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Boron Lewis Acid Promoted Ruthenium-Catalyzed Hydrogenation of Amides: An Efficient Approach to Secondary Amines

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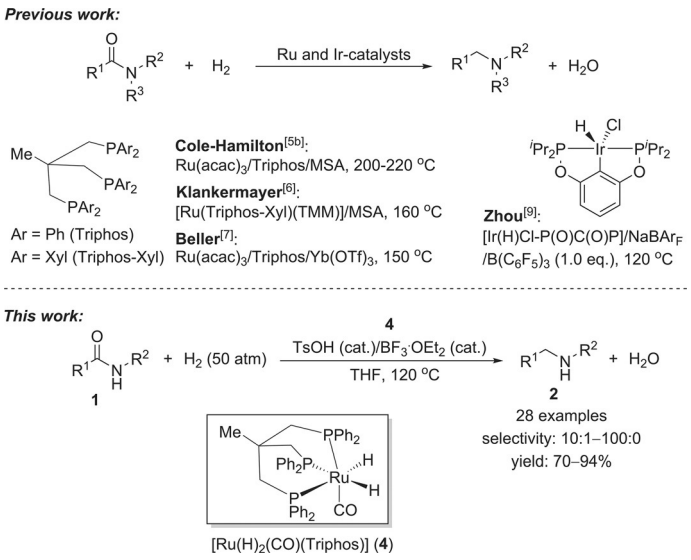
The hydrogenation of amides to amines has been developed by using the catalyst [Ru(H)$_2$(CO)(Triphos)] (Triphos = 1,1,1-tri(diphenylphosphinomethyl)ethane) and catalytic boron Lewis acids such as B(C$_6$F$_5$)$_3$ or BF$_3$·Et$_2$O as additives. The reaction provides an efficient method for the preparation of secondary amines from amides in good yields with high selectivity.

Transition-metal-catalyzed hydrogenation of amides to amines, which avoids the use of stoichiometric hydride reagents and the generation of large amounts of waste, has received intensive study in recent years.[1] The big challenge for this transformation is to find efficient catalysts that can selectively hydrogenate amides to the corresponding amines without generation of alcohols and lower amines.[2] Several bifunctional/bimetallic heterogeneous catalysts have been developed for the hydrogenation of amides to amines with high selectivity, albeit the substrate scope is narrow and the reaction conditions are generally harsh.[3] In contrast, homogeneous catalytic hydrogenation of amides can performed under milder conditions, but most of the reported examples produced a mixture of alcohols and lower amines.[4] A breakthrough was made in 2007 by Cole-Hamilton et al., who introduced the ruthenium complex of the Triphos ligand (1,1,1-tri(diphenylphosphinomethyl)-ethane) into the hydrogenation of *N*-phenyl amide to secondary amine with excellent selectivity, but relatively harsh reaction conditions (164 °C, 40 bar; or 210 °C, 10 bar) are required.[5] Recently, Klankermayer et al. modified the Triphos ligand and found that ruthenium complexes of Xyl-Triphos ligands containing 3,5-dimethylphenyl groups have high activity and selectivity for the hydrogenation of lactams to cyclic amines in the presence of a catalytic amount of methanesulfonic acid as a co-catalyst. However, a high reaction temperature and high H_2 pressure (160 °C, 100 bar) are still needed.[6] In addition, with the Ru/Triphos catalyst and expensive metal triflate Yb(OTf)$_3$ as a co-catalyst, Beller et al. realized the hydrogenation of a range of secondary and tertiary amides to the corresponding amines with moderate to good selectivities under milder reaction conditions (150 °C, 5–15 bar).[7] Therefore, the development of highly efficient and easily accessible catalysts for selective hydrogenation of amides to the corresponding amines is highly desired.

As a part of our ongoing research on the development of efficient catalysts for the hydrogenation of carboxylic acid derivatives under mild reaction conditions,[8] we have recently reported an iridium catalyst with a P(O)C(O)P pincer ligand and B(C$_6$F$_5$)$_3$ as a Lewis acid for the hydrogenation of *N*-arylamides and lactams to amines with excellent selectivity under relatively mild conditions.[9] However, one equivalent of B(C$_6$F$_5$)$_3$ was required to activate the amide substrates in that reaction. In the search for low-cost, efficient, and practical catalysts for the hydrogenation of amides to amines, we found that catalytic boron Lewis acids can promote the hydrogenation of amides catalyzed by Ru/Triphos complexes. We herein report the boron Lewis acid promoted Ru-catalyzed hydrogenation of amides in excellent selectivity (Scheme 1).



Scheme 1. Catalysts for the homogeneous hydrogenation of amides to amines.

We initially evaluated a series of ruthenium catalysts in the reduction of *N*-phenylacetamide (**1a**) to *N*-ethylaniline (**2a**) in the presence of 10 mol% of B(C$_6$F$_5$)$_3$. The [Ru(H)$_2$(CO)(Triphos)]

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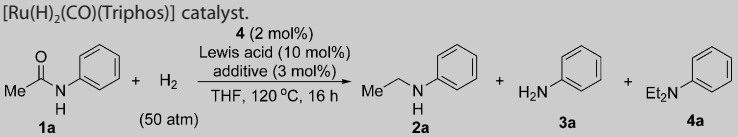
(**4**) complex was found to be the most efficient catalyst among the ruthenium complexes currently available in our laboratory (see Table S1 in the Supporting Information). Under the conditions of 50 atm of H_2 at 120 °C for 16 h, the amide **1a** was hydrogenated to amine **2a** in 90% conversion with 84% yield and 24:1 C–O/C–N selectivity (**2a**/**3a**). The *N*-alkylation of **2a** to form the byproduct *N*,*N*-diethylaniline (**4a**) was also detected in 2% yield (Table 1, entry 2). No hydrogenation was observed under the same reaction conditions without $B(C_6F_5)_3$ (entry 1). This result indicated that the addition of a catalytic amount of boron Lewis acid is necessary for the reaction. Several boron-based Lewis acids were then compared, and $BF_3{\cdot}OEt_2$ also gave good results (85% conv., 78% yield, **2a**/**3a**/**4a** = 23:1:0.7; entry 5). Because $BF_3{\cdot}OEt_2$ is more accessible, we used it for optimizing the reaction conditions. Brønsted acids have been reported to increase the activity of catalysts in reactions that involve a dehydration process (C–O cleavage).[10] When 3 mol% TsOH was added to the hydrogenation of **1a**, full conversion was achieved, the yield of **2a** was increased to 90%, and the selectivity was almost retained (**2a**/**3a**/**4a** = 18:1:0.8, entry 7). Addition of $HNTf_2$ and HBF_4 also increased the conversion of the reaction, but markedly decreased the selectivity (entries 8 and 9). In addition to THF, other ether solvents such as dioxane and 1,2-dimethoxyethane (DME) can also be used for this transformation, albeit with lower conversion, yield, as well as selectivity. However, non-coordinating solvents such as toluene or 1,2-dichloroethane (DCE) gave very low conversions or no reaction (see the Supporting Information, Table S2). When the reaction was performed at 100 °C, the amide **1a** was hydrogenated in 98% conversion with 88% yield and **2a**/**3a**/**4a** selectivity of 19:1:0.7 was achieved, albeit with a longer reaction time (entry 10). The hydrogenation of **1a** can also be performed under 30 atm of H_2, and a comparable result was obtained (entry 11).

Under the optimized reaction conditions, a series of amides were hydrogenated. The results summarized in Table 2 show that all *N*-arylacetamides (**1a**–**l**) give high yields (80–95%) and excellent C–O/C–N selectivities (12:1–38:1). The substituents on the phenyl ring of the substrates had little effect on the yield and selectivity of the reaction (entries 1–12). The *N*-phenylamides with other aliphatic or aromatic acyl groups (**1m**–**u**) also worked well, affording the corresponding amines (**2m**–**u**) in high yield (72–95%) and high C–O/C–N selectivity (10:1–45:1; entries 13–21). The amide with a bulky acyl group, isobutyl (**1n**), has a relatively low yield (70%), but higher C–O/C–N selectivity (45:1; entry 14). The reaction has good tolerance for oxygen atoms and heterocycles in the acyl group (entries 18, 19, and 21). The hydrogenation of lactams afforded cyclic amines exclusively, however,

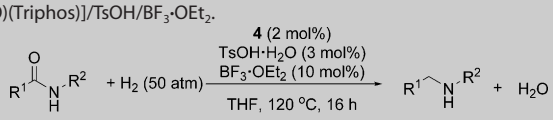
Table 1. Optimization of the reaction conditions for the hydrogenation of **1a** with $[Ru(H)_2(CO)(Triphos)]$ catalyst.



Entry[a]	Lewis acid	Additive	Conversion [%][b]	Yield [%][b]	Selectivity (**2a**:**3a**:**4a**)[b]
1	–	–	0	0	–
2	$B(C_6F_5)_3$	–	90	84	24:1:0.5
3[c]	BEt_3	–	2	2	100:0:0
4	BPh_3	–	3	3	100:0:0
5	$BF_3{\cdot}OEt_2$	–	85	78	23:1:0.7
6[d]	BCl_3	–	0	0	–
7	$BF_3{\cdot}OEt_2$	$TsOH{\cdot}H_2O$	>99	90 (87)	18:1:0.8
8	$BF_3{\cdot}OEt_2$	$HNTf_2$	99	85	12:1:0.9
9	$BF_3{\cdot}OEt_2$	HBF_4	98	84	12:1:0.8
10[e]	$BF_3{\cdot}OEt_2$	$TsOH{\cdot}H_2O$	98	88	19:1:0.7
11[f]	$BF_3{\cdot}OEt_2$	$TsOH{\cdot}H_2O$	>99	89	18:1:0.8

[a] Reaction conditions: 0.5 mmol *N*-phenylacetamide (**1a**), 2 mol% $[Ru(H)_2(CO)(Triphos)]$ (**4**), 5–10 mol% boron Lewis acids, 2–4 mol% Brønsted acid, 2 mL THF, 50 atm H_2, 120 °C, 16 h. [b] Conversions, yields, and selectivities were determined by GC analysis by using triphenylamine as an internal standard; the isolated yield is given in parentheses. [c] BEt_3 used as a 1 M solution in THF. [d] BCl_3 used as a 1 M solution in *n*-heptane. [e] 100 °C, 24 h. [f] 30 atm H_2, 24 h.

Table 2. Substrate scope of the hydrogenation of amides catalyzed by $[Ru(H)_2(CO)(Triphos)]$/TsOH/$BF_3{\cdot}OEt_2$.



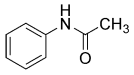
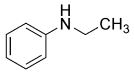
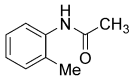
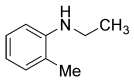
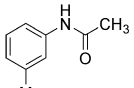
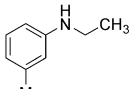
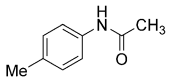
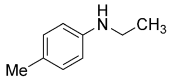
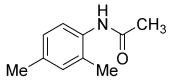
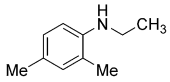
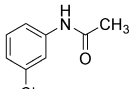
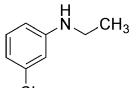
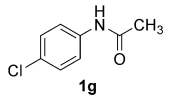
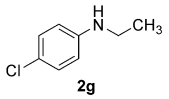
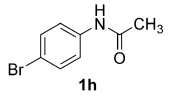
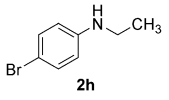
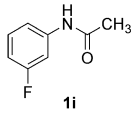
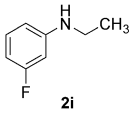
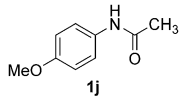
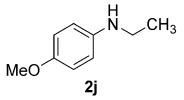
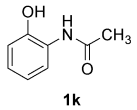
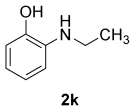
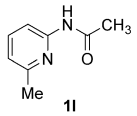
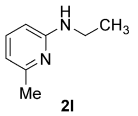
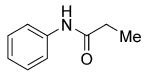
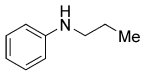
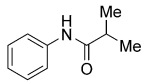
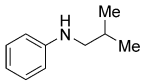
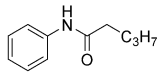
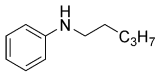
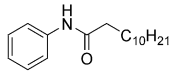
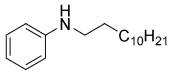
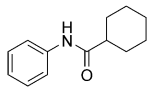
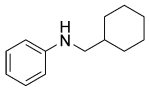
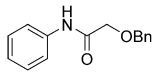
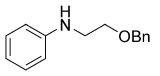
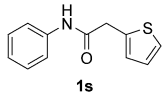
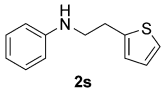
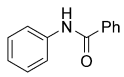
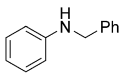
Entry[a]	1	2	Yield [%][b]	Selectivity (C–O/C–N)[b]
1[c]	 **1a**	 **2a**	87	18:1
2	 **1b**	 **2b**	94	38:1
3[c]	 **1c**	 **1c**	88	20:1
4[c]	 **1d**	 **2d**	86	18:1
5	 **1e**	 **2e**	93	36:1
6[c]	 **1f**	 **2f**	84	16:1

Table 2. (Continued)

Entry[a]	1	2	Yield [%][b]	Selectivity (C–O/C–N)[b]
7[c]	 **1g**	 **2g**	85	17:1
8[c]	 **1h**	 **2h**	80	12:1
9[c]	 **1i**	 **2i**	83	15:1
10[c]	 **1j**	 **2j**	88	20:1
11	 **1k**	 **2k**	80	–
12	 **1l**	 **2l**	75	14:1
13[c]	 **1m**	 **2m**	85	17:1
14	 **1n**	 **2n**	70	45:1
15[c]	 **1o**	 **2o**	87	20:1
16	 **1p**	 **2p**	92	34:1
17	 **1q**	 **2q**	80	40:1
18[c]	 **1r**	 **2r**	91	21:1
19	 **1s**	 **2s**	86	13:1
20[d]	 **1t**	 **2t**	78	10:1

one equivalent of BF_3·OEt_2 was necessary for the full conversion of azepan-2-one (**1w**; entry 23).[11] It was delightful to find that the ester groups, which could be hydrogenated to alcohol by the Ru/Triphos catalyst,[12] were stable in our reaction. The *N*-acylanilines **1x**–**1ab** containing an ester group either in the phenyl ring or in the acyl moiety were hydrogenated to the corresponding amines **2x**–**2ab** in high yields (83–92%) with the ester groups unchanged (entries 24–28). This high selectivity of amide hydrogenation over ester hydrogenation was attributed to the fact that the BF_3 favors the formation of BF_3–amide adducts.[13]

To demonstrate the utility of this efficient ruthenium-catalyzed hydrogenation of amides, we synthesized tetracaine hydrochloride, a potent local anesthetic and antipruritic.[14] Under the optimal reaction conditions, ethyl 4-butyramidobenzoate (**1z**) was hydrogenated on the gram-scale to the amine **2z** in 89% yield. The amine **2z** was converted to tetracaine hydrochloride in 85% yield through an ester exchange reaction with 2-(dimethylamino)-ethan-1-ol (Scheme 2).

To understand the role of BF_3·OEt_2, the adduct (**1a**)–BF_3 was prepared by heating **1a** at reflux with one equivalent of BF_3·OEt_2 in toluene in quantitative yield (for details, see the Supporting Information). Hydrogenation of the adduct (**1a**)–BF_3 by catalyst **4** under the optimized conditions afforded the desired product **2a** in 99% yield with 50:1 C–O/C–N selectivity (Scheme 3). This result strongly indicated that the amide–boron adduct is the key intermediate in the reaction. Although water is produced in the reaction, and the BF_3·OEt_2 could be hydrolyzed to HF and other Brønsted acids; the ^{19}F NMR spectrum shows that the product of the hydrogenation of **1a** with stoichiometric BF_3·OEt_2 is the adduct (**2a**)–BF_3. This experiment showed that BF_3·Et_2O is stable under the reaction conditions and functionalized as a Lewis acid.

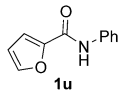
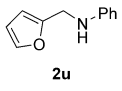
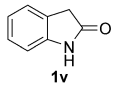
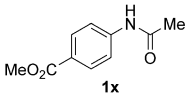
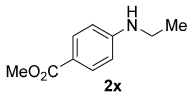
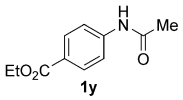
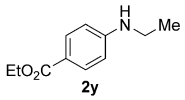
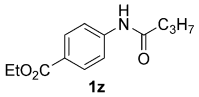
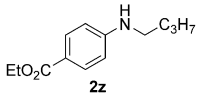
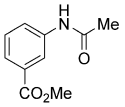
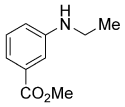
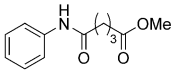
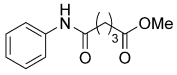
In summary, a catalytic amount BF_3·OEt_2 significantly improved the performance of the catalyst [$Ru(H)_2(CO)$(Triphos)] in the hydrogenation of amides. Both aromatic and aliphatic amides were hydrogenated to secondary amines in good yields and high selectivity under mild conditions. Ester groups are tolerated in the hydrogenation of amides.

Experimental Section

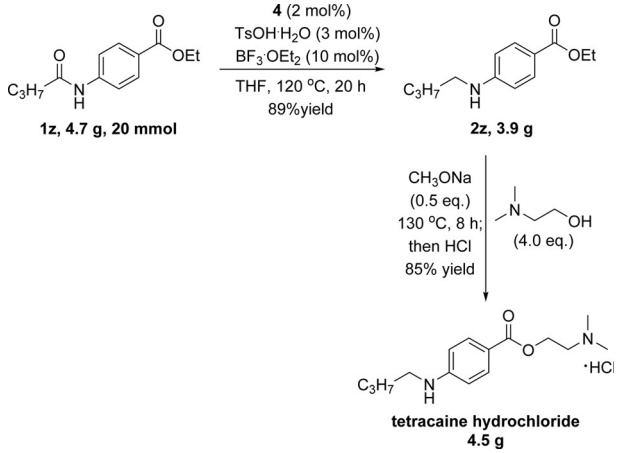
General procedure for the Ru-catalyzed hydrogenation of amides

In a glovebox, a glass vessel was charged with [$Ru(H)_2(CO)$(Triphos)] (7.8 mg, 10 μmol), TsOH·H_2O (2.8 mg, 15 μmol), and amide (0.5 mmol). The vessel was placed into an autoclave and BF_3·OEt_2 (5 μL) in dry THF (2 mL) was added under an argon atmosphere. The auto-

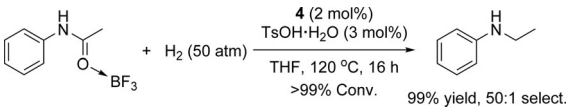
Table 2. (Continued)

Entry[a]	1	2	Yield [%][b]	Selectivity (C–O/C–N)[b]
21[d]	 1u	 2u	80	11:1
22[e]	 1v	 2v	82	100:0
23[f]	 1w	 2w	73	100:0
24[c,g]	 1x	 2x	85	13:1
25[c,g]	 1y	 2y	86	14:1
26[c,g,h]	 1z	 2z	89	14:1
27[c,g]	 1aa	 2aa	83	11:1
28[c,g]	 1ab	 2ab	92	20:1

[a] Reaction conditions: 0.5 mmol amide (**1**), 2 mol% $[Ru(H)_2(CO)(Triphos)]$ (**4**), 10 mol% $BF_3{\cdot}OEt_2$, 3 mol% $TsOH{\cdot}H_2O$, 2 mL THF, 50 atm H_2, 120 °C, 16 h. [b] Isolated yield after column chromatography on silica gel. Selectivity is determined by GC analysis by using triphenylamine as an internal standard. [c] Traces of *N,N*-dialkylanilines were detected as byproduct. [d] 5 mol% $[Ru(H)_2(CO)(Triphos)]$ (**4**), 7.5 mol% $TsOH{\cdot}H_2O$, 15 mol% $BF_3{\cdot}OEt_2$. [e] Indole was detected as a byproduct in 11% yield. [f] 100 mol% of $BF_3{\cdot}OEt_2$ was used. [g] No ester reduction product was detected. [h] 20 mmol amide, 20 h.



Scheme 2. The synthesis of tetracaine hydrochloride.



Scheme 3. Hydrogenation of the **1a**–BF_3 adduct.

clave was purged three times with hydrogen and finally charged to 50 atm. The reaction mixture was stirred at 120 °C for 16 h, then cooled to room temperature. The pressure was released, and triphenylamine was added as an internal standard. The mixture was filtered through a short silica column and submitted for analysis of the yield and selectivity of the reaction by GC. The pure product was obtained by column chromatography on silica gel (petroleum ether/ethyl acetate (PE/EA) = 10:1, v/v).

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Keywords: amide · boron · homogeneous catalysis · hydrogenation · Lewis acids · ruthenium

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