From Ruthenium to Iron for the Catalytic Reduction of Ketones: Catalysis and Mechanistic Insights

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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A range of air- and moisture-stable phosphonium salts was prepared. Compounds were isolated in high yield and fully characterized. The properties of these compounds and the nature of their formation were explored. The phosphonium salts react with base to give phosphino-aldehydes which are important building blocks in the synthesis of PNNP ligands. The condensation reaction between phosphino-aldehydes and a diamine usually employed for the preparation of PNNP ligands was not applicable to the phosphino-aldehydes derived from these phosphonium salts as a result of the high reactivity of the nucleophilic phosphorus causing uncontrollable side-reaction.

In order to resolve this problem, a template reaction with iron(II) Lewis acid was used to suppress the reactivity of the phosphorus via coordination. The reaction was successful and gave rise to bis-tridentate complexes with PNN ligands ([Fe(Ph₂PCH₂CH=N---NH₂)₂][BPh₄]₂, where N---NH₂ depends on diamine used) as the kinetic product and to desired tetradoentate complexes with PNNP ligands (trans-[Fe(Ph₂PCH₂CH=N---N=CHCH₂PPh₂)(CH₃CN)₂][BPh₄]₂, where N---N depends on diamine used) as a thermodynamic product of the reaction. The reaction appeared to be very general; complexes
with various diamines incorporated in the ligand backbone were prepared in high yield and fully characterized.

Mono-carbonylation reaction of the complexes containing tetradentate PNNP ligands resulted in the formation of the precatalysts with a general formula (trans-[Fe(Ph$_2$PCH$_2$CH=N--N=CHCH$_2$PPh$_2$)(CO)(Br)][BPh$_4$]. These precatalysts give active (TOF up to 28000 h$^{-1}$) and enantioselective (up to 95 % ee) catalytic systems for the ATH of ketones when activated with base in a solution of 2-propanol as the reducing agent.

On the basis of a kinetic study and other evidence, we propose a mechanism of activation and operation of the catalytic system involving the precatalyst trans-[Fe(CO)(Br)(Ph$_2$CH$_2$CH=N-((S,S)-C(Ph)H-C(Ph)H)-N=CHCH$_2$PPh$_2$)][BPh$_4$] and acetophenone as a model substrate. We determined that the activation of the precatalyst to the active species involves the stereoselective reduction of one imine group of the ligand, since when the active species are quenched with acid, the complex trans-[Fe(CO)(Cl)(Ph$_2$CH$_2$CH-(H)N-((S,S)-C(Ph)H-C(Ph)H)-N=CHCH$_2$PPh$_2$)][BPh$_4$] containing amine and imine functionalities in the backbone is produced.
Acknowledgements

I would like to say a special thank you to my supervisor, Professor Bob Morris, who guided me through my graduate studies, was always helpful in all possible aspects of the research and significantly influenced my personal and professional development. His kindness and patience made my stay in Morris group a pleasant and fruitful experience that I will never forget.

I would like also to thank past and present members of the Morris group for their involvement and dedication to the research projects that we were involved in as well as friendly and professional environment that they created inside and outside of the laboratory.

I would like to acknowledge the staff personal in the Department of Chemistry at the University of Toronto for their help hard and dedicated work, in particular, Dr. Alan Lough in the X-ray crystallography and Dr. Tim Burrow in the NMR laboratories.

At the end I want to say thank you to my family and friend who supported me throughout my studies.
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<tbody>
<tr>
<td>ATH</td>
<td>Asymmetric Transfer Hydrogenation</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>bn</td>
<td>ortho-phenylenediamine</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bu₄N</td>
<td>tetrabutylammonium</td>
</tr>
<tr>
<td>C/B/S</td>
<td>catalyst to base to substrate</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>(L)-DOPA</td>
<td>(L)-3,4-dihydroxyphenylalanine</td>
</tr>
<tr>
<td>dpen</td>
<td>1,2-diphenylethlenediamine</td>
</tr>
<tr>
<td>dach</td>
<td>trans-1,2-diaminocyclohexane</td>
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<tr>
<td>en</td>
<td>ethylenediamine</td>
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<tr>
<td>eq</td>
<td>equation/equilibrium</td>
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<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>Electrospray Ionization Mass Spectrometry</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td>fac</td>
<td>facial</td>
</tr>
<tr>
<td>FID</td>
<td>flame ionization detector</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
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<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple-bond Correlation</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single-quantum Correlation</td>
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<tr>
<td>iPr</td>
<td>isopropyl</td>
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<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>KIE</td>
<td>kinetic isotope effect</td>
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<tr>
<td>mer</td>
<td>meridional</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge Thermal-Ellipsoid Plot</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium Chlorochromate</td>
</tr>
<tr>
<td>PCy₃</td>
<td>tricyclohexylphosphine</td>
</tr>
<tr>
<td>PiPr₃</td>
<td>triisopropylphosphine</td>
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<tr>
<td>PNNP</td>
<td>tetradentate diphosphinediimine ligand</td>
</tr>
<tr>
<td>P₂(NH)₂</td>
<td>tetradentate diphosphinediamine ligand</td>
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<tr>
<td>PPh₃</td>
<td>triphenylphosphine</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>py</td>
<td>pyridine</td>
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<tr>
<td>rac</td>
<td>racemic</td>
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<tr>
<td>ROMP</td>
<td>ring opening metathesis polymerization</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tmen</td>
<td>2,3-dimethylbutane-2,3-diamine</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>TMSCl</td>
<td>Trimethylsilyl chloride</td>
</tr>
<tr>
<td>TOF</td>
<td>turnover frequency</td>
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<tr>
<td>tot</td>
<td>total</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>UV-vis</td>
<td>ultraviolet</td>
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Chapter 1: Introduction

The reduction of carbon-oxygen double bonds is an important transformation in organic chemistry. Its importance is reflected in many different catalytic and stoichiometric methodologies that have been developed in this field. As in any process, the reduction of a polar double bond has to be atom economical, selective, fast, efficient, cheap and environmentally friendly.\textsuperscript{1-3} The major breakthrough towards creating a process that would address most of these issues was made by Noyori and coworkers in the mid 1990s when they discovered a group of highly active and selective ruthenium-based catalysts.\textsuperscript{4-7} Since that time many other processes, which utilize complexes containing metals of the platinum group in the catalyst, have been developed and shown to have excellent selectivity and efficiency. Their mechanisms of action were intensively studied in order to further optimize the ligand structure and the catalysts to achieve better performance.\textsuperscript{8-11} Nevertheless, there is still place for improvement. The limited availability of platinum group metals as well as their toxicity are problematic for some applications because these unwanted properties increase the price and limit the scope of their application. The use of less toxic and more abundant transition metals such as iron would be beneficial. In addition, the discovery of new catalytic systems is important since new reactivity and science can be explored and cost of the process can be reduced by avoiding patented protocols. The design, synthesis, catalytic activity and mechanistic investigations of the processes involving iron-based catalysts for the asymmetric reduction of ketones are now being developed in order to make this transformation more sustainable.\textsuperscript{12-17}

1.1 The importance of chiral alcohols

The alcohol functional group is very common in molecular structures. Compounds containing a hydroxyl group are employed in various processes in industry and in research as a solvent, reagent or versatile energy carrier. A secondary alcohol that contains different substituents at the carbon attached to the hydroxyl group has a chiral center and can thus exist
as a left- or right- handed isomer. The physical properties of the stereoisomers are identical apart from their interaction with circularly polarized light. For this reason their separation or preparation in an enantiopure form is a challenging task. For the same reason the utilization of the racemic mixture of chiral alcohols (a mixture containing equal amounts of the right- and left-handed isomers) is acceptable in many processes that do not have biological or medicinal applications. On the other hand, when these alcohols are prepared in an enantiopure form, they are highly valuable for these latter uses since here the spatial orientation of atoms in the molecule will often influence the biological action of the alcohol. Therefore, industries which prepare agrochemicals, flavors, fragrances and pharmaceutical goods are particularly interested in the development of asymmetric synthesis or methodologies aimed to separate racemic mixtures of stereoisomers to produce alcohols in an enantiopure form.

Chiral molecules are of a particular interest to the pharmaceutical industry.\textsuperscript{18} The efficiency of drugs depends on their ability to bind to the biologically important target molecules such as proteins, nucleic acids and membranes. The binding usually occurs via a non-covalent interaction of the drug molecule with a three dimensional matrix of the target molecules. For that reason, the molecular configuration of a pharmaceutical is highly important to produce a desired effect.\textsuperscript{19} In the last decade the regulations for the production and utilization of racemic pharmaceuticals by drug manufacturers have become more restrictive, to avoid side effects that can be induced by an unwanted activity of one of the enantiomers of the drug. This has forced pharmaceutical companies to produce more and more drugs in an enantiopure form. The orientation of the alcohol functional group in a bioactive molecule is of special significance since hydroxyls form non-covalent interactions via hydrogen bonding. It is not surprising that about 20\% of the drugs that are available on the market contain this functionality. Examples of a few popular drugs derived from enantiopure alcohols are shown in Figure 1.1.\textsuperscript{20-22}

Odor and taste receptors are highly selective with respect to binding of the signaling molecules on the basis of their three dimensional structure. For this reason, a molecule that is used as a food additive or fragrance product usually has to possess a specific chiral orientation to induce the desired odor or taste. Thus, small volatile alcohols that are enantiopure are extensively used in the fragrance and flavor industries (Figure 1.1).\textsuperscript{23, 24}
Many popular agrochemicals containing functional groups with a chiral center are produced and utilized as a racemic mixture in order to significantly reduce the price of the product.\textsuperscript{25} The potency as well as the effect on the environment of the stereoisomers can be different as in the case of pharmaceuticals and fragrances as discussed above. Given the worldwide concern about artificial chemicals populating the environment,\textsuperscript{26} it is important to study the potency and the side effects on biological ecosystems of each stereoisomer. An agrochemical should be produced as a single isomer in the case when one of the isomers is less effective for its anticipated role or is more toxic.\textsuperscript{27, 28} This approach has been applied for several classes of synthetic agrochemicals such as pyrethroid insecticides, aryloxypropanoate
herbicides and triazole fungicides, all of which are now utilized as enantiopure products. This also applies to agrochemicals that contain, or are derived from, chiral alcohols (Figure 1.2). For example, classes of synthetic pyrethroids which contain an ester with a chiral substituent are prepared as one diastereomer after recrystallization of the reaction mixture of an enantiopure acid and a racemic secondary alcohol. On the other hand, the practice of using enantiopure chemicals in agriculture is not common, mostly due to the fact that the methodologies for the preparation of enantioenriched chemicals are expensive compared to the synthesis of racemic mixtures.

![Figure 1.2 Examples of synthetic pyrethroids containing chiral secondary alcohol moieties.](image)

Enantiopure alcohols can also be used as versatile building blocks, synthetic intermediates and chiral ancillaries. The hydroxyl group when activated with an acid or converted into a mesylate or tosylate group via standard reactions becomes a good leaving group. A subsequent stereospecific, second order, nucleophilic substitution (SN$_2$) reaction with practically any nucleophile can produce a large variety of enantiopure products of choice.
1.2 Synthesis of Chiral alcohols: Stoichiometric Reactions

Alcohols can be synthesized starting from a variety of reagents. They can be produced from alkenes via a range of reactions which includes acid-catalyzed hydration, epoxidation, oxymercuration-demercuration, hydroboration, and hydroxylation with potassium permanganate or osmium tetraoxide. They can also be made from alkylhalides via SN$_2$ reactions with hydroxides and from carboxylic acid derivatives via reduction reactions. The most versatile and abundant starting materials, on the other hand, are carbonyl compounds, since they are readily available through condensations and Friedel-Crafts-type reactions. The reduction of carbonyl compounds using aluminum and boron hydrides can produce secondary and primary alcohols of interest.$^{31,32}$ Chiral secondary alcohols can be obtained as a racemic mixture of two stereoisomers by the reduction of prochiral ketones. Post-synthetic manipulations such as enantioselective preparatory chromatography or use of chiral auxilaries can efficiently separate two isomers from the reaction mixture to obtain enantiopure products. These processes are reliable and well investigated; thus, they are commonly applied in industry and academia.$^{33}$ Nevertheless, they have several severe disadvantages including the production of waste, since the hydride reagents are used in stoichiometric amounts, the lack of stereoselectivity and the requirement of an expensive separation of stereoisomers.

Taking into consideration the relative inexpensiveness of aluminum and boron hydrides, it is not surprising that a lot of researchers have attempted to make this reaction asymmetric. Two major approaches were investigated: the use of chiral aluminum or boron hydrides$^{34}$ or the use of a chiral auxiliary in combination with boron or aluminum hydrides.$^{35}$ Although several highly enantioselective processes were developed, these transformation suffer a common important problem of producing stoichiometric amounts of borate or aluminate by-products.

To resolve this issue, researchers have looked for alternative reducing agents. The most atom economical choice is hydrogen gas, which upon the reduction of a ketone produces absolutely no by-product. The other choices are secondary alcohols or formate salts, which produce non-toxic and readily removable nontoxic by-products: ketones and carbon dioxide,
respectively. These reducing agents are unreactive towards the reduction of ketones unless a catalyst is present.

1.3 Synthesis of Chiral alcohols: Catalytic Reactions

The general mode of action of the catalytic reduction can be described as follows. The reaction of catalyst molecule with a reducing agent generates a highly reactive intermediate which is capable of reducing a carbonyl functional group. After the reaction with the ketone, the catalyst is regenerated to repeat the activation step. The catalysts often contain a chiral functionality to induce the stereoselective reduction of the ketone to give an enantiopure alcohol as the product. Catalysts which are useful for the catalytic asymmetric reduction of ketones can be divided into three major classes: bio-catalysts, organocatalysts and transition metal based catalysts. Every class has its advantages and limitations and currently these are being explored to develop the most sustainable, efficient and selective processes.

Bio-catalytic reactions employ enzymes as catalysts to reduce the corresponding ketones to alcohols. The system may contain an isolated enzyme or whole cells of microorganisms which contain the enzyme of interest. The synthetic preparation of the catalyst is not required since the enzymes are synthesized by microorganisms. The catalytic reaction is highly chemo and stereoselective, because the three dimensional recognition of the substrate by the enzyme is employed in the reaction. On the other hand, this property of the bio-catalyst limits the scope of substrates that can be reduced by a particular enzyme. This problem was partially solved since the modification of the enzyme’s structure is a relatively straightforward task involving the selective mutation of the enzyme-encoding genes. Enzymatic catalytic reactions commonly use naturally occurring alcohols as reducing agents such as ethanol, lactate or glycerol. Bio-catalysis operates under the mild conditions associated with enzymatic activity under physiological conditions. Enzyme-catalyzed reductions have one major drawback compared to the other types of catalytic systems – the reactions are typically slow and do not permit high substrate loadings, attributes which are especially problematic for their industrial application.
Organocatalysts are typically small to medium-sized molecules which contain functional groups that are capable of activating the substrate to reduction via weak interactions. They can be Brønsted acids that, by protonation of the substrate, form an ion-pair which is further reduced asymmetrically. The Hantzsch ester can be used as a reducing agent in these reactions. Asymmetric hydrosilylation reductions of aryl–alkyl ketones have also been reported. The system of achiral silanes as a reducing agent in combination with enantiopure phase-transfer quaternary ammonium salt produced enantioenriched alcohols with enantiomeric excess up to 70%. The limitations of this catalytic process are typically associated with a high catalytic loading, moderate enantiomeric excess, the high price of the reagents and the difficulty in regenerating the reducing agent.

Catalytic systems involving transition metal complexes are very popular in homogeneous catalysis in general and specifically in the asymmetric hydrogenation of unsaturated polar double bonds. Such popularity can be explained by the exceptionally high activity, stereoselectivity and wide substrate scope of these catalysts. The theme of this thesis is directly related to this class of catalytic reduction reactions; thus, it will be discussed in more detail in the following section.

1.4 Transition metal catalyzed asymmetric reduction of ketones

1.4.1 Dihydrogen complexes

The reduction of ketones by dihydrogen does not occur at room temperatures although it is a thermodynamically favorable process. This can be explained by the high stability of H-H bond (103 kcal/mol) and symmetry forbidden nature of the reaction determined by the relationship between the HOMO of the dihydrogen and the LUMO of the carbon oxygen bond, a π*orbital; this makes activation barrier for the process inaccessibly high (Figure 1.3).

The discovery that molecular hydrogen can be activated using transition metals to produce metal-hydride compounds opened the possibility to destabilize the H-H bond and make the reaction described in Figure 1.3 possible. The isolation of dihydrogen-metal complexes, which are intermediates in the process of the metal-hydride formation, allowed a deeper
mechanistic understanding of the interaction of transition metals with molecular hydrogen. The two bonding interactions between the metal and side-on bonded dihydrogen are a σ-interaction involving HOMO electrons of the dihydrogen and empty d-orbital of the metal with a matching symmetry and a π-bonding interaction of electrons from a metal d-orbital into the σ* orbital of the dihydrogen.\textsuperscript{50-52} The extent of bonding via one or the other mode depends on the electronic properties of the metal. A stronger π-donation from the metal to the dihydrogen usually results in an elongation and weakening of the H-H bond as a result of populating the σ* orbital of the dihydrogen.\textsuperscript{53}

![Figure 1.3 HOMO of hydrogen and LUMO of the C=O bond.](image)

The extent of activation of the dihydrogen upon coordination is an important concept for catalysis. Several indirect techniques were used to establish the dependences of the dihydrogen activation on the metal type, the metal oxidation states and ligands. The elongation of the H-H bond is proportional to the extent of the activation. The H-H distances of many complexes were determined using diffraction methods (X-ray or neutron)\textsuperscript{51, 54, 55} as well as NMR techniques by determining correlations between the distance and T\textsubscript{1} values and J\textsubscript{HD} coupling constants.\textsuperscript{56, 57} The kinetic and thermodynamic acidity of metal dihydrogen and hydride complexes were investigated to determined the dependence of the pK\textsubscript{a} values on various structural and electronic properties of the metal complexes.\textsuperscript{58, 59 60-62}
1.4.2 Formation of metal hydrides: oxidative addition

The use of electron-rich transition metal complexes in dihydrogen activation results in significant donation of the electron density into the σ* orbital of the dihydrogen. This forces the reactants to undergo oxidative addition to give a dihydride complex with a metal center with an oxidation state increased by two units. Rhodium dihydride complexes were found to be particularly active towards the hydrogenation of unsaturated organic molecules such as terminal alkenes.\textsuperscript{43} When the hydrogen gas and the alkene are part of the reaction mixture then the process can become catalytic. This catalytic scheme was proven to be operational in the famous Wilkinson catalytic reduction of alkenes\textsuperscript{63} and other similar reactions. The detailed mechanism of this process is schematically represented in Scheme 1.1.\textsuperscript{64} The catalytic reduction of the alkenes was also successfully accomplished using ruthenium (II),\textsuperscript{65,66} and Ir(I)\textsuperscript{67} complexes containing monophosphines in the coordination sphere.

The asymmetric versions of the catalytic hydrogenation systems were developed using chiral bidentate diphosphate ligands\textsuperscript{68} and phosphinooxazolines.\textsuperscript{69} One of the earliest examples of the utilization of catalytic asymmetric reduction on an industrial scale was implemented by Knowles for the preparation of L-3,4-dihydroxyphenylalanine (L-DOPA) using [Rh(COD)(R, R)-DIPAMP)][BF\textsubscript{4}], where COD is cyclooctadiene and DIPAMP is a diphosphine with chiral centers at the phosphorus.\textsuperscript{70}

Scheme 1.1 Proposed mechanism of catalytic reduction of alkenes using Wilkinson’s catalyst.
Electron rich complexes are able to efficiently add dihydrogen in an oxidative addition reaction to give dihydride complexes. In contrast, the last step of the catalytic process, a reductive elimination, is favored when the metal center is electron poor. Therefore, the efficient catalysts are usually metal complexes that have unique electronic properties to favor both reductive elimination from, and oxidative addition to, the different oxidation states.

1.4.3 Formation of metal hydrides: deprotonation of dihydrogen complexes

Upon coordination to transition metal dihydrogen becomes acidic, as was discussed above. The addition of a base to these complexes may result in the formation of metal hydrides (Scheme 1.2, A). Such hydrides, in the presence of a suitable substrate, can undergo hydride transfer reactions.

![Scheme 1.2 Deprotonation of a metal hydride with a base: A, intermolecular reaction; B, intramolecular reaction.](image)

Crabtree and coworkers recently reported a catalytic process for the reduction of quinolines using molecular hydrogen as a reducing agent with an [Ir(I)-(NHC)(PPh₃)(COD)]⁺ complex as the precatalyst, where NHC is an N-heterocyclic carbene. The reaction of the precatalyst with hydrogen resulted in the formation of an Ir (III) octahedral complex with two hydrides and an η²-H₂ ligand. Intensive mechanistic studies showed that the imine nitrogen of the quinoline acts as an external base to deprotonate the Ir(III)- η²-H₂ to give Ir(III)-trihydride species. The subsequent hydride delivery to the activated cationic quinoline resulted in the formation of the reduced product. This mechanism, which is usually referred to as an ionic
hydrogenation, was also observed by other researchers\textsuperscript{72-74} in the catalytic reductions of imines. The synthesis of the herbicide (S)-Metolachlor catalyzed by iridium may also involve such a mechanism.\textsuperscript{1}

\[
\begin{align*}
\text{Scheme 1.3} & \quad \text{A part of the proposed catalytic cycle for quinoline reduction using an Ir-based catalyst.}
\end{align*}
\]

The intramolecular deprotonation of dihydrogen complexes can also take place when the basic functionality is a part of the ligand (Scheme 1.2, B). A well known example of such reactivity is the reversible deprotonation of dihydrogen on ruthenium(II) by a dimethyl amine functional group linked to the ligand in a Ru-diphosphine aminocyclopentadienyl complex.\textsuperscript{75, 76} The intermolecular heterolytic splitting of dihydrogen by ruthenium amide complexes is exceptionally important for the catalytic reduction of ketones, since here the hydride and proton are brought into close proximity and have the required symmetry and energy for a favorable addition to the substrate.

\subsection{1.4.4 Catalytic reduction of ketones}

Although the reduction of C=C bond using molecular hydrogen activated with transition metal catalysts has been an established and efficient process since the 1970s, the asymmetric reduction of the polar unsaturated bonds was still a challenge before 1995.\textsuperscript{77} Early examples of catalytic systems based on Ru(η\textsuperscript{2}-H\textsubscript{2})(PPh\textsubscript{3})\textsubscript{3},[Ru(H)\textsubscript{3}(PPh\textsubscript{3})\textsubscript{3}]\textsuperscript{78} and cis-RuH\textsubscript{2}(PPh\textsubscript{3})\textsubscript{4}\textsuperscript{79} showed that the reduction of the carbonyl functionality occurs efficiently only for a selected
group of ketones. Later investigations of the catalytic reduction of ketones using Ru-BINAP diacetate complexes that are activated by hydrogen halides (HX) and RuX(BINAP)(arene) complexes, where X = halides, showed exceptional enantioselectivity but required harsh conditions (p(H$_2$) up to 100 atm, 30ºC) to produce the desired alcohol in high yields.\textsuperscript{80} These results can be explained by the intrinsic properties of the C=O bond: weak coordination bond strength and low hydride affinity. According to the proposed mechanism for these systems (Scheme 1.4), the transfer of the hydride from metal to the carbonyl carbon requires the coordination of the ketone to the metal center, that is, in the inner coordination sphere. The coordination is less favourable than that of alkene coordination. This limitation of the weak interaction of ketones with the metal is consistent with the observation that ketones containing directing groups such as dialkylamino, hydroxyl, siloxyl, keto, alkoxy carbonyl, alkylthiocarbonyl, dialkylaminocarbonyl or β-ketoesters, which increase coordination ability of the substrate, in general were reduced more efficiently.\textsuperscript{81-84} When substrates that are tridentatesuch such as certain α-ketoesters were used in the catalytic transformation, the reaction rate was strongly dependent on the acidity of the reaction solution (more acidic solution gives faster rate). This observation indicates that the rate limiting step in this case was not the coordination of the ketone to the metal center but the hydrogenolysis of the Ru-alkoxide species.\textsuperscript{77a}

![Scheme 1.4 Inner sphere mechanism for the hydrogenation of ketones](image-url)
Noyori and coworkers in 1995 demonstrated that the reduction of aromatic ketones using RuX₂(diphosphine)(solvent)₂ can be efficiently achieved under mild conditions (p(H₂) = 4 atm) using relatively low catalyst loading (substrate:cat = 500:1), when a primary diamine is added to the reaction mixture.⁸⁵,⁸⁶ The dramatic increase in catalytic activity was attributed to the so-called “NH-effect,” that was imposed by the amine group of the diamine. Further investigations of the mechanism of this catalytic system (Scheme 1.5) revealed that the coordinated diamine is deprotonated by the external base, which is required for the catalyst activation, to form an amido complex. The intramolecular reaction of coordinated dihydrogen with the basic amido nitrogen gives hydride (MH) and amine (NH₂). Noyori and coworkers also proposed that the MH/NH complex transfers the H⁻ and H⁺ from the metal and amine to the carbonyl carbon and oxygen, respectively, in an outer sphere six-membered transition state.⁴,⁶,⁹

Noyori and coworkers prepared a group of catalysts with the general formula *trans*-RuCl₂(diphosphine)(diamine). In the case when a chiral diphosphine (BINAP or its derivatives) and a primary diamine (1,2-diphenylethylenediamine or its derivatives) with matching chirality (eg. *S*-diphosphine with *S*,*S*-diamine) were used, the reduction of aromatic prochiral ketones was carried out with exceptional enantioselectivity (ee up to 99 %) and efficiency (sub:cat = 2,400,000:1; 48 hours) under mild conditions (p(H₂) = 4 atm, 30°C).⁸⁶

Scheme 1.5 Outer sphere bifunctional mechanism for the hydrogenation of ketones.
The precatalysts that were discussed above required *in situ* activation with base (10-100 equivalents relative to the catalyst) for a successful reaction to occur. Morris and coworkers investigated the process of activation of the precatalysts with the intention of gaining important information about the mechanism and isolating active species in the catalytic cycle.\(^{87,89}\) One of the isolated species \(1.1\) (Figure 1.4), which contains *trans*-hydrides coordinated to the ruthenium metal center, appeared to be highly active for the hydrogenation without activation with base. The researchers postulated that the presence of two hydrides in a *trans* disposition enhances the hydricity via the trans-influence of the hydrides; and therefore, the activity of the catalyst. Moreover, the stoichiometric reaction of \(1.1\) with acetophenone resulted in the formation of corresponding amido complex and 1-phenethanol. This outcome of the reactions supports the idea that the transfer of \(H^+ / HF\) from \(1.1\) to the ketone occurs via the concerted process.

Conversely, Bergens and coworkers, who investigated similar reaction using ruthenium complex with the \((R,R)\)-dpen (\(1.2\)) at low temperature (-80° C), discovered that the product of the reaction was a Ru-alkoxide complex, suggesting that the reduction of acetophenone does not occur simultaneously with the transfer of the proton.\(^{90,91}\) The difference in reactivity of the complexes \(1.1\) and \(1.2\) was explained by the electronic and steric properties imposed by the diamines. Further investigations of Bergens and coworkers, including the base assisted formation of the Ru-amido complex from the Ru-alkoxide\(^{90}\) and intramolecular trapping experiments,\(^{92}\) support the idea that the reduction and proton transfer to acetophenone is a step-wise rather than a concerted process. Recently, Gusev and coworkers have also reported evidence for the step-wise process. Their group was able to isolate and structurally characterize a Ru(II)-alkoxide complex with a PNP-pincer ligand, indicating its stability.\(^{93}\)

Figure 1.4 The structure of ruthenium dihydride catalysts.
1.5 Transfer hydrogenation of ketones

Molecular hydrogen is the most atom-economical reducing agent, since no oxidized by-product is formed in the course of the reaction. On the other hand, the reductions using molecular hydrogen are associated with an increased level of danger. Transfer hydrogenation reactions,\textsuperscript{43, 94, 95} which utilize safe, benign, operationally simple and low cost reducing agents such as 2-propanol or formates have become quite popular in recent years and are employed for academic and in some cases industrial applications.

The process of transfer hydrogenation is illustrated in general terms in Scheme 1.6. A hydrogen donor ($DH_2$) transfers the H\textsubscript{2} equivalent to the activating molecule or promoter (transition metal complex) to form the oxidized by-product D and promoter carrying H\textsubscript{2}. In the next step, the H\textsubscript{2} is transferred to the substrate to give the product alcohol with the regeneration of the activating molecule for the next cycle. The donor molecules commonly contain hydridic and protic hydrogens which are transferred to the substrate sequentially: hydride to the carbonyl carbon and proton to the oxygen. The main drawback of this process compared to, for example, hydrogenations using molecular hydrogen is that the transfer hydrogenation is an equilibrium process, when secondary alcohols are used as reducing agents. The formation of the product in good to excellent yield can be accomplished by increasing the concentration of the reducing agent relative to the product or by removing the by-product of the reaction. This problem also can be solved when formic acid or its salts are used as a donor molecule, since the reaction is irreversible due to the formation of CO\textsubscript{2} gas as the by-product.\textsuperscript{96}

![Scheme 1.6 A general reaction for the hydrogen transfer reaction of ketones](image-url)

Scheme 1.6 A general reaction for the hydrogen transfer reaction of ketones
One of the first catalysts for the transfer hydrogenation of carbonyl compounds was based on aluminum alkoxide complexes. The proposed mechanism for this transformation, which is known as a direct hydride transfer, is the coordination of the alkoxide and ketone to the aluminum metal center, promoting a transfer of the hydride to give the corresponding products. The metal center in this process plays a dual role: it acts as a Lewis acid to activate the carbonyl carbon and allows the formation of a highly ordered six-membered transition state to lower the activation barrier of the process. When the reaction produces alcohol from the ketone, it is known as a Meerwein – Ponndorf – Verley (MPV) reduction. The reverse reaction that leads to the formation of the ketone is called an Oppenauer oxidation. The asymmetric version of this reaction was recently reported.

The other class of transfer hydrogenation catalyst, which usually entails a transition metal complex with diphosphine ligands, is known to operate by a hydride mechanism. In the case when the reducing agent is 2-propanol, it involves the coordination of the isopropoxide to the transition metal followed by intramolecular β-hydrogen transfer to the metal to produce a metal-hydride with coordinated acetone. The acetone then is exchanged with the ketone of interest at the metal. The hydride is then transferred to the carbonyl carbon to produce alkoxide of the product, which is then exchanged with 2-propanoxide to repeat the cycle (Scheme 1.7).

![Scheme 1.7 Hydridic mechanism of the transfer hydrogenation using 2-propanol as a reducing agent.](image-url)
The most valuable class of the transfer hydrogenation reaction is the one that produces the alcohol in enantioenriched form; this is usually referred to as asymmetric transfer hydrogenation (ATH). Higher reduction rates of the catalytic systems with transition metals and a ligand containing a primary amine group\textsuperscript{70} were observed for the transfer hydrogenation reaction similar to the hydrogenations using molecular hydrogen. These catalysts also were found to be exceptionally enantioselective when enantiopure diamines\textsuperscript{103} or amino alcohols\textsuperscript{104} were used as ligands.\textsuperscript{105} Noyori and coworkers proposed that these systems also operate by an outer sphere bifunctional mechanism (Scheme 1.5) except, that in the step where the hydrogen is added across metal-amido bond, in the transfer hydrogenation reaction an alcohol donates a proton to the amine nitrogen and hydride to the metal and is reduced to a ketone.\textsuperscript{103, 104, 106, 107}

The catalytic systems which are especially relevant to the topic of this thesis and to the field of ATH were described by Noyori group in 1996 (Figure 1.5).\textsuperscript{108} The catalysts in this reaction are based on Ru(II) complexes with a tetradeinate \textit{C}$_2$-symmetric diphosphine/diamine ligands. Two precatalysts were prepared and tested for the transfer hydrogenation of aromatic ketones: (\textit{S},\textit{S})-1 and (\textit{S},\textit{S})-2 containing imine and secondary amine functionalities, respectively. The catalysts were activated by the addition of one or less equivalents of \textit{iso}-propoxide, which is a relatively low amount compared to the 10-50 equivalents of base that are usually required for the activation of the bifunctional \textit{H}$_2$-hydrogenation precatalysts described in Section 1.4. Complex (\textit{S},\textit{S})-2 showed excellent catalytic activity and enantioselectivity, whereas (\textit{S},\textit{S})-1 was almost inactive catalyst in the same reaction. The low activity of complex (\textit{S},\textit{S})-1 was explained by the absence of an amine functionality in the structure of the complex, thus precluding the operation of an NH mechanism.

It also has to be noted that the precatalyst (\textit{S},\textit{S})-2 was also found to be highly active for the hydrogenation of ketones using molecular hydrogen as a reducing agent.\textsuperscript{6, 109} Interestingly, the enantiomeric excess of the 1-phenethanol was opposite and lower compared to the reduction using 2-propanol. This implies that the catalytically active species may be different for the transfer and the direct hydrogenations, even when the precatalyst is the same.
Figure 1.5 Examples of Ru-based precatalysts for transfer hydrogenation containing PNPN ligands.

In recent years several research groups have shown that the presence of the amine functionality in the coordination sphere of the catalyst does not always indicate that the system operates by the outer sphere bifunctional mechanism. They report highly active transfer hydrogenation catalysts containing amine groups that are now thought to operate by alternative pathways in both hydrogenation and transfer hydrogenation of ketones (as discussed in more details in Chapter 5).\(^\text{91, 92, 110, 111}\) Nevertheless, the importance of a primary or secondary amine group in catalyst design is widespread since the NH group can participate in the activation of the carbonyl group of the substrate by hydrogen bonding and/or protonation.

### 1.6 Iron as an alternative metal for the catalytic asymmetric transfer hydrogenation of ketones.

As was briefly mentioned in the introductory remarks to this Chapter, the transition metal catalyzed transformations, which rely on PGM, are problematic due to the toxicity and expense of the metals that are utilized in the process. The toxicity of the catalyst is an especially important parameter in asymmetric synthesis, since the chiral products of the reaction, which are used in bio-related industries, have to contain low levels of toxic materials. Recently,
substantial restrictions on the allowable levels of various materials have been placed on products such as drugs and food additives, which are directly administered to humans. According to US Pharmacopeia (the agency for the quality and purity control of pharma-related products), the amounts of the metals such as Ru, Os, Rh, and Ir should not exceed the level of 100 µg/day/50 kg person. The acceptable limit of iron daily intake is much higher (15000 µg/day/50 kg person), which makes the utilization of this particular metal in asymmetric transformations highly beneficial.

Ruthenium metal, which is the most popular metal for the asymmetric reduction reactions of carbonyl compounds, is a rare element, only the 74th abundant metal on the Earth.\textsuperscript{112} Even taking into consideration the exceptional catalytic activity of certain ruthenium complexes in hydrogenation reactions, the limited availability of this metal constrains its adoption for industrial-scale processes. Hand in hand with low availability, the price for this metal is high (on average 14 USD/g according to the current market of rare metals), making it a less attractive candidate for intensive exploitation. From the point of view of the price and availability, iron, which is extremely cheap (0.0001 USD/g) and very abundant (constituting 5% of Earth’s crust), would be an excellent candidate for use in catalysis. Of course iron catalysts are already widely used in the Haber-Bosch process for ammonia production, the largest chemical process on the planet.

Although these benefits of iron were known for a long time, it was only recently that the reactivity of iron complexes in homogeneous catalysis was discovered in several highly efficient transformations (see further discussion of this in Chapter 5). This activity had been overlooked due to a common believe that the easily attainable oxidation states of iron such as (II) and (III), which are different by one electron, might initiate radical processes and would result in uncontrollable and unselective transformations. The discovery of transition metal complexes with suitable ligands that are able to catalyze the reactions via a bifunctional mechanism opened the possibility for the metal centers of the complexes to operate without changing the oxidation state of the metal. For this reason, it is not surprising that the most active iron-based catalytic systems contain ligands that are designed to directly participate in the catalytic transformation.\textsuperscript{12-17,113} A detailed discussion of the recent trends and developments in the field of iron catalysis, especially in the asymmetric transfer hydrogenation of aromatic ketones, is presented in the introductory sections of Chapters 4 and 5.
1.7 Thesis outline

The main goal of the research project which is described in this thesis, was to prepare and explore the catalytic activity of a library of related iron-based complexes containing tetradeatate ligands with two phosphorus and two nitrogen donor atoms (PNNP) in the catalytic asymmetric transfer hydrogenation (ATH) of alkyl-aryl and alkyl-alkyl prochiral ketones. Another objective was to examine possible mechanisms of this transformation. Previous members of the Morris group determined that monocarbonyl iron(II) complexes containing PNNP ligands that were prepared by the condensation reaction of chiral diamines and \( \text{o-phosphinobenzaldehyde} \) are highly active and are moderately enantioselective in ATH reactions.\(^{114,115}\) In order to improve the efficiency and selectivity of this process, we decided to design and synthesise a new set of iron(II) complexes containing PNNP ligands that were prepared by the condensation reaction of chiral diamines and \( \text{o-phosphinobenzaldehyde} \) that are different from \( \text{o-phosphinobenzaldehyde} \).

Chapter 2 describes high-yielding, one pot syntheses of air- and moisture-stable phosphonium salts from commercially available starting materials (Scheme 1.8). A library of these compounds was prepared and fully characterized. The phosphonium salts upon reaction with base form desired phosphino-aldehydes, which were observed by NMR. The amphoteric nature of the phosphino-aldehydes makes them highly reactive; they easily get oxidized when exposed to air and react with themselves unselectively to give rise to oligomeric and polymeric structures upon standing. The salts containing \( \text{Et}, \text{iPr} \) and \( \text{p-Tol} \) substituents on the phosphorus were synthesized by P. O. Lagaditis and P. E. Sues. The results that are described in this chapter were published in *Inorganic Chemistry*,\(^{116}\) and *Journal of Organometallic Chemistry*.\(^{117}\)
Phosphonium salts, when reacted with a base, form the phosphinoaldehydes, which can be directly used in multicomponent template reactions in acetonitrile as a solvent with iron (II) precursors and diamines to give bis-tridentate complexes containing corresponding PNN ligands (1.3) as the kinetic products of the reaction. When the reaction was conducted at elevated temperatures the formation of complexes containing tetradentate PNNP and trans acetonitrile ligands (1.4) (thermodynamic product) was observed. If the reaction was conducted in the solvent mixture of acetonitrile and methanol, the iron(II) complexes 1.4 can be prepared in good yields at room temperature. The complexes with various diamines incorporated into the ligand backbone were prepared using the procedure described above and fully characterized. The results that are described in this chapter were published in 2008 (Inorganic Chemistry) and in 2010 (Inorganic Chemistry).
The preparation of active precatalysts for the ATH of aromatic ketones and a study of their catalytic activity are described in Chapter 4. Monocarbonylation of 1.4 in acetone under one atmosphere of carbon monoxide leads to the formation of complexes 1.5 (Figure 1.7). The reduction of aromatic prochiral ketones using 2-propanol as a solvent and reducing agent was conducted under an inert atmosphere using 1.5 activated by eight equivalents of KOtBu. The complex containing the ligand with (S,S)-1,2-diphenylethlyenediamine incorporated into the backbone of the tetradequate ligand showed exceptional activity (TOF up to 30000 h⁻¹) and enantioselectivity (eel up to 99 %). The influence of steric and electronic properties of various diamines on the rate and stereoselectivity of the ATH reaction was investigated by comparing the performance of complexes 1.5 containing various diamines incorporated into the ligand structure. The results that are described in this Chapter were published in 2009 (Journal of the American Chemical Society)¹²⁰ and 2010 (Inorganic Chemistry).¹¹⁸
Figure 1.7 Structure of iron(II) active precatalysts studied in Chapters 4 and 5.

Mechanistic investigations of the catalytic process are described in Chapter 5. Kinetic studies of the ATH of acetophenone by 2-propanol as a solvent and reducing agent catalyzed by the complex 1.4 with (S,S)-1,2-diphenylethylenediamine incorporated in the ligand backbone were conducted by monitoring the formation of 1-phenethanol over time with respect to the initial concentrations of the reagents. The results of this study were used to propose a mechanistic model that was verified by performing numerical simulations of the reaction profiles. Rate constants for individual steps of the process along with the activation parameters of the reaction were determined from the simulations. The activation of the precatalyst by reaction with basic 2-propanol was investigated and was shown to proceed by the stereoselective reduction of one of the imine groups of the ligands by transfer from 2-propanol. The composition of the catalytically active species was proposed based on the structures of isolated and fully characterized the complexes that arise from the protonation of active species.

All of the X-ray diffraction data was collected and solved by Dr. Alan Lough. The program for the numerical simulations, which was used in the kinetic studies, was developed by Dr. Shun Lo.
97. Meerwein, H.; Schmidt, R., Liebig's Annalen der Chemie 1925, 444, 221-238.

Chapter 2: Cyclic Phosphonium Salts as Versatile Ligand Precursors: Synthesis and Characterization

2.1 Abstract

Various cyclic phosphonium structures are formed in high yield by the deprotection of unstable phosphine-aldehydes in acidic solution. When there is a methylene spacer between the phosphine and the aldehyde, a dimeric phosphonium ion is obtained as a mixture of two diastereomers. Reaction of the precursors \([\text{PHR}_2\text{CH}_2\text{CH(OEt)}_2]\text{Br}, R = i\text{Pr, Et}\) with water produces the dimers \([-\text{PR}_2\text{CH}_2\text{CH(OH)}-\text{]}_2[\text{Br}]_2, R = i\text{Pr, Et}\). When there is an ethylene spacer as in \(\text{PPh}_2\text{CH}_2\text{CH}_2\text{CH(OCH}_2\text{CH}_2\text{O)}\), a remarkable tetramer with a 16-membered ring \([-\text{PPh}_2\text{CH}_2\text{CH}_2\text{CH(OH)}-\text{]}_4[\text{Cl}]_4\) forms as one diastereomer in hydrochloric acid solution. Reaction of HCl with the protected phosphine-aldehyde with a propylene spacer \((\text{PPh}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH(OCH}_2\text{CH}_2\text{O)})\) results in the formation of the monomeric phosphonium salt \([-\text{PPh}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH(OH)}-\text{]}\text{Cl}\) with a 5-membered ring. Solid state structures of different ring types were determined using single crystal X-ray diffraction experiment.

2.2 Introduction

Phosphines are particularly versatile ligands in organometallic chemistry because of the ease in changing the substituents at phosphorus to vary their coordination abilities.\(^1,2\) The substituent effects on electronic and steric characteristics of phosphines can be quantitatively predicted using available Tolman’s parameters.\(^3,4\) This makes it possible to predict and rationalize the properties and behaviour of coordination compounds in catalytic
transformations. Additional donor groups can be attached to make mixed donor chelating ligands such as phosphorus-nitrogen\textsuperscript{5-12} or phosphorus-oxygen ligands.\textsuperscript{13-17} On the other hand, the synthesis and reactions of molecules with a phoshpine group and an electrophilic group such as an aldehyde are less explored. Such amphoteric molecules may undergo oxidation and unselective polymerization by the formation of carbon-phosphorus bonds and for this reason they require specific handling and are difficult to prepare in good yield and high purity.\textsuperscript{18-23}

One of the promising synthetic protocols for the preparation of the amphoteric phosphino-aldehydes is based on the ability of phosphines to form air and moisture stable adducts with boranes.\textsuperscript{24} This protecting group can be removed under mild conditions using secondary amines. This methodology was successfully applied for the preparation of bidentate ligands containing chiral phosphorus donor.\textsuperscript{25} The example of the preparation of the phosphino-aldehydes using this methodology was reported by Pellon and coworkers and summarized in (Scheme 2.1).\textsuperscript{20, 26}

Scheme 2.1 Preparation of the phosphino-aldehyde using the borane-protection method.

Matt and co-workers observed that under acidic conditions a particular amphoteric phosphine-aldehyde selectively forms a stable phosphonium dimer (2.1, Scheme 2.2, $M = Li, R = Et$).
Scheme 2.2 Synthesis and behaviour of phosphine-aldehydes under acidic and basic conditions.

A particularly useful phosphine-aldehyde, ortho-diphenylphosphinobenzaldehyde (2.2), was initially synthesised by the reaction of protected ortho-bromomagnesium-benzaldehyde with chlorodiphenyl phosphine followed by deprotection of the aldehyde functional group (Scheme 2.3). This method is relatively efficient although other preparations have been reported. Phosphino-aldehyde 2.2 is a particularly useful starting material for the synthesis of chiral PNNP and PNN ligands by Schiff base condensation reactions with enantiopure amines and diamines. These ligands were utilized in various catalytic transformations, especially as catalysts for the reduction of ketones and aldehydes. The reason for the popularity of phosphine-aldehyde 2.2 relative to others is its stability. The phosphorus atom of 2.2 is bonded to three aryl groups, which by steric and inductive effects stabilize the otherwise highly nucleophilic lone pair on the phosphorus.
Scheme 2.3 Synthesis of o-phosphinobenzaldehyde.

Recently, our group showed that less stable phosphine-aldehydes derived by reaction of a base with dimeric phosphonium salts 2.1 can also be used for the synthesis of iron(II) pre-catalysts (Chapter 4). These pre-catalysts were found to be particularly active in the enantioselective transfer hydrogenation of ketones using iso-propanol as the reducing agent (Chapter 4).

The ease of formation of the phosphorus-carbon bonds in the synthesis of dication 2.1 might also be exploited for the synthesis of macrocyclic molecules (Scheme 2.2) to produce porous materials, anionic sensors or macrocycles. In recent years macrocyclic molecules have attracted more attention from the chemical community as a result of developments in areas of molecule signaling, molecular motors and organometallic catalysis. Macrocycles are commonly synthesized from linear molecules containing terminal reactive functional groups or from short amphoteric molecules that oligomerize into cyclic structures. Both approaches demand a high level of selectivity towards the formation of cyclic molecules over the linear ones and towards a specific size of the ring. One of the solutions to the selectivity problem is the synthesis involving a template pre-organization. Here a host molecule (receptor) brings together two or several molecules with reactive functionalities by non-covalent interactions to form a highly organized structure that further undergoes chemoselective reactions.

Host molecules are typically cationic because their coordination chemistry is well studied and understood. Anions are less often employed as hosts in template syntheses because of their undesirable features, which include a high solvation energy, a low charge to radius ratio and a high pH dependence. Several examples of an anion-assisted formation of rotaxanes and similar macromolecules are found in the literature. The only multi-component anionic template to our knowledge was reported by Rubio and co-workers in the synthesis of macrocycles.
derived from amino acids. Unfortunately, this methodology usually gives low to moderate yields of the desired product.

The ease of formation of the dimeric phosphonium compound, 2.1, (Scheme 2.2) instead of other cyclic oligomers prompted us to explore this reaction in more detail. We wanted to investigate (a) how is the chemoselectivity and diastereoselectivity controlled in the process of the formation of dimer 2.1 and (b) whether this knowledge could be used to prepare more complex and diverse molecules. This led us to discover an even simpler method of producing such phosphonium compounds when the phosphorus atoms bear electron-donating substituents and a high yielding method for the selective formation of a tetrameric macrocycle.

2.3 Results and Discussion

2.3.1 One carbon spacer between the phosphorus and reactive carbon centre

Cyclic phosphonium dimers similar to that of 2.1 but with iso-propyl or ethyl substituents at the phosphorus atoms (2.3a, 2.3b) were prepared in a new, direct reaction of the secondary phosphine with the protected bromoacetoaldehyde diethyl acetal (BrCH₂CH(OEt)₂) to give an intermediate phosphonium salt that was then hydrolyzed (Scheme 2.4).

![Scheme 2.4 Direct preparation of phosphonium dimers 2.3a, 2.3b and 2.3c using secondary phosphines containing electron-donating alkyl substituents.](image-url)
The yields of the white solids \(2.3a, 2.3b\) and \(2.3c\) are 81, 86 and 40\%, respectively. Compound \(2.3a\) is an air- and moisture-stable white solid that is completely soluble in methanol or/and water and insoluble in other common organic solvents. Therefore, it possesses similar physical properties compared to the dimer \(2.1\). The dimers \(2.3b\) and \(2.3c\), on the other hand, adsorb water on prolonged exposure to atmosphere, and are soluble only in water. All dimers \(2.3\) are stable toward oxidation by molecular oxygen.

This direct reaction does not work for the less nucleophilic phosphines such as diphenylphosphine (HPPh\(_2\)) and di(p-tolyl)phosphine (HP(p-tol)\(_2\)). These need to be converted into their corresponding more nucleophilic phosphides by reaction with potassium hydride before successful nucleophilic attack on the protected aldehyde BrCH\(_2\)CH(OEt)\(_2\) can take place (see Scheme 2.2 and Scheme 2.5). Deprotection of the phosphine-aldehyde diethyl acetics in acidic media gives the desired dimers with diphenyl (\(2.1\), Scheme 1) or di-p-tolyl substituents (\(2.3d\), Scheme 2.5). The new dimeric compound \(2.3d\) was obtained as a white, air-stable solid in 88 \% yield.

\[\text{Scheme 2.5 General preparation of phosphonium dimers } 2.1 \text{ and } 2.3d \text{ from potassium phosphide.}\]

Hence the high yields and chemoselectivity in the formation of \(2.1\) and \(2.3\) are not affected by varying the electronic and steric properties of the phosphines. An explanation for the selectivity must lie in the favourable geometry of the 6-membered rings. Thus, the selectivity of the reaction appears to be primarily controlled by thermodynamic factors rather than kinetic ones.
The new dimers 2.3 were fully characterized by NMR spectroscopy. These compounds show two characteristic singlets in the $^{31}$P {$^{1}$H} NMR spectra in the region between 11 and 40 ppm; the two singlets observed in the $^{31}$P {$^{1}$H} NMR arise from the rac and meso diastereomers. As for the $^{1}$H NMR spectra, there is a characteristic multiplet in the region between 5.3 and 6.2 ppm for the proton on the carbon with the hydroxyl group –CH(OH)–, and the absence of the aldehyde hydrogen resonance, which is expected in the 9-10 ppm region.

Crystals of 2.3a and 2.3d have been analyzed by single crystal X-ray diffraction (Figure 2.1). Both structures are meso diastereomers with the hydroxyl groups in equatorial positions for 2.3a and in axial positions for 2.3d. The P-C1 bond lengths are similar in both dimers and are slightly elongated compared to all other phosphorus carbon bonds in the structures probably as a result of electron-withdrawing effect of the neighbouring oxygen atom. The bond between P1 and C6 in 2.3a is longer than the bond between P1 and C3 in 2.3d as expected from the larger cone angle of the iso-propyl group compared to p-tolyl group. All of the angles and bond lengths of both 2.3a and 2.3d are comparable to those observed by Matt and co-workers. 18

Crystals that were used for the X-ray diffraction studies were also analyzed by $^{31}$P NMR spectroscopy in order to assign peaks and determine the ratio of diastereomers formed in the reaction. The $^{31}$P {$^{1}$H} NMR spectra obtained for the crystals (Table 2.1) showed peaks for both diastereomers at 36.8 and 34.5 ppm for 2.3a and at 16.1 and 11.2 ppm for 2.3d with integration ratios of 1:2 and 3:4, respectively. On the other hand, Matt and co-workers were able to selectively crystallize dimer 2.1 as a meso diastereomer and determine the structure by X-ray diffraction. A signal at 16.6 ppm in the $^{31}$P {$^{1}$H} NMR spectrum was observed indicating that it is a minor diastereomer in the mixture of 2.1. A possible explanation to the difference in distribution of diastereomers of 2.3d and 2.3d resulting from X-ray diffraction and $^{31}$P {$^{1}$H} NMR analyses is that the diastereomers have similar solubility and both diastereomers co-crystallize. Thus the crystals containing the meso diastereomer were chosen for the X-ray diffraction by chance. It is however possible that racemization of the pure meso diastereomer occurred in methanol-d$_4$ into a mixture of meso and rac diastereomers prior to $^{31}$P {$^{1}$H} NMR analysis.
Figure 2.1 ORTEP views of the molecular structures of 2.3a (bottom) and 2.3d (top). Thermal ellipsoids are drawn at 30% probability. Some hydrogen atoms, solvent molecules and counter ions are omitted for clarity. Selected interatomic distances [Å] and angles [°]: 2a P1-C1 1.835(3), P1-C2 1.813(3), P1-C6 1.825(3), P1-C3 1.819(3), C1-O1 1.410(3); C1-P1-C2 103.7(1), C1-P1-C3 108.4 (1); 2c P1-C1 1.847(5), P1-C2 1.804(4), P1-C3 1.783(3), C1-O1 1.394(4); C1-P1-C2 104.7(2), C10-P1-C3 109.1(2).
Table 2.1 Selected spectroscopic data and properties of the dimers 2.1, 2.3a, 2.3b and 2.3d.

<table>
<thead>
<tr>
<th>Dimer</th>
<th>$^{31}$P {$^1$H} NMR minor diastereomer (ppm)</th>
<th>$^{31}$P {$^1$H} NMR major diastereomer (ppm)</th>
<th>Ratio of diastereomers minor/ major$^{[a]}$</th>
<th>Yield (%) total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1$^{[18]}$</td>
<td>16.6</td>
<td>11.9</td>
<td>3:4</td>
<td>93</td>
</tr>
<tr>
<td>2.3a</td>
<td>36.8</td>
<td>34.5</td>
<td>1:2</td>
<td>81</td>
</tr>
<tr>
<td>2.3b</td>
<td>35.5</td>
<td>32.7</td>
<td>1:2</td>
<td>87</td>
</tr>
<tr>
<td>2.3d</td>
<td>16.1</td>
<td>11.2</td>
<td>3:4</td>
<td>88</td>
</tr>
</tbody>
</table>

$^{[a]}$ Ratios of diastereomers were determined by $^1$H NMR.

In order to test each of these assumptions, equimolar amounts of 2.1 and 2.3a were mixed together in methanol-d$_4$ and the solution was monitored by $^{31}$P {$^1$H} NMR spectroscopy. After 12 hours a spectrum showed only peaks at 16.63 and 11.97 ppm (dimer 2.1) and at 36.80 and 34.54 ppm (dimer 2.3a). Since no mixed-substituent phosphonium dimer was produced it indicates that the dissociation of dimers or racemization does not take place in solution.

The various substituents at the phosphorus atom have a minor effect on the chemoselectivity of the reaction and six-membered dimers are formed over other possible species (Scheme 2.2). More electron-rich substituents (iso-propyl and ethyl) considerably increase the formation of one diastereomer over the other and thus make the reaction more diastereoselective. One can argue that the selectivity comes from the formation of the more thermodynamically favorable six-membered ring instead of less stable cyclic or linear oligomers and polymers. In order to investigate such an assumption, we decided to increase the size of the hydrocarbon spacer between the carbonyl and phosphine groups in the phosphine-aldehyde and study the oligomerization under acidic conditions.

### 2.3.2 Two carbon spacer between the phosphorus and reactive carbon centre

The synthesis of 2-(2-chloroethyl)-1,3-dioxolane was previously reported by the Lugtenburg and co-workers.$^{47}$ The addition of the $\beta$-chloropropionaldehyde ethylene glycol to a freshly-prepared solution of the KPPh$_2$ in THF resulted in the formation of the tertiary phosphine 2.5 with a protected aldehyde in situ. Instead, the addition of a degassed,
concentrated, aqueous hydrochloric acid solution to the reaction mixture gave \textbf{2.5} as a white precipitate (Scheme 2.6).

Scheme 2.6 Synthesis of tetramer \textbf{2.5} from 2-(2-chloroethyl)-1,3-dioxolane and potassium phosphide.

The molecular structure of a crystal from the isolated white solid was determined in a preliminary X-ray diffraction experiment to be cyclic and tetrameric (Scheme 2.6). The elemental analysis and \textsuperscript{1}H NMR spectra show that the crystals contain approximately 3 water molecules per tetramer. All attempts to completely remove water from the solid tetramer failed, probably due to high affinity of the chloride ions for water. Since the \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectrum of \textbf{2.5} in methanol-d\textsubscript{4} solution shows a single resonance at 27.08 ppm, we may conclude that the reaction leading to this tetrameric structure is highly diastereoselective.

The formation of the specific ring size of \textbf{2.5} might suggest that the selectivity toward its formation may be due to a template effect of monomers around the chloride ion. If this assumption is correct then the use of a more bulky counter ion in the synthesis should lead to the formation of a larger ring. To check this assumption, we synthesized the phosphine-aldehyde monomer PPh\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}C(O)H (\textbf{2.6}) by reacting the tetramer with base and extracting the product with diethyl ether. Spectral data of compound \textbf{2.6} were found to be
similar to those reported by Vaughn and Gladysz\textsuperscript{21} who synthesized and characterized this compound previously by a different method.

The reaction of 2.6 in THF with hydrochloric acid resulted in complete conversion of the monomer to the tetramer 2.5. Similar reactions were performed with HBr, HBF\textsubscript{4} and p-TsOH in methanol-d\textsubscript{4}. The \textsuperscript{31}P{\textsuperscript{1}H} NMR spectra of the reaction mixtures showed complete consumption of the starting phosphine 2.6 and production of the tetramer 2.5 along with other oligomeric species as minor products. Attempts to vary the conditions of the reaction in order to increase the yield of non-tetrameric species such as by changing the solvent, temperature and rate of addition of the reagents, failed probably as a result of the high stability of the tetramer 2.5 relative to the other oligomers.

### 2.3.3 Three carbon spacer between the phosphorus and reactive carbon centre

The synthesis of the protected phosphine-aldehyde precursor was carried out in a similar fashion to the previous compounds (Scheme 2.7).

![Scheme 2.7 Synthesis of 2.7 from 2-(3-chloropropyl)-1,3-dioxolane and potassium phosphide.](image)

Commercially available 2-(3-chloropropyl)-1,3-dioxolane (ClCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH(OCH\textsubscript{2}CH\textsubscript{2}O)) was reacted with a freshly-prepared solution of KPP\textsubscript{2} in THF. Quenching of the reaction with concentrated hydrochloric acid gave rise to a species in
solution that produced a strongly downfield-shifted resonance in the $^{31}\text{P} \{^1\text{H}\}$ NMR spectrum at 38.0 ppm. The X-ray diffraction study revealed that 2.7 is a monomeric phosphonium salt. Here the molecule has clearly “bitten its tail” to form a stable five-membered ring structure (Figure 2.2). The structure of 2.7 revealed that bond lengths in the molecule are in a comparable range to those observed in the previous cyclic oligomers. However, the C1-P1-C4 angle is smaller in compound 6 which is consistent with observed five-membered cyclic geometry.

![Figure 2.2 ORTEP views of the molecular structure of 2.7. Thermal ellipsoids are drawn at 30% probability. Some hydrogen atoms and solvent molecules are omitted for clarity. Selected interatomic distances [Å] and angles [°]: 6 P1-C1 1.870(3), P1-C4 1.799(3), P1-C5 1.782(3), C1-C2 1.519(4), C2-C3 1.523(4), C1-O1 1.410(4); C1-P1-C4 97.2(1), C1-P1-C5 111.8(1), C1-C2-C3 108.1(2).]

2.5 Conclusions

In conclusion, a series of oxygen-stable, cyclic phosphonium salts, derived from unstable phosphine-aldehydes were synthesized and fully characterized. Chemoselective cyclization reactions strongly depended on the stability of the final product, although in case of tetramer 2.5, an anionic template effect might be operational. The variation of the carbon distance between phosphorus and carbonyl carbon from 2.3 to 2.7 resulted in the formation of different phosphonium salts: dimers with six-membered rings (compounds 2.1 and 2.3), a tetramer with a 16-membered ring (compound 2.5) and a monomer with a five-membered ring
(compound 2.7), respectively. All of the phosphine-aldehydes react in the presence of acid to form carbon phosphorus bonds chemoselectively. High diastereoselectivity of oligomerization was observed in the process of formation of the dimers with electron-donating alkyl substituents at phosphorus (dimers 2.3a and 2.3d) and tetrameric oligomer 2.5. The high chemoselectivity that was observed is controlled by the thermodynamic stability of the structures formed compared to other possible species (Scheme 2.2). This conclusion arises from observations that the dimers do not dissociate in solution into monomers and that their yields are not affected by changes in the reaction conditions as would be expected in case of kinetic control.

2.4 Experimental

2.4.1 General comments

All manipulations that involved air- or moisture-sensitive materials were performed using Schlenk techniques or a glovebox under an argon or nitrogen atmosphere. Solvents of high purity (ACS grade or higher) were purchased from Caledon Laboratory Chemicals and were further degassed and dried using standard procedures prior to all manipulations and reactions. Deuterated solvents were purchased from Cambridge Isotope Laboratories, INC and distilled and dried over activated molecular sieves. The reagents used were purchased from commercial sources and utilized without further purifications. NMR spectra of the samples that were prepared under argon in degassed solvents were recorded at ambient temperature and pressure using a 400 MHz Varian Gemini [\(^1\)H (400 MHz), \(^{13}\)C\{\(^1\)H\} (100 MHz), and \(^{31}\)P\{\(^1\)H\} (161 MHz)]. \(^1\)H NMR spectra were internally referenced to tetramethylsilane (TMS, 0 ppm). \(^{13}\)C NMR spectra were internally referenced to the carbon resonances of the solvent. The ESI-MS data on samples in methanol/water were done on an AB/Sciex QStar mass spectrometer with an ESI source. The elemental analyses were performed at the Department of Chemistry, University of Toronto, on a Perkin-Elmer 2400 CHN elemental analyzer. Single crystal X-ray diffraction was performed at the University of Toronto X-ray Laboratory using a Nonius Kappa-CCD System.
2.4.2 General procedure for preparation of the dimers 2.3a and 2.3b

In an Ar-filled glovebox diisopropylphosphine (for 2.3a) or diethylphosphine (for 2.3b) (15 mmol) was dissolved in 5 mL of dry THF. Bromoacetadehyde diethyl acetal (15 mmol) was added to the resulting mixture on Ar line and resulting solution was stirred for 1 h. The reaction was quenched with degassed H$_2$O (20 mmol) and heated for overnight at 70 °C. The solvent was partially removed under vacuum and gave colourless solution with white precipitate. The solution was stored for 3 h at 5 °C. The precipitate then was filtered and washed with diethyl ether (2 x 5 mL) to give an analytically pure sample. Crystals suitable for X-ray diffraction experiments were obtained by slow diffusion of diethyl ether into a saturated solution of 2.3a in methanol.

2.4.3 Dimer 2.3a

Yield: 2.93 g, 81 %. The diastereomeric ratio was found to be 1:2, as determined by $^1$H NMR. $^1$H NMR (400 MHz, CD$_3$OD, resonances of two diasteriomers of 2a overlap in region δ 3.50-1.40; see below): δ 5.60 (pseudo ddd, $^3$J$_{HH}$ = 6.4 Hz, $^2$J$_{HP}$ = 22.3Hz, 2H, CH(OH), major diastereomer; $^{31}$P{$^1$H}, 5.60 (pseudo d, $^3$J$_{HH}$ = 6.5Hz)), 5.44 (ddd, 1H, $^3$J$_{HH}$ = 3.0Hz, $^3$J$_{HH}$ = 9.3 Hz, $^2$J$_{HP}$ = 12.0 Hz, 2H, CH(OH), minor diastereomer; $^1$H{$^{31}$P}, 5.44 (dd, $^3$J$_{HH}$ = 3.0 Hz, $^3$J$_{HH}$ = 9.3 Hz)), 3.50-2.85 (m, overlap of 4H, CH(OH)CH$_2$P and 4H, (CH$_3$)$_2$CHP (both diastereomers); $^1$H{$^{31}$P}, same), 1.60-1.40 (m, 12H, (CH$_3$)$_2$CHP, (both diasteriomers); $^1$H{$^{31}$P}, same). $^{31}$P{$^1$H} NMR (161 MHz, CD$_3$OD): δ 36.81 (s, minor diastereomer), 34.54 (s, major diastereomer). $^{13}$C{$^1$H} NMR (100 MHz, CD$_3$OD, signals of carbon atoms appear as a multiplets with complex splitting patterns that arise from coupling to two magnetically inequivalent phosphorus atoms in the structure ): δ 58.61 (m, CH(OH), minor diastereomer), 57.69 (m, CH(OH), major diastereomer), 22.93 (m, CH$_2$P, major diastereomer), 22.93 (m, CH$_2$P, minor diastereomer), 21.23 (m, CH$_2$P, major diastereomer), 21.62 (d, $^2$J$_{CP}$ = 21.8 Hz, C(CH$_3$)$_2$P, minor diastereomer) 19.71 (d, $^2$J$_{CP}$ = 40.5 Hz, C(CH$_3$)$_2$P, major diastereomer), 16.45-15.35 (m, overlapping peaks of iso-propyl methyl groups, both diasteriomers). Anal. Calcd for C$_{16}$H$_{36}$P$_2$O$_2$Br$_2$: C, 39.85; H, 7.52. Found: C, 39.35; H, 7.32.
2.4.4 Dimer 2.3b

Yield: 2.78 g, 87%. The diastereomeric ratio was found to be 1:2, as determined by $^1$H NMR. $^1$H NMR (400 MHz, D$_2$O with a CDCl$_3$/TMS insert, resonances of two diastereomers of 2b overlap; see below): $\delta$ 5.45-510 (m, 2H, CH(OH)), diastereomers overlap; $^1$H $^{31}$P, 5.36 (pseudo d, 2H, CH(OH), $^2$J$_{H-P}$ = 5.8 Hz, major diastereomer), 5.29 (pseudo dd, 2H, CH(OH), $^3$J$_{H-H}$ = 3.4Hz, $^2$J$_{H-P}$ = 9.2 Hz, minor diastereomer)), 3.31-2.87 (m, 4H, CH(OH)CH$_2$P, overlap of diastereomers; $^1$H $^{31}$P, same), 2.58-2.08 (m, 8H, (CH$_3$CH$_2$P, overlap of diastereomers; $^1$H $^{31}$P, same), 1.32-0.90 (m, 12H, CH$_3$CH$_2$P, overlap of diastereomers; $^1$H $^{31}$P, same).

$^{31}$P $^1$H NMR (161 MHz, D$_2$O with a CDCl$_3$/TMS insert): $\delta$ 35.59 (s, minor diastereomer), 32.72 (s, major diastereomer). $^{13}$C $^1$H NMR (100 MHz, D$_2$O with a CDCl$_3$/TMS insert, complex coupling of several carbon atoms results from coupling to two magnetically inequivalent phosphorus atoms in the structure ): $\delta$ 58.10 (m, CH(OH), minor diastereomer), 57.85 (m, CH(OH), major diastereomer), 19.54 (m, CH$_2$P, minor diastereomer), 18.35 (m, CH$_2$P, major diastereomer), 12.50-9.12 (m, CH$_3$CH$_2$P, overlap of diastereomer), 5.42-3.72 (m, CH$_3$CH$_2$P, overlap of diastereomer). Anal. Calcd for C$_{12}$H$_{28}$P$_2$O$_2$Br$_2$: C, 33.82; H, 6.62. Found: C, 33.92; H, 6.38.

2.4.5 Procedure for preparation of the dimer 2.3d

In an Ar glovebox, potassium hydride (0.521 g; 13.0 mmol) was partially dissolved in 13 mL of THF. On a Schlenk line, di(p-tolyl)phosphine (2.31 g; 10.8 mmol) was slowly added to the mixture. The color of the solution changed to red-orange and H$_2$ gas was evolved. The solution was stirred for about 30 min until no more hydrogen generation was observed. The reaction mixture was then cooled to -78 °C and bromoacetdehyde diethyl acetal (2.12 g; 10.8 mmol) was added over a 20 min period. The temperature was brought to 25 °C and 2.5 g of 48% HBr (14.8 mmol) was added. The mixture was heated at 45 °C for 2 h, and left in the freezer for 5 hours. The precipitate was filtered off in the air and washed twice with 7 mL of cold water, as well as 15 mL of a 1:1 mixture of cyclohexanol:ethyl acetate. The precipitate was
then recrystallized by slow diffusion of ether into in of a solution of 2.3d in 1:1 methanol:toluene. The purified solid was dried under high vacuum. Yield: 2.70 g, 87.8%. Anal. Calcd for [C$_{32}$H$_{36}$P$_2$O$_2$][Br]$_2$[CH$_3$OH][H$_2$O]: C, 54.71; H, 5.84. Found: C, 54.65; H, 6.04. The diastereomeric ratio was found to be 3:4, as determined by $^1$H NMR, and $^{31}$P NMR.

**2.4.6 Major diastereomer of 2.3d**

$^1$H NMR (400 MHz, CD$_3$OD): δ 8.06 (dd, $^3$J$_{HH}$= 8.2 Hz, $^3$J$_{HP}$= 12.3 Hz, 4H, ArH), 7.63-7.58 (m, 8H, ArH), 7.48 (dd, $^3$J$_{HH}$= 8.2 Hz, $^3$J$_{HP}$= 2.5 Hz, 4H, ArH), 6.19 (dd, $^3$J$_{HH}$= 6.6 Hz, $^3$J$_{HP}$= 21.5, 2H, PCH(OH)), 4.37-4.15 (m, 2H, PCH(OH)CH$_2$), 3.99-3.81 (m, 2H, PCH(OH)CH$_2$), 2.53 (s, 6H, C$_{6}$H$_3$), 2.44 (s, 6H, C$_{6}$H$_3$). $^1$H{${^{31}$P}} NMR (400 MHz, CD$_3$OD): δ 8.06 (d, $^3$J$_{HH}$= 8.2 Hz, 4H, ArH), 7.63-7.58 (m, 8H, ArH), 7.48 (d, $^3$J$_{HH}$= 6.6 Hz , 2H, PCH(OH)), 4.18 (dd, $^3$J$_{HH}$= 6.9, 16.3 Hz, 2H, PCH(OH)CH$_2$), 3.93 (dd, $^3$J$_{HH}$= 2.2, 16.3 Hz, 2H, PCH(OH)CH$_2$), 2.53 (s, 6H, C$_{6}$H$_3$), 2.44 (s, 6H, C$_{6}$H$_3$). $^{31}$P{${^1$H}} NMR (161 MHz, CD$_3$OD): δ 11.12 (s). $^{13}$C{${^1$H}} NMR (100 MHz, CD$_3$OD): δ 146.9-146.8 (m, p-F of ArP), 146.7 (m, p-F of ArP), 133.7-133.6 (m, o-F of ArP), 133.1-133.0 (m, o-F of ArP), 114.0-113.8 (m, ipso-F of ArP), 113.0-112.9 (m, ipso-F of ArP), 61.5-60.7 (m, CH(OH)), 22.3-21.6 (m, CH$_2$CH(OH)), 20.5 (s, CH$_3$), 20.3 (s, CH$_3$).

**2.4.7 Minor diastereomer of 2.3d**

$^1$H NMR (400 MHz, CD$_3$OD): δ 7.96 (dd, $^3$J$_{HH}$= 8.3 Hz, $^3$J$_{HP}$= 12.5 Hz, 4H, ArH), 7.86 (dd, $^3$J$_{HH}$= 8.3 Hz, $^3$J$_{HP}$= 12.0 Hz, 4H, ArH), 7.63-7.58 (m, 4H, ArH), 7.56 (dd, $^3$J$_{HH}$= 8.1 Hz, $^3$J$_{HP}$= 3.2 Hz, 4H, ArH), 5.81 (ddd, $^3$J$_{HH}$= 2.7, 9.3 Hz, $^3$J$_{HP}$= 16.3 Hz, 2H, PCH(OH)), 4.37-4.15 (m, 2H, PCH(OH)CH$_2$), 3.99-3.81 (m, 2H, PCH(OH)CH$_2$), 2.50 (s, 6H, C$_{6}$H$_3$), 2.49 (s, 6H, C$_{6}$H$_3$). $^1$H{${^{31}$P}} NMR (400 MHz, CD$_3$OD): δ 7.96 (d, $^3$J$_{HH}$= 8.3 Hz, 4H, ArH), 7.86 (d, $^3$J$_{HH}$= 8.3 Hz, 4H, ArH), 7.63-7.58 (m, 4H, ArH), 7.56 (d, $^3$J$_{HH}$= 8.1 Hz, 4H, ArH), 5.81 (dd, $^3$J$_{HH}$= 2.7, 9.3 Hz, 2H, PCH(OH)), 4.27 (dd, $^3$J$_{HH}$= 9.3, 16.2 Hz, 2H, PCH(OH)CH$_2$), 3.83 (dd, $^3$J$_{HH}$= ...
2.7, 16.2 Hz, 2H, PCH(OH)CH₂), 2.50 (s, 6H, CH₃), 2.49 (s, 6H, CH₃). ³¹P{¹H} NMR (161 MHz, CD₃OD): δ 16.06 (s). ¹³C{¹H} NMR (100 MHz, CD₃OD): δ 147.5 (m, p-C of ArP), 147.0-146.9 (m, p-C of ArP), 133.4-133.3 (m, m-C of ArP), 132.9-132.8 (m, m-C of ArP), 131.4-131.3 (m, o-C of ArP), 130.5-130.4 (m, o-C of ArP), 112.8-112.3 (m, ipso-C of ArP), 111.9-111.5 (m, ipso-C of ArP), 62.2 (pdd, CH(OH)), 23.6 (pdd, CH₂CH(OH)), 20.4 (s, CH₃).

2.4.8 Procedure for preparation of the tetrimer 2.5

The procedure for the preparation of 2-(2-chloroethyl)-1, 3-dioxolane was used as described by Gil⁴⁹ without major changes. Potassium hydride (3.86 g; 96.3 mmol) was partially dissolved in 25 mL of THF in Ar glovebox. At a Schlenk line under Ar, diphenylphosphine (14.9 g; 80.0 mmol) was slowly added to the mixture. The color of the solution changed to red-orange and H₂ gas has evolved. The solution was stirred until no more hydrogen generation was observed. The reaction mixture was then cooled to 0 °C and the 2-(2-chloroethyl)-1, 3-dioxolane (10.9 g; 80.2 mmol) was added over a 20 min period. The mixture was warmed to 25 °C and 20 mL of 5M HCl was added. The mixture was heated at 45 °C over night. Volume of the solution was reduced to 2/3 of the original volume to give a milky white solution that was left in the cooler (T ~ 0 to -5 °C) overnight to give a white precipitate. The precipitate was filtered and washed twice with 7 mL of cold H₂O and diethyl ether (10 mL). The precipitate was then recrystallized from a saturated solution in MeOH by slow diffusion of diethyl ether. White rhombic crystals were filtered and washed with diethyl ether and pentanes to give analytically pure product as the trihydrate. Yield: 19.6 g, 88 %. ¹H{³¹P} NMR (400 MHz, CD₃OD): δ 7.95-7.55 (m, 40H, ArH), 6.60 (dd, ³JHH=11.2 Hz, 4H, PCH(OH)), 4.41-4.23 (m, 4H, CH₂CH (OH)), 3.03-2.84 (m, 4H, CH₂CH (OH)), 2.80-2.63 (m, 4H, PCH₂CH₂), 1.30-1.22 (m, 4H, PCH₂CH₂). ¹H NMR (400 MHz, CD₃OD): 7.95-7.55 (m, 40H, ArH), 6.60 (pd (pseudo doublet), ³JHH=10.4 Hz, 4H, PCH(OH)), 4.41-4.23 (pq, 4H, CH₂CH (OH)), 3.03-2.84 (pq, 4H, CH₂CH (OH)), 2.80-2.63 (pt, 4H, PCH₂CH₂), 1.30-1.22 (bs, 4H, PCH₂CH₂),δ ³¹P{¹H} NMR (161 MHz, CD₃OD): δ 27.08 (s). ¹³C{¹H} NMR (100 MHz, CD₃OD): δ 135.0 (s, p-C of PhP), 134.8 (s, p-C of Ph’P), 134.0 (m, m-C of PhP), 133.4 (m, m-C of Ph’P), 129.9 (m, o-C of PhP), 129.5 (m, o-C of Ph’P), 115.7 (d, JCP=85 Hz, ipso-C of PhP), 114.7 (d, JCP=84 Hz, ipso-C of
Ph’P), 63.1 (m, PCH(OH)), 23.7 (m, PCH₂CH₂CH(OH)), 16.5 (m, PCH₂CH₂CH(OH)). Anal. Calcd for [C₆₀H₆₄P₄O₄Cl₄][2MeOH][2H₂O] C, 61.29; H, 6.30. Found: C, 61.23; H, 5.84.

2.4.9 Procedure for preparation of the monomer 2.7

Diphenylphosphine (0.500 g, 2.69 mmol) was added to a mixture of partially dissolved potassium hydride (0.129 g, 3.22 mmol) in 15 mL of THF. The color of the solution changed to red-orange and H₂ gas evolution was observed. The solution was stirred until no more hydrogen generation was observed. The reaction mixture was then cooled to 0 °C and ClCH₂CH₂CH₂CH(OCH₂CH₂O) (0.404 g, 2.69 mmol) was added over a 20 min period. The mixture was warmed to 25 °C and then 10 mL of 5M HCl was added. The mixture was heated at 45 °C overnight. The solvent was completely evaporated under vacuum to give a yellow-white solid. The solid was redissolved in a minimum amount of MeOH and diethyl ether was slowly diffused into the solution. White crystals were collected by quick filtration in air and taken into a glovebox where the recrystallization was repeated to give the analytically pure product. Yield: 0.645 g, 82 %. \(^1\)H NMR (400 MHz, CD₃OD): \(\delta\) 8.02-7.62 (m, 10H, ArH), 5.48 (dt, \(^3J_{HH}=6.0\) Hz, \(^3J_{HP}=7.6\) Hz 1H, CH(OH)), 3.22-2.99 (m, 2H, CH₂CH(OH)), 2.59-2.12 (m, 4H, PCH₂ and PCH₂CH₂). \(^1\)H\(^{31}\)P NMR (400 MHz, CD₃OD): \(\delta\) 8.02-7.62 (m, 10H, ArH), 5.48 (t, \(^3J_{HH}=6.0\) Hz, 1H, CH(OH)), 3.22-2.99 (m, 2H, CH₂CH(OH)), 2.59-2.12 (m, 4H, PCH₂ and PCH₂CH₂). \(^{31}\)P\(^{1}\)H NMR (161 MHz, CD₃OD): \(\delta\) 38.0 (s). \(^{13}\)C\(^{1}\)H NMR (100 MHz, CD₃OD): \(\delta\) 134.7 (d, \(J_{CP}=3.0\) Hz, p-C of PhP), 134.4(d, \(J_{CP}=3.2\) Hz, p-C of Ph’P), 133.7 (d, \(J_{CP}=9.0\) Hz, o-C of PhP), 132.8 (d, \(J_{CP}=9.0\) Hz, o-C of Ph’P), 130.1 (d, \(J_{CP}=11.8\) Hz, m-C of PhP), 129.4 (d, \(J_{CP}=12.4\) Hz, m-C of PhP), 118.4 (d, \(J_{CP}=73.3\) Hz, ipso-C of PhP), 115.5 (d, \(J_{CP}=78.2\) Hz, ipso-C of Ph’P), 72.5 (d, \(J_{CP}=55.9\) Hz, C(OH)), 34.5 (d, \(J_{CP}=18.0\) Hz, CH₂CH(OH)), 21.3 (d, \(J_{CP}=38.6\) Hz, PCH₂), 21.4 (d, \(J_{CP}=17.2\) Hz, PCH₂CH₂). Anal. Calcd for [C₁₆H₁₈POCl][MeOH]: C, 62.80; H, 6.83. Found: C, 62.33; H, 6.18. Crystals suitable for the X-ray diffraction experiment were obtained by slow diffusion of the diethyl ether into a saturated solution of 2.7 in methanol.
2.4.10 Structure determination of 2.3a, 2.3d and 2.7 by X-ray diffraction

X-ray crystallographic data were collected on a Bruker–Nonius Kappa-CCD
diffractometer with use of monochromated MoKa radiation (λ = 0.71073 Å) and were measured
with a combination of φ scans and ω scans with k offsets, to fill the Ewald sphere.

Crystals of the tetramer 2.5 were obtained by slow diffusion of diethyl ether into a
saturated solution of 2.5 in methanol. The presence of large cavities in the lattice that originate
from the tetrameric nature of the phosphonium ion allowed co-crystallization of a large number
of solvent molecules (water and methanol as determined from 1H NMR studies) that appeared
to be highly disordered. Attempts to model the solvent molecules were not successful. If the
SQUEEZE option in PLATON was used to minimize the overall level of the disorder in the
lattice, then the density of the crystal was found to be lowered by a significant amount because
of the formation of large cavities. As a result, we cannot report the crystal structure of 2.5 in
this chapter. On the other hand, this preliminary X-ray analysis result confirms the proposed
structure with a high level of confidence.
Table 2.2 Summary of crystal data and details of intensity collection and least-squares refinement parameters for 2.3a, 2.3d and 2.7.

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<td>3817 [R(int) = 0.060]</td>
<td>3832 [R(int) = 0.0975]</td>
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<td>data; parameters</td>
<td>2862; 128</td>
<td>3817; 175</td>
<td>3832; 208</td>
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<td>R1; wR2</td>
<td>0.03356; 0.087</td>
<td>0.0554; 0.1532</td>
<td>0.0556; 0.1392</td>
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2.6 References

Chapter 3: Template Syntheses of Iron(II) Complexes Containing Chiral PNNP and PNN Ligands

3.1 Abstract

The highly unstable phosphino-aldehyde (Ph₂CH₂C(O)H) was prepared from an air and moisture stable phosphonium salt by the reaction with a strong base. This phosphino-aldehyde was used in multicomponent template reactions with various diamines in the presence of iron(II) precursors in neat acetonitrile to give mer-[Fe(PNN)₂]²⁺ complexes as kinetic products in high yields. Enantioselective reactions involving chiral diamines led to the formation of bis-tridentate complexes that were chiral at the metal center. If the reactions were conducted for a long period of time (several days) or at an elevated temperatures then the tetradentate iron(II) complexes with general structure [Fe(PNNP)(CH₃CN)₂]²⁺ were obtained as thermodynamic products. If the reactions were carried out in the solvent mixture of methanol and acetonitrile as opposed to neat acetonitrile then the formation of the tetradentate complexes is faster at room temperature. The complexes were purified by selective precipitation from methanol solution by use of NaBPh₄ and fully characterized.

3.2 Introduction

Complexes containing tetradentate PNNP ligands are important in catalysis.¹ Those based on platinum metals are catalysts for asymmetric transfer hydrogenation,²⁻⁵ direct hydrogenation,⁵ kinetic resolution of racemic alcohols,⁶ Michael addition,⁷ epoxidation and oxidation,⁸⁻¹⁰ cyclopropanation,¹¹,¹² and fluorination, both nucleophilic¹³ and electrophilic.¹⁴
Those based on iron(II) were recently shown to be catalysts for the asymmetric hydrogenation and transfer hydrogenation of aromatic ketones\textsuperscript{15-18} and of selected ketimines.\textsuperscript{19} This is significant because iron-based catalysts are potentially of lower cost, toxicity and environmental impact than those of platinum metals.\textsuperscript{20-24}

Conventionally, the preparation of PNNP ligands (Scheme 3.1) involves the condensation of a phosphine-aldehyde with the desired diamine. The method is highly versatile since a number of diamines are available (including enantiopure ones with chiral centers) and can be incorporated in the ligand backbone (Figure 3.1). This versatility allows the preparation of a library of similar ligands for further fine tuning of catalytic processes. The advantages of ligand synthesis were used in our laboratory by Dr. C. Sui-Seng\textsuperscript{15} and Dr. N. Meyer\textsuperscript{25} to prepare a library of PNNP ligands and their corresponding complexes with the general structure $\text{trans-}[\text{Fe(PNNP)(CO)(CH}_3\text{CN)}][\text{BF}_4]_2$. Their catalytic activities were investigated in the process of transfer hydrogenation of aromatic ketones. The complex containing dpen and phosphine-aldehyde 3.1 in the backbone of the ligand compared to the complexes with en and dach, was more enantioselective, although enantiomeric excess was still moderate in cases when non-bulky substrates were used.

![Scheme 3.1 Conventional synthetic route to PNNP ligands.](image-url)
With the intention to further improve the performance of the catalytic system and knowing that the catalyst activity and selectivity are highly dependent on the ligand structure, it was interesting to vary the phosphine-aldehyde in the ligand. The replacement of phosphino-aldehyde counterpart, on the other hand, is problematic because they are oxygen sensitive. As was described in Chapter 2, phosphino-aldehydes are amphoteric molecules and contain electrophilic (aldehyde) and nucleophilic (phosphorus(III)) functional groups, which may react with each other uncontrollably to produce a mixture of oligomers and polymers. The low nucleophilicity of the phosphorus in ortho-phosphinobenzaldehyde (3.1) suppresses these type of reactivities and makes this phosphine-aldehyde a precursor of choice for the preparation of PNNP ligands. The phosphino-aldehydes with the general structure 3.2 are less stable and therefore are more difficult to handle; they have not been used in the synthesis of PNNP ligand.

Moreover, the condensation reaction of phosphino-aldehydes with general structure 3.2 with the diamines to form imines may be difficult for the following reasons. A reactive phosphorus lone pair may compete with the nitrogen of the diamine for the attack on the aldehyde and therefore lead to the formation of multiple products. The absence of an aromatic group next to the aldehyde functional group of 3.2 means that the resonance stabilization of the imine is lost compared to the imine formed from 3.1. In order to overcome this limitation the method of the ligand templating on a metal center can be particularly useful.

The metal-template effect is usually referred to a class of chemoselective reactions in which the selectivity is controlled via coordination of the reagents or products to the metal center.26-28 This effect was initially observed in late 1800’s by Ettling and later by Schiff in the reaction of salicylaldehydes with ammonia.26 The presence of divalent metals gives a single
product, although a metal-free reaction usually would produce multiple products. It was not until the 1960s that the role of the metal in similar reactions was identified and supported by qualitative data by Busch. Later investigations identified two major origins of this effect: kinetic and thermodynamic (Scheme 3.2). The kinetic effect arises from the pre-organization of reagents by coordination to the metal. The resulting special orientation of the reactive functional groups favours a particular pathway by lowering its activation energy resulting in a chemo- and stereospecific reaction. The metal-template effect can be thermodynamic. It is usually observed when the multicomponent reaction is fast but is not chemoselective and results in formation of several products, which are in equilibrium with each other. An added metal may react with one of the products selectively (for example as a result of chelating effect) and remove the coordinated product from the equilibrium, thus shifting the reaction to a single product. These approaches were efficiently used in the synthesis of macromolecules and cage structures with a high degree of selectivity. Template synthesis was also used as a particularly efficient method for the synthesis of phosphorus-donor ligands.

Scheme 3.2 General representation of kinetic and thermodynamic metal-template effects.
In this chapter the phosphino-aldehydes 3.2 in combination with various diamines will be used in preparation of Fe(II)-based complexes using a multicomponent template reaction. The advantages of this method compared to the conventional metal-free condensation reaction and the properties of complexes that are formed will be discussed.

### 3.3 Results and Discussion

#### 3.3.1 Attempt to prepare PNNP ligands from phosphonium salts and diamines using conventional condensation reactions.

The dissociation of the dimeric phosphonium salt 3.3 was investigated prior the study of the condensation reactions of corresponding phosphino-aldehyde 3.4 with diamine (Scheme 3.3). The phosphonium salt 3.3 was reacted with strong and weak non-nucleophilic bases (KO\text{t}Bu or NaHCO\text{3}) in dry methanol for 20 min and the solvent was evaporated to give a white, oily solid that was re-dissolved in dichloromethane. The insoluble salts were filtered off and the solvent was evaporated to give an oily residue. The products from reactions with strong and weak bases were analyzed by $^{31}$P{$^{1}$H} NMR and showed similar results. The spectrum showed a singlet resonance at -16 ppm, which was assigned to the desired phosphino-aldehyde. The spectrum also showed several resonances in the region from 10 to 30 ppm, which were assumed to be a minor by-products. The sample was analyzed by $^{31}$P{$^{1}$H} NMR after one day of standing under an inert atmosphere to show that the by-products peaks grew in intensity relative to the peak at -16 ppm. The structures of the by-products were not determined, since it was difficult to separate them. It can be assumed that they contain [PR$_3$H]$^+$, [PR$_4$]$^+$ or P(O)R$_3$ functional groups based on their chemical shifts.$^{41}$ The by-products containing [PR$_3$H]$^+$ or P(O)R$_3$ may form under the reaction conditions but would not account for all of the resonances in the 10-30 ppm region of the spectrum. The phosphorus-containing functionality [PR$_4$]$^+$, on the other hand, may arise from the non-chemoselective reaction of a phosphine with an aldehyde to generate oligomeric structures uncontrollably. This may explain the presence of the remaining by-product peaks in the spectra.
Scheme 3.3 Reaction of the phosphonium dimer 3.3 with base and the possible decomposition products of the phosphino-aldehyde.

The mixture of 3.4 and possible oligomers can be treated with aq. HBr in THF to give the dimer 3.3 after purification. This experiment indicates that the formation of oligomers from the phosphino-aldehyde 3.4 at neutral conditions is an equilibrium process and can drive the reaction towards the formation of more stable dimeric phosphonium salt by making the conditions acidic. For that reason, it is possible that the condensation of the phosphino-aldehyde 3.4 with a diamine may lead to the formation of the desired PNNP ligand if it will be more thermodynamically stable compared to the other possible products.

The condensation of the ethylene diamine with the phosphino-aldehyde was conducted using a Dean-Stark setup (Scheme 3.4), because removal of water is required to drive the reaction to completion. We initially used acidic conditions for this reaction, since the condensation requires protonation of the –OH group, to make it a better leaving group. After 12 hours the reaction mixture was analyzed by $^{31}\text{P}^{1\text{H}}$ NMR. The spectrum showed two singlet resonances that correspond to the diastereomers of the phosphonium dimer 3.3, as a major product. This result indicates that the dimeric structure is highly stable under acidic condition and does not allow the formation of the condensation product. The condensation reaction was also attempted with addition of two equivalents of KO'Bu. The $^{31}\text{P}^{1\text{H}}$ spectrum of crude reaction mixture showed the formation of multiple products. This outcome of the reaction can be attributed to an unselective reaction of the phosphorus with the aldehyde and/or imine in the course of the reaction.
Scheme 3.4 The condensation reactions of the phosphino-aldehyde and diamine under acidic, basic and neutral conditions.

The above findings show that the high reactivity of the phosphorus lone pair is problematic for the condensation reaction. In order to resolve this problem, we further looked into different techniques to reduce its nucleophilic abilities without altering the core structure of the phosphino-aldehyde. The most common method of PR$_3$ functional groups protection from unwanted reactivity at the phosphorus was developed by Imamoto and co-workers in 1985.\textsuperscript{43} This involves the reaction of PR$_3$ with boranes such as BH$_3$ to give stable Lewis acid-base adduct. The deprotection is usually achieved by reaction with an excess of a Lewis base such as a secondary amine. This methodology was successfully used in various transformations including the preparation of molecules chiral at the phosphorus\textsuperscript{44} and the synthesis of phosphino-aldehydes and phosphino-ketones.\textsuperscript{45}

The protected phosphino-aldehyde 3.5 was prepared in moderate yields (~60 %). The reaction is summarized in Scheme 3.5. The product was partially characterized to show a broad resonance for the phosphorus atom at 13 ppm. The chemical shift is similar to the values observed by Pellon for the same compound, which was prepared using different passway.\textsuperscript{45}
Scheme 3.5 Preparation of BH$_3$ protected phosphino-aldehyde.

The condensation reaction of **3.5** with diamines using similar conditions, which were used for the previous condensation reactions, resulted in the formation of multiple products. The addition of a strong Lewis base such as diamine most likely deprotected the phosphorus atom by the formation of adduct with BH$_3$. This explains the unsuccessful outcome of the reaction. Therefore, Lewis acid protection is not compatible with the condensation reactions.

### 3.3.2 Template synthesis: formation of *bis*-tridentate iron complexes

The nucleophilicity of the phosphorus lone pair which affects the selectivity of condensation reaction can be suppressed via its coordination to the Lewis acidic metal. Moreover, the condensation reaction of phosphino-aldehyde with a diamine may also occur faster and more selectively in the presence of metal center as a result of the template effect that was described earlier.

In an argon glovebox the phosphonium salt **3.3** was dissociated into monomeric phosphino-aldehydes by the reaction with two equivalents of KO'Bu in CH$_3$CN. The iron(II) precursor ([Fe(H$_2$O)$_6$][BF$_4$]) was added to the reaction mixture. The solution was analyzed by $^{31}$P{$^1$H} NMR using a D$_2$O insert as a reference. The spectrum showed the presence of the phosphine-aldehyde and several iron(II)-phosphine complexes with peaks in the 20-45 ppm region. A subsequent addition of 1 equivalent of ethylene diamine resulted in an instantaneous change of the color of the solution from colorless to a deep purple. The solvent was evaporated to give a purple solid that was soluble in acetonitrile, dichloromethane and methanol, but
insoluble in ethers, benzene and hexanes. The $^{31}\text{P}_1(\text{H})$ NMR spectrum of the solid in CD$_3$CN showed a singlet resonance at 62 ppm. The $^1\text{H}$ NMR spectrum of the solid in CD$_3$CN did not give reliable information about the structure of the product due to the broadening of the peaks, which can be explained by the presence of paramagnetic impurities and/or salts, which were formed in the course of the template reaction.

The purification of the product was initially attempted by washing the solid with various solvents, but was not successful enough to produce an analytically pure sample. The recrystallization of the product from the solution of acetonitrile with slow diffusion of diethyl ether gave micro-crystals that were suitable for a single crystal X-ray diffraction. The structure of the product is a dicationic iron complex with mer-bis-tridentate tridentate PNN ligands (see below). The counter-ion of the obtained complex was tetrabromoferrate (FeBr$_4^{2-}$) instead of the expected tetrafluoroborates. The FeBr$_4^{2-}$ forms from the reaction of iron(II) and bromides, which come from the phosphonium salts. The formation of this by-product diminishes the total amount of iron(II) available for the desired complex formation. The template reaction using an altered stoichiometry to account for the formation of the FeBr$_4^{2-}$ (1.5 equivalent of [Fe(H$_2$O)$_6$][BF$_4$]$_2$ relative to the phosphonium dimer) gave a higher yield. The recrystallization of the crude reaction mixture produced an analytically pure sample of the product but was not high yielding (15-20 % recovered). On the other hand, the desired complex can be selectively precipitated from methanol solution by the addition of NaBPh$_4$ to give the bis-tridentate iron complex with BPh$_4^-$ as counter-ions in 75-79 % yield (Scheme 3.6).
This multicomponent one pot template reaction was conducted using several diamines: en, dach and dpn (Figure 3.1). The reaction appeared to be very general and the corresponding iron(II) bis-tridentate complexes with PNN ligands were isolated in very good yields (Figure 3.1).

All of the complexes were isolated and fully characterized using $^1$H, $^{13}$C and $^{31}$P NMR spectroscopy, electrospray ionization mass spectrometry (ESI$^+$ MS) and elemental analysis (EA). The elemental analysis showed a slightly low carbon percentage than was expected for the proposed structures. This can be attributed to the known combustion problem of the compounds containing a boron atom in their structure. The addition of the combustion agents such as V$_2$O$_5$ did not improve the carbon percentage of the EA.
Table 3.1 Preparation of [Fe(PNN)$_2$][BPh$_4$]$_2$: summary of synthetic and characterization data.

| Entry | Diamine | Complex | Yield (%) | $^{31}$P{$^1$H}NMR ppm | Configuration at iron | Optical rotation $[\alpha]_D^{27}$  
<table>
<thead>
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<th></th>
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<tbody>
<tr>
<td>1</td>
<td>en</td>
<td>3.6a</td>
<td>78</td>
<td>62.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-dach</td>
<td>3.6b</td>
<td>75</td>
<td>60.8</td>
<td>S (Λ)</td>
<td>+1423$^\circ$ (c=0.22M, CH$_3$CN)</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-dpen</td>
<td>3.6c</td>
<td>79</td>
<td>59.2</td>
<td>S (Λ)</td>
<td>+1087$^\circ$ (c=0.48M, CH$_3$CN)</td>
</tr>
</tbody>
</table>

The template reaction that results in the formation of two tridentate ligand coordinated to the metal center can produce several geometrical and stereo isomers (Figure 3.2). The complexes containing PNN ligands arranged in non-planar manner are known as facial (fac) isomer. The fac complex can have cis or trans orientation relative to the phosphorus atoms in case of the PNN ligands. The meridian (mer) isomer corresponds to the complexes with planar PNN ligands. On top of that, every geometrical isomer can exist as a mirror image of itself to give rise to stereo isomers.

![Figure 3.2 Several possible geometrical and stereo isomers of bis-tridentate complexes.](image-url)
The molecular structures of complexes **3.6a** derived from **en** (Figure 3.3) and **3.6c** derived from **dpen** (Figure 3.4) were determined using X-ray diffraction study. From the structures it follows that the iron(II) complexes have a *mer* configuration. Since $^{31}$P NMR spectrum of the bulk material showed only one singlet resonance, it can be concluded that the template reaction selectively leads to the formation of one diastereomer. Taking into consideration the number of isomers that can be formed, it is remarkable that the template reaction is so selective in all studied cases. This selectivity may be explained by the preference of sp$^2$-hybridization nitrogen and carbon of the central imine group of the ligand to maintain a planar geometry.

![ORTEP diagram of 3.6a](image)

Figure 3.3 ORTEP diagram of 3.6a depicted with thermal ellipsoids at 30 % probability. The counter-ions solvent molecules and hydrogens have been omitted for clarity. Selected bond distances (Å) and bond angles (deg): Fe(1)-P(1) 2.224(2); Fe(1)-P(2) 2.261(2); Fe(1)-N(1) 1.947(4); Fe(1)-N(2) 2.053(4); Fe(1)-N(3) 2.059(5); Fe(1)-N(4) 1.939(4); P(1)-Fe(1)-P(2) 93.41(6); N(1)-Fe(1)-P(2) 82.0(1); N(1)-Fe(1)-N(2) 82.1(2); P(1)-Fe(1)-N(4) 81.9(1); N(3)-Fe(1)-N(4) 82.8(2).
Figure 3.4 ORTEP diagram of 3.6c depicted with thermal ellipsoids at 30 % probability. The counter-ions solvent molecules and hydrogens have been omitted for clarity. Selected bond distances (Å) and bond angles (deg): Fe(1)-P(1) 2.249(3); Fe(1)-P(2) 2.246(3); Fe(1)-N(1) 2.059(8); Fe(1)-N(2) 1.969(6); Fe(1)-N(3) 2.072(8); Fe(1)-N(4) 1.971(6); P(1)-Fe(1)-P(2) 93.81(9); N(2)-Fe(1)-P(1) 83.2(2); N(1)-Fe(1)-N(2) 82.2(3); P(2)-Fe(1)-N(4) 82.2(2); N(3)-Fe(1)-N(4) 82.5(3).

Complexes 3.6a and 3.6c possess a slightly distorted octahedral geometry as follows from P-Fe-N and N-Fe-N angles (81-83) and P-Fe-P angles (93-94). Bond distances between iron(II) and the donor atoms of ligands (nitrogen and phosphorus) are within the expected range. The iron complexes that were obtained contain a chiral center at the metal. The template reaction involving non-chiral components cannot be enantioselective. Based on that, we can assume that the template reaction with en gives a racemic mixture of two enantiomers, which are chiral at the iron. The complex 3.6a crystallized in non-chiral space group C2/c. The unit cell contains eight units; four of which poses Λ orientation and the other four are Δ. The Λ enantiomer is shown in Figure 3.3. The $^{31}$P NMR spectra of the chiral complexes 3.6b and 3.6c show only one singlet resonance. They indicate that these complexes form with complete diastereoselectivity at iron. Thus, the template reactions involving the chiral diamines $(R,R)$-dach and $(R,R)$-dpen are completely stereoselective. The X-ray crystal structure of 3.6c shows that the configuration at iron is S (Λ) (For complex 3.6c P1 has priority #1, P2 has #2, N4 (attached to P2) has #3. N4 is found counterclockwise from P2 around the P1-Fe axis.
Therefore, the configuration of the complex is Λ with the phenyl ring of the diamine in equatorial position. These are the first enantiopure mer-bis-tridentate complex of iron. The synthesis of mer-bis-tridentate N-glucoside complexes of Ni$^{2+}$ and Zn$^{2+}$ derived from diamines and D-glucosamine is the only other example that uses a template approach to make chiral mer-bis-tridentate complexes.

3.3.3 Template synthesis: formation of tetradentate iron complexes

The template reaction was initially anticipated to produce iron(II) complexes with tetradentate ligands. Although bis-tridentate complexes that were formed are important, they are less likely to become a good pre-catalyst compared to the tetradentate complexes, taking into consideration that they are coordinatively saturated. For that reason, the conditions of the reaction were systematically modified with intention to obtain tetradentate complexes.

The reaction mixture containing bis-tridentate complex with en in the backbone of the ligands (singlet at 62 ppm) was left in acetonitrile for several hours. The $^{31}$P NMR spectrum of this reaction mixture with a D$_2$O insert as a reference showed a new singlet resonance at 74 ppm. The same reaction mixture was heated for 24 hours at 50°C to obtain a complete conversion of the bis-tridentate complex to a new product (Scheme 3.7, Route A). The color of the clear solution was changed from a deep purple to a pale orange-pink during the reaction. The formation of a noticeable amount of white precipitate was observed. The crude product was isolated by solvent evaporation and analysed by ESI$^+$ MS. One of the masses in the spectrum corresponded to the M$^+$ ion of the desired PNNP ligand and suggested that the new product is the tetradentate complex. The above experiments led us to the conclusion that the desired tetradentate complex is the thermodynamic product of the template reaction, while the bis-tridentate complex is the kinetic product.

The temperature and the reaction time were varied to determine the optimal conditions for the reaction. The yields of the reaction were found to be lower at longer reaction time and at higher temperature. To avoid using harsh conditions the reaction was done in protic solvent. In particularly, the reaction conducted in MeOH with the addition of stoichiometric amounts of acetonitrile gave the desired product in several hours at room temperature. NaOMe was used as
a base instead of KO‘Bu, in order to eliminate the formation of the HO‘Bu. The tetradentate complexes were isolated in analytically pure form by selective precipitation of the desired dication with NaBPh₄ from MeOH solution.

The optimized conditions of the template reaction, which leads to the formation of the tetradentate PNNP complexes with iron(II), are summarized in Scheme 3.7, Route B and were used to prepare complexes with various diamines: en, ((R,R)-dach, (R,R)-dpen and bn.

Scheme 3.7 Preparation of complexes trans- [Fe(PNNP)(CH₃CN)₂][BPh₄]₂ with various diamines.
The complexes 3.7 were isolated in good yields and characterized by 1H and 31P NMR spectroscopy, mass spectrometry (ESI+ MS) and elemental analysis (EA) (Table 3.2).

Table 3.2 Preparation of [Fe(PNNP)(CH3CN)2][BPh4]2: summary of synthetic and characterization parameters.

<table>
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<tr>
<th>Entry</th>
<th>Diamine</th>
<th>Complex</th>
<th>Yield (%)</th>
<th>$^{31}$P{1H}NMR ppm</th>
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<td>1</td>
<td>en</td>
<td>3.7a</td>
<td>82</td>
<td>62.9</td>
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<tr>
<td>2</td>
<td>(R,R)-dach</td>
<td>3.7b</td>
<td>54</td>
<td>60.8</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-dpen</td>
<td>3.7c</td>
<td>76</td>
<td>72.6</td>
</tr>
<tr>
<td>4</td>
<td>bn</td>
<td>3.7d</td>
<td>86</td>
<td>68.3</td>
</tr>
</tbody>
</table>

The dications of 3.7a, 3.7b and 3.7c crystallized from the reaction mixture as BF4-, FeBr42- and BF4- salts, respectively, in low yield. These crystals were used for the X-ray diffraction studies. The determined molecular structures of dications of 3.7a, 3.7b and 3.7c are shown in Figure 3.5, Figure 3.6 and Figure 3.7, respectively.

Figure 3.5 ORTEP diagram of 3.7a depicted with thermal ellipsoids at 30 % probability. The counter-ions, solvent molecules and hydrogens have been omitted for clarity. Selected bond distances (Å) and bond angles (deg): Fe(1)-P(1) 2.256(1); Fe(1)-P(2) 2.2429(9); Fe(1)-N(1) 1.964(3); Fe(1)-N(2) 1.956(3); Fe(1)-N(3) 1.914(3); Fe(1)-N(4) 1.914(3); P(1)-Fe(1)-P(2) 111.84(4); N(1)-Fe(1)-P(1) 83.19(9); N(1)-Fe(1)-N(2) 82.5(1); P(2)-Fe(1)-N(2) 82.52(9); P(2)-Fe(1)-N(4) 94.03(8); P(2)-Fe(1)-N(3) 88.01(9).
Figure 3.6 ORTEP diagram of 3.7b depicted with thermal ellipsoids at 30 % probability. The counter-ions, solvent molecules and hydrogens have been omitted for clarity. Selected bond distances (Å) and bond angles (deg): Fe(2)-P(2) 2.256(1); Fe(2)-P(2') 2.245(1); Fe(2)-N(3) 1.924(4); Fe(2)-N(3') 1.971(4); Fe(2)-N(4) 1.924(3); Fe(2)-N(4') 1.924(3); P(2)-Fe(2)-P(2') 109.81(6); N(3)-Fe(2)-P(2) 83.9(1); N(3)-Fe(2)-N(3') 82.7(2); P(2)-Fe(2)-N(4) 88.9(1); P(2)-Fe(1)-N(4') 91.7(1).
Complexes 3.7a, 3.7b and 3.6c have tetradentate PNNP ligands arranged in one plane around the metal center with two acetonitrile ligands trans to each other. All of the complexes possess slightly distorted octahedral geometry as follows from P-Fe-N, N-Fe-N and P-Fe-P angles, which are different from the expected for the octahedral geometry 90 degrees. Although 3.7a, 3.7b, 3.7c and the previously reported complexes 3.8a, 3.8b and 3.8c are prepared using diamines en, (R,R)-dach and (R,R)-dpen, respectively, they have a significant structural difference (Figure 3.8).
Figure 3.8 Comparison between P-Fe-P angles of iron(II) complexes with PNNP ligands.\textsuperscript{15,25,49}

Complexes 3.7\textit{a}, 3.7\textit{b} and 3.7\textit{c} have a P-Fe-P angle in a range from 108.77° to 111.84°, which are much wider than the corresponding P-Fe-P angle observed for the complexes 3.8 (100.24°-102.98°). This is attributed to the 5-, 5- and 5-membered chelate rings in 3.7 compared to the 6-, 5- and 6-membered rings in 3.8. Interestingly enough, the complexes 3.7\textit{aCy} and 3.7b\textit{Cy},\textsuperscript{49} which contain cyclohexyl (Cy) groups on the phosphorus instead of the phenyl groups compared to 3.7\textit{a} and 3.7\textit{b}, respectively, have even larger P-Fe-P angles; 112.92(2)° and 111.96(4)°, respectively. Bond distances between iron(II) and the donor atoms of ligands (nitrogen and phosphorus) are within the expected range, although P-Fe bonds are slightly elongated for the complexes 3.7 compared to the complexes 3.6 and 3.8.

The phenyl groups on the diamine of the PNNP ligand with (\textit{R,R})-\textit{dpen} might be arranged in equatorial or axial positions. We determined that the phenyl groups in 3.7\textit{c} are in equatorial positions, whereas in the similar complex 3.8\textit{c}, which was prepared from \textit{o}-phosphinobenzaldehyde 3.1, they are in axial positions, at least in the solid state. Morris and
coworkers postulated that the axial orientation of the phenyl group in the 3.8c is more favorable compared to the equatorial due to the sterics imposed by the CH=N protons. The CH=N protons in the complex 3.7c do not interfere with the substituents in equatorial position. For this reason the orientation of the phenyl groups in 3.7c is controlled by the sterics imposed by the 1-3 interaction in 5-membered ring, which forces the structure to adopt more favourable equatorial orientation. The formation of particular isomer indicates that the axial orientation is preferred in the complexes containing phosphino-aldehydes 3.4 and equatorial orientation in the complexes with the phosphino-aldehyde 3.1. The orientation of the phenyl groups may be important for the performance of the catalyst.

3.3.4 The effect of conditions and reagents on the outcome of template reaction

Imine bond-forming reactions are highly important in organic chemistry, especially in the selective preparation of secondary amines via reductive amination. The reaction is an equilibrium process, thus, the formation of the product is usually predetermined by the stability of the imine bond. In the case when water and the imine are less stable compared to the starting ketone and primary amine, water is removed from the reaction mixture to drive the reaction to completion. An acid catalyst is employed to increase the rate of the reaction by formation of a small amount of a highly electrophilic oxonium ion by protonation of the carbonyl oxygen to increase the rate of the nucleophilic attack by the amine. The protonation of –OH in the last step of the mechanism is also important because it makes –OH$_2^+$, which is a better leaving group. A Lewis acidic metal ion, when added to amine and ketone, may assist in the process of imine bond formation in several ways. It acts as an acid to catalyze the reaction. In the case when the carbonyl group is covalently linked to a donor atom, the metal ion also 1) brings the reactants together to form the thermodynamically stable chelate product; 2) increases the rate of the reaction; 3) drives the reaction to completion.

The high rates and selectivity of the template reaction described in this Chapter are indicative of metal-ion involvement in the process. The electronic configuration of iron(II) ion, d$^6$, forces the complexes to adopt a six coordinate, octahedral geometry. Based on that, we can
postulate that the productive preorganization of the ligands involves coordination of two
equivalents of the diamine (4 donors) and two equivalents of the phosphino-aldehyde **3.4** to the
iron(II) to give rise to a *bis*-tridentate complex upon condensation reaction. Complexes **3.6**
form as major products, even when the stoichiometry of the reactions was 2:1 phosphino-
aldehyde to diamine (optimal for the formation of the complex with tetradeionate ligand). The
formation of complexes **3.7** was only observed when harsh conditions were used or the reaction
was conducted in more polar, protic solvent. Most likely, that under these conditions the
dissociation of one of the ligands occurs to induce further reactivity.

These assumptions are supported by the observed reactivity of the phosphino-aldehydes,
which contain bulky cyclohexyl or *i*-propyl substituents on the phosphorus, in template
reactions as reported elsewhere by our group. These phosphino-aldehydes did not form the
expected *bis*-tridentate complexes even when the stoichiometry of diamine used (2 equivalents
relative to the phosphonium dimer) and conditions (room temperature, CH$_3$CN) was adjusted to
force the formation of such complex. On the other hand, the tetradeionate complexes were
formed and isolated in an analytically pure form. This led us to the conclusions that the initial
preorganization of two diamines and two phosphino-aldehydes is impossible when bulky
phosphines are used due to the limited space around the metal ion.

Changing the substituents on phosphorus from phenyl to cyclohexyl and *i*-propyl influences not only steric but also makes phosphorus more electron rich. The change in
electronics may also have an effect on outcome of the template reaction. To verify this
assumption the phosphonium dimer containing ethyl substituents on the phosphorus was used
in the template reaction. The analysis of the reaction mixture showed the formation of the *bis-
tridentate complex, indicating that steric created by the substituents on the phosphorus has a
major effect on the outcome of the template reaction.

The use of various diamines also has a dramatic consequence on the rate and result of
the template reaction. The formation of the *bis*-tridentate complex with **(R,R)-dach** in MeOH
occurs instantaneously after the addition of the diamine in CH$_3$CN to the reaction mixture,
similar to the reaction of **en** and **(R,R)-dpen**. The conversion to the tetradeionate complex **3.7b**, in contrast, occurs much slower than the reactions with **en** and **(R,R)-dpen**, possibly because
**(R,R)-dach** is more rigid and basic. The template reaction of non-chiral *o*-phenylenediamine in
either acetonitrile or methanol as the solvent gives only the tetradeionate PNPN complex **3.7d**.
The extended conjugation of the tetradeutant ligand in 3.7d likely increases its stability relative to the bis-tridentate complex.

### 3.4 Conclusions

In conclusions, we attempted to synthesize tetradeutant PNNP ligands derived from the phosphonium dimer 3.3 and ethylenediamine. The desired phosphino-aldehyde 3.4 was prepared by the reaction of corresponding phosphonium salt with two equivalents of base and observed by NMR. 3.4 appeared to be highly reactive due to high nucleophilicity of the phosphorus, which caused unsselective reactions with the aldehyde. The attempts to react phosphinoaldehyde 3.4 with diamine to obtain the desired condensation product were not successful, since the reaction under basic conditions was not-selective giving rise to multiple products. The protection of the phosphorus with BH$_3$ did not solve the problem, since the protecting group was sensitive to the diamine, causing deprotection.

In order to suppress the reactivity of the phosphorus, a Lewis acidic iron(II) precursor was added to the reaction of the phosphino-aldehyde and the diamine. The resulting product appeared to be iron(II) bis-tridentate complex containing PNN ligands 3.6. A library of similar complexes with different diamines were prepared in high yield (75-79 %), isolated as a BPh$_4^-$ salts and fully characterized. These complexes are chiral at the metal center. The formation of only one diastereomer was observed when the template reaction was conducted with chiral diamines, indicating that the reaction is highly stereospecific.

When the template reaction was heated for a long period of time, the formation of iron(II) complex 3.7 containing PNNP ligand was observed. If the reaction was conducted in MeOH as a solvent than 3.7 was formed at room temperature. A library of complexes 3.7 with various diamines incorporated in the backbone of the ligand was prepared and isolated as BPh$_4^-$ salts in moderate to high yield (54-86 %). All complexes were fully characterized.
3.5 Experimental

3.5.1 General comments

All manipulations that involved air- or moisture-sensitive materials were performed using Schlenk techniques or a glovebox under an argon or nitrogen atmosphere. Solvents of high purity (ACS grade or higher) were purchased from Caledon Laboratory Chemicals and were further degassed and dried using standard procedures prior to all manipulations and reactions. Deuterated solvents were purchased from Cambridge Isotope Laboratories, INC and distilled and dried over activated molecular sieves. The phosphonium dimers were synthesized according to the procedure previously reported by our group. Other reagents used were purchased from commercial sources and utilized without further purifications. NMR spectra of the samples that were prepared under argon in degassed solvents were recorded at ambient temperature and pressure using a 400 MHz Varian Gemini [\textsuperscript{1}H (400 MHz), \textsuperscript{13}C {\textsuperscript{1}H} (100 MHz), and \textsuperscript{31}P {\textsuperscript{1}H} (161 MHz)]. \textsuperscript{1}H NMR spectra were internally referenced to tetramethylsilane (TMS, 0 ppm). \textsuperscript{13}C NMR spectra were internally referenced to the carbon resonances of the solvent. The ESI-MS data on samples in methanol/water were done on an AB/Sciex QStar mass spectrometer with an ESI source. The elemental analyses were performed at the Department of Chemistry, University of Toronto, on a Perkin-Elmer 2400 CHN elemental analyzer. Some complexes gave a low carbon analysis but acceptable hydrogen and nitrogen contents because of a combustion problem that is common for the compounds containing boron atoms. Single crystal X-ray diffraction was performed at the University of Toronto X-ray Laboratory using a Nonius Kappa-CCD System.

3.5.2 Preparation of stock solution A that was used in the synthesis of PNN \textit{bis}-tridentate complexes

The dimer 3.3 (200 mg, 0.324 mmol) was partially dissolved in CH\textsubscript{3}CN (6 mL) in a glove-box under a N\textsubscript{2} atmosphere. After 5 min of stirring [Fe(H\textsubscript{2}O)\textsubscript{6}][BF\textsubscript{4}]\textsubscript{2} (164 mg, 0.485
mmol) was added to the reaction mixture. KOtBu (74.0 mg, 0.645 mmol) was added and the color of solution changed from colorless to yellow. The mixture was stirred at room temperature for 15 min without any observable changes.

### 3.5.3 Synthesis of mer-[Fe(Ph₂PCH₂CH=NCH₂CH₂NH₂)₂][BPh₄]₂ (3.6a).

A stock solution of diamine was prepared by dissolving 62.1 mg of the 1, 2-ethylenediamine (en) in 0.90 mL of CH₃CN. The stock solution (0.552 mL, 38.0 mg, 0.647 mmol) was added drop-wise over the course of 3 minutes to the precursor solution A. The color of the solution changed to a deep purple at the moment of the addition and a small amount of insolubles formed. The mixture was filtered through a pipette with a cotton ball. The solvent was removed under reduced pressure to give a red-purple solid. The solid was dissolved in 5 mL of MeOH and the resulting purple solution was added to the solution of NaBPh₄ (250 mg, 0.658 mmol) in 1 mL of MeOH to cause the formation of a pink-orange precipitate. The solid was filtered and washed with MeOH (0.50 mL) and with Et₂O (0.50mL) three times and dried under vacuum. Yield: 78% (3.1 g); ¹H NMR (400 MHz, CD₃CN) δ: 1.88 (br, 2H, HN), 2.38 (m, 2H, HCP), 2.62 (m, 2H, HCP), 3.20 (br, 2H, HN), 3.52 (m, 4H, HC-N), 3.68 (m, 4H, HC-N), 6.8-7.5 (m, 60H, HAr), 8.53 (m, 2H, HC=N). ³¹P ¹H NMR (121 MHz; CD₃CN): 62.87 ppm (s). Anal. Calcd for C₈₀H₇₈N₄P₂FeB₂: C, 77.82; H, 6.37; N, 4.53. Found: C, 77.19; H, 6.40; N, 4.61. MS (ESI⁺) Calcd for [C₃₂H₃₈N₄P₂Fe]²⁺: 298.2 m/z. Found: 298.1 m/z. MS (ESI⁻) Calcd for [B(Ph)₄]⁻: 319.2 m/z. Found: 319.2 m/z. The red-purple solid (10 mg) that was obtained before the addition of NaBPh₄ was dissolved in 1 mL of MeOH:CH₃CN (1:1 by volume). Crystals were obtained by diffusion of Et₂O (1.0 mL) into this solution. The structure of the cation of mer-[Fe(Ph₂PCH₂CH=NCH₂CH₂NH₂)₂][BPh₄]₂ is shown in Figure 3.3.
3.5.4 Synthesis of mer-(R, R)-[Fe(Ph₂PCH₂CH=N(C₆H₁₀)NH₂₂][BPh₄]₂ (3.6b).

Solution of (1R,2R)-(−)-1,2-diaminocyclohexane (73.9 mg, 0.647 mmol in 1 mL of CH₃CN) was added drop-wise over the course of 3 min to the precursor solution A (mL). The color of the solution changed to deep purple at the moment of the addition and a small amount of precipitate formed. The mixture was filtered through a pipette with a cotton ball. Solvent was removed under reduced pressure to give red-purple solid. The solid was dissolved in 2 mL of MeOH and resulting purple solution was added to the solution of NaBPh₄ (250 mg, 0.658 mmol) in 1 mL of MeOH to cause the formation of a purple-red precipitate. The solid was filtered and washed with MeOH (0.25 mL) and with Et₂O (0.50 mL) three times and dried under vacuum. Yield: 75% (0.33 g); ¹H NMR (400 MHz, CD₃CN) δ: 1.01-1.79 (m, 16 H, H of C₆H₁₀), 2.27-2.36 (m, 2H, HC-N), 2.46-2.59 (m, 2H, HC-N), 3.17-3.27 (m, 2H, -NH), 3.42-3.54 (m, 2H, HCP), 3.66-3.78 (m, 2H, HCP), 4.59-4.72 (m, 2H, NH), 6.80-7.58 (m, 60H, ArH), 8.43-8.62 (m, 2H, HC=N). ³¹P {¹H} NMR (121 MHz; CD₃CN): 61.08 ppm (s). Anal. Calcd for
C₈₄H₆₄N₄P₂FeB₂: C, 78.69; H, 6.76; N, 4.17. Found: C, 73.03; H, 6.60; N, 4.32. MS (ESI⁺)
Calcd for [C₃₆H₄₄N₄P₂Fe]²⁺: 325.3 m/z. Found: 325.2 m/z. MS (ESI⁺) Calcd for [B(Ph)₄]⁺: 319.2 m/z. Found: 319.2 m/z.
3.5.5 Synthesis of mer-[Fe(Ph₂PCH₂CH=NCH(Ph)CH(Ph)NH₂)₂][BF₄]₂ (3.6c).

A solution of the (1R,2R)-(−)-1,2-diphenylethylene-diamine (137 mg, 0.647 mmol in 1 mL of CH₃CN) was added drop-wise over the course of 3 minutes to the precursor solution A (6 mL). The color of the solution changed to a deep purple at the moment of the addition and a small amount of precipitate formed. The mixture was filtered through a pipette with a cotton ball. The solvent was removed under reduced pressure to give a red-purple solid. The solid was dissolved in 4 mL of MeOH and the resulting purple solution was added to a solution of NaBPh₄ (250 mg, 0.658 mmol) in 1 mL of MeOH to cause the formation of the precipitate. The solid was filtered and washed with 0.35 mL of MeOH three times and dried under vacuum. Yield: 79% (0.39 g); ¹H NMR (400 MHz, CD₃CN) δ: 3.55 (m, 2H, -NH), 3.56 (d, 2H, J 12 Hz, HC-P), 3.72 (m, 2H, HC-N), 4.67 (m, 2H, NH), 5.23 (d, 2H, J 16 Hz, HC-P), 6.6-7.8 (m, 60H, ArH), 7.96 (m, 2H, HC=N). ³¹P{H} NMR (121 MHz; CD₃CN): δ 59.1 (s). MS (ESI⁺) Calcd for [C₅₆H₅₄N₄P₂Fe]²⁺: 450.4 m/z. Found: 450.2 m/z. MS (ESI⁻) Calcd for [B(Ph)₄]⁻: 319.2 m/z. Found: 319.2 m/z. The red-purple solid (10 mg) that was obtained before the addition of NaBPh₄ was dissolved in 1 mL of MeOH:CH₃CN (1:1 by volume). Crystals were obtained by diffusion of Et₂O (1.0 mL) into this solution. The structure of the cation of mer-[Fe(Ph₂PCH₂CH=NCHPhCHPhNH₂)₂][BF₄]₂ is shown in Figure 3.4.
3.5.6 Preparation of stock solution (B) for the template synthesis of tetradequate ligand complexes.

The phosphonium dimer 3.3 (200 mg, 0.324 mmol) was completely dissolved in MeOH (6 mL). [Fe(H₂O)₆][BF₄]₂ (164 mg, 0.485 mmol) was added to the reaction mixture. NaOMe (34.9 mg, 0.647 mmol) was added as a MeOH (1 mL) solution and the color of the solution changed from colorless to clear yellow. After 10 min of stirring, 1 mL of acetonitrile was added.

3.5.7. Synthesis of trans-(R, R)-[Fe(Ph₂PCH₂CH=NCH₂CH₂N=CHCH₂PPh₂) (CH₃CN)₂] [BPh₄]₂ (3.7a).

A stock solution of the diamine was prepared by dissolving 85.5 mg of 1, 2-ethylenediamine in 1.1 mL of acetonitrile. Portion (0.250 mL) of stock solution was added to the stock solution B (6 mL) over the course of 20 min. The solution changed color to red-orange after the addition. After 3 h the solution became a deep orange. The solution was added to a solution of NaBPh₄ (250 mg, 0.658 mmol) in 1.5 mL of MeOH to cause the formation of the precipitate. The orange-pink solid was filtered and washed with 0.35 mL of MeOH three times and dried under vacuum. Yield: 82% (0.33 g); ¹H NMR (400 MHz, CD₃CN) δ: 1.36 (s, 6H, CH₃CN ), 4.10-4.25 (m, 4H, HCP), 4.10-4.25 (m, 4H, HCFN), 6.80-7.55 (m, 60H, ArH), 8.65-8.80 (m, 2H, HC=N). ³¹P {H} NMR (121 MHz; CD₃CN): 74.01 ppm (s). Anal. Calcd for C₈₂H₇₆N₄P₂FeB₂: C, 78.38; H, 6.08; N, 4.46. Found: C, 77.58; H, 6.03; N, 4.26. MS (ESI⁺) Calcd. for [C₃₄H₃₆N₄P₂Fe-2(CH₃CN)]²⁺: 268.2 m/z. Found: 268.1 m/z. MS (ESI⁺) Calcd for [B(Ph)₄]⁺: 319.2 m/z. Found: 319.2 m/z. The crystals were obtained by diffusion of Et₂O (1.0
mL) into the deep orange solution of crude product in CH$_3$CN:MeOH (4:1, 2 mL). The structure of the cation of trans-(R, R)-Fe(Ph$_2$PCH$_2$CH=NCH$_2$CH$_2$N=CHCH$_2$PPh$_2$)(CH$_3$CN)$_2$][BF$_4$]$_2$ is shown in Figure 3.5.

### 3.5.8 Synthesis of trans-(R, R)-
[Fe(Ph$_2$PCH$_2$CH=N(C$_6$H$_{10}$)N=CHCH$_2$PPh$_2$)(CH$_3$CN)$_2$][BPh$_4$]$_2$ (3.7b).

(1R,2R)-(-)-1,2-diaminocyclohexane (37 mg, 0.32 mmol) was dissolved in 0.5 mL of acetonitrile and was added to the precursor solution B (6 mL) over the course of 20 min. The solution changed color to purple after the addition. The resulting solution was heated at 40 °C for 20 h to give deep orange solution. The solvent volume was reduced by one half and the resulting solution was added to a solution of NaBPh$_4$ (250 mg, 0.65 mmol) in 1.5 mL of MeOH to cause the formation of a precipitate. An orange-red solid was recovered by filtration and washed with 0.15 mL of MeOH three times and dried with vacuum. Yield: 54% (0.23 g); $^1$H NMR (400 MHz, CD$_3$CN) δ: 1.33 (s, 6H, CH$_3$CN), 1.29-1.39 (m, 2H, H of C$_6$H$_{10}$), 1.68-1.76 (m, 2H, H of C$_6$H$_{10}$), 1.98-2.28 (m, 2H, H of C$_6$H$_{10}$), 2.70-2.78 (m, 2H, H of C$_6$H$_{10}$), 3.54-3.58 (m, 2H, HC-N), 3.88-4.01 (m, 2H, HCP), 4.34-4.49 (m, 2H, HCP), 6.8-7.5 (m, 60H, ArH), 8.60-8.74 (m, 2H, HC=N). $^{31}$P {H} NMR (121 MHz; CD$_3$CN): 73.96 ppm (s). Anal. Caled for C$_{84}$H$_{82}$N$_4$P$_2$FeB$_2$: C, 78.78; H, 6.31; N, 4.27. Found: C, 77.00; H, 5.99; N, 4.34. MS (ESI$^+$) Caled for [C$_{38}$H$_{45}$N$_4$P$_2$Fe-2(CH$_3$CN)]$^{2+}$: 268.1 m/z. Found: 268.1 m/z. MS (ESI$^+$) Caled for [B(Ph)$_4$]$^+$: 319.2 m/z. Found: 319.2 m/z. The crystals were obtained by diffusion of Et$_2$O (2.0 mL) into the deep orange solution of crude product in CH$_3$CN:MeOH (5:1, 2 mL). The
structure of the cation of trans-(R, R)-
Fe(Ph_2PCH_2CH=NCH_2CH_2N=CHCH_2PPh_2)(CH_3CN)_2][BF_4]_2 is shown in Figure 3.6.

3.5.9 Synthesis of trans-(R, R)-
[Fe(Ph_2PCH_2CH=NCH(Ph)CH(Ph)N=CHCH_2PPh_2)(CH_3CN)_2][BPh_4]_2 (3.7c)

The phosphonium compound (200 mg, 0.324 mmol) was completely dissolved in MeOH (6 mL). [Fe(H_2O)_6][BF_4]_2 (164 mg, 0.485 mmol) was added to the reaction mixture. NaOMe (34.9 mg, 0.647 mmol) was added as a MeOH (1 mL) solution and the color of the solution changed from colorless to clear yellow. After 10 min of stirring, 1 mL of acetonitrile was added. To this solution was added, over the course of 20 min, a solution of (1R,2R)-(+) 1,2-diphenylethylenediamine (69 mg, 0.323 mmol) in 0.5 mL of acetonitrile. The solution changed color to purple after the addition. After 20 h the resulting solution was added to a solution of NaBPh_4 (250 mg, 0.658 mmol) in 1 mL of MeOH to cause the formation of the precipitate. A pink solid was recovered by filtration and dried under vacuum. Yield: 76% (0.35 g); ^1H NMR (400 MHz, CD_3CN) δ: 1.54 (s, 6H, CH_2CN), 3.95-4.15 (m, 2H, HCP), 4.26-4.38 (m, 2H, HCP), 5.43 (m, 2H, HC=N), 6.80-7.75 (m, 70H, ArH), 8.10-8.27 (m, 2H, HC=N); ^31P {^1H} NMR (121 MHz; CD_3CN): 72.63 ppm (s); Anal. Calcd for C_{94}H_{84}N_4P_2FeB_2: C, 80.14; H, 6.01; N, 3.98; Found: C, 79.20; H, 6.08; N, 4.65; MS (ESI^+) Calcd for [C_{46}H_{44}N_4P_2Fe-2(CH_3CN)]^{2+}: 344.3 m/z. Found: 344.1 m/z. MS (ESI) Calcd for [B(Ph)_4]^+: 319.2 m/z. Found: 319.2 m/z. The orange solid (10 mg) that was obtained before the addition of NaBPh_4 was dissolved in 1 mL of MeOH:CH_3CN (1:1 by volume). Crystals were obtained by diffusion of
Et₂O (1.0 mL) into this solution. The structure of the cation of complex 3.7c is shown in Figure 3.7.

3.5.10 Synthesis of 
Fe(Ph₂PCH₂CH=N(C₆H₄)N=CHCH₂PPh₂)(CH₃CN)₂][BPh₄]₂ (3.7d).

Ortho-phenylenediamine (35 mg, 0.32 mmol) was dissolved in 0.5 mL of acetonitrile and was added to the precursor solution B (6 mL) over the course of 20 minutes. The solution changed color to orange after the addition. The resulting residue was added to the solution of NaBPh₄ (250 mg, 0.658 mmol) in 1 mL of MeOH to cause the formation of the precipitate. The red-orange solid was isolated by filtration and washed with 0.15 mL of MeOH three times and dried under vacuum. Yield: 86% (0.36 g); ¹H NMR (400 MHz, CD₃CN) δ: 2.10 (s, 6H, CH₃CN), 4.52-4.60 (m, 4H, HCP), 6.80-8.20 (m, 64H, HAr), 9.32-9.44 (m, 2H, HC=N). ³¹P {H} NMR (121 MHz; CD₃CN): 68.33 ppm (s). Anal. Calcd for C₃₈H₇₆N₄P₂FeB₂: C, 79.19; H, 5.87; N, 4.29. Found: C, 76.83; H, 5.80; N, 4.15. MS (ESI⁺) Calcd for [C₆₀H₇₆N₄P₂Fe₂(CH₃CN)₂]⁺: 292.2 m/z. Found: 292.1 m/z. MS (ESI⁻) Calcd for [B(Ph)₄]⁻: 319.2 m/z. Found: 319.2 m/z.
3.5.11 Structure determination of the complexes 3.6a, 3.6c, 3.7a, 3.7b and 3.7c.

X-ray crystallographic data were collected on a Bruker–Nonius Kappa-CCD diffractometer with use of monochromated MoKa radiation (λ = 0.71073Å) and were measured with a combination of φ scans and ω scans with k offsets, to fill the Ewald sphere. The summary of crystal lattice parameters can be found in Table 3.3.

Table 3.3 Summary of crystal data parameters for 3.6a, 3.6c, 3.7a, 3.7b and 3.7c.

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3.6 References

Chapter 4: The Use of Iron(II) Complexes Containing Chiral PNNP Ligands in the Asymmetric Transfer Hydrogenation of Ketones

4.1 Abstract

The asymmetric transfer hydrogenation of aromatic ketones can be efficiently accomplished using catalysts that are based on platinum group metals. These are more toxic and less abundant than iron. For that reason, the discovery of iron-based catalysts for this purpose is important. In order to address this issue, an iron(II)-based pre-catalyst trans-[Fe(CH$_3$CN))(CO)(PPh$_2$CH$_2$CH=NCH(Ph)CH(Ph)N=CHCH$_2$PPh$_2$)][BPh$_4$]$_2$ was prepared by a monocarbonylation reaction of the corresponding bis-acetonitrile complex and was tested for catalytic activity in the asymmetric transfer hydrogenation of various aromatic and aliphatic prochiral ketones. The pre-catalyst lead to a very efficient and stereo-selective catalyst for this transformation and produced chiral alcohols in high yields (up to 90%) and high enantiomeric excess (up to 97 %) using low catalyst loadings (0.05%). In order to explore the effect of the various diamines incorporated into the backbone of the ligand on the activity of the catalyst, the complexes trans-[Fe(Br)(CO)(PPh$_2$CH$_2$CH=NCHRCHRN=CHCH$_2$PPh$_2$)]BPh$_4$ were prepared using the following diamines: (R,R)-1,2-diaminocyclohexane, (R,R)-1,2-diphenyl-1,2-diaminoethane, (R,R)-1,2-di(4-methoxyphenyl)-1,2-diaminoethane and ethylenediamine. All of the complexes, when activated with a base, show a very high activity in the transfer hydrogenation catalysis of acetophenone, using 2-propanol as the reducing agent under mild conditions. A comparison of the TOF of complexes shows that catalytic activity of the complexes increase as the size of the substituents on the backbone of ligands increases.
4.2 Introduction

The reduction of ketones to alcohols is an important process for both industrial and academic purposes, especially the enantioselective reduction of prochiral ketones for the production of enantioenriched alcohols (Scheme 4).\textsuperscript{1-3} This transformation can be efficiently accomplished using catalysts that are based on platinum group metals (PGM) in combination with different reducing agents.\textsuperscript{4-33}

![Scheme 4.1 General scheme for the reduction of pro-chiral ketones using platinum group metal catalysts.](image)

Although these catalytic systems are very active, well investigated and highly enantioselective, the use of less toxic, more abundant and inexpensive metals would be highly beneficial. Iron, in particular, is an interesting alternative because of its chemical properties such as easily varied oxidation states, well investigated coordination properties and Lewis acidity as well as low toxicity and high abundance. Some other reactions such as cross-coupling, cycloadditions and polymerization that are important for industrial and synthetic applications can now be accomplished using iron-based catalytic systems,\textsuperscript{34} although harsh
conditions such as high temperature, high catalyst loading and additives are often required for a successful reaction. The catalytic reduction of carbonyl-containing compounds to the corresponding alcohols using iron-based catalysts is a rapidly growing field, one that was relatively unexplored only seven years ago.\textsuperscript{35-39}

Several major directions were taken by researchers in an attempt to develop iron(II)ketone hydrogenation catalysts. The first common trend is to use well studied ligand systems that have proven to be effective in combination with ruthenium or other PGM. The most interesting candidates are ligands which are known to operate via a metal-ligand assisted mechanism.\textsuperscript{11} These ligands are known not only to increase the rates of the catalytic reaction, but also to allow the metal to stay in one oxidation state during hydrogen activation and hydrogen transfer steps. This is especially important for iron catalysts because the interchange between readily attainable oxidation states (III) and (II) may lead to radical pathways, which are usually difficult to control and give unselective reactivity. The second common direction is associated with the attempt to mimic naturally occurring iron-based enzymes, hydrogenases, which are responsible for the reversible oxidation of molecular hydrogen in the anaerobic metabolism of various microorganisms.\textsuperscript{40} The presence of carbon monoxide (CO) and cyanide (CN\textsuperscript{-}) ligands in the coordination sphere of the [Fe-Fe] and [Ni-Fe] hydrogenases\textsuperscript{41, 42} is known to play a crucial role in their biological activity by the stabilization of electron rich intermediates via metal to ligand pi-back donation, trans-influence and other factors.\textsuperscript{43, 44} For this reason, iron-carbonyl compounds were intensively investigated in the hydrogen transfer reactions.

One of the first examples of the hydrogenation of ketones was reported in the 1980s by the group of Marcò.\textsuperscript{45, 46} The direct hydrogenation using molecular hydrogen was catalyzed by iron carbonyl hydride [HFe(CO)\textsubscript{4}]\textsuperscript{-} that was formed \textit{in situ} from Fe(CO)\textsubscript{5} and molecular hydrogen in the presence of a base under high pressure (100 bar) and temperature (150 °C) (Scheme 4.2, A). The salt of hydrido tetracarbonyl ferrate with tetraethyl ammonium was prepared separately and was found to be an efficient stoichiometric reductant of acetone, supporting the fact that [HFe(CO)\textsubscript{4}]\textsuperscript{-} is an active species in catalysis (Scheme 4.2, B). Following the success of this reaction, Vancheeseen\textsuperscript{47, 48} reported the transfer hydrogenation using secondary alcohols (2-PrOH, 1-phenethanol and others) as a hydrogen donor. The catalytically active species were similarly generated \textit{in situ} from different iron carbonyl starting materials
with the general structure Fe₅(CO)₉ under mild conditions (room temperature, no pressure). The iron carbonyl cluster Fe₅(CO)₁₂ was found to be the most active pre-catalyst. Long induction periods (10-20 min) were observed in both the direct hydrogenation and the transfer hydrogenation reactions reported by Marcò and Vancheesan when the catalytic reductions were conducted using the pre-catalysts. This observation was explained by long activation times of the pre-catalyst to the active species.

Scheme 4.2 A Activation of an iron carbonyl complex in situ, and its proposed catalytic cycle as described by Marcò. B Preparation of the possible active complex.

It is very surprising that the importance of these reports was relatively unnoticed for almost 20 years. Gao and co-workers used the pre-made iron carbonyl cluster ([NEt₃][HFe₅(CO)₁₁]) in combination with a chiral dianinodiphosphine ligands under the transfer hydrogenation condition with 2-PrOH as a reducing agent to hydrogenate several pro-chiral ketone (Scheme 4.3). It is important to note that the ligands used were previously utilized in a similar process using Ru(II) as the metal center. The process was enantioselective and the resulting alcohols were isolated with a moderate to high enantiomeric excess (63-98 %) depending on the substrate used. The catalytic system was not very efficient, giving low yields (18-87 %) if bulky ketone were used although relatively mild conditions were applied.
The strategy of using carbonyl clusters in combination with phosphorus and nitrogen donor ligands was further investigated by Beller and co-workers.\textsuperscript{52-54} Unidentified catalytically active species were prepared by the reaction of various iron carbonyl complexes or iron-containing salts by reaction with 2-PrOH in the presence of tridentate NNN terpyridine and phosphine or porphyrin ligands for a long period of time (10-16 h) at elevated temperatures (65°C). The resulting reaction mixture was further activated by a strong base (both organic and inorganic) prior to the addition of the substrate. The reactions at high temperatures (100°C) were found to be very efficient in the chemoselective reduction of various ketones (aryl-alkyl and alkyl-alkyl) using low catalyst loadings.

Scheme 4.3 Examples of iron-based catalytic systems prepared \textit{in situ}. 
Interestingly, the reactions that were carried out with iron precursors containing metal center in different oxidation states (Fe(0), Fe(II) and Fe(III)) often showed very similar activity, especially in the case when porphyrin-type ligands were used. Unfortunately, the structure and the pathway of formation of the catalytically active species were not reported in order to conclusively explain this outcome. Attempts to isolate and determine the structure of the active species that are generated in the process of activation of iron-containing precursors did not produce any conclusive results. Vancheesan and co-worker postulated that the catalytically active species in his transfer hydrogenation reaction contain iron in the zero oxidation state, by conducting a Mössbauer study before and after the reaction. Assuming that Beller’s active species have similar origins, then iron(II) and iron(III) pre-catalysts are activated by the reduction with 2-PrOH. In all cases of iron catalyzed reduction of ketones the addition of base was required for the activation of the pre-catalyst. It was also observed that the reactivity of the systems is dependent on the base concentration.

Knowledge of the structure of the active species would greatly assist in the optimization of the activity and enantioselectivity of the catalysts based on iron. A step in this direction is the use of well-defined iron-based pre-catalysts. Casey and Guan investigated the reactivity of Knölker’s complex, the structure of which resembles a Ru-based catalyst, in the chemoselective hydrogenation of various ketones under mild conditions (Scheme 4.4, A). Mechanistic studies were conducted to show that the iron-based catalyst behaved in a similar fashion to its ruthenium analog. The studies were also supported by the separately conducted density function theory (DFT) investigations.

Recently, another highly active hydrogenation system containing iron as the central metal with a pincer-type PNP ligand was described by Milstein and co-workers (Scheme 4.4, B). The importance of the carbonyl ligand in the coordination sphere of the catalyst is especially great in this example, since the complexes without CO, which were previously prepared, were not catalytically active for the hydrogenation of ketones. A ligand-assisted mechanism involving the aromatization/dearomatization of the ligand in hydrogen cleavage step was proposed for this catalytic system, but was not strongly supported by the experimental data. On the other hand, Yang found in DFT calculations that the direct reduction of the ketone
by the Fe-hydride is a lower energy pathway, compared to the mechanism proposed by Milstein.\textsuperscript{65}

\begin{center}
\begin{tabular}{ll}
\textbf{Conditions} & \textbf{Results} \\
\hline
Cat 2 mol \% & Yield = 83 \%

\textbf{A} & \\
$\text{p (H}_2\text{)} = 3$ atm & \\
$T = 25 ^\circ \text{C}$ & \\
Toluene & \\
Time = 20 hours & \\

\textbf{B} & \\
Cat 0.05 mol \% & Yield = 94 \%

\textbf{4.1} & \\
$\text{p (H}_2\text{)} = 4.1$ atm & \\
$T = 20 ^\circ \text{C}$ & \\
EtOH & \\
K$\text{O}^+$Bu 0.1 \% & \\
Time = 20 hours & \\

\textbf{C} & \\
Cat 0.44 mol \% & Yield = 95 \%

\textbf{4.2} & \\
$\text{p (H}_2\text{)} = 25$ atm & \\
$T = 50 ^\circ \text{C}$ & \\
EtOH & \\
K$\text{O}^+$Bu 3.2 \% & \\
Time = 18 hours & \\
\end{tabular}
\end{center}

Scheme 4.4 Iron-based well-defined catalysts for the direct hydrogenation of acetophenone: \textbf{A} by Casey and Guan, \textbf{B} Milstein and co-workers, \textbf{C} Morris and co-workers.

Our group reported several well-defined iron-based pre-catalysts containing tetradeutate PNNP ligands.\textsuperscript{66, 67} The structures of the ligands were similar to those which were previously used with ruthenium\textsuperscript{50, 51} and iridium\textsuperscript{50, 51, 68} for the transfer hydrogenation of aromatic ketones. The iron(II) complexes were prepared by reacting a neutral PNNP ligands with an iron(II) containing precursor ($\text{FeCl}_2$ or $[\text{Fe(H}_2\text{O})_6][\text{BF}_4]_2$) in acetonitrile (Scheme 4.5, Method B). The template method, which was described in detail in Chapter 3, can also be used in the
preparation of complexes 4.3 (Scheme 4.5, Method A). Complexes 4.3 and complex 4.4 were tested for catalytic activity in the direct hydrogenation of aromatic ketones. A high conversion of acetophenone, which was used as a model substrate, to a corresponding alcohol was achieved only under harsh conditions \( (p(H_2) = 25 \text{ atm}, T = 50^\circ\text{C}) \) (Scheme 4.4, C). A strong base in a 1:8 ratio relative to the catalyst was required in all cases for the pre-catalyst activation. The reactivity of the complex 4.4 containing amine groups in the ligand backbone was found to be only slightly more active compared to its analog 4.3a bearing imine functional groups. This observation indicates that the both pre-catalysts form similar active species upon activation.

Scheme 4.5 Synthesis of iron(II) complexes 4.3 and 4.4.
The enantiomeric excess of the product was found to be low (27 %) when pre-catalyst 4.3b containing a chiral backbone was used in the hydrogenation of acetophenone. Although this result is far from optimal it is important since it is the only well-defined asymmetric iron-based hydrogenation catalyst. Complexes 4.3 and 4.4 showed no activity in the transfer hydrogenation of ketones using 2-PrOH as the solvent and reducing agent.

Complexes 4.5 and 4.6 can be prepared in almost quantitative yields by exposing the solution of complexes 4.3 in acetone or dichloromethane to a CO atmosphere or by reacting it with tBuNC, respectively (Scheme 4.6).

The presence of the pi-accepting ligands CO or 'BuNC in the coordination sphere of the metal complex dramatically increased the catalytic activity of the iron PNPN complexes in the transfer hydrogenation of ketones (Table 4.1). Complexes 4.5 showed extremely high initial turn over frequencies (TOF) up to 2400 h⁻¹ when activated with base. The enantiomeric excess of alcohols ranged from 50 to 99 %, increasing when more bulky pro-chiral ketones were used. Complex 4.5c containing the most sterically bulky diamine in the backbone of the ligand, showed higher enantioselectivity compared to the complex 4.5b. Complex 4.6b showed the lowest activity; on the other hand, it showed the highest enantioselectivity in the reduction of acetophenone.
Table 4.1 Summary of the catalytic activity of complexes 4.5 and 4.6b in the transfer hydrogenation of acetophenone.

![reaction_diagram]

<table>
<thead>
<tr>
<th>Pre-catalyst</th>
<th>TOF (h⁻¹)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5a</td>
<td>2160</td>
<td>-</td>
</tr>
<tr>
<td>4.5b</td>
<td>2520</td>
<td>39</td>
</tr>
<tr>
<td>4.5c</td>
<td>1980</td>
<td>63</td>
</tr>
<tr>
<td>4.6b</td>
<td>26</td>
<td>67</td>
</tr>
</tbody>
</table>

Although the activities of the complexes 4.5 were exceptionally high even in comparison with the most active ruthenium-based asymmetric transfer hydrogenation catalysts, the enantioselectivity of the process needs significant improvement. The important structural components of the catalyst can be elucidated from the above described studies. A successful candidate for the role of the catalyst needs to have four neutral donors and at least one good pi-accepting ligand such as a carbonyl of isocyanide. It is also preferable to have a donor atom which is potentially capable of metal-ligand cooperation. Based on these principles, we decided to prepare iron-based pre-catalysts containing ligands with different phosphino-imine linkers. This chapter will highlight how the bis-acetonitrile iron(II) complexes, which were prepared via the multicomponent template reaction (Chapter 3) from the phosphonium salts (Chapter 2) can be monocarbonylated to give rise to highly active and enantioselective catalysts for the transfer hydrogenation of aromatic and aliphatic pro-chiral ketones.
4.3 Results and Discussion

4.3.1 Synthesis of complex 4.8

The carbonyl complex pre-catalyst trans-[Fe(CO)(NCMe)(PPh\(_2\)CH\(_2\)CHNCHPhCHPhNCHCH\(_2\)PPh\(_2\))]\((\text{BPh}_4)_2\) (4.8) is prepared by treating complex 4.7, which was previously synthesized as described in Chapter 3, in acetone with carbon monoxide (2 atm) and is isolated as a yellow solid in 92% yield (Scheme 4.7).

![Scheme 4.7 Preparation of complex 4.8.](image)

It displays a carbonyl vibration in the IR spectrum at 2001 cm\(^{-1}\). The asymmetry of the molecule is reflected in the observation of two doublets (\(^2J_{P,P} = 30\) Hz) in the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum of its (CD\(_3\))\(_2\)CO solution. It reacts slowly with air as a solid and as a solution. It reacts with neat acetonitrile over a 5 hour period and converts back to complex 4.7.

4.3.2 Asymmetric transfer hydrogenation of ketones and aldimines using complex 4.8

Complex 4.8 in basic iso-propanol was tested for the asymmetric transfer hydrogenation of acetophenone at room temperature (Table 4.2). It shows excellent activity for the hydrogenation of acetophenone to (S)-1-phenylethanol in 82% ee (entry 1-5). This is a great
improvement in enantioselectivity and TOF compared to that displayed by the system with catalyst precursor 4.5c (Table 4.1). The sense of asymmetric induction (S) is the same as that of Noyori- and Noyori-like catalysts utilizing (R,R)-dpn. A significant racemization of 1-phenethanol is observed when the acetophenone concentration is low (Table 4.2, Entry 1 and 2). The enantioselectivity and activity of the system is marginally dependant on the type of the base that was used (Table 4.2, Entry 4-6). The reaction is efficient in the case when KOH was used as a base, which produce water as a by-product upon reaction with 2-PrOH, indicating that the system is not water sensitive. The optimal amount of the base required for the activation of the pre-catalyst was determined to be 8 equivalents. A lower conversion is observed when 4 equivalents are used and no conversion is observed when base is not added (Table 4.2, Entry 3 and 4).

Table 4.2 Transfer hydrogenation of acetophenone catalyzed by complex 4.8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>S/C/B</th>
<th>Base</th>
<th>Time (min)</th>
<th>Conv (%)</th>
<th>ee (%)</th>
<th>TOF (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600/1/8</td>
<td>KOtBu</td>
<td>8</td>
<td>75</td>
<td>83</td>
<td>3400</td>
</tr>
<tr>
<td>2</td>
<td>600/1/8</td>
<td>KOtBu</td>
<td>30</td>
<td>90</td>
<td>12</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>600/1/4</td>
<td>KOtBu</td>
<td>20</td>
<td>75</td>
<td>81</td>
<td>1350</td>
</tr>
<tr>
<td>4</td>
<td>600/1/0</td>
<td>-</td>
<td>40</td>
<td>&lt; 1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2000/1/8</td>
<td>KOtBu</td>
<td>30</td>
<td>90</td>
<td>82</td>
<td>3600</td>
</tr>
<tr>
<td>6</td>
<td>2000/1/8</td>
<td>NaOtBu</td>
<td>30</td>
<td>75</td>
<td>83</td>
<td>3000</td>
</tr>
<tr>
<td>7</td>
<td>2000/1/8</td>
<td>KOH</td>
<td>30</td>
<td>80</td>
<td>83</td>
<td>3200</td>
</tr>
</tbody>
</table>

The substrate scope of the asymmetric transfer hydrogenation reaction using pre-catalyst 4.8 was investigated. The reaction was found to be very general (Table 4.3). The reduction of the more hindered aromatic ketones (Table 4.3, Entry 1-3) proceeded with
excellent enantioselectivity, although the expected trend of a decrease in conversion for the more bulky 'Bu substituent was also observed. If the methyl group of the acetophenone is replaced with a bulkier cyclohexyl group (Table 4.3, Entry 4), then the ee of the reaction drops significantly. Hydrogenation of the ketone with the 2-phenylethyl group (Table 4.3, Entry 5) proceeds with reduced enantioselectivity. This result illustrates the importance of bulky groups next to the carbonyl for obtaining high enantioselectivity.

The aromatic ketone (Table 4.3, Entry 6) with a strong σ-electron withdrawing and weak π-electron donating chloro group in the para position showed a higher TOF compared to that with acetophenone. Substrates with the π-electron donating methoxy group (Table 4.3, Entry 8), on the other hand, showed lower selectivity and activity. Aromatic ketones with methoxy and chloride substituents (Table 4.3, Entry 7 and 9) in the meta position both showed comparable conversion and selectivity to acetophenone. These results indicate that meta substitution has a minor effect on the catalytic process. The acetonaphthone isomers were also efficiently reduced (Table 4.3, Entries 10 and 11).
Table 4.3 Reactivity of various aromatic ketones in the transfer hydrogenation reaction using pre-catalyst 4.8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>S/C/B</th>
<th>Time (min)</th>
<th>Conv (%)</th>
<th>ee (%)</th>
<th>TOF (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-CO-Et</td>
<td>1500/1/8</td>
<td>25</td>
<td>90</td>
<td>94</td>
<td>3375</td>
</tr>
<tr>
<td>2</td>
<td>Ph-CO-²Bu</td>
<td>500/1/8</td>
<td>200</td>
<td>35</td>
<td>99</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>Ph-CO-(C₆H₇)</td>
<td>1000/1/8</td>
<td>40</td>
<td>95</td>
<td>94</td>
<td>1425</td>
</tr>
<tr>
<td>4</td>
<td>Ph-CO-(C₆H₁₁)</td>
<td>1000/1/8</td>
<td>85</td>
<td>76</td>
<td>26</td>
<td>536</td>
</tr>
<tr>
<td>5</td>
<td>Ph-CH₂-CH₂-CO-Me</td>
<td>1000/1/8</td>
<td>30</td>
<td>98</td>
<td>14</td>
<td>1960</td>
</tr>
<tr>
<td>6</td>
<td>(4'-Cl-C₆H₄)-CO-Me</td>
<td>1500/1/8</td>
<td>18</td>
<td>96</td>
<td>80</td>
<td>4800</td>
</tr>
<tr>
<td>7</td>
<td>(3'-Cl-C₆H₄)-CO-Me</td>
<td>1000/1/8</td>
<td>13</td>
<td>98</td>
<td>80</td>
<td>4523</td>
</tr>
<tr>
<td>8</td>
<td>(4'-MeO-C₆H₄)-CO-Me</td>
<td>1000/1/8</td>
<td>40</td>
<td>65</td>
<td>54</td>
<td>930</td>
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<tr>
<td>9</td>
<td>(3'-MeO-C₆H₄)-CO-Me</td>
<td>1500/1/8</td>
<td>30</td>
<td>80</td>
<td>85</td>
<td>2400</td>
</tr>
<tr>
<td>10</td>
<td>1-acetonaphthone</td>
<td>1500/1/8</td>
<td>60</td>
<td>93</td>
<td>92</td>
<td>1380</td>
</tr>
<tr>
<td>11</td>
<td>2-acetonaphthone</td>
<td>1000/1/8</td>
<td>11</td>
<td>90</td>
<td>84</td>
<td>4900</td>
</tr>
</tbody>
</table>

Non-aromatic ketones are challenging substrates for enantioselective reduction. Catalyst 4.8 was found to be active for such a ketone (Scheme 4.8, A) and showed moderate enantioselectivity. An aldimine (Scheme 4.8, B) was reduced with low activity. The reduction of trans-4-phenyl-3-buten-2-one to trans-4-phenyl-3-buten-2-ol using the precatalyst 4.8 shows a high chemoselectivity (Scheme 4.8, C). This supports the idea that an outer sphere attack by an H-Fe-N-H motif on the ketone group might be operational.⁶⁹,⁷⁰
Scheme 4.8 Reactivity of special ketones and an aldimine in the transfer hydrogenation reaction using pre-catalyst 4.8.

4.3.3 Synthesis of iron(II) complexes containing various diamines incorporated into the backbone of the ligand

Our previous studies related to the preparation iron PNNP carbonyl complexes derived from o-diphenylphosphinobenzaldehyde and their use in the transfer hydrogenation process showed that the activity and enantioselectivity of the reaction significantly depended on the type of diamine incorporated in the ligand backbone.\(^\text{67, 71}\) In order to investigate similar effects for the complexes derived from the phosphino-aldehyde Ph\(_2\)PCH\(_2\)C(O)H, we decided to prepare a library of complexes with various diamines, using the advantage of a versatile template approach. One problem that detracts from the convenience of the method is the separation of the complex \(\text{trans-[Fe(NCMe)}_2\text{(PNNP)}\text{]}^{2+}\) from stoichiometric amounts of salts that are formed in the reaction by the selective precipitation of the bis(acetonitrile) complex as the
tetraphenylborate salt. To resolve this limitation, we attempted to carbonylate the crude product of the template reaction by reacting it in acetone under a CO atmosphere.

The test reaction was conducted using (S, S)-dpen and gave the product as an orange solid, similarly to that observed before (Scheme 4.7). The solution of product of the reaction in (CD$_3$)$_2$CO was analyzed by $^{31}$P{$_1$H} NMR. The spectrum showed the formation of the expected complex 4.8 as was determined from two doublet resonances at 65.7 and 69.3 ppm with a coupling $^2J_{P-P} = 30$ Hz. On the other hand, a significant amount of a by-product with two doublet resonances at 64.2 and at 65.6 ppm with a coupling $^2J_{P-P} = 39$ Hz was observed. The ESI-MS spectrum of the mixture had a significant peak at 795.098 m/z, showing that one of the products contained bromide coordinated to the iron along with carbonyl and the expected P-N-N-P ligand. Our group has recently reported the synthesis and characterization by single crystal X-ray diffraction of similar iron(II) complexes with bromide $trans$ to carbonyl. This observation directed us to a new optimized one pot synthesis of active iron(II) complexes 4.9 (Scheme 4.9).

![Scheme 4.9 One pot synthesis of complexes 4.9 starting from the phosphonium dimer.](image-url)
The template synthesis starting from the dimer 2.1, diamine and iron(II) precursor was performed in an identical fashion to the previously reported template procedure, but the isolation of the bis(acetonitrile) complex was omitted. The solvent mixture of acetonitrile and methanol was evaporated and replaced with acetone and the resulting solution was subjected to a CO atmosphere. The Br⁻/CO complexes 4.9 are more thermodynamically stable compared to the CH₃CN/CO complexes 4.8, since the formation of 4.9 was observed when Br⁻ was present in small quantity in the reaction mixture containing a large excess of acetonitrile. The greater stability of complex 4.9 compared to the complex 4.8 can be explained by the strong, ionic Fe²⁺-Br⁻ bond relative to the weaker ion-dipole Fe²⁺-Nδ⁻ bond of an acetonitrile ligand. The selective precipitation of the resulting complex with NaBPh₄ from methanol yielded the desired compounds 4.9 contaminated with salts. A convenient purification method is the filtering of a dichloromethane solution of the crude product through Celite. This general procedure was used to successfully synthesize and purify complexes 4.9a-4.9d in moderate to good yields using a range of diamines as shown in Scheme 4.9.

4.3.4 Properties of the complexes 4.9.

Complexes 4.9a-4.9d were isolated as yellow, slightly air-sensitive solids. They demonstrate similar solubility properties: soluble in dichloromethane, acetone and acetophenone, but insoluble in other common solvents. The complexes were characterized by ¹H, ³¹P, ¹³C NMR, HRMS, EA and FTIR. Selected properties are listed in Table 4.4. Complexes 4.9a-4.9c that contain a chiral diamine incorporated into the backbone have inequivalent phosphorus atoms due to the lack of symmetry. This was signaled in the ³¹P{¹H} NMR spectra by the appearance of two doublets as opposed to the singlet observed for the C₂-symmetrical bis(acetonitrile) complex 4.7. The carbonyl ¹³C NMR resonance was only detected for complexes 4.9b (at 214.9 ppm) and 4.9c (215.1 ppm). The resonance of 4.9c was the expected doublet of doublets due to coupling to two inequivalent phosphorus atoms. The long relaxation time of the carbonyl carbon of 4.9a and 4.9d presumably prevented the detection of their carbonyl resonances. On the other hand, the presence of this functionality was supported
by the strong peak of the carbonyl stretch in the IR spectrum and the detection of the parent ion peak by mass spectroscopy. The carbonyl stretching wavenumbers of the compounds were observed in a range from 1974 to 1981 cm\(^{-1}\). The monocationic bromide-carbonyl complex (4.9b) has a lower carbonyl stretching frequency compared to the dicationic acetonitrile-carbonyl complex 4.8 at 2001 cm\(^{-1}\), consistent with an increase in iron-carbon backdonation on going from the dication to the monocation. Attempts were unsuccessful in obtaining crystals of complexes suitable for X-ray diffraction analysis.

Table 4.4 Yields of complexes 4.9a-4.9d using the method described on Scheme 4.9 and selected IR and NMR data.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Yield (%)</th>
<th>IR CO stretch (cm(^{-1}))</th>
<th>(^{31})P NMR ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9a</td>
<td>48</td>
<td>1974</td>
<td>65.2(d), 66.2(d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J_{PP} = 38.2\text{Hz})</td>
</tr>
<tr>
<td>4.9b</td>
<td>53</td>
<td>1975</td>
<td>64.2(d), 65.6(d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J_{PP} = 39.5\text{Hz})</td>
</tr>
<tr>
<td>4.9c</td>
<td>55</td>
<td>1974</td>
<td>64.6(d), 66.0(d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J_{PP} = 39.1\text{Hz})</td>
</tr>
<tr>
<td>4.9d</td>
<td>82</td>
<td>1981</td>
<td>67.6</td>
</tr>
<tr>
<td>4.8</td>
<td>92(^a)</td>
<td>2001</td>
<td>69.3 (d), 65.7(d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(J_{p,p} = 30\text{Hz});</td>
</tr>
</tbody>
</table>

\(^a\) The yield of the reaction is starting from complex 4.7.
4.3.5 Catalytic activity of complexes 4.9.

The catalytic hydrogenation of acetophenone to 1-phenethanol was conducted in an argon glove-box using precatalysts 4.9a-4.9d. The reaction was performed at 28-30 °C using acetophenone, catalyst and base (KOTBu) in a ratio 6000/1/8, respectively. After precatalysts 4.9a-4.9d are activated by the base they become extremely air sensitive and must be handled under N₂ or Ar. Samples were taken by injection of small portions of the reaction mixture into a sealed vial containing air and aerated 2-propanol to ensure successful quenching of the oxygen-sensitive catalyst system. They were then analyzed using gas chromatography. The reaction using each precatalyst was performed three times. The rate of the reaction was obtained by plotting the concentration of 1-phenethanol vs. time and determining the slope of the linear part of the graph. The turn-over frequency (TOF) values were calculated using least-squared fit equations at 15-50 % conversion and are summarized in Table 4.5.

Table 4.5 The transfer hydrogenation of acetophenone catalyzed by complexes 5a-5d in basic 2-propanol.

<table>
<thead>
<tr>
<th>Complexes</th>
<th>TOF (h⁻¹)ᵃ</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9a</td>
<td>4.9×10³</td>
<td>60</td>
</tr>
<tr>
<td>4.9b</td>
<td>2.0×10⁴</td>
<td>81</td>
</tr>
<tr>
<td>4.9c</td>
<td>2.0×10⁴</td>
<td>82</td>
</tr>
<tr>
<td>4.9dᵇ</td>
<td>2.1×10³</td>
<td>-</td>
</tr>
<tr>
<td>4.8</td>
<td>2.1×10⁴</td>
<td>82</td>
</tr>
</tbody>
</table>

ᵃ TOF at 15-50 % conversion, b. 15 % conversion.
The catalytic activity of the pre-catalyst \textbf{4.8} was reinvestigated under the conditions used for \textbf{4.9b} in order to identify the effect of the ligand, bromide vs acetonitrile, in the \textit{trans} position relative to the carbonyl (Table 4.5). The activation and the maximum constant rate of the transfer hydrogenation using \textbf{4.9b} and \textbf{4.8} were found to be the same within experimental error. A lower TOF of $3.6 \times 10^3 \text{ h}^{-1}$ was reported earlier for \textbf{4.8} (Table 4.2), but this refers to a lower temperature and a lower substrate loading than for the present conditions. This observation also shows that the dissociation of the ligand \textit{trans} to carbonyl most likely is taking place during the activation of the precatalyst and that bromide and acetonitrile do not participate in the process of the reduction of acetophenone to 1-phenethanol.

The incorporation of different diamines into the backbone of the ligand of complexes \textbf{4.9a-4.9e} influences both the electronic and steric properties of the complexes. The basicity of the nitrogen donors decrease in the order \textit{dach} = \textit{MeO-dpen} = \textit{dpen} > \textit{en} as interpreted from the wavenumbers of the carbonyl absorptions listed in Table 4.4 -- the more basic the donor, the lower the CO stretching wavenumber. The TOF values of the corresponding complexes do not correlate well with the basicity of the donors. The sterically bulky diamines might be expected to increase the enantioselectivity but decrease the activity of ruthenium complexes. This was the observation when the sterically more crowded precatalyst \textit{RuCl}_2(\textit{daipen})(\textit{xylBinap}) was used in place of \textit{RuCl}_2(\textit{dpen})(\textit{tolBinap}) in the catalytic hydrogenation of acetophenone.\cite{73}

However there is also a report where the substitution of the diamine backbone with phenyl groups in the 1- and 2-positions results in an increase in eee and an increase in rate compared to diamines with only mono-substitution at the 1- or 2-positions.\cite{74} No explanation was provided for the rate enhancement. But the activity trend within this group of iron catalysts is different with the more bulky phenyl and substituted phenyl ligands of \textbf{4.9b} and \textbf{4.9c} producing more active precatalysts than the less bulky diaminocyclohexane- and ethylenediamine-derived ligands of \textbf{4.9a} and \textbf{4.9d}. This shows that the steric effect of the diamine has a larger influence on the activity of the catalyst than electronic factors.

In order to gain a deeper understanding of this process, the conversion of the substrate to the product was monitored by taking samples of the reaction mixture at short time intervals. Catalysts \textbf{4.9a-4.9d} showed similar reaction profiles in the reduction of acetophenone to 1-phenethanol; the profile for complex \textbf{4.9a} is depicted in Figure 4.1. The reaction starts with the activation of the pre-catalyst to the so far unknown active catalyst, a process with continuously increasing rate. The activation period varies for different catalysts, but in general takes place...
during the first 5 minutes of the reaction. The following turnover step produces 1-phenethanol at a constant rate before the reaction reaches 60% conversion in case of complexes 4.9a-4.9c and 15% conversion in case of the complex 4.9d. A reduction of the rate is observed later in the reaction to give, at the end, more than 80% of the product in case of the complexes 4.9a-4.9c and 40% in case of the complex 4.9d.

Figure 4.1 The reaction profile of the catalytic reduction of acetophenone to 1-phenethanol catalyzed by the pre-catalyst 4.9b under Ar at 28-30°C. a. cat/sub/base = 1/6000/8, b. 4800 equivalents of acetophenone was added to the reaction mixture after 23 min of reaction, c. reaction conducted with cat/sub/acetone/base = 1/6000/6000/8

We wondered whether the observed rate reduction is associated with the decomposition of the catalyst after a certain number of turnovers in the catalytic cycle. In order to check that assumption, extra acetophenone was added after 23 minutes of the reaction (Figure 4.1, b). Since the rate increases to the value comparable to that observed during the turnover step, we conclude that the catalyst decomposition cannot be the reason for the rate reduction.
A mixture (50-50 % by mol) of acetophenone and acetone was subjected to the catalytic conditions in order to see how acetone influences the rate of the reaction (Figure 4.1, c). There was almost a three-fold decrease in rate for the reaction with extra acetone compared to the rate of the initial reaction. This unambiguously shows that acetone is competing with acetophenone for the active site on the catalyst.

4.4. Conclusions

The complex 4.8 was synthesized using the enantiopure diamine (R,R)-dpen and found to provide, after condition optimization, a very active and enantioselective catalytic system for the reduction of a variety of ketones and an aldimine. Bulkier arylketones were reduced with higher enantioselectivity, up to 99% (S) for PhCO\text{t-Bu}, but at lower rates. The TOF depended on the electronic properties of the aryl groups on the ketones with electron withdrawing chlorine in the para position giving the higher rates. The selective reductive of an alpha-beta unsaturated ketone to the unsaturated alcohol provides evidence for an outersphere bifunctional reduction mechanism as observed for Noyori catalysts with amine and hydride ligand motifs.

We were able to synthesize and characterize the bromide-containing iron(II) complexes (4.9a-4.9d) containing P-N-N-P ligands with different diamines incorporated into the backbone in order to compare their activity and enantioselectivity in asymmetric catalytic transfer hydrogenation of acetophenone to 1-phenethanol using 2-propanol as a reducing agent. A highly efficient one pot procedure allowed us to prepare those compounds in high purity and in moderate to good yields starting from readily available starting materials. The activities, of pre-catalyst 4.8 and 4.9b indicate that ligand trans to CO has no effect on the reaction rate. All of the complexes show very high TOF (up to $2.0 \times 10^4$ h$^{-1}$) and enantioselectivity (up to 82 % ee), using very low catalyst loadings (0.016 % relative to the substrate). Monitoring the formation of product in a course of the reaction illustrated that the catalytic process consists of three stages: activation of the pre-catalyst to an active catalyst (increasing rate of product formation), turnover step (formation of the product at a constant rate) and termination step (decreasing rate of product formation). A series of experiments has proven that the decrease in the rate when approaching the end of the reaction may be associated with the fact that the reaction
approaching equilibrium. The comparison of the TOF of complexes 4.9a-4.9d showed that the catalytic activity of the complexes increases as the steric influence of the groups in the backbone of ligand increases.

In accompanying papers our group showed how various substituents on the phosphorus of the ligand may influence the activity of the transfer hydrogenation of acetophenone (Table 4.6).\textsuperscript{72,75} Substituting phosphorus atoms with highly sterically bulky groups (4.10c, 4.10h and 4.10i) produced inactive complexes and therefore indicated that there cannot be too much steric bulk on the phosphorus. Strongly electron donating (4.10g) and electron withdrawing groups (4.10e and 4.10f) also resulted in significant reduction of the activities of the complexes. Complexes 4.9b, 4.10b and 4.10d, which produced both exceptional activity and selectivity, possess a narrow region of electronic and steric properties for the successful catalytic reaction. Further studies of the mechanism of these interesting catalytic systems are described in following chapter.
Table 4.6 The effect of various substituents on the phosphorus atoms of the ligand in ATH of acetophenone. Complexes 4.10 were prepared and tested for the catalytic activities by P. E. Sues and P. O. Lagaditis.\textsuperscript{72, 75}

<table>
<thead>
<tr>
<th>Complex</th>
<th>Activity</th>
<th>TOF (h(^{-1}))</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9b</td>
<td>active</td>
<td>28000\textsuperscript{a}</td>
<td>82</td>
</tr>
<tr>
<td>4.10b</td>
<td>active</td>
<td>30000</td>
<td>84</td>
</tr>
<tr>
<td>4.10c</td>
<td>inactive</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.10d</td>
<td>active</td>
<td>26000</td>
<td>90</td>
</tr>
<tr>
<td>4.10e</td>
<td>inactive</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.10f</td>
<td>inactive</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.10g</td>
<td>slightly active</td>
<td>Not determined</td>
<td>56</td>
</tr>
<tr>
<td>4.10h</td>
<td>inactive</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.10i</td>
<td>inactive</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Higher concentrations of the catalyst and the substrate used in the experiments conducted by P. Sues resulted in increased TOF value compared to the value in Table 4.5.
4.5 Experimental

4.5.1 General comments

All manipulations that involved air- or moisture-sensitive materials were performed using Schlenk techniques or a glovebox under an argon or nitrogen atmosphere. Solvents of high purity (ACS grade or higher) were purchased from Caledon Laboratory Chemicals and were further degassed and dried using standard procedures prior to all manipulations and reactions.\(^76\) Deuterated solvents were purchased from Cambridge Isotope Laboratories, INC and distilled and dried over activated molecular sieves. Liquid ketones were distilled under argon and stored under molecular sieves in a glovebox prior reduction reaction. Solid ketones were recrystallized using common techniques. The phosphonium dimer 2.1 was synthesized according to the procedure described in Chapter 2.\(^77\) Complex 4.7 was synthesised as described in Chapter 3.\(^78\) Other reagents used were purchased from commercial sources and utilized without further purification. NMR spectra of the samples that were prepared under argon in degassed solvents were recorded at ambient temperature and pressure using a 400 MHz Varian Gemini \([\text{\textsuperscript{1}H} (400 \text{ MHz}), \text{\textsuperscript{13}C} \{\text{\textsuperscript{1}H}\} (100 \text{ MHz}), \text{and} \text{\textsuperscript{31}P} \{\text{\textsuperscript{1}H}\} (161 \text{ MHz})]\). \textsuperscript{1}H NMR spectra were internally referenced to tetramethylsilane (TMS, 0 ppm). \textsuperscript{13}C NMR spectra were internally referenced to the carbon resonances of the solvent. The ESI-MS data on samples in methanol/water were done on an AB/Sciex QStar mass spectrometer with an ESI source. The elemental analyses were performed at the Department of Chemistry, University of Toronto, on a Perkin-Elmer 2400 CHN elemental analyzer. The infrared spectra of the KBr pellets containing pre-catalysts 4.9a-4.9d was measured on Paragon 500 (Spectral Range 4600 cm\(^{-1}\) to 400 cm\(^{-1}\)) using Perkin Elmer's SPECTRUM for Windows system for data collection and processing at 25°C. Some complexes gave a low carbon analysis but acceptable hydrogen and nitrogen contents because of a combustion problem that is common for the compounds containing boron atoms.\(^79\)
4.5.2 Synthesis of trans-
(R,R)[Fe(Ph₂PCH₂CH=NC(H)(Ph)CH(Ph)N=CHCH₂PPh₂)(CH₃CN)(CO)]
[BPh₄]₂ (4.8)

\[
\begin{align*}
\text{In the N₂ glovebox complex 4.7 (500 mg, 0.355 mmol) was dissolved in 9 mL of acetone. Resulting homogeneous solution was transferred to the high pressure reactor that was perched with CO gas. The reaction mixture was stirred for 2 hours under 2 atm of CO. Solvent was evaporated under vacuum in order to evaporate released acetonitrile. After complete evaporation 9 mL of acetone was added to the resulting solid and solution was placed under CO atmosphere for 2 hours. Procedure was repeated three times. Isolated orange solid and was washed with diethyl ether (5 mL) three times. Yellow solid was dried under vacuum. Yield: 92% (455 mg);} \\
\text{H NMR (400 MHz, acetone-d₆) δ: 1.54 (s, 3H, CH₃CN), 4.42-4.57 (m, 2H, HC-N), 5.58-5.76 (m, 4H, HCP), 6.80-7.75 (m, 70H, ArH), 8.14-8.23 (m, 2H, HC=N);} \\
\text{P \{H\} NMR (121 MHz; acetone-d₆): 69.3 ppm (d, Jₚ₋ₚ=30Hz); 65.7 ppm (d, Jₚ₋ₚ=30Hz);} \\
\text{Anal. Calcd for C₉₃H₈₁N₄P₂FeB₂: C 80.01, H 5.85, N 3.01; Found: C 76.75, H 5.85, N 3.15 (repeated attempts gave similar results); MS (ESI⁺) Calcd for [C₄₆H₄₄N₄P₂Fe-(CO+CH₃CN)]²⁺: 344.3 m/z; Found: 344.3 m/z; MS (ESI⁻) Calcd for [B(Ph)₄]⁻: 319.2 m/z, Found: 319.2 m/z; IR (KBr) 2294 cm⁻¹ (v C≡N, MeCN), 2001 cm⁻¹ (v CO).}
\end{align*}
\]

4.5.3 General procedure of ketone reduction using complex 4.8

In an Ar glovebox, complex 4.8 (2 mg, 0.0014 mmol) was added to a 30 mL vial charged with a stirring bar. A required amount of ketone relative to the catalyst was dissolved in 2-PrOH (5 mL). A stock solution of base was prepared by dissolving 25 mg of KOtBu in 10 mL of 2-PrOH. 0.5 mL of the resulting stock solution was further diluted with 5 ml of 2-PrOH. The
reaction was initiated by the addition of the substrate solution to the pre-catalyst followed by the base solution. The samples of the reaction mixture were analyzed by $^1$H NMR spectroscopy and GC using a Perkin Elmer Autosystem XL chromatograph with a chiral column (CP chirasil-Dex CB 25 m x 2.5 mm) and hydrogen was used as a mobile phase at a column pressure of 5 psi. The injector temperature was 250 °C, and a FID temperature was 275 °C. The retention times and column temperatures for various substrates are summarized in Table 4.7 and Table 4.8.

Table 4.7 GC retention times of ketones and alcohols ($t_{st}$ = retention time of the starting material; $t_R$, $t_S$ = retention times of the products).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Oven Temp. (°C)</th>
<th>$t_{st}$ (min)</th>
<th>$t_R$ (min)</th>
<th>$t_S$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-CO-Me</td>
<td>130</td>
<td>5.02</td>
<td>8.73</td>
<td>9.42</td>
</tr>
<tr>
<td>Ph-CO-Et</td>
<td>118</td>
<td>5.82</td>
<td>10.0</td>
<td>10.3</td>
</tr>
<tr>
<td>Ph-CO-Bu</td>
<td>140</td>
<td>5.73</td>
<td>13.2</td>
<td>14.0</td>
</tr>
<tr>
<td>Ph-CO-(C$_4$H$_7$)</td>
<td>120</td>
<td>19.3</td>
<td>40.8</td>
<td>42.0</td>
</tr>
<tr>
<td>Ph-CO-(C$<em>6$H$</em>{10}$)</td>
<td>135</td>
<td>19.6</td>
<td>36.1</td>
<td>37.2</td>
</tr>
<tr>
<td>Ph-CH$_2$-CH$_2$-CO-Me)</td>
<td>125</td>
<td>11.8</td>
<td>19.0</td>
<td>19.9</td>
</tr>
<tr>
<td>(4'-MeO-C$_6$H$_4$)-CO-Me</td>
<td>135</td>
<td>13.6</td>
<td>19.0</td>
<td>20.2</td>
</tr>
<tr>
<td>(4'-Cl-C$_6$H$_4$)-CO-Me</td>
<td>145</td>
<td>6.46</td>
<td>12.7</td>
<td>13.7</td>
</tr>
<tr>
<td>(3'-MeO-C$_6$H$_4$)-CO-Me</td>
<td>135</td>
<td>11.3</td>
<td>17.2</td>
<td>18.4</td>
</tr>
<tr>
<td>(3'-Cl-C$_6$H$_4$)-CO-Me</td>
<td>140</td>
<td>7.4</td>
<td>13.9</td>
<td>14.1</td>
</tr>
<tr>
<td>i-Pr-CO-Me</td>
<td>60</td>
<td>3.8</td>
<td>9.4</td>
<td>9.8</td>
</tr>
<tr>
<td>1-acetonaphthone</td>
<td>140</td>
<td>24.1</td>
<td>63.6</td>
<td>73.9</td>
</tr>
<tr>
<td>2-acetonaphthone</td>
<td>150</td>
<td>23.5</td>
<td>41.3</td>
<td>43.2</td>
</tr>
</tbody>
</table>
Table 4.8 GC retention times of trans-4-phenyl-3-buten-2-one and its hydrogenation products by use of 2. (Oven temperature was 120 °C).

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.8 (min)</td>
<td>37.1 / 38.4</td>
<td>14.1</td>
<td>25.7 / 26.3</td>
</tr>
</tbody>
</table>

4.5.4 Synthesis of

\((R,R)\)-[Fe(\(\text{Ph}_2\text{PCH}_2\text{CHN}(<\text{C}_6\text{H}_{10})\text{NCHCH}_2\text{PPh}_2\)\(\text{Br}(\text{CO})\)][\text{BF}_4\] (4.9a).

In an Ar glovebox dimer 2.1 (5.41 g, 8.75 mmol), [Fe(H\(\text{O}_2\)\(\text{C}_6\)]\[\text{BF}_4\] (4.43 g, 13.1 mmol) and NaOMe (0.946 g, 17.5 mmol) were dissolved in 20 mL of MeOH to give a slightly yellow transparent solution after 15 min of stirring. A solution of (1\(R,2R\))-diaminocyclohexane (1.00 g, 8.75 mmol) in acetonitrile (5mL) was added to the reaction mixture to give a bright purple solution instantaneously. After 48 hours the solution became orange in color with an orange-pink precipitate. The solvent was removed under vacuum and the resulting orange-pink solid was washed with diethyl ether (10 mL) and re-dissolved in 15 mL of acetone and 1 eq of KBr relative to [Fe(H\(\text{O}_2\)\(\text{C}_6\)]\[\text{BF}_4\] was added. The resulting pink-orange solution with a white precipitate was stirred under 1 atm of carbon monoxide at 30 °C for 48 hours to give a bright yellow solution with a white precipitate that was filtered. The solvent of the eluate was removed under vacuum and the resulting solid was re-dissolved in 40 mL of MeOH. The solution of Na\[\text{BPh}_4\] (2.99 g, 8.75 mmol) in 5 mL of MeOH was slowly added to a yellow solution to give a yellow precipitate that was filtered and washed with diethyl ether (10 mL) three times. The resulting solid was dissolved in 5 mL of dichloromethane to give a brown-
yellow solution and a white precipitate that was filtered through the glass frit and then through a bed of Celite. The solvent of eluate was removed under vacuum to give a bright-yellow precipitate that was mixed with diethyl ether and the mixture stirred for 20 hours. The precipitate was filtered and washed with 10 mL of diethyl ether three times to give microcrystals containing diethylether (NMR evidence). Yield: 48 % (8.91 mg); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ: 1.2-1.4 (m, 1H, NCHCH$_2$; 2H, NCHCH$_2$CH$_2$), 1.4-1.6 (m, 1H, NCHCH$_2$), 1.7-2.8 (m, 1H, NCHCH$_2$; 2H, NCHCH$_2$CH$_2$), 2.2-2.5 (m, 1H, NCHCH$_2$), 3.3-3.5 (m, 1H, NCH; 1H, PCH$_2$), 3.6-3.8 (m, 1H, PCH$_2$), 3.8-4.0 (m, 1H, NCH; 1H, PCH$_2$), 4.1-4.2 (m, 1H, PCH$_2$), 6.7-7.8 (m, 40H, ArH), 7.9-7.7 (m, 1H, N=CH), 7.9-8.1 (m, 1H, N=CH); $^{13}$C{H} NMR (100 MHz; CD$_2$Cl$_2$) δ: 23.7 (s, CH$_2$CH$_2$), 23.7 (s, CH$_2$CH$_2$), 29.4 (s, CHCH$_2$), 30.0 (s, CHCH$_2$), 47.2-47.9 (m, PCH$_2$), 70.1 (s, NCH), 74.0 (s, NCH), 122 (s, BPhCH), 126 (m, BPhCH), 127-134 (m, ArCH), 131 (s, BPhCH), 136 (s, BPhCH), 164 (m, $J_{CB}$=49.3 Hz, BPhCH), 169-170 (m, N=CH); $^{31}$P{H} NMR (161 MHz; CD$_2$Cl$_2$): 65.2 (d, $J_{PP}$=38.2 Hz), 66.2 (d, $J_{PP}$=38.2 Hz); HRMS (ESI-TOF) m/z calculated for [C$_{35}$H$_{36}$N$_2$P$_2$FeOBr]$^+$: 697.0830, found: 697.0828 m/z. Anal. Calcd for C$_{59}$H$_{56}$N$_2$P$_2$FeBrOBC$_4$H$_{10}$O: C, 69.31; H, 6.09; N, 2.56. Found: C, 70.79; H, 6.06; N, 2.93.

4.5.5 Synthesis of (S,S)-
[Fe(Ph$_2$PCH$_2$CHNC(Ph)HC(Ph)HNCHCH$_2$PPh$_2$)(Br)(CO)][BPh$_4$] (4.9b).

Complex 4.9b was synthesized similarly to the complex 4.9a using the following amounts of starting materials: dimer 2.1 (5.24 g, 8.47 mmol), [Fe(H$_2$O)$_6$][BF$_4$]$_2$ (4.29 g, 12.7 mmol), NaOMe (0.916 g, 16.9 mmol), (1S,2S)-1,2-diphenyldiaminoethane (1.80 g, 8.47 mmol) and NaBPh$_4$ (2.90 g, 8.47 mmol). Yield: 53 % (5.01 g); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ: 3.41-3.55 (m, 1H, PCH$_2$), 3.59-3.74 (m, 1H, PCH$_2$), 3.76-3.91 (m, 1H, PCH$_2$), 3.99-4.13 (m, 1H, PCH$_2$), 5.15-5.25 (m, 1H, NC(Ph)H), 5.62-5.72 (m, 1H, NC(Ph)H), 6.70-7.57 (m, 50H, ArH).
7.52-7.66 (m, 1H, NCH), 7.73-7.87 (m, 1H, NCH); $^{13}$C {H} NMR (100 MHz; CD$_2$Cl$_2$) δ: 47.05-47.71 (m, PCH$_2$), 78.07 (s, NC(Ph)H), 81.42 (s, NC(Ph)H), 122.03 (s, BPh), 125.96 (m, BPh), 127.9-129.7 (m, ArCH), 130.17 (s, BPh), 130.3-136.52 (m, ArCH), 136.2 (s, BPh), 164.62 (m, $J_{CB}$=49.3 Hz, BPh), 174.2-174.5 (m, NCH), 214.89 (s, weak, CO); $^{31}$P {H} NMR (161 MHz; CD$_2$Cl$_2$): 64.24 (d, $J_{PP}$=39.5 Hz), 65.62 (d, $J_{PP}$=39.5 Hz); HRMS (ESI-TOF) m/z calculated for [C$_{43}$H$_{38}$N$_2$P$_2$FeOBr]$^+$: 795.0986, found: 795.0983. Anal. Calcd for C$_{67}$H$_{58}$N$_2$P$_2$FeBrOB: C, 72.13; H, 5.24; N, 2.51. Found: C, 69.21; H, 5.30; N, 2.75.

4.5.5 Synthesis of (R,R)-[Fe(Ph$_2$PCH$_2$CHNC(p-MeO-Ph)HC(p-MeO-Ph)HNCHCH$_2$PPh$_2$)(Br)(CO)][BPh$_4$] (4.9c).

Complex 4.9c was synthesized similarly to the complex 4.9a using the following amounts of starting materials: dimer 2.1 (2.25 g, 3.64 mmol), [Fe(H$_2$O)$_6$][BF$_4$]$_2$ (1.83 g, 5.45 mmol), NaOMe (0.393 g, 7.27 mmol) (1R,2R)-1,2-di(4'-methoxyphenyl)-1,2-diaminoethane (0.990 g, 3.64 mmol) and NaBPh$_4$ (1.24 g, 3.64 mmol). Yield: 55 % (2.35 g); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ: 3.40-3.57 (m, 1H, PCH$_2$), 3.60-3.90 (m, 2H, PCH$_2$), 3.74 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.94-4.11 (m, 1H, PCH$_2$), 5.00-5.23 (m, 1H, NC(Ph)H), 5.50-5.73 (m, 1H, NC(Ph)H), 6.50-7.70 (m, 48H, ArH), 7.73-7.97 (m, 1H, NCH), 7.48-7.72 (m, 1H, NCH); $^{13}$C {H} NMR (100 MHz; CD$_2$Cl$_2$) δ: 47.14-47.84 (m, PCH$_2$), 55.8 (s, OCH$_3$), 55.9 (s, OCH$_3$), 77.36 (s, NC(Ph)H), 81.00 (s, NC(Ph)H), 122.1 (s, BPh), 124.9-136.2 (m, ArCH), 125.4 (m, BPh), 136.16 (s, BPh), 164.62 (m, $J_{CB}$=49.3 Hz, BPh), 173.7-174.5 (m, NCH), 215.1 (dd, $J_{CP}$=30.2 Hz, CO); $^{31}$P {H} NMR (161 MHz; CD$_2$Cl$_2$): 64.6 (d, $J_{PP}$=39.1 Hz), 66.0 (d, $J_{PP}$=39.1 Hz); HRMS (ESI-TOF) m/z calculated for [C$_{43}$H$_{42}$N$_2$P$_2$FeO$_3$Br]$^+$: 855.1197, found: 855.1196 m/z. Anal. Calcd for C$_{69}$H$_{62}$N$_2$P$_2$FeBrO$_3$B: C, 70.49; H, 5.32; N, 2.38. Found: C, 68.49; H, 5.48; N, 2.34.
4.5.6 Synthesis of [Fe(Ph$_2$PCH$_2$CHNCH$_2$CH$_2$NCHCH$_2$PPh$_2$)(Br)(CO)][BPh$_4$] (4.9d).

Complex 4.9d was synthesized similarly to the complex 4.9a using the following amounts of starting materials: dimer 2.1 (1.20 g, 1.94 mmol), [Fe(H$_2$O)$_6$][BF$_4$]$_2$ (0.98 g, 2.91 mmol), NaOMe (0.21 g, 3.88 mmol), ethylenediamine (0.12 g, 1.94 mmol) and NaBPh$_4$ (0.66 g, 1.94 mmol). Yield: 82 % (1.53 g); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$: 3.47-3.59 (m, 2H, NCH$_2$), 3.58-3.69(m, 2H, PCH$_2$ ), 3.75-3.86 (m, 2H, PCH$_2$), 3.85-3.97 (m, 2H, NCH$_2$), 6.75-7.68 (m, 40H, ArH; 2H, NCH); $^{13}$C {$^1$H} NMR (100 MHz; CD$_2$Cl$_2$) $\delta$: 48.3-48.8 (m, PCH$_2$), 61.1 (s, NCH$_2$), 121.6 (s, BPhCH), 125.4 (m, BPhCH), 127.5 (PPhCH), 128.3 (PPhCH), 130.7 (PPhCH), 131.0 (PPhCH), 131.4 (PPhCH), 133.3 (PPhCH), 135.3 (s, BPhCH), 162.9 (m, $J_{CB}$=48.5 Hz, BPhCH), 172.5 (s, NCH); $^{31}$P {$^1$H} NMR (161 MHz; CD$_2$Cl$_2$): 67.58 ppm (s); HRMS (ESI-TOF) m/z calculated for [C$_{31}$H$_{50}$N$_2$P$_2$FeOBr]$:^+$: 643.0360 m/z. Found: 643.0356 m/z. Anal. Calcd for C$_{55}$H$_{50}$N$_2$P$_2$FeBrOB: C, 68.56; H, 5.23; N, 2.91. Found: C, 66.70; H, 5.55; N, 3.27.
4.5.7 Catalytic reduction of acetophenone using catalysts 4.9a-4.9d

4.5.7.1 General procedure for the catalytic reduction of the acetophenone using catalysts 4.9a-4.9d and 2-propanol as a reducing agent.

In an Ar glovebox, two stock solutions were prepared. The stock solution 1 (1SS) contains $4.48 \times 10^{-6}$ moles of the catalyst (4.9a-4.9d) dissolved in $4.64 \times 10^{-3}$ mole of the acetophenone. The stock solution 2 (2SS) contains $8.91 \times 10^{-5}$ mole of the KO'Bu dissolved in $1.70 \times 10^{-2}$ moles of 2-propanol. For every catalytic run, 0.110 g of 1SS was diluted with acetophenone (0.527 g) and 2-propanol (8.0 g). The 0.081 g 2SS was diluted with 2-propanol (0.50 g). Resulting solutions were mixed in order to initiate the reaction. Final concentrations of reagents in the reaction mixture appeared to be as follows: $[\text{cat}] = 7.7 \times 10^{-5}$ (mol/L), $[\text{substrate}] = 0.45$ (mol/L). Samples were taken by injection of small portions of the reaction mixture into a sealed vial containing air and aerated 2-propanol to ensure successful quenching of the oxygen-sensitive catalyst system. They were then analyzed using gas chromatography using a Perkin Elmer Autosystem XL chromatograph with a chiral column (CP chiral-Sil-Dex CB 25 m x 2.5 mm). Hydrogen was used as a mobile phase at a column pressure of 5 psi. The injector temperature was 250 °C, a FID temperature was 275 °C and an oven temperature was 130 °C. GC retention times were 5.02 min, 8.73 and 9.42 for ketone, alcohol R-isomer and alcohol S-isomer, respectively.

4.5.7.2 Catalytic hydrogenation of the acetophenone to 1-phenethanol using 4.9a

The reaction was carried out as described in section 4.5.7.1. The rates of 1-phenethanol formation of three catalytic runs were calculated using LINEST function in EXCEL. The corresponding turn over frequencies (TOF) were determined by dividing the rates of 1-phenethanol formation by the number of moles of the pre-catalyst. The average TOF and the
standard deviation were obtained using AVERAGE function and statistical functions for an error propagation using EXCEL, respectively. The results are summarized in Table 4.9.

Table 4.9 TOF calculation for the catalytic reduction of acetophenone using pre-catalyst 4.9a.

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</tr>
<tr>
<td>2</td>
<td>4830</td>
</tr>
<tr>
<td>3</td>
<td>4968</td>
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<tr>
<td>Average TOF</td>
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<td>St.dev. of Average TOF</td>
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</table>

4.5.7.3 Catalytic hydrogenation of the acetophenone to 1-phenethanol using 4.9b

![Chemical reaction](image)

The reaction was carried out as described in section 4.5.7.1. The TOF was determined as described in section 4.5.7.2. The results are summarized in Table 4.10.
Table 4.10 TOF calculation for the catalytic reduction of acetophenone using pre-catalyst 4.9b.

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<td>2</td>
<td>21124</td>
</tr>
<tr>
<td>3</td>
<td>19426</td>
</tr>
<tr>
<td>Average TOF</td>
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<tr>
<td>St.dev. of Average TOF</td>
<td>0.16×10⁴</td>
</tr>
</tbody>
</table>

4.5.7.4 Catalytic hydrogenation of the acetophenone to 1-phenethanol using 4.9c

![Chemical Reaction](image)

The reaction was carried out as described in section 4.5.7.1. The TOF was determined as described in section 4.5.7.2. The results are summarized in Table 4.11.
Table 4.11 TOF calculation for the catalytic reduction of acetophenone using pre-catalyst 4.9c.

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<tr>
<td>3</td>
<td>21340</td>
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<tr>
<td></td>
<td>Average TOF</td>
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<tr>
<td></td>
<td>St.dev. of Average TOF</td>
</tr>
</tbody>
</table>

4.5.7.5 Catalytic hydrogenation of the acetophenone to 1-phenethanol using 4.9d.

The reaction was carried out as described in section 4.5.7.1. The TOF was determined as described in section 4.5.7.2. The results are summarized in Table 4.12.
Table 4.12 TOF calculation for the catalytic reduction of acetophenone using pre-catalyst 4.9d.

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<td>2</td>
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<td>3</td>
<td>2379</td>
</tr>
<tr>
<td>Average TOF</td>
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<tr>
<td>St.dev. of Average TOF</td>
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4.6 References

Chapter 5: The Asymmetric Transfer Hydrogenation of Acetophenone Using an Iron(II) Complex Containing A P-N-N-P Ligand: Exploring the Mechanism by Experiment

5.1 Abstract

On the basis of a kinetic study and other evidence, we propose a mechanism of activation and operation of a highly active system generated from the precatalyst [Fe(CO)(Br)(Ph₂CH₂CH=N-((S,S)-C(Ph)H-C(Ph)H)-N=CHCH₂PPh₂)][BPh₄] (5.2) for the asymmetric transfer hydrogenation of aromatic ketones. Acetophenone is used as the model substrate. The prolonged induction period prior to the catalytic cycle suggests that the process consists of two dependent reactions: the activation of the precatalyst 5.2 and the catalytic production of 1-phenethanol. The dependencies of these processes on the initial concentrations of acetophenone, pre-catalyst, base and acetone, which forms as a by-product in the reaction, were separately determined from the experimentally obtained reaction profiles and were used to propose mechanistic model. Numerical simulations were used to verify the kinetic model and estimate the rate constants associated with it. A unique set of rate constants was found that gave a good agreement between the experimentally determined reaction profiles and those simulated. According to the model, the active catalyst is generated continuously and its concentration increases with a variable rate. The activation parameters of the reaction were determined using numerical simulation. The large negative entropy of activation supports the proposal of an outer-sphere bifunctional iron hydride/amine proton attack on the acetophenone in the hydrogenation step. The reaction of the pre-catalyst 5.2 with KO₂Bu led to the formation of a highly reactive bis(eneamido) complex Fe(CO)(Ph₂PCH=CH-N-(S,S-CH(Ph)CH(Ph))-N-...
CH=CHPh₂) 5.5 that was partially characterized. We show that 5.5 is only an intermediate in the process of activation of 5.2, and is not within the catalytic cycle. Instead, the reaction of 5.5 with i-PrOH results in the formation of an active catalytic species, which upon quenching with HCl, gives the complex [Fe(CO)(Cl)(Ph₂PCH₂CH₂N((S,S)-CH(Ph)CH(Ph))-N=CHCH₂PPh₂)][BPh₄] (5.7). From the structure of 5.7 it follows that the pre-catalyst activation involves the selective reduction of one of the imine functionalities of the ligand.

When compound 5.7 is treated with base it directly enters the catalytic cycle with no induction period. A study involving the use of deuterated reactants shows that there is a larger kinetic isotope effect (2.5±0.1) for the transfer of the hydride from the metal to the carbonyl carbon and a smaller one (1.3±0.1) for the transfer of the proton. Several features of this catalytic system are indicators of a homogeneous catalyst as opposed to an iron nanoparticle catalyst.

### 5.2 Introduction

The asymmetric reduction of polar unsaturated compounds allows the production of valuable chiral secondary alcohols and amines for use as chiral building blocks in industry and academia.¹ The complexes containing platinum group metals (such as Ru, Rh and Ir) and chiral ligands are especially active and have been developed to be highly enantioselective.²⁻⁵ The information gained from mechanistic studies on these catalytic systems greatly assists in the optimization and scaling-up of the process for industrial application.⁵,¹¹⁻¹³ Nevertheless, there are some negative features of these catalytic systems such as the high price, low availability and high toxicity of the metal that make them undesirable for some applications. Recent developments to overcome these drawbacks involve the use of first row transition metals for asymmetric catalysis. Low-valent iron is an especially attractive candidate for this role, since it is cheap, abundant and non-toxic compared to ruthenium. Iron-containing catalysts for asymmetric reduction reactions are proving to be promising (see Chapter 4 for discussion).¹⁴⁻¹⁷ Highly reactive and selective catalytic systems for the direct¹⁸⁻²⁰ and transfer hydrogenation²¹⁻
26, hydrosilylation\textsuperscript{26-28} of ketone and recently ketimines\textsuperscript{29} using iron have now been developed. On the other hand, there are only a few studies of their mechanism of action.\textsuperscript{30-32}

Complex 5.1 (Figure 5.1) was the first fully characterized iron-based pre-catalyst for the effective asymmetric transfer hydrogenation (ATH) of aromatic ketones.\textsuperscript{19, 33} A second generation of precatalyst (5.2) was designed with a ligand that maintained the key phosphorus and nitrogen chelates, which are known to be important for bifunctional catalysis. Although the resulting structure was found to be distorted from an octahedral geometry, the pre-catalyst 5.2 showed exceptionally high activity and enantioselectivity in the catalytic reduction of ketones.\textsuperscript{34} The effect on the catalyst activity by changing substituents on the ligand (Chapter 4) was also explored, a task that was relatively straightforward due to the ease of the template synthesis of the complexes (Chapter 3).\textsuperscript{35} A variation of the substituents at the phosphorus atom showed that only a narrow range of structures result in active catalysts; the effective substituents were ethyl, phenyl, or aryl groups substituted with methyl groups in the meta or para positions.\textsuperscript{36, 37} Bulky substituents at phosphorus such as cyclohexyl, isopropyl or ortho-tolyl prevented catalysis. This is evidence against mechanisms that require the breaking of an iron-phosphorus bond such as a Meerwein Ponndorf Verley mechanism.\textsuperscript{37} A study of the use of different diamines serving as the backbone of the ligand demonstrated that the (R,R) or (S,S) stilbenyl (CHPhCHPh) backbone gave optimum activity and enantioselectivity in the ATH of acetophenone while, surprisingly, the ethylene backbone gave a reduced activity.\textsuperscript{35}

![Figure 5.1](image_url)

Figure 5.1 The structures of highly active iron(II)-based precatalysts for the ATH of aromatic ketones.

The ligands of precatalysts 5.1 and 5.2 are constructed from different phosphino-aldehyde precursors. The smaller phosphino-aldehyde used for 5.2 results in a PNNP ligand
that forms smaller ring sizes with the metal (5,5,5 in 5.2 vs 6,5,6 in 5.1) and a wider P-Fe-P angle.\textsuperscript{38, 39} The most interesting difference, on the other hand, is associated with the presence of the acidic β-hydrogens in ligand of 5.2. Recently, our group discovered that dicationic complexes, identical to 5.2 but with electron-donating substituents on phosphorus, undergo double deprotonation when reacted with base in non-polar solvents to give neutral ene-amido iron complexes, for example, complex 5.3 (Scheme 5.1).\textsuperscript{40} The neutral complex 5.3, without pre-activation by base, showed good activity in the catalytic reduction of acetophenone. The role in catalysis of such an ene-amido complex formed from 5.2 will be described in this Chapter.

![Scheme 5.1 Synthesis of complex 5.3 by the deprotonation of β-hydrogens.](image)

Ruthenium complexes containing tetradentate ligands with two phosphorus and two nitrogen donors have been used in a variety of catalytic transformations\textsuperscript{41, 42} including the catalytic asymmetric reductions of ketones.\textsuperscript{43-46} Interestingly enough, transfer hydrogenation with the catalysts bearing P-N(H)-N(H)-P ligands are much more active due to their ability to form amido-metal species after activation with base, compared to the complexes with imine P-N-N-P ligands.\textsuperscript{6} By contrast iron-based catalysts for the asymmetric reduction of aromatic ketones, including complexes 5.1 and 5.2, do not follow this rule, since they contain P-N-N-P ligands with imine functionalities. It is important in the current study to determine whether the ligand on iron can be reduced under the catalytic conditions to the diamine ligand. The reduction of ketones could then proceed according to the bifunctional outer-sphere mechanism similar to that observed for the ruthenium-based complexes where a metal hydride and an amine proton attack the ketone in the carbonyl reduction step.
This Chapter will describe a study of the mechanism of action of a catalyst system that is highly active and selective for the ATH of ketones. It is based on pre-catalyst 5.2 (Figure 5.1) which has iron(II) coordinated by a PNNP ligand.

5.3 Results

5.3.1 Kinetics of the process

The catalytic reduction of acetophenone to 1-phenethanol was chosen for study because it is the standard reaction used to test ATH catalysts. The optimized conditions for the ATH of acetophenone to produce enantioenriched 1-phenethanol using \textit{i}-PrOH as a solvent and a reducing agent were previously reported by our group and are summarized in Scheme 5.2.\textsuperscript{35} The iron precatalyst 5.2 was synthesized by a template reaction followed by substitution with carbon monoxide (Chapter 4).\textsuperscript{35} A strong base such as KO\textsubscript{t}Bu is required for the activation of the catalyst and is used in 8 fold excess relative to the catalyst.

Scheme 5.2 General reaction of the catalytic reduction of acetophenone.

5.3.2 Reaction profile

The reaction profile shown in Figure 2 (the run at standard conditions) was previously reported and was obtained by monitoring the formation of the product as a function of time. The reaction consists of three stages: initiation (increasing rate of the reaction), maximum rate
of the reaction (a linear region) and culmination (decreasing rate of the reaction). A prolonged induction period is not common in homogeneous catalysis, since the activation of the catalyst is usually a fast process. However, the induction periods for activation have been observed, for example, for phosphine-rhodium(I), iridium(I) and arene ruthenium(II) complexes. Such an induction period might also indicate the formation of soluble or insoluble metal particles and/or nanoparticles that serve as heterogeneous catalysts. This induction process, identified by Finke and co-workers, has two steps for particle formation: first slow nucleation and then fast agglomeration.

The observed sigmoidal kinetics of our system forced us to explore the true nature of the catalytic species. One of the most commonly reported methods in the literature for differentiating between hetero- and homogeneous catalysts is the mercury test that was first proposed by Whitesides and co-workers. It is based on the property of metals to form an amalgam with Hg(0). Therefore, if mercury is added to the catalytic mixture it should deactivate a heterogeneous catalyst but not affect the activity of a homogeneous catalyst. This test can be efficiently applied to the Pt, Pd, and Ni metals that form an amalgam with elemental mercury. On the other hand, this test can be misleading when applied to the catalytic systems that are based on Ir, Rh, Ru and Fe because they may not form an amalgam with Hg(0). Nevertheless, examples of successful quenching of the heterogeneous catalysis using Hg(0), for example with rhodium complexes, are known. Even though our system is based on iron, this test was applied by adding 300 equivalents of mercury to the reaction mixture containing initially acetophenone, KOtBu and i-PrOH at 28.0 °C in argon glove box after 6.90 minutes of reaction (Figure 5.2, Hg(0)). The reaction progression was unaffected by the addition. Thus, the catalyst is either homogeneous or catalytic Fe particles were not deactivated by Hg(0).

The inconclusive outcome of the Hg(0) test forced us to perform additional testing.
Figure 5.2 The effect of the addition of Hg(0) and substoichiometric amounts of trimethylphosphine on the reaction rate of the transfer hydrogenation of acetophenone (Hg(0) was added at 6.9 min, and PMe₃ at 6.5 min, after reaction was initiated).

A “fractional poisoning” experiment is rarely reported in the literature but can be a powerful technique to differentiate between hetero- and homogeneous catalysis. The reasoning behind this test is that metal particles have only a fraction of the active metal on the surface of the particle to perform catalysis. Therefore, a heterogeneous catalyst can be poisoned with less than one equivalent of the quenching agent relative to the catalyst, compared to the homogeneous catalyst that would usually require one equivalent of poisoning agent for the quenching or more than one if reversible inhibition is taking place. Trimethylphosphine was chosen to be a poisoning agent for our system, since it binds strongly to low valent metals and is not a sterically demanding ligand. This additive poisons our first generation catalysts which are thought to form active iron nanoparticles. The test was conducted using the same conditions as were used for Hg(0) poisoning experiment except 0.5 equivalents of PMe₃ relative to the catalyst was added at 6.5 min of reactions time (Figure 5.2, PMe₃). The reaction slowed a little but was not poisoned completely. This observation supports the proposal that the active catalytic species are sterically hindered homogeneous complexes and are not surface atoms of nanoparticles. The reproducibility of the kinetics and the high enantioselectivity of the
process also argue for a homogenous process. Finally, we will show below that a well-defined complex can be isolated that serves as an extremely active catalyst without the induction period.

When a high loading of the substrate (6000 equivalents relative to the catalyst) is used, the turn over frequency of the process decreases after 60 % of the acetophenone is converted to the corresponding alcohol. The decomposition of the catalyst is not the cause of this slow down because the addition of substrate to the reaction mixture after 60 % conversion increases the rate of reaction to the expected value (Chapter 4). Instead it appears that the slower rate results from the system approaching equilibrium. Whether a high (0.1%) or low (0.01%) catalyst loading is employed, the reaction attains about 88% conversion at 28.0 °C. This corresponds to an equilibrium constant $K_{eq}$ of 0.24 (eq. 1).

\[
K_{eq} = \frac{[acetone]_{eq}[1−phenethanol]_{eq}}{[i Pr OH]_{eq}[acetophenone]_{eq}} = 0.24 \pm 0.02
\]  

5.3.3 Maximum rate determination and analysis

A systematic variation of the reaction conditions was conducted in an attempt to determine rate laws for the catalyst activation and 1-phenethanol formation. The kinetics method of measuring initial rates cannot be used to explore the mechanism of this reaction because of the induction period. However, a constant, maximum rate of 1-phenethanol production is observed in the region between approx. 10 and 60% conversion (Figure 5.2 and Figure 5.3) and the variation in this rate with changes in the initial concentrations of the reagents provides useful information. The process of pre-catalyst activation cannot be monitored directly, since the concentrations of active species are very difficult to measure accurately. For that reason, we used the intercept of the 1-phenethanol formation line with the time axes (Figure 5.3). The intercept is a measure of the time required for the pre-catalyst to be activated in order to produce the maximum rate of catalysis.
To ensure the reproducibility of results, the catalytic reductions of acetophenone were conducted at 28.0±0.3°C in an argon glovebox using the following standard concentrations of reagents, which were achieved using a series of dilutions, unless otherwise stated: the concentrations of acetophenone, 5.2, KO\textsuperscript{t}Bu and \textit{i}-PrOH were 0.412, 6.73x10\textsuperscript{-5}, 5.45x10\textsuperscript{-4} and 12.4 M, respectively (detailed procedures, initial concentration and experimental results can be found in the Experimental section). The reactions were initiated by addition of the base solution to a mixture containing 5.2, \textit{i}-PrOH and acetophenone.

A plot of the maximum rate of 1-phenethanol formation versus the precatalyst concentration is non-linear (Figure 5.4, (a)). Nevertheless, it can be seen that the rate is positively dependent on the precatalyst concentration. The time required for the activation of the catalyst is inversely proportional to the concentration of 5.2 (Figure 5.4, (b)), when its concentration is significantly lower than the base concentration (below 7 x10\textsuperscript{-5} M). At higher concentrations the activation step becomes almost independent of the concentration of 5.2. This can be attributed to the fact that the number of equivalents of the precatalyst relative to the base falls to less than a 1:5 ratio; thus, the base becomes a rate-limiting reagent.

Figure 5.3 Plot showing how the maximum rate and activation period were determined.
Figure 5.4 Plots of (a) the maximum rate of 1-phenethanol formation versus the precatalyst concentration and (b) the time for catalyst activation versus the precatalyst concentration. Conditions: [acetophenone] = 0.412 M; [2] = 1.07x10^{-4}, 8.58x10^{-5}, 6.74x10^{-5}, 4.29x10^{-5}, 1.53x10^{-5} M; [KO'Bu] = 5.45x10^{-4} M, [i-PrOH] = 12.4 M; temperature 28°C.
Attempts were made to activate the catalyst before the addition of the ketone. Initially, we reacted the catalyst with the base for 12 minutes followed by the addition of substrate and obtained a complete shutdown of reactivity. An approximately one minute reduction in the activation period compared to the standard run was observed when the catalyst was reacted with the base for 2 minutes prior to the addition of the ketone and showed comparable activity to the standard run. The color of solutions in both experiments changed from yellow to green instantaneously after the addition of the base. The color of the reaction mixture gradually changed to a yellow-brown over the course of 12 minutes. These observations indicate that the formation of the active catalyst by the reaction of the precatalyst and basic $i$-PrOH is the cause of the induction period and that the active species decomposes in the presence of excess of base, when the ketone is not part of the reaction mixture.

There is a positive dependence of the maximum rate on acetophenone concentration (Figure 5.5(a)). Figure 5.5(b) shows that increasing the concentration of acetophenone causes a decrease in the rate of the precatalyst activation.

The interference by acetophenone on the activation of the catalyst is an unexpected outcome; ketones are poor ligands and are unlikely to prevent the $iso$-propoxide from coordinating to the iron and activating the catalyst. On the other hand, the enolate form of acetophenone, which can be easily formed under the experimental conditions,$^{58}$ would be a much better ligand. Support for inhibition by the enolate comes from a previously reported experiment where benzophenone, a non-enolizable ketone, was found to have no effect on the reaction rate.$^{37}$
Figure 5.5 a) The dependence of maximum rate of 1-phenethanol formation on the acetophenone concentration. b) The dependence of the time required for the precatalyst to be activated on the acetophenone concentration. Conditions: [acetophenone] = 0.263, 0.313, 0.412, 0.513, 0.562, 0.662 M; [2] = 6.74x10^{-5} M; [KO\textsuperscript{t}Bu] = 5.45x10^{-4} M, [i-PrOH] = 12.4 M; temperature 28°C.
During the course of the reaction another ketone, acetone, is produced as a by-product, and this, in its enolate form, may also interfere with the catalyst activation. Figure 5.6 verifies the fact that acetone has a weak inhibitory effect on the activation.

![Figure 5.6](image)

Figure 5.6 The dependence of the catalyst activation time on acetone concentration. Conditions: \([\text{acetophenone}] = 0.412 \text{ M; } [2] = 6.74 \times 10^{-5} \text{ M; } [\text{KO}^\text{Bu}] = 5.45 \times 10^{-4} \text{ M, } [\text{i-PrOH}] = 1.24 \times 10^{-1} \text{ M; } [\text{acetone}] = 4.12 \times 10^{-2}, 8.42 \times 10^{-2}, 1.24 \times 10^{-1}, 1.64 \times 10^{-1} \text{ M; temperature } 28^\circ \text{C.}

In our previous studies,\textsuperscript{34} different bases such as NaO\text{t}Pr, KOH and NaO\text{t}Bu were tested as activating agents for this process. The variation had a minor effect on the rate of the reaction and it was concluded that neither the base nor its cation (Na\textsuperscript{+} or K\textsuperscript{+}) participate in the actual catalytic cycle and only play an active role during the activation of the catalyst. Indeed, the data of Figure 5.7 (a) show that the maximum rate is independent of the base (KO\textsuperscript{Bu}) concentration as long as at least six times greater than that of the catalyst. The experiments with less than six equivalents of base per iron complex showed slower maximum rates because the activation of the catalyst took a longer time than the time for the reaction to go to completion. The dependence of the precatalyst activation time on the base concentration showed the expected inverse dependence (Figure 5.7 (b)). These observations are in agreement with our previous conclusions that the base is only important for the activation of the catalyst.
Figure 5.7 a) The dependence of maximum rate of 1-phenethanol formation on the base concentration. b) The dependence of catalyst activation time on the base concentration. Conditions: [acetophenone] = 0.413 M; [2] = 6.74x10^{-5} M; [KO'Bu] = 4.08x10^{-4}, 4.71x10^{-4}, 5.44x10^{-4}, 8.16x10^{-4}, 1.35x10^{-3} M, [i-PrOH] = 12.4 M; temperature 28°C.

The attempts to investigate the dependence of the maximum rate on i-PrOH concentration were not successful. We searched for a suitable solvent that was inert, weakly-
coordinating and with a dielectric constant similar to that of \( i\hspace{-0.5mm}-\hspace{-0.5mm}PrOH \). When mixtures of THF and \( i\hspace{-0.5mm}-\hspace{-0.5mm}PrOH \) or benzene and \( i\hspace{-0.5mm}-\hspace{-0.5mm}PrOH \) were used, the rates were much lower than those expected based on the standard runs. These observations show that the polarity and protic nature of the solvent are important factors in this catalytic reaction.

### 5.3.4 The kinetic model

The kinetic studies indicate that the catalyst activation is directly proportional to the pre-catalyst and the base concentrations. It is also inversely proportional to the concentration of the substrate and acetone. These findings are schematically represented in Scheme 5.3. The non-activated iron complex (\( Fe_p \)) participates in an irreversible reaction with \( i\hspace{-0.5mm}-\hspace{-0.5mm}PrO^- \) to give catalytically active complexes (\( Fe_{Ta} \)) (eq (2)) and in two quickly established equilibria with the enolate of acetone (\( A^e \)) (eq (3)) and the enolate of acetophenone (\( S^e \)) (eq (4)) to give non-productive iron-enolate species (\( Fe-A^e \) and \( Fe-S^e \)). The formation of the enolates \( A^e \) and \( S^e \) are described in terms of rapidly established equilibria with base and acetone (eq (5)) or base and acetophenone (eq (6)), respectively.

\[
\begin{align*}
Fe_p + i\hspace{-0.5mm}-\hspace{-0.5mm}PrO^- & \xrightleftharpoons[\text{k_{act}}]{\text{K}} Fe_{Ta} \quad \text{eq (2)} \\
A^e + Fe_p & \xrightleftharpoons[K_{eq1}]{\text{K}_{eq1}} Fe-A^e \quad \text{eq (3)} \\
S^e + Fe_p & \xrightleftharpoons[K_{eq2}]{\text{K}_{eq2}} Fe-S^e \quad \text{eq (4)} \\
A^e + i\hspace{-0.5mm}-\hspace{-0.5mm}PrO^- & \xrightleftharpoons[K_{eq3}]{\text{K}_{eq3}} i\hspace{-0.5mm}-\hspace{-0.5mm}PrOH + A^e \quad \text{eq (5)} \\
S^e + i\hspace{-0.5mm}-\hspace{-0.5mm}PrO^- & \xrightleftharpoons[K_{eq4}]{\text{K}_{eq4}} i\hspace{-0.5mm}-\hspace{-0.5mm}PrOH + S^e \quad \text{eq (6)}
\end{align*}
\]

Scheme 5.3 Schematic representation of the activation of 5.2.
The rate of formation of Fe\textsubscript{Ta} can be represented in terms of the concentrations of 5.2 ([Fe\textsubscript{p}]\textsubscript{0}, Fe\textsubscript{Ta}, \textit{i}-PrO\textsuperscript{-}, A and S and described by eq (7) (See Experimental section for derivation).

\begin{equation}
\frac{d[Fe_{Ta}]}{dt} = \frac{k_{act} \times \{[Fe_{p}]_{0} - [Fe_{Ta}]\} \times [\textit{i}PrO^{-}]}{1 + \frac{[\textit{i}PrO^{-}]}{[\textit{i}PrOH]} \times \left(K_{eq}^{-1} K_{eq}^{-2} [A] + K_{eq}^{-2} K_{eq}^{-4} [S]\right)} \tag{eq (7)}
\end{equation}

The rate of 1-phenethanol formation depends on the concentrations of activated catalyst, substrate and possibly the hydrogen source, \textit{i}-PrOH. Similar dependences were previously observed by Adolfsson and co-workers for the ruthenium-based catalytic system containing pseudo-dipeptide ligands for the asymmetric transfer hydrogenation of acetophenone\textsuperscript{,59} and thus this model can be applied to our catalytic process. The reduction can be represented in terms of two dependent equilibria (Scheme 5.4): an iron-containing active complex (Fe\textsubscript{a}) reacts with \textit{i}-PrOH (R) to give a complex with activated hydrogen or hydride (Fe\textsubscript{a}H) and acetone (A) (eq (8)) and reaction of Fe\textsubscript{a}H with acetophenone (S) to give 1-phenethanol and regenerate Fe\textsubscript{a} (eq (9)). The total amount of active iron species Fe\textsubscript{Ta} is equal to Fe\textsubscript{a}+Fe\textsubscript{a}H.

Scheme 5.4 Schematic representation of the hydrogen transfer process.
Adolfsson and co-workers in their kinetic study assumed that the formation of the active ruthenium complex from the precatalyst is an instantaneous process; thus, the concentration of the precatalyst is equal to the concentration of the active species.\textsuperscript{59} This assumption in combination with the derived rate law allowed the determination of all of the rate constants from the kinetic data. Unfortunately, in our iron-catalyzed reaction this assumption is not valid and $[\text{Fe}_p]_0 \neq [\text{Fe}_\text{Ta}]$. Moreover, $[\text{Fe}_\text{Ta}]$ is changing throughout the catalytic reaction and depends on the initial concentrations of the reagents.

### 5.3.5 The simulation of the rate processes

In order to verify the legitimacy of the proposed kinetic model and estimate rate constants associated with it, numerical simulations were used. A change in concentration of every component of the reaction mixture in small intervals of time ($\Delta t = 0.00025$ s) can be determined from the equations which arise directly from the kinetic model (Scheme 5.3 and Scheme 5.4); these equations are given in the Appendix (eq 10-20). The concentrations of base and $i$-PrOH are assumed to be constant during the reaction, since they are used in large excess compared to the other reagents, and are assumed to be equal to their initial concentrations.

The experimental data consisting of 18 catalytic runs (180 data points) conducted with various initial concentrations of precatalyst, acetophenone, acetone and base were globally fitted by numerical simulations to determine an optimized, consistent set of the rate constants (Table 5.1). The plots showing both the experimental and fitted data points are presented in Figure 5.8.
Table 5.1 Estimated rate constants from simulated reaction profiles using the proposed model (the error is less than 10 %).

<table>
<thead>
<tr>
<th>Rate constants</th>
<th>(M⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_1 )</td>
<td>6.5x10²</td>
</tr>
<tr>
<td>( k_{-1} )</td>
<td>2.7x10⁴</td>
</tr>
<tr>
<td>( k_2 )</td>
<td>1.4x10⁴</td>
</tr>
<tr>
<td>( k_{-2} )</td>
<td>1.4x10⁷</td>
</tr>
<tr>
<td>( k_{\text{act}} )</td>
<td>2.7x10²</td>
</tr>
</tbody>
</table>

\[ K_{\text{eq}}^{-1} K_{\text{eq}}^{-3} = K_{\text{eq}}^{-2} K_{\text{eq}}^{-4} \]

1.2x10⁵
Figure 5.8 Experimental and simulated reaction profiles using the proposed model. Solid lines represent simulated reaction profiles. Plots A, B, C and D represent experiments with various concentrations of acetone, acetophenone, precatalyst and base, respectively. Plot E shows simulated concentrations of iron species in the reaction mixture as a function of time (simulated for the standard conditions: concentrations of acetophenone, 5.2, base and $i$-PrOH were 0.412, 6.73x10^{-5}, 5.45x10^{-4} and 12.4 M, respectively).

The simulated reaction profiles are in good agreement with the experimental data points. A slight variation between the simulated and the experimental data can be seen in Figure 5.8 C with the lowest concentration of catalyst. Slower formation of 1-phenethanol can be explained by possible decomposition of the catalyst, which only becomes evident at low catalyst loadings (1.53x10^{-5} M); this was not taken in account in the simulation. Figure 5.8 E shows the simulated concentrations of the iron pre-catalyst (Fe$_p$ in Scheme 5.4), and the active iron species with and without a hydride equivalent (Fe$_a$H and Fe$_a$ in Scheme 5.4, respectively) during the reaction with standard initial concentrations. From the plot it is evident that the active species have similar concentrations during the initiation and propagation segments of the reaction, but at equilibrium the active species without the hydride is predominant. Clearly, the formation of the active species is a continuous process that takes place with a diminishing rate over the course of the entire reaction.
5.3.6 Temperature dependence

Catalytic reductions were conducted at various temperatures between 229.1 and 314.1 K in order to obtain corresponding reaction profiles. The maximum rates of these reactions result from the combined effects of different rate constants, and therefore cannot be used to determine the activation parameters of the rate limiting step of the reaction. The rates constants of individual steps can be estimated by numerical simulations of the reaction profiles in a similar fashion to that done for the determination of rate constants, except that various $K_{eq}$ values, which were experimentally determined, were used in equation (14) for the determination of the $r_2$ (see Appendix). The simulated profiles along with the experimental data are presented in Figure 5.9. Five sets of rate constants that were used in the simulations of temperature variation reaction profiles are summarized in Table 5.2. These values were used to determine activation parameters of individual steps (Table 5.2) of the reaction using Eyring-Polanyi plots (Experimental section).

Figure 5.9 Experimental and simulated reaction profiles of temperature dependence experiments. Solid lines represent simulated reaction profiles. Conditions: [acetophenone] = 0.412 M; [2] = 6.74x$10^{-5}$ M; [KO'Bu] = 5.45x$10^{-4}$ M, [i-PrOH] = 1.24x$10^{-4}$ M; temperature 292.1, 296.1, 298.1, 300.1, 303.1, 306.2, 314.1 K.
Table 5.2 Estimated rate constants of the process at different temperatures and the calculated activation parameters of individual steps of the reaction.

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>$k_{\text{act}} \times 10^2$ (M$^{-1}$min$^{-1}$)</th>
<th>$k_1 \times 10^2$ (M$^{-1}$min$^{-1}$)</th>
<th>$k_{-1} \times 10^4$ (M$^{-1}$min$^{-1}$)</th>
<th>$k_2 \times 10^4$ (M$^{-1}$min$^{-1}$)</th>
<th>$k_{-2} \times 10^4$ (M$^{-1}$min$^{-1}$)</th>
<th>$K_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>292.1</td>
<td>1.43</td>
<td>4.61</td>
<td>2.10</td>
<td>1.01</td>
<td>0.830</td>
<td>0.256</td>
</tr>
<tr>
<td>296.1</td>
<td>2.15</td>
<td>5.81</td>
<td>2.24</td>
<td>1.17</td>
<td>1.23</td>
<td>0.248</td>
</tr>
<tr>
<td>298.1</td>
<td>2.48</td>
<td>6.26</td>
<td>2.42</td>
<td>1.32</td>
<td>1.40</td>
<td>0.244</td>
</tr>
<tr>
<td>300.1</td>
<td>2.74</td>
<td>6.48</td>
<td>2.72</td>
<td>1.36</td>
<td>1.36</td>
<td>0.240</td>
</tr>
<tr>
<td>303.1</td>
<td>3.25</td>
<td>6.95</td>
<td>3.17</td>
<td>1.59</td>
<td>1.49</td>
<td>0.234</td>
</tr>
<tr>
<td>306.2</td>
<td>3.68</td>
<td>7.80</td>
<td>3.56</td>
<td>1.64</td>
<td>1.58</td>
<td>0.228</td>
</tr>
<tr>
<td>314.1</td>
<td>6.19</td>
<td>10.4</td>
<td>4.76</td>
<td>2.19</td>
<td>2.27</td>
<td>0.212</td>
</tr>
<tr>
<td>Rate (M/min)$^*$</td>
<td>0.078</td>
<td>0.036</td>
<td>0.035</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta H^{\ddagger}$ (kcal/mol)</td>
<td>10.9</td>
<td>5.76</td>
<td>6.65</td>
<td>5.74</td>
<td>6.67</td>
<td></td>
</tr>
<tr>
<td>$\Delta S^{\ddagger}$ (cal/molK)</td>
<td>-2.96</td>
<td>-18.3</td>
<td>-7.96</td>
<td>-12.4</td>
<td>-13.9</td>
<td></td>
</tr>
<tr>
<td>$\Delta G^{\ddagger}_{298}$ (kcal/mol)</td>
<td>11.7</td>
<td>11.2</td>
<td>9.02</td>
<td>9.42</td>
<td>10.8</td>
<td></td>
</tr>
</tbody>
</table>

$^*$Rates of the reaction at 7 min of reaction time were calculated using following concentrations of the reagents that were determined from experimental and simulated reaction profiles: [Fe$_a$H] = 1.00x10$^{-5}$ M, [Fe$_a$] = 1.00x10$^{-5}$ M, [Acetone] = 0.15 M, [1-phenethanol] = 0.15 M, [Acetophenone] = 0.262 M, [i-PrOH] = 12.4 M.

The Gibbs free energies of activation of all of the steps of the process are relatively low. This is consistent with the observed high rate of the process. The activation energies of the catalytic steps are in a similar range, thus allowing the system to be driven by the thermodynamic equilibrium of the process. The highest energy point in the catalytic cycle is the reaction of acetophenone with the Fe$_a$H, although the free energy that is required to get to this
transition state is smaller than the energy needed to activate Fe₇₇ by reaction with i-PrOH (11.7 kcal/mol) and the energy of the reaction of Fe₆ with i-PrOH (Figure 5.10).

![Reaction coordinate diagram](image)

Figure 5.10 Reaction coordinate diagram for the catalytic step of the process.

The rates of individual steps at seven minutes of reaction time can be approximated by multiplying corresponding rate constants by the concentrations of reagents participating in particular step of the reaction at a given time. The concentrations of the reagents were determined from the experimental and simulated reaction profile of the standard run and are summarized in Table 5.2. The rates of forward reactions, which correspond to k₁ and k₂ (equations (8) and (9)) were faster compared to the reverse reactions, which correspond to k₋₁ and k₋₂. The rate of forward reaction described by equation (8) was found to be almost twice as fast as the rate of the forward reaction described by the equation (9). This observation allows us to assume that at a given set of conditions the step involving the reduction of acetophenone is a rate determining event in the catalytic cycle. Our previous studies also showed that the rate of reaction is highly dependent on the nature of the ketone used. This supports the idea that the reaction of Fe₆ with the ketone is the rate determining step under experimental conditions. On the other hand, it is possible that the reaction of i-PrOH with Fe₆ can be a rate determining step when concentration of acetophenone is high or the concentration of i-PrOH is low.
5.3.7 Kinetic isotope effect

The kinetic isotope effect (KIE), as a ratio of the rates of hydrogen and deuterium transfer, was determined for the standard catalytic reductions that were conducted at constant temperatures using different hydrogen/deuterium donor sources: \((\text{CH}_3)_2\text{C}(\text{H})\text{OH}\), \((\text{CD}_3)_2\text{C}(\text{D})\text{OD}\) and \((\text{CH}_3)_2\text{C}(\text{H})\text{OD}\). It has to be noted that the rates of the entire process, which are influenced by several rate constants, were used in the determination of the KIE but not the rate constants of individual steps, because at this point of investigation the isolation of intermediates and measuring the rates of individual steps of the process is difficult. For that reason, the determined values of KIE may result from combined KIE of the individual steps of the reaction. On the other hand, it can be assumed that the rate of the process is proportional to the rate constant associated with the rate-limiting step of the reaction, which is the reduction of the acetophenone with \(\text{FeH}\). The formation of \(1\)-phenethanol over time is plotted in Figure 5.11. The resulting rates were used to calculate the KIE (Chart 1).

![Figure 5.11](image-url)  
Figure 5.11 The rates of ATH of acetophenone using \(i\)-PrOH deuterated at different positions.
Chart 5.1 Calculation of the kinetic isotope effects using (CD$_3$)$_2$C(D)OD (KIE) and (CH$_3$)$_2$C(H)OD (KIE$_2$).

\[
KIE = \frac{k_{obs}[(CH_3)_2C(H)OH]}{k_{obs}[(CD_3)_2C(D)OD]} = 2.5 \pm 0.1
\]

\[
KIE_2 = \frac{k_{obs}[(CH_3)_2C(H)OH]}{k_{obs}[(CH_3)_2C(H)OD]} = 1.3 \pm 0.1
\]

A primary kinetic isotope effect (KIE$_1$ = 2.5) was observed when fully deuterated iPrOD was used and a smaller kinetic isotope effect (KIE$_2$ = 1.3) was detected when iPrOD-d$_1$ was used. The different intercepts of the rate lines on the time axis show that the activation period was longer when iPrOD-d$_8$ is used compared with the reactions involving iPrOD-d$_1$ and iPrOH. These observations indicate that the transfer of the hydridic hydrogen of 2-propanol, as opposed to the hydroxyl hydrogen, dominates the rate of activation of the precatalyst, and that a hydride transfer likely also dominates the rate of catalyst turnover. More data will be needed in order the separate the relative contributions of these processes to the KIE values.

5.3.8 The preparation and reactivity of the complex 5.4 containing a diamine ligand

The complex 5.4 that contains a PNNP ligand with amine groups instead of imines can be synthesized as described in Scheme 5.5. It was fully characterized using spectroscopic methods. Single crystals of 5.4 were analyzed by X-ray diffraction (Figure 12). The monocationic complex 5.4 has a distorted octahedral geometry with carbonyl and bromide ligands trans to each other. The phenyl groups of the diamine are in equatorial positions and the amine hydrogens are axial, anti with respect to each other. The bond lengths between ligand donor atoms and the iron are within the expected range. A wide P-Fe-P angle (108°) results from the structure of the ligand, which forms three five-membered ligand-metal rings. This is comparable to P-Fe-P angles observed for similar iron complexes prepared in our laboratory.
The reduction of acetophenone using complex 5.4 was performed under standard conditions that were used for the kinetic studies of complex 5.2. After 2 hours of reaction only 10% of the ketone was converted to the corresponding alcohol with an enantiomeric excess of 82 % (R).

Scheme 5.5 The synthesis of complex 5.4.
Figure 5.12 ORTEP plot of the cation of 5.4. Thermal ellipsoids are drawn at 50% probability. Some hydrogen atoms, solvent molecules and counter ions are omitted for clarity. Selected interatomic distances [Å] and angles [°]: N1a-Fe1a 2.065(5), P1a-Fe1a 2.259(2), C7a-Fe1a 1.745(9), Br1a-Fe1a 2.490(1), P1a-Fe1a-P2a 107.99(7).

5.3.9 Preparation and properties of the ene-amido complex 5.5

Complex 5.2 was reacted with 2.5 equivalents of the base KOtBu in benzene at room temperature to produce a green solid after purification. The $^1$H NMR spectra of the product in benzene-$d_6$ shows that the resonances corresponding to the hydrogen atoms of the complex 5.2 are absent but a new set of multiplets was observed. These peaks were assigned to the hydrogens $H_a'$, $H_d'$, $H_c'$ and $H_n'$ of the neutral bis(ene-amido) iron complex 5.5 (Figure 13). Coupling between $H_a'$-$H_c'$ and $H_f'$-$H_h'$ were identified using 2D COSY experiments to locate the resonances of $H_c'$ and $H_f'$ that were overlapping with aromatic peaks. An absence of the resonances arising from tetraphenylborate in the $^{11}$B NMR spectrum and in the aromatic region of $^1$H NMR spectra peaks is consistent with the formulation of 5.5 as a neutral complex. This highly soluble complex showed AB pattern in the $^{31}$P{$^1$H} NMR spectrum at 68.9 and 68.6 ppm with $^2J_{PP} = 25$ Hz, which is consistent with structure having two inequivalent phosphorus atoms. The reaction of the complex 5.5 with a 1 M solution of HCl in diethyl ether (excess was added) resulted in the formation of complex 5.6, the structure of which was confirmed by $^{31}$P{$^1$H} NMR (two doublets at 64.9 and 67.0 ppm, $^2J_{PP} = 40.4$ Hz) and HRMS ESI$^+$ (full monocation of the complex 5.6). This reversibility of the reaction of the precatalyst 5.2 with base and acid further supports the structure of the complex 5.5.
The stability of complex 5.5 was lower than that of the bis(eneamido) complex 5.3 (Scheme 5.1) as expected since precatalyst 5.2 when activated with base produces a far more reactive catalytic solution than 5.3.\textsuperscript{40} The decomposition of compound 5.5 in solution or in the solid state under an inert atmosphere occurred after days but after seconds in the air. Decomposition in solution is signalled by a broadening of the peaks in the \textsuperscript{1}H NMR spectra, resulting from the formation of paramagnetic species, and by a change of color from a deep green to a brown-green. This high reactivity prevented the full characterization of this compound using elemental analysis, high resolution mass spectroscopy or X-ray diffraction.

Compound 5.5 was directly reacted with a mixture of the acetophenone in \textit{i}-PrOH (standard conditions applied) without the addition of base to test whether it is within the catalytic cycle. The observed reaction profile in terms of the formation of 1-phenethanol with time is presented in Figure 5.14, Run 1. The reactivity and enantioselectivity of the complex 5.5 in the process of acetophenone reduction are comparable to those observed with complex 5.2 activated by base. On the other hand, the apparent activation period indicates that complex 5.5
needs to be activated prior to the catalytic cycle to take place; thus it is not within the catalytic cycle.

![Graph showing concentration of 1-phenethanol over time for different runs](image)

**Figure 5.14** The catalytic reduction of acetophenone using complex 5.5. Run 1: complex 5.5 reacted with a solution of acetophenone in $i$-PrOH. Run 2: complex 5.5 reacted with $i$-PrOH for 4 minutes prior the addition of acetophenone. Run 3: complex 5.5 reacted with acetophenone for 4 minutes prior the addition of $i$-PrOH. Run 4: complex 5.5 was reacted with $i$-PrOH for 12 minutes prior the addition of acetophenone.

Since the reaction of complex 5.5 with $i$-PrOH and acetophenone led to the formation of the active catalyst (Figure 5.14, Run 1), it can be concluded that one of these reagents is responsible for the activation of 5.5. Each was reacted with the complex 5.5 for four minutes prior to the addition of the other in order to identify, which of the two substances is an activating agent (Figure 5.14, Run 3 and Run 2, respectively). The induction period disappeared when 5.5 is pre-reacted with $i$-PrOH, but is very pronounced when acetophenone is reacted with 5.5 before $i$-PrOH is added. These observations show that the activation of the green complex 5.5 results from its reaction with $i$-PrOH. The longer induction period of Run 3 relative to Run 1 (Figure 5.14) is consistent with the finding of the kinetic study that the enolate of acetophenone prolongs the period of activation of the catalyst. The kinetic studies also predict that the formation of the active species in the solution is a continuous process that takes place during the entire acetophenone reduction step of the reaction. This implies that the
concentration of the active catalytic species and the rate of 1-phenethanol formation will be greater if the pre-activation of the green compound 5.5 with i-PrOH is allowed to occur for a longer period of time, keeping other conditions the same. The reaction where 5.5 is pre-activated with i-PrOH for 12 min (Figure 5.14, Run 4) verifies that this is the case.

5.3.10 Protonation of the active catalytic species and synthesis of complex 5.7

In order to gain information about the structures of the catalytically active complexes, i-PrOH was added to the complex 5.5. The green solution turned an orange-red color after 20 min. The $^{31}$P{¹H} NMR spectrum of the reaction mixture showed a complicated pattern of broad resonances, indicating that several species were formed. These species might be Fe₆, Fe₆H, 5.5 and decomposition products. The isolation and characterization of the observed complexes is difficult due to their high reactivity. On the other hand, when the reaction was quenched with a 1 M solution of HCl in diethyl ether (excess was added) the solution became bright yellow. The solvent was evaporated to give a yellow solid. The major species in the $^{31}$P{¹H} NMR spectrum of the solid dissolved in CD₂Cl₂ had two doublet resonances at 56.2 and 66.0 ppm with $J_{P,F} = 39.3$ Hz (~85% relative to all the species that produced $^{31}$P resonances). The solid was purified by precipitation with NaBPh₄ from MeOH solution and identified as the amino-imino complex 5.7 (Scheme 5.6) on the basis of HRMS ESI⁺, ¹H and $^{31}$P{¹H} NMR spectroscopy. The structure of complex 5.7 is similar to the structure of complex 5.6 except that one of the imine functionalities of the ligand is reduced to the amine. The reduction possibly occurred via selective transfer of the hydrogen equivalent from i-PrOH to one of the imines of the ligand as described in Scheme 5.6, since no other reducing agents were present in the reaction mixture. It also has to be noted that only one diastereomer of complex 5.7 was observed (two possible diastereomers may arise from reduction of one or the other imine of the ligand), since two doublets were observed in $^{31}$P {¹H} NMR spectra, indicating that the reaction is stereospecific.
Scheme 5.6 Proposed formation of the complex 5.7.

5.3.11 Catalytic activity of complex 5.7

The use of complex 5.7 as a catalyst precursor under the standard conditions results in the rapid catalytic reduction of acetophenone without an induction period (Figure 5.15; see the Experimental section for the conditions). The TOF is 55,000 h\(^{-1}\) at 25% conversion compared to 28,000 h\(^{-1}\) using complex 5.2 under standard conditions. The e.e. of the 1-phenylethanol produced in each case was 82% (\(R\)).
5.4 Discussion

5.4.1 Summary of findings.

The presence of the activation period prior the catalytic cycle of the reaction makes it difficult to use conventional techniques to determine the rates of individual steps of the reaction, since it is impossible to enforce the conditions such that the active catalyst would be at steady-state. Hartmann and Chen have used an alternative approach, which was initially outlined by Boudart, to investigate the catalytic cycle of asymmetric transfer hydrogenation of Noyori’s precatalyst RuCl$_2$(diamine)(diphosphine). The approach is based on utilization of coupled differential rate laws of individual steps of the process, which arise directly from the proposed mechanistic model, in numerical integrations, instead of entire rate law. If these numerical integrations are fitted to the experimentally obtained reaction profiles, then the rate constants and rates of the individual steps of the process can be determined.
In order to propose the kinetic model, we established the dependences of the rates of activation of the catalyst and 1-phenethanol formation on concentrations of the reagents. The mechanistic model (Scheme 5.3 and Scheme 5.4) was used to derive coupled differential rate laws (eq 7, eq (10)-eq (20)), for elementary steps of the catalytic process. The extent of 1-phenethanol production with time was simulated using these rate laws. The simulated reaction profiles, which were obtained using the rate constants summarized in Table 5.1, are in good agreement with the data obtained experimentally (Figure 5.8). This implies that the proposed model effectively describes the catalytic process. Simulations were also used to show that the formation of the active species is a prolonged process (Figure 5.8, E). It suggests that the activation is a complex process involving major changes in the structure of the complex going from the precatalyst to the catalyst. A similar approach was used to determine the activation parameters of individual steps of the reaction from the reaction profiles that were obtained by conducting the catalytic reductions at different temperatures.

A logical explanation for the activation period is that the imine groups are reduced to amines to produce an iron complex with hydride and amine groups to allow the hydride-protic amine outer sphere reduction of the ketone that is observed for PNNP ruthenium catalysts. Complex 5.4, which contains a ligand with two amine groups, is a significantly less active precatalyst compared the complex 5.2. This indicates that the complete reduction of the ligand does not lead to the formation of the active catalyst. The enantiomeric excess of the 1-phenethanol produced using 5.4 as a precatalyst is identical to that using complex 5.2. This may be explained by the fact that both 5.2 and 5.4 upon activation give the same active species, but complex 5.2 is activated faster to provide more of the active catalyst for the reaction. A complete reduction of the ligand from imine to amine may in fact be one of the possible catalyst deactivation pathways. Indeed deactivation is especially pronounced when the concentration of the substrate is low, but the concentration of iso-propoxide is high.

The reaction of complex 5.2 with KOtBu in non-protic and non-reducing benzene as a solvent led to the formation of the bis(ene-amido) complex 5.5. This reaction can be reversed if a strong acid such as HCl is added to the solution to give the chloro-carbonyl complex 5.6 containing the PNNP ligand identical to that of the complex 5.2. It is evident that complex 5.5 is only an intermediate in the process of the catalyst activation since the induction period is still observed when 5.5 is reacted with a mixture of i-PrOH and acetophenone to start catalysis.
The active catalyst is actually formed by the reaction of the complex 5.5 and $i$-PrOH; thus when 5.5 is pre-activated with $i$-PrOH and then acetophenone is added (Figure 5.14, Run 2), the reaction proceeds without an induction period.

The structures of the catalytically active species that form during the course of the reaction of 5.5 with $i$-PrOH are very difficult to identify or isolate due to their high reactivity. They have been indirectly identified by quenching the catalyst solution with HCl and isolating complex 5.7 in good yield. Complex 5.7 has a PNPN ligand with both amine and imine functionalities. This strongly suggests that under the basic conditions of reaction the catalyst has a ligand with an ene-amido structure on one side and a saturated amido structure on the other side (complex 5.8). Indeed, when complex 5.7 is treated with base under standard catalytic conditions, there is rapid catalysis without an induction period (Figure 5.15).

### 5.4.2 Proposed mechanism of the ATH of acetophenone using complex 5.2

The above findings lead us to propose the mechanism that is depicted in Scheme 5.7. The catalytic process is initiated by the fast reaction of complex 5.2 with the base to give Fe<sub>p</sub> (complex 5.5). The slow step in the activation process is the reaction of Fe<sub>p</sub> with $i$-PrOH to give Fe<sub>a</sub> (complex 5.8). The equilibria with Fe<sub>p</sub> and the enolates of acetophenone and acetone (in later stage of the reaction) establish and interfere with the activation step. The activated catalyst Fe<sub>a</sub> reacts with $i$-PrOH, presumably in an outer-sphere fashion, to give acetone and an iron hydride complex (Fe<sub>a</sub>H) which contains an $H^+H^-$ pair with the hydride bound to the iron and proton to the nitrogen. The subsequent reaction of the Fe<sub>a</sub>H with acetophenone produces 1-phenethanol and regenerates the complex Fe<sub>a</sub>.  


Scheme 5.7 Proposed mechanism of the transfer hydrogenation of acetophenone using 5.2.

In the investigation of ketone reduction reactions using RuCl$_2$(PPh$_3$)$_3$,$^6^2$ Backvall and coworkers proposed that the hydride transfer to the ketone occurs via its coordination to the metal followed by the insertion into the metal-hydride bond to give the alkoxide intermediate.$^6^3$, $^6^4$ This mechanism, as well as the Meerwein-Ponndorf-Verley mechanism, which involves a direct transfer of the hydride between ketone and alkoxide when they are simultaneously coordinated to the metal,$^6^5$, $^6^6$ are less likely to be operational in the catalytic system under investigation, since both of them require two or more vacant coordination sites. The outer-sphere mechanism that involves metal-ligand cooperation in transferring of the hydrogen equivalent is more probable. The mechanism involving a concerted hydride/proton transfer (H$^-$/H$^+$) from the metal and nitrogen to the carbon and oxygen of the ketone, respectively, was originally proposed by Noyori and co-workers$^6^7$, $^6^8$ and is operational in many highly active catalytic reductions. A stepwise outer-sphere transfer of the hydrogen molecule (SWTH) is also known. In this mechanism the ketone is activated and oriented by non-covalent interaction with
NH group of the ligand for the following attack of the metal-hydride. If the acidity of the ligand’s amine group is low then the formation of the NH/alkoxide pair after the hydride transfer would be more favourable compared to the formation of alcohol/amido that is expected in a concerted outer-sphere mechanism. This mechanism was recently proposed by Baratta for a Ru(C-N-N)(P-P)Cl/base system\(^69,70\) and by Bergens for a \(\text{trans-Ru(P-P)(H}_2\text{N-NH}_2)(\text{H})_2\) system.\(^10\) Gusev and co-workers were able to characterize in the solid state a ruthenium-secondary alkoxide complex also containing a P-N(H)-P and a carbonyl ligand; in solution this dissociates into a ruthenium hydride and ketone.\(^71-73\)

It is a challenging task to differentiate between the concerted and step-wise outer-sphere mechanisms. The most direct method was used by Baratta\(^74\) and Bergens\(^10\) groups and involves direct observation of the metal-alkoxide intermediate. Baratta and co-workers also investigated the effect of the base that is present in the solution during transfer hydrogenation on the alkoxide/NH\(_2\) intermediate. They suggested that \(i\)-PrOH is competing with \(i\)-PrO\(^-\) for the coordination to the NH\(_2\)-Ru complex; high base concentration favours the formation of the active alkoxide/NH\(_2\) complex thus, increasing the rate of the catalytic reduction of ketones. Our iron system showed no dependence on the base concentration when the ratio of base to 5.2 is greater than 5:1. It was also shown that the decrease in rate of 1-penethanol formation when the ratio of the base: 5.2 is smaller than 5:1 resulted from the slower rate of activation of the catalyst and not due to a slower rate of the catalytic reduction process. Complex 5.5, without the addition of any base, can be activated by \(i\)-PrOH to produce a highly active catalyst (Figure 5.14). In addition, the activation entropy value for the hydride transfer step reported by Baratta et al. (-3.2 eu)\(^74\) in the system operating via a ruthenium-alkoxide/amine intermediate is more positive than the activation entropy observed for our system (-12 eu for the k\(_2\) step, Table 5.2). Thus a bimolecular attack of an iron hydride on the ketone is more consistent with this value than an intramolecular reaction involving an iron alkoxide complex.\(^66,75,76\)

The secondary amido nitrogen of complex 5.8 is highly basic. The adjacent ene-amido part of the ligand makes this amido nitrogen even more basic. Therefore, it is reasonable to assume that complex 5.8, when exposed to an excess of protic solvent such as \(i\)-PrOH, would be protonated at the amido nitrogen and give a coordinatively unsaturated mono-cationic iron complex. Accordingly the process of hydride transfer would be a more difficult step than the transfer of the proton and this would explain why there is a small KIE for the transfer of the
proton but a significant KIE for the transfer of the hydride. The observed KIE of 2.5 is comparable to other KIE measured for HM-NH vs DM-ND attack on ketones.\textsuperscript{77} Casey and Johnson concluded in a detailed study of Noyori’s transfer hydrogenation catalyst that the both the observed isotope effects of 1.79 for transfer of OH to nitrogen and of 2.86 for transfer of CH to ruthenium from isopropanol are much too large to be equilibrium isotope effects. They argued for a concerted transfer of the hydride and proton.\textsuperscript{75} We propose that the transfer of a proton from $i$-PrOH to the amido complex is a fast process but does not lead to the formation of a metal-alkoxide intermediate of the type observed by Baratta, Bergens and Gusev. The transfer of the hydride from iron(II) to the ketone is the slowest step. This explains why the rate of catalytic reduction is sensitive to the nature of the ketone that is used.\textsuperscript{77}

With only a cursory glance at the activation parameters of Table 5.2 one might think that the $k_1$ step, the formation of the iron-hydride, should be rate determining since it has a greater free energy of activation. However, under experimental conditions where the concentration of $i$-PrOH is significantly higher than the concentration of acetophenone, the slowest rate of the process is the hydride transfer from the metal center to the ketone.

### 5.5 Conclusions

The current study provides evidence that the activation of precatalyst 5.2 with base results in the selective reduction of one of the imine groups of the starting PFNFNFP ligand to give a highly active catalyst 5.8 for the enantioselective transfer hydrogenation of acetophenone. This catalyst likely contains a PNNP ligand with amido and ene-amido functionalities. Only the presence of both functionalities in the structure results in high catalytic activity; the \textit{bis}(amine) complex 5.4, and the \textit{bis}(enamido) complex 5.5 require activation. The proposed structure of the amido(ene-amido) catalyst 5.8 is supported by its reaction with acid to give complex 5.7 that contains a PNNP ligand with an amine and imine functionality. Precatalyst 5.7 under our mild standard conditions leads to the most active catalyst known for the asymmetric reduction of acetophenone without activation period.

The determined activation parameters suggest that the catalytic reduction of acetophenone occurs via an outer-sphere mechanism. The determined KIE for the transfer of
the hydride to the carbonyl carbon indicates that the rate determining step may not involve a concerted hydride/proton transfer but rather a stepwise hydride addition then proton transfer mechanism. The kinetics studies provided rate constants for the proposed mechanism. DFT results that support the proposed mechanism over alternatives are in hand and will be published in near future.78

5.6 Experimental Section

5.6.1 General information

All manipulations that involved air- or moisture-sensitive materials were performed using Schlenk techniques or a glovebox under an argon or nitrogen atmosphere. Solvents of high purity (ACS grade or higher) were purchased from Caledon Laboratory Chemicals and were further degassed and dried using standard procedures prior to all manipulations and reactions.79 Deuterated solvents were purchased from Cambridge Isotope Laboratories, INC and distilled and dried over activated molecular sieves. Acetophenone was distilled under argon and stored under molecular sieves in a glovebox prior reduction reaction. The complex 5.2 was synthesised as described in Chapter 4.35 Other reagents used were purchased from commercial sources and utilized without further purification. NMR spectra of the samples that were prepared under argon in degassed solvents were recorded at ambient temperature and pressure using a 400 MHz Varian Gemini \(^{1}H\) (400 MHz), \(^{13}C\)\(^{1}H\) (100 MHz), and \(^{31}P\)\(^{1}H\) (161 MHz)]. \(^{1}H\) NMR spectra were internally referenced to tetramethylsilane (TMS, 0 ppm). \(^{13}C\) NMR spectra were internally referenced to the carbon resonances of the solvent. The ESI-MS data on samples in methanol/water were done on an AB/Sciem QStar mass spectrometer with an ESI source. The elemental analyses were performed at the Department of Chemistry, University of Toronto, on a Perkin-Elmer 2400 CHN elemental analyzer. Some complexes gave a low carbon analysis but acceptable hydrogen and nitrogen contents because of a combustion problem that is common for the compounds containing boron atoms.80
5.6.2 General procedure for the reduction of acetophenone using iron based precatalysts 5.2, 5.4 and 5.7

The stock solution 1 (SS1) was prepared by dissolving the precatalyst in acetophenone. The stock solution 2 (SS2) was prepared by dissolving KOtBu in i-PrOH. These solutions were used only after all the solids were completely dissolved and for less than two days. A required mass of the SS1 was added to a vial containing i-PrOH charged with a stirring bar and acetophenone to form mixture 1 (M1). A required mass of SS2 was added to a second vial containing i-PrOH to give mixture 2 (M2). In order to ensure a constant temperature of the experiment inside a glovebox, M1 and M2 were placed into a sand bath with a coil connected to the Fisher Scientific temperature control unit for 15 minutes (Figure 5.16). To initiate the reaction, M1 and M2 were efficiently mixed by transferring the solutions from vial to vial and placed into a sand bath attached to the stirring plate. The final concentrations of the reagents were adjusted to be as follows [acetophenone] = 0.412 M, [5.2], [5.4], or [5.7] = 6.73x10^{-5} M, [KOtBu] = 5.45x10^{-4} M and [i-PrOH] = 12.4 M (standard conditions). The samples were taken by injecting small portions of the reaction mixture into septa-sealed GC-vials containing aerated i-PrOH for efficient quenching of the reaction. Samples were analyzed using a Perkin Elmer Autosystem XL chromatograph with a chiral column (CP chirasil-Dex CB 25 m x 2.5 mm). Hydrogen gas was used as a mobile phase at a column pressure of 5 psi. The injector temperature was 250 °C, and the FID temperature was 275 °C. The amount of 1-phenethanol in the sample was determined relative to the acetophenone. The retention times of acetophenone, 1-phenethanol (R) and 1-phenethanol (S) were found to be 5.02, 8.73 and 9.42 min. respectively, if the temperature of the oven was kept at 130 °C.
Figure 5.16 A picture of the typical reaction setup for the kinetic studies.

### 5.6.3 Poisoning experiments

The procedure outlined in section 5.6.2. was used to prepare the reaction solutions with the initial concentrations of reagents that are summarized in Table 5.3. The reactions were conducted in an argon glovebox at a constant temperature of 28.0 °C. Figure 5.2 summarizes the results of the quenching experiments.

Table 5.3 A summary of the reagent concentrations used in attempted catalyst poisoning experiments.

<table>
<thead>
<tr>
<th>Run</th>
<th>[5.2] (M) x10⁻⁵</th>
<th>[KOTBu] (M) x10⁻⁴</th>
<th>[Acetophenone] (M) x10⁻¹</th>
<th>[i-PrOH] (M) x10</th>
<th>Hg(0) (eq.)</th>
<th>P(Me)₃ (eq.)</th>
<th>Time added (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>6.74</td>
<td>5.45</td>
<td>4.13</td>
<td>1.24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hg(0)</td>
<td>6.74</td>
<td>5.45</td>
<td>4.11</td>
<td>1.24</td>
<td>300</td>
<td>-</td>
<td>6.90</td>
</tr>
</tbody>
</table>
5.6.4 Variation of the base concentration

The procedure outlined in the section 5.6.2. was used to determine the maximum rates of the reaction at different concentrations of KOtBu. The concentrations of reagents used are summarized in Table 5.4. The rate of every reaction was obtained by plotting the concentration of 1-phenethanol with respect to time and determining the slope of the resulting tangent line (Figure 5.17). These rates along with the standard deviations were determined using the LINEST function in EXCEL (here and in the following plots) and are tabulated in Table 5.5. The dependence of rate of the reaction on the concentration of base is depicted on Figure 5.7 a. The dependence of catalyst activation on the base concentration is represented on Figure 5.7 b by plotting the x- intercept extrapolated from the linear region of 1-phenethanol vs time plots.

Table 5.4 The initial concentrations of the reagents that were used in the base dependence experiments.

<table>
<thead>
<tr>
<th>Run</th>
<th>[Acetophenone] (M) x 10^{-1}</th>
<th>[5.2] (M)x10^{-5}</th>
<th>[KOtBu] (M) x 10^{-4}</th>
<th>[i-PrOH] (M) x 10^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>4.13</td>
<td>6.74</td>
<td>5.44</td>
<td>1.24</td>
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<td>1</td>
<td>4.12</td>
<td>6.74</td>
<td>4.08</td>
<td>1.24</td>
</tr>
<tr>
<td>2</td>
<td>4.13</td>
<td>6.74</td>
<td>4.71</td>
<td>1.24</td>
</tr>
<tr>
<td>3</td>
<td>4.12</td>
<td>6.74</td>
<td>8.16</td>
<td>1.24</td>
</tr>
<tr>
<td>4</td>
<td>4.13</td>
<td>6.74</td>
<td>13.5</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Figure 5.17 The rate determination for base concentration dependence experiments (only linear portions of reaction profiles are shown).

Table 5.5 The rates of reaction at different concentrations of base.

<table>
<thead>
<tr>
<th>Run</th>
<th>[Base] (M) x10^{-4}</th>
<th>Rate (M/min) x10^{-2}</th>
<th>Rate Standard deviation (M/min) x10^{-4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stand.</td>
<td>5.44</td>
<td>3.15</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>4.08</td>
<td>3.13</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4.71</td>
<td>3.27</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>8.16</td>
<td>3.26</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>13.5</td>
<td>3.25</td>
<td>6</td>
</tr>
</tbody>
</table>

5.6.5 Variation of the precatalyst concentration
The procedure outlined in the section 5.6.2. was used to determine the dependence of reaction rate on the precatalyst concentration. The initial concentrations of all components of the reactions are summarized in Table 5.6. The slope of the linear dependence of 1-phenethanol on time represents the maximum rate of the reaction. These rates were determined from Figure 5.18 (Table 5.7). The standard deviations of the rates were determined from the relative linearity of the 1-phenethanol vs. time lines. The dependence of the maximum rates on precatalyst concentration was determined by plotting the rate of the reaction against the catalyst concentration (Figure 5.4, a). The dependence of catalyst activation rate on precatalyst concentration was estimated by plotting x-intercept values, which were obtained by extrapolation of the line through the linear region of the plot of phenethanol concentration vs the precatalyst concentration (Figure 5.4 b).

Table 5.6 The initial concentrations of reagents used for the precatalyst concentration dependence experiments.

<table>
<thead>
<tr>
<th>Run</th>
<th>[5.2] (M)x10^{-5}</th>
<th>[KOtBu] (M)x10^{-4}</th>
<th>[Acetophenone] (M) x10^{-1}</th>
<th>[i-PrOH] (M)x10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>6.74</td>
<td>5.45</td>
<td>4.13</td>
<td>1.24</td>
</tr>
<tr>
<td>1</td>
<td>1.53</td>
<td>5.45</td>
<td>4.12</td>
<td>1.24</td>
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<td>4.29</td>
<td>5.45</td>
<td>4.12</td>
<td>1.24</td>
</tr>
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<td>8.58</td>
<td>5.45</td>
<td>4.12</td>
<td>1.24</td>
</tr>
<tr>
<td>4</td>
<td>10.7</td>
<td>5.45</td>
<td>4.12</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Figure 5.18 The rate determination for precatalyst concentration dependence experiments (only linear portions of reaction profiles are shown).

Table 5.7 The rates of the precatalyst concentration dependence reactions.

<table>
<thead>
<tr>
<th>Run</th>
<th>Rate (M/min) x10^{-2}</th>
<th>Rate Standard deviation (M/min) x10^{-4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
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</tr>
<tr>
<td>1</td>
<td>1.21</td>
<td>1</td>
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<td>2</td>
<td>2.60</td>
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<td>3</td>
<td>3.88</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>4.17</td>
<td>9</td>
</tr>
</tbody>
</table>
The order with respect to the precatalyst concentration was determined by plotting $\ln(\text{Rate})$ vs $\ln([\text{catalyst}])$ and determining a slope of the obtained linear dependence (Figure S8). The order was found to be equal to $0.65 \pm 0.04$.

Figure 5.19 The determination of order of the reaction with respect to the catalyst.

5.6.6 Variation of the acetophenone concentration

The procedure outlined in Section 5.6.2. was used to determine the dependence of the maximum reaction rate on the acetophenone concentration. The initial concentrations of all components of the reactions are summarized in Table 5.8. The rates of reactions are equal to the slope of the linear part of the plot of $[1\text{-phenethanol}]$ vs time (Figure 5.20) and were determined (Table 5.9) and plotted in Figure 5.5, a. The standard deviations of the rate were determined from the relative linearity of the rate plots. The dependence of catalyst activation time on the concentration of acetophenone was estimated by plotting the $x$-intercept values from Figure 5.20 against the initial acetophenone concentrations (Figure 5.5, b).

Table 5.8 The initial concentrations of reagents used for the acetophenone dependence experiments.
<table>
<thead>
<tr>
<th>Run</th>
<th>[Acetophenone] (M)x10⁻¹</th>
<th>[5.2] (M)x10⁻⁵</th>
<th>[KOTBu] (M)x10⁻⁴</th>
<th>[i-PrOH] (M)x10⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>4.12</td>
<td>6.74</td>
<td>5.45</td>
<td>1.24</td>
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<td>1</td>
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<td>5</td>
<td>6.62</td>
<td>6.73</td>
<td>5.45</td>
<td>1.21</td>
</tr>
</tbody>
</table>

Figure 5.20 The maximum rate determination plots for the acetophenone concentration dependence experiments (only linear portions of reaction profiles are shown).

Table 5.9 The dependence of the maximum rates on the acetophenone concentration.
The procedure outlined in the section 5.6.2. (except that a certain amount of the acetone was added to the M1 prior to the initiation of the reaction) was used to determine the dependence of the reaction rate on acetone concentration. The initial concentrations of all of the reagents in the reaction mixture are tabulated in Table 5.10. The rates of every reaction were obtained by plotting the concentration of 1-phenethanol with respect to time (Figure 5.21). They are tabulated in Table 5.11. The rate dependence on the acetone concentration is presented in Figure 5.22. The dependence of the time required for the precatalyst activation on the acetone concentration was estimated by plotting x-intercept values from the plot in Figure 5.21 against the initial acetone concentrations Figure 5.6.

Table 5.10 The initial concentrations of reagents used for the acetone dependence experiments.

<table>
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<tr>
<th>Standard</th>
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<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.29</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>2.71</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3.46</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>3.59</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>4.00</td>
<td>5</td>
</tr>
<tr>
<td>Run</td>
<td>[Acetophenone] (M) x10^{-1}</td>
<td>[5.2] (M) x10^{-5}</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Standard</td>
<td>4.12</td>
<td>6.73</td>
</tr>
<tr>
<td>1</td>
<td>4.12</td>
<td>6.73</td>
</tr>
<tr>
<td>2</td>
<td>4.12</td>
<td>6.72</td>
</tr>
<tr>
<td>3</td>
<td>4.12</td>
<td>6.72</td>
</tr>
<tr>
<td>4</td>
<td>4.12</td>
<td>6.72</td>
</tr>
</tbody>
</table>

Figure 5.21 The rate determination for acetone dependence experiments (only linear portions of reaction profiles are shown).

Table 5.11 The maximum rates of the acetone dependence reactions.
<table>
<thead>
<tr>
<th>Run</th>
<th>[acetone] (M x10^2)</th>
<th>Rate (M/min) x10^2</th>
<th>Rate Standard deviation (M/min) x10^4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>0.00</td>
<td>3.29</td>
<td>9.5</td>
</tr>
<tr>
<td>1</td>
<td>4.12</td>
<td>3.06</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>8.42</td>
<td>2.71</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>1.24</td>
<td>2.59</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>1.67</td>
<td>2.40</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 5.22 The dependence of the maximum rate on the acetone concentration.

5.6.9 Derivation of the catalyst activation rate equation
The model for the catalyst activation can be described in terms of equations eq(2)-eq(6) (Scheme 5.3) as it follows from the kinetic data. The precatalyst iron complex \( \text{Fe}_p \) participates in an irreversible reaction with iso-propoxide \( (i\text{-PrO}^-) \) to give the active iron containing complex \( \text{FeTa} \) (eq(2)) and in two fast-established equilibria with the enolate of acetone \( \text{A}^e \) (eq(3)) and the enolate of acetophenone \( \text{S}^e \) (eq(4)) to give non-productive iron-enolate species \( \text{Fe-A}^e \) and \( \text{Fe-S}^e \). The formation of the enolates of \( \text{A}^e \) and \( \text{S}^e \) are described in terms of fast-established equilibria with the base, acetone (eq(5)) and acetophenone (eq(6)), respectively.

The rate of active catalyst formation can be described as follows:

\[
\frac{d[\text{FeTa}]}{dt} = k_{act} \text{[Fe}_p \text{][i Pr O}^-] 
\]

\text{eq(21)}

The equilibriums can be described as follows:

\[
K_{eq}^1 = \frac{[\text{FeA}^e]}{[\text{Fe}_p][\text{A}^e]} 
\]

\text{eq(22)}

\[
K_{eq}^2 = \frac{[\text{FeS}^e]}{[\text{Fe}_p][\text{S}^e]} 
\]

\text{eq(23)}

\[
K_{eq}^3 = \frac{[\text{A}^e][i \text{Pr OH}]}{[\text{A}][i \text{Pr O}^-]} 
\]

\text{eq(24)}

\[
K_{eq}^4 = \frac{[\text{S}^e][i \text{Pr OH}]}{[\text{S}][i \text{Pr O}^-]} 
\]

\text{eq(25)}

From eq(24):
\[
[A^e] = \frac{K_{eq}^3 [A][i Pr O^-]}{[i Pr OH]} \quad \text{eq}(26)
\]

From eq(25):
\[
[S^e] = \frac{K_{eq}^4 [S][i Pr O^-]}{[i Pr OH]} \quad \text{eq}(27)
\]

From eq(22) and eq(26):
\[
K_{eq}^1 = \frac{[i Pr OH][FeA^e]}{[Fe_p]K_{eq}^3 [A][i Pr O^-]} \Leftrightarrow [FeA^e] = \frac{K_{eq}^1 K_{eq}^3 [Fe_p][A][i Pr O^-]}{[i Pr OH]} \quad \text{eq}(28)
\]

From eq(23) and eq(27):
\[
K_{eq}^2 = \frac{[i Pr OH][FeS^e]}{[Fe_p]K_{eq}^4 [S][i Pr O^-]} \Leftrightarrow [FeS^e] = \frac{K_{eq}^2 K_{eq}^4 [Fe_p][S][i Pr O^-]}{[i Pr OH]} \quad \text{eq}(29)
\]

From mass balance it follows, with \([Fe_T]_0 = \text{total initial amount of 5.2}:
\[
[Fe_T]_0 = [Fe_{ta}] + [Fe_p] + [FeS^e] + [FeA^e] \quad \text{eq}(30)
\]

From eq(30), eq(28) and eq(29):
\[
[Fe_T]_0 = [Fe_{ta}] + [Fe_p] + \left(\frac{K_{eq}^1 K_{eq}^3 [Fe_p][A][i Pr O^-]}{[i Pr OH]} + \frac{K_{eq}^2 K_{eq}^4 [Fe_p][S][i Pr O^-]}{[i Pr OH]} \right) + \left(1 + \frac{[i Pr O^-]}{[i Pr OH]} \times (K_{eq}^1 K_{eq}^3 [A] + K_{eq}^2 K_{eq}^4 [S]) \right) \Leftrightarrow
\]
\[
[Fe_T]_0 - [Fe_{ta}] = [Fe_p] \left(1 + \frac{[i Pr O^-]}{[i Pr OH]} \times (K_{eq}^1 K_{eq}^3 [A] + K_{eq}^2 K_{eq}^4 [S]) \right) \Leftrightarrow
\]
\[
[Fe_p] = \frac{[Fe_T]_0 - [Fe_{ta}]}{1 + \frac{[i Pr O^-]}{[i Pr OH]} \times (K_{eq}^1 K_{eq}^3 [A] + K_{eq}^2 K_{eq}^4 [S])} \quad \text{eq}(31)
\]

From eq(11) and eq(31):
$$\frac{d[Fe_{Ta}]}{dt} = \frac{k_{ac} \{[Fe_{Ta}]_0 - [Fe_{Ta}]\} \times [iPrO^-]}{\left(1 + \frac{[iPrO^-]}{[iPrOH]} \times K_{eq}^{-1} K_{eq}^{-3} [A] + K_{eq}^{-2} K_{eq}^{-4} [S]\right)}$$  \hspace{1cm} \text{eq}(7)$$

5.6.10 The equilibrium constant determination

The equilibrium constant was found experimentally from the equilibrium concentrations of the reagents at the end of the reaction using high loadings of the catalyst \((c/s/b=1/1000/8)\). The results of the experiments are summarized in Table 5.12.

<table>
<thead>
<tr>
<th>Concentrations</th>
<th>Run 1</th>
<th>Run 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>[phenethanol] (M)</td>
<td>0.257</td>
<td>0.259</td>
</tr>
<tr>
<td>[acetophenone] (M)</td>
<td>0.0231</td>
<td>0.0207</td>
</tr>
<tr>
<td>[iPrOH] (M)</td>
<td>12.4</td>
<td>12.4</td>
</tr>
<tr>
<td>[acetone] (M)</td>
<td>0.257</td>
<td>0.259</td>
</tr>
<tr>
<td>Keq</td>
<td>0.230</td>
<td>0.262</td>
</tr>
</tbody>
</table>

Keq (avg) Standard deviation

$$\frac{[A]_{eq} \cdot [P]_{eq}}{[R]_{eq} \cdot [S]_{eq}} = K_{eq(28^0 C)} = 0.24 \pm 0.02$$
5.6.11 The determination of the deuterium kinetic isotope effect (KIE)

The rates of the catalytic reduction of acetophenone using $i$-PrOH, $i$-PrOD-$d_8$ and $i$-PrOD-$d_1$ were determined experimentally following the procedure described in Section 5.6.2. The initial concentrations of the reagents are summarized in Table 5.13. The formation of the 1-phenethanol as a function of time is summarized on a Figure 5.11. The rates of reactions were calculated along with a corresponding standard deviations using the LINEST function in EXCEL and are summarized in Table 5.14.

Table 5.13 Initial concentration of the reagents for the KIE experiments.

<table>
<thead>
<tr>
<th>Run</th>
<th>[Acetophenone] (M)</th>
<th>[Precat] (M) x10^{-5}</th>
<th>[KO$'$Bu] (M) x10^{-4}</th>
<th>[i-PrOH] (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard 1</td>
<td>0.412</td>
<td>6.75</td>
<td>5.44</td>
<td>12.5</td>
</tr>
<tr>
<td>Standard 2</td>
<td>0.412</td>
<td>6.75</td>
<td>5.44</td>
<td>12.5</td>
</tr>
<tr>
<td>Standard 3</td>
<td>0.412</td>
<td>6.74</td>
<td>5.44</td>
<td>12.5</td>
</tr>
<tr>
<td>$i$-PrOD-$d_1$ 1</td>
<td>0.412</td>
<td>6.74</td>
<td>5.44</td>
<td>12.4</td>
</tr>
<tr>
<td>$i$-PrOD-$d_1$ 2</td>
<td>0.413</td>
<td>6.74</td>
<td>5.44</td>
<td>12.5</td>
</tr>
<tr>
<td>$i$-PrOD-$d_8$ 1</td>
<td>0.412</td>
<td>6.74</td>
<td>5.45</td>
<td>12.4</td>
</tr>
</tbody>
</table>
Table 5.14 Maximum rates obtained for the KIE experiments.

<table>
<thead>
<tr>
<th>Run</th>
<th>Maximum rate (M/min) x10^2</th>
<th>Maximum rate standard deviation (M/min) x10^4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard 1</td>
<td>3.27</td>
<td>5</td>
</tr>
<tr>
<td>Standard 2</td>
<td>3.30</td>
<td>6</td>
</tr>
<tr>
<td>Standard 3</td>
<td>3.37</td>
<td>8</td>
</tr>
<tr>
<td><em>i</em>-PrOD-d_8 1</td>
<td>2.52</td>
<td>5</td>
</tr>
<tr>
<td><em>i</em>-PrOD-d_8 2</td>
<td>2.86</td>
<td>6</td>
</tr>
<tr>
<td><em>i</em>-PrOD-d_8 1</td>
<td>1.28</td>
<td>3</td>
</tr>
<tr>
<td><em>i</em>-PrOD-d_8 2</td>
<td>1.38</td>
<td>3</td>
</tr>
</tbody>
</table>

5.6.12 Determination of the thermodynamic parameters of the process

The influence of the temperature on the maximum rates of reaction was investigated by performing the catalytic reaction in a range from 291.15 to 314.05 K. The initial concentrations of the reagents are summarized in Table 5.15. The maximum rates of the reactions were determined by plotting the concentration of 1-phenethanol over time and finding a slope of resulting tangent line using LINEST function in EXCEL. The results are summarized in Table 5.15 and Figure 5.23.
Table 5.15 Initial concentrations of the reagents for temperature dependence experiments.

<table>
<thead>
<tr>
<th>Run</th>
<th>Temperature (K)</th>
<th>[Pretalyst] (M) x10⁻⁵</th>
<th>[Acetophenone] (M) x10⁻¹</th>
<th>[Base] (M) x10⁻⁴</th>
<th>[i-PrOH] (M) x10⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>300.15</td>
<td>6.74</td>
<td>4.12</td>
<td>5.44</td>
<td>1.24</td>
</tr>
<tr>
<td>1</td>
<td>292.15</td>
<td>6.74</td>
<td>4.12</td>
<td>5.45</td>
<td>1.24</td>
</tr>
<tr>
<td>2</td>
<td>296.15</td>
<td>6.74</td>
<td>4.12</td>
<td>5.44</td>
<td>1.24</td>
</tr>
<tr>
<td>3</td>
<td>298.15</td>
<td>6.74</td>
<td>4.12</td>
<td>5.44</td>
<td>1.24</td>
</tr>
<tr>
<td>4</td>
<td>303.15</td>
<td>6.74</td>
<td>4.12</td>
<td>5.44</td>
<td>1.24</td>
</tr>
<tr>
<td>5</td>
<td>306.25</td>
<td>6.74</td>
<td>4.12</td>
<td>5.44</td>
<td>1.24</td>
</tr>
<tr>
<td>6</td>
<td>314.05</td>
<td>6.74</td>
<td>4.13</td>
<td>5.45</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Figure 5.23 The maximum rates of the temperature dependence reactions

<table>
<thead>
<tr>
<th>Run</th>
<th>Temperature (K)</th>
<th>Rate (M/min) x10^{-2}</th>
<th>Rate Standard deviation (M/min) x10^{-4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>300.15</td>
<td>3.36</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>292.15</td>
<td>2.12</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>296.15</td>
<td>2.95</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>298.15</td>
<td>3.13</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>303.15</td>
<td>3.44</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>306.25</td>
<td>3.72</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>314.05</td>
<td>5.37</td>
<td>20</td>
</tr>
</tbody>
</table>

The resulting reaction profiles were mathematically simulated using the proposed model to obtain rate constant for individual steps of the reaction. Figure 5.9 shows the results of the simulations conducted using Igor Pro6 software (see details in the main part of manuscript).
The rate constants are summarized in Table 5.2. The rate constants were used in Eyring equation to determine activation parameters (Table 5.2) associated with each step of the reaction. Eyring-Polanyi plots are summarized on the Figure 5.24.

![Eyring-Polanyi plots of individual steps of the reaction.](image)

5.6.13 The synthesis of the ligand precursors (diphenylvinyl phosphine and diphenylvinyl phosphine oxide)

The procedures for the synthesis of the ligand precursors (diphenylvinyl phosphine and diphenylvinyl phosphine oxide) and for the preparation and reduction of O=P-N-N-P=O ligand were adopted with modifications from work of Rahman et al. and Cook et al. \(^{81,82}\)

**Diphenylvinyl phosphine oxide.** Chlorodiphenyl phosphine (5.45 mL, 30 mmol) was dissolved in 65 mL of THF under an Ar atmosphere. The resulting solution was cooled to -78°C. A solution of vinyl magnesium bromide in THF (1.6 M, 22.5 mL, 1.2 eq) was added drop-wise over the course of 30 min. The reaction mixture was brought to room temperature after the addition was complete and stirred for an additional 5 hours. The solvent was removed under vacuum and the resulting mixture was re-dissolved in hexanes to give a yellow solution.
and white precipitate that was filtered off. The solvent was removed from the remaining solution to give diphenylvinyl phosphine as yellow oil that was used without further purification.

The diphenylvinyl phosphine (1.25 mL) was dissolved in dichloromethane (60 mL). To the resulting solution a hydrogen peroxide solution (10% v/v, 11.7 mL) was added drop-wise and the solution was stirred in air overnight. After the reaction was completed (monitored by $^{31}$P $^1$H NMR of the reaction mixture with benzene-d$_6$ insert, product resonance found to be at 24 ppm) the product was extracted with dichloromethane and washed with water (3x20 mL). After drying with magnesium sulfate the solvent was removed on a rotary evaporator to give diphenyl vinylphosphine oxide as a white solid (1.11 g, Yield = 77 %).

$((S,S)-1,2$-diphenyl-ethylamine-$N,N'$-bis-diphenylethylphosphine oxide). The diphenylvinyl phosphine oxide (0.935 g, 4.09 mmol) and $(S,S)$-1,2-diphenyl-ethylamine (0.435 g, 2.05 mmol) were dissolved in dry $i$-PrOH (25 mL) in the Schlenk flask charged with a stirring bar. The reaction mixture was refluxed for 5 days to obtain complete conversion (determined by $^{31}$P $^1$H NMR of the reaction mixture with benzene-d$_6$ insert, product resonance detected at 31.8 ppm). The crude product $((S,S)$-1,2-diphenyl-ethylamine-$N$-bis-diphenylethlyphoshine oxide) was isolated by removal of the solvent under vacuum and used in the next step without further purification.

$((S,S)-1,2$-diphenyl-ethylamine-$N,N'$-bis-diphenylethylphosphine) $((S,S)$-1,2-diphenyl-ethylamine-$N,N'$-bis-diphenylethylphosphine oxide) (0.935 g, 1.40 mmol) and degassed triethylamine (0.892 g, 8.80 mmol) were dissolved in 40 mL of acetonitrile in a Schlenk flask charged with a stirring bar. The resulting mixture was cooled to 0°C and trichlorosilane (1.39 g, 10.3 mmol) was added dropwise. After 10 minutes the solution was brought to room temperature and refluxed for 1 day. At room temperature the reaction was quenched by addition of a degassed aqueous 10 % solution of NaOH. The solution was separated from the precipitate using the cannula method and solvent was evaporated to give a yellow-white solid. The solid was further purified by performing water/dichloromethane extraction under inert atmosphere. The organic phase was washed with water and dried with magnesium sulfate to give a crude product $((S,S)$-1,2-diphenyl-ethylamine-$N,N'$-bis-diphenylethlyphoshine) as an oily solid after solvent was removed under vacuum. The formation of the desired product was identified by $^{31}$P
\{^1\text{H}\} \text{NMR} \text{ that showed a single resonance at -20.3 ppm. Isolated product was used in further reactions without purification.}

5.6.14 Synthesis of Complex [Fe(CO)(Br)(Ph2PCH2CH2-N(H)-((S,S)-CH(Ph)CH(Ph)-N(H)-CH2CH2-PPh2)][BPh4] (5.4)

The P-N-N-P ligand (S,S)-1,2-diphenyl-ethylamine-\(N,N'\)-bis-diphenylethylphosphine (0.260 g, 0.410 mmol) was dissolved in 15 mL of acetonitrile in 20 mL vial charged with a stirring bar. Hexafluoroboron (0.138 g, 0.410 mmol) was added drop-wise to the reaction mixture as a solution in acetonitrile (3 mL) to give an instantaneous change in color from colorless to deep purple. After 3 hours the solvent was removed from the reaction mixture to give a deep purple solid that was mixed with potassium bromide (0.073 g, 0.61 mmol) and re-dissolved in acetone (15 mL) and placed under atmosphere of carbon monoxide (1.1 atm) and stirred overnight at 38°C to give a yellow solution with a white precipitate that was filtered through Celite. Solvent was removed under vacuum to give yellow solid that was re-dissolved in methanol (10 mL). A solution of NaBPh₄ (0.14 g, 0.41 mmol) in 3 mL of methanol was added drop-wise to give an instantaneous formation of the yellow precipitate. The precipitate was filtered and washed with methanol (3x1 mL), dried and washed with diethyl ether (3x2 mL) to give complex 5.4 as a yellow-orange solid (0.093 g, 20 % yield). Crystals suitable for the X-ray analysis were obtained by the diffusion of diethyl ether into solution of 5.4 in dichloromethane and methanol mixture. ^1\text{H} \text{NMR} (400 MHz, CD₂Cl₂) δ: 2.19-2.40 (m, 1H, PCH\(H\)), 2.45-2.64 (m, 1H, PCH\(H\)), 2.76-2.97 (m, 1H, PCH\(H\)), 1H, NCH\(H\)), 3.04-3.33 (m, 1H, PCH\(H\)), 1H, NCH\(H\)), 1H, NCH\(H\)), 3.62-3.86 (m, 1H, NCH\(H\)), 1H, NH), 4.15-4.30 (m, 1H, NC(Ph)\(H\)), 4.48-4.62 (m, 1H, NC(Ph)\(H\)), 5.05-5.20 (m, 1H, NH), 6.75-7.60 (m, 50H, Ar\(H\)); ^13\text{C} \{^1\text{H}\} \text{NMR} (100 MHz; CD₂Cl₂) δ: 33.24-33.62 (m, PCH₂), 34.78-33.62 (m, PCH₂), 46.21 (s,
NCH₂), 50.69 (s, NCH₂), 71.08 (s, NC(Ph)H), 75.28 (s, NC(Ph)H), 121.6 (s, BPh), 125.5-125.6 (m, BPh), 128.9-135.6 (m, ArCH), 135.0-135.9 (m, BPh), 163.9 (m, \( J_{CB} = 49.3 \) Hz, BPh), 216.6 (m, CO); \(^{31}\)P{\(^1\)H} NMR (161 MHz; CD₂Cl₂): 55.18 (d, \( J_{pp} = 39.3 \) Hz), 58.03 (d, \( J_{pp} = 39.3 \) Hz); HRMS (ESI-TOF) m/z calculated for [C₄H₄N₂P₂FeOBr]⁺: 799.1299, found: 799.1315. Anal. Calcd for C₆₇H₄₂N₂P₂FeBrOB: C, 71.87; H, 5.58; N, 2.5. Found: C, 71.52; H, 6.25; N, 2.58.

### 5.6.15 Synthesis of complex Fe(CO)(Ph₂PCH=CHN-((S,S)-CH(Ph)CH(Ph))-N-CH=CHPPh₂) (5.5)

![Diagram of complex Fe(CO)(Ph₂PCH=CHN-((S,S)-CH(Ph)CH(Ph))-N-CH=CHPPh₂) (5.5)](image)

In an argon glovebox a solution of KO\(^{1}\)Bu (sublimed, 0.013 g, 0.112 mmol) in 5 mL of benzene was added to a vial charged with a stirring bar containing complex 5.2 (0.050 g, 0.044 mmol). The solution instantaneously became green and a white precipitate was observed. The reaction mixture was stirred for an additional 10 min, filtered through the glass-frit and the solvent was evaporated from the resulting green solution to give a bright green powder. The powder was redissolved in 5 mL of hexanes upon the addition of a few drops of benzene. This solution was filtered through the Celite and the solvent was evaporated. Yield: 0.019 g, 59.3 %. \(^1\)H NMR (400 MHz, C₆D₆) δ: 4.49-4.57 (m, 1H, PCH), 4.59-4.68 (m, 1H, PCH, 1H, NC(Ph)H), 5.06-5.16 (m, 1H, NC(Ph)H), 6.94-7.50 (m, 30H, ArH), 7.31-7.51 (m, 2H, NCH); \(^{31}\)P{\(^1\)H} NMR (161 MHz; C₆D₆) δ: 68.9 (d), 68.6 (d) ppm \(^2\)\( J_{pp} = 25 \) Hz.

### 5.6.16 Synthesis of complex [Fe(CO)(Cl)(Ph₂PCH₂CH₂N(H)-((S,S)-CH(Ph)CH(Ph))-N=CHCH₂PPh₂)][BPh₄] (5.7)

![Diagram of complex [Fe(CO)(Cl)(Ph₂PCH₂CH₂N(H)-((S,S)-CH(Ph)CH(Ph))-N=CHCH₂PPh₂)][BPh₄] (5.7)](image)
$i$-PrOH (3 mL) was cooled to -25° in a freezer in an argon glovebox and added to a vial charged with stirring bar containing complex 5.2 (0.014 g, 0.020 mmol). The reaction mixture was stirred and allowed to warm up to 25°C. A gradual change of color of the solution was observed from green to orange-red over the course of 25 min of the reaction. The reaction was quenched with a 1M solution of HCl in diethyl ether (excess added), which instantaneously gave a yellow solution. The solvent was evaporated from the reaction mixture to give a yellow solid as a product. The $^{31}$P{$^1$H} NMR spectrum of the crude product in CD$_2$Cl$_2$ showed that the major product had doublet resonances at 55.15 and 64.92 ppm with $J_{pp} = 39.4$ Hz, which was accounted for more than 85% of the material present. The compound was further purified. The crude product was dissolved in 1 mL of methanol followed by the addition of a solution (1 mL) of NaBPh$_4$ (0.013 g, 0.038 mmol) in methanol. The product was isolated as a yellow solid (yield: 0.011 g, 53%). $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$: 2.61-2.77 (m, 2H, NCH$_2$), 3.09-3.33 (m, 2H, PCH$_2$ amine side), 3.81-3.95 (m, 2H, PCH$_2$ imine side), 4.38-4.49 (m, 1H, C(Ph)H amine side), 4.57-4.69 (m, 1H, NH), 4.93-5.02 (m, 1H, C(Ph)H imine side), 7.70-7.82 (m, 1H, N=C), 6.84-7.67 (m, 50H, ArH); $^{13}$C{$^1$H} NMR (100 MHz; CD$_2$Cl$_2$) $\delta$: 46.72-47.11 (m, PCH$_2$), 49.46 (s, HNCH$_2$), 49.51-49.92 (m, PCH$_2$), 76.50 (s, NC(Ph)H), 77.69 (s, NC(Ph)H), 121.3 (s, BPh), 124.-125.1 (m, BPh), 129.9-135.6 (m, ArCH), 135.2-136.2 (m, BPh), 163.7 (m, $J_{CB}=49.3$ Hz, BPh), the resonances for the carbonyl (CO) and imine (N=C) carbons were not detected in the spectra due to their longer relaxation times compared to the other carbons in the structure and the lower intensity of the signal due to the expected multiple splitting by $^{31}$P nuclei; $^{31}$P{$^1$H} NMR (161 MHz; CD$_2$Cl$_2$): 55.15 (d, $J_{pp}=39.4$ Hz), 64.92 (d, $J_{pp}=39.4$ Hz); HRMS (ESI-TOF) m/z calculated for [C$_{43}$H$_{40}$N$_2$P$_2$FeOCl]$^+$: 753.1648, found: 753.1637.

5.6.17 General procedure for the reduction of acetophenone using complex 5.5

In an argon glovebox complex 5.5 (0.019 g, 0.027 mmol) was dissolved in benzene (2.00 g). The resulting green, clear solution (0.050 g) was added to vials charged with stirring bars. The benzene was evaporated to give solid samples of complex 5.5 (0.48 mg, 0.000665 mmol) in the vials. These were used in reduction reactions with acetophenone and $i$-PrOH. Run 1: A solution of acetophenone (0.476 g, 3.96 mmol) in $i$-PrOH (7.192 g) was prepared in an argon glovebox and the temperature of the solution equilibrated to 28°C. The solution was added to the vial with complex 5.5 to initiate the reaction. The reaction progress was monitored
by taking samples of the reaction mixture and quenching them by injection into aerated \(i\)-PrOH in a sealed GC vial. **Run 2:** The solvent \(i\)-PrOH (7.192 g) was thermostatted at 28°C and added to the vial containing complex 5.5 and stirred for 4 min. Acetophenone (0.476 g, 3.96 mmol) was added to the reaction mixture to initiate the reaction. The reaction progress was monitored in a similar fashion as in Run 1. **Run 3:** Acetophenone (0.476 g, 3.96 mmol) was thermostatted at 28°C and added to the vial containing complex 5.5 and stirred for 4 min. Isopropanol (7.192 g) was added to the reaction mixture to initiate the reaction. The reaction progress was monitored in a similar fashion as in Run 1. **Run 4:** Same as Run 2, but the activation reaction with \(i\)-PrOH was left for 12.4 min before adding the substrate.

### 5.7 Appendices

Equations used in the numerical simulation of the kinetic processes by use of the program Igor Pro 6:

\[
\begin{align*}
  r_0 &= \frac{k_{act}[i \text{Pr } O^-][Fe_{p}]-[Fe_{T,a}]}{1+rac{[i \text{Pr } O^-]}{[i \text{Pr } OH]}(K_{eq}^{A} + K_{eq}^{2}K_{eq}^{4}[S])} \\
  r_1 &= k_1[i \text{Pr } OH][Fe_{p}]	imes\Delta t \\
  r_{-1} &= k_{-1}[A][Fe_{p}H]	imes\Delta t \\
  r_2 &= k_2[S][Fe_{p}H]	imes\Delta t
\end{align*}
\]

(eq 10)

(eq 11)

(eq 12)

(eq 13)
\[ r_{-2} = \frac{k_1k_2[P][Fe_{eq}]}{K_{eq} \times k_{-1}} \times \Delta t, \]  

(eq 14)

\( K_{eq} \) was experimentally determined at different temperatures

\[ [Fe_{eq}]_i = [Fe_{eq}]_{i-1} - r_0 \]  

(eq 15)

\[ [Fe_aH]_i = [Fe_aH]_{i-1} + r_i - r_{-1} - r_2 + r_{-2} \]  

(eq 16)

\[ [Fe_a]_i = [Fe_a]_{i-1} - r_i + r_{-1} + r_2 - r_{-2} + r_0 \]  

(eq 17)

\[ [A]_i = [A]_{i-1} + r_i - r_{-1} \]  

(eq 18)

\[ [S]_i = [S]_{i-1} - r_2 + r_{-2} \]  

(eq 29)

\[ [P]_i = [P]_{i-1} + r_2 - r_{-2} \]  

(eq 20)
5.8 References

Chapter 6: Conclusions and Future work

6.1 Conclusions

Phosphino-aldehydes are useful building blocks for the preparation of tri- and tetradeutate PNN and PNNP ligands, which are commonly utilized in the synthesis of transition metal catalysts.\(^1\) The amphoteric nature of these compounds, especially when the phosphorus atom is nucleophilic, makes them unstable towards unselective polymerization reactions. This makes their preparation and handling a challenging task. It was previously observed that Ph\(_2\)PCH\(_2\)C(O)H can react with an acid to give a cyclic dimeric phosphonium salt 2.1, which is moisture and air stable solid.\(^2\) The reaction can be reversed if base is reacted with the phosphonium dimer to give Ph\(_2\)PCH\(_2\)C(O)H in high yield. For this reason, the phosphonium salts can useful synthetic precursors of the phosphino-aldehydes.

We investigated this reaction to show that this highly chemoselective cyclization is driven by the thermodynamic stability of the product. The phosphonium salts with aryl substituents at the phosphorus were prepared by the reaction of corresponding potassium phosphides with X-(CH\(_2\))\(_n\)CH(OR)\(_2\) (where X is bromide or chloride and n is 1, 2 or 3) followed by the addition of acid. The variation of the carbon distance between phosphorus and carbonyl carbon from 1 to 3 resulted in the formation of different phosphonium salts: dimers with six-membered rings (compounds [PPh\(_2\)CH\(_2\)CHOH]\(_2\)(Br)\(_2\) 2.1 and [PCy\(_2\)CH\(_2\)CHOH]\(_2\)(Br)\(_2\) 2.3), a tetramer with a 16-membered ring (compound [PPh\(_2\)CH\(_2\)CH\(_2\)CHOH]\(_4\)(Br)\(_2\) 2.5) and a monomer with a five-membered ring (compound [PPh\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CHOH]Br 2.7), respectively. The procedure for the formation of the phosphonium dimers 2.3, which are prepared from alkylphosphines, does not require the addition of a strong base unlike the synthesis of 2.3, 2.5 and 2.7, since the phosphine is nucleophilic enough to undergo \(S_N2\) reaction with bromoacetaldehyde diethyl acetal. High diastereoselectivity of oligomerization was observed in the process of formation of the dimers with electron-donating alkyl substituents at the phosphorus (dimers 2.3a and 2.3d) and tetrameric oligomer 2.5.

We attempted to utilize the phosphonium dimer 2.1 in the condensation reaction with ethylene diamine in order to prepare the corresponding PNNP ligand. The high stability of the
phosphonium salt under acidic conditions prevented any reaction even at elevated temperatures. Under basic conditions the reaction was not selective giving rise to multiple products. The cause of unselective reactivity was the nucleophilic nature of the phosphorus atom. In an attempt to suppress the nucleophilic reaction at the phosphorus, we attempted to use the protection methodology utilizing BH₃. This did not solve the problem, since the protecting group was sensitive to the diamine, causing deprotection.

In order to suppress the reactivity of the phosphorus, a Lewis acidic iron(II) precursor was added to the reaction of the phosphino-aldehyde and the diamine. The resulting product was an iron(II) bis-tridentate complex containing PNN ligands [Fe(PNN)₂](BF₄)₂ 3.6. A library of similar complexes with different diamines were prepared in high yield (75-79 %), isolated as BPh₄ salts and fully characterized. These complexes are chiral at the metal center. The formation of only one diastereomer was observed when the template reaction was conducted with chiral diamines, indicating that the reaction is highly stereospecific.

In order to obtain likely catalyst precursors, complexes containing PNNP ligands were prepared by conducting the template reaction at elevated temperatures in acetonitrile or using methanol as the solvent at room temperature. A range of complexes trans-[Fe(NCMe)₂(PNNP)](BPh₄) 3.7 with various diamines incorporated in the backbone of the ligand was prepared and isolated as BPh₄ salts in moderate to high yield (54-86 %). All of the complexes were fully characterized.

The solution of complexes 3.7 containing the enantiopure diamine (R,R)-dp en in acetone can be reacted with carbon monoxide (CO) to give the mono-carbonylated complex trans-[Fe(NCMe)(CO)(PNNP)](BPh₄)₂ 4.8 in a good yield after the selective precipitation with BPh₄⁻. This complex is highly active and enantioselective when activated with eight equivalents of base in the ATH reactions of ketones and an aldimine using 2-propanol as a solvent and reducing agent. The scope of the reaction was investigated to show that the reaction is very general. Bulkier arylketones were reduced with higher enantioselectivity, up to 99% (S) for PhCOTBu, but at lower rates. The TOF depended on the electronic properties of the aryl groups on the ketones with electron withdrawing chlorine in the para position giving the higher rates. The chemoselective reductive of an alpha-beta unsaturated ketone to the unsaturated alcohol provides evidence for an outer sphere bifunctional mechanism.
Complexes that are analogous to 4.8, which contain a bromide ligand trans to the carbonyl and PNNP ligands with different diamines incorporated into the backbone of the ligand (trans-[Fe(CO)(Br)(PNNP)]BPh₄ 4.9a-4.9d), were synthesized and characterized in order to compare their activity and enantioselectivity in the ATH of acetophenone using 2-propanol as a reducing agent and solvent. The activities of precatalyst 4.8 and 4.9b indicate that ligand trans to CO has no effect on the reaction rate. This implies that the activation of the precatalyst involves decoordination of the ligand that is trans to CO. All of the complexes show very high TOF (up to $2.0 \times 10^4$ h⁻¹) and enantioselectivity (up to 82 % ee), using very low catalyst loadings (0.016 % relative to the substrate). The comparison of the TOF of complexes 4.9a-4.9d showed that the catalytic activity of the complexes increases as the steric influence of the groups in the backbone of ligand increases.

The mechanism of the ATH of acetophenone as a model substrate and precatalyst 4.9a was investigated. The rates dependences of the 1-phenethanol formation on the initial concentrations of the reagents were determined. These dependencies were used to propose a mechanistic model of the process, which was used to derive coupled differential rate laws for the elementary steps of the catalytic process. The extent of 1-phenethanol production with time was calculated using these rate laws in numerical simulations. A consistent set of the rate constants was found to give a good fit of the experimental and the simulated reaction profiles. This implies that the proposed model effectively describes the catalytic process. Simulations were also used to show that the formation of the active species is a prolonged process.

A similar approach was used to determine the rate constants of individual steps of the process at different temperatures. This data was used to determine the activation parameters of individual steps of the reaction from Eyring–Polanyi plots. From these results we determined that under experimental conditions (high concentration of 2-propanol relative to the acetophenone) the rate-limiting step of the reaction is the transfer of the hydride to the substrate.

In order to propose possible structures of the catalytically active species, the process of precatalyst activation was investigated. The reaction of the precatalyst with a non-nucleophilic base in benzene as the solvent resulted in the formation of complex (S,S)-[Fe(CO)(PPh₂CHCHNCHPhCHPhNCHCHPPh₂)] 5.5, which was partially characterized. This complex showed comparable catalytic activity in the process of ATH of acetophenone without
the addition of base to the activity displayed by 5.2 activated by base under otherwise identical conditions. The activation period was observed in both reactions indicating that 5.5 needs to be activated prior to the catalytic cycle to take place; thus it is not within the catalytic cycle. The preactivation of 5.5 with 2-propanol resulted in the formation of the active species, which showed high catalytic activity in the reaction without the activation period. We proposed that the activation of the precatalyst involves the reduction of the imine functionality of the ligand backbone, which causes the activation period.

To verify this assumption complex 5.4 identical to 5.2 but with a saturated PNPN ligand backbone was synthesised and fully characterized. This complex when activated with base was found to be significantly less active for the ATH of acetophenone compared to the 5.2, indicating that the reduction of both imines in the ligand of 5.2 does not lead to the active catalytic species.

Complex 5.5 was reacted with 2-propanol for 25 minutes to cause the solution of the reaction to change from a green to an orange-red colour. The reaction was quenched with HCl in diethyl ether. Complex trans-(S,S)-[Fe(CO)(Cl)(PPh₂CH₂CH₂NHCHPhCHPhNCHCHPPh₂]BPh₄ 5.7 was isolated as the main product of this reaction and fully characterized. From the structure of 5.7 it follows that one of the imine functionality of the ligand was stereospecifically reduced by 2-propanol. Complex 5.7 was found to be an extremely active catalyst precursor for the ATH of acetophenone (TOF = 55,000 h⁻¹ at 25% conversion) when activated with base. No induction period was observed, indicating that the deprotonation of 5.7 gives an active species in an instantaneous reaction.

From the structure of 5.7 we assumed that one of the active species contains a PNPN ligand with amido and ene-amido functionalities ([Fe(CO)(PPh₂CH₂CH₂NCHPhCHPhNCHCHPPh₂] 5.8). Only the presence of both functionalities in the structure results in high catalytic activity; the bis(amine) complex [Fe(CO)(Br)(PPh₂CH₂CH₂NHCHPhCHPhNHCH₂CH₂PPh₂]BPh₄ 5.4, and the bis(ename) complex 5.5 require activation.

The determined activation parameters suggest that the catalytic reduction of acetophenone occurs via a mechanism where a proton and hydride are transferred from an iron hydride complex to the ketone in the outer coordination sphere. The determined KIE for the transfer of the hydride to the carbonyl carbon indicates that the rate determining step may not involve a concerted hydride/proton transfer but rather a stepwise mechanism involving first
hydride addition and then proton transfer. The kinetics studies provided rate constants for the proposed mechanism. DFT results that support the proposed mechanism over alternatives are in hand and will be published in near future.³

6.2 Future work

Chiral iron(II) complexes containing PNNP ligands that were described in this thesis are the most efficient iron-based catalysts for the ATH of ketones when activated by base. Their activities and enantioselectivities are comparable and in case of 5.2 are higher compared to the best Ru-based catalysts.⁴ Nevertheless, the catalyst performance still need to be improved in order to be feasible for the industrial scale applications.⁵,⁶

The mechanistic studies that were presented in Chapter 5 are important for further developments in the ligand design. Complex 5.7, which we assume requires only to be deprotonated in order to produce an active species, showed extremely high TOF for the ATH of acetophenone. On the other hand, its synthesis is very low yielding and inefficient. For this reason, the main direction in the development of industrially applicable catalyst based on iron is to develop the synthetic protocol, which will give complex 5.7 and similar complexes containing the important functionality in the ligand structure in high yield. In order to efficiently synthesize a library of such compounds the following synthetic pathway can be proposed.

The template reaction of the diamines and the phosphino-aldehydes when conducted at low temperature in acetonitrile allows a selective mono-functionalization of the diamines (Chapter 3). Complexes 6.1 (Scheme 6.1) can be reduced using various mild reducing agents to give bis-tridentate complexes 6.2 containing PNN ligands with an amine group connecting carbon and nitrogen. The addition of the equivalent of the iron(II) precursor and phosphino-aldehyde of choice in MeOH would potentially give the complex containing tetradentate ligand. Following mono-carbonylation will give the desired complexes. Our group is currently investigating the reactions in Scheme 6.1. The activity of these complexes in the ATH of ketones will be determined.
Scheme 6.1 Proposed synthesis of new iron(II) complexes.

The catalysts that were described in this thesis can be also useful in other catalytic transformations such as hydrogenation using molecular hydrogen and imine reductions. Recently, Beller and coworkers reported that an in situ formed iron catalyst derived from the iron carbonyl clusters and chiral PNNP ligand (Scheme 6.2), was particularly active and enantioselective in the process of the transfer hydrogenation of imines using 2-propanol as a reducing agent.\(^7\) It would be important to explore reactivity of our complexes in this transformation.

Scheme 6.2 ATH of imines described by Beller and coworkers.
6.3 References