Proton-Responsive Pyridine-Based Ligands. Synthesis, Coordination Chemistry and Catalysis

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Summary

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Synthesis, Coordination Chemistry and Catalysis

Catalysts are indispensable for society as they are applied in the majority of industrial processes to produce e.g. pharmaceuticals, fuels and plastics. Catalysts 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 side products or waste, resulting in more efficient, atom-economical and environmentally benign processes. In homogeneous catalysis, the catalyst often consists of a transition metal that is surrounded by ligands. 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 they do not actively participate in bond making and breaking processes. 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 bond activation processes and may undergo a reversible chemical transformation. In synthetic chemistry and especially catalysis, reactive ligands may be envisioned to operate in a synergistic way with the metal to facilitate a chemical process. This concept of metal-ligand cooperation (MLC) has gained a lot of interest over the past decade and is currently a rapidly expanding field of homogeneous catalysis.

The research described in this thesis is focused on the development of new metal complexes bearing different proton-responsive ligand systems. More specifically, several bidentate and tridentate types of pyridine-based ligands are described, which exhibit a cooperative character in their own specific way. The coordination to mainly 2nd row late-transition metals (Ru, Rh, and Pd) is studied, along with the behavior of their bifunctional character and application in several catalytic transformations. **Chapter 1** provides an overview of different types of reported cooperative ligands based on phosphinomethylpyridines, pyridones and pyrazoles (Figure 1), along with their corresponding metal complexes. These systems have been influential for the research described in this thesis and are therefore reviewed in detail, along with the aims for the thesis itself.

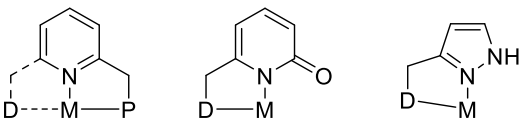
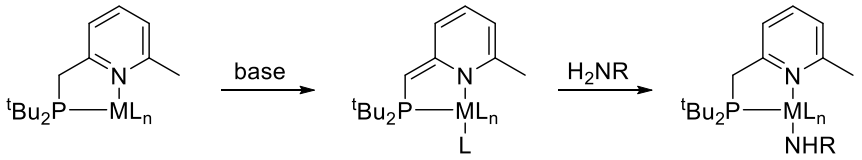


Figure 1. *General structure of a phosphinomethylpyridine, pyridone and pyrazole ligand, coordinated to a metal center.*

In **Chapter 2** a bidentate reactive phosphinomethylpyridine is described as well as its coordination to $Pd(CH_3)(Cl)(cod)$, $[Rh(CO)_2(\mu\text{-}Cl)]_2$, and $[Rh(acetone)_2(coe)_2]BF_4$. Tridentate PNP pincer analogues are known, but the use of a bidentate ligand allows for an additional vacant site at the metal center that could be utilized for further reactivity. Deprotonation of the resulting complexes with a strong base provided the ligand-activated complexes that could be efficiently stabilized by coordination of various additional phosphine ligands or solvent molecules (Scheme 1). Backbone reactivity is shown in N-H activation, as amines can be activated using the dearomatization-rearomatization strategy of this ligand. This resulted in the formation of novel Pd(II)- and Rh(I)-amido species.



Scheme 1. *Deprotonation of these complexes results in stabilized dearomatized complexes that can undergo activation of N-H bonds via MLC.*

Application of these bidentate complexes in the catalytic intra- and intermolecular hydroamination of aminoalkenes, which we envisioned to have a benefit over their tridentate analogous, was unfortunately unsuccessful, suggesting that coordination of a substrate *trans* to the phosphorus atom of the ligand is not a productive intermediate to acquire the desired reactivity.

Chapters 3 and **4** describe the synthesis and coordination properties of novel tridentate PNN(O) ligands that feature two different reactive sites, *i.e.* a phosphinomethyl arm and a hydroxy-pyridine functionality (Figure 2). The acidity of the unequal reactive sites is shown by bases of different strength, which lead to site-selective dearomatization. These systems could benefit from their more accessible cooperative site compared to analogous PNP pincer systems.

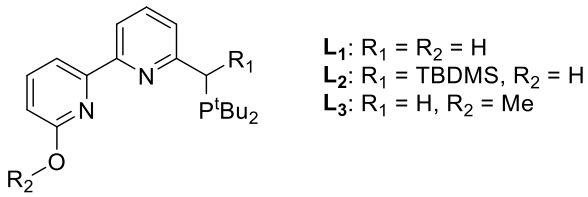
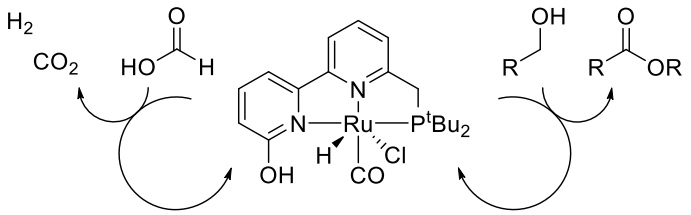


Figure 2. *General structure of the ligands discussed in Chapters 3 and 4.*

In **Chapter 3** the synthesis of the ligands is described, as well as their coordination to ruthenium. As expected, selective deprotonation of Ru**L1**, having both a hydroxyl and a benzylic acidic proton, occurs with both weak and strong bases, whereas Ru**L3**, the O-methyl

protected variant of **L1**, was only deprotonated by the stronger bases. Application of Ru**L1** in the dehydrogenation of formic acid resulted in rather poor turnover frequencies, but did produce clean, CO-free dihydrogen. It also turned out to be a robust catalyst, as it did not decompose after several reactions. Using Ru**L1** in the dehydrogenative coupling of alcohols into esters, resulted in 90% conversion for benzyl alcohol and full conversion for 1-butanol (Scheme 2). The more challenging dehydrogenative coupling of benzyl alcohol and benzyl amine into benzyl benzamide led only to small amounts of amide, as the main product proved to be the ester.

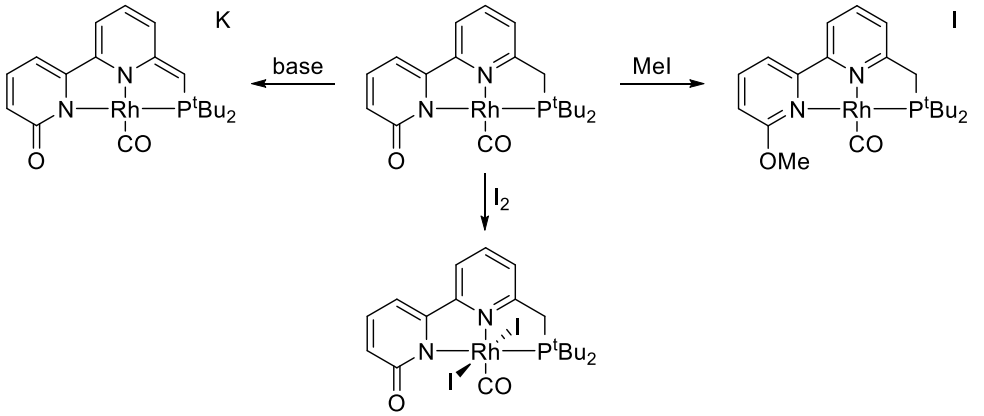


Scheme 2. *Application of ruthenium complex Ru**L1** in the dehydrogenation of formic acid (left) and dehydrogenative coupling of alcohols into esters (right).*

Calculations indicate that this ligand system should have enhanced reactivity compared to the parent pincers, which is not observed experimentally. The reason why the catalytic activity is not higher, especially in the formic acid dehydrogenation, remains unknown. The calculations we have performed only concern the step that involves the formation of dihydrogen. Whereas the results indicate that this step is indeed lower in activation energy, it implies that another step of the catalytic cycle is higher in energy, or a competing, non-productive pathway is active. For example, coordination of the substrate or activation of the O-H bond could be challenging steps, but those stages have not been calculated.

Chapter 4 describes the coordination of these PNN(O) ligands to different Rh(I) and Pd(II) precursors. Depending on the rhodium precursor, spontaneous deprotonation of the pyridone side arm to generate an anionic ligand or dissociation of the halide from the precursor material was observed. Additionally, these complexes proved susceptible to (further) deprotonation (dearomatization) upon reaction with both weak or strong bases, even generating the formation of an anionic doubly deprotonated species. Oxidative addition of molecular iodine to these complexes gives rise to the formation of Rh(III) complexes. Addition of iodomethane illustrates the reactive nature of the ligand, as the methyl moiety reacts with the pyridone to form the methoxy derivative (Scheme 3). We envisioned these novel complexes to have a benefit from their hydroxyl-functional group as cooperative site compared to analogous pincer systems. However, application of these rhodium complexes in the transfer hydrogenation of acetophenone (with 2-propanol as hydrogen donor) demonstrated moderate activity for only some of the complexes.

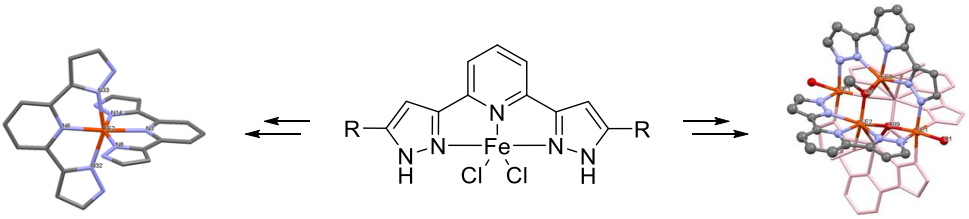
The palladium complexes were studied in the catalytic intramolecular hydroamination of (*N*-substituted) aminoalkenes, but unfortunately no cyclization was observed (isomerization of the starting material was commonly detected). The envisioned advantage of the additional pyridone site over known systems failed to give the desired reactivity. One plausible reason might be steric hindrance induced by the *tert*-butyl groups on the phosphorus donor, preventing coordination of the substrate double bond and/or proton-transfer from the amino moiety.



Scheme 3. *Deprotonation of the rhodium complex leads to the doubly deprotonated species (left), oxidative addition of I_2 generates a Rh(III) complex (bottom) and addition of iodomethane forms the methoxyl derivative of the ligand (right).*

In **Chapter 5** we discuss the formation of tridentate NNN ligands and their coordination chemistry with several 1st row (Fe, Co) and 2nd row (Ru, Pd) transition metals. This ligand structure can be doubly deprotonated, and also possesses a relatively facile reversible process of proton transfer compared to the previously discussed phosphinomethylpyridines. Due to the close proximity of its reactive sites to a given metal center and the relatively easily deprotonation by mild bases, this may significantly aid the process of metal-ligand bifunctional activation.

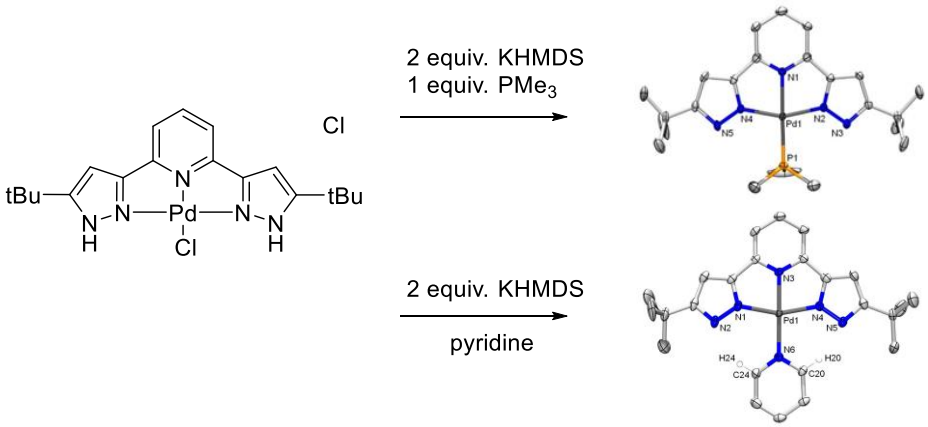
Coordination of the ligands to $Fe(II)Cl_2$ smoothly leads to the five-coordinated iron complexes, but subsequent deprotonation of the pyrazolyl moieties produces a mixture of products, including the desired deprotonated complexes. Formation of homoleptic species and even hexanuclear structures is also observed. The latter ones are thermodynamically more stable than the deprotonated complex (Scheme 4).



Scheme 4. *Deprotonation of the iron complexes leads to undesired byproducts.*

When coordinated to ruthenium, this ligand showed activity in the transfer hydrogenation of acetophenone. The analogous complex with protected cooperative sites was not able to convert acetophenone, demonstrating the assistance of its proton-responsive sites during the catalysis.

The palladium complex can be doubly deprotonated and is stabilized by different co-ligands such as PMe_3 and pyridine (Scheme 5). Furthermore, a rare Pd(IV) species can be obtained via the oxidative addition of I_2. A trigonal bipyramidal cobalt(II) complex shows to be stable under deprotonation conditions. Reduction to Co(I) led to a disproportionation and formation of similar homoleptic complex as was observed for iron.



Scheme 5. *Stabilization of the deprotonated complex by trimethylphosphine or pyridine.*

Application of the Pd complexes in the intramolecular hydroamination reaction of a CBz-functionalized aminoalkene resulted in a yield of 58%. Unfortunately, other functionalized aminoalkene substrates failed to cyclize. When both the Co and Pd complexes were applied in the intramolecular hydroamination of aminoalkynes, formation of the dihydro-pyrrole was obtained under all circumstances.

With the research described in this thesis we have demonstrated the coordination chemistry of several different proton-responsive ligands to mainly 2nd row late-transition metals. These complexes can benefit to some extent from their accessible bifunctional site in catalytic

reactions, but the resulting discoveries have not led to the anticipated reactivity and catalytic activity. Whereas the above discussed systems are all rather rigid, inducing severe strain into a complex, more flexible ligands could provide a complex with more freedom, hereby improving its reactivity towards the envisioned theories.