Catalytic Amide Synthesis

Efficient Hydration of Nitriles to Amides in Water, Catalyzed by Ruthenium Hydroxide Supported on Alumina**

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Hydration of nitriles to the corresponding amides is an important reaction in academia and industry because of their usefulness in a wide variety of applications such as intermediates in organic syntheses and as raw materials for engineering plastics, detergents, and lubricants.[1–4] For example, hydration of acrylonitrile produces annually more than 2×10^5 tons of acrylamide and is the most important technology for the production of this chemical.[4–6] Homogeneous hydration of nitriles is traditionally carried out with acids and bases such as H_2SO_4 and NaOH. However, carboxylic acids are formed as undesirable by-products by hydrolysis of the starting nitriles and amide products, especially under strongly basic conditions. In addition, many functional groups, for

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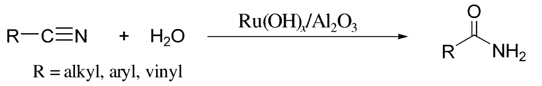
example, carbon–carbon double bonds, do not tolerate such forcing conditions, which results in decreased selectivity for amides. Only under carefully controlled conditions with one of equivalent water with respect to the nitrile could hydration of a nitrile to an amide be selectively catalyzed by H_2SO_4 to give the corresponding amide sulfate salt. Since a stoichiometric amount of ammonia (two equivalents with respect to amide sulfate) is required to isolate the free amide, ammonium sulfate is produced as waste. Therefore, the development of an efficient, intrinsically non-waste-producing catalytic hydration system is of great importance.

Many efficient methods that use microorganisms for enzymatic hydration of nitriles[5,6] or homogeneous complexes of transition metals such as cobalt,[7] copper,[8] molybdenum,[9] ruthenium,[10] rhodium,[11] palladium,[12,13] and platinum[14,15] have been reported. However, these systems have disadvantages: difficulty in catalyst/product separation and necessity of special handling of microorganisms and metal complexes. Despite the advantages of heterogeneous hydration, for example, easy catalyst/product separation and recycling, only a few examples have been reported. Unactivated neutral alumina (stoichiometric hydration without water),[16] Raney copper,[4] KF/Al_2O_3,[17] KF/phosphate,[18] MnO_2/SiO_2,[19,20] Ru-substituted hydroxyapatite ($(RuCl)_2Ca_8(PO_4)_6(OH)_2$),[21] and $NaNO_3$ on fluoroapatite ($NaNO_3$/FAP)[22] are examples. However, turnover numbers are still very low (≤ 6) or stoichiometric, catalysts can not be reused, and/or the type of nitrile is limited. In this context, efficient, widely usable, reusable catalysts are so far unknown, although heterogeneous hydration systems are environmentally and technologically the most desirable.[23–25] Herein we report that the easily prepared, inexpensive supported ruthenium hydroxide catalyst $Ru(OH)_x/Al_2O_3$[26–28] is effective for the hydration of various nitriles to amides in water[29] under conditions that are entirely free of explosive, hazardous, or carcinogenic organic solvents, even in the workup steps [Eq. (1)].



(1)

Table 1: Hydration of benzonitrile to benzamide with various catalysts.[a]

Entry	Catalyst	Conversion of benzonitrile [%]	Selectivity to benzamide [%]	Rate × 10^3 [M min^{-1}]
1	$Ru(OH)_x/Al_2O_3$	47	> 99	1.74
2[b]	$(RuCl)_2Ca_8(PO_4)_6(OH)_2$	7	> 99	0.10
3	$Ru(OH)_3 \cdot n\,H_2O$	7	> 99	0.24
4	RuO_2	2	> 99	0.06
5	$RuCl_3 \cdot n\,H_2O$	28	> 99	0.79
6	[Ru(acac)$_3$]	no reaction	–	0.00
7	[$RuCl_2(PPh_3)_3$]	no reaction	–	0.00
8	[$RuCl_2$(DMSO)$_4$]	no reaction	–	0.00
9	[{$RuCl_2$(*p*-cymene)}$_2$]	no reaction	–	0.00
10	[$RuCl_2$(bpy)$_2$]	no reaction	–	0.00
11[c]	Al_2O_3	no reaction	–	0.00
12[c]	Al_2O_3 treated with NaOH	no reaction	–	0.00
13	NaOH	3	> 99	0.05
14	H_2SO_4	no reaction	–	0.00
15	None	no reaction	–	0.00

[a] Reaction conditions: benzonitrile (1 mmol), catalyst (2 mol%), water (3 mL), 403 K, 3 h. Conversion and selectivity were determined by GC with an internal standard. [b] Prepared according to the procedure in ref. [20]. [c] 0.2 g. Wilgus et al.[16] reported that unactivated alumina could act as a stoichiometric reagent (two hydroxy functions for hydration of one nitrile molecule) for the hydration of nitriles in the absence of water. If the alumina used can act as a stoichiometric reagent in the same way, the maximum yield is estimated to be ca. 5%. However, alumina was completely inactive under these conditions, probably because of the presence of water in the present system.

First, the catalytic activity and selectivity for the hydration of benzonitrile to benzamide in water at 403 K were compared with those of a variety of ruthenium catalysts (Table 1). Hydration did not proceed in the absence of catalyst. γ-Al_2O_3 and γ-Al_2O_3 treated with NaOH did not show any catalytic activity under the present reaction conditions. Among the ruthenium catalysts tested, $Ru(OH)_x/Al_2O_3$ had the highest catalytic activity and selectivity for the hydration of benzonitrile to benzamide, and no benzoic acid could be detected. Under the same conditions, it was confirmed that $Ru(OH)_x/Al_2O_3$ did not catalyze the hydrolysis and dehydration of benzamide. The yield of benzamide was higher than those of heterogeneous catalysts such as anhydrous RuO_2, $Ru(OH)_3 \cdot n\,H_2O$, and $(RuCl)_2Ca_8(PO_4)_6(OH)_2$, and of homogeneous ruthenium catalysts such as $RuCl_3 \cdot n\,H_2O$ and [$RuCl_2(PPh_3)_3$] 18-Electron ruthenium complexes such as [$RuCl_2$(dmso)$_4$], [$RuCl_2$(bpy)$_2$], and [{$RuCl_2$(*p*-cymene)}$_2$] were completely inactive.

When the hydration of benzonitrile was carried out at 413 K (see Experimental Section), a quantitative yield of benzamide was obtained after 6 h, as determined by GC analysis. The $Ru(OH)_x/Al_2O_3$ catalyst could be easily separated from the reaction mixture by filtration (Figure 1 a and b). After separation of the catalyst, the filtrate was cooled to 273 K, and analytically pure white crystals of benzamide appeared (Figure 1 c). The crystals were isolated from the water solvent by filtration or decantation in 90% yield. Recovered $Ru(OH)_x/Al_2O_3$ could be reused at least twice for the hydration of benzonitrile without appreciable loss of catalytic performance (entries 1–3 in Table 2). After the catalytic hydration of benzonitrile was completed under the conditions in Table 2, the reaction mixture was filtered to remove the $Ru(OH)_x/Al_2O_3$ and product amide. It was confirmed that no ruthenium was present in the filtrate by inductively coupled plasma atomic emission spectroscopy (ICP-AES; detection limit of 7 ppb). Then, benzonitrile (1 mmol) was again added to the filtrate and the solution was heated to 413 K. No conversion of benzonitrile was observed. These results show that any contribution to the observed catalysis from ruthenium species that leached into the reaction solution can be ruled out, and the observed catalysis is truly heterogeneous in nature.[30]

The scope of the present $Ru(OH)_x/Al_2O_3$ catalyst system with regard to various kinds of nitriles was examined. The results are summarized in Table 2. $Ru(OH)_x/Al_2O_3$ has high catalytic activity for hydrations of activated, unactivated, and

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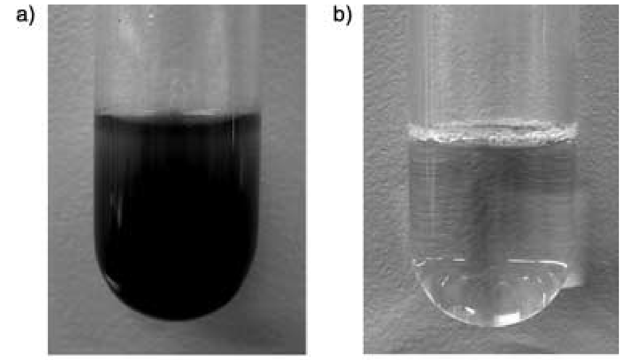
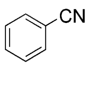
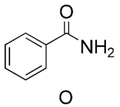
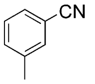
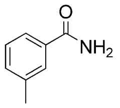
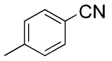
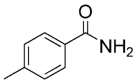
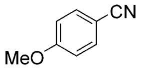
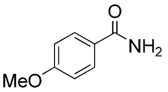
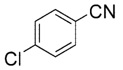
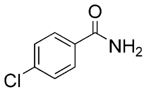
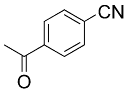
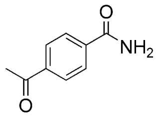
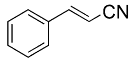
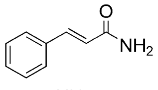
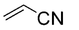
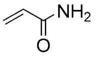
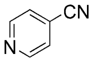
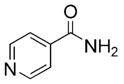
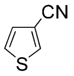
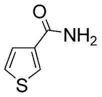
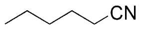
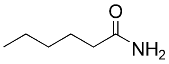
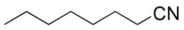
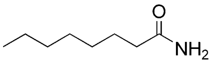



Figure 1. Hydration of benzonitrile to benzamide. a) Reaction mixture, b) filtrate after removal of Ru(OH)$_x$/Al$_2$O$_3$ by filtration at 363 K, and c) benzamide crystals obtained after cooling the filtrate.

heterocyclic nitriles in water. Benzonitriles were smoothly hydrated to give the corresponding benzamides in excellent yields (entries 1–8). The rates were not much influenced by the electronic effects of the substituents on the aromatic ring of benzonitriles. A larger scale experiment (tenfold scale-up, 0.4 mol% Ru) for benzonitrile at 423 K showed a turnover frequency (TOF) of 13 h^{-1}, and the turnover number (TON) reached 234. These values are the highest of those reported for the heterogeneous hydration of benzonitrile so far: KF/Al$_2$O$_3$ (TOF 0.2 h^{-1}, TON 0.5 based on KF),[17] KF/phosphate (0.2 h^{-1}, 0.9 based on KF),[18] MnO$_2$/SiO$_2$ (0.2 h^{-1}, 0.7 based on MnO$_2$),[19] (RuCl)$_2$Ca$_8$(PO$_4$)$_6$(OH)$_2$ (0.2 h^{-1}, 6 based on Ru),[21] and NaNO$_3$ on fluoroapatite (NaNO$_3$/FAP; 2 h^{-1}, 6 based on NaNO$_3$).[22] Hydration of the α,β-unsaturated nitrile cinnamonitrile proceeded only at the cyano group to afford the corresponding α,β-unsaturated amide (entry 9). Notably, the industrially important hydration of acrylonitrile proceeded with 2.3 mol% of Ru(OH)$_x$/Al$_2$O$_3$ at 393 K to afford a quantitative yield of acrylamide. Neither hydration of the carbon–carbon double bond nor polymerization of acrylonitrile and/or acrylamide occurred (entry 10). Ru(OH)$_x$/Al$_2$O$_3$ successfully catalyzed the hydration of various nitriles containing heteroatoms such as oxygen, nitrogen, and sulfur to the corresponding amides in high yields (entries 6, 8, 11, and 12). The less reactive aliphatic nitriles could also be hydrated to the corresponding aliphatic amides (entries 13 and 14).

In the hydration of toluonitriles, the lower reaction rate of *o*-tolunitrile (79% yield after 24 h) relative to *m*- and *p*-

Table 2: Hydration of various nitriles catalyzed by Ru(OH)$_x$/Al$_2$O$_3$.[a]

Entry	Substrate	Product	*t* [h]	Conversion [%]	Selectivity [%]
1			6	99	> 99
2[b]			6	99	> 99
3[b]			6	99	> 99
4			6	96	> 99
5			6	> 99	99
6			6	> 99	> 99
7			6	> 99	> 99
8			6	> 99	99
9			5	> 99	99
10[c]			24	> 99	> 99
11			6	91	98
12			6	> 99	> 99
13[d]			10	92	99
14[d]			24	91	97

[a] Reaction conditions: nitrile (1 mmol), Ru(OH)$_x$/Al$_2$O$_3$ (4 mol% Ru), water (3 mL), 413 K. The conversion and selectivity were determined by GC with an internal standard. Traces of the corresponding carboxylic acids, formed by hydrolysis of starting nitriles or amide products, were found as by-products in some cases. Carbon balance for each reaction was greater than 95%. [b] These experiments used a recycled catalyst: 1st reuse (entry 2), 2nd reuse (entry 3). The reaction conditions were the same as in entry 1. The initial rates for the recycle runs were the same as that for the first run with fresh catalyst. [c] Reaction conditions: acrylonitrile (10 mmol), Ru(OH)$_x$/Al$_2$O$_3$ (2.3 mol% Ru), water (20 mL), 393 K. The conversion and selectivity were determined by ^{1}H NMR spectroscopic analysis with an internal standard. [d] The reaction was carried out at 403 K.

toluonitrile indicates a steric effect. This observation strongly suggests that nitriles coordinate to the ruthenium center on the surface of $Ru(OH)_x/Al_2O_3$ and that hydration of nitriles proceeds by intramolecular attack of a ruthenium hydroxide species on the coordinated nitrile (steps 1 and 2). When the hydration of *o*-, *m*-, and *p*-toluonitriles was catalyzed by NaOH, the reactivity did not vary. In addition, the ρ value for NaOH-catalyzed hydration in water (external attack of water on the nitrile carbon atom catalyzed by free OH^-) should be positive, in contrast to the negative ρ value for the present $Ru(OH)_x/Al_2O_3$-catalyzed hydration (see below). The above observations show that free OH^- is not the active species. It was reported that cobalt(III) hydroxide undergoes coordination of a nitrile and that this favors nucleophilic attack of the metal hydroxide on the proximal nitrile carbon atom rather than on the distal carbon–carbon double bond, hydration of which is thus prevented. These results are in agreement with those for the present system and support coordination of a nitrile to Ru^{n+} (**II**). Competitive hydration of benzonitrile and *p*-substituted benzonitriles was carried out in water at 413 K. The order of reactivity was *p*-OCH_3 ($k_X/k_H = 1.28$) > *p*-CH_3 (1.01) > *p*-H (1.00) > *p*-Cl (0.79) > *p*-$COCH_3$ (0.70). The good linearity of Hammett plots ($\lg(k_X/k_H)$ versus Brown–Okamoto σ^+, see the Supporting Information) suggests that the present hydration proceeds with a single mechanism. The slope of the linear line gave a Hammett ρ value of -0.21. The negative Hammett ρ value might be due to the formation of a positively charged transition state at the carbon atom adjacent to the phenyl ring.

On the basis of these results, we propose the possible mechanism given in Figure 2 for the $Ru(OH)_x/Al_2O_3$-catalyzed hydration of nitriles. This catalytic hydration can be divided into steps 1–3: Initially, coordination of a nitrile to the ruthenium center proceeds to form **II** (step 1). Then, intramolecular nucleophilic attack of hydroxide species in **II** on the nitrile carbon atom takes place to afford the ruthenium iminolate species **III** or ruthenium η^2-amidate species **IV** (step 2). Step 2 may include the formation of a carbocation-type transition state. Regeneration of ruthenium hydroxide species **I** proceeds by the ligand exchange between water and **III** or **IV** together with the formation of the amide product (step 3).

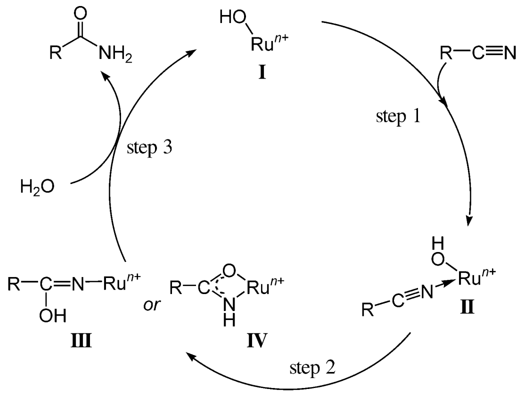


Figure 2. A proposed reaction mechanism for the $Ru(OH)_x/Al_2O_3$-catalyzed hydration of nitriles.

Kinetic studies revealed a zero-order dependence of the reaction rate on the concentration of water and a first-order dependence on both the amount of $Ru(OH)_x/Al_2O_3$ and the nitrile concentration (Supporting Information). The Arrhenius plots (observed rate constant k_{obs} versus T^{-1}) are also shown in the Supporting Information (383–423 K). Good linearity was observed for the Arrhenius plots, which gave the following activation parameters: $E_a = 71.5\ \text{kJ mol}^{-1}$, $\Delta H^{\ddagger}_{413\,K} = 68.1\ \text{kJ mol}^{-1}$, $\Delta S^{\ddagger}_{413\,K} = -155.3\ \text{J mol}^{-1}\text{K}^{-1}$, and $\Delta G^{\ddagger}_{413\,K} = 132.2\ \text{kJ mol}^{-1}$. The activation energy E_a is lower than that of hydration with H_2SO_4 ($E_a = 150.7\ \text{kJ mol}^{-1}$).[31] The hydration rate was independent of the content of D_2O (Supporting Information). These results show that O–H bond dissociation (step 3) is not included in the rate-limiting step under the present conditions.[32] The value of the activation entropy $\Delta S^{\ddagger}_{413\,K}$ suggests that a bimolecular transition state (step 2) is included in the rate-limiting step.[32]

In summary, $Ru(OH)_x/Al_2O_3$ can act as a heterogeneous catalyst for the hydration of nitriles in water. The hydration of both activated and unactivated nitriles can be performed with high conversion and selectivity to give the corresponding amides. Furthermore, catalyst/product separation is easy, and $Ru(OH)_x/Al_2O_3$ is recyclable.

Experimental Section

The $Ru(OH)_x/Al_2O_3$ catalyst was prepared by the procedure reported previously.[26–28] A typical $Ru(OH)_x/Al_2O_3$-catalyzed hydration was carried out as follows: Benzonitrile (5 mmol), $Ru(OH)_x/Al_2O_3$ (4 mol%), and water (15 mL) were placed in a Teflon vessel with a magnetic stir bar. Next, the Teflon vessel was quickly inserted into an autoclave, and then the autoclave was heated at 413 K (bath temperature). The reaction rates were not affected by stirring rates from 500 to 2000 rpm. After 6 h, benzamide was formed in > 99% yield, as determined by GC analysis. $Ru(OH)_x/Al_2O_3$ was removed by filtration at 363 K. The filtrate was cooled to 273 K, and white crystals precipitated from the filtrate. The crystalline product was collected by simple filtration and dried in vacuo to give analytically pure benzamide in 90% yield. The recovered $Ru(OH)_x/Al_2O_3$ was further washed with hot water and an aqueous NaOH solution (pH 13) and then dried in vacuo before reuse.

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Keywords: amides · cyanides · heterogeneous catalysis · hydration · ruthenium

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