Amide Synthesis

Heterogeneously Catalyzed Efficient Oxygenation of Primary Amines to Amides by a Supported Ruthenium Hydroxide Catalyst**

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*Dedicated to the Catalysis Society of Japan on the occasion of its 50th Anniversary*

Amides are a very important class of compounds in chemistry and biology that have been used as intermediates in peptide and protein synthesis, intensifiers of perfume, anti-block reagents, color pigments for inks, detergents, and lubricants.[1] Traditionally, amides have been synthesized by the reaction of activated carboxylic acid derivatives, such as acid chlorides, anhydrides, and esters with amines including ammonia[2] or by the acid-catalyzed rearrangements of ketoximes.[2] However, these traditional methods often produce vast amounts of toxic chemical by-products. Therefore, the development of efficient procedures for the synthesis of amides that avoid the wasteful use of stoichiometric reagents and/or acidic and basic media is highly desirable and still a great challenge in modern organic synthesis.[3]

In general, it is very difficult to oxygenate the α-methylene groups of amines to the corresponding amides.[4,5] For example, the stoichiometric oxidant RuO_4 (generated by the reaction of RuO_2 with $NaIO_4$) has been used alongside the protection of NH_2 groups.[5] To date, to our knowledge, no efficient catalytic oxygenation of amines to produce amides have been reported. Herein, we report the oxygenation of primary amines to primary amides by molecular oxygen (from air) in water, in the presence of an easily prepared, supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$.[6] This catalytic oxygenation has the following significant advantages from the standpoint of green chemistry:[7] 1) high atom efficiency and no production of toxic waste materials (theoretically, only water is formed as a by-product). Eq. (1)], 2) the use of air as the sole oxidant,

3) the use of water as a solvent, 4) applicability to various kinds of substrates, and 5) heterogeneous catalysis, allowing facile catalyst/product separation and reusability of the $Ru(OH)_x/Al_2O_3$ catalyst.

Initially, various metal hydroxide catalysts were prepared and applied to the transformation of benzylamine to benzamide in water using air as a sole oxidant (Table 1). The $Ru(OH)_x/Al_2O_3$ catalyst showed the highest catalytic activity and selectivity for the transformation of benzylamine to benzamide (Table 1, entries 1–9). Various ruthenium catalysts were also applied to the desired oxidation. $Ru(OH)_x/Al_2O_3$ again showed the highest catalytic activity and selectivity (Table 1, entries 1, 10–18). The catalyst precursor $RuCl_3 \cdot n\,H_2O$[4] showed lower catalytic activity than the $Ru(OH)_x/Al_2O_3$ catalyst and gave a mixture of benzamide, benzonitrile, benzaldehyde, and benzoic acid (Table 1, entry 14). Complexes such as $[Ru_3(CO)_{12}]$, $[RuCl_2(PPh_3)_3]$, $[\{RuCl_2(p\text{-cymene})\}_2]$, and $[Ru(acac)_3]$ were similarly ineffective (Table 1, entries 15–18). Heterogeneous ruthenium catalysts, such as Ru/C (Ru metal on activated carbon), RuHAP (Ru^{3+}-exchanged hydroxyapatite),[8] and anhydrous RuO_2 (bulk oxide) did not show high catalytic activity (Table 1, entries 11–13). Pretreatment of the catalyst with base significantly increased the activity (Table 1, entry 1 cf. entry 10), as a result of the generation of the active ruthenium hydroxide species on the surface of the Al_2O_3 support. Benzamide was not formed in the absence of any catalyst (Table 1, entry 21), in the presence of just Al_2O_3 (Table 1, entry 19) or with Al_2O_3 pretreated with an aqueous NaOH solution (Table 1, entry 20).

The scope of the $Ru(OH)_x/Al_2O_3$-catalyzed transformations of amines to amides was examined (Table 2). The transformation of benzylamines, which contain electron-donating as well as electron-withdrawing substituents, proceeded efficiently to give the corresponding benzamides in high yields (Table 2, entries 1–6). In the transformations of methoxybenzylamines, the lower reaction rate of *o*-methoxybenzylamine relative to *m*- and *p*-analogues indicates a steric effect (Table 2, entry 5 cf. entries 3 and 4). This fact suggests the coordination of substrates to the metal center on the $Ru(OH)_x/Al_2O_3$ catalyst and that the transformation proceeds through intramolecular attack by the ruthenium hydroxide species on the coordinated (activated) substrates. A similar steric effect was evident for the $Ru(OH)_x/Al_2O_3$-catalyzed hydration of nitriles.[6c] Furthermore, non-activated linear, branched, and cyclic aliphatic amines were converted into the corresponding aliphatic amides in high yields (Table 2, entries 7–10). Nicotinamide was obtained from picolylamine

$$R\diagdown NH_2 + O_2 \xrightarrow[\text{in water}]{Ru(OH)_x/Al_2O_3} R\diagup\!\!\!\overset{\displaystyle O}{C}\!\!\diagdown NH_2 + H_2O \qquad (1)$$
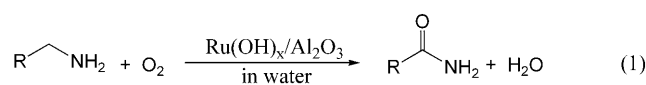
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Table 1: Transformation of benzylamine to benzamide using various catalysts.[a]

Entry	Catalyst	Yield [%]				
		1a	1b	1c	1d	1e
1	Ru(OH)$_x$/Al$_2$O$_3$	87	8	nd	3	nd
2	Ir(OH)$_x$/Al$_2$O$_3$	8	11	18	nd	nd
3	Au(OH)$_x$/Al$_2$O$_3$	3	3	28	3	3
4	Cu(OH)$_x$/Al$_2$O$_3$	1	2	25	nd	9
5	Rh(OH)$_x$/Al$_2$O$_3$	nd	1	3	nd	3
6	Pt(OH)$_x$/Al$_2$O$_3$	nd	nd	21	nd	10
7	Pd(OH)$_x$/Al$_2$O$_3$	nd	nd	15	nd	6
8	Co(OH)$_x$/Al$_2$O$_3$	nd	nd	5	nd	7
9	In(OH)$_x$/Al$_2$O$_3$	nd	nd	5	nd	7
10	RuCl$_x$/Al$_2$O$_3$[b]	9	25	2	nd	nd
11	Ru/C	28	20	1	3	nd
12	RuHAP	20	42	5	3	nd
13	RuO$_2$ anhydrous	nd	2	8	11	nd
14	RuCl$_3$·nH$_2$O	38	15	6	1	nd
15	[Ru(acac)$_3$]	25	22	7	nd	nd
16	[RuCl$_2$(PPh$_3$)$_3$]	11	21	18	2	nd
17	[{RuCl$_2$(p-cymene)}$_2$]	44	22	7	2	nd
18	[Ru$_3$(CO)$_{12}$]	26	30	9	nd	nd
19[c]	Al$_2$O$_3$	nd	nd	9	nd	2
20[c]	Al$_2$O$_3$[d]	nd	nd	2	nd	2
21	none	nd	nd	3	nd	4

[a] Reaction conditions: catalyst (metal: 5 mol%), **1** (0.25 mmol), water (1 mL), air (5 atm), 140°C, 6 h. Yields were based on **1** and determined by GC analysis. nd = not detected (<1%). [b] Prepared without base pretreatment (see Supporting Information). [c] 53 mg. [d] Pretreated with an aqueous NaOH solution (0.1 M).

(Table 2, entry 11). After the reaction was complete, the Ru(OH)$_x$/Al$_2$O$_3$ catalyst could be easily retrieved from the reaction mixture, by a simple filtration, and reused without

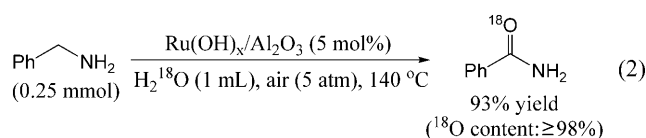significant loss of its catalytic performance (83% yield of isolated benzamide).

The transformation of *p*-methoxybenzylamine was carried out under the conditions described in Table 2, and Ru(OH)$_x$/Al$_2$O$_3$ and product were removed from the reaction mixture by filtration. Further substrate was then added to the filtrate and the mixture heated at 140°C. In this case, the corresponding amide was hardly formed. In addition, no ruthenium species were detected in the reaction solution (ICP-AES (inductively coupled plasma atomic emission spectroscopy) analysis, below the detection limit of 7 ppb), ruling out any contribution to the catalysis from ruthenium species that leached into the reaction solution, and confirming the catalysis to be truly heterogeneous.[9]

In the oxidation of benzylamine, the amount of molecular oxygen consumed was the same as those of benzamide produced and benzylamine consumed, in agreement with Equation (1). The Ru(OH)$_x$/Al$_2$O$_3$-catalyzed transformation of benzylamine in ^{18}O-labeled water (^{18}O content: ≥98%) led to the selective formation of ^{18}O-labeled benzamide in almost quantitative yield [Eq. (2)],

Table 2: Transformation of various primary amines to primary amides using Ru(OH)$_x$/Al$_2$O$_3$.[a]

Entry	Substrate	T [°C]	t [h]	Conversion [%][b]	Selectivity [%][b]				
					a	b	c	d	e
1	1	140	10	>99	94 (92)	3	nd	3	nd
2	2	140	10	>99	94 (82)	6	nd	nd	nd
3	3	140	10	>99	93 (89)	7	nd	nd	nd
4	4	140	10	>99	94 (87)	2	4	nd	nd
5	5	140	24	>99	90 (86)	10	nd	nd	nd
6	6	140	10	>99	98 (92)	nd	2	nd	nd
7	7	130	24	>99	94 (87)	1	nd	5	nd
8	8	140	24	>99	93 (86)	6	nd	1	nd
9	9	130	24	>99	84 (83)	5	nd	11	nd
10	10	160	24	>99	91 (77)	9	nd	nd	nd
11	11	140	24	>99	90 (90)	10	nd	nd	nd

[a] Reaction conditions for benzylamines and picolylamine (**1–6** and **11**): Ru(OH)$_x$/Al$_2$O$_3$ (5 mol% of Ru), amine (0.25 mmol), water (1 mL), air (5 atm); for alkyl amines (**7–10**): Ru(OH)$_x$/Al$_2$O$_3$ (5 mol% of Ru), amine (0.5 mmol), water (2 mL), air (5 atm). [b] Conversion and selectivity were determined by GC analysis. Values in the parentheses were the yields of isolated product. nd = not detected (<1%).

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$$Ph\diagup NH_2 \xrightarrow[\text{H}_2^{18}\text{O (1 mL), air (5 atm), 140 °C}]{\text{Ru(OH)}_x/\text{Al}_2\text{O}_3 \text{ (5 mol\%)}} Ph\overset{^{18}O}{\diagdown} NH_2 \qquad (2)$$

(0.25 mmol)

93% yield
(^{18}O content: ≥98%)

suggesting that the oxygen atom incorporated into benzamide originates from water. When the reaction of a secondary amine, *N*-phenylbenzylamine, was carried out under the conditions described in Table 1, the corresponding amide was not produced.[10] These facts show that water and the NH_2 group in primary amines are significant in the reaction mechanism for this transformation. In addition, the reaction profile for the oxygenation of benzylamine showed that, initially, benzonitrile was formed, followed by the formation of benzamide (See Supporting Information, Figure S1), indicating that the Ru(OH)$_x$/Al$_2$O$_3$-catalyzed transformation possibly proceeds by a tandem process of the oxidative dehydrogenation of amines to nitriles[6b,11] followed by hydration to produce the corresponding amides.[6c,11] Detailed mechanistic studies are now in progress.

In summary, Ru(OH)$_x$/Al$_2$O$_3$ acts as an efficient heterogeneous catalyst for the synthesis of primary amides by oxygenation of primary amines with water and air. The results presented herein open up a new avenue for the green synthesis of primary amide motifs, which completely avoids the use of conventional toxic stoichiometric reagents.

Experimental Section

The supported ruthenium hydroxide catalyst was prepared as follows:[6] Powdered Al$_2$O$_3$ (2.0 g) was pretreated at 550 °C for 3 h, vigorously stirred at room temperature with aqueous RuCl$_3$ (8.3 mM, 60 mL). After 15 min, the pH value of the solution was adjusted to 13.2 by addition of an aqueous sodium hydroxide solution (1M) and the resulting slurry stirred for 24 h. The solid was then removed by filtration, washed with a large amount of water, and dried in vacuo to afford the supported ruthenium hydroxide catalyst. The ruthenium content was 2.1–2.2 wt%. A general procedure for the synthesis of primary amides from primary amines was as follows. An amine (0.25–0.5 mmol), Ru(OH)$_x$/Al$_2$O$_3$ (Ru: 5 mol%), and water (1–2 mL) were placed in a Teflon vessel with a magnetic stir bar. The Teflon vessel was sealed inside an autoclave and the reaction was carried out at 130–160 °C (bath temperature) in 5 atm of air. After the reaction was complete, used Ru(OH)$_x$/Al$_2$O$_3$ catalyst was separated by filtration, washed with aqueous sodium hydroxide (0.1M) and water, and then dried in vacuo prior to being recycled. The amide products were isolated by column chromatography on silica gel using ethanol as an eluent. The products were confirmed by the comparison of their GC retention time, mass spectra, and ^{1}H and ^{13}C NMR spectra with those of authenticated data.

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[10] Under the conditions, the substrate was mostly consumed. *N*-Benzylideneaniline, aniline, and benzaldehyde were produced in 29, 26, and 33% yields, respectively.

[11] In contrast with the transformation in water, in common organic solvents such as toluene and *p*-xylene, nitriles were formed as major products.[6b] In addition, the hydration of nitriles to primary amides proceeded easily under similar conditions.[6c]