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

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Abstract The coordination chemistry and reactivity of tridentate bis(pyrazolyl)pyridine ligands is described with various late transition metals. Coordination to iron(II) and cobalt(II) precursors occurs smoothly, but subsequent deprotonation of the pyrazolyl-NH moieties leads to disproportionation with formation of homoletic complexes, or self-assembled hexanuclear structures, rather than well-defined isolable heteroleptic mononuclear compounds. The Pd(II)-bis(pyrazolyl)pyridine complexes can be doubly deprotonated, and are stabilized by different co-ligands. Moreover, a Pd(IV) species was generated using molecular iodine. Application of the Co(II) and Pd(II) complexes in the intramolecular hydroamination of N-substituted aminoalkenes resulted in the discovery of a single combination of an active complex and reactive aminoalkene. When these complexes were applied in the intramolecular hydroamination of aminoaalkynes, formation of the N-heterocyclic dihydro-pyrrole product was obtained in all cases. This denotes the second report of Co(II) mediated hydroamination.
5.1 Introduction

Metal-ligand cooperative bifunctional catalysts have proven to be attractive candidates for the efficient, selective and atom-economical conversion of a variety of substrates.\textsuperscript{1,2} Within the last fifteen years, pyrazole and pyridone ligand systems have gained a lot of interest.\textsuperscript{3,4} Pyrazoles bear a Brønsted acidic β-NH group and these systems undergo a relatively facile reversible proton transfer (Scheme 1). Due to the close proximity and directionality (in the equatorial plane) of their reactive sites to the metal center and the reversible deprotonation by mild bases, this may significantly aid the process of metal-ligand bifunctional activation, especially when compared to earlier discussed PNP/N systems. It is envisioned that the combination of smooth proton transfer and the more accessible site will likely abate the need for high temperatures and high pressures. Indeed, these systems have shown to be highly efficient in catalytic transformations.\textsuperscript{3,4}

![Scheme 1. Tautomerization between a pyrazolato and a pyrazole with reversible protonation of the β-nitrogen.](image)

Pyrazole ligands have been known for a while, and so is their ability to be deprotonated, even when coordinated to a metal.\textsuperscript{5} However, the benefit of this feature was only applied in catalysis in 2010. Bidentate and tridentate pyrazole ligands were coordinated to ruthenium precursors and their activity in the hydrogenation and transfer hydrogenation of acetophenone has been reported (Figure 1).\textsuperscript{6} The ruthenium complexes contain both a hydride and a pyrazole with an acidic N-H group, which is important for their specific reactivity.

![Figure 1. Three different Ru(II)pyrazole complexes which are active in transfer hydrogenation.](image)

Ikariya and Kuwata reported the formation of an iridium complex and described the well-defined ligand-based deprotonation-reprotonation process, and its involvement in the catalytic intramolecular hydroamination of aminoalkenes (Scheme 2).\textsuperscript{7} 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 2. Intramolecular hydroamination via MLC of an Ir-pyrazole complex.

Most attention has been given to (substituted) 2,6-bis-(pyrazol-3-yl)pyridine ligands, as these systems have two proton-responsive pyrazole arms. When coordinated to ruthenium, dinuclear complexes were formed that are active in the transfer hydrogenation of ketones, whereas a double-deprotonated monomeric complex facilitates the side-on coordination of O$_2$ and end-on coordination of N$_2$. The combination of this ligand with first-row transition metals has been explored to some extent for iron, cobalt and manganese. The Fe$^{II}$(NNN) complex is able to cleave the N-N bond of (substituted) hydrazines, which leads to facile reduction and oxidation of hydrazine, generating ammonia and dinitrogen (Scheme 3).

However, these tridentate ligands remain underexplored to date regarding catalytic conversions.

Scheme 3. Reduction and oxidation of hydrazine leads to NH$_3$ and N$_2$, respectively.

In this chapter we will discuss the coordination chemistry, ligand-based reactivity and catalytic applications of tridentate bis(pyrazolyl)pyridine NNN ligands when coordinated to different metals, with an initial focus on first-row transition metals. As these complexes undergo an easier proton transfer and also have the reactive site in closer proximity to the metal compared to PNP, we envision enhanced reactivity for the NNN complexes in catalytic applications. Therefore, different metal-ligand combinations (Fe, Co, Ru, and Pd) have been
utilized and compared. The Pd(II) and Co(II) complexes were selected for investigation in the intramolecular hydroamination reaction of both aminoalkenes and aminoalkynes.

5.2 Results and Discussion

5.2.1 Ligand synthesis

Bis(pyrazolyl)pyridine NNN-ligands (L1 and L2), which should both be capable of reversible proton transfer from the protic sidearms, have been synthesized according to literature procedures (Figure 2).

![Figure 2. Specific tridentate bis(pyrazolyl)pyridine ligands explored throughout this chapter.](image)

The 2-step syntheses of the bis(pyrazolyl)pyridine ligands L1 and L2 were straightforward,\textsuperscript{9,13} starting from either the diethyl 2,6-pyridinecarboxylate (for L2) or 2,6-diacetyl pyridine (for L1) with a final ring-closure using hydrazine monohydrate (Scheme 4). The tridentate ligands were obtained in 82% (L1) and 74% (L2) isolated yield and are characterized by NMR spectroscopy and mass spectrometry. In these ligands, the 6 π-electron pyrazole is susceptible to deprotonation of the NH. The difference between these two ligands is the tert-butyl group on the 5-position of the pyrazole rings for L2, which renders the ligand more electron-rich, induces some steric bulk, and enhances the ligand solubility compared to the ‘parent’ ligand L1.

![Scheme 4. Synthesis of bis(pyrazolyl)pyridine ligands L1 and L2.](image)

To distinguish between ligand-assisted cooperativity and metal-based catalysis in later studies, the NH fragments of the protic pyrazolyl side arms of L2 were methylated.\textsuperscript{14} L2 was reacted with sodium hydride and methyl iodide in refluxing DMF over two days to obtain
ligand L2Me in 83% isolated yield (Scheme 5). The structure of L2Me was established using spectroscopic studies, which shows selective methylation on the outer nitrogen atom.

Scheme 5. Methylation of NH of the pyrazolyl groups, providing ligand L2Me.

5.2.2 Coordination and reactivity studies with iron

Coordination of L1 and L2 to FeCl₂ afforded complexes 1 and 2, respectively, which were characterized by NMR spectroscopy and mass spectrometry (Scheme 6). The 1H NMR spectra obtained indicate the formation of diamagnetic species in both cases, but during overnight acquisition of the 13C NMR spectra, coordination of a molecule of DMSO (NMR solvent) likely occurred, generating NMR-silent octahedral paramagnetic species. Mass spectrometry proved more conclusive with respect to the molecular composition of these species, supporting the formation of FeCl₂(L) in both cases. Addition of two equivalents of silver hexafluorophosphate to both complexes in MeCN solution generated bright-yellow paramagnetic complexes [1]PF₆ and [2]PF₆ bearing three acetonitrile ligands. Determination of the magnetic susceptibility by means of the Evans method in acetonitrile at 25 °C, with dichloromethane as standard, yielded a μeff value of 5.76 μB for [2]PF₆, which indicates a high-spin (S = 2) Fe(II) complex.


Mass spectrometry (m/z calcd. 701.3491; found 701.3424) unveiled that in solution not only these tris-acetonitrile complexes were formed, but also the corresponding paramagnetic dicationic homoleptic iron complexes that bear two bis(pyrazolyl)pyridine ligands. The formation of these species is expected to involve disproportionation, with co-generation of 'ligand-less' Fe(II) salts. Single crystal X-ray diffraction confirmed the formulation of complex 3 (for L1) as [Fe(L1)₂](PF₆)₂ (Figure 3).
A slightly distorted octahedral geometry around the iron center is found. Such homoleptic iron complexes with bis(pyrazolyl)pyridine ligands are known and Mössbauer and SQUID studies have shown that these species can undergo temperature-induced low-spin/high-spin transitions.\textsuperscript{15,16} However, these coordinatively saturated complexes are not expected to exhibit the envisioned metal-ligand-bifunctional reactivity, due to the coordinatively saturated nature of the Fe center. Hence, we studied the halide abstraction to form complexes [1]PF\textsubscript{6} and [2]PF\textsubscript{6} in the presence of stabilizing co-ligands. Reaction with base under 5 bars of CO pressure provided a mixture of compounds, but IR spectroscopy did not indicate coordination of carbon monoxide to the iron center. In the presence of two equivalents of trimethylphosphine, species [1]PF\textsubscript{6} and [2]PF\textsubscript{6} converted into 4 and 5. Complex 5, which is already described as the bis(triflate) species,\textsuperscript{12} was characterized by a singlet in \textsuperscript{31}P NMR at \( \delta \) 17.3 ppm and a broad singlet for the pyrazole NH protons at \( \delta \) 11.86 in the \textsuperscript{1}H NMR spectrum. Slow diffusion of pentane into a concentrated solution of dichloromethane afforded orange-red single crystals that were suitable for X-ray structure determination. The molecular structure is depicted in Scheme 7. An octahedral geometry around the iron center is revealed, with the two trimethylphosphine ligands coordinated in the axial positions, with identical metric parameters as for the reported triflate analogue.\textsuperscript{12}
Deprotonation of either complex 1 or 2, to probe the reactivity of these cooperative ligands, using one equivalent of base (either NaOAc, KO\(^{1}\)Bu, or KHMDS), led to a color change from dark-yellow to a brown solution. Upon addition of a second equivalent of base, purple mixtures were obtained. When a solution of hydrochloric acid or tetrafluoroboric acid (one or two molar equivalents) was added to these purple, presumably doubly deprotonated species, the reaction mixtures reverted to brown and subsequently yellow, indicating a clean and reversible proton transfer (Scheme 8). The same trend is observed with dicationic complexes [1]PF\(_6\) and [2]PF\(_6\). This process was also probed via UV-Vis spectroscopy, as depicted in Figure 4. Complex 2 exhibits a band at 314 nm (blue line), which disappeared upon addition of one molar equivalent of base (yellow line). When one equivalent of acid was subsequently added, this absorption band reappeared (green line), confirming the reversible deprotonation. However, consecutive addition of two equivalents of base and acid did not lead to regeneration of the original UV-Vis spectrum, indicating the formation of other species, presumably the homoleptic complexes.

Scheme 8. The reversible proton transfer explored with complexes 1, [1]PF\(_6\), 2 and [2]PF\(_6\), which show different colors for the different states in which they can be found.

Unfortunately, both the mono- and bis-deprotonated species were only accessible in solution, as isolation led to intractable mixtures. In situ stabilization of the doubly-deprotonated species with two equivalents of trimethylphosphine resulted in the formation of dark-red complexes 6 and 7 (Scheme 9). Both complexes displayed a singlet at \(\delta 19.2\) in the \(^{31}\)P NMR spectrum and the coordinated acetonitrile ligand was clearly detected in the \(^1\)H NMR spectrum.
at 1.07 ppm. However, when complex 5 was subjected to deprotonation, a mixture of products was obtained after work-up, but no signals related to complex 7 were detected spectroscopically, although *in situ* monitoring of this reaction via NMR spectroscopy did provide indication for its formation.

![Scheme 9](image)

**Scheme 9.** Formation of doubly-deprotonated stabilized species 6 and 7.

As catalysts, we envisioned the iron complexes could show their potential in catalytic reactions like hydrogenation and transfer hydrogenation of ketones, provided that the corresponding iron-hydride could be accessible. Therefore, starting from complex 4, we made different attempts to generate complex 8 (Scheme 10). Addition of LiBEt₃H and NaBH₄ did not show the formation of a hydride species but rather decomposition of the complex, as dissociation of trimethylphosphine was observed. When NaH was used as hydride source, the ³¹P NMR spectrum also displayed the signal for free trimethylphosphine. In addition, a doublet (JₚH = 60 Hz) at 21.3 ppm was detected, along with a signal at -10.89 ppm in the ¹H NMR spectrum. However, this species was not stable enough for isolation.

![Scheme 10](image)

**Scheme 10.** Formation of hydrido complex 8, via the reaction with different hydride sources.

When 2 equivalents of KOtBu and a balloon of hydrogen gas were applied to complex 4, the color of the solution changed from dark orange to deep-red (deprotonated species) and subsequently back to dark orange. In agreement with the anticipated formation of a hydride containing species, the obtained ¹H NMR spectrum displayed a signal at δ -10.53 ppm again. Slow addition of diethyl ether to the concentrated methanol solution afforded crystals, which were suitable for X-ray structure determination (Figure 5). However, the centrosymmetric molecular structure was not the desired species, but a surprisingly large hexanuclear structure, that involves six iron(III) centers and four ligands. Its full formula reads [Fe₆(L₁)₄(µ₃-O)₃(µ-OMe)₄(OH)]₂, with bridging methoxy and oxo-ligands. Four iron atoms (Fe2 and Fe3) display a pseudo-octahedral geometry and are coordinated to ligand L₁ in the usual tridentate fashion. Furthermore, these metals are also linked to four µ-OMe groups. The iron centers on the outside (Fe1) display a perfect octahedral geometry and are coordinated to
the pyrazolato nitrogen atoms of all four ligands $\textbf{L}_1$. All three different iron atoms are coordinated to a $\mu_3$-oxo fragment and the Fe1 centers are furthermore occupied by a hydroxyl group, generating an overall neutral hexanuclear structure. The targeted formation of a very similar structure ($\text{Fe}_6(\textbf{L}_1)_4(\mu_3-O)_2(\mu-\text{OMe})_3(\mu-\text{OH})\text{Cl}_2$) was described by Plaul et al. in high yield. As the reactivity of these ligands in combination with iron was more challenging than expected, we decided to focus on cobalt systems.

**Figure 5.** Left: ORTEP plot (50% probability displacement ellipsoids) of complex 8, obtained by X-ray diffraction. Only two out of four ligands and four out of six iron atoms of the hexamer are highlighted, and all hydrogen atoms have been omitted for clarity. Approximate bond lengths (Å): Fe1-N4 2.103; Fe1-N7 2.124; Fe1-N11 2.111; Fe1-N12 2.117; Fe2-N5 2.179; Fe2-N8 2.210; Fe2-N16 2.060; Fe2-O2 1.997; Fe2-O4 1.963; Fe3-N1 2.061; Fe3-N6 2.163; Fe3-N13 2.213; Fe3-O2 1.983; Fe3-O4 1.963; O99-Fe1 1.929; O99-Fe2 1.991; O99-Fe3 2.012. Right: Part of the structural motif of complex 8.

### 5.2.3 Coordination and reactivity of Co(NNN) complexes

Cobalt complex 9 was synthesized according to a reported literature procedure by Ikariya and coworkers, which involved a reaction of CoCl$_2$-6H$_2$O and $\textbf{L}_2$ in ethanol (Scheme 11). Pentane was added slowly to the concentrated reaction mixture and this afforded blue crystalline needles, which were suitable for X-ray structure determination (Figure 6). This complex was also characterized by mass spectrometry ($m/z$ calcld. 417.1130; found 417.1128 [M-Cl]). The magnetic susceptibility was estimated by the Evans method, as this species is paramagnetic. In DMSO at 25 °C, with dichloromethane as standard, a $\mu_{\text{eff}}$ value of 3.51 µB was observed, which is consistent with a high spin Co(II) ($S = \frac{3}{2}$) complex.
Scheme 1. Formation of complex 9.

Figure 6. ORTEP plot (50% probability displacement ellipsoids) of complex 9. Hydrogen atoms have been omitted for clarity, except for the NH and OH groups. Selected bond lengths (Å) and angles (°): Co1-Cl1 2.302(1); Co1-Cl2 2.302(1); Co1-N2 2.166(3); Co1-N3 2.073(3); Co1-N4 2.172(3); N1-N2 1.3491(1); N4-N5 1.3425(4); O1---N1H 1.91(2); O1H---Cl1 2.36(3); O2---N5H 1.94(3); O2H---Cl2 2.38(4).

The molecular structure reveals a distorted trigonal bipyramidal geometry (τ = 0.73) around the cobalt atom and a crystallographically imposed C2 axis was found that passes through Co1, N3 and C10. The angles of the equatorial plane (N3-Cl1-Cl2) are totaling 360°, but not 120° each. The two chloride atoms are bent more towards each other with an angle of 106.6(2)° for Cl1-Co1-Cl2. The angles of the chloride atoms to N3 of the pyridine are 117.14(7)° and 136.20(7)° for Cl1-Co1-N3 and Cl2-Co1-N3, respectively. The axial positions are occupied by the pyrazolyl groups. The angle of the axial plane totals 150.4(1)° for N2-Co1-N4; this distortion is due to the rigid structure of the flat pincer ligand. When the structure of this complex is compared to the related complex CoCl2(L1), it was found that all bond lengths and angles are similar, except for the angles in the equatorial plane. All the angles found in this structure are approximately 120°, whereas in 9 the chloride atoms are in closer proximity of each other. Similarly, the Co-N and Co-Cl bond lengths in 9 are all shorter than those found in the analogous MnCl2(L2) complex, which is consistent with cobalt being more electronegative and larger. When compared to a related octahedral Co(L2)(OTf)2(MeCN) complex, it was found that the bond lengths and angles of 9 are all in the same range. The angles inside the pyrazolyl rings assure the structural comparison between pyrazolyl and the pyrazolato analogue. The N1-N2-C7 angle is rather small (105.27(3)°) compared to the larger N2-N1-C5 angle (111.93(2)°), which is consistent with the coordination of the pyrazolyl rings as neutral donors, still bearing the proton on N1. This is further confirmed by the presence of
a hydrogen bonding network between 9 and two molecules of ethanol. The oxygen O1 of the alcohol binds to the N1H of the pyrazole (1.91(2) Å) and the O1H binds to Cl1 (2.36(3) Å). Analogous Co(II)PNP complexes are well-known\(^\text{22}\) and their reduction to Co(I) species leads to diamagnetic complexes that can be further converted into a Co(I)-hydride (Scheme 12). Application of such complexes can be found in the hydrogenation of ketones or carbon dioxide,\(^\text{23-25}\) similar to comparable iridium catalysts.

\[
\text{Scheme 12. Reduction of a CoCl}_2(\text{PNP}) \text{ complex to Co(I)Cl and Co(I)H species.}^\text{22}
\]

Reduction of complex 9 with 1 or 2 equivalents of NaBEt\(_3\)H did not lead to the desired species 10 and 11 (Scheme 13). \(^1\)H NMR measurements showed that a mixture of both paramagnetic and diamagnetic species is present, which were unfortunately inseparable. An attempt to separate these complexes via crystallization resulted in the molecular structure as depicted in Figure 7. The molecular structure of 12 reveals an octahedral geometry around the cobalt ion that is coordinated to two bis(pyrazolyl)pyridine ligands. Only one out of four of the pyrazole rings contains a proton, which is also shown in the bond length of Co1-N21. As this pyrazole nitrogen atom coordinates as a neutral donor, and the other as anionic donor, the cobalt has been oxidized to Co(III). This species may have formed via elimination of H\(_2\) from the hydride of sodium triethylborohydride and a proton of the ligand. Whereas the plan was to reduce the metal, it is actually oxidized into a semi-homoleptic structure. Homoleptic complexes are not uncommon for first-row transition metals as was already shown in the paragraph about iron,\(^\text{15,16}\) but subsequent reactivity is hindered as this system lacks vacant sites.
Figure 7. ORTEP plot (50% probability displacement ellipsoids) of complex 12. Hydrogen atoms have been omitted for clarity, except for the one on N11. Selected bond lengths (Å) and angles (°): Co1-N21 1.9618(16); Co1-N31 1.8857(16); Co1-N41 1.9002(15); Co1-N22 1.9285(16); Co1-N32 1.8878(16); Co1-N42 1.9228(16); N11-N21 1.3463(21); N41-N51 1.3415(22); N12-N22 1.3480(21); N42-N52 1.3514(21). N21-Co1-N31 80.22(7); N41-Co1-N31 81.59(7); N21-Co1-N41 161.81(7); N22-Co1-N32 81.40(7); N42-Co1-N32 81.45(7); N22-Co1-N42 162.84(7).

This system does, however, show that double deprotonation of the ligand is successful when coordinated to cobalt and this is observed when complex 9 is exposed to base. Two equivalents of KOtBu to the turquoise solution resulted in the formation of an azure solution of 13, which could be converted into 9 again by the addition of 2 equivalents of HCl (Scheme 14 and Figure 8). Deprotonated cobalt species will be applied in catalysis (Paragraph 5.2.6).

5.2.4 Coordination and reactivity with ruthenium

Because the coordination chemistry of ligands $L_1$ and $L_2$ with iron and cobalt with respect to deprotonation and dehalogenation did not provide much controlled reactivity (except for the direct deprotonation of CoCl$_2$($L_2$), we decided to move to some second-row analogues. Coordination of $L_2$ to RuCl(CO)(H)(PPh$_3$)$_3$ was envisioned to be analogous to what has been reported for PNP and PNN pincer complexes. However, the NMR spectra demonstrated that a mixture of species was formed, which were identified by mass spectrometry (Figure 9). Complex 14 is the desired neutral species in which $L_2$ is coordinated in the expected tridentate fashion, together with the hydrido, chloride and carbonyl co-ligands ($m/z$ calcd. 454.1181; found 454.1184 [M-Cl]). The other complex 15 appeared to be the cationic analogue in which the bis(pyrazolyl)pyridine coordinates as a bidentate ligand via the pyridine and one of the pyrazole arms. The additional ligands are the hydride, carbonyl and two triphenylphosphine moieties, with the chloride ligand acting as non-coordinating counter ion ($m/z$ calcd. 978.3004; found 978.3104). The group of Thiel attempted to synthesize a similar complex 14 with a tBu-substituted $L_2$, but also reported the formation of a mixture of complexes.6

Figure 9. Complexes 9 and 10 that could not be separated from each other.

Figure 8. UV-Vis spectrum of the deprotonation and reprotonation of complex 9.
Therefore, we synthesized complex 16 from L2 and precursor RuCl₂(PPPh₃)₃ via a procedure reported by Ikariya and co-workers (Figure 10, left). They have described the ability of mono and double deprotonation of this complex, alongside the coordination of O₂ and N₂, but any further investigation in the reactivity of this complex remains unknown to date. To access a Ru-H species, complex 16 was deprotonated by two equivalents of base and subsequently exposed to hydrogen gas. However, the obtained green mixture did not show the formation of hydride species 17 according to ¹H NMR spectroscopy, but several unidentified species were formed instead. We therefore decided not to focus on hydride species but explore the reactivity of complex 16.

![Figure 10. Cationic complex 16 (left) and hypothesized neutral mono-deprotonated hydrido complex 17 (right).](image)

Because Ru-pincer complexes are known to activate N-H bonds via metal-ligand cooperation, we chose to explore complex 16 in this reaction (Scheme 15). Addition of 2 equivalents of base to 16 and in situ addition of an acidic amine resulted in the formation of several species, which makes it unclear whether one of the desired species (18, 19 or 20) is formed at all. According to ³¹P NMR, free triphenylphosphine is formed during all three reactions, showing a high degree of decomposition of the complex.

![Scheme 15. Activation of N-H bonds on complex 16 was unsuccessful for all three amines.](image)

Besides the activation of N-H bonds, the activity of this complex was also studied in the transfer hydrogenation of acetophenone using 2-propanol (iPrOH) as both hydrogen donor and solvent. To study if the reaction goes via ligand-assisted catalysis, complex 16Me with methyl-protected pyrazole arms was synthesized and used for comparison. We assumed the coordination of this ligand would be similar as in complex 16, but unfortunately this complex was not obtained in pure form. Mass spectrometry and NMR spectroscopy suggested the complex was the main product in the mixture (m/z calc. 1012.2978; found 1012.2993), therefore the mixture was used in the transfer hydrogenation reaction. Acetophenone was chosen as benchmark substrate and the conversion was determined by GC analysis with p-xylene as internal standard. Table 1 shows the results of the catalysis. Indeed, complex 16
shows 95% conversion for acetophenone into 1-phenylethanol,\(^6\) whereas complex \(16\text{Me}\), which has no proton-responsive sites, shows no conversion at all. This suggests the active role of the ligand in this catalytic reaction. However, in comparison to Noyori’s ruthenium catalyst, it is less active as this catalyst requires only half the amount of catalyst to achieve the same conversion.\(^{27}\) Complex \(16\) is certainly active, but not as fast as known systems.

**Table 1. Results of the catalytic transfer hydrogenation of acetophenone in the presence of 2-propanol as hydrogen source.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>t (h)</th>
<th>Conv [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(16)</td>
<td>KO(^t)Bu</td>
<td>16</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>(16\text{Me})</td>
<td>KO(^t)Bu</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>3(^a)</td>
<td>Noyori</td>
<td>KOH</td>
<td>15</td>
<td>95</td>
</tr>
</tbody>
</table>

Conditions: 1.0 mmol acetophenone, 1 mol% catalyst, 10 mol% base. The conversion was determined by GC analysis with \(p\)-xylene as internal standard. \(^a\) 0.5mol% catalyst was used in this reaction.

### 5.2.5 Coordination and reactivity with palladium

The coordination of \(\text{L2}\) to \(\text{PdCl}_2(\text{MeCN})_2\) occurred smoothly at room temperature to produce the cationic complex \(21\) as a yellow solid in quantitative yield. This complex, which was fully characterized by NMR and IR spectroscopy and mass spectrometry, could be reacted with both 1 and 2 equivalents of \(\text{TIPF}_6\) to replace the chloride anion and chloride ligand, respectively (Scheme 16, complexes \(22\) and \(23\)). Subtle differences were observed in the \(^1\)H NMR spectrum for the different complexes, especially for complex \(23\) to which an acetonitrile ligand is now coordinated.

**Scheme 16.** Chloride abstraction from complex \(21\) leads to the formation of \(\text{PF}_6\)-complexes \(22\) and \(23\).
Deprotonation of these complexes with 2 equivalents of KHMDS and \textit{in situ} addition of 2 equivalents of HCl regenerates complex 21, displaying the metal-ligand cooperativity. \textit{In situ} addition of trimethylphosphine to the doubly deprotonated species resulted in the formation of complex 24, of which single crystals suitable for X-ray structure determination were obtained via slow diffusion of diethyl ether into a concentrated solution of acetonitrile. Furthermore, complex 24 was fully characterized, showing the molecular ion peak in HR-MS (m/z 504.15084 (calcd); 504.15478 (found)) and a singlet in the $^{31}$P NMR spectrum at $\delta$ -4.6 ppm. The molecular structure of 24 is depicted in Figure 1 and reveals a slightly distorted square planar geometry around the palladium center with a crystallographically imposed C$_2$ axis that passes through P1, Pd1, N1 and C10. The angles and bond lengths are slightly larger than those in the cobalt complexes.

![ORTEP plot of complex 24](image)

Figure 1. ORTEP plot (50% probability displacement ellipsoids) of complex 24. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Pd1-N1 2.0086(24); Pd1-N2 2.0051(25); Pd1-N4 2.0161(24); Pd1-P1 2.2505(9). N1-Pd1-N2 79.22(10); N1-Pd1-N4 79.59(10); P1-Pd1-N2 99.63(8); P1-Pd1-N4 101.48(7).

The smooth reversible proton transfer is evident from the addition of 2 equivalents of HCl to complex 24, which exclusively generates complex 25 (Scheme 17). This dicationic complex displays a small shift downfield to 0.86 ppm in the $^{31}$P NMR spectrum and shows the protonation of both pyrazole rings as indicated by the N-H signals in the $^1$H NMR spectrum at 11.54 ppm. Moreover, this complex 25 could also be obtained from the addition of 1 equivalent of PMe$_3$ to complex 21, illustrating that the chloride ligand is only weakly coordinated to the palladium center.
Scheme 17. Deprotonation (and in situ addition of PMe₃) of complex 21 leads to complex 24 that can be protonated to generate complex 25. This complex can also be synthesized by the addition of PMe₃ to a solution of 21.

Next, we examined the coordination of other ligands than PMe₃ for the stabilization of the doubly deprotonated species. Tri-isopropylphosphine proved to be too sterically hindered for coordination, but pyridine appeared to be a suitable ligand. This is, however, only when pyridine was applied as the solvent and not when one or more equivalents were added to a reaction mixture. The ¹H NMR spectrum of 26 shows the downfield shift of the ortho-hydrogen atoms of the coordinated pyridine, as a doublet (J = 4.9 Hz) at 10.25 ppm (Figure 12, ortho-hydrogens of free pyridine are found at δ 8.61 ppm). The structure was furthermore confirmed by HR-MS, showing an m/z value of 506.13903 (calc. m/z 506.14103).

Figure 12. ¹H NMR spectrum of complex 26.

Slow addition of pentane onto a concentrated dichloromethane solution of complex 26 resulted in single crystals which were suitable for X-ray structure determination. The molecular structure of 26 is depicted in Figure 13 and reveals a slightly distorted square planar geometry around the palladium center with a crystallographically imposed C2 axis that passes through C6, N3, Pd1, N6 and C22. The angles and bond lengths are all comparable to those in
complex 24. Moreover, this structure is in agreement with the $^1$H NMR spectrum, as the pyridine ligand and the deprotonated tridentate ligand lie in one plane, verifying the interaction between the ortho-hydrogens of the pyridine and the nitrogen atoms of the pyrazole moiety.

![Image of ORTEP plot](image)

**Figure 13.** ORTEP plot (50% probability displacement ellipsoids) of complex 26. Hydrogen atoms have been omitted for clarity, except for H20 and H24. Selected bond lengths (Å) and angles (°): Pd1-N1 2.030(5); Pd1-N3 1.980(9); Pd1-N4 2.001(5); Pd1-N6 2.040(1); N1-Pd1-N3 79.88(3); N3-Pd1-N4 80.00(3); N1-Pd1-N4 159.85(2); N1-Pd1-N6 99.89(4); N4-Pd1-N6 100.19(4).

Most catalytic cycles that involve palladium go through a Pd(0)/Pd(II) cycle, and Pd(IV) intermediates are not very common, although several examples appeared in recent years.28 Several Pd(IV) complexes have been isolated and characterized, and understanding the behavior of Pd(IV) complexes could lead to the development of novel reactions involving such species. Starting from complex 24, we studied the possible formation of a Pd(IV) species with this ligand system. Addition of 1 (or 2) equivalents of methyl triflate resulted in a mixture of undefined products, and addition of iodomethane displayed only the formation of oxidized trimethylphosphine, besides the starting materials. Also (diacetoxyiodo)benzene, which is commonly used for the oxidation of palladium(II) species, does not give the desired palladium(IV) compound. However, addition of molecular iodine (Scheme 18) led to a clear color change from yellow to dark red, concomitant with a large shift in $^{31}$P NMR from -4.6 to 37.4 ppm. The structure of complex 27 was furthermore confirmed by HR-MS, showing an $m/z$ value of 630.0450 (calc. $m/z$ 630.0475) [M-I]. Although further investigations regarding mechanistics and catalysis should be performed, we have shown the possible formation of Pd(IV) species of complexes based on a bis(pyrazolyl)pyridine ligand system.

![Diagram of Scheme 18](image)

**Scheme 18.** Formation of Pd(IV) complex 27 via the oxidative addition of I$_2$ on complex 24.
5.2.6 Intramolecular hydroamination

In Chapters 2 and 4 we examined various complexes as catalyst in the intramolecular hydroamination of aminoalkenes. Unfortunately, none of these complexes was able to accomplish the ring closure, as only isomerization of the alkene double bond occurred. Since a pyrazole-iridium catalyst is known for its bifunctional behavior in this catalytic reaction, we selected several of the cobalt and palladium complexes reported in this Chapter as potential catalyst for the hydroamination reaction, of which the results are displayed in Table 2. Palladium complexes have been known for a while as hydroamination catalyst and recently a study has been reported on a Co(II) complex, although the precise mode of action for this catalyst system has not been established and various additives are required. All aminoalkenes are derivatives of 2,2-diphenyl-4-pentenylamine, including triflic-, tosyl- and CBz-functionalized amines and the yields are determined by 1H NMR spectroscopy. Products a and b would correlate to the anti-Markovnikov and Markovnikov products, respectively, while iso is formed via double bond isomerization of the terminal alkene into the internal derivative.

Entries 1 – 5 show the results for the parent aminoalkene. When complex 21 is used as catalyst in the presence of AgBF₄ and with toluene as solvent, full conversion into the isomerization product is observed (entry 1). Complex 23 shows no reactivity at all, which can be explained by the coordinated acetonitrile ligand. Apparently, its strong coordination prevents substrate binding or activation (entry 2). The same observation is made when 2 equivalents of base are added to either complex in dichloromethane, as the palladium complexes do not show any activity when deprotonated (entries 3 and 4). In entry 5, also cobalt complex 9 shows no conversion when pre-treated with 2 equivalents of base. The more acidic triflic-functionalized aminoalkene does not show formation to either of the desired products. Palladium complex 21, in the presence of AgBF₄, shows 38% conversion to the isomerization product, whereas 2 equivalents of base at 70 ºC apparently led to an inactive complex (entries 6 and 7). Entries 8 – 15 show the outcome of the catalysis done with the tosyl-functionalized aminoalkene as substrate. Under different conditions, the applied palladium and cobalt complexes are inactive (entries 11 – 15), except for complex 21 in the presence of AgBF₄. Entries 8 – 10 show almost full conversion to the isomerization product in both toluene and dichloromethane. A possible explanation for this inactivity could lie in the initial amine activation prior to the cyclization event, or the inhibition of proton-transfer from the amino moiety to the coordinated double bond of the substrate. Therefore, we probed stoichiometric reactions of palladium complex and aminoalkene. Reaction of complex 21 in combination with 2 equivalents of KOtBu and CBz-functionalized aminoalkene did not result in activation of the amine N-H bond. This cannot be related to the substituent on the amine, as Table 2 shows that none of the aminoalkenes reacts with the deprotonated complexes. Therefore, initial amine activation can be excluded as pathway of cyclization. When complex 21 in the presence of AgBF₄ is reacted with the tosyl-functionalized aminoalkene, we do not find evidence of the coordinated alkene species, as the 1H NMR spectrum does not show a shift of the alkene signals. However, some isomerization has already occurred, indicating the alkene must have been coordinated initially.
Table 2. The results of the intramolecular hydroamination reaction for different aminoalkenes using cobalt complexes 9 and 9Me, and palladium complexes 21 and 23.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>additive</th>
<th>solvent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Yield [%]</th>
<th>iso</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>21</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
<td>rt</td>
<td>15</td>
<td>100%</td>
<td>iso</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>23</td>
<td>-</td>
<td>toluene</td>
<td>50</td>
<td>14</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H</td>
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<td>2 equiv. KHMDS</td>
<td>dcm</td>
<td>rt</td>
<td>15</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>21</td>
<td>2 equiv. KOtBu</td>
<td>dcm</td>
<td>rt</td>
<td>16</td>
<td>SM</td>
<td></td>
</tr>
<tr>
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<td>H</td>
<td>9</td>
<td>2 equiv. KOtBu</td>
<td>dcm</td>
<td>rt</td>
<td>14</td>
<td>SM</td>
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</tr>
<tr>
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<td>toluene</td>
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<td>14</td>
<td>70%</td>
<td>iso</td>
</tr>
<tr>
<td>9</td>
<td>Ts</td>
<td>21</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
<td>50</td>
<td>14</td>
<td>100%</td>
<td>iso</td>
</tr>
<tr>
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<td>Ts</td>
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<td>dcm</td>
<td>rt</td>
<td>17</td>
<td>SM</td>
<td></td>
</tr>
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<td>12</td>
<td>Ts</td>
<td>21</td>
<td>2 equiv. KOtBu</td>
<td>toluene</td>
<td>50</td>
<td>16</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Ts</td>
<td>23</td>
<td>-</td>
<td>toluene</td>
<td>50</td>
<td>14</td>
<td>SM</td>
<td></td>
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<tr>
<td>14</td>
<td>Ts</td>
<td>9</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
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<td>Ts</td>
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<td>toluene</td>
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<td>15</td>
<td>SM</td>
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<tr>
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<td>CBz</td>
<td>21</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
<td>50</td>
<td>14</td>
<td>13%</td>
<td>iso</td>
</tr>
<tr>
<td>17</td>
<td>CBz</td>
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<td>2 equiv. KOtBu</td>
<td>dcm</td>
<td>rt</td>
<td>16</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>CBz</td>
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<td>14</td>
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<td>b</td>
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<td>dcm</td>
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<td>14</td>
<td>42%</td>
<td>iso</td>
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</table>

The reason why the cyclization does not occur might be related to the functional group on the amine. Whereas the parent aminoalkene and triflic- and tosyl-functionalized aminoalkenes only show (partial) isomerization, the CBz-functionalized amine (a carbamate) shows formation of product b (entries 16 – 19). In toluene with AgBF₄, a small amount of isomerization product is formed when complex 21 is applied as catalyst, and in dichloromethane with base only starting material was obtained. However, when a mixture of 21 and AgBF₄ was applied in dichloromethane, 32% of product b was formed along with byproduct iso (entry 18). Moreover, when the temperature was increased to 40 °C, the major product turned out to be b, in 58% yield (entry 19). Whereas this is still a rather moderate yield, cyclization of the aminoalkene is able to occur when this palladium complex is applied as catalyst.
Beside the intramolecular hydroamination of aminoalkenes, the metal-catalyzed hydroamination of aminoalkynes is also considered as a potent way of synthesizing nitrogen-containing heterocycles.³⁰ Palladium complexes have been known as hydroamination catalysts for both alkenes and alkynes. We therefore examined the palladium complexes as well as the cobalt complexes as catalysts for this cyclization reaction. The results are presented in Table 3. When applying Pd-complex 21 with AgBF₄ in toluene at 50 ºC, full conversion into the five-membered heterocycle was obtained (entry 1). To our delight, at lower temperature and in the presence of base, also full conversion was obtained when complex 21 was used as catalyst (entry 2). Moreover, when the temperature was increased, full conversion was obtained in only 3.5 hours (entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>additive</th>
<th>solvent</th>
<th>T [ºC]</th>
<th>t [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
<td>50</td>
<td>15</td>
<td>100% b</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>2 equiv. KOtBu</td>
<td>dcm</td>
<td>rt</td>
<td>17</td>
<td>100% b</td>
</tr>
<tr>
<td>3</td>
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<td>dcm</td>
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<td>100% b</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
<td>50</td>
<td>19</td>
<td>100% b</td>
</tr>
<tr>
<td>5</td>
<td>9Me</td>
<td>2 equiv. AgBF₄</td>
<td>toluene</td>
<td>50</td>
<td>19</td>
<td>100% b</td>
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<td>6</td>
<td>9</td>
<td>2 equiv. KOtBu</td>
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<td>rt</td>
<td>46a</td>
<td>37% b</td>
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<td>7</td>
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<td>dcmᵇ</td>
<td>rt</td>
<td>46a</td>
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<td>dcm</td>
<td>40</td>
<td>23a</td>
<td>100% b</td>
</tr>
</tbody>
</table>

ᵃ aliquots were taken during the reaction and measured, this time indicates the last measurement. ᵇ this reaction is carried out in half of the usual volume, to create a more concentrated solution.

Both cobalt complexes 9 and 9Me, the protected-ligand analogue, show full conversion in the presence of AgBF₄ in toluene at 50 ºC (entries 4 and 5). Since the palladium complex facilitated full conversion of the aminoalkyne in only 3.5 hours, we were curious about the required time of cobalt complex 9. Entries 6 – 8 of Table 3 correlate with the plot in Figure 14. A reaction using 9 in the presence of base in dichloromethane at room temperature resulted in a slow conversion of the aminoalkyne, as only 37% of the heterocycle was obtained after nearly 2 days. Using higher concentration of the reagents did increase the product yield by a factor of 1.5, although 40 hours were still required for conversion of half the amount of the substrate. When the temperature was increased to 40 ºC, 71% of product b was already obtained after 7 hours and after 23 hours its full conversion was achieved. Both cobalt complex 9 and palladium complex 21 show their value in this catalytic hydroamination, where slightly elevated temperatures are required for a fast conversion of aminoalkyne into methyl-dihydropyrrole.
Figure 14. Conversion of aminoalkyne over time, catalyzed by Co complex 9 under different conditions.

5.3 Conclusions

The coordination chemistry, (ligand-induced) reactivity and catalytic applications of tridentate bis(pyrazolyl)pyridine ligands are underexplored when compared to closely resembling PNP pincer systems. We herein described the versatile chemistry of these NNN-ligands with iron, cobalt, ruthenium, and palladium precursors. Formation of penta-coordinated iron complexes 1 and 2 occurs smoothly, but subsequent deprotonation of the pyrazolyl moieties produces not only the desired deprotonated complexes. Formation of homoleptic species and even hexanuclear structures is also observed as well. The synthesized cobalt complex 9 is stable under deprotonation conditions, however, reduction to Co(I) led to a similar (semi)-homoleptic complex as was also observed with iron. Ruthenium complex 16 was able to perform well in the transfer hydrogenation of acetophenone. Its proton-responsive sites aid the metal during the catalysis, as the protected complex 16Me was not able to convert the acetophenone, proving the metal-ligand cooperation. Palladium complex 21 can be doubly deprotonated and is stabilized by different co-ligands such as PMe₃ and pyridine. Furthermore, a Pd(IV)-species was generated via the oxidative addition of I₂. Application of the Pd complexes in the intramolecular hydroamination reaction of a CBz-functionalized aminoalkene resulted in a yield of 58%. Unfortunately, the other functionalized substrates did not react. Whether this system is limited to carbamate-functionalized aminoalkenes, should be investigated in more detail. When both the Co and Pd complexes were applied in the intramolecular hydroamination of aminoalkynes, formation of the dihydro-pyrrole was obtained in all cases. Whereas we envisioned the ligands in these complexes to undergo an easier deprotonation/reprotonation process than the PNP systems, we discovered that they also coordinate and behave in a different way. Especially in the complexes of the first row TMs, the coordinated acetonitrile ligands are rapidly displaced by ligands L1 or L2, which makes its ensuing chemistry more difficult. However, it has been shown that these complexes can benefit to some extent from their accessible bifunctional site in catalytic reactions and despite its difficult nature, pyrazole-pyridine systems are interesting ligands. 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.

5.4 Experimental Section

**General procedures**

Solvents were either distilled over suitable drying agents or dried using an MBraun SPS (Solvent Purification System). All experiments were carried out under an inert gas atmosphere using standard Schlenk techniques. All chemicals were commercially available and used without further purification, unless described otherwise. The \(^1\)H, \(^1\)H\{\(^{31}\)P\}, \(^{31}\)P\{\(^1\)H\} and \(^{13}\)C\{\(^1\)H\} NMR spectra were recorded at room temperature on a Bruker AV400 (at 400, 162, and 100 MHz, respectively) and on a Bruker DRX500 (at 500, 202, and 126 MHz, respectively) and calibrated to the residual proton and carbon signals of the solvent. High resolution mass spectra were recorded on a JEOL AccuTOF GC v 4g, JMS-T100GCV mass spectrometer (FD) and on a JEOL AccuTOF LC, JMS-T100LP mass spectrometer (CSI). IR spectra were recorded with a Bruker Alpha-p FT-IR spectrometer operated in the ATR mode.

**Syntheses and characterization**

**Ligand L1.** This ligand was prepared according to a reported procedure,\(^6\) starting from 2,6-diacetylpyridine (0.83 g, 5.08 mmol) and obtained as an off-white powder (82%). \(^1\)H NMR (400 MHz, DMSO-\(d_6\), ppm): δ 13.51 (br s, 1H), 13.05 (br s, 1H), 7.86 – 7.63 (m, 5H), 6.97 (s, 2H). HR-MS (FAB\(^+\)) (C\(_{11}\)H\(_9\)N\(_5\)): m/z calcd. 212.0936; found 212.0934.

**Ligand L2.** This ligand was synthesized according to a reported procedure,\(^9\) starting from diethyl 2,6-pyridinecarboxylate (3.00 g, 13.44 mmol) and obtained as a white crystalline powder (74%). \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 7.72 (t, \(J_{HH} = 7.5\) Hz, 1H), 7.60 (d, \(J_{HH} = 6.7\) Hz, 2H), 6.64 (s, 2H), 1.39 (s, 18H). HR-MS (CSI\(^+\)) (C\(_{19}\)H\(_{25}\)N\(_5\)): m/z calcd. 324.2188; found 324.2162.

**Ligand L2Me.** This ligand was synthesized according to a reported procedure, starting from L2 (221.7 mg, 0.685 mmol),\(^14\) and obtained as a grey powder (83%). \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 7.79 (m, 3H), 6.79 (s, 2H), 4.01 (s, 6H), 1.45 (s, 18H). HR-MS (CSI\(^+\)) (C\(_{21}\)H\(_{29}\)N\(_5\)): m/z calcd. 352.2501; found 352.2502.

**Complex 1, FeCl\(_2\)(L1).** Anhydrous FeCl\(_2\) (1.63 g, 7.7 mmol) was dissolved in 60 mL acetonitrile and L1 (0.98 g, 7.7 mmol) in 30 mL acetonitrile was added. The solution was stirred at room temperature for 20 hours before all volatiles were evaporated. A dark yellow powder was obtained in quantitative yield. \(^1\)H NMR (400 MHz, DMSO-\(d_6\), ppm): δ 13.53 (br s, 1H), 13.06 (br s, 1H), 7.94 – 7.62 (m, 5H), 7.02 (s, 2H). HR-MS (FAB) (C\(_{10}\)H\(_9\)Cl\(_2\)FeN\(_5\)): m/z calcd. 336.9585; found 336.9586. IR (ATR cm\(^{-1}\)):

\[1609 \text{ (m)}, \quad 1568 \text{ (m)}\]
Complex 2, FeCl₂(L₂). Anhydrous FeCl₂ (185.0 mg, 1.46 mmol) was dissolved in 40 mL acetonitrile and L₂ (472.1 mg, 1.46 mmol) in 20 mL acetonitrile was added. This mixture was stirred for 20 hours at room temperature before all volatiles were evaporated. A dark yellow powder is obtained in quantitative yield. \(^1\)H NMR (400 MHz, DMSO-\(d_6\), ppm): \(\delta\) 13.04 (s, 1H), 12.75 (s, 1H), 7.82 (s, 2H), 7.66 (d, \(J = 9.1\) Hz, 1H), 6.99 (s, 1H), 6.82 (s, 1H), 1.31 (s, 18H). HRMS (CSI\(^+\)) \((\text{C}_{28}\text{H}_{50}\text{ClFeN}_3)\): \(m/z\) calcd. 449.0837; found 449.0851. IR (ATR \(\text{cm}^{-1}\)): 1613 (m), 1578 (m).

Complex 9, CoCl₂(L₂). This complex was synthesized according to a literature procedure,\(^9\) starting from L₂ (210.1 mg, 0.65 mmol) and obtained as blue crystalline needles (67%). \(\mu_{\text{eff}} = 3.51\) \(\mu\)B. HR-MS (CSI\(^+\)) \((\text{C}_{25}\text{H}_{55}\text{ClCoN}_3)\): \(m/z\) calcd. 417.1130; found 417.1128 [M-Cl]. IR (ATR \(\text{cm}^{-1}\)): 1612 (m), 1573 (m).

Complex 9Me, CoCl₂(L₂Me). This complex was synthesized according to a literature procedure,\(^9\) starting from L₂Me (245.1 mg, 0.697 mmol) and obtained as turquise crystalline needles (61%). \(\mu_{\text{eff}} = 4.27\) \(\mu\)B. HR-MS (CSI\(^+\)) \((\text{C}_{25}\text{H}_{55}\text{ClCoN}_3)\): \(m/z\) calcd. 415.1444; found 415.1508 [M-Cl]. IR (ATR \(\text{cm}^{-1}\)): 1609 (m), 1574 (m).

Complex 16, [RuCl(PPh₃)₃(L₂)]Cl. This complex was synthesized according to a literature procedure,\(^9\) starting from L₂ (51.8 mg, 0.16 mmol) and obtained as an orange powder (75%). \(^1\)H NMR (400 MHz, chloroform-\(d\), ppm): \(\delta\) 10.83 (s, 2H), 7.48 (t, \(J = 7.8\) Hz, 1H), 7.41 – 7.02 (m, 32H), 6.42 (d, \(J = 1.9\) Hz, 2H), 1.22 (s, 18H). \(^{31}\)P NMR (162 MHz, chloroform-\(d\), ppm): \(\delta\) 24.2 (s). HR-MS (CSI\(^+\)) \((\text{C}_{35}\text{H}_{55}\text{ClN}_3\text{P}3\text{Ru})\): \(m/z\) calcd. 984.2676; found 984.2599. IR (ATR \(\text{cm}^{-1}\)): 1608 (m), 1556 (m).

Complex 21, [PdCl(L₂)]Cl. Ligand L₂ (210.8 mg, 0.652 mmol) and PdCl(MeCN)₂ (169.1 mg, 0.652 mmol) were dissolved in 20 mL anhydrous acetonitrile, producing a dark-yellow solution that was stirred for 20 hours at room temperature. Subsequently, all volatiles were evaporated and a dark-yellow solid was obtained (71%). \(^1\)H NMR (400 MHz, acetonitrile-\(d_3\), ppm): \(\delta\) 12.20 (br s, 2H), 8.26 (t, \(J = 8.0\) Hz, 1H), 7.84 (d, \(J = 8.0\) Hz, 2H), 6.99 (s, 2H), 1.43 (s, 18H). \(^{13}\)C NMR (100 MHz, acetonitrile-\(d_3\), ppm): \(\delta\) 159.2 (s), 153.7 (s), 150.08 (s), 143.3 (s), 120.5 (s), 103.2 (s), 31.9 (s), 29.9 (s). HR-MS (CSI\(^+\)) \((\text{C}_{29}\text{H}_{55}\text{ClN}_3\text{Pd})\): \(m/z\) calcd. 464.0838; found 464.0890. IR (ATR \(\text{cm}^{-1}\)): 1611 (m), 1569 (m).

Complex 22, [PdCl(NCMe)(L₂)](PF₆). Complex 21 (15.0 mg, 0.03 mmol) and TIPF₆ (10.4 mg, 0.03 mmol) were dissolved in 5 mL anhydrous acetonitrile, producing a dark-yellow solution that was stirred for 20 hours at room temperature. Subsequently, the mixture was filtered and all volatiles were evaporated to produce a dark-yellow solid in quantitative yield. \(^1\)H NMR (400 MHz, acetonitrile-\(d_3\), ppm): \(\delta\) 12.13 (s, 2H), 8.25 (t, \(J = 8.0\) Hz, 1H), 7.81 (d, \(J = 8.0\) Hz, 2H), 6.97 (d, \(J = 1.9\) Hz, 2H), 1.43 (s, 18H). \(^{31}\)P NMR (162 MHz, chloroform-\(d_3\), ppm): \(\delta\) 98.4 (s). HR-MS (CSI\(^+\)) \((\text{C}_{29}\text{H}_{55}\text{ClN}_3\text{Pd})\): \(m/z\) calcd. 524.1080; found 524.1080. IR (ATR \(\text{cm}^{-1}\)): 1611 (m), 1569 (m).
acetonitrile-$d_3$, ppm): δ -144.6 (hept, $J = 707$ Hz). HR-MS (CSI$^+$) (C$_{9}$H$_{13}$ClN$_{3}$Pd): $m/z$ calcd. 464.0838; found 464.0868. IR (ATR, cm$^{-1}$): 1614 (m), 1578 (m).

**Complex 23, [Pd(NCMe)(L$_2$)](PF$_6$)$_2$.** Complex 21 (17.9 mg, 0.036 mmol) and TIPF$_6$ (24.9 mg, 0.071 mmol) were dissolved in 5 mL anhydrous acetonitrile, producing a dark-yellow solution that was stirred for 20 hours at room temperature. Subsequently, the mixture was filtered and all volatiles were evaporated to produce a dark-yellow solid in quantitative yield. $^1$H NMR (400 MHz, acetonitrile-$d_3$, ppm): δ 12.06 (s, 2H), 8.36 (t, $J = 8.0$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 1.9$ Hz, 2H), 1.46 (s, 18H). $^3$P NMR (162 MHz, acetonitrile-$d_3$, ppm): δ -146.8 (hept, $J = 707$ Hz). $^{13}$C NMR (126 MHz, acetonitrile-$d_3$, ppm): δ 159.8 (s), 153.6 (s), 150.7 (s), 145.0 (s), 121.4 (s), 103.8 (s), 32.1 (s), 28.9 (s). HR-MS (CSI$^+$) (C$_{9}$H$_{13}$ClN$_{3}$Pd): $m/z$ calcd. 429.11448; found 429.10269 [M-MeCN] IR (ATR, cm$^{-1}$): 1616 (m), 1560 (m).

**Complex 24, Pd(PMe$_3$)(L$_2$)**. Complex 21 (97.3 mg, 0.194 mmol) was dissolved in 10 mL acetonitrile and KHMDS (0.5M in toluene) (0.78 mL, 0.389 mmol) was added. PMe$_3$ (22 mL, 0.2 mmol) was added and the yellow mixture was stirred for 2 hours. The mixture was filtered and all volatiles were evaporated to yield a yellow powder (65%). $^1$H NMR (400 MHz, acetonitrile-$d_3$, ppm): δ 7.82 (t, $J = 7.9$ Hz, 1H), 7.23 (dd, $J = 7.9, 1.7$ Hz, 2H), 6.53 (s, 2H), 1.83 (d, $J = 12.2$ Hz, 9H), 1.32 (s, 18H). $^3$P NMR (162 MHz, acetonitrile-$d_3$, ppm): δ -4.6 (s). $^{13}$C NMR (100 MHz, acetonitrile-$d_3$, ppm): δ 153.0 (s), 151.4 (s), 141.6 (s), 113.2 (s), 100.1 (s), 99.9 (s), 31.9 (s), 30.3 (s), 12.6 (d, $J = 32.5$ Hz). HR-MS (CSI$^+$) (C$_{22}$H$_{32}$N$_{3}$Pd): $m/z$ calcd. 504.14387; found 504.14520. IR (ATR, cm$^{-1}$): 1597 (m), 1562 (m).

**Complex 25, [Pd(PMe$_3$)(L$_2$)Cl].** Complex 21 (103.7 mg, 0.21 mmol) was dissolved in 10 mL acetonitrile and PMe$_3$ (23.6 mL, 0.22 mmol) was added. The yellow solution was stirred for 3 hours before all volatiles were evaporated. Alternatively, complex 24 (12.1 mg, 0.024 mmol) was dissolved in 1 mL acetonitrile and HCl (1.0M solution in diethyl ether) (24 µL, 0.024 mmol) was added. The solution was stirred for 1 hour before all volatiles were evaporated. $^1$H NMR (400 MHz, acetonitrile-$d_3$, ppm): δ 11.54 (s, 2H), 8.08 (t, $J = 7.9$ Hz, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 7.8$ Hz, 1H), 6.83 (d, $J = 10.2$ Hz, 2H), 1.73 (d, $J = 11.7$ Hz, 9H), 1.09 (s, 18H). $^3$P NMR (162 MHz, acetonitrile-$d_3$, ppm): δ 0.86 (s). HR-MS (CSI$^+$) (C$_{22}$H$_{32}$N$_{3}$Pd): $m/z$ calcd. 504.15084; found 504.15478. IR (ATR, cm$^{-1}$): 1597 (m), 1572 (m).

**Complex 26, Pd(pyridine)(L$_2$)**. Complex 21 (20.9 mg, 0.04 mmol) and KHMDS (16 mg, 0.08 mmol) were dissolved in 2 mL pyridine. The solution, which turned bright yellow, was stirred for 3 hours before filtration and evaporation. $^1$H NMR (400 MHz, methylene chloride-$d_3$, ppm): δ 10.26 (d, $J = 5.6$ Hz, 2H), 8.03 (t, $J = 7.5$ Hz, 1H), 7.75 (t, $J = 7.9$ Hz, 1H), 7.61 (t, $J = 6.9$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 6.56 (s, 2H), 1.42 (s, 18H). $^{13}$C NMR (101 MHz, methylene chloride-$d_3$, ppm): δ 160.6 (s), 153.2 (s), 152.4 (s), 150.8 (s), 140.5 (s), 138.5 (s), 124.9 (s), 112.6 (s), 100.0 (s), 32.23 (s), 30.6 (s). HR-MS (CSI$^+$) (C$_{24}$H$_{18}$N$_{3}$Pd): $m/z$ calcd. 506.14103; found 506.13903. IR (ATR, cm$^{-1}$): 1603 (m), 1561 (m).
Complex 27, Pd(PMe$_3$)$_2$(L$_2$)**. Complex 24 (16.8 mg, 0.04 mmol) and iodine (9.0 mg, 0.04 mmol) were dissolved in 1 mL deuterated acetonitrile. Within an hour, the yellow solution turned dark-red. $^1$H NMR (400 MHz, acetonitrile-$d_3$, ppm): δ 7.90 (t, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 6.83 (br s, 1H), 1.81 (d, $J = 12.3$ Hz, 9H), 1.32 (s, 18H). $^{31}$P NMR (162 MHz, acetonitrile-$d_3$, ppm): δ 37.4 (s). $^{13}$C NMR (126 MHz, acetonitrile-$d_3$, ppm): δ 160.0 (s), 159.2 (s), 155.1 (s), 143.4 (s), 120.8 (s), 103.8 (s), 32.0 (s), 28.9 (d, $J = 8.4$ Hz), 15.1 (d, $J = 72.6$ Hz). HR-MS (CSI$^+$) (C$_{22}$H$_{32}$IN$_5$PPd): m/z calcd. 630.0475; found 630.0450 [M-I]. IR (ATR, cm$^{-1}$): 1605 (m), 1563 (m).

General procedure for catalytic transfer hydrogenation
To a Schlenk containing a magnetic stirrer, 1 mol% of catalyst, and 10 mol% of base were added distilled acetophenone (1 mmol) as substrate, 10 µL p-xylene as internal standard, and 2 mL isopropanol. The mixture was stirred at 75 ºC. Aliquots were taken from the mixture during the reaction, which were subsequently filtered over a plug of silica and analyzed by GC.

General procedure for intramolecular hydroamination
Typically, the relevant Pd or Co complex (0.01 mmol) and the additives (0.02 mmol) were dissolved in the desired solvent (2 mL) and stirred for 10 minutes. The aminoalkene substrate (0.1 mmol) was added to the mixture and the reaction was stirred at room temperature, unless stated otherwise. Reaction times varied from 16 to 20 hours. The yields of the products were determined by NMR analysis.

X-ray crystallography
X-ray intensities were measured on a Bruker D8 Quest Eco diffractometer equipped with a Triumph monochromator ($\lambda = 0.71073$ Å) and a CMOS Photon 50 detector at a temperature of 150(2) K. Intensity data were integrated with the Bruker APEX2 software. Absorption correction and scaling was performed with SADABS. The structures were solved with the program SHELXL. Least-squares refinement was performed with SHELXL-2013 against F$^2$ of all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. The H atoms were placed at calculated positions using the instructions AFIX 13, AFIX 43 or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times U$^{eq}$ of the attached C atoms. N-H hydrogen atoms were refined freely with isotropic displacement parameters.

5.5 References

[34] G. M. Sheldrick, SHELXL2013, University of Göttingen, Germany, 2013.
5.6 Appendix

The original idea for this research was the comparison between tridentate NNN ligands based on pyrazoles and hydroxy-pyridines (Scheme 19). They both have a similar tautomerization for proton transfer, have their reactive sites in close proximity to the metal center and also direct in the equatorial plane.

![Scheme 19. Tautomerization between a pyrazolato and a pyrazole (left) and a pyridone and a hydroxy-pyridine (right), with reversible protonation of the β-nitrogen.]

Although the synthesis of ligand L3 is reported, we could not synthesize the targeted product. Starting from the 6,6′-dibromo-terpyridine, a palladium(II)-catalyzed coupling with sodium tert-butoxide was performed and should afford the 6,6′-di-tert-butoxy-terpyridine, from where hydrolysis of the tert-butoxide groups is carried out to obtain the final 6,6′-dihydroxy-terpyridine ligand. Although several attempts were carried out, not once was the desired intermediate obtained.

The tert-butoxide, which is a very strong base, cannot attack the 2-position of the pyridine since it is a very poor nucleophile. Therefore, the bromide will not be replaced, leaving only starting material left (Scheme 20, left). An alternative route was tested where the 6,6′-dibromo-terpyridine was reacted with n-butyl lithium, followed by in situ borylation and subsequent hydrolysis. Unfortunately, this did not give the desired product either. A possible explanation is the fact that in this synthesis the aromatic ring that is attacked is a pyridine, where mostly phenyl rings are reported for this type of reactions (Scheme 20, right).

![Scheme 20. a) Attack of the tert-butoxide on the pyridine is very unlikely, since it is a very poor nucleophile. b) Alternative synthesis to 6,6′-dihydroxy-terpyridine, where the bromides are substituted by boranes, followed by hydrolysis.]

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Because this ligand was still valued as worthy, it was reasoned we could synthesize this via a multicomponent reaction. In 2012, the group of Orru described the synthesis of benzo[a]quinolizines via the four-component reaction of 3,4-dihydro-pyridin-2-ones.\textsuperscript{37} We envisioned the synthesis of the 6,6'-dihydroxypyridine should be straightforward, although two ring closing events had to occur in this situation to form both hydroxyl-pyridine side-arms of $L_3$, compared to the single heterocycle formation that was reported. Starting from diethyl methyl phosphonate $a$, methyl isocyanoacetate $b$, benzaldehyde $c$ and half an equivalent of 2,6-pyridinedinitrile $d$, the isocyanide-containing 3,4-dihydropyridin-2-one $L_3^{NC}$ should have been synthesized easily (Scheme 21).

Unfortunately, it appeared very difficult to form a pyridone on both sides of the central pyridine ring. From $^1$H and $^{13}$C NMR spectra and $^1$H-$^{13}$C HMQC correlation we concluded that the desired product was not obtained but that the formed species was compound $L_4^{NC}$, which we considered as an intermediate that could lead to a very interesting ligand (Scheme 22). Deprotonation with an excess of NaH should provide the corresponding 2-pyridone via facile elimination of the isocyano group, but ligand $L_4$ was not obtained.

\textbf{Scheme 21.} Retro synthesis of 2,6-pyridine-(3,4-dihydropyridin-2-one) $L_3^{NC}$ from diethyl methyl phosphonate $a$, methyl isocyanoacetate $b$, benzaldehyde $c$ and half an equivalent of 2,6-pyridinedinitrile $d$.

\textbf{Scheme 22.} Ligand $L_4^{NC}$ was the product obtained from the multicomponent reaction. Deprotonation with an excess of NaH to obtain ligand $L_4$ was unfortunately unsuccessful.