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Copper Iodide Mediated Cyanation of Arylboronic Acids and Aryl Iodides with Ethyl (Ethoxymethylene)cyanoacetate as Cyanating Agent

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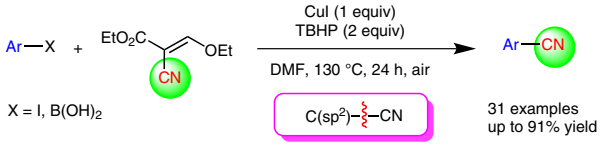

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Abstract An efficient copper iodide mediated cyanation of arylboronic acids and aryl iodides with ethyl (ethoxymethylene)cyanoacetate as cyanating agent has been developed. The reaction involves a C(sp^2)–CN bond cleavage and tolerates a wide range of functional groups, affording the corresponding aryl nitriles in moderate to excellent yields.

Key words copper, nitriles, transition metals, cleavage, arenes

The transition-metal-catalyzed or -mediated C–CN bond activation and cleavage has emerged as an attractive research topic in recent years, not only because C–CN bonds are widely present in many functional molecules but also it can provide novel strategies for the synthesis of a variety of structurally diverse compounds through a series of new reactions, including a) decyanative cross-coupling reactions, b) carbocyanation reactions with unsaturated hydroncarbons, and c) cyanation reactions (Figure 1).[1]

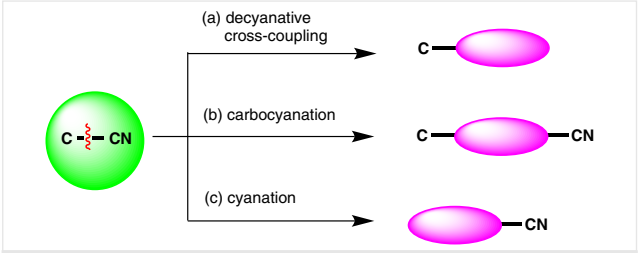
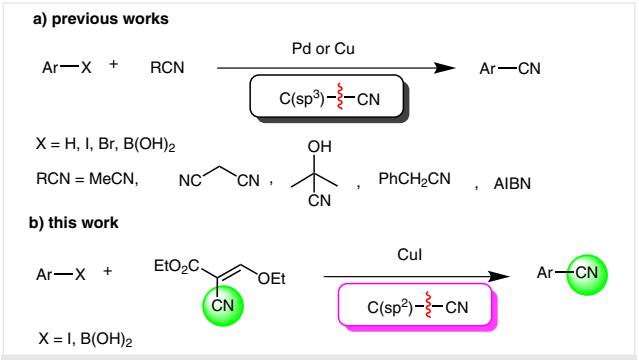


Figure 1 The application of C–CN bond cleavage in organic synthesis

In particular, due to the importance of nitriles in natural products, dyes, pharmaceuticals, and herbicides,[2] cyanation reactions via C–CN bond cleavage are of greatly synthetic interest, as it allows to establish many elegant alternative routes to aryl nitriles, while avoiding the use of toxic metal cyanides as cyano-group sources frequently employed by conventional synthetic methods.[3] Different organic compounds, such as acetonitrile,[4] acetone cyanohydrins,[5] malononitrile,[6] benzyl cyanide,[7] and 2,2′-azobisisobutyronitrile (AIBN),[8] were successfully utilized as efficient cyanating agent for the transition-metal-catalyzed or -mediated cyanantion of various substrates (Scheme 1, a). Although great progress has been made, the development of novel, nontoxic, and easily available cyanating agents for the cyanation is still highly desirable. Moreover, in most of the cases mentioned above, the cyano group transfers from C(sp^3) to C(sp^2). In sharp contrast, cyanation reaction involving cyano-group migration from C(sp^2) to C(sp^2) has less been explored.



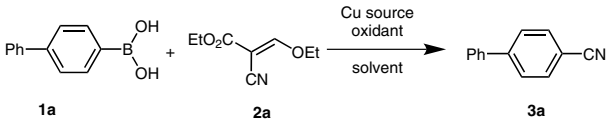
Scheme 1 Synthesis of aryl nitriles through C–CN bond cleavage

Ethyl (ethoxymethylene)cyanoacetate is a versatile synthetic building block,[9] but its application to cyanation reaction as a nonmetallic cyano-group source has never been explored. Recently, we found that ethyl (ethoxymethylene)cyanoacetate could react with α-hydroxy ketones to furnish 2,2,4-trisubstituted 3(2*H*)-furanones in good yields in the presence of copper iodide as the catalyst.[10] We envi-

sioned that ethyl (ethoxymethylene)cyanoacetate might serve as an efficient cyanating agent for the synthesis of aryl nitriles. Herein, we wish to report our investigation on the cyanation of arylboronic acids and aryl iodides with ethyl (ethoxymethylene)cyanoacetate in detail (Scheme 1, b).

Initially, we chose 4-biphenylboronic acid (**1a**) as the model substrate for the optimization of the reaction conditions, and the results are summarized in Table 1. When the reaction was performed in the presence of 20 mol% of CuI as catalyst, two equivalents of TBHP as oxidant in DMF at 100 °C under air for 24 hours, the desired product **3a** was obtained in 29% yield (Table 1, entry 1). To our delight, the yield of **3a** was increased to 82% when we used one equivalent of CuI and increased the reaction temperature to 130 °C (Table 1, entry 2). Control experiments showed that the reaction could not occur in the absence of CuI (Table 1, entry 3). Moreover, only low yield or trace amount of **3a** was observed when the reaction was conducted without TBHP or under a nitrogen atmosphere, indicating that both TBHP and air are necessary for the reaction (Table 1, entries 4 and 5).

Table 1 Optimization of Copper-Mediated Cyanation of Arylboronic acid with **2a** as Cyanating Agent[a]



1a **2a** **3a**

Entry	Cu (equiv)	Oxidant	Solvent	Temp (°C)	Yield (%)[b]
1	CuI (0.2)	TBHP	DMF	100	29
2	CuI (1.0)	TBHP	DMF	130	82 (72)
3	–	TBHP	DMF	130	N.D.[c]
4	CuI (1.0)	–	DMF	130	15
5[d]	CuI (1.0)	TBHP	DMF	130	trace
6[e]	CuI (1.0)	TBHP	DMF	130	trace
7	CuBr (1.0)	TBHP	DMF	130	N.D.
8	CuCl (1.0)	TBHP	DMF	130	N.D.
9	$CuSO_4$ (1.0)	TBHP	DMF	130	N.D.
10	$Cu(OAc)_2$ (1.0)	TBHP	DMF	130	N.D.
11	CuI (1.0)	TBHP	DMSO	130	55
12	CuI (1.0)	TBHP	DMA	130	50
13	CuI (1.0)	BQ	DMF	130	28
14	CuI (1.0)	DTBP	DMF	130	31
15[f]	CuI (1.0)	O_2	DMF	130	10

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Cu source, oxidant (2 equiv), solvent (2 mL), 24 h, air.
[b] GC yield with dodecane as internal standard. Number in parentheses is the yield of isolated product.
[c] N.D. = not detected.
[d] Under N_2 atmosphere.
[e] Without **2a**.
[f] Under 1 atm of O_2.

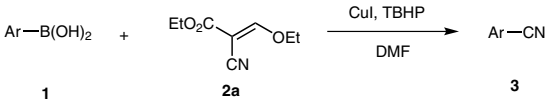
Considering that DMF have previously been employed as the CN source,[11] we performed a control experiment in the absence of **2a**. The result showed that only trace amount of **3a** was detected in this case (Table 1, entry 6), confirming that **2a** indeed act as a source of cyano group in this transformation. Further screening of different copper salts revealed that only CuI was effective for the reaction, and other copper salts such as CuBr, CuCl, $CuSO_4$, or $Cu(OAc)_2$ failed to give the desired product (Table 1, entries 7–10). We also investigated the influence of different solvents on the reaction. DMF was found to be the best media for the reaction while the use of dimethyl sulfoxide (DMSO) or dimethylacetamide (DMA) as solvent resulted in a dramatic decrease in the yield (entries 11 and 12). The oxidant also has an important influence on the reaction. For example, when TBHP was replaced by benzoquinone (BQ) or di-*tert*-butylperoxide (DTBP), only a low yield of **3a** was obtained (Table 1, entries 13 and 14). The use of molecular oxygen (1 atm) as the sole oxidant afforded **3a** only in 10% yield (Table 1, entry 15).

The scope of the copper iodide promoted cyanation reaction was subsequently investigated with various arylboronic acids (Table 2).[12] To our delight, both electron-deficient and electron-rich arylboronic acids underwent the reaction and gave the corresponding products **3b**–**o** in moderate to high yields, although in some cases a longer reaction time (48 h) is required for the reaction to complete. It is noteworthy that all halogen substituents (F, Cl, Br, and I) are tolerated in the reaction conditions, which is advantageous for further transformations (products **3g**–**j**). The results also shows that steric hindrance has a significant influence on the reaction since the substrates with substituent in the 3- or 4-position gave the desired products in higher yields than their 2-substituted analogues. Fused aryl ring such as naphthalene and anthracene derivatives **1p**–**s** could also work well to furnish the corresponding products **3p**–**s** in satisfactory yields.

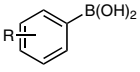
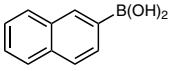
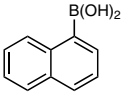
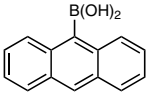
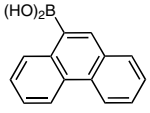
In order to further explore the scope of our protocol, aryl iodides were also examined as the coupling partner for the reaction, and the experimental results are given in Table 3. Pleasingly, under the standard conditions, a variety of aryl iodides could efficiently react with **2a**, forming the desired product in good to excellent yields. Both electron-donating groups such as methoxy and methyl, and electron-withdrawing groups such as trifluoromethyl, nitro, cyano, fluro, and chloro on the aromatic moiety could be tolerated. It is noteworthy that 2-iodophenol (**4k**), whose molecule contains an active proton, entered into the reaction smoothly to give the expected product **3u** in 61% yield.

We suggested that the cyanation of arylboronic acids might proceed through an aryl iodide intermediate. To verify the hypothesis, we investigated the reaction profile of the copper-mediated cyanation of **1a** under the standard conditions. As can be seen from Figure 2, the iodination

Table 2 Copper-Mediated Cyanation of Arylboronic Acids with **2a** as Cyanating Agent[a]

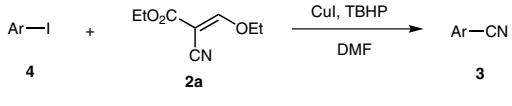


1 **2a** **3**

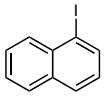
Entry	**1**		Yield of **3** (%)[b]
1		**1b** R = 4-*i*-Pr	**3b** 86
2		**1c** R = 4-OMe	**3c** 47[c]
3		**1d** R = 4-F_3C	**3d** 90[c]
4		**1e** R = 4-O_2N	**3e** 70
5		**1f** R = 4-NC	**3f** 45
6		**1g** R = 4-F	**3g** 68, 95[c]
7		**1h** R = 4-Cl	**3h** 85[c]
8		**1i** R = 4-Br	**3i** 70[c]
9		**1j** R = 4-I	**3j** 68[c,d]
10		**1k** R = 3-O_2N	**3k** 88
11		**1l** R = 2-O_2N	**3l** 65
12		**1m** R = 2-Ph	**3m** 60
13		**1n** R = 2-Me	**3n** 44
14		**1o** R = 2-F	**3o** 58
15		**1p**	**3p** 54
16		**1q**	**3q** 61
17		**1r**	**3r** 52[c]
18		**1s**	**3s** 69

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), CuI (1 equiv), TBHP (2 equiv), DMF (2 mL), 130 °C, 24 h, air.
[b] Isolated yield.
[c] The reaction was carried out in 48 h.
[d] **3f** was also isolated in 20% yield as a byproduct.

Table 3 Copper-Mediated Cyanation of Aryl Iodides with **2a** as Cyanating Agent[a]



4 **2a** **3**

Entry	**4**		Yield of **3** (%)[b]
1		**4a** R = 4-MeO	**3c** 65
2		**4b** R = 4-F_3C	**3d** 73
3		**4c** R = 4-O_2N	**3e** 82
4		**4d** R = 4-CN	**3f** 91
5		**4e** R = 4-F	**3g** 81
6		**4f** R = 4-Cl	**3h** 83
7		**4g** R = 3-O_2N	**3k** 61
8		**4h** R = 2-Me	**3n** 91
9		**4i** R = 2-F	**3o** 69
10		**4j** R = H	**3t** 82
11		**4k** R = 2-HO	**3u** 61
12		**4l**	**3q** 87

[a] Reaction conditions: **4** (0.3 mmol), **2a** (0.6 mmol), CuI (1 equiv), TBHP (2 equiv), DMF (2 mL), 130 °C, 24 h, air.
[b] Isolated yield.

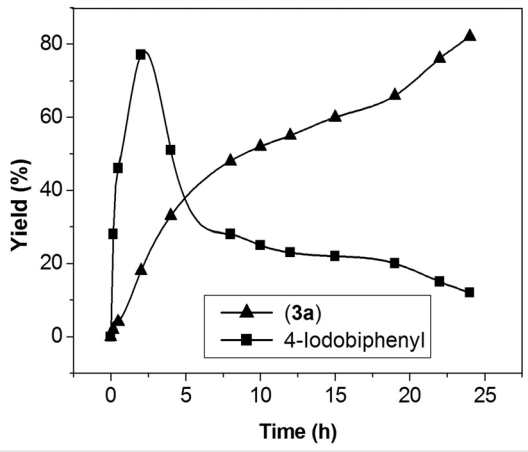
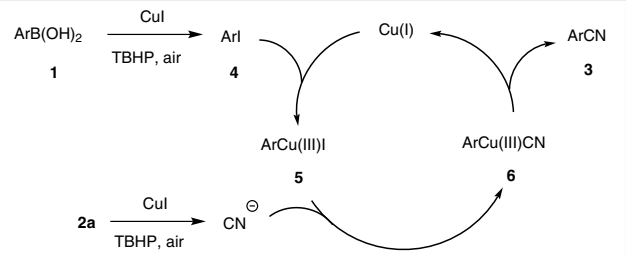


Figure 2 Reaction profile in the copper-mediated cyanation of **1a** with **2a** as cyanating agent

product, 4-iodobiphenyl, was formed as the major product at the initial stage of the reaction. The yield of 4-iodobiphenyl reached a maximum value (77% yield) after two hours and then decreased gradually. At the same time, the cyanated product **3a** was gradually produced after a short period of induction (0.5 h). Therefore, the iodination products were proved to be the key reaction intermediates toward the expected aryl nitriles, and copper(I) iodide acted also as a supplier of iodide anions in this transformation.

In order to gain more insight into the mechanism of the reaction, we also attempted to test the existence of cyanide anions formed in situ during the reaction. As expected, when the reaction was performed in the absence of **1a** under standard reaction conditions, the cyanide anions could be detected by using a picric acid strip (see Supporting information for more details).

Based on the above-mentioned results and previous reports,[4b,c,7c] we proposed a possible mechanism for the cyanation of arylboronic acids (Scheme 2). Initially, the iodination of arylboronic acid **1** occurred in the presence of CuI and TBHP, giving rise to aryl iodide **4** as the key intermediate. Then, the oxidative addition of **4** to Cu(I) took place to form ArCu(III)I species **5**, which could further react with the cyanide anion generated in situ from the C(sp^2)–CN bond cleavage of **2a** to furnish species **6**. Finally, the reductive elimination of **6** would yield the target product **3** and regenerated the copper catalyst.



Scheme 2 Possible reaction mechanism

In summary, we have successfully developed an efficient approach for the synthesis of aryl nitriles via a copper iodide mediated cyanation of arylboronic acids or aryl iodines with ethyl (ethoxymethylene)cyanoacetate as the cyanating agent. The reaction involves a C(sp^2)–CN bond cleavage and tolerates a wide range of functional groups, affording the corresponding aryl nitriles in moderate to excellent yields. Further investigation on the reaction mechanism and the synthetic application of the new method are ongoing in our laboratory.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562112.

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(12) **Typical Procedure for the Synthesis of Compound 3a**
To a 25 mL round-bottom flask was added the mixture of boronic acid **1a** (0.3 mmol), ethyl 2-cyano-3-ethoxyacrylate (**2a**, 0.6 mmol), CuI (0.3 mmol), *t*-BuOOH (0.6 mmol) in DMF (2 mL) successively. The mixture was stirred at 130 °C for 24 h under air. After the reaction was completed, the mixture was cooled to room temperature, diluted with H_2O (15 mL), and then extracted with CH_2Cl_2 (3 × 5 mL). The organic extract was washed with H_2O (3 × 10 mL) and dried over anhydrous Na_2SO_4. After removal of the CH_2Cl_2 in vacuum, the crude product thus obtained was purified by column chromatography on silica gel using PE–EtOAc as eluent to give the desired product **3a** as a white solid; yield 72%; mp: 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.66 (m, 4 H), 7.59 (d, *J* = 7.3 Hz, 2 H), 7.51–7.43 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 139.0, 132.5, 129.0, 128.6, 127.6, 127.1, 118.8, 110.8. IR (KBr): 2227, 1605, 1484, 1400, 844, 769, 736, 699, 564, 518 cm^{-1}. MS (EI): *m/z* = 179 (100) [M^+], 151, 126, 113, 89, 76, 63.