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# Photoinduced Hydroxylation of Organic Halides under Mild Conditions

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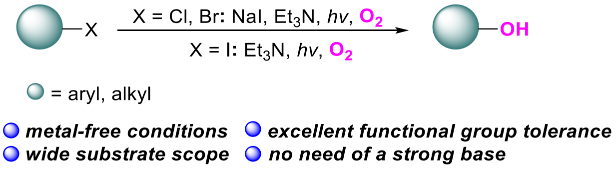
*Supporting Information*

**ABSTRACT:** Presented in this paper is photoinduced hydroxylation of organic halides, providing a mild access to a range of functionalized phenols and aliphatic alcohols. These reactions generally proceed under mild reaction conditions with no need for a photocatalyst or a strong base and show a wide substrate scope as well as excellent functional group tolerance. This work highlights the unique role of NaI that allows a challenging transformation to proceed under mild reaction conditions.



Phenols and their derivatives are prevalent structures in pharmaceutical, agrochemical, material, and natural products as well as versatile intermediates in organic chemistry.[1] Over the past decades, much effort to develop the methods for the preparation of phenols has been devoted.[2] Among these existing methods, hydroxylation of aryl halides has been widely recognized as one of the most attractive approaches to access phenols because of its advantages including the accessibility and abundance of haloarenes, control of the regioselectivity, as well as no need for protecting groups. Traditional conditions for hydroxylation of aryl halides relied on the use of transition metals such as copper salts,[3] nickel,[4] and palladium salts.[5] However, these transition-metal-catalyzed hydroxylation reactions typically suffered from high temperatures, the demand of complex ligands and strong bases, as well as the requirement of microwaves in some case. Specifically, the employment of strong base as a hydroxide nucleophile usually led to a number of side reactions such as hydrolysis of esters and amides, hydration of nitriles, and dehydration of alcohols, thus causing functional groups incompatibility. Furthermore, it is worth noting that most of the existing methods were only effective for aryl iodines and aryl bromides but ineffective for aryl chlorides. On the other hand, other hydroxide sources including acetohydroxamic acid[6] and oxime[7] were also successfully applied to the hydroxylation of haloarenes in the presence of stoichiometric $K_2CO_3$ or $Cs_2CO_3$. To take account of the concept of green and sustainable chemistry, the development of a mild and efficient strategy to construct phenols and their derivatives is still quite desirable.

Over the past decade, some work on photoinduced C−X bond homolytic cleavage of haloarenes under photocatalyst-free conditions has been reported.[8] For example, Li and co-workers disclosed a photoinduced halogen exchange and carbohalogenation of haloarenes via a radical intermediate in the absence of a photocatalyst.[9] In 2016, the groups of both Li and Larionov developed photoinduced C−X borylation with homolytic cleavage of the Ar−X bond being the key step.[10] Furthermore, this photocatalyst-free strategy could be extended to phosphinylation of heteroaryl halides.[11] With these items in mind, we envisage that the homolytic cleavage of the Ar−X bond would be enabled by ultraviolet irradiation under photocatalyst-free conditions to in situ generate an aryl radical intermediate which can be further trapped by molecular oxygen, thus providing a direct and mild entry to phenols.

To test our proposal, 4-bromobenzonitrile (**1a**) was chosen as the model substrate to screen the optimal reaction conditions (Table 1). The hydroxylation of **1a** was conducted under $O_2$ atmosphere with UV irradiation for 24 h in the presence of $Et_3N$.

To our delight, the hydroxyated product **2a** was successfully formed in 35% yield (entry 1). Inspired by Li's work[9] on photoinduced carboiodination and halogen exchange with NaI, we speculated that the addition of NaI will impart a high degree of efficiency into the hydroxylation of challenging substrates such as aryl bromides and chlorides. As expected, it more than doubled the yield of the desired product **2a** in the presence of a catalytic amount of NaI (entry 2). The use of KI as an additive also resulted in an increased yield with a growth rate approaching 50% (entry 3), whereas the addition of $NH_4I$ did not improve the reaction efficiency (entry 4). Replacement of $Et_3N$ with other amines such as $^i\mathrm{Pr}_2\mathrm{NEt}$, *N*,*N*-dimethylaminobutane, triethylenediamine, and 1-ethylpiperidine led to no improvement in the yield (entries 5−8). The absence of the amines resulted in a significant decrease in the yield of product **2a**, demonstrating its important role in the reaction (Table 1, entry 9). Screening of solvents (entries 10−13) revealed that the use of $CH_3CN$ was still the best choice. Interestingly, nonpolar solvent such as cyclohexane proved to be an

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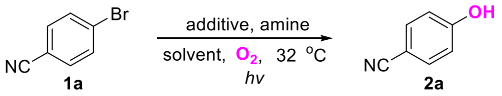
### Table 1. Reaction Optimization[a]



| entry | additive | amine | solvent | yield[b] (%) |
|---|---|---|---|---|
| 1 | | $Et_3N$ | $CH_3CN$ | 35 |
| 2 | NaI | $Et_3N$ | $CH_3CN$ | 75 |
| 3 | KI | $Et_3N$ | $CH_3CN$ | 54 |
| 4 | $NH_4I$ | $Et_3N$ | $CH_3CN$ | 34 |
| 5 | NaI | $^i Pr_2NEt$ | $CH_3CN$ | 64 |
| 6 | NaI | $\boldsymbol{N}^1$ | $CH_3CN$ | 65 |
| 7 | NaI | $\boldsymbol{N}^2$ | $CH_3CN$ | 42 |
| 8 | NaI | $\boldsymbol{N}^3$ | $CH_3CN$ | 60 |
| 9 | NaI | | $CH_3CN$ | 30 |
| 10 | NaI | $Et_3N$ | cyclohexane | 0 |
| 11 | NaI | $Et_3N$ | DMSO | 16 |
| 12 | NaI | $Et_3N$ | $^i$PrOH | 14 |
| 13 | NaI | $Et_3N$ | THF | 39 |
| 14[b] | NaI | $Et_3N$ | $CH_3CN$ | 67 |
| 15[c] | NaI | $Et_3N$ | $CH_3CN$ | 45 |
| 16[d] | NaI | $Et_3N$ | $CH_3CN$ | 0 |
| 17[e] | NaI | $Et_3N$ | $CH_3CN$ | 0 |
| 18[f] | NaI | $Et_3N$ | $CH_3CN$ | 13 |

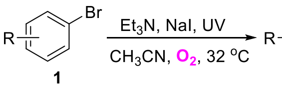
[a] Standard conditions: **1a** (0.2 mmol), additive (0.2 equiv), amine (1.5 equiv), solvent (4.0 mL), UV light (15 W), under $O_2$ atmosphere, 32 °C, 24 h, isolated yield. [b] $Et_3N$ (1.0 equiv). [c] $Et_3N$ (0.5 equiv). [d] Blue light (15W). [e] Green light (15W). [f] Under air atmosphere. $\boldsymbol{N}^1$ = *N,N*-dimethylaminobutane. $\boldsymbol{N}^2$ = triethylenediamine. $\boldsymbol{N}^3$ = 1-ethylpiperidine.

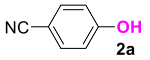
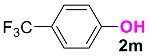
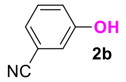
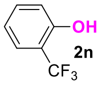
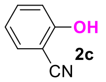
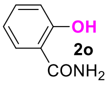
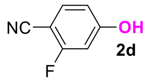
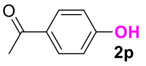
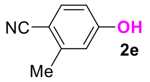
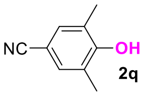
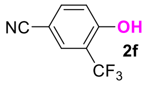
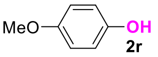
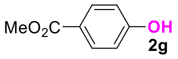
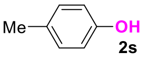
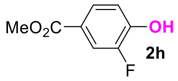
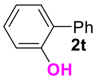
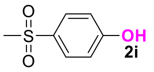
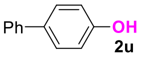
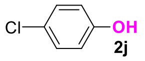
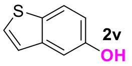
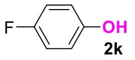
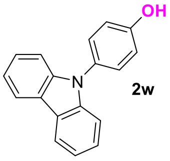
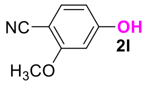
unsuitable solvent for the hydroxylation of 4-bromobenzonitrile (entry 10). Reducing the amount of $Et_3N$ significantly decreased the reaction efficiency (entries 14 and 15). Subsequently, the effect of light source on the efficiency was investigated. It was found that neither blue light nor green light promoted the reaction at all (entries 16 and 17). When the reaction was performed under air atmosphere, a sharp decrease in the yield was observed (entry 18).

With the optimized conditions determined, a series of commercially available aryl bromides reacted well to give functionalized phenols (Table 2). A broad range of functional groups such as cyano, fluoro, trifluoromethyl, ester, mesyl, amide, acyl, methoxy, and methyl groups were compatible with the reaction conditions to deliver the corresponding products in moderate to good yields, emphasizing the generality and excellent functional group tolerance (entries 1−19). It was found that electron-withdrawing substituents at the *para* position of the phenyl ring (entries 1 and 13) resulted in higher yields compared with those at the *meta* (entry 2) and *ortho* positions (entries 3 and 14). In the case of *p*-chloroiodobenzene and *p*-fluoroiodobenzene, the reactions proceeded chemoselectively to give the desired products, with chloro and fluoro groups being intact (entries 4, 10, and 11). This reaction was also operable with sterically hindered aryl bromide (entry 17). In addition, electron-rich aryl bromides afforded lower yields of the desired products (entries 18 and 19). The aryl bromides with an electrically neutral group or a heterocyclic ring proved to be a suitable substrate (entries 20−23).

The possibility of extending the protocol to aryl chlorides was explored under the standard reaction conditions (Table 3). The transformation could be effective for the aryl chlorides

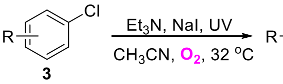
### Table 2. Scope of Aryl Bromides[a]

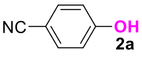
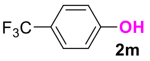
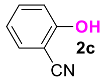
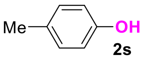
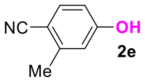
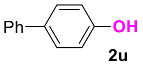
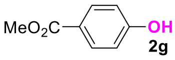


| entry | product | yield (%)[b] | entry | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  2a | 75% | 13 |  2m | 76% |
| 2 |  2b | 60% | 14 |  2n | 50% |
| 3 |  2c | 64% | 15 |  2o | 59% |
| 4 |  2d | 61% | 16 |  2p | 45% |
| 5 |  2e | 68% | 17 |  2q | 42% |
| 6 |  2f | 62% | 18 |  2r | 39% |
| 7 |  2g | 75% | 19 |  2s | 42% |
| 8 |  2h | 47% | 20 |  2t | 91% |
| 9 |  2i | 95% | 21 |  2u | 43% |
| 10 |  2j | 78% | 22 |  2v | 35% |
| 11 |  2k | 60% | 23 |  2w | 40% |
| 12 |  2l | 54% | | | |

[a] Reaction conditions: aryl bromides (0.2 mmol), NaI (0.2 equiv), $Et_3N$ (1.5 equiv), $CH_3CN$ (4.0 mL), UV light (15 W), $O_2$ atmosphere, 32 °C, 24 h. [b] Isolated yields.

### Table 3. Scope of Aryl Chlorides[a]



| entry | product | yield (%)[b] | entry | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  2a | 60% | 5 |  2m | 70% |
| 2 |  2c | 52% | 6 |  2s | 35% |
| 3 |  2e | 57% | 7 |  2u | 37% |
| 4 |  2g | 26% | | | |

[a] Reaction conditions: aryl chlorides (0.2 mmol), NaI (0.2 equiv), $Et_3N$ (1.5 equiv), $CH_3CN$ (4.0 mL), UV light (15 W), $O_2$ atmosphere, 32 °C, 24 h. [b] Isolated yields.

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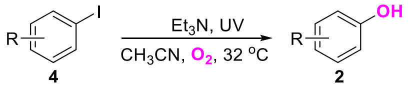
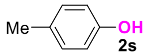
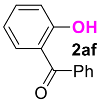
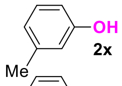
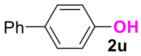
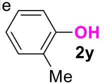
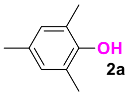
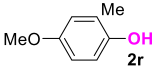
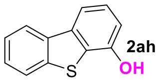
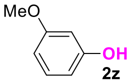
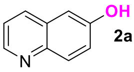
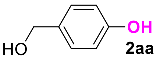
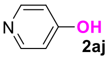
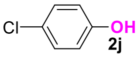
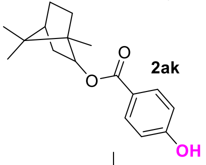
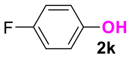
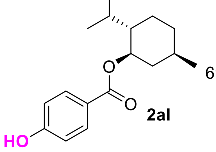
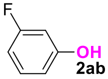
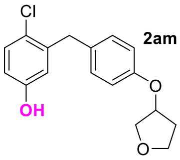
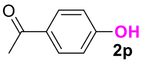
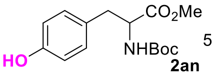
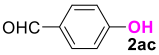
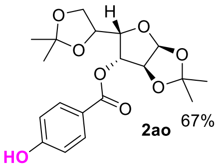
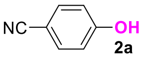
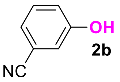
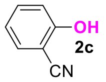
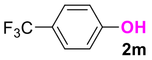
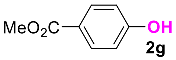
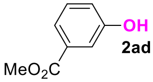
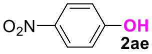
bearing cyano, trifluoromethyl, ester, methyl, and phenyl groups, despite them being recognized as challenging substrates for other hydroxylation, providing the desired products with 26−70% yields (entries 1−7). The low-to-moderate yields for aryl chlorides were attributed to low conversions and side reactions such as dehalogenation.

In addition to aryl bromides and chlorides, we next accessed the scope of aryl iodines (Table 4). A preliminary investigation showed that the addition of NaI had no influence on the reaction efficiency for aryl iodines, and thus, the hydroxylation of aryl iodines was performed in the absence of NaI. A wide range of electronically distinct aryl iodides could be transformed into the corresponding phenols with various functional groups. The substrates bearing electron-neutral substituents such as methyl (entries 1−3) and phenyl groups (entry 20), electron-donating substituents such as methoxy (entries 4 and 5) and methylol groups (entry 6), as well as electron-withdrawing substituents such as acyl (entries 10, 11, and 19), cyano (entries 12−14), trifluoromethyl (entry 15), ester (entries 16 and 17), and nitro (entry 18) groups proved to be amenable to the standard reaction conditions. In particular, sensitive moieties including alcohol (entry 6) and aldehyde (entry 11) could be well tolerated and led to good yields. The reaction was slightly sensitive to sterical hindrance as trimethyl-substituted iodobenzene offered lower yield in comparison to unsubstituted iodobenzene (entry 1 vs entry 21). The substrates bearing a heterocyclic ring were also effective under the standard conditions (entries 22−24). Notably, upon exposing aryl iodines to a high-pressure mercury lamp irradiation instead of UV irradiation, we observed increased yields (entries 1−5, 12, 17, and 22). To further study the group compatibility and practicability of the transformation, several complex molecules with sensitive and bioactive groups were subjected to the standard conditions. Gratifyingly, these molecules reacted smoothly, affording the desired products in 51−73% yields (entries 25−29). Nevertheless, in the case of secondary and tertiary alkyl halides, poor yields were observed (Scheme S6a,b, see the Supporting Information). Interestingly, the reactions of benzyl halides gave a mixture of benzyl alcohol and benzaldehyde (Scheme S6c).

### Table 4. Scope of Aryl Ioides[a]

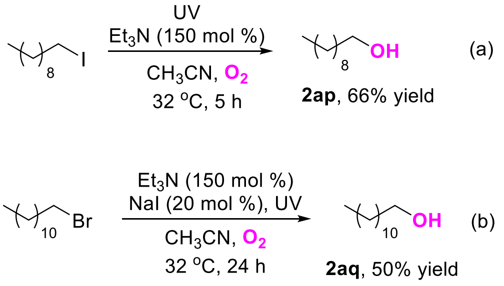


| entry | product | yield (%)$^b$ | entry | product | yield (%)$^b$ |
|---|---|---|---|---|---|
| 1 |  **2s** | 53%, 80%$^c$ | 19 |  **2af** | 83% |
| 2 |  **2x** | 57%, 63%$^c$ | 20 |  **2u** | 68% |
| 3 |  **2y** | 54%, 63%$^c$ | 21 |  **2ag** | 40% |
| 4 |  **2r** | 42%, 72%$^c$ | 22 |  **2ah** | 37%, 46%$^c$ |
| 5 |  **2z** | 55%, 74%$^c$ | 23 |  **2ai** | 48% |
| 6 |  **2aa** | 53% | 24 |  **2aj** | 39% |
| 7 |  **2j** | 57% | 25 |  **2ak** | 73% |
| 8 |  **2k** | 80% | 26 |  **2al** | 69% |
| 9 |  **2ab** | 78% | 27 |  **2am** | 51% |
| 10 |  **2p** | 78% | 28 |  **2an** | 58% |
| 11 |  **2ac** | 77% | 29 |  **2ao** | 67% |
| 12 |  **2a** | 71%, 83%$^c$ | | | |
| 13 |  **2b** | 73% | | | |
| 14 |  **2c** | 67% | | | |
| 15 |  **2m** | 81% | | | |
| 16 |  **2g** | 81% | | | |
| 17 |  **2ad** | 55%, 74%$^c$ | | | |
| 18 |  **2ae** | 56% | | | |

[a] Reaction conditions: aryl bromides (0.2 mmol), $Et_3N$ (1.5 equiv), $CH_3CN$ (4.0 mL), UV light (15 W), $O_2$ atmosphere, 32 °C, 24 h. [b] Isolated yields. [c] Under high pressure mercury lamp irradiation (500 W).

The hydrolysis of alkyl halides is known as one of important laboratory synthetic methods for preparation of aliphatic alcohols. Traditional methods[12] to aliphatic alcohols from aliphatic halides usually relied on a two-step procedure involving the use of nucleophilic oxygenated reagents such as acetate or formate,[13] superoxide radical ions,[14] and bis(tributyltin)oxide.[15] Most of these approaches suffered from high temperature, the employment of dangerous reagents, and Ag catalysts. Herein, the possibility of extending the protocol to alkyl halides also was explored (Scheme 1). Delightfully, alkyl halides including alkyl iodine and bromide were efficiently functionalized with the photoinduced protocol. For example, 1-iodododecane could be converted into the corresponding aliphatic alcohol (**2ap**) in 66% yield even in the absence of NaI (Scheme 1a). Moreover, the reaction of 1-bromododecane under the standard conditions successfully took place to afford the desired product (**2aq**) in 50% yield (Scheme 1b). Therefore, the protocol provided a mild route to aliphatic alcohol from alkyl halides using molecular oxygen as the oxygen source.

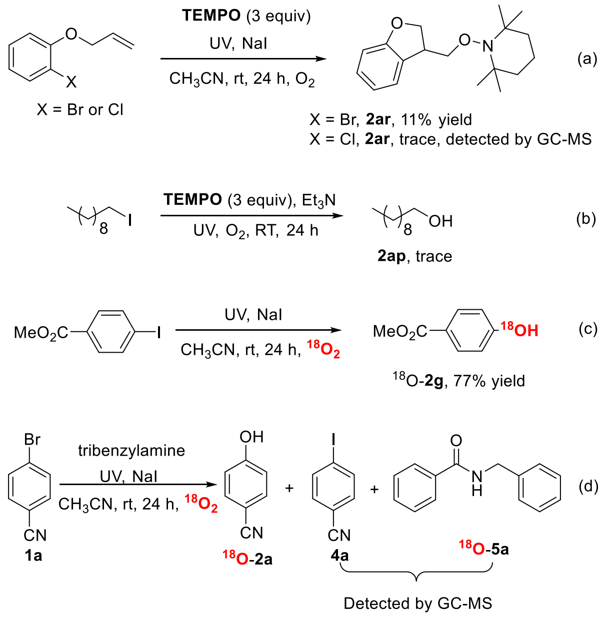
### Scheme 1. Hydroxylation of Alkyl Halides



DOI: 10.1021/acs.orglett.9b03317
Org. Lett. XXXX, XXX, XXX−XXX

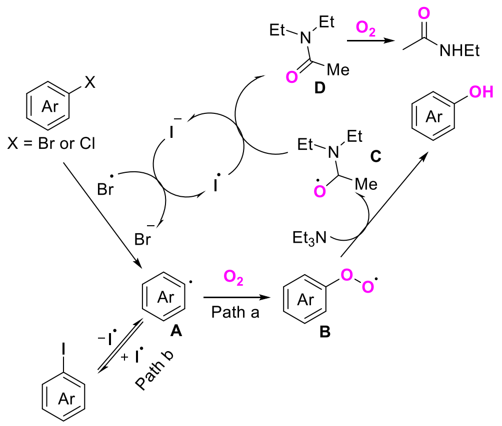
To obtain a better understanding of this photoinduced hydroxylation of aryl halides, several control experiments were conducted (Scheme 2). The presence of TEMPO enabled the reaction of 1-(allyloxy)-2-bromobenzene or 1-(allyloxy)-2-chlorobenzene to provide the product **2ar** instead of the hydroxyated product, suggesting that the reaction process involved an aryl radical intermediate (Scheme 2a). A radical process for the hydroxylation of alkyl halide was also supported by control experiments (Scheme 2b). Upon conducting the hydroxylation of methyl 4-iodobenzoate under $^{18}O_2$ atmosphere (Scheme 2c), we obtained $^{18}$O-labeled product with 77% yield (Figure S1), demonstrating that the molecule oxygen rather than water served as the oxygen source. When triethylamine was replaced with tribenzylamine in the reaction of 4-bromobenzonitrile (Scheme 2d), some products including 4-iodobenzonitrile and $^{18}$O-labeled amide were detected by GC–MS (Figure S2).

**Scheme 2. Some Control Experiments**



On the basis of these results and the previous references,[9] a plausible mechanism for the hydroxylation of aryl bromides and chlorides was proposed (Scheme 3). At the beginning, the C−Br (Cl) bonds of aryl bromides (chlorides) were cleaved homolytically, which reacted with $Et_3N$ to afford intermediate **C** and phenol. In addition, intermediate **C** underwent single-electron-transfer under the standard conditions to produce aryl radicals and bromine (chloride) radicals. The resulting bromine (chloride) radicals were further reduced by iodine anions to form bromine (chloride) anions, while iodine anions were converted into iodine radicals. On the other hand, the in situ generated aryl radicals can be trapped by a molecule of oxygen to generate intermediate **B** with iodine radicals to deliver amide **D**, while iodine radicals are changed back into iodine anions, thus enabling a complete catalytic cycle. Alternatively, the in situ generated aryl radicals reacted with iodine radicals to afford aryl iodides in a reversible way.

**Scheme 3. Plausible Mechanism**



In summary, we have disclosed a photoinduced hydroxylation of organic halides under mild conditions with the use of cheap and green $O_2$ as the oxygen source, providing a mild access to functionalized phenols and aliphatic alcohols. This reaction displays satisfied efficiency and excellent functional group tolerance toward a wide range of aryl and alkyl halides and features no need for a strong base. Central to this protocol is the addition of sodium iodide, which enables the significantly increased activity for the hydroxylation of aryl bromides and chlorides due to its ability to promote homolytic cleavage of the C−Br(Cl) bond.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03317.

> Experimental procedures, full characterization of compounds, MS data of $^{18}$O labeling experiments, computational details, and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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