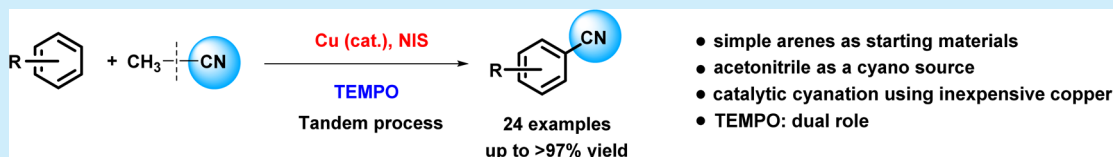


# Acetonitrile as a Cyanating Reagent: Cu-Catalyzed Cyanation of Arenes

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**S** Supporting Information

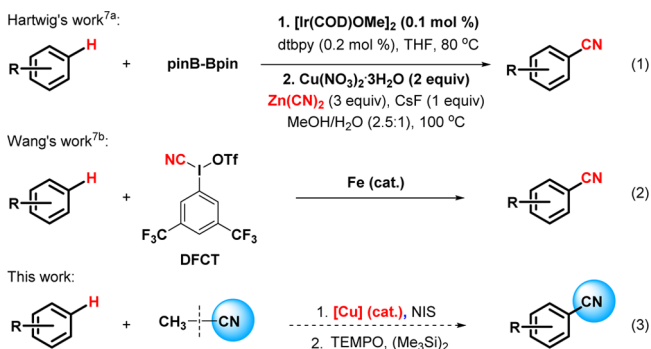


**ABSTRACT:** A novel approach to the Cu-catalyzed cyanation of simple arenes using acetonitrile as an attractive cyano source has been documented. The C–H functionalization of arenes without directing groups involves a sequential iodination/cyanation to give the desired aromatic nitriles in good yields. A highly efficient Cu/TEMPO system for acetonitrile C–CN bond cleavage has been discovered. TEMPO is used as a cheap oxidant and enables the reaction to be catalytic in copper. Moreover, TEMPOCH<sub>2</sub>CN **6** has been identified as the active cyanating agent and shows high reactivity for forming the –CN moiety.

Aromatic nitriles are versatile functional units in many dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.<sup>1</sup> Furthermore, the cyano group serves as a valuable intermediate for transformation into aldehydes, amines, amidines, tetrazoles, amides, and their carboxyl derivatives.<sup>2</sup> In recent decades, significant progress has been achieved in the transition-metal catalyzed synthesis of benzonitriles.<sup>3</sup> Notably, the cyanations of aryl (pseudo)halides,<sup>3</sup> activated arenes,<sup>4,6f</sup> and arenes with directing groups<sup>5</sup> have been elegantly developed. In most cases, metal cyanides were often used as cyanating reagents. A significant problem 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, Zn(CN)<sub>2</sub>, and TMSCN, have notorious toxicity. Recently, the investigation of combined cyano sources as an alternative strategy, such as ammonium salts in combination with DMF or DMSO, has attracted considerable attention.<sup>6</sup>

The cyanation of simple arenes, that is arenes without a directing group, is an attractive and modern approach to making benzonitriles. This strategy avoids the need for prefunctionalization of substrates, and importantly, simple arenes are abundant starting materials. Thus far, few examples have been reported in this field due to their low reactivity. In 2010, Hartwig and co-workers documented an elegant example of the cyanation of unactivated arenes (Scheme 1, eq 1).<sup>7a</sup> In this case, an Ir-catalyzed C–H borylation is followed by a stoichiometric Cu-promoted cyanation using Zn(CN)<sub>2</sub> as the cyano source. Recently, Wang and co-workers reported the Fe-catalyzed direct cyanation of arenes using aryl(cyano)iodonium triflate (DFCT) as a cyano source (Scheme 1, eq 2).<sup>7b</sup> In considering this challenge, our laboratory was interested in developing a complementary method that exploits the common solvent, acetonitrile, as the cyano source. Herein, we report a copper-catalyzed cyanation of simple arenes using acetonitrile via an initial iodination. Studies reveal

## Scheme 1. Strategies for Cyanation of Arenes



that a Cu/TEMPO system plays a crucial role in the activation of acetonitrile.

From the viewpoint of safety and atom-economy, acetonitrile is a rather attractive “CN” source, avoiding the employment of toxic metal cyanides and structurally complex electrophilic “CN” sources. However, this type of C–C bond activation is challenging due to a high CH<sub>3</sub>–CN bond dissociation energy (133 kcal/mol) relative to alkane C–C bonds (ca. 83 kcal/mol).<sup>8</sup> Given our interest in cyanation studies, our group recently disclosed the Cu-catalyzed cyanation of aromatic C–H bonds bearing a directing group using acetonitrile as the “CN” source.<sup>9</sup> Notably, the identification of (Me<sub>3</sub>Si)<sub>2</sub> as a suitable Lewis acid was crucial for activating the relatively inert acetonitrile C–CN bond. Based on this work, we envisioned a strategy for the cyanation of simple arenes by using CH<sub>3</sub>CN as a “CN” source (Scheme 1, eq 3). This strategy involves a sequential process to activate simple arenes via initial iodination followed by cyanation. However, the iodination

Received: March 26, 2015

Table 1. Parameters for Cyanation of Arenes<sup>a</sup>

entry	LA (10 mol %)	2a (%) <sup>b</sup>	[Cu] (20 mol %)	oxidant	3a (%) <sup>b</sup> (o:p)
1	none	—	Cu(NO <sub>3</sub> ) <sub>2</sub>	none	—
2	AlCl <sub>3</sub>	31	Cu(NO <sub>3</sub> ) <sub>2</sub>	TEMPO	9 (1:1)
3	BF <sub>3</sub> ·Et <sub>2</sub> O	97	Cu(NO <sub>3</sub> ) <sub>2</sub>	TEMPO	31 (1.8:1)
4	Bi(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	TEMPO	67 (1.4:1)
5	Sc(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	TEMPO	77 (1:1)
6	Fe(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	TEMPO	49 (1.3:1)
7	Yb(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	TEMPO	94 <sup>c</sup> (1:1.1)
8 <sup>d</sup>	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	>99	none	TEMPO	91 <sup>c</sup> (1.1:1)
9 <sup>e</sup>	Cu(OTf) <sub>2</sub>	>99	none	TEMPO	83 <sup>c</sup> (1.1:1)
10	Yb(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	Ag <sub>2</sub> CO <sub>3</sub> (1 equiv)	40 (1.3:1)
11	Yb(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	Oxone (1 equiv)	—
12	Yb(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	BQ (1 equiv)	—
13	Yb(OTf) <sub>3</sub>	>99	Cu(NO <sub>3</sub> ) <sub>2</sub>	TBHP (1 equiv)	—
14	Yb(OTf) <sub>3</sub>	>99	Cu(OAc) <sub>2</sub>	TEMPO	77 (1.3:1)
15 <sup>f</sup>	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	>99	none	TEMPO	29 (1.2:1)

<sup>a</sup>Conditions: the first step: Lewis acid (10 mol %), NIS (1.05 equiv), CH<sub>3</sub>CN, 150 °C, O<sub>2</sub>, 2 h; the second step: [Cu] catalyst (20 mol %), 1,10-phenanthroline (20 mol %), (Me<sub>3</sub>Si)<sub>2</sub> (1 equiv), TEMPO (2,2,6,6-tetramethylpiperidinyloxy, 2 equiv), 150 °C, O<sub>2</sub>, 2–2.5 d. <sup>b</sup>GC yield using dodecane as an internal standard. <sup>c</sup>Isolated yield. <sup>d</sup>Cu(ClO<sub>4</sub>)<sub>2</sub> (20 mol %). <sup>e</sup>Cu(OTf)<sub>2</sub> (20 mol %). <sup>f</sup>Without (Me<sub>3</sub>Si)<sub>2</sub>.

of simple arenes is normally carried out under harsh conditions such as the use of strong acids, excess amounts of oxidants, and special reagents.<sup>10</sup> Therefore, the one-pot cyanation using CH<sub>3</sub>CN as a cyanating reagent via a iodination process would be a challenging strategy.

We chose readily available toluene as a test substrate. To identify conditions for this transformation, a series of Lewis acids, copper catalysts, and oxidants were examined (Table 1). First, we found that no product was formed under Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O/(Me<sub>3</sub>Si)<sub>2</sub> catalytic conditions (Table 1, entry 1), while acetonitrile C–CN cleavage successfully proceeded to release the CN<sup>−</sup> anion with this system,<sup>11</sup> showing acetonitrile is an effective cyano source in the presence of (Me<sub>3</sub>Si)<sub>2</sub>. Accordingly, various Lewis acids were screened for the cyanation of toluene in the presence of an iodinating agent. Pleasingly, Yb(OTf)<sub>3</sub> showed good reactivity for the sequential iodination/cyanation using NIS as an iodinating source, giving the desired cyanated product **3a** in 94% yield with 1:1.1 regioselectivity for *ortho* and *para* substitution (entry 7). Other M(OTf)<sub>3</sub> salts (M = Bi, Sc, Fe) can efficiently promote the iodination of toluene, whereas these triflate salts had an inferior effect on the cyanation process (Table 1, entries 4–6). It is worth noting that the use of Cu(ClO<sub>4</sub>)<sub>2</sub> (10 mol %) or Cu(OTf)<sub>2</sub> (10 mol %) as a Lewis acid facilitated not only the iodination but also the cyanation reaction to provide **3a** in 91% and 83% yields, respectively (Table 1, entries 8–9). No other Cu catalysts were required in the cyanation step, making this system simple and efficient. These results mean that Cu(ClO<sub>4</sub>)<sub>2</sub> and Cu(OTf)<sub>2</sub> could efficiently serve three roles: a Lewis acid for iodination, a catalyst for C–CN bond cleavage, and a promoter for new C–CN bond formation. By varying oxidants (entries 10–13), we found that TEMPO is the best oxidant for this sequential transformation. Ag<sub>2</sub>CO<sub>3</sub>, a good oxidant in previous reports,<sup>6e,12</sup> gave **3a** in moderate yield (entry 10). In the absence of (Me<sub>3</sub>Si)<sub>2</sub>, the yield of **3a** dramatically decreased to 29%, indicating disilane is still important for acetonitrile C–CN bond scission (Table 1, entry 15). Consequently, the optimal conditions for this

sequential iodination/cyanation in a one-pot process are entry 8 (conditions A) and entry 7 (conditions B).

With the optimal conditions in hand, the generality and limitations of this Cu-catalyzed cyanation of simple arenes with acetonitrile were explored, as shown in Table 2. Pleasingly, benzene smoothly underwent cyanation under the standard conditions, giving benzonitrile **3b** (39% yield under conditions A, 47% yield under conditions B) (entry 2). A variety of substituents on the arene, from Me to the bulky *t*-Bu group (**1a**, **1c–1e**), were well tolerated, furnishing the corresponding products in 76–96% yields (entries 2–5). Interestingly, a trend was observed where selectivity for *para*-substitution increased as the bulk of the substituent increases. For simple disubstituted arenes such as *o*-, *m*-, and *p*-xylene, these reactions performed well to provide the desired cyanated products **3f–h** under both conditions A and B (75–95% yields) (entries 6–8). The cyanation in products **3f–g** occurred primarily at the less hindered and electron-rich positions. *p*-Xylene **1h** exclusively provided 2,5-dimethylbenzonitrile **3h** in high yield (entry 8). The electron-withdrawing fluoro substituent on the aryl ring did not influence the reactivity to give **3i** in 56% and 81% yields under system A and B, respectively (entry 9). Besides phenyl rings, fused aromatic rings such as phenanthrene **1j** could also smoothly transfer to 1-naphthonitrile **3j** in 74% and 82% yields under conditions A and B (entry 10). The reactions of analogous methyl substituted phenanthrenes **1k–1l** produced the corresponding cyanated products **3k** and **3l** in good yields with a high level of regioselectivity (entries 11–12).

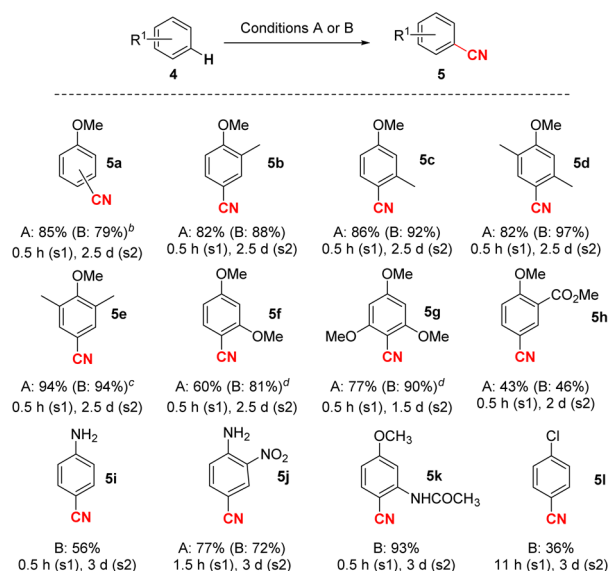
Encouraged by the positive results of simple arenes, we next focused on the scope of functional groups on aromatic rings (Scheme 2). Note that arenes (**4a–e**) with an electron-donating OMe group resulted in fast iodination within 30 min and efficiently furnished the cyanated products **5a–e** with predominant *para* selectivity to the OMe group in excellent yields (85–97%). In particular, we found that 4-cyano-2,6-dimethylphenol **See** deprotected from **5e** (**See**: 83% yield) is a valuable intermediate that can be used for the preparation of pharmaceutical etravirine for the treatment of HIV.<sup>13</sup> Unexpect-

**Table 2. Scope of Simple Arenes in the Sequential Iodination/Cyanation Using Acetonitrile as Cyano Unit<sup>a</sup>**

$\text{R-C}_6\text{H}_4\text{-H} \xrightarrow[\text{2. 1,10-phen (15-20 mol \%), TEMPO (2 equiv) (Me}_3\text{Si)}_2 \text{ (1 equiv), 150 }^\circ\text{C, O}_2]{\text{1. Cu(ClO}_4\text{)}_2 \cdot 6\text{H}_2\text{O (15-20 mol \%) NIS (1.05 equiv), CH}_3\text{CN}} \text{R-C}_6\text{H}_4\text{-CN}$						
entry	substrate	product	time (1)	time (2)	yield (%) <sup>b</sup>	ratio
1	<b>1b</b>	<b>3b</b>	1 h	4 d	39 (A) 47 (B)	
2	<b>1a</b> (R = CH <sub>3</sub> )	<b>3a</b>	2 h	2 d	87 (A) 96 (B)	<i>p</i> : <i>o</i> = 1:1
3	<b>1c</b> (R = Et)	<b>3c</b>	1 h	2.5 d	76 (A) 85 (B)	<i>p</i> : <i>o</i> = 2.1:1
4	<b>1d</b> (R = <i>i</i> -Pr)	<b>3d</b>	1 h	2.5 d	90 (A) 80 (B)	<i>p</i> : <i>o</i> = 6:1
5	<b>1e</b> (R = <i>t</i> -Bu)	<b>3e</b>	1 h	2.5 d	91 (A) 83 (B)	<i>p</i> : <i>o</i> = 13:1
6	<b>1f</b>	<b>3f</b>	2 h	2 d	79 (A) 81 (B)	4-CN:3-CN = 3:1 4-CN:3-CN = 3:1
7	<b>1g</b>	<b>3g</b>	2 h	2 d	75 (A) 95 (B)	4-CN:2-CN = 9:1 4-CN:2-CN = 9:1
8	<b>1h</b>	<b>3h</b>	2 h	2 d	76 (A) 84 (B)	
9	<b>1i</b>	<b>3i</b>	2 h	2 d	56 (A) 81 (B)	
10	<b>1j</b>	<b>3j</b>	1.75 h	2.5 d	74 (A) 82 (B)	
11	<b>1k</b>	<b>3k</b>	4 h	3.25 d	77 (A) 73 (B)	$\alpha'$ : $\beta$ = 11:1 $\alpha'$ : $\beta$ = 11:1
12	<b>1l</b>	<b>3l</b>	3.5 h	3 d	77 (A) 81 (B)	$\alpha$ : $\alpha'$ = 10:1 $\alpha$ : $\alpha'$ = 10:1

<sup>a</sup>Conditions A: the first step: substrate **1** (0.5 mmol), Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (15–20 mol %), NIS (1.05 equiv), CH<sub>3</sub>CN (1.2 mL), O<sub>2</sub>, 150 °C; the second step: 1,10-phen (15–20 mol %), TEMPO (2 equiv), (Me<sub>3</sub>Si)<sub>2</sub> (1 equiv), 150 °C, O<sub>2</sub>. Conditions B: the first step: Yb(OTf)<sub>3</sub> (10 mol %), NIS (1.05 equiv), CH<sub>3</sub>CN (1.2 mL), O<sub>2</sub>, 150 °C; the second step: Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (15–20 mol %), 1,10-phen (15–20 mol %), TEMPO (2 equiv), (Me<sub>3</sub>Si)<sub>2</sub> (1 equiv), 150 °C, O<sub>2</sub>. <sup>b</sup>Isolated yield.

edly, the iodination reaction for more electron-rich arenes (**4f–g**) containing two or three OMe groups worked sluggishly under either system A or B. To solve this issue, we added KOH (1 equiv) to the first step to promote the iodination process and observed the sequential iodination/cyanation reactions proceeded smoothly, producing the cyanated products **5f–g** in 60–90% yields. The electron-withdrawing COOMe installed in substrate **4h** was accommodated and resulted in a moderate yield. To our delight, not only the protected AcNH– (**4k**) but also the free NH<sub>2</sub> group in substrate **4i–j** was compatible under the standard conditions, giving the desired products **5i–k** in moderate to high yields. In Hartwig's report, however, various protected anilines could not form the corresponding products.<sup>7a</sup> On the other hand, the reactions of electron-deficient arenes such as benzonitrile, benzaldehyde, or methyl benzoate did not take place under the standard conditions because the initial iodination hardly

**Scheme 2. Scope of Substrates<sup>a</sup>**


<sup>a</sup>Isolated yield. s1 means the first step; s2 means the second step. <sup>b</sup>A 5:1 ratio of 4-methoxybenzonitrile and 2-methoxybenzonitrile. <sup>c</sup>Trace 3-methoxy-2,4-dimethylbenzonitrile was isolated. <sup>d</sup>KOH (1 equiv) was added into the first step.

**Table 3. Using **6** instead of TEMPO for Cyanation**

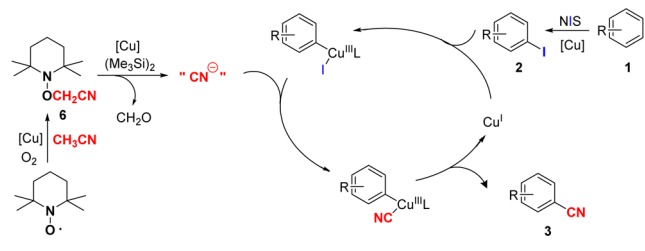
$\text{H}_3\text{C-C}_6\text{H}_4\text{-I} + \text{TEMPO-CH}_2\text{CN} \xrightarrow[\text{Condition A without NIS}]{\text{6 instead of TEMPO}} \text{H}_3\text{C-C}_6\text{H}_4\text{-CN}$			
entry	6 instead of TEMPO	time	3a (%)
1	2 equiv of <b>6</b> under O <sub>2</sub>	41 h	90
2	2 equiv of <b>6</b> under N <sub>2</sub>	2 d	62
3	2 equiv of <b>6</b> using 1,4-dioxane as sol. under O <sub>2</sub>	2 d	38

proceeded. However, chlorobenzene (**4l**) could undergo cyanation albeit with a 36% yield.

The Cu/TEMPO system efficiently allowed access to the catalytic cyanation of simple arenes via a tandem process. For the catalytic cyanation, TEMPO acted as an important oxidant. Fortunately, a key intermediate, TEMPO–CH<sub>2</sub>CN **6**, was observed by GC during the course of reaction, and this species was confirmed by NMR and HRMS. Interestingly, when TEMPO–CH<sub>2</sub>CN **6** was used in place of TEMPO under an oxygen or nitrogen atmosphere, the reaction of 1-iodo-4-methylbenzene **p-2a** with acetonitrile still proceeded to give the cyanated product **p-3a** in 90% and 62% yields, respectively (Table 3, entries 1 and 2). Next, an experiment was designed to test the hypothesis that **6** is the active cyanating agent: the reaction was carried out in 1,4-dioxane as solvent using **6** instead of TEMPO (Table 3, entry 3). Incredibly, a 38% yield of cyanated product **p-3a** was obtained. These studies support the proposal that intermediate **6** is indeed the direct supplier of the “CN” unit and oxidant for catalytic cyanation, and oxygen most likely enables formation of TEMPO–CH<sub>2</sub>CN **6**. Consequently, a tentative mechanism for Cu-catalyzed sequential iodination/cyanation was outlined in Scheme 3. TEMPO–CH<sub>2</sub>CN **6** might be formed by the reaction of TEMPO and acetonitrile in the presence of a Cu species and oxygen, which acts as a “CN” supplier by C–CN cleavage promoted by (Me<sub>3</sub>Si)<sub>2</sub> and the Cu catalyst. The in situ generated cyanide anion would subsequently take part in the



## Scheme 3. Tentative Reaction Mechanism



cyanation of aryl iodides from initial iodination of simple arenes to provide the desired aromatic nitriles **3**. Detailed mechanistic investigation of the reaction is underway in our laboratory.

In summary, we have designed and executed a new approach for the Cu-catalyzed cyanation of simple arenes using acetonitriles as a cyano source via C–CN bond cleavage. This C–H functionalization strategy involves a sequential iodination/cyanation process to furnish the corresponding aromatic nitriles in good to excellent yields. Moreover, we found a highly efficient Cu/TEMPO system for acetonitrile C–CN bond cleavage. TEMPO plays a significant role in promoting this cyanation transformation: (1) TEMPO, a cheap oxidant, allows the reaction to be catalytic in copper; (2) TEMPOCH<sub>2</sub>CN is formed in situ and acts as the active cyanating agent. This system represents a new avenue to breaking the relatively inert C–CN bond. Notably, in system A, Cu(ClO<sub>4</sub>)<sub>2</sub> is required alone and it serves three roles: a Lewis acid for initial iodination, a catalyst for C–CN bond cleavage, and a promoter for new C–CN bond formation. The development of new cyanation reactions with acetonitrile is in progress in our laboratory.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

All characterization data, including spectra and GC traces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00886.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the NSFC (21272001), Shanghai Education Committee (13ZZ014). We thank Prof. Vy M. Dong (UCI) and Dr. Peter K. Dornan (CIT) for helpful discussions.

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