

Communication

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Direct Synthesis of Amides by Acceptorless Dehydrogenative Coupling of Benzyl Alcohols and Ammonia Catalyzed by a Manganese Pincer Complex: Unexpected Crucial Role of Base

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ABSTRACT: Amide synthesis is one of the most important transformations in chemistry and biology. The direct use of ammonia for the incorporation of nitrogen functionalities in organic molecules is an attractive and environmentally benign method. We present here a new synthesis of amides by acceptorless dehydrogenative coupling of benzyl alcohols and ammonia. The reaction is catalyzed by a pincer complex of earth-abundant manganese in the presence of stoichiometric base, making the overall process economical, efficient and sustainable. Inter-

tions, indicating the crucial role of the base, are provided.

esting mechanistic insights based on detailed experimental observa-

The synthesis of amides is among the most significant transformations in organic synthesis, as they are widely used as precursors for the synthesis of polymers, biologically-active compounds, and pharmaceuticals.¹ Conventional methods for the preparation of amides include coupling of amines with carboxylic acid derivatives, nitrile hydrolysis, and rearrangement of ketoximes, generating copious waste in most of the cases. In 2007 our group reported the synthesis of amides by dehydrogenative coupling of alcohols and amines, generating hydrogen gas as the only byproduct, catalyzed by a PNN-Ru-pincer complex.² This dehydrogenative coupling method opened up a new era for the atom economic and environmental benign synthesis of amides, and was followed by several groups employing various catalysts for this reaction.3

The direct incorporation of a nitrogen atom in organic molecules by use of ammonia is an attractive and step-efficient process. The selective synthesis of primary amines by coupling of primary alcohols and ammonia homogeneously catalyzed by an acridine-based PNP-Ru pincer complex was reported by our group in 2008.⁴ Subsequently several other groups reported on the selective formation of primary, secondary and tertiary amine by use of alcohols and ammonia catalyzed by noble metal complexes.5 We recently published the direct synthesis of Nheteroaromatics from diols and ammonia (Scheme 1).6

Due to the high abundance and lower cost, development of basemetal catalysts is desirable. Manganese is earth's third most abundant transition metal, and considerable progress has been made by several groups⁷ including our's⁸ in employing manganese complexes in various (de)hydrogenation reactions. Direct synthesis of amides by dehydrogenative coupling of primary amines with alcohols or esters catalyzed by a manganese complex was recently reported by our group.^{8d} We also reported the dehydrogenative coupling of diols and amines to form cyclic imides using a manganese complex.8g

Intrigued by these recent developments in the synthesis of amides, we explored the possibility of acceptorless dehydrogenative coupling of alcohols and ammonia as the only nitrogen source, avoiding the use of preformed amines. Such a process would be more step economic, efficient, and effective compared to other amide synthesis pathways. It should be noted that acceptorless dehydrogenative coupling reactions of alcohols are generally driven by efficient H₂ removal, making such reactions using ammonia in a closed system quite challenging.⁶ To the best of our knowledge, formation of amides by coupling of alcohols and ammonia with the extrusion of H2 and water, using any catalyst, has not been reported. Herein, we present the synthesis of secondary amides by manganese catalyzed coupling of benzyl alcohols and gaseous ammonia.

Scheme 1. Transition Metal Catalyzed Dehydrogenative Coupling of Alcohols and Amines or Ammonia

Dehydrogenative coupling of alcohols and amines



Direct amide formation from benzyl alcohols and ammonia



Reaction of benzyl alcohol (0.5 mmol) with ammonia (7 bar) in the presence of complex 2^{8k} (2 mol%) and KH (3 mol%) at 150°C in toluene resulted after 24 h in the formation of Nbenzylidenebenzylamine (A, Table 1) in 25% yield and Nbenzylbenzamide (B) in 13% yield (Table 1, entry 1). Complex 1 (see SI) as catalyst afforded N-benzylidenebenzylamine in 26% yield as the only product under similar conditions (Table 1, entry 2). Increasing the base loading to 25 mol%, using 1 under the same reaction conditions resulted 32% yield of (A) and 12% of N-benzylbenzamide (B), whereas using an equivalent amount of KH (with respect to the alcohol) resulted in the formation of 48% of N-benzylidenebenzylamine and 38% of N-benzylbenzamide, the overall conversion being 90% (Table 1, entries 3 and 4 respectively). Quite remarkably, using complex **2** and a stoichiometric amount of KH (relative to the alcohol) under 7 bar ammonia at 150°C for 24 h resulted in 92% conversion with 100% selectivity to N-benzylbenzamide (Table 1, entry 5). Thus, the amount of base used in the catalysis has a crucial effect on the selectivity towards amide formation.

Table 1. Optimization of the reaction conditions for the amidation of benzyl alcohol with ammonia^a

| \bigcirc | H <mark>+ NH₃ (7 bar) -</mark> To | [Mn] (2 mol%) KH (Y mol%) (2ml), 150°C, 24h | [∧] N ∕) A | Ŭ Å Û B | |
|-----------------|--|---|-------------------------|--------------------|------|
| Entry | Catalyst (2 mol%) | Base(Y mol%) | Conv. (%) | Yield ^b | |
| | | | | A(%) | B(%) |
| 1 | 2 | KH (3) | 40 | 25 | 13 |
| 2 | 1 | KH (3) | 28 | 26 | 0 |
| 3 | 1 | KH (25) | 48 | 32 | 12 |
| 4 | 1 | KH (100) | 90 | 48 | 38 |
| 5 | 2 | KH (100) | 92 | 0 | 90 |
| 6° | 2 | KH (100) | 90 | 0 | 88 |
| 7^{d} | 2 | KH (100) | 99 | 0 | 90 |
| 8 ^e | 2 | KH (100) | 99 | 70 | 28 |
| 9 | 2 | 'BuOK (100) | 90 | 0 | 89 |
| 10 | 2 | KHMDS (100) | 65 ^f | 05 | 35 |
| 11 ^g | - | KH (100) | 5 | 0 | 0 |
| 12 ^h | 3 | KH (100) | 99 | 04 | 92 |

Substrate Scope:



^aReaction conditions: Catalyst (2 mol%), benzyl alcohol (0.5 mmol), KH (specified amounts), NH₃ (7 bar), 150°C, 24h, toluene, the reaction quenched with methanol. ^bGC yield with mesitylene as internal standard. ^cIn presence of 300 eq. of Hg. ^dSolvent 1,4-dioxane. ^eSolvent THF. ^fOther unidentified products formed. ^gWithout any catalyst, a small amount benzaldehyde was formed. ^hCatalyst **3** (2 mol%). ⁱOptimized reaction conditions: catalyst **2** (2 mol%), primary alcohol (0.5mmol), KH (0.5 mmol), NH₃ (7 bar), 150°C, 24h, toluene (2 ml).

Significantly, addition of 300 equivalents of Hg to the reaction solution showed no decrease in the product formation or selectivity (Table 1, entry 6), suggestive of a homogeneous catalytic pathway. Changing the solvent to 1,4-dioxane using catalyst **2** under the optimized conditions resulted in a similar yield of the amide product (entry 7) whereas low yield of the amide was observed when THF was used (28 %) (entry 8). A possible reason for the observed different selectivity of the product with 1,4-dioxane and THF as solvents is their coordination ability, which competes with coordination of the hemiaminal intermediate, required for its dehydrogenation, as opposed to the noncoordinating nonpolar toluene. Using an equivalent amount of 'BuOK resulted in a similar yield and selectivity of the amide (entry 9) whereas using KHMDS as base, lower conversion (65%) and also selectivity (35%) to the amide was observed and some unidentified products were formed (entry 10). Under similar conditions, using stoichiometric KH and no catalyst, no conversion of benzyl alcohol was observed (entry 11). Analysis of the gas phase by gas chromatography indicated the formation of H_2 (see Figure S1).

Using the optimized reaction conditions, in the presence of a stoichiometric amount of KH with respect to the alcohol (toluene, 150°C, 2 mol% 2), the scope of this new dehydrogenative coupling reaction was explored. Electron-rich benzyl alcohols showed very good reactivity, forming the corresponding N-substituted amides as the major products (Table 1). Benzyl alcohol and its derivatives 4-methyl, 3methyl, 4-ethyl, 4-isopropyl, 4-tert-butyl benzyl alcohols afforded good yields of the corresponding amides with high selectivity (Table 1, entry A-F). 2-menthyl benzyl alcohol also showed good conversion with 47% of the amide product and 45% of the 2,4,5-trisubstituted imidazole as the side product (Entry G, and also see later for details). The sterically hindered 2,4,6-trimethylbenzyl alcohol was completely inactive under the optimized reaction conditions and unreacted alcohol was recovered (See SI, Table S2). 4-Methoxy benzyl alcohol and 3-(N,N-dimethyl amine)benzyl alcohol also afforded the corresponding amides in good yields and high selectivity (Table 1, entries H, I). Employing benzyl alcohols bearing electron withdrawing substituents such as 4trifluoromethyl benzyl alcohol resulted in poor yield of the secondary amide and moderate yield of the primary amide, in addition to the unreacted alcohol (see SI, Table S2). In case of 1-hexanol, Nhexylhexan-1-imine was obtained as the major product along with other unidentified condensation products (due to the enolizeable aliphatic aldehyde intermediate) and no amide product was detected. The electron rich aliphatic alcohol lacking enolizeable protons, neopentyl alcohol, formed 2,4,5-tri(tert-butyl)-imidazole as the major product (see SI Table S2). Formation of imidazole derivatives was reported in case of the ruthenium catalyzed reductive amination of carbonyl compounds with ammonia in under hydrogen.9

To gain mechanistic insight into this unprecedented amidation reaction, some control experiments were performed. Reaction of an equimolar amount of benzyl alcohol with either benzyl amine or 1hexylamine in the presence of catalyst 2 (2 mol%) and a catalytic amount of KH (3 mol%) at 150°C for 24 h in a closed system resulted in quantitative formation of the corresponding imine as the only product and no corresponding amide was observed (Scheme 2a). However, when the same reaction was performed using benzyl alcohol and benzyl amine, but in presence of a stoichiometric amount of KH, Nbenzylbenzamide was observed as the major product (Scheme 2b). Although dehydrogenative coupling of alcohols and amines to form amides using a manganese catalyst was reported by us, the substrate scope for this reaction was limited to aliphatic alcohols and benzyl amines.^{8d} Thus, this is the first example of amide formation by dehydrogenative coupling of benzyl alcohols and benzyl amines catalyzed by an earth-abundant metal complex.

One possible mechanism for amide formation could involve addition of water to an intermediate imine¹⁰. To explore this possibility, we performed a reaction of N-benzylidenebenzylamine (0.05 mmol) with catalyst **2** (2 mol%) in the presence of KH (catalytic or stoichiometric amount with respect to substrate) in a 1,4-dioxane-water mixture (1:1) at 150°C for 24h. However, no amide product was observed and the unreacted imine was isolated with some aldehyde and amine as hydrolysis products at the end of reaction. Based on this, we exclude the possibility of formation of amide by the addition of water to an imine intermediate (Scheme 2c). 1

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Scheme 2. Using catalyst 2, effect of amount of base on amide formation from benzyl alcohol and benzyl amine (a, b), and lack of reaction of imine upon heating in dioxane/water (c).



Another possibility is that benzyl alcohol reacts with ammonia to form benzyl amine,⁴ followed by reaction of the latter with benzyl alcohol to form an amide via dehydrogenation of a hemiaminal intermediate. To explore this possibility, a control experiment was carried out (Scheme 3). Reaction of equimolar amounts of 4-methylbenzyl alcohol and benzyl amine with a stoichiometric amount of KH (with respect to the alcohol) under the optimized conditions afforded a minor amount of 4-methyl-N-(4-methylbenzyl)benzamide as the only amide product, along with a major amount of a mixture of imine products (Scheme 3, A; see SI for details). This suggests that under these catalytic conditions, benzyl alcohol and the amine do not couple to form an amide. Furthermore, treatment of equivalent amounts of benzyl alcohol and 4methyl benzyl alcohol with ammonia (7 bar), in the presence of two equivalents of KH (with respect to both alcohols) and complex 2 under similar conditions afforded a mixture of all four possible amides as the major products (Scheme 3, B). This suggests that the reaction proceeds via the formation of a 1-aminoalkoxide intermediate followed by its dehydrogenation to the primary amide, and finally its N-alkylation by the alcohol (see details in the mechanistic description). To establish the initial alkoxide formation, an independently prepared potassium salt of benzyl alcohol was treated with ammonia under similar conditions. Analysis of the reaction mixture at the end of the reaction showed the formation of N-benzylbenzamide with a similar yield (80%) (Scheme 3, C). Additionally, N-benzylbenzamide was formed quantitatively by treatment of benzamide with benzyl alcohol in the presence of catalyst 2 (2 mol%) using a catalytic amount of KH (3 mol%) (Scheme 3, D), supporting that the reaction proceeds via the Nalkylation of the amide. To our knowledge, this is the first report of manganese catalyzed N-alkylation of an amide.11

Scheme 3. Control catalytic experiments



Based on the aforementioned observations, a plausible mechanism is proposed in Scheme 4. Reaction of an equivalent amount of base (KH)

with the alcohol generates the corresponding alkoxide salt (I), which could be in some equilibrium with the large excess of ammonia at the high reaction temperature to regenerate some alcohol and form potassium amide. Reaction of the alcohol with the Mn complex forms the corresponding aldehyde, through β-hydride elimination.^{8k} This is followed by the attack of ammonia (or formed potassium amide), on the aldehyde to form a hemiaminal that undergoes deprotonation by the base to form an 1-aminoalkoxide (II). We believe that the 1aminoalkoxide is an important intermediate for the second dehydrogenation, likely via the amido intermediate (III), leading to the selective formation of the amide by retarding the water elimination and disfavoring the imine formation. The second dehydrogenation step leads to the corresponding primary amide salt (IV or V, Scheme 4). Nalkylation of the formed amide with the primary alcohol via dehydrogenative coupling and borrowing hydrogenation affords the final amide salt product (VI).

Scheme 4. Proposed mechanism for the formation of secondary





In order to gain evidence about the ionic nature of the product and intermediate, the precipitate from the reaction mixture of benzyl alcohol with an equivalent of KH and catalyst **2** with ammonia (7 bar) was isolated. HRMS showed a mass peak at 210 (M/Z) corresponding to the amido anion (VI) in the negative scanning mode whereas a mass peak at 250 (M/Z) corresponding to the K salt of N-benzylbenzamide was detected in the positive scanning mode (See SI). Recently we reported that the bridged BH₃ moiety of complex **2** is easily eliminated by its reaction with gaseous ammonia or any primary amine.^{8k} When the ammonia bound complex **3** was synthesized and used as catalyst of the reaction of benzyl alcohol with ammonia, 92% (Table 1, entry 12) yield of N-benzylbenzamide was formed under the optimized reaction conditions, which is comparable to the catalytic activity of complex **2**, indicating that ammonia bound complex **3** is likely an active organometallic intermediate during the reaction (See SI).

In conclusion, for the first time, the synthesis of amides via dehydrogenative coupling of an alcohol and ammonia is reported, ammonia serving as the nitrogen source. The reaction is catalyzed by a complex of the first row, earth-abundant transition metal manganese. An unusual, plausible mechanism is proposed in which the role of stoichiometric base is to form a 1-aminoalkoxide hemiaminal intermediate (II, Scheme 4), which leads to selective amide formation by retarding water elimination from the hemiaminal intermediate. Further investigation regarding the mechanism of this reaction is underway. We believe that this reaction provides an attractive new pathway to the synthesis of secondary amides from benzyl alcohols and ammonia using a basemetal catalyst.

ASSOCIATED CONTENT

Experimental procedure, and control experiments were describe in the SI "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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