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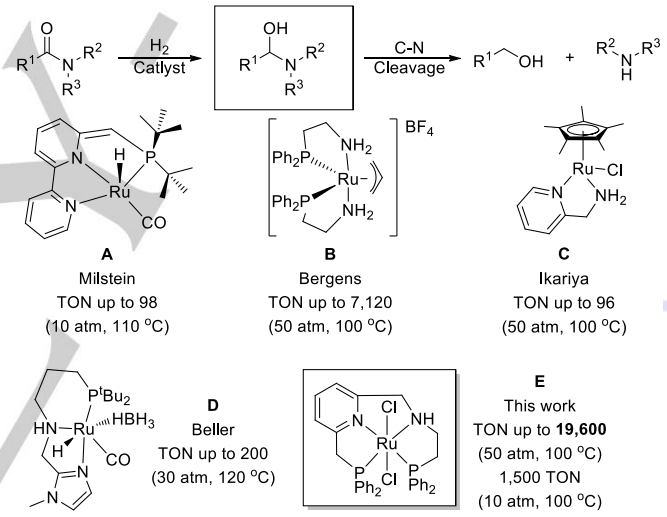
Direct Catalytic Hydrogenation of Simple Amides: A Highly Efficient Approach from Amides to Amines and Alcohols

Liyang Shi, Xuefeng Tan, Jiao Long, Xiong Xiong, Song Yang, Peng Xue, Hui Lv*, and Xumu Zhang*

Abstract: Highly chemoselective and reactive direct catalytic reduction of various amides to amines and alcohols has been developed with a tetradentate ruthenium complex. The catalytic system shows excellent activities (TONs up to 19,600) and great functional group tolerance under mild reaction conditions, comparing with several bidentate and tridentate ruthenium catalytic systems.

The reduction of carboxylic acid derivatives plays an important role in organic synthesis. Especially, simple amides with a less electrophilic carbonyl group are still one of the major challenging targets in reduction of carboxylic acid derivatives.[1] However, this transformation still relies heavily on the stoichiometric use of metal hydride reagents despite of the difficult handling of large amount of waste.[2] Therefore, considerable efforts have been devoted to developing efficient catalytic systems for hydrogenation of amides with molecular hydrogen. Over the past decades, numerous heterogeneous catalysts have been successfully used to reduce amides.[3] However, many heterogeneous catalysts have limitations, such as, harsh conditions, high catalytic loading, and small substrate scope. In contrast, homogeneous systems are often considered to be more active at low reaction temperatures and hydrogen pressures, which might lead to high reactivity and selectivity.[4]

Since the first example was described in 2003 by Crabtree,[5] several homogeneous systems have been reported.[6] But, selective, direct hydrogenation of amides to form amines and alcohols has rare been reported. In this field, progress have been made by Ikariya[7], Milstein[8], Bergens[9] and Beller[10] *et al*. For related reactions of net C-N cleavage, progress was developed by Ikariya and co-workers since 2007.[7] In 2010, a breakthrough based on a PNN-Ru pincer complex was presented by David Milstein.[8] In this system, amides can be selectively and directly reduced to amines and alcohols with TONs (Turnover number) up to 100 under mild conditions (Scheme 1, **A**). Almost the same time, Bergens developed a π-allyl ruthenium complex (Scheme 1, **B)** which exhibited good performance in the reduction of secondary and tertiary amides as well as lactams.[9a] Remarkably, using the π-allyl ruthenium complex, the TONs can reach up to 1000 for several lactams and 7120 for N-phenylpyrrolidin-2-one. In 2011, Ikariya and co-workers used [Cp*RuCl(LN)] (Cp* =η-$C_5(CH_3)_5$, LN = 2-$C_5H_4NCH_2NH_2$), for the reduction of lactams, and amides (Scheme 1, **C**)[7d]. In 2015, a base-free catalytic system with moderate TONs (>300) was also provided by Bergens.[9b] Then in 2016, Beller and co-workers synthesized two novel ruthenium pincer complexes (Scheme 1, **D**) bearing an imidazolylaminophosphino ligand.[10] More recently, some systems based on earth-abundant metal complexes were also reported.[11] *So far, general and efficient catalytic system for amides reduction with TON over 10,000 and broad substrate scope has far less established.*



Scheme 1. Catalytic hydrogenation of simple amides

Recently, our group successfully designed and synthesized a new tetradentate ruthenium complex (Scheme 1, **E**) for the hydrogenation of esters with high efficiency (TONs up to 80,000).[12] We attribute the great catalytic activity to the hydridic character of the metal hydride and the acidity of the N−H group in our catalytic precursor **E**. According to the bifunctional concept and the mechanism study,[13] high acidity of the N−H group in complex **E** is helpful to activate the C=O group and high hydridity of the Ru-H in active species is profitable to attack the C=O group. And the tetradentate coordination model with two electron-donating phosphine groups makes the complex not easy to be deactivated under a variety of catalytic conditions.[14] Intrigued by the success of the catalytic model, we envision that catalyst **E** may also achieve amide reduction with high efficiency. *Herein, we report that complex* **E** *showed outstanding performance in the catalytic hydrogenation of a variety of simple amides with TONs up to 19,600.*

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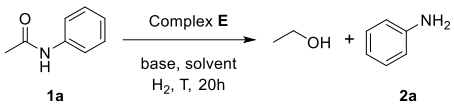
Initially, acetanilide **1a** was chosen as a model substrate for the hydrogenation (Table 1). When the reaction was carried out at 100 °C and 50 bar of hydrogen with the assistance of *t*-BuOK, it proceeded smoothly and an unexpected TON as high as 11,800 was obtained (Table 1, entry 1). It is noteworthy that only trace of *N*-ethyl aniline (<1%) was detected. Encouraged by this excellent result, further examination on the effect of the reaction media was conducted (Table 1, entries 1-5). It revealed that the solvent THF gave the best result in terms of TONs (Table 1, entry 5). Subsequently, exploration of various bases and the corresponding amount showed that *t*-BuOK was the best base (Table 1, entry 5). Then temperature and pressure of H_2 were also systematically investigated, and found that the reaction worked very well in low pressure (1500 TON, 10 atm, entry 10). Generally, high temperature and high hydrogen pressure led to high TONs, but no further improvement when the temperature was higher than 100 °C and the pressure of H_2 is higher than 50 atm (see supporting information). Therefore, the optimal condition were established as: substrate : t-BuOK = 100 : 1 ~ 100 : 2, 4 mL of THF, 100 °C, 50 bar of H_2.

Table 1. Optimization for hydrogenation of **1a**[a]



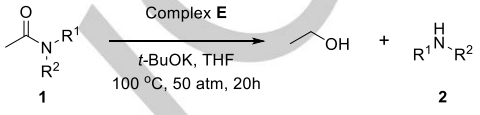
1a **2a**

entry	Solvent	Base (%)	T (°C) / P (bar)	TON[b]
1	Toluene	*t*-BuOK (1.3)	100/50	11,800
2	MeOH	*t*-BuOK (1.3)	100/50	1,200
3	*i*-PrOH	*t*-BuOK (1.3)	100/50	10,100
4	1,4-Dioxane	*t*-BuOK (1.3)	100/50	18,800
5	THF	*t*-BuOK (1.3)	100/50	19,700
6	THF	*t*-BuOK (3)	100/50	19,600
7	THF	MeONa (5)	100/50	10,100
8	THF	EtONa (5)	100/50	11,900
9	THF	$CsCO_3$ (5)	100/50	3,000
10[c]	THF	*t*-BuOK (5)	100/10	1,500

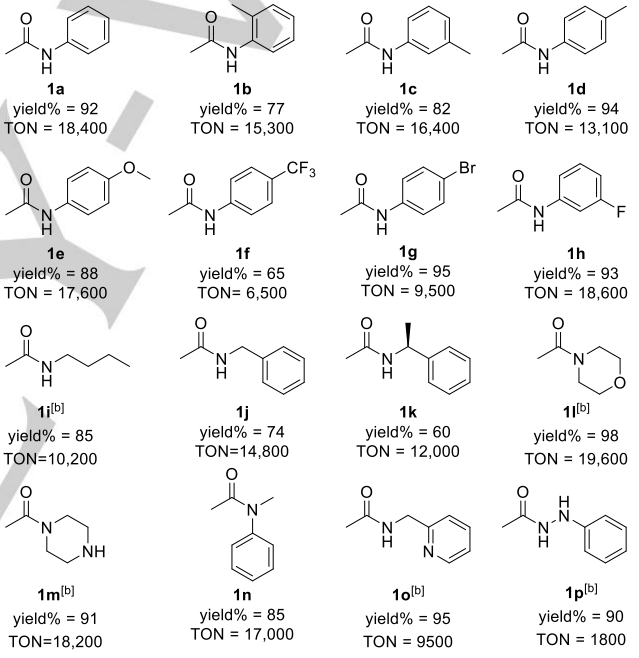
[a] Conditions: **1a** (10 mmol), Complex **E** (0.0005 mmol), base, solvent (4 mL), 100 °C, 50 atm H_2, 20h. [b] Determined by GC analysis with internal standard. [c] 10 atm H_2, Complex **E** (0.005 mmol)

The substrate scope of various *N*-substituted acetamides was investigated under the optimal reaction conditions. As listed in table 2, *N*-aryl acetamides were efficiently hydrogenated with excellent TONs (10,000-20,000) under mild reaction conditions regardless of the substituents on the phenyl ring were electron donating (Table 2, **1b-1e**), electron withdrawing (Table 2, **1f-1h**), or substituted with halogen (Table 2, **1g** and **1h**). And different substitution positions on the phenyl ring of the methyl group did not influence the reaction activity (Table 2, **1b-1d**). Then, we switched our attention to the fatty amides (Table 2, **1i-1k**), tertiary amides (Table 2, **1l-1n**), and other special amides (Table 2, **1o** and **1p**). As expected, good to excellent TONs (9,500-19,600) were obtained (Table 2, **1i-1o**). It is remarkable that the chiral center of the amine product **2k** is still retained. To our delight, this catalytic system works well for substrate **1o** with TON up to 9,500, although the product **2o** with strongly coordinating substituents may interfere with the catalysis. Moreover, our catalytic hydrogenation system is also compatible for hydrazides, such as **1p**.

Table 2. Substrate scope of various N-substituted acetamides.[a]



1 **2**



1a yield% = 92, TON = 18,400
1b yield% = 77, TON = 15,300
1c yield% = 82, TON = 16,400
1d yield% = 94, TON = 13,100
1e yield% = 88, TON = 17,600
1f yield% = 65, TON= 6,500
1g yield% = 95, TON = 9,500
1h yield% = 93, TON = 18,600
1i[b] yield% = 85, TON=10,200
1j yield% = 74, TON=14,800
1k yield% = 60, TON = 12,000
1l[b] yield% = 98, TON = 19,600
1m[b] yield% = 91, TON=18,200
1n yield% = 85, TON = 17,000
1o[b] yield% = 95, TON = 9500
1p[b] yield% = 90, TON = 1800

[a] The reaction was conducted in 10 mmol scale in 4 mL of THF, Complex **E** was used as catalytic precursor, Complex **E** 0.0005mmol, *t*-BuOK (1%-2% of substrates), 100 °C, 50 bar of H_2, 20 h, unless otherwise noted. The reaction scale: 10 mmol of **1a-1c**, **1e**, **1h**, **1i-1n**; 7 mmol of **1d**; 5 mmol of **1f**; 5 mmol of **1g**; 6 mmol of **1i**; 5 mmol of **1o**; 1 mmol of **1p**. Isolated yields. [b] GC yields.

In order to gain more insights into this catalytic system, hydrogenation of more substrates were also conducted as shown in table 3. *N*- aryl substituted amines bearing not only electron-donating groups, such as methoxy and methyl, but also electron-withdrawing groups, could be well converted by complex **E** with high activities (Table 2, **3a-3d**). To our delight, it also worked well for trifluoro-*N*-phenylacetamide (Table 2, **3e**), imide (Table 2, **3f**) and benzoyl benzylamine (Table 2, **3g**).

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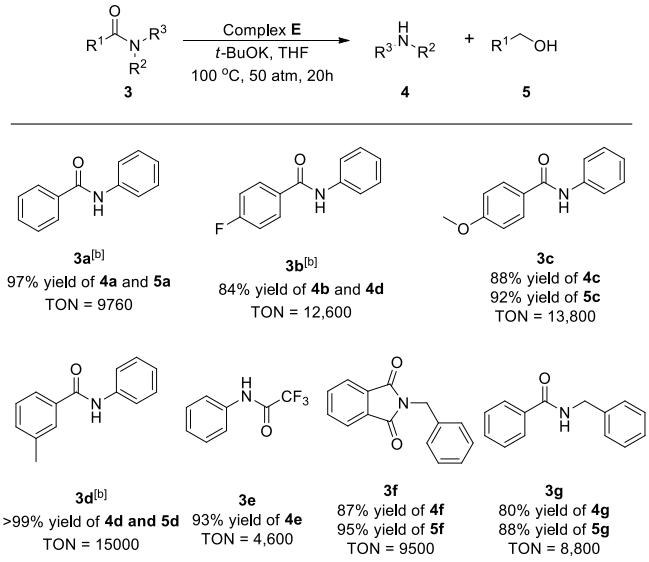
Table 3. Substrate scope using Complex E as the catalytic precursor.[a]



[a] The reaction was conducted in 4 mL of THF, Complex **E** was used as catalytic precursor, Complex **E** 0.0005mmol, *t*-BuOK (1%-2% of substrates), 100 °C, 50 bar of H_2, 20 h, unless otherwise noted. The reaction scale: 5 mmol of **3a**, 7.5 mmol of **3b-3d**, 2.5 mmol of **3e**, 5 mmol of **3f** and **3g**. Isolated yields. [b] GC yields.

In summary, we have developed a practical strategy for the highly selective convertion of simple amides to amines and alcohols. This reaction features high reaction activity (TONs up to 19,600), wide substrate scope, mild reaction conditions, and simple operation. It can be served as an outstanding and general method to remove amide protecting group and should have broad interest for organic communities. Studies on the substrate scope of this system, catalyst variations, and the mechanism are undergoing in our laboratory.

Experimental Section

In an argon-filled glove box, a 5 mL vial equipped with a magnetic stirring bar, was added the required amount of complex **D** (0.023 mg/mL in THF), substrate (10 mmol) and base successively. Additional THF was added to bring the total reaction volume to 4 mL. The vials were subsequently transferred into an autoclave which was charged with hydrogen (50 bar). The reaction was then stirred at 100 °C for 20 h. The hydrogen gas was released slowly and carefully. The solution was passed through a short column of silica gel (eluent: EtOAc) to remove the metal complex. The yields of compounds **1** and **3** were then determined by GC analysis.

Keywords: Amides • Hydrogenation • Chemoselectivity • Amines • Alcohols

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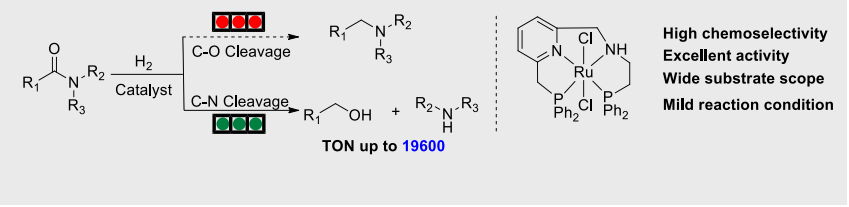

A general and efficient protocol for the reduction of various amides to amines and alcohols have been achieved by a tetradentate ruthenium complex catalyzed hydrogenation. The catalytic system displays excellent activities (TONs up to 19,600) and wide substrate scope under mild reaction conditions which provides an outstanding and general method to remove amide protecting group.

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