Asymmetric Hydrogenations using N, P - Ligated Iridium Complexes

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Dissertation presented at Uppsala University to be publicly examined in B41, Husargatan 3, BMC, Uppsala, Friday, June 8, 2012 at 10:15 for the degree of Doctor of Philosophy. The examination will be conducted in English.

Abstract

The research described in this thesis focuses on the catalytic asymmetric hydrogenation of prochiral olefins using N, P – chelated iridium catalysts. This catalytic system is tolerant to a wide range of substrates and performs better than the well-known ruthenium- and rhodium-catalytic systems for substrates devoid of coordinating groups in proximity of the olefin.
Low catalytic loadings (often <1 %) and the high atom efficiency of this reaction make it a synthetically useful method of chiral molecule synthesis. The primary aim of this thesis was to develop new catalysts that rapidly and efficiently hydrogenate a broad range of alkenes asymmetrically. Papers I and II describe the synthesis and evaluation of new, highly efficient, chiral N, P – ligated iridium complexes. These catalysts were obtained in relatively few steps, while leaving open possibilities to modify and fine-tune their structure. Their versatility is ideally suited to both industrial uses and to equip any catalyst box. Paper III deals with a common problem of defluorination of vinylic fluorides during the hydrogenation. The catalyst designed in that work performs well for several substrates giving very low defluorination rates making it a good starting point for further improvements to cover a broader scope of vinyl fluorides. The structures of the catalysts from papers I and III also offers an easy approach to attach the catalyst ligands to a solid support. Paper IV explores hydrogenation of vinyl boronates, which gives synthetically interesting borane compounds with high enantioselectivities. Taking into account the rich chemistry of organic boranes, these compounds are very important. Paper V deals with hydrogenation of diphenyl/vinylphosphine oxides and vinyl phosphonates, another important classes of substrates that give chiral phosphorous containing compounds of interest in many fields of chemistry: such as medicinal chemistry and organocatalysis. In papers VI and VII we explore the Birch reaction as a source of prochiral olefins. By combining asymmetric hydrogenation with it, we obtain a powerful method to create chiral compounds with excellent enantioselectivities that are next to impossible to make by other routes. The products of the asymmetric hydrogenation are further modified by other well-known transformation to create other induced stereogenic centres.

Keywords: asymmetric hydrogenation, iridium, birch, boronates, fluorine


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ISSN 1651-6214
ISBN 978-91-554-8380-7
urn:nbn:se:uu:diva-173459 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-173459)
To my parents
List of Papers

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


IV Alexander Paptchikhine; Pradeep Cheruku; Mattias Engman and Pher G. Andersson. Iridium-catalyzed enantioselective hydrogenation of vinyl boronates. *Chemical Communications*, **2009**, 5996-5998


VI Alexander Paptchikhine; Kaori Itto and Pher G. Andersson. Sequential Birch reaction and asymmetric Ir-catalyzed hydrogenation as a route to chiral building blocks. *Chemical Communications*, **2011**, *47*, 3989-3991
VII Alexander Paptchikhine; Byron Peters; Thavendran Govender and Pher G. Andersson. The Birch reaction as a source of substrates for asymmetric hydrogenation. 
Manuscript in preparation (Supporting information)

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Contribution report
The author wishes to clarify his contribution to the papers I-VII in this thesis

I) Performed part of catalyst synthesis and screening of substrates. Contributed to the interpretation of results and part of the writing of the manuscript.

II) Contributed partly with the original idea. Developed the synthesis of the catalysts used in this study and took an important part in the synthesis of the catalysts.

III) Developed the synthesis of catalyst used in this study. Synthesized catalyst and performed part of the hydrogenations and was partially involved in preparation of the manuscript.

IV) Performed all experimental work and synthesis of catalysts. Contributed significantly to the interpretation of the results and wrote the entire paper.

V) Prepared catalyst used in this study. Performed a small part of the synthetic work. Contributed in part to the interpretation of the results.

VI) Performed all experimental work and synthesis of catalysts. Contributed significantly to the interpretation of the results and wrote the entire paper.

VII) Performed most of the experimental work and synthesis of catalysts. Contributed significantly to the interpretation of the results and wrote the entire manuscript.
Not Included Publications

*Comptes Rendus Chimie, 2007, 10, 213-219*

IX. Päivi Tolstoy; Mattias Engman; Alexander Paptchikhine; Jonas Bergquist; Tamara L. Church; Abby W.-M. Leung and Pher G. Andersson. Iridium-Catalyzed Asymmetric Hydrogenation Yielding Chiral Diarylmethines with Weakly Coordinating or Noncoordinating Substituents. 
*Journal of the American Chemical Society, 2009, 131, 8855-8860*

X. Javier Mazuela; Alexander Paptchikhine; Päivi Tolstoy; Oscar Pàmies; Montserrat Diéguez and Pher G. Andersson. A New Class of Modular P,N-Ligand Library for Asymmetric Pd-Catalyzed Allylic Substitution Reactions: A Study of the Key Pd–pi-Allyl Intermediates 
*Chemistry - A European Journal, 2010, 16, 620-638*

XI. Javier Mazuela; Alexander Paptchikhine; Oscar Pàmies; Pher G. Andersson and Montserrat Diéguez. Adaptative Biaryl Phosphite–Oxazole and Phosphite–Thiazole Ligands for Asymmetric Ir-Catalyzed Hydrogenation of Alkenes 
*Chemistry - A European Journal, 2010, 16, 4567-4576*

XII. J. Johan Verendel; Taigang Zhou; Jia-Qi Li; Alexander Paptchikhine; Oleg Lebedev and Pher G. Andersson. Highly Flexible Synthesis of Chiral Azacycles via Iridium-Catalyzed Hydrogenation. 
*Journal of the American Chemical Society, 2010, 132, 8880-8881*

XIII. Alban Cadu; Alexander Paptchikhine and Pher G. Andersson. Birch Reaction Followed by Asymmetric Iridium-Catalysed Hydrogenation. 
*Synthesis, 2011, 3796-3800*
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Abbreviations

* Stereogenic center
Abs. Conf. Absolute configuration
Ac Acetyl
Ar Aryl
BArF Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Cat. Catalyst
cod Cyclooctadiene
Conv. Conversion
Cy Cyclohexyl
de Diastereomeric excess
DCM Dichloromethane
DIBAL Diisobutylaluminium hydride
ee Enantiomeric excess
Et Ethyl
EWG Electron withdrawing group
GC Gas chromatography
h Hour(s)
HPLC High performance liquid chromatography
Pr Isopropyl
LAH Lithium aluminium hydride
mCPBA meta-Chloroperoxybenzoic acid
Me Methyl
MS Mass spectrometer
n-BuLi n-Butyllithium
NBS N-Bromosuccinimide
NMR Nuclear magnetic resonance
o.n. Overnight
Pd/C Palladium on carbon
Ph Phenyl
PVP Poly(4-vinylpyridine)
rac Racemic
RT Room temperature
Bu tert-Butyl
THF Tetrahydrofuran
Catalysts used in this thesis:

A1: Ar = R = Ph

B1: Ar = R = Ph

C1: Ar = oTol, R' = H, R'' = tPr
C2: Ar = R' = R'' = Ph
C3: Ar = Ph, R' = H, R'' = tBu
C4: Ar = Ph, R' = H, R'' = tPr

26a: R = Benzyl
26b: R = Methyl
26c: R = Allyl

43a: R = Me, Ar = Ph
43b: R = tBu, Ar = Ph
43c: R = Ph, Ar = Ph
43d: R = Ph, Ar = o-Tol
1 Introduction

Chirality is a fundamental concept in organic chemistry since nature is full of chiral molecules. The term chirality was first used by Lord Kelvin in 1904 and was defined as a specific geometrical property in an object: an object is chiral if its mirror image (enantiomer) is not super-imposable with itself. Such as for example right and left hands, which are mirror images of each other, but in fact have different geometrical properties.

Because all living organisms are built out of chiral molecules, many essential life-processes are regulated by specific enantiomers. In many cases a biological process can have a greater response to one of the two enantiomers. For example, the history of medicinal compounds is littered with examples of two opposite enantiomers having a significant difference in their biological activity. An example would be propranolol where both of its enantiomers show local anaesthetic and histamine releasing properties but only the (R)-propranolol that acts as a β-adrenergic agent, Figure 1. The ability to synthesize optically pure chiral compounds is therefore of vital importance.

![Figure 1](image.png)

Figure 1. Example of a chiral drug propranolol, used to treat hypertension, anxiety and panic.

1.1 Sources of Chirality

Numerous reviews and books cover the different routes to introduce chirality, discussing all aspects of this field here is simply of too great magnitude even for an entire thesis. However, below are summarized the most common approaches that an organic chemist use to obtain chiral building blocks:

- Use of the chiral pool
- Resolution of a racemic mixture
- Asymmetric synthesis
The chiral pool approach uses chiral compounds found in nature. Although this often gives starting materials of high optical purity and complexity, the choice of compounds is limited and often only one enantiomer is available.

Resolution of racemic mixtures is another widely used approach, it simplifies synthetic work and often provides both enantiomers, however the separation of enantiomers is often time consuming, requires a lot of effort and in most cases wasteful. To solve the aforementioned problems, an organic chemist often resorts to asymmetric synthesis. In this powerful approach the new chiral centers are induced by means of chiral auxiliaries, reagents or catalysts. From the economic point of view asymmetric synthesis is often catalytical, where a small amount of a chiral material (the catalyst) does an enantioselective transformation generating large quantities of a chiral product, obviously a preferred approach in the industry.

The development of efficient chiral catalysts is therefore the crux of the field of asymmetric synthesis.

The preferred properties of a good catalyst are:

- Simplicity of preparation
- Low cost
- High activity and selectivity
- Tolerance for a wide variety of substrates
- Long lifetime
- High chemical stability
- Simplicity of removal

1.2 Enantioselective Reduction of C=C Bonds

The catalytic enantioselective hydrogenation is a powerful method to create chiral centers. Its first commercial application (1974), developed by William Knowles, was done on the synthesis of the anti-Parkinson’s drug L-DOPA using a rhodium-DIPAMP catalyst, Scheme 1. Since then, transition metal catalyzed asymmetric hydrogenation has played an important role in chemical industry.
Scheme 1. The key steps in Knowles’ synthesis of L-DOPA

The ruthenium- and rhodium-catalyzed hydrogenations have been known and studied for a long time. Although excellent results were obtained both in terms of enantioselectivity and catalytic activity, the substrate scope is limited. These catalytic systems require olefins with proximal polar groups that are able to coordinate to the metal, while non-functionalized olefins generally show low reactivity and enantioselectivity. This problem was overcome in 1998, when Pfaltz and co-workers introduced an N, P – chelated iridium complexes able to reduce non-functionalised olefins with high enantioselectivity, Figure 2. The basic structure of these complexes was inspired by the non-chiral Crabtree’s catalyst [Ir(pyridine)(Cy3P)(cod)]PF6, Figure 2.

Figure 2. Crabtree’s catalyst (1979), Pfaltz’s catalyst (1998) and the BArF anion.

A well-known problem with the Crabtree’s and other N, P – chelated iridium catalysts is their rapid deactivation in presence of hydrogen to give stable hydride bridged trinuclear complexes. It has been shown that this deactivation is accelerated in absence of olefinic substrates. With the substitution of the PF6 in favour of the less coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF) counterion, this deactivation process is considerably slowed down. The more loosely coordinated BArF also enables faster hydrogenation, presumably owing to easier accessibility for substrate coordination to the metal. This improvement made it possible to reduce the catalyst loadings to as low as 0.02 mol % while maintaining both high conversions and enantiomeric excess.

Since then, numerous reports have been made of successful N, P – chelated iridium catalysts that resemble Pfaltz catalyst. Figure 3 shows a selection of N, P ligands that work well in iridium catalyzed asymmetric hydrogenation of nonfunctionalised olefins.
Figure 3. Examples of common N, P ligands used in iridium catalyzed asymmetric hydrogenation. For more details on substitution see the corresponding references. $^{9b-f}$

Despite numerous studies on the mechanism of iridium-catalyzed hydrogenations, $^{10,16}$ there are uncertainties as to which is the actual mechanism. Two possible catalytic cycles have been studied involving either Ir(I)/Ir(III) $^{10d}$ or an Ir(III)/Ir(V) $^{16}$ pathway. Both cycles having a common Ir(III) intermediate that forms when hydrogen is applied to the catalyst precursor 1, Scheme 2.

Scheme 2. Proposed Ir(I)/Ir(III) (left) and Ir(III)/Ir(V) (right) catalytic cycles for the N, P–ligated iridium hydrogenation of alkenes. For simplicity the N, P ligand is not drawn out completely. S = Solvent.

Both catalytic cycles starts with addition of the olefin to the active catalyst 2, trans to the phosphorous. In the Ir(III)/Ir(V) cycle one of the solvent molecules is then replaced by a hydrogen molecule to give intermediate 3. The olefin then does a migratory insertion into Ir–H bond with simultaneous oxidative addition of the hydrogen molecule to give complex 4. After reductive elimination the hydrogenated product is released. In the Ir(I)/Ir(III) cycle coordination of the olefin is followed by the migratory insertion and reductive elimination to release the hydrogenated product.
1.3 Research Performed in This Thesis

The aim of this thesis is to explore the iridium catalyzed asymmetric hydrogenation, an important branch of the asymmetric synthesis. Based on research previously conducted in this group, syntheses of efficient N, P – ligand chelated iridium catalysts were developed. The substrate scope of these catalysts has been widened to include various heteroatom-containing vinylic compounds.

The well-known Birch reaction was explored as a convenient source of prochiral olefins for the asymmetric hydrogenation.
2 Development of Catalyst Backbones for Asymmetric Hydrogenation (Papers I, II and III)

2.1 Previously Developed Catalysts

The successful ligand structural backbones in catalysts A, B and C have been previously developed in our group, Figure 4. In particular catalysts A1 and B1 have shown exceptional enantioselectivity in the asymmetric reduction of non-functionalized alkenes.\textsuperscript{11} Catalysts of type C provide excellent stereoselectivities in hydrogenation of aromatic N-arylimines\textsuperscript{12a,b} and enol phosphinates.\textsuperscript{12c,d}

**Figure 4.** General structures of previously reported catalyst frameworks. Tuning of performance is achieved by varying Ar, R and for A value of n; A1: \( \text{Ar} = \text{R} = \text{Ph}, n = 1 \); B1: \( \text{Ar} = \text{R} = \text{Ph} \); C1: \( \text{Ar} = \text{oTol, R = H, R’ = iPr} \); C2: \( \text{Ar} = \text{R’ = R” = Ph} \); C3: \( \text{Ar = Ph, R’ = H, R” = tBu} \); C4: \( \text{Ar = Ph, R’ = H, R” = iPr} \).

General routes to complexes A-C are seen in Scheme 3, highlighting the most important intermediates and conversion of these into chiral ligand backbones. The chirality of catalyst A1 is introduced by resolution of the racemic key intermediate 10 with L-DBTA (dibenzoyl-L-tartaric acid). Pure S enantiomer 11 and optically enriched R enantiomer are obtained by this method. Equilibration in basic conditions of the latter provides a racemate that can be resolved again, increasing overall yield of the S enantiomer 11. Several subsequent steps allow the transformation of compound 11 into the class of catalysts A, Scheme 3, (a).\textsuperscript{11a}

Catalyst B is a mimic of A with several major changes in the backbone: the thiazole moiety is exchanged for an oxazole and the CH\(_2\)-linker to the phosphine replaced by O-linker. Both of these factors directly impact on the coordination properties of the ligand to the metal. The key step in the syn-
thesis differs in that CBS reduction is applied to introduce the chirality to give alcohol 14 in 90% ee, Schem 3, (b). Interestingly, only Ph-substituted (R = Ph) oxazoline 14 could be enantiomerically enriched by crystallization to give product with >99% ee. The 1'Bu-, CH$_3$C$_6$H$_4$- and CF$_3$C$_6$H$_4$-substituted oxazolines were obtained in 70-80 % ees after CBS reduction of the corresponding ketones. The ees of these alcohols were enriched to >99% using chiral chromatography.

A totally different chiral backbone was constructed for catalyst C through a highly stereoselective aza-Diels Alder reaction, which can be scaled up to a multigram scale, Scheme 3, (c).

Scheme 3. Abridged synthetic schemes of the most used catalysts previously prepared in our group.

2.2 Synthesis of the New Complexes (Paper I)

Inspired by the previous work done in our group, it was decided to modify the framework of catalyst A by opening up the rigid six-membered cyclohexyl backbone and thereby making the N, P ligand more flexible, Figure 5.

The synthesis starts from the bromination of ethyl acetoacetate 17 in chloroform, Scheme 4. At the end of the reaction HBr was removed by bubbling a stream of air through the solution. Under these conditions the bromine migrated from α- to γ-carbon affording the more thermodynamically stable γ-bromo-β-ketoester. The latter underwent Hantzsch cyclisation with
thiobenzamide to afford thiazole 18, which was coupled to Me₃Al-activated Oppolzer sultam. Interestingly, the ethyl ester 18 coupled at a much lower rate giving only 23% yield, even after 7 days of reflux, compared to the methyl ester 22 which yielded >85% of the desired product after only 24 hours of reflux. The obtained chiral amide 19 was enolised with LiHMDS and treated with different alkyl bromides in presence of DMPU to afford compounds 20a-c with very high diastereomeric ratios (>95%). The reductive cleavage of the Oppolzer sultam was achieved with LAH, affording alcohols 23a-c and a good recovery rate of the sultam. Tosylation of the alcohols 23a-c, followed by the displacement of OTs with LiP(BH₃)Ph₂ and removal of the BH₃-group provided N, P ligands. Finally the N, P ligands were complexed with [Ir(cod)Cl]₂ and the resulting complex was subjected to ion exchange in two phase system (DCM/water) where Cl⁻ was exchanged by BArF⁻ to give complexes 26a-c.

The enrichment towards optical purity could be done either by recrystallisation of 20a or, at a later stage of the tosylates 24b-c giving >99% ees.

![Diagram of the synthesis of new iridium complexes.](image)

**Scheme 4.** Synthesis of new iridium complexes.

Reagents and conditions: i) Br₂, CHCl₃, 0 °C, 16 h; ii) Thiobenzamide, ethanol, pyridine, reflux, 4 h; iii) MeSO₃H, methanol, reflux, 2 h; iv) Oppolzer sultam, Me₃Al, DCM, reflux, 24 h; v) LiHMDS, THF, −78 °C, RBr, DMPU, 4 h; vi) LiAlH₄, THF, −10 °C to RT, 4 h; vii) TsCl, pyridine, DCM, 0 °C to RT, 16 h; viii) HP(BH₃)Ph₂, n-BuLi, −78 °C to 0 °C, 40 min, then 24a-c, DMF, −78 °C to RT, 16 h; ix) Et₂NH (excess), RT, 16 h; x) [Ir(cod)Cl]₂, DCM, reflux, 40 min; xi) H₂O, NaBARF, RT, 2 h.

### 2.2.1 Evaluation of the New Complexes

Complexes 26a and 26b were stable in air, at ambient temperature, for months, whereas complex 26c decomposed after only a few days, even at low temperatures (-20 °C). Due to its instability, complex 26c has to be used immediately after its preparation.
Table 1. Iridium-catalyzed asymmetric hydrogenation of substrates 27-37.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>26a</th>
<th>26b</th>
<th>26c</th>
<th>A1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conv.</td>
<td>ee</td>
<td>Conv.</td>
<td>ee</td>
</tr>
<tr>
<td>1</td>
<td>Ph-Ph</td>
<td>&gt;99</td>
<td>96(R)</td>
<td>&gt;99</td>
<td>&gt;99(R)</td>
</tr>
<tr>
<td>2</td>
<td>p-MeO-C6H4</td>
<td>&gt;99</td>
<td>94(R)</td>
<td>&gt;99</td>
<td>99(R)</td>
</tr>
<tr>
<td>3</td>
<td>MeO-phen</td>
<td>&gt;99</td>
<td>80(S)</td>
<td>&gt;99</td>
<td>57(S)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>&gt;99</td>
<td>98(R)</td>
<td>&gt;99</td>
<td>94(R)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>&gt;99</td>
<td>78(S)</td>
<td>&gt;99</td>
<td>78(S)</td>
</tr>
<tr>
<td>6</td>
<td>Ph-OH</td>
<td>&gt;99</td>
<td>90(R)</td>
<td>&gt;99</td>
<td>97(R)</td>
</tr>
<tr>
<td>7</td>
<td>Ph-OH</td>
<td>&gt;99</td>
<td>79(R)</td>
<td>&gt;99</td>
<td>91(R)</td>
</tr>
<tr>
<td>8</td>
<td>Ph-COOEt</td>
<td>&gt;99</td>
<td>51(R)</td>
<td>&gt;99</td>
<td>32(R)</td>
</tr>
<tr>
<td>9</td>
<td>Ph-COOEt</td>
<td>&gt;99</td>
<td>97(R)</td>
<td>&gt;99</td>
<td>98(R)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>75</td>
<td>56(S)</td>
<td>75</td>
<td>23(S)</td>
</tr>
<tr>
<td>11</td>
<td>Ph-N-Ph</td>
<td>70</td>
<td>51(S)</td>
<td>27</td>
<td>49(S)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reagents and conditions: 50 bar H₂, RT, DCM, 0.5 mol% catalyst. <sup>b</sup> Determined by ¹H NMR spectroscopy. <sup>c</sup> Determined by chiral HPLC or chiral GC and compared to the literature data. Absolute configuration is given in parentheses. <sup>d</sup> Not attempted. <sup>e</sup> 1 mol% catalyst loading.

The new complexes were evaluated for the hydrogenation of various trisubstituted alkenes, to offer a comparison of performance with previously synthesized complex A1. The summarized results in Table 1, entries 1-10, show that complexes 26a and 26b have comparable stereo selectivity to the
cyclic analogue A1. Complex 26c is clearly less selective, and this might be linked to its instability.

2.2.2 Origin of Enantioselectivity – Application of the Selectivity Model

The known absolute configuration of the complex 26a, deduced from X-ray analysis of 20a (Figure 6, left), and the trend in absolute configurations of the hydrogenation products tells us that catalyst 26a and R enantiomer of A1 have similar conformations during the coordination of the substrate, see Figure 6 (right). As shown elsewhere (Part 1), the initial coordination of the substrate plays a key role in the outcome of the stereochemistry of the hydrogenated product.

Figure 6. X-Ray of compound 20a (left) and superimposition of catalyst 26a and R enantiomer of catalyst A1 (right) light and dark grey, respectively. Hydrogens and coordinating substrate are omitted for clarity.

As expected, the new complexes follow the same trends of selectivity, obeying the selectivity model proposed previously by Andersson and co-workers.11,16 The key steps of the catalytic cycle presented in Part 1 (Scheme 2) are shown in Scheme 5, (a). First the substrate 35 (blue) displaces a solvent molecule on the active complex, trans to the phosphorous. This coordination plays a crucial role in the enantiodetermination of the hydrogenation, as the alkene coordinates in such way as to point the smallest substituent H towards the bulky R substituent of the ligand (red). The ligand has been simplified for the sake of clarity. After several subsequent steps the hydrogenation product is released.

Scheme 5, (b), shows in more detail the steric repulsion between the H substituent of the substrate and Ph substituent of the ligand. This interaction is also represented as a 3D quadrant model, which is simplified as a 2D model.
The catalytic site is composed of one hindered quadrant with steric bulk from the Ph substituent of the ligand, one semi-hindered quadrant with slight hindrance from the substituents of phosphorous and finally the two remaining open quadrants with least hindrance.

Apart from the steric discrimination, the catalyst also possesses polarity recognition. In transition state 38 the alkene makes a migratory insertion into the axial Ir-H bond – a delivery of hydride that preferably takes place on the \( \partial^+ \) side of the alkene. The steric and electronic match and mismatch can be clearly seen in Scheme 5, (c).

Scheme 5. Selectivity model adapted from previously published material for catalysts 26a-c. (a) Coordination of the substrate (blue) to the active catalyst, followed by several steps to release the hydrogenated product. The N, P ligand (red) is not drawn out completely for legibility. (b) Catalytic site represented as a four-quadrant model. Only the smallest substituent (H) of the substrate is shown. (c) Above model applied to substrate 35.

By applying the aforementioned selectivity model on the hydrogenation results of catalysts 26a-c it is possible to see that all studied substrates obey this model. It is also interesting to confirm that substrate 34 (entry 8) having electronically mismatched polarity gives significantly lower ee values (32-51 \% \%) for all tested complexes in this study, Figure 7, (a). Substrate 36 (entry 10) suffered from lower ee values (0-56 \%) due to steric mismatch, having its bulky Ph substituent forced into the semi-hindered quadrant of the catalytic site, Figure 7, (b).
2.2.3 Conclusions

A convenient approach to synthesize new enantiomerically pure N,P-chelated iridium catalysts 26a-c via diastereoselective alkylation was designed. The new catalysts reduced a wide variety of prochiral alkenes in very high conversions and stereoselectivities, comparable to the previously reported complex A1. Given the similarities in results of catalysts A1 and 26a-c, it is evident that backbone flexibility is not a necessity in our catalytic system.

The synthetic route investigated here appear to be tolerant to a number of different substituents in the alkylation step, as was shown in the benzylation, allylation and alkylation reactions, giving very high diastereoselectivities. This gives a simple methodology to produce a wide variety of different catalysts.

Further investigations should be done to attach catalyst intermediate 25c to solid support, thus expanding into the realm of heterogeneous catalysis.

2.3 Development of Bicyclic Thiazole Complexes (Paper II)

To further alter the stereo-environment of catalyst C we decided to exchange oxazoline moiety with a substituted thiazole. This would also make the backbone more chemically resistant and simplify the synthesis and purification of the intermediates.
2.3.1 Synthesis of the New Catalysts

Previously reported bicyclic thioamide 39 underwent Hantzsch cyclization with a selection of α-bromo ketones. Deprotection of the amine and coupling with different diaryl phosphine chlorides afforded N, P ligands 42a-d which were complexed with [Ir(cod)Cl]2 and resulting complexes were subjected to ion exchange in a biphasic system (DCM/water) to give the desired catalysts 43a-d, Scheme 6.

Scheme 6. Synthesis of iridium complexes 43a-d.
Reagents and conditions: i) MeOH, α-bromoketone, CaCO3, reflux, 4 h; ii) THF, 12 M HCl, 2 h; iii) Ar2PCl, iPr2NEt, THF, 0 °C then 4 °C overnight; iv) [Ir(cod)Cl]2, DCM, reflux 1 h then H2O, NaBArF, RT, 2 h.

2.3.2 Evaluation of the New Complexes

The new complexes 43a-d were evaluated for the hydrogenation of several standard tri-substituted alkenes, Table 2, entries 1-9. Complexes 43a-b are shown to be less stereoselective compared to the other catalysts in the series, while complexes 43c-d were comparable to C2 both in terms of stereoselectivity and conversions. Interestingly, replacing Ph- by o-Tol-groups on the phosphorous improved both conversions and ee values for most substrates, compare hydrogenation results for complexes 43c and 43d.
Table 2. Iridium-catalyzed asymmetric hydrogenation of standard substrates.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv.\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
<th>Conv.\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
<th>Conv.\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
<th>Conv.\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
<th>Conv.\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-MeO-C\textsubscript{6}H\textsubscript{4}</td>
<td>99</td>
<td>82(R)</td>
<td>99</td>
<td>22(R)</td>
<td>99</td>
<td>97(R)</td>
<td>99</td>
<td>97(R)</td>
<td>99</td>
<td>99(R)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>83</td>
<td>97(R)</td>
<td>45</td>
<td>97(R)</td>
<td>99</td>
<td>99(R)</td>
<td>99</td>
<td>98(R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>99</td>
<td>32(S)</td>
<td>28</td>
<td>47(S)</td>
<td>97</td>
<td>83(S)</td>
<td>99</td>
<td>76(S)</td>
<td>36</td>
<td>38(S)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>98</td>
<td>85(R)</td>
<td>0</td>
<td>66</td>
<td>92(R)</td>
<td>99</td>
<td>98(R)</td>
<td>99</td>
<td>69(R)</td>
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</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>58</td>
<td>54(R)</td>
<td>0</td>
<td>82</td>
<td>15(R)</td>
<td>99</td>
<td>84(R)</td>
<td>99</td>
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<td>45(R)</td>
<td>0</td>
<td>99</td>
<td>93(R)</td>
<td>95</td>
<td>93(R)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>99</td>
<td>49(S)</td>
<td>96</td>
<td>20(R)</td>
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<td>99</td>
<td>83(S)</td>
<td>99</td>
<td>81(S)</td>
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<td>99</td>
<td>15(S)</td>
<td>99</td>
<td>3(S)</td>
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<td>44(S)</td>
<td>99</td>
<td>50(S)</td>
<td>99</td>
<td>28(S)</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>99</td>
<td>2(S)</td>
<td>99</td>
<td>3(S)</td>
<td>99</td>
<td>2(S)</td>
<td>99</td>
<td>17(S)</td>
<td>99</td>
<td>3(S)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: 0.25 M substrate in DCM, 0.5 mol\% catalyst, 50 bar H\textsubscript{2}, RT, overnight. 
\textsuperscript{b} Determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{c} Determined by chiral GC or HPLC compared to the literature.

2.3.3 Conclusions

A new family of thiazole N, P–ligated iridium complexes was synthesized employing a rigid bicyclic backbone. In comparison to their oxazoline analogue C\textsubscript{2}, complexes 43c-d gave better results for most tested substrates. The synthesis was more robust and simpler than for the corresponding catalysts of type C. This is partially due to the difference in the stability of the thiazole moiety compared to that of the oxazoline. The synthetic scheme proposed here could be easily used for a scaled up production of these com-
plexes and provide an easy way to alter the properties of the catalyst by changing substituents on the thiazole moiety and phosphorous atom.

2.4 Towards Fluorine-Containing Stereogenic Centers (Paper III)

Use of fluorine in biologically active molecules has become more popular in recent decades. The inclusion of fluorine into a drug molecule can alter properties such as its bioavailability, toxicity and metabolism. Many of these properties hinge on the lipophilicity of the compound and the high electronegativity of fluorine.¹⁷

There are few methods to create F-containing stereogenic centers,¹⁸ which can be the reason why few drugs contain this functionality. To date, F-containing stereogenic centers have been used only in steroid-like molecules where fluorine is introduced by opening a chiral epoxide with various fluoride sources, Figure 8.¹⁹ Aside from these examples there are almost no drugs that contain a stereogenic center with a fluorine, however, a great number of drugs with fluorine in the non-stereogenic centers are appearing on the market, and this trend does not seem to slow down. This makes research in this field of asymmetric synthesis very valuable.

![Figure 8. Examples of two anti-inflammatory steroids featuring fluorinated stereocenters.](image)

Most reports on synthesising chiral fluorine centers in literature involve asymmetric fluorination of β-ketoesters and β-keto phosphonates²⁰ and very few report the use of asymmetric hydrogenation in this field. Saburi et al. has investigated the ruthenium-catalyzed asymmetric hydrogenation of 2-fluoro-2-alkenoic acids achieving ees of up to 90 % and excellent conversions, Scheme 7.²¹

![Scheme 7. An example of asymmetric hydrogenation of a vinyl fluoride reported by Saburi et al.](image)
2.4.1 Hydrogenation of Vinyl Fluorides

A common problem encountered with the hydrogenation of vinyl fluorides is the C-F bond cleavage, which is observed with most transition metals in both hetero- and homogeneous catalytic systems. In preliminary testing of our catalysts, similar problem was encountered.

![Figure 9. Overview of conversions and C-F bond cleavage in the hydrogenations of vinyl fluoride 47.](image)

The initial screening against the library of catalysts prepared previously in our group revealed that bicyclic catalysts of type C give less C-F bond cleavage (5-12 %) than A and B catalyst types (32-40 %). Figure 9 shows a comparison of catalysts A1 and B1, as well as catalysts of type C that performed best. A possible explanation for difference in defluorination between these catalysts could be varying electron density on the iridium metal. The C-F cleavage proceeds most probably with initial coordination of the metal to the double bond and an oxidative addition of the iridium metal into the vinylic C-F bond. Both steps would highly depend on the electronic environment at the iridium.

Factors that should play a significant role on the electron density of the metal are the relative basicity of the chelated N and P atoms. It is understood that the N-P bond in catalysts of type C plays an important role in the control of the electron density on the phosphorous and therefore on the metal.

Keeping in mind that type A and B catalysts usually perform better with tri-substituted alkenes than type C catalysts, it was inferred that maintaining the structural motif of catalyst A whilst adding an N-linker to the phosphorous was likely to yield a useful complex, Figure 10.
Figure 10. The new N-linker catalyst derived from two previously synthesized N, P ligands.

2.4.2 Synthesis of the New N-linker Catalyst

As the structure of 54 is closely related to our previously prepared type A catalysts, we decided to use a common precursor to make the amide 50 and then performing a Hoffmann-type reaction using Pb(OAc)\textsubscript{4} to introduce the nitrogen onto the cyclohexyl moiety, giving compound 51. Furthermore, reduction of the Boc-group with LAH and resolution on Chiralpak OD column afforded both enantiomers of 52 with ee >99%. The enantiomerically pure secondary amine (R)-52 was coupled with Ph\textsubscript{2}PCl, then complexed with [Ir(cod)Cl]\textsubscript{2}. The resulting complex was subjected to an ion exchange in a biphasic system (DCM/water) to give complex 54.

Scheme 8. Synthesis of iridium complex 54.
Reagents and conditions: i) Pb(OAc)\textsubscript{4}, Et\textsubscript{3}N, DMF/\textbf{t}BuOH, 70 °C, 42 h; ii) LAH, THF, reflux 1.5 h; iii) Chiral HPLC; iv) Ph\textsubscript{2}PCl, DIPEA, toluene, 0 °C, o.n.; v) [Ir(cod)Cl]\textsubscript{2}, DCM, reflux 1 h then H\textsubscript{2}O, NaBArF\textsubscript{4}, RT, 2 h.

2.4.3 Evaluation of the New N-linker Complex

Since complex C1 afforded the least C-F cleavage and better conversions than any of the compared complexes previously reported in our group, we decided to screen substrates against both complexes C1 and 54. The new complex has shown excellent selectivity (≥99 % ees) with tri-substituted vinyl fluorides, Table 3, entries 2 and 3. However, complex C1 remained superior to 54 when it comes to tetrasubstituted vinyl fluorides, Table 3,
The addition of hydrogen proceeds syn across the double bonds for all tetrasubstituted substrates studied.

Table 3. Iridium-catalyzed asymmetric hydrogenation of substrates 55-60.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Complex C1</th>
<th>Complex 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{PhCOOC_2}H)</td>
<td>99</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>(\text{PhCOOAc_2}H)</td>
<td>78</td>
<td>88:12</td>
</tr>
<tr>
<td>3</td>
<td>(\text{PhCOOEt_2}H)</td>
<td>99</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>(\text{PhCOOEt_2}H)</td>
<td>21</td>
<td>100:0</td>
</tr>
<tr>
<td>5</td>
<td>(\text{PhCOOEt_2}H)</td>
<td>25</td>
<td>100:0</td>
</tr>
<tr>
<td>6</td>
<td>(\text{PhCOOEt_2}H)</td>
<td>24</td>
<td>71:29</td>
</tr>
</tbody>
</table>

\(\text{R} = \text{Ph}, \text{R' = F}\)

General conditions: 0.5-2.0 mol % catalyst, RT to 40 °C, dry DCM, 20-100 bar \(\text{H}_2\). Ratio and conversion were determined by \(^1\text{H}\) NMR.

2.4.4 Conclusions

We were able to design an iridium complex that could hydrogenate several vinyl fluorides with low defluorination rates, high stereo selectivity and low catalyst loadings. The synthetic route offers a simple way to functionalise the nitrogen in the ligand (Scheme 9), thus creating possibilities to tune the performance of the final catalyst further, or, use the N-linker to attach the catalyst to solid support.

Scheme 9. Possibility to functionalise the N-linker.
Reagents and conditions: i) NaH, BnBr, DMF, RT, o.n., 62 %; ii) HCl, H\(_2\)O/THF, RT, 95 %.
Further investigations are required to deduce the relationship between the defluorination and the combined basicity of the nitrogen and the phosphorous electron donors.
3 Heteroatom Substituted Vinylic Compounds as Substrates for Asymmetric Hydrogenation (Papers IV and V)

Obviously, heteroatom containing stereocenters are interesting due to their widespread occurrence in nature. The functionality of heteroatoms such as N, O and P, as well as their ease of modification makes them suitable as reacting/ recognition sites in biologically active molecules. These compounds have therefore gained plenty of attention from organic chemists and a wide range of chemical reactions on heteroatoms have been explored.

3.1 Hydrogenation of Vinyl Boronates (Paper IV)

Chiral borane compounds are useful building blocks in organic chemistry because of the wide range of available methods to convert C–B bonds to C–O, C–N or C–C bonds with retention of chirality, Scheme 10.\textsuperscript{25,26a-c} Additionally, the widely known reaction sequence of attack by a carbon or heteroatom nucleophile on achiral (α-haloalkyl)boronic ester followed by intramolecular rearrangement offers a practical method of chain elongation at the boron atom, and has been used in the total synthesis of natural products.\textsuperscript{27} The Suzuki–Miyaura coupling is another synthetically useful transformation involving chiral secondary boranes. This reaction proceeds with high enantioselectivity.\textsuperscript{28}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

\textbf{Scheme 10.} Illustration of the versatility of boronates. Chirality is retained in many transformations.\textsuperscript{25-28}
Chiral boranes are usually prepared by the hydroboration of olefins using a stoichiometric amount of a chiral borane. With this approach, non-polarized terminal alkenes give predominantly primary boranes, whereas 1,2-substituted alkenes produce mixtures of regioisomers. Only styrenes give satisfactory regioselectivity in hydroboration reactions yielding secondary borane-containing compounds. Styrenes have also shown promising results in enantioselective Rh-catalyzed hydroboration.

Knochel et al. published the Pd/C-catalyzed hydrogenation of a vinyl boronate having an achiral directing group near the double bond which yielded the product with a diastereomeric excess of 86 %. Miyaura et al. reported the first asymmetric hydrogenation of 1-phenylethynylboronic acid and related esters using [Rh(cod)$_2$]BF$_4$ with various chiral diphosphine ligands. The best result was achieved with the BI-NAP ligand (80 % ee).

Morgan and Morken reported the catalytic asymmetric hydrogenation of 1,2-bis-B$_{pin}$ (pin = pinacolato) substituted alkenes using Rh complexes with chiral P, P ligands, obtaining ee values up to 93 %. They later used the same catalysts to hydrogenate terminal aliphatic vinyl pinacol boranes in excellent enantioselectivities, and used the chiral borane products in transformations that yielded chiral C–N and C–C bonds with almost complete retention of chirality.

At the time of writing, it has been shown that 1-chloro-1-akaryl boronic esters can be reduced using N, P – chelated iridium catalysts with very good enantioselectivities to give useful building blocks. Substrates with both aromatic and aliphatic substituents have given ees of 88 to 94 % with low levels of dechlorination.

In this work, N, P – chelated iridium catalysts were applied to the asymmetric hydrogenation of vinyl boronates, for the first time.

3.1.1 Evaluation of Vinyl Boronate Hydrogenation

Encouraged by the excellent results from hydrogenation of vinyl phosphinates and other heteroatom-containing alkenes, we used our previously synthesized complexes of types A-C to screen several commercially available vinyl boronates. Preliminary screening of solvents (DCM, toluene and THF) with complex C1 revealed DCM as the best choice. Hence DCM was used exclusively in the process of catalyst screening. The ees were determined by first oxidising the hydrogenation product by H$_2$O$_2$ in presence of NaOH, Scheme 11. For substrate 63, NaOAc was used as base to avoid any hydrolysis of the ester. The obtained alcohols were analyzed either with chiral GC or HPLC.

![Scheme 11. Oxidation of boronates for determination of the ee.](attachment:image.png)
Bicyclic catalysts C1, 43c and C3 performed best in terms of stereoselectivity and conversion, see Table 4. As can be seen from the results obtained, the presence of either electron donating or withdrawing groups on the aromatic substituents of the substrate influenced negatively the stereoselectivity of the hydrogenation.

Table 4. Asymmetric hydrogenation of vinyl boronates 62-70 with catalysts C1, 43c and C3. 0.2 M solution of substrates were used.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>P/bar</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R_Bpin</td>
<td>50</td>
<td>&gt;99</td>
<td>75S</td>
<td>&gt;99</td>
<td>17S</td>
<td>&gt;99</td>
<td>89S</td>
</tr>
<tr>
<td>2</td>
<td>C2H5_Bpin</td>
<td>50</td>
<td>&gt;99</td>
<td>14S</td>
<td>78</td>
<td>44R</td>
<td>53</td>
<td>48R</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>1</td>
<td>&gt;99</td>
<td>70</td>
<td>88R</td>
<td>trace</td>
<td>21R</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Ph_Bpin</td>
<td>50</td>
<td>&gt;99</td>
<td>60R</td>
<td>&gt;99</td>
<td>67S</td>
<td>&gt;99</td>
<td>12R</td>
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<tr>
<td>5</td>
<td>C2H5_Bpin</td>
<td>1</td>
<td>&gt;99</td>
<td>70</td>
<td>64</td>
<td>98S</td>
<td>12</td>
<td>93S</td>
</tr>
<tr>
<td>6</td>
<td>C2H5_Bpin</td>
<td>50</td>
<td>&gt;99</td>
<td>11S</td>
<td>&gt;99</td>
<td>4R</td>
<td>&gt;99</td>
<td>12S</td>
</tr>
<tr>
<td>7</td>
<td>p-MeOC6H4</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>&gt;99</td>
<td>76S</td>
</tr>
<tr>
<td>8</td>
<td>p-MeOC6H4</td>
<td>50</td>
<td>–</td>
<td>85</td>
<td>88S</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>p-F3CC6H4</td>
<td>1</td>
<td>–</td>
<td>&gt;99</td>
<td>82</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Good stereoselectivities (ee values of 76-98 %) were obtained with vinyl groups having aromatic and/or polarizing groups (substrates 62-65 and 68-70). However, aliphatic alkenes were less successful, giving 48 % ee at most (substrates 66 and 67).
Interestingly, pressure of hydrogen had a significant impact on the stereoselectivity. For most substrates the selectivity decreased with pressure, or even reversed, which suggested that different mechanisms are predominating at different pressures of hydrogen. This might also explain why results could not be correlated with the previously established selectivity model for variety of olefinic substrates (Section 2.2.2).\textsuperscript{11,16}

![Figure 11. Comparison of results from hydrogenation of substrate 65 and trans-methyl stilbene with catalyst 43c.](image)

A consistency in absolute configurations could be seen for substrate 65: with the S configuration obtained for all three catalysts and at different pressures, Table 4, entry 4. This result correlates with the selectivity model when compared with the hydrogenation of trans-methyl stilbene that gives R configuration with catalyst 43c, Figure 11.

### 3.1.2 Conclusions

A range of vinyl boronates was hydrogenated with Ir-N,P catalysts. This can be a convenient method to prepare chiral building blocks with high enantiomeric purity that can be used for further modification. The sensitivity of this reaction to hydrogen pressure is yet not explained, however, it can be speculated that different mechanisms are predominating at different pressures. This explanation is preferred, especially for cases when there is an inversion of the absolute configuration (ex: Table 4, entry 2, catalyst 43c).

This pressure effect and inconsistency in absolute configurations amongst the different complexes are some of the important points that need further investigation.

The pinacol group of the boronate is another variable that can be altered to achieve better results in the hydrogenation of the aliphatic substrates that has shown to be troublesome for our catalytic system.

### 3.2 Hydrogenation of Vinylphosphonates and Phosphine Oxides (Paper V)

Recently, chiral phosphorous containing compounds have gained much attention due to many applications in various fields of chemistry.\textsuperscript{35,36}
Chiral phosphines are frequently used in a wide range of transition metal catalyzed asymmetric reactions. Figure 12 shows several examples of chiral organophosphorous compounds.

It was therefore interesting to apply our previously reported catalysts in synthesis of chiral phosphorous containing compounds.

![Figure 12. Several examples of useful chiral phosphorous containing compounds.](image)

At the time when we published paper V, only one catalytic asymmetric reduction of diphenylvinylphosphine oxides has been reported, where Matteoli and co-workers synthesized the chiraphos ligand via asymmetric hydrogenation of 2,3-bis(diphenylphosphinoyl)buta-1,3-diene.

3.2.1 Catalyst Screening and Evaluation of Substrates

Initial screening of three catalysts with substrate 71 have given promising results with full conversions to the desired product, Scheme 12. Catalyst 54 has shown exceptional stereoselectivity of >99 %, and was used in further studies.

![Scheme 12. Catalyst screening with substrate 71.](image)

The scope of the substrate class was extended by using varying substitution patterns on the aromatic substituent as well as replacing the aromatic moiety with completely aliphatic substituents, Table 5. Surprisingly the catalyst 54 has shown outstanding performance in stereoselectivity (ee values above 99 % for most substrates) both for substrates with aromatic and aliphatic substituents. The latter class is known to be a demanding set of substrates; hydrogenations of similar aliphatic substrates usually give low ees. For exam-
ple hydrogenation results of aromatic and aliphatic substrates can be compared for the vinyl boronates (Paper IV). Electron donating substituents on the aromatic moiety of the substrate seemed to have no effect on the stereoselectivity of the hydrogenation (entries 1-4 and 6). However, introduction of an electron withdrawing group somewhat reduces the ee (entry 5). Bulky substitution in close proximity to the alkene reduced slightly the conversion and ee (entry 8).

**Table 5. Asymmetric hydrogenation of diphenylvinylphosphine oxides by complex 54.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Entry</th>
<th>Substrate</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_R)</td>
<td>6</td>
<td>Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_+)</td>
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<tr>
<td>2</td>
<td>Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_+)</td>
<td>7</td>
<td>Ph(O)Ph2</td>
<td>&gt;99</td>
<td>99(_+)</td>
</tr>
<tr>
<td>3</td>
<td>MeO-Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_+)</td>
<td>8</td>
<td>Ph(O)Ph2</td>
<td>98</td>
<td>90(_+)</td>
</tr>
<tr>
<td>4</td>
<td>F-Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_+)</td>
<td>9</td>
<td>Ph(O)Ph2</td>
<td>80_d,e</td>
<td>92(_-)</td>
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<tr>
<td>5</td>
<td>F3C-Ph(O)Ph2</td>
<td>&gt;99</td>
<td>93(_+)</td>
<td>10</td>
<td>Ph(O)Ph2</td>
<td>&gt;99_e</td>
<td>&gt;99(_-)</td>
</tr>
<tr>
<td>6</td>
<td>Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_+)</td>
<td>11</td>
<td>Ph(O)Ph2</td>
<td>&gt;99</td>
<td>&gt;99(_+)</td>
</tr>
</tbody>
</table>

a Determined by 1H NMR spectroscopy. b Determined by chiral HPLC. Optical rotations are given in parentheses. c Determined by comparing optical rotation with a literature value. d Using 1 mol% catalyst loading. e P(H2) = 100 bar.

The substrate scope was expanded by introducing an alcohol group, as can be seen with substrate 80. At 0.5 mol% of catalyst and 50 bar only 80 % conversion and 92 % ee was obtained, however, increasing catalyst loading to 1 mol% and pressure to 100 bar resulted in >99% conversion and ee. For the acetyl protected alcohol 81, only 0.5 mol% of catalyst was required to achieve >99 % conversion and ee. The obtained product 83 could be easily deprotected with K2CO3 in ethanol to give the corresponding alcohol.

A successful attempt was made to perform a hydrogenation of substrate 81 on a larger scale: 0.94 g was converted to the corresponding product 83 with >99 % ee and 95 % isolated yield, Scheme 13.
Scheme 13. An example of up scaled hydrogenation to give an interesting building block.

Chiral phosphine oxides allow for direct access to the corresponding phosphines upon reduction. In Scheme 14 it can be seen how compound 84 could be easily converted in several steps to chiral N, P and P, P ligands. For example, the chiral ligand chairphos 87 was originally synthesized through a tedious route starting from malic acid. Using our methodology we were able to reach the key intermediate 84 in two steps, with >99 % ee and 87 % isolated yield.

Scheme 14. Examples of possible applications of products 84 and 88.

To test further the versatility of catalyst 54 we exchanged diphenylphosphine moiety by diethoxy phosphonate which gives another interesting class of heterosubstituted vinylic compounds. These have already been reported in asymmetric hydrogenation by Pfalz and co-workers. Good ees (up to 95 %) were obtained although only diethyl 1-arylethenylphosphonates were examined.

The asymmetric hydrogenations of ester substituted vinyl phosphonates remains barely explored. Kadyrov et al. constitutes one of the few examples of such research, with the investigation of the hydrogenation of terminal and internal 3-phosphonobutenoates using Rh(bppm) catalyst.

We tested our catalyst system on both carboxyethylvinylphosphonates and 1-arylvinylphosphonates. In this study substrate 90 was hydrogenated with catalysts 54 and C1. Catalyst 54 proved superior giving >99 % conversion and ee. Substrate 93 was however more demanding: requiring 100 bar H2, 1 mol% catalyst and 48 h to reach 79 % conversion with 91 % ee. The hydrogenation product 94 resembles a phosphorous analogue of Naproxen, Scheme 15.
Scheme 15. Hydrogenation of two diethyl 1-arylvinylphosphonates.

The carboxyethylvinylphosphonates are highly electron deficient, complete conversion was achieved with 1 mol% of catalyst and 100 bar of H₂, Table 6. Hydrogenation of (E)-95 appeared to be especially slow, giving <10 % conversion after 24 h providing satisfactory ee of 90 %. However, Z isomers of 95 and 96 gave >99 % conversions and ees. Interestingly, hydrogenation of E/Z mixtures of 95 and 96 respectively provided >99 % conversions and ees. Both E and Z isomers of 95 and 96 have given products of the same absolute configuration, according to the optical rotations of the hydrogenation products, Table 6, entries 1-3 and 4-5. This shows that the enantioselectivity is not governed by the relative configuration of the third R substituent (=CHR) of the olefin, as was previously observed for many tri-substituted alkenes and substrates in Papers I-III. This result might be explained by the coordinating nature of the phosphonate group being more stereodetermining than steric interactions between substrate and catalyst.

Table 6. Asymmetric hydrogenation of carboxyethylvinylphosphonates by complex 54.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Isomer</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Opt. rot.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>E</td>
<td>&lt;10</td>
<td>90</td>
<td>(–)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Z</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>(–)</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
<td>E/Z (1:4)</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>(–)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Z</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>(–)</td>
</tr>
<tr>
<td>5</td>
<td>96</td>
<td>E/Z (1:6)</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>(–)</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>E</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>(+)</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR spectroscopy. b Determined by chiral HPLC. Optical rotations are given in parentheses.
This effect was previously observed for Ru catalyzed hydrogenation of fluorinated alkenes\textsuperscript{42} but never for Ir. As such, this method is synthetically useful since separation of $E$ and $Z$ isomers is not required to obtain excellent $ees$.

Surprisingly, the substitution of an aromatic substituent in favor of a benzylic one, as in substrate 97 lead to the hydrogenation of the $E$ isomer with >99\% conversion and $ee$.

It has been reported that $\alpha$-aryl-substituted fosmidomycin analogues, such as FR900098 (Scheme 16), show higher antimalarial activity than fosmidomycin, however most derivatives were tested as racemates.\textsuperscript{43} The hydrogenation of compounds 95-97 give both $\beta$-aryl and $\beta$-alkyl substituted precursors to FR900098 as single enantiomers (>99 \% $ee$), and these can be easily transformed into the corresponding fosmidomycin analogues, Scheme 16.

![Scheme 16. Iridium-catalyzed asymmetric hydrogenation in the synthesis of Fosmidomycin analogues.](image)

3.2.2 Conclusions

A range of vinylic phosphine oxides and phosphonates was evaluated with our previously synthesised Ir complex, obtaining practically enantiopure products. The $E$ isomers of trisubstituted carboxyethylphosphonates hydrogenated slower and with lower $ees$ than $Z$ isomers, however mixtures of $E$ and $Z$ isomers gave complete conversions with excellent $ees >99 \%$.

This is a novel phenomenon to iridium-catalyzed hydrogenations which should be studied in greater detail due to the synthetic value of this asymmetric hydrogenation.

The excellent enantioselectivities of these hydrogenations yields a powerful tool in the development of efficient total syntheses, which should be explored further.
4 Synthesis of Prochiral Dienes Through Birch Reaction (Papers VI and VII)

4.1 Sources of Alkenes for Hydrogenation

It has been previously shown for most substrates that the stereoselectivity of the N, P-chelated iridium catalysts in hydrogenation depends highly on E/Z configuration of the alkene. Therefore to design an elegant synthesis where chirality is introduced by an asymmetric hydrogenation of an alkene requires a regioselective synthesis of the prochiral alkene. Eliminations and Wittig reaction, constituting the most commonly used methods to create alkenes, often give unsatisfactory E/Z selectivity for asymmetric hydrogenation. Although the isomers can be often separated by chromatography or crystallization both of these methods waste time and material. Several strategies exist to create alkenes with high regioselectivity. Some of the approaches discussed in this thesis are illustrated in Scheme 17 together with most common alkene syntheses.

Scheme 17. Examples of the most known syntheses of alkenes. Elimination, Wittig and Birch reactions, as well as ring closing metathesis (RCM) of dienes and Cu mediated alkylation of alkynes.

Generally the elimination reactions give poor E/Z selectivity, while metathesis, the Wittig reaction and other types of ylide based condensations give good selectivities. The latter two types of reactions give excellent selec-
tivities when performed intramolecularly. Also, the cis selective addition of copper alkanes across a triple bond, followed by alkyl halide quench of the resulting vinylic copper complex yields alkenes with very high regioselectivity.

The Birch reaction discussed in this chapter gives excellent regioselectivity providing that the right substitution pattern is selected. Mentioned above are only a few examples of alkene syntheses, numerous reviews exists on this matter.

It was previously shown that the absolute configuration of the final product of the hydrogenation depends highly on the configuration of the substituents on the alkene. In tri-substituted alkenes, the best results in terms of stereoselectivity were obtained when the most bulky substituents were in trans positions relative to each other. The third R substituent (=CHR) is usually the one that governs the stereoselectivity, as predicted by previously mentioned selectivity model, see section 2.2.2.

It should be noted that for carboxyethylvinylphosphonates, the E/Z isomerism is less important to achieve good stereoselectivity in the hydrogenation.

4.2 The Birch Reaction

The aim was to find efficient and synthetically robust methods to produce isomerically pure substrates. With this in mind we examined the well known Birch reaction, which converts aromatic compounds into non-conjugated dienes. This transformation has been used to synthesize precursors for many natural products and other important building blocks. The rich and varied chemistry of aromatic compounds, combined with the powerful functionalisation that is provided by the Birch reduction, makes the latter an important tool for producing complex molecules.

Products of the Birch reaction have been used for many years to create molecules with new chiral centers. There are also many reports of chiral centers being introduced during the Birch reaction by means of chiral auxiliaries, or simply by using chiral aromatic substrates. The Birch reaction’s high regioselectivity and superb tolerance for substitution make it an excellent source of prochiral, unsaturated substrates for asymmetric hydrogenation.
4.3 Origin of Regioselectivity

Birch reduction of substituted benzenes generally gives non-conjugated dienes. The electron donating groups (EDG) favor vinylic positions while electron withdrawing groups (EWG) prefer allylic, Scheme 18.

Scheme 18. Generalised regioselectivity of the Birch reaction.

The mechanism of this reduction has been studied in great detail, since its discovery in 1944, to this day. Scheme 19 demonstrate the most probable course of the reaction shown on a mono-substituted benzene with an electron donating group. Initially a solvated electron is added to the aromatic system to give a negatively charged radical 99 which is in a fast equilibrium with the reactant 98. The radical anion then undergoes a rate limiting protonation that comprise the first regiodetermining step. Several computational and experimental investigations have been made to show that the negative charge is distributed with preference to ortho and meta positions, and the ortho protonation is dominating. A second electron is then added to the neutral radical 100 thus generating a delocalized anion 101, followed by a second regiodetermining protonation to give the final diene 102. Theoretical calculations have shown that the electron density of the anion 101 is greater at the center carbon, which governs the selectivity of the second protonation.

Scheme 19. Mechanism of the Birch reaction (R = electron donating group).

In the case of benzenes with π-electron withdrawing groups the resonance stabilization of the negative charge allows the substrate to consecutively accept two electrons to give -3 charged anion 105. In the presence of t-BuOH, the anion is protonated to give compound 106, Scheme 20.

Scheme 20. Mechanism of the Birch reaction exemplified on benzoic acid.
4.4 Asymmetric Reduction of Substituted 1,4-Cyclohexadienes (Paper VI)

A range of cyclohexadienes was prepared from aromatic compounds using Na or Li in liquid ammonia, Table 7. In the case of compounds 109a and 109f, a near-stoichiometric amount of tert-butanol was used as proton source, and a co-solvent (THF or Et₂O) was also used. The more hindered substrates 109c-109e and 109g-o required a large excess of Na and ethanol to achieve satisfactory conversions. The dienes thus obtained were purified by distillation or column chromatography, then screened as substrates for asymmetric hydrogenation against our library of N, P – chelated Ir catalysts.¹¹,¹²,³³

The best catalysts were found out to be A1 and 108, Figure 13. In contrast to our previous observations on benzyl enol ethers,⁵⁶ the methoxy enol ethers studied here were hydrogenated without noticeable hydrolysis.

![Figure 13. Catalysts used in this study.](image-url)

Yields from the Birch reactions and the results of the subsequent asymmetric hydrogenations are summarized in Table 7. For most substrates, high trans:cis ratios (>70:30) were observed, and the trans isomers were hydrogenated in excellent ee values (94-99%). Low ee values were observed for the minor cis isomers.

Most interestingly, substrate 112 was hydrogenated with exceptional regio-(>99:1) and stereoselectivity (>99.9%). The tetra-substituted double bond remained intact, leaving the obtained chiral product available for further modifications. For example, oxidation with RuCl₃/NaIO₄ produced compound 114, Scheme 21.

![Scheme 21. Reduction of substituted naphthalene.](image-url)

**Scheme 21.** Reduction of substituted naphthalene. i) Li, NH₃(l), ethanol, 93 %; ii) A1, H₂ (20 bar), DCM, 18 h, 72 %; iii) RuCl₃•nH₂O, NaIO₄, 54 %. Absolute configuration was deduced from the selectivity model, see section 2.2.2.
Table 7. Results of the Birch reductions followed by the asymmetric hydrogenations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R’</th>
<th>R''</th>
<th>R''’</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>trans:cis&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (trans)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>ee (cis)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Compl.&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO</td>
<td>Me</td>
<td>H</td>
<td>110a 63&lt;sup&gt;f&lt;/sup&gt;</td>
<td>76:24</td>
<td>97</td>
<td>48</td>
<td>108</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>MeO</td>
<td>110b 76&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40:60</td>
<td>-</td>
<td>-</td>
<td>A1</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>iPr</td>
<td>H</td>
<td>110c 60&lt;sup&gt;f&lt;/sup&gt;</td>
<td>86:14</td>
<td>94</td>
<td>21</td>
<td>108</td>
</tr>
<tr>
<td>4</td>
<td>iPrO</td>
<td>Me</td>
<td>H</td>
<td>110d 48&lt;sup&gt;f&lt;/sup&gt;</td>
<td>75:25</td>
<td>94</td>
<td>77</td>
<td>108</td>
</tr>
<tr>
<td>5</td>
<td>MeO</td>
<td>CH(OH)Bu</td>
<td>H</td>
<td>110e, R’’’= n-C₅H₁₁</td>
<td>70 81</td>
<td>83:17</td>
<td>98</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>110f 40&lt;sup&gt;f&lt;/sup&gt;</td>
<td>91:9</td>
<td>97</td>
<td>-</td>
<td>A1</td>
</tr>
<tr>
<td>7</td>
<td>CH(OH)Me</td>
<td>CH(OH)Me</td>
<td>H</td>
<td>110g, R’=R’’=Et</td>
<td>41</td>
<td>54:46&lt;sup&gt;d&lt;/sup&gt;</td>
<td>75</td>
<td>A1</td>
</tr>
<tr>
<td>8</td>
<td>Me₂(OH)C</td>
<td>Et</td>
<td>H</td>
<td>110h, R’=iPr</td>
<td>61</td>
<td>56:44&lt;sup&gt;d&lt;/sup&gt;</td>
<td>96</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>iPr</td>
<td>iPr</td>
<td>H</td>
<td>110i 45 76</td>
<td>75:25</td>
<td>&gt;99</td>
<td>-</td>
<td>108</td>
</tr>
<tr>
<td>10</td>
<td>MeO</td>
<td>iBu</td>
<td>H</td>
<td>110j 52 68</td>
<td>82:18</td>
<td>98</td>
<td>66</td>
<td>A1</td>
</tr>
<tr>
<td>11</td>
<td>MeO</td>
<td>CH(OH)Ph</td>
<td>H</td>
<td>110k&lt;sup&gt;g&lt;/sup&gt;</td>
<td>82 84</td>
<td>78:22</td>
<td>&gt;99</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td>MeO</td>
<td>MeO</td>
<td>H</td>
<td>110l 65 56</td>
<td>&gt;99:1</td>
<td>&gt;99</td>
<td>-</td>
<td>108</td>
</tr>
<tr>
<td>13</td>
<td>MeO</td>
<td>Me</td>
<td>Me</td>
<td>110m 77</td>
<td>-</td>
<td>-</td>
<td>97&lt;sup&gt;h&lt;/sup&gt;</td>
<td>A1</td>
</tr>
<tr>
<td>14</td>
<td>MeO</td>
<td>Me</td>
<td>iPr</td>
<td>110n 51</td>
<td>-</td>
<td>-</td>
<td>89&lt;sup&gt;h&lt;/sup&gt;</td>
<td>A1</td>
</tr>
<tr>
<td>15</td>
<td>MeO</td>
<td>iPr</td>
<td>Me</td>
<td>110o 69 60&lt;sup&gt;i&lt;/sup&gt;</td>
<td>-</td>
<td>97&lt;sup&gt;h&lt;/sup&gt;</td>
<td>A1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Same substituents as in compounds 109a-o unless otherwise stated. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by NMR unless otherwise stated. <sup>d</sup> Determined by chiral GC-MS; see Supporting Information. <sup>e</sup> 0.5 mol% catalyst loading. <sup>f</sup> Literature procedures were used; see Supporting Information. <sup>g</sup> Ph group is reduced to cyclohexa-1,4-diene. <sup>h</sup> Poly(4-vinylpyridine) used as additive; see Supporting Information; Methoxy-substituted double bond remains intact. <sup>i</sup> Isolated yield of the corresponding ketone.

To add another layer of selectivity, the catalysts could be deactivated towards methoxy-substituted olefins using poly(4-vinylpyridine) (PVP)<sup>57</sup> as an additive. This allowed compounds 115e (69% yield) and 115m-o to be prepared, Scheme 22. Other bases such as pyridine, NEt₃, iPr₂NEt, aniline, Ph₃P, 1,10-phenanthroline, and Cy₂NH, (5 eq with respect to catalyst) completely poisoned the catalyst and discolored reaction solution. Results using KOAc as a base were comparable to those with PVP. Compound 115o could be easily hydrolyzed by an acid, then equilibrated under basic conditions<sup>58</sup> to
give a disubstituted cyclohexanone 116 which can be used in turn to prepare a 7-membered lactone 117, in high ee, Scheme 22.

Scheme 22. Synthesis of optically active disubstituted cyclohexanone. i) A1, H₂ (20 bar), DCM, PVP; ii) (COOH)₂, MeOH, RT, 2 h, cis:trans = 48:52; iii) NaOEt, EtOH, 30 min, cis:trans = 11:89; iv) Brevibacterium, β-cyclodextrin, 71%.⁵⁹

4.4.1 Selectivity in the Hydrogenation of Dienes

The trans preference observed for substrates 110a, 110c-l and 112 suggests that, after reduction of the first double bond, the substrate dissociates from the catalyst before undergoing the second reduction. The selection of which olefin face the catalyst binds to and hydrogenates is based on steric, as was previously shown in our selectivity model, see section 2.2.2.¹⁶

As shown in Scheme 23, the ee of the preferred trans isomer increases at the expense of the trans:cis selectivity. Whenever the catalyst reduces the double bond on the unwanted face, producing 118a, the mistake is quickly corrected by the fast reduction of 118a to the cis isomer. The result is a decreased trans:cis selectivity but a high ee for the major trans isomer.

Scheme 23 Origin of the ee amplification due to the second reduction step that converts the unwanted enantiomer 118a to the corresponding cis isomer. The quadrant models show if reaction will be relatively fast or slow.

The enantiomeric amplification is demonstrated in the incomplete hydrogenation of 110e. After hydrogenation at 20 bar of H₂ for 12 min with 1 mol% of A1, this reaction formed a 90:10 mixture of mono- and dihydrogenated compounds, displaying 95 and 98% ee respectively, Scheme 24 (a). This reveals that the unwanted enantiomer (S)-115e gets reduced to the re-
pective cis isomer faster than to the unwanted enantiomer of 111e. This explains why the ee of 111e is higher than that of 115e.

![Scheme 24](image)

Scheme 24. Examples of ee enrichment after two subsequent reductions.

The same effect can be observed when substrates 119 and 112 are reduced. The mono-substituted substrate 119 gives 98.9 % ee, while its di-substituted analogue 112 gives, quite exceptionally, only one enantiomer at the expense of the formation of the cis isomer (<1%).

![Scheme 25](image)

Scheme 25. Reversal of trans:cis selectivity explained by the selectivity model, adopted for catalyst A1. Numbers present the experimental results. (a) Hydrogenation of substrate 110a and (b) of 110b.

The experimental trans:cis hydrogenation product ratios of 1,4- and 1,5-disubstituted dienes 110a and 110b reveal trans selectivity (65:35) for the former and cis selectivity (40:60) for the latter, Table 7, entries 1 and 2. The previously established selectivity model is used to explain these selectivity trends, Scheme 25.

Initially, the substrate coordinates to the catalytic site in such a way as to keep the steric interactions to a minimum, directing the smallest substituent H into the most hindered quadrant. After addition of the hydrogen from beneath the plane, the mono-hydrogenated product is released. Coordination of the remaining double bond proceeds in a similar fashion as to keep the steric
interactions to a minimum. At this point, compounds 115a and 115b coordinate to the catalyst with the opposite sides respectively. After the final addition of the hydrogen the products are released, giving reversed trans:cis selectivities.

4.4.2 Conclusions

The methodology here expounded provides a convenient synthetic route to chiral substituted cyclohexanes and cyclohexanones. This method is not restricted to monocyclic aromatics, and high selectivities can readily be achieved, according to the substitution pattern of the aromatic system. Many of the chiral products prepared in this work are nigh on impossible to make by other methods, which makes this a very valuable synthetic methodology. The enantiomeric excesses of the products tolerate a wide range of aliphatic substituents.

4.5 Investigating the Applicability of the Birch Reaction
Further (Paper VII)

To widen the scope and applicability of the asymmetric reduction of the Birch products, several hydrogenation products were subjected to further reactions, Scheme 26. These include oxidative cleavage to make 1,6-dicarbonyl compounds, epoxidation and reduction. The two latter transformations generate two new chiral centers and can be regioselective, providing appropriate reagents are chosen.

![Scheme 26.](image-url) Oxidative and reductive transformations of the tetra-substituted double bond.

4.5.1 Synthesis of 1,6-Diketones

Several substituted benzenes and naphthalenes were subjected to the Birch reaction followed by an asymmetric reduction with catalyst A1 to afford products 115e, 115n, 120, 123 and 127 with high enantioselectivities (93-99 % ee), Scheme 27.
Scheme 27. Transformation of aromatic compounds into corresponding 1,6-dicarbonyl alkenes. Reagents and conditions: i) Na or Li, NH₃(l), EtOH; ii) A1, H₂ (20 bar), DCM; iii) O₃, DCM/MeOH, -78 °C, then Me₂S, warm up to RT.

The remaining tetra-substituted double bond was subjected to oxidative cleavage by ozonolysis, which generated acyclic (128-130) and cyclic (131 and 132) 1,6-dicarbonyl compounds, Figure 14. The absolute configuration of compound 129 was inferred from comparative optical rotation with literature value.⁶⁰ Because this enantiomer was also predicted by the selectivity model it was assumed that compounds 128-132 possesses the same relative configuration, Scheme 28. The yields reported are over two steps: asymmetric hydrogenation and oxidative cleavage. The noticeable volatility of these compounds is the cause of the low yields.

Figure 14. Chiral 1,6-dicarbonyl compounds. Shown are the isolated yields over two steps: asymmetric hydrogenation and ozonolysis. Ees were determined after asymmetric hydrogenation. The absolute configuration was obtained by comparing literature value of optical rotation. The absolute configuration was inferred from the selectivity model, see section 2.2.2.

Scheme 28. Selectivity model for catalyst A1 deduces the absolute configuration of the compound 110n.
4.5.2 Epoxidation of the Chiral Olefinic Products

Numerous reports exist on the use of transition metal catalyzed neighboring group directed epoxidation of olefins. Some of the best known catalytic systems use vanadium and molybdenum complexes in presence of tBuOOH, Scheme 29.\(^\text{61}\)

![Scheme 29](image)

**Scheme 29.** Literature examples of directed metal catalyzed epoxidations, compared to mCPBA.

To our surprise, in an attempt to epoxidise compound (S)-120, the *endo* isomer 134 was formed exclusively. The presence of water did not alter the regio selectivity, however, when this reaction was conducted in presence of air, considerable amount of the *exo* isomer was formed. Epoxidation using mCPBA resulted in slight preference (45:55 *endo:exo*) to the directed *exo* product, probably due to hydrogen bonding interaction.

![Scheme 30](image)

**Scheme 30.** Directed and non-directed epoxidations of compound (S)-120 (prepared from hydrogenation of compound 119 with catalyst 108). Reagents and conditions: i) mCPBA, Na\(_2\)HPO\(_4\), DCM, 0 °C; ii) Mo(CO)\(_6\), tBuOOH, toluene, 90 °C.

To confirm its relative configuration, compound 134 was subjected to an epoxide opening reaction with NaN\(_3\) in presence of NH\(_4\)Cl in ethanol\(^\text{62}\) to give the azidoalcohol 135 as the only product (70 % isolated yield). The structure was deduced from X-ray analysis, Scheme 31.
4.5.4 Conclusions

Sequential Birch reaction and asymmetric reduction can be used as a source of chiral building blocks. It has been shown with several examples that introduced chirality can be used to conveniently create new stereogenic centers, making more complex molecules. A convenient synthesis of 1,6-diketones with chiral substituents has been introduced. It has been also shown on a chiral olefinic substrate 120 that a methoxy group did not act as a chelating group in the Mo-catalyzed epoxidation. In fact the regioselectivity of this metal-oxidant is governed by the steric hindrance of this particular olefinic substrate.
5 Conclusions and Outlook

The iridium N, P – ligated chiral catalysts are a good complement to the well known ruthenium and rhodium catalysts: it transcends the need for the adjacent coordinating group allowing for a wider range of substrates to be hydrogenated. Any well-stocked toolbox of catalysts for asymmetric hydrogenation should include a few N, P – ligated iridium catalysts.

The work described in this thesis consists of the several catalysts I co-developed as well as synthesized based on ligands previously studied in our group. Catalysts 26a-c and 43a-d were prepared by somewhat simpler synthetic routes than their predecessors, while performance in asymmetric hydrogenation was comparable.

Adjustments were made to the electronic properties of iridium in catalyst A1 by replacing the CH₂-linker of the ligand by a N-linker. This has given a promising catalyst 54 that performed well in asymmetric hydrogenation of vinyl fluorides, diphenylvinylphosphine oxides and carboxyethylvinyl phosphonates. To explore the heteroatom containing vinylic substrates we have also applied catalysts C1, 43c and C3 in the asymmetric hydrogenation of vinyl boronates obtaining very good results in terms of enantioselectivity and conversion. The new catalysts of type 26a-c and 43a-d were prepared through relatively short and robust synthetic routes, giving a possibility to modify and tune the structure of the final catalyst. This makes these synthetic routes perfect for the creation of small libraries of catalysts for optimization studies. The synthesis also allows an easy incorporation of a linker to the catalyst for attachment to solid support.

In search of robust synthetic methods to obtain prochiral olefins we have also explored the Birch reaction. In combination with asymmetric hydrogenation this highly regioselective transformation opens a convenient synthetic route to substituted cyclohexanes of high optical purity. The chiral compounds obtained by this methodology are almost impossible to make by other methods, which make the Birch reaction an invaluable source of prochiral olefins.

The results obtained in this study can be applied when choosing a suitable catalyst for an asymmetric hydrogenation of prochiral alkenes, be it in total synthesis of drugs or fine chemicals.
The Birch reaction is a convenient method to prepare alkenes, which ought to be explored further to produce compounds directed towards useful chiral molecules.
Acknowledgements

I would like to express my sincere gratitude to my supervisor Prof. Pher G. Andersson for accepting me as a Ph. D. student in his group at Uppsala University. I thank him for his patience and wise advise through all the years and for letting me be in his lab and doing interesting chemistry.

Thanks to all collaborators outside the Uppsala University:

*Dr. Montserrat Diéguez, Dr. Oscar Pámies* and *Javier Mazuela.*

I would also like to thank past and present members of the PGA group:

*Johan V.* for being so awesome. It's been fun to discuss chemistry and all the philosophical things in life. Call me when you start your own research group. *Alban C.* for making these last months of phd-ing more interesting. I'm looking forward to your defense and when you'll become Dr. Alban! *Taigang Z.* (Mr T), working hard and publish in JACS. *Byron P.*, I'm really glad that you joined us. *Jia-Qi L.*, it was nice to share the lab with you! *Xu Q.* (Jazzman) you are an inspiration! Keep up the good work! *Simone D.* for translating Toto Cutugno songs. *Dr. Päivi T.*, it was fun being your fume hood neighbor and discussing life and chemistry. The lab and I are missing you. *Dr. Mattias E.*, I still have a lot to learn from you, especially about determination and discipline. *Dr. Jarle D.*, you are probably the most missed guy at our department. We still can hear the echoes of your laugh. *Dr. Pradeep C.*, it was fun doing chemistry and teaching together. *Dr. Tamara C.*, you are amazing and should come back to us. *Dr. Klas K.*, hope they treat you well, as we did. Johan and me think about you all the time. *Dr. Eskender*, wish you stayed at our department for longer. *Dr. Ian M.*, *Muhammad Ali*, *Dr. Anna T.*

This thesis would probably never be complete if not for combined effort of *Christian D.* and especially *Alban C.*. Thanks to Johan for proofreading the Swedish summary.

Many thanks go also to the other people at the BMC:
Supaporn S., you've made it more interesting to be at our department. Thanks for all the help with chemistry and all delicious Thai food. Hao, you are almost like a member of PGA-group. Thanks for being a cool dude and for all the help with the 2D NMR. Maxim G., it would be more awesome if you didn't move to the other group. Adam S., it was always fun having you around and talk about some very important subjects, including chemistry. We've never had anyone like you.

Special thanks go to Johanna J. for being the coolest administrator. You are like a sunbeam in our corridor, and I'm happy that you chose our department.

Sara N., thanks for all the help and advises. Classe A. (one of my idols). Christian D., you are a wise man and I would consider having you as my third supervisor. Rikard E., it's always fun to see you so you should visit our lab more often. Laura M., thanks for taking over the NMR club. Michael N., I'm happy that you started at our department. Dr. Julius T., we miss you. Alma, for making it more fun to go to the teaching labs. Lina, I still have your banana and I've taken proper care of it. Jesper, it's been long time since we played blues in E. Prof. Adolf G., thanks for all your help with the NMR and other instruments. You are the reference to all of my NMR peaks. Prof. Lars B., you always have a solution to any problem. Prof. Mikael W., for signing my ‘end-use license agreements’ for all kinds of interesting chemicals that we needed for the research purposes... Gunnar S. for supplying us with solvents and equipment, and for always being so kind.

And the rest of the people at the department: Alvi M., Magnus B., Huan M., Marcus K., Dr. Andreas., Dr. Miranda, Dr. Diana, Dr. Henrik, Dr. Johan L., Prof. Josef S., Prof. Peter D., Prof. Henrik O., Prof. Helena G., Prof. Olle M., Thomas N., Tomas K., Inger and Eva.

And of course my parents, brother and Olga. Especially thanks to my dad for all support and wise advises. Also thanks to sweet Josefin.

Other thanks go to:

My fume-hood for being there through all the years no matter what and keeping me alive. My new Furch Durango guitar for having so beautiful sound. BMC for being like a second home. Yngwie Malmsteen for shredding some awesome arpeggios and making it look so easy (making us mortal people to feel like giving up the guitar and stop trying). And of course Dr. Tong.

Väldigt mycket forskning har gjorts för att förstå de processer som pågår i levande organismer och man har länge försökt kartlägga de kemiska föreningar som styr och reglerar levande organismer. Resultatet av denna forskning har gett mediciner som under mer än hundra år har ökat medellivslängden hos människor.

Därför är det viktigt att fortsätta underhålla och utveckla kunskapen om kemi på alla plan.

En viktig del av organisk kemi är kunskapen om hur man framställer kirala molekyler. Dessa är viktiga eftersom nästan alla interaktioner i levande organismer sker mellan kirala molekyler som proteiner, DNA, hormoner och diverse signalsubstanser som reglerar våra liv och sådana känslor som t.ex. humör, smak eller lukt.


Detta är ett av många exempel som visar hur vår kirala kropp uppfattar olika spegelbild-molekyler.

För att selektivt kunna framställa en molekyl som luktar apelsin kan vi avända asymmetrisk syntes. Vårt arbete går ut på att utveckla och förbättra metoder i detta fält – att kunna framställa bara en av den kirala molekylens spegelbilder. För att åstadkomma detta använder vi speciella katalysatorer som inför kiralitet i molekyler (substrat). Katalysatorerna som vi utvecklar är uppbygda av en iridium atom som är bunden till en kiral molekyl (en kiral

Förutom utveckling av katalysatorer (Artiklar I, II och III) håller vi på med utforskning av olika substrat (Artiklar IV och V) och utforskning av nya substratkällor (Artiklar VI och VII).
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