

RESEARCH ARTICLE

View Article Online

View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2024, **11**, 3442Received 12th March 2024,
Accepted 29th April 2024

DOI: 10.1039/d4qo00460d

rsc.li/frontiers-organic

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

Zhe Meng,^a Min Shi ^{a,b} and Yin Wei ^a

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.

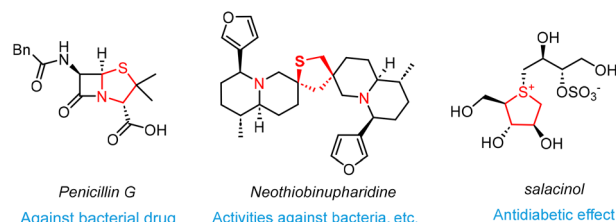
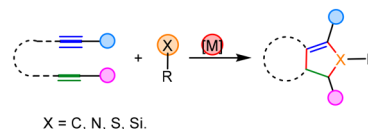
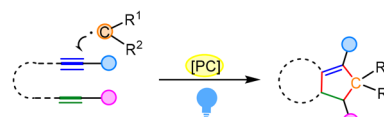
Introduction

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

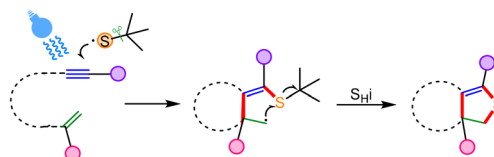
The synthesis of complex polycyclic molecules has always been a momentous research subject in synthetic chemistry, especially the preparation of multiple cyclic systems in one step.⁴ One of the common synthetic strategies for constructing these structures is the [2 + 2 + *m*] annulation of 1,*n*-enynes (*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 catalysis⁶ (Scheme 1b) or photo-induced catalysis⁷ (Scheme 1c). On the basis of transition-

a) Examples of sulfur-containing polycyclic bioactive compounds and pharmaceutical molecules

b) Transition-metal-mediated 1,*n*-enynne [2 + 2 + 1] cyclization (*n* = 6 or 7)c) Photoredox catalyzed 1,*n*-enynne [2 + 2 + 1] cyclization (*n* = 6 or 7)

d) This work



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

^aState Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

^bKey Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China.
E-mail: mshi@mail.sioc.ac.cn, weiyin@sioc.ac.cn

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of new compounds. CCDC 2222581. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4qo00460d>



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 precursors⁷ 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, K₂CO₃ (0.2 mmol, 2.0 equiv.) is used as a base, *p*-toluenethiol is employed as an additive and Ir[(dFCF₃ppy)₂(dtbpy)]PF₆ 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(dtbpyp)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 Cs₂CO₃, NEt₃, and Na₂CO₃, but none of them performed better than K₂CO₃ (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	<i>fac</i> -Ir(ppy) ₃ as PC	15
3	Ir(dtbpyp) ₂ as PC	50
4	Cs ₂ CO ₃ instead of K ₂ CO ₃	72
5	NEt ₃ instead of K ₂ CO ₃	0
6	Na ₂ CO ₃ instead of K ₂ CO 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 <i>p</i> -toluenethiol	67

2b

2c

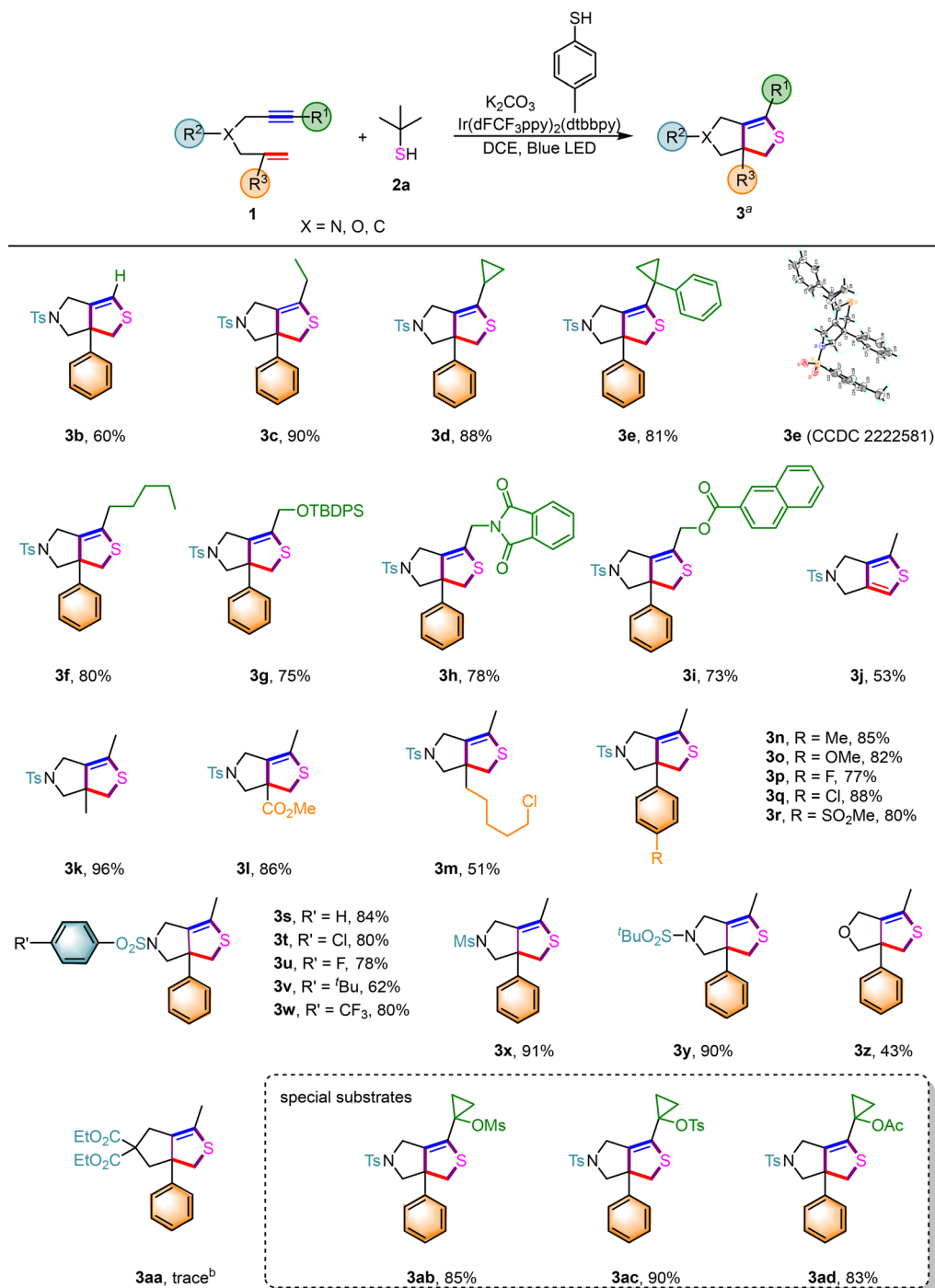
2d

^a Reaction was carried out with **1a** (0.1 mmol), **2a** (2.0 equiv.), K₂CO₃ (2.0 equiv.), *p*-toluenethiol (0.2 equiv.), Ir[(dFCF₃ppy)₂(dtbpy)]PF₆ (3.0 mol%) in DCE (5.0 mL) at ambient temperature under 30 W blue LED irradiation. ^b ¹H 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 (R¹ = 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.), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (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

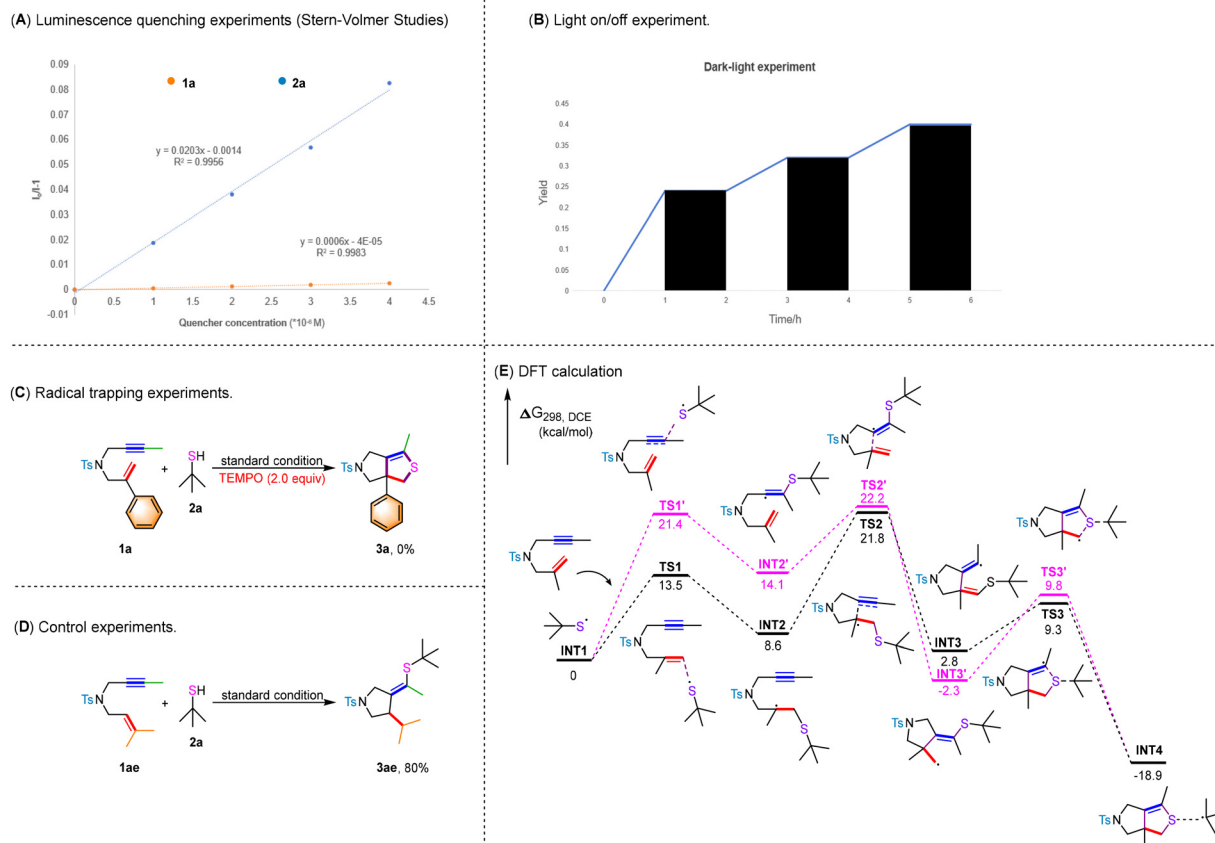
addition, substrate **1g** having a protected hydroxy group, substrate **1h** containing an imino group and substrate **1i** with an ester group were all well compatible, giving the desired products **3g**, **3h** and **3i** in 75%, 78% and 73% yields, respectively. Notably, in the case of substrate **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** ($R^1 = \text{Me}$) 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 $(\text{C}(\text{CO}_2\text{Et})_2)$ -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 $\text{Ir}[(\text{dFCF}_3\text{ppy})_2\text{dtbpy}]\text{PF}_6$, suggesting that **2a** is an effective quencher for the excited state of $\text{Ir}[(\text{dFCF}_3\text{ppy})_2\text{dtbpy}]\text{PF}_6$

(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 $\Phi = 0.13$ 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-

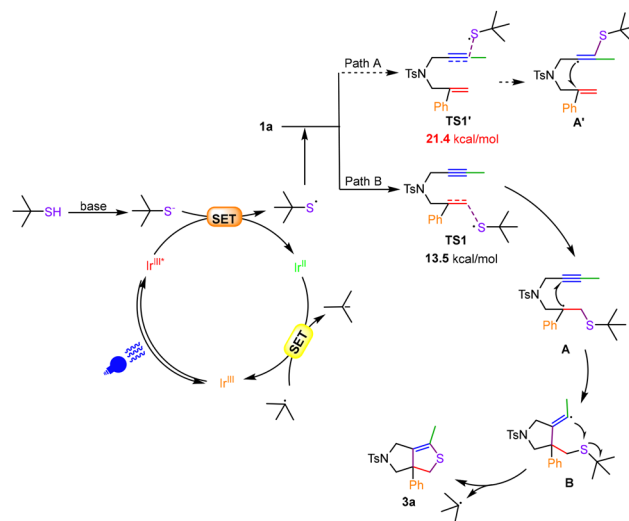


Scheme 3 Mechanistic studies. (A) Luminescence quenching experiments (Stern–Volmer studies). (B) Light on/off experiment. (C) Radical trapping experiments. (D) Control experiment. (E) DFT calculations.



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).

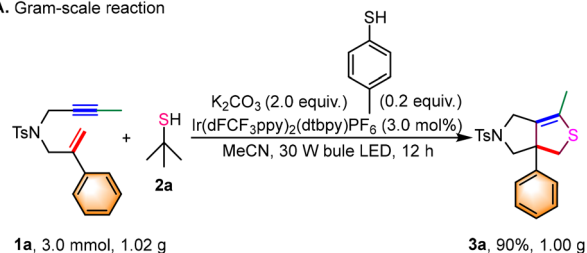
On the basis of control experiments and DFT calculations, we proposed a plausible mechanism to elucidate this visible light-induced photochemical reaction (Scheme 4). Upon irradiation with blue light, the ground state of the photosensitizer Ir[(dFCF₃tpy)₂dtbpy]PF₆ is converted into its excited state, which can further oxidize Me₃CS⁻ 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.



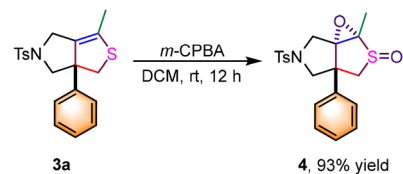
Scheme 4 Proposed reaction mechanism.

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

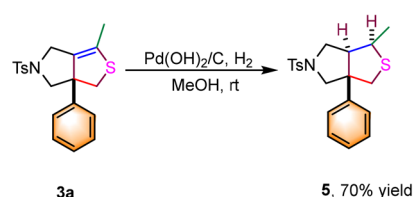
A. Gram-scale reaction



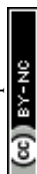
B. Epoxidation reaction



C. Hydrogenative reduction reaction



Scheme 5 Synthetic transformations. (A) **1a** (3.0 mmol, 1.0 equiv.), **2a** (2.0 equiv.), K₂CO₃ (2.0 equiv.), *p*-toluenethiol (0.2 equiv.), [Ir(dFCF₃ppy)₂dtbpy]PF₆ (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, H₂.



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 photo-redox 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.

Acknowledgements

We are grateful for the financial support from the National Key R & D Program of China (2022YFC2303100), the National Natural Science Foundation of China (21372250, 21121062, 21302203, 21772037, 21772226, 21861132014, 91956115 and 22171078) and the Fundamental Research Funds for the Central Universities 222201717003.

References

- (a) A. K. Franz and S. O. Wilson, Organosilicon Molecules with Medicinal Applications, *J. Med. Chem.*, 2013, **56**, 388–405; (b) N. Z. Wang, P. Saidharedy and X. F. Jiang, Construction of sulfur-containing moieties in the total synthesis of natural products, *Nat. Prod. Rep.*, 2020, **37**, 246–275; (c) A. A. Bhat, N. Tandon, I. Singh and R. Tandon, Structure-activity relationship (SAR) and antibacterial activity of pyrrolidine based hybrids: A review, *J. Mol. Struct.*, 2023, **1283**, 135175; (d) T. C. Adams, J. N. Payette, J. H. Cheah and M. Movassaghi, Concise total synthesis of (+)-luteoalbusins A and B, *Org. Lett.*, 2015, **17**, 4268–4271; (e) K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Strohm, P. A. Keifer, F. Sun, L. H. Li and D. G. Martin, Ecteinascidins 729, 743, 745, 759A, 759B, and 770: potent antitumor agents from the caribbean tunicate ecteinascidia turbinata, *J. Org. Chem.*, 1990, **15**, 4512–4515; (f) B. R. Beno, K. S. Yeung, M. D. Bartberger, L. D. Pennington and N. A. Meanwell, A survey of the role of noncovalent sulfur interactions in drug design, *J. Med. Chem.*, 2015, **11**, 4383–4438; (g) A. A. Bhat, N. Tandon and R. Tandon, Pyrrolidine derivatives as antibacterial agents, current status and future prospects: a patent review, *Pharm. Pat. Anal.*, 2022, **11**, 187; (h) A. A. Bhat, N. Tandon and R. Tandon, Pyrrolidine derivatives as anti-diabetic agents: current status and future prospects, *ChemistrySelect*, 2022, **7**, e202103757.
- (a) T. Morikawa, K. Ninomiya, G. Tanabe, H. Matsuda, M. Yoshikawa and O. Muraoka, A review of antidiabetic active thiosugar sulfoniums, salacinol and neokotalanol, from plants of the genus Salacia, *J. Nat. Med.*, 2021, **75**, 449–466.
- (a) C. X. Li, R. J. Liu, K. Yin, L. R. Wen and M. Li, Synthesis of disulfides tethered pyrroles from β -ketothioamides via a bicyclization/ring-opening/oxidative coupling reaction, *Org. Biomol. Chem.*, 2017, **15**, 5820–5823; (b) Y. A. Zhang, Z. Ding, P. Liu, W. S. Guo, L. R. Wen and M. Li, Access to SCN-containing thiazolines via electrochemical regio-selective thiocyanothiocyclusation of *N*-allylthioamides, *Org. Chem. Front.*, 2020, **7**, 1321–1326; (c) B. B. Liu, H. W. Bai, H. Liu, S. Y. Wang and S. J. Ji, Cascade trisulfur radical anion ($S_3^{\cdot-}$) addition/electron detosylation process for the synthesis of 1,2,3-thiadiazoles and isothiazoles, *J. Org. Chem.*, 2018, **17**, 10281–10288; (d) J. X. Feng, Y. Zhang, X. D. Wang, J. Liu, V. Benazzi, K. Lu, X. Zhao and S. Protti, Recent advances in visible-light-driven C–S bond formation, *Adv. Synth. Catal.*, 2023, **365**, 3413–3431; (e) Z. C. Shi, R. H. Li, W. Q. Lan, H. S. Wei, S. R. Sheng and J. M. Chen, Visible-light-induced intramolecular C–S bond formation for practical synthesis of 2,5-disubstituted 1,3,4-thiadiazoles, *Synth. Commun.*, 2023, **53**, 40–48; (f) W. K. Abdelbasset, M. Q. Sultan, A. F. Alkaim, T. A. Ashurov, U. S. Altimari, B. A. Hussein, Y. F. Mustafa and A. T. Hammid, Intramolecular cascade C–S bond formation: a safe and new strategy for the synthesis of riluzole analogues catalyzed by $K_2S_2O_8$, *Polycyclic Aromat. Compd.*, 2023, **43**, 7970–7978; (g) M. Z. Wu, C. X. Yan, D. J. Zhuang and R. L. Yan, Metal-free C–S bond formation in elemental sulfur and cyclobutanol derivatives: the synthesis of substituted thiophenes, *Org. Lett.*, 2022, **24**, 5309–5313.
- (a) T. Nakata, Total synthesis of marine polycyclic ethers, *Chem. Rev.*, 2005, **105**, 4314–4347; (b) R. A. Craig and B. M. Stoltz, Polycyclic furanobutenolide-derived cembranoid and norcembranoid natural products: biosynthetic



- connections and synthetic efforts, *Chem. Rev.*, 2017, **117**, 7878–7909; (c) M. Hirai, N. Tanaka, M. Sakai and S. Yamaguchi, Structurally constrained boron-, nitrogen-, silicon-, and phosphorus-centered polycyclic π -conjugated systems, *Chem. Rev.*, 2019, **119**, 8291–8331; (d) G. Mehta and A. Srikrishna, Synthesis of polyquinane natural products: an update, *Chem. Rev.*, 1997, **97**, 671–720; (e) H. C. Guo and J. A. Ma, Catalytic asymmetric tandem transformations triggered by conjugate additions, *Angew. Chem., Int. Ed.*, 2006, **45**, 354–366; (f) Z. T. Li, Y. X. Gao, Z. D. Jiao, N. Wu, D. Z. Wang and Z. Yang, Diversity-oriented synthesis of fused pyran γ -lactones via an efficient Pd-thiourea-catalyzed alkoxyacylation annulation, *Org. Lett.*, 2008, **10**, 5163–5166; (g) X. M. Zhang, Y. Q. Tu, Y. J. Jiang, Y. Q. Zhang, C. A. Fana and F. M. Zhang, Tandem reactions of cis-2-acyl-1-alkynyl-1-aryl cyclopropanes tuned by gold(I) and silver(I) catalysts: efficient synthesis of pyran-fused indene cores and 2,4,6-trisubstituted phenols, *Chem. Commun.*, 2009, 4726–4728; (h) T. Bach and J. P. Hehn, Photochemical reactions as key steps in natural product synthesis, *Angew. Chem., Int. Ed.*, 2011, **50**, 1000–1045.
- 5 (a) C. Aubert, O. Buisine and M. Malacria, The Behavior of 1,*n*-enynes in the presence of transition metals, *Chem. Rev.*, 2002, **102**, 813–834; (b) S. T. Diver and A. J. Giessert, Enyne metathesis (enyne bond reorganization), *Chem. Rev.*, 2004, **104**, 1317–1382; (c) P. A. Inglesby and P. A. Evans, Stereoselective transition metal-catalysed higher-order carbocyclisation reactions, *Chem. Soc. Rev.*, 2010, **39**, 2791–2805; (d) C. Raviola, S. Protti, D. Ravelli and M. Fagnoni, (Hetero)aromatics from dienes, enedienes and enyne-allenes, *Chem. Soc. Rev.*, 2016, **45**, 4364–4390; (e) J. Xuan and A. Studer, Radical cascade cyclization of 1,*n*-enynes and diynes for the synthesis of carbocycles and heterocycles, *Chem. Soc. Rev.*, 2017, **46**, 4329–4346; (f) M. H. Huang, W. J. Hao and B. Jiang, Recent advances in radical-enabled bicyclization and annulation/1,*n*-bifunctionalization reactions, *Chem. – Asian J.*, 2018, **13**, 2958–2977; (g) X. F. Tong, M. Beller and M. K. Tse, A palladium-catalyzed cyclization-oxidation sequence: synthesis of bicyclo[3.1.0]hexanes and evidence for SN2 C–O bond formation, *J. Am. Chem. Soc.*, 2007, **129**, 4906–4907; (h) Y. Liu, J. L. Zhang, R. J. Song, P. C. Qian and J. H. Li, Cascade nitration/cyclization of 1,7-enynes with ^tBuONO and H₂O: one-pot self-assembly of pyrrolo[4,3,2-*de*]quinolinones, *Angew. Chem., Int. Ed.*, 2014, **53**, 9017–9020; (i) Y. Li, G. H. Pan, M. Hu, Ba. Liu, R. J. Song and J. H. Li, Intermolecular oxidative decarbonylation [2 + 2 + 2] carbocyclization of *N*-(2-ethynylaryl)acrylamides with tertiary and secondary alkyl aldehydes involving C(sp₃)-H functionalization, *Chem. Sci.*, 2016, **7**, 7050–7054.
- 6 (a) K. Matsui, M. Shibuya and Y. Yamamoto, Catalytic [2 + 2] synthesis of fused thiophenes using thiocarbonyls as sulfur donors, *Angew. Chem., Int. Ed.*, 2016, **55**, 15397–15400; (b) Y. Park, S. Ahn, D. Kang and M. H. Baik, Mechanism of rh-catalyzed oxidative cyclizations: closed versus open shell pathways, *Acc. Chem. Res.*, 2016, **49**, 1263–1270; (c) J. K. Qiu, B. Jiang, Y. L. Zhu, W. J. Hao, D. C. Wang, J. Sun, P. Wei, S. J. Tu and G. G. Li, Catalytic dual 1,1-*H*-abstraction/insertion for domino spirocyclizations, *J. Am. Chem. Soc.*, 2015, **137**, 8928–8931; (d) Y. F. Qiu, X. Y. Zhu, Y. X. Li, Y. T. He, F. Yang, J. Wang, H. L. Hua, L. Zheng, L. C. Wang, X. Y. Liu and Y. M. Liang, AgSCF₃-mediated trifluoromethylthiolation/radical cascade cyclization of 1,6-enynes, *Org. Lett.*, 2015, **17**(15), 3694–3697; (e) J. X. Yu, F. Teng, J. N. Xiang, W. Deng and J. H. Li, One-carbon incorporation using cyclobutanone oxime ester enabled [2 + 2 + 1] carboannulation of 1,7-enynes by C–C/N–O bond cleavage and C–H functionalization, *Org. Lett.*, 2019, **21**, 9434–9437; (f) S. Suzuki, S. Nishigaki, Y. Shibata and K. Tanaka, Rhodium-catalyzed enantioselective [2 + 2 + 1] cycloaddition of 1,6-enynes with cyclopropylideneacetamides, *Org. Lett.*, 2018, **20**, 7461–7465; (g) Y. Y. Zhao, Y. C. Hu, H. L. Wang, X. C. Li and B. S. Wan, Transition-metal controlled diastereodivergent radical cyclization/azidation cascade of 1,7-enynes, *J. Org. Chem.*, 2016, **81**, 4412–4420; (h) Y. Liu, J. L. Zhang, R. J. Song and J. H. Li, Sulfur incorporation: copper-catalyzed cascade cyclization of 1,7-enynes with metal sulfides toward thieno [3,4-*c*]quinolin-4(5*H*)-ones, *Org. Lett.*, 2014, **16**, 5838–5841; (i) T. Ohmura, I. Sasaki and M. Sugimoto, Catalytic generation of rhodium silylenoid for alkene-alkyne-silylene [2 + 2 + 1] cycloaddition, *Org. Lett.*, 2019, **21**, 1649–1653; (j) M. Hu, R. J. Song, X. H. Ouyang, F. L. Tan, W. T. Weia and J. H. Li, Copper-catalyzed oxidative [2 + 2 + 1] annulation of 1,*n*-enynes with α -carbonyl alkyl bromides through C–Br/C–H functionalization, *Chem. Commun.*, 2016, **52**, 3328–3331; (k) M. Hu, H. X. Zou, R. J. Song, J. N. Xiang and J. H. Li, Copper-catalyzed C–H oxidative radical functionalization and annulation of aniline-linked 1,7-enynes: evidence for a 1,5-hydride shift mechanism, *Org. Lett.*, 2016, **18**, 6460–6463; (l) M. Hu, M. Li, F. L. Tan, R. J. Song, Y. X. Xie and J. H. Li, Oxidative divergent bicyclizations of 1,*n*-enynes through α -C(sp₃)-H functionalization of alkyl nitriles, *Adv. Synth. Catal.*, 2017, **359**, 120–129; (m) Y. Liu, R. J. Song and J. H. Li, Palladium-catalyzed dearomatization [2 + 2 + 1] carboannulation of 1,7-enynes with aryl diazonium salts and H₂O: facile synthesis of spirocyclohexadienone-fused cyclopenta[*c*]quinolin-4(5*H*)-ones, *Chem. Commun.*, 2017, **53**, 8600–8603.
- 7 (a) J. J. Luo, G. H. Zeng, X. H. Cao and B. L. Yin, Visible-light-induced [2 + 2 + 1] dearomative cascade cyclization of indole/furan alkynes to synthesize sulfonyl polycycles, *Adv. Synth. Catal.*, 2022, **364**, 2197–2204; (b) Y. Li, B. Liu, R. J. Song, Q. A. Wang and J. H. Li, Visible light-initiated C(sp₃)-Br/C(sp₃)-H functionalization of α -carbonyl alkyl bromides through hydride radical shift, *Adv. Synth. Catal.*, 2016, **358**, 1219–1228; (c) M. J. Jiao, D. Liu, X. Q. Hu and P. F. Xu, Photocatalytic decarboxylation [2 + 2 + 1] annulation of 1,6-enynes with *N*-hydroxyphthalimide esters for the synthesis of indene-containing polycyclic compounds, *Org. Chem. Front.*, 2019, **6**, 3834–3838; (d) Y. Qu, W. T. Xu, J. J. Zhang, Y. X. Liu, Y. Q. Li, H. J. Song and Q. M. Wang,



- Visible-light-mediated $[2 + 2 + 1]$ carbocyclization reactions of 1,7-enynes with bromofluoroacetate to form fused mono-fluorinated cyclopenta[*c*]quinolin-4-ones, *J. Org. Chem.*, 2020, **85**, 5379–5389; (e) J. X. Yu, F. Teng, J. N. Xiang, W. Deng and J. H. Li, One-carbon incorporation using cyclobutanone oxime ester enabled $[2 + 2 + 1]$ carboannulation of 1,7-enynes by C-C/N-O bond cleavage and C-H functionalization, *Org. Lett.*, 2019, **21**, 9434–9437; (f) F. Gao, C. Yang, N. Ma, G. L. Gao, D. Z. Li and W. J. Xia, Visible-light-mediated 1,7-enyne bicyclizations for synthesis of cyclopenta[*c*]quinolines and benzo[*j*]phenanthridines, *Org. Lett.*, 2016, **18**, 600–603; (g) X. H. Ouyang, R. J. Song, Y. Liu, M. Hu and J. H. Li, Copper-catalyzed radical $[2 + 2 + 1]$ annulation of benzene-linked 1,*n*-enynes with azide: fused pyrroline compounds, *Org. Lett.*, 2015, **17**, 6038–6041; (h) G. B. Deng, R. L. Zhong, J. X. Song, P. Y. Choy and F. Y. Kwong, Assembly of furazan-fused quinolines via an expeditious metal-free $[2 + 2 + 1]$ radical tandem cyclization process, *Org. Lett.*, 2021, **23**, 6520–6524; (i) Y. Liu, R. J. Song, S. L. Luo and J. H. Li, Visible-light-promoted tandem annulation of *N*-(*o*-ethynylaryl)acrylamides with CH_2Cl_2 , *Org. Lett.*, 2018, **20**, 212–215.
- 8 (a) H. Jiang and A. Studer, Intermolecular radical carboamination of alkenes, *Chem. Soc. Rev.*, 2020, **49**, 1790–1811; (b) H. W. Xiao, H. G. Shen, L. Zhu and C. Z. Li, Copper-catalyzed radical aminotrifluoromethylation of alkenes, *J. Am. Chem. Soc.*, 2019, **141**, 11440–11445; (c) X. W. Lan, N. X. Wang and Y. L. Xing, Recent advances in radical difunctionalization of simple alkenes, *Eur. J. Org. Chem.*, 2017, 5821–5851; (d) B. Zhang, T. T. Li, Z. C. Mao, M. Jiang, Z. H. Zhang, K. Zhao, W. Y. Qu, W. J. Xiao and J. R. Chen, Enantioselective cyanofunctionalization of aromatic alkenes via radical anions, *J. Am. Chem. Soc.*, 2024, **146**, 1410–1422; (e) J. Wang, X. X. Wu, Z. Cao, X. Zhang, X. X. Wang, J. Li and C. Zhu, E-selective radical difunctionalization of unactivated alkynes: preparation of functionalized allyl alcohols from aliphatic alkynes, *Adv. Sci.*, 2024, 2309022; (f) P. Wang, H. H. Zhang, M. Q. Zhao, S. S. Ji, L. Lin, N. Yang, X. L. Nie, J. S. Song and S. H. Liao, Radical hydro-fluoro-sulfonylation of unactivated alkenes and alkynes, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207684; (g) E. R. Lopat'eva, L. B. Krylov, S. A. Paveliev, D. A. Emtsov, V. A. Kostyagina, A. A. Korlyukov and A. O. Terent'ev, Free Radicals in the Queue: Selective Successive Addition of Azide and N-Oxyl Radicals to Alkenes, *J. Org. Chem.*, 2023, **88**, 13225–13235; (h) M. H. Huang, W. J. Hao, G. G. Li, S. J. Tu and B. Jiang, Recent advances in radical transformations of internal alkynes, *Chem. Commun.*, 2018, **54**, 10791–10811; (i) C. W. Hu, J. Mena and I. V. Alabugin, Design principles of the use of alkynes in radical cascades, *Nat. Rev. Chem.*, 2023, **7**, 405–423; (j) W. Q. Su, P. Xu, R. Petzold, J. Y. Yan and T. Ritter, Ligand-to-copper charge-transfer-enabled C-H sulfoximation of arenes, *Org. Lett.*, 2023, **25**, 1025–1029; (k) W. Z. Fu, N. M. Neris, Y. Fu, Y. L. Zhao, B. K. Hansen, P. Liu and Y. Yan, Enzyme-controlled stereoselective radical cyclization to arenes enabled by metalloredox biocatalysis, *Nat. Catal.*, 2023, **6**, 628–636.
- 9 (a) D. Crich, Homolytic substitution at the sulfur atom as a tool for organic synthesis, *Helv. Chim. Acta*, 2006, **89**, 2167–2182; (b) F. Dénès, Heteroatom-centred radicals for the synthesis of heterocyclic compounds, *Top. Heterocycl. Chem.*, 2018, **54**, 151–230; (c) A. L. J. Beckwith and D. R. Boate, Stereochemistry of intramolecular homolytic substitution at the sulphur atom of a chiral sulphoxide, *J. Chem. Soc., Chem. Commun.*, 1986, 189–190; (d) D. C. Harrowven, J. C. Hannam, M. C. Lucas, N. A. Newman and P. D. Howes, A thiyl radical mediated cascade sequence for the co-cyclisation of 1,6-hexadienes with sulfur atom transfer, *Tetrahedron Lett.*, 2000, **41**, 9345–9349; (e) P. James, K. Schenk and Y. Landais, Radical-mediated 5-exo-trig cyclizations of 3-silylhepta-1,6-dienes, *J. Org. Chem.*, 2006, **71**, 3630–3633; (f) J. A. F. Salas, M. M. R. Fernández, M. C. Maestro and J. L. G. Ruano, Stereochemical aspects and the synthetic scope of the SHi at the sulfur atom. Preparation of enantiopure 3-substituted 2,3-dihydro-1,2-benzisothiazole 1-oxides and 1,1-dioxides, *Chem. Commun.*, 2014, **50**, 6046–6048; (g) J. A. Kampmeier and T. R. Evans, Radical reactions of organic sulfides. II. behavior of the 2-(2'-methylthio)biphenyl radical, *J. Am. Chem. Soc.*, 1966, **88**, 4096–4097; (h) A. L. J. Beckwith and D. R. Boate, formation of fused tricyclic azetidinones and pyrrolidinones by intramolecular SH₂ processes, *J. Org. Chem.*, 1988, **53**, 4339–4348; (i) L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo and S. Strazzari, Generation and intramolecular reactivity of acyl radicals from alkynylthiol esters under reducing tin-free conditions, *Org. Lett.*, 2003, **5**, 1313–1316; (j) P. Carta, N. Puljic, C. Robert, A. L. Dhimane, L. Fensterbank, E. Lacote and M. Malacria, Generation of phosphorus-centered radicals via homolytic substitution at sulfur, *Org. Lett.*, 2007, **9**, 1061–1063; (k) S. H. Kyne, H. M. Aitken, C. H. Schiesser, E. Lacote, M. Malacria, C. Olliviere and L. Fensterbank, Intramolecular homolytic substitution of sulfinates and sulfinamides—a computational study, *Org. Biomol. Chem.*, 2011, **9**, 3331–3337.
- 10 (a) Q. Z. Li, X. T. Gu, Y. Wei and M. Shi, Visible-light-induced indole synthesis via intramolecular C-N bond formation: desulfonylative C(sp²)-H functionalization, *Chem. Sci.*, 2022, **13**, 11623–11632; (b) Z. Liu, Y. Wei and M. Shi, Visible-light-mediated regioselective ring-opening hydrogenolysis of donor-acceptor cyclopropanes with DIPEA and H₂O, *Org. Chem. Front.*, 2022, **9**, 1960–1966.
- 11 (a) J. Yan, Z. Q. Yu, H. Z. Wei, M. Shi and Y. Wei, Visible light-mediated hydrogen atom transfer and proton transfer for the conversion of (2-vinylaryl) methanol derivatives to aryl aldehydes or aryl ketones, *Org. Chem. Front.*, 2023, **10**, 5876; (b) Z. Meng, X. Y. Zhang and M. Shi, Visible-light mediated cascade cyclization of ene-vinylidenecyclopropanes: access to fluorinated heterocyclic compounds, *Org. Chem. Front.*, 2021, **8**, 3796–3801.
- 12 X. Y. Zhang, X. Y. Wu, B. Zhang, Y. Wei and M. Shi, Silyl Radical-mediated carbocyclization of acrylamide/vinyl sul-



- fonamide-attached alkylidenecyclopropanes via photoredox catalysis with a catalytic amount of silane reagent, *ACS Catal.*, 2021, **11**, 4372–4380.
- 13 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, *Gaussian 16, Revision A.03*, Gaussian, Inc., Wallingford CT, 2016.
 - 14 (a) Y. S. Chen, X. X. Wu, S. Yang and C. Zhu, Asymmetric radical cyclization of alkenes by stereospecific homolytic substitution of sulfinamides, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201027.
 - 15 (a) A. Luridiana, A. Frongia, M. A. Scorciapino, G. Mallocci, B. Manconi, S. Serrao, P. C. Ricci and F. Secci, Z-selective synthesis of α -sulfanyl carbonyl compounds from internal alkynes and thiols via photoredox catalysis, *Adv. Synth. Catal.*, 2022, **364**, 124–131; (b) S. S. Zaleskiy, N. S. Shlapakova and V. P. Ananikov, Visible light mediated metal-free thiol-yne click reaction, *Chem. Sci.*, 2016, **7**, 6740–6745; (c) L. Benati, L. Capella, P. C. Montecvecchi and P. Spagnolo, Free-radical addition of alkanethiols to alkynes. rearrangements of the intermediate .beta.-(vinylthio) radicals, *J. Org. Chem.*, 1994, **59**, 2818–2823; (d) M. H. Huang, W. J. Hao, G. G. Li, S. J. Tu and B. Jiang, Recent advances in radical transformations of internal alkynes, *Chem. Commun.*, 2018, **54**, 10791–10811; (e) X. F. Xia, G. W. Zhang and S. L. Zhu, Visible-light-induced synthesis of benzothiophenes and benzoselenophenes via the annulation of thiophenols or 1,2-diphenyldisilane with alkynes, *Tetrahedron*, 2017, **73**, 2727–2730.

