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

Práxedes Sánchez, a Martin Hernández-Juárez, b Nuria Rendón, b **a Eleuterio Álvarez, a Laura L. Santos, a Joaquín López-Serrano, d a Margarita Paneque a and Andrés Suárez d **a

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, a considerable diversity of ligands containing Brønsted acid/base functionalities have been developed. 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. Both lutidine- and NH-containing pincer complexes have provided highly active and selective catalysts for a broad variety of hydrogenation and dehydrogenation reactions.

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. 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, which according to DFT calculations catalyzes the dehydrogenative coupling of alcohols solely through amine-metal/amido-metal interconversion.

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. 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-PNHP (M = Fe, Co) complexes or costly Cpr derivatives.

Pincer complexes based on N-heterocyclic carbenes (NHCs) have received an increased attention as catalysts in hydrogenation and dehydrogenation reactions. An interesting modification of the structure of lutidine-derived PNP and PNN ligands consists on the substitution of the P-donors by NHC cations of the structure of lutidine-derived PNP and PNN complexes. 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 Ag2O in CH2Cl2 to yield the silver complexes 2a-c (Scheme 1). Subsequent reactions of 2a-c with RuHCl(CO)(PPh3)3 in THF, followed by treatment with NaBF4 and PPh3 in CH2CN, allowed the isolation of the...
Similarly, using 0.5 mol% of above conditions with high conversions in 24 h (entry 4). For example, 2-methylquinoxaline (3a) was tested in the hydrogenation of a series of N-heterocycles.

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\textsubscript{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 other N-heterocyclic substrates. 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).\textsuperscript{11} Moreover, the performance of 3a is superior to that of the Fe-PN\textsubscript{H}P catalyst in the hydrogenation of N-heterocycles (3 mol% Fe, 80 °C, 5 bar H\textsubscript{2}).
Dalton Transactions

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

| Entry | Substrate | Product | Yield (%) |
|-------|-----------|---------|-----------|
| 1<sup>a</sup> | ![Image](image1.png) | ![Image](image2.png) | >99 (24 h) |
| 2     | ![Image](image3.png) | ![Image](image4.png) | 85 (24 h)  |
| 3     | ![Image](image5.png) | ![Image](image6.png) | 76 (48 h)  |
| 4     | ![Image](image7.png) | ![Image](image8.png) | 94 (24 h)  |
| 5     | ![Image](image9.png) | ![Image](image10.png) | >99 (24 h) |
| 6     | ![Image](image11.png) | ![Image](image12.png) | 50 (48 h)  |
| 7     | ![Image](image13.png) | ![Image](image14.png) | 27 (48 h)  |
| 8     | ![Image](image15.png) | ![Image](image16.png) | 27 (48 h)  |
| 9     | ![Image](image17.png) | ![Image](image18.png) | 74 (48 h)  |

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

while it is slightly poorer in the dehydrogenation reactions (3 mol% Fe, xylene reflux).<sup>10</sup>

To investigate the likely Ru species formed under catalytic conditions, complex 3a was treated with KO'Bu (1.3 equiv.) in THF-d<sub>8</sub> producing the instantaneous dark red coloring of the initially clear solution. Formation of the deprotonated complex 6 was ascertained by <sup>1</sup>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 <sup>2</sup>J<sub>HP</sub> of 140.2 Hz, indicative of its trans coordination to PPh<sub>3</sub>. Selective deprotonation of the CH<sub>2</sub>-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 (<sup>2</sup>J<sub>HH</sub> = 12.0 Hz, <sup>3</sup>J<sub>HH</sub> = 12.0 Hz) and 3.09 (<sup>2</sup>J<sub>HH</sub> = 12.0 Hz, <sup>3</sup>J<sub>HH</sub> = 1.9 Hz) ppm, attributable to the CH<sub>2</sub>-NMe moiety.

Scheme 2  Generation of Ru complexes 6–8.

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

| Entry | Substrate | Product | Yield (%) |
|-------|-----------|---------|-----------|
| 1<sup>a</sup> | ![Image](image1.png) | ![Image](image2.png) | >99 (24 h) |
| 2     | ![Image](image3.png) | ![Image](image4.png) | 85 (24 h)  |
| 3     | ![Image](image5.png) | ![Image](image6.png) | 76 (48 h)  |
| 4     | ![Image](image7.png) | ![Image](image8.png) | 94 (24 h)  |
| 5     | ![Image](image9.png) | ![Image](image10.png) | >99 (24 h) |
| 6     | ![Image](image11.png) | ![Image](image12.png) | 50 (48 h)  |
| 7     | ![Image](image13.png) | ![Image](image14.png) | 27 (48 h)  |
| 8     | ![Image](image15.png) | ![Image](image16.png) | 27 (48 h)  |
| 9     | ![Image](image17.png) | ![Image](image18.png) | 74 (48 h)  |

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

THF-d<sub>8</sub> solutions pressurized with H<sub>2</sub> (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<sub>2</sub> activation. However, noticeable changes in their <sup>1</sup>H NMR experiments were not observed. Alternatively, pressurization of solutions of complexes 6 and 7 with D<sub>2</sub> (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<sub>3</sub> decoordination) and 7 to produce the reversible activation of H<sub>2</sub> 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).<sup>11</sup> The <sup>1</sup>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 (<sup>2</sup>J<sub>HP</sub> = 3.7 Hz). The <sup>13</sup>C<sup>1</sup>H NMR spectrum presents the resonances...
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 \(31P\{^1H\} NMR\) 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 \textit{et al.} (Scheme 3).\(^{14,15}\) 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, hydrogenation 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, 6-31g(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 \textit{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 \(^3\)RuOH resulting from the deprotonation of 3a with KO\(^2\)Ru (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.

Acknowledgements

Financial support (FEDER contribution) from the Spanish Ministry of Science and Innovation (CTQ2016-80814-R) and Junta de Andalucía (PY18-3208), and the use of computational facilities of the Supercomputing Center ofGalicia (CESGA) are gratefully acknowledged. We thank support of the publication fee by the CSIC Open Access Publication Support Initiative through its Unit of Information Resources for Research (URICI).

Notes and references

1 B. Zhao, Z. Han and K. Ding, \textit{Angew. Chem., Int. Ed.}, 2013, 52, 4744.
2 J. R. Khushnutdinova and D. Milstein, \textit{Angew. Chem., Int. Ed.}, 2015, 54, 12236.
3 D. Milstein, \textit{Philos. Trans. R. Soc., A}, 2015, 373, 20140189.
4 A. Suárez, \textit{Phys. Sci. Rev.}, 2018, 3, 20170028.
5 R. H. Crabtree, \textit{Chem. Rev.}, 2017, 117, 9228.
6 E. Fogler, J. A. Garg, P. Hu, G. Leitus, L. J. W. Shimon and D. Milstein, \textit{Chem. – Eur. J.}, 2014, 20, 15727; S. Kar, M. Rauch, A. Kumar, G. Leitus, Y. Ben-David and D. Milstein, \textit{ACS Catal.}, 2020, 10, 5511.
7 P. Hu, E. Fogler, Y. Diskin-Posner, M. A. Iron and D. Milstein, \textit{Nat. Commun.}, 2015, 6, 6859; A. Kumar, T. Janes, N. A. Espinosa-Jalapa and D. Milstein, \textit{J. Am. Chem. Soc.}, 2018, 140, 7453.
8 C. Hou, J. Jiang, Y. Li, C. Zhao and Z. Ke, \textit{ACS Catal.}, 2017, 7, 786.
9 Z. X. Giustra, J. S. Ishibashi and S. Y. Liu, \textit{Coord. Chem. Rev.}, 2016, 314, 134; R. H. Crabtree, \textit{ACS Sustainable Chem. Eng.}, 2017, 5, 4491.
10 S. Chakraborty, W. W. Brennessel and W. D. Jones, \textit{J. Am. Chem. Soc.}, 2014, 136, 8564; R. Xu, S. Chakraborty, H. Yuan and W. D. Jones, \textit{ACS Catal.}, 2015, 5, 6350.
11 R. Yamaguchi, C. Ikeda, Y. Takahashi and K. Fujita, \textit{J. Am. Chem. Soc.}, 2009, 131, 8410; K. Fujita, Y. Tanaka, M. Kobayashi and R. Yamaguchi, \textit{J. Am. Chem. Soc.}, 2014, 136, 4829; K. Fujita, T. Wada and T. Shiraiishi, \textit{Angew. Chem., Int. Ed.}, 2017, 56, 10886; J. Wu, D. Talwar, S. Johnston, M. Yan and J. Xiao, \textit{Angew. Chem., Int. Ed.}, 2013, 52, 6983; á. Vivancos, M. Beller and M. Albrecht, \textit{ACS Catal.}, 2018, 8, 17; B. Maji and J. Choudhury, \textit{Chem. Commun.}, 2019, 55, 4574.
12 D. A. Hey, R. M. Reich, W. Baratta and F. E. Kühn, \textit{Coord. Chem. Rev.}, 2018, 374, 114.
13 C. del Pozo, M. Iglesias and F. Sánchez, Organometallics, 2011, 30, 2180; E. Fogler, E. Balaraman, Y. Ben-David, G. Leitus, L. J. W. Shimon and D. Milstein, Organometallics, 2011, 30, 3826; Y. Sun, C. Koehler, R. Tan, V. T. Annibale and D. Song, Chem. Commun., 2011, 47, 8349; G. A. Filonenko, D. Smykowski, B. M. Szyja, G. Li, J. Szczygieł, E. J. M. Hensen and E. A. Pidko, ACS Catal., 2015, 5, 1145; M. Hernández-Juárez, J. López-Serrano, P. Lara, J. P. Morales-Cerón, M. Vaquero, E. Álvarez, V. Salazar and A. Suárez, Chem. – Eur. J., 2015, 21, 7540; X. Wu, L. Ji, Y. Ji, E. H. M. Elageed and G. Gao, Catal. Commun., 2016, 85, 57.

14 T. He, J. C. Buttner, E. F. Reynolds, J. Pham, J. C. Malek, J. M. Keith and A. R. Chianese, J. Am. Chem. Soc., 2019, 141, 17404.

15 A. Anaby, M. Schelwies, J. Schwaben, F. Rominger, A. S. K. Hashmi and T. Schaub, Organometallics, 2018, 37, 2193; A. Ezawa, S. Nishimura, K. Arashiba, K. Nakajima and Y. Nishibayashi, Organometallics, 2018, 37, 3086; D. J. Tindall, M. Menche, M. Schelwies, R. A. Paciello, A. Schäfer, P. Comba, F. Rominger, A. S. K. Hashmi and T. Schaub, Inorg. Chem., 2020, 59, 5099; N. Govindarajan, V. Sinha, M. Trincado, H. Grützmacher, E. J. Meijer and B. de Bruin, ChemCatChem, 2020, 12, 2610.