Copper-Mediated Sequential Cyanation of Aryl C−B and Arene C−H Bonds Using Ammonium Iodide and DMF

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S *Supporting Information*

ABSTRACT: The cyanation of aromatic boronic acids, boronate esters, and borate salts was developed under copper-mediated oxidative conditions using ammonium iodide and DMF as the source of nitrogen and carbon atom of the cyano unit, respectively. The procedure was successfully extended to the cyanation of electron-rich benzenes, and regioselective introduction of a cyano group at the arene C−H bonds was also achieved. The observation that the reaction proceeds via a two-step process, initial iodination and then cyanation, led us to propose that ammonium iodide plays a dual role to provide iodide and nitrogen atom of the cyano moiety.

Nitriles are a ubiquitous structural motif frequently found in natural products and synthetic intermediates, and their facile access is important in the manufacture of pharmaceuticals, agrochemicals, and dyes.[1] Cyano unit is a key precursor for diverse functional groups including aldehydes, amines, amidines, tetrazoles, or amides.[2] Recently, the synthetic utility of organonitriles has been investigated relying on the catalytic cleavage of carbon−cyano bond.[3] Whereas traditional methods such as Sandmeyer[4] or Rosenmund−von Braun reaction[5] are routinely employed for the preparation of nitriles, metal-mediated approach has also been investigated in the coupling of aryl (pseudo)halides with metal cyano reagents such as MCN (M = K, Na, or Zn), TMSCN, or K$_3$Fe(CN)$_6$.[6−11] In those reactions, not only aryl halides but also C−H bonds of (hetero)arenes bearing suitable directing groups can be directly cyanated under various conditions mainly using metal cyanides.[12] Recently, certain organic precursors such as acetone cyanohydrin have been employed in catalytic cyanations to release cyanide *in situ* although a careful control of its concentration was required.[13,14]

We recently reported that aqueous ammonia and *N*,*N*-dimethylformamide (DMF) were used in combination to afford "cyano" unit *in situ* under copper-mediated oxidative conditions, and this protocol was successfully utilized in the Pd-catalyzed C−H cyanation of 2-phenylpyridines.[15] Labeling experiments revealed that nitrogen and carbon atom of "CN" were originated from ammonia and the *N*,*N*-dimethyl moiety of DMF, respectively. Similar approaches of generating the cyano unit by using ammonium salts and DMF (or DMSO) were subsequently applied to the Pd-catalyzed cyanation of indoles[16] and Cu-mediated cyanation of aryl halides.[17]

Although aryl boronic acids are readily available and convenient coupling reagents, their conversion to nitriles has been rarely studied. Only in recent years, Hartwig[18a] and Cheng[18b] independently reported the Cu-mediated cyanation of aryl boronates and boronic acids using Zn(CN)$_2$ and CuCN (or TMSCN/CuI), respectively. Herein, we present our new cyanation protocol of aryl boronic acids, boronates, and borate salts using ammonium iodide and DMF under Cu-mediated oxidative conditions (Scheme 1). The reaction was revealed to
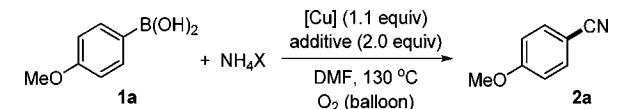
Scheme 1
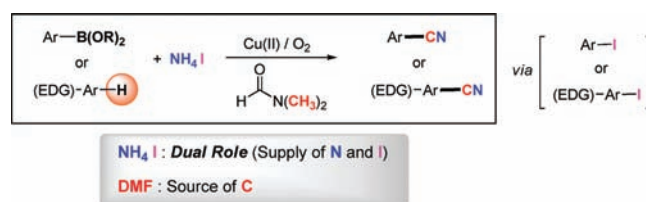
proceed via a two-step process: initial iodination and then cyanation.[12a,19] The procedure was successfully applied also to the cyanation of electron-rich arene C−H bonds. In this study, ammonium iodide was found to play a dual role to supply both iodide and nitrogen atom of the cyano unit. *This is the first example, to the best of our knowledge, of utilizing both cationic and counteranionic part of ammonium iodide in metal-mediated reactions.*

Using 4-methoxyphenylboronic acid (1a) as a test substrate, optimal conditions were first sought for the cyanation (Table 1). When aqueous ammonia was employed as in our previous case,[15] 4-methoxybenzonitrile (2a) was not formed irrespective of copper species (entries 1−2). On the other hand, the use of NH$_4$I offered 2a albeit in varied yields depending on copper salts (entries 3−6).[20] Among those metal species screened, Cu(NO$_3$)$_2$·3H$_2$O (2.0 equiv to 1a) was most effective for the cyanation in the presence of acetic acid additive (entries 7−11). No cyanated product was obtained if a base was added (entry 9). Interestingly, similar efficiency was also obtained by the combined use of NH$_4$OAc and I$_2$ (entry 12), which has an important clue for the mechanistic details (*vide infra*).

With the optimal conditions in hands, we next examined the scope and limitations of our method (Table 2). In general, reaction of aryl boronic acids bearing e-donating groups gave
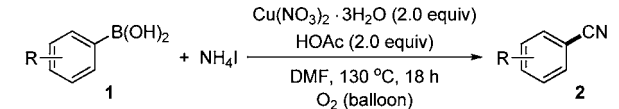
Table 1. Optimization of Copper-Mediated Cyanation[a]

entry	Cu	NH₄X	additive	yield (%)[b]
1	CuBr₂	NH₃ (aq)	–	0
2	Cu(OAc)₂	NH₃ (aq)	–	0
3	Cu(OAc)₂	NH₄I	–	28
4	CuBr₂	NH₄I	–	0
5	CuSO₄	NH₄I	–	7
6	Cu(NO₃)₂·3H₂O	NH₄I	–	55
7	Cu(NO₃)₂·3H₂O	NH₄I	HOAc	72
8[c]	Cu(NO₃)₂·3H₂O	NH₄I	HOAc	90
9[c]	Cu(NO₃)₂·3H₂O	NH₄I	K₂CO₃	0
10[c]	CuI	NH₄I	HOAc	21
11[c]	CuCN	NH₄I	HOAc	30
12[c]	Cu(NO₃)₂·3H₂O	NH₄OAc	I₂	92

[a]Conditions: 1a (0.3 mmol), NH₄X (0.6 mmol), Cu salt, and additive (2.0 equiv) in DMF (1.5 mL) under O₂ balloon at 130 °C for 18 h. [b]Determined by ¹H NMR (internal standard: 1,1,2,2-tetrachloroethane). [c]2.0 equiv of copper species was used.
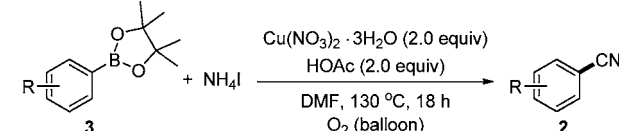
Table 2. Cu-Mediated Cyanation of Boronic Aicds[a]

[a]Conditions: 1 (0.3 mmol), NH₄I (0.6 mmol), Cu(NO₃)₂·3H₂O (2.0 equiv) and HOAc (2.0 equiv) in DMF (1.5 mL) under O₂ balloon at 130 °C for 18 h. [b]Determined by ¹H NMR.

slightly higher product yields than those containing e-withdrawing moieties (2a–2f). It is notable that a wide range of functional groups were compatible with the conditions. Aryl boronic acids substituted at the *para*-, *meta*-, and *ortho*-position were all smoothly cyanated in good yields (2a, 2g, and 2h). The reaction of disubstituted aryl boronic acids was also efficient (2i–2k). Polyaryl substrates such as 1- or 2-naphthalene- and 9-phenanthreneboronic acid were readily cyanated (2l–2n). In addition, heteroaryl substrates such as 3-pyridineboronic acid underwent the cyanation albeit in moderate yield (2o). Cinnamonitrile was obtained with a slight decrease of the stereosense from (*E*)-styreneboronic acid (2p).[21]

The aspect that boronic esters are less polar and easier to handle than boronic acids has resulted in the increased utility of boronates in organic synthesis.[22] When aryl pinacolboronates were examined, we were pleased to find that the cyanation occurred readily to afford comparable or higher product yields when compared to the corresponding boronic acids (Table 3).

Table 3. Cu-Mediated Cyanation of Aryl Boronate Esters[a]

[a]Conditions: 3 (0.3 mmol), NH₄I (0.6 mmol), Cu(NO₃)₂·3H₂O (2.0 equiv), and HOAc (2.0 equiv) in DMF (1.5 mL) under O₂ balloon at 130 °C for 18 h.

The fact that borate salts such as potassium trifluoroborates are a new class of air-stable and easily accessible compounds[23] led us to test the suitability of borates in the cyanation (Scheme 2). It was found that phenylborate salts were readily

Scheme 2
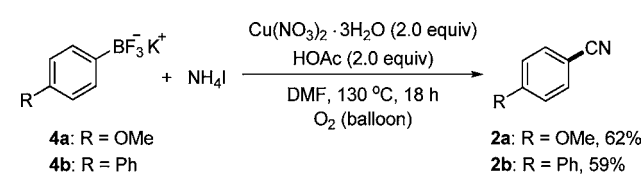
cyanated under the optimal conditions although yields were slightly lower than the corresponding boronic acids or boronate esters.

In order to investigate reaction pathways, a series of mechanistic studies were next carried out. First, a reaction profile was obtained in the cyanation of 4-methoxyphenylboronic acid (1a) under the standard conditions (Figure 1).[24] Within 1 h, 4-iodoanisole (5a) was detected to form over than 70%, and then 4-methoxybenzonitrile (2a) started to be produced with the concomitant disappearance of 5a, thus implying the intermediacy of 5a in the course of the cyanation. Indeed, separately prepared 5a underwent the cyanation almost quantitatively when ammonium acetate instead of its iodide salt was allowed to react under the otherwise identical conditions (eq 1).

Moreover, *in situ* formation of cyanide anion was confirmed by the cyanide-detecting test with a picric acid strip.[24] When
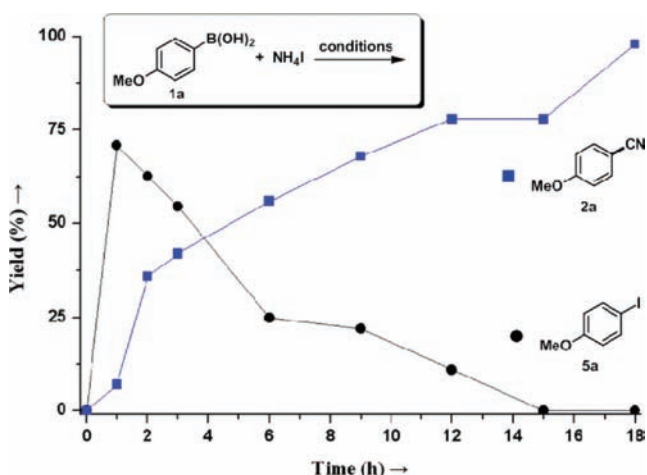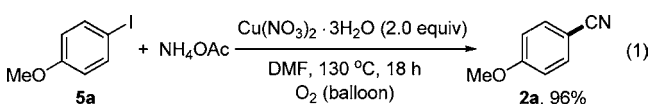
Figure 1. Reaction profile in the Cu-mediated cyanation of **1a**.

NH$_4$I was treated with equivalent Cu(NO$_3$)$_2$·3H$_2$O in DMF under O$_2$ at 130 °C, colorless precipitate was produced, and its structure was identified as CuI by a XRD analysis.[25]

The above results led us to propose a sequential cyanation pathway going through the initial formation of an aryl iodo intermediate followed by subsequent cyanation (Scheme 3). As

**Scheme 3. Proposed Mechanistic Pathways of the Cyanation**
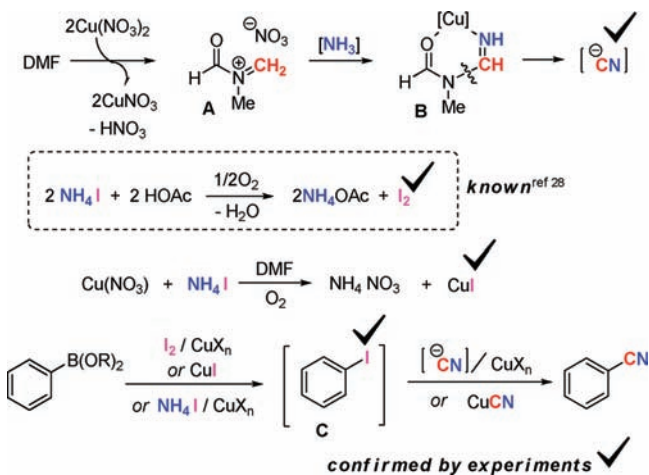
we previously proposed in the cyanation of 2-phenylpyridines,[15] it is assumed that DMF is initially oxidized to its iminium species **A** upon the reduction of Cu(II) salts to Cu(I).[26] Cyanide ion is envisioned to form upon the reaction of **A** with ammonia presumably via an amidinyl species **B**.[27] Since ammonium iodide is known to undergo decomposition to give ammonia and iodine,[28] the role of acetic acid additive is assumed to capture the released ammonia leading to its acetate salt.[29]

Formation of the key intermediate iodoarene **C** would be feasible through the reaction of boronates with certain plausible iodide sources such as CuI, I$_2$, or NH$_4$I where copper species might facilitate its conversion in the latter two cases. Finally, cyanation of intermediate **C** would take place presumably

upon the reaction with either naked cyanide anion under copper-mediated conditions or CuCN that might be formed by the ligand exchange of CuI with cyanide anion.[30]

Based on the above mechanistic proposal, we envisaged that cyanation of electron-rich benzenes would be possible since they are prone to undergo the initial iodination step.[31] Indeed, we were delighted to see *the first example of the sequential cyanation of arene C−H bonds under the oxidative copper-mediated conditions using NH$_4$I and DMF* (Table 4). 1,3,5-Trimethoxybenzene was

Table 4. Cu-Mediated Cyanation of Electron-Rich Arenes[a]
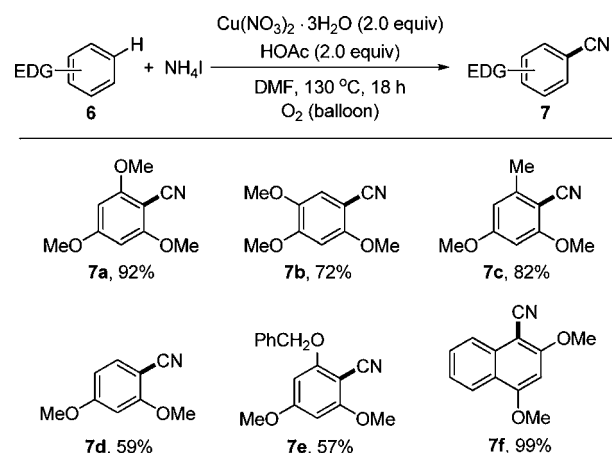
[a]Conditions: **6** (0.3 mmol), NH$_4$I (0.6 mmol), Cu(NO$_3$)$_2$·3H$_2$O (2.0 equiv), and HOAc (2.0 equiv) in DMF (1.5 mL) under O$_2$ balloon at 130 °C for 18 h.

cyanated in high yield (**7a**). Interestingly, 1,2,4-trimethoxybenzene and 1,3-dimethoxy-5-methylbenzene underwent the cyanation preferentially at the coinciding C−H bond from two *ortho-* and *para-*methoxy groups although the exact reason for this regioselectivity is not clear at the present stage (**7b** and **7c**). As expected on the analogy with this argument, 1,3-dimethoxybenzene was cyanated indeed exclusively at the 4-position albeit with slightly lower yield (**7d**). Likewise, selective reaction was also observed with 1,3-dimethoxy-5-(benzyloxy)benzene (**7e**), and no cyanation occurred at the unsubstituted phenyl side of the benzyloxy moiety. When 1,3-dimethoxynaphthalene was subjected to the conditions, cyanation took place smoothly, as anticipated, at the coinciding C−H bond positioned from two *ortho-* and *para-*methoxy groups, and the desired product **7f** was obtained in excellent yield.

It needs to be addressed that a similar reaction profile was also obtained from this arene C−H cyanation,[24] thereby suggesting that the same two-step pathway going through the initial iodination followed by subsequent cyanation operates in both cyanations of aryl boronate C−B and arene C−H bonds.

Recently, Hartwig et al. reported a one-pot method of two-step cyanation of arenes *via* Ir-catalyzed borylation and Cu-mediated cyanation of initially formed aryl boronates with zinc cyanide.[18a] After obtaining 1,3-dimethoxy-5-pinacolboronate according to the Hartwig C−H borylation protocol, we successfully applied our present method for the subsequent cyanation using NH$_4$I/DMF either in one-pot or in a two-step manner to give **8d** (Scheme 4, route **A**). On the other hand, *a regioselective cyanation of 6d was also realized using our method leading to 7d, a regioisomer of 8d* (route **B**). This is a nice

Scheme 4. Regioselective Cyanation of Arene C−H Bonds

8d, 35% (one-pot)
52% (two separate steps)

6d

7d, 59%
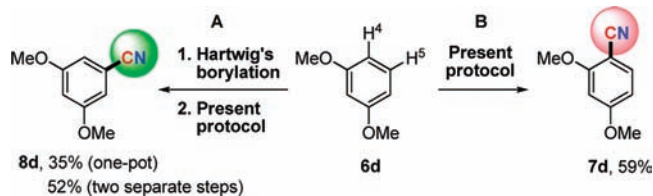
example of *how our approach can readily be utilized for the generation of isomeric benzonitriles upon the choice of cyanation routes.*

In conclusion, we have developed a new procedure of the copper-mediated cyanation using ammonium iodide and DMF. Boronic acids, boronate esters, borate salts, and electron-rich arenes were efficiently cyanated with broad substrate scope and high functional group tolerance. The reaction was proposed to proceed in two steps *via* initial iodination and subsequent cyanation. Ammonium iodide plays a dual role to supply iodide and nitrogen atom of the cyano unit, thus representing the first example of utilizing both cationic and anionic species of ammonium salts in metal-mediated reactions. Further studies on the details of the cyanide-generating process are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedure and characterization of new compounds, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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