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# Organophotoredox Assisted Cyanation of Bromoarenes via Silyl-Radical-Mediated Bromine Abstraction

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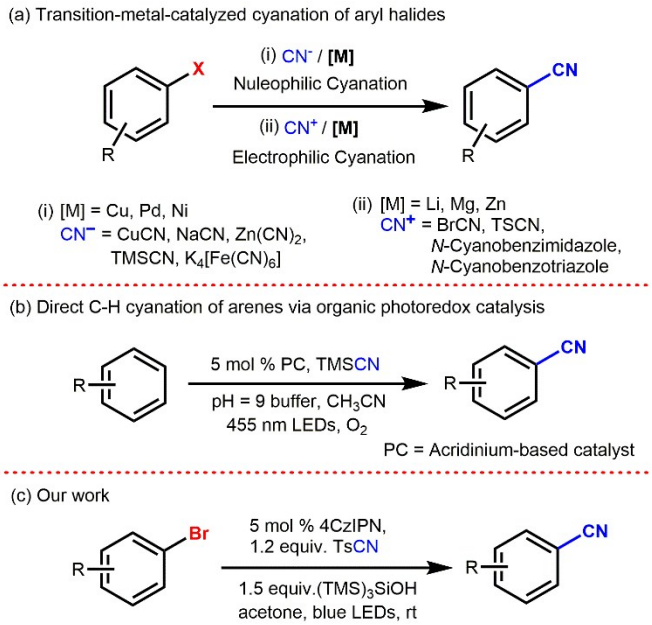
**Insertion of nitrile (-CN) group to arenes through direct functionalization of C($sp^2$)-Br bond is a challenging reaction. Herein, we report an organophotoredox method for the cyanation of aryl bromides using organic photoredox catalyst 4CzIPN and Tosyl cyanide (TsCN) as the nitrile source. Photogenerated silyl radical, via single electron transfer (SET) mechanism, was employed to abstract bromine from aryl bromide to provide aryl radical, which concomitantly intercepted by TsCN to afford the aromatic nitrile. A range of substrates containing electron-donating and -withdrawing groups, were demonstrated to undergo cyanation at room temperature in good yield.**

The presence of aromatic nitriles in pharmaceuticals, agrochemicals, natural products, pesticides, and fine chemicals reflects their utmost importance.[1] Cyanoarenes are treated as valuable functional group precursors for the late stage installation of acids,[2] aldehydes or amines,[3] ketones or imines,[4] and amides.[5] Aromatic nitriles are synthesized by numerous methods such as Sandmeyer reaction using diazonium salt,[6] Rosenmund–von Braun reaction from aryl halides and copper catalyst.[7] In addition to classic approaches several transition metal catalyzed cross-coupling of aryl halides and cyano precursors are utilized for the synthesis of cyanoarenes.[8] Primarily copper and palladium catalysts are used to couple aryl halides with cyanating reagents to provide cyanoarenes (a, Scheme 1).[9] Buchwald's works on palladium-and copper-catalyzed cyanation of aryl halides are noteworthy.[10] Although these methods are efficient, the requirement of toxic reagents, high temperature, expensive metal catalysts, and ligands are serious drawbacks. Development of a transition metal free method at room temperature for the direct conversion of aryl halides to aryl nitriles would be attractive. This motivated us to focus on the photocatalytic method to synthesize aromatic nitriles.

In the last decade, photoredox catalysis has been exploited for the synthetically challenging reactions.[11] Notably, facile generations of reactive intermediates such as arene radical cations, α-carbonyl radicals, trifluoromethyl radicals, enone radical anions, iminium ions via SET under photocatalytic condition ease the synthesis of complex molecules.[12]




**Scheme 1.** Cyanation Methods for Aromatic Ring.

Interestingly, photocatalytic cyanation of organic molecules is a synthetically viable method. In 2015, Fu and Peter groups developed photoinduced copper-catalyzed cyanation of unactivated secondary alkyl chlorides at room temperature in the presence of UV light.[13] Later on, several decarboxylative cyanation of carboxylic acids using visible light has been developed.[14a-c] Recently, König and co-workers achieved cyanation of aliphatic carboxylic acids via decarboxylation method using tosyl cyanide as a cyanating agent and Flavin as a photocatalyst.[14d] These photocatalytic cyanation restricted to aliphatic systems. Nicewicz et al. reported cyanation of arenes

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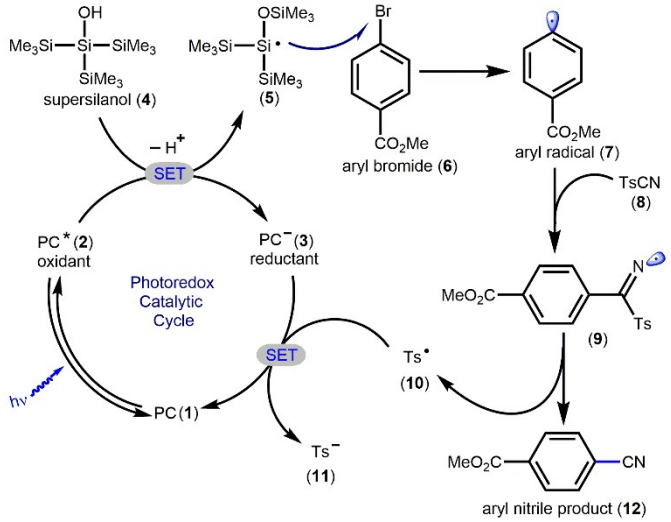
by direct functionalization of C-H bonds assisted by an acridinium based photoredox catalyst and nucleophile trimethylsilyl cyanide (TMSCN) under aerobic condition (b, Scheme 1).[15] This procedure was successful with electron rich arenes and showed regioselectivity problem. Limited access to synthesize aromatic nitriles led us to develop a direct cyanation method under visible light irradiation. With this intention, we were interested to functionalize C($sp^2$)-Br bond of aryl bromide via radical mediated Br abstraction to generate aryl radical, which would then intercept by TsCN as a cyanating agent to produce desire aromatic nitrile (c, Scheme 1).

Inspired by the literature reports,[12,14,15] we hypothesized that the visible-light promoted cyanation of aryl bromide based on our methodology proceed following the photocatalytic cycle depicted in the Scheme 2.




**Scheme 2.** Proposed mechanism for silyl radical mediated cyanation of aryl bromides via photoredox catalysis.

The catalytic cycle will follow the sequence as, (i) Visible-light excitation of photocatalyst (PC) 4CzIPN [1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene] (**1**) will produce excited state species (**2**), (ii) the excited photocatalyst (**2**) [$E_{red}$ ($PC^*/PC^-$) = +1.43 V vs SCE in $CH_3CN$][16] will then oxidize tris-(trimethylsilyl) silanol (supersilanol, **4**) [$E_{red}$ [$(TMS)_3SiOH^{+\bullet}/(TMS)_3SiOH$] = +1.54 V vs SCE in MeCN][17] via SET mechanism to generate reduced form of the photocatalyst (**3**), (iii) oxidized form of supersilanol will then generate silicon-centered radical (**5**), after deprotonation followed by radical Brook rearrangement,[18] (iv) silyl radical (**5**), known as potent abstractor of bromine atom from C($sp^2$)-Br bonds[19,20] ($k \approx 5\times 10^6$ $M^{-1}s^{-1}$ to $1.1 \times 10^8$ $M^{-1}s^{-1}$ for bromobenzene)[21] will result in the formation of aryl radical (**7**), (v) weakly nucleophilic aryl radicals will then attack the highly electrophilic TsCN (**8**) to furnish the expected key intermediate (**9**), which then affords the desired nitrile compound (**12**) through Barton nitrile transfer[14a,b] along with the formation of *p*-toluenesulfonyl radical ($Ts^\bullet$, **10**), (vi) finally, the reduced photocatalyst ($PC^-$) [$E_{red}$ ($PC^-/PC$) = −1.24 V vs SCE in $CH_3CN$][16] will donate single electron to $Ts^\bullet$ [$E_{red}$ ($Ts^\bullet/Ts^-$) = −0.50 V vs SCE in $CH_3CN$][22] to provide $Ts^-$ (**11**) and the photocatalyst (**1**).

To implement our hypothesized photocatalytic cyanation reaction, we focused on the cyanation of methyl 4-bromobenzoate **6** (Table 1).

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**Table 1**. Optimization of Reaction Conditions.[a]


| entry | conditions | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | as shown | $CH_3CN$ | 48 |
| 2 | as shown | DMF | 14 |
| 3 | as shown | DMSO | 19 |
| 4 | as shown | DME | 5 |
| 5 | as shown | Acetone | 71 |
| 6[c] | TMSCN | Acetone | <5 |
| 7 | 1 equivTsCN | Acetone | 63 |
| 8 | 2 equivTsCN | Acetone | 75 |
| 9 | 4CzTPN as PC | Acetone | 55 |
| 10 | 4DPAIPN as PC | Acetone | 0 |
| 11[d] | $TMS_3SiH$ | Acetone | 43 |
| 12 | Presence of air | Acetone | 9 |
| 13 | no PC | Acetone | 0 |
| 14 | no $(TMS)_3SiOH$ | Acetone | 0 |
| 15 | no visible light | Acetone | 0 |
| 16 | no TsCN | Acetone | 0 |

[a]Reaction conditions: Aryl bromide **6** (0.25 mmol, 1 equiv), 4CzIPN (5 mol %), TsCN (0.30 mmol, 1.2 equiv), base (107 mg, 0.50 mmol, 2 equiv), $(TMS)_3SiOH$ (0.375 mmol, 1.5 equiv), solvent (3 mL), irradiated under inert condition with blue LEDs for 12 h at room temperature. [b]Isolated products. [c]TMSCN used instead of TsCN as a -CN source. [d]1.5 equiv of $TMS_3SiH$ used in place of $(TMS)_3SiOH$.

A reaction mixture of **6** (1 equiv), organic photocatalyst 4CzIPN (5 mol %), silyl radical source $(TMS)_3SiOH$, and cyanating agent TsCN were added to $CH_3CN$ under $N_2$ atmosphere and exposed to blue LED for 12 h at room temperature. The desired nitrile-bearing product **12** was obtained in 48 % yield (Table 1, entry 1). Solvent screening showed that acetone afforded the cyano product with maximum yield (Table 1, entry 5). Further studies revealed that the use of 4CzTPN [2,3,5,6-Tetra(carbazol-9-yl)terephthalonitrile] as an organic photocatalysts provided satisfactory yield whereas 4DPAIPN [1,3-Dicyano-2,4,5,6-tetrakis(diphenylamino)-benzene] found to be ineffective photocatalyst (Table 1, entries 9, 10). When we used TMSCN as a cyanating reagent trace amount of product was formed (Table 1, entry 6). Further, change in the reaction parameters like substrate and reagents' concentrations and catalyst loading had an adverse impact on the yield of the product (Table 1, entry 7, 8). Under aerobic condition cyanation reaction provided drastically reduced product yield due to interference of $O_2$ with the catalytic cycle (Table 1, entry 12). Control experiments revealed that photocatalyst, silanol, TsCN, and visible light were all individually necessary for the success of the reaction (Table 1, entries 13–16, 0% yield). Additionally, the exclusion of base resulted in lower product yield (supporting information, SI, Figure S2, entry 6, 32% yield).

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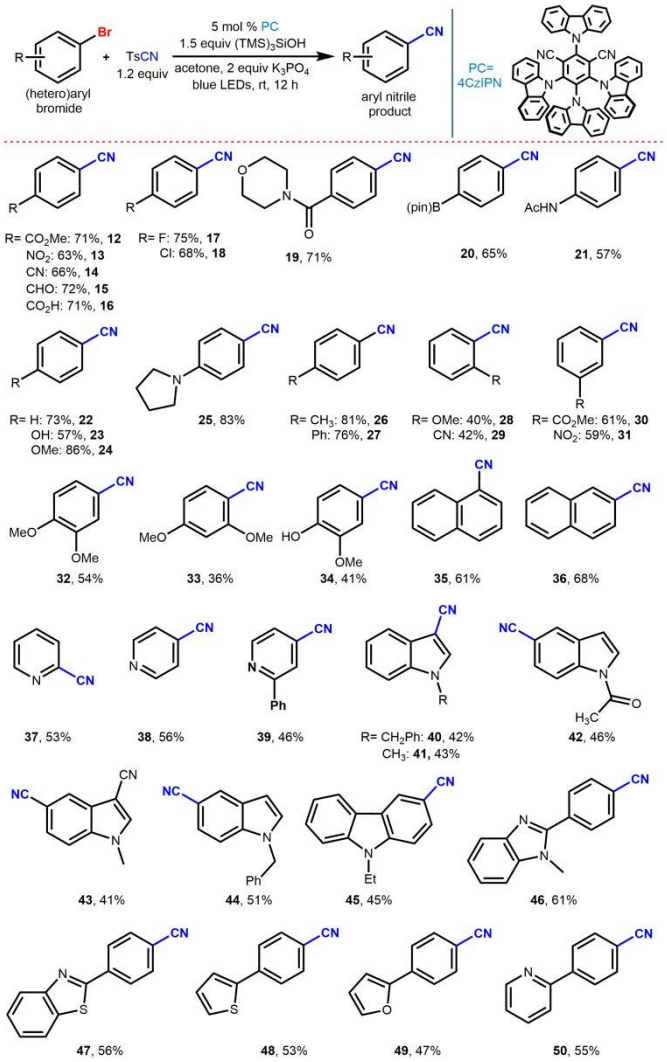
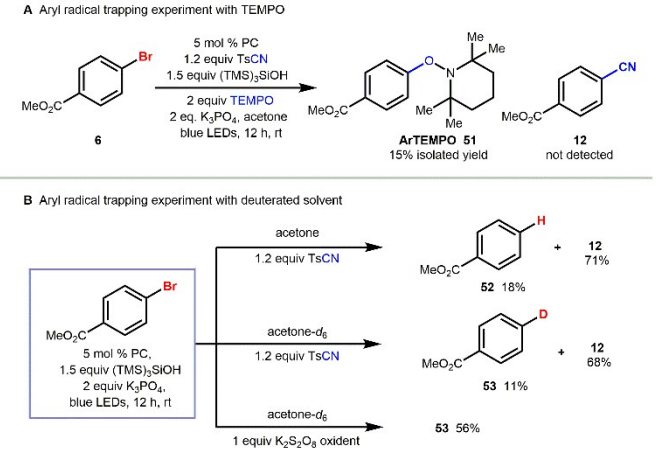



**Scheme 3**. Scope of the Cyanation Reaction of Aryl Bromides: Aryl bromide (0.5 mmol, 1 equiv), 4CzIPN (5 mol %), TsCN (0.60 mmol, 1.2 equiv), base (1.00 mmol, 2 equiv), $(TMS)_3SiOH$ (0.75 mmol, 1.5 equiv), solvent (6 mL), irradiated under inert condition with blue LEDs for 12 h at room temperature. Isolated products yields were reported.

Having optimized conditions in hand, we explored the scope of this photocatalytic cyanation method with diverse aromatic and hetero aromatic bromides (Scheme 3). Electronically varied bromoarenes with para substitution provided good product yields (**12**–**27**, 57–86%). ortho- and meta-substituted substrates were well tolerated and gave moderate yields (**28**–**31**, 40–61%). Notably, substrates containing electron-withdrawing groups (e.g. $NO_2$, CN) did not hinder the reaction and furnished good product yields (**12**–**21**, 57–75%). Similarly, electron-donating group bearing substrates afforded high yield of the desired products (**23**–**28**, 40–86%). Interestingly, substrates containing other halogen (fluoro and chloro) groups proceeded smoothly and furnished nitrile products with good yields (**17** and **18**, 75% and 68%). Disubstituted aryl bromides produced slightly lower product yields (**32**–**34**, 36–54%). Bromonaphthalenes were suitable substrates for the cyanation reactions (**35** and **36**, 61% and 68%). We were pleased to find that heteroaryl bromides such as bromo derivatives of pyridines, *N*-substituted indoles, and carbazole yielded cyano products moderately (**37**–**45**, 41–56%). To our delight, heterocycles e.g. benzodiazole, benzothiazole, thiophene, furan attached to para postion of the aromatic bromides delivered the cyano products under the presented photocatalytic method (**46**–**50**, 47–61%). The reason for the moderate yields is due the formation of dehalogenation product. The dibromide substrates provided moderate to lower yield along with minimum amount of dicyano products (SI, for details).

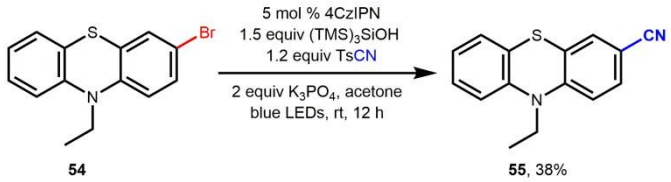
To shed light on the reaction mechanism, we have carried out some control experiments. Formation of the aryl radical intermediate was checked by conducting the photocatalytic cyanation reaction under the optimized reaction condition in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (A, Scheme 4).




**Scheme 4**. Mechanistic studies on aryl radical.

As expected, the formation of aryl nitrile was completely suppressed, whereas aryl-TEMPO adduct (**51**) was obtained in 15% yield (see the SI for details). Further, the dehalogenation product (**52**) was obtained in 18% yield under the optimized reaction condition due to hydrogen atom abstraction from solvent (B, Scheme 4). When the same reaction was conducted in acetone-$d_6$, 11% deuterium incorporated product (**53**) was observed. Furthermore, the standard reaction was carried out using $K_2S_2O_8$ as an oxidant instead of TsCN in acetone-$d_6$ solvent resulted in high incorporation of deuterium to the arene (56% yield of **53**), further supporting the intermediacy of an aryl radical.

The utility of this method was shown by inserting -CN group to *N*-substituted bromo-phenothiazine (**54**) to synthesize compound **55** (Scheme 5). Nitrile containing phenothiazine moiety constitute several drug molecules e.g. pericyazine and cyamemazine which are antipsychotic drugs.[1a] Cyano-phenothiazine molecules exhibits strong luminescent property. These redox-active chromophores also found application in photocatalysis and dye-sensitized solar cells (DSSC).[23] Compound **55** shows strong yellow fluorescent color.




**Scheme 5.** Direct insertion of -CN group to phenothiazine.

In conclusion, we have developed a metal-free photocatalytic method for the direct cyanation of aryl bromides. Silyl-radical-mediated halogen abstraction strategy has been employed to functionalize the C($sp^2$)-Br bond. Organic photoredox catalyst 4CzIPN and cyanating reagent TsCN effectively accomplish the reactions. A range of aryl and heteroaryl bromides were tested successfully. The developed photocatalytic cyanation reaction proceeded at room temperature and provided moderate to good product yields. Wide variety of functional groups e.g. ester, acid, amide, and protected amines were well tolerant towards the proposed photocatalytic conditions. To the best of our knowledge, this is the first time we have shown a metal-free direct cyanation of (hetero)aryl bromides. Additionally, the application of this direct cyanation was demonstrated by incorporating -CN group to arene ring of phenothiazine. This Mild and simple protocol can be used to synthesize pharmaceuticals, organic precursors, and natural products.

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## Conflicts of interest

There are no conflicts to declare.

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