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Metallaphotoredox-Mediated C_{sp2}−H Hydroxylation of Arenes under Aerobic Conditions

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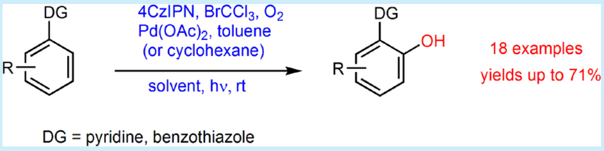
Supporting Information

ABSTRACT: The direct hydroxylation of 2-arylpyridines and 2-arylbenzothiazoles via the merger of organic photoredox and metal catalysis is reported where 4CzIPN is used as the visible-light photocatalyst and $Pd(OAc)_2$ as the metal catalyst. This method has been employed to synthesize organic molecules exhibiting excited-state intramolecular proton transfer properties for generating tunable luminescence responses.



Owing to its mild and renewable nature, light-induced catalysis has gained considerable attention over the past few decades.[1] Metal and organic photocatalysts have been used independently to synthesize medicinal agents and bioactive molecules.[2] Recently, the merger of transition-metal catalysis and photocatalysis, known as metallaphotocatalysis, has emerged as a powerful method for cross-coupling reactions.[3] MacMillan, Sanford, Molander, and various research groups have utilized metallaphotocatalysis for C−N, C−S, C−O, and C−C bond formations.[2,4−10]

To date, significant effort has been dedicated to synthesizing phenol and hydroxylated arenes, as they are the building blocks of many bioactive molecules, pharmaceuticals, polymers, and light-emitting materials.[11−13] The direct C−H oxidation leading to hydroxylation is an attractive method for generating important phenol products.[14,15] In 2009, Yu et al. showed carboxylic group directed ortho-hydroxylation of benzoic acids using a Pd-catalyst with 1 atm of O_2 or air.[16a] The same group has also explored the Cu(II)-catalyzed ortho-C−H hydroxylation of aryl C−H bonds.[16b] Further, carbonyl-directed hydroxylation of arenes has been achieved successfully by the groups of Ackermann[14a] and others.[14b,c] Of late, Jiao et al. have described C_{sp2}−H hydroxylation of 2-phenylpyridines using $PdCl_2$ and NHPI (*N*-hydroxyphthalimide) co-catalysts (Scheme 1, entry a).[17] Guin et al. also showed direct C−H hydroxylation of 2-arylpyridines using *n*-butyraldehyde as a hydroxy radical source.[18] Generally, these hydroxylation methods required the use of stoichiometric oxidants and high temperature as well as limited substrate scope (Scheme 1, entry b).

Thus, the development of a mild and clean method for the C_{sp2}−H hydroxylation of arenes would be attractive (Scheme 1, entry c).

Based on the literature survey, we hypothesized that a metallaphotocatalysis protocol could be used for the hydroxylation reactions. Here, we report for the first time, the direct hydroxylation of 2-arylpyridines and 2-arylbenzothiazoles via the merger of photocatalyst, 4CzIPN [1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene] and metal catalyst, $Pd(OAc)_2$, under visible-light irradiation in the presence of O_2. To check the viability of our proposed metallaphotocatalysis, an initial study was carried out by using 4CzIPN (2 mol %) as the organic photocatalyst in a reaction mixture of 2-phenylpyridine (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $BrCCl_3$ (0.4 mmol), and toluene (1.5 mL) under visible-light irradiation in the presence of O_2. The reaction provided the hydroxylation product **2a** in 25% yield (Table 1, entry 1). This encouraged us to optimize the reaction conditions. Solvent studies revealed that the maximum hydroxylation product was

Scheme 1. Hydroxylation of Arenes under Various Conditions

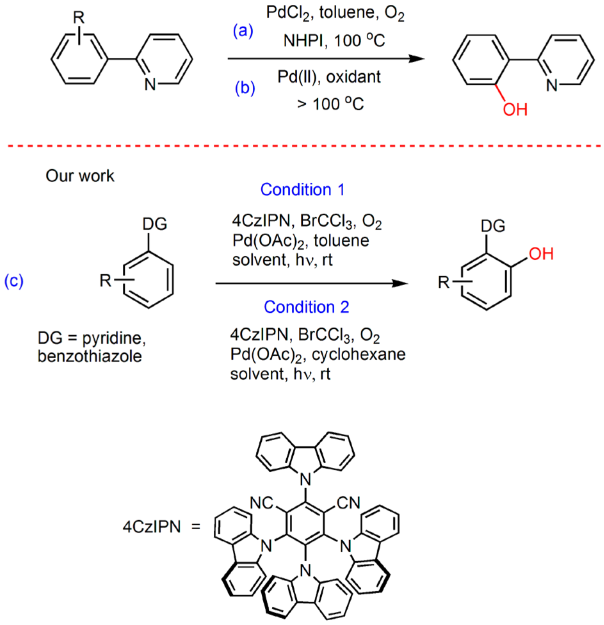


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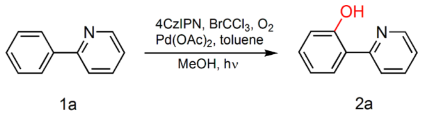
Table 1. Screening of the Reaction Conditions[a]



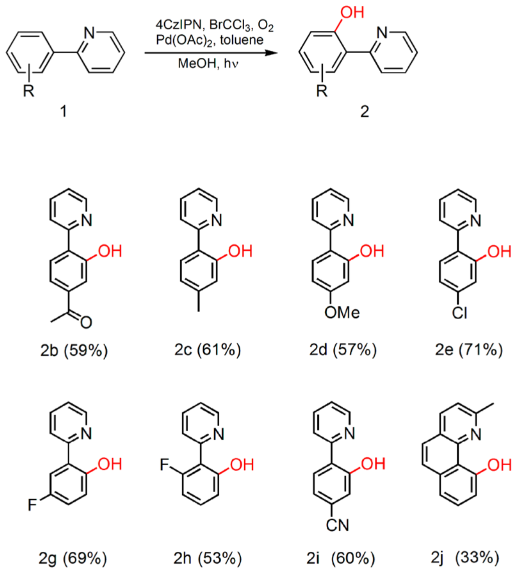
entry	conditions	solvent	yield[b] (%)
1	as shown	DCE	25
2	as shown	CH_3CN	5
3	as shown	DMF	0
4	as shown	DMSO	0
5	as shown	MeOH	67, 49,[c] 21[d]
6	air instead of O_2	MeOH	41
7	EY as photocatalyst	MeOH	45
8	RB as photocatalyst	MeOH	23
9	RhB as photocatalyst	MeOH	33
10	CBr_4 instead of $BrCCl_3$	MeOH	60
11	TBHP instead of $BrCCl_3$	MeOH	37
12	no $BrCCl_3$	MeOH	12
13	BTF instead of toluene	MeOH	0
14	no toluene	MeOH	0
15	no photocatalyst	MeOH	0
16	no $Pd(OAc)_2$	MeOH	0
17	no light	MeOH	0
18	N_2 in place of O_2	MeOH	0
19	as shown	MeOH	41[e]

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), 4CzIPN (2 mol %), $BrCCl_3$ (2 equiv), O_2, toluene (1.5 mL), solvent (1.5 mL), under exposure from a 23 W CFL lamp for 24 h. [b] Isolated products. [c] 5 mol % of $Pd(OAc)_2$. [d] In the absence of solvent. EY = eosin Y, RB = rose bengal, RhB = rhodamine b, TBHP = *tert*-butyl hydroperoxide, BTF = benzotrifluoride. [e] Large-scale reaction: **1a** (1.5 mmol).

obtained in MeOH (Table 1, entry 5), while DMF or DMSO failed to execute the reaction (Table 1, entries 3 and 4). Reducing the mol % of $Pd(OAc)_2$ produced lower yield (Table 1, entry 5). Next, the use of atmospheric air instead of O_2 reduced the yield (Table 1, entry 6). Interestingly, the use of other organic photocatalysts (EY, RB, and RhB) instead of 4CzIPN provided a moderate yield (Table 1, entries 7–9). Further, the use of CBr_4 or TBHP as a hydrogen abstractor instead of $BrCCl_3$ furnished a lower yield (Table 1, entries 10 and 11). However, in the absence of $BrCCl_3$, **2a** was produced in 12% yield (Table 1, entry 12). This phenomenon is due to the hydrogen-abstracting ability of $O_2^{\bullet-}$.[19] It is worth noting that, in the absence of toluene, or the use of BTF instead of toluene, the reaction was completely inhibited (Table 1, entries 13 and 14). The reported method yielded moderately at large scale (Table 1, entry 19). The screening of the reaction conditions disclosed that photocatalyst, $Pd(OAc)_2$, $BrCCl_3$, toluene, O_2, and visible light were all crucial for the accomplishment of the hydroxylation of 2-arylpyridine.

With the optimized conditions in hand, the hydroxylation scope of the substituted 2-phenylpyridines was investigated (Scheme 2). Electron-donating and electron-withdrawing groups attached to the benzene ring provided good yields. Remarkably, the present method has executed the hydroxylation of the substrates containing a halogen group smoothly (**2e–h**). The productivity of this transformation was not impeded by the substituents at the ortho, meta, or para positions (**2f–h**). Moreover, hydroxylation of 2-methylbenzo[*h*]quinoline gave **2j** only in 33% yield.

Scheme 2. Visible-Light-Induced Hydroxylation of 2-Arylpyridines.[a]



[a] Palladium-catalyzed hydroxylation of 2-phenylpyridine with 4CzIPN in the presence of O_2 under visible-light irradiation. Standard reaction conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.1 equiv), 4CzIPN (2 mol %), $BrCCl_3$ (2 equiv), toluene (3 mL), O_2 (1 atm), 24 h. Yields of isolated products given.

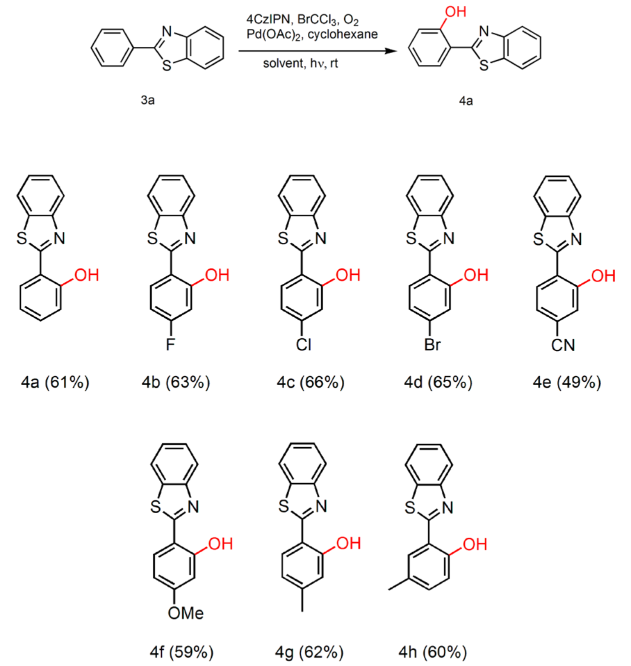
To check the generality of this reaction, we were curious to explore the effect of other directing groups on the hydroxylation of arenes. For this purpose, we chose benzothiazole-directed arenes. The above-mentioned metallaphotocatalysis methods were unable to give any satisfactory results and provide some acylation products.

This prompted us to search for an alternative hydroxyl radical generator. Surprisingly, the use of cyclohexane in place of toluene provided the expected hydroxylation product **4a** (Table S1, Supporting Information (SI)). The solvent studies showed that the maximum yield was obtained in DCE (Table S1, entry 2). No product was formed in the absence of catalyst, oxidant, air, cyclohexane, and light (Table S1, entries 3–7). With the optimization conditions in hand, the substrate scope was explored (Scheme 3). In this case, the electron-donating and electron-withdrawing groups provided good yield. The present method performed equally well with the substrates containing a halogen group (**4b–d**). Satisfactory results have been obtained for substrates containing methyl and methoxy groups (**4g,h**).

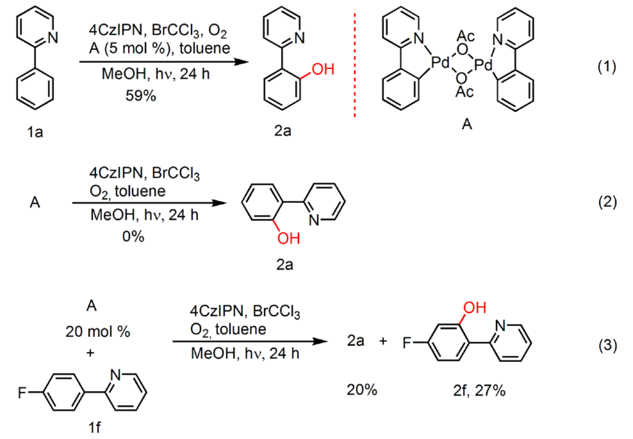
To shed light on the reaction mechanism, control experiments were carried out. The reactions were monitored in the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). The present method was unable to produce **2a** or **4a** in the presence of 2 equiv of TEMPO (Scheme S1, SI). The above experiment implied the involvement of a radical species in the hydroxylation process.

Further mechanistic studies were carried out using Pd^{II} complex (**A**) as the catalyst instead of $Pd(OAc)_2$. The product **2a** was obtained in 59% yield (eq 1). However, the reaction of **A** in the absence of **1a** (or any other substrates) failed to produce **2a** under the standard reaction conditions (eq 2). Furthermore, when the reaction of **A** was carried out in the presence of **1f**, products **2a** and **2f** were obtained in 20 and 27% yields, respectively (eq 3). The above results indicate that

Scheme 3. Visible-Light-Induced Hydroxylation of 2-Arylbenzothiazoles[a]



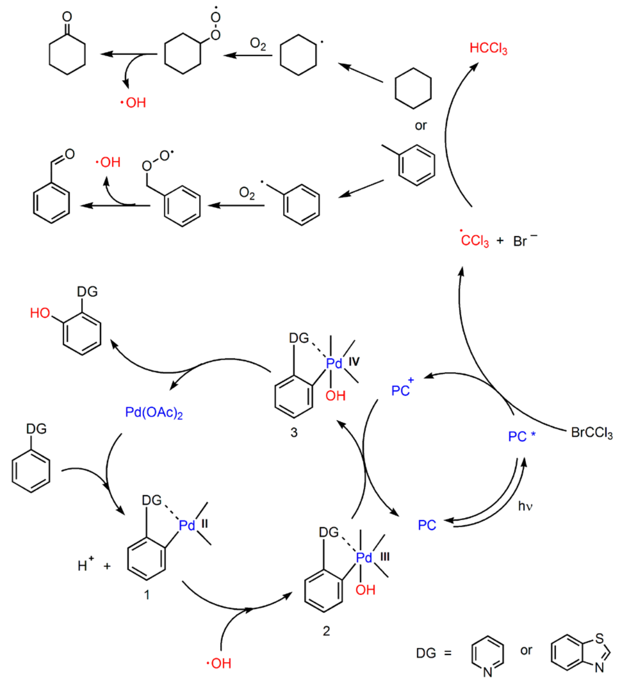
[a]Reaction conditions: **3** (0.3 mmol), Pd(OAc)$_2$ (0.1 equiv), 4CzIPN (2 mol %), BrCCl$_3$ (2 equiv), O$_2$, cyclohexane (1.5 mL), DCE (1.5 mL), under exposure from a 23 W CFL lamp for 24 h. [b]Isolated products.



the formation of a monomeric $\mathrm{Pd^{II}}$ intermediate by breaking the dimeric $\mathrm{Pd^{II}}$ complex **A** is essential for the hydroxylation.[20c]

On the basis of the reaction conditions and a literature survey, we proposed the hydroxylation mechanism (Scheme 4).[6,17,20] The catalytic cycle includes the following steps: (i) PC (4CzIPN) excites under visible light exposure to its excited state PC*. (ii) Single-electron transfer from PC* to BrCCl$_3$ generates $^{\bullet}CCl_3$ radical and PC$^+$. (iii) $^{\bullet}CCl_3$ radical abstracts a hydrogen from toluene (or cyclohexane) leading to the formation of benzyl radical (or cyclohexyl radical). (iv) Benzyl radical (or cyclohexyl radical) is then trapped by O$_2$ to produce the intermediate peroxo radical, which in turn forms the hydroxyl radical (HO$^{\bullet}$) and benzaldehyde (or cyclohexanone).[21] The HO$^{\bullet}$ was detected by EPR experiments using DMPO as the trapping agent (SI). Further, the H source in HO$^{\bullet}$ was verified by carrying out the hydroxylation reaction in toluene-d_8). The byproduct benzaldehyde (or cyclohexanone) was detected using GC–MS. (v) Reaction of HO$^{\bullet}$ with palladacycle **1** (formed by C–H activation of the substrate) furnishes the $\mathrm{Pd^{III}}$ intermediate **2**. (vi) Single-electron oxidation of **2** by PC$^+$ regenerates the PC and forms the $\mathrm{Pd^{IV}}$ intermediate **3**. Finally, (vii) C–O bond formation by reductive elimination produces the hydroxylation product and regenerates the $\mathrm{Pd^{II}}$ catalyst.

Scheme 4. Plausible Mechanism for the Photocatalytic Hydroxylation of Arenes



To show the application of our direct hydroxylation method, we synthesized fluorophores (**4a**, **4f**, and **2j**) and studied their fluorescence behavior. The newly generated fluorophores exhibited emission colors ranging from blue to orange (Figure 1). This large Stoke's shift fluorescence of our fluorophores is due to the existence of the ESIPT phenemenon.[22]

In conclusion, we have disclosed a metallaphotoredox method for the hydroxylation of 2-arylpyridines and 2-

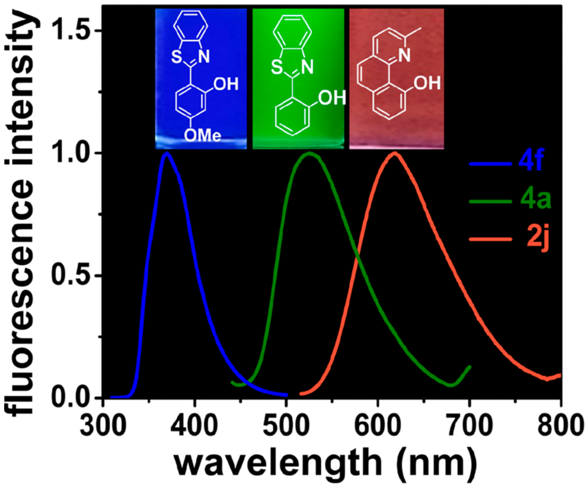


Figure 1. Fluorescence behavior of **4a**, **4f**, and **2j**.

arylbenzothiazoles. We demonstrated that by integrating photocatalyst, 4CzIPN, and metal catalyst, $Pd(OAc)_2$, the hydroxylation reactions of arenes can be carried out smoothly at room temperature under visible-light conditions. The utility of this hydroxylation reaction was addressed by developing fluorophores with interesting ESIPT properties.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01973.

General experimental procedures and characterization data of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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