Catalytic Asymmetric Ketone and Alkene Reductions Using Transition Metal Complexes

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Abstract

This thesis contains seven papers dealing with iridium and ruthenium based catalytic asymmetric reductions, either of ketones into chiral alcohols, or olefins into chiral alkanes. The first part of the thesis describes how we have designed and evaluated new bicyclic ligands containing either $N,S$ or $N,N$ chelating atoms. The ligands have been evaluated in the asymmetric Ir-catalyzed transfer hydrogenation of acetophenone. The complexes evaluated induced good enantioselectivity of the product. Moreover we have also utilized a commercially available chiral diamine (QCD-amine) as a ligand in the Ru-catalyzed hydrogenation of prochiral ketones, with excellent enantioselectivity for some of the substrates used. As part of this work we investigated, both theoretically and experimentally, the mechanism of this hydrogenation. Based on these results we have proposed a new reaction mechanism for this type of hydrogenations which involves active participation of the solvent in the catalytic cycle. The last part of the thesis describes the design, synthesis and evaluation of $N,P$ and $N,C$-carbene, $N$ ligands for the Ir-catalyzed hydrogenation of carbon-carbon double bonds. The selectivities obtained in these investigations are among the best reported so far for a broad variation of substrates. A selectivity model for this hydrogenation has been derived and used in the rationalization of the results. As a part of this work we have synthesized and evaluated a new class of substrates, vinyl silanes, and showed that the scope of the hydrogenation reaction can be expanded to this new substrate class.

Keywords: Catalytic, Asymmetric, Reductions, Ketones, Alkenes, Transition metal Complexes

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List of Papers

This thesis is based on the following publications and appendix

I  Synthesis and evaluation of N,S-compounds as chiral ligands for transfer hydrogenation of acetophenone. Ekegren, Jenny; Roth, Peter; Källström, Klas; Tarnai, Tibor; Andersson, Pher G.; Organic & Biomolecular Chemistry 2003, 1, 358-366.

II Development of a new class of (1S,3R,4R)-2-azabicyclo[2.2.1]heptane-oxazoline ligands and their application in asymmetric transfer hydrogenation. Trifonova, Anna; Källström, Klas; Andersson, Pher G.; Tetrahedron 2004, 60, 3393-2403.

III Mechanistic Insights into the Phosphine free RuCp*-Diamine Catalyzed Hydrogenation of Arylketones: Experimental and Theoretical Evidence for an Alcohol-Mediated Dihydrogen Activation Hedberg, Christian; Källström, Klas; Arvidsson, Per I.; Andersson, Pher G.; Brandt, Peter; Journal of the American Chemical Society. 2005, 127, 15083-15090.

IV Rationally Designed Ligands for Asymmetric Iridium-Catalyzed Hydrogenation of Olefins. Källström, Klas; Hedberg, Christian; Brandt, Peter; Bayer, Annette; Andersson, Pher G.; Journal of the American Chemical Society 2004, 126, 14308-14309.


VI Asymmetric Hydrogenation of Trisubstituted Olefins with Ir-NHC-Thiazole Complexes Källström, Klas; Andersson, Pher G.; Advanced Synthesis and Catalysis, submitted.


VIII Appendix: Supplementary Material. Källström, Klas
Publications not included in this thesis

I  **Ir catalysed asymmetric hydrogenation: ligands, substrates and mechanism** Källström, Klas; Munslow, Ian J.; Andersson, Pher G.; *Chemistry: a European Journal*. **2006**, 12, 3194-3200.

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Contribution Report

The author wishes to clarify his contributions to the papers I-VII in the thesis:

I  Performed a significant part of the experimental work; contributed partly to the formulation of the research problem; main contribution to interpretation of the results.

II Partly formulated the research problem; performed a significant part of the experimental work; contributed significantly to the interpretation of the results.

III Contributed with the original idea concerning the experimental system; performed all experimental work; contributed significantly to the interpretation of the experimental results and to a significant extent in writing of the paper. Dr. Peter Brandt and Prof. Pher G. Andersson performed the DFT-calculations.

IV Contributed partly with the original idea; significantly formulated the research problem; performed a major part of the experimental work; contributed significantly to the interpretation of the results; wrote the paper. Dr. Peter Brandt performed the DFT-calculations. Dr. Annette Bayer and Prof. Lars-Kristian Hansen performed the X-ray crystallographic diffraction experiments.

V Contributed partly with the original idea; significantly formulated the research problem; performed a significant part of the experimental work; contributed significantly to the interpretation of the results; significantly contributed in writing of the paper. Prof. Pher G. Andersson and Dr. Peter Brandt performed the DFT-calculations. Dr. Annette Bayer and Prof. Lars Kristian Hansen performed the X-ray crystallographic diffraction experiments.

VI Formulated the original research idea; performed all experimental work and interpretation of results; wrote the paper.

VII Formulated the original research idea; significantly contributed to the experimental work and interpretation of results; played a significant part in writing of the paper.
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Abbreviations

Abs. Config.  Absolute Configuration
Ac            Acetyl
BARf          tetrakis[3,5-(trifluoromethyl)-phenyl]borate
Bn            Benzyl
Boc           tert-Butoxycarbonyl
Cbz           Benzylxycarbonyl
Cbz-p-NO₂     para-Nitrobenszyloxycarbonyl
COD           1,5-Cyclooctadiene
Conv          Conversion(s)
Cp*           Pentamethyl Cyclopentadienyl
DFT           Density Functional Theory
DIBAL         Diisobutylaluminium Hydride
DMAP          4-Dimethylaminopyridine
DoE           Design of Experiments
EDC           1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide
ee            Enantiomeric Excess
Equiv.        Equivalent(s)
h.             Hour(s)
HPLC          High Performance Liquid Chromatography
HOBt          1-Hydroxybenzotriazole
i-Pr          iso-Propyl
LAH           Lithium Aluminium Hydride
Me            Methyl
Me-CBS        Methyl- Oxazaborolidine Catalyst
MeCN          Acetonitrile
Ms            Methane Sulphonyl
n-Bu          n-Butyl
NMR           Nuclear Magnetic Resonance
o.n.          Over Night
Ph            Phenyl
rt            Room Temperature (23°C)
t-Bu          tert-Butyl
Temp.         Temperature
TFA           Trifluoroacetic acid
THF           Tetrahydrofuran
TMS           Trimethylsilane
TOF  
Toluenesulphonyl
Å  
Angström(s)

Turn Over Frequency
p-


Populärvetenskaplig Sammanfattning på Svenska

Begreppet organiska ämnen infördes på 1780-talet av uppsalaprofessorn Torbern Bergman och uttrycket organisk kemi är 1806 av Jöns Jacob Berzelius. Distinktionen mellan oorganisk och organisk kemi grundades då på uppfattningen att organiska ämnen (karaktäristiska för levande organismer) var förknippade med en livskraft och därför inte kunde uppstå ur oorganiska ämnen (tillhörande mineralriket). Efter 1800-talets mitt kom organisk kemi att definieras som kolföreningarnas kemi, sedan teorin om livskraften visat sig ohållbar. Ända sedan organisk kemi blev ett mer eller mindre väldefinierat område inom kemin på slutet av 1700-talet har organiska kemister syntetiserat nya föreningar på ett mer systematiskt sätt. Idag överstiger de syntetiserade, icke naturligt förekommande, föreningarna vida de som isolerats ur naturliga material.

Den organiska kemin har under det senaste seklet genomgått en häpnadsväckande utveckling. I gränslandet mellan organisk kemi och andra vetenskaper t.ex. biologi och fysik, har enastående tekniska och farmaceutiska applikationer tillkommit.

En viktig egenskap hos vissa kemiska föreningar, i synnerhet hos organiska, är att de uppvisar kiralitet, spegelbildisomeri (Figur 1).

![Figur 1. Spegelbilder av en schematisk molekyl.](image)

Molekylära spegelbilder har samma fysikaliska och kemiska egenskaper i en icke kiral miljö. Skillnader uppstår bara när de interagerar med andra kirala objekt, molekyler, eller planpolariserat ljus. Biologiska system är uppbygda av kirala molekyler, vilket medför att enantiomerer växelverkar olika i dessa system. Detta har en avgörande effekt för t.ex. läkemedel. Det är därför av stor betydelse för läkemedelsindustrin att kunna framställa rätt enantiomer av ett läkemedel.

Den här avhandlingen behandlar just detta område, hur kan vi styra en reaktion till att bara producera den ena enantiomeren av en molekyl. Mer pre-
cist har nya system för reduktion av kol-syre samt kol-koldubbelbindningar undersöks (Figur 2), med hjälp av asymmetrisk katalys.

![Figur 2. Reduktion av kol syre (1) samt kol kol dubbelbinding (2).](image)

Fördelen med att inducera kiralitet genom att använda en katalysator, jämfört med ett stökiometriskt reagens, är att en ytterst liten mängd kirtalt material (katalysatorn) behövs för att åstadkomma en kiral produkt. I de olika delarbeterna (I-VII) har vi utvecklat nya kiralra katalysatorer som med hög selektivitet har utfört den önskade reduktionen.

I delarbete I har nya svavel och kväveinhållande Kirala katalysatorer utvecklats och utvärderats i asymmetrisk iridiumkatalyserad transferhydrogenering av en keton. Transferhydrogeneringmetoden kan enklast beskrivas som överföring av en hydrid från ett organiskt ämne till ett annat. Den molekyl som överför hydriden oxideras medan den mottagande molekylen reduceras. I detta arbete har god selektivitet uppnåts. Delarbete II är en fortsättning på arbete I, där en ny typ av kväveinhållande kiralra ligander syntetiseras. Utvärdering av transferhydrogenering visade att dessa ligander är ungefär lika effektiva som de i arbete I.


I delarbete IV-VII återvänder vi till iridium men denna gång utvecklas nya katalysatorer för reduktion av kol-koldubbelbindningar. Syftet med dessa arbeten är att i ett längre perspektiv systematiskt undersöka de faktorer som reglerar aktivitet och selektivitet hos de katalytiska system som vi har utarbetat. Arbetet har sin utgångspunkt i ett mekanistiskt förslag om hur den här typen av hydrogenering fungerar. Utifrån kunskapen om den bakomliggande mekanismen utvecklar vi en hypotes om hur liganderna i dessa kataly-
satorer ska vara uppbyggda samt en selektivitetsmodell som kan rationalisera och förklara den uppkomna selektiviteten. Med den första generationens ligander (arbete IV) testar vi vår hypotes samt validiteten av selektivitetsmodellen. Detta görs genom syntes av olika ligander som utvärderas i den iridiumkatalyserade asymmetriska hydrogeneringen av kol-koldubbelbindningar av olika substrat. I delarbete V används resultaten från arbete IV för att förbättra ligandstrukturer, andra generationens ligander, genom att införa större diversitet och stabilitet hos liganderna. Selektivitetsmodellen förfinas ytterligare genom att studera substrat innehållande en polariserad kol-koldubbelbindung Resultaten är mycket intressanta och för första gången har bra selektivitet med substrat som tidigare har ansetts som "omöjliga" uppnåtts. I arbete VI undersöker vi effekten av att byta ut fosforatomen i ligandstrukturen mot en kolatom. Denna manipulation gör att vi kan tillgodogöra oss ytterligare kunskap om selektivitetsmodellen samt uppnå förbättrade resultat med substrat som tidigare har uppvisat dålig selektivitet, i överensstämme med selektivitetsmodellen. I arbete VII använder vi oss av den andra generationens ligander i asymmetrisk hydrogenering av vinyl silaner, en typ av substrat som aldrig tidigare har använts för denna typ av katalys. Genom detta visar vi att asymmetrisk iridiumkatalyserad hydrogenering inte är begränsad till de tidigare studerade substraten. Ett mycket viktigt bidrag eftersom om katalysatorm skulle vara begränsad till de tidigare använda modellsystemen, skulle det innebära en kraftig begränsning i användbarheten. Arbetet i dessa två delarbeten har gett en djupare förståelse för det katalytiska systemet och vilka substrat som kan användas.
1 Introduction

1.1 History of Organic Chemistry

The intent of chemistry is the exploration of the nature and the materials that fabricate our physical environment, why molecules hold the different properties that depict them, how the atomic structures of molecules may be fathomed and how molecular structures may be manipulated and changed. Although organic reactions have been conducted by man since the discovery of fire, the science of organic chemistry did not develop until the turn of the eighteenth century. The person to introduce the term “Organic Chemistry” was Jöns Jacob Berzelius in 1806.[1] At that time organic substances were understood as being materials produced by living organisms: wood, bone, cloth, food, medicines, and the complex substances that configure the human body. Inorganic material was believed to come from the Earth: salt, metals and rock, just to name a few. Because of human’s wonder of natural life, organic materials were believed to possess an enigmatic “vital force”. [2] The “vital force” theory was immensely discredited by Friedich Wöhler who in 1828 succeeded in synthesizing urea starting from inorganic materials, thus rendering the “vital force” theory to be with flaws. He made this from a non-living chemical substance, ammonium cyanate, by evaporating a solution of ammonium cyanate.[3] The theory of vitalism, like many other scientific theories, disappeared slowly under the weight of accumulated evidence.

Structural theory, which developed in the 1860’s, started the second major period of growth in the field of organic chemistry. Almost at the same point in time, Kekule and Couper suggested that atoms in molecules are fused together by bonds.[2] Their theory was that every atom is distinguished by having the same number of bond availability or valence number, wherever that particular atom appears in any compound. The main notability of organic compounds is that they posses strong carbon-carbon bonds. This was recognized in the theory and was help in understanding large molecules possessing many bonded carbon atoms. So far, this theory has gone through rigorous testing, and has not been proven inadequate to this day. Kekule and Couper’s theory was not all without fault; they did not recognize atoms as three-dimensional objects. It was not until 1874 when van’t Hoff and LeBel proposed their hypothesis of compounds and atoms taking up space.[2] The four bonds of carbon are located at equal angles to each other in space, resulting in a regular tetrahedron. The power of this theory is demonstrated by
the fact that there has been no chemical observation that cannot be basically understood by structural theory. Finally, although structural logic is extremely rigorous, it involves no mathematics. The third and presently used theory in the history of organic chemistry ends with the description of chemical bonds as electron pairs, an idea Lewis formulated in 1916.[2] Although a great amount of chemical reactions were already known and in active use to synthesize organic compounds, only with the understanding about the nature of chemical bonding did a clear reason of the nature of reaction mechanisms begin to appear. Thus if the nineteenth century was devoted to revealing the fixed structures of molecules, the twentieth century was devoted to the study of their transformations. The research in organic chemistry expanded enormously during this century and the subject had to be divided into more specialized branches such as metal organic chemistry, carbohydrate chemistry and heterocyclic chemistry just to mention a few.

1.2 History of Chirality

Optically active compounds have been known since the early nineteenth century. In 1801, the French mineralogist Haeü noticed that quartz crystals exhibited hemihedral phenomena. In 1812 another French scientist, Biot, found that plates of quartz crystals cut of right angles to its symmetry axis rotated plane polarized light in opposite directions, depending on the original symmetry. Biot extended his investigations to solutions of organic compounds and found that many compounds of natural origin behaved in a similar manner.[4] At the time, the phenomenon was explained by the fact that the compounds were of natural origin, produced by living organisms. In 1848 Pasteur was able to separate the two enantiomorphous crystal forms of racemic sodium ammonium tartrate (Figure 1) manually, with a pair of tweezers, by a simple assignment of the crystal shape through a lens.[5] He found that a solution of the enantimorphous crystals rotated the polarized light in equal intensity but in opposite directions. Pasteur then made an important statement that the rotation of polarized light caused by the different tartaric acid salt crystals was the property of chiral molecules. The two forms of optically active tartaric acid were related to each other as three-dimensional mirror images.

![Figure 1. The two enantiomers of sodium ammonium tartrate.](image-url)
Enantiomers have identical physical and chemical properties when acting in a non-chiral environment. The differences only occur when interacting with another chiral object (molecule) or plane-polarized light. Biological systems are built up by chiral molecules (e.g. DNA, RNA, sugars and proteins). As an example, 19 out of the 20 naturally occurring amino acids that make up proteins in living organisms are chiral. Because of this chirality has been extensively investigated. The major breakthrough in the synthesis of chiral compounds was made in the late 1960’s, when the synthetic and analytic tools of organic chemistry became more sophisticated, development of organometallic chemistry, chiral catalysis, NMR and mass spectroscopy. Advances in chiral methodologies have resulted in industrial applications. Several asymmetric processes are operating in chemical plants around the world today. The first large-scale processes were based on enzymatic systems, but during the 1990’s several metal catalyzed asymmetric reactions were setup for pharmaceutical- and speciality-chemical production.\textsuperscript{6} The use and demand for optically active substances is greater today than ever, since the recognition that enantiomers of a specific molecule can interact differently in biological systems and thereby cause different actions.

1.3 Enantiomerically Pure Compounds

Today we know that chiral compounds are fundamental for the existence of life. The majority of biological processes are consequences of the fact that different enantiomers react with receptors in different ways, depending on their absolute configuration. As mentioned above, life itself is in many ways chiral. For example, the mechanism of smell is based on stereogenic interactions between the sensor, our nose, and a volatile compound, i.e. the enantiomers of carvone smells different the (S)-enantiomer have a caraway odor and the (R)-enantiomer smells of spearmint. This is also the case in taste, i.e. the enantiomers of the \(-\)amino acid aspargine taste bitter or sweet, depending on the absolute configuration (Figure 2).

\[ \text{H}_2\text{N} \quad \text{COOH} \quad \text{NH}_2 \]
\[ \text{HOOC} \quad \text{NH}_2 \quad \text{O} \]

Figure 2. The two enantiomers of aspargine the (R)-enantiomer tastes bitter (left) whereas the (S)-enantiomer tastes sweet (right).

Another more drastic and tragic example of different biological activity of enantiomers is the drug thalidomide, sold under the tradename Neurocedyd in Sweden, where the (R)-enantiomer is a mild tranquilizer whereas the (S)-enantiomer is teratogen, causing abnormalities in human embryos. To be able to prevent future drawbacks of optically active drugs the pharma indus-
try must develop safe and efficient pharmaceuticals and gain control over which enantiomer of a potential drug that possesses the desired effect. This is necessary not only from a safety reason but also from an economical perspective. Producing only the active enantiomer of a drug or other fine chemicals may reduce production costs, and from an environmental perspective, if less solvent is required the environmental stress can be diminished. With this in mind it is clear that a change to single enantiomer pharmaceutical and agricultural chemicals will change the market, increase patient safety and decrease environmental impact. The market of single enantiomer compounds is growing fast. Out of the 60% of all drugs that contain a chiral center, a percentage that has remained relatively unchanged over the last 20 years, racemates dominated in 1983 (60%) and the drug compounds that were marketed as single enantiomers at that time were mainly of natural origin. In 2002 only (10%) of the drugs that contained a chiral compound were racemates, with the rest sold as single enantiomers. Since 1992, new chemical pharma compounds possessing chirality must have each enantiomer individually screened and evaluated as different chemical entities during the drug approval process.\[7\]

1.4 Methods to Obtain Enantiomerically Pure Compounds

There are several ways to obtain enantiomerically pure or enriched compounds. The basic strategies can be divided into the following three categories:

1. Resolution of racemates
2. The “Chiral pool”
3. Asymmetric synthesis

1.4.1 Resolution of Racemates

This classic way of obtaining enantiopure or enriched compounds relies on a racemate being temporarily converted into diastereomers, this is often obtained by formation of diastereomeric salts, using an enantiomerically pure compound. The obtained diastereomers possess different physiochemical properties making a separation possible. An example is the resolution by recrystallization of (S)-propranolol, a \(\beta\)-receptor antagonist (Scheme 1).\[8\]
The reagents used to resolve a compound are often of natural origin i.e. tartaric acid, lactic acid, brucine, quinidine and other related alkaloids. Enzymatic methods, like lipase catalyzed reactions are also employed especially on large scale. Resolution of racemates suffers from some drawbacks such as the need for stoichiometric amounts of the enantiopure compound and the maximum theoretical yield is only 50%. Recovery and racemization of the unwanted isomer can in some cases overcome this problem. A good method for this is a dynamic kinetic resolution, where the unwanted isomer is racemized in situ and then transformed again into the desired enantiomer via resolution.

1.4.2 The “Chiral Pool”

The fundamental of the naturally occurring “chiral pool” approach is that non-racemic compounds occurring in nature, can serve as chiral starting materials for a synthesis. Nature provides a vast diversity of chiral species in several types of compound classes of which amino acids, carbohydrates, terpenes, carboxylic acids and alkaloids play important roles (Figure 3).

Many chiral compounds have been synthesized from the “chiral pool” approach. One example is oseltamivir phosphate, Tamiflu®. This compound is a potent antiviral agent and can be synthesized from the naturally occurring (-)-shikimic acid (Scheme 2), extracted from the Chinese star anis plant.
1.4.3 Asymmetric Synthesis

This way of producing chiral compounds is a very efficient methodology and it has become the most used strategy for obtaining chiral compounds. In order to produce an enantiomerically enriched product at least one part of the reacting system must be chiral itself. Hence, chiral substrates, chiral auxiliaries, chiral reagents or a chiral catalyst can be used to achieve an asymmetric synthesis:

1. In the substrate controlled asymmetric synthesis a chiral compound is used as a starting material, not necessarily a naturally occurring material. The formation of the new chiral centre is induced by the presence of a stereogenic fragment on the substrate.

2. In the auxiliary controlled asymmetric strategy an enantiomerically pure compound, chiral auxiliary, is temporarily attached to the starting material. After a diastereoselective reaction the auxiliary is removed, obtaining the product in an enantiomerically pure form.

3. In the reagent controlled asymmetric synthesis the enantioselectivity is induced by a chiral reagent e.g. base, reducing agent or hydroboration reagent.

4. In asymmetric catalysis the enantioselectivity is induced by a catalyst, present in sub stociometric amounts, the catalyst lowers the activation energy of one diastereomeric TS and thereby enhances the reaction rate and asymmetry in the product. Asymmetric catalysis is described in more detail below.

1.4.4 Asymmetric Catalysis

Ever since the first report of a catalytic reaction by Michael Faraday in 1834 the field of catalysis has grown tremendously and in 1904 Markwald reported the first catalytic asymmetric synthesis, a decarboxylation of a prochiral, -disubstituted malonic acid, catalyzed by the naturally occurring alkaloid brucine. The first synthetically useful asymmetric catalysis was reported in the late 1950s. Izumi et al. reported the hydrogenation of methyl acetoacetate into methyl -hydroxybutyrate with enantioselectivities up to 80%, using Raney nickel modified with tartaric acid.
The first industrial application employing asymmetric catalysis was Monsanto's production of L-DOPA, an important anti-Parkinson's drug. The process is an asymmetric hydrogenation of an acyl amine with a modified Wilkinson catalyst, developed by William Knowles (Scheme 3).[16, 17]

\[
\begin{array}{c}
\text{AcO} \quad \text{OAc} \\
\text{NHAc} \\
\text{COOH} \\
\text{H}_2, [\text{Rh(DIPAMP)}_2\text{cod}] \\
\text{AcO} \quad \text{OAc} \\
\text{NHAc} \\
\text{COOH} \\
\text{H}_2\text{O}^+ \\
\text{HO} \quad \text{OH} \\
\text{L-DOPA, 95% ee}
\end{array}
\]

Scheme 3. Monsanto’s L-DOPA process.

A few years later, Ryoji Noyori introduced the binaphthalene based BINAP-ligand (Scheme 4) that coordinated to Ru or Rh is especially successful in enantioselective hydrogenation of unsaturated carbon-carbon bonds and ketones.[18-21]

\[
\begin{array}{c}
\text{COOH} \\
\text{H}_2, [\text{Ru(OAc)}_2\text{BINAP}] \\
\text{COOH} \\
\text{HO} \quad \text{OH} \\
\text{(S)-Naproxen, 97% ee}
\end{array}
\]


After the introduction of a large number of ligands suitable for asymmetric hydrogenation reactions, enantioselective hydrogenation has become an established reaction. Catalytic asymmetric oxidations have also been studied and developed. Reactions such as epoxidations, dihydroxylation and aminoxylation have been reported; Sharpless and Katsuki introduced the first practical useful asymmetric oxidation in 1980.[22, 23] It involves epoxidation of allylic alcohols and is still one of the most popular oxidative asymmetric processes. Today there are also a variety of asymmetric reductions, addition reactions and other miscellaneous methods available, some of them highly useful. At present, asymmetric hydrogenation is the most used cata-
lytic asymmetric transformation,\textsuperscript{24, 25} with several companies offering asymmetric hydrogenation technology on a license basis.\textsuperscript{26}

1.5 Research Performed in This Thesis

This thesis contains seven papers all dealing with asymmetric reductions, either of ketones into chiral alcohols, (papers I-III), or olefins into chiral alkanes (papers IV-VII). In papers I and II we have designed new bicyclic ligands containing either N,S- (paper I) or N,N- (paper II) chelating atoms. The ligands have been evaluated in the asymmetric Ir-catalyzed transfer hydrogenation of acetophenone. In paper III we utilized a commercially available chiral diamine (QCD-amine) as ligand in the Ru-catalyzed hydrogenation of prochiral ketones. As part of this work we investigated, both theoretically and experimentally, the mechanism of this hydrogenation. In paper IV-VII we have designed and evaluated N,P and N\textsubscript{2}C-carbene,N-ligands for the Ir-catalyzed hydrogenation of carbon-carbon double bonds. A selectivity model for this hydrogenation has been derived and used in rationalizing the results (paper IV). In paper V we have further refined the ligand structure from paper IV as well as the selectivity model. In paper VI we designed and evaluated N\textsubscript{2}C-carbene,N-ligands and showed that the chelating atoms in the ligand moiety do not need to be restricted to phosphorus and nitrogen. In paper VII we have hydrogenated a new class of substrates, vinyl silanes, and showed that the scope of this reaction does not need to be restricted to previously investigated substrates.
2 Asymmetric Reduction of C=O Bonds

2.1 Asymmetric Transfer Hydrogenation

The transfer hydrogenation reaction is the abstraction of hydrogen from a hydrogen donor followed by re-addition to the hydrogen acceptor. The reaction is reversible if the oxidation potentials of the donor and the acceptor are of similar magnitude i.e. Meerwein-Pondorff-Verley reduction and the Oppenauer oxidation. Both these processes are catalyzed by Al(O-i-Pr)₃, and the equilibrium can be shifted towards reduction by the use of a donor in excess. The most common donor in transfer hydrogenation is i-PrOH but the azeotrope of formic acid with triethyl amine is also frequently used (Scheme 5).

Scheme 5. Asymmetric transfer hydrogenation of acetophenone using i-PrOH as hydrogen donor.

It was not until 1980 that the first asymmetric reduction of a prochiral ketone using i-PrOH as the hydrogen donor appeared in the literature, the reduction of 3-methyl-1-phenyl-butan-1-one with only 10% optical yield. At this time phosphine and pyridine ligands in combination with ruthenium, rhodium and iridium complexes were frequently used. However the catalytic reactions suffered from the need of high temperatures to obtain reasonably turn over frequency. It was not until it was found that addition of a base dramatically increased the TOF that the research in this field took off.

In the 90’s the results improved with regard to both catalyst activity and enantioselectivity and in 1995 Noyori reported that [RuCl₂(arene)]₂-complexes in combination with a chiral amino alcohol or mono-tosylated diamine ligands catalyzed the transfer hydrogenation of various prochiral aromatic ketones with excellent enantioselectivity for a vide range of substrates, not only ketones but also imines. This discovery led to the exploration of new ligands containing NH functions in combination with [RuCl₂(arene)]₂ as a metal precursor. Some important examples are shown below (Scheme 6). The most efficient ligands used for this reaction are based
on β-amino alcohols or N-sulfonyl-β-diamines together with Ru-arene or Rh/Ir-cyclopentadiene complexes.\textsuperscript{[38, 40-45]}

\[ \text{Ar} \text{R} \text{O} \text{NHTs} \text{RuCl}_2(\text{mesitylene})_2, 0.5 \text{ mol}\% \text{ base}, 15 \text{ h.} \]

\[ 95\% \text{ conv. 97\% ee.} \]

\[ \text{Ar} \text{R} \text{O} \text{NH}_2 \text{RuCl}_2(\text{p-cymene})_2, 0.1 \text{ mol}\% \text{ base}, 4 \text{ min.} \]

\[ 98\% \text{ conv. 97\% ee.} \]

\textbf{Scheme 6. Asymmetric transfer hydrogenation. Noyori's mono tosylated diamine system (left)\textsuperscript{[38]} and a 2-azonboronyl alcohol system developed by our group (right).\textsuperscript{[46]}}

A mechanistic and computational study of a Ru\textsuperscript{II} amino alcohol system identified three possible mechanistic pathways:\textsuperscript{[47]}

1. Concerted transfer of the proton from the NH-moiety in the ligand and the hydride coordinated to the metal onto the prochiral ketone.
2. Migratory insertion of the prochiral ketone into the metal-hydride bond.
3. Direct transfer of the -hydrogen of the metal-alkoxide complex to the prochiral ketone.

Recently it has been shown that for Ir\textsuperscript{I}-amino alcohol and Ir\textsuperscript{I}-amino sulfide complexes the reaction proceeds \textit{via} direct transfer from alcohol to ketone which are simultaneously coordinated, these findings corresponds to the concerted transfer mechanism.\textsuperscript{[48]}

\section{2.2 Synthesis and Evaluation of N,S-Compounds as Chiral Ligands for Transfer Hydrogenation of Acetophenone (Paper I)}

Sulfur containing ligands have been studied in a variety of applications in asymmetric catalysis.\textsuperscript{[49]} The different electronic properties of sulfur compared to oxygen\textsuperscript{[50]} as a chelating atom, coordinated to a metal have challenged many scientists.\textsuperscript{[51-54]} Utilization of nitrogen and sulfur as chelating atoms in ligands have afforded moderate to excellent results in e.g. allylic alkylation, hydrogenation, diethylzinc addition, conjugate addition to enones, metal catalyzed cross-coupling and hydrosilylation of imines and ketones.\textsuperscript{[49]}

Van Leeuwen and Lemaire recently reported the use of N,S-ligands in asymmetric transfer hydrogenation of ketones.\textsuperscript{[55-60]} Prior to these publications very little had been reported in the literature regarding sulfur containing ligands for transfer hydrogenation.\textsuperscript{[49]} In this work (Paper I) we report the
synthesis and evaluation of two new classes of N,S-ligands for transfer hydrogenation. The first class relies on the 2-azanorbornyl structure that has been previously investigated in our group.\cite{46} Aiming for access to active ligands that would be easy to prepare and modify we also developed a class of cyclohexyl based ligands. In earlier reports on N,S-ligands in asymmetric transfer hydrogenation, it has been showed that [Ir(COD)Cl]$_2$ yielded the most active catalysts.\cite{59}

These ligands were done in cooperation with Solvias AG and aimed for new ligands that could be patented.

2.2.1 Synthesis of Ligands

A synthetic strategy affording -amino sulfides containing a 2-aza-norbornyl scaffold was developed (Scheme 7). Starting from 1, hydrogenation and hydrogenolysis gave amino ester 2 in quantitative yield. Boc-protection of the secondary amine followed by reduction of the methyl-ester afforded 3 in good yield. Tosylation of the alcohol followed by nucleophilic substitution with BnSLi afforded 5 in 47\% yield, over two steps. Deprotection of the amine afforded ligand 6 in 31\%, overall yield.

![Scheme 7. Synthesis of ligand 6.](image)

Reagents and conditions: i) H$_2$, (10 bar), Pd/C, MeOH, rt. o.n.; ii) Boc$_2$O, Et$_3$N, THF, rt, o.n.; iii) LAH, THF, 0°C, 2 h.; iv) TsCl, pyridine, CH$_2$Cl$_2$, 0°C to rt, 5 h.; v) BnSH, n-BuLi, THF, 0°C to rt, o.n.; vi) TFA, CH$_2$Cl$_2$, rt, 2 h.

To extend the properties of ligand 6, monooxidation of the sulfur atom, which introduces a new center of chirality into the ligand, was performed by sodium periodate oxidation of 5 in a MeOH/H$_2$O solution. The product was formed as a 3:2 mixture of diastereomers that were separated by HPLC (Chiracel-OD). Deprotection of the amine yielded sulfoxides major-8 and minor-8 (Scheme 8)

![Scheme 8. Mono oxidation of 5 introduces a new chiral center in the ligand structure.](image)

Reagents and conditions: i) NaIO$_4$, MeOH:H$_2$O, 1:1 0°C to rt, 2 h.; ii) TFA, CH$_2$Cl$_2$, rt, 2 h.
To further expand the scope of this ligand class we decided to synthesize easier accessible, via a shorter synthetic pathway, ligands. This would open up a broader substitution pattern on the heteroatoms. Ligands still possessing a cyclic backbone was preferable, in order to reduce flexibility within the ligand structure. We therefore decided to synthesize ligands having trans-cyclohexyl backbones. Having the heteroatoms trans to each other has earlier proved to be favorable in the transfer hydrogenation reaction.\[38\] The synthesis started with ring opening of cyclohexene epoxide 9 by NaN₃ followed by a triphenylphosphine mediated Staudinger reaction afforded aziridine 10 in 57% yield over two steps (Scheme 9). Nucleophilic ring opening of the aziridine afforded the primary amines 11-13. At this stage chiral separation of the racemic amines into their corresponding enantiomers proved to be difficult. Instead the corresponding Cbz-protected amines were synthesized and separated by chiral HPLC followed by deprotection of the amine. Reductive amination of the enantiomerically pure material afforded ligands 16 and 17 in good yields (Scheme 9). Nucleophilic ring opening of 10 with tert-butyl thiol failed; a different approach was considered. Activation of the aziridine moiety by CbzCl then nucleophilic ring opening with tert-butyl thiol, facilitated by BF₃(OEt₂), followed by separation of the enantiomers by chiral HPLC afforded 19. Subsequent deprotection of the amine yielded ligand 20.

\[
\begin{align*}
\text{Scheme 9. Synthesis of ligands 16, 17 and 20.}
\end{align*}
\]

Reagents and conditions: i) NaN₃, H₂O, rt. o.n.; ii) PPh₃, CH₃CN, reflux, o.n.; iii) RSH, MeOH, reflux, 7 h; iv) CbzCl, Et₃N, Et₂O, 0 °C, 2 h, HPLC (Chiracel-OD); v) 6 M HCl, reflux, o.n.; vi) CbzCl, Et₃N, Et₂O, 0 °C, 1.5 h; vii) tert-BuSH, BF₃(OEt₂), CH₂Cl₂, 0 °C, 3 h, rt, o.n., HPLC (Chiracel-OD); viii) Pd/C, NH₄⁺COO⁻, MeOH, rt, 1 h.

To broaden the diversity of the ligand structures, compounds 11-13 were converted into secondary amines by reductive amination (Scheme 10).
Reagents and conditions: i) Acetone, NaCNBH₃, MeOH, rt, o.n.; ii) benzaldehyde, NaCNBH₃, MeOH, rt, o.n., HPLC (Chiracel-OD); iii) benzaldehyde, MgSO₄, EtOH, rt, 4 h; iv) NaBH₄, rt o.n., HPLC (Chiracel-OD).


A third chiral center in ligand 16 was introduced by treating cyclohexene epoxide 9 with (S)-1-phenylethylamine resulting in aziridine 24 followed by nucleophilic ring opening with benzylthiol to give 25 (Scheme 11, I). The effect of a smaller ring size in the ligand backbone was investigated by synthesizing compound 28 using the same methodology used to prepare ligands 16 and 17 (Scheme 11, II).


Faster access to the N-benzyl amino sulfides such as 23 was obtained using aziridine 29, derived from cyclohexene oxide and benzylamine. Compound 29 was ring opened with four different substituted phenyl thiols resulting in compounds 30-33. These ligands enabled a steric and/or electronic investigation by different substituents on the phenyl ring attached to the sulfur atom (Scheme 11, III).

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2.2.2 Results and Discussion

In total 16 new ligands were prepared and evaluated in the Ir-catalyzed asymmetric transfer hydrogenation of acetophenone, the results are summarized in Table 1.

Table 1. Results of the asymmetric transfer hydrogenation of acetophenone, using i-PrOH as hydrogen donor.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h.)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Abs. Config.</th>
</tr>
</thead>
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<td>1</td>
<td>95</td>
<td>63</td>
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<td>Major-6</td>
<td>1</td>
<td>10</td>
<td>55</td>
<td>(S)</td>
</tr>
<tr>
<td>3</td>
<td>Minor-6</td>
<td>1</td>
<td>52</td>
<td>80</td>
<td>(R)</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>0.5</td>
<td>97</td>
<td>59</td>
<td>(S)</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>2.5</td>
<td>&gt;99</td>
<td>16</td>
<td>(S)</td>
</tr>
<tr>
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<td>20</td>
<td>1</td>
<td>41</td>
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<tr>
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<td>1</td>
<td>96</td>
<td>63</td>
<td>(S)</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>0.5</td>
<td>98</td>
<td>70</td>
<td>(S)</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>0.5</td>
<td>79</td>
<td>33</td>
<td>(S)</td>
</tr>
<tr>
<td>10</td>
<td>Major-25</td>
<td>1</td>
<td>94</td>
<td>24</td>
<td>(R)</td>
</tr>
<tr>
<td>11</td>
<td>Minor-25</td>
<td>1</td>
<td>20</td>
<td>32</td>
<td>(S)</td>
</tr>
<tr>
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<td>28</td>
<td>1</td>
<td>89</td>
<td>38</td>
<td>(S)</td>
</tr>
<tr>
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<td>30</td>
<td>1</td>
<td>80</td>
<td>35</td>
<td>(S)</td>
</tr>
<tr>
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<td>31</td>
<td>1</td>
<td>91</td>
<td>35</td>
<td>(S)</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>1</td>
<td>92</td>
<td>44</td>
<td>(S)</td>
</tr>
<tr>
<td>16</td>
<td>33</td>
<td>1</td>
<td>59</td>
<td>29</td>
<td>(S)</td>
</tr>
</tbody>
</table>

Conditions: Acetophenone: [IrCl(COD)]_2:ligand:i-PrOK = 200:1:2.5:6.25, 0.1 M in substrate, rt.

Amino sulfide 6 reduced acetophenone with high rate but with moderate ee (Entry 1). One of the mono oxidized ligands, minor-7, proved to increase the ee (Entry 3). Both these diastereomers were found to yield less active catalysts compared to 6, (10 respectively 52% conversion after 1 h). Amine 16 gave rise to a more efficient catalyst than the bicyclic ligands 6 and minor-7 (97% conversion in 0.5 h), but less selective, 59% ee. The amines with more bulky substituents on the sulfur atom, 17 and 20, showed a decrease in both activity and selectivity of the catalyst (Entries 5 and 6). Amino sulfides 21 and 22, secondary amines, gave higher ee’s than the corresponding primary amine 16, 63 and 70% ee respectively (Entries 7 and 8). For 22 the same rate as for amine 16 was observed (~ full conversion in 0.5 h, Entries 4 and 8). Ligand 23 afforded a lower ee (33%, Entry 9) compared to 21 and 22, probably due to unfavorable electronic density on the sulfur atom in this ligand. The results obtained with the aryl-substituted analogues of 23, 30-33, (Entries 13-16) revealed that electron-donating aryl substituents give a slight increase of the ee (Entries 13-15) whilst an electron-withdrawing group low-
ered the ee (Entry 16). Introducing steric bulk at the ortho-position in the aryl did not significantly affect the selectivity (Entry 13). This is likely due to the fact that the methyl group is able to orient itself away from the metal center and therefore the effective steric bulk between ligands 23 and 30 are comparable. Ligands major- and minor-25 (Entries 10 and 11) differed significantly in rate, 94 and 20% conversion in 1 h respectively, but both of them gave very low ee. Decreasing the ring size by one-carbon (ligand 28, Entry 12) significantly lowered the selectivity (38% ee); one reason might be the change in dihedral angle between the heteroatoms.

In addition, ligands 6 and minor- and major-7 were also evaluated in the asymmetric transfer hydrogenation of acetophenone using formic acid as hydrogen donor instead of i-PrOH (Table 2). With ligand 6, full conversion was reached after 6 h at 60 °C and the enantiomeric excess of the (R)-product was 15%. At room temperature the reaction was very slow, 30% conversion after 96 h, but interestingly this lead to a reversal of the stereoselectivity and the (S)-product was obtained in 28% ee. With ligands minor- and major-7 no reaction was observed.

Table 2. Results of the asymmetric transfer hydrogenation of acetophenone using HCOOH:Et3N as hydrogen donor.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h.)</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Abs. Config.</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>96</td>
<td>23</td>
<td>30</td>
<td>28</td>
<td>(S)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>6</td>
<td>60</td>
<td>&gt;99</td>
<td>15</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>Major-7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Minor-7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Conditions: Acetophenone:[IrCl(COD)]2:ligand = 200:1; 2.5; 0.67 M in substrate.

2.2.3 Conclusions

In conclusion, we have synthesized and evaluated two new classes of N,S-ligands. These new ligands were evaluated in the asymmetric transfer hydrogenation of acetophenone. Bicyclic ligand minor-7 gave rise to a catalyst that induced good enantioselectivity, 80% ee. A synthetic protocol for rapid access to a number of monocyclic ligands, open to different ligand modifications, was also developed. The Ir-complex having dibenzyl ligand 22 showed the fastest rate of all complexes evaluated in this study, 98% conversion in 0.5 h using a substrate to catalyst ratio of 200:1. This is probably due to favorable electronic and steric properties of this complex compared to the other complexes.
2.3 Design and Evaluation of Amino-Oxazoline Ligands (Paper II)

Among other nitrogen containing ligands, oxazoline compounds have been used as ligands in different catalytic reactions. Chelating atoms, beside the nitrogen in the oxazoline ring, could be phosphorus, amino nitrogen, aromatic nitrogen or sulfur. Bis-oxazolines are also widely employed as ligands. Noyori et al. has showed that a chelating NH-function is crucial to have within the ligand structure to obtain good activity in the transfer hydrogenation of ketones. Several C₂-symmetric chiral bis-oxazoline methyamine ligands have been reported as efficient ligands in the Ru²⁺ catalyzed asymmetric transfer hydrogenation. However there are only a few reports on the use of C₁-symmetric amine and oxazoline containing ligands for the asymmetric transfer hydrogenation of prochiral ketones. The only examples are the 1,2,3,4-tetrahydroquinolinyl-oxazoline ligands developed by Zhou et al., used together with Ru²⁺ complexes and the proline derived amino-oxazolines used together with Ir³ complexes (Figure 4).

![Figure 4. Schematic picture of the amino-oxazolines used in asymmetric transfer hydrogenation.](image)

As previously mentioned, the 2-aza-norbornyl scaffold has extensively been utilized by our research group. In this study we took advantage of the fact that compound easily can be converted into an amino acid and then transformed into an amino-oxazoline compound via a short synthetic route. This allows for studying the influence of size and configuration of the substituent on the oxazoline 5´-position and also the influence of a more sterically demanding backbone compared to the general structure.

2.3.1 Synthesis of Bicyclic Amino-Oxazoline Ligands

The synthesis of these ligand starts from amino acid, easily prepared by a stereoselective aza-Diels-Alder reaction. To be able to execute the synthetic strategy envisioned the amine function in the bicyclic scaffold must be protected (Scheme 12). Initial studies showed that a Boc protecting group was not beneficial, as this resulted in low yields of the oxazoline formation.
Instead, the Cbz protecting group was used. Compound 37 smoothly underwent amide coupling with chiral amino alcohols under standard conditions affording the corresponding hydroxylamides 38-43 in good yields.\textsuperscript{[73, 74]} These compounds were converted into N-protected oxazolines 44-49 by treatment with mesyl chloride under basic conditions.\textsuperscript{[73]} Deprotection of the amine function was accomplished by hydrogenation over Pd/C yielding ligands 50-55 in good yields.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{synthesisScheme.png}
\end{scheme}


However, if the substituent in the 5´-position on the oxazoline was either a dimethyl, phenyl or benzyl group, deprotection of the secondary amine failed as decomposition of the oxazoline ring occurred under these conditions. It was therefore necessary to use a different protecting group, which could be removed under basic conditions or cleaved off under milder hydrogenation conditions. Initial studies with the 9-Fluorenylmethoxycarbonyl (Fmoc) group, commonly used in peptide synthesis, was unsuccessful as it
was not possible to deprotect the amine by treatment with piperidine, diethyl amine or tert-butyl ammonium fluoride.[75] Instead the p-nitrobenzyloxy carbonyl group was considered. This Cbz analogue is more easily cleaved, under less harsh conditions than the Cbz group. Alternatively, deprotection can be accomplished by treatment with sodium dithionite.[76] Both procedures were investigated and the hydrogenation protocol proved to be the most efficient, as deprotection of the secondary amine by sodium dithionite led to decomposition of the oxazoline ring even under basic conditions. Amino acid 56 underwent amide coupling under the same conditions as used for compound 36. The hydroxyl amides 57-61 were cyclized by treatment with mesyl chloride under basic conditions to give the protected oxazolines in good yields (Scheme 13). Deprotection of the amine was performed by hydrogenolysis over Pd/C as a catalyst to afford ligands 67-71 in good yields.

2.3.2 Ligand Evaluation

To be able to find an efficient catalytic system, a number of metal precursors together with ligand 51 were screened for transfer hydrogenation of acetophenone using \( \text{\textit{i}}\text{-PrOH} \) as hydrogen donor and \( \text{\textit{i}}\text{-PrOK} \) as base (Table 3). We found that complexes prepared from Rh-precursors were active for this transformation whereas those prepared from Ru-precursors showed no catalytic activity at all. The most efficient and selective complex was formed from \([\text{IrCl}_2(\text{COD})]_2\) (Entry 3) and was therefore chosen as the metal precursor for the ligand screening.

Table 3. Transfer hydrogenation of acetophenone using different metal precursor and ligand 51.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal precursor</th>
<th>Conv. 16 h. (%)</th>
<th>ee (%) (^b)</th>
<th>Abs. Config.</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>([\text{RhCl}(\text{PPh}_3)_3]</td>
<td>3</td>
<td>25</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>([\text{IrCl}(\text{COD})]_2]</td>
<td>18</td>
<td>71</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>([\text{IrCl}(\text{COD})]_2]</td>
<td>32</td>
<td>79</td>
<td>(R)</td>
</tr>
<tr>
<td>4</td>
<td>([\text{RuCl}_2(\text{benzene})]_2]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>([\text{RuCl}_2(\text{PPh}_3)_3]</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>6</td>
<td>([\text{RuCl}_2(\text{DMSO})]_2]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Conditions: Acetophenone:metal precursor:ligand:i-PrOK=200:1:2.5:6.25, 0.1 M in substrate. \(^b\)Determined by chiral GC.

We then became interested to investigate how the substituent in the 5’-position influenced the rate and selectivity of the transfer hydrogenation (Table 4). The Ir-complex formed from compound 69 (Entry 9) catalyzed the reduction of acetophenone to 1-(R)-phenylethanol in 73% conversion and with a moderate ee of 53%. The use of diastereomeric complexes derived from 50 and 53 reduced acetophenone less efficiently than the complex derived from 69.
Table 4. Transfer hydrogenation of acetophenone using ligands 50-55 and 67-71.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv. 16 h. (%)</th>
<th>ee (%)</th>
<th>Abs. Config.</th>
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<tr>
<td>1</td>
<td>50</td>
<td>20</td>
<td>41</td>
<td>(R)</td>
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<td>(R)</td>
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<td>(S)</td>
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<tr>
<td>11</td>
<td>71</td>
<td>83</td>
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<td>(R)</td>
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</table>

Conditions: Acetophenone:[IrCl(COD)]2:ligand:i-PrOK:i-PrOH = 200:1:2.5:6.25, 0.1 M in substrate. rt. aDetermined by chiral GC.

These results suggest that small substituents at the 5'-position, regardless of configuration, have no significant effect on rate or stereochemical outcome of the reaction. These parameters are dictated only by the bulk provided by the bicyclic backbone at the 1 and 3 positions, for ligands having small substituents at the 5'-position. Of the ligands, 51 and 54, possessing larger steric bulk on the oxazoline ring, 51 provided better selectivity than 54. Also different absolute configuration of the product was observed between the two diastereomeric complexes. Further increasing the steric bulk of the oxazoline moiety did not result in better enantioselectivity. Catalysts prepared from ligands 52 and 55 having tert-butyl substituents at the 5'-position induced the lowest ee of all catalysts evaluated, probably due to unfavorable steric interactions between the catalyst and the substrate. In general, catalysts formed from D-amino alcohols showed notably higher conversion. The most selective catalyst in this study was formed from ligand 51 (Entry 2) although conversion in this case was relatively low, 32%.

We also found that the enantiomeric composition of the product changed during the course of reaction (Table 5). For example the Ir-complex prepared from ligand 51 produced 1-(R)-phenylethanol in 38% ee after 1 h. After 16 hours the ee unexpectedly increased to 79% (Entry 1). Similar behaviour was observed with the diastereomeric analogue 54, where the ee increased from 16% after one hour to 27% after 16 hours (Entry 2).
Table 5. Change of ee over time.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h.)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Abs. Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>1</td>
<td>1</td>
<td>38</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>16</td>
<td>32</td>
<td>79</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>16</td>
<td>14</td>
<td>14</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>16</td>
<td>13</td>
<td>42</td>
<td>(R)</td>
</tr>
</tbody>
</table>

Conditions: Acetophenone:[IrCl(COD)]2 ligand:i-PrOK = 200:1:2.5:6.25, 0.1 M in substrate. rt. a Determined by chiral GC.

The same was also observed for the Ir complex of compound 67, the ee increased from 14% after one hour to 24% after 16 hours (Entry 3). The reversed behavior was observed for the Ir-complex of 71 where the ee substantially dropped after 16 hours from 42% after one hour to 28% (Entry 5). In recent published reports the mechanisms for Ru- and Ir-catalyzed asymmetric transfer hydrogenations have been studied, by means of computational calculations of the reaction mechanisms. The calculations suggests that Ru- based systems proceeds via a concerted mechanism while the Ir-catalyzed reaction proceeds via direct hydrogen transfer between simultaneously coordinated ketone and alcohol (Scheme 14).

Scheme 14. Proposed mechanism for the Ir-catalyzed transfer hydrogenation.

The unexpected change in product enantioselectivity over time for some of these catalytic systems might be the result of the chiral environment, around the metal center changing over time. Additionally, degradation of the catalyst took place during the reaction course and the catalyst was totally inactive after 16 hours.

2.3.3 Conclusions

In conclusion, we have developed a synthetic route towards a new class of (1S,3R,4R)-2-aza-bicyclo[2.2.1]heptane-oxazoline compounds. This route can be used to prepare various derivatives of these new compounds in enan-
tiomerically pure forms from commercially available starting materials. We have also demonstrated that these compounds can be employed as ligands in the Ir-catalyzed asymmetric transfer hydrogenation of acetophenone with ee’s ranging from moderate to good. It was found that [IrCl₂(COD)]₂ was the best catalyst precursor and use of the oxazoline 51 as a ligand gave rise to a catalyst of good selectivity, 79 % ee. We were also able to demonstrate that the ee increased during the course of reaction.

2.4 Catalytic Asymmetric Hydrogenation of Ketones by Phosphine Free Ruthenium Catalysts (Paper III)

Catalytic asymmetric synthesis is, according to a newly published report,⁷⁷ the most important method for the production of chiral products. Definitely, catalytic enantioselective hydrogenation is the reaction most widely used for this purpose, both industrially and in the laboratory. This interest has made homogeneous hydrogenation of functionalized olefins the best-studied enantioselective catalytic reaction.

Of comparable practical interest to the enantioselective reduction of C,C-double bonds is the hydrogenation of C,O- and C,N- double bonds.⁷⁸ One method to achieve this is asymmetric transfer hydrogenation as already mentioned in this thesis. Another method is the direct use of molecular hydrogen, hydrogenation, which has the advantage of using a cheaper hydrogen source and no excess of hydrogen is, in principle, needed to obtain full conversion.

The most efficient catalysts for the hydrogenation of activated ketones with H₂ are based on Ru¹¹-diphosphine catalysts (Figure 5, A).⁷⁹ The system of choice for reducing unactivated ketones, on the other hand, is Noyori’s recently developed bifunctional Ru-diphosphine/diamine catalyst system (B).⁸⁰-⁸⁴

![Figure 5. Previous used systems for ketone hydrogenation.](image)

Although both Ru-diphosphine/diamine complexes (B) and the widely used Ru-arene/diamine complex (C) contain a characteristic NH-functionality, the catalytic activity of these two catalytic systems differs. The Ru-
arene/diamine complex widely used in transfer hydrogenation, hardly reacts with H₂,[41] while the Ru-diphosphine/diamine complex does so easily. Recently, Ikariya et al. demonstrated that Cp*RuCl₁,₂-diamine complexes of type (D) which are isoelectronic to the transfer hydrogenation catalyst (C), were active catalysts for the hydrogenation of ketones with H₂ as hydrogen source.[85] This finding is interesting, as it appears to be one of the few known examples of a homogeneous hydrogenation catalyst, which is capable of activating molecular hydrogen without having at least one phosphine ligand around the metal center.[86, 87] This study also concluded that the most active catalyst was obtained with a diamine having one tertiary and one primary amino function.

Based on these results, we became interested to investigate the role of the Lewis basicity[88] of the tertiary nitrogen center of the ligand. One possibility to achieve this would be to include a quinuclidine function into the ligand. Gratifyingly, two pseudo-enantiomeric 1,₂-diamines containing a quinuclidine and a primary amino function are commercially available. The quincoridine-amine (QCD-amine) 72 and quincorine-amine (QCI-amine) 73 are derived from the Cinchona alkaloids quinine and quinidine, respectively (Scheme 15).[89]

![Scheme 15. Preparation of QCI/QCD-amines.](image)

These β-diamines, having four stereogenic centers each, including a fixed stereogenic (S)-configured N-bridgehead, and have previously been used as ligands in Ir-catalyzed asymmetric transfer hydrogenation of ketones,[90] and as chiral acylation catalysts.[91] Other ligands based on the quincorine and quincoridine scaffold, including N,P-ligands, have also been described.[92-94] However no QCI/QCD-based ligands have previously been used in asymmetric hydrogenation reactions.

### 2.4.1 Results and Discussion

**2.4.1.1 Hydrogenation of Aryl Alkyl Ketones; Results**

In an initial study of the rate of the hydrogenation, we compared the two diamines employed by Ikariya and co-workers, 74 and 75 with 72, employ-
ing almost identical reaction conditions. Interestingly the observed reaction rates for 74 and 75 were faster than reported by Ikariya; the metal precursor used by us probably generates a more active catalyst. To our satisfaction, it was also found that 72 reacted approximately 24 times faster (relative rate) than 74 with comparable enantioselectivity (Figure 6).

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

**Figure 6.** Initial results comparing QCD-amine 72 with previously reported ligands 74 and 75 in the phosphine free asymmetric hydrogenation of unfunctionalized ketones.

Inspired by the high reaction rates obtained by the initial studies on acetophenone with the QCD-amine 72, we preceded our investigation by reducing a wide variety of sterically and electronically different aryl-alkyl ketones (Table 6). Interestingly, pseudoenantiomeric QCI-amine 73 induces lower enantioselectivity, probably due to a steric miss-match between the vinyl group and the substrate (Entry 2). Good activity in terms of conversion was achieved for both 72 and 73 with 72 being more selective than 73, 75 and 41% ee respectively (Entries 1 and 2).

* We used [Cp*RuCl]_4 instead of Cp*Ru(COD)Cl as catalyst precursor
Table 6. Results of the asymmetric hydrogenation of aryl alkyl ketones by 72 (QCD) /73 (QC1)-amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar</th>
<th>R</th>
<th>Diamine</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Abs. Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>72</td>
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<td>2</td>
<td>76</td>
<td>C₆H₅</td>
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<td>73</td>
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<td>i-C₆H₇</td>
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<td>99</td>
<td>74</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>C₆H₅</td>
<td>t-C₆H₉</td>
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<td>99</td>
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<td>(S)</td>
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<td>5</td>
<td>79</td>
<td>C₆H₅</td>
<td>n-C₆H₉</td>
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<td>99</td>
<td>81</td>
<td>(S)</td>
</tr>
<tr>
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<td>80</td>
<td>C₆H₅</td>
<td>i-C₆H₉</td>
<td>72</td>
<td>99</td>
<td>90</td>
<td>(S)</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
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<td>CH₃</td>
<td>72</td>
<td>+99</td>
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<td>(S)</td>
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<td>+99</td>
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<td>(S)</td>
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<td>(S)</td>
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<td>90</td>
<td>1-naphthyl</td>
<td>CH₃</td>
<td>72</td>
<td>+99</td>
<td>81</td>
<td>(S)</td>
</tr>
</tbody>
</table>

Conditions: 1 mol% catalyst, 25 bar H₂, 0.47M substrate in i-PrOH, rt, 2h.

2.4.1.2 Rationalizing Mechanism and Enantioselectivity

It has been postulated earlier that the mechanism of the ketone hydrogenation by Ru-catalysts that contains at least one sp³-hybridized NH donor proceeds via a concerted proton-hydride transfer from the complex to the substrate.\[95, 96\] This mechanism can be regarded as commonly accepted, considering the reduction step, but very little is known about how the dihydrogen is heterolytically activated into a metal bound hydride and a nitrogen bound proton. This part of the reaction is of considerable interest as its calculated barrier is estimated to be high (ca. 20 kcal mol⁻¹) and probably overall rate determining (Figure 7, pathway A).\[97\] In contradiction with the calculated barrier, Morris et al. reported an experimental activation enthalpy of only 7.6 to 8.6 kcal mol⁻¹.\[98, 99\] The difference between the calculated and experimentally observed barriers could be an effect of the active participation of an alcohol molecule in the coordination and cleavage of dihydrogen (Figure 7, pathway...
Such a mechanism has been proposed and experimentally supported by deuterium labeling experiments by Ikariya and coworkers in 2001.\textsuperscript{[85]} However, the possibility for \textit{i}-PrOH-assisted heterolytic dihydrogen activation at the Ru-center has been overlooked in computational studies so far, although often mentioned in a tentative way.\textsuperscript{[97, 100]} We have used our \textit{Cp*Ru\textsuperscript{II}(QCD)Cl}-catalyst to investigate the possibility of such mechanism by theoretical and experimental methods (Figure 7, pathway B).

Figure 7. Relative energy diagram depicting the addition of \textit{H}_2 to the 16-electron Ru-complex and subsequent heterolytic cleavage in a diamine model system. \textbf{A}: Nonalcohol-mediated pathway. \textbf{B}: alcohol-mediated pathway.

As the first step in the experimental mechanistic evaluation, we performed a kinetic investigation into the \textit{Cp*Ru\textsuperscript{II}(QCD)Cl} catalyzed reaction. According to DFT-calculations, it should be first order with respect to catalyst and hydrogen pressure. In a series of experiments, 1.9 mmol of \textit{70} was reduced at hydrogen pressures of 5.0, 10.0, 15.0, 20.0 and 25.0 bar using 1.00 mol\% of \textit{Cp*Ru\textsuperscript{II}(QCD)Cl} at 0.470 M in \textit{i}-PrOH. This revealed a first order dependence in hydrogen pressure (Figure 8, a).
We also experimentally verified the expected zero order dependence in substrate concentration (Figure 8, b).

Figure 8. a) Pressure dependence on rate for the hydrogenation of acetophenone with Cp*Ru\textsuperscript{II}(QCD)Cl under the conditions used in Table 6. (Slope=9.8x10\textsuperscript{-5}, I=-3.3x10\textsuperscript{4}, R\textsuperscript{2} = 0.995) b) Plot of initial rates as a function of substrate concentration; the slope shows reaction order zero with respect to acetophenone.

The importance of a protic solvent for this reaction was supported by performing the hydrogenation in a nonprotic solvent (THF), where the hydrogenation was found to be substantially slower, as was also observed in Ikariya’s initial report.\textsuperscript{[85]} However it should be noted that the solubility of H\textsubscript{2} varies with solvent.

In order to see how well the proposed mechanism correlates with the experimental results we next compared the selectivities obtained for the ketones with the catalyst structure derived from the DFT-calculations. This is greatly facilitated by the presence of the \textsuperscript{\textsuperscript{5}}-bonded Cp*-ligand, since it occupies three coordination sites on the octahedral Ru and thus reduces the number of possible diastereomeric complexes. Starting from the planar zwitter-ionic 16e-complex C, (Figure 9) addition of dihydrogen can take place from two sides, leading to two diastereomeric complexes. Calculations favor formation of intermediate A which has a lower activation energy for the heterolytic, alcohol mediated cleavage of the coordinated dihydrogen (8.8 kcal mol\textsuperscript{-1} for A compared to 11.6 kcal mol\textsuperscript{-1} for B.)
The modeled transition state of the reduction is a concerted, but asynchronous, addition of a hydride to the carbonyl carbon, followed by the transfer of a proton from nitrogen to oxygen. In this model, the addition to the Si-face of the ketone is favored by 2.2 kcal mol$^{-1}$ since this will avoid interactions between the phenyl and the Cp*-ligand of the complex that takes place in the corresponding addition to the Re-face (Figure 10).

The lower selectivities obtained (Table 6) for the QCI-amine, 73, originates from a collision between the vinyl group in the ligand and the phenyl ring in the substrate. This interaction leads to destabilization of the transition state giving Re-addition and the calculated energy difference between the two diastereomeric transition states is now only 1.2 kcal mol$^{-1}$, compared to 2.2 kcal mol$^{-1}$ for the QCD-complex, 72, (Figure 11).
We also found that the enantioselectivity strongly depends on the electronic character of aromatic substituent pattern in the substrates. By decreasing the electron density of the aromatic moiety, a strong negative effect on the enantioselectivity was observed (Table 6). Recalculating the enantiomeric excess value (ee), into the corresponding enantiomeric ratio value (er) and plotting the \( \ln(\text{er}) \) against literature values of (MeO<Me<H<Cl<CF\(_3\))\(^{[101]} \) gives a good correlation (Figure 12).

This fact can be explained by the influence of a dipole-dipole stabilizing/destabilizing interaction in the enantiodetermining transition state, de-
pending on the electron density and dipole moment of the aromatic ring and its recognition of the strongly negative Cp*-ligand. This leads to an attractive interaction in case of an electron deficient aromatic ring and the opposite repulsive effect, in case of an electron rich aromatic substrate. As the aromatic substituent points away from the Cp*-ligand in the transition state, leading to the major enantiomer, the repulsive effect can be considered as positive in terms of enantioselectivity. Similar electrostatic effects, but in the opposite direction, have been observed by our group in the Ru-catalyzed transfer hydrogenation of a series of substituted acetophenones.\cite{102}

In contrast to other asymmetric ketone hydrogenation catalysts, alkyl-aryl ketones having bulkier alkyl groups reacted with higher enantioselectivity than those having smaller alkyl groups. While acetophenone was hydrogenated to (S)-1-phenyl ethanol in 75\% ee, the sterically more demanding 2,2-dimethylpropioophenone and valerophenone (Table 6, Entries 4 and 6) gave the corresponding alcohols in 90\% ee. This fact can be explained by the DFT-calculations, showing a difference between the Re- and Si-face reduction of 2,2-dimethylpropioophenone of 5.5 kcal mol\textsuperscript{-1}, compared to 2.2 kcal mol\textsuperscript{-1} for acetophenone (75\% ee), which corresponds well to the observed 90\% ee of substrate 78 (Table 7). This can be attributed to the almost perfect fit of the tert-butyl group into the pocket formed between the coordinated carbonyl and the Cp*-ligand.

Table 7. Comparison between experimental and calculated enantioselectivities for the diamine-Ru-Cp* catalyzed hydrogenation of acetophenone and 2,2-dimethylpropioophenone. Energies in kcal/mol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>$\Delta G(R-S)_\text{calc}$ \textsuperscript{a}</th>
<th>$\Delta G(R-S)_\text{Exp}$ \textsuperscript{b}</th>
<th>ee (%$R$ or $S$)\textsubscript{Exp}</th>
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<tr>
<td>1</td>
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<td>76</td>
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<td>1.15</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>76</td>
<td>-2.0</td>
<td>-1.07</td>
<td>72</td>
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<td>73</td>
<td>76</td>
<td>-1.1</td>
<td>-0.52</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>78</td>
<td>5.6</td>
<td>1.74</td>
<td>90</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Refers to the absolute configuration of the alcohol product.

\textsuperscript{b} All calculations were performed on the full structures. Energies reported are from the B3LYP/LACV3P**/B3LYP/LACVP** including zero-point correction.

\textsuperscript{c} Calculated from the observed ee.
2.4.2 Conclusions

In conclusion, we have shown that the complex formed between [RuCp*Cl]₄ and the commercially available chiral diamine quincorine-amine, originally derived from quinine, is a highly reactive catalyst for the phosphine-free enantioselective hydrogenation of aryl ketones. A detailed mechanistic investigation revealed that the quinuclidine based ligand is approx. 24 times more reactive than previously described catalysts, and the enantioselectivities obtained are modest to good (up to 90 \% ee). Interestingly, the diastereomer of quincorine-amine 72, i.e. quincoridine-amine 73, also showed high activity. However, the enantioselectivities obtained with this catalyst were lower. This finding represents a rare exception where these diastereoisomers do not function as pseudo-enantiomeric reagents for an asymmetric reaction. The reason for the lower, but opposite stereoselectivity seen with the quincoridine-amine, as compared to the quincorine-amine, could be rationalized through a computational study of the mechanism of the reaction. In addition to providing a working selectivity model, these calculations also revealed that the activation energy for the dihydrogen split involved is significantly lowered when a solvent alcohol molecule mediates the process. This finding provides an explanation for the reported discrepancy between experimental and theoretical activation energies reported for Noyori’s diphosphine/diamine mediated enantioselective hydrogenation system. \[80-84\]
3 Asymmetric Reduction of C=C Bonds

3.1 Iridium-Catalyzed Asymmetric Hydrogenation of Olefins

Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis. While ruthenium- and rhodium-catalyzed asymmetric hydrogenations of chelating olefins have a long history,[103] unfunctionalized olefins still represent a challenging class of substrates. In 1977 Crabtree reported the first successful achiral Ir-catalyzed hydrogenation of unfunctionalized olefins.[104, 105] The so-called Crabtree catalyst 91 (Figure 13) have successfully been used for the hydrogenation of substrates not suitable for treatment with heterogeneous catalysts like Pd/C or Adams catalyst (PtO2).

Although very general in its application, the major drawbacks of 91 have been high catalyst loadings and sensitivity towards heteroatom functionalities in the substrates. It took a further 21 years from Crabtree’s first report on homogeneous achiral iridium catalysis, with a few exceptions using Rh, Ru or titanocenes as catalysts for hydrogenations,[106, 107] until Pfaltz and co-workers reported the successful asymmetric Ir catalyzed hydrogenation of unfunctionalized olefins.[108] Utilizing the previously reported phosphine oxazoline ligand 92 (Figure 13).[109, 110] The most important discovery made by Pfaltz was that through a simple exchange of the PF6− counter ion with the even more weakly coordinating anion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF) (Figure 13) the Ir-complexes became more robust and allowed for lower catalyst loadings.[108]

![Figure 13. Crabtree’s catalyst 91 and chiral analogue 92 by Pfaltz et al.](image)

The mechanisms of hydrogenation of activated olefins with cationic rhodium complexes have been studied in detail and most of the mechanistic aspects are known.[111] In the case of Crabtree’s iridium catalyst 91 and the chiral
analogues by the groups of Pfaltz, Zhang, Knochel and Burgess, very little is known about the catalytic cycle. Nevertheless, the importance of a coordinating diene like 1,5-cyclooctadiene (COD) or norbornadiene (NBD) in the metal precursor has been stated earlier in the literature. The presence of these dienes in the precursor ensures irreversible formation of free coordination sites at the metal. Thus, in the activation of the catalyst, this ligand is reduced and the corresponding saturated compound is released. Several studies have been devoted to the understanding of this process and the oxidative addition of dihydrogen to Ir-(COD) complexes is known in some detail. However, the knowledge of the real catalyst and the exact mechanism for the Ir-catalyzed hydrogenation of olefins is very limited. Our group recently undertook a kinetic and computational study to bring further understanding about the operating mechanism in the Ir-catalyzed hydrogenation of unfunctionalized olefins.

Based on the findings from Brandt et al., the reaction mechanism (Scheme 16), was assumed to be operating in the hydrogenation of alkenes using Ir(N,P-ligand)(diene) catalyst precursors.

The catalytic cycle starts with a stable IrIII-dihydride complex (A). In the following step, an olefin is coordinated trans to phosphorous and in an endergonic step, dihydrogen coordinates in the remaining axial position (B C). The coordination of dihydrogen might be either dissociative with an energy cost of the iridium-dichloromethane bond, or associative as shown in $T_{SB}$. The olefin in this complex can then undergo a migratory insertion into the axial Ir-H bond, a reaction that occurs simultaneously with an oxidative addition of dihydrogen to the other axial position (C D). The resulting

Ir^v-species (D) is now labile and the reductive elimination occurs with an insignificant barrier (D E).

A recent publication by Burgess and co-workers suggests a similar mechanism to that described in Scheme 16, also involving a Ir^v-transition species, but differing slightly in character, probably due to that the system studied involves a seven member Ir-chelate and a N2C-carbene instead of phosphorous. [124]

3.2 Rational Design of New Catalysts; First Generation (Paper IV)

With the knowledge from the mechanistic studies of Pfaltz system in our hands we became interested in designing new, even more potent, catalysts. We also wanted to give a rational for the observed enantioselectivity, envisioned in a selectivity model (Figure 14), where it would be possible to determine the important factors governing selectivity in the Ir-catalyzed hydrogenation of olefins.

In order to obtain high selectivity and reactivity the following specifications of the catalyst should be met: the ligand should (i) contain an aromatic nitrogen atom and a phosphorous atom to get a significant trans-effect and reaction site discrimination, (ii) be able to form a six membered chelate ring upon complex formation and (iii) contain a rigid backbone fused to the aromatic heterocycle to reduce conformational flexibility. These criteria can be fulfilled in the ligand design by envisioning a schematic 3D picture of the catalyst prior to migratory insertion (Figure 14, A) if assuming that the center of the 2D quadrant model (Figure 14, B) is the olefin coordinating site, located trans to phosphorus. By filling the lower left quadrant in the 2D model with a steric bulk, an enantiofacial discrimination is established. The large trans-substituents of the substrate are forced into the open quadrants and the unsubstituted olefin position will be orientated towards the filled quadrant. In order to design a ligand structure from the quadrant model, including the features listed above, the following manipulations were performed as seen in Figure 14:

1. The P- and N-coordinating atoms are connected through a three-atom linker, giving C.
2. Stereochemistry of the catalyst complex is established by the following manipulations: (2.1) incorporation of coordinating N-atom into a five membered heteroaromatic group, (2.2) conformationally locking of the chelate and heteroaromatic substituent with a cyclic backbone, (2.3) establishing the stereogenic center within the chelate, preferably at the site where the backbone and chelate connect to each other. and (2.4) adding the steric bulk located in the lower left
quadrant to the five-member heteroaromatic substituent, giving hypothetic structure D.

3. In order to turn D into a possible structure, steric bulk is added in terms of a R- or Ar-group, fused to the five-member heteroaromatic moiety including the coordinating N-atom. The heteroaromatic moiety is chosen as a 1,3-heterocycle, locating the steric bulk at the 2-position. The correct twist angle of the ligand, locating the steric bulk as close to the Ir-center as possible, is achieved by the cyclic backbone of the ligand.

![Figure 14. Rational ligand design from quadrant model to ligand structure.](image)

Turning structure E into a possible chemical structure is done by adding oxygen atoms to the X positions. This results in the oxazole phosphinite structure F (Figure 15).

![Figure 15. Creation of oxazole based ligand from model E.](image)
One noticeable conclusion from this schematic representation is that the R- or Ar- group must offer enough steric hindrance to discriminate between different possible substrate catalyst interactions.

3.2.1 Synthesis and Evaluation of First Generation Ligands

Retrosynthetic analysis of structure F shows, that after disconnection of the phosphinite moiety, introduction of chirality by an asymmetric reduction of corresponding ketone is possible (Scheme 17). Disconnection of the heterocyclic moiety in the ketone points at a 1,3-dipolar intermediate, available from a Rh2(OAc)4-catalyzed [3+2] dipolar cycloaddition over nitriles.\cite{125}

With the diazoketone easily prepared from the corresponding 1,3-dicarbonyl compound by diazotation of an enolate by sulfonyl azide.

In the synthesis we first started with two different symmetric diketones, dimedone and 1,3-cyclohexanedione. Initial studies on the formation of 2-diazo-1,3-carbonyl compounds revealed that dimedone 93 was a much more convenient starting material for the synthesis of its diazocompound than 1,3-cyclohexanedione and was therefore chosen as starting material for the synthesis. Treatment of 93 with tosyl azide (TsN$_3$) in the presence of triethylamine at 0 °C gave diazodimedone 94 in excellent yield.\cite{126}

Decomposition of 94 in the presence of various nitriles by a catalytic amount of Rh$_2$(OAc)$_4$ yielded ketones 95-98 in moderate yields.\cite{127}

It was found that the purity of reactants was of importance for the outcome of this reaction. Performing the reaction at temperatures higher than 60 °C resulted in the formation of large amounts of byproducts. Ketones 95-98 were then reduced by slow addition to a solution of (R)-Me-CBS catalyst\cite{128} (10 mol%), employing BH$_3$·SMe$_2$ (2 equiv.) as stochiometric reductant, in THF at room temperature. Recrystallization from 95% ethanol of the obtained alcohols did not result in an increase of the enantiomeric excesses for 99-101 but for 102 a single recrystallization yielded in enantiomerically pure material (>99.5% ee) with 86% recovery of 102 (Scheme 18).

It is known from literature that the enantioselectivity obtained with these borane reduction systems is highly dependent on solvent and temperature, usually THF at rt. are optimal conditions. [129] We therefore decided to study the temperature dependence on enantioselectivity for the asymmetric reduction of ketone 98 (Scheme 19).

Scheme 19. Temperature dependence upon enantioselectivity in the (R)-Me-CBS borane reduction of ketone 98.

As seen in Scheme 19, the optimal temperature for obtaining high enantioselectivity was, as expected, rt. The other alcohols 99-101 could not be obtained with higher ee employing different temperatures. Given this and the fact that the ee could not be increased by recrystallization for alcohols 99-101, alcohol 102 was chosen as a “lead compound”. Treatment of 102 with n-BuLi/TMEDA at low temperature (-78°C), followed by addition of Ar₂PCl and stirring at rt. over night yielded the ligands 103-105 in good yields (Scheme 20). At this point the phosphinite moiety of the ligands was found to be sensitive to both oxidation and hydrolysis so the final ligands had to be rapidly filtered through a short silica column. Therefore 103-105 were converted into their corresponding iridium complexes 106-108 immediately after preparation by treatment with 0.5 equivalents of [IrCl(COD)]₂ in re-
fluxing dichloromethane, directly followed by ion exchange from Cl\(^-\) to BAr\(^{+}\) under aqueous two-phase conditions. Complexes 106-108 were isolated in good yields after precipitation from an absolute ethanol solution, by careful addition of water (Scheme 20).

In order to determine the absolute configuration of complexes 106-108, an X-ray of either an Ir-complex or the enantiomerically pure alcohol was needed, a diastereomeric derivative of alcohol 102 turned out to be the easiest way. Treatment of alcohol 102 with (S)-phenethylamine isocyanate in the presence of a catalytic amount of DMAP in toluene at 80 °C gave the corresponding diastereomeric crystalline carbamate 109 in high yield (scheme 21). Crystallization from 95% ethanol gave crystals suitable for X-ray crystallography. From the X-ray structure of 109, the absolute configuration of the alcohol 102 was established to be (S) (Figure 16).\(^{[130]}\)

Reagents and conditions: i) TMEDA, n-BuLi, THF, -78\(^\circ\) C, then Ar\(_2\)PCl, raise to rt, 16h; ii) [IrCl(COD)]\(_2\), CH\(_2\)Cl\(_2\), reflux 30 min, then H\(_2\)O, NaBAR+F3H\(_2\)O, rt, 1h.


Reagents and conditions: i) (S)-phenethylamine isocyanate, toluene, DMAP, 80°C, 2h, 85%.

3.2.2 Evaluation of Complexes in Asymmetric Ir-Catalyzed Hydrogenation

The potential of these new N-heterocyclic catalysts were evaluated in the asymmetric Ir-catalyzed hydrogenation of olefins (Table 8). Hydrogenation of 110 using 0.5 mol% of 106 under standard conditions at different pressures showed 30 bars to be optimal for this substrate. At 1 bar no conversion could be detected after two hours. For substrate 112 the ee increased slightly, 91 % to 93 %, when going from 30 to 50 bars. Substrate 114 reacted slowly at 50 bars so over night reaction at 100 bars was used instead. These new complexes also proved to be highly efficient in the hydrogenation of other substrates (Entries 1-9) with complex 107 as the overall best. As expected, according to the selectivity model, 2-(4-methoxyphenyl)-3-methyl-but-2-en 114 (Entry 5) showed poor enantioselectivity.
Table 8. Results from asymmetric hydrogenation of olefins 110-118 by Ir complexes 106-108.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>106 conv(%)</th>
<th>106 ee(%)</th>
<th>107 conv(%)</th>
<th>107 ee(%)</th>
<th>108 conv(%)</th>
<th>108 ee(%)</th>
<th>Abs. Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMePh</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>p-MeO-C₆H₄MeMePh</td>
<td>&gt;99</td>
<td>89</td>
<td>&gt;99</td>
<td>96</td>
<td>&gt;99</td>
<td>97</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>p-MeO-C₆H₄MeMePh</td>
<td>&gt;99</td>
<td>95</td>
<td>&gt;99</td>
<td>96</td>
<td>&gt;99</td>
<td>96</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>p-MeO-C₆H₄MeMePh</td>
<td>&gt;99</td>
<td>92</td>
<td>&gt;99</td>
<td>94</td>
<td>&gt;99</td>
<td>90</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>p-MeO-C₆H₄MeMePh</td>
<td>37</td>
<td>15</td>
<td>46</td>
<td>rac.</td>
<td>47</td>
<td>rac.</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>PhMeOH</td>
<td>96</td>
<td>92</td>
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<td>98</td>
<td>95</td>
<td>97</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>PhMeOAc</td>
<td>&gt;99</td>
<td>99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>99</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>PhMeCO₂Et</td>
<td>&gt;99</td>
<td>66</td>
<td>&gt;99</td>
<td>93</td>
<td>&gt;99</td>
<td>72</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>PhMeCO₂Et</td>
<td>50</td>
<td>rac.</td>
<td>50</td>
<td>33</td>
<td>48</td>
<td>38</td>
<td>R</td>
</tr>
</tbody>
</table>

Conditions: pressures: 30 bar (entry 1), 50 bar (entries 2-4, 6-9), 100 bar (entry 5); All reactions were performed at room temperature for 2h, except for entries 5 and 6, where the reaction was run over night; Catalyst loading 0.5 mol% in all entries, except 5 and 6 where 1 mol% were used. All reactions were performed in freshly distilled (CaH₂, ethanol free) CH₂Cl₂ as 0.25 M solutions.

The results, clearly shows that the newly developed catalysts are highly efficient catalysts for the Ir-catalyzed asymmetric hydrogenation of tri-substituted olefins. The results also agree with the proposed selectivity model, trans-olefins are reduced with much better selectivity than cis and tetra-substituted substrates are reduced with low ee. All the used substrates gave products with the same absolute configuration as the selectivity model predicts. To get a better understanding of the substrate-catalyst interactions in the enantio-determining transition state of these systems, designed according to Figure 14, (Chap. 3.2) we calculated the coupled migratory insertion/oxidative addition step for the full system of complex 106 with substrate 110. The calculated transition state structure where found to be very similar to those reported.[123] This clearly shows a chiral pocket well suited to accommodate a tri-substituted alkene according to our selectivity model. As
depicted, the enantiofacial selectivity is primarily based on discrimination between a larger and a smaller geminal substituent (Figure 17).

Figure 17. Structure of the selectivity determinating transition state of the coupled olefin migratory insertion / dihydrogen oxidative addition (left). Selectivity model using the ligand structure of the energy optimized transition state and a schematic substrate molecule (right).

3.2.3 Conclusions

In conclusion we have proposed a selectivity model for the Ir-catalyzed hydrogenation of olefins. This model can be used to predict the stereochemical outcome of the hydrogenation, by overlapping a substrate on to the empty quadrant model. In order to validate the model we designed synthesized and evaluated a new type of heteroaromatic N,P-ligands. The results obtained with these new complexes are in the range of best so far reported. With the aid of calculations we have established a deeper understanding of the selectivity and reactivity governing factors involved in these kinds of hydrogenations. The calculations can be used as a tool in designing new and even more efficient catalytic systems.

3.3 Design and Modifications Leading to Second Generation Ligands (Paper V)

Encouraged by the results from the oxazole based ligands we became interested in further investigating the structure-selectivity relationship of these systems. We therefore decided to develop a new set of ligands that relies on
the same structural principle (Figure 18). These new ligands are highly modular and allow for the late stage diversity of the structure. The structural variations can be used to study how structural changes influences the enantioselectivity of the hydrogenation. Moreover the selectivity model derived in this study can be used to rationalize the results. The preparation of thiazoles is much more expedient than oxazoles and introduction of a halogen at the 2-position allows for more structural variation in the ligand structure. It was also desirable to change the labile P-O bond into the more stable P-CH$_2$ bond and thereby gain a more stable ligand structure compared to the previously utilized ligands (Figure 18).

Figure 18. Synthetic modifications on first generation ligands.

Retrosynthetic analysis of A suggests that, after removal of the tosylate group, reduction of an ester to get the corresponding bromoalcohol, followed by a diazotation to introduce the halogen at the 2-position on an amino thiazole. The thiazole ring is then constructed by a Hantzsch condensation with a bromoketone and thiourea. As it is known in literature that -keto esters are brominated at the least substituted activated position by Br$_2$ under anhydrous acidic conditions, the bromoketone can be synthesized by direct bromination of commercially available ethyl 2-oxocyclohexane carboxylate 119 (Scheme 22).

Scheme 22. Retrosynthetic analysis of intermediate A.

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3.4 Synthesis and Evaluation of Second Generation Ligands

3.4.1 Initial Study, Variation of Backbone Ring Size

To systematically vary the critical selectivity governing factors of the ligand structure, we started to evaluate the importance of the cyclic backbone by calculating the distance between the \emph{ipso}-carbon of the substituent in the 2-position on the heterocycle and the Ir atom. These calculations were performed on five, six and seven membered cyclic backbones as well as for the oxazole complex (Figure 19).

![Figure 19. Calculated complex structures, from left thiazole complex five (a) six (b) and seven (c) membered cyclic backbone and the oxazole complex (d).](image)

The calculated structures showed a large difference between the five and six membered ring size and a smaller difference between the six and seven membered rings, suggesting that altering the ring size of the backbone may have a major impact on the stereochemical outcome. It is also favorable to
change the oxygen atom to a sulfur in the heterocyclic backbone since this results in a shorter distance between the ipso-carbon and the Ir atom, resulting in a more congested complex.

To investigate any differences between the five-, six-, and seven-membered cyclic backbone, the ligands were synthesized and the corresponding Ir-complexes evaluated in the hydrogenation of olefins. Synthesis of the complexes, starts with treatment of 119-121 with Br2 \( \text{[133]} \) followed by a Hantzsch condensation with PhC(S)NH\(_2\) to give the corresponding thiazole esters 122-124. Reduction of 122-124 with LiAlH\(_4\) gave the corresponding racemic alcohols 125-128 in good yields, followed by resolution of racemates 125-128 into their enantiomers by preparative chiral HPLC (Chiracel OD). The resolved alcohols were then converted to their corresponding tosylates 129-131, followed by substitution with Ph\(_2\)P(BH\(_3\))Li and deprotection with Et\(_2\)NH gave the free phosphines 135-137, which were subsequently transformed into their corresponding Ir-complexes 138-140 according to the standard procedure (Scheme 23). \( \text{[108]} \)

Initial hydrogenation results revealed a difference in selectivity between complexes 138-140, with complex 139 as the overall most selective catalyst (Table 9). For substrate 110 (Entry 1) a slight effect on enantioselectivity could be detected at 10 bars, in favor of catalyst 139 over 138 and 140. However, at 50 bars (Entry 2) the structural differences between the catalysts do not affect the enantioselectivity for substrate 110; this was also the case
for substrate 111 (Entry 3). For substrate 117 (Entry 4), catalyst 139 is superior to 138, and slightly better than 140. Substrate 118 gave, as expected, close to racemic material and low conversions, (Entry 5), in agreement with the selectivity model (Figure 14, Chap. 3.2).

Table 9. Comparison between Catalysts 138-140 and the corresponding Oxazole complex 106.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>138 conv.(%)</th>
<th>ee (%)</th>
<th>139 conv.(%)</th>
<th>ee (%)</th>
<th>140 conv.(%)</th>
<th>ee (%)</th>
<th>106 conv.(%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MePhPh</td>
<td>&gt;99</td>
<td>94 (S)</td>
<td>&gt;99</td>
<td>98 (S)</td>
<td>&gt;99</td>
<td>98 (S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MePhPh</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PhMeO-C$_6$H$_4$Me</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph$_2$CO$_2$Et</td>
<td>99</td>
<td>86 (S)</td>
<td>&gt;99</td>
<td>98 (S)</td>
<td>99</td>
<td>95 (S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph$_2$CO$_2$Et</td>
<td>99</td>
<td>3 (R)</td>
<td>85 rac.</td>
<td>97</td>
<td>3 (S)</td>
<td>50 rac.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conditions: $^a$Pressure 10 bar (entry 1) 50 bar (entries 2-6); All reactions were performed at room temperature over night; Catalyst loading 0.5 mol% in all entries. All reactions were performed in freshly distilled (CaH$_2$, ethanol free) CH$_2$Cl$_2$ as 0.25 M solutions.$^{b}$ Reaction time 2h.

The results in Table 9 show that a six-membered cyclic backbone is preferable and also the thiazole moiety proved to be much better than the oxazole for some substrates. Therefore a synthetic protocol, that allows for more structural variations, leading to the enantiomerically pure six-membered cyclic backbone was developed (Scheme 30, Chap. 3.4.2).

3.4.2 Synthesis of Enantiomerically Pure Six Membered Ring Backbone Ligands

To obtain ligands having more structural variations, compared to the ligands synthesized in the initial study (Chap. 3.4.1) the use of thiobenzamide had to be omitted. Instead Hantzsch condensation between 141 and thiourea was utilized (Scheme 24). With the encouraging results from the initial hydrogenations (Table 9, Chap. 3.4.1) the synthesis of second generation ligands was outlined in the following way: bromination of ketoester 120 with Br$_2$ in anhydrous Et$_2$O at 0 °C gave the corresponding 3-bromo derivative 141 in
almost quantitative yield. Treatment of 141 with thiourea in absolute ethanol at room temperature gave aminothiazole hydrobromide 143 in excellent yield.\[^{[134, 135]}\]

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{N} \\
\text{Br} & \quad \text{Br} & \quad \text{NH}_3\text{Br} & \quad \text{NH}_2 \\
\end{align*}
\]

Reagents and conditions: \(|i| \text{Br}_2, \text{Et}_2\text{O}, 0^\circ\text{C}, 3\text{h}, 95\%; |i| \text{thiourea, abs. EtOH, rt, 18h, 94\%; |i| K}_2\text{CO}_3 \text{(aq.), CHCl}_3, 40^\circ\text{C}, 30 \text{min., quantitative.}|


A question mark in the synthesis of the second generation ligands was when, and how, to introduce the chiral center. The initial synthetic study (Scheme 23, Chap. 3.4.1) established that a hydroxy intermediate i.e. 126 easily could be resolved by preparative chiral HPLC. Such a methodology is considered as a serious drawback, thus we synthesized rac-145 (Scheme 25) and investigated lipase-catalyzed kinetic resolution of rac-145 as a possible route into enantiopure material.\[^{[136, 137]}\]

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{S} & \quad \text{S} & \quad \text{S} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{Br} & \quad \text{Br} & \quad \text{Br} \\
\end{align*}
\]

Reagents and conditions: \(|i| \text{HBr, CuBr}_2, \text{t-BuONO, MeCN, 0^\circ\text{C}, 2h, 78\%; |i| 2.2 \text{equiv. DIBAL, THF, -40^\circ\text{C}, 1.5h, 85\%|}


Several different lipases were evaluated for the kinetic resolution of racemic 145, but the selectivities achieved were low. The step forward came when it was found that racemic aminothiazole 143 could be resolved as its dibenzoyl tartaric acid salt (Scheme 26). This is, according to our knowledge, the first example of a resolution of a chemical compound by salt formation on a remote aminothiazole moiety. The free base 143 was then resolved as its (L)-dibenzoyltartrate salt, formed by addition of (L)-DBTA·H$_2$O to 146 in a carefully controlled volume of hot 80% aqueous MeCN. The resolution step was optimized in terms of mass yield and enantioselectivity by initial DoE screening, followed by steepest ascent method.\[^{[138]}\] It was found that the yield of pure 146 could be increased even further from 37% up to 42%, but at the cost of the robustness. The reaction conditions giving 37% yield proved to be the best compromise, producing a crystal crop of 95-98% enantiomeric

Best result: *Pseudomonas Cepacia*, vinyloctanoate, rt. \(_i\)-Pr$_2$O, \(E = 9\).
excess, directly from the racemic mixture, if filtered at the right temperature. One single recrystallization yielded material of more than 99% enantiopurity. Treatment of 146 with aqueous potassium carbonate gave the enantiopure free base 147. The unwanted enantiomer of 147, could be recycled by racemization employing a catalytic amount of sodium ethoxide in refluxing absolute ethanol (typically 2 hours and 5 mol% sodium ethoxide).

**Scheme 26. Resolution of 143.**

At this point in the synthetic sequence it was necessary to investigate if, as originally planned, tosylate rac-148 could undergo nucleophilic displacement with Ph2P(BH3)Li directly on the tosylate (Scheme 27, A), or if nucleophilic displacement would take place on the heterocycle instead (Scheme 27, B). It was found that the only product obtained was formed from nucleophilic displacement on the heterocycle. The original idea with a single intermediate, only two steps from the final ligand, had to be changed.

**Scheme 27. Nucleophilic displacement with Ph2P(BH3)Li on rac-148.**

Converting 147 in situ to its hydrogen bromide salt, followed diazotation under anhydrous conditions employing t-BuONO in acetonitrile with CuBr₂ as halogen source, gave enantiomerically pure 144 in good yield (Scheme 25).[139] Intermediate 144 could then be converted either into bromothiazole alcohol 145 by treatment with two equivalents of DIBAL at -40 °C, or into the debrominated 2-H-thiazole derivative 149 by the action of excess DIBAL at 0 °C. (Scheme 28).[140]
Compound **145** smoothly underwent Suzuki coupling with PhB(OH)₂ according to a standard protocol, which gave **126** in high yield. No racemization of any of the enantiomerically pure material could be detected by chiral HPLC during the synthetic sequence. Alcohols **126** and **149** were then converted into their corresponding tosylates **130** and **150** in good yields (Scheme 29).

Treatment of tosylates **126** and **150** with Ar₂P(BH₃)Li at 0 °C, followed by stirring at room temperature overnight in THF/DMF yielded P-borane protected phosphines **133** and **151-153** in high yields. At this point, **133** and **151-153** are completely stable to hydrolysis and oxidation, compared to the first generation phosphinite ligands. Removal of the borane-protecting group by stirring in neat Et₂NH gave the deprotected phosphines **135** and **154-156**. Complex formation according to the previously employed protocol worked excellent, and complexes **139** and **157-159** were isolated in high yields (Scheme 30).
Reagents and conditions: i) Ar$_2$P(BH$_3$)$_2$, n-BuLi, THF, DMF, -78°C to rt, 16h; ii) Et$_2$NH (large excess), 18h, rt; iii) [IrCl(COD)$_2$, CH$_2$Cl$_2$, reflux 30 min, then H$_2$O, NaBArF•3H$_2$O, rt, 1h.


As all attempts to obtain crystals suitable for single crystal X-ray analysis from aminothiazole-(L)-DBTA salt 146 failed, thus a heavier atom derivative was considered instead. Treatment of 147 with one equivalent tosyl chloride in pyridine gave ca 45% yield of the bis-tosylated aminothiazole 160, and only a trace of the originally considered mono-N-tosylated derivative (Scheme 31). Increasing the amount of tosyl chloride to 2.1 equivalents yielded the highly crystalline bis-tosylate 160 in excellent isolated yield.

Scheme 31. Synthesis of heavy atom derivative 160 for determination of absolute configuration by single crystal X-ray diffraction.

The absolute configuration of 147, determined via its derivative 160, proved to be (S) (Figure 20). Comparison of the HPLC elution order and optical rotation of the five, six and seven membered structures also established (S)-configuration of the five and seven membered structures.
3.4.3 Results and Discussion

The new complexes 139 and 157-159 also proved to be highly efficient, for the asymmetric hydrogenation of a vide variety of tri-substituted olefins (Table 10). As expected, the steric bulk of the heteroaromatic substituent is important for achieving high enantioselectivity, which is clearly seen in (Entry 1) for substrate 110, where a remarkable drop in enantioselectivity is observed for complexes 158 and 159, lacking the phenyl group. Also the size of the phosphine substituents, occupying the semi-hindered quadrant, is of importance for some substrates like 111 and 161 (Entries 2 and 3) where changing from 139 into 157 leads to a dramatic loss of enantioselectivity in both cases. One example of an electron rich enol ether is included in the study, substrate 162 (Entry 4) clearly demonstrating its mesomeric effect, leading to low conversion and poor enantioselectivity. Between Entries 5 and 6, a slight change of a single methoxy group makes a large difference in enantioselectivity between substrates 113 and 163 for complex 139. Allylic alcohol 115 (Entry 8) worked surprisingly well with all complexes. Allylic acetate 116 (Entry 9) gave disappointingly low conversions with all of the evaluated complexes and poor enantioselectivity, with reversed asymmetric induction than expected. This was unexpected as substrate 116 provided excellent results with the oxazole phosphinite complexes 106-108 (Table 8, Entry 7, Chap. 3.2.2). Ethyl -methyl trans-cinnamate 165 (Entry 10) gave good enantioselectivities with o-Tol-complexes 157 and 159, while its cyclic analogue 166 (Entry 11) gave low conversions and poor enantioselectivity.
Only for substrate 118 (Entry 12) did the 2-H-thiazole complexes 158 and 159 prove to be superior, giving high conversions and excellent enantioselectivities for this previously very unreactive substrate. Substrate 117 (Entry 13) gave excellent conversions and enantioselectivities with all complexes.

Table 10. Asymmetric hydrogenation with complexes 139 and 157-159.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>139 conv.(%):</th>
<th>ee (%)</th>
<th>157 conv.(%):</th>
<th>ee (%)</th>
<th>158 conv.(%):</th>
<th>ee (%)</th>
<th>159 conv.(%):</th>
<th>ee (%)</th>
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<td>&gt;99</td>
<td>&gt;99 (S)</td>
<td>&gt;99</td>
<td>77 (S)</td>
<td>&gt;99</td>
<td>48 (S)</td>
</tr>
<tr>
<td>2</td>
<td>p-MeO-C6H4</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99</td>
<td>58 (S)</td>
<td>&gt;99</td>
<td>98 (S)</td>
<td>&gt;99</td>
<td>30 (S)</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>99</td>
<td>60 (S)</td>
<td>35</td>
<td>16 (S)</td>
<td>30</td>
<td>rac.</td>
</tr>
<tr>
<td>4</td>
<td>MePhMe</td>
<td>162</td>
<td>16</td>
<td>35³</td>
<td>rac.</td>
<td>11</td>
<td>2³</td>
<td>10</td>
<td>rac.</td>
</tr>
<tr>
<td>5</td>
<td>MeO</td>
<td>&gt;99</td>
<td>93 (R)</td>
<td>99</td>
<td>31 (R)</td>
<td>&gt;99</td>
<td>78 (R)</td>
<td>&gt;99</td>
<td>40 (R)</td>
</tr>
<tr>
<td>6</td>
<td>MeO</td>
<td>163</td>
<td>99</td>
<td>55 (R)</td>
<td>99 (S)</td>
<td>74</td>
<td>50 (R)</td>
<td>90</td>
<td>15 (R)</td>
</tr>
<tr>
<td>7</td>
<td>MeO</td>
<td>164</td>
<td>99</td>
<td>98 (S)</td>
<td>99 (S)</td>
<td>99</td>
<td>26 (S)</td>
<td>99</td>
<td>rac.</td>
</tr>
<tr>
<td>8</td>
<td>PhMeOH</td>
<td>115</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99 (S)</td>
<td>&gt;99</td>
<td>99 (S)</td>
<td>&gt;99</td>
<td>99 (S)</td>
</tr>
<tr>
<td>9</td>
<td>PhMeOAc</td>
<td>116</td>
<td>6</td>
<td>64 (R)</td>
<td>8</td>
<td>72 (R)</td>
<td>8</td>
<td>65 (R)</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>PhMeOAc</td>
<td>165</td>
<td>&gt;99</td>
<td>40 (S)</td>
<td>&gt;99 (S)</td>
<td>&gt;99</td>
<td>80 (S)</td>
<td>50</td>
<td>40 (S)</td>
</tr>
<tr>
<td>11</td>
<td>PhMeOAc</td>
<td>166</td>
<td>5</td>
<td>72³</td>
<td>47</td>
<td>46³</td>
<td>21</td>
<td>32</td>
<td>rac.</td>
</tr>
<tr>
<td>12</td>
<td>PhMeOAc</td>
<td>118</td>
<td>85</td>
<td>rac</td>
<td>99 (R)</td>
<td>99</td>
<td>95 (R)</td>
<td>99</td>
<td>95 (R)</td>
</tr>
<tr>
<td>13</td>
<td>PhMeOAc</td>
<td>117</td>
<td>&gt;99</td>
<td>98 (S)</td>
<td>&gt;99 (S)</td>
<td>98</td>
<td>98 (S)</td>
<td>91</td>
<td>87 (S)</td>
</tr>
</tbody>
</table>

Absolute configurations of products given in paranthesis after ee-value. *Absolute configuration not known. Conditions: Pressures: 50 bar in all entries; All reactions were performed at rt. for 2 h., except entries 8 and 12 were reactions were ran o.n. instead; Catalyst loading 0.5 mol% in all entries, except 10-13 where 1 mol% were used. All reactions were performed in freshly distilled (CaH2, ethanol free) CH2Cl2 as 0.25 M solutions.
3.4.4 Further Refinements of the Selectivity Model

The different geometrical variations of cinnamyl esters enables us to derive a further refined selectivity model. In order to do so, calculations where first performed on the full-sized catalyst 139, with 110 as the substrate to validate the already proposed model. Adding a quadrant scheme over the catalyst with the olefin coordination site centered over the origin in front of the iridium atom (c.f. Figure 14, Chap. 3.2), creates a almost perfect chiral pocket to host tri-substituted trans-olefins (Figure 21).

The bulky substituent in the 2-position of the heterocycle on the ligand creates an almost perfect pocket; especially well adapted to host tri-substituted olefins. In this case the least sterically demanding substituent i.e. the proton, will face the steric bulk of the ligand. The catalyst then offers two open sites, located in a *trans* position to each other, and a forth site facing one of the aryl groups of the phosphine. This forth site can accommodate smaller olefin substituents.

Coordination of a olefin into the empty quadrant model, reveals that the olefin will preferentially coordinate to the catalyst from the Re-side, as the opposite coordination mode will result in unfavorable interactions between one of the large *trans*-substituents with the steric bulk of the ligand. This determines the stereochemical outcome of the reaction and sets the facial recognition of an electronically neutral tri-substituted olefin.

Substrates possessing a polarized double bond, such as _-unsaturated esters add a complicating electronic effect. DFT-calculations with methyl *trans-* -methyl cinnamate 116 show a strong preference for _-addition of the hydride in the migratory insertion step (13 kcal mol⁻¹) whereas calculations on the oxazole complex 105 revealed that this preference is about 5 kcal mol⁻¹ for this complex. The migration of the substrate into the Ir-H bond leads to a tilt of the C-C double bond towards the hydride. For steric reasons, this means that migratory insertions into an axial hydride pointing up will be preferred over insertion into an axial hydride pointing down, since the former leads to a less congested transition state where the substrate is moving away from the close proximity of the phenyl ring on the thiazole. For sub-
strate **117** this results in TS **A** which is both sterically as well as electronically favored over TS **B** (Figure 22). As seen -addition is much more favored than -addition, resulting in a lower energy of the TS due to minimized steric repulsions and a matched electronic polarization of the substrate.

![Figure 22. Calculated enantio-determining migratory-insertion TS of methyl trans-\(\text{methyl cinnamate}\) (A) Sterically and electronically favored -addition. (B) Sterically and electronically unfavored -addition.](image)

In the case of methyl trans-\(\text{methyl cinnamate}\), **165**, a -addition of the hydride will require a migratory insertion step in an iridium-hydride bond pointing in the same direction as the steric bulk of the thiazole moiety (Figure 23, **D**). Thus, there will be a substantial steric interaction between substrate and catalyst. For this substrate the steric and electronic effects will be mismatched and result in a reduced reaction rate and a deterioration of the enantioselectivity. Competitive experiments between the two substrates revealed that **117** was indeed hydrogenated 6.7 times faster than **165**.
This gives another tool for predicting enantioselectivity and reactivity of substrates towards asymmetric hydrogenation by Ir-(N,P) systems. For successful reaction, a steric and electronic match between substrate and catalyst is necessary. This fact can be rationalized by the addition of a direction to the enantio-determinating migratory insertion step, in the quadrant selectivity model. A substrate possessing a conjugated electron-withdrawing group (EWG) will show a strong -preference for the initial hydride addition (Figure 24). Substrate 165 orients into a sterically matched but electronically mis-matched orientation hence the lower selectivities obtained with this substrate compared to 117. Substrate 117 however possesses perfect overlap for catalysts 139 and 157 resulting in exceptionally high selectivity for those catalysts (Figure 24).
3.4.5 Conclusions

In conclusion, we have developed a new type of heterocyclic (N,P)-ligands for the asymmetric Ir-catalyzed hydrogenation of olefins. The results, in terms of enantioselectivities for typically difficult substrates, are among the best reported so far. The results obtained for the second-generation thiazole ligands have allowed a more detailed selectivity model to be derived, revealing the relation between steric and electronic effects and their importance for activity and enantioselectivity. The effect of the substituent on the thiazole ring, which is situated in the blocked quadrant, was also studied and it was found that its presence is important for the stereoselectivity of the catalysts. Decreasing the bulk of this substituent generally results in decreased ee of the products with the exception of cis-substrates, which are better accommodated in catalysts having a small substituent on the thiazole ring.
3.5 Chiral NHC Phosphine Ligands in Ir-Catalyzed Hydrogenation of Olefins (Paper VI)

N-heterocyclic carbenes (NHCs) and their transition metal complexes have recently attracted much interest in organic and organometallic chemistry. Due to strong carbon-metal bonds NHCs are well suited to act as ligands in various transition metal catalyzed reactions. The organometallic complexes derived from NHC tends to be air stable and the carbene binds to the metal more strongly than electron rich phosphines. Their powerful donating and weak accepting properties results in metal centers that are electron rich compared to the corresponding phosphate complexes. Chiral imidazolylidenes were first reported several decades ago by Müller et al. and several others have been reported more recently. Even so, there has been relatively few reports on optically active electron rich carbene ligands in asymmetric catalysis; some examples include Ru-catalyzed methathesis, Rh-catalyzed hydrosilylation, and conjugate addition of arylboronic acid derivatives to enones.

Recently, Burgess et al. reported that chiral Ir-imidazol-2-ylidene-oxazoline complexes can be used for the asymmetric hydrogenation of olefins with great success, ee’s over 99% were obtained. Complexes containing carbene based ligands tend to be highly active in oxidative addition reactions and hence are attractive alternatives to phosphine based ligand systems. Inspired by this we decided to synthesize an imidazole analogue of our phosphine-thiazole ligand (Scheme 30, Chap. 3.4.2). We reasoned that exchanging the diaryl phosphine with a sterically less bulky N-phenyl-imidazole would reduce the steric bulk located in the semi-hindered quadrant in the selectivity model (Figure 24, Chap. 3.4.4). This might lead to improved enantioselectivity for more bulky substrates like 4-methyl-1,2-dihydro-naphthalene.

3.5.1 Synthesis of Ligands

The synthesis of the new NHC ligand starts from tosylate via a Finkelstein reaction by treatment with 5 eqv. Nal in refluxing acetone. Nucleophilic substitution with N-phenyl-imidazole (1 eqv.) proceeded smoothly in DMF at 60°C for 48 h and gave in reasonable yield (Scheme 32). Complex formation was accomplished by dissolving the ligand, [IrCl(COD)], and tert-BuOLi, to generate the carbene, in refluxing THF for 1 h. and then stirring at rt o.n. The solvent was then evaporated and the residue dissolved in 5 ml CH2Cl2, ion exchange was accomplished by addition of 2 ml H2O followed by 1.2 eqv. of NaBArF and stirring vigorously for 30 min. This gave complex in 30% isolated yield (Scheme 32).
Scheme 32. Synthesis of Ir-complex 171.

The major byproduct observed in this reaction was the elimination product 170 (Scheme 33).

Scheme 33. Nucleophilic substitution between iodide 163 and N-phenyl-imidazole under different conditions.

DFT-calculations on this complex suggests that the semi-hindered quadrant in this new carbene complex differs from thiazole complex 139 (Figure 25).
3.5.2 Results and Discussion

This new complex proved to be efficient in the hydrogenation of various standard substrates with ee’s ranging from 34 to 90 % (Table 11). Hydrogenation of 110 at different pressures of H₂ showed 50 bars to be optimal for this substrate and this pressure was therefore used for all subsequent experiments. Substrate 163 (Entry 6) was reduced with better enantioselectivity, 70% ee, than for the previously used phosphine thiazole complexes, 55% ee. Presumably due to the less sterically hindered semi-hindered quadrant that in this system can accommodate more bulky substituents. Interestingly, with this complex tetra-substituted olefins (Entry 5) showed no conversion at all under the conditions used. Substrate 173 (Entry 11) was reduced with both low selectivity and conversion. This is probably due to an electronic mismatch of the polarization over the double bond. The differences in enantioselectivity compared to the phosphine-thiazole complexes may be explained by the fact that the N-phenyl-imidazole provides a less efficient chiral environment around the Ir atom for the substrates that do not provide enough steric bulk themselves. Substrates 163 and 118 (Entries 6 and 9) orientate the R₂-substituent into the semi-hindered quadrant and we find that catalyst 171 performs better when compared to 139. Also substrates, trans- (117) and cis- (118) -methyl cinnamate (Entries 8 and 9) show reversed enantiofacial selectivity when compared to the phosphine thiazole complexes. A reason for this might be that the complex forms a seven membered chelate and that the semi-hindered quadrant is more open as compared to the phosphine thiazole ligand 139, thus opening for a different geometrical orientation of these substrates around the Ir atom.
3.5.3 Conclusions

In conclusion we have synthesized and evaluated a new Ir-NHC thiazole complex in the asymmetric hydrogenation of olefins. This new complex proved to be efficient in the hydrogenation of various tri-substituted olefins, with ee values ranging from 34 to 90% depending on the geometry around the double bond in the substrates. We were also able to show that increasing
the chelate size, from a six to seven-membered ring, and decreasing the steric bulk in the semi-hindered quadrant of the selectivity model is beneficial for substrates that contain bulky substituents.

3.6 Expanding the Substrate Scope in the Ir-Catalyzed Hydrogenation (Paper VII)

As mentioned earlier the asymmetric Ir-catalyzed hydrogenation of olefins is to date highly substrate demanding. This can be due to a number of reasons but mainly two distinct factors can be recognized.

1. The catalysts, so far developed, only tolerate a narrow scope of substrates.
2. Very little effort has been put into the search for new suitable substrates.

With a few exceptions the substrates used have been limited to substituted styrenes, dihydro naphthalenes, various derivatives of cinnamyl esters and their corresponding alcohols. Knochel *et al.*, \[118\] has reported asymmetric hydrogenation enamides utilizing Ir-catalyzed hydrogenation. Also very recently Pfaltz *et al.*\[154\] reported that simple alkenes, having no aromatic moiety, worked well as substrate for this kind of asymmetric hydrogenation.\[155\] Another important class of substrates that has shown to give high selectivity and activity is imines and quite a few reports of Ir-catalyzed asymmetric hydrogenation of imines\[156, 157\] and substituted pyridines\[158\] can be found in the literature.\[6\]

We decided to synthesize a range of vinyl silanes that has, to the best of our knowledge, never been used as substrates in any asymmetric hydrogenation before. In order to find a catalyst that can hydrogenate these substrates with both satisfactory rate and enantioselectivity, we started with a comparison of three different ligand classes, thiazole complex 139, Pfaltz Ir-PHOX complex 92\[108\] and the phosphine-oxazoline complex 174, previously used by our research group in Ir-catalyzed asymmetric hydrogenation of imines (Figure 26).\[157\]

![Figure 26. Ir-complexes used for asymmetric hydrogenation of vinyl silanes.](image-url)
3.6.1 Results and Discussion

The results of the hydrogenations of vinyl silanes are summarized in Table 12. All of the catalysts evaluated gave full conversion within 12 h. Complex 139 proved to induce the highest enantioselectivity of the evaluated substrates. Complexes 92 and 174 hydrogenated substrate 175 (Entry 1) with slightly lower selectivities 25 % and 26 % respectively, when compared to complex 139, 28%. When the TMS group was moved into the non prochiral position (Entry 2), complex 139 still proved to be the most selective catalyst (98% ee), although to our surprise Pfaltz Ir-PHOX complex 92 resulted in racemic product, whereas complex 174 gave a slightly lower ee (96%). Complex 139 was therefore evaluated with a range of vinyl silanes.

Table 12. Asymmetric reduction of vinyl silanes.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>92</th>
<th>139</th>
<th>174</th>
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<tbody>
<tr>
<td></td>
<td>conv. (%)</td>
<td>ee (%)</td>
<td>conv. (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>&gt;99</td>
<td>25 (R)</td>
<td>&gt;99</td>
<td>28a (S)</td>
</tr>
<tr>
<td>2</td>
<td>rac.</td>
<td>&gt;99</td>
<td>98a (R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>&gt;99</td>
<td>58a (S)</td>
<td></td>
</tr>
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<td></td>
<td>&gt;99</td>
<td>48a (-)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>&gt;99</td>
<td>55a (+)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>99</td>
<td>70b (S)c</td>
<td></td>
</tr>
</tbody>
</table>

Conditions: Pressures: 50 bar in all entries; All reactions were performed at rt. for 12 h.; Catalyst loading 0.5 mol% in all entries. Reactions were performed in freshly distilled (CaH2, ethanol free) CH2Cl2 as 0.25 M solutions. GC-MS (G-TA, 90 °C, 20 min, 100 kPa). Determined by conversion into chiral alcohol. The abs. config. were determined by optical rotation.

The observed range in selectivities can be rationalized by the previously derived selectivity model (Figure 24, Chap. 3.4.4). With a substrate such as 175 (Entry 1) one is unable to successfully arrange the TMS and phenyl groups, into electronic and steric favorable arrangement. Instead such a substrate will be arranged onto the catalyst in an electronically match but a sterically mismatched fashion. These unfavorable interactions result in an observed ee of only 28%. Compared with substrate 176 (Entry 2) where the
bulky substituents are able to occupy the two open quadrants on the selectivity model in both a sterically and electronically favorable arrangement, resulting in an observed ee of 98% of the predicted, correct absolute configuration. Interestingly substrate 179 (Entry 5) is one of the few examples known where the substrate lacks an aromatic substituent. Unfortunately we were unable to separate the cis and trans isomers obtained in the synthesis of this substrate, hence the low enantioselectivity reported. The lower selectivity obtained with substrate 180 (Entry 6) is in agreement with the findings that substrates possessing a polarized double bond, like unsaturated esters and vinyl silanes, add a complicated electronic effect. As mentioned before DFT-calculations on trans- -methyl cinnamate suggest a strong preference for -addition of the hydride in the migratory insertion step whereas for trans- -methyl cinnamate this preference is substantially lower leading to lower enantioselectivity for this substrate. We have reasons to believe that this is also the case for the electron withdrawing vinyl silanes.

In conclusion we have performed the first successful hydrogenation of a range of vinyl silanes and shown that the reduction of simple olefins need not be restricted to the model substrates that so far have dominated the field of Ir- catalyzed asymmetric hydrogenations. The catalyst used in this study is sensitive to unfavorable steric interactions, which can be rationalized via our proposed selectivity model, resulting in a loss of selectivity.

3.6.2 Conclusions

In conclusion we have performed the first successful hydrogenation of a range of vinyl silanes and shown that the reduction of simple olefins need not be restricted to the model substrates that so far have dominated the field of Ir- catalyzed asymmetric hydrogenations. The catalyst used in this study is sensitive to unfavorable steric interactions, which can be rationalized via our proposed selectivity model, resulting in a loss of selectivity.
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Last but not least: My parents Jan-Erik and Birgitta and my wife Nina.
5 References


[26] Examples of such companies are: Solvias AG, Chirex Rhodia, Chimia Spa, Takasago, Degussa, OMG and others.


[130] Crystallographic data compounds 109 and 160 have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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