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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700213

Link to VoR: http://dx.doi.org/10.1002/adsc.201700213

Advanced Synthesis & Catalysis
10.1002/adsc.201700213

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Photoinduced Copper(I)-Catalyzed Cyanation of Aromatic Halides at Room Temperature

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Received: ((will be filled in by the editorial staff))

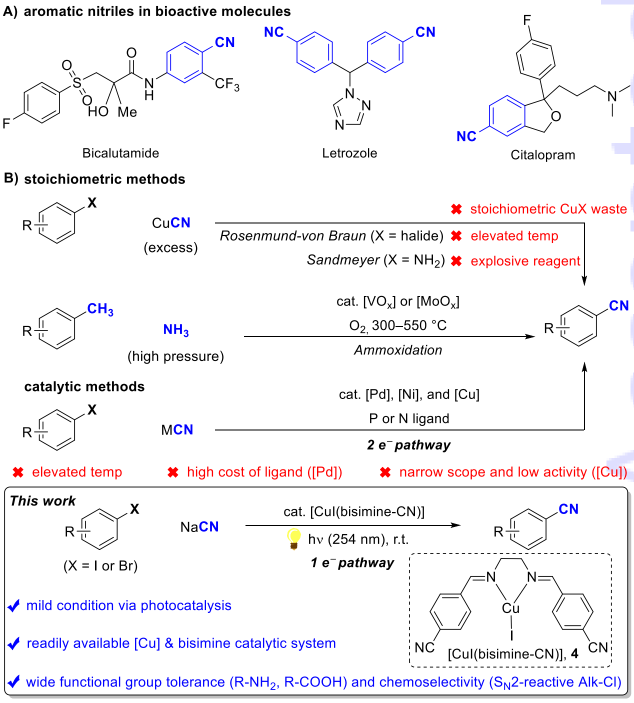
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The first photoinduced Cu(I)-catalyzed cyanation of aromatic halides at room temperature has been developed. The sp^2 cyanation reaction exhibits outstanding tolerance to functional groups including primary amines and carboxylic acids, and chemoselectivity to S_N2-reactive alkyl chlorides. Mechanistic investigations indicate that the reaction occurs via single-electron transfer (SET) between the aryl halide and an excited Cu(I) cyanide catalytic intermediate.

Keywords: Copper; Photocatalysis; Cross-coupling; Cyanides; Radical reactions

Aromatic nitriles have gained significant attention as versatile synthetic intermediates and functional motifs in dyes, pharmaceuticals, and agrochemicals (Scheme 1A).[1] Because of their importance, various synthetic protocols have been developed following “addition of one carbon onto the target aromatic ring” concept (Scheme 1B).[2] Among the traditional methods, the Rosenmund–von Braun reaction is efficient, but suffers from the use of excess CuCN, tedious purification of Cu wastes, and high reaction temperature (150–280 °C).[3] Another common method, the Sandmeyer reaction involving the diazotization of anilines suffers from explosion hazard. In industry, ammoxidation with toluene derivatives under high-pressure O_2 and toxic NH_3 at highly elevated temperatures (300–550 °C) is commonly used but restricted in narrow scope due to such harsh conditions.[4]

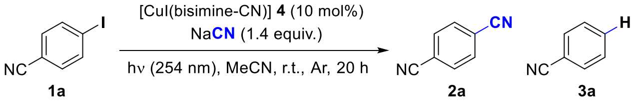
In aromatic nitrile synthesis, catalytic cyanation of aryl (pseudo)halides has been achieved using mainly Pd,[1a,1b,5] Ni,[6] and Cu[7] complexes based on the conventional reactivity of aryl electrophiles with nucleophilic cyanides at elevated temperatures. Other catalytic methods via oxidative nitrogenation or C–H cyanation have also been developed.[8] With the advantages of low cost and chemical diversity,[9] Cu-catalyzed C(sp^2)-cyanation methods have been actively developed in the last decade based on a two-electron pathway utilizing $Cu^{n+}/Cu^{(n+2)+}$ catalytic cycles.[6] CuI and diamine ligand-based catalytic system, developed by the Buchwald group, has shown the widest scope of aryl bromides with high activity among the reported Cu-based catalysts for sp^2-cyanation.[10] Inspired by recent developments by Fu and Peters,[11],[12] we envisioned that photoinduced Cu-catalyzed SET may expand the scope of the reaction, especially with polar and coordinating substrates that could interfere with two-electron-based inner-sphere-type catalytic systems. Herein, we report the first photoinduced Cu(I)-catalyzed cyanation of aryl halides with readily available NaCN at ambient temperature. Notably, this protocol is compatible with diverse aryl halides, polar reactive functional groups including free amino and carboxylic acid groups, and even S_N2-reactive alkyl chlorides.



Scheme 1. Aromatic nitriles: utility and syntheses.

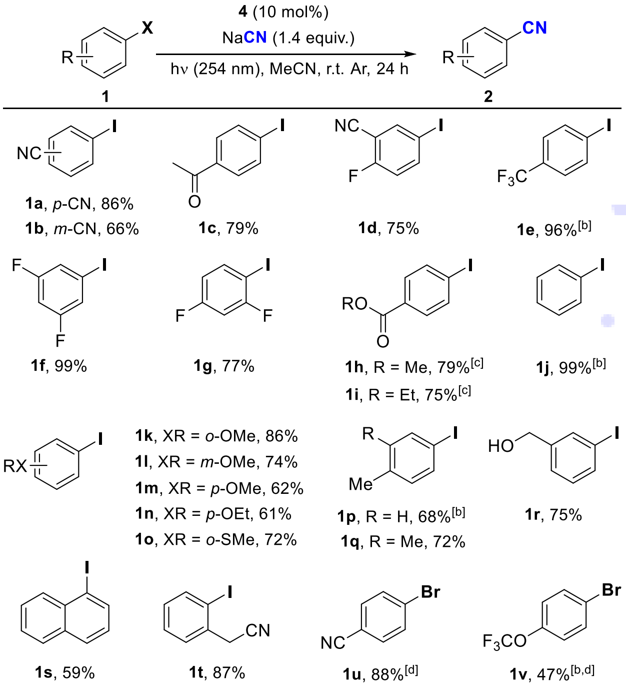
Recently, the Lectka group reported that bisimine ligands were especially effective in Cu(I)-catalyzed sp^3 C–H fluorination via SET.[13] We envisioned that such bisimine ligands would improve catalytic activity by preventing the formation of inactive metal percyanides[14] and by varying the solubility and electronic properties of the catalysts.[14a] Inspired by the photoinduced Cu-catalyzed C(sp^3)-cyanation of secondary alkyl chlorides,[11,15] the reaction of 4-iodobenzonitrile **1a** with tetra-*n*-butylammonium cyanide (TBACN) was conducted using [CuI(bisimine-CN)] **4** as the photocatalyst under UV-C irradiation (λ_{max} = 254 nm). The desired product **2a** was obtained in a moderate yield at room temperature (entry 1, Table 1). To our delight, readily available NaCN was identified as the best cyanide source among the tested cyanide sources including $K_4[Fe(CN)_6]$ (entry 2, see Table S2 for further details). Simple Cu(I) salts gave lower yields, especially in the reactions with other aryl iodides (entries 3–5).[16] Visible-light irradiation was not effective (entry 6). The exclusion of Cu, light, or cyanide did not produce any product (entries 7–9). Recently, MeCN was reported as a nucleophilic cyanide source when Cu catalysts and oxidants such as O_2 and TEMPO were used.[17] However, the reaction did not produce the cyanated product without NaCN (entry 9). To our delight, the reaction was comparably efficient even in presence of air and moisture, demonstrating excellent tolerance of the developed conditions (entries 10 and 11). Reductive dehalogenated product **3a** was observed as the byproduct probably by the abstraction of one hydrogen from the solvent from the generated aryl radical. Thus, deuterated solvent with stronger C–D bonds than C–H bonds was used to prevent the side reaction, but diminished yield was obtained (entry 12).

Table 1. Optimization of reaction conditions.[a]



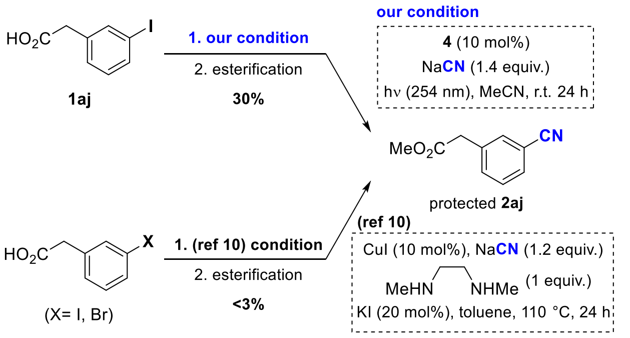
Entry	Deviation from above	Conv [%]	2a [%]	3a [%]
1	2.0 equiv. TBACN instead of NaCN	100	59	41
2	none	100	88	12
3	[CuI] instead of **4**	100	84	16
4	[CuBr] instead of **4**	100	86	14
5	[CuCl] instead of **4**	100	74	26
6	hν (visible light, 34W blue LED)	0	0	0
7	no [Cu]	0	0	0
8	no hν	0	0	0
9	no NaCN	59	0	0
10	under air	100	87	13
11	1.0 equiv. H_2O	100	86	14
12	CD_3CN instead of MeCN	100	82	0

[a] Conditions: **1a** (0.1 mmol), NaCN (1.4 equiv.), **4** (10 mol%), MeCN (0.4 mL), Ar, irradiation using four 15W UV germicidal CFL lamps, r.t. 20 h. Average of 3 runs; determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

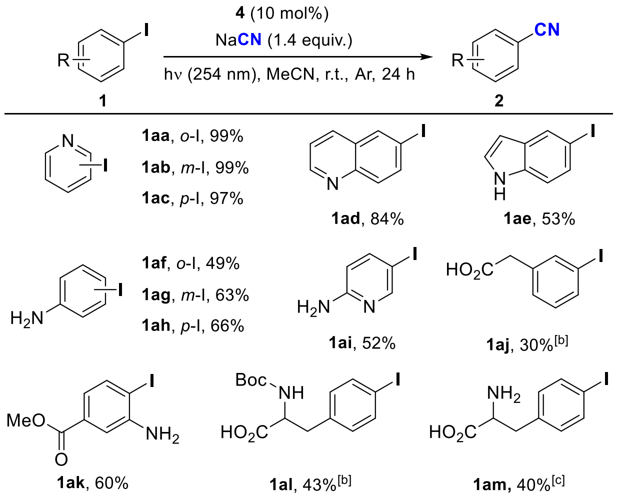


Scheme 2. Scope of aryl halides. [a] [a] Conditions: **1** (0.3 mmol), NaCN (1.4 equiv.), **4** (10 mol%), MeCN (1.2 mL), Ar, irradiation using four 15W UV germicidal CFL lamps, r.t. 24 h. Isolated yields. [b] NMR yield due to low boiling point of the product. [c] 36 h. [d] 2 equiv. NaCN and 30 mol% NaI were used.

With the optimized reaction conditions, diverse aromatic iodides and bromides were explored (Scheme 2). Both electron-rich and -deficient aromatic iodides reacted, affording the products in moderate-to-excellent yields regardless of substitution position. Electron-withdrawing cyano (**1a** and **1b**), acetyl (**1c**), trifluoromethyl (**1e**), fluoro (**1f** and **1g**), and ester groups (**1h** and **1i**) as well as electronically neutral iodobenzene (**1j**) were tolerated. In the case of electron-donating substituents, ether (**1k**–**n**), thioether (**1o**), alkyl (**1p** and **1q**), and alcoholic (**1r**) groups were compatible. In addition, the developed methods also afforded cyanation with aryl bromides (**1u** and **1v**) in the presence of 30 mol % NaI.

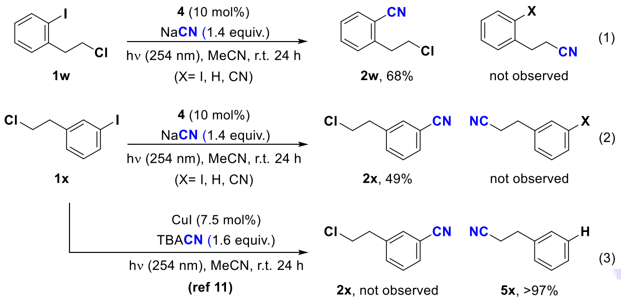


Scheme 3. Cu catalyzed cyanation: our method and the method in reference 10.



Scheme 4. Scope of aryl iodides with polar functional groups. [a] [a] Conditions are same with Scheme 2. Isolated yields. [b] After the cyanation, the carboxylic acid was esterified [c] After the cyanation, the amine was Boc-protected, and then the carboxylic acid was esterified.

A carboxylic acid, 3-iodophenylacetic acid (**1aj**), which was not compatible in the previously reported Cu^+/Cu^{3+}-based catalytic system,[10] was cyanated although the isolated yield (30%) after esterification was not so high (Scheme 3). Encouraged by the result, we applied the developed method to highly polar functional groups which were usually less compatible in transition-metal catalysis. The developed method tolerated amino groups, free carboxylic acid, amino acids, and medicinally relevant heterocycles[1c] (Scheme 4). Pyridine derivatives including quinolone (**1aa**–**1ad**) successfully afforded the coupling products in good-to-quantitative yields despite their high affinity toward a transition metal center. Even free indole (**1ae**) and free anilines (**1af**–**1ai**) were smoothly transformed to the desired products in moderate yields. However, the reactions with thiophene derivatives such as 2-iodothiophene did not give any desired product, affording dehalogenated thiophene only. Notably, amino acid derivatives including unprotected amino acid (**1ak**–**1am**) tolerated the catalytic conditions. It is worthwhile to note that reactions with amino acids such as **1al** under the previously reported Cu^+/Cu^{3+}-based catalytic conditions did not afford the corresponding nitrile at all.



Scheme 5. Chemoselectivity to C(sp^2)-cyanation over S_N2.

To illustrate the chemoselectivity of the method,[18] two reactions with S_N2-reactive alkyl chlorides, substituted aryl iodides (**1w** and **1x**) were carried out [Eqs. (1) and (2), Scheme 5]. To our delight, this Cu(I) bisimine catalytic system selectively afforded C(sp^2)-cyanated products **2w** and **2x** without C(sp^3)-cyanation on alkyl chlorides, which is difficult to achieve with the previously reported catalytic systems operated at high temperatures. The reaction of **1x** under the reported photoinduced C(sp^3)-cyanation conditions[11] furnished only the C(sp^3)-cyanated and reductively dehalogenated product **5x** in a quantitative yield [Eq. (3), Scheme 5]. These results clearly indicate that this method can be used to selectively functionalize aryl rings differently with the traditional S_N2 and recently reported photocatalytic C(sp^3)-cyanation protocols.

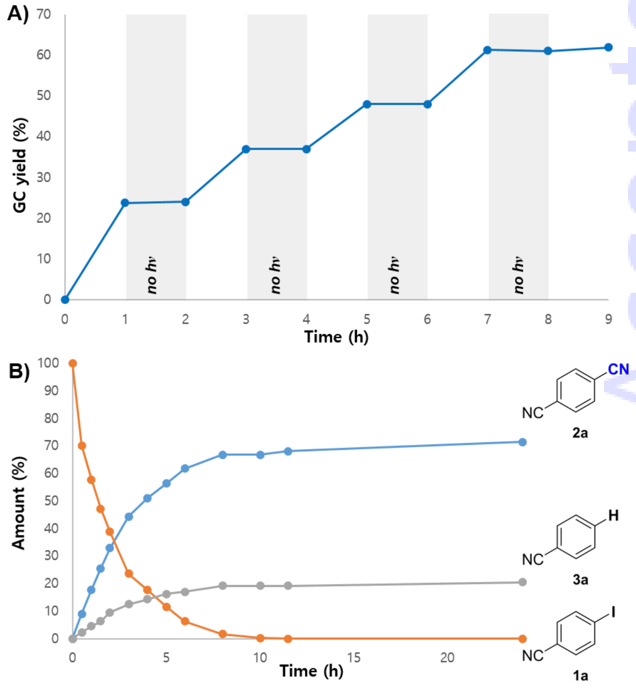
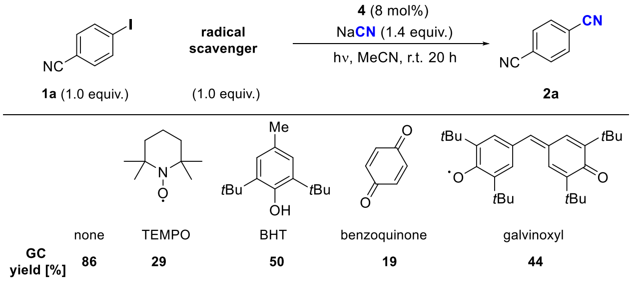
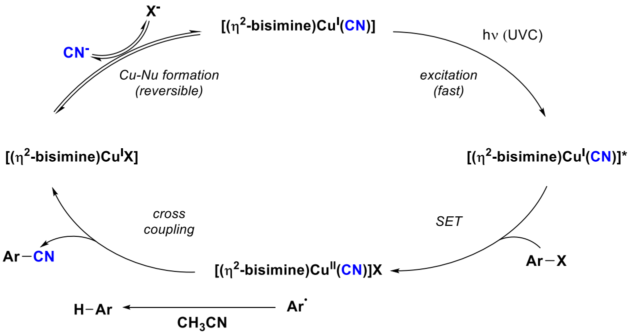


Figure 1. Investigation of photocatalysis. A) light-dark experiment. B) reaction profile during catalysis.

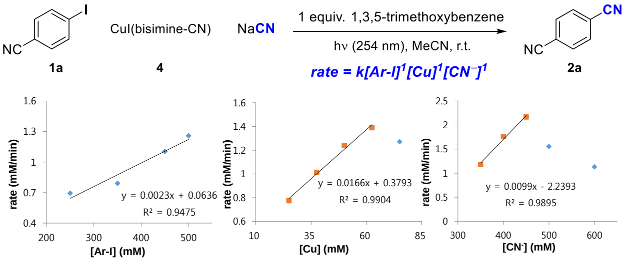
Photoirradiation is essential in the developed method as no conversion occurred without light (entry 8, Table 1). Light–dark experiment with **1a** further confirmed that the reaction proceeded only with irradiation (Figure 1A). The involvement of radical intermediates in photocatalysis was also investigated using four radical scavengers such as TEMPO (Scheme 6). All the reactions with **1a** were arrested in moderate-to-high degree (36–67% decrease in yield). Regarding the gradual conversion of aryl iodide (Figure 1B) and incomplete inhibition by radical scavengers, a catalytic amount of aryl radical may be present within the solvent cage following closed catalytic cycle rather than a rapid chain process.



Scheme 6. Inhibition with radical scavenger.



Scheme 7. Plausible mechanism.



Scheme 8. Kinetic study.

Based on the experiments and the previous reports,[11,12h] a plausible mechanism was proposed (Scheme 7).[12h] Cu(I) cyanide is formed from Cu(I) halide via anion exchange. The adduct is first photoexcited and then quenched with the aryl halide via SET, furnishing Cu(II) cyanide and an aryl radical. Next, they combine to generate an aromatic nitrile and Cu(I) halide. To gain a deeper mechanistic insight, a kinetic study was performed (Scheme 8). All the reaction species (aryl iodide **1a**, Cu **4**, and cyanide) showed first-order dependence on the concentration. These results indicate that the reaction of copper cyanide adduct with aryl species is the turnover limiting step, which could be the SET or the cross-coupling step in the proposed mechanism. Besides, Cu(I) halide seems to be a catalyst resting state in equilibrium via reversible cyanide exchange, regarding the first order of cyanide. Interestingly, relatively large equivalence of cyanide (up to 1.8 equiv.) compared to copper catalyst did not hamper the reactions. Chelation of the bidentate bisimine ligand presumably inhibits the formation of percyanide complex. Much higher concentrations of Cu and cyanide hindered the reactions. In high concentrations of Cu, comproportionation of Cu(I) might occur, giving catalytically inactive Cu(0) and Cu(II) species.[19] In the presence of excess cyanides, Cu percyanide species could be formed as dead-end species similar to Pd catalysis.[14a]

In conclusion, we developed a novel mild cyanation method for aryl halides at room temperature using a Cu(I) photocatalytic system. This method tolerates various functional groups including reactive free amino and carboxylic groups, which were previously incompatible in two-electron-based $Cu^{n+}/Cu^{(n+2)+}$ sp^2 cyanation reactions. The method also exhibited excellent chemoselectivity in the cyanation of aryl halides even in presence of S_N2-reactive alkyl chlorides.

Experimental Section

To an oven-dried quartz tube (10 cm in height, fitted with a 14/20 septum) equipped with a stir bar, (if solid) **1** (1 equiv., 0.3 mmol), **4** (10 mol%), and NaCN (1.4 equiv.) were added in an Ar-filled glovebox. The quartz tube was capped with a 14/20 septum after CH_3CN (1.2 mL) was added via a syringe. After removing from the glovebox, the reaction tube was sealed again with a black-vinyl-electrical tape (if **1** is liquid, it was added via a microsyringe at this time). The resulting mixture was stirred vigorously and irradiated in the center of the lamps at room temperature for 24 h. Then, the reaction mixture was transferred to a round-bottom flask using acetone or CH_2Cl_2 and then concentrated under reduced pressure. The residue was purified by column chromatography using a mixture of hexane/ethyl acetate or CH_2Cl_2/methanol eluents used.

Acknowledgements

We thank Jaewoon Kim in our group for helpful discussion. This work was supported by Samsung Science and Technology Foundation under Project Number SSTF-BA1601-12.

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[16] Although CuI and CuBr exhibited comparable activity in the cyanation of **1a**, their efficiency decreased significantly with other substrates such as **1c**, **1k**, **1n**, and **1ah**. see the Supporting Information (Table S4).

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