Highly selective aerobic oxidation of primary amines to nitriles by ruthenium hydroxide

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ABSTRACT

A highly selective ruthenium catalyzed aerobic oxidation of primary amines to corresponding nitriles was developed in water and organic solvents. The catalyst system was highly efficient and widely applicable, and several functional groups were tolerated under the reaction conditions employed.

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1. Introduction

Nitriles are important building blocks of dyes, natural products, herbicides, agrochemicals, pharmaceuticals, and various fine chemicals [1,2]. In addition, nitriles are versatile intermediates in synthetic organic chemistry, since they can be easily converted into other functional groups, such as carboxylic acids, amides, aldehydes and heterocycles, etc. [3–6] For these reasons, much attention has been given to the development of efficient and practical methods for the synthesis of nitriles. Nitriles can be prepared in numerous ways. Traditional methods for the preparation of benzonitriles on laboratory as well as on industrial scale are the Rosenmund–von Braun reaction of aryl halides [7,8] and the diazotization of anilines and subsequent Sandmeyer reaction [9]. However, such processes do not meet the criteria of today's sustainable synthesis due to stoichiometric amounts of metal waste generated and toxic cyanides used. And recently, Pd and Cu catalyzed cyanation of aryl halides was established for synthesis of benzonitriles [10–15]. Nevertheless, the development of improved and environmental friendly ways to aromatic and aliphatic nitriles continues to be a challenging goal.

We have reported Pd and Ru nano-catalysts for efficient hydrogenation reactions recently, [16–19] and we are also interested in transition metal catalyzed aerobic oxidation reactions. Oxide supports play an important role in noble metal catalyzed aerobic oxidations. TiO$_2$ and CeO$_2$ are typically good supports and commercial

available. Herein, we reported a highly selective oxidation of primary amines to nitriles by O$_2$ in water or organic solvents (Scheme 1), in the presence of ruthenium catalyst Ru(OH)$_x$/anatase or Ru(OH)$_x$/ceria.

Aerobic oxidation is an important method for the synthesis of chemical intermediates in the manufacture of high-tonnage commodities, high-value fine chemicals, agrochemicals and pharmaceuticals [20–26]. The introduction of transition-metal catalytic systems using oxygen or air is preferred for green processing. In industry, nitriles are produced in large scale by ammoxidation, [27–29] whereby the corresponding arene or alkene is reacted with oxygen and ammonia at 300–550 °C in the presence of heterogeneous fixed-bed catalysts. However, the method is poorly tolerant with functional groups and less suitable for functionalized nitriles because of its harsh reaction conditions. Aerobic oxidation of primary amines to nitriles was reported with Ru(OH)$_x$/Al$_2$O$_3$ system and RuHAP system in organic solvents [30,31]. But in water, Ru(OH)$_x$/Al$_2$O$_3$ catalyzed oxidation of primary amines gave amides presumably via nitriles hydrolysis [32]. To the best of our knowledge, there is no aerobic oxidation of primary amines to nitriles reported in water. As an alternative solvent, water is not only inexpensive and environmentally benign, but also offers the easy approach for separation of organic reagents or catalysts from aqueous phase.
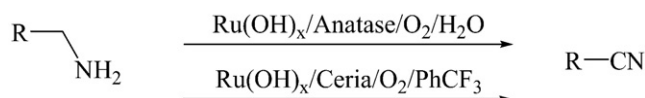
2. Experimental

2.1. Reagents and general consideration

Anatase (aggregated material from particles with diameter of average 20 nm; BET surface area: 75 m^2/g) and ceria (aggregated

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Scheme 1. Ru catalyzed aerobic oxidation primary amines to nitrils in water or in PhCF$_3$.

material from particles with diameter of average 40 nm, BET surface area: 60 m^2/g) were purchased from Nanjing Emperor Material Co. Ltd. The other reagents were purchased from Aladdin Reagent, Sigma-Aldrich Company and Alfa-Aesar Company without further purification.

2.2. General procedure for preparation of Ru(OH)$_x$/anatase and Ru(OH)$_x$/ceria

The anatase powder (0.5 g) was added to a 10 mL of aqueous solution of RuCl$_3$ (10.9 mM) with vigorously stirring at room temperature. After 0.5 h, the pH value of the solution was adjusted to 13 by addition of an aqueous solution of NaOH (3.0 M) and the resulting slurry was stirred for 24 h at room temperature. The solid was then filtered off, washed with a large amount of water, and dried in vacuum to afford 0.35 g of Ru(OH)$_x$/anatase as a pale green powder (Ru content: 2.19 wt.%). The ceria supported ruthenium hydroxide was prepared in the same way and 0.30 g of Ru(OH)$_x$/ceria was obtained as a brown powder (Ru content: 2.09 wt.%). The content of Ru was detected by ICP-OES (inductively coupled plasma optical emission spectroscopy). The ICP-OES analyses were performed with Perkin Elmer OPTIMA 2000DV.

2.3. Procedure for Ru(OH)$_x$ catalyzed aerobic oxidation of amines

An amine (0.25 mmol), Ru(OH)$_x$/anatase (Ru: 5 mol%), and water (1.0 mL) were placed in a Schlenk tube with a magnetic stir bar, and the reaction was carried out at 100 °C under 1 atm of O$_2$ or air (with a balloon). After the reaction was completed, the Ru(OH)$_x$/anatase was separated by filtration, and the products were extracted by 3 × 1.0 mL diethyl ether. The conversion and yield were determined by GC with an internal standard (C$_{16}$H$_{34}$). Ru(OH)$_x$/ceria (Ru: 3 mol%) catalyzed aerobic oxidation of amines in PhCF$_3$ was performed in a similar way. GC analyses were performed on a Hewlett Packard 5890 instrument with a FID detector and Hewlett Packard 24 m × 0.2 mm i.d. HP-5 capillary column.

3. Results and discussion

3.1. Aerobic oxidation of amines to nitriles in water

Oxidation of benzylamine was performed as a model reaction with O$_2$ in water. Ru(OH)$_x$/anatase catalyst showed the highest catalytic activity and selectivity for the transformation of benzylamine to benzonitrile. Ru(OH)$_x$/anatase catalyzed oxidation of benzylamine gave benzonitrile in 93% yield with benzamide (7%) by-product under 1 atm O$_2$ at 100 °C in water (Table 1, Entry 1). And at a higher temperature, 120 °C, the oxidation gave benzonitrile in 80% yield and benzamide in 19% yield under 1 atm O$_2$ (Table 1, Entry 2), which implied some benzonitrile was hydrolyzed to benzamide. At a lower temperature, 80 °C, besides benzonitrile (78%) and benzamide (6%), N-benzylbenzamide was obtained in 10% yield, which indicated that benzonitrile reacted with benzylamine before completion of the oxidation (Table 1, Entry 3). Air used as oxidant instead of O$_2$, the reaction proceeded with a slight loss of the product selectivity (76%) (Table 1, Entry 4), and some N-benzylbenzamide (12%) formed also. Compared to Ru(OH)$_x$/anatase, Ru(OH)$_x$/ceria exhibited lower selectivity, and the oxidation afforded benzonitrile in 57% yield with benzamide (6%), benaldehyde (15%) and N-benzylbenzamide (10%)

Table 1
Aerobic oxidation of benzylamine to benzonitrile and benzyamide in water.

Entry	Catalyst	Conv. [%]	1a [%]	1b [%]
1	**Ru(OH)$_x$/anatase**	**100**	**93**	**7**
2[a]	Ru(OH)$_x$/anatase	100	80	19
3[b]	Ru(OH)$_x$/anatase	98	78	6
4[c]	Ru(OH)$_x$/anatase	94	76	5
5[d]	Ru(OH)$_x$/ceria	100	57	6
6	Ru(OH)$_x$/Al$_2$O$_3$	100	83	13
7[f]	Ru(OH)$_x$/anatase	100	90	10
8	No	0	0	n. d

Reaction conditions: benzylamine, 0.25 mmol; Ru catalyst (Ru: 5 mol%); water, 1.0 mL, 100 °C; under 1 atm O$_2$; reaction time: 10 h. Conversion and selectivity were determined by GC using an internal standard.
[a] At 120 °C, 1 atm O$_2$ in a sealed pressure tube.
[b] At 80 °C, N-benzylbenzamide (10%).
[c] 1.0 atm air, N-benzylbenzamide (12%).
[d] Benzaldehyde (15%) and N-benzylbenzamide (10%).
[f] The reaction scaled up to 1.0 mmol benzylamine, isolated yield.

(Table 1, Entry 5). As reported by Mizuno, the oxidation gave mainly benzamide by Ru(OH)$_x$/Al$_2$O$_3$ at 140 °C in water, [32] but under our condition (100 °C), the oxidation by Ru(OH)$_x$/Al$_2$O$_3$ afforded mainly benzonitrile in 83% yield with benzamide in 13% yield (Table 1, Entry 6). The results indicated that higher temperature enhanced the hydrolysis of benzonitrile to benzamide for both Ru(OH)$_x$/Al$_2$O$_3$ and Ru(OH)$_x$/anatase (Table 1, Entry 1, 2, 6). But Ru(OH)$_x$/Al$_2$O$_3$ was more active for the hydrolysis of benzonitrile than Ru(OH)$_x$/anatase (Table 1, Entry 1, 6), thus the Ru(OH)$_x$/anatase was more selective for benzonitrile. In fact, Mizuno reported the hydrolysis of benzonitrile to benzamide at 140 °C with Ru(OH)$_x$/Al$_2$O$_3$ [3]. Although this issue is still to be solved, the experimental fact is that at high reaction temperature Ru(OH)$_x$/Al$_2$O$_3$ was more active for hydrolysis of nitriles to amides than Ru(OH)$_x$/anatase. Through screening of the catalyst systems, the best catalyst system was found to be the Ru(OH)$_x$/anatase, although the role of the supports was not investigated thoroughly. The scaled-up oxidation of benzylamine (1.0mmol) by Ru(OH)$_x$/anatase afforded benzonitrile in 90% yield (Table 1, Entry 7), which showed the practicality of the oxidation method. Benzonitrile was easily extracted by diethyl ether from the water solution with >90% purity, and it can be further purified by column chromatography on silica gel. Benzonitrile was not formed in the absence of Ru catalyst or in the presence of supports only.

With optimized reaction conditions in hand, we investigated the application scope of the aerobic oxidation reaction. Several amines were examined for oxygenation with Ru(OH)$_x$/anatase in water (Table 2). The transformation of benzylamines, which contain methoxy, chloro and alkyl groups, proceeded efficiently to give the corresponding benzonitriles in high yields (Table 2, Entry 2–5). Oxidation of aliphatic amine requires longer time, and octan-1-amine was converted into octanenitrile smoothly in 86% yield within 16 h (Table 2, Entry 6).

3.2. Aerobic oxidation of amines to nitriles in benzotrifluoride

Afterwards, we tested the aerobic oxidation of amines also in organic solvents. Ru(OH)$_x$/ceria was found the best catalyst for the transformation of benzylamine to benzonitrile among several catalysts examined in benzotrifluoride. Ru(OH)$_x$/ceria catalyzed oxidation of benzylamine afforded benzonitrile in 94%, 93% and 85% yields at 120, 100 and 80 °C respectively in 10 h (Table 3, Entry 1, 2, 7). Instead of Ru(OH)$_x$/ceria, Ru(OH)$_x$/anatase and Ru/Al$_2$O$_3$ [30] exhibited slightly lower selectivity in benzotrifluoride (Table 3, Entry 3, 8).

Table 2
Aerobic oxidations of various amines catalyzed by Ru(OH)$_x$/anatase in water.

Entry	Amine	Nitriles	Conv. [%]	Yield [%]
1			100	93
2			100	88
3			100	88
4			93	83
5			100	85
6[a]			99	86

Reaction conditions: amine, 0.25 mmol; Ru(OH)$_x$/anatase (Ru: 5 mol%); water, 1.0 mL; 100 °C; under 1 atm O$_2$; reaction time: 10 h. Conversion and selectivity were determined by GC using an internal standard.

[a] 16 h.

The oxidation of benzylamine was almost completed in 6 hours and gave benzonitrile in 90% yield (Table 3, Entry 4). Toluene was not so good a solvent as benzotrifluoride and benzonitrile was obtained in 80% yield in toluene (Table 3, Entry 5). Instead of O$_2$, the oxidation

Table 3
Ru(OH)$_x$/ceria catalyzed aerobic oxidations of various amines in benzotrifluoride.

Entry	Catalyst	Amine	Nitriles	T/°C	Conv. [%]	Yield [%]
1	Ru(OH)$_x$/ceria			100	100	93
2[a]	Ru(OH)$_x$/ceria			120	100	94
3	Ru(OH)$_x$/anatase			100	93	75
4[b]	Ru(OH)$_x$/ceria			100	99.5	90
5[c]	Ru(OH)$_x$/ceria			100	100	80
6[d]	Ru(OH)$_x$/ceria			100	100	89
7	Ru(OH)$_x$/ceria			80	98	85
8	Ru(OH)$_x$/Al$_2$O$_3$			100	100	77
9[e]	Ru(OH)$_x$/ceria			100	100	90
10	Ru(OH)$_x$/ceria			100	100	95
11	Ru(OH)$_x$/ceria			100	100	97
12	Ru(OH)$_x$/ceria			100	98	90
13	Ru(OH)$_x$/ceria			100	100	94
14[f]	Ru(OH)$_x$/ceria			100	94	89

Reaction conditions: amines, 0.25 mmol; Ru catalyst (Ru: 3 mol%); PhCF$_3$, 1.25 mL, under 1 atm O$_2$; reaction time: 10 h. Conversion and selectivity were determined by GC using an internal standard.

[a] 1.0 atm O$_2$ in a sealed pressure tube.
[b] 6 h.
[c] 1.25 mL toluene as solvent.
[d] 1.0 atm air instead of O$_2$.
[e] The reaction scaled up to 1.0 mmol benzylamine, isolated yield.
[f] 16 h.

with air also gave benzonitrile in high yield (89%) (Table 3, Entry 6). The scaled-up oxidation of benzylamine (1.0 mmol) in benzotrifluoride afforded benzonitrile in good yield (90% isolated yield) (Table 3, Entry 9). Under the optimized reaction conditions, several amines were oxygenated in benzotrifluoride, and Ru(OH)$_x$/ceria catalyzed oxidation of benzylamines proceeded efficiently to give the corresponding benzonitriles in excellent yields (Table 3, Entry 10–13). And aliphatic octanenitrile was also obtained in good yield (89%) within a longer time (16 hours) (Table 3, Entry 14). Accordingly, the Ru(OH)$_x$/ceria also exhibited excellent activity and selectivity for oxidation of primary amines to nitriles in PhCF$_3$, which was comparable to Ru/Al$_2$O$_3$ [30] and RuHAP [31] systems reported.

3.3. Catalyst reusability

Ru(OH)$_x$/ceria and Ru(OH)$_x$/anatase were ready to be separated by filtration directly, and the recycled catalysts were used again for the aerobic oxidation of benzylamine to benzonitrile. Comparing to the 'fresh' catalyst, we found that the oxidation of benzylamine afforded benzonitrile in nearly the same yield (91% from first time 93% yield) by recycled Ru(OH)$_x$/anatase in water. And the oxidation of benzylamine gave benzonitrile in similar yield (92% from first time 94% yield) by the recycled Ru(OH)$_x$/ceria in benzotrifluoride. The good reusability of the catalysts can facilitate possible fixed bed reactors with long durability. It was confirmed by ICP-OES that no ruthenium (below detection limit) was detected in the filtrates (for reactions in water and PhCF$_3$ Table 1, Entry1 and Table 3, Entry 1). In addition, the oxidation processes were terminated by the removal of Ru(OH)$_x$/anatase or Ru(OH)$_x$/ceria from the reaction solutions. Thus, the observed catalysis is intrinsically heterogeneous.

4. Conclusions

In summary, we demonstrated a highly selective Ru catalyst system for aerobic oxidation of primary amines to corresponding nitriles, and Ru(OH)$_x$/anatase and Ru(OH)$_x$/ceria were found excellent catalysts for the aerobic oxidation in water and in benzotrifluoride respectively. The catalyst systems were highly selective and widely applicable, and several functional groups were tolerated under the reaction conditions employed. The oxidation in water provided a green and convenient method for nitrile synthesis, and it was also helpful to understand the oxidation mechanism. Work on mechanism study and on practical application for the oxidation is now in progress.

Acknowledgements

References

[1] T.M. Harris, C.M. Harris, T.A. Oster, L.E. Brown Jr., Y.C. Lee, J. Am. Chem. Soc. 110 (1988) 6180–6186.
[2] V.V. Grushin, H. Alper, Chem. Rev. 94 (1994) 1047–1062.
[3] K. Yamaguchi, M. Matsushita, N. Mizuno, Angew. Chem., Int. Ed. 43 (2004) 1576–1580.
[4] J.N. Moorthy, N. Singhal, J. Org. Chem. 70 (2005) 1926–1929.
[5] G.K. Jnaneshwara, V.H. Deshpande, M. Lalithambika, T. Ravindranathan, A.V. Bedekar, Tetrahedron Lett. 39 (1998) 459–462.
[6] P. Benz, R. Muntwyler, R. Wohlgemuth, J. Chem. Technol. Biotechnol. 82 (2007) 1087–1098.
[7] G.P. Ellis, T.M. Romney-Alexander, Chem. Rev. 87 (1987) 779–794.
[8] R.G.R. Bacon, H.A.O. Hill, J. Chem. Soc. (1964) 1097–1107.
[9] T. Sandmeyer, Ber. Dtsch. Chem. Ges. 17 (1884) 2650–2653.
[10] H.J. Cristau, A. Ouali, J.F. Spindler, M. Taillefer, Chem. Eur. J. 11 (2005) 2483–2492.
[11] M. Sundermeier, A. Zapf, S. Mutyala, W. Baumann, J. Sans, J. Weiss, M. Beller, Chem. Eur. J. 9 (2003) 1828–1836.
[12] J. Zanon, A. Klapars, S.L. Buchwald, J. Am. Chem. Soc. 125 (2003) 2890–2891.

[13] T. Schareina, A. Zapf, W. Magerlein, N. Muller, M. Beller, Tetrahedron Lett. 48 (2007) 1087–1090.
[14] Y. Ren, Z. Liu, S. Zhao, X. Tian, J. Wang, W. Yin, S. He, Catal. Commun. 10 (2009) 768–771.
[15] T. Schareina, A. Zapf, W. Magerlein, N. Muller, M. Beller, Chem. Eur. J. 13 (2007) 6249–6254.
[16] J. Huang, T. Jiang, B.X. Han, H.X. Gao, Y.H. Chang, G.Y. Zhao, W.Z. Wu, Chem. Commun. (2003) 1654–1655.
[17] J. Huang, T. Jiang, B.X. Han, W.Z. Wu, Z.M. Liu, Z.L. Xie, J.L. Zhang, Catal. Letters 103 (2005) 59–62.
[18] J. Huang, T. Jiang, H.X. Gao, B.X. Han, Z.M. Liu, W.Z. Wu, Y.H. Chang, G.Y. Zhao, Angew. Chem., Int. Ed. 43 (2004) 1397–1399.
[19] S.D. Miao, Z.M. Liu, B.X. Han, J. Huang, Z.Y. Sun, J.L. Zhang, T. Jiang, Angew. Chem., Int. Ed. 45 (2005) 266–269.
[20] F. Shi, M.K. Tse, X. Cui, D. Gordes, D. Michalik, K. Thurow, Y. Deng, M. Beller, Angew. Chem., Int. Ed. 48 (2009) 5912–5915.
[21] F. Shi, M.K. Tse, S. Zhou, M.M. Pohl, J. Radnik, S. Huebner, K. Jaehnisch, A. Brueckner, M. Beller, J. Am. Chem. Soc. 131 (2009) 1775–1779.
[22] F. Shi, M.K. Tse, M.M. Pohl, A. Brueckner, S. Zhang, M. Beller, Angew. Chem., Int. Ed. 46 (2007) 8866–8868.
[23] Z. Hou, N. Theyssen, A. Brinkmann, W. Leitner, Angew. Chem., Inter. Ed. 44 (2005) 1346–1349.
[24] B. Feng, Z. Hou, X. Wang, Y. Hu, H. Li, Y. Qiao, Green Chem. 11 (2009) 1446–1452.
[25] Y. Gorbanev, S.K. Klitgaard, J. Woodley, C.H. Christensen, A. Riisager, ChemSusChem 2 (2009) 672–675.
[26] B. Jorgensen, S.B. Kristensen, A.J. Kunov-Kruse, R. Fehrmann, C.H. Christensen, A. Riisager, Top. Catal. 52 (2009) 253–257.
[27] A. Martin, N.V. Kalevaru, B. Lücke, J. Sans, Green Chem. 4 (2002) 481–485.
[28] G.Y. Popova, T.V. Andrushkevich, Y.A. Chesalov, L.M. Plyasova, L.S. Dovlitova, E.V. Ischenko, G.I. Aleshina, M.I. Khramov, Catal. Today 144 (2009) 312–317.
[29] W.I. Denton, R.B. Bishop, H.P. Caldwell, H.D. Chapman, Ind. Eng. Chem. 42 (1950) 796–800.
[30] K. Yamaguchi, N. Mizuno, Angew. Chem., Int. Ed. 42 (2003) 1480–1483.
[31] K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, Chem. Commun. (2001) 461–462.
[32] J.W. Kim, K. Yamaguchi, N. Mizuno, Angew. Chem., Int. Ed. 47 (2008) 9249–9251.