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Communications

Transition-metal-free, visible-light-mediated cyclization of *o*-azidoarylalkynes with aryl diazonium salts

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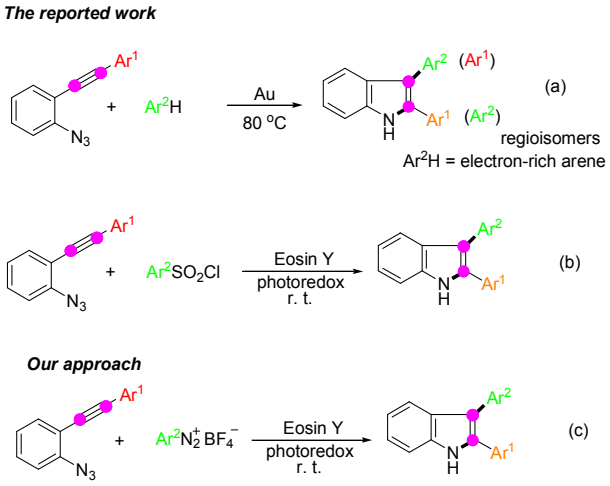
Visible light along with 3 mol% eosin Y catalyzes the cyclization reaction of *o*-azidoarylalkynes with aryl diazonium salts by a photoredox process. We have investigated the scope of the reaction for several aryl diazonium salts and *o*-azidoarylalkynes. The general and easy procedure provides a transition-metal-free alternative for the formation of unsymmetrical 2,3-diaryl-substituted indoles.

The prevalence of the indole ring system that represents a key structural component in natural products and pharmaceutical chemistry is well-established.[1] Moreover, functionalized indoles have also found wide utility as versatile starting materials for the synthesis of a broad range of heterocyclic compounds.[2] For this reason, it is not surprising that since Fischer's pioneering indole synthesis in 1883, numerous methodologies have been reported for the construction and functionalization of the indole skeleton.[3,4] As important members of the indole family, 2,3-disubstituted indole derivatives are core structures in some bioactive natural products. In this regard, there are many reports on the synthesis of 2,3-disubstituted indole derivatives.[5] Generally, the complimentary synthesis of indole derivatives with a predictable 2,3-substitution pattern meets with certain restrictions. For the case of unsymmetrical 2,3-diarylated derivatives, the use of transition-metal catalysis has enabled some elegant solutions to this problem. Recently, Zhang developed a gold-catalyzed annulation of *o*-azidoarylalkynes with electron-rich arenes for the synthesis of unsymmetrical 2,3-disubstituted indoles (Scheme 1a).[6] Very recently, the group of Wan reported a rhodium-catalyzed C-H annulation of nitrones with alkynes for the formation of unsymmetrical 2,3-diaryl-substituted indoles.[7] Despite these advances, current unsymmetrical 2,3-diarylated indole synthesis methodologies face the following problems: (i) the need for stoichiometric amounts of oxidants or transition-metal catalysis, which in stoichiometric quantities, can produce undesirable byproducts; (ii) high reaction temperature.

Aryl diazonium salts, which can be synthesized from commercial available aniline, have proven to be good aryl radical providers. Aryl diazonium salts are prone to undergo a homolytic dediazoniation to provide aryl radicals, and the in situ generated aryl radicals can be trapped by other reactive species to form the desired products. Among many different approaches to aryl radicals, the photoinduced reduction of aryl diazonium salts through electron transfer using photoredox catalysis are particularly attractive.[8] Recently, many examples for radical arylation by photoredox catalysis have been reported.[8c] The group of König developed an efficient visible-light-mediated arylation of heteroarenes, enones, enol acetates, alkenes and alkynes using diazonium salts by photoredox catalysis.[8c] Recently, Gu reported a visible-light-catalyzed synthesis of unsymmetrical 2,3-diarylsubstituted indoles from arylsulfonyl chlorides and *o*-azidoarylalkynes (Scheme 1b).[9] Inspired by these pioneering works and given the importance of unsymmetrical 2,3-diarylated indoles, Herein, we disclose our preliminary results on the visible-light-promoted transformation of aryl diazonium salts and *o*-azidoarylalkynes for the synthesis of unsymmetrical 2,3-diaryl-substituted indoles at room temperature without the requirement of strong acids, strong bases or organometallic reagents. This new method offers rapid access to unsymmetrical 2,3-diaryl-substituted indoles from simple and readily available aryl diazonium salts (Scheme 1c).



Scheme 1 Synthesis of unsymmetrically 2,3-diaryl substituted indoles via cyclization of *o*-azidoarylalkynes.

Our initial investigations began with the reaction of *o*-azidophenylalkyne **1a** with benzenediazonium tetrafluoroborate **2a** in the presence of 3 mol% of photocatalyst and 1,4-cyclohexadiene (1,4-CHD) under visible-light irradiation with blue LEDs (5 W) for reaction optimization. Treatment of *o*-azidophenylalkyne **1a** with benzenediazonium tetrafluoroborate **2a**, 1,4-CHD, eosin Y, and Na_2CO_3 in MeCN at room temperature for 14 h afforded the desired 2,3-diphenyl-1H-indole **3aa** in 33% yield (Table 1, entry 1). Switching the base to K_2HPO_4 resulted in a significant improvement in the yield (Table 1, entries 2-6). Among the solvents evaluated, the best result was achieved when the reaction was conducted in DMSO (Table 1, entries 7-10). It was found that eosin Y was superior to other photocatalysts for this cascade cyclization process (Table 1,

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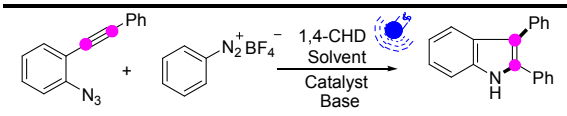
entries 7, 11-13). Reducing the photocatalyst loading to 1 mol% slightly reduced the product yield (Table 1, entry 14). To improve the reaction yield, different hydrogen sources were tested (Table 1, entries 15 and 16). However, no higher yield of **3aa** was observed. The control experiment showed that the reaction could not proceed in the absence of either the photocatalysts or additional visible light (Table 1, entries 17 and 18).

Table 1 Optimization of the Reaction Conditions[a]



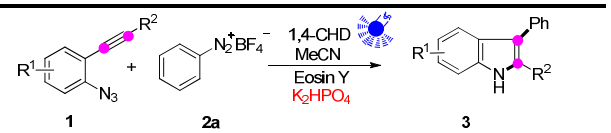
1a 2a 3aa

Entry	Catalyst	Solvent	Base	Yield (%)[b]
1	Eosin Y	MeCN	Na_2CO_3	33
2	Eosin Y	MeCN	$NaHCO_3$	26
3	Eosin Y	MeCN	K_2CO_3	30
4	Eosin Y	MeCN	Na_2HPO_4	47
5	Eosin Y	MeCN	K_2HPO_4	59
6	Eosin Y	MeCN	Et_3N	11
7	Eosin Y	DMSO	K_2HPO_4	77
8	Eosin Y	DMF	K_2HPO_4	34
9	Eosin Y	EtOAc	K_2HPO_4	23
10	Eosin Y	THF	K_2HPO_4	trace
11	Rose Bengal	DMSO	K_2HPO_4	trace
12	$[Ru(bpy)_3Cl_2]$	DMSO	K_2HPO_4	15
13	$[Ir(ppy)_3]$	DMSO	K_2HPO_4	trace
14[c]	Eosin Y	DMSO	K_2HPO_4	68
15[d]	Eosin Y	DMSO	K_2HPO_4	34
16[e]	Eosin Y	DMSO	K_2HPO_4	39
17[f]	Eosin Y	DMSO	K_2HPO_4	0
18	none	DMSO	K_2HPO_4	0

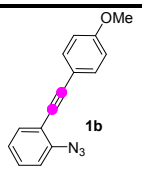
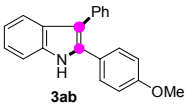
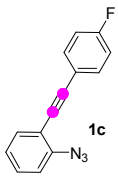
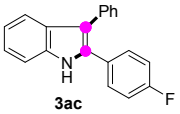
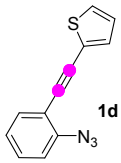
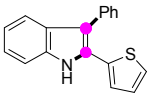
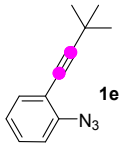
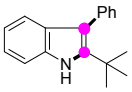
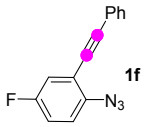
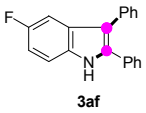
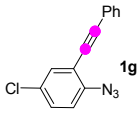
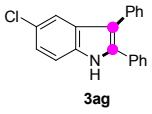
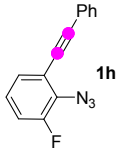
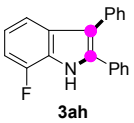
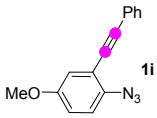
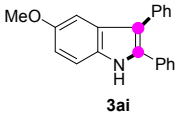
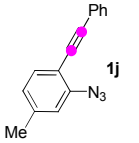
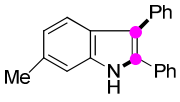
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.35 mmol), base (0.3 mmol), catalyst (3 mol%), solvent (2.0 mL), room temperature, Ar atmosphere, 1,4-CHD (0.45 mmol), 5 W blue LED light (λ_{max} = 455 nm) for 14 h. [b]Isolated yield. [c]eosin Y (1 mol%). [d]Hantzsch ester (0.45 mmol) used instead of 1,4-CHD. [e]Ph_3SiH (0.45 mmol) used instead of 1,4-CHD. [f]Without additional light.

With the optimized conditions in hand, we next investigated the generality of this transition-metal-free cyclization reaction with respect to a range of *o*-azidoarylalkynes **1 (Table 2)**. Interestingly, both electron-donating and electron-withdrawing aromatic substituents were tolerated at the terminal alkyne (**1b** and **1c**). Furthermore, heteroaryl-substituted alkyne **1d** was compatible under the standard conditions, leading to the desired product **3ad** in 59% yield. However, the optimized reaction conditions were not applicable to substrate **1e**, which bears an alkyl group at the terminal alkyne. To highlight the utility of this transformation, representative 2-phenylethynyl arylazides were selected to illustrate the tolerance for substituents on the aryl ring of the 1-(azido)benzene moiety. To our delight, substrates with different substitutions such as fluoro, chloro, methoxy and methyl groups at different positions are well tolerated, providing 54-79% yields.

Table 2 *o*-azidoarylalkynes **1**[a]



1 2a 3

Entry	*o*-Azidoarylalkynes **1**	Product **3**	Yield (%)[b]
1	 **1b**	 **3ab**	80
2	 **1c**	 **3ac**	73
3	 **1d**	 **3ad**	59
4[c]	 **1e**	 **3ae**	0
5[c]	 **1f**	 **3af**	79
6	 **1g**	 **3ag**	72
7	 **1h**	 **3ah**	54
8	 **1i**	 **3ai**	67
9	 **1j**	 **3aj**	70

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.35 mmol), K_2HPO_4 (0.3 mmol), eosin Y (3 mol%), DMSO (2.0 mL), room temperature, Ar atmosphere, 1,4-CHD (0.45 mmol), 5 W blue LED light (λ_{max} = 455 nm) for 14 h. [b]Isolated yield.

The substrate scope was further investigated by reacting *o*-azidophenylalkyne **1a** with different aryldiazonium tetrafluoroborates **2 (Table 3)**. It is noted that the broad availability of substituted aryldiazonium tetrafluoroborates **2** rendered us access to various substituted unsymmetrical 2,3-diaryl-substitued indoles. Notably, halo-substituted aryldiazonium tetrafluoroborates were demonstrated to be well-tolerated under our standard conditions, thereby enabling subsequent modifications at the halogenated positions. We found that aryl diazonium salt bearing CN on the aryl ring could give the desired product in a moderate yield (**3da**). Moreover, aryldiazonium tetrafluoroborates with electron-rich substituents (like Methyl and Methoxyl) on the aromatic rings could proceed smoothly. The substituents at the *ortho*-, *meta*-, or *para*-position

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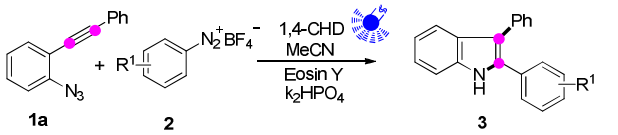
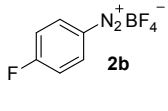
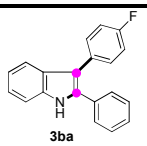
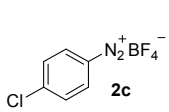
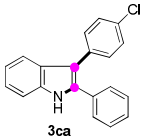
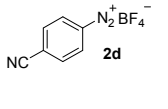
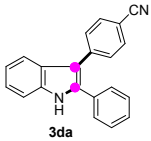
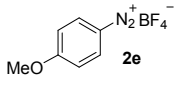
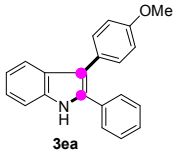
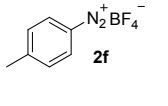
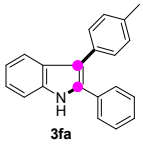
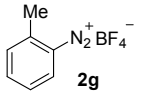
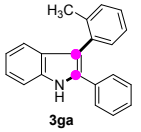
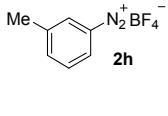
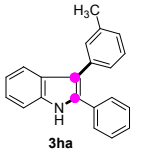
have no distinct influence on the reaction. For example, substrates **2f-2h** with a Methyl group were transformed into products **3fa-3ha** with similar yields.

Table 3 Scope of aryl diazonium salts 2[a]

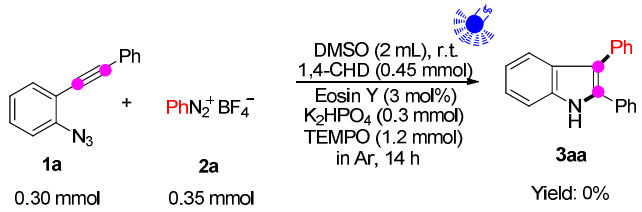


1a 2 3

Entry	Aryl diazonium salts **2**	Product **3**	Yield (%)[b]
1	 **2b**	 **3ba**	70
2	 **2c**	 **3ca**	75
3	 **2d**	 **3da**	49
4	 **2e**	 **3ea**	72
5	 **2f**	 **3fa**	64
6	 **2g**	 **3ga**	60
7	 **2h**	 **3ha**	62

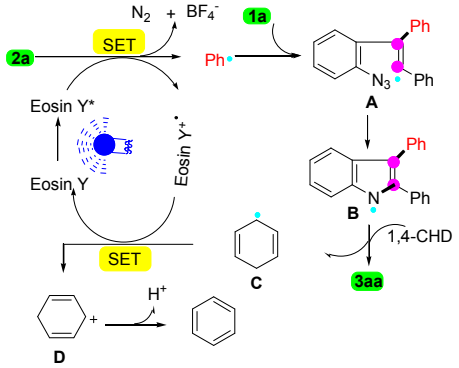
[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.35 mmol), K_2HPO_4 (0.3 mmol), eosin Y (3 mol%), DMSO (2.0 mL), room temperature, Ar atmosphere, 1,4-CHD (0.45 mmol), 5 W blue LED light (λ_{max} = 455 nm) for 14 h. [b]Isolated yield.

To understand the mechanism, the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 4 equiv), was added to the reaction, leading to its inhibition (Scheme 2). These results suggest that a radical process may be involved in this transformation. Furthermore, the product yield dropped precipitously when no photocatalyst was present in the reaction and/or under dark conditions.



Scheme 2 Experiments for mechanistic studies.

Proposed reaction mechanisms based on the above results and previous reports are shown in Scheme 3. Initially, addition of phenyl radical (Ph•), which is generated in situ from benzenediazonium tetrafluoroborate **2a** via the SET reduction, to the carbon-carbon triple bond of the *o*-azidophenylalkyne **1a** gives alkenyl radical intermediate **A**, which cyclizes to form intermediate **B** with extrusion of N_2 gas. H-atom abstraction from 1,4-CHD will form the product **3aa** and generate the radical **C**, which closes the photoredox cycle by SET with [eosin Y]$^{\bullet+}$.



Scheme 3 Plausible Mechanism.

In summary, we have developed a novel transition-metal-free cascade reaction for the synthesis of unsymmetrical 2,3-diaryl-substitued indoles at room temperature from readily available aryldiazonium tetrafluoroborates and *o*-azidoarylalkynes in good yields. These reactions exhibit excellent substrate scope and predictable regioselectivity. The use of inexpensive eosin Y as the catalyst with easy operation makes this protocol very practical. Further investigations on the mechanism of the reaction and its application are ongoing in our laboratory.

Notes and references

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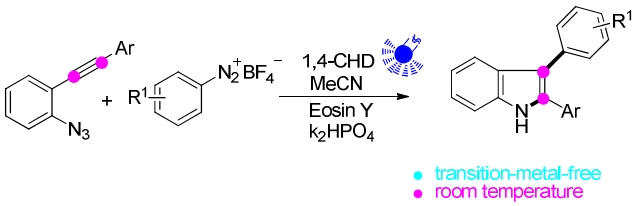

A visible-light promoted transformation of *o*-azidoarylalkynes and aryl diazonium salts for the synthesis of unsymmetrical 2,3-diarylsubstituted indoles under transition-metal-free was described.