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Manganese oxide-catalyzed transformation of primary amines to primary amides through the sequence of oxidative dehydrogenation and successive hydration†

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Manganese oxide octahedral molecular sieves (OMS-2) could act as an efficient, reusable heterogeneous catalyst for transformation of various primary amines to the corresponding primary amides through the sequence of oxidative dehydrogenation and successive hydration.

Amides are one of the most important chemicals that have widely been used as intermediates in organic synthesis, raw materials for engineering plastics, detergents, and lubricants.[1] The development of green procedures for synthesis of amides from various starting materials is a very important subject in modern organic synthesis (instead of antiquated procedures using activated carboxylic acid derivatives and amines). The Beckmann rearrangement of ketoximes is one of the most commonly utilized procedures for synthesis of *N*-substituted amides.[2,3] In particular, the vapor-phase Beckmann rearrangement of cyclohexanone oxime using high silica zeolite catalysts has been industrialized.[3] Dehydrogenative synthesis of *N*-substituted amides directly from alcohols and amines can be realized by using several precious metal complexes.[4] Hydration of nitriles[5] and rearrangement of aldoximes[6] are two of the most attractive procedures for synthesis of primary amides. Quite recently, we have reported that manganese oxide octahedral molecular sieves (OMS-2)[7] can act as an efficient, reusable heterogeneous catalyst for synthesis of various kinds of primary amides from alcohols (or aldehydes) and aqueous ammonia.[8]

With regard to synthesis of primary amides, primary amines are also desirable starting materials because they are readily available and inexpensive. However, in general, it is very difficult to oxygenate primary amines, and reactive stoichiometric reagents are necessary.[9,10] For example, Nishinaga's procedure requires a stoichiometric amount of 2,6-di-*tert*-butyl-*p*-benzoquinone (Fig. 1).[9] In Yoshifuji's procedure, amines with the Boc (Boc = *tert*-butoxycarbonyl) protection are oxygenated using *in situ*-generated RuO_4, followed by deprotection of the Boc group (Fig. 1).[10] In contrast, the dehydrogenation–hydration sequence with molecular oxygen (air) as a sole oxidant theoretically produces only water as a co-product (Fig. 1). As far as we know, only one system using the supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$, has previously been reported for this dehydrogenation–hydration strategy.[11] Various kinds of primary amines can be converted into the corresponding amides, while a large amount of water (reactant) is indispensable because of the very low catalytic activity of $Ru(OH)_x/Al_2O_3$ for nitrile hydration.[5a,11] We demonstrate herein that it is possible to realize oxygenation of primary amines to primary amides through the sequence of oxidative dehydrogenation and hydration with OMS-2, and that the catalytic performance of OMS-2 is much superior to that of $Ru(OH)_x/Al_2O_3$ (see Table 1).

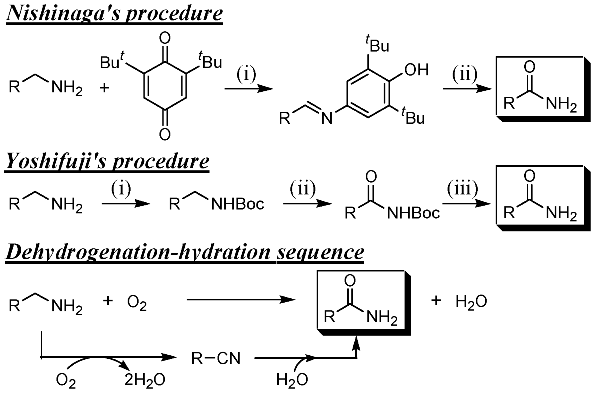

Fig. 1 Transformation of primary amines to primary amides. Nishinaga's procedure:[9] (i) reflux in ethanol, (ii) ^{t}BuOK (or KOH), O_2. Yoshifuji's procedure:[10] (i) *tert*-butyl *S*-4,6-dimethylpyrimidyl-2-thiocarbonate, triethylamine, (ii) $RuO_2{\cdot}nH_2O$, $NaIO_4$, (iii) trifluoroacetic acid.

First, various kinds of catalysts were applied to the transformation of benzylamine (**1a**) to benzamide (**2a**) using air (as an oxidant) and aqueous ammonia (Table 1).‡ 1,4-Dioxane was the suitable solvent because of the high solubilities of substrates, ammonia, and water.[8] When the transformation was carried out with OMS-2, 83% yield of **2a** was obtained with a small amount of benzonitrile (**3a**, 3% yield). In the presence of commercially available activated MnO_2 (generally utilized for organic oxidations), **1a** was converted into the corresponding nitrile **3a** as a major product (72% yield) with 12% yield of **2a**. Other manganese-based oxides such as β-MnO_2, β-MnOOH, and birnessite-type MnO_2 gave **3a** and **4a** in moderate yields, and **2a** was hardly produced. $KMnO_4$ and $MnSO_4{\cdot}H_2O$ (precursors for OMS-2) were not effective for

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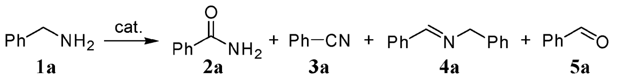
† Electronic supplementary information (ESI) available: Experimental details and Table S1. See DOI: 10.1039/c2cc17499e

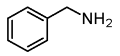
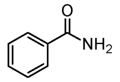
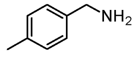
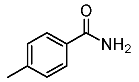
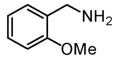
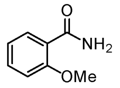
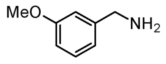
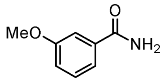
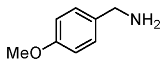
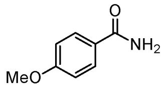
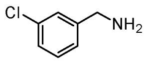
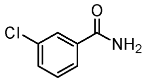
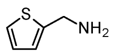
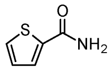
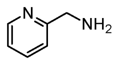
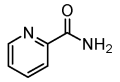
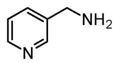
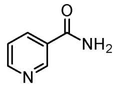
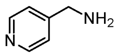
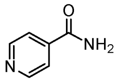
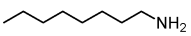
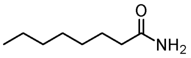
Table 1 Effect of catalysts on the transformation of **1a** to **2a**[a]



Entry	Catalyst	Yield (%) 2a	3a	4a	5a
1	OMS-2	83	3	1	<1
2	Activated MnO_2[b]	12	72	2	2
3	β-MnO_2	5	63	19	<1
4	β-MnOOH	<1	9	39	2
5	Birnessite-type MnO_2	6	29	10	<1
6[c]	$KMnO_4$	7	37	22	2
7[c]	$MnSO_4{\cdot}H_2O$	<1	<1	4	<1
8	$Ru(OH)_x/Al_2O_3$[d]	<1	80	13	2
9	RuHAP[e]	<1	46	10	1

[a] Reaction conditions: catalyst (100 mg), **1a** (0.5 mmol), aqueous ammonia (28 wt%, 100 μL), 1,4-dioxane (1 mL), 130 °C (bath temperature), air (6 atm), 3 h. Yields were determined by GC using naphthalene as an internal standard. [b] Commercially available (see the ESI). [c] Mn salt (0.5 mmol). [d] 100 mg, Ru: 5 mol%, prepared according to ref. 11. [e] 100 mg, Ru: 18 mol%, commercially available (see the ESI).

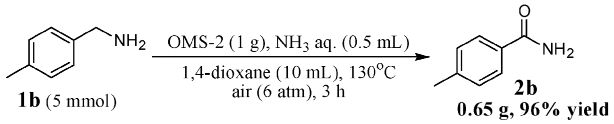
Table 2 Scope of the OMS-2 catalyzed transformation of primary amines to primary amides[a]

Entry	Substrate		Product		Time/h	Yield (%)
1		**1a**		**2a**	3	87
2[b]		**1a**		**2a**	3	82
3		**1b**		**2b**	3	98
4[b]		**1b**		**2b**	3	90
5		**1c**		**2c**	3	92
6		**1d**		**2d**	3	89
7		**1e**		**2e**	3	96
8		**1f**		**2f**	3	82
9		**1g**		**2g**	3	93
10		**1h**		**2h**	3	65
11		**1i**		**2i**	3	91
12[b]		**1i**		**2i**	3	84
13		**1j**		**2j**	3	90
14[c]		**1k**		**2k**	8	66

[a] Reaction conditions: OMS-2 (100 mg), substrate (0.5 mmol), aqueous ammonia (28 wt%, 50 μL), 1,4-dioxane (1 mL), 130 °C (bath temperature), air (6 atm). Yields were determined by GC using diphenyl or naphthalene as an internal standard. See Table S1 in the ESI for more details. [b] Reuse experiment. [c] OMS-2 (200 mg), aqueous ammonia (28 wt%, 200 μL), 160 °C.

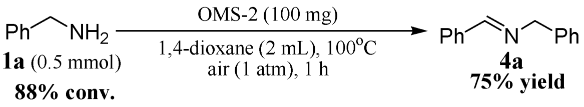
the transformation. Supported ruthenium catalysts such as $Ru(OH)_x/Al_2O_3$[11] and RuHAP (Ru on hydroxyapatite)§[12] gave **3a** as a major product without formation of **2a**.

The results of the OMS-2-catalyzed transformations of various primary amines to the corresponding primary amides under optimized conditions are summarized in Table 2. Transformations of benzylamine derivatives (**1a–1f**), which contain electron-donating as well as electron-withdrawing substituents at different positions, efficiently proceeded to give the corresponding benzamide derivatives in high yields. In the present transformation, the steric effect of substrates was not significant (**1c–1e**). Heteroatom-containing amines such as thiophene (**1g**) and pyridine (**1h–1j**) methylamines efficiently proceeded to afford the corresponding heteroaromatic amides. An aliphatic amine (**1k**) also gave the corresponding amide in moderate yield. The large scale transformation (10-fold scaled-up) was also effective; the transformation of **1b** efficiently proceeded without any decrease in the performance in comparison with the small-scale transformation given in Table 2, and **2b** was produced in 99% yield (by GC). OMS-2 was separated by filtration and washed with ethanol and acetone. Evaporation of the combined filtrate gave a crude product, followed by rinsing with a mixed solvent of *n*-hexane and acetone (20 : 1 v/v, *ca.* 5 mL), giving 0.65 g of **2b** (96% isolated yield, >99% purity by GC and NMR) [eqn (1)]. The observed catalysis was truly heterogeneous,¶ and the retrieved OMS-2 catalyst could be reused without a significant loss of its high catalytic performance (see entries 2, 4, and 12 in Table 2).

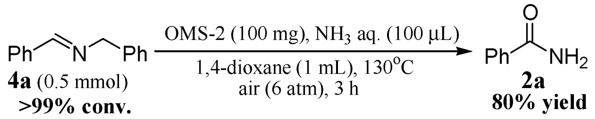


(1)

The reaction of **1a** at 100 °C without aqueous ammonia gave **4a** as a major product (75% yield) with small amounts of **3a** (6% yield) and **5a** (3% yield) [eqn (2)]. The alkylimine **4a** is possibly produced through hydrolytic decomposition of the aldimine intermediate to **5a**, followed by condensation with **1a** (Scheme 1). When the same reaction was carried out in the presence of aqueous ammonia (28 wt%, 100 μL), **2a**, **3a**, and **4a** were obtained in 10%, 21%, and 52% yields, respectively. In addition, **4a** was also converted into **2a** (major product) and **3a** in 80% and 18% yields, respectively, in the presence of OMS-2 and aqueous ammonia [eqn (3)].



(2)



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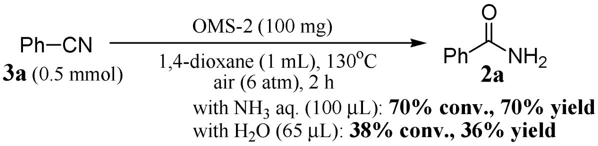
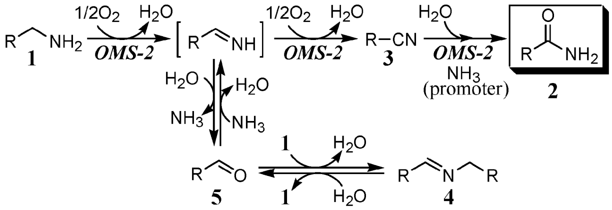


(4)



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

Therefore, aqueous ammonia plays a crucial role; even if the side-reaction to the corresponding alkylimine takes place during the transformation, the alkylimine (undesirable by-product) can efficiently be decomposed to the aldimine (desirable intermediate to the corresponding amides) in the presence of aqueous ammonia, resulting in the selective formation of the desired primary amides. Notably, the reaction rate for the hydration of **3a** with aqueous ammonia was larger than that with just water, as shown in eqn (4). We confirmed that the hydration did not proceed at all with aqueous ammonia alone (in the absence of OMS-2). Thus, the OMS-2-catalyzed nitrile hydration is also promoted by the presence of ammonia. The possible reaction pathway for the OMS-2-catalyzed transformation of primary amines to primary amides is summarized in Scheme 1.

In summary, OMS-2 could act as an efficient heterogeneous catalyst for synthesis of primary amides from primary amines in the presence of aqueous ammonia. The catalyst/product separation was very easy. The observed catalysis was truly heterogeneous, and OMS-2 could be reused without an appreciable loss of its high catalytic performance. The dual catalytic functions of OMS-2 make oxygenation of primary amines possible through the sequence of oxidative dehydrogenation and successive hydration. Aqueous ammonia also plays two important roles, that is, transforming back alkylimines (by-products) to aldimines (intermediates) and promotion of nitrile hydration.

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Notes and references

‡ Procedure for transformation of primary amines: OMS-2 (100–200 mg), amine (0.5 mmol), 1,4-dioxane (1 mL), aqueous ammonia (28 wt%, 50–200 µL) 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 130–160 °C (bath temperature) in 6 atm of air. For safety reasons, explosion-proof apparatus should be used for the reactions. The turnover numbers based on OMS-2 were 1.2–3.6 under standard reaction conditions. After the reaction was completed, the spent OMS-2 catalyst was separated by filtration, washed with ethanol and acetone, and dried at 150 °C for 1 h prior to being used for the reuse experiment (> 95% catalyst recovery). The products (amides) could simply be isolated by evaporation of volatiles (combined filtrate), followed by rinsing with a mixed solvent of *n*-hexane and acetone (20 : 1 v/v, *ca.* 5 mL). The products were confirmed by the comparison of their GC retention times, GC-MS spectra, and/or ^{1}H and ^{13}C NMR spectra with those of authentic data.

§ The step-by-step synthesis of nicotinamide (**2i**) from 3-picolylamine (**1i**) using RuHAP catalyst has been reported.[12]

¶ We confirmed that no further production of **2a** (amide) and **3a** (nitrile) proceeded after removal of OMS-2 by hot filtration for the transformation of **1a** and that no manganese species was detected in the filtrate (by inductively coupled plasma atomic emission spectroscopy analysis, below 0.003%).

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