Heterogeneous Catalysis

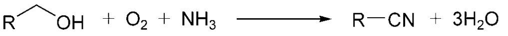
DOI: 10.1002/anie.200900418

Catalytic Oxidative Synthesis of Nitriles Directly from Primary Alcohols and Ammonia**

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

Nitriles are a very important class of compounds in chemistry as well as biology, and they are widely used in the production of pharmaceuticals, agricultural chemicals, and fine chemicals.[1] Aromatic nitriles can be synthesized by the Sandmeyer reaction and gas-phase ammoxidation in laboratories and industry, respectively.[1] The nucleophilic substitution of alkyl halides with a stoichiometric amount of hazardous inorganic cyanides is a general procedure for the synthesis of alkylnitriles and is frequently accompanied by the elimination of hydrogen halides especially in the case of bulky alkyl halides.[1] Unsaturated nitriles can be synthesized by the Wittig reaction of the corresponding aldehydes with cyanoalkyl phosphates.[1] The above antiquated procedures often produce large amounts of inorganic salts as waste, which is not desirable from the standpoint of green chemistry.[2] Therefore, the development of new environmentally friendly procedures is very important. The transition-metal-catalyzed dehydration of aldoximes or amides under neutral conditions is a good candidate for green nitrile synthesis.[3] Recently, excellent examples for the catalytic dehydration have been reported.[3]

An alternative approach to the synthesis of nitriles is the oxidative reaction directly from alcohols and ammonia.[4,5] The direct synthesis is very difficult, and reported procedures require the use of stoichiometric amounts of reactive oxidants and reagents such as I_2,[4a,b] 1,3-diiodo-5,5-dimethylhydantoin (DIH),[4a,c] $NiSO_4/K_2S_2O_8/NaOH$,[4d] $MnO_2/MgSO_4$,[4e] and $(Bu_4N)_2S_2O_8/Cu(HCO_2)_2/Ni(HCO_2)_2/KOH$.[4f] Therefore, if the catalytic oxidative synthesis of nitriles directly from alcohols and ammonia using molecular oxygen (or air) as the sole oxidant could be realized, it would be a desirable transformation because of its high atom efficiency and the lack of toxic waste (theoretically, only water is formed as a by-product [Eq. (1)].



(1)

We have recently reported the efficient aerobic oxidative dehydrogenation of alcohols[6a,b] and amines,[6a,c] and the catalytic oxygenation of amines to amides[6d] catalyzed by an easily prepared supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$. During the course of our investigations, we discovered that the liquid-phase aerobic oxidative synthesis of nitriles directly from alcohols and ammonia can be realized in the presence of the supported ruthenium hydroxide catalyst.[7] Various kinds of aromatic and heteroaromatic primary alcohols can be converted into the corresponding nitriles in high to excellent yields, and the observed catalysis is heterogeneous.[8]

Initially, various kinds of supported metal hydroxide catalysts and ruthenium-based catalysts were applied to the transformation of 2-naphthalenemethanol (**1a**) into 2-naphthonitrile (**2a**) in a solution of ammonia in THF (0.45 M, NH_3/**1a** = 1.8) using air as an oxidant (Table 1). Among various catalysts examined, $Ru(OH)_x/Al_2O_3$ showed the highest catalytic activity and selectivity (Table 1, entry 1). Ruthenium complexes such as [Ru(acac)$_3$], [$RuCl_2(PPh_3)_3$], [{$RuCl_2$(*p*-cymene)}$_2$], and [$Ru_3(CO)_{12}$] were not effective for the present transformation (Table 1, entries 10–13). Similarly, heterogeneous ruthenium catalysts such as Ru/C (Ru metal on activated carbon), RuHAP (Ru^{3+}-exchanged hydroxyapatite),[9] and RuO_2 anhydrous (bulk oxide) did not show high catalytic activity (Table 1, entries 6–8). Among the catalysts examined, only $Ru(OH)_x/Al_2O_3$ gave the desired nitrile **2a** in high yield. Under the present conditions, no reaction proceeded in the absence of the catalyst (Table 1, entry 15), or in the presence of just Al_2O_3 (Table 1, entry 14) or the catalyst precursor of $RuCl_3 \cdot nH_2O$ (Table 1, entry 9).

To verify whether the observed catalysis is derived from solid $Ru(OH)_x/Al_2O_3$ or leached ruthenium species, the transformation of **1a** into **2a** was carried out under the conditions described in Table 1 and the $Ru(OH)_x/Al_2O_3$ catalyst was removed from the reaction mixture by filtration at approximately 30 % conversion of **1a**. After removal of the $Ru(OH)_x/Al_2O_3$ catalyst, a solution of ammonia in THF (1 mL, 0.45 M) was added to the filtrate and the solution was again heated at 120 °C under 6 atmospheres of air. In this case, no reaction proceeded. It was confirmed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) that no ruthenium was in the filtrate (below 0.03 %). All these facts rule out any contribution to the observed catalysis from ruthenium species that leached into the reaction solution, and the observed catalysis is intrinsically heterogeneous.[10]

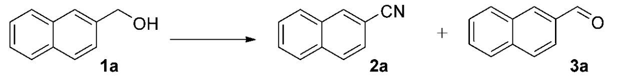
---

[*] T. Oishi, Dr. K. Yamaguchi, 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)
Fax: (+81) 3-5841-7220
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp
Dr. K. Yamaguchi, Prof. Dr. N. Mizuno
Core Research for Evolutional Science and Technology (CREST)
(Japan) Science and Technology Agency
4-1-8 Honcho, Kawaguchi, Saitama, 332-0012 (Japan)

[**] This work was supported in part by the Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), the Core Research for Evolutional Science and Technology (CREST) program of the Japan Science and Technology Agency (JST), and Grants-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900418.

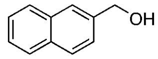
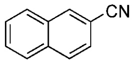
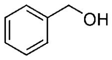
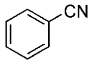
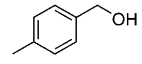
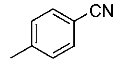
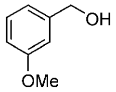
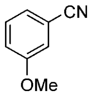
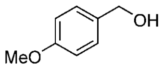
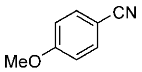
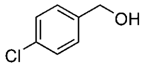
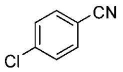
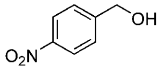
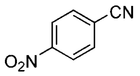
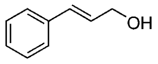
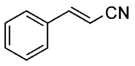
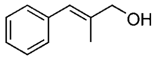
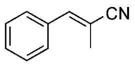
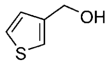
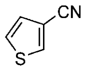
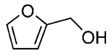
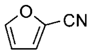
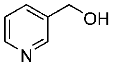
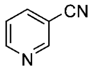
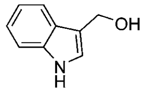
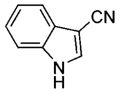
Table 1: Transformation of 2-naphthalenemethanol (**1a**) into 2-naphthonitrile (**2a**).[a]



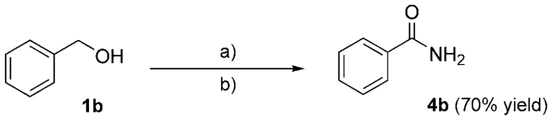
Entry	Catalyst	Yield [%][b]	
		2a	**3a**
1	$Ru(OH)_x/Al_2O_3$	74	17
2	$Au(OH)_x/Al_2O_3$	10	29
3	$Pd(OH)_x/Al_2O_3$	n.d.	1
4	$Pt(OH)_x/Al_2O_3$	n.d.	5
5	$Rh(OH)_x/Al_2O_3$	n.d.	2
6	Ru/C	22	30
7	RuHAP	4	11
8	RuO_2 anhydrous	n.d.	n.d.
9	$RuCl_3 \cdot nH_2O$	n.d.	n.d.
10	$[Ru(acac)_3]$	n.d.	n.d.
11	$[RuCl_2(PPh_3)_3]$	2	4
12	$[\{RuCl_2(p\text{-cymene})\}_2]$	2	6
13	$[Ru_3(CO)_{12}]$	n.d.	3
14[c]	Al_2O_3	n.d.	2
15	none	n.d.	n.d.

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (metal: 0.05 mmol), 0.45 M solution of ammonia in THF (2 mL, NH_3/**1a** = 1.8), air (6 atm), 120 °C, 1 h. [b] Yields were determined by GC and ^1H NMR analyses. n.d. = not detected (< 1 %). [c] 200 mg. acac = acetylacetonate.

Table 2: Scope of the $Ru(OH)_x/Al_2O_3$-catalyzed transformation of primary alcohols into nitriles.[a]

Entry	Substrate		*t* [h]	Product		Yield [%][b]
1		**1a**	3		**2a**	96 (91)
2		**1b**	5		**2b**	72
3		**1c**	5		**2c**	80
4		**1d**	5		**2d**	85
5		**1e**	5		**2e**	83
6		**1f**	5		**2f**	92 (82)
7		**1g**	6		**2g**	82
8		**1h**	5		**2h**	82
9		**1i**	5		**2i**	76
10		**1j**	7		**2j**	80
11		**1k**	7		**2k**	67
12		**1l**	6		**2l**	81
13[c]		**1m**	12		**2m**	65

[a] Reaction conditions: primary alcohol (0.5 mmol), catalyst (Ru: 0.05 mmol), 0.45 M THF solution of ammonia (2 mL, NH_3/alcohol = 1.8), air (6 atm), 120 °C. [b] Yields were determined by GC and ^1H NMR analyses (also see Table S1 in the Supporting Information). Values in the parentheses are the yields of the isolated products. [c] 130 °C.

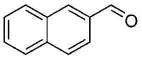
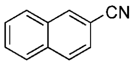
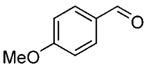
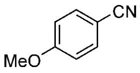
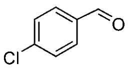
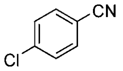
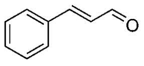
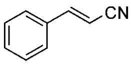
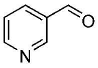
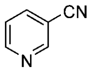


Scheme 1. One-pot synthesis of benzamide. Reaction conditions: a) alcohol (0.5 mmol), catalyst (Ru: 0.05 mmol), 0.45 M solution of ammonia in THF (2 mL, NH_3/alcohol = 1.8), air (6 atm), 120 °C, 5 h; b) addition of water (2 mL), Ar (5 atm), 150 °C, 24 h.

Next, the scope of the present $Ru(OH)_x/Al_2O_3$-catalyzed reaction with regard to various kinds of structurally diverse primary alcohols was examined. $Ru(OH)_x/Al_2O_3$ showed high catalytic activities for the transformation of benzylic, allylic, and heteroatom-containing alcohols, as summarized in Table 2. The transformation of benzylic alcohols **1a**–**1g**, which contain electron-donating as well as electron-withdrawing substituents, efficiently proceeded to afford the corresponding aromatic nitriles in high yields (Table 2, entries 1–7). In the transformation of allylic alcohols **1h** and **1i**, the corresponding unsaturated nitriles could be obtained without isomerization, hydrogenation, and hydration of the double bonds (Table 2, entries 8 and 9). Also, heteroatom-containing alcohols **1j**–**1m** were converted into the corresponding nitriles in high yields (Table 2, entries 10–13). Additionally, the present $Ru(OH)_x/Al_2O_3$ catalyst could be employed for the one-pot synthesis of amides through the oxidative synthesis of nitriles from alcohols and ammonia and the subsequent hydration of the nitriles formed.[11] For example, the corresponding amide **4b** could be obtained in 70 % yield for the transformation of **1b** under the conditions described in Scheme 1. After the reaction was completed, the $Ru(OH)_x/Al_2O_3$ catalyst could easily be retrieved from the reaction mixture by filtration (or centrifugation). In the recycling experiment using the retrieved catalyst, an 81 % yield of **2a** was obtained from the transformation of **1a** by using the reaction conditions described in Table 2.

The reaction profile for the transformation of **1a** into **2a** showed that the corresponding aldehyde **3a** was initially produced, followed by the formation of **2a**. In addition, $Ru(OH)_x/Al_2O_3$ showed high catalytic performance for the oxidative transformation of various kinds of structurally diverse aldehydes including benzylic, allylic, heteroatom-containing, and aliphatic aldehydes in the presence of ammonia and air (Table 3). Thus, the present $Ru(OH)_x/Al_2O_3$-catalyzed transformation possibly proceeds through three sequential reactions, that is, the aerobic oxidative dehydrogenation of alcohols to aldehydes,[6a,b] the dehydrative condensation of the aldehydes and ammonia into imines,[12] and the aerobic oxidative dehydrogenation of the imines to produce the corresponding nitriles.[6b,c] A possible reaction mechanism for the present transformation is given in Scheme S1 in the Supporting Information.

Table 3: Scope of the $Ru(OH)_x/Al_2O_3$-catalyzed transformation of aldehydes into nitriles.[a]

Entry	Substrate		t [h]	Product		Yield [%][b]
1		**3a**	3		**2a**	93
2		**3e**	5		**2e**	85
3		**3f**	5		**2f**	90
4		**3h**	5		**2h**	82
5		**3l**	6		**2l**	76
6[c]	$CH_3(CH_2)_6CHO$	**3n**	16	$CH_3(CH_2)_6CN$	**2n**	71
7[c]	$CH_3(CH_2)_8CHO$	**3o**	16	$CH_3(CH_2)_8CN$	**2o**	81

[a] Reaction conditions: aldehyde (0.5 mmol), catalyst (Ru: 0.05 mmol), 0.45 M THF solution of ammonia (2 mL, NH_3/aldehyde = 1.8), air (6 atm), 120 °C. [b] Yields were determined by GC and ^1H NMR analyses (also see Table S2 in the Supporting Information). [c] 130 °C.

In conclusion, $Ru(OH)_x/Al_2O_3$ served as an efficient heterogeneous catalyst for the aerobic oxidative synthesis of nitriles directly from alcohols (or aldehydes) and ammonia. Furthermore, the one-pot synthesis of amides could also be realized. The observed catalysis was truly heterogeneous. The results demonstrated herein will open up a new avenue for the green nitrile synthesis, which avoids the use of the conventional hazardous reagents, such as inorganic cyanides, in stoichiometric amounts.

Experimental Section

General procedure: An alcohol (or an aldehyde) (0.5 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 0.05 mmol), and a solution of ammonia in THF (2 mL, 0.45 M, NH_3/substrate = 1.8) were placed in a Teflon vessel with a magnetic stir bar. The Teflon vessel was placed inside an autoclave, and the reaction was carried out at 120–130 °C (bath temperature) under 6 atm of air. The reaction rates were not affected by stirring rates ranging from 500 to 1000 rpm. After the reaction was completed, the used $Ru(OH)_x/Al_2O_3$ catalyst was removed by filtration (or centrifugation), washed with acetone, an aqueous solution of NaOH (0.1 M), and water, and then dried in vacuo prior to being recycled. The product nitrile was isolated after purification using silica gel column chromatography (diethyl ether). The products were confirmed by the comparison of their GC retention times, GC mass spectra, and ^1H and ^{13}C NMR spectra with those of authentic samples.

Received: January 22, 2009

Keywords: alcohols · ammonia · heterogeneous catalysis · nitriles · ruthenium

---

[1] a) A. J. Fatiadi in *Preparation and Synthetic Applications of Cyano Compounds* (Eds.: S. Patai, Z. Rappaport), Wiley, New York, **1983**; b) J. S. Miller, J. L. Manson, *Acc. Chem. Res.* **2001**, *34*, 563; c) P. Magnus, D. A. Scott, M. R. Fielding, *Tetrahedron Lett.* **2001**, *42*, 4127; d) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed., Wiley, Hoboken, NJ, **2007**.

[2] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, London, **1998**; b) R. A. Sheldon, *Green Chem.* **2000**, *2*, G1; c) P. T. Anastas, L. B. Bartlett, M. M. Kirchhoff, T. C. Williamson, *Catal. Today* **2000**, *55*, 11.

[3] a) K. Ishihara, Y. Furuya, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 3109; *Angew. Chem. Int. Ed.* **2002**, *41*, 2983; b) P. Yan, P. Batamack, G. K. S. Prakash, G. A. Olah, *Catal. Lett.* **2005**, *101*, 141; c) S. H. Yang, S. Chang, *Org. Lett.* **2001**, *3*, 4209; d) E. Choi, C. Lee, Y. Na, S. Chang, *Org. Lett.* **2002**, *4*, 2369; e) K. Yamaguchi, H. Fujiwara, Y. Ogasawara, M. Kotani, N. Mizuno, *Angew. Chem.* **2007**, *119*, 3996; *Angew. Chem. Int. Ed.* **2007**, *46*, 3922.

[4] a) S. Iida, H. Togo, *Tetrahedron* **2007**, *63*, 8274; b) N. Mori, H. Togo, *Synlett* **2005**, 1456; c) S. Iida, H. Tago, *Synlett* **2007**, 407; d) S. Yamazaki, Y. Yamazaki, *Chem. Lett.* **1990**, 571; e) G. D. McAllister, C. D. Wilfred, R. J. K. Taylor, *Synlett* **2002**, 1291; f) F.-E. Chen, Y.-Y. Li, H.-Q. Jia, *Synthesis* **2002**, 1804.

[5] Very recently, excellent examples for the homogeneous transition-metal-catalyzed direct synthesis of amines[5a] and amides[5b] from alcohols using gaseous ammonia (typically 7.5 atm) and liquid ammonia, respectively, have been reported: a) C. Gunanathan, D. Milstein, *Angew. Chem.* **2008**, *120*, 8789; *Angew. Chem. Int. Ed.* **2008**, *47*, 8661; b) T. Zweifel, J.-V. Naubron, H. Grützmacher, *Angew. Chem.* **2009**, *121*, 567; *Angew. Chem. Int. Ed.* **2009**, *48*, 559.

[6] a) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2002**, *114*, 4720; *Angew. Chem. Int. Ed.* **2002**, *41*, 4538; b) K. Yamaguchi, N. Mizuno, *Chem. Eur. J.* **2003**, *9*, 4353; c) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2003**, *115*, 1518; *Angew. Chem. Int. Ed.* **2003**, *42*, 1480; d) J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2008**, *120*, 9389; *Angew. Chem. Int. Ed.* **2008**, *47*, 9249; e) K. Yamaguchi, T. Koike, J. W. Kim, Y. Ogasawara, N. Mizuno, *Chem. Eur. J.* **2008**, *14*, 11480.

[7] The gas-phase ammoxidations of small alcohols (reaction temperature ≥350 °C) have been reported: a) B. M. Reddy, B. Manohar, *J. Chem. Soc. Chem. Commun.* **1993**, 234; b) S. J. Kulkarni, R. R. Rao, M. Subrahmanyam, A. V. R. Rao, *J. Chem. Soc. Chem. Commun.* **1994**, 237.

[8] The development of easily recovered and recycled heterogeneous catalysts, especially for oxidation reactions, has received interest and can solve the problems associated with the homogeneous systems: a) R. A. Sheldon, H. van Bekkum, *Fine Chemical through Heterogeneous Catalysis*, Wiley, Weinheim, **2001**; b) G. Centi, F. Cavani, F. Trifiro, *Selective Oxidation by Heterogeneous Catalysis*, Kluwer, New York, **2001**; c) I. V. Kozhevnikov, *NATO Science Series, II: Mathematics, Physics and Chemistry*, Kluwer, New York, **2003**, pp. 351–380; d) B. Warren, S. T. Oyama, *Heterogeneous Hydrocarbon Oxidation*, ACS, Washington, DC, **1996**; e) A. Bhan, E. Iglesia, *Acc. Chem. Res.* **2008**, *41*, 559.

[9] K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2000**, *122*, 7144.

[10] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485.

[11] K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem.* **2004**, *116*, 1602; *Angew. Chem. Int. Ed.* **2004**, *43*, 1576.

[12] During the transformation of **1a** into **2a**, the corresponding imine of 2-naphthalenemethanimine could be detected by GC–MS (MS (EI): m/z (%): 156 (12), 155 (100) [M^+], 154 (92), 153 (18), 128 (32), 127 (44), 126 (18), 77 (18)) albeit in an only small amount (below 1 % yield).