

# Iron(II)-Catalyzed Direct Cyanation of Arenes with Aryl(cyano)-iodonium Triflates\*\*

Zhibin Shu, Wenzhi Ji, Xi Wang, Yujing Zhou, Yan Zhang, and Jianbo Wang\*

Dedicated to Professor Max Malacria on the occasion of his 65th birthday

**Abstract:** A direct oxidative cyanation of arenes under  $\text{Fe}^{\text{II}}$  catalysis with 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (DFCT) as the cyanating agent has been developed. The reaction is applicable to wide range of aromatic substrates, including polycyclic structures and heteroaromatic compounds.

The aromatic cyano group is widely applied in functional-group transformations, including the formation of aromatic acids, aldehydes, amines, amides, and heterocycles.<sup>[1]</sup> Aryl nitriles are also found as integral parts of many dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.<sup>[2]</sup> Consequently, the development of efficient methods for the synthesis of aryl nitriles has been pursued for many decades.

The Sandmeyer and Rosenmund–von Braun reactions are two classical functional-group transformations for the synthesis of aromatic nitriles.<sup>[3]</sup> However, both reactions require toxic copper(I) cyanide as the cyano source and occur under rather harsh reaction conditions. The nucleophilic cyanation of aryl halides under the catalysis of transition metals with KCN or NaCN,<sup>[4]</sup>  $\text{Zn}(\text{CN})_2$ ,<sup>[5]</sup> acetone cyanohydrin,<sup>[6]</sup> trimethylsilyl cyanide,<sup>[7]</sup> and  $\text{K}_4[\text{Fe}(\text{CN})_6]$ <sup>[8]</sup> as cyanating agents has emerged as an alternative route to aryl nitriles. Moreover, directing-group-assisted transition-metal-catalyzed C–H bond functionalization has enabled the direct cyanation of aromatic C–H bonds.<sup>[9]</sup>

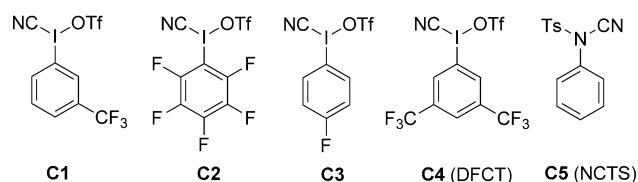
Although much effort and remarkable progress has been made in this area, some drawbacks remain with these reactions. The major drawback is the high affinity of the cyanide ion for the transition metal, which often results in rapid deactivation of the catalyst. Moreover, most of the cyano sources, in particular KCN, CuCN,  $\text{Zn}(\text{CN})_2$ , and TMSCN, have notorious toxicity. Recently, the search for

alternative cyano sources, such as ammonium salts, DMSO, and DMF, has attracted considerable attention, and significant progress has been made.<sup>[10,11]</sup>

As an alternative to nucleophilic cyanation, electrophilic cyanation has become a promising strategy for the synthesis of aromatic nitriles. So far, electrophilic cyanation reactions of reactive aryl nucleophiles, such as aryl stannanes and Grignard, zinc, and lithium reagents, have been documented.<sup>[11b,12]</sup> However, in most of the established electrophilic cyanation processes, highly toxic cyanogen halides are unavoidable: They are used either to prepare the cyanating reagent or as a direct cyano source. Moreover, direct C–H bond cyanation of arenes without a directing group is still very limited.<sup>[13]</sup> Recently, Ohe and co-workers reported an interesting  $\text{GaCl}_3$ -catalyzed electrophilic cyanation of electron-rich aromatic compounds with cyanogen bromide as the cyano source.<sup>[13c]</sup>

We recently reported a  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed cyanation of indoles and pyrroles with *N*-cyano-*N*-phenyl-*para*-toluenesulfonamide (NCTS) as the electrophilic cyano source.<sup>[14]</sup> However, this reaction system failed when applied to substituted benzene derivatives. In our continued search for new and efficient cyanation systems,<sup>[15]</sup> we noticed that hypervalent iodine(III) reagents have been widely applied to direct oxidative nucleophilic substitution reactions of aromatic compounds with various nucleophiles, such as  $-\text{CN}$ ,  $-\text{N}_3$ ,  $-\text{OAc}$ , and  $-\text{SCN}$ , under mild conditions.<sup>[16]</sup> In particular, Kita and co-workers reported the direct cyanation of aromatic compounds in a reaction mediated by hypervalent iodine(III) reagents generated in situ.<sup>[17]</sup> However, this direct cyanation system is only compatible with electron-rich heteroaromatic compounds. Herein, we demonstrate an efficient iron(II)-catalyzed direct cyanation of arenes under mild conditions with aryl(cyano)iodonium triflates as the cyano source.

The aryl(cyano)iodonium triflates **C1–4** (Scheme 1) were developed by Stang and co-workers.<sup>[18,19]</sup> These reagents, which are prepared by the treatment of  $\text{ArI}(\text{CO}_2\text{CF}_3)_2$  with



**Scheme 1.** Aryl(cyano)iodonium triflates and NCTS. Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

[\*] Z. Shu, W. Ji, X. Wang, Y. Zhou, Prof. Dr. Y. Zhang, Prof. Dr. J. Wang Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of the Ministry of Education, College of Chemistry, Peking University Beijing 100871 (China)  
E-mail: wangjb@pku.edu.cn

Prof. Dr. J. Wang  
The State Key Laboratory of Organometallic Chemistry, SIOC  
Chinese Academy of Sciences  
Shanghai 200032 (China)

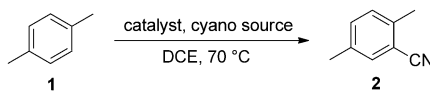
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Me<sub>3</sub>SiOTf and Me<sub>3</sub>SiCN, are relatively stable and can be stored for months in a refrigerator without evident decomposition. These reagents have found application as useful iodonium-transfer reagents in the synthesis of various alkynyl iodonium and alkenyl iodonium salts.<sup>[18a]</sup> To the best of our knowledge, they have not been used as electrophilic cyanating agents.

At the outset, the hypervalent iodine(III) reagent **C1** was tested for the direct cyanation of *p*-xylene (**1**; Table 1). A series of catalysts, including BF<sub>3</sub>·Et<sub>2</sub>O, CuBr, CuCl, CoCl<sub>2</sub>,

**Table 1:** Cyanation reaction of *p*-xylene (**1**).<sup>[a]</sup>

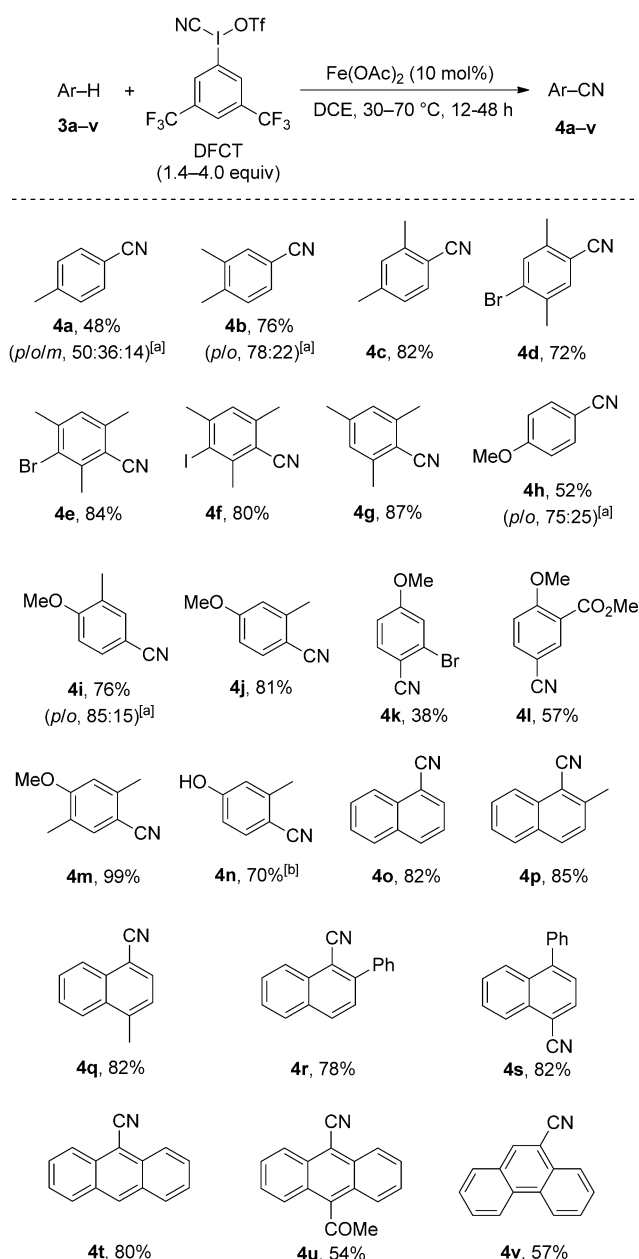
			
Entry	Catalyst (mol %)	Cyanating agent (equiv)	Yield [%] <sup>[b]</sup>
1	CuBr (10)	<b>C1</b> (2)	0
2	CuCl (10)	<b>C1</b> (2)	0
3	CoCl <sub>2</sub> (10)	<b>C1</b> (2)	0
4	SnCl <sub>2</sub> (10)	<b>C1</b> (2)	0
5	FeCl <sub>2</sub> (5)	<b>C1</b> (2)	trace <sup>[c]</sup>
6	FeBr <sub>2</sub> (5)	<b>C1</b> (2)	trace <sup>[c]</sup>
7	FeF <sub>2</sub> (5)	<b>C1</b> (2)	trace
8	Fe(OTf) <sub>2</sub> (5)	<b>C1</b> (2)	trace
9	Fe(OAc) <sub>2</sub> (5)	<b>C1</b> (2)	trace
10	Fe(OAc) <sub>2</sub> (5)	<b>C2</b> (2)	20
11	Fe(OAc) <sub>2</sub> (5)	<b>C3</b> (2)	trace
12	Fe(OAc) <sub>2</sub> (5)	<b>C4</b> (2)	47
13	Fe(OAc) <sub>2</sub> (10)	<b>C4</b> (4)	73
14	none	<b>C4</b> (4)	N.R. <sup>[d]</sup>

[a] Reaction conditions: **1** (0.2 mmol), catalyst, cyanating agent, 1,2-dichloroethane (DCE; 2 mL), 12 h. [b] Yield of the isolated product.

[c] The main products were halogenated arenes. [d] N.R.: no reaction.

and SnCl<sub>2</sub>, were examined; however, no expected cyanation product **2** could be identified (Table 1, entries 1–4). When Fe<sup>II</sup> catalysts were examined, we observed the formation of a trace amount of the desired product (Table 1, entries 5–9). With Fe(OAc)<sub>2</sub> (5 mol %) as the catalyst, other cyanating agents **C2–4** were then examined. To our delight, the cyanation product **2** could be isolated in improved yield with these cyanating agents (Table 1, entries 10–12). With 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (**C4**, DFCT) as the cyanating agent, the yield was further improved by increasing the loading of the catalyst from 5 to 10 mol % (Table 1, entry 13). A control experiment indicated that in the absence of a metal catalyst, no reaction occurred (Table 1, entry 14). Finally, for comparison, NCTS (**C5**) was also examined. No desired cyanation product was identified with NCTS under otherwise identical conditions, or under our previous conditions for indole cyanation with BF<sub>3</sub>·OEt<sub>2</sub> (100 mol %).<sup>[14]</sup>

Having optimized the reaction conditions, we next proceeded to explore the scope of the reaction. The cyanation of benzene derivatives with various electron-donating substituents proceeded smoothly (Scheme 2), whereby the reaction temperature and the amount of DFCT required varied depending on the reactivity of the arene substrate.<sup>[20]</sup> The



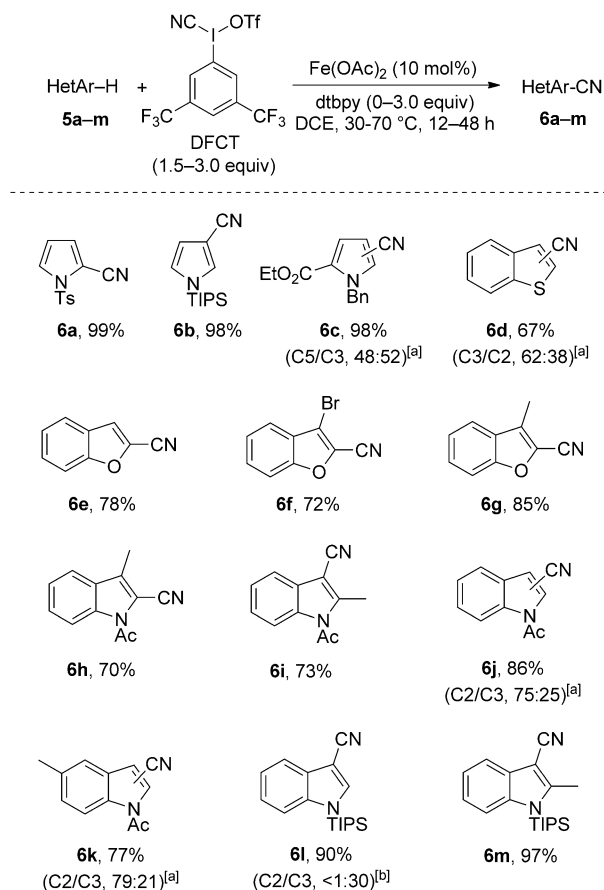
**Scheme 2.** Scope of the cyanation of arenes. [a] The ratio was determined by <sup>1</sup>H NMR spectroscopy. [b] The starting material was *m*-tolyl acetate.

cyanation of toluene gave a mixture of three regioisomers (product **4a**). Similar results were observed for the cyanation of *o*-xylene (product **4b**). The regioselectivity of the cyanation reaction is governed by both electronic and steric effects of the substituents, in a similar manner to the hypervalent-iodine-induced nucleophilic substitution reactions reported by Kita and co-workers.<sup>[16]</sup> The reaction with electron-rich mesitylene afforded the product **4g** in nearly quantitative yield. The cyanation was also successful with methoxy-substituted benzene derivatives (products **4h–m**) and a hydroxy-substituted substrate (**4n**).

Notably, the cyanation reaction with polycyclic aromatic substrates, such as naphthalene derivatives (products **4o–s**),

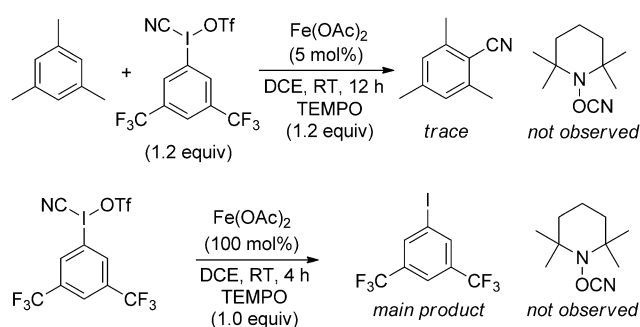
anthracene derivatives (**4t,u**), and phenanthrene (product **4v**), all proceeded well and afforded the corresponding cyanation products as single regioisomers in moderate to high yields. The results are in accordance with the high reactivity of these positions for electrophilic substitution.

Next, we extended the cyanation reaction to heteroaromatic compounds (Scheme 3). Heteroaromatic compounds



**Scheme 3.** Cyanation of heteroarenes. [a] The ratio was determined by <sup>1</sup>H NMR spectroscopy. [b] The ratio was determined by GC. Bn = benzyl, dtbpy = 2,6-di-*tert*-butylpyridine, TIPS = triisopropylsilyl.

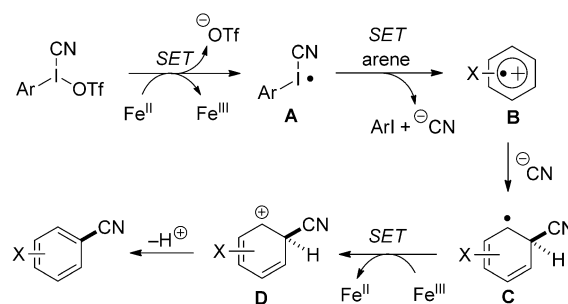
were generally more reactive toward electrophilic cyanation, although the regioselectivity was significantly affected by the structure of the substrate. The amount of the cyanating agent DFCT required also varied depending on the substrate, and in most cases 2,6-di-*tert*-butylpyridine was needed to optimize the yield.<sup>[20]</sup> In the case of pyrroles, it was possible to control the cyanation to occur at either the C2 or the C3 position through fine-tuning of the substituent on the nitrogen atom (products **6a,b**). The control of regioselectivity can be interpreted in terms of steric effects of the substituent. Interestingly, benzofuran and benzothiophene showed different selectivities for C2 and C3 cyanation (products **6d,e**). For indole derivatives, the C2 cyanation showed high reactivity; however, the selectivity could be controlled by the substituent on the nitrogen atom (products **6j–l**).



**Scheme 4.** Radical-trapping experiments. TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

We carried out experiments to elucidate the reaction mechanism (Scheme 4). When the reaction of mesitylene and DFCT was conducted in the presence of a stoichiometric amount of TEMPO, the transformation of mesitylene was almost completely inhibited, but no adduct derived from the trapping of cyano radical by TEMPO could be observed. When the reaction of DFCT and TEMPO was carried out in the absence of mesitylene and with stoichiometric Fe(OAc)<sub>2</sub>, the TEMPO–CN adduct was also not observed.

On the basis of these preliminary experiments and the studies by Kita and co-workers,<sup>[17]</sup> we propose a reaction mechanism which involves a single-electron-transfer (SET) sequence (Scheme 5). The highly reactive radical species **A** is



**Scheme 5.** Proposed reaction mechanism.

initially produced through single-electron transfer from Fe<sup>II</sup> to DFCT. A pathway via a free cyano radical can be ruled out because cyano radical was not trapped by TEMPO. Instead, we suggest SET from the radical species **A** to the arene substrate to form intermediate **B**; nucleophilic addition of cyanide ion to **B** then generates radical intermediate **C**. Finally, SET occurs to give cation intermediate **D**, the deprotonation of which affords the final product.<sup>[17]</sup>

In summary, we have developed a direct oxidative cyanation of arenes under Fe<sup>II</sup> catalysis by using DFCT as the cyanating agent. The procedure has been successfully applied to the direct cyanation of a wide range of aromatic substrates, including polycyclic structures and heteroaromatic compounds. Further studies are ongoing to expand the reaction scope and identify more reactive cyanating agents.

## Experimental Section

Typical procedure: Under a nitrogen atmosphere, a mixture of *p*-xylene (**1**; 32.0 mg, 0.3 mmol), DFCT (618 mg, 1.2 mmol, 4.0 equiv), and iron(II) acetate (2.6 mg, 0.015 mmol, 0.05 equiv) in 1,2-dichloroethane (3 mL) was stirred at 70 °C for 12 h. After cooling, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed with aqueous saturated NaHCO<sub>3</sub> and then aqueous FeCl<sub>3</sub>. The aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and the combined organic phases were dried with anhydrous MgSO<sub>4</sub> and then concentrated in vacuo. Purification of the crude residue by column chromatography afforded pure **2** (29 mg, 73 % yield) as a solid.

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- [20] See the Supporting Information for the details of each reaction.