Iron catalyzed oxidative cyanation of tertiary amines†‡

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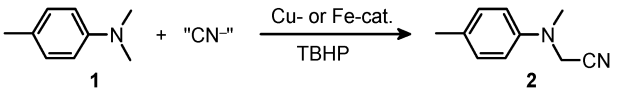
Iron(II) and iron(III) salts catalyze the oxidative α-cyanation of tertiary amines by trimethylsilyl cyanide in the presence of *tert*-butylhydroperoxide under acid-free conditions at room temperature.

The formation of new carbon–carbon bonds is the most important transformation in organic chemistry.[1] Transition metal catalyzed activation of C(sp^3)–H bonds and subsequent C–C bond formation which avoids the use of prefunctionalized starting material is therefore a valuable and straightforward synthetic strategy.[2–4] In contrast to many toxic and/or rare metals previously used for this transformation, iron is ubiquitous in the geosphere with 4.7% wt abundance and in the biosphere where it is often found as part of catalytic systems. Consequently, in recent years iron catalysts have been used for a multitude of organic syntheses, including oxidations and cross couplings.[5] So far, C–C bond forming reactions *via* iron catalyzed functionalization of C(sp^3)–H bonds generally require elevated temperatures (60 to 100 °C),[6–9] and we are not aware of a synthetic iron-based system sufficiently active to catalyze C(sp^3)–H cross couplings at room temperature.

Metal-catalyzed oxidative α-cyanation of tertiary amines *via* direct functionalization of C(sp^3)–H bonds provides access to α-aminonitriles.[10,11] $RuCl_3$[12a,c,4] and V_2O_5[13] catalyzed α-cyanation of amines with NaCN and molecular O_2 in acetic acid required heating to 60 °C. Recently, Murahashi *et al.* reported analogous $RuCl_3$ catalyzed oxidative cyanations of tertiary amines with hydrogen peroxide and experimentally confirmed the participation of HCN, which is formed *in situ* from NaCN and acetic acid (in MeOH, r.t.).[4,12b,c]

Copper and iron salts in the presence of oxidants, such as organic peroxides, O_2, or DDQ, are also capable of activating C(sp^3)–H bonds adjacent to nitrogen in amines.[3,7,8] Iron-containing heme and non-heme enzymes catalyze a variety of oxidative transformations,[14] and it is interesting to note that under conditions which avoid cytochrome P450 inhibition by CN^-, *N*,*N*-dimethylaniline reacts with NaCN in the presence of rat liver microsomes to form (*N*-methyl-*N*-phenyl-amino)-acetonitrile.[15] Miura *et al.* described the reactions of *N*,*N*-dimethylanilines with iron(III) chloride as catalyst (5 mol%), O_2 as oxidant, and benzoyl cyanide as cyanide source (MeOH, 50 °C, 16 h) to furnish mainly α-cyano compounds accompanied by *N*-methylformanilides and traces of *N*-benzoyl-*N*-methylanilines.[16]

Table 1 Oxidative α-cyanation of *N*,*N*-dimethyl-*p*-toluidine (**1**) in MeOH[a]



1 **2**

	Catalyst (mol%)	Cyanide source (equiv.)	Equiv. TBHP	*t*/h	Yield[b] (%)
1	CuBr (5)[c]	n-$Bu_4N^+CN^-$ (1.2)	1.2	24	9
2	$CuBr_2$ (10)	n-$Bu_4N^+CN^-$ (1.2)	1.2	24	15
3	CuBr (10)	n-$Bu_4N^+CN^-$ (1.5)	1.5	24	21
4	CuBr (10)	TMSCN (2.0)	2.5	10	26
5	$FeCl_2$ (10)	n-$Bu_4N^+CN^-$ (1.5)	1.5	24	10
6	$FeCl_2$ (10)	$K_3[Fe(CN)_6]$ (0.25)	1.5	24	25
7	$FeCl_2$ (10)	TMSCN (2.0)	1.5	24	86
8	**$FeCl_2$ (10)**	**TMSCN (2.0)**	**2.5**	**10**	**92**
9	None	TMSCN (2.0)	2.5	10	19
10	FeF_2 (10)	TMSCN (2.0)	2.5	10	37
11	$FeSO_4$ (10)	TMSCN (2.0)	2.5	10	43
12	$Fe(gluconate)_2$ (10)	TMSCN (2.0)	2.5	24	51
13	$Fe(OAc)_2$ (10)	TMSCN (2.0)	2.5	10	63
14	$Fe(acac)_3$ (10)	TMSCN (2.0)	2.5	10	59
15	$FeCl_3$ (10)	TMSCN (2.0)	2.5	10	90
16	$FeCl_3 \cdot 6H_2O$ (10)	TMSCN (2.0)	2.5	10	82
17	$FeBr_3$ (10)	TMSCN (2.0)	2.5	10	88

[a] *Reaction conditions*: *N*,*N*-dimethyl-*p*-toluidine (1.0 mmol), MeOH (2.0 mL), room temperature, dry N_2 atmosphere. [b] Yield of isolated product after column chromatography on silica gel. [c] Without methanol.

Herein we report the selective synthesis of α-aminonitriles under mild and acid-free conditions by oxidation of tertiary amines in the presence of inexpensive and non-toxic iron salts without designed ligands.

In a first series of experiments, we studied the catalytic efficiency of various copper and iron salts for the oxidative cyanation of *N*,*N*-dimethyl-*p*-toluidine (**1**) with different cyanide sources using *tert*-butylhydroperoxide (TBHP) as oxidant (Table 1).

Low yields of **2** were obtained by Cu(I) or Cu(II) bromide-catalyzed cyanation reactions with tetra-*n*-butylammonium cyanide or trimethylsilyl cyanide (TMSCN) (Table 1, entries 1–4). Similarly, the $FeCl_2$-catalyzed reaction of **1** with tetra-*n*-butylammonium cyanide or potassium hexacyanoferrate(III) (entries 5 and 6) gave only low yields,[17] but the conversion to the α-cyano derivative **2** was significantly improved when we employed 2 equiv. of TMSCN (86%). Optimum yields of **2** and shorter reaction times were obtained with 2.5 equivalents of TBHP (entry 8).[18–20]

The α-cyanation was achieved with different iron(II) and iron(III) salts. Whereas catalysis by FeF_2 or $FeSO_4$

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(entries 10 and 11) increased the yields only moderately above the level that was reached without catalyst (entry 9), catalysis by Fe(gluconate)$_2$ and Fe(OAc)$_2$ (entries 12 and 13) produced already acceptable yields of the α-cyanoamine **2**. Iron(III) salts $FeCl_3$, $FeCl_3 \cdot 6H_2O$, or $FeBr_3$ (entries 15–17) were comparably in activity (82–90% yield) to $FeCl_2$.

The combination of $FeCl_2$ with di-*tert*-butylperoxide, which had been reported to induce C(sp^3)–H bond activation adjacent to nitrogen,[7,8] was found to be ineffective for the cross-coupling reaction with TMSCN.

The addition of 5 or 100 mol% of the radical inhibitor 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) to the $FeCl_2$ (10 mol%)/TBHP/TMSCN mixture did not hinder the conversion of **1** into the corresponding α-cyanoamine **2** (87% and 60% isolated yields, respectively). This result is in agreement with previous reports on analogous $FeCl_3$-catalyzed oxidations of tertiary amines,[16,21] but differs from the observations of Sain and co-workers[13] on the V_2O_5-catalyzed formation of α-aminonitriles from tertiary amines and NaCN–AcOH under aerobic conditions. A detailed mechanistic study of the iron-catalyzed α-cyanations of tertiary amines presented in this paper is subject to future investigations.

In order to explore the functional group tolerance of the oxidative cyanations by $FeCl_2$/TMSCN/TBHP, a series of tertiary anilines were investigated as substrates in methanol at room temperature (Table 2).

Ring-substituted *N*,*N*-dimethylanilines in general reacted analogously and furnished the corresponding (*N*-aryl-*N*-methyl-amino)acetonitriles in high yield. The reaction times were found to be only loosely correlated with the electronic donor or acceptor properties of the substituents at the phenyl moiety.

The $FeCl_2$-catalyzed cross-coupling of tertiary amines with terminal alkynes using di-*tert*-butylperoxide as oxidant was recently described by Rao Volla and Vogel.[8] We found that under our conditions the presence of a *para*-ethynyl group at the phenyl ring did not disturb the high selectivity for the oxidative cyanation reaction at the *N*-methyl group (Table 2, entry 8).

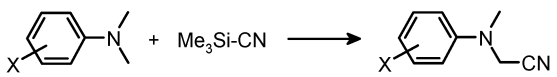
N,*N*-Dimethyl-*p*-nitroso-aniline was converted after 12 h at room temperature in high yield to the corresponding *p*-nitro compound, illustrating the incompatibility of the NO group with the oxidative reaction conditions, in accord with the finding that introducing an α-cyano group at the thus formed *p*-NO_2 derivative requires higher reaction temperatures (entry 9 and footnote *c* of Table 2).

As shown in Table 3, the α-cyano derivatives of 2-aryl-1,2,3,4-tetrahydro-isoquinolines (aryl = phenyl,[22] *p*-anisyl) and *N*-phenyl-substituted cyclic amines could also be obtained in high yield under reaction conditions similar to those optimized for the conversion of **1**. With a higher excess of TMSCN (4 equiv.) double cyanation of *N*-phenyl-pyrrolidine was observed.

Metal-catalyzed α-cyanations of tertiary alkyl amines have not been described so far.[8,23] GC-MS analysis of the oxidative cyanation of *N*,*N*-dimethyl benzylamine at room temperature (24 h, 63% conv.) indicated a C(sp^3)–H activation of similar extent for the two different α-positions adjacent to nitrogen.

In summary, we have demonstrated that environmentally benign iron salts activate C(sp^3)–H bonds adjacent to nitrogen in tertiary amines selectively to allow for efficient cross-coupling reactions with cyanide at room temperature. Future studies will further explore the substrate scope and selectivities of iron catalyzed C(sp^3)–H bond functionalizations.

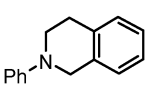
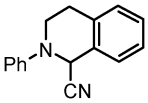
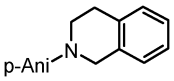
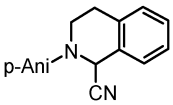
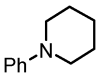
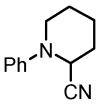
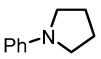
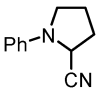
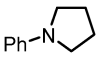
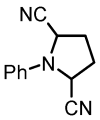
Table 2 $FeCl_2$-catalyzed oxidative cyanations of X-substituted *N*,*N*-dimethyl anilines[a]



Entry	X	*t*/h	Yield[b] (%)
1	*p*-OMe	14	87
2	*p*-Me	10	92
3	*m*-Me	10	89
4	*o*-Me	24	76
5	H	13	90
6	*p*-Br	10	78
7	*o*-Br	24[c]	85
8	*p*-C≡CH	5[c]	83
9	*p*-NO_2	24[c]	45
10	*m*-NO_2	15	80
11	*p*-NO	12	—[d]

[a] *Reaction conditions*: amine (1.0 mmol), $FeCl_2$ (0.10 mmol), TMSCN (2.0 mmol), TBHP (2.5 mmol), MeOH (2.0 mL), r.t., dry N_2 atmosphere. [b] Yields of isolated products after column chromatography on silica gel (for the characterization of new compounds, see the ESI‡). [c] The reaction mixture was heated to reflux. [d] The isolated product was *N*,*N*-dimethyl-*p*-nitro-aniline (84% yield).

Table 3 $FeCl_2$-catalyzed oxidative cyanations of tertiary amines[a]

Amine	*t*/h	Product	Yield[b] (%)
	13		85
	12		83[c]
	24[d]		~70[e]
	24[d]		82
	24[f]		54

[a] *Reaction conditions*: see footnote *a* of Table 2. [b] Yield of isolated product after column chromatography on SiO_2 (for the characterization of new compounds see the ESI‡). [c] *p*-Ani: *p*-MeO-C_6H_4–. [d] Without methanol. [e] Contaminated by *ca.* 15% of unknown byproducts that could not be separated by column chromatography. [f] 4 equiv. of TMSCN was used.

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18 Under similar conditions the use of other solvents was less efficient (isolated yields of **2**): *tert*-butanol (47%), ethanol (53%), acetonitrile (52%), 2,2,2-trifluoroethanol (71%), isopropanol (78%).

19 Reducing the excess of TMSCN (1.5 equiv.) required extended reaction times (24 h, 85% yield), and the use of equimolar amounts of TMSCN affected the yield of **2** (24 h, 69%).

20 The presence of additional n-$Bu_4N^+CN^-$ (1.0 equiv.) under otherwise optimized reaction conditions (*cf.* entry 8 of Table 1) resulted in a slight retardation of the cyanation reaction (63% isolated yield of **2** after 12 h) possibly because of a decrease in the concentration of the active catalyst.

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