Homogeneous Catalysis

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A Highly Active Catalyst for the Hydrogenation of Amides to Alcohols and Amines**

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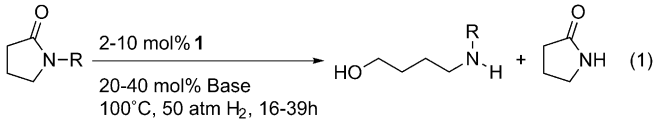
Alcohols and amines are ubiquitous in the synthesis of agrochemicals, pharmaceuticals (e.g. protection, deprotection), flavorings, fragrances, and advanced materials.[1] One approach to accessing these compounds is through the reduction of amides. Amides are, however the most stable carboxylic acid derivative.[2] Consequently, the reduction of amides typically requires stoichiometric amounts of active Al–H,[3] B–H,[3] or Si–H[4] reducing agents that often cause reductive cleavage of the C=O bond.

Numerous heterogeneous catalysts have been developed to hydrogenate amides. These include copper/chromite systems that give mixtures of amine products under 350 atm of H_2 at temperatures of 250–400 °C.[5] Co-catalysts of Rh or Ru with Re, W, or Mo hydrogenate amides either by reductive cleavage of the C=O bond (100 atm H_2, 160–180 °C),[6] or by selectively hydrogenating primary amides to the corresponding primary amines (20–100 atm H_2, 130–160 °C).[7]

There are a handful of homogeneous systems that catalyze the hydrogenation of amides or amide derivatives. The first is a Ru/triphos system (triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane) that hydrogenates primary amides with a preference for the reductive cleavage of the C=O bond in the presence of NH_3 (40 atm H_2, 140–164 °C, 14 h).[8] Beginning in 2006, Ikariya et al. reported dihydrogenations of cyclic imides,[9a,c] *N*-acylcarbamates, *N*-sulfonyllactams, *N*-acylsulfonamides,[9b] *N*-phenyllactams, and benzamides[9d,e] with reductive cleavage of the C–N bond catalyzed by [Cp*RuCl(*P*N)] (Cp* = η^5-$C_5(CH_3)_5$, e.g. *P*N = $Ph_2P(CH_2)_2NH_2$) or [Cp*RuCl(*L*N)] (e.g. *L*N = 2-$C_5H_4NCH_2NH_2$) under the reported reaction conditions (*t*BuOH or 2-PrOH, 80–100 °C, 30–50 atm, KO*t*Bu 1–2.5 equiv, 2–72 h). Our group recently reported the enantioselective monohydrogenation of *meso*-cyclic imides to give hydroxy lactams using *trans*-[Ru(H)$_2$(binap)(dpen)] (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dpen = 1,2-diphenylethylenediamine) and related complexes in THF at low temperatures (0.1 mol% [Ru], 0 °C, 50 atm H_2, 9 mol% *t*BuOK, 17–57 h).[10] The most active system to date, reported by Milstein and co-workers, is the dearomatized, bipyridyl-based PNN/Ru complex (PNN = (2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine) that hydrogenates a variety of secondary amides, and tertiary amides having ether groups to give the alcohol and amine products (1 mol% [Ru] in THF, base free, 110 °C, 10 atm H_2, 48 h).[11]

We recently reported the low-temperature preparation and study of the Noyori ketone hydrogenation catalyst *trans*-[Ru((*R*)-binap)(H)$_2$((*R,R*)-dpen)] (**1**).[12] Compound **1** is remarkably active towards carbonyl reduction. For example, **1** adds acetophenone upon mixing and adds γ-butyrolactone within minutes at −80 °C to form the alkoxide *trans*-[Ru((*R*)-binap)(H)(OCH(CH$_3$)(Ph))((*R,R*)-dpen)],[12b] and the corresponding Ru/hemiacetaloxide of γ-butyrolactone. The complex **1** also catalyzes the hydrogenation of ethyl hexanoate under 4 atm H_2 below a temperature of 0 °C,[13] and the monohydrogenation of *meso*-cyclic imides at 0 °C.[10] We report herein the results of our study of **1** and related compounds as catalysts for the hydrogenation of amides.

We found that the activity of **1** towards the activated amides *N*-methylsulfonylpyrrolidin-2-one (**2a**) and *N*-acetylpyrrolidin-2-one (**2b**) was low to moderate. Compound **2a** was hydrogenated with a turnover number (TON) of approximately 27 to give the ring-opened *N*-methanesulfonyl amino alcohol product when using 2 mol% [Ru] in THF (100 °C, 50 atm, 20 mol% KO*t*Bu, 39 h) [Eq. (1); Ms = methanesulfonyl]. Substrate **2b** formed mixtures of pyrrolidine-2-one (major) and the ring-opened N-acetyl amino alcohol with a TON of approximately 45 using 2 mol% [Ru] (80 °C, 50 atm H_2, 20 mol% KN[Si(CH$_3$)$_3$]$_2$, 16 h). *N*-phenylpyrrolidin-2-one (**2c**) was inactive under our reaction conditions.



2a: R = Ms
2b: R = C(O)CH$_3$
2c: R = Ph

These results are in contrast to the high activity of **1** towards the reduction of ketones, esters, and imides in THF.[10,12,13] We reasoned that catalysts such as **1** are intrinsically active towards amide hydrogenation, but they decompose[12] at the higher temperaturerequired for this transformation. We hypothesized that tethering the amine and

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phosphine groups would maintain activity, and prevent dissociative loss of the diamine at high temperatures. We found that reaction between 2 equivalents of $Ph_2P(CH_2)_2NH_2$ (**3**) and the Ru precursor *cis*-$[Ru(CH_3CN)_2(\eta^3\text{-}C_3H_5)(cod)]BF_4$ (**4**; cod = 1,5-cyclooctadiene) in THF at 60 °C forms isomers of the π-allyl complex **5** in near-quantitative yield (in solution) by displacement of the cod and MeCN ligands [Eq. (2)].[14,15,17]

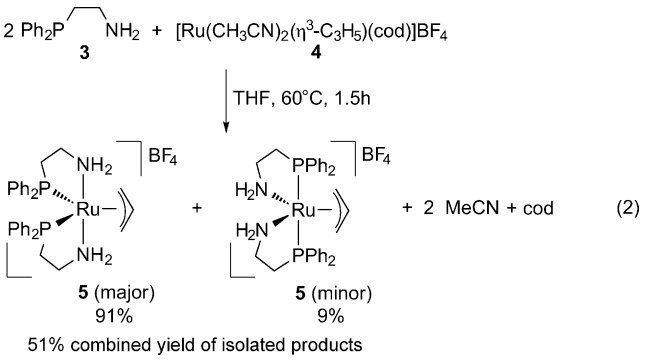
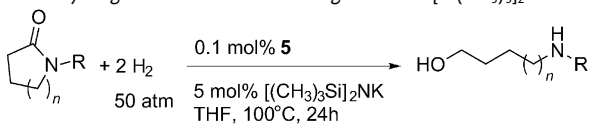


Table 1 and Table 2 summarize the results of our amide hydrogenations using **5** and $KN[Si(CH_3)_3]_2$ as the added base in THF. All hydrogenations were carried out with 0.1 mol% [Ru] , 4–5 mol% $KN[Si(CH_3)_3]_2$, and 50 atm H_2 at 100 °C, for 24 hours. To our pleasant surprise, *N*-phenylpyrrolidin-2-one (**2c**) was hydrogenated to give *N*-phenyl-4-aminobutan-1-ol in 100% yield, or with a TON of 1000 under these reaction conditions (entry 1, Table 1). The N–Me (entry 2) and N–H (entry 3) derivatives were much less active than **2c**, whereas the six-membered N–Ph derivative **6** reacted in 100% yield (entry 4). The seven-membered unsubstituted lactam **7** (entry 5) was more reactive than the five-membered lactam **2e** (entry 3), as expected from the greater stability of five- over seven-membered rings.

Table 1: Hydrogenation of lactams using **5** and $KN[Si(CH_3)_3]_2$.[a,b]



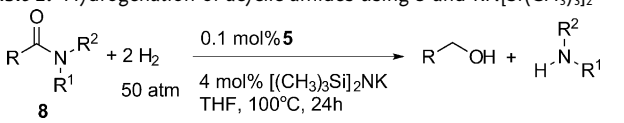
2c: R = Ph, *n* = 1 **2e**: R = H, *n* = 1 **6**: R = Ph, *n* = 2
2d: R = Me, *n* = 1 **7**: R = H, *n* = 3

Entry	Substrate	Yield [%][c]	TON
1	**2c**	100	1000
2	**2d**	5	50
3	**2e**	0	0
4	**6**	100	1000
5	**7**	23	230

[a] Performed using in situ prepared catalyst precursor **5**. [b] Reaction conditions: H_2 at 50 atm, 100 °C, **5**/$KN[Si(CH_3)_3]_2$ = 1:50, [Substrate] = 0.626 M in THF. [c] Determined by ^{1}H NMR spectroscopy.

The order of reactivity among the acyclic benzamides was $-N(Ph)_2 \approx -N(Ph)Me > -N(Me)_2$ (entries 1–3, Table 2). This

Table 2: Hydrogenation of acyclic amides using **5** and $KN[Si(CH_3)_3]_2$[a,b]



Entry	Substrate	R	R^1	R^2	Yield [%][c]	TON
1	**8a**	Ph	Ph	Ph	100[d]	1000
2	**8b**	Ph	Ph	Me	96	960
3	**8c**	Ph	Me	Me	50	500
4	**8d**	Ph	$-(CH_2)_5-$	–	82	820
5	**8e**	Ph	Ph	H	50	500
6	**8f**	Ph	Me	H	27	270
7	**8g**	Me	Ph	Ph	100	1000
8	**8h**	Me	Ph	Me	100	1000
9	**8i**	Me	Me	Me	50[e]	500
10	**8j**	Me	Ph	H	70	700

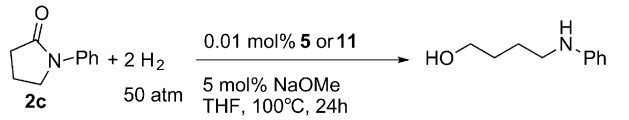
[a] Performed using in situ prepared catalyst precursor **5**. [b] Reaction conditions: H_2 at 50 atm, 100 °C, **5**/$KN[Si(CH_3)_3]_2$ = 1:40, [Substrate] = 0.626 M in THF. [c] Determined by ^{1}H NMR spectroscopy. [d] 72% benzyl alcohol, 14% benzyl benzoate. [e] Anthracene used as an internal standard.

order is consistent with the differences in the extent of donation from the lone pair of electrons on the nitrogen atom to the carbonyl carbon center of these substrates. 1-Benzoylpiperidine (**8d**; entry 4) was more active than **8c** (entry 3), whereas secondary amides were somewhat less reactive than tertiary amides (entry 5 versus entry 1 and entry 6 versus entry 3). Similar results were obtained with acyclic acetamides. Specifically, the reactivity was on the order of $-N(Ph)_2 \approx -N(Ph)Me > -N(Me)_2$ (entries 7–9). The secondary acetamide $-N(Ph)H$ **8j** (entry 10) was less reactive than the corresponding tertiary amide (entry 8). The lower reactivity of secondary versus tertiary amides may arise from reaction of the secondary amide with the added base.

In preliminary experiments, we found that **5** reacts with H_2 (ca. 1 atm) and $KN[Si(CH_3)_3]_2$ (ca. 3 equiv) in $[D_8]$THF starting at approximately 0 °C to form propylene and three ruthenium monohydrides.[16] The known[17] dichloride $[Ru(Cl)_2(Ph_2P(CH_2)_2NH_2)_2]$ (**11**) gives a similar mixture of monohydride species under these reaction conditions. This mixture reacts further (ca. 4 atm H_2, ca. 10 equiv $KN[Si(CH_3)_3]_2$) at room temperature to generate a symmetrical dihydride as the major product, which we tentatively assign to be an isomer of *trans*-$[Ru(H)_2(Ph_2P(CH_2)_2NH_2)_2]$ (**9**).[18,19] Saudan et al. reported that **11** forms an active ester hydrogenation catalyst with NaOMe as the base in THF.[17] Indeed, we found that **5** and **11** (0.01 mol%) both hydrogenate **2c** with remarkable TONs of 7120 and 6760, respectively, in the presence of 5 mol% NaOMe (Table 3).

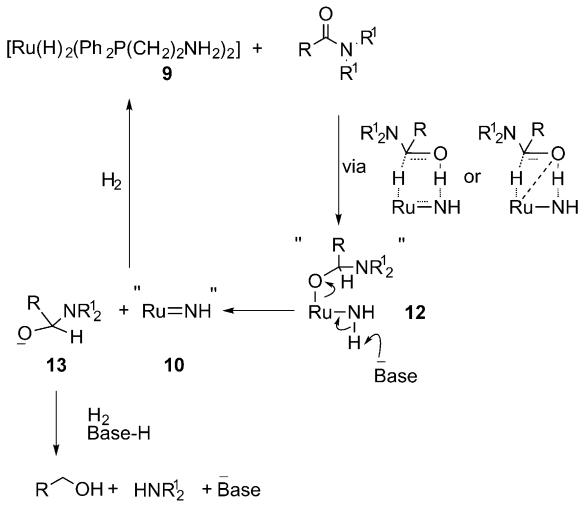
On the basis of prior studies with ketone and ester substrates and **1**,[12,13] we propose the following mechanism for the hydrogenation of amides with **9** (Scheme 1). The first step is a bifunctional-type addition of the amide to **9**, thus forming the ruthenium hemiaminaloxide **12** as the net product. Base-assisted elimination from **12** forms the ruthenium/amide **10**, and the free hemiaminaloxide **13** which regenerates the base and eliminates aldehyde and H-NR^1_2. Addition of H_2 to **10**

Table 3: Hydrogenation of *N*-phenylpyrrolidin-2-one using **5** or **11** and NaOMe.[a,b]



Entry	Catalyst precursor	Yield [%][c]	TON
1	**5**	71.2	7120
2	**11**	67.6	6760

[a] Performed using the isolated catalyst precursor **5**. [b] Reaction conditions: H_2 at 50 atm, 100 °C, **5** or **11**/NaOMe = 1:500, [Substrate] = 2.08 M in THF. [c] Determined by ^{1}H NMR spectroscopy.



Scheme 1. Proposed mechanism for the hydrogenation of amides.

regenerates **9** and hydrogenation of the aldehyde forms the alcohol. Consistent with this mechanism is the formation of benzyl benzoate by the Tishchenko reaction of benzaldehyde during the hydrogenation of **8a** (entry 1, Table 2).We have shown that **5** and **11** are remarkably active towards the hydrogenation of a series of amides without strongly activating functional groups. Significantly, the commonly inert, unfunctionalized amide dimethyl acetamide was hydrogenated with TONs of 500, and *N*-phenylpyrrolin-2-one was hydrogenated with TONs of up to 7120. Studies on catalyst variations, the mechanism, and the synthetic scope of these hydrogenations are underway in our laboratories.

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[15] Compound **5** was identified by ^{1}H, ^{31}P, gCOSY, ^{1}H{^{31}P} gCOSY, ^{1}H-^{31}P gHSQC, TROESY, and gTOCSY NMR experiments, mass spectrometry, and elemental analysis.

[16] Overlap among the signals corresponding to the arene, N–H, and aliphatic protons in the ^{1}H NMR spectra made a conclusive identification impossible. Their reactivity with H_2, and that they are formed from **5** and **11** suggests that they are isomers of the ruthenium/amide $[Ru(H)(Ph_2P(CH_2)_2NH_2)(Ph_2P(CH_2)_2NH)]$ (**10**).

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[18] This preliminary assignment is based upon the similarities between the $^{31}P\{^{1}H\}$ and ^{1}H (hydride) NMR spectra between **9** and **1** (see Ref. [12]). The peaks for compound **9** were assigned using ^{1}H, ^{31}P, gCOSY, ^{1}H–^{31}P gHSQC, and gTOCSY NMR experiments. $^{31}P\{^{1}H\}$ NMR (161.903 MHz, $[D_8]$THF, 27 °C): 56.2 ppm (s). ^{1}H NMR (399.951 MHz, $[D_8]$THF, 27 °C): $\delta =$ 8.26 ppm (Ru-*H*, t, $J = 14.8$ Hz), $\delta = 1.25$ ppm, $\delta = 2.43$ ppm, $\delta = 2.73$ ppm.

[19] Use of **4** as a catalyst precursor, or **5** without added base (both at 10 mol%), did not result in hydrogenation. Use of Ru black (10 mol%) resulted only in hydrogenation of the arene ring in **2c**. It is therefore unlikely that Ru nanoparticles are the active catalyst in these hydrogenations.

