Direct Synthesis of Amides from Alcohols and Amines with Liberation of H_2

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Direct Synthesis of Amides from Alcohols and Amines with Liberation of H_2

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Given the widespread importance of amides in biochemical and chemical systems, an efficient synthesis that avoids wasteful use of stoichiometric coupling reagents or corrosive acidic and basic media is highly desirable. We report a reaction in which primary amines are directly acylated by equimolar amounts of alcohols to produce amides and molecular hydrogen (the only products) in high yields and high turnover numbers. This reaction is catalyzed by a ruthenium complex based on a dearomatized PNN-type ligand [where PNN is 2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine], and no base or acid promoters are required. Use of primary diamines in the reaction leads to bis-amides, whereas with a mixed primary-secondary amine substrate, chemoselective acylation of the primary amine group takes place. The proposed mechanism involves dehydrogenation of hemiaminal intermediates formed by the reaction of an aldehyde intermediate with the amine.

Amide formation is a fundamental reaction in chemical synthesis (*1*). The importance of amides in chemistry and biology is well recognized and has been studied extensively over the past century (*2*–*4*). Although several methods are known for the synthesis of amides, preparation under neutral conditions and without the generation of waste is a challenging goal (*1*, *5*). Synthesis of amides is mostly based on activated acid derivatives (acid chlorides and anhydrides) or rearrangement reactions induced by an acid or base, which often produce toxic chemical waste and involve tedious procedures (*5*). Transition metal–catalyzed conversion of nitriles into amides was reported (*6*–*8*). Catalytic acylation of amines by aldehydes in the presence of a stoichiometric amount of oxidant and a base is known (*9*, *10*). Recently, oxidative amide synthesis was achieved from terminal alkynes (*11*). Cu(I)-catalyzed reaction of sulfonyl azides with terminal alkynes is a facile method for the synthesis of sulfonyl amides (*12*, *13*). A desirable goal is the direct catalytic conversion of alcohols and amines into amides and dihydrogen (Eq. 1)

$$R\text{–}NH_2 + RCH_2OH \xrightarrow[R = \text{alkyl, aryl}]{\text{catalyst, } \Delta} RNHCOR + 2H_2 \quad (1)$$

This unknown, environmentally benign reaction (*14*–*18*) might lead to a diverse library of amides from very simple substrates, with high atom

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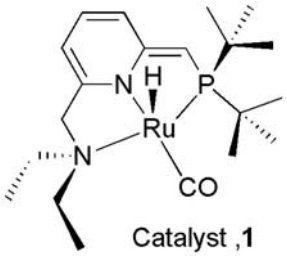


Fig. 1. Structure of dearomatized PNN pincer complex **1**.

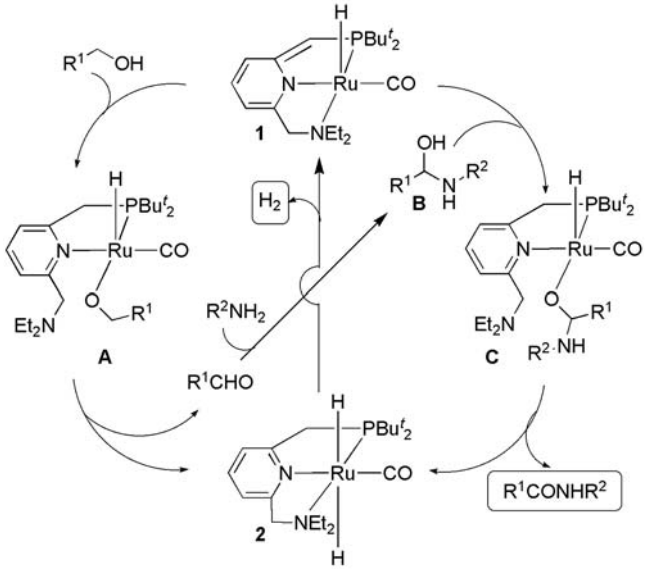
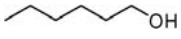
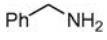
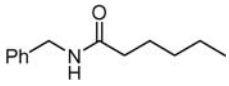
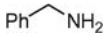
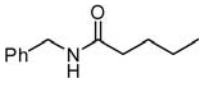
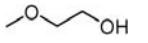
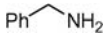
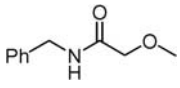
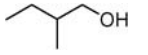
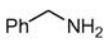
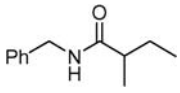
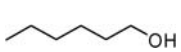
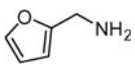
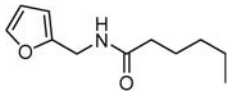
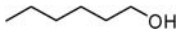
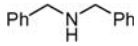
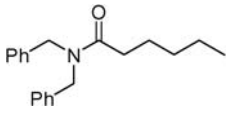
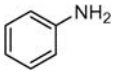
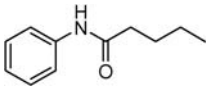
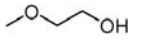
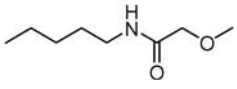
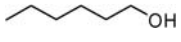
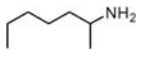
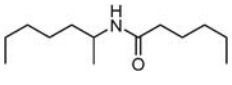
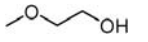
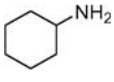
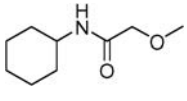


Fig. 2. Proposed mechanism for the direct acylation of amines by alcohols catalyzed by complex **1**.

economy and no stoichiometric activating agents, generating no waste. Although such a reaction is expected to be thermodynamically uphill, it is envisioned that the liberated hydrogen gas (valuable in itself) will shift the equilibrium and drive the reaction.

We recently reported the dehydrogenation of alcohols catalyzed by 2,6-bis-(di-*tert*-butylphosphinomethyl)pyridine (PNP)–Ru(II) and PNN-Ru(II) hydride complexes (*19*). Whereas secondary alcohols lead to ketones (*20*, *21*), primary alcohols are efficiently converted into esters and dihydrogen (*19*–*21*). The dearomatized PNN pincer complex **1** (Fig. 1) is particularly efficient (*19*, *22*); it catalyzes this process in high yields under neutral conditions, in the absence of acceptors or promoters. We have now discovered that complex **1** catalyzes the reaction of alcohols with amines to form amides and H_2, leading to a variety of amides (Table 1).

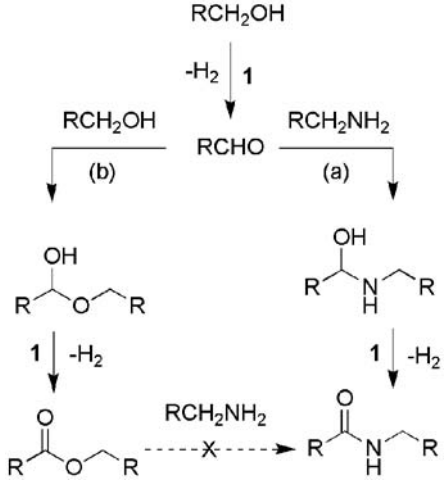
Table 1. Direct dehydrogenative acylation of amines with alcohols catalyzed by the ruthenium complex **1**. Catalyst **1** (0.01 mmol), alcohol (10 mmol), amine (10 mmol), and toluene (3 ml) were refluxed under Ar flow (*33*). Conversion of alcohols was 100% [by gas chromatography (GC) analysis]. The following reaction illustrates the transformation: $R^1CH_2OH + R^2{-}NH_2 \xrightarrow[\text{Toluene,Reflux,-2H}_2]{\mathbf{1}\ (0.1\ \text{mol}\ \%)} R^2NHCOR^1$

Entry	R^1CH_2OH	R^2NH_2	Time (hours)	Amide	Yield* (%)
1			7		96
2			7		97
3			9		99
4			12		70†
5			8		78†
6			8		0†
7			8		58†
8			8		99
9			8		72†
10			8		99

*Isolated yields. †The remaining alcohol was converted into the corresponding ester. In the reactions involving hexanol and pentanol, trace amounts of the corresponding secondary amines were detected (GC–mass spectrometry).

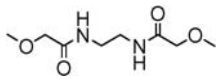
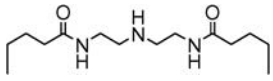
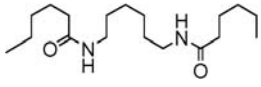
At the outset, when a toluene solution of complex **1** (0.2 mole percent) with benzylamine and 1-hexanol (1:1 ratio) was refluxed in a closed system for 6 hours, 63% conversion of 1-hexanol to *N*-benzylhexanamide was observed. Continuing the reaction up to 40 hours resulted in a mixture of products. In order to facilitate formation of the product amide by hydrogen removal, we heated 1-hexanol and benzylamine with complex **1** (0.1 mol %) under a flow of argon in refluxing toluene for 7 hours. This setup resulted in the formation of *N*-benzylhexanamide in 96% yield and a trace of *N*-benzyl-hexyl-1-amine (1%). We observed no formation of hexyl hexanoate, which forms quantitatively in the absence of amine (Table 1, entry 1). Repeating the reaction with 1-pentanol under identical conditions led to selective direct amidation, providing *N*-benzylpentanamide in 97% yield (Table 1, entry 2). 2-Methoxyethanol underwent clean dehydrogenative acylation by reaction with the primary amines benzylamine, pentylamine, and cyclohexylamine to give methoxy-acetylated amides in almost quantitative yields (Table 1, entries 3, 8, and 10).

The amidation reactions are sensitive to steric hindrance at the α positions of either the alcohol or the amine. Thus, when 2-methyl-1-butanol reacted with benzylamine, the corresponding amide was obtained in 70% yield, with the rest of the alcohol being converted to the ester 2-methylbutyl 2-methylbutanoate (Table 1, entry



Scheme 1.

Table 2. Bis-acylation of diamines with alcohols catalyzed by complex **1**. Catalyst **1** (0.01 mmol), alcohol (10.5 mmol), diamine (5 mmol), and toluene (5 ml) were refluxed under Ar flow (*33*).

Entry	Diamine	Time (hours)	Bis-amide	Yield (%)
1	Ethylenediamine	9		99
2	Diethylenetriamine	8		88
3	Hexamethylenediamine	9		95

4). A similar pattern was also observed when 2-methylhexylamine reacted with hexanol, leading to 72% yield of the corresponding amide (Table 1, entry 9). 1-(2-Furyl)methylamine provided 78% yield of amide when it reacted with 1-hexanol (Table 1, entry 5). When aniline was subjected to acylation with 1-pentanol, the amide was obtained in 58% yield (Table 1, entry 7). The lower reactivity of aniline may be attributed to its lower nucleophilicity as compared with that of the alkylamines. Secondary amines do not react. Thus, heating dibenzylamine with 1-hexanol under the experimental conditions resulted in a quantitative yield of hexyl hexanoate (Table 1, entry 6).

We have also examined the scope of this method with respect to bis-acylation processes with diamines. Upon refluxing a slight excess of a primary alcohol and catalyst **1** with diamines (500 equivalents relative to catalyst **1**) in toluene under argon, we produced bis-amides in high yields. Thus, reaction of 2-methoxyethanol with ethylenediamine, and 1-hexanol with hexamethylene diamine, resulted in quantitative yields of the corresponding bis-amides (Table 2, entries 1 and 3). The high selectivity of the dehydrogenative amidation reaction to primary amine functionalities enabled the direct bis-acylation of diethylenetriamine with 1-hexanol to provide the bis-amide in 88% yield without the need to protect the secondary amine functionality (Table 2, entry 2).

The direct acylation of amines to amides with H_2 liberation may in principle proceed in two ways, as shown in Scheme 1: ("a") dehydrogenation of the alcohol to the aldehyde followed by its reaction with a primary amine to form a hemiaminal that is subsequently dehydrogenated to the amide and ("b") formation of a hemiacetal (from the aldehyde and alcohol) that is subsequently dehydrogenated to the ester (*19*), which reacts with the amine to form the amide (*23*). The latter possibility was ruled out because refluxing a toluene solution of hexyl hexanoate (1.25 mmol) and benzylamine (2.5 mmol) under argon for 8 hours, either in the presence or absence of catalyst **1**, did not result in the formation of *N*-benzylhexanamide. Thus, the reaction probably proceeds via the hemiaminal pathway.

On the basis of the above results and the known chemistry of PNN-type and PNP-type pincer complexes (*19*, *22*, *24*), we tentatively propose the mechanism depicted in Fig. 2. After a catalytic cycle for dehydrogenation of the alcohol to the corresponding aldehyde, reaction with the amine can form the hemiaminal **B**, which (upon reaction with complex **1**) can lead to the aromatic intermediate **C**. β-H elimination from **C** can form the observed product amide and generate the known *trans* Ru dihydride complex **2** (*19*, *22*). Elimination of dihydrogen from complex **2** (*19*, *22*) would regenerate catalyst **1**, completing the catalytic cycle. The dehydrogenation of the hemiaminal **B** to the amide prevails relative to the expected facile water elimination to give an imine, which on hydrogenation would provide the secondary amine (*25*–*27*), that was observed in our system only in trace amounts.

These results highlight the substantial scope for the preparation of the fundamental amide motif by direct acylation of amines with alcohols, which is a clear departure from the conventional synthetic procedures.

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15. 1-Butanol was acylated with amines by means of stoichiometric amount of imidazole (via carbonyl imidazole). Reaction time and yield were not reported (*28*).
16. For a procedure based on three separate reactions, involving aldehyde synthesis by alcohol dehydrogenation, reaction of the aldehyde with hydroxylamine hydrochloride to form an oxime, and rearrangement of the oxime to an amide, see (*29*).
17. In the presence of an excess of a sacrificial hydrogen acceptor, ruthenium-catalyzed lactamization of amino alcohols with a total of 16 turnovers was reported (*30*).
18. Rhodium-catalyzed lactamization of aryl amino alcohols in the presence of base and hydrogen acceptor with a total of 20 turnovers was reported (*31*).
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33. Materials and methods are available as supporting material on *Science* Online.

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