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Photoredox catalytic alkylarylation of alkynes with arylsulfonylacetate as bifunctional reagent

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Difunctionalization of alkynes represents a powerful and straightforward approach to the synthesis of complex molecules. However, the radical difunctionalization of alkynes mediated by bifunctional reagents remains challenging and underexplored, despite significant progress having been made in alkene difunctionalization. Here, we report a novel arylsulfonylacetate skeleton in which aryl rings are attached to acetates through SO_2, serving as a powerful bifunctional reagent for the alkylarylation of alkynes *via* vinyl-radical intermediate under photoredox conditions. This modular bifunctional reagent enables the simultaneous incorporation of a wide range of functional groups, including (hetero)aryl ring and alkyl carboxylate into alkynes, resulting in synthetically valuable all-carbon tetrasubstituted alkene derivatives. This transformation is distinguished by its redox-neutral nature, readily accessible starting materials, compatibility with diverse functional groups and its capacity to facilitate convergent synthesis. The utility of this approach was further demonstrated by the late-stage functionalization of complex molecules and the preparation of fluorescent molecules and anti-cancer drugs.

bifunctional reagent, photoredox catalysis, Smiles rearrangement, alkylarylation, tetrasubstituted acyclic all-carbon olefins

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1 Introduction

Difunctionalization of unsaturated carbon-carbon bonds provides a robust tool for the conversion of simple alkenes or alkynes into complex molecules, which is consistently of high interest and challenging from both academic and industrial perspectives [1]. Thanks to significant advances in photocatalysis [2] and electrosynthesis [3], radical-mediated difunctionalization has received considerable attention from synthetic chemists, because of its inherent features of high efficiency in increasing molecular complexity and product diversity [4]. As an important subset, several brilliantly designed bifunctional reagents (BFRs), which employ a linker to bind two individual components, have recently been used for the rapid difunctionalization of unsaturated carbon-carbon bonds [5]. In particular, sulfonyl bifunctional reagents mediated difunctionalization procedures involving a Smiles-Truce rearrangement have been extensively investigated for the derivatization of alkenes by Zhu *et al*. [6] and Stephenson *et al*. [7] independently (Figure 1a). Recently, Nevado *et al*. [8] described enantioenriched arylsulfinylamides for the asymmetric aminoarylation of alkenes. In stark contrast, the utilization of bifunctional reagents for the difunctionalization of alkynes has been rarely documented. This disparity is particularly surprising considering the wide application of alkynes as radical acceptors in organic reactions [9]. The

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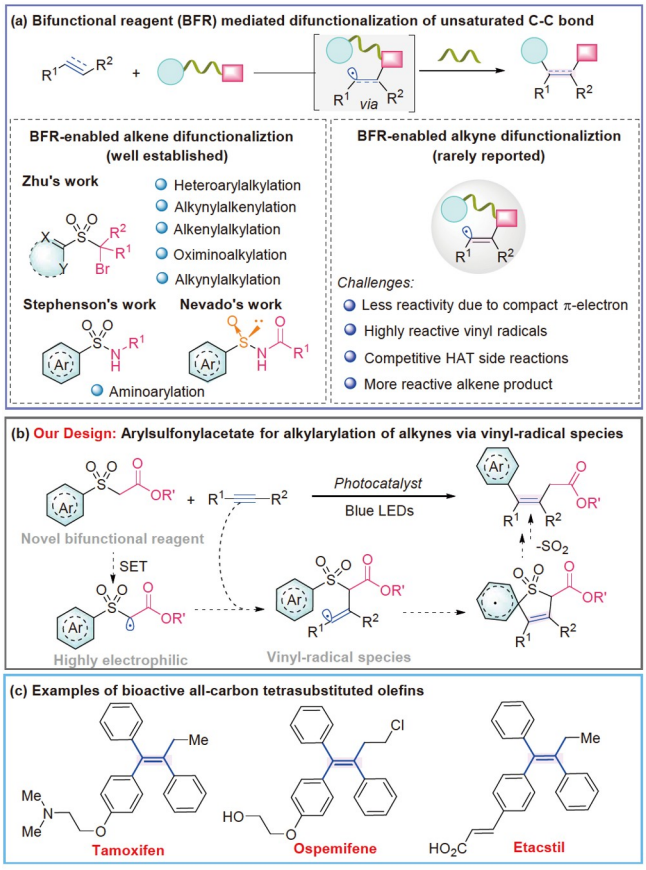


Figure 1 General radical difunctionalization of alkenes and examples of functional-group-migration (FGM) strategies (color online).

scarcity of such a strategy in alkyne difunctionalization can be attributed to the rather bulky skeleton of internal alkynes, their inherent compact π electrons, the instability of vinyl radical intermediates and the presence of various competitive side reactions (Figure 1a) [10].

Given that the introduction of more electron-withdrawing groups would enhance the electrophilicity of radicals, thus facilitating their addition to the compact π electrons of alkynes, and considering that a sequential intramolecular cascade transformation might effectively suppress undesired side reactions, we envisioned the idea of utilizing bifunctional reagents for the difunctionalization of alkynes (Figure 1b). Inspired by the above-mentioned seminal works [6–8] and our previous reports on radical difunctionalizations [11], we conceived the idea that aryl rings anchored to acetates *via* SO_2 could serve as a potential bifunctional reagent. Theoretically, single-electron oxidation of the sulfonyl acetate generates a highly electrophilic radical, which can then be incorporated into alkynes *via* radical addition. Next, the nascent vinyl radical triggers a sequential Smiles rearrangement to yield the final difunctionalized products. If successful, two valuable functional groups, alkyl carboxylate and aryl rings would be installed across an alkyne, ultimately resulting in the formation of synthetically useful all-carbon tetrasubstituted alkenes which are commonly found in natural products, pharmaceuticals and organic functional materials [12] (Figure 1c).

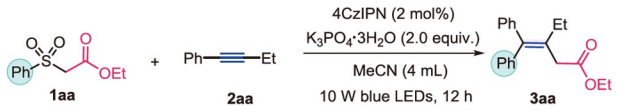
As a result, we hereby report the successful implementation of this strategy to develop arylsulfonylacetate as a bifunctional reagent for the efficient difunctionalization of alkynes, allowing for concomitant incorporation of alkyl carboxylates and aryl groups into alkynes [13]. This novel approach is compatible with both internal and terminal alkynes, manifesting an excellent functional group tolerance. Moreover, the advantages of these bifunctional reagents are highlighted by their modular structure diversity and high efficiency for the difunctionalization of alkynes in a straightforward single-step operation, which would further inspire the future development of the concept.

2 Results and discussion

We initiated our study by employing ethyl 2-(phenylsulfonyl)acetate **1aa** as a bifunctional reagent and but-1-yn-1-ylbenzene **2aa** as the radical acceptor. To our delight, a promising 68% yield of the difunctionalized tetrasubstituted olefin **3aa** was obtained using the organic fluorophore 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) as the photocatalyst and 1.5 equiv. of K_3PO_4 as the base (Table 1, entry 1). Next, different photocatalysts, including 2,4,6-triphenylpyrylium tetrafluoroborate (TPT), $Ru(bpy)_3Cl_2·6H_2O$, and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ were tested, but none of them gave superior results (Table 1, entries 2–4). It is noteworthy that the choice of base had a significant impact on the reaction. A series of base screenings finally led us to figure out that 2.0 equiv. of $K_3PO_4·3H_2O$ yielded 89% of the product (Table 1, entries 5–9). In addition, we also explored the solvent effect. However, neither *trans*-1,2-dichloroethylene (DCE), tetrahydrofuran (THF) nor *N*,*N*-dimethylformamide (DMF) could further improve the reaction yield (Table 1, entries 10 and 11). Further control experiments revealed that the photocatalyst, light irradiation and $K_3PO_4·3H_2O$ were critical, as no desired product formation was observed in the absence of any of these parameters (Table 1, entry 12).

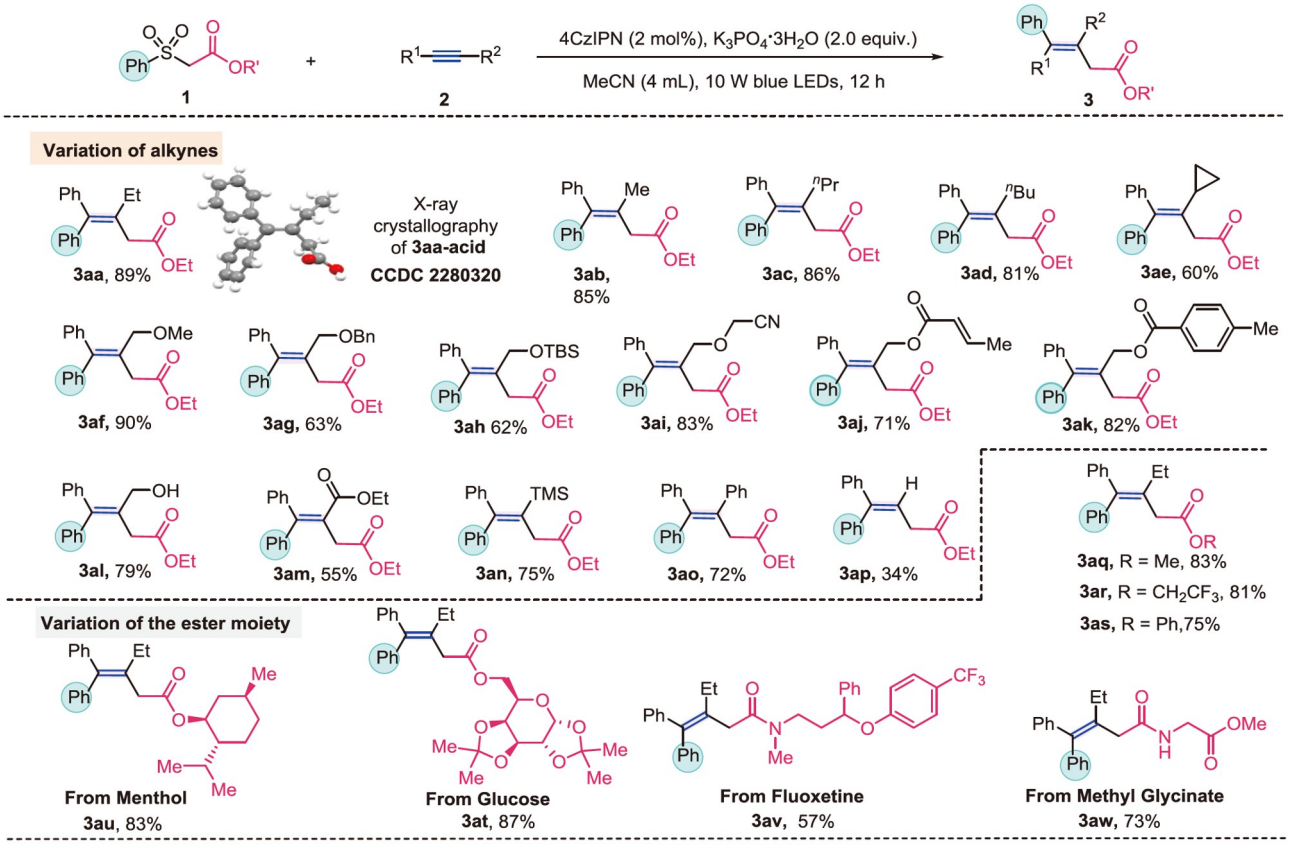
Having identified the optimal reaction conditions, we set out to investigate the generality of this protocol (Scheme 1). First, we screened a variety of alkynes with different functionalities. Increasing the length of the alkyl chain on the alkyne did not significantly affect the reaction efficiency. All the corresponding alkenes were obtained in good yields with excellent regioselectivities (**3aa**–**3ad**), which was attributed to the resonance stabilization of the nascent vinyl radicals through p-π conjugation. It is worth noting that the structure of **3aa** was unambiguously confirmed by X-ray analysis of

Table 1 Optimization of reaction conditions[a)]



Entry	Variations of the standard conditions	Yield of **3aa** (%)[b)]
1	1.5 equiv. of K_3PO_4 was used as base for 24 h	68
2[c)]	TPT instead of 4CzIPN	0
3[c)]	$Ru(bpy)_3Cl_2·6H_2O$ instead of 4CzIPN	55
4[c)]	1 mol% $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ instead of 4CzIPN	61
5	1.5 equiv. of Na_2CO_3 was used as base for 24 h	16
6	1.5 equiv. of K_2CO_3 was used as base for 24 h	70
7	1.5 equiv. of $K_3PO_4·3H_2O$ was used as base for 24 h	73
8	Running for 24 h	89
9	None	89
10	DCE or DMF instead of MeCN	<5
11	THF instead of MeCN	15
12	Without $K_3PO_4·3H_2O$ or 4CzIPN or in dark	0

a) Reaction conditions: **1aa** (0.2 mmol, 1.0 equiv.), **2aa** >(0.4 mmol, 2.0 equiv.), 4CzIPN (2 mol%), $K_3PO_4·3H_2O$ (0.4 mmol), in CH_3CN (4.0 mL) irradiated with 10 W blue LED for 12 h. b) Isolated yield. c) 1.5 equiv. of K_3PO_4 was used as the base. For experimental details, see the Supporting Information online.

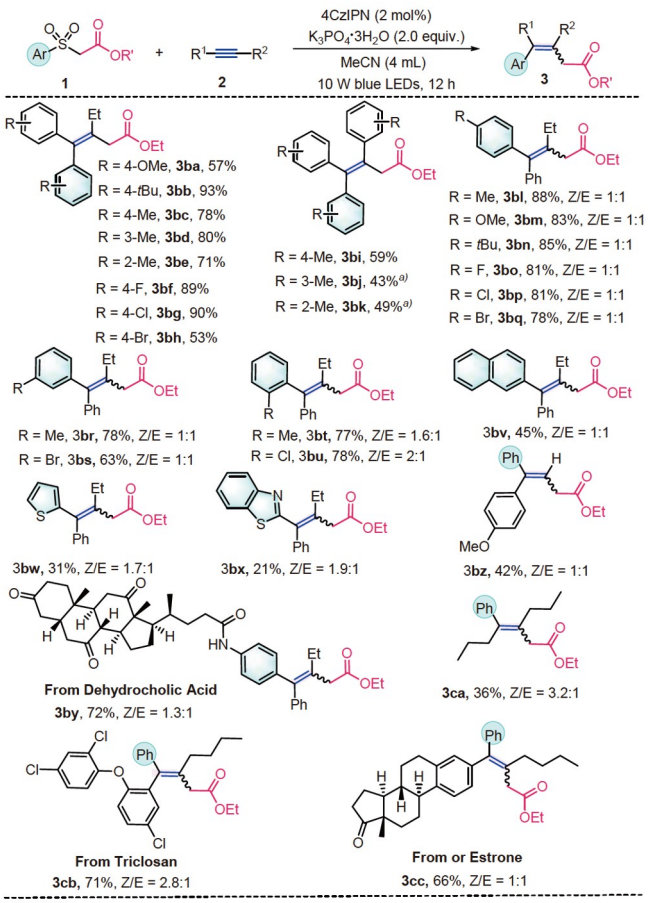


Scheme 1 Substrate scope investigation. Reactions were carried out on 0.2 mmol scale and isolated yields were given. For details see Supporting Information online (color online).

the corresponding acid derivative [14]. When cyclopropane-bearing internal alkyne was subjected to the standard conditions, the expected alkene (**3ae**) was obtained in a 60% yield. Alkynyl alcohols with different protecting groups, including methyl, benzyl, *tert*-butyldimethylsilyl, cyanomethyl and esters (**3af**–**3ao**), were all amenable to providing the desired tetrasubstituted alkenes in moderate to good yields. The double bond in the substrate was also tolerated, as exemplified by the successful conversion of the acrylate alkyne into **3aj** in a 71% yield. The inert reactivity of **1aa** toward the double bond in acrylate was attributed to the mismatched polarity between the electrophilic radical intermediate and electron-poor acrylate. Although alkyne with free alcohols was incompatible under the standard conditions, *p*-sulfonyl chloride was shown to act as a traceless protecting group under the standard conditions, providing the alcohol-substituted alkene **3al** in a 79% yield from the sulfonate-protected substrate. In addition, alkynes with electron-withdrawing ester groups could also proceed smoothly under the optimal reaction conditions, delivering the desired product (**3am**) in a 55% yield. Intriguingly, it was found that the trimethylsilyl group remained intact during this photocatalyzed difunctionalization cascade to give a 75% yield of **3an**. Moreover, 1,2-diphenylethyne was successfully applied in this reaction to render the corresponding product (**3ao**) in a moderate 72% yield. Terminal alkyne and ethynylbenzene could also be used, albeit with a poor 34% yield of product **3ap** formation. This lower yield is mainly ascribed to the less electron-rich nature of terminal alkynes compared with internal ones.

Next, we evaluated the variation of the ester moieties in the bifunctional reagents. As shown in Scheme 1, different alkyl esters (**3aq** and **3ar**) and phenolate (**3as**) could be incorporated into alkynes within our method. Furthermore, bifunctional reagents derived from complex molecules such as protected glucose, menthol, sulfonylacetamide-bearing drug molecules and amino acid derivatives were all compatible to efficiently afford the desired all-carbon tetrasubstituted alkenes in moderate to good yields and good regioselectivities (**3at**–**3aw**). These results highlight the modular structure diversity of the bifunctional reagents and the robustness of their application in alkyne difunctionalization.

We further examined the scope of the BFRs consisting of different aromatic rings and alkyl acetate groups (Scheme 2). Phenyl rings bearing both electron-donating groups, including methyl, *tert*-butyl, and methoxy groups, and electron-withdrawing halogens all underwent the difunctionalization reaction smoothly to provide the alkenes **3ba**–**3bh** in yields ranging from 53% to 93%. Reactions of BFRs with 1,2-diphenylethynes also occurred efficiently to produce **3bi**–**3bk** in moderate yields, regardless of the steric effect of the substrates. Furthermore, a series of BFRs with



Scheme 2 Substrate scope investigation. Reactions were carried out on 0.2 mmol scale and isolated yields were given. a) Reaction for 24 h. For details see Supporting information (color online).

different aryl substituents were evaluated with but-1-yn-1-ylbenzene. In general, the reaction exhibits high efficiency for the difunctionalization of the alkyne. Phenyl rings with either electron-donating or electron-withdrawing groups, naphthalene (**3bv**), thiophene (**3bw**), benzothiazole (**3bx**) and BFR derived from dehydrocholic acid (**3by**), have all been explored under the standard conditions, leading to the desired products in moderate yields. Internal alkynes derived from triclosan or estrone were also effective substrates to furnish the desired alkenes (**3cb** and **3cc**) in 71% and 66% yields. However, in most cases, a nearly 1:1 mixture of the two stereoisomers was obtained. Attempts to enhance the stereoselectivity of this reaction by introducing bulky substituents on the substrates [15] were unsuccessful, although some of the relatively bulky substrates (**3bu** and **3ca**) give Z/E ratios of 2:1 or 2.8:1. Given the propensity of olefins to undergo photosensitization [16], we assumed that the diminished stereoselectivity of the products might be attributed to the photoisomerization process under the standard conditions.

To validate our hypothesis, two mixtures containing dif-

ferent Z/E ratios of the product **3bm** were isolated and submitted to the standard conditions. As expected, both reactions gave a similar 1:1 mixture of the Z/E stereoisomers. Moreover, either a 4:1 mixture of the Z/E stereoisomers of **3bw** or a mixture of 1.3:1 ultimately reached the same result with a ratio of 1.7:1, which is consistent with the outcome of the difunctionalization reaction (Figure 2a). We speculated that this ratio of Z/E stereoisomer is closely related to the photostationary state [17] of the generated alkene. These results clearly demonstrate that the photoisomerization process occurred and photostationary states of those tetrasubstituted alkenes could be reached and maintained under the standard conditions [18].

The utility of this chemistry was then demonstrated by the gram-scale synthesis of **3ao** in a moderate 61% yield (Figure 2b). Furthermore, preliminary investigations into the optical properties of **3ao** and the other three analogs (**3bi**–**3bk**) were conducted. The fluorescence spectra showed that these molecules exhibited emissions peaks at 418 nm, falling within the blue light region (Figure 2c). Due to the good photostability and the presence of readily derivatizable carboxylate groups on these molecules, they may serve as fluorescent probes and warrant further investigation. To further illustrate the potential application of this approach, readily available BFR **4** was efficiently converted to tetrasubstituted alkene **5** under standard conditions. Subsequent reduction and chlorination steps yielded compound **6**, which could then be further transformed into the anti-cancer drug Etacstil **8** *via* a Heck reaction followed by hydrolysis or into Toremifene and Ospemifene *via* documented cross-coupling reactions [19] (Figure 2d).

To shed light on the reaction mechanism, a series of control experiments were carried out. First, the radical nature of the reaction was confirmed through a radical trapping experiment. When 2.0 equiv. of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was introduced into the reaction mixture, the reaction was completely halted, and the TEMPO adduct **9** was detected. In addition, 1,1-diphenylethene was also demonstrated to be a good radical capture reagent to give adduct **10** in an excellent 97% yield (Figure 3a). Then, a deuterium labeling experiment was performed. When the reaction was carried out in the presence of 5 equiv. of D_2O, we isolated an 18% yield of the deuterated product **3aa'** alongside a 71% yield of **3aa**. Conversely, treating **3aa** with D_2O under the standard conditions did not result in any deuterium labeling, suggesting that the H/D exchange of

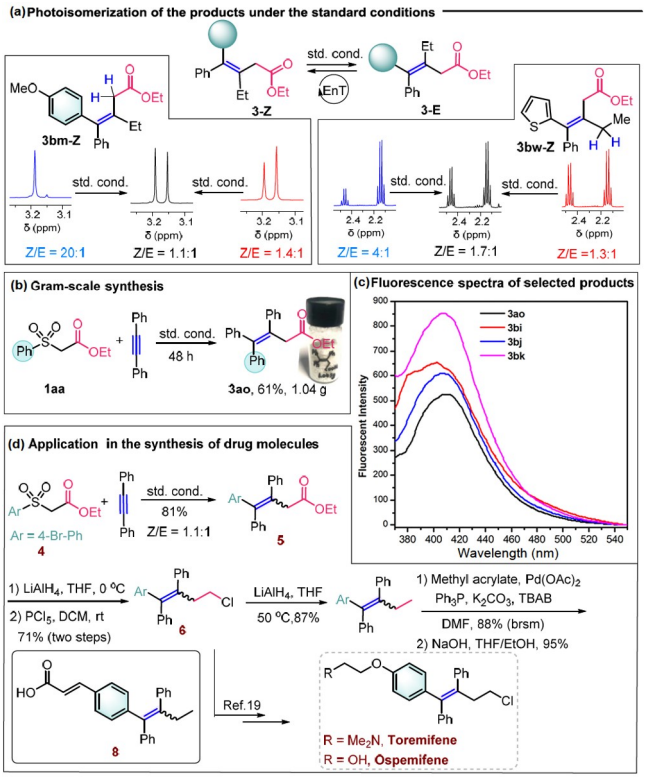


Figure 2 Photoisomerization and synthetic application (color online).

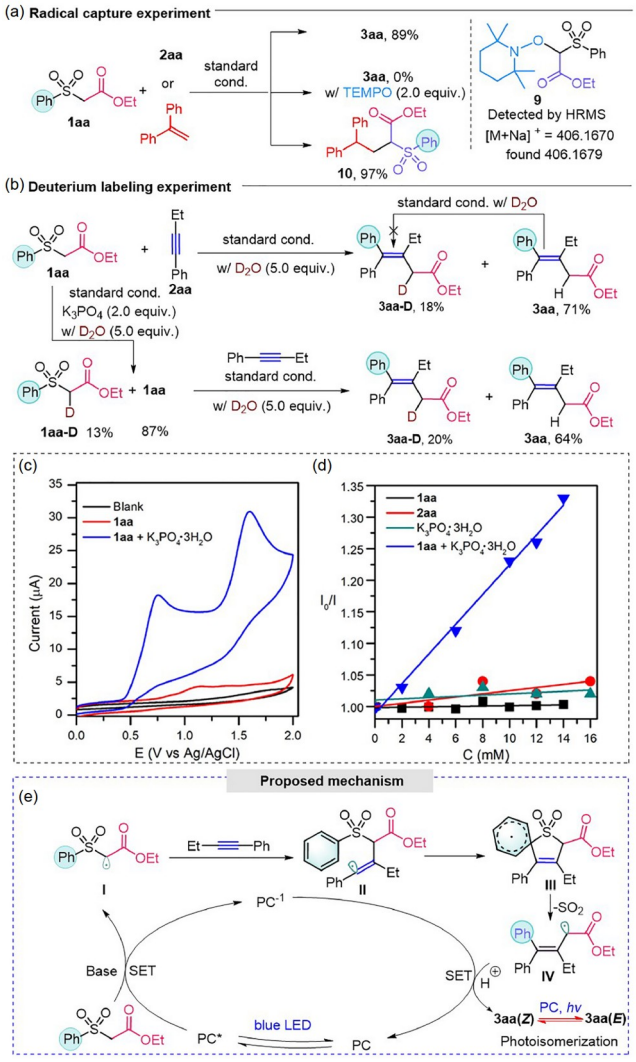


Figure 3 Mechanism investigation (color online).

product **3aa** did not take place in the reaction system. In addition, when substrate **1aa** was exposed to the standard conditions in the presence of 5 equiv. of D_2O, 13% of deuterium labeling was observed. Further difunctionalization of **2aa** with the mixture of **1aa-D** and **1aa** within D_2O provides a 20% yield of deuterium-labeled product **3aa-D**. Starting with 13% of deuterium-labeled **1aa**, obtaining a 20% yield of deuterium-labeled **3aa-D**, clearly indicates that deuterium labeling was operational during the cascade process (Figure 3b). Taken together, these results suggest that a radical polar cross-over process enabled protonation was operational. Subsequently, cyclic voltammetry (CV) experiments were carried out to gain insight into the oxidative process (Figure 3c). Compound **1aa** exhibited a broad peak at 1.2 V and displayed the first distinct oxidation peak at 0.76 V in the presence of a base. These results indicate that the oxidation of **1aa** by the excited state *4CzIPN ($E_{1/2}$(*P/P$^-$) = 1.35 V *vs.* SCE is thermodynamically feasible [20], especially in the presence of a base. This is also consistent with the fact that the fluorescence of the excited photocatalyst could be efficiently quenched by the mixture of **1aa** and base (Figure 3d). Additionally, the light on/off experiment, as well as a measured quantum yield of 0.31 for the reaction, led us to rule out the possibility of a radical chain mechanism (See Supporting Information online).

Based on the control experiments and previous literature [21], a plausible mechanism was proposed (Figure 3e). The photocatalyst (PC) is irradiated by blue light to its excited state, which undergoes a single electron transfer event with **1aa** to afford alkyl radical **I**. Electrophilic radical addition to the triple bond of alkyne forms vinyl radical **II**. Subsequently, radical **II** undergoes *ipso*-radical addition to the phenyl ring to form a spiro radical species **III**. Fragmentation, accompanied by the extrusion of SO_2, produces alkyl radical **IV**. This transient species is then reduced *via* another SET event from PC^{-1} followed by protonation to give the desired alkene **3**, concomitantly regenerating PC to complete the photo-redox cycle. Once product **3** is formed in the reaction system, photoinduced isomerization of the generated alkene occurs, which accounts for the diminished Z/E ratio of the obtained products.

3 Conclusions

In conclusion, we have disclosed a novel arylsulfonylacetate skeleton in which aryl rings are tethered to acetates through SO_2, as a powerful bifunctional reagent for the alkylarylation of alkynes under photoredox conditions. This modular bifunctional reagent allows for the simultaneous incorporation of (hetero)aryl ring and alkyl carboxylate into alkynes, facilitating the synthesis of a diverse library of synthetically valuable all-carbon tetrasubstituted alkene derivatives. This method features mild reaction conditions, high atom- and step-economy, excellent functional group compatibility and great structural diversity. Given the current easy availability of arylsulfonylacetate bifunctional reagents, along with the ubiquity of alkynes as feedstock substrates, we anticipate this method would serve as a highly enabling platform for research endeavors aimed at synthesizing synthetically useful all-carbon tetrasubstituted alkenes in a single operation. The success of this strategy using bifunctional reagents for the difunctionalization of alkynes *via* vinyl-radical species is expected to stimulate further investigation of the concept. Further investigations are currently underway in our laboratory to address the application of these bifunctional reagents in a stereo-controlled manner.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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18 DFT calculations revealed that the energy barrier between the E/Z isomers of alkene **3bm** was found to be extremely low (less than 0.1 kcal/mol). This finding aligns with the obtained poor E/Z ratios of the generated alkenes (for details, see Supporting Information)

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