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Hydrogenation of amides catalyzed by a combined catalytic system of a Ru complex with a zinc salt†

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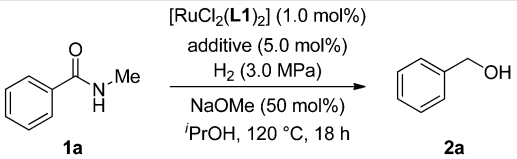
Addition of catalytic amounts of zinc salts facilitated the hydrogenation of amides catalyzed by a ruthenium complex bearing 2-(diphenylphosphino)ethanamine (L1). The combined catalytic system of the ruthenium complex $[RuCl_2(L1)_2]$ with a zinc salt such as $Zn(OCOCF_3)_2$ mediated hydrogenation of various amides under mild conditions to afford the corresponding primary alcohols.

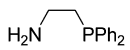
Amide reduction is a widely utilized synthetic protocol to prepare primary alcohols and amines. In general, amide reduction is achieved using stoichiometric reduction reagents such as lithium aluminum hydride[1] or borane,[2] although significant amounts of waste are produced with the workup. The most straightforward approach to address this issue is the use of molecular hydrogen as the reducing reagent.[3] Reduction of amides using hydrogen gas in the presence of heterogeneous catalysts, such as copper chromite,[4] ReO_3,[5] RANEY® Ni,[6] PtO_2,[7] Rh–Re,[8] Cu,[9] Rh/Mo,[10] Ru/Re,[11] Pt–Re/TiO_2,[12] Pt/Re/graphite,[13] and Re/TiO_2,[14] has been successfully applied to afford the corresponding amines instead of the primary alcohols; however, these systems typically require high temperatures and high pressures. On the other hand, some homogeneous catalysts based on ruthenium exhibit catalytic activities for hydrogenation of amides to give the corresponding primary alcohols. In some reports, however, a mixture of secondary amines, alcohols, and alkylated amides was formed when using a ruthenium complex with a tridentate phosphine ligand.[15] Recently, pincer ligands,[16,17] a pyridyl amine ligand,[18] and P,N ligands[19,20] were utilized to synthesize ruthenium catalysts active for amide hydrogenation, but rather severe reduction conditions were required. We found that the addition of catalytic amounts of zinc salt, such as $Zn(OCOCF_3)_2$, dramatically increased the yield of the hydrogenated product for Ru-catalyzed hydrogenation of amides under mild conditions.

Table 1 Optimization of reaction conditions for hydrogenation of **1a** catalyzed by the ruthenium complex[a]



1a **2a**

Entry	Additive	Yield[b] (%)
1	None	Not detected
2	$Zn(OTf)_2$	53
3	$ZnCl_2$	73
4	$ZnBr_2$	39
5	ZnI_2	19
6	$Zn(OAc)_2$	64
7	$Zn(OCOCF_3)_2$	74
8	$Zn_4(OCOCF_3)_6O$	56
9[c]	$Zn(OCOCF_3)_2$	95



L1

[a] Reaction conditions: a mixture of the $[RuCl_2(L1)_2]$ catalyst (0.010 mmol), *N*-methylbenzamide (1.0 mmol), NaOMe (0.50 mmol), and additives (0.050 mmol) in isopropyl alcohol (5.0 mL) was stirred under 3.0 MPa hydrogen pressure at 120 °C, 18 h. [b] GC yield. [c] 1.0 mol% of the catalyst, 2.0 mol% of additives, 20 mol% of K^tOBu as a base and 1,4-dioxane (3.0 mL) as a solvent were used and run at 100 °C.

We began with catalytic hydrogenation of *N*-methylbenzamide using a ruthenium complex bearing a P,N ligand (**L1**)[21] with NaOMe in isopropyl alcohol under hydrogen pressure (3.0 MPa) at 120 °C for 18 h, and almost no reaction was observed (Table 1, entry 1). The addition of catalytic amounts of zinc triflate for the hydrogenation of *N*-methylbenzamide dramatically increased the yield (53%) of benzyl alcohol (entry 2). Based on the positive effect of the addition of a zinc salt, we screened a variety of zinc salts (Table 1). Zinc chloride increased the yield of the product (entry 3), whereas zinc bromide and zinc iodide did not (entries 4 and 5).

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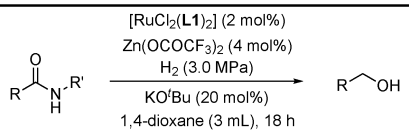
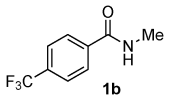
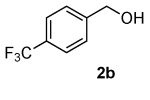
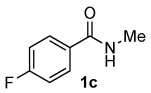
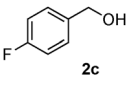
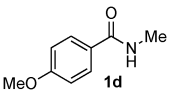
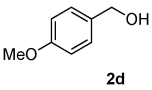
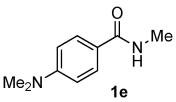
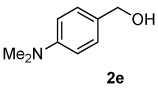
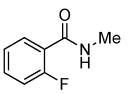
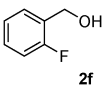
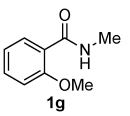
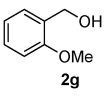
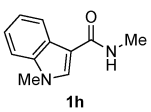
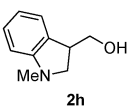
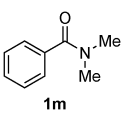
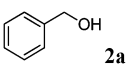
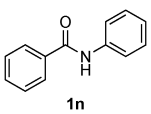
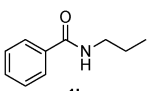
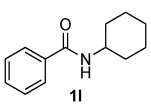
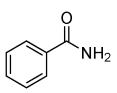
$Zn(OAc)_2$ and $Zn(OCOCF_3)_2$ were also effective for the present system (entries 6 and 7). We previously reported that tetranuclear zinc clusters exhibit higher activity in transesterification than mononuclear zinc salts.[22] Thus, we used a tetranuclear zinc cluster as an additive and observed moderate effects for the present reaction (entry 8). We finally selected $Zn(OCOCF_3)_2$ as the best additive for amide hydrogenation.[23] The additive/catalyst ratio was also important for determining the efficiency of the present reaction. Changing the additive/catalyst ratio to 2 : 1 had little effect on the yield of the desired product, and large amounts of additive were detrimental (see ESI†). To achieve a more efficient catalytic system, we screened both the base and solvent. The highest yield was produced using KO^{t}Bu as the base. Among the solvents we examined (*i.e.*, toluene, hexane, CH_2Cl_2, MeCN, and THF), we selected 1,4-dioxane as the best solvent. Further optimization provided a high yield (95%), even at a lower temperature (100 °C) (entry 9). Consequently, we selected the optimized conditions with KO^{t}Bu as the base and 1,4-dioxane as the solvent at 100 °C for 18 h.

We next explored the scope of amides under the optimized conditions (Table 2). Initially, we examined *N*-methyl benzamide derivatives. An electron-withdrawing group at the *para*-position enhanced the reactivity of the substrates for hydrogenation (entries 1 and 2). On the other hand, substrates with an electron-donating group required a relatively longer reaction time (entries 3 and 4). Sterically congested substrates such as *ortho*-substituted substrates retarded the reaction (entries 5 and 6). In the hydrogenation of 3-carbamoyl indole (**1h**), both the amide bond and indole skeleton were hydrogenated to give **2h** selectively (entry 7). We then turned our attention to the substituents on the nitrogen. A tertiary amide was a good substrate for the present hydrogenation (entry 8). With regard to the substituent on the secondary amides, an aryl group accelerated the reaction, probably due to a decrease in amide resonance (entry 9), whereas a bulky normal propyl and a cyclohexyl group retarded the reaction (entries 10 and 11). Unfortunately, a primary amide could not be applied to the present system (entry 12).

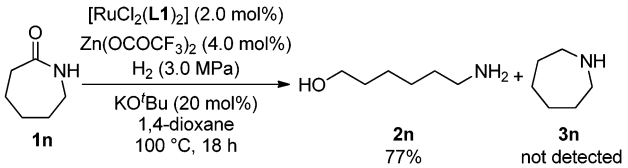
We conducted a lactam reduction to evaluate the mechanism for which there are two possible routes, C–N bond cleavage and C=O bond cleavage, depending on the catalysis and ring size.[20] In our system, C–N bond cleavage was observed using a seven-membered lactam. Hydrogenation of ε-caprolactam proceeded to afford aminoalcohol in 77% yield and no C=O bond cleavage product [eqn (1)]. In contrast, cyclic amine was obtained using a six-membered lactam with the concomitant formation of aminoalcohol [eqn (2)]. The selectivity between C=O cleavage and C–N cleavage was similar to that in a previously reported Ru-catalyzed amide hydrogenation.[20] This selectivity can be explained by the elimination step from the hemiaminal intermediate. Based on the results observed in Table 2, the major route is nitrogen elimination from the hemiaminal intermediate to initially produce the corresponding aldehyde, which is further hydrogenated to give the corresponding alcohol (C–N bond cleavage). In the case of the six-membered lactam, oxygen elimination competed with nitrogen elimination, probably due to the re-formation of the hemiaminal intermediate by an intramolecular attack of the amine on the aldehyde oriented in a suitable position for intramolecular attack. Oxygen elimination gave cyclic imine, and subsequent hydrogenation afforded cyclic amine (C=O bond cleavage).

Table 2 Hydrogenation of amides catalyzed by $[RuCl_2(\mathbf{L1})_2]$[a]

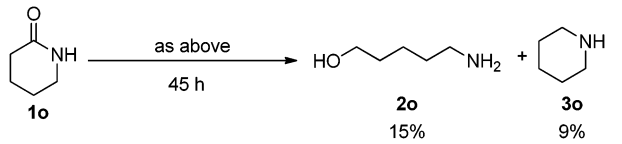


Entry	Amide		Product	Yield[b] (%)
1[c]		**1b**		99[e]
2[c]		**1c**		80[e]
3[d]		**1d**		81
4[d]		**1e**		28
5[d]		**1f**		13[e]
6[d]		**1g**		68
7[d]		**1h**		55
8[c]		**1i**	 **2a**	>99[f]
9[c]		**1j**	**2a**	>99[f]
10[c]		**1k**	**2a**	80[f]
11[c,d]		**1l**	**2a**	61[f]
12[c]		**1m**	**2a**	Trace[f]

[a] Reaction conditions: a mixture of $[RuCl_2(\mathbf{L1})_2]$ (0.020 mmol), amide (1.0 mmol), KO^{t}Bu (0.20 mmol), and $Zn(OCOCF_3)_2$ (0.040 mmol) in 1,4-dioxane (3.0 mL) was stirred under 3.0 MPa hydrogen pressure at 100 °C, 18 h. [b] Isolated yield. [c] 0.010 mmol of the catalyst and 0.020 mmol of the zinc salt were used. [d] Run for 45 h. [e] NMR yield. [f] GC yield.

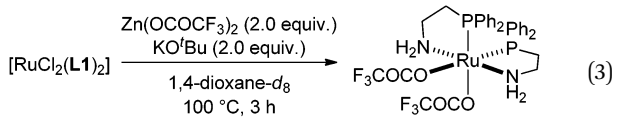


(1)

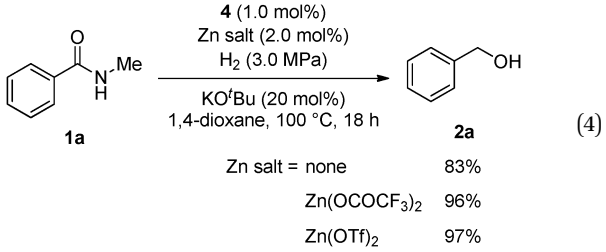


(2)

To gain additional insight into the effects of the best additive $Zn(OCOCF_3)_2$, we performed controlled NMR experiments. When the ruthenium complex $[RuCl_2(\mathbf{L1})_2]$ was mixed with $Zn(OCOCF_3)_2$ in the presence of KO^{t}Bu in 1,4-dioxane-d_8, a new singlet peak appearing at 62.6 ppm in its $^{31}P\{^1H\}$ NMR spectrum was assigned to complex **4** bearing two trifluoroacetates in the *cis* position based on X-ray crystallographic analysis [eqn (3)]. In contrast to the observation that $[RuCl_2(\mathbf{L1})_2]$ without any additives showed no catalytic activity (Table 1, entry 1), the isolated complex **4** exhibited catalytic activity for hydrogenation of **1a** in the absence of a zinc salt to afford **2a** in 83% yield, suggesting that incorporation of a trifluoroacetate ligand into the ruthenium center was essential for the catalytic activity [eqn (4)]. The addition of $Zn(OCOCF_3)_2$ and $Zn(OTf)_2$ to the hydrogenation catalyzed by complex **4** increased the yield of **2a** to 96% and 97%, respectively, indicating an important role of the zinc ion in activating the amide bonds through its coordination to the carbonyl group. Thus, $Zn(OCOCF_3)_2$ had dual functions, as a source of a trifluoroacetate ligand and as a Lewis-acid to activate the amide bonds.



(3)



(4)

In conclusion, we found that $Zn(OCOCF_3)_2$ had unique additive effects on Ru-catalyzed hydrogenation of amides under mild conditions. This catalytic system could be applied to the hydrogenation of various amides, giving the corresponding primary alcohols in good yield. Such a simple combination of the ruthenium complex and the zinc salt provides a conventional synthetic protocol for hydrogenating amides. Further application of the ruthenium complex–zinc salt combination is currently under investigation in our laboratory.

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