Catalytic Amide Synthesis

DOI: 10.1002/anie.201107110

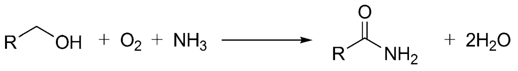
Heterogeneously Catalyzed Synthesis of Primary Amides Directly from Primary Alcohols and Aqueous Ammonia**

*Kazuya Yamaguchi, Hiroaki Kobayashi, Takamichi Oishi, and Noritaka Mizuno**

Amides are a very important class of compounds in chemistry as well as biology that have widely been utilized as intermediates in peptide and protein synthesis, intensifiers of perfume, anti-block reagents, color pigments for inks, detergents, and lubricants.[1] The most common procedure for amide synthesis is the reaction of activated carboxylic acid derivatives such as acid chlorides, anhydrides, and esters with amines including ammonia.[2] The Beckmann rearrangement, the Aube–Schmidt rearrangement, and the Staudinger ligation are also commonly utilized procedures.[2] However, these procedures require stoichiometric amounts of (hazardous) reagents, and at least equimolar amounts of by-products are formed. Therefore, the development of new environmentally friendly procedures[3] for amide synthesis is a very important subject in modern organic synthesis.

In 2007, Milstein and co-workers reported the direct synthesis of secondary amides from primary alcohols and amines with a PNN pincer-type ruthenium complex.[4] Alcohols are desirable starting materials because they are readily available and inexpensive and theoretically produce only hydrogen or water as a by-product. The reaction reported by Milstein and co-workers is initiated by the dehydrogenation of an alcohol to an aldehyde. Then, condensation of the aldehyde with an amine proceeds to form a hemiaminal intermediate, followed by dehydrogenation to the corresponding secondary amide.[4] Since then, several precious-metal-based complexes have been developed for the synthesis of secondary amides.[5–7] However, widely applicable procedures for the direct synthesis of primary amides from primary alcohols and ammonia are very challenging because dehydration, rather than dehydrogenation, of the hemiaminal from ammonia readily occurs and/or catalysts are deactivated in the presence of ammonia and/or water in some cases.[8]

Herein, we demonstrate that it is possible to realize the direct synthesis of primary amides from primary alcohols and aqueous ammonia [Eq. (1)] in the presence of manganese oxide based octahedral molecular sieves (KMn_8O_{16}; OMS-2), which have a 2×2 hollandite structure with a one-dimensional pore.[9] This transformation can be realized by the triple catalytic functions of OMS-2: 1) dehydrogenation of alcohols to aldehydes, 2) dehydrogenation of NH aldimines to nitriles, and 3) hydration of nitriles.[10] The procedures herein have the following significant advantages in comparison with previously reported procedures for the synthesis of primary amides: 1) only water is formed as a by-product [Eq. (1)], 2) easily handled aqueous ammonia can be used, 3) a variety of primary alcohols can be used as starting materials (the use of a variety of aldehydes and nitriles is also possible), 4) separation of the catalyst and product is very easy, 5) a manganese-based oxide is rather inexpensive in comparison with precious-metal-based catalysts, and 6) OMS-2 can be reused many times without an appreciable loss of its high catalytic performance.



(1)

Initially, a range of catalysts were applied to the transformation of benzyl alcohol (**1a**) to benzamide (**2a**) in 1,4-dioxane using aqueous ammonia and O_2 (see Table S1 in the Supporting Information). Among the various catalysts examined, only OMS-2 gave the corresponding amide **2a**, for example, when the transformation was carried out using aqueous ammonia (28 wt %, ca. 2.6 equiv to **1a**) and O_2 (3 atm) at 130 °C (bath temperature), after 3 hours 96% yield of **2a** was obtained as well as a small amount of benzonitrile (**3a**, 2% yield; Table 1, entry 1). In the case of other manganese-based oxides, such as β-MnO_2, birnessite-type MnO_2, and spinel-type Mn_3O_4, no **2a** was produced, and **3a** and benzaldehyde (**4a**) were formed in moderate yields. In the presence of activated MnO_2 (for organic oxidations, Aldrich), **1a** was selectively converted into the corresponding nitrile **3a** (95% yield).[11] Other metal oxides, such as Co_3O_4 and CeO_2, did not give **2a**. $KMnO_4$ and $MnSO_4{\cdot}H_2O$, which are precursors for OMS-2, were not effective for the transformation. The supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$,[12] gave **3a** and **4a** in 18% and 22% yields, respectively, without formation of **2a** under the reaction conditions described above (see Table S1 in the Supporting Information). 1,4-Dioxane and *N*,*N*-dimethylformamide were good solvents for the transformation, thus giving **2a** in high yields (see Table S1, in the Supporting Information). Toluene, dichloromethane, 1,2-dichloroethane, and water gave **3a** as a major product with moderate yields of **2a** (see Table S1 in the Supporting Information).

To verify whether the observed catalysis is derived from solid OMS-2 or a leached manganese species, the trans-

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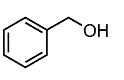
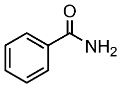
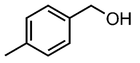
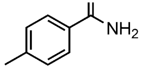
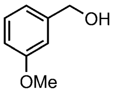
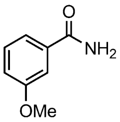
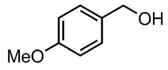
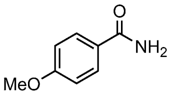
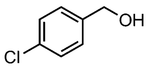
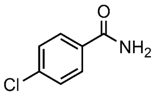
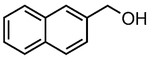
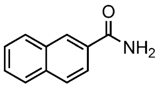
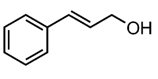
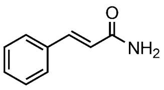
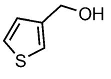
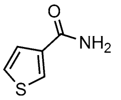
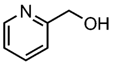
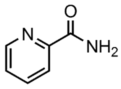
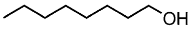
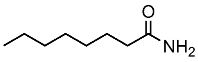
[*] Dr. K. Yamaguchi, H. Kobayashi, T. Oishi, Prof. Dr. N. Mizuno
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp

[**] This work was supported in part by the Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering) and Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology. T.O. is grateful for a JSPS Research Fellowship for Young Scientists.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107110.

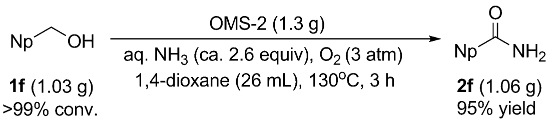
Table 1: Synthesis of amides from primary alcohols and ammonia.[a]

Entry	Substrate		t [h]	Product		Yield [%]
1		**1a**	3		**2a**	96
2		**1b**	3		**2b**	97
3		**1c**	3		**2c**	96
4		**1d**	3		**2d**	98
5		**1e**	3		**2e**	97
6		**1f**	3		**2f**	95
7		**1g**	3		**2g**	99
8		**1h**	3		**2h**	87
9		**1i**	1		**2i**	95
10[b]		**1j**	24		**2j**	65

[a] Reaction conditions: OMS-2 (100 mg), substrate (0.5 mmol), 28% aq. ammonia (100 μL, ca. 2.6 equiv), 1,4-dioxane (2 mL), O_2 (3 atm), 130°C (bath temp.). See Table S2 in the Supporting Information for more details. Yields were determined by GC using biphenyl or naphthalene as an internal standard. [b] OMS-2 (200 mg).

formation of **1a** to **2a** was carried out under the reaction conditions described in Table 1, and OMS-2 was removed from the reaction mixture by filtration at 50–60% conversion of **1a**. Then, the filtrate was heated at 130°C in 3 atm of O_2. In this case, no further production of **2a** and **3a** was observed. This result was confirmed by inductively coupled plasma atomic-emission spectroscopy (ICP-AES) analysis, as no manganese species was detected in the filtrate (below 0.001%). All these facts can rule out any contribution to the observed catalysis from a manganese species that has leached into the reaction solution; thus the observed catalysis is intrinsically heterogeneous.[13]

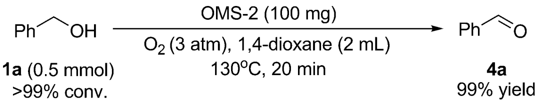
Next, the scope of the present OMS-2 catalytic system with regard to a range of structurally diverse primary alcohols was examined. OMS-2 showed high catalytic activities for the transformation of benzylic, allylic, heteroatom-containing, and aliphatic alcohols (Table 1). The transformation of benzylic alcohols **1a**–**1f**, which contain electron-donating as well as electron-withdrawing substituents at different positions, efficiently proceeded to afford the corresponding substituted benzamide derivatives in almost quantitative yields (≥95% yields). In the transformation of an allylic alcohol (**1g**), the corresponding unsaturated amides could be obtained without isomerization and hydrogenation of the double bond. Heteroatom-containing alcohols such as thiophene (**1h**) and pyridine (**1i**) methanols afforded the corresponding heteroaromatic amides in excellent yields. Also, an aliphatic alcohol (**1j**) could be converted into the corresponding aliphatic amide. To show the practical value of the present procedure, a gram-scale transformation of **1f** (1.03 g; 13-fold scale) was carried out [Eq. (2)]. The transformation efficiently proceeded without any decrease in the performance in comparison with the small-scale transformation in Table 1, and **2f** and **3f** (nitrile) were produced in 97% and 3% yields (by GC analysis), respectively. OMS-2 was separated by filtration and washed with ethanol (ca. 50 mL). Evaporation of the combined filtrate gave a crude product, which was washed with n-hexane (ca. 10 mL) to afford 1.06 g of **2f** (95% yield, >98% purity by GC and NMR spectroscopy).[14]



(2)

After the reaction was completed, OMS-2 was recovered from the reaction mixture by filtration (>95% recovery). The retrieved OMS-2 catalyst could be reused for the transformation of **1i** at least eleven times without an appreciable loss of its high catalytic performance (see Figure S1 in the Supporting Information). The structure of OMS-2 was preserved even after the eleventh reuse (see Figure S2 in the Supporting Information), showing the high durability of OMS-2.

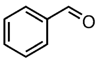
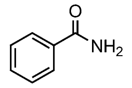
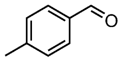
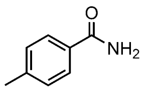
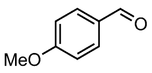
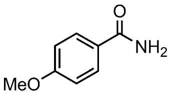
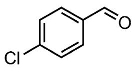
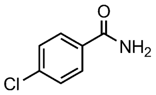
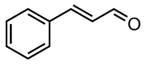
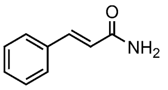
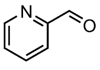
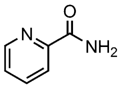
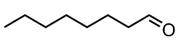
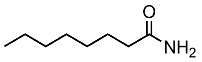
When amines, e.g., methylamine (40% aqueous solution), instead of ammonia were used in the transformation of **1a** under the reaction conditions described in Table 1, the corresponding secondary amides were not produced at all. Therefore, it can be concluded that the present transformation does not proceed through direct dehydrogenation of hemiaminal intermediates as has been reported for the precious-metal catalytic systems.[4,5] The reaction profile for the transformation of **1a** into **2a** showed that the corresponding nitrile **3a** was initially produced as a major product, followed by the formation of **2a** (see Figure S3 in the Supporting Information). During the transformation, the corresponding aldehyde and aldimine[15] were also detected, albeit in only small amounts (below 1%). Under the reaction conditions described in Table 1, the absence of ammonia resulted in the quantitative conversion of **1a** into the corresponding aldehyde **4a** within 20 minutes [Eq. (3)].[10] OMS-2 showed high catalytic performance for the transformation of a variety of structurally diverse aldehydes, including benzylic, allylic, heteroatom-containing, and aliphatic ones, into the corresponding amides in the presence of



(3)

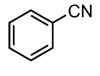
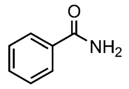
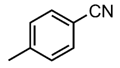
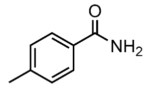
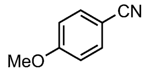
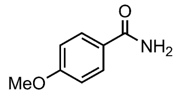
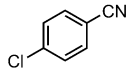
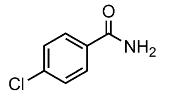
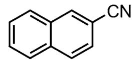
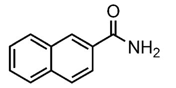
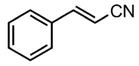
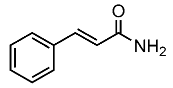
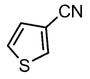
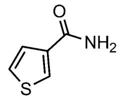
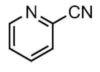
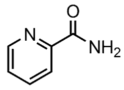
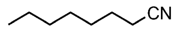
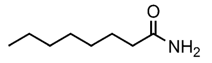
ammonia (Table 2). In addition, the OMS-2-catalyzed hydration of various nitriles proceeded efficiently to give the corresponding amides in excellent yields (Table 3). Among the catalysts examined, only OMS-2 promoted the nitrile hydration (see Table S1 in the Supporting Information).[10]

Table 2: Synthesis of amides from aldehydes and ammonia.[a]

Entry	Substrate		t [h]	Product		Yield [%]
1		**4a**	3		**2a**	89
2		**4b**	3		**2b**	91
3		**4d**	3		**2d**	97
4		**4e**	3		**2e**	98
5		**4g**	3		**2g**	87
6		**4i**	1		**2i**	94
7[b]		**4j**	24		**2j**	77

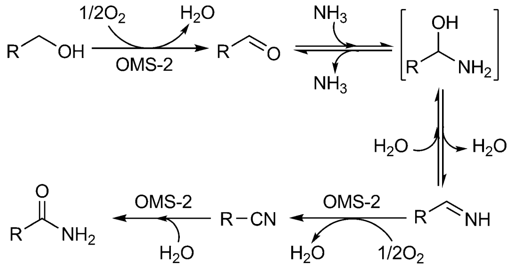
[a] Reaction conditions: OMS-2 (100 mg), substrate (0.5 mmol), 28% aq. ammonia (100 μL, ca. 2.6 equiv), 1,4-dioxane (2 mL), O_2 (3 atm), 130 °C (bath temp.). See Table S3 in the Supporting Information for more details. Yields were determined by GC using biphenyl or naphthalene as an internal standard. [b] OMS-2 (200 mg).

Table 3: Hydration of nitriles.[a]

Entry	Substrate		t [h]	Product		Yield [%]
1 2[b]		**3a**	3 3		**2a**	91 81
3		**3b**	3		**2b**	98
4		**3d**	3		**2d**	94
5		**3e**	3		**2e**	97
6		**3f**	3		**2f**	97
7		**3g**	3		**2g**	93
8		**3h**	3		**2h**	88
9		**3i**	1		**2i**	96
10[c]		**3j**	24		**2j**	98

[a] Reaction conditions: OMS-2 (100 mg), substrate (0.5 mmol), 28% aq. ammonia (100 μL, ca. 2.6 equiv), 1,4-dioxane (2 mL), Ar (3 atm), 130 °C (bath temp.). See Table S4 in the Supporting Information for more details. Yields were determined by GC using biphenyl or naphthalene as an internal standard. [b] Water (50 μL, ca. 5.5 equiv) was used instead of aq. ammonia. [c] OMS-2 (200 mg).

All the above-mentioned experimental evidences indicate that the present OMS-2-catalyzed transformation possibly proceeds through the following sequence of reactions (Scheme 1): 1) aerobic oxidative dehydrogenation of an alcohol to an aldehyde, 2) dehydrative condensation of the aldehyde and ammonia to an aldimine via a hemiaminal intermediate, 3) aerobic oxidative dehydrogenation of the aldimine to a nitrile, and 4) successive hydration to the desired primary amide.



Scheme 1. Possible reaction pathway for the OMS-2-catalyzed transformation of primary alcohols to primary amides.

In summary, OMS-2 acted as an efficient heterogeneous catalyst for a widely applicable synthesis of primary amides directly from primary alcohols and ammonia. The synthesis from aldehydes or nitriles was also possible in the presence of OMS-2. The separation of the catalyst and product was very easy. The observed catalysis was truly heterogeneous, and OMS-2 could be reused many times without an appreciable loss of its high catalytic performance. The heterogeneously catalyzed reaction using OMS-2 described herein will provide a new route for sustainable amide synthesis, which can completely avoid utilization of conventional (hazardous) stoichiometric reagents and the formation of vast amounts of inorganic by-products.

Experimental Section

OMS-2 was prepared according to the literature procedure (see the Supporting Information).[9a] A typical procedure for the synthesis of the amides was as follows: **1a** (0.5 mmol), OMS-2 (100 mg), 1,4-dioxane (2 mL), an aqueous solution of ammonia (28 wt %, 100 μL, ca. 2.6 equiv with respect to **1a**) were placed in a Teflon vessel with a magnetic stir bar. The Teflon vessel was attached inside an autoclave and the reaction was carried out at 130 °C (bath temperature) in O_2 (3 atm). The reaction rates were not affected by stirring rates from 500 to 1000 rpm. After the reaction was completed (3 h), the OMS-2 catalyst was separated by filtration, washed with acetone, and then dried at 150 °C prior to its use in the reuse experiment. The products (amides) could be isolated by evaporation of volatiles, followed by a wash with *n*-hexane (column chromatography on silica gel, if necessary; initial eluent: *n*-hexane, after elution of by-products: ethyl acetate). The products were confirmed by the comparison of their GC retention times, GC mass spectra, and/or ^{1}H and ^{13}C NMR spectra with those of authentic data.

Received: October 7, 2011

Keywords: alcohols · amides · ammonia · heterogeneous catalysis · manganese oxide

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[8] Very recently, three catalytic systems for the synthesis of primary amides from alcohols and ammonia have been reported. In the catalytic system with a rhodium diolefin amido complex, methylmethacrylate (3 equiv with respect to the alcohol) is required to promote the reaction, and easily handled aqueous ammonia is not used.[8a] Although various secondary amides can be synthesized from alcohols and amines in water with the water-soluble gold/DNA catalyst and $LiOH \cdot H_2O$ (indispensable additive, 1.1 equiv with respect to an alcohol), the applicability of this catalytic system to the synthesis of primary amides is limited to **2a**, and the yield is low (50 %).[8b] After Wang's report, Kobayashi and co-workers reported a similar gold catalytic system.[8c] In this system also, the applicability is limited to **2a**, and NaOH (1 equiv) is required. Thus, as far as we know, widely applicable, efficient procedures for the direct aerobic synthesis of primary amides from alcohols and ammonia without additives are previously unknown, and the development is a challenging subject: a) T. Zweifel, J.-V. Naubron, H. Grützmacher, *Angew. Chem.* **2009**, *121*, 567; *Angew. Chem. Int. Ed.* **2009**, *48*, 559; b) Y. Wang, D. Zhu, L. Tang, S. Wang, Z. Wang, *Angew. Chem.* **2011**, *123*, 9079; *Angew. Chem. Int. Ed.* **2011**, *50*, 8917; c) J.-F. Soulé, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2011**, 133, 18550.

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[12] Recently, we have reported the direct synthesis of nitriles from alcohols and ammonia by the supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$. In the presence of $Ru(OH)_x/Al_2O_3$, the direct synthesis of amides was very difficult (see Table S1, entry 18 in the Supporting Information) because of the low ability of $Ru(OH)_x/Al_2O_3$ for nitrile hydration (a large amount of water is required to attain high yields) in comparison with OMS-2: a) T. Oishi, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2009**, *121*, 6404; *Angew. Chem. Int. Ed.* **2009**, *48*, 6286; b) T. Oishi, K. Yamaguchi, N. Mizuno, *Top. Catal.* **2010**, *53*, 479.

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[14] Nitriles, aldehydes, and alcohols are soluble in *n*-hexane while the solubilities of amides are very low. By exploiting this solubility difference, amides can be simply purified by washing crude products with *n*-hexane.

[15] During the transformation of **1f** to **2f**, the corresponding aldimine intermediate could be detected by GC-MS analysis (see Figure S4 in the Supporting Information).