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COMMUNICATION

Visible-light-induced cascade dearomatization cyclization between alkynes and indole-derived bromides: a facile strategy to synthesize spiroindolenines

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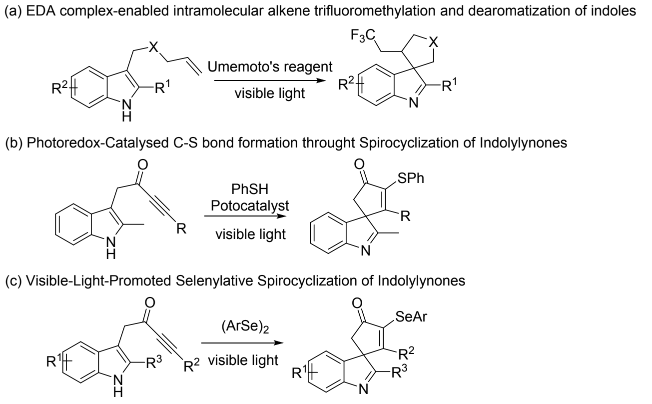
A visible-light-initiated intermolecular dearomatization cyclization cascade reaction between alkynes and indole-derived bromides has been explored. This transformation exhibits a wide substrates scope and significant functional groups tolerance, providing an efficient way to access a variety of spiroindolenines under mild conditions.

Synthesizing spiroindolenines is vital importance in organic and medicinal chemistry since spiroindolenines scaffolds are widely embedded in pharmaceuticals and natural products.[1] Therefore, it is not surprising that many efforts have been devoted to construct such useful skeletons.[2] However, these protocols often suffer from harsh reaction conditions or a limited substrate scope. Hence, the development of practical and green methods for the straightforward construction of these spiroindolenine frameworks is still an urgent and attractive task.

Nowadays, the visible-light-induced catalysis cascade dearomatization cyclization strategy has emerged as a uniquely powerful and straight forward tool for the assembly of novel and complex cyclic molecular architectures from simple precursors under mild reaction conditions.[3-5] However, only a handful of examples on the syntheses of spiroindolenines have been reported via visible-light photoredox catalysis. In 2018, You and coworkers discovered a novel cascade alkene trifluoromethylation and dearomatization of indole derivatives, and mechanistic studies suggested an electron donor-acceptor (EDA) complex formed between indole derivatives and Umemoto's reagent (**Scheme 1a**).[6a] Later, Unsworth's group reported a radical spirocyclization of indolyl-tethered ynones leading to sulfur-containing spiroindolenines under the air condition (**Scheme 1b**).[6b] A similar visible-light-promoted selenylative spirocyclization of indolyl-tethered ynones was subsequently demonstrated by Xu and co-workers (**Scheme 1c**).[6c]


(a) EDA complex-enabled intramolecular alkene trifluoromethylation and dearomatization of indoles

(b) Photoredox-Catalysed C-S bond formation throught Spirocyclization of Indolylynones

(c) Visible-Light-Promoted Selenylative Spirocyclization of Indolylynones

Scheme 1 Photoredox-based synthesis of spiroindolenines

Furthermore, another particularly intriguing transformation is the photocatalytic cascade radical functionalization of aryl alkynes followed by intermolecular cyclization reaction which can easily construct many important heterocycles.[7,8] In 2016, Xiao group has demonstrated a photo-driven intermolecular formal (4+2) cycloaddition for the efficient synthesis of carbazole using alkynes and indole-derived bromides as the substrates (**Scheme 2a**).[8b]

Inspired by these works and our continuous efforts devoted to visible-light-induced dearomatization reactions,[9] we would like to present a visible-light-mediated intermolecular cascade dearomatization cyclization reaction between alkynes and indole-derived bromides, with this strategy, several series of spiroindolenines frameworks could be obtained under facile conditions (**Scheme 2b**).

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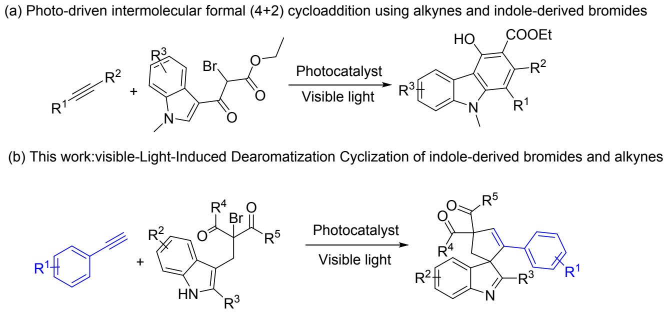
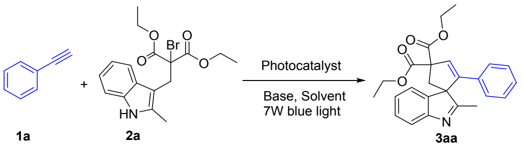


Scheme 2 Photoredox reaction based alkynes and indole-derived bromides.

Table 1 Optimization of the reaction conditions[a]

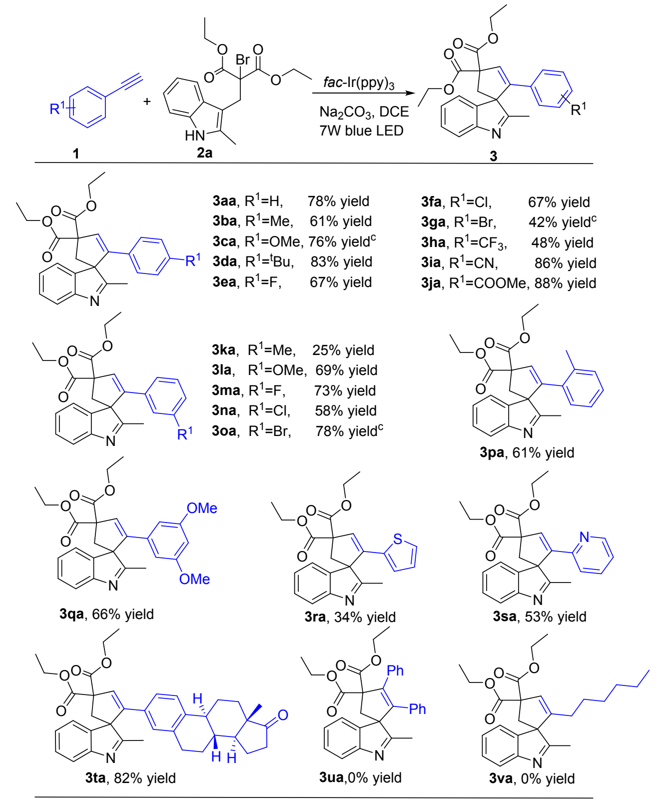


entry	photocatalyst	base	solvent	yield[b]
1	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	74
2	*fac*-Ir(ppy)$_3$	-	CH_3CN	0
3	Ir(ppy)$_2$(dtbpy)PF$_6$	Na_2CO_3	CH_3CN	8
4	Ru(bpy)$_3$Cl$_2$·6H$_2$O	Na_2CO_3	CH_3CN	0
5	Eosin Y	Na_2CO_3	CH_3CN	0
6	*fac*-Ir(ppy)$_3$	Li_2CO_3	CH_3CN	8
7	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3CN	73
8	*fac*-Ir(ppy)$_3$	$NaHCO_3$	CH_3CN	65
9	*fac*-Ir(ppy)$_3$	Na_2HPO_4	CH_3CN	4
10	*fac*-Ir(ppy)$_3$	K_2HPO_4	CH_3CN	65
11	*fac*-Ir(ppy)$_3$	Et_3N	CH_3CN	60
12	*fac*-Ir(ppy)$_3$	2,6-Lutidine	CH_3CN	51
13	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMF	72
14	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMA	64
15	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMSO	57
16	*fac*-Ir(ppy)$_3$	Na_2CO_3	Toluene	52
17	*fac*-Ir(ppy)$_3$	Na_2CO_3	MeOH	0
18	*fac*-Ir(ppy)$_3$	Na_2CO_3	DCM	76
19	*fac*-Ir(ppy)$_3$	Na_2CO_3	DCE	82(78)[c]
20	*fac*-Ir(ppy)$_3$	Na_2CO_3	$CHCl_3$	74
21	*fac*-Ir(ppy)$_3$	Na_2CO_3	THF	63
22	*fac*-Ir(ppy)$_3$	Na_2CO_3	EA	54
23	*fac*-Ir(ppy)$_3$	Na_2CO_3	1,4-dioxane	72
24	none	Na_2CO_3	DCE	0
25[d]	*fac*-Ir(ppy)$_3$	Na_2CO_3	DCE	0

[a] Reaction conditions: **1a** (30.6 mg, 0.3 mmol), **2a** (229.3 mg, 0.6 mmol), base (0.6 mmol), catalyst (0.006 mmol), solvent (3 mL), rt, 24 h, under N_2 atmosphere. [b] Determined by ^{1}H NMR analysis with benzyl ether as an internal standard. [c] The value in parentheses was isolated yield. [d] In the dark.

Initially, we investigated this reaction using phenylacetylene **1a** and indole-derived bromide **2a** as the starting materials with Na_2CO_3 as the base and *fac*-Ir(ppy)$_3$ (2 mol%) as the catalyst. To our delight, the reaction proceeded smoothly after 24 h of irradiation with a 7 W blue LED in CH_3CN at room temperature, affording the desired spiroindolenines **3aa** in 74 % yield (**Table 1**, entry 1). However, no **3aa** was detected when the reaction was performed in the absence of a base, which indicated that the base played a key role for a successful outcome in this transformation. (**Table 1**, entry 2). Encouraged by this result, the reaction conditions were further optimized. Firstly, we screened other photocatalysts such as Ru(bpy)$_3$Cl$_2$•6H$_2$O, Ir(ppy)$_2$(dtbpy)PF$_6$ and Eosin Y, which gave inferior results (**Table 1**, entries 3–5). To further improve the reaction efficiency, many inorganic and organic bases were subsequently screened, but none of the other bases gave a higher yield than Na_2CO_3 (**Table 1**, entries 6–12). Considering that the identity of solvents sometimes play a key role in photoredox catalysis, we further screened many commonly solvents (**Table 1**, entries 13–23). To our delight, when DCE replaced CH_3CN as the solvent, the yield of the desired product **3aa** increased to 82%. Control experiments suggested that photocatalyst and visible light irradiation are indispensable to this transformation (**Table 1**, entries 24 and 25).

Scheme 3 Substrates scope of alkynes.[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (229.3 mg, 0.6 mmol), Na_2CO_3 (63.6 mg, 0.6 mmol), *fac*-Ir(ppy)$_3$ (3.9 mg, 0.006mmol), DCE (3 mL), irradiation with a 7W blue LED light, rt, 24 h. [b] Isolated yields. [c] Irradiation with a 7 W blue LED for 48 h.

With the optimized cyclization reaction conditions in hand, the substrate scope of this reaction was investigated (**Scheme 3**). Firstly, different substituent groups on the aryl alkynes were examined. Gratifyingly, both electron-donating group (*e.g.*, Me, OMe, ^{t}Bu) and electron-withdrawing group (*e.g.*, CF_3, CN, COOMe) substituents at the *para* position of aryl alkynes proceeded efficiently to afford the spiroindolenines **3aa-3ja** in moderate to excellent yields. Notably, synthetically attractive

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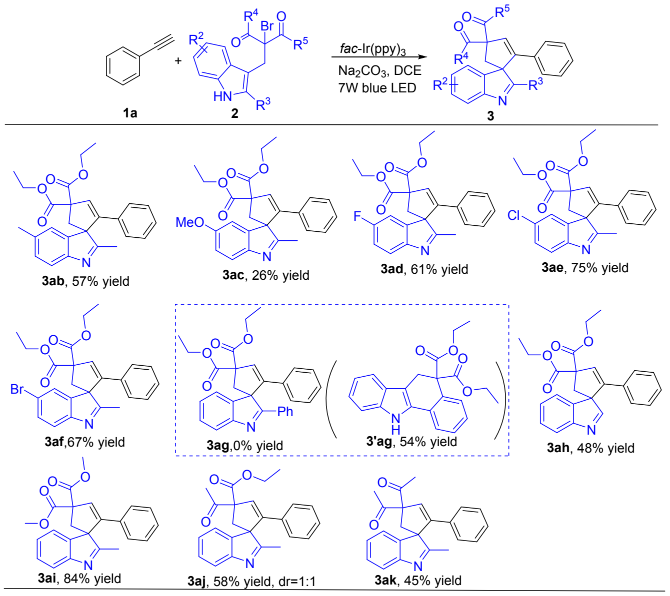
groups (F, Cl, Br) in substrates were also tolerated in this reaction providing the products **3ea-3ga** in moderate to good yields. Subsequently, for a *meta*-substituent aryl alkynes also underwent cyclization smoothly to give spiroindolenines **3ka-3oa**. Nevertheless, the *meta*-Me-substituent aryl alkynes was obtained corresponding product **3ka** in only 25% yield. Other substituents such as *ortho*-Me and 3,5-di-OMe on aryl alkynes could also delivered the desired products **3pa** and **3qa** in satisfactory yields. In addition, heteroaryl thiophene and pyridine-based acetylenes were well tolerated with this mild system affording the spiroindolenines **3ra** and **3sa** in 34% and 53% yield, respectively. Remarkably, the aryl alkyne with a natural product estrone steroid skeleton was also amenable to this reaction under the standard conditions giving the corresponding product **3ta** in 82% yield, which may be applied in the late-stage functionalization of a bioactive molecule. Unfortunately, for the substrate internal alkynes diphenyl acetylene **1u** or aliphatic alkyne 1-octyne **1v** failed to give the target compound, and starting material **1u** and **1v** was recovered.

Scheme 4 Substrates scope of indole-derived bromide.[a,b]

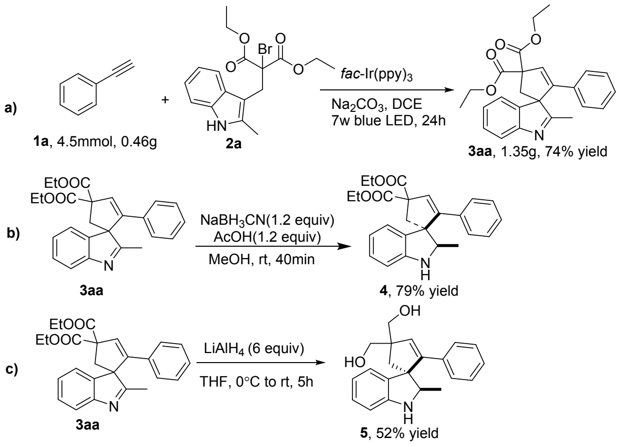


[a] Reaction conditions: **1a** (30.6 mg, 0.3 mmol), **2** (0.6 mmol), Na_2CO_3 (63.6 mg, 0.6 mmol), *fac*-Ir(ppy)$_3$ (3.9 mg, 0.006 mmol), DCE (3 mL), irradiation with a 7W blue LED light, rt, 24 h. [b] Isolated yield.

To further expand the substrate scope of this transformation, we then examined the substituents on the indole-derived bromides (**Scheme 4**). A range of C5-substituted on indoles also showed good applicability for this reaction affording their corresponding dearomatized products in moderate yields (**3ab-3af**). However, somewhat lower yield was obtained with the 5-OMe-indole derived bromide **2c**. When indoles C2 position bearing phenyl group, we only got **2g** direct cyclization byproduct **3ag′** in 54% yield. In addition, when indoles C2 position bearing hydrogen moiety was also achieved desired spiroindolenines **3ah** in 48% yield. Moreover, dimethyl malonate indole-derived bromide **2i** was also applicable to this system, delivering the desired product **3ai** in 84% yield. Finally, other bromocarbonyl indoles, such as keto esters **2j** or diketones **2k**, were also effective in this transformation affording the spiroindolenines **3aj** and **3ak** in 58% and 45% yield, respectively.

When we scaled the reaction of **1a** in a 4.5 mmol with **2a**, to our delight, the reaction proceeded smoothly delivering product **3aa** in 74% yield, which highlights practicality of this method (**Scheme 5a**). In addtion, several transformations based on spiroindolenine **3aa** were carried out. Spirocycle **4** could be obtained in 79% yield as a single diastereoisomer through the reduction of the imine moiety of **3aa** in the presence of $NaBH_3CN$ and AcOH (**Scheme 5b**). Moreover, the product **3aa** could be readily converted to spirocycle diol compound **5** in 54% yield using $LiAlH_4$ as reducing agent (**Scheme 5c**).

Scheme 5. Gram-scale reaction and transformations of product **3aa**



To gain additional mechanistic insights, 3 equiv. of TEMPO relative to **1a** was added to the reaction system, no desired product **3aa** was observed, indicating that a radical process is probably involved in this reaction. The Stern-Volmer analysis revealed that the photoluminescence of *fac*-Ir(ppy)$_3$ was quenched by indole-derived bromides **2a** in DCE at room temperature (see SI). Meanwhile, we also ruled out the radical-chain propagation mechanism based on the light on/off experiments (see SI).

On the basis of experimental observations and previous literature reports,[9] a plausible mechanism was proposed for this transformation (**Scheme 6**). Initially, Ir(III) photocatalyst was excited to generate the excited species Ir(III)* under blue light irradiation, which underwent single electron transfer (SET) process with indole-derived bromide **2a** generate radical **A** and Ir(IV) metal complex. Subsequently, radical **A** underwent a rapid addition with phenylacetylene **1a** afforded radical intermediate **B**, followed by intramolecular cyclization lead to radical intermediate **C**, which was further oxidized through SET process to give key carbocation **D** and regenerated Ir(III) photocatalyst.[5d-5f] Finally, deprotonation of intermediate **D** under basic condition gave the desired product **3aa**.

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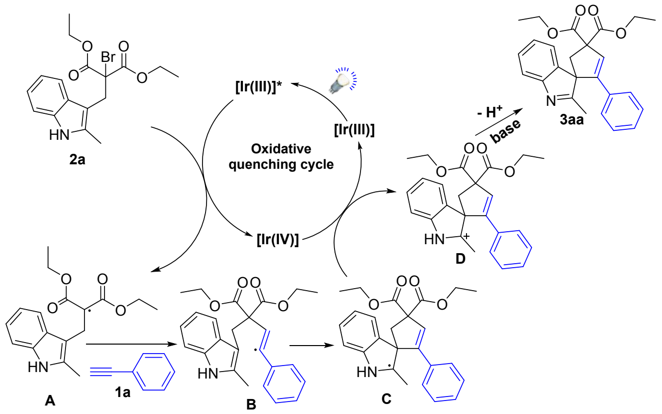
Scheme 6 Postulated cyclization reaction mechanism.



In summary, we have disclosed an operationally convenient visible-light photocatalytic intermolecular dearomatization cyclization cascade reaction between indole-derived bromides and alkynes, which cyclization process features a broad substrate scope and high reaction efficiency. This protocol also presents a mild and efficient way to furnish a variety of spiroindolenines.

Conflicts of interest

There are no conflicts to declare.

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