

Photoredox Catalytic Alkylarylation of Alkynes with Arylsulfonylacetate as Bifunctional Reagent

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Abstract: The radical difunctionalization of alkynes represents a powerful and straightforward approach for the synthesis of sophisticated molecules. However, the difunctionalization of alkynes mediated by bifunctional reagents remains unexplored, 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 SO₂, serving as a powerful bifunctional reagent for the alkylarylation of alkynes 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 synthetic 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, the preparation of fluorescent molecules and anti-cancer drugs.

Alkynes are among the most fundamental and versatile structural motifs utilized in organic synthesis¹⁻⁴. The difunctionalization of alkynes represents one of the most efficient and straightforward strategies for the rapid assembly of diverse alkenes, which is consistently of high interest and challenging from both academic and industrial perspectives⁵⁻¹⁰. Thanks to significant advances in photocatalysis¹¹⁻¹⁸ and electrocatalysis¹⁹⁻²¹, the radical difunctionalization of alkynes has gained considerable attention due to its high efficiency, substrate versatility and operational simplicity. In general, most of the developed radical difunctionalization reactions of alkynes proceed through one of the following mechanisms²²⁻²⁴: 1) In situ generated radical species initiate an addition onto the π system of internal alkynes to form highly reactive vinyl radicals. Subsequently, intermolecular radical capture occurs, resulting in the formation of the difunctionalized products. 2) In case where alkynes contain radical acceptors, the vinyl radical intermediates can be intercepted by the intramolecular unsaturated system, leading to cyclic products via radical addition/cyclization cascade (Fig. 1 A). Despite significant progress made in the recent years, these methods are limited by multi-step substrate manipulation, insufficient substrate scope, low atom-economy and restricted product diversity. Therefore, the development of new models for the radical difunctionalization of alkynes remain highly sought-after.

Bifunctional reagent, which employs a linker to bind two individual components, have recently been used for the rapid difunctionalization of unsaturated carbon-carbon bond²⁵⁻³³. Several brilliantly designed molecules have demonstrated powerful capacity as surrogates for both radical donors and acceptors, enabling the efficient difunctionalization of alkenes by Zhu³⁴⁻³⁸, Stephenson³⁹⁻⁴¹, Nevado⁴² and Hong⁴³⁻⁴⁵. In stark contrast, the use of bifunctional reagents for the difunctionalization of alkynes remains unexplored. The 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 reactions⁴⁶.

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

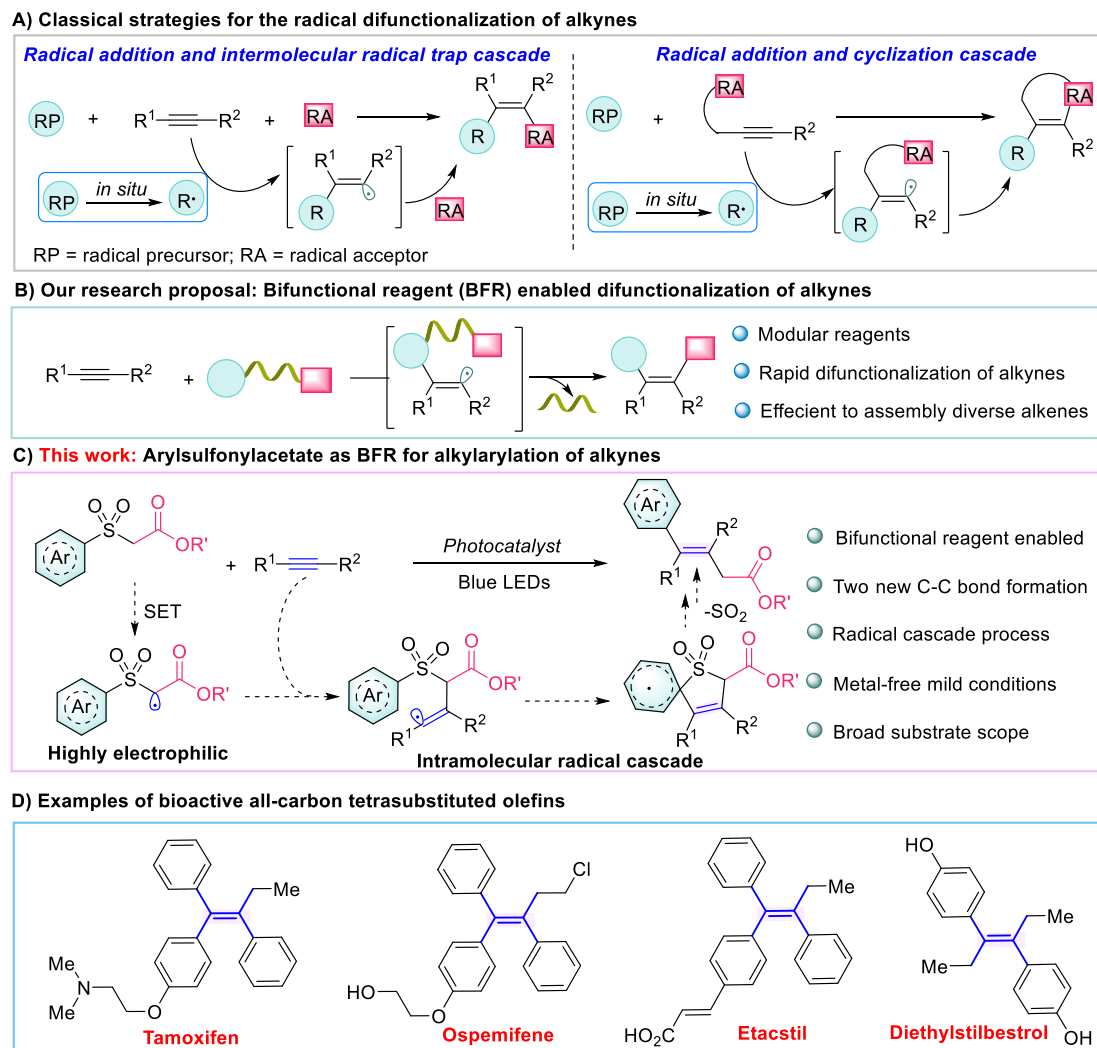


Fig. 1 Overview of radical difunctionalization of alkynes and our bifunctional reagents mediated strategy

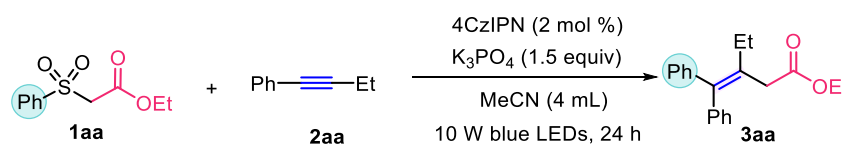
difunctionalization of alkynes (**Fig. 1 B**). Inspired by the above-mentioned seminal works and our previous reports on the radical difunctionalizations⁴⁷⁻⁴⁹, we conceived the idea that aryl rings anchored to acetates via SO_2 could serve as a potential bifunctional reagent. Theoretically, a single-electron 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 (**Fig. 1 C**). 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 materials⁵⁰⁻⁵⁴ (**Fig. 1 D**).

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 methyl carboxylate and aryl groups into alkynes (Fig. 1 C). To the best of our knowledge, this represents the first example of bifunctional reagents mediated difunctionalization of alkynes through a photoredox cascade reaction. 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.

Results

Reaction optimization. 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 K_3PO_4 as the base (Table 1, entry 1). Next, different photocatalyst including 2,4,6-triphenylpyrylium tetrafluoroborate (TPT), $Ru(bpy)_3Cl_2 \cdot 6H_2O$, 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 screening finally led us to figure out that 2.0 equiv of $K_3PO_4 \cdot 3H_2O$ provided the best yield of 89% for the product (Table 1, entries 5-9). In addition, we also explored the solvent effect. However, neither DCE, THF nor DMF could further improve the reaction yield (Table 1, entry 10 and 11). Further control experiments revealed that the photocatalyst, light irradiation and $K_3PO_4 \cdot 3H_2O$ 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 (Fig. 2). First, we screened a variety of alkynes with different functionalities. Increasing the length of 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 ambiguously confirmed by X-ray

Table 1 Optimization of the reaction conditions^a


Entry	Variations of the standard conditions	Yield of 3aa (%) ^b
1	None	68
2	TPT instead of 4CzIPN	0
3	Ru(bpy) ₃ Cl ₂ ·6H ₂ O instead of 4CzIPN	55
4	1 mol% [Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆ instead	61
5	Na ₂ CO ₃	16
6	K ₂ CO ₃ instead of K ₃ PO ₄	70
7	K ₃ PO ₄ ·3H ₂ O instead of K ₃ PO ₄	73
8	2.0 equiv of K ₃ PO ₄ ·3H ₂ O was used	89
9	With 2.0 equiv of K ₃ PO ₄ ·3H ₂ O for 12h	89
10 ^c	DCE or DMF instead of MeCN	< 5
11 ^c	THF instead of MeCN	15
12 ^c	Without K ₃ PO ₄ ·3H ₂ O or 4CzIPN or in dark	0

^aReaction conditions: **1aa** (0.2 mmol, 1.0 equiv.), **2aa** (0.4 mmol, 2.0 equiv.), 4-CzIPN (2 mol%), K₃PO₄ (0.3 mmol), in CH₃CN (4.0 mL) irradiated with 10 W blue LED for 24 h. ^bIsolated yield. ^c Reaction for 12 h. For experimental details, see the Supplementary Information.

analysis of the corresponding acid derivative⁵⁵. 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. 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 75% yield of **3an**. Moreover, 1,2-

diphenyl ethyne was successfully applied in this reaction to render the corresponding product (**3ao**) in a moderate 72% yield. Terminal alkyne, ethynylbenzene, could also be used, albeit with a poor 34% yield of product **3ap** formation.

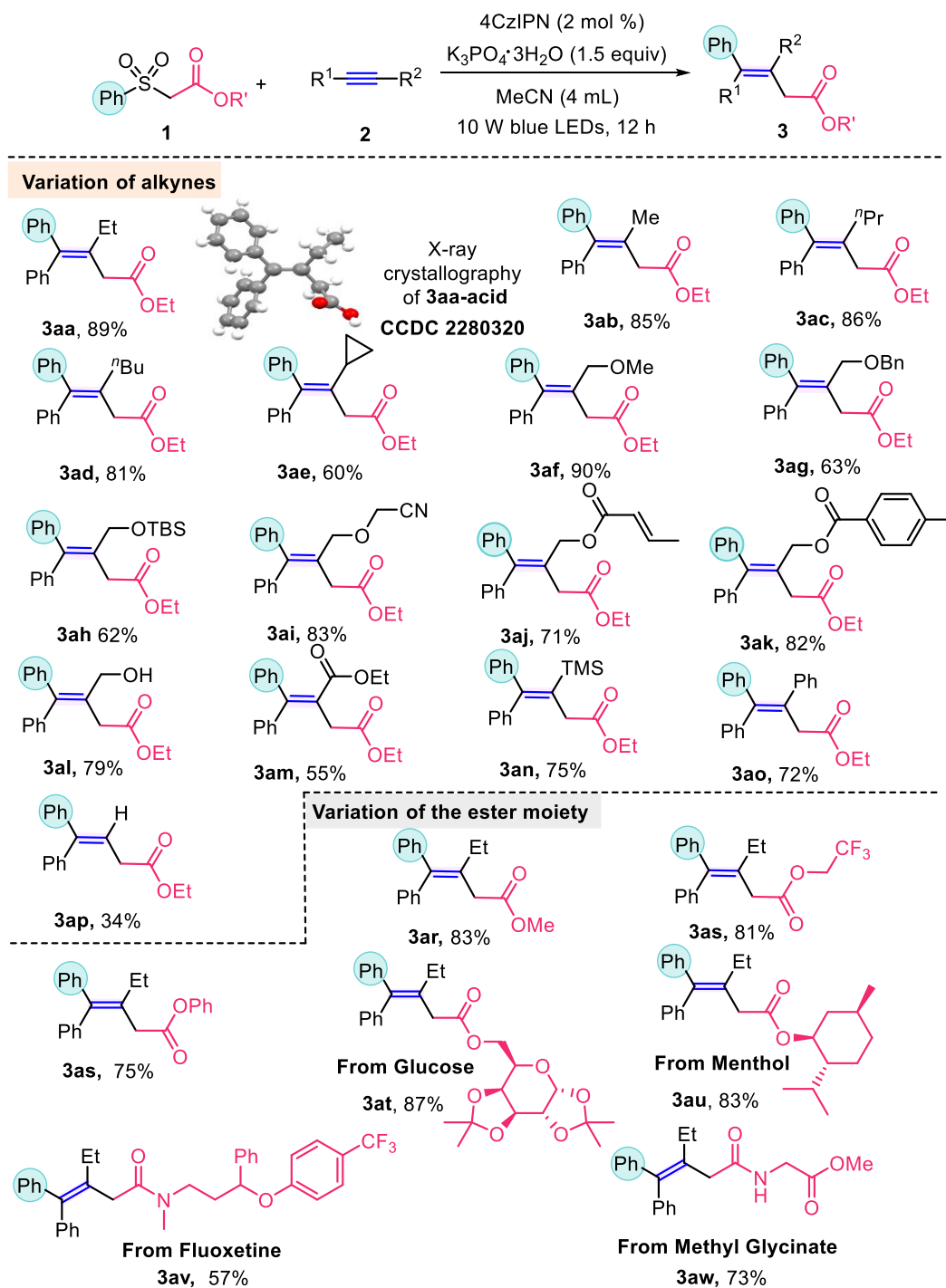


Fig.2 Substrate scope investigation. ^a Reactions were carried out on 0.2 mmol scale and isolated yields are given.

for details see Supplementary Information.

Next, we evaluated the variation of the ester moieties in the bifunctional reagents. As shown in **Fig. 2**, 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, sulfonamide-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 (**Fig.3**). 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-diphenylethyne also occurs efficiently to produce **3bi-3bk** in moderate yields, regardless of steric effect of the substrates. Furthermore, a series of BFRs with different aryl substitutions 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 were obtained. Attempts to enhance the stereoselectivity of this reaction by introducing bulky substitutions on the substrates⁵⁶⁻⁵⁷ 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 photosensitization⁵⁸, 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 different *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

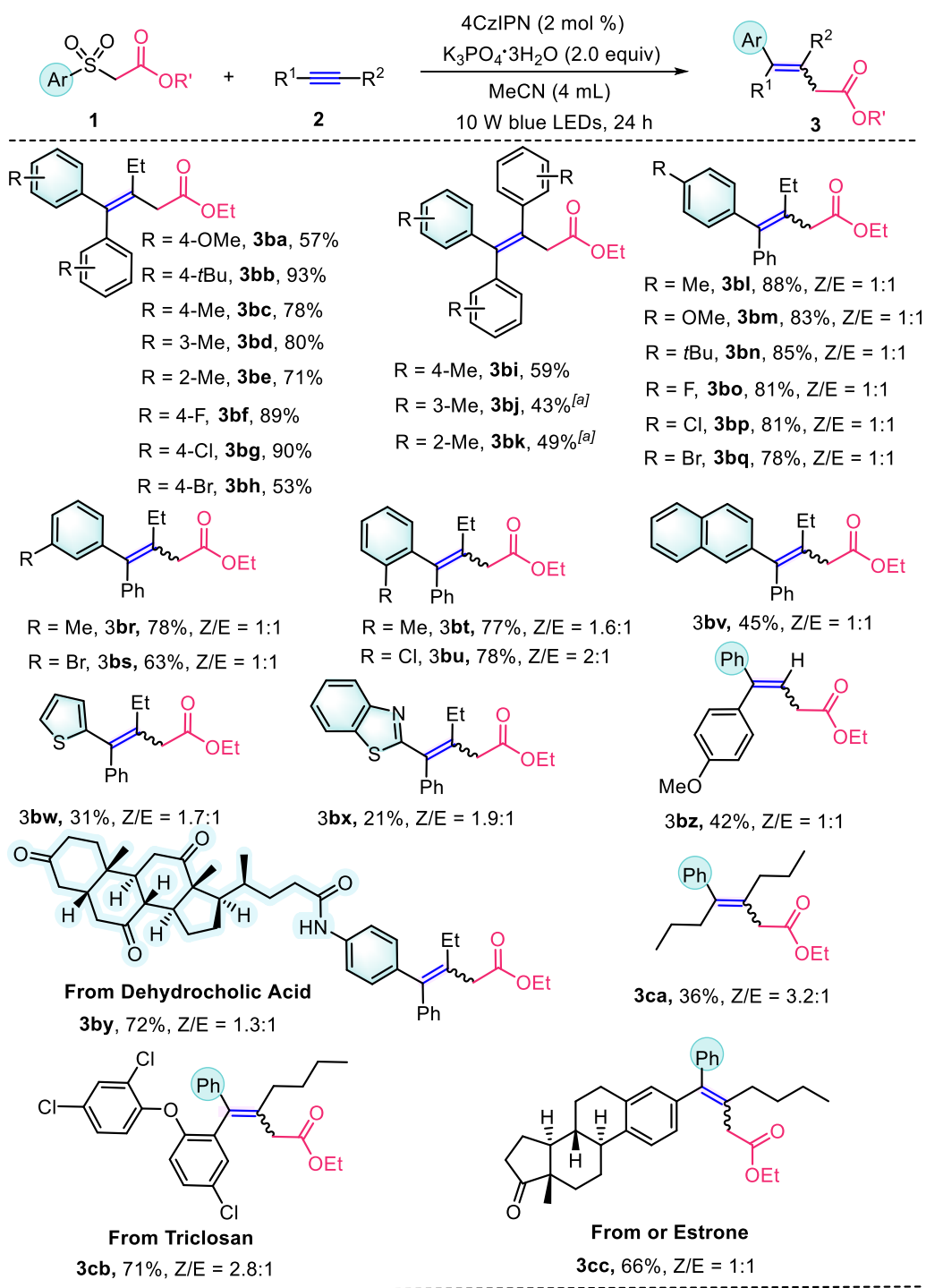
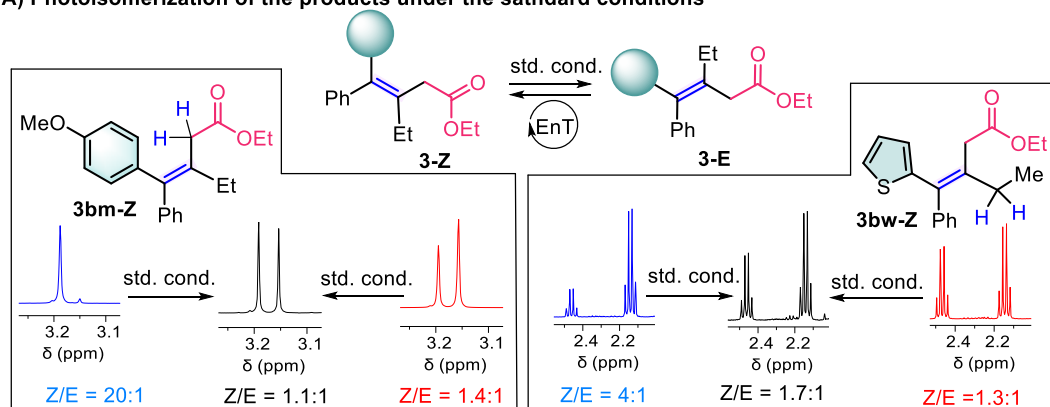


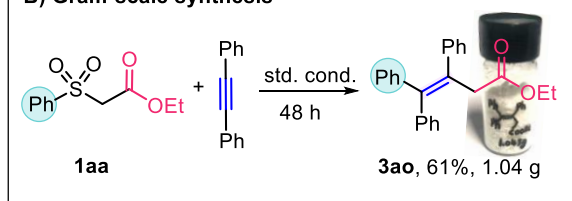
Fig.3 Substrate scope investigation. a Reactions were carried out on 0.2 mmol scale and isolated yields are given. for details see Supplementary Information.

with the outcome of the difunctionalization reaction. We speculated that this ratio of Z/E stereoisomer is closely related to the photostationary state⁵⁹⁻⁶⁰ of the generated alkene. These results clearly demonstrate that photoisomerization process occurred and photostationary states of those tetrasubstituted alkenes could be reached and maintained under the standard conditions⁶¹ (**Fig. 4 A**).

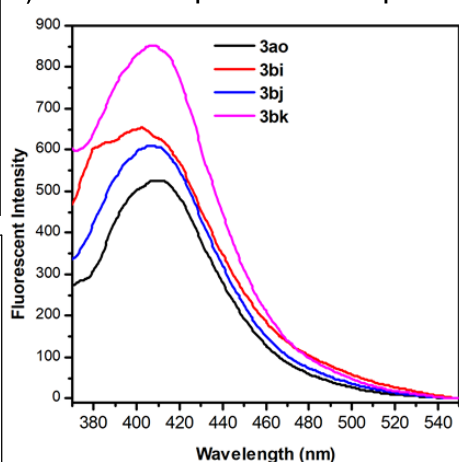
A) Photoisomerization of the products under the standard conditions



B) Gram-scale synthesis



C) Fluorescence spectra of selected products



D) Application in the synthesis of drug molecules

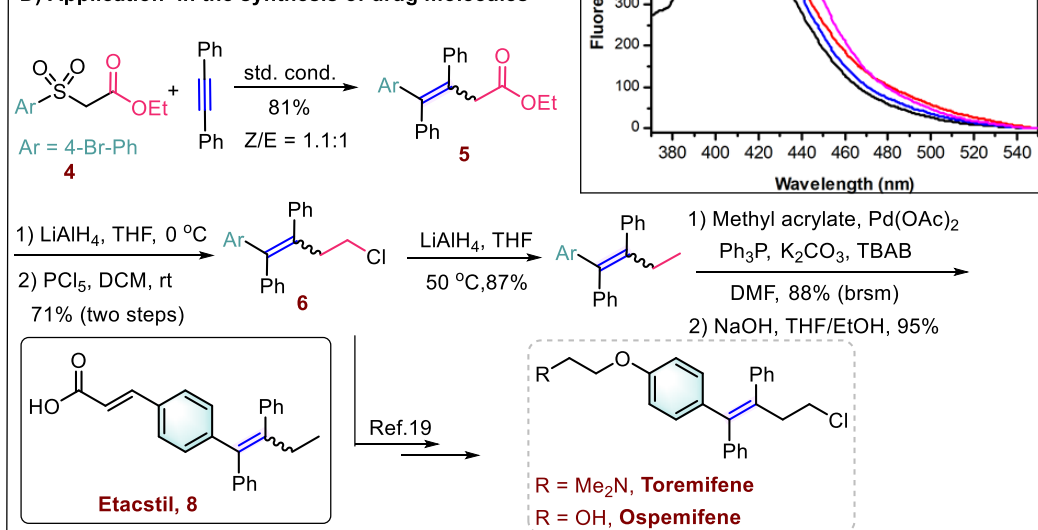


Fig.4 Photoisomerization and synthetic application. For details, see Supplementary Information.

The utility of this chemistry was then demonstrated by the gram-scale synthesis of **3ao** in moderate 61% yield (**Fig. 4 B**). Furthermore, preliminary investigations into the optical properties of **3ao** and the other three analogs (**3bi-3bk**) were conducted. The fluorescence spectrum showed that these molecules exhibited emissions peaks at 418 nm, falling within the blue light region (**Fig. 4 C**). Due to the good photostability and the presence of readily derivative 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 the 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 reactions⁶²⁻⁶⁴ (Fig. 4 D).

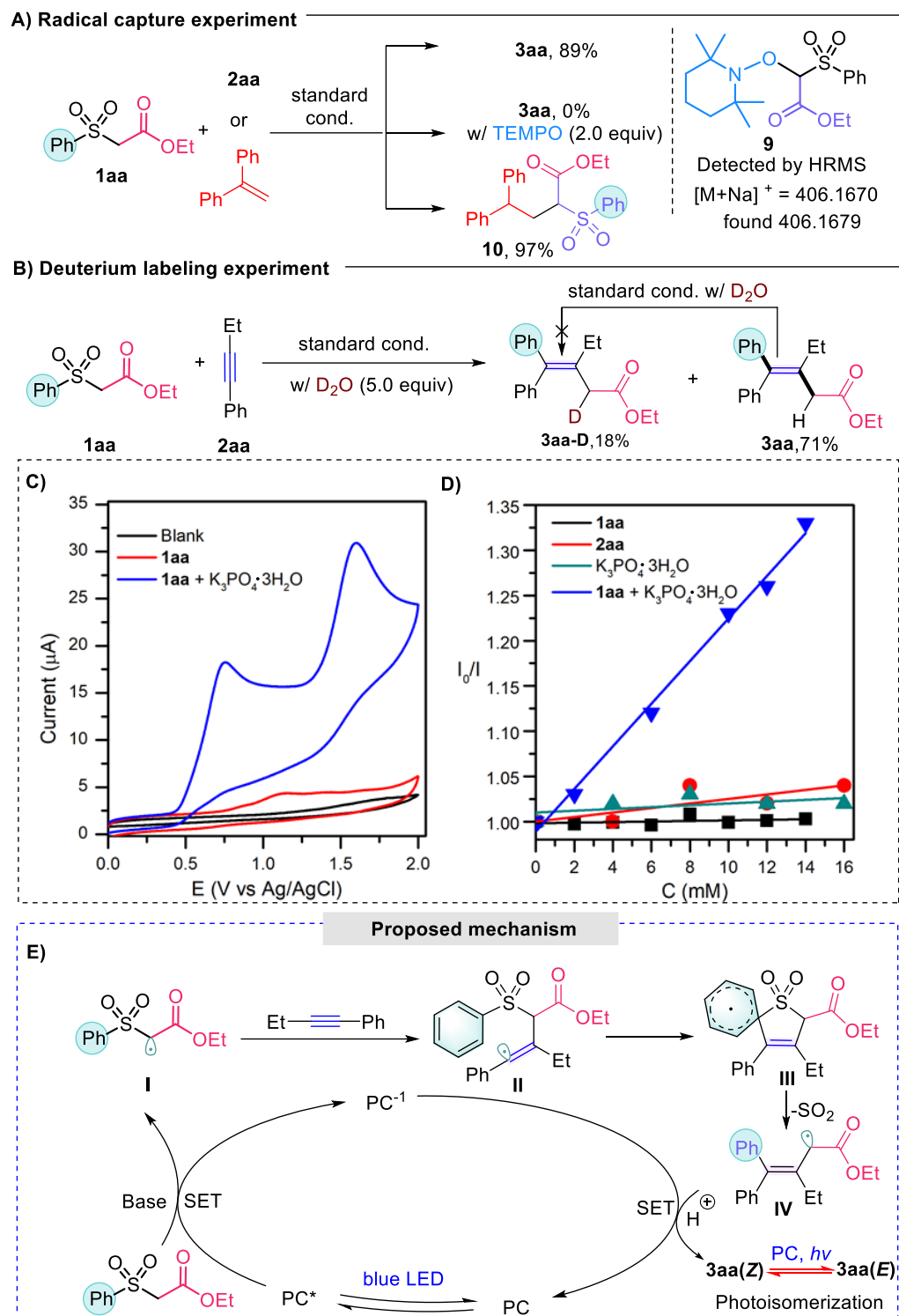


Fig. 5 Mechanism investigation

Mechanistic studies

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 equivalent 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 (**Fig. 5 A**). Then, a deuterium labeling experiment was performed. When the reaction was carried out in the presence of 5 equiv of D₂O, we isolated an 18% yield of the deuterium product **3aa'** alongside a 71% yield of **3aa**. Conversely, treating of **3aa** with D₂O under the standard conditions did not result in any deuterium labelling, suggesting that H/D exchange of product **3aa** did not take place in the reaction system (**Fig. 5 B**). This observation suggests 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 (**Fig. 5 C**). The blank consisted of 0.1 M *n*-Bu₄NPF₆ in CH₃CN (black line, **Fig. 5 C**). 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 base. These results indicate that the oxidation of **1aa** by the excited state *4CzPIN ($E_{1/2}(*P/P^-) = 1.35$ V vs SCE) is thermodynamically feasible⁶⁵, especially in the presence of 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 (**Fig. 5 D**). Additionally, light on/off experiment as well as a measured quantum yield of 0.31 for the reaction led us to rule out the possible of radical chain mechanism (See SI).

Based on the control experiments and previous literature²¹, a plausible mechanism was proposed (**Fig. 5 E**). 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 SO₂, 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 diminished Z/E ratio of the obtained products.

Discussion

In conclusion, we have disclosed a novel arylsulfonylacetate skeleton in which aryl rings are tethered to acetates through SO₂, 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 synthetic 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 synthetic useful all-carbon tetrasubstituted alkenes in a single operation. Further investigations are currently underway in our laboratory to address the application of these bifunctional reagents in a stereo controlled manner.

Methods

To a 5 mL Shlenck tube containing a PTFE-coated stirring bar was charged with ethyl 2-(phenylsulfonyl)acetate **1a** (0.2 mmol, 1.0 equiv), 4-CzIPN (2 mol %), and K₃PO₄•3H₂O (0.4 mmol, 106 mg, 2.0 equiv). The vessel was then evacuated and filled with nitrogen three times. Then, MeCN (4 mL) was added, followed by the addition of alkyne **2a** (0.4 mmol, 2.0 equiv) under nitrogen flow. Finally, the tube was sealed and placed in the photoreactor about 2 cm away from a 10 W 460 nm LEDs light irradiation with a chiller to maintain the temperature at 25 °C. After 12 hours, the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel to give the corresponding pure products.

Data availability

Data relating to the materials and methods, optimization studies, experimental procedures, mechanistic studies, DFT calculations, NMR spectra, and mass spectrometry are available in the Supplementary Information. Crystallographic data for compounds **3aa-acid** is available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC 2280320. All other data are available from the authors upon reasonable request.

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Author contributions

L. Liu conceptualized the project. L. Liu and X.-H. Duan supervised the investigation. C. He, M. Wang, Y. Wang, L. Zhao, Y. Zhou and K. Zhang performed the experiments. S. Shen and Y. Su conducted the DFT calculations. L. Liu, C. He, M. Wang, L. Zhao, Y. Zhou and K. Zhang analyzed the data co-wrote the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.