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Visible-Light-Promoted Redox Neutral C−H Amidation of Heteroarenes with Hydroxylamine Derivatives

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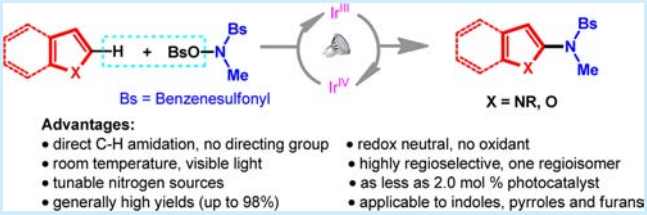
Supporting Information

ABSTRACT: A room temperature redox neutral direct C−H amidation of heteroarenes has been achieved. Hydroxylamine derivatives, which are easily accessed, have been employed as tunable nitrogen sources. These reactions were enabled by a visible-light-promoted single-electron transfer pathway without a directing group. A variety of heteroarenes, such as indoles, pyrroles, and furans, could go through this amidation with high yields (up to 98%). These reactions are highly regioselective, and all the products were isolated as a single regioisomer.

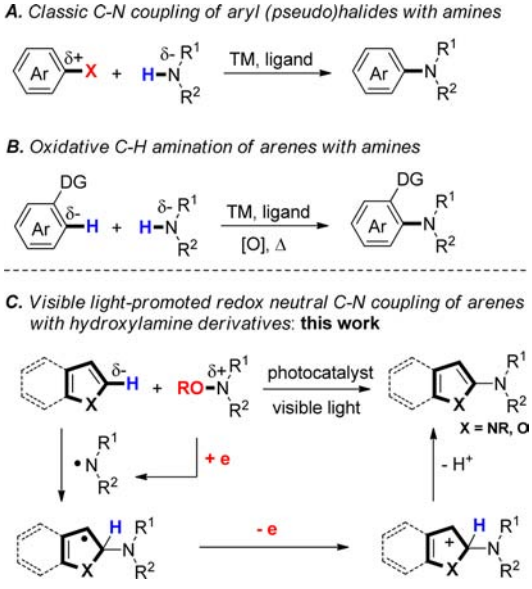


Aryl and heteroarylamines, which widely exist in natural products, pharmaceuticals, and functional materials, have attracted increasing attention from synthetic and medicinal chemists.[1] As essential structural fragments, they often exhibit biological activities. Therefore, synthesis of (hetero)arylamines is always one of the most important tasks of the synthetic community.[2−6]

A conventional method to incorporate an amino group into organic molecules is aromatic nitration followed by reduction.[2] Recently copper-mediated Ullmann-type[3] and palladium-catalyzed Buchwald−Hartwig amination/amidation[4] have emerged as more powerful tools for C−N bond formation (Scheme 1A). However, prefunctionalized arenes and normally high temperature are necessary. More recently, oxidative direct C−H amination of arenes with amines has been achieved (Scheme 1B).[5,6] This atom economical approach usually requires directing groups and stoichiometric oxidants, which restrains its applications. This has led us to explore more efficient C−H amination/amidation under mild conditions.

Nitrogen-centered radicals have been involved in a wide variety of useful organic transformations, which has received increasing attention from the synthetic community.[7] In 2013, MacMillan and co-workers reported that a nitrogen-centered radical generated from a hydroxylamine derivative assisted by visible light could add to the C−C double bond of an enamine.[8] Inspired by this work, as well as our recent research on visible-light-promoted C−H functionalization of enamides,[9] we envisaged that reductive cleavage of a hydroxylamine derivative could give a nitrogen-centered radical. The nitrogen-centered radical could add to a (hetero)arene to generate a C−N bond and a carbon-centered radical. The resultant carbon-centered radical could be oxidized to a carbocation followed by deprotonation to regenerate the aromatic ring (Scheme 1C). Based on this scenario, we would like to report our efforts in the photoredox neutral direct C−H amidation of heteroarenes using hydroxylamine derivatives as nitrogen sources.[10]

Scheme 1. Major Strategies for C−N Coupling



Our efforts toward this hypothesis focused on the use of *N*-methylindole (**1a**) and *N*, *O*-ditosyl-*N*-methylhydroxylamine (**2a**) as model substrates. The photocatalyst *fac*-Ir(ppy)$_3$ (**I**) was chosen as the photocatalyst because of its superior reduction capacity in the excited state.[11] When a solution of **1a** and **2a** in DMSO was irradiated by a white LED strip in the presence of photocatalyst **I** and Na_2HPO_4 for 24 h, the desired amido indole **3a** was isolated in 58% yield as one regioisomer (Table 1, entry 1). After NMR comparison,[12] the structure of **3a** was established ambiguously as a 2-amido indole derivative.

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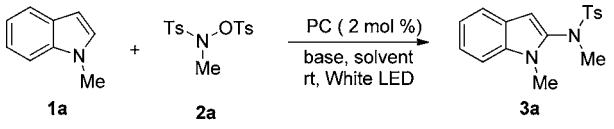
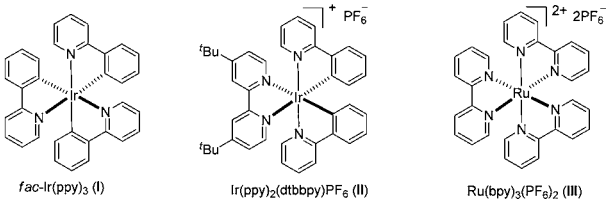
Table 1. Reaction Condition Optimization[a]




fac-Ir(ppy)3 (I)
Ir(ppy)2(dtbbpy)PF6 (II)
Ru(bpy)3(PF6)2 (III)

entry	PC	base	solvent	yield (%)[b]
1	**I**	Na_2HPO_4	DMSO	58
2	**I**	Na_2HPO_4	DMA	56
3	**I**	Na_2HPO_4	CH_3CN	32
4	**I**	Na_2HPO_4	CH_2Cl_2	46
5	**I**	Na_2HPO_4	DMF	61
6	**I**	**$NaHCO_3$**	**DMF**	**66**
7	**I**	K_3PO_4	DMF	59
8	**I**	K_2HPO_4	DMF	62
9	**I**	K_2CO_3	DMF	54
10	**II**	$NaHCO_3$	DMF	13
11	**III**	$NaHCO_3$	DMF	19
12	**I**	none	DMF	56%
13	none	$NaHCO_3$	DMF	no rxn
14[c]	**I**	$NaHCO_3$	DMF	no rxn

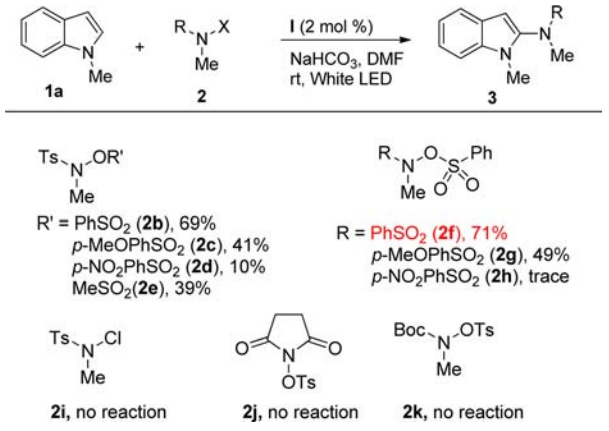
[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.2 mmol, 2.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv), and photocatalyst (0.002 mmol, 2.0 mol %) in dry solvent (1.5 mL) were irradiated by a white LED strip. [b]Isolated yield. [c]No irradiation. PC = photocatalyst.

Other solvents, such as DMA, CH_3CN, and CH_2Cl_2, could not give improved results (entries 2−4). To our delight, a 61% yield was achieved when DMF was used as solvent (entry 5). A variety of bases were then examined (entries 6−9); $NaHCO_3$ turned out to be a better base with a 66% yield (entry 6). Several other photocatalysts, such as $Ir(ppy)_2(dtbbpy)PF_6$ (**II**) and $Ru(bpy)_3(PF_6)_2$ (**III**), were not superior to *fac*-$Ir(ppy)_3$ (**I**) (entries 10−11). Control experiments verified the necessity of the base, irradiation, and photocatalyst (entries 12−14).

In order to improve this reaction further, different nitrogen-centered radical precursors were then investigated, as shown in Scheme 2. First, activated groups on the hydroxyl group proved to be very important. An electron-neutral benzenesulfonyl group (**2b**) gave a slightly better result (69% yield). Both electron-rich and -deficient aromatic sulfonyl groups (**2c** and **2d**) gave worse yields. An aliphatic sulfonyl group (**2e**) was not as efficient as a tosyl group. The protecting groups of amine were then examined. When benzenesulfonyl (**2f**) was used instead of the tosyl group, the yield could be improved to 71%. Neither electron-rich (**2g**) nor -deficient sulfonyl (**2h**) groups could give better results. Other types of radical precursors, such as *N*-chloride (**2i**), a *N*-hydroxyl succinimide derivative (**2j**), and a *N*-Boc hydroxylamine derivative (**2k**), did not work at all.

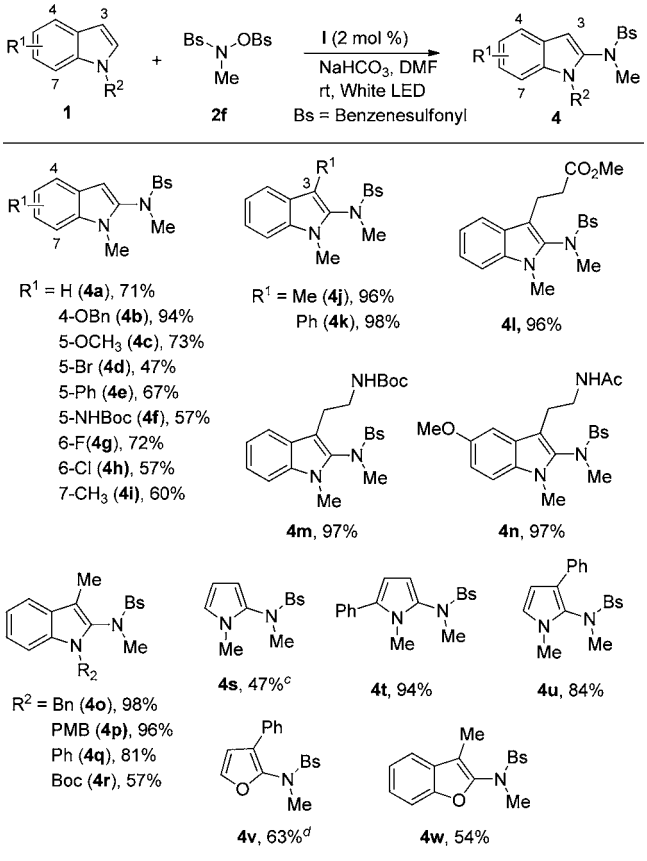
We next sought to establish the scope of the heteroarenes coupling partners in this transformation. A variety of indoles were tested with the hydroxylamine derivative **2f**, as shown in Scheme 3. It was found that indoles bearing various substituents at the C4−C7 positions (indole numbering) gave the amido indole derivatives **4a−i** with satisfactory to excellent

Scheme 2. Optimization of Nitrogen Radical Precursors[a,b]



[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.2 mmol, 2.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv), and *fac*-$Ir(ppy)_3$ (0.002 mmol, 2.0 mol %) in dry DMF (1.5 mL) were irradiated by a white LED strip. [b] The yields were isolated yields.

Scheme 3. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2f** (0.2 mmol, 2.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv), and *fac*-$Ir(ppy)_3$ (0.002 mmol, 2.0 mol %) in dry DMF (1.5 mL) were irradiated by a white LED strip. [b] The yields were isolated yields. [c] Na_2HPO_4 (1.2 equiv) was used as a base in DMSO (1.5 mL). [c] 4 equiv of **2f** were used.

yields (47−94%). Electron-donating groups, such as 4-OBn (94% yield), worked better than electron-withdrawing groups, such as 5-Br (47% yield). Substitutions at the C3 position had a positive influence on this transformation. 3-Methyl and 3-phenyl indole derivatives could go through this reaction

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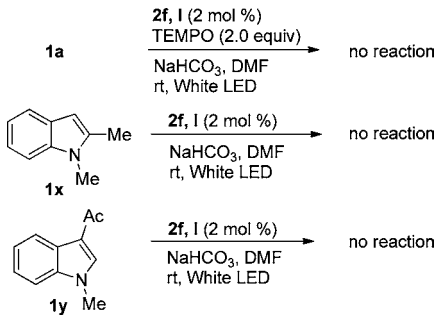
perfectly to give amido indoles **4j** and **4k** with excellent yields (96% and 98% respectively). More biologically important indole derivatives, such as indole propanoic acid, tryptamine, and melatonin derivatives, could also be amidated fluently under standard conditions to give corresponding amido indoles **4l**–**n** with 96–97% yields. The protecting groups at the N1 position were next explored. Indoles with more easily removable groups, such as Bn and PMB, worked quite well to give the desired products **4o** and **4p** in nearly quantitative yields. *N*-Phenyl and Boc indoles could also undergo this transformation with slightly lower yields (87% for **4q** and 57% for **4r**). Pyrrole and furan derivatives could also be amidated with the hydroxylamine derivative **2f** to give the corresponding amido pyrroles **4s**–**t** and furans **4v**–**w** with good to excellent yields (47–94%). It is noteworthy that all the desired products were isolated in a single regioisomer exclusively without other regioisomers. However, attempts to amidation of benzene, pyridine, and thiophene derivatives under standard conditions failed (for the substrates we tried, see Supporting Information).

Several control experiments were then conducted to gain some insights into the reaction mechanism (Scheme 4). The

Scheme 4. Control Experiments



reaction could be terminated completely if TEMPO was introduced to the reaction mixture, which suggested a one-electron transfer pathway. 1,2-Dimethylindole (**1x**) could not go through this reaction which implies that nitrogen-centered radical attacks the C2 position of indoles. Compared to 3-alkyl or aryl substituted indoles, which can undergo this transformation perfectly, electron-deficient 3-acetyl indole (**1y**) could not work at all. This phenomenon could be explained by the formation of a carbon cation intermediate at the C3 position.

Although, at this stage, an electrophilic aromatic substitution mechanism through an amine radical cation cannot be ruled out completely, a more likely radical pathway is proposed based on the aforementioned observations and literature precedents[8,10,11] (Figure 1). First, the photocatalyst *fac*-$Ir^{III}(ppy)_3$ is irradiated to the excited state *fac*-$Ir^{III}(ppy)_3$* and then oxidatively quenched by hydroxylamine derivative **2f** with generation of *fac*-$Ir^{IV}(ppy)_3^+$ and nitrogen-centered radical species **5** respectively. Radical **5** adds onto *N*-methylindole **1a** to generate radical intermediate **6**, which is oxidized by *fac*-$Ir^{IV}(ppy)_3^+$ to form cation intermediate **7** and regenerate *fac*-$Ir^{III}(ppy)_3$. Ultimately, amido indole **4a** is formed by deprotonation.

We have reported herein that a room temperature redox neutral direct C–H amidation of heteroarenes proceeded without a directing group. The hydroxylamine derivatives were used as tunable nitrogen sources. The external oxidants could be avoided due to the overall redox neutral process. The visible-light-promoted radical pathway enabled that these amidations could be carried out at room temperature. A series of heteroarenes, including indoles, pyrroles, furans, and benzofurans, could undergo this amidation with high yields (up to 98%). These reactions are highly regioselective, and all the products were isolated as a single regioisomer.

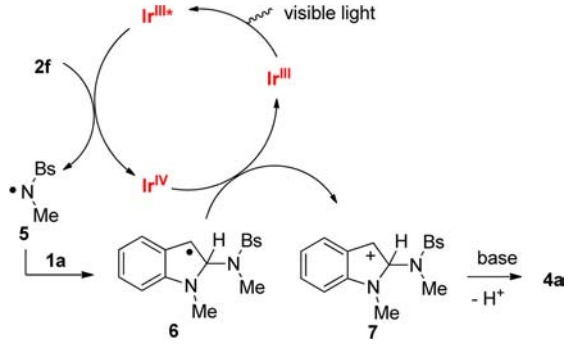


Figure 1. Proposed mechanism.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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