Oxidative Cyanations

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Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Hydrogen Peroxide and Sodium Cyanide**

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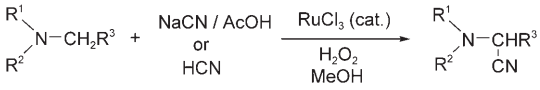
There has been much interest in the development of clean and environmentally benign methods for the transformation of amines into the corresponding α-functionalized compounds. These compounds have proven to be versatile intermediates and have been widely used in the construction of biologically active nitrogen compounds such as alkaloids.[1] Direct introduction of a substituent at the α position of tertiary amines is performed in two steps: α-C–H activation to produce iminium ion intermediates and subsequent reaction with nucleophiles.[2–4] The initial C–H activation has been achieved by two methods, that is, with low-valent transition metals by oxidative addition[2,5] or with metal–oxo species.[2,3]

Although various compounds can be used for the oxidation of amines, hydrogen peroxide is the oxidant that satisfies recent environmental and sustainable demands, because water is the sole by-product. Therefore, catalytic oxidation of substrates such as alkenes, alcohols, amines, sulfides, and alkanes with H_2O_2 has been explored extensively.[6,7] However, there are few examples for the introduction of an external functional group to substrates upon H_2O_2 oxidation.[7r,8] We report here that a carbon–carbon bond forms at the α position (with respect to the nitrogen atom) of tertiary amines under the H_2O_2 oxidation conditions. Thus, the ruthenium-catalyzed oxidative cyanation of tertiary amines with H_2O_2 in the presence of sodium cyanide or hydrogen cyanide gives the corresponding α-aminonitriles with high efficiency [Eq. (1)]. The reaction is, to the best of our knowledge, the first example of direct C–H activation and C–C bond formation under H_2O_2 oxidation conditions.



(1)

The catalytic activity for the oxidative cyanation of *N*,*N*-dimethylaniline with H_2O_2 in the presence of sodium cyanide was examined. $RuCl_3$ was found to be the most effective catalyst. $[RuCl_2(PPh_3)_3]$ and $Pr_4N[RuO_4]$ show moderate catalytic activity, while $K_4[Ru(CN)_6]$ retards the reaction. Methanol is the most effective solvent, although ethanol, ethyl acetate, and acetonitrile can also be used. The addition of acetic acid is necessary for the reaction with sodium cyanide, as otherwise no reaction takes place.

As shown in Table 1, various tertiary amines can be efficiently converted into the corresponding α-aminonitriles[9] with H_2O_2 in the presence of sodium cyanide. Reaction of substituted *N*,*N*-dimethylanilines bearing both electron-donating and electron-withdrawing substituents gave the corresponding cyanated products (entries 1–3). In the presence of other alkyl groups, the *N*-methyl group reacts predominantly. For example, the reaction of *N*-methyl-*N*-ethylaniline gave *N*-cyanomethyl-*N*-ethylaniline (**8**) along with a small amount of *N*-(1-cyanoethyl)-*N*-methylaniline (**9**; entry 4). The reaction can also be applied efficiently to cyclic amines: Piperidine, pyrrolidine, and tetrahydroisoquinoline derivatives can be converted into the corresponding α-cyanoamines (entries 5–8). In terms of the substrate, oxidative cyanation with H_2O_2 is more versatile than with molecular oxygen;[10] for example, molecular oxygen cannot be used for reactions with piperidine and pyrrolidine derivatives. The ruthenium-catalyzed oxidative cyanation of *N*-(4-methoxyphenyl)pyrrolidine (**14**) with H_2O_2 gave the corresponding α-cyanated amine **15** in 80% yield (entry 7), while the same reaction with molecular oxygen provided the product in only 23% yield.

To gain insight into the reaction mechanism, the relative reaction rates for the oxidative cyanation of four *para*-substituted *N*,*N*-dimethylanilines (p-$XC_6H_4NMe_2$; X = MeO,

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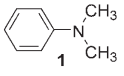
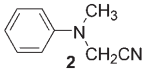
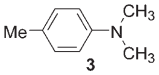
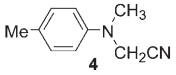
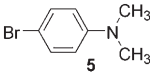
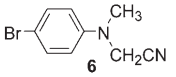
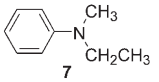
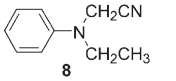
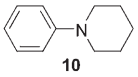
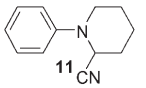
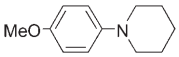
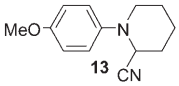
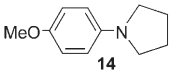
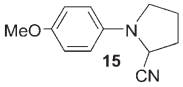
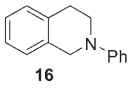
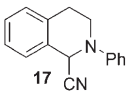
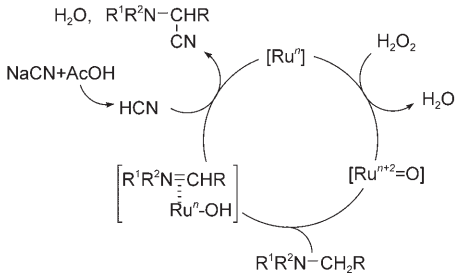
Table 1: Results of the ruthenium-catalyzed oxidative cyanation of tertiary amines with hydrogen peroxide and NaCN [see Eq. (1)].[a]

Entry	Substrate	*t* [h]	Product	Yield [%][b]
1	 **1**	2	 **2**	90 (80)[c]
2	 **3**	1.5	 **4**	81
3	 **5**	3	 **6**	67
4[d]	 **7**	1.5	 **8**	63
5	 **10**	2	 **11**	69[e]
6[f]	 **12**	1.5	 **13**	73[e]
7[g]	 **14**	1.5	 **15**	80[e]
8	 **16**	1.5	 **17**	83[e]

[a] The reaction was carried out as follows: A 30% aqueous solution of H_2O_2 (2.5 mmol) was added dropwise over a period of 1 h to a mixture of amine (1.0 mmol), $RuCl_3$ (0.05 mmol), NaCN (1.2 mmol), and CH_3CO_2H (6 mmol) in MeOH (1.2 mL). The reaction mixture was then stirred for the given amount of time. [b] Determined by GLC using an internal standard. [c] Yield of the isolated product. [d] A small amount of **9** was also formed. [e] Determined by ^{1}H NMR spectroscopy. [f] 1.5 mmol of H_2O_2 was used. [g] 1.0 mmol of H_2O_2 was used.

Me, H, Br) with H_2O_2 in the presence of sodium cyanide were determined by ^{1}H NMR spectroscopy of the resulting cyanated products. The rate data correlate well ($R^2 = 0.998$) with the Hammett linear free energy relationship with use of σ values (Figure 1).

The ρ value was determined to be -3.61, indicating a cationic intermediate at the rate-determining step. The intramolecular deuterium isotope effect for the ruthenium-catalyzed oxidative cyanation of *N*-methyl-*N*-(trideuteriomethyl)aniline was found to be 4.1 by ^{1}H NMR spectroscopy. Similarly, the intermolecular deuterium isotope effect for the oxidative cyanation of an equimolar mixture of *N*,*N*-dimethylaniline and *N*,*N*-bis(trideuteriomethyl)aniline was determined to be 3.7. These intra- and intermolecular isotope effects are larger than those observed for *N*-demethylation with cytochrome P450 (1.6–3.1,[11] and 1.0–1.1[12]), suggesting that cleavage of the C–H bond proceeds via an intermediate bearing more ionic character. Under consideration of these data, the present reaction can be rationalized by assuming the cytochrome P450 type mechanism, as shown in Scheme 1. The



Scheme 1. The proposed reaction mechanism for the ruthenium-catalyzed oxidative cyanation of tertiary amines with H_2O_2.

low-valent ruthenium species [Ru^n] undergoes reaction with H_2O_2 to give the oxo–ruthenium species [Ru^{n+2}=O], which produces an iminium ion intermediate by electron transfer and subsequent hydrogen transfer. Nucleophilic attack by hydrogen cyanide on the iminium ion intermediate provides the corresponding α-cyanated products, water, and the [Ru^n] species to complete the catalytic cycle.

The participation of hydrogen cyanide, which is formed from sodium cyanide and acetic acid under the reaction conditions,[13] was confirmed by the following reactions: The ruthenium-catalyzed oxidation of *N*,*N*-dimethylaniline with H_2O_2 in the presence of hydrogen cyanide in methanol gave the corresponding α-aminonitrile **2** in 80% yield (Scheme 2). The analogous reaction with *N*-phenyltetrahydroisoquinoline provided the α-cyanated tetrahydroisoquinoline **17** in 97% yield.

The oxidative cyanation of tertiary amines provides a convenient method for synthesizing various compounds,

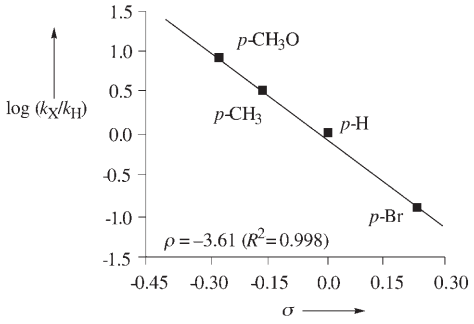
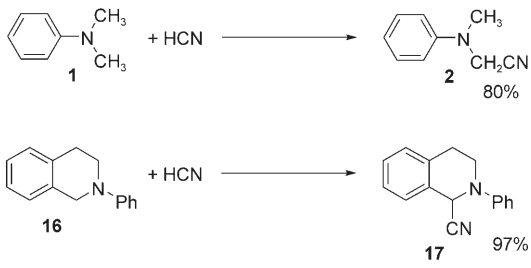


Figure 1. Hammett plot for the $RuCl_3$-catalyzed oxidative cyanation of the *para*-substituted *N*,*N*-dimethylanilines *p*-$XC_6H_4NMe_2$ (X = MeO, Me, H, Br) with H_2O_2 in the presence of NaCN.



Scheme 2. The ruthenium-catalyzed oxidative cyanation of tertiary amines with H_2O_2 in the presence of HCN. Reaction conditions: $RuCl_3$ (5 mol%), H_2O_2 (1.5 equiv), MeOH, RT, 24 h (**1**→**2**) or 4 h (**16**→**17**).

including *N*-aryl-α-amino acids[14,15] and *N*,*N*-disubstituted 1,2-diamines. Upon hydrolysis, 2-cyano-*N*-4′-methoxyphenyl)pyrrolidine (**15**) can be converted into *N*-(4′-methoxyphenylproline (**18**) in 69% yield, while the reduction of **15** with $LiAlH_4$ provides 2-aminoethyl-*N*-(4′-methoxyphenyl)-pyrrolidine (**19**) in 99% yield. Quinoline skeletons can also be constructed from tertiary arylamines by iminium ion cyclization. Typically, the $TiCl_4$-promoted reaction of α-aminonitrile **2**, derived from oxidative cyanation of **1** with allyltrimethylsilane in CH_2Cl_2 at −78 °C, gave 1-methyl-4-trimethylsilylmethyl-1,2,3,4-tetrahydroquinoline (**20**) in 75% yield.

In conclusion, we have demonstrated the novel ruthenium-catalyzed oxidative cyanation of tertiary amines with hydrogen peroxide. The reaction proceeds with high efficiency to give the corresponding α-cyanated amines, and thus provides a useful method for the synthesis of various nitrogen compounds from tertiary amines. Research is currently underway to elucidate the mechanism and to apply the principle to other catalytic systems.

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