Cobalt-Catalyzed Oxidative α-Cyanation of Tertiary Aromatic Amines with Trimethylsilyl Cyanide and *tert*-Butyl Hydroperoxide

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Abstract: In this Letter is described that a cobalt(II)–*tert*-butyl hydroperoxide oxidizing system was used to catalyze the α-cyanation of aromatic tertiary amines in the presence of trimethylsilyl cyanide to produce the corresponding α-aminonitriles in good yields.

Key words: cobalt, oxidation, cyanation, aminonitriles, tertiary amines

α-Aminonitriles have been used to constitute the basic skeleton, or a useful precursor, of natural products, biologically active substances, and functional materials.[1] Thus, the development of a facile and effective method for the preparation of nitriles has attracted considerable attention in the field of applied chemistry. Thus far, the demand has been satisfied by substituting amines that have a leaving group with a cyano source[2] or by using Strecker-type reaction with an imine intermediate, which can be generated from an amine and an aldehyde.[3] During the past two decades, direct C–H functionalization at the α-position of tertiary amines with an appropriate cyano source, such as sodium cyanide or trimethylsilyl cyanide (TMSCN), in the presence of a transition metal has been developed as a straightforward and clean approach. For example, Murahashi and co-workers initially developed the ruthenium-catalyzed oxidative α-cyanation of tertiary amines with molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) in the presence of sodium cyanide.[4] Also Sain and Jain et al. reported that a vanadium or an iron catalyst would catalyze the cyanation of tertiary amines with O_2 or H_2O_2 in the presence of sodium cyanide to produce aminonitriles.[5] Ofial and Zhu disclosed the iron- or gold-complex-catalyzed oxidative α-cyanation of tertiary amines with TBHP in the presence of TMSCN.[6] Recently, Prabhu found that a molybdenum catalyst had a similar catalytic effect for the α-cyanation of amines with O_2 in the presence of TMSCN.[7] In recent interesting examples, several groups reported that either a visible-light photoredox system,[8] or some promoters, such as a tropylium ion and an iodine molecule, have been used to mediate the α-cyanation of tertiary amines.[9]

We report herein the α-cyanation of the C(sp^3)–H bond of tertiary amines catalyzed by a novel cobalt–TBHP oxidizing system. As far as we know, there has been no reported example of the α-cyanation of tertiary amines using the combination of a cobalt chloride catalyst and TBHP, with the noted exception of one report[10] wherein Murahashi et al. described the possibility of the cyanation of tertiary amines with $CoCl_2$ and molecular O_2, but an actual investigation has not been demonstrated.[11]

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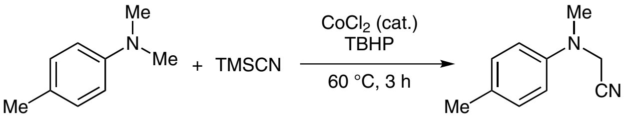
Table 1 Examinations of Reaction Conditions



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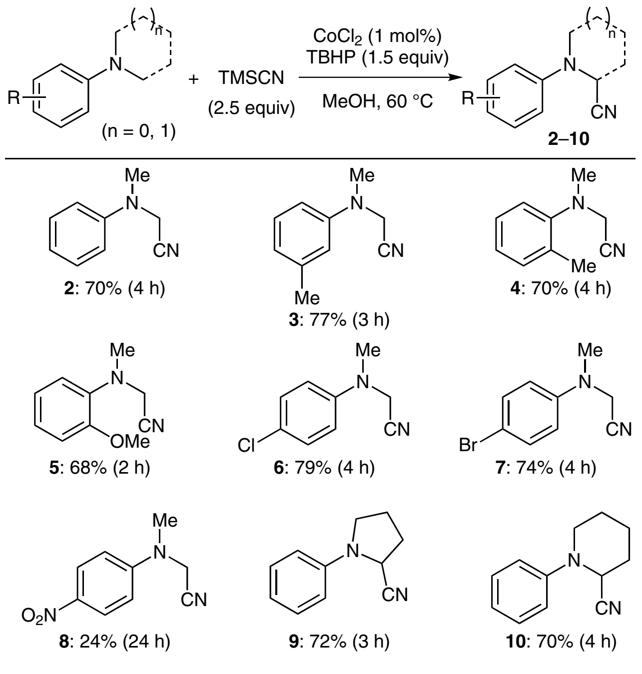
Entry	$CoCl_2$ (mol%)	TBHP (equiv)	TMSCN (equiv)	Solvent	Yield (%)[a]
1	5	1.5	2	$CHCl_3$	25
2	5	1.5	2	MeCN	27
3	5	1.5	2	THF	9
4	5	1.5	2	MeOH	75
5	5	1.5	2.5	MeOH	80
6	2	1.5	2.5	MeOH	83
7	1	1.5	2.5	MeOH	(80)

[a] GC (isolated) yield.

Based on conventional methods, the cyanation of *N*,*N*-dimethyl-*p*-toluidine with trimethylsilyl cyanide in the presence of a cobalt catalyst and an oxidizing agent, *tert*-butyl hydroperoxide (TBHP) was examined as the initial model (Table 1).[12] When the reaction was conducted with 5 mol% of $CoCl_2$ and 1.5 equivalents of TBHP in chloroform at 60 °C, the expected cyanation proceeded to produce the desired α-aminonitrile (**1**) in a 25% yield (Table 1, entry 1). This result showed that the oxidizing system, which consisted of $CoCl_2$ and TBHP readily activated the α-C(sp^3)–H bond adjacent to a nitrogen atom in a tertiary aromatic amine to generate an iminium intermediate. Thus, to improve the yield, a solvent effect was investigated using several solvents. A typical coordinative solvent, such as acetonitrile and tetrahydrofuran, was ineffective for this cyanation (Table 1, entries 2 and 3). However, gratifyingly, when a similar reaction was carried out in methanol, the yield was remarkably improved to a 75% yield (Table 1, entry 4). Finally, the loading of only

1 mol% of $CoCl_2$ and 1.5 equivalents of TBHP promoted sufficient cyanation to produce the expected aminonitrile in a good yield (Table 1, entries 5–7).

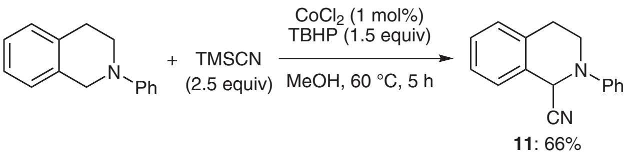
With the optimal conditions shown in Table 1, the scope of this oxidation was examined with a variety of tertiary aromatic amines (Scheme 1). When substrates bearing an electron-donating group, such as a methyl or methoxy group, were treated with TMSCN under these conditions, the corresponding α-aminonitriles **3**–**5** were obtained in good yields. Also for substrates having a relatively weak electron-withdrawing group, such as halogens, oxidative cyanation proceeded cleanly, producing the desired aminonitriles **6** and **7**.



Scheme 1 $CoCl_2$-catalyzed α-cyanation of various tertiary aromatic amines; isolated yields are given

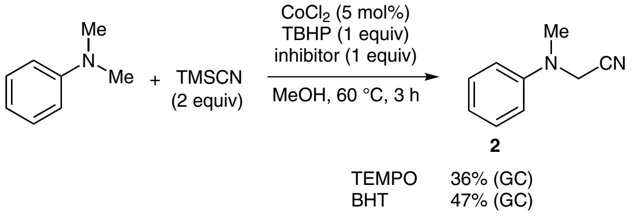
In contrast, this oxidative system was affected by a nitro group, which led to a decrease in the yield and to the recovery of the starting material. Moreover, this cyanation could be extended to the α-cyanation of cyclic tertiary amines. For example, when the oxidative cyanation was performed using a tertiary amine with pyrrolidine and piperidine rings, the corresponding products **9** and **10** were obtained in good yields. In contrast, although there is no clear explanation except a steric repulsion around the reaction site, use of *N*,*N*-diethylaniline as a substrate did not produce the corresponding α-aminonitrile at all.

In addition, as application, the substrate embedded in a tetrahydroisoquinoline skeleton could also be converted into the expected aminonitrile derivative **11** in a 66% yield, in which the α-cyanation at the benzyl position preferentially occurred (Scheme 2).



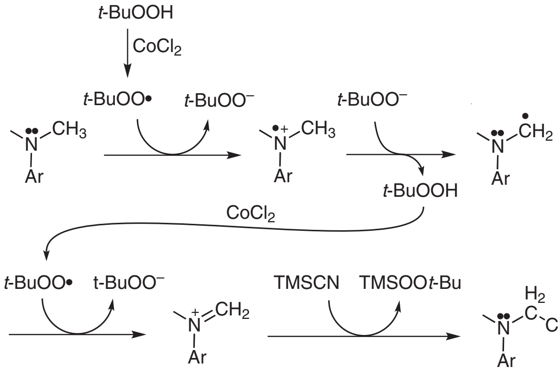
Scheme 2 α-Cyanation onto a tetrahydroisoquinoline skeleton

To better understand the reaction pathway for the cyanation series, control experiments were conducted (Scheme 3). When the reaction was carried out with radical scavengers, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di(*tert*-butyl)-*p*-cresol (BHT), a decrease in the yield of **2** was observed in both cases. Thus, it was implied that the reaction rate of the α-cyanation with a $CoCl_2$–TBHP system was mainly controlled by a single electron transfer (SET) rather than by an ionic path.



Scheme 3 Control experiments with a radical inhibitor

A plausible mechanism is shown in Scheme 4. The cobalt catalyst initially reacted with TBHP to produce a *tert*-butylperoxy radical, which undertook the SET reaction of a tertiary aromatic amine to form a radical cation intermediate.[11,13,14] The radical cation intermediate was converted into an iminium intermediate through both proton transfer (PT) and SET in the presence of the cobalt catalyst. Finally, the trimethylsilyl cyanide attacked the iminium intermediate to produce the final α-aminonitrile derivative.



Scheme 4 Plausible reaction path for cobalt-catalyzed α-cyanation of tertiary aromatic amines with TBHP

In conclusion, we demonstrated the cobalt-catalyzed oxidative cyanation of aromatic tertiary amines in the presence of TBHP leading to the preparation of aminonitriles. Further investigation into the mechanism of this reaction is now in progress.

Acknowledgment

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(12) **General Procedure**
To a 5 mL screw vial containing freshly distilled MeOH (0.6 mL) were successively added 1.0 M $CoCl_2$ in a MeOH solution (6.0 μL, 0.0060 mmol), aromatic tertiary amine (0.60 mmol), TMSCN (188 μL, 2.50 mmol), and 5.5 M TBHP in decane solution (164 μL, 0.900 mmol) under an ambient atmosphere. The resultant mixture was stirred at 60 °C (bath temperature), and consumption of the starting amine was monitored by GC analysis. After the reaction the resultant mixture was quenched with a aqueous solution of Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2, then the organic phases were dried over anhyd Na_2SO_4, filtered, and evaporated under a reduced pressure. The crude product was purified by silica chromatography (hexane–EtOAc, 4:1) to give the corresponding α-aminonitrile.
Selected Data for the Prepared Aminonitriles
***N*-Methyl-*N*-(4-methylphenyl)aminoacetonitrile (1)**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.95 (s, 3 H), 4.12 (s, 2 H), 6.78 (d, 2 H, *J* = 9.0 Hz), 7.11 (d, 2 H, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 39.4, 42.8, 115.3, 115.4, 129.8, 129.9, 145.6. MS (EI): *m/z* (%) = 160 (100) [M$^+$].
***N*-Methyl-*N*-(4-bromophenyl)aminoacetonitrile (7)**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.99 (s, 3 H), 4.15 (s, 2 H), 6.72 (d, 2 H, *J* = 9.0 Hz), 7.38 (d, 2 H, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.3, 42.1, 112.5, 115.1, 116.4, 132.2, 146.7. MS (EI): *m/z* (%) = 224 (100) [M$^+$]. The characterization of other α-aminonitriles was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis.

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(14) One reviewer pointed out that a reaction of $CoCl_2$ with TBHP initially generated $Co(III)Cl_2(OH)$ and a *tert*-butyloxy radical (*t*-BuO•, Equation 1, a). Those species are acceptable. However, both species would be promptly oxidized by an excess amount of TBHP to finally produce a *tert*-butylperoxy radical (*t*-BuOO•) through the following plausible oxidation steps (Equation 1, b and c).
Also, several groups reported that ruthenium-, rhodium-, or copper-catalyzed oxidative substitution of amines with TBHP, producing not the *N*,*O*-aminal derivative, but the amino peroxide derivative.[4f,13b,15] Moreover, Doyle et al. showed that $Co(OAc)_2$ converted TBHP into the *tert*-butylperoxy radical.[11] Therefore, we proposed the initial formation of the *tert*-butylperoxy radical by $CoCl_2$ as the plausible reaction path.

$$\mathrm{CoCl_2} + t\text{-}\mathrm{BuOOH} \longrightarrow \mathrm{Co(III)Cl_2(OH)} + t\text{-}\mathrm{BuO}\bullet \qquad \text{(a)}$$

$$\mathrm{Co(III)Cl_2(OH)} + t\text{-}\mathrm{BuOOH} \longrightarrow \mathrm{CoCl_2} + \mathrm{H_2O} + t\text{-}\mathrm{BuOO}\bullet \qquad \text{(b)}$$

$$t\text{-}\mathrm{BuO}\bullet + t\text{-}\mathrm{BuOOH} \longrightarrow \text{t-BuOH} + t\text{-}\mathrm{BuOO}\bullet \qquad \text{(c)}$$

Equation 1

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