

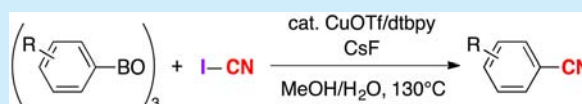
# Copper-Catalyzed Cyanation of Aryl- and Alkenylboronic Reagents with Cyanogen Iodide

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**S** Supporting Information

**ABSTRACT:** Direct catalytic cyanation of organoboronic acids with cyanogen iodide has been achieved by using a copper–bipyridine catalyst system. The cyanation reaction is likely to occur through two catalytic cycles: copper(II)-catalyzed iodination of organoboronic acids and the following cyanidocopper(I)-mediated cyanation of organic iodides.

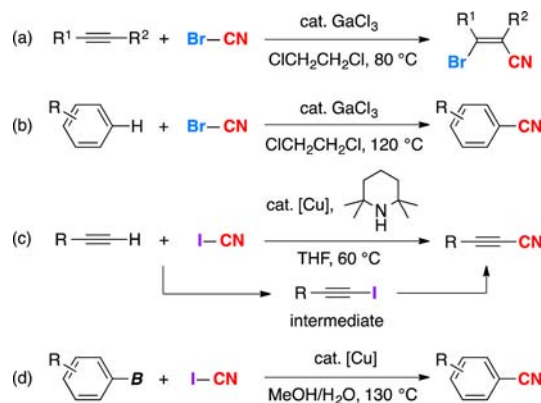


Aromatic and  $\alpha,\beta$ -unsaturated nitriles constitute an important class of compounds that are seen in many organic electronic materials,<sup>1</sup> medicinal compounds,<sup>2</sup> and natural resources.<sup>3</sup> These compounds are also important as synthetic intermediates for the development of useful organic molecules because the cyano group can be transformed into a range of functional groups such as carboxylic acids, esters, amides, and aldehydes.<sup>4</sup> Conventional cyanation methods for the synthesis of nitriles typically employ the corresponding organic halides or diazonium salts with copper cyanide,<sup>5</sup> or the combination of cyanide anion equivalents and transition-metal catalysts.<sup>6,7</sup>

In contrast to these nucleophilic cyanation reagents, cyanogen bromide and cyanogen iodide usually behave as electrophilic cyanation reagents, and such species can be used for the cyanation of carbon nucleophiles without any additional oxidant.<sup>8,9</sup> Therefore, cyanation reactions using cyanogen halides are regarded as complementary to traditional cyanation methods using cyanide anion reagents. We have previously reported that gallium(III) chloride acts as an efficient catalyst for the activation of cyanogen bromide in both bromocyanation of alkynes and Friedel–Crafts-type aromatic cyanation (Scheme 1a,b).<sup>10</sup> We have also shown that copper(I) triflate can effectively catalyze the C–H cyanation of terminal alkynes with cyanogen iodide (Scheme 1c).<sup>11</sup> In the latter reaction, remarkably, the cyanation proceeds indirectly through the intermediary formation of alkynyl iodide rather than through direct cyanation from copper acetylide.

Organoboronic acid derivatives are the most widely used class of building blocks for transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions.<sup>12</sup> Conventional methods for the synthesis of organoboronic compounds typically start from the corresponding halide.<sup>13</sup> However, in 2002, Ishiyama, Miyaura, and Hartwig developed an iridium-catalyzed C(sp<sup>2</sup>)–H borylation reaction of arenes that enabled the halide-free synthesis of arylboronic compounds with completely different regioselectivity to that generated by using halide-based methods.<sup>14</sup> Given the rapid development in the chemistry of organoboronic acids, much attention has been paid to the direct catalytic oxidative cyanation of arylboronic acid derivatives as a

## Scheme 1. Catalytic Transformation of Hydrocarbons with Cyanogen Halides

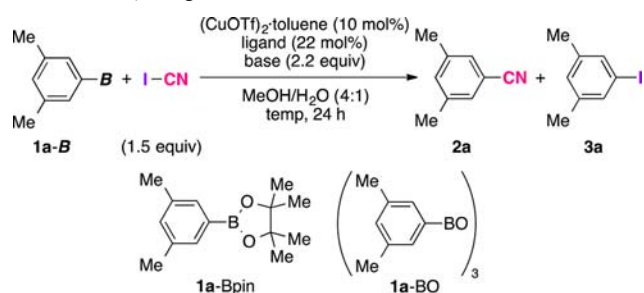


method to access aromatic nitriles.<sup>15,16</sup> However, the reported methods for such reactions leave much room for development because of the use of highly expensive rhodium catalyst<sup>15c</sup> or because of the requirement for a stoichiometric amount of copper or silver salt. Based on our previous report, we envisioned that the catalytic cyanation of organoboronic reagents could be achieved by utilizing a combination of copper catalyst and cyanogen iodide. Herein, we detail a methodology that can be used for the copper-catalyzed cyanation of organoboronic acids with cyanogen iodide and provide some mechanistic insights on the activation of cyanogen iodide and boronic acids by the copper catalyst (Scheme 1d).

Initially, the reaction conditions were optimized by using 3,5-dimethylphenylboronic acid pinacol ester (**1a-Bpin**), cyanogen iodide, base, and copper catalyst (Table 1). Initial attempts at the cyanation of **1a-Bpin** were performed with cyanogen iodide (1.5 equiv), 2,2,6,6-tetramethylpiperidine (TEMP; 2.2 equiv), and (CuOTf)<sub>2</sub>·toluene (10 mol %) in THF at 60 °C for 24 h;

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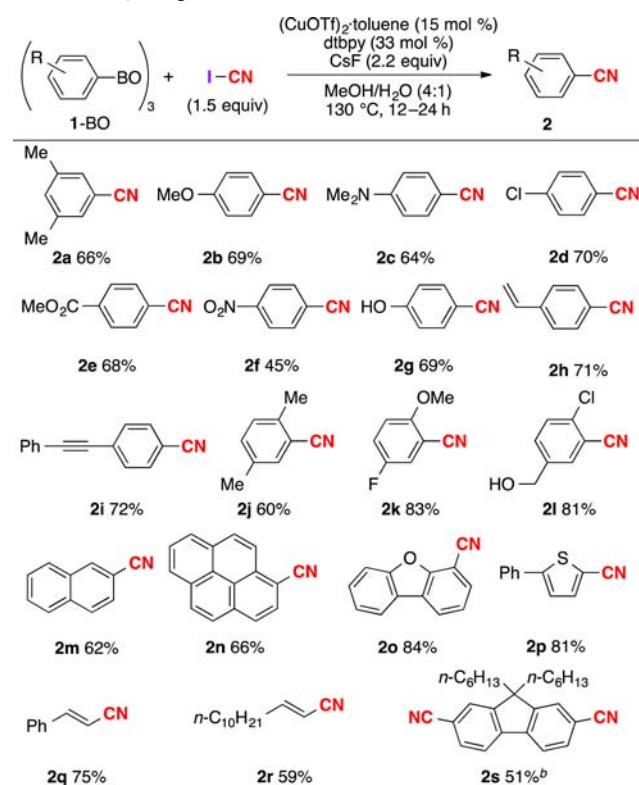
Table 1. Copper-Catalyzed Cyanation of Arylboronic Reagent 1a-B with Cyanogen Iodide<sup>a</sup>

entry	ligand	base	temp (°C)	boronic reagent	yield (%) <sup>b</sup>	
					2a	3a
1 <sup>c</sup>	none	TEMP	60	1a-Bpin	0	2
2	none	TEMP	60	1a-Bpin	8	21
3	dtbpy	TEMP	60	1a-Bpin	27	25
4	dtbpy	TEMP	110	1a-Bpin	42	12
5	dtbpy	Et <sub>3</sub> N	110	1a-Bpin	8	3
6	dtbpy	K <sub>2</sub> CO <sub>3</sub>	110	1a-Bpin	39	10
7	dtbpy	CsF	110	1a-Bpin	45	14
8	dtbpy	CsF	130	1a-Bpin	61	16
9	dtbpy	CsF	130	1a-BO	54	25
10 <sup>d</sup>	dtbpy	CsF	130	1a-BO	73 (66 <sup>e</sup> )	8
11 <sup>d</sup>	dtbpy	none	130	1a-BO	1	68

<sup>a</sup>Standard conditions: 3,5-dimethylphenylboronic reagent (1a-B) (0.20 mmol per amount of boron atoms), cyanogen iodide (0.30 mmol), (CuOTf)<sub>2</sub>-toluene (10 mol %), ligand (22 mol %), and base (0.44 mmol) in MeOH/H<sub>2</sub>O (4:1 v/v, 1.5 mL). <sup>b</sup>Yields were determined by <sup>1</sup>H NMR spectroscopic analysis using 1,4-dioxane as internal standard. <sup>c</sup>THF was used as solvent instead of MeOH/H<sub>2</sub>O. <sup>d</sup>(CuOTf)<sub>2</sub>-toluene (15 mol %) and dtbpy (33 mol %) were used. <sup>e</sup>Isolated yield.

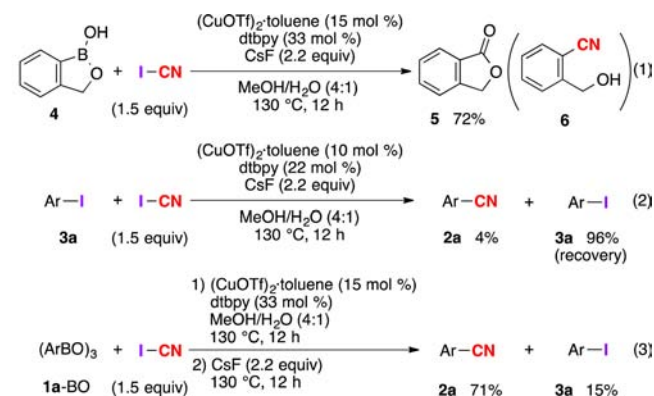
however, the reaction did not afford the expected cyanation product 2a (Table 1, entry 1). When the solvent was changed from THF to a 4:1 mixture of MeOH and H<sub>2</sub>O, a small amount of nitrile 2a (8% yield) was observed, together with iodoarene 3a (21% yield) (entry 2). The use of 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbpy) as a ligand for the copper catalyst increased the yield of 2a to 27% (entry 3). Performing the reaction at higher temperature (110 °C) led to an improved yield of 2a (entry 4). When the effect of base was examined, cesium fluoride (CsF) was found to be superior (entries 5–7). At higher temperature (130 °C), the use of either boronic pinacol ester (1a-Bpin) or boroxine (1a-BO) afforded nitrile 2a in moderate yield (entries 8 and 9).<sup>17</sup> Finally, use of the catalyst precursor (CuOTf)<sub>2</sub>-toluene (15 mol %) afforded cyanide 2a in 66% isolated yield (entry 10). In contrast to these results, iodide 3a was formed as the major product (68% yield) when the reaction was conducted in the absence of CsF (entry 11).

With the optimized conditions in hand, the substrate scope of the cyanation reaction was explored (Scheme 2). The reaction was found to tolerate a range of arylboroxine derivatives bearing a variety of functional groups including methoxy, *N,N*-dimethylamino, chloro, methoxycarbonyl, nitro, and hydroxyl groups, to afford the cyanation products 2b–g in good yields. The reaction also succeeded with boroxine derivatives bearing an alkene or alkyne moiety at the *para*-position (2h and 2i) and *ortho*-substituted boroxines (2j–l). In addition, polyaromatic or heteroaromatic boroxines also underwent cyanation efficiently to give the corresponding nitriles 2m–p in good yield. Cyanation

Scheme 2. Copper-Catalyzed Cyanation of Arylboroxine 1-BO with Cyanogen Iodide<sup>a</sup>

<sup>a</sup>The reaction was carried out with boroxine 1-BO (0.40 mmol per amount of boron atoms), cyanogen iodide (0.60 mmol), (CuOTf)<sub>2</sub>-toluene (15 mol %), dtbpy (33 mol %), and CsF (0.88 mmol) in MeOH/H<sub>2</sub>O (4:1 v/v; 3.0 mL). Isolated yields are shown. <sup>b</sup>(CuOTf)<sub>2</sub>-toluene (30 mol %) and dtbpy (66 mol %) were used.

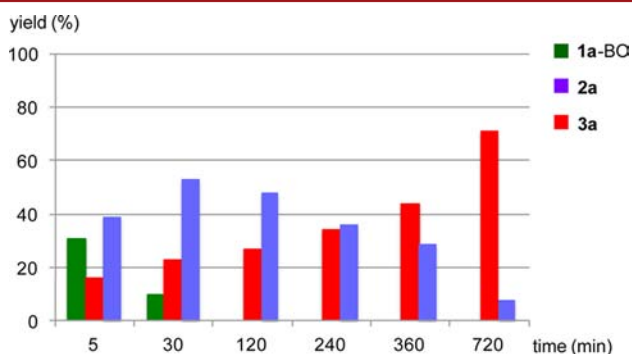
of alkenylboronic acids gave the corresponding  $\alpha,\beta$ -unsaturated nitriles 2q and 2r. Double cyanation of a diboronic acid with a fluorene framework to give 2s also proceeded successfully by using double the amount of reagent. Cyclic boronic compound 4 was also used in this cyanation reaction and gave lactone 5, which can be generated by solvolysis of nitrile 6 in 72% yield (eq 1).



The formation of aryl iodide 3a as the principle component when the reaction was performed in the absence of CsF (Table 1, entry 11) suggests the involvement of iodide 3a in the present cyanation.<sup>18</sup> To investigate this hypothesis, we performed two control experiments. First, in the absence of arylboroxine 1a-BO, the standard reaction conditions were applied to aryl iodide 3a, which was prepared separately; unexpectedly this afforded a

crude mixture containing only 4% nitrile **2a** together with 96% recovered iodide **3a** (eq 2). Second, when CsF was subsequently added to the mixture obtained from the reaction performed in the absence of CsF, and the reaction was continued at 130 °C for a further 12 h, nitrile **2a** was observed as a major product (eq 3). These contrasting results imply that the cyanation of iodide **3a** requires both CsF and the boronic moiety to proceed.

We then performed the reaction in several batches under the same conditions to determine how the distribution of aromatic compounds (**1a-BO**, **2a**, and **3a**) evolved as the reaction progressed (Figure 1). It was found that even at the beginning

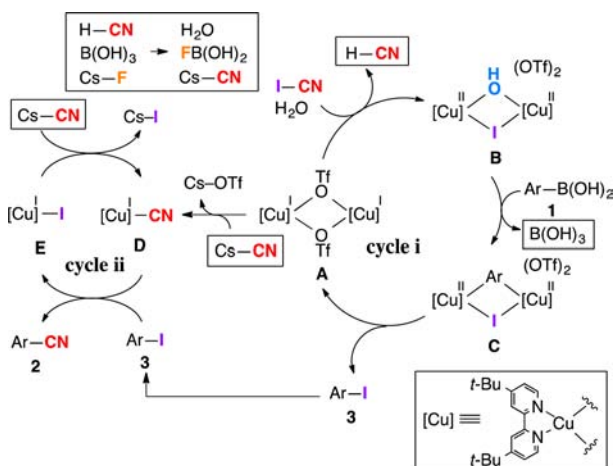


**Figure 1.** Time-dependent distribution of the recovered reactant **1a-BO** and the products **2a** and **3a**.

of the reaction (5–30 min), detectable amounts of nitrile **2a** were already formed. When the starting arylboronic compound had been consumed, the amount of nitrile **2a** then increased in proportion to the decrease in the amount of iodide **3a**. Such time-dependent behavior implies that nitrile **2a** is formed through both direct cyanation of an arylboronic compound and cyanation of iodide **3a**.

Based on the results presented above, we propose the reaction mechanism shown in Scheme 3. During the earlier stages of the reaction, Cu(I)–dtbpy complex **A**, which is initially generated by complexation, is readily oxidized to Cu(II) cationic complex **B**, which is accompanied by the generation of hydrogen cyanide (HCN). Aqueous protic solvent may be necessary in this step. Even in the absence of cesium fluoride (CsF), complex **B** undergoes transmetalation with arylboronic acid **1** to form

**Scheme 3.** Proposed Mechanism for Copper-Catalyzed Cyanation



arylcopper(II) complex **C**. Reductive elimination from complex **C** releases aryl iodide **3**, regenerating copper(I) complex **A** (cycle (i)). With the reaction proceeding through cycle (i), HCN and boric acid (B(OH)<sub>3</sub>) accumulate in the reaction mixture, which then generates cesium cyanide (CsCN) as the active cyanation agent in the presence of CsF. CsCN reacts readily with dimeric copper(I) triflate **A** to form cyanidocopper(I) complex **D**, which would be an irreversible step. Complex **D** can also catalyze the cyanation of aryl iodide **3** with consumption of CsCN to form nitrile **2** (cycle (ii)).<sup>19,20</sup>

In conclusion, we have demonstrated a copper-catalyzed cyanation reaction of aryl- and alkenylboronic acids using cyanogen iodide. The reaction proceeds efficiently under aqueous conditions with a combination of copper(I) triflate and a bipyridine ligand in the presence of cesium fluoride as base. Aryl- and alkenylboronic acids with a range of functional groups at the ortho-, meta-, or para-positions reacted with cyanogen iodide under the optimized conditions to give the corresponding nitriles in moderate to high yields. Control experiments and an analysis of the time-dependent behavior of the species present in the reaction enabled us to propose a reasonable reaction mechanism that involves multiple catalytic cycles producing iodides or nitriles.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01924.

Experimental procedures and compounds characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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