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Copper-catalyzed cyanation of arenes using benzyl nitrile as a cyanide anion surrogate†

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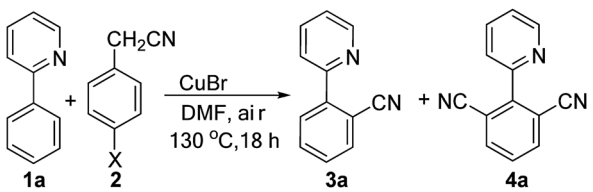
The copper-catalyzed cyanation of arenes using benzyl nitrile as a cyanide anion surrogate furnishes aromatic nitriles in moderate to good yields. The cascade process involves a copper-catalyzed aerobic C–H oxidation, a retro-cyanohydrination, and a copper-catalyzed aerobic oxidative C–H functionalization.

The C–H bond functionalizations have attracted much attention because they could directly convert a C–H bond into a C–C or C–FG bond without the assistance of transfer groups, such as halogens. In this blooming field, the palladium-catalyzed C–H bond activation/C–C bond-forming reactions,[1] the copper-catalyzed cross-dehydrogenative coupling (CDC),[2] and the copper-catalyzed aerobic oxidative C–H bond functionalization[3] are the most popular perspectives. On the other hand, aryl nitriles are the subunits[4] or the key intermediates[5] of a number of important drugs. They are also versatile building blocks in organic synthesis and can be transformed into various compounds such as imines, amines, aldehydes, carboxylic acids, amides, and tetrazoles.[6] Consequently, the transition metal-catalyzed cyanation of aryl halides and the cyanation through C–H bond functionalization of arenes have been significantly developed in the last few decades. The cyanation reagents used in these processes are metal cyanides, such as CuCN,[7] KCN,[8] NaCN,[9] $Zn(CN)_2$,[10] TMSCN,[11] and $K_2Fe(CN)_4$.[12] Organoreagents are seldom reported. A few examples include acetone cyanohydrin,[13] nitromethane,[11] malononitrile,[14] and *N*,*N*-dimethylformamide.[15] More recently, the combination of ammonium salts and DMF or DMSO as the surrogate of cyanide anions was reported,[16] which could effectively convert Ar–H with directing groups or Ar–X into the corresponding aryl nitriles. Enlightened by these results and our recent finding that benzyl cyanide could work as a cyanide anion surrogate for the palladium-catalyzed cyanation of aryl halides,[17] we envisaged that the combination of benzyl cyanide with a copper-catalyzed aerobic oxidative C–H functionalization might lead to the development of a practical method for the cyanation of arenes. Herein, we report the results of this effort.

During the screening of reaction conditions (Table S1, ESI†), we discovered that the reaction of 2-phenylpyridine (**1a**) with 1.5 equiv. of benzyl cyanide (**2a**) in DMF under 1.2 equiv. of CuBr and air atmosphere at 130 °C for 18 h gave aryl nitrile **3a** in 83% yield (Scheme 1). For the electron-withdrawing group substituted benzyl cyanides **2b** and **2c**, the yield of **3a** was decreased apparently. For the electron-donating group substituted benzyl cyanide **2d**, we obtained **3a** (55% yield) along with dicyanated product **4a** (39% yield).

With our optimized reaction conditions in hand, we next explored the substrate scope and the limitation of this reaction (Scheme 2). The substituent effect on the phenyl ring of 2-phenylpyridines was not apparent. Products **3b–h** were obtained in yields ranging from 52% to 73%. Steric hindrance was high when the methyl group occupied the *ortho* position of the phenyl ring of 2-phenylpyridine. As a result, **3i** was obtained in lower yield (31%). 2-(Naphthalen-1-yl)pyridine afforded **3m** in 66% yield, while 2-(naphthalen-2-yl)pyridine gave a mixture of **3na** and **3nb** in a 1 : 2 ratio (63% yield) along with a dicyanated product **4b** (21% yield). With other directing groups, such as pyrimidine, pyrazole, and 3-methylpyrazole, **3o**, **3p**, and **3q** were prepared in 42%, 43%, and 39% yields, respectively. Benzo[*h*]quinoline, in which the free rotation of the C–C bond between phenyl and pyridinyl was blocked by a covalent C=C bond, could proceed the reaction to afford the desired product **3r** in 51% yield.

We also examined the sterically hindered substrates, such as 2,6-diphenylpyridine (**1s**), 2-methyl-6-phenylpyridine (**1t**) and



2	X	3a	4a
2a	H	83%	trace
2b	F	71%	trace
2c	NO_2	62%	trace
2d	OMe	55%	39%

Scheme 1 Substituent effect of benzyl cyanides.

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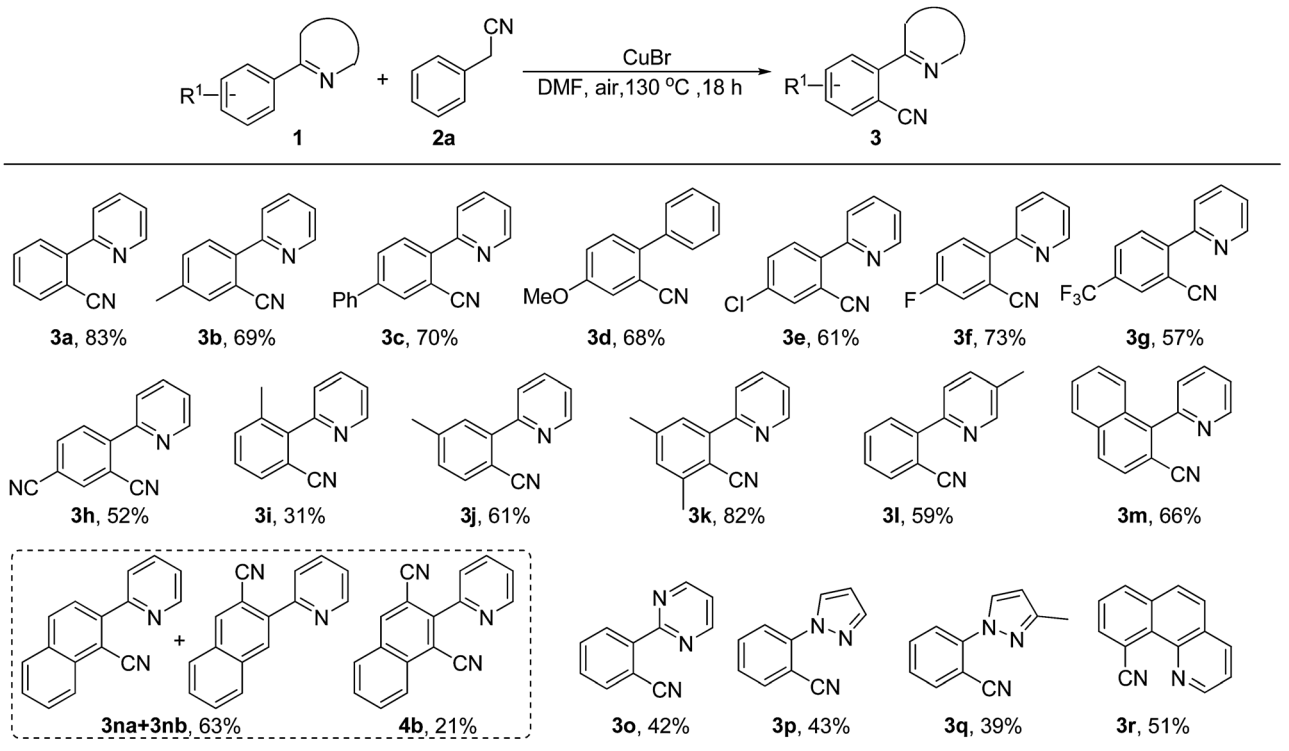
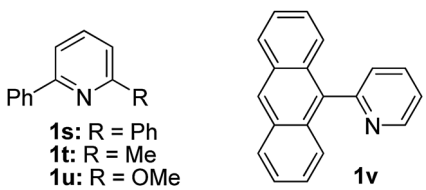
† Electronic supplementary information (ESI) available: Experimental details, optimization of reaction conditions, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products. See DOI: 10.1039/c2cc35046g



Scheme 2 Preparation of aromatic nitriles **3a–r** and **4b** from arenes using benzyl cyanide.

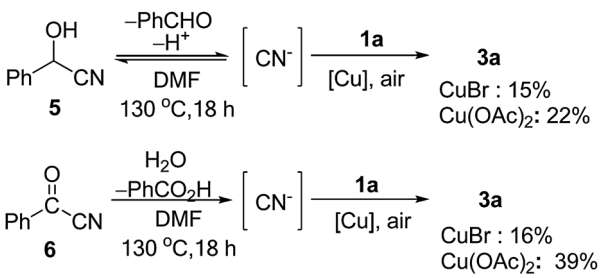


Scheme 3 Structures of substrates **1s–v**.

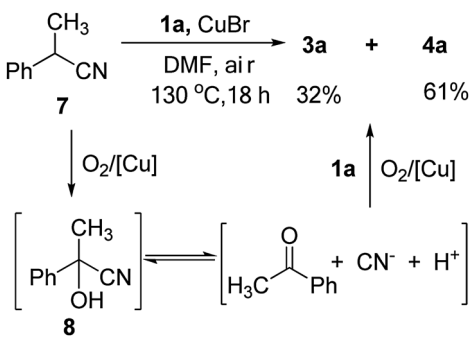
2-methoxy-6-phenylpyridine (**1u**) (Scheme 3). It was found that these reactions did not proceed because the substituent at the 6-position of pyridine inhibited the coordination of the nitrogen of pyridine to copper. Furthermore, 2-(anthracen-9-yl)-pyridine (**1v**) did not react due to the inappropriate ring size for the copper-catalyzed C–H activation.

Since cyanide anion (CN^-), 2-hydroxy-2-phenylacetonitrile (**5**) and several by-products, such as benzaldehyde, benzoic acid, *N*,*N*-dimethylbenzamide and *cis*-/*trans*-2,3-diphenylfumaronitrile, were detected from the reaction mixture (see ESI†), we speculated that the cyanide reagent **2a** might undergo a copper-catalyzed aerobic C–H oxidation[18] to form cyanohydrin **5** and benzoyl cyanide (**6**), which could release free cyanide anions. In order to demonstrate this process, we utilized **5** and **6** as cyanation reagents to carry out the reaction with **1a** (Scheme 4). In the presence of CuBr, **5** and **6** afforded **3a** in 15% and 16% yields, respectively. $Cu(OAc)_2$ could also catalyze these reactions to give improved yields (22% and 39%).

2-Phenylpropanenitrile (**7**), which can be oxidized into α-cyanohydrin **8**, but cannot be further oxidized into ketone, was also examined (Scheme 5). We found that CuBr could efficiently catalyze the reaction between **7** and **1a**. These results suggested that α-cyanohydrins can provide cyanide anions *via* a retro-cyanohydrination.



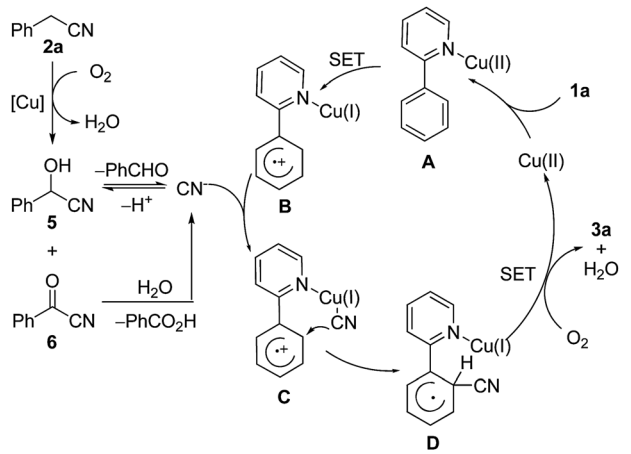
Scheme 4 Reaction of cyanation reagents **5** and **6**.



Scheme 5 Reaction of cyanation reagent **7** with **1a**.

With the CN^- indicator strip,[16,17] we monitored the *in situ* generated cyanide anion from the cyanation reagents **2a** and **5–7** in DMF (Table S2, ESI†). For **2a** and **7**, both Cu(I) and air were found to be necessary for the formation of free cyanide anions. However, **5** and **6** could release cyanide anions without the copper catalyst.

In the reaction kinetics investigations, we observed that **1a** consumed steadily along with a steady formation of **3a** in the



Scheme 6 Possible mechanism for the Cu-catalyzed reaction between **1a** and **2a**.

CuBr-catalyzed cyanation of **1a** with **2a** (Fig. S2, ESI†). The half conversion of **1a** was determined at 12 h, while the reaction completed at 18 h. However, for the CuBr-catalyzed cyanation of **1a** with **6**, a rapid increment of **3a** and a rapid decrement of **1a** appeared after the reaction took place for 4 hours (Fig. S3, ESI†). In this case, there was an initiation period for the reaction, in which Cu(I) needs to be oxidized to Cu(II) for the C–H functionalization of 2-phenylpyridine. For the $Cu(OAc)_2$ catalyzed reaction, a steady increment of **3a** was observed (Fig. S4, ESI†). These results suggest that Cu(I) is responsible for the oxidation of benzyl cyanide, while Cu(II) is responsible for the C–H functionalization of 2-phenylpyridine. The activated Cu(II) could be *in situ* generated from the Cu(I) salt in our reaction system. Moreover, the copper catalyzed oxidation step from **2a** to **5** is critical for a high yield of **3a**. Both **5** and **6** could rapidly release cyanide anions without the oxidation step, but they gave the cyanated product in poor yields (Scheme 4). In these cases, the formation of cyanide anions might be so fast that most of them were oxidized to OCN^- under air in the presence of Cu(I).[19] For the same reason, the reaction using oxygen or other oxidants also gave poor yields (Table S1, entries 23–25, ESI†).

Based on these results, a possible mechanism is proposed in Scheme 6. Firstly, **2a** undergoes a copper-catalyzed oxidation with air to generate **5** and **6**,[18] accompanying the generation of Cu(II) species. Then, a cyanide anion is formed through a retro-cyanohydrination of **5** and hydrolysis of **6**. Finally, the cyanide anion participates in the copper-catalyzed-cyanation cycle. This cycle is initiated with the coordination of Cu(II) to the pyridine, which forms Cu(II) complex **A**. Subsequently, a single electron transfer (SET) from the aryl ring to the coordinated Cu(II) leads to the cation-radical intermediate **B**,[11] which coordinates with the *in situ* generated cyanide anion to form Cu(I) complex **C**. Then, **C** undergoes an intramolecular anion transfer to form radical **D**. Finally, **D** is oxidized by O_2 to **3a** and Cu(II).

In conclusion, we demonstrated an efficient transformation from arenes to aryl cyanides using benzyl cyanide as the cyanide anion surrogate. The cascade cyanation involves a copper-catalyzed aerobic oxidation of benzyl cyanide, a retro-cyanohydrination, and a copper-catalyzed aerobic oxidative C–H functionalization. We believe that matching two copper-catalyzed reaction rates is the key for the success of this transformation. Further investigations on the reaction mechanism and synthetic applications of the present method are currently underway in our laboratory.

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