

**DEVELOPMENTS IN THE HYDROGENATION OF
CHALLENGING SUBSTRATES UTILISING TRANSITION
METAL COMPLEXES**

Ian Carpenter

**A Thesis Submitted for the Degree of PhD
at the
University of St Andrews**



2014

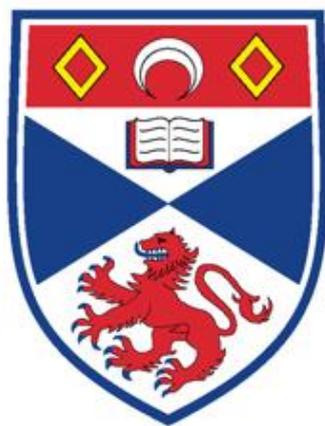
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Developments in the Hydrogenation of Challenging Substrates Utilising Transition Metal Complexes



University
of
St Andrews

School of Chemistry

A thesis submitted for the degree of PhD by

Ian Carpenter

2014

Under the Supervision of Dr Matthew Clarke

Declarations

I, Ian Carpenter, hereby certify that this thesis, which is approximately 38,000 words in length, has been written by me, that it is the record of work carried out by me or principally by myself in collaboration with others as acknowledged, and that it has not been submitted in any previous application for a higher degree.

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“Insanity: doing the same thing over and over again and expecting different results.”

Albert Einstein (1879-1955).

“L’univers est dissymétrique.”

Louis Pasteur (1822-1895)

Acknowledgements

There are a lot of people that require thanks for helping making this thesis come to fruition. First of all, I must thank Dr Matthew Clarke for the opportunity to study at St Andrews and carry out this research project. Matt I thank you for your constant input and most of all your patience over the last few years.

I wish to thank all the members of the Clarke group over my time at St Andrews. From the first day I started I was made to feel welcome and the environment in the lab has made it a great place to work. I would especially like to thank; Gary Noonan, Scott Phillips, Charlotte Jones, Ed Milton, Tina Konrad, Jamie Durrani, Laura Mitchell, and Rebecca How. I would like to thank all the post-doctoral researchers in the group who have provided vital help and guidance. A very big thanks to; Jose Fuentes, Piotr Warwrzyniak and Arnald Grabulosa.

I need to thank all the technical staff at the School of Chemistry at St Andrews, who make all the research at St Andrews possible. Thanks to; Melanja Smith, Tomas Lebl, Caroline Horsburgh, Sylvia Williamson.

I would like to thank all my family for all their support during and before my time at St Andrews. Thank you all very much.

The most important person that requires my gratitude is the love of my life. Thank you Morag, without your constant support (and possibly occasional nagging), I would never have got to the end.

Abstract

This thesis describes the developments of new protocols for the hydrogenation of challenging substrates. Three specific substrates were highlighted for study after an initial review of the literature; benzofurans, esters and bulky ketones.

Chapter 1 details a review of the hydrogenation of challenging unsaturated substrates, highlighting areas where development is still required.

Chapter 2 describes studies on the hydrogenation of 2,3-benzofuran. While a benzofuran hydrogenation catalysts was optimised, severe conditions were required to facilitate the reaction, and not found to be applicable for more elaborate substrates. We therefore considered an alternative process of enantioselective hydrogenation of benzofuranyl ketones followed by heterogeneous hydrogenation. A good process for transfer hydrogenation of a range of these hitherto unstudied substrates was developed along with greater understanding.

The hydrogenation of esters is another challenge in the catalytic reduction field, so was also selected for study, with the results described in Chapter 3. After screening a range of catalysts of types $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ and $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$, good catalysts were identified. Successful hydrogenation of a range of esters, under mild conditions was achieved using $[\text{RuCl}_2(1,3\text{-bis(diphenylphosphine)propane})(2\text{-aminomethylpyridine})]$ using high concentrations of base co-catalyst. $[\text{RuCl}_2((2\text{-(diphenylphosphanylbenzyl)ethane-1,2-diamine})(\text{DMSO}))]$ combined with 15-25 mol% of a basic co-catalyst have been shown to be active at near ambient conditions in the hydrogenation of aromatic esters.

Chapter 4 related to studies where the activity of Ru, Ir and Rh complexes of the same tridentate ligand were tested in the hydrogenation of ketones that would be regarded as sluggish substrates. Highly active and selective catalysts for the hydrogenation of bulky acetophenone derivatives were found using iridium complexes of PNX ligands (formed *in situ*). The highest selectivity was obtained with acetophenone substrates containing *iso*-propyl and cyclohexyl substituents, or medically important piperdiny groups. In the best cases over 90% e.e. was observed with high conversions and with only 0.1 mol% of catalyst.

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Acronyms and Abbreviations

Ac	Acetyl group or $-(C=O)CH_3$
Ar	Aromatic group
NaBAR ^F	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAL	2,2'-Dihydroxy-1,1'-binaphthyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
bis	Indicates the presence of two identical groups
Bn	Benzyl group or $-CH_2Ph$
Boc	<i>tert</i> -butyloxycarbonyl
Bu	Butyl group or $-C_4H_9$
<i>c</i>	Concentration
°C	Degrees Celsius
C ₂	Symmetry operation
<i>cf</i>	<i>Confer imper</i> , Latin meaning compared to
CI	Chemical Ionisation
<i>Cis</i>	Highest priority substituents located on the same side of a double bond
COD	Cyclooctadiene
Cp*	Cyclopentadienyl ligand
cy	Cyclic compound
cyclo	Cyclic compound
<i>d</i>	Doublet
δ	Chemical shift
DAIPEN	1,1- <i>bis</i> (4-methoxyphenyl)-3-methyl-1,2-butanediamine
DiBPF	Di- <i>tert</i> -butylphosphinoferrocene
DCM	Dichloromethane
d.e.	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarisation Transfer
DIOP	((4 <i>R</i> ,5 <i>R</i>)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(diphenylphosphine)
DIPAMP	1,2-Bis-(<i>o</i> -anisylphenylphosphino)ethane
DMAPEN	2-Dimethylamino-1-phenylethylamine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DPEN	1,2-Diphenylethylenediamine
<i>E</i>	Entgegen, german meaning opposite side, see <i>trans</i>
EDG	Electron donating group
e.e.	Enantiomeric excess
EI	Electron Impact
EPSRC	Engineering and Physical Sciences Research Council
ES	Electrospray
et al.	Latin meaning “and others”

Et	Ethyl group or -CH ₂ CH ₃
eq.	Equivalents
EWG	Electron withdrawing group
g	Gram
hrs	Hours
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
<i>in situ</i>	In this place
<i>in vacuo</i>	Under reduced pressure
<i>i</i> -Pr	Isopropyl group or -CH(CH ₃) ₂
IR	Infrared
<i>J</i>	Coupling constant
KO <i>t</i> -Bu	Potassium <i>tert</i> - butoxide
l	Litre
lit	Literature value
<i>m</i>	Multiplet
m	Metre or milli
<i>m</i> -	<i>Meta</i> substituted
M	Moles per litre
Me	Methyl group or -CH ₃
min	Minute
mol	Moles
MOM	Methoxymethyl group or -CH ₂ OCH ₃
Mp	Melting point
Ms	Methanesulfonyl group or -SO ₂ Me
MS	Mass Spectrometry
MeTHF	2-Methyltetrahydrofuran
naphth	Naphthalene
NCS	<i>N</i> -Chlorosuccinimide
NMR	Nuclear magnetic resonance
Np	Naphthyl group or -C ₁₀ H ₇
Nu	Nucleophile
μW	Microwave radiation
<i>o</i> -	<i>Ortho</i> substituted
<i>p</i> -	<i>Para</i> substituted
PEG	Polyethylene glycol
pH	The decimal logarithm of the reciprocal of the hydrogen ion activity
Ph	Phenyl group or -C ₆ H ₅
PICA	α-Picolylamine
p <i>K</i> _a	The negative logarithm of the acid dissociation constant, <i>K</i> _a
PNN	A tridentate ligand containing a phosphorus donor and two nitrogen donors

PNX	A tridentate ligand containing a phosphorus donor, a nitrogen donor and another heteroatom donor (e.g O, N, S).
poly	Polymeric
ppm	Parts per million
Pr	Propyl group or $-C_3H_7$
Pro	Proline
PTFE	Polytetrafluoroethylene
py	Pyridine
q	Quartet
R	<i>Rectus</i> , the substituent priority decreases in a clockwise manner, as according to the Cahn-Ingold-Prelog rules
rac	Racemic
rt	Room temperature
s	Seconds
s	singlet
S	<i>Sinister</i> , the substituent priority decreases in a counterclockwise manner, as according to the Cahn-Ingold-Prelog rules
t	Triplet or Tertiary
<i>t</i> -Bu	Tertiary butyl group or $-C(CH_3)_3$
<i>tert</i>	Tertiary
TfO/OTf	Triflate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl group or $-Si(CH_3)_3$
TOF	Turnover Frequency
Tol	Tolyl group or $-(4-CH_3)C_6H_4$
TON	Turnover number
<i>trans</i>	Highest priority substituents on opposite sides of a double bond
Ts	Toluenesulfonyl group or $CH_3C_6H_4SO_2-$
TS	Transition State
UV	Ultraviolet
vs	Versus
Xyl	Xylyl group or $3,5-di-(CH_3)C_6H_3-$
Z	Zusammen, German for together, see <i>cis</i>

I. CHAPTER I: INTRODUCTION

1.1. The Use of Catalysts in Synthesis

Catalysts in different guises have been used for centuries, in such processes as making bread, soap and fermenting wine. The term catalyst was derived by Berzelius a Swedish chemist. It was derived from the Greek words, *kata* and *lyein*, meaning ‘down’ and ‘loosen’ respectively. Berzelius believed that the catalyst gave an inherent force to the reaction which “awakened the activities that are slumbering in the molecules.”¹

A more detailed definition for catalysis was proposed in 1895 by Ostwald who later won the nobel prize for his work in catalysis. “A catalyst is a substance that changes the rate of a chemical reaction without itself appearing in the product.”²

Catalysis is a widely researched area of chemistry, due to the great improvement of the rate of a reaction that can be produced by adding sub-stoichiometric amounts of the catalyst. This is beneficial for both industrial and academic work; they can improve costs, reduce time frames, affect the selectivity of the reaction and also lessen the environmental effects of a particular experiment. Due to the large amount of research directed towards catalysis, modern catalysts are used widely in the production of a variety of different every day products, including plastics, fuels, fine chemicals and pharmaceuticals.

Most catalysts belong to one of two broad classes; heterogeneous and homogeneous and each has pro’s and con’s. Heterogeneous catalysts are compounds that are present in different phase from the substrate (i.e. solid vs. liquid). In general, they are cheap, recoverable/ recyclable, with good thermal stability. Heterogeneous catalysts in certain cases have issues with selectivity and will often transform multiple functionalities within the substrate. They also have intrinsic activity issues as a phase separation exists and there are limited active surface sites present.

Homogeneous catalysts are present in the same phase as the substrate, so can be very active catalysts. The largest group of homogeneous catalysts are those represented by organometallic coordinated compounds. These are also easier to modify and control when compared with heterogeneous catalysts, which means they can be created to be highly selective. Catalysts can be chemoselective, regioselective, enantioselective or combination of all of these. There are significant disadvantages to homogeneous catalysts also, these types of catalysts are often difficult to separate from the product, are often toxic and can be expensive to synthesise.

Catalysts are used in a number of different chemical reactions that would not be possible without them. One such reaction is hydrogenation. Hydrogenation is the addition of a hydrogen molecule to an unsaturated functional group. The most common and atom efficient source is to use gaseous molecular hydrogen. The process requires the use of a catalyst, and early examples discovered by Crabtree and Wilkinson are shown below and are named Crabtree's catalyst and Wilkinson's catalyst respectively shown in Figure 1.1.^{3,4}

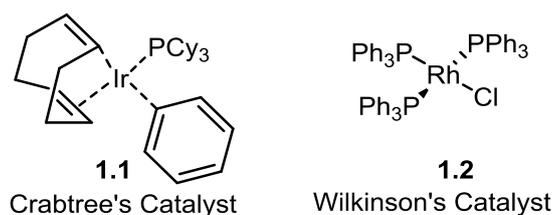


Figure 1.1: Crabtree's and Wilkinson's catalysts^{3,4}

These catalysts can hydrogenate a large variety of alkenes, and have led to the development of more elaborate catalysts.

1.2. Catalytic Asymmetric Hydrogenation

Chirality is a property of specific molecules that means a number of isomers of a chiral molecule can exist. This has interesting effects in nature due to the specificity of enzymes and receptors, as one isomer will often have a different physical effect on an organism. There are many examples of this, for instance Naproxen (shown in figure 1.2) is sold worldwide as an analgesic, but the opposite enantiomer causes liver damage with no analgesic effect. The market share of single enantiomer chiral drugs was 39% in 2002 and has increased since then to an estimate \$15 billion market.⁵

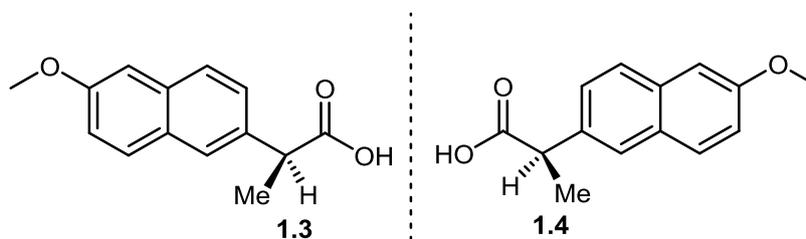
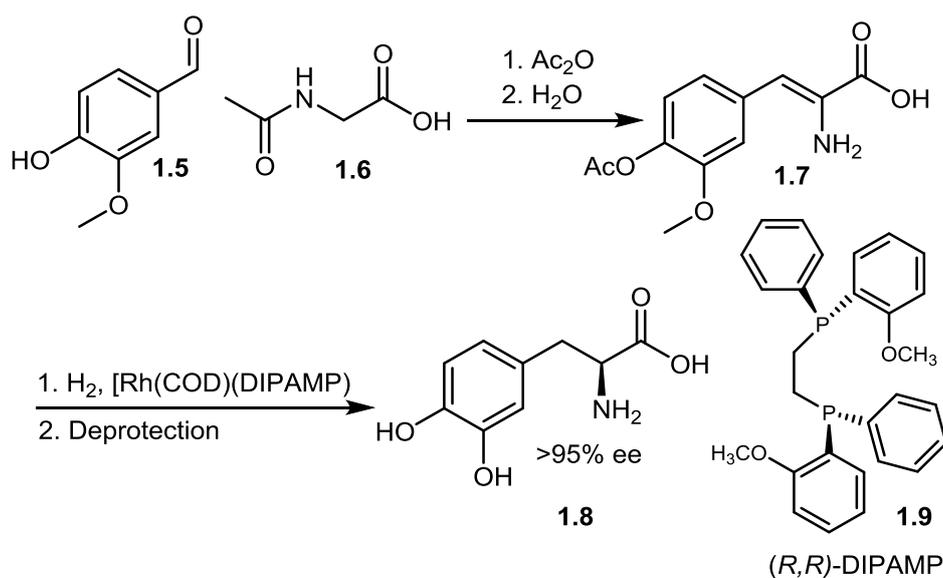


Figure 1.2: Enantiomers of Naproxen⁵

The selective synthesis of one enantiomer (asymmetric synthesis) is a very important area of organic chemistry, as numbers of active pharmaceutical products are found that contain one or more stereogenic centre. As a result there is becoming a greater need to produce pure forms of chiral molecules. Conventional methods for producing such molecules often require the aid of; chiral auxiliaries, resolutions, asymmetric catalysis or making molecules from the chiral pool. All these methods are can be combined to produce a certain product.

An early, industrially relevant, example of the use of catalytic asymmetric hydrogenation, is in the synthesis of (S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid or L-3,4-dihydroxyphenylalanine (L-DOPA). L-DOPA is used as a drug for the treatment of Parkinson's disease. The synthesis of L-DOPA was developed by Knowles while working at Monsanto. Knowles won the Nobel Prize (jointly with Noyori and Sharpless) in 2001 for the development of the asymmetric hydrogenation. Knowles showed that you could start with a prochiral olefin and treat it with a chiral catalyst in a hydrogen atmosphere, to achieve a highly selective hydrogenation of an alkene substrate to produce a product that could be further modified to produce L-DOPA.^{6,7} Knowles and co-workers experimented with a number of different chiral phosphines before they eventually managed to optimise the process and produce L-DOPA with an e.e of >95%⁶ using the P- Chiral diphosphine DIPAMP, shown below in scheme 1.1.



Scheme 1.1: Synthesis of L-DOPA⁶

This reaction has been used on an industrial scale since 1974 and has given inspiration for many other research groups to investigate hydrogenation of a variety of prochiral unsaturated substrates not just olefins.

In contrast to the Knowles ligand, BINAP (see below Figure 1.3) has the stereogenic information contained in the backbone of the diposphine due to axial chirality present in the ligand due to the restriction of rotation of the aryl-aryl bond.

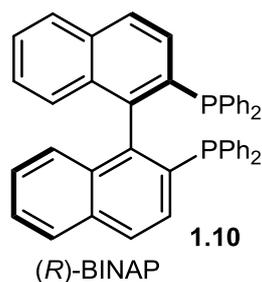
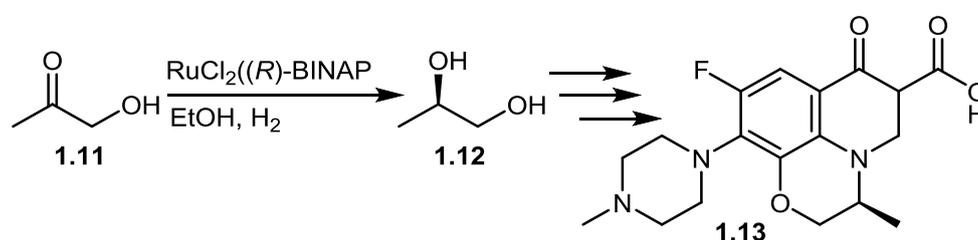


Figure 1.3: Structure of (*R*)-BINAP

Complexes formed from the BINAP ligand and transition metals such as ruthenium have been shown to hydrogenate a number of olefins, which can then be used in total synthesis or the synthesis of pharmaceuticals e.g. α -tocopherol, morphine, naproxen.^{8,9,10}

The ruthenium (II) / BINAP complexes can also be used to catalyse the reduction of a variety of ketones with good enantioselectivity.^{8, 9,10} These also have commercial applications in the pharmaceutical industry. It is required that there be some other donor atom 2 to 3 bonds away from the ketone moiety in the molecule to give the selectivity (such as an oxygen atom). The donor atom is required as this can chelate with the metal centre and creates a preferential face of the transition state for the carbonyl group to be reduced.

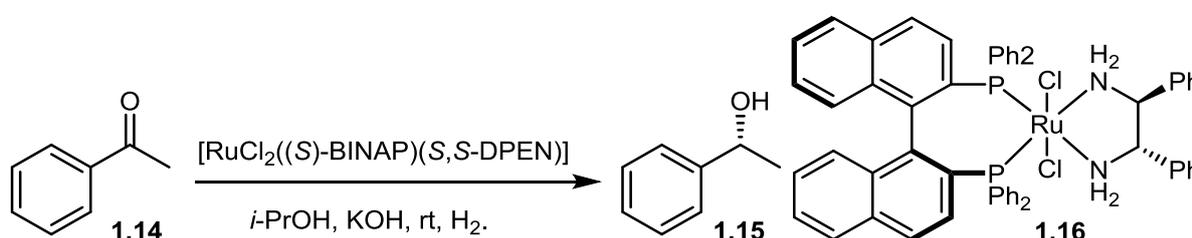


Scheme 1.2: The role of hydrogenation in the total synthesis of Levofloxacin¹⁰

The example given is the hydrogenation of hydroxypropanone to give enantioenriched *R*-propanediol, used in the industrial production of an anti-bacterial drug, *S*-levofloxacin, illustrated in Scheme 1.2.¹⁰

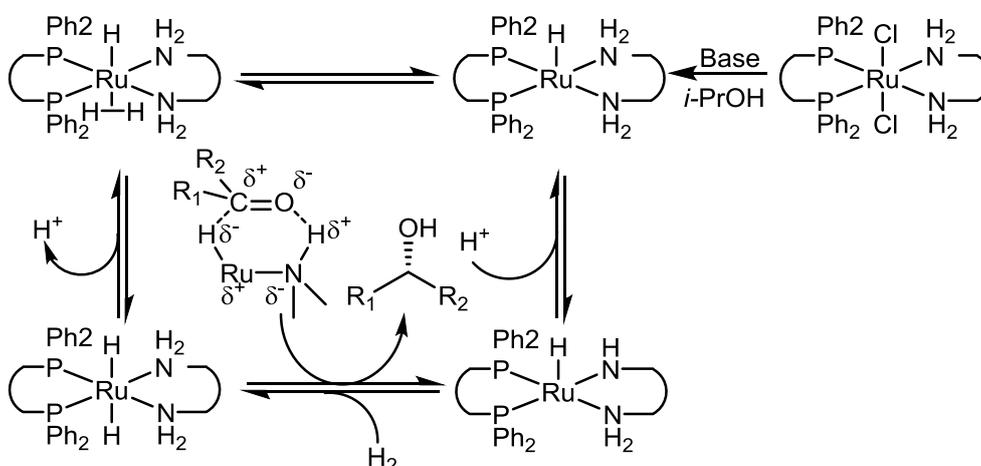
The limitation of this catalyst is that the substrate scope is not very wide. A donor atom is required within the molecule at certain positions relative to the ketone, so many potentially interesting substrates that lack a donor moiety are not hydrogenated selectively with this catalyst.

Noyori and co-workers were able to extend the reaction to unfunctionalised ketones, using a new ruthenium-BINAP complex which contained an additional diamine ligand.¹⁰



Scheme 1.3: Hydrogenation of acetophenone using $[RuCl_2((S)\text{-BINAP})(S,S\text{-DPEN})]$ ¹⁰

The addition of a diamine ligand to the complex increased the substrate scope of the reaction, to many other molecules without donor atoms, as illustrated in the case of acetophenone (scheme 1.3). The mechanism proposed is a bifunctional process where one of the hydrogen molecules comes from a ruthenium hydride and the other from one of the amines on the diamine ligand, as shown in Scheme 1.4.^{10, 44}



Scheme 1.4: Mechanism of the Noyori catalyst^{10,11}

There are a many reactions now in the literature that have built on the theme of this complex. By experimenting with the ligand backbone, enantiomeric excesses of >90% with large turnover frequencies can be achieved with these types of catalysts. Most aryl-alkyl ketones can be hydrogenated with relatively small amount of optimisation and the method is now used widely in academia and industry. However, there are still whole classes of unsaturated compounds that cannot effectively be hydrogenated.

1.3 Asymmetric Hydrogenation of Challenging Ketones

The class of catalysts with the general structure $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ has been shown to be extremely reactive and selective in the hydrogenation of ketones. Examples of catalysts include $[\text{RuCl}_2((S)\text{-Xyl-BINAP})((S)\text{-DAIPEN})]$ or $[\text{RuCl}_2((S)\text{-BINAP})((S,S)\text{-DPEN})]$ (shown in Figure 1.4), although these catalysts show superb results for a large range of ketones, there are a number of ketone substrates that show low reactivity, selectivity or both.¹²

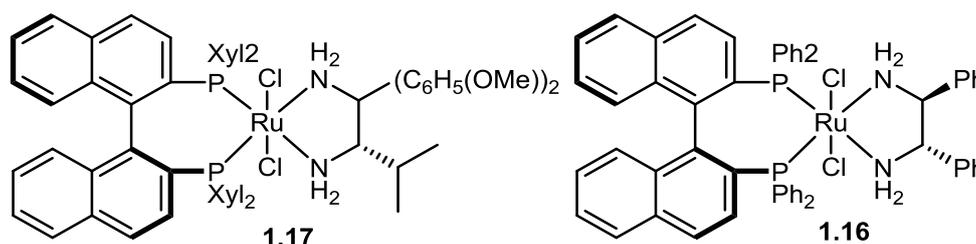


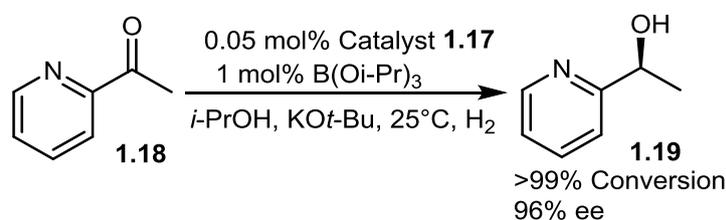
Figure 1.4: $[\text{RuCl}_2((S)\text{-Xyl-BINAP})((S)\text{-DAIPEN})]$ and $[\text{RuCl}_2((S)\text{-BINAP})((S,S)\text{-DPEN})]$ complexes¹²

Types of challenging ketones are included below in a summary of the literature, and include heteroaromatic ketones, ketones with large substituents (or “bulky” ketone), aryl-aryl ketones, and alkyl-alkyl ketones. These ketones are of interest as the secondary alcohol products could be used to create a large number of possible fine chemicals or pharmaceuticals.

1.3.1 Heteroaromatic Ketones

Ketones with substituents containing heteroatoms prove difficult for conventional ketone hydrogenation catalysts. This is presumed to be because the heteroatoms can act as a ligand or a hydrogen bond acceptor, and deactivate the active catalytic species. Recent research has

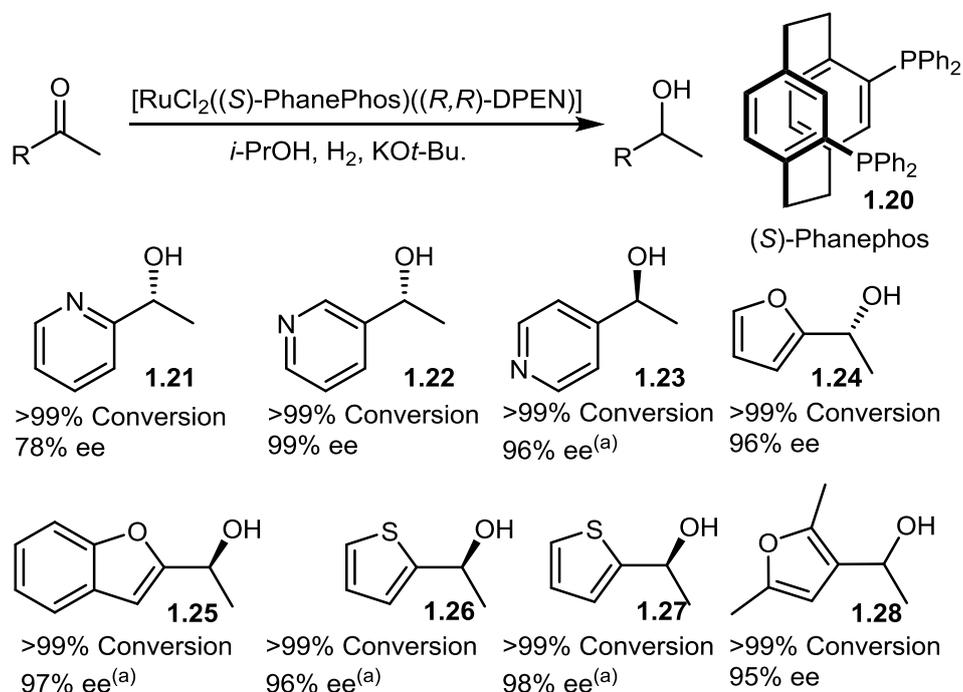
shown certain catalysts or additives can be used for the hydrogenation of heteroaromatic ketones. Work by Noyori and co-workers has shown that the addition of 1 mol% of a borate ($\text{B}(\text{O}i\text{-Pr})_3$) greatly improves the reactivity of the 2-pyridyl substrate and other problematic heteroaromatic substrates, shown in Scheme 1.5.¹²



Scheme 1.5: Hydrogenation of 2-actyl pyridine¹³

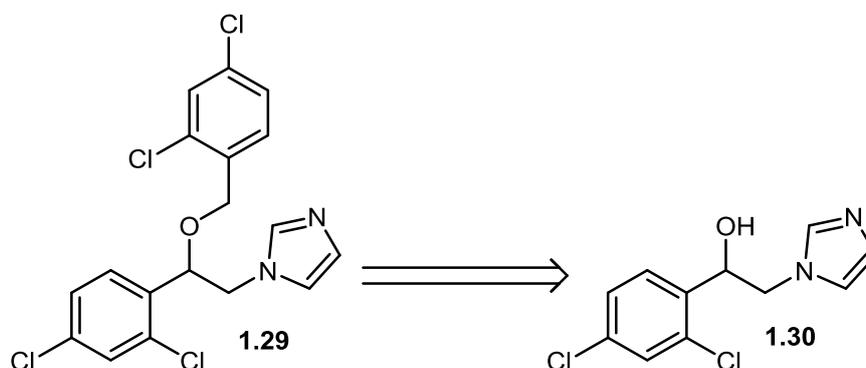
The addition of the borate provides an efficient reaction with quantitative conversion in as little as 3 hours, and with significantly improved selectivity when compared with other catalysts, (such as the PhanePhos catalyst, shown below in Scheme 1.6).

Researchers at Chirotech have shown the use of $[\text{RuCl}_2(\text{PhanePhos})(\text{DPEN})]$ catalytic system is able to hydrogenate a range of acetophenone analogues containing heteroatoms without additives, shown in Scheme 1.6.¹⁴



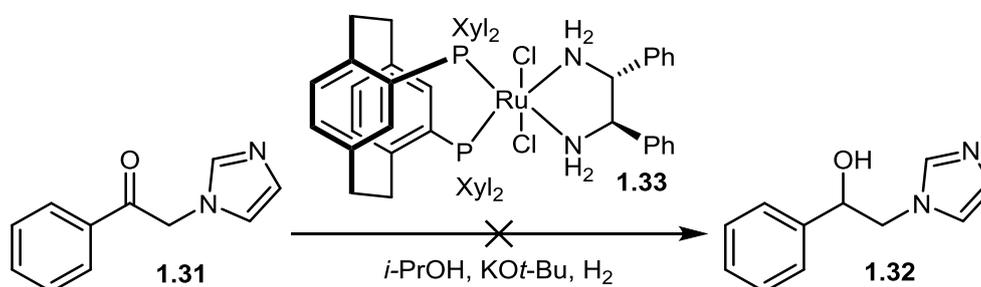
Scheme 1.6: Hydrogenation of heteroaromatic acetophenone analogues (^(a) $[\text{RuCl}_2((\text{R})\text{-PhanePhos})(\text{S,S})\text{-DPEN}]$ used instead).¹⁴

Lennon and Ramsden investigated the hydrogenation of ketones bearing an imidazole substituent; the authors chose the substrate as it was a potential precursor for an antifungal agent, miconazole.¹⁵ Illustrated below in Scheme 1.7



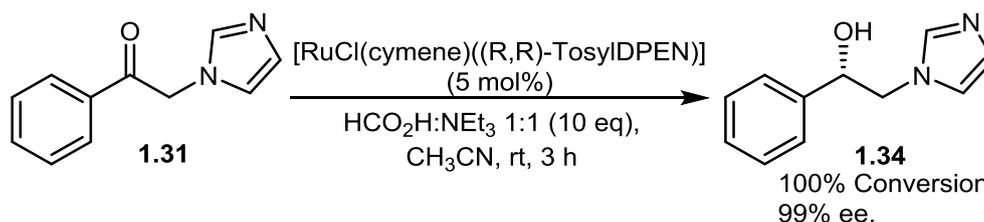
Scheme 1.7: Retrosynthesis of Miconazole¹⁵

Investigations into the hydrogenation of the imidazole substrate showed no reactivity with the $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ type complex, as shown in scheme 1.8.



Scheme 1.8: Unsuccessful hydrogenation of a ketone with an imidazole substituent¹⁵

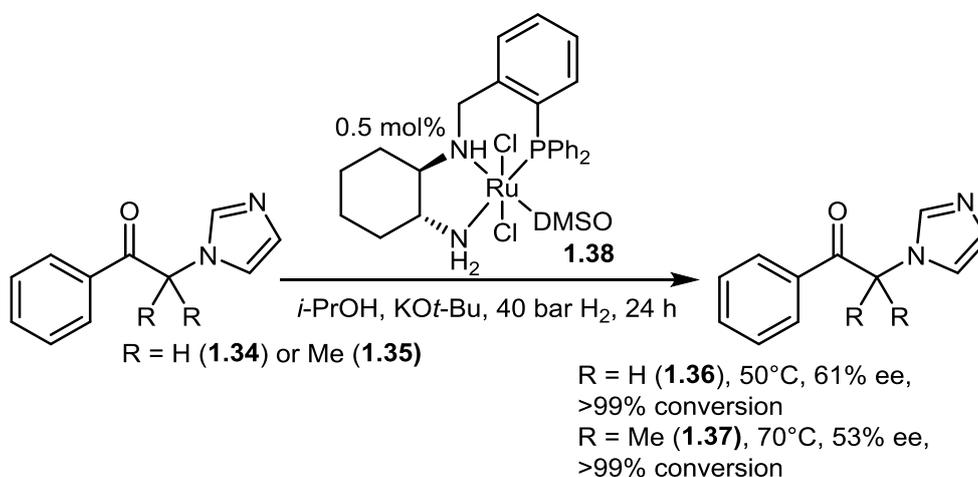
No product was observed in the reaction, even after addition of triisopropyl borate. Further investigation by the researchers showed that the product can be formed from the reaction if the transfer hydrogenation catalyst $[\text{RuCl}(\text{cymene})((R,R)\text{-DPEN})]$ was used instead, with high selectivity achieved, shown below in Scheme 1.9.



Scheme 1.9: Transfer hydrogenation of an acetophenone derivative with an imidazole substituent¹⁵

The downside for the use of a transfer hydrogenation catalyst in this case is the high catalyst loading required to observe the product in good yield.

Clarke and co-workers demonstrated the use of the $[RuCl_2(PNN)(DMSO)]$ class of catalysts in the hydrogenation of the imidazole substrate, with high conversion to product and moderate selectivity.¹⁶ Even the geminal dimethyl analogue (**1.37**) could be hydrogenated with excellent conversion and moderate selectivity, as shown in Scheme 1.10.



Scheme 1.10: Hydrogenation of ketones with an imidazole substituent using a $[RuCl_2(PNN)(DMSO)]$ complex¹⁶

The authors have also demonstrated the compatibility of other compounds containing hetero atoms with the $[RuCl_2(PNN)(DMSO)]$ type catalyst, with the successful hydrogenation of a range of substrates, shown in Figure 1.5.

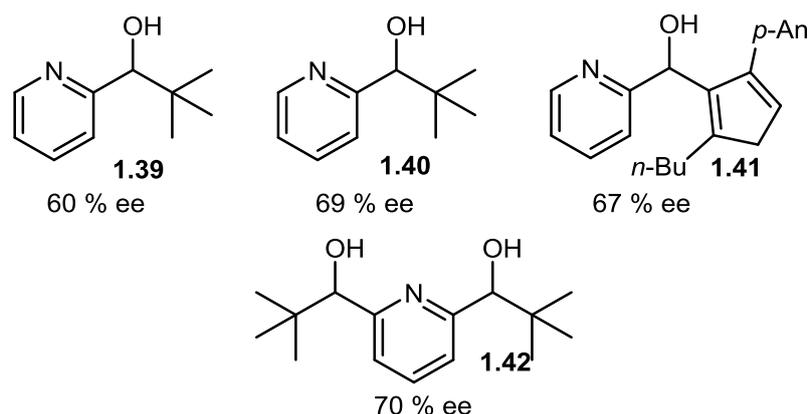
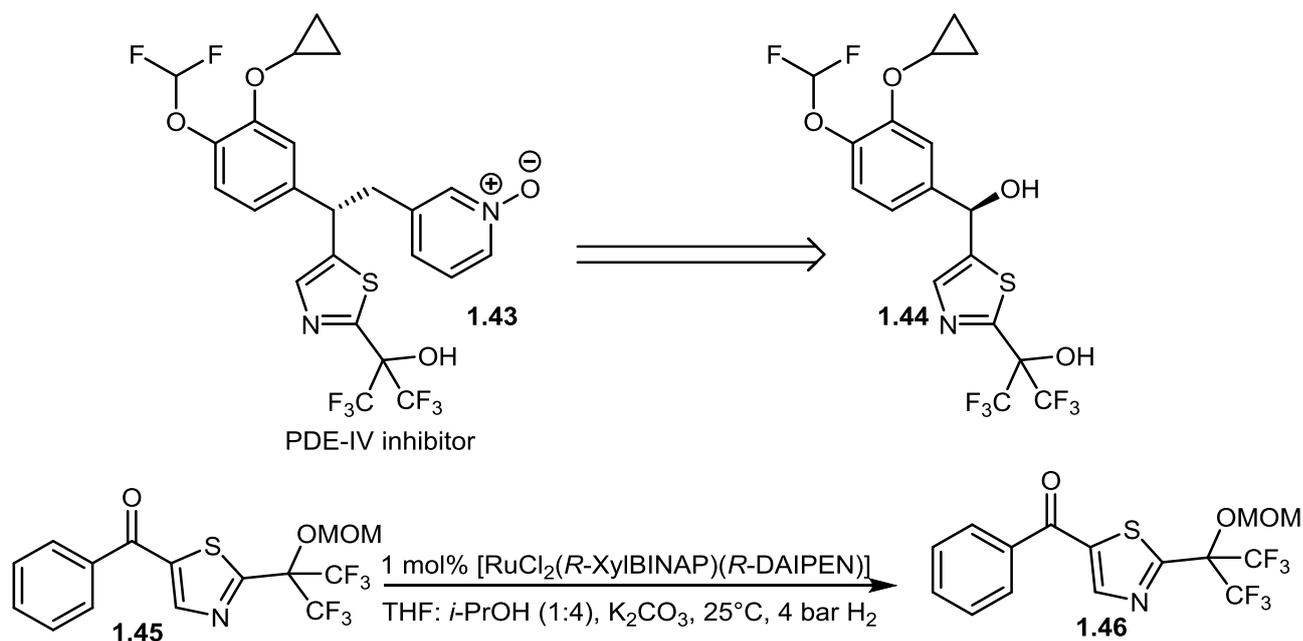


Figure 1.5: Hydrogenation of heterocyclic ketones using a $[\text{RuCl}_2(\text{PNN})(\text{DMSO})]^{16}$

Researchers at Merck¹⁷ have demonstrated the successful hydrogenation of aryl–aryl ketones (shown in scheme 1.11), where one of the substituents is a 5 membered heterocycle. The research was initiated in the attempt to synthesis a potential PDE-IV inhibitor, that have uses in the treatment of asthma, depression, Alzheimer’s, Parkinson’s and a number of other diseases.



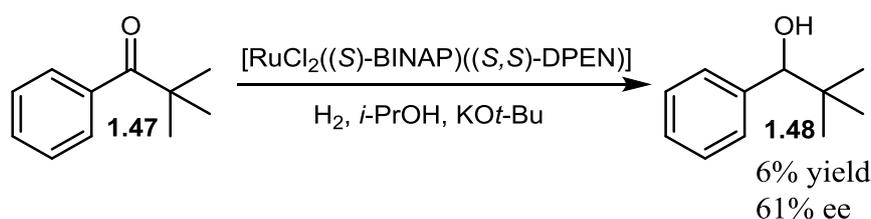
Scheme 1.11: Hydrogenation of a heterocyclic ketone in the total synthesis of a PDE-IV inhibitor¹⁷

The researchers showed that alcohol intermediates in the synthesis of the PDE-IV inhibitor could be synthesised by the hydrogenation of ketone precursors. A range of other aryl–aryl ketones were also described with good enantioselectivity achieved.

1.3.2 Bulky Ketones

Ketones with large substituents are generally difficult to hydrogenate with conventional catalysts. The large steric bulk of substrates such as isobutyrophenone or 2,2 dimethylpropiophenone, presumably disrupt or prevent the formation of the substrate-catalyst transition state, therefore slowing down the reaction.

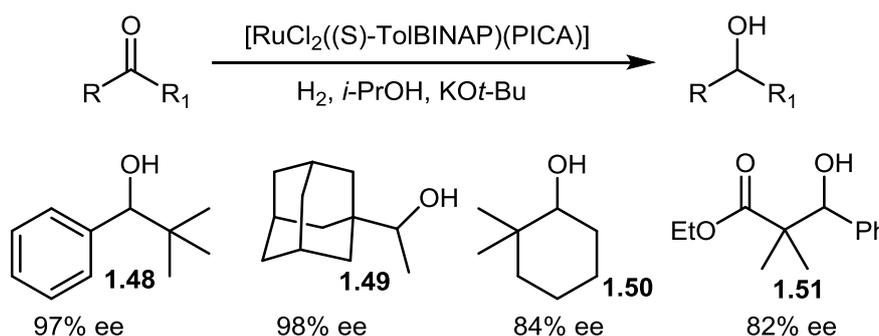
An example of which is shown in scheme 1.12, where $[\text{RuCl}_2(\text{BINAP})(\text{DPEN})]$ catalyst is used in the attempted hydrogenation of 2,2 dimethylpropiophenone.¹²



Scheme 1.12: Hydrogenation of 2,2 dimethylpropiophenone¹²

The reaction only results in a 6% yield and 61% enantiomer excess, and other catalysts such as $[\text{RuCl}_2(\text{ToIbINAP})(\text{DAIPEN})]$ or $[\text{RuCl}_2(\text{XylBINAP})(\text{DAIPEN})]$ proved inactive. This supports the hypothesis that the large substituents disrupt the catalytic cycle as the simplest/less sterically hindered catalyst was marginally active.

In 2004 Noyori reported an improved catalytic system, utilising the achiral unsymmetrical NN ligand, picolyamine (PICA).¹⁸ Shown below in Scheme 1.13.



Scheme 1.13: Hydrogenation of a range of bulky ketones¹⁸

With this new catalyst, a range of bulky ketones could be hydrogenated with high selectivity and yields.

The $[\text{RuCl}_2(\text{PNN})(\text{DMSO})]$ type of catalyst, which has been developed by Clarke and co-workers, has also been shown to be active and selective in the hydrogenation of large bulky

ketones. In the case of 2,2 dimethylpropiophenone, the $[\text{RuCl}_2(\text{PNN})(\text{DMSO})]$ catalyst can hydrogenate the substrate in high yield and good selectivity, either with the use of a pressure hydrogenation or transfer hydrogenation. Representative examples are shown in Figure 1.6.^{16,19}

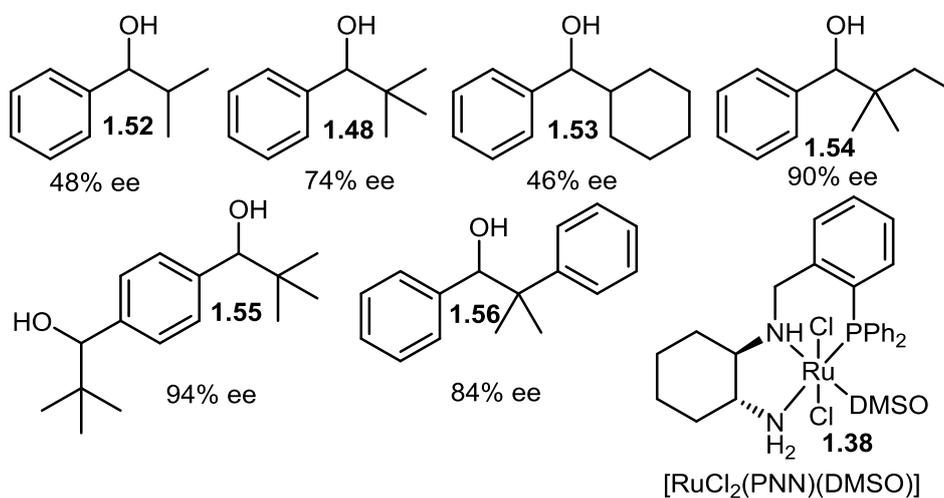
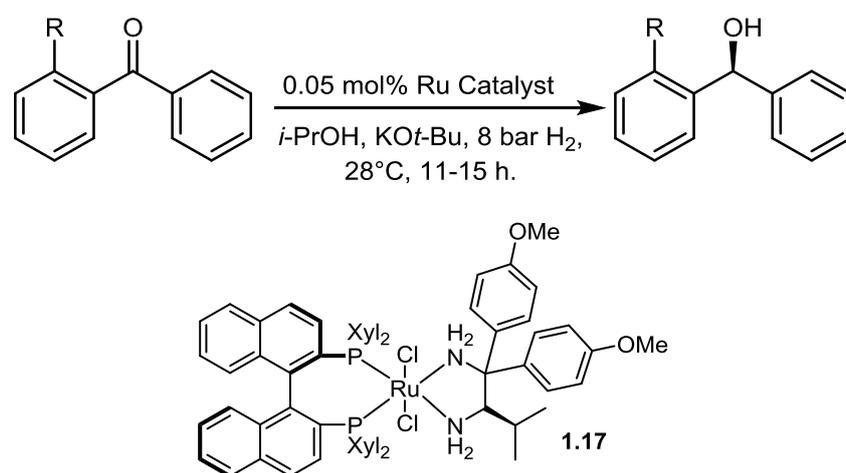


Figure 1.6: Hydrogenation of a range of bulky ketones using a $\text{RuCl}_2(\text{PNN})(\text{DMSO})$ catalyst^{16,19} Conditions: 0.5 mol% catalyst, 1 mol% $\text{KO}t\text{-Bu}$, 50°C , 50 bar H_2 , *i*-PrOH.

Extremely short reaction times can be achieved when the transfer hydrogenation is carried out with microwave heating. As little as 20 minutes was required for high conversions to be achieved for the hydrogenation of 2,2 dimethylpropiophenone when using the microwave technology, with very similar selectivity achieved. The short time scale of the reaction makes for a very convenient process, and the expected drop in selectivity is not observed if the optimal temperature is used, in this case 90°C .

1.3.3. Aryl-Aryl Ketones

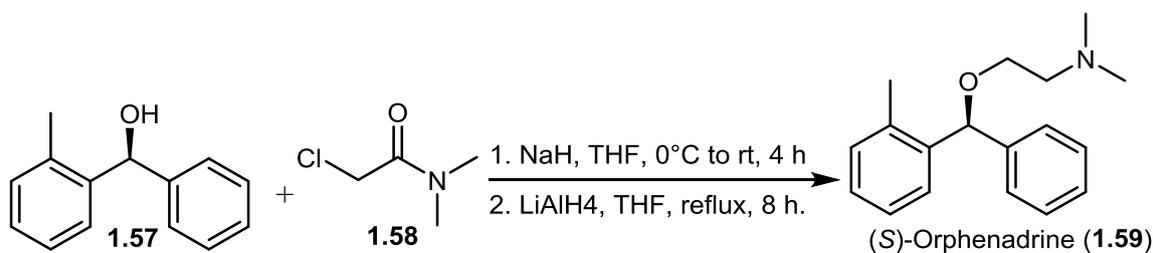
Initial attempts to hydrogenate aryl-aryl ketones have had mixed results. Success can be achieved with substrates containing *ortho* substituents, that can be hydrogenated in high enantioselectivity using [RuCl₂(diphosphine)(diamine)] catalysts. This was demonstrated by Noyori and co-workers as shown below in Table 1.1.²⁰



Entry	R	Conversion (%)	ee (%)
1	Me	99	93 (<i>S</i>)
2	MeO	100	99 (<i>S</i>)
3	F	99	97 (<i>S</i>)
4	Cl	99	97 (<i>S</i>)
5	Br	99	96 (<i>S</i>)

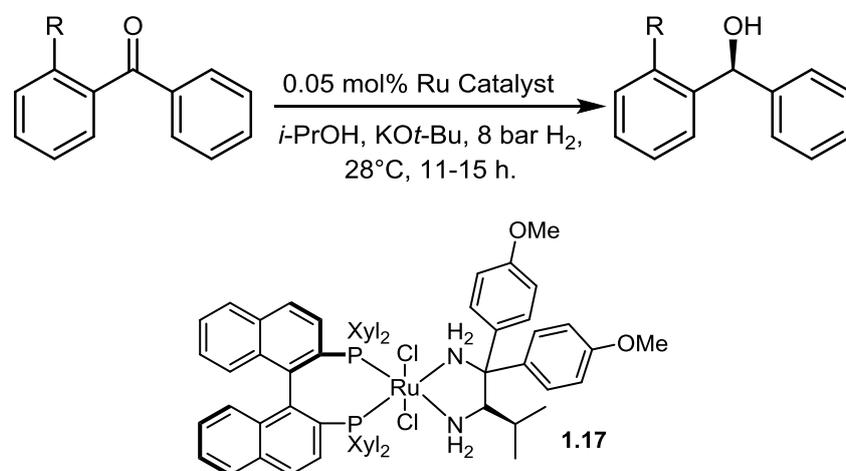
Table 1.1: Hydrogenation of aryl-aryl ketones²⁰

High yields and conversions could be achieved with the range of *ortho* substituted substrates tested. The authors demonstrated that product of the *o*-methyl substrate (entry 1) can be easily converted into orphenadrine by a literature procedure, illustrated in scheme 1.14.²¹ Orphenadrine is a known antihistaminic or anticholinergic compound.



Scheme 1.14: The synthesis of (*S*)-orphenadrine from a chiral secondary alcohol.²¹

Unfortunately when Noyori and co-workers attempted the hydrogenation of *meta* and *para* substituted substrates the selectivity of the reaction dropped dramatically, and only moderate enantioselectivity observed (8-47% ee), shown in Table 1.2.



Entry	R	Conversion (%)	Ee (%)
1	<i>m</i> -Me	98	33 (-)
2	<i>p</i> -Me	98	8 (<i>R</i>)
3	<i>p</i> -MeO	95	35 (<i>R</i>)
4	<i>p</i> -Cl	97	9 (<i>S</i>)
5	<i>p</i> -CF ₃	99	47 (<i>S</i>)

Table 1.2: Hydrogenation of *para* substituted aryl-aryl ketones²¹

Comparison of the *para* substituents (entry 2, 3, 4, and 5, Table 1.2) shows that for enantioselectivity is influenced by electronic factors (see entry 3 and 5, Table 1.2), which differs from the *ortho* substrates where steric effects are the contributing factor to selectivity.

The requirement for an *ortho* substituted ketone is further exemplified with the hydrogenation of pyridinyl aryl methanones, highlighted in Figure 7.²²

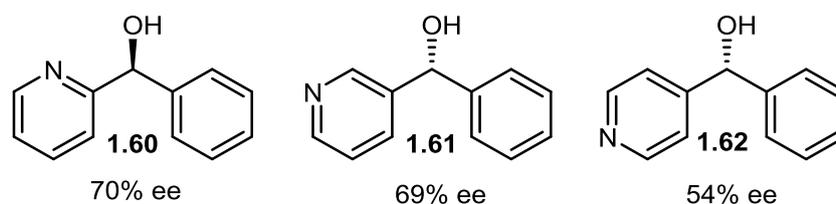


Figure 7: Pyridinyl aryl methanones made using 0.1% [RuCl₂(*R*-BINAP)(*R*-DAIPEN)], *i*-PrOH, KOH, 30°C and 20 bar H₂.²²

There is a remarkable difference between the catalyst selectivity of the 2-pyridyl methanone and the 3 and 4-pyridyl substrates. A similar enantiomeric excess is observed between the 2 and 3-pyridyl substrates, though the opposite enantiomers are produced. The authors speculate that this could be due to a stabilisation of an intermediate caused by favourable hydrogen bonding interactions. The substrate and the hydrogen atom of the amine of the catalyst can form a stable hydrogen bonded intermediate, leading to the formation of the opposite enantiomer. The hydrogenation of the 4-pyridyl substrate leads to a lower enantioselectivity.

1.3.4. Alkyl-Alkyl Ketones

Examples of aryl-alkyl ketones are prevalent in the literature, with a wide range of catalysts investigated. Conversely only a few examples of alkyl-alkyl ketones have been described in the literature, mainly these consist of substrates containing one large bulky group, allowing stereo recognition. Examples of which are shown below in Scheme 1.7, which were reduced using $[\text{RuCl}_2((S)\text{-BINAP})(\alpha\text{-picolylamine})]$.^{16, 23}

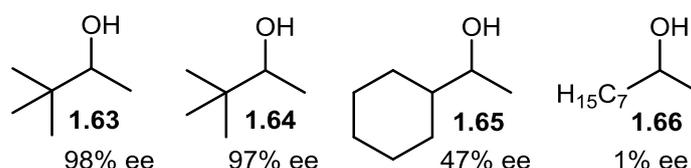
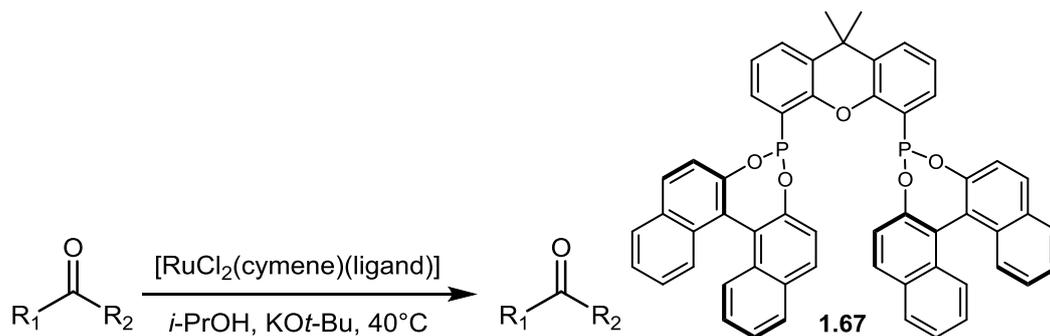


Figure 1.7: Hydrogenation of alkyl-alkyl ketones using $[\text{RuCl}_2((S)\text{-BINAP})(\text{diamine})]$ catalysts.^{16,23}

Specific substrates have been described in the literature. Selectivity problems occur when the substituent is less bulky or when both substituents are of similar steric bulk, for example the cyclohexyl substrate shown above in Scheme 1.7. An example of a transfer hydrogenation catalytic system has been described in which a range of alkyl-alkyl ketones have been hydrogenated with high selectivity, shown below in Table 1.3.²⁴



Entry	R ₁	R ₂	Conversion (% (hrs))	ee (%)
1	Cyclohexyl	Me	97 (22)	99
2	<i>i</i> -Pr	Me	99 (22)	99
3	<i>n</i> -hexyl	Me	96 (16)	90
4	(CH ₃) ₂ CHCH ₂	Me	83 (40)	79
5	BenzylCH ₂	Me	97 (26)	76
6	<i>n</i> -Pr	Me	96 (26)	82

Table 1.3: Transfer hydrogenation of alkyl-alkyl ketone²⁴

The transfer hydrogenation catalyst can achieve alkyl-alkyl alcohol products in high conversion and with high selectivity. Branched ketones give higher selectivity (compare entry 2 and 6, or 1 and 3, Table 1.3), which is to be expected as the branched compounds will have higher steric bulk, therefore stereodiscrimination is easier. Unfortunately high catalyst loadings (0.5 mol% Ru precursor, 1.25 mol% ligand), and long reaction times (1-2 days) are required.

A more elaborate water soluble rhodium “surfactant” transfer hydrogenation catalyst has been described in the literature. The researchers modified TsDPEN and created a surfactant analogue shown below in Scheme 1.8.²⁵

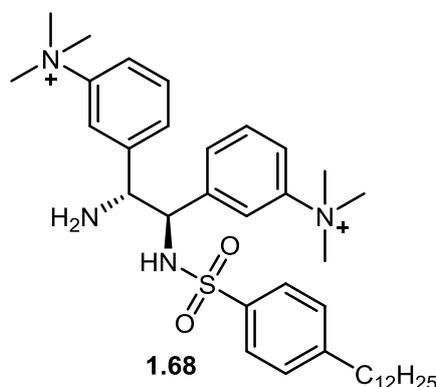


Figure 1.8: Surfactant modified Ts-DPEN²⁵

The modified DPEN ligand when used in combination with $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$ forms an active water soluble transfer hydrogenation catalyst that can reduce large range of alkyl-alkyl ketones in high conversion and selectivity.

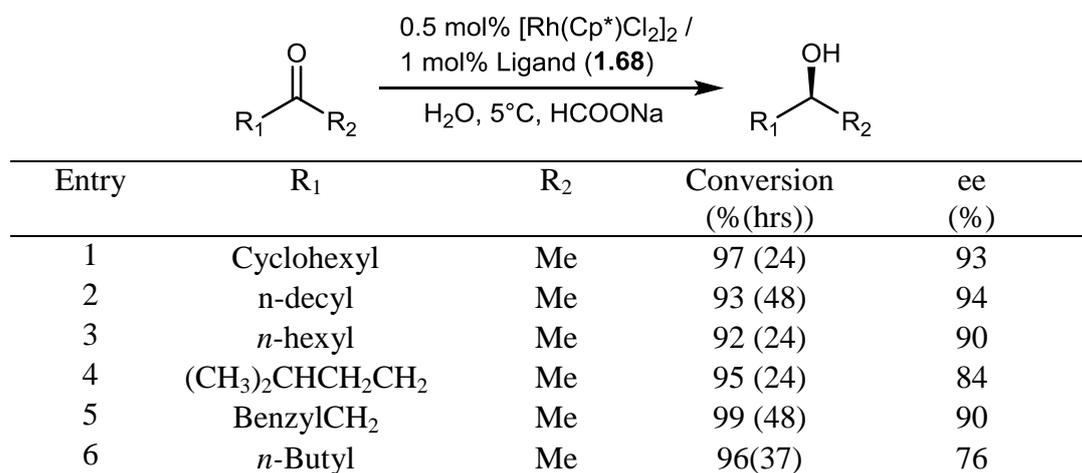


Table 1.4: Hydrogenation of alkyl-alkyl ketones²⁵

The authors propose that the selectivity is due to the formation of metallomicelles. The micelles provide an environment which allows favourable hydrophobic interactions between the large alkyl chains of both the substrate and the ligand, allowing for high enantiomeric excess to be achieved. The proposed mechanism is supported by the fact that longer chain alkyl ketones show higher selectivity when compared with shorter chain ketones (compare entry 6 and 2).

The hydrogenation of acetophenone is also described with high selectivity (96% ee), but the opposite enantiomer (*R*) is formed when compared with the alkyl substrates (*S*). This is proposed to be due to the fact that the selectivity is due to CH- π interactions, instead of the hydrophobic interactions of the alkyl substrates.

The use of low temperatures, long reactions times and high catalysts loadings are again limiting factors for the reaction (1 mol% ligand, 0.5 mol% Rh precursor, 5°C and 24-72 hours).

The papers presented here, show there is potential for the hydrogenation of alkyl-alkyl ketones, particularly the transfer hydrogenation examples. Despite these developments, there is still major room from for improvement, and the area requires more in depth research.

1.3.4. Imine Hydrogenation

Alkenes and ketones make up a significant part of the literature on catalytic hydrogenation, but other unsaturated functionalities can be hydrogenated. For example the hydrogenation of the C=N functionality is a promising way to produce new chiral building blocks, but unfortunately the problem is not as simple. When contrasted with the hydrogenation of olefins and ketones, which have a large amount of literature precedent showing good activity and selectivity, this is not the case with imine hydrogenation. None the less a number of good catalysts have been reported in recent times.

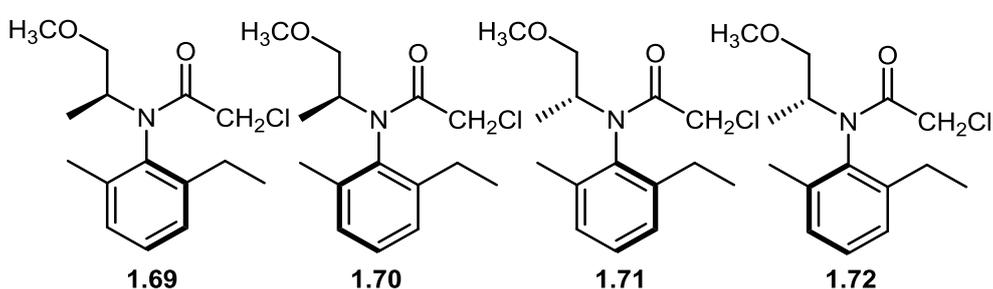
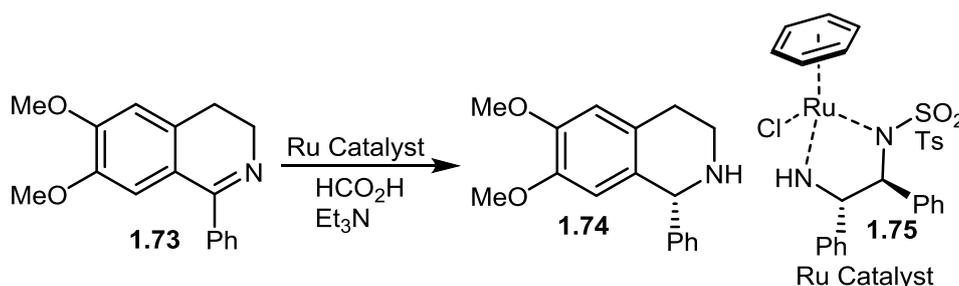


Figure 1.9: Isomers of Metolachlor^{26,27}

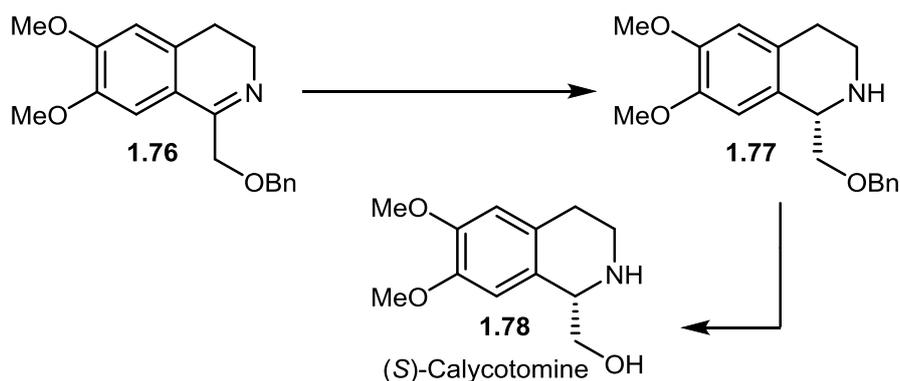
By far the best example is the hydrogenation of imines which was used in the synthesis of Metolachlor.^{26,27} Metolachlor is the active ingredient in the herbicide Dual made by Syngenta since the 1970's. The product was initially marketed as a mixture of 4 stereoisomers shown in figure 1.9, but it was found the activity only came from one diastereoisomer. Therefore it was considered advantageous to investigate a method for producing an enantioenriched product. This process is used on 10000 ton scale per year. Syngenta developed an iridium catalyst which is amazingly active with a huge TOF of $>400000 \text{ h}^{-1}$ and TON of 2000000.^{26,27,28} The e.e of 80% obtained in the reaction is sufficient for direct use as agrochemicals. This level of selectivity would not be directly acceptable for use in the synthesis of pharmaceuticals, and would require a separate purification procedure.

A variety of imines have been shown to be hydrogenated in the literature. It is also possible to hydrogenate cyclic imines as shown below in Scheme 1.15.



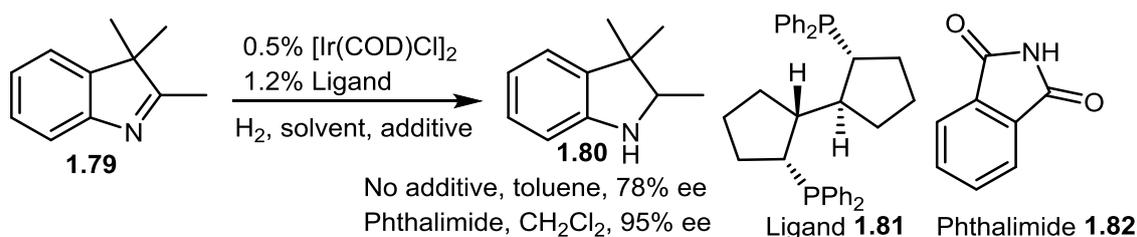
Scheme 1.15: Transfer hydrogenation of a cyclic imine²⁹

This is a successful example of an asymmetric transfer hydrogenation of a cyclic imine by Noyori and co-workers²⁹. The use of the azeotropic mixture of formic acid and triethylamine is used as a hydrogen source with conversions of over 99% and an ee of 95% in 3hrs. The reaction requires the use of a high catalyst to substrate ratio and long reaction times. It reaction has been shown that the reaction can be used in the total synthesis calycotomine. Illustrated below in Scheme 1.16.³⁰



Scheme 1.16: The use of ketone hydrogenation in the synthesis of calycotomine³⁰

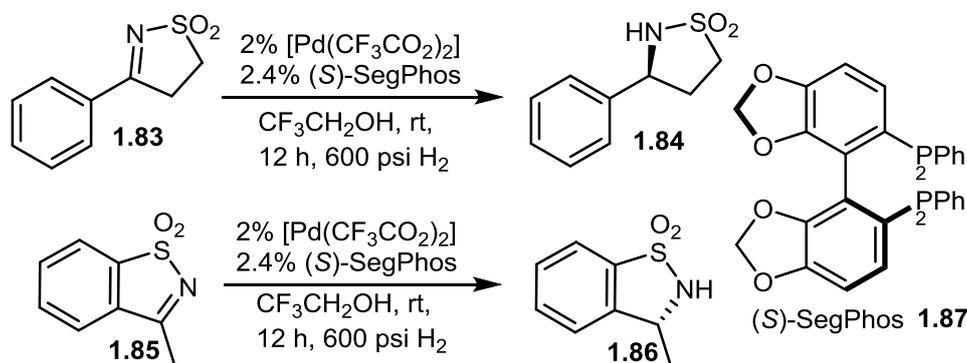
In the example shown in Scheme 1.17, the researchers³¹ attempted to experiment with the addition of additives and changes of solvent in the above reaction to see what improvement could be made.



Scheme 1.17: The use of an additive in the hydrogenation of a cyclic imine³¹

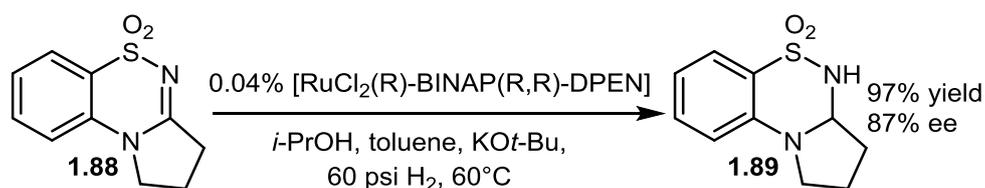
Without an additive the reaction went to complete conversion in 96 hrs, with an ee of 78%. The result could be improved with the addition of phthalimide in dichloromethane, giving an ee of 95%, albeit after a reaction time of 100 hrs.

Due to the difficulty of reducing imines, research has been conducted into the hydrogenation of activated imines. Such as this example in Scheme 1.18³² of the reduction of sulfonyl imines, this uses a palladium catalyst and gives a moderate ee and high reactivity. However, this needs a high catalyst loading (2 mol %) and long reaction time (12hrs).



Scheme 1.18: Hydrogenation of cyclic sulfonyl imines.³²

Scheme 1.19 demonstrates another example of sulfonyl imine³³ that has been hydrogenated. This produces a product with a considerable better ee, and can be achieved with relatively low catalyst loading.



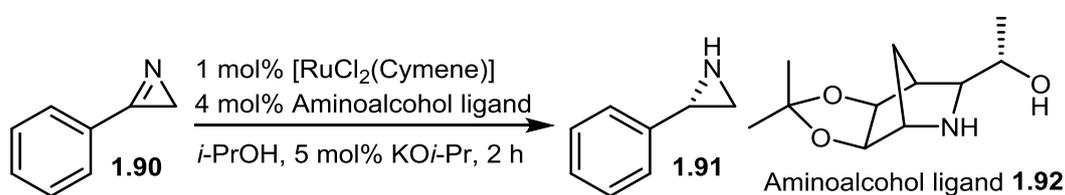
Scheme 1.19: Hydrogenation of a cyclic sulfonyl imine³³

The racemic product of the above hydrogenation is a potential drug candidate for the treatment of certain neurological disorders³³. Therefore it was deemed important to synthesise enantiomerically enriched product for further investigation. It was demonstrated that the compound could be produced in good yield and selectivity using the $[\text{RuCl}_2((R)\text{-BINAP})((R,R)\text{-DPEN})]$.

At the beginning of this research project, the area of imine hydrogenation was relatively underdeveloped, with most literature examples of catalysts having poor substrate scope and required the use of large catalyst loadings and forcing conditions. However a number of good imine hydrogenation catalysts have appeared in the last 5 years that have attempted to overcome these problems.³⁴⁻⁴⁰

1.3.5 Azirines

Aziridines are good building blocks for organic synthesis as they can be ring opened stereoselectively and regioselectively to potential produce chiral amines. A potential route to produce aziridines is to reduce azirines with a chiral catalyst.

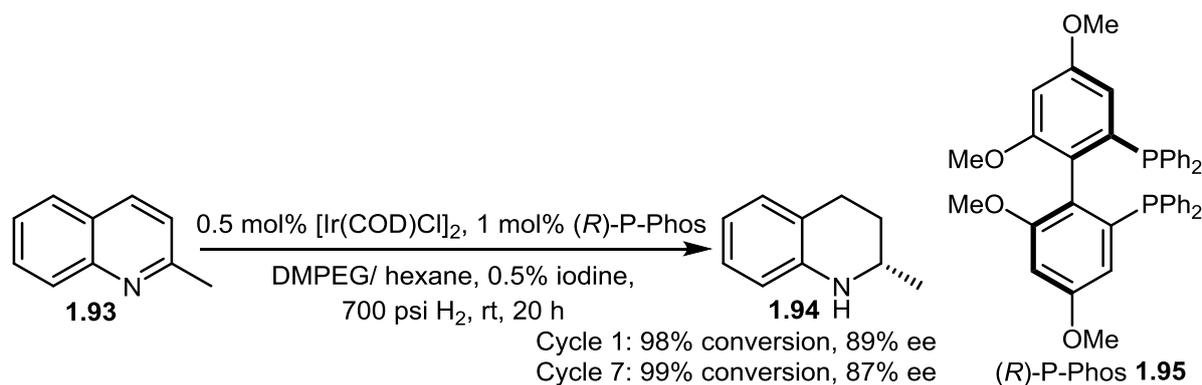


Scheme 1.20: Hydrogenation of an azirine⁴¹

In the investigation summarised in Scheme 1.20⁴¹ the researchers use an amino alcohol ligand and ruthenium catalyst to carry out the transfer hydrogenation. This catalyst is the only example that can be found in the literature of azirine hydrogenation. The authors attempted the pressure hydrogenation of this type of substrate with no success.

1.3.6. Quinolines

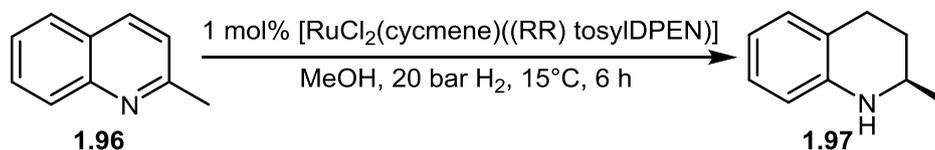
Tetrahydroquinolines are an important functional group for synthetic chemistry, as there are a number of different biologically active molecules that contain the tetrahydroquinoline moiety. In this example shown in Scheme 1.21 the catalyst is iridium based⁴² and is used to hydrogenate the quinoline. The reaction is complete after 20 hrs (97% yield) with an ee of 89%. Iodine is used as an additive to prevent catalyst deactivation.



Scheme 1.21: Hydrogenation of a quinoline using a recyclable catalyst⁴²

This reaction provides good ee's and yields with a reasonably low catalyst loading (0.5 mol%) for this type of reaction, although turnover frequency and selectivity need to be improved. What is interesting in this article is that they used a biphasic system of DMPEG and hexane. The catalyst is then immobilized on to the liquid polymer allowing the system to be used to recycle the catalyst and reproduce the result with reused catalyst, with only a slight drop in ee (87%).

Research from the same group has more recently shown the use of ruthenium catalysts that gives quantitative conversions and high selectivities, shown in Scheme 1.22.⁴³

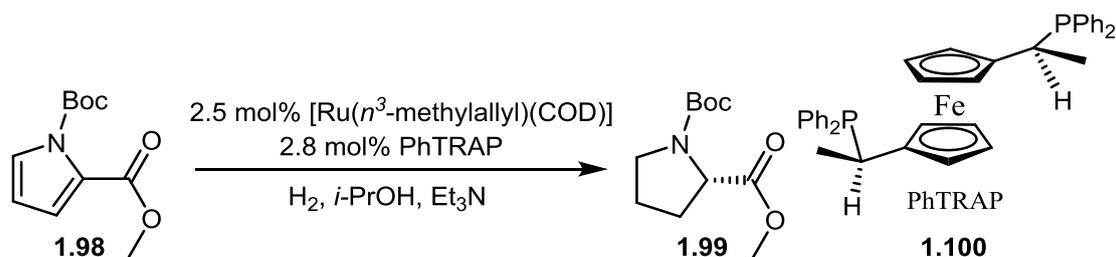


Scheme 1.22: Improved hydrogenation of a quinoline⁴³

The catalyst demonstrates a large substrate scope, including 2 substituted alkyl and aryl quinolines, even 2,3 substituted quinolines could be hydrogenated. The researchers have also shown the use of the reaction in the synthesis of natural products.

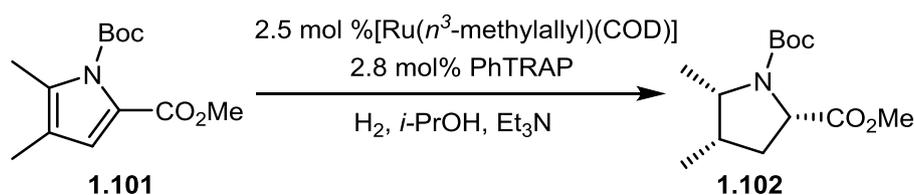
1.3.7. Pyrroles

Another useful reaction that gives products widely found in natural products is the hydrogenation of pyrroles to pyrrolidines.



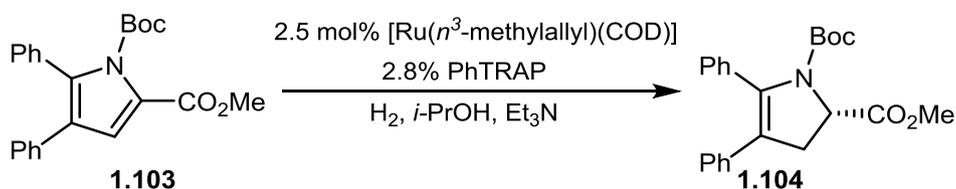
Scheme 1.23: Hydrogenation of a pyrrole⁴⁴

In this case⁴⁴ shown in Scheme 1.23, is an example of a mono substituted pyrrole that can be effectively hydrogenated, with a conversion of 92% and an ee of 79%. It can be noted that the addition of a base (triethylamine) to the reaction results in an increase in ee (without base ee = 73%). However enantioselectivity and activity need to be improved further to be useful industrially.



Scheme 1.24: Hydrogenation of a trisubstituted pyrrole⁴⁴

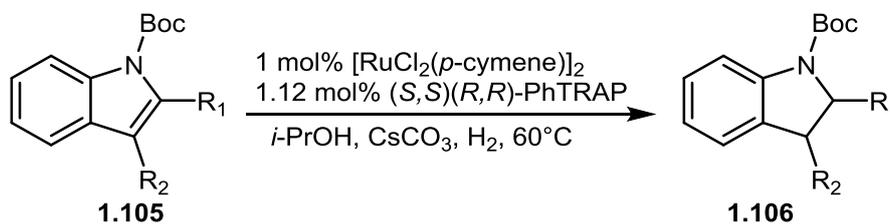
In the same paper⁴⁴ it was also shown that a tri-substituted pyrrole can also be hydrogenated, giving 3 new chiral centres in one reaction with an ee of 96%, as illustrated in Scheme 1.24. It was possible in some cases to isolate a mixture of mono- and di-hydrogenated products. If you increase the steric hindrance around the molecule as shown in Scheme 1.25, the reaction only gives the single reduced product and the other double bond is left untouched.



Scheme 1.25: Mono hydrogenation of a sterically hindered pyrrole⁴⁴

1.3.8. Indoles

Substituted indoles are a group of aromatic heterocycles that may also be hydrogenated with reasonable success⁴⁵, although once again require further studies.



Entry	R1	R2	Conversion	ee
1	Me	H	99	95
2	H	Me	87	92
3	Me	Me	59	72

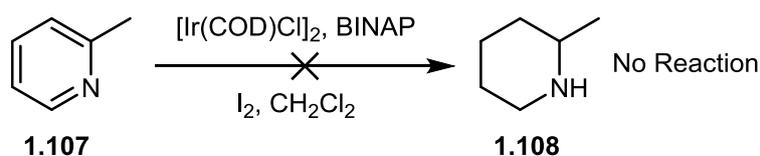
Table 1.5: Hydrogenation of substituted indoles⁴⁵

In the example shown in Table 1.5 the hydrogenation of the substrate occurs with a conversion of 99% and ee of 95% in two hours. The main down side is the catalyst loading of 1 mol %. Unfortunately this is only the case for this substrate, if other functional groups are present the ee and reactivity is decreased. Even changing the position of the methyl group from carbon-1 to carbon-2 reduces the reactivity and enantioselectivity. Interestingly the other enantiomer is formed, with the above reaction. As mentioned the ee drops to 87% and 92% conversion after 24 hours. When the disubstituted substrate is used, the conversion is 59% after 72 hrs and the ee is 72%. This shows the initial result of 95% ee has dropped dramatically when the substrate has only been made marginally more complicated.

1.3.9. Pyridines

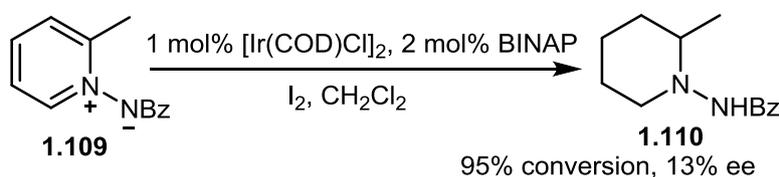
Hydrogenation of pyridines is of interest as the piperidine products are found in a number of different natural products.

Research by Legault and Charette,⁴⁶ initially attempted to hydrogenate the unmodified pyridine, using an iridium/ BINAP complex. Unfortunately it was found to be unsuccessful with no product formed.



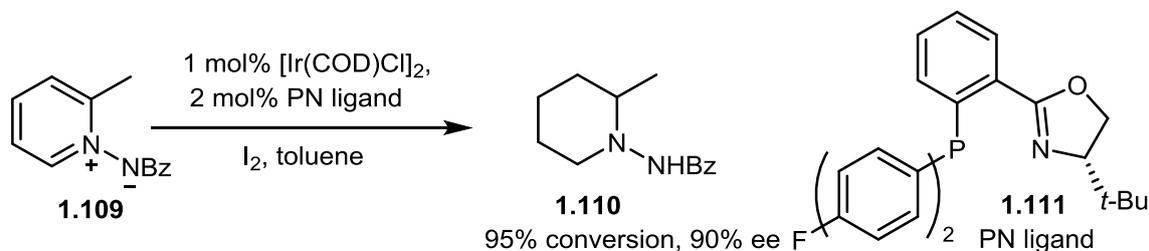
Scheme 1.26: Attempted hydrogenation of a pyridine⁴⁶

The researchers found it possible to hydrogenate pyridine derivatives. The active derivatives were the benzoyliminopyridinium ylides, and high conversions were observed when using iodine as an additive. It is thought that the iodine is required to act as an oxidising agent, converting Ir(I) species into the Ir(III) species which are known to be active as hydrogenation catalysts.



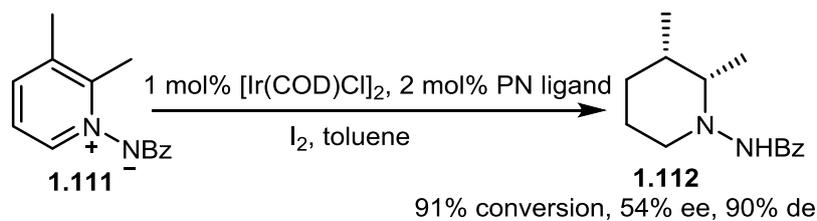
Scheme 1.27: Hydrogenation of a pyridine derivative⁴⁶

The catalyst was found to be active, but unfortunately the BINAP ligand used was not successful in inducing a high enantiomeric excess, but further study found that by changing the ligand the results could be optimised, as shown below.



Scheme 1.28: Improved hydrogenation of a pyridine derivative⁴⁶

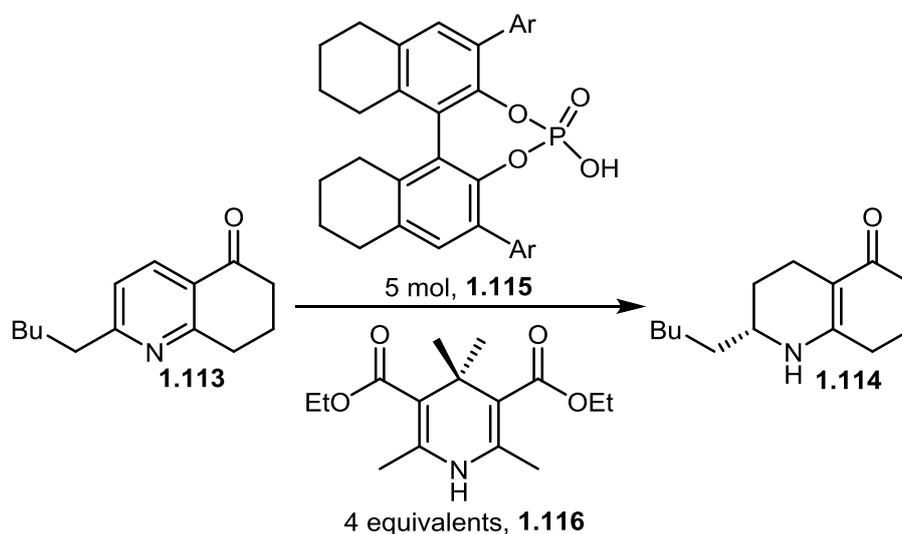
Using a chiral PN oxazoline ligand, high selectivity and conversions could be achieved. After the hydrogenation it was possible to generate the piperidine product by cleaving the N-N bond by using either lithium in NH_3 or Raney nickel to give the reduced pyridine product. Investigation into the substrate scope showed that it is also possible to reduce difunctionalised pyridines in the same manner.



Scheme 1.29: Hydrogenation of a disubstituted pyridine⁴⁶

High diastereoselectivity and conversions could be achieved in this reaction, although the enantiomeric excess was only moderate, and high catalyst loadings are required.

Work has also been demonstrated on the use of an organocatalyst for the hydrogenation of pyridines. The substrate itself (shown below) can be used to synthesise a number of biologically active molecules and a number of different alkaloids found in nature.⁴⁷

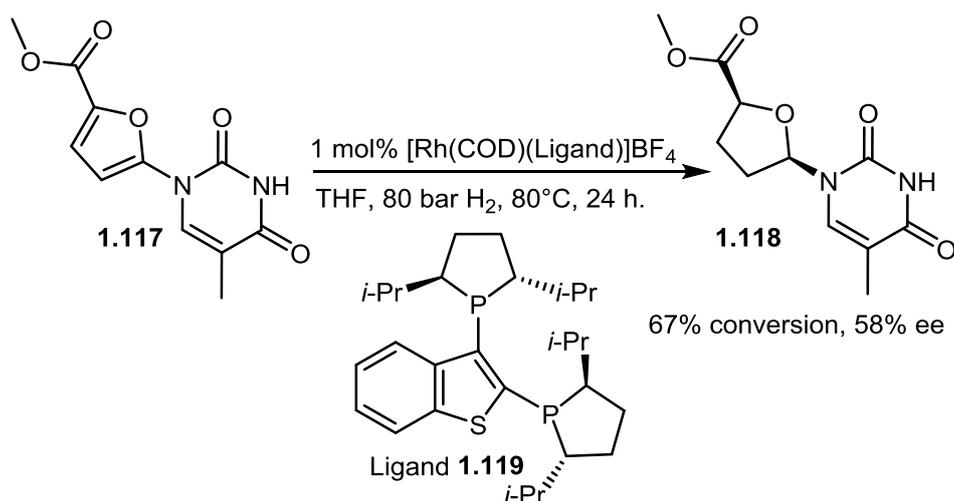


Scheme 1.30: Organocatalytic hydrogenation of a pyridine⁴⁷

The organocatalyst used was a chiral bronsted acid catalyst and a dihydropyridine hydrogen source. The reaction gives good enantiomeric excess of 91% with an acceptable yield of 81%. Unfortunately this requires a high catalyst loading of 5 mol% and the use of 4 equivalents of the dihydropyridine, which is expensive to synthesise so is unlikely to be an alternative to H₂ or simple hydrogen donors on a commercial scale. The authors described only a limited substrate scope for this reaction.

1.3.10 Furans

Attempts have been made in the literature to hydrogenate furan substrates. In this example the authors were attempting to synthesise nucleoside analogues from a substituted furan.⁴⁸



Scheme 1.31: Hydrogenation of a furan⁴⁸

The results are moderate; with 1 mol% catalyst the best ee achieved is 58%. The catalyst loading was quite high for this reaction at 1 mol% and it still required 24 hrs to get to 67% conversion, under harsh conditions. The results can be achieved if 10 mol% catalyst is used with higher conversions and selectivity observed, although this would only be a viable option for small scale reactions.

Pfaltz and co-workers developed the catalyst below⁴⁹ and have used it in the hydrogenation of alkenes. It was also possible to hydrogenate some furans and benzofurans.

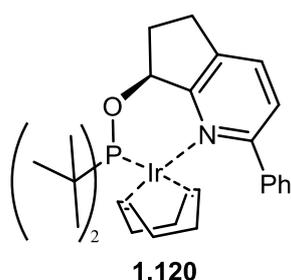
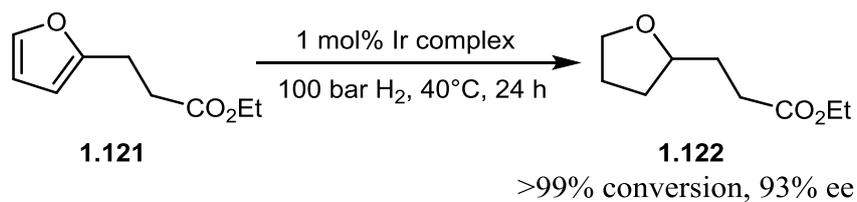


Figure 1.10: Pfaltz's iridium complex⁴⁹

The furan hydrogenation below gave a good ee and conversion. Although this is only one of two furans stated in the paper and the other example only gave 84% conversion and 78% ee. There is, therefore, a poor substrate scope for this reaction at present.



Scheme 1.32: Hydrogenation of a mono substituted benzofuran⁴⁹

1.3.11. Benzofurans

Benzofurans are another challenging heterocycle to hydrogenate and are discussed in depth at the beginning of Chapter 2. It is worthwhile addressing here, that there are only a few examples of homogeneous catalysts in the literature for the successful hydrogenation of benzofurans and further research in the area is required.^{49,50}

Aromatic heterocycles have been the focus of a number of research projects. There are examples of most aromatic heterocycles, although the requirement for substantial catalyst loadings and forcing conditions are often required for good conversions to product. Due to this there is still a need for more in depth research for these types of unsaturated substrates.

1.4. Other Unreactive Substrates

1.4.1. Esters

Esters are not a prochiral substrate, so the product of the reaction would not generate a new chiral centre within the product. Still the substrate is of interest as it can be challenging to hydrogenate. The general procedure for the hydrogenation of esters is to use excess amounts of metal hydrides. Use of homogeneous catalysts for the hydrogenation of esters is often difficult and there are few examples in the literature that do not require high temperatures and catalyst loadings.⁵¹ for a review of the area please refer to chapter 3.

1.4.2. Amides

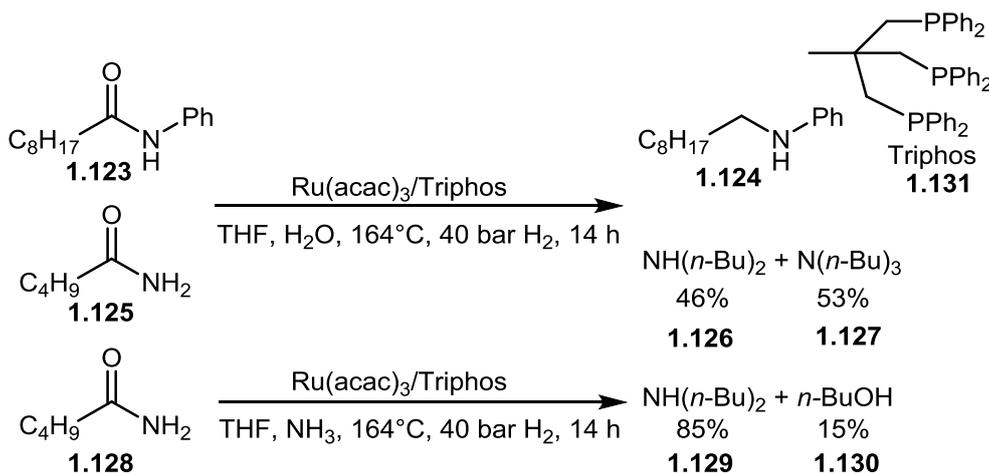
It has been considered that there is an order of reactivity of unsaturated substrates, with the following order of activity.⁵²



Amides represent the one of the most difficult class of unsaturated compounds to hydrogenate. There are two potential routes for the hydrogenation of amides. One route is to

cleave the CO carbonyl bond via an imine intermediate, resulting in a secondary amine product. The other route is to break the CN bond resulting in the production of a primary amine and alcohol products.

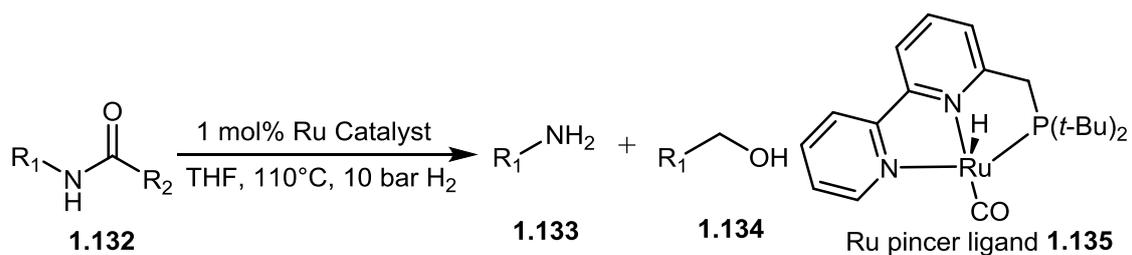
Cole-Hamilton and co workers have shown that amides can be reduced with homogeneous ruthenium catalysts using TRIPHOS as a ligand, selectively either producing the primary or secondary amine depending on the reaction conditions.⁵³



Scheme 1.33: Hydrogenation of amides with a ruthenium/triphos catalyst⁵³

The addition of aqueous ammonia to the reaction mixture can change the selectivity of the reaction from the secondary/ tertiary amine product, to the primary amine compound.

Milstein and co-workers have shown the use of ruthenium complexes of dearomatised pincer ligands in the hydrogenation of amides, to form a mixture of primary amine and alcohol. The reaction does not require any addition of additives.⁵⁴

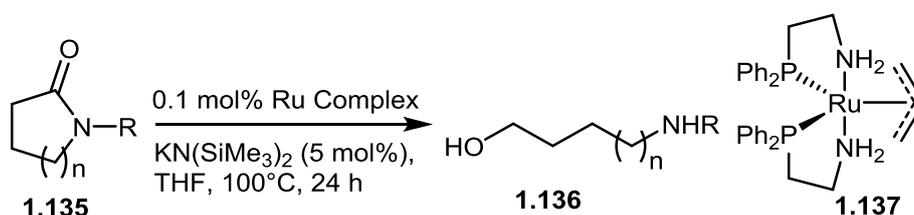


Entry	R ₁	R ₂	Yield amine (%)	Yield alcohol (%)
1	benzyl	CH ₂ OCH ₃	90	89
2	<i>n</i> -hexyl	CH ₂ OCH ₃	90	91
3	<i>n</i> -hexyl	2-(furanyl)	68	69
4	benzyl	Phenyl	57	57
5	phenyl	Phenyl	91	92
6	cyclohexyl	CH ₂ OCH ₃	87	88

Table 1.6: Reduction of a range of amides⁵⁴

A range of amides were tested, with a representative selection shown above. The pincer catalyst has been shown to hydrogenate the amides selectively towards the primary amine products, with good yields after 48 hours, with a broad substrate scope. The reaction is however, a hydrogenolysis, and a reduction, rather than a simple reduction of the carbonyl bond.

John and Burgen have shown the use of a ruthenium catalyst combined with a PN ligand, with the addition of a base additive. The researchers demonstrate the use of the catalytic system for the hydrogenation of lactams to produce products with terminal alcohol and amine functional groups.⁵⁵



Entry	R ₁	n	Yield (%)
1	Ph	1	100
2	Me	1	5
3	H	1	0
4	Ph	2	100
5	H	3	23

Table 1.7: Hydrogenation of cyclic lactams⁵⁵

The five and six membered phenyl substituted amides (entry 1 and 4) reacted well giving 100% yield after 24 hours. The methyl substituted and straight amide analogues are less reactive giving only small amounts of product, although the seven membered ring amide (entry 5) does give an increased yield (23%). The difference between the five membered ring (entry 2) was proposed by the authors to be due to the greater stability of the 5 membered ring analogue.

There have been only a few catalytic systems described in the literature for the hydrogenation of amides. As shown in the examples above high yields can be obtained, and with careful selection of catalyst and reaction conditions either primary or secondary amines can be produced. Unfortunately all of the catalysts require high temperatures and pressures for good reactivity. In most cases high catalyst loadings are required. The examples described in the literature are very promising but further research is required to reduce the cost of the process.

1.5. Aims

The overall aim of the research described within this thesis, was to explore the reaction of challenging substrates in catalytic hydrogenation chemistry.

Catalytic hydrogenation has undergone a vast amount of research, with numerous papers in the literature. Still there are significant substrate classes that prove challenging with modern catalysts, as has been demonstrated in the review of the literature in Chapter 1.

At the beginning of this project, the areas of benzofuran hydrogenation, ester hydrogenation and bulky ketone hydrogenation had relatively little research described in the literature. Effective catalysts and procedures for the efficient hydrogenation of these types of substrates would have both industrial and academic interest as it could provide new routes to the synthesis of a number of different compounds.

The literature for the catalytic homogeneous asymmetric hydrogenation of benzofurans at the beginning of this project had one paper, with only three substrates examined⁴⁹. Due to the small substrate scope and the high catalysts loadings required in this work, it was decided to undertake a research project to find a catalytic system that could hydrogenate benzofurans. Initially it was decided to investigate achiral catalysts, and explore different types of metal/ligand combinations to try and get a better understanding of the reaction. The overall aim was to hopefully produce an optimised and efficient achiral catalytic system. Once this was achieved research into a stereoselective process could be undertaken.

There was literature precedent in the area of ester hydrogenation before this project was started, and is discussed in Chapter 3. Unfortunately most substrates described were either an activated species or the reaction required high catalyst loadings and high reaction temperatures to achieve good conversions to product. Work within the research group had produced a protocol for quickly and easily screening $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ complexes, so it was decided to carry out a complex screen with the aim of finding new catalysts for the hydrogenation of esters. It was also of interest to investigate the $[\text{RuCl}_2(\text{PNN})(\text{DMSO})]$ type complex using higher basic co-catalyst concentrations than had previously been examined. This type of catalyst had previously shown activity in the hydrogenation of activated esters using low base concentrations. Since the base concentration has been found to be an important parameter, often requiring $>25\text{mol}\%$, then it was thought that using high base concentration then the substrate scope could be increased to non activated substrates. The overall aim for this part of the project was to produce and optimise new catalysts for the hydrogenation of esters, with the hope of reducing the high catalysts loadings and temperatures that were required in the literature examples.

The area of bulky ketone hydrogenation, had a few interesting examples, but most substrates react sluggishly and a more active catalytic system are needed. Research at St Andrews had previously shown new $[\text{RuCl}_2(\text{PNN})(\text{DMSO})]$ catalysts for the hydrogenation of these substrates, and previous research has shown that the reaction could effectively and efficiently reduce a large range of bulky ketones, that had previously not been possible. Researchers have demonstrated the use of different metals, other than ruthenium can have effects on the reaction rates and selectivity of other catalytic systems, but no such research had been carried out on the $[\text{RuCl}_2(\text{PNN})(\text{DMSO})]$ type catalysts. The aim of this part of the project was to investigate different catalysts formed from other metals such as iridium or rhodium, with the hope of producing an even more active and selective catalytic system.

The overriding goal that links the three separate projects is to find new catalytic systems for the hydrogenation for substrates that are a significant challenge. At the same time a reduction of the cost of the processes will be attempted, by trying to use low temperature and low catalyst loading reaction, if possible.

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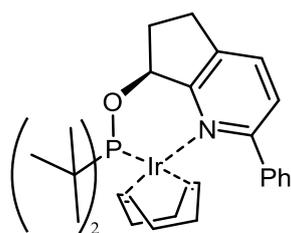
II. CHAPTER II: A STUDY INTO THE HYDROGENATION OF BENZOFURANS.

2.1. Hydrogenation of Benzofurans

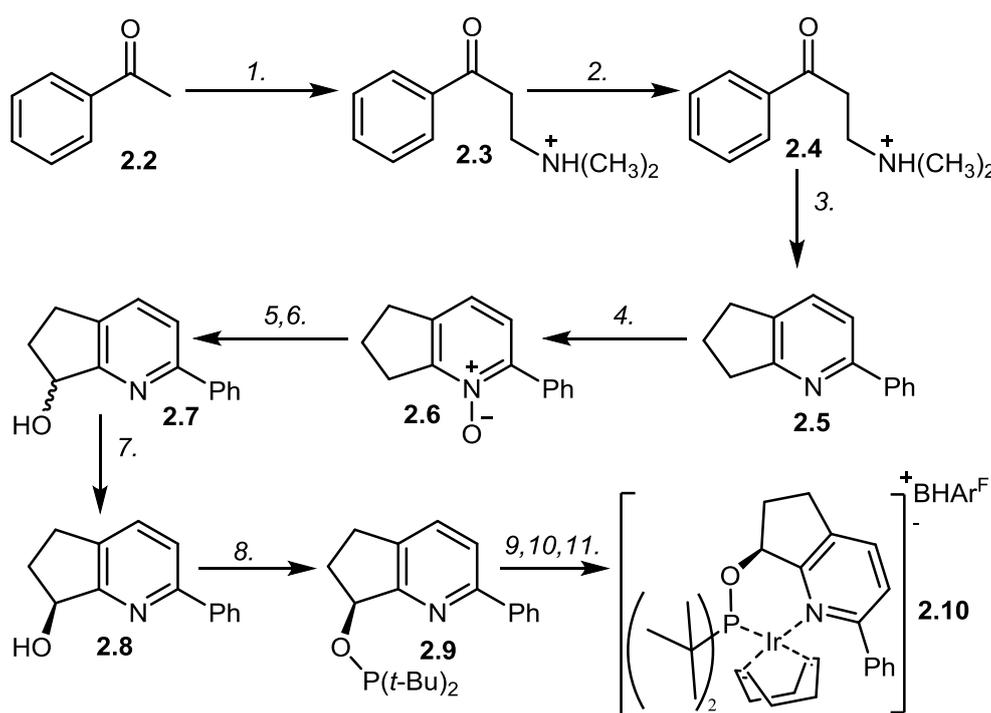
The asymmetric hydrogenation of heterocycles is an area of chemistry which is relatively underdeveloped when compared with other unsaturated functional groups such as ketones and olefins. There are only a few examples in the literature where there has been any appreciable enantioselectivity recorded. Even when enantioselectivity over 90% has been achieved, the activity for the reaction is usually poor; conversely highly active catalysts often give reduced selectivity.

Heterocycles are difficult to hydrogenate with homogeneous catalysts as they can often datively coordinate to the metal, acting as a poison to potential catalytically active species. Aromatic heterocycles such as pyridines or benzofurans, are even more challenging substrates. The low reactivity of aromatic heterocycles is primarily due to the inherent resonance stabilisation, making the substrate unusually stable, compare to other substrate classes.

There has been some research in this area over the last few decades as the potential products could be used to produce a wide variety of new chiral molecules. Substrates including cyclic imines, azirines, quinolines, pyrroles, and indoles, have been the subjects of significant investigation with representative examples not shown in the introduction chapter. Unfortunately even though there are ranges of heterocyclic compounds that can be hydrogenated using homogeneous catalysis with good selectivities, there are still few whole groups of substrates that have shown success in the literature. Benzofurans are an example of an under researched substrate class, when compared with other heterocyclic compounds. A promising paper by Pfaltz and co-workers¹, describes the enantioselective hydrogenation of a small selection of both furans and benzofurans. The catalyst type highlighted in the paper is shown below and was developed for the hydrogenation of substituted alkenes. However it was shown to also hydrogenate a limited number of furans and benzofurans, albeit at relatively high catalyst loadings.

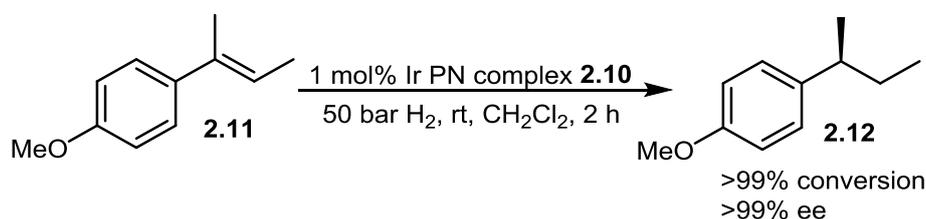

2.1
Figure 2.1: Pfaltz's iridium PN catalyst structure¹

The researchers designed the catalyst type shown in Figure 2.1 to closely mimic Crabtree's catalyst $[\text{Ir}(\text{COD})(\text{Py})(\text{Cy}_3\text{P})]\text{PF}_6$. The researchers sought to combine the phosphine and pyridine ligand of the Crabtree catalyst into one combined PN bidentate ligand. This type of ligand has been shown to be synthesised in a 7 step procedure from acetophenone; the product of which can then be complexed with an iridium precursor to form the precatalytic complex (**2.10**). See Scheme 2.1 below for details of the synthetic pathway utilised.



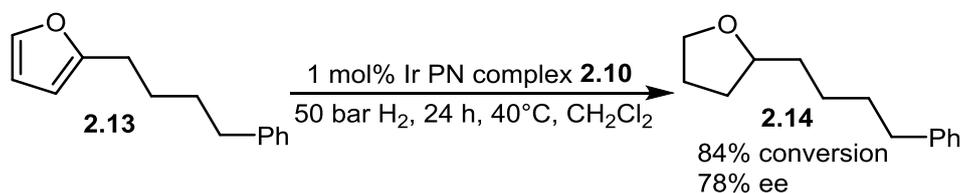
Scheme 2.1: Synthesis of Pfaltz PN phosphinite ligand (**2.10**).¹ **1.** $[\text{H}_2\text{C}=\text{N}(\text{CH}_3)_2]\text{Cl}$, MeCN, reflux, 1h. **2.** Cyclopentanone morpholine enamine, dioxane, reflux, 16 hrs. **3.** HO-NH₃Cl, EtOH, reflux, 3 hrs. **4.** *m*-CPBA, CH₂Cl₂, 0°C to rt, overnight. **5.** TFAA, CH₂Cl₂, 0°C to rt, 4 hrs. **6.** LiOH, CH₂Cl₂, rt, 3 hrs. **7.** Resolution with preparative HPLC. **8.** $(t\text{-Bu})_2\text{PCl}$, NaH, THF/DMF (9:1), 0°C to rt, 1-4 days. **9.** $[\text{Ir}(\text{COD})\text{Cl}]_2$, CH₂Cl₂, 50°C, 2 hrs. **10.** NaBARF, rt, 2 mins. **11.** H₂O, rt, 15 mins.

The catalyst type (**2.10**) was initially developed for the hydrogenation of olefins, an example is shown in scheme 2.2.



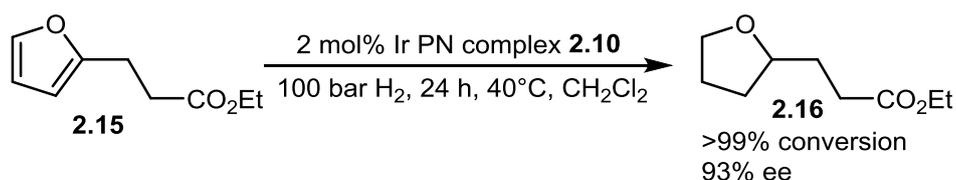
Scheme 2.2: Asymmetric hydrogenation of alkene **2.11** using Ir PN complex **2.10**.¹

The iridium complexes have been shown to hydrogenate a wide variety of alkenes readily, the main advantage of these complexes are that they can hydrogenate unfunctionalised alkenes enantioselectively. A lower selectivity was observed with tetra substituted alkenes, but this is a particularly challenging substrate. Due to such a success with alkene substrate hydrogenation, Pfaltz and co-workers investigated hydrogenation of further unsaturated compounds including furans and benzofurans.¹



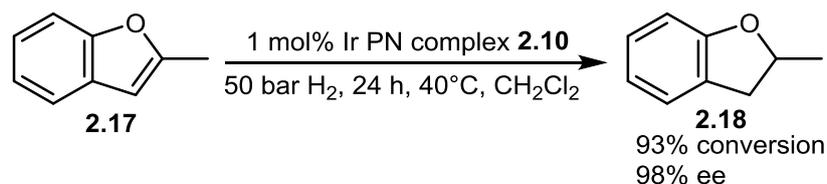
Scheme 2.3: Asymmetric hydrogenation of furan **2.13** using Ir PN complex **2.10**.¹

Experiments have shown activity in the hydrogenation of furans, a substrate with an alkyl chain terminated with a phenyl group was tested (scheme 2.3). The reaction only resulted in an 84% conversion in a 24 hour time period at 1 mol% catalyst loading and good enantiomeric excess achieved.



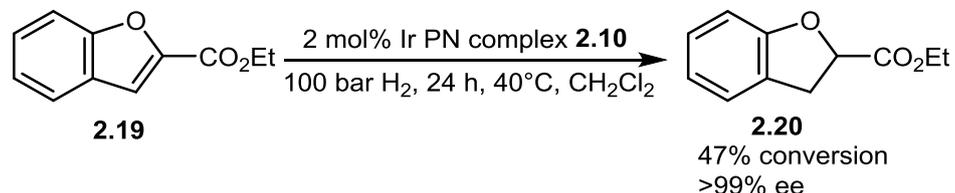
Scheme 2.4: Asymmetric hydrogenation of furan **2.15** using Ir PN complex **2.10**.¹

An additional substrate with an ester terminated side chain was hydrogenated giving the fully reduced furan in quantitative yield and high enantiomeric excess (see scheme 2.4). A higher catalyst loading and initial hydrogen pressure were required for the reaction to work. At the same time a small number benzofurans were also investigated, showing the iridium complex was also active in the hydrogenation this difficult substrate class. The results of which are illustrated below in Scheme 2.5.



Scheme 2.5: Asymmetric hydrogenation of 2-methylbenzofuran (**2.17**) using an Ir PN complex.¹

The simple methyl benzofuran was hydrogenated in good yield and high selectivity in 24 hours. The hydrogenation of an ester substituted benzofuran was also tested as shown below in Scheme 2.6.

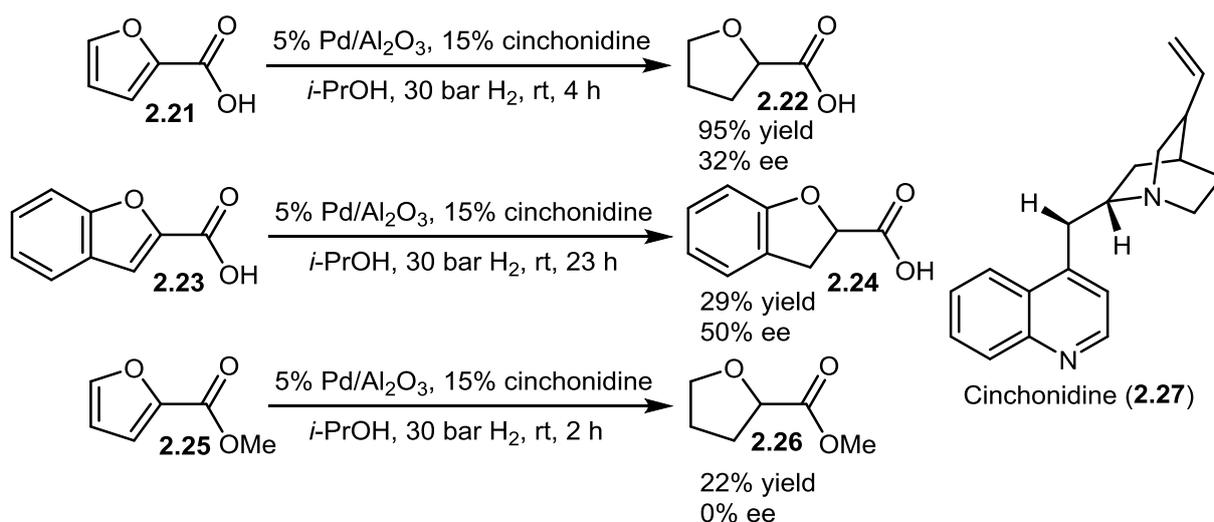


Scheme 2.6: Asymmetric hydrogenation of benzofuran **2.19** using an Ir PN complex **2.10**.¹

This experiment resulted in an enantiopure product, but the reaction has poor conversion to product. It is also necessary to use higher catalyst loading and hydrogen pressure, to only achieve a 47% conversion after 24 hours.

This initial work into the catalytic homogeneous hydrogenation of benzofurans is ground breaking work, despite this there are significant areas for improvement. Only a total of 5 furan/ benzofuran substrates described in the paper, so the substrate scope of the reaction needs improvement and further investigation, as this substrate class is almost unstudied using homogeneous catalysts. Currently high catalyst loadings are required for the reaction to be successful. To make the process more viable, these need to be lowered significantly; as most industrial hydrogenations use between 0.0005 and 0.1 mol% catalyst.

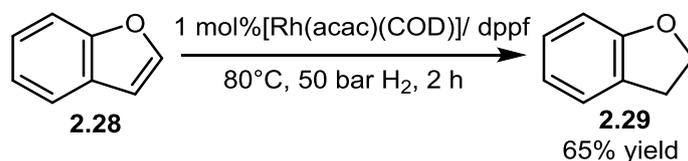
In addition to this example of homogeneous iridium catalysed hydrogenation, there are also examples of the heterogeneous hydrogenation² of furans and benzofurans in the literature. One example is shown in Scheme 2.7 below, in this instance the palladium on alumina catalyst was modified with the addition of cinchonidine, which is a chiral alkaloid found in nature.



Scheme 2.7: Heterogeneous hydrogenation of furans and benzofurans, utilising modified palladium on alumina.²

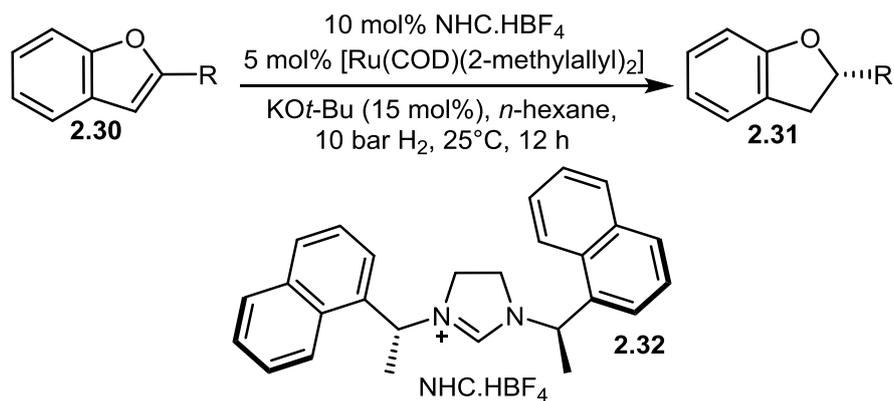
The results for the hydrogenation are modest, with an ee of only 32% for the furan and 50% for the benzofuran. The yield for the benzofuran is low at 29% over a 23 hour period (scheme 2.7). The carboxylic acid functionality is required for the enantioselectivity observed in the reaction as demonstrated by the hydrogenation of ester **2.25**. The ester analogues show no selectivity, the loss in enantioselectivity is suggested by the authors to be due to an acid-base relationship between the carboxylic acid substrate and the cinchonidine that does not occur with the ester substrate.

The hydrogenation of unsubstituted benzofuran itself proves difficult to hydrogenate using homogenous catalysts, with only a modest yield of 65% with high temperatures, pressures and catalyst loadings required as shown in Scheme 2.8.



Scheme 2.8: Literature example of the hydrogenation of benzofuran with a rhodium catalyst³

More recent research published after the research described in this chapter, by Glorius and co-workers^{4,5}, has shown the use of a ruthenium N-heterocyclic carbene (NHC) complex in the hydrogenation of substituted benzofurans at low pressures and ambient temperatures. If the reaction was carried out at increased reaction temperatures and pressure (80°C, 60 bar H₂), only starting material was present after the end of the experiment. The supposition for this given by the authors, is that the catalyst decomposes under such conditions. A total of 18 substrates (shown below) were described in the publication, all of those giving high conversions and selectivities, up to 98% ee. This is illustrated below in Table 2.1



Entry	Substrate/ Product 2.30 a-j/ 2.31 a-j (R=)	Conversion (%)	Enantioselectivity (%)
1	H	99	NA
2	Me ^a	99	92
3	<i>n</i> -Dec	99	88
4	<i>n</i> -Bu	99	90
5	Ph	99	98
6	<i>i</i> -Pr	99	87
7	<i>t</i> -Bu	38	75
8	Benzyl	99	84
9	2-pyridinyl	99	58
10	3-pyridinyl	99	98

a. Reaction performed using 0.5 mol% catalyst, for 2 hours.

Table 2.1: Hydrogenation of benzofuran and derivatives with a NHC ruthenium catalyst.^{4,5}

These results are very promising; the catalyst has been shown to work over a large substrate scope. Lower yield and selectivity was observed when using the bulky tertiary butyl substrate (see entry 7, **2.30g**). High catalyst loadings and base concentrations were required for good reactivity. Generally 5 mol% was used and the lowest loading was for the hydrogenation of the methyl substrate (entry 2, **2.30b**) where the reaction was successful using 0.5 mol%, and went to complete conversion in 2 hours.

2.2 Aims

At the initiation of this project the number of papers in the literature describing the homogeneous hydrogenation of benzofurans is very small. Due to this it was decided to investigate this challenging class of substrates with the aim of producing a selective and efficient catalytic system for asymmetric hydrogenation of substituted benzofurans.

Initially it was decided to perform the initial catalyst screen on the simple unsubstituted 2,3-benzofuran, to probe the reaction with a cheap and easily obtainable starting material. The aim would then be to follow up with stereoselective examples using the knowledge learned.

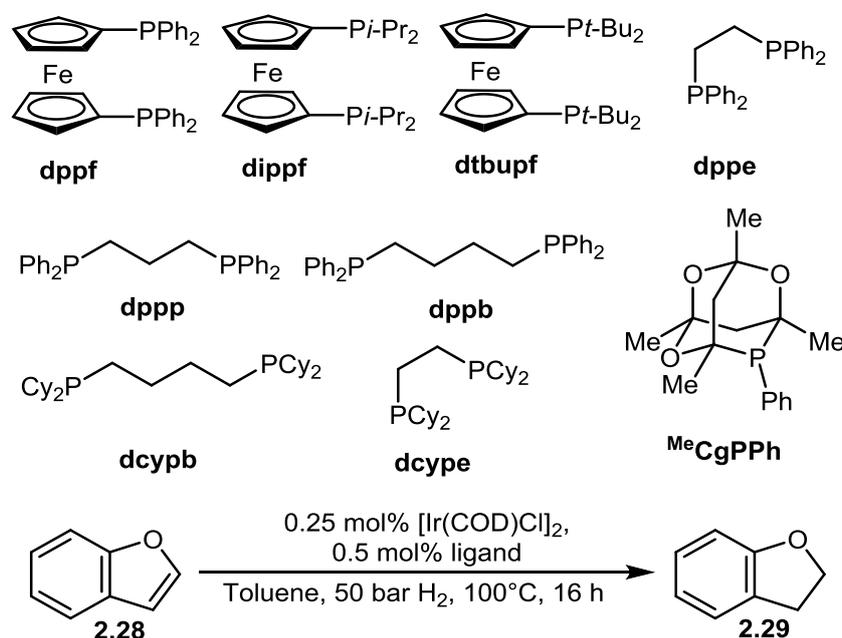
During the course of this research it became of interest to also study the asymmetric hydrogenation of benzofuranyl-aryl ketones to aid in the stereoselective hydrogenation benzofurans. At the beginning of this research the hydrogenation benzofuranyl-aryl ketone had even less precedent than for benzofuran hydrogenation, with no literature examples and only a few examples of aryl-aryl ketone hydrogenation and heterocycle ketone hydrogenation (see Chapter 1 for details) to base the research on. Therefore a major aim of this chapter was to develop active and selectivity catalytic species for the hydrogenation of ketones with benzofuranyl substituents.

2.3. Screens of Metal Complexes for the Hydrogenation of Benzofuran

Benzofurans represent a group of aromatic bicycles. The functionality is found widely in nature, contained within a number of drug molecules and natural products. Dihydrobenzofurans, the products of the hydrogenation of benzofuran are also found in a number of natural products and drug molecules. Dihydrobenzofurans have also been used as isosteres of aromatic methoxy groups, to be used as analogues of hallucinogens.⁶ The work by Pfaltz and co-workers has clearly shown that the benzofuranyl substrates can be hydrogenated using iridium based homogeneous catalysts.

To help with investigations into the enantioselective hydrogenation of benzofurans, a study was performed on the hydrogenation of 2,3-benzofuran to compare ligand, solvent and temperature effects on reactivity to optimise the reaction conditions and explore potential ligand effects, please refer to the experimental for full details of the experiment set up. The

reactions were carried out on a 0.45 mmol scale with $[\text{Ir}(\text{COD})\text{Cl}]_2$ as the metal precursor with a variety of different types of diphosphine ligands, as shown in Table 2.2.



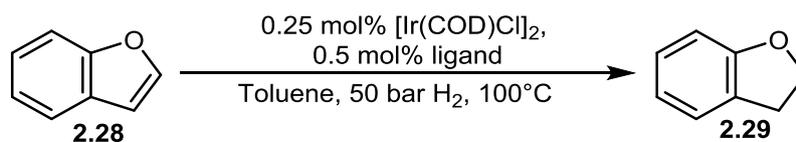
Entry	Metal complex	Ligand	Solvent	Conversion (%)
1	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dppf	Toluene	5.5
2	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dippf	Toluene	<0.5
3	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dcype	Toluene	9.5
4	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dppe	Toluene	8.5
5	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dtbdpf	Toluene	8
6	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dppp	Toluene	Nil
7	$[\text{Ir}(\text{COD})\text{Cl}]_2$	dppb	Toluene	Nil

Conditions: 0.45 mmols of substrate, 0.25 mol % $[\text{Ir}(\text{COD})\text{Cl}]_2$, 0.5 mol%, ligand, 3ml solvent, 50 bar of hydrogen, 100°C, 16 hrs. Conversion calculated by ^1H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

Table 2.2: Diphosphine ligand study on the hydrogenation of 2,3-benzofuran

This experiment shows that most of the catalysts used are, at best, only slightly active toward the hydrogenation of benzofuran, with the best conversion being only 9.5%.

To determine if the poor reactivity was due to catalyst poisoning/ deactivation, the reaction time was extended to 64 hours, as shown in Table 2.3.



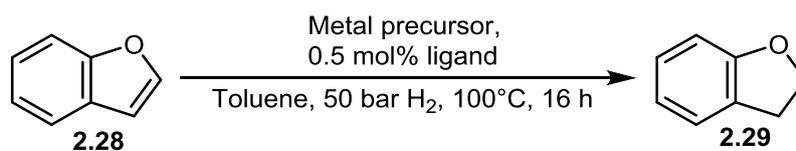
Entry	Metal complex	Ligand	Time (hrs)	Conversion (%)
1	[Ir(COD)Cl] ₂	dcype	16	9.5
2	[Ir(COD)Cl] ₂	dcype	64	25
3	[Ir(COD)Cl] ₂	dppe	16	8.5
4	[Ir(COD)Cl] ₂	dppe	64	32

Conditions: 0.45 mmols of substrate, 0.25 mol % [Ir(COD)Cl]₂, 0.5 mol%, ligand, toluene (3 ml), 50 bar of hydrogen, 100°C 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

Table 2.3: Time study on the hydrogenation of benzofuran

After 64 hours (4 times the previous experiments reaction time), the reaction had gone more towards completion but still did not give high conversions. The experiment does show that the catalysts are not becoming excessively poisoned and are just not very active for this particular substrate.

Iridium was chosen for this initial screen as the work by Pfaltz and co-workers¹ had shown an iridium complex to be active in the hydrogenation of benzofurans. The initial experiments have shown that the iridium had not proved to be very effective as all results had given poor conversions over 16 hours and required forcing conditions required. Due to the poor conversions observed in this initial screen, a small metal precursor screen was performed to study the use of different metal complexes in the hydrogenation of benzofuran. This included iridium complexes with different counterion and other transition metal complexes. Ruthenium and rhodium precursor were chosen as they have already been shown to be active in the hydrogenation of other substrate classes such as ketones and olefins. The results of this metal screen are shown below in Table 2.4.



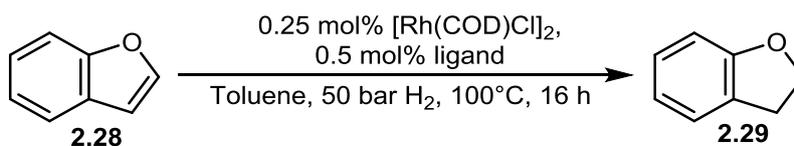
Entry	Metal complex	Ligand	Solvent	Conversion (%)
1	[Ir(COD ₂)]BF ₄	dcype	Toluene	5
2	[Ru(COD)Cl ₂] _n	dcype	Toluene	2.5
3	[Ir(COD)Cl] ₂	dcype	Toluene	9.5
4	[Rh(COD)Cl] ₂	dcype	Toluene	16

Conditions: 0.45 mmols of substrate, 0.25 mol % dimeric precursor or 0.5 mol % monomeric/ polymeric precursor, 0.5 mol%, ligand, toluene (3ml), 50 bar of hydrogen, 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

Table 2.4: Metal precursor screen on the hydrogenation of benzofuran

The ligand, 1,2-bis(dicyclohexylphosphino)ethane was chosen as this proved to work the best when combined with iridium in the initial screening experiments. The results are still meagre, but promising as an increase in reactivity was observed when a rhodium precursor was used instead of the other metal complexes. The alternative [Ir(COD₂)]BF₄ also showed poor performance when compared with [Ir(COD)Cl]₂.

As the rhodium precursor proved the most active in the hydrogenation of benzofuran, further investigation was required with the aim of improving the conversions. As a previous ligand screen had shown that the dcype ligand was the best when combined with iridium, it was decided to carry out a further ligand screen to see if this was also the case with rhodium or if a better combination could be found. A further array of diphosphine and some mono phosphine ligands were examined, shown in Table 2.5.



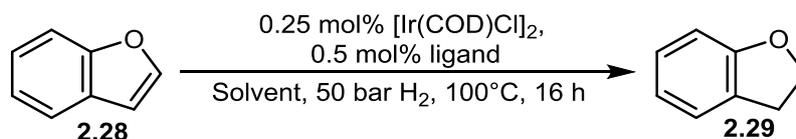
Entry	Metal complex	Ligand	Time (hrs)	Conversion (%)
1	[Rh(COD)Cl] ₂	dcype	16	16
2	[Rh(COD)Cl] ₂	dcype	64	71
3	[Rh(COD)Cl] ₂	dppe	64	28
4	[Rh(COD)Cl] ₂	dippf	16	85
5	[Rh(COD)Cl] ₂	dppp	16	5
6	[Rh(COD)Cl] ₂	dppb	16	21
7	[Rh(COD)Cl] ₂	dcypb	16	45
8	[Rh(COD)Cl] ₂	^{me} CgPPh	16	70
9	[Rh(COD)Cl] ₂	PPh ₃	16	55

Conditions: 0.45 mmols of substrate, 0.25 mol % [Rh(COD)Cl]₂, 0.5 mol%, ligand, toluene (3 ml), 50 bar of hydrogen, 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methyl-naphthalene as an internal standard.

Table 2.5: Phosphine ligand screen on the hydrogenation of benzofuran using a rhodium based precursor.

This ligand screen shows a dramatic increase in reactivity relative to the iridium catalysed reactions. The result of particular interest is the rhodium/dippf combination which resulted in high conversion to product in an overnight reaction. There is a dramatic increase in reactivity when compared to the Ir/dippf combination where no reactivity was observed. Although the iridium/dippf catalyst proved to be the best under these conditions a few other examples of high conversions were achieved including when using the monodentate methyl cage phosphine (meCgPPh) and the simple triphenylphosphine.

Experiments were performed to see if the solvent could affect the product conversions.

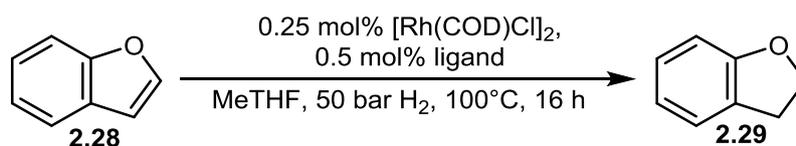


Entry	Metal complex	Ligand	Solvent	Conversion (%)
1	[Ir(COD)Cl] ₂	dcype	Toluene	9.5
2	[Ir(COD)Cl] ₂	dppf	Toluene	5.5
3	[Ir(COD)Cl] ₂	dcype	THF	10
4	[Ir(COD)Cl] ₂	dppf	THF	Nil
5	[Ir(COD)Cl] ₂	dcype	Me-THF	5.5
6	[Ir(COD)Cl] ₂	dppf	Me-THF	17
7	[Ir(COD)Cl] ₂	dcype	EtOH	2
8	[Ir(COD)Cl] ₂	dppf	EtOH	Nil

Conditions: 0.45 mmols of substrate, 0.25 mol % [IrCODCl]₂, 0.5 mol%, ligand, 3ml solvent, 50 bar of hydrogen, 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

Table 2.6: Solvent screen on the hydrogenation of benzofuran using iridium/ diphosphine catalytic species.

The results in Table 2.6 show an increase in reactivity when using 2-methyltetrahydrofuran (MeTHF) and bis(diphenylphosphino)ferrocene, (dppf). This is an intriguing result as the dppf shows generally lower activity when using previous solvents compared with other ligands such as dcype. It was noted that there was an increase in reactivity when the solvent was changed to MeTHF in the iridium results. It was decided to perform a reaction in which the rhodium precursor was used to perform an additional ligand screen. This time the ligand screen was investigated with MeTHF as the solvent of choice, as this has the potential to significantly increase the reactivity.



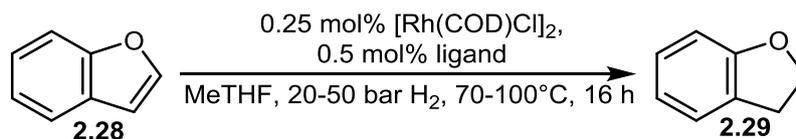
Entry	Metal complex	Ligand	Conversion (%)
1	[Rh(COD)Cl] ₂	dippf	>99
2	[Rh(COD)Cl] ₂	dcypb	>99
3	[Rh(COD)Cl] ₂	dppf	30
4	[Rh(COD)Cl] ₂	^{me} CgPPh	14
5	[Rh(COD)Cl] ₂	PPh ₃	23
6	[Rh(COD)Cl] ₂	dppe	35
7	[Rh(COD)Cl] ₂	dcype	30

Conditions: 0.45 mmols of substrate, 0.25 mol % [Rh(COD)Cl]₂, 0.5 mol%, ligand, MeTHF (3 ml), 50 bar of hydrogen, 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

Table 2.7: Ligand screen in the hydrogenation of benzofuran using a rhodium based precursor.

When the reactions were carried out in Me-THF shown in Table 2.7 above, complete conversion to benzofuran was achieved using dippf and dcypb as ligands. In general, the reactivity of the *in situ* formed rhodium complexes increased with MeTHF as the solvent when compared when carried out in toluene, although this was not the case with the monodentate ^{me}CgPPh.

As the reaction conditions so far used were forcing, a temperature and pressure optimisation was performed for the new MeTHF solvent system as it showed good reactivity over 16 hours at 100°C. It was felt that as quantitative conversions were obtained, the reaction conditions may be able to be altered so that such extreme conditions are no longer necessary.



Entry	Metal complex	Ligand	Temperature (C)	Pressure (bar H ₂)	Conversion (%)
1	[Rh(COD)Cl] ₂	dippf	70	50	21
2	[Rh(COD)Cl] ₂	dippf	90	50	25
3	[Rh(COD)Cl] ₂	dippf	100	20	94
4	[Rh(COD)Cl] ₂	dippf	100	50	>99
5	[Rh(COD)Cl] ₂	dcypb	70	50	19
6	[Rh(COD)Cl] ₂	dcypb	90	50	47
7	[Rh(COD)Cl] ₂	dcypb	100	20	65
8	[Rh(COD)Cl] ₂	dcypb	100	50	>99
9	[Rh(COD)Cl] ₂	dppf	70	50	13
10	[Rh(COD)Cl] ₂	dppf	90	50	29
11	[Rh(COD)Cl] ₂	dppf	100	20	10
12	[Rh(COD)Cl] ₂	dppf	100	50	30

Conditions: 0.45 mmols of substrate, 0.25 mol % [IrClCOD]₂, 0.5 mol%, ligand, MeTHF (3 ml), 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methyl naphthalene as an internal standard.

Table 2.8: Temperature and pressure study on the hydrogenation of benzofuran using a rhodium/ diphosphine catalyst.

The results in Table 2.8 show that when the temperature is decreased by just ten degrees there is a dramatic fall in reactivity. At a 100°C using dippf and dcypb, the reaction goes to completion. At 90°C the reactivity drops and the catalyst converts less than a quarter of the starting material during the same time period in some cases (entry 2, Table 2.8).

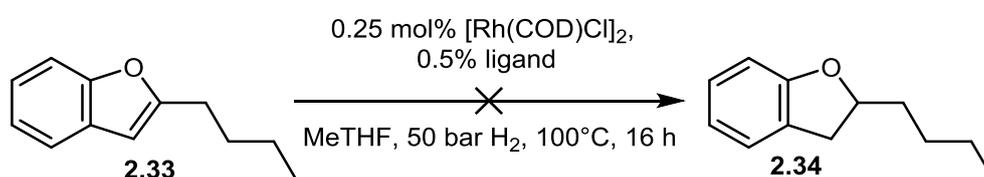
The same dramatic effect is not observed when reducing the pressure. The hydrogen pressure could be reduced to 20 bar with only a mild reduction in conversion, as shown above only a small drop to 94% conversion with dippf. The results show that using dcypb and dippf combined with [Rh(COD)Cl]₂ makes for an efficient benzofuran hydrogenation catalyst at 100°C and at pressures as low as 20 bar. These ligands share similar properties that the less reactive ligands do not have. They are both considered strongly electron donating, both are bulky at phosphorus, and both have a relatively large natural bite angle (i.e. the angle that the diphosphines would prefer to adopt when coordinated to a hypothetical metal centre).

The purpose of these reactions was to provide comparative results of different reaction conditions; as such the experiments were carried out on a small scale that has the side effect

of inefficient stirring and heating. This was sufficient for the aim this research, but if the reaction was to be optimised full it should be carried out on a larger scale using overhead stirring.

2.4. Substituted Benzofurans

As it was possible to hydrogenate benzofuran successfully albeit with high reaction temperatures, it was decided to determine if it was possible to hydrogenate a substituted benzofuran with the same reaction conditions. 2-Butyl benzofuran was chosen as it was an inexpensive commercially available compound, and the results are shown below in Table 2.9.



Entry	Ligand	Temperature (°C)	Conversion (%)
1	dippf	100	0
2	dcype	100	0
3	dcypb	100	0
4	dppf	100	0
5	dippf	130	0
6	dcype	130	0
7	dcypb	130	0
8	dppf	130	0

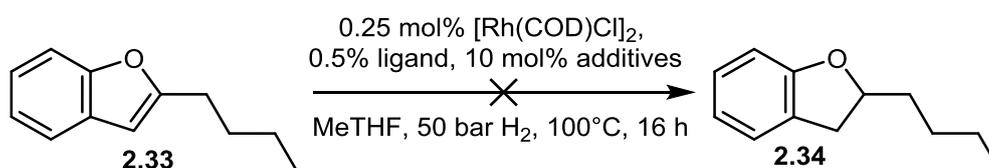
Conditions: 0.3mmols of substrate, 0.25 mol % [RhCODCl]₂, 0.5%, ligand, MeTHF (3ml), 50 bar of hydrogen, 100°C, 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

Table 2.9: Hydrogenation of 2-butyl benzofuran

The substrate was tested under the same reaction conditions as with benzofuran, with a range of the most successful diphosphine ligands tested thus far. Unfortunately no conversion was observed with any of the ligands after 16 hours, with only starting material present after the reaction. The temperature of the reaction was increased to 130°C but still there was no

conversion to product observed. As the aim of the research was to produce a stereoselective reaction it was decided not to increase the reaction temperature further as any selectivity at higher temperatures would be unlikely.

It was believed that the benzofuran could be potentially activated by using a lewis acid co-catalyst. Bases were also investigated as they have also been used as co-catalysts in certain hydrogenations. To explore these hypotheses a range of different bases and lewis acids were added at substoichiometric amounts (10 mol%) to the reaction mixture, shown below in Table 2.10.



Entry	Ligand	Additive	Conversion (%)
1	dippf	NEt ₃	0
2	dcype	NEt ₃	0
3	dcypb	NEt ₃	0
4	dppf	NEt ₃	0
5	dippf	CsCO ₃	0
6	dcype	CsCO ₃	0
7	dcypb	CsCO ₃	0
8	dppf	CsCO ₃	0
9	dippf	Sc(OTf) ₃	0
10	dcype	Sc(OTf) ₃	0
11	dippf	Bi(OTf) ₃	0
12	dcype	Bi(OTf) ₃	0
13	dippf	I ₂	0
14	dcype	I ₂	0

Conditions: 0.3mmols of substrate, 0.25 mol % [RhCODCl]₂, 0.5%, ligand, MeTHF (3 ml), 50 bar of hydrogen, 100°C, 16 hrs. Conversion calculated by ¹H NMR, using 1/3 equivalent of methylnaphthalene as an internal standard.

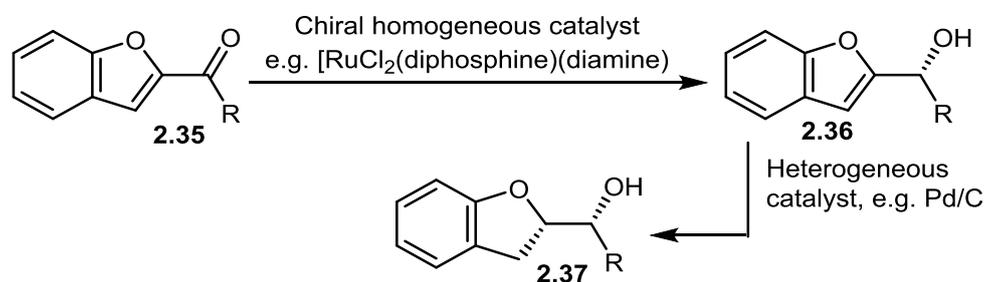
Table 2.10: The effect of additives on the hydrogenation of 2-butyl benzofuran.

The range of additives tested did not produce any product with only starting material observed post reaction.

Unfortunately after a number of attempts, even with an addition of a base, a Lewis acid or an increasing the temperature, no reaction was observed. This is a relatively simple substrate and the lack of success is unfortunately likely to preclude the use of this catalytic system in more elaborate substrates.

2.5. Asymmetric Hydrogenation of Benzofuranyl Aryl Ketones

Due to these issues it was decided to take a different approach, instead of homogeneous hydrogenation. The hypothesis for this new approach was that by taking a benzofuran with a ketone side chain, and reducing the ketone with a chiral catalyst, then an enantioenriched alcohol would be produced. The chiral alcohol side chain could then act as a directing group and the benzofuran could potentially be reduced diastereoselectively with a heterogeneous catalyst. This process should be easier since the heterogeneous hydrogenation of aromatic compounds normally proceeds to give some product, so it is just the investigation of the asymmetric ketone hydrogenation and inducing the diastereoselectivity that is required. The illustration of a generic example is shown below in Scheme 2.9.



Scheme 2.9: Proposed alternative hydrogenation pathway

A small number of benzofurans with ketone substituents are commercially available. The two chosen for initial experimentation are shown below in Figure 2.3.

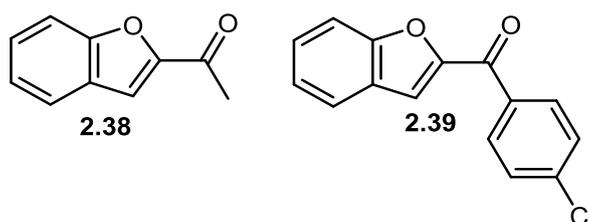
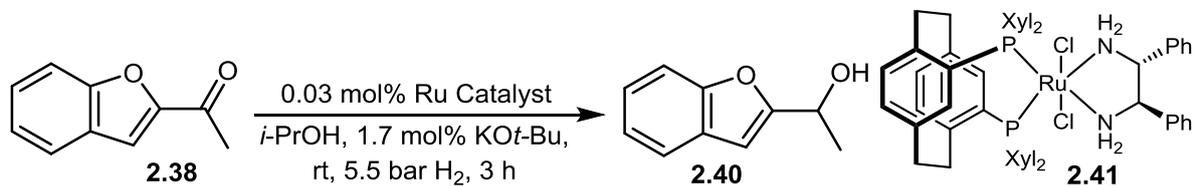


Figure 2.3: Commercially available benzofuranyl ketones

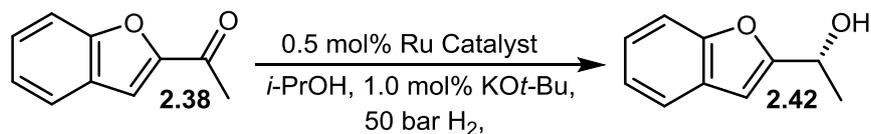
There are a few examples of the hydrogenation of ketones substrates containing heterocycles, for representative examples refer to Chapter 1. 2-Acetyl benzofuran has been previously been hydrogenated, and described in the literature as shown below in Scheme 2.10.⁷



Scheme 2.10: Literature example of the asymmetric hydrogenation of benzofuran ketone.⁷

The results with this substrate are good, with high selectivity and conversions with mild conditions. Due to this example, it was apparent that there was the potential to hydrogenate ketones with the benzofuran moiety in the substrate. There were no other examples of benzofuran hydrogenation shown, therefore there seemed to be a case for developing a broad protocol for the asymmetric hydrogenation of ketones containing benzofuran groups.

It was attempted to hydrogenate these substrates with a range of chiral ruthenium catalysts, as shown below. First the simplest methyl benzofuran-2-yl ketone was tested shown in Table 2.11.

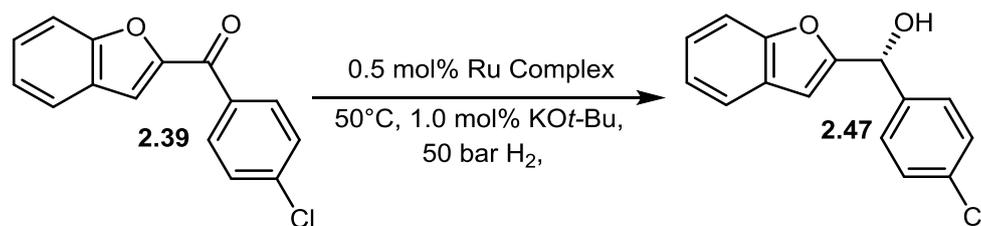


Entry (Catalyst)	Catalyst	Temperature (°C)	Time (hrs)	Conv (%)	ee (%)
1 (2.41)		r.t	6	96	97 ^a
2 (2.43)		r.t	6	95	94
3 (2.44)		r.t	6	95	92
4 (2.45)		40	16	81	9
5 (2.46)		40	16	4	Racemic

Conditions: 0.3 mmols of substrate, 0.5 mol % Ru complex, *i*-PrOH, 1 mol% KO*t*-Bu, initial hydrogen pressure of 50 bar. Conversion calculated by ¹H NMR, using methylnaphthalene, or tetraethylsilane as an internal standard. Enantioselectivity calculated by HPLC (see chapter 5, for details). (a) Reaction conditions modified from literature example.

Table 2.11: Asymmetric hydrogenation of benzofuran-2-yl methyl ketone using various ruthenium catalysts.

This substrate is hydrogenated with good conversions and enantiomeric excess using the $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ type catalysts, as had already been demonstrated.⁶ However the $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ complexes tested were less successful, with low selectivity and conversions observed. The selectivity difference between the two catalysts is to be expected, as when compared with the analogous acetophenone substrate the two different types of catalyst show a similar trend, with high enantioselectivity observed with the $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ catalysts and low selectivity with $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ complexes. It was thought that the $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ complexes could give good selectivity for the *para* chlorophenyl benzofuranyl ketone, as this type of catalyst has shown increase selectivity for ketone with large substituents when compared with the $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ complexes. So we next investigated the aryl benzofuranyl ketone, since to the best of our knowledge these types of substrates had never been investigated, shown below in Table 2.12.



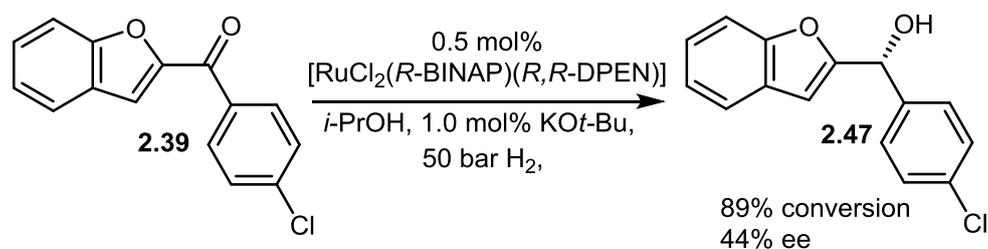
Entry (Catalyst)	Catalyst	Solvent	Conversion (%)	ee (%)
1 (2.41)		<i>i</i> -PrOH /CH ₂ Cl ₂	81	0
2 (2.41)		<i>i</i> -PrOH	76	0
3 (2.43)		<i>i</i> -PrOH /CH ₂ Cl ₂	74	0
4 (2.43)		<i>i</i> -PrOH	75	0
5 (2.44)		<i>i</i> -PrOH /CH ₂ Cl ₂	71	0
6 (2.44)		<i>i</i> -PrOH	69	0
7 (2.46)		<i>i</i> -PrOH	57	0

Conditions: 0.3 mmols of substrate, 0.5 mol % complex, 3ml solvent (either *i*-PrOH or 8:1 *i*-PrOH:CH₂Cl₂), initial pressure of 50 bar hydrogen, 1 mol% KO*t*-Bu, 16 hrs. Conversion calculated by ¹H NMR, using tetraethylsilane or methylnaphthalene as an internal standard. Enantioselectivity calculated by HPLC (see chapter 5, for details).

Table 2.12: Asymmetric hydrogenation of (4-chlorobenzoyl) benzofuran using various ruthenium catalysts.

Unfortunately this substrate is not as active towards hydrogenation as the methyl ketone substrate. The reactivity is lower, which is possibly due to the lower solubility of the substrate in *i*-PrOH. To counter act this drop in reactivity, the reaction was carried out in a mixture of isopropanol and dichloromethane (8:1). Unfortunately the addition of dichloromethane only mildly increased the conversions achieved.

The substrate reactivity is not the main issue as the reaction conditions could be altered to improve the reaction rate. The major issue with the catalytic systems used is that there was no selectivity with any of the catalysts used. This is possibly due to the phenyl ring being flat, and not dissimilar in shape and size as a benzofuran group. The reaction was also carried out using $[\text{RuCl}_2(\text{R-BINAP})(\text{R,R-DPEN})]$, as shown below in Scheme 2.11.



Scheme 2.11: Asymmetric pressure hydrogenation of 2-(*p*-chlorobenzoyl)benzofuran.

Using the more conventional $[\text{RuCl}_2(\text{R-BINAP})(\text{R,R-DPEN})]$ catalyst showed better result. The reaction gives higher conversions and even gives some selectivity.

To address the problem of low enantiomeric excess, it was decided to use a transfer hydrogenation catalyst which has previously given greater enantiomeric excess in substrates with two similar shaped substituents. It has been shown that certain transfer hydrogenation catalysts control selectivity primarily by favourable electronic interactions between the π -system of the substrate and the C-H bond of the aryl ligand, as opposed to the induction being controlled by steric effects in the $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ catalyst systems. This effect is illustrated in Figure 2.4 below.^{8,9}

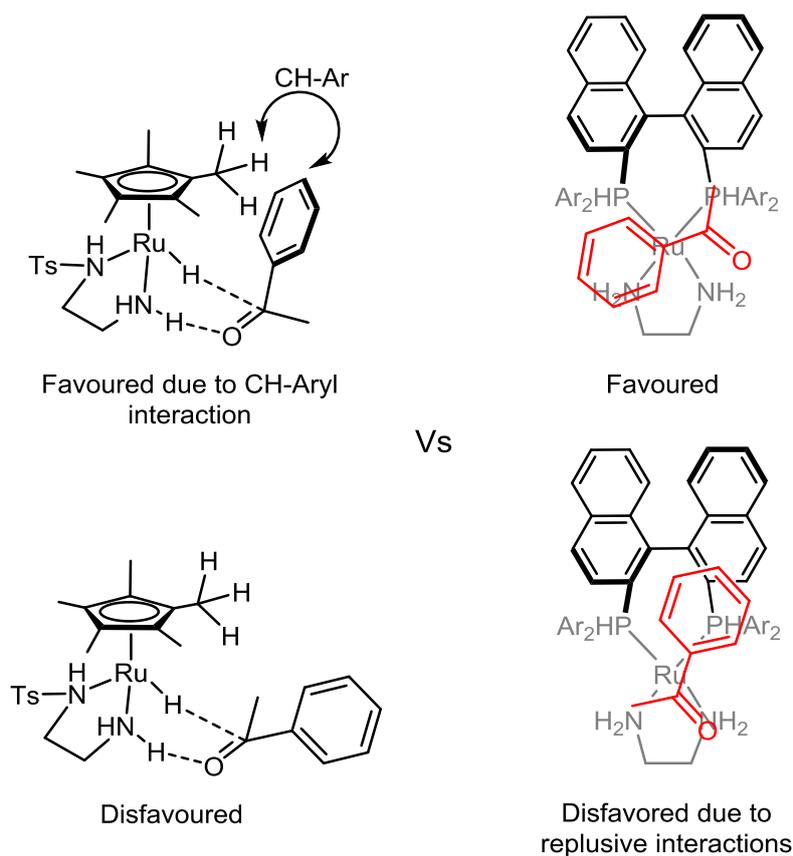


Figure 2.4: The different origins of selectivity of the classes of catalyst^{8,9}

Initial hydrogenations with transfer hydrogenation were carried out using [RuCl(cymene)(Ts-DPEN)] shown below in Table 2.13.

Entry	Substrate	Catalyst	Conv (%)	ee (%)
1			73	64
2			85	92

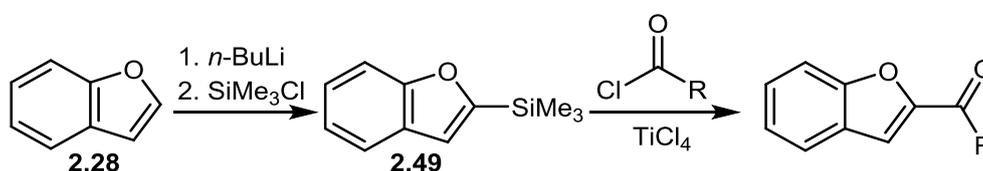
Conditions: 0.3 mmols of substrate, 0.25mol % [RuCl₂(cymene)], 0.5%, ligand, 3ml of *i*-PrOH, 1 mol% KO^t-Bu, 40°C, for 16 hrs. Conversion calculated by ¹H NMR, using tetraethylsilane as an internal standard. Enantioselectivity calculated by HPLC (see chapter 5, for details).

Table 2.13: Transfer hydrogenation of benzofurans **2.39** and **2.38**

The transfer hydrogenation of the two substrates was relatively successful with moderate selectivity and conversions. The enantiomeric excess given for the *p*-chlorobenzoyl benzofuran substrate is very promising as the result as the previous pressure hydrogenation catalysts had only given racemic products.

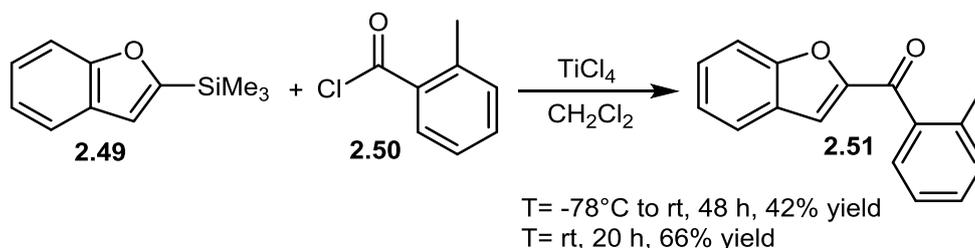
2.6. Synthesis and Hydrogenation of Aryl-Benzofuranyl Ketones.

Due to the success with the *p*-chlorobenzoyl benzofuran substrate **2.39**, it was decided to investigate other substituted benzofurans. Additional benzofuran substrates that were not commercially available were synthesised from benzofuran itself, as shown below in Scheme 2.12, using a method adapted from the literature.¹⁰



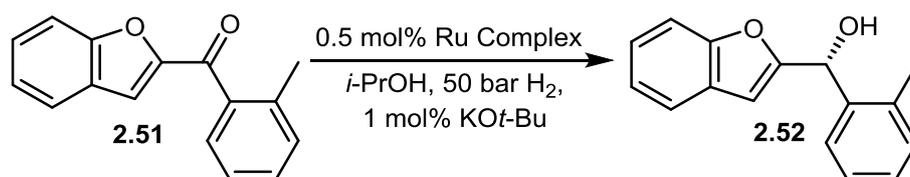
Scheme 2.12: Synthesis of a range of substituted benzofurans.¹⁰

This type of Friedel-Crafts synthesis has been described for a number of different acid chlorides included alkyl and phenyl side chains. This reaction has been shown to give high yields for alkyl acid chlorides in as little as 5 minutes. The reaction does not give as good yields for phenyl substituted side chains when compared to the alkyl acid chlorides mainly used in the article. This is argued in the article by the author as to be due to the decrease in solubility of the TiCl_4 -acid chloride complex formed, so the reaction is very slow at -78°C .¹⁰ As solubility was an issue at low temperatures, when using this procedure the reaction was required to stir for 48 hours and resulted in 42% yield after work up and purification, shown below in Scheme 2.13.



Scheme 2.13: Synthesis of 2-(*o*-Methylbenzoyl)benzofuran

The product yield was improved upon with a minor change to the literature procedure, by performing the acylation at room temperature instead of -78°C , and the reaction was left to stir overnight (66% for the above substrate). The *o*-tolyl benzofuran was chosen for synthesis, to test the hypothesis that the chiral induction of the pressure hydrogenation catalyst was due to steric factors. If this is true increasing the steric bulk around the ketone would result in a greater stereo induction when compared with the *p*-chlorobenzoyl benzofuran substrate, the results of which are shown in Table 2.14.



Entry (Catalyst)	Catalyst	Conversion (%)	e.e (%)
1 (2.41)		94	63
2 (2.44)		95	85
3 (2.53)		>99	83

Conditions: 0.45 mmols of substrate, 0.5 mol % Ru complex, 3ml *i*-PrOH, 50 bar of hydrogen, 1 mol% KO*t*-Bu, 16 hrs. Conversion calculated by ^1H NMR, using tetraethylsilane as an internal standard. Enantioselectivity calculated by HPLC (see chapter 5, for details).

Table 2.14: Pressure hydrogenation of *o*-toluoyl benzofuran using a range of ruthenium catalysts

When comparing the pressure hydrogenations from the *o*-tolyl and the *p*-chloro substrates, it is obvious to see that there is an increase in enantiomeric excess for the *o*-tolyl compound, but there is also an increase in reactivity. This could be due to the difference in solubility of the substrates, as the *p*-chloro substrate is difficult to dissolve in a number of solvent systems, whereas the same issue is not observed for the *o*-tolyl substrate.

Further substrates were synthesised using the same synthesis procedure as the *o*-tolyl substrate with similar yields achieved, except in the case of the *ortho* and *para* substituted trifluoromethyl compounds, where lower yields were shown due to issue during the work up procedure. The products and yields are shown below in Figure 2.5.

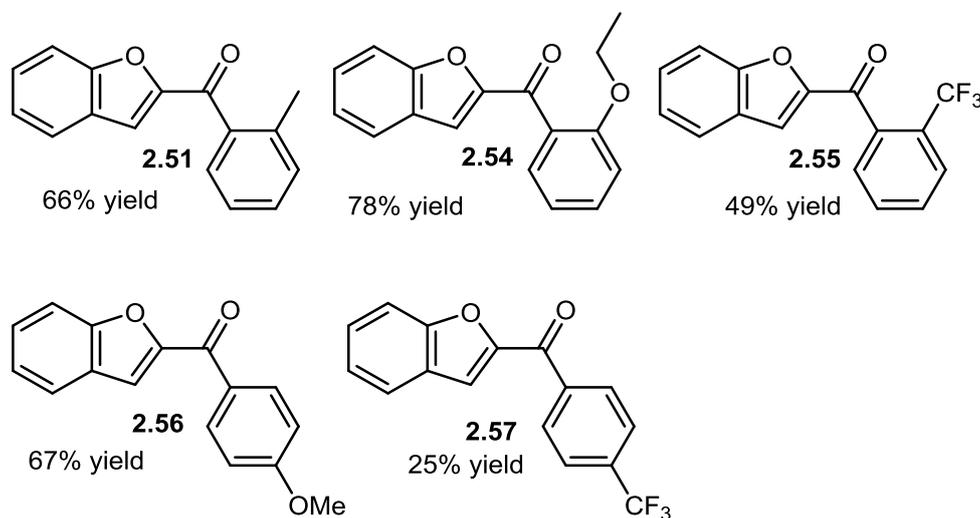
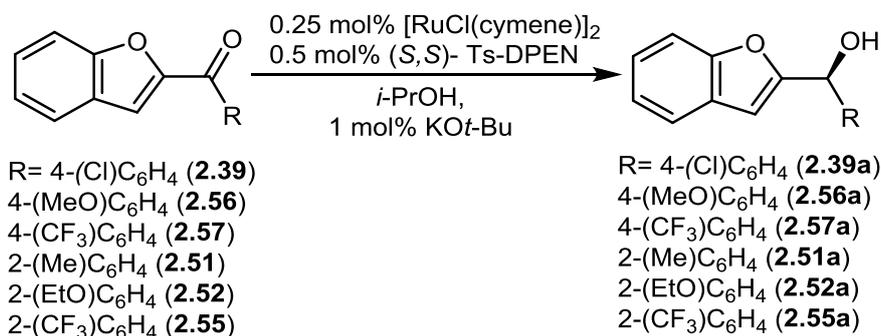


Figure 2.5: The range of benzofuran-2-yl ketones synthesised and yields.

These substrates were tested using the ruthenium cymene transfer hydrogenation catalyst, shown below in Table 2.15.



Entry	Substrate/ Product (R=)	Temperature (°C)	Conversion (%)	ee (%)
1	4-(Cl)C ₆ H ₄	40	73	64
2	4-(MeO)C ₆ H ₄	40	46	55
3	4-(CF ₃)C ₆ H ₄	40	>99	69
4	2-(Me)C ₆ H ₄	40	0	ND
5	2-(EtO)C ₆ H ₄	80	7	ND
6	2-(CF ₃)C ₆ H ₄	80	2	ND

Unless otherwise stated, the reactions were carried out using 0.25 mol% [RuCl₂(cymene)]₂, 0.5 mol% (*S,S*)-tosyl dpen, 1 mol% KO*t*-Bu as base, at 40 °C at an initial pressure of 50 bar using 0.45 mmol of substrate. Conversions were measured by NMR with the aid of an internal standard and selectivity was determined using HPLC (see chapter 5, for details).

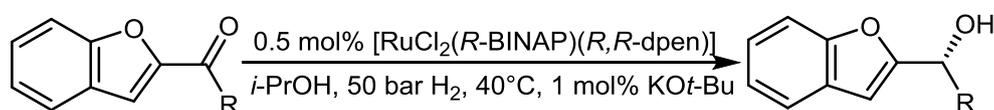
Table 2.15: Asymmetric hydrogenation of various benzofuran-2-yl ketones using a ruthenium transfer hydrogenation catalyst.

These results showed that good selectivity can be achieved with a range of other *para* substituted substrates using the transfer hydrogenation catalyst. Unfortunately the *ortho* substituted benzofurans give poor conversions with little alcohol products observed after the reaction. The reactivity of the *ortho* substrates was predicted to be lower but the yields observed were disappointing.

The hypothesis that the selectivity of the [RuCl(cymene)]₂ complex is based on the electronic interactions between the metal complex and the substrate is supported when comparing the selectivity of entry 2 and 3. The *para*-trifluoromethyl substituent is a strong electron withdrawing group, and leads to the highest selectivity, whereas the electron donating group (*para*-methoxy) gives the lowest selectivity. The selectivity of the arene- metal complex is postulated to be due to the CH/π interaction by Noyori and co-workers⁷ and supported by experimental evidence.⁸ The CH/π edge/ face interaction arises between the arene C-H of the catalyst and π system of the substrate. The π in most cases needs to be an aryl group, but

work by Wills and co-workers⁸ has also demonstrated the phenomena in unsaturated carbocycle groups. Presumably the reason for increased selectivity for electron deficient *para*-trifluoromethyl substrates is due to a larger energy difference between transition states, favouring CH/ π interaction between the electron rich benzofuran substituent, leading to higher selectivity.

The pressure hydrogenation of these substrates was also of interest. This was especially the case with the *ortho* substituted compounds which in theory should give a good selectivity due to the high steric bulk surrounding the carbonyl group. It was also hoped that the *ortho* substrate would be more reactive under pressure hydrogenation conditions.



R= 4-(Cl)C₆H₄ (**2.39**)
 4-(MeO)C₆H₄ (**2.56**)
 4-(CF₃)C₆H₄ (**2.57**)
 2-(Me)C₆H₄ (**2.51**)
 2-(EtO)C₆H₄ (**2.52**)
 2-(CF₃)C₆H₄ (**2.55**)

R= 4-(Cl)C₆H₄ (**2.39a**)
 4-(MeO)C₆H₄ (**2.56a**)
 4-(CF₃)C₆H₄ (**2.57a**)
 2-(Me)C₆H₄ (**2.51a**)
 2-(EtO)C₆H₄ (**2.52a**)
 2-(CF₃)C₆H₄ (**2.55a**)

Entry	Substrate/ Product (R=)	Conversion (%)	ee (%)
1	4-(Cl)C ₆ H ₄	89	44
2	4-(MeO)C ₆ H ₄	>99	48
3	4-(CF ₃)C ₆ H ₄	83	42
4	2-(Me)C ₆ H ₄	>99	83
5	2-(EtO)C ₆ H ₄	>99	86
6	2-(CF ₃)C ₆ H ₄	77	81

Unless otherwise stated, the reactions were carried out using 0.5 mol% [RuCl₂(R-binap)(R,R-dpen)], 1 mol% KO_t-Bu as base, at 40 °C at an initial pressure of 50 bar using 0.45 mmol of substrate. Conversions were measured by NMR with the aid of an internal standard and selectivity was determined using HPLC (see chapter 5, for details).

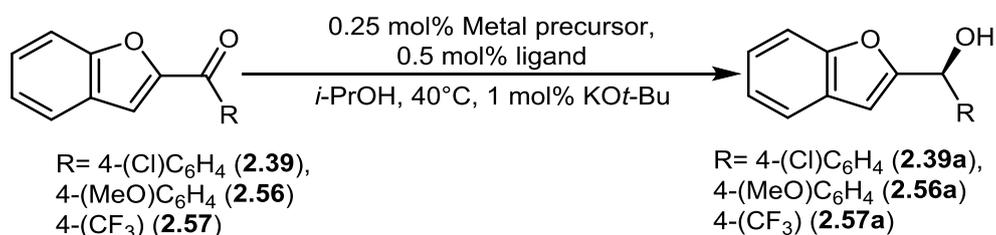
Table 2.16: Asymmetric hydrogenation of a range of benzofuran ketones using a ruthenium pressure hydrogenation catalyst.

From the results summarised in Table 2.16, it is observed that the conversion to alcohol product was increased with most substrates compared with the transfer hydrogenation catalysts (Table 2.15), except the *para*-tri fluoromethyl substrate, which gave lower yields. The selectivity of the hydrogenation reaction showed lower selectivity than transfer

hydrogenation of the *para* substituted substrates, although only marginally in the case of the methoxy substrate.

The substrates with the *ortho* substituents showed much higher selectivity, in the 80% range. This confirms the hypothesis that the selectivity of the pressure hydrogenation [RuCl₂(diphosphine)(diamine)] type complexes is due to steric interactions and there is a reduced electronic factor compared to the transfer hydrogenation with the [RuCl(cymene)(diamine)] catalysts.

Further investigation into the transfer hydrogenation catalysts was carried out and shown in Table 2.17, with a screen performed of a number of different metal precursors and ligands, including the [RhCp*Cl₂] system that has been used industrially.^{11,12}



Entry	Substrate/ Product (R=)	Metal precursor	Ligand	Conv (%)	ee (%)
1	4-(Cl)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>S,S</i>)-tosyl dpen	73	64
2	4-(MeO)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>S,S</i>)-tosyl dpen	46	55
3	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>S,S</i>)-tosyl dpen	>99	69
4	4-(Cl)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>S,S</i>)-tosyl dpen	86	59
5	4-(MeO)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>S,S</i>)-tosyl dpen	71	32
6	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>S,S</i>)-tosyl dpen	20	64
7	4-(Cl)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>R,S</i>)-Aminoindanol	95	33
8	4-(MeO)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>R,S</i>)-Aminoindanol	87	26
9	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>R,S</i>)-Aminoindanol	>99	42
10	4-(Cl)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>R,S</i>)-Aminoindanol	89	30
11	4-(MeO)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>R,S</i>)-Aminoindanol	59	29
12	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>R,S</i>)-Aminoindanol	98	57
13	4-(Cl)C ₆ H ₄	[RhCl ₂ (Cp*)] ₂	(<i>R,S</i>)-Aminoindanol	>99	47
14	4-(MeO)C ₆ H ₄	[RhCl ₂ (Cp*)] ₂	(<i>R,S</i>)-Aminoindanol	>99	28
15	4-(CF ₃)C ₆ H ₄	[RhCl ₂ (Cp*)] ₂	(<i>R,S</i>)-Aminoindanol	>99	55

Unless otherwise stated, the reactions were carried out using 0.25 mol% [RuCl₂(cymene)]₂, 0.5 mol% (*S,S*)-tosyl dpen, 1 mol% KO*t*-Bu as base, at 40 °C at an initial pressure of 50 bar using 0.45 mmol of substrate. Conversions were measured by NMR with the aid of an internal standard and selectivity was determined using HPLC (see chapter 5, for details).

Table 2.17: Asymmetric hydrogenation of a range of benzofuranyl ketones using various transfer hydrogenation catalysts.

The catalyst screen showed very promising results. Catalyst activity could be improved with the use of (*R,S*)-aminoindanol over (*S,S*)-Ts DPEN. The combination of a rhodium precursor ($[\text{RhCl}(\text{Cp}^*)]_2$) and (*R,S*)-aminoindanol, resulted in the highest conversions achieved with quantitative conversions for all of the three substrates. The same electronic effect on selectivity was observed with all the catalysts tested, although this was more pronounced in certain cases (see entry 5 and 6, table 2.17).

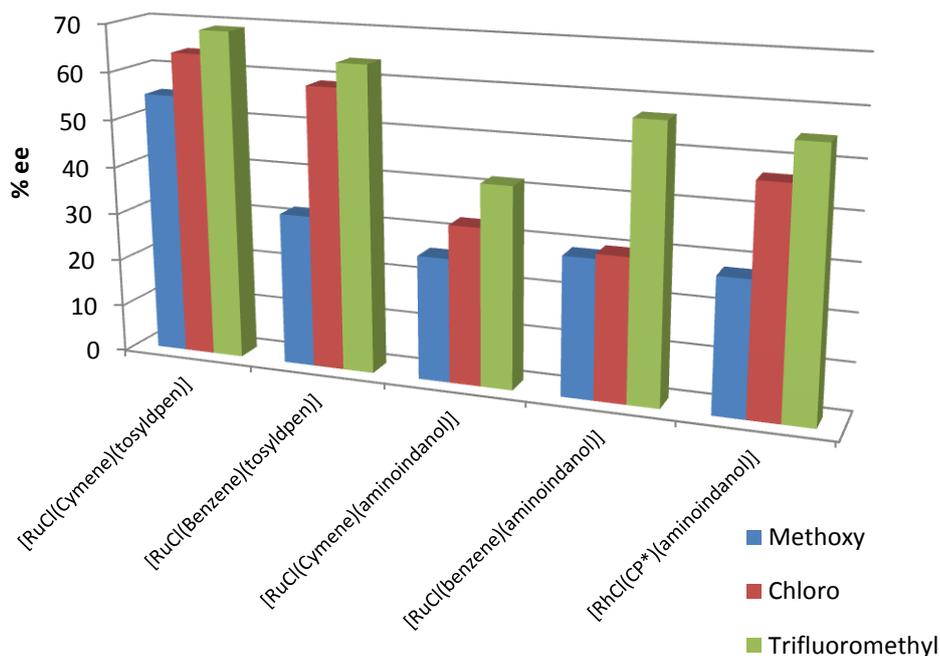
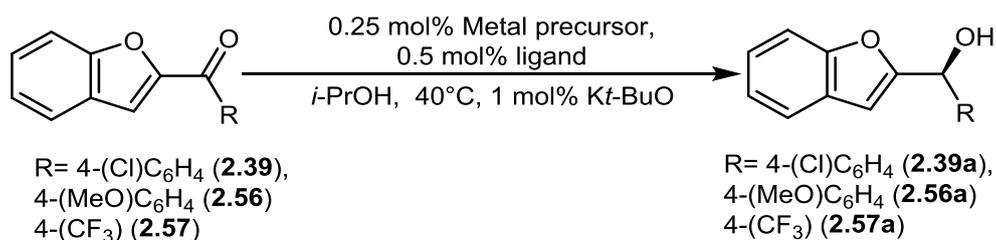


Figure 2.6: A graph demonstrating the trend in selectivity with respect to electronic substituents of the substrate.

The graph above in Figure 2.6 clearly shows the following order of enantioselectivity with all transfer hydrogenation catalyst used;



This is in agreement with the electronegativity of the substrates and supports the hypothesis of electronic control of the selectivity in transfer hydrogenations. As greater activity (particularly with the rhodium complex) was achieved using these new catalysts, it was decided to test the ortho substituted substrates further. The rhodium catalyst was particularly promising in terms of activity.



Entry	Substrate/ Product (R=)	Metal precursor	Ligand	Conv (%)	ee (%)
1	4-(Cl)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>S,S</i>)-tosyl dpen	0	ND
2	4-(MeO)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>S,S</i>)-tosyl dpen	7	ND
3	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>S,S</i>)-tosyl dpen	2	ND
4	4-(Cl)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>S,S</i>)-tosyl dpen	0	ND
5	4-(MeO)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>S,S</i>)-tosyl dpen	28	58
6	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>S,S</i>)-tosyl dpen	12	52
7	4-(Cl)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>R,S</i>)-Aminoindanol	17	73
8	4-(MeO)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>R,S</i>)-Aminoindanol	20	61
9	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (Cymene)] ₂	(<i>R,S</i>)-Aminoindanol	36	53
10	4-(Cl)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>R,S</i>)-Aminoindanol	87	87
11	4-(MeO)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>R,S</i>)-Aminoindanol	32	47
12	4-(CF ₃)C ₆ H ₄	[RuCl ₂ (benzene)] ₂	(<i>R,S</i>)-Aminoindanol	16	25
13	4-(Cl)C ₆ H ₄	[RhCl ₂ (Cp*)] ₂	(<i>R,S</i>)-Aminoindanol	>99	74
14	4-(MeO)C ₆ H ₄	[RhCl ₂ (Cp*)] ₂	(<i>R,S</i>)-Aminoindanol	66 ^a	45
15	4-(CF ₃)C ₆ H ₄	[RhCl ₂ (Cp*)] ₂	(<i>R,S</i>)-Aminoindanol	75	76

Unless otherwise stated, the reactions were carried out using 0.25 mol% [RuCl₂(cymene)]₂, 0.5 mol% (*S,S*)-tosyl dpen, 1 mol% *Kt*-BuO as base, at 40 °C at an initial pressure of 50 bar using 0.45 mmol of substrate. Conversions were measured by NMR with the aid of an internal standard and selectivity was determined using HPLC (see chapter 5, for details). ^a, >99% conversion and 45% ee achieved with 1 mol% catalyst.

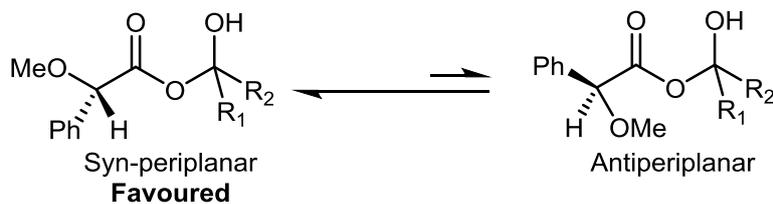
Table 2.18: Asymmetric hydrogenation of an array of substituted benzofuranyl ketones using a range of transfer hydrogenation catalysts.

The results summarised in Table 2.18 show that the *ortho* substituted substrates again reacted sluggishly with low conversions to product generally achieved. The rhodium catalyst was the exception, with high conversions and high selectivity achieved. The most challenging substrate both in terms of reactivity and selectivity proved to be the *ortho* ethoxy substrate. The low reactivity observed is probably due to the excess steric hindrance caused by the ethyl chain.

2.7. Determination of Absolute Stereochemistry.

The absolute configuration of the benzofuranyl alcohols formed in the hydrogenations was assigned by NMR experiments. There is literature precedent¹³ for the determination of secondary alcohols by NMR using enantiopure methoxyphenylacetic acid (MPA). The ester

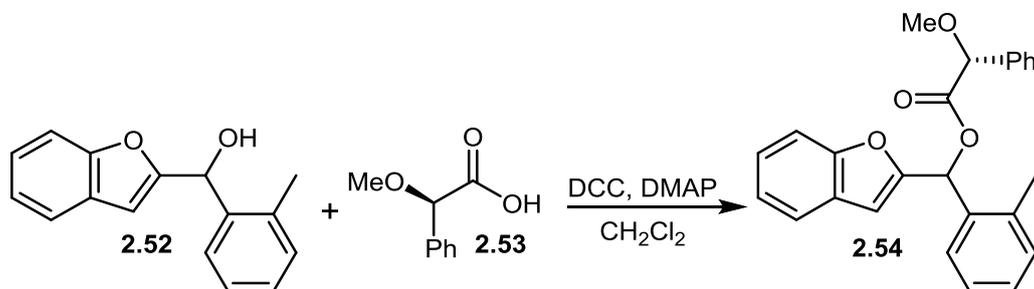
formed from secondary alcohols and MPA (using DCC and DMAP in CH_2Cl_2), is favoured towards one conformation (*syn*-periplanar) in solution, as illustrated in Scheme 2.14.



Scheme 2.14: The major conformers of MPA esters.¹³

As the ester exists predominately as the *syn*-periplanar isomer in solution, shielding effects from the π system of the phenyl groups can be observed with certain diastereotopic protons. By comparing the NMR of the esters formed from racemic and enantioenriched alcohol products it is often possible to determine the absolute configuration of an alcohol product.

The *ortho*-tolyl substrate was chosen as a representative alcohol to undergo the esterification, mainly as the substrate gave one the highest selectivities in the ketone hydrogenation, but also as the CH_3 proton would be clearly identifiable in the crude NMR. The enantioenriched alcohol was produced using $[\text{RuCl}_2((R)\text{-BINAP})((R,R)\text{-DPEN})]$ as a catalyst with an enantiomeric excess of 86%. The esterification of which is shown in Scheme 2.15.



Scheme 2.15: Determination of the absolute configuration of benzofuranyl secondary alcohols.

The crude NMR of the reaction had two areas of interest. Firstly the tolyl proton gave a clear peak in the 2-3 ppm region and also the proton for the benzofuranyl olefinic bond, which also gave a clear peak at 6-7 ppm. These clear peaks in the racemic sample gave two peaks with a 50:50 ratio. When you compare the enantioenriched sample with the racemic, it is clear to see

that the prominent tolyl group of the major isomer is downfield (i.e. not shielded by the phenyl group). This observation is confirmed by the benzofuranyl proton, where the predominant peak is upfield, therefore shielded by the phenyl group of the MPA, as shown in Figure 2.7.

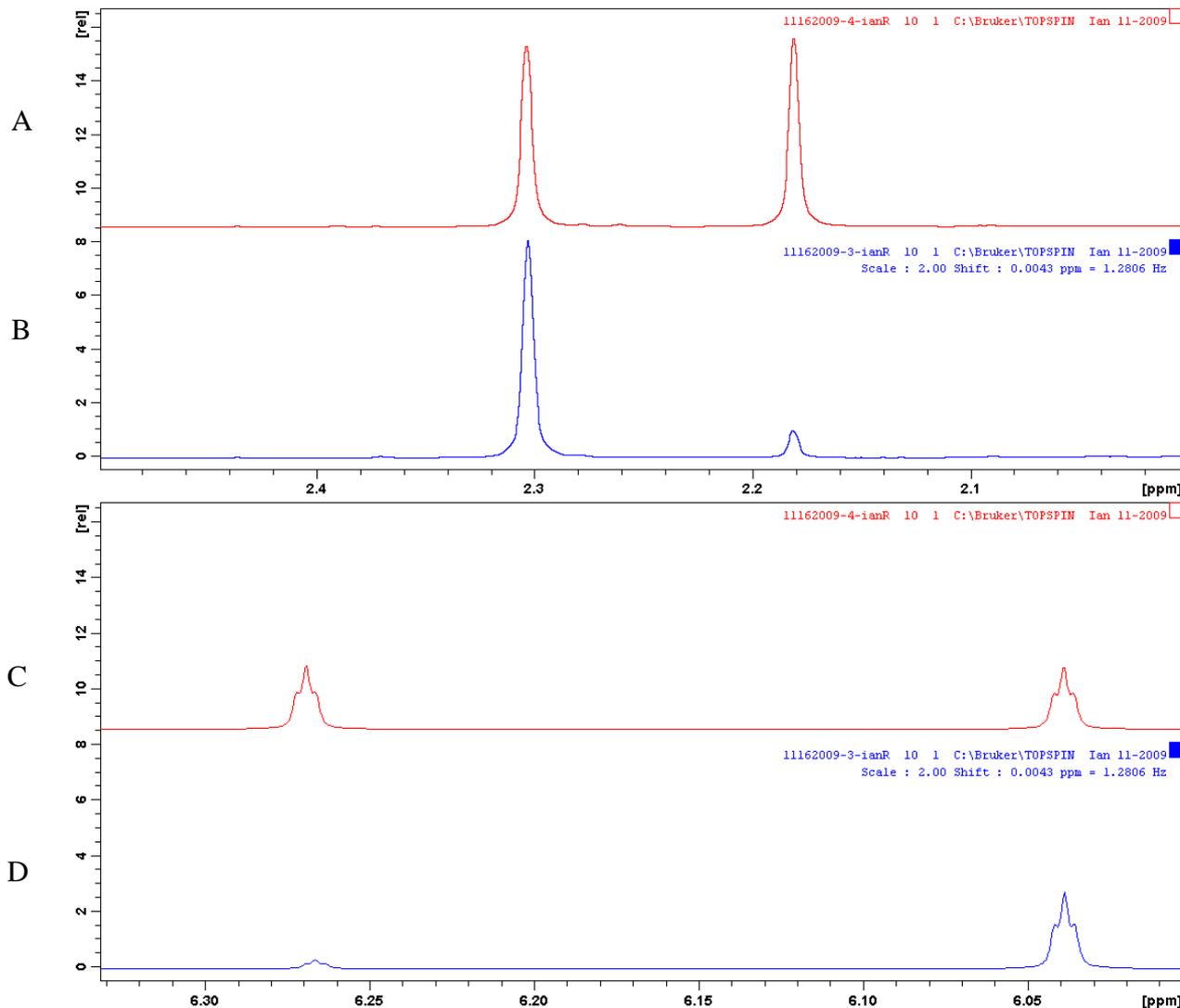
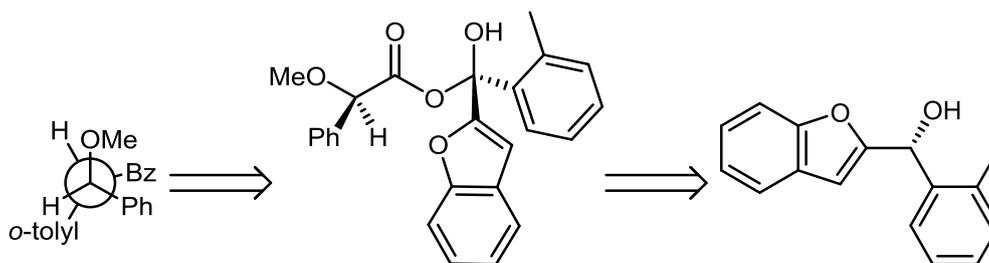


Figure 2.7: Expanded NMR's of the ester formed from (*R*)-MPA. The racemic (A+C) and enantioenriched (B+D) alcohol synthesised from the reduction of 2-(*o*-methylbenzoyl)benzofuran. A+B shows the tolyl protons and C+D shows the benzofuranyl olefinic protons.

From these observations the structure of the syn-periplanar ester can be determined, and from that structure the absolute stereochemistry of the alcohol can be assigned, as illustrated in Scheme 2.16



Scheme 2.16: Determining the absolute configuration of benzofuranyl secondary alcohols.

The absolute stereochemistry of the *ortho* tolyl substrate was assigned as the *R* enantiomer. The [RhCl(Cp*)(1*R*,2*S*)aminoindanol] gave the opposite enantiomer product (determined by comparison of the sign of the optical rotation and HPLC data).

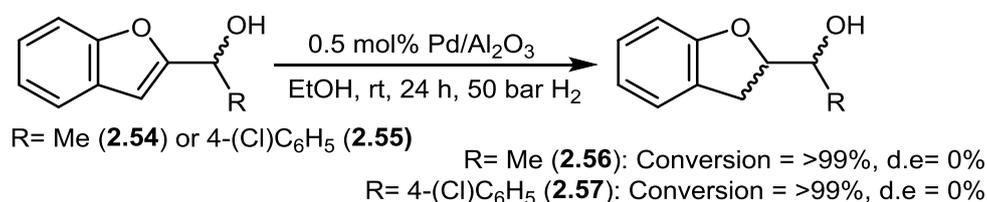
Since it is reasonable to assume the catalyst will show the same sense of enantioselection for what are very similar substrates, and since these all gave the same sign of optical rotation, then we assign [RuCl₂((*R*)-BINAP)((*R*,*R*)-DPEN)] to give *R* products and [RhCl(Cp*)(*R*,*S*)aminoindanol] giving *S* products. The trifluoromethyl substituted compounds gave the opposite sign of optical rotation than to the other product. To confirm the absolute stereochemistry of these products, the same esterification was carried out and the results showed that the product of the transfer hydrogenation of *para*-trifluoromethyl substrate using the [RhCl(Cp*)(*R*,*S*)aminoindanol] catalyst does give the expected (*S*)-enantiomer even though the sign of the optical rotations was reversed.

The investigation into the different phenyl substituted benzofurans, proved interesting with some thought provoking challenges that needed to be addressed. The challenges were greater as this type of aryl-aryl ketones had not been previously hydrogenated in the literature.

Despite this, the initial goal of this part of the project was successfully achieved, with the ability to produce a variety of benzofuran compounds with enantioenriched, secondary alcohol side chains. If the right catalyst/ substrate combinations are used, alcohols can be produced in high conversion and selectivity. Due to this it was decided to proceed with the next step, to attempt the diastereoselective hydrogenation of the benzofuran olefinic bond.

2.8. Attempted Diastereoselective Hydrogenation

The diastereoselective hydrogenation of substituted benzofurans was attempted using heterogeneous catalysis. The catalyst chosen in initial screening was palladium on alumina, as it gave the higher conversions to product when compared with palladium on carbon. The reaction needed to be kept at room temperature otherwise unwanted by-products were formed, due to the unselective nature of the catalyst. It was decided to start with optimising the conditions with racemic product, as the diastereoselectivity would still be observed, and the starting materials would be easier to synthesis in the amounts required to optimise the conditions. The two commercially available benzofurans were reduced using sodium borohydride to produce the racemic benzofuranyl alcohols that were tested under the conditions shown below in Scheme 2.17.



Scheme 2.17: Attempted diastereoselective heterogeneous hydrogenation of racemic benzofuranyl secondary alcohols.

In both cases the required product was observed in the NMR, with no starting material observed after 24 hours. Unfortunately the products of the reactions had an even mix of diastereomers in both cases.

A number of protecting groups were added to the alcohol such a silane, acetyl, and benzyl group. It was thought that increasing the size or type of the substituents would possibly lead to a selective reaction, but again no selectivity was observed.

2.9. Conclusions

Initial experiments showed that benzofuran can be hydrogenated with high conversions using rhodium based catalysts, with MeTHF is used as a solvent. Unfortunately the same catalysts are no longer active if the benzofuran is substituted, even with the relatively simple substrates.

Para substituted aryl-benzofuranyl ketones have selectivity issues when the hydrogenation is carried out with conventional pressure hydrogenation catalysts. This problem can be solved with the use of transfer hydrogenation catalysts, which have a different mode of initiating selectivity, and appear to be able to differentiate between the very similar phenyl and benzofuranyl groups, especially when electron withdrawing groups are present on the phenyl group. Transfer hydrogenation catalysts have their own complications; ruthenium transfer hydrogenation catalysts show poor reactivity. This can be overcome with the use of rhodium catalysts instead, that results in significantly improve the conversions. With the careful selection of catalyst, it has been demonstrated that a range of different aryl-benzofuranyl ketones can be hydrogenated in high selectivity and conversion. Pressure hydrogenation catalysts should be used for substrates with large substituents surrounding the carbonyl group. If that is not the case then the best choice is to use a transfer hydrogenation catalyst, of which $[\text{RhCl}(\text{Cp}^*)((R,S)\text{-aminoindanol})]$ is the most reactive catalyst tested. The selectivity of the transfer hydrogenation catalysts can be increased if there is a large difference in electron density between the two aryl groups.

The absolute chemistry of the alcohol products formed could be determined with NMR experiments using a facile formation of diastereomeric esters

Enantioenriched samples of a number of different benzofuranyl compounds were produced, although it was not possible to carry out a diastereoselective heterogeneous hydrogenation of the benzofuranyl olefinic bond.

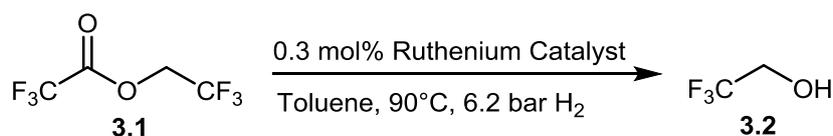
2.10. References

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III. CHAPTER III: EXPLORING THE USE OF RUTHENIUM CATALYSTS IN THE HYDROGENATION OF ESTERS.

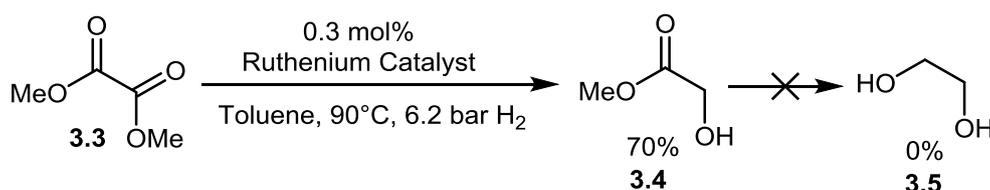
3.1. Catalytic Ester Hydrogenation.

The hydrogenation of esters is often performed using metal hydrides in stoichiometric amounts, for example lithium aluminium hydrides. These reagents have significant disadvantages, such as creating large quantities of waste by-products. At best the process requires the use of a stoichiometric reducing agent and commonly the use of an excess is needed, which only increases the waste and clean up required. These factors have relatively little effect in small scale laboratory reactions as the cost and time lost is small. If you extrapolate these factors to an industrial setting, the economic and environmental costs start to become major concerns and may make it unviable. A potentially more efficient method for the hydrogenation of esters is to use a catalytic process. Heterogeneous catalysts are widely used on a commercial scale for ester hydrogenation. These catalytic processes have advantages over the use of hydride reagents as they produce very little waste products, and are cheap to run since the catalysts can be used in sub-stoichiometric amounts. Unfortunately heterogeneous catalysts have limited use, as they will often hydrogenate other unsaturated moieties within the substrate molecule. This is particularly relevant in the case of the ester functionality as it is a relatively stable moiety, and means only relatively simple esters can be reduced successfully using this approach. Catalytic homogenous hydrogenation methodologies potentially have advantages over both metal hydrides and heterogeneous catalysts, where a catalyst can be used at sub-stoichiometric amounts and can reduce the ester functionality selectively. Until recently such catalysts required high temperatures and pressures, and often only hydrogenated activated substrates. For example, Grey *et. al.*¹ demonstrated one of the first attempts of the hydrogenation of esters using a ruthenium hydride species, and was able to hydrogenate the highly activated trifluoroethyl trifluoroacetate with quantitative conversion and 98% alcohol in 4 hours with 162 turnovers.



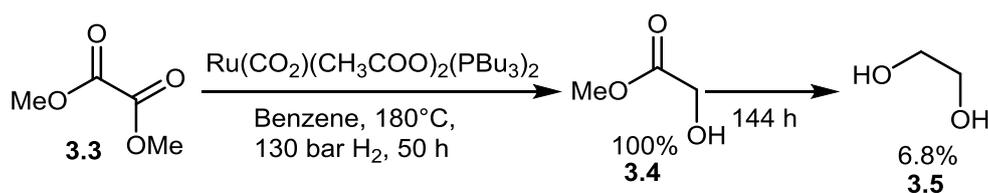
Scheme 3.1: Hydrogenation of trifluoroethyl trifluoroacetate¹

The requirement for an activating side chain is exemplified by Grey *et. al.*¹ with the hydrogenation of dimethyl oxalate. The oxalate is hydrogenated with the same ruthenium catalyst and conditions, although the reaction stops at the first hydrogenation to methyl glycolate (70% conversion, shown in Scheme 3.2) with no ethylene glycol was formed. The full hydrogenation to ethylene glycol is not possible due to electronic factors. Other esters were also tested under the same conditions, but with less success such as the unactivated methyl acetate which only gave a small conversion (22%).



Scheme 3.2: Hydrogenation of dimethyl oxalate¹

Scheme 3.3 shows works perform by Matteoli *et. al.*², who examined this reaction further in the presence of $[\text{Ru}(\text{CO}_2)(\text{CH}_3\text{COO})_2(\text{PBU}_3)_2]$ and was able to convert dimethyl oxalate to methyl glycolate quantitatively, although at high temperatures and pressures. Matteoli did observe a small amount (6.8% ethylene glycol, 93.2% methyl glycolate) of ethylene glycol formed but only after 6 days. Higher amounts of ethylene glycol (26.7%) could be formed by the use of methanol as a solvent instead of benzene.



Scheme 3.3: Hydrogenation of dimethyl oxalate²

Other alkyl oxalates have also been tested under the same conditions and left to react for 6 days, with the general trend that longer chain esters are less reactive. The only ester to produce ethylene glycol in the reaction was the dimethyl oxalate (see Table 3.1).

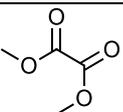
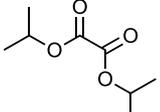
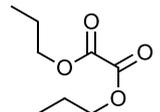
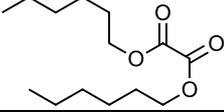
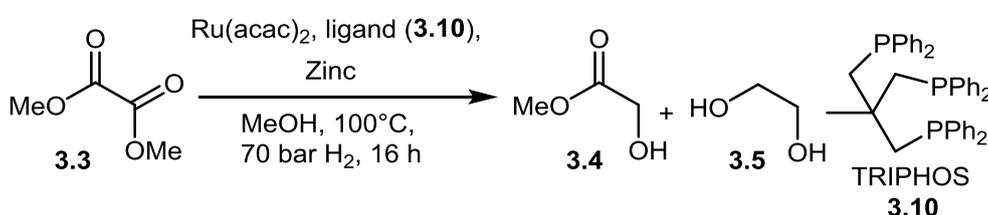
Entry	Substrate	Conversion (%)	Glycolate (%)	Ethylene glycol (%)
1 (3.6)		100	93.2	6.8
2 (3.7)		100	100	0
3 (3.8)		93.7	100	0
4 (3.9)		69.7	100	0

Table 3.1: Hydrogenation of oxalate esters²

An investigation into different ligands for this reaction by Elsevier and co-workers showed that the reaction could be performed under milder conditions using the tridentate TRIPHOS ligand, as described in Table 3.2.³ Mono and bidentate ligands show less activity for the hydrogenation of dimethyl oxalate, and only give the methyl glycolate product. The tridentate TRIPHOS ligand gives complete conversion and 95% ethylene glycol.



Entry	Ligand	Conversion (%)	Glycolate (%)	Ethylene glycol (%)
1	None	18	2	0
2	PPh ₃	73	36	0
3	dppe	18	11	0
4	TRIPHOS	100	1	95
5	[CH ₂ P(Ph)C ₂ H ₄ PPh ₂] ₂	91	85	0

Table 3.2: Hydrogenation of dimethyl oxalate with a variety of ligands³

Elsevier and co-workers, in a subsequent paper^{4,5} described the hydrogenation of other even less reactive species such as dimethyl phthalate (DMP), benzyl benzoate (BZB), dimethyl maleate (DMM) and methyl palmitate (MP), with good yields and reaction rates, although the use of larger amounts of additives was required and very specific solvents. Use of high

temperatures and pressures are required for reactivity. The ligands and results are shown in Figure 3.1 and Table 3.3.

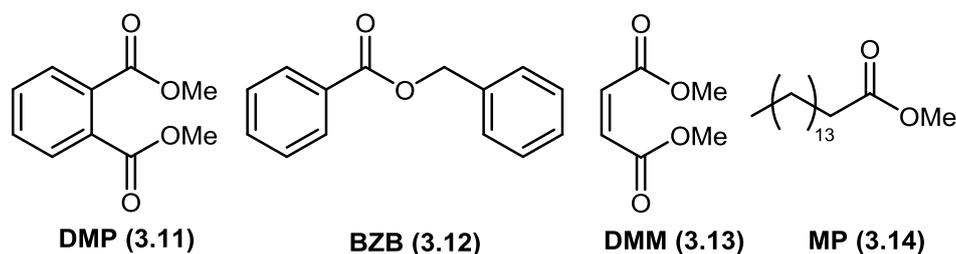
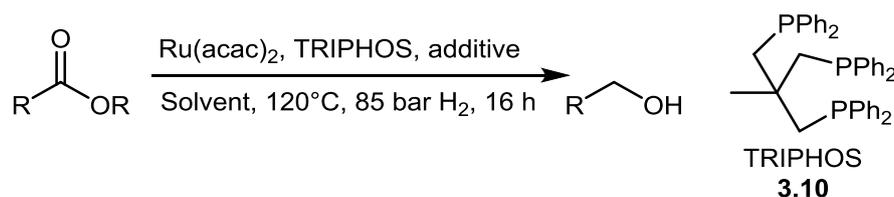


Figure 3.1: A range of ester substrates



Entry	Ester	Solvent	Additive	Conversion (%)	Yield (%)
1	DMP (3.11)	<i>i</i> -PrOH	HBF ₄	100	78(18 ^a)
2	BZB (3.12)	FIPA	NEt ₃	97	95
3	BZB (3.12)	TFE	NEt ₃	65	53
4	DMM (3.13)	FIPA	NEt ₃	100	100 ^b
5	MP (3.14)	FIPA	NEt ₃	94	94

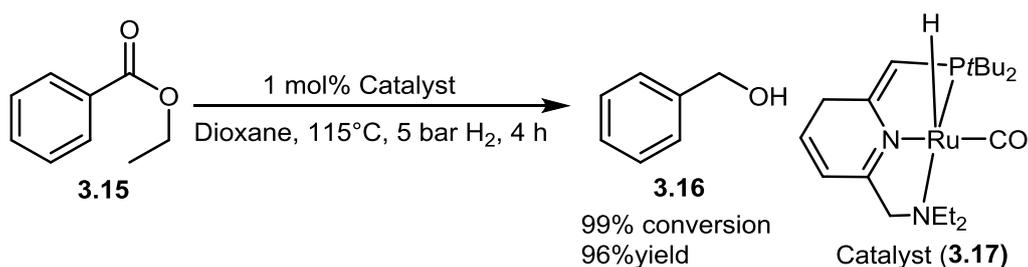
^a= The number in brackets corresponds to the amount of phthalide produced in the reaction.

^b= The fully reduced butane-1,4-diol is obtained as the product.

Table 3.3: Hydrogenation of a range of esters^{4,5}

The dimethyl phthalate (**3.11**) reaction produces a significant amount of the product from the initial first hydrogenation to phthalide. This is due to the same effect as is in dimethyl oxalate hydrogenation, as there is no longer an electron withdrawing functionality to the molecule, the second hydrogenation is much more difficult. The hydrogenation of dimethyl maleate is not chemoselective, with the fully reduced butane-1,4-diol produced as the product (entry 4, Table 3.3). It is proposed that the use of 1,1,1,3,3,3-hexafluoropropan-2-ol (FIPA) for the hydrogenation of the other substrates is required due to an initial transesterification, which produces a compound that is much more readily hydrogenated due to the electron withdrawing nature of the fluorinated alcohol (*cf* yields of entry 2 and 3).

More recent advances in the field have looked at unactivated esters trying to reduce the harsh conditions required to attempt to make it a more viable reaction. They have also exploited the apparent trend shown by Elsevier that the use of tridentate ligands is required for good activity. Milstein and co-workers⁶ demonstrated the use of a ruthenium complex formed from a deprotonated “pincer” PNN ligand. The PNN catalyst was able to hydrogenate simple unactivated esters readily, albeit without additives still at over 100°C. This is shown below in Scheme 3.3.



Scheme 3.3: Hydrogenation of an unactivated ester⁶

Saudan et al.,⁷ working at Firmenich, have patented the use of Noyori [RuCl₂(BINAP)(DPEN)] type catalysts for the hydrogenation of esters with good reactivities. Saudan also demonstrated a number of different catalysts were active in the ester hydrogenation as illustrated below in the hydrogenation of methyl benzoate, summarised below in Figure 3.2.⁷

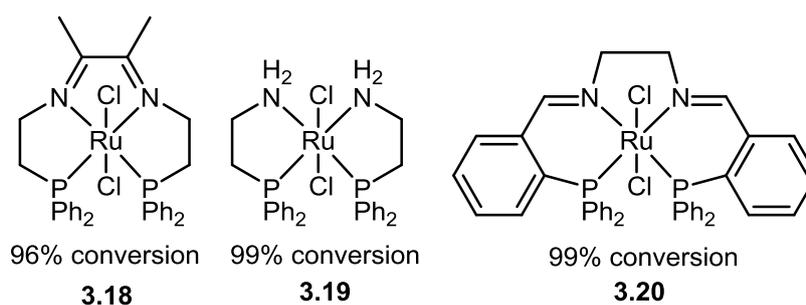


Figure 3.2: Different catalysts used in the hydrogenation of methyl benzoate. (0.05 mol% catalyst, 5 mol% NaOMe, THF, 50 bar H₂, 100°C, 1 hr).⁷

The catalysts in Figure 3.2 are active, as long as high amounts of base (5 mol%, base:catalyst 100:1) are used as co-catalyst and can be used in the hydrogenation of a range of substrates,

highlighted below in Figure 3.3. Even the selective hydrogenation of esters containing alkenes substituents gave high amounts of the unsaturated alcohol products and alkyl esters.

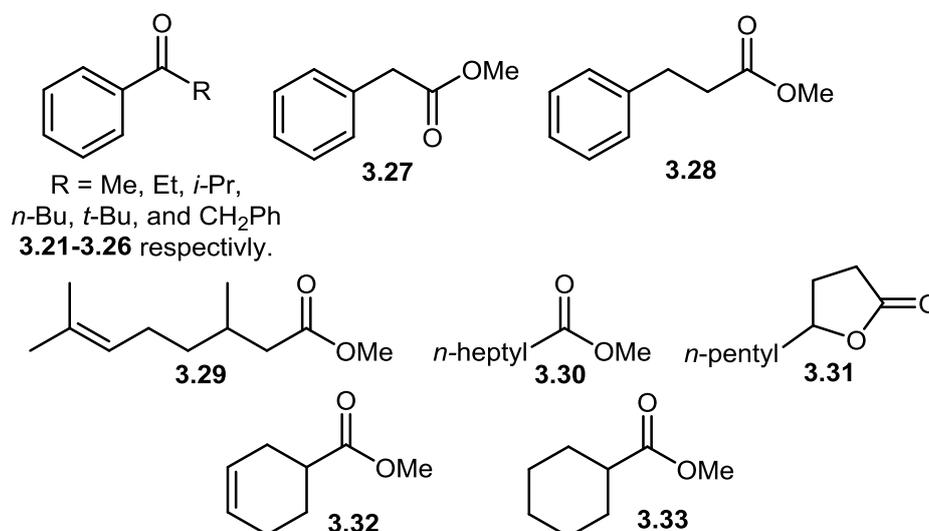
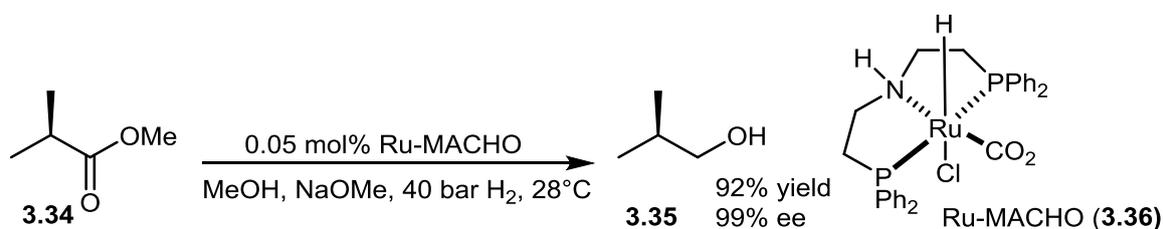


Figure 3.3: Substrates hydrogenated by Saudan et al., using the catalysts shown in the previous Figure 3.2, all giving yield >80% and often above 90%.⁷

Kuriyama et. al., working at Takasago in Japan has recently demonstrated the use of ruthenium PNP complex in the hydrogenation of a variety of esters, including a large scale multi ton ester hydrogenation at low reaction temperatures, shown below in Scheme 3.4.⁸



Scheme 3.4: Large scale hydrogenation of a chiral ester⁸

The industrially viable reaction proceeds to completion after 12 hours and after purification an excellent 92% yield is achieved with a total of 1.5 metric tons per batch of 1,2-propanediol produced. The catalyst system shows good compatibility with chiral substrates as only a minor racemation was observed (starting material = 99.6% ee).

Other recent work at Takasago show/ [Ru(diphosphine)(diamine)] type complexes that utilise DPPP and (*R,R*)-DPEN ([Ru(H)(η¹-BH₄)(DPPP)(DPEN)] to hydrogenate simple esters such as methyl benzoate with high conversions at 80°C.⁹

Clarke and Daiz¹⁰ discovered a single example of a ruthenium tridentate PNN complex hydrogenated activated esters such as methyl heptafluorobutanoate, with high conversion but under forcing conditions. Aromatic esters gave low conversions even at 160°C. These reactions used base/ catalyst ratios of 2:1, since this was found to be ideal in asymmetric ketone hydrogenation.

Recent developments highlighted here, particularly using large base/ catalyst ratios suggest that [RuCl₂(diphosphine)(diamine)] and ruthenium tridentate ligands are both classes of catalyst to investigate further.

3.2 Aims

The original aim of the work described in this chapter was to develop and expand on a procedure for the *in situ* synthesis of [RuCl₂(diphosphine)(diamine)] complexes to allow for a facile and efficient screen of various complexes for the hydrogenation of esters.

Once a method was optimised for the synthesis of *in situ* ruthenium complexes, a screen of various diphosphine and diamine ligands was planned to probe the reaction and develop an understanding of the properties required for an efficient ligand or catalyst.

A second aim of the project to investigate the ruthenium/ tridentate catalysts developed in the Clarke group for ketone hydrogenation, for ester hydrogenation. The use of significant quantities of a basic co-catalyst and a broader range of catalysts now available was hoped to deliver a fully active catalyst.

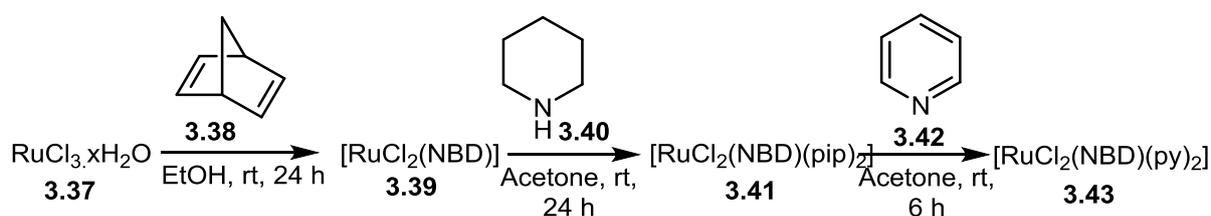
3.3 Screen of Diphosphine/Diamine Ruthenium Complexes:

Researchers such as Saudan⁷ and Kuriyama⁸ have demonstrated the use of [RuCl₂(BINAP)(DPEN)] and [Ru(H)(η¹-BH₄)(DPPP)(DPEN)] in the hydrogenation of esters. A wide screen of diphosphines was not reported, so it was decided to perform a screen of a range of different [RuCl₂(diphosphine)(diamine)] complexes in this reaction with the aim to discover improved catalysts.

Within the research group, a method was discovered in which [RuCl₂(diphosphine)(diamine)] ligands could be prepared *in situ*. Using this method it was possible to make a library of catalysts of this type, that would usually be time consuming and expensive to produce.

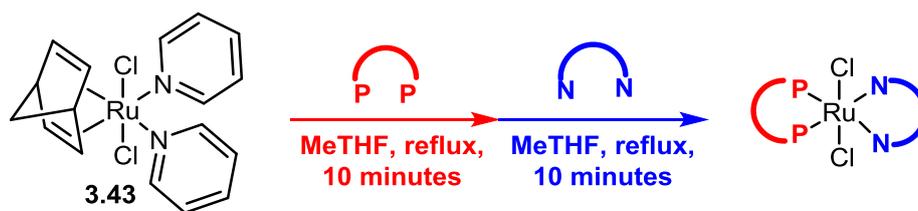
The initial procedure developed was a stepwise process in which you first take the ruthenium precursor [RuCl₂(norbornadiene)(pyridine)₂] and mix this with the required diphosphine in

dichloromethane. The mixture was heated with the use of a microwave reactor for 15 mins or until all the all free diphosphine was consumed. The diamine was then added as a solution in dichloromethane and heated again under microwave heating for 15 mins. The solvent was then removed *in vacuo* and the substrate (methyl 4-fluorobenzoate) was added to the residue along with the reaction solvent, and then transferred to a autoclave and pressurised to 50 bar H₂ and heated to 100°C for 16 hours. The best solvent found in these initial screens was found to be MeTHF. The precursor [RuCl₂(norbornadiene)(pyridine)₂] can easily be synthesised from ruthenium trichloride as shown below in Scheme 3.5.



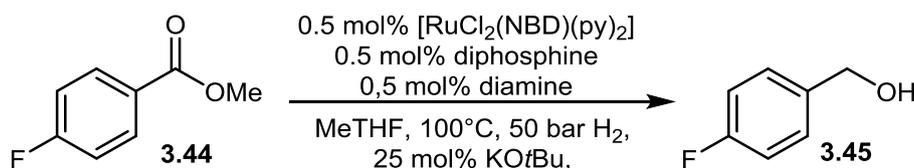
Scheme 3.5: Synthesis of the precursor [RuCl₂(norbornadiene)(pyridine)₂]

This *in situ* catalyst preparation process was relatively cumbersome and required additional evaporation stages after the catalyst preparation and the use of multiple solvents. The requirement to use a microwave is a potential downside when considering scaling up and also not all research groups has access to microwave which would limit the procedure's viability for other researchers. The starting point for this project was to refine the process and simplify it to use one solvent throughout. This would reduce the need for several time consuming evaporations, and give the option of using conventional glassware and heating. 2-methyltetrahydrofuran (MeTHF) was chosen as the ideal reaction solvent as the actual hydrogenation performed the best in this solvent. This solvent also has a significant advantage when compared to THF or CH₂Cl₂ as the boiling point is higher, so heating at reflux could be enough to drive the reaction. The new method summarised below in Scheme 3.6 was developed with these considerations taken into account. If desired the microwave method also gave similar results when MeTHF was used.



Scheme 3.6: *In situ* preparation of [RuCl₂(diphosphine)(diamine)] complex

The hydrogenation of methyl 4-fluorobenzoate, using the *in situ* generated [RuCl₂(BINAP)(DPEN)] complex (0.5 mol%), gave an initial result of 80% conversion after 16 hours at 100°C and 50 bar H₂. The *in situ* formation procedure was comparable to the previous procedure. It was decided to perform a ligand screen to try and probe the reaction to determine if new catalysts for the hydrogenation of esters could be developed. A combination of different diphosphines and diamines were tested, and the results are summarised in Table 3.4.



Entry	Diphosphine	Diamine	Product (%)	Conversion (%)	Other (%)
1	Rac-BINAP	(<i>R,R</i>)- DPEN	83	93	10
2	dppp	(<i>R,R</i>)- DPEN	99	100	1
3	dppe	(<i>R,R</i>)- DPEN	28	46	18
4	dppb	(<i>R,R</i>)- DPEN	44	62	18
5	dcypb	(<i>R,R</i>)- DPEN	10	32	22
6	dippf	(<i>R,R</i>)- DPEN	4	26	22
7	dppp	(<i>R,S</i>) Aminoindanol	1	17	16
8	dppp	2-(Methylthio)aniline	4	22	18
9	dppp	Ethylenediamine	48	70	21
10	dppp	Diaminopropane	2	25	23
11	dppp	1,2-Diaminobenzene	9	33	24
12	dppp	<i>N,N</i> -Dimethylethylenediamine	2	22	20
13	dppp	2,4-Diaminopyridine	2	25	23
14	dppp	(<i>R,R</i>)-Ts-DPEN	7	29	22
15	dppp	2-Picolylamine	96	100	4

The reactions were carried out using 0.5 mol% [Ru(Cl)₂(NBD)(Py)₂], 25 mol% KO^t-Bu as base at 100 °C at an initial pressure of 50 bar using 0.5 mmol of methyl 4-fluorobenzoate in 3 ml of Me-THF as solvent with a 16 hour reaction time. The catalysts were formed by pre-stirring the [Ru(Cl)₂(NBD)(Py)₂] precursor and the P-ligand for 10 mins at reflux, followed by the addition of the N-ligand and stirring for a further 10 mins.

Table 3.4: Summary of diphosphines used in the hydrogenation of methyl 4-fluorobenzoate catalyst screen

Initially a diphosphine screen was performed using (*R,R*)-DPEN as a control diamine as the Saudan patent showed it to be an effective ligand. This initial screen showed that racemic BINAP and dppp were the most effective ligands when combined with DPEN. All of the other ligands showed some performance, but were not worth developing further. The bite angle of BINAP and dppp are similar (93° and 91° respectively¹¹), which might account for the similar reactivity. When the conversion vs. bite angle data of selected ligands were plotted (BINAP, dppp, dppe, dppb, and dippf), there is an apparent trend with a maximum conversion reached at 91° for dppp, illustrated in Figure 3.4.

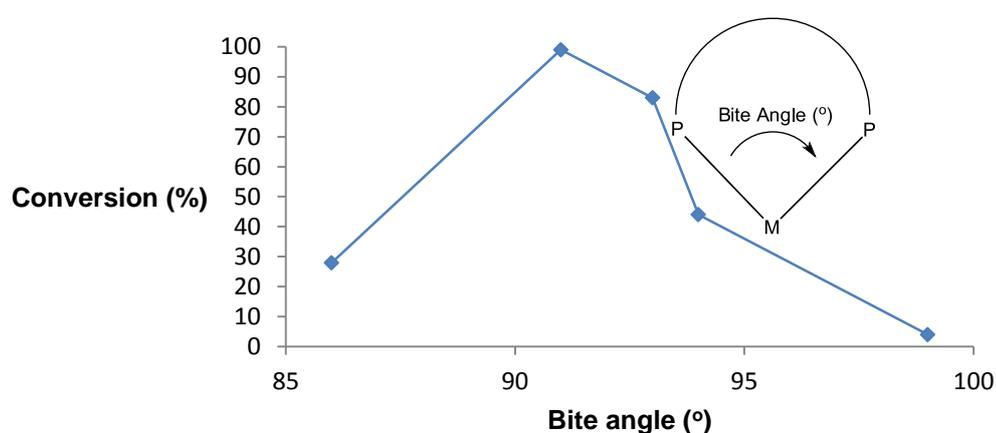


Figure 3.4: Graph of conversion vs. bite angle of representative diphosphine ligands in the hydrogenation of methyl 4-fluorobenzoate.

After the initial phosphine screen dppp was chosen as the ligand to develop the reaction further since this gave the highest conversion, and has the advantage of being a simple, cheap commercially available ligand.

Unfortunately the screen with various diamines was not particularly successful and only two diamines were found that gave good conversions, (*R,R*)-DPEN and 2-picoylamine (see Figure 3.5 for structures). The only other ligand that gave any appreciable conversion was ethylenediamine (but only 48% alcohol).

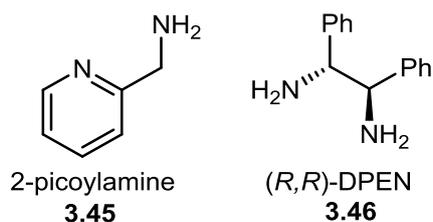


Figure 3.5: The best amine ligands found from the ligand screen

It has been shown in the literature that the hydrogenation of esters requires large amounts of basic additives (in this case potassium *tert* butoxide), for an efficient reaction to take place. It was important to probe this issue further and find the point in which the reactivity would diminish if the base concentration was decreased. The reason for this is very simple; if the reaction was to be scaled up, the benefits of even a small drop in additive used would have significant cost implications.

The catalyst loading was halved for the reaction so that any changes in reactivity that would occur from reducing the base concentration, could be examined. Some reactions at higher base concentration were also performed to see if there is a drop-off in reactivity caused from increased amounts of additive.

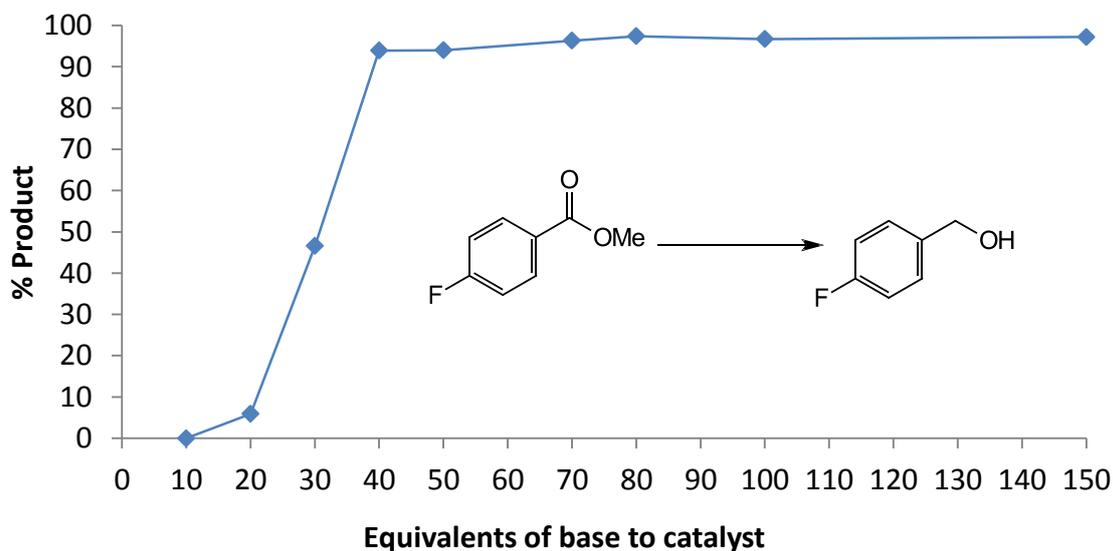


Figure 3.6: The effect of basic co-catalyst on reaction conversion. (Reaction performed using 0.4 mmol methyl 4-fluorobenzoate, 0.25 mol% in situ formed $[\text{RuCl}_2(\text{dppp})(R,R)\text{-DPEN}]$ and 1.25-18.8 mol% $\text{KO}t\text{-Bu}$ at 100°C and 50 bar H_2).

The results shown in Figure 3.6 show that the minimum amount of base required is 40 equivalents of $\text{KO}t\text{-Bu}$ to catalyst for an appreciable conversion to be achieved. A significant drop in conversion is shown when going to concentrations less than 40 equivalents, (at 30 equivalents 47% alcohol is observed and a further drop to 20 equivalents gives only 6% alcohol). Increasing the base concentration above 50 equivalents does not depreciate the

reaction at all and only gives a mild increase in conversion (94% alcohol at 50 eq and 97% at 150 eq).

3.4 The use of Ruthenium PNN and PNO Tridentate Complexes in the Hydrogenation of Esters.

Previous work in the Clarke group¹⁰ has shown that complex **3.47** (Figure 3.7) has some activity in ester hydrogenation, but using low base: catalyst ratios, that now seem an unwise choice for the hydrogenation of esters. Due to the results already described it was decided to investigate the use of these PNN type complexes further in the hydrogenation of esters, with higher amounts of co-catalyst.

Initially the original chiral diamine PNN (**3.47**)¹⁰ was tested with an increased base concentration, with good results obtained in the hydrogenation of methyl 4-fluorobenzoate. When tested over 16 hours at 100°C a 94% conversion to product was obtained. Due to this success it was decided to test a range of different PNX catalysts that have been synthesised within the Clarke group over the last decade, that have been reported as catalyst for the hydrogenation of ketones.^{10,12} A summary of the structures is shown below in Figure 3.7.

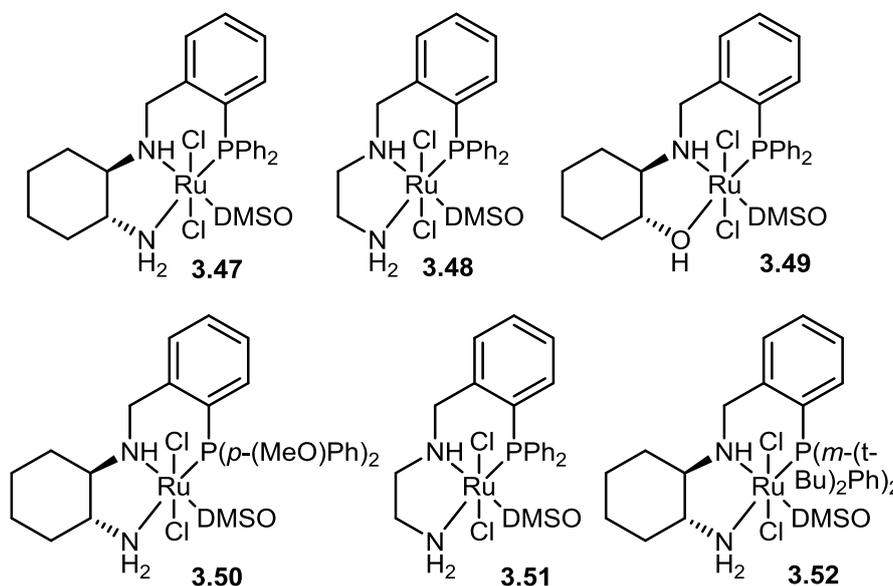
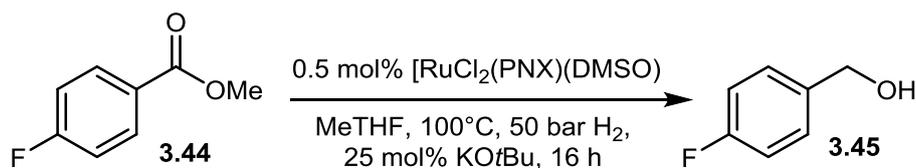


Figure 3.7: The range of $\text{RuCl}_2(\text{PNX})(\text{DMSO})$ complexes used.

The catalysts shown in Figure 3.7 were tested in the hydrogenation of methyl 4-fluorobenzoate, with a base/ catalyst ratio of 50:1, and the results are summarised below in Table 3.4.

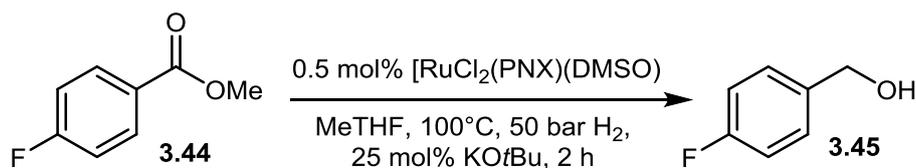


Entry	Catalyst	Temperature (°C)	Product (%)	Ester (%)
1	3.47	100	94	2
2	3.48	100	99	0
3	3.49	100	98	0
4	3.50	100	76	13
5	3.51	100	43	46
6	3.52	100	26	54
7	3.48	50	99	0

The reactions were carried out using 0.5 mol% $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$, KOtBu as base (50:1, base:catalyst) at 100 °C at an initial pressure of 50 bar using 0.5 mmol of methyl 4-fluorobenzoate in 3 ml of Me-THF.

Table 3.4: Hydrogenation of methyl 4-fluorobenzoate using $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ complexes

The best PNN ruthenium catalysts under the conditions tested appears to be the very simple PNN catalyst **3.48**, with the chiral PNN and PNO catalysts also giving very high conversions to product. Altering the phosphine substituents resulted in a drop in reactivity. The most severe case of this was with the *meta-tert*-butyl substituted catalyst **3.52**, which gave little product after 16 hours. Steric hindrance possibly has a very important role in the reactivity of the catalyst, as it is observed that increasing the steric hindrance on phosphine or even the backbone (cyclohexyl backbone) results in a drop in reactivity, although only very slightly in when you compare the catalysts **3.47** and **3.48** (table 3.4, entry 1+2). Catalyst **3.48** proved the most promising therefore this catalyst was also tested at 50°C and the same 99% yield in product was observed (table 3.4, entry 7). From these reactions three catalysts (**3.47**, **3.48** and **3.49**) were highlighted as the most promising so the reactivity of these catalysts were examined further. The catalysts were tested over a shorter time period, shown in Table 3.5.



Entry	Catalyst	Time (hrs)	Product (%)	Ester (%)
1	3.47	2	99	0
2	3.48	2	97	0
3	3.49	2	98	1

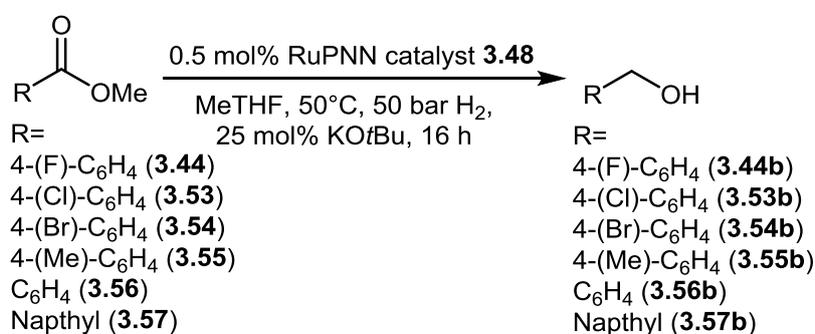
The reactions were carried out using 0.5 mol% [RuCl₂(PNX)(DMSO)], KO*t*-Bu as base (50:1, base:catalyst) at 100 °C at an initial pressure of 50 bar using 0.5 mmol of methyl 4-fluorobenzoate in 3 ml of Me-THF.

Table 3.5: Hydrogenation of methyl 4-fluorobenzoate over 2 hours

All three catalysts gave very similar results to the 16 hour experiments, with catalyst **3.47** giving the highest amount of alcohol product, as the other two catalysts gave higher amounts of other minor reaction by-products (~1-2%).

3.5 Investigation into the Substrate Scope of the [RuCl₂(PNN)(DMSO)].

A range of different substrates for ester hydrogenation were examined, these were mainly aromatic esters, the results of which are shown below in Table 3.6.



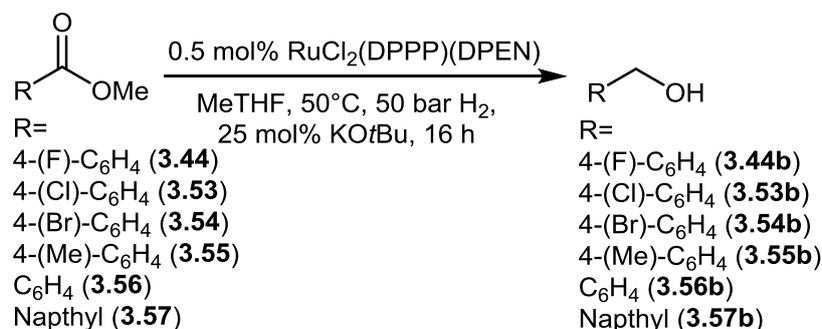
Entry	Substrate (R=)	Conversion (%)
1	4-(F)-C ₆ H ₄ (3.44)	99
2	4-(Cl)-C ₆ H ₄ (3.53)	>99
3	4-(Br)-C ₆ H ₄ (3.54)	>99
4	4-(Me)-C ₆ H ₄ (3.55)	>99
5	C ₆ H ₄ (3.56)	>99
6	Naphthyl (3.57)	>99

The reactions were carried out using 0.5 mol% [RuCl₂(PNN)(DMSO)] catalyst 3.48, KO*t*-Bu as base (50:1, base:catalyst) at 50 °C at an initial pressure of 50 bar using 0.5 mmol of methyl 4-fluorobenzoate in 3 ml of Me-THF.

Table 3.6: Substrate scope of the [RuCl₂(PNX)(DMSO)] complexes in ester hydrogenation

The results have shown that the catalyst system is successful and hydrogenates a range of aromatic esters even at relatively low reaction temperatures of 50°C and giving full conversion to product in 16 hours.

The same range of substrates was also tested using the *in situ* prepared [RuCl₂(dppp)(DPEN)] catalyst; the results of which are shown below in Table 3.7.



Entry	Substrate (R=)	Conversion/(yield) (%)
1	4-(F)-C ₆ H ₄ (3.44)	99 (97)
2	4-(Cl)-C ₆ H ₄ (3.53)	>99 (98)
3	4-(Br)-C ₆ H ₄ (3.54)	>99 (95)
4	4-(Me)-C ₆ H ₄ (3.55)	>99 (96)
5	C ₆ H ₄ (3.56)	>99 (97)
6	Naphthyl (3.57)	>99 (95)

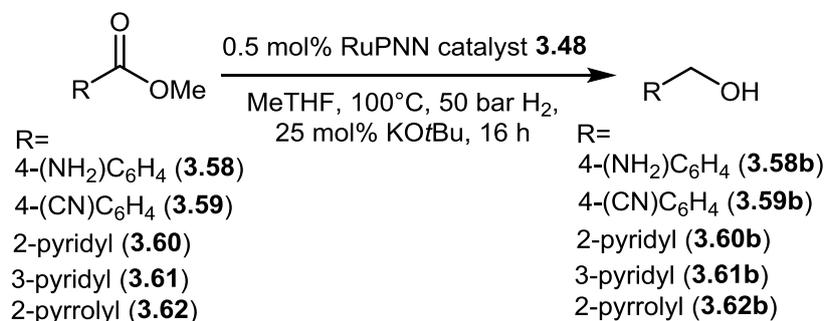
The reactions were carried out using 0.5 mol% *in situ* formed [RuCl₂(DPPP)(DPEN)] catalyst, KO*t*-Bu as base (50:1, base:catalyst) at 50 °C at an initial pressure of 50 bar using 0.5 mmol of methyl 4-fluorobenzoate in 3 ml of Me-THF.

Table 3.7: Substrate scope of RuCl₂(DPPP)(DPEN) complex.

The [RuCl₂(DPPP)(DPEN)] catalyst was able to hydrogenate the same range of substrates as the [RuCl₂(PNN)(DMSO)] catalyst **3.48** with quantitative conversion and high yields achieved in all cases.

To explore the substrate scope further, compounds containing nitrogen substituents were examined, as often these types of substrates can have a dramatic decrease on catalyst activity.

A summary of the results is shown in Table 3.8 below.



Entry	Substrate (R=)	Temperature (°C)	Conversion (%)
1	4-(NH ₂)-C ₆ H ₄ (3.58)	50	0
2	4-(NH ₂)-C ₆ H ₄ (3.58)	100	0
3	4-(CN)-C ₆ H ₄ (3.59)	50	0
4	4-(CN)-C ₆ H ₄ (3.59)	100	0
5	2-pyridyl (3.60)	50	0
6	2-pyridyl (3.60)	100	0
7	3-pyridyl (3.61)	50	0
8	3-pyridyl (3.61)	100	>99
9	2-pyrrolyl (3.62)	50	0
10	2-pyrrolyl (3.62)	100	0

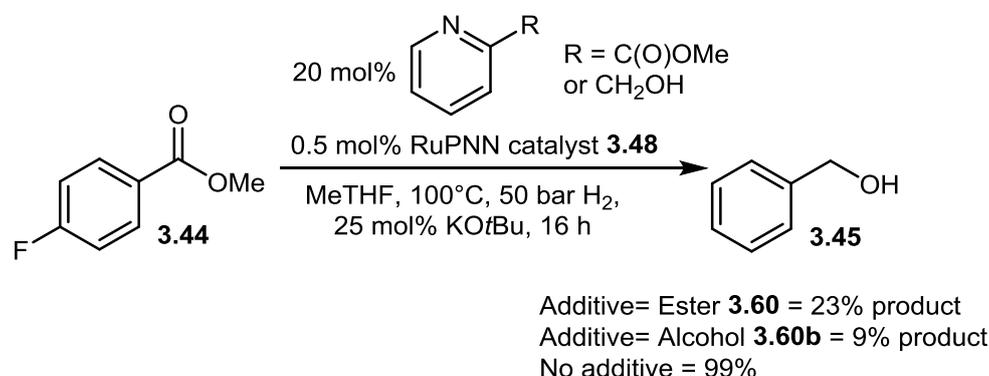
The reactions were carried out using 0.5 mol% [RuCl₂(PNN)(DMSO)] catalyst **3.48**, KO^t-Bu as base (50:1, base:catalyst) at 50 °C at an initial pressure of 50 bar using 0.5 mmol of substrate in 3 ml of Me-THF.

Table 3.8: Attempted hydrogenation of substrates containing heteroatoms

The results showed that most of the nitrogen containing substrates tested were not hydrogenated with this catalytic system, at 50°C. When the reaction temperature was increased to 100 °C there was still no reactivity after 16 hours. The only exception is the 3-pyridyl substrate which gave quantitative conversion after 16 hours. It is a point worth noting that this is not the trend observed in the case of ketone hydrogenation, as the St Andrews RuPNN system shows a good tolerance to ketones containing heterocyclic and nitrogen containing substituents.

Experiments were conducted to determine the detrimental effects that the 2-pyridyl substituted substrate was having on the catalyst activity as there was a marked difference when compared with the 3-pyridyl substituent. It was hypothesised that the 2-pyridyl substrate or its alcohol product could act as a good ligand to the ruthenium complex and may

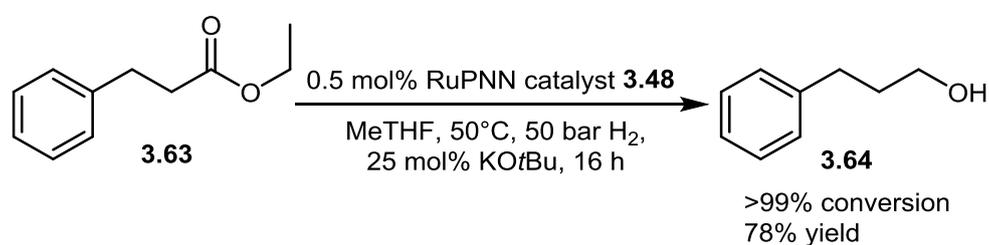
act as a poison in the catalytic cycle. To test this hypothesis two experiments were carried out in which the hydrogenation of methyl 4-fluorobenzoate was attempted with the addition of 20 mol % of either the 2-pyridyl ester or the product 2-pyridyl-methyl alcohol to the reaction mixture. These reactions are summarised below in Scheme 3.7.



Scheme 3.7: Effects of the inhibitory effect of pyridyl alcohols and esters on the hydrogenation of esters.

The condition chosen would normally give 99% conversion, although the results show that the reaction containing the ester additive gave 23% conversion. When the alcohol additive was added only 9% conversion was observed. This suggests that the 2-pyridyl alcohol and ester are having an inhibitory effect on the catalytic system, with the predominate effect caused by the alcohol product. This is presumably because they are very good ligating species that poisons the catalyst.

An alkyl ester was also tested to determine if it was possible to hydrogenate esters that did not contain an aromatic group directly adjacent to the ester moiety, as this could have an electronic activating affect, shown below in Scheme 3.8.



Scheme 3.8: Hydrogenation of an alkyl ester

3-Phenylpropionate was successfully hydrogenated after 16 hours at 50°C. The alkyl substrate hydrogenated fully to the alcohol product using typical conditions used for the

aromatic ester hydrogenation. An example of a more elaborate alkyl ester was tested but was unsuccessful (see figure 3.8).

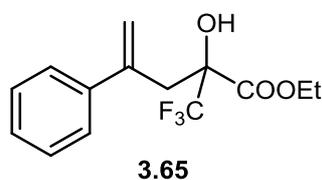
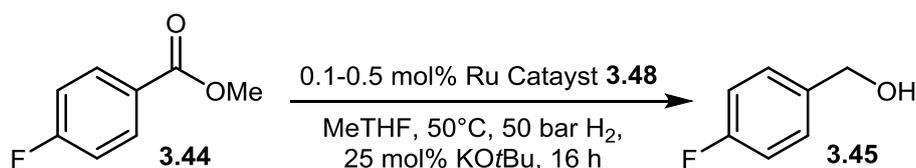


Figure 3.8: Unreactive ester substrate

3.6 Optimisation of Reaction Conditions for the [RuCl₂(PNN)(DMSO)] Catalyst:

Optimisation reactions shown in Table 3.9 were carried out to discover if the catalyst loading of the reaction could be reduced. 0.5 mol% is a relatively high catalyst loading when compared with industrial viable catalysts that often have catalyst loadings of 0.05 mol% or below.



Entry	Catalyst loading (Mol%)	Temperature (°C)	Conversion (%)
1	0.5	50	>99
2	0.4	50	>99
3	0.3	50	>99
4	0.2	50	>99
5	0.1	100	0

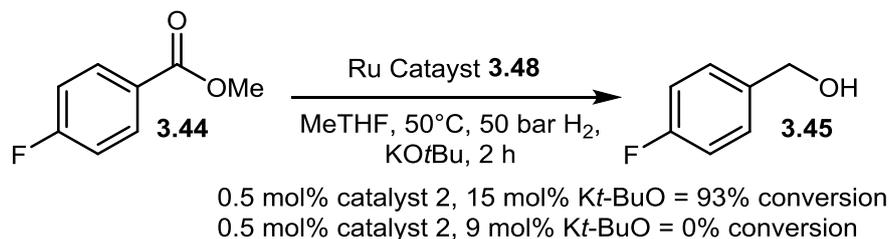
The reactions were carried out using 0.5 -0.1mol% Ru catalyst **3.48**, KO*t*-Bu as base (50:1, base:catalyst) at 50 or 100 °C at an initial pressure of 50 bar using 0.5 mmol of methyl 4-fluorobenzoate in 3 ml of Me-THF.

Table 3.9: Attempts to lower the catalyst loading

Good reactivity was observed down to as low as 0.2% loading, although a reduction of catalyst loading further to 0.1% resulted in loss of reactivity.

To further optimise the reaction conditions, it was decided to see if the same trend in base concentration was observed in the case of the [RuCl₂(diphosphine)(diamine)] catalyst (i.e

>30:1, Figure 3.6). As such the base loading in the tridentate ruthenium PNN system was investigated to see if the PNN system was reactive with 30 equivalents of base (scheme 3.9).

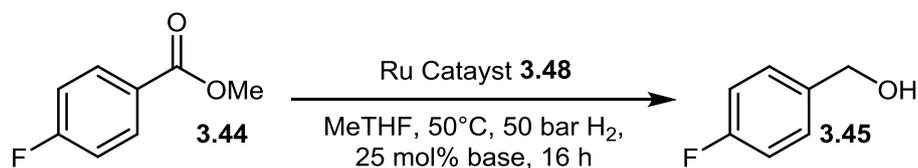


Scheme 3.9: Optimisation of reaction conditions

This result shows that using 30 equivalents of base to catalyst gave a good conversion to product, although not the same conversion as when compared with when 50 equivalents of base used. The combination of lowering both the catalyst loading and base concentration was not successful. Even increasing the reaction temperature to 100°C gave no product after 16 hours.

As the catalytic system proves to be very active at moderate reaction temperatures of 50°C further reducing the reaction temperature was examined. Initial experiments at a near ambient temperature of 30°C showed that the catalyst was active, but only gave very small conversions (5%) during the normal timescale of 16 hours. If left for a much longer time frame (64 hrs and 100 hrs), higher conversions could be achieved, resulting in 69% and quantitative conversion to alcohol respectively.

The type of base used was investigated, to evaluate what basic co-catalysts could be used. The different bases were tested at the same concentration (25 mol%) as usually used for *KOt*-Bu. The results of which are shown below in Table 3.10.



Entry	Base	Conversion (%)
1	NaOH	0
2	NaOMe	0
3	KOH	0
4	KPF ₆ + 1mol% <i>KOt</i> -Bu	0
5	<i>KOt</i> -Bu in PrOH	>99
6	<i>KOt</i> -Bu solid	68

The reactions were carried out using 0.5 mol% [RuCl₂(PNN)(DMSO)] catalyst **3.48**, at 50 °C at an initial pressure of 50 bar using 0.5 mmol of substrate in 3 ml of Me-THF.

Table 3.10: Different bases in the hydrogenation methyl 4-fluorobenzoate .

The bases NaOH, NaOMe, KOH were examined, in addition to these bases we also attempted an ester hydrogenation using 25 mol % KPF₆ (in the case of KPF₆, we also added 1 mol% *KOt*-Bu) to determine if the cation concentration is important in the catalytic cycle. In all cases no reactivity was observed after 16 hours at 50 °C. Experiments shown previously in this chapter under these same conditions resulted in full conversion when using 25 mol% *KOt*-Bu. This result is possibly partially due to the solubility issue of the base in MeTHF, as catalytic system requires a large amount of base in solution for reactivity. An additional experiment that supports this hypothesis was conducted in which solid *KOt*-Bu (25 mol%) was used, instead of a solution of *KOt*-Bu (1M in *t*-BuOH) which was normally used. When solid *KOt*-Bu (RuPNN catalyst 3.48, MeTHF, 50°C, 16 hours) was used the reaction gave a conversion to product of only 68%, compared with 99% using a solution of *KOt*-Bu. This may provide a partial answer to the drop in conversion when using NaOH, NaOMe and KOH, although the use of a solid base does not account fully for the complete drop in catalyst reactivity observed.

3.7 Conclusions:

An easy, quick and efficient method for producing $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ complexes *in situ* directly prior to ester hydrogenation has been demonstrated. The use and importance of such a procedure has been shown in the screening of a variety of different ligand combinations in the hydrogenation of esters.

From these screens it was shown that the most effective combination of phosphines and amines to form $[\text{RuCl}_2(\text{diphosphine})(\text{diamine})]$ complexes, were $[\text{RuCl}_2(\text{BINAP})(\text{DPEN})]$, $[\text{RuCl}_2(\text{dppp})(\text{DPEN})]$, and $[\text{RuCl}_2(\text{dppp})(\text{picolyamine})]$. All three catalysts resulted in good conversions to the alcohol product. In the case of the two DPPP complexes, higher overall conversions were noted and less side product was formed.

High base concentrations (>15 mol%) are required for good catalytic activity with the $[\text{RuCl}_2(\text{diphosphine})(\text{amine})]$ complexes. It has also been demonstrated that the St Andrews $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ catalysts are also active in the hydrogenation of ester when these relatively high amounts of basic co-catalyst, where they had previously been shown to be relatively unreactive when tested with small amounts of base (1 mol%).

The investigation described here was limited to mainly benzoate esters, although other substrates have shown promise such as a specific nitrogen containing substrate and an example of a simple alkyl ester has been shown to be reactive towards hydrogenation with $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ catalysts.

From these optimisation experiments it has been shown that the reaction conditions can be improved upon. Reduced temperature, catalyst loading and base concentration can all be achieved with the ruthenium PNN catalyst system, although a combination of all these is problematic. The most beneficial condition in terms of cost is probably to use the conditions with reduced catalyst loadings, lowering the catalyst loading down to 0.2 mol%. It is worth noting that it would be anticipated that further optimisation of the system could be achieved particularly if using an optimised reactor in terms of agitation, such as overhead stirring. Scaling up the reaction is likely to be beneficial since trace impurities in the solvent poison a catalyst far less when the amount of catalyst per ml of solvent is higher.

3.8 References.

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IV. CHAPTER IV: INVESTIGATION OF IRIIDIUM IN THE HYDROGENATION OF PRO-CHIRAL KETONES USING A CHIRAL P[^]N[^]N LIGAND.

4.1 Iridium Complexes used in the Hydrogenation Ketones.

Chiral secondary alcohols are made by a number of different processes, including the use of enzymes, or the use of chiral resolution reactions to enrich a racemic mixture of an alcohol. Both of these methods are used industrially and in research, but often have issues with substrate scope and cost. An alternative method involves the reduction of a corresponding pro-chiral ketone to form the required alcohol using catalytic homogenous hydrogenation, which has the potential if designed and optimised correctly to be a green and cost efficient process.

Homogenous hydrogenation reactions utilise metal complexes such as the catalyst shown below in Figure 4.1, a ruthenium catalyst invented by Noyori and co-workers.¹

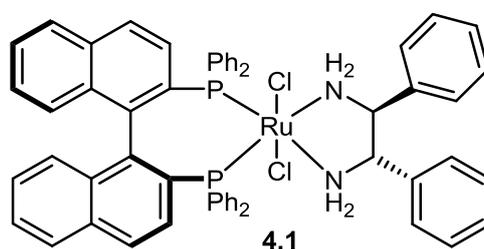


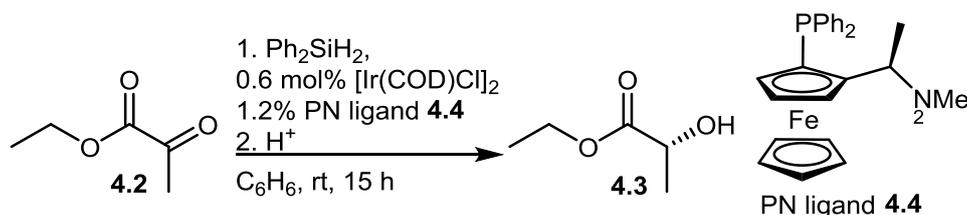
Figure 4.1: Structure of $[\text{RuCl}_2(\text{S-BINAP})(\text{S,S-DPEN})]$ complex (4.1).¹

Ruthenium is the most popular choice of metal for catalytic homogenous hydrogenations of ketones, although other metals are often used including rhodium, iridium and iron. Compared with ruthenium there are relatively few examples which utilise iridium.²

4.2 Asymmetric Hydrosilylation.

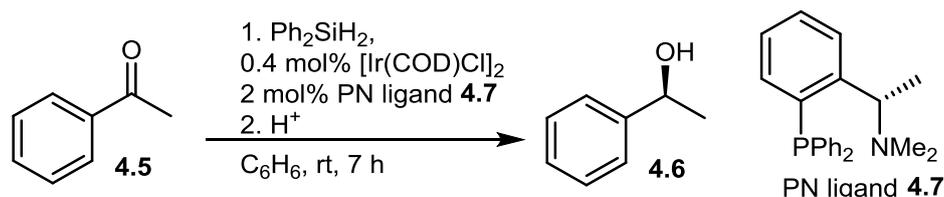
One of the original attempts to transform ketones to chiral secondary alcohols using iridium complexes was in 1985, and was performed by an asymmetric hydrosilylation reaction, followed by an acidic work up to form the required alcohol. The work by Apple and co-workers.³ (see scheme 4.1), resulted in good yields at room temperature after 15 hours using an iridium precursor and a ferrocenyl PN ligand shown below. The yield of the reaction was

satisfactory, although the enantioselectivity of the product was poor with only a minimal selectivity of 7%, shown below in Scheme 4.1.



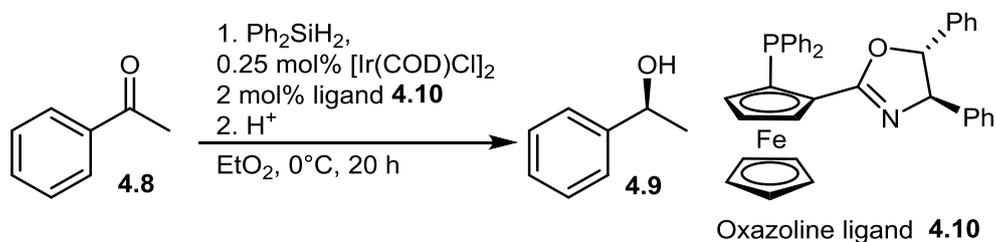
Scheme 4.1: The first attempted hydroosilylation of a ketone with iridium³

The researchers at the same time tried the asymmetric hydroosilylation of acetophenone using the same catalytic system, resulting in only a 1% enantiomeric excess. A few years later the hydroosilylation of acetophenone was improved upon. This time a phenyl PN ligand was used by Kreuzfeld and co-workers⁴, which resulted in a good yield although still a disappointing selectivity of 16.5% enantiomeric excess, as shown below in Scheme 4.2.



Scheme 4.2: Hydroosilylation of acetophenone using iridium PN ligand.⁴

The hydroosilylation of acetophenone was greatly improved by Uemura and co-workers,^{5,6} the researchers used a PN ferrocene ligand with an oxazoline side chain and $[\text{Ir}(\text{COD})\text{Cl}]_2$ precursor, The experiment showed an excellent enantioselectivity (96% ee) and proceeded to give quantitative conversion in 20 hours, as illustrated below in Scheme 4.3.



Scheme 4.3: Hydroosilylation of acetophenone using iridium PN ferrocene complex.^{5,6}

Uemura also tested a variety of acetophenone derivatives with the same catalyst, which progressed with high yields and moderate to high enantioselectivities. These include a heteroaromatic ketone and an alkyl alkyl ketone. The selectivity was high except for substrates with large side groups (isopropyl, **4.15**) and dialkyl ketones (**4.16**) that showed poor selectivities, as highlighted in Table 4.1.

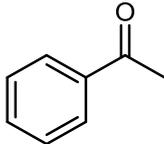
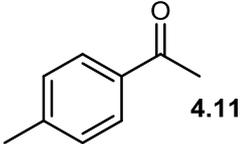
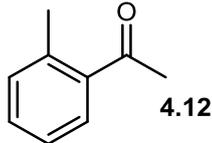
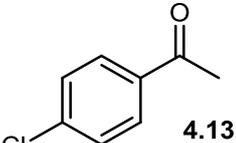
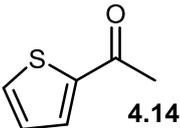
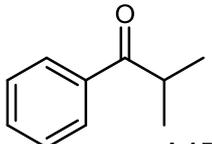
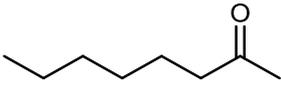
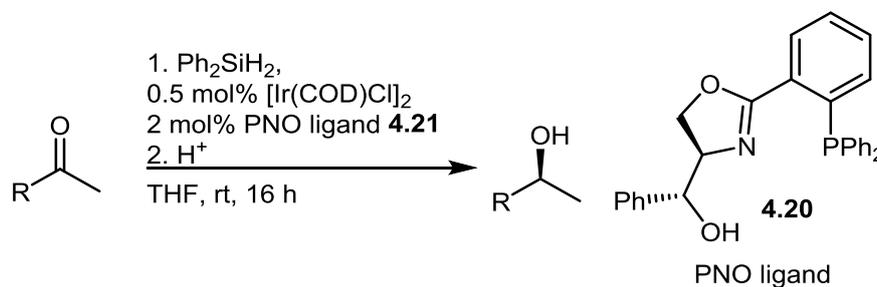
Substrate	Conversion (%)	ee (%)
 4.8	100	96
 4.11	100	91
 4.12	98	88
 4.13	100	89
 4.14	100	83
 4.15	78	9
 4.16	100	19

Table 4.1: Hydrosilylation of acetophenone derivatives using iridium ferrocene PN complex^{5,6}

A PNO ligand containing a chiral oxazoline was demonstrated as being effective in the hydrosilylation of ketones by Frolander Moberg,⁷ giving high conversions and good enantioselectivities in some cases, as shown below in Table 4.2.



Substrate	Conversion (%)	ee (%) with Ir	ee (%) with Rh
4.17	98	69	81
4.18	97	62	85
4.16	98	13	67
4.19	100	9	55

Table 4.2: Hydrosilylation of a variety of ketones using an iridium PNO complex⁷

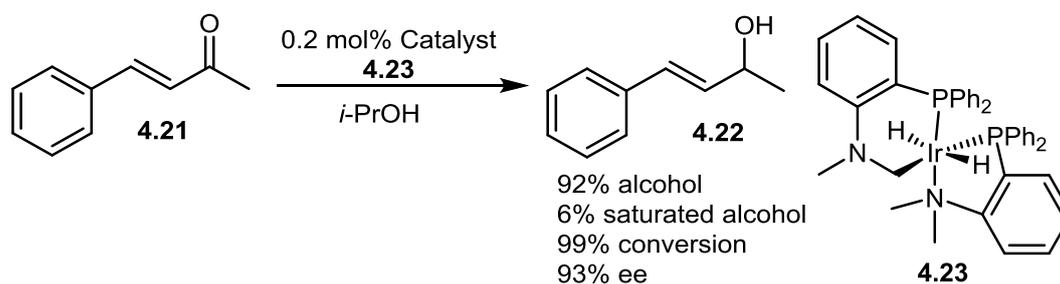
Interestingly when rhodium was used as the metal precursor it gave higher selectivity and the opposite enantiomer was produced.

As this summary shows, asymmetric hydrosilylation provides a good method of ketone reduction and can result in a selectivity and active reduction. Unfortunately the reaction comes with inherent downsides. The requirement for the use of stoichiometric amounts of

silanes, and an additional acid work up make this process not viable from an industrial perspective for economic and environmental reasons.

4.3 Asymmetric Transfer Hydrogenation.

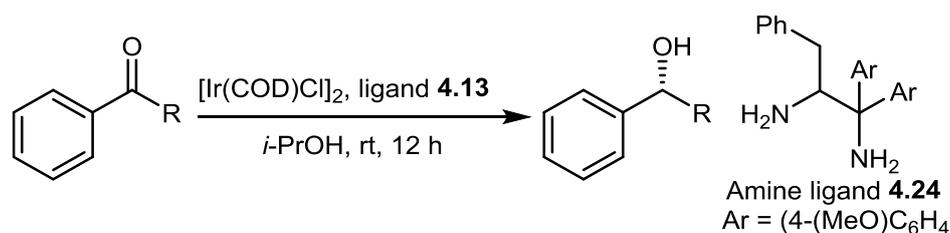
Iridium catalysed hydrogenation of ketones using transfer hydrogenation conditions have been described in the literature. An example of the reaction is shown below,⁸ that uses an iridium based catalyst in the hydrogenation of α,β -unsaturated ketones both chemoselectively and enantioselectively. The results of which are shown below in Scheme 4.4.



Scheme 4.4: Transfer hydrogenation of an unsaturated ketone⁸

The hydrogen source in this reaction is the solvent. Isopropanol acts in the catalytic cycle to regenerate the catalytically active hydride species. In most cases a basic co-catalyst is also required such as sodium methoxide, potassium tertiary butoxide or a hydroxide.

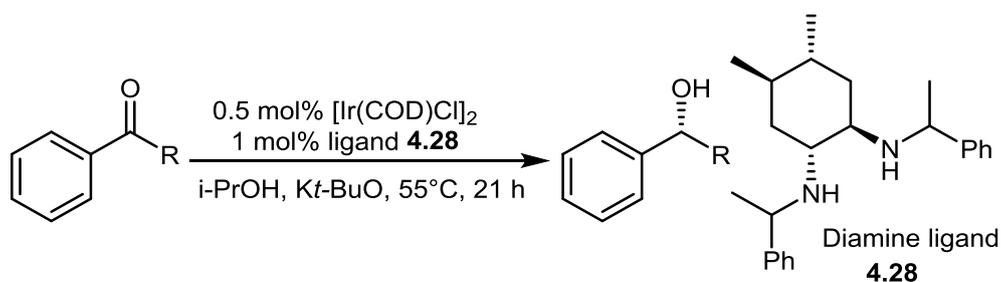
A large number of examples in the literature of iridium transfer hydrogenation utilise a diamine ligand such as the example shown below in Table 4.3.



Substrate	ee (%)
Me (4.8)	78
Et (4.25)	93
<i>i</i> -Pr (4.15)	93

Table 4.3: Transfer hydrogenation of acetophenone⁹

This catalyst demonstrated by Inoue et al.⁹ gives excellent enantioselectivities and good yields, although there is a marked lowering of selectivity in the case of acetophenone. Another example of a diamine complex system includes the cyclodiamine ligand¹⁰ as shown below, that when complexed *in situ* with an iridium precursor gave an active transfer hydrogenation catalyst giving moderate enantioselectivity over a range of acetophenone type substrates using potassium tertiary butoxide as a co catalytic base. As shown below in Table 4.4



Substrate	ee (%)
Me (4.18)	49
Cy (4.26)	58
<i>i</i> -Pr (4.15)	53
<i>t</i> -Bu (4.27)	60

Table 4.4: Transfer hydrogenation of acetophenone derivatives¹⁰

Marginally higher enantioselectivities were achieved with larger substituents such as cyclohexyl or tertiary butyl groups (**4.27**).

Further examples of chiral symmetrical ligands include this bis oxazoline ligand (PYBOX, Figure 4.2). The iridium (III) complex shown in Figure 4.2, reduces acetophenone with 96% conversion to alcohol over 1.5 hours and a good selectivity (70 % ee).¹¹

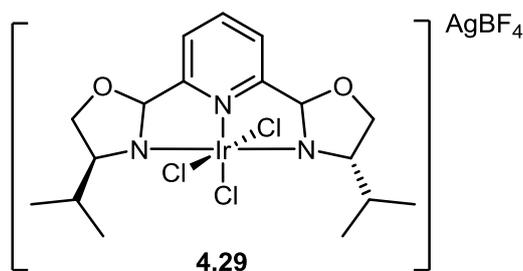
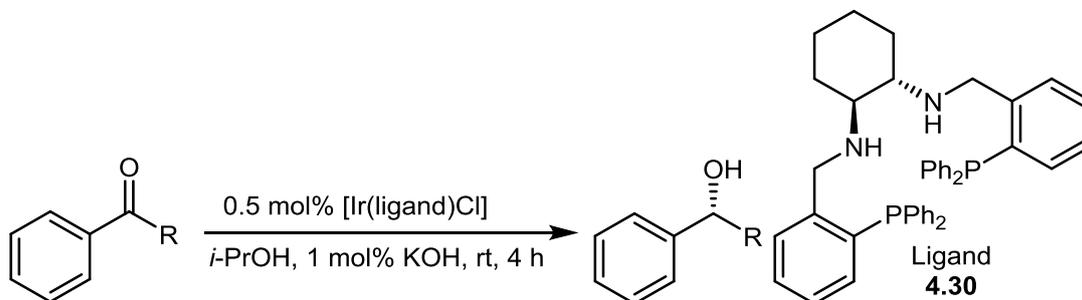


Figure 4.2: Tridentate (PYBOX) iridium complex¹¹

An interesting tetradentate PNNP compound has been developed by Gao and co-workers,^{12,13,14} that is active in transfer hydrogenation catalysis, the results are shown below in Table 4.5.



Substrate	ee (%)
Me (4.8)	83
Et (4.25)	94
Cy (4.26)	98
<i>i</i> -Pr (4.15)	99
<i>t</i> -Bu (4.27)	82

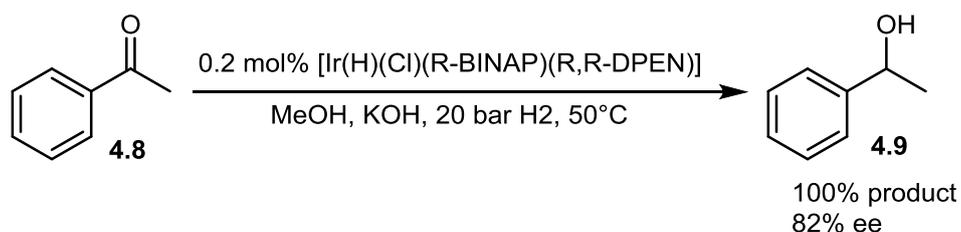
Table 4.5: Transfer hydrogenation of acetophenone derivatives^{12,13,14}

The iridium PNNP catalyst shows very high selectivity with specific substrates such as cyclohexyl and isopropyl. The catalyst shows improved selectivity with the medium sterically hindered substituents such as ethyl, cyclohexyl and isopropyl. A reduction in selectivity was observed with the larger tertiary butyl and the smaller methyl substituent.

Transfer hydrogenation is a great method for the enantioselective reduction of ketones, although there are some significant downsides to the process. Certain substrates are not compatible with the necessary reaction conditions. Substrates that are not soluble or incompatible with alcoholic solvents can also be an issue as it is required to regenerate the active catalytic species. Economical and environmental issues often arise due to the large amounts of basic co-catalyst and the fact that relatively dilute conditions are often needed. In some cases the best selectivity can only be realised at incomplete conversion. Finally, while the use of *i*-PrOH as the hydrogen source is cheap, it is not quite as cost efficient as hydrogen.

4.4. Homogenous Hydrogenation using Hydrogen.

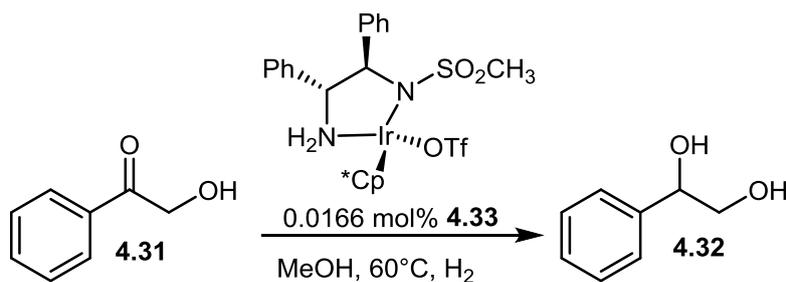
The use of gaseous hydrogen as the hydrogen sources can be beneficial as such reactions are potentially atom efficient so therefore have less of an environmental effect when compared with the hydrogenation methods already described. Iridium catalysts for asymmetric hydrogenation have been described in the literature. An iridium (III) hydride complex that is an analogue to the famous Noyori ruthenium catalyst was investigated by Dahlenburg et al.¹⁵ Dalenburg used the $[\text{Ir}(\text{H})(\text{Cl})(R\text{-BINAP})(R,R\text{-DPEN})]\text{BF}_4$ hydride species to successfully hydrogenate acetophenone to 1-phenylethanol with a quantitative yield in 1.5 hours. The selectivity of 82% ee is higher when compared with the ruthenium hydride equivalent ($[\text{Ru}(\text{H})(\text{Cl})(R\text{-BINAP})(R,R\text{-DPEN})]$ (0.02 mol%)) that produces 1-phenylethanol in 73% ee, although ten times the amount of catalyst is required for good conversions to be achieved. This is illustrated below in Scheme 4.5.



Scheme 4.5: Hydrogenation of acetophenone using an iridium analogue of the Noyori catalyst¹⁵

A slightly higher selectivity can be achieved with an *in situ* formed complex from a chloride bridged iridium/BINAP dimer as the iridium precursor and (*R,R*)-DPEN that generated an enantiomer excess of 84%, although higher catalyst loadings (0.4 mol% *cf.* 0.2 mol%) are required.

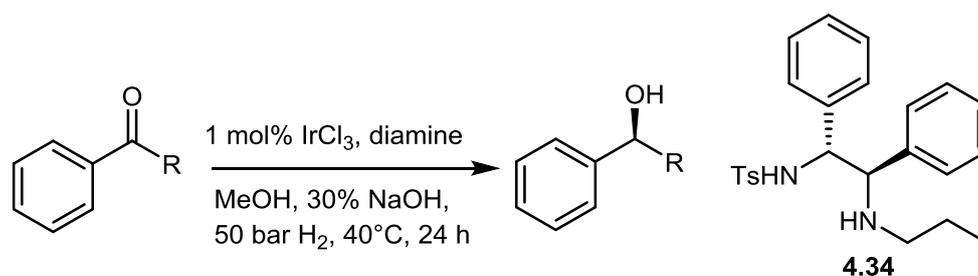
An iridium diamine complex (shown below in Scheme 4.6) has been used in the asymmetric hydrogenation of hydroxyl ketones.¹⁶



Scheme 4.6: Hydrogenation of a functionalised ketone¹⁶

High reactivity was described with relatively low catalyst loading of 6000:1, giving good selectivity over a range of different hydroxyl ketones. Only hydroxyl ketones were described, and simple ketones were not investigated.

Martins et al.¹⁷ described the use of iridium (III) complexes with chiral diamines in the hydrogenation of a range of ketone substrates, as shown in Table 4.6.



Substrate	Conversion (%)	ee (%)
Me (4.8)	100	60
Et (4.25)	100	66
Cy (4.26)	73	69
<i>i</i> -Pr (4.15)	97	73
<i>t</i> -Bu (4.27)	100	73

Table 4.6: Hydrogenation of acetophenone derivatives utilising a chiral diamine¹⁷

This catalytic system gave the required alcohols in good conversion and moderately high enantioselectivity. The selectivity was slightly higher for large groups such as tertiary butyl. The catalytic system does require large amounts of base to maximise selectivity and long reaction times to achieve high conversion. The largest enantioselectivity was achieved using the same conditions as above but using *ortho* methyl substituted acetophenone as the substrate, and resulting in 84% ee.

Recent Work by Xie et al.¹⁸ is probably the best example of asymmetric hydrogenation using iridium complexes in the literature. Xie has shown that a chiral iridium PNN catalyst (**4.35**, shown in Scheme 4.9) was extremely active in ketone hydrogenation at low catalyst loadings of 5,000,000:1 (substrate: catalyst). However, only the relatively easy acetophenone and its close derivatives were examined.

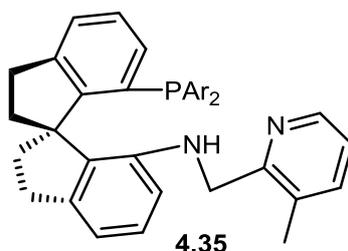


Figure 4.3: Spiro PNN ligand

Such high turnovers are rarely seen in the literature and because of this it was decided to further investigate the iridium catalysed hydrogenation of ketones.

4.5 Aims

Previous work within the research Clarke group¹⁹ demonstrated that when the PNN ligand (**4.36**, Scheme 4.10) is complexed with ruthenium, it forms an active catalyst in the hydrogenation of ketones. The complex is able to hydrogenate ketones with large substituents with high enantioselectivity that had previously not been possible at that point in time. The catalysts have proved to be selective with a variety of interesting substrates, but unfortunately this selectivity was limited to sterically hindered substrates and usually required the use of around 0.2-0.5 mol% of catalyst. As a result it was decided that it was an ideal ligand to experiment, as it would be interesting to see if the specific selectivity could be maintained while hopefully increasing the activity. As such the aim of this project was to develop

catalysts of **4.36** using other transition metals, to achieve efficient and selective catalysts for the hydrogenation of a range of ketones.

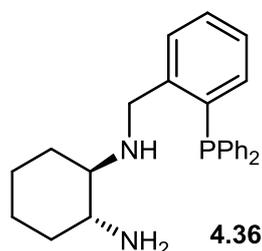
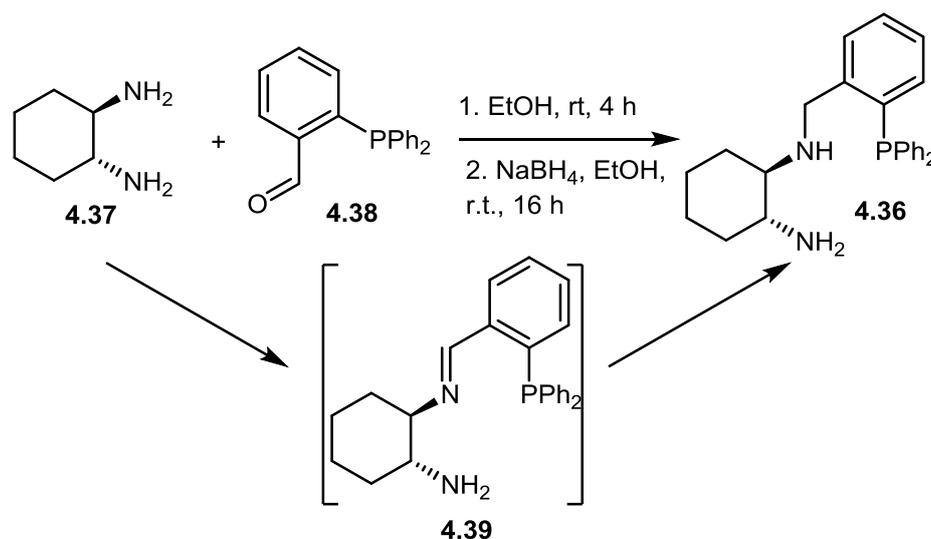


Figure 4.4: Chiral PNN ligand **4.36**.

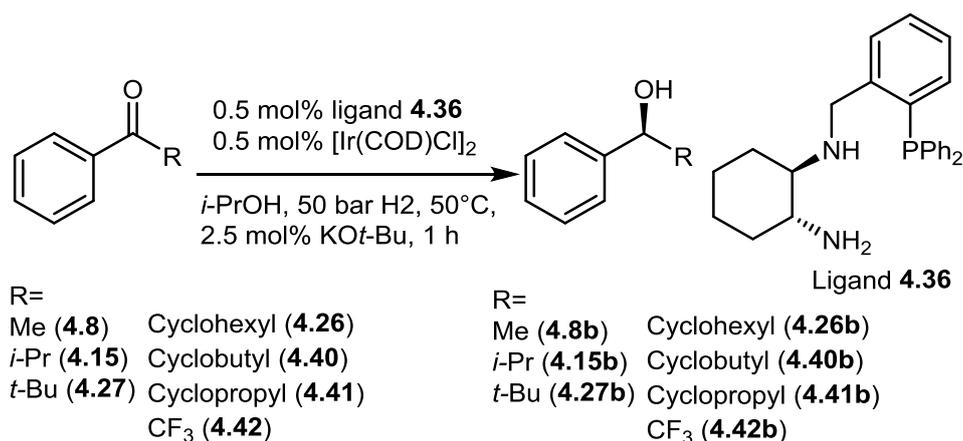
4.6 Hydrogenation of Acetophenone, Isobutylphenone and Tertbutylphenone.

The PNN ligand can be easily synthesised from readily available commercial starting materials¹⁹, as illustrated in Scheme 4.7.



Scheme 4.7: Synthesis of PNN ligand

It was to the use of an alternative metal, this selectivity profile could change; as such it was decided to perform an initial reaction screen with substrates with a range of different steric profiles as shown in Table 4.6.



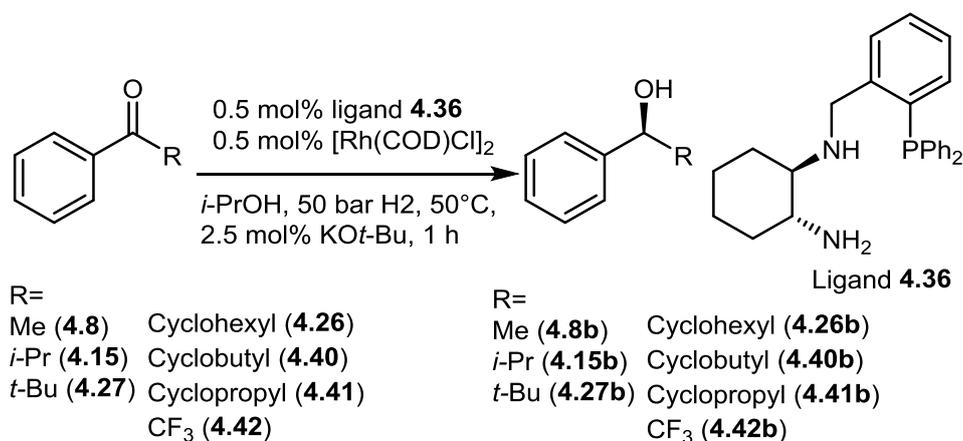
Entry	Substrate (R=)	Conversion (%)	ee (%)
1	Me	>99	23 (<i>S</i>)
2	<i>Iso</i> -propyl	>99	89 (<i>S</i>)
3	<i>Tert</i> -butyl	>99	48 (<i>S</i>)
4	Cyclohexyl	>99	91 (<i>S</i>)
5	Cyclobutyl	87	78 (<i>S</i>)
6	Cyclopropyl	97	45 (<i>S</i>)
7	CF ₃	>99	1 (<i>S</i>)

The reaction conditions used were: 0.3 mmols substrate, 0.5 mol% ligand, 0.5 mol% [Ir(COD)Cl]₂, 2.5 mol% KO*t*-Bu, 3 ml *i*-PrOH, 50°C and 50 bar H₂, 1 hour.

Table 4.6: Asymmetric hydrogenation of various ketones with an Ir(PNN) complex of **4.36**.

The initial screen of iridium catalysts showed very high reaction rates, achieving quantitative conversions of most substrates tested in one hour. The selectivity of the iridium catalysts gave interesting results with enantiomeric excess of greater than 90 in one case, with the cyclohexyl substituent (**4.26**).

The same substrates were also tested using ruthenium and rhodium based PNN catalysts, under similar conditions, as shown below in Table 4.7.



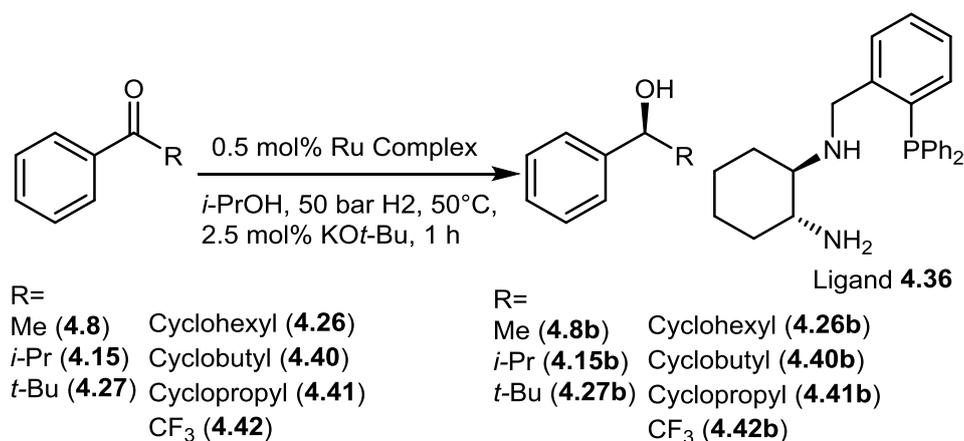
Entry	R=	Conversion (%)	ee (%)
1	Me	>99	50 (<i>S</i>)
2	<i>Iso</i> -propyl	58	45 (<i>S</i>)
3	<i>Tert</i> -butyl	79	55 (<i>S</i>)
4	Cyclohexyl	64	72 (<i>S</i>)
5	Cyclobutyl	14	72 (<i>S</i>)
6	Cyclopropyl	28	21 (<i>S</i>)
7	CF ₃	6	ND

The reaction conditions used were: 0.3 mmols substrate, 0.5 mol% ligand, 0.5 mol% [Rh(COD)Cl]₂, 2.5 mol% KO*t*-Bu, 3 ml *i*-PrOH, 50°C and 50 bar H₂, 1 hour.

Table 4.7: Asymmetric hydrogenation of various ketones with an Rh(PNN) complex of ligand **4.36**.

In general the reactivity of the rhodium catalyst was less active at hydrogenating the substrates tested (compare Table 4.6, entries 1-7 and Table 4.7, 1-7), although when left to react over a 16 hour period quantitative conversions could be achieved. The enantioselectivity of the rhodium based catalyst was lower, which is the most pronounced in the case of entry 2 and 6.

The ruthenium complex was tested under the same conditions so that the results are the readily comparable, as shown in Table 4.8.



Entry	R=	Conversion (%)	ee (%)
1	Me	>99	3 (<i>S</i>)
2	<i>Iso</i> -propyl	17	14 (<i>S</i>)
3	<i>Tert</i> -butyl	38	73 (<i>S</i>)
4	Cyclohexyl	49	51 (<i>S</i>)
5	Cyclobutyl	9	ND
6	Cyclopropyl	97	18 (<i>S</i>)
7	CF ₃	98	1 (<i>S</i>)

The reaction conditions used were: 0.3 mmols substrate, 0.5 mol% ruthenium complex, 2.5 mol% KO*t*-Bu, 3 ml *i*-PrOH, 50°C and 50 bar H₂, 1 hour.

Table 4.8: Hydrogenation of various ketones with a Ru(PNN) complex with ligand **4.36**.

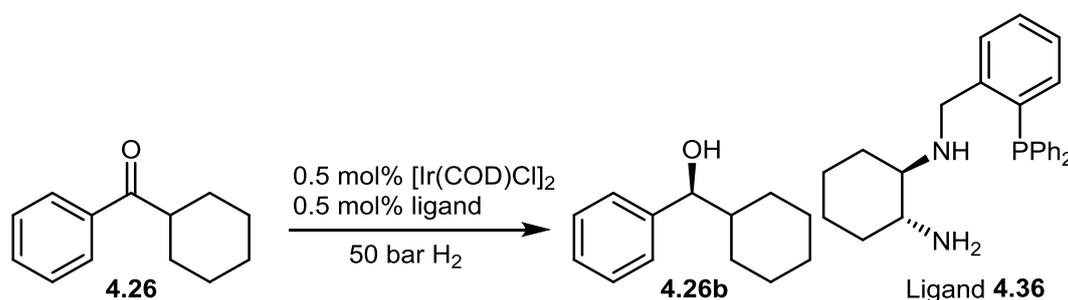
As expected the conversions were highest for the smaller less sterically hindered compounds, such as acetophenone and 2,2,2-trifluoroacetophenone, but in this short reaction time moderate reactivity was observed with larger substrates. Noyori catalysts are reported to give as little as 6% yield for this type of substrates.²⁰

The selectivity showed the expected trend of higher enantiomeric excesses for the most sterically hindered ketones, (refer to entry 3 and 4, Table 4.8). The selectivity of 73% ee obtained for the tertiary butyl ketone is similar to previous work (99% conversion, 2-16 hrs, up to 77% ee).¹⁹

4.7 Modifications of Reaction Conditions.

It is often possible to optimise reaction conditions for specific catalysts by varying a number of parameters. By performing an optimisation screen it can be possible to improve the reactivity and selectivity, increasing the potential financial and commercial viability of a catalytic system.

The main aim of the initial optimisation was to improve the selectivity and try to reach the maximum enantiomeric excess, and to then investigate if high e.e is possible at low catalyst loadings. The initial screen is shown below in Table 4.9.



Entry	Solvent	KO <i>t</i> -Bu (mol %)	Temperature* (°C)	Time (hrs)	Conv (%)	ee (%)
1	<i>i</i> -PrOH	2.5	50	1	>99	91
2	<i>i</i> -PrOH	2.5	25	2	>99	94
3	<i>i</i> -PrOH	2.5	3	2	>99	94
5	<i>i</i> -PrOH	5	25	1	98	90
6	<i>i</i> -PrOH	1	25	1	98	87
7	Ethanol	2.5	25	1	>99	81
8	Methanol	2.5	25	1	>99	93
9	MeTHF: <i>i</i> -PrOH (2:1)	2.5	25	1	69	91
10	DCM: <i>i</i> -PrOH (2:1)	2.5	25	1	>99	89

The reaction conditions were: 0.3 mmols substrate, 0.5 mol% ligand, 0.5 mol% [Ir(COD)Cl]₂, 1-5 mol% KO*t*-Bu, 3 ml *i*-PrOH, 50 bar H₂. * The temperatures are of the cooling/ heating solutions containing the vessel. For the low temperature reaction the autoclave and reaction solutions were precooled, before the addition of substrate and hydrogen.

Table 4.9: Investigation of the effect of temperature and co-catalyst concentration on enantioselectivity and activity of the IrPNN catalyst.

The simplest and often most effective method of improving enantioselectivity is to lower the temperature of the reaction, but this has the unfortunate side effect of also lowering the reaction rate. By lowering the reaction temperature to near ambient (25°C), it was possible to achieve quantitative conversion in two hours with a higher enantiomeric excess of 94% (see entry 1 and 2, Table 4.9). Lowering the temperature further by submerging the autoclave in an ice bath did not improve the selectivity further.

The amount of base used was also varied in an attempt to affect an increase in selectivity. The amount of base was both increased and decreased, however in both cases a drop in selectivity was observed.

Changing the solvent can often have an effect on reactivity and selectivity of a reaction as solvents with different polarities can have an effect on the catalytic cycle. A solvent screen of some common solvents was performed. In the case of the dichloromethane and methyltetrahydrofuran a co-solvent was assumed to be required as the catalytic cycle of the hydrogenation requires an alcohol present to regenerate the catalytically active species.

Unfortunately in all cases changing the solvent lowered the selectivity and in the case of methyltetrahydrofuran lowered the activity substantially and the reaction only went to 69% conversion. The effect of Me-THF is possibly due to the solubility of the substrate.

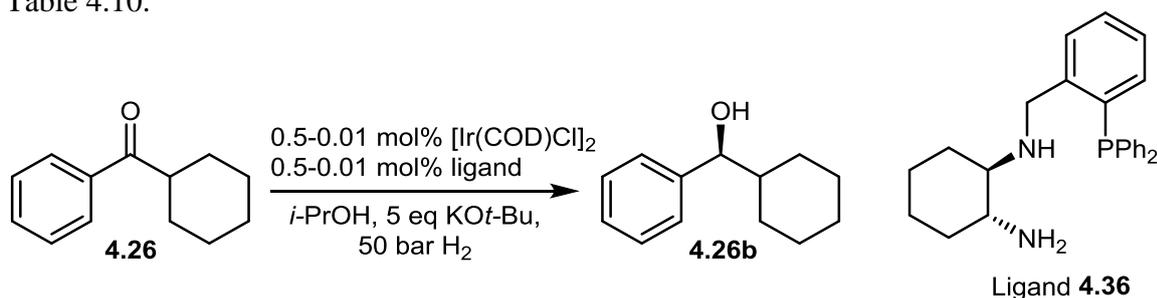
From this optimisation it is apparent that the original conditions used were the best for achieving both high conversions and high enantioselectivity. This demonstrates that even though the metal of the catalytic complex has been changed, there is no requirement for modification of the reaction conditions in this case.

It should be noted that an unusual metal to ligand ratio of 2:1 has been used throughout this work. This stemmed from getting the best results during initial trial reactions at this ratio, and different ratios gave inferior results. Follow-up studies by Fuentes²¹ established that in fact iridium/ligand ratio of 2:1 always gives the best selectivity.

To demonstrate an industrially viable catalytic system, a number of factors are important. High enantioselectivity is necessary, which has already been demonstrated.

A major factor for industrial viability is the substrate to complex ratio. For cost and environmental reasons it is necessary for a catalyst to be sufficiently active so that the substrate to metal ratio is as small as possible. For this reason it was necessary to investigate

the catalyst loading of the reaction further, the investigation of which is shown below in Table 4.10.



Entry	Substrate:Catalyst	KO <i>t</i> -Bu (mol%)	Temperature (°C)	Time (hrs)	Conv (%)	ee (%)
1	200:1	2.5	50	1	>99	91
2	2000:1	2.5	50	2	43	90
3	2000:1	2.5	80	2	89	90
4	2000:1	2.5	80	6	>99	90
5	2000:1	2.5	50	24	>99	90
6	10000:1	2.5	80	16	0.6	ND
7	10000:1	5	80	16	1	ND
8	5000:1	5	80	2	2	ND
9	5000:1	2.5	80	2	0	ND

The reaction conditions used were: 0.3 mmols substrate, 2.5-5 mol% KO*t*-Bu, 3 ml *i*-PrOH, and 50 bar H₂, 1 hour.

Table 4.10: The catalyst to substrate ratio was also modified to probe the selectivity and rate of the reaction

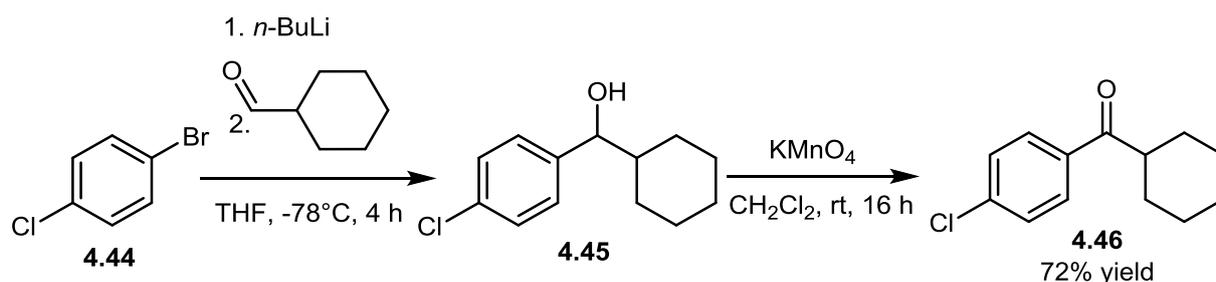
Decreasing the catalyst loading from 0.5 mol% by tenfold was successful, as the catalyst is still active at 0.05 mol%, with 43% conversion in just two hours and full conversion after 24 hours. This could be improved upon by increasing the reaction temperature to 80°C, which gives 89% conversion over 2 hours and complete conversion in 6 hours. Lowering the catalyst loading results in only a slight drop in enantioselectivity to (90% ee).

It was decided to determine if decreasing the substrate to catalyst ratio further would still result in high conversions to product. Unfortunately, this resulted in a complete drop in conversion with only a small amount of alcohol observed post reaction, even when increasing both the temperature and reaction time. At present, the lowest effective catalyst loading is 2000:1.

4.8 Substrate Modification to Probe Substrate Scope:

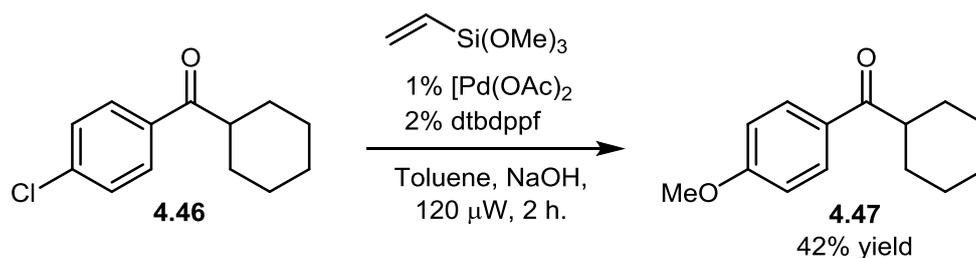
To determine the scope of the highly enantioselective ketone hydrogenation further experimentation was performed.

It has previously been observed that altering the electron environment of the ketone substrate can affect the enantioselectivity. Noyori demonstrated that electron rich compounds led to more selective reactions due to the stabilisation of the substrate-catalyst intermediate.^{22, 23} To determine if it would be possible to improve the enantiomeric excess of the reaction by changing the electronic environment two cyclohexyl phenyl ketone derivatives were synthesised; one with an electron withdrawing *para* chloro substituent and another with an electron donating *para* methoxy group. First the *para* chloro compound was synthesised by initially lithiating **4.44**, followed by reaction with cyclohexane carboxaldehyde, leading to racemic alcohol **4.45**, which was then be oxidised using potassium permanganate to yield the required ketone. The synthetic pathway is shown below in Scheme 4.8.



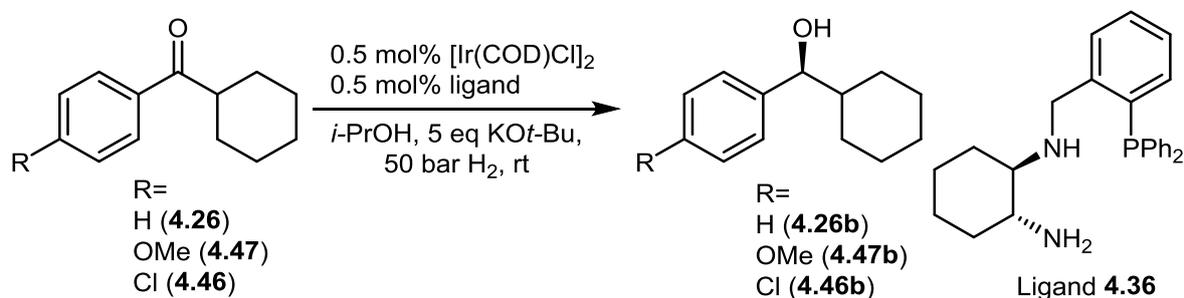
Scheme 4.8: Synthesis of *para*-chloro ketone **4.46**.

This ketone can then be modified to form the *para* methoxy derivative via a cross coupling reaction developed by the Clarke group.²⁴ It was found that using a combination vinyl trimethoxysilane, palladium catalyst and sodium hydroxide, it was possible to couple an aryl halide with the silane to produce an aryl-methyl ether, instead of the expected aryl alkene. As shown in Scheme 4.9.



Scheme 4.9: Synthesis of *para*-methoxy ketone **4.47**.

The *para*-methoxy and *para*-chloro (**4.47** and **4.46**) substituted substrates were evaluated in tandem with **4.26** to probe the substrate scope, and determine if the electronic properties of the substituents may affect the selectivity or reactivity of the reaction. These results are summarised in Table 4.11.

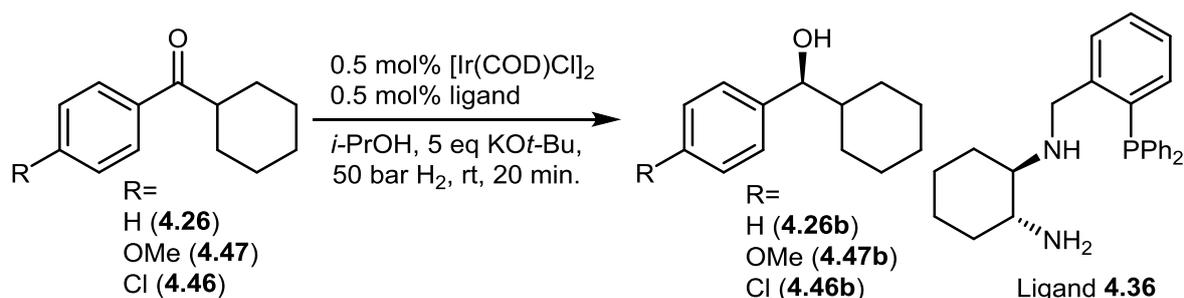


Entry	Substrate (R=)	Conversion (%)	ee (%)
1	H	>99	94
2	OMe	78	55
3	Cl	95	91

The reaction conditions used were: 0.3 mmols substrate, 0.5 mol% ligand, 0.5 mol% [Ir(COD)Cl]₂, 5 eq KO*t*-Bu, 3 ml *i*-PrOH, 50°C and 50 bar H₂, 1 hour.

Table 4.11: Asymmetric hydrogenation of ketone substrates with differing electronic environments, with Ir(PNN) complexes to investigate the effect on selectivity and reaction rate.

Interestingly the electron rich, *para* methoxy substituent resulted in a lower enantioselectivity when compared to cyclohexyl phenyl ketone, but the *para* chloro electron withdrawing substituent gave the same selectivity. In both cases the conversion was lower, although this was more pronounced with the *para* methoxy substituent. To investigate this further the reaction was stopped after a shortened reaction time of 20 minutes, as shown in Table 4.12.



Entry	R=	Conversion (%)	ee (%)
1	H	85	N.D.
2	OMe	59	N.D.
3	Cl	74	N.D.

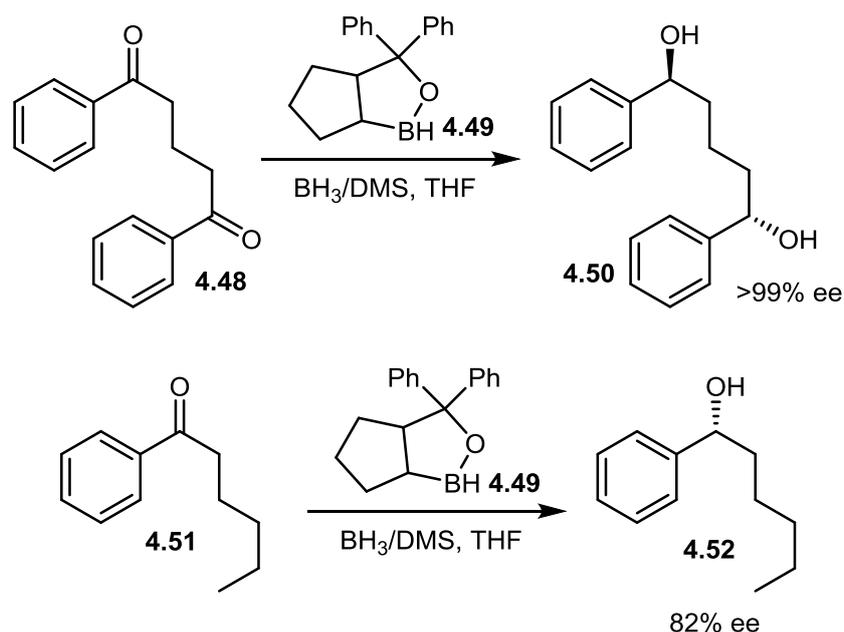
The reaction conditions used were: 0.3 mmols substrate, 0.5 mol% ligand, 0.5 mol% [Ir(COD)Cl]₂, 5 eq KOt-Bu, 3 ml *i*-PrOH, at room temperature, 50 bar H₂, 20 mins. N.D. = not determined

Table 4.12: Asymmetric hydrogenation of ketone substrates with differing electronic environments, with Ir(PNN) complex to investigate the effect on reaction rate over a 20 minute time period.

The results showed that there was indeed a small difference of in reaction rate showing that the control (R=H) was the most reactive, and the electron rich was least reactive.

Both Noyori²⁰ and Phillips²⁵ similar effects, for example Noyori showed that the rate of reaction of the electron deficient *para*-trifluoromethylbenzophenone can hydrogenated 11 times faster than the analogous *para*-methoxy ketone. These iridium catalysts may well reduce electron rich ketones slower, but the differences are not very pronounced.

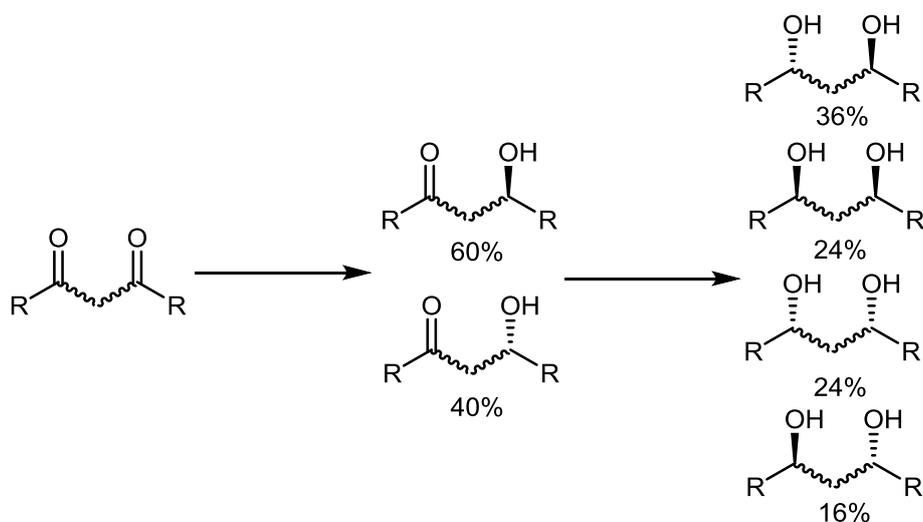
It was decided to investigate a diketone substrate. This type of selective hydrogenation exploit the Horeau effect;³² if there are a number of stereo centres created by the same reaction; there can be an amplification in enantioselectivity. The Horeau effect can be seen in the case of the reduction of C₂ symmetric ketones to form symmetric diols.



Scheme 4.10: Comparative example of the Horeau effect with mono and diketones analogues.²⁷

The above examples in Scheme 4.10²⁷ show that a significant increase in selectivity can arise when using an analogous symmetrical diketone.

An estimate of the potential amplification produced from the phenomenon can even be calculated, if the assumption is made that there is no effect of the substrate on the selectivity of the reaction. A schematic of the phenomenon is shown below in Scheme 4.11.

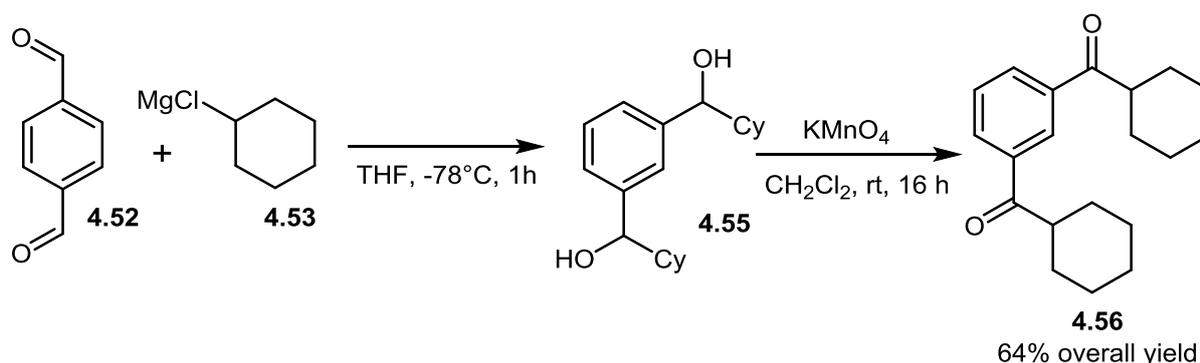


Scheme 4.11: A hypothetical amplification of selectivity by the Horeau effect

For example, in this hypothetical example of a reaction with a mediocre 20% enantiomeric excess generated of a monoalcohol, (i.e. 60% S and 40% R), then the subsequent full reduction to the dialcohol would give an enantiomeric excess of 38.5%, which is almost double of that of a monoalcohol. A downside to this is a large amount of *meso* compound is produced, in this case 48% of the final product would be the *meso* compound, although this may often be removed by purification methods such as flash chromatography.

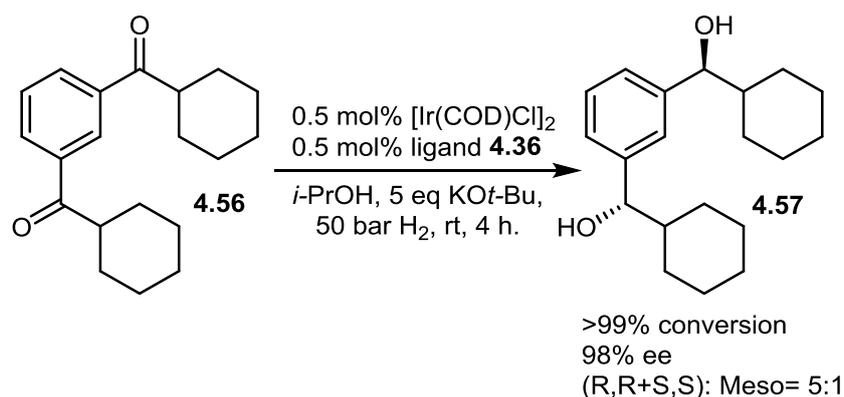
It is also the case that the higher the selectivity of a particular reaction the lower the amount of *meso* compound produced and hence there is a less dramatic increase in selectivity, for example if the initial selectivity was 91% as in the case of the cyclohexyl ketone hydrogenation then the calculated selectivity would be 99.6% enantiomeric excess, assuming no factors such as steric hindrance or electronic effects had an involvement in the reaction.

The synthesis of the diketone **4.56** (shown below in Scheme 4.12) was chosen to synthesised, as this would be a C₂ symmetric variation of the cyclohexyl ketone.



Scheme 4.12: Synthesis of a C₂ symmetric analogue of cyclohexyl phenyl ketone.

This was synthesised by the Grignard reaction of cyclohexylmagnesium chloride with isophthalaldehyde (**4.52**), which generates the dialcohol (**4.55**), this can then be oxidised to the required product using an excess of potassium permanganate. When hydrogenated using the IrPNN complex, the reaction proceeded to full conversion after 4 hours at room temperature as shown in Scheme 4.13.



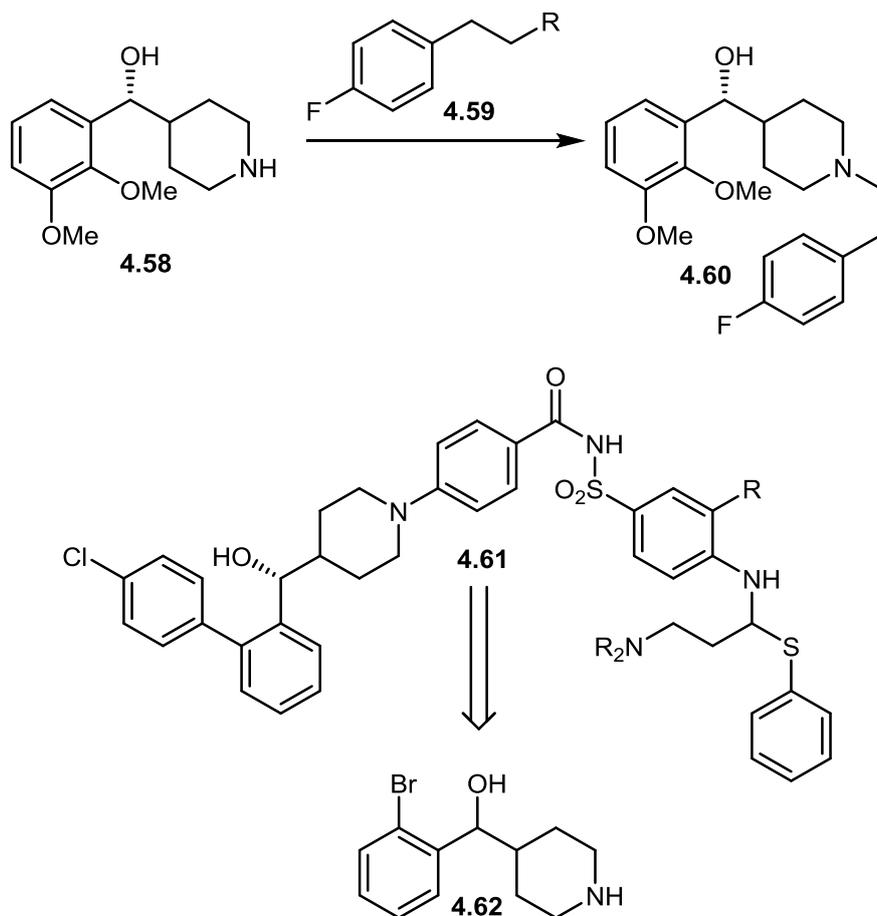
Scheme 4.13: Hydrogenation of C₂ symmetric diketone **4.56**.

The enantioselectivity of the reaction was lower than expected possibly due to substrate effects, but there was still a significant increase in selectivity from 94% to 98% ee, when compared with the analogous mono ketone and a ratio of (*R,R+S,S*):Meso of 5:1 (calculated using HPLC and NMR data).

4.9 Demonstration of the Potential Utility of the IrPNN System.

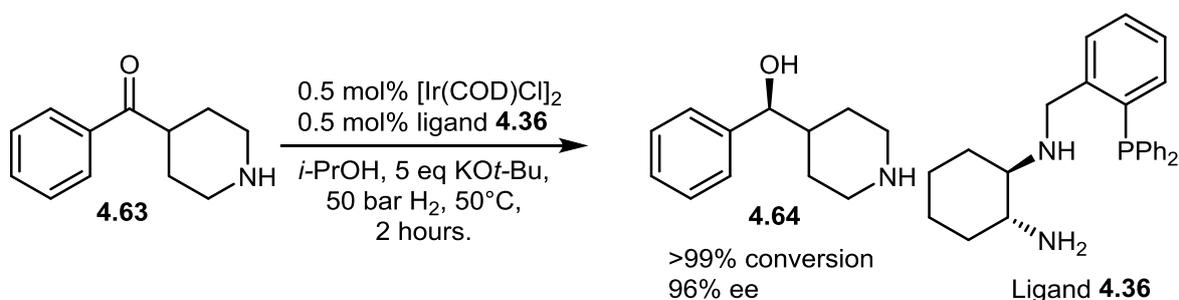
As discussed at the beginning of the chapter chiral alcohols are very important building blocks in the fine chemistry and pharmaceutical industries. A structural moiety that is quite prevalent in a number of different potential drug moles is a secondary alcohol with a piperidine substituent such as the alcohol shown below. As the [RuCl₂(PNN)(DMSO)] type catalysts have previously been shown to be compatible with substrates containing heteroatoms and the IrPNN catalyst has been shown to give high selectivity with ketones bearing cyclohexyl substituents it was decided to look into the hydrogenation of 4-benzoylpiperidine, which is commercially available.

This type of chiral secondary alcohol, appears in many drugs and drug leads. Two examples are; (*R*)- α -(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol a 5HT₂ (serotonin) antagonist, and the Bcl-2/ Bcl-X₁, inhibitors, that are potential candidates for cancer treatments.^{28, 29} The structures, and potential synthetic pathways for synthesis form secondary alcohols are shown in Scheme 4.14.



Scheme 4.14: Use of piperidyl alcohols in the synthesis of drug molecules, such as 5HT₂ (serotonin) antagonist, and the Bcl-2/ Bcl-X₁, inhibitors.^{28,29}

The 4-benzoylpiperidine substrate was subjected to the standard hydrogenation conditions used for cyclohexyl acetophenone derivative (**4.26**), as shown below in Scheme 4.15. The reaction went to full conversion within 2 hours at 50°C. The reaction temperature and slightly longer reaction time were chosen as the ligating nature of the piperidine substituent has the potential to affect the reaction rate.



Scheme 4.15: Hydrogenation of ketone substituted with a piperidine

The selectivity of the reaction was higher than expected, giving an enantioselectivity of 96% ee, which is very slightly higher than when compared with the cyclohexyl analogue. This increase in selectivity might reflect that the piperidine group is the right shape to act as ligating species leading to a more rigid catalytic transition state and hence improving selectivity, although the increase is only minor.

4.10 Conclusions

This work has demonstrated that using iridium instead of ruthenium based catalysts in the asymmetric hydrogenation of ketones has the potential to not only increase the reactivity of a the hydrogenation, it also has the potential to increase the selectivity for certain substrates. It is therefore possible to use different metals as a tool to essentially tune a complex to achieve the best selectivity and reactivity for a specific substrate. Further investigation into other metals for the hydrogenation of ketones and other substrates would be of significant interest to expand the versatility of the PNN type ligands. The catalyst seems to have a ‘sweet spot’ for aryl-secondary alkyl ketones. While some of these probably could be reduced by Noyori catalysts, the level of reactivity and enantioselectivity observed here is especially high. After this thesis was submitted further experiments have been done in the group that reveal that the Ir/PNN system simultaneously catalyses hydrogenation and transfer hydrogenation, and the latter is especially fast and selective.²¹

The best results can be achieved using the *in situ* formed IrPNN catalyst at 25°C, 50 bar H₂, in *i*-PrOH, and using 5 equivalents of KO^{*t*}-Bu. Currently the lowest effective catalyst loading is at 2000:1.

It has been demonstrated that the IrPNN catalytic system is able to hydrogenate a variety of different substrates and is even able to hydrogenate compounds that contain hetero atoms that usually prove difficult, including unprotected piperidine substituents.

4.11 References

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V: CHAPTER V: EXPERIMENTAL

5.1 GENERAL INFORMATION

Except where stated, otherwise all reactions were performed under an atmosphere of dry nitrogen, Schlenk techniques were used to maintain an inert environment. Where applicable for reasons of moisture and air sensitivity, solvents were dried and degassed before use. Technical grade solvents were used for work up or purification procedures. Unless stated, commercially procured starting materials and reagents were used as received without further purification.

Pressurised reactions were carried out in stainless steel autoclaves fitted with either a glass liner or in sealed microwave vials perforated with syringe needles. The autoclave was pressurised with hydrogen gas to the required pressure in bar and checked for leaks before use. If required the autoclave was heated with the aid of an oil bath or a heating jacket.

NMR spectra for ^1H , ^{13}C , ^{19}F and ^{31}P nuclei, was obtained on a Bruker AVANCE III 500, Bruker AVANCE II 400 or a Bruker AVANCE 300 spectrometer. Chemical shifts are quoted as ppm and referenced to residual solvent protons. Proton multiplicity are given using the following abbreviations; singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), multiplet (*m*), broad (*br*) and coupling constants (*J*) are quoted as Hz.

Mass spectrometry measurements were obtained by Mrs Caroline Horsburgh at the University of St Andrews using a Micromass GCT (electrospray ionisation spectra (ESI)) operating in positive or negative mode, from solutions of methanol, acetonitrile or water. For electron impact (EI) spectra and chemical ionisation (CI) spectra, a VG platform spectrometer was used.

Infrared spectra were carried out on a Perkin Elmer Paragon 1000 Spectrum GX FT-IR system. Compounds were analysed either as a nujol mull or as a thin film.

Elemental microanalysis was performed by Mr Stephen Boyer at London Metropolitan University or by Ms Sylvia Williamson at the University of St Andrews.

Enantiomeric excesses were determined from traces obtained using high performance liquid chromatography, performed on a Varian Prostar system operated by Galaxie workstation software. A variety of chiral columns were employed with mixtures of HPLC grade hexane and isopropanol used as the mobile phase (details of which are outlined in the experimental section below).

Specific rotation values were calculated from optical rotation measurements, carried out on a Perkin Elmer 341 Polarimeter using a 5 ml quartz cell with a 1 cm path length. Experiments were carried out at room temperature using the sodium D-line and a suitable solvent.

Thin layer chromatography (TLC) was performed on pre-coated Aldrich TLC plates (G/UV254). Visualisation was carried out by absorption of ultraviolet light and/or thermal decomposition after dipping in an aqueous solution of potassium permanganate/sodium hydroxide.

Flash column chromatography was carried out using Davisil Silica- Flash Gel 35 – 70 μm , eluting with solvents applied under a positive pressure generated with the aid of bellows.

5.2 EXPERIMENTAL FOR CHAPTER II

Reagent Information.

2,3-Benzofuran, 2-(*p*-chlorobenzoyl)benzofuran, titanium tetrachloride, *n*-butyllithium, chlorotrimethylsilane, benzeneruthenium(II) chloride dimer, (1*R*,2*S*)-(+)-cis-1-amino-2-indanol were all obtained from Sigma-Aldrich. (1*S*,2*S*)-(+)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine was obtained from Alfa Aesar. Dichloro(*p*-cymene)ruthenium(II) dimer was obtained from Strem Chemicals. [RuCl₂(*R*-HEXAPHEMP)(*R,R*-DPEN)], [RuCl₂(*S*-PhanePhos)(*R,R*-DPEN)], [RuCl₂(*S*-(*xy*l)-PhanePhos)(*R,R*-DPEN)], were donated by Dr Reddy's Chirotech Technology. Pentamethylcyclopentadienyl iridium dichloride dimer, [RuCl₂(*R*-BINAP)(*R,R*-DPEN)], the ruthenium PNN complexes were prepared using literature procedures.^{1,2,3,4}

General Methods

General Procedure for the Acylation of 2-(Trimethylsilyl)benzofuran.

To a solution of an acid chloride (1.1 eq) in dry CH_2Cl_2 under a nitrogen atmosphere, trimethylsilylbenzofuran (1.0 eq) was added dropwise. The solution was stirred vigorously at room temperature, whilst TiCl_4 (1.25 eq) was added carefully in a dropwise fashion. The resulting suspension was stirred at room temperature for 48 hrs, followed by addition of water. The solution was extracted with diethyl ether, dried and concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography or recrystallisation.⁵

General Procedure for Transfer Hydrogenation:

Under a nitrogen atmosphere the substrate, internal standard (1-methylnaphthalene), 0.25 mol% metal complex, 0.5 mol% ligand and KO*t*-Bu (1 M solution in BuOH) were transferred into a glass vial and dissolved in 3 ml of dry and degassed solvent and left to stir for 2 minutes. The reaction was then heated and left to stir using an oil bath and hotplate/magnetic stirrer. After 16 hrs the vials were cooled, the crude reaction mixture was then analysed by ^1H NMR using 1-methylnaphthalene as an internal standard to calculate the conversion to product. The conversion was calculated by comparing the ratio of the methylnaphthalene and the substrate proton integrals, before and after the reaction. The product was then isolated by column chromatography (SiO_2 ; hexane/ ethyl acetate).

General Procedure for Pressure Hydrogenation:

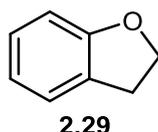
Under a nitrogen atmosphere the substrate, internal standard, metal complex and ligand are transferred into seal glass vial and dissolved in 3 ml of dry and degassed solvent and left to stir for 2 minutes. The vials kept in an inert atmosphere before being transferred to a steel autoclave and pressurised to the required pressure with H_2 gas. The reaction was then heated using a oil bath and left to stir for 16 hours (stirring via small magnetic bars). After 16 hours, the autoclave was immersed in cold water, then once cooled was depressurised. The crude reaction mixture was then analysed by ^1H NMR using 1-methylnaphthalene as an internal standard to calculate the conversion to product. The conversion was calculated by comparing the ratio of the methylnaphthalene and the substrate proton integrals, before and after the reaction. The product was then isolated by column chromatography (SiO_2 ; Hexane/ ethyl

acetate). Note this methodology has been used hundreds of times within the research group, and generally provide similar results to mechanically stirred vessels, although higher pressures are often required.

Enantiomeric Excess Determination:

Enantiomeric excess were calculated using chiral HPLC, with a Varian Prostar apparatus. The equipment was optimised in each case by evaluation of the racemic product produced from a NaBH₄ reduction of the specific ketone. This was performed to confirm good separation of each of the enantiomeric products and to determine the retention times of the enantiomers. Various columns (OD, AD, OD-H, AD-H, AS-H), flow rates and solvent ratios of hexane and *i*-PrOH were used to achieve a good separation of the enantiomers. The specific conditions for each products are stated below.

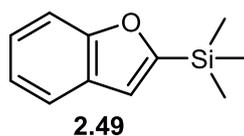
2,3-Dihydrobenzofuran. (2.29)



Under a nitrogen atmosphere, benzofuran (500 mg, 4.23 mmol) was dissolved in MeTHF (2ml) and added to microwave vial containing dippf (8.8mg, 21 μmol, 0.5 mol %) and [Rh(COD)Cl]₂ (5.2mg, 10 μmol, 0.25 mol %) dissolved in MeTHF (3ml). The vial was then transferred to an autoclave, pressurised to 50 bar with hydrogen, and heated to 100°C. After 16 hours the autoclave was cooled, and depressurised. The solvent was then evaporated under vacuum. The residue was purified by column chromatography (8:1 hexane: ethyl acetate), to give a brown/yellow oil (0.31g, 2.58mmols, 61.1% yield, 97% conversion).

δ_{H} (400 MHz, CDCl₃) 7.29-7.17 (2H, m, C_{Ar}H), 6.95-6.86 (2H, m, C_{Ar}H), 4.62 (2H, OCH₂CH₂), 3.27 (2H, t, OCH₂CH₂). δ_{C} (100 MHz, CDCl₃) 160.1, 128.0, 126.9, 125.0, 120.4, 109.4, 71.0, 29.8. m/z (ES⁺) 143.08 ((M+Na)⁺ 100%). This data agrees with the literature.⁵

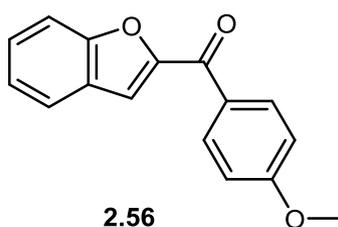
2-(Trimethylsilyl)benzofuran. (2.49)



2-(Trimethylsilyl)benzofuran was synthesised from a method adapted from the literature⁵ 2,3-benzofuran (5.1 ml, 46 mmol) was dissolved in dry THF (50ml) and cooled to -78°C , under a nitrogen atmosphere. *n*-BuLi (40 ml, 1.6M in hexanes, 64 mmol) was added drop wise to the solution over the course of 10 minutes. The resulting suspension was stirred at -78°C for 1 hour, after which chlorotrimethylsilane (9.5 ml, 75 mmol) was added and the mixture was left to stir at -78°C for an additional hour. The solution was then allowed to warm to room temperature, and stirred for a further 16 hrs. After this period the reaction mixture was diluted with hexanes, filtered and evacuated *in vacuo* to give a crude yellow oil (9.108g). The crude product was purified by column chromatography (hexane), to give a colourless oil (7.368g, 39 mmol, 85% yield).

δ_{H} (400 MHz, CDCl_3) 7.60-7.45 (*s*, 2H, ArH), 7.29-7.13 (*m*, 2H, ArH), 6.84 (*s*, 1H, ArCH), 0.34 (*s*, 9H, SiCH₃). δ_{C} (75 MHz, CDCl_3) 165.3 (ArC), 159.9 (ArC), 129.8 (ArC), 126.1 (ArCH), 124.1 (ArCH), 122.8 (ArCH), 117.8 (ArCH), 113.1 (ArCH), 0.1 (Si(CH₃)₃). *m/z* (ES+) 213.12 (M+Na⁺). The data are in agreement with the literature⁶

2-(*p*-Methoxybenzoyl)benzofuran. (2.56)

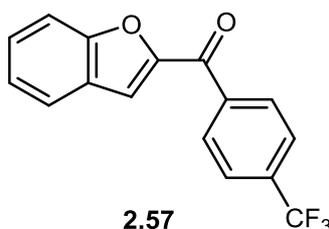


2-(*p*-Methoxybenzoyl)benzofuran was synthesised from a method adapted from the literature¹. *p*-Methoxybenzoylchloride (4.92 g, 28.9 mmol), was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. Trimethylsilylbenzofuran (5.01 g, 26 mmol) was added and the solution was stirred vigorously at room temperature. Titanium tetrachloride (3.6 ml, 33 mmol), was added to the solution in a drop wise manner over the course of 1 hour. The resulting suspension was stirred at room temperature for 48 hrs, followed by addition of water. The solution was extracted with diethyl ether, the combined

organic layers were dried (MgSO_4) and concentrated *in vacuo* to give a crude product. The crude product was purified by recrystallisation (hexane: ethyl acetate), to give a pale yellow crystalline solid (4.42 g, 17.5 mmol, yield 67%).

Mp 95-97 °C. δ_{H} (400 MHz, CDCl_3) 3.91 (*s*, 3H, OCH_3), 7.03 (*d*, 2H, $J = 8.9$, ArH), 7.34 (*t*, $J = 7.7$, 1H, ArH), 7.46-7.51 (*m*, 1H, ArH), 7.52 (*s*, 1H, ArH), 7.63 (*d*, $J = 8.5$, 1H, ArH), 7.72 (*d*, $J = 7.8$, 1H, ArH), 8.09-8.14 (*d*, $J = 8.9$, 2H, ArH). δ_{C} (75 MHz, CDCl_3) 55.9 (OCH_3), 112.8 (ArCH), 114.3 (2x ArCH), 115.9 (ArCH), 123.5 (ArCH), 124.3 (ArCH), 127.5 (ArC), 128.4 (ArCH), 130.2 (ArC), 132.4 (2x ArC), 153.1 (ArCO), 156.2 (ArCO), 164.0 (ArCO), 183.2 (C=O). m/z (ES^+) 274.82 ($\text{M}+\text{Na}^+$). The data are in agreement with the literature.⁷

2-(*p*-(Trifluoromethyl)benzoyl)benzofuran. (2.57)

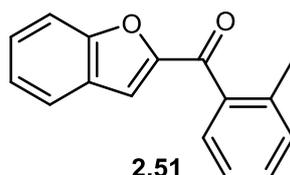


2-(*p*-(Trifluoromethyl)benzoyl)benzofuran was synthesised from a method adapted from the literature¹. *p*-Trifluoromethylbenzoylchloride (3.56 g, 17.1 mmol), was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. Trimethylsilylbenzofuran (2.95g, 15.5 mmol), was added and the solution was stirred vigorously at room temperature. Titanium tetrachloride (2.1 ml, 19.6 mmol), was added to the solution in a drop wise manner over the course of 1 hour. The resulting suspension was stirred at room temperature for 48 hrs, followed by addition of water. The solution was extracted with diethyl ether, the combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give a crude product. The crude product was purified by recrystallisation (hexane: ethyl acetate), to give a white crystalline solid (1.13 g, 3.9 mmol, 25% yield).

Mp 102-103 °C. δ_{H} (300 MHz, CDCl_3) 7.29 (*t*, $J = 7.4$, 1H, ArH), 7.40-7.79 (*m*, 5H, 5x ArH), 8.09 (*d*, $J = 8.0$, 2H, ArH). δ_{C} (75 MHz, CDCl_3) 113.0 (ArCH), 117.5 (ArCH), 123.9 (ArCH), 124.6 (ArCH), 126.0 (ArCH), 127.3 (ArC), 129.3 (ArCH), 130.2 (ArCH), 134.4 (ArC), 134.9 (ArC), 140.5 (ArCO), 152.3 (ArCO), 156.6 (ArCO), 183.6 (C=O). m/z (ES^+) 312.82 ($\text{M}+\text{Na}^+$). **HRMS** found 313.0452, $\text{C}_{16}\text{H}_9\text{O}_2\text{NaF}_3$ requires 313.0452.

IR ($\nu_{\text{max}}/\text{cm}^{-1}$), 3313, 3071, 1950, 1668, 1613, 1582, 1550, 1478, 1448, 1316, 1217, 1131, 1060, 1035, 1006.

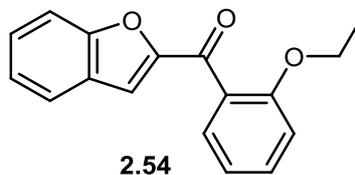
2-(*o*-Methylbenzoyl)benzofuran. (2.51)



2-(*o*-Methylbenzoyl)benzofuran was synthesised from a method adapted from the literature.¹ *o*-Methylbenzoylchloride (4.39 g, 28.5 mmol), was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. Trimethylsilylbenzofuran (5.00 g, 26.3 mmol), was added and the solution was stirred vigorously at room temperature. Titanium tetrachloride (3.6 ml, 33.2 mmol), was added to the solution in a drop wise manner over the course of 1 hour. The resulting suspension was stirred at room temperature for 48 hrs, followed by addition of water. The solution was extracted with diethyl ether, the combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (hexane: ethyl acetate, 10:1), to give a pale yellow oil (4.10 g, 17.4 mmol, yield 66%).

δ_{H} (400 MHz, CDCl_3) 2.43 (*s*, 3H, CH_3), 7.26-7.33 (*m*, 4H, ArH), 7.40-7.45 (*m*, 1H, ArH), 7.46-7.51 (*m*, 1H, ArH), 7.56 (*m*, 1H, ArH), 7.62 (*m*, 1H, ArH), 7.60-7.64 (*m*, 1 H, ArH), 7.66-7.69 (*m*, 1H, ArH). δ_{C} (75 MHz, CDCl_3) 20.2 (CH_3), 113.2 (ArCH), 117.9 (ArCH), 123.9 (ArCH), 124.4 (ArCH), 125.7 (ArCH), 127.5 (ArC), 128.9 (ArCH), 129.0 (ArCH), 131.4 (ArCH), 131.7 (ArCH), 137.8 (ArC), 153.1 (ArCO), 156.7 (ArCO), 187.4 (C=O). **m/z** (ES^+) 258.85 ($\text{M}+\text{Na}^+$). **HRMS** found 259.0732, $\text{C}_{16}\text{H}_{12}\text{O}_2$ Na requires 259.0735. **IR** ($\nu_{\text{max}}/\text{cm}^{-1}$), 3064, 1939, 1660, 1549, 1445, 1328, 1219, 1186, 1114; **CHN**: C: 81.39, H: 5.05. ($\text{C}_{16}\text{H}_{12}\text{O}_2$ requires C: 81.34, H: 5.12).

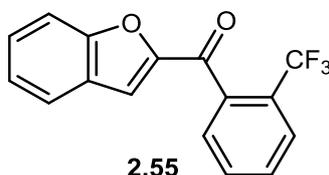
2-(*o*-(Ethoxy)benzoyl)benzofuran. (2.54)



2-(*o*-(ethoxy)benzoyl)benzofuran was synthesised from a method adapted from the literature¹. *o*-Ethoxybenzoylchloride (3.32 g, 18.0 mmol), was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. Trimethylsilylbenzofuran (3.09 g, 16.3 mmol), was added and the solution was stirred vigorously at room temperature. Titanium tetrachloride (2.7 ml, 22.4 mmol), was added to the solution in a drop wise manner over the course of 1 hour. The resulting suspension was stirred at room temperature for 48 hrs, followed by addition of water. The solution was extracted with diethyl ether, the combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (hexane: ethyl acetate, 20:1), to give a yellow oil (3.697 g, 12.75 mmol, 78% yield).

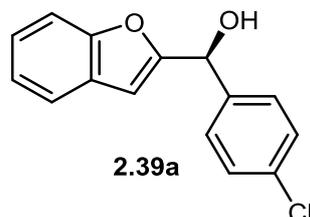
δ_{H} (300 MHz, CDCl₃) 1.21 (*t*, *J* = 7.0, 3H, OCH₂CH₃), 4.07 (*q*, *J* = 7.0, 2H, CH₂), 6.99-7.04 (*m*, 2H, ArCH), 7.27-7.36 (*m*, 2H, ArH), 7.44-7.53 (*m*, 3H, ArH), 7.57-7.60 (*m*, 1H, ArH), 7.66-7.71 (*m*, 1H, ArH); δ_{C} (75 MHz, CDCl₃) 14.9 (CH₂CH₃), 64.7 (CH₂CH₃), 112.9 (ArCH), 113.1 (ArCH), 116.5 (ArCH), 120.7 (ArCH), 123.7 (ArCH), 124.2 (ArCH), 127.6 (ArC), 128.5 (ArC), 128.6 (ArCH), 130.1 (ArCH), 133.0 (ArCH), 153.6 (ArCO), 156.4 (ArCO), 157.5 (ArCO), 185.6 (C=O); *m/z* (ES⁺) 288.87 (M+Na⁺). HRMS found 289.0847, C₁₇H₁₄O₃Na requires 289.0841. IR (ν_{max} /cm⁻¹), 2981, 1947, 1799, 1659, 1598, 1551, 1475, 1450, 1393, 1350, 1329, 1301, 1247, 1185, 1115, 1043, 1005; CHN: C: 76.59, H: 5.27. (C₁₇H₁₄O₃ requires C: 76.68, H: 5.30).

2-(*o*-(Trifluoromethyl)benzoyl)benzofuran. (2.55)



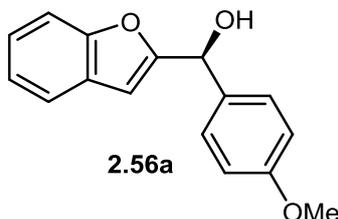
2-(*o*-(Trifluoromethyl)benzoyl)benzofuran was synthesised from a method adapted from the literature¹. *o*-Trifluoromethylbenzoylchloride (2.98 g, 15.7 mmol), was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. Trimethylsilylbenzofuran (2.98 g, 15.7 mmol), was added and the solution was stirred vigorously at room temperature. Titanium tetrachloride (2.7 ml, 22.4 mmol), was added to the solution in a drop wise manner over the course of 1 hour. The resulting suspension was stirred at room temperature for 48 hrs, followed by addition of water. The solution was extracted with diethyl ether, the combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (hexane: ethyl acetate, 8:1). A yellow oil was obtained (2.248 g, 7.75 mmol, 49% yield).

δ_{H} (300 MHz, CDCl₃) 7.18-7.27 (*m*, 2H, ArH), 7.41-7.46 (*m*, 1H, ArH), 7.49-7.54 (*m*, 2H, ArH), 7.56-7.64 (*m*, 3H, ArH), 7.69-7.76 (*m*, 1H, ArH). δ_{C} (75 MHz, CDCl₃) 112.7 (ArCH), 118.0 (ArCH), 122.2 (ArC), 123.6 (ArCH), 124.2 (ArCH), 126.8 (ArC) 126.9 (ArCH), 128.6 (ArCH), 129.1 (ArCH), 130.6 (ArCH), 131.5 (ArCH), 136.7 (ArC), 151.9 (ArCO), 156.5 (ArCO), 184.3 (C=O). δ_{F} (376 MHz, CDCl₃) -58.43. **m/z** (ES⁺) 312.78 (M+Na⁺). **HRMS** found 313.0448, C₁₆H₉O₂NaF₃ requires 313.0452. **IR** (ν_{max} /cm⁻¹), 2924, 1651, 1459, 1377, 1326, 1165, 1109, 1067, 1004. **CHN**: C: 66.31, H: 3.04. (C₁₆H₉O₂ requires C: 66.21, H: 3.13).

(S)-p-Chlorophenyl(benzofuran-2-yl)methanol. (2.39a)


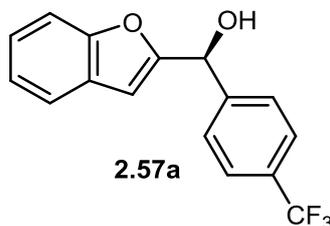
Under a nitrogen atmosphere, a stock solution (1 ml, in *i*-PrOH) containing pentamethylcyclopentadienylrhodium(III) chloride dimer, ([RhCp*Cl₂]₂, 0.3 mg/ml, 0.5 μmol, 0.25 mol%) and (1*R*,2*S*)-cis-aminoindanol (0.15 mg/ml, 1 μmol, 0.5 mol%) was added to dry and degassed *i*-PrOH (2 ml), and left to stir for 1 hour at 40°C. 2-(*p*-Chlorobenzoyl)benzofuran (50.1 mg, 0.2 mmol), potassium *tert*-butoxide (1 mol%, 1 M solution in *t*-BuOH) were added to the stirred solution and the reaction mixture was then heated to 40°C. The reaction was left to stir for 16 hrs, after which the vials were left to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, hexane: ethyl acetate, 3:1). A yellow oil was obtained (49 mg, 0.189 mmol, 95% yield, >99% conversion, 47% ee (determined by HPLC: AD-H (hexane: *i*-PrOH, 95:5, flow: 0.5 ml/min)).

$[\alpha]_{\text{D}}^{20} +3.4$ (CHCl₃, *c* = 2.1 g/100 ml). δ_{H} (300 MHz, CDCl₃) 2.55 (br *s*, 1H, **OH**), 5.85 (*s*, 1H, **CHOH**), 6.44 (*s*, 1H, **ArH**), 7.09-7.23 (*m*, 2H, **ArH**), 7.24-7.38 (*m*, 5H, **ArH**), 7.41-7.47 (*m*, 1H, **ArH**). δ_{C} (75 MHz, CDCl₃) 70.4 (**CHOH**), 104.8 (**ArCH**), 111.8 (**ArCH**), 121.7 (**ArCH**), 123.5 (**ArCH**), 125.1 (**ArCH**), 125.9 (**ArCH**), 127.5 (**ArCH**), 128.2 (**ArC**), 130.6 (**ArC**), 144.5 (**ArC**), 155.6 (**ArC**), 158.0 (**ArC**). **m/z** (ES+) 281.01 (M+Na⁺). Data are in agreement with the literature.⁸

(S)-*p*-Methoxyphenyl(benzofuran-2-yl)methanol. (2.56a)


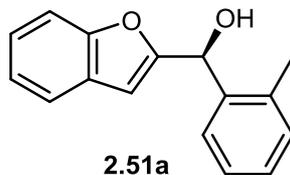
Under a nitrogen atmosphere, a stock solution (1ml, in *i*-PrOH) containing pentamethylcyclopentadienylrhodium(III) chloride dimer, ([RhCp*Cl₂]₂, 0.4 mg/ml, 0.6 μmol, 0.25 mol%) and (1*R*,2*S*)-cis-aminoindanol (0.18 mg/ml, 1.2 μmol, 0.5 mol%) was added to dry and degassed *i*-PrOH (2 ml), and left to stir for 1 hour at 40°C. 2-(*p*-methoxybenzoyl)benzofuran (57.4mg, 0.23 mmol), potassium *tert*-butoxide (1 mol%, 1 M solution in *t*-BuOH) were added to the stirred solution and the reaction mixture was then heated to 40°C. The reaction was left to stir for 16 hrs, after which the vials were left to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, hexane: ethyl acetate, 3:1). A yellow oil was obtained (50 mg, 0.20 mmol, 87% yield, >99% conversion, 28% ee (determined by HPLC: OD-H (*i*-PrOH/hexane: 5/90, flow: 1.0 ml/min))).

$[\alpha]_{\text{D}}^{20} +6.3$ (CHCl₃, *c* = 2.0 g/100 ml); δ_{H} (300 MHz, CDCl₃) 2.45 (br s, 1H, OH), 3.73 (s, 3H, OCH₃), 5.82 (s, 1H, CHOH), 6.45 (s, 1H, ArH), 6.84 (d, *J* = 8.8, 2H, ArH), 7.09-7.21 (m, 2H, ArH), 7.30-7.39 (m, 3H, ArH), 7.40-7.46 (m, 1H, ArH). δ_{C} (75 MHz, CDCl₃) 55.7 (OCH₃), 70.8 (CHOH), 104.2 (ArCH), 111.8 (ArCH), 114.4 (ArCH), 121.5 (ArCH), 123.2 (ArCH), 124.6 (ArCH), 128.5 (ArC ipso-CH), 128.6 (ArCH), 133.0 (ArC), 155.5 (ArCO), 159.2 (ArCO), 160.1 (ArCO). *m/z* (ES⁺) 276.86 (M+Na⁺). Data are in agreement with the literature.⁷

(S)-p-(Trifluoromethyl)phenyl(benzofuran-2-yl)methanol. (2.57a)


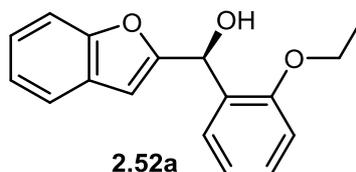
Under a nitrogen atmosphere, a stock solution (1ml, in *i*-PrOH) containing pentamethylcyclopentadienylrhodium(III) chloride dimer, ([RhCp*Cl₂)₂, 0.3 mg/ml, 0.4 μmol, 0.25 mol%) and (1*R*,2*S*)-cis-aminoindanol (0.13 mg/ml, 0.85 μmol, 0.5 mol%) was added to dry and degassed *i*-PrOH (2 ml), and left to stir for 1 hour at 40°C. 2-(*p*-trifluoromethylbenzoyl)benzofuran (50.7mg, 0.174 mmol), potassium *tert*-butoxide (1 mol%, 1 M solution in *t*-BuOH) were added to the stirred solution and the reaction mixture was then heated to 40°C. The reaction was left to stir for 16 hrs, after which the vials were left to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, hexane: ethyl acetate, 3:1). A pale yellow powder was obtained (50 mg, 0.171 mmol, 98% yield, >99% conversion, 76% ee (determined by HPLC: OD-H (*i*-PrOH/hexane: 5/95, flow: 1.0 ml/min))). Analysis of the diastereomeric ester formed after the treatment with methoxyphenylacetic acid (DCC and DMAP) shows this to have the (*S*) configuration.

$[\alpha]_{\text{D}}^{20} -1.8$ (CHCl₃, *c* = 1.5 g/100 ml). δ_{H} (300 MHz, CDCl₃) 2.66 (br *s*, 1H, OH), 5.93 (*s*, 1H, CHOH), 6.46 (*s*, 1H, ArH), 7.08-7.25 (*m*, 2H, ArH), 7.36 (*d*, *J* = 8.2, 1H, ArH), 7.44 (*d*, *J* = 7.8, 1H, ArH), 7.48-4.61 (*m*, 4H, 4xArH). δ_{C} (75 MHz, CDCl₃) 70.4 (CHOH), 104.6 (ArCH), 111.8 (ArCH), 121.6 (ArCH), 123.4 (ArCH), 125.0 (ArCH), 128.3 (ArC), 128.6 (2xArCH), 129.2 (2xArCH), 134.6 (ArC), 139.1 (ArC), 155.5 (ArCO), 158.4 (ArCO). δ_{F} (282 MHz, CDCl₃) -63.01. **m/z** (ES-) 290.87 (M-H); **HRMS** found 291.0623, C₁₆H₁₀O₂F₃ requires 291.0633. **IR** (ν_{max} /cm⁻¹), 3260, 2854, 1479, 1454, 1411, 1329, 1256, 1167, 1124, 1069, 1013.

(S)-*o*-Methylphenyl(benzofuran-2-yl)methanol. (2.51a)


Under a nitrogen atmosphere, a stock solution (1ml, in *i*-PrOH) containing pentamethylcyclopentadienylrhodium(III) chloride dimer, ([RhCp*Cl₂]₂, 0.4 mg/ml, 0.6 μmol, 0.25 mol%) and (1*R*,2*S*)-cis-aminoindanol (0.17 mg/ml, 1.2 μmol, 0.5 mol%) was added to dry and degassed *i*-PrOH (2 ml), and left to stir for 1 hour at 40°C. 2-(*o*-methylbenzoyl)benzofuran (58.3mg, 0.23 mmol), potassium *tert*-butoxide (1 mol%, 1 M solution in *t*-BuOH) were added to the stirred solution and the reaction mixture was then heated to 40°C. The reaction was left to stir for 16 hrs, after which the vials were left to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, hexane: ethyl acetate, 3:1). A yellow semi-solid was obtained (69 mg, 0.228 mmol, 99% yield, >99% conversion, 74% ee (determined by HPLC: OD-H (hexane: *i*-PrOH: 90:10, flow: 0.5 ml/min))). Analysis of the diastereomeric ester formed after the treatment with methoxyphenylacetic acid (DCC and DMAP) shows this to have the (*S*) configuration.

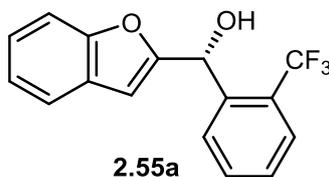
[α]_D²⁰ +28.2 (CHCl₃, c = 2.2 g/100 ml); δ_H(300 MHz, CDCl₃) 2.28 (*s*, 3H, CH₃), 2.42 (*br s*, 1H, OH), 6.07 (*s*, 1H, CHOH), 6.34 (*s*, 1H, ArH) 7.08-7.24 (*m*, 5H, ArH), 7.35-7.45 (*m*, 2H, ArH), 7.46-7.53 (*m*, 1H, ArH); δ_C (75 MHz, CDCl₃) 19.1 (CH₃), 67.5 (CHOH), 104.6 (ArCH), 111.5 (ArCH), 121.3 (ArCH), 122.7 (ArCH), 124.5 (ArCH), 126.3 (ArCH), 128.4 (ArC), 128.7 (ArCH), 130.9 (ArCH), 136.0 (ArC), 138.7 (ArC), 156.0 (ArCO), 159.2 (ArCO); *m/z* (ES⁺) 260.77 (M+Na⁺). Data are in agreement with the literature.⁷

(S)-o-Ethoxyphenyl(benzofuran-2-yl)methanol. (2.52a)


Under a nitrogen atmosphere, a stock solution (1ml, in *i*-PrOH) containing pentamethylcyclopentadienylrhodium(III) chloride dimer, ([RhCp*Cl₂]₂, 0.3 mg/ml, 0.6 μmol, 0.25 mol%) and (1*R*,2*S*)-cis-aminoindanol (0.14 mg/ml, 1.0 μmol, 0.5 mol%) was added to dry and degassed *i*-PrOH (2 ml), and left to stir for 1 hour at 40°C. 2-(*o*-ethoxybenzoyl)benzofuran (51.3mg, 0.193 mmol), potassium *tert*-butoxide (1 mol%, 1 M solution in *t*-BuOH) were added to the stirred solution and the reaction mixture was then heated to 40°C. The reaction was left to stir for 16 hrs, after which the vials were left to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, hexane: ethyl acetate, 3:1). An orange oil was obtained (51 mg, 0.190 mmol, 99% yield, >99% conversion, 45% ee (determined by HPLC: AD-H (*i*-PrOH/hexane: 10/90, flow: 0.5 ml/min))).

[α]_D²⁰ +7.6 (CHCl₃, c = 2.3 g/100 ml); δ_H(400 MHz, CDCl₃) 1.37 (*t*, *J* = 6.9 Hz, 3H, CH₂CH₃), 3.42 (*d*, *J* = 7.2, 1H, OH), 4.01 (app *dq*, 2H, CH₂CH₃), 6.14 (*d*, *J* = 6.6, 1H, CHOH), 6.51 (*s*, 1H, ArH), 6.92 (*d*, *J*₁ = 8.3, 1H, ArH), 6.98 (*td*, *J*₁ = 7.5, *J*₂ = 1.1, 1H, ArH), 7.16-7.25 (*m*, 2H, ArH), 7.28-7.34 (*m*, 1H, ArH), 7.36 (*dd*, *J*₁ = 7.5, *J*₂ = 1.7 1H, ArH), 7.43-7.46 (*m*, 1H, ArH), 7.48-7.53 (*m*, 1H, ArH). δ_C (75 MHz, CDCl₃) 14.8 (CH₂CH₃), 63.9 (CH₂CH₃), 67.8 (CHOH), 103.4 (ArCH), 111.3 (ArCH), 111.8 (ArCH), 120.8 (ArCH), 120.9 (ArCH), 122.6 (ArCH), 123.9 (ArCH), 128.4 (ArCH), 128.6 (ArC), 129.4 (ArCH), 155.0(ArCO), 156.4 (ArCO), 158.7 (ArCO). **m/z** (ES+) 290.86 (M+Na⁺). **HRMS** found 291.0997, C₁₇H₁₆O₃Na requires 291.0997. **IR** (ν_{max}/cm⁻¹), 3419, 2851, 1475, 1454, 1326, 1163, 1122, 1062, 1009; **CHN**: C: 75.94, H: 6.01. (C₁₇H₁₆O₃ requires C: 76.1, H: 6.01).

(R)-o-(Trifluoromethyl)phenyl(benzofuran-2-yl)methanol. (2.55a)



Under a nitrogen atmosphere, a stock solution (1ml, in *i*-PrOH) containing [RuCl₂(*R*-BINAP)((*R,R*)-DPEN)] (0.8mg/l, 0.8 μmol, 0.5 mol%) was added to dry and degassed *i*-PrOH (2 ml), and left to stir for 1 hour at 40°C. 2-(*o*-trifluoromethylbenzoyl)benzofuran (51 mg, 0.16 mmol), potassium *tert*-butoxide (1 mol%, 1 M solution in *t*-BuOH) were added to the stirred solution and the reaction mixture was then heated to 40°C. The reaction was left to stir for 16 hrs, after which the vials were left to cool to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, hexane: ethyl acetate, 3:1). A brown oil was obtained (29mg, 0.099 mmol, 62% yield, 77% conversion, 81% ee (determined by HPLC: AD-H (*i*-PrOH/hexane: 10/90, flow: 0.5 ml/min))).

$[\alpha]_D^{20}$ -24.7 (CHCl₃, c = 0.75 g/100 ml). δ_H (300 MHz, CDCl₃) 2.69 (br *s*, 1H, OH), 6.30 (*s*, 1H, CHOH), 6.37 (*s*, 1H, ArH), 7.08-7.22 (*m*, 2H, ArH), 7.34-7.44 (*m*, 3H, ArH), 7.55 (*t*, *J* = 7.6, 1H, ArH), 7.62 (*d*, *J* = 7.6, 1H, ArH), 7.84 (*d*, *J* = 7.8, 1H, ArH). δ_C (75 MHz, CDCl₃) 66.5 (CHOH), 105.0 (ArCH), 111.8 (CHCC=O), 121.6 (ArCH), 122.8 (ArC), 123.3 (ArCH), 124.9(ArCH), 126.1 (ArCH), 126.5 (ArC), 128.3 (ArC), 128.9 (ArCH), 129.7 (ArCH), 132.8 (ArCH), 139.3 (ArC), 155.5 (ArCO), 157.9 (ArCO). δ_F (282 MHz, CDCl₃) -58.57. **m/z** (ES+) 314.81 (M+Na⁺). **HRMS** found 315.0597, C₁₆H₁₁O₂F₃Na requires 315.0609.

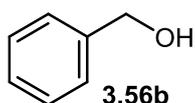
5.3 EXPERIMENTAL FOR CHAPTER III

Reagent Information:

Methyl benzoate, methyl 4-methylbenzoate, methyl 4-fluorobenzoate, methyl 4-chlorobenzoate, methyl 4-bromobenzoate, methyl 2-naphthoate were all obtained from Sigma-Aldrich. Methyl 4-bromobenzoate was obtained from Alfa Aesar. $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ and the $[\text{RuCl}_2(\text{PNX})(\text{DMSO})]$ complexes were prepared using literature procedures.^{9,3,4}

General Procedure for Pressure Hydrogenation: Under a nitrogen atmosphere the metal complex and phosphine ligand (if required) are transferred into a glass vial and dissolved in 2 ml of dry and degassed solvent and refluxed for 10 minutes, If required a stock solution containing the diamine was then added to the vial and refluxed for a further 10 minutes. The ester starting material, and base ($\text{KO}t\text{-Bu}$) were then added. The vials were then transferred to a steel autoclave and pressurised with H_2 gas. The reaction was then heated using a oil bath and left to stir for 16 hours (stirring via small magnetic bars). After 16 hours, the autoclave was immersed in cold water, then depressurised. The crude reaction mixture was then analysed by ^1H NMR using 1-methylnaphthalene as an internal standard to calculate the conversion to product. The conversion was calculated by comparing the ratio of the methylnaphthalene and the substrate proton integrals, before and after the reaction. The product was then isolated by column chromatography (SiO_2 ; Hexane/ ethyl acetate).

Benzyl alcohol. (3.56b)

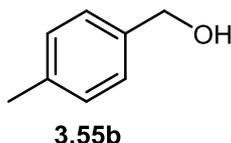


Under a nitrogen atmosphere, $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ (1.8 mg, 4.27 μmol , 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol , 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picolylamine (0.5 $\mu\text{l/ml}$, 4.41 μmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl benzoate (124 μl , 0.84 mmol), and $\text{KO}t\text{-Bu}$ (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 50 $^\circ\text{C}$ temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo*

and the resulting residue was purified by flash column chromatography (silica, hexane: ethyl acetate, 5:1). A yellow oil was obtained (88 mg, 0.81 mmol, 97 % yield).

δ_{H} (400 MHz, CDCl_3) 2.14 (br *s*, 1H, *OH*), 4.67 (*s*, 2H, CH_2), 7.27-7.34 (*m*, 1H, *ArH*), 7.34-7.38 (*m*, 4H, *ArH*). δ_{C} (75 MHz, CDCl_3) 65.3 (CH_2), 127.0 (2x*ArCH*), 127.7 (*ArCH*), 128.6 (2x*ArCH*), 140.9 (*ArC*). *m/z* (GCMS) 108 (*M*⁺). Data are in agreement with the literature.¹⁰

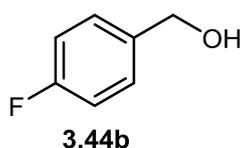
4- Methylbenzyl alcohol. (3.55b)



Under a nitrogen atmosphere, $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ (1.8 mg, 4.27 μmol , 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol , 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picoylamine (0.5 $\mu\text{l/ml}$, 4.41 μmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl 4-methylbenzoate (123.4 mg, 0.82 mmol), and *KOt*-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 50°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 5:1). A white solid was obtained (96 mg, 0.79 mmol, 96 % yield).

Mp 59-60 °C. δ_{H} (400 MHz, CDCl_3) 1.87 (br *s*, 1H, *OH*), 2.26 (*s*, 3H, CH_3), 4.53 (*s*, 2H, CH_2), 7.15 (*dd*, $J_1= 7.8$, $J_2= 26.7$, 4H, *ArH*). δ_{C} (75 MHz, CDCl_3) 21.2 (CH_3) 65.2 (CH_2), 127.1 (2x*ArCH*), 129.2 (2x*ArCH*), 137.4 (*ArC*), 137.9 (*ArC*). *m/z* (ES⁺) 145.01 (*M*+*Na*⁺). Data are in agreement with the literature.¹⁰

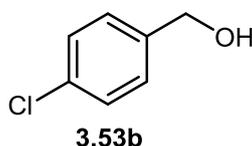
4-Fluorobenzyl alcohol. (3.44b)



Under a nitrogen atmosphere, $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ (1.8 mg, 4.27 μmol , 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol , 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picolylamine (0.5 $\mu\text{l}/\text{ml}$, 4.41 μmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl 4-fluorobenzoate (156 μl 0.85 mmol), and KOt-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 50°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 5:1). A yellow oil was obtained (103 mg, 0.82 mmol, 96 % yield).

δ_{H} (400 MHz, CDCl_3) 2.02 (br s, 1H, OH), 4.63 (s, 2H, CH_2), 7.03 (t, $J=8.7$, 2H, ArCH) 7.28-7.36 (m, 2H, ArCH). δ_{C} (75 MHz, CDCl_3) 64.6 (CH_2), 115.3 (ArCH), 115.5 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 136.6 (CCH_2OH), 161.1 (CF). δ_{F} (377 MHz, CDCl_3) 115.4. m/z (GCMS) 126 (M+). Data are in agreement with the literature.¹¹

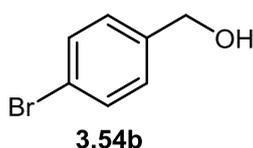
4-Chlorobenzyl alcohol. (3.53b)



Under a nitrogen atmosphere, $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ (1.8 mg, 4.27 μmol , 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol , 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picolylamine (0.5 $\mu\text{l}/\text{ml}$, 4.41 μmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl 4-Chlorobenzoate (143.4mg, 0.84 mmol), and KOt-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 50°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 5:1). A white solid was obtained (117 mg, 0.82 mmol, 98 % yield).

Mp 69-72 °C. δ_{H} (400 MHz, CDCl_3) 1.96 (br *s*, 1H, *OH*), 4.64 (*s*, 2H, *CH*₂), 7.31 (*dd*, $J_1=8.8$, $J_2=12.1$, 4H, *ArCH*). δ_{C} (75 MHz, CDCl_3) 64.5 (*CH*₂), 128.3 (2x*ArCH*), 128.7 (2x*ArCH*), 133.3 (*CCH*₂*OH*), 139.3 (*CCl*). *m/z* (GCMS) 142 (*M*⁺). Data are in agreement with the literature.¹⁰

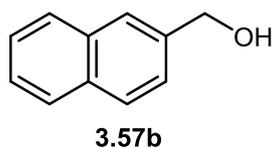
4-Bromobenzyl alcohol: (3.54b)



Under a nitrogen atmosphere, $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ (1.8 mg, 4.27 μmol , 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol , 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picolylamine (0.5 $\mu\text{l/ml}$, 4.41 μmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl 4-bromobenzoate (180.6, 0.84 mmol), and *KOt*-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 50°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 5:1). A white solid was obtained (149 mg, 0.80 mmol, 95 % yield).

Mp 77-78 °C. δ_{H} (400 MHz, CDCl_3) 2.28 (br *s*, 1H, *OH*), 4.60 (*s*, 2H, *CH*₂), 7.20 (*d*, $J=8.6$, 2H, *ArCH*) 7.45 (*d*, $J=8.6$, 2H, *ArCH*). δ_{C} (75 MHz, CDCl_3) 64.5 (*CH*₂), 121.5 (*CCH*₂*OH*), 128.6 (2x*ArCH*), 131.6 (2x*ArCH*), 139.8 (*CBr*). *m/z* (GCMS) 186 (*M*⁺). Data are in agreement with the literature.¹⁰

2-Naphthylmethanol. (3.57b)

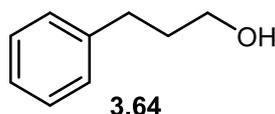


Under a nitrogen atmosphere, $[\text{RuCl}_2(\text{NBD})(\text{Py})_2]$ (1.8 mg, 4.27 μmol , 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol , 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes.

A stock solution (1ml, in MeTHF) of 2-picolyamine (0.5µl/ml, 4.41 µmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl 2-naphthoate (186.1, 0.84 mmol), and KOt-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 50°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 5:1). A white solid was obtained (121 mg, 91 % yield).

Mp 79-81 °C. δ_{H} (400 MHz, CDCl₃) 2.50 (br s, 1H, OH), 4.81 (s, 2H, CH₂), 7.42-7.53 (m, 3H, ArCH), 7.77 (s, 1H ArCH), 7.80-7.86 (m, 3H, ArCH). δ_{C} (75 MHz, CDCl₃) 65.3 (CH₂), 125.2 (ArCH), 125.4 (ArCH), 125.9 (ArCH), 126.2 (ArCH), 127.8 (ArCH), 127.9 (ArCH), 128.3 (ArCH), 132.9 (ArC), 133.4 (ArC), 138.4 (CCH₂OH). m/z (ES⁺) 180.94 (M+Na⁺). Data are in agreement with the literature.¹³

Benzenepropanol. (3.64)

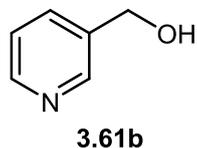


Under a nitrogen atmosphere, [RuCl₂(NBD)(Py)₂] (1.8 mg, 4.27 µmol, 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 µmol, 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picolyamine (0.5µl/ml, 4.41 µmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Ethyl 3-phenylpropionate (147 µl, 0.84 mmol), and KOt-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 100°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 8:1). A colourless oil was obtained (87 mg, 78 % yield).

δ_{H} (400 MHz, CDCl₃) 1.50 (1H, br s, OH), 1.75-1.87 (2H, m, CH₂), 2.63 (1H, t, J₁= 7.7, CH₂), 3.60 (1H, t, CH₂), 7.10-7.15 (3H, m, ArCH), 7.18-7.25 (2H, m, ArCH). δ_{C} (125 MHz, CDCl₃) 32.1 (CH₂), 34.3 (CH₂), 62.3 (CH₂OH), 125.9 (ArCH), 128.4 (2xArCH), 128.5

(2xArCH), 141.8 (ArC). m/z (ES+) 135.96 (M+Na) Data are in agreement with the literature.¹⁴

3-Pyridinemethanol. (3.61b)



Under a nitrogen atmosphere, [RuCl₂(NBD)(Py)₂] (1.8 mg, 4.27 μmol, 0.5 mol%), and 1,3-bis(diphenylphosphino)propane (1.8 mg, 4.37 μmol, 0.5 mol%), was dissolved in 2-methyltetrahydrofuran (2 ml) in a microwave vial, the mixture was refluxed for 10 minutes. A stock solution (1ml, in MeTHF) of 2-picolylamine (0.5μl/ml, 4.41 μmol) was added to the reaction mixture, followed by an additional reflux for 10 minutes. Methyl nicotinate (114.2, 0.83 mmol), and KOt-Bu (25 mol%) was added. The reaction mixture was then pressurised to an initial pressure of 50 bar with hydrogen gas and heated to 100°C temperature and left to stir. After 16 hours the autoclave was cooled to room temperature by submerging in cold water, after cooling the autoclave was depressurised. The solvent was then removed *in vacuo* and the resulting residue was purified by flash column chromatography (Silica, hexane: ethyl acetate, 2:1). A colourless oil was obtained (86 mg, 95 % yield).

δ_H (400 MHz, CDCl₃) 2.48 (1H, br s, OH), 4.74 (2H, s, CH₂), 7.30 (1H, ddd, $J_1=0.7$, $J_2=4.9$, $J_3=7.8$, ArCH), 7.71-7.76 (1H, m, ArCH), 8.51 (1H, dd, $J_1=1.7$, $J_1=4.9$, ArCH), 8.57 (1H, d, $J_1=1.7$, ArCH). δ_C (75 MHz, CDCl₃) 62.7 (CH₂), 123.7 (ArCH), 135.4 (ArCH), 138.2 (ArC), 148.2 (ArCH), 148.5 (ArCH). m/z (GCMS) 109 (M+) Data are in agreement with the literature.¹⁵

5.4 EXPERIMENTAL FOR CHAPTER IV

Reagent Information.

Acetophenone, isobutyrophenone, cyclohexylphenyl ketone, phenyl cyclobutyl ketone, and phenyl cyclopropyl ketone were all procured from Sigma-Aldrich. 2,2-dimethylpropiophenone, 4-benzoylpiperidine, chloro(1,5-cyclooctadiene)iridium(I) dimer, and chloro(1,5-cyclooctadiene)rhodium(I) dimer, were obtained from Alfa Aesar. (*R,R*)-(Diphenylphosphino)benzyl)cyclohexane-1,2-diamine and the ruthenium PNN complexes were prepared according to the literature.¹⁶

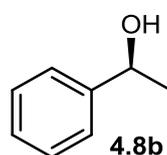
General Methods

General Procedure for Transfer Hydrogenation: Under a nitrogen atmosphere the substrate, internal standard, 0.25 mol% metal complex, 0.5 mol% ligand and KO^t-Bu (1 M solution in pentane) were transferred into a glass vial and dissolved in 3 ml of dry and degassed solvent and left to stir for 2 minutes. The reaction was then heated and left to stir. After 16 hrs the vials were cooled, the crude reaction mixture was then analysed by ¹H NMR using 1-methylnaphthalene as an internal standard to calculate the conversion to product. The conversion was calculated by comparing the ratio of the methylnaphthalene and the substrate proton integrals, before and after the reaction. The product was then isolated by column chromatography (SiO₂; hexane/ ethyl acetate).

General Procedure for Pressure Hydrogenation: Under a nitrogen atmosphere the substrate, internal standard, metal complex and ligand are transferred into a glass vial and dissolved in 3 ml of dry and degassed solvent and left to stir for 2 minutes. The sealed vials were kept in an inert environment, and then transferred to a steel autoclave and pressurised with H₂ gas. The reaction was then heated using a oil bath and left to stir for 16 hours (stirring via small magnetic bars). After 16 hours, the autoclave was immersed in cold water, then depressurised. The crude reaction mixture was then analysed by ¹H NMR using 1-methylnaphthalene as an internal standard to calculate the conversion to product. The conversion was calculated by comparing the ratio of the methylnaphthalene and the substrate proton integrals, before and after the reaction. The product was then isolated by column chromatography (SiO₂; Hexane/ ethyl acetate). Note this methodology has been used hundreds of times within the research group, and generally provide similar results to mechanically stirred vessels, although higher pressures are often required.

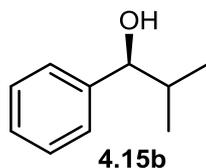
Enantiomeric Excess Determination:

Enantiomeric excess were measured using chiral HPLC, with a Varian Prostar apparatus. The equipment was optimised in each case by evaluation of the racemic product produced from a NaBH₄ reduction of the specific ketone. This was to confirm good separation of each of the enantiomeric products and to determine the retention times of each enantiomer. Various columns (OD, AD, OD-H, AD-H, AS-H), flow rates and solvent ratios of hexane and *i*-PrOH were used to achieve a good separation of the enantiomers. The specific conditions for each product are stated below.

(S)-1-Phenylethanol. (4.8b)

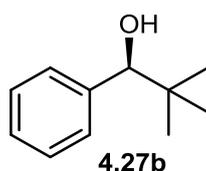
Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μ mol, 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μ mol, 0.5 mol%) was dissolved in *i*-PrOH (3 ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour, acetophenone (58 μ l, 0.5 mmol) and KOt-Bu (2.5 mol%) was added. The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was heated to 50°C with the aid of an oil bath, and left to stir for 1 hour. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). The product was obtained as a colourless oil. (55.2 mg, 0.45 mmol, 90% yield, >99% conversion, 23% ee). Enantioselectivity determined by HPLC, OD-H, 0.5 mlmin⁻¹, Hexane:isopropanol, 95:5. (major 21 mins, minor 17 mins).

$[\alpha]_{\text{D}}^{20}$ -9.8 (CHCl₃, *c* = 1.1 g/100 ml) (-45.0, for 99% ee, *c* = 5.0)². δ_{H} (400 MHz, CDCl₃), 7.31-7.15 (5H, *m*, ArCH), 4.82 (1H, *q*, *J* = 6.5, CHOH), 2.02 (1H, br *s*, OH), 1.41 (3H, *d*, *J* = 6.5, CH₃). δ_{C} (101 MHz, CDCl₃), 146.2 (ArC), 128.9 (2xArCH), 127.9 (ArCH), 125.8 (2xArCH), 70.8 (CHOH), 25.6 (CH₃). *m/z* (ES⁺) 144.23 (M+Na⁺). Data are in agreement with the literature.¹³

(S)-2-Methyl-1-phenylpropanol. (4.15b)


Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (3 ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour, isobutyrophenone (75 μl , 0.5 mmol) and KOt-Bu (2.5 mol%) was added. The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was heated to 50°C with the aid of an oil bath, and left to stir for 1 hours. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A colourless oil was obtained (72.8 mg, 97% yield, >99% conversion, 89% ee). Enantioselectivity determined by HPLC, AS-H, 0.5 mlmin⁻¹, Hexane:isopropanol, 95:5. (major 6.5 mins, minor 5.5 mins).

$[\alpha]_{\text{D}}^{20}$ -31.6 (CHCl₃, *c* = 0.6 g/100 ml) (-28.6, for 48% ee, *c* = 0.16)³. δ_{H} (400 MHz, CDCl₃) 7.44-7.27 (5H, *m*, ArH), 4.39 (1H, *d*, *J*=7.0, CHOH), 2.06-1.92 (1H, *m*, (CH₃)₂CH), 1.05 (3H, *d*, *J*=6.9, CH₃), 0.84 (3H, *d*, *J*=6.9, CH₃). δ_{C} (101 MHz, CDCl₃), 143.7 (ArC), 128.2 (2xArCH), 127.4 (ArCH), 126.6 (2xArCH), 80.0 (CHOH), 35.3 (CH(CH₃)₂), 19.0 (CH₃), 18.3 (CH₃), *m/z* (ES+) 172.11 (M+Na⁺). Data are in agreement with the literature.¹⁷

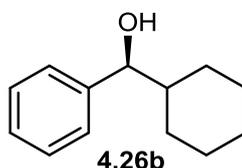
(S)-2,2-Dimethyl-1-phenylpropan-1-ol. (4.27b)


Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (3 ml) and prestirred at 50°C, at an initial

hydrogen pressure of 50 bar. After prestirring for 1 hour, 2,2-dimethylpropiophenone (84 μl , 0.5 mmol) and KOt-Bu (2.5 mol%) was added. The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was heated to 50°C with the aid of an oil bath, and left to stir for 1 hours. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A colourless oil was obtained (80.2 mg, 0.49 mmol, >99% conversion, 98% yield, 48% ee). Enantioselectivity determined by HPLC, OD-H, 0.5 mlmin⁻¹, Hexane:isopropanol, 95:5, (major 11 mins, minor 15 mins).

$[\alpha]_{\text{D}}^{20}$ -17.2 (CHCl₃, c = 0.5 g/100 ml) (-30.3, for >99% ee, c = 0.36).^{3,4} δ_{H} (400 MHz, CDCl₃), 7.32-7.13 (5H, *m*, ArCH), 4.34 (1H, *m*, CHOH), 1.78 (1H, br *s*, OH), 0.85 (9H, *s*, C(CH₃)₃). δ_{C} (101 MHz, CDCl₃), 143.1 (ArC), 128.0 (2xArCH), 127.9 (2xArCH), 127.7 (ArCH), 82.8 (CHOH), 35.9 (C(CH₃)₃), 26.3 (C(CH₃)₃). *m/z* (ES+) 186.48 (M+Na). Data are in agreement with the literature.¹⁸

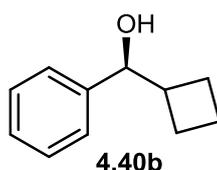
(S)-Cyclohexyl(phenyl)methanol. (4.26b)



Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (2 ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour, cyclohexylphenyl ketone (94.1mg, 0.5 mmol) as a solution in *i*-PrOH (1ml) and KOt-Bu (2.5 mol%) was added. The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was to stir for 2 hours at room temperature. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A colourless oil was obtained (94.3 mg, 0.496 mmol, >99% conversion, 99% yield, 94% ee). Enantioselectivity determined by HPLC, OD-H, 0.5 mlmin⁻¹, Hexane:isopropanol, 98:2, (major 29 mins, minor 32 mins).

$[\alpha]_{\text{D}}^{20}$ -14.6 (CHCl_3 , $c = 1.1$ g/100 ml) (-16.3, for 99% ee, $c = 3.3$)¹⁹. δ_{H} (400 MHz, CDCl_3) 7.33-7.19 (5H, *m*, ArCH), 4.34 (1H, *d*, $J=7.4$, CHOH), 1.98-1.44 (6H, *m*, CyCH), 1.34-0.77 (6H, *m*, CyCH). δ_{C} (101 MHz, CDCl_3) 144.0 (ArC), 128.6 (2xArCH), 127.8 (2xArCH), 127.1 (ArCH), 79.8 (CHOH), 45.4 (CH), 29.7 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 26.4 (CH_2). m/z (ES+) 213.39 (M+Na⁺). Data are in agreement with the literature.¹⁹

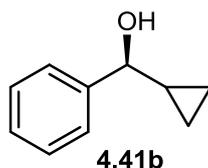
(S)-Cyclobutyl(phenyl)methanol. (4.40b)



Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzylcyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (3 ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour phenyl cyclobutyl ketone (76 μl , 0.5 mmol) and KOt-Bu (2.5 mol%). The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was heated to 50°C with the aid of an oil bath, and left to stir for 1 hour. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A yellow oil was obtained (74.8 mg, 0.463 mmol, 87% conversion, 93% yield, 78% ee). Enantioselectivity determined by HPLC, OD-H, 0.5 mlmin⁻¹, Hexane:isopropanol, 95:5. (major 18 mins, minor 16 mins).

$[\alpha]_{\text{D}}^{20}$ -31.2 (CHCl_3 , $c = 0.9$ g/100 ml) (-23.5, for 75% ee, $c = 0.8$)¹⁹. δ_{H} (400 MHz, CDCl_3), 7.37-7.22 (4H, *m*, ArCH), 7.29-7.24 (1H, *m*, ArCH), 4.56 (1H, *d*, $J = 7.1$, CHOH), 2.68-2.54 (1H, *m*, CH), 2.14-1.96 (2H, *m*, CH_2), 1.94-1.74 (4H, *m*, CH_2). δ_{C} (101 MHz, CDCl_3) 143.2 (ArC), 128.3 (2xArCH), 127.4 (ArCH), 126.2 (2xArCH), 78.4 (CHOH), 42.4 (CH), 24.9 (CH_2), 24.4 (CH_2), 17.7 (CH_2). Data are in agreement with the literature.¹⁹

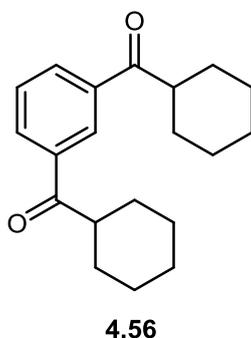
(S)-Cyclopropyl(phenyl)methanol. (4.41b)



Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (3 ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour phenyl cyclopropyl ketone (69 μl , 0.5 mmol) and KOt-Bu (2.5 mol%). The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was heated to 50°C with the aid of an oil bath, and left to stir for 1 hour. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A colourless oil was obtained (56.4 mg, 0.38 mmol, 97% conversion, 45% ee, 76% yield). Enantioselectivity determined by HPLC, AD-H, 0.5 mlmin⁻¹, Hexane:isopropanol, 95:5, (major 21 mins, minor 19 mins).

$[\alpha]_{\text{D}}^{20}$ -13.6 (CHCl₃, *c* = 1.1 g/100 ml). δ_{H} (400 MHz, CDCl₃), 7.43-7.21 (5H, *m*, ArCH), 3.99 (1H, *d*, *J* = 8.6, CHOH), 1.24-1.17 (1H, *m*, CH), 0.66-0.36 (4H, *m*, CH₂). δ_{C} (101 MHz, CDCl₃) 144.1 (ArC), 128.5 (2xArCH), 127.5 (ArCH), 126.2 (2xArCH), 78.9 (CHOH), 18.8 (CH), 3.6 (CH₂), 2.8 (CH₂). *m/z* (ES+) 171.14 (M+Na). Data are in agreement with the literature.¹⁹

1,3-Phenyl-bis(cyclohexylmethanone). (4.56)

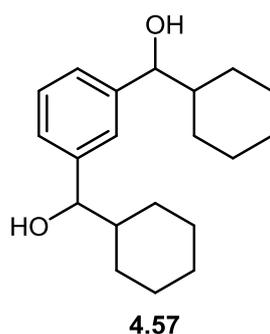


To a stirred solution of isophthalaldehyde (1.0g, 7.4 mmol) at -78°C in THF (25 ml), a solution of cyclohexylmagnesium chloride (4.8 ml, of 2M solution in diethyl ether, 9.6

mmol) was added dropwise over the course of 1 hr. The reaction was then left to warm to room temperature. The reaction was quenched with water, and then extracted with diethyl ether. The organic layer was dried and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (50 ml). To this solution potassium permanganate (2.35 g, 12.9 mmol) was added and stirred overnight. The reaction mixture was then filtered through a pad of silica and the filtrate was concentrated *in vacuo* and purified by column chromatography (silica, hexane:ether, 9:1). A pale yellow oil was obtained (1.42 g, 4.7 mmol, 64 %).

δ_{H} (400 MHz, CDCl_3) 8.43-8.40 (1H, *s*, ArCH), 8.04 (2H, *dd*, $J_1 = 2.0$ ArCH), 7.50 (1H, *t*, $J = 7.8$, ArCH), 3.29- 3.19 (2H, *m*, CyCH), 1.88-1.60 (10H, *m*, CyCH₂), 1.49-1.09 (10H, *m*, CyCH₂). δ_{C} (75 MHz, CDCl_3) 202.4 (C=O), 137.2 (ArC), 129.2 (ArCH), 127.7 (ArCH), 126.7 (ArCH), 45.6 (CyCH), 29.5 (CyCH₂), 26.3 (CyCH₂), 25.9 (CyCH₂).²⁰

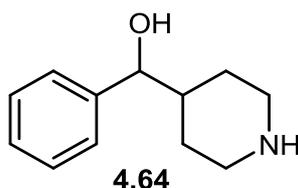
1,3-Phenyl-bis(cyclohexylmethanol). (4.57)



Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (2ml) and prestirred for 1 hour at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour the substrate (149 mg, 0.5 mmol) was added as a solution in *i*-PrOH (1ml). The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was left at room temperature to stir for 4 hours. At the end of the reaction the hydrogen was vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). (87.1 mg, 0.288 mmol, 58% yield, >99% conversion, 98% ee, (*R,R+S,S*): Meso = 5:1 (calculated by HPLC and NMR data). Enantioselectivity determined by HPLC, AD-H, 0.5 mlmin^{-1} , Hexane: isopropanol, 98:2, (major 43 mins, minor 29 mins, meso 39 mins).

δ_{H} (400 MHz, CDCl_3), 7.26-7.21 (1H, *m*, ArCH), 7.16-7.11 (3H, *m*, ArCH), 4.30 (1H, $J=7.4$, CHOH), 2.03-1.95 (2H, *m*, CyCH), 1.88 (2H, *br s*, CHOH), 1.84-1.74 (2H, *m*, CyCH), 1.73-1.58 (6H, *m*, CyCH), 1.43-1.34 (2H, *m*, CyCH), 1.30-1.11 (6H, *m* CyCH), 1.08-0.89 (4H, *m*, CyCH). δ_{C} (75 MHz, CDCl_3) 143.5 (ArC), 128.1 (ArCH), 125.6 (ArCH), 124.9 (ArCH), 79.3 (CHOH), 45.0 (CyCH), 29.3 (CyCH₂), 28.8 (CyCH₂), 26.1 (CyCH₂), 26.0 (CyCH₂), 25.3 (CyCH₂).²⁰

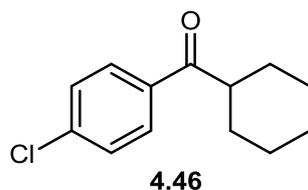
Phenyl(piperidin-4-yl)methanol. (4.64)



Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (2ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour 4-benzoylpiperidine (95 mg, 0.5 mmol) as a solution in *i*-PrOH (1ml) and KO*t*-Bu (2.5 mol%). The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was heated to 50°C with the aid of an oil bath, and left to stir for 2 hours. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (silica, CH_2Cl_2). A yellow/ orange oil was obtained (59.7 mg, 0.31 mmol, 62% yield, >99 conversion, 96% ee). Enantioselectivity determined by HPLC, AD-H, 0.5 mlmin^{-1} , Hexane: isopropanol. 98:2 (with 0.5% diethanolamine) (major 34 mins, minor 42 mins).

$[\alpha]_{\text{D}}^{20}$ -26.7 (MeOH, $c = 0.2$ g/100 ml). δ_{H} (400 MHz, CD_3OD), 7.36-7.25 (5H, *m*, 5xArCH), 4.31 (1H, *d*, $J = 7.4$, CHOH), 2.99 (2H, *dd*, $J_1=13.1$, $J_2=42.7$, CyCH), 2.55-2.39 (2H, *m*, CyCH), 1.94 (1H, *d*, $J = 13.1$, CyCH), 1.72-1.63 (1H, *m*, CyCH), 1.26-1.1 (3H, *m*, CyCH). δ_{H} (101 MHz, CD_3OD) 142.2 (ArC), 127.8 (2xArCH), 126.7 (ArCH), 125.5 (2xArCH), 78.6 (CHOH), 50.6 (CH₂), 50.1 (CH₂), 41.9 (CH), 33.3 (CH₂), 32.8 (CH₂). m/z (GCMS) 191 (M+). Data are in agreement with the literature.²¹

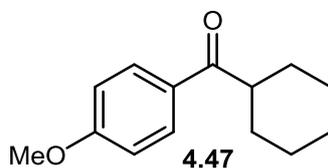
Cyclohexyl(4-chlorophenyl)methanone. (4.46)



A solution of 1-Bromo-4-chlorobenzene (2.29 g, 12 mmol) in dry and degassed THF (10 ml), the solution was then cooled to -78°C . To the cooled solution *n*-BuLi (8.25ml, 1.6 M in hexanes, 13.2 mmol, 1.1 eq) was added and left to stir at -78°C . After 1 hour cyclohexanecarboxaldehyde (1.45 ml, 12 mmol) was added and left to stir for 1 hour at -78°C . After this the solution was allowed to warm to room temperature and left to stir for 4 hours. At the end of the reaction water was added, and the reaction solution was extracted with diethyl ether. The solvent was then dried (MgSO_4), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 ml) and potassium permanganate (3.80g, 24 mmol, 2 eq) was added and left to stir at room temperature. After 16 hours the solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (hexane: ether, 15:1). A pale green powder was obtained (1.92g, 8.6 mmol 72% yield).

Mp $60\text{-}62^{\circ}\text{C}$. δ_{H} (400 MHz, CDCl_3) 7.84 (2H, *d*, $J = 8.6$, ArCH), 7.39 (2H, *d*, $J = 8.6$, ArCH), 3.13 (1H, *m*, CyCH), 1.85-1.61 (5H, *m*, CyCH), 1.49-1.17 (5H, *m*). δ_{C} (75 MHz, CDCl_3) 202.5 (C=O), 139.1 (ArC), 134.6 (ArC), 129.7 (2xArCH), 128.9 (2xArCH), 45.6 (CyCH), 29.4 (2xCyCH₂), 25.9 (2xCyCH₂), 25.8 (CyCH₂). **m/z** (ES+) 224.32 (M+H). Data are in agreement with the literature.²²

Cyclohexyl(4-methoxyphenyl)methanone. (4.47)

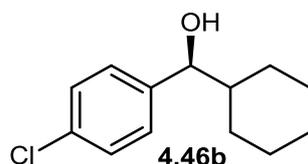


Under a nitrogen atmosphere, cyclohexyl(4-chlorophenyl)methanone (0.96 g, 4.3 mmol) and vinyl trimethoxysilane (1 ml, 6.5 mmol, 1.5 eq) were dissolved in toluene (3 ml). The solution was then added via a syringe to sodium hydroxide (0.220 mg, 5.5, 1.25 eq) palladium acetate (10 mg, 0.4 mmol, 1 mol%), 1-di-*tert*-butylphosphino-1'-diphenylphosphinoferrocene (44 mg, 0.8 mmol 2 mol%), contained in a microwave vial. The

reaction mixture was heated to 120°C by microwave irradiation. After 2 hours the solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was then purified by column chromatography (silica, hexane: diethyl ether, 20:1). A yellow solid was obtained (417 mg, 1.91 mmol, 44% yield).

Mp 66-67 °C. δ_{H} (400 MHz, CDCl₃) 7.92 (2H, *d*, *J*= 8.6, ArCH), 6.90 (2H, *d*, *J*= 8.6, ArCH), 3.81 (3H, *s*, OCH₃), 3.21-3.12 (1H, *m*, CyCH), 1.90-1.70 (5H, *m*, CyCH), 1.56-1.20 (5H, *m*, CyCH). δ_{C} (75 MHz, CDCl₃) 202.6 (C=O), 163.5 (ArC), 130.7 (ArC), 128.9 (2xArCH), 113.5 (2xArCH), 55.6 (CH₃O), 45.1 (CyCH), 29.4 (2xCyCH), 25.9 (2xCyCH₂), 25.8 (CyCH₂). **m/z** (ES+) 219.67 (M+H). Data are in agreement with the literature.²²

(S)-Cyclohexyl(4-chlorophenyl)methanol. (4.46b)

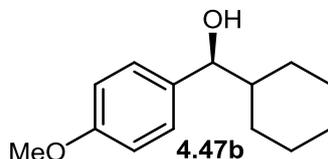


Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol , 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol , 0.5 mol%) was dissolved in *i*-PrOH (2ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour cyclohexyl(4-chlorophenyl)methanone (111 mg, 0.5 mmol) as a solution in *i*-PrOH (1ml) and KO*t*-Bu (2.5 mol%). The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was left to stir for 2 hours at room temperature. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A pale green oil obtained (93.7 mg, 0.42 mmol, 84% yield, 95% conversion, 91% ee). Enantioselectivity determined by HPLC, OD-H, 0.5 mlmin⁻¹, Hexane: isopropanol, 95:5, (major 21 mins, minor 26 mins).

δ_{H} (400 MHz, CDCl₃) 7.30 (4H, *dd*, *J*₁= 8.3, *J*₂=22.8, ArCH), 4.39 (1H, *d*, *J*= 6.6, CHOH), 2.11-1.52 (6H, *m*, CyCH), 1.48-0.87 (6H, *m*, CyCH). δ_{C} (75 MHz, CDCl₃) 140.9 (ArC), 132.8 (ArC), 128.0 (ArCH), 127.7 (ArCH), 78.3 (CHOH), 44.8 (CyCH), 28.9 (CyCH₂), 28.3

(CyCH₂), 25.9 (CyCH₂), 25.8 (CyCH₂), 25.7 (CyCH₂). **m/z** (ES+) 247.43 (M+Na⁺). Data are in agreement with the literature.²³

(S)-Cyclohexyl(4-methoxyphenyl)methanol. (4.47b)



Under a nitrogen environment, bis(1,5-cyclooctadiene)diiridium(I) dichloride (1.7 mg, 2.5 μmol, 0.5 mol%) and (*R,R*)-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (1.0 mg, 2.5 μmol, 0.5 mol%) was dissolved in *i*-PrOH (2ml) and prestirred at 50°C, at an initial hydrogen pressure of 50 bar. After prestirring for 1 hour cyclohexyl(4-methoxyphenyl)methanol (109 mg, 0.5 mmol) was added as a solution in *i*-PrOH (1ml). The reaction solution was transferred to a steel autoclave and pressurised to an initial hydrogen pressure of 50 bar. The autoclave was left to stir for 2 hours at room temperature. At the end of the reaction the autoclave was cooled to room temperature and the hydrogen vented. The reaction solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate, 10:1). A yellow oil was obtained (62.5 mg, 0.28 mmol, 78% conversion, 56% yield, 55% ee). Enantioselectivity determined by HPLC, OD-H, 0.5 mlmin⁻¹, Hexane: isopropanol, 95:5 (major 33 mins, minor 36 mins).

δ_H (400 MHz, CDCl₃) 7.21 (2H, *d*, *J*= 8.5, ArCH), 6.81 (2H, *d*, *J*= 8.5, ArCH), 4.22 (1H, *d*, *J*= 7.1, CHOH), 3.74 (3H, *s*, OCH₃), 2.01-1.53 (6H, *m*, CyCH), 1.38-0.84 (6H, *m* CyCH). **δ_C** (75 MHz, CDCl₃) 158.8 (ArC), 135.6 (ArC), 128.3 (ArCH), 113.9 (ArCH), 79.4 (CHOH), 55.3 (CH₃O), 44.9 (CyCH), 29.7 (CyCH₂), 29.4 (CyCH₂), 26.7 (CyCH₂), 26.4 (CyCH₂), 26.2 (CyCH₂). **m/z** (ES+) 243.65 (M+Na⁺). Data are in agreement with the literature.²⁴

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