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Manganese-Catalyzed Direct Conversion of Ester to Amide with Liberation of H_2

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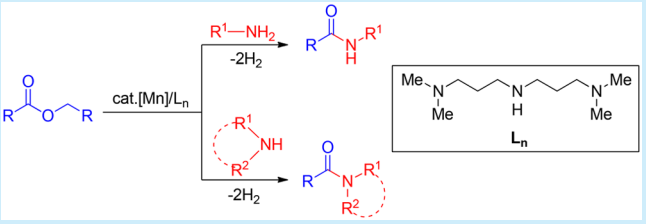
Supporting Information

ABSTRACT: A simple and efficient Mn-catalyzed acylation of amines is achieved using both acyl and alkoxy functions of unactivated esters with the liberation of molecular hydrogen as a sole byproduct. The present protocol provides an atom-economical and sustainable route for the synthesis of amides from esters by employing an earth-abundant manganese salt and inexpensive phosphine-free tridentate ligand.

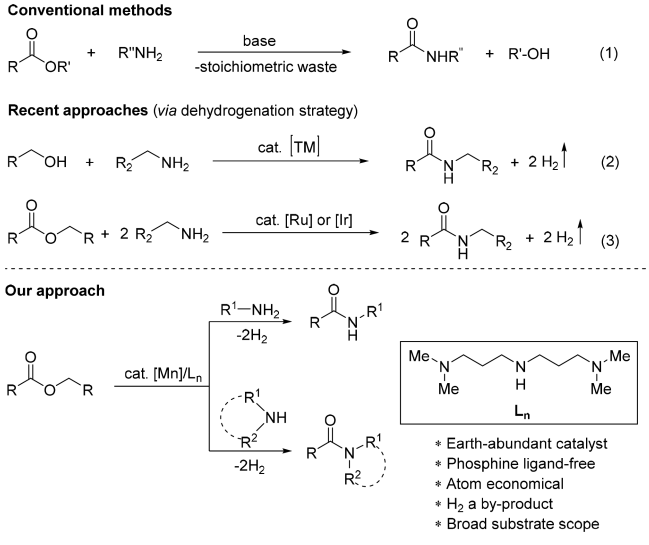


Amides are common in nature and have found widespread applications in the pharmaceutical industry.[1] Amide linkages (or peptide bonds) are omnipresent in biomolecules, fine chemicals, and drug candidates. For instance, approximately 25% of drug molecules contain an amide moiety in their structural composition.[2] The classical approach to prepare amides involves coupling of carboxylic acids with amines at elevated temperature or aminolysis of activated carboxylic acid derivatives such as halides, anhydrides, and azides.[3] However, such protocols are limited by a narrow substrate scope, poor atom economy, need of reactive substrates, and cumulative waste generation. In this regard, catalytic aminolysis of esters is one of the elegant methods for the construction of amides, as this protocol involves the direct conversion of ubiquitous esters into biologically significant amides.[4] Indeed, aminolysis of esters results in alcohols as undesired byproducts, limiting the scope of the process. An efficient and newer strategy for amide synthesis that avoids byproduct formation and utilizes earth-abundant resources is highly demanding and challenging in chemical production.

In 2007, the pioneering work on highly atom-economical and direct synthesis of amides from alcohols and amines was reported by the research group of Milstein.[5] This reaction is catalyzed by a dearomatized PNN−Ru pincer complex and operates via the acceptorless dehydrogenative coupling (ADC) pathway with the liberation of molecular hydrogen as the sole byproduct. Subsequently, several interesting reports on ADC for the preparation of amides were developed using expensive and less-abundant noble-metal-based catalytic systems.[6] In continuation of earlier work, Milstein and co-workers reported the direct synthesis of amides by dehydrogenative coupling of esters and amines with the liberation of hydrogen gas using the same PNN−Ru(II) catalytic system.[7a] However, the ester substrates had to be purified prior to the reaction in order to eliminate carboxylic acid impurities that were responsible for catalyst deactivation even in the presence of the amine partner.

In contrast to conventional approaches, the dehydrogenative coupling of esters with amines provides a sustainable protocol for the synthesis of amides since both the acyl part and the alkoxy part of the ester are incorporated into the product amide.[7] Though unprecedented progress has been achieved on catalytic aminolysis of esters using the ADC strategy with expensive, less abundant, toxic noble metals, the use of a catalytic system derived from and earth-abundant, economical, and biorelevant system is highly desirable in contemporary science.[8,9] In this regard, we report a facile protocol for the direct conversion of esters to amides with the liberation of molecular hydrogen using a base metal (manganese) as a catalyst featuring an inexpensive phosphine-free tridentate ligand.[10] The present protocol was successfully applied for various unactivated esters and amines (Scheme 1).

Scheme 1. Strategies for Amide Bond Formation



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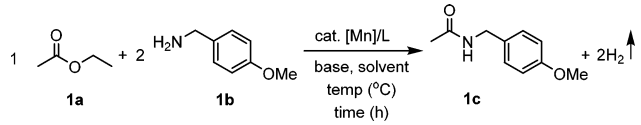
Inspired by Mn-catalyzed acceptorless dehydrogenation of alcohols,[9] we started by using simple, commercially available $MnBr(CO)_5$ as the catalyst along with the tridentate ligand 3,3′-iminobis(*N*,*N*-dimethylpropylamine) (L_n) for the dehydrogenative coupling of esters with amines. The unactivated ester ethyl acetate (**1a**) and 4-methoxybenzylamine (**1b**) as the amine coupling partner were selected as benchmark substrates for the optimization process. Thus, the initial reaction was carried out in the presence of $MnBr(CO)_5$ (5 mol %), L_n (10 mol %), and *t*-BuOK (1 mmol) in toluene at 90 °C. After 16 h, quantitative conversion of **1b** was observed, and amide **1c** was obtained in 87% isolated yield (Table 1, entry 1). Gratifyingly,

Table 1. Optimization of the Conditions for Ester Amidation[a]



entry	temp (°C)	time (h)	ligand	solvent	conv of amine (%)[b]	yield (%)[b]
1	90	16	L_n	toluene	99	87[c]
2	90	16	L_n	decane	41	32[c]
3	90	16	L_n	1,4-dioxane	53	34[c]
4	90	16	L_n	CH_3CN	50	39[c]
5	130	22	L_n	toluene	71	47[c]
6	90	16	L_n	toluene	NQ	trace[d]
7	90	22	L_n	toluene	NQ	18[e]
8	110	16	–	toluene	NQ	26
9	90	16	L_n	toluene	NQ	15[f,j]
10	90	16	L_n	toluene	NQ	20[g,j]
11	90	16	L_n	toluene	NQ	40[h,j]
12	90	16	L_n	toluene	NQ	63[i,j]
13	90	22	L_1	toluene	33	14
14	90	22	L_2	toluene	49	18
15	90	22	L_3	toluene	26	17
16	90	22	L_4	toluene	21	9
17	90	22	L_5	toluene	73	41[c]
18	90	22	L_6	toluene	57	33
19	90	22	L_7	toluene	40	NQ
20	90	22	L_8	toluene	44	21
21	90	22	L_9	toluene	55	39[c]

[a]Reaction conditions: ethyl acetate (1.5 mmol), 4-methoxybenzylamine (2.6 mmol), *t*-BuOK (1 mmol), $MnBr(CO)_5$ (5 mol %), ligand (10 mol %), and solvent (2 mL) in an open argon atmosphere. [b]Conversions of amine and (unless noted otherwise) yields of amide **1c** were determined by GC using *m*-xylene as an internal standard. NQ = not quantified. [c]Isolated yield. [d]In the absence of base. [e]In the absence of Mn catalyst. [f]10 mol % *t*-BuOK was used. [g]The potassium salt of L_n was used. [h]KH (1 mmol) was used. [i]*t*-BuONa (1 mmol) was used. [j]NMR yield.

the generation of molecular hydrogen was qualitatively analyzed by gas chromatography. Indeed, the possibility of competing imine formation (self-dehydrogenative coupling of benzylamine) was not observed. The screening of other solvents such as decane, 1,4-dioxane, and acetonitrile under the same reaction conditions provided poor yields of **1c** (Table 1, entries 2–4). When the reaction temperature was increased to 130 °C, a lower yield of **1c** (47%) was obtained (Table 1, entry 5). The control experiment illustrated that there was no formation of **1c** in the absence of the base (Table 1, entry 6). Similarly, the absence of the Mn catalyst and the ligand (L_n) significantly affected the aminolysis process, which gave a trace amount of **1c** under standard conditions (Table 1, entries 7 and 8). Notably, the quantity (mol %) and nature of the base have a significant effect on the present Mn-catalyzed direct amidation of esters, and also, the potassium salt of ligand L_n showed an unsatisfactory yield of amide **1c** (Table 1, entries 9–12). These results revealed that the presence of the catalyst, ligand, and base are necessary for the effective formation of the desired amide via ADC. Among various ligand systems employed for the amidation reaction (Table 1, entries 13–21, and Figure 1), the phosphine-free tridentate ligand L_n was found to be optimal.

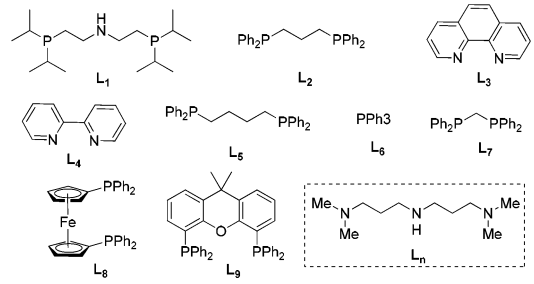


Figure 1. Ligands used for the optimization.

With the optimized reaction conditions in hand, the scope with respect to alkyl and aryl esters and amines were investigated. As shown in Table 2, a diverse range of unactivated alkyl esters such as ethyl acetate, pentyl pentanoate, and hexyl hexanoate as well as activated esters (e.g., benzyl benzoate) were smoothly converted into the corresponding amides in excellent yields (up to 87%) using the optimized conditions. The present catalytic system was compatible with a range of 1° and 2° aliphatic amines and afforded the corresponding amides in varying yields of 35–81% (Table 2). Several benzylamines underwent the catalytic aminolysis with esters to afford the corresponding amides in good to excellent yields (Table 2, products **1c** in 87%, **2c** in 82%, **9c** in 60%, **22c** in 61%, and **23c** in 73% isolated yield). In particular, biomass-derived heretocyclic furfurylamine was well-tolerated under our catalytic conditions and gave the expected product **10c** in 85% yield.

Notably, cyclic secondary amines such as morpholine, pyrrolidine, piperidine, and *N*-methylpiperazine showed good reactivity with various esters and yielded the corresponding amides **11c**–**19c** in moderate yields (up to 57%). The reaction of anilines containing both electron-donating and -withdrawing substituents afforded the corresponding amides **21c** (51%), **29c** (51%), **31c** (43%), and **32c** (35%). Regrettably, aniline containing an electron-withdrawing group (−CN at the *para* position or $-NO_2$ at the *meta* position) failed to give the corresponding amides under the optimized reaction conditions. However, the reaction of 2-(aminomethyl)aniline with ethyl acetate under the standard conditions led to the bisacylated product *N*-(2-acetamidobenzyl)acetamide (**26c**) in 36% yield with the liberation of hydrogen gas. Interestingly, the scope of this protocol was explored with 1,4- and 1,2-amino alcohols (e.g., 4-aminobutan-1-ol and (*S*)-2-amino-3-phenylpropan-1-ol) under mild catalytic conditions. Interestingly, 4-aminobutan-1-ol underwent the acylation of both the amine and alcohol functional groups to afford **27c** under Mn-catalyzed

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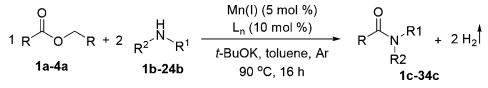
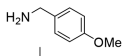
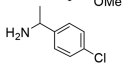
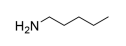
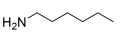
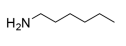
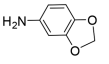
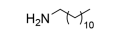
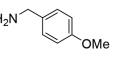
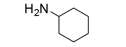
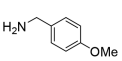
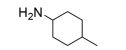
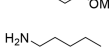
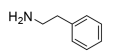
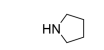
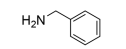
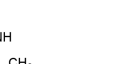
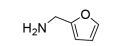
Table 2. Substrate Scope for Ester Aminolysis[a]



entry	ester	amine	yield[b] (%)	entry	ester	amine	yield[b] (%)
1			87	18			35
2			82	19			58
3			78	20			60
4			81	21			51
5			81	22			61
6			57	23			73
7			55	24			70
8			70	25			69
9			60	26			36[c]
10			85	27			33[c]
11			53	28			35[c]
12			53	29			51
13			57	30			55
14			42	31			43
15			56	32			35
16			42	33			trace
17			40	34			trace

[a]Reaction conditions: ester (1.5 mmol), amine (2.6 mmol), *t*-BuOK (1 mmol), $MnBr(CO)_5$ (5 mol %), L_n (10 mol %), and toluene (2 mL) heated at 90 °C under an argon atmosphere. [b]Isolated yields. [c]The yield was calculated with respect to the amine.

reaction conditions. It is worth mentioning that the chiral molecule (*S*)-2-amino-3-phenylpropan-1-ol was tolerated in the present Mn-catalyzed acylation process, providing N- and O-acylated product **28c** with retention of configuration.

A series of experiments were carried out (Scheme 2) to gain insight into the mechanisms of ester aminolysis. A mercury poisoning study revealed that the active catalytic system in the amidation of esters is homogeneous in nature. The benchmark reaction of **1a** and **1b** in the presence of a radical scavenger (TEMPO) showed the formation of amide **1c** in 72% yield with the liberation of molecular hydrogen, which completely eliminates a radical mechanism. Upon treatment of *n*-hexanol under the Mn-catalyzed reaction conditions (5 mol % [Mn], 10 mol % L_n, and 1 equiv of *t*-BuOK in toluene at 110 °C), the formation of hexyl hexanoate (36%) with the liberation of molecular hydrogen was observed. This result clearly indicates that the present Mn catalytic system follows the dehydrogenative coupling pathway. Heating equimolar amounts of the alcohol and amine partners in the presence of manganese

Scheme 2. Control Experiments

catalysis led to the amide 1-morpholinoethan-1-one in 38% isolated yield and ethyl acetate (8%). Next, the intermolecular competitive reaction of an ester and alcohol with an amine partner was performed under standard catalytic conditions. The results revealed that the present catalytic system is more suitable for aminolyis of the ester (62%) than the alcohol (10%).

As shown in Scheme 3, the present Mn-catalyzed direct conversion of esters to amides proceeds via Mn-catalyzed

Scheme 3. Proposed Mechanisms for Direct Conversion of Esters to Amides

activation of the ester for nucleophilic addition of the amine to give the amide and alcohol, followed by dehydrogenative coupling of the alkoxy part of the ester moiety with an amine, thus resulting in dihydrogen as the greener waste. Indeed, acceptorless self-dehydrogenative coupling of the alcohol to the ester is also operative.

In summary, a facile protocol for the direct conversion of esters to amides with the liberation of molecular hydrogen using a base metal (manganese) as a catalyst and an inexpensive phosphine-free tridentate ligand is reported. Interestingly, the activated symmetric esters were selectively transformed into the corresponding N-acylated amines as a result of incorporation of both the acyl and alkoxy functions of ubiquitous esters into the product amides. This reaction operates via catalytic ester activation for the amine addition, followed by dehydrogenative coupling of the alkoxy part of the ester with the amine.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental section, mechanistic investigation, characterization data, ^{1}H and ^{13}C NMR spectra, HRMS spectra, and GC analyses (PDF)

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Notes

The authors declare no competing financial interest.

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(10) During the preparation of our manuscript, a similar work was reported by Milstein and co-workers using an electron-rich phosphine-based ligand system. See: Kumar, A.; Espinosa-Jalapa, N. A.; Leitus, G.; Diskin-Posner, Y.; Avram, L.; Milstein, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 14992−14996.

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