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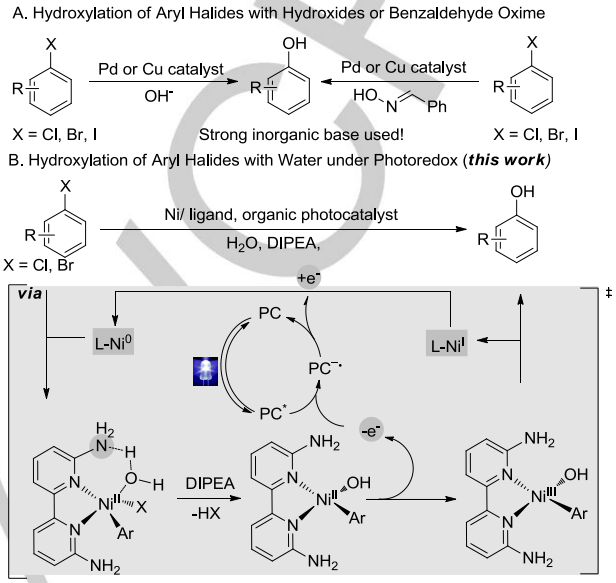
Synthesis of Phenols: Organophotoredox/Ni Dual Catalytic Hydroxylation of Aryl Halides with Water

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 the synergistic merger of organophotoredox and nickel-catalysis is reported. The OH group of 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 can serve as effective substrates, affording phenols with a wide range of functional groups. Using no strong inorganic bases and no expensive noble metal catalysts, this process can be applied to the efficient preparation of diverse phenols and enables the hydroxylation of several multifunctional pharmaceutical aryl halides.

Phenols and their derivatives are important organic functional groups, prevalent in many pharmaceuticals, agrochemicals, materials and natural products.[1] Although the efficient synthesis of phenols has been realized from different strategies,[2,3] one of the most attractive methods is the metal-catalyzed hydroxylation of aryl halides due to the abundance of various haloarenes (Scheme 1A).[4] The coupling of hydroxide anions from strong inorganic bases with aryl halides catalyzed by copper,[5] iron[6] and palladium[7] has been successfully developed and 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[5p,7j] recently reported the Pd- and Cu-catalyzed hydroxylation of aryl halides to access phenols with benzaldehyde oxime as the hydroxide surrogate and Cs_2CO_3 as the base (Scheme 1A). Despite these achievements, the coupling of aryl halides with *water* as nucleophile catalyzed by cheap metals is believed to be an ideal strategy for the synthesis of phenols.

With the background above in mind, we envisaged a strategy for the synthesis of phenols that would involve the synergistic merger of organophotoredox (PC)[9] and nickel catalysis[10] for the hydroxylation of aryl halides with water, as illustrated in Scheme 1B. Although water is an ideal hydroxyl source for hydroxylation, a highly challenging issue is that water is a weak nucleophilic reagent. This problem could be tackled by introducing 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 via hydrogen bonding and deprotonation (Scheme 1 B).[11] The Ni-catalyzed photochemical C-O bond formation from aryl



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

alcohols has witnessed significant advance.[12] However, the hydroxylation of aryl halides with water using easily 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. In addition, the typical photocatalysts applied in the photoredox-nickel catalyzed reactions are expensive ruthenium and iridium complexes.[13] Cheap organic dyes have seldom been used as photocatalysts in this type of reactions.[14] Herein, we report an effective organophotoredox-Ni dual catalytic hydroxylation of aryl halides with water under visible light using BODIPY[15-17] as the organic photocatalyst and *N,N*-diisopropylethylamine (DIPEA) as a mild organic base.

Following on from our previous study[16], we explored the hydroxylation reaction of 3,5-dimethylbromobenzene **1** with water, identifying the readily accessible organic dye BODIPY as the most efficient photocatalyst (Table 1).[18,19] The effect of ligands for nickel and other conditions on the reaction under the standard conditions is shown in Table 1. In particular, amongst all the ligands examined, 6,6'-diamino-2,2'-bipyridyl (**L_2**) gave the best result. Of particular note is that the electronically similar 4,4'-diamino analogue **L_8** afforded a much lower activity, indicating a neighboring effect from the amino group in **L_2**. Comparing the effect of ligands with NH_2 (**L_2**), acidic analogues such as OH (**L_3**), COOH (**L_4**) and NHAc (**L_5**) groups failed to afford the desired products, led us to believe that the 6,6'-amino group plays an important role in the activation of water, likely acting as hydrogen bonding acceptor and base to facilitate proton transfer (Scheme 1 B).[11] Interestingly, the *N*-ethyl substituted **L_6** which was supposed to be a stronger hydrogen

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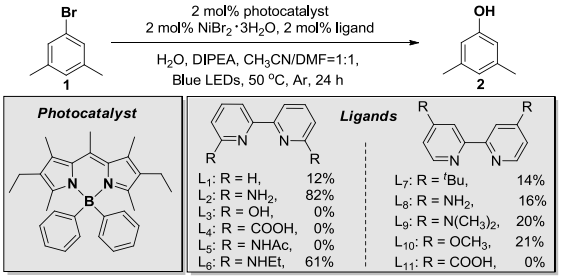
10.1002/anie.201710698

bonding acceptor, surprisingly gave low yield (61% Vs 82%). These unexpected results may stem from the crowded nickel center which was surrounded by a bulky bipyridine **L_6**. The sensitively steric hindrance was further demonstrated by introducing a slightly more bulky NMe_2 group. When 6,6'-di-NMe_2 analogue with higher electron density but bulkier than **L_6** was used as a ligand suggested by a referee, it did not afford any observable conversion of **1** to **2** (See the SI, Table S4). Further examination of Ni salts, photocatalysts, bases, solvents

Table 1. Optimization of reaction conditions for identifying lead catalyst [a]

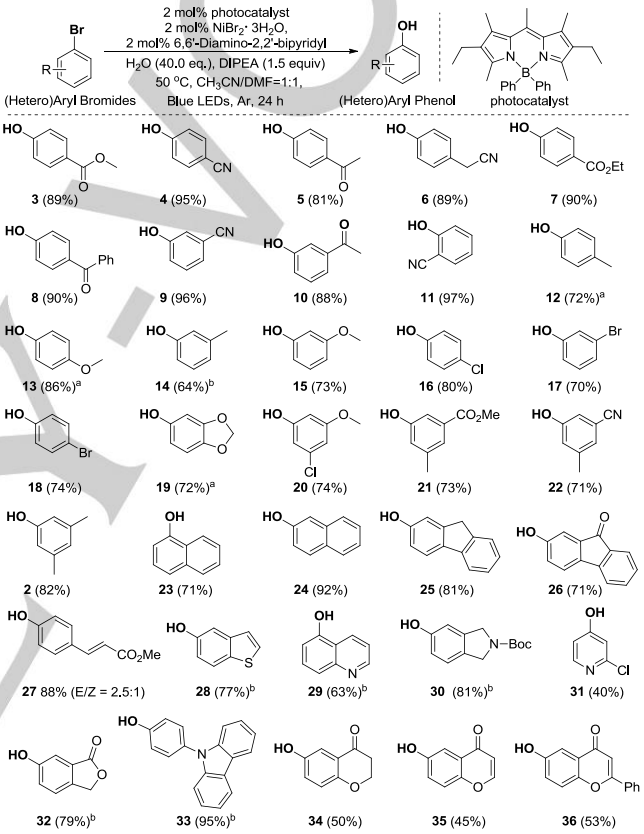


entry	variation from standard conditions[i,j]	yield (%)
1	standard conditions	82
2	$NiBr_2$ instead of $NiBr_2{\cdot}3H_2O$	26
3	$NiCl_2$ instead of $NiBr_2{\cdot}3H_2O$	75
4	$NiBr_2{\cdot}$glyme instead of $NiBr_2{\cdot}3H_2O$	72
5	$Ni(cod)_2$ instead of $NiBr_2{\cdot}3H_2O$	81
6	$Ni(cod)_2$, no photocatalyst	0
7	no photocatalyst	0
8	no light	0
9	no $NiBr_2{\cdot}3H_2O$	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 condition A: 1 (1.0 eq., 0.5 mmol), H_2O (40.0 eq.), $NiBr_2{\cdot}3H_2O$ (2.0 mol%), ligand (2.0 mol%), BODIPY (2.0 mol%), DIPEA (1.5 eq., 0.75 mmol), CH_3CN/DMF = 1 : 1 (3 mL), isolated yield. [b] Standard conditions B: 6,6'-Diamino-2,2'-bipyridyl (2.0 mol%) was used, other conditions were same as reaction condition A.

and light sources demonstrated the combination of $NiBr_2{\cdot}3H_2O$, L_2, BODIPY and DIPEA in DMF/CH_3CN (1:1) to be the best with respect to the product yield.[20] Thus, the desired product 3,5-dimethylphenol **2** was obtained with an isolated yield of 82% at 50 °C with blue LEDs in 24 h. Other nickel catalysts could also catalyze the reaction, but with low efficiency (Table1, entries 2-4). Control experiments revealed that the reaction does not proceed in the absence of nickel, BODIPY, light or ligand (Table 1, entries 7-12). The critical role of DIPEA and water was demonstrated by the absence of any desired product when either of these two components was omitted (entries 11 and 12). To the best of our knowledge, this is the first hydroxylation reaction of aryl halides with tertiary amines as base. It is noted that the presence of oxygen dramatically decreased the reaction efficiency (entry 14).

With the optimized conditions in hand, a wide range of aryl bromides were investigated to explore the reaction efficiency and scope of this nickel-catalyzed hydroxylation reaction. As shown in Scheme 2, bromoarenes with a variety of functional groups reacted efficiently in this synergistic protocol, delivering the desired phenols with good to excellent yields (**3**-**36**). For electron-deficient substrates, all the para-, meta-, and ortho-substituted aryl bromides containing ketones, cyano and esters groups worked well, providing phenols (**3**-**11**) in 81%-97%. For electron-neutral and electron-rich aryl bromides, the reaction appears to be difficult, with the desired hydroxylation product obtained with good yields at a higher temperature or longer reaction time (**12**-**15**). Notably, for aryl bromides bearing a chloro or an additional bromo substituent, the corresponding



Scheme 2. The hydroxylation of (hetero)aryl bromides. For standard reaction condition, see SI. [a] 120 °C, [b] 36 h. Isolated yields.

mono-substituted hydroxylated products were the only observed products (**16**-**18**), demonstrating that a high degree of chemoselectivity can be achieved in this hydroxylation reaction. This is likely a result of the installation of the electron-rich hydroxyl group, which makes the second C-X (X = Br, Cl) bond difficult to undergo oxidative addition (Scheme 1B). The di-substituted aryl bromides bearing either electron-donating or withdrawing groups were all applicable, delivering the desired products (**2, 19**-**22**). Notably, in the case of aryl bromides with a fused ring and bromo cinnamate as the substrates, excellent yields of hydroxylated products were achieved (**23**-**26**, **27**). Hydroxylated heteroarenes are important bioactive intermediates in medicinal chemistry. We next explored the scope of (hetero)aryl bromides. To our delight, a wide range of (hetero)aryl bromides are compatible, affording the desired

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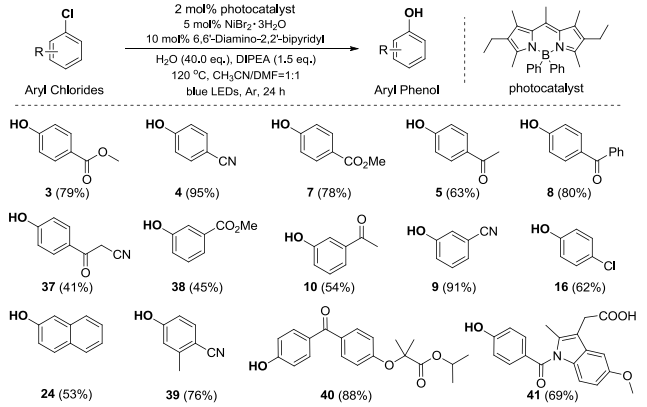
hydroxylated products under the same reaction conditions. Hydroxylated heteroarenes containing benzothiophene (**28**), quinoline (**29**), isoindole (**30**), pyridine (**31**), phthalide (**32**), carbazole (**33**), chroman-4-one (**34**) and chromen-4-one (**35**) were all obtained with good to excellentyields. Finally, we demonstrated that the standard reaction condition is suitable for the synthesis of the natural product flavonoid (**36**).

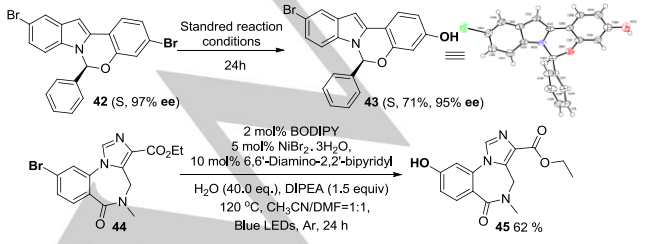
To find more applications of our methodology, we attempted to expand the reaction scope to cheaper but more challenging



Scheme 3. The hydroxylation with aryl chlorides. For standard reaction condition, see SI. Isolated yields.

aryl chlorides. Considering the stronger C-Cl bond, it was not unexpected to find that reaction temperature plays a vital role in the reaction. Thus, phenol products were obtained with low yields under conditions used for aryl bromides; however, by increasing the temperature to 120 °C, satisfactory yields could be achieved. As shown in Scheme 3, the reaction provides the phenol products in high yields with aryl chlorides containing ester (**3**, **7** and **38**), ketone (**5**, **8** and **10**) or nitrile units (**4**, **9** and **37**), as well as with fused-aromatic (**24**) and di-substituted aryl chlorides (**39**). Similar to the bromides, when 1,4-dichlorobenzene was used as the substrate, the corresponding mono-substituted hydroxylated product was obtained (**16**). Of particular note is that more complex, biologically relevant substrates are also tolerated in this transformation, as demonstrated by the hydroxylation of Fenofibrate (**40**)[21] and Indomethacin (**41**)[22] with excellent yields.

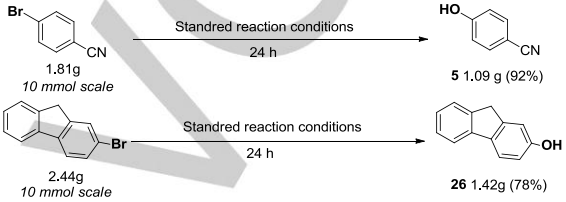
To further demonstrate the utility of this new hydroxylation protocol, more challenging polyfunctional, drug-like aryl halides were studied (Scheme 4). A key intermediate of Elbasvir,[23] which has been approved for the treatment of Hepatitis C virus (HCV) infection, the mono-substituted hydroxylated product



Scheme 4. Hydroxylation of polyfunctional, drug-like aryl halides.

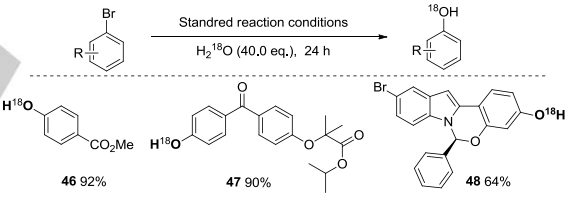
(**43**) was achieved in 71% yield with little loss of enantioselectivity. In the case of the challenging *N*-heterocycle substrate **44**,[24] the desired phenol **45** was also formed in good yield. These examples showcase the significant potential of this method in the synthesis of complex molecules.

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



Scheme 5. Scaling up the hydroxylation reaction.

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 with good yields. The protocol thus also provides a methodology for the synthesis of ^{18}O labeled drug-like complex molecules.



Scheme 6. Synthesis of ^{18}O labelled phenols.

The mechanism of this dual catalytic system remains to be delineated. Our working hypothesis (Scheme 1B) offers a brief explanation, which finds support in the work reported by MacMallian and co-wokers.[12,27] It is also backed by the high reduction and oxidation potentials of the photo-excited state of BODIPY (E^{*ox} = −1.45 V vs SCE, E^{*red} = +0.74 V vs SCE), making the photocatalyst both a strong single-electron oxidant and reductant upon irradiation under visible light.[18,20] Furthermore, replacing $NiBr_2.3H_2O$ with $Ni(COD)_2$ led to a similar result (Table 1, entry 5), indicating the involvement of a Ni(0) species in the catalytic cycle. A catalytically active Ni(0) species could be formed in situ via the reduction of (dtbbpy)Ni(II)Br_2 by the organic photocatalyst ($E_{1/2}^{red}$ [B/B^-] = −1.45 V versus SCE, $E_{1/2}^{red}$ [Ni^{II}/Ni^0] = −1.2 V versus SCE).[28] Indeed, when BODIPY was omitted, no desired product was obtained (Table 1, entry 6). Additional experiments revealed that only DIPEA could quench the excited state of BODIPY, with the nickel catalyst or 1 showing no effect (See the SI,

Figure S7-9). These observations shed new light on the hypothesized mechanism (Scheme 1B): the excited photocatalyst PC* oxidizes DIPEA to form the PC^- and $DIPEA^{\cdot+}$, 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 lab, aiming to elucidate the role of BODIPY, DIPEA and nickel catalyst.

In summary, we have developed a nickel-catalyzed hydroxylation of aryl halides with water under visible light with BODIPY as the 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 inexpensive metal catalyst, organic photosensitizer and organic base, this feature makes the protocol practically valuable for the synthesis of phenols.

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

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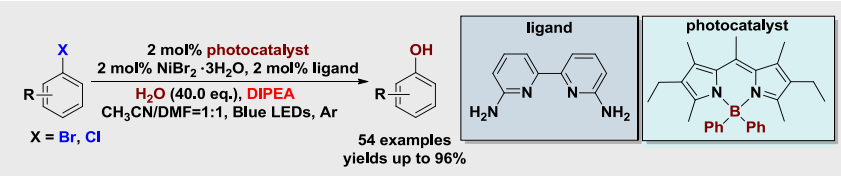

A highly effective hydroxylation reaction of aryl halides with water under the synergistic merger of organophotoredox and nickel catalysis is reported.

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Page No. – Page No.
Synthesis of Phenols: Organophotoredox/Ni Dual Catalytic Hydroxylation of Aryl Halides with Water