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Cross-Dehydrogenative C−H Amination of Indoles under Aerobic Photo-oxidative Conditions

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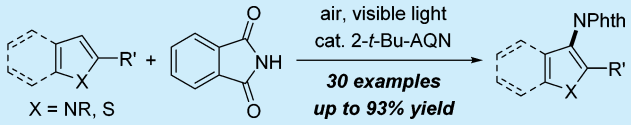
Supporting Information

ABSTRACT: A novel cross-dehydrogenative C(sp^2)−H amination catalyzed by an organic photocatalyst is reported. The reaction is mediated by 2-*tert*-butylanthraquinone as a photocatalyst, harmless visible light, and aerobic oxygen as the sole oxidant without a transition-metal catalyst and or external oxidant.

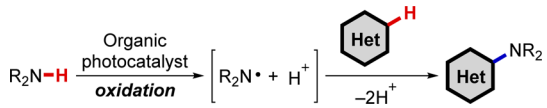


Direct C−H bond functionalization is one of the most challenging reactions in organic chemistry, and many researchers have developed various reactions to tackle the problem.[1] In particular, intra- and intermolecular C−H aminations are explored energetically because aromatic and heteroaromatic amines are frequently present in pharmaceuticals, agrochemicals, and organic materials.[2] Generally, these molecules are generated by nucleophilic aromatic substitution, reduction of nitroarenes, or a cross-coupling reaction such as Buchwald−Hartwig amination and Ullmann-type coupling reaction.[3] These typical methodologies are valuable and used frequently; however, they require prefunctionalization of starting materials. In contrast, direct C−H amination does not require prefunctionalization of arenes, and various reactions such as ligand-directed, intramolecular, and intermolecular reactions have been reported.[4] Furthermore, the direct amination of simple arenes and heteroarenes with *N*-centered radicals using visible light and photoredox catalysts has been achieved.[5] These photoreactions do not need directing groups in substrates or high temperature; however, they require preparation of amine derivatives and expensive iridium or ruthenium photocatalysts. Therefore, the development of a simpler and more economical method is desired.

Meanwhile, the cross-dehydrogenative coupling (CDC) reaction is an ideal reaction system because preactivation of both substrates is unnecessary, reducing the reaction waste and steps. Thus, C−H aminations via the CDC reaction have been developed by using a transition-metal catalyst such as palladium, copper, and iron or an organic reagent such as Bu_4NI and $PhI(OAc)_2$.[6] These reactions are superior but require transition-metal catalysts, a stoichiometric or large excess amount of the oxidant, and harsh reaction conditions. With such a background, we propose to use the CDC reaction with a *N*-centered radical, e.g., amidyl radical, to develop a novel reaction that overcomes the above problems. Specifically, a superior C−H amination can be achieved if a radical species is formed by single-electron oxidation of a secondary amine. Very recently, visible-light-induced oxidative C−H amidation has been reported by Yu, Zhang et al.[7] However, the methodologies of catalytic C(sp^2)−H amination under mild conditions are still rare; therefore, the development of catalytic and oxidative formation of *N*-radicals is important in organic chemistry.

Furthermore, we are involved in the development of photo-organo-catalytic oxidative reactions employing aerobic oxygen.[8] We have already reported the cross-dehydrogenative coupling reaction via the aerobic photo-oxidative generation of an iminium intermediate from tertiary amines followed by addition of a nucleophile.[9] In this reaction, single-electron transfer was mediated by a photocatalyst, and the amines were converted into radical cation species. Accordingly, we envisioned that oxidative C−H amination of heterocycles with amidyl radicals, which are often used as radical intermediates in photoreactions,[10] could be achieved if the single-electron transfer of secondary amines proceeds by our oxidation system. Our oxidative strategy does not require preactivation of amines and keeps byproducts to a minimum because molecular oxygen is used as a sole oxidant (Scheme 1). Hence, this method will be

Scheme 1. Oxidative Generation of *N*-Centered Radicals and the C−H Amination of Heterocycles



superior to others in atom and step economy if it can be applied to the intermolecular C−H amination of heterocycles. In particular, we focused on the amination of indoles, which are important for both biological and functional material chemistries. 3-Aminoindoles have received a lot of attention as a significant structure in drug design for various diseases.[11] Herein, we describe the catalytic amination of indoles via the CDC reaction under aerobic photo-oxidative conditions.

Initially, we examined the C−H amination of 1-methyl-2-phenylindole (**2a**) with phthalimide (**1a**) using 2-*tert*-butylanthraquinone (2-*t*-Bu-AQN) and potassium carbonate

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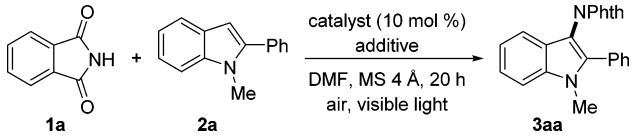
Table 1. Optimization of the Oxidative C−H Amination of 2a[a]



1a 2a 3aa

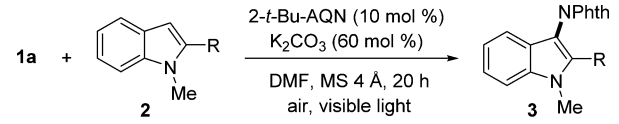
entry	catalyst	additive (mol %)	3aa[b] (%)
1	2-*t*-Bu-AQN	K_2CO_3 (50)	85 (80)
2		K_2CO_3 (50)	0
3	2-*t*-Bu-AQN		42
4[c]	2-*t*-Bu-AQN	K_2CO_3 (50)	0
5[d]	2-*t*-Bu-AQN	K_2CO_3 (50)	26
6	AQN	K_2CO_3 (50)	68
7	AQN-2-CO_2H	K_2CO_3 (50)	54
8	9,10-DCA	K_2CO_3 (50)	56
9	$Ru(bpy)_3Cl_2$[e]	K_2CO_3 (50)	0
10	2-*t*-Bu-AQN	K_2CO_3 (60)	(82)
11	2-*t*-Bu-AQN	K_2CO_3 (100)	(81)

[a]Reaction conditions: mixture of **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst, additive, and MS 4 Å (50 mg) in DMF (3 mL) was stirred for 20 h under an aerobic atmosphere irradiated with a 21-W fluorescent lamp. [b]Yields were determined by ^1H NMR analysis. Numbers in parentheses refer to isolated yields. [c]Reaction performed in the dark. [d]Reaction performed under an argon atmosphere. [e]$Ru(bpy)_3Cl_2$ (5 mol %) was used as a catalyst.

in *N*,*N*-dimethylformamide (DMF) under an aerobic atmosphere with visible light irradiation (Table 1, entry 1). The amination of indole at the C3 position proceeded well, and pure **3aa** was obtained in 80% yield. In the absence of the photocatalyst or base, the product yield decreased (entries 2 and 3). Control experiments verified the necessity of both visible light irradiation and molecular oxygen in the reaction (entries 4 and 5). Solvent and base screening revealed that DMF and potassium carbonate were well suited to this reaction (for detailed results, see the Supporting Information). Photocatalyst screening revealed that anthraquinones and 9,10-dicyanoanthracene provided the product in moderate yield, but a commonly used photocatalyst tris(bipyridine)ruthenium(II) chloride was found to be ineffective (entries 6−9) Moreover, the amination reaction did not proceed well with other photocatalysts such as eosin Y, rose bengal, or acridine (for detailed results, see the SI). The product yield decreased by reducing the loading of 2-*t*-Bu-AQN (for detailed results, see the SI). With an increased amount of potassium carbonate, the desired aminated product was obtained in 82% isolated yield (entry 10). However, the yield of product was not improved by addition of 100 mol % of base (entry 11).

After determining the optimal conditions, we investigated the reaction of **1a** with indoles bearing various substituents (Table 2). The desired product **3ab** was obtained in moderate yield when 1,2-dimethylindole was used as the substrate (entry 2). Furthermore, the product yield was low when the electron poor indole (**2c**) was used as a substrate (entry 3). These results suggested that the stability of the generated radical at C2 is crucial in this reaction. Next, we examined the effect of substituents on the phenyl group. Electron-donating groups such as alkyl and methoxy were suitable for this method, and C3-aminated products were obtained in good to excellent yields (entries 4−6). Furthermore, the direct C−H amination proceeded well to yield the desired products in the presence of electron-withdrawing groups (entries 7−10). Silyl-protected

Table 2. Oxidative C−H Amination of 2 Bearing Various Substituents at C2[a,b]



2 3

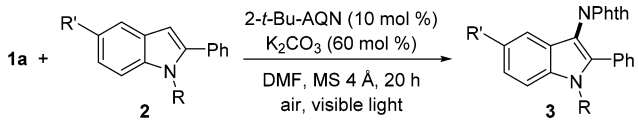
entry	R	yield (%)
1	Ph (**3aa**)	82
2	Me (**3ab**)	55
3	CO_2Me (**3ac**)	29
4	4-Me-C_6H_4 (**3ad**)	80
5	4-*t*-Bu-C_6H_4 (**3ae**)	70
6	4-OMe-C_6H_4 (**3af**)	87
7	4-CHO-C_6H_4 (**3ag**)	86
8	4-CO_2Me-C_6H_4 (**3ah**)	72
9	4-Br-C_6H_4 (**3ai**)	60
10	4-CF_3-C_6H_4 (**3aj**)	69
11	4-CH_2OTBS-C_6H_4 (**3ak**)	77
12	3-OMe-C_6H_4 (**3al**)	93
13	2-Me-C_6H_4 (**3am**)	83
14	2-thienyl (**3an**)	77
15	4-pyridinyl (**3ao**)	42
16	H (**3ap**)	n.d.

[a]Reaction conditions: mixture of **1a** (0.3 mmol), **2** (0.6 mmol), 2-*t*-Bu-AQN (10 mol %), K_2CO_3 (60 mol %), and MS 4 Å (50 mg) in DMF (3 mL) was stirred for 20 h under an aerobic atmosphere irradiated with a 21-W fluorescent lamp. [b]Isolated yields.

aldohol could be employed under the reaction conditions without any deprotection (entry 11). When the position of the substituent was changed from *para* to *meta* or *ortho*, the desired products were produced in high yield (entries 12 and 13). Thienyl- or pyridinyl-substituted indole was converted into the corresponding aminated indole in moderate to good yields (entries 14 and 15). Unfortunately, *N*-methylindole (**2p**) was not suited to these reaction conditions (entry 16).

We next investigated the effect of the substituent at the C1 position (Table 3). Starting materials and byproducts, which

Table 3. Oxidative C−H Amination of Substituted Indoles[a,b]



2 3

entry	R	R′		yield (%)
1	H	H	(**3aq**)	0
2	Ac	H	(**3ar**)	0 (13)[c]
3	Ph	H	(**3as**)	82
4	Bn	H	(**3at**)	89
5	MOM	H	(**3au**)	88
6	CH_2CO_2Me	H	(**3av**)	72
7	Me	OMe	(**3aw**)	69
8	Me	Me	(**3ax**)	75
9	Me	Cl	(**3ay**)	77

[a]Reaction conditions: mixture of **1a** (0.3 mmol), **2** (0.6 mmol), 2-*t*-Bu-AQN (10 mol %), K_2CO_3 (60 mol %), and MS 4 Å (50 mg) in DMF (3 mL) was stirred for 20 h under an aerobic atmosphere irradiated with a 21-W fluorescent lamp. [b]Isolated yields. [c]The yield of 2-phenyl-3-phthalimidoindole (**3aq**).

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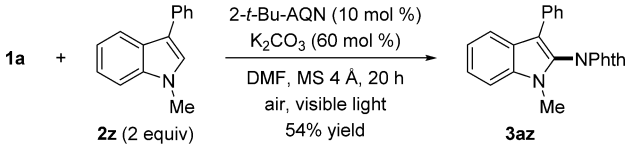
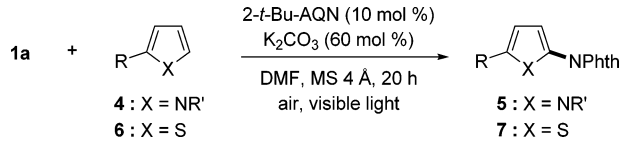
could not be detected, were observed when 2-phenylindole (**2q**) was used as substrate (entry 1). Furthermore, **2r** could not be converted to the desired compound (**3ar**) but gave 2-phenyl-3-phthalimidoindole (**3aq**) in low yield (entry 2). By contrast, 1,2-diphenylindole (**2s**) underwent this transformation with good yield (entry 3). These results suggested that the electron density of indole is an important factor for this reaction. Furthermore, indoles with removable groups, such as Bn and MOM, worked well to give the 3-aminated products in excellent yields (entries 4 and 5). Next, we investigated the effect of the substituents at C5 of indoles. As a result, the desired products were obtained in moderate yields regardless of the electron density (entries 7−9). When the position of the phenyl group was changed from C2 to C3, the C−H amination proceeded at C2 in moderate yield (Scheme 2).

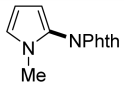
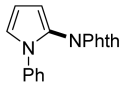
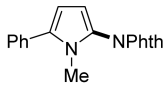
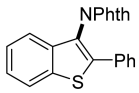
Scheme 2. Direct C−H Functionalization of 2z



In addition, we applied this catalytic system for other heterocycles (Table 4). The aminated products were formed in

Table 4. Oxidative C−H Amination of Pyrroles and Benzo[*b*]thiophene[a,b]



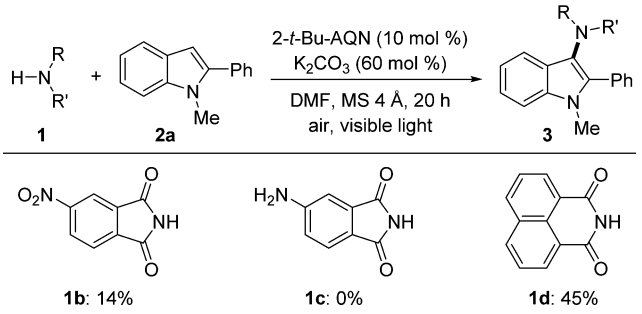
entry	substrate	product	yield (%)
1	**4a**		(**5aa**) 55
2	**4b**		(**5ab**) 21
3	**4c**		(**5ac**) 50
4	**6**		(**7a**) 22

[a]Reaction conditions: mixture of **1a** (0.3 mmol), **4** or **6** (0.6 mmol), 2-*t*-Bu-AQN (10 mol %), K_2CO_3 (60 mol %), and MS 4 Å (50 mg) in DMF (3 mL) was stirred for 20 h under an aerobic atmosphere irradiated with a 21-W fluorescent lamp. [b]Isolated yields.

low to moderate yields when substituted pyrroles were used as substrates (entries 1−3). Moreover, 2-phenylbenzo[*b*]-thiophene (**6**) could be employed for this reaction even though the yield was low (entry 4).

Furthermore, we examined the amination of **2a** with various substituted phthalimides (Scheme 3). As a result, the desired product yields decreased in the presence of electron-donating and -withdrawing substituents at C4 of phthalimide (**1b** and

Scheme 3. Oxidative C−H Amination of 2a with Various Substituted 1[a,b]

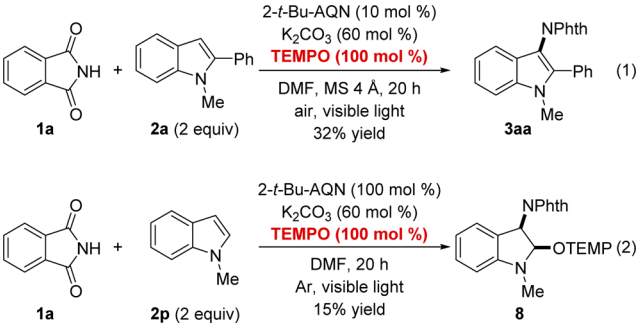


[a]Reaction conditions: mixture of **1** (0.3 mmol), **2a** (0.6 mmol), 2-*t*-Bu-AQN (10 mol %), K_2CO_3 (60 mol %), and MS 4 Å (50 mg) in DMF (3 mL) was stirred for 20 h under an aerobic atmosphere irradiated with a 21-W fluorescent lamp. [b]Isolated yields.

1c). On the other hand, moderate yield was observed when 1,8-naphthalimide (**1d**) was used as a nitrogen source.

Several control experiments were conducted to investigate the reaction mechanism. The yield of **3aa** was decreased to 32% by addition of TEMPO, which is a radical scavenger (Scheme 4,

Scheme 4. Control Experiments



eq 1). Furthermore, TEMPO adduct (**8**) was obtained when 1-methylindole (**2p**) was used instead of **2a** (Scheme 4, eq 2). These results suggested that the amination proceeded by the generation of an *N*-centered radical, followed by an addition to indoles. The aminated product was obtained in excellent yield regardless of the presence of potassium carbonate when potassium phthalimide was used as a nitrogen source. This result indicated that deprotonation of phthalimide may be assisted by K_2CO_3 (for detailed results, see the SI). Moreover, the generation of peroxide was detected by iodometry, suggesting that molecular oxygen was converted to hydrogen peroxide in this reaction (for detailed results, see the SI).

Figure 1 shows a plausible mechanism for this reaction, which is postulated by considering all of the above results. Initially, an *N*-centered radical is formed by deprotonation of **1a** and single-electron transfer to AQN*. The radical species adds to indoles, followed by one-electron oxidation and aromatization. On the other hand, $AQN^{\bullet-}$ is oxidized by molecular oxygen in the air to AQN, which is then converted by visible light to AQN* to complete the catalytic system. However, another path, such as AQN* quenched with **2**, could not be ruled out.[12]

In conclusion, we have achieved the catalytic C−H amination of indoles at room temperature. This methodology uses harmless visible light, cheap and commercially available

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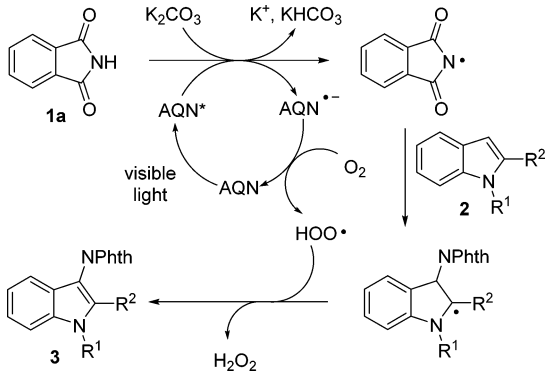

Figure 1. Plausible reaction mechanism.

photocatalyst and nitrogen source, and molecular oxygen as the sole oxidant. Further applications of the *N*-centered radical for other heterocycles and the nitrogen sources are being studied at our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00026.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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