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Highly Selective, Efficient Deoxygenative Hydrogenation of Amides Catalyzed by a Manganese Pincer Complex via Metal–Ligand Cooperation

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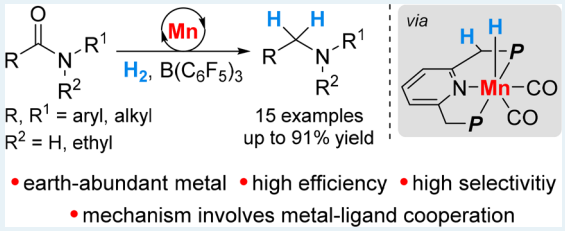
Supporting Information

ABSTRACT: Deoxygenative hydrogenation of amides to amines homogeneously catalyzed by a complex of an Earth-abundant metal is presented. This manganese-catalyzed reaction features high efficiency and selectivity. A plausible reaction mechanism, involving metal–ligand cooperation of the manganese pincer complex, is proposed based on NMR studies and relevant stoichiometric reactions.



KEYWORDS: *deoxygenative hydrogenation, amide, manganese pincer complex, metal–ligand cooperation, amine*

Metal–ligand cooperation (MLC) is a powerful activation mode in transition-metal catalysis, which has fascinated chemists for many years.[1] It has grown into, and will continue to be, a popular and flourishing research field. In this regard, our group developed a mode of MLC involving aromatization/dearomatization by metal pincer complexes, which found broad applications in the activation of C–H, N–H, O–H, B–H, B–B, Si–H, as well as H–H bonds.[2] This novel bond activation mode enables the environmentally benign, sustainable synthesis of numerous important and useful chemicals from simple starting materials. However, in most of those reactions, complexes of precious metals are used. Currently, there is growing research interest in the development of catalytic reactions based on complexes of Earth-abundant metals.[3] In 2016, our group reported the manganese-catalyzed acceptorless dehydrogenative coupling of alcohols and amines to aldimines.[4a] Seminal works employing manganese-based pincer complexes were subsequently disclosed by the groups of Beller, Kempe, Kirchner, and others, including the dehydrogenation of alcohols[4b−e,5] and hydrogenation of ketones,[6] esters,[4f,7] and C–N bond hydrogenolysis of amides,[8] as well as conjugate addition of nonactivated nitriles.[4g]

Amine skeletons are prevalent in many biologically important natural products, pharmaceuticals, and agrochemicals. They also serve as versatile building blocks in organic synthesis, which can be easily elaborated into various fine and useful complex molecules.[9] In addition, amines are widely used as dyes, surfactants, anticorrosive agents, detergents in industrial production.[9] Given the importance of amine compounds, the development of effective protocols for their synthesis is highly desirable. In this context, deoxygenative hydrogenation (reduction) of amides (C–O bond cleavage) represents a straightforward method to access the corresponding amines.[10]

Conventional methods for the deoxygenative reduction of amides to amines are largely based on the use of (over)-stoichiometric amounts of reductants such as lithium aluminum hydride ($LiAlH_4$), silanes, or boranes.[10] However, these methods suffer from the hazardous reductive agents, tedious workup procedures, and generation of a large amount of waste. To address these issues, catalytic deoxygenative reduction of amides using hydrogen as the terminal reductant, forming water, is ideal. The relatively low electrophilicity of the amide carbonyl group and the competitive C–N bond cleavage (deaminative reduction) make this transformation more challenging, compared to the hydrogenation of aldehydes, ketones, and esters. While *heterogeneously* catalyzed deoxygenative reduction of amides were reported,[11] they were often stricken with high pressure,[11f−i] high temperature,[11a,b,f,g] and poor selectivity.[11a,d,e] Only few reports of homogeneously catalyzed reaction were disclosed during the past decade (Scheme 1a).[12] Homogeneously catalyzed reactions are generally attractive, because of potential high selectivity and being more amenable for mechanistic understanding. In 2007, Cole-Hamilton and co-workers reported a ruthenium-triphos complex-catalyzed hydrogenation of amides to primary and secondary amines with good to excellent selectivities.[12a,b] Later, the Klankermayer group synthesized a rationally designed ruthenium-triphos η^4-trimethylenemethane complex and successfully applied it to the hydrogenation of lactams.[12c] Shortly after, similar ruthenium-based catalytic systems were

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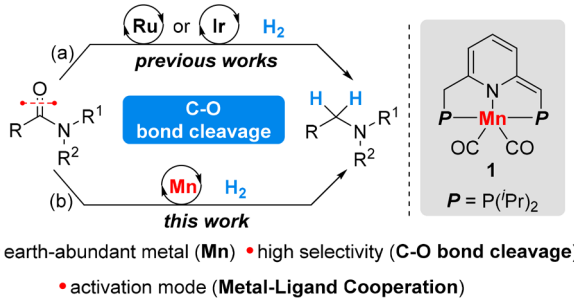
Scheme 1. Transition-Metal-Catalyzed Deoxygenative Hydrogenation of Amides to Amines

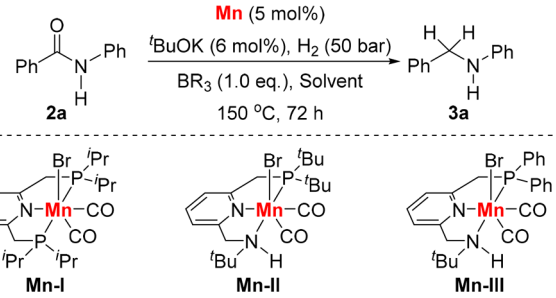


disclosed by the groups of Beller[12d] and Zhou,[12e] using $Yb(OTf)_3{\cdot}H_2O$ and $BF_3{\cdot}OEt_2$ as the additives, respectively. In addition, the Zhou group also described a selective deoxygenative hydrogenation of amides catalyzed by an iridium pincer complex, where $B(C_6F_5)_3$ was used as the Lewis acid additive.[12f] Despite these advances, all the above transformations are using catalysts based on the precious metals ruthenium or iridium. The development of novel methods for the deoxygenative hydrogenation of amides without noble metals is of great importance.

As part of our ongoing research program on sustainable homogeneous catalysis, we herein report a more environmentally benign strategy for the deoxygenative hydrogenation of amides catalyzed by a pincer complex of Earth-abundant manganese (Scheme 1b). We envisioned that the dearomatized manganese complex **1** could heterolytically split dihydrogen via MLC, and the resulting manganese hydride will hydrogenate amides to amines with the aid of a proper Lewis acid. To the best of our knowledge, there has hitherto been no report on deoxygenative hydrogenation of amides to amines homogeneously catalyzed by a complex of a base metal.

Our initial studies were focused on examining the feasibility of the deoxygenative hydrogenation of *N*-phenylbenzamide (**2a**) and optimization of the reaction conditions for the application to various amides. Encouragingly, the hydrogenation of **2a** did indeed occur in the presence of the manganese PNP complex **Mn-I**[5e] (5 mol %), ^{t}BuOK (6 mol %) and one equivalent of BPh_3 under 50 bar H_2 at 150 °C in *m*-xylene, to afford the desired product *N*-benzylaniline (**3a**) in 53% GC yield after 72 h (Table 1, entry 1). The transformation is highly selective and only trace amounts of the C−N bond cleavage products aniline (<1%) and benzyl alcohol (<1%) were detected by GC (see the Supporting Information for details). Control experiments indicated that without manganese complex or Lewis acid no hydrogenation reaction occurred (entries 2 and 3). Encouraged by this promising result, we started to optimize the reaction conditions to improve the conversion and yield. Two manganese PNNH complexes **Mn-II**[4c,f] and **Mn-III**[4d] showed lower catalytic performance and produced the product in 23% and 37% yield, respectively (entries 4 and 5). Lowering the reaction temperatures led to dramatically decreased conversions and yields (entries 6 and 7). Interestingly, both conversion and yield were increased by using the stronger Lewis acid $B(C_6F_5)_3$ as the additive (74% conversion and 63% yield, entry 8). Further screening the solvents indicated that dioxane and THF were not suitable reaction media, probably due to their coordination to $B(C_6F_5)_3$ (entries 9 and 10). Increasing the Lewis acid loading to 1.5 equiv provided the

Table 1. Optimizing of the Reaction Conditions[a]



entry	Mn	BR_3	solvent	conversion[b] (%)	yield[b] (%)
1	**Mn-I**	BPh_3	*m*-xylene	53	53
2		BPh_3	*m*-xylene	<5	0
3	**Mn-I**		*m*-xylene	0	0
4[c]	**Mn-II**	BPh_3	*m*-xylene	38	23
5[c]	**Mn-III**	BPh_3	*m*-xylene	45	37
6[d]	**Mn-I**	BPh_3	*m*-xylene	26	24
7[e]	**Mn-I**	BPh_3	*m*-xylene	19	20
8	**Mn-I**	$B(C_6F_5)_3$	*m*-xylene	74	63
9	**Mn-I**	$B(C_6F_5)_3$	dioxane	23	17
10	**Mn-I**	$B(C_6F_5)_3$	THF	<1	0
11[f]	**Mn-I**	$B(C_6F_5)_3$	*m*-xylene	95	95 (89)
12[f,g]	**Mn-I**	$B(C_6F_5)_3$	*m*-xylene	89	75

[a]Reaction conditions: **2a** (0.2 mmol), Mn cat. (5 mol %), ^{t}BuOK (6 mol %), Lewis acid BR_3 (0.2 mmol), H_2 (50 bar), and solvent (1.0 mL) at 150 °C (bath temperature) for 72 h. [b]Conversions and yields were determined by GC analysis using biphenyl as an internal standard; isolated yield is given in parentheses. [c]12 mol % of ^{t}BuOK was used. [d]Reaction was performed at 130 °C. [e]Reaction was performed at 110 °C. [f]$B(C_6F_5)_3$ (0.3 mmol) was used. [g]Reaction was performed for 48 h.

best results: 95% conversion and 89% isolated yield of product **3a** (see entry 11). Under shorter reaction time (48 h), the reaction efficiency was slightly decreased (see entry 12).

Next, we selected the conditions of entry 11 to examine the generality of this catalytic hydrogenation system by evaluating a variety of amides. As highlighted in Table 2, benzamides bearing substituents of different electronic nature on the *N*-phenyl group were applicable to this reaction, and the corresponding secondary amines **3a**-**3f** were obtained in good to excellent isolated yields (Table 2, entries 1−6). The hydrogenation of *N*-benzyl-, cyclohexyl-, and hexyl-benzamides in **2g**−**2i** also proceeded smoothly to give the desired products in good yields (68%−83% yields, entries 7−9). Aliphatic *N*-phenyl amides such as *N*-phenylacetamide (**2j**), *N*-phenylpropionamide (**2k**) and *N*-phenylisobutyramide (**2l**) were compatible with the optimal conditions, furnishing the products **3j**−**3l** in 52%−70% isolated yields (entries 10−12). Notably, the lactams 2-pyrrolidinone (**2m**) and 2-piperidinone (**2n**) were also suitable substrates, and good results were observed (entries 13 and 14). Deoxygenation of formamides resulted in low yields (see the SI for details). In order to further extend the substrate scope, we evaluated the reaction of the tertiary amide **2o**; deoxygenative hydrogenation also occurred to give the fully aliphatic tertiary amine **3o**, albeit in lower conversion (47%) and yield (21%) (entry 15). Significantly, all the reactions selectively gave the C−O bond cleavage products.

In order to get some insight into the mechanism of this transformation, we first treated complex **Mn-I** with 1.2 equiv of

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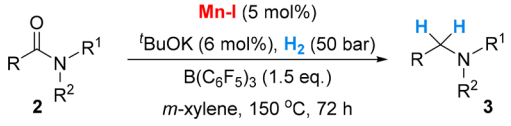
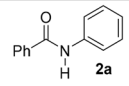
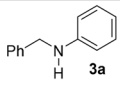
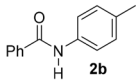
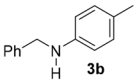
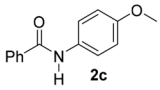
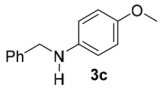
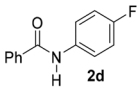
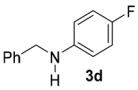
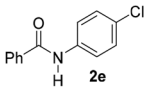
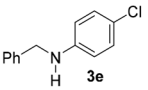
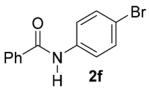
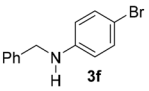
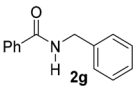
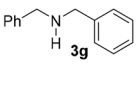
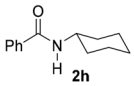
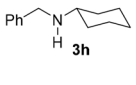
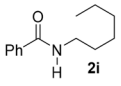
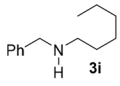
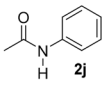
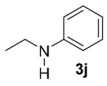
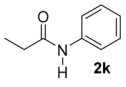
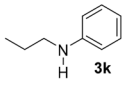
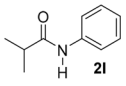
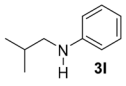
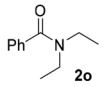
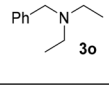
Table 2. Deoxygenative Hydrogenation of Amides 2 to Amines 3 Catalyzed by Mn-I



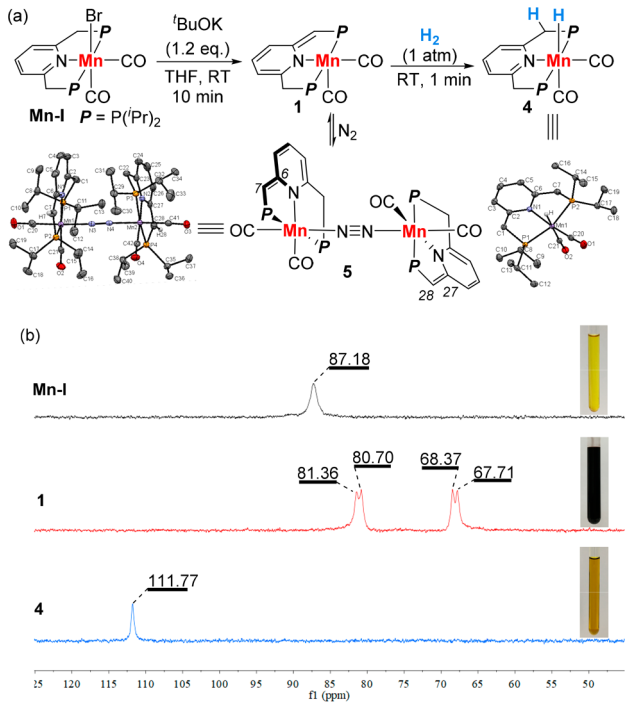
entry[a]	Amide 2	Amine 3	conv. (%)[b]	isolated yield (%)[c]
1	 2a	 3a	95	89
2	 2b	 3b	98	81
3	 2c	 3c	89	69
4	 2d	 3d	97	86
5	 2e	 3e	97	87
6	 2f	 3f	91	76
7	 2g	 3g	93	83
8	 2h	 3h	90	71
9	 2i	 3i	70	68
10	 2j	 3j	100	52
11	 2k	 3k	100	70
12	 2l	 3l	75	55
13	 2m	 3m	100	81[d]
14	 2n	 3n	68	63[d]
15	 2o	 3o	47	21

[a]Reaction conditions: **2** (0.2 mmol), **Mn-I** (5 mol %), ^{t}BuOK (6 mol %), $B(C_6F_5)_3$ (0.3 mmol), H_2 (50 bar), and *m*-xylene (1.0 mL) at 150 °C (bath temperature) for 72 h. [b]Conversions were determined by GC analysis using biphenyl as an internal standard. [c]Yields of isolated products after flash chromatography. [d]Yields were determined by GC analysis using biphenyl as an internal standard.

Table 2. continued

^{t}BuOK at room temperature in THF, upon which the transparent yellow solution immediately changed to a dark brown homogeneous solution (Scheme 2b; see SI for details)

Scheme 2. (a) Dearomatization of Mn-I, Activation of H_2 by Complex 1, and Related X-ray Crystal Structures and (b) ^{31}P NMR Spectra



and two sharp AB doublets appeared at δ = 81.03 ($^2J_{P-P}$ = 79.9 Hz) and 68.04 ($^2J_{P-P}$ = 79.9 Hz) ppm in the ^{31}P NMR (THF as the solvent), attributable to complex **1** (Scheme 2a).[13] Recrystallization of **1** gave the new N_2-bridged dinuclear manganese complex **5** (N_2 is from the glovebox), the only example of a dearomatized N_2-bridged complex (Scheme 2a). The bond lengths of C6−C7 and C27−C28 are 1.385 and 1.384 Å, respectively, which clearly indicate double-bond characters.[14]

On the other hand, upon treatment of the above reaction mixture with 1 atm dihydrogen, an orange solution was formed (Scheme 2b), generating the new hydride complex **4**, as indicated by the ^{31}P{^{1}H} NMR spectrum in THF, which exhibited a singlet at δ = 111.77 ppm (see the SI for details), and the ^{1}H NMR spectrum exhibited a hydride resonance at δ = −4.34 ppm (t, $^2J_{P-H}$ = 48.5 Hz). The IR spectrum of **4** showed two strong absorption bands at 1878.4 (ν_{asym}) and 1804.0 cm^{-1} (ν_{sym}). The structure of complex **4** was further confirmed by X-ray crystal analysis.[14] Importantly, when complex **4** was employed as catalyst for the hydrogenation of amide **2a**, full conversion was observed and the product **3a** was isolated in 91% yield (see Scheme 3).

We also examined the manganese complex **Mn-I** catalyzed hydrogenation of the imine *N*-benzylideneaniline **6**.[15] As

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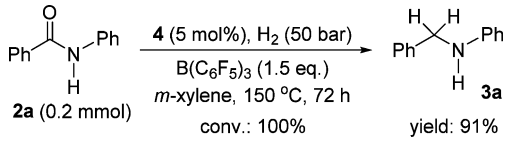
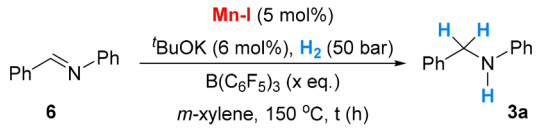
Scheme 3. Deoxygenative Hydrogenation of Amide 2a Catalyzed by Complex 4



shown in Table 3, the hydrogenation of **6** did occur under the above optimal hydrogenation conditions, without Lewis acid,

Table 3. Hydrogenation of Imine 6 Catalyzed by Mn-I



entry[a]	$B(C_6F_5)_3$	t (h)	conversion[b] (%)	isolated yield[c] (%)
1		24	60	51
2		72	80	72
3	0.2 equiv	48	88	83
4	0.5 equiv	48	100	81

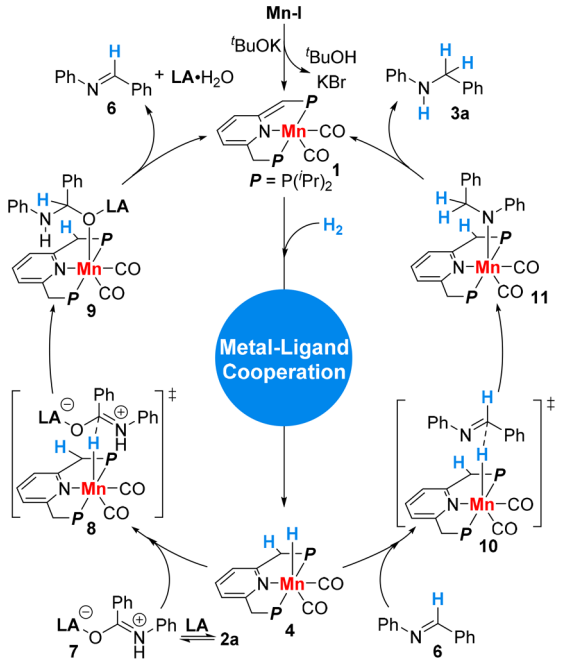
[a]Reaction conditions: **6** (0.2 mmol), **Mn-I** (5 mol %), ^{t}BuOK (6 mol %), H_2 (50 bar), and *m*-xylene (1.0 mL) at 150 °C (bath temperature). [b]Conversions were determined by GC analysis using biphenyl as an internal standard. [c]Yields of isolated products after flash chromatography.

resulting in 60% conversion within 24 h and the amine **3a** was isolated in 51% yield (Table 3, entry 1). Prolonging the reaction time to 72 h, the conversion was increased to 80% (entry 2). When 0.2 equiv of $B(C_6F_5)_3$ was used, the reaction reached 88% conversion within 48 h (entry 3). Increasing the loading of $B(C_6F_5)_3$ to 0.5 equiv, 100% conversion was recorded and the desired product was isolated in 81% yield (entry 4). These results indicate that imine **6** could be an intermediate in the hydrogenation of amide **2a**, and Lewis acid may also accelerate the hydrogenation of the imine.[16]

Based on our experimental results and previous work, we propose a possible reaction mechanism for the Mn-catalyzed deoxygenative hydrogenation of amides. As we have shown, in the presence of ^{t}BuOK, the pincer complex **Mn-I** undergoes deprotonation to give the dearomatized complex **1**, which is very likely the actual catalyst (Scheme 4). Subsequently, complex **1** heterolytically splits dihydrogen by MLC, generating the aromatized complex **4**. The carbonyl group of the Lewis acid activated amide **7** then may electrophilically attack the Mn−H moiety of the coordinatively saturated **4** through an outer-sphere pathway, leading to formation of the hemiaminal intermediate **9** via transition state **8**.[17] Later, the Lewis-acid-assisted dehydration of **9** occurs to produce imine **6**, accompanied by the regeneration of the dearomatized complex **1**.[18] Once imine **6** is formed, it may react with the hydride complex **4** to afford intermediate **11** through transition state **10** via a similar outer-sphere process.[16] At last, elimination of the desired product **3a** from **11** releases the complex **1**, which then re-enters the catalytic cycle.

In conclusion, we have developed the first Earth-abundant-based metal complex for homogeneously catalyzed deoxygenative hydrogenation of amides to amines. This synthetically important, highly selective C−O bond cleavage reaction is catalyzed by a dearomatized pincer complex of manganese. A

Scheme 4. Proposed Reaction Mechanism for Manganese-Catalyzed Deoxygenative Hydrogenation of Amides to Amines



plausible catalytic cycle, involving metal−ligand cooperation, is supported by nuclear magnetic resonance (NMR) studies, stoichiometric reactions, X-ray crystallography, and isolation of plausible intermediates. Further detailed mechanistic investigations and applications of this methodology are underway in our laboratory, and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02902.

Experimental and spectroscopic details of the catalytic reactions (PDF)

Crystallographic information files for **4** and **5** (CIF)

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Notes

The authors declare no competing financial interest.

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