Advanced Synthesis & Catalysis

Accepted Article

Title: Ru-catalyzed Deoxygenative Transfer Hydrogenation of Amides to Amines with Formic acid/triethylamine

Authors: Yixiao Pan, zhenli luo, Xin Xu, Haoqiang Zhao, Jiahong Han, Lijin Xu, Qing-Hua Fan, and Jianliang Xiao

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900406

Link to VoR: http://dx.doi.org/10.1002/adsc.201900406

10.1002/adsc.201900406

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Ru-catalyzed Deoxygenative Transfer Hydrogenation of Amides to Amines with Formic acid/Triethylamine

Yixiao Pan,[a] Zhenli Luo,[a] Xin Xu,[a] Haoqiang Zhao,[a] Jiahong Han,[a] Lijin Xu, *[a] Qinghua Fan *[b] and Jianliang Xiao*[c]

[a] Department of Chemistry, Renmin University of China, Beijing 100872, China.
Phone: 86-10-62511528, Fax: 86-10-62516444, E-mail: 20050062@ruc.edu.cn
[b] Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, P. R. China
E-mail: fanqh@iccas.ac.cn
[c] Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, United Kingdom
E-mail: J.Xiao@liverpool.ac.uk

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A ruthenium(II)-catalyzed deoxygenative transfer hydrogenation of amides to amines using HCO_2H/NEt_3 as the reducing agent is reported for the first time. The catalyst system consisting of [Ru(2-methylallyl)$_2$(COD)], 1,1,1-tris(diphenylphosphinomethyl) ethane (triphos) and Bis(trifluoromethane sulfonimide) ($HNTf_2$) performed well for deoxygenative reduction of various secondary and tertiary amides into the corresponding amines in high yields with excellent selectivities, and exhibits high tolerance toward functional groups including those that are reduction-sensitive. The choice of hydrogen source and acid co-catalyst is critical for catalysis. Mechanistic studies suggest that the reductive amination of the in situ generated alcohol and amine via borrowing hydrogen is the dominant pathway.

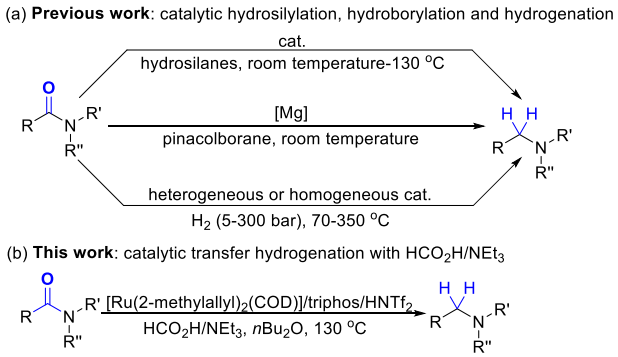
Keywords: Transfer Hydrogenation, Formic acid/ Triethylamine, Amide, Amine, Ruthenium, Triphos.

Introduction

The ubiquity of amines in drugs, natural products, agrochemicals, dyes, polymers and other fine chemicals and in diverse organic transformations has resulted in a great demand for the efficient preparation of these compounds.[1] Among these existing methods, the deoxygenative reduction of readily accessible amides is recognized as one of the most convenient and straightforward routes for the construction of amines.[2] Though useful, traditional methods strongly rely on the use of (over)stoichiometric amounts of highly reactive lithium aluminum hydride or borane to realize this transformation are generally fraught with many drawbacks, such as the use of hazardous chemicals, tedious workup procedures, narrow substrate scope, low functional group tolerance and the generation of large amounts of waste by-products.[3] In this context, a catalytic reduction approach that overcomes these drawbacks would be more attractive and atom-economic. Recently impressive advances in catalytic hydrosilylation[4] and hydroborylation[5] of amides into amines via C-O bond cleavage have been reported (Scheme 1a), but the concomitant generation of copious amounts of undesired byproducts remains problematic. There has been a long standing interest in the development of transition-metal catalysts for deoxygenative hydrogenation of amides to amines (Scheme 1a).[6] Although appealing, heterogeneous catalytic deoxygenative hydrogenation of amides is often plagued by harsh conditions and poor selectivity.[7] Recently, there has been increasing interest in developing homogeneous catalysts which could operate more selectively under milder reaction conditions for deoxygenative hydrogenation of amides.[8] Pioneering work by Cole-Hamilton and co-workers revealed that a homogeneous catalyst generated in situ from Ru(acac)$_3$ and triphos could work well for deoxygenative hydrogenation of amides with good to excellent selectivities, and introduction of an acid co-catalyst could improve the catalytic efficiency.[8a,b] Subsequently, the research groups of Klankermayer,[8c,g] Beller[8d] and Zhou[8f] independently developed similar Ru catalytic systems for highly selective deoxygenative hydrogenation of secondary, tertiary amides and lactams in the presence of acid co-catalysts. Zhou and coworkers also accomplished highly selective deoxygenative hydrogenation of secondary amides and lactams with an iridium pincer catalyst and B(C_6F_5)$_3$ co-catalyst.[8e] Saito et al. reported highly selective deoxygenative hydrogenation of ε-caprolactam catalyzed by a sterically confined bipyridine-ruthenium complex.[8h] Recently, Milstein et al. described the combination of

10.1002/adsc.201900406

a manganes pincer catalyst with $B(C_6F_5)_3$ co-catalyst for hydrogenation of secondary, tertiary amides and lactams into amines with excellent selectivity.[8i] More recently, Paradies et al. achieved metal-free frustrated Lewis pair catalyzed highly selective deoxygenative hydrogenation of tertiary amides with the assistance of oxalyl chloride.[8j] Despite these advances, the low electrophilicity of the amide carbonyl carbon and the difficulty in the control of C-O bond cleavage selectivity render this transformation rather challenging.[6-8] Therefore, the search for new efficient methods for deoxygenative reduction of amides is still an interesting and current research topic.



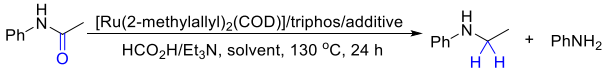
Scheme 1. Catalytic Reduction of Amides to Amines via C-O Bond Cleavage.

The catalytic transfer hydrogenation using a hydrogen donor other than molecular hydrogen has been rapidly developed over the past decades as a promising alternative to the catalytic hydrogenation because of its safety, low cost, operational simplicity and abundant availability of hydrogen sources.[9] Consequently, a variety of catalytic systems have been established for transfer hydrogenation of polar functional groups, and alcohols, formic acid and formates rank among the most commonly used hydrogen donors in these reactions. While remarkable progress has been made in this field, there has been surprisingly little attention paid to the development of catalytic transfer hydrogenation of carboxylic acid derivatives.[10] In particular, catalytic deoxygenative transfer hydrogenation of amides to amines has not been realized so far. Charette et al. reported a highly chemoselective and metal-free transfer reduction of amides pre-activated by Tf_2O to amines with Hantzsch ester.[11] However, this process is non-catalytic, and the requirement of overstoichiometric amounts of expensive Tf_2O and Hantzsch ester greatly hampers its wider application in organic synthesis. Given the synthetic potential of catalytic transfer hydrogenation reactions and on the basis of our own experience[12] in this field, we became interested in exploring catalytic deoxygenative reduction of amides to amines with convenient and inexpensive hydrogen sources. Herein we present for the first time an efficient Ru-catalytic system which enables highly chemoselective reduction of differently substituted amides into the corresponding amines with good to excellent yields and high tolerance of functional groups by using HCO_2H/NEt_3 as the hydrogen source (Scheme 1b)

Results and Discussion

We commenced our investigations by surveying reaction conditions employing *N*-phenylacetamide (**1a**) as the substrate and HCO_2H/NEt_3 (n/n = 5/2) as the hydrogen source (Table 1 and supporting information (SI)). We first examined the catalytic performance of the ruthenium catalyst generated in situ from triphos and [Ru(2-methylallyl)$_2$(COD)] in the absence of any additive at 130 °C in THF in a sealed flask. The reaction generated a mixture of the target product *N*-ethylaniline (**2a**) (33%) and aniline (**2a'**) (17%) after 24 h (Table 1, entry 1). Obviously, both the reactivity and selectivity for the C-O bond cleavage needed to be improved. Several other frequently employed ruthenium complexes were then examined in this reaction, but none of them outperformed [Ru(2-methylallyl)$_2$(COD)] (see SI). It was reported that using Lewis or Bronsted acid additive could enhance the catalytic efficiency of Ru/triphos-catalyzed deoxygenative hydrogenation of amides[8] and *N*-alkylation of amines.[13] Indeed, evaluation of various acid additives in this reaction showed that the additive turned out to be the critical parameter (Table 1, entries 2-10), and $HNTf_2$ was the best choice with 79% yield of **2a** and 79:13 C-O / C-N cleavage selectivity (Table 1, entry 5). Further optimization revealed that both the yields and selectivities decreased when performing the reaction in 1, 4-dioxane, toluene, MTBE or DCE (Table 1, entries 11, 13-15). Gratefully, nBu_2O exhibited superior performance, delivering **2a** in 91% yield with almost complete suppression of the C-N cleavage (Table 1, entry 12). The hydrogen source also played an important role in this reaction. Comparable results were observed when using HCO_2H alone as the reductant, but switching to HCO_2Na or HCO_2NH_4 significantly diminished the catalytic activity (Table 1, entries 16-18). Finally, control experiments indicated that no reaction occurred in the absence of either triphos or [Ru(2-methylallyl)$_2$(COD)] (Table 1, entries 19 and 20).

Table 1. Optimization of reaction conditions.[a,b]



1a 2a 2a'

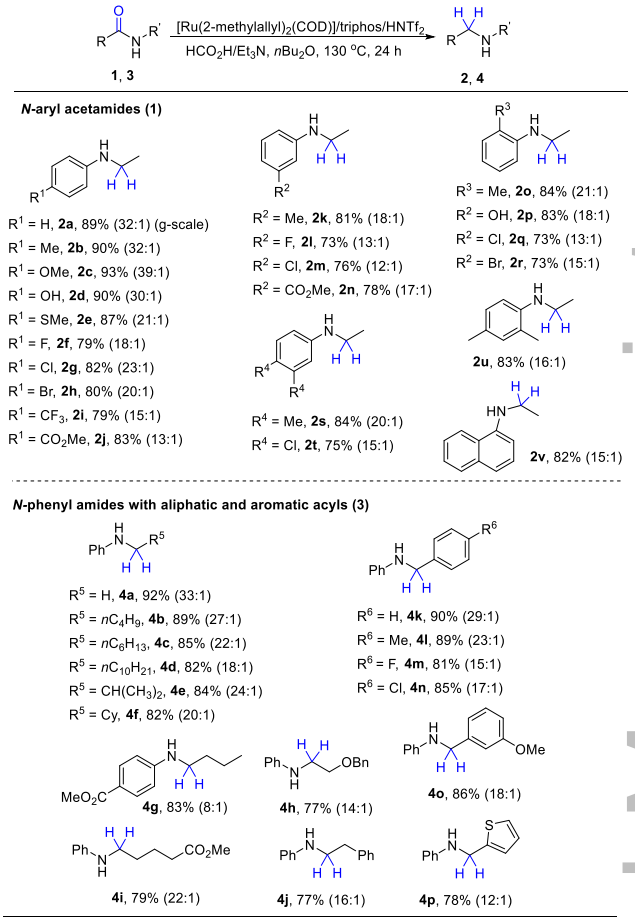
Entry	Solvent	Additive	Conv. (%)[b]	**2a** (%)[b]	**2a'** (%)[b]
1	THF	none	52	33	17
2	THF	TfOH	68	46	20
3	THF	MSA	82	58	8
4	THF	TsOH•H$_2$O	53	17	30
5	THF	$HNTf_2$	93	79	13
6	THF	BF_3•Et_2O	66	38	25

10.1002/adsc.201900406

7	THF	$Al(OTf)_3$	72	49	20
8	THF	$In(OTf)_3$	78	52	22
9	THF	$Yb(OTf)_3$ •H_2O	80	67	12
10	THF	$In(OAc)_3$	68	53	12
11	dioxane	$HNTf_2$	72	58	14
12	nBu_2O	$HNTf_2$	96	91	3
13	toluene	$HNTf_2$	74	44	29
14	MTBE	$HNTf_2$	85	71	13
15	DCE	$HNTf_2$	45	25	20
16[c]	nBu_2O	$HNTf_2$	90	73	15
17[d]	nBu_2O	$HNTf_2$	35	15	18
18[e]	nBu_2O	$HNTf_2$	67	42	21
19[f]	nBu_2O	$HNTf_2$	NR	0	0
20[g]	nBu_2O	$HNTf_2$	NR	0	0

[a] Reaction conditions: **1a** (0.25 mmol), [Ru(2-methylallyl)$_2$(COD)] (5.0 mol %), triphos (10.0 mol %), additive (10.0 mol %), HCO_2H/NEt_3 (n/n = 5/2, n(HCO_2H) = 1.25 mmol, n(Et_3N) = 0.5 mmol, 135 μL), solvent (1.0 mL) at 130 °C for 24 h. NR: no reaction. TfOH: trifluoromethanesulfonic acid; MSA: methyl sulfonic acid; TsOH: 4-methyl benzenesulfonic acid; $HNTf_2$: bis(trifluoromethane sulfonimide). [b] Conversion and yield were determined by GC with Ph_3N as an internal standard. [c] HCO_2H (1.25 mmol) was employed as the reductant. [d] HCO_2Na (1.25 mmol) was employed as the reductant. [e] HCO_2NH_4 (1.25 mmol) was employed as the reductant. [f] No triphos. [g] No Ru(2-methylallyl)$_2$(COD).

With the optimized conditions in hand, we then examined the reactivity of various secondary amides. As shown in Scheme 2, various *N*-aryl acetamides (**1b-1v**) underwent smooth reduction to afford the corresponding amine products (**2b-2v**) in good to excellent yields (73-93%) and C-O/C-N bond cleavage selectivities (12:1-39:1). Gratifyingly, the sensitive functional groups, such as -F, -Cl, -Br, -OH, -SMe, -CO_2Me and -CF_3, were well-tolerated under the reaction conditions, providing ample opportunities for further chemical diversification. The reduction appears to be affected by the position of the substituent on the aryl ring, and better yields and selectivities were observed in the reduction of substrates with para-substituent on the aryl ring. The deoxygenative transfer hydrogenation of aliphatic *N*-phenyl amides (**3a-3f**) also proceeded well to provide the target products (**4a-4f**) in high yields with high selectivities, and variation of length and size of the alkyl groups did not significantly affect the reaction outcome. Notably, ethyl 4-butyramidobenzoate (**3g**) reacted well to furnish **4g** in 83% yield and a 8:1 selectivity, which is an intermediate for the synthesis of tetracaine hydrochloride, a potent local anesthetic and antipruritic.[14] The *N*-phenyl amides **3h** and **3i** were competent reaction partners with the ether and ester groups kept intact throughout the reaction. The *N*- phenyl amides with aromatic acyls (**3k-3p**) also successfully engaged in the reduction. Notably, a gram-scale reduction of **1a** was conducted smoothly under the optimized conditions to give **2a** in 89% yield. However, no reaction was observed when unactivated amides such as *N*-benzyl acetamide or *N*-benzyl benzamide was employed.



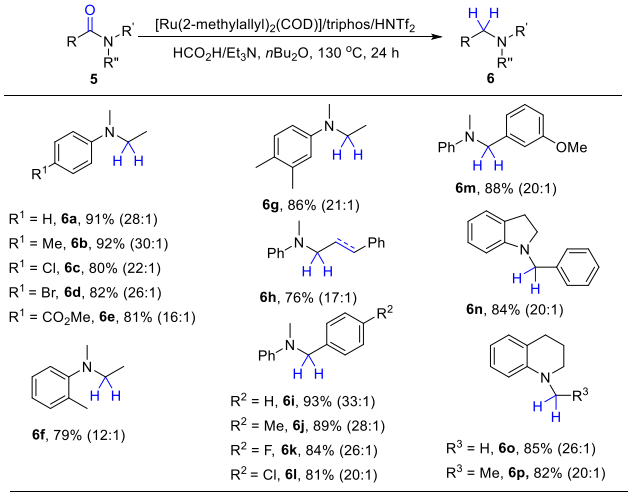
[a] Reaction conditions: **1** or **3** (0.25 mmol), [Ru(2-methylallyl)$_2$(COD)] (5.0 mol %), triphos (10.0 mol %), $HNTf_2$ (10.0 mol %), HCO_2H/NEt_3 (n/n = 5/2, n(HCO_2H) = 1.25 mmol, n(Et_3N) = 0.5 mmol, 135 μL), nBu_2O (1.0 mL) at 130 °C for 24 h. [b] Isolated yield. The ratio of C-O/C-N cleavage in parentheses was determined by GC with Ph_3N as an internal standard.

Scheme 2. Transfer Hydrogenation of Secondary Amides.[a,b]

To further explore the scope of this reaction, we then evaluated the deoxygenative reduction of various tertiary amides under the optimized reaction conditions (Scheme 3). It was found that both the *N*-aryl acetamides (**5a-5g**) and *N*-phenyl amides (**5i-5m**) performed well, affording the corresponding amine products (**6a-6g, 6i-6m**) in 80-93% yields and 12:1-33:1 C-O/C-N bond cleavage selectivities. When *N*-methyl-*N*-phenylcinnamamide (**5h**) was employed, both the amide and the C=C moieties were reduced to give the product **6h** in 76% yield with a 17:1 selectivity. The *N*-heterocyclic amides (**5n-5p**) were also readily converted to the target products (**6n-6p**)

10.1002/adsc.201900406

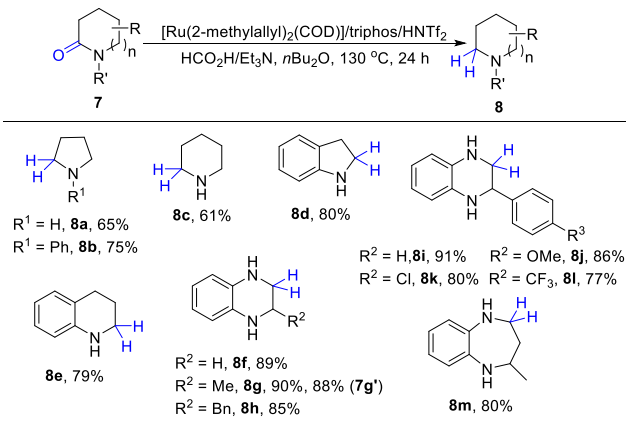
in high yields and selectivities. Finally, primary amides such as benzamide and butyramide were investigated under the optimized conditions, but no reaction took place.



[a] Reaction conditions: **5** (0.25 mmol), [Ru(2-methylallyl)$_2$(COD)] (5.0 mol %), triphos (10.0 mol %), $HNTf_2$ (10.0 mol %), HCO_2H/NEt_3 (n/n = 5/2, n(HCO_2H) = 1.25 mmol, n(Et_3N) = 0.5 mmol, 135 μL), *n*Bu_2O (1.0 mL) at 130 °C for 24 h. [b] Isolated yield. The ratio of C-O/C-N cleavage in parentheses was determined by GC with Ph_3N as an internal standard.

Scheme 3. Transfer Hydrogenation of Tertiary Amides.[a,b]

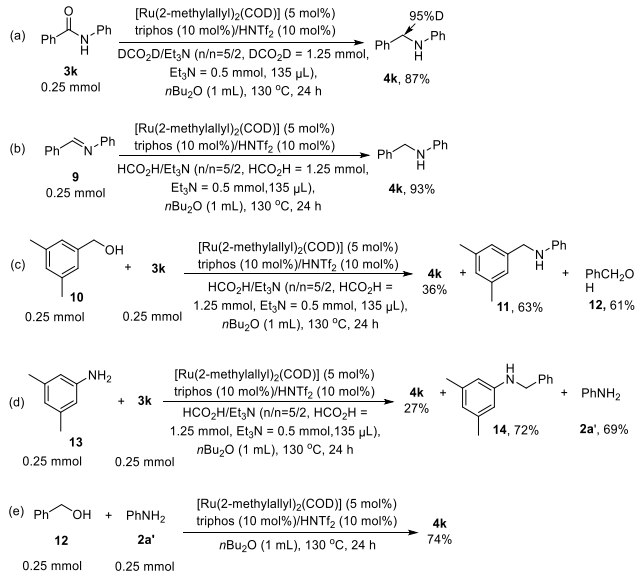
Afterward, we turned to testing this deoxygenative reduction with lactams (Scheme 4). Good yields were achieved for products **8a-8c** derived from pyrrolidin-2-ones (**7a, 7b**) and piperidin-2-one (**7c**). The reaction with indolin-2-one (**7d**) and 3,4-dihydroquinolin-2(*1H*)-one (**7e**) worked well, delivering **8d** and **8e** in 80% and 79% yields, respectively. Notably, an array of 3-substituted-3,4-dihydro-quinoxalin-2(*1H*)-ones (**7f-7l**) underwent the reduction smoothly in good to excellent product yields, and the *N*(4)-amino group showed no deleterious effect on the reaction efficiency. Furthermore, when 3-methylquinoxalin-2(*1H*)-one (**7g'**) was employed, the imine functionality was not tolerated, and the reduction product **8g** was isolated in 88% yield. Similarly, the lactam **7m** with a seven-membered ring afforded the target product **8m** in 80% yield. Importantly, side products from C-N bond cleavage were not detected in these reactions.



[a] **7** (0.25 mmol), [Ru(2-methylallyl)$_2$(COD)] (5.0 mol %), triphos (10.0 mol %), $HNTf_2$ (10.0 mol %), HCO_2H/NEt_3 (n/n = 5/2, n(HCO_2H) = 1.25 mmol, n(Et_3N) = 0.5 mmol, 135 μL), *n*Bu_2O (1.0 mL) at 130 °C for 24 h. [b] Isolated yield.

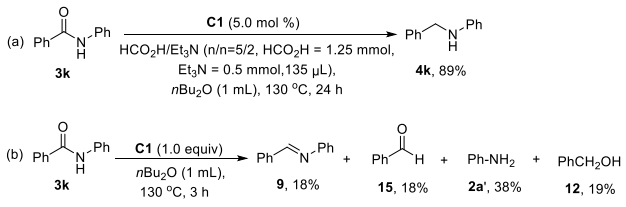
Scheme 4. Transfer Hydrogenation of Lactams.[a,b]

Two reaction pathways have been proposed for the homogeneous deoxygenative reduction of amides into amines: (1) direct reduction via imine intermediates;[4,8a,8e,8i,8j] (2) initial redcution of amides to form amines and alcohols vial hemiaminal intermedates and subsequent redcutive amination via a borrowing hydrogen process.[8d] In order to gain insight into the reaction mechanism, additional experiments were performed. Under the standard reaction conditions, the deoxygenative reduction of **3k** with DCO_2D/NEt_3 afforded the product **4k** in 87% yield with 95% deuterium incorporation exclusively at the α-CH_2 position (Scheme 5a). This result indicates the involvement of an imine key intermediate in this reaction. The successful conversion of *N*,1-diphenylmethanimine (**9**) into **4k** under the same reaction conditions supports this (Scheme 5b). Moreover, under the standard reaction conditions, the reaction of **3k** with 3,5-dimethylbenzyl alcohol (**10**) afforded a mixture of **4k** (36%), *N*-(3,5-dimethylbenzyl)aniline (**11**) (63%) and benzyl alcohol (**12**) (61%) (Scheme 5c), and a mixture of **4k** (27%), *N*-benzyl-3,5-dimethylaniline (**14**) (72%) and aniline (**2a'**) (69%) was obtained in the reaction of 3,5-dimethylaniline (**13**) and **3k** (Scheme 5d). These results suggest that the reductive amination of the in situ generated alcohol and amine via a borrowing hydrogen process may be the dominant pathway. This was further supported by the fact that alkylation of **2a**' with **12** gave the expected product **4k** in 74% yield (Scheme 5e).



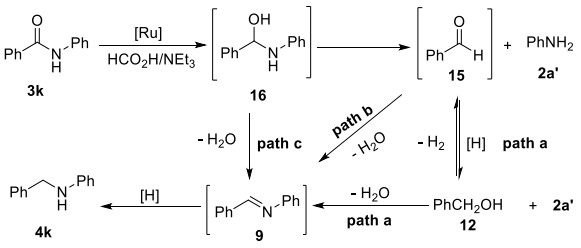
Scheme 5. Experiments Aimed to Probe the Reaction Mechansim.

Futhermore, the ESI-HRMS analysis of the reaction system of **3k** under the standard conditions indicated the formation of the cationic $[(triphos)Ru(\eta^2\text{-}O_2CH)(S)]^+$ (S = solvent, undetected) complex during the reaction. When using the separately prepared $[(triphos)Ru(\eta^2\text{-}O_2CH)(THF)(NTf_2)]$ (**C1**)[15] alone as the catalyst for transfer reduction of **3k**, the desired product **4k** was obtained in 89% yield (Scheme 6a). In addition, the stoichiometric reaction of **C1** with **3k** resulted in the formation of a mixture of imine **9**, aldehyde **15**, amine **2a'** and alcohol **12** (Scheme 6b). This is consistent with the reduction proceeding via a hemiaminal intermediate, although other possibilities cannot be excluded. The ESI-HRMS result and the effect of **C1** appear to suggest that a **C1** analogue is the resting state of catalytic cycle.



Scheme 6. Catalytic and Stoichiometric Reactions of **C1**.

Based on these results and previous reports,[4,8a,8d,8e,8i,8j] a plausible reaction mechanism is depicted in Scheme 7. Initially, the Ru-catalyzed transfer hydrogenation of amide **3k** leads to the generation of the hemiaminal intermediate **16**. The collapse of **16** forms aldehyde **15** and amine **2a**'. The following reduction of **15** furnishes alcohol **12**. The subsequent alkylation of **2a'** with **12** via borrowing hydrogen affords imine **9** (path a). Alternatively, **9** could be generated through reductive amination of **15** and **2a'** (path b) or direct dehydration of **16** (path c). Finally, reduction of **9** gives the target product **4k**.



Scheme 7. Proposed Reaction Mechanism.

Conclusion

In conclusion, we have developed a new, general and efficient protocol for the deoxygenative transfer hydrogenation of various amides into the corresponding amines with HCO_2H/NEt_3 as the hydrogen source under Ru catalysis. The reaction is generally high-yielding, highly selective for C-O bond cleavage and tolerant of diverse functionality. This operationally simple method offers a valuable alternative to the currently known methods for amide reduction. Further studies to develop more efficient catalytic systems based on earth-abundant transition-metals with wider substrate scope under milder conditions for these transformations are currently underway in our laboratory.

Experimental Section

For details of instruments used and the general experimental procedures, see the Supporting Information.

General procedure for deoxygenative reduction of amides

To a pressure tube were sequentially added amide **1** (0.25 mmol), $[Ru(2\text{-methylallyl})_2(COD)]$ (7.19 mg, 5.0 mol %), triphos (15.62 mg, 10 mol %), HCO_2H/NEt_3 (n/n = 5/2, $n(HCO_2H)$ = 1.25 mmol, $n(Et_3N)$ = 0.5 mmol, 135 μL), $HNTf_2$ (7.05 mg, 10 mol %) and dibutyl ether (1.0 mL). Then the reaction mixture was stirred at 130 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with EtOAc (5.0 mL). Then aqueous NaOH (5.0 mL, 4.0 M) was added to the reaction mixture, which was extracted with EtOAc three times (5.0 mL each). The combined organic phases were dried over Na_2SO_4, then filtered and evaporated under reduced pressure. After the removal of volatile materials by rotary evaporation, the resultant mixture was purified by silica gel column chromatography using a mixture of EtOAc and Petroleum ether to give the corresponding pure product.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21372258), and the Fundamental Research Funds for the Central Universities, and the Research Funds of Renmin University of China (Program 16XNLQ04) is greatly acknowledged.

References

[1] S. A. Lawrence, *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, UK, **2004**.

[2] a) B. M. Trost, I. Fleming, Eds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, U.K. **1991**; b) A. Ricci, Ed. *Modern Amination Methods*; Wiley-VCH: Weinheim, Germany, **2000**; c) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337-2347; d) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, H. L. Leazer, R. J. Linderman Jr., K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T.-Y. Zhang, *Green Chem.* **2007**, *9*, 411-420; e) A. Chardon, E. Morisset, J. Rouden, J. Blanchet, *Synthesis* **2018**, *50*, 984-997.

[3] a) J. SeydeN-Penne, *Reductions by the Alumino- and Boro-hydrides in Organic Synthesis*; John Wiley & Sons, Inc: New York, **1997**; b) W. G. Gribble, *Chem. Soc. Rev.* **1998**, *27*, 395-404; c) A. M. Smith, R. Whyman, *Chem. Rev.* **2014**, *114*, 5477-5510.

[4] For reviews of catalytic hydrosilylation of amides to amine, see: a) S. Das, S. Zhou, D. Addis, S. Enthaler, K. Junge, M. Beller, *Top. Catal.* **2010**, 53, 979-984; b) D. Addis, S. Das, K. Junge, M. Beller, *Angew. Chem., Int. Ed.* **2011**, *50*, 6004-6011; c) A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo, H. Adolfsson, *Chem. Soc. Rev.* **2016**, *45*, 6685-6697; d) B. Li, J. B. Sortaisa, C. Darcel, *RSC Adv.* **2016**, *6*, 57603-57625; e) S. Hanada, T. Ishida, Y. Motoyama, H. Nagashima, *J. Org. Chem.* **2007**, *72*, 7551-7559; f) P.-Q. Huang, Q.-W. Lang, Y.-R. Wang, *J. Org. Chem.* **2016**, *81*, 4235-4243; g) Y. Sunada, H. Nagashima, *Dalton Trans.* **2017**, *46*, 7644-7655.

[5] N. L. Lampland, M. Hovey, D. Mukherjee, A. D. Sadow, *ACS Catal.* **2015**, *5*, 4219-4226.

[6] S. Werkmeister, K. Junge, M. Beller, *Org. Process Res. Dev.* **2014**, *18*, 289-302.

[7] For heterogeneous deoxygenative hydrogenation of amides, see: a) H. Adkins, B. Wojcik, *J. Am. Chem. Soc.* **1934**, *56*, 247; b) H. J. Schneider, H. Adkins, S. M. McElvain, *J. Am. Chem. Soc.* **1952**, *74*, 4287-4290; c) H. S. Broadbent, W. J. Bartley, *J. Org. Chem.* **1963**, *28*, 2345-2347; d) A. Guyer, A. Bieler, G. Gerliczy, *Helv. Chim. Acta.* **1955**, *38*, 1649-1654; e) C. Hirosawa, N. Wakasa, T. Fuchikami, *Tetrahedron Lett.* **1996**, *37*, 6749-6752; f) G. Beamson, A. J. Papworth, C. Philipps, A. M. Smith, R. Whyman, *J. Catal.* **2010**, *269*, 93-102; g) G. Beamson, A. J. Papworth, C. Philipps, A. M. Smith, R. Whyman, *J. Catal*. **2011**, *278*, 228-238; h) R. Burch, C. Paun, X.-M. Cao, P. Crawford, P. Goodrich, C. Hardacre, P. Hu, L. McLaughlin, J. Saa, J. M. Thompson, *J. Catal.* **2011**, *283*, 89-97; i) J. Coetzee, H. G. Manyar, C. Hardacre, D. J. Cole-Hamilton, *ChemCatChem* **2013**, *5*, 2843-2847; j) Stein, M.; Breit, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2231-2234; k) T. Mitsudome, K. Miyagawa, Z. Maeno, T. Mizugaki, K. Jitsukawa, J. Yamasaki, Y. Kitagawa, K. Kaneda, *Angew. Chem., Int. Ed.* **2017**, *56*, 9381-9385.

[8] For homogeneous deoxygenative hydrogenation of amides, see: a) A. A. N. Magro, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, *43*, 3154-3156; b) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin, D. J. Cole-Hamilton, *Chem. Eur. J.* **2013**, *19*, 11039-11050; c) M. Meuresch, S. Westhues, W. Leitner, J. Klankermayer, *Angew. Chem., Int. Ed.* **2016**, *55*, 1392-1395; d) J. R. Cabrero-Antonino, E. Alberico, K. Junge, H. Junge, M. Beller, *Chem. Sci.* **2016**, *7*, 3432-3442; e) M.-L. Yuan, J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *ACS Catal.* **2016**, *6*, 3665-3669; f) M.-L.Yuan, J.-H. Xie, Q.-L. Zhou, *ChemCatChem* **2016**, *8*, 3036-3040; g) S. Westhues, M. Meuresch, J. Klankermayer, *Angew. Chem. Int. Ed.* **2016**, *55*, 12841-12844; h) T. Miura, M. Naruto, K. Toda, T. Shimomura, S. Saito, *Sci. Rep.* **2017**, *7*, 1586; i) Y.-Q. Zou, S. Chakraborty, A. Nerush, D. Oren, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *ACS Catal.* **2018**, *8*, 8014-8019; j) N. A. Sitte, M. Bursch, S. Grimme, J. Paradies, *J. Am. Chem. Soc.* **2019**, *141*, 159-162.

[9] For recent reviews on catalytic transfer hydrogenation, see: a) J. Ito, H. Nishiyama, *Tetrahedron Lett.* **2014**, *55*, 3133-3146; b) D. Wang, D. Astruc, *Chem. Rev.* 2015, *115*, 6621-6686; c) Y. Wei, X. Wu, C. Wang, J. Xiao, *Catal. Today* 2015, *247*, 104-116; d) Y.-M. He, Q.-H. Fan, *ChemCatChem* **2015**, *7*, 398-400; e) F. Foubelo, C. Najera, M. Yus, *Tetrahedron: Asymmetry* **2015**, *26*, 769-790.

[10] Only catalytic transfer hydrogenation of esters are known in the literature, see: a) S. H. Kim, S. H. Hong, *ACS Catal.* **2014**, *4*, 3630-3636; b) A. Dubey, E. Khaskin, *ACS Catal.* **2016**, *6*, 3998-4002.

[11] a) G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008** *130*, 18-19; b) G. Pelletier, W. S. Bechara, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 12817-12819.

[12] a) J. Tan, W. J. Tang, Y. Sun, Z. Jiang, F. Chen, L. Xu, Q. Fan, J. Xiao, *Tetrahedron* **2011**, *67*, 6206-6213;. b) L. Zhang, R. Qiu, X. Xue, Y. Pan, C. Xu, H. Li, L. Xu, *Adv. Synth. Catal.* **2015**, *357*, 3529-3537; c) C. Xu, L. Zhang, C.-N. Dong, J. Xu, Y. Li, H. Zhang, H. Li, Z. Yu, L. Xu, *Adv. Synth. Catal*. **2016,** *358*, 567-572; d) Y. Pan, C. Chen, X. Xu, H. Zhao, J. Han, H. Li, L. Xu, Q. Fan, J. Xiao, *Green Chem.* **2018**, *20*, 403-411.

[13] a) S. Savourey, G. Lefevre, J.-C. Berthet, T. Cantat, *Chem. Commun.* **2014**, *50*, 14033-14036; b) I. Sorribes, J. R. Cabrero-Antonino, C. Vicent, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 13580-13587; c) R. Adam, J. R. Cabrero-Antonino, K. Junge, R. Jackstell, M. Beller, *Angew. Chem., Int. Ed.* **2016**, *55*, 11049-11053; d) Y. Shi, P. C. J. Kamer, D. J. Cole-Hamilton, M. Harvie, E. F. Baxter, K. J. C. Lim, P. Pogorzelec, *Chem. Sci.* **2017**, *8*, 6911-6917; e) Y. Shi, P. C. J. Kamer, D. J. Cole-Hamilton, *Green Chem.* **2017,** *19*, 5460-5466.

[14] S. Gyorke, V. Lukyanenko, I. Gyçrke, *J. Physiol.* **1997**, *500*, 297-309.

[15] S. Wesselbaum, V. Moha, M. Meuresch, S. Brosinski, K. M. Thenert, J. Kothe, T. vom Stein, U. Englert, M.

10.1002/adsc.201900406

Holscher, J. Klankermayer, W. Leitner, *Chem. Sci.* **2015**, *6*, 693-704.

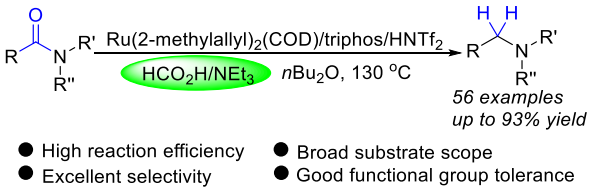
10.1002/adsc.201900406

FULL PAPER

Ru-catalyzed Deoxygenative Transfer Hydrogenation of Amides to Amines with Formic acid/Triethylamine

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Yixiao Pan,[a] Zhenli Luo,[a] Xin Xu,[a] Haoqiang Zhao,[a] Jiahong Han,[a] Lijin Xu,*[a] Qinghua Fan *[b] and Jianliang Xiao*[c]



- High reaction efficiency
- Excellent selectivity
- Broad substrate scope
- Good functional group tolerance