the aqueous phase extracted with DCM (10 ml). The combined organic phases were washed with brine (10 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 20% ethyl acetate in petrol) to afford the title compound (133) as a pale yellow oil; Rf(25% ethyl acetate in petrol) 0.31

\[ ^{1}H-NMR \delta_{H}: 8.03-7.17 (19H, m, PhH), 5.19 (1H, d, J 7, PhCHCH₂OCH₃), 4.21 (1H, m, PhCHCH₂OCH₃), 3.43 (1H, dd, J 9.5 and 4.6, PhCHCH₂HOCH₃), 3.27 (3H, s, PhCHCH₂OCH₃), 2.95 (1H, d, J 9.5 and 8.1, PhCHCH₂HOCH₃) \]

\[ ^{13}C-NMR \delta_{C}: 163.6 (C=N), 140.6, 138.1, 134.7, 134.4, 134.0, 133.8, 130.7, 130.2, 128.8, 128.6, 128.6, 128.5, 128.4, 128.0, 125.8, 83.8, 74.7, 74.2, 59.1 \]

IR (film) \( \nu_{max}: 3059, 2929 (s), 2252 (s), 1718, 1652 (s, C=N), 1603, 1471, 1435, 1381 (w), 1318, 1193, 1133, 1093, 1039, 962 \)

LRMS (FAB) m/z: 452 (M⁺+H, 12%), 396 (7), 305 (100), 149 (77)

HRMS (FAB) m/z: Found for C₂₉H₂₇NPO₂ (M⁺+H), 451.1760; Required 451.1779

2,2-Bis-[(4S)-4-isopropyl-1,3-oxazoline-2-yl]-propane

\[ (127) \]

In a 100 ml Schlenk flask, zinc chloride (45 mg, 0.33 mmol) was melted under high vacuum, then cooled to room temperature. 2,2-Dimethylmalonitrile (188 mg, 2.00 mmol), (S)-(+)2-amino-3-methyl-1-butanol (560 µl, 515 mg, 5.00 mmol) and chlorobenzene (10 ml) were added to the flask and the mixture heated to reflux for 48 hours. The solvent was removed under reduced pressure and the oily residue dissolved in DCM (10 ml). The solution was washed with water (3 x 10 ml) and the combined aqueous washings were extracted with DCM (15 ml). The combined organic phase was dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was filtered through a pad of silica and chromatographed (HPLC; Mobile phase: EIOAc, eluting at 3.8-4.0ml/min⁻¹) to afford the title compound (127) as an oil (containing an inseparable impurity).

\[ ^{1}H-NMR \delta_{H}: 4.18-4.23 (2H, m, 2 x OCH₂CH₃), 3.94-4.02 (4H, m, 2 x OCH₂CH₃), 1.79-1.84 (2H, m, CH(CH₃)₂), 1.52 (6H, s, 2 x C(CH₃)₂), 0.92 (6H, d, J 6.8, 2 x CH₃), 0.85 (6H, d, J 6.8, 2 x CH₃) \]

\[ ^{13}C-NMR \delta_{C}: 168.8 (C=N), 71.6, 70.0, 38.6, 32.2, 24.5, 18.6, 17.4 \]
D-Glucose (2.00 g, 11.1 mmol) was added in one portion to a solution of iodine (600 mg, 2.36 mmol) in acetone (100 ml), and the mixture stirred at room temperature for 48 hours, then added to a saturated sodium thiosulfate solution (50 ml). The acetone was removed under reduced pressure, and then the aqueous phase extracted with DCM (2 x 50 ml). The organic phases were combined, then washed with water (50 ml), brine (50 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 25% ether in petrol) to afford the title compound (151) as a white needles (m.p. 107-109°C; lit.: 109-110°C); Rₚ (25% ether in petrol) 0.29

**¹H-NMR** δH: 5.96 (1H, d, J 3.7, C(1)-H), 4.55 (1H, d, J 3.7, C(2)-H), 4.38-4.32 (2H, m, C(4,5)-H), 4.18 (1H, dd, J 8.6 and 6.2, C(6)-H), 4.08 (1H, dd, J 7.6 and 2.8, C(3)-H), 3.99 (1H, dd, J 8.6 and 5.4, C(6)-H), 2.50 (1H, m, OH), 1.51, 1.45, 1.37, 1.33 (12H, 4 x s, 4 x CH₃)

**¹³C-NMR** δC: 109.5, 108.7, 96.3, 71.6, 70.7, 68.0, 62.4, 26.0, 25.9, 24.9, 24.3, 15.3

**IR** (film) νmax: 3598 (s, OH), 2990, 2932, 2896, 1379, 1268, 1217, 1164, 1075, 1020, 847

**LRMS** (FAB) m/z: 267 (M⁺+H, 100%), 69 (30), 41 (33)

**1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose**

![Structural formula](image)
1,2:5,6-Di-O-isopropylidene-3-O-diphenylphosphino-α-D-glucofuranose

A mixture of 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (151) (500 mg, 1.92 mmol) and triethylamine (15 ml) was stirred for 10 minutes. Chlorodiphenylphosphine (350 µl, 1.95 mmol) was then added dropwise, and slurry then stirred for 48 hours. The mixture was filtered through a pad of celite, then the pad rinsed through with triethylamine. The solvent was then removed under reduced pressure and the residue chromatographed (SiO_2, 30% ethyl acetate in petrol) to afford the title compound (144)^25 (6.45 g, 1.45 mmol, 76%) as a clear, colourless, viscous oil; R_f (50% ethyl acetate in petrol) 0.72.

\[ ^1H-NMR \delta: 7.50-7.29 (10H, m, PhH), 5.85 (1H, d, J 3.4, C(1)-H), 4.55 (1H, dd, J 3.4 and 1.2, C(2)-H), 4.50 (1H, dd, J 9.4 and 2.8, C(3)-H), 4.26 (1H, ddd, J 8.1, 6.1 and 6.0, C(5)-H), 4.13 (1H, ddd, J 8.1, 2.8 and 1.2, C(4)-H), 4.04 (1H, dd, J 8.4 and 6.1, C(6)-H), 3.94 (1H, d, J 8.4 and 6.0, C(6)-H), 1.47, 1.38, 1.24 and 1.22 (12H, 4 x s, 4 x CH_3) \]

\[ ^13C-NMR \delta: 130.8, 130.6, 130.3, 130.1, 129.6, 128.5, 128.4, 128.2, 112.1, 109.1, 105.2, 83.9, 82.3, 81.9, 72.3, 67.6, 26.9, 26.7, 26.3, 25.1 \]

\[ IR (film) \nu_{max}: 3055, 2986 (s), 2933, 1481 (s), 1481 (w), 1435 (P-Ph), 1368, 1251, 1216, 1164, 1074 (s), 1026 (s, P-O), 954, 841, 698 \]

\[ LRMS (FAB) m/z: 445 (M^++H, 42%), 403 (26), 345 (15), 285 (1), 219 (100), 203 (45), 201 (44) \]

\[ HRMS (FAB) m/z: \text{Found for } C_{24}H_{30}O_6P (M^++H), 445.1770; \text{Required } 445.1780 \]

1-(6-Bromopyridin-2-yl)-ethanone

\[ n\text{-Butyllithium (6.55 ml, 10.5 mmol, 1.60M in hexanes) was added dropwise to a stirred suspension of 2,6-dibromopyridine (2.50 g, 10.6 mmol) in ether (35 ml) at -78°C. After 30 minutes at this temperature, a solution of N,N-dimethylacetamide (1.08 ml, 11.6 mmol) in ether (10 ml) was added dropwise and the mixture stirred for 90 minutes. After warming the solution to room temperature and stirring for 1 hour, 1M HCl (18 ml) was added dropwise, and the phases} \]
then separated. The aqueous phase was extracted with ether (3 x 40 ml), then the organic phases combined, washed with brine (30 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was recrystallised from ether at 0°C to afford the title compound (1.35 g, 6.73 mmol, 64%) as pale yellow prisms (152)\textsuperscript{214} (m.p. 53-54°C); $R_t$ (25% ether in petrol) 0.50

$^1$H-NMR $\delta$: 7.99 (1H, dd, $J$ 7.2 and 1.4, pyH), 7.72-7.65 (2H, m, pyH), 2.71 (3H, s, CH$_3$)

$^{13}$C-NMR $\delta$: 198.5, 154.3, 141.4, 139.2, 131.8, 120.5, 25.8

IR (film) $\nu_{max}$: 3044, 2003, 1695 (s, C=O), 1572, 1552, 1430, 1396, 1362, 1306, 1239, 1160, 1127, 1074, 988, 961, 807, 729, 654

LRMS (FAB) m/z: 174 (28%), 146 (6), 110 (11), 91 (21), 78 (C$_5$H$_4$N$^+$, 4%), 66 (100)

HRMS (FAB) m/z: Found for C$_7$H$_6$NOBr$^+$ (M$^+$), 198.9640; Required 198.9633

\[ \text{(6-Bromopyridin-2-yl) phenyl ketone} \]

\[ \text{(153)} \]

$n$-BuLi (2.75 ml, 4.25 mmol, 1.55M in hexanes) was added dropwise to a stirred suspension of 2,6-dibromopyridine (1.00 g, 4.22 mmol) in ether (18 ml) at -78°C. After 30 minutes at this temperature, neat benzonitrile (520 $\mu$l, 5.09 mmol) was added dropwise and the mixture stirred for 2 hours. After warming the solution to room temperature, 2M H$_2$SO$_4$ (10 ml) was added dropwise, and the mixture heated to reflux for 2 hours. After cooling to room temperature, the phases were separated and the aqueous phase was extracted with ether (3 x 15 ml). The organic phases were then combined, washed with saturated Na$_2$CO$_3$ solution (30 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 5% ether in petrol), then recrystallised from ether/petrol to afford the title compound (153)$^{214}$ (963 mg, 3.67 mmol, 87%) as clear, colourless prisms (m.p. 64-66°C); $R_t$ (10% ether in petrol) 0.21

$^1$H-NMR $\delta$: 8.11-8.07 (2H, m, aromatic), 7.96 (1H, dd, $J$ 17.4 and 2.3, aromatic), 7.76-7.72 (1H, m, aromatic), 7.67-7.64 (1H, m, aromatic), 7.61-7.57 (1H, m, aromatic), 7.50-7.45 (2H, m, aromatic)

$^{13}$C-NMR $\delta$: 191.6, 155.7, 140.7, 139.3, 135.4, 133.3, 131.1, 130.8, 128.2, 123.4

IR (film) $\nu_{max}$: 3063, 2959, 1667 (s, C=O), 1598, 1573, 1556 (s), 1450, 1431, 1396, 1320, 1302, 1243, 1168, 1156, 1124, 1079, 1028, 1101, 988, 948, 916, 891, 823, 786, 765, 688, 636

LRMS (El) m/z: 262 (M$^+$+H, 100%), 184 (16), 154 (48), 136 (49), 105 ([PHCHO]$^+$, 50)
n-Butyllithium (4.35 ml, 4.66 mmol, 1.07M in hexanes) was added dropwise to a stirred suspension of 2,6-dibromopyridine (1.00 g, 4.22 mmol) in ether (18 ml) at -78°C. After 30 minutes at this temperature, neat pivalonitrile (560 μl, 5.07 mmol) was added dropwise and the mixture stirred for 2 hours. After warming the solution to room temperature, 2M H₂SO₄ (10 ml) was added dropwise, and the mixture heated to reflux for 2 hours. After cooling to room temperature, the phases were separated and the aqueous phase was extracted with ether (3 x 15 ml). The organic phases were then combined, washed with saturated Na₂CO₃ solution (30 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 4% ether in petrol) to afford the title compound (156) as clear, colourless prisms; Rf (4% ether in petrol) 0.14.

¹H-NMR δH: 7.89-7.58 (3H, m, pyH), 1.43 (9H, s, 'Bu)

¹³C-NMR δC: 204.9, 154.7, 139.7, 139.0, 130.5, 122.5, 44.3, 27.4

IR (film) νmax: 2970, 1688 (s, C =O), 1555, 1480, 1427, 1405, 1297, 1204, 1153, 1122, 1038, 972, 817, 753

LRMS (FAB) m/z: 243 (M⁺+H, 24%), 242 (M⁺, 100%), 226 (12), 186 (M⁺+H⁻Bu, 4%), 157 (M⁺+H⁻CO'Bu, 7%), 133 (25), 57 (‘Bu⁺, 83%)

HRMS (FAB) m/z: Found for C₁₀H₁₃NOBr⁺⁺ (M⁺+H), 242.0170; Required 242.0181

(1R)-1-(6-Bromopyridin-2-yl)-ethanol

(+)-DIP-Chloride (394 mg, 1.23 mmol) was added in one portion to a solution of 1-(6-Bromopyridin-2-yl)-ethanone (152) (199 mg, 996 μmol) in THF (1.5 ml) at -20°C. The solution was slowly warmed to room temperature (over 3 hours) then stirred for a further 3 hours. The mixture was diluted with ether (2 ml) and diethanolamine (325 mg, 3.09 mmol) was added in one portion. After stirring for 3 hours, the mixture was filtered through a pad of celite, then the pad
rinsed through with ether. The ether solution was dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 20% ethyl acetate in petrol) to afford the title compound (154)²¹⁴ (190 mg, 940 μmol, 94%) as a clear colourless oil; Rf (25% ethyl acetate in petrol) 0.14

¹H-NMR δH: 7.56 (1H, m, pyH), 7.39 (1H, m, pyH), 7.29 (1H, m, pyH), 4.88 (1H, qd, J 6.6 and 5.1, CH(OH)CH₃), 3.43 (1H, d, J 5.1, CH(OH)CH₃), 1.51 (3H, d, J 6.6, CH(OH)CH₃)

¹³C-NMR δc: 165.2, 141.2, 139.2, 126.6, 118.5, 69.1, 24.1

IR (film) νmax: 3378 (s, OH), 2975, 2929, 2360 (s), 1702 (w), 1583, 1556, 1433, 1407, 1318 (w), 1157, 1131, 1075, 1020, 986, 909 (w), 794, 741, 675

LRMS (FAB) m/z: 202 (M⁺, 4%), 186 (M⁺-O, 100%), 174 (6), 167 (16), 158 (26), 149 (47), 121 (5), 106 (26), 104 (24), 91 (11), 83 (11)

HRMS (FAB) m/z: Found for C₁₂H₁₅NOBr⁷⁹ (M⁺-CH₃), 185.9560; Required 185.9554

(R)-1-(6-Bromopyridin-2-yl)-1-phenylmethanol

(+)-DIP-Chloride (305 mg, 949 μmol) was added in one portion to a solution of (6-Bromopyridin-2-yl) phenyl ketone (153) (200 mg, 765 μmol) in THF (1.5 ml) at -20°C. The solution was slowly warmed to room temperature (over 3 hours) then stirred for a further 3 days. The mixture was diluted with ether (2 ml) and diethanolamine (325 mg, 3.09 mmol) was added in one portion. After stirring for 3 hours, the mixture was filtered through a pad of celite, then the pad rinsed through with ether. The ether solution was dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 15% ethyl acetate in petrol) to afford the title compound (157)²¹⁴ (131 mg, 496 μmol, 65%) as a white crystalline powder; Rf (15% ethyl acetate in petrol) 0.17

¹H-NMR δH: 7.51-7.12 (8H, m, aromatic), 5.76 (1H, s, CH(OH)Ph), 4.46 (1H, s, CH(OH)Ph)

¹³C-NMR δc: 163.0, 142.2, 140.9, 139.2, 128.7, 128.1, 127.0, 126.8, 120.1, 75.0

IR (film) νmax: 3606, 3447 (s, OH), 3067, 2927, 1583, 1557, 1494, 1436, 1407, 1194, 1161, 1126, 1077, 1050, 1028, 991, 908, 783, 750

LRMS (FAB) m/z: 264 (M⁺+H, 20%), 246 (M⁺-OH, 16), 219 (11), 167 (23), 149 (100), 113 (21)

HRMS (FAB) m/z: Found for C₁₂H₁₄NOBr⁹³ (M⁺+H), 264.0030; Required 264.0024
(+) Menthylchloroformate (35.0 µl, 163 µmol) was added in one portion to a solution of 2-(1-hydroxyethyl)-6-bromopyridine (154) (32.0 mg, 158 µmol) and pyridine (100 µl, 1.24 mmol) in DCM (1 ml). The solution was stirred for 2 hours at room temperature then added to water (1 ml). The aqueous phase was extracted with ether (2 ml), then the organic phases combined, washed with brine (2 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 10% ethyl acetate in petrol) to afford the title compound (155) [(+)-Menthyl-1-(6-bromopyridin-2-yl)-1-methoxyethane] (59.2 mg, 154 µmol, 97%) as a clear colourless oil; R₇ (10% ethyl acetate in petrol) 0.12.

**¹H-NMR** δ: 7.58-7.31 (3H, m, pyH), 5.72 (1H, q, J 6.3, CHCHOCO₂CH₃), 4.51 (1H, m, CH₃CHOCO₂CH₃), 2.13-0.79 (9H, m, 3 x OH and 3 x CH₂), 1.63 (3H, d, J 6.3, CH₃CH₂CO₂), 0.93 (3H, d, J 6.7, CH₃), 0.91 (3H, d, J 6.7, CH₃), 0.74 (3H, d, J 6.7, CH₃)

**¹³C-NMR** δ: 162.1, 154.1, 141.5, 139.1, 127.1, 118.3, 78.8, 75.7, 47.0, 40.7, 34.1, 31.4, 26.2, 23.4, 22.0, 21.0, 20.7, 16.3

**IR** (film) νₚₚ: 2960, 2929, 2872, 2252 (w), 2241 (w), 1736 (s, C=O), 1585, 1559, 1456, 1435, 1409, 1369, 1337, 1312, 1286, 1262 (s), 1182, 1159, 1132, 1079, 1064, 1039, 1009, 981, 956, 814 (w), 793

**LRMS** (FAB) m/z: 386 (46%), 384 (M⁺+H, 49%), 248 (94), 246 (100%), 186 (63), 184 (63)

**HRMS** (FAB) m/z: Found for C₁₉H₂₇NO₃Br⁺ (M⁺+H), 384.1160; Required 384.1174

(1R)-1-(6-Bromopyridin-2-yl)-1-methoxyethane

A solution of (1R)-1-(6-Bromopyridin-2-yl)-ethanol (154) (100 mg, 497 µmol) in THF (2 ml) was added dropwise to a stirred suspension of sodium hydride (24 mg, 60% wt disp. in oil, 600 µmol) in THF (1 ml) at 0°C. After 45 minutes, methyl iodide (80.0 µl, 1.29 mmol) was added. The mixture was stirred at room temperature for 2 hours, then added to water (2 ml). The layers were separated and the aqueous phase was extracted with ether (3 x 3 ml). The organic phases combined, washed with brine (4 ml), dried (Na₂SO₄) and the solvent removed under reduced
pressure. The residue was chromatographed (SiO₂, ether) to afford the title compound (158) (105 mg, 484 µmol, 97%) as a clear colourless oil; Rᵣ (10% ethyl acetate in petrol) 0.25

\(^1\)H-NMR δ: 7.59-7.27 (3H, m, pyH), 4.40 (1H, q, J 6.6, CH\(\text{OCH}_3\)CH₃), 3.32 (3H, s, CH\(\text{OCH}_3\)CH₃), 1.45 (3H, d, J 6.6, CH\(\text{OCH}_3\)CH₃)

\(^1^3\)C-NMR δ: 165.2, 141.3, 139.2, 126.6, 118.5, 80.3, 57.1, 22.4

IR (film) vₘₐₓ: 2980, 2930, 2823, 2361 (w), 1712 (w), 1581, 1556, 1432, 1406, 1367, 1332, 1261 (w), 1202, 1155, 1122 (s), 1058, 988, 872 (w), 797, 741, 678

LRMS (FAB) m/z: 202 (M⁺-CH₂, 15%), 187 (M⁺-CH₂CH₃, 97%), 185 (100%), 174 (9), 158 (8), 149 (13), 104 (18), 91 (8), 78 (26), 66 (34), 59 (42)

HRMS (FAB) m/z: Found for C₁₃H₁₂BrNO (M⁺), 278.1090; Required 278.1081

(R)-1-(6-Bromopyridin-2-yl)-1-phenyl-1-methoxymethane

A solution of (R)-1-(6-Bromopyridin-2-yl)-1-phenylmethanol (157) (120 mg, 454 µmol) in THF (3 ml) was added dropwise to a stirred suspension of sodium hydride (23 mg, 60% wt disp. in oil, 575 µmol) in THF (2 ml) at 0°C. After 45 minutes, methyl iodide (70.0 µl, 1.12 mmol) was added. The mixture was stirred at room temperature for 2 hours, then added to water (2 ml). The layers were separated and the aqueous phase was extracted with ether (3 x 3 ml). The organic phases combined, washed with brine (4 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, ether) to afford the title compound (159) (124 mg, 446 µmol, 98%) as a clear colourless oil; Rᵣ (15% ethyl acetate in petrol) 0.34

\(^1\)H-NMR δ: 7.56-7.21 (8H, m, aromatic), 5.36 (1H, s, CH\(\text{OCH}_3\)), 3.43 (3H, s, CH₃O)

\(^1^3\)C-NMR δ: 165.3, 141.2, 140.2, 139.2, 128.5, 127.9, 126.8, 126.7, 119.3, 85.8, 57.3

IR (film) vₘₐₓ: 3032 (w), 2993 (w), 2934, 2828, 2249 (w), 1581 (s), 1557 (s), 1494 (w), 1454, 1434, 1406, 1315 (w), 1196, 1153, 1123, 1098, 1030, 988, 922 (s), 788

LRMS (FAB) m/z: 278 (M⁺, 75%), 248 (M⁺-CH₂O, 100%), 219 (32), 202 (22), 167 (37), 149 (30)

HRMS (FAB) m/z: Found for C₁₃H₁₂NOBr (M⁺), 278.1090; Required 278.1081
(1R)-1-(Pyridin-2-yl)-1-ethanol

\[ \text{(160)} \]

A solution of 1-(6-Bromopyridin-2-yl)-ethanone (152) (56.6 mg, 280 µmol) and AIBN (15.3 mg, 93.2 µmol) in toluene (10 ml) was purged with nitrogen for 15 minutes. Neat tributyltinhydride (150 µl, 558 µmol) was added, and the mixture then heated to 100°C for 4 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was dissolved in chloroform (3 ml) and treated with iodine (ca. 75 mg, 295 µmol), and allowed to stir for 45 minutes. The solvent was removed under reduced pressure and the residue stirred in ethyl acetate (3 ml) and 1M aqueous KF for 2 hours. The phases were separated and the aqueous phase extracted with ethyl acetate (3 x 3 ml). The organic phases were combined, washed with brine (30 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (SiO$_2$, 50% ethyl acetate in petrol) to afford the title compound (160) (26.2 mg, 213 µmol, 76%) as a clear, pale yellow oil, contaminated by tin residues; R$_f$(50% ethyl acetate in petrol) 0.14

$^1$H-NMR $\delta$: 8.51 (1H, m, pyH), 7.69-7.75 (1H, m, pyH), 7.26-7.24 (1H, m, pyH), 7.19-7.16 (1H, m, pyH), 4.87 (1H, q, J 6.5, CHOH), 4.26 (1H, brs, OH), 1.48 (3H, d, J 6.5, CH$_3$)

$^{13}$C-NMR $\delta$: 162.9, 128.1, 136.7, 122.2, 119.8, 68.8, 24.2

(R,R)-6,6'-Bis(1-methoxyethyl)-2,2'-bipyridine

\[ \text{(145)} \]

Triphenylphosphine (600 mg, 2.29 mmol), followed by zinc powder (40.6 mg, 621 µmol) was added to a solution of nickel chloride hexahydrate (136 mg, 572 µmol) in degassed DMF (3 ml) at 80°C. The mixture was stirred that temperature for 1 hour. A solution of (1R)-1-(6-Bromopyridin-2-yl)-1-methoxyethane (158) (100 mg, 463 µmol) in degassed DMF (1 ml) was added and the mixture heated at 80°C for 3.5 hours. An aqueous solution of ammonia (5%, 4 ml) was added and the mixture filtered through a pad of celite, then the pad rinsed through with water and DCM. The phases were separated and the aqueous phases extracted with 1 : 2 mixture of ether: DCM (3 x 5 ml). The organic phases were combined, washed with brine (10 ml), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The residue was
chromatographed (SiO₂, 5-50% ethyl acetate in petrol) to afford the title compound (145) (42.3 mg, 155 μmol, 67%) as a pale cream crystalline solid; Rᵥ (10% ethyl acetate in petrol) 0.10

1H-NMR δ: 8.32 (2H, d, J 7.8, pyH), 7.81 (2H, t, J 7.8, pyH), 7.42 (2H, t, J 6.5, 2 x CHCH₃), 4.51 (2H, q, J 6.5, 2 x CHCH₃), 3.34 (6H, s, 2 x OCH₃), 1.51 (6H, d, J 6.5, 2 x CHCH₃)

13C-NMR δ: 162.5, 155.5, 137.5, 119.7, 119.6, 80.9, 56.9, 22.3

IR (film) νmax: 3064, 2983, 2933, 2826, 2248, 1718 (w), 1579, 1572, 1436, 1396, 1371, 1331 (w), 1306, 1235 (w), 1207, 1150 (w), 1116 (s), 1080, 1059, 998, 920 (s), 868 (w), 807, 784 (w)

LRMS (FAB) m/z: 242 (M⁺-CH₃, 81%), 209 (56), 183 (16), 174 (10), 167 (32), 149 (100), 128 (22), 105 (25), 91 (25)

HRMS (FAB) m/z: Found for C₁₅H₁₇N₂O₂ (M⁺-CH₃), 275.1280; Required 275.1290

(R,R)-6,6′-Bis(1-methoxy-1-phenylethyl)-2,2′-bipyridine

Triphenylphosphine (393 mg, 1.50 mmol), followed by zinc powder (27.0 mg, 413 μmol) was added to a solution of nickel chloride hexahydrate (89.0 mg, 374 μmol) in degassed DMF (3 ml) at 80°C. The mixture was stirred at that temperature for 1 hour. A solution of (R)-1-(6-Bromopyridin-2-yl)-1-phenyl-1-methoxymethane (159) (84.3 mg, 303 μmol) in degassed DMF (1 ml) was added and the mixture heated at 80°C for 3.5 hours. An aqueous solution of ammonia (5%, 4 ml) was added and the mixture filtered through a pad of celite, then the pad rinsed through with water and DCM. The phases were separated and the aqueous phases extracted with 1 : 2 mixture of ether : DCM (3 x 10 ml). The organic phases were combined, washed with brine (10 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 15-20% ethyl acetate in petrol) to afford the title compound (146) (17.9 mg, 45.1 μmol, 30%) as a yellow oil (containing an inseparable impurity); Rᵥ (15% ethyl acetate in petrol) 0.08

1H-NMR δ: 8.52 (2H, d, J 4.3, aromatic), 7.68-7.12 (14H, m, aromatic), 5.36 (2H, s, 2 x CHOCH₃), 3.41 (6H, s, 2 x CHOCH₃)

13C-NMR δ: 161.5, 149.0, 136.8, 130.9, 128.5, 127.7, 126.9, 122.4, 120.5, 86.5, 57.2
Isomerisations using \( \text{NiCl}_2(\text{DIPHOS})/\text{PrMgCl} \)

Isomerisation of 1,4-dimethoxybut-2-ene (89)

\[
\text{MeO} - \text{CH=CHMe} - \text{OMe} \quad \rightarrow \quad \text{MeO} - \text{CH=CHMe} - \text{OMe} + \text{MeO} - \text{CH=CHMe} - \text{OMe}
\]

A solution of isopropyl magnesium chloride (10.0 \( \text{µL}, 20.0 \text{µmol}, 2\text{M in THF} \)) was added dropwise to a mixture of \( \text{NiCl}_2(\text{DIPHOS}) \) (5.00 mg, 9.50 \( \text{µmol} \)) and 1,4-dimethoxybut-2-ene (89) (54.0 mg, 473 \( \text{µmol} \)) in THF (1 ml) at 0°C. After warming to ambient temperatures the mixture was quenched with saturated \( \text{NH}_4\text{Cl} \) solution and extracted with ether. The extracts were combined and the solvent removed under reduced pressure. Analysis of the isolated residue by \( ^1\text{H-NMR} \) revealed starting material (4%) and a mixture of (\( Z \)) and (\( E \))-1,4-dimethoxybut-1-ene, (275) and (276) \( ^{303} \) respectively (96%; 3.6 : 1); \( R_f \) (50% ether in petrol) 0.52

\( ^1\text{H-NMR} \ \delta \text{H}: \)

(275) 5.94 (1H, d, \( J 6.2, \text{C=CHMe} \)), 4.36 (1H, dt, \( J 6.2 \) and 6.1, \( \text{C=CHCH}_2 \)), 3.58 (3H, s, \( \text{CH}_3\text{OCH=CH} \)), 3.45 (2H, t, \( J 6.8 \) and 6.1, \( \text{CH}_2\text{OCH=CH} \)), 3.33 (3H, s, \( \text{CH}_2\text{OCH}_2 \)), 2.32 (2H, td, \( J 6.8 \) and 6.1, \( \text{CH}_2\text{CH}=\text{C} \)); (276) 6.34 (1H, d, \( J 14.0, \text{C=CHMe} \)), 4.71 (1H, dt, \( J 14.0 \) and 6.1, \( \text{C=CHCH}_2 \)), 3.57 (3H, s, \( \text{CH}_3\text{OCH=CH} \)), 3.37 (2H, t, \( J 6.2 \), \( \text{C=CHMe} \)), 3.32 (3H, s, \( \text{CH}_2\text{OCH}_2 \)), 2.18 (2H, td, \( J 6.2 \) and 6.1, \( \text{CH}_2\text{CH}=\text{C} \))

Isomerisation of 1,4-benzyloxybut-2-ene (90)

\[
\text{BnO} - \text{CH=CHMe} - \text{O} \quad \rightarrow \quad \text{BnO} - \text{CH=CHMe} - \text{O} + \text{BnO} - \text{CH=CHMe} - \text{O}
\]

A solution of isopropyl magnesium chloride (10.0 \( \text{µL}, 20.0 \text{µmol}, 2\text{M in THF} \)) was added dropwise to a mixture of \( \text{NiCl}_2(\text{DIPHOS}) \) (5.00 mg, 9.50 \( \text{µmol} \)) and 1,4-dibenzylxybut-2-ene (90) (127 mg, 473 \( \text{µmol} \)) in THF (1 ml) at 0°C. After warming to ambient temperatures the mixture was quenched with saturated \( \text{NH}_4\text{Cl} \) solution and extracted with ether. The extracts were combined and the solvent removed under reduced pressure. Analysis of the isolated residue by \( ^1\text{H-NMR} \) revealed starting material (5%) and a mixture of (\( Z \)) and (\( E \)) benzyl enol ethers, (277) and (278) \( ^{303} \) respectively (95%; 8 : 1)

\( ^1\text{H-NMR} \ \delta \text{H}: \)

(277) 7.37-7.26 (10H, m, PhH), 6.09 (1H, dt, \( J 6.2 \) and 1.4, \( \text{C=CHO} \)), 4.80 (2H, s, \( \text{C=CHOCH}_2\text{Ph} \)), 4.52 (2H, s, \( \text{CH}_2\text{Ph} \)), 4.48 (1H, td, \( J 7.0 \) and 6.2, \( \text{CH}_2\text{CH}=\text{C} \)), 3.48 (2H, t, \( J 7 \), \( \text{BnOCH}_2 \)), 2.46 (2H, qd, \( J 7.0 \) and 1.4, \( \text{CH}_2\text{CH}=\text{C} \)); (278) Peaks too weak for assignment.
A solution of n-BuLi (1.94 ml, 2.98 mmol, 1.54M in hexanes) was added dropwise to a solution of 1-phenyl-2-propen-1-ol (88) (400 mg, 2.98 mmol) (91) in THF (10 ml) at 0°C. The yellow solution was warmed and stirred at room temperature before the addition of solid NiCl₂(DIPHOS) (72.0 mg, 136 pmol). The mixture was heated to reflux, whereupon a solution of isopropyl magnesium chloride (149 μl, 298 pmol, 2M in THF) was added dropwise. After 4 hours, the mixture was cooled to room temperature then quenched with saturated NH₄Cl solution (10 ml) and the phases separated. The aqueous phase was extracted with ether (2 x 10 ml), and then the combined organic phases washed with brine (15 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (SiO₂, 20% ether in petrol) to afford propiophenone (91)° (165 mg, 1.23 mmol, 41%) as a clear colourless oil; Rf (20% ether in petrol) 0.45

\[ \text{H-NMR} \delta: 7.97-7.45 (5H, m, PhH), 3.02 (2H, q, J 7.3, CH₂CH₃) 1.24 (3H, t, J 7.3, CH₂CH₃) \]

\[ \text{C-NMR} \delta: 200.8 (C=O), 136.9, 132.8, 128.5, 127.9, 31.8 (CH₂), 8.2 (CH₃) \]

\[ \text{IR (film) v}_{\text{max}}: 3061, 2979, 2938, 1686 (C=O), 1597, 1583, 1449, 1353, 1279, 1220, 1181, 952 \]

\[ \text{LRMS (El) m/z: 134 (M⁺, 10%), 130 (23), 117 (23), 105 (100), 91 (15), 77 (35)} \]

Isomerisations using NiCl₂(DIPHOS)/LiBE₃H or NiCl₂(DIPHOS)/KB₃EtH

The catalyst, in THF (2 ml), was prepared from potassium triethylborohydride (70.0 μl, 70.0 μmol, 1M in THF) and NiCl₂(DIPHOS) (37.3 mg, 71.0 μmol). The alkoxide, in THF (3 ml), was prepared with n-BuLi (967 μl, 1.49 mmol, 1.54M in hexanes) and 1-phenyl-prop-2-en-1-ol (88) (200 mg, 1.49 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 3 hours then quenched with saturated NH₄Cl solution (4 ml). The isolated residue was chromatographed
(SiO₂, 20% ether in petrol) to afford propiophenone (91) (161 mg, 1.20 mmol, 81%) as a clear colourless oil.

Isomerisation of 1-phenyl-2-propen-1-ol (88)

The catalyst, in THF (1 ml), was prepared from potassium triethylborohydride (40.0 μl, 40.0 μmol, 1M in THF) and NiCl₂(DIPHOS) (21.0 mg, 39.7 μmol). The alkoxide, in THF (1 ml), was prepared with n-BuLi (485 μl, 747 μmol, 1.54M in hexanes) and 1-phenyl-prop-2-en-1-ol (88) (100 mg, 0.74 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 3 hours then quenched with acetic anhydride. The isolated residue was chromatographed (SiO₂, 10% ether in petrol) to afford an inseparable mixture of (Z) and (E)-1-phenyl-1-acetoxypropene, (92) and (93) respectively (94.6 mg, 0.54 mmol, 73%; 24 : 1) as a clear colourless oil; Rf (10% ether in petrol) 0.36

^H-NMR δH: (92) 7.42-7.27 (5H, m, PhH), 5.91 (1H, q, J 7.0, C=CH), 2.32 (3H, s, CH₃CO₂), 1.73 (3H, d, J 7.0, CH₃CH=C)

^C-NMR δC: (92) 168.6 (C=O), 146.9, 135.0, 128.5, 128.1, 124.3, 112.7, 20.7, 11.6

IR (film) v max : 3061, 2980, 2936, 2860, 1755 (C=O), 1665, 1495, 1445, 1372, 1269, 1207, 1115, 1078, 1027, 993

LRMS (El) m/z: 177 (M⁺+H, 41%), 117 (100), 105 (40), 91 (25), 77 (15), 43 (45)

Isomerisation of 1-penten-3-ol (94)

The catalyst, in THF (2 ml), was prepared from lithium triethylborohydride (75 μl, 75 μmol, 1M in THF) and NiCl₂(DIPHOS) (40.0 mg, 75.8 μmol). The alkoxide, in THF (3 ml), was prepared with n-BuLi (984 μl, 1.51 mmol, 1.54M in hexanes) and 1-penten-3-ol (94) (130 mg, 1.51 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 6 hours then quenched with benzaldehyde (115 μl, 1.67 mmol). The isolated residue was chromatographed (SiO₂, 20-30% ether in petrol) to afford the inseparable mixture of cis and trans 1-phenyl-1-hydroxy-2-methyl-3-
pentanone, (95) and (96)\textsuperscript{138} respectively (212 mg, 1.10 mmol, 73%; 4 : 1) as a clear colourless oil; \( R_f(20\% \text{ ether in petrol}) 0.21 \)

\[ ^1H-NMR \delta_H (95) 7.37-7.27 (5H, m, PhH), 5.07 (1H, m, \text{CHOH}), 3.14 (1H, d, J 2.0, \text{OH}), 2.83 (1H, m, \text{CHMe}), 2.50 (2H, q, J 7.3, \text{CH}_2\text{C}=\text{O}); \]

(96) 7.37-7.27 (5H, m, PhH), 4.78 (1H, m, \text{CHOH}), 2.95 (1H, m, \text{CHMe}), 2.35 (2H, q, J 7.2, \text{CH}_2\text{C}=\text{O}), 1.63 (1H, s, \text{OH}), 1.04 (3H, t, J 7.5, \text{CH}_2\text{CH}_3\text{C}=\text{O}), 0.95 (3H, d, J 7.2, \text{CH}_3\text{CH})

\[ \text{IR (film) } \nu_{max}: \text{Mixture of (95) and (96)}: 3456 (\text{OH}), 3064, 2977, 2938, 2879, 1708 (\text{C}=\text{O}), 1495, 1377, 1112, 1015, 975 \]

\[ \text{LRMS (FAB) } m/z: 193 (M^+\text{H}, 20%), 175 (62), 107 (34), 105 (19), 57 (100) \]

Isomerisation of 1-methoxy-1-phenyl-2-propene (97)

The catalyst, in THF (1 ml), was prepared from lithium triethylborohydride (40\l, 40 \mu\text{mol}, 1M in THF) and NiCl\(_2\)(DIPHOS) (21 mg, 40 \mu\text{mol}). The allylic ether, in THF (2 ml), was 1-methoxy-1-phenyl-2-propene (97) (118.6 mg, 0.80 mmol). The resulting catalyst/allylic ether mixture was heated to reflux for 3 hours then quenched with saturated NH\(_4\)Cl solution (3 ml). The isolated residue was chromatographed (Si\(_2\)O\(_2\), 5% ether in petrol) to afford starting material (73.5 mg, 496 \mu\text{mol}, 62%) and the inseparable mixture of (Z) and (E)-1-methoxy-1-phenyl-1-propene, (98) and (99)\textsuperscript{138} respectively (18 mg, 134 \mu\text{mol}, 17%; 1.5 : 1) as a clear colourless oil; \( R_f(10\% \text{ ether in petrol}) 0.64 \)

\[ ^1H-NMR \delta_H (98) 7.48-7.27 (5H, m, PhH), 5.40 (1H, q, J 6.8, \text{C}=\text{CHCH}_3), 3.56 (3H, s, \text{OCH}_3), 1.82 (3H, d, J 6.8, \text{C}=\text{CHCH}_3); (99) 7.48-7.27 (5H, m, PhH), 4.82 (1H, q, J 7.2, \text{C}=\text{CHCH}_3), 3.65 (3H, s, \text{OCH}_3), 1.71 (3H, d, J 7.2, \text{C}=\text{CHCH}_3) \]

Isomerisation of (E)-3-penten-2-ol (100)

The catalyst, in THF (2 ml), was prepared from lithium triethylborohydride (75 \l, 75 \mu\text{mol}, 1M in THF) and NiCl\(_2\)(DIPHOS) (40 mg, 75.8 \mu\text{mol}). The alkoxide, in THF (3 ml), was prepared with n-
BuLi (984 µl, 1.51 mmol, 1.54M in hexanes) and 3-penten-2-ol (100) (130 mg, 1.51 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 6 hours then quenched with benzaldehyde (115 µl, 1.67 mmol). Analysis of the isolated residue by $^1$H-NMR revealed a complex mixture of products, none of which were isolated.

**Isomerisation of (E)-1-phenyl-1-buten-3-ol (279)**

\[
\begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array}
\rightarrow
\text{Complex Mixture}
\]

The catalyst, in THF (3 ml), was prepared from lithium triethylborohydride (100 µl, 100 µmol, 1M in THF) and NiCl$_2$(DIPHOS) (52.8 mg, 1.00 µmol). The alkoxide, in THF (3 ml), was prepared with n-BuLi (767 µl, 986 µmol, 1.29M in hexanes) and E-1-phenyl-1-buten-3-ol (279) (146, 984 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 18 hours then quenched with saturated NH$_4$Cl solution (4 ml). The isolated residue was chromatographed (SiO$_2$, 20% ether in petrol) to afford a mixture of compounds, analysis of which by $^1$H-NMR and GCMS indicated only polymeric material.

**Isomerisation of 1-phenyl-4-buten-3-ol (102)**

\[
\begin{array}{c}
\text{OH} \\
\text{Ph}
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{C} \\
\text{O} \\
\text{C}
\end{array}
\]

The catalyst, in THF (3 ml), was prepared from lithium triethylborohydride (100 µl, 100 µmol, 1M in THF) and NiCl$_2$(DIPHOS) (52.7 mg, 100 µmol). The alkoxide, in THF (4 ml), was prepared with n-BuLi (775 µl, 996 µmol, 1.29M in hexanes) and 1-phenyl-4-buten-3-ol (102) (161 mg, 992 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 90 minutes then quenched with benzaldehyde (75 µl, 1.09 mmol). The isolated residue was chromatographed
(SiO₂, 25% ether in petrol) to afford the ketone (104) (22 mg, 14%), cis and trans 1,5-diphenyl-1-
hydroxy-2-methyl-3-pentanone, (105) and (106) respectively (3.2 : 1), and cis and trans 1-phenyl-
2-(1-phenyl-1-hydroxymethyl)-3-pentanone, (107) and (108) respectively (1 : 1.1). The
inseparable hydroxyketones (157 mg, 586 mmol, 59%) were isolated as a clear colourless oil in
an overall regiochemical ratio of [(105) + (106)] : [(107) + (108)] 1 : 1.4; Rf (10% ether in petrol) 0.41

\[ ^1H-NMR \delta: (105) 7.38-7.05 (10H, m, PhH), 5.03 (1H, dd, J 3.4 and 2.8, C(5)-H), 3.0-2.6 (5H, m,
C(1,2 and 4)-H), 1.81 (1H, m, OH), 1.05 (3H, d, J 7.2, CH₂CH); (106) 7.38-7.05 (10H, m, PhH), 4.77 (1H, dd, J 8.1 and 4.0, C(5)-H), 3.0-2.6 (5H, m, C(1,2 and 4)-H), 1.85 (1H, m, OH), 0.90 (3H, d, J 7.2, CH₂CH); (107) 7.38-7.05 (10H, m, PhH), 4.84 (1H, t, J 6.3, CHOH),
3.0-2.6 (5H, m, C(1,2 and 4)-H), 2.02 (1H, m, OH), 0.73 (3H, t, J 7.1, CH₂CH₂); (108) 7.38-
7.05 (10H, m, PhH), 4.95 (1H, dd, J 3.9 and 1.8, CHOH), 3.0-2.6 (5H, m, C(1,2 and 4)-H),
2.09 (1H, m, OH), 0.64 (3H, t, J 7.1, CH₂CH₂)

LRMS (FAB) m/z: 250 (10%, [M-OH]⁺), 193 (63), 177 (45), 163 (25), 146 (51), 134 (25), 118 (39)
IR (film) v_max: 3444 (OH), 3063, 3029, 2975, 2936, 1704 (C=O), 1604, 1495, 1454, 1404, 1377,
1133, 1029, 910

HRMS (EI) m/z: Found for C₁₈H₂₇O₂ (M⁺), 268.1458; Required 268.1463

Isomerisation of geraniol (61)
using 5 mol% catalyst

The catalyst, in THF (2 ml), was prepared from potassium triethylborohydride (70.0 μl, 70.0 μmol,
1M in THF) and NiCl₂(DIPHOS) (37.0 mg, 70.0 μmol). The alkoxide, in THF (3 ml), was
prepared with n-BuLi (907μl, 1.40 mmol, 1.54M in hexanes) and geraniol (61) (216 mg, 1.40
mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 20 hours then quenched
with saturated NH₄Cl solution (4 ml). Analysis of the residue by \(^1H\text{-NMR}\) and GC (7.5 psi column
head pressure; 100°C for 2 min, then 15°C/min to 250°C) revealed only starting material (61);
(GC: 4.99 min) and citronellol (112)_{329} (GC: 4.72 min) (ratio 2 : 1), which were isolated by
chromatography (SiO₂, 40% ether in petrol) as an inseparable mixture (84 mg, ca. 84%).

\[ ^1H-NMR \delta: (112) 5.12 (1H, m, C=CH), 3.71 (2H, m, CH₂OH), 2.19-2.00 (2H, m, C=CHCH₂), 1.71
(3H, s, CH₃), 1.64 (3H, s, CH₃), 1.44-1.09 (5H, m, CH₂CH(CH₃)CH₂), 0.93 (3H, d, J 6.6,
CH₃CH(CH₃)CH₂)

\[ ^13C-NMR \delta: 131.3, 124.7, 61.3, 39.9, 37.2, 29.2, 25.7, 25.5, 19.6, 17.7 \]
Isomerisation of geraniol (61)

using 20 mol% catalyst

The catalyst, in THF (1.5 ml), was prepared from potassium triethylborohydride (130.0 µl, 130.0 µmol, 1M in THF) and NiCl₂(DIPHOS) (68.5 mg, 129 µmol). The alkoxide, in THF (1 ml), was prepared with n-BuLi (421 µl, 648 µmol, 1.54M in hexanes) and geraniol (61) (100 mg, 648 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 3 hours then quenched with saturated NH₄Cl solution (3 ml). Analysis of the residue by ¹H-NMR and GC (7.5 psi column head pressure; 100°C for 2 min, then 15°C/min to 250°C) revealed citronellal (62) (22%, GC: 3.88 min), starting material (61) (38%, GC: 4.99 min) and citreneol (112) (13%, GC: 4.72 min), none of which were isolated.

¹H-NMR δ: (62) 9.76 (1H, t, J 2.2, CHO), 5.08 (1H, m, C=CH), 2.40 (1H, ddd, J 13.4, 5.5 and 2.2, CHCHO), 2.29 (1H, ddd, J 13.4, 7.9 and 2.2, CHCHO), 2.13-1.94 (2H, m, C=CHCH₂), 1.69 (3H, s, CH₃), 1.60 (3H, s, CH₃), 1.41-1.25 (3H, m, CH₂CH(CH₃)₂CH₂CHO), 0.98 (3H, d, J 6.6, CHCH₃)

¹³C-NMR δ: (62) 203.1, 131.8, 124.0, 36.9, 33.6, 27.8, 25.7, 25.4, 19.9, 17.7

Isomerisation of geraniol (61)
in benzene

The catalyst, in benzene (1.5 ml), was prepared from potassium triethylborohydride (33.0 µl, 33.0 µmol, 1M in THF) and NiCl₂(DIPHOS) (17.1 mg, 32.4 µmol). The alkoxide, in benzene (1 ml), was prepared with n-BuLi (421 µl, 648 µmol, 1.54M in hexanes) and geraniol (61) (100 mg, 648 µmol).
µmol) at 5°C. The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated NH₄Cl solution (3 ml). Analysis of the residue by ¹H-NMR and GC revealed citronellal (62) (13%), starting material (61) (18%) and citronellol (112) (18%), none of which were isolated.

**Isomerisation of geraniol (61) in toluene**

\[
\begin{align*}
\text{(61)} & \rightarrow \text{(61)} + \text{(112)} \\
& \text{(62)}
\end{align*}
\]

The catalyst, in toluene (2 ml), was prepared from potassium triethylborohydride (65.0 µl, 65.0 µmol, 1M in THF) and NiCl₂(DIPHOS) (34.5 mg, 65.3 µmol). The alkoxide, in toluene (3 ml), was prepared with n-BuLi (819 µl, 1.26 mmol, 1.54M in hexanes) and geraniol (61) (195 mg, 1.26 mmol). The resulting catalyst/alkoxide mixture was heated to 60°C for 17 hours then quenched with saturated NH₄Cl solution (3 ml). Analysis of the residue by ¹H-NMR and GC revealed citronellal (62) (7%), starting material (61) (10%) and citronellol (112) (21%), none of which were isolated.

**Isomerisation of (E)-1-phenyl-1-propen-3-ol (280)**

\[
\begin{align*}
\text{(280)} & \rightarrow \text{No Reaction}
\end{align*}
\]

The catalyst, in THF (3 ml), was prepared from lithium triethylborohydride (88 µl, 88 µmol, 1M in THF) and NiCl₂(DIPHOS) (46.3 mg, 88 µmol). The alkoxide, in THF (3 ml), was prepared with n-BuLi (638 µl, 1.02 mmol, 1.6M in hexanes) and (E)-1-phenyl-1-propen-3-ol (280) (137 mg, 1.02 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 10 hours then quenched with saturated NH₄Cl solution (4 ml). Analysis of the residue by ¹H-NMR and GC revealed predominantly starting material, which was not isolated.
**Isomerisation of \((E)-3\text{-phenyl-2-buten-1-ol}\) (63)**

\[
\text{Ph} - \text{CH}-\text{CH}_2\text{CH} = \text{CH}_2 \text{OH} \quad \rightarrow \quad \text{No Isomerisation Products} + \quad \text{Ph} - \text{CH}-\text{CH}_2\text{CH} = \text{CH}_2 \text{OH}
\]

The catalyst, in THF (3 ml), was prepared from lithium triethylborohydride (95 µl, 95 µmol, 1M in THF) and NiCl₂(DIPHOS) (50.3 mg, 95 µmol). The alkoxide, in THF (3 ml), was prepared with n-BuLi (778 µl, 1.00 mmol, 1.29M in hexanes) and \(E\)-3-phenyl-2-buten-1-ol (63) (148.2 mg, 1.00 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 18 hours then quenched with saturated NH₄Cl solution (4 ml). The isolated residue was chromatographed (SiO₂, 55% ether in petrol) to afford an inseparable mixture of starting material and 3-phenyl-1-butanol (281) as a clear colourless oil (105 mg, 71%, 19 : 1).

\(^1\text{H-NMR} \delta_H (281)\): 7.44-7.19 (5H, m, PhH), 3.50 (2H, m, \text{CH}_2\text{CH}_2\text{OH}), 2.90 (1H, m, J 6.7, PhCH), 1.86 (2H, m, \text{CH}_2\text{CH}_2\text{OH}), 1.52 (1H, br, OH), 1.29 (3H, d, J 6.7, CH₃)

\(^13\text{C-NMR} \delta_C\): 146.8, 128.5, 128.3, 126.9, 61.2, 40.9, 36.4, 22.4

**Isomerisations using Ni(COD)₂**

**Isomerisation of geraniol (61) with 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)**

\[
\begin{align*}
\text{CH}_2\text{=CH}_2 \text{OH} & \quad \rightarrow \quad \text{CH}_2\text{=CH}_2\text{CH} \equiv \text{C(OAc)} \quad + \quad \text{CH}_2\text{=CH}_2\text{CH} \equiv \text{C(OAc)}
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (23.6 mg, 80.0 µmol) and Ni(COD)₂ (22.0 mg, 80.0 µmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.03 ml, 1.45 mmol, 1.41M in hexanes) and geraniol (61) (224 mg, 1.45 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 90 minutes then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of \((E)\) and \((Z)\) enol acetates, respectively, (199 mg, 1.01 mmol, 70%, 4.1 : 1). Ratio determined by \(^1\text{H-NMR}\) and by GC: 7.5 psi column head pressure; 100°C for 2 min, then 5°C/min to 250°C; rt \(Z = 7.27 \text{ min, } E = 8.48 \text{ min}\) as a clear colourless oil. Rf(25% ether in petrol) 0.61

\(^1\text{H-NMR} \delta_H (115)\): 7.06 (1H, dd, J 12.5 1.0, CH=CHOAc), 5.29 (1H, dd, J 12.5 8.9, CH=CHOAc), 5.10-5.01 (1H, m, C=CH), 2.14 (1H, m, CHCH₃), 2.11 (3H, s, CH₃O), 1.96 (2H, m, CH₂CH₂CH=CH₂), 1.68 (3H, s, CH₃C=C), 1.58 (3H, s, CH₃C=C), 1.40-1.21 (2H, m,
Experimental

\[ \text{CH}_2\text{CH}_{2}\text{CH}=\text{C}, \, 1.10 \, (3\, \text{H}, \, \text{d}, \, J \, 6.8, \, \text{CH}_2\text{CH}); \, \text{(116)} \, 6.98 \, (1\, \text{H}, \, \text{dd}, \, J \, 9.6 \, 1.0, \, \text{CH}=\text{CHOAc}), \]
\[ 5.10-5.01 \, (1\, \text{H}, \, \text{m}, \, \text{C}=\text{CH}), \, 4.67 \, (1\, \text{H}, \, \text{dd}, \, J \, 9.6 \, 6.5, \, \text{CH}=\text{CHOAc}), \, 2.14 \, (1\, \text{H}, \, \text{m}, \, \text{CHCH}_3), \, 2.11 \]
\[ (3\, \text{H}, \, \text{s}, \, \text{CH}_3\text{O}), \, 1.96 \, (2\, \text{H}, \, \text{m}, \, \text{CH}_2\text{CH}_2\text{CH}=\text{C}), \, 1.68 \, (3\, \text{H}, \, \text{s}, \, \text{CH}_3\text{C}=\text{C}), \, 1.58 \, (3\, \text{H}, \, \text{s}, \, \text{CH}_3\text{C}=\text{C}), \]
\[ 1.40-1.21 \, (2\, \text{H}, \, \text{m}, \, \text{CH}_2\text{CH}_2\text{CH}=\text{C}), \, 0.98 \, (3\, \text{H}, \, \text{d}, \, J \, 6.8, \, \text{CH}_2\text{CH}) \]

IR (film) \( \nu_{\text{max}} \): Mixture of (115) and (116) 2964, 2916, 2854, 1759, 1673, 1454, 1371, 1223, 1096

MS (El) \text{m/z}: \) Mixture of (115) and (116): 196 (M+, <1%), 154 (41%), 136 (43), 121 (45), 109 (44),
\[ 101 \, (43), \, 95 \, (46), \, 84 \, (50), \, 71 \, (55) \]

Isomerisation of geraniol (61) with
2,2-bis-[(4S)-4-phenyl-1,3-oxazoline-2-yl]-propane (140)

The catalyst, in THF (8 ml), was prepared from 2,2-bis-[(4S)-4-phenyl-1,3-oxazoline-2-yl]-propane (140) (30.4 mg, 90.9 \text{mmol}) and Ni(COD)$_2$ (25.0 mg, 90.9 \text{mmol}). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.04 ml, 1.47 mmol, 1.49M in hexanes) and geraniol (61) (227 mg, 1.47 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO$_2$, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (198 mg, 1.01 mmol, 69%, 4.4 : 1) as a clear colourless oil. \( R_{f}(25\% \text{ ether in petrol}) \, 0.61 \)

Isomerisation of geraniol (61) with
2,6-bis-[(4S)-4-isopropyl-1,3-oxazoline-2-yl]-pyridine (143)

The catalyst, in THF (8 ml), was prepared from 2,6-bis-[(4S)-4-isopropyl-1,3-oxazoline-2-yl]-pyridine (20.0 mg, 66.4 \text{mmol}) and Ni(COD)$_2$ (18.0 mg, 65.4 \text{mmol}). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.22 ml, 1.32 mmol, 1.08M in hexanes) and geraniol (61) (203 mg, 1.32 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO$_2$, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (186 mg, 948 \text{mmol}, 72%, 4.4 : 1) as a clear colourless oil. \( R_{f}(25\% \text{ ether in petrol}) \, 0.61 \)
Experimental

Isomerisation of geraniol (61) with (4S)-2-(2-diphenylphosphinophenyl)-4-(1-methylethyl)-1,3-oxazoline (129)

\[ \text{(61)} \quad \text{\xrightarrow{\text{\textit{OAc}}} \quad (115) + (116)} \]

The catalyst, in THF (8 ml), was prepared from (4S)-2-(2-diphenylphosphinophenyl)-4-(1-methylethyl)-1,3-oxazoline (129) (32.8 mg, 87.9 μmol) and Ni(COD)\(_2\) (24.0 mg, 87.2 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.05 ml, 1.48 mmol, 1.49M in hexanes) and geraniol (61) (228 mg, 1.48 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO\(_2\), 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (96.3 mg, 490 μmol, 33%, 3.7 : 1) as a clear colourless oil. \(R_f(25\%\text{ ether in petrol}) 0.61\)

Isomerisation of geraniol (61) with (4S,5S)-2-(2-diphenylphosphinophenyl)-4-(methoxymethyl)-5-phenyl-1,3-oxazoline (133)

\[ \text{(61)} \quad \text{\xrightarrow{\text{\textit{OAc}}} \quad \text{No isomerisation product} + \quad \text{(61)}} \]

The catalyst, in THF (8 ml), was prepared from (4S, 5S)-2-(2-diphenylphosphinophenyl)-4-(methoxymethyl)-5-phenyl-1,3-oxazoline (133) (30.0 mg, 66.4 μmol) and Ni(COD)\(_2\) (19.0 mg, 69.1 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (835 μl, 1.29 mmol, 1.55M in hexanes) and geraniol (61) (199 mg, 1.29 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated NH\(_4\)Cl solution (8 ml). Analysis of the isolated residue by \(^1\text{H}-\text{NMR}\) and GC indicated only starting material (61)

Isomerisation of geraniol (61) with 5 equivalents of 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)

\[ \text{(61)} \quad \text{\xrightarrow{\text{\textit{OAc}}} \quad (115) + (116)} \]

The catalyst, in THF (8 ml), was prepared from 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (46.8 mg, 159 μmol) and Ni(COD)\(_2\) (8.70 mg, 31.6 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (600 μl, 709 μmol, 1.18M in hexanes) and geraniol (61) (109 mg, 705
μmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2.5 hours then quenched with acetic anhydride (600 μl, 6.36 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (24.3 mg, 123 μmol, 18%, 5.0 : 1) as a clear colourless oil. Rf(25% ether in petrol) 0.61

Isomerisation of geraniol (61) with mercury and 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)

The catalyst, in THF (8 ml), was prepared from 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (13.0 mg, 44.2 μmol) and Ni(COD)₂ (12.0 mg, 43.6 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (631 μl, 745 μmol, 1.18M in hexanes) and geraniol (61) (115 mg, 746 μmol). Mercury (50 μl, 3.37 mmol) was added to the resulting catalyst/alkoxide mixture, which was then heated to reflux for 2.5 hours, then quenched with acetic anhydride (600 μl, 6.36 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (95.4 mg, 486 μmol, 65%, 4.2 : 1) as a clear colourless oil. Rf(25% ether in petrol) 0.61

Isomerisation of geraniol (61) with 2 equivalents of pyridine

The catalyst, in THF (8 ml), was prepared from pyridine (10.6 μl, 137 μmol) and Ni(COD)₂ (18.0 mg, 65.4 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.25 ml, 1.3 4 mmol, 1.07M in hexanes) and geraniol (61) (206 mg, 1.34 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (174 mg, 885 μmol, 66%, >25 : 1) as a clear colourless oil. Rf(25% ether in petrol) 0.61
Isomerisation of geraniol (61) with bipyridyl

\[
\begin{align*}
(61) & \rightarrow \underset{\text{(E)}}{\text{(115)}} + \underset{\text{(Z)}}{\text{(116)}} \\
\text{(E)} & \quad \text{(Z)}
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from bipyridyl (10.1 mg, 64.7 \( \mu \)mol) and Ni(COD)\(_2\) (19.0 mg, 69.1 \( \mu \)mol). The alkoxide, in THF (8 ml), was prepared with \( n \)-BuLi (1.25 ml, 1.34 mmol, 1.07 M in hexanes) and geraniol (61) (208 mg, 1.35 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (Si\(_2\)O\(_2\), 2\% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (121 mg, 618 \( \mu \)mol, 46\%, 4.5 : 1) as a clear colourless oil. \( R_f(25\% \text{ ether in petrol}) 0.61 \)

Isomerisation of geraniol (61) with 1,2:5,6-Di-O-isopropylidene-3-O-diphenylphosphino-\( \alpha \)-D-glucofuranose (144)

\[
\begin{align*}
(61) & \rightarrow \underset{\text{(E)}}{\text{(115)}} + \underset{\text{(Z)}}{\text{(116)}} \\
\text{(E)} & \quad \text{(Z)}
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from 1,2:5,6-Di-O-isopropylidene-3-O-diphenylphosphino-\( \alpha \)-D-glucofuranose (144) (39.5 mg, 88.9 \( \mu \)mol) and Ni(COD)\(_2\) (23.5 mg, 85.4 \( \mu \)mol). The alkoxide, in THF (8 ml), was prepared with \( n \)-BuLi (1.01 ml, 1.43 mmol, 1.49 M in hexanes) and geraniol (61) (220 mg, 1.43 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 75 minutes then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (Si\(_2\)O\(_2\), 2\% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (98 mg, 499 \( \mu \)mol, 35\%, 4.7 : 1) as a clear colourless oil. \( R_f(25\% \text{ ether in petrol}) 0.61 \)

Isomerisation of geraniol (61) with 2 equivalents of 1,2:5,6-Di-O-isopropylidene-3-O-diphenylphosphino-\( \alpha \)-D-glucofuranose (144)

\[
\begin{align*}
(61) & \rightarrow \underset{\text{(E)}}{\text{(115)}} + \underset{\text{(Z)}}{\text{(116)}} \\
\text{(E)} & \quad \text{(Z)}
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from 1,2:5,6-Di-O-isopropylidene-3-O-diphenylphosphino-\( \alpha \)-D-glucofuranose (144) (58.2 mg, 131 \( \mu \)mol) and Ni(COD)\(_2\) (18.0 mg, 65.4 \( \mu \)mol).
The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.22 ml, 1.32 mmol, 1.08M in hexanes) and geraniol (61) (203 mg, 1.32 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 75 minutes then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (127 mg, 645 µmol, 49%, 4.8 : 1) as a clear colourless oil. Rf(25% ether in petrol) 0.61

**Isomerisation of geraniol (61) with**

![Chemical structure](image)

The catalyst, in THF (5 ml), was prepared from (1R,1R)-6,6′-bis(1-methoxyethyl)-2,2′-bipyridine (145) (10.0 mg, 36.7 µmol) and Ni(COD)₂ (10.0 mg, 36.4 µmol). The alkoxide, in THF (5 ml), was prepared with n-BuLi (480 µl, 742 µmol, 1.55M in hexanes) and geraniol (61) (114 mg, 741 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (600 µl, 6.36 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (85.1 mg, 434 µmol, 59%, 5.7 : 1) as a clear colourless oil. Rf(25% ether in petrol) 0.61

**Isomerisation of geraniol (61) with hydroquinidine-4-methyl-2-quinidyl ether (148)**

![Chemical structure](image)

The catalyst, in THF (8 ml), was prepared from hydroquinidine-4-methyl-2-quinidyl ether (148) (30.2 mg, 64.6 µmol) and Ni(COD)₂ (19.0 mg, 69.1 µmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.28 ml, 1.37 mmol, 1.07M in hexanes) and geraniol (61) (208 mg, 1.35 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (72.7 mg, 370 µmol, 27%, 8.2 : 1) as a clear colourless oil. Rf(25% ether in petrol) 0.61
Isomerisation of geraniol (61) with 2 equivalents of (S)-nicotine (149)

\[
\text{CH}_3\text{CH}=\text{CH}_2\text{CH}(_2\text{OH}) \quad \Rightarrow \quad \text{CH}_3\text{CH}=\text{CH}_2\text{CH}_2\text{OAc} \quad \text{and} \quad \text{CH}_3\text{CH}=\text{CH}_2\text{CH}_2\text{OAc}
\]

The catalyst, in THF (6 ml), was prepared from (S)-nicotine (149) (18.0 mg, 111 µmol) and Ni(COD)_2 (13.5 mg, 49.1 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (614 µl, 982 µmol, 1.60M in hexanes) and geraniol (61) (151 mg, 982 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 1.75 hours then quenched with acetic anhydride (900 µl, 9.54 mmol). The isolated residue was chromatographed (SiO\textsubscript{2}, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (97.5 mg, 497 µmol, 51%, 5.3 : 1) as a clear colourless oil. R\text{f}(25\% ether in petrol) 0.61

Isomerisation of geraniol (61) with 2 equivalents of (4S,5S) 2-methyl-5-phenyl-1,3-oxazoline (150)

\[
\text{CH}_3\text{CH}=\text{CH}_2\text{CH}(_2\text{OH}) \quad \Rightarrow \quad \text{CH}_3\text{CH}=\text{CH}_2\text{CH}(_2\text{OH}) \quad \text{and} \quad \text{CH}_3\text{CH}=\text{CH}_2\text{CH}(_2\text{OH})
\]

The catalyst, in THF (6 ml), was prepared from (4S,5S) 2-methyl-5-phenyl-1,3-oxazoline (150) (20.2 mg, 98.4 µmol) and Ni(COD)_2 (13.5 mg, 49.1 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (614 µl, 982 µmol, 1.60M in hexanes) and geraniol (61) (151 mg, 982 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 1.75 hours then quenched with saturated NH\textsubscript{4}Cl solution (8 ml). Analysis of the residue by \textsuperscript{1}H-NMR and GC revealed only starting material (61) and citronellol (112) (4.9 : 1), which were isolated by chromatography (SiO\textsubscript{2}, 40% ether in petrol) as an inseparable mixture (129 mg, ca. 85%); R\text{f}(30\% ether in petrol) 0.14

Isomerisation of geraniol (61) with 5 equivalents of 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) at room temperature

\[
\text{CH}_3\text{CH}=\text{CH}_2\text{CH}(_2\text{OH}) \quad \text{No isomerisation product} \quad \text{and} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(_2\text{OH})
\]

No isomerisation product + (61)
The catalyst, in THF (8 ml), was prepared from 2,2-bis-[4(S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (47.0 mg, 160 μmol) and Ni(COD)$_2$ (8.80 mg, 32.0 μmol). The solution of geraniol (61) (109 mg, 705 μmol) in THF (8 ml) was added to the catalyst solution. The resulting mixture was heated to reflux for 2.5 hours then quenched with acetic anhydride (600 μl, 6.36 mmol). Analysis of the residue by $^1$H-NMR and GC indicated starting material (61) (68%) as the only identifiable compound, which was not isolated.

**Isomerisation of (E)-3-phenyl-2-buten-1-ol (63) with 2,2-bis-[4(S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)**

![Chemical structure](image)

The catalyst, in THF (6 ml), was prepared from 2,2-bis-[4(S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (15.0 mg, 50.9 μmol) and Ni(COD)$_2$ (14.0 mg, 50.9 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (595 μl, 1.02 mmol, 1.72M in hexanes) and E 3-phenyl-2-buten-1-ol (63) (151 mg, 1.02 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO$_2$, 10% ether in petrol) to afford a mixture of (E) and (Z) enol acetates, and 3-phenylbutanal, (169), (170)$^{331}$ and (282)$^{309}$ respectively, (33.8 mg, ca. 17%, 5.0 : 1 : 16.4) containing co-running impurities; $R_f$(50% ether in petrol) 0.58

$^1$H-NMR $\delta$: (169) 7.40-7.10 (6H, m, PhH and CH=CHOCH$_3$), 5.65 (1H, dd, J 12.5 and 7.5, CH=CHOCH$_3$), 3.52 (1H, m, PhCH$_3$), 2.12 (3H, s, CH=CHOCH$_3$), 1.42 (3H, d, J 7.0, PhCH$_2$H); (170) 7.40-7.10 (6H, m, PhH and CH=CHOCH$_3$), 5.07 (1H, dd, J 9.6 and 6.4, CH=CHOCH$_3$), 4.05 (1H, m, PhCH$_3$), 2.18 (3H, s, CH=CHOCH$_3$), 1.39 (3H, d, J 6.0, PhCH$_2$H); (282) 9.73 (1H, t, J 1.9, CH$_2$CHO), 7.38-7.21 (5H, m, PhH), 3.45-3.24 (1H, m, PhCH$_3$), 2.74 (2H, qd, J 6.8 and 1.9, CH$_2$CHO), 1.35 (3H, d, J 7.0, PhCH$_2$H)

IR (film) $\nu_{max}$: 3085, 3028, 2967, 2931, 2874, 1748 (s, C=O), 1672, 1602, 1494, 1452, 1372, 1223, 1110, 1080, 1047, 1028, 934, 910
Isomerisation of 3,5,5-trimethyl-2-cyclohexen-1-ol (162) with 2,2-bis-[\((4S)-4-t\text{-butyl-1,3-oxazoline-2-yl}\)]-propane (128)

The catalyst, in THF (6 ml), was prepared from 2,2-bis-[\((4S)-4-t\text{-butyl-1,3-oxazoline-2-yl}\)]-propane (128) (16.0 mg, 54.3 \(\mu\)mol) and Ni(COD)\(_2\) (15.0 mg, 54.5 \(\mu\)mol). The alkoxide, in THF (6 ml), was prepared with \(n\)-BuLi (631 \(\mu\)l, 1.09 mmol, 1.72M in hexanes) and 3,5,5-trimethyl-2-cyclohexen-1-ol (162) (152 mg, 1.09 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO\(_2\), 25% ether in petrol) to afford 3,3,5-trimethylcyclohexanone (171) (145 mg, 884 \(\mu\)mol, 83%) as a clear colourless oil. \(R_f\) (50% ether in petrol) 0.44

\(^1\text{H-NMR}\) \(\delta\): 232 (1H, ddt, \(J\) 11.3 3.9 2.0, C(6)-H), 2.16 (1H, d, \(J\) 13.3, C[2]-H), 2.06 (1H, dt, \(J\) 13.3 2.0, C[2]-H), 2.05-1.95 (1H, m, C[5]-H), 1.85 (1H, dt, \(J\) 13.0 0.6, C[4]-H), 1.58 (1H, ddt, \(J\) 13.5 3.4 2.0, C[6]-H), 1.30 (1H, t, \(J\) 13.0, C[4]-H), 1.06 (3H, s, CH\(_3\))

\(^{13}\text{C-NMR}\) \(\delta\): 212.0 (C=O), 54.2, 49.3, 47.3, 35.4, 32.2, 29.7, 25.8, 22.5

IR (film) \(\nu_{\text{max}}\): 2956 (s), 2909 (s), 2871 (s), 2251 (w), 1712 (s, C=O), 1455, 1419, 1368, 1336, 1275, 1225, 1177 (w), 1082, 984 (w)

Isomerisation of 3-phenyl-2-cyclohexen-1-ol (161) with 2,2-bis-[\((4S)-4-t\text{-butyl-1,3-oxazoline-2-yl}\)]-propane (128)

The catalyst, in THF (6 ml), was prepared from 2,2-bis-[\((4S)-4-t\text{-butyl-1,3-oxazoline-2-yl}\)]-propane (128) (16.0 mg, 54.3 \(\mu\)mol) and Ni(COD)\(_2\) (15.0 mg, 54.5 \(\mu\)mol). The alkoxide, in THF (6 ml), was prepared with \(n\)-BuLi (620 \(\mu\)l, 1.07 mmol, 1.72M in hexanes) and 3-phenyl-2-cyclohexen-1-ol (161) (186 mg, 1.07 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO\(_2\), 40% ether in petrol) to afford 3-phenylcyclohexanone (168) (154 mg, 884 \(\mu\)mol, 83%) as a clear colourless oil. \(R_f\) (50% ether in petrol) 0.44
\[ ^1H\text{-NMR} \; \delta_H: 7.35-7.16 \; (5H, m, \text{PhH}) \; m \; 2.99 \; (1H, \text{tt}, \; J \; 11.8 \; 4.2, \; CH\text{Ph}), \; 2.61-2.32 \; (4H, m, \; CH_2C\{=O\}CH_2), \; 2.19-2.04 \; (2H, m, \; CH_2CH\text{Ph}), \; 1.90-1.72 \; (2H, m, \; CH_2CH_2CO) \]

\[ ^{13}C\text{-NMR} \; \delta_C: 211.1 \; (C=O), \; 144.3, \; 128.7, \; 126.7, \; 126.5, \; 48.9, \; 44.7, \; 41.2, \; 32.8, \; 25.5 \]

\[ \text{IR} \; \nu_{\text{max}}: 3062, \; 3028, \; 2937, \; 2866, \; 1712 \; (s, \; C=O), \; 1603, \; 1496, \; 1452, \; 1421, \; 1314, \; 1250, \; 1224, \; 1182, \; 1099, \; 1030, \; 973, \; 918 \]

\[ \text{LRMS (FAB) m/z: 173 (M*-H, 100%), 157 (19), 149 (12), 117 (15), 105 (12)} \]

\[ \text{HRMS (FAB): Found for C}_{12}\text{H}_{13}O_3 (M*-H), \; 173.0960; \text{ Required 173.0966} \]

**Isomerisation of (3S)-1-trimethylsilyloxy-3,7-dimethyl-2,6-octadiene with 2,2-bis-[\{(4S)-4-t-butyl-1,3-oxazoline-2-yl\}-propane (128)**

\[
\begin{align*}
\text{(273)} & \quad + \\
\text{(274)} & \quad \rightarrow \\
\text{(115)} & \quad + \\
\text{(116)}
\end{align*}
\]

The catalyst, in THF (6 ml), was prepared from 2,2-bis-[\{(4S)-4-t-butyl-1,3-oxazoline-2-yl\}-propane (128) (15.0 mg, 50.9 \text{ mol}) and Ni(COD)_2 (13.0 mg, 47.3 \text{ mol}). The alkoxide, in THF (6 ml), was prepared with MeLi (560 \text{ mL}, 974 \mu\text{L}, 1.74M in hexanes) and (3S)-1-trimethylsilyloxy-3,7-dimethyl-2,6-octadiene (273) and (274) (109 mg, 705 \mu\text{mol}; \; E:Z \text{ ratio} \; 1.7 : 1). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO_2, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (81.4 mg, 415 \mu\text{mol}, 43\%, 6.2 : 1) and citronellal (6 mg, 38.9 \mu\text{mol}, 3\%) as clear colourless oils.

**Isomerisation of geraniol (61) with 2,2-bis-[\{(4S)-4-t-butyl-1,3-oxazoline-2-yl\}-propane (128) in benzene**

\[
\begin{align*}
\text{(61)} & \quad \rightarrow \\
\text{(115)} & \quad + \\
\text{(116)}
\end{align*}
\]

The catalyst, in benzene (6 ml), was prepared from 2,2-bis-[\{(4S)-4-t-butyl-1,3-oxazoline-2-yl\}-propane (128) (14.0 mg, 47.5 \mu\text{mol}) and Ni(COD)_2 (13.5 mg, 49.1 \mu\text{mol}). The alkoxide, in benzene (6 ml), was prepared with n-BuLi (608 \mu\text{L}, 973 \mu\text{mol}, 1.60M in hexanes) and geraniol (61) (150 mg, 972 \mu\text{mol}) at 5°C. The resulting catalyst/alkoxide mixture was stirred at room
temperature for 2.5 hours then quenched with acetic anhydride (850 µl, 9.01 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (88.6 mg, 451 µmol, 46%, >20 : 1) as a clear colourless oil. Rₓ(25% ether in petrol) 0.61

Isomerisation of geraniol (61) with 2,2-bis[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) in benzene at room temperature

The catalyst, in benzene (6 ml), was prepared from 2,2-bis[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (14.0 mg, 47.5 µmol) and Ni(COD)₂ (13.5 mg, 49.1 µmol). The alkoxide, in benzene (6 ml), was prepared with n-BuLi (608 µl, 973 µmol, 1.60M in hexanes) and geraniol (61) (150 mg, 972 µmol) at 5°C. The resulting catalyst/alkoxide mixture was stirred at room temperature for 2.5 hours then quenched with acetic anhydride (850 µl, 9.01 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (32.2 mg, 164 µmol, 17%, >20 : 1) as a clear colourless oil. Rₓ(25% ether in petrol) 0.61

Isomerisation of geraniol with NiCl₂(Cy₃P)₂/n-BuLi

The catalyst, in THF (4 ml), was prepared from n-BuLi (87 µl, 112 µmol, 1.29M in hexanes) and NiCl₂(Cy₃P)₂ (51.5 mg, 74.6 µmol). The alkoxide, in THF (4 ml), was prepared with n-BuLi (580 µl, 745 mmol, 1.29M in hexanes) and geraniol (61) (114.9 mg, 745 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 6 hours then quenched with acetic anhydride (400 µl, 4.24 mmol) at -78°C. The isolated residue was chromatographed (SiO₂, 3-4% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (96 mg, 490 µmol, 65%, 4.4 : 1) as a clear colourless oil. Rₓ(25% ether in petrol) 0.61
Isomerisation of geraniol (61) with NiCl₂(C₅H₃P)₂/ n-BuLi and 1,2:5,6-di-O-isopropylidene-3,4 di-O-methyl-D-mannitol (183)

The catalyst, in THF (3 ml), was prepared from n-BuLi (88 μl, 113 μmol, 1.29M in THF) and NiCl₂(C₅H₃P)₂ (52 mg, 75.3 μmol). The alkoxide, in THF (3 ml), was prepared with n-BuLi (600 μl, 771 μmol, 1.29M in hexanes) and geraniol (61) (118.8 mg, 770 μmol). A solution of 1,2:5,6-di-O-isopropylidene-3,4 di-O-methyl-D-mannitol (183) (224 mg, 760 μmol) in THF (2 ml) was added to the alkoxide solution prior to degassing. The solution was then degassed, added to the catalyst, heated to reflux for 18 hours then quenched with saturated NH₄Cl solution (5 ml). Analysis of the residue by ¹H-NMR and GC revealed predominantly the mannitol derivative (183) and acetylated starting material, geranyl acetate (283), neither of which were isolated.

¹H-NMR δH: (283) 5.37 (2H, t, J 7.1, CH₂OAc), 5.08 (1H, m, C(5)-H), 4.60 (1H, d, J 7.1, C(2)-H), 2.10 (4H, m, CH₂CH₂), 2.05 (3H, s, CH₃CO₂), 1.70 (3H, s, CH₃), 1.68 (3H, s, CH₃), 1.61 (3H, s, CH₃-CH=CH)

IR (film) νmax: 2968, 2926, 2858, 1742, 1670, 1446, 1378, 1366, 1232, 1024, 955

MS (EI) m/z: 196 (M⁺, <1%), 154 (8), 136 (70), 121 (89), 107 (31), 93 (92), 85 (57), 80 (87), 67 (97), 53 (100), 39 (98), 43 (87), 41 (89), 29 (98), 27 (97)

Isomerisation of geraniol (61) with bipyridine and 1,2,3,4,5,6-Hexa-O-methyl-D-mannitol (184)

The catalyst, in THF (8 ml), was prepared from bipyridine (10.2 mg, 65.3 μmol) and Ni(COD)₂ (19.0 mg, 69.1 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (845 μl, 1.31 mmol, 1.55M in hexanes) and geraniol (61) (204 mg, 1.32 mmol). 1,2,3,4,5,6-Hexa-O-methyl-D-mannitol (184) (72.4 mg, 272 μmol) was added to the alkoxide prior to degassing. The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of (E) and (Z) enol acetates, (115) and (116) respectively, (169 mg, 860 μmol, 64%, 4.7 : 1) as a clear colourless oil. Rf (25% ether in petrol) 0.61
Isomerisation of geraniol (61) with DIPHOS (284) and tetra-t-butylammonium bromide (285)

\[
\begin{align*}
\text{(61)} & \quad \rightarrow \quad \text{(62)} + \text{(61)}
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from DIPHOS (284) (26.0 mg, 65.3 μmol) and Ni(COD)_2 (18.0 mg, 66.4 μmol). A solution of geraniol (61) (200 mg, 1.30 mmol) in THF (4 ml) and tetra-t-butylammonium bromide (418 mg, 1.30 mmol) was added dropwise to a stirred suspension of sodium hydride (61.0 mg, 60% wt disp. in oil, 1.53 mmol) in THF (4 ml) at 0°C, and the mixture stirred at room temperature for 30 minutes. The supernatant solution was then transferred to a clean, dry argon filled Schlenk vessel, using a filter-tipped cannulae. The mixture was degassed twice, added to the catalyst solution, heated to reflux for 3.5 hours then quenched with acetic anhydride (1.20 ml, 12.7 mmol). Analysis of the residue by ^1H-NMR and GC revealed predominantly citronellal (62) (11%) and starting material (61) (39%), neither of which were isolated.

Isomerisation of geraniol (61) with DIPHOS (284) and tetrahexylammonium bromide (285)

\[
\begin{align*}
\text{(61)} & \quad \rightarrow \quad \text{(62)} + \text{(61)}
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from DIPHOS (284) (26.5 mg, 66.5 μmol) and Ni(COD)_2 (18.0 mg, 66.0 μmol). A solution of geraniol (61) (200 mg, 1.30 mmol) in THF (4 ml) and tetrahexylammonium bromide (565 mg, 1.30 mmol) was added dropwise to a stirred suspension of sodium hydride (62.0 mg, 60% wt disp. in oil, 1.55 mmol) in THF (4 ml) at 0°C, and the mixture stirred at room temperature for 30 minutes. The supernatant solution was then transferred to a clean, dry argon filled Schlenk vessel, using a filter-tipped cannulae. The mixture was degassed twice, added to the catalyst solution, heated to reflux for 3.5 hours then quenched with acetic anhydride (1.20 ml, 12.7 mmol). Analysis of the residue by ^1H-NMR and GC revealed predominantly citronellal (62) (31%) and starting material (61) (23%), neither of which were isolated.
Isomerisation of geraniol (61) with DIPHOS (284) and 1 equivalent of 9-BBN-triflate

The catalyst, in THF (6 ml), was prepared from DIPHOS (284) (19.6 mg, 49.2 μmol) and Ni(COD)$_2$ (13.5 mg, 49.1 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (905 μl, 975 μmol, 1.08M in hexanes) and geraniol (61) (150 mg, 975 μmol). 9-BBN-triflate (1.95 ml, 975 μmol, 0.5M in hexane) was added to the alkoxide and stirred at room temperature for 1 hour prior to degassing and addition to the catalyst solution. The resulting mixture was heated to reflux for 18 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed starting material (61) (57%) and citronellol (112) (10%), neither of which were isolated.

Isomerisation of geraniol (61) with DIPHOS (284) and 1.2 equivalents of 9-BBN-triflate

The catalyst, in THF (6 ml), was prepared from DIPHOS (284) (20.3 mg, 50.9 μmol) and Ni(COD)$_2$ (14.0 mg, 50.9 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (905 μl, 975 μmol, 1.08M in hexanes) and geraniol (61) (150 mg, 975 μmol). 9-BBN-triflate (2.34 ml, 1.17 mmol, 0.5M in hexane) was added to the alkoxide and stirred at room temperature for 1 hour prior to degassing and addition to the catalyst solution. The resulting mixture was heated to reflux for 18 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed starting material (61) (40%) and citronellol (112) (12%), neither of which were isolated.
The catalyst, in THF (8 ml), was prepared from DIPHOS (284) (26.0 mg, 65.3 μmol) and Ni(COD)$_2$ (18.0 mg, 65.4 μmol). A solution of geraniol (61) (202 mg, 1.31 mmol) in THF (4 ml) was added dropwise to a stirred suspension of sodium hydride (66.0 mg, 60% wt disp. in oil, 1.65 mmol) in THF (4 ml) at 0°C, and the mixture stirred at room temperature for 30 minutes. 9-BBN-triflate (2.34 ml, 1.17 mmol, 0.5M in hexane) was then added, and after a further 30 minutes, the supernatant solution was transferred to a clean, dry argon filled Schlenk vessel, using a filter-tipped cannulae. The mixture was degassed twice, added to the catalyst solution, heated to reflux for 18 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed predominantly starting material (61) (80%), which was not isolated.

**Isomerisation of 1-t-butyldimethylsilyloxy-3,7-dimethyl-2,6-octadiene (187) with 2,2-bis-[4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)**

The catalyst, in THF (6 ml), was prepared from 2,2-bis-[4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (6.00 mg, 20.3 μmol) and Ni(COD)$_2$ (5.50 mg, 20.0 μmol). A solution of 1-t-butyldimethylsilyloxy-3,7-dimethyl-2,6-octadiene (187) (100 mg, 372 μmol) in THF (6 ml) was added to the catalyst solution at 0°C and the mixture heated to reflux for 16 hours, then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed predominantly starting material (187).

**Isomerisation of geraniol (61) with 2 equivalents of triphenylphosphine (286) and triphenylphosphine copper(I)chloride (287)**

The catalyst, in THF (8 ml), was prepared from triphenylphosphine (286) (34.4 mg, 131 μmol) and Ni(COD)$_2$ (18.0 mg, 65.4 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.20 ml, 1.32 mmol, 1.10M in hexanes) and geraniol (61) (202 mg, 1.31 mmol). Triphenylphosphine copper(I)chloride (47.3 mg, 131 μmol), followed by the alkoxide solution, was added to the catalyst mixture. The resulting mixture was then stirred at room temperature for 6 hours, at reflux for 6 hours, then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed predominant starting material (61) (55%), which was not isolated.
Isomerisation of geraniol (61) with 
NiCl₂(DIPHOS)/LiBE₃H and triphenylphosphine copper(I)chloride (287)

\[ \text{No Isomerisation Products} \]


The catalyst, in benzene (8 ml), was prepared from lithium triethylborohydride (70.0 μl, 70.0 μmol, 1M in THF) and NiCl₂(DIPHOS) (36.7 mg, 69.5 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.28 ml, 1.40 mmol, 1.10M in hexanes) and geraniol (61) (215 mg, 1.40 mmol). Triphenylphosphine copper(I)chloride (75.6 mg, 209 μmol), followed by the alk oxide solution, was added to the catalyst mixture. The resulting mixture was then heated to reflux for 2 hours, then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by \(^1\)H-NMR and GC revealed predominant starting material (61) (81%), which was not isolated.

Isomerisation of geraniol (61) with 
DIPHOS (284) and 4 equivalents of triethylborane

\[ \text{No Isomerisation Products} \] + \[ \text{(61)} \]

The catalyst, in THF (8 ml), was prepared from DIPHOS (284) (26.4 mg, 66.3 μmol) and Ni(COD)$_2$ (18.5 mg, 67.3 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.22 ml, 1.32 mmol, 1.10M in hexanes) and geraniol (61) (202 mg, 1.31 mmol). Triethylborane (270 μl, 270 μmol, 1M in hexanes) was added to the alkoxide solution before addition to the catalyst solution. The resulting alkoxide/catalyst/borane mixture was heated to reflux for 20 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the residue by \(^1\)H-NMR and GC revealed starting material (61) (28%) and citronellol (112) (30%), neither of which were isolated.

Isomerisation of geraniol (61) with 
DIPHOS (284) and 24 equivalents of triethylborane

\[ \text{No Isomerisation Products} \] + \[ \text{(61)} \] + \[ \text{(112)} \]

The catalyst, in THF (8 ml), was prepared from DIPHOS (284) (26.4 mg, 66.3 μmol) and Ni(COD)$_2$ (18.5 mg, 67.3 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.22 ml, 1.32 mmol, 1.10M in hexanes) and geraniol (61) (202 mg, 1.31 mmol). Triethylborane (270 μl, 270 μmol, 1M in hexanes) was added to the alkoxide solution before addition to the catalyst solution. The resulting alkoxide/catalyst/borane mixture was heated to reflux for 20 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the residue by \(^1\)H-NMR and GC revealed starting material (61) (28%) and citronellol (112) (30%), neither of which were isolated.
Experimental

The catalyst, in THF (8 ml), was prepared from DIPOHOS (284) (26.6 mg, 66.8 μmol) and Ni(COD)$_2$ (18.5 mg, 67.3 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (1.22 ml, 1.32 mmol, 1.10M in hexanes) and geraniol (61) (202 mg, 1.31 mmol). Triethylborane (1.60 ml, 1.60 mmol, 1M in hexanes) was added to the alkoxide solution before addition to the catalyst solution. The resulting alkoxide/catalyst/borane mixture was then heated to reflux for 20 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed citronellal (62) (6%), starting material (61) (17%) and citronellol (112) (34%), none of which were isolated.

Isomerisation of (E)-3-phenyl-2-propen-1-ol (58) with 2 equivalents of pyridine

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

The catalyst, in THF (6 ml), was prepared from pyridine (8.5 µl, 105 µmol) and Ni(COD)$_2$ (14.0 mg, 50.9 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (590 µl, 1.01 mmol, 1.72M in hexanes) and (E)-3-phenyl-2-propen-1-ol (58) (150 mg, 1.01 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 3 hours then quenched with acetic anhydride (600 µl, 6.36 mmol). The isolated residue was chromatographed (SiO$_2$, 15% ether in petrol) to afford acetylated starting material, (E)-1-acetoxy-3-phenyl-2-propene, (288)$_{335}$ (39.5 mg, 224 μmol, 22%) as the only identifiable product.

$^1$H-NMR $\delta$H: 7.43-7.19 (5H, m, PhH), 6.68 (1H, dd, J 15.9 and 1.3, PhCH=CHCH$_2$O), 6.31 (1H, dd, J 15.9 and 6.4, PhCH=CHCH$_2$O), 4.75 (2H, dd, J 6.4 and 1.3, PhCH=CHCH$_2$O), 2.13 (3H, s, CH$_3$CO$_2$)

Isomerisation of (E)-2-dodecen-1-ol (192) with 2 equivalents of pyridine

The catalyst, in THF (6 ml), was prepared from pyridine (12.5 µl, 139 µmol) and Ni(COD)$_2$ (20.0 mg, 72.7 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (790 µl, 1.36 mmol, 1.73M in hexanes) and (E)-2-dodecen-1-ol (192) (250 mg, 1.36 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 3 hours then quenched with acetic anhydride
(1.25 ml, 13.2 mmol). Analysis of the residue by $^{1}H$-NMR and GC indicated no trace of the enol acetates, (E) and (Z)-1-acetoxy-1-dodecene.

**Isomerisation of (E)-4-benzyloxy-2-buten-1-ol (191) with 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)**

The catalyst, in THF (8 ml), was prepared from 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (18.5 mg, 62.8 µmol) and Ni(COD)$_2$ (17.0 mg, 61.8 µmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (700 µl, 1.19 mmol, 1.70M in hexanes) and (E)-4-benzyloxy-2-buten-1-ol (191) (200 mg, 1.12 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 1.5 hours then quenched with acetic anhydride (1.20 ml, 12.7 mmol). The isolated residue was chromatographed (SiO$_2$, 25-50% ether in petrol) to afford benzyl acetate (193) (4.6 mg, 30.6 µmol, 3%) and starting material (191) (42.1 mg, 236 µmol, 21%) as clear colourless oils.

$^{1}H$-NMR $\delta$: (193) 7.40-7.28 (5H, m, PhH), 5.14 (2H, s, PhCH$_2$O), 2.13 (3H, s, CH$_3$CO$_2$)

$^{13}C$-NMR $\delta$: (193) 170.9, 135.9, 128.6, 128.3, 128.2, 66.3, 21.1

IR (film) $\nu_{max}$: (193) 3066, 3035, 2956, 2894, 1732 (s, C=O), 1608, 1498, 1456, 1381, 1228 (s), 1081, 1027, 1081, 1027, 967

**Isomerisation of (E)-3-phenyl-2-buten-1-ol (63) with 2 equivalents of pyridine**

The catalyst, in THF (6 ml), was prepared from pyridine (8.5 µl, 105 µmol) and Ni(COD)$_2$ (14.0 mg, 50.9 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (595 µl, 1.02 mmol, 1.72M in hexanes) and (E)-3-phenyl-2-buten-1-ol (63) (150 mg, 1.01 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO$_2$, 10% ether in petrol) to afford a mixture of (E) and (Z)-1-acetoxy-3-phenyl-1-butene, (169) and (170) respectively, (103 mg, 53%, 15:1) as a clear colourless oil.
Isomerisation (E)-1-phenyl-2-buten-1-ol (199) with 2 equivalents of pyridine

The catalyst, in THF (6 ml), was prepared from pyridine (8 µl, 99 µmol) and Ni(COD)₂ (12.0 mg, 43.6 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (485 µl, 829 µmol, 1.71M in hexanes) and (E)-phenyl-2-buten-1-ol (199) (123 mg, 829 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (800 µl, 8.48 mmol). The isolated residue was chromatographed (SiO₂, 5-20% ether in petrol) to afford 1-phenyl-1-butanone (203)\(^°^\) (52.9 mg, 357 pmol, 43%) an inseparable mixture of (Z) and (E)-\(^\ddagger\)phenyl-3-acetoxy-2-pentene, (201)\(^\ddagger\) and (202) respectively (33.1 mg, 174 pmol, 21%, >20 : 1), and acetylated starting material, (E)-1-phenyl-1-acetoxy-2-butene (204)\(^°\) (51.9 mg, 273 pmol, 33%) as clear colourless oils.

\(^1\)H-NMR \(\delta_{HS} (201)\) 7.61-7.20 (5H, m, Ph), 5.81 (1H, t, J 7.4, C=CHCH\(_2\)CH\(_3\)), 2.29 (3H, s, OCH\(_3\)), 2.15 (2H, m, C=CHCH\(_2\)CH\(_3\)), 1.07 (3H, t, J 7.6, C=CHCH\(_2\)CH\(_3\)); (202) 5.42 (1H, t, J 8.3, C=CHCH\(_2\)CH\(_3\)), other signals obscured; (204) 7.55-7.20 (5H, m, PhH), 6.20 (1H, m, PhCHOAc), 5.78-5.61 (2H, m, CH=CHCH\(_3\)), 1.71 (3H, dd, J 5.6 and 0.9, CH=CHCH\(_3\)); (203) 7.97-7.21 (5H, m, PhH), 2.93 (2H, t, J 7.2, CH\(_2\)CH\(_2\)CH\(_3\)), 1.75 (2H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 0.99 (3H, t, J 7.4, CH\(_2\)CH\(_2\)CH\(_3\))

IR (film) \(\nu_{max}\): (203) 3062, 2963, 2934, 2875, 1967, 1905, 1817, 1687, 1598, 1581, 1449, 1369, 1274, 1213, 1180, 1002, 966, 754, 736, 691, 668; Mixture (201) and (202): 3034, 2968, 2936, 1760, 1665, 1601 (w), 1494, 1447, 1370, 1207, 1035, 751, 691; (204) 2969, 2936, 1722, 1675, 1597, 1448, 1357, 1273, 1211, 735, 695

LRMS (El) m/z: (203) 148 (M⁺, 49%), 120 (38%), 105 (100), 91 (11), 77 (90), 65 (7), 55 (10), 51 (82), 39 (31), 27 (54); Mixture (201) and (202): 190 (M⁺, 12%), 148 (100), 133 (18), 105 (10), 77 (15), 51 (8), 43 (21)

HRMS (El) m/z: Mixture (201) and (202): Found for C\(_{12}\)H\(_{14}\)O\(_2\) (M⁺), 190.0994; Required 190.1002
Isomerisation of (E)-2,2-dimethyl-4-hexen-3-ol (200) with 2 equivalents of pyridine

The catalyst, in THF (6 ml), was prepared from pyridine (8 μl, 99 μmol) and Ni(COD)_2 (12.0 mg, 43.6 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (460 μl, 787 μmol, 1.73M in hexanes) and (E)-2,2-dimethyl-4-hexen-3-ol (200) (101 mg, 787 μmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (800 μl, 8.48 mmol). The isolated residue was chromatographed (SiO₂, 20% ether in petrol) to afford an inseparable mixture of (Z)-2,2-dimethyl-3-acetoxy-3-hexene (205) (Z:E >20 : 1) and acetylated starting material, (E)-2,2-dimethyl-3-acetoxy-4-hexene, (206) (59.6 mg, 350 μmol, 45%; 1 : 3.4) as a clear colourless oils.

^H-NMR δ: (136) 5.03 (1H, t, J 7.0, C=CHCH₃CH₂), 2.15 (3H, s, CH₃CO₂), 2.11 (2H, m, C=CHCH₃CH₂), 1.03 (3H, peaks obscured, C=CHCH₃CH₂), 0.87 (9H, s, C(CH₃)₃); (206) 5.66 (1H, dq, J 16.0 and 6.5, CHCH=CHCH₃), 5.39 (1H, ddq, J 16.0, 7.9 and 1.5, CHCH=CHCH₃), 4.91 (1H, d, J 7.9, CHCH=CHCH₃), 2.13 (3H, s, CH₃CO₂), 1.67 (3H, dd, J 6.5 and 1.5, CHCH=CHCH₃), 0.87 (9H, s, C(CH₃)₃)

IR (film) ν max: Mixture of (205) and (206) : 2968, 2873, 1760 (s, C=0), 1738 (s, C=O), 1704, 1674, 1480, 1464, 1369 (s), 1241, 1221, 1208, 1143, 1086, 1053, 1020, 969, 934, 900, 609

LRMS (FAB) m/z: Mixture of (205) and (206) : 363 (2M^+Na, 35%), 323 (2M^+-OH, 18%), 154 (49), 136 (72), 127 (M^+-Ac, 84%), 111 (M^+-OAc, 67%)

Isomerisation of 3-methyl-1-phenyl-2-buten-1-ol (207) with 2 equivalents of pyridine

The catalyst, in THF (8 ml), was prepared from pyridine (10 μl, 124 μmol) and Ni(COD)_2 (17.0 mg, 61.8 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (816 μl, 1.31 mmol, 1.61M in hexanes) and 3-methyl-1-phenyl-2-buten-1-ol (207) (213 mg, 1.31 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2.5 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the residue by ^H-NMR and GC indicated predominantly starting material (94%), which was not isolated.
Isomerisation of (E)-2-methyl-1-phenyl-2-buten-1-ol (208) with 2 equivalents of pyridine

\[ \text{PhCH} = \text{CH} - \text{CHCH}_2 - \text{OH} \rightarrow \text{PhCH} = \text{CH} - \text{CHCH}_2 - \text{OAc} + \text{PhCH} = \text{CH} - \text{CHCH}_2 - \text{OAc} \]

The catalyst, in THF (8 ml), was prepared from pyridine (10 μl, 124 μmol) and Ni(COD)$_2$ (17.0 mg, 61.8 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (773 μl, 1.24 mmol, 1.61M in hexanes) and (E)-2-methyl-1-phenyl-2-buten-1-ol (208) (201 mg, 1.24 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 1.5 hours then quenched with acetic anhydride (1.20 ml, 12.7 mmol). The isolated residue was chromatographed (SiO$_2$, 5% ether in petrol) to afford 2-methyl-1-phenyl-1-butanone (209) (39.5 mg, 243 pmol, 20%) and an inseparable mixture of (Z) and (E)-1-phenyl-1-acetoxy-2-methyl-1-butene, (213) and (214) respectively (137 mg, 671 pmol, 54%; 5.0 : 1) as clear colourless oils.

$^1$H-NMR δH: (209) 7.95-7.92 (1H, m, PhH), 7.56-7.41 (4H, m, PhH), 3.38 (1H, m, PhCHCH$_3$), 1.82 (1H, m, CHHCH$_3$), 1.48 (1H, m, CHHCH$_3$), 1.17 (3H, d, J 6.7, PhCHCH$_3$), 0.90 (3H, t, J 7.3, CH$_2$CH$_3$); (213) 7.41-7.25 (5H, m, PhH), 2.13 (3H, s, OCH$_3$), 2.12 (2H, q, J 7.5, CH$_2$CH$_3$); 1.73 (3H, s, C=CHH$_3$), 1.08 (3H, t, J 7.5, CH$_2$CH$_3$); (214) 7.41-7.25 (5H, m, PhH), 2.14 (3H, s, OCH$_3$), 2.14 (2H, q, J 7.5, CH$_2$CH$_3$), 1.79 (3H, s, C=CHH$_3$), 1.06 (3H, t, J 7.5, CH$_2$CH$_3$);

$^{13}$C-NMR δC: (209) 206.1, 136.8, 132.8, 128.6, 128.2, 42.1, 26.7, 16.8, 11.8; Mixture of (213) and (214): 169.2, 169.2, 141.3, 140.7, 136.0, 135.9, 128.9, 128.9, 128.6, 128.1, 128.0, 127.9, 127.7, 127.3, 26.1, 26.1, 25.3, 20.9, 17.1, 15.1, 12.9, 12.0

IR (film) νmax: (209) 2969, 2934, 1680 (s, C=O), 1597, 1581, 1448, 1378, 1219, 972, 702; Mixture of (213) and (214): 3059, 2972, 2937, 2877, 2099, 1955, 1890, 1686, 1602, 1576, 1493, 1444, 1369, 1215, 1117, 1046, 1026, 961, 898, 780, 700;

LRMS (FAB) m/z: Mixture of (213) and (214): 205 (M$^+H$, 13%), 204 (M$^+$, 20%), 176 (9), 162 (M$^+$+H-CH$_3$CHO, 100%);

HRMS (FAB) m/z Mixture of (213) and (214): Found for C$_{13}$H$_{16}$O$_2$·(M$^+$), 204.1140; Required 204.1150

Isomerisation of 2-ethyl-1-phenyl-2-propen-1-ol (210) with 2 equivalents of pyridine

\[ \text{PhCH} = \text{CH} - \text{CHCH}_2 - \text{OH} \rightarrow \text{PhCH} = \text{CH} - \text{CHCH}_2 - \text{OAc} + \text{PhCH} = \text{CH} - \text{CHCH}_2 - \text{OAc} \]
The catalyst, in THF (8 ml), was prepared from pyridine (10 μl, 124 μmol) and Ni(COD)$_2$ (17.0 mg, 61.8 μmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (773 μl, 1.24 mmol, 1.61M in hexanes) and 2-ethyl-1-phenyl-2-propen-1-ol (210) (202 mg, 1.24 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 1.5 hours then quenched with acetic anhydride (1.20 ml, 12.7 mmol). The isolated residue was chromatographed (SiO$_2$, 5% ether in petrol) to afford 2-methyl-1-phenyl-1-butanone (209)$^{337}$ (42.6 mg, 263 μmol, 21%) and an inseparable mixture of (Z) and (E)-1-phenyl-1-acetoxy-2-methyl-1-butene, (213) and (214) respectively (125 mg, 610 μmol, 49%; 2.5 : 1) as clear colourless oils.

**Isomerisation of (E)-2-methyl-1-phenyl-2-buten-1-ol (208) with 2 equivalents of pyridine in benzene**

![Diagram]

The catalyst, in benzene (7 ml), was prepared from pyridine (7 μl, 86.5 μmol) and Ni(COD)$_2$ (12.0 mg, 43.6 μmol). The alkoxide, in benzene (7 ml), was prepared with n-BuLi (539 μl, 924 μmol, 1.71M in hexanes) and (E)-2-methyl-1-phenyl-2-buten-1-ol (208) (150 mg, 925 μmol) at 5°C. The resulting catalyst/alkoxide mixture was heated to reflux for 1.5 hours then quenched with acetic anhydride (500 μl, 5.30 mmol). The isolated residue was chromatographed (SiO$_2$, 5% ether in petrol) to afford 2-methyl-1-phenyl-1-butanone (209)$^{337}$ (34.5 mg, 213 μmol, 23%) and an inseparable mixture of (Z) and (E)-1-phenyl-1-acetoxy-2-methyl-1-butene, (213) and (214) respectively (103 mg, 503 μmol, 54%; 2.4 : 1) as clear colourless oils.

**Isomerisation of 2-ethyl-1-phenyl-2-propen-1-ol (210) with 2 equivalents of pyridine in benzene**

![Diagram]
249 Experimental

petrol) to afford 2-methyl-1-phenyl-1-butanone \((209)^{397}\) (28.5 mg, 176 \(\mu \)mol, 19\%) and an inseparable mixture of \((Z)\) and \((E)\)-1-phenyl-1-acetoxy-2-methyl-1-butene, \((213)\) and \((214)\) respectively (98.4 mg, 482 \(\mu \)mol, 52\%; 2.4 : 1) as clear colourless oils.

**Isomerisation of 2,2-dimethyl-4-ethyl-4-penten-3-ol \((215)\) and \((E)\)-2,2,4-trimethyl-4-hexen-3-ol \((216)\) with 2 equivalents of pyridine**

\[
\begin{align*}
  \text{(215)} \quad + \quad \text{(216)} & \quad \rightarrow \quad \text{(217)} \\
\end{align*}
\]

The catalyst, in THF (8 ml), was prepared from pyridine (10 \(\mu\)l, 124 \(\mu\)mol) and Ni(COD)\(_2\) (17.0 mg, 61.8 \(\mu\)mol). The alkoxide, in THF (8 ml), was prepared with \(n\)-BuLi (800 \(\mu\)l, 1.29 mmol, 1.61M in hexanes), 1-phenyl-2-ethyl-2-propen-1-ol \((215)\) and \((E)\)-1-phenyl-2-methyl-2-buten-1-ol \((216)\) (183 mg, 1.29 mmol; 2.2 : 1). The resulting catalyst/alkoxide mixture was heated to reflux for 2.5 hours then quenched with saturated \(\text{NH}_4\text{Cl}\) solution (8 ml). Analysis of the residue by \(^1\text{H}-\text{NMR}\) and GC indicated both starting materials, \((215)\) and \((216)\) (57\%, 1.9 : 1) and 2,2,4-trimethyl-3-hexanone \((217)^{398}\) (18\%), none of which were isolated.

\(^1\text{H}-\text{NMR}\) \(\delta_h\): \((217)\) 2.89 (1H, m, \(\text{C}[-\text{O}]\text{CHCH}_3\), other peaks obscured.

**Isomerisation of 1,6-heptadien-3-ol \((219)\) with 2 equivalents of pyridine**

\[
\begin{align*}
  \text{(219)} & \quad \rightarrow \quad \text{(220)} \\
\end{align*}
\]

The catalyst, in THF (6 ml), was prepared from pyridine (12.5 \(\mu\)l, 139 \(\mu\)mol) and Ni(COD)\(_2\) (20.0 mg, 72.7 \(\mu\)mol). The alkoxide, in THF (6 ml), was prepared with \(n\)-BuLi (790 \(\mu\)l, 1.36 mmol, 1.73M in hexanes) and 1,6-heptadien-3-ol \((219)\) (250 mg, 1.36 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 3 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO\(_2\), 10\% ether in petrol) to afforded 6-hepten-3-one \((220)^{399}\) (27.7 mg, 247 \(\mu\)mol, 18\%) containing an impurity.

\(^1\text{H}-\text{NMR}\) \(\delta_h\): \((220)\) 5.82 (1H, ddt, \(J\) 17.1, 10.1 and 6.4, \(\text{CH}=\text{CH}_2\)), 5.03 (1H, dq, \(J\) 17.1 and 1.6, \(\text{CH}=\text{CH}\text{H}_{\text{trans}}\)), 4.96 (1H, dq, \(J\) 10.1 and 1.6, \(\text{CH}=\text{CH}\text{H}_{\text{cis}}\)), 2.43 (2H, q, \(J\) 7.3, \(\text{CH}_2\text{CH}_2\)), 2.54-2.31 (4H, m, \(\text{CH}_2\text{CH}_2\text{CO}\)), 1.03 (3H, t, \(J\) 7.2, \(\text{CH}_3\text{CH}_2\)).
Isomerisation of $N,N$-diethylgeranylamine (64) with 2 equivalents of pyridine

The catalyst, in THF (6 ml), was prepared from pyridine (8.5 μl, 105 μmol) and Ni(COD)$_2$ (14.0 mg, 50.9 μmol). A solution of $N,N$-diethylgeranylamine (64) (212 mg, 1.01 mmol) in THF (6 ml) was degassed twice then added to the catalyst solution. The resulting mixture was heated to reflux for 16 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed predominantly starting material (64) (92%), which was not isolated.

Isomerisation of $N,N$-diethylgeranylamine (64) with DIPHOS (284)

The catalyst, in THF (6 ml), was prepared from DIPHOS (284) (19.0 mg, 47.7 μmol) and Ni(COD)$_2$ (13.0 mg, 47.3 μmol). A solution of $N,N$-diethylgeranylamine (64) (200 mg, 955 μmol) in THF (6 ml) was degassed twice then added to the catalyst solution. The resulting mixture was heated to reflux for 16 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed predominantly starting material (64) (91%), which was not isolated.

Isomerisation of $N,N$-diethylgeranylamine (64) with bipyridyl

The catalyst, in THF (6 ml), was prepared from bipyridyl (7.8 mg, 49.9 μmol) and Ni(COD)$_2$ (13.0 mg, 47.3 μmol). A solution of $N,N$-diethylgeranylamine (64) (200 mg, 955 μmol) in THF (6 ml) was degassed twice then added to the catalyst solution. The resulting mixture was heated to reflux for 16 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the residue by $^1$H-NMR and GC revealed predominantly starting material (64) (83%), which was not isolated.
Isomerisation of 1-phenyl-4-penten-3-ol (102) with 2 equivalents of pyridine

The catalyst, in THF (8 ml), was prepared from pyridine (7.9 µl, 97.7 µmol) and Ni(COD)$_2$ (13.4 mg, 48.7 µmol). The alkoxide, in THF (8 ml), was prepared with n-BuLi (578 µl, 925 µl, 1.60M in hexanes) and 1-phenyl-4-penten-3-ol (102) (150 mg, 925 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 1.75 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO$_2$, 20-50% ether in petrol) to afford an inseparable mixture of (E) and (Z)-1-phenyl-3-acetoxo-3-pentene, (227) and (228) respectively (12%, 8.2 : 1), of (E) and (Z)-1-phenyl-3-acetoxo-2-pentene, (229) and (230) respectively (14%, 2.3 : 1), (total: 49.1 mg, 241 µmol, 26%), 1-phenyl-3-pentanone (226)$^{340}$ (25.3 mg, 169 µmol, 17%) and starting material (102) (32.0 mg, 197 µmol, 21%) as clear colourless oils.

$^1$H-NMR $\delta_H$: (227) 7.34-7.15 (5H, m, PhH), 5.09 (1H, q, $J_6.8$, C=CHCH$_3$), 2.75 (2H, t, $J_7.9$, PhCH$_2$CH$_2$), 2.50 (2H, t, $J_7.9$, PhCH$_2$CH$_2$), 2.20 (3H, s, CH$_3$CO$_2$), 1.49 (3H, d, $J_6.8$, C=CHCH$_3$); (228) 7.34-7.15 (5H, m, PhH), 5.29 (1H, q, $J_6.8$, C=CHCH$_3$) other peaks obscured; (229) 7.34-7.15 (5H, m, PhH), 5.20 (1H, t, $J_7.3$, C=CHCH$_2$Ph), 3.29 (2H, d, $J_7.3$, C=CHCH$_2$Ph), 2.26 (2H, q, $J_7.5$, CH$_2$CH$_3$), 2.15 (3H, s, CH$_3$CO$_2$), 1.07 (3H, t, $J_7.5$, CH$_2$CH$_3$); (230) 7.34-7.15 (5H, m, PhH), 3.43 (2H, d, $J_8.1$, PhCH$_2$);

IR (film) $\nu_{max}$: Mixture of (227), (228), (229) and (230): 3085, 3062, 3028, 2974, 2937, 2360 (w), 1949 (w), 1753 (s, C=O), 1715 (s, C=O), 1604, 1496, 1454, 1370, 1219 (s), 1156, 1074, 1022, 967, 947, 910, 851, 795, 748, 700 (s)

HRMS (EI) $m/z$: Mixture acetates: 205 (M$^+$/H, 14%), 161 (M$^+$/Ac, 51%), 145 (25), 91 (100), 77 (47)

HRMS (EI) $m/z$: Mixture acetates: Found for C$_{13}$H$_7$O$_2$ (M$^+$/H), 205.1220; Required 205.1229
Isomerisation of 3-phenyl-2-cyclohexen-1-ol (161) with 2 equivalents of pyridine

The catalyst, in THF (6 ml), was prepared from pyridine (8 μl, 102 μmol) and Ni(COD)$_2$ (14.0 mg, 50.9 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (595 μl, 977 μmol, 1.64M in hexanes) and 3-phenyl-2-cyclohexen-1-ol (161) (170 mg, 976 μmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO$_2$, 5-50% ether in petrol) to afford 3-phenylcyclohexanone (168) (81.6 mg, 468 μmol, 48%) and an inseparable mixture of 3-phenyl-1-acetoxy-1-cyclohexene and 4-phenyl-2-acetoxy-1-cyclohexene, (231) and (232) respectively (61.2 mg, 283 μmol, 29%; 2.0 : 1) as clear colourless oils.

$^1$H-NMR δ: (231) 7.32-7.16 (5H, m, PhH), 5.41 (1H, d, J 2.6, C=CH), 3.55 (1H, m, Ph-CH), 2.30-1.49 (6H, m, CH$_2$CH$_2$CH$_2$), 2.13 (3H, s, CH$_3$O); (232) 7.32-7.16 (5H, m, PhH), 5.44 (1H, m, C=CH), 3.55 (1H, m, PhCH), 2.30-1.49 (6H, m, CH$_2$CH$_2$CH$_2$), 2.10 (3H, s, CH$_3$O)

$^{13}$C-NMR δ: (231) 169.4, 149.6, 145.4, 128.3, 127.7, 126.2, 117.2, 51.2, 40.2, 31.8, 26.8, 20.9; (232) 169.4, 147.7, 145.5, 128.4, 126.9, 126.3, 113.8, 38.9, 34.5, 29.0, 23.7, 21.1

IR (film) ν$_{max}$: Mixture of (231) and (232): 3060, 3027, 2936, 2861, 1950 (w), 1756 (s, C=O), 1688, 1602, 1492, 1452, 1365, 1220 (s), 1121 (s), 1044, 1010, 911, 883, 846 (w), 758, 701 (s), 603 (w), 531

LRMS (FAB) m/z: Mixture of (231) and (232): 175 (M$^+$+H-CH$_3$CO), 174 (14), 157 (20), 154 (38), 117 (100), 115 (97), 107 (31), 103 (53)

HRMS (FAB) m/z: Found for C$_{12}$H$_{15}$O (M$^+$+H), 175.1130; Required 175.1123

Isomerisation of 3-phenyl-2-cyclohexen-1-ol (161) with 2 equivalents of triphenylphosphine

The catalyst, in THF (6 ml), was prepared from pyridine (8 μl, 102 μmol) and Ni(COD)$_2$ (14.0 mg, 50.9 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (595 μl, 977 μmol, 1.64M in hexanes) and 3-phenyl-2-cyclohexen-1-ol (161) (170 mg, 976 μmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO$_2$, 5-50% ether in petrol) to afford 3-phenylcyclohexanone (168) (81.6 mg, 468 μmol, 48%) and an inseparable mixture of 3-phenyl-1-acetoxy-1-cyclohexene and 4-phenyl-2-acetoxy-1-cyclohexene, (231) and (232) respectively (61.2 mg, 283 μmol, 29%; 2.0 : 1) as clear colourless oils.

$^1$H-NMR δ: 7.32-7.16 (5H, m, PhH), 5.41 (1H, d, J 2.6, C=CH), 3.55 (1H, m, Ph-CH), 2.30-1.49 (6H, m, CH$_2$CH$_2$CH$_2$), 2.13 (3H, s, CH$_3$O); 7.32-7.16 (5H, m, PhH), 5.44 (1H, m, C=CH), 3.55 (1H, m, PhCH), 2.30-1.49 (6H, m, CH$_2$CH$_2$CH$_2$), 2.10 (3H, s, CH$_3$O)

$^{13}$C-NMR δ: 169.4, 149.6, 145.4, 128.3, 127.7, 126.2, 117.2, 51.2, 40.2, 31.8, 26.8, 20.9; 169.4, 147.7, 145.5, 128.4, 126.9, 126.3, 113.8, 38.9, 34.5, 29.0, 23.7, 21.1

IR (film) ν$_{max}$: Mixture of (231) and (232): 3060, 3027, 2936, 2861, 1950 (w), 1756 (s, C=O), 1688, 1602, 1492, 1452, 1365, 1220 (s), 1121 (s), 1044, 1010, 911, 883, 846 (w), 758, 701 (s), 603 (w), 531

LRMS (FAB) m/z: Mixture of (231) and (232): 175 (M$^+$+H-CH$_3$CO), 174 (14), 157 (20), 154 (38), 117 (100), 115 (97), 107 (31), 103 (53)

HRMS (FAB) m/z: Found for C$_{12}$H$_{15}$O (M$^+$+H), 175.1130; Required 175.1123
hexanes) and 3-phenyl-2-cyclohexen-1-ol (161) (170 mg, 976 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with acetic anhydride (1.00 ml, 10.6 mmol). The isolated residue was chromatographed (SiO₂, 5-50% ether in petrol) to afford 3-phenylcyclohexanone (168) (74.8 mg, 429 µmol, 44%) and an inseparable mixture of 3-phenyl-1-acetoxy-1-cyclohexene and 4-phenyl-2-acetoxy-1-cyclohexene, (231) and (232) respectively (46.4 mg, 215 µmol, 22%; 2.1 : 1) as clear colourless oils.

**Isomerisation of 1-[²H]-1-phenyl-2-propen-1-ol (233) with 2 equivalents of tricyclohexylphosphine (286)**

![Diagram](image)

The catalyst, in THF (6 ml), was prepared from tricyclohexylphosphine (286) (29 mg, 103 µmol) and Ni(COD)₂ (14.0 mg, 50.9 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (280 µl, 479 µmol, 1.71M in hexanes) and 1-[²H]-1-phenyl-2-propen-1-ol (233) (65.0 mg, 481 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4.5 hours then quenched with saturated NH₄Cl solution (8 ml). The isolated residue was chromatographed (SiO₂, 20% ether in petrol) to afford 3-[²H]-1-phenyl-1-propanone (235)1346.1 mg, 193 µmol, 40%) as a clear colourless oil.

**Isomerisation of 1-[²H]-1-phenyl-2-propen-1-ol (233) with 2,2-*bis*-[4S]-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)**

![Diagram](image)

The catalyst, in THF (6 ml), was prepared from 2,2-*bis*-[4S]-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (15 mg, 50.9 µmol) and Ni(COD)₂ (14.0 mg, 50.9 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (281 µl, 961 µmol, 1.71M in hexanes) and 1-[²H]-1-phenyl-2-propen-1-ol (233) (65.0 mg, 481 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4.5 hours then quenched with saturated NH₄Cl solution (8 ml). The isolated residue was chromatographed (SiO₂, 20% ether in petrol) to afford 3-[²H]-1-phenyl-1-propanone (235)1345.9 mg, 192 µmol, 40%) as a clear colourless oil.
Isomerisation of \((E)-1,1\text{-di}[{}^2\text{H}]\text{-3-phenyl-2-buten-1-ol (238)}\) with \(2,2\text{-bis-}[\{4S\}4\text{-t-butyl-1,3-oxazoline-2-y1}\text{-propane (128)}\)

\[
\begin{align*}
\text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
\rightarrow & & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
\text{(238)} & & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
& & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
\text{(241)} & & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
\text{(238)} & & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
& & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH} \\
\text{(242)} & & & \quad \text{Ph} & \quad \text{D} & \quad \text{D} & \quad \text{OH}
\end{align*}
\]

The catalyst, in THF (6 ml), was prepared from \(2,2\text{-bis-}[\{4S\}4\text{-t-butyl-1,3-oxazoline-2-y1}\text{-propane (128)}\) (15.0 mg, 50.9 µmol) and Ni(COD)\(_2\) (14.0 mg, 50.9 µmol). The alkoxide, in THF (6 ml), was prepared with \(n\)-BuLi (595 µl, 1.02 mmol, 1.72M in hexanes) and \((E)-1,1\text{-di}[{}^2\text{H}]\text{-3-phenyl-2-buten-1-ol (238)}\) (153 mg, 1.02 mmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated NH\(_4\)Cl solution (8 ml). The isolated residue was chromatographed (SiO\(_2\), 10% ether in petrol) to afford 1,3-di[\(^2\text{H}\)]-3-phenylbutanal (241)\(^{322}\) (39.2 mg, 261 µmol, 26%) and an inseparable mixture of starting material and 1,1,3-tri[\(^2\text{H}\)]-3-phenyl-1-butanol, (238) and (242)\(^{322}\) respectively, (21.0 mg, ca. 14%, 1 : 1) as clear colourless oils. 

\[^1\text{H-NMR}\] \(\delta\): (241) 7.38-7.25 (5H, m, PhH), 2.78 (1H, d, \(J = 15.7\), CHHCDO), 2.66 (1H, d, \(J = 15.7\), CHHCDO), 1.35 (3H, s, CH\(_3\)CD); (242) 7.43-7.19 (5H, m, PhH), 1.84 (2H, s, CH\(_2\)CD\(_2\)OH), 1.28 (3H, s, CH\(_3\)CD) 

\[^{13}\text{C-NMR}\] \(\delta\): (241) 210.0, 143.0, 128.7, 126.7, 126.6, 33.6, 22.1; (242) 146.8, 128.5, 128.3, 126.9, 36.4, 22.4 

\[^{\text{IR (film)}}\] \(\nu\): max (241) 3083, 3059, 3025, 2964, 2928, 2872, 2600 (w), 2077, 1948 (w), 1873 (w), 1803 (w), 1711 (s, C=O), 1603, 1494 (s), 1447 (s), 1377, 1182, 1092, 1028, 910, 759, 734, 700, 544 (w); Mixture of (238) and (242): 3370 (s, OH), 3082, 3025, 2963, 2871, 2182 (w), 2010 (w), 1948 (w), 1879 (w), 1728, 1673, 1601, 1494, 1446, 1377, 1264, 1139, 1078, 1028, 1003, 958, 908, 811, 759, 699 (s), 588 (w), 548. 

\[^{\text{LRMS (FAB)}}\] m/z: 138 (M\(^+\), 3%), 106 (PhCDCH\(_2\)\(^+\), 100%)
Experimental

Isomerisation of (E) 1,1-Di-[3H]-3-phenyl-2-buten-1-ol (238) with NiCl$_2$(Cy$_3$P)$_2$/n-BuLi

The catalyst, in THF (6 ml), was prepared from n-BuLi (90.0 µl, 153 µmol, 1.70 M in hexanes) and NiCl$_2$(Cy$_3$P)$_2$ (70.0 mg, 101 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (395 µl, 672 µmol 1.70M in hexanes) and (E) 1,1-di-[3H]-3-phenyl-2-buten-1-ol (238) (100 mg, 666 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 6 hours then quenched with saturated NH$_4$Cl solution (8 ml). The isolated residue was chromatographed (SiO$_2$, 10-50% ether in petrol) to afford predominantly starting material (238) (28.4 mg, 189 µmol, 28%) as a clear colourless oil.

Isomerisation of (E)-1,1-di-[3H]-3,7-dimethyl-2,6-octadien-1-ol (239) with 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128)

The catalyst, in THF (6 ml), was prepared from 2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane (128) (12.5 mg, 42.4 µmol) and Ni(COD)$_2$ (11.0 mg, 40.0 µmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (462 µl, 795 µmol, 1.72 M in hexanes) and (E)-1,1-di-[3H]-3,7-dimethyl-2,6-octadien-1-ol (239) (124 mg, 794 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated NH$_4$Cl solution (8 ml). The isolated residue was chromatographed (SiO$_2$, 5-50% ether in petrol) to afford 1,3-di-[3H]-3,7-dimethyl-6-octenal (243) (16.7 mg, 107 µmol, 13%), and an inseparable mixture of starting material and 1,1,3-tri-[3H]-3,7-dimethyl-6-octen-1-ol, (239) and (244) respectively, (31.8 mg, 204 µmol, 26%, 1 : 2.73) as clear colourless oils.

$^1$H-NMR δ (ppm)

- (239): 5.11 (1H, m, C=CH), 2.42 (1H, d, J 16.0, CH=CD), 2.24 (1H, d, J 16.0, CH=CD), 2.06-1.98 (2H, m, C=CHCH$_2$), 1.71 (3H, s, CH$_3$), 1.62 (3H, s, CH$_3$), 1.58-1.21 (2H, m, C=CHCH$_2$CH$_3$), 0.99 (3H, s, CH$_3$CD); (244) 5.16-5.04 (1H, m, CH$_2$CH=CH$_3$), 2.14-1.91 (2H, m, CH$_2$CH=CH$_3$), 1.69 (3H, s, CH$_3$), 1.61 (3H, s, CH$_3$), 1.72-1.17 (5H, m, CH$_2$CD(CH$_3$)CH$_2$CD$_2$OH), 0.91 (3H, s, CH$_3$CD)
\(^{13}\text{C-NMR}\) \(\delta_{C}\): (243) 203.4, 131.8, 124.1, 36.9, 25.7, 25.4, 19.8, 17.7; (244) 131.3, 124.7, 39.6, 37.1, 25.7, 25.5, 19.4, 17.7; \(\text{IR (film)}\) \(\nu_{\text{max}}\): (243) 2966 (s), 2917 (s), 2073 (s), 2055 (s), 270 (w), 2255 (w), 2067, 1714 (s), 1666, 1624, 1556, 1454, 1377, 1096, 984 (w), 914, 831, 735 (s), 648 (w); Mixture (239) and (244): 3333 (s, OH), 2966, 2916, 2856, 2730 (w), 2199 (w), 2092, 1665, 1451, 1377, 1258 (w), 1137, 1081, 1049 (w), 970, 890 (w), 826 (w), 735 (w)

\(\text{LRMS (FAB)}\) \(m/z\): (243) 156 (M\(^+\), 3%), 139 (M\(^+\) - OH, 14%), 110 (26), 83 (20), 70 (32), 69 (100), 55 (41); Mixture (239) and (244) 159 (M\(^+\), <1%), 142 (M\(^+\)-OH, 2%), 141 (M\(^+\)-H\(_2\)O, 4%), 102 (7), 110 (32), 98 (7), 96 (16), 84 (9), 83 (21), 82 (46), 71 (11), 69 (100), 55 (20), 43 (23), 41 (57)

\(\text{HRMS (FAB)}\) \(m/z\): On recovered (239): Found for \(\text{C}_{10}\text{H}_{15}\text{D}_2\) (M\(^+\)OH), 139.1450; Required 139.1456; (243): Found for \(\text{C}_{10}\text{H}_{15}\text{D}_2\) (M\(^+\)OH), 139.1450; Required 139.1456

**Isomerisation of (\(E\)-1,1-di-[^H\(^2\)]-3,7-dimethyl-2,6-octadien-1-ol (239) with 2 equivalents of pyridine**

The catalyst, in THF (6 ml), was prepared from pyridine (7 \(\mu\)l, 86.0 \(\mu\)mol) and Ni(COD\(_2\)) (11.0 mg, 40.0 \(\mu\)mol). The alkoxide, in THF (6 ml), was prepared with \(n\)-BuLi (462 \(\mu\)l, 795 \(\mu\)mol, 1.72M in hexanes) and (\(E\)-1,1-di-[^H\(^2\)]-3,7-dimethyl-2,6-octadien-1-ol (239) (124 mg, 794 \(\mu\)mol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated \(\text{NH}_4\text{Cl}\) solution (8 ml). The isolated residue was chromatographed (SiO\(_2\), 5-50% ether in petrol) to afford 1,3-di-[^H\(^2\)]-3,7-dimethyl-6-octenal (243) (20.4 mg, 131 \(\mu\)mol, 16%), and an inseparable mixture of starting material and 1,1,3-tri-[^H\(^2\)]-3,7-dimethyl-6-octen-1-ol, (239) and (244) respectively, (34.5 mg, 221 \(\mu\)mol, 28%, 1:3.0) as clear colourless oils.
**Isomerisation of (E)-1,1-di-[²H]-3,7-dimethyl-2,6-octadien-1-ol (239) with 2 equivalents of tricyclohexylphosphine (289)**

The catalyst, in THF (6 ml), was prepared from tricyclohexylphosphine (289) (22.5 mg, 80.2 μmol) and Ni(COD)₂ (11.0 mg, 40.0 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (475 μL, 818 μmol, 1.72M in hexanes) and (E)-1,1-di-[²H]-3,7-dimethyl-2,6-octadien-1-ol (239) (128 mg, 817 μmol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated NH₄Cl solution (8 ml). The isolated residue was chromatographed (SiO₂, 5-50% ether in petrol) to afford an inseparable mixture of starting material and 1,1,3-tri-[²H]-3,7-dimethyl-6-octen-1-ol, (239) and (244) respectively, (41.3 mg, 264 μmol, 32%, 1.4 : 1) as a clear colourless oil.

**Isomerisation of (E) 1,1-Di-[²H]-3,7-dimethyl-2,6-octadien-1-ol (239) with NiCl₂(Cy₃P)₂/n-BuLi**

The catalyst, in THF (6 ml), was prepared from n-BuLi (90.0 μL, 153 μmol, 1.70M in hexanes) and NiCl₂(Cy₃P)₂ (70.0 mg, 101 μmol). The alkoxide, in THF (6 ml), was prepared with n-BuLi (405 μL, 689 μmol, 1.70M in hexanes) and (E)-1,1-di-[²H]-3,7-dimethyl-2,6-octadien-1-ol (239) (106 mg, 680 μmol). The resulting catalyst/alkoxide mixture was heated to reflux for 6 hours then quenched with saturated NH₄Cl solution (8 ml). The isolated residue was chromatographed (SiO₂, 5-50% ether in petrol) to afford 1,3-di-[²H]-3,7-dimethyl-6-octenal (243) (22.0 mg, 141 μmol, 21%), and an inseparable mixture of starting material and 1,1,3-tri-[²H]-3,7-dimethyl-6-octen-1-ol, (239) and (244) respectively, (39.2 mg, 251 μmol, 37%, 1.1 : 1) as a clear colourless oil.
Isomerisation of \((E)\)-4,4,4-tri-[\(^2\)H]-3-phenyl-2-buten-1-ol (252) with 2 equivalents of pyridine

The catalyst, in THF (6 ml), was prepared from pyridine (8.5 \(\mu\)l, 105 \(\mu\)mol) and \(\text{Ni(COD)}_2\) (14.0 mg, 50.9 \(\mu\)mol). The alkoxide, in THF (6 ml), was prepared with \(n\)-BuLi (570 \(\mu\)l, 986 \(\mu\)mol, 1.73M in hexanes) and \((E)\)-4,4,4-tri-[\(^2\)H]-3-phenyl-2-buten-1-ol (252) (149 mg, 986 \(\mu\)mol). The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated \(\text{NH}_4\text{Cl}\) solution (8 ml). The isolated residue was chromatographed (SiO\(_2\), 10-50% ether in petrol) to afford 4,4,4-tri-[\(^2\)H]-3-phenylbutanal (254)\(^{32}\) (51.1 mg, 338 \(\mu\)mol, 34%) and starting material (252) (38.9 mg, 257 \(\mu\)mol, 26%) as clear colourless oils.

\(^1\)H-NMR \(\delta\)c: (254) 9.74 (1H, m, \(\text{CH}_2\text{CHO}\)), 7.51-7.14 (5H, m, PhH), 3.37 (1H, br t, \(J\) 6.8, PhCHCD\(_3\)), 2.70 (2H, m, \(\text{CH}_2\text{CHO}\)), 1.34 (H, m, CD\(_3\), 87% Deuterium content)

Isomerisations using \(\text{NiCl}_2\)(Ligands)

Isomerisation of 1-phenyl-2-propen-1-ol (88) with \(\text{NiCl}_2\text{Py}_2/n\)-BuLi

The catalyst, in THF (5 ml), was prepared from \(n\)-BuLi (30.0 \(\mu\)l, 51.4 \(\mu\)mol, 1.71M in hexanes) and \(\text{NiCl}_2\text{Py}_2\) (10.0 mg, 34.7 \(\mu\)mol) at -78\(^\circ\)C. The alkoxide, in THF (5 ml), was prepared with \(n\)-BuLi (378 \(\mu\)l, 648 \(\mu\)mol 1.71M in hexanes) and 1-phenyl-2-propen-1-ol (88) (87.0 mg, 648 \(\mu\)mol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated \(\text{NH}_4\text{Cl}\) solution (8 ml). Analysis of the isolated residue by \(^1\)H-NMR and GC revealed starting material (88) (59%) and propiophenone (91) (33%)
Isomerisation of 1-phenyl-2-propen-1-ol (88) with NiCl$_2$Py$_2$/LiBEt$_3$H

The catalyst, in THF (5 ml), was prepared from LiBEt$_3$H (37.5 µl, 37.5 µmol, 1M in THF) and NiCl$_2$Py$_2$ (10.0 mg, 34.7 µmol). The alkoxide, in THF (5 ml), was prepared with n-BuLi (378 µl, 648 µmol 1.71M in hexanes) and 1-phenyl-2-propen-1-ol (88) (87.0 mg, 648 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the isolated residue by $^1$H-NMR and GC revealed starting material (88) (71%) and propiophenone (91) (17%)

Isomerisation of geraniol (61) with NiCl$_2$Py$_2$/n-BuLi

The catalyst, in THF (5 ml), was prepared from n-BuLi (30.0 µl, 51.4 µmol, 1.71M in hexanes) and NiCl$_2$Py$_2$ (10.0 mg, 34.7 µmol) at -78°C. The alkoxide, in THF (5 ml), was prepared with n-BuLi (378 µl, 648 µmol 1.71M in hexanes) and geraniol (61) (100 mg, 648 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the isolated residue by $^1$H-NMR and GC revealed predominantly starting material (61).

Isomerisation of geraniol (61) with NiCl$_2$Py$_2$/LiBEt$_3$H

The catalyst, in THF (5 ml), was prepared from LiBEt$_3$H (30.0 µl, 51.4 µmol, 1.71M in hexanes) and NiCl$_2$Py$_2$ (10.0 mg, 34.7 µmol). The alkoxide, in THF (5 ml), was prepared with n-BuLi (378 µl, 648 µmol 1.71M in hexanes) and geraniol (61) (100 mg, 648 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the isolated residue by $^1$H-NMR and GC revealed predominantly starting material (61).
solution (8 ml). Analysis of the isolated residue by $^1$H-NMR and GC revealed predominantly starting material (61) (68%) and several unidentifiable products.

**Isomerisation of 1-phenyl-2-propen-1-ol (88) with (2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride/n-BuLi**

![Chemical structure]

The catalyst, in THF (5 ml), was prepared from n-BuLi (30.0 µl, 51.4 µmol, 1.71M in hexanes) and (2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride (14.5 mg, 34.2 µmol) at -78°C. The alkoxide, in THF (5 ml), was prepared with n-BuLi (383 µl, 656 µmol 1.71M in hexanes) and 1-phenyl-2-propen-1-ol (88) (88.0 mg, 656 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the isolated residue by $^1$H-NMR and GC revealed starting material (88) (81%) and propiophenone (91) (11%)

**Isomerisation of 1-phenyl-2-propen-1-ol (88) with (2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride/LiBEt$_3$H**

![Chemical structure]

The catalyst, in THF (5 ml), was prepared from LiBEt$_3$H (35.0 µl, 35.0 µmol, 1M in THF) and (2,2-bis-[(4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride (14.5 mg, 34.2 µmol). The alkoxide, in THF (5 ml), was prepared with n-BuLi (379 µl, 649 µmol 1.71M in hexanes) and 1-phenyl-2-propen-1-ol (88) (87.1 mg, 649 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH$_4$Cl solution (8 ml). Analysis of the isolated residue by $^1$H-NMR and GC revealed starting material (88) (45%) and several unidentifiable products.
Isomerisation of geraniol (61) with (2,2-bis-[4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride/n-BuLi

The catalyst, in THF (5 ml), was prepared from n-BuLi (30.0 µl, 51.4 µmol, 1.71M in hexanes) and (2,2-bis-[4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride (14.5 mg, 34.2 µmol) at -78°C. The alkoxide, in THF (5 ml), was prepared with n-BuLi (383 µl, 656 µmol 1.71M in hexanes) and geraniol (61) (101 mg, 656 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (61) (46%) and several unidentifiable products.

Isomerisation of geraniol (61) with (2,2-bis-[4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride/LiBEt₃H

The catalyst, in THF (5 ml), was prepared from LiBEt₃H (35.0 µl, 35.0 µmol, 1M in THF) and (2,2-bis-[4S)-4-t-butyl-1,3-oxazoline-2-yl]-propane)nickel(II)chloride (14.5 mg, 34.2 µmol). The alkoxide, in THF (5 ml), was prepared with n-BuLi (383 µl, 656 µmol 1.71M in hexanes) and geraniol (61) (102 mg, 661 µmol). The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (61) (54%) and several unidentifiable products.
Isomerisations using [Rh(COD)BINAP]^+ClO_4^-

**Isomerisation of geraniol (61) using [Rh(R)-(BINAP)]^+**

A pre-hydrogenated solution of [Rh(COD)-(R)-(BINAP)]^+ClO_4^- (15.0 mg, 14.9 μmol, Supplier: Aldrich) in THF (6 ml) was added to a solution of geraniol (61) (51.5 mg, 334 μmol) in THF (3 ml). The resulting catalyst/alkoxide mixture was heated to reflux for 24 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by GC (7.5 psi column head pressure; 100°C for 2 min, then 15°C/min to 250°C) and GCMS revealed starting material (61) (43%, GC: 4.99 min), citronellol (112) (1%, GC: 4.72 min), diastereoisomers of pulegol (266) (15%, GC: 3.18 min) and limonene (265) (12%, GC: 2.58 min), none of which were isolated. Note that these are the same conditions used by Noyori and co-workers who were able to isomerise geraniol to citronellal in 70% yield and 37% ee. Only trace amounts of citronellal (<1%) were detected in all our attempts to repeat this reaction. Noyori and co-workers did not report the formation of pulegol nor limonene.

**LRMS (EI) m/z:** (266) 154 (M^+, 8%), 136.2 (M^-H_2O, 12), 121 (31), 93 (33), 69 (71), 41 (CH_3CHCH_2^+, 100%); (265) 136 (M^+, 12%), 121 (12), 93 (52), 79 (31), 68 (100), 53 (27)

The alkoxide, in THF (3 ml), was prepared with n-BuLi (275 μl, 325 μmol, 1.18M in hexanes) and geraniol (61) (51.5 mg, 334 μmol). A pre-hydrogenated solution of [Rh(COD)-(R)-(BINAP)]^+ClO_4^- (15.0 mg, 14.9 μmol, Supplier: Aldrich) in THF (6 ml) was then added. The resulting catalyst/alkoxide mixture was heated to reflux for 24 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by ^1H-NMR and GC revealed starting material (61) (49%) and citronellol (112) (21%) as the only identifiable compounds, neither of which were isolated.
Isomerisation of geraniol (61) using [Rh(COD)(S)-(BINAP)]^+ClO_4^-.

The alkoxide, in THF (8 ml), was prepared with n-BuLi (805 μl, 1.36 mmol, 1.70M in hexanes) and geraniol (61) (210 mg, 1.36 mmol). A solution of [Rh(COD)-(S)-BINAP)]^+ClO_4^- (15.0 mg, 14.9 μmol) in THF (8 ml) was then added. The resulting catalyst/alkoxide mixture was heated to reflux for 24 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by ^1H-NMR and GC revealed starting material (61) (81%) and citronellol (112) (5%) as the only identifiable compounds, neither of which were isolated.

Isomerisation of geraniol (61) using [Rh(COD)(S)-(BINAP)]^+ClO_4^-.

A solution of [Rh(COD)-(S)-BINAP)]^+ClO_4^- (12.0 mg, 11.9 μmol) in THF (6 ml) was added to a solution of geraniol (61) (200 mg, 1.30 mmol) in degassed THF (6 ml). The resulting mixture was heated to reflux for 20 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by GC and by chiral GC revealed starting material (61) (16%), iso-pulegol (266a) (7%, 49.6% ee), iso-iso-pulegol (266b) (7%, 48% ee), and limonene (265) (18%) as the major compounds, none of which were isolated.

Isomerisation of geraniol (61) using [Rh(COD)(S)-(BINAP)]^+ClO_4^- at room temperature.

A solution of [Rh(COD)-(S)-BINAP)]^+ClO_4^- (12.0 mg, 11.9 μmol) in THF (6 ml) was added to a solution of geraniol (61) (200 mg, 1.30 mmol) in degassed THF (6 ml). The resulting mixture was heated to reflux for 20 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by GC and by chiral GC revealed starting material (61) (16%), iso-pulegol (266a) (7%, 49.6% ee), iso-iso-pulegol (266b) (7%, 48% ee), and limonene (265) (18%) as the major compounds, none of which were isolated.
A solution of \([\text{Rh(COD)}-(S)\text{-BINAP}])^+\text{ClO}_4^-\) (16.0 mg, 15.9 μmol) in THF (6 ml) was added to a solution of geraniol (61) (202 mg, 1.31 mmol) in degassed THF (6 ml). The resulting mixture stirred at room temperature for 20 hours. An aliquot was subject to analysis by GC which revealed predominantly starting material (61) (91%). The reaction mixture was therefore heated to reflux for 20 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by GC revealed starting material (61) (26%), diastereoisomers of pulegol (266) (17%) and limonene (265) (16%) as the major compounds, none of which were isolated.

### Isomerisation of \(N,N\)-diethylgeranylamine (64) using \([\text{Rh(COD)}(S)\text{-BINAP}])^+\text{ClO}_4^-\)

\[
\begin{align*}
\text{(64)} & \quad \text{NET}_3 & \quad \rightarrow & \quad \text{(62)}
\end{align*}
\]

A solution of \([\text{Rh(COD)}-(S)\text{-BINAP}])^+\text{ClO}_4^-\) (12.0 mg, 11.9 μmol) in THF (6 ml) was added to a solution of \(N,N\)-diethylgeranylamine (64) (204 mg, 972 μmol) in degassed THF (6 ml). The resulting mixture was heated to reflux for 20 hours. An aliquot was worked-up with saturated NH₄Cl solution and subject to analysis by GC which revealed predominantly citronellal (62) (95%). The reaction mixture was treated with solution of 1M HCl (10 ml) and stirred for 30 minutes. The isolated residue was chromatographed (SiO₂, 7.5% ether in petrol) to afford citronellal (62) (101 mg, 655 μmol, 67%) as a clear colourless oil. \(R_f(5\%\text{ ether in petrol})\) 0.26.

### Isomerisation of geraniol (61) and 1.07 equivalents of \(n\text{-BuLi}\) using \([\text{Rh(COD)}(S)\text{-BINAP}])^+\text{ClO}_4^-\) at room temperature

The alkoxide, in THF (8 ml), was prepared with \(n\text{-BuLi}\) (530 μl, 1.43 mmol, 2.70M in hexanes) and geraniol (61) (206 mg, 1.34 mmol). A solution of \([\text{Rh(COD)}-(S)\text{-BINAP}])^+\text{ClO}_4^-\) (16.0 mg, 15.9 μmol) in THF (8 ml) was then added. The resulting catalyst/alkoxide mixture was stirred at room temperature for 20 hours then quenched with acetic anhydride (1.25 ml, 13.2 mmol). The isolated residue was chromatographed (SiO₂, 2% ether in petrol) to afford an inseparable mixture of \(E\) and \(Z\) enol acetates, (115) and (116) respectively, (182 mg, 927 μmol, 69%, 4.3 : 1) as a clear colourless oil. \(R_f(25\%\text{ ether in petrol})\) 0.61.
Isomerisations using [Rh(Ligands)]^+

Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(DIPHOS)]^+

\[
\begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{C} \\
(88) \\
\end{array} \rightarrow \\
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
(91) \\
\end{array}
\]

The alkoxide, in THF (5 ml), was prepared with n-BuLi (570 µl, 790 µmol, 1.39M in hexanes) and 1-phenyl-2-propen-1-ol (88) (105 mg, 782 µmol). A pre-hydrogenated solution of [Rh(COD)-(DIPHOS)]^+ClO_4^- (15.0 mg, 14.2 µmol) in THF (5 ml) was then added. The resulting catalyst/alkoxide mixture was heated to reflux for 7 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by ^1H-NMR and GC revealed starting material (88) (<1%) and 1-phenyl-1-propanone (91) (>98%) as the only compounds, neither of which were isolated.

Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(COD)Cl]_2/DIPHOS

\[
\begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{C} \\
(88) \\
\end{array} \rightarrow \\
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
(91) \\
\end{array}
\]

The alkoxide, in THF (5 ml), was prepared with n-BuLi (570 µl, 790 µmol, 1.39M in hexanes) and 1-phenyl-2-propen-1-ol (88) (105 mg, 782 µmol). Anhydrous silver(I) perchlorate (10.0 mg, 48.3 µmol), was added to a solution of [Rh(COD)Cl]_2 (4.0 mg, 8.1 µmol) in THF (5 ml) and the mixture stirred for 15 minutes. DIPHOS (6.5 mg, 16.3 µmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described), then transferred via filter tipped cannulae to the alkoxide solution. The resulting catalyst/alkoxide mixture was heated to reflux for 4.5 hours then quenched with saturated NH_4Cl solution (8 ml). Analysis of the isolated residue by ^1H-NMR and GC revealed starting material (88) (1%) and 1-phenyl-1-propanone (91) (>98%) as the only compounds, neither of which were isolated.

Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(COD)Cl]_2/Ph_3P

\[
\begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{C} \\
(88) \\
\end{array} \rightarrow \\
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{C} \\
(91) \\
\end{array}
\]
The alkoxide, in THF (5 ml), was prepared with n-BuLi (330 μl, 784 μmol, 2.38M in hexanes) and 1-phenyl-2-propen-1-ol (88) (105 mg, 782 μmol). Anhydrous silver(I) perchlorate (5.0 mg, 24.1 μmol) was added to a solution of [Rh(COD)Cl]₂ (5.6 mg, 11.4 μmol) in THF (5 ml) and the mixture stirred for 15 minutes. Triphenylphosphine (12.0 mg, 45.7 μmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described) then transferred via filter tipped cannulae to the alkoxide solution. The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (88) (21%) and 1-phenyl-1-propanone (91) (77%) as the only compounds, neither of which were isolated.

**Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(COD)Cl]₂/pyridine**

![Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(COD)Cl]₂/pyridine](image)

The alkoxide, in THF (5 ml), was prepared with n-BuLi (328 μl, 779 μmol, 2.38M in hexanes) and 1-phenyl-2-propen-1-ol (88) (104 mg, 775 μmol). Anhydrous silver(I) perchlorate (5.0 mg, 24.1 μmol) was added to a solution of [Rh(COD)Cl]₂ (5.6 mg, 11.4 μmol) in THF (5 ml) and the mixture stirred for 15 minutes. Dipyridyl (3.5 mg, 22.4 μmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described) then transferred via filter tipped cannulae to the alkoxide solution. The resulting catalyst/alkoxide mixture was heated to reflux for 4 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (88) (6%) and 1-phenyl-1-propanone (91) (92%) as the only compounds, neither of which were isolated.

**Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(COD)Cl]₂/DMAP**

![Isomerisation of 1-phenyl-2-propen-1-ol (88) using [Rh(COD)Cl]₂/DMAP](image)

The alkoxide, in THF (5 ml), was prepared with n-BuLi (327 μl, 776 μmol, 2.38M in hexanes) and 1-phenyl-2-propen-1-ol (88) (104 mg, 775 μmol). Anhydrous silver(I) perchlorate (5.0 mg, 24.1 μmol) was added to a solution of [Rh(COD)Cl]₂ (5.6 mg, 11.4 μmol) in THF (5 ml) and the mixture stirred for 15 minutes. N,N,N4-(Dimethylamino)-pyridine (5.6 mg, 45.8 μmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described)
then transferred via filter tipped cannulae to the alkoxide solution. The resulting catalyst/alkoxide mixture was heated to reflux for 2 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (88) (10%) and 1-phenyl-1-propanone (91) (80%) as the only compounds, neither of which were isolated.

**Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/DMAP**

![Chemical structure](image)

The alkoxide, in THF (5 ml), was prepared with n-BuLi (328 μl, 779 μmol, 2.38M in hexanes) and geraniol (61) (120 mg, 778 μmol). Anhydrous silver(I) perchlorate (5 mg, 24.1 μmol) was added to a solution of [Rh(COD)Cl]₂ (5.6 mg, 11.4 μmol) in THF (5 ml) and the mixture stirred for 15 minutes. N,N 4-(Dimethylamino)-pyridine (5.6 mg, 45.8 μmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described) then transferred via filter tipped cannulae the alkoxide solution. The resulting mixture was heated to reflux for 24 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (61) (76%) and citronellol (112) (8%), neither of which were isolated.

**Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/DMAP**

![Chemical structure](image)

Anhydrous silver(I) perchlorate (5 mg, 24.1 μmol) was added to a solution of [Rh(COD)Cl]₂ (5.6 mg, 11.4 μmol) in THF (5 ml) and the mixture stirred for 15 minutes. N,N 4-(Dimethylamino)-pyridine (5.6 mg, 45.8 μmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described) then transferred via filter tipped cannulae to a solution of geraniol (61) (120 mg, 778 μmol) in degassed THF (5 ml). The resulting mixture was heated to reflux for 24 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed predominantly starting material (61) (>95%), which was not isolated.
Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/bis(oxazoline) (128)

![Chemical structure diagram]

The alkoxide, in THF (8 ml), was prepared with n-BuLi (940 µl, 1.30 mmol, 1.38M in hexanes) and geraniol (61) (200 mg, 1.30 mmol). Anhydrous silver(I) perchlorate (10.0 mg, 48.3 µmol) was added to a solution of [Rh(COD)Cl]₂ (13.0 mg, 26.4 µmol) in THF (8 ml) and the mixture stirred for 15 minutes. 2,2-bis-[(4S)-4-tert-butyl-1,3-oxazoline-2-yl]-propane (128) (13.0 mg, 44.2 µmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described) then transferred via filter tipped cannulae to the alkoxide solution. The resulting catalyst/alkoxide mixture was heated to reflux for 21 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (61) (41%) and citronellol (112) (13%), neither of which were isolated.

Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/bis(oxazoline) (128)

![Chemical structure diagram]

Anhydrous silver(I) perchlorate (8 mg, 38.6 µmol) was added to a solution of [Rh(COD)Cl]₂ (9.6 mg, 19.5 µmol) in THF (8 ml) and the mixture stirred for 15 minutes. 2,2-bis-[(4S)-4-tert-butyl-1,3-oxazoline-2-yl]-propane (128) (11.5 mg, 39.1 µmol) was then added, and the mixture stirred for a further 15 minutes, hydrogenated (as previously described) then transferred via filter tipped cannulae to a solution of geraniol (61) (195 mg, 1.26 mmol) in degassed THF (8 ml). The resulting mixture was heated to reflux for 24 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed predominantly starting material (61) (>95%), which was not isolated.

Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/DIPHOS in benzene

![Chemical structure diagram]
The alkoxide, in benzene (6 ml), was prepared with n-BuLi (405 µl, 648 µmol, 1.60M in hexanes) and geraniol (61) (100 mg, 648 µmol) at 5°C. A solution of [Rh(COD)-(DIPHOS)]⁺ClO₄⁻ (10.0 mg, 9.5 µmol) in benzene (6 ml) was added to the alkoxide solution. The resulting mixture was heated to reflux for 22 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed starting material (61) (16%) and citronellol (112) (19%) as the only identifiable compounds, neither of which were isolated.

**Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/DIPHOS in benzene**

\[ \text{OH} \]
\[ \text{OH} \]
\[ \text{OH} \]

\[ (61) \]
\[ (61) \]
\[ (265) \]
\[ (266) \]

A solution of [Rh(COD)-(DIPHOS)]⁺ClO₄⁻ (10.0 mg, 9.5 µmol) in benzene (6 ml) was added to a solution of geraniol (61) (100 mg, 648 µmol) in degassed benzene (6 ml). The resulting mixture was heated to reflux for 20 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by GC and GCMS revealed starting material (61) (70%), 5-methyl-2-(2-propen-2-yl)-1-cyclohexanol (266) (8%) and limonene (265) (16%) as the major compounds, none of which were isolated.

**Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/DIPHOS in toluene**

\[ \text{OH} \]
\[ \text{OH} \]
\[ \text{OH} \]

\[ (61) \]
\[ \text{No Isomerisation} \]
\[ \text{Products} \]
\[ (61) \]

The alkoxide, in toluene (6 ml), was prepared with n-BuLi (405 µl, 648 µmol, 1.60M in hexanes) and geraniol (61) (100 mg, 648 µmol) at 5°C. A solution of [Rh(COD)-(DIPHOS)]⁺ClO₄⁻ (10.0 mg, 9.5 µmol) in toluene (6 ml) was added to the alkoxide solution. The resulting mixture was heated to reflux for 20 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by ¹H-NMR and GC revealed citronellol (112) (16%) as the only identifiable compound, which was not isolated.
Experimental

Isomerisation of geraniol (61) using [Rh(COD)Cl]₂/DIPHOS in toluene

A solution of [Rh(COD)²DIPHOS]⁺ClO₄⁻ (10.0 mg, 9.5 µmol) in benzene (6 ml) was added to a solution of geraniol (61) (100 mg, 648 µmol) in degassed benzene (6 ml). The resulting mixture was heated to reflux for 20 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by GC revealed limonene (265) (32%) and 5-methyl-2-(2-propen-2-yl)-1-cyclohexanol (266) (20%) as the only identifiable compounds, neither of which were isolated.

Isomerisation of TBDMS geranyl ether (187) using [Rh(COD)Cl]₂/DIPHOS

A pre-hydrogenated solution of [Rh(COD)²DIPHOS]⁺ClO₄⁻ (12.0 mg, 11.4 µmol) in THF (5 ml) was added to a solution of TBDMS-geranyl ether (187) (150 mg, 559 µmol) in degassed THF (5 ml). The resulting mixture was heated to reflux for 22 hours then quenched with saturated NH₄Cl solution (8 ml). Analysis of the isolated residue by GC and GCMS revealed starting material (187) (2%), geraniol (61) (3%), 3-ethyl-2-methyl-1,3-heptadiene (268) (6%), 1-methyl-4-(prop-2-yl)-benzene (269) (10%), limonene (265) (21%) and 2-carene (270) (14%) as the major compounds, none of which were isolated.

LRMS (El) m/z: (268) 138 (M⁺, 37%), 109 (M⁺-Et, 100%), 81 (39), 67 (80); (269) 134 (M⁺, 30%), 119 (M⁺-Me, 100%), 91 (28); (270) 136 (M⁺, 42%), 121 (M⁺-Me, 100%), 93 (83)
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