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Catalytic hydrogenation of unactivated amides enabled by hydrogenation of catalyst precursor

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ABSTRACT

A general method for catalytic hydrogenation of unactivated amides was achieved. During the catalyst induction period, a novel structural change was observed involving full hydrogenation of the interior unsaturated bonds of the pyridines of the Ru-containing catalyst precursor. Based on this observation, the mechanism of amide hydrogenation may involve a two-step pathway, wherein the Ru catalyst having an H–Ru–N–H functionality is generated in the first step, followed by the amide carbonyl group interacting with the outer, rather than the inner, sphere of the Ru catalyst.

Amides[1a] are abundant functional groups which can be found, for example, in the repeating units of polypeptide macromolecules and artificial polymeric materials (e.g., polyacrylamide), nylons, Kevlar), and their respective monomers (e.g., α,β-unsaturated carboxamides, caprolactams), which can be produced on an enormous scale via existing industrial processes. They also exist as potent pharmacophores,[1d,e,g–i] which are useful building blocks accessible via many synthetic methods.[1b,c,f,j,k] Were it possible to develop catalytic transformations of amide resources without the salt-containing wastes formed in stoichiometric amounts with respect to the amide, such chemical processes would provide a shortcut or alternative route to presently known and/or unknown materials or chemicals. However, the salt-free transformation of amides[2] is a significant challenge, as there is a lack of basic knowledge concerning the catalytic activation. Such activation is frequently hampered by high thermodynamic stability[3] and kinetic inertness due to the low electrophilicity of the amide carbonyl carbon among carbon(x)yl functionalities.[1a] In particular, the catalytic hydrogenation of unactivated amides has rarely been accomplished using existing homogeneous catalysis methods. Recently, Cole-Hamilton,[4] Ikariya,[5] Milstein,[6a] and Bergens[7] reported different ruthenium (Ru) complexes, which hydrogenate a range of strongly or moderately activated amides, including *N*-phenyl-, *N*-acyl-, α-alkoxy[8] amides, morpholino ketones, and relatively small unactivated amides. Heterobimetallic clusters are able to hydrogenate larger, more inert amides, whereby dehydrative cleavage of the C=O bonds affords higher amines, albeit with accompanying dearomatic hydrogenation.[9] As part of our research on the catalytic transformation of amides,[10] herein is reported a more general and selective method for the hydrogenation of unactivated amides, affording selective C–N or C=O bond cleavage using a new Ru complex **1a** (Scheme 1).

Since the need for harsh reaction conditions was anticipated for this otherwise difficult unactivated amide hydrogenation, the 'structural robustness' of the catalyst precursor was the foremost consideration in the initial molecular design of a Ru complex catalyst. Such robustness may obviate the facile detachment of the ligands from the Ru center during the induction period of the catalyst. Accordingly, the emphasis was placed on imposing a 'coordinatively saturated Ru center' on a catalyst precursor with sterically demanding and strongly coordinative ligand(s), with the additional expectation that only an H_2 molecule could make easy access to the narrow space (though large enough to accept an H_2) around the metal center of an intermediate active species that subsequently forms a metal hydride. Indeed, the derivation of a metal hydride species from H_2 is frequently rate-determining.[11] To satisfy such primary criteria for catalyst design, a bidentate (*P*,*N*)-ligand[12,13] as in **1a** was chosen first. Additional Ru complexes **1b** and **1c** were also prepared for control experiments.[14] Since *N*-benzylbenzamide (**3a**) was hydrogenated previously in moderate yield [**4a**: 57%; ruthenium complex (1 mol %), H_2 pressure (P_{H2}) = 1 MPa, 110 °C, 48 h],[6a] examination of **3a** is thought to be a good starting point for analysis.

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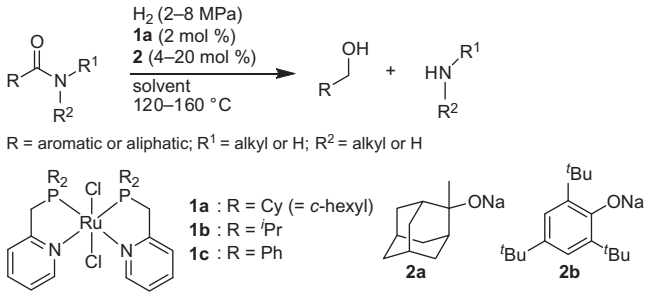


Scheme 1. Hydrogenation of unactivated amides using **1** and **2**.

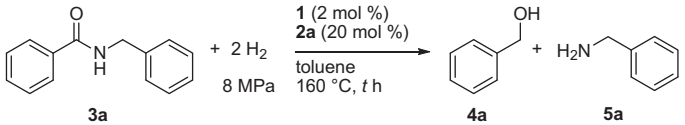
Treatment of a toluene solution of **3a** and **1a** (2 mol %) with sterically bulky base **2a** (20 mol %) under P_{H2} = 8 MPa at 160 °C for 24 h gave both **4a** and **5a** in 92% yield (Table 1, entry 1). The steric bulkiness of the base was more important than its basicity under similar conditions ([**1a**]$_0$ = 6.7 mM; P_{H2} = 6 MPa, 160 °C, 24 h): use of phenoxide **2b** in place of **2a** gave **4a** with similar effectiveness (entry 2), while either NaO^{t}Bu, KO^{t}Bu, NaOMe, or NaOH was less satisfactory (**4a**: 43%, 27%, ~2%, and 31%, respectively; **5a**: 44%, 26%, ~1%, and 26%, respectively). Although toluene was the best solvent of those tested in terms of enabling smooth conversion of **3a**, a sterically more demanding alcohol solvent was better than a smaller one [**4a**: <1% (MeOH); 4% (EtOH); 45% (^{i}PrOH); 61% (^{t}BuOH). [**1a**]$_0$ = 6.7 mM; P_{H2} = 8 MPa, 160 °C, 24 h]. Ru complex **1b** showed a similar effectiveness but with formation of a byproduct (entry 3), while the reaction using **1c**[15] led to the formation of a fine, black powder precipitate, and almost full recovery of **3a** (entry 4). Obviously, the combined use of **1a** and a base additive such as **2a** or **2b**, both being sterically demanding, is crucial for selective hydrogenation. The preference for formation of Ru–OR with alkoxides of 1° alcohols [or partial formation of the Ru–O bond as in Ru$^+$(HOR)] was recently explained as being due to their higher acidity and lower steric congestion,[16] and this preference may be detrimental to the initiation of a catalytically active RuH species in the present system. In contrast, 4 mol % instead of 20 mol % of **2a** was satisfactory to obtain a high conversion of **3a** by prolonging the reaction time to 36 h (**4a**: 88%; **5a**: 88%) under regular conditions.

This hydrogenation method was more selective (i.e., negligible dearomatization) and showed a wider substrate scope with respect to unactivated amides (Table 2) than the established methods. Selective C–N bond cleavage of linear amides was uniformly observed.[5–7] The active species maintained its catalytic integrity even after a lengthy reaction time (entries 3, 4, 17, and 18). The hydrogenation of ε-caprolactam (**3l**), a cyclic amide, which serves as the monomer of nylon-6, showed a similar pattern of bond cleavage (entry 14). Hydrogenation was rather sluggish with **3m** derived by N-methylation of **3l** (entry 15). Products **4l** and **4m** could be a synthetic precursor of *N*,*N*-dimethyl-6-amino-1-hexanol, a polymerization initiator.[17] In contrast, C=O bond cleavage predominated with five- and six-membered lactams **3n**,**o** (entries 16 and 17). This apparent C=O bond scission can be explained by a multistep reaction sequence consisting of hydrogenative C–N bond cleavage of the amides giving $NH_2(CH_2)_nOH$, followed by oxidation of the $HOCH_{2-}$ group giving $NH_2(CH_2)_{n-1}CHO$, then intramolecular imine formation, and finally, imine hydrogenation. In fact, when **4n** was used as the starting material in the absence of H_2 or with P_{H2} = 8 MPa under otherwise identical conditions (160 °C, 24 h), amide **3n** and piperidine (**5n**) were obtained in 53% and 25%, and 28% and 48% yields, respectively. Primary and tertiary amides **3c** and **3b**, and simple aliphatic amides **3i** and **3j**, were also applicable substrates, but marginal hydrogenation took place with more bulky **3k** (entry 13). Hydrogenation of urea[6c] **3p** (entry 18) is important with respect to the methanol economy,[6b,18] since ureas are excellent chemical reservoirs and carriers of CO_2. However, a larger amount of base (20 mol %) only ensured a reasonable reaction rate for the more inert aliphatic amides. In addition, hydrogenation was sluggish and required harsh reaction conditions (entries 3, 4, 17, and 18), so additional optimized conditions for generating catalytic species were evaluated.

Such a catalytic species could be generated following a deprotonation pathway similar to those disclosed by Milstein (Fig. 1),[6,19] in which a base deprotonates the methylene group vicinal to the phosphorous atom (PyCH$_2$P) of **1a**. However, the primary (**3c**) and secondary (**3a**, **3d**–**l**, and **3n**,**o**) amides used here have acidic hydrogens in excess quantity relative to **1a**. Thus, deprotonation of the NH hydrogen of those **3** would prevail over that of **1a**. Due to the less basic nature of the deprotonated form (the conjugate base) of **3**, deprotonation of **1a** might be sluggish, and thus, a high temperature and a high P_{H2} may be required either to produce a catalytic species from **1a**, or for the hydrogenation of **3**.

To probe this speculation, **2a** (4 mol %) was exposed to a toluene solution of **1a** (2 mol %) in the absence of amide **3** (160 °C, 5 h, P_{H2} = 8 MPa) for preactivation of the catalyst, and the resulting matured catalyst was used for the hydrogenation of **3a** under milder conditions with a shortened reaction time (140 °C, P_{H2} = 4 MPa, 12 h). Indeed, **4a** and **5a** were produced in 89% and 89% yields, respectively. Another important aspect is that both **2a** and H_2 are critical to inducing the catalyst. When preactivation was carried out in the absence of H_2 (toluene, 160 °C, 5 h), **1a** was recovered almost unchanged. This feature, namely the structural robustness of **1a** toward bulky base **2a**, is in contrast to previous observation,[6,19] in which the PyCH$_2$P moiety was deprotonated below 0 °C without H_2, giving, for example, **1d**.[19]

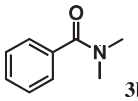
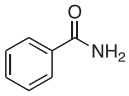
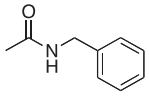
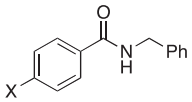
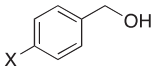
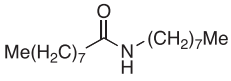
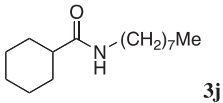
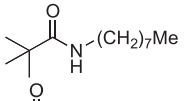
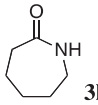
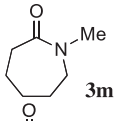
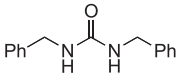
Table 1
Different Ru complexes **1a**–**c** for hydrogenation of **3a**[a]



Entry	Ru complex	t (h)	Conversion[b] (%)	Yield[b] (%) **4a**, **5a**
1	**1a**	24	92	92, 92
2[c]	**1a**	24	75 (94)[d]	74 (94)[d],75 (86)[d]
3	**1b**	24	98[e]	84, 92
4	**1c**	24	<5	0, 0

[a] Reaction was carried out in toluene at 160 °C using **1a**:**2a**:**3a** = 2:20:100; [**1a**]$_0$ = 6.7 mM; P_{H2} = 8 MPa.
[b] Determined by ^{1}H NMR.
[c] **2b** instead of **2a**; P_{H2} = 6 MPa.
[d] t = 48.
[e] PhCH$_2$NH(CH$_2$)Ph (6%) was obtained.

Table 2
Hydrogenation of **3** using **1a** and **2a**[a]

Entry	Amide **3**	Conditions	Products **4** and **5** (yield[b]%) [conversion[b]% of **3**]
1	 **3b**	A	**4a** (83) [84]
2	**3b**	B	**4a** (85) [92]
3	 **3c**	A[c]	**4a** (74) [87]
4	**3c**	B[d]	**4a** (71) [96]
5	 **3d**	A	**5a** (95) [95]
6	**3d**	B	**5a** (87) [99]
7	 **3e** (X = CF_3)	A[e]	 **4e** (99), **5a** (99) [99]
8	**3f** (X = Ph)	A[e]	**4f** (83), **5a** (76) [83]
9	**3g** (X = Me)	A[e]	**4g** (73), **5a** (70) [74]
10	**3h** (X = OMe)	A	**4h** (62), **5a** (67) [67]
11	 **3i**	A[f]	$Me(CH_2)7OH$ (**4i** (88)) $Me(CH_2)7NH_2$ (**5i** (94)) [94]
12	 **3j**	A[f]	$(C_6H_{11})CH_2OH$ (**4j** (66)), **5i** (59) [66]
13	 **3k**	A	 **4K** (9), **5i** (6) [9]
14	 **3l**	A[e]	$HO(CH_2)_6NH_2$ (**4l** (92)) [94]
15	 **3m**	A	$HO(CH_2)_6NHMe$ (**4m** (64)) [64]
16	 **3n**	A[f]	 **5n** (78)[g] [88]
17	 **3o**	A[c]	 **5o** (62)[h] [73]
18	 **3p**	B	**5a** (74)[i] [97]; (97)[d] [99]

[a] Unless otherwise specified, reaction was carried out at 160 °C, P_{H2} = 8 MPa with: conditions A: **1a**:**2a**:**3** = 2:20:100, *t* = 24 (h); or conditions B: **1a**:**2a**:**3** = 2:4:100, *t* = 36 (h).
[b] Determined by ^1H NMR.
[c] *t* = 216 (h).
[d] *t* = 168 (h).
[e] P_{H2} = 6 MPa.
[f] *t* = 48 (h).
[g] $HO(CH_2)_5NH_2$ (**4n**) (4%) was obtained.
[h] $HO(CH_2)_4NH_2$ (5%) was obtained.
[i] $(CHO)NHCH_2Ph$ (13% based on **3p**) was obtained.

The mercury test[20] was also employed, in which Hg(0) was added during the hydrogenation step to probe the possibility of catalysis by a Ru nanoparticle. The catalytic activity was not perturbed during the course of the reaction (**4a**: 94%; **5a**: 92%).[14] This preactivation procedure using 4 mol % of **2a** also improved the yields of **4h** and **4i** obtained previously using 20 mol % of **2a** (Table 2, entries 10 and 11, 62% and 88%, respectively) to 80% (160 °C, 19 h) and 92% (160 °C, 30 h), respectively, with shorter reaction times (P_{H2} = 8 MPa). When even milder conditions were used for the hydrogenation of **3a** (120 °C, P_{H2} = 2 MPa), a high yield of **4a** (93%) and **5a** (92%) was still obtained by prolonging the reaction time to 60 h. Preactivation of **1a** over a shorter time (1 h, 160 °C, P_{H2} = 8 MPa) or keeping the induction period at 5 h but at a lower temperature and P_{H2} (140 °C, 4 MPa) was found to be less promising

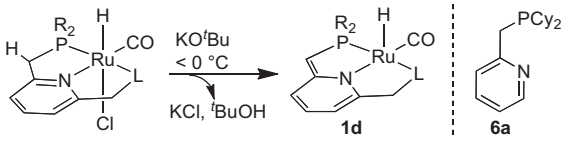


Figure 1. Milstein's mechanism for pyridine dearomatization (L = Et_2N or $^iPr_2P$) and the ligand used here, **6a**.

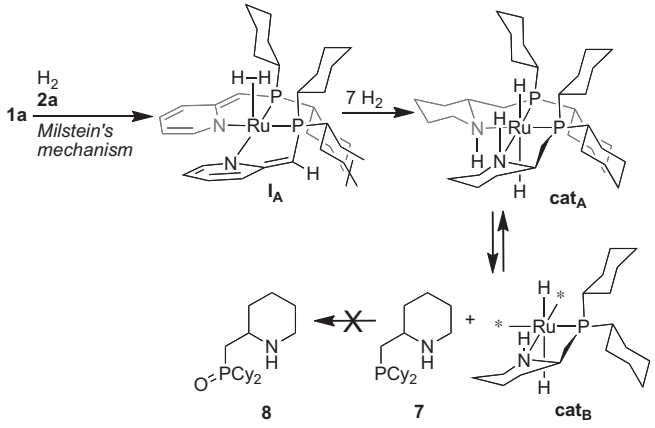


Figure 2. Plausible pathway giving prospective catalytic species $\mathbf{cat_A}$/$\mathbf{cat_B}$ via formation of $\mathbf{I_A}$. Hydrogen atoms may occupy * positions afterward.

(**4a**: ~55% with hydrogenation conditions: 140 °C, P_{H2} = 4 MPa, 12 h).

The $^{31}P\{^1H\}$ NMR (toluene-d_8, ppm) spectrum (Fig. S1) of the reaction mixture obtained after the optimal induction period of the catalyst showed a medium intensity singlet at δ −15.2 corresponding to **7** (Fig. 2), with an additional set of small signals (δ 45.8, 71.0, 73.3, 88.1), which are all different from that of **1a** (δ 66.2) and the free ligand **6a** (δ 4.3) (Fig. 1).[14] A ^1H NMR of the same sample lacks signals in the 6–9 ppm region which would correspond to the protons of the original Py of **1a** or of partially decomposed products. In order to further confirm the identity of the catalytic species involving **7**, the reaction mixture was quenched with excess BH_3·THF (25 °C, 12 h) and was analyzed via electrospray ionization mass spectroscopy (ESI-MS).[14] The base peak obtained matched fully hydrogenated **7** complexed with BH_3 (Found: m/z = 310.2837; Calcd for **7**·BH_3+H^+: 310.2829) (Fig. S2).[21] The mixture obtained following a shorter induction period (1 h) showed a negligible ESI-MS signal for **7**·BH_3 and an intense signal consistent with unreacted **1a** (Found: m/z = 750.2335; Calcd for $\mathbf{1a}^+$: 750.2334) (Fig. S4). These results, with the Hg test, suggest that $\mathbf{cat_A}$ or $\mathbf{cat_B}$ is likely to be responsible for the hydrogenation of amides.[22] Based on the fact that at least 2 equiv of **2a** relative to **1a** was required to ensure a high reaction rate,[23] **1a** is first converted into $\mathbf{I_A}$ (16e complex) upon η^2-coordination of H_2. The olefins of the two partially decomposed Pys of $\mathbf{I_A}$ are in turn hydrogenated (intramolecularly), and finally, the structure is fully saturated, giving piperidines as in $\mathbf{cat_A}$, $\mathbf{cat_B}$, and **7** during the induction period of catalyst (Fig. 2).

In summary, a sterically congested and coordinatively saturated Ru complex **1a** (catalyst precursor), combined with a bulky base, has been demonstrated to be effective for the hydrogenation of a range of unactivated amides. A novel structural change involving multiple hydrogenation of the interior Py of **1a** during the catalyst induction period was also clarified. Such insight into a catalytic species reinforces the promise of further improvement of molecular catalysts for the hydrogenation of even more kinetically inert and thermodynamically stable unsaturated chemical bonds.

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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.2013.03.047.

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21. Direct injection of a similar sample into an ESI-MS instrument under air, skipping the BH_3 treatment, gave an intense signal corresponding to **8** (Found: m/z = 312.2482; Calcd for 8+H+: 312.2451) (Supplementary Fig. S6). The structure of **7**, **7**·$(BH_3)_2$, and **8** was unambiguously ascertained in reference to $^{31}P\{^1H\}$ NMR and/or ESI-MS data of a set of authentic samples prepared separately. An attempt to purify and to isolate the complex $(RuCl_2)$·$\mathbf{7}_2$ is unsatisfactory so far; however, a crude mixture of **7** and $[RuCl_2(cod)]_n$ ($[\mathbf{7}]_0$:$[Ru]_0$ = ca. 2:1) also enabled the hydrogenation of **3a**. See Supplementary data.
22. ^1H NMR (toluene-d_8) of a preactivated catalyst (P_{H2} = 8 MPa, 160 °C, 5 h) showed several signals within a range from d −7 to −24 ppm, corresponding to RuH species; however, they are variable depending on technical conditions.
23. When 2 mol % instead of 4 mol % of **2a** was used for the hydrogenation of **3a** under conditions B in Table 2 (160 °C, P_{H2} = 8 MPa, 36 h), NMR yields of **4a** and **5a** were 9% and 8%, respectively.