Enantioselective Hydrogenation Using
Ruthenium Complexes of Tridentate
Ligands

University of St Andrews
School of Chemistry

Scott D. Phillips
PhD Thesis
March 2011

Supervisor: Dr Matthew L. Clarke
Thesis Declaration

I, Scott Phillips, hereby certify that this thesis, which is approximately 56,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in March 2007, and as a candidate for the degree of PhD in March 2008; the higher study for which this is a record was carried out in the University of St Andrews between 2007 and 2011.

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of PhD in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date …………… Signature of candidate ………………………………..

Date …………… Signature of supervisor ………………………………..
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Date …………… Signature of supervisor ………………………………………
It is in truth not for glory, nor riches, nor honours that we fight, but for freedom alone, which no honest man gives up but with life itself.

Declaration of Arbroath, 1320
A number of people must be thanked for the huge input they have had in making this work possible. Firstly, I wish to thank Dr Matt Clarke for giving me the chance to carry out this exciting project, and supporting my efforts throughout. I admire his dedication and enthusiasm for chemistry, which motivates the excellent research and great atmosphere in his group.

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I have many friends in the Carnoustie & District Pipe Band, whom I have the honour of representing as Pipe Major. With over 30 members from the age of 9 to nearly 90, it’s impossible to thank each individually but I am in awe of the work they put and their dedication to producing good music. We’ve had lots of fun together over the last three years and I can’t thank everyone involved enough.

Finally I’d like to express my thanks to the people I love in life, for all their encouragement and support throughout my studies. I had the fortune to meet Miss Elisabetta Spano during the course of my studies and look forward to spending many more years together, as perfect as those so far. My family, as always, stick by me every step of the way and I can’t put into words the thanks I must give them. My mum and dad have been a rock through my work and their enthusiasm for me to do well drives me on. My sister and her delightful family are a pleasure to spend time with, and looking after my niece and nephew keep me on my toes! My grandparents have always generously helped me along the way throughout my studies, and I’m extremely grateful for such loving support. My Gran unfortunately passed away last year: she was an inspirational woman, and I must thank her too for the love and support she has given me.


Abstract

This thesis describes the development of the [RuCl₂(P^N^N)L] catalytic system for asymmetric hydrogenation. It has been demonstrated that the current system is efficient in preparing a range of bulky chiral alcohols in good enantioselectivity, many of which are likely to be inaccessible using the more classic [RuCl₂(P^P)N^N)] system developed by Noyori and coworkers. It has been shown that the current system is tolerant of a range of substrate electronic effects as well as the presence of heteroaromatic functionality, thus showing its applicability in synthesis. This has been extended to prepare a number of bulky derivatives of synthetically important molecules. The demonstration of this is significant as in drug design, for example, studies that aim to extend lipophilicity or steric bulk make the ability to prepare alcohols across the full range of steric properties important. We have shown that chiral alcohols with adjacent gem-dimethyl groups can be prepared in high enantioselectivity and their conversion into other valuable molecules, such as chiral lactones has been demonstrated.

Detailed mechanistic studies have been undertaken for the present system in order to aid rational design of new, more active and selective catalysts. A number of achiral variants of the original system have been prepared and the key features of ligand structure for efficient catalysis have been identified. This was accomplished by rigorous kinetic analysis of each complex, using specialist gas-uptake monitoring equipment. The key features of catalyst structure and optimal reaction conditions for efficient asymmetric hydrogenation have been identified.

Our greater understanding of the present system allowed us to rationally design new catalysts of for enantioselective hydrogenation. Our aim was to be able to tune the catalyst structure to carry out hydrogenation of a greater variety of ketone substrate with high activity and selectivity. We have successfully prepared second generation catalysts that show enhanced enantioselectivity for a variety of substrates, many of which were problematic with the Noyori system.
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# Abbreviations and Acronyms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Ångstrom</td>
</tr>
<tr>
<td>AABPY</td>
<td>3-amino-5-aminomethyl-Boc-pyrrolidine</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl group (-COCH₃)</td>
</tr>
<tr>
<td>Ala</td>
<td>alanine</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic group</td>
</tr>
<tr>
<td>BICP</td>
<td>bis(diphenylphosphanyl)dicyclopentane</td>
</tr>
<tr>
<td>BINAL</td>
<td>2,2'-dihydroxy-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>bis</td>
<td>signifies presence of two identical but separate groups</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl group (-CH₂Ph)</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl group (C₄H₉)</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>C</td>
<td>catalyst</td>
</tr>
<tr>
<td>°C</td>
<td>degrees celsius</td>
</tr>
<tr>
<td>C₂</td>
<td>symmetry operation</td>
</tr>
<tr>
<td>cat</td>
<td>catalyst</td>
</tr>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata reagent</td>
</tr>
<tr>
<td>CCD</td>
<td>Charge Coupled Device (X-ray diffraction)</td>
</tr>
<tr>
<td>cf</td>
<td>confer imper (Latin), compared to</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionisation, ionisation technique (Mass spectrometry)</td>
</tr>
<tr>
<td>cis</td>
<td>highest priority substituents on the same side of a double bond</td>
</tr>
<tr>
<td>COD</td>
<td>cyclooctadiene</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy (NMR Spectroscopy)</td>
</tr>
<tr>
<td>C₆p</td>
<td>cyclopentadienyl ligand</td>
</tr>
<tr>
<td>cyclo</td>
<td>cyclic compound</td>
</tr>
<tr>
<td>d</td>
<td>day(s); doublet (spectroscopy); deuterated</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift (NMR)</td>
</tr>
<tr>
<td>Δ</td>
<td>treatment at reflux</td>
</tr>
<tr>
<td>DACH</td>
<td>1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>DAMDO</td>
<td>2,3-dimethoxy-2,3-dimethyl-5,6-diaminomethyl-1,4-dioxane</td>
</tr>
<tr>
<td>DAIPEN</td>
<td>1,1'-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>D'BPF</td>
<td>di-tert-butylphosphinoferrocene</td>
</tr>
<tr>
<td>Dₜb</td>
<td>conjugate base-assisted dissociative mechanism</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>d.e.</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>decomp.</td>
<td>decomposition observed</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer (NMR)</td>
</tr>
<tr>
<td>DIOPT</td>
<td>((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis (diphenylphosphine)</td>
</tr>
<tr>
<td>DIP</td>
<td>disopropylamocampheryl</td>
</tr>
<tr>
<td>DiPAMP</td>
<td>1,2-bis-(o-anisylphosphono)ethane</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>DMAPEN</td>
<td>2-dimethylamino-1-phenylethylamine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DOPA</td>
<td>3,4-dihydroxy-L-phenylalanine</td>
</tr>
</tbody>
</table>
NCS  \( N \)-chlorosuccinimide
NK₁  Neurokinin 1
NMR  nuclear magnetic resonance
Np  naphthyl group (-C₁₀H₇)
Nu  nucleophile
μW  microwave radiation
\( o- \)  \textit{ortho} substituted
\( p- \)  \textit{para} substituted
PEG  polyethylene glycol
pH  power of hydrogen
Ph  phenyl group (-C₆H₅)
PICA  \( \alpha \)-picolyamine
p\( K_a \)  the negative logarithm of the acid dissociation constant, \( K_a \)
poly  polymeric
ppm  parts per million
Pr  propyl group (-C₃H₇)
Pro  proline
prod  product
PTFE  polytetrafluoroethylene
py  pyridine
q  quartet (NMR spectroscopy)
\( R \)  \textit{rectus}, priorities of substituents decrease in a clockwise direction according to the Cahn-Ingold Prelog
\( R_2 \)  coefficient of determination
rac  racemic
\( Re \)  face of a prochiral ketone where the priorities of the substituents on the trigonal carbon atom decrease in a counterclockwise direction according to the Cahn-Ingold Prelog
rt  room temperature
s  seconds; singlet (NMR spectroscopy); strong absorption (IR spectroscopy)
S  solvent; substrate
\( S \)  \textit{sinister}, priorities of substituents decrease in a counterclockwise direction according to the Cahn-Ingold Prelog
SDP  spiro diphosphine ligand
\( Si \)  face of a prochiral ketone where the priorities of the substituents on the trigonal carbon atom decrease in a counterclockwise direction according to the Cahn-Ingold Prelog
\( S_{N1} \)  nucleophilic substitution with a unimolecular rate-determining step
\( S_{N1} \)_{CB}  conjugate base-assisted nucleophilic substitution with a unimolecular rate-determining step
\( S_{N2} \)  nucleophilic substitution with a bimolecular rate-determining step
t  triplet (NMR spectroscopy)
\( t-\text{Bu} \)  tertiary butyl group (-C(CH₃)₃)
tert.  tertiary
THF  tetrahydrofuran
TLC  Thin Layer Chromatography
TMEDA  tetramethylethylenediamine
TMS  trimethysilyl group (-Si(CH₃)₃)
TOF  Turnover Frequency
Tol  tolyl group (4-CH₃C₆H₄)
TON  Turnover number
\( trans \)  highest priority substituents on opposite sides of a double bond
Ts        toluenesulfonyl group (CH$_3$C$_6$H$_4$SO$_2$-)
TS       Transition State
υ        wavenumbers (IR spectroscopy)
UV       Ultraviolet
vs       versus
w        weak (IR spectroscopy)
wrt      with respect to
Xyl      xylyl group (3,5-di-CH$_3$C$_6$H$_3$)
Z        zusammen (German), together (isomerism, corresponds to cis)
Chapter I

Introduction

1.1 Catalytic Asymmetric Hydrogenation

The chirality, or “handedness”, of molecules is of fundamental importance in both science and technology. In particular, the biological activity of many pharmaceuticals and agrochemicals is often specific to a single enantiomer. The demand for enantiopure compounds has escalated in recent times and has motivated intensive research to develop improved methods for the synthesis of optically pure compounds. Catalytic asymmetric hydrogenation, using molecular hydrogen to reduce prochiral olefins, ketones and imines, has become one of the most efficient, practical and atom-economical methods for the construction of homochiral compounds and as such, much work is focused on designing original catalysts with enhanced activity and selectivity.

Catalytic asymmetric hydrogenation has its origins in the 1960s when William Knowles and his colleagues at Monsanto demonstrated that rhodium complexes containing enantioenriched phosphine ligands could catalyse the enantioselective addition of hydrogen to a prochiral olefinic substrate (Scheme I-1). Knowles’ work integrated the newly established methods to prepare chiral phosphines of Mislow and Horner with Wilkinson’s groundbreaking discovery of [RhCl(PPh$_3$)$_3$] as a hydrogenation catalyst. Knowles demonstrated that hydrogenation of α-phenylacrylic acid 1 could be accomplished using [RhL$_3$Cl] (L = (R)-(−)-methyl-n-propylphenylphosphine 3 of 69% optical purity) with a 15% enantiomeric excess observed in the acid product.

![Scheme I-1](image)

Scheme I-1 The hydrogenation of α-phenylacrylic acid with a ruthenium complex of the optically active phosphine (−)-methylpropylphenylphosphine 3. Reaction conditions: α-phenylacrylic acid 1 (1 eq.), [RhCl$_3$] (0.15 mol%), NEt$_3$ (0.53 mol%), H$_2$ (20–30 bar), benzene/ethanol (1:1), 60°C.

Although not comparable with enantioselectivities obtained in asymmetric catalysis today, this
initial result, together with work by Horner, provided the clue that catalytic asymmetric hydrogenation could be an efficient tool for the preparation of enantioenriched compounds. An important breakthrough, in terms of levels of enantioselectivity, came later when Kagan found that a rhodium complex containing the enantiopure diphosphine \(((4R,5R)-2,2\text{-dimethyl}-1,3\text{-dioxolane}-4,5\text{-diyl})\text{bis}(\text{methylene})\text{bis}(\text{diphenylphosphine}))\), (-)-DIOP 6, prepared in two steps from (+)-ethyl tartrate, catalyses the enantioselective reduction of unsaturated prochiral acids in up to 72\% e.e. (Scheme I-2). Kagan proposed that two factors were necessary in order to obtain such stereoselectivity in catalysis: the ligand conformations must have maximum rigidity with the ligands staying firmly bound to the metal, and that the acid function of the substrates was important.

Extensive mechanistic studies by Halpern suggested that the substrate binds to the metal centre through the olefinic bond and the carbonyl oxygen, producing ring-stabilised diasteromeric intermediates (TS1, Scheme I-2), supporting Kagan’s claim that a remote functionality such as the acid function is salient. A more detailed discussion of the complex chemistry discovered on this mechanism can be found elsewhere.

![Scheme I-2](image)

Scheme I-2 The hydrogenation of \(\alpha\)-functionalised olefins with a ruthenium complex of the diphosphine \((R,R)-6\), showing the transition state proposed by Halpern. Reaction conditions: 1 or 4 (1 eq.), [RhCl(solvent)] (0.02-3 mol\%), NEt\(_3\) (0.06 mol\%), H\(_2\) (1 bar), benzene/ethanol (1:2), r.t.

Knowles noted the importance of the diphosphine to enantioselectivity and developed a new breed of chiral diphosphines. It was found that employing a cationic rhodium complex of the diphosphine \((R,R)-\text{DiPAMP} 10\), enantioselectivity of up to 95\% could be obtained in the hydrogenation of \(\alpha\)-acylaminocrylic acids (Scheme I-3). This led to the development of the first industrial application of catalytic asymmetric hydrogenation, in the synthesis of \(L\)-DOPA 9, a compound found to be useful in the treatment of Parkinson’s disease.

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1 Kagan’s work was also insightful in that he showed that the chirality did not have to be at the phosphorus centre and could be incorporated in the ligand backbone, further from the metal centre.
The success of this process - operated on an industrial scale since 1974 - opened the door to a new era in asymmetric catalysis. In subsequent years, the discovery of a variety of ligands, in combination with various metals, has led to several processes for alkene hydrogenation running on a commercial scale\textsuperscript{13,14} and a number of recently launched drugs, such as Tipranavir,\textsuperscript{15} Rozerem,\textsuperscript{16} Sitagliptin\textsuperscript{17} and Aliskiren\textsuperscript{18} are reported to use asymmetric hydrogenation in their synthesis. The asymmetric hydrogenation of ketones, however, is a newer field and its origins lie in the 1980s, in particular in the work of Ryoji Noyori.

Scheme I-3 The hydrogenation of $\alpha$-acylaminoacrylic acids with the ruthenium complex of the diphosphine ($R,R$)-DiPAMP 9. Deprotection of the aryl substituents and the amide component of compound 8 (steps (i) and (ii)) yields L-DOPA, produced on an industrial scale via this route. 

Reaction conditions: 4 or 7 (1 eq.), [Rh($R,R$-10)\textsuperscript{1,5-COD}]+BF\textsubscript{4} (0.001 mol%), H\textsubscript{2} (3 bar), MeOH, 50°C. (i) 9, HCl (aq); (ii) HBr (5 eq.), H\textsubscript{2}O, reflux, 3 h.

1.2 Asymmetric Hydrogenation of Functionalised Ketones

Despite the tremendous success in the hydrogenation of prochiral olefins, until the 1980s attempts at catalytic asymmetric ketone hydrogenation had been generally fruitless. The breakthrough came about with the discovery of a new ligand, the atropisomeric chiral diphosphine ligand $2,2'$-bis(diphenylphosphino)-1,1'-binaphtyl (BINAP) 11, which when employed with ruthenium, was found to be remarkably effective not only in the enantioselective hydrogenation of a wide variety range of olefinic substrates such as enamides,\textsuperscript{19,20} $\alpha$-(acylamino)acrylic acids, alkyl- and aryl-substituted acrylic acids,\textsuperscript{21} $\beta,\gamma$-unsaturated carboxylic acids,\textsuperscript{21} allylic and homoallylic alcohols,\textsuperscript{22} but also in the hydrogenation of ketones with proximal functional groups, which act as a tether to the ruthenium centre.\textsuperscript{23} A number of functional groups were shown to tether the substrate to the catalyst leading to highly enantioselective hydrogenation, for example: dialkylamino, hydroxyl, alkoxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, dialkylaminocarbonyl, and carboxyl groups - a number of which are represented in Table I-1.

Noyori proposed that the hydrogenation of such substrates is possible due to an alternative
mechanism operating compared to hydrogenation using rhodium complexes. It was proposed that the reaction proceeds via a Ru monohydride intermediate formed by heterolysis of molecular hydrogen by the Ru complex (Scheme I-4). The ruthenium centre remains in the +II oxidation state throughout the catalytic cycle; rhodium on the other hand oxidatively adds H₂ and the catalytic cycle thus involves a +I/+III redox process. Heteroatoms in the functional groups are needed to tether the substrate to the catalytic ruthenium centre and enantiodifferentiation is brought about by a combination of the 5 or 6 membered chelate ring formed between the substrate and the catalyst, and the unique dissymmetric template created by ruthenium and the C₂ symmetric chiral diphosphine (Scheme I-4, TSₐ and TSₐ).

![Scheme I-4](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tether</th>
<th>Ru Catalyst</th>
<th>Catalyst Loading [mol%]</th>
<th>P[H₂] [bar]</th>
<th>Time [h]</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{CH}_2\text{NMe}_2)</td>
<td>[Ru((S)-11)(OAc)]_2</td>
<td>0.13</td>
<td>50</td>
<td>12</td>
<td>72</td>
<td>96 (S)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CH}_2\text{OH})</td>
<td>[RuCl₂((R)-11)]</td>
<td>0.43</td>
<td>93</td>
<td>32</td>
<td>&gt;99</td>
<td>92 (R)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{CO}_2\text{Me})</td>
<td>[RuCl₂((R)-11)]</td>
<td>0.13</td>
<td>96</td>
<td>46</td>
<td>97</td>
<td>83 (R)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CH}_2\text{CH}_2\text{OH})</td>
<td>[RuCl₂((R)-11)]</td>
<td>0.11</td>
<td>70</td>
<td>42</td>
<td>&gt;99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CH}_2\text{CO}_2\text{Et})</td>
<td>[RuBr₂((R)-11)]</td>
<td>0.08</td>
<td>86</td>
<td>51</td>
<td>&gt;99</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>6</td>
<td>(\text{CH}_2\text{COSPh})</td>
<td>[RuCl₂((R)-11)]</td>
<td>0.19</td>
<td>95</td>
<td>86</td>
<td>(42)</td>
<td>93 (R)</td>
</tr>
<tr>
<td>7</td>
<td>(\text{o-BrC}_6\text{H}_4)</td>
<td>[RuBr₂((R)-11)]</td>
<td>0.09</td>
<td>100</td>
<td>62</td>
<td>97</td>
<td>92 (R)</td>
</tr>
</tbody>
</table>

Table I-1 Hydrogenation of functionalised ketones using ruthenium complexes of the C₂-symmetric diphosphine BINAP 11. General conditions: functionalised ketone, ruthenium catalyst, MeOH or EtOH, H₂, rt.

This development proved to be extremely efficient for the asymmetric hydrogenation of a wide variety of functionalised ketones resulting in the industrial production of synthetic intermediates of antibiotic carbapenems and antibacterial Levofloxacin. However, simple unfunctionalised ketones are not hydrogenated using such catalytic systems because the substrates are unable to stabilise the transition state by forming the chelate structure depicted in Scheme I-4.
In spite of extensive studies, only a limited number of transition metal catalysts were known to exhibit any activity in the hydrogenation of simple ketones up until the 1990s, and even fewer were noted to induce stereoinduction. Until this point, enantioselective reduction of achiral ketones was affected by chiral stoichiometric reagents including BINAL-H, DIP chloride and Alpine Borane, or by CBS reduction using borane/catechol borane and a chiral oxazaborolidine catalyst. For technical and economic reasons, particularly in large scale reactions in industry, homogenous hydrogenation is obviously more desirable than stoichiometric hydride reduction.

The major breakthrough in the catalytic asymmetric hydrogenation of simple ketones using transition metals was made by Noyori in the mid-1990s by the development of ruthenium catalysts bearing both BINAP and a chiral 1,2-diamine on the metal centre. Noyori proposed that employing protic ligands, for example ligands containing an NH₂, could improve the activity and selectivity of the BINAP-Ru(II) catalyst by forming a secondary, hydrogen bonding interaction with the C=O moiety. Indeed it was shown that the reactivity of [RuCl₂(PPh₃)₃] was significantly enhanced by the addition of one equivalent of ethylene diamine and an excess of potassium hydroxide, with TOF increasing from less than 5 to 6700 mol cat⁻¹ mol prod⁻¹ h⁻¹ in the hydrogenation of acetophenone. Turnover frequency was enhanced further using the anisotropic diphosphate BINAP and its derivatives. It was shown that maximum turnover frequencies of over 250,000 mol cat⁻¹ mol prod⁻¹ h⁻¹ could be obtained using a preformed

**Scheme 1-4** Mechanism of BINAP-Ru catalysed hydrogenation of β-keto esters and the diastereomeric transition states involved (naphthalene rings omitted for clarity). S = solvent

### 1.3 Asymmetric Hydrogenation of Simple Ketones
ruthenium catalyst comprising TolBINAP in combination with DPEN, and 200 equivalents of KO'Bu relative to ruthenium.\textsuperscript{32}

The asymmetric version of this reaction, employing (S)-TolBINAP and (S,S)-DPEN, was found to give good enantioselectivity in the hydrogenation of acetophenone and 1'acetonaphthone (Scheme I-5).\textsuperscript{32} However, this could be significantly increased by employing the more sterically demanding (S)-XylBINAP and the diamine (S)-DAIPEN - readily obtainable from leucine - and this combination remains the best system for a many enantioselective hydrogenations.\textsuperscript{33} High enantioselectivity is dependent upon using the ‘matched’ diphosphine/diamine combination i.e. the (S)/(R)-combination of XylBINAP and DPEN gives substantially lower selectivity.

\begin{equation}
\begin{array}{c}
\text{A wide range of simple alcohols have subsequently been prepared with high levels of enantioenrichment and the catalytic system has been shown to be tolerant of a number of functionalities (Table I-2).}\textsuperscript{31,32,33} \text{Substitution of different electronic groups of the phenyl ring had little effect on enantioselectivity and hydrogenation of the ketone proceeded while leaving groups such as NH}_2, \text{NO}_2, \text{ester groups, and halogens untouched.}
\end{array}
\end{equation}

The [RuCl\(_2\)(P\(^\bullet\)P)(N\(^\bullet\)N)] system has also been found to be efficient in the highly enantioselective hydrogenation of unsymmetrical, sterically differentiated benzophenones,\textsuperscript{34} some heteroaromatic ketones,\textsuperscript{135} conjugated\textsuperscript{33} and unconjugated ketones\textsuperscript{36} – leaving the olefinic bond intact – cycloalkyl methyl ketones,\textsuperscript{33} dialkoxymethyl methyl ketones\textsuperscript{24} and \(\alpha\)-amino aromatic ketones.\textsuperscript{37} Thus this system has given unprecedented access to a wide variety of synthetically valuable chiral secondary alcohols (Scheme I-6). Noyori has also demonstrated the synthesis of a number of biologically relevant molecules using [RuCl\(_2\)(P\(^\bullet\)P)(N\(^\bullet\)N)] catalysts (Scheme I-7). None-the-less, there were some rather significant gaps in the substrate scope that will be discussed later. It should also be noted that some of the same principles have been applied in the asymmetric

\begin{equation}
\begin{array}{c}
\text{‡ The hydrogenation of some heteroaromatic ketones is accomplished successfully with the heterocycle remaining intact. However, borate additives are often required to prevent deactivation of the catalyst.}\textsuperscript{35}
\end{array}
\end{equation}
transfer hydrogenation of simple ketones, but the interested reader is directed to other reviews on this related field of study.38-41

![Chemical Structures](image)

Table I-2 Hydrogenation of an unprecedented range of simple ketones using diphosphine/diamine-ruthenium complexes. *6% conversion.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>R or X</th>
<th>e.e. [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>99 91 87</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>C₂H₅</td>
<td>99 92</td>
</tr>
<tr>
<td>n-C₃H₇</td>
<td>n-C₃H₇</td>
<td>94</td>
</tr>
<tr>
<td>n-C₄H₉</td>
<td>n-C₄H₉</td>
<td>90</td>
</tr>
<tr>
<td>CH₂Ph</td>
<td>CH₂Ph</td>
<td>98</td>
</tr>
<tr>
<td>CH(CH₃)₂</td>
<td>CH(CH₃)₂</td>
<td>99</td>
</tr>
<tr>
<td>C(CH₃)₃</td>
<td>C(CH₃)₃</td>
<td>61⁺</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>97 82</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>98 94</td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
<td>96 98</td>
</tr>
<tr>
<td>CF₃</td>
<td>CF₃</td>
<td>99 99</td>
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<tr>
<td>CH₂O</td>
<td>CH₂O</td>
<td>92 82</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>&gt;99 87</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>98 88</td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
<td>&gt;99 77</td>
</tr>
<tr>
<td>CF₃</td>
<td>CF₃</td>
<td>99 83</td>
</tr>
<tr>
<td>CH₂O</td>
<td>CH₂O</td>
<td>99 88</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>99 99</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>97 77</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>96 94</td>
</tr>
<tr>
<td>CF₃</td>
<td>CF₃</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

*Table I-2* Hydrogenation of an unprecedented range of simple ketones using diphosphine/diamine-ruthenium complexes. *6% conversion.*
1.4 Mechanism of Hydrogenation of Unfunctionalised Ketones

The rational design of efficient homogeneous catalysts is greatly accelerated by an in-depth knowledge of the mechanism of the desired process, especially of the underlying origin of activity and selectivity. The mechanism of the hydrogenation of unfunctionalised ketones has undergone extensive study in an attempt to fully delineate the catalytic process. Such an
understanding is of huge importance in the design of new asymmetric hydrogenation catalysts, not only in the optimisation of the original Noyori catalyst scaffold, but in discovering and developing new breeds of catalysts. Here, the current understanding of the mechanism by which Noyori’s [(P^P)(N^N)RuCl_2] catalytic system is believed to operate, and the proposed origin of enantioselectivity in the asymmetric process, is discussed.

1.4.1 Noyori’s Proposed Mechanism

The fundamental principle behind the high activity and enantioselectivity of [RuCl_2 (P^P)(N^N)] catalysts first presented by Noyori, was the need for a terminal N-H functionality to facilitate hydride transfer between the Ru-H species and the ketone. Noyori realised that the ketone must somehow interact with the catalyst structure in a way such that it is geometrically possible for hydride delivery to the carbonyl functionality. It was postulated that since electrophilic metal centres tend to form σ-complexes rather than π-complexes with carbonyl compounds the relative locations of the nucleophile and the carbonyl carbon are inappropriate for a reaction to occur. Thus he accounted for the lack of reactivity of simple ketones with [RuCl_2(P^P)]-type catalysts, which are efficient catalysts for the hydrogenation of functionalised ketones. In the case of functionalised ketones, coordination of an adjacent heteroatom allowed the positioning of the metal hydride for efficient hydride transfer to the ketone. Noyori proposed that increased activity in the hydrogenation of simple, or unfunctionalised ketones, could be achieved by addition of diamine additives, with ligand-substrate hydrogen bonding interactions holding the substrate in place for efficient hydride transfer.

As discussed, this conceptually new idea for the hydrogenation of simple ketones was borne out experimentally allowing for a highly efficient process, and a greater understanding of the mechanism has developed from the original idea. Noyori has proposed a mechanism for the hydrogenation of acetophenone using catalyst (S),(S,S)-37, structurally similar to the original catalyst precursor (S),(S,S)-14 (Scheme I-8) based on detailed experimental observations. The catalytic cycle is made of two distinct modes: catalyst generation from precatalysts and the catalytic cycles leading to turnover of substrate.

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^Noyori makes use of this precatalyst in preference to the original precatalyst (S),(S,S)-14 as it is claimed that the activation of (S),(S,S)-37 is considerably more complex than that of (S),(S,S)-14. However, both catalyst precursors are believed to generate the same stereo-determining reactive species, and thus operate by the same mechanism, both giving identical enantioselectivities in the hydrogenation of a variety of ketonic substrates.
(i) Catalyst Generation

Noyori proposed that hydrogenation proceeded first by generation of real catalysts from the precatalyst $A$, then subsequent dual-operating catalytic cycles 1 and 2 (Scheme I-8).$^{42}$ The generation of the real catalytic species from the 18 electron species $A$ can follow two reversible pathways. A ligand can dissociate to form the cationic species $B$ which can then be deprotonated to form the 16e Ru amide complex $E$. Alternatively $E$ can be be formed through species $D$ via a $D_{3b}$ mechanism (akin to SN$_{1CB}$) whereby the ligand elimination is facilitated by deprotonation of the amine, to give species $E$. Noyori postulates that the formation of $H_2$, $RO^-$ and $B(OR)_3$ from the destruction of $BH_4$ in alcoholic solvent, or chloride salts when catalyst precursors such as $(S),(S)-14$ are used, shifts the equilibrium in these reversible steps towards the formation of species $B$ and $E$ which can be considered ‘true catalysts,’ with their relative amounts dependent on base concentration.$^{42}$

![Scheme I-8 Mechanism of the hydrogenation of unfunctionalised ketones as proposed by Noyori.](image)

Mechanism described in reference $^{42}$ for system where $P-P = (S)$-TolBINAP, $HN-NH = (S,S)$-DPEN, $L^1 = BH_4$, $L^2 = H$, with isopropanol as solvent.
Noyori suggests that once the catalytic species B and E are generated, two cycles are in operation, dependant on the reaction conditions. Under standard conditions, i.e. in alcoholic media and in the presence of base, catalytic cycle 1 is the major pathway and is thought to be responsible for the exceedingly high catalytic turnover in isopropanol. The cationic 16e complex B first reacts with H₂ to form the 18e complex C which can undergo deprotonation to generate species F. Reaction of F with ketone substrate gives the 16e amido Ru species E as well as the alcoholic product. Protonation of E by the alcohol solvent regenerates B, thus completing catalytic cycle 1. Alternatively, F can also be regenerated by direct reaction of E with H₂, giving the less significant catalytic cycle 2. However, this cycle becomes important when hydrogenations are carried out in aprotic solvents or at high base concentration.

It is important to note that the proposed catalytic cycles make assumptions on the relative basicity and acidity of reaction intermediate such that relative basicity:

\[ :\text{NH (G)} > :\text{NH (E)} > (\text{RO-})(\text{isopropanol})_n \]

and the relative acidity of

\[ \eta^2\text{-H}_2 (\text{C}) > \text{NH}_2 (\text{B}) \geq \text{isopropanol} > \text{NH}_2 (\text{A}) > \text{NH}_2 (\text{F}) \]

Thus under standard conditions, i.e. catalytic cycle 1, B and C are the resting states, where a high concentration of C and its easy deprotonation are required for high catalyst efficiency. In catalytic cycle 2, E is the resting species.

(iii) Origin of Enantioselectivity

Noyori’s proposed mechanism is based on a metal-ligand dual functionality first proposed in 2001. It was postulated that the hydride transfer step, i.e. the stereodirecting step, involves the two ground state components F and E linked by transition step TS1. The NH proton in F plays a pivotal role in hydrogen delivery to ketones.
In the ground state species $F$ (Scheme I-9), the NH moiety has an excellent hydrogen bonding ability which can activate carbonyl substrates, and this combined with the sufficiently nucleophilic hydride in a $\textit{fac}$ relationship sets up a charge-alternating $\text{H}^\delta-\text{Ru}^\delta-\text{N}^\delta-$ $\text{H}^\delta$ arrangement which fits well with the C=O dipole. Only the axial N-H protons are involved in this arrangement due to stereoelectronic reasons. The Ru center can then deliver a hydride to the electrophilic C=O carbon, while the nitrogen supplies a proton to the oxygen atom simultaneously to give $E$.

The origin of enantioselectivity can be seen by consultation of the possible diastereomeric transition states for $\text{TS}_1$ (Scheme I-10). The prochiral ketone approaches 38 so as to minimise nonbonded repulsion with the substituents upon phosphorus, in this case the tolyl ring, and to maximise the electronic attraction between the equatorial NH and the ketone phenyl group. This
allows transfer of the hydride to the Si prochiral face of the ketone resulting in the formation of the (R) form of the alcohol product using the (S),(S,S) catalyst.

1.5 Evidence for Noyori’s Proposed Mechanism

1.5.1 Role of Diamine Ligand

When Noyori first reported the efficient enantioselective hydrogenation of unfunctionalised ketones in 1995 by diphosphine-diamine-Ru(II) complexes he noted that at least one primary amine end is necessary to facilitate reaction after diamine ligand screening experiments and reported that N,N,N’,N’-tetramethylenediamine (TMEDA) is totally ineffective in catalysis. This led to the proposal that the NH proton in catalyst such as (S,SS)-14 plays a key role in the catalytic cycle.

Noyori proposed that diamine-substrate hydrogen bonding was important and this was backed up by later work which showed remarkable selectivity for the ketone functionality over the alkene functionality (lacking a hydrogen bond acceptor) in the hydrogenation of alkenyl ketones. This was particularly remarkable as diamine-free BINAP-Ru complexes were shown to have good catalytic activity for hydrogenation of the C=C unit of allylic alcohols.

Scheme I-10 shows that as well as forming a hydrogen bond with the ketone substrate, that the diamine may also be responsible for an electrostatic interation with the phenyl group of the substrate through the equatorial proton of the ‘other’ NH group. Noyori backed up this claim by showing that in competition experiments, electron poor derivatives of acetophenones were hydrogenated faster than acetophenone itself, which in turn was hydrogenated faster than electron rich derivatives, although substituent effects were significantly less pronounced than simple sodium borohydride reduction. Noyori also noted that this is consistent with the poor performance of NH₂/pyridine hybrid ligands instead of bis-NH₂ ligands such as DPEN, in the hydrogenation of acetophenone.
1.5.2 Role of Base

The base plays a crucial role in the rate of the catalytic reaction. Noyori initially reported that at least two equivalents of base are needed for sufficient activity, and that the role of base is to neutralise HCl formed in the catalyst generation step. Noyori showed that the addition of base reduces the incubation period and proposed that this was due to the enhanced acceleration of the D elimination step in the formation of species B. Further work however showed that the base also facilitates the catalytic cycle itself. It was shown that the reaction rate after the incubation period is accelerated by increasing the base concentration (Figure I-2). Noyori postulated that the base facilitates the deprotonation of C to F which readily catalyses the reduction of ketone. However, there is an optimum base concentration and above this, deprotonation of B to E is also evident, decreasing the effective concentration of C, thus reducing the accelerative effects.

Noyori initially proposed that the nature of the base was not important and showed that productive hydrogenation could be accomplished using alkaline bases such KOH, KOPr and KO’Bu as well as strong organic bases such as phosphazenes (sterically hindered neutral nitrogen bases). However, a subsequent study by Chen showed that an alkali metal cation is in fact important for high activity, with reactivity in the order K > Na ~ Rb > Li. Chen proposed that such acceleration in activity is a result of rapid hydrogen cleavage as similar trends are not
observed in transfer hydrogenation catalysts. Chen’s results led to the suggestion that in hydrogenation catalysts, the amine nitrogen and two aryl rings create a cation binding site for potassium in species C/G (Scheme I-11). Binding of potassium increases the acidity of bound dihydrogen and brings the alkoxide base into close proximity to dihydrogen, thus facilitating efficient hydrogen cleavage to give the real catalyst F.

![Scheme I-11 Importance of metal cation in dihydrogen cleavage in Noyori catalysts.](image)

Despite having such a profound impact on reaction rate, the concentration of base has no effect upon the level of enantioselectivity. This is consistent with the proposal that the stereodetermining step proceeds via the same Ru reducing species, F.

1.5.3 Effect of Solvent

The solvent was noted to be of particular importance in the original work by Noyori. While the reaction can be carried out in methanol, ethanol, *n*-butanol, toluene or even DMF, isopropanol is the solvent of choice and gives rise to enhanced reaction rates. This led to the proposition that the solvent was implicit in the reaction mechanism. One proposal for the alcohol dependency is thought to be the formation of diphosphine/diamine-RuH(OR) or -Ru(OR)₂ species that act as a reservoir to the active catalyst. Noyori proposed that the stability of such species and the ease of such to be transformed into active catalysts would depend on the properties of the RO groups.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>TOF [h⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>isopropanol</td>
<td>2650</td>
</tr>
<tr>
<td>2</td>
<td><em>n</em>-butanol</td>
<td>1170</td>
</tr>
<tr>
<td>3</td>
<td>1-phenyethanol</td>
<td>920</td>
</tr>
<tr>
<td>4</td>
<td>ethanol</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>methanol</td>
<td>8</td>
</tr>
</tbody>
</table>

*Table I-3 Solvent Effect on Catalysis*

Alcoholic solvent has also been proposed to participate in the hydrogen activation step. Ikariya first suggested - based on deuterium labelling experiments using the phosphine-free
[RuCl(NH$_2$CH$_2$CH$_2$NMe$_2$)Cp*] system - that isopropanol was implicit in the splitting of hydrogen probably via the hydrogen bonding network shown in Scheme I-12, thus leading to enhanced activity versus hydrogenation in aprotic solvent.$^{47}$ This was supported by theoretical studies by Andersson, who showed that there is a significantly lower activation barrier for the alcohol-mediated splitting of hydrogen compared to the non-alcohol mediated process for the same system.$^{48}$ Morris has since presented both experimental and theoretical work showing similar alcohol effects using [Ru(H)$_2$(BINAP)PICA] derivatives.$^{49}$

The nature of the solvent is also of importance to the degree of enantioselectivity. Bergens showed that isopropanol is by far the more superior solvent when compared to THF in terms of enantioselectivity with the e.e. of reactions in THF decreasing as the reaction proceeds. The basis of this is in the reversibility of each step of the catalytic cycle. Bergens postulated that the huge excess of isopropanol can intercept the ruthenium intermediate 42 which pushes the reaction in the forward direction and prevents the reverse reaction and thus racemisation (Scheme I-13). Any small amount of the Ru amide present is therefore converted back to the dihydride species or ‘stored’ as the Ru isopropoxide species. In the absence of isopropanol, the reaction of 1-phenylethanol with the Ru-amide species 42 occurs, leading to racemisation of the alcohol product, is in competition with the regeneration of 41.

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**Scheme I-12** Alcohol-assisted hydrogen activation

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**Scheme I-13** Reaction equilibria leading to high enantioselectivity for reactions in isopropanol.
1.5.4 Source of Hydrogen/Effect of Hydrogen Pressure

The transfer hydrogenation of ketones by transition metals with isopropanol as the hydrogen donor is a well known process and it was conceivable that the [RuCl₂(P^P)(N^N)] system operates without the need for molecular hydrogen. It was found by Noyori however that the presence of diamine retarded transfer hydrogenation - i.e. when no molecular hydrogen was present - and accelerated H₂-hydrogenation, and is thus a net H₂-hydrogenation. This was confirmed by deuterium labelling experiments using d₈-iPrOH as solvent (and potential hydride source), which yielded no deuterated 1-phenylethanol in the H₂-hydrogenation of acetophenone. Complex E, although potentially reactive towards isopropanol, must preferentially form B which reacts with molecular hydrogen in a more rapid process with transfer hydrogenation unable to compete.

The rate of catalysis is particularly sensitive to hydrogen pressure since an increase in hydrogen concentration in solution facilitates the conversion of B to C thus reducing the incubation period. The rate is intrinsically linked to the base concentration however as base is need to convert C into the reducing species F. Without base the rate is insensitive to hydrogen pressure whereas even with small concentrations, the rate rapidly increases.

As is expected from the proposed catalytic cycle, the levels of enantioselectivity in the reaction are unaffected by hydrogen pressure.

1.5.5 Kinetic Evidence

Noyori showed that for the hydrogenation of acetophenone with catalyst precursor (S),(S,S)-14, consumption of the substrate as a function of time was sigmoidal in nature. This is consistent with the presence of an incubation period, i.e. the generation of the real catalytic species B and E from precatalyst A. This incubation period is largely diminished by addition of base, due to the enhanced Dₐₘ elimination.

The consumption of acetophenone by the system was shown to be pseudo-first order, once the incubation period was taken into account, with pseudo-zero order observed at high substrate:catalyst ratios where saturation kinetics were in effect.
1.5.6 Ligand Structure

The effect of ligand structure upon catalyst activity and enantioselectivity, and the resultant development of new catalysts, is discussed throughout this review. Experimental results, by in large, have supported the mechanistic proposal and origin of enantioslectivity proposed by Noyori. The need for an amine group has already been discussed but modification of the phosphine components has also supported Noyori’s proposals. The 3,5-dialkyl meta effect has been demonstrated to give higher enantioselectivity suggesting that the phosphine substituents are implicit in enantioinduction.\(^{33}\) The configuration of the alcohol products in all cases are consistent with hydrogen bonding interaction between the diamine and the substrate in such a way as orientate the bulkier aryl group of the substrate away from the phosphine substituents allowing facially selective hydride transfer, i.e. \((S)\text{-BINAP}/(S,S)\text{-DPEN}\) combination always gives \((S)\)-configured product (unless group priorities are different). This mode of enantioselection has been backed up by the theoretical work of Harvey who, making use of DFT calculations, has shown that the approach of acetophenone with the phenyl group oriented away from the phosphine ligands is favoured both by steric interactions and weak hydrogen bonding between the phenyl ring and ruthenium bound NH\(_2\). Harvey reproduced the magnitude of enantioselectivity obtained in the experimental findings semiquantatively and has demonstrated that the much reduced enantioselectivity of the mismatched diphosphine/diamine combination can also be reproduced.\(^ {50}\)

1.5.7 Identification, Isolation and Synthesis of Catalytic Intermediates

Since the disclosure of Noyori’s highly active and selective catalytic system in the mid-1990s, much effort has gone into the identification, isolation and synthesis of intermediates in order to scrutinise the proposed reaction mechanism. Noyori noted early on however, that a number of problems existed which prevented the isolation or even observation of key intermediates. The inherent instability of the ruthenium complexes due to their reactive nature was the principal problem to be overcome. A second problem was the solvent: despite isopropanol being the solvent of choice in terms of reactivity and enantioselectivity, H-D exchange between \(d_8\)-isopropanol and the hydride/dihydrogen ligands on Ru species prevented detailed NMR observations.

These problems have been overcome in many cases however by tuning catalyst structure for maximum stability and it has become possible to prepare both ruthenium monohydride and
dihydride complexes (examples in Scheme I.14). Analysis of the performance of such complexes in catalysis has led to the suggestion that the dihydride is more likely to be the active catalytic species as the preformed dihydride complexes such as 45 do not need base to function whereas monohydride species, such as 44, do.\(^{51}\) It has also been proposed that the hydride must have a *fac* relationship with the diamine ligand in the active species to give the most active catalysts (e.g., 46 and 47) and for highly enantioselective catalysis both the diamine and phosphine must be meridional (46).\(^{24}\)

![Scheme I-14](image)

\textbf{Scheme I-14} Ruthenium monohydride and dihydride species that have been studied.

How such hydride species are formed in the catalytic cycle has also received attention although isolation and even identification of ruthenium complexes of bound dihydrogen, believed to precede the hydride species, is very difficult due to the inherent instability of such complexes. Bergens and coworkers have however observed species 49 (Scheme I-15) at low temperatures, which could be converted into an active catalyst (presumably the dihydride species) with the addition of base.\(^{52}\)

![Scheme I-15](image)

\textbf{Scheme I-15}

The ruthenium species that are present after the transfer of the hydride to the ketone substrates have also been identified although similar problems with stability have been encountered. Morris has proposed that the amido species 50 is the product after hydride-transfer\(^{53}\) although Bergens and coworkers have provided evidence for the presence of alkoxide intermediates such
as 51 that proceed the formation of such species.\textsuperscript{54} Intermediates similar to 51 have also been observed in ester hydrogenation\textsuperscript{55} and computational models have backed up Bergens’ proposal.\textsuperscript{56}

![Scheme I-16 Ruthenium intermediates believed to be the result of hydride transfer.](image)

### 1.6 Extensions of the Noyori System

Noyori’s discovery of an efficient catalytic system for the enantioselective hydrogenation of simple ketones, and a greater understanding of its mechanism of operation, prompted a huge research effort in the area. A number of novel catalysts have been designed by modification of the diphosphine and diphosphine components but few catalysts rival the \([\text{RuCl}_2(\text{XylBINAP})(\text{DAIPEN})]\) system in terms of activity and selectivity. However, the search for more active/highly selective catalysts are still fuelled by the desire for a universal process, overcoming some significant limitations of the system such as the inability to hydrogenate bulkier substrates efficiently as well as many heteroaromatic ketones without the need for additives.\textsuperscript{57} Ketones with sterically similar substituents have also been shown to be problematic in hydrogenation, including dialkyl ketones for example. More practically useful catalysts for adoption into industrially-viable processes are also highly desirable.

#### (i) Phosphine Modification

Noyori’s original work implied, and mechanistic studies later supported (See section 1.4), that the aryl substituents upon phosphorus play a crucial role in determining enantioselectivity. Indeed a significant increase in enantioselectivity of the alcohol product is seen as the steric bulk upon the phosphorus aryl ring is increasing from \(-\text{PPh}_2\) to \(-\text{P(tol)}_2\) to \(-\text{P(xyl)}_2\) (See Table I-2 for examples). Pregosin has described this as the 3,5-dialkyl meta effect, and shown that it is common in a number of enantioselective processes catalysed by phosphine-ligated transition metals.\textsuperscript{58,59} Research on modification of the diphosphine component has mainly been focussed upon exploiting this phenomenon by using new diphosphines with either axial, planar, or backbone chirality, in the hydrogenation of
ketones with the goal of improved activity/selectivity, or by discovering catalysts which are more easily prepared and thus more industrially viable.

Due to the unprecedented success of binaphthyl ligands in a wide range of processes that goes far beyond hydrogenation chemistry, early attempts at improvement of catalyst structure were based on diphosphines with similar axial chirality. Lin showed that even subtle changes to the binaphthyl ring could lead to an improvement in enantioselectivity. Lin demonstrated that the 3,5-dialkyl meta effect can be mimicked by substituents on the binaphthyl ring in the 4/4’ positions. Catalysts containing the 4,4’-disubstituted diphosphines \((S)-60, (S)-61\) and \((S)-62\) gave elevated enantioselectivity comparable with that obtained using catalysts made from the xylyl-based phosphine for a range of simple ketones (Scheme I-17). Lin suggested that unlike xylyl-based phosphines, the 4,4’ substituents are readily tunable for practical asymmetric hydrogenation of different substrates.

![Scheme I-17](image)

Modification of the atropisomeric diphosphine in order to narrow the dihedral angle between phosphorus atoms when bound to ruthenium has also been shown to increase enantioselectivity, by apparently maximising interactions between the phosphine substituents and the substrate. Genêt showed that enantioselectivity increased going from \((R)\)-BINAP \((\theta = 80^\circ)\) to the smaller dihedral angle ligand \((R)\)-SYNPHOS 63 \((\theta = 75^\circ)\) for a wide range of substrates. Enantioselectivity obtained with \((R)\)-SYNPHOS 63 was again comparable to hydrogenation using \((R)\)-XylBINAP 18 without the need for large phosphorus substituents, and thus a simplified synthetic route to the desired diphosphine.

\[\text{\textsuperscript{**}} \text{Other smaller bite angle ligands, as determined by computational modelling, were also shown to have a positive effect upon enantioselectivity in this study with SYNPHOS being the most active and selective.}\]
Most of the early attention regarding the diphosphine component centred on the binaphthyl system due to its conformational rigidity when bound to ruthenium, thus controlling the dihedral angle between phosphorus donors, which has been shown to be key. Since then, other axial chiral ligands have been employed with some success based on the biaryl system. Chan paved the way in this area by employing the ruthenium complex of dipyridylphosphine ligand XylP-Phos (R)-66 in combination with (R,R)-DPEN in the hydrogenation of simple ketones (Scheme I-18).61 This ligand, as well as its diphenylphosphino- and ditolylphosphino- derivatives (S)-64 and (S)-65, had been previously used in the highly enantioselective hydrogenation of functionalised ketones, and the methoxy groups, while being necessary to block the pyridyl nitrogen from coordinating to the metal centre, could also conceivably act to anchor the biphosphine in one conformer.62,63 Chan showed that using XylP-Phos (R)-66 in combination with (R,R)-DPEN, enantioselectivities were obtained on par with that with Xyl-BINAP/DAIPEN.

This idea opened the way for the development of a range of atropisomeric biaryl diphosphines for use in ketone hydrogenation on an industrial scale. Researchers at Chirotech (now Dr Reddys) have developed a highly efficient protocol for enantioselective hydrogenation with diphosphine ligands based on the BIPHEMP motif (Scheme I-18, 67-70).64 It was observed that ruthenium complexes of biaryl phosphines (R)-OMeBIPHEP 67 and (R)-HexaPHEMP 68 in combination with (R,R)-DPEN/(R)-DAIPEN/(R,R)-DACH proved to be active and highly enantioselective catalysts. (R)-OMeBIPHEP 67 proved to give less active catalysts but it emerged that making use of the 3,5-dialkyl meta effect, ruthenium complexes of (S)-Xyl-HexaPHEMP 69 in combination with (S)-DAIPEN gave a catalyst that performed as well as, if not better than, the corresponding BINAP ligand in the enantioselective hydrogenation of functionalised ketones. Problematic syntheses of both enantiomers of Xyl-HexaPHEMP 69 have led to the development of the more accessible Xyl-TetraPHEMP 70, which gives equally
excellent performance and has the advantage that best results are obtained in combination with DPEN, a more economically viable alternative to DAIPEN.\textsuperscript{65}

\begin{center}
\includegraphics[width=\textwidth]{tune-phos.png}
\end{center}

\textit{Scheme I-19} TunePhos ligands

Zhang has developed a related system employing the atropisomeric bridged biaryl ligand (S)-C\textsubscript{3}-XylTunePHOS 71 (Scheme I-19),\textsuperscript{66} which has also shown great activity and selectivity in hydrogenation, rivalling that of the corresponding BINAP system when used in conjunction with (S)-DAIPEN.\textsuperscript{67} Zhang reasoned that this ligand is more easily accessible than Chan’s P-Phos ligands, and its modular nature allows tuning (thus deriving its name) for the hydrogenation of specific substrate classes.\textsuperscript{67} This has been extended to (R)-C\textsubscript{3}-TunePhos 72\textsuperscript{68} but this class of ligand has so far failed to deliver the high levels of enantioselectivity accomplished by C\textsubscript{3}-TunePHOS.

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

\textit{Scheme I-20} Other axial chiral diphosphine ligands employed in enantioselective hydrogenation of ketones.

Other structurally different diphosphines containing axial symmetry have also been demonstrated to be highly efficient catalysts. Zhang showed that diphosphines based on the dicyclopentane structure could be used as ligands for ruthenium in combination with DPEN (Scheme I-20, (R,R)-73), giving enantioselectivities of up to 93\%, although this level of enantioinduction could not be replicated over a large range of substrates.\textsuperscript{69} More luck was had employing the unusual chiral spiro diphosphine (SDP) ligands in the work of Zhou.\textsuperscript{70} When combined with (R,R)-DPEN upon ruthenium, the xylyl-derivative (S)-74 gave enantioselectivity on par with that of the corresponding BINAP-derived diphosphine.
While diphosphines base on axial chirality have proved hugely successful in such enantioselective transformations, synthesis of such structures, especially with xylil substituents that appear in the best catalysts, remains tricky. Thus, structurally different diphosphines are desirable. Researchers at Chirotech have developed an excellent system based on a diphosphine with planar chirality and this still remains the only efficient alternative to atropisomeric phosphines for the highly enantioselective hydrogenation of a diverse range of simple ketones. Screening of a variety of diphosphines showed (S)-PhanePhos 77 (Scheme I-21) to have both the high catalytic activity and high enantioselectivity needed for efficient catalysis. Making use of the 3,5-dialkyl meta effect, the most efficient ligand (S)-XylPhanePhos 78 was discovered. The best results have been obtained when used in conjunction with (S,S)-DPEN, with results comparable to that obtained using the XylBINAP/(S)-DAIPEN system, i.e. enantioselectivities generally above 90% for a range of substrates - including simple, some heteroaromatic, and unsaturated ketones - and catalysis carried out with substrate:catalyst ratios of up to 40,000.

(ii) Diamine Modification

While many diphosphines have been developed for enantioselective hydrogenation with [RuCl₂(P^P)(N^N)] systems, relatively little research has been aimed at modifications of the diamine component. Most catalysts are based on the vicinal 1,2-diamines DPEN and DAIPEN, which have allowed for highly active and enantioselective hydrogenation of a wide range of simple ketones. A limited number of other diamines have been discovered however with niche applications and others with practical advantages in synthesis.

Work undertaken by researchers at Johnson Matthey looked at the development of the 1,3-analogue of DPEN. The ruthenium complex of the C₃-diamine DPPN in combination with (R)-XylP-Phos ((R)(S,S)-79) (Scheme I-22), displayed reactivity and selectivity on par of its C₃ derivative DPEN, in the hydrogenation of a range of simple ketones. ⁷¹ This suggests that the structural modification associated with the expansion of the diamine-Ru chelate ring from a five membered ring to six does not impart radical new properties on the system.
However, it was found – subsequent to the work of the Noyori and coworkers\textsuperscript{72} and research in this group\textsuperscript{73} in this challenging area – that such complexes were more adept at the enantioselective hydrogenation of \textit{tert}-butyl alkyl ketones, attaining enantioselectivity up to 74% with catalyst \((R)(S,S)\)-\textsuperscript{80}. Complexes containing 1,2-diamines that are generally poor in such transformations.\textsuperscript{74} This is likely due to the more open environment created by the lengthening of the diamine chain length (the enantioselective hydrogenation of bulky ketones will be discussed further in section 1.7.2).

![Scheme I-22 Ruthenium catalysts of 1,3-diamines and diphosphines developed by Johnson Matthey.](image)

This idea is furthered when using 1,4-diamines, such as IPBAN \textsuperscript{84} and IPHAN, derived from tartaric acid and mannitol, respectively. Ruthenium complexes of IPBAN \textsuperscript{84} in combination with chiral diphosphines have been shown to be more selective for more bulky secondary alkyl ketones such as isobutyrophenone compared to acetophenone and its derivatives (Table I-4).\textsuperscript{74,75} Unlike catalysis with complexes of 1,2-diamines/diphosphines, the 3,5-dialkyl \textit{meta} effect of the phosphine is not observed.

![Table I-4 Hydrogenation of simple ketones by [RuCl\(_2\)(diphosphine)((S)-IPBAN)] catalysts. \textit{General conditions:} Ketone 81 or 82 (1 eq.), Ru catalyst (0.1 mol%), KO\(^{13}\)Bu (4 mol%), \(^1\)PrOH, H\(_2\) (10 bar), rt.](image)
Ruthenium complexes of IPHAN combined with diphosphine ligands have been shown to be efficient in the hydrogenation of other bulkier substrates, in particular of substituted tetralones.\(^\text{76}\) Noyori showed that a whole range of the corresponding chiral alcohols could be prepared in greater than 90% e.e. using (S)-XylBINAP/(R,R)-IPHAN-ruthenium complex \(\text{85}\) (Scheme I-23). Hems and coworkers at Johnson Matthey have also employed complexes of the 1,4-diamine DAMDO \(\text{96}\) (Scheme I-25) for such transformations, obtaining good enantioselectivities of up to 81% in the hydrogenation of tetralone \(\text{86}\), but note that such complexes are prone to decomposition.\(^\text{74}\)

**Scheme I-23**  Enantioselective hydrogenation of tetralones using \([\text{RuCl}_2(\text{diphosphine})(\text{IPHAN})]\) complexes.

Ruthenium complexes of IPHAN and BINAP have also been used in the hydrogenation of tricky bicyclo [2.2.2] and [2.2.1] ketones. This is particularly worthy of mention as such sterically congested frameworks require highly active catalytic species and the ability to discriminate between tertiary and secondary alkyl groups to achieve selectivity (Scheme I-24).\(^\text{77}\) Noyori showed that 2-diphenylmethyl-3-quinuclidine could be hydrogenated giving the cis isomer exclusively in greater than 99% enantioselectivity.\(^\text{77}\) It was noted that the product is a useful intermediate for the synthesis of a series of human NK\(_1\) antagonists.\(^\text{78}\)

**Scheme I-24** Hydrogenation of bicyclic systems with \([\text{RuCl}_2(\text{IPHAN})(\text{BINAP})]\)

Johnson Matthey have also developed the 1,4-diamine \((R,R)\)-AABPY \(\text{97}\), which it has felt would provide rigidity to the ligand compared to the other diamines discussed (Scheme I-25).\(^\text{74}\) Despite good activity, it was found that only moderate enantioselectivity could be imparted to alcohol
products (20-84% e.e. for hydrogenation of a range of simple ketones) when complexes of 97 in
combination with P-Phos or BINAP were used (the matched complexes).

![Scheme I-25](image)

Scheme I-25 1,4-Diamines employed in enantioselective hydrogenation.

Compared to development of the phosphine component, the diamine has received relatively
little attention. The examples described have shown however has shown that the diamine has a
very significant role in the formation of enantiopure secondary alcohols and further
developments are likely to ensue.

**(iii) Base-free hydrogenation**

Many of the hydrogenation catalysts described thus far have required a base to catalyst ratio
of up to 20:1 in order for efficient catalysis to proceed,\(^{42}\) which can be incompatible with
certain functionalities. A significant development of the \([\text{RuCl}_2(\text{P}^\text{P})(\text{N}^\text{N})]\) system was its
extension to allow the enantioselective hydrogenation of base-sensitive substrates such as
ketones with remote ester and epoxide functionality. Noyori demonstrated that catalysis
using the diphosphine-diamine ruthenium complexes such as \((S),(S,S)-98\) could proceed
without the need for any added base (Scheme I-26).\(^{79}\) Not only did these catalysts allow the
highly enantioselective preparation of base sensitive products such as those shown, an
increase in activity of around one order of magnitude was observed compared to the original
catalyst precursors in the hydrogenation of acetophenone under identical conditions. Noyori
later attributed this to a less complex and more rapid formation of the catalytic species (See
section 1.4.1).\(^{42}\)

![Scheme I-26](image)

Scheme I-26 Hydrogenation of base-sensitive substrates.

27
(iv) Supported Catalysts

There is considerable interest in the development of catalysts which are immobilised to a solid support so that they can be removed from the reaction mixture easily and recycled. This is particularly important when the metal complexes used are expensive and toxic. Both the diphosphine and diamine component have been immobilised to a support with varying degrees of success.

Noyori employed the polystyrene-supported BINAP ligands of Bayston\textsuperscript{80} to form ruthenium complexes along with DPEN (Scheme I-27, 102).\textsuperscript{81} The supported catalyst was found to be highly active in the hydrogenation of simple ketones, although longer induction periods were observed than the homogenous system. Enantioselectivity was found to be on par with the homogeneous system for the hydrogenation 1'-acetonaphthone (97-98\% e.e.) and the catalyst could be reused several times with enantioselectivity reported to remain constant up until the 14\textsuperscript{th} use. Lemaire and coworkers adopted a different strategy by incorporating BINAP into the backbone of a polyurea-based polymer.\textsuperscript{82} However, the most efficient ligand, \textit{poly}-NAP (\textit{R})-103, when employed with [RuCl\textsubscript{2}(C\textsubscript{6}H\textsubscript{6})] and (\textit{R},\textit{R})-DPEN, could only hydrogenate acetophenone in 68\% e.e. compared to 87\% in the homogenous system.

\textbf{Scheme I-27} Polymer supported diphosphines/diamines
Other groups have employed this strategy with more success however. The work of Pu has shown that polymeric BINAP, linked by aryl or biaryl spacers, when used along with a ruthenium precursor and enantiopure diamine, are efficient enantioselective catalysts. Pu demonstrated that polymer (R)-104 along with [RuCl₂(C₆H₆)] and (R,R)-DPEN could hydrogenate a range of simple ketones with enantioselectivity approaching that observed for the homogenous system.⁸³ Catalyst containing the polymer (R)-105, composed of alternating BINAP/BINOL monomers, gave similar results in hydrogenation.⁸⁴ However, the best results to date appear to be obtained using the more flexible Noyori system, rather than where the diphosphine is incorporated in the rigid polymer itself, although enantioselectivity with the Pu system is approaching that of the homogeneous system.

The diamine component of the catalytic system has also shown to be of use when immobilised to a solid support. Itsuno has shown that (S,S)-DPEN can be attached to polystyrene via a benzyl ether linkage through both its phenyl rings, to form a cross-linked polymer (Scheme I-27).⁸⁵ Ruthenium catalysts derived from such polymeric ligands and BINAP-derived diphosphines were shown to be active in the hydrogenation of a range of simple ketones, carried out in a isopropanol/DMF mixture.⁸⁶ Enantioselectivities were almost at the same level as the corresponding homogeneous system. Itsuno reported that the polymeric catalysts were easily separated from the reaction mixture and recycled a several times without loss of activity (although he never commented on the effect of recycling of selectivity).⁸⁶

Ding has developed a ‘self-supported’ polymer, whereby catalysts are heterogenised by homocombination of ligands that are subsequently linked by the metal centre, for example ligands (S)-110 and (S,S)-111 linked together by ruthenium (Scheme I-28).⁸⁷ The resultant polymer are active in the hydrogenation of simple ketones and are easily recovered due to their insolubility in isopropanol. The polymeric catalyst (S),(S,S)-109 was found to give activity and enantioselectivity on par with the corresponding homogenous system. Seven cycles of hydrogenation could be completed with the polymer before any sign of diminished activity/selectivity was observed and ruthenium leaching was reported to be extremely low (<0.1 ppm).
The diphosphine and diamine components of the [RuCl₂(P^P)(N^N)] catalytic system have also been immobilised as dendrimers. Fan and coworkers have shown that high enantioselectivity with the catalyst immobilised through the binaphthyl part of BINAP (Scheme I-29, (S,S-112-115). Little difference was observed in e.e using the different generations of dendrimer, with the supported catalyst removed easily by precipitation and separation. The immobilised catalyst could be recycled but activity and e.e. diminished after only the 3rd use. Fan also demonstrated that the diamine can also be immobilised to good effect as a dendrimer, (S,S)-116-119. When ruthenium complexes of such and (S)-BINAP were used in hydrogenation, even higher enantioselectivities were observed compared to the corresponding homogeneous system.
The diphosphine/diamine ligands have also been immobilised, with some success, on inorganic materials. Chan showed that silica could be used as a support and BINAP was immobilised by covalent linkage through the binaphthyl moiety and the ruthenium complex formed with DPEN (Scheme I-30, 120). Hydrogenation of acetophenone and 1’-acetonaphthone was accomplished successfully however, whilst enantioselectivity was on par with that for the homogeneous process for the reduction of 1’-acetonaphthone (95 cf 97% e.e.), it was significantly diminished for acetophenone (25 cf. 87% e.e.). The catalyst was easily separated by filtration using a glass frit and subsequent washing and the catalyst could be reused up to 5 times with no loss of enantioselectivity and little loss of activity. DPEN has also been shown to function successfully as a ligand while immobilised on an inorganic material. DPEN has been attached to the inner surfaces of mesoporous silicates MCM-41 and MCM-48 materials through organic tether groups, and the corresponding ruthenium catalysts formed with the matched BINAP enantiomer (Scheme I-30, 121). The supported catalysts were shown to be highly active (TOFs ~ 500 h⁻¹) in the hydrogenation of a large range of simple ketones, although the homogeneous reactions were twice as fast. No difference in enantioselectivity was observed between the homogenous system and the supported catalysts, and was solely dependent on the ligand combination.

Most attempts at immobilisation have relied upon phase differences that have allow the catalyst to be easily separated from the reaction mixture and reused. The diphosphine has also been shown to be immobilised on ionic liquids, which can be easily removed from the reaction medium and reused. Lin and coworkers 92 have demonstrated that the polar catalysts (R),(R,R)-122 and (R),(R,R)-123 can be immobilised to a range of ionic liquids, with DMPIIm 124 being the most efficient in terms of activity with full conversion within 24 hours at 48 bar hydrogen pressure. Very high enantioselectivity – on par of that with the best homogeneous systems – were observed when using catalyst (R),(R,R)-122, consistent
with the work on other 4,4'-disubstituted BINAP (Section I-31). The immobilised catalyst could be recycled up to 6 times without significant loss of enantioselectivity and no appreciable leaching of ruthenium was observed.

![Scheme I-31 Ionic liquid-supported catalysts](image)

Chan has also shown that immobilisation of diphosphines upon polyethylene glycol, such as (R)-\textbf{125} (Scheme I-32), is also possible and the product can removed from the catalyst via extraction into organic solvent.\textsuperscript{93} Hydrogenation of acetophenone and derivatives gave enantioselectivities comparable to, if not better than, the corresponding homogenous systems, when the ruthenium complexes of PEG-supported diphosphines (R)-BINAP, (S)-BINAP, (R)-XylBINAP, and (S)-XylP-Pho, and (R,R)-DPEN were used. Recycling of the catalyst allowed it to be reused up to four times without a significant decrease in enantioselectivity, and leaching of the ruthenium into the organic was shown to be less than 0.85 ppm. Catalysts have similarly been immobilised on polyethylene glycol through the phenyl groups of DPEN. In collaborative work between Johnson Matthey and the University of Liverpool, ruthenium complexes of PhanePhos and PEG-supported DPEN have been shown to be highly effective in the hydrogenation of simple aromatic ketones, with enantioselectivity over 90% with all substrates reported.\textsuperscript{94} Catalysis could be repeated 3 times with the same supported catalyst with little decrease in activity and no loss of selectivity. Leaching of ruthenium resulted in less than 3 ppm presence in the product.

![Scheme I-32 PEG-supported (R)-BINAP](image)
1.7 Deviations from the Noyori Blueprint

Recent years has seen the emergence of active and selective catalysts which have deviated quite significantly from the original Noyori blueprint. New, structurally distinct catalysts are important in overcoming the significant limitations of the \([\text{RuCl}_2(\text{P}^2\text{P})(\text{N}^2\text{N})]\) system, such as the expense and synthetic challenges of preparing such catalysts, as well as their limitation in substrate scope, which hindered the efficient hydrogenation of useful classes of molecule such as tetralones, bulky ketones, some heterocyclic ketones and alkyl-alkyl substrates. The need for more practically useful catalysts, with less expensive, easily accessible building blocks, can also be exploited, by moving away from the original manifold. The design of catalysts significantly different to the \([\text{RuCl}_2(\text{P}^2\text{P})(\text{N}^2\text{N})]\) structure is also of great interest to industry as all diphosphine/di-primary-amine complexes of ruthenium are currently covered by the Noyori patents and can only be used under license from Takasago International Corporation. 95

1.7.1 More Practically Useful/Industrially Relevant Catalysts

(i) Achiral diphosphines

The use of achiral phosphines in combination with homochiral diamines in catalysis is very appealing due to the expense and often extended routes for preparation of homochiral diphosphines. Mikami and Noyori first proposed that achiral ligands could be used in combination with enantiopure diamine in enantioselective hydrogenation by fine control of relative amount of the matched and mismatched diastereomers of the ruthenium complex in solution. 96 They proposed that the greater presence of the matched diastereomer would lead to enhanced activity and enantioselectivity. It was shown that using the conformationally flexible \(\text{rac-BIPHEP}\) ligand in combination with \((S,S)\)-DPEN, high levels of enantioselectivity could be imparted upon the substrate. Heating a 1:1 mixture of the matched catalyst \((S),(S,S)\)-126 and mismatched catalyst \((R),(S,S)\)-127, prepared from racemic BIPHEP and enantiopure DPEN, at 80°C was shown to lead to a 3:1 excess of the \((S),(S,S)\) catalyst (matched) in solution (Scheme I-33). 96 Use of the solution led to enantioenrichment in the hydrogenation of acetophenone of 92%, in contrast to 63% if the solution was used before heating. Further improvement in the relative amounts of matched:mismatched diastereomers was accomplished later by Mikami by use of the racemic...
triphos ligand along with (S,S)-DPEN, with the matched complex (S),(S,S)-127 being prepared almost exclusively and imparting enantioselectivity of up to 85% on the reduction of 1-acetonaphthone.\textsuperscript{97}

Mikami expanded this work to show that the achiral tropos ligand 2,2’bis(diphenylphosphino)benzophenone (DPBP) in combination with (S,S)-DPEN, formed the matched ruthenium complex 128 exclusively.\textsuperscript{98} This complex demonstrated high levels of stereoinduction, in some cases in excess of those obtained with the corresponding enantiopure BINAP complex. This complex remains the benchmark in enantioselective hydrogenation with achiral diphosphines but work by Li has also shown that moderate to good levels of enantioselectivity (up to 87% e.e.) could be obtained even when simple, inexpensive achiral diphosphines such as 129 and 130 are employed in catalysis with enantiopure diamines (Scheme I-34).\textsuperscript{99}

![Scheme I-33](image)

Scheme I-33 Active hydrogenation catalysts prepared from racemic diphosphines.

![Scheme I-34](image)

Scheme I-34 Achiral diphosphines used in the ruthenium-catalysed hydrogenation of simple ketones giving moderate to good levels of steroinduction (41-87% e.e.) when used in combination with (S,S)-DPEN.
(ii) Aminophosphine Ligands

The group of Morris has demonstrated the hydrogenation of simple ketones by ruthenium complexes of β-aminophosphine ligands, which, it is reported, are easily accessible from readily available chiral pool amino acids (Scheme I-35, \((R)-131/(S)-132\) or \((R)\)-norephedrine \((R,R)-133\)). The complexes \([\text{RuCl}_2(\text{P}_{\text{ala}})_2]\), \([\text{RuHCl}(\text{P}_{\text{ala}})_2]\) and \([\text{RuHCl}(\text{P}_{\text{pro}})]_2\) were all shown to be extremely active in the hydrogenation of acetophenone and derivatives, however, enantioinduction was negligible.\(^1\) Combining the aminophosphine \((R)-131\) with \((R)\)-BINAP \((R)-\text{BINAP}\) did give a modest e.e. of 40%, however, in the hydrogenation of acetophenone. The bis-complex of ligand \(133\) \([\text{RuHCl}((R)-133)]_2\) gave enantioselectivities of up to 51% e.e in the hydrogenation of acetophenone, and this could be enhanced to up to 72% by replacing one of the ligands with \((S)\)-BINAP.\(^1\)

\[\text{Scheme I-35 β-Aminophosphine ligands}\]

(iii) Other PX Bidentate Ligands

As well as aminophosphine ligands, a number of other bidentate phosphine ligands have been developed with different secondary donors. Some of these have found application due to their ease of synthesis and remarkably high activity/selectivity. The QUINAPHOS family of ligands (Scheme I-36) - with a phosphine and phosphoramidite donor - which have been shown to be very efficient ligands in a variety of asymmetric processes,\(^2\) and described in some circles as a privileged ligand,\(^3\) have also been employed in ketone hydrogenation. The ruthenium complex of \((R,S_C)\)-enantiomer and \((S,S)\)-DPEN was shown to be highly enantioselective in the hydrogenation of acetophenone and derivatives. Although the full scope of this catalyst system has not been explored, and its activity not quantified, QUINAPHOS is another addition to the toolbox of highly selective ligands.
Phosphine-oxazoline ligands have also been shown to be remarkably efficient ligands, despite not having an N-H group, which was deemed to be a prerequisite for activity and good enantioselectivity in the hydrogenation of simple ketones (see section 1.4). Such ligands have received attention due to their ease of synthesis and favourable coordinating properties. The best of these ligands, 135 (Scheme I-36), when employed in situ with \([\text{RuCl}_2(\text{PPh}_3)_2]\) has been shown to give remarkably high enantioselectivity, above 95% e.e., for a range of acetophenone derivatives and TON of up to 40,000. More recently, the ruthenocycle derivative of 135 (replacement of Fe with Ru) has also been shown to be highly active and enantioselective in the hydrogenation of simple ketones.

(iv) Monodentate Phosphorus Donors

A major deviation from the original \([\text{RuCl}_2(\text{P}^\text{P})(\text{N}^\text{N})]\) blueprint has been to replace the diphosphine component with two monophosphine donors. It has been proposed that the use of monophosphines has a significant advantage in terms of practicality as such ligands are less expensive and more readily available than most bidentate ligands, and as such, potentially more relevant to industrial application. The work in this area was triggered by the observations of Noyori and Morris that active and enantioselective catalysis could still occur with replacement of the diphosphine component by two simple triphenylphosphine ligands. Although enantioselectivity was only 60% in the hydrogenation of acetophenone, Ding subsequently demonstrated that, analogous to the parent Noyori system, increasing the steric bulk upon the phosphorus substituents led to more selective catalysts, with enantioselectivity of up to 96% (Table I-5).
Enantioselective Hydrogenation Using Ruthenium Complexes of Tridentate Ligands

Scott Phillips

Table I-5 Hydrogenation of acetophenone using ruthenium complexes of monodentate achiral phosphines and chiral diamines, as reported by Morris (entry 1) and Ding (entries 2-7). General conditions: ruthenium catalyst (0.1 mol%), KO\textsubscript{t}Bu (2 mol%), iPrOH, H\textsubscript{2} (21 bar), 25°C, 10 h. \textsuperscript{a} neat, no iPrOH, 3 bar H\textsubscript{2}, < 8 h. \textsuperscript{b} n-propanol as solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphine</th>
<th>Diamine</th>
<th>Conversion [%]</th>
<th>ee [%]</th>
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<td>1\textsuperscript{a}</td>
<td>136</td>
<td>(R,R)-DACH</td>
<td>&gt;99</td>
<td>60 (S)</td>
</tr>
<tr>
<td>2</td>
<td>136</td>
<td>(R,R)-DPEN</td>
<td>&gt;99</td>
<td>77 (S)</td>
</tr>
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<td>96</td>
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<td>(R,R)-DPEN</td>
<td>&gt;99</td>
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<td>&gt;99</td>
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<tr>
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<td>140</td>
<td>(R,R)-DPEN</td>
<td>&gt;99</td>
<td>96 (S)</td>
</tr>
</tbody>
</table>

This work has been extended to employ chiral monophosphines with bulky substituents. Wills conceived that the MonoPhos ligand 143 – shown to have outstanding activity and selectivity in the hydrogenation of C=C bonds when two such ligands are complexed to rhodium\textsuperscript{110,111} - could be employed as the monophosphine component in ruthenium complexes for ketone hydrogenation. Similar binaphthophosphine ligands have also been employed in the highly enantioselective hydrogenation of β-keto esters.\textsuperscript{112} Indeed MonoPhos was found to give moderate selectivity in the hydrogenation of simple ketones (Table I-6), but optimisation of the catalyst structure, and strategic placement of an ortho substituent on the phosphine’s phenyl substituent gave the most selective catalyst, with enantioselectivity up to 99%.\textsuperscript{106,113,114} Wills commented that while enantioselectivities are generally excellent in such systems, catalyst loading (typically in the range 0.05-0.02 mol%) and pressures were higher (50-80 bar) than those employed with BINAP-based catalysts.\textsuperscript{24} Since then the easy accessibility of such phosphoramidite ligands through robotic parallel synthesis protocols has allowed the screening of a diverse range of potential ligands.\textsuperscript{77} Feringa and de Vries identified ligand (S)-145 via such studies, which gave a catalyst on complexation with ruthenium/chiral diamine that can hydrogenate simple ketones whilst maintaining enantioselectivity above 90% for a range of substrates.\textsuperscript{108} However, the problems of higher
catalyst loadings and high hydrogen pressure remain pertinent for the bulkier phosphoramidite ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphine</th>
<th>Diamine</th>
<th>Catalyst Loading (mol%)</th>
<th>$P_H_2$ (bar)</th>
<th>Ar =</th>
<th>Conversion [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-143</td>
<td>(S,S)-DPEN</td>
<td>0.1</td>
<td>10</td>
<td>Me</td>
<td>&gt;99</td>
<td>54 (R)</td>
</tr>
<tr>
<td>2</td>
<td>(S)-144</td>
<td>(S,S)-DPEN</td>
<td>0.1</td>
<td>10</td>
<td>Me</td>
<td>&gt;99</td>
<td>88 (R)</td>
</tr>
<tr>
<td>3</td>
<td>(S)-145</td>
<td>(S,S)-DPEN</td>
<td>0.05</td>
<td>50</td>
<td>Me</td>
<td>&gt;99</td>
<td>90 (R)</td>
</tr>
<tr>
<td>4</td>
<td>(S)-145</td>
<td>(S,S)-DPEN</td>
<td>0.05</td>
<td>10</td>
<td>$p$-CH$_3$Ph</td>
<td>&gt;99</td>
<td>96 (R)</td>
</tr>
<tr>
<td>5$^a$</td>
<td>(S)-145</td>
<td>(S,S)-DPEN</td>
<td>0.05</td>
<td>50</td>
<td>$\alpha$-BrPh</td>
<td>&gt;99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>6$^b$</td>
<td>(S)-145</td>
<td>(S,S)-DPEN</td>
<td>0.05</td>
<td>60</td>
<td>$\alpha$-IPh</td>
<td>&gt;99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>7$^b$</td>
<td>(S)-146</td>
<td>(S,S)-DACH</td>
<td>0.1</td>
<td>25</td>
<td>Me</td>
<td>&gt;99</td>
<td>97 (R)</td>
</tr>
</tbody>
</table>

Table I-6: Hydrogenation of simple ketones using ruthenium complexes of BINOL-derived chiral monophosphine ligands and chiral diamines, as reported by Morris (entries 1-6) and Feringa and De Vries (entry 7). General conditions: ruthenium catalyst, KO$_{t}$Bu (10 eq wrt catalyst loading), i$PrOH$, H$_2$, rt, 20 h. $^a$ 8 h. $^b$ 24 h, 5 equivalent of KO$_{t}$Bu wrt catalyst loading.

Work has also been undertaken in using monophosphine ligands that are chiral at phosphorus but enantioselectivities have so far only been modest, with high catalyst loading and high pressure (although ligands were used in situ and the catalyst wasn’t isolated) (Scheme I-37).$^{115}$ This remains an underdeveloped area, and is perhaps limited by the synthetic challenges associated with P-chiral phosphines.

Scheme I-37: Hydrogenation of acetophenone with the ruthenium complex of P-chiral phosphine (R,R)-148 and 1,4-diaminobutane. Reaction conditions: [Ru(C$_6$H$_5$)$_2$Cl$_2$] (1 mol%), (±)-1,4-diaminocyclobutane (1mol%), ligand (R,R)-148 (1.1 mol%), KO$_{t}$Bu (10 mol%), i$PrOH$, H$_2$ (30 bar), rt, 18 h.
(iv) Phosphine Free Catalysis

There has been relatively little attention paid to the development of phosphine free catalysts, despite the obvious benefits to catalyst synthesis. The most successful transfer hydrogenation catalysts of the type \([\text{RuCl}(\text{TsDPEN})(\eta^6\text{-arene})]\) contain no phosphine ligand\(^{38}\) but tend to be inactive in \(\text{H}_2\)-hydrogenation (and vice versa, \([\text{RuCl}_2(\text{P}^\text{P})(\text{N}^\text{N})]\) are generally inactive in transfer hydrogenation). This difference in reactivity has been attributed to the electronic properties of the Ru centre; \(\text{H}_2\)-hydrogenation catalysts need electron donating phosphorus donors (presumably to facilitate hydrogen activation) whereas transfer hydrogenation catalysts have an electron-withdrawing tosylimido ligand.\(^{47}\) Ikariya has shown that ligands isoelectronic to those employed in transfer hydrogenation, but with less electron-withdrawing characteristics, such as ligand (S)-\(^{150}\) (Scheme I-38), are however active in \(\text{H}_2\)-hydrogenation with enantioselectivity in the range 64-95\%.\(^{47}\)

\[\text{Scheme I-38 Transfer hydrogenation catalysts that can be employed in } \text{H}_2\text{-hydrogenation.}\]

It has also been shown that more typical phosphine-free transfer hydrogenation catalysts, such as (S,S)-\(^{151}\) and (S,S)-\(^{152}\) (Scheme I-38), can be transformed into active \(\text{H}_2\)-hydrogenation catalysts. Noyori has reported that such complexes, can be converted into \(\text{H}_2\)-hydrogenation catalysts by switching to acidic conditions.\(^{116}\) The theoretical work of Lei and Fang,\(^{117}\) and kinetic evidence of Rauchfuss,\(^{118}\) has suggested that the addition of acid facilitates the coordination of dihydrogen to the ruthenium centre in such cases compared to the acid free process. Excellent enantioselectivity has been obtained in the hydrogenation of the tricky 4-chromanone substrates, generally over 95\% e.e.\(^{116}\) although to date this area of study remains underdeveloped and the full substrate scope has not been delineated.

A further example of a phosphine-free hydrogenation system was reported by Kitamura, employing the tetradentate Goodwin-Lions type ligands (Scheme I-39).\(^{119}\) In combination with \([\text{Ru}(\pi\text{-CH}_2\text{C(\text{CH}_3)CH}_2)_2(\text{COD})]\), ligand (R)-\(^{153}\) was shown to be highly active and enantioselective in the reduction of a range of acetophenone derivatives (generally above 86\% e.e.). The system has the advantage over the original diphosphine/diamine system in
that base is not required for reactions to proceed and so is useful in the hydrogenation of configurationally unstable substrates.\textsuperscript{119} Lemaire demonstrated that tetradentate ligands derived from (\(R,R\))-DPEN (Scheme I-39), could be also used as a ligands in the asymmetric hydrogenation of acetophenone although enantioselectivities were generally only moderate (below 80\% e.e.).\textsuperscript{120} Substitution of the aryl groups with bulky substituents did not enhance enantioselectivity but the best selectivities were obtained with the \(N\)-substituted tosyl derivative 155.

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_I-39}
\end{center}

\textbf{Scheme I-39} Tetradentate Amine Ligands

(v) \textbf{Hydrogenation with Other Metals}

In recent years, a plethora of research has taken place into enantioselective hydrogenation using catalysts based on metals other than ruthenium, including Rh(II),\textsuperscript{121} Cu(I),\textsuperscript{14} Ir(I)\textsuperscript{122} and Fe(II)\textsuperscript{123}, in an attempt to discover more efficient, more commercially viable alternatives. To date, ruthenium catalysts still set the standard as regards high catalytic activity and enantioselectivity. An in-depth discussion of alternative metal systems is outwith the remit of this review, however such systems have been reviewed in the references given.

1.7.2 Catalysts for Difficult Substrates

(i) Bulky substrates

Noyori reported that the original [RuCl\(_2\)(P\(^\text{P}\))(N\(^\text{N}\))] catalytic system was poor for the hydrogenation of bulkier ketones, with hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone being achieved in only 6\% yield using [RuCl\(_2\)((S\text{-})\text{-BINAP})((S,S\text{-})\text{-DPEN})].\textsuperscript{24} It was postulated that this was due to steric congestion near the mechanistically important NH\(_2\) groups.\textsuperscript{72} The hydrogenation of bulky ketones is a comparatively underdeveloped area of research compared to acetophenone and derivatives, despite the utility of the corresponding alcohol
products (see Chapter II). Study in this area has focussed on the preparation of new catalysts with a more open coordination environment to allow the approach of bulkier ketones to the ruthenium hydride. Work in this group has found a highly efficient system to hydrogenate such ketones with good enantioselectivity (up to 94% e.e.) using ruthenium complexes of tridentate P^N^N ligands,\textsuperscript{73,124,125} and this shall be discussed in detail in chapter II.

Subsequent to our work which began in 2004, Noyori has also reported a highly enantioselective system for the hydrogenation of tert-alkyl ketones, making use of the unsymmetrical NH\textsubscript{2}/pyridine ligand, α-picolylamine (PICA).\textsuperscript{72} This ligand incorporates the terminal amine deemed to be required for efficient catalysis with a planar pyridine secondary donor, which allows for the approach of bulkier substrates. Noyori also notes that ethanol is the solvent of choice for this system, whereas isopropanol was used in the original [RuCl\textsubscript{2}(P\textsuperscript{P})(N\textsuperscript{N})] system.\textsuperscript{72}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Conversion [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>157</td>
<td>&gt;99</td>
<td>97 (S)</td>
</tr>
<tr>
<td>2</td>
<td>158</td>
<td>&gt;99</td>
<td>97 (S)</td>
</tr>
<tr>
<td>3\textsuperscript{a}</td>
<td>159</td>
<td>&gt;99</td>
<td>97 (R)</td>
</tr>
<tr>
<td>4</td>
<td>160</td>
<td>&gt;99</td>
<td>97 (R)</td>
</tr>
<tr>
<td>5</td>
<td>161</td>
<td>&gt;99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>6</td>
<td>162</td>
<td>&gt;99</td>
<td>97 (S)</td>
</tr>
<tr>
<td>7</td>
<td>163</td>
<td>&gt;99</td>
<td>98 (R)\textsuperscript{b}</td>
</tr>
<tr>
<td>8</td>
<td>164</td>
<td>&gt;99</td>
<td>98 (S)</td>
</tr>
<tr>
<td>9\textsuperscript{c}</td>
<td>165</td>
<td>&gt;99</td>
<td>90 (S)</td>
</tr>
<tr>
<td>10</td>
<td>166</td>
<td>&gt;99</td>
<td>98 (S)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>&gt;99</td>
<td>97 (S)</td>
</tr>
<tr>
<td>12</td>
<td>168</td>
<td>&gt;99</td>
<td>82 (S)</td>
</tr>
</tbody>
</table>

Table I-7 Hydrogenation of tert-alkyl ketones using [RuCl\textsubscript{2}(S)-BINAP](PICA)\textsubscript{156}. General conditions: substrate (1 eq.), ruthenium catalyst (0.05 mol%), KO\textsubscript{B}u (1 mol%), EtOH, H\textsubscript{2} (5-8 bar), 25-27°C, 5 h.\textsuperscript{a} 12 h,\textsuperscript{b} 5:1 E:Z, data for E-isomer.\textsuperscript{c} 20 h.

A number of tert-alkyl ketones have been reduced with good enantioselectivity using this system (Table I-7) with ee’s generally above 90%.\textsuperscript{72} The system has been found to be
tolerant of aliphatic, aromatic, heteroaromatic and olefinic ketones, and reactions proceed smoothly with S/C ratios as high as 100,000.

Noyori and coworkers have extended the hydrogenation of more bulky substrates using ruthenium complexes of the related DMAPEN ligand and BINAP. It has been shown that hydrogenation of α-branched aromatic ketones can be accomplished in over 90% e.e and >98% d.e. (Table I-8). The absence of steric bulk upon the ligand away from the mechanistically important NH₂ appears to give a more open coordination environment for the approach of more bulky ketones, with enantioselectivity determined by steric interactions between the phosphine substituents and the substrates in the original system. Indeed, Ohkuma has shown that incorporating more bulky N-dimethyl substituents upon DMAPEN (giving a more congested active site) leads to a decrease in activity and reduced enantioselectivity.

![Enantioselective Hydrogenation Using Ruthenium Complexes](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Isolated Yield [%]</th>
<th>ee [%]</th>
<th>dr</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>170</td>
<td>95</td>
<td>97</td>
<td>na</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>171</td>
<td>97</td>
<td>93</td>
<td>na</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>172</td>
<td>91</td>
<td>97</td>
<td>na</td>
<td>(R)</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>94</td>
<td>95</td>
<td>na</td>
<td>(S)</td>
</tr>
<tr>
<td>5</td>
<td>173</td>
<td>90</td>
<td>98</td>
<td>&gt;99:1</td>
<td>(1R,2R)</td>
</tr>
</tbody>
</table>

Table I-8 Hydrogenation of α-branched ketones using [RuCl₂((S)-BINAP)((R)-DMAPEN)] 

*General conditions: substrate (1 eq.), ruthenium catalyst (0.05-0.1 mol%), KO'Bu (1 mol%), EtOH, H₂ (5-8 bar), 25-30°C, 10-24 h.*
(ii) Dialkyl ketones

The enantioselective hydrogenation of dialkyl ketones remains a challenging problem in asymmetric catalysis with only isolated examples in the literature, where one alkyl group is bulky allowing for sufficient stereodifferentiation. To date, only the alkyl-alkyl ketones reduced in high enantiopurity via ruthenium catalysed hydrogenation are pinacolone and cyclopropyl and cyclohexyl methyl ketones 24 and 25 (Scheme I-5).‡‡ This remains an under-developed area of research despite the huge value of potential chiral products.

1.8 Project Aims

When this project commenced in 2004, only simple model ketones could be hydrogenated effectively using the Noyori system, and the hydrogenation of bulky ketones was completely underdeveloped. As mentioned in section 1.7.2, work in this group led to the discovery of an efficient system for the enantioselective hydrogenation of bulky compounds, based on ruthenium complexes of tridentate P^N^N ligands. The scope of the original work was somewhat limited, but exhibited potential for the hydrogenation of a range of substrates. The current worked aimed to fully delineate the scope of this new breed of catalyst and demonstrate its utility in preparing synthetically useful chiral molecules. It was felt that due to the modular nature of the ligand design there was potential for tuning of the ligand structure, not just to improve activity/selectivity, but in order to hydrogenate difficult substrates, many of which still remain problematic for the Noyori and the other systems discussed in this chapter. In order to do this rationally, it was felt a greater understanding of the reaction mechanism and origin of enantioselectivity was highly desirable. Thus the principal aims of this work were to (a) delineate the full substrate scope of the present system, (b) gain a detailed understanding of the reaction mechanism and origin of enantioselectivity, leading to (c) the tuning of catalyst structure to give both more active/selective catalysts as well as catalysts capable of hydrogenating difficult substrates, including bulky, heteroaromatic and dialkyl ketones. The work carried out to further these aims will be presented in the ensuing pages.

‡‡ There are also limited examples of ruthenium catalysed transfer hydrogenation of alkyl-alkyl ketones. 128
1.9 References

Enantioselective Hydrogenation Using Ruthenium Complexes

Chapter I

of Tridentate Ligands

Scott Phillips

89. W. Liu, X. Cui, L. Cun, J. Wu, J. Zhu, J. Deng, and Q. Fan, Synlett, 2005, 10, 1591-
1595.
Chapter II

Exploring the Scope and Application of [RuCl\(_2\)(P^N^N)L] Catalysts

Preliminary work from this group\(^1\) has shown that the [RuCl\(_2\)(P^N^N)L] catalyst \((R,R)-174\) is active and enantioselective in the hydrogenation of bulky ketones (Table II-1); substrates which were shown to be problematic using [RuCl\(_2\)(P^P)(N^N)] systems. It was proposed that the more open coordination environment created by combining the chiral diamine and phosphine components – shown to be crucial for successful catalysis in the Noyori system – into one chiral tridentate ligand, would allow easier access for such ketones, and thereby increase their activity in hydrogenation. This was indeed the case and it was shown that enantioselectivity improved as steric bulk of the R group was increased (Table II-1). The Noyori [RuCl\(_2\)(P^P)(N^N)] catalyst \((S),(S,S)-14\) is almost completely inactive in the hydrogenation of bulky ketones such as \(\alpha,\alpha,\alpha\)-trimethylacetophenone (Table II-1, Entry 4).\(^2\)

\[
\text{Entry} \quad \text{R} \quad \text{Catalyst} \quad \text{Conversion (yield) [\%]} \quad \text{ee [\%]}
\begin{align*}
1 & \quad \text{Me} \quad (R,R)-174 \quad >99 \ (99) \quad 0 \\
2 & \quad \text{iPr} \quad (R,R)-174 \quad 93 \quad 48 \ (S) \\
3 & \quad \text{tBu} \quad (R,R)-174 \quad >99 \ (99) \quad 74 \ (S) \\
4 & \quad \text{Bu} \quad (S),(S,S)-14 \quad 6 \quad 61 \\
5 & \quad -\text{C(CH}_3\text{)}_2\text{CH}_2\text{CH}_3 \quad (R,R)-174 \quad >99 \ (99) \quad 90 \ (S)
\end{align*}
\]

Table II-1 The hydrogenation of bulky ketones using catalyst \((R,R)-174,^1\) and comparison with hydrogenation using Noyori’s catalyst \((S),(S,S)-14.\)\(^3\)

The scope of ketone substrate that could be hydrogenated using catalyst \((R,R)-174\) had not been fully explored in the original work. In order to be a synthetically useful catalyst, it must be demonstrated that the catalyst can hydrogenate a variety of substrates, not just selected model substrates such as entries 1-5 in Table II-1. It is also important to demonstrate the utility of the catalyst and its ability to prepare chiral secondary alcohols which are of direct synthetic use. In this chapter, the need for chiral secondary alcohols and their derivatives in organic synthesis
will be outlined, and how catalyst \((R,R)-174\) can be employed to prepare such useful molecules. The preparation of several chiral secondary alcohols with direct synthetic use will be examined in this chapter, but more generally the compatibility of various functional groups with the \([\text{RuCl}_2(\text{P}^\text{N}^\text{N}\text{N})\text{L}]\) catalytic system has also been a key part of this study.

### 2.1 Chiral Secondary Alcohols in Organic Synthesis

Chiral secondary alcohols are of vast importance in organic synthesis as not only are they a structural motif that is ubiquitous in a range of biologically relevant molecules, they also serve as a functional group which can be transformed into a plethora of important chiral products. Thus, to the synthetic organic chemist, chiral secondary alcohols can be both a crucial target in the synthesis of complex products, and a vital precursor, opening the door to the synthesis of other important molecules.

A brief search of the chemical literature displays a variety of natural products and biologically relevant molecules containing the secondary alcohol functionality. It can be seen from Scheme II-1 that chiral secondary alcohols are a salient feature of a variety of important classes of compound (although only a tiny fraction of important chiral secondary alcohols (probably <<1%) are depicted here). Whereas technology exists to prepare a number of these in homochiral form by catalytic asymmetric hydrogenation,\(^4\) extended syntheses, often involving the use of stoichiometric amounts of reagent for chiral induction, is required to incorporate the chiral secondary alcohol component in large molecules such as epothilone A \(175,\) for example.

![Scheme II-1 Examples of chiral secondary alcohols which are salient features of both natural products (175-179) – many of which having important therapeutic properties – and other biologically-relevant molecules, such as the important pharmaceuticals 180 and 181.](image-url)
Chiral secondary alcohols are also often manipulated by the organic chemist to take part in a multitude of functional group transformations, and are thus vital precursors in the synthesis of many important molecules. As depicted in Scheme II-2, chiral secondary alcohols can be transformed by nucleophilic substitution (via the mesylate or tosylate ester) into a number of chiral products such as amines and phosphines. Synthetically important chiral esters, carbamates and ethers can also be prepared from these valuable precursors. There are hundreds, probably thousands, of commercially available chiral molecules that can be made from chiral secondary alcohols.

Scheme II-2 Some of the most important synthetic transformations of chiral secondary alcohols and potential targets which could be made via such valuable precursors.

Introducing chirality into molecules by preparing chiral secondary alcohols has become an important tool of the synthetic chemist in recent times due to their straightforward preparation from prochiral ketones via asymmetric hydrogenation. However, as discussed previously, the range of substrates that can be hydrogenated with good activity and high enantioselectivity is limited. Thus there is a considerable interest in widening the scope of asymmetric hydrogenation catalysts in order to be able to prepare every class of chiral secondary alcohol. In this chapter, the substrate scope of the [RuCl₂(P^N^N)L] catalyst (R,R)-174 is explored, with particular regard for functional group compatability and the preparation of useful chiral molecules.
2.2 Preparation of Sterically Demanding Chiral Secondary Alcohols

The conclusions of the original work using catalyst \((R,R)-174\) were based on a relatively small pool of model substrates. It was felt that in order to gain a better understanding of the catalyst’s capabilities, as well as showing its synthetic use, other ketonic substrates needed to be explored in hydrogenation. It was postulated that by increasing the steric bulk, or ‘volume’, of the R substituent of the ketone (Scheme II-3), the extent of the catalyst’s capability could be assessed. The chiral alcohol products of such reactions, despite being potentially useful synthetic intermediates, had never been prepared previously via enantioselective hydrogenation due to the inactivity of Noyori and related catalysts in the hydrogenation of such sterically demanding substrates. In the design and optimisation of drugs, for example, studies that aim to extend lipophilicity or steric bulk make the ability to prepare alcohols across the full range of steric properties important. From a more fundamental point of view, there was considerable interest in how big the R group substituent on the ketone could be before diminished activity and/or enantioselectivity was observed. Previous work in this group demonstrated that enantioselectivity of 90% can be achieved for substrate 182 but the significantly bulkier ketone 185 was found to be totally resistant to hydrogenation with catalyst \((R,R)-174.\) Thus, it was decided that compounds 183 and 184 would be prepared – more sterically demanding than substrate 182 but less so than 185 – in order to probe whether catalyst \((R,R)-174\) could tolerate such bulk in hydrogenation, and to observe whether selectivity was diminished, or indeed enhanced.

![Scheme II-3 More sterically demanding ketone substrates for hydrogenation with [RuCl₂(P^N^N)L] catalyst 174.](image)

2.2.1 Synthesis

It was envisaged that the substrate 2-methyl-1,2-diphenylpropan-1-one 183, could be prepared in a variety of ways, from the commercially-available compounds, isobutyrophenone 82 or 1,2-diphenylethanone 186. Initially, the palladium-catalysed \(\alpha\)-arylation of isobutyrophenone with bromobenzene, as developed by Hartwig, was employed due to the scope of the methodology for preparing a wide variety of other substrates (Scheme II-4). This method successfully
furnished the ketone 183, albeit in a moderate yield of 49% after column chromatography. Increased temperature, prolonged reaction times, higher catalyst loading and substitution of the aryl bromide for iodobenzene failed to increase the conversion to the arylated product.

This synthesis was not optimised further due to the discovery of a higher yielding, although less elaborate and less customisable, alternative route. This involved the exhaustive methylation of 1,2-diphenylethanone 186, via its potassium enolate, with iodomethane. Use of 2.2 equivalents of base and alkylating agent, converted all starting material to the desired product in 16 h (Scheme II-5). Purification was carried out in a facile manner by short-path distillation using Kugelrohr apparatus to give ketone 183 in 83% yield. Samples of 183 made via both routes were employed in subsequent hydrogenation reactions.

The synthesis of methyl-1,2-diphenylpropan-1-one 184 was accomplished in a similar manner, by alkylation of 1,2-diphenylethanone, via its potassium enolate, with iodoethane (Scheme II-6).

2.2.2 Catalysis

Hydrogenation of substrates 183 and 184 was carried out using the original catalyst precursor (R,R)-174, prepared according to the literature. Both ketones were reduced quantitatively by catalyst (R,R)-174 in 16 h using 40 bar hydrogen pressure at 70°C. It was found that while a
high degree of enantioselectivity was maintained in the secondary alcohol products (Table II-2),
there was a small but significant decrease from that observed for the hydrogenation product of
ketone 184 (the stereochemical configuration of alcohols 187 and 188 was tentatively assigned
as (S) akin to that of entries 2,3 and 5 in Table II-1. All products display the same sense of
optical rotation and order of elution from the chiral HPLC).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R =</th>
<th>$P_{H2}$ [bar]</th>
<th>$T$ [°C]</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>40</td>
<td>70</td>
<td>&gt;99 (79)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>40</td>
<td>70</td>
<td>62</td>
<td>75</td>
</tr>
</tbody>
</table>

Table II-2 The hydrogenation of ketones 183 and 184 using catalyst
(R,R)-174. General conditions: ketone (~1 mmol), catalyst (R,R)-174
(0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL),
molecular $H_2$, 16 h.

The results suggest that as the R substituent of the ketone substrate gets larger than that of
ketone 183, the preference for the attack of the ruthenium hydride at the $Si$-face of the ketone is
somewhat diminished, perhaps due to enhanced steric repulsion between the ligand and the
bulky substrate. Thus, as well as showing that catalyst (R,R)-174 is effective in producing useful
bulky secondary alcohols with good enantioselectivity, these results give clues to the possible
direction of catalyst optimisation, which shall be discussed more extensively in Chapter IV.

The reductions of substrates 183 and 184 were also studied in a microwave-assisted transfer
hydrogenation protocol, developed in this group, employing isopropanol as the hydride source.
It was gratifying to observe that alcohols 187 and 188 could be furnished with good
enantioselectivity (Table II-3). Reaction temperatures had to be tuned to give enantioselectivities
approaching that of the $H_2$-hydrogenation system for the hydrogenation of 183 but this led to
poor conversions when the temperature was lowered. Good enantioselectivity was also obtained
in the transfer hydrogenation of 184 but the conversion was again poor. It is likely that further
optimisation of reaction conditions, in particular increasing the reaction time and base loading,
would improve the yield of enantiomerically enriched product. However, this was not
considered an important objective given that this has been demonstrated for other substrates by
Diaz and Clarke. We have nevertheless demonstrated that the transfer hydrogenation procedure,
albeit requiring further optimisation, gives an alternative route to chiral secondary alcohol building blocks, without the need for high pressure equipment. This is particularly convenient in the research laboratory which does not always have the facilities for \(\text{H}_2\)-hydrogenation. \(\text{H}_2\)-hydrogenation however, is normally preferred at a commercial scale and having a catalyst which can operate in both systems is highly beneficial.

The similarly high enantioselectivity observed for substrates 183 and 184 in \(\text{H}_2\)-hydrogenation and transfer hydrogenations also suggests a common pathway in the enantio-determining step in each process, and this shall be discussed further in Chapter III.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R = )</th>
<th>(t) [min]</th>
<th>(T) [°C]</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>20</td>
<td>120</td>
<td>55</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>40</td>
<td>100</td>
<td>31</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>20</td>
<td>120</td>
<td>18</td>
<td>83</td>
</tr>
</tbody>
</table>

*Table II-3* The transfer hydrogenation of ketone 183 and 184 using catalyst \((R,R)-174\). General conditions: ketone (~1 mmol), catalyst \((R,R)-174\) (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL).

### 2.3 Preparation of Chiral Secondary Alcohols with Distinct Electronic Properties

In light of the proposed mechanism for ketone hydrogenation with Noyori’s \([\text{RuCl}_2(\text{P}^\text{P})(\text{N}^\text{N})]\) catalyst system, it is conceivable that altering the electronic environment at the substrate carbonyl functionality could impact both activity and enantioselectivity in such reactions. For a catalyst to be synthetically useful it must be shown that it can tolerate a variety of electronically different substrates as well as steric bulk. Studies into the effect of substituents upon catalysis can also shed light upon the mechanism by which the catalytic cycle operates. It was shown for the Noyori system that electron-poor substrates, such as \(p\)-trifluoromethylacetophenone, were hydrogenated up to 11 times faster than electron-rich substrates such as \(p\)-methoxyacetophenone, although this is a smaller effect than the substituent effect on reduction with sodium borohydride.² It was also demonstrated by Noyori that the electronic effects of
*para* substituents on enantioselectivity are relatively small and thus efficient enantioselective hydrogenation with such catalysts can tolerate a range of ring substituents.\(^8\) Noyori does suggest, however, that substrates with an electron donating substituent gives rise to high enantioselectivity due to the greater stabilisation of an NH/π interaction between the diamine ligand and the aryl component of the substrate.\(^9\)

In order to investigate this issue for the hydrogenation of bulky ketones with the \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) catalytic system, a range of derivatives of \(\alpha,\alpha,\alpha\)-trimethylacetophenone were prepared, to cover a spectrum of electronic influences on the carbonyl functionality of the substrate (Scheme II-8). The *para*-methoxy derivative \(197\) was prepared as an example of a relatively electron-rich substrate compared to \(\alpha,\alpha,\alpha\)-trimethylacetophenone \(159\), while *para*-chloro and *para*-trifluoromethyl derivatives, \(198\) and \(199\), were prepared as relatively electron-poor substrates, and their performance in catalysis was compared and contrasted. To investigate whether *ortho* substitution can also be tolerated by the \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) system, where steric influences also becomes a factor, the *ortho*-methoxy derivative \(200\) was prepared and its performance in catalysis was explored.

![Scheme II-8 Para- and *ortho*-substituted \(\alpha,\alpha,\alpha\)-trimethylacetophenone derivatives prepared to probe the effect of the electronic environment at the carbonyl group upon productivity and enantioselectivity.](image)

### 2.3.1 Synthesis

The syntheses of the *tert*-butyl ketones \(197-200\) were carried out in moderate to good yields from commercially available acid chlorides by adaptation of literature procedures (Scheme II-9).\(^{10,11}\) The *tert*-butyl cuprate was first generated by reaction of copper(I) bromide dimethylsulfide complex with *tert*-butyllithium in THF at 0°C. Addition of the requisite aroyl chloride and stirring overnight yielded the desired product in each case. Purification by short-path distillation using Kugelrohr apparatus was carried out before each substrate was investigated in catalysis.
2.3.2 Catalysis

Hydrogenation of the substituted α,α,α-trimethylacetophenone derivatives 197-200 with catalyst (R,R)-174 at 50 bar hydrogen pressure and 50°C resulted in the quantitative conversion in each case to the corresponding alcohol (Table II-4). The para-substituted derivatives show consistently high levels of enantioselectivity, generally slightly higher than that of α,α,α-trimethylacetophenone itself. The similarities in selectivity suggests that modifying the electronic environment at the carbonyl functionality has little effect on selectivity in hydrogenation with catalyst (R,R)-174. Unlike in the [RuCl₂(P^P)(N^N)] system, there is a small but significant drop in enantioselectivity for the ortho-substituted methoxy-derivative 200. This may be attributed to the increase in steric bulk near the carbonyl functionality, making differentiation between each face of the ketone substrate more challenging for the present catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>X=</th>
<th>P_H₂ (bar)</th>
<th>T (°C)</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>159</td>
<td>H</td>
<td>50</td>
<td>50</td>
<td>&gt;99 (99)</td>
<td>74 (S)</td>
</tr>
<tr>
<td>2</td>
<td>197</td>
<td>p-OMe</td>
<td>50</td>
<td>50</td>
<td>&gt;99 (79)</td>
<td>77 (S)</td>
</tr>
<tr>
<td>3</td>
<td>198</td>
<td>p-Cl</td>
<td>50</td>
<td>50</td>
<td>&gt;99 (97)</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>199</td>
<td>p-CF₃</td>
<td>50</td>
<td>50</td>
<td>&gt;99 (84)</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>o-OMe</td>
<td>50</td>
<td>50</td>
<td>&gt;99 (69)</td>
<td>69</td>
</tr>
</tbody>
</table>

Table II-4 The hydrogenation of para- and ortho-substituted α,α,α-trimethylacetophenone derivatives 197-200 using catalyst (R,R)-174. General conditions: ketone (~1 mmol), catalyst (R,R)-174 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂, 16 h.
The catalytic performance of substrates 197-200 has shown that hydrogenation \[\text{[RuCl}_2\text{(P}^\text{N}^\text{N})\text{L]}\] catalyst (R.R)-174 can tolerate a range of substrate electronic effects, as all substrates were hydrogenated quantitatively in 16 hours and differences in enantioselectivity with the unsubstituted \(\alpha,\alpha,\alpha\)-trimethylacetophenone were minimal; in some cases enantioselectivity was elevated, perhaps due to steric effects. Our results bode extremely well for the catalysts applicability in synthesis, expanding the scope of substrate greatly.

### 2.4 Preparation of Heteroaromatic Chiral Secondary Alcohols

Heterocycles are so-called “privileged structures” in medicinal chemistry and provide a scaffold for many pharmaceutically active molecules. “Privileged structures” commonly consist of the rigid heteroaromatic ring, which presents appended residues in well defined orientations required for target recognition. Thus, it is incredibly important to be able to control the stereochemistry adjacent to the heterocyclic core in order to control the orientation of appended residues. Heteroaromatic chiral secondary alcohols are thus a versatile building block in preparing pharmaceutically active molecules, an example of which is depicted in Scheme II-10.

Despite the importance of such heteroaromatic chiral secondary alcohols, their preparation by the enantioselective hydrogenation of heteroaromatic ketones is an underdeveloped area, and wasteful resolution techniques are still often required. Heteroaromatic substrates have proved problematic in catalytic hydrogenation as they can preferentially bind to the metal centre through heteroatoms at the expense of the carbonyl group, thus deactivating the catalyst.\(^{13}\) There is also precedent for hydrogenation of the heteroaromatic ring itself\(^{13}\) and under some conditions, cleavage of the ring.\(^{14}\) While some good solutions now exist for the enantioselective catalytic hydrogenation of simple heteroaromatic ketones,\(^{12,15}\) there are still no efficient catalysts for the reduction of bulky, heteroaromatic ketones, and inefficient resolution procedures are still commonplace (Scheme II-11).
Enantioselective Hydrogenation Using Ruthenium Complexes

Chapter II

of Tridentate Ligands

Scott Phillips

Scheme II-11 The bulky heteroaromatic chiral alcohol 207 is a precursor to the potent cathepsin K inhibitor 208, but is prepared in racemic form and then separated by chiral preparatory HPLC.\(^{16}\)

In light of the success of catalyst (\(R,R\))-174 in the enantioselective hydrogenation of sterically-demanding aromatic ketones, it was thought worthwhile to investigate the catalyst’s performance in hydrogenation of bulky ketones containing heteroaromatic functionality. A panel of heteroaromatic ketones were chosen to explore the catalyst’s tolerance of a range of heteroaromatic functionalities (Scheme II-12).

Of the heteroaromatic scaffolds to be investigated, the pyridine structure is of particular importance in medicinal chemistry as the conformational space around the scaffold can be explored in a variety of ways by varying the substituent at the five positions around the ring.\(^{17}\) Introducing a chiral ‘handle’ through asymmetric hydrogenation of prochiral pyridyl ketones is worthwhile in order to equip the medicinal chemist with the tools to fully explore this space. It was decided to look at the hydrogenation of 4-pyridyl ketone 209 in hydrogenation with catalyst (\(R,R\))-174 to expand the scope of this technology in preparing synthetically valuable chiral alcohols.

2.4.1 Synthesis

It was envisaged that the 4-pyridyl ketone 209 could be prepared by adaption of a procedure described by Moberg,\(^ {18}\) in which the 4-lithiopyridine is first prepared by reaction of 4-bromopyridine with \(n\)-butyllithium. It was thought that subsequent addition of pivalonitrile then
hydrolysis would furnish the desired product 209. However, in practice this was not the case and a complex mixture of products was obtained. This was potentially a result of competing ortho-lithiation of the pyridine ring, and subsequent reaction, rather than lithium-halogen exchange as desired. Attention was thus diverted to a more practical route into compound 209. Preparation of the desired 4-pyridyl ketone 209 was furnished in moderate yield by exhaustive methylation of 4-acetylpyridine 213, employing sodium hydride as base (Scheme II-13). While conversion to product was typically high in this reaction, isolated yields were only moderate due to the affinity of the product for silica, employed during purification, and this remains un-optimised.

Scheme II-13 Preparation of 2,2-dimethyl-1-(pyridin-4-yl)propan-1-one 209. Reaction Conditions: 213 (1 eq.), NaH (10 eq.), MeI (10 eq.), THF, 0°C → rt, 16 h, 57%.

The furyl ketone 210 was prepared by Clarke and Fuentes in this group following a previously described route, by addition of t-butylmagnesium chloride to 2-formylfuran, and subsequent oxidation of the secondary alcohol.

A facile route to the thienyl ketone 211 was achieved through the Friedel Crafts acylation of thiophene 214, using stannic chloride and pivaloyl chloride. Acylation was selective at the 2-position and furnished the desired product in excellent yield.

Scheme II-14 Preparation of 1-(thien-2-yl)-2,2-dimethylpropan-1-one 211. Reaction Conditions: 214 (1 eq.), SnCl₄ (1 eq.), pivaloyl chloride (1 eq.), toluene, 0°C → rt, 2 h, 95%.

The final example on the test panel of heteroaromatic substrates, was the elaborate isoxazolyl-based substrate 212. Not only was this substrate chosen to investigate the tolerance of the catalytic system to such a heteroaromatic group but also whether hydrogenation could be accomplished on a relatively large complex molecule, without fragmentation or other possible side reactions.
Substrate 212 was prepared via a recently published literature procedure. The synthesis culminated in the microwave-assisted 1,3-dipolar cycloaddition of alkyne 220 – prepared by Sonagashira coupling of acid chloride 218 and terminal alkyne 219 – with the in-situ generated nitrile oxide 221, prepared in two steps from para-methoxybenzaldehyde 215. This gave the desired product in poor overall yield, but in sufficient quantities for subsequent use in catalysis. The protocol was hampered by the competing dimerisation of nitrile oxide 221 in the microwave-assisted step.

The procedures described all furnished the desired heteroaromatic ketones in sufficient yield and purity for investigation in catalysis with catalyst (R,R)-174.

2.4.2 Catalysis

Hydrogenation of the pyridyl ketone 209 with catalyst (R,R)-174 at 70 bar hydrogen pressure and 70°C resulted in the quantitative conversion to alcohol product (Table II-5). The reaction was sluggish compared to hydrogenation of the phenyl derivative 159 and thus elevated temperature and pressure were required to drive the reaction to full conversion. It was gratifying however that moderate/good enantioselectivity was observed for such a substrate, for which no efficient catalyst exists. It was also pleasing that the ketone could be hydrogenated quantitatively without signs of catalyst deactivation, although the sluggish reaction at low temperatures may be attributed to prohibitive heteroatom-catalyst interactions. Indeed, Noyori

![Scheme II-15 Preparation of isoxazolyl ketone 212. Reaction Conditions: (i) 215 (1 eq.), NH₂OH.H₂O (1.1 eq.), NaOH, H₂O, EtOH, 25-30°C, 1 h, 71%; (ii) 216 (1 eq.), NCS (1 eq.), DMF, 0°C, 1 h, 65%; (iii) 218 (1 eq.), 219 (1 eq.), (PPh₃)₂PdCl₂ (2 mol%), CuI (4 mol%), NEt₃ (1.1 eq.), THF, rt; (iv) 220 (1 eq.), 221 (1 eq.), μW, 90°C, 30 min, 21% (two steps).](image-url)
found the need to use a borate additive to prevent such interactions when investigating the hydrogenation of simple pyridyl ketones.\textsuperscript{12} Isolated yields were low for pyridyl alcohols in our study due to their affinity for silica, which was encountered during purification.

The 2-furyl derivative \textit{210} was also hydrogenated quantitatively using catalyst \((R,R)-174\), at 50 bar hydrogen pressure and 50°C, giving the chiral secondary alcohol product \textit{223} with enantioselectivity on par with the non-heteroaromatic derivative \textit{159}. The milder reaction conditions in comparison with those needed for the hydrogenation of pyridyl ketone \textit{209} may be down to the lone pair on the furan oxygen being less available for interaction with the metal catalyst, and thus less energy is needed to overcome such an interaction. Disappointingly, however, it was found that the 2-thienyl derivative \textit{211} was totally resistant to hydrogenation with catalyst \((R,R)-174\), even at elevated temperature and pressure. This may be attributed to the greater availability of the lone pair upon sulfur to interact with the metal catalyst. This problem was overcome somewhat by Fuentes and Clarke in this group,\textsuperscript{20} who made use of a \((R,R)-[\text{RuCl}_2(\text{P}^\text{N}^\text{O})\text{L}]\) catalyst that could hydrogenate ketone \textit{211} with 65\% conversion in 65 h, and with 64\% enantioselectivity (S-enantiomer), at 50 bar hydrogen pressure and 50°C.\textsuperscript{23} This suggests that perhaps rather than an interaction between the heteroatom lone-pair and the metal centre prohibiting efficient hydrogenation, that interaction between the heteroaromatic ring and the amine ligand may be important.

Hydrogenation of the more elaborate isoxazolyl ketone \textit{212} with catalyst \((R,R)-174\) was successfully accomplished, almost quantitatively, at 70 bar hydrogen pressure and 40°C.
without any competing side reactions. Pleasingly, alcohol 225 was also furnished with 67% enantiomeric excess. The mere fact that alcohols containing heteroaromatic function as well as sterically demanding structures can be hydrogenated with catalyst \((R,R)-174\) is extremely gratifying as few, if any, catalysts exist that can tackle such substrates. The additional bonus of good enantioselectivity bodes well for the development of second generation \([\text{RuCl}_2(P^\text{N^N}L)]\) catalysts, which can deliver such complex structures with enhanced enantio-enrichment (see chapter IV).

![Scheme II-16](image)

Scheme II-16 The hydrogenation of heteroaromatic ketone 212 using catalyst \((R,R)-174\). Reaction conditions: ketone 212 (1 eq.), catalyst \((R,R)-174\) (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular \(\text{H}_2\) (70 bar), 40°C 16 h, 98%.

It has been demonstrated in this work that a range of heteroaromatic functionalities can be tolerated by the present catalytic system: pyridyl,\(^1\) furyl and isoxazyl ketones can be hydrogenated by catalyst \((R,R)-174\), in many cases with good enantioselectivity. Such reactions can be used to produce valuable chiral heteroaromatic scaffolds, which are privileged structures in medicinal chemistry.

### 2.4.3 Preparation of Heteroaromatic Bis-Diols

There is a huge scope in asymmetric synthesis for the use of \(C_2\)-symmetric diols as chiral ‘inducers,’ whether it be in the preparation of chiral auxiliaries - for a range of reactions such as stereoselective additions to \(\text{C=O}, \text{C=N}\) or \(\text{C=C-C=O}\) - or as chiral ligands, for important catalytic processes such as the enantioselective addition of diethylzinc to aldehydes or titanium-catalysed asymmetric oxidation and Diels Alder reactions.\(^2\) In addition to this, such diols are

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\(^1\) In collaboration with Professor Marcia B. France, Washington and Lee University, VA, United States, and Mary E. Gunn, University of St Andrews, during a summer training project, it was found that 2,2-dimethyl-1-(pyridin-2-yl)propan-1-one could also be hydrogenated quantitatively by catalyst \((R)-174\), with 60% e.e. (S) at 70 bar \(\text{H}_2\) and 70°C, after 16 h.
synthons in the synthesis of important chiral diamines and diphosphines. This makes $C_2$-symmetric diols one of the “most sought after molecules in the area of asymmetric synthesis.”

Many $C_2$-symmetric diols are prepared directly from chiral pool precursors but such resources are limited in scope. Asymmetric hydrogenation provides a convenient route into such molecules from prochiral bis-ketones. Previous work in this laboratory has demonstrated that chiral $C_2$-symmetric diols can be prepared in up to 93% e.e. by using catalyst ($R,R$)-174 to hydrogenate bis-ketones. In light of the current work of the hydrogenation of heteroaromatic ketones, it was decided to investigate catalyst ($R,R$)-174 in the hydrogenation of bis-ketones with a heteroaromatic core. This would furnish a $C_2$-symmetric diol that might find use as a tridentate ligands, either as itself or after further manipulation.

The bis-ketone 226 was prepared in this laboratory by Clarke and Fuentes. It was found that the diol 227 could be furnished quantitatively from bis-ketone 226 using catalyst ($R,R$)-174 in 16 h at 50 bar hydrogen pressure and 50°C (Scheme II-17).

![Scheme II-17](image)

**Scheme II-17** The hydrogenation of bis-ketone 226 using catalyst ($R,R$)-174.

**Reaction conditions:** ketone 226 (1 eq.), catalyst ($R,R$)-174 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H$_2$ (50 bar), 50°C, 16 h, >99% conversion.

Enantioselectivity in the reaction was hugely amplified relative to the hydrogenation of related monoketone 210 (Table II-5, entry 3) with the major enantiomer produced in almost enantiopure form. This amplification is accounted for by the Horeau effect, whereby multiple enantioselective transformations on the same molecule by the same catalyst, lead to an increase in product e.e. relative to that expected for a single reaction, due to the formation of the meso diastereomer which allows for the removal of racemic material (Scheme II-18). Based on 74% enantioselectivity for a single transformation, statistical analysis predicts that 95% e.e. will be obtained after hydrogenation of the two ketones. This assumes that the catalyst selectivity is the same at both sites, i.e. the first formed stereocentre has no influence on further selectivity. This may not be the case in our system and the slightly higher selectivity obtained may be accounted
for by the steric impact of the bulky substituents at the first stereocentre influencing selectivity at the second centre. The diastereomeric ratio \((R,R):(+S,S):\text{meso})\) for our system is slightly lower than what is predicted and this may be explained by similar reasoning.

Scheme II-18 The Horeau Effect and its statistical impact on product distribution in the hydrogenation of the *bis*-ketone 226.

The price paid for such an amplification of enantioselectivity however is the large material lost as the *meso* compound (which increases relative to the magnitude of enantioselectivity). While this can often be separated easily by column chromatography, it is not desirable to produce such quantities of undesired material, and in this case, efficient separation was problematic in initial attempts.

Despite this, utility of \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}] \) catalysts in preparing synthetically useful, almost enantiopure diols has been demonstrated, products with a variety of potential uses, whether it be as chiral ligands, or as precursors to a range of other important chiral products. Diol 227 has potential use as a chiral ligand as it contains a third potential metal coordination point, through the oxygen lone pair, which one would assume would more a conformationally rigid structure, ideal for the relay of stereochemical information to other molecules in catalysis. This is just another example of the range of valuable chiral products that the current technology has the potential to exploit.
2.5 Preparation of Chiral Secondary Alcohols with an Adjacent Gem-Dimethyl Group

Geminal dimethyl groups are key features of many biologically important molecules and their analogues (Scheme II-19). Such groups can lock structures in certain conformations thus maximising receptor affinity compared to their CH$_2$ analogues. Gem-dimethyl groups are also effective in increasing metabolic stability by blocking parts of molecules to nucleophilic attack. As well as this, gem-dimethyl groups are also salient in organic synthesis as they can be exploited in a variety of ways, whether it be by preventing nucleophilic attack at sensitive functionality, or in aiding the relay of stereochemical information by providing conformational rigidity in chiral auxiliaries/ligands, or even enhancing the rate of some ring-forming reactions (Thorpe-Ingold Effect).

Scheme II-19 Biologically important molecules containing gem-dimethyl substituents (a) for structural rigidity and maximising receptor affinity (175 and 176), (b) for metabolic stability (228) and (c) for both prevention of endocyclic cleavage of the ring by nucleophilic attack, and structural rigidity for transfer of stereochemical information in this important class of chiral auxiliary (231).

Despite being extraordinarily useful molecules, there is little precedent in the literature for the preparation of chiral secondary alcohols with an adjacent gem-dimethyl group via asymmetric hydrogenation. This is primarily due to the limitations of the Noyori [RuCl$_2$(P$^P$)(N$^N$)] catalytic system in the hydrogenation of such bulky ketones. The [RuCl$_2$(P$^N$N)L] has shown great potential, however, for the enantioselective hydrogenation of this class of substrate, giving quantitative conversion of ketone 183 to alcohol product in 84% e.e. (Table II-2). It was decided to explore the performance of catalyst (R)-174 further in the hydrogenation of such ketones. The aim of this study was both to demonstrate the activity and selectivity of the [RuCl$_2$(P$^P$)(N$^N$)] in preparing chiral secondary alcohols with adjacent gem-dimethyl groups, but also to furnish molecules as potential analogues of biologically important compounds.

It was felt that as well as having adjacent gem-dimethyl substituents, chiral secondary alcohols with ‘handles’ for further modification must be prepared in order to exhibit the catalyst’s potential in preparing useful products which were previously inaccessible by asymmetric
hydrogenation. Two substrate targets were in mind: ketones 230 and 231, with a distal nitrile
group and benzyl ether-protected alcohol group, respectively, for further chemical modification,
(Scheme II-20).

\[
\begin{align*}
\text{230} & \quad \text{CN} \\
\text{231} & \quad \text{O} \text{Ph}
\end{align*}
\]

Scheme II-20 Chiral secondary alcohols containing synthetically-useful remote functionality.

Nitriles such as 230 are of extreme versatility in synthesis as they can be transformed to a
number of useful products: hydrolysis of 230 yields carboxylic acids; reduction leads to primary
amines or imines (aldehydes upon hydrolysis); alcohol nucleophiles can furnish esters upon
hydrolysis, and alkyl/aryl based nucleophiles can give ketones. Nitrile groups can also undergo
displacement via S_N2 reactions with certain nucleophiles, which opens the door to a whole new
range of useful products. Likewise, deprotection of the benzyl ether 231 unlocks the primary
alcohol functionality which can be manipulated in a variety of ways to give an array of chiral
products.

It was also desirable to investigate the potential of the present catalytic system in preparing
gem-dimethyl analogues of antifungal agents such as econazole 232 and miconazole 233
(Scheme II-21). To date, the only successful preparation of the precursor to such compounds,
chiral alcohol 234, via asymmetric hydrogenation was accomplished using a transfer
hydrogenation system employing [RuCl(N-tosylDPEN)(cymene)] and formic acid as hydride
source, in up to 99% e.e.\textsuperscript{34} Whilst transfer hydrogenation is a mild and convenient technique to
prepare such chiral alcohols in the research lab, pressure hydrogenation is preferred in industry
due to its scaleability, as well as molecular hydrogen being a relatively cheap and readily
available hydride source. Thus, efficient H\textsubscript{2}-hydrogenation catalysts are still desirable for the
enantioselective reduction of such ketones and analogues.
Previous work in this group has demonstrated that the CH$_2$ analogue 235 can be prepared quantitatively in 61% e.e by H$_2$-hydrogenation with catalyst (R)-174 (Scheme II-22). In light of the present catalytic system’s ability to hydrogenate bulky substrates, and its tolerance of heteroaromatic functionality, it was decided to investigate the hydrogenation of ketone 236, to demonstrate the catalyst’s utility in preparing useful chiral analogues of biologically important molecules.

The strategy for preparation of the ketone precursors to 230 and 231 was by functionalisation of the α-carbon of isobutyrophenone 82. It was envisaged that substrate 237 could be prepared by the conjugate addition of the potassium enolate of isobutyrophenone 82 to acrylonitrile, in a procedure similar to that reported by Campbell et al.\textsuperscript{35} This was successfully accomplished, albeit in low un-optimised yield, and the desired product was easily recovered, giving the pure ketone in sufficient quantities for investigation in catalysis (Scheme II-23). It should be noted here that this is a quick and facile route into such compounds and it can be imagined that a large number of functionalised derivatives could be prepared by such methods from relatively cheap,
commercially-available starting materials. Thus, there is potential to create a expanded range of functionalised chiral secondary alcohol products.

![Chemical structure](image)

**Scheme II-23** Preparation of 4,4-dimethyl-5-oxo-5-phenylpentanenitrile 237. *Reaction Conditions*: 82 (1 eq.), acrylonitrile (1 eq.), methanolic KOH solution (30%), dioxane, 50°C, 24 h, 21%.

The preparation of substrate 239 proved more troublesome. Isobutyrophenone 82 was first converted to the keto-alcohol 238 in good yield by aldol condensation with paraformaldehyde in the presence of trifluoroacetic acid, and subsequent base hydrolysis of the trifluoracetate ester (Scheme II-24). Multiple attempts to prepare the benzyl protected form of the alcohol (thought to be required to provide steric bulk for efficient enantioselective catalysis) failed however. This was likely due to retro-Aldol reaction taking place under the forcing basic conditions needed in ether synthesis, yielding isobutyrophenone as the primary product.

![Chemical structure](image)

**Scheme II-24** Attempted preparation of substrate 239. *Reaction Conditions*: (i) 82 (1 eq.), paraformaldehyde (1.3 eq.), trifluoroacetic acid, 60°C, 16 h then 2M NaOH, rt, 2 h, 74%; (ii) 238 (1 eq.), BnBr (1 eq.), tBuNI (0.015 eq.) H₂O, Me-THF, reflux, 16 h or 238 (1 eq.), BnBr (1 eq.), NaH (2.5 eq.), THF or DMF, reflux, 16 h.

A second route was thus needed, which could prepare substrate 239 in a good yield in few steps, but which could be customisable in preparing a range of derivatives. It was decided to make use of the catalytic monoalkylation protocol of Onomura and co-workers to first prepare the monobenzylated 1,3-diol 241 in an easy, high-yielding and customisable step (Scheme II-25). Subsequent oxidation, addition of arylmagnesium bromide reagent (opening the door to potential preparation of substituted derivatives), and final oxidation step, furnished the desired product. Although this is not an elegant process, the product is delivered using easy, high-yielding reactions.
The imidazole-functionalised ketone substrate 244 was prepared by modification of a procedure by Bildstein (Scheme II-26), presumably via an S_N_1 mechanism, with the second equivalent of imidazole acting to neutralise the HBr which is formed. This procedure provided ketone 244 in good yield and purity for subsequent use in catalysis.

**Scheme II-26** The synthesis of 2-(1H-imidazol-1-yl)-2-methyl-1-phenylpropan-1-one 244. Reaction conditions:

243 (1 eq.), imidazole (2 eq.), EtOH, reflux, 3 d, 62%.

### 2.5.2 Catalysis

Hydrogenation of both the functionalised ketone substrates 237 and 239 with catalyst (R,R)-174 at 50 bar hydrogen pressure and 50°C resulted in the quantitative conversion in each case to alcohol product (Table II-6). It was gratifying to find that substrate 237 was hydrogenated with enantioselectivity on par with that of the model ketone α,α,α-trimethylacetophenone 159. The uses of the chiral alcohol product 237 will be underlined further in section 2.5.3. It was pleasing to find that catalysis is tolerant of the useful nitrile functionality, given that ruthenium catalysed nitrile hydrogenation is a well known reaction.38,39
Enantioselective Hydrogenation Using Ruthenium Complexes

Chapter II

of Tridentate Ligands

Scott Phillips

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**Table II-6** The hydrogenation of ketones with gem-dimethyl substituents using catalyst (R,R)-174. General conditions: ketone (−1 mmol), catalyst (R,R)-174 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂, 16 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>R=</th>
<th>(P_{\text{H}_2}) [bar]</th>
<th>(T) [^\circ\text{C}]</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>237</td>
<td>CH₂CH₂CN</td>
<td>50</td>
<td>50</td>
<td>&gt;99</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>239</td>
<td>CH₂OBn</td>
<td>50</td>
<td>50</td>
<td>&gt;99</td>
<td>50</td>
</tr>
</tbody>
</table>

Chiral alcohol 231 was furnished in only moderate enantioselectivity upon hydrogenation with catalyst (R,R)-174. This may be due to the significant extension of the substrate structure away from the ketone function, resulting in unfavourable interactions with the catalyst structure. However, bearing in mind the limited number of catalysts which can hydrogenate such ketones with bulk around the carbonyl group, this result is still promising and catalyst optimisation has the potential of leading to more selective catalysts.

Hydrogenation of the gem-dimethyl substituted ketone 244 was again accomplished quantitatively in 16 h by catalyst (R,R)-174 at 70 bar hydrogen pressure and 40° C. Disappointingly, however, levels of enantioselectivity were slightly diminished for this substrate, relative to that obtained in producing the less sterically demanding derivative 235.

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**Scheme II-27** The hydrogenation of 2-((1H-imidazol-1-yl)-2-methyl-1-phenylpropan-1-one 244 using catalyst (R,R)-174. Reaction conditions: ketone 244 (1 eq.), catalyst (R,R)-174 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂ (70 bar), 40° C, 16 h, >99% conversion, 86% yield.
Despite achieving only moderate enantioselectivity, these results are encouraging bearing in mind that this class of substrate is envisaged to be of low reactivity using Noyori-type catalysts, and such useful chiral products cannot be prepared by existing H₂-hydrogenation technology. Hopefully, the moderate level of enantioselectivity can be elevated by catalyst optimisation, and some important preliminary steps towards this have been achieved in chapter IV.

2.5.3 Practical Uses of Chiral Alcohol Products

It has been demonstrated that useful chiral secondary alcohol 237, with gem-dimethyl substituents, and remote functionality, can be prepared with good enantioselectivity using catalyst (R,R)-174. In order to showcase the utility of such chiral products, it was undertaken to employ 237 in the preparation of the chiral cyclic ester (δ-butyrolactone) 248, and show that enantioselectivity could be preserved throughout the process.

Scheme II-28

The cyclic ester component constitutes a frequently encountered structural motif within a huge variety of natural products and biologically active compounds. Furthermore, the lactone functionality exists in common flavour components and is thus employed in the perfumery and food industry.

40,41 Derivatives of lactones also play important roles as sex attraction pheromones of different insects, and plant regulators as well as being building blocks in the synthesis of natural products, such as alkaloids and terpenoids, and other biologically active compounds, such as antitumour, antidepressant and antiviral agents (Scheme II-29).

While a variety of methods exist for the preparation of enantiomeric pure γ- (five membered ring) and δ-lactones (six-membered), many of these rely on asymmetric induction from stoichiometric amounts of chiral auxiliary or chiral reducing agent, or require problematic enzyme based reductions.

48,47,49 The use of a metal-based catalyst to hydrogenate functionalised ketones enantioselectively and subsequent intermolecular ring closing is an underdeveloped technology, and only limited reports of such exists in the literature to date, making use of first generation Noyori [Ru(P^P)L₂] catalysts to enantioselectively hydrogenate β-ketoesters and γ-ketoacids.

50,51 To the best of our knowledge, enantioselective synthesis of δ-lactones from enantio-enriched hydroxy nitriles is unprecedented. Our plan was to employ the chiral
secondary alcohol 237, prepared via enantioselective hydrogenation using catalyst \((R,R)-174\), in a ring-closing reaction to prepare lactone 248, whilst maintaining the enantioselectivity introduced in the hydrogenation step.

![Scheme II-29 Examples of the cyclic ester motif in biologically active compounds including perfumery ingredients, insect pheromones and compounds of pharmaceutical interest.](image)

**Scheme II-29** Examples of the cyclic ester motif in biologically active compounds including perfumery ingredients, insect pheromones and compounds of pharmaceutical interest.

![Scheme II-30 The intermolecular ring-closing of functionalised chiral alcohol 237 to give the chiral \(\delta\)‐lactone 248. Reaction Conditions: 237 (1 eq.), KOH (5 eq.), ethylene glycol, reflux, 24 h then 10% HCl (aq), 76%. The HPLC traces show the retention of the high levels of enantioselectivity in the ring‐closing step.](image)

**Scheme II-30** The intermolecular ring-closing of functionalised chiral alcohol 237 to give the chiral \(\delta\)‐lactone 248. Reaction Conditions: 237 (1 eq.), KOH (5 eq.), ethylene glycol, reflux, 24 h then 10% HCl (aq), 76%. The HPLC traces show the retention of the high levels of enantioselectivity in the ring‐closing step.
It was pleasing to find that ring-closing to form the lactone \(248\) could be accomplished by treating the chiral alcohol \(237\) with excess potassium hydroxide in ethylene glycol and refluxing the mixture for 24 h. Subsequent treatment with 10% aqueous hydrochloric acid furnished the desired product in good yield. Analysis of the product lactone by chiral HPLC, showed that enantioselectivity was indeed retained during the ring-closing step (Scheme II-30).

Having developed a method for preparing enantio-enriched δ-lactones from the products of \([\text{RuCl}_2(P^N^N)]\)-catalysed enantioselective hydrogenation, it was felt worthwhile to widen the scope of potential lactone products. It was envisaged that by making use of Noyori-type \([\text{RuCl}_2(P^P)(N^N)]\) catalysts to prepare highly enantio-enriched chiral secondary alcohols containing the nitrile functionality, a wider range of chiral lactone products could be prepared using this approach. It was thus necessary to demonstrate the use of Noyori-type catalysts in such protocols.

Ketone \(252\) was prepared in two good yielding steps from the vinyl ketone \(249\) (Scheme II-31), making use of protocols developed by Wessig.\(^52\) The conjugate addition of the stabilised anion of \(250\) to \(249\) yielded ketone \(251\) which underwent facile Krapcho decarboxylation to yield the desired functionalised ketone \(252\).

\[\text{Scheme II-31 Preparation of 5-oxo-5-phenylpentanenitrile 252. Reaction Conditions: (i) 249 (1 eq.), 250 (2 eq.), K}_2\text{CO}_3 (0.11 eq.), 18\text{-crown-6} (0.12 eq.), \text{THF, rt, 1 h; (ii) 251, NaCl (1.1 eq.), H}_2\text{O, DMSO, reflux, 24 h, 62\% over two steps).}\]

Despite the success of this methodology, it was felt that the development of a more customisable route into ketones such as \(252\) from commercially available starting materials was highly desirable (Scheme II-32). Making use of a method described in a very early patent,\(^53\) ketone \(252\) could indeed be prepared in one step from acetophenone via an amine-catalysed Michael addition. This opens the door to a wide variety of analogues of \(252\) and this type of organocatalytic Michael addition to acrylonitrile without over-addition would be an interesting topic for further investigation. Ketone \(252\) prepared by both methods were used in subsequent hydrogenation.
Scheme II-32 Preparation of 5-oxo-5-phenylpentanenitrile 252 in one step from acetophenone 81. Reaction Conditions: (i) acetophenone 81 (4 eq.), acrylonitrile 237 (1 eq.), cyclohexylamine (0.2 eq.), hydroquinone (0.02 eq.), acetic acid, Δ, 16 h, 62%.

Attempts at the hydrogenation of substrate 252 employing Noyori-type catalysts 254-256 and 14 that had previously been shown to be active in the hydrogenation of a wide range of simple aromatic ketones,54,55 proved to be unsuccessful, with low levels of conversion to product (Table II-7, entries 1-5) even with more forcing conditions (entry 4). It was thought that the distal nitrile functionality may lend to its use to efficient catalysis without the need for the diamine component. However, attempts using [RuCl$_2$((S)-BINAP)]$_n$ 257 again proved futile (Entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>$P_{H_2}$ [bar]</th>
<th>B:C</th>
<th>$T$ [°C]</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S),(R,R)-254</td>
<td>50</td>
<td>50:1</td>
<td>50</td>
<td>5</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>(S),(R,R)-255</td>
<td>50</td>
<td>50:1</td>
<td>50</td>
<td>&lt;5</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>(S),(S,S)-256</td>
<td>50</td>
<td>50:1</td>
<td>50</td>
<td>14</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>(S),(S,S)-256</td>
<td>70</td>
<td>50:1</td>
<td>70</td>
<td>21</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>(S),(S,S)-14</td>
<td>50</td>
<td>50:1</td>
<td>50</td>
<td>&lt;5</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>(S)-257</td>
<td>50</td>
<td>-</td>
<td>50</td>
<td>&lt;5</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>(S,S)-151</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>(R,R)-174</td>
<td>50</td>
<td>2:1</td>
<td>50</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>(R,R)-174</td>
<td>70</td>
<td>2:1</td>
<td>70</td>
<td>&gt;99</td>
<td>49</td>
</tr>
</tbody>
</table>

Table II-7 Hydrogenation of simple nitrile functionalised ketones. General conditions using $H_2$-hydrogenation catalysts: Ru catalyst (0.5 mol%), KO'Bu (if required), PrOH, $H_2$, 16 h. Conditions using transfer hydrogenation catalyst: Catalyst (S,S)-151, HCO$_2$H (3 eq.), NEt$_3$ (2.6 eq.), 3 d.
The only literature examples of the hydrogenation of ketones with nitrile functionality, are transfer hydrogenations using catalysts such as (S,S)-151.56,57 The transfer hydrogenation of 252, using catalyst (S,S)-151 and formic acid/triethylamine as hydride source, was attempted but no product was observed (Entry 7).

Since the [RuCl₂(P^N^N)] catalytic system did show activity in the hydrogenation of the bulky ketone 237 with distal nitrile functionality, it was decided to employ catalyst (R,R)-174 in the hydrogenation of the simple derivative 252. Pleasingly, this proceeded quantitatively and in 49% e.e at 70 bar and 70°C. Although enantioinduction was only moderate, these results are significant as no other system was capable of the reduction of such ketones and thus has a number of potential uses.

The nitrile functionalised alcohol 253 could be ring-closed to give the chiral δ-lactone 258 by treatment at reflux with potassium hydroxide in ethylene glycol for 3 days followed by acidic work-up (Scheme II-33). The level of enantioinduction was preserved throughout the process.

![Scheme II-33](image)

**Scheme II-33** The intermolecular ring-closing of functionalised chiral alcohol 253 to give the chiral δ-lactone 258. Reaction Conditions: 253 (1 eq.), KOH (5 eq.), ethylene glycol, reflux, 3 d then 10% HCl (aq), 62%.

It has been demonstrated that using this hydrogenation/ring-closure methodology, both simple chiral δ-lactones, and those with more sterically demanding substituents, can be prepared in moderate to good enantioselectivity from readily accessible starting materials. There is thus potential to prepare a variety of valuable chiral lactone products. The tolerance of such catalysts for a variety of electronically-distinct and heteroaromatic substituents, as well as the potential to form different sized lactone rings, increases the scope of this methodology significantly (Scheme II-34).
2.6 Conclusions

The current work has demonstrated the huge potential of \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) catalysts in preparing a wide range of enantio-enriched chiral products. The current system is complementary to the Noyori system, being particularly efficient in the enantioselectivity of more bulky aromatic ketones, giving ee’s of up to 98%. The system is tolerant of a wide range of electronically and sterically demanding substituents and can hydrogenate a wide range of both aromatic and heteroaromatic substrates, giving rise to an exponentially large substrate scope. The utility of the system has been demonstrated and has been shown to be effective in the preparation of a number of synthetically useful chiral alcohols, whether it be for use as a functionalised scaffold in medicinal chemistry, or to undergo further elaboration to give other valuable chiral products such as lactones, or for use as chiral inducers in asymmetric synthesis.

2.7 Progression

While enantioselective hydrogenation with catalyst (\(R,R\))-\textbf{174} has allowed the preparation of a range of important chiral products, scope still exists for the optimisation of catalyst structure to prepare alcohols in close to enantiopurity. The modular nature of the ligand structure allows the ligand to be tuned in a variety of ways to potentially improve reactivity and selectivity. It was decided that in order to aid the rational design of new ligands, a better understanding of the mechanism of hydrogenation by \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) catalysts, and the origin of enantioselectivity in these reactions, must be gained through detailed experimental observations. A proposed mechanism for hydrogenation using the \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) catalytic system, and the experimental evidence which supports this, is described in full in Chapter III. The rational design of new ligands, based on this improved mechanistic understanding, is subsequently presented in Chapter IV.
2.8 References

Chapter III


The work to date in this group has shown catalyst (R,R)-174 to be very effective in the asymmetric hydrogenation of a variety of ketone substrates, tolerating a wide variety of electronically and sterically demanding functionalities, and having the ability to prepare a range of useful chiral products, inaccessible via other hydrogenation protocols. However, while enantioselectivities in the reactions have been very encouraging - typically in the range 50-90% for substrates with one ketone functionality - it is believed that optimisation of the catalyst structure would lead to increased selectivity, approaching that needed to be generally appliable (>90% e.e.).¹ Also, more active catalysts are highly desirable due to the need for low catalyst loading driven by economic factors.

The modular design of the [RuCl₂(P^N^N)L] catalyst (R,R)-174 allows for tuning at a number of positions to facilitate catalyst optimisation. A greater understanding of the reaction mechanism allows this to be done more rationally from the development of catalyst structure-activity relationships.

The modular ligand design employed in this research allows for the preparation of a range of catalyst derivatives in order to improve activity and enantioselectivity (Scheme III-1). However, rather than preparing a large library of new [RuCl₂(P^A^N^N)L] catalysts, it was felt that an investigation of catalyst structure-activity relationships would be of more benefit, leading to rational catalyst design. In particular, we were interested in the role of the diamine component of the ligand structure, since Noyori identified the primary diamine as crucial to activity and enantioselectivity using [RuCl₂(P^A^P)(N^A^N)] systems. This shall play a large part in an extensive study into the mechanism of hydrogenation using [RuCl₂(P^A^N^N)L] catalysts, with the principal
aim of aiding the design of more active and selective catalysts for a wider range of ketone substrates.

3.1 The Role of Diamine Component in Catalyst Productivity

The initial design of $[\text{RuCl}_2(P^\text{N^N})L]$ catalyst ($R,R$)-174 envisaged hydrogenation would be facilitated by the primary amine terminus of the ligand, in a coordination environment that is more accessible for bulky substrates. However, the presence of a secondary amine component in the ligand structure offers a second potential hydrogen bond donor for interaction with an incoming ketone substrate, which could similarly facilitate hydrogenation via the bifunctional mechanism. A third possibility exists that neither outer sphere mechanism is operational, and the $[\text{RuCl}_2(P^\text{N^N})L]$ system operates by a completely independent mechanism, perhaps via coordination of the substrate to the metal centre itself. Knowledge of the precise mechanism by which the catalytic system proceeds could allow rational tuning of the catalyst structure shown in Scheme III-1.

In order to probe whether the terminal amine or the secondary amine component is responsible for productivity in $[\text{RuCl}_2(P^\text{N^N})L]$ catalysts, it was decided that a number of achiral derivatives of catalyst ($R,R$)-174 would be prepared (Scheme III-2). We aimed to investigate the effect of removing the hydrogen bond donor capacity of first the terminal NH$_2$ group (Catalyst 264) and then both the terminal and secondary amine component (Catalyst 265), by the incorporation of methyl groups at the requisite positions. The achiral derivative of catalyst ($R,R$)-174, 263, was also prepared for a direct comparison with derivatives 264 and 265. This was all done assuming that the increased steric bulk created by the appended methyl group had little effect other than to block potential hydrogen bonding interactions.

It was envisaged that kinetic analysis of each catalyst in the hydrogenation of $\alpha,\alpha,\alpha$-trimethylacetophenone would shed light on the relative activity of each catalyst and would give
clues as to the requirements of catalyst structure, in particular the diamine component, for maximum TOF.

3.1.1 Synthesis of Catalysts

The new achiral ligands 263-265 were all prepared from commercially available starting materials. Ligand 263 was prepared following a procedure performed previously in this group by Lamb, by careful dropwise addition of a solution of 2-(diphenylphosphino)benzaldehyde 266 in degassed ethanol to a dilute solution of ethylenediamine 267 also in degassed ethanol, and the reaction mixture stirred under a nitrogen atmosphere (Scheme III.3). It was ensured that diamine 267 was present in a suitably large excess to prevent the undesired difunctionalisation of the diamine. Monitoring of the reaction mixture by $^1$H and $^{31}$P NMR spectroscopy showed the disappearance of signals corresponding to 2-(diphenylphosphino)benzaldehyde 266 ($\delta_H$ (C$_6$H$_6$) = 10.3 ppm (CHO, d, J 5), $\delta_p$ (C$_6$H$_6$) = -10.8 ppm) and the appearance of a signal at $\delta_H$ (C$_6$H$_6$) = 9.51 ppm (CH=N, d, J 4) and $\delta_p$ (C$_6$H$_6$) = -12.0 ppm corresponding to that of the imine species. Complete conversion of 2-(diphenylphosphino)benzaldehyde 266 to the imine was accomplished after 5 h. The imine was reduced to the secondary amine by addition of sodium borohydride to the mixture and was complete within 12 h. This was indicated by the disappearance of the signal corresponding to the CH=N proton of the imine species in the $^1$H NMR spectrum, and the appearance of a new signal at -16.0 ppm in the $^{31}$P NMR spectrum, corresponding to the reduced species 268. Careful aqueous work-up under a nitrogen atmosphere, removed the excess ethylenediamine furnishing ligand 268 in 72% yield and in sufficient purity (>95%) for complexation. An analytically pure sample for characterisation could be obtained by formation of the hydrochloride salt of the ligand and crystallisation from dichloromethane.

Scheme III-3 The synthesis of complex 263, the achiral derivative of the original [RuCl$_2$(P$_2$N$_2$N)$_2$] catalyst 174. Reaction conditions: 2-(diphenylphosphino)benzaldehyde 266 (1 eq.), ethylenediamine 267 (3 eq.), EtOH, 45°C → rt, 5 h; (ii) NaBH$_4$ (4 eq.), EtOH, rt, 12 h; (iii) 268 (1 eq.), [RuCl$_2$(DMSO)$_2$] (1 eq.), THF, μw, 120°C, 20 min.
Complexation of ligand 268 was successfully accomplished employing the microwave-assisted protocol developed in this group.³ Ligand 268 and [RuCl₂(DMSO)₄] were dissolved in degassed THF in an inert environment and microwave heating for 20 min at 120°C resulted in the quantitative conversion to complex 263. Complexation was confirmed by the appearance of a signal with a downfield shift in the ³¹P NMR spectrum at +44.5 ppm (CDCl₃) and disappearance of the signal corresponding to the unbound ligand at -16.1 ppm (CDCl₃). Signals corresponding to the protons upon carbon atoms adjacent to the coordinating nitrogens are also shifted downfield when the ligand is bound to ruthenium. Each of these protons also becomes inequivalent due to the formation of the stereogenic centre at the secondary amine atom in the complex and thus individual signals appear for each. The one dimethylsulfoxide molecule that remains bound to the ruthenium centre becomes desymmetrised as a result of this and signals corresponding to the two methyl groups appear at 2.98 and 2.56 ppm in the ¹H NMR. This pattern is characteristic of complexes with meridional P^N^N and DMSO ligands, with chloride ligands occupying the remaining axial positions. All NMR observations were consistent with that seen for catalyst 174, for which an X-ray crystal structure has been obtained, giving us confidence that the coordination mode of ligands are analogous to that of the original catalyst, and as shown in Scheme III-3. Accurate mass analysis of the pure complex confirmed the molecular ion ([M+Na]⁺) to be that of the desired complex, with an excellent match to the theoretical isotope model.

The dimethylated ligand 270 was prepared in a similar manner to that of ligand 268, although without the possible complications of difunctionalisation of the diamine. Thus, equimolar amounts of N’N’-dimethylethylenediamine 269 and 2-(diphenylphosphino)benzaldehyde 266 were dissolved in degassed ethanol and the reaction mixture stirred at room temperature (Scheme III-4). Again the reaction was monitored by ¹H and ³¹P NMR spectroscopic analysis of the crude reaction mixture and the characteristic signals are presented in Scheme III-4. After aqueous work-up, the ligand was deemed of good purity and reacted immediately with [RuCl₂(DMSO)₄], giving analytically pure complex 264 in 95% yield after column chromatography. Similar trends in the spectroscopic data were observed to those described for complex 263, supporting the assignment.
Recrystallisation by vapour diffusion from CHCl₃/hexane gave crystals of 264 which despite being small allowed X-ray diffraction studies to be conducted by Prof. Alexandra Slawin. The representation of the molecular structure that was produced (Figure III-1, (a)) supports the expected ligand coordination mode to ruthenium, where the P^N^N ligand is coordinated in a meridional manner with a sulfur-bound dimethylsulfoxide molecule occupying the final meridional site. Chloride ligands in a trans-relationship are present at the remaining coordination sites. An interesting molecular structure was observed when the complex was crystallised from acetonitrile (Figure III-1, (b)). The dimethylsulfoxide ligand was replaced by a nitrogen bound acetonitrile molecule, with the chloride ligands now having a cis-relationship. This suggests that the DMSO ligand is labile and may not remain bound to the metal centre throughout catalysis.

Figure III.1 (a) Representation of the molecular structure of 264, from X-ray diffraction studies, supporting the expected coordination mode of the ligands. Two molecules of chloroform omitted for clarity. (b) Representation of the molecular structure of the complex that was crystallised from acetonitrile.
A modified procedure was required in order to furnish ligand 265 containing methyl groups both on the primary and secondary amine component. The original methodology failed to promote the full conversion to the intermediate iminium species. The transformation was accomplished by the direct reductive amination of 2-(diphenylphosphino)benzaldehyde 266 and \( N,N',N' \)-trimethylethylenediamine 271 in dichloromethane, employing sodium triacetoxyborohydride as the reducing agent and acetic acid as the proton source. The mixture of these components was stirred at room temperature for 4 hours, after which \(^1\)H and \(^{31}\)P NMR spectroscopic analyses showed the complete conversion of aldehyde to a new species at \( \delta_{P} = -17.8 \) ppm (C\(_6\)D\(_6\)). Flash chromatography, using a basic triethylamine/acetone mixture as eluting solvent, allowed the separation of the product from the reaction mixture and ligand 272 was obtained in high yield. Complexation was accomplished in a straightforward manner as before using [RuCl\(_2\)(DMSO)\(_4\)] as metal precursor, and flash chromatography of the crude product yielded analytically pure complex 265 for use in catalysis. Complex 265 appeared to be somewhat unstable in solution in acetone and column fractions needed to be concentrated immediately to give pure material.

Complexation was again indicated by the downfield shift of the signal in the \(^{31}\)P NMR spectrum to \( \delta_{P} (\text{CDC}_3) = +49.7 \) ppm and the characteristic pattern of signals corresponding to inequivalent DMSO methyl groups in the \(^1\)H NMR spectrum (CDCl\(_3\)) at 2.80 and 2.40 ppm. Accurate mass analysis on the molecular ion was not possible for this complex despite being identified in low resolution studies. However, it was possible to obtain accurate mass for the fragment \([ \text{M-DMSO-Cl} ]^+\), a common fragmentation mode for such complexes.

\[
\text{Scheme III-5} \quad \text{The synthesis of complex 265, the trimethylated derivative of complex 265. Reaction conditions: 2-(diphenylphosphino)benzaldehyde 266 (1 eq.), } \quad N,N',N' \quad \text{trimethylethylenediamine 272 (1 eq.), NaBH(OAc)}_3 (1.5 \text{ eq.), AcOH (3 eq.), DCM; (ii) 273 (1 eq.), [RuCl}_2(DMSO)\_4] (1 eq.), THF, } \mu_w, 120^\circ C, 20 \text{ min.}
\]
Each of the new complexes were used in subsequent kinetic studies as analytical pure material, together with pure samples of catalyst (\textit{R,R})-174 which was prepared according to the original procedures.\textsuperscript{3}

3.1.2 Hydrogenation of \textit{\alpha,\alpha,\alpha}-Trimethylacetophenone

It was found that each complex – the original catalyst (\textit{R,R})-174, the achiral derivative 263, and the di- and tri- methylated derivatives 264 and 265 respectively – all hydrogenated the bulky ketone 165 quantitatively within 16 hours at 50\textdegree C and 50 bar hydrogen pressure, with a 0.5 mol\% base loading. These initial findings were intriguing as it is generally accepted that hydrogenation with related Noyori catalysts of the type [RuCl\textsubscript{2}(\textit{P^\textit{P}})(\textit{N^\textit{N}})] requires a terminal amine functionality to be productive, and the same was anticipated to be true for the [RuCl\textsubscript{2}(\textit{P^\textit{N^\textit{N}}})L] system.

Kinetic analysis of the hydrogenation of \textit{\alpha,\alpha,\alpha}-trimethylacetophenone using each of the catalysts was undertaken using data obtained from specialist pressure equipment whereby the hydrogen consumption was measured over the course of the reaction. As hydrogen gas was consumed in the reaction vessel, it was replaced from a linked burette containing an elevated hydrogen pressure, separated from the main vessel by a non-return valve, thus maintaining the desired pressure in the reaction vessel. The decrease in hydrogen pressure in the burette ‘reservoir,’ corresponding to that uptaken by the reaction mixture, was monitored using an electronic probe and visualised through Picolog software.

Prior to commencing each experiment, it was necessary to check the system for the presence of leaks, due to the high pressures typically involved. A control experiment was thus carried out before each experiment, over a period of no less than one hour, to make sure no hydrogen was ‘consumed,’ i.e. leaked from the system, at the desired pressure and temperature. Once the system was ascertained to be leak-free, the reaction mixture – composed of the requisite catalyst, the ketone substrate and isopropanol under a nitrogen atmosphere – was first injected with potassium \textit{tert}-butoxide to initiate the reaction, then immediately transferred to the autoclave (depressurised to allow transfer of the reaction mixture, under a hydrogen atmosphere), which was subsequently repressurised. Experiments were carried out with 70 bar pressure of hydrogen gas in the autoclave, and an initial pressure of 100-120 bar hydrogen gas in the burette. This was found to be optimal conditions for the comparison of the activity of the
four catalysts. Measurement of hydrogen consumption was commenced immediately after repressurisation with hydrogen and continued until no more hydrogen was consumed.\(^1\)

The crude data for hydrogen consumption was normalised by assuming 100% conversion of ketone to alcohol product at maximum hydrogen uptake, and this was checked by \(^1\)H NMR spectroscopy of the crude reaction mixture. Crude reaction profiles of conversion versus time allows a qualitative comparison of each of the four catalysts used in this study, and from such plots average initial turnovers frequencies were abstracted for a quantitative comparison. Processing of the crude data allowed the reaction rate to be plotted over the course of the reaction profile. This gave more clear insights into individual events of the catalytic cycle, i.e. the induction period of each catalyst, the point at which maximum TOF is reached and its magnitude, and the point at which catalyst decomposition becomes evident. To give an approximation of reaction order with respect to substrate concentration, and the rate constant for each reaction, the data were also processed as ‘graphical rate equations’ as proposed by Blackmond in her work on reaction profile kinetic analysis.\(^5\) The assignment of reaction order was substantiated by the classical fitting to the requisite rate equation.\(^6\)

The unprocessed reaction data for hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone, together with average initial turnover frequencies for each of the four complexes are presented in Figures III-2 and III-3. Comparison of the performance of each catalyst shows that the original catalyst \((R,R)-174\) turns over substrate quickest with the reaction complete in 50 min with an initial average TOF of 350.46 mol prod.mol cat\(^{-1}\)h\(^{-1}\). This is in good agreement with a previous limited study which showed the reaction to be complete in approximately 40 min under similar conditions.\(^4\)

\(^1\) Although theoretically the reaction may have commenced prior to pressurisation with hydrogen due to transfer hydrogenation processes, these were deemed negligible as previous work has shown pressure hydrogenation to be the dominant factor in this system.\(^4\) All attempts were made to ensure quick transfer of the reaction mixture to the autoclave immediately once potassium tert-butoxide solution was added to initiate the reaction.

\(^\) No product was observed in the absence of catalyst.
There is a significant drop in activity going from catalyst \((R,R)-174\) to its achiral variant catalyst \(263\). The reaction goes to completion in around 5.6 hours, nearly 7 times longer than catalyst \((R,R)-174\), and turns over at 106.27 mol prod.mol cat\(^{-1}\).h\(^{-1}\). The decrease in productivity going from catalyst \((R,R)-174\) to catalyst \(263\) suggests importantly that the shape of the catalyst, and perhaps the geometry at the ruthenium centre, has a very significant influence on catalyst productivity (this will be discussed more in chapter IV). Unpublished work by Fuentes and Clarke has also demonstrated that productivity is diminished even further by substituting the 2 carbon backbone of catalyst \(263\) for a 3 carbon backbone, further supporting the proposition that a well-defined geometry at ruthenium is important for productivity. These observations suggest that if an N-H bond (whether it be secondary or terminal) is crucial for productivity then its orientation, controlled by the geometry around ruthenium, is also salient.

Replacing the NH\(_2\) on complex \(263\) for a NMe\(_2\) group (catalyst \(264\)) gives a catalyst with very similar average initial TOF (114.66 mol prod.mol cat\(^{-1}\).h\(^{-1}\)). However, this catalyst takes longer to reach completion (7.8 h, off-scale), likely due to catalyst decomposition events. The similarity of the reaction rates of catalyst \(263\) and \(264\), suggest that a terminal NH\(_2\) is not of critical importance to turnover. This is surprising due to the fact that Noyori states that a terminal NH\(_2\) group is crucial for activity in hydrogenation with the closely related \([RuCl_2(P^P)(N^N)]\) system.\(^7,8\) These observations cast significant doubt upon the primary amine-assisted transition state that would have seemed likely with \([RuCl_2(P^N^N)L]\) catalysts and point toward the secondary NH component being important to productivity.

Of most surprise, was that catalyst \(265\), containing no N-H containing groups at all for association with an incoming substrate, should catalyse hydrogenation of unfunctionalised ketones. The premise of Noyori’s work was that in order for such a reaction to take place, a secondary binding point, i.e. a N-H group to form a hydrogen bond, must be available, thus orienting the substrate in the correct manner for successful transfer of hydride. Despite this, the trimethylated catalyst \(265\), successfully catalysed the hydrogenation of \(\alpha,\alpha,\alpha\)-
trimethylacetophenone, albeit after a prolonged reaction time compared to the catalysts containing hydrogen bond donors. The reaction was complete after 18.6 hours (offsce).

3.1.3 Kinetic Analysis of Hydrogenation with Catalyst (R,R)-174

More detailed kinetic analysis of the hydrogenation of \( \alpha, \alpha, \alpha \)-trimethylacetophenone with each catalyst provided further information about the reaction profile, in particular individual events that make up the catalytic process. Kinetic analysis of the reaction using catalyst (R,R)-174 is presented in Figure III-4. Scrutiny of the reaction rate over time (Figure III-4 (c)), constructed from the data in plots (a) and (b), shows that the reaction rate increases to a maximum around 600 s (20% of the total reaction time) after initiation of the reaction. By referring back to graph (a), the maximum turnover frequency can be abstracted by differentiation of the curve around this point and was shown to be 655 moles of product per mole of catalyst per hour. Although this is two orders of magnitude slower than the best [RuCl\(_2\)(P\(^n\)P)(N\(^n\)N)] catalysts in the hydrogenation of acetophenone,\(^7,8\) it is worth reiterating that such catalysts are practically inactive for the hydrogenation of \( \alpha, \alpha, \alpha \)-trimethylacetophenone. Graph (c) also presents clearly an induction period in the first 600 s of the reaction as the reaction rate gradually rises towards its maximum. It is believed that this induction period involves the formation of ‘real’ catalyst from the precatalyst (R,R)-174. The nature of the ‘real’ catalyst will be discussed further in section 3.4.

Processing the data as a graphical rate equation (graph (d)) gives further kinetic information about the reaction. Excluding the induction period, it can be seen that the reaction follows positive order kinetics, with the rate increasing as substrate concentration increases. The data has a good fit to the first order integrated rate equation (graph (e), \( k = 0.002 \) s\(^{-1}\), \( R^2 = 0.99 \)). We can say that the reaction with catalyst (R,R)-174 is following pseudo-first order kinetics, if we incorporate the catalyst concentration, base concentration and hydrogen concentration – which are all assumed to be constant throughout the reaction – into the rate constant. The rate law for such reactions, if we assume that the reaction is practically irreversible due to the abundance of isopropanol to take part in the reverse reaction, takes the form:

\[
\frac{d[substrate]}{dt} = k_1[substrate][cat]^{-1}[base]^{-1}[H_2]^{-2}k_2
\]  

The operation of first order kinetics is insightful as it suggests that the reaction is limited by an event involving the substrate, and not by the harnessing of molecular hydrogen. This suggests
that either the association of the substrate with the catalyst, the transfer of the hydride to the substrate, or the release of the substrate after hydride transfer is implicit is limiting the reaction.

3.1.4 Kinetic Analysis of Hydrogenation with Catalyst 263

By conducting similar kinetic analysis on the hydrogenation of $\alpha,\alpha,\alpha$-trimethylacetophenone using the achiral derivative 263, it can be seen that the reaction profiles are very similar, albeit progressing more slowly towards completion (Scheme III-5).
Processing of the data in graphs (a) and (b) gives the plot of rate against time shown in graph (c). From this we can see that the maximum rate is achieved after approximately 2000s and the TOF at this point can be calculated, as before, to be 652 mole product per mole catalyst per hour. This is broadly similar to the maximum rate achieved by the original catalyst \((R,R)-174\). However, it can be clearly seen that a longer induction period is involved (first 2000s) and the
reaction takes longer to proceed to completion. This implies that the shape of the catalyst, and geometry around Ru, are important both during the induction period, i.e. for formation of the real catalytic species, and in catalysis itself.

Observing the graphical rate equation (graph d), it can be seen that positive order kinetics are being followed and the data has a good fit to the first order rate equation \( k = 0.0003 \text{ s}^{-1}, R^2 = 0.98 \), bearing in mind previous assumptions. We can consider catalyst 263 as also following the rate law set out in equation (1). These results suggest that like catalyst \((R,R)-174\), the rate of reaction with catalyst 263 is limited by an event involving the ketone substrate. Further to this, since similar kinetics appear to be observed (suggesting a similar reaction mechanism), this supports our proposition that the shape of the catalyst and geometry around Ru is important for the productivity of such catalysts as the rate constant for the reaction is roughly one order of magnitude less compared to catalyst \((R,R)-174\).

### 3.1.5 Kinetic Analysis of Hydrogenation with Catalyst 264

Kinetic analysis was also carried out for the reaction with the dimethylated complex 264. Observing the plot of rate versus time (Scheme III-6, graph (c)), constructed from data in graphs (a) and (b), it can be seen that the maximum TOF occurs after 2000 s and is slightly diminished compared to catalysts \((R,R)-174\) and 263, turning over at 403 mol prod.mol cat\(^{-1}\).h\(^{-1}\). The induction time of 2000s is similar to that of catalyst 263 suggesting that the presence of methyl groups on the terminal amine has no effect on the formation of the active catalyst. This plot also shows that while broadly similar rates of reaction are observed to catalyst 263 there is a dramatic drop in catalyst activity after 4000 s, perhaps due to catalyst deactivation/decomposition. Data obtained in the early part of the reaction (2000-4000 s) and the latter part (13000-28500 s) do hint at the presence of pseudo-first order kinetics (more obvious in graph (d)) and the data does have a fit to the first order rate equation albeit with a reduced \(R^2\) value. However, positive order kinetics appear to be predominant and again this suggests that the reaction is limited by an event involving the substrate.

The similarities in the behaviour of catalyst 264, containing the primary amine functionality, and catalyst 263, without such, argues that the terminal amine is not as important to productivity in this system as one would expect from knowledge of the Noyori system. Although this system is complicated by the decomposition/dramatic slowing of reaction rate, the most substantial part of the reaction behaves similar to the \(\text{NH}_2\) catalyst 263. In particular, the first 50% of the reaction is similar, which would seem to rule out demethylation of the ligand, and the \(\text{NH}_2\)
species operating. This points towards the potential involvement of the secondary amine function in a bifunctional mechanism as it would allow the well-defined transition state required both for productivity (see previous section) and for high enantioselectivity. Work in this laboratory by Fuentes and Clarke has also shown that replacing the terminal NH$_2$ in the original catalyst 174 for a hydroxyl group gives an equally efficient catalyst with marginally enhanced enantioselectivities (Table III-1), supporting this hypothesis.$^9$

![Figure III-6](image)

**Figure III-6** Kinetic analysis of the hydrogenation of $\alpha$-$\alpha$-$\alpha$-trimethylacetophenone employing complex 264. Reaction conditions: $\alpha$-$\alpha$-$\alpha$-trimethylacetophenone ($0.615$ mol L$^{-1}$), complex 264 (0.5 mol%), potassium tert-butoxide (1 mol%), iPrOH (20 mL), H$_2$ (70 bar), 70°C.
### Table III-1

Comparison of the hydrogenation of α,α,α-trimethylacetophenone with complex (R,R)-174 and (R,R)-274 (work carried out by Fuentes and Clarke). *Reaction conditions:* α,α,α-trimethylacetophenone, complex (R,R)-174 or (R,R)-274 (0.5 mol%), potassium tert-butoxide (1 mol%), tPrOH, H₂ (50 bar), 50°C, 3 h. a 2.5 mol% KO’Bu. b 5 mol% KO’Bu.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ketone</th>
<th>R=</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-174</td>
<td>81</td>
<td>Me</td>
<td>&gt;99 (99)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-274</td>
<td>81</td>
<td>Me</td>
<td>&gt;99 (99)</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-174</td>
<td>82</td>
<td>iPr</td>
<td>93</td>
<td>48 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-274</td>
<td>82</td>
<td>iPr</td>
<td>99 (97)</td>
<td>52 (S)</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-174</td>
<td>159</td>
<td>tBu</td>
<td>&gt;99 (99)</td>
<td>74 (S)</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-274</td>
<td>159</td>
<td>tBu</td>
<td>98</td>
<td>80 (S)</td>
</tr>
</tbody>
</table>

### 3.1.6 Kinetic Analysis of Hydrogenation with Catalyst 265

Finally, the hydrogenation of α,α,α-trimethylacetophenone with the trimethylated complex 265 was subjected to kinetic analysis. It can be seen by first glance at the reaction profile (Scheme III-7, graph (a)) that the reaction follows different kinetics from the preceding three catalysts, and there seems little dependency of rate upon substrate concentration. Indeed, there is a good fit of the data to the classic zero order raw equation as shown in graph (b). Although the rate remains fairly constant throughout the reaction, in the initial period it is slower with an average initial TOF of 35 mol prod.mol cat⁻¹.h⁻¹, rising to 187 mol prod.mol cat⁻¹.h⁻¹ as the reaction nears completion. This is perhaps due to an elongated induction period. The graphical rate equation shows more clearly that reaction rate is independent of ketone concentration and that the reaction likely follows pseudo-zero order kinetics. This proposal is supported by separate batch experiments carried out at different concentrations of ketone substrate. The data, presented in graph (d) also shows that the rate is independent of the concentration of the substrate. The kinetics for hydrogenation with catalyst 265, outwith the induction period, can be expressed:
\[
\frac{d[\text{substrate}]}{dt} = k_1 = [\text{cat}]^x[\text{base}]^y[H_2]^z k_2
\]

These findings suggest that hydrogenation with catalyst 265 follows a different mechanism to that employed by the catalysts containing NH hydrogen bond donors. Rather than being limited by an event involving the substrate, it is more likely that the reaction is limited by another process, perhaps by the harnessing of molecular hydrogen. This may implicate the presence of a hydrogen bond donor in the activation of hydrogen with the original catalyst (R,R)-174, as has already been suggested.

### 3.1.7 Hydrogenation with Other Catalysts with No Hydrogen Bond Donors

The observation that catalyst 265 with no hydrogen bond donors still catalyses the hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone with zero order dependence on substrate was intriguing and it was felt worthwhile exploring Noyori-type catalysts without hydrogen bond donor groups to compare their activity with catalyst 265. A search of current literature only furnished one example of a \([\text{RuCl}_2(P^\text{P})(N^\text{N})]\) catalyst which was shown to efficiently catalyse the hydrogenation of unfunctionalised ketones despite having no H-bond donors. Bergens and
coworkers reported that complexes such as 277 and 278 could catalyse the hydrogenation of acetophenone and 1'-acetonaphthone (Scheme III-6).

The small but significant e.e. values in these reactions – the correct values are published in an erratum to reference 12 - suggest that enantioselectivity is induced in a different manner to Noyori catalysts containing N-H hydrogen bond donors.

It was decided to prepare complex 285 by methods already described by the groups of Wilkinson 13 and Bergens 12 (Scheme III-7) in order to examine its behaviour in the hydrogenation of acetophenone. It was found that the final step could be more conveniently carried out using microwave assisted heating for 1 hour and subsequent crystallisation of the precipitate from dichloromethane/hexane. This gave small orange crystals which gave a single signal in the $^{31}$P NMR spectrum at +41.0 ppm (CDCl$_3$)( lit. 12 +40.9 (CD$_2$Cl$_2$)), that were of analytical purity as determined by microanalysis.

It was found that catalyst 285 was active in the hydrogenation of acetophenone - a substrate the catalysts of the type [RuCl$_2$(P^P)(N^N)] typically hydrogenate with high TOF and in high selectivity -with 91% conversion being obtained after 5.5 h, giving an average TOF of 33 mol prod.mol cat$^{-1}$.h$^{-1}$, several orders of magnitude slower than the best N-H containing catalysts. 8 This process gave a modest e.e. of 15%. The performance of complex 285 in the hydrogenation...
of acetophenone was examined at different substrate concentrations in batch experiments and, akin to hydrogenation with catalyst 265, it was found that reaction rates appeared to have no dependence upon ketone concentration (Figure III-8).

These results show that the reactions are pseudo-zero order in ketone concentration, and this is in contrast to the kinetics described for [RuCl₂(BINAP)(DPEN)] which shows pseudo-first order kinetics under similar conditions.⁵ Like in hydrogenation with catalyst 265, hydrogenation with catalyst 285 is not limited by a ketone binding/reduction process, and in terms of activity, a hydrogen activation step is the most important feature. This work also potentially opens the door to a new variety of non-NH catalysts, once potential problems with hydrogen activation are overcome.

### 3.1.8 Hydrogenation of Styrene

It was felt worthwhile exploring the activity of each of the four catalysts in the hydrogenation of substrates which are thought to operate by a different mechanism. The hydrogenation of unfunctionalised alkenes by ruthenium complexes is thought to proceed exclusively via an inner sphere mechanism whereby the alkene coordinates directly to the metal centre.¹⁵ Simple alkenes do not have hydrogen bond acceptors to form ligand-substrate interactions in the outer sphere. We therefore postulated that the presence/absence of hydrogen bond donor groups would have no effect upon the hydrogen transfer step of the hydrogenation of alkenes such as styrene. The activation of hydrogen could involve the NH functionality (and so similar ligand effects as before) or could be completely independent of the NH function since there is no longer such potential for acid/base chemistry.

It was found that hydrogenation of styrene with each of the four catalysts proceeded to full conversion within 12 hours (Scheme III-9, graph (a)). The initial and maximum turnover

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⁵ First order kinetics are observed, but at very low catalyst loadings these can become independent of ketone.¹⁴
frequencies (Graphs (b) and (c) respectively) are very similar for each of the four catalysts, with the presence or absence of NH$_2$ functionality having no effect upon reaction rate.

These results argue that the effect of the secondary NH group (and the sensitivity to ligand shape) is specific for ketone hydrogenation where an outer sphere bifunctional mechanism can take place. From this, it is likely that the alkene hydrogenation catalytic cycle shares little with that of ketone hydrogenation, with the cycle operating being relatively insensitive to ligand structure.

3.1.9 Summary

From the rigorous kinetic analysis outlined, a number of proposals can be made:

1. The shape of the catalyst/geometry at Ru is crucial for productivity in ketone hydrogenation. It has been shown that going from the original catalyst 174 to its achiral derivative 265 has a significant impact on productivity.

2. The terminal NH$_2$ is not important to productivity; the secondary N-H is implicated. Blocking the hydrogen bonding capacity of the terminal amine (catalyst 264) has negligible impact on productivity compared to catalyst 263, but blocking both the secondary and terminal amines (catalyst 265) significantly reduces productivity. The induction times are
similar for catalysts with a NH function but are elongated in the absence of a secondary amine. We propose that the secondary amine is important in the binding/reduction of the ketone substrate, which limits the rate of these reactions and this secondary amine also facilitates hydrogen activation significantly. Work carried out by Fuentes and Clarke in this group has also demonstrated that derivatives of the original catalyst containing a hydroxyl group in the place of the primary amine group, can catalyse the reduction of \( \alpha,\alpha,\alpha \)-trimethylacetophenone quantitatively in 3 hours, with enantioselectivity marginally higher than with the original catalyst. This suggests that this catalyst operates by the same mechanism as the original catalyst and supports our conclusion that the terminal amine is not responsible for catalyst productivity (or enantioselectivity) and that the secondary NH is perhaps more important.

3. **Non-NH catalysts can still catalyse hydrogenation of unfunctionalised ketones; a different mechanism is operational.** Catalyst 265 is still productive but with slower TOFs then NH containing catalyst. Rates are not limited by ketone binding/reduction suggesting that another process is severely hampered by the lack of an NH, most likely the activation of hydrogen.

4. **The ketone hydrogenation cycles using all four catalysts are likely to have a different mechanism than alkene hydrogenation, which we would suggest is a classic inner sphere hydrogenation.**

### 3.2 The Role of Base

Hydrogenation of unfunctionalised ketones using \([\text{RuCl}_2(\text{P}^\alpha\text{P})(\text{N}^\alpha\text{N})]\) catalysts is highly dependent upon base concentration. Noyori has suggested that base plays an important role not just in formation of the real catalytic species but also in accelerating the catalytic cycle itself (Chapter II, section 1.5.1). It was felt in order to get a better understanding of the mechanism of hydrogenation employing \([\text{RuCl}_2(\text{P}^\alpha\text{N}^\alpha\text{N})\text{L}]\) catalysts, it would be remiss not to include a more detailed study of concentration effects upon catalyst activity. Previous work in this group demonstrated, in a limited study, that at least two equivalents of potassium tert-butoxide were required in order for the reaction with catalyst \((R,R)-174\) to proceed at 50°C and 50 bar hydrogen pressure. Using less than 2 equivalents resulted into no reaction occurring. This suggests that the 2 equivalents of base are required to form the real catalysts from precatalyst
due to the apparent non-linear relationship between productivity and base concentration at base concentrations less than 2.

It was felt worthwhile to examine the behaviour of the reaction at increased base concentration to determine whether elevation of base has effect on the turnover of the catalytic cycle itself. Noyori observed that reaction rates increase towards a maximum when the base to catalyst ratio is 20 and suddenly drops at higher concentrations (Chapter I, Figure I-2). Hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone using catalyst \((R,R)-174\) was thus carried out with base loading in the range 2-20 equivalents per ruthenium complex, and the reaction mixture was sampled throughout the course of the reaction to determine the reaction profile (Scheme III-10).

Figure III-10 Reaction profiles of the hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone with complex \((R,R)-174\), with 2-20 equivalents of base with respect to catalyst in (a) the first 16 h and (b) the first 8 h. Reaction conditions: \(\alpha,\alpha,\alpha\)-trimethylacetophenone, complex \((R,R)-174\) (0.5 mol%), potassium tert-butoxide (1-10 mol%), \(i\)PrOH, \(H_2\) (50 bar), 50\(^\circ\)C.

From graphs (a) and (b) is can be seen that increasing the base loading from 2 to 10 equivalents per ruthenium leads to a reduction in the time taken for the reaction to go to completion. Increasing this further to 20 equivalents however results in a loss of activity and the reaction is still uncomplete after 16 hours.

A closer look at the reaction profiles using 2 and 10 equivalents indicates that pseudo-first order kinetics are still in operation and substrate concentration is still limiting turnover. Rates of reaction in the initial part of the reaction (first 20%) seem to be very similar at both base loadings but further base, beyond the two equivalents needed to form the active species, do not speed up the induction period. It appears that increasing the base loading increases turnover after the induction period, implicating base effects in the catalytic cycle itself. However, when even more base is used, 20 equivalents relative to ruthenium complex, the rate of reaction is significantly diminished. A potential explanation for these observation is perhaps that the addition of base facilitates deprotonation of a hypothetical dihydrogen complex giving active
dihydride species, but too much base hinders productive proton transfer between solvent and amido complex, stalling the catalytic cycle.

The enantioselectivity of the reaction remains unaffected by these changes in base loading. These results are insightful as not only do they give valuable clues to the mechanism of the reaction they also allow the tuning of base concentration to give higher turnover, without any effect upon the selectivity in the reaction.

3.3 Electronic Environment at the Metal Centre

It is quite likely that the electronic environment at the metal centre plays an important part in the operation of the catalytic cycle, and tuning of this could lead to more active, and perhaps more selective catalysts. Indeed, since the reaction rate is believed to be limited by an event involving ketone coordination/hydride transfer, it is plausible that rates could be enhanced by fine tuning of the electron density upon the ruthenium metal.

To get a better understanding of the effect of changing the electronic environment at the ruthenium centre, it was decided to explore the effect of electronically different substituents on the phosphorus aryl groups upon the rate of hydrogenation. [RuCl₂(P^N^N)L] catalysts with both electron-rich and electron-deficient components were targeted. The ruthenium complex (R,R)-286, somewhat deactivated by para-chloro substituents, was prepared in this laboratory by Kuntz et al (Scheme III-9). They found that this complex was totally inactive in hydrogenation of α,α,α-trimethylacetophenone, even at elevated temperature and pressure.

It was decided to focus on preparing an electron-rich derivative of this complex and testing its performance in hydrogenation. With the requisite 2-(diarylphosphino)benzaldehyde 287 in hand (prepared by Wawrzyniak and Clarke), the ruthenium complex was prepared in a analogous manner to the published route into these compounds (Scheme III-8). The ligand could only be prepared in 80% purity due to the sensitive nature of the electron rich phosphine, thus it was complexed immediately and after column chromatography, analytically pure complex (R,R)-290 was obtained. The usual characteristics of the complexed ligand were observed.
Complex (R,R)-290 hydrogenated α,α,α-trimethylacetophenone cleanly at 50°C and 50 bar H₂ pressure (Scheme III-9). Kinetic analysis of the reaction suggests that hydrogenation is less positive order, with respect to ketone concentration, than the parent catalyst (R,R)-174, and is perhaps tending towards zero order kinetics (Figure III-10). This was checked by experiments at different substrate concentrations that showed that the reaction rate was indeed dependent upon ketone concentration and is more likely following pseudo-first order kinetics (Figure III-11), albeit proceeding slower than the original catalyst (R,R)-174. Enantioselectivity is practically identical using both catalysts.

Scheme III-9 Hydrogenation with catalysts (R,R)-286 and (R,R)-290. General conditions: ketone 159, catalyst (R,R)-286 or (R,R)-290 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂ (50 bar), 50°C, 16 h.
The observation that pseudo-first order kinetics are still in operation in hydrogenation with catalyst (R,R)-290, and that enantioselectivities are almost identical to those obtained with catalyst (R,R)-174, suggest that a similar mechanistic pathway exists for both species. The decrease in activity, with the half-life of catalyst (R,R)-290 almost double that of the original catalyst (R,R)-174, suggests that the increase in electron density at the metal centre, brought about by the electron-donating substituents upon the phosphorus aryl ring, retards the rate limiting step, believed to involve either the coordination of the ketone substrate or transfer of the hydride to the ketone.

The observations made here, accompanied by that made by Kuntz et al, suggest that a fine balance between electron rich and electron poor properties is required in the most efficient catalysts, and the best to date is the original catalyst (R,R)-174. More subtle modification of the phosphorus substituents is needed to find the optimal electronic environment but this is outwith the scope of the current work. It is gratifying however that enantioselectivity remains similar when using catalysts (R,R)-174 and (R,R)-290 as it would be expected that further modification of the electronic properties of the ligand could be carried out with erosion of enantioselectivity.

3.4 Comparisons with Transfer Hydrogenation

Much of the original work looking at the mechanism of ruthenium-catalysed hydrogenation of unfunctionalised ketones was conducted on the related transfer hydrogenation system. Such systems, despite employing a different hydride source, such as isopropanol or a formic acid/triethylamine mixture, were thought to transfer the hydride to the ketone substrate through the same transition state. Not many catalysts have been identified as being able to catalyse both
transfer and H₂-hydrogenation however, suggesting different pathways leading to the formation of the real catalyst. Some catalysts, including the present system, have the capability of catalysing both. Previous work in this group by others, and that described in chapter II, has shown that catalyst \((R,R)-174\) can hydrogenate a variety of substrates with enantioselectivities broadly similar to those obtained by H₂-hydrogenation in rapid time using microwave heating. This indeed implies that a similar transition state exists, between substrate and catalyst, in the hydride transfer step when using the present catalytic system in both transfer and H₂-hydrogenation.

The microwave-accelerated transfer hydrogenation protocol does not so easily lend itself to kinetic investigation, but conversion to product using the four catalysts – \((R,R)-174, 263, 264\) and \(265\) – was compared after 20 and 40 minutes of heating at 90°C. It was found that all four catalysts are active in the microwave-assisted transfer hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone to some degree (Figure III-12). Like in H₂-hydrogenation, the original catalyst \((R,R)-174\) was superior in terms of productivity, with complete conversion to product in around 20 minutes. The achiral derivative \(263\) catalyses the reaction with diminished rate although goes to full conversion within 40 minutes. The absence of terminal NH₂ groups appears to have a larger effect. The dimethyl catalyst \(264\) is significantly less productive than catalyst \(263\) and the trimethyl derivative \(265\) is slightly slower again.

More firm conclusions would require further kinetic investigation but this was felt to be of little value. However, these results suggest that the terminal NH₂ is more important to productivity in the transfer hydrogenation system than in the H₂-hydrogenation system.

![Figure III-12](image)

**Figure III-12** The transfer hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone employing complex \((R,R)-174\), complex \(263\), complex \(264\) and complex \(265\) (8 individual experiments). Reaction conditions: \(\alpha,\alpha,\alpha\)-trimethylacetophenone (1 mmol), Ru complex (1 mol%), potassium tert-butoxide (2 mol%), iPrOH (3 mL), μW, 90°C.

**This is in agreement with work by Fuentes and Clarke\(^{10}\) that has shown that the [RuCl₂(P^N^O)L] system is considerably less active in transfer hydrogenation (non microwave-assisted) than their corresponding [RuCl₂(P^N^N)L] catalysts, indicating that the terminal NH₂ is salient to productivity in the transfer process.**
3.5 Conclusions

We have drawn a number of conclusions from our work which will assist us with the rational design of novel, more active, more selective catalysts based on the original ligand design. For good activity in H₂-hydrogenation, a catalyst needs a well-defined shape with the geometry at ruthenium perhaps also being salient. The vicinal nature of the two amine coordinating group has also been shown to be required for productive catalysis. The secondary amine seems to facilitate hydrogen activation making this step facile. The rate limiting step of the reaction is probably the ketone coordination/hydride transfer step and the transition state formed between the secondary N-H and a ketone substrate is likely to be important in determining the enantioselectivity of the alcohol product, and a potential model is represented in Scheme III-11.

![Scheme III-11 A potential model for the origin of enantioselectivity in hydrogenation with [RuCl₂(P^N^N)L] catalysts.](image)

We have found the optimal base concentration for efficient catalysis, noting that at least 2 equivalents of base are required for efficient catalysis and above 10 equivalents appears to retard the reaction rate. A fine balance of electronics at the metal centre is required in order for the best rates, with electron poor metal centre leading to a complete loss of activity. These are all crucial considerations in rational tuning of the catalyst to produce more efficient catalysts, which shall be discussed in the next chapter.

3.6 References

Chapter IV

Rational Design of Novel [RuCl₂(P^N^N)L] Catalysts

Our knowledge of the present system, as well as the closely related [RuCl₂(P^P)(N^N)] system, combined with the detailed kinetic studies described in Chapter III, put us in a position to rationally design new catalysts, with the potential for enhanced productivity and selectivity, and for hopefully accessing some new, previously inaccessible, chiral alcohols. Fine tuning of the ligand structure has the potential to create more selective and highly enantioselective catalysts for a range of sometimes difficult substrates. In this chapter, the preparation of a number of rationally designed, novel catalytic systems are described, and their performance in catalysis scrutinised. To allow this work to take place, a facile screening method was developed, and this will first be described.

4.1 In situ screening method

It was highly desirable to develop an in situ protocol which could be used to analyse the performance of potentially useful P^N^N ligands in hydrogenation. Often such ligands are very air sensitive, forming the phosphine oxide rapidly, even after minimal exposure to air. Therefore, the use of the protected form of such ligands, i.e. their borane adduct, directly in catalysis was felt to be useful. The in situ deprotection and complexation of the ligand would hopefully lead to the same catalytic species. Conveniently, it was known that heating phosphine-boranes in the presence of alcoholic solvents can lead to the deprotection of phosphine-boranes. As isopropanol is the reaction solvent it was anticipated that this could be achieved in a straightforward manner before subsequent complexation and catalysis in situ.

A number of ruthenium precursors were screened in the hydrogenation of α,α,α-trimethylacetophenone with the borane protected form of the original ligand, (R,R)-293 (Table IV-1). A solution of the phosphine borane 293 and the ruthenium precursor in isopropanol was first stirred at rt, before addition of α,α,α-trimethylacetophenone and potassium tert-butoxide. The reaction mixture was then placed under 50 bar hydrogen pressure and stirred for 16 hours at 50°C.

† This was prepared by adding borane.THF complex dropwise to a solution of the original ligand in THF over a period of two hours. This gave one main broad signal in the 31P NMR spectrum at +18.3 ppm (CDCl₃), in the characteristic range for phosphine boranes. This adduct was used directly in catalysis.
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Table IV-1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ru Precursor</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl$_3$</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>2$^a$</td>
<td>RuCl$_3$</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ru(acac)$_3$</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>4$^a$</td>
<td>Ru(acac)$_3$</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>RuCl$_2$(DMSO)$_4$</td>
<td>&gt;99</td>
<td>78 (S)</td>
</tr>
<tr>
<td>6$^a$</td>
<td>RuCl$_2$(DMSO)$_4$</td>
<td>&lt;5</td>
<td>-</td>
</tr>
</tbody>
</table>

Table IV-1 The in situ hydrogenation of $\alpha,\alpha,\alpha$-trimethylacetophenone using a ruthenium precursor and phosphine borane $(R,R)$-293. General conditions: $\alpha,\alpha,\alpha$-trimethylacetophenone 159, Ru precursor (0.5 mol%), Ligand $(R,R)$-293 (0.7 mol%), KO'Bu (1 mol%), tPrOH, H$_2$ (50 bar), 50°C, 16 h. $^a$ Without KO'Bu.

It was found that efficient hydrogenation was only apparent when the ruthenium precursor $[\text{RuCl}_2\text{(DMSO)}_4]$ was employed in the presence of base. Gratifyingly, similar high levels of stereoinduction to hydrogenation using the preformed catalyst were obtained, indicating that the same active catalyst was being formed. The relative activities of the two systems were not measured in this study, but these results were pleasing as the use of $[\text{RuCl}_2\text{(DMSO)}_4]$ as the precursor led to quantitative conversion of ketone to product within a practical timescale, and thus this protocol can be considered as a useful alternative to the use of well-defined catalysts.

4.2 Novel Catalysts by Modification of Phosphorus Substituents

4.2.1 P-Chiral Phosphine Component

From our knowledge of the mechanism of hydrogenation using $[\text{RuCl}_2(P^N^N)L]$ catalysts, a working model for the origin of enantioselectivity has been constructed and was presented in Chapter III. The hydride transfer step is believed to be aided by a hydrogen bonding interaction between the secondary N-H group of the ligand and the carbonyl oxygen of the incoming ketone (Chapter III, Scheme III-11). The transition state can be visualised more easily by superimposing the incoming ketone substrate upon the molecular structure of catalyst $(R,R)$-
174. derived from X-ray diffraction studies. The representation shown in Figure IV-1 illustrates the transition state which is believed to lead to the major enantiomer in the hydrogenation of α,α,α-trimethylacetophenone ((S)-enantiomer), which makes use of hydrogen bonding interactions between the substrate and the secondary N-H component of the ligand structure. We cannot categorically say which interactions lead to the preferred facial selectivity (although potential clashes between the bulky ketone R group and the diamine backbone is possible), however from the model it can be seen that tweaking of the phosphorus substituents that are in close proximity to the ‘active site’ of the catalysts, could have a large effect upon the enantioselectivity of the reaction.

In order to probe the effect of placing sterically different phosphorus substituents in close spacial proximity to the mechanistically important secondary N-H, a number of P-chiral P^N^N ligands were trialled in the hydrogenation of unfunctionalised ketones. These ligands, available as phosphine-boranes, were prepared by Dr Nina Kann and Kristian Andersson at the Chalmers University in Gothenburg, Sweden, who specialise in the synthesis of P-chirogenic molecules. The ligands were employed in the in situ hydrogenation protocol described previously, and their performance in the reduction of acetophenone and α,α,α-trimethylacetophenone examined (Table IV-2).

It was interesting to observe similar levels of enantioselectivity in the hydrogenation of α,α,α-trimethylacetophenone 159 when employing ligand (R,R),(S)-294 in combination with [RuCl₂(DMSO)₄], as with the original P^N^N catalyst (R,R)-174. It appears that changing the linker between the diamine component and the phosphine component to a simple three-carbon alkyl chain has no effect on enantioselectivity. The ortho-methyl group on the phosphorus aryl substituent, expected to be in close spacial proximity to the mechanistically important secondary N-H, has little observable effect on the enantioselectivity of this reaction. However, quite interestingly, enantioselectivity is significantly enhanced in the hydrogenation of acetophenone, relative to that of hydrogenation with the original catalyst (R,R)-174, in which racemic material
was produced. The configuration of product observed suggests that the bulkier \( o \)-OMe group of ligand \((R,R)(S)-294\) creates a clash between phenyl group of acetophenone and the phosphorus substituents that clearly is not present in the parent catalyst. If we remove the steric bulk at this position, i.e. replace the \( o \)-OMePh group for a simple methyl substituent, ligand \((R,R),(S)-295\), then enantioselectivity is considerably eroded for both substrates, supporting this proposal. Incorporating the more bulky cyclohexyl substituent upon phosphorus, as in ligand \((S,S),(S)-296\), elevates enantioselectivity for both substrates once again but activity decreases, possibly due to increased steric congestion at the active site.

These results suggest that modifying the substituents on phosphorus, particularly those close to the mechanistically important secondary N-H, has a significant effect on the enantioselectivity of hydrogenation. It was envisaged that strategic placement of steric bulk upon the phosphorus substituents could lead to enhanced enantioselectivity in the hydrogenation of such unfunctionalised ketones.
4.2.2 Bulky Phosphorus Substituents

It was thought that the use of ligands \((R,R)-297\) and \((R,R)-298\) (Scheme IV-1) would show particularly enhanced enantioselectivity in the reduction of acetophenone and \(\alpha,\alpha,\alpha\)-trimethylacetophenone, since increased steric bulk on the phosphine aryl substituents proximal to the catalyst’s ‘active site’ upon complexation, would increase the preference for the phenyl ring of the substrate to be on the opposite side of the catalyst to the phosphine group.

\[
\text{Scheme IV-1 P}^\text{N}^\text{N} \text{ ligands containing bulkier aryl substituents.}
\]

In was envisaged that both of these ligands could be prepared by condensation of the requisite 2-(diarylphosphinobenzaldehyde with \((R,R)\)-diaminocyclohexane. The aldehyde precursor to \((R,R)-297\) is commercially available, however, the precursor to \((R,R)-298\) needed to be first prepared. This was achieved by adapting a procedure previously developed in this group for certain other diarylphosphinobenzaldehydes, by the reaction of the freshly prepared lithio-derivative of 2-bromobenzaldehyde ethylene acetal 299 with a 10-fold excess of phosphorus trichloride in tetrahydrofuran at -78°C to give the dichloride species 300 (Scheme IV-2). The solvent and excess phosphorus chloride were then removed before the residue was redissolved in THF immediately and reacted with two equivalents of (3,5-di-\text{tert}-butylphenyl)lithium, freshly prepared from 3,5-di-\text{tert}-butylbromobenzene and \(n\)-butyllithium. This furnished the protected aldehyde 301 after column chromatography, in moderate yield, which was easily converted to the aldehyde 302 by treatment at reflux with \(p\)-toluenesulfonic acid in acetone for 2 hours, in a high yielding process. After column chromatography, this gave analytically pure aldehyde 302 as a bright yellow solid.
Ligands 297 and 298 were then prepared by dropwise addition of a solution of the requisite aldehyde in degassed ethanol to a dilute solution of (R,R)-diaminocyclohexane 294, also in degassed ethanol. It was ensured that diamine 294 was present in a suitably large excess to prevent the undesired difunctionalisation of the diamine. This furnished the imine species after stirring for 2-5 hours. Subsequent reduction with sodium borohydride yielded ligands (R,R)-304 and (R,R)-305 after careful work-up in an inert atmosphere. The reactions were monitored using $^1$H and $^{31}$P NMR spectroscopy and the key signals are shown in Table IV-3. Ligand (R,R)-298 could only be obtained in ~60% purity due to the sensitivity of the phosphine and thus full characterisation data could not be obtained. Despite this, both ligands were complexed with [RuCl$_2$(DMSO)$_4$] following the usual microwave-assisted protocol and analytically pure material was obtained after column chromatography. Complexation was confirmed by the downfield shift of the signal in the $^{31}$P NMR spectrum as well as the downfield shifts of the CHN protons in the $^1$H NMR spectrum. The remaining coordinated DMSO ligand becomes desymmetrised by the process and individual signals are seen for the protons attached to each methyl group. The methyl/tert-butyl groups upon the phosphorus aryl substituents also become inequivalent upon complexation due to restricted rotation/exchange between face-on/edge-on rings.
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Table IV-3 Synthesis of bulky catalysts (R,R)-297 and (R,R)-298. General conditions: (i) 303 or 302 (1 eq.), (R,R)-diaminocyclohexane (3 eq.), EtOH, 45°C → rt, 2 h; NaBH₄ (4 eq.), EtOH, rt, 8 h; (ii) (R,R)-304 or (R,R)-305 (1 eq.), [RuCl₂(DMSO)₄] (1 eq.), THF, μw, 120°C, 20 min. Table shows NMR signals corresponding to each species formed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Complex</th>
<th>δₚ(CDCl₃) (aldehyde)</th>
<th>δₚ(C₆D₆) (CH=N, imine species)</th>
<th>δₚ(C₆D₆) (amine species)</th>
<th>δₚ(C₆D₆) (Ru complex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-297</td>
<td>-13.4</td>
<td>9.52 (d, J 4)</td>
<td>-12.2</td>
<td>-15.7</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-298</td>
<td>-11.8</td>
<td>9.50 (d, J 4)</td>
<td>-8.6</td>
<td>-13.5</td>
</tr>
</tbody>
</table>

The relative performance of each catalyst in the hydrogenation of model substrates 81 and 159 was examined (Table IV-4). Pleasingly, increasing the steric bulk on the phosphine substituents led to increased enantioselectivity in the hydrogenation of both acetophenone 81 and α,α-dimethylpropiophenone 159 as predicted. This effect was more pronounced in the reduction of acetophenone with catalyst (R,R)-298, yielding the (S)-enantiomer of phenethyl alcohol in up to 60% e.e. despite the original catalyst (R,R)-174 only giving racemic material. However, an undesirable consequence of this was the accompanying decrease in activity brought about by increased steric bulk on the catalyst structure. Quantitative conversion to product employing catalysts (R,R)-297 and (R,R)-298 could only be accomplished by elevation of temperature in the hydrogenation of α,α,α-trimethylacetophenone. This resulted in the erosion of enantioselectivity in the case of hydrogenation with the bulky catalyst (R,R)-298.

Although highly efficient catalysts exist for the hydrogenation of acetophenone 81 and derivatives, and the preparation of further catalysts was not our aim, these results demonstrated that the catalyst scaffold can be tuned for particular substrates. A significant increase in enantioselectivity was observed from 0% e.e. when using the original catalyst to 60% e.e. when the bulky derivative (R,R)-298 was employed.
Table IV-4 The effect of increasing steric bulk on the phosphine component of the ligand structure upon hydrogenation of ketones 81 and 159. General conditions: ketone 81 or 159, catalyst (R,R)-297 or (R,R)-298 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂ (50 bar), 50°C, 16 h. a 70°C, b 70°C, 24 h. c 90°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ketone</th>
<th>R=</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-174</td>
<td>81</td>
<td>Me</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-297</td>
<td>81</td>
<td>Me</td>
<td>&gt;99</td>
<td>35 (S)</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-298</td>
<td>81</td>
<td>Me</td>
<td>24</td>
<td>56 (S)</td>
</tr>
<tr>
<td>4a</td>
<td>(R,R)-298</td>
<td>81</td>
<td>Me</td>
<td>84</td>
<td>60 (S)</td>
</tr>
<tr>
<td>5b</td>
<td>(R,R)-298</td>
<td>81</td>
<td>Me</td>
<td>&gt;99</td>
<td>58 (S)</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-174</td>
<td>159</td>
<td>1Bu</td>
<td>&gt;99</td>
<td>74 (S)</td>
</tr>
<tr>
<td>7</td>
<td>(R,R)-297</td>
<td>159</td>
<td>1Bu</td>
<td>&gt;99</td>
<td>77 (S)</td>
</tr>
<tr>
<td>8</td>
<td>(R,R)-298</td>
<td>159</td>
<td>1Bu</td>
<td>5</td>
<td>83 (S)</td>
</tr>
<tr>
<td>9a</td>
<td>(R,R)-298</td>
<td>159</td>
<td>1Bu</td>
<td>21</td>
<td>85 (S)</td>
</tr>
<tr>
<td>10c</td>
<td>(R,R)-298</td>
<td>159</td>
<td>1Bu</td>
<td>&gt;99</td>
<td>67 (S)</td>
</tr>
</tbody>
</table>

4.3 Novel Catalysts by Modification of Diamine Component

It has been shown that the shape of [RuCl₂(P^N^N)₂L] catalysts, and the geometry at the ruthenium centre, are highly important to catalyst productivity. A vicinal diamine is preferable and maximum TOF is obtained when the diamine component is locked in conformation by a cyclic carbon backbone. It is likely that this ‘locking’ of conformation orients the N-H bond in such a manner that promotes efficient interaction with an incoming ketone substrate and in such a way that the hydride can be easily transferred from the metal centre. DPEN is one of the most important chiral ligands and has been combined with many transition metals to give highly enantioselective catalysts for a range of organic transformations. It was envisaged that the complexation of DPEN to ruthenium would give a catalyst with a similar or smaller bite angle than the original catalyst (R,R)-174, as the vicinal phenyl groups would orientate themselves as far away spacially as possible after complexation, reducing the dihedral angle between the...
vicinal amine groups, creating a rigid structure around the ruthenium centre. It was felt worthwhile therefore to incorporate DPEN as the diamine component of [RuCl₂(P^N^N)L] cataysts.

Ligand \((R,R)-301\) was prepared, first by the condensation of \((R,R)-1,2\)-diphenylethlenediamine, \((R,R)-299\), (a three-fold excess in ethanol) with 2-(diphenylphosphino)benzaldehyde 266, furnishing the corresponding imine species \((R,R)-300\) after 4 hours (Scheme IV-3). The presence of the imine species was indicated by the appearance of a signal at \(\delta_P (C_6D_6) = -7.9 \text{ ppm} \) in the \(^{31}\text{P}\) NMR spectrum and a signal at \(\delta_H (C_6D_6) = 9.17 \text{ ppm} \) (d, \(J_5\)), corresponding to the \(CH=N\) proton, in the \(^1\text{H}\) NMR spectrum. Reduction of the imine with sodium borohydride resulted in the formation of species \((R,R)-301\) after stirring for 16 hours, shown by a signal at \(\delta_P (C_6D_6) = -9.6 \text{ ppm} \) in the \(^{31}\text{P}\) NMR spectrum. However, after aqueous work-up, two further species were observed, with signals at \(\delta_P (C_6D_6) = -15.9 \text{ and } -16.2 \text{ ppm} \). Due to the apparent inseparability of these species it was decided to use the crude mixture directly in the complexation reaction. This gave phosphorus containing species with signals observed at \(\delta_P (CDCl_3) = +42.4, -16.4 \text{ and } -16.9 \text{ ppm} \ (-3:1:1)\). It was believed that the species at \(\delta_P (CDCl_3) = +42.4 \) corresponded to the desired complex and indeed following column chromatography on silica, analytically pure complex \((R,R)-302\) was furnished.

![Scheme IV-3](image)

**Scheme IV-3** The synthesis of complex \((R,R)-302\). Reaction conditions: 2-(diphenylphosphino)benzaldehyde 266 (1 eq.), \((R,R)-1,2\)-diphenylethlenediamine \((R,R)-299\) (3 eq.), EtOH, rt, 4 h; (ii) \((R,R)-300\) (1 eq.), NaBH₄ (3 eq.), EtOH, rt, 16 h; (iii) \((R,R)-301\) (1 eq.), [RuCl₂(DMSO)$_4$] (1 eq.), THF, μw, 120°C, 20 min.

Pleasingly, catalyst \((R,R)-302\) was found to be active in the hydrogenation of a number of ketone substrates (Scheme IV-5). The hydrogenation of acetonophenone produced practically racemic material when employing catalyst \((R,R)-302\). However, like the original catalyst \((R,R)-174\), the new catalyst was found to be highly selective in the reduction of bulkier ketones. A meaningful but small increase in enantioselectivity was observed in the hydrogenation of \(\alpha,\alpha,\alpha\)-
trimethylacetophenone compared to the original catalyst (80% e.e. versus 74% e.e.). The enantioselectivity was slightly diminished in the reduction of the more bulky ketone 183.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Conversion (yield) [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>&gt;99</td>
<td>3 (S)</td>
</tr>
<tr>
<td>2</td>
<td>159</td>
<td>&gt;99</td>
<td>80 (S)</td>
</tr>
<tr>
<td>3</td>
<td>183</td>
<td>&gt;99</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>244</td>
<td>&gt;5</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>226</td>
<td>&gt;99</td>
<td>98a</td>
</tr>
<tr>
<td>6</td>
<td>303</td>
<td>&gt;99</td>
<td>9</td>
</tr>
<tr>
<td>7b</td>
<td>304</td>
<td>&gt;99</td>
<td>na</td>
</tr>
</tbody>
</table>

Table IV-5 Hydrogenation with the catalyst (R,R)-302. General conditions: ketone (1 eq.), catalyst (R,R)-302 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂ (50 bar), 70°C, 16 h.  

Disappointingly, catalyst (R,R)-302 was found to be practically inactive in the hydrogenation of the heteroaromatic ketone 244 despite encouraging results using catalyst (R,R)-174. However, hydrogenation of the heteroaromatic diketone 226 gave the useful alcohol product 327 in near enantiopurity. Ketones with sterically similar groups proved to be active substrates but little stereoinduction was observed. It was also demonstrated that the reduction of the achiral ketone 304 could be accomplished with good regioselectivity using catalyst (R,R)-302.

These studies show that the DPEN-derived catalyst is a viable alternative to the original catalyst and is worth screening when new hydrogenations are attempted in the future. Catalysts derived from other small bite angle chiral diamines are also well worth investigation.

### 4.4 Conclusions

This work has shown that tuning of the ligand design in [RuCl₂(PNN)L₂] systems, directed by experimental observations, can lead to more enantioselective catalysts for the hydrogenation of model substrates. We have shown that such catalysts are efficient in preparing chiral secondary alcohols in up to 98% e.e., many of which are important precursors in synthesis and of biological significance. It is anticipated that further catalyst optimization, by tuning of the
modular ligand design, has the potential to lead to very active and selective catalysts for preparing a variety of chiral secondary alcohols, based on this knowledge and current observations.

4.5 References

Conclusions and Future Work

The first aim of his work was to fully delineate the substrate scope of hydrogenation catalysed by [RuCl₂(P^N^N)] complexes. The scope of the technology was successfully extended to even bulkier substrates than those outlined in the original work. Phenyl, dimethyl phenyl ketones were shown to be reduced quantitatively using catalyst (R,R)-174 giving the corresponding alcohol in 84% e.e. Even bulkier phenyl, diethyl phenyl ketones were also hydrogenated effectively albeit in slightly lower e.e. The catalytic system was shown to be tolerant of a range of electronically different substituents upon the phenyl group of the substrate – para-OMe, -Cl and –CF₃ as well as ortho-OMe substituents – giving the corresponding alcohol quantitatively in each case whilst maintaining high levels of enantioenrichment in the product (69-80% e.e.). The system was also tolerant of heteroaromatic functions – pyridyl, furanyl and isoxazolyl bulky ketones were all hydrogenated quantitatively with good to excellent enantioselectivity (67-98% e.e.), giving products often unobtainable by other methods. It was demonstrated that analogues of synthetically useful chiral alcohols with adjacent gem-dimethyl groups could be prepared in good enantioselectivity using catalyst (R,R)-174. We also successfully showed that the current technology could be employed to prepare nitrile functionalised chiral secondary alcohols in 74% e.e. that could be transformed further into chiral lactones, a class of compound that is important in the fragrance industry, and despite its ubiquity has not previously been accessible through asymmetric hydrogenation/lactonisation techniques.

The current system has been shown to be of great use as a synthetic tool, and a complimentary method to the use of the Noyori catalysts. Although the current research aimed to illustrate the wide scope of potential substrates - and the wealth of chiral products that can potentially be furnished - future work would aim to demonstrate that the current system could be used in the preparation of current commercial targets, showing that this methodology can fulfil its potential in the industrial synthesis of chiral molecules.

The design of second generation [RuCl₂(P^N^N)] catalysts was also an important aim of this work, to increase the activity and selectivity of catalysts. We decided that a good way of doing this was using a rational approach based on a greater understanding of the mechanism of the system. We felt that knowledge of the role of the diamine component of the ligand, and whether interactions between the ligand and the substrate in hydrogenation exist, was key to future catalyst design. Achiral derivatives of the original [RuCl₂(P^N^N)] catalyst were prepared: one containing a simple two carbon backbone between the primary and secondary amine...
components, another analogous to the first but with the primary NH$_2$ replaced with an NMe$_2$ group, and a third complex analogous to the second but with the secondary amine group also replaced with NMe. Kinetic analysis of each catalyst, including the original, in the hydrogenation of $\alpha,\alpha,\alpha$-trimethylacetophenone, gave a number of valuable insights. Firstly, for good activity the catalyst needs a well-defined shape, with the geometry around ruthenium being important. Secondly, the presence of a terminal NH$_2$ group is not as salient as the presence of a secondary N-H for good activity. Thirdly, the absence of the terminal and secondary amine functions dramatically diminished activity although hydrogenation still progresses slowly. In the hydrogenation of styrene (where no substrate/ligand interactions are likely) there were no differences in the reaction profile of each catalyst. These observations allowed us to postulate that hydrogenation using the [RuCl$_2$(P$^N$N$^N$)] system proceeds via an interaction between the secondary N-H component and the incoming substrate, and that the secondary amine is particularly good at promoting hydride activation.

The mechanistic evidence gave us a more focussed, rational approach for the design of new catalysts: consulting the possible transition state, modification of the ligand phosphine substituents would likely have an effect on enantioselectivity. Indeed, 3,5-di-substitution of the phosphine aryl groups led to more enantioselective hydrogenation in many cases. This was most evident in the hydrogenation of acetophenone, where the incorporation of 3,5-di-tert-butyl groups led to an increase in enantioselectivity of 60% compared with hydrogenation using the original catalyst, which furnished racemic material. An unfortunate consequence of the increase in bulk on the phosphorus substituents, however, was a reduction in activity in the hydrogenation of more bulky compounds.

Our mechanistic work also pointed to the need of catalysts for vicinal diamines with a well defined geometry around the metal centre. A catalyst based on the diamine DPEN, was prepared. Such a diamine is likely to have a well defined conformation when bound to a metal centre due to the repulsion between adjacent phenyl groups, locking it in its conformation. The new catalyst was found to be active in the hydrogenation of several substrates, with increased enantioselectivity compared to the diaminocyclohexane catalysts for a number of substrates (for example 80% vs. 74% for the hydrogenation of $\alpha,\alpha,\alpha$-trimethylacetophenone).

The work has shown that due to the modular nature of the ligands, the catalyst structure can be tuned for greater selectivity, based on a greater mechanistic understanding. Future work is anticipated to extend this further and modification of the DPEN catalyst framework, possibly combining DPEN with a more bulky phosphine substituent, has the potential to lead to even
greater selectivities. A greater understanding of the mechanism over time will lead to other avenues of potential catalyst modification.

I feel that this work has contributed significantly to the understanding of the current system – its scope, likely mechanism, and possibilities for catalyst tuning - and gives a sound basis for the development of the next generation of catalyst for preparation of such important chiral building blocks.
Chapter V

Experimental

5.1 General

Dry, degassed solvents were used for reactions that were carried out under an N₂ atmosphere unless otherwise indicated. Normal grade solvents were used for chromatography and work-up procedures under aerobic conditions. Solvents were removed by rotary evaporation on a Heidolph labtota 4000. Flash column chromatography (eluents given in brackets) was performed using Davisil silica gel Fluorochem 60 Å, particle size 35-70 micron. Thin-layer chromatography (TLC) was performed on pre-coated Aldrich TLC plates (POLYGRAM SIL G/UV₂₅₄). All microwave syntheses were carried out in a Biotage Initiator Microwave reactor using 5ml heavy-walled vials equipped with an air tight septum. Melting points were determined with a Gallenkamp melting point apparatus Nº 889339 and are uncorrected. ¹H NMR, ¹³C NMR, ³¹P NMR and ¹⁹F NMR spectra were recorded either on a Bruker Avance 300 (¹H 300 MHz, ¹³C 75.5 MHz, ³¹P 121.4 MHz and ¹⁹F 282 MHz) or Bruker Avance 400 (¹H 400 MHz, ¹³C 100 MHz and ³¹P 162 MHz) instrument. ¹³C NMR spectra were recorder using the DEPTQ sequence and internal deuterium lock. Chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard. Chemical shift values for ³¹P spectra are reported downfield of phosphoric acid, and chemical shifts values for ¹⁹F spectra are relative to CFCl₃. Proton resonance multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of them. When appropriate, coupling constants (J) are quoted in Hz and are reported to the nearest 0.1Hz. All spectra were recorded at room temperature and the solvent for a particular spectrum is given in parentheses. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 Spectrum GX FT-IR system. Compounds were analysed using disposable PTFE IR card with an aperture diameter of 15mm obtained from Aldrich. When disposable IR cards were not available, liquids were analysed as films, and solids were analysed as KBr disks. Absorptions maxima are reported in wavenumbers (cm⁻¹). The characteristic absorption is reported as strong (s), medium (m) or weak (w). Mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea University, using Waters ZQ4000, Thermofisher LTQ Orbitrap XL and Finnigan MAT 900 XLT instruments, or by Mrs Caroline Horsburgh at the University of St Andrews using a Waters Micromass GCT (Time of flight) fitted with lockspray for accurate mass (ESI) or GCT (CI). Only major peaks are reported and intensities are quoted as
percentages of the base peaks. Isotope profiles for ruthenium complexes are presented in Appendix B. Optical rotations were measured on a Perkin Elmer 241 polarimeter using a 1ml cell with a 1 dm path length at room temperature using the sodium D-line, and a suitable solvent that is reported along with the concentration ($c = g/100ml$). Microanalysis for carbon, hydrogen and nitrogen were performed using a EA 1110 CHNS CE instruments elemental analyser by Mrs Sylvia Williamson or Miss Donna McColl at the University of St Andrews or by Mr Stephen Boyer at the London Metropolitan University. X-Ray crystallography data were recorded at the University of St Andrews by Alex Slawin in a Bruker SMART CCD Diffractometer and the data are presented in Appendix B. HPLC analysis has been determined using a Varian Prostar operated by Galaxie workstation PC software.

5.2 General Reagents

**Dichlorotetrakis(dimethyl sulfoxide) ruthenium (II)**

Prepared by modification of a literature procedure.¹ Ruthenium trichloride trihydrate (0.86 g, 4.13 mmol) was refluxed in dimethyl sulfoxide (5 mL) for 5 min under nitrogen. The volume was then reduced to half *in vacuo* and acetone added prompting formation of a yellow solid. The precipitate was filtered off, washed with acetone and dried *in vacuo*. Recrystallisation from dimethyl sulfoxide yielded complex (0.87 g, 44 %) as yellow crystals, mp 190 °C (lit.¹ 193 °C).

5.3 General Procedures

5.3.1 Preparation of [RuCl₂(P^N^X)L] Complexes

To dichlorotetrakis(dimethylsulfoxide) ruthenium(II) (1 equivalent) in a sealed microwave tube under nitrogen was added a solution of the requisite ligand (1 equivalent) in tetrahydrofuran (3 mL). The reaction was heated in the microwave for 15 min at 120 °C. The mixture was filtered to removed excess ruthenium(II) precursor and the solvent was removed *in vacuo*. Purification by column chromatography yielded pure complex, unless otherwise stated.

5.3.2 Hydrogenation Using [RuCl₂(P^N^X)L] Catalysts

A solution of substrate (ca 1 mmol), catalyst and potassium tert-butoxide (1 M solution in pentane) in degassed isopropanol (3 mL) was prepared in a microwave vial under an atmosphere of nitrogen. The microwave tube was then placed inside a steel autoclave with two syringe
needles piercing the lid of the vial. The autoclave was then sealed and flushed three times with hydrogen before being charged with hydrogen to the required pressure. The reactions were stirred at the same speed for the desired times at the required temperature using a stainless steel heating jacket connected to a thermocouple and heater. After the desired time passed, the autoclave was opened and the reaction mixture concentrated in vacuo. The conversion of substrate to product was calculated by $^1$H NMR spectroscopy (In these experiments only starting material and product were observed negating the use of an internal standard). The products were isolated by column chromatography or short-path distillation and characterised by comparison of NMR, IR, MS, optical rotation and where appropriate melting point data, with authentic samples. The enantiopurity of the product (where applicable) was determined using high performance liquid chromatography with the chiral stationary phase noted for each product.

5.3.3 Microwave-Accelerated Transfer Hydrogenation Using RuCl$_2$(P$^N$X)L Catalysts

A solution of substrate (ca 1 mmol), catalyst and potassium tert-butoxide (1 M solution in pentane) in degassed isopropanol (3 mL) was prepared in a microwave vial under an atmosphere of nitrogen. The vial was then place inside the heating cavity of the microwave and heated for the required period at the desired temperature. After the desired time passed, the microwave vial was opened and the reaction mixture concentrated in vacuo. The conversion of substrate to product was calculated by $^1$H NMR spectroscopy. The products were isolated by column chromatography or short-path distillation and characterised by comparison of NMR, IR, MS, optical rotation and, where appropriate melting point data, with authentic samples. The enantiopurity of the product (where applicable) was determined using high performance liquid chromatography.

5.3.4 Racemic Reduction with Sodium Borohydride

To a solution of the substrate (1 equivalent) in absolute ethanol was added powdered sodium borohydride (3 equivalents) in small portions to avoid vigorous reaction and the mixture stirred. The reaction was monitored by thin layer chromatography and upon completion quenched with 10 % hydrochloric acid solution. The mixture was then extracted with dichloromethane and washed with water and brine before drying with magnesium sulfate, filtration and concentration in vacuo yielded the product.
5.3.5 Kinetic Analysis of Hydrogenation Using [RuCl₂(P^N^X)L] Catalysts

The requisite ruthenium precatalyst (0.5 mol%) was dissolved in isopropanol (20 mL) and to this was added substrate (0.0123 mol) under a nitrogen environment at rt. The solution was stirred for 15 min and immediately prior to the transfer of the solution, potassium tert-butoxide (1M solution in tert-butanol, 1 mol%) was added. All hydrogenation experiments were performed under isobaric conditions in a Parr autoclave using an automatic gas-measuring apparatus. Experiments were carried out at 70 °C and 70 bar pressure of hydrogen. Prior to commencing each experiment, a control experiment was carried out in order to detect leaks at the same temperature and pressure. This was typically carried out over a period of no less than one hour. Once it was ascertained that the system was leak-free, the reaction mixture, immediately after addition of potassium tert-butoxide, was transferred to the autoclave, which was repressurised and gas-uptake was measured immediately. The method of data collection used means that, despite the heating jacket being adaptive to the internal temperature, there will be a short period of time where the temperature of the solution is stabilising. However, we estimate this to be the first minute of reaction, and thus conclude the induction period observed (in some cases 30 minutes) is not a result of this equilibration, but a chemical process (i.e. formation of Ru-hydride). The main source of error in the experiments stems from temperature control of the laboratory and consequently the ballast vessel, and is not considered to have any significant implication to the conclusions made. Measurements were continued until no more hydrogen was consumed. The data were normalised by assuming 100% conversion at maximum gas uptake (confirmed by ¹H NMR). Analysis of the data was conducted in a similar manner to the graphical rate equation tutorial of Blackmond.²

5.4 Synthesis of 2-(Diarylphosphino)benzaldehyde Ligand Precursors

2-(Diphenylphosphinobenzaldehyde 266 and 2-[bis(3,5-dimethylphenyl)phosphino]benzaldehyde 303 were purchased commercially and used as received.2-(bis(4-Methoxyphenyl)phosphino)benzaldehyde was prepared by Piotr Wawrzyniak in this group.³
A solution of 2-bromobenzaldehyde ethylene acetal \(299\) (0.277 mL, 1.9 mmol) in dry THF (5 mL) was cooled to -78 °C, and to this, \(n\)-butyllithium (1.25 mL, 1.6 M solution in THF, 2.0 mmol) was added slowly. The resulting mixture was stirred at this temperature for 2h. The creamy/white suspension was then transferred portionwise via cannula to a solution of phosphorus trichloride (1.66 mL, 19 mmol) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min then warmed to rt. The solvent and excess phosphorus trichloride were removed in vacuo at 60 °C before the residue was redissolved in THF (5 mL) immediately. To this was added a solution prepared by adding \(n\)-butyllithium (2.5 mL, 1.6 M solution in THF, 40 mmol) to a solution of 3,5-di-tert-butylbenzene (1.00 g, 37 mmol) in dry THF (10 mL), after stirring for 2 h at -78 °C. This addition was achieved via cannula keeping all reactants at -78 °C and the resultant mixture was stirred for a further 30 min at -78 °C. The reaction mixture was then warmed to rt. The reaction mixture was concentrated and applied directly to a silica column. Flash chromatography (dichloromethane:hexane 1:1) afforded the title compound as a sticky white solid (0.435 g, 41 %), mp 102-103.5 °C. \(\nu_{\text{max}}/\text{cm}^{-1}\) (film) 3420 (m), 3059 (w), 2963 (s), 1589 (s), 1477 (s), 1420 (m), 1394 (m), 1363 (m), 1249 (m), 1129 (m), 1091 (s) 945 (m), 875 (m), 738 (m) and 710 (m); \(\delta_{\text{H}}\) (CDCl\(_3\), 300 MHz) 7.66-7.56 (1H, m, \(\text{C}_\text{Ar}H\)), 7.34-7.13 (4H, m, \(\text{C}_\text{Ar}H\)), 7.06-6.97 (4H, m, \(\text{C}_\text{Ar}H\)), 6.90-6.81 (1H, m, \(\text{C}_\text{Ar}H\)), 6.40 (1H, d, \(J = 5\), \(\text{C}, \text{CH}\)), 4.07-3.86 (4H, m, \(\text{CH}_2\)) and 1.15 (36H, s, \(\text{C(CH}_3)_3\)); \(\delta_{\text{C}}\) (CDCl\(_3\), 101 MHz) 150.4 (d, \(J = 6\), \(\text{C}_\text{q}\)), 141.8 (\(\text{C}_\text{q}\)), 137.4 (\(\text{C}_\text{q}\)), 135.9 (d, \(J = 8\), \(\text{C}_\text{q}\)), 133.8 (\(\text{C}_\text{Ar}H\)), 128.9 (d, \(J = 25\), \(\text{C}_\text{Ar}H\)), 128.1 (d, \(J = 20\), \(\text{C}_\text{Ar}H\)), 126.1 (d, \(J = 7\), \(\text{C}_\text{Ar}H\)), 122.5 (\(\text{C}_\text{Ar}H\)), 122.3 (\(\text{C}_\text{Ar}H\)), 101.7 (d, \(J = 25\), \(\text{CH}\)), 65.4 (\(\text{CH}_2\)), 34.9 (\(\text{C(CH}_3)_3\)) and 31.4 (\(\text{C(CH}_3)_3\)); \(\delta_{\text{p}}\) (CDCl\(_3\), 162 MHz) -13.7; \(m/z\) (ES+) 581.03 ([M+Na\(^+\), 100%] and 597.03 ([M=O+Na\(^+\), 40%]); HRMS (ES+) found 581.3520, \(\text{C}_{37}\text{H}_{51}\text{O}_2\text{NaP}\) requires 581.3524.
To a solution of 301 (0.106 g, 1.90 mmol) in degassed acetone (10 mL) was added p-toluenesulfonic acid monohydrate (0.036 g, 0.19 mmol). The reaction was stirred at rt for 4h. The solvent was then evaporated, and the residue purified by column chromatography on silica (dichloromethane:hexane 1:1) to furnish the pure compound as a yellow viscous liquid which solidified upon standing (0.090 g, 92 %), mp 135-136°C. v_max/cm⁻¹ (film) 3441 (w), 2962 (s), 1698 (m), 1586 (m), 1477 (w), 1419 (w), 1393 (w), 1363 (m), 1249 (m), 1198 (m), 1131 (w), 875 (w), 758 (w) and 710 (m); δ_H (CDCl₃, 300 MHz) 10.63 (1H, d, J 6, CHO), 7.95-7.88 (1H, m, C₆H₄H), 7.34-7.30 (2H, m, C₆H₄H), 7.03 (2H, d, J 2, C₆H₄H), 7.00 (2H, d, J 2, C₆H₄H), 6.94-6.88 (1H, m, C₆H₄H) and 1.15 (36H, s, C(CH₃)₃); δ_C (CDCl₃, 101 MHz) 191.9 (C=O), 150.9 (d, J 7, C=O), 134.9 (d, J 9, C=O), 133.6 (d, J 17, C₆H₄H), 128.8 (C₆H₄H), 128.7 (C₆H₄H), 128.3 (d, J 21, C₆H₄H), 123.6 (C₆H₄H), 122.9 (C₆H₄H), 34.9 (C(CH₃)₃) and 31.4 (C(CH₃)₃); δ_P (CDCl₃, 121 MHz) -11.8; m/z (ES+) 536.90 ([M+Na]⁺, 100%); HRMS (ES+) found 537.3256, C₃₅H₄₇ONaP requires 537.3262.

5.5 Synthesis of Diamines

Ethylenediamine 267, N',N'-dimethylethylenediamine 269, N,N',N'-trimethylethylenediamine 271 and (R,R)-(−)-1,2-diphenyletheylenediamine 299 were purchased commercially and used as received. (1R,2R)-Cyclohexane-1,2-diamine was either purchased commercially or prepared by the method below.

(1R,2R)-Cyclohexane-1,2-diamine

Using a procedure adapted from the work of Zhang and Walsh,¹ a mixture of cis- and trans-1,2-diaminocyclohexane (52.6 mL, 50.0 g, 0.44 mol) was added dropwise to a solution of L-(R,R)-(−)-tartaric acid (66.0 g, 0.44 mol) in H₂O (175 mL) at 90°C. Further water (up to 660 mL total)
was added to dissolve precipitate that was formed. The solution was gradually cooled to rt and stood overnight at 4°C. The crystals formed were filtered off, washed with ice water and methanol, and dried under vacuum to give the tartrate salt of the title compound as a white solid. This solid was then dissolved in a minimum amount of 10% methanolic HCl, and diethyl ether was added dropwise until a white precipitate appeared. The precipitate was filtered and dried under vacuum to give the hydrochloride salt. This was redissolved in a minimum amount of saturated sodium hydroxide solution and then extracted with diethyl ether. The organic layer was separated, filtered and concentrate in vacuo to give the title compound as a white solid (22.11 g, 44%) in >99% diastereomeric and enantiomeric excess, mp 41-42 °C (lit. 5 40-43°C).

\([\alpha]_D^{20}-23.9 \,(c \,5, \,1M \,HCl), \, \text{lit.}^6 \,[\alpha]_D^{20}-25.0 \,(c \,5 \,1M \,HCl); \, \delta_H (300 MHz, CDCl_3) 2.25-2.13 \,(2H, \, m, \, CHN), \, 1.82-1.71 \,(2H, \, m, \, cyclohexyl \, CH), \, 1.67-1.52 \,(6H, \, m, \, 2 \times NH_2, \, 2 \times \, cyclohexyl \, CH) \, \text{and} \, 1.28-0.94 \,(4H, \, m, \, cyclohexyl \, CH); \, \text{Enantioselectivity determined by chiral HPLC of the bis-m-toluoyl amide derivative.}^7 \, \text{ChiralPak AD, 1.0 mL/min, 90:10 hexane:2-propanol. Retention times: 6.4 min ((S,S)), 17.3 min (R,R) and 29.9 min ((S,S)+(R,R)). Data are in agreement with the literature.}^7,^8

5.6 Synthesis of Ligands

\((1R, \, 2R)-N-(2-(\text{Diphenylphosphino})\text{benzyl})\text{cyclohexane-1,2-diamine (307)}\)

Prepared by modification of a literature procedure.9 A solution of 2-(diphenylphosphino)benzaldehyde 266 (0.136 g, 0.45 mmol) in absolute ethanol (13 mL) at 45°C was added over a period of 5 h to a solution of \((1R,2R)\)-cyclohexane-1,2-diamine (0.153 g, 1.34 mmol) in absolute ethanol (23 mL) at 0°C. The reaction was monitored by \(^1\text{H}\) and \(^{31}\text{P}\) NMR and upon completion, sodium borohydride (0.068 g, 1.79 mmol) was added and the reaction stirred for 12 h at rt. Once \(^1\text{H}\) and \(^{31}\text{P}\) NMR spectroscopy had indicated complete reduction of the imine, the reaction was concentrated under reduced pressure. The residue was dissolved by stirring with saturated ammonium chloride solution and dichloromethane. The aqueous phase was then extracted with dichloromethane and the organic phases were washed with water, dried over magnesium sulfate, filtered and concentrated to yield the product as a yellow oil (0.073 g, 40%). \(\delta_H (400 MHz, CDCl_3) 7.47-7.34 \,(m, \, 1H, \, C_A\text{H}), \, 7.31-7.14 \,(m, \, 11H, \, C_A\text{H}), \, 7.12-7.06 \,(m, \, 1H, \, C_A\text{H}), \, 6.83-6.78 \,(m, \, 1H, \, C_A\text{H}), \, 4.04 \,(1H, \, d, \, AB \, system, \, J_{AB} \, 14.1, \, CH_2\text{H}_2\text{NH}), \, 3.84 \,(1H,
d, AB system, $J_{AB} 14.1$, CH$_A$H$_B$NH), 2.29-2.17 (m, 1H, NCH), 2.06-1.92 (m, 2H, NCH, CH$_2$), 1.84-1.76 (m, 1H, CH$_2$), 1.64-1.52 (m, 3H, CH$_3$), 1.24-0.94 (m, 5H, CH$_3$, NH, N$_H$) and 0.90-0.75 (1H, m, CH$_2$); $\delta_p$ (121 MHz, CDCl$_3$) –16.4. Data are in agreement with the literature.$^9$

$N'$-(2-(Diphenylphosphino)benzyl)ethane-1,2-diamine (268)

A solution of 2-(diphenylphosphino)benzaldehyde (0.20 g, 6.9 mmol) in absolute ethanol (26 mL) at 45°C was added dropwise over a period of 5 h to a solution of ethylene diamine (0.14 mL, 20.7 mmol) in absolute ethanol (46 mL). The reaction was monitored by $^1$H and $^{31}$P NMR and upon completion, sodium borohydride (0.10 g, 27.6 mmol) was added portionwise and the reaction was stirred for 12 h at rt. Once $^1$H NMR had shown complete reduction of the imine, the reaction was quenched by addition of acetone and the solvent was removed under reduced pressure. The residue was dissolved by stirring with saturated ammonium chloride solution and dichloromethane. The organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated to yield the crude product as a yellow oil. For the purposes of purification, the hydrochloride salt of the ligand was prepared by reaction of the crude product with concentrated hydrochloric acid solution and dichloromethane. The organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated to yield the crude product as a yellow oil. For the purposes of purification, the hydrochloride salt of the ligand was prepared by reaction of the crude product with concentrated hydrochloric acid solution and subsequent removal of solvent. The salt was washed with dichloromethane, before reaction with aqueous sodium hydroxide and extraction into dichloromethane gave the pure product as a colourless oil (0.164 g, 72 %). $\nu_{\text{max}}$/cm$^{-1}$ (film) 3423, 3051, 2978, 2672, 2477, 1719, 1585, 1477, 1434 , 1261, 1180, 1118, 1093, 1026, 804, 746, 698, 547 and 507; $\delta_h$ (CD$_3$OD, 400 MHz) 7.54-7.48 (1H, m, C$_{Ar}$H), 7.42-7.33 (7H, m, C$_{Ar}$H), 7.29-7.17 (5H, m, C$_{Ar}$H), 6.91-6.84 (1H, m, C$_{Ar}$H), 3.98 (2H, s, NHC$_H$Ar), 2.89-2.82 (2H, m, CH$_2$CH$_3$) and 2.78-2.71 (2H, m, CH$_2$CH$_3$); $\delta_c$ (CD$_3$OD, 75 MHz) 143.6 (d, $J_{CP}$ 24, C$_{ipso}$C), 136.7 (d, $J_{CP}$ 9, C$_{ipso}$P), 136.1 (d, $J_{CP}$ 13, C$_{ipso}$P), 134.0 (C$_{Ar}$H), 133.7 (C$_{Ar}$H), 129.5 (d, $J_{CP}$ 5, C$_{Ar}$H), 129.2 (C$_{Ar}$H), 129.0 (C$_{Ar}$H), 128.8 (d, $J_{CP}$ 7, C$_{Ar}$H), 127.6 (C$_{Ar}$H), 51.5 (d, $J_{CP}$ 21, NHCH$_2$Ar), 50.0 (CH$_3$) and 40.3 (C$_H$); $\delta_p$ (CD$_3$OD, 162 MHz) –18.2; $m/z$ (ES+) 335.11 ((M+H)$^+$, 100%) and 275.06 (20); HRMS (ES+) found 335.1677, [C$_{21}$H$_{24}$N$_2$P]$^+$ requires 335.1687.
N-(2-(Diphenylphosphino)benzyl)-N',N'-dimethylethane-1,2-diamine (270)

A solution of 2-(diphenylphosphino)benzaldehyde (0.150 g, 0.52 mmol) in absolute ethanol (10 mL) at 45°C was added dropwise to a solution of N',N'-dimethylethane-1,2-diamine (0.056 mL, 0.52 mol) in absolute ethanol (20 mL) at rt. The reaction was monitored by $^1$H and $^{31}$P NMR and upon completion, sodium borohydride (0.079 g, 2.08 mmol) was added portionwise and the reaction was stirred for 12 h at rt. Once $^1$H NMR had shown complete reduction of the imine, the reaction was quenched by addition of acetone and the solvent was then removed under reduced pressure. The residue was dissolved by stirring with saturated ammonium chloride solution and dichloromethane. The organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated to yield the product as a yellow oil (0.122 g, 65%) which was deemed sufficiently pure for complexation. $\nu_{\text{max}}$/cm$^{-1}$ (film) 3437, 3052, 2940, 2817, 1457, 1434, 1264, 1182, 745 and 696; $\delta_\text{H}$ (CDCl$_3$, 400 MHz) 7.47-7.33 (2H, m, C$_\text{Ar}$H), 7.29-7.13 (10H, m, C$_\text{Ar}$H), 3.91 (2H, s, C$_2$H), 2.52 (2H, t, $J$ 6.4, C$_2$H), 2.33 (1H, br s, NH), 2.16 (3H, m, N(C$_3$H$_7$)$_2$), 1.95 (7H, br s, NCH$_2$), and 2.06 (6H, s, N(C$_3$H$_7$)$_2$); $\delta_\text{C}$ (CDCl$_3$, 101 MHz) 144.5 (d, $J_{CP}$ 23.5, C$_{ipso}$CH$_2$), 136.8 (m, C$_\text{Ar}$H), 135.7 (d, $J_{CP}$ 9.7, C$_{ipso}$P), 133.9 (d, $J_{CP}$ 19.7, C$_\text{Ar}$H), 132.0 (d, $J_{CP}$ 9.7, C$_\text{Ar}$H), 129.1 (d, $J_{CP}$ 5.4, C$_\text{Ar}$H), 128.7 (d, $J_{CP}$ 11.1, C$_\text{Ar}$H), 128.6 (C$_\text{Ar}$H), 127.2 (C$_\text{Ar}$H), 59.0 (CH$_2$NMe$_2$), 52.4 (d, $J_{CP}$ 23.0, ArCH$_2$NH), 46.6 (CH$_3$NH) and 45.5 (N(CH$_3$)$_2$); $\delta_\text{P}$ (CDCl$_3$, 121 MHz) -16.1; $m/z$ (Cl+) 363.20 ($\text{M}^+H^+$, 25%) and 286.00 (100); HRMS (Cl+) found 363.1995, [C$_{23}$H$_{28}$N$_3$P]$^+$ requires 363.1990.

N-(2-(Diphenylphosphino)benzyl)-N,N',N'-trimethylethane-1,2-diamine (272)

To a solution of 2-(diphenylphosphino)benzaldehyde (0.21 g, 0.73 mmol) in dichloromethane (20 mL) at rt was added N,N,N'-trimethylethlenediamine (0.09 mL, 0.73 mmol) followed by sodium triacetoxyborohydride (0.23 g, 1.10 mmol). To the mixture was then added glacial acetic acid (0.13 mL, 2.20 mmol) and the reaction stirred at room temperature for 4 h. Once $^1$H NMR had shown complete reduction of the imine, the reaction was quenched by addition of acetone and the solvent was then removed under reduced pressure. The residue was dissolved
by stirring with saturated ammonium chloride solution and dichloromethane. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Azeotropic distillation with toluene allowed removal of residual acetic acid. Purification by flash chromatography on silica (acetone:triethylamine 98:2) yielded the title compound as a colourless oil (0.276 g, 95%).

\[ \text{max} \nu/\text{cm}^{-1} (\text{KBr}) 3423, 3051, 2957, 2788, 2672, 2477, 1719, 1585, 1477, 1362, 1262, 1180, 1118, 1093, 1069, 1026, 805, 746, \text{and} \ 698; \delta \text{H} (\text{CDCl}_3, 300 \text{ MHz}) \ ^{\uparrow} 7.41-7.32 (1 \text{H}, \text{ m, C}_\text{Ar} \text{H}), 7.31-7.22 (6 \text{H}, \text{ m, C}_\text{Ar} \text{H}), 7.19-7.08 (6 \text{H}, \text{ m, C}_\text{Ar} \text{H}), 6.89 (1 \text{H}, \text{ dd, J 4, 1, C}_\text{Ar} \text{H}), 3.72 (2 \text{H}, \text{ s, -NMeCH}_2\text{C}_\text{ipso}), 2.77-2.61 (4 \text{H}, \text{ m, -NMeCH}_2\text{CH}_2\text{NMe}_2), 2.52 (6 \text{H}, \text{ s, N(C}_\text{H}_3)_2 \text{and} \ 2.08 (3 \text{H}, \text{ s, -NC}_\text{H}_3). \delta \text{C} (\text{CDCl}_3, 101 \text{ MHz}) \ ^{\uparrow} 144.1 (\text{d, } \text{J} \text{ 23, C}_\text{ipsoCH}_2), 137.7 (\text{d, J 10, 2 x C}_\text{ipsoP}), 136.5 (\text{d, J 15, C}_\text{ipsoP}), 134.0 (\text{C}_\text{Ar} \text{H}), 133.9 (\text{C}_\text{Ar} \text{H}), 133.7(\text{C}_\text{Ar} \text{H}), 129.2 (\text{d, J 5, C}_\text{Ar} \text{H}), 128.6 (\text{C}_\text{Ar} \text{H}), 128.4 (\text{C}_\text{Ar} \text{H}), 128.4 (\text{d, J 3, C}_\text{Ar} \text{H}), 127.1 (\text{C}_\text{Ar} \text{H}), 61.1 (\text{d, J 19, -N(CH}_3)-\text{CH}_2\text{Ar}), 56.9 (\text{CH}_2\text{NMe}_2), 54.9 (\text{CH}_2\text{N(Me)-}), 45.8 (\text{N(CH}_3)_2) \text{ and} \ 41.9 (\text{N}_\text{C}_\text{H}_3); \delta \text{P} (\text{CDCl}_3, 300 \text{ MHz}) -15.7; \text{m/z (ES+)} 377.10 ([M+H]^+, 100%). HRMS (ES+) found 377.2142, [C\text{24H}_30\text{N}_2\text{P}]^+ \text{requires} 363.2147. \ ^{\uparrow} \text{Assignments supported by} ^1\text{H-}^{13}\text{C HSQC and HMBC correlations}

\((1\text{R,2R})\text{-N1-(2- (bis(4-methoxyphenyl)phosphino)benzyl) cyclohexane-1,2-diamine (289)}\)

Prepared using the same procedure as for ligand 307 giving \((R,R)-289\) as gummy solid. Due to the sensitivity of the phosphine, this material could only be obtained in ~80% purity (~20% ligand oxide) and was thus complexed immediately without any further purification. \delta \text{H} (\text{CDCl}_3, 300 MHz) 7.52-7.33 (2H, m, C\text{Ar} \text{H}), 7.30-7.21 (1H, m, C\text{Ar} \text{H}), 7.16-7.01 (4H, m, C\text{Ar} \text{H}), 6.96-6.87 (1H, m, C\text{Ar} \text{H}), 6.83-6.71 (4H, m, C\text{Ar} \text{H}), 4.09-3.84 (1H, m, CH\text{ArH}_2\text{Ar}), 3.72 (6H, s, -OC\text{H}_3 \times 2), 3.50 (1H, dd, J 14, 7, CH\text{H}_2\text{Ar}), 2.48-2.35 (1H, m, CHN), 2.30-1.47 (5H, m, CHN, cyclohexyl CH) and 1.25-0.72 (4H, m, cyclohexyl CHN); \delta \text{C} (101 MHz, CDCl_3) 162.0 (C\text{ipso}), 160.4 (C\text{ipso}), 143.9 (C\text{ipso}), 135.2 (C\text{Ar} \text{H}), 133.5 (C\text{Ar} \text{H}), 131.4 (C\text{Ar} \text{H}), 129.0 (C\text{Ar} \text{H}), 127.7 (C\text{ipso}), 127.3 (C\text{Ar} \text{H}), 114.5 (C\text{ipso}), 63.4 (CH), 61.1 (CH), 55.2 (OCH_3), 49.3 (d, J 21, CH\text{H}_2\text{Ar}), 31.5 (cyclohexyl CH_2), 29.7 (cyclohexyl CH_2), 25.2 (cyclohexyl CH_2) and 24.5 (cyclohexyl CH_2); \delta \text{P} (\text{CDCl}_3, 121 MHz) -18.8; \text{m/z (CI+)} 449.24 ([M+H]^+, 90%), 337.14 (66), 261.11 (45), 203.15 (79) and 95.05 (100); HRMS (CI+) found 449.2374, C\text{35H}_{49}\text{ONaP requires 449.2358.}
(1R,2R)-N1-(2-(bis(3,5-dimethylphenyl)phosphino)benzyl)cyclohexane-1,2-diamine (297)

Prepared using the same procedure as for ligand 307 giving (R,R)-297 as a pale yellow solid (0.181 g, 67 %), mp 125-127°C. ν_max/cm⁻¹ (IR card) 3383 (s), 3028 (w), 2859 (m), 1622 (m), 1599 (m), 1446 (s), 1379 (m), 1272 (s), 1159 (m), 1128 (s), 1038 (m), 872 (w), 851 (s), 800 (m), 694 (s), 579 (s), 534 (w) and 486.8 (m) ; δ_H (CDCl₃, 300 MHz) † 7.47-7.36 (1H, m C Ar H), 7.27-7.19 (1H, m C Ar H), 7.12-7.03 (2H, m C Ar H), 6.87 (2H, s C Ar H), 6.83-6.71 (4H, m, C Ar H), 4.70 (2H, br s, NH₂), 4.05 (1H, d (AB system, J 12, ArC H A H B NH), 3.77 (1H, d (AB system, J 12, ArCH₂H₃NH), 2.54-2.34 (1H, m, CHN), 2.19 (12H, s, Ar-CH₃), 2.11-1.93 (1H, m, CHN), 1.73-0.67 (9H, m, cyclohexyl CH and NH); δ_C (75 MHz, CDCl₃) † 143.8 (C ipso), 138.6 (C ipso), 138.2 (C ipso), 136.2 (C ipso), 134.0 (C Ar H), 131.8 (d, J 14, C Ar H), 131.5 (d, J 14, C Ar H), 130.7 (C Ar H), 129.1 (C Ar H), 127.4 (C Ar H), 60.9 (CHN), 55.8 (CHN), 49.5 (d, J 22, CH₂Ar), 32.3 (cyclohexyl CH₂), 31.1 (cyclohexyl CH₂), 25.0 (cyclohexyl CH₂), 24.7 (cyclohexyl CH₂) and 21.4 (Ar-CH₃); δ_P (CDCl₃, 121 MHz) -16.1; m/z (ES+) 445.24 ([M+H]+, 100%); HRMS (ES+) found 445.2758, [C₂₉H₃₈N₂P]⁺ requires 445.2773. †Assignments supported by ¹H-¹³C HMBC correlations.

(1R,2R)-N1-(2-(bis(3,5-di-tert-butylphenyl)phosphino)benzyl)cyclohexane-1,2-diamine (298)

Prepared using the same procedure as for ligand 307 giving (R,R)-298 as gummy solid. Due to the sensitivity of the phosphine, this material could only be obtained in ~60% purity and was thus complexed immediately without any further purification. δ_P (CDCl₃, 121 MHz) -11.8; m/z (ES+) 613.46 ([M+H]+, 100%); HRMS (ES+) found 613.4651, C₄₁H₆₂N₂P requires 613.4651.
5.7 Synthesis of Ruthenium Complexes

[RuCl₂((S)-BINAP)]ₙ was purchased commercially and used as received. [RuCl₂(NBD)]₂, trans-[RuCl₂(NBD)(pip)]₂, trans-[RuCl₂(NBD)(py)]₂, [RuCl₂((S)-BINAP)((R,R)-DPEN)] and [RuCl₂((S)-TolBINAP)((R,R)-DPEN)] were prepared following literature procedures exactly. [RuCl₂((S)-XylPhanePhos)((R,R)-DPEN)] and [RuCl₂((R)-HEXAPHEMP) ((R,R)-DPEN)] were kindly donated by Dr Reddys (formerly Chirotech).

Complex (R,R)-174

Prepared using the general procedure outlined in section 5.3.1 giving complex (R,R)-174, after purification by column chromatography (9:1 dichloromethane:acetone), as a brown powder (0.048 g, 83 %), mp 169-171°C (lit. 14 170°C). [α]₂₀° + 59.1 (c 0.5, chloroform), lit. 14 [α]₂₀° + 60.0 (c 0.5 chloroform); δH (400 MHz, CDCl₃) 7.59-7.09 (14H, m, C₆H₄H), 4.41-3.91 (2H, m, ArCH₂NH), 3.64-3.74 (1H, m, NH), 3.47-3.26 (2H, m, CHNH, CHNH₂), 2.99 (6H, s, SO(CH₃)₂), 2.72-2.52 (1H, m, cyclohexyl CH), 2.72-2.52 (1H, m, cyclohexyl CH), 1.83-1.66 (2H, m, cyclohexyl CH), 1.55 (2H, br s, NH₂) and 0.91-1.29 (4H, m, cyclohexyl CH); δp (121 MHz, CDCl₃) +42.5. Data are in agreement with the literature. 14

Complex 263

Prepared using the general procedure outlined in section 5.3.1 giving complex 263 as a brown/red solid (0.050 g, 86 %), m.p. 166-167.5°C (decomp.). Found: C, 43.55; H, 4.24; N, 3.97%; C₂₅H₃₃Cl₂N₂OPRuS + 1 CH₂Cl₂ requires C, 43.06; H, 4.67; N, 4.18%; νmax/cm⁻¹ (KBr disc) 3449, 2924, 2854, 1637, 1459, 1434, 1095, 1020, 752, 697, 536 and 425; δH (300 MHz, CDCl₃) 7.76-7.45 (2H, m, C₆H₄H), 7.43-7.20 (11H, m, C₆H₄H), 7.08 (1H t, J 9, C₆H₄H), 4.48 (1H, app dd, J 11, 11, NHCH₃H₃Ar), 4.02 (1H, br s, NH₂H₂), 3.94 (1H, app dd, J 11, 11, NH, 3.94 (1H, app dd, J 11, 11, NH, 3.94 (1H, app dd, J 11, 11, NH, 3.94 (1H, app dd, J 11, 11, NH,
3.77-3.65 (2H, m, NHCH₃HβAr + NH₃H₈), 3.53-3.36 (1H, m, CH₃CH₈NH₂), 3.02-2.74 (6H, m, C(H₃)₂SO₂C(H₈)₃ + CH₃CH₈NH₂ + CH₃CH₈NH- + CH₃CH₈NH-) and 2.56 (3H, s, C(H₃)₂SO₂C(H₈)₃); δ C (75.5 MHz, CDCl₃) † 141.3 (d, J 15, C(ipso)₂CH₂), 135.9 (d, J 42, C(ipso)₂P), 135.5 (d, J 10, C₈H₈), 134.3 (d, J 10, C₈H₈), 133.4 (d, J 2, C₈H₈), 132.8 (d, J 40, C(ipso)₂P), 131.8 (d, J 8, C₈H₈), 131.0 (d, J 2, C₈H₈), 130.8 (d, J 42, C(ipso)₂P), 130.3 (d, J 3, C₈H₈), 130.3 (d, J 2, C₈H₈), 129.3 (d, J 2, C₈H₈), 128.6 (d, J 6, C₈H₈), 128.1 (d, J 9, C₈H₈), 57.9 (d, J 7, NHCH₂Ar), 54.2 (NHCH₂CH₂NH₂), 47.1 (C₈H₈SO₂C₁₈H₃₅), 45.9 (C₈H₈SO₂C₁₈H₃₅) and 41.9 (NHCH₂CH₂NH₂); δ p (121 MHz, CDCl₃) +44.5; HRMS (ES+) found 584.0162 ([M⁺]), [C₈H₁₂N₂O₆RuS₁₅Cl₂]** requires 584.0153. †Assignments supported by ¹H-¹H COSY and ¹H-¹³C HSQC correlations.

 whistleblower supported by ¹H-¹³C HSQC correlations.

**Complex 264**

![Complex 264](image)

Prepared using the general procedure outlined in section 5.3.1 giving complex 264 as a brown/red solid (0.058 g, 95 %), m.p. 174-176°C (decomp.). Found: C, 49.25; H, 5.18; N, 4.34%; C₁₂H₃₃Cl₂N₂O₆RuS requires C, 49.02; H, 5.43; N, 4.57%; ν max/cm⁻¹ (KBr) 3449, 2921, 1637, 1435, 1307, 1261, 1017, 923, 724, 508 and 425; δ H (400 MHz, CDCl₃) 7.78-7.51 (2H, m, C₈H₈), 7.48-7.10 (11H, m, C₈H₈), 6.95-6.80 (1H, t, J 8.5 Hz, C₈H₈), 4.67-4.54 (1H, m, NHCH₃HβAr), 4.12-3.95 (1H, m, NHCH₂CH₂H₂CH₂NMe₂), 3.70-3.60 (1H, m, NHCH₃HβAr), 3.55-3.38 (1H, m, NHCH₂CH₂H₂CH₂NMe₂), 3.00 (3H, s, C₈H₈SO₂C₁₈H₃₅), 2.96 (7H, m, N(CH₃)₂, NHCH₂HβCH₂NMe₂), 2.77 (3H, s, C₈H₈SO₂C₁₈H₃₅) and 2.20-2.09 (NHCH₂CH₂H₂NMe₂); ν C (75 MHz, CDCl₃) 139.6 (d, J 15, C(ipso)₂), 134.4 (d, J 8, C₈H₈), 133.9 (d, J 43, C(ipso)₂), 133.5 (d, J 9, C₈H₈), 131.7 (d, J 2, C₈H₈), 131.5 (d, J 42, C(ipso)₂), 129.7 (C₈H₈), 129.6 (d, J 3, C₈H₈), 129.1 (d, J 2, C₈H₈), 128.8 (d, J 2, C₈H₈), 128.6 (d, J 43, C(ipso)₂), 127.8 (d, J 7, C₈H₈), 127.2 (d, J 9, C₈H₈), 126.4 (d, J 9, C₈H₈), 61.9 (CH₂), 56.1 (d, J 7, NHCH₂Ar), 51.3 (CH₂), 49.7 (N(C₈H₈)₃C₁₈H₃₅), 49.0 (N(C₈H₈)₃C₁₈H₃₅), 47.5 (C₈H₈SO₂C₁₈H₃₅) and 45.5 (C₈H₈SO₂C₁₈H₃₅); δ p (121 MHz, CDCl₃) +42.5; HRMS (ES+) found 607.0577 ([M+H⁺]), [C₂₅H₉₃N₂O₆RuS₁₅Cl₂]** requires 607.0574.
Complex 265

Prepared using the general procedure outlined in section 5.3.1 giving complex 265 as a brown/red solid (0.040 g, 65 %), m.p. > 170°C (decomp.). Found: C, 49.96; H, 5.59; N, 4.44%; C_{26}H_{35}Cl_{2}N_{2}OPRuS requires C, 49.84; H, 5.63; N, 4.47%; \nu_{max}/\text{cm}^{-1} (KBr) 3054, 2918, 1944, 1482, 1435, 1128, 1072, 1013, 958, 840, 751, 697 and 536; \delta_{H} (300 MHz, CDCl_{3}) 7.76-7.58 (2H, m, C_{Ar}H), 7.50-7.24 (6H, m, C_{Ar}H), 7.23-7.08 (5H, m, C_{Ar}H), 6.95 (1H, t, J 9, C_{Ar}H), 5.86 (1H, d, J 14, NHC_{A}H_{C_{B}}H_{A}), 3.38-3.11 (4H, m, -N(Me)C_{H}2C_{H}2NMe_{2}), 3.01 (6H, s, N(CH_{3})_{2}), 2.80 (3H, s, N(CH_{3})CH_{2}Ar), 2.61 (3H, s, C_{A}H_{3}SOC_{B}H_{3}), 2.40 (3H, s, C_{A}H_{3}SOC_{B}H_{3}) and 2.22 (1H, J 14, NHC_{A}H_{C_{B}}H_{A}); \delta_{C} (75 MHz, CDCl_{3}) 142.0 (d, J 14, C_{ipso}), 137.1 (d, J 42, C_{ipso}), 136.3 (C_{A}H), 134.2 (d, J 9, C_{A}H), 132.9 (d, J 9, C_{A}H), 129.7 (d, J 39, C_{ipso}), 129.2 (d, J 10, C_{A}H), 129.2 (d, J 10, C_{A}H), 128.6 (d, J 45, C_{ipso}), 128.6 (d, J 15, C_{A}H), 128.6 (d, J 15, C_{A}H), 127.0 (d, J 9, C_{A}H), 126.3 (d, J 9, C_{A}H), 125.3 (d, J 6, C_{A}H), 65.4 (CH_{2}), 63.2 (CH_{2}), 59.2 (NMeCH_{2}Ar), 49.4 (NCH_{3}), 48.8 (NCH_{3}), 48.3 (NCH_{3}), 46.0 (C_{A}H_{3}SOC_{B}H_{3}) and 43.9 (C_{A}H_{3}SO_{3}C_{B}H_{3}); \delta_{P} (121 MHz, CDCl_{3}) +49.7; m/z (EI) 628.1 ([M+H]^+, 100 %), 548.1 ([M-DMSO]^+, 20) and 512.1 ([M-DMSO-HCl]^+, 95). Assignments supported by ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC correlations. Assignments supported ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC correlations.

Complex (R)-285

A solution of trans-[RuCl_{2}(NBD)(py)]_{2} 284 (0.056 g, 0.13 mmol) and (R)-BINAP (0.083 g, 0.13 mmol) in dichloromethane was heated at 120°C for 1 h in the microwave. The mixture was concentrated in vacuo and the residue recrystallised from dichloromethane/hexane to give the title compound as orange crystals (0.087 g, 69%). \delta_{H} (300 MHz, CDCl_{3}) 8.14-8.04 (2H, m, C_{A}H), 7.95-7.83 (4H, m, C_{A}H), 7.68-7.56 (6H, m, C_{A}H), 7.46 (2H, d, J 8, C_{A}H), 7.19-7.03 (4H, m, C_{A}H), 6.85 (2H, app t, J 8, C_{A}H), 6.75 (4H, app t, J 8, C_{A}H), 6.66-6.58 (2H, m C_{A}H)
and 6.26 (2H, d, J 8, C_AH); δ_p (121 MHz, CDCl_3) +41.0. Data are in agreement with the literature.¹⁵

**Complex (R,R)-290**

Prepared using the general procedure outlined in section 5.3.1 giving Complex (R,R)-290, after column chromatography (silica, DCM:acetone 100:0 → 50:50), as a brown/red solid (0.092 g, 85 %), m.p. 177-180 °C (decomp.). Found: C, 49.75; H, 5.52; N, 3.98%; C_{29}H_{39}Cl_2N_2O_3PRuS requires C, 49.86; H, 5.63; N, 4.01%; [α]_D^{20} +37.9 (c 0.4, CHCl_3); ν_{max}/cm⁻¹ (PTFE Card) 3906 (w), 3403 (m), 2928 (m), 2855 (w), 1567 (s), 1593 (m), 1440 (m), 1401 (w), 1287 (m), 1251 (m), 1183 (s), 1144 (m), 1094 (s), 1056 (w), 1024 (m), 827.8 (m), 798.0 (m), 758.5 (w), 718.9 (w), 680.8 (m), 539.8 (m), 431.3 (w) and 435.2 (w); δ_H (300 MHz, CDCl_3) 7.43-7.22 (7H, m, C_AH), 7.12 (1H, app ddd, J 9,8,1, C_AH), 6.78 (4H, app ddd, J 13,9,2, C_AH), 4.35 (1H, t, J 11, C_H), 4.00 (1H, dd, J 12,6, CH), 3.97-3.89 (1H, m, NH), 3.74 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.24 (1H, t, J 12, CH), 3.11 (1H, qd, J 14, 4, CH), 2.98 (3H, s, C(H_A)SOC(H_B)), 2.67-2.58 (1H, m, NH), 2.54 (3H, s, C(H_A)SOC(H_B)), 1.78-1.62 (4H, m, NH + cyclohexyl CH), 1.38 (1H, m, cyclohexyl CH), 1.24-1.08 (3H, m, cyclohexyl CH) and 0.99 (1H, m, cyclohexyl CH); δ_C (300 MHz, CDCl_3) 160.8 (d, J 7, C_ipso), 140.8 (d, J 19, C_ipso), 136.9 (d, J 13, C_AH), 135.6 (d, J 11, C_AH), 134.0 (d, J 38, C_ipso), 132.4 (C_AH), 131.0 (d, J 9, C_AH), 130.5 (C_AH), 128.8 (d, J 9, C_AH), 126.6 (d, J 46, C_ipso), 122.2 (d, J 46, C_ipso), 119.1 (C_ipso), 113.7 (d, J 14, C_AH), 113.2 (d, J 14, C_AH), 63.7 (CHN), 57.1 (CHN), 55.2 (OCH_3), 55.1 (OCH_3), 52.4 (d, J 8, CH_2Ar), 46.9 (C(H_A)SOC(H_B)), 45.5 (C(H_A)SOC(H_B)), 36.0 (cyclohexyl CH_2), 30.6 (cyclohexyl CH_2), 24.8 (cyclohexyl CH_2) and 24.4 (cyclohexyl CH_2); δ_p (121 MHz, CDCl_3) + 39.6 ; m/z (ES+) 584.63 ([M-Cl-DMSO]^+, 100%); HRMS (ES+) found 585.1008, [C_{27}H_{35}ClN_2O_3PRu]^+ requires 585.1012.
Prepared using the general procedure outlined in section 5.3.1 giving Complex \((R,R)-297\), after column chromatography (silica, DCM:acetone 75:25), as a brown/red solid (0.141 g, 70 %), m.p. 175-176°C (decomp.). This complex showed a single peak in the \(^{31}\text{P}\) NMR, and the expected spectroscopic data that confirm its structure and purity, but held onto some residual solvents even after drying preventing good microanalysis. \([\alpha]_{\text{D}}^{20} +28.2 \ (c \ 0.2, \text{CDCl}_3)\); \(\nu_{\text{max}}/\text{cm}^{-1}\) (IR card) 2921 (m), 2857 (w), 1583 (m), 1446 (m), 1268 (m), 1194 (m), 1131 (m), 1045 (s), 999 (s), 852 (m), 758 (m), 694 (s), 574 (m) and 467 (m); \(\delta_{\text{H}}(400 \text{ MHz, } \text{C}_6\text{D}_6)\) \(7.40-7.05 \ (6\text{H, m, } \text{C}_\text{Ar}H), \ 7.02-6.87 \ (4\text{H, m, } \text{C}_\text{Ar}H), \ 4.32 \ (1\text{H, app t, } J = 10, \text{C}_\text{H}A \text{H}_B \text{Ar}), \ 4.10-3.95 \ (2\text{H, m, } \text{N}_\text{H}+ \text{CH}_A \text{H}_B \text{Ar}), \ 3.82-3.65 \ (1\text{H, br s, } \text{N}_\text{H}), \ 3.34-3.09 \ (2\text{H, m, } \text{N}_\text{H}+ \text{C}_\text{H}A \text{H}_B \text{Ar}), \ 3.05 \ (3\text{H, s, } \text{C}(\text{H}_A)_3 \text{SOC}(\text{H}_B)_3)), \ 2.66-2.58 \ (1\text{H, m, } \text{CH}), \ 2.43 \ (3\text{H, s, } \text{C}(\text{H}_A)_3 \text{SOC}(\text{H}_B)_3)), \ 2.17 \ (6\text{H, 2 x Ar-CH}_3),\ 2.14 \ (6\text{H, 2 x Ar-CH}_3), \ 1.80-1.58 \ (3\text{H, m, cyclohexyl CH}), \text{ and } 1.42-0.90 \ (5\text{H, m, cyclohexyl CH}); \delta_{\text{C}}(101 \text{ MHz, } \text{C}_6\text{D}_6) \ 139.9 \ (d, J = 15, \text{C}_\text{ipso}), \ 136.5 \ (d, J = 16, \text{C}_\text{ipso-CH}_3), \ 135.7 \ (d, J = 10, \text{C}_\text{ipso-CH}_3), \ 134.0 \ (d, J = 10, \text{C}_\text{ipso-CH}_3), \ 132.4 \ (d, J = 10, \text{C}_\text{ipso-CH}_3), \ 132.0 \ (C_\text{Ar}H), \ 131.9 \ (C_\text{Ar}H), \ 131.6 \ (C_\text{Ar}H), \ 130.7 \ (C_\text{Ar}H), \ 130.5 \ (d, J = 11, \text{C}_\text{Ar}H), \ 129.8 \ (d, J = 7, \text{C}_\text{Ar}H), \ 129.5 \ (d, J = 14, \text{C}_\text{Ar}H), \ 129.4 \ (C_\text{Ar}H), \ 127.7 \ (d, J = 6, \text{C}_\text{Ar}H), \ 62.9 \ (\text{CHN}), \ 55.9 \ (\text{CHN}), \ 51.5 \ (d, J = 8, \text{CH}_2\text{Ar}), \ 45.7 \ (\text{C}(\text{H}_A)_3 \text{SOC}(\text{H}_B)_3)), \ 34.9 \ (\text{cyclohexyl CH}_2), \ 29.6 \ (\text{cyclohexyl CH}_2), \ 23.8 \ (\text{cyclohexyl CH}_2), \ 23.4 \ (\text{cyclohexyl CH}_2), \ 20.5 \ (\text{Ar-CH}_3) \text{ and } 20.4 \ (\text{Ar-CH}_3); \delta_{\text{P}}(121 \text{ MHz, } \text{CDCl}_3) +40.6; \ m/z \ (\text{ES+}) \ 717.11 \ [\text{M}+\text{Na}]^+, \ 100\%); \text{ HRMS (ES+)} \text{ found 717.1176, } \ [\text{C}_3\text{H}_3\text{Cl}_2\text{N}_2\text{PRuSNa}]^+ \text{ requires 711.1179.} \ ^1\text{Assignments supported by } ^1\text{H}-^1\text{H COSY, } ^1\text{H}-^13\text{C HSQC and } ^1\text{H}-^13\text{C HMBC correlations.} \ ^2\text{Assignments supported by } ^1\text{H}-^13\text{C HSQC and HMBC correlations.} \n
\text{Complex } (R,R)-298 \n
Prepared using the general procedure outlined in section 5.3.1 giving Complex \((R,R)-298\), after column chromatography (silica, DCM:acetone 80:20), as a brown/red solid (0.030 g, 50 %),
m.p. 180-181°C (decomp.). This complex showed a single peak in the $^{31}$P NMR, and the expected spectroscopic data that confirm its structure and purity, but held onto some residual solvents even after drying preventing good microanalysis. $[\alpha]_{D}^{20} +50.0$ (c 0.2, CDCl$_3$); $\nu_{max}$/cm$^{-1}$ (IR card); 3287 (br s), 2960 (m), 2140 (w), 1634 (m), 1476 (w), 1362 (w), 1263 (w), 1201 (m), 1147 (w), 1015 (m), 798 (w), 752 (w), 709 (w), 637 (w), 601 (w) and 489 (w); $\delta_h$ (400 MHz, C$_6$D$_6$) 7.87-7.78 (2H, m, C$_{Ar}H$), 7.68 (1H, app t, $J$ 8, C$_{Ar}H$), 7.42-7.39 (1H, m, C$_{Ar}H$), 7.36-7.33 (1H, m, C$_{Ar}H$), 7.10-6.96 (4H, m, C$_{Ar}H$), 6.80 (1H, dd, $J$ 7, 3, C$_{Ar}H$), 4.53 (1H, t, $J$ 12, C$_{H}$), 4.14 (1H, br s, N$_H$), 3.87-3.76 (1H, m, C$_{H}$), 3.44 (1H, dd, $J$ 12, 4, C$_{H}$), 3.21 (3H, s, C($H_A$)$_3$SOC($H_B$)$_3$), 2.94 (1H, dd, $J$ 12, 4, C$_{H}$), 2.26 (3H, s, C($H_A$)$_3$SOC($H_B$)$_3$), 1.76 (1H, d, J 12, cyclohexyl $CH$), 1.27-0.73 (9H, m, cyclohexyl C$_H$), 1.17 (18H, s, 2 x C(CH$_3$)$_2$) and 1.10 (18H, s, 2 x C(CH$_3$)$_2$); $\delta_C$ (300 MHz, C$_6$D$_6$) 150.4 (d, $J$ 9, C$_{ipso}$), 150.1 (d, $J$ 9, C$_{ipso}$), 141.8 (d, J 17, C$_{ipso}$), 135.9 (d, J 40, C$_{ipso}$), 134.9 (d, J 36, C$_{ipso}$), 132.6 (C$_{Ar}H$), 132.1 (d, J 40, C$_{ipso}$), 131.1 (C$_{Ar}H$), 131.1 (C$_{Ar}H$), 130.9 (C$_{Ar}H$), 129.9 (C$_{Ar}H$), 123.4 (C$_{Ar}H$), 122.4 (C$_{Ar}H$), 63.8 (CHN), 56.6 (CHN), 52.6 (d, J 8, CH$_2$Ar), 46.7 (C($H_A$)$_3$SOC($H_B$)$_3$), 44.3 (C($H_A$)$_3$SOC($H_B$)$_3$), 35.1 (cyclohexyl CH$_2$), 35.1 (cyclohexyl CH$_2$), 34.9 (cyclohexyl CH$_2$), 31.4 (C(CH$_3$)$_3$), 31.2 (C(CH$_3$)$_3$), 24.4 (C(CH$_3$)$_3$) and 24.1 (C(CH$_3$)$_3$); $\delta_p$ (162 MHz, CDCl$_3$) +45.2; $m/z$ (ES+) 748.71 ([M-Cl-DMSO]$^+$, 100%); HRMS (ES+) found 749.3304, [C$_{41}$H$_{61}$ClN$_2$PRu]$^+$ requires 749.3302.

**Complex (R,R)-302**

The DPEN-derived ligand (R,R)-301 was prepared in the same manner as ligand (R,R)-307 and NMR analysis of the reaction mixture after treatment with sodium borohydride for 16 h showed complete conversion to one phosphorus containing species believed to be the desired product ($\delta_p$ = -7.9 ppm (C$_6$D$_6$)), disappearance of imine proton at 9.17 ppm in $^1$H NMR spectrum). Upon work-up however, the $^{31}$P NMR spectrum showed the presence of three species at $\delta_p$ (C$_6$D$_6$) = -9.6, -15.9 and -16.2 ppm ($\sim$ 3:1:1). Due to the apparent inseparability of the species and the sensitive nature of such compounds, it was decided to use the crude mixture directly in the complexation reaction, as described in the general procedure. This gave phosphorus containing species at $\delta_p$ (CDCl$_3$) = +42.4, -16.4 and -16.9 ppm ($\sim$ 3:1:1). It was believed that the species at $\delta_p$ (CDCl$_3$) = +42.4 corresponded to the desired complex and indeed following column...
chromatography on silica (DCM:acetone 80:20), analytically pure complex \((R,R)-302\) was furnished as a red/orange solid (0.100 g, 62 %), m.p. 187-189°C (decomp.). Found: C, 56.86; H, 4.82; N, 3.68%; \(C_{33}H_{31}Cl_2N_2OPRu\)S requires C, 57.06; H, 5.06; N, 3.80%; \(\alpha D^{20} +79.3 \text{ (c 0.2, CHCl}_3)\); \(\delta_{\text{IR card}}\) 3411 (br, s), 1278 (br, s), 1179 (s), 1061 (m), 700 (m), 573 (w), 534 (w), 432 (w) and 415 (w); \(\delta_{\text{H (400 MHz, CDCl}_3)}\)† 7.59-7.41 (4H, m, \(C_AH\)), 7.37-7.22 (10H, m, \(C_AH\)), 7.18-7.03 (8H, m, \(C_AH\)), 6.77-6.67 (1H, m, \(C_AH\)), 4.78-4.70 (1H, m, \(CHN\)), 4.51 (1H, br s, \(NH\)), 4.43-4.27 (3H, m, \(CH_AH\_BAr +NH_2\)), 4.13-4.06 (1H, m, \(CHN\)), and 3.54-3.44 (1H, m, \(CH_AH\_BAr\)); \(\delta_{\text{C (100 MHz, CDCl}_3)}\)‡ 140.6 (d, \(J_{Cipso} 16\), \(Cipso\)), 139.4 (\(Cipso\)), 136.7 (\(Cipso\)), 135.6 (\(Cipso\)), 135.3 (\(C_AH\)), 135.2 (\(C_AH\)), 134.0 (\(C_AH\)), 132.9 (\(Cipso\)), 132.7 (\(C_AH\)), 132.5 (\(Cipso\)), 130.8 (\(C_AH\)), 130.7 (\(Cipso\)), 130.0 (\(C_AH\)), 128.9 (\(C_AH\)), 128.6 (\(Cipso\)), 128.3 (\(C_AH\)), 128.2 (\(C_AH\)), 128.2 (\(Cipso\)), 127.8 (\(Cipso\)), 127.6 (\(C_AH\)), 127.4 (\(C_AH\)), 71.6 (CHN), 63.2 (CHN), 54.1 (d, \(J 7\), \(CH_2Ar\)), 47.0 (\(CH_AH\_BAr +NH_2\) and 45.3 (\(CH_AH\_BAr +NH_2\)); \(\delta_{\text{P (162 MHz, CDCl}_3)}\) +42.4; \(m/z\) (ES+) 623.1 ([M-Cl-DMSO]+, 100%); HRMS (ES+) found 623.0956, \([C_{33}H_{31}Cl_2N_2PRu]^+\) requires 623.0956. †Assignments supported by \(^1H-^1H\) COSY, \(^1H-^{13}C\) HSQC and \(^1H-^{13}C\) HMBC correlations. ‡Assignments supported by \(^1H-^{13}C\) HSQC and HMBC correlations.

5.8 Preparation of Substrates

Acetophenone 81, isobutyrophenone 82, trimethylacetophenone 159 and styrene 286 were purchased commercially and used as received. 2,2-Dimethyl-1-(2-furyl)-1-propanone 210 and 1,1’-(Furan-2,5-diyl)bis(2,2-dimethylpropan-1-one) 226 were prepared in this laboratory by Jose A. Fuentes.

2-Methyl-1,2-diphenylpropan-1-one (183)

Prepared following a literature procedure.\(^\text{16}\) To a suspension of bis(dibenzylideneacetone)palladium (0) (53.0 mg, 0.09 mmol), 1,1’-di-tert-butylphosphino)ferrocene (69.0 mg, 0.12 mmol) and sodium tert-butoxide (660 mg, 6.89 mmol) in tetrahydrofuran were added bromobenzene (721 mg, 4.59 mmol) and isobutyrophenone (749 mg, 5.05 mmol). The reaction mixture was then warmed to 50°C for 6 h. The mixture was subsequently diluted with ether and washed with water and brine. The organic layer was dried over MgSO\(_4\) and concentrated \(in\ vacuo\). The residue was chromatographed on silica gel (95:5
hexane:diethyl ether) to give the pure product as a colourless solid (0.55 g, 49 %), m.p. 45-46°C (lit. 17 46-47°C). δH (300 MHz, CDCl3) 7.46-7.37 (2H, m, CArH), 7.33-7.23 (5H, m, CArH), 7.22-7.08 (3H, m, CArH) and 1.53 (6H, s, C(CH3)2); δC (75 MHz CDCl3) 202.7 (C=O), 144.2 (COCipso), 135.2 (C(CH3)2Cipso), 130.6 (CArH), 128.8 (CArH), 128.0 (CArH), 126.9 (CArH), 125.7 (CArH), 124.7 (CArH), 50.4 (C(CH3)2) and 26.8 (C(CH3)2); m/z (ES+) 247.08 ((M+Na)+, 100 %). Data are in agreement with the literature.

2-Ethyl-1,2-diphenylbutan-1-one (184)

To a suspension of sodium hydride (0.37 g, 15.29 mmol) in tetrahydrofuran (40 mL) at 0°C was added a solution of deoxybenzoin (1.00 g, 5.10 mmol) in tetrahydrofuran (10 mL), dropwise via cannula. The mixture was allowed to warm to rt and stirred for one hour before recooling to 0°C. Iodoethane (1.22 mL, 15.29 mmol) was then added dropwise and the mixture allowed to warm to rt over 16 h with stirring. Excess sodium hydride was then quenched with cautious addition of ethyl acetate and followed by water. The reaction mixture was partitioned between water and diethyl ether and the organic fractions collected. Subsequent drying of the organic phase over magnesium sulfate, filtration and concentration of the filtrate yielded the product. NMR examination of the product showed it to be a mixture of the mono- and di-alkylated ketone. This crude material was then resubjected to the initial reaction conditions, first by dropwise addition to a suspension of sodium hydride (0.37 g, 15.29 mmol) in tetrahydrofuran (40 mL) at 0°C, then after a period of stirring between 0°C and rt, addition of iodoethane (1.22 mL, 15.29 mmol) and continuation of stirring for 16 h. Quenching of the reaction followed by work-up as described previously furnished the dialkylated ketone exclusively. Purification by short-path distillation yielded the ketone (0.86 g, 67 %) as a colourless oil. δH (400 MHz, CDCl3) 7.34-7.25 (5H, m, CArH), 7.23-7.17 (3H, m, CArH), 7.15-7.09 (2H, m, CArH), 2.14-1.98 (4H, m, C(CH2CH3)2 and 0.57 (6H, t, J 7.5, C(CH2CH3)2); δC (75 MHz CDCl3) 215.9 (C=O), 143.0 (COCipso), 137.4 (Cipso), 131.5 (CArH), 129.3 (CArH), 128.8 (CArH), 127.9 (CArH), 127.0 (CArH), 126.8 (CArH), 58.6 (C(CH2CH3)2), 26.4 (C(CH2CH3)2) and 7.8 (C(CH2CH3)2); m/z (ES+) 275.18 ((M+Na)+, 100 %). Data are in agreement with the literature.
1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one (197)

Prepared by modification of literature procedures.\textsuperscript{19,20} To a suspension of copper bromide dimethyl sulfide complex (1.33 g, 6.49 mmol) in tetrahydrofuran (20 mL) at -78°C was added a 1.7 M solution of tert-butyllithium in pentane (4.33 mL, 6.49 mmol). After stirring for 30 min, a solution of 4-methoxybenzoyl chloride (1.00 g, 5.86 mmol) in tetrahydrofuran (5 mL) was added slowly via cannula. After stirring for 4 h, the reaction was quenched by addition of saturated ammonium chloride solution and the organic layer separated. The aqueous layer was extracted with diethyl ether and the organic fractions combined, dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. The residue was purified by short-path distillation to yield the product as a colourless oil (0.73 g, 65 %). $\delta_{H}$ (300 MHz, CDCl\textsubscript{3}) 7.81-7.74 (2H, d, $J_{C_{Ar}-H}$), 6.85-6.79 (2H, d, $J_{C_{Ar}-H}$), 3.78 (3H, s, $OC_{H_{3}}$) and 1.30 (9H, s, $C(CH_{3})_{3}$); $\delta_{C}$ (75 MHz CDCl\textsubscript{3}) 206.3 (C=O), 162.0 (CO$C_{ipso}$), 131.0 ($C_{Ar}$H), 130.1 ($C_{ipso}$OMe), 113.2 ($C_{Ar}$H), 55.4 ($OCH_{3}$), 43.9 ($C(CH_{3})_{3}$) and 28.4 ($C(CH_{3})_{3}$); m/z (CI+) 193.1 ((M+H)$^{+}$, 100 %), 135.1, 109.1 and 85.1. Data are in agreement with the literature.\textsuperscript{21}

1-(4-Chlorophenyl)-2,2-dimethylpropan-1-one (198)

Prepared by same method as for compound 197 giving the product as a colourless oil (0.75 g, 67 %). $\delta_{H}$ (300 MHz, CDCl\textsubscript{3}) 7.62-7.56 (2H, m, $C_{Ar}$H), 7.32-7.26 (2H, m, $C_{Ar}$H) and 1.26 (9H, s, $C(CH_{3})_{3}$); $\delta_{C}$ (75 MHz CDCl\textsubscript{3}) 207.7 (C=O), 137.2 ($C_{ipso}$), 136.5 ($C_{ipso}$OMe), 129.6 ($C_{Ar}$H), 128.4 ($C_{Ar}$H), 44.2 ($C(CH_{3})_{3}$) and 28.0 ($C(CH_{3})_{3}$); m/z (ES+) 219.02 ((M+H)$^{+}$, 100 %). Data are in agreement with the literature.\textsuperscript{22}

1-(4-Trifluoromethyl)-2,2-dimethylpropan-1-one (199)

Prepared by same method as for compound 197 giving the product as a colourless oil (0.83 g, 49 %). $\delta_{H}$ (400 MHz, CDCl\textsubscript{3}) 7.66-7.61 (2H, m, $C_{Ar}$H), 7.59-7.55 (2H, m, $C_{Ar}$H) and 1.24 (9H, s,
C(CH$_3$)$_3$; $\delta$C (101 MHz, CDCl$_3$) 208.9 (C=O), 142.1 (COC$_{ipso}$), 127.8 (q, $^2$J$_{CF}$ 32.9, C$_{ipso}$CF$_3$), 125.1 (q, $^3$J$_{CF}$ 3.6, C$_{ipso}$HCCF$_3$), 123.7 (q, $^1$J$_{CF}$ 272.6, CF$_3$), 44.4 (C(CH$_3$)$_3$) and 27.7 (C(CH$_3$)$_3$); $\delta$F (376 MHz, CDCl$_3$) - 63.5; m/z (CI+) 231.10 (M+H$^+$, 100 %). Data are in agreement with the literature.$^{21}$

1-(2-Methoxyphenyl)-2,2-dimethylpropan-1-one (200)

![Chemical Structure](image)

Prepared by same method as for compound 197 giving the product as a colourless oil (1.62 g, 70 %). $\delta$H (300 MHz, CDCl$_3$) 7.28-7.20 (1H, m, C$_{Ar}$H), 6.98-6.90 (1H, m, C$_{Ar}$H), 6.89-6.78 (2H, m, C$_{Ar}$H), 3.71 (3H, s, OCH$_3$) and 1.14 (9H, s, C(CH$_3$)$_3$); $\delta$C (101 MHz CDCl$_3$) 213.9 (C=O), 155.3 (COC$_{ipso}$), 129.9 (C$_{ipso}$OMe), 126.3 (C$_{Ar}$H), 120.2 (C$_{Ar}$H), 110.9 (C$_{Ar}$H), 55.3 (OCH$_3$), and 26.8 (C(CH$_3$)$_3$); m/z (ES+) 215.11 ((M+Na)$^+$, 100 %). Data are in agreement with the literature.$^{23}$

2,2-Dimethyl-1-(pyridin-4-yl)propan-1-one (209)

![Chemical Structure](image)

To a suspension of sodium hydride (1.72 g, 71.75 mmol) in tetrahydrofuran (120 mL) at 0°C was added a solution of 4-acetylpyridine (0.91 mL, 8.21 mmol) in tetrahydrofuran (10 mL) dropwise via cannula. The mixture was allowed to warm to rt and stirred for one hour before recooling to 0 °C. Iodomethane (4.48 mL, 72.00 mmol) was then added dropwise and the mixture stirred between 0 °C and rt for 16 h. Excess sodium hydride was then quenched with cautious addition of ethyl acetate followed by water. The reaction mixture was partitioned between water and diethyl ether and the organic fractions collected. Subsequent drying of the organic phase over magnesium sulfate, filtration and concentration of the filtrate yielded the product. NMR examination of the product showed it to be a mixture of the tri- and di-alkylated ketone. This crude material was then resubjected to the initial reaction conditions, first by dropwise addition to a suspension of sodium hydride (1.72 g, 71.75 mmol) in tetrahydrofuran (120 mL) at 0°C, then after a period of stirring between 0°C and rt, addition of iodomethane (4.48 mL, 72.00 mmol) and continuation of stirring for 16 h. Quenching of the reaction followed by work-up as described previously, furnished the trialkylated ketone exclusively.
Purification by short-path distillation yielded the ketone (1.35 g, 57 %) as a colourless oil. \( \delta_H \) (300 MHz, CDCl\(_3\)) 8.65-8.58 (2H, m, C\(_{\text{Ar}}\)H), 7.33-7.29 (2H, m, C\(_{\text{Ar}}\)H) and 1.23 (9H, s, C(CH\(_3\)_3)); \( \delta_C \) (75 MHz CDCl\(_3\)) 209.1 (C=O), 150.3 (C\(_{\text{ipso}}\)H), 146.4 (C\(_{\text{Ar}}\)H), 146.4 (C\(_{\text{Ar}}\)H), 121.4 (C\(_{\text{Ar}}\)H), 44.8 (C(CH\(_3\)_3)) and 27.6 (C(CH\(_3\)_3)); m/z (Cl+) 164.11 ((M+H)\(^+\), 100 %). Data are in agreement with the literature.\(^{24}\)

1-(Thien-2-yl)-2,2-dimethylpropan-1-one (211)

To a solution of thiophene (3.20 mL, 40 mmol) and pivaloyl chloride (4.92 mL, 40 mmol) in toluene (40 mL) at 0°C was added a solution of stannic chloride (10.5 g, 40 mmol) dropwise over a period of 15 min. The reaction mixture was stirred for a further 1 h at rt. It was then diluted with diethyl ether and added to 2M hydrochloric acid solution (30 mL). The organic layer was separated and washed thoroughly with water, dried with magnesium sulfate, filtered and concentrated \textit{in vacuo}. Purification by short-path distillation furnished the pure product as a colourless oil (5.04 g, 75 %). \( \delta_H \) (CDCl\(_3\), 400 MHz) 7.71 (1H, dd, \( J \) 4, 1, C\(_{\text{Ar}}\)H), 7.49 (1H, dd, J 5, 1, C\(_{\text{Ar}}\)H), 7.04 (1H, dd, J 5, 4, C\(_{\text{Ar}}\)H) and 1.33 (9H, s, C(CH\(_3\)_3)); \( \delta_C \) (CDCl\(_3\), 75 MHz) 199.0 (C=O), 142.6 (C\(_{\text{ipso}}\)H), 132.4 (C\(_{\text{Ar}}\)H), 131.9 (C\(_{\text{Ar}}\)H), 127.8 (C\(_{\text{Ar}}\)H), 43.9 (C(CH\(_3\)_3)) and 28.2 (C(CH\(_3\)_3)); m/z (ES+) 190.96 ([M+Na]\(^+\), 100%) and 358.97 ([M+Na]\(^+\), 50). Data are in agreement with the literature.\(^{25}\)

\textit{N}-Hydroxy-4-methoxybenzimidoyl chloride (217)

Prepared by modification of literature procedures.\(^{26,27}\) To a mixture of 4-methoxybenzaldehyde 215 (6.09 mL, 50.00 mmol) in water (12.5 mL), absolute ethanol (12.5 mL) and ice (ca. 10 mL) was added hydroxylamine hydrochloride (3.82 g, 55.00 mmol). To this was added 50 % sodium hydroxide solution (125.00 mmol) and the mixture was stirred for 1 h whilst maintaining the temperature between 25-30°C by the addition of further ice. The mixture was then extracted with diethyl ether, acidified with concentrated hydrochloric acid then further extracted with diethyl ether (x2). The latter two extracts were combined, dried with magnesium sulfate, filtered and concentrated to give solid oxime (5.35 g, 71 %). \( \delta_H \) (400 MHz, CDCl\(_3\)) 8.68 (1H, br s,
NOH), 8.14 (1H, s, N=CHAr), 7.57-7.53 (2H, m, C_ArH), 6.97-6.91 (2H, m, C_ArH) and 3.86 (3H, s, OCH_3). The oxime 216 (5.35 g, 40.00 mmol) was dissolved in N,N-dimethylformamide (50 mL) and to this was added N-chlorosuccinimide (5.35 g, 40.00 mmol) portionwise, allowing for an initial induction period and avoiding vigorous reaction by cooling using a dry ice bath. Completion of the reaction was indicated by the cessation of the exotherm and the reaction mixture was then poured into four volumes of ice water. The mixture was extracted twice with diethyl ether, washed with water, dried over magnesium sulfate, filtered and concentrated to yield the product 217 as a yellow solid (4.83 g, 65 %), mp 106-108°C (lit. 112-112.5°C. δ_H (400 MHz, CDCl_3) 9.35 (1H, br s, NOH), 7.84-7.76 (2H, m, C_ArH), 6.97-6.89 (2H, m, C_ArH) and 3.86 (3H, s, OCH_3). Data are in agreement with the literature.

[5-n-Butyl-3-(4-methoxyphenyl)isoxazol-4-yl](4-methoxyphenyl)methanone (212)

Prepared following a literature procedure. To a solution of bis(triphenylphosphine)palladium(II) dichloride (0.022 g, 0.03 mmol) and copper (I) iodide (0.012 g, 0.06 mmol) in degassed tetrahydrofuran (4 mL) in a microwave vial under nitrogen was added 4-methoxybenzoyl chloride 218 (0.21 mL, 1.53 mmol), hex-1-yne 219 (0.18 mL, 1.53 mmol) and triethylamine (0.22 mL, 1.60 mmol). The mixture was stirred for 1 h before N-hydroxy-4-methoxybenzimidoyl chloride 217 (0.28 g, 1.53 mmol) and triethylamine (0.23 mL, 1.68 mmol) were added. The mixture was then heated under microwave conditions at 90°C for 30 min. After cooling to room temperature, the solvent was removed in vacuo and the crude product was purified by flash column chromatography (hexane:diethyl ether, 3:1) to yield the pure product as a viscous colourless oil (0.117 g, 21 %). δ_H (400 MHz, CDCl_3) 7.67-7.62 (2H, m, C_ArH), 7.39-7.34 (2H, m, C_ArH), 6.77-6.69 (4H, m, C_ArH), 3.75 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 2.72 (2H, t, J 7.5, -CH_2CH_2CH_2CH_3), 1.68-1.55 (2H, m, -CH_2CH_2CH_2CH_3), 1.25 (2H, sext, J 8, -CH_2CH_2CH_2CH_3) and 0.80 (3H, t, J 7, -CH_2CH_2CH_2CH_3); δ_C (101 MHz, CDCl_3) 188.0 (C_quat), 174.1 (C_quat), 162.9 (C_quat), 160.0 (C_quat), 159.6 (C_quat), 131.0 (C_ArH), 129.3 (C_quat), 128.8 (C_ArH), 119.7 (C_quat), 114.0 (C_quat), 113.0 (C_ArH), 112.8 (C_ArH), 54.5 (OCH_3), 54.2 (OCH_3), 28.6 (-CH_2CH_2CH_2CH_3), 25.3 (-CH_2CH_2CH_2CH_3), 21.2 (-CH_2CH_2CH_2CH_3) and 12.5 (-CH_2CH_2CH_2CH_3); m/z (ES+) 388.15 ((M+Na)^+, 100 %). Data are in agreement with the literature.
3-(Benzyloxy)-2,2-dimethylpropan-1-ol (241)

Following the literature procedure of Onomura, neopentyl glycol (0.277 g, 2.7 mmol) and potassium carbonate (0.55 g, 4.0 mmol) were added to a solution of p-fluorophenylboronic acid (0.038 g, 0.27 mmol) and benzyl bromide (0.48 mL, 4.0 mmol) in DMF (10 mL) and the reaction stirred at rt for 36 h. After this time, the mixture was poured into water and extracted with ethyl acetate. The organic component was dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product as colourless oil (0.420 g, 80%), which was deemed sufficiently pure for the next step. δH (CDCl₃, 300 MHz) 7.31-7.17 (5H, m, CArH), 4.44 (2H, s, CH₂Ph), 3.38 (2H, s, CH₂), 3.25 (2H, s, CH₂), 2.56 (1H, br s, OH) and 0.86 (6H, s, C(CH₃)₂). Data are in agreement with the literature.

3-(Benzyloxy)-2,2-dimethylpropanal (242)

To a solution of oxalyl chloride (0.30 mL, 3.50 mmol) in dichloromethane (6 mL) at -78°C was added dimethylsulfoxide (0.50 mL, 7.00 mmol) and the mixture stirred for 5 min. To this, 3-(benzyloxy)-2,2-dimethylpropan-1-ol (241) (0.340 g, 1.75 mmol) was added and the reaction stirred for a further 30 min at -78°C, before addition of triethylamine (0.93 mL, 7.00 mmol) and stirring again for 45 min. After this period, the mixture was warmed to rt and 2M HCl (3 mL) was added. The mixture was extracted with dichloromethane, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica (19:1 hexane:ethyl acetate) gave the title compound as a colourless oil (0.272 g, 81%). δH (CDCl₃, 300 MHz) 9.46 (1H, s, CHO), 7.29-7.13 (5H, m, CArH), 4.40 (2H, s, CH₂Ph), 3.36 (2H, s, CH₂) and 0.99 (6H, s, C(CH₃)₂). Data are in agreement with the literature.
3-(Benzyloxy)-2,2-dimethyl-1-phenylpropan-1-ol (231)

![Chemical Structure](image)

To a solution of 3-(benzyloxy)-2,2-dimethylpropanal 242 (0.105 g, 0.55 mmol) in diethyl ether at -78°C was added phenylmagnesium bromide (0.219 mL, 3M solution in Et₂O, 0.66 mmol) and stirred for 1 h. The reaction was allowed to warm to rt and stirred for 16 h. After this time, the reaction was quenched with water, then extracted with diethyl ether. The organic component was dried over magnesium sulfate, filtered and concentrated in vacuo to give the product as a colourless oil which was used directly in the next step. δ_H (CDCl₃, 300 MHz) 7.31-7.14 (10H, m, C_ArH), 4.53 (1H, s, CH₂OH) 4.49 (2H, s, C_H₂Ph), 3.87 (1H, br s, CHO_H), 3.31 (1H, d, AB system, J=9, CAHₐHₐB), 3.23 (1H, d, AB system, J=9, CHₐHₐB), 0.82 (3H, s, C((C₃A)₃)(C₃B)₃) and 0.81 (3H, s, C((C₃A)₃)(C₃B)₃); δ_C (CDCl₃, 300 MHz) 139.9 (C_ipso), 138.5 (C_ipso), 128.5 (C_ArH), 128.3 (C_ArH), 127.7 (C_ArH), 127.7 (C_ArH), 127.6 (C_ArH), 127.2 (C_ArH), 81.5 (CHOH), 79.7 (CH₂), 74.0 (CH₂), 33.1 (C(CH₃)₂), 23.3 C(C₃A)(C₃B) and 20.1 C(C₃A)(C₃B); m/z (ES+) 293.07 ([M+Na]⁺, 100%) and 563.16 ([2M+Na]⁺, 100); HRMS (ES+) found 293.1518, C₁₈H₂₂O₂Na requires 293.1517.

3-(Benzyloxy)-2,2-dimethyl-1-phenylpropan-1-one (239)

![Chemical Structure](image)

To a solution of oxalyl chloride (0.094 mL, 1.09 mmol) in dichloromethane (6 mL) at -78°C was added dimethylsulfoxide (0.170 mL, 2.18 mmol) and the mixture stirred for 5 min. To this, 3-(benzyloxy)-2,2-dimethyl-1-phenylpropan-1-ol 231 (0.148 g, 0.55 mmol) was added and the reaction stirred for a further 30 min at -78°C, before addition of triethylamine (0.304 mL, 2.18 mmol) and stirring again for 45 min. After this period, the mixture was warmed to rt and 2M HCl (3 mL) was added. The mixture was extracted with dichloromethane, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica (19:1 hexane:ethyl acetate) gave the title compound as a colourless oil (0.102 g, 69%). δ_H (CDCl₃, 300 MHz) 7.56-7.49 (2H, m, C_ArH), 7.40-7.14 (8H, m, C_ArH), 4.39 (2H, s, CH₂Ph), 3.54 (2H, s, CH₂) and 1.27 (6H, s, C(CH₃)₂); δ_C (CDCl₃, 75 MHz) 208.9 (C=O), 139.5 (C_ipso), 138.2 (C_ipso), 130.5 (C_ArH), 128.3 (C_ArH), 128.0 (C_ArH), 127.5 (C_ArH), 127.5 (C_ArH), 127.2 (C_ArH), 73.5 (CH₂), 48.9 (CH₂), 25.4 (C(CH₃)₂) and 23.4 (C(CH₃)₂).
**4,4-Dimethyl-5-oxo-5-phenylpentanenitrile (237)**

In a similar procedure to that reported by Campbell,\textsuperscript{29} acrylonitrile (2.62 mL, 0.04 mol) was added dropwise with stirring to a solution of isobutyrophenone (6.00 mL, 0.04 mol) in dioxane (10 mL) containing 30 % solution of potassium hydroxide in methanol (0.5 mL). This solution was heated at 50 °C for 24 h. After this time, the mixture was poured into water and the oil separated. Column chromatography of this oil on silica (Hexane:EtOAc 9:1) yielded the title compound as a colourless oil (1.71 g, 21 %). Δ\textsubscript{H} (CDCl\textsubscript{3}, 300 MHz) 7.72-7.65 (2H, m, C\textsubscript{Ar}H), 7.55-7.40 (3H, m, C\textsubscript{Ar}H), 2.39-2.30 (2H, m, CH\textsubscript{2}), 2.18-2.10, (2H, m, CH\textsubscript{2}) and 1.42 (6H, s, C(CH\textsubscript{3})\textsubscript{2}); Δ\textsubscript{C} (CDCl\textsubscript{3}, 75 MHz) 207.0 (C=O), 137.9 (C\textsubscript{ipso}), 131.6 (C\textsubscript{Ar}H), 128.4 (C\textsubscript{Ar}H), 127.8 (C\textsubscript{Ar}H), 119.8 (C≡N), 47.0 (C(CH\textsubscript{3})\textsubscript{2}), 36.4 (CH\textsubscript{2}), 25.8 (C(CH\textsubscript{3})\textsubscript{2}) and 13.1 (CH\textsubscript{2}); m/z (ES+) 224.01 ([M+Na]\textsuperscript{+}, 100 %) and 425.03 ([2M+Na]\textsuperscript{+}, 25). Data are in agreement with the literature.\textsuperscript{30}

**2-(1H-Imidazol-1-yl)-2-methyl-1-phenylpropan-1-one (244)**

Prepared by modification of a literature procedure.\textsuperscript{33} A solution of imidazole (3.40 g, 49.90 mmol) and 2-bromo-2-methylpropiophenone (4.00 mL, 23.80 mmol) in absolute ethanol (40 mL) was refluxed for 3 days. The mixture was then partitioned between diethyl ether and water and the organic phase collected, dried with magnesium sulfate, filtered and concentrated to yield a yellow sticky solid. Recrystallisation from dichloromethane/hexane (1:2) afforded the desired ketone (3.14 g, 62 %) as a yellow solid, mp 118-119°C (lit. 117-119°C) Δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 7.63 (1H, br s, C\textsubscript{Ar}H), 7.43-7.35 (1H, m, C\textsubscript{Ar}H), 7.26-7.21 (4H, m, C\textsubscript{Ar}H), 7.08 (1H, br s, C\textsubscript{Ar}H), 6.90 (1H, br s, C\textsubscript{Ar}H) and 1.79 (6H, s, C(CH\textsubscript{3})\textsubscript{2}); Δ\textsubscript{C} (75 MHz CDCl\textsubscript{3}) 198.5 (C=O), 134.8 (C\textsubscript{Ar}H), 134.5 (C\textsubscript{ipso}), 132.9 (C\textsubscript{Ar}H), 130.3 (C\textsubscript{Ar}H), 128.6 (C\textsubscript{Ar}H), 128.5 (C\textsubscript{Ar}H), 117.4 (C\textsubscript{Ar}H), 64.9 (C(CH\textsubscript{3})\textsubscript{2}) and 27.2 (C(CH\textsubscript{3})\textsubscript{2}); m/z (Cl+) 215.12 ((M+H)+, 100 %). Data are in agreement with the literature.\textsuperscript{33}
Ethyl 2-cyano-5-oxo-5-phenypentanoate (251)

Prepared following the procedure of Wessig. To a solution of 1-phenylprop-2-ene-1-one (0.841 g, 6.40 mmol) and ethyl cyanoacetate (0.677 mL, 6.40 mmol) in tetrahydrofuran was added potassium carbonate (0.089 g, 6.50 mmol) and 18-crown-6 (0.142 mL, 0.66 mmol) and the mixture stirred for 2 h. After this period, water was added and the mixture diluted with diethyl ether. The organic component was separated, washed with further water, dried over magnesium sulfate, filtered, and concentrated in vacuo giving product that was deemed pure enough for direct use in the next step. δ_H (400 MHz, CDCl₃) 8.00-7.94 (2H, m, C_ArH), 7.62-7.56 (1H, m, C_ArH), 7.50-7.44 (2H, m, C_ArH), 4.26 (2H, q, J 7, C_H₂CH₃), 3.82 (1H, dd, J 10, 7, CH), 3.25 (2H, t, J 7, COCH₂), 2.56-2.24 (2H, m, COCH₂CH₂) and 1.32 (3H, t, CH₂CH₃). Data are in agreement with the literature.

5-Oxo-5-phenypentanenitrile (252)

Following the procedure of Wessig, the ester (0.90 g, 3.7 mmol), sodium chloride (0.20 g, 3.8 mmol) and water (2 mL) in dimethylsulfoxide (20 mL) were refluxed for 24 h. After this time, the mixture was diluted with further water and extracted with diethyl ether. The organic component was dried over magnesium sulfate, filtered and the solvent removed in vacuo. Flash chromatography on silica (10:2 petroleum ether:ethyl acetate) furnished the product as a colourless oil (0.320 g, 50%); δ_H (300 MHz, CDCl₃) 7.99 (2H, d, J 7, C_ArH), 7.66-7.55 (1H, m, C_ArH), 7.55-7.44 (2H, m, C_ArH), 3.20 (2H, t, J 7, CH₂), 2.54 (2H, t, J 7, CH₂) and 2.13 (2H, app pent, J 7, CH₂); δ_C (75 MHz, CDCl₃) 198.3 (C=O), 136.5 (C_ipso), 133.6 (C_ArH), 128.8 (C_ArH), 128.1 (C_ArH), 119.6 (CN), 36.5 (CH₂), 19.9 (CH₂) and 16.6 (CH₂). m/z (ES+) 196.07 ((M+Na)^+, 100%); HRMS (ES+) found 196.0743, [C_11H_11NONa]^+ requires 196.0738. Data are in agreement with the literature.
5.9 Data for Hydrogenation Products

1-Phenylethanol (12)

\[
\begin{align*}
\text{[α]}_D^{20} & -32.0 \text{ (60\% e.e., } c 2.5, \text{ CHCl}_3) \text{ (lit.}^{31} \text{ [α]}_D^{25} \text{ -45.0 (S, 99\% e.e., } c 5.0, \text{ methanol}) ; \delta_H (400 \\
& \text{MHz, CDCl}_3) 7.18-7.33 \text{ (5H, m, } C_ArH), 4.84 \text{ (1H, q, } J 6, \text{ CHOH), 1.63 \text{ (1H, br s, } -OH) \text{ and 1.43} \\
& \text{ (3H, d, } J 6, \text{ CH}_3). \text{ Enantioselectivity determined by HPLC, ChiralPak OD-H, 0.5 mL/min, 95:5} \\
& \text{hexane:2-propanol. Retention times: 17.4 min ((R)-(+) enantiomer) and 21.2 min ((S)-(--) enantiomer). Data are in agreement with the literature.}^{50}
\end{align*}
\]

2-Methyl-1-phenylpropan-1-ol (83)

\[
\begin{align*}
\text{[α]}_D^{20} & -30.1 \text{ (48\% e.e., } c 1, \text{ acetone) (lit.}^{14} \text{ [α]}_D^{25} \text{ -28.6 (S, 48\% e.e., } c 0.16, \text{ acetone}) ; \delta_H (300 \\
& \text{MHz, CDCl}_3) 7.24-7.11 \text{ (5H, m, ArCH); 4.18 (1H, d, } J 6.8, \text{ CHOH), 2.23 (br s, 1H, CHOH),} \\
& 1.82 \text{ (1H, m, CH(CH}_3)_2), 0.87 \text{ (3H, d, } J 6.8, \text{ CH(C}_AHH)_3(C}_BHH)_3) \text{ and 0.67 (3H, d, } J 6.8,} \\
& \text{CH(C}_AHH)_3(C}_BHH)_3). \text{ Enantioselectivity determined by HPLC. ChiralPak OD-H, 0.5 ml/min,} \\
& 90:10 \text{ hexane:2-propanol. Retention times: 10.8 min (S, major enantiomer) and 11.8 min (R, minor enantiomer). Data are in agreement with the literature.}^{48}
\end{align*}
\]

2-Methyl-1,2-diphenylpropan-1-ol (187)

\[
\begin{align*}
\text{[α]}_D^{20} & -34.0 \text{ (84\% e.e., } c 0.1, \text{ chloroform); } \delta_H (300 \text{ MHz, CDCl}_3) 7.36-7.21 \text{ (4H, m, } C_ArH), \\
& 7.20-7.14 \text{ (4H, m, } C_ArH), 7.09-7.03 \text{ (2H, m, } C_ArH), 4.69 \text{ (1H, s, CHOH), 1.63 (1H, br s,} \\
& \text{CHOH), 1.25 (3H, s, C(C}_AHH)_3(C}_BHH)_3) \text{ and 1.21 (3H, s, C(C}_AHH)_3(C}_BHH)_3) ; \delta_C (75 \text{ MHz CDCl}_3) \\
& 145.3 \text{ (C}_ipso), 139.8 \text{ (C}_ipso), 127.1 \text{ (C}_AHH), 126.8 \text{ (C}_AHH), 126.3 \text{ (C}_AHH), 126.3 \text{ (C}_AHH), 125.9 \text{ (}
\end{align*}
\]

\[
\begin{align*}
& \text{(C}_AHH), 125.3 \text{ (C}_AHH), 81.0 \text{ (CHOH), 42.1 (C(CH}_3)_2), 24.7 \text{ (C(C}_AHH)_3(C}_BHH)_3) \text{ and 21.4} \\
& \text{(C(C}_AHH)_3(C}_BHH)_3); \text{ m/z (ES+) 249.09 ((M+Na)^+)}, 100 \text{ %). Enantioselectivity determined by chiral} \\
& \text{HPLC. ChiralPak AD, 1.0 mL/min, 95:5 hexane:2-propanol. Retention times: 9.5 min (major}
\end{align*}
\]
enantiomer) and 11.1 min (minor enantiomer). Data are in agreement with the literature for the racemic compound that has been reported before.\textsuperscript{35}

2-Ethyl-1,2-diphenylbutan-1-ol (188)

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

\([\alpha]^{20}_D -28.1 \text{ (75\% e.e., c 0.2, chloroform); } \delta_H (400 \text{ MHz, CDCl}_3) 7.21-7.14 \text{ (3H, m, } C_AH) , \ 7.11-7.02 \text{ (5H, m, } C_AH) , \ 6.64-6.59 \text{ (2H, m, } C_AH) , \ 4.68 \text{ (1H, s, } CHOH) , \ 2.13 \text{ (1H, dq, ABX system, } J_{AB} 15.2, J_{AX} 7.4, C(CH_3)H(CH_2)D), 1.70 \text{ (1H, br s, } CHOH) , \ 1.69-1.53 \text{ (2H, m, } C(CH_3)_2H(CH_2)D)\), 0.84 (3H, t, J 7.4, C(CH_3)H(CH_2)D) and 0.77 (3H, t, J 7.4, C(CH_3)H(CH_2)D); \delta_C (101 \text{ MHz CDCl}_3) 140.6 (C_{ipso}), 140.4 (C_{ipso}), 127.8 (C_AH), 126.7 (C_AH), 126.4 (C_AH), 126.3 (C_AH), 126.1 (C_AH), 125.1 (C_AH), 78.0 (CHOH), 47.9 (C(CH_3)H_2), 23.9 (C(CH_3)H(CH_2)H_3), 23.1 (C(CH_3)H(CH_2)H_3)(C(CH_2)C(CH_2)H_3), 7.30 (C(CH_3)H(CH_2)H_3)(C(CH_2)C(CH_2)H_3)) \text{ and 7.2 (C(CH_3)H(CH_2)H_3)(C(CH_2)C(CH_2)H_3)). Enantioselectivity determined by chiral HPLC. ChiralPak AD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 12.8 min (major enantiomer) and 13.7 min (minor enantiomer).}

1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one (201)

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

\([\alpha]^{20}_D -16.3 \text{ (77\% e.e., c 4.24, toluene); lit}\textsuperscript{36} \text{ (S, 99\% e.e.) } [\alpha]^{20}_D -21.6 \text{ (c 4.24, benzene); } \delta_H (400 \text{ MHz, CDCl}_3) 7.47-7.09 \text{ (2H, m, } C_AH) , \ 6.77-6.72 \text{ (2H, m, } C_AH) , \ 4.23 \text{ (1H, s, } CHOH) , \ 3.70 \text{ (s, 3H, } OCH_3) , \ 1.92 \text{ (1H, br s, } CHOH) \text{ and 0.81 (9H, s, } C(CH_3)H); \delta_C (75 \text{ MHz, CDCl}_3) 158.8 (C_{ipso}), 134.5 (C_{ipso}), 128.7 (C_AH), 112.9 (C_AH), 82.0 (CHOH), 55.2 (OCH_3), 35.7 (C(CH_3)H), and 25.9 (C(CH_3)H)\); m/z (CI+) 195.1 ((M-H_2O), 100 \%) and 177.1 ((M+H)^+, 33 \%). Enantioselectivity determined by chiral HPLC. Chiralpak AD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 16.8 min (minor enantiomer) and 18.0 min (major enantiomer). Data are in agreement with the literature.\textsuperscript{37}
1-(4-Chlorophenyl)-2,2-dimethylpropan-1-ol (202)

\[ \text{[\(\alpha\)]\text{D}}^{20} -22.9 \text{ (80\% e.e., } c\ 1.0, \text{ chloroform)}; \delta_{\text{H}} \text{ (300 MHz, CDCl}_3\text{)} 7.25-7.14 \text{ (4H, m, C}_\text{Ar}H\text{)}, 4.30 \text{ (1H, s, CHO)}\text{), 1.73 (1H, br s, CHO) and 0.84 (9H, s, C(CH}_3\text{)_3}); \delta_{\text{C}} \text{ (75.5 MHz CDCl}_3\text{)} 133.1 \text{ (C}_\text{ipso}\text{), 129.0 (C}_\text{ipso}\text{CF), 127.7 (C}_\text{Ar}H\text{), 127.5 (C}_\text{Ar}H\text{), 81.7 (CHOH), 35.7 (C(CH}_3\text{)_3}), and 25.8 (C(CH}_3\text{)_3}); m/z (CI+) 181.1 ((M-H}_2\text{O), 100 \%)) and 199.9 ((M+H)}^+\text{, 7 \%). Enantioselectivity determined by chiral HPLC. Chiralcel OD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 10.3 min (major enantiomer) and 12.4 min (minor enantiomer). Data are in agreement with the literature for the racemic compound that has been reported before. \]

1-(4-(Trifluoromethyl)phenyl)-2,2-dimethylpropan-1-ol (203)

\[ \text{[\(\alpha\)]\text{D}}^{20} -11.3 \text{ (76\% e.e., } c\ 0.50, \text{ chloroform)}; \delta_{\text{H}} \text{ (300 MHz, CDCl}_3\text{)} 7.45-7.40 \text{ (2H, m, C}_\text{Ar}H\text{), 7.32-7.26 (2H, m, C}_\text{Ar}H\text{), 4.31 (1H, s, CHOH), 1.76 (1H, br s, CHOH) and 0.78 (9H, s, C(CH}_3\text{)_3}); \delta_{\text{C}} \text{ (75.5 MHz CDCl}_3\text{)} 146.5 \text{ (C}_\text{ipso}\text{), 129.1 (q, J}_{\text{CF}}\text{ 4.3, C}_\text{ipso}\text{CF), 127.9 (C}_\text{Ar}H\text{), 124.5 (q, J}_{\text{CF}}\text{ 3.8, C}_\text{Ar}HCCF}_3\text{), 123.7 (q, J}_{\text{CF}}\text{ 271.1, CF}_3\text{), 81.7 (CHOH), 35.7 (C(CH}_3\text{)_3)) and 25.8 (C(CH}_3\text{)_3)); m/z (ES-) 231.1 ((M-H}_2\text{O}, 100 \%)) and 199.9 ((M+H)}^+\text{, 7 \%). Enantioselectivity determined by chiral HPLC. Chiralcel OD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 9.5 min (major enantiomer) and 11.0 min (minor enantiomer). Data are in agreement with the literature. \]

1-(2-Methoxyphenyl)-2,2-dimethylpropan-1-ol (204)

\[ \text{[\(\alpha\)]\text{D}}^{20} -24.3 \text{ (69\% e.e., } c\ 0.1, \text{ CHCl}_3\text{)}; \delta_{\text{H}} \text{ (400 MHz, CDCl}_3\text{)} 7.24-7.20 \text{ (1H, m, C}_\text{Ar}H\text{), 7.19-\text{7.13 (1H, m, C}_\text{Ar}H\text{), 6.90-6.85 (1H, m, C}_\text{Ar}H\text{), 6.81-6.78 (1H, m, C}_\text{Ar}H\text{), 4.66 (1H, d, J 6.0, CHOH), 3.74 (s, 3H, OCH}_3\text{), 2.57 (1H, br s, CHOH) and 0.86 (9H, s, C(CH}_3\text{)_3}); \delta_{\text{C}} \text{ (101 MHz, CDCl}_3\text{)} 157.0 \text{ (C}_\text{ipso}\text{), 130.0 (C}_\text{ipso}\text{), 129.4 (C}_\text{Ar}H\text{), 128.1 (C}_\text{Ar}H\text{), 120.2 (C}_\text{Ar}H\text{), 110.5 (C}_\text{Ar}H\text{), 77.9 (CHOH), 55.1 (-OCH}_3\text{), 36.7 (C(CH}_3\text{)_3) and 26.0 (C(CH}_3\text{)_3)); m/z (ES+) 217.15 ((M+Na)}^+, \]
100 %). Enantioselectivity determined by chiral HPLC. Chiralpak AD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 17.2 min (major enantiomer) and 25.5 min (minor enantiomer). Data are in agreement with the literature.\(^\text{39}\)

**2,2-Dimethyl-1-(pyridin-4-yl)propan-1-ol (222)**

\[
\begin{align*}
\text{[}\alpha\text{]}_{D}^{20} & = -8.9 \ (69\% \ e.e., \ c \ 1.0, \ \text{CHCl}_3) ;
\delta_H \ (400 \ MHz, \ \text{CDCl}_3) \ 8.39-8.35 \ (2H, \ m, \ C_AH) , 7.17-7.13 \ (2H, \ m, \ C_AH) , 4.29 \ (1H, \ s, \ CHO) , 3.15 \ (1H, \ br \ s, \ CHO) \ and \ 0.85 \ (9H, \ s, \ C(CH_3)_3) ;
\delta_C \ (101 \ MHz \ \text{CDCl}_3) 151.4 \ (C_{ipso}) , 148.8 \ (C_AH) , 122.9 \ (C_AH) , 80.9 \ (CHO) , 35.6 \ (C(CH_3)_3) , and \ 25.8 \ (C(CH_3)_3) ; m/z \ (ES-) \ 164.1 \ ((M-H)^{-}, \ 100 \% ).
\end{align*}
\]

Enantioselectivity determined by chiral HPLC. Chiralpak AS, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 13.8 min (minor enantiomer) and 17.9 min (minor enantiomer). Data are in agreement with the literature.\(^\text{40}\)

**1-(Furan-2-yl)-2,2-dimethylpropan-1-ol (223)**

\[
\begin{align*}
\text{[}\alpha\text{]}_{D}^{20} & = -13.5 \ (74\% \ e.e., \ c \ 2.0, \ \text{toluene}) \ (\text{lit.} \ [\alpha]_{D}^{25} \ +19.7 \ (R, \ 98 \% \ e.e., \ c \ 2.2, \ \text{benzene}) ;
\delta_H \ (300 \ MHz, \ \text{CDCl}_3) \ 7.34-7.26 \ (1H, \ dd, \ J 2, 1, \ C_AH) , 6.31-6.24 \ (1H, \ dd, \ J 3, 2, \ C_AH) , 6.18-6.11 \ (1H, \ d, \ J 3, \ C_AH) , 4.31 \ (1H, \ s, \ CHO) , 1.85 \ (1H, \ br \ s, \ CHO) \ and \ 0.89 \ (9H, \ s, \ C(CH_3)_3) ;
\delta_C \ (101 \ MHz \ \text{CDCl}_3) 155.7 \ (C_{ipso}) , 141.4 \ (C_AH) , 110.0 \ (C_AH) , 107.0 \ (C_AH) , 76.5 \ (CHO) , 35.8 \ (C(CH_3)_3) , and \ 25.8 \ (C(CH_3)_3) ; m/z \ (ES+) 177.0 \ ([M+Na]^+, \ 100 \% ).
\end{align*}
\]

Enantioselectivity determined by chiral HPLC. Chiralcel OD-H, 0.5 mL/min, 98:2 hexane:2-propanol. Retention times 13.4 min (major enantiomer), 14.8 min (minor enantiomer). Data are in agreement with the literature.\(^\text{41}\)

**2,2-Dimethyl-1-(thiophen-2-yl)propan-1-ol (224)**

\[
\begin{align*}
\delta_H \ (\text{CDCl}_3, \ 300 \ MHz) & = 7.23 \ (1H, \ dd, \ J 5, 1, \ C_AH) ; 6.99-6.93 \ (2H, \ m, \ C_AH) , 4.66 \ (1H, \ s, \ CHO) , 2.00 \ (1H, \ s, \ CHO) , 0.99 \ (9H, \ s, \ C(CH_3)_3) ;
\delta_C \ (\text{CDCl}_3, \ 75 \ MHz) 146.2 \ (C_{ipso}) , 126.5 \ (C_AH) , 125.6 \ (C_AH) , 124.6 \ (C_AH) , 79.4 \ (CHO) , 36.1 \ (C(CH_3)_3) , and \ 26.3 \ (C(CH_3)_3) ; m/z
\end{align*}
\]
(ES+) 193.00 ([M+Na]+, 100%). Enantioselectivity determined by chiral HPLC. Chiralcel OD-H, 0.5 mL/min, 98:2 hexane:2-propanol. Retention times 20.9 min (major enantiomer), 29.5 min (minor enantiomer). Data are in agreement with the literature. 41

(5-n-Butyl-3-(4-methoxyphenyl)isoxazol-4-yl)(4-methoxyphenyl)methanol (225)

\[ \frac{\text{[a]} D}{18} = -38.1 \text{ (67\% e.e., c 0.1, CHCl}_3); \nu_{\text{max}} / \text{cm}^{-1} (\text{film}) 3367, 2960, 2932, 1611, 1510, 1459, 1435, 1296, 1255, 1175, 1110, 1033 and 834; \delta H (400 MHz, CDCl}_3) 7.43-7.38 (2H, m, C\_Ar\_H), 7.18-7.13 (2H, m, C\_Ar\_H), 6.85-6.81 (2H, m, C\_Ar\_H), 6.80-6.76 (2H, m, C\_Ar\_H), 5.78 (1H, s, CHO\_H), 3.75 (3H, s, OCH\_3), 3.73 (3H, s, OCH\_3), 2.63-2.50 (2H, m, -CH\_2CH\_2CH\_2CH\_3), 2.08 (1H, br s, CHO\_H), 1.62-1.42 (2H, m, -CH\_2CH\_2CH\_2CH\_3), 1.29-1.12 (2H, m, -CH\_2CH\_2CH\_2CH\_3) and 0.80 (3H, t, J 7.3, -CH\_2CH\_2CH\_2CH\_3); \delta C (101 MHz, CDCl}_3) 170.7 (C\_quat), 161.0 (C\_quat), 159.5 (C\_quat), 158.0 (C\_quat), 133.1 (C\_quat), 129.1 (C\_Ar\_H), 126.3 (C\_Ar\_H), 120.5 (C\_quat), 114.4 (C\_quat), 113.0 (C\_Ar\_H), 112.8 (C\_Ar\_H), 76.3 (CH\_O), 65.7 (-OCH\_3), 54.3 (-OCH\_3), 28.8 (-CH\_2CH\_2CH\_2CH\_3), 25.2 (-CH\_2CH\_2CH\_2CH\_3), 21.4 (-CH\_2CH\_2CH\_2CH\_3) and 12.7 (-CH\_2CH\_2CH\_2CH\_3); m/z (ES+) 390.23 ([M+Na]+, 100 %); HRMS (ES+) found 390.1678, \C\_22\_H\_25\_NNaO\_4 requires 390.1681. Enantioselectivity determined by chiral HPLC. Chiralcel AD, 1.0 mL/min, 85:15 hexane:2-propanol. Retention times: 16.7 min (major enantiomer) and 27.1 min (minor enantiomer).

1,1’-(Furan-2,5-diyl)bis(2,2-dimethylpropan-1-ol) (227)

\[ \frac{\text{[a]} D}{18} = -38.1 \text{ (67\% e.e., c 0.1, CHCl}_3); \nu_{\text{max}} / \text{cm}^{-1} (\text{film}) 3367, 2960, 2932, 1611, 1510, 1459, 1435, 1296, 1255, 1175, 1110, 1033 and 834; \delta H (400 MHz, CDCl}_3) 6.07 (2H, s, C\_Ar\_H), 4.23 (2H, s, CH\_O\_H), 2.40 (2H, s, OH\_H) and 0.87 (18H, s, CH\_3); [Meso: \delta H (400 MHz, CDCl}_3) 6.03 (2H, s, C\_Ar\_H), 4.20 (2H, s, CH\_O\_H), 2.80 (2H, s, OH\_H) and 0.87 (18H, s, CH\_3); Enantioselectivity determined by chiral HPLC. ChiralPak AD, 1.0 miL/min, 93:7 hexane:2-propanol. Retention times 10.4 min (major enantiomer (-)), 14.8 min (meso), 21.4 min (minor enantiomer (+)). Data are in agreement with the literature for the racemic compound that has been reported before. 42
5-Hydroxy-4,4-dimethyl-5-phenylpentanenitrile (230)

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

\([\alpha]_D^{20}\) -3.6 (74% ee, c 1.7, CHCl\(_3\)); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.32-7.17 (5H, m, C\(_{\text{Ar}}\)H), 4.35 (1H, s, CHO\(_2\)), 2.33 (1H, app dd, \(J\) 7, 2, C(H\(_A\))(H\(_B\))CN), 2.31 (1H, app dd, \(J\) 7, 1, C(H\(_A\))(H\(_B\))CN), 1.92 (1H, br s, CHO\(_2\)), 1.84-1.75 (1H, m, C(H\(_A\))(H\(_B\))CH\(_2\)CN), 1.64-1.54 (1H, m, C(H\(_A\))(H\(_B\))CH\(_2\)CN), 0.82 (3H, s, C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\))) and 0.81 (3H, s, C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\))); \(\delta_C\) (CDCl\(_3\), 101 MHz) 141.3 (C\(_{\text{ipso}}\)), 127.9 (C\(_{\text{Ar}}\)H), 127.8 (C\(_{\text{Ar}}\)H), 127.6 (C\(_{\text{Ar}}\)H), 127.2 (C\(_{\text{Ar}}\)H), 120.8 (C\(_{\text{ar}}\)), 80.9 (CHO\(_2\)), 37.9 (C(CH\(_3\))\(_2\)), 34.4 (CH\(_2\)), 23.4 C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\)), 22.3 C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\)) and 12.6 (CH\(_2\)); \(m/z\) (ES+) 226.12 ([M+Na]\(^+\), 100%). Enantioselectivity determined by chiral HPLC. Chiralpak AD, 1 mL/min, 90:10 hexane:2-propanol. Retention times 12.2 min (minor enantiomer), 15.2 min (major enantiomer). Data are in agreement with the literature for the racemic compound that has been prepared previously.

3-(Benzyloxy)-2,2-dimethyl-1-phenylpropan-1-ol (231)

\[
\begin{align*}
\end{align*}
\]

\([\alpha]_D^{20}\) -20.6 (50% ee, c 0.06, CHCl\(_3\)); \(\delta_H\) (CDCl\(_3\), 300 MHz) 7.31-7.14 (10H, m, C\(_{\text{Ar}}\)H), 4.53 (1H, s, CHO\(_2\)), 4.49 (2H, s, CH\(_2\)Ph), 3.87 (1H, br s, CHO\(_2\)), 3.31 (1H, d, AB system, \(J\) 9, CH\(_A\)H\(_B\)), 3.23 (1H, d, AB system, \(J\) 9, CH\(_A\)H\(_B\)), 3.00 (2H, s, C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\))) and 0.81 (3H, s, C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\))); \(\delta_C\) (CDCl\(_3\), 300 MHz) 139.9 (C\(_{\text{ipso}}\)), 138.5 (C\(_{\text{ipso}}\)), 128.5 (C\(_{\text{Ar}}\)H), 128.3 (C\(_{\text{Ar}}\)H), 127.7 (C\(_{\text{Ar}}\)H), 127.7 (C\(_{\text{Ar}}\)H), 127.6 (C\(_{\text{Ar}}\)H), 127.2 (C\(_{\text{Ar}}\)H), 81.5 (CHO\(_2\)), 79.7 (CH\(_2\)), 74.0 (CH\(_2\)), 33.1 (C(CH\(_3\))\(_2\)), 23.3 C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\)) and 20.1 C(C\(_A\)H\(_3\))(C\(_B\)H\(_3\)); \(m/z\) (ES+) 293.07 ([M+Na]\(^+\), 100%) and 563.16 ([2M+Na]\(^+\), 100); HRMS (ES+) found 293.1518, C\(_{18}\)H\(_{22}\)O\(_2\)Na requires 293.1517. Enantioselectivity determined by chiral HPLC. Chiralpak AD, 0.5 mL/min, 98:2 hexane:2-propanol. Retention times 33.6 min (major enantiomer), 39.8 min (minor enantiomer).
2-(1H-Imidazol-1-yl)-2-methyl-1-phenylpropan-1-ol (236)

\[
\text{m.p. 166-168 °C (lit.)}^{44} 167-168 °C; \; [\alpha]^D_{20} = -20.0 \; (53\% \; \text{e.e., c} \; 2.9, \; \text{CHCl}_3); \; \delta_H (300 \; \text{MHz, CDCl}_3) \; 7.31 \; (1H, \text{br s, NCHN}), \; 7.24-7.13 \; (4H, \text{m, C}_A\text{H}), \; 6.97-6.83 \; (4H, \text{m, C}_A\text{H}), \; 4.60 \; (1H, \text{s, CHOH}), \; 2.42 \; (1H, \text{br s, CHO}), \; 1.49 \; (3H, \text{s, C(C}_A\text{H}_3(C}_B\text{H}_3)) \; \text{and} \; 1.46 \; (3H, \text{s, C(C}_A\text{H}_3(C}_B\text{H}_3)); \; \delta_C (101 \; \text{MHz, CDCl}_3) \; 140.0 \; (\text{C}_{\text{ipso}}), \; 135.6 \; (\text{N=C-N}), \; 128.0 \; (\text{C}_A\text{H}), \; 127.9 \; (\text{C}_A\text{H}), \; 127.7 \; (\text{CH=CH}), \; 127.3 \; (\text{C}_A\text{H}), \; 118.0 \; (\text{CH=CH}), \; 80.2 \; (\text{CHOH}), \; 60.9 \; (\text{C(CH}_3)_2), \; 25.0 \; (\text{C}(\text{C}_A\text{H}_{23})), \; 24.2 \; (\text{C}(\text{C}_A\text{H}_{23}))); \; \text{m/z (ES+) 217.2 (M+H), 100%); HRMS (ES+) found 217.1346 (± 0.9 ppm), C_{13}H_{17}N_2O requires 217.1341. Enantioselectivity determined by chiral HPLC. Chiralcel OD, 1.0 mL/min, 93:7 hexane:2-propanol. Retention times: 35.6 min (minor enantiomer) and 40.9 min (minor enantiomer). Data are in agreement with the literature.}^{44}

5,5-Dimethyl-6-phenyltetrahydro-2H-pyran-2-one (248)

\[
\text{m.p. 103-104 °C (lit.)}^{30} 102-103 °C; \; [\alpha]^D_{20} = -17.2 \; (74\% \; \text{ee, c} \; 0.5, \; \text{CHCl}_3); \; \delta_H (\text{CDCl}_3, \; 400 \; \text{MHz}) \; 7.29-7.22 \; (2H, \text{m, C}_A\text{H}), \; 7.21-7.14 \; (3H, \text{m, C}_A\text{H}), \; 5.00 \; (1H, \text{s, CHO}), \; 2.65-2.60 \; (2H, \text{m, CH}_2\text{CO}), \; 1.86-1.75 \; (1H, \text{m, C(H}_A\text{)(H}_B\text{)CH}_2\text{CO}), \; 1.70 \; (1H, \text{m, C(H}_A\text{)(H}_B\text{)CH}_2\text{CO}), \; 0.87 \; (3H, \text{s, C(C}_A\text{H}_3(C}_B\text{H}_3)) \; \text{and} \; 0.77 \; (3H, \text{s, C(C}_A\text{H}_3(C}_B\text{H}_3)); \; \delta_C (\text{CDCl}_3, \; 75 \; \text{MHz}) \; 171.6 \; (C=O), \; 136.3 \; (\text{C}_{\text{ipso}}), \; 128.2 \; (\text{C}_A\text{H}), \; 127.8 \; (\text{C}_A\text{H}), \; 127.5 \; (\text{C}_A\text{H}), \; 89.1 \; (1H, \text{s, CHO}), \; 34.2 \; (\text{CH}_2), \; 33.3 \; (\text{C(CH}_3)_2), \; 27.5 \; (\text{CH}_2), \; 26.8 \; (\text{C}(\text{C}_A\text{H}_3(C}_B\text{H}_3)) \; \text{and} \; 19.4 \; (\text{C}(\text{C}_A\text{H}_3(C}_B\text{H}_3)); \; \text{m/z (Cl+) 205.12 ([M+H]^+, 68%), 187.11 (100), 145.10 (80), 127.08 (39), 105.07 (30) and 91.05 (15); HRMS (Cl+) 205.1237 ([M+H]^+), [C_{13}H_{18}O]^+ requires 205.1229. Enantioselectivity determined by chiral HPLC. Chiralpak AD, 1 mL/min, 95:5 hexane:2-propanol. Retention times 19.9 min (minor enantiomer), 28.0 min (major enantiomer). Data are in agreement with the literature for the racemic compound that has been reported before.}^{30}
5-Hydroxy-5-phenylpentanenitrile (252)

\[
\begin{align*}
\text{[\(\alpha\)\text{]}}_{D}^{20} & \text{ -20.4 (49% ee, c 4.5, CHCl}_3) ;
\delta_h (\text{CDCl}_3, 300 MHz) 7.40-7.18 (5H, m, C\_\text{Ar}\_H), 4.69-4.63
(1H, s, CHO\_OH) , 2.34-2.28 (2H, m, CH\_2\_CN), 4.69-4.63 (1H, br s, CHO\_OH) and 1.90-1.67 (4H, m, CH\_2\_CH\_2) ;
\delta_c (\text{CDCl}_3, 75 MHz) 144.0 (C\_ipso) , 128.8 (C\_\text{Ar}\_H) , 128.0 (C\_\text{Ar}\_H), 125.8 (C\_\text{Ar}\_H) , 119.7 (CN) , 73.7 (CHO\_OH) , 37.7 (CH\_2) , 21.9 (CH\_2) and 17.2 (CH\_2) ; m/z (ES\text{+}) 198.09 ([M+Na]^\text{+}, 100 %); HRMS (ES\text{+}) 198.0894 ([M+Na]^\text{+}), [C\text{\textsubscript{11}}H\text{\textsubscript{13}}N\text{\textsubscript{Na}}]^\text{+} requires 198.0895. Enantioselectivity determined by chiral HPLC. Chiralcel OD-H, 1 mL/min, 90:10 hexane:2-propanol. Retention times 20.2 min (major enantiomer), 22.1 min (minor enantiomer). Data are in agreement with the literature for the racemic compound that has been reported before.\textsuperscript{45}
\end{align*}
\]

6-Phenyltetrahydro-2H-pyran-2-one (258)

\[
\begin{align*}
\text{[\(\alpha\)\text{]}}_{D}^{20} & \text{ -16.6 (48 % e.e., c 0.1, CHCl}_3) (\text{lit.}\textsuperscript{46} \text{[\(\alpha\)\text{]}}_{D}^{25} +38.5 (R, 98 % e.e., c 1.0, CHCl}_3) ;
\delta_h (\text{CDCl}_3, 400 MHz) 7.45-7.24 (5H, m, C\_\text{Ar}\_H), 5.30 (1H, dd, J 11.3, CHO) , 2.80-2.46 (2H, m, CH\_2) , 2.20-2.10 (1H, m, CH\_A\_H) , 2.00-1.81 (3H, m, CH\_A\_H + CH\_2) ; 
\end{align*}
\]

Enantioselectivity determined by chiral HPLC. Chiralcel OD-H, 1 mL/min, 90:10 hexane:2-propanol. Retention times 28.7 min (minor enantiomer) and 32.8 min (major enantiomer). Data are in agreement with the literature.\textsuperscript{47}

2,2-Dimethyl-1-phenylpropan-1-ol (273)

\[
\begin{align*}
\text{m.p. 45 °C (lit.}\textsuperscript{48} 45 °C) ; \text{[\(\alpha\)\text{]}}_{D}^{20} & \text{ -19.3 (74% e.e., c 0.3, acetone) (lit.}\textsuperscript{49} \text{[\(\alpha\)\text{]}}_{D}^{25} -30.3 (S, >99% e.e., c 0.36, acetone) ; 
\delta_h (300 MHz, \text{CDCl}_3) 7.25-7.19 (5H, m, C\_\text{Ar}\_H) , 4.31 (s, 1H, CH\_OH) , 1.97 (1H, br s, CHO\_H) and 0.85 (9H, s, C(CH\_3)\_3) ; 
\end{align*}
\]

Enantioselectivity determined by chiral HPLC. Chiralpak OD-H, 1 mL/min, 98:2 hexane:2-propanol. Retention times: 10.5 min (S, major enantiomer) and 15.0 (R, minor enantiomer). Data are in agreement with the literature.\textsuperscript{50}
5.10 References

42. J. A. Fuentes and M. L. Clarke, Unpublished Work, University of St Andrews.
Appendix A

Other Active [RuCl$_2$(P$^N$X)L] catalysts

A number of other ruthenium complexes of P$^N$X (X=N,O) were prepared in this work and shown to be active catalysts but fall outwith the scope of the work discussed so far. These shall be outlined in the following addendum.

A.1 Alternative Precatalysts -Imine Complexes as Precursors to the Active Catalyst

Preliminary attempts by Diaz and Clarke, using uncharacterised and unpurified complex, suggests that the imine variant of the original catalyst gives similar results to the amine catalysts in terms of productivity and enantioselectivity in the hydrogenation of $\alpha,\alpha,\alpha$-trimethylacetophenone. This is likely due to in situ hydrogenation of the imine bond to give equivalent active species. If this is the case, it is desirable to be able to use the imine variant in such cases where it is impossible to prepare the amine ligand. In order to verify this, the imine variant of the original catalyst ($R,R$)-174 was first prepared and its performance in catalysis analysed.

Ligand ($R,R$)-307 was prepared as a mixture with the difunctionalised diamine ($R,R$)-308 (3:1 monofunctionalised:difunctionalised species) by reacting equimolar amounts of 2-(diphenylphosphino)benzaldehyde 266 and ($R,R$)-diaminocyclohexane in dichloromethane for 5 hours (Scheme A1-1). Conversion to imine was shown by the presence of signals at $\delta_H$ (CDCl$_3$) = 8.72 ppm (d, $J$ 4, monofunctionalised species) and 8.55 ppm (d, $J$ 4, difunctionalised species) corresponding to the C$\text{H}=\text{N}$ proton, and signals at -12.7 ppm and -13.8 ppm in the $^{31}$P NMR, corresponding to the monofunctionalised and difunctionalised species respectively. The solvent was removed and the crude mixture immediately reacted with [RuCl$_2$(DMSO)$_4$] in the usual complexation protocol to furnish two complexes: the known [RuCl$_2$(N$^P$P$^A$P$^N$)] complex ($R,R$)-310 ($\delta_P$ (CDCl$_3$) = +47.3 ppm),$^1$ and the desired [RuCl$_2$(P$^N$P$^A$N)L] complex ($R,R$)-309 ($\delta_P$ (CDCl$_3$) = +51.5 ppm). These complexes were easily separated by column chromatography. It is worthwhile noting that the chemical shift in the $^{31}$P NMR spectrum of these imine variants are typically downfield of those associated with complexes of the original amine ligands ($\delta_P$ (CDCl$_3$) = +43.6 ppm).$^2$ The identity of complex ($R,R$)-309 was supported by x-ray diffraction studies of the crystal structure and is represented in Figure A1-1. This shows the tridentate...
ligand bound at three of the four meridional sites with DMSO occupying the final site, as in catalyst \((R,R)-174\). The final two coordination sites are occupied by \textit{trans}-chloride ligands.

\[ \text{Scheme A1-1} \text{ The synthesis of complex } (R,R)-309, \text{ the imine variant of complex } (R,R)-174. \]

**Reaction conditions:**
1. 2-(diphenylphosphino)benzaldehyde 266 (1 eq.), \((R,R)\)-diaminocyclohexane (1 eq.), DCM, rt, 5 h;
2. \((R,R)\)-307 and 308 (1 eq.), \([\text{RuCl}_2(\text{DMSO})_4] \) (1 eq.), THF, \(\mu_w\), 120°C, 20 min.

\[ \text{Figure A1-1} \text{ Representation of the molecular structure of } (R,R)-309, \text{ from x-ray diffraction studies, supporting the expected coordination mode of the ligands.} \]

Hydrogenation with catalyst \((R,R)-309\) was shown to give very similar results to the original catalyst \((R,R)-174\) with reactions typically complete within an hour and with equivalent or enhanced enantioselectivities (Table A1-1).
Table A1-1 Comparison of the hydrogenation of ketones 81, 82 and 198 with catalyst (R,R)-174 and its imine derivative (R,R)-309. General conditions: ketone (~1 mmol), catalyst (R,R)-174 or (R,R)-309 (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂ (50 bar), 50°C, 16 h. a From reference 2

<table>
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<td>81 (S)</td>
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Since the enantioselectivity obtained using the imine derivative (R,R)-309 was on par with, if not better than, that obtained with catalyst (R,R)-174, using such derivatives in hydrogenation, in situations when it was impossible to make the amine variant, seemed feasible. The enhanced selectivity obtained for the hydrogenation of ketone 82 was mysterious if the stereoinduction step is equivalent. We felt it necessary to examine further whether the imine function is indeed reduced during hydrogenation, forming the same active species in solution.

In order to do this, stoichiometric amounts of complex (R,R)-309 were reacted with potassium tert-butoxide in isopropanol in the presence of 70 bar hydrogen at 70°C for 16 hours. NMR analysis of the resulting material showed one main species in the 31P NMR spectrum (CDCl₃) at +42.3 ppm, shifted upfield from +51.5 ppm. The signal in the 1H NMR (CDCl₃) of the imine complex at 8.53 ppm disappeared from the spectrum after this treatment, while signals corresponding to the other ligand protons remained. This suggests that the imine component is being hydrogenated to reform the original amine species, thus why similar activities and enantioselectivities are observed. Mass spectrometry studies of the mixture failed to identify molecular ions corresponding to species (R,R)-309 or its reduced form. However, a signal with a molecular weight corresponding to the potassium adduct of the reduced ligand was the predominant species in positive electrospray studies, suggesting the ligand is indeed reduced in the process.
It was concluded that in the cases where it was impossible to prepare the amine variety of the desired catalyst, the imine variant may be used to give clues as to whether the ligand in question is useful in catalysis.

### A.2 Further Modification of Diamine Component

It was felt that by altering the bite angle of the diamine component in the $[\text{RuCl}_2(P\text{^N\text{^N}})\text{L}]$ system, one could not only tune the orientation of the N-H bond to maximise interaction with the incoming substrate, the enantioselectivity of the reaction could be enhanced as the spacial proximity of the phosphine substituents to the mechanistically important N-H group is consequently modified. It was envisaged that the bite angle of the diamine component could be varied by adjustment of the ring size and the conformational constraints in the diamine. In the first instance, attempts were made to widen the bite angle of the diamine component by increasing the dihedral angle between the vicinal amine groups. Basic computational calculations (Table A1-2), based on the MM2 force field, showed that reducing the ring size of the diamine component, increases the dihedral angle between the vicinal amine groups ($312 \text{ cf } 311 \text{ cf } 310$). Constraining the ring in bicyclic system ($313$) also increases the dihedral angle.

Our immediate targets were the ligands shown in Scheme A1-2: ($R,R$)-$314$ with five-membered cyclic backbone and ($S,S$)-$315$ with a fused bicyclic backbone: both expected to have larger bite angles than present in the original catalyst once complexed.

![Scheme A1-2: Target ligands to explore the effect of increased bite angle upon performance of $[\text{RuCl}_2(P\text{^N\text{^N}})\text{L}]$ catalysts in hydrogenation](image)

| Entry | Diamine | Diamine (viewed along ring bond) | Dihedral angle
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<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
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*Table A1-2* Comparison of theoretical bite angles for unbound diamines based on MM2 calculations.

The nature of the metal centre, as well as the ligand dihedral angle, has a significant impact on the bite angle once the ligand is bound. This analysis allows for a rough appreciation of the relative bite angles of each of the diamines.
The five-membered cyclic backbone of ligand \((R,R)\)-314 was chosen in preference to 1,2-diaminocyclopentane 311 due to the significant instability of 311, which rapidly reacts with carbon dioxide in the atmosphere to give the carbamate ester. A secondary advantage of \((R,R)\)-314 is that the tertiary amine is a handle which can potentially be exploited to attach the ligand/catalyst to a solid support to aid catalyst recovery. It was envisaged that \((R,R)\)-314 could be prepared in an analogous manner to the original ligand by the condensation of diamine \((R,R)\)-222 with 2-(diphenylphosphino)benzaldehyde 266.

The enantiopure diamine \((R,R)\)-322 was first prepared in a number of steps from L-(\(R,R\)\)-\((+\)-tartaric acid 317 (Scheme A1-3). The pyrrolidindione 318 was obtained on multigram scale by reacting \((R,R)\)-317 with benzylamine 316 in xylene at reflux, making use of the procedures of Skarzevski and Gupka. Reduction of the amide proved to be tricky and all attempts using diborane, generated \textit{in situ} from sodium borohydride and iodine, proved futile. The reduced product was obtained however, albeit in poor yield, by addition of 318 to a large excess (6-10 equivalents) of lithium hydride in THF and the reaction stirred overnight. Research published while this work was ongoing, combined with personal correspondence with the authors, led to increased yields for this reaction. Maximum yields were accomplished by the portion-wise addition of 318 to a dilute solution of lithium aluminium hydride (three-fold excess) in THF.

![Scheme A1-3](image.png)

\textbf{Scheme A1-3} Preparation of diol \((S,S)\)-319. \textit{Reaction conditions:} (i) benzylamine 316 (1 eq.), L-(\(R,R\)\)-\((+\)-tartaric acid \((R,R)\)-317 (1 eq.), xylene, \(\Delta\), 6 h; (ii) \((R,R)\)-318 (1 eq.), LiAlH\(_4\) (3-10 eq.), THF, \(0^\circ\text{C} \rightarrow \Delta\), 16 h.

It is reported in the literature that the diol \((R,R)\)-319 can be transformed into the corresponding diamine by Mitsunobu reaction followed by hydrogenation with palladium on carbon. However, Fuentes reports that this method is unreliable and instead employed a two step procedure to access the diazido compound \((R,R)\)-321 as described for the preparation of 1,2-diazidocyclopentane, which was successfully employed here (Scheme A1-4). The hydroxyl groups of \((S,S)\)-319 were first activated by reaction with methanesulfonyl chloride in the presence of triethylamine to give the \textit{bis}-mesylate \((S,S)\)-320. Subsequent treatment of \((S,S)\)-320 with sodium azide furnished the diazido compound \((R,R)\)-321 with inversion of configuration at each stereocentre. Reduction of this compound was accomplished easily by hydrogenation with...
palladium on carbon and 1 bar hydrogen pressure, and monitoring of the reaction by thin layer chromatography indicated that the reaction was complete within 16 hours.

\[
\text{Scheme A1-4 Preparation of diamine } \left(\text{R,R}\right)-322. \text{ Reaction conditions: (i) } (S,S)-319 \ (1 \text{ eq.}), \text{ methanesulfonyl chloride (3 eq.), triethylamine (3 eq.), dichloromethane, } 0^\circ\text{C} \rightarrow \text{rt}, \ 5 \text{ h; (ii) } (S,S)-320 \ (1 \text{ eq.)}, \text{ sodium azide (4 eq.), DMF, } 100^\circ\text{C}, \ 4 \text{ h then rt, } 24 \text{ h; (iii) } (R,R)-321 \ (1 \text{ eq.}, \text{ 10\% Pd/C (0.1 eq.), H}_2 \ (1 \text{ bar}, \text{ EtOH, rt, } 16 \text{ h.})}
\]

Attempts to prepare the \( \text{P}^\text{N}^\text{N} \text{N} \) ligand \( \left(\text{R,R}\right)-314 \) from diamine \( \left(\text{R,R}\right)-322 \) were unsuccessful (Scheme A1-5). Condensation of the diamine \( \left(\text{R,R}\right)-322 \) with 2-(diphenylphosphino)benzaldehyde 266 in ethanol, using a three-fold excess of the amine to avoid difunctionalisation, furnished the imine \( \left(\text{R,R}\right)-323 \), indicated by the appearance of a signal in the \( ^1\text{H} \) NMR spectrum at \( \delta_H (\text{C}_6\text{D}_6) = 9.41 (\text{d, } J = 5) \), corresponding to the \( \text{CH}=\text{N} \) proton, and a signal at \( \delta_P (\text{C}_6\text{D}_6) = -11.2 \) in the \( ^3\text{P} \) NMR spectrum. However, attempts at the reduction of this species resulted in the formation of a significant amount of a phosphine oxide species \( (\delta_P (\text{C}_6\text{D}_6) = +34.6) \) as well as the desired phosphine ligand \( (\delta_P (\text{C}_6\text{D}_6) = -15.8) \), despite rigorous exclusion of air from the system. Aqueous work-up in an inert environment, necessary to remove the excess diamine, resulted in almost complete conversion of the desired phosphine to the phosphine oxide species. Multiple attempts at this procedure failed to yield significant amounts of the desired phosphine ligand for complexation, as did attempts at reduction of the phosphine oxide.

\[
\text{Scheme A1-5 Attempted preparation of ligand } \left(\text{R,R}\right)-314. \text{ Reaction conditions: (i) } 2\text{-(diphenylphosphino)benzaldehyde 266 (1 eq.), } \left(\text{R,R}\right)-322 \ (3 \text{ eq.), EtOH, rt, } 3 \text{ h; (ii) } \left(\text{R,R}\right)-323 \ (1 \text{ eq.), NaBH}_4 \ (4 \text{ eq.), EtOH, rt, } 16 \text{ h.})}
\]
Since the problematic oxidation of the phosphine appeared to occur after the reduction of the imine species, it was decided to prepare the ruthenium complex of the imine species itself. It has been shown that complexes of such are likely reduced under the hydrogenation conditions to give similar active species to those obtained from the corresponding amine species (See previous section). Ligand \((R,R)-324\) was prepared by the slow, dropwise addition of a solution of 2-(diphenylphosphino)benzaldehyde 266 in dichloromethane over a period of 16 hours to a dilute solution of diamine \((R,R)-322\) in dichloromethane. The monofunctionalised diamine was formed almost exclusively, with identical signals as previously (Scheme A1-6). Once the solvent was removed the ligand was complexed immediately using the standard complexation protocol and, after silica flash chromatography (1:1 DCM:acetone), pure complex \((R,R)-324\) was obtained. The identity of the complex was supported by the appearance of a single peak at \(\delta_{P} (\text{CDCl}_3) = +53.7\) in the \(^{31}\text{P}\) NMR spectrum, in the characteristic region for such complexes, and two signals in the \(^1\text{H}\) NMR for the inequivalent protons of the remaining bound DMSO ligand. Although microanalysis data could not obtained due to residual solvent molecules, the complex was deemed pure from NMR data, and accurate mass analysis identified the molecular ion corresponding to the structure presented.

Scheme A1-6 Preparation of complex \((R,R)-324\). Reaction conditions:
(i) 2-(diphenylphosphino)benzaldehyde 266 (1 eq.), \((R,R)-322\) (1 eq.), EtOH, rt, 16 h; (ii) \((R,R)-323\) (1 eq.), \([\text{RuCl}_2(\text{DMSO})_4]\) (1 eq.), THF, \(\mu\text{W}, 120^\circ\text{C}, 20\text{ min.}\)

Complex \((R,R)-324\) was found to hydrogenate \(\alpha,\alpha,\alpha\)-trimethylacetophenone quantitatively within 16 hours at 50\(^\circ\text{C}\) and 50 bar hydrogen pressure (Scheme A1-7). Unfortunately, an erosion of enantioselectivity was observed, with the \((S)\)-alcohol produced in just 40\% e.e.
We next turned our attention to catalysts derived from 11,12-diamino-9,10-dihydro-9,10-ethanoanthracene. It was predicted that ligand \((S,S)-315\) could be prepared in a similar manner to the original ligand \((R,R)-174\) from the diamine \((S,S)-331\). Racemic diacid 327 was first prepared by heating fumaric acid 326 and anthracene 325 in dioxane at reflux over a period of three days using the methods of Bachman and Scott\(^8\) (Scheme A1-8). Resolution by formation of the diastereomeric salts of the diacid with the alkaloid brucine 328, and subsequent fractional recrystallisation, yielded the desired \((S,S)\)-diastereomer \((S,S)-327\) in 34% yield upon decomposition of the salt with sodium hydroxide.\(^9,10\) The optical purity of the diacid was analysed by HPLC analysis of its isopropyl ether derivative, and was shown to be greater than 99% enantiomerically and diasteromerically pure.

The diacid \((S,S)-327\) was converted to the diamine \((S,S)-331\) by first conversion to the corresponding bis-azide via the bis-acid chloride, then subsequent Curtius Rearrangement, following the methods of Trost\(^11\) and modifications made by Fuentes (Scheme A1-9).\(^7\) Curtius
rearrangement yielded the hydrochloride salt of diamine (S,S)-331, and the free amine was liberated by treatment with sodium hydroxide and extraction into dichloromethane.‡

Under strictly inert conditions,§ condensation of (S,S)-331 (a three-fold excess in ethanol) with 2-(diphenylphosphino)benzaldehyde 266 furnished the imine species (S,S)-332, indicated by the appearance of a signal at δ_p (C_6D_6) = -11.6 ppm in the ^31_P NMR spectrum and a signal at δ_H (C_6D_6) = 9.46 ppm (d, J 5), corresponding to the CH=N proton, in the ^1_H NMR spectrum (Scheme A1-10). Reduction of the imine species was achieved by addition of sodium borohydride to the reaction mixture and stirring for 4 h. Complete reduction was indicated by disappearance of signals in the ^1_H and ^31_P NMR spectra corresponding to the imine species and appearance of a new signal at δ_p (C_6D_6) = -15.9 ppm in the ^31_P NMR spectrum. However, aqueous work-up failed to remove the excess diamine from the reaction mixture. Purification procedures resulted in the complete oxidation of the phosphine (δ_p (CDCl_3) = +34.8 ppm). It was decided to subject the reaction mixture to the complexation protocol, and purify the resultant complex. This appeared to yield the desired complex (S,S)-333, with the appearance of the principal signal at δ_p (CDCl_3) = +45.3 ppm in the ^31_P NMR spectrum. However, column chromatography to remove the organic impurities, resulted in the apparent degradation of the complex, with the appearance of a second signal at δ_p (CDCl_3) = +54.2. This unknown species could not be removed and has hampered full characterisation of complex (S,S)-333.

‡ Enantiomerically and diastereomerically pure (R,R)-331 could also be prepared by first preparing racemic 331, using identical procedures as shown in Scheme A1-9, from racemic diacid 327, then resolving the diamine by diastereomeric salt formation with (S)-mandelic acid, and subsequent base hydrolysis. Both the the (S,S) and the (R,R) forms were employed in attempts to prepare P^N^N ligands.
§ Initial attempts at this transformation encountered significant problems with phosphine oxidation, particularly in the condensation step. This was overcome to a great extent by meticulous exclusion of air from the system and minimising reaction times, i.e. the time components spent in solution.
It was decided to employ the mixture of what appeared to be complex \((S,S)\)-323, based on the characteristic chemical shift of the species in the \(^{31}\text{P} \) NMR, and the unknown complex (5:1 mixture), in the hydrogenation of \(\alpha,\alpha,\alpha\)-trimethylacetophenone 159. Pleasingly full conversion was obtained at 50°C and 50 bar hydrogen pressure (Table A1-3). However, the reaction yielded racemic alcohol 273. Due to the absence of full characterisation of complex \((S,S)\)-333 to confirm its identity, and the presence of an unknown complex in the reaction mixture, limited conclusions can be drawn from this result.

Due to the problems encountered with formation of the ruthenium complex of ligand \((S,S)\)-315, it was decided to prepare the borane-protected form of the ligand and employ it in the \textit{in situ} hydrogenation protocol described in section 4.1, and compare the results with that of the impure precatalyst. We had the \((R,R)\)-diastereomer of diamine 331 to hand and decided to use this to first prepare the amide \((R,R)\)-335 (Scheme A1-11). This was accomplished using an amide coupling protocol described by Santos and coworkers.\(^{12}\) \(N\)-[2-(Diphenylphosphanyl)benzoyloxy]sucinimide 334\(^{13}\) was added dropwise to a solution of diamine \((R,R)\)-331 in dichloromethane to give the amide \((R,R)\)-335, which was air stable and could be purified by column chromatography. Treatment of \((R,R)\)-335 with 5 equivalents of borane tetrahydrofuran complex yielded the borane adduct of the \(\text{P}^\text{N}^\text{N}\) ligand \((R,R)\)-336, \(\delta_\text{p} \) (CDCl\(_3\)) = +18.9 ppm (br s). Reduction of the amide was indicated by disappearance of the signal at \(\delta_\text{H} \) (CDCl\(_3\)) = 5.71 ppm (d, J 8) corresponding to the amide NHCO.

\[\text{Scheme A1-10 Synthesis of complex } (S,S)-333. \text{ Reaction conditions: (i) 2-} \]
\[\text{(diphenylphosphino)benzaldehyde 266 (1 eq.), (S,S)-331 (3 eq.), EtOH, 45^\circ \text{C} \rightarrow \text{rt, 2 h; (ii) 332, NaBH}_4 \text{ (3 eq.), EtOH, rt, 4 h; (iii) (S,S)-315 (1 eq.), [RuCl}_2(DMSO)_4 \text{ (1 eq.), THF, } \mu \text{w, 120^\circ \text{C, 20 min.}}\]
Scheme A1-11 Synthesis of borane-protected ligand (R,R)-336. Reaction conditions:
(i) N-[2-(diphenylphosphanyl)benzoyloxy]succinimide 334 (1 eq.), (R,R)-331 (2 eq.),
DCM, rt, 3 h; (ii) (R,R)-336 (1 eq.), BH₃·THF (5 eq.), rt, 16 h.

Borane-protected ligand (R,R)-336 was used in the in situ hydrogenation protocol in combination with [RuCl₂(DMSO)₄], and successfully reduced α,α,α-trimethylacetophenone 159 cleanly in 16 hours at 50°C and 50 bar hydrogen pressure (Table A1-3). Again, however, no enantioselectivity was observed in the product alcohols.

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Table A1-3 Hydrogenation employing wide-bite angle ligands. General conditions: ketone 81, 82 or 159, catalyst (S,S)-333 (0.5 mol%) or [RuCl₂(DMSO)₄] (0.5 mol%)/Ligand (R,R)-336, potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular H₂ (50 bar), 50°C, 16 h.

It is worth noting that whilst poor for the enantioselective hydrogenation of α,α,α-trimethylacetophenone, and other simple ketones, it is conceivable that these catalysts may have niche application in the hydrogenation of other substrates. To date this remains a relatively unstudied, but worthwhile area of research. These results, in combination with catalysis using complex (R,R)-324, might suggest that widening the ligand bite angle has a negative effect upon
enantioselectivity. However, these are different catalyst structures and it is important to interpret these findings with some caution.

A.3 Further Attempted Tuning of Catalyst Structure

Although highly efficient catalysts exist for the hydrogenation of acetophenone and derivatives, and the preparation of further catalysts was not our aim, the results shown in section 4.2.2 demonstrated that the catalyst scaffold can be tuned for particular substrates. A significant increase in enantioselectivity was observed from 0% e.e. when using the original catalyst to 60% e.e. when the bulky derivative \((R,R)-298\) was employed. We decided to explore the tunability of the catalyst structure further by preparing the bulky derivative of catalyst \((R,S)-337\), which was shown in work by Fuentes and Clarke, to give 51% e.e. in the hydrogenation of acetophenone (Scheme A1-12). If a similar increase in enantioselectivity was brought about by the incorporation of bulk on the phosphine substituents, then industrially viable levels of selectivity may be approached for such substrates.

![Scheme A1-12](image)

Scheme A1-12 Hydrogenation of acetophenone with complex \((R,S)-337\)
(work carried out by Fuentes and Clarke). Reaction conditions:
acetophenone, complex \((R,S)-337\) (0.5 mol%), potassium tert-butoxide (5 mol%), \(i\)PrOH, \(H_2\) (50 bar), 50°C, 16 h.

The bulky derivative of complex \((R,S)-337\) was prepared by condensation of equimolar amounts of \((1R,2S)-(+)-\text{cis-1-amino-2-indanol}\) and \(2-(\text{bis}(3,5\text{-di-tert-butylphenyl})\text{phosphino})\text{benzaldehyde}\) in degassed ethanol of a period of 3 hours (Scheme A1-13). Formation of the imine species was indicated by the disappearance of the signal corresponding to the aldehyde species in the \(^{31}\text{P}\) NMR spectrum (\(\delta_p (C_6D_6) = -10.2\) ppm) and the appearance of a signals at \(\delta_{1H} (C_6D_6) = 9.75\) ppm (d, J 5) and at \(\delta_p (C_6D_6) = 7.9\) ppm in the \(^1\text{H}\) and \(^{31}\text{P}\) NMR spectra respectively. Treatment with sodium borohydride resulted in the disappearance of these signals and a new signal in the \(^{31}\text{P}\) NMR spectrum at \(\delta_p (C_6D_6) = -14.0\) ppm. Due to the sensitivity of the ligand, full characterisation was not possible. The molecular ion of the phosphine oxide was observed however after positive electrospray mass spectrometry.
The synthesis of \([\text{RuCl}_2(\text{P}^\text{N}^\text{O})\text{L}]\) complex 341. Reaction conditions: 2-(bis(3,5-di-tert-butylphenyl)phosphino)benzaldehyde 302 (1 eq.), \((R,S)-1\)-amino-2-indanol 338 (1 eq.), EtOH, rt, 3 h; (ii) \((R,S)-339\) (1 eq.), NaBH₄ (4 eq.), EtOH, rt, 12 h; (iii) \((R,S)-340\) (1 eq.), \([\text{RuCl}_2(\text{DMSO})_4]\) (1 eq.), THF, μw, 120°C, 20 min.

The ligand was thus complexed immediately with \([\text{RuCl}_2(\text{DMSO})_4]\), making use of the standard microwave assisted protocol, and purified by column chromatography. Complexation was verified by the downfield shift of the signal corresponding to the phosphorus nuclei to \(\delta_p (\text{C}_6\text{D}_6) = +58.6\) ppm in the \(^{31}\text{P}\) NMR spectrum. This appears further downfield than typical shifts for \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) complexes but matched well with data for previously prepared \([\text{RuCl}_2(\text{P}^\text{N}^\text{O})\text{L}]\) complexes, with signals typically in the range 57-60 ppm. Like the analogous \([\text{RuCl}_2(\text{P}^\text{N}^\text{N})\text{L}]\) complexes, signals for \(\text{CHX} \ (X = \text{N}, \text{O})\) protons were shifted downfield by complexation, and previously equivalent dimethylmethoxide protons again became inequivalent, giving two distinct singlets at \(\delta_H (\text{CDCl}_3) = 2.85\) and 2.65 ppm. Coordination of the hydroxyl group was supported by the broad singlet at \(\delta_H (\text{CDCl}_3) = 5.96\) ppm corresponding to the –OH proton: the unbound signal appears downfield at 6.29 ppm. X-ray diffraction studies on similar \([\text{RuCl}_2(\text{P}^\text{N}^\text{O})\text{L}]\) complexes prepared by Fuentes and Clarke, also indicates that the oxygen atom in such ligands does indeed coordinate to the ruthenium centre.
Enantioselective Hydrogenation Using Ruthenium Complexes of Tridentate Ligands

Scott Phillips

xxvii

\((R,S)-341\)

\(\text{R} = \text{Me} 81, \text{R} = \text{tBu} 159\)

\(\text{R} = \text{Me} 43, \text{R} = \text{tBu} <5\)

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<td>159</td>
<td>tBu</td>
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Table A1-4 Hydrogenation with the \([\text{RuCl}_2(\text{P}^N^O)L]\) catalyst \((R,S)-341\). General conditions: ketone 81 or 159, catalyst \((R,S)-341\) (0.5 mol%), potassium tert-butoxide (1 mol%), isopropanol (3 mL), molecular \(\text{H}_2\) (50 bar), 70°C, 16 h. \(^a\) 5 mol% KO'Bu.

Like the complex \((R,R)-298\), also with bulky substituents upon phosphorus, catalyst \((R,S)-341\) was also found to be less active than its non-bulky parent catalyst. Temperatures of 70°C and increased base loading were required to get above 70% conversion in the hydrogenation of acetophenone 81 (Table A1-4). The bulky substrate \(\alpha,\alpha,\alpha\)-trimethylacetophenone 159 was practically inactive to hydrogenation with catalyst \((R,S)-341\). Disappointingly, only racemic material was obtained on reduction of acetophenone. The results suggest, since enantioselectivity is completely eroded, and activity is significantly diminished, that this catalyst may operate by a different mechanism, i.e. the bulky substituents may block the mechanistically important secondary NH, and hydrogenation may occur via pathways more akin to non-NH complexes. Our rationale that bulky substituents near the ‘active site’ may still hold true, but up to a point where they hinder the approach of the ketone substrate.

A.4 Experimental

Complex \((R,R)-309\)

\((JR,2R\)-Cyclohexane-1,2-diamine (0.105 g, 0.91 mmol) and 2-(diphenylphosphino)benzaldehyde 266 (0.267 g, 0.91 mmol) were dissolved in ethanol and the mixture stirred for 5 h. The solvent was removed and the resultant residue was redissolved in tetrahydrofuran (3 mL) and to this \([\text{RuCl}_2(\text{DMSO})_4]\) (0.441 g, 0.91 mmol) was added. The
mixture was heated at 120°C for 20 min in the microwave and the solvent was then removed. Flash chromatography of the residue (8.2 g) dichloromethane:acetone isolated the desired complex \((R,R)-309\) as a red solid (0.110 g, 19%). Recrystallisation from CHCl₃/tetrahydrofuran gave small microcrystals which were used in x-ray diffraction studies. \([\alpha]_D^{20} = +140 (c = 0.1, \text{CHCl}_3)\); Found: C, 44.98; H, 4.59; N, 3.77%; \(C_{27}H_{31}Cl_2N_2OPRu\) + 1 CHCl₃ requires C, 44.43; H, 4.66; N, 3.70%; \(\nu_{\text{max}}\)/cm⁻¹ (KBr) 3578 (br), 3058 (w), 2923 (s), 1798 (s), 1615 (s), 1558 (s), 1481 (m), 1434 (s), 1301 (m), 1089 (s), 1018 (s), 699 (s), 534 (s) and 488 (m); \(\delta_H\) (400 MHz, CDCl₃) 8.53 (1H, s, -N=CH), 7.96-7.86 (3H, m, C₆H₅), 7.52 (1H, t, \(J_6=8\)), 7.42 (1H, t, \(J_7=7.5\)), 7.38-7.31 (1H, m, C₆H₅), 7.30-7.15 (7H, m, C₆H₅), 7.11 (1H, t, \(J_9=7.5\)), 6.42 (1H, br s, NH₃H), 4.07 (1H, app t, J 11, CHN), 3.99-3.87 (1H, m, NH₃H), 2.94 (3H, s, C₆H₅SOC₃H₃), 2.65-2.51 (1H, m, CHN), 2.46 (3H, s, C₆H₅SOC₃H₃), 2.36-2.25 (2H, m, cyclohexyl CH₃), 1.91-1.72 (2H, m, cyclohexyl CH₂) and 1.70-1.41 (4H, m, cyclohexyl CH₂); \(\delta_C\) (75 MHz, CDCl₃) 162.1 (d, \(J_6=15.01\), C₆H₅H), 135.1 (d, \(J_{10}=13.57\), C₆H₅H), 133.6 (C₆H₅H), 131.3 (d, \(J_{10}=132.4\), C₆H₅H), 131.6 (C₆H₅H), 130.8 (d, \(J_{10}=129.7\), C₆H₅H), 129.7 (d, \(J_{12}=129.0\), C₆H₅H), 128.7 (d, \(J_{12}=128.7\), C₆H₅H), 127.3 (d, \(J_{10}=126.7\), C₆H₅H), 126.7 (d, \(J_{12}=116.4\), C₆H₅H), 114.5 (C₆H₅H), 72.7 (CH₃), 54.0 (CH₃N), 43.6 (CH₃SOC₃H₃), 41.7 (CH₃SOC₃H₃), 35.2 (cyclohexyl CH₃), 29.6 (cyclohexyl CH₂), 24.1 (cyclohexyl CH₂) and 23.0 (cyclohexyl CH₂); \(\delta_\text{PMR}\) (121 MHz, CDCl₃) + 51.5; \(\nu_{\text{max}}\) (El) 637.2 [M⁺H]⁺ (20 %), 558.1 ([M-DMSO]+), 523.1 ([M-Cl]⁺, 20) and 486.2 ([M-DMSO-2HCl]⁺, 80); HRMS (ESI) found 637.0538 ([M⁺]), [C₇H₅Cl₂N₃O₆P₆RuS₄Cl₂]⁺ requires 637.0545.

\[(3R,4R)-1\text{-Benzyl-3,4-di-hydroxy-pyrrolidine-2,5-dione \((R,R)-318\)}\]

Prepared according to the procedure of Skarzewski and Gupka and modifications made by Fuentes. A mixture of benzylamine (10.72 g, 0.1 mol) with L-(R,R)-(+-)Tartric acid 317 (15.01 g, 0.1 mol) in xylene (60 mL) was refluxed using Dean-Stark apparatus for 6 h and was subsequently left to cool to rt for 16 h. The crystalline product was filtered off and washed with acetone to give compound \((R,R)-318\) as white solid (15.51 g, 70%), mp 196-197°C (lit. 197-198°C). \(\delta_\text{PMR}\) (300 MHz, d₆-DMSO) 7.38-7.21 (5H, m, C₆H₅H), 6.33 (2H, br s, 2 x OCH), 4.56 (2H, d, \(J_5=5.02\), C₆H₅H), and 4.40 (2H, s, C₂H₃Ph); \(\delta_C\) (101 MHz, CDCl₃) 179.8 (C=O), 141.2 (C₆H₅H), 133.7 (C₆H₅H), 132.7 (C₆H₅H), 79.7 (CH₂OH), 46.4 (CH₂Ph). Data are in agreement with the literature. 6,7

\[(3S,4S)-1\text{-Benzylpyrrolidin-3,4-diol \((S,S)-319\)}\]

Prepared following the procedure of Cardona. Compound \((R,R)-318\) was added portionwise to a suspension of lithium aluminium hydride (1.02 g, 0.027 mol) in tetrahydrofuran (100 mL) at rt. The mixture was then heated at reflux for 16 h. This was then cooled to 0°C and a saturated solution of sodium sulfate was added until no more gas was evolved. The mixture was filtered through Celite, washing with ethyl acetate, and was then concentrated in vacuo to give compound \((S,S)-319\) after recrystallisation, as a white solid (0.855 g, 49%), mp 72-73°C (lit. 70-71.5); \(\delta_\text{PMR}\) (300 MHz, CDCl₃) 7.27-7.14 (5H, m, C₆H₅H), 4.03-3.97 (2H, m, 2 x CHO), 3.55 (2H, d, \(J_5=5.02\), C₂H₃Ph), 3.02 (2H, br s, 2 x OH), 2.87 (2H, dd, \(J_10=10.06\), C₆H₅H), 2.37 (2H, dd, \(J_10=6.2\), 2 x CH₃H), \(\delta_C\) (101 MHz, CDCl₃) 132.6 (C₆H₅H), 123.7 (C₆H₅H), 123.1 (C₆H₅H), 122.0...
(C<sub>Ar</sub>H), 73.2 (CHOH), 54.9 (CH<sub>2</sub>) and 54.8 (CH<sub>2</sub>Ph). Data are in agreement with the literature.  

(3<sup>R</sup>,4<sup>R</sup>)-3,4-Di(methanesulfonyloxy)-1-benzylpyrrolidine ([S,S]-320)

Following the procedure of Fuentes, triethylamine (2.68 mL, 19.2 mmol) was added dropwise to a solution of ([S,S]-319) (1.23 g, 6.4 mmol) in DCM at 0°C and the reaction mixture stirred for 10 min. To this, methanesulfonyl chloride (1.49 g, 19.2 mmol) was added dropwise over 5 min. The reaction was stirred at 0°C for 4 h and then was allowed to warm to rt over 1 h. The mixture was filtered and the filtrate was washed with water, before being dried over magnesium sulfate, filtered and concentrated in vacuo, to afford the bis-mesylate ([S,S]-320) as a white solid (1.46 g, 65%), mp 56-58°C (lit. 56°C). δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.28-7.15 (5H, m, C<sub>Ar</sub>H), 5.06-5.00 (2H, m, 2 x C<sub>H</sub>OMs), 3.55 (2H, app d, J 2, C<sub>H</sub>2Ph), 3.01 (2H, app dd, J 11, 6, 2 x C<sub>Ar</sub>H<sub>B</sub>), 2.98 (6H, s, 2 x SO<sub>2</sub>C<sub>H</sub>3) and 2.67 (2H, dd, J 11, 4, 2 x CH<sub>2</sub>H<sub>B</sub>). Data are in agreement with the literature.

(3<sup>R</sup>,4<sup>R</sup>)-3,4-Diazido-1-benzylpyrrolidine ([R,R]-321)

Following the procedure of Fuentes, the bis-mesylate ([S,S]-320) (0.186 g, 0.53 mmol) was dissolved in DMF (10 mL) and to this, sodium azide (0.138 g, 0.53 mmol) was added, and the mixture heated to 100°C for 4 h. The reaction mixture was then stirred for another 16 h at rt, before dichloromethane was added. The organic component was washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product. Flash chromatography (100% dichloromethane) gave the bis-amide as a colourless liquid (0.039 g, 30%). δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.26-7.16 (5H, m, C<sub>Ar</sub>H), 3.81-3.76 (2H, m, 2 x C<sub>H</sub>N<sub>3</sub>), 3.57 (2H, d, J 13, C<sub>H</sub>2Ph), 2.90 (2H, dd, J 10, 6, 2 x C<sub>Ar</sub>H<sub>B</sub>) and 2.52 (2H, dd, J 10, 5, 2 x CH<sub>2</sub>H<sub>B</sub>). Data are in agreement with the literature.

(3<sup>R</sup>,4<sup>R</sup>)-1-Benzylpyrrolidine-3,4-diamine ([R,R]-322)

Following the procedure of Skareski and Gupta, 10% Pd on carbon (0.040 g) was added to a solution of ([R,R]-321) (0.357 g, 15 mmol) in absolute ethanol (10 mL) and the mixture was stirred at rt for 16 h under a hydrogen atmosphere (1 bar). The mixture was subsequently filtered through Celite, washing with ethyl acetate, and concentrated in vacuo to give the title compound as a sticky solid (0.230 g, 82%). [α]<sup>20</sup> D -15.5 (c 1.0, MeOH), lit. [α]<sup>20</sup> D -15.0 (c 1.0, MeOH); δ<sub>δH</sub> (400 MHz, CDCl<sub>3</sub>) 7.28-7.13 (5H, m, C<sub>Ar</sub>H), 3.62-3.45 (2H, m, CH<sub>2</sub>Ph), 3.05-2.93 (2H, m, 2 x C<sub>Ar</sub>H<sub>B</sub>), 2.91-2.79 (2H, m, 2 x CH<sub>2</sub>H<sub>B</sub>), 2.30-2.18 (2H, m, 2 x CHNH<sub>2</sub>) and 1.71 (4H, br s, J 10, 5, 2 x NH<sub>2</sub>). m/z (ES+) 192.07 ([M+H]+, 100%); HRMS (ES+) found 192.1502, [C<sub>11</sub>H<sub>18</sub>N<sub>3</sub>]+ requires 192.1501. Data are in agreement with the literature.
Complex (R,R)-324

A solution of 2-(diphenylphosphino)benzaldehyde 266 (0.082 g, 0.28 mmol) in ethanol at 45°C was added dropwise to a solution of (3R,4R)-1-benzylpyrrolidine-3,4-diamine (R,R)-322 (0.054 g, 0.28 mmol) in the same solvent over a period of 16 h. The solvent was then removed and the residue stirred with 2.5 M sodium bicarbonate solution for 2 h. The mixture was filtered and concentrated hydrochloric acid was added to the filtrate until it reached pH 7 and extracted with toluene (2 x 100 mL). The aqueous layer was acidified with concentrated hydrochloric acid causing the product to precipitate. The mixture was filtered and the precipitate was with chloroform to leave compound (±)-trans-9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid ((±)-327)

Following the procedure of Bachmann and Scott, a solution of anthracene (24.0 g, 130 mmol) and fumaric acid (5.2 g, 44.80 mmol) in dioxane (250 mL) was refluxed for 3 days. The solvent was then evaporated in vacuo and the residue stirred with 2.5 M sodium bicarbonate solution for 2 h. The mixture was filtered and concentrated hydrochloric acid was added to the filtrate until it reached pH 7 and extracted with toluene (2 x 100 mL). The aqueous layer was acidified with concentrated hydrochloric acid causing the product to precipitate. The mixture was filtered and the precipitate was with chloroform to leave compound (±)-327 as a white solid (23.16 g, 61 %). mp 248 - 250°C (lit. 105 253 -254°C). δH (400 MHz, CDCl3) 8.18 (1H, s, N=CH), 7.70-7.04 (19H, m, C̸ArH), 5.07 (1H, br s, NH₃H₄B), 3.86-3.66 (4H, NCH₂Ar† + CHNH₂† + NH₃H₄B), 3.19-3.08 (1H, m, pyrrolidine C₂H₂B) †, 3.07-2.99 (2H, m, pyrrolidine C₂H₂B + pyrrolidine C₂H₂B) †, 2.98-2.87 (2H, m, pyrrolidine C₂H₂B + CHN=C) †, 2.56 (3H, s, C(H₃)₃SOC(H₄B)₃) and 2.51 (3H, s, C(H₃)₃SOC(H₄B)₃); δC (400 MHz, CDCl3) 163.3 (N=CH), 137.1 (C ipso), 136.2 (d, J 9, C₆H), 135.8 (C ipso), 134.9 (C₆H), 134.1 (d, J 10, C₆H), 133.6 (d, J 10, C₆H), 132.1 (d, J 7, C₆H), 131.8 (d, J 11, C ipso), 130.9 (C₆H), 130.2 (C₆H), 129.8 (C₆H), 128.5 (C₆H), 128.5 (C₆H), 127.7 (d, J 10, C₆H), 127.2 (C ipso), 116.0 (C ipso), 116.3 (NCH₂Ph), 58.5 (CHNH₂), 54.5 (pyrrolidine C₂H₂), 50.8 (pyrrolidine C₂H₂), 44.7 (CHN=C), 43.0 (C₆H₂SOC₆H) and 41.1 (C₆H₂SOC₆H); δp (121 MHz, CDCl₃) +53.7; HRMS (ES+) found 708.0845, [C₃₂H₂₇Cl₂N₂O₆RuS] requires 708.0842. Observed from ¹H-¹H HSQC correlations.

(±)-trans-9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid ((±)-327)

Following the procedure of Bachmann and Scott, a solution of anthracene (24.0 g, 130 mmol) and fumaric acid (5.2 g, 44.80 mmol) in dioxane (250 mL) was refluxed for 3 days. The solvent was then evaporated in vacuo and the residue stirred with 2.5 M sodium bicarbonate solution for 2 h. The mixture was filtered and concentrated hydrochloric acid was added to the filtrate until it reached pH 7 and extracted with toluene (2 x 100 mL). The aqueous layer was acidified with concentrated hydrochloric acid causing the product to precipitate. The mixture was filtered and the precipitate was with chloroform to leave compound (±)-327 as a white solid (23.16 g, 61 %). mp 248 - 250°C (lit. 105 253 -254°C). δH (400 MHz, d⁶ DMSO) 12.54 (2H, br s, OH), 7.41-7.36 (2H, m, C₆H), 7.27-7.23 (2H, m, C₆H), 7.13-7.03 (4H, m, C₆H), 4.71 (2H, s, 2 x CHCO₂H) and 3.10 (2H, s, 2 x CH); δC (75 MHz, d⁶ DMSO) 45.9 (CH), 47.3 (CH), 123.5 (C₂H), 124.6 (C₂H), 125.8 (C₂H), 126.0 (C₂H), 140.5 (C₂H), 142.7 (C₂H) and 173.3 (CO₂H); m/z (CI+) 294.09 (M⁺, 10 %), 207.12 (M-(2 x (CO₂H))⁺, 10) and 179.07 (M-(HO₂CCH₂CH₂CO₂H)⁺, 100). Data are in agreement with the literature.
(-)-9,10-Dihydro-9,10-ethanoanthracene-11(S),12(S)-dicarboxylic acid ((S,S)-327)

Following a procedure introduced by Brienne and Jaques and later modified by Allenmark, (±)-trans-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid 327 (10.48 g, 35.60 mmol) and brucine (28.01 g, 71.20 mmol) were stirred in a 35 % solution of absolute ethanol in water (v/v) (300 mL). The resulting mixture was warmed until all the solids dissolved. The solution was then allowed to cool to room temperature and was kept at 4°C for 24 h. The white precipitate was collected by suction filtration and the same procedure was repeated again, this time using 200 mL of a 35 % solution of absolute ethanol in water. The solution was allowed to stand for 4 h at 4°C and the precipitate collected by suction filtration, washed with cold 35 % solution of absolute ethanol in water (2 x 20 mL) and dried. The brucine salt was stirred with 1M NaOH (100 mL) for 30 min before the free brucine was filtered off. The filtrate was acidified to pH < 2 by addition of concentrated hydrochloric acid and the resulting precipitate was filtered, washed with chloroform, and dried in vacuo to leave the desired product as a white powder (3.56 g, 34 %). Characterisation data matched that of the racemate.

(-)-9,10-Dihydro-9,10-ethanoanthracene-11(S),12(S)-diacid chloride ((S,S)-329)

By adaption of the procedure of Allenmark, thionyl chloride (0.79 mL, 10.80 mmol) was added dropwise to a stirred slurry of (-)-9,10-dihydro-9,10-ethanoanthracene-11(S),12(S)-dicarboxylic acid ((S,S)-327) (1.06 g, 36.00 mmol) in anhydrous toluene (8 mL). The mixture was heated at reflux until the entire solid had disappeared and then for 16 h at 60°C. The solution was allowed to cool to room temperature and the solvent and thionyl chloride were removed under reduced pressure to afford the bis-acid chloride ((S,S)-329) as a sticky clear solid (0.94 g, 79 %), of >99% enantiomeric excess. δH (400 MHz, CDCl3) 7.36-7.26 (4H, m, CArH), 7.15-7.10 (4H, m, CArH), 4.88 (2H, s, 2 x CHH) and 3.75-3.74 (2H, m, 2 x CHH). Enantioselectivity determined by chiral HPLC of the isopropyl ester derivative of (S,S)-338. ChiralPak AD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 6.0 min (R,R) and 9.7 min (S,S). Data are in agreement with the literature.

(+)-(11S,12S)-11,12-Diamino-9,10-dihydro-9,10-ethanoanthracene ((S,S)-331)

By modification of the procedures of Trost and Fuentes, a solution of (+)-(11S,12S)-11,12-Diamino-9,10-dihydro-9,10-ethanoanthracene diacid chloride ((S,S)-329) (1.10 g, 3.32 mmol) in toluene (15 mL) was added dropwise to a solution of sodium azide (0.76 g, 11.60 mmol) in water (15 mL) cooled to 0°C. The mixture was stirred 4 h while warming up from 0°C to rt. The organic layer was separated and washed with dilute sodium hydrogen carbonate (15 mL) and water (2 x 10 mL), dried over anhydrous magnesium sulfate and filtered to give a solution of the corresponding bis-azide. The solution was diluted further with toluene and heated to 80°C for 1 h then cooled to rt to give a solution of the bis-isocyanate. To this solution was added 6M hydrochloric acid (6 mL) and the mixture heated to 80°C for 3 h and then stirred at rt for 16 h.
The two layers were separated and the aqueous phase washed with toluene then concentrated to give the diamine hydrochloride as a brownish solid. This was dissolved in water and sodium hydroxide was added until the solution became milky (~ pH 14). The solution was extracted with dichloromethane and the organic solution was washed with water then brine before being separated, dried over magnesium sulfate and concentrated to give the title compound as a beige solid (0.157 g, 20 %), which was used without further purification, mp 151-153 °C (lit. 11153-156 °C). [α]20D + 19.9 (c 2.0, MeOH), lit. [α]20D + 21.2 (c 2.3, MeOH); δH (400 MHz, CDCl3) 7.23-7.09 (4H, m, CArH), 7.05-6.92 (4H, m, CArH), 3.86 (2H, s, 2 x CH2), 2.45 (2H, s, 2 x CH) and 1.12 (4H, br s, 2 x NH2); m/z (ES+) 237.08 ([M+H]+, 5 %) and 220.06 ([M-NH2]+, 100).

Data are in agreement with the literature.

N-[2-Diphenylphosphanyl]benzoyloxy]succinimide (334)

Following the procedure of Santos and coworkers, 12 2-(diphenylphosphanyl)benzoic acid (0.984 g, 3.2 mmol) and N-hydroxysuccinimide (0.737 g, 6.4 mmol) were dissolved in dichloromethane (20 mL) at rt, and a solution of dicyclohexylcarbodiimide (1.32 g, 6.4 mmol) was added dropwise. After 3 h, the mixture was filtered through Celite, washing with further dichloromethane, and concentrated in vacuo. Column chromatography (4:1 ethyl acetate:hexane) afforded the pure material as a yellowish solid (1.16 g, 90%). mp 142-144 °C.

δH (300 MHz, CDCl3) 8.27-8.20 (1H, m, CArH), 7.44-7.34 (3H, m, CArH), 7.27-7.10 (9H, m, CArH), 6.95-6.88 (1H, m, CArH) and 2.68 (4H, s, 2 x CH2); δP (121 MHz, CDCl3) -10.1.

Data are in agreement with the literature.

[(11R,12R)-N-(12-Amino-9,10-dihydro-9,10-ethanoanthracen-11-yl)]-2-(diphenylphosphino) benzamide (335)

By modification of a literature procedure of Santos and coworkers, 12 N-[2-(diphenylphosphanyl)benzoyloxy]succinimide 334 (0.100 g, 0.42 mmol), dissolved in dichloromethane (10 mL), was added dropwise to a solution of (+)-(11S,12S)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene (R,R)-331 in the same solvent (25 mL). After 4 h, the mixture was washed with water and the organic phase separated. The aqueous phase was extracted with further dichloromethane. The combined organic fractions were dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica (95:5→9:1 DCM:MeOH) and subsequent recrystallisation furnished the product as yellowish crystals (0.137 g, 75%), mp 129-130°C. δH (CDCl3, 300 MHz) 7.37 (1H, ddd, J 8, 4, 2, CArH), 7.30-7.08 (16H, m, CArH), 7.07-6.94 (4H, m, CArH), 6.79 (1H, ddd, J 8, 4, 1, CArH), 5.71 (1H, d, J 8, NHCO), 4.08 (1H, d, J 3, CH), 4.00 (1H, d, J 3, CH), 3.66-3.59 (1H, m, CH), 2.43 (1H, t, J 3, CH) and 1.53 (2H, br s, NH2); δP (CDCl3, 400 MHz) 169.2 (C=O) 142.4 (Cipso), 140.9 (d, J 26, Cipso), 140.3 (Cipso), 139.2 (Cipso), 138.5 (Cipso), 136.8 (Cipso), 136.7 (Cipso), 135.8 (d, J 21, Cipso), 134.1 (Cipso), 134.0 (Cipso), 133.9 (Cipso), 133.9 (Cipso), 133.7 (Cipso), 130.3 (Cipso), 129.0 (d, J 6, Cipso), 128.8 (app d, J 6, Cipso), 128.7 (app d, J 6, Cipso), 128.6 (Cipso), 127.9 (d, J 5, Cipso), 126.7 (Cipso), 126.6 (d, J 5, Cipso), 126.3 (Cipso), 126.2 (Cipso), 125.4 (Cipso), 124.5 (d, J 9, Cipso), 60.7 (CHN), 60.3 (CHN), 51.5 (CH) and 48.6 (CH); δP (CDCl3, 121 MHz) -10.1;
Enantioselective Hydrogenation Using Ruthenium Complexes

Appendix
of Tridentate Ligands
Scott Phillips

$m/z$ (ES+) 524.92 ((M+H)$^*$, 100%); HRMS (ES+) found 525.2089. [C$_{35}$H$_{30}$N$_2$OP]$^*$ requires 525.2096. $^\dagger$ Assignments supported by $^1$H-$^1$H COSY and $^1$H-$^{13}$C HSQC correlations. $^\ddagger$ Assignments supported by $^1$H-$^{13}$C HSQC correlations.

Complex (S,S)-333

A solution of 2-(diphenylphosphino)benzaldehyde 266 (0.099 g, 0.34 mmol) in ethanol at 45°C was added dropwise to a solution of (+)-(11S,12S)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene (S,S)-331 (0.250 g, 1.03 mmol) in the same solvent over a period of 2 h at rt. To this, sodium borohydride (0.051 g, 1.36 mmol) was added and the solution stirred for a further four hours at rt. The solvent was removed and the ligand complexed immediately using the protocol described in section 5.2.1. Attempts at purification of the crude product by flash chromatography on silica (100:0 to 50:50 DCM:acetone) only furnished the product as an 80:20 mixture with an unidentified species. Product: $\delta$ (121 MHz, CDCl$_3$)$^+$ +45.3; Unidentified side product $\delta$ (121 MHz, CDCl$_3$)$^+$ +54.2. We therefore have only made tentative conclusions regarding the performance of this complex.

(11S,12S)-N$^{11}$-(2-(Diphenylphosphino)benzyl)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine borane adduct (336)

(R,R)-331 and borane tetrahydrofuran complex were stirred together under nitrogen for 16 h. Evaporation of the solvent and recrystallisation from dichloromethane yielded the title compound (0.067 g, 59%) in around 90% purity by NMR. $\delta$H 7.70-7.14 (22H, m, C$_{Ar}$H), 4.60 (2H, br s, NH$_2$), 4.44-4.40 (1H, m, NH or CH), 4.36-4.32 (2H, m, NH or CHN), 4.23-4.17 (2H, m, 2 x NH or CHN), 3.16-3.15 (CH) and 2.83-2.80 (CH); $\delta$P (CDCl$_3$, 300 MHz) +18.9; $\delta$B (McOD, 400 MHz) = -1.3.

(1R,2S)-1-((2-(bis(3,5-di-tert-butylphenyl)phosphino)benzyl)amino)-2,3-dihydro-1H-inden-2-ol (340)

(1R,2S)-(+) cis-1-amino-2-indanol 338 (0.022 g, 0.195 mmol) and 2-(bis(3,5-di-tert-butylphenyl)phosphino)benzaldehyde 302 (0.100 g, 0.195 mmol) were dissolved in ethanol (20 mL) and stirred at rt for 3 h. After this period, sodium borohydride (0.030 g, 0.780 mmol) was added and the mixture stirred for a further 16 h. The solvent was then removed under reduced pressure. The residue was dissolved by stirring with saturated ammonium chloride solution and dichloromethane. The organic layer was separated, washed with water and brine, dried over
magnesium sulfate, filtered and concentrated in vacuo to give the crude product as a sticky colourless solid. Due to the sensitivity of the phosphine to air, full characterisation was not possible and the ligand complexed immediately. \( \delta_H \) (CDCl\(_3\), 300 MHz) 7.71-6.75 (14H, m, C\(_{Ar}\)H), 6.29 (1H, d, J 7, OH), 4.39-4.32 (1H, m, CHO or CHN), 4.18-4.11 (2H, m, CH\(_2\)CHOH), 3.97-3.90 (1H, m, CHO or CHN), 2.96-2.83 (3H, m, CH\(_2\)Ar + NH) and 1.13 (36H, s, 4 x C(CH\(_3\))\(_2\)); \( \delta_C \) (CDCl\(_3\), 75 MHz) 149.9 (d, J 7, Cipso), 149.8 (d, J 7, Cipso), 142.6 (d, J 20, Cipso), 140.9 (Cipso), 140.0 (Cipso), 136.1 (d, J 12, Cipso), 134.9 (d, J 9, Cipso), 134.4 (d, J 10, Cipso), 132.8 (Cipso), 129.0 (Cipso), 127.9 (Cipso), 127.2 (Cipso), 126.9 (Cipso), 126.6 (Cipso), 126.5 (Cipso), 125.4 (Cipso), 124.3 (Cipso), 122.5 (Cipso), 121.7 (Cipso), 121.6 (Cipso), 69.3 (CHN or CHO), 64.1 (CHN or CHO), 50.2 (d, J 18, NHCH\(_2\)Ar), 38.6 (CH\(_2\)CHOH). 33.9 (C(CH\(_3\))\(_3\)) and 30.3 (C(CH\(_3\))\(_3\)); \( \delta_P \) (CDCl\(_3\), 121 MHz) -14.2; \( m/z \) (ES+) 664.26 ((M=O+H)*, 100%).

**Complex (R,S)-341**

Prepared using the general procedure outlined in section 5.3.1 giving complex (R,S)-341 as a brown solid (0.138 g, 79 %), m.p. > 187°C (decomp.). Microanalysis was not possible as the complex held on to some solvent even after exhaustive drying preventing good microanalysis.

\( \delta_H \) (300 MHz, CDCl\(_3\)) 7.46-7.40 (1H, m, Cipso), 7.31-7.04 (13H, m, Cipso), 5.96 (1H, br 2, OH), 5.08 (1H, br s, NH), 4.89 (1H, dd, J 11; 6, CHN), 4.68-4.52 (1H, m, CH\(_3\)H\(_3\)CHOH), 4.34-4.23 (1H, m, CH\(_3\)H\(_3\)CHOH)\(^+\), 4.15 (1H, t, J 11, CHO), 3.64-3.47 (1H, m, CH\(_3\)H\(_3\)NH)\(^+\), 3.11-2.96 (1H, m, CH\(_3\)H\(_3\)NH)\(^+\), 2.85 (3H, s, Cipso), 2.65 (3H, s, Cipso), 1.18 (18H, s, 2 x C(CH\(_3\))\(_3\)) and 1.10 (18H, s, 2 x C(CH\(_3\))\(_3\)); \( \delta_C \) (75 MHz, CDCl\(_3\)) 149.9 (d, J 14, Cipso), 140.9 (Cipso), 139.0 (Cipso), 134.1 (Cipso), 133.3 (d, J 11, Cipso), 133.1 (Cipso), 132.7 (Cipso), 132.0 (Cipso), 131.8 (Cipso), 131.0 (Cipso), 129.4 (Cipso), 128.8 (Cipso), 128.4 (Cipso), 128.3 (Cipso), 127.5 (Cipso), 126.5 (Cipso), 126.0 (Cipso), 124.0 (Cipso), 123.4 (Cipso), 68.7 (CHN)\(^+\), 64.8 (CHO)\(^+\), 54.6 (d, J 7, NHCH\(_2\)Ar), 45.9 (Cipso), 45.4 (Cipso), 37.0 (CH\(_2\)CHOH)\(^+\), 31.8 (C(CH\(_3\))\(_3\)), 31.8 (C(CH\(_3\))\(_3\)) and 31.6 (C(CH\(_3\))\(_3\)); \( \delta_P \) (121 MHz, CDCl\(_3\)) +58.6; HRMS (ES+) found 898.2889, \([C_{46}H_{66}Cl_3\text{NOPR}_{25}]^+\) requires 898.2894. \(^1\) Observed from \( ^1H-^1H \) COSY correlations. \(^2\) Observed from \( ^1H-^1^3C \) HSQC and HMBC correlations.

### A.5 References

Appendix B

Mass Spectrometry Isotope Profiles for Ru Complexes

Complex 264

Complex (R,R)-297
Complex \((R,R)-309\)

Complex \((R,R)-324\)
Complex (R,S)- 341
Appendix C

X-ray Crystallographic Data

X-ray crystallographic data were collected at 93 K using a Rigaku MM007 High Brilliance RA generator and Mercury/Saturn CCD systems using Mo Kα radiation. Intensities were corrected for Lorentz-polarisation and for absorption. The structures were solved by direct methods. All hydrogen atoms were refined as idealised riding geometries and structural refinements were obtained with full-matrix least squares based on $F^2$ by using the program SHELXTL. Full crystallographic data in CIF format are available on the CD attachment.

B.1 Crystal data and structure refinement for Complex 264.2CHCl₃ (Shown in Figure III.1 (a))

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<td>Empirical formula</td>
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<td>Formula weight</td>
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<tr>
<td>Wavelength</td>
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<tr>
<td>Crystal system</td>
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<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 10.9133(11) Å  γ = 83.876(7)°.</td>
</tr>
<tr>
<td></td>
<td>c = 15.9236(16) Å</td>
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<tr>
<td>Volume</td>
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</tr>
<tr>
<td>Z</td>
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<tr>
<td>Density (calculated)</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
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<td>Crystal size</td>
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</tr>
<tr>
<td>Index ranges</td>
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<tr>
<td>Reflections collected</td>
<td>16641</td>
</tr>
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Independent reflections 6257 [R(int) = 0.1380]
Completeness to theta = 25.00° 98.6 %
Absorption correction Multiscan
Max. and min. transmission 1.0000 and 0.71446
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 6257 / 72 / 371
Goodness-of-fit on F^2 1.122
Final R indices [I>2sigma(I)] R1 = 0.1944, wR2 = 0.4185
R indices (all data) R1 = 0.2028, wR2 = 0.4257
Extinction coefficient 0.021(3)
Largest diff. peak and hole 3.453 and -1.995 e.Å^{-3}

**B.2 Crystal data and structure refinement for complex formed upon attempted crystallisation of Complex 264 from MeCN (Shown in Figure III.1 (b))**

Empirical formula C25 H30 Cl2 N3 P Ru
Formula weight 575.46
Temperature 93(2) K
Wavelength 0.71073 Å
Crystal system Triclinic
Space group P-1
Unit cell dimensions a = 12.409(5) Å α= 90.79(4)°.
b = 15.030(5) Å β = 100.49(4)°.
c = 15.379(5) Å γ = 114.17(5)°.
Volume 2560.8(16) Å^3
Z 4
Density (calculated) 1.493 Mg/m^3
Absorption coefficient 0.901 mm^{-1}
F(000) 1176
Crystal size 0.1200 x 0.1200 x 0.0800 mm³
Theta range for data collection 1.35 to 25.31°.
Index ranges -14≤h≤14, -17≤k≤18, -18≤l≤18
Reflections collected 24631
Independent reflections 9190 [R(int) = 0.0894]
Completeness to theta = 25.00° 99.0 %
Absorption correction Multiscan
Max. and min. transmission 1.0000 and 0.5235
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 9190 / 0 / 579
Goodness-of-fit on F² 1.070
Final R indices [I>2sigma(I)] R1 = 0.1004, wR2 = 0.2730
R indices (all data) R1 = 0.1206, wR2 = 0.2985
Largest diff. peak and hole 2.063 and -2.013 e.Å⁻³

B.3 Crystal data and structure refinement for Complex (R,R)-309

Empirical formula C27 H33 Cl2 N2 O P Ru S
Formula weight 636.55
Temperature 93(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)
Unit cell dimensions a = 8.981(4) Å  α= 90°.
b = 11.235(4) Å  β= 102.690(17)°.
c = 13.362(5) Å  γ = 90°.
Volume 1315.2(9) Å³
Z 2
Density (calculated) 1.607 Mg/m³
Absorption coefficient 0.964 mm⁻¹
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<th>Description</th>
<th>Value/Details</th>
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<tr>
<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<td>Index ranges</td>
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<td>Completeness to theta = 25.00°</td>
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<tr>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
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<td>Goodness-of-fit on F$^2$</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<td>R indices (all data)</td>
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<tr>
<td>Absolute structure parameter</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.818 and -0.838 e.Å$^{-3}$</td>
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</table>
Appendix D

Publications


