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Hydrogenation/dehydrogenation of N-heterocycles catalyzed by ruthenium complexes based on multimodal proton-responsive CNN(H) pincer ligands†

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Ru complexes based on lutidine-derived pincer CNN(H) ligands having secondary amine side donors are efficient precatalysts in the hydrogenation and dehydrogenation of N-heterocycles. Reaction of a Ru-CNN(H) complex with an excess of base produces the formation of a Ru(0) derivative, which is observed under catalytic conditions.

Following pioneering work by Noyori *et al.* on the use of metal complexes based on ligands bearing primary or secondary amine donors capable of getting involved in reversible metal-amine/metal-amido interconversion,[1] a considerable diversity of ligands containing Brønsted acid/base functionalities have been developed.[2] Among others, lutidine-derived metal complexes, which are readily deprotonated at the pincer methylene arms with concomitant dearomatization of the pyridine central moiety, have received significant attention.[3] Both lutidine- and NH-containing pincer complexes have provided highly active and selective catalysts for a broad variety of hydrogenation[4] and dehydrogenation reactions.[5]

Recently, the Milstein group has reported novel Ru complexes incorporating lutidine-based PNN(H) ligands containing secondary amines as side donors that are efficient catalysts in the (de)hydrogenation of polar substrates.[6,7] These complexes are active ester and amide hydrogenation catalysts under very mild conditions, and catalyze the dehydrogenative coupling of alcohols to esters at low temperatures. Interestingly, reaction of a Ru-PNN(H) complex with 2 equiv. of base produced the formation of an enamino anionic Ru(II) species,[6] which according to DFT calculations catalyzes the dehydrogenative coupling of alcohols solely through amine-metal/amido-metal interconversion.[8]

On the other hand, hydrogenation and acceptorless dehydrogenation are low environmental impact processes for the reduction of aromatic N-heterocycles to their corresponding saturated derivatives and the oxidation of the latter products to the parent N-heteroarenes, respectively.[9] Although the principle of microscopic reversibility dictates that species able to catalyze the hydrogenation of N-heterocycles should also be active in the reverse dehydrogenation process, the number of catalytic systems that are able to perform both transformations is scarce, being these mainly based on M-PN^{H}P (M = Fe, Co) complexes[10] or costly CpIr derivatives.[11]

Pincer complexes based on N-heterocyclic carbenes (NHCs) have received an increased attention as catalysts in hydrogenation and dehydrogenation reactions.[12] An interesting modification of the structure of lutidine-derived PNP and PNN ligands consists on the substitution of the P-donors by NHC groups.[13] Herein, we report a series of Ru complexes stabilized with lutidine-derived CNN(H) pincer ligands incorporating secondary amino groups that are suitable catalytic precursors in both the hydrogenation and dehydrogenation of N-heterocycles. Because of the presence of two acidic functionalities in the ligands, these complexes might exhibit metal–ligand cooperation based on pyridine aromatization/dearomatization or amine-metal/amido-metal interconversion. However, preliminary NMR spectroscopic data revealed the unexpected formation of a zero-valent Ru complex under catalytic conditions.

Aiming to synthesize Ru-CNN(H) complexes, the imidazolium salts **1a–c** were made react with Ag_2O in CH_2Cl_2 to yield the silver complexes **2a–c** (Scheme 1). Subsequent reactions of **2a–c** with $RuHCl(CO)(PPh_3)_3$ in THF, followed by treatment with $NaBF_4$ and PPh_3 in CH_3CN, allowed the isolation of the

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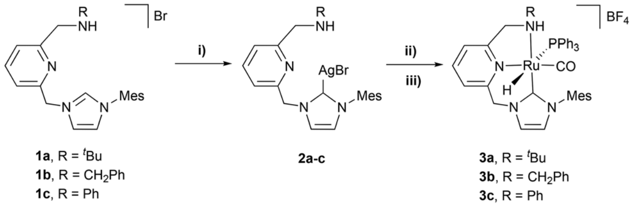
† Electronic supplementary information (ESI) available: Experimental procedures; X-ray diffraction analysis; and DFT calculations details. CCDC 1968868 [**3a**·CH_2Cl_2] and 1968869 [**3b**·$2CH_3OH$]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0dt02326d



i) Ag_2O, CH_2Cl_2; ii) $RuHCl(CO)(PPh_3)_3$, THF; iii) $NaBF_4$, PPh_3, MeCN

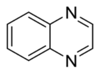
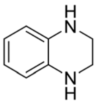
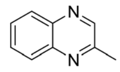
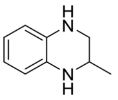
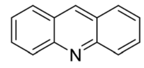
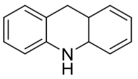
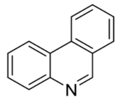
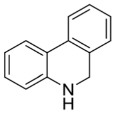
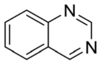
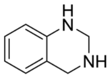
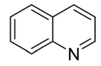
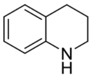
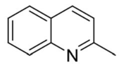
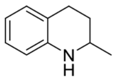
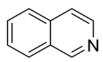
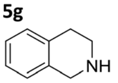
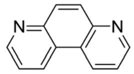
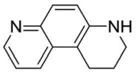
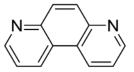
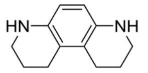
Scheme 1 Synthesis of Ru–CNN(H) complexes.

Ru-CNN(H) complexes **3a–c** in moderate to good yields (33–85%). In the ^{1}H NMR spectrum, the hydrido ligand of **3a** gives rise to a doublet resonance at −7.79 ppm with a large $^2J_{HP}$ of 114.0 Hz, evincing the *trans* arrangement of the hydrido and PPh_3 ligands. Similar NMR features are observed for complexes **3b** and **3c**. This structural arrangement was further confirmed in the solid state by an X-ray diffraction study of **3a** and **3b** (ESI†).

Next, the catalytic behavior of **3a–c** in the hydrogenation of N-heterocycles was examined (Table 1). In the presence of KO^{t}Bu (5 mol%), complex **3a** (0.5 mol%) catalyzed the hydrogenation of quinoxaline (**4a**) under 4 bar of H_2 at 80 °C leading to full conversion in 6 h (entry 1). However, under the same conditions, complexes **3b** and **3c** were found to be less active than **3a** (entries 2 and 3). Based on these results, complex **3a** was tested in the hydrogenation of a series of N-heterocycles. For example, 2-methylquinoxaline (**4b**) was reduced under the above conditions with high conversions in 24 h (entry 4). Similarly, using 0.5 mol% of **3a**, acridine (**4c**) and phenanthridine (**4d**) were hydrogenated with elevated conversions in 19 h (entries 5 and 6). However, the hydrogenation of quinazoline (**4e**), quinoline (**4f**) and quinaldine (**4g**) required harsher reaction conditions (1.0 mol% **3a**, 95 °C, 48 h) to proceed to higher than 95% conv (entries 7–9). Under the later conditions, an increase of the H_2 pressure to 10 bar was used for the hydrogenation of isoquinoline (**4h**) (entry 10). Finally, under 4 bar of H_2, selective reduction of one of the N-containing rings of 4,7-phenanthroline (**4i**) was achieved, while the hydrogenation of both N-heterocycles was accomplished at 10 bar of H_2 (entries 11 and 12).

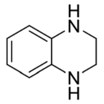
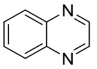
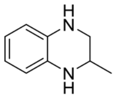
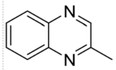
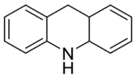
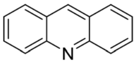
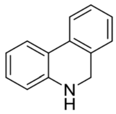
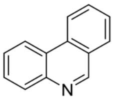
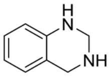
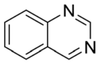
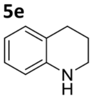
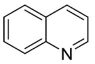
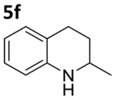
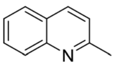
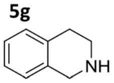
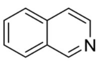
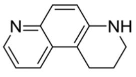
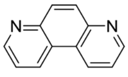
The catalytic performance of **3a** in the dehydrogenation of the N-heterocycles **5** was also investigated (Table 2). Initially, dehydrogenation of 1,2,3,4-tetrahydroquinoxaline (**5a**) was examined using 4.0 mol% of **3a** and 60 mol% of KO^{t}Bu in 2-methyltetrahydrofuran at 85 °C, leading to complete formation of **4a** after 24 h (entry 1). However, a higher temperature was required for the reaction of **5b** (160 °C, *o*-xylene) (entry 2). In addition, the oxidation of other N-heterocyclic substrates was examined. 9,10-Dihydroacridine (**5c**) was dehydrogenated in refluxing *o*-xylene with moderate catalytic activity (entry 3). Meanwhile, under the same conditions, hydrogen release from **5d** and **5e** took place with higher than 94% conv. (entries 4 and 5). The dehydrogenation of **5f**, **5g** and **5h** proceeded with only low to moderate conversions after 48 h (entries 6–8); whereas **5i** yielded 4,7-phenanthroline in 74% NMR yield (entry 9). To the best of our knowledge, complex **3a** is the first example of a Ru derivative that catalyzes both the hydrogenation and dehydrogenation of a series of N-heterocycles. In addition, the catalytic activity of **3a** in the reduction of N-heteroarenes lies in the range of most CpIr systems, although it is less efficient in the dehydrogenation reactions (0.1–5 mol% Ir, 74–160 °C).[11] Moreover, the performance of **3a** is superior to that of the Fe-PN^{H}P catalyst in the hydrogenation of N-heterocycles (3 mol% Fe, 80 °C, 5 bar H_2),

Table 1 Hydrogenation of N-heterocycles catalyzed by **3a–c**

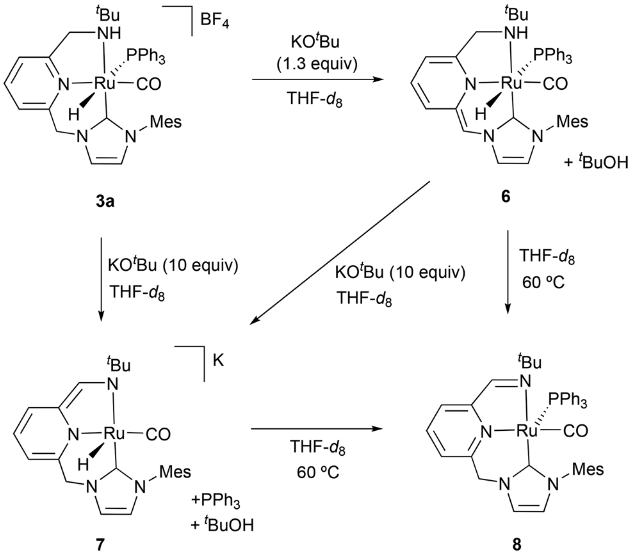
Entry	Substrate	Product	Cat.	Yield (%)
1	 **4a**	 **5a**	**3a**	>99 (6 h)
2			**3b**	23 (6 h)
3			**3c**	22 (6 h)
4	 **4b**	 **5b**	**3a**	>99 (24 h)
5	 **4c**	 **5c**	**3a**	98 (19 h)
6	 **4d**	 **5d**	**3a**	92 (19 h)
7^{a,b}	 **4e**	 **5e**	**3a**	98 (48 h)
8^{a,b}	 **4f**	 **5f**	**3a**	>99 (48 h)
9^{a,b}	 **4g**	 **5g**	**3a**	95 (48 h)
10^{a,b,c}	 **4h**	 **5h**	**3a**	74 (24 h)
11^{a,b}	 **4i**	 **5i**	**3a**	>99 (24 h)
12^{a,b,c}	 **4i**	 **5ii**	**3a**	93 (72 h) (+7% **5i**)

Reaction conditions: Unless otherwise noted: 4 bar H_2, 80 °C, 2-methyltetrahydrofuran, 0.5 mol% Ru–CNN(H), 5 mol% KO^{t}Bu; [*S*] = 0.24 M. Yields were determined by ^{1}H NMR spectroscopy using mesitylene as internal standard. ^{a} 95 °C. ^{b} 1.0 mol% **3a**. ^{c} 10 bar H_2.

Table 2 Dehydrogenation of N-heterocycles catalyzed by complex **3a**

Entry	Substrate	Product	Yield (%)
1^a	 **5a**	 **4a**	>99 (24 h)
2	 **5b**	 **4b**	85 (24 h)
3	 **5c**	 **4c**	76 (48 h)
4	 **5d**	 **4d**	94 (24 h)
5	 **5e**	 **4e**	>99 (24 h)
6	 **5f**	 **4f**	50 (48 h)
7	 **5g**	 **4g**	27 (48 h)
8	 **5h**	 **4h**	27 (48 h)
9	 **5i**	 **4i**	74 (48 h)

Reaction conditions, unless otherwise noted: 160 °C, *o*-xylene, 4.0 mol% **3a**, 60 mol% KO^{t}Bu. [*S*] = 0.12 M. Yields were determined by ^{1}H NMR spectroscopy using mesitylene as internal standard. ^{a} 85 °C, 2-methyltetrahydrofuran. [*S*] = 0.06 M.



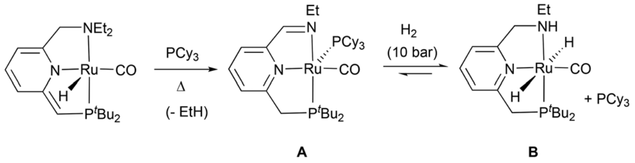
Scheme 2 Generation of Ru complexes **6–8**.

while it is slightly poorer in the dehydrogenation reactions (3 mol% Fe, xylene reflux).[10]

To investigate the likely Ru species formed under catalytic conditions, complex **3a** was treated with KO^{t}Bu (1.3 equiv.) in THF-d_8 producing the instantaneous dark red coloring of the initially clear solution. Formation of the deprotonated complex **6** was ascertained by ^{1}H NMR spectroscopy (Scheme 2), which shows the hydrido ligand of **6** giving rise to a broad doublet at −7.64 ppm with a large $^2J_{HP}$ of 140.2 Hz, indicative of its *trans* coordination to PPh$_3$. Selective deprotonation of the CH$_2$-NHC arm of **3a** was evident from the observation of a singlet signal at 4.38 ppm (integrating to 1H), due to the methyne =CH–NHC bridge, and two doublets of doublets at 3.43 ($^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 12.0 Hz) and 3.09 ($^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 1.9 Hz) ppm, attributable to the CH$_2$-NH moiety. Subsequent treatment of the same THF-d_8 solution of complex **6** with an excess of KO^{t}Bu (10 equiv.) or KHMDS (3 equiv.) produced a dark violet coloring of the sample (Scheme 2). The NMR spectra of the reaction mixture pointed out to the formation of the anionic complex **7**, which is structurally related to an enamino Ru(II) complex previously reported by Milstein *et al.*[6] The hydride and the enamino =CH–N^{t}Bu hydrogens of the pincer ligand resonate as singlets at −17.09 and 6.69 ppm, respectively, in the ^{1}H NMR experiment, while the inequivalent methylene protons of the CH$_2$–NHC bridge appear as mutually coupled doublets at 4.83 and 4.56 ppm ($^2J_{HH}$ = 12.7 Hz). Also of note, the hydrogens of the pincer dearomatized central ring produce upfield shifted resonances in the range between 5.33 and 6.54 ppm.

THF-d_8 solutions pressurized with H$_2$ (3 bar) of the *in situ* generated complexes **6** and **7** were analyzed by NMR spectroscopy in order to determine the potential of these species to perform H$_2$ activation. However, noticeable changes in their ^{1}H NMR experiments were not observed. Alternatively, pressurization of solutions of complexes **6** and **7** with D$_2$ (3 bar) produced the H/D exchange of the hydride ligands and the protons of the methylene and methyne bridges (ESI†), evincing the ability of complexes **6** (after PPh$_3$ decoordination) and **7** to produce the reversible activation of H$_2$ in a ligand-assisted process or through the participation of an external base.

Unexpectedly, heating to 60 °C solutions of the *in situ* formed species **6** or **7** produces the clean generation of a new species, which has been spectroscopically characterized as the Ru(0) imine complex **8** (Scheme 2).[14] The ^{1}H NMR spectrum of the resulting dark blue solutions indicates the presence of the imine moiety by the appearance of a doublet at 7.92 ppm ($^4J_{HP}$ = 3.7 Hz). The ^{13}C{^{1}H} NMR spectrum presents the resonances



Scheme 3 Complexes A and B reported by Keith, Chianese *et al.*

corresponding to the CO ligand and the C^2–NHC carbon as doublets at 216.1 (J_{CP} = 10 Hz) and 191.3 (J_{CP} = 7 Hz) ppm, respectively. Finally, the coordination of PPh_3 is manifested in the $^{31}P\{^1H\}$ NMR experiment by the appearance of a singlet at 50.5 ppm. Complex **8** can be regarded as derived from **6** by the formal loss of a H_2 molecule.

It is worth noting that imine Ru(0) complexes structurally related to **8** have been recently reported by Keith, Chianese *et al.* (Scheme 3).[14] These derivatives (such as **A**), which were shown to be highly active ester hydrogenation catalysts, were isolated from the reactions with base of Ru–PNN and –CNN complexes bearing dialkylamino side donors. Moreover, hydrogen activation by **A** led to the formation of a Ru dihydride complex (**B**) in which the imine ligand fragment was hydrogenated to amine. Interestingly, solutions of the Ru(0) derivative **8** were active in the hydrogenation of N-heterocycles.[14,15] Thus, THF-d_8 solutions containing this complex were able to hydrogenate (3 bar H_2) 2-methylquinoxaline (10 equiv.) at 60 °C, being **8** the only detectable metal species during the catalytic reaction and suggesting that this is the catalyst resting state (ESI†). Similarly, addition of 2-methylquinoxaline (10 equiv.) to a THF-d_8 solution of a 1 : 1 mixture of **6** and **7** produced the instantaneous formation of **8**. Subsequent pressurization with H_2 (3 bar) and heating to 65 °C the resulting solution brought about the hydrogenation of the N-heteroarene (ESI†).

In an attempt to determine the likely formation of dihydride species similar to **B**, a THF-d_8 solution of complex **8** was pressurized with H_2 (4 bar) and analyzed by NMR spectroscopy. Contrary to previously observed in the reaction of **A** with H_2,[14] the ^1H NMR spectrum of this solution did not reveal changes in the temperature range between −80 and 55 °C. DFT calculations (B3LYP-D3, 6-31 g(d,p)/SDD) showed that hydrogen activation by **8** to yield a dihydride Ru complex analogous to **B** is endergonic by 9.5 kcal mol^{-1} (ESI†). Moreover, H/D exchange upon exposure to D_2 (3 bar) of an *in situ* generated solution of **8** did not occur even after prolonged (72 h) heating to 65 °C. However, in the latter experiment, formation of HD was observed, what can be ascribed to the generation of deuteride species (Ru-D) under the NMR detection limit that react with ^{t}BuOH resulting from the deprotonation of **3a** with KO^{t}Bu (ESI†).

In conclusion, ruthenium complexes **3** incorporating CNN(H) pincer ligands are efficient catalyst precursors in the hydrogenation of N-heteroarenes and in the acceptorless dehydrogenation of N-heterocycles. Although complexes **3** contain two potential sites for metal–ligand cooperation, reaction of **3a** with base ultimately furnishes the Ru(0) complex **8**, whose formation is observed under catalytic conditions. Further studies to determine the nature of the metal species participating in the catalytic cycle are being carried out.

Conflicts of interest

There are no conflicts to declare.

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