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Visible-Light-Promoted Direct Amination of Phenols via Oxidative Cross-Dehydrogenative Coupling Reaction

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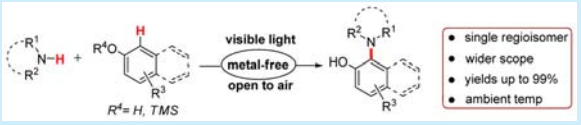
Supporting Information

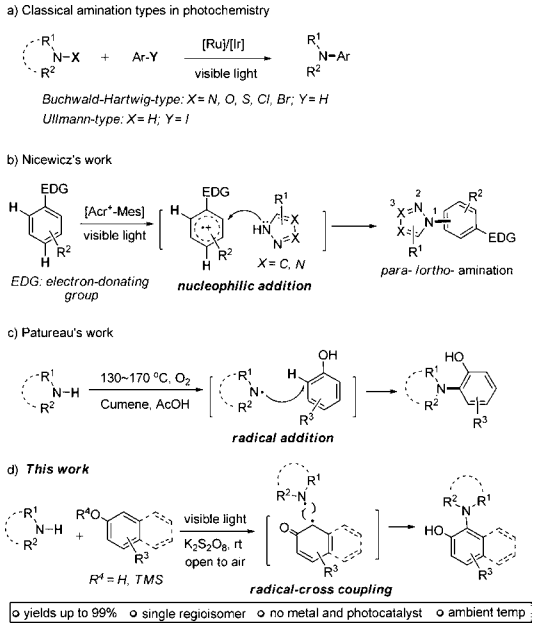
ABSTRACT: A transition-metal-free approach was disclosed for intermolecular aryl C−N bonds formation between phenols and cyclic anilines via cross-dehydrogenative coupling (CDC) amination that was mediated by visible light, wherein $K_2S_2O_8$ served as an external oxidant. The salient features of this protocol include circumventing the requirement for prefunctionalized starting materials and achieving single regioselectivity of amination adducts at room temperature.



The development of efficient methods to construct aryl C−N bonds is a pivotal goal in organic synthesis owing to their ubiquitous and indispensable presence in pharmaceutical, agrochemical, and material science.[1] In the field of transition-metal-catalyzed aryl amination reactions, significant achievements have been made by the well established palladium-catalyzed Buchwald−Hartwig amination and the copper-catalyzed Ullmann-type coupling reaction.[2] During recent research on photochemistry, visible-light photoredox catalysis provided optional approaches for aromatic C−N bonds formation through the generated N-radicals from reductive cleavage of weak N−X (X = N, O, S, Cl, and Br) bonds carrying on radical addition to arenes (Scheme 1a).[3] Alternatively, the aryl C−N bonds were produced via amine agents reacted with a metal complex which was derived from aryl halides by merging photocatalysis with a metal catalyst.[4]

Compared with the above-mentioned aryl amination methods that required preactivation of either C−H or N−H coupling partners, the C−N bonds formation by cross-dehydrogenative coupling (CDC)[5] is quite appealing in terms of atom and step economy, albeit with few examples realized to date.[6] Over the past decades, new strategies in direct amination of arenes have been propelled by employing other metallic catalysts such as Ru besides Pd and Cu to activate aryl C−H bonds.[7] However, metal-catalyzed intermolecular CDC-amination reactions generally suffer from scope limitations, as a result of the requirement of a directing group as an appendage to arene. Beyond the metal-catalyzed methods, stoichiometric hypervalent iodine reagents such as $PhI(OAc)_2$, DMP, and IBX provided metal-free direct amination avenues.[8] Despite these advances, the visible-light induced intermolecular CDC-amination reaction is still in its early stages, and examples in this realm via scission of the strong N−H bonds into *N*-radicals are extremely rare. In this regard, the pioneering work reported by Nicewicz's group was achieved by employing heteroaromatic azoles as strong nucleophiles to attack the electron-enriched arene cation radicals through a photoredox catalytic process (Scheme 1b).[9] Accordingly, the resonance property of an arene cation radical gave rise to moderate site selectivity of the amination adduct. Moreover, the distributed potential N-nucleophilic centers of azoles resulted in diverse isomers. Recently, more wonderful work from Patureau's group disclosed O_2-mediated dehydrogenative amination of phenol with phenothiazine (PTZ) (Scheme 1c)[10] in their continuous pursuit of intermolecular CDC-amination, wherein cumene organically activated O_2 at high temperature to form α-hydroxycumene which could oxidize PTZ to produce a *N*-radical added to the phenol ring, basically affording the *ortho*-position

Scheme 1. Intermolecular Aryl Amination Reactions



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amination products. Conclusively, development of intermolecular aryl CDC-amination remains significantly challenging with respect to extending the scope of the two coupling partners and achievement of site selectivity.

Phenols were documented to be readily oxidized by persulfate ($S_2O_8^{2-}$) under heating or light irradiation to produce phenol cation radicals, which would then enable formation of a phenoxonium radical intermediate[11] that, we hypothesized, might be capable of coupling with a nitrogen centered radical to furnish a C−N bond. Moreover, high regioselectivity might be feasible owing to the putative α-carbonyl radical intermediate of phenol. Herein, we describe a visible-light mediated CDC-amination reaction via a radical/radical cross-coupling pathway using $K_2S_2O_8$ for dual oxidation (Scheme 1d). This reaction benefits from mild conditions (e.g., open to air, room temperature), high regioselectivity, and the absence of metal and/or photocatalysts.

Our initial effort toward this goal focused on applying the photoredox catalytic technique that was previously utilized in [3 + 2] cycloaddition of phenols,[11b,c] by irradiating a mixture of PTZ (**1a**, 0.78 V vs SCE in CH_3CN, Figure 1), 4-methoxypheol

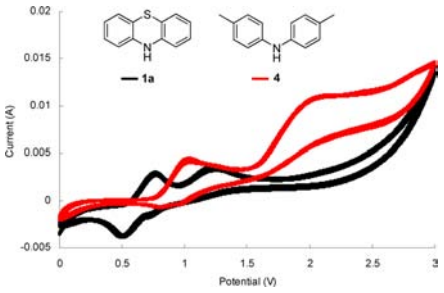
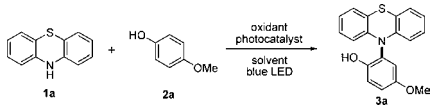


Figure 1. Cyclic voltammograms for **1a** (PTZ) and **4** (di-*p*-tolylamine).

(**2a**, 1.17 V vs SCE),[12] and $Na_2S_2O_8$ ($SO_4^{-\bullet}$, 2.6 V)[11a] in the presence of $Ru(bpy)_3Cl_2$ with visible light. To our delight, the original trial afforded the anticipated adduct **3a** promisingly despite low efficiency (Table 1, entry 1). Control experiments revealed that light illumination was indispensable in retaining the reaction efficacy while the photocatalyst was not (entries 2−3 and 8). Subsequently we attempted to examine other kinds of oxidants. Nevertheless, PTZ almost remained intact after irradiation, and **3a** was not observed (entries 4−5). Screening of persulfate salts demonstrated the superiority of potassium persulfate in this reaction (entries 6−7). Furthermore, the reaction atmosphere was investigated and air could slightly improve the yield (entries 9−10). In addition, the TMS-protected **2a** was exposed for irradiation and the desired product **3a** was obtained in comparable yield (entry 11), which clarified the naked −OH was dispensable.

Apart from the CDC-amination adduct, 1,4-benzoquinone that was derived from oxidation of **2a** was detected as well. We speculated that the low yield of **3a** was possibly attributed to the fate of the phenol radical resulting from **2a** that was preferentially oxidized to form 1,4-benzoquinone. Of course, another factor of the further oxidation of **3a** to decompose into other compounds also could not be excluded. To verify this hypothesis, we subjected other phenols such as sesamol (0.76 V vs SCE) to the reaction conditions. Pleasantly, the desired cross-coupling product **3b** was achieved in an excellent yield of up to 97% (Scheme 2). We thereby were inspired to extend the scope of CDC-amination beyond **2a**. Electron-enriched substituents such

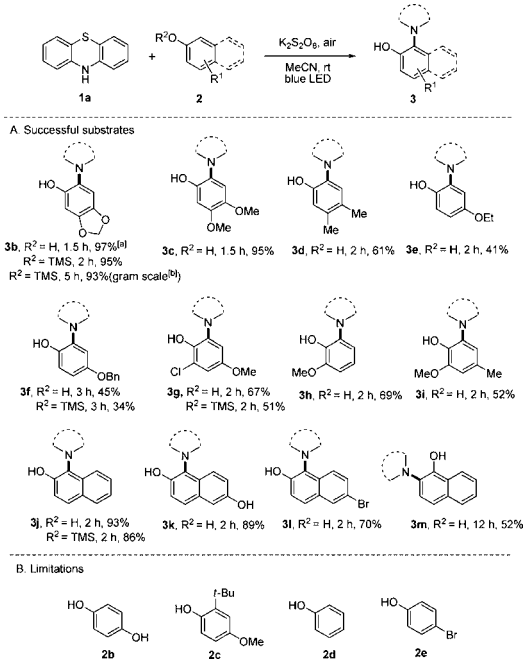
Table 1. Optimization of Reaction Conditions



entry[a]	photocatalyst	oxidant	yield (%)[b]	conv **1a** (%)[b]
1	$Ru(bpy)_3Cl_2$	$Na_2S_2O_8$	28	100
2[c]	$Ru(bpy)_3Cl_2$	$Na_2S_2O_8$	<5	28
3	none	$Na_2S_2O_8$	26	100
4	none	O_2	0	0
5	none	TEMPO	0	<5
6	none	$(NH_4)_2S_2O_8$	21	100
7	none	$K_2S_2O_8$	30	100
8[c]	none	$K_2S_2O_8$	<5	35
9[d]	**none**	**$K_2S_2O_8$**	**32**	**100**
10[e]	none	$K_2S_2O_8$	24	92
11[f]	none	$K_2S_2O_8$	30	100
12[g]	none	$K_2S_2O_8$	11	62

[a]Unless otherwise noted, all reactions were irradiated for 2 h under 8 W blue LED strips, using 0.2 mmol of **1a**, 0.4 mmol of **2a**, 0.6 mmol of oxidant, and 0.005 mmol of photocatalyst in 4 mL of MeCN with tube closed. [b]Isolated yields were indicated, and conversions of **1a** were based on recovered **1a**. [c]Reaction performed in the dark. [d]Reaction performed in air. [e]Reaction performed in N_2. [f]**2a** was protected with TMS; reaction conditions were same as those in entry 7. [g]Reaction performed in DCM.

Scheme 2. Scope of Phenols for CDC-Amination



[a]Standard conditions: using 0.4 mmol of **1a**, 0.8 mmol of **2**, 1.2 mmol of $K_2S_2O_8$ in 8 mL of MeCN under 8 W blue LED strips in air. Isolated yields were indicated. [b]Reaction performed with 2.5 mmol of **1a** (0.5 g); isolated yield was indicated.

as methoxy or methyl on phenols enabled the coupling reaction to proceed in good to prominent efficacy (Scheme 2, **3c**, **3d**, **3h**, and **3i**). Ethyl and benzyl ethers were applicable in furnishing the corresponding products (Scheme 2, **3e** and **3f**). A halide was also tolerated to provide a moderate yield (Scheme 2, **3g**). Polycyclic phenols proved to be excellent substrates as well, even with two

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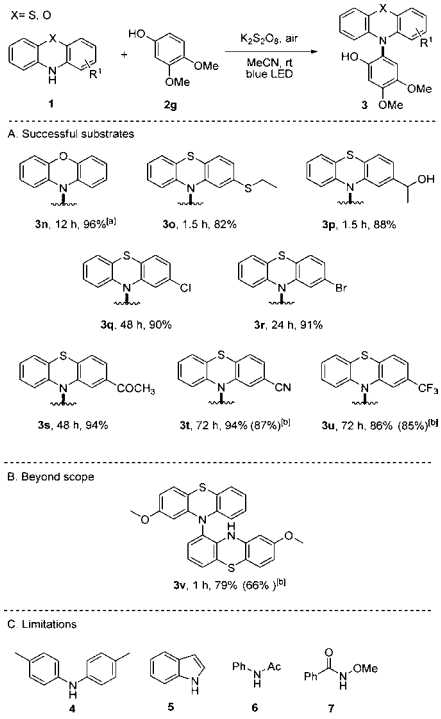
free −OH groups (Scheme 2, **3j**−**3m**). Furthermore, some TMS-protected phenols were examined as well in this protocol which led to the corresponding products in moderate to good yields (Scheme 2, **3b**, **3f**, **3g**, and **3j**), among which the gram scale CDC-amination between TMS-protected sesamol and **1a** provided a high yield of up to 93%. Besides, Ac- and Bz-protected sesamols were also examined but failed to afford the desired product, which could be attributed to their higher oxidation potentials (see the Supporting Information). However, phenol exhibiting strong reducibility was susceptible to being oxidized into the corresponding benzoquinone and no C−N coupling product was observed (Scheme 2, **2b** and **2c**). In addition, a reaction conducted with a less electron-rich or electron-deficient phenol which was difficult to oxidize by persulfate[11b,c] failed to produce the desired product (Scheme 2, **2d** and **2e**). Those unsuccessful results suggested that the engagement of phenol oxidation was indispensible for C−N bond formation, and mere *N*-radical addition to phenol made little sense in product formation.

Various commercial derivates of PTZs were also explored, including phenoxazine which finally afforded corresponding product **3n** in 96% yield (Scheme 3). Results revealed that the

Scheme 3. Scope of PTZs for CDC-Amination

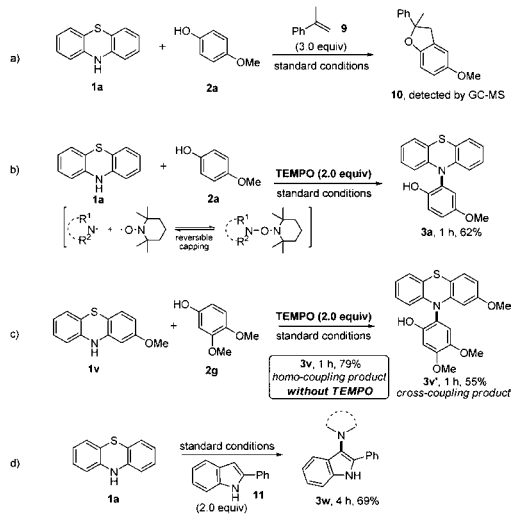


[a]Unless otherwise noted, isolated yields were based on full conversion of **1**. [b]Isolated yields were based on conversion of **1**; percentage in parentheses refers to conversion of **1**.

electronic effect had certain impacts on the reaction time and the conversion of PTZs, probably due to its effect on the rate of generation of *N*-radicals. PTZs with modest electron-donating groups were smoothly coupled with phenol, providing desired products in good to high yields (Scheme 3, **3o** and **3p**). However, a reaction performed with PTZ that was substituted with a strong electron-rich group, e.g. methoxy, resulted in complicated products. We therefore terminated the reaction before full consumption of substrate to isolate the labile intermediate, which was characterized as a homocoupling product of PTZ (Scheme 3, **3v**). A prolonged reaction time was needed for PTZs containing halides, yet the yields of the products remained outstanding (Scheme 3, **3q** and **3r**). Notably, various electron-deficient functional groups were impregnable during reaction to provide respective products in good to excellent efficiencies (Scheme 3, **3s**−**3u**). Beyond the cyclic PTZs scope, noncyclic diphenylamine (Scheme 3, **4**) possessing higher bond dissociation energy (BDE)[10,13] was evaluated under this simple oxidative condition, but no expected amination product was observed. To gain further insight into the reactivity between **1a** and **4**, the oxidation potential of **1a** and **4** was tested by using cyclic voltammetry as shown in Figure 1. Due to the higher oxidation potential value, diphenylamine **4** (1.04 V vs SCE) experienced more difficultly in being oxidized than **1a** (0.78 V vs SCE). Further investigation indicated other selected aminating candidates were unsuitable for the reaction conditions (Scheme 3, **5**−**7**).

Several control experiments were carried out to explore the reaction mechanism. To add more credence to the involvement of a phenol radical during the reaction, α-methyl-styrene **9** was added to the standard reaction conditions to obtain benzofuran **10**,[11c] a reported cycloaddition product of the phenol radical being added to styrene.[14] As expected, **10** was detected by GC-MS after 72 h (Scheme 4a). Additionally, TEMPO was added to

Scheme 4. Control Experiments



the standard conditions. To our surprise, far from being impeded by a radical scavenger, the reaction worked smoothly and the yield of **3a** was dramatically improved to 62%, without any TEMPO-trapping product obtained (Scheme 4b).[15] Since the independent TEMPO could not move this reaction forward (Table 1, entry 5), the role of oxidant that it played in this case could thus be excluded. Encouraged by precedent literature on nitroxides regulating living radical polymerization,[16] we speculate that TEMPO might play an important role in prolonging the lifetime of the transient *N*-radical in a covalent and reversible way (Scheme 4b). Once generated, the phenoxonium radical broke the reversible balance by coupling with *N*-radical to form the strong and stable C−N bond. To verify our hypothesis, we subjected **1v**, which initially afforded the labile homocoupling product **3v** (Scheme 3), to standard conditions with further addition of TEMPO, which successfully afforded the cross-coupling product **3v′** as expected (Scheme 4c). For more credence to the existence of *N*-radical, indole **11** was utilized in

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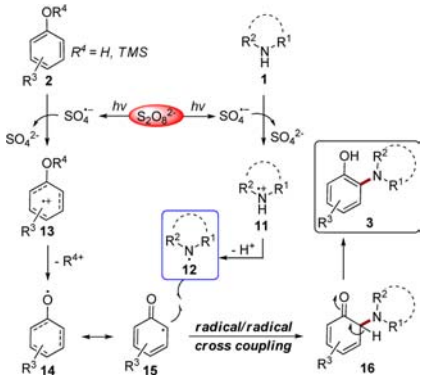
the standard conditions instead of **2a** to furnish the *N*-radical addition product **3w** (Scheme 4d).[17]

Based upon the above experimental results, a plausible mechanism is proposed and described in Scheme 5. Under

Scheme 5. Putative Mechanism for CDC-Amination



irradiation with visible light, the phenol **2** and amine **1** were both oxidized by $S_2O_8^{2-}$ to form the radical intermediates **15** and **12** respectively. Then the radical/radical cross-coupling reaction occurred to furnish intermediate **16** which was isomerized to afford the final product **3**.

In summary, we presented an oxidative CDC-amination route to construct intermolecular aryl C−N bonds between phenols and cyclic anilines at room temperature employing neither a metal catalyst nor a photocatalyst. This protocol was highlighted by avoiding preactivation of starting materials and acquiring single regioselectivity of the product. Furthermore, an expensive oxidant as well as elevated temperature was averted. Wider substrate scopes were demonstrated with moderate to excellent efficiency under very mild conditions. Continuous studies are ongoing concentrating on expanding the aminating partners in benign chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01371.

Experimental procedures, product characterizations, and ^1H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Styrene **9** was also used, but the addition product with **1a** was unidentified.

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