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A visible light promoted cascade cyclization reaction *via* a PCET process: easy access to indolinone-fused polycycles

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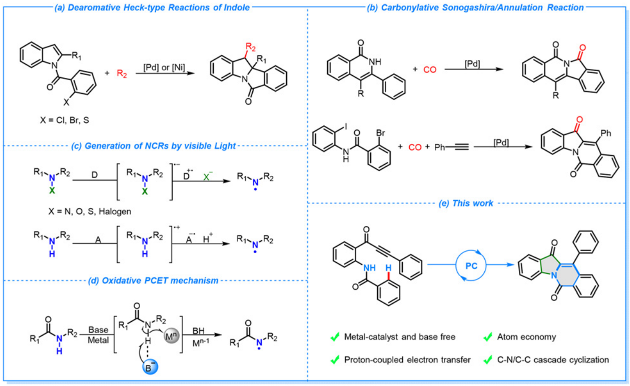
An efficient protocol for the synthesis of indolinone-fused polycycles initiated by nitrogen-centered radicals (NCRs) has been developed. The amide radical was generated by proton-coupled electron transfer (PCET) under visible light. A series of indole[1,2-*b*] isoquinolinones were synthesized in up to 99% yield in "one-pot" construction of C–N/C–C bonds through cascade cyclization. This protocol features excellent step and atom economy, obviating the use of transition metals and Brønsted bases, offering a mild and efficient photochemical pathway to synthesize polycyclic indolinones.

Green foundation

1. We disclose a step- and atom-economic protocol for the rapid synthesis of indolinone-fused polycycles through a PCET process under Brønsted base- and translation metal-free conditions, forming C–N and C–C bonds in one pot.
2. This sustainable approach employs a cheap acridine photosensitizer as the electron transfer reagent and molecular oxygen in the air as a clean oxidant and produces water as the sole by-product, in which the atomic utilization rate is up to 98%.
3. Further development of radical cascade cyclization strategies based on the Brønsted base-free PCET mechanism, such as those involving sulfur-centered radicals and carbon-centered radicals, may be beneficial for expanding the application of the PCET mechanism in organic synthesis.

Indolinone-fused polycycles are essential nitrogen-containing heterocyclic compounds with broad-spectrum biological and pharmacological activities.[1–7] Therefore, building this framework has drawn great attention from organic chemists.[8] Transition metal-catalyzed dearomatizing Heck-type reactions of indoles[9–14] (Scheme 1a) and carbonylative Sonogashira/annulation reactions[15,16] (Scheme 1b) are recognized as elegant methods for constructing such a skeleton. However, the requirement of transition metals and pre-activated starting materials results in poor atomic economy and potential environmental concerns. Recently, visible light-promoted radical processes have been rapidly developed in organic chemistry.[17–19] Among them, the formation of nitrogen-centered radicals (NCRs) has emerged as a powerful approach for constructing nitrogen-containing heterocycles.[20–22] Currently, producing NCRs mainly relies on single-electron reduction. This process requires the cleavage of the N–X bond through transferring a single electron from a donor orbital to the N–X (X = N, O, or halogen) σ*-acceptor orbital.[23,24] From the perspective of atom and step economy, the direct cleavage of the N–H bond to form NCRs is the most ideal approach. However,



Scheme 1 Construction of an indolinone-fused polycyclic skeleton and generation of NCRs.

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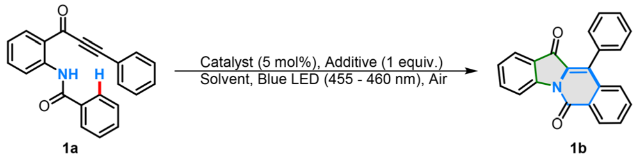
strong stoichiometric oxidants or bases as proton acceptors are necessary due to the high bond-dissociation free energy (BDFE) of the N–H bond (typically >100 kcal mol^{-1}) (Scheme 1c).[25–28]

Inspired by proton-coupled electron transfer (PCET) in biological redox processes, Knowles' group first synthesized azacyclic compounds through oxidative PCET (Scheme 1d).[29,30] The amide radical could be generated directly from readily available amides using a catalytic amount of metal–Brønsted base combination. Subsequently, a series of cyclization and functionalization reactions based on the PCET pathway were reported,[31–37] providing an environmentally friendly approach for the synthesis of functionalized molecules. Recently, Zhang reported the direct PCET reduction of dioxygen *via* weak interactions between electron donors and proton donors, thereby confirming molecular oxygen as the potential electron and proton acceptor in this process.[38] We envisioned that oxygen could be used as a clean oxidant to oxidize the quenched photocatalyst; subsequently, the generated superoxide radical could act as a proton acceptor to cleave the N–H bond and produce NCRs through a Brønsted base-free PCET process. Continuing our interest in green synthesis of heterocycles,[39–46] herein, we describe a mild and efficient PCET process for generating NCRs (Scheme 1e). The amide nitrogen radical was generated through stepwise electron transfer, followed by a proton transfer (ETPT) process in the absence of transition metals and Brønsted bases, using visible light as the sole energy source,[47–49] and then constructing C–N and C–C bonds in a "one pot" manner to synthesize 6/5/6/6 fused indolinones.

At the beginning of the investigation, *N*-(2-(3-phenylpropioloyl)phenyl)benzamide **1a** was selected as the substrate to optimize the reaction conditions. The desired product **1b** was obtained in 35% yield in the presence of 5 mol% Mes–Acr–BF$_4$ as the photocatalyst and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as the additive in acetonitrile under the irradiation of a blue LED (455–460 nm) and an air atmosphere for 3 hours (Table 1, entry 1). When Mes–Acr–BF$_4$ was replaced with Mes–Acr–ClO$_4$, the yield of **1b** increased to 58% (Table 1, entry 2). However, increasing the loading of TEMPO dramatically reduced the formation of **1b** (Table 1, entry 3). K$_2$S$_2$O$_8$ was used as the additive, yielding better results than those of Na$_2$S$_2$O$_8$ and (NH$_4$)$_2$S$_2$O$_8$ (Table 1, entries 4–6). To our delight, the yield of **1b** could reach 80% without any additive (Table 1, entry 7). Control experiments confirmed that both visible light and photocatalysts were essential (Table 1, entries 8 and 9). The yield of the product slightly decreased under oxygen (Table 1, entry 10). This transformation was blocked under the protection of N$_2$ (Table 1, entry 11). During the optimization of the reaction medium (Table 1, entries 12–18), it was found that protic solvents (MeOH and EtOH, Table 1, entries 15 and 16) were more favorable compared to other solvents, such as acetonitrile (CH$_3$CN), 1,4-dioxane, dimethyl sulfoxide (DMSO), and ethyl acetate (EA) (Table 1, entries 7 and 12–14). Since substrate **1a** was poorly soluble in alcohol, leading to incomplete conversion, a mixture of methanol with ethyl acetate or acetonitrile was used as the reaction medium. In the EA : MeOH (1 : 1) mixture, a satisfactory yield of 98% was achieved (Table 1, entry 17).

Table 1 Optimization of the reaction conditions[a]

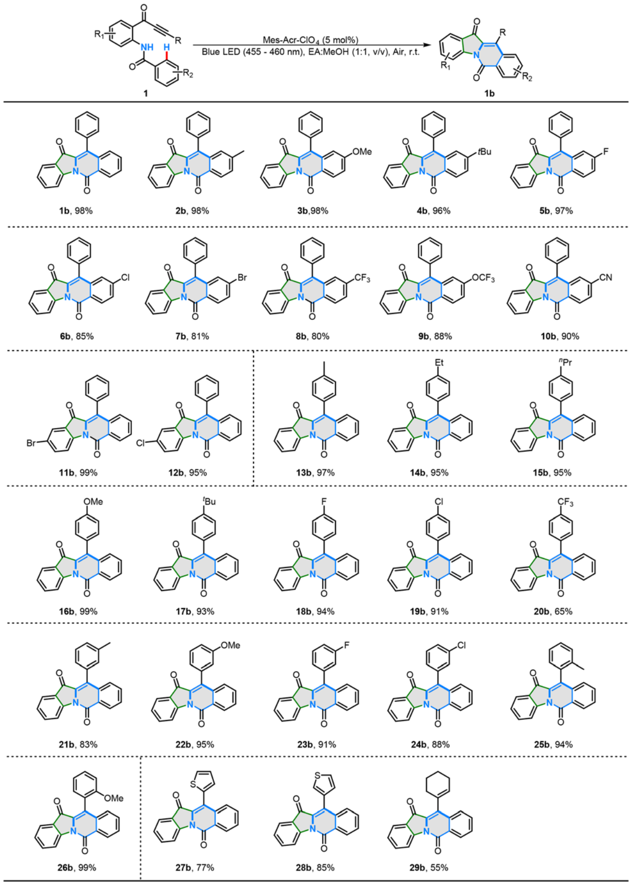


Entry	Pc.	Additive	Solvent	Yield[b] (%)
1[c]	Pc 1	TEMPO	CH$_3$CN	35
2[c]	Pc 2	TEMPO	CH$_3$CN	58
3	Pc 2	TEMPO	CH$_3$CN	Trace
4	Pc 2	Na$_2$S$_2$O$_8$	CH$_3$CN	71
5	Pc 2	K$_2$S$_2$O$_8$	CH$_3$CN	78
6	Pc 2	(NH$_4$)$_2$S$_2$O$_8$	CH$_3$CN	63
7	Pc 2	—	CH$_3$CN	80
8	—	K$_2$S$_2$O$_8$	CH$_3$CN	NR
9[d]	Pc 2	K$_2$S$_2$O$_8$	CH$_3$CN	NR
10[e]	Pc 2	—	CH$_3$CN	78
11[f]	Pc 2	—	CH$_3$CN	NR
12	Pc 2	—	1,4-Dioxane	58
13	Pc 2	—	DMSO	72
14	Pc 2	—	EA	81
15	Pc 2	—	MeOH	91
16	Pc 2	—	EtOH	90
17	Pc 2	—	EA/MeOH (1 : 1, v/v)	98
18	Pc 2	—	CH$_3$CN/MeOH (1 : 1, v/v)	91

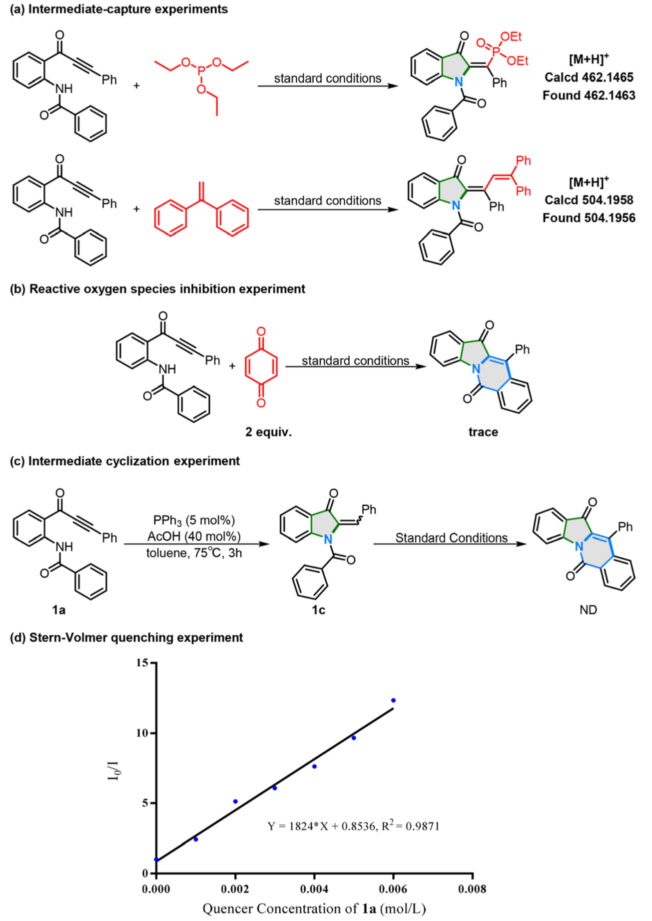
[a] Reaction conditions: **1a** (0.1 mmol), Pc. (photocatalyst, 5 mol%), additive (0.1 mmol, 1 equiv.), solvent (2.0 mL), 10 W blue LED (455–460 nm), air, rt, and 3 h. [b] Isolated yield. [c] Additive (0.02 mmol, 20 mol%). [d] Dark. [e] O$_2$. [f] N$_2$. Pc 1 = Mes–Acr–BF$_4$ and Pc 2 = Mes–Acr–ClO$_4$.

With the optimized reaction conditions in hand (Table 1, entry 17), the applicability of the photocatalytic cascade cyclization was explored. The electron-donating groups (–Me, –OMe, and –^{t}Bu) at the *para*-position of the C–benzene ring in amides yielded the corresponding fused indolinones (**2b–4b**) in excellent yields (>96%). Substrates with halogen atoms (–F, –Cl, and –Br) at the *para*-position smoothly underwent cyclization reactions, resulting in good to excellent yields (**5b–7b**, 81–97%). Introducing electron-withdrawing groups, such as –CF$_3$, –OCF$_3$, and –CN, at the *para*-position also resulted in corresponding products in good to excellent yields (**8b–10b**, 80–97%). When –Cl and –Br were introduced at the *para*-position of the *N*-phenyl group, the cyclized products (**11b–12b**) were obtained in excellent yields of 95% and 99%, respectively, possibly because the conjugated effect of the *N*-aromatic ring stabilized the NCR. The obtained results suggested that this mild photocatalytic cascade annulation was compatible with various valuable functional groups, including –F, –Cl, and –Br, showcasing potential late-stage modifications (Scheme 2).

Then, the impact of substituted ynones on the reaction was further explored. Gratifyingly, both electron-rich groups (Me, OMe, ^{t}Bu, Et, and ^{n}Pr) and halogens (F and Cl) at the *para*-position of the benzene ring yielded the corresponding products in excellent yields (**13b–19b**, 91–99%). A strong



Scheme 2 Scope of the substrates. Reaction conditions: **1** (0.1 mmol), photocatalyst (5 mol%), solvent (2.0 mL), 10 W blue LED (455–460 nm), under air, r.t., and 3 h.

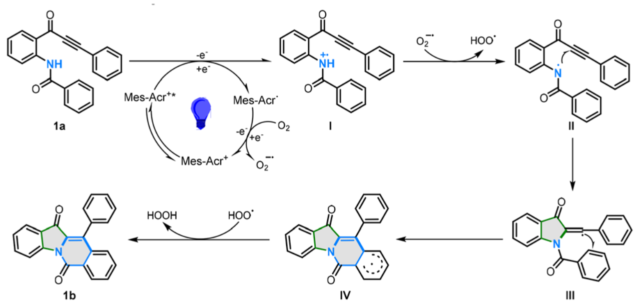


Scheme 3 Reaction mechanistic studies.

electron-withdrawing group (–CF$_3$) was also suitable (**20b**, 65%). Introducing groups at the *meta*- and *ortho*-positions minimally impacted the reaction. Groups such as –Me, –OMe, –F and –Cl at the *meta*-position, and –Me and –OMe at the *ortho*-position, led to efficient cascade cyclization affording good to excellent yields (**21b–26b**, 83–99%). The 2-thiophene- and 3-thiophene-substituted alkynones were then investigated. The corresponding cyclization products **27b** and **28b** were afforded in 77% and 85% yields, respectively. The cascade cyclization product was obtained in moderate yield from an alkenyl-substituted alkynone (**29b**, 55%), potentially due to the lower stability of alkenyl-substituted vinyl radicals.

To clarify the reaction process, intermediate-capture experiments were conducted. Based on the optimization of the reaction conditions (Table 1, entry 3), the presence of TEMPO (1 equiv.) under standard conditions significantly inhibited the reaction, suggesting that a radical process might be involved in this reaction. The addition of 2 equiv. of benzoquinone (BQ) as a superoxide radical quencher also well blocked the reaction (Scheme 3b), indicating the essential role of the superoxide radical. Under the standard conditions, equal amounts of free radical scavengers were reacted with the substrates (Scheme 3a). Triethyl phosphate-[50] and 1,1-diphenylethylene-captured vinyl carbon radical species were detected by high-resolution mass spectrometry (HRMS). To verify the cyclization process, substrate **1a** was subjected to PPh$_3$-catalyzed cyclization, yielding indole ketone **1c**. The product **1b** was not detected under the standard reaction conditions starting from indole ketone **1c** (Scheme 3c), indicating that this photocatalytic cyclization might proceed *via* a cascade rather than a tandem cyclization mechanism.[50,51] A Stern–Volmer quenching study demonstrated that the fluorescence intensity of the photocatalyst was effectively quenched by **1a** (Scheme 3d). Moreover, the generation of hydrogen peroxide during the reaction was confirmed using hydrogen peroxide test strips (see the SI).

Based on the results from the mechanism experiments, a possible reaction mechanism was proposed (Scheme 4). First, the acridinium salt was converted into an excited state under light irradiation and then quenched by substrate **1a** as an electron transfer agent to form a cationic intermediate **I**. The quenched catalyst returned to the ground state by electron transfer with molecular oxygen from air, thereby completing the catalytic cycle and generating superoxide anion radicals. **I** underwent hydrogen atom transfer (HAT) with the superoxide



Scheme 4 Proposed mechanism.

anion to form a peroxide radical and amide nitrogen radical **II**. The subsequent 5-*exo*-dig cyclization of **II** afforded vinyl radical **III**, which then electrophilically attacked the benzene ring to form the intermediate **IV**. Intermediate **IV** further underwent HAT with the peroxide radical, ultimately resulting in the formation of hydrogen peroxide and phenylindole[1,2-*b*] isoquinolinone **1b**.

Conclusions

In summary, we have developed a mild, stepwise PCET process for synthesizing 6/5/6/6 fused indolinones. Mes–Acr–ClO_4 was engaged in the electron transfer with the substrate, while the N–H bond was cleaved by the reactive oxygen species *in situ* generated under visible light. This atom economic transformation occurs at room temperature, avoiding the use of transition metals and Brønsted bases. The C–N/C–C bonds were constructed in one pot *via* a cascade cyclization reaction initiated by a nitrogen-centered free radical.

Author contributions

C.-X. L. conceived the project. H.-Y. X. designed and performed the experiments and drafted the first version of the manuscript. C. J. and Z. H. prepared some starting materials. C.-X. L. administered the project and revised the manuscript. All authors have discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its online SI: experimental details, spectral data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: https://doi.org/10.1039/d5gc03208c.

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