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Ruthenium(II) pincer complexes with oxazoline arms for efficient transfer hydrogenation reactions

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ABSTRACT

Well-defined P^NN^CN pincer ruthenium complexes bearing both strong phosphine and weak oxazoline donors were developed. These easily accessible complexes exhibit significantly better catalytic activity in transfer hydrogenation of ketones compared to their PN^3P analogs. These reactions proceed under mild and base-free conditions via protonation–deprotonation of the 'NH' group in the aromatization–dearomatization process.

Transition metal complexes with rigid tridentate pincer ligands have been studied extensively because their chemical and physical properties can be tuned by varying the steric and electronic parameters of the donor groups to afford interesting and useful reactivities.[1] Many of these complexes have been employed to facilitate a variety of organic transformations, including carbon dioxide reduction,[2] catalytic dehydrogenation of alkanes,[3] catalytic hydrogenation of ketones,[4] hydrosilylation of aldehydes and ketones,[5] transfer hydrogenation of ketones,[6] cross-coupling,[7] selective decarbonylation reactions of alkyl formates and alkynyl aldehydes,[8] dehydrogenation of alcohols to ketones,[9] dehydrogenative homocoupling of primary alcohols to esters,[10] direct amidation from alcohols and amines,[11] light-induced water splitting,[12] etc. Among these applications, the concept of cooperative catalysis has received increasing attention. One of the most remarkable examples is Milstein's PNN–Ru system.[13] The unprecedented reactivities of the PNN system are believed to be attributed to the introduction of a hemi-labile donor in the pincer ligand and the ability of the pyridine ring to undergo dearomatization and rearomatization, resulting in a ligand that can act cooperatively with the metal center for substrate activation. Based on a similar concept, analogous ruthenium complexes using *N*-heterocyclic carbenes as an alternative to phosphine donors have also been reported (Fig. 1).[14]

Compared to C–H bonds, N–H bonds are in general more acidic.[15] Replacement of the CH_2 spacer of the phosphine arm with an NH may favor the deprotonation/dearomatization of the PNN-pincer ligand and offer different reactivities. Pincer ligands with N–H spacers have been synthesized,[16] but their involvement in catalytic reactions has not been studied until our recent work. We have demonstrated that a dearomatized ruthenium complex based on a PN^3P ligand employing an NH spacer displays good catalytic activities in transfer hydrogenation of ketones at 82 °C.[17] It was envisaged that replacement of one of the phosphine groups with a weaker donor may allow the ligand to dissociate from the metal center more easily and to facilitate the hydride elimination of a plausible isopropoxide intermediate,[12] and may consequently increase the catalytic activities of this type of pincer catalyst. Oxazolines, derived from amino alcohols, are a sub-class of azole heterocycles, which commonly act as weak donors. Pincer complexes containing one or two oxazoline groups have received increasing attention due to their easy accessibility from a wide variety of commercially available aminoalcohols.[18] With this consideration in mind, we combined a phosphine ligand using NH as the linker and an oxazoline ring as a relatively weaker donor to create new ligands. Herein, we report the synthesis of novel hemilabile P^NN^CN pincer ligands and their Ru(II) complexes, which show significantly improved activities in transfer hydrogenation of ketones compared to those of analogous complexes with the symmetric PN^3P ligand.

Starting from commercially available 6-bromopicolinic acid (**1**), *N*-(di-*tert*-butylphosphino)-6-(4,5-dihydrooxazol-2-yl)pyridin-2-amine (P^NN^CN **6a**) and *N*-(di-*tert*-butylphosphino)-6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)pyridin-2-amine (P^NN^CN **6b**) were prepared conveniently in high yields (Scheme 1). Upon treatment with oxalyl chloride in tetrahydrofuran (THF), acid **1** reacted with amino alcohols in the presence of triethylamine to afford

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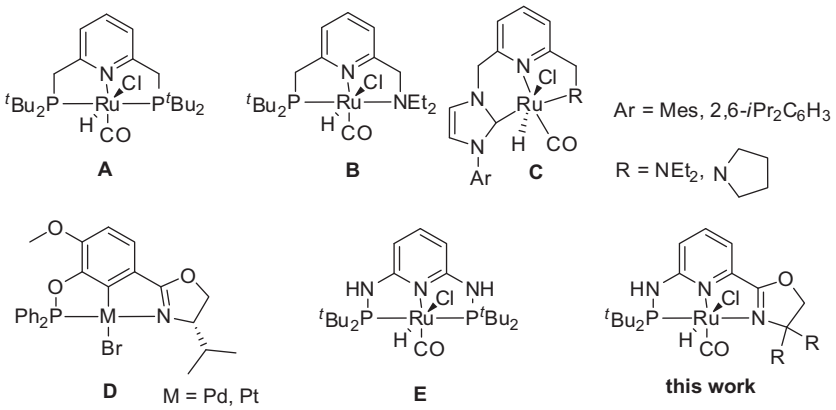
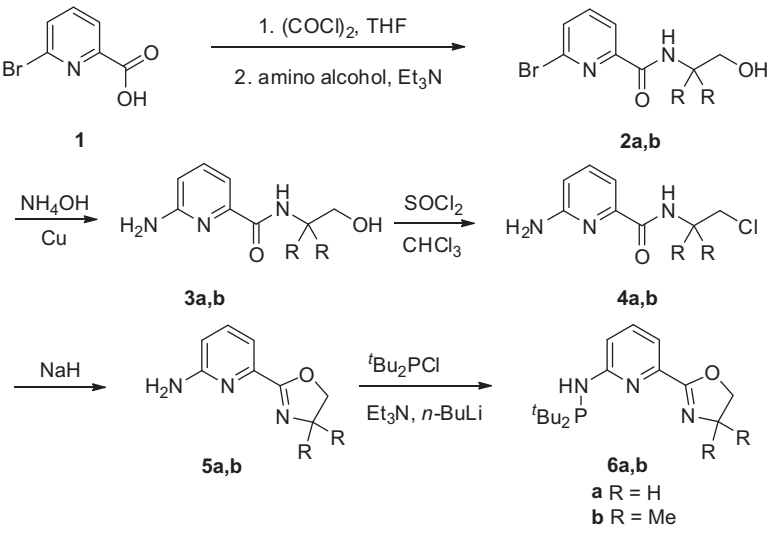


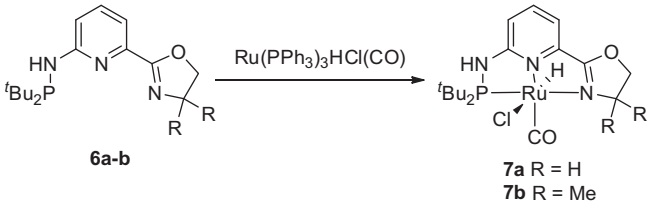
Figure 1. Various pincer complexes.



Scheme 1. Synthetic route for the preparation of ligands **6a**–**b**.

compounds **2a**,**b** in 76% and 81% overall yields, respectively. Amides **2a**,**b** were then heated with ammonium hydroxide in the presence of copper in a pressure tube at 100 °C for 24 h to give amino compounds **3a**,**b** as white solids in 70% and 72% yields. It was noted that the oxazoline group could undergo ring-opening under the above-mentioned conditions, so the amination must be conducted before constructing the oxazoline. Substitution of the hydroxy group of **3a**,**b** with a chlorine was achieved by reaction with thionyl chloride in chloroform at reflux to produce compounds **4a**,**b** in 96% and 95% yields.[19] The oxazoline rings were generated by deprotonating **4a**,**b** with sodium hydride followed by intramolecular nucleophilic substitution to afford **5a**,**b** in 72% and 81% yields. The phosphine donors were introduced according to Benito-Garagorri's strategy by treating **5a**,**b** with one equivalent of di-*tert*-butylchlorophosphine in the presence of triethylamine and *n*-butyllithium to give oxazolines **6a**,**b**, which were sufficiently pure to be used without purification.[16a]

Reaction of the new pincer ligands **6a**,**b** with $Ru(PPh_3)_3HCl(CO)$ in THF at reflux for 16 h resulted in the formation the hydrido chlororuthenium pincer complexes **7a**,**b** as red solids (Scheme 2). The appearance of a doublet at −16.58 ppm (J = 19.8 Hz) in the ^1H NMR spectrum of **7b** indicated the existence of a hydride ligand, which was further confirmed by the absorptions at 2041 cm^{-1} (Ru-H) in the IR spectrum. The $^{13}C\{^1H\}$ NMR signal at 206.78 ppm and the absorption at 1926 cm^{-1} in the IR were indicative of the existence of a CO ligand. $^{31}P\{^1H\}$ NMR spectroscopy of **7b** showed a singlet at 162.6 ppm, 53.9 ppm more downfield compared to the similar ruthenium complex (108.7 ppm) of 2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl) pyridine, mainly due to the replacement of the CH_2 spacer by NH.[10] Complex **7a** showed similar spectra to those of **7b**. Suitable crystals for single-crystal X-ray analysis were obtained by recrystallization of **7b** from dichloromethane/*n*-pentane (Fig. 2). The molecular structure shows a distorted octahedral geometry around the Ru(II) center, with the CO ligand coordinated *trans* to the pyridine nitrogen and the hydride *trans* to the chloride.



Scheme 2. Synthesis of ruthenium complexes **7a** and **7b**.

Treatment of **7b** with one equivalent of KO^{t}Bu under an argon atmosphere in THF resulted in an immediate color change from bright-red to dark-red and increased solubility (Scheme 3). In the

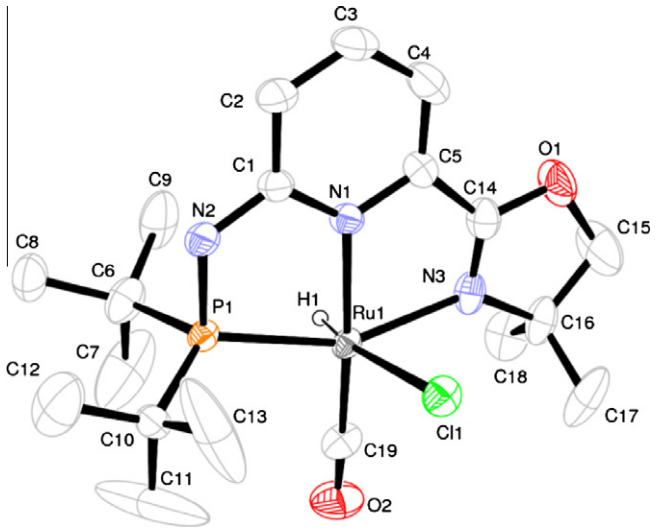
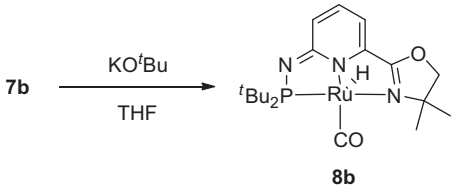


Figure 2. ORTEP representation of complex **7b** with thermal ellipsoids drawn at the 30% probability level. Hydrogen atoms (except hydride) are omitted for clarity.

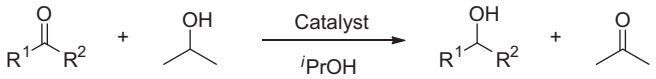


Scheme 3. Synthesis of ruthenium complex **8b**.

^{1}H NMR spectrum of **8b**, the disappearance of the broad NH signal at 8.10 ppm indicated that the N–H bond was deprotonated and the signals at 7.05, 6.61, and 6.25 ppm confirmed the dearomatization of the pyridine ring in the complex. The deprotonated and dearomatized complex **8b** was isolated as a brown-red solid in 97% yield. The hydride of **8b** appeared as a doublet at −26.83 ppm (J = 19.5 Hz), an upfield shift of 10.25 ppm, suggesting that the *trans* chloride ligand had been removed. The IR spectrum showed a CO absorption at 1897 cm^{-1} (Ru-CO), in good agreement with a more electron-rich ruthenium center.

The reduction of ketones employing catalytic hydrogenation transfer conditions with 2-propanol as the hydrogen source has been extensively investigated, and several ruthenium complexes have been proven to be efficient catalysts/catalyst precursors in transfer hydrogenation reactions.[20] In this regard, a number of pincer ruthenium complexes have also been employed as catalysts in the transfer hydrogenation of ketones. Selected recent examples include ruthenium CNN pincer complexes,[21] pincer-type pyridine-based (NHC)NN–Ru(II) complexes,[14a] and ruthenium(II) complexes bearing an unsymmetrical NNN ligand.[22] The activities of our new P^{N}N^{C}N–Ru complexes **7a**,**b** toward transfer hydrogenation were examined (Table 1). Initial experiments were conducted using cyclohexanone as the substrate with 2-propanol as the hydrogen source. Ruthenium complexes **7a**,**b** were found to be efficient catalysts in the presence of a base at 40 °C: 96% and 98% yields were achieved respectively in 16 h (entries 2 and 4). However, in the absence of a base, the reaction failed to proceed under similar reaction conditions (entries 1 and 3), suggesting that deprotonation of ruthenium complexes **7a**,**b** was necessary for the transfer hydrogenation reactions. Consistent with these observations, the deprotonated ruthenium complex **8b** displayed excellent catalytic activity under base-free conditions: 99% yield at 40 °C in 16 h (entry 5), a clearly improved result was achieved at

Table 1
Transfer hydrogenation of ketones with Ru complexes **7a**,**b** and **8b**[a]



Entry	Catalyst	Substrate	Time (h)	Yield[b] (%)
1	**7a**	Cyclohexanone	16	0
2[c]	**7a**	Cyclohexanone	16	96
3	**7b**	Cyclohexanone	16	0
4[c]	**7b**	Cyclohexanone	16	98
5	**8b**	Cyclohexanone	16	99
6	**8b**	Cyclohexanone	16	91
7	**8b**	2-Hexanone	16	94
8	**8b**	2-Heptanone	16	91
9[d]	**8b**	3-Hexanone	16	99
10[d]	**8b**	4-Heptanone	16	99
11	**8b**	4-*tert*-Butylacetophenone	16	61
12	**8b**	Acetophenone	16	74 (70)
13	**8b**	4-Bromoacetophenone	10	87 (85)
14[d]	**8b**	1-Acetonaphthone	5	93 (92)

[a] Reaction conditions: 0.5 mmol of ketone, 1.0 mol % of Ru complex in 1 mL of ^{i}PrOH at 40 °C.
[b] Determined by GC–MS or ^{1}H NMR spectroscopy, isolated yield in parenthesis.
[c] 1.0 mol % of KO^{t}Bu was added.
[d] Reactions were conducted at 82 °C.

a lower reaction temperature and in a shorter reaction time compared to the results of similar complexes with the PN^{3}P ligand.[17]

To explore the scope of the reaction catalyzed by ruthenium complex **8b**, a variety of ketones were examined (Table 1, entries 5–14). In general, the P^{N}N^{C}N-Ru complex **8b** showed significantly improved catalytic activity compared to the complex with the symmetric PN^{3}P ligand. Excellent yields (91 to >99%) were achieved for cycloketones and 2-alkylketones (entries 5–8) at 40 °C. For 3-hexanone and 4-heptanone, the reactions were a little slow, but more than 99% yields were obtained in 16 h at elevated temperature (entries 9 and 10). Aromatic ketones can be hydrogenated to the corresponding alcohols in moderate to good yields (61–93%, entries 11–14). An aromatic ketone with an electron-withdrawing substituent at the *para* position gave better results than those with electron-donating substituents.

In summary, we have reported the design, synthesis, and characterization of novel P^{N}N^{C}N pincer ligands with oxazoline arms and their corresponding ruthenium complexes. By introducing an oxazoline arm, the dearomatized ruthenium complexes exhibited much increased catalytic activities for the transfer hydrogenation of ketones compared to similar ruthenium complexes with a PN^{3}P ligand. Further modification of the ligand to tune the steric environment and hemi-lability, and the exploration of their applications are ongoing in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.041.

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