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EDGE ARTICLE

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Cite this: DOI: 10.1039/d6sc01281g

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Photoinduced intramolecular S-α-C(sp^3)–H functionalization enabled by an electron donor–acceptor complex-Mediated radical relay

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Received 13th February 2026
Accepted 25th February 2026

DOI: 10.1039/d6sc01281g

rsc.li/chemical-science

We describe a consecutive reaction of 2-alkynylthioanisoles and 4-cyanopyridine enabled by EDA complex photoactivation, which facilitates the sequential S-α-C(sp^3)–H bond activation, cyclization and radical coupling under mild conditions. A variety of 3-(4-pyridylbenzyl)benzothiophenes and benzoselenophenes were synthesized *via* a single-step process. Mechanistic investigations indicate that EDA complexes between thioethers and 4-cyanopyridines are crucial to this process.

Introduction

Sulfur-containing molecules are widely present in biologically active natural products, pharmaceutical compounds, and functional materials.[1] The direct α-C(sp^3)–H functionalization of sulfides has emerged as an atom-economical and environmentally benign strategy for the efficient construction of diverse sulfur-containing compounds.[2] Compared to the activation of α-C(sp^3)–H bonds adjacent to oxygen or nitrogen atoms, the functionalization of α-sulfur C(sp^3)-H bonds is considerably more challenging due to the susceptibility of thioethers toward oxidation and their strong coordinating ability.[3] Notably, significant progress has been achieved over the past decade in the direct α-C(sp^3)–H functionalization of thioethers, primarily through methods such as catalysis by rare-earth complexes[4] or alkali metal amides,[5] electrochemical oxidation-enabled S-α-C(sp^3)–H functionalization,[6] and photoinduced S-α-C(sp^3)–H activation and modification (Scheme 1a).[7–12] The generation of α-thioalkyl radicals from thioethers can be accomplished *via* a photoinduced single-electron transfer (SET) oxidation/deprotonation sequence or through direct hydrogen-atom transfer (HAT).[7] MacMillan's group has developed a selective α-C(sp^3)–H alkylation of sulfides with alkyl bromides *via* the combination of photoredox, nickel and hydrogen-atom transfer (HAT) catalysis.[8] In addition, Alfonzo and Hande disclosed an α-C(sp^3)–H activation of thioethers to generate nucleophilic α-thioalkyl radicals through dual photoredox/weak base catalysis, followed by coupling with pyridinium salts or addition with electron deficient olefins.[9] Recently, Feng and Liu have reported a photoinduced chemo-, site- and stereoselective α-C(sp^3)–H functionalization of sulfides using isatins as the photoredox reagent and coupling partner catalyzed by a chiral gallium(III)–*N*,*N*′-dioxide complex.[10] The same group subsequently developed an enantioselective radical hydrofunctionalization of α-substituted vinylphosphine oxides or α,β-unsaturated pyrazoleamide through photoactivation of α-C(sp^3)–H of sulfides using naphthacene-6,11-quinone (NQ) as photocatalyst.[11] Very recently, Sawama reported a highly chemoselective α-C(sp^3)–H deuteration of sulfides using a thioxanthone or anthraquinone as photocatalyst and D_2O as an inexpensive deuterium source under 390 nm irradiation.[12] Despite these advances, the photocatalyst-free and HAT reagent-free strategies for direct α-C(sp^3)–H modification of sulfides remain highly desirable and still not realized.

In the past few years, the EDA complex photochemistry,[13] especially the catalytic EDA complex strategy[14] has attracted the interest of a growing number of chemists, and which has been recognized as a powerful approach for expanding the potential of photo-driven radical synthetic chemistry. The most straightforward synthetic application of EDA complex photoactivation is based on light-driven intermolecular charge transfer, which generates a radical ion pair and leads to the coupling of stoichiometric donor and acceptor substrates. The transformation could conduct in the absence of external photocatalysts with high atomic economy because the moieties of the substrates will eventually end up in the core of the corresponding products. Among the reported strategies, amine has been extensively employed as donor of the EDA complex and successfully applied in organic synthesis.[15] In 2020, Xu and coworkers realized the visible-light-promoted *N*-α-C(sp^3)–H alkylation through intermolecular charge transfer within a glycine Katritzky salt EDA complex, providing a simple method for preparation of unnatural α-amino acids and late-stage modification of peptides.[16] Subsequently, the group has also disclosed a photo-promoted C(sp^3)-H bicyclopentylation

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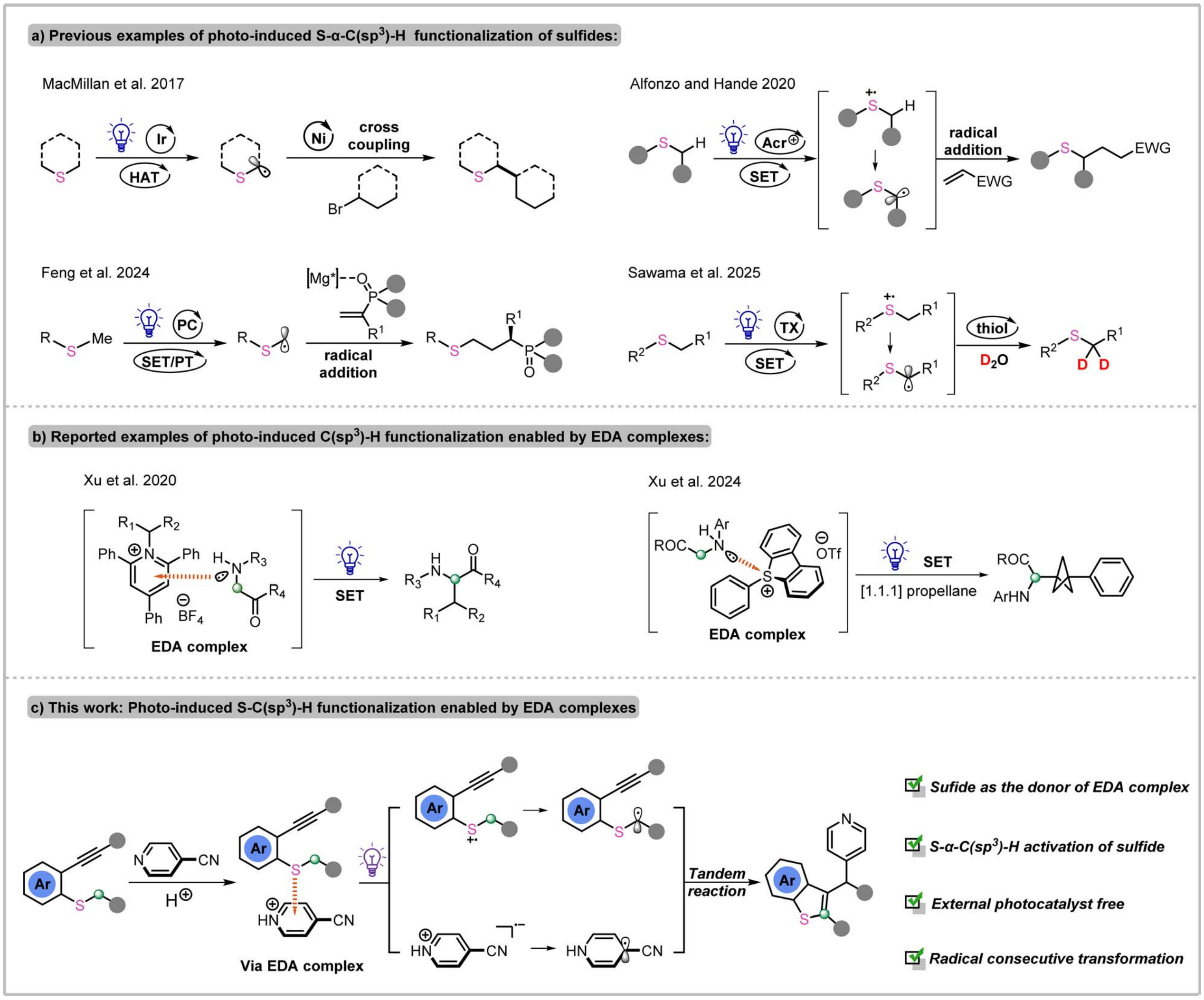


Scheme 1 Photo-induced C(sp^3)-H functionalization adjacent to S/N atom.

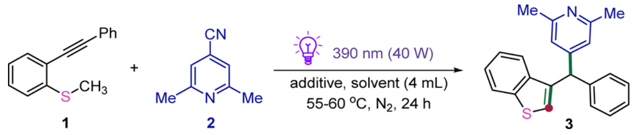
enabled by an electron donor–acceptor complex-mediated chemoselective three component radical relay (Scheme 1b).[17]

However, these seminal strategies are frequently found in amine-based EDA complexes,[18] and to the best of our knowledge, using sulfides as donors in EDA complexes for direct α-C(sp^3)–H functionalization has rarely reported.[19] Based on our ongoing interest in organic photochemistry[20] and inspired by recent progress on visible-light excited EDA complex-enabled selective α-C(sp^3)–H functionalization, we hypothesized that an electron-poor 4-cyanopyridine and an electron-rich sulfide could generate an EDA complex. Excitation of such an EDA complex under visible-light irradiation would promote single-electron transfer to generate a radical ion pair intermediate, and which will undergo further transformation for new molecular construction. To our pleasure, we have achieved this assumed process. Herein, we will present a novel photoinduced cascade radical annulation of 2-alkynylthioanisoles with 4-cyanopyridines through S-α-C(sp^3)–H activation enabled by an electron donor–acceptor complex–mediated radical relay, providing an efficient approach to synthesize 3-(4-pyridylbenzyl) benzothiophenes and benzoselenophenes which are difficult to obtain *via* traditional methods (Scheme 1c). This protocol features photocatalyst-free and HAT reagent-free, simple operation, broad scope and good yield. Moreover, late-stage modification of pharmaceutical derivatives further highlights the utility of this strategy.

Results and discussion

We initially investigated the cascade radical annulation using methyl(2-(phenylethynyl)phenyl)sulfane (**1**) and 4-cyano-2,6-lutidine (**2**) as the model substrate (Table 1). Unfortunately, the reaction of **1** and **2** could not happen under irradiation of 390 nm (40 W) LEDs without any additives in acetonitrile and nitrogen atmosphere (entry 1). To our pleasure, the desired product **3** was obtained in 11–50% yield after a suitable acid, such as trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (TsOH) and racemic 1,1′-binaphthyl-2,2′-diylhydrogenphosphate (BNDHP) was added to the reaction system (entries 2–4). Regrettably, the racemic products were still obtained when

Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Additives	Yield[b] (%)
1	CH_3CN	—	n.d
2	CH_3CN	20% mol TFA	11
3	CH_3CN	20% mol TsOH	17
4	CH_3CN	20% mol BNDHP	51
5	CH_3CN	—	50[c]
6	CH_3COOH	—	65
7	CH_3CN/CH_3COOH (1 : 2)	—	23
8	CH_3COOH (2 mL or 6 mL)	—	32[d], 69[e]
9	CH_3COOH	—	53[f]
10	CH_3COOH	—	n.d[g]
11	CH_3COOH	—	n.d[h]
12	CH_3COOH	—	12[i], 21[j], 32[k]
13	CH_3COOH	—	38[l], 51[m]
14	CH_3COOH	—	78[n], 78[o]
15	CH_3COOH	—	48[p], 76[q]

[a] Reaction conditions: 1 (0.20 mmol) and 2 (4-cyano-2,6-lutidine, 0.24 mmol) in solvent were irradiated with 390 nm Kessil LED (40 W) in a reaction tube under N_2 atmosphere at 55–60 °C for 24 h unless otherwise stated. [b] Isolated yield. [c] 20% mol of (*S*)-3,3′-bis(2-naphthalenyl)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate was used, 0%ee. [d] 2 mL CH_3COOH was used. [e] 6 mL CH_3COOH was used. [f] With a fan, the reaction temperature is about 35–40 °C. [g] dark. [h] 80 °C in the dark. [i] 390 nm (10 W). [j] 390 nm (20 W). [k] 390 nm (30 W). [l] 370 nm (40 W). [m] 427 nm (40 W). [n] 0.24 mmol 1 was used. [o] 0.22 mmol 1 was used. [p] 12 h. [q] 36 h; BNDHP = 1,1′-binaphthyl-2,2′-diylhydrogenphosphate (racemic), n.d. = not detected.

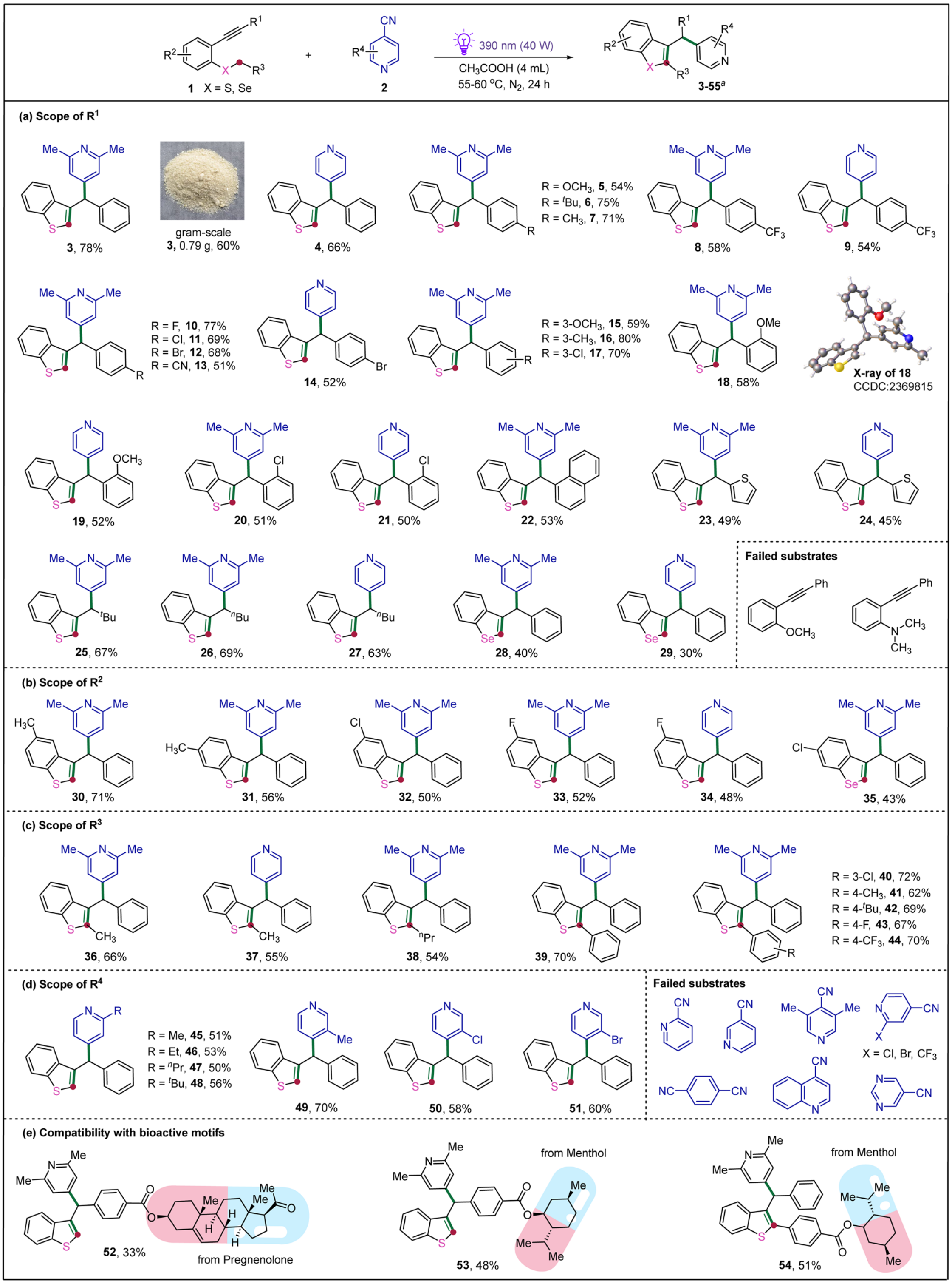
a chiral phosphoric acid, (*S*)-3,3′-bis(2-naphthalenyl)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate was involved in this transformation (entry 5). Given that a weak acid proved beneficial for this reaction, we employed acetic acid as the solvent, achieving the target product **3** in 65% yield (entry 6). However, the yield of the desired product was dramatically decreased when the reaction was performed in the mixture of acetonitrile and acetic acid (entry 7). Interestingly as comparations, the amount of acetic acid also has a significant impact on the yield of the desired product (entry 8). Control experiments revealed that the acid, light and reaction temperature were vital for this transformation (entries 9–11). Further screening of the wavelength and power of the LEDs, the reaction temperature, the ratio of **1** and **2**, as well as the reaction times were optimized, as also shown in Table 1 (entries 12–15).

With the optimized conditions in hand, we next sought to investigate the scope of this EDA complex-promoted cascade radical annulation. As shown in Scheme 2a, a broad range of 2-alkynylthioanisoles with different groups on the aryl rings (R^1) readily underwent annulation with 4-cyano-2,6-lutidine or 4-cyanopyridine, affording the desired products (**3–21**) in moderate to good yields, and the structure of **18** was further confirmed by X-ray single crystal analysis. Notably, the electronic effect and position of the substituents had a significant influence on the cascade radical annulation, both strong electron-donating group (OCH_3) and strong electron-withdrawing substituent (CN) decrease the reaction efficiencies, and the *ortho*-substituted substrates also afford the desired products in lower yields, probably due to the steric hindrance. Moreover, when R^1 was replaced with naphthyl and thiophenyl group, the two substrates could also be tolerated well, undergoing the tandem reaction smoothly to give desired products **22–24** in 45–53% yields. Fortunately, when R^1 was an alkyl substituent, such as *tert*-butyl and *n*-butyl group, the corresponding products **25–27** were also obtained in good yields. Moreover, 2-alkynylselenoanisoles were also suitable substrates to deliver the desired products **28** and **29** in 40% and 30% yields, respectively. Additionally, the reaction could be easily scalable, and when the reaction was carried out on 4.8 mmol (1.08 g) scale, **3** was isolated in 60% yield. Unfortunately, 1-methoxy-2-(phenylethynyl)benzene and *N*,*N*-dimethyl-2-(phenylethynyl)aniline failed in this reaction under present conditions, no targeted products were observed, and the starting materials were quantitatively recovered.

Subsequently, different substituents (R^2) on the aromatic ring of thioanisole were also investigated, both electronic and steric effects appear negligible in this transformation, affording the desired products **30–34** in 48–71% yields. Pleasingly, the substituted benzoselenophene **35** was also obtained in 43% yield under the optimized conditions (Scheme 2b).

Encouraged by our success with cascade radical annulation of 2-alkynylthioanisoles and 4-cyano-2,6-lutidine or 4-cyanopyridine, we further wondered whether this protocol could be applied to other 2-alkynylphenyl alkylsulfanes (Scheme 2c). We were delighted to find that a variety of 2-alkynylphenyl alkylsulfides, such as ethyl phenyl sulfide, butyl phenyl sulfide and benzyl phenyl sulfide, all underwent such an annulation to generate desired products **36–39** in moderate-to-good yield. Noteworthy, for benzyl phenyl sulfide, different kinds of substitutes on the phenyl ring of benzyl group, such as chloro, fluoro, trifluoromethyl, methyl and *tert*-butyl, did not significantly affect the reaction, providing the desired products **40–44** in 62–72% yields.

To further extend the reaction scope, we focused on evaluating substituted 4-cyanopyridines. As shown in Scheme 2d, 2-methyl, 2-ethyl, 2-^{n}propyl and 2-^{t}butyl, 3-methyl, 3-chloro and 3-bromo substituted 4-cyanopyridine showed good compatibility with the reaction, delivering the corresponding products **45–51** in good yields (50–70%). To our surprise, 2,6-dimethylisonicotinonitrile, along with the 2-chloro, 2-bromo, and 2-CF_3 substituted 4-cyanopyridines, did not undergo the desired transformation, and the starting materials were recovered. Unfortunately, 2-cyanopyridine and 3-cyanopyridine also failed to react under the current conditions, no desired products were detected, and the starting materials were recovered unchanged. Furthermore, when 1,4-dicyanobenzene, 4-cyanoquinoline, and 5-pyrimidinecarbonitrile were employed as substrates, no new products were observed and the starting materials were recovered in all cases. To demonstrate the utility of this EDA complex mediate S-α-C(sp^3)–H activation strategy, the late-stage modification of segments of pharmaceutical molecule derivatives were



Scheme 2 Substrate Scope. Reaction conditions: **1** (0.22 mmol), **2** (0.2 mmol), CH_3COOH (4.0 mL), under N_2 atmosphere, 55–60 °C, 390 nm Kessil lamp (40 W), 24 h, Isolated yield.

also evaluated. The drug modified substrates, from pregnenolone and menthol, delivered the corresponding products **52–54** in 33–51% yields (Scheme 2e).

In order to gain a deeper mechanistic understanding of this annulation, a series of mechanistic studies were conducted. Firstly, we examined the ultraviolet-visible spectra of the reaction components and their mixture. As shown in Fig. 1a, both the appearance of a noticeable colour change and a bathochromic displacement absorption spectrum in the visible region were observed upon mixing **1** with **2** in the presence of

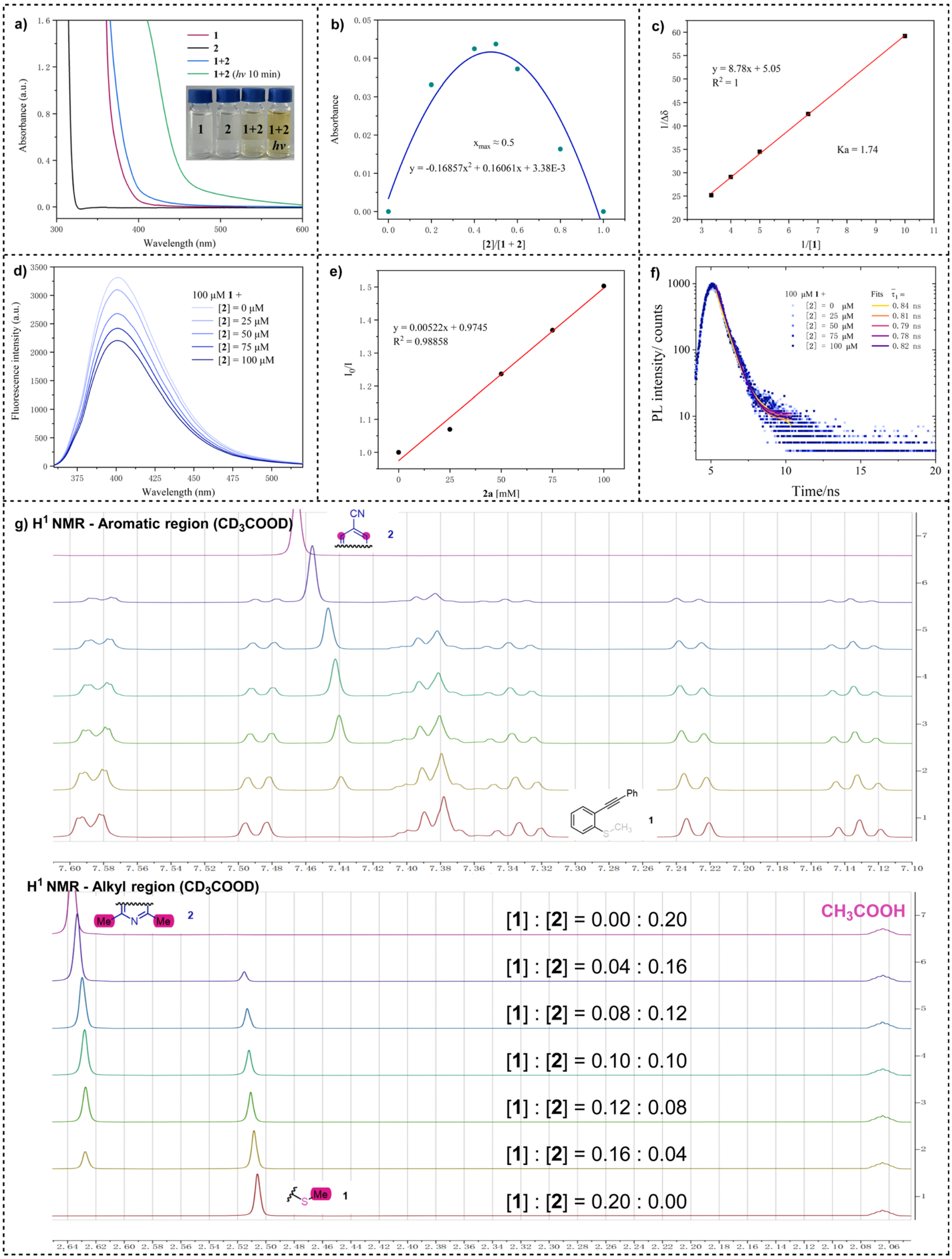
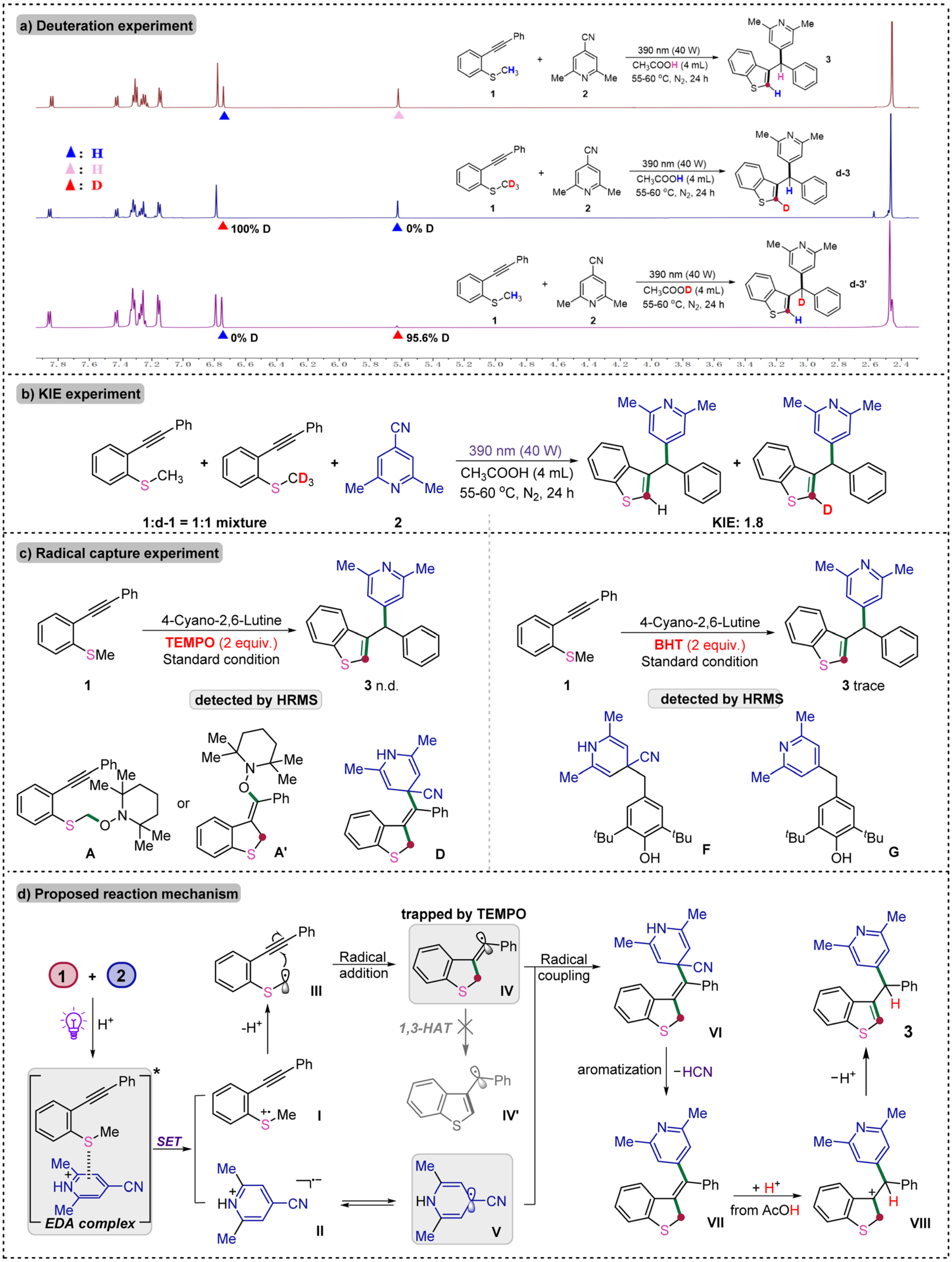


Fig. 1 (a) UV/Vis absorption spectra of the reaction components and their mixture; (b) Job's plot analysis; (c) association constant determination; (d) fluorescence quenching of **1** (1×10^{-4} M) by increasing concentrations of 4-cyano-2,6-lutidine; (e) Stern–Volmer plot of **1** quenching with 4-cyano-2,6-lutidine; (f) time-correlated single-photon counting decays of **1** in CH_3COOH in the presence of different concentrations of 4-cyano-2,6-lutidine, indicative of a static quenching process; (g) changes observed in the aromatic and aliphatic regions of the proton NMR spectra of the mixture during the NMR titration experiment.

acetic acid. Based on the UV-vis absorption of the EDA complex and the reaction conditions employed, we monitored the absorbance at 390 nm and plotted it as a function of the mole fraction of **2**. The results confirmed the formation of a 1 : 1 complex between **1** and **2** (Fig. 1b). The association constant (K_a) was determined to be 1.74 M^{-1} by ^1H NMR analysis in CD_3COOD (Fig. 1c). On the other hand, the Stern–Volmer quenching experiment showed the exited state of **1** could be reductively quenched by **2**, and the Stern–Volmer plot for **1** was fitted linearly with a quenching constant of $K_{sv} = 5.22 \times 10^{-3}$ M^{-1}



Scheme 3 (a) Deuteration experiment; (b) KIE experiment; (c) radical capture experiment; (d) proposed reaction mechanism.

(Fig. 1d and e). Notably, the fluorescence lifetime of **1** (τ_1–0.8 ns) is not affected by the increasing concentration of 4-cyano-2,6-lutidine (**2**), which shows the static character of the quenching and further confirms the formation of an EDA complex (Fig. 1f). Moreover, NMR titration experiments revealed that upon complexation, the acceptor (**2**) exhibited upfield shifts in both its aliphatic and aromatic regions, while the donor (**1**) underwent corresponding downfield shifts (Fig. 1g). To elucidate the reaction mechanism, density functional theory (DFT) calculations were carried out to investigate the reaction pathway. Weak-interaction analysis of the most populated conformer revealed a pronounced interaction between the lone-pair electrons on the sulfur atom and the pyridinium ring (SI for details). All of these observations confirm an EDA complex of **1** and **2** was formed in this reaction system. In addition, the switching light experiment suggested that the continuous irradiation of visible light is needed (Fig. S5), and the quantum yield for the process was determined and calculated as $\Phi = 0.29$, which suggested a photoinitiated chain transfer process could be excluded. It is worth noting that the isotope labeling experiments of the model reaction (Scheme 3a) revealed the 4-pyridylbenzyl hydrogen in the product **3** come from the reaction medium (acetic acid), ruling out the possibility of 1,3-HAT pathway to form the benzyl radical intermediate (**IV′**). Furthermore, to gain deeper insight into the rate-limiting step, we conducted a kinetic isotope effect (KIE) study of the reaction. The observed intermolecular competition KIE value of 1.8 suggests that deprotonation of the sulfur α-carbon is not the rate-determining step in this EDA-mediated transformation (Scheme 3b). Additionally, we found that radical scavengers, such as 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) and 2,6-ditert-butyl-4 methylphenol (BHT), inhibited the formation of the product (**3**), and the adducts of TEMPO or BHT with various radical species (**A**, **A′**, **F**, **G**) and the reaction intermediate **D** were all detected by high-resolution mass spectrometry (HRMS) analysis, demonstrating the radical intermediates in this cascade annulation process (Scheme 3c).

Based on the results of experimental investigations, we considered that the formation and excitation of an EDA complex of **1** and **2** are involved in the reaction, and a reasonable mechanism of this transformation was proposed, as shown in Scheme 3d. Initially, the interaction between methyl(2-(phenylethynyl)phenyl)sulfane (**1**) and 4-cyano-2,6-lutidine (**2**) with the assistant of acetic acid, resulting the formation of an EDA complex. Next, excitation of such an EDA complex under visible-light irradiation accelerates the single-electron transfer, leading to the formation of radical ion pairs, a sulfide radical cation (**I**) and a pyridinium radical anion (**II**). Then, the intermediate **I** undergoes deprotonation to deliver a S-α-alkyl radical **III**, which then generate the vinyl radical intermediate **VI** through intramolecular radical addition. Under acidic conditions, **II** equilibrates with **V**. Subsequently, the radical–radical cross coupling of **VI** and **V** producing intermediate **VI**, which simultaneously eliminating a HCN to give the intermediates **VII**, which is then protonated to obtain a cation intermediate **VIII**, and ultimately yield the desired product **3** by deprotonation.

Conclusions

In summary, our study presents an efficient and mild strategy for the construction of various 3-(4-pyridylbenzyl)benzothiophenes and benzoselenophenes from 2-alkynylthioanisoles and their derivatives using substituted 4-cyanopyridines as pyridination reagents under mild conditions. This photochemical protocol features photocatalyst-free and HAT reagent-free, broad substrate scope, good yields, high step and atom economy, transition-metal-free reaction conditions. Notably, the late-stage modification of pharmaceutical derivatives highlights the potential application of this strategy. Mechanistically, visible-light induced the intermolecular charge transfer within the EDA complex of 2-alkynylthioanisole and 4-cyano-2,6-lutidine enabled the single electron transfer (SET), accomplishing the sequential reactions of selective S-α-C(sp^3)–H bond activation, cyclization and radical coupling. Ongoing researches including further mechanism and the new applications of this photo-induced EDA complex mediated transformation are currently underway in our laboratory.

Author contributions

P. L. and M. W. conceived and supervised the project, and edited the manuscript. T. X. designed and carried out the experiments, analyzed the data, and prepared the manuscript. R. H. performed the computational studies presented in this paper. T. L. and D. Z. provided valuable assistance with the synthesis of compounds. J. Y. contributed to experimental testing and analysis. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6sc01281g.

Acknowledgements

We gratefully acknowledge the Young Talent Key Project of Anhui Province (No. 170808J02), the University Synergy Innovation Program of Anhui Province (No. GXXT-2020-078) and the Research Fund of Anhui Polytechnic University (No. 2023YQQ0001, S022024011) for financial support of this work.

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