

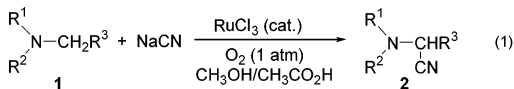
## Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide

Shun-Ichi Murahashi,<sup>\*,†,‡</sup> Naruyoshi Komiya,<sup>†</sup> Hiroyuki Terai,<sup>†</sup> and Takahiro Nakae<sup>†</sup>

Department of Chemistry, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan, and Department of Applied Chemistry, Faculty of Engineering, Okayama University of Science, 1-1 Ridaicho, Okayama, Okayama 700-0005, Japan

Received October 13, 2003; E-mail: murahashi@high.ous.ac.jp

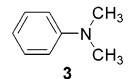
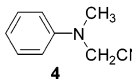
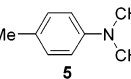
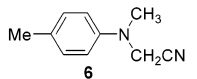
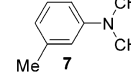
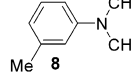
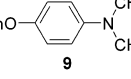
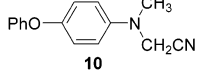
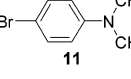
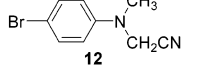
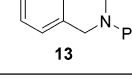
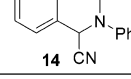
Oxidative transformation of tertiary amines is of importance in both its enzymatic and synthetic aspects.<sup>1</sup> During simulation of the functions of cytochrome P-450 enzyme with transition-metal complexes,<sup>2</sup> we found that ruthenium-catalyzed oxidations of amines,<sup>3,4</sup> amides,<sup>5</sup> and  $\beta$ -lactams<sup>5</sup> with peroxides occur efficiently. The ruthenium-catalyzed oxidation of tertiary amines with *t*-BuOOH gives  $\alpha$ -*tert*-butyldioxyamines by trapping the iminium ion intermediates, which are derived from the reaction with ruthenium oxo species.<sup>3,5</sup> Similarly, the ruthenium-catalyzed oxidation of  $\beta$ -lactams with peracetic acid in acetic acid gives 4-acetoxy-2-azetidinones highly efficiently.<sup>5</sup> In a search for an environmentally benign and effective method for oxidative transformation of amines, we aimed at accomplishing two tasks at once: (1) oxidation with molecular oxygen in place of peroxides and (2) direct carbon–carbon bond formation by trapping of the iminium ion intermediates with a carbon nucleophile under oxidative conditions. Catalytic oxidation with molecular oxygen under mild conditions is one of the current problems of interest in chemistry.<sup>6</sup> However, to our knowledge, there is no reported example of efficient aerobic oxidative transformation of amines.<sup>7</sup> We report that aerobic, ruthenium-catalyzed oxidative cyanation of tertiary amines with sodium cyanide occurs to give the corresponding  $\alpha$ -aminonitriles<sup>8</sup> (eq 1), which are useful for synthesis of compounds such as  $\alpha$ -amino acids and 1,2-diamines.



Catalytic activity of various ruthenium catalysts was examined for the oxidative cyanation of *N,N*-dimethylaniline. RuCl<sub>3</sub>·*n*H<sub>2</sub>O has proved to be the best catalyst. Ruthenium complexes such as K<sub>2</sub>[RuCl<sub>5</sub>(H<sub>2</sub>O)] and [Ru<sub>2</sub>( $\mu$ -CH<sub>3</sub>CO<sub>2</sub>)<sub>4</sub>Cl] are also useful. Acetic acid is essential, and a 3:1 mixture of methanol and acetic acid was an excellent solvent.

Typical results of the aerobic ruthenium-catalyzed oxidative transformation of tertiary amines are shown in Table 1. The reaction of *N,N*-dimethylaniline with sodium cyanide (1.2 equiv) in the presence of RuCl<sub>3</sub>·*n*H<sub>2</sub>O catalyst (5 mol %) in a 3:1 mixture of methanol and acetic acid under molecular oxygen (1 atm, balloon) at 60 °C for 2 h gave *N*-methyl-*N*-phenylaminoacetonitrile in 88% isolated yield (93% GLC yield) (entry 1). The other products formed were *N*-methylaniline (less than 3% GLC yield) and *N*-methylformanilide (trace). The reaction can be used for substituted *N,N*-dimethylanilines with either electron-donating or -withdrawing groups (entries 2–5). Cyclic amines such as tetrahydroisoquinoline can be converted into the corresponding  $\alpha$ -cyanated compound (entry 6).

**Table 1.** Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide<sup>a</sup>

entry	substrate	time (h)	conv (%) <sup>b</sup>	product	yield (%) <sup>c</sup>
1		2	99		88% (93%) <sup>b</sup>
2		1	99		94% (97%) <sup>b</sup>
3		1.5	99		84%
4		2	94		81%
5		2	98		88%
6		4	91 <sup>d</sup>		76%

<sup>a</sup> A mixture of a tertiary amine (1.0 mmol), RuCl<sub>3</sub>·*n*H<sub>2</sub>O (0.05 mmol), and NaCN (1.2 mmol) in methanol/acetic acid (3:1, 1.6 mL) was stirred under O<sub>2</sub> (1 atm) at 60 °C. <sup>b</sup> Found by GLC analysis using an internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> Found by <sup>1</sup>H NMR analysis.

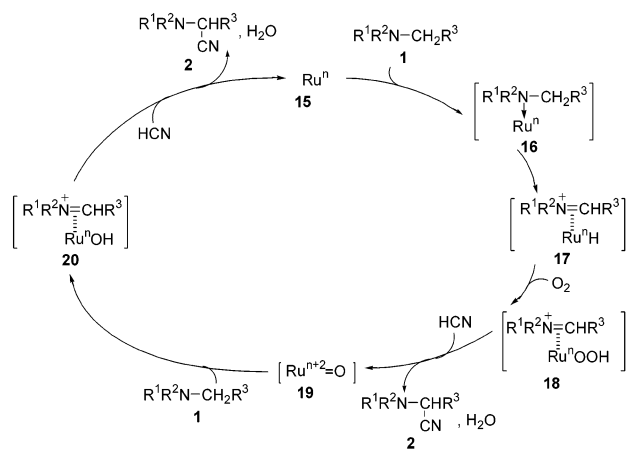
*N*-Methyl groups are oxidized chemoselectively in the presence of other alkyl groups. Thus, the reaction of *N*-ethyl-*N*-methylaniline gave *N*-ethyl-*N*-phenylaminoacetonitrile in 57% yield along with 2-(*N*-methyl-*N*-phenylamino)propionitrile (4%) as with cytochrome P-450 oxidation.<sup>3</sup>

Such oxidative cyanation of tertiary amines provides a novel and convenient method for synthesis of  $\alpha$ -amino acids from tertiary amines because the  $\alpha$ -aminonitriles thus obtained are precursors for synthesis of amino acids.<sup>9</sup>  $\alpha$ -Aminonitriles can be readily converted to *N*-aryl- $\alpha$ -amino acids.<sup>10</sup> Typically, alkaline hydrolysis of *N*-methyl-*N*-phenylaminoacetonitrile and *N*-methyl-*N*-(4-methoxyphenyl)aminoacetonitrile gave *N*-methyl-*N*-phenylglycine and *N*-methyl-*N*-(4-methoxyphenyl)glycine in 87% and 82% yield, respectively. Furthermore, the  $\alpha$ -aminonitriles thus obtained can be converted into unsymmetrical 1,2-diamines, which are important as ligands and precursors of biologically active compounds. Typically, treatment of *N*-methyl-*N*-phenylaminoacetonitrile with lithium aluminum hydride gave *N*-methyl-*N*-phenylethylenediamine in 92% yield.

In an exploration of the mechanism, the relative rates of the oxidative cyanation of para-substituted *N,N*-dimethylanilines (*p*-X-C<sub>6</sub>H<sub>4</sub>NMe<sub>2</sub>, X = MeO, Me, H, and Br) with molecular oxygen

<sup>†</sup> Osaka University.  
<sup>‡</sup> Okayama University of Science.

Scheme 1



in the presence of sodium cyanide were examined by  $^1\text{H}$  NMR analysis of the corresponding cyanated products. The rates correlate well ( $r^2 = 0.999$ ) with the Hammett linear free-energy relationship with  $\sigma$  values. The  $\rho$  value is  $-3.35$ , which is close to the value,  $-3.60$ , obtained by the  $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -catalyzed oxidation of *p*-substituted anilines with  $\text{H}_2\text{O}_2$  in methanol to give  $\alpha$ -methoxy compounds<sup>4</sup> and is larger than the value,  $-0.84$ , obtained by the  $\text{RuCl}_2(\text{PPh}_3)_3$ -catalyzed oxidation of the same amines with *tert*-butyl hydroperoxide to give *tert*-butyldioxyamines.<sup>3</sup> In the present reaction, the oxo-ruthenium species seems to form as an active species to generate iminium ion intermediates. The intramolecular deuterium isotope effects,  $k_{\text{H}}/k_{\text{D}}$ , for the *para*-substituted *N*-methyl-*N*-trideuteriomethylanilines are dependent on the  $\sigma$  values of substituents and decrease going from electron-donating to electron-withdrawing substituents. The  $k_{\text{H}}/k_{\text{D}}$  values of the reactions of four *para*-substituted *N*-methyl-*N*-trideuteriomethylanilines (*p*-X- $\text{C}_6\text{H}_4\text{N}(\text{Me})\text{CD}_3$ , *p*-MeO, *p*-Me, H, and *p*-Br) obtained are 4.2, 3.1, 2.4, and 1.1, respectively, indicating that electron transfer from the amine to ruthenium would take place at the initial step.<sup>11</sup>

Results of measurement of molecular oxygen uptake show that 1 mol of molecular oxygen is consumed for the oxidation of 2 mol of *N,N*-dimethylaniline under the standard reaction conditions, indicating that one molecule of molecular oxygen is used for the formation of two iminium ion intermediates, which are trapped with cyanide to give the corresponding  $\alpha$ -aminonitriles. The reaction can be rationalized in terms of the mechanism shown in Scheme 1.

Ruthenium species **15** would coordinate to tertiary amines to give **16**. Electron transfer and subsequent hydrogen transfer from the amine to ruthenium result in the formation of [iminium ion]-ruthenium hydride complex **17**.<sup>12</sup> The ruthenium hydride species **17** undergoes reaction with molecular oxygen to form an [iminium ion]- $\text{Ru}^{\text{n}}\text{OOH}$  complex **18**, likewise the formation of  $\text{PdOOH}$  from  $\text{PdH}$ .<sup>13</sup> Subsequent reaction of the [iminium ion]- $\text{Ru}^{\text{n}}\text{OOH}$  complex **18** with HCN, which is generated from NaCN and acetic acid under the conditions used,<sup>14</sup> gives  $\alpha$ -aminonitrile **2**,  $\text{H}_2\text{O}$ , and a  $\text{Ru}^{\text{n}+2}=\text{O}$  species **19**. The  $\text{Ru}^{\text{n}+2}=\text{O}$  species **19** thus formed reacts with another tertiary amine, **1**, to give iminium ion intermediate **20** by electron transfer and subsequent hydrogen transfer.<sup>3–5</sup> The iminium ion intermediate **20** can be trapped with cyanide to afford  $\alpha$ -aminonitrile, **2**, and  $\text{Ru}^{\text{n}}$ , **15**, to complete the catalytic cycle. At the stage of transformation from **18** to **19**, a two-step pathway with

formation of  $\text{H}_2\text{O}_2$  by protonolysis of **18** and subsequent formation of **19** from  $\text{H}_2\text{O}_2$  and Ru may be an alternative. Actually, it was confirmed that the oxidative cyanation of tertiary amines with  $\text{H}_2\text{O}_2$  occurred similarly to give  $\alpha$ -aminonitriles. Control experiments showed that the corresponding *N*-oxide of *N,N*-dimethylaniline was not detected under the reaction conditions, although the  $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -catalyzed aerobic oxidation of tertiary amines has been reported.<sup>15</sup> The mechanism that involves oxidation with the *N*-oxide thus formed can therefore be excluded.

In conclusion, the aerobic ruthenium-catalyzed oxidative cyanation of tertiary amines can be done efficiently under simple and mild conditions and should be an environmentally benign and useful process.

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**Supporting Information Available:** Detailed experimental procedures including analytical and spectroscopic data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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