Proton-responsive pyridine-based ligands: Synthesis, coordination chemistry and catalysis

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Chapter 1

The Reactivity and Application of Cooperative Bifunctional Phosphinomethylpyridine, Pyridone and Pyrazole Ligands in Catalysis
1.1 Introduction

Catalysis as used by mankind dates back to the dawn of civilization, when people started to produce alcohol from fermentation. Nowadays, catalysts are indispensable for society as they are applied in the majority of industrial processes to produce a variety of chemicals for e.g. pharmaceuticals, fuels and plastics. Catalysts affect chemical reactions in an efficient, economical and environmentally friendly way, as they can increase the rate at which a reaction proceeds, but can also selectively produce only one product, thereby preventing side reactions and the production of byproducts or waste. Catalysts do not change the thermodynamics (i.e. the outcome), but change the kinetics (which comes from the ancient Greek “movement”).

In homogeneous catalysis, reactions occur in solution, and often consist of transition metals that are surrounded by ligands. The ligands, generally organic molecules, influence the properties of the metal center, and indirectly steer the activity and selectivity of the catalyst. Traditionally, ligands act merely as spectators rather than actors, and thus only modify the reactivity of the metal center by their steric properties and electronic donating/accepting abilities, but do not actively participate by undergoing bond making and breaking processes themselves. In biological systems, enzymes exploit protein-based ligands or other organic co-factors in combination with earth-abundant metals for cooperative substrate activation. In the active site, these ligands often participate directly in a bond activation reaction and may undergo a reversible chemical transformation. In synthetic chemistry and especially catalysis, so-called cooperative ligands have gained a lot of interest over the past decade, by collaborating in a synergistic way with the metal to facilitate a chemical process. This concept of metal-ligand cooperation (MLC) is a rapidly expanding field of homogeneous catalysis and this chapter provides an overview of different types of cooperative ligands along with their corresponding metal complexes that have been influential for the systems discussed in this thesis.

1.2 Cooperative vs. bifunctional vs. proton-responsive

Nowadays, cooperative ligands go by many names as they are also called “reactive”, “bifunctional” or “non-innocent”. The additional groups they bear are able to change the properties of the ligand, but the assistance depends on their specific functionality, for which they can be divided into the following categories:

1. Proton-responsive ligands; capable of accepting or donating one or more protons.
2. Hydrogen-bonding ligands; implying partial proton transfer or substrate orientation
3. Electron-responsive ligands; capable of gaining or losing one or more electrons, also called redox-active.
4. Photo-responsive ligands; capable of undergoing changes upon irradiation.
5. Ligands that have molecular recognition.
In this thesis, the focus lies on proton-responsive ligands in combination with 2nd row late transition metals (Ru, Rh, Pd). The first example of such systems dates back to 1985, where a cyclopentadienone-ruthenium complex was applied in the hydrogenation of ketones (Scheme 1).\textsuperscript{5,6} The hydrogenation of ketones is among one of the most widely studied reactions in chemistry and especially the catalytic hydrogenation is interesting as it is atom-efficient. Here, dihydrogen is activated through MLC by the Ru ($\eta^4$-Ph$_4$C$_4$CO)(CO)$_2$ complex, Shvo’s catalyst, which generates RuH($\eta^5$-Ph$_4$C$_5$OH)(CO)$_2$. In this form, the proton and hydride can be transferred to the carbonyl of a ketone, forming the corresponding alcohol. The transition in this system is redox neutral, as the formal oxidation state of the ruthenium does not change, but it is rather the cyclopentadienone ligand that undergoes a charge switch from neutral to mono-anionic.

![Scheme 1. The first example of a cooperative ruthenium complex.\textsuperscript{5,6}](image)

Notable breakthroughs in the asymmetric ketone hydrogenation were realized by Noyori and co-workers in 1995, using several cooperative Ru(II)-diamine complexes (Scheme 2).\textsuperscript{7-10} These catalysts also contain a nucleophilic hydride and an adjacent ligand-based electrophilic proton. The mechanism is promoted by a cyclic transition state, in which the proton and hydride transfer occurs simultaneously via an outer-sphere mechanism. Especially the BINAP/1,2-diamine complexes are extremely successful, as they show very high conversion rates and ee’s for the hydrogenation of ketones. Moreover, these robust catalysts promote the enantioselective reaction under base-free conditions.\textsuperscript{9,10} Once more, the transition is redox neutral, as the amine ligand switches between neutral and anionic. The ability to donate or accept protons without change of formal charge is one of the trademarks of metal-ligand cooperativity and this feature has quickly evolved since.

![Scheme 2. Ru-diamine complexes, especially with BINAP/1,2-diamine ligands, are excellent catalysts for the hydrogenation of ketones, for which the transition state goes via an outer-sphere mechanism.](image)
1.3 Tridentate lutidine-based pincer ligands

Among several other ligand structures that are actively involved in metal substrate interactions, lutidine-based pincer complexes are particularly interesting because of their versatility. Within a decade, the range of reactions facilitated by these systems has expanded very rapidly, and new applications are still being discovered. The concept of these cooperative pincer complexes is depicted in Scheme 3 and is based on an aromatization/dearomatization process of the neutral ligand scaffold. The ligand backbone is susceptible to selective deprotonation at the methylenic position, hereby inducing dearomatization of the pyridine ring. Upon dearomatization, the ligand undergoes a formal charge switch from neutral to monoanionic, and can be reprotonated by the addition of a substrate. This process occurs with no formal change in the metal oxidation state. The chemistry of three cooperative ligand systems, namely PNP, PNN and bipy-PNN pincers, with ruthenium, rhodium and palladium will be discussed in this paragraph (Scheme 3, box).11-13 Interesting derivatives based on aminopyridine building blocks have also been extensively probed with a large set of (late) transition metals, including Ru and Pd.14-17 Furthermore, these lutidinyl or picolinyl-derived ligands have also been investigated in combination with several other metals (e.g. Fe, Co, Ni).18-21 However, these explorations are beyond the scope of this thesis and will not be discussed.

Scheme 3. Schematic representation of the cooperativity of pyridine-based pincer ligands via an aromatization/dearomatization process, and three types of pincers (box).

1.3.1 PNP complexes

The PNP ligand motif as derived from lutidine was first reported in 1971 by the group of Nelson22 and it took nearly 20 years before its cooperative characteristics were observed.23 These proton-responsive ligands have long been overlooked and underappreciated as a tool for catalytic activity, as another 20 years would pass before these ligands would be truly recognized. Early studies on the application of these complexes focused on the ruthenium-catalyzed acceptorless dehydrogenation of alcohols into ketones (Scheme 4), yet no remarks were made regarding the contribution of the ligand.24 The first reactivity was observed when complex 2 was deprotonated with a strong base (complex 3) and subsequently treated with H₂, generating complex 4 (Scheme 5).25
Not only dihydrogen can be heterolytically activated by dearomatized complex 3, but also O-H, B-H, C-H and N-H bonds. The activation of N-H bonds is demonstrated for electron-poor anilines and the breaking of the N-H bonds seems to be reversible, as complex 3 is still observed in the presence of an excess of amine. This suggests that the barrier for N-H bond activation is low enough for the reaction to occur rapidly at room temperature and that product amines could be eliminated in potential catalytic cycles based on such systems. Moreover, the activation of ammonia is displayed through deuteration experiments. Although NH₃ prefers to be coordinated rather than activated, DFT studies show that the barrier for exchange between the two formations is low and accessible at room temperature (Figure 1).

The activation of O-H bonds is the first step in many reactions catalyzed by complex 3 (Scheme 6). An efficient method is developed for the formation of imines, important compounds with a diverse reactivity, from alcohols and amines. This atom-efficient reaction occurs under neutral conditions with the liberation of molecular hydrogen as the only byproduct. A variety
of alcohols and amines can be applied and high turnovers can be achieved. Complex 3 is also highly active in the acceptorless dehydrogenative coupling of primary alcohols into aldehydes and esters, and secondary alcohols into their corresponding ketones. The dehydrogenative cyclization of diols to lactones is achieved as well.26

![Scheme 6. Possible products from the activation of R-OH bonds with complex 3.](image)

When the dehydrogenation of alcohols was probed at low temperatures, the resulting aldehyde was not found in solution, but it was coordinated to the catalyst instead.31 NMR experiments revealed a new mode of MLC, which involves a Ru-O bond and a C-C bond between the aldehyde and the ligand backbone. This binding process was found to be highly reversible and experiments with carbon dioxide displayed the same reactivity.32-34 The group of Pidko investigated the catalytic hydrogenation of CO₂ in combination with this deprotonated system, but they discovered that pathways involving the ligand backbone are not contributing to the catalytic cycle. The product in which CO₂ is activated by MLC is actually an inactive state that inhibits catalytic performance. However, the reversible hydrogenation of CO₂ by this highly active system shows the highest TOFs up to date (1,1·10⁶ h⁻¹), producing formic acid under mild conditions.

Another example of this versatile complex illustrates the facile addition of boranes to complex 3, which resulted in the Lewis acidic boron atom to bind to the ligand, whereas the hydride coordinates to the ruthenium center.28 This demonstrates that not only protons can bind to the methylene spacer of the ligand backbone, but this feature will be discussed further on.

The first Rh(I)PNP complexes were described in 2007,35,36 but the reactivity they displayed was not based on MLC. Cooperativity for such complexes was only displayed in the activation of H-H,37 arene C-H37-38 and aniline N-H39 bonds but no catalytic applications have been reported thus far.

The PNP ligands are much more valuable in combination with palladium precursors. Although MLC is not exhibited in those systems, Pd(II)PNP Ph⁶ is a highly active catalyst for the intramolecular hydroamination of a range of aminoalkenes (Scheme 7).40-44 The reactions are performed at room temperature and the products were obtained in high yields and with high selectivity.

A recent publication showed how the stereoselectivity could be controlled by using a P-stereogenic pincer complex (Figure 2). Complex 7 was used in the asymmetric intramolecular hydroamination of amino-1,3-dienes, in which the desired products were obtained in high yields and with excellent regioselectivities, showing that chiral N-heterocycles can be obtained from this process at room temperature.

Figure 2. Complex 7 is highly active in the asymmetric hydroamination of amino-1,3-dienes.

The first example of reactive ligands in palladium PNP complexes was shown in 2009 by van der Vlugt et al. They coordinated the ligand via transmetalation of cationic AgPNP to different Pd precursors which afforded cationic Pd(II)PNP tBu complexes. Mono-deprotonation of these species with NaN(SiMe₃)₂ provided their neutral analogues and the reactivity of these complexes was investigated in the Suzuki-Miyaura coupling of bromoarenes and phenylboronic acid pinacol ester. Besides mono-deprotonation, cationic Pd(II)PNP systems are also able to undergo double deprotonation, generating an anionic complex (Scheme 8).

An excess of MeLi to either 8 or 9 leads to the methylated anionic complex 10, which is easily and irreversibly reprotonated to the neutral species with only a trace of water or methanol (Scheme 10). Conversely, the neutral species can be reversible reprotonated to the cationic analogue. As metal hydride species are important reactive intermediates and also participate in numerous fundamental organometallic reactions, both the cationic (8), neutral (9) and anionic (11) Pd species were reacted with hydrido-compounds to generate the three metal-hydride equivalents (12, 13 and 14).
1.3.2 PNN complexes

Complex 16 was prepared by the group of Milstein, as they were aiming to improve the catalytic activity of the dehydrogenation of alcohols.\textsuperscript{49} Beside the reactive methylene, this novel complex has an additional feature, \textit{i.e.} the nitrogen donor is hemilabile, and this enables the ligand to create a vacant coordination site on the metal center if necessary (Scheme 9). The importance of this characteristic is demonstrated in the dehydrogenation of alcohols. Whereas complex 2\textsuperscript{iPr} (\textit{i.e.} \textit{i}Pr substituents on the P-donors of PNP ligand) gave only moderate yields (67.2%), complex 15 and 16 showed outstanding performance (99%).

Complex 16 (or 15 in the presence of base) is a very versatile catalyst, as it is able to efficiently catalyze a range of reactions. Not only can it catalyze the dehydrogenation of alcohols into ketones and esters,\textsuperscript{49-51} but also the reverse reaction, \textit{i.e.} the hydrogenation of esters into alcohols (Scheme 10).\textsuperscript{25} Likewise, secondary alcohols can be acylated by using non-activated esters under neutral conditions,\textsuperscript{52} and organic carbonates, carbamates and formates are efficiently hydrogenated as well, indicating alternative routes to methanol based on CO\textsubscript{2} and CO.\textsuperscript{53}

\textbf{Scheme 8.} Formation of cationic, neutral and anionic palladium hydride complexes.

\textbf{Scheme 9.} Complex 15 has two cooperative characteristics: the ligand backbone is susceptible for deprotonation (left), and the \textit{NEt}_2 donor is hemilabile, which may create a vacant site for substrate coordination (right).
Related to the formation of esters from alcohols is the formation of amides from alcohols and amines\textsuperscript{54} and the formation of cyclic dipeptides,\textsuperscript{55} which are both isolated in high yields using 15. In case of the dipeptides, a method was developed using the dehydrogenative self-coupling of β-amino alcohols. Surprisingly, when the closely related PNP complex 2 was applied, pyrazines were selectively formed, showing ligand-controlled selectivity (Scheme 11).

Regarding the ability of the ligand to participate in substrate activation reactions, not only protons can bind to the methylene spacer of the ligand backbone.\textsuperscript{56} Like complex 3, facile addition of boranes to complex 16 resulted in the Lewis acidic boron atom to bind to the ligand, whereas the hydride coordinated to the ruthenium center.\textsuperscript{28} The group of Sanford describes the cooperative activation of CO\textsubscript{2} at 16 via C-C coupling with the ligand in combination with the formation of a Ru-O bond.\textsuperscript{57,58} As was seen for PNP complex 3, they observed that the C-C bond-forming event at the phosphine arm is reversible at room temperature, but formation of the C-C bond at the nitrogen arm is irreversible, signifying the kinetic and thermodynamic product, respectively (Scheme 12). Both isomers are catalytically competent for the hydrogenation of carbon dioxide to formate in the presence of base with TOF’s up to 2200 h\textsuperscript{-1}.\textsuperscript{59} Formate is the anionic form of formic acid, which may provide an interesting storage-release system for the energy carrier H\textsubscript{2}.\textsuperscript{60}
Complex 16 was also reported as an efficient mediator for the sunlight-driven splitting of water into O₂ and H₂. Water was activated in a similar fashion as alcohols, which resulted in the reprotonation of the ligand backbone, generating complex 17 (Scheme 13). Thermal activation of a second water molecule leads to the formation of H₂ and dihydroxo Ru species 18. When N₂O was used as O-atom transfer agent, complex 18 was formed even more rapidly and also more cleanly.

Upon photolysis of complex 18, hydrogen peroxide was liberated in a reductive elimination step from the two hydroxo ligands, and rapid intramolecular proton transfer from a non-detected intermediate regenerates complex 16. Labeling studies showed that the O-O bond remains intact via disproportionation of H₂O₂, generating light-induced oxygen. No comments were made regarding the potential role of the hemilabile ligand arm, which could lead to the hypothesis that other cooperative tridentate ligands systems could afford the same activity.
Complex 16 has also been applied by de Vries and co-workers as catalyst for the room temperature isomerization of alkenes. The isomerization process was found to be slow, but the rate increased when isopropanol was used as additive. The activity at low temperature is surprising, as most other catalysts operate at higher temperatures. Coordination of β-substituted nitriles to 16 led to tautomerization of the methine proton from the P-arm to the N-arm of 16. The nitrile nitrogen coordinates to the Ru center, while the adjacent carbon binds to the N-side of ligand backbone (Scheme 14). Subsequent oxa-Michael addition of alcohols to the nitrile gave the product in good yield, with no external base required.

![Scheme 14](image)

**Scheme 14.** Intermolecular oxa-Michael additions to unsaturated nitriles via MLC.

Like the PNP ligand, only one system is known for the PNN ligand in combination with rhodium. For this complex 19 (and Rh(PNP)PPr as well) N-H activation of anilines is observed, which is accomplished via metal-ligand cooperation (Scheme 15). The obtained anilido complex can subsequently react with ancillary ligands such as PEt₃ or CO to eliminate anilines and regenerate the dearomatized complex. However, no catalytic application has been discovered for this system yet.

![Scheme 15](image)

**Scheme 15.** Activation of anilines by metal-ligand cooperation.
1.3.3 Bipy-PNN complexes

In 2010, the group of Milstein prepared a new reactive bipyridine-based PNN pincer. When coordinated to Ru(II) (Figure 3), it efficiently catalyzes the selective hydrogenation of amides to form amines and alcohols under mild pressure and neutral conditions.\(^{65}\)

![Figure 3. Bipyridine-based PNN pincer complexes.](image)

Both complexes 20 and 21 exhibit remarkable catalytic activity in numerous hydrogenation reactions, such as the hydrogenation of organic carbonates, carbamates and formates into methanol,\(^{53}\) but also the hydrogenation of urea derivatives into amines and methanol,\(^{66}\) and the hydrogenation of biomass-derived cyclic di-esters into 1,2-diols.\(^{67}\) The scope of these Ru(II)-PNN complexes can be extended beyond hydrogenation reactions to e.g. the dehydrogenative cross-coupling between primary alcohols and secondary alcohols under neutral conditions.\(^{68}\) Also the formation of tertiary amides and dihydrogen by dehydrogenative coupling of primary alcohols with secondary amines\(^{69}\) and the coupling of nitriles and amines to form imines have been accomplished with this system.\(^{70}\) Complex 21 was also found to be an efficient catalyst for the transformation of primary alcohols into carboxylates with catalyst loadings of only 0.2 mol% and water as the oxygen source.\(^{71}\)

The synthesis of N-heterocycles has attracted much attention, because of their prevalence in natural products and drugs. A protocol described by Milstein and co-workers enables an environmentally friendly, atom-economical and efficient condensation reaction that converts readily available starting materials under mild conditions. Complexes 20 and 21 are able to catalyze the direct synthesis of N-heterocycles via acceptorless dehydrogenative coupling of aminoalcohols and secondary alcohols,\(^ {72,73}\) generating substituted pyridines, quinolines and pyrroles in high yields.

The group of de Bruin\(^ {74}\) was the first to coordinate this bipyridine PNN ligand to a rhodium precursor, generating complex 22 (Scheme 16). Upon reaction with sodium azide, complex 23 is formed, from which the dearomatized open-shell nitride-bridged rhodium complex 24 could be isolated, which exhibits predominant nitridyl radical character.
Scheme 16. A dearomatized open-shell nitride-bridged rhodium complex is formed from a (PNN)Rh(I)azide.

1.4 Hydroxy-pyridine / Pyridone

As was already shown by Shvo’s catalyst, ligands functionalized with hydroxyl groups have attracted significant interest for the design of versatile complexes. Lately, hydroxypyridines or pyridones have gained increasing attention because of their interesting properties and excellent coordination abilities. The equilibrium between the two tautomers has a significant influence on the electronic properties of the ligand, and thus the metal. Among the different hydroxypyridines, 2-hydroxypyridine is of particular interest. These ligands are well-known in coordination chemistry since the 1960s, but its cooperative nature was only revealed twenty years ago. Due to its close proximity to the metal center, the hydroxyl group can transfer protons via a proton-relay, which significantly may significantly aid the process of metal-ligand bifunctional activation. 2-Hydroxypyridine was coordinated to an iridium precursor, generating complex 25 (Scheme 17). Upon the addition of strong acid HX (X = Cl, Br, I) halogen-hydride species 26 was formed, wherein the oxygen atom is protonated. This is followed by dissociation of the –OH from the metal, which allows the halide to coordinate. For 26, two isomers are observed with the hydroxyl group hydrogen bonding to the halide and hydride, respectively. Addition of a weak base (NEt₃) to either 26X or 26H quantitatively yields 25 within 1 minute. This suggests that the exchange of isomers also occurs almost instantaneously, as the dissociation of XNHEt₃ only happens from 26X.

Scheme 17. Hydrogen bonding of a hydroxy-pyridine to a metal-hydride or -halide.

Hydroxy-pyridine ligands have a low tautomeric barrier for proton transfer and they can therefore be deprotonated relatively easily by a mild base. Furthermore, the hydroxyl group is in close proximity to the metal center, which may significantly aid the process of metal-ligand bifunctional activation, compared to the earlier discussed PNP/N systems. It is suggested that the combination of smooth proton transfer and the more accessible site will diminish the
necessity of high temperatures and high pressures. This is demonstrated by Kelson and Phengsy, who discovered that ruthenium complex 27 is an efficient transfer hydrogenation catalyst for ketones under basic conditions and with isopropanol or formate as H$_2$-donor (Figure 4). A TOF of 780 h$^{-1}$ was achieved and the complex also proved to be selective for ketones in the presence of alkene substrates.

![Figure 4. Complex 27 efficiently catalyzes the transfer hydrogenation of ketones.](image)

A bidentate bipyridine ligand with two hydroxyl groups at both 6-positions, 6,6'-dihydroxy-2,2'-bipyridine, has been reported. Whereas bipyridine itself had already acquired a legendary status in both coordination chemistry and catalysis, this small adjustment was only reported in 2011 by two groups independently. In combination with rhodium (28, Scheme 18, left), its bifunctional behavior was demonstrated and the efficient carbonylation of methyl acetate was presented. When coordinated to a ruthenium precursor (29, Scheme 18, right), the transfer hydrogenation of selected ketones was reported in various media, including isopropanol, methanol and water. Analogous Ir, Rh and Ru-pianostool complexes have been efficiently used in the acceptorless alcohol dehydrogenation of benzyl alcohol and the aldehyde-water shift reaction, with high selectivities up to 95%.

![Scheme 18. Formation of rhodium and ruthenium dihydroxy-bipyridine complexes.](image)

After these publications on hydroxy-substituted bipyridines, the number of metal complexes and applications of this system increased rapidly. Iridium complex 30 with a proton-responsive bipyridine ligand was published (Figure 5, left), that is capable of converting hydrogen and carbon dioxide to formic acid. This system is energy-efficient and green because it operates near ambient conditions, uses water as a solvent, produces high-pressure, CO-free hydrogen, and uses pH to control hydrogen production or consumption. A TOF of 228,000 h$^{-1}$ at 90 °C was observed, and a TON of 308,000 at 80 °C.
Figure 5. Structure of binuclear complex 30 (left) and catalyst 31 (right).

Quickly after complex 30 was published, Fujita and Himeda and co-workers designed iridium complex 31 (Figure 5, right), with the 6,6'-dihydroxy-2,2'-bipyridine ligand, which was successfully applied in the hydrogenation of CO$_2$ in water as well.$^{84}$ Since then, this complex has been shown to have a large variety of applications. Additional publications appeared on the hydrogenation of CO$_2$ in water,$^{85}$ but also on formic acid dehydrogenation in which CO-free dihydrogen is produced with a TOF of 39,500 h$^{-1}$. The cobalt analogue of complexes 29 and 31, which is water-soluble as well, exhibits notable catalytic activity in the hydrogenation of CO$_2$ to formate in aqueous bicarbonate media and at moderate temperature.$^{88}$ Although the TOF and TON are not as high as for the iridium complexes, the activities are definitely promising for earth-abundant metal catalysts.

Not only formic acid can be used as a hydrogen storage system, but also N-heterocycles. Iridium catalyst 31 was demonstrated to be highly active and selective in the perdehydrogenation of 2,6-dimethyldecahydro-1,5-naphthyridine and perhydrogenation of 2,6-dimethyl-1,5-naphthyridine with release and uptake of five molecules of H$_2$ (Scheme 19). Only a few systems are known that use a single metal catalyst for both the dehydrogenation and hydrogenation, and this system proved to be very efficient.$^{89}$

Scheme 19. Iridium complex 31 efficiently catalyzes both the perdehydrogenation and hydrogenation of naphthyridines.

Conversion of complex 32 with NaOH in water generated anionic complex 33, which is highly soluble in water. The interconversion between complex 31, 32 and 33 is achieved by changing the pH value. When refluxing a mixture of methanol and water in the presence of 33, a mixed gas of dihydrogen and carbon dioxide was formed. Formation of the products turned out to be
dependent on the different species. Complex 33 forms H₂, whereas CO₂ formation can be described to 32. By keeping the pH at high levels, hydrogen production of 84% yield was obtained.⁹⁰

**Scheme 20. pH-Dependent interconversion of iridium complexes 31, 32 and 33.**

A catalytic system was developed for the dehydrogenative oxidation of alcohols with the watersoluble complex 31. This allowed the catalysis to be performed in aqueous media, under mild conditions. Primary alcohols were converted to aldehydes, whereas secondary alcohols could be converted into ketones, marking this as the first example of dehydrogenative oxidation of alcohols in aqueous media.⁹¹ This chemistry allows easy access to several glucocorticoid derivatives, which may be useful in studies of steroid metabolism or as possible chemotherapeutics and drug conjugates.⁹² Lactones can be produced from the dehydrogenative lactonization of diols, producing 2 equivalents of dihydrogen as byproduct⁹³ and the selective dehydrogenation of the biopolymer lignin was conducted as well, with dihydrogen being trapped by 1-decene.⁹⁵ Furthermore, a new prototype for hydrogen storage was designed based on the interconversion between acetone and isopropanol. First, the dehydrogenation of isopropanol was conducted, affording acetone and dihydrogen. When a balloon of hydrogen gas was attached to the Schlenk flask, isopropanol was formed in 100% yield (Scheme 21).⁹⁴

**Scheme 21. Reversible transformation between isopropanol and acetone in one Schlenk, via the dehydrogenation and hydrogenation, catalyzed by complex 31.**

Iridium catalyst 31 shows also high activity in water oxidation, in combination with pH switching.⁹⁶-⁹⁷ This framework offers insight into how hydrogen bonds and acid/base-sensitive groups can impact organometallic catalysis. These features and pH-dependent solubility properties can enable green chemistry applications based upon water oxidation, as the activities are the highest ever reported for iridium catalysts.
Sulfonamide derivatives display biological activities, and especially N-alkylsulfonamides are important as they are active as inhibitors for tuberculosis or as pro-drug for cancer therapy. The formation of N-alkylsulfonamides used to involve sulfonyl chlorides, which are highly toxic and cannot be stored for long. A new catalytic system based on complex 32 shows the N-alkylation of poor nucleophilic sulfonamides with alcohols as alkylating agents. The catalysis is performed in water and the catalytic activity was found to be depending on the hydroxyl units of the ligand. The group of Li also reported the alkylation of ketones with primary alcohols using this iridium complex, generating α-alkylated ketones. The reactions are conducted under mild conditions and in air. Besides α-alkylation, this complex also exhibits high levels of catalytic activity for the α-methylation of ketones with methanol. Recently, they designed a new strategy for the synthesis of α-alkylated ketones via a tandem acceptorless dehydrogenation/α-alkylation from secondary and primary alcohols (Scheme 22). Compared to their previously reported methods, this approach includes complete selectivity for α-alkylated ketones and is performed under more environmentally benign conditions.

![Scheme 22](image)

**Scheme 22.** α-Alkylated ketones are synthesized via a tandem acceptorless dehydrogenation/α-alkylation from secondary and primary alcohols, catalyzed by 32.

Recently, two related tridentate bifunctional ligands and ruthenium complexes thereof were presented. Both 6,6'-dihydroxy-terpyridine (34) and bis(2'-hydroxy-6'-iminopyridyl)isoindoline (35) are rigid pincer-type ligands with two reactive sites and their tautomerism provides accessible proton donors or acceptors in the second coordination sphere of the metal center. Complex 34 (Figure 6) efficiently catalyzes the transfer hydrogenation of a variety of ketones in isopropanol and, moreover, the reduction of carbonyl groups was catalyzed in the presence of substituted olefins, showing high chemoselectivity. Complex 35 displays high activity in the hydroboration of aryl nitriles, producing diborylamines under mild conditions. The catalytic activity of this complex is one of the fastest reported for ketone hydroboration at room temperature (initial TOF = 1.2(3) s⁻¹).
Figure 6. Tridentate hydroxy-pyridine complexes 34 and 35 catalyze the transfer hydrogenation of ketones and the hydroboration of nitriles, respectively.

1.5 Pyrazoles: β-NH-based bifunctional catalysts

Related to the hydroxy-pyridine/pyridone ligands are N-H acidic pyrazoles, as they exhibit a similar fashion of reversibly donating protons when part of a metal complex. They have been used as ligands for a while, and also their ability to be deprotonated has been well-known. However, this feature was only applied for catalytic reactions in 2010. Coordination of an N-H pyrazole to a transition metal brings the β-NH group in close proximity to the metal site, and it becomes even more acidic due to the coordination of the Lewis-acidic metal site to the pyrazole moiety (Scheme 23). Most reported structures reveal an extended hydrogen-bonded network that involves the uncoordinated N-H group of the pyrazole, coordinated halides or solvent molecules.

Scheme 23. Interconversion between a pyrazolato and a pyrazole, with reversible protonation of the β-nitrogen.

The group of Thiel was the first to prepare ruthenium complexes based on bidentate and tridentate N-H acidic pyrazole ligands, and apply them in catalytic studies (Figure 7). They demonstrate the formation of ruthenium complexes that bear both the acidic N-H and a ruthenium hydride, and prove the activity of these complexes in the hydrogenation and transfer hydrogenation of acetophenone.

Figure 7. Three different Ru(II)pyrazole complexes use MLC in transfer hydrogenation.
A dinuclear ruthenium complex was described, with an analogous tridentate bis-pyrazolylpyridine as reported by Thiel and co-workers. Complex 39 is the first bimetallic ruthenium complex that is crystallographically characterized, with one of the β-N atoms of the pyrazole arms being coordinated to the other ruthenium center, leaving only one cooperative site available (Figure 8). The transfer hydrogenation of a variety of ketones with isopropanol is catalyzed very efficiently, even with 0.02 mol% catalyst loading.\textsuperscript{106} In combination with ruthenium, the parent tridentate ligand and substituted pyrazoles demonstrated the ability of direct and stepwise double deprotonation. The substituted ligands generate monomeric complexes involved in hydrogen bonding. The parent ligand however, is bridged between two ruthenium centers. Reaction of complex 36\textsuperscript{Ir} in reaction with O\textsubscript{2} afforded a side-on coordinated peroxo ligand, whereas dinitrogen coordinates end-on.\textsuperscript{107}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Reprinted with permission,\textsuperscript{106} copyright 2011 American Chemical Society. A dinuclear ruthenium complex of bis-pyrazolepyridine.}
\end{figure}

Kuwata and Ikariya reported the formation of iridium complex 40 and describe its well-defined deprotonation-reprotonation process, and also in relation to its activity in the catalytic intramolecular hydroamination of aminoalkenes.\textsuperscript{108} The activated olefin undergoes nucleophilic attack of the amine, which is assisted by secondary interactions of the pyrazolato ligand. Subsequent proton transfer from the pyrazole ligand generates the cyclization product in nearly quantitative yield (Scheme 24).
The combination of first row transition metals with bis-pyrazole pyridine ligands have recently also been reported. Several iron, cobalt and manganese species were synthesized\(^{109,110}\), of which a metal-ligand bifunctional iron complex is able to cleave the N-N bond of (substituted) hydrazines. This leads to facile reduction and oxidation of hydrazine, generating ammonia and dinitrogen (Scheme 25).\(^{111}\)

Iron complex 41 and ruthenium complex 42 bearing a novel tridentate ligand with two different functionalities have been reported recently (Scheme 26).\(^{112}\) One side arm consists of a proton-responsive pyrazole, while the other contains the hemilabile diethylamine donor. However, when examined in the catalytic hydrogenation of acetophenone, the use of 42 leads to only 36% of product formation and complex 41 exhibited no catalytic activity at all (complex 36 afforded a yield of 86%). Nonetheless, this unsymmetrical ligand is very fascinating and further work should find a suitable catalytic application.
Scheme 26. Unsymmetrical complexes 41 and 42 consist of both a proton-responsive pyrazole and an hemilabile diethylamine donor.

1.6 Aim and outline of the thesis

Cooperative systems have gained a lot of interest in the last decade. Such reactive complexes have proven their effectiveness in atom-economical activation reactions and they exhibit remarkable catalytic activity in a range of transformations and under mild conditions. In this thesis, the development of several bidentate and tridentate types of pyridine-based ligands is described. The coordination to mainly 2\textsuperscript{nd} row late-transition metals is studied, along with the behavior of their bifunctional character and application in several catalytic transformations.

In Chapter 2 the synthesis of a bidentate PN-ligand is described as well as its coordination to PdCl(Me)(cod) and [Rh(CO)\textsubscript{2}(\mu-Cl)]\textsubscript{2}. The resulting complexes show ligand backbone reactivity relevant to N-H activation, which leads to novel Pd(II)- and Rh(I)-amido complexes and they are applied in the catalytic intramolecular hydroamination of aminoalkenes. The next two chapters discuss in detail novel tridentate PNN(O) ligands that feature two different reactive sites, i.e. a phosphinomethyl arm and a hydroxy-pyridine functionality. The acidity of the unequal donors is shown by reactions with bases of different strength and site-selective dearomatization can be achieved. In Chapter 3 the coordination to ruthenium is described. These complexes are explored in the cooperative dehydrogenation of formic acid, the dehydrogenative coupling of alcohols into esters and in the dehydrogenative coupling of alcohols and amines into amides. Chapter 4 shows the coordination of the PNN(O) ligands to different Rh(I) and Pd(II) precursors. The rhodium complexes are applied in the transfer hydrogenation of ketones, whereas the palladium analogues have been studied in the intramolecular hydroamination of aminoalkenes.

Chapter 5 describes the formation of tridentate NNN ligands and their coordination chemistry with several 1\textsuperscript{st} row (Fe and Co) and 2\textsuperscript{nd} row (Ru, Pd) transition metals. The ligand can be doubly deprotonated, which is a rare feature. The ruthenium complex is studied in the transfer hydrogenation of ketones and the activity of the cobalt and palladium complexes is examined in the catalytic intramolecular hydroamination of both aminoalkenes and aminoalkynes.
1.7 References