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Metal-free, C–H arylation of indole and its derivatives with aryl diazonium salts by visible-light photoredox catalysis

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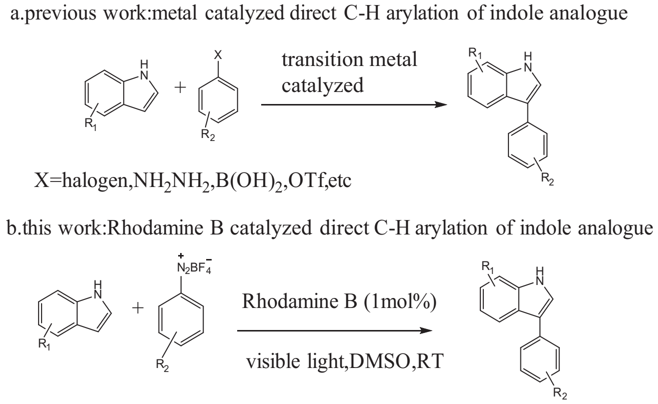
ABSTRACT

In this Letter, we present the Rhodamine B catalyzed direct C–H arylation of indole with aryl diazonium salts. This method only requires green light and room temperature.

Introduction

Indole and its derivatives are often found in functional materials, pesticides, drugs, and natural products.[1–4] C-arylindole shows better medicinal value, especially in the aspect of cancer is more outstanding. Since it was found in 1860s, scientists had been committed to seek different synthesis methods for further functionalization.[5–7] The most efficient synthesis of arylindole is the direct arylation of indole by C–H bond activation. Recently, much focus has been devoted to transition-metal-catalyzed processes such as direct arylation of indoles with activated arenes. The method avoids the need for prefunctionalization of indole derivatives and thus can potentially provide a promising synthetic route.[8–17] Under such conditions, aromatic halohydrocarbon is one of the most commonly used coupling partners for the direct arylation of indole derivatives. In addition, different aromatic coupling partners as arylation agents have been successfully applied[18–26] (Scheme 1a).


a.previous work:metal catalyzed direct C-H arylation of indole analogue

b.this work:Rhodamine B catalyzed direct C-H arylation of indole analogue

Scheme 1. Metal catalyzed and photocatalytic approaches for direct C–H arylation of indole analogue. (a) Previous work: metal catalyzed direct C–H arylation of indole analogue. (b) This work Rhodamine B catalyzed direct C–H arylation of indole analogue.

However, the above mentioned reaction process suffers from several drawbacks, such as the need for a large catalyst, high cost, ligands and restriction to aqueous reaction media. More recently reports had appeared showing the direct arylation of furans and thiophenes using EsoinY as catalyst.[27] This method avoids the high temperature, ligands, and the use of transition-metal. Thus, photocatalyst is likely the most promising approach for direct C-arylation of the diazonium salt and indole.

In the past ten years, the free radical reaction has played an important role in organic synthesis for formation of C–C bonds. Aryl diazonium salt was selected as a good free radical source due to its high reduction potential.[4,28] Aryl diazonium salts are

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well-known oxidative quenchers in photoredox chemistry. It was first applied by Cano-Yelo and Deronzier to synthesize phenanthrene derivatives using $Ru(bpy)_3^{2+}$ as a photoredox catalyst.[29–31] In this Letter, we present the Rhodamine B catalyzed direct C–H arylation of indole with aryl diazonium salts. This method only requires green light and room temperature.

Results and discussion

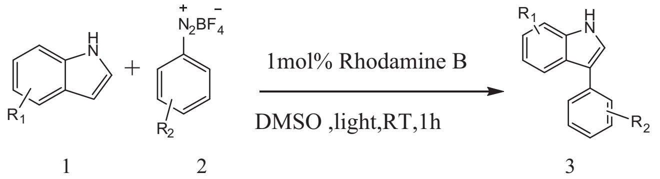
Initially, we examined the direct arylation using indole (**1a**) and aryl diazonium salts (**2a**) as the model. The reaction was carried out under 25 W white light-emitting diode (LED) irradiation with 1 mol % Rhodamine in *N*,*N*-dimethylformamide (DMF). The desired product **3a** was obtained in 69% yield after 1 h (Table 1, entry1). Inspired by this result, we screened other parameters. Firstly, the reaction of organic solvents such as THF, EtOH,CH_3CN,MeOH, DMSO, and CH_2Cl_2 was investigated. Different yields were obtained in such cases (Table 1, entries 2–7). The results show that dimethyl sulfoxide (DMSO) is a more suitable solvent for the photoreaction (Table 1, entry 7). Aromatic product was obtained in better yields using a bit more indole **1a** (Table 1, entries 8 and 9). Yield of the control reactions was significantly reduced in the absence of photocatalyst or light (Table 1, entries 10 and 11). The reaction can also be performed in the presence of water (Table 1, entry 15).

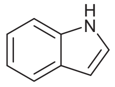
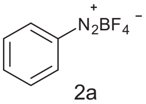
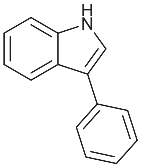
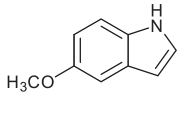
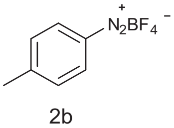
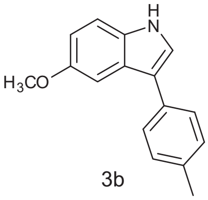
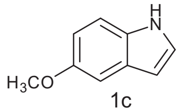
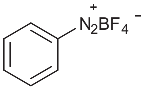
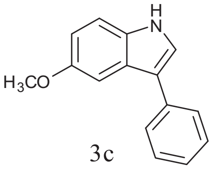
Table 1
Optimization of reaction conditions[a]

Entry	Conditions	Yield (%)
1	Rhodamine B, DMF	69
2	Rhodamine B, EtOH	26
3	Rhodamine B, MeOH	23
4	Rhodamine B, CH_3CN	54
5	Rhodamine B,THF	19
6	Rhodamine B, CH_2Cl_2	21
7	Rhodamine B, DMSO	79
[b]8	Rhodamine B, DMSO	81
[c]9	Rhodamine B, DMSO	81
10	Without light, DMSO	Trace
11	Without catalyst, DMSO	Trace
12	EsoinY, DMSO	66
13	Rose Bengal, DMSO	69
14	Rhodamine 6G, DMSO	73
15	Rhodamine B, DMSO/H_2O (4:1)	47

[a] Yields were determined by column chromatography.
[b] 1.5 equiv of indole was used.
[c] 2 equiv indole was used.

Table 2
Scope of aryl diazonium salts and indole[a]



Entry	Substrate **1**	Substrate **2**	Product	Yield[b] (%)
1	 1a	 2a	 3a	81
2	 1b	 2b	 3b	71
3	 1c	 2c	 3c	72

(*continued on next page*)

Table 2 (*continued*)

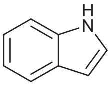
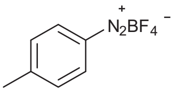
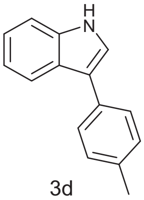
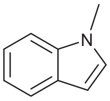
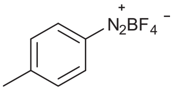
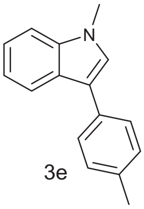
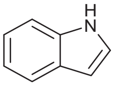
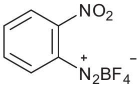
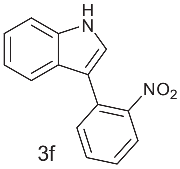
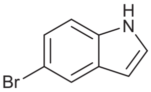
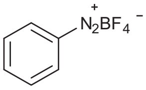
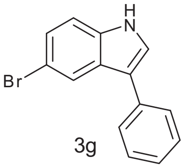
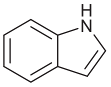
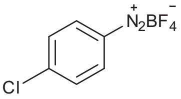
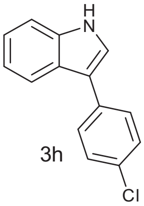
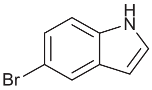
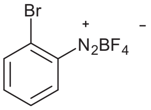
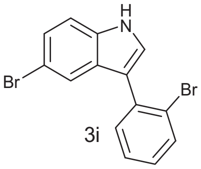
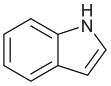
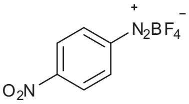
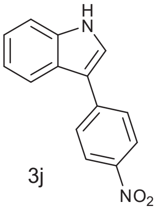
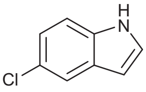
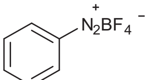
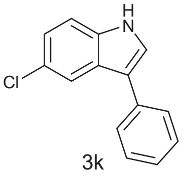
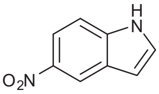
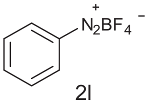
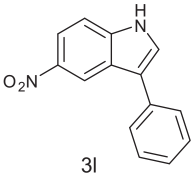
Entry	Substrate **1**	Substrate **2**	Product	Yield[b] (%)
4	 1d	 2d	 3d	73
5	 1e	 2e	 3e	70
6	 1f	 2f	 3f	54
7	 1g	 2g	 3g	53
8	 1h	 2h	 3h	66
9	 1i	 2i	 3i	47
10	 1j	 2j	 3j	57
11	 1k	 2k	 3k	22
12	 1l	 2l	 3l	25

Table 2 (*continued*)

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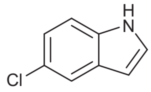
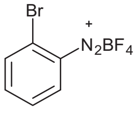
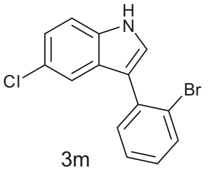
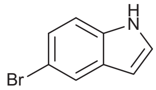
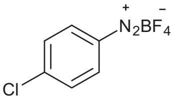
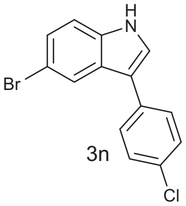
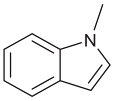
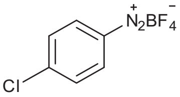
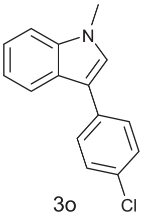
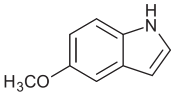
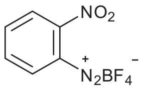
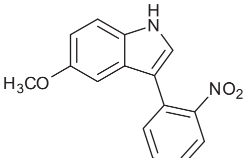
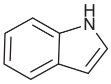
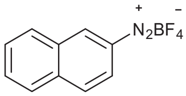
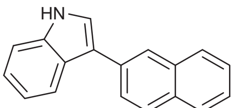
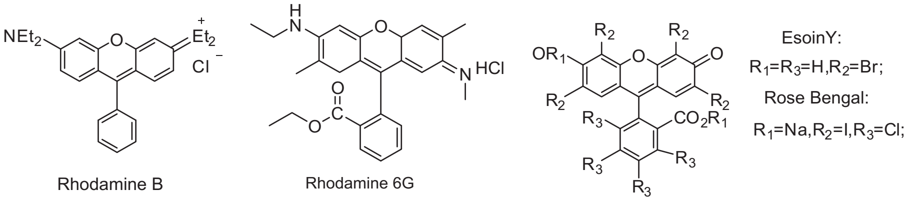
13	 1m	 2m	 3m	14
14	 1n	 2n	 3n	31
15	 1o	 2o	 3o	62
16	 1p	 2p	 3p	60
17	 1q	 2q	 3q	17

[a] The reaction was performed with **1** (0.5 mmol), **2a** (1.5 equiv), and Rhodamine B (0.01 equiv) in 2.0 mL of DMSO.

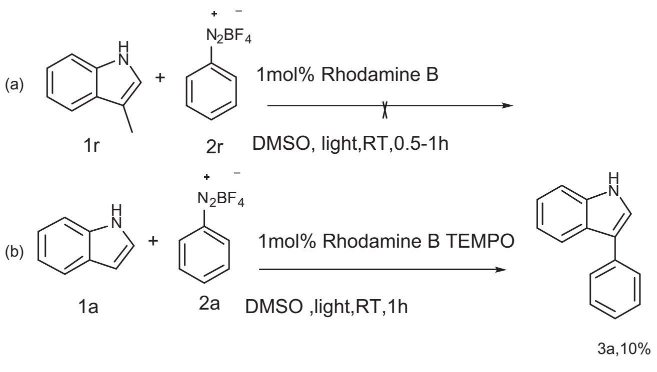
[b] Isolated yields after purification on SiO_2.



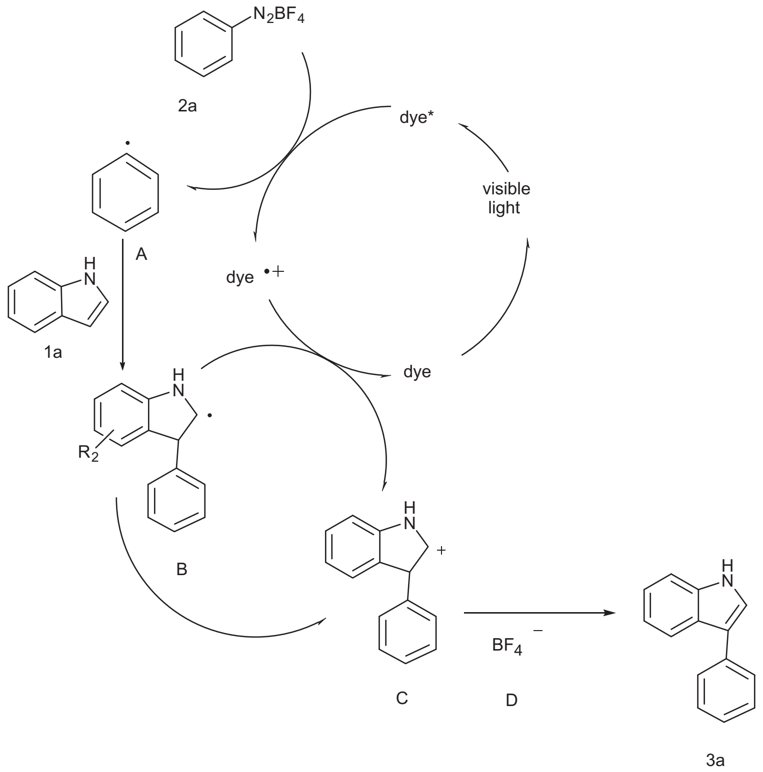
In addition, other organic dyes except Rhodamine B such as eosin Y, Rose Bengal and its sodium salt, and Rhodamine 6G were also successful in accelerating this indole arylation process, albeit with somewhat lower efficiencies (Table 1, entries 12–14).

Based on the optimized conditions, we examined the scope and generality of the indole (**1a**) with diazonium salt (**2a**), various indole derivatives and diazonium salt have been successfully applied in this reaction. The results are listed in Table 2. Electron-donor indole and diazonium salt (Table 2, entries 2–5), were found to be more effective in the formation of the product than electron-acceptor substituted (Table 2, entries 6–14). For *N*-substituted indoles, the corresponding 3-arylindole products were also obtained (Table 2, entries 5 and 15). Moreover, electron-donor indole and electron-acceptor diazonium salt also gained a good 60% yield (Table 2, entry 16). Not surprisingly, for the indole with a naphthyl group diazonium salt, 3-(naphthalen-2-yl)-1*H*-indole (Table 2, entry 17) was formed under identical conditions. In addition, nitro, bromide and chloride were successfully introduced in the photochemical reaction, which is useful for further synthesis elaboration.

In order to better understand the mechanism of this reaction, two kinds of control experiments were performed, and the results are presented in Scheme 2. Preliminary studies have verified this



Scheme 2. Control experiments.



Scheme 3. Plausible reaction mechanism. Dye = Rhodamine B.

hypothesis. As expected, no desired product was obtained when 3-methylindole was subjected to this reaction (Scheme 2a). Reaction was conducted while a widely known radical-scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy(TEMPO) was added led to complete inhibition of the intended reactivity, only a 10% yield of product was obtained (Scheme 2b). Which shows that a radical intermediate involves in this reaction.

Based on the above observations and literature reports a plausible mechanism for this photoreaction is proposed (Scheme 2). Initially, aryl radical **A** is formed from the excited state of Rhodamine B to aryldiazonium salt **2a**. Addition of aryl radical **A** to indole **1a** gives radical intermediate **B**, which is transformed into a carbocation intermediate C by a Possible route oxidation of the radical intermediate **B** by the Rhodamine B radical cation to give **C**. Finally, intermediate **C** is deprotonated, Regeneration systems of aromatic results in the desired coupling product **3a** (Scheme 3).

Conclusions

In summary, we have presented a novel, general synthesis strategy for 3-arylindoles. The procedure was entirely metal free and was carried out at room temperature. This reaction described in this Letter is an efficient and environmentally benign synthesis strategy.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.051.

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