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Photoredox-catalyzed cascade [2 + 2 + 1] cyclization of 1,6-enynes with thiols†

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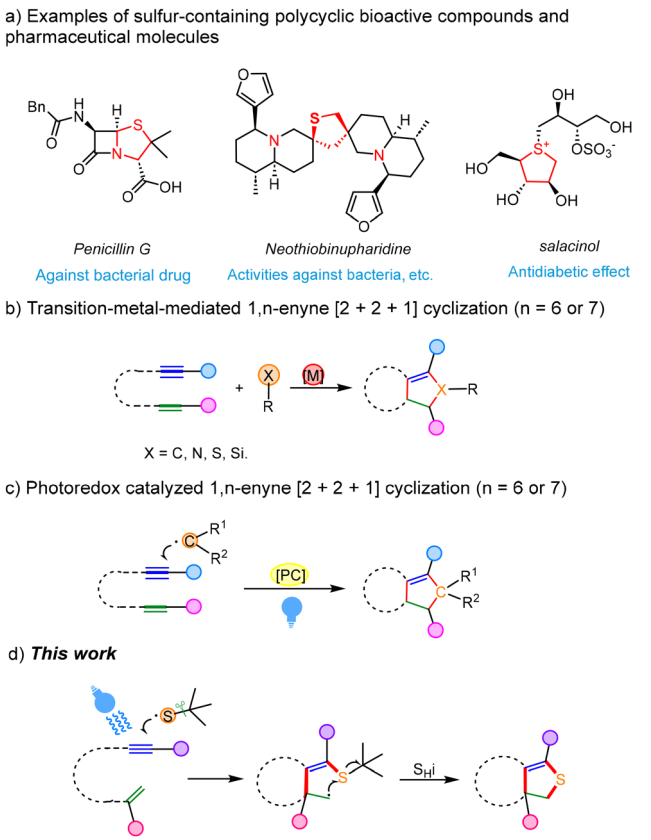
Here, we report a visible-light-mediated [2 + 2 + 1] cascade cyclization of 1,6-enynes with thiols, providing a new synthetic protocol for the rapid construction of sulfur-containing polycyclic derivatives in moderate to good yields along with a broad substrate scope. Mechanistic investigations were also performed through control experiments and Stern–Volmer analysis as well as DFT calculations, suggesting that this cascade cyclization reaction stems from a sulfur radical addition to the alkynyl moiety of 1,6-enyne along with a cascade cyclization with the alkenyl unit. Then, the formation of sulfur-containing polycyclic molecules can be achieved by homolytic S_Hi-type substitution at the thioether unit, stripping away a sulfur atom. Further transformations of the obtained product have also been disclosed.

Introduction

Five- and six-membered heterocyclic rings are key fragments that can be found in numerous compounds of natural sources, presenting potent biological activities.[1] In particular, a number of sulfur-containing heterocyclic natural products, such as penicillin, neothiobinupharidine, and salacinol, have been applied as anticancer, antibacterial and antidiabetic drugs (Scheme 1a).[1b,2] However, obtaining sufficient amounts of sulfur-containing natural products from natural sources for biomedical studies remains a considerable challenge. Considering the above factors, the design and synthesis of sulfur-containing polycyclic compounds have attracted great interest in recent years.[3]

The synthesis of complex polycyclic molecules has always been a momentous research subject in synthetic chemistry, especially the preparation of multiple cyclic systems in one step.[4] One of the common synthetic strategies for constructing these structures is the [2 + 2 + *m*] annulation of 1,*n*-enynes (*n* = 6 or 7) with various *m*-atom units to form complex polycyclic compounds with high atom and step economy.[5] Over the past decades, numerous [2 + 2 + 1] cascade annulations have been reported with transition-metal catalysis[6] (Scheme 1b) or photoinduced catalysis[7] (Scheme 1c). On the basis of transition-



Scheme 1 Sulfur-containing cyclic compounds, previous work and this work.

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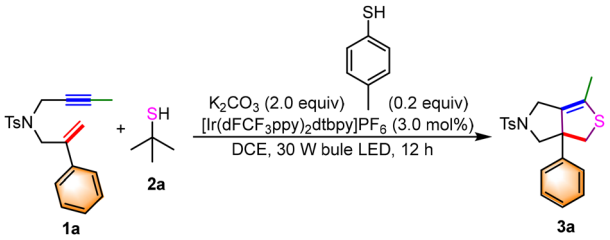
metal catalysis, 1,*n*-enynes (*n* = 6 or 7) can be used as feedstock materials to accept the addition of X-atom units, affording five- or six-membered ring fused polycyclic molecules. For example, the [2 + 2 + 1] cyclization reaction between 1,*n*-enynes and C-atom units can use CO as a C-atom reagent under transition metal catalysis (Paulson Handel type cyclization reaction), delivering the desired polycyclic products in good yields (Scheme 1b).[6b] Other functional groups can also be utilized as C-atom units in [2 + 2 + 1] cyclization, such as alkanes,[6c] arenes,[6d] and imines.[6e] However, it is more difficult for heteroatom units to undergo such [2 + 2 + 1] cyclization with 1,*n*-enynes than for C-atom units (Scheme 1b). Only three heteroatoms such as N,[6g] S,[6h] and Si[6k] have been developed for the synthesis of heterocyclic compounds through [2 + 2 + 1] cyclization with 1,*n*-enynes under transition-metal catalysis with limited examples thus far (Scheme 1b). On the other hand, radical species can also be utilized to synthesize complex polycyclic molecules through [2 + 2 + 1] cyclization with 1,*n*-enynes. For instance, the cascade addition of carbon-centered radicals generated from fluoroalkanes[7d] or other alkyl radical precursors[7] upon photoredox catalysis to 1,6-enyne can afford polycyclic compounds under mild conditions (Scheme 1c). Nevertheless, the synthesis of sulfur-containing polycyclic compounds *via* visible-light mediated [2 + 2 + 1] heterocyclization with 1,*n*-enynes has never been reported before.

It has been well known that radical species allow the formation of cyclic structures *via* the cyclization of a radical species onto an unsaturated partner (*e.g.* alkene, alkyne, or arene).[8] In addition, the formation of sulfur-containing heterocycles can be achieved by homolytic substitution at the sulfur atom.[9] Inspired by these findings, we attempted to utilize *tert*-butylthiol **2a** as a sulfur radical precursor for the reaction with 1,6-enynes **1** to realize a cascade [2 + 2 + 1] heterocyclization *via* photoredox catalysis under mild conditions (Scheme 1d).

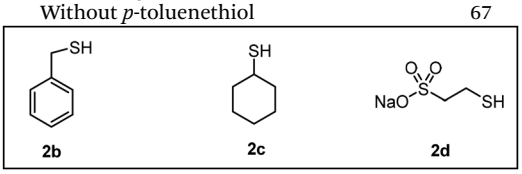
Results and discussion

We first utilized substrate **1a** as the model substrate for the initial investigation and subsequently optimized the reaction conditions. The results are shown in Table 1. After several initial experimental examinations, the optimal reaction conditions are identified as follows: 1,6-enyne **1a** (0.1 mmol, 1.0 equiv.) is used as the substrate, *tert*-butylthiol **2a** (0.2 mmol, 2.0 equiv.) is employed as a reagent, K_2CO_3 (0.2 mmol, 2.0 equiv.) is used as a base, *p*-toluenethiol is employed as an additive and Ir[(dFCF$_3$ppy)$_2$(dtbpy)]PF$_6$ is utilized as a photosensitizer in dichloroethane (DCE) (5.0 mL) and irradiated with a 30 W blue LED for 12 h, affording the desired product **3a** in 97% NMR yield and 95% isolated yield (Table 1, entry 1). In addition, other photosensitizers such as *fac*-Ir(ppy)$_3$ and Ir(dtbpy)ppy$_2$ gave **3a** in low and moderate yields of 15% and 50%, respectively (entries 2 and 3) (see Table S2 in the ESI† for more information). Moreover, attempting to improve the yield, we evaluated other bases including Cs_2CO_3, NEt_3, and Na_2CO_3, but none of them performed better than K_2CO_3 (entries 4–6)

Table 1 Optimization of the reaction conditions[a,b]



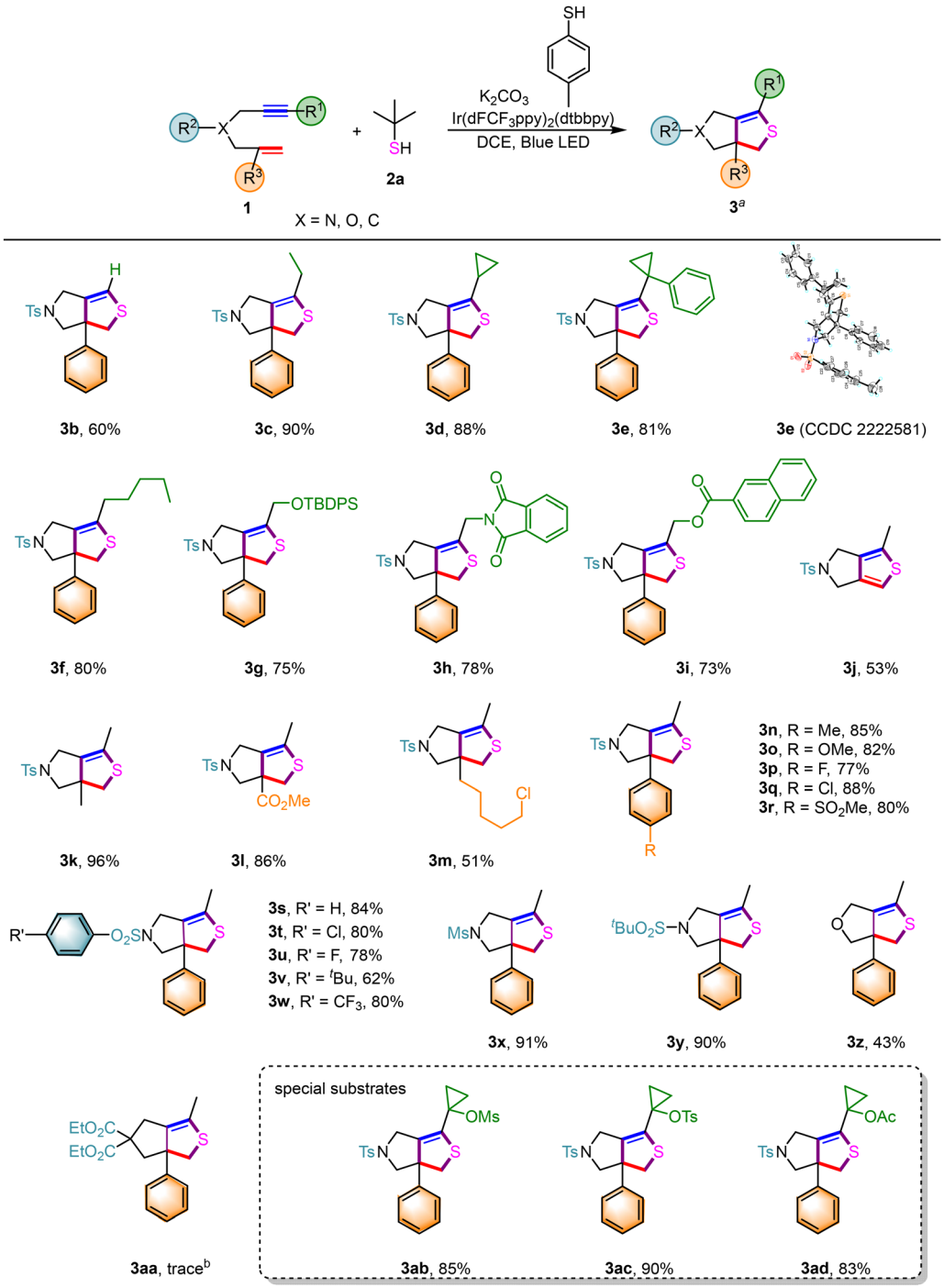
Entry	Variation from the standard conditions	**3a**, yield[b] [%]
1	None	97 (95)[c]
2	fac-Ir(ppy)$_3$ as PC	15
3	Ir(dtbpy)ppy$_2$ as PC	50
4	Cs_2CO_3 instead of K_2CO_3	72
5	NEt_3 instead of K_2CO_3	0
6	Na_2CO_3 instead of K_2CO_3	77
7	DCM instead of OGE	58
8	MeCN instead of OGE	60
9	1.0 ml OGE instead of 5.0 ml OGE	59
10	**2b** instead of **2a**	43
11	**2c** instead of **2a**	66
12	**2d** instead of **2a**	10
13	Without base	40
14	Without light or PC	0
15	Without *p*-toluenethiol	67



[a] Reaction was carried out with **1a** (0.1 mmol), **2a** (2.0 equiv.), K_2CO_3 (2.0 equiv.), *p*-toluenethiol (0.2 equiv.), [Ir(dFCF$_3$ppy)$_2$(dtbpy)]PF$_6$ (3.0 mol%) in DCE (5.0 mL) at ambient temperature under 30 W blue LED irradiation. [b] ^{1}H NMR yield using dimethyl terephthalate as an internal standard. [c] Isolated yield.

(see Table S4 in the ESI† for more information). We further examined solvent effects on this photochemical transformation and found that the use of other solvents, such as DCM and MeCN, afforded **3a** in moderate yields ranging from 58% to 60%, demonstrating that the best solvent for the reaction was DCE (entries 7 and 8) (see Table S3 in the ESI† for more information). When the solvent volume was changed to 1.0 mL, the yield of **3a** decreased to 59% (entry 9). Benzylthiol **2b**, cyclohexylthiol **2c** and mesna **2d** could also be used as the sulfur radical precursor to react with **1a**, affording the desired product in 43%, 66% and 10% yields, respectively (Table 1, entries 10–12). Furthermore, the control experiments revealed that base, *p*-toluenethiol, photosensitizer, and light were essential for this reaction (entries 13–15) (see Table S5 in the ESI† for more information).

With the reaction conditions optimized, we explored the generality of this cascade annulation reaction, and the results are summarized in Scheme 2. It was found that most of the substrates successfully underwent these reactions smoothly, providing the desired products in moderate to good yields. Substrate **1b** having a terminal alkyne unit (R^1 = H) was tolerated in this reaction, delivering the corresponding product **3b**

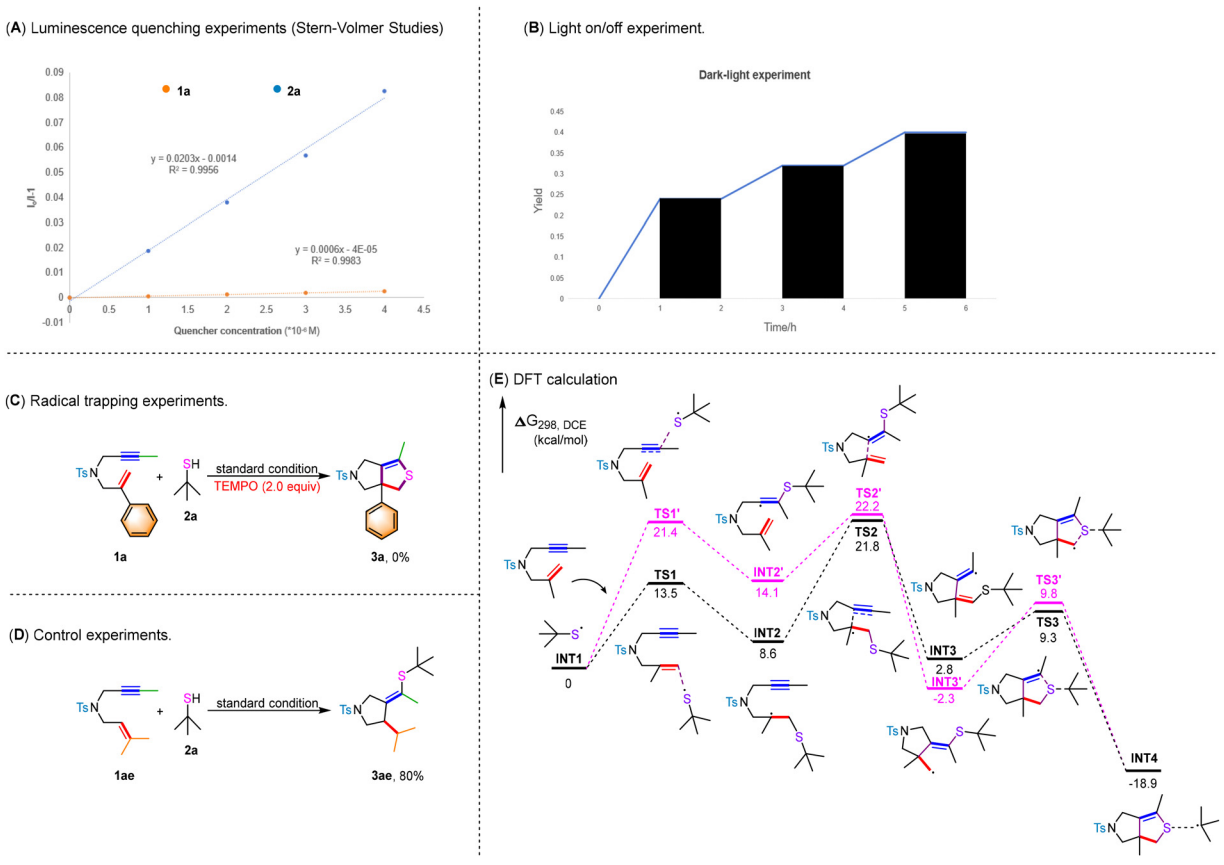


Scheme 2 [a] Standard conditions: substrate **1** (0.1 mmol, 1.0 equiv.), **2a** (2.0 equiv.), K_2CO_3 (2.0 equiv.), *p*-toluenethiol (0.2 equiv.), [Ir(dFCF$_3$ppy)$_2$(dtbpy)]PF$_6$ (3.0 mol%) in DCE (5.0 mL) at ambient temperature under 30 W blue LED irradiation for 12 hours. [b] The desired product was obtained in a complex mixture.

in 60% yields. Utilizing 1,6-enyne substrates **1c–1f** (R^1 = alkyl group, R^2 = Ts, and R^3 = Ph), the desired products **3c–3f** were obtained in 80%–90% yields. It is worth noting that an increase of the steric hindrance of the alkyl group decreased the yield of the corresponding products **3**. The structure of **3e** was unambiguously determined by X-ray crystallographic analysis and its ORTEP drawing is shown in Scheme 2. In addition, substrate **1g** having a protected hydroxy group, substrate **1h** containing an imino group and substrate **1i** with an ester group were all well compatible, giving the desired products **3g**, **3h** and **3i** in 75%, 78% and 73% yields, respectively. Notably, in the case of substrate **1j** containing a terminal alkenyl group, the thiophene product **3j** was formed in 53% yield presumably due to the further oxidation in the reaction

system. Next, we shifted our attention to examine the R^3 group in 1,6-enynes **1** (R^1 = Me) and found that introducing an alkyl group, ester group and aryl substituent in the R^3 group of 1,6-enynes **1k–1r** afforded the desired products **3k–3r** in 51%–96% yields. Moreover, the R^2 sulfonyl group was also exploited under the standard conditions and we identified that substrates **1s–1y** with a variety of sulfonated groups in R^2 all provided the desired products in good yields. To our delight, upon changing the linker atom to an oxygen atom, the desired product **3z** was obtained in 43% yield. However, when the $(C(CO_2Et)_2)$-linked substrate **1aa** was utilized to carry out the reaction, the desired product **3aa** was not obtained perhaps due to the steric effect. Further investigation revealed that this reaction also tolerated 1,6-enynes with several leaving groups (OMs, OTs, and OAc) such as substrates **1ab**, **1ac** and **1ad**, giving the corresponding products **3ab**, **3ac** and **3ad** in 85%, 90% and 83%, respectively, probably due to the mild reaction conditions.

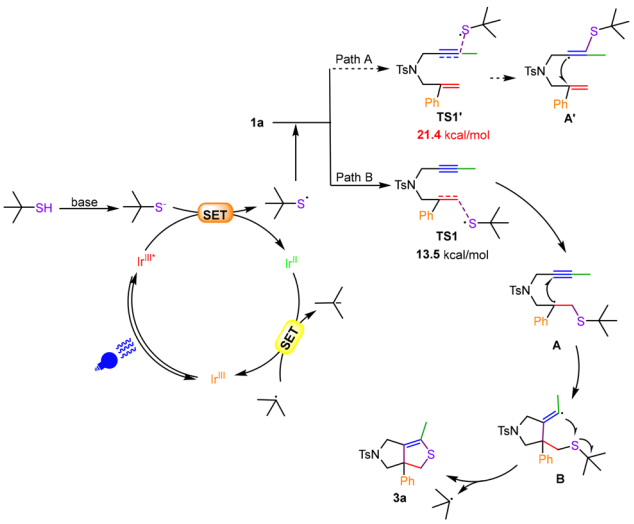
To gain more insights into the reaction mechanism, we carried out several control experiments (Scheme 3). First, Stern–Volmer luminescence quenching analysis using **1a** and **2a** showed that **2a** can more effectively quench the emission of $Ir[(dFCF_3ppy)_2dtbpy]PF_6$, suggesting that **2a** is an effective quencher for the excited state of $Ir[(dFCF_3ppy)_2dtbpy]PF_6$ (Scheme 3A).[10] To test whether the sulfur radical initiated a radical chain reaction, we analyzed the exclusive light-dependence of the reaction, in which the reaction basically stopped under dark conditions and continued when light was restored, indicating that visible light irradiation is a necessary condition for this reaction (Scheme 3B),[11] and the quantum yield was measured as Φ = 0.13 in this reaction (see page S15 in the ESI†), also suggesting that the intervention of a radical chain mechanism is unlikely. The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as a radical scavenger significantly inhibited the reaction. However, the TEMPO-trapped adduct cannot be characterized by HRMS spectrometry in our attempted experiment (Scheme 3C, also see page S16 in the ESI†).[12] Moreover, we utilized **1ae** as a substrate which has large steric hindrance in the alkenyl moiety, giving the corresponding product **3ae** instead of the [2 + 2 + 1] cyclization product (Scheme 3D). We subsequently embarked on DFT calculations to gain further insight into the reaction mechanism. All calculations have been performed at the SMD(dichloroethane)/B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level with the Gaussian 16 program.[13] The solvation Gibbs free energy profile in dichloroethane (DCE) for the suggested reaction pathway is shown in Scheme 3E (see Table S6 in the ESI† for more information). We investigated the reaction pathway start-



Scheme 3 Mechanistic studies. (A) Luminescence quenching experiments (Stern–Volmer studies). (B) Light on/off experiment. (C) Radical trapping experiments. (D) Control experiment. (E) DFT calculations.

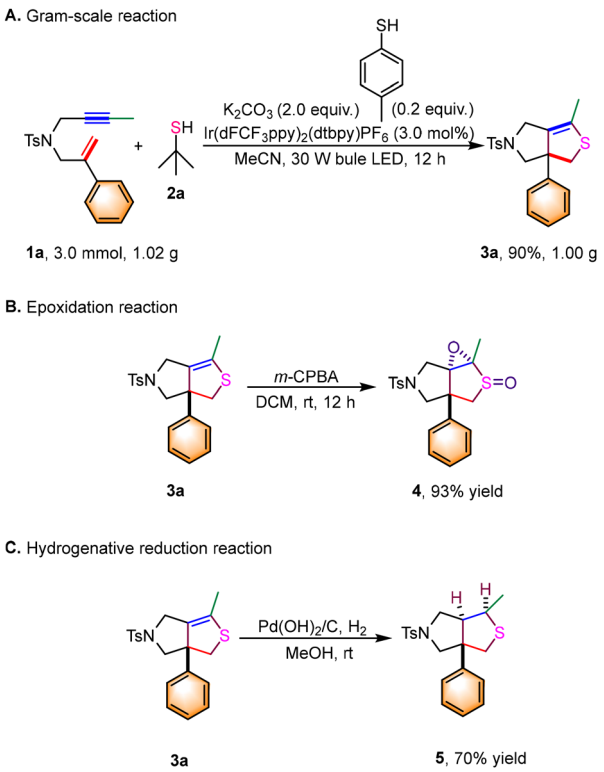
ing from a *tert*-butyl sulfur radical intermediate **INT1** shown in Scheme 3E. First, the intermediate **INT1** undergoes addition to the alkenyl moiety of **1k** *via* **TS1** with an energy barrier of 13.5 kcal mol^{-1} to generate a radical intermediate **INT2**. Subsequently, the intermediate **INT2** produces another carbon-centered cyclized radical intermediate **INT3** through an intramolecular cyclization with an energy barrier of 13.2 kcal mol^{-1}. Passing through transition state **TS3**, the radical intermediate **INT3** undergoes the S_Hi process with an energy barrier of 6.5 kcal mol^{-1} to afford the product complex **INT4**. According to the previous reports, the LUMO of **INT3** is located at the S center which is more easily prone to intermolecular attack by the alkyl radical.[14] Another possible reaction pathway was also investigated theoretically. Instead of starting from the terminal alkenyl moiety, **INT1** undergoes addition to the alkynyl moiety of **1k** *via* **TS1′** with an energy barrier of 21.4 kcal mol^{-1} to produce a radical intermediate **INT2′**, which is higher than that of addition on the alkenyl moiety by 7.9 kcal mol^{-1}. The energy of intermediate **INT2′** is higher than that of **INT2** by 5.5 kcal mol^{-1}. Therefore, the addition of the alkenyl moiety is more favorable kinetically and thermodynamically. Next, the intermediate **INT2′** similarly produces another carbon-centered cyclized radical intermediate **INT3′** through an intramolecular cyclization with an energy barrier of 8.1 kcal mol^{-1}. The radical intermediate **INT3′** also undergoes the S_Hi process through transition state **TS3′**, with an energy barrier of 12.1 kcal mol^{-1} to afford the product complex **INT4**. In general, the reaction prefers to start from the addition of a *tert*-butyl sulfur radical to the alkenyl moiety of the substrate, and an intramolecular cyclization and an S_Hi process follow to generate the desired product. For special substrates having bulky substituents on the alkenyl moiety, the reaction may start from the alkynyl moiety since a side product **3ae** was obtained when using **1ae** as a substrate under the standard reaction conditions (see Scheme 3D).

On the basis of control experiments and DFT calculations, we proposed a plausible mechanism to elucidate this visible light-induced photochemical reaction (Scheme 4). Upon irradiation with blue light, the ground state of the photosensitizer $Ir[(dFCF_3tppy)_2dtbpy]PF_6$ is converted into its excited state, which can further oxidize Me_3CS^- through a SET process to afford the *tert*-butyl sulfur radical, which reacts with the alkenyl moiety of 1,6-enyne *via* **TS1** with an energy barrier of 13.5 kcal mol^{-1} to furnish a radical intermediate **A**.[15] Based on the calculation result, the *tert*-butyl sulfur radical *via* **TS1′** with an energy barrier of 21.4 kcal mol^{-1} forms an intermediate **A′**. Thus, we exclude Path A. Then, intramolecular cyclization takes place to afford radical intermediate **B**. Subsequently, intermediate **B** undergoes intramolecular cyclization *via* S_Hi-type substitution, which strips away a sulfur atom from the *tert*-butylthioether unit, affording the desired product **3a** and a *tert*-butyl radical. The *in situ* generated Ir^{II} species reduces the *tert*-butyl radical to the corresponding *tert*-butyl anion, which is quenched by H^+ in the reaction system. In this photochemical catalytic system, *p*-toluenethiol is utilized to increase the concentration of H^+ in the reaction system, thereby improving the reaction efficiency.



Scheme 4 Proposed reaction mechanism.

To demonstrate the synthetic applicability of this protocol, a gram-scale reaction was conducted by employing 1.02 g (3.0 mmol) of **1a**, delivering the desired product **3a** in 90% yield (1.0 g) under the standard conditions (Scheme 5A). Epoxidation of **3a** with *m*-CPBA as an oxidant furnished the product **4** in 93% yield (Scheme 5B). Moreover, hydrogenation



Scheme 5 Synthetic transformations. (A) **1a** (3.0 mmol, 1.0 equiv.), **2a** (2.0 equiv.), K_2CO_3 (2.0 equiv.), *p*-toluenethiol (0.2 equiv.), $[Ir(dFCF_3ppy)_2dtbpy]PF_6$ (3.0 mol%) in DCE (30.0 mL) at ambient temperature under 30 W blue LED irradiation for 12 hours; (B) *m*-CPBA (3.0 equiv.), DCM; (C) $Pd(OH)_2/C$, MeOH, rt, H_2.

of the obtained product **3a** effectively afforded the corresponding product **5** in 70% yield (Scheme 5C).

Conclusions

In summary, we have developed a novel and practical photoredox catalytic methodology for cascade [2 + 2 + 1] cyclization of 1,6-enynes with thiols, delivering sulfur-containing polycyclic derivatives in moderate to good yields with broad substrate scope and good functional group tolerance under mild conditions. Moreover, this S- and carbon-centered radical reaction could be achieved on a gram scale, and the products could be further functionalized to afford other novel polycyclic compounds. The reaction mechanistic paradigm has been proposed on the basis of control experiments and photophysical analysis as well as DFT calculations. Further exploration of this visible light photoinduced synthetic strategy for the synthesis of medicinally useful heteropolycyclic products is underway.

Data availability

Experimental and computational data have been made available in the ESI.†

Author contributions

Z. Meng contributed to the investigation. Z. Meng, Y. Wei and M. Shi contributed to the conceptualization and writing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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