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Asymmetric Hydrogenations of Imines, Vinyl Fluorides, Enol Phosphinates and Other Alkenes Using N,P-Ligated Iridium Complexes

JARLE SIDNEY DIESEN



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Abstract

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The research described in this thesis is directed toward the efficient, enantioselective synthesis of chiral products that have useful functionality. This goal was pursued through catalytic asymmetric hydrogenation, a reaction class that selectively introduces one or two stereocenters into a molecule in an atom-efficient step. This reaction uses a small amount (often <1 mol%) of a chiral catalyst to impart stereoselectivity to the product formed. Though catalytic asymmetric hydrogenation is not a new reaction type, there remain many substrate classes for which it is ineffective. The present thesis describes efforts to extend the reaction to some of these substrate classes. Some of the products synthesized in these studies may eventually find use as building blocks for the production of chiral pharmaceuticals, agrochemicals, or flavouring or colouring agents. However, the primary and immediate aim of this thesis was to develop and demonstrate new catalysts that are rapid and effective in the asymmetric hydrogenation of a broad range of compounds.

Paper I describes the design and construction of two new, related chiral iridium compounds that are catalysts for asymmetric hydrogenation. They each contain an N,P-donating phosphinoxazoline ligand that is held together by a rigid bicyclic unit. One of these iridium compounds catalyzed the asymmetric hydrogenation of acyclic aryl imines, often with very good enantioselectivities. This is particularly notable because acyclic imines are difficult to reduce with useful enantioselectivity. The second catalyst was useful for the asymmetric hydrogenation of two aryl olefins. In Paper II, the class of catalysts introduced into Paper I is expanded to include many more related compounds, and these are also applied to the asymmetric hydrogenation of prochiral imines and olefins. By studying a range of related catalysts that differ in a single attribute, we were able to probe how different parts of the catalyst affect the yield and selectivity of the hydrogenation reactions.

Whereas iridium catalysts had been applied to the asymmetric hydrogenation of imines and largely unfunctionalized olefins prior to this work (with varied degrees of success), they had not been used to reduce fluoroolefins. Their hydrogenation, which is discussed in Paper III, was complicated by concomitant defluorination to yield non-halogenated alkanes. To combat this problem, several iridium-based hydrogenation catalysts were applied to the reaction. Two catalysts stood out for their ability to produce chiral fluoroalkanes in good enantioselectivity while minimizing the defluorination reaction, and one of these bore a phosphinoxazoline ligand of the type described in Papers I and II.

Enol phosphinates are another class of olefins that had not previously been subjected to iridium-catalyzed asymmetric hydrogenation. They do, however, constitute an attractive substrate class, because the product chiral alkyl phosphinates can be transformed into chiral alcohols or chiral phosphines with no erosion of enantiopurity. Iridium complexes of the phosphinoxazoline ligands described in Papers I and II were extremely effective catalysts for the asymmetric hydrogenation of enol phosphinates. They produced alkyl phosphinates from di- and trisubstituted enol phosphinate, β -ketoester-derived enol phosphinates, and even purely alkyl-substituted enol phosphinates, in very high yields and enantioselectivities.

Keywords: Catalysis, Asymmetric, Hydrogenations, Reductions, Alkenes, Imines, Vinyl fluorides, Enolphosphinates, Transition metal, Complexes, Iridium

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*First there is the forest
and inside the forest the clearing and
inside the clearing the cabin
and inside the cabin the mother and
inside the mother the child
and inside the child
the mountain.*

Jeanette Winterson, *Gut Symmetries* (1997)

Til mor og far

List of publications:

This thesis is based on the following papers:

- I Application of Phosphine-Oxazoline Ligands in Ir-Catalyzed Asymmetric Hydrogenation of Acyclic Aromatic N-Arylimines. Trifonova, Anna; **Diesen, Jarle S.**; Chapman, Christopher J.; Andersson, Pher G. *Org. Lett.* **2004**, *6(21)*, 3825-3827.
- II Hydrogenation of Imines and Olefins Using Phosphine-Oxazoline Iridium Complexes as Catalysts. Trifonova, Anna; **Diesen, Jarle S.**; Andersson, Pher G. *Asymmetric Chem. Eur. J.* **2006**, *12(8)*, 2318-2328.
- III Iridium-Catalyzed Asymmetric Hydrogenation of Fluorinated Olefins Using N,P-Ligands: A Struggle with Hydrogenolysis and Selectivity. Engman, M.; **Diesen, J. S.**; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536-4537.
- IV Asymmetric Hydrogenation of Di- and Trisubstituted Enol Phosphinates with N,P-Ligated Iridium Complexes. Pradeep Cheruku, **Jarle Diesen**, and Pher G. Andersson *J. Am. Chem. Soc.* **2008**, *130(16)*, 5595-5599.
- V Appendix: Supplementary information

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Publications not included in this thesis:

- Hydrogenation of unfunctionalised alkenes. **Jarle S. Diesen** and Pher Andersson, p. 39-64 (book chapter) in *Modern Reduction Methods*, by Andersson, Pher (editor) and Munslow, Ian (editor), Wiley VCH, Verlag GmbH & Co. KGaA, Weinheim **2008**, 522 pages. ISBN: 978-3527318629.
- Evaluation of the tracer-pulse method for high performance liquid chromatography combined with mass spectrometry. Validation of the tracer-pulse method for high performance liquid chromatography combined with mass spectrometry. Samuelsson, J., Arnell, R.; **Diesen, J. S.**; Tibbelin, J.; Paptckhikhine, A.; Fornstedt, T.; Sjöberg, P. *J. R. Anal. Chem.* **2008**, *80*, 2105-2112.

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Abbreviations

Ac	acetyl
Ar	aryl
BAr _F ⁻	<i>tetrakis</i> [3,5- <i>bis</i> (trifluoromethyl)phenyl]borate
bdpp	[(1 <i>R</i> ,3 <i>R</i>)-1,3-dimethyl-1,3-propanediyl]bis-(diphenylphosphine)
BINAP	(2 <i>R</i> ,3 <i>S</i>)-2,2'-bis(diphenylphosphine)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
<i>t</i> -Bu	<i>tert</i> -butyl
Cbz	benzyloxycarbonyl
<i>p</i> -NO ₂ -Cbz	<i>para</i> -nitrobenzyloxycarbonyl
COD	cyclooctadiene
Conv.	conversion
Cy	cyclohexyl
DET	diethyl tartrate
DIOP	[[<i>(4R,5R)</i> -2,3-dimethyl-1,3-dioxolane-4,5-diyl]- <i>bis</i> (methylene)] <i>bis</i> (diphenylphosphine)
DIPEA	diisopropylethylamine
DIPAMP	<i>bis</i> (methylphenyl- <i>ortho</i> -anizylphosphine)
DNA	deoxyribonucleic acid
DOPA	3,4-diol-phenylalanine
EDC	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide
<i>ee</i>	enantiomeric excess
<i>E</i>	Entgegen
Et	ethyl
GC	Gas Chromatography
HOBt	1-hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
Me	methyl
Ms	methane sulphonyl
NMR	Nuclear Magnetic Resonance
Ph	phenyl
<i>i</i> -Pr	<i>iso</i> -propyl
RNA	ribonucleic acid
<i>S/C</i>	substrate-to-catalyst ratio

stoich.	stoichiometric
Tf	trifluoromethane sulphonyl
TFA	trifluoroacetic acid
TOF	Turnover frequency
Ts	<i>p</i> -toluene sulphonyl
(<i>R,R</i>)-Walphos	(<i>R,R</i>)-1-[1-(Dicyclohexylphosphino)ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene

1 Introduction

The concept of chirality plays an important role in chemistry. Chiral objects are ubiquitous in Nature. Lord Kelvin (1824-1907) defined a chiral object as *any* object that is not superimposable on its mirror image.¹ The word *chiral* derives from the Greek word *cheir* ($\rho\epsilon\iota\chi$), meaning *hand*, and the term *chirality* refers to the "handedness" of an object — analogously to a hand, it cannot be placed on its mirror image so that all parts coincide.

According to the above definition, chirality is not confined to physics, chemistry or biology; it belongs to the area of geometry and the only requirement for an object to be chiral is the lack of a plane or axis of symmetry.² Any object that possesses one or both of these will be superimposable on its mirror image, and is called achiral. A chiral molecule and its mirror image are called *enantiomers*. Chiral objects exist on both microscopic and macroscopic levels (Figure 1).

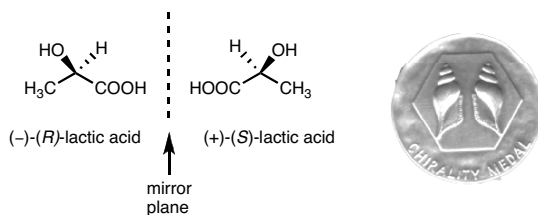


Figure 1. Chirality is encountered everywhere in Nature, as demonstrated by the enantiomers of a lactic acid molecule (left) and the enantiomorphous sea shells (right).

1.1 Stereochemistry

1.1.1 Historical development

Dominated by French scientists, the pioneering work in the field of stereochemistry started early in the nineteenth century. In 1801, the French mineralogist René-Just Haüy (1743-1822) observed that quartz crystals displayed

hemihedral phenomena.³ Another important contribution during this early stage was provided eight years later when Haüy's countryman, the physicist Étienne-Louis Malus (1775-1812), observed that quartz crystals could induce the polarization of light.³ Just a few years later, in 1812, Jean-Baptiste Biot (1774-1862), discovered the optical activity in nature.⁴ He demonstrated that a quartz plane rotated the plane of polarised light to an angle proportional to the thickness of the quartz plane. Three years later, he found that an analogous effect was also produced by some pure organic liquids and solutions.

Louis Pasteur (1822-1895), a student of Biot, obtained the first separation of enantiomers in 1848 when he managed to separate enantiomorphous crystals of the sodium ammonium salt of tartaric acid manually (Figure 2).⁵ Two years earlier he had observed that all the crystals of dextrotatory tartaric acid salt had hemihedral faces with the same orientation and thus assumed that the structure of the tartaric acid salt was related to its optical rotatory properties.

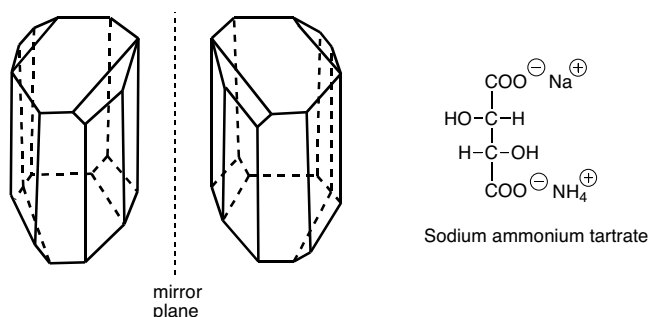


Figure 2. Pasteur separated the enantiomorphous crystals of sodium ammonium tartrate in 1848.

An important milestone was reached on the molecular level in 1874 when J. H. van't Hoff (1852-1911) and J. A. Le Bel (1847-1930) independently proposed a three-dimensional orientation of atoms.⁶ They claimed that the four bonds attached to a carbon atom were oriented tetrahedrally, and that the dissymmetry and optical rotation observed for organic compounds was caused by this tetrahedral arrangement. Seminal work was performed by the German chemist E. Fisher (1852-1919), who investigated the structure and stereochemistry of sugars in the end of the 1890s.⁷ In 1891 he had already made the decision to relate the configurations of optical isomers of compounds having chiral carbon atom(s) to that of glyceraldehyde.⁸

1.1.2 Chiral molecules – concepts and properties⁹

Chiral molecules rotate the plane of polarized monochromatic light - a phenomenon called *optical activity*. Two enantiomers rotate plane-polarized light to exactly the same degree, but in *opposite* directions. By convention, the the composition of a sample of enantiomers (i.e. its optical purity) is given by the enantiomeric excess (*ee*), a measure that describes the excess of one enantiomer over the other and is given by the following formula:

$$ee = \frac{|[R] - [S]|}{[R] + [S]} \cdot 100\%$$

where $[R]$ and $[S]$ are amounts of the two isomers. *Ee* values are usually determined by HPLC, GC, NMR and optical methods. Two enantiomers have identical physical and chemical properties when acting in a non-chiral environment; their differences appear only when interacting with other chiral species or with plane-polarized light. Biological systems are, in general, highly chiral as they are by and large composed of chiral molecules (e.g. DNA, RNA, sugars and proteins). For example, 19 of the 20 amino acids that make up natural proteins and enzymes are chiral. Consequently, a chiral compound will interact in a stereospecific manner with a living organism. This has been demonstrated for a variety of chemical species; a fragrance, flavor, drug etc. can trigger a completely different effect in a living biological organism (Figure 3) than its chiral sibling, which makes the field stereochemistry very important.

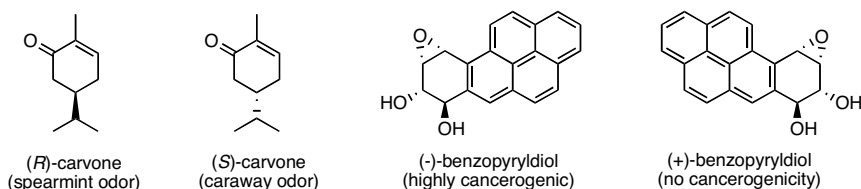


Figure 3. Examples of enantiomers that show different behavior *in vivo*.

One example of a drug that shows different effects *in vivo* in humans is Darvon.¹⁰ Darvon is a painkiller whereas its enantiomer, called Novrad, is an anticough agent (Figure 4).

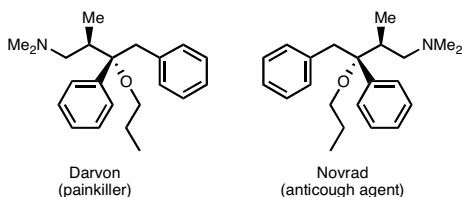


Figure 4. The enantiomers Darvon and Novrad show very different effects *in vivo* in humans.

The importance of obtaining enantiopure compounds is underlined by considering that ca. 80% of the active compounds produced by the pharmaceutical industry are chiral.¹¹

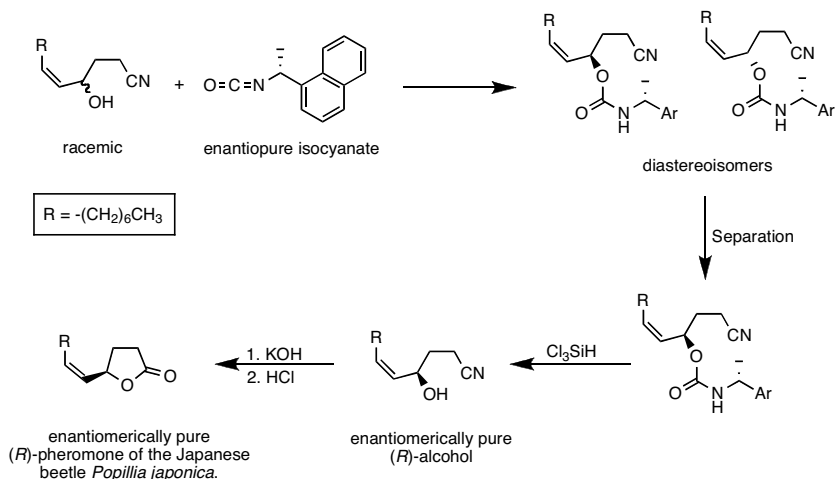
1.2 How to obtain enantiomerically pure compounds

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

- Resolution of racemates (a mixture of enantiomers);
- Chiral pool (naturally chiral starting materials);
- Asymmetric synthesis

1.2.1 Resolution of racemates

A classic strategy to obtain an enantiopure or enantioenriched compound is the resolution of racemates. In this method, a mixture of racemates is temporarily converted into diastereoisomers (often diastereoisomeric salts) through reaction with an enantiomerically pure compound. The resulting diastereoisomers possess different physicochemical properties, making their separation possible. An example is the resolution presented in Scheme 1.¹²



Scheme 1. The resolution of a racemic nitrilo alcohol used in the synthesis of the (R)-enantiomer of the pheromone from the Japanese beetle *Popillia japonica*. The (S)-enantiomer of the pheromone is biologically inactive.

The resolution of racemates suffers from several drawbacks: equimolar amounts of the enantiopure compound must be applied and can not always

be recycled and the maximum theoretical yield is only 50%. In addition, the resolution of racemates often requires more work compared to other available methodologies.

1.2.2 The “chiral pool” or “Chiron” approach¹³

The basis for the “chiral pool” (“Chiron”) approach is naturally occurring, chiral, non-racemic compounds that can serve as enantiomerically pure starting materials for synthesis. Nature provides such chiral species in several compound classes; amino acids, carbohydrates, terpenes and alkaloids play prominent roles in synthesis (Figure 5).

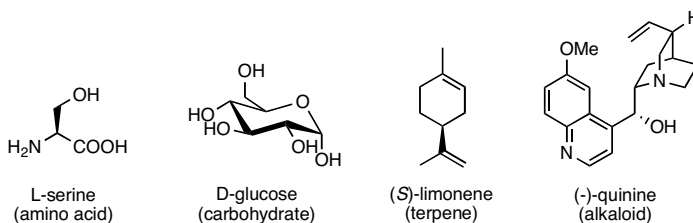
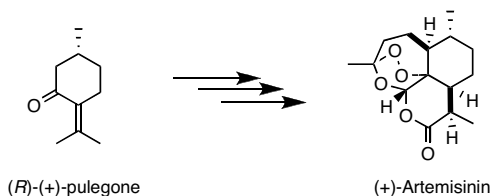


Figure 5. Some examples of naturally occurring chiral molecules that are useful in the synthesis using the Chiron approach.

Many compounds have successfully been synthesized by the chiral pool approach. An example is the synthesis of (+)-artemisinin, a potent anti-malaria agent, which is synthesized starting from the simple monoterpene (*R*)-(+)-pulegone (Scheme 2).¹⁴



Scheme 2. Synthesis of (+)-artemisinin starting from the naturally occurring monoterpene (*R*)-(+)-pulegone.

The limited number of starting materials available, including the lack of availability of both enantiomers provided by Nature, restricts the synthetic application of the chiral pool approach.

1.2.3 Asymmetric synthesis

A third approach to the production of chiral non-racemic molecules is asymmetric synthesis. This is a very effective methodology and has developed into the most commonly used strategy for obtaining chiral molecules. In order to produce an asymmetric product, at least one part of the reacting system must be chiral and non-racemic. Hence, one can use a chiral substrate, a chiral auxiliary, a chiral reagent or a chiral catalyst to achieve asymmetric synthesis:

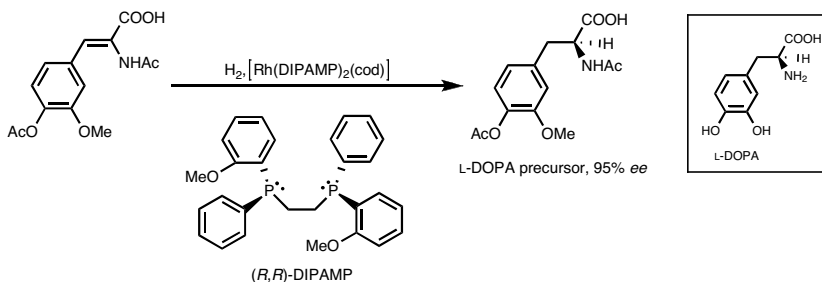
- In *substrate-controlled asymmetric synthesis*, a chiral compound is used as starting material. The formation of the new chiral centre is controlled by the presence of the stereogenic fragment on the substrate.
- In the *auxiliary-controlled asymmetric strategy*, an enantiomerically pure compound, called a chiral auxiliary is temporarily attached to the starting material. After a diastereoselective reaction is carried out, the chiral auxiliary is removed, leaving the product as a single enantiomer. The chiral auxiliary is usually derived from a simple natural product such as an optically active amino acid, terpene or α -hydroxy acid. The two extra steps required to attach and remove the chiral auxiliary are drawbacks to this strategy.
- In the *reagent-controlled asymmetric synthesis*, enantioselectivity is induced by a chiral non-racemic reagent e.g. base, reducing agent or hydroboration reagent.
- A catalyst is a species, present in a small amount compared with the reactants, that accelerates a reaction without being consumed. In *asymmetric catalysis*, a chiral catalyst both speeds up the reaction and induces enantioselectivity. Asymmetric catalysis is described in more detail in section 1.2.3.1

1.2.3.1 Asymmetric catalysis

Since the first published study on a catalytic reaction by Michael Faraday (1791-1867) in 1834, there has been tremendous development in the field of catalysis.¹⁵

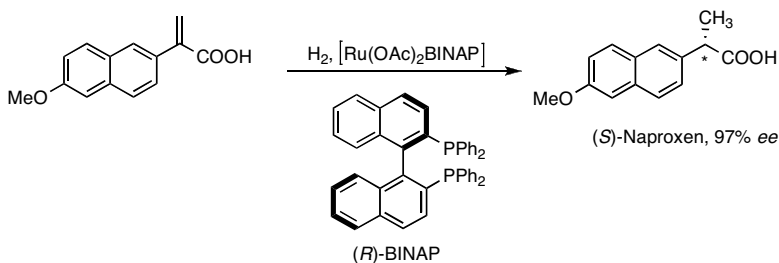
The first attempts to obtain enantiomerically enriched products using such catalysts can be traced back to the beginning of the 20th century. In 1908, Rosenthaler reported the synthesis of optically active mandelonitrile using an enzyme.¹⁶ Four years later, Bredig prepared the same compound in an 10% *ee* by applying an alkaloid as a chiral catalyst.¹⁷ The first synthetically useful asymmetric catalysis was not performed until the late 1950s, when Izumi *et al.* reported the hydrogenation of methyl acetoacetate into methyl β -hydroxybutyrate with *ee* values up to 80%.¹⁸ He used Raney nickel that had been modified with tartaric acid as catalyst for this reaction.

About two decades later, in 1974, an important milestone was reached, when William Knowles of Monsanto, developed a Rh-DIPAMP catalyst for the industrial production of the important anti-Parkinson's drug L-DOPA (Scheme 3).¹⁹ This was the first commercial application of asymmetric transition metal catalysis.



Scheme 3. Knowles' Monsanto L-DOPA process. The product of the asymmetric hydrogenation can be converted to L-DOPA.

Further progress in enantioselective hydrogenation was made with Ryoji Noyori's versatile BINAP ligand (Scheme 4); complexes of this ligand are especially successful in the enantioselective hydrogenation of unsaturated carbon-carbon bonds and ketones.²⁰ For example, an organometallic complex between (R)-BINAP and ruthenium can be used to prepare the anti-inflammatory drug (S)-naproxen in high yield (92%) and with excellent enantiomeric excess (97%) (Scheme 4).

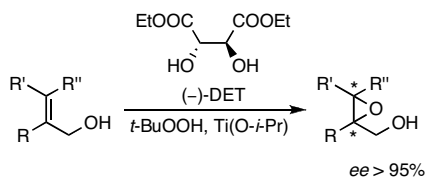


Scheme 4. Synthesis of the anti-inflammatory drug (S)-naproxen using an asymmetric catalyst based on Noyori's (R)-BINAP. The catalyst loading in the reaction is 0.5 mol%.

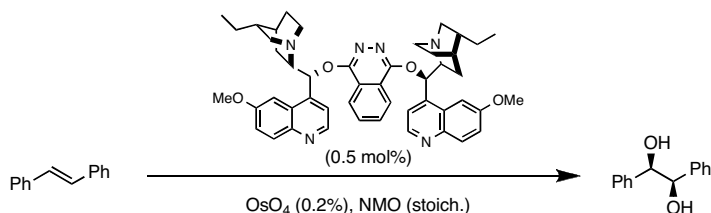
The field of asymmetric catalysis has been extended to encompass many reaction types, and the amount of catalyst needed for such reactions is often very low (> 1 mol%). Two particularly successful oxidation reactions are the

Sharpless epoxidation of allylic alcohols²¹ and the Sharpless asymmetric dihydroxylation of olefins²² which both are widely used as synthetic tools in organic synthesis (Scheme 5).

(a) Sharpless asymmetric epoxidation of allylic alcohols



(b) Sharpless asymmetric dihydroxylation of olefins

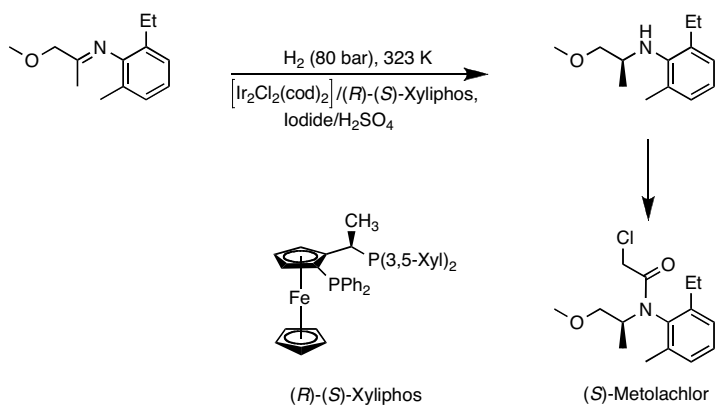


Scheme 5. Asymmetric reactions by Sharpless.

The significance of asymmetric catalysis was recognized when Knowles²³, Noyori²⁴ and Sharpless²⁵ received the 2001 Nobel Prize in chemistry for their merits in this field.

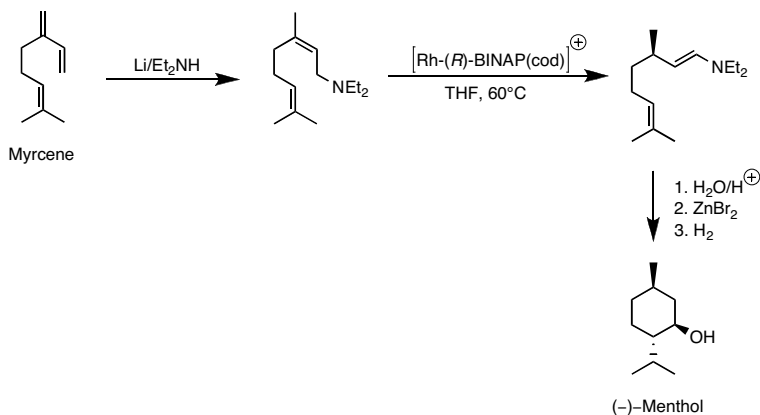
Today, asymmetric catalysis is well-established in the chemical, agrochemical and pharmaceutical industries. In the pharmaceutical industry, new chiral drugs are being synthesised as one enantiomer, and existing drugs are being replaced by single-enantiomer versions (a process called the ‘chiral switch’).²⁶

Two bulk-scale industrial productions that use asymmetric catalysis are the syntheses of the herbicide (*S*)-Metolachlor²⁷ by Syngenta (Scheme 6) and of (–)-menthol²⁸ by Takasago (Scheme 7). (*S*)-Metolachlor is sold under the trade name Dual MagnumTM as a selective herbicide primarily for the protection of corn and sorghum and more than 10,000 tons are produced per year. The chirality in the product is introduced by using an organometallic complex of the ligand xyliphos and an iridium-(cod) moiety.



Scheme 6. Industrial synthesis of the important grass herbicide Metolachlor (Dual Magnum™) by Syngenta.

(-)-Menthol is a bulk chemical for the food and pharmaceutical industries where it serves mainly as a flavoring and fragrance agent. It is produced on a multi-ton scale by Takasago. One of the chemical transformations crucial to the process involves asymmetric catalysis. The chiral catalyst is based on Noyori's (*R*)-BINAP ligand together with a rhodium(cod) group.



Scheme 7. Takasago's industrial synthesis of (-)-menthol.

2 Synthesis of Chiral Bicyclic Ligands

2.1 Introduction

Metal complexes with chiral, non-racemic ligands that are based on amino acids have proven interesting in asymmetric catalysis. The amino acid, L-proline contains a rigid pyrrolidine ring, and this has caused ligands derived from it to receive a lot of heed. In order to create even greater backbone rigidity, our research group started to explore chiral ligands based on the 2-aza-norbornene scaffold (Figure 6), a structure that has successfully been applied by us and others in several types of asymmetric catalysts.²⁹ The 2-aza-norbornene scaffold is obtained via a highly stereoselective aza-Diels-Alder reaction, and is the starting point of the ligand syntheses described in this thesis.

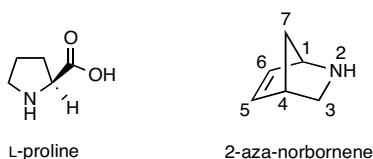
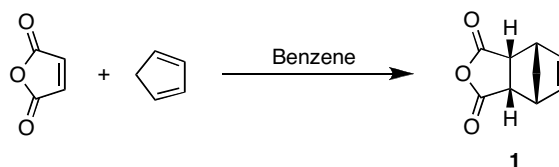


Figure 6. The structures of the amino acid L-proline and the 2-aza-norbornene scaffold.

2.2 The Diels-Alder reaction

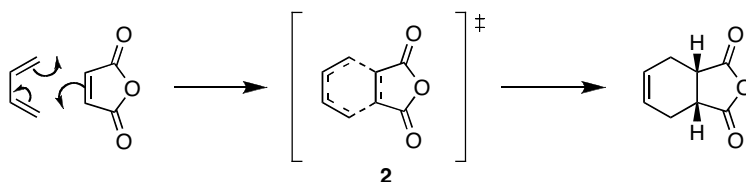
2.2.1 The classic Diels-Alder reaction

In 1928, Otto Diels (1876-1954) and Kurt Alder (1902-58), published a powerful organic synthesis that later became known as the Diels-Alder reaction and that earned them the 1950 Nobel Prize in chemistry.³⁰ Their first publication on this reaction reported the quantitative formation of the bicyclic compound (**1**) from the reaction of maleic anhydride and cyclopentadiene (Scheme 8).



Scheme 8. The first reported example of a Diels-Alder reaction.

Formally the Diels-Alder reaction is a [4+2] cycloaddition where the reactants are a diene component with 4π -electrons and a dienophile with 2π -electrons (Scheme 10). One of the reasons for why the reaction proceeds so well is that its transition state (**2**, Scheme 9) has six delocalized π electrons and thus is aromatic in character.³¹

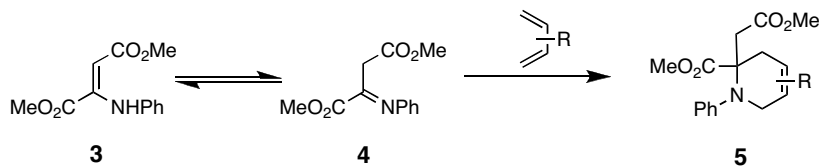


Scheme 9. The Diels-Alder reaction is formally a [4+2] cycloaddition proceeding via the six-membered cyclic transition state **2**, which is aromatic in character.

The Diels-Alder reaction displays a high degree of regio- and stereoselectivity and, because it can create up to four stereocenters simultaneously,³² it is an important reaction in organic chemistry, and especially in the total synthesis of natural products.³³

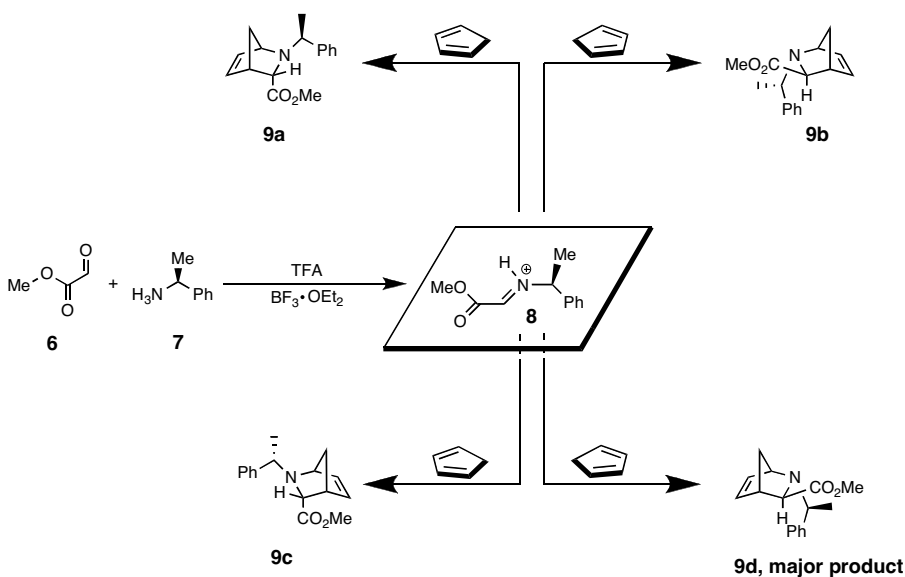
2.2.2 The aza-Diels-Alder reaction

A variant of the classical Diels-Alder reaction is the hetero Diels-Alder in which the diene and/or dienophile contains one or more heteroatoms. When the heteroatom is nitrogen the reaction is named the aza-Diels-Alder reaction. The imino-Diels-Alder reaction is an aza-Diels-Alder reaction in which an imino group is acting as a diene or dienophile. In 1943, Alder described an example of this reaction,³⁴ in which the amino diester **3** reacted with aliphatic dienes to produce the tetrahydropyridines **5** via the imino tautomer **4**, rather than the carbocyclic adducts one might have expected (Scheme 10). In synthetic organic chemistry, the imino-Diels-Alder reaction is a useful tool for obtaining functionalized nitrogen-containing compounds such as amino acids, peptides and alkaloids.³⁵



Scheme 10. The first published aza-Diels-Alder reaction.

Our synthesis of the 2-aza-norbornene scaffold is performed in accordance with a published method³⁶ and starts with the reaction between methyl glyoxylate **6** and the optically pure (*S*)-phenylethylamine **7** to form the imine **8** (Scheme 11). When the imine undergoes the subsequent aza-Diels-Alder reaction with cyclopentadiene, four possible adducts **9a-d** are formed. The desired adduct **9d** is the major product, and is reported to constitute ca. 96% of the product mixture.³⁷



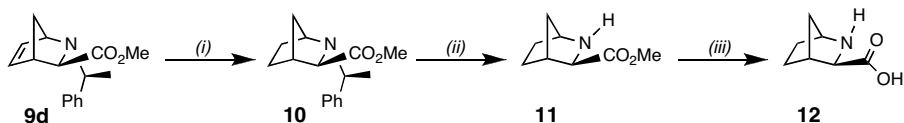
Scheme 11. Synthesis of the 2-aza-norbornene scaffold.

2.3 Synthesis of amino-oxazoline compounds based on the 2-aza-norbornane scaffold

2-Aza-norbornane-oxazolines compounds are precursors to the phosphine-oxazoline ligands investigated in this thesis. The synthesis of the 2-aza-

norbornane-oxazoline compounds is based methods recently published by our group.³⁸ In brief, the synthesis of the phosphine-oxazoline ligands starts from the 2-aza-norbornene **9d** (Scheme 11) and proceeds via the corresponding amino-oxazolines to the final reaction with a suitable diaryl-/dialkylphosphine chloride.

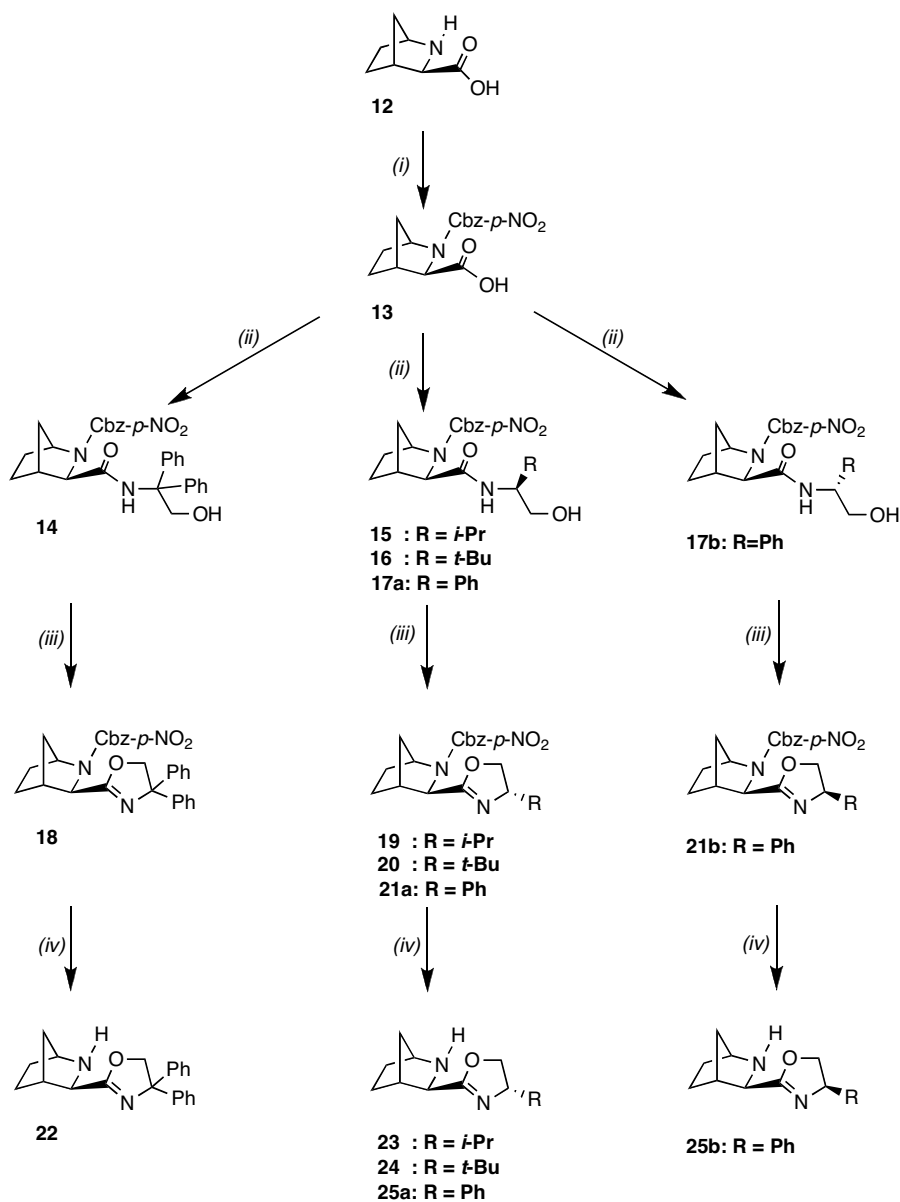
After the 2-aza-norbornene product **9d**, is formed in the aza-Diels-Alder reaction described section 2.2.2, its carbon-carbon double bond is catalytically hydrogenated producing compound **10** (Scheme 12). Subsequent hydrogenolysis of the chiral auxiliary yields the free amine **11** whose ester group is subsequently hydrolysed using LiOH in water to thus producing the (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid **12**.



Conditions and reagents: (i) Pd/C (10 wt%), H₂ (20 bar), EtOH, rt, overnight; (ii) Pd(OH)₂ (10 wt%), H₂ (1 atm), EtOH, rt, overnight; (iii) LiOH, H₂O/CH₂Cl₂, rt, overnight.

Scheme 12. Outline of the synthetic transformations that lead from the aza-Diels-Alder adduct **9d** to (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid, **12**.

Scheme 13 illustrates the syntheses of several 2-aza-norbornane-oxazoline compounds starting from **12**. First, the cyclic secondary amine of **12** is protected through reaction with *p*-nitrobenzyloxycarbonyl chloride (*p*-NO₂-CbzCl) under basic conditions forming the *p*-NO₂-Cbz protected **13**. Amide couplings of the acid **13** with suitable aminoalcohols produced the corresponding hydroxylamides **14**, **15**, **16**, **17a-b**, which produced the oxazolines **18**, **19**, **20**, **21a-b** upon a subsequent treatment with mesyl chloride under basic conditions. Finally, the *p*-NO₂-Cbz protecting group was cleaved off of the secondary amine by hydrogenolysis over palladium on carbon, producing **22**, **23**, **24**, **25a-b**. The yields of these reactions were consistent with the reported values.³⁸



Conditions and reagents: (i) *p*-NO₂-CbzCl, 2.0 M NaOH in dioxane/H₂O, rt, overnight; (ii) EDC, HOBT, aminoalcohol, CH₂Cl₂, rt, overnight; (iii) MsCl, Et₃N, CH₂Cl₂, 0 °C → rt, overnight; (iv) Pd/C (10 wt%), H₂ (1 atm), EtOH, rt, overnight.

Scheme 13. Synthesis of the chiral amino-oxazoline compounds that serve as precursors to the phosphine-oxazoline ligands.

2.4 Synthesis of phosphine-oxazoline ligands based on 2-aza-norbornane-oxazolines (*Paper I and II*)

To date, most phosphine-oxazoline ligands that have been successfully applied in catalytic hydrogenation have featured steric bulk in the positions as indicated on the generic structure **26a** (Figure 7). The aza-2-norbornane backbone can provide significant steric bulk, and this led us to explore the using of this motif in ligands for these reactions. Structure **26b** (Figure 7) shows how this bicyclic skeleton can form the sterically bulky basis of interesting phosphine-oxazoline candidates to test in enantioselective hydrogenation reactions.

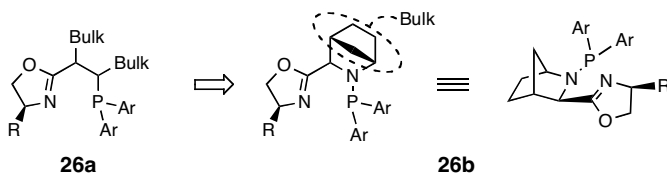
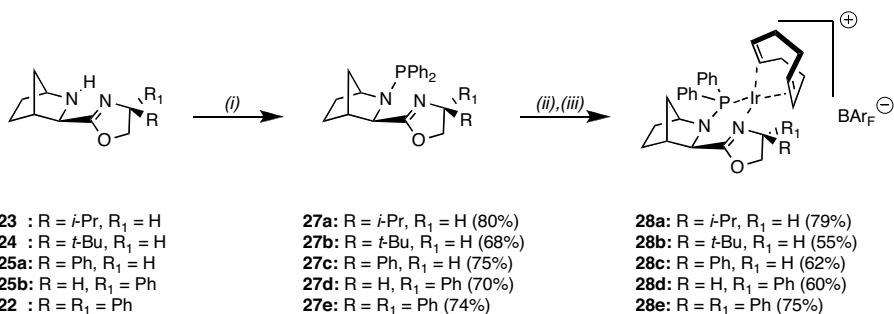


Figure 7. Compound **26a** is a proposed generic structure of phosphine-oxazoline ligands that have proven to be efficient in many iridium-catalyzed enantioselective hydrogenations of imines and olefins. Structure **26b** demonstrates how our bicyclic ligand could be an interesting ligand candidate for catalysts of this type.

Our group's novel 2-aza-norbornane-oxazoline ligands, which are discussed in the previous section, provided the basis for the novel phosphine-oxazoline ligands. By functionalizing of the 2-aza-norbornane-oxazoline compounds with phosphine groups one obtains set of new chiral phosphine-oxazoline ligands that are in congruence with the desired structure **26b**. *Paper I* and *Paper II* in this thesis describe the synthesis of these compounds and *Paper I-IV* their application as ligands in iridium-catalyzed hydrogenations. The synthesis of the iridium complexes used in catalysis is depicted in Scheme 14.

Phosphines **27a-e** were produced in high yields (70-80%) from the corresponding 2-aza-norbornane-oxazoline compounds upon treatment with a CH_2Cl_2 solution of diphenylphosphine chloride and diisopropylethylamine. The corresponding iridium complexes **28a-e** were formed by heating the **27a-e** and $[\text{Ir}(\text{COD})\text{Cl}]_2$ in CH_2Cl_2 at reflux, then stirring with NaBAR_F in a $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ mixture to replace the Cl^- anion by BAR_F^- (Figure 8). The complexes **28a-e** were purified by column chromatography on silica gel and isolated as bright orange crystalline solids that were stable for months when stored at low temperatures ($-30\text{ }^\circ\text{C}$).



Conditions and reagents: (i) PPh₂Cl, DIPEA, toluene, 4 °C overnight; (ii) [Ir(COD)Cl]₂, CH₂Cl₂, reflux, 2h; (iii) NaBAR_F, H₂O/CH₂Cl₂.

Scheme 14. Synthesis of the Ir complexes **28a-e** from the phosphine-oxazoline ligands **27a-e**.

To explore the influence of the phosphine substituents on the enantioselectivities of imine and olefin hydrogenations, Ir complexes bearing various phosphine substituents were prepared.

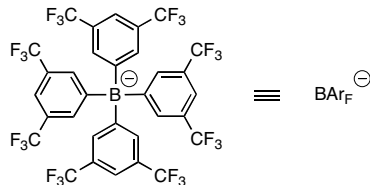
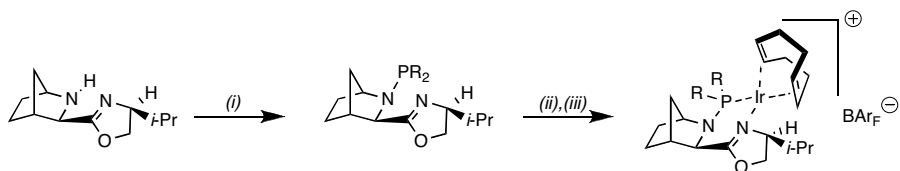


Figure 8. The structure of the weakly coordinating BAR_F⁻ ion which frequently serves as counter anion in the Ir catalysts used in asymmetric hydrogenations.

The complexes **29a-e** were prepared upon treatment of the amino-oxazoline **23** with different dialkyl- and diarylphosphine chlorides (Scheme 15). The amino-oxazoline **23** was chosen as the N-donor component of these ligands based on the hydrogenation experiments described in section 3.3 (see Table 1 and the corresponding discussion). The phosphorylation yields were sensitive to the steric bulk of the alkyl or aryl groups on the phosphine. The bulkiest phosphine chlorides which had di-*t*-butyl-, di(2-trifluoromethylphenyl)-, di(2,6-dimethylphenyl) and di(1-naphthyl) groups did not react with **23**, whereas di(3,5-dimethylphenyl) chloride reacted cleanly to give the desired product. The Ir complexes **29a-e** were prepared as crystalline bright orange

orange solids in good yields following the same procedure as described for the complexes **28a-e**.



- 29a:** R = cyclohexyl (47%)
29b: R = 2-methylphenyl (52%)
29c: R = 3,5-dimethylphenyl (62%)
29d: R = 2-methoxyphenyl (61%)
29e: R = 4-methoxyphenyl (30%)

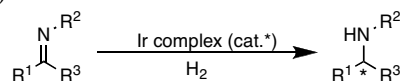
Conditions and reagents: (i) PR_2Cl , DIPEA, toluene, 4°C overnight; (ii) $[\text{Ir}(\text{COD})\text{Cl}]_2$, CH_2Cl_2 , reflux, 2h; (iii) NaBARF , $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$.

Scheme 15. Synthesis of Ir complexes **29a-e**, which bear a variety of phosphine groups.

3 Application of phosphine-oxazoline ligands in Ir-catalyzed asymmetric hydrogenation of imines

3.1 Introduction

Chiral amines are important targets in synthetic organic chemistry. Attempts to enantioselectively reduce the C=N double bond can be traced back to the early 1940s. The reaction still represents a great challenge with many of the complicating features being inherent in the imines. For example, some imines exhibit facile *syn/anti* isomerization, and both the starting material and product of imine hydrogenation (imine and amine, respectively) can complex to homogeneous catalyst.³⁹ This chapter describes the evaluation of the new chiral phosphine-oxazoline complexes, **28** and **29**, whose syntheses were described in the previous chapter, in catalytic asymmetric imine hydrogenation (Scheme 16).

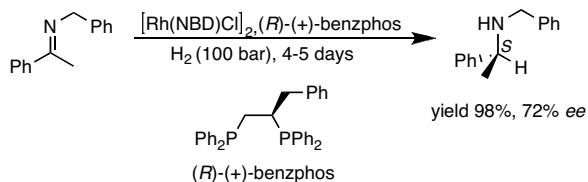


Scheme 16. Asymmetric iridium-catalyzed hydrogenation of imines.

3.2 Asymmetric hydrogenation of imines – an overview

The first report of enantioselective C=N reduction was published in 1941 by Nakamura,⁴⁰ who used a heterogenous catalyst (Pt black) and menthoxyacetic acid as a chiral auxiliary to reduce an oxime. The reaction displayed low enantioselectivity, giving only 3% *ee*. The first homogenous asymmetric catalytic hydrogenations of imines, published in 1975, used Ru⁴¹ or Rh⁴² metals with diop as chiral auxiliary. The *ee* values observed, however, were low, reaching only 15% for the Ru-catalyzed reaction and 22% in the Rh-catalyzed reaction. Nine years later, the first useful enantioselectivities were obtained when Marko *et al.*⁴³ obtained *ee* values up to 72% using Rh cata-

lysts and benzphos and analogues as chiral auxiliaries in the hydrogenation of *N*-benzyl-(1-phenylethylidene)amine (Scheme 17).



Scheme 17. The first asymmetric imine hydrogenation to produce useful enantioselectivity.

Even higher enantioselectivities were reported five years later when an acyclic imine was reduced with a Rh-bdpp_{sulf} complex in *ee* 94%.⁴⁴ During and since the 1990s, several chiral metal catalysts have been successfully applied in the asymmetric hydrogenation of acyclic and cyclic imines, although the latter substrates are, in general, easier to hydrogenate effectively (Figure 9). The metals involved in these catalysts are Ir, Ru, Rh, Ti, Au and Zr; among these, Ir plays an increasingly dominating role. Buchwald *et al.*^{45a,b} developed chiral titanocene catalysts that are particularly effective for the enantioselective hydrogenation of cyclic imines, and the zirconium analogues, developed by Brintzinger *et al.*^{45c} have shown similar results. Imines have also been hydrogenated by using gold complexes: in a recent publication anti-*N*-benzyl(1-phenylethylidene)imine was reduced in 75% *ee* by $\{(\text{AuCl})_2[(\text{R},\text{R})\text{-Me-Duphos}]\}$ (Figure 9).^{45d} Complexes based on Ru^{46,47} and Rh⁴⁸ are effective in both in direct imine hydrogenations using hydrogen gas^{47,49a-d,49f} and in transfer hydrogenation using a small organic molecule as the H₂ donor.^{48,49d} These catalysts worked well in the reduction of cyclic and acyclic imines and the reduction of sulfonimines,^{47a,48c} and in the reductive amination of ketones.^{49b,f} Iridium has gradually become the metal of choice in the catalytic asymmetric hydrogenation of imines as its complexes have proven to be highly effective for this purpose.⁴⁹ For example, Zhang *et al.* recently reported the reduction of acyclic imines with *ee* values up to >99% using an Ir complex of f-binaphane.^{49g} Ir complexes have also found their applications in large-scale chemistry production, as exemplified by the synthesis of (*S*)-metolachlor that Syngenta implemented in 1996 (Scheme 7).

In 1977, Crabtree *et al.*⁵⁰ initiated the development of a whole new line of iridium-based catalysts when they reported that the (pyridine)(phosphine)-iridium-complex **30** (Figure 10) was a highly active hydrogenation catalyst. Since then, several groups have developed analogues of the Crabtree catalyst and evaluated them in enantioselective reactions.^{51,52} Twenty years after Crabtree's discovery, Pfaltz *et al.*^{53a} reported that iridium complexes of

phosphine-oxazoline **31** are highly effective catalysts for imine hydrogenation (Figure 11).

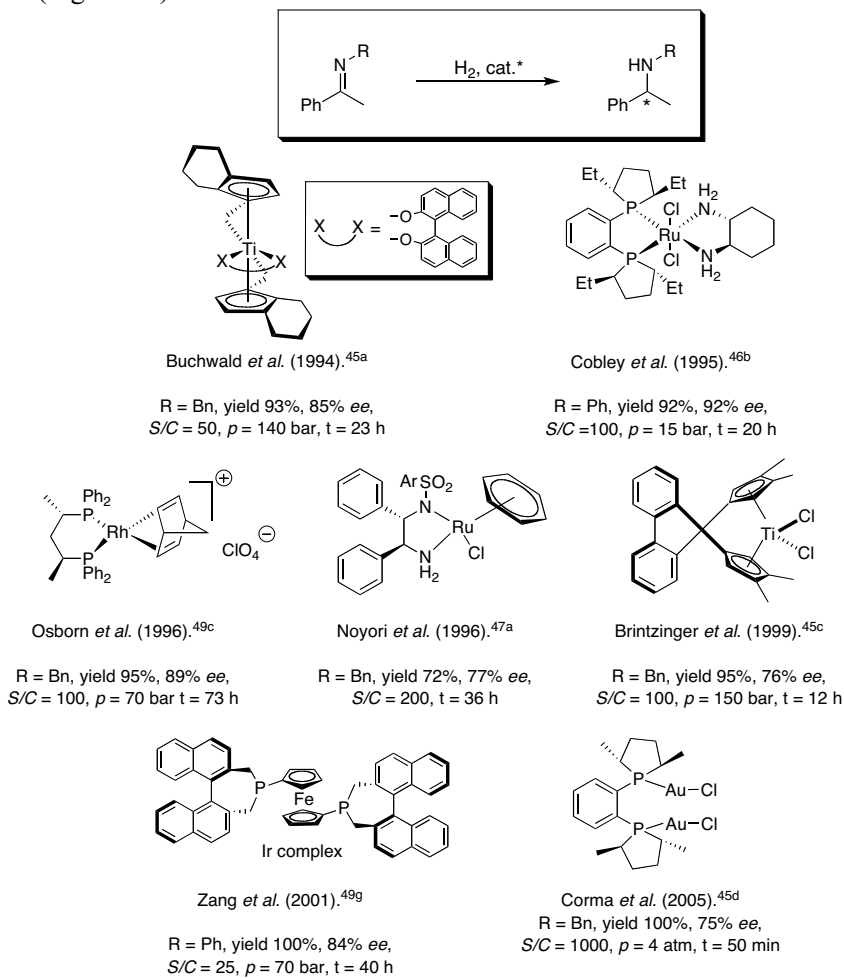


Figure 9. Some complexes applied to the catalytic asymmetric hydrogenation of imines.

In the following years, a whole array of this type of *P,N*-ligand was developed and evaluated in imine reductions, by Pfaltz' and several other research groups (Figure 11).⁵³

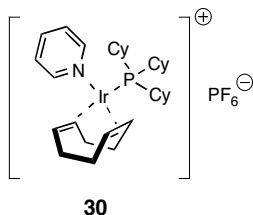


Figure 10. The structure of Crabtree's catalyst, which was published in 1977.

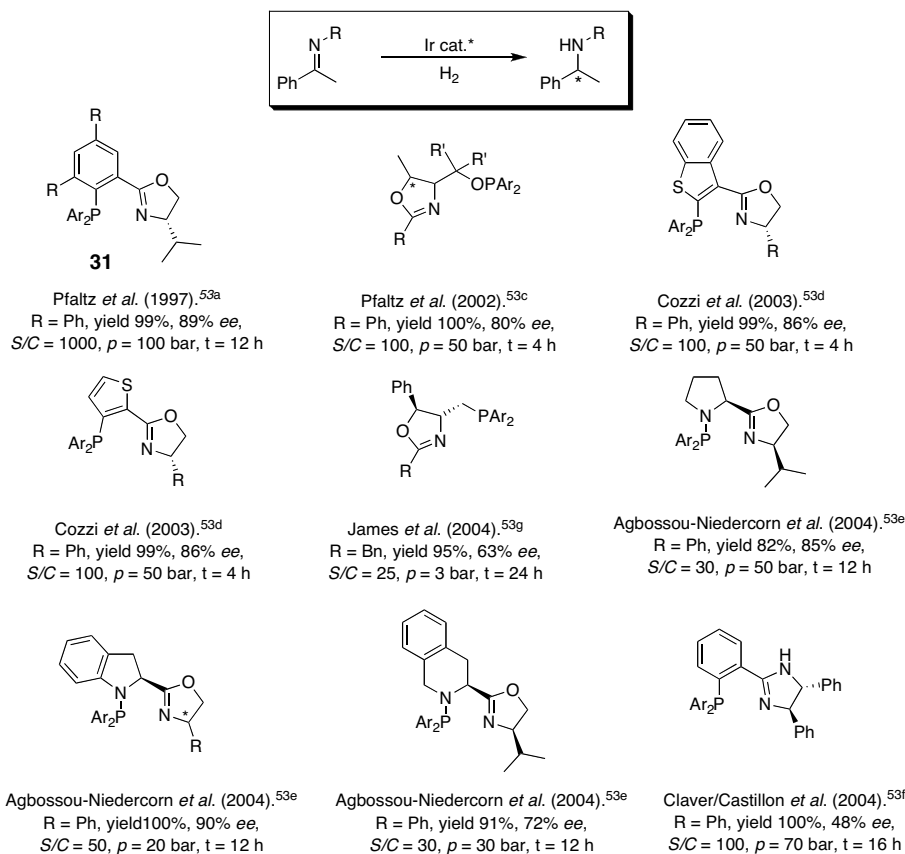


Figure 11. Overview of some phosphine-oxazoline ligands used in Ir-catalyzed asymmetric imine hydrogenation.

There remains, however, room for improvement. Most of the (phosphine-oxazoline)Ir catalytic systems for imine hydrogenation demand high catalyst loadings, elevated pressures (often $P \geq 50$ bar) and long reaction times to produce the corresponding chiral amines in high yields. Furthermore, there is also potential for improvement when it comes to the substrate scope, in particular acyclic imines. There are a number of useful methods for reducing cyclic imines (e.g. Buchwald's and Brintzinger's metallocene ligands): the same arsenal does not exist for the acyclic imines.

3.3 Phosphine-oxazoline ligands applied in Ir-catalyzed asymmetric hydrogenation of imines (*Paper I and II*)

The complexes described in section 3.2 were evaluated in the asymmetric hydrogenation of imines. Firstly, the influence of the size and the configuration of the oxazoline's 5' substituent were investigated. Complexes **28a-e** were applied in the reduction of *N*-(1-phenylethylidene)aniline **32**, a compound often used as a model substrate in these reactions, to the corresponding *N*-phenyl-*N*-(1-phenylethyl)amine (Table 1). The results of these reactions, which were performed in CH₂Cl₂ under a hydrogen pressure of 20 bar and using a catalyst loading of 0.5 mol%, are summarized in Table 1.

Table 1. Asymmetric hydrogenation of *N*-(1-phenylethylidene)aniline using Ir complexes **28a-e**.

Entry	Ligand	Complex	time (h)	Conv., % ^a	% <i>ee</i> ^b	Abs. Conf. ^c
1.		28a	2	98	90	(<i>R</i>)
2.		28b	12	88	73	(<i>R</i>)
3.		28c	12	66	57	(<i>R</i>)
4.		28d	12	67	52	(<i>R</i>)
5.		28e	12	0	n.d.	(<i>R</i>)

^a Determined by ¹H NMR. ^{b,c} Determined by chiral HPLC, absolute configuration is assigned by comparison of retention times with literature values.^{53a}

Complex **28a** reduced **32** to (*R*)-*N*-phenyl-*N*-(1-phenylethyl)amine in 90% *ee* and 98% conversion in 2 hours (Table 1, entry 1). When the reaction was performed under milder conditions (5 bar) and lower catalyst loading (0.05 mol%), the high enantioselectivity was maintained but a drop in reaction rate

was observed. Complex **28b** produced the (*R*)-enantiomer of *N*-phenyl-*N*-(1-phenylethyl)amine in 73% *ee* and 88% conversion after 12 hours (Table 1, entry 2). Notably, the hydrogenations using the complexes **28c** and **28d** both, oddly, gave the (*R*)-enantiomer of *N*-phenyl-*N*-(1-phenylethyl)amine. Furthermore, these two complexes produced very similar *ee* values (57% and 52%, respectively) and conversion (66% and 67%, respectively) (Table 1, entry 3 and 4) in the hydrogenation. When the steric bulk at the 5' position on the oxazoline ring was increased by including two phenyl groups (Table 1, entry 5) no catalytic activity for imine reduction was detected under the standard conditions. Of the catalysts evaluated in this study the complex **28a**, based on ligand **27a**, was the best imine hydrogenation catalyst, yielding 90% *ee* and 98% conversion within 2 hours (Table 1, entry 1). It was therefore chosen to be tested with several acyclic and cyclic imines.

Several acyclic imines that were structurally similar to **32** were tested as substrates for asymmetric hydrogenation with catalyst **28a**, and the results of these hydrogenations are presented in Table 2. Imines **33** and **34** (Table 2, entries 1 and 2), which have *ortho*-methyl groups on their C- and N-aromatic rings, respectively, were hydrogenated more slowly than the unsubstituted model substrate **32**. The corresponding observed drop in enantioselectivity for these substrates was, however, small (80-83% *ee*). Substrates **35-39** have electron-withdrawing and electron donating groups at the *para*-positions of their aromatic rings (Table 2, entries 3-7). These imines were reduced almost as enantioselectively as was imine **32** (86-89% *ee*), and moreover, full conversion was achieved for all of them (**35-39**) within 1.5-3 hours. Thus substituents at these positions do not influence the reaction rate or selectivity significantly. Substrate **40**, *N*-(1-phenylethylidene)benzylamine (Table 2, entry 9), was reduced to the corresponding amine less successfully. With twice the catalyst loading (1 mol% rather than 0.5 mol%) used in the preceding reaction, (*R*)-*N*-benzyl-*N*-(1-phenylethyl)amine was formed with in 63% conversion and 66% *ee* in 12 hours.

The good results obtained in the asymmetric hydrogenation of the simple, mainly planar imine substrates **32-39** by catalyst **28a** (Tables 1 and 2) led us to test it with more complicated imine structures (Table 3 and Figure 11). More puckered substrates influenced on both the *ee* values and conversions significantly with even a minor deviation from substrate planarity resulting in lower conversion and selectivity. This is illustrated by the hydrogenation of imine **41** (Table 3, entry 1), which differs from the model imine **32** by only one extra methyl group. The hydrogenation of imine **41** under standard conditions using Ir complex **28a** needed 6 hours to achieve full conversion (cf 2 hours for imine **32**; Table 1, entry 1). The enantioselectivity of this reduction was also slightly lower (78% *ee*) than that of **32** (90% *ee*).

Table 2. Asymmetric hydrogenation of various imines using Ir complex **28a**.

$$\text{R}^1\text{-C(R}^2\text{)=N-R}^3 \xrightarrow[0.5 \text{ mol\% Ir-complex } \mathbf{28a}]{\text{H}_2 (20 \text{ bar}), \text{rt, CH}_2\text{Cl}_2} \text{R}^1\text{-CH(R}^2\text{)-NH-R}^3$$

Entry	Imine	time (h)	Conversion, % ^a	% <i>ee</i> ^b
1.	 33	12	52	83 (-)
2.	 34	3	99	80 (-)
3.	 35	2	99	89 (-)
4.	 36	3	99	86 (-)
5.	 37	1.5	99	89 (+)
6.	 38	2	99	86 (+)
7.	 39	1.5	99	89 (+)
8. ^c	 40	12	63	66 (<i>R</i>)

^a Determined by ¹H NMR. ^b Determined by chiral HPLC, absolute configuration is assigned by comparison of retention times with literature values.^{53a} ^c 1 mol% of catalyst used.

Imine **42** (Table 3, entry 2) is more flexible than **41**, and was hydrogenated in 95% conversion after 12 hours with a moderate *ee* of 58%. The 1-

tetralone derivative **43** (Table 3, entry 3) is even more flexible than the 1-indanone derivative **42**, and was hydrogenated to 50% conversion after 12 hours, with a correspondingly moderate *ee* (53%). The planar imine **44** (Table 3, entry 4) was as anticipated, efficiently hydrogenated reaching full conversion and high enantioselectivity (90.5% *ee*) after only 1 hour. When the aromatic ring of the C=N double bond was substituted with the bulky, flexible aliphatic group cyclohexyl (imine **45**, Table 3, entry 5), hydrogenation could only be achieved with relatively low *ee* (30%), implying that bulky three-dimensional substituents at the double bond might interfere with the steric bulk of the chiral catalyst.

Table 3. Asymmetric hydrogenation of various imines using Ir-complex **28a**.

Entry	Imine	time (h)	Conversion, % ^a	% <i>ee</i> ^b
1.	 41	6	99	78 (+)
2.	 42	12	95	58 (+)
3.	 43	12	50	53 (+)
4.	 44	1	99	90.5 (+)
5.	 45	12	70	30 (+)

^a Determined by ¹H NMR. ^b Determined by chiral HPLC, the sign of the optical rotation is reported.

The acyclic imines **46-49** were inert in to hydrogenation under the standard conditions using Ir complex **28a** (Figure 11). The steric bulk and deviation from planarity seen in imines **46** and **47** explains why they do not react. The inactivity of imines **48** and **49** in the reduction could be due to their electron deficient C=N double bonds (relative to that of **32**), which result in a reduced ability to coordinate to iridium. Several cyclic imines were also subjected to hydrogenation, but **50-54** were all inert under standard conditions (Fig.12).

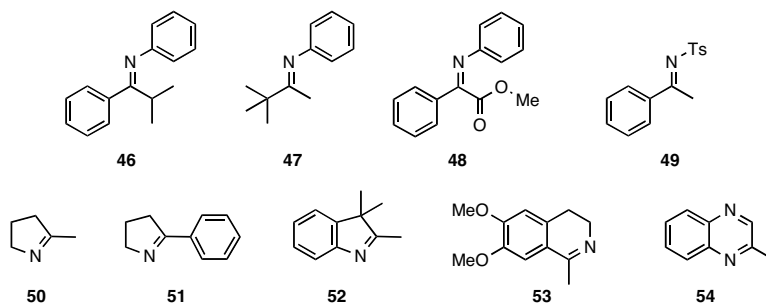


Figure 12. Imines that did not undergo Ir-catalyzed asymmetric hydrogenation under standard conditions.

A further goal was to explore how the phosphine substituents influence enantioselectivities and reaction rates of the hydrogenation. Ir complexes **29a-e**, which are based on the amino-oxazoline **23** but have various phosphine substituents, were synthesized (Scheme 15) and subsequently evaluated in the reduction of the model imine *N*-(1-phenylethylidene)aniline (**33**). The results of these asymmetric hydrogenation reactions are presented in Table 4. Ir-complex **29a**, bearing a di(cyclohexylphosphine) substituent, hydrogenated **32** to (*R*)-*N*-benzyl-*N*-(1-phenylethyl)amine in full conversion and 86% *ee* after 4 hours (Table 4, entry 1). Exchanging dicyclohexylphosphine substituent in **29a** with a di(*ortho*-tolyl)phosphine (**29b**, Table 4, entry 2) or di(3,5-dimethylphenyl)phosphine (**29c**, Table 4, entry 3) increased the selectivity (92% *ee* obtained for both complexes), and produced 99% conversion after 3 and 4 hours, respectively. When an Ir complex with a di(*ortho*-methoxyphenyl)phosphine (**29d**, Table 4, entry 4) was applied in the reduction of **32**, the enantioselectivity was still high (90% *ee*) but the reaction suffered from a drop in effectiveness taking 20 hours to reach 61% conversion. When the methoxy substituent was located at *para*-position instead, as for **29e** (Table 4, entry 5), the catalytic activity increased yielding full conversion after 6 hours. The results indicate that the substituents on the phosphine aromatics do not have a strong influence on the enantioselectivity in the asymmetric hydrogenation of the standard substrate **32**. Notably, the enantioselectivities (92% *ee*), obtained with complexes **29b** and **29c** are

among the best reported in the literature for the asymmetric hydrogenation of imines. Also noteworthy is the moderate hydrogen pressure needed in this reaction.

Table 4. Asymmetric hydrogenation of *N*-(1-phenylethylidene)aniline using Ir-complexes **29a-e**.

CC(=Nc1ccccc1)c2ccccc2
 $\xrightarrow[0.5 \text{ mol\% Ir-complex}]{\text{H}_2 (20 \text{ bar}), \text{rt}, \text{CH}_2\text{Cl}_2}$
CC(Nc1ccccc1)c2ccccc2

32

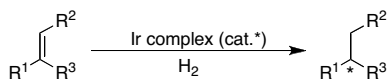
Entry	Ligand	Complex	time (h)	Conv., % ^a	% <i>ee</i> ^b	Abs. Config. ^c
1.		29a	4	99	86	(<i>R</i>)
2.		29b	4	99	92	(<i>R</i>)
3.		29c	3	99	92	(<i>R</i>)
4.		29d	20	61	90	(<i>R</i>)
5.		29e	6	99	90	(<i>R</i>)

^a Determined by ¹H NMR. ^{b,c} Determined by chiral HPLC, absolute configuration is assigned by comparison of retention times with literature values.^{53a}

4 Application of phosphine-oxazoline ligands in Ir-catalyzed asymmetric hydrogenation of ‘unfunctionalized’ olefins

4.1 Introduction

The asymmetric hydrogenation of olefins is of major importance in organic synthesis, and is also one of the topics with the longest history in enantioselective catalysis. In this chapter the phosphine-oxazoline complexes whose syntheses were described in chapter 2 are evaluated in the Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins (Scheme 18).⁵⁴



Scheme 18. Asymmetric iridium-catalyzed hydrogenation of olefins.

4.2 Overview of asymmetric hydrogenation of olefins

The field of enantioselective hydrogenation of olefins is one of the most explored areas in asymmetric catalysis.⁵⁵ The discovery of Wilkinson’s catalyst played an essential role in the development of this field, as it demonstrated the possibility of homogeneous asymmetric catalysis. Methods for the asymmetric hydrogenations of both functionalized and unfunctionalized alkenes have been developed, but the functionalized olefins, which containing coordination functionality (e.g. heteroatoms) near the double bond, are easier to hydrogenate because they can chelate the metal centre of the chiral complex. Catalysts based on various metals (Rh, Ru, Ti, Zr, Ln and Ir) have been successfully applied to these reactions, and recently Ir complexes have received increasing attention. Tri- and tetrasubstituted alkenes that lack additional coordination functionality have proven difficult to reduce by asym-

metric catalysis, and only few examples involving Rh and Ru have been reported.⁵⁶ Metallocene complexes of Ti, Zr, and various lanthanides have produced very good enantioselectivities and yields for unfunctionalized olefins (Figure 13), but these all suffer from low turnover frequencies and turnover numbers.⁵⁷

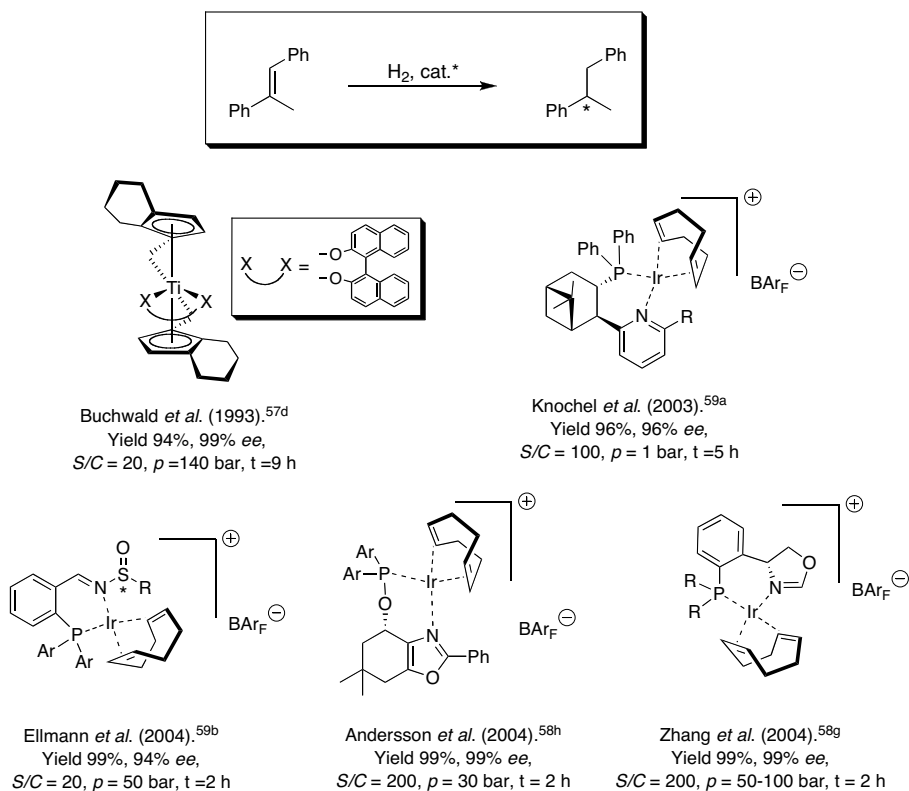
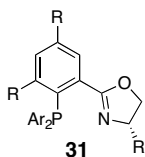
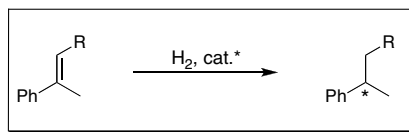
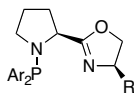


Figure 13. Complexes used in the catalytic asymmetric hydrogenation of olefins.

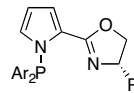
Pfaltz *et al.*^{53a} published a seminal continuation of Crabtree's work in 1997. In it, they described the effective enantioselective hydrogenation of imines using an iridium catalyst with a P,N-type ligand (**31**, Figure 14); this work was soon extended to the area of unfunctionalized olefins.⁵⁸ In the following years a number of such chiral P,N-ligands^{58,59,60,62} were used in the Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins (Figures 13 and 14). During the 1990s iridium complexes with phosphine-oxazoline⁵⁸ and phosphine-imidazole⁶⁰ ligands were synthesized and evaluated in this reaction. In many cases, these produced excellent yields (99%) and *ee* values (>99%).



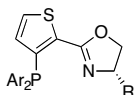
Pfaltz *et al.*^{58a}
Yield 99%, 97% *ee*,
S/C = 1000, *p* = 50 bar, *t* = 2 h



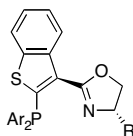
Gilbertson *et al.*^{58f}
Yield 99%, 92% *ee*,
S/C = 300, *p* = 50 bar, *t* = 2 h



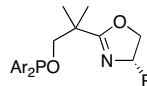
Cozzi/Pfaltz.^{58c}
Yield 100%, 99% *ee*,
S/C = 100, *p* = 50 bar, *t* = 2 h



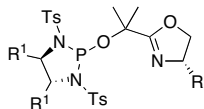
Cozzi *et al.*^{53d}
Yield 99%, 99% *ee*,
S/C = 100, *p* = 50 bar, *t* = 2 h



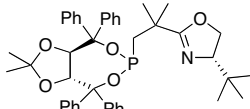
Cozzi *et al.*^{53d}
Yield 99%, 94% *ee*,
S/C = 100, *p* = 50 bar, *t* = 2 h



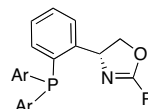
Pfaltz *et al.*^{58j}
Yield 99%, 98% *ee*,
S/C = 1000, *p* = 50 bar, *t* = 2 h



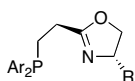
Pfaltz *et al.*^{58b}
Yield 99%, 87% *ee*,
S/C = 25, *p* = 100 bar, *t* = 2 h



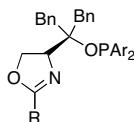
Pfaltz *et al.*^{58b}
Yield 100%, 75% *ee*,
S/C = 25, *p* = 100 bar, *t* = 2 h



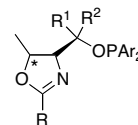
Zhang *et al.*^{58g}
Yield 99%, 99% *ee*,
S/C = 200, *p* = 50-100 bar, *t* = 2 h



Burgess *et al.*^{60b}
Yield 99%, 95% *ee*,
S/C = 500, *p* = 50 bar, *t* = 2 h



Pfaltz *et al.*^{58d}
Yield 100%, 98% *ee*,
S/C = 250, *p* = 50 bar, *t* = 2 h



Pfaltz *et al.*^{53c}
Yield 99%, 99% *ee*,
S/C = 2000, *p* = 50 bar, *t* = 2 h

Figure 14. Overview of some phosphine-oxazoline ligands used in the Ir-catalyzed asymmetric hydrogenation of olefins.

4.3 Phosphine-oxazoline ligands applied to the iridium-catalyzed asymmetric hydrogenation of olefins (*Paper II*)

In the first series of hydrogenation experiments, Ir complexes **28a-e** were tested on the commonly used unfunctionalized model substrate *trans*- α -methylstilbene (**55**). The results of these reactions, which were performed in CH₂Cl₂ under 20 bar hydrogen pressure and with a catalyst loading of 0.5 mol%, are presented in Table 5.

Table 5. Asymmetric hydrogenation of *trans*- α -methylstilbene (**55**) using Ir-complexes **28a-e**.

Entry	Ligand	Complex	time (h)	Conv., % ^a	% <i>ee</i> ^b	Abs. Conf. ^c
1.		28a	<0.5	99	82	(<i>R</i>)
2.		28b	<0.5	99	92	(<i>R</i>)
3.		28c	0.5	99	73	(<i>R</i>)
4.		28d	0.5	99	74	(<i>R</i>)
5.		28e	12	81	96	(<i>R</i>)

^a Determined by ¹H NMR. ^{b,c} Determined by chiral HPLC, absolute configuration is assigned by comparison of retention times with literature values.^{58a}

Complex **28a**, prepared from the *iso*-propyl-substituted ligand **23**, catalytically hydrogenated **55** to (*R*)-1,2-diphenylpropane with full conversion and 82% *ee* in <0.5 hour (Table 5, entry 1). When the *iso*-propyl substituent was exchanged with a *tert*-butyl group (complex **28b**) the enantiomeric excess of

the same catalytic hydrogenation was 92%, and was also complete in less than 0.5 hour (Table 5, entry 2). Ir complexes **28c** and **28d** (Table 5, entries 3 and 4) also reduced the model substrate to full conversion in less than 0.5 hour, but the reaction suffered from a drop in enantioselectivity; (*R*)-1,2-diphenylpropane was produced with enantiomeric excesses of 73% and 74%, respectively. As observed in asymmetric imine hydrogenation, catalysts **28c** and **28d** yielded very similar results for olefin hydrogenation, including producing the same configuration in the product. Of the catalysts tested it was **28e**, based on the 5',5'-diphenyloxazolinebased ligand, that produce the best enantioselectivity. For example, **28e** hydrogenated **55** in 96% *ee* and 81% conversion in 12 hours. In general, the complexes produced promising results and the hydrogenation results imply that the steric bulk on the oxazoline ring has a profound influence on the stereoselectivity.

The high enantioselectivities produced by **28e** led us to test this Ir complex in reactions with other olefins (Table 6). With an elevated hydrogen pressure (80 bar) and a reaction time of 12 hours, complex **28e** hydrogenated *trans*- α -methylstilbene (**55**), to complete conversion and 98% *ee* (Table 6, entry 1). Even higher selectivity was observed for (*E*)-2-(4-methoxyphenyl)-2-butene (**56**), which reached 99% *ee* and full conversion within 12 hours (Table 6, entry 2). The same high degree of enantioselectivity was not displayed when the acrylic ester **57** (Table 6, entry 3) was subjected to these reaction conditions. Full conversion was obtained after 12 hours, but the *ee* was only a moderate 69%. A pronounced improvement was observed when the hydrogenation of the same substrate was catalyzed by Ir complex **28a** at a lower hydrogen pressure (20 bar) — complete conversion was reached in less than 0.5 hour, and the *ee* was 88% (Table 6, entry 4). The acrylic ester **58** was reduced in 90% *ee* using **28e** (Table 6, entry 5). High selectivity was observed for substrate **59** (6-methoxy-1-methyl-3,4-dihydronaphthalene), which was reduced to its (*S*) isomer with 95% *ee* and full conversion (Table 6, entry 6). Olefin **60** is an analog of **59** that lacks the methoxy group on the aromatic ring. It showed low conversion and poor *ee* values when subjected to hydrogenation by both Ir complexes **28a** and **28e** (Table 6, entries 7 and 8). Like **59**, the major reduction product from substrate **60** possessed the *S* configuration. Olefin **61**, an isomer of **60**, was converted rather cleanly to the reduced product, giving a 94% *ee*.

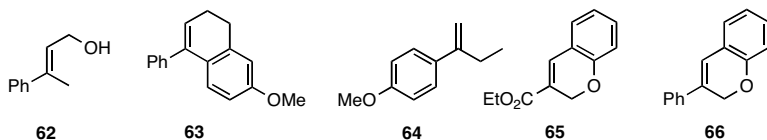
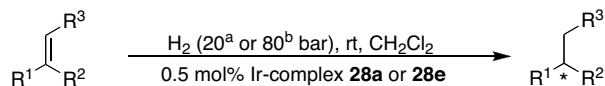
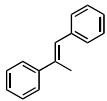
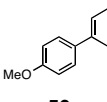
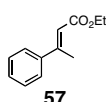
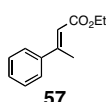
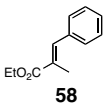
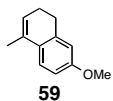
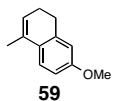
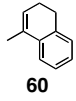
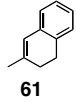


Figure 15. Structures of olefins inert in Ir-catalyzed asymmetric hydrogenation with catalysts **28a** and **28e**.

Some of the substrates we evaluated, however, turned out to be inert in the Ir-catalyzed asymmetric hydrogenation with catalysts **28a** and **28e** (Figure 15). Olefins **62-66** were not hydrogenated under the standard conditions.

Table 6. Asymmetric hydrogenation of different alkenes using the Ir complexes **28a-e**.



Entry	Olefin	Complex	time (h)	Conversion, % ^c	% ee ^d
1.	 55	28e	12	99	98 (<i>R</i>)
2.	 56	28e	12	99	99 (<i>R</i>)
3.	 57	28e	12	99	69 (<i>R</i>)
4.	 57	28a	<0.5	99	88 (<i>R</i>)
5.	 58	28e	12	99	90 (<i>R</i>)
6.	 59	28e	12	99	95 (<i>S</i>)
7.	 59	28a	12	99	21 (<i>S</i>)
8.	 60	28e	12	99	38 (<i>S</i>)
9.	 61	28e	12	99	95 (<i>R</i>)

^a For hydrogenation with Ir-complex **28a**. ^b Pressure applied for hydrogenations using Ir-complex **28e**.

^c Determined by ¹H NMR. ^d Determined by chiral HPLC, absolute configuration is assigned by comparison of retention times with literature values.^{58a}

As the final part of this work with olefins, the Ir complexes **29a-e**, which bore various phosphine substituents, were evaluated in the hydrogenation of the model *trans*- α -methylstilbene (**55**) (Table 7). Ir complex **29a**, which had a di(cyclohexyl)phosphine substituent, hydrogenated **55** into (*R*)-1,2-diphenylpropane with 99% conversion and high optical purity (92%) after 0.5 hours (Table 7, entry 1). This was also the highest enantiomeric excess observed for these complexes.

Table 7. Asymmetric hydrogenation of *trans*- α -methylstilbene (**55**) using Ir-complexes **29a-e**.

55

Entry	Ligand	Complex	time (h)	Conv., % ^a	% <i>ee</i> ^b	Abs. Config. ^c
1.		29a	0.5	99	92	(<i>R</i>)
2.		29b	0.5	99	78	(<i>R</i>)
3.		29c	0.5	99	82	(<i>R</i>)
4.		29d	20	84	10	(<i>R</i>)
5.		29e	6	99	84	(<i>R</i>)

^a Determined by ¹H NMR. ^{b,c} Determined by chiral HPLC, absolute configuration is assigned by comparison of retention times with literature values.^{58a}

29b and **29c**, prepared from di(*ortho*-tolyl)phosphine chloride (Table 7, entry 2) and di(3,5-dimethylphenyl)phosphine chloride (Table 7, entry 3), respectively, gave *ee* values of 78% and 82%. Full conversion was achieved in 0.5 hour with both these complexes. A dramatic drop in selectivity was observed when complex **29d**, which contains the di(*ortho*-methoxyphenyl)phosphine group, was the catalyst; only a poor enantiomeric excess (10%) was observed, though 84% conversion was reached after 20 hours (Table 7, entry 4). Complex **29e**, which differed from **29d** in that it had the methoxy group at the *para* position, reduced *trans*- α -methylstilbene with good enantioselectivity (84% *ee*) and full conversion in six hours (Table 7, entry 5). From these experiments, complex **28e** stands out as the most efficient catalyst in the reduction of unfunctionalized olefins.

5 Asymmetric hydrogenation of fluorinated olefins using N,P-Ligated Iridium Complexes (*Paper III*)

5.1 Introduction

Over the past decades, organofluorine compounds have been increasing in popularity within the agrochemical and pharmaceutical industry.⁶¹ In 2005, approximately 30-40% of agrochemicals and 20% of pharmaceuticals were estimated to contain fluorine.⁶² Today many of the top-selling pharmaceuticals contain fluorine; well-known drugs like the anti-depressant Prozac[®], the cholesterol-reducing Lipitor[®] and the selective COX-2 inhibitor Celebra[®] (used for rheumatoid arthritis) are some examples of highly successful pharmaceutical products that are containing one or more atoms of this element (Figure 16).⁶³

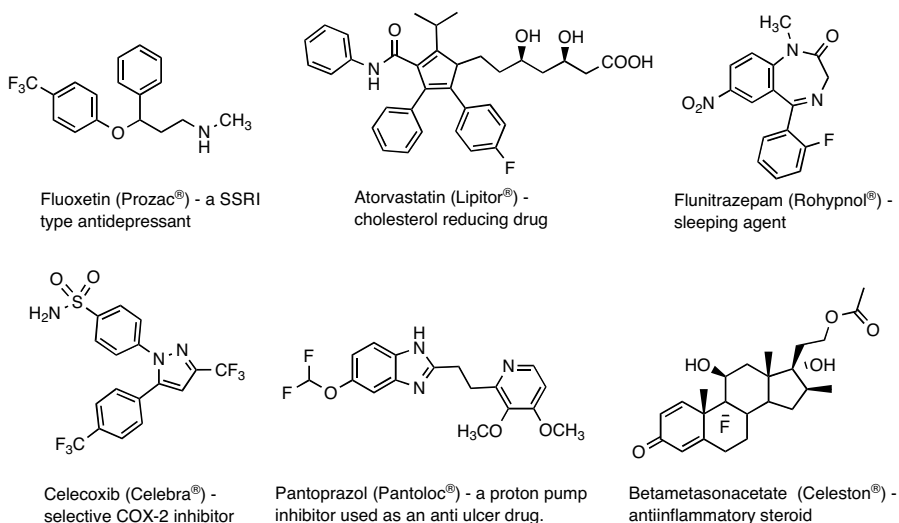
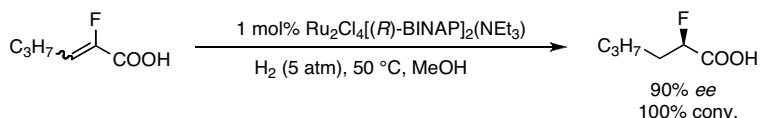


Figure 15. Examples of top-selling drugs containing fluorine.

The incorporation of fluorine in a structure can alter the properties of the molecule significantly and therefore modify the activity or the toxicity of a drug molecule. For instance, fluorination usually increases lipophilicity of a molecule.⁶⁴

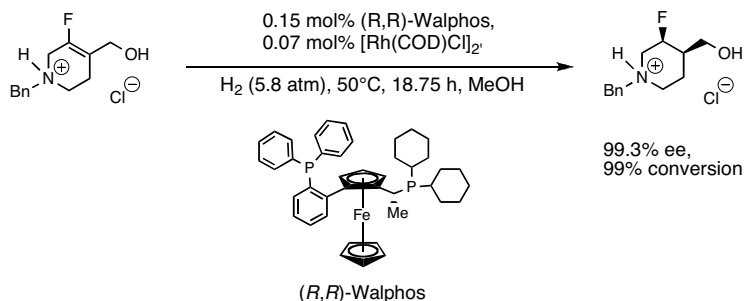
5.2 Creating fluorine-bearing stereocenters

The synthetic methods for creating a fluorine-containing stereocenter are still few. Most literature reports involve asymmetric fluorination of β -ketoesters or β -keto phosphonates.⁶⁵ The use of asymmetric hydrogenation to produce a CHF-bearing stereocenter has been only sparsely reported. Saburi *et al.* published work on the ruthenium-based asymmetric hydrogenation of 2-fluoroalkenoic acids using (*R*)-BINAP as a chiral ligand in 1992.⁶⁶ They were able to obtain *ee* values up to 90% accompanied by full conversion.



Scheme 20. Saburi *et al.* reported good results on the asymmetric hydrogenation of 2-fluoroalkenoic acids using a ruthenium-BINAP system in 1992.

Recently, Nelson *et al.* published a patent on the asymmetric hydrogenation of a cyclic vinyl fluoride using Rh-Walphos, and reported excellent enantioselectivity (99.3% *ee*, Scheme 21).⁶⁷

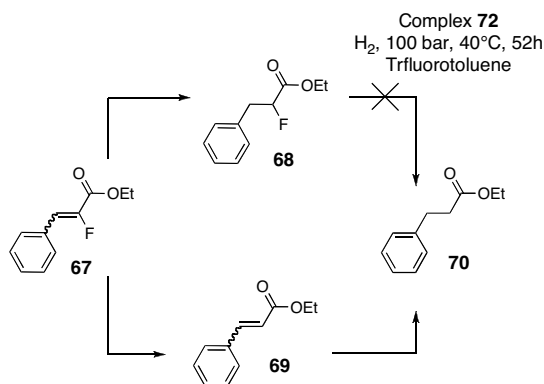


Scheme 21. Using (*R,R*)-Walphos Nelson *et al.* obtained an impressive 99.3% *ee* in the rhodium-based hydrogenating of a cyclic vinyl fluoride.

5.3 Loss of fluorine: a challenge in the hydrogenation of vinyl fluorides

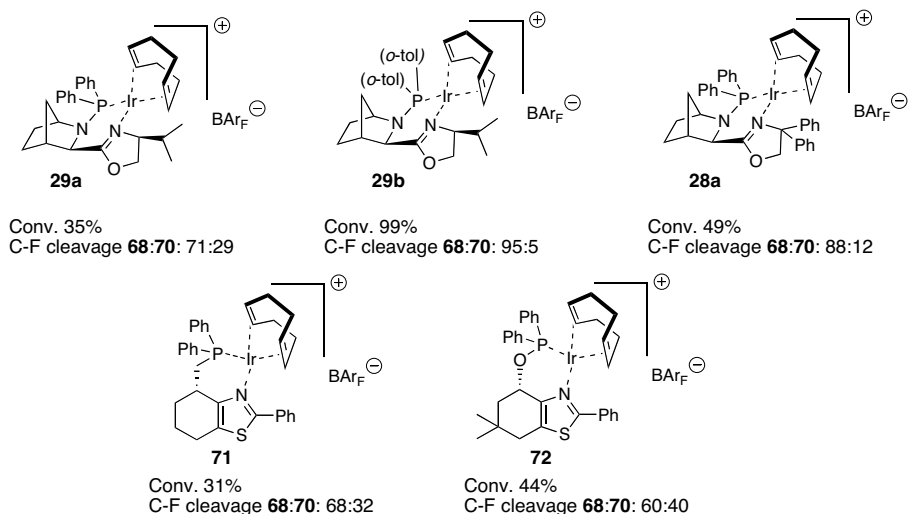
Preliminary hydrogenation experiments using different Ir complexes to reduce vinyl fluorides revealed that fluorine loss was a significant problem in the hydrogenation of these substrates. For example, fluorine loss was as high as 62%, when using complex **72** (Figure 17) to hydrogenate ester **67** (Scheme 19).

There are two likely routes leading to the defluorinated hydrogenated product **70** (Scheme 19) from **67**. In one possible path, the vinyl fluoride **67** first undergoes hydrogenation of the C=C double bond to yield **68**, from which the fluorine is subsequently cleaved off (Scheme 19, upper pathway). In another plausible route, the fluorine is cleaved off **67** prior to the hydrogenation of the C=C double bond of **69** (Scheme 19, lower pathway). The latter path seems more likely, as the vinylic fluorine is less stable than its saturated counterpart. Indeed, when the (\pm)-**68** was prepared and subjected to hydrogenation with complex **72**, only the starting compound **68** was detected. This suggests that the latter route in Scheme 19 is the likely defluorination path.



Scheme 19. Loss of fluorine is an unwanted side reaction in the iridium-catalyzed hydrogenation reaction of vinyl fluorides. Experiments indicate that the latter route for this reaction is the most plausible one.

Several iridium complexes were prepared and screened in the hydrogenation of an *E/Z*-mixture of vinyl fluoride **67** in order to find a catalyst that caused minimal C-F bond cleavage and maximal conversion (Figure 17). The observed C-F bond cleavage and conversions varied quite a bit for the different complexes and the choice of solvent was also important. When using α,α,α -trifluorotoluene as solvent, the thiazole-based catalyst **72** produced 62% defluorination in the hydrogenation of vinyl fluoride **67**, and only a disappointing 44% conversion. However, the observed defluorination was reduced from 62% to 40% when the reaction was run in dichloromethane.



Conditions: 100 bar H₂, 72 h, 40 °C in CH₂Cl₂.

Figure 17. Overview of conversions and C-F bond cleavage in the hydrogenations of vinyl fluoride **67** using different Ir catalysts. The highest conversion and the lowest C-F bond cleavage were achieved with complex **29b**.

The analogous complex **71** produced similarly dissatisfying levels of C-F bond hydrogenolysis and conversion. More successful results were obtained using the complexes **28a**, **29a** and **29b**, based on the aza-norbornyl scaffold, as they all caused much less defluorination. With only a 5% loss of fluorine, and 99% conversion, complex **29b** clearly performed best among the three, and was chosen for the further studies in the hydrogenation of fluorinated olefins.

5.4 Application of N,P-ligated iridium complexes in the asymmetric hydrogenation of fluorinated olefins

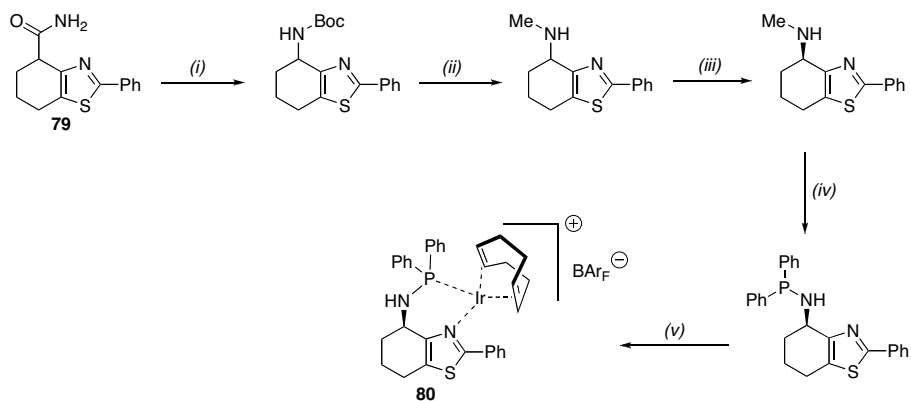
In a series of hydrogenation experiments, iridium complex **29b** was used to hydrogenate several tri- and tetrasubstituted vinyl fluorides (Table 9). The reactivities varied greatly among the different substrates. The ester (entry 1, Table 9) required high pressures and elevated temperatures (40 °C) to hydrogenate; this was in contrast to the acetate (entry 2) and the alcohol (entry 3) substrates. The latter underwent full conversion within 24 hours at room temperature using 20 bar H₂ and 0.5 mol% catalyst. The observed *ee* values varied from poor (29%, entry 1) to good (87% for entry 2 and 80% for entry 3).

Table 9. Hydrogenation of vinyl fluorides using Ir complexes **29b** and **80**.

Entry	Substrate	Complex 29b				Complex 80			
		Conv. ^a	Ratio ^a A : B	<i>ee</i> ^b (%)	Abs. Conf. ^c	Conv. ^a	Ratio ^a A : B	<i>ee</i> ^b (%)	Abs. Conf. ^c
1.		99	98.2	29	(<i>R</i>)	0	–	–	–
2.		78	88:12	87	(<i>R</i>)	82	95:5	>99	(<i>R</i>)
3.		99	94:6	80	(<i>R</i>)	97	100:0	99	(<i>R</i>)
4.		21	100:0	57	(+)- (2 <i>R</i> ,3 <i>S</i>)	30	53:47	rac	–
5.		25	100:0	74	(+)- (2 <i>S</i> ,3 <i>S</i>)	25	70:30	rac	–
6.		24	71:29	90	(+)- (2 <i>S</i> ,3 <i>S</i>)	69	91:9	90	(+)- (2 <i>S</i> ,3 <i>S</i>)

^a Determined by ¹H NMR. ^b Determined by chiral GC or HPLC. ^c See Appendix: Supplementary information

In an attempt to improve these results, we synthesized a modified ligand, **80** (Scheme 22). The complexes **28a**, **29a**, and **29b**, which in general caused less defluorination and overall higher reactivity than **71** and **72**, all possess a nitrogen atom that links the ligand backbone to the phosphine group, whereas **71** and **72** have a methylene group and an oxygen atom linker, respectively. Recent work shows that thiazole-based catalysts are more effective than their oxazole-based counter parts for catalytic asymmetric olefin hydrogenation.^{58h,68} Therefore, we chose to make a thiazole-based ligand with nitrogen linker. The outline of the synthesis of complex **80** starting from the amide precursor **79** is depicted in Scheme 22.



Conditions and reagents: (i) DMF/*t*-BuOH (16:13), Pb(OAc)₄, Et₃N, 70 °C, 42 h; (ii) LiAlH₄, THF, reflux 1.5 h CH₂Cl₂; (iii) Chiral HPLC; (iv) Ph₂PPh, DIPEA, toluene, 0 °C overnight; (v) [Ir(COD)Cl]₂, CH₂Cl₂, reflux under N₂, 1 h; NaBARF, H₂O/CH₂Cl₂, rt, 30 min.

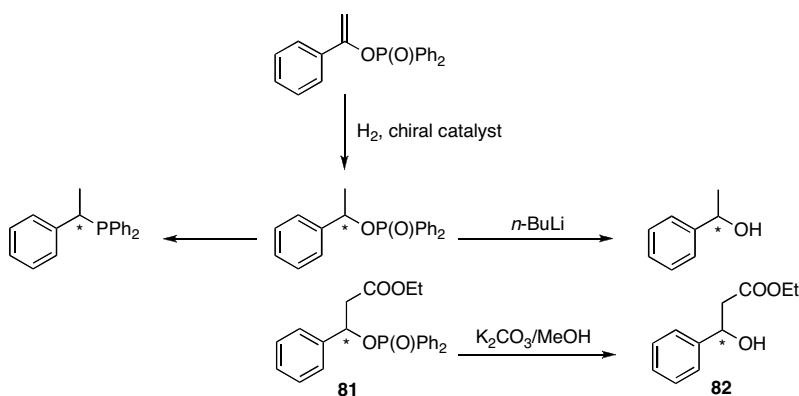
Scheme 22. Synthesis of Ir complex **80**.

When tested in the hydrogenation of vinyl fluorides **73-78** (Table 9), complex **80** showed improved enantioselectivity compared to complex **29b** for both the acetate, **74**, and the alcohol, **75**, (entry 2 and 3). Contrary to the aza-norbornyl based catalysts, complex **80** was not able to catalyze the hydrogenation of the trisubstituted ester (entry 1). This was a surprise as its tetrasubstituted counterpart underwent hydrogenation with 30% conversion (entry 4).

6 Iridium-catalyzed asymmetric hydrogenation of di- and trisubstituted enol phosphinates (*Paper IV*)

6.1 Introduction

As a continuation of our work on the iridium-based asymmetric hydrogenation of imines, olefins and fluorinated olefins, we wanted to expand this reaction's substrate scope to also include enol phosphinates. Enol phosphinates are structural analogues of enol acetates, and are synthetically useful because the resulting chiral alkyl phosphinates easily can be transformed into the corresponding alcohols or phosphanes with preservation of the stereogenic center (Scheme 23).⁶⁹ For instance, the phosphinate group of **81** could be cleaved off under mild conditions using K_2CO_3 in dry methanol, yielding **82** with the carboxylic ester group intact.



Scheme 23. Chiral alkylphosphinates can be transformed into different products with conservation of the stereochemistry.

Similarly to largely unfunctionalized olefins, the ester groups of enol esters and enol phosphinates coordinate only weakly to metal centers, making them a more difficult substrate class for rhodium- and ruthenium-catalyzed asymmetric hydrogenation than their topological counterparts, enamides. The

most successful enantioselective hydrogenation of enol esters to date, used rhodium catalysts with ligands like DIPAMP, DuPhos, KetalPhos and Tang-Phos.⁷⁰ Published work on the asymmetric hydrogenation of enol phosphinates is rare. In 1981, Kumada and co-workers reported the rhodium-catalyzed asymmetric hydrogenation of enol phosphinates, and obtained moderate enantioselectivities.⁷¹ More recently Andersson *et al.* published a communication reporting the iridium-based asymmetric hydrogenation of terminal phosphinates.⁷² Catalyst **29b** produced high conversions and good to excellent enantioselectivities (*ee* values: 85% to >99%) for this reaction within few hours of reaction.

6.2 Asymmetric hydrogenation of enol phosphinates

6.2.1 Asymmetric hydrogenation of trisubstituted aryl-alkyl and ester-functionalized enol phosphinates

A variety of trisubstituted enol phosphinates were subjected to asymmetric hydrogenation using catalyst **29b**, and the results are presented in Table 11. When increasing the size of the alkyl group (R^2) in the enol phosphinates (**83a-83c**, entries 1-3, Table 11), we observed a decrease in conversion and a small drop in the enantioselectivity. The methyl-substituted substrate **83a** proceeded to completion with a 96% *ee* within 3 hours, whereas the conversion and selectivity observed in the hydrogenation of the ethyl-substituted substrate **83b** under the same conditions were 90% and 92%, respectively. For the *iso*-propyl analogue **83c**, the observed conversion was 89% and the selectivity was 91% *ee*.

Table 10. Initial asymmetric hydrogenation of enol phosphinate **83** with Ir complexes **29b** and **80**.

Entry	Ligand	Ir-complex	Conv. ^a , %	<i>ee</i> ^b , %
1.		29b	>99	96
2.		28a	>99	74
3.		28e	>99	93

^a Determined by ¹H NMR spectroscopy. ^b Determined by chiral HPLC.

A variety of trisubstituted enol phosphinates were subjected to asymmetric hydrogenation using catalyst **29b**. The results from these experiments are presented in Table 11. When increasing the size of the alkyl group (R^2) in the enol phosphinates (**83a-83c**, entry 1-3, Table 11) we observed a decrease in the conversion accompanied with a small drop in the enantioselectivity. The methyl-substituted substrate **83a** proceeded to completion with a 96% enantioselectivity within 3 hours whereas the conversion and selectivity for the hydrogenation of the ethyl-substituted substrate **83b** under the same conditions was 90% and 92%, respectively. For the *iso*-propyl analogue **83c** the observed conversion was 89% and selectivity 91% ee.

Table 11. Hydrogenation of aryl-alkyl enol phosphinates using Ir-complex **29b**.

Entry	Substrate	Conv. ^b (%)	ee ^c (%)	Config. ^d	Entry	Substrate	Conv. ^b (%)	ee ^c (%)	Config. ^d
1		>99	96	<i>R</i>	8		>99	99 ^e	<i>R</i>
2		90	92	<i>R</i>	9		>99	>99	<i>S</i>
3		89	90	<i>R</i>	10		>99	99	<i>S</i>
4		>99	>99	<i>R</i>	11		>99	>99	<i>S</i>
5		>99	>99	<i>R</i>	12		58	92	(+) ^f
6		>99	99	<i>R</i>	13		98	93	<i>S</i>
7		>99	98	<i>R</i>	14		50	58	(+) ^f

^a Conditions: CH_2Cl_2 , 0.5 mol% catalyst, 30 bar H_2 (entries 1-3) or 50 bar (entries 4-14). ^b Determined by ^1H NMR spectroscopy. ^c Determined by chiral HPLC. ^d Determined by hydrolyzing the product to the corresponding alcohol and comparing its optical rotation with that of the known alcohol. ^e Determined for the corresponding alcohol by chiral HPLC. ^f Absolute configurations were not determined. ^g 2 mol% catalyst loading.

Substituting the alkyl group with a carboxylic ester to give **84a** increased the selectivity to >99% ee. Unfortunately, the reaction proceeded at a much

slower rate (90% conversion in 12 h), but this could be compensated for by elevating the hydrogen pressure from 30 to 50 bar; this led to full conversion in 6 hours without lowering the enantioselectivity. In order to maximize conversions, the remaining reactions were run at a 50-bar hydrogen pressure. Notably, introducing electron-donating (**84b**) or electron-withdrawing (**84c** and **84d**) groups at the phenyl group's *para* position did not change the reactivity or the selectivity, and all substrates were completely hydrogenated with excellent enantioselectivities (98–>99% *ee*). The phosphorus triester **84e** was also hydrogenated in 99% *ee* and to full conversion. It did so without any cleavage of the phosphorous triester, which was an issue when hydrogenating terminal enol phosphinate triesters.⁷²

An array of ester-substituted enol phosphinates in which the aryl group (R^1) was replaced by an alkyl group (**85a–85e**, entries 9–13, Table 11), was also screened. Substrate **85a** (entry 9, Table 11), in which the phenyl ring of **4a** has been substituted with a methyl group ($R^1 = \text{Me}$), was hydrogenated to completion with 99% *ee*. Interestingly, the bulkiness of the alkyl group did not influence the selectivity significantly. Therefore, when the methyl group was replaced with an ethyl (**85b**, entry 10) or *iso*-propyl group (**85c**, entry 11), the hydrogenation reaction went to completion with excellent enantioselectivities ($\geq 99\%$ *ee*). Even substrate **85e**, which has a bulky *tert*-butyl group, gave 98% conversion and 93% *ee*. Introducing a halogen atom in the alkyl chain had a considerable effect on the reactivity. For the chloroalkyl-substituted enol phosphinate **85d** (entry 12), a conversion of 58% was obtained; whereas the corresponding ethyl analogue **85b** was hydrogenated to >99% conversion. The selectivity (92% *ee*) was also lower than for the corresponding ethyl analogue (99% *ee*). However, by increasing the catalyst loading from 0.5 mol% to 2 mol%, we were able to improve the conversion for **85d** from 58% to 95% without losing any selectivity. When comparing entries 4–7 with entries 9–13, we see no significant reactivity difference between alkyl- and aryl-substituted β -ketoester-derived enol phosphinates; both types were completely hydrogenated in 6 hours with >99% *ee* using 0.5 mol% catalyst. For enol phosphinate **85f** (entry 14), which has a conjugated double bond system, 50% conversion and moderate enantioselectivity 58% *ee* was observed.

6.2.2 Asymmetric hydrogenation of purely alkyl-substituted enol phosphinates

The asymmetric hydrogenation of prochiral alkyl-alkyl ketones to chiral alcohols by ruthenium and rhodium catalysts is still challenging because of the difficulty in differentiating two alkyl groups.⁷³ This is reflected by the chemical literature, which reports that only a few purely alkyl-substituted ketones have been hydrogenated with good enantioselectivity.⁷⁴ Recently, Noyri and co-workers achieved 98% *ee* in the hydrogenation of *tert*-

butylmethylketone.⁷⁵ The products of the asymmetric hydrogenation of enol phosphinates are chiral alkyl phosphinates that can be transformed into the corresponding alcohols, so the reaction could be considered as an alternative to the direct hydrogenation of ketones. In this study, alkylketones were converted to the corresponding enol phosphinates and subjected to hydrogenation by Ir complex **29b**. The products were converted to the corresponding alcohols by treatment with *n*-BuLi. The results are summarized in Table 12. All the substrates were hydrogenated to completion with good to excellent enantioselectivities ($\geq 90\%$ *ee*). For the hydrogenations of the disubstituted alkyl enol phosphinates **86a-86d** (entries 1-4, Table 12) we obtained some of the highest *ee* values (92%, >99%, 92%, and 98%) ever reported for this class of compounds. Also, the trisubstituted alkyl enol phosphinates **86e** and **86f** (entries 5 and 6) displayed good enantioselectivities (90-91% *ee*) and were interesting because the asymmetric hydrogenation of their ketone counterparts to give the same chiral alcohols has not been reported in the literature.

Table 12. Hydrogenation of alkyl-substituted enol phosphinates using Ir complex **29b**.

Entry	Substrate	Conv. ^a (%)	<i>ee</i> ^b (%)	Config. ^c
1		>99	92	<i>R</i>
2		>99	>99	<i>R</i>
3		>99	92	<i>R</i>
4		>99	98	(+) ^d
5		>99	90 ^e	(+) ^d
6		>99	91 ^e	(+) ^d

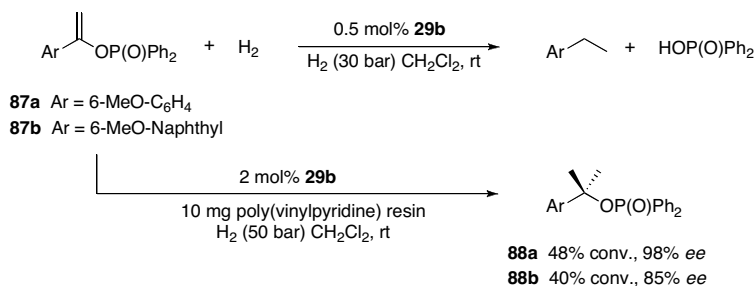
^a Determined by ¹H NMR spectroscopy. ^b Determined by chiral HPLC.

^c Determined by hydrolyzing the product to the corresponding alcohol and comparing its optical rotation with that of the known alcohol. ^d Absolute configuration was not determined. ^e Determined after conversion to the corresponding 3,5-dinitrobenzoate.

We also hydrogenated the chiral, racemic substrate **86d** (entry 4) and found that no kinetic resolution was caused by the pre-existing chiral center — both enantiomers were reduced with an enantioselectivity of 98%.

6.2.4 Asymmetric hydrogenation of acid-sensitive enol phosphinates

Hydrogenolysis is a known issue for the iridium-catalyzed asymmetric hydrogenation of acid-sensitive substrates.⁷⁶ When the acid-sensitive enol phosphinates **87a** and **87b** were hydrogenated under standard conditions, the resulting products were the hydrogenolyzed products and not the expected corresponding alkyl phosphinates (Scheme 23).⁷² By using a tiny amount of a proton scavenger (poly(4-vinylpyridine)resin) and a higher catalyst loading (because the proton scavenger deactivates the catalyst), the acid-sensitive substrates **87a** and **87b** could be hydrogenated to the alkyl phosphinates **88a** and **88b** with good or excellent *ee* values, albeit in low conversion (Scheme 23).



Scheme 23. The asymmetric hydrogenation of especially acid-sensitive enol phosphinates could be accomplished by adding a proton scavenger, poly(4-vinylpyridine), to the reaction.

7. Summary in Swedish

Människan har sedan urminnes tider använt sig av kemi för att överleva och förbättra sina livsvillkor; konservering av mat, förbränning, alkemi, samt bruk av elixir för att bota och lindra olika åkommor är några exempel. Den gren av kemin som kallas organisk kemi kom ursprungligen från idén att djur och växter hade en livskraft som inte kunde skapas från mineraler och andra oorganiska material. Allteftersom förståelsen för materiens uppbyggnad och uppbyggnaden av levande organismer ökade kom organisk kemi att definieras som kolföreningarnas kemi. Denna typ av kemiska föreningar innehåller grundämnena kol och väte och utgör fundamentet i biologiska system. Organisk kemi idag innefattar manipulation av organiska föreningar för att framställa exempelvis plaster, läkemedel, bränslen, färger m.m. Den organiska kemin har nära band till andra områden inom naturvetenskapen som fysik, biologi, nanoteknik och medicin. Vetenskapsområden som biokemi, polymerkemi och läkemedelskemi är sprungna ur den organiska kemin.

En viktig egenskap hos organiska föreningar är spegelbildsisomeri eller kiralitet. Kiralitet innebär att två stycken näst intill identiska molekyler är varandras spegelbilder, de kallas då enantiomerer. Enantiomerer har samma fysiska och kemiska egenskaper i en akiral miljö men de kan ha helt olika egenskaper då andra kirala element finns närvarande. Som exempel kan tas en vänsterhand och en högerhand, de är i grunden identiska men varandras spegelbilder. Endast högerhanden kan hälsa på en annan högerhand, de har alltså olika egenskaper i närvaro av ett annat kiralt objekt. Biologiska system är uppbyggda av kirala organiska molekyler där endast en av de två spegelbilderna (enantiomererna) förekommer. Därför kan två enantiomerer av en kiral substans ha helt olika effekt i människokroppen. Vid läkemedelsframställning är det alltså väsentligt att endast generera den önskade enantiomeren i så hög renhet som möjligt för att få bästa möjliga effekt och undvika bieffekter.

Vid framställningen av organiska molekyler bildas som regel biprodukter och andra restprodukter. I den kemiska industrin är det därför väsentligt att optimera förhållandena i en kemisk reaktion för att erhålla maximal mängd produkt och minimalt med biprodukter på kortast möjliga tid. Effektivisering av kemiska reaktioner är alltså viktigt både av praktiska, ekonomiska och miljömässiga skäl. Många kemiska reaktioner kan snabbas upp med hjälp av

katalysatorer. Katalysatorer tillsätts vanligtvis i små mängder och kan vara av många olika slag. Vanligt är att man använder sig av metaller exempelvis platina, koppar, nickel och palladium. Metallernas egenskaper är helt olika de för organiska ämnen och möjliggör reaktioner att äga rum som annars hade varit omöjliga.

Denna avhandling behandlar asymmetrisk katalys d.v.s. katalys av kemiska reaktioner där huvudsakligen en av de möjliga enantiomererna bildas. Mer precist har hydrogeneringsreaktioner, reaktioner där en vätgasmolekyl adderas till en större molekyl, studerats. Katalysatorerna som undersökts är baserade på metallen iridium bunden till en kiral organisk molekyl (ligand). Iridium snabbar upp överföringen av vätgas till målmolekylen (substratet) och liganden styr överföringen så att huvudsakligen en enantiomer bildas. I de olika arbetena har vi utvecklat nya katalysatorer av detta slag som med effektivt och med hög selektivitet kan utföra den önskade reaktionen. Hydrogenering av olika typer av substrat som inte har behandlats tidigare har också undersökts.

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– *Soli Deo Gloria* –

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