Photoredox Catalysis

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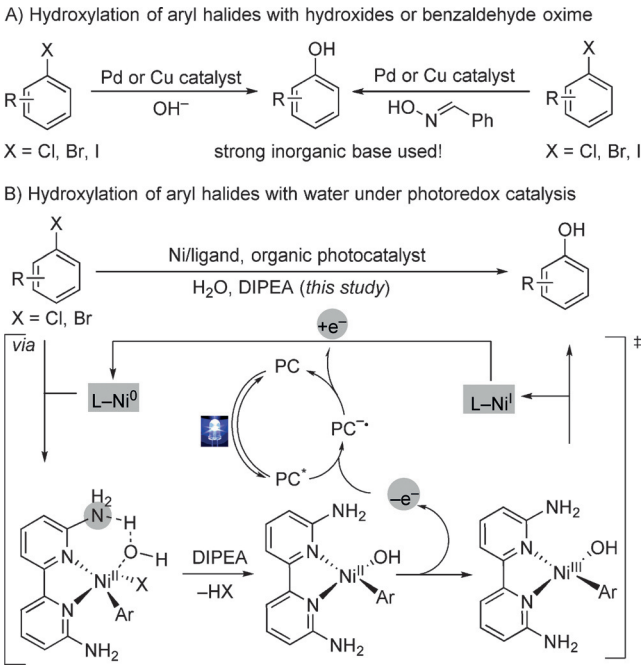
Synthesis of Phenols: Organophotoredox/Nickel Dual Catalytic Hydroxylation of Aryl Halides with Water

*Liu Yang, Zhiyan Huang, Gang Li, Wei Zhang, Rui Cao, Chao Wang, Jianliang Xiao, and Dong Xue**

Abstract: *A highly effective hydroxylation reaction of aryl halides with water under synergistic organophotoredox and nickel catalysis is reported. The OH group of the resulting phenols originates from water, following deprotonation facilitated by an intramolecular base group on the ligand. Significantly, aryl bromides as well as less reactive aryl chlorides served as effective substrates to afford phenols with a wide range of functional groups. Without the need for a strong inorganic base or an expensive noble-metal catalyst, this process can be applied to the efficient preparation of diverse phenols and enables the hydroxylation of multifunctional pharmaceutically relevant aryl halides.*

Phenols and their derivatives are important organic functional groups, prevalent in many pharmaceuticals, agrochemicals, materials, and natural products.[1] Although phenols have been synthesized efficiently by different strategies,[2,3] one of the most attractive methods is the metal-catalyzed hydroxylation of aryl halides owing to the abundance of various haloarenes (Scheme 1 A).[4] The coupling of hydroxide anions from strong inorganic bases with aryl halides under the catalysis of copper,[5] iron,[6] and palladium[7] has been successfully developed and is recognized as one of the most valuable approaches to phenols. However, the use of strong inorganic bases or organic superbases[8] is problematic, especially for substrates bearing base-sensitive functionalities. To overcome this limitation, Fier and Maloney[5l,7h] recently reported the palladium- and copper-catalyzed hydroxylation of aryl halides to access phenols with benzaldehyde oxime as the hydroxide surrogate and Cs_2CO_3 as the base (Scheme 1 A). Despite these achievements, the coupling of aryl halides with water as the nucleophile under the catalysis of cheap metals is believed to be an ideal strategy for the synthesis of phenols.

With this background in mind, we envisaged a strategy for the synthesis of phenols that would involve the synergistic combination of organophotoredox[9] and nickel catalysis[10] for the hydroxylation of aryl halides with water (Scheme 1 B). Although water is an ideal hydroxy source for hydroxylation, a highly challenging issue is that water is a weak nucleophilic reagent. This problem could be tackled by including an intramolecular hydrogen-bond acceptor or basic group in the ligand, which would facilitate the generation of the hydroxide nucleophile in situ from the coordinated water through hydrogen bonding and deprotonation (Scheme 1 B).[11] Nickel-catalyzed photochemical C–O bond formation from aryl alcohols has been advanced significantly.[12] However, the hydroxylation of aryl halides with water by the use of readily available Ni catalysts with or without synergistic photocatalysis has only been sparsely studied.[12] Notably, cheap but less reactive aryl chlorides have not been investigated thus far. Furthermore, the typical photocatalysts applied in photoredox–nickel-catalyzed reactions are expensive ruthenium and iridium complexes.[13] Cheap organic dyes have seldom been used as photocatalysts in this type of reaction.[14] Herein, we report an effective organophotoredox–nickel dual-catalytic hydroxylation of aryl halides with water under visible light with BODIPY[15–17] as the organic photocatalyst and *N*,*N*-diisopropylethylamine (DIPEA) as a mild organic base.



Scheme 1. Synthesis of phenols from aryl halides under various conditions and a working hypothesis for the reaction in this study. PC = photocatalyst.

[*] L. Yang, Prof. Dr. Z. Huang, Dr. G. Li, Prof. Dr. W. Zhang, Prof. Dr. R. Cao, Prof. Dr. C. Wang, Prof. Dr. J. Xiao, Prof. Dr. D. Xue
Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education and School of Chemistry and Chemical Engineering
Shaanxi Normal University
Xi'an, 710062 (China)
E-mail: xuedong_welcome@snnu.edu.cn
Prof. Dr. J. Xiao
Department of Chemistry, University of Liverpool
Liverpool, L69 7ZD (UK)

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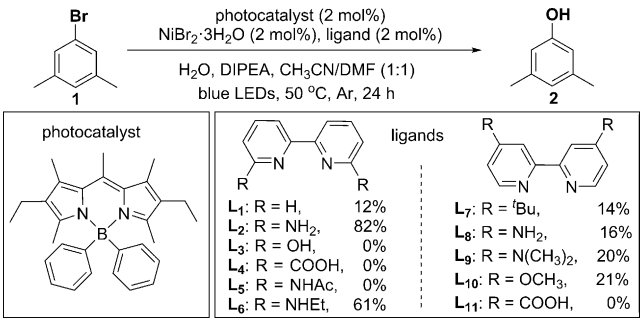
Following on from our previous study,[16] we explored the hydroxylation reaction of 3,5-dimethylbromobenzene (**1**) with water and identified the readily accessible organic dye BODIPY as the most efficient photocatalyst (Table 1).[18,19] In

Table 1: Optimization of the reaction conditions.[a]



Entry	Variation from the standard conditions[b]	Yield [%][c]
1	standard conditions	82
2	$NiBr_2$ instead of $NiBr_2{\cdot}3\,H_2O$	26
3	$NiCl_2$ instead of $NiBr_2{\cdot}3\,H_2O$	75
4	$NiBr_2$·glyme instead of $NiBr_2{\cdot}3\,H_2O$	72
5	$Ni(cod)_2$ instead of $NiBr_2{\cdot}3\,H_2O$	81
6	$Ni(cod)_2$, no photocatalyst	0
7	no photocatalyst	0
8	no light	0
9	no $NiBr_2{\cdot}3\,H_2O$	0
10	no ligand	0
11	no DIPEA	0
12	no H_2O	0
13	$N(Et)_3$ instead of DIPEA	25
14	air instead of Ar	trace

[a] Reaction conditions A: **1** (1.0 equiv, 0.5 mmol), H_2O (40.0 equiv), $NiBr_2{\cdot}3\,H_2O$ (2.0 mol%), ligand (2.0 mol%), BODIPY (2.0 mol%), DIPEA (1.5 equiv, 0.75 mmol), CH_3CN/DMF (1:1; 3 mL). [b] Standard conditions B: 6,6′-diamino-2,2′-bipyridyl (2.0 mol%) was used, other conditions were the same as reaction conditions A. [c] Yield of the isolated product. BODIPY = boron-dipyrromethene, cod = 1,5-cyclooctadiene, DMF = *N*,*N*-dimethylformamide.

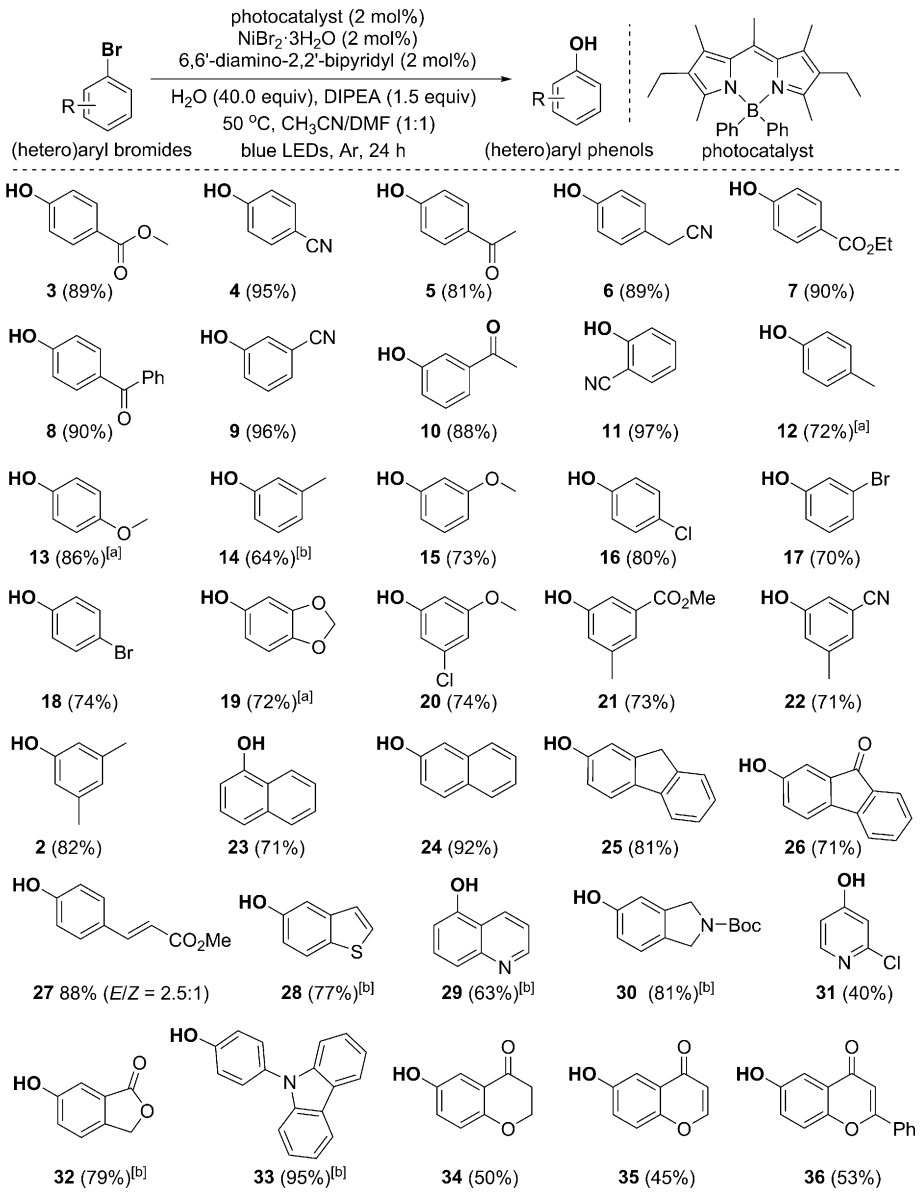
particular, of all ligands examined, 6,6′-diamino-2,2′-bipyridyl (**L_2**) gave the best result. Notably, the electronically similar 4,4′-diamino analogue **L_8** showed much lower activity, thus indicating a neighboring effect of the amino groups in **L_2**. Ligands with acidic groups, such as OH (ligand **L_3**), COOH (ligand **L_4**), and NHAc (ligand **L_5**), at the 6,6′-positions failed to afford the desired products, which led us to believe that the 6,6′-amino group plays an important role in the activation of water, probably acting as hydrogen-bond acceptor and base to facilitate proton transfer (Scheme 1 B).[11] Interestingly, *N*-ethyl-substituted **L_6**, which was supposed to be a stronger hydrogen-bond acceptor, gave a low yield (61 vs. 82 %). This unexpected result may stem from crowding of the nickel center by the bulky bipyridine **L_6**. The sensitivity to steric hindrance was further demonstrated by introducing a slightly bulkier NMe_2 group. When the 6,6′-di-NMe_2 analogue, which has higher electron density but is bulkier than **L_6**, was used as a ligand, no conversion of **1** into **2** was observed (see Table S4 in the Supporting Information).

Further examination of Ni salts, photocatalysts, bases, solvents, and light sources demonstrated the combination of $NiBr_2{\cdot}3\,H_2O$, **L_2**, BODIPY, and DIPEA in DMF/CH_3CN (1:1) to be optimal with respect to the product yield.[20] Thus, the desired product 3,5-dimethylphenol (**2**) was isolated in 82 % yield when the reaction was carried out at 50 °C with blue LEDs for 24 h. Other nickel catalysts could also catalyze the reaction, but with low efficiency (Table 1, entries 2–4). Control experiments revealed that the reaction does not proceed in the absence of nickel, BODIPY, light, or a ligand (Table 1, entries 7–12). The critical role of DIPEA and water was demonstrated by the absence of the desired product when either of these two components was omitted (entries 11 and 12). To the best of our knowledge, this reaction is the first hydroxylation of aryl halides with a tertiary amine as the base. The presence of oxygen dramatically decreased the reaction efficiency (entry 14).

We investigated a wide range of aryl bromides under the optimized reaction conditions to explore the efficiency and scope of this nickel-catalyzed hydroxylation reaction. Bromoarenes with a variety of functional groups reacted efficiently in this synergistic protocol to deliver the desired phenols in good to excellent yields (Scheme 2, products **3**–**36**). In the case of electron-deficient substrates, *para*-, *meta*-, and *ortho*-substituted aryl bromides containing ketone, cyano, and ester groups were all suitable, providing phenols **3**–**11** in 81–97 % yield. The reaction appears to be difficult for electron-neutral and electron-rich aryl bromides, with a higher temperature or longer reaction time required for the desired hydroxylation product to be obtained in good yield (products **12**–**15**). Notably, for aryl bromides bearing a chloro or an additional bromo substituent, the corresponding monosubstituted hydroxylated products **16**–**18** were the only observed products, thus demonstrating that a high degree of chemoselectivity is possible in this hydroxylation reaction. It is likely that the installation of the electron-rich hydroxy group makes oxidative addition of the second C–X bond (X = Br, Cl) difficult (Scheme 1 B). Disubstituted aryl bromides bearing either electron-donating or electron-withdrawing groups were all applicable, delivering the desired products **2** and **19**–**22**. Notably, aryl bromides with a fused ring and methyl 4-bromocinnamate were hydroxylated in excellent yields to give products **23**–**27**.

Hydroxylated heteroarenes are important bioactive intermediates in medicinal chemistry. We next explored the scope of the reaction of heteroaryl bromides and substrates with additional heteroatom-containing rings (Scheme 2). To our delight, a wide range of (hetero)aryl bromides were compatible, affording the desired hydroxylated products under the same reaction conditions. Hydroxylated heteroarenes containing benzothiophene (product **28**), quinoline (product **29**), isoindole (product **30**), pyridine (product **31**), phthalide (product **32**), carbazole (product **33**), chroman-4-one (product **34**), and chromen-4-one moieties (product **35**) were all obtained in good to excellent yields. Finally, we demonstrated that the standard reaction conditions were suitable for the synthesis of the natural product 6-hydroxyflavone **36**.

To find more applications of our methodology, we attempted to expand the reaction scope to cheaper but



Scheme 2. Hydroxylation of (hetero)aryl bromides. For the standard reaction conditions, see the Supporting Information. Yields are for the isolated product. [a] The reaction was carried out for 120 °C. [b] Reaction time: 36 h.

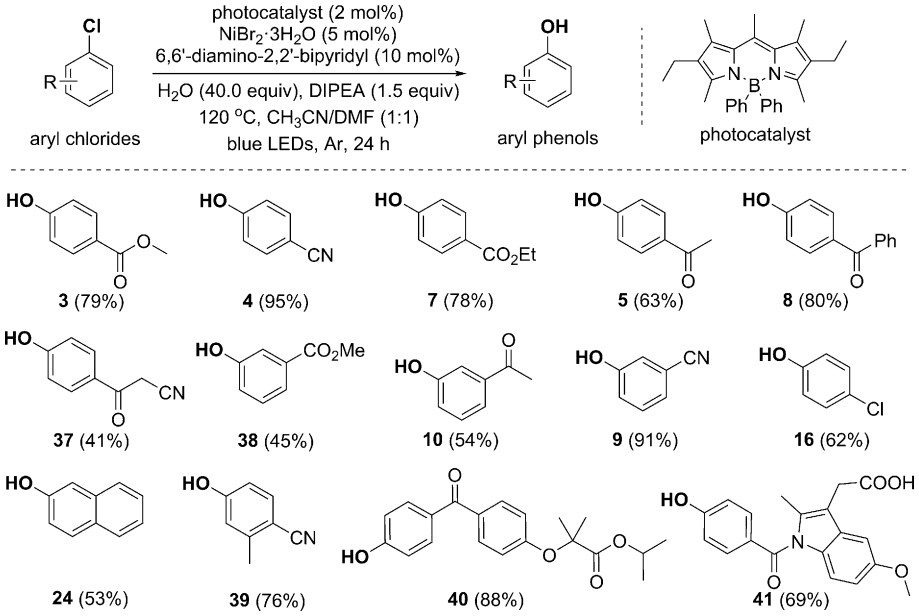
more challenging aryl chlorides. Considering the stronger C–Cl bond, it was not unexpected to find that reaction temperature played a vital role in the reaction. Thus, phenol products were obtained in low yields under the conditions used for aryl bromides; however, by increasing the temperature to 120 °C, satisfactory yields could be attained (Scheme 3). The reaction provided the phenol products in good yields with aryl chlorides containing ester (products **3**, **7**, and **38**), ketone (products **5**, **8**, and **10**), or nitrile units (products **4**, **9**, and **37**), as well as with fused-aromatic (product **24**) and disubstituted aryl chlorides (product **39**). Similar to the reaction of bromides, when 1,4-dichlorobenzene was used as the substrate, the corresponding monosubstituted hydroxylated product **16** was obtained. Notably, more complex, biologically relevant substrates were also tolerated, as demonstrated by the hydroxylation of fenofibrate to give **40**[21] and indomethacin to give **41**[22] in excellent yields.

To further demonstrate the utility of this new hydroxylation protocol, more challenging polyfunctional, druglike aryl halides were studied (Scheme 4). A key intermediate in the synthesis of elbasvir,[23] which has been approved for the treatment of hepatitis C virus (HCV) infection, the monohydroxylated product **43** was formed in 71 % yield with little loss of enantiomeric purity. In the case of the challenging N-heterocyclic substrate **44**,[24] the desired phenol **45** was also formed in good yield. These examples showcase the significant potential of this method in the synthesis of complex molecules.

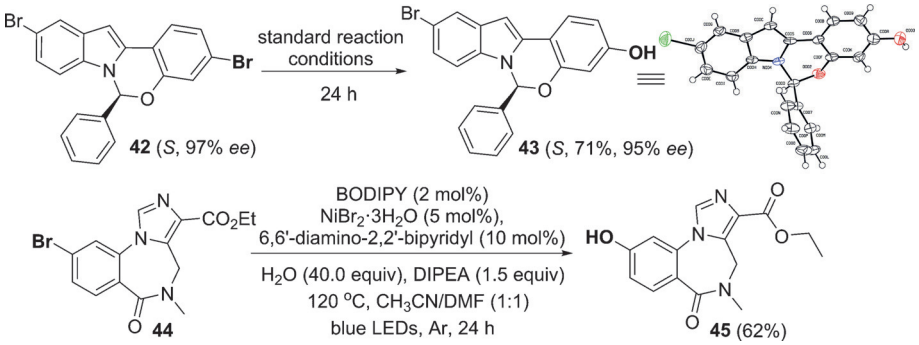
To show the scalability of this new hydroxylation protocol, we performed gram-scale reactions (Scheme 5). Gratifyingly, starting with 4-bromobenzonitrile (1.81 g), the desired product **5** was isolated in 92 % yield. Furthermore, the hydroxylation of 2-bromofluorene (2.44 g) led to the desired product **26**, which can be used as a versatile synthetic intermediate,[25] in 78 % yield. The commercial availability of **26** is limited,[26] probably because of the low reactivity of 2-bromofluorene.

To verify that the OH moiety of the phenolic products originates from water, we carried out reactions in which H_2O was replaced with $H_2{}^{18}O$. As shown in Scheme 6, the ^{18}O labeled phenols **46**, **47**, and **48** were obtained in good yields. The protocol thus also provides a methodology for the synthesis of ^{18}O-labeled druglike complex molecules.

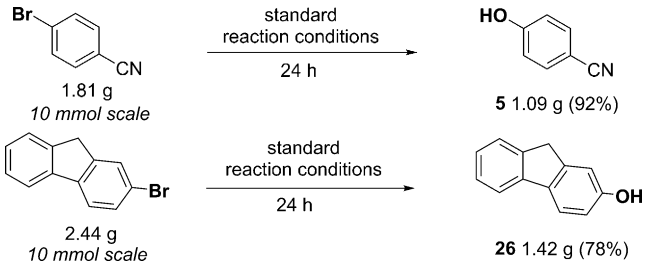
The mechanism of this dual catalytic system remains to be delineated. Our working hypothesis (Scheme 1 B) offers a brief explanation, which finds support in the work reported by MacMillan and co-workers.[12,27] It is also backed by the high reduction and oxidation potentials of the photoexcited state of the BODIPY catalyst ($E^{*ox} = -1.45$ V vs. SCE, $E^{*red} = +0.74$ V vs. SCE), which make the photocatalyst both a strong single-electron oxidant and a strong single-electron reductant upon irradiation with visible light.[18,20] Furthermore, the replacement of $NiBr_2{\cdot}3H_2O$ with $Ni(COD)_2$ led to a similar result (Table 1, entry 5), thus indicating the involvement of a Ni^0 species in the catalytic cycle. A catalytically active Ni^0 species could be formed in situ through the



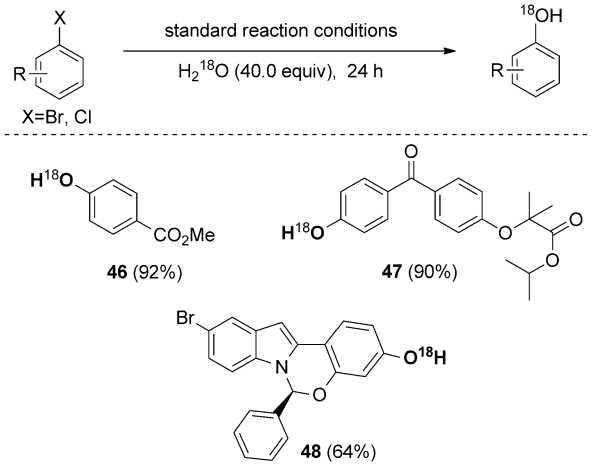
Scheme 3. Hydroxylation of aryl chlorides. For the standard reaction conditions, see the Supporting Information. Yields are for the isolated product.



Scheme 4. Hydroxylation of polyfunctional, druglike aryl halides.



Scheme 5. Scaling up of the hydroxylation reaction.



Scheme 6. Synthesis of ^{18}O-labeled phenols.

reduction of (dtbbpy)Ni^{II}Br$_2$ by the organic photocatalyst ($E_{1/2}^{red}$ [B/B$^-$] = −1.45 V vs. SCE, $E_{1/2}^{red}$ [Ni^{II}/Ni^0] = −1.2 V vs. SCE).[28] Indeed, when the BODIPY catalyst was omitted, no desired product was obtained (Table 1, entry 6). Additional experiments revealed that only DIPEA could quench the excited state of the BODIPY catalyst; the nickel catalyst and **1** showed no effect (see Figures S7–S9). These observations shed new light on the mechanistic hypothesis (Scheme 1B): The excited photocatalyst PC* oxidizes DIPEA to form PC$^-$ and DIPEA$^{\bullet+}$, and the latter oxidizes Ni^{II} to Ni^{III}, while the former reduces the Ni^I to Ni^0 following reductive elimination to form the phenol product at the Ni^{III} center. However, direct oxidation of Ni^{II} to Ni^{III} by the excited photocatalyst is also possible.[29] More detailed studies are ongoing in our laboratory, aiming to elucidate the role of BODIPY, DIPEA, and the nickel catalyst.

In summary, we have developed a nickel-catalyzed hydroxylation of aryl halides with water under visible light with a BODIPY photocatalyst and DIPEA as the base. This methodology enables the hydroxylation of a wide range of aryl bromides, and even less-active aryl chlorides, with various functionalities. Together with the use of an inexpensive metal catalyst, an organic photosensitizer, and an organic base, this feature makes the protocol practically valuable for the synthesis of phenols.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aryl halides · hydroxylation · nickel catalysis · phenols · photoredox catalysis

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