Iridium Catalysed Asymmetric Hydrogenation of Olefins and Isomerisation of Allylic Alcohols

Byron Peters
Abstract

The work described in this thesis is focused on exploring the efficacy of asymmetric iridium catalysis in the hydrogenation of challenging substrates, including precursors to chiral sulfones and chiral cyclohexanes. Furthermore, iridium catalysis was used to isomerise allylic alcohols to aldehydes, and in a formal total synthesis of Aliskiren (a renin inhibitor). A large variety of unsaturated sulfones (cyclic, acyclic, vinylic, allylic and homoallylic) were prepared and screened in the iridium catalysed hydrogenation reaction using a series of previously developed N,P-ligated Ir-catalysts. The outcome was a highly enantioselective (>90% ee) protocol to prepare sulfones bearing chiral carbon scaffolds, sometimes having purely aliphatic substituents at the stereogenic centre. Furthermore, performing the Ramberg-Bäcklund reaction on the chiral products, under optimised conditions, produced cyclic and acyclic unsaturated derivatives without erosion of enantiomeric excess. This hydrogenation protocol was also successful in the hydrogenation of a number of cyclohexene-containing compounds. Minimally functionalised, functionalised and heterocycle-containing cyclohexenes were hydrogenated in up to 99% ee. Hitherto, both chiral sulfones and chiral cyclohexanes have been challenging targets for most catalytic asymmetric methodologies. Although the preparation of aldehydes and ketones by isomerisation of the corresponding allylic alcohol is well established, there has been limited success in the development of good enantioselective protocols. For the isomerisation of a number γ,γ-allylic alcohols to the corresponding chiral aldehydes, high enantioselectivities (up to >99% ee) and modest yields were achieved using an N,P-iridium catalyst. Noteworthy is the high selectivity obtained for isomerisation of Z and dialkyl γ,γ-allylic alcohols, which prior to this study had been difficult to isomerise in high enantioselectivity. Preparation of a key intermediate used in the synthesis of Aliskiren, a renin inhibitor drug was also accomplished. Using a convergent synthesis strategy, two allylic alcohol fragments were hydrogenated with high enantiomeric excess (>92% ee). These fragments were then joined using a Julia-Kocienski reaction, providing >95% E geometry around the C=C bond, which was crucial for the subsequent steps in the synthesis.
## Contents

1) Introduction .................................................................................................................. 1  
   a) Chirality and Asymmetric Synthesis[1] ...................................................................... 1  
   b) Catalytic Asymmetric Hydrogenation .................................................................... 4  
   c) Aims of this Thesis ............................................................................................... 8  

2) Asymmetric Hydrogenation of Sulfones ................................................................. 9  
   a) Sulfones ................................................................................................................... 9  
      i) Organocatalytic Methods .................................................................................... 9  
      ii) Transition Metal Catalysed Methods ............................................................... 10  
   b) Synthesis ................................................................................................................ 11  
   c) Evaluation of Unsaturated Sulfones in the Asymmetric Hydrogenation Reaction ................................................................................................................................. 13  
   d) Conclusion .............................................................................................................. 20  

3) Asymmetric Isomerisation of Allylic Alcohols ...................................................... 21  
   a) Isomerisation of Allylic Alcohols ............................................................................ 21  
   b) Evaluation of Iridium Catalysts in the Isomerisation ............................................. 24  
   c) Conclusion .............................................................................................................. 28  

4) Formal Total Synthesis of Aliskiren ........................................................................ 29  
   a) Introduction ............................................................................................................ 29  
   b) Synthesis of Key Intermediate in the Preparation of Aliskiren ............................. 30  
   c) Asymmetric Hydrogenation of the Allylic Alcohol Fragments ............................... 32  
   d) Connecting the Pieces ......................................................................................... 35  
   e) Conclusions .......................................................................................................... 37  

5) Enantio- and Regioselective Hydrogenation of Minimally and Densely Decorated Unsaturated Carbocycles ............................................................... 38  
   a) Introduction ............................................................................................................ 38  
   b) Discussion .............................................................................................................. 39  
   c) Conclusion ............................................................................................................ 42  

6) Concluding Remarks and Outlook ........................................................................ 44  

7) Summary in Swedish ................................................................................................ 45  

8) Acknowledgements ................................................................................................... 46  

9) References .................................................................................................................. 48
List of Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


Reprints were made with permission from the respective publishers.
Contribution Report

I. Contribution: Synthesized six of the substrates and performed 20 % of their evaluation in the hydrogenation. Prepared one of the catalysts reported in the paper. Contributed to the discussion of the selectivity model. Carried out the Ramberg-Bäcklund reaction on three of the compounds reported in the paper. Carried out characterization of a portion of the synthesis of novel compounds.

II. Contribution: Prepared two substrates. Synthesized the most selective and active catalyst. Carried out 20 % of the testing and optimization of the reaction conditions. Participated only in a small part of the writing of the paper.

III. Contribution: Carried out preparation of a major portion of the starting materials (65 %, 20 substrates). Conducted all testing of substrates I prepared as well as characterisation of most of my substrates. Wrote the introduction, the origins of selectivity and 50 % of the discussion.

IV. Contribution: Had a major contribution to the synthesis. Prepared one of the two fragments, performed the coupling of the fragments, also completed the synthesis all the way to the key intermediate (our target). Synthesised the representative substrate that was used as a mimic to optimise the Julia-Kocienski conditions. Also performed all of the optimisations for the Julia-Kocienski reaction. Took part in some of the characterisation of novel compounds. Co-wrote the paper with my supervisor.

V. Contribution: Had a major contribution to the synthesis. Prepared all compounds presented in the chapter. Carried out 25 % of the characterisation of the novel compounds.
Papers not Included in this Thesis


Abbreviations

* Stereogenic centre
Ac Acetyl
Ar Aryl
BArF Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BOX-ligand Bisoxazoline ligand
Cat. Catalyst
COD 1,5-Cyclooctadiene
Conv. Conversion
Cy Cyclohexyl
DIBAL-H Diisobutylaluminium hydride
DME 1,2-dimethoxyethane
DMSO Dimethylsulfoxide
ee Enantiomeric excess
Et Ethyl
FDA US Food and Drug Administration
GC Gas Chromatography
HPLC High Performance Liquid Chromatography
hr(s) Hour(s)
i-Pr Isopropyl
L Ligand
Me Methyl
m-CPBA meta-chloroperoxybenzoic acid
Ms Methanesulfonyl
MHMDS Metal hexamethyldisilazide
n-Bu n-Butyl
n-BuLi n-Butyl lithium
NMR Nuclear Magnetic Resonance
o.n. Overnight
o-Tol ortho-Tolyl
PCC Pyridinium chlorochromate
Pd/C Palladium on carbon
PF6 Hexafluorophosphate
Ph Phenyl
PHOX Phosphine-Oxazoline
rt. Room temperature
S/C Substrate/Catalyst
t-Bu tert-Butyl
THF Tetrahydrofuran
TFA Trifluoroacetic acid
Catalysts mentioned in this thesis

A, \( R^1 = \text{Pr}, R^2 = H \)
B, \( R^1 = \text{t-Bu}, R^2 = H \)
C, \( R^1 = \text{Ph}, R^2 = \text{Ph} \)
D, \( R = \text{Me} \)
E, \( X = \text{Ph} \)
F, \( G \), antipode
H, \( Ar = \text{Ph} \)
I, \( Ar = o\text{-tol} \)
J, \( Ar = \text{Ph} \)
K, \( Ar = o\text{-Tol} \)
L, \( Ar = \text{Ph} \)
M, \( Ar = o\text{-Tol} \)
N
O, \( O^\text{--}O = \text{(R)-BINOL} \)
1) Introduction

a) Chirality and Asymmetric Synthesis\(^1\)

In a chemical context, chirality is a property of molecules. A simple example explaining the concept of chirality is presented in Figure 1.1. Despite appearing identical, structures 1 and 2 are mirror images of each other but they cannot be superimposed on their mirror image. These structures are referred to as enantiomers. Both 1 and 2 have identical physical properties in an achiral environment, and usually chemical reactivity. The importance of chirality is apparent when two stereogenic centres (centre of chirality) are brought together. If 1 and 2 react and are bound together at A-A, 3 is the result. If 1 and 2 are absolutely identical, then the same reaction with two molecules of 1 would also generate 3. However, as seen from structure 4, the result is quite different. Structure 3 has a mirror plane (perpendicular A-A) and 4 has a \(C_2\) rotation axis (180° about A-A). These properties are not shared by both molecules, but are specific to 3 and 4, that is, they will have different physical properties, and will react at different rates for the same transformation.

![Figure 1.1: Illustration of chirality.](image)

Hence, compounds 3 and 4 are known as diastereomers and in most cases possess measurably different physical properties and chemical reactivity. It is this transition (enantiomeric → diastereomeric) that allows the distinction from one enantiomer to another. Enzymes and proteins in our bodies are chiral. Proteins are vital for a number of reasons, one being they serve as drug recep-
tors. Hence, one can appreciate how important it is to produce selectively one enantiomer of a drug.

Firstly, it is necessary to understand how both enantiomers are formed. A simple retrosynthesis of 1 and 2 produces 5 as a possible intermediate, where A has been removed (Figure 1.2). Compound 5 is not chiral (it is superimposable on its mirror image), and is flat. The reagent bearing A (R-A unit) added to 5 can attack either from the left- (L) or right- (R) side. The right-side attack generates 1, while the left-side attack generates 2. Since neither 5 nor the reagent is chiral, there can be no distinction in the chiral transition state between the L or R attack (E_L = E_R). Therefore both occur equally as fast, and a 1:1 mixture of 1 and 2 is formed – known as a racemate. This result is obtained when using the classical, achiral synthetic route.

Figure 1.2: Difference between classical, achiral synthesis and asymmetric synthesis.

However, this is not always the case. If a stereogenic centre is already present, that is B* in structure 6, then addition from L or R will no longer be equally favoured, i.e. E_L ≠ E_R. This is due to the enantio → diastereo transition (vide supra) upon addition of A. If the R approach is arbitrarily chosen as the least favoured face for the addition of A, then faster addition will take place from L (E_R > E_L). As a result, less of 7 (minor) and more of 8 (major) will be formed rendering the process stereoselective. This concept is known as asymmetric synthesis.

There are many categories in asymmetric synthesis. The classical and asymmetric synthetic route described in Figure 1.2 is an example of substrate controlled asymmetric induction. If the chiral unit on B* in compound 6, is removed post addition of A (B* → B) to yield either 1 or 2, this would be an example of auxiliary controlled asymmetric induction. If instead, the
reagent (R*-A) were chiral rather than the substrate, then chiral induction would be classified as *reagent controlled*.

Another strategy, although not considered a part of asymmetric synthesis, is *resolution of racemates*. This strategy essentially functions along the same principle demonstrated in **Figure 1.1**. However, it focuses on one enantiomer in a racemate that reacts faster with the chiral material/species, or forming a diastereomer having chemical properties that are different to that formed by the other enantiomer.

Chiral molecules can also be derived from nature (*chiral pool*), which uses enzymes and proteins to produce these molecules. However, the major drawback of this strategy has always been availability – chiral molecules are often only present in small quantities – and the difficulty is in the isolation from natural sources.†

The major drawback of all these strategies is that a stoichiometric amount of chiral material is needed to produce the chiral product. In many cases, the reaction generates several unwanted side-products as well, and this complicates purification and increases the cost of production. Another branch of *asymmetric synthesis* is *asymmetric catalysis*, which attempts to solve this problem through the action of a chiral catalyst. A catalyst is a species that lowers the activation energy of a chemical process, and is regenerated after the transformation has taken place. Hence, a catalyst can be present in sub-stoichiometric amounts, and in some cases recycled. Due to this, *asymmetric catalysis* is not affected by many of the problems associated with other *asymmetric synthesis* methods. The most well studied and typical example of *asymmetric catalysis* is catalytic homogenous asymmetric hydrogenation of olefins.

---

† For a more detailed discussion on chirality, asymmetric synthesis (also strategies within) and related methods on routes to obtain optically pure compounds, see references [1].
b) Catalytic Asymmetric Hydrogenation

In Figure 1.3 pioneering work by Halpern\(^2\) (efficacy), Wilkinson\(^3\) (1st generation), Schrock and Osborn\(^4\) (1st generation), Knowles and Sabacky\(^5\) (2nd and 3rd generation), Horner\(^6\) (2nd generation), Dang and Kagan\(^7\) (3rd generation), laid the foundation for modern day asymmetric hydrogenation. Nearly all the breakthroughs made during this pioneering work, were with rhodium catalysis. The high catalytic activity of achiral Wilkinson catalyst for the hydrogenation of olefins provided motivation for the development of chiral versions of the catalyst. This resulted in an investigation of chiral phosphine ligands. Despite some success in the initial studies on chiral monodentate phosphine ligands, focus steadily moved towards chiral bidentate phosphine ligands. Many years of fine-tuning and development of new chiral bidentate phosphine ligand scaffolds, have resulted in the highly selective hydrogenation of an enormous variety of olefin substrates.\(^8\)

Figure 1.3: Evolution of asymmetric hydrogenation of olefins.

Iridium as a hydrogenation catalyst did not receive much attention, primarily due to its lower activity when compared to rhodium. However, in 1977 Robert Crabtree studied the effects of mixing ligands, and found that for both rhodium and iridium, a more active catalyst was produced when he exchanged one of the phosphine coordinating functionalities to a pyridine group. Interestingly, he noted that the catalytic efficiency was increased when poorly or weakly-coordinating solvents (CH\(_2\)Cl\(_2\), CHCl\(_3\) and chlorobenzene) were used especially for iridium. Crabtree proposed that the stable iridium dihydride species would coordinate strongly to polar solvents (EtOH, acetone, THF) therefore the olefin was unable to displace the solvent molecule from the metal. The best combination was a tricyclohexylphosphine and pyridine ligand, using PF\(_6^-\) as the counterion (Figure 1.4),

![Figure 1.3: Evolution of asymmetric hydrogenation of olefins.](image-url)
which is nowadays known as Crabtree’s catalyst.\textsuperscript{[9]} The most important outcome of his study, was a highly active iridium catalyst (highest homogenous hydrogenation catalyst at that time). In addition, both tri- and even tetra-substituted olefins were hydrogenated rapidly, which was not possible for rhodium catalysts at that time.

\textbf{Figure 1.4: Crabtree’s catalyst and polyhydride type species formed in the hydrogenation.}

A major drawback of Crabtree’s work was that these iridium catalysts rapidly and irreversibly form polyhydride hydride species in the presence of dihydrogen, and were not active hydrogenation catalysts (\textbf{Figure 1.4}). This was possibly due to a lack of stabilization by the poorly coordinating solvent, an effect that is enhanced when a very weakly coordinating, or extremely bulky olefin substrate is present.\textsuperscript{[9c]}

It was Andreas Pfaltz and co-workers who in 1997 introduced the asymmetric version of the iridium catalysed system devised by Crabtree (\textbf{Figure 1.5}). Employing the PHOX ligand that had originally been used in other catalytic systems, a number of non-functionalised olefins were hydrogenated in high enantioselectivity. Later they discovered that using the weakly coordinating, extremely bulky BArF anion slowed down the polyhydride formation significantly, but enhanced catalytic activity, possibly due to the higher affinity for olefin coordination by the iridium BArF catalysts.\textsuperscript{[10]} The same group has also developed a series of efficient fused-heterocyclic catalysts.

\textbf{Figure 1.5: PHOX ligand, BArF anion and fused-heterocyclic ligand.}
The mechanism of the iridium catalysed hydrogenation has also been under inspection (Figure 1.6). It was first believed that it may proceed via an Ir(I)/Ir(III) cycle which is similar to that of the rhodium pathway.\textsuperscript{[10c, 11]} However, it is possible that an Ir(III)/Ir(V) cycle is active, as suggested from computational studies by Andersson, and recent experimental studies by Pfaltz, respectively.\textsuperscript{[12]} In Figure 1.6 homolytic oxidative addition of dihydrogen to give the Ir(III)-dihydride 10 occurs. Coordination of the olefin and a dihydrogen molecule occurs to form 11. Migratory insertion of the hydride trans to dihydrogen occurs together with an oxidative addition of the dihydrogen, to produce the transient Ir(V) species 12 (rate and selectivity determining step). Reductive elimination gives 13, which upon displacement of the alkane product with two molecules of solvent, regenerates 10.

\textbf{Figure 1.6:} Proposed Ir(I)/Ir(III) and Ir(III)/Ir(V) pathways in the iridium hydrogenation. Counterion omitted for clarity.

The Andersson group has been very active in this field of research. Highly efficient and selective catalysts have been developed with some of the more successful catalysts shown on page x.\textsuperscript{[13]} This has allowed for significant expansion of the substrate scope to include vinyl phosphonates, enamines, vinyl-CF\textsubscript{3}, vinyl silanes, $\alpha$,$\beta$-unsaturated esters, enol ethers, heteroaromatic rings, vinyl fluorides and enol phosphinates.\textsuperscript{[13b, 13c, 14]}
The Andersson group, based on the mechanistic studies, has developed a selectivity model to explain the absolute configuration of the hydrogenation products (Figure 1.7). The model focuses on the degree of steric hindrance of the four quadrants. Two of these quadrants are recognized as being significantly occupied by an aryl group of the phosphine and another by the substituent of the nitrogen heterocycle. A third quadrant is semi-occupied by the other aryl group on the phosphine, while the remaining quadrant is almost empty. Placing the olefin in a vertical position (calculated to give the lowest energy pathway of the reaction) and orientating it to the most sterically favoured conformation: the hydrogen, the smallest substituent, will occupy the bulkiest quadrant i.e. where the substituent of the heterocycle resides. Adding hydrogen from the face the iridium is coordinated to determines the absolute configuration of the product. Experimentally, this selectivity model has proved reliable for a wide variety of tri-substituted olefins (for ee’s >90%), thus making it a useful tool for the hydrogenation reaction.\[12c\]

\textbf{Figure 1.7: Use of the selectivity model to predict the absolute configuration of the hydrogenation product}
c) Aims of this Thesis

The rhodium and ruthenium systems have been shown to rely on coordinating groups in the vicinity of the olefin to assure high enantioselectivities. The iridium catalysed hydrogenation on the other hand, does not rely on a chelation to the substrate to ensure high enantioselectivities, which makes it suitable for the highly selective hydrogenation of olefins not having a coordinating group. The investigation of the substrate scope for this reaction will form a part of this thesis. The application of this work in the synthesis of Aliskiren and the isomerisation of allylic alcohols to chiral aldehydes will also be discussed.
2) Asymmetric Hydrogenation of Sulfones

a) Sulfones

The sulfonyl group has important applications in both C-C and C=C bond formation reactions.\cite{15} In many cases sulfones are generated as intermediates towards C=C bond forming reactions specifically the Julia reaction and Ramberg-Bäcklund reaction that is frequently used in total synthesis of natural products.\cite{16} A number of biologically active compounds possess sulfone/s functionality and a few examples are presented in Figure 2.1.\cite{17} Hence, efficient and highly selective asymmetric methods for their preparation are highly desirable.

![Tazobactam](image1)

![Remikiren](image2)

![Trusopt](image3)

*Figure 2.1: Some biologically active chiral compounds possessing a sulfone*

There are several catalytic methods available to prepare chiral sulfones. These can be sub-divided into organocatalysed and transition metal catalysed methods:

i) Organocatalytic Methods

Acyclic chiral sulfones have been produced using organocatalysis in high enantiomeric excess. Pioneering work by Alexakis\cite{18} and Deng\cite{19} (Scheme 2.1) has introduced several examples of acyclic chiral sulfone syntheses, by Michael addition reactions of nucleophiles to vinyl sulfones. However, high catalyst loadings are necessary (20-25 mol%), and in some cases a large
excess of one reagent (10 equiv.). In addition to the sub-optimal reaction conditions, enantioselectivities range from being acceptable to good.

**Scheme 2.1:** Organocatalytic methods to prepare chiral sulfones.

### ii) Transition Metal Catalysed Methods

Carretero et al. ([Scheme 2.2](#)) were amongst the first to use Rh catalysis to carry out asymmetric *Michael Addition reactions* of unsaturated sulfones with aryl boronic acids being added to 1,2-disubstituted-α,β-unsaturated sulfones with a Rh-(S,S)-Chiraphos catalyst. Reasonable stereoselectivity was attained. [20] They later employed this methodology to prepare acyclic analogues bearing quaternary chiral centres. [21] However, in both cases a 2-pyridyl group on the sulfone substrate was necessary for the reaction to take place. Watanabe [22] has developed an enantioselective catalytic radical addition method that makes use of a zinc based Lewis acid catalyst bearing a BOX-ligand.

There have been several investigations of the preparation of chiral sulfones via asymmetric hydrogenation ([Scheme 2.2](#)). Ru [23] and Rh [24] based catalysts have been employed, particularly in the hydrogenation of acyclic α-ketosulfones to produce β-hydroxysulfones in reasonable enantiomeric excess. A less common strategy is the reduction of prochiral C=C bonds near the sulfone to produce the desired chiral sulfone. Pfaltz and Misun have used a semicorrin Co-catalyst in combination with NaBH₄ as hydride source, to reduce an α,β-unsaturated sulfone. [25] Carretero et al. have developed a reduction method of α,β-unsaturated sulfones using a Cu-(R)-BINAP and
Yuasa has also hydrogenated an acrylic acid sulfone using a Ru-BINAP catalyst and hydrogen gas.\[27\]

Ir-catalysed hydrogenation has proven to be a useful method for hydrogenation of unfunctionalised as well as functionalised olefins. In this chapter, unsaturated sulfones are hydrogenated using chiral N,P-ligated Ir-catalysts to produce the corresponding unsaturated chiral sulfone. Our aim is to demonstrate that regardless of the substituents on the olefin or if the olefin is one, two and three bonds away from the sulfonyl group, high enantioselectivity is obtained using only two Ir-catalysts.

b) Synthesis

Three main synthetic pathways were chosen to prepare the substrates used in this investigation. First are the cyclic substrates presented in Scheme 2.3. Both the cyclic vinylic and allylic sulfones of type 14 and 15 begin from a ring expansion (Tiffeneau-Demjanov reaction) of the readily available ketone 16. The products, a 1:1 mixture of isomers 17 and 18 are then separated via flash chromatography and pure 17 was decarboxylated (Krapcho decarboxylation). Ketone 19 was arylated using an aryl Grignard reagent, followed by dehydration with TFA to produce both vinyl 20 and allylic thioethers 21. These thioethers were separated by flash chromatography. Oxidation of 20 and 21 yielded the desired sulfones 14 and 15.

Preparation of acyclic allylic sulfones 22, (Scheme 2.4) proceeded via a Horner-Wadsworth-Emmons reaction on the corresponding ketone 23. The E-ester 24 was reduced to the allylic alcohol, and then converted to allylic bromide 25 using PBr₃. Reaction of 25 with the corresponding thiol (Williamson ether synthesis) under basic conditions formed the thioether, and oxidation using m-CPBA procured the allylic sulfones 22.
Scheme 2.2: Access to chiral sulfones via transition metal catalysis.

\[
\text{R=SO}_2\text{Py} \xrightarrow{\text{Rh(aceo)(C}_2\text{H}_4)_2, (S,S)-chiralphosphate}} \text{R=SO}_2\text{Py} \quad \text{Carretero 2004}
\]

76-92% ee

\[
\text{O=S=O} \quad 1) \text{Zn(OTf)_2, bisoxazoline} \\
\text{2) allylthiol, t-Bu, Et_3B} \\
\xrightarrow{} \quad \text{O=S=O} \\
\text{up to 84% ee} \quad \text{Watanabe 2001}
\]

41-85% ee

\[
\text{O=S=O} \quad \text{Cu}^{1-}\text{Taniaphose (5 mol%)} \\
\xrightarrow{} \quad \text{O=S=O} \\
\text{up to 66% ee} \quad \text{Carreto 2007}
\]

Ph\text{SCH}_2\text{CN, diglyme, CoCl}_2 (2 mol%) \text{OTBDMS}

Psaltz 1996

\[
\text{Ph=SO}_2\text{R} \xrightarrow{\text{PhSH}_2 (4 equiv), CuCl/d-BuUNa (5 mol%), \text{(R)-BINAP (5 mol%)}}} \text{Ph=SO}_2\text{R} \quad \text{up to 94% ee} \quad \text{Carretero 2007}
\]

Scheme 2.3: Preparation of cyclic sulfones.

ea) \text{N}_2\text{CHCOOEt, BF_3, Et}_2\text{O, DCM, -78 °C, 4 hrs}
\text{b) LiCl, H}_2\text{O, DMSO, 180 °C, 5 hrs}

c) \text{ArMgX, CeCl}_3, \text{THF, reflux, o.n.}
\text{d) TFA, -78 °C, o.n.}
\text{e) m-CPBA, CH}_2\text{Cl}_2, 0 °C, 2 hrs
Scheme 2.4: Preparation of acyclic allylic sulfones.

The acyclic vinyl sulfones 26 (Scheme 2.5) were prepared by reaction of the relevant acetylene 27 with a disulfide (R²SS²R) under basic conditions (n-BuLi) to produce the necessary thioacetylene. Oxidation using a stoichiometric amount of m-CPBA produced the sulfoxide 28. Addition of R³ was accomplished by reaction of 28 with R³Li and CuI at low temperature to yield the vinyl sulfoxide. Treatment of the vinyl sulfoxide with m-CPBA produced acyclic vinylic substrates of type 26 that were used in the hydrogenation.

c) Evaluation of Unsaturated Sulfones in the Asymmetric Hydrogenation Reaction

The 7-membered allylic cyclic sulfone 29 was used as a model substrate for evaluation in the asymmetric hydrogenation reaction.
Figure 2.2: Ligands used in this investigation.

Six catalysts A, C, F, I, J and N (Figure 2.2) were used to screen 29 under standard conditions. The results are presented in Table 2.1. In general, catalysts bearing thiazole moieties showed high enantioselectivity (entries 3, 5 and 6, all ee’s >95%) whereas, ligands bearing oxazoline and imidazole moieties were less enantioselective (entries 1, 2 and 4, ee’s <90%).

Table 2.1: Screening of catalysts in the asymmetric hydrogenation of substrate 29

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Catalyst</th>
<th>% Conv[b]</th>
<th>% ee[c],[d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>25</td>
<td>14 (S)</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>30</td>
<td>87 (R)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>&gt;99</td>
<td>96 (R)</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>&gt;99</td>
<td>83 (S)</td>
</tr>
<tr>
<td>5</td>
<td>J</td>
<td>49</td>
<td>96 (S)</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>42</td>
<td>97 (S)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol substrate, 0.5 mol% catalyst, 2 mL CH2Cl2, 50 bar H2, 17 hrs, rt.[b] Conversion, determined by 1H NMR spectroscopy. No side products were detected.[c] Determined by chiral HPLC or GC analyses. [d] Absolute configuration determined by analogy with the corresponding alkenes obtained from Ramberg-Bäcklund rearrangement.

The promising results encouraged a continued investigation of the allylic sulfones. A variety of cyclic and acyclic allylic sulfones were prepared with
emphasis on the steric and electronic diversity of the substrates. Catalyst F, which had the best overall performance for the model substrate 29 was chosen for testing the allylic sulfones (Table 2.2). Enantioselectivity was high (>89% ee) for β-substituted 6- and 7-membered, and γ-7-membered aryl-allylic sulfones (entries 1, 2, 4 and 6, respectively). However, aliphatic substitutions resulted in a decrease in enantioselectivity for both 7- and 6-membered substrates (entries 3 and 5, respectively). Acyclic allylic sulfones were hydrogenated in high selectivity (>96% ee, entries 7, 8, 10, 11 and 12), showing a wide tolerance to the group on the sulfone. However, heterocycles such as pyridine were not tolerated, and no reaction occurred (entry 9).

The next focus of interest was the vinylic substrates. E-vinyl sulfones 43 were used as a model substrate (Table 2.3). Catalyst F again performed satisfactorily for the vinylic sulfone 43 in the hydrogenation.

For the acyclic vinylic substrates (Table 2.4), enantioselectivity was high regardless of the substitution (aryl, aliphatic, sterically demanding) on the sulfone (>90% ee, entries 1-3) or on the olefin (>90% ee, entries 4-7). Changing the geometry of the olefin from E to Z did not affect the high selectivity however the hydrogenation decreased (61% conv., 96% ee, entry 8). The cyclic vinylic system resulted in a slightly lower enantioselectivity (<90% ee, entry 9).

In this investigation an attempt was also made to convert the chiral sulfones from asymmetric hydrogenation into their corresponding chiral alkenes using the Ramberg-Bäcklund reaction (Table 2.5). The 7-membered chiral sulfones (54-56 and 58) were converted to their corresponding chiral unsaturated carbocyclic derivatives with ease using the modified conditions developed by Chan.[28] Under the same conditions, the 6-membered chiral carbocycles (63-65 and 67) were also furnished in high yield. There was no detectable loss in enantiomeric excess (entries 1-3 and 5). As expected, formation of the rigid 5-membered carbocycle 66 proved to be more difficult. However, no loss in ee was observed (entry 4). Acyclic sulfones possessing chirality at the β-position (59-61) were also successfully transformed to the corresponding E-α-chiral alkenes (68-70). Yields were greater when R = aryl (entries 6 and 7) vs. R = alkyl (entry 8). Enantiomeric excesses remained high in all cases. Astonishingly, even 62 having chirality at the γ-position was transformed to give the isomerically pure E-β-chiral alkene 71, albeit, in a somewhat lower yield than the E-α-chiral alkenes (68-70).
Table 2.2: Screening of some allylic sulfones in the asymmetric hydrogenation with catalyst $F$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$R^2$ or $R^3$</th>
<th>% Conv</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>4-MeOC$_6$H$_4$</td>
<td>&gt;99</td>
<td>97 (-)</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>4-Fl$_3$C$_6$H$_4$</td>
<td>91</td>
<td>95 (-)</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>Me</td>
<td>&gt;99</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>Ph</td>
<td>43</td>
<td>90 (-)/(R)</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>Me</td>
<td>&gt;99</td>
<td>95 (-)/(R)</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td></td>
<td>&gt;99</td>
<td>89 (-)</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>Bn</td>
<td>&gt;99</td>
<td>97 ( )</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>Ph</td>
<td>&gt;99</td>
<td>95 ( )</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>Py</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>$n$-Bu</td>
<td>&gt;99</td>
<td>98 ( )</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>$t$-Bu</td>
<td>&gt;99</td>
<td>98 ( )</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>2,0-MeOC$_6$H$_3$</td>
<td>&gt;99</td>
<td>99 ( )</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol substrate, 0.5 mol% catalyst, 2 mL CH$_2$Cl$_2$, 50 bar H$_2$, 17 hrs, rt.

[b] Conversion, determined by $^1$H NMR spectroscopy. No side products were detected.

c] Determined by chiral HPLC or GC analyses.

d] Absolute configuration determined by analogy with the corresponding alkenes obtained from Ramberg-Bäcklund reaction.
**Table 2.3: Screening of catalysts in the asymmetric hydrogenation of substrate 43**

![Catalyst, 50 bar H₂, CH₂Cl₂, rt, 17 hrs]

<table>
<thead>
<tr>
<th>Entry[α]</th>
<th>Ligand</th>
<th>% Conv.[β]</th>
<th>% ee[c][d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>45</td>
<td>76 (S)</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>24</td>
<td>41 (S)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>&gt;99</td>
<td>96 (S)</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>&gt;99</td>
<td>27 (R)</td>
</tr>
<tr>
<td>5</td>
<td>J</td>
<td>90</td>
<td>74 (R)</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>27</td>
<td>50 (R)</td>
</tr>
</tbody>
</table>

[α] Reaction conditions: 0.25 mmol substrate, 0.5 mol% catalyst, 2 mL CH₂Cl₂, 50 bar H₂, 17 hrs, rt. [β] Conversion, determined by ¹H NMR spectroscopy. No side products were detected.
[c] Determined by chiral HPLC or GC using chiral stationary phases. [d] Absolute configuration determined on the corresponding alkenes obtained from Ramberg-Bäcklund reaction.

Having a substituent α to the sulfone (Scheme 2.6, 72) also afforded high enantioselectivity (97% ee) and had little influence on the activity of catalyst F (94% conv.).

An interesting example was the diene substrate (Scheme 2.7, 74). The diallylic sulfone was completely reduced selectively to the chiral diastereomer (75) in 96% ee.
Table 2.4: Screening of some vinylic sulfones in the asymmetric hydrogenation with catalyst F.

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry[^a]</th>
<th>Substrate</th>
<th>R</th>
<th>% Conv[^b]</th>
<th>% en[^c][^d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>n-Bu</td>
<td>&gt;99</td>
<td>91 (-)</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>Cy</td>
<td>&gt;99</td>
<td>94 (-)</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>Ph</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>4-MeOC₆H₄</td>
<td>&gt;99</td>
<td>92 (+)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>4-ClC₆H₄</td>
<td>&gt;99</td>
<td>95 (+)</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>n-Bu</td>
<td>&gt;99</td>
<td>93 (+)(R)</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td></td>
<td>&gt;99</td>
<td>91 (+)</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td></td>
<td>61</td>
<td>96 (R)</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td></td>
<td>&gt;99</td>
<td>89 (-)</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: 0.25 mmol substrate, 0.5 mol% catalyst, 2 mL CH₂Cl₂, 50 bar H₂, 17 hrs, rt.
[^b]: Conversion, determined by ¹H NMR spectroscopy. No side products were detected.
[^c]: Determined by chiral HPLC or GC analyses.
[^d]: Absolute configuration determined by analogy with the corresponding alkenes obtained from Ramberg-Bäcklund reaction.
**Table 2.5**: Evaluation of some product chiral sulfones from the asymmetric hydrogenation in the Ramberg-Bäcklund reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>R</th>
<th>% Yield[a]</th>
<th>% ee[b] [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>63</td>
<td>Ph</td>
<td>88</td>
<td>96 (-)(S)</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>64</td>
<td>Me</td>
<td>&gt;99</td>
<td>96 (-)(S)</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>65</td>
<td>4-MeOC₆H₄</td>
<td>90</td>
<td>97 (-)</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>66</td>
<td>Ph</td>
<td>30</td>
<td>90 (-)(S)</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>67</td>
<td>Ph</td>
<td>90</td>
<td>89 (-)</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>68</td>
<td>Ph</td>
<td>91</td>
<td>96 (+)(R)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>69</td>
<td>4-MeOC₆H₄</td>
<td>93</td>
<td>92 (+)</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>70</td>
<td>nBu</td>
<td>78</td>
<td>93 (+)(S)</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>71</td>
<td>Ph</td>
<td>75</td>
<td>97 (-)</td>
</tr>
</tbody>
</table>

[a] Isolated yields. [b] Determined by chiral HPLC or GC using chiral stationary phases. [c] Absolute configuration determined by comparison with the optical rotation from literature.

**Scheme 2.6**: Asymmetric hydrogenation of α,β-substituted unsaturated sulfone.

**Scheme 2.7**: Asymmetric hydrogenation of α,β-substituted unsaturated sulfone.

Successful hydrogenation of both allylic and vinylic substrates prompted an investigation to move the alkene one bond further from the sulfone group (E-homoallylic sulfones). Two E-homoallylic sulfones were prepared and tested in the hydrogenation (**Table 2.6**). As expected, the enantioselectivity was
high (>90% ee) where benzyl 76 substitution was slightly better than 2,6-dimethyl phenyl 77 (99 vs 94% ee, entry 1 vs 2).

**Table 2.6**: Screening of some homo-allylic sulfones in the asymmetric hydrogenation with catalyst F.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>R</th>
<th>% Conv.[b]</th>
<th>% ee[c], [d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>&gt;99</td>
<td>99 (-)</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>&gt;99</td>
<td>94 (-)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol substrate, 0.5 mol% catalyst, 2 mL CH₂Cl₂, 50 bar H₂, 17 hrs, rt. [b] Conversion, determined by ¹H NMR spectroscopy. No side products were detected. [c] Determined by chiral HPLC or GC analyses. [d] Absolute configuration determined by analogy with the corresponding alkenes obtained from Ramberg-Bäcklund reaction.

d) Conclusion

A variety of cyclic and acyclic sulfones were successfully hydrogenated. The resultant chiral sulfones were produced in high optical purity. Furthermore, it was also shown that these chiral sulfones can be converted to the corresponding chiral alkenes in high yield and stereoselectivity (E/Z ratio) using the Ramberg-Bäcklund reaction. In addition, α-substitution, symmetric diallylic and homoallylic configuration were tolerated and high enantioselectivity was achieved. Therefore, this methodology offers a useful and practical route to sulfone and alkene containing chiral molecules.
3) Asymmetric Isomerisation of Allylic Alcohols

a) Isomerisation of Allylic Alcohols

The isomerisation of allylic alcohols involves the transformation of an allylic alcohol into its corresponding saturated aldehyde or ketone (Figure 3.1). This redox reaction has significant value in organic synthesis since, in theory, it can be performed with perfect atom economy requiring no added reagents, which evokes interest in the catalysis of this reaction. Although there are different types of isomerisation reactions, only the reactions concerning allylic alcohols will be discussed.

![Figure 3.1: Isomerisation of an allylic alcohol.](image)

The first example showing that a homogenous metal species could effect the isomerisation of allylic alcohols was in 1962 using an iron catalyst, Fe(CO)\textsubscript{5} (Figure 3.2). However, after numerous investigations, it proved difficult to overcome the high catalyst loading which in many cases was approximately 20 mol\%, and the high temperatures needed for the iron systems. Therefore, focus was shifted to other metals.\textsuperscript{[29]}
Metals such as rhodium,\cite{30} ruthenium,\cite{31} nickel,\cite{32} iridium,\cite{31b, 31d, 33} osmium\cite{34} and molybdenum\cite{35} have been investigated in the isomerisation of allylic alcohols. \textbf{Table 3.1} summarises some allylic alcohol substrates together with the results obtained for the different metals. It is clear that rhodium is well suited for this reaction. Ruthenium and iridium also prove useful for a variety of allylic alcohols. The $\gamma$,\$-dialkyl and alkyl,aryl substituted allylic alcohols are challenging substrates, which thus far have been isomerised only by rhodium and iridium. These substrates are of particular interest as they form chiral aldehydes and ketones.\cite{36}

\textbf{Table 3.1: Summary of the scope of some metals in the isomerisation of allylic alcohols.}

<table>
<thead>
<tr>
<th>Metal</th>
<th>$\omega$</th>
<th>$\beta$</th>
<th>$\alpha$</th>
<th>$\gamma$</th>
<th>$\delta$</th>
<th>$\gamma$</th>
<th>$\tau$</th>
<th>$\tau$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Ru</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Ni</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ir</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Mo</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Several mechanisms have been proposed for this reaction, and are largely dependent on the metal used. Two of the most common pathways are presented in \textbf{Figure 3.3}. Pathway P1 proceeds via the formation of a H-M-$\pi$-allyl species which upon migratory insertion forms the enolate that tautomerises to the desired ketone/aldehyde. In pathway P2, a metal hydride species either pre-formed or formed as a result of autocatalysis, (perhaps from pathway P1, where both mechanisms could be occurring simultaneously), coordinates to the olefin. Migratory insertion of the hydride forms the alkyl-metal species, which then does a $\beta$-hydride elimination to form the enol. Tautomerism generates the ketone/aldehyde. It is important to note that both these mechanisms may be occurring simultaneously, and even along with
others. Furthermore, migratory insertions and β-hydride abstraction steps are likely to be occurring reversibly, making mechanistic investigation difficult due to scrambling. The reaction has been known to generate a number of side products, such as α,β-unsaturated aldehydes and ketones, aldol condensation products, esters and Z/E isomerised products.\cite{36} Mazet has also conducted some mechanistic studies for the iridium N,P-system.\cite{37}

![Figure 3.3: General mechanistic pathways, proposed for a majority of the metal catalysts used in the isomerisation reaction.](image)

Rhodium catalysts bearing phospha-ferrocene ligands are highly enantioselective in the isomerisation of γ,γ-alkyl,aryl allylic alcohols, as demonstrated by Fu. They observed that higher selectivities were obtained for Z-γ,γ-alkyl,aryl substrates than for the E alcohols. After modifying the ligand, Fu achieved very good results for E-γ,γ-alkyl,aryl allylic alcohols (Figure 3.4).\cite{38}

![Figure 3.4: Highly active and selective catalysts in the rhodium catalysed isomerisation of γ,γ-substituted allylic alcohols developed by Fu.](image)

Iridium based catalysts have been investigated by Mazet. He began by exploring the ligand effects focusing primarily on achiral, mono-dentate lig-
ands. From among the many observations made, Mazet concluded that, to achieve significant activity, a phosphine having bulky dialkyl groups such as cyclohexyl and adamantyl, is required. Furthermore, a weakly coordinating BArF counterion proved superior to PF₆. Utilizing these properties in a chiral ligand, Mazet successfully isomerised a number of $E$-$\gamma,\gamma$-alkyl,aryl allylic alcohols with excellent enantioselectivities (Figure 3.5). However, the Z and dialkyl allylic alcohol substrates still proved a challenge for his system.\textsuperscript{[37, 39]}

![Figure 3.5: Optimized catalyst design for Mazet’s system.](image)

Some work has been conducted using the enolate intermediate. Martín-Matute has added electrophiles such as $N$-halo succinimides in combination with an iridium catalyst (Figure 3.6). The corresponding $\alpha$-halo ketone is produced in high yield in a mixture of acetone and water. An asymmetric version has not yet been developed.\textsuperscript{[40]}

![Figure 3.6: Tandem isomerisation-halogenation reaction.](image)

b) Evaluation of Iridium Catalysts in the Isomerisation

A number of the chiral N,P-iridium catalysts that Mazet tested in the isomerisation, had been shown previously to also be successful catalysts for the asymmetric hydrogenation of olefins. Mazet had been successful in the isomerisation of $E$-$\gamma,\gamma$-alkyl,aryl allylic alcohols, but not the corresponding Z and dialkyl allylic alcohols. Hence, it was decided to conduct an investigation in the isomerisation of allylic alcohols, using a series of chiral N,P-iridium catalysts (Figure 3.7).
For the analysis, \((E)-4\text{-methyl-3-phenylpent-2-en-1-ol}\) \(78\) was used as a model substrate (Table 3.2). With the exception of catalysts \(B\) and \(E\) (bicyclic ligands, entries 1 and 3), the majority of catalysts screened had almost no activity for isomerisation (entries 2 and 4 – 6). Both \(B\) and \(E\) produced the corresponding aldehyde with very high enantioselectivities (both \(>99\%\) ee). Catalyst \(B\) had the highest activity, and was chosen to screen more substrates.

A number of both \(Z\)- and \(E\)-configured \(\gamma,\gamma\)-alkyl,aryl substituted allylic alcohols (Table 3.3) were prepared and screened in the isomerisation using catalyst \(B\). Interestingly, the corresponding \(Z\)-isomer \(79\) was isomerised with equally high selectivity as \(E\)- \(78\) albeit in a lower yield (both \(>99\%\) ee, entries 1 and 2).
Table 3.2: Screening catalysts for the asymmetric isomerisation of \((E)\)-4-methyl-3-phenylpent-2-\(E\)-ol 78.

The same observations were made in the case of the cyclohexyl, phenyl \(E/Z\)-isomers 80 and 81 (both >99% ee, entries 3 and 4), which both isomerised with excellent selectivity. Curiously, with an ethyl group, the \(E\)-alcohol 82 was isomerised less efficiently than the \(Z\)- 83 (21% yield, 97% ee and 38% yield, >99% ee, entries 5 and 6, respectively). When alkyl = Me (84 and 85), the isomerisation became more difficult (less chemoselective) and the products were obtained in lower yields: 84 -<5% and 85 -14% yield (entries 5-8). For the \(Z\)-alcohols the enantioselectivity remained remarkably high regardless of the alkyl substituent (all >99% ee, entries 2, 4, 6 and 8).

<table>
<thead>
<tr>
<th>Entry(^{[a]})</th>
<th>Catalyst</th>
<th>Yield(^{[b]}) (%)</th>
<th>ee(^{[c]}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>88</td>
<td>&gt;99 (S)</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>&lt;5</td>
<td>n.a.(^{[d]})</td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>44</td>
<td>&gt;99 (S)</td>
</tr>
<tr>
<td>4</td>
<td>L</td>
<td>&lt;5</td>
<td>n.a.(^{[d]})</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>&lt;5</td>
<td>n.a.(^{[d]})</td>
</tr>
<tr>
<td>6</td>
<td>O</td>
<td>&lt;5</td>
<td>n.a.(^{[d]})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Each result is the average from two reactions.\(^{[b]}\) Isolated yield.\(^{[c]}\) Determined by GC/MS using chiral stationary phases.\(^{[d]}\) Not applicable.
Table 3.3: Asymmetric isomerisation of both Z- and E-configured γ,γ-alkyl,aryl substituted allylic alcohols using catalyst B.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Configuration</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>E</td>
<td>88</td>
<td>&gt;99 (S)</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>Z</td>
<td>42</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>E</td>
<td>86</td>
<td>&gt;99 (S)</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>Z</td>
<td>50</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>5</td>
<td>82</td>
<td>E</td>
<td>21</td>
<td>97 (R)</td>
</tr>
<tr>
<td>6</td>
<td>83</td>
<td>Z</td>
<td>38</td>
<td>&gt;99 (S)</td>
</tr>
<tr>
<td>7</td>
<td>84</td>
<td>E</td>
<td>&lt;5</td>
<td>91 (R)</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>Z</td>
<td>14</td>
<td>&gt;99 (S)</td>
</tr>
</tbody>
</table>

[a] Each result is the average from two reactions. [b] Isolated yield. [c] Determined by GC/MS using chiral stationary phases.

Some E- and Z-dialkyl allylic alcohols were also tested (Table 3.4). Geraniol 86 and nerol 87 were isomerised with high enantioselectivity despite low yields of the aldehyde product (entries 1 and 2). Similar observations were made when comparing the results of 78 and 79 to those of 88 and 89 (Table 3.4 and Table 3.3, entries 3 and 4, respectively).
Table 3.4: Asymmetric isomerisation of both Z- and E-configured γ,γ-dialkyl substituted allylic alcohols using catalyst B.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Substrate</th>
<th>Configuration</th>
<th>Yield[b] (%)</th>
<th>ee[c] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>E</td>
<td>11</td>
<td>94 (S)</td>
</tr>
<tr>
<td>2</td>
<td>87</td>
<td>Z</td>
<td>&lt;5</td>
<td>n.a.[d]</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>E</td>
<td>79</td>
<td>96 (R)</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>Z</td>
<td>50</td>
<td>98 (S)</td>
</tr>
</tbody>
</table>

[a] Each result is the average from two reactions. [b] Isolated yield. [c] Determined by GC/MS using chiral stationary phases. [d] Not applicable.

c) Conclusion

Catalyst B was found to be very enantioselective (>91% ee) for the isomerisation of a variety of Z- and E- allylic alcohol substrates. The high enantioselectivity for both Z- and E- allylic alcohols – tested in this study – makes this methodology a useful tool for asymmetric synthesis.
4) Formal Total Synthesis of Aliskiren

a) Introduction

Asymmetric hydrogenation using N,P-ligated iridium catalysts is a field of significant interest. Bulky olefins, in particular those that do not possess a sufficiently strong coordination group in the vicinity of the olefin, have remained a challenge for chiral rhodium and ruthenium di-phosphine catalysts. This limitation is not shared by the iridium-N,P catalysts.\(^{[41]}\)

Considerable attention has been given to explore the substrate scope for these unique catalysts. However, it should be noted that, the implementation of this useful chemistry in the total synthesis of natural products or biologically interesting molecules is still scarce. Pfaltz’s group, however, have successfully applied this chemistry in the synthesis of several natural products.\(^{[42]}\) Using the iridium N,P-catalysts developed in their group, they have used asymmetric hydrogenation as a key strategy to install stereogenic centres in the synthesis of \(\alpha\)-tocopherol,\(^{[42a]}\) (+)-torrubellone C\(^{[42b]}\) and (-)-pyridovericin\(^{[42c]}\) and others (Scheme 4.1).

These studies have been a motivation in the Andersson group and interest was focused on Aliskiren (Tekturna®) (Figure 4.1): an efficient renin in-
hibitor drug used to treat hypertension and renal failure. FDA approval and desirable administration via oral intake of the drug have made it an attractive challenge to many chemists in the field of asymmetric synthesis and catalysis.\textsuperscript{[43]}

\begin{center}
\includegraphics[height=1cm]{aliskiren.png}
\end{center}

\textbf{Figure 4.1: Structure and absolute stereochemistry of Aliskiren.}

In Aliskiren there are four stereogenic centres: C-2, C-4, C-5 and C-7. Several syntheses have been reported.\textsuperscript{[44]} Many of these strategies arrive at compound 90 (\textbf{Scheme 4.2}), using stereoselective methods to install chirality at positions C-2 and C-7. Another important feature of compound 90 is that there is an \textit{E}-C=C masking C-4 and C-5, which has a crucial role in their formation. Various halo-lactonisation, or epoxidation-ring opening methods have been investigated to prepare 91,\textsuperscript{[44h-j]} where the dimethyl amide (at C-2) offers the best results.\textsuperscript{[44n]} The “X” at C-5, is typically a leaving group (or converted to one: -OH to -OMs etc.), which is formed directly after the lactonisation. This leaving group is substituted with inversion of configuration, by a nucleophilic source of nitrogen. Since these reactions are stereospecific, the \textit{Z}-C=C isomer would produce the undesired opposite stereochemistry (\textit{R},\textit{R}). Since two of the stereogenic centres (C-4 and C-5) were installed from compound 90, in an approach that is both selective and elegant, it was chosen as the target compound.

\begin{center}
\includegraphics[height=3cm]{aliskiren_intermediates.png}
\end{center}

\textbf{Scheme 4.2: Key intermediates used in the preparation of Aliskiren.}

\textbf{b) Synthesis of Key Intermediate in the Preparation of Aliskiren}

Disconnection of the C=C bond renders fragments 92 and 93, where intermediate 90 would be produced using an olefination protocol (\textbf{Scheme 4.3}).
Various olefination strategies are capable of doing this, for example: McMurry coupling (92 and 93: X = O), Cross Metathesis (3 and 4: X = CH₂) and the Wittig reaction (92: X = ‘P(Ar)₃Br, 93: X = O, and vice versa). However, the Julia-Kocienski olefination was chosen (92: X = SO₂R, 93: X = O, and vice versa), since it has been shown to have high E selectivity (very high when R = 1-phenyl-1H-tetrazole).[45]

![Scheme 4.3: Retrosynthetic analysis of key intermediate 90.](image)

Further analysis showed that chirality on 92 and 93 can be installed by asymmetric hydrogenation of the corresponding olefins. Both the sulfone (X = SO₂R) and aldehyde (X = O) can be readily prepared from the respective alcohols. The Andersson group has prepared several N,P-iridium catalysts, that hydrogenate allylic alcohols with impressive enantioselectivity.[13b, 13e, 46] Therefore, the aim of this study focused on the preparation of 94 and 95, where R = Et (Scheme 4.3).

Perhaps one of the greatest challenges faced in most asymmetric hydrogenation reactions is control of the geometry about the C=C (E or Z). Hence, preparation of the olefin had to be carried out using stereospecific transformations. Addition of organocuprates to acetylenes is well established and highly selective for many substituted acetylenes. With this in mind, the goal was first to synthesise 97 (Scheme 4.4). Once the preparation of compound 96 (Maibaum et. al.[47] was complete, 97 was furnished by reaction of 96, methyl propiolate and K₂CO₃ in the presence of CuI.[48] The key step in forming an olefin of pure Z geometry via an organocuprate reaction was screened under a number of different conditions. A combination of i-PrMgCl, LiBr and CuBr to form the organocuprate facilitated an efficient reaction (complete in <1 hr). It was discovered that both the solvent and the reaction temperature had an impact on the Z:E selectivity. The best results were obtained at low temperature in THF forming essentially only the de-

**Scheme 4.4: Preparation of allylic alcohol fragment 94.**

Using a protocol developed by Valenta et al. (Me vs i-Pr), alkylation of ethyl 3-butenoate (Scheme 4.5) with an i-Pr group afforded 99. This was followed by epoxidation of 99 using m-CPBA which resulted in the formation of 100 in high yield. With the aid of base (K$_2$CO$_3$), 100 underwent rearrangement furnishing the alcohol fragment 95 in the desired E geometry. Any formed Z-isomer is likely to cyclize into the corresponding lactone, which was detected in the crude reaction mixture.

**Scheme 4.5: Preparation of allylic alcohol fragment 95.**

c) Asymmetric Hydrogenation of the Allylic Alcohol Fragments

The results for the asymmetric hydrogenation of compounds 94 and 95 are presented in Table 4.1. Catalyst screening was carried out using CH$_2$Cl$_2$ as a solvent. The conversions obtained ranged from poor to high (entries 1-6).
Enantioselectivities also varied, however, 93% ee (entry 2) for the hydrogenation of 94 using G, and 97% ee (entry 3) in the hydrogenation of 95 using H, could be achieved.

It has been reported that enantioselectivity can increase when the hydrogenation is carried out in solvents such as ClCH₂CH₂Cl and CF₃-C₆H₅. Xumu et al. have shown that the asymmetric hydrogenation of cyclic imines using Ir-diphosphine catalysts had higher selectivity in a mixture of EtOAc and CH₂Cl₂. A number of weakly coordinating solvents (entries 7-11) were tested. Two catalysts G and H having either an imidazole or a thiazole heterocyclic backbone were evaluated in the hydrogenation of 94 and 95. The screening was carried out using CH₂Cl₂ as a solvent and the results for the asymmetric hydrogenation are presented in Table 4.1.
Figure 4.2: Catalysts used in this study (black).

Table 4.1: Evaluation of the hydrogenation of allylic alcohols 94 and 95 with some N,P-ligated Ir-complexes.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>% conv.</th>
<th>% ee</th>
<th>catalyst</th>
<th>% conv.</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>CH₂Cl₂</td>
<td>30</td>
<td>61</td>
<td>B</td>
<td>99</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>G</td>
<td>CH₂Cl₂</td>
<td>99</td>
<td>83</td>
<td>G</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CH₂Cl₂</td>
<td>99</td>
<td>83</td>
<td>H</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>CH₂Cl₂</td>
<td>99</td>
<td>83</td>
<td>I</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>J</td>
<td>CH₂Cl₂</td>
<td>31</td>
<td>67</td>
<td>J</td>
<td>31</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>CH₂Cl₂</td>
<td>57</td>
<td>75</td>
<td>N</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>G</td>
<td>CHCl₂CH₂Cl</td>
<td>99</td>
<td>91</td>
<td>H</td>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>G</td>
<td>Toluene</td>
<td>99</td>
<td>91</td>
<td>H</td>
<td>71</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>G</td>
<td>CF₃C₆H₅</td>
<td>99</td>
<td>91</td>
<td>H</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>G</td>
<td>EtOAc:CH₂Cl₂, 1:10</td>
<td>99</td>
<td>89</td>
<td>H</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>G</td>
<td>CF₃CH₂OH</td>
<td>99</td>
<td>92</td>
<td>H</td>
<td>25</td>
<td>82</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.065 mmol of substrate, 1.0 mol% catalyst, 0.5 mL of solvent, 50 bar H₂ for 94, 100 bar for 95, 20 °C, 17 hrs. For 95, 1.5 mg of polyvinyl pyridine (PVP) was added.[b] Determined by ¹H NMR spectroscopy.[c] Determined by HPLC or GC analyses using a chiral stationary phase.[d] 97% yield (+)-(S).[e] 91% yield (-)-(S).

All other solvents screened had a negative effect on the conversion and enantioselectivity when compared to CH₂Cl₂. More strongly coordinating sol-
vents, such as MeOH and i-PrOH completely inhibited the hydrogenation. The best solvent for both cases was CH$_2$Cl$_2$, where 92 and 93 were isolated in a yield of 91% and 97%, respectively with both having (S)-configuration [(+)-(S)-92 and (-)-(S)-93]. This assignment supported experimental data (comparison of optical rotation data reported for 90).$^{[51]}$

d) Connecting the Pieces

Having prepared the two chiral fragments, it was necessary to test the efficacy of the *Julia-Kocienski reaction* of the installation of the necessary *E*-olefin geometry for our target (vide supra). A study was conducted to determine the optimal reaction conditions using two isoamyl fragments (101 and 102) as mimics to the chiral γ,γ-scaffolds (*Table 4.2*). These bases: Li, Na and KHMDS were evaluated in different solvents: toluene, Et$_2$O, THF and DME. Li and NaHMDS gave unsatisfactory *E* selectivity (<80%) in the less polar solvents (toluene and Et$_2$O). Using KHMDS in these solvents, was considerably selective (~85% *E*). In more polar solvents (THF and DME), Li and NaHMDS both gave high *E* selectivity. However, KHMDS produced the most satisfactory results (>95% *E*) with DME as the solvent, where essentially only the *E* isomer of 103 was detected.
Table 4.2: Optimization of MHMDS and solvent for the Julia-Kocienski reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent</th>
<th>MHMDS</th>
<th>E/Z</th>
<th>% E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>1.5:1</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Iodone</td>
<td>Na</td>
<td>1:1</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>K</td>
<td>7:1</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Li</td>
<td>2.9:1</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Et₂O</td>
<td>Na</td>
<td>2.1:1</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>K</td>
<td>6.3:1</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Li</td>
<td>6.1:1</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>Na</td>
<td>6.5:1</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>K</td>
<td>25.1:1</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Li</td>
<td>8.1:1</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>DME</td>
<td>Na</td>
<td>14.8:1</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>K</td>
<td>88.2:1</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

The final stage for the preparation of 90 (Scheme 4.6) was facilitated by oxidation of 93 using PCC to yield 104 (91%). Substitution of the alcohol in 92, was preceded by tosylation and formed 105 (91%). Oxidation of the thioether produced sulfone 106 that was required to complete the assembly of 90. These steps were high yielding and the products easy to purify. Combining 104 and 106 using the optimised Julia-Kocienski reaction conditions (KHMDS, DME) furnished 90 in 63% isolated yield.
Scheme 4.6: Construction of key intermediate 90, from chiral fragments 92 and 93.

e) Conclusions

The successful construction of a late-stage intermediate 90 in the synthesis of Aliskiren was accomplished in 11 steps. An overall yield of 18% for intermediate 96 was achieved. Despite not being the shortest route to prepare Aliskiren, this route offers both highly selective and operation friendly protocols. The key steps in the synthesis; installation of chirality (C-2 and C-7), and the construction of an E di-substituted olefin (C-4 and C-5), were completed using stereoselective methodologies. These methodologies afforded 97% ee and 93% ee at C-2 and C-7, respectively, and at least 95% E geometry about C-4 and C-5. The synthesis developed in this work is also protecting-group free.
5) Enantio- and Regioselective Hydrogenation of Minimally and Densely Decorated Unsaturated Carbocycles

a) Introduction

For a long time saturated and partially saturated carbocycles bearing stereogenic centres have been challenging targets in organic synthesis. From a retrosynthetic analysis (Figure 5.1) these compounds (107) are easily prepared from an asymmetric hydrogenation of an olefin (108). Compounds such as 108, can be in the form of 1,4-dienes, which are versatile and simple to prepare via the well-established Birch reduction\textsuperscript{[52]} and Diels-Alder reactions.\textsuperscript{[53]} Therefore, in a few steps these compounds can be prepared using the asymmetric hydrogenation reaction to install the chirality needed.

\[ R^* \text{AH} \rightarrow R \xrightarrow{\text{Birch}} \xrightarrow{\text{Diels-Alder}} R + \]

Figure 5.1: Retrosynthesis of a chiral saturated cyclohexane.

These chiral units are themselves versatile building blocks and are present in many biologically active compounds. A few examples are: the dehydro-decalins unit is ubiquitous in sesquiterpenes such as Eudesmane and Eremophilan (Figure 5.2). The tetrahydrocarbazole scaffold is of great importance in the biologically active compound Frovatriptan, a drug for the treatment of migraines.\textsuperscript{[54]}
Andersson and co-workers carried out an investigation on the hydrogenation of minimally functionalised compounds of Class 1 (Figure 5.3) with great success. The purpose of this chapter is to investigate possible expansion of the substrate scope to include functional groups (Class 2) and heterocycles (Class 3).

b) Discussion

Three classes of cyclic substrates were investigated (Figure 5.3); minimally functionalised (Class 1), functionalised (Class 2) and heterocycle fused (Class 3). As mentioned, these compounds were easily prepared from either a Birch reduction of the corresponding aromatic precursor, or a Diels-Alder reaction. A series of catalysts used in this study is presented in Figure 5.4.
Minimally functionalised olefin substrates (Table 5.1) were well tolerated and required only 0.5 mol% of catalyst to complete the hydrogenation. With catalyst M, excellent enantioselectivity was obtained for the hydrogenation of 109 (entry 1, 92% ee). Catalyst J hydrogenated the dehydronaphthalene substrates successfully (entries 2 and 3, 95 and 99% ee, respectively). However, the enantioselectivity was higher for an OMe (111) substituent than the Me (110). These scaffolds are pro sesquiterpene, which have been shown to be active anticancer agents. In addition to high enantioselectivity, hydrogenation of the tetra-substituted olefin was not observed.

Substrates having functional groups directly attached to the carbocycle were also screened (Table 5.2). Interestingly, despite the steric hindrance imposed by the carboxyl groups, excellent enantioselectivity was maintained using catalyst J. However, higher catalyst loading (1 vs 0.5 mol%) was necessary at 100 bar of hydrogen. Substrate 112 was hydrogenated with excellent enantioselectivity (entry 2, 99% ee). A fused cyclohexanone (113) did not affect the high enantioselectivity either (entry 3, 98% ee). In this case the catalyst gave equally high selectivity for both diastereomers. No reduction of the ketone was observed.
Table 5.1: Asymmetric hydrogenation of Class 1 substrates

<table>
<thead>
<tr>
<th>Entry[^a]</th>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst</th>
<th>% Conv[^b]</th>
<th>% ee[^c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[109]</td>
<td>[Me, Me]</td>
<td>[Me]</td>
<td>&gt;99</td>
<td>92 (+)</td>
</tr>
<tr>
<td>2</td>
<td>[110]</td>
<td>[Me, Me]</td>
<td>[J]</td>
<td>&gt;99</td>
<td>95 (-)</td>
</tr>
<tr>
<td>3</td>
<td>[111]</td>
<td>[OMe, OMe]</td>
<td>[J]</td>
<td>&gt;99</td>
<td>99 (-)</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: 0.25 mmol of substrate, 1 mol% catalyst, 2 mL of CH₂Cl₂, 50 bar of H₂, 17 hrs, rt.
[^b]: Conversion determined by ¹H NMR spectroscopy. No side products were detected.
[^c]: Determined by chiral GC analyses.

There have been only a few reports of asymmetric iridium catalysts that can hydrogenate tetra-substituted olefins with reasonable enantioselectivity. Pfaltz and co-workers[56] have achieved some success in the hydrogenation of these very bulky substrates. In their investigation they report that more room is available on the metal for these bulky olefins using a 5-membered N-Ir-P chelate which directs the groups on the phosphine and nitrogen outward whereas in the traditional 6-membered N-Ir-P chelate, the bulky groups tends to fold inward. However, our interest was to retain the tetra-substituted olefin, so that it can be used for further transformation such as; epoxidation, oxidative cleavage or dihydroxylation.[55]

Two heterocyclic substrates (pyrrole and indole, Table 5.3) were tested. These substrates also resulted in high ee’s (up to 99%, catalyst loading: 1-2 mol%). The dehydro-indole, bearing a 5-methyl substituent (indole nomenclature) [114] was hydrogenated with catalyst [J] in high enantiomeric excess (entry 1, 98 % ee). Using catalyst [H], a dehydro-indole, bearing a 5-methoxy substituent [115] was hydrogenated in >99% ee. When catalyst [J] was used, a small amount of ketone product was observed. No reduction of the pyrrole was observed.
Table 5.2: Asymmetric hydrogenation of Class 2 substrates.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst</th>
<th>% Conv.[b]</th>
<th>% ee[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>112</td>
<td>COOH</td>
<td>J</td>
<td>&gt;99</td>
<td>99[g] (+)</td>
</tr>
<tr>
<td>2</td>
<td>113</td>
<td>COOH</td>
<td>J</td>
<td>&gt;99</td>
<td>99[g] (-)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol of substrate, 1 mol% catalyst, 2 mL of CH₂Cl₂, 100 bar of H₂, 17 hrs, rt. [b] Conversion determined by ¹H NMR spectroscopy. No side products were detected. [c] Determined by chiral GC analyses. [d] For the trans-Me product. [e] For both cis-fused diastereomers.

Table 5.3: Asymmetric hydrogenation of Class 3 substrates.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst</th>
<th>% Conv.[b]</th>
<th>% ee[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>114</td>
<td>NR</td>
<td>J</td>
<td>&gt;99</td>
<td>98 (+)</td>
</tr>
<tr>
<td>2</td>
<td>115</td>
<td>NR</td>
<td>H</td>
<td>&gt;99</td>
<td>99 (+)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol of substrate, 1 mol% catalyst, 2 mL of CH₂Cl₂, 50-100 bar of H₂, 17 hrs, rt. [b] Conversion determined by ¹H NMR spectroscopy. No side products were detected. [c] Determined by chiral GC analyses.

c) Conclusion

Several cyclic prochiral olefins were successfully hydrogenated (>99% conv., up to >99% ee) using N,P-ligated iridium catalysts. Minimally functionalised substrates (Class 1) were hydrogenated rapidly and in high ee, which was consistent with earlier reports. Substrates having functional groups (Class 2) and heterocycles (Class 3) attached to the unsaturated cycle,
were hydrogenated gradually over a period of time, however, high enantioselectivity was still maintained (up to >99% ee). This methodology is a highly practical, general and selective means of preparing chiral cyclohexanes.
This thesis describes the application of N,P-ligated iridium catalysts in the preparation of chiral molecules.

In Chapters 2 and 5, the asymmetric hydrogenation of some unsaturated sulfones and cyclohexenes was carried out using a series of previously developed N,P-ligated iridium catalysts in the Andersson group. The sulfones (Chapter 2) were observed to undergo a clean and selective hydrogenation (>90% ee), regardless of the substitution pattern. Bulky groups and purely aliphatic substitution were also tolerated. The Ramberg-Bäcklund reaction was used to generate chiral olefin containing compounds after the hydrogenation. This two-step, orthogonal approach proved effective in furnishing either E or Z geometry about the C=C bond without loss in enantiomeric excess from the hydrogenation. It was discovered that the hydrogenation reaction was sensitive to heterocycles such as pyridines, which still require investigation. However, given the large scope covered by these two strategies there is potential for their use in the preparation of biologically interesting molecules.

Challenging cyclohexene substrates (Chapter 5) were also found to undergo a selective hydrogenation. Although successful reports from the Andersson group are recognized, functionality of the substrates was low. Several cyclohexenes and fused heterocycles were prepared and hydrogenated in high enantiomeric excess (>91% ee). Given the high selectivity, this work could be extended into the preparation of sesquiterpenes and chiral tetrahydrocarbazole type drugs.

The preparation of chiral aldehydes is an invaluable tool for organic synthesis. Catalytic isomerisation of allylic alcohols to aldehydes is an efficient and atom economical method to achieve this. Although there are efficient and selective catalysts for the isomerisation of E-configured alkyl,aryl-substituted allylic alcohols, both dialkyl (E and Z) substituted, and Z alkyl,aryl-substituted allylic alcohols remained a challenge. In Chapter 3 an iridium N,P-ligated hydrogenation catalyst, developed in the Andersson group, was used and up to >99% ee was achieved for the isomerisation of the aforementioned allylic alcohol substrates. However more work has to be conducted to understand the origins of the high selectivity in this reaction.
Denna avhandling behandlar två stereoselektiva reaktioner, hydrogenering samt isomerisering av olefiner, som båda katalyseras av en iridium katalysator med kväve-fosfor-ligander. Särskilt fokus har riktats mot studier och utveckling av reaktionernas användningsområde och ett resultat av detta är att ett flertal nya substrat nu framgångsrikt kan användas som startmaterial. Reaktionsprodukterna som bildas är svåra att framställa med andra metoder vilket i kombination med den höga stereoselektiviteten (90 – 99% ee) gör reaktionerna mycket användbara inom kemisk syntes.

Resultaten som presenteras i avhandlingen är av intresse inte bara inom grundvetenskaplig forskning utan kan även komma till användning inom kommersiell framställning av värdefulla produkter vilket exempliferas genom en selektiv syntes av Aliskiren som är en effektiv medicin för behandling hjärt-kärl sjukdomar.
I would like to express my sincerest gratitude to the following people:

My supervisor Prof. Pher Andersson, a great mentor. I have always admired your knowledge, honesty and unique way of putting things into perspective. I have very much enjoyed doing chemistry under your guidance. I have learned a lot from you. Thank you for always encouraging me to peruse new ideas.

Johan Verendel, a man of tremendous knowledge and insight. During your studies, no challenge was too great; no task was beyond your scope and each endeavour tactfully performed. A great scientist and friend, whom I admire candidly. Alexander Paptchikhine, also a great chemist, with a good sense of humour. I learnt a lot from you, especially about bicycles. Thanks for all the good times in Uppsala. JiaQi Li, a truly spirited researcher; passionate about chemistry; always well-informed and you were work focused and steady. I enjoyed all our chemistry discussions, especially when they were accompanied with whisky and beer. Taigang Zhou, always cool and calm; a hard worker; very thorough and accommodating; and most of all a legend at chromatography. Xu Quan, the splendid enigma; a talented experimentalist as well as a knowledgeable chemist, whom I envy. Thank you for all the great times in and outside the lab: they are priceless. I sincerely hope that we continue our drunken mayhem for a long time to come. Alban Cadu, a witty fellow; always good for a conversation; sharp and to the point. I enjoyed sharing a hood next to yours. Thanks for the good times.

Thishana Singh, the benevolent angel. Your attention to detail, multifaceted skill set and unwavering capacity to help people has always evoked my greatest admiration for you. Most importantly and for many reasons, you truly are someone special to me. Thank you for proofreading this thesis. Janjira Rujirawanich (Nan), always very organised, and probably why all the projects you handled simultaneously didn’t drive you crazy. My utmost gratitude for your help on the sulfone project. I couldn’t have completed it without you. Vijay Singh Parih, very friendly and considerate. I enjoyed working in the hood next to you. Puspesh Kumar Upadhyay, I really appreciate your support during the move to Stockholm. Jianguo Liu, my dearest friend. I’m sorry for all the hard times I have given you, it’s only because I envy your potential. You have always been my go-to-guy in the lab and I’m very grateful for it. I wish
you and your family all the best for the future. Wangchuk Rabten, a fantastic listener and an understanding person. You are competent and considerate, well suited as the lab boss. Someone I have deep respect for and I sincerely hope we will be able to work together again someday. Thank you for all the chemistry discussions and the good times in Stockholm. Sutthichat Kerdpphon, always happy and smiling. The multitude of strange and funny things you say and do is well compensated for by your brilliant mind. Thank you for your help and the good times. Suppachai Krajangsri, you have the makings of a great chemist: skilled in the lab and always willing to try new ideas. Keep singing and be happy, it’s a great opposition to any problem. Cristiana Margarita, someone very witty and talented. I have always admired how quickly you learn. Always arriving so rapidly at answers. You are simply brilliant. Someone who I have enjoyed many discussions about life with. I’m grateful for this, and hope that we will have the opportunity to have more such discussions in the future. Maxim G., Alexey V. and Supaporn S. for good times and great chemistry discussions. Dr. Joseph Samec., a good researcher and teacher, who helped me improve my knowledge of organic reactions with his excellent lectures.

Profound appreciation to the people at Stockholm University:

Deep gratitude to all the friends and colleagues in the Department of Organic Chemistry for an unforgettable time spent here. I enjoyed the guest lectures, seminars, presentations and discussions at the SDM. It has been good spending time with you.

Prof. Kálmán Szabó, for agreeing to be my co-supervisor and helpful chemistry suggestions. Dr. Abraham Mendoza and Dr. Eric Johnston for helpful discussions and considerate suggestions about my future plans in academic research.


Many thanks to Dr. Thishana Singh and Prof. David Tanner for their contribution in the proofreading and suggestions for this thesis.

Finally I would like to thank my parents for their consistent support throughout my studies.
9) References


