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Direct Hydrogenation of Amides to Alcohols and Amines under Mild Conditions

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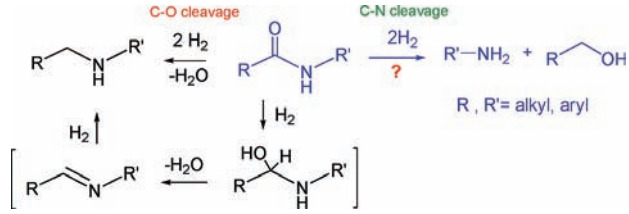
Abstract: The selective, direct hydrogenation of amides to the corresponding alcohols and amines with cleavage of the C−N bond was discovered. The expected products of C−O cleavage are not formed (except as traces in the case of anilides). The reaction proceeds under mild pressure and neutral, homogeneous conditions using a dearomatized, bipyridyl-based PNN Ru(II) pincer complex as a catalyst. The postulated mechanism involves metal−ligand cooperation by aromatization−dearomatization of the heteroaromatic pincer core and does not involve hydrolytic cleavage of the amide. The simplicity, generality, and efficiency of this environmentally benign process make it attractive for the direct transformations of amides to alcohols and amines in good to excellent yields.

Reduction of carboxylic acids and their derivatives plays an important role in organic synthesis, in both laboratory and industrial processes. Traditionally, the reduction is performed using stochiometric amounts of hydride reagents, generating stochiometric amounts of waste.[1] A much more attractive, atom-economical approach is a catalytic reaction using H_2; however, hydrogenation of carboxylic acid derivatives under mild conditions is a very challenging task,[2] with amides presenting the highest challenge among all classes of carbonyl compounds. Very few examples of the important hydrogenation of amides to amines, in which the C−O bond is cleaved with the liberation of water (Scheme 1), were reported.[3] C−O cleavage of amides can also be affected with silanes as reducing agents.[4] In addition, the interesting hydrogenation of cyclic *N*-acylcarbamates and *N*-acylsulfonamides, which involves cleavage of the C−N bond, but does not form amines, was recently reported by Ikariya.[5] On the other hand, to the best of our knowledge, selective, direct hydrogenation of amides to form amines and alcohols has not been reported.[6] Amines and alcohols are used extensively in the chemical, pharmaceutical, and agrochemical industries.[7] Design of such a reaction is conceptually challenging, since the first mechanistic step in amide hydrogenation is expected to be H_2 addition to the carbonyl group to form a very unstable hemiaminal which, in the case of primary or secondary amides, spontaneously liberates water to form an imine; further hydrogenation of the imine then leads to amine formation (Scheme 1). This is the basis of the amide hydrogenation mentioned above. For amine and alcohol formation, cleavage of the C−N bond in preference to the C−O bond would be required.

We have recently developed new catalytic reactions of alcohols, based on a new mode of metal−ligand cooperation, involving aromatization−dearomatization of pyridine-[8] and acridine-derived[9] pincer ligands. The dearomatized pyridine-based PNN Ru complex

Scheme 1. General Scheme for Hydrogenation of Amides



1 (Figure 1) efficiently catalyzes the dehydrogenative coupling of alcohols to form esters,[8b,d,h] the hydrogenation of esters to alcohols under mild conditions,[8c,h] and the novel coupling of alcohols and amines to form amides and H_2.[8e,h] The dearomatized PNP complex **2** is an efficient catalyst for the dehydrogenative coupling of alcohols and amines to form imines.[8f] Complex **1** is also effective in N−H activation[10] and in the unique light-induced splitting of water to hydrogen and oxygen.[11]

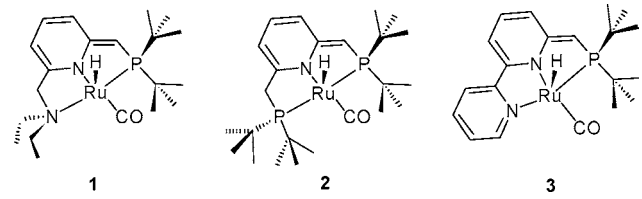
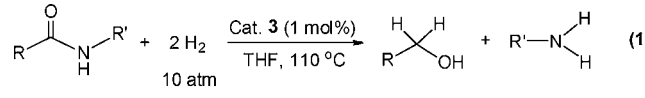


Figure 1. Dearomatized Ru-pincer complexes.

We have now prepared the new, dearomatized, bipyridine-based pincer complex **3**. Remarkably, **3** efficiently catalyzes the selective hydrogenation of amides to form amines and alcohols (eq 1). The reaction proceeds under mild pressure and neutral conditions, with no additives being required. Since the reaction proceeds well under anhydrous conditions, hydrolytic cleavage of the amide is not involved in this process.



(1)

R = Aryl, and alkyl
R' = Aryl, alkyl, and Aryalkyl

Reaction of the new, electron-rich tridentate ligand, BPy-^{t}PNN (**5**),[12] with [RuHCl(PPh$_3$)$_3$(CO)] in THF at 65 °C for 8 h results in substitution of the PPh$_3$ ligands to yield the hydrido chloride pincer complex **4**.[12] The fully characterized **4** gives rise to a singlet at 107.01 ppm in the ^{31}P{^{1}H}NMR spectrum, and the hydride ligand appears as a doublet at −15.26 ppm ($^2J_{PH}$ = 24.6 Hz) in the ^{1}H NMR spectrum. The "arm" methylene protons give rise to signals at 3.06 and 3.75 ppm ($^2J_{HH}$ = 16.8 Hz and $^2J_{PH}$ = 10.2 Hz). The carbonyl ligand appears as a doublet at 207.37 ppm (J_{PC} = 15.0

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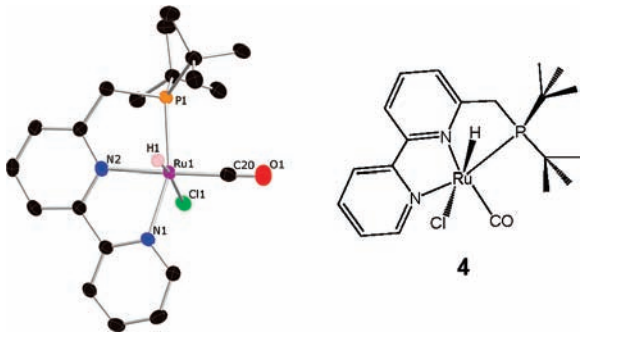


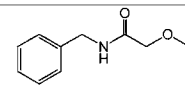
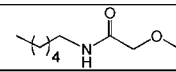
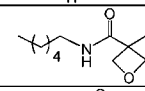
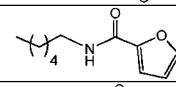
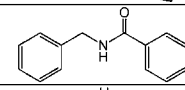
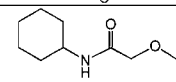
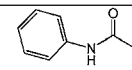
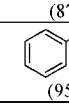
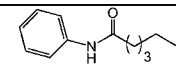
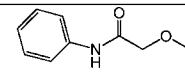
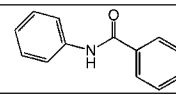
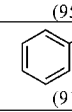
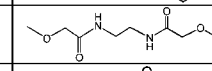
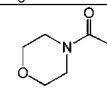
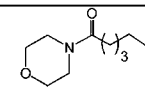
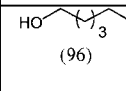
Figure 2. X-ray structure of complex **4** (50% probability level). Hydrogen atoms (except hydride) were omitted for clarity. Selected bond distances (Å): Ru1−N1 2.124(2), Ru1−N2 2.086(2), Ru1−P1 2.2859(7), Ru1−C20 1.861(3). Selected angles (deg): N2−Ru1−C20 173.34(10), N2−Ru1−H1 86.4(9), Cl1−Ru1−H1 170.4(9), N1−Ru1−P1 159.65(6).

Hz) in the $^{13}C\{^{1}H\}$NMR spectrum. The structure of **4** was confirmed by a single-crystal X-ray diffraction study (Figure 2), which reveals a distorted octahedral geometry around the ruthenium center, with the CO ligand coordinated *trans* to the central nitrogen atom of the pincer system and the hydride *trans* to the chloride.

Deprotonation of complex **4** with KO^{t}Bu at −32 °C gave the dearomatized, coordinatively unsaturated complex **3** in 94% yield (see Supporting Information (SI)). The hydride ligand of the resulting complex **3** exhibits a doublet at −20.93 ppm ($^{2}J_{PH}$ = 25.0 Hz) in the ^{1}H NMR spectrum. The "arm" vinylic proton appears as a singlet at 3.36 ppm and a doublet at 66.56 ppm (J_{PC} = 48.8 Hz) in the $^{13}C\{^{1}H\}$ NMR spectrum, indicating formation of an anionic PNN system. The CO ligand absorbs at 1907 cm^{-1} in the IR spectrum.

We have reported the dehydrogenative coupling of alcohols with amines to form amides, catalyzed by complex **1**, with liberation of hydrogen gas.[8e,h,13,14] Exploring whether it might be possible to reverse this reaction by the application of H_2 pressure, complexes **1**−**4** were tested as catalysts for the hydrogenation of amides. Thus, upon treatment of *N*-benzyl-2-methoxyacetamide with H_2 (10 atm) at 110 °C (bath temperature) in dry THF for 48 h with a catalytic amount of **1** (1 mol %), 63% of 2-methoxyethanol and 62% of benzyl amine were obtained. Performing the reaction at 140 °C using 1,4-dioxane as solvent did not significantly improve the yield (alcohol yield 66%). Although a modest yield was obtained, it was significant that the reaction was selective and the corresponding secondary amine was not formed. Under the same conditions complex **2** was inactive.[8c] Importantly, employing complex **3** (1 mol %) as catalyst, hydrogenation of *N*-benzyl-2-methoxyacetamide under identical conditions (THF, 110 °C) resulted in considerably higher yields of 89% 2-methoxyethanol and 90% benzyl amine (Table 1, entry 1), with C−O hydrogenolysis not taking place at all. Of practical significance, the *air-stable* complex **4** (stable in air for at least 2 days) in the presence of 1 equiv (relative to Ru) of base also efficiently catalyzes the hydrogenation of amides to alcohols and amines, by generation of the catalyst **3** *in situ*. Thus, upon heating a THF solution of **4** (0.01 mmol) with KO^{t}Bu (0.01 mmol) and *N*-benzyl-2-methoxyacetamide (1 mmol) at 110 °C under H_2 (10 atm) for 48 h, 80% of alcohol and 82% of amine were formed. No reaction took place in the absence of base. Hydrogenation of *N*-hexyl-2-methoxyacetamide catalyzed by **3** yielded 2-methoxy ethanol and hexyl amine in 91% and 90% yields, respectively (entry 2). Interestingly, *N*-hexyl-3-methyloxetane-3-carboxamide underwent hydrogenation to the alcohol and amine without hydrogenolysis of the strained oxetane ring (entry 3). The heterocyclic amide, *N*-hexylfuran-2-carboxamide, was hydrogenated to yield 69% of furfuryl alcohol and 68% of hexylamine (entry 4). The aromatic nonactivated amide, *N*-benzylbenzamide, was hydrogenated to benzyl

Table 1. Hydrogenation of Amides to Alcohols and Amines Selectively Catalyzed by BPy-PNN-Ru(II) Pincer Complex **3**[a]

Entry	Amide	Products (yield [%])[b]	
		Alcohol	Amine
1		 Cat.**1**; (63)[a] Cat.**1**; (66)[c] Cat **2**; (0)[a] Cat.**3**; (89)[a] Cat.**4**; (80)[a,d]	 Cat.**1**; (62)[a] Cat. **1**; (67)[c] Cat. **2**; (0)[a] Cat.**3**; (90)[a] Cat.**4**; (82)[a,d]
2		 (91)	 (90)
3		 (74)	 (74)
4		 (69)	 (68)
5		 (57)	 (57)
6		EtOH (71)	$EtNH_2$[e]
7		 (68)	$MeNH_2$[e]
8		 (88)	 (87)
9		EtOH (94)	 (95)[f]
10		 (92)	 (92)
11		 (95)	 (95)
12		 (92)	 (91)
13		 (78)	 (77)[g]
14		EtOH (97)	 (98)
15		 (96)	(96)
16		(97)	(97)
17		MeOH (97)	(98)[h]

[a] Complex **1**, **2**, or **3** (0.01 mmol), amide (1 mmol), H_2 (10 atm), and dry THF (2 mL) were heated in a Fischer−Porter tube at 110 °C (bath temperature) for 48 h. [b] Yields of products were analyzed by GC (*m*-xylene as internal standard). [c] 1,4-Dioxane (2 mL) at 140 °C. [d] 1 equiv (relative to Ru) of base was used. [e] The amines ($EtNH_2$ and $MeNH_2$ for entries 6 and 7 respectively) were analyzed in the gas phase by GC-MS. [f] In the reactions involving anilide derivatives (entries 9−12), trace amounts of the corresponding secondary amines were detected by GC-MS. [g] 0.5 mmol of bis-amide was used. [h] Yield after 32 h.

alcohol and benzyl amine (entry 5) in a lower yield (57%), probably because of steric reasons. Significantly, the aliphatic nonactivated amides, *N*-ethylacetamide and *N*-methylpropionamide, also underwent hydrogenation to yield the corresponding alcohols and amines (71% of ethanol and ethylamine for entry 6 and 68% of *n*-propanol and methylamine for entry 7). The product gaseous amines were characterized by GC-MS of the gas phase and not quantified. Anilide derivatives were converted into their corresponding alcohols and aniline in excellent yields (91−95%; entries 9−12) along with trace amounts of the secondary amines (detected by GC-MS) under similar conditions. The reaction is also effective for bis-amides. Thus, *N*,*N*′-(ethane-1,2-diyl)bis(2-methoxyacetamide) (0.5 mmol) was hydrogenated selectively to diamine (77%) and alcohol (78%) using catalyst **3** without formation of monoamine-monoamide (entry 13).[15] Noteworthy, *tert*-amides also underwent hydrogenation almost quantitatively to yield alcohols and secondary amines in equivalent amounts (entries 14−16). Gratifyingly, heating a solution of *N*-formymorpholine (1 mmol) and complex **3** in THF at 110 °C yielded after 32 h 97% of methanol and 98% of morpholine, formyl decarbonylation not being observed. These results highlight the substantial scope of the selective hydrogenation of amides catalyzed by **3**, or by the air-stable **4** with an equivalent of base (which generates **3** *in situ*).

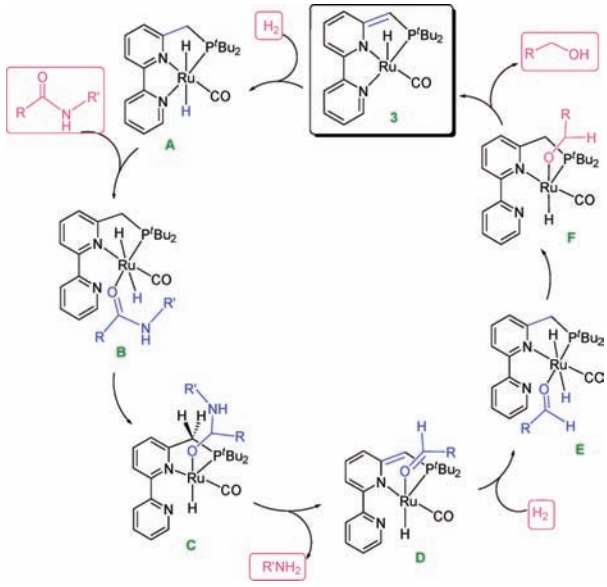


Figure 3. Postulated mechanism for hydrogenation of amides to amines and alcohols catalyzed by complex **3**.

On the basis of the above results and the known chemistry of the pincer complexes **1** and **2**[8,10] we propose the mechanism depicted in Figure 3. Initially, dihydrogen addition by metal−ligand cooperation[8,10,16] to complex **3** results in aromatization, to form the coordinatively saturated, *trans* dihydride complex **A**, as reported for complex **1**.[8c] Decoordination of the pyridyl "arm" can provide a site for amide coordination, to give the intermediate **B**. Subsequent hydride transfer to the carbonyl group of the amide ligand leads to a hemiaminoxy intermediate **C**, with no formation of free hemiaminal. Deprotonation of the benzylic arm by the adjacent NH group leads to the amine product and a dearomatized intermediate **D**, bearing a coordinated aldehyde. H_2 addition to **D** forms the aromatic dihydride **E**, followed by hydride transfer to the aldehyde to generate the alkoxy intermediate **F**. Deprotonation of the benzylic arm by the alkoxy ligand generates the product alcohol and regenerates catalyst **3**. The overall process does not involve a change in the metal oxidation state. We postulate that key to the success of this process is that it does not involve intermediacy of free hemiaminal, avoiding water elimination to give an imine and, subsequently, a secondary amine.

In conclusion, amides can be selectively and directly hydrogenated to alcohols and amines (including under anhydrous conditions) for the first time. The reaction proceeds under mild pressure and neutral, homogeneous conditions using a BPy-PNN-Ru(II) hydride pincer catalyst and dihydrogen by a mechanism involving metal−ligand cooperation. This new catalytic protocol exhibits a broad substrate scope providing a variety of amines and alcohols in good to excellent yields.[17] The analogous Py-PNN complex **1** is less efficient. The reasons for this are being explored.

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Supporting Information Available: Experimental procedures and X-ray data for complex **4** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Catalytic hydrogenation of amides to amines (*via* C−O cleavage, generating water) can be accompanied by hydrolytic C−N cleavage as a side reaction, presumably resulting from catalytic hydrolysis of the amides to acids and amines, followed by hydrogenation of the acids to alcohols: see refs 3b,c.
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(12) See SI for full details.
(13) Coupling of alcohols with amines to form amides and H_2 reported after our publication (ref 8e): (a) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (b) Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H. *Organometallics* **2010**, *29*, 1374.
(14) Coupling of alcohols with amines to form amides using hydrogen acceptors: (a) Zweifel, T.; Naubron, J. V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559. (b) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667.
(15) The fact that the monoamine-monoamide was not observed, while some starting diamide was still present, suggests that it reacts faster than the diamide, perhaps as a result of coordination of the amine group.
(16) (a) Grützmacher, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1814. (b) van der Vlugt, J. I.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 8832.
(17) Complex **3** catalyzes also amide formation by dehydrogenative coupling of alcohols with amines: Balarman, E.; Milstein D. to be published.

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