Radical Bifunctionalization of Alkenes with Arylsulfonylacetate as Bifunctional Reagent via Photoredox Radical Addition/Smiles Rearrangement Cascade

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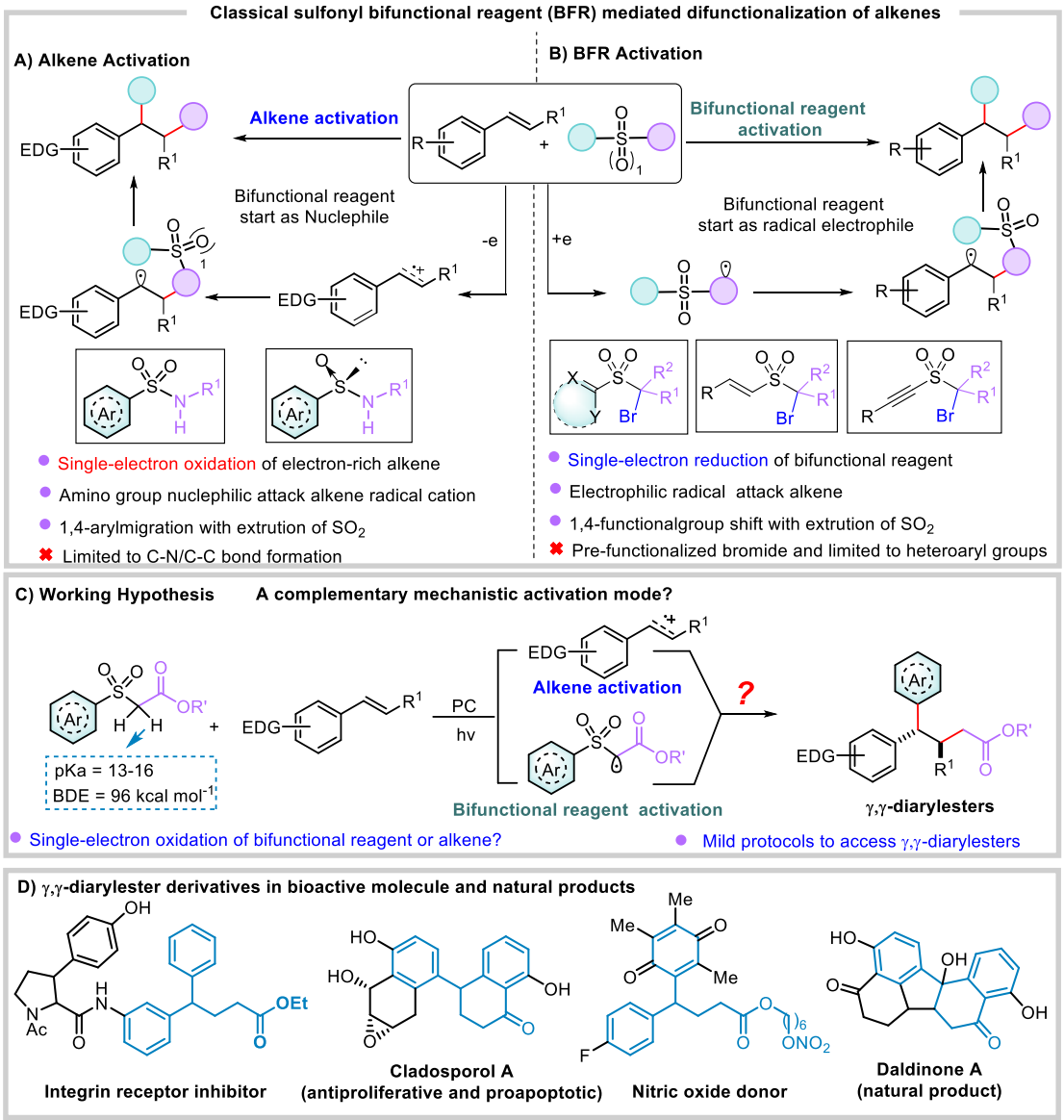
Abstract: We present herein a modular photoredox strategy for the difunctionalization of alkenes employing arylsulfonyl acetate as the bifunctional reagents. Under photoredox conditions, the electrophilic carbon-centered radical, generated from bifunctional reagent, add to alkenes followed by 1,4-aryltranlocation, providing a robust alternative to synthetic valuable γ,γ-diaryl and γ-aryl ester compounds. This method features mild reaction conditions, high atom- and step- economy, excellent functional group compatibility and great structural diversity. A complementary oxidative bifunctional reagents activation mode governs the radical cascade reactions, facilitating the simultaneous incorporation of aryl and carboxylate bearing alkyl groups into the alkenes.

Difunctionalization of alkenes provides a robust tool for the converting simple alkenes into complex molecules, consistently of high interest and challenging from both academic and industrial perspectives.[1] The simultaneous formation of multiple bonds using just one bifunctional reagent has become state-of-the-art in achieving this target.[2] Numerous examples of introducing bifunctional reagents-mediated difunctionalization of alkenes have been extensively disclosed in recent decades due to the rapid development of electrocatalysis[3] and photocatalysis.[4] Among them, sulfonyl bifunctional reagent mediated difunctionalization of alkenes via the radical-induced functional group migration process represents one of the most efficient strategies.[5] In general, those reactions could be summarized as the following two categories with respect to the mechanistic profiles: 1) Single-electron oxidation of the electron-rich alkenes to generate the key active radical cation species. Then, bifunctional reagents act as nucleophile to attach the radical species and engage in the following intramolecular Smiles rearrangement to achieve difunctionalization of alkenes (Scheme 1A).[6] 2) Instead of alkene oxidation, single-electron reduction of sulfonyl alkyl bromide bifunctional reagents yields the electrophilic radical species, which subsequently undergo radical addition to styrenes. Then, the benzyl radical undergoes *ipso* attack, leading to 1,4-functional group migration to deliver the difunctionalized products (Scheme 1B).[7] Pioneered by Stephenson and Zhu, various efficient desulfonylative difunctionalization of alkenes with these activation modes have been reported for incorporating amino or alkyl units and (her)aryl units across alkenes. In addition, an asymmetric radical difunctionalization was also realized by the Nevado group, employing chiral sulfinamide as the auxiliary.[8] Nevertheless, both the mechanistic activation mode and the substrate scopes in alkene radical

difunctionalizations are still limited. More easily accessible and functional group-compatible bifunctional reagents, as well as complementary mechanistic activation modes, are still highly desirable.

Recently, arylsulfonylacetate has been independently developed as a bifunctional reagent for the difunctionalization of unsaturated carbon-carbon bonds by both our research group[9] and others.[10] As an extension of our ongoing exploration into radical cemistry,[11] we have conceived a strategy employing arylsulfonylacetate as a bifunctional reagent for the difunctionalization of styrene derivatives. This proposed methodology is designed to provide a direct and efficient route to γ,γ-diaryl and γ-aryl ester compounds, a structural motif frequently encountered in bioactive compounds and natural products (Scheme 1D).[12] Subsequently, a crucial mechanistic question arose, specifically concerning the activation mode that would govern the anticipated transformation (Scheme 1C). This consideration holds significant implications for both the substrate scope and the



Scheme 1. Previous work on sulfonyl bifunctional reagent mediated difunctionalization of

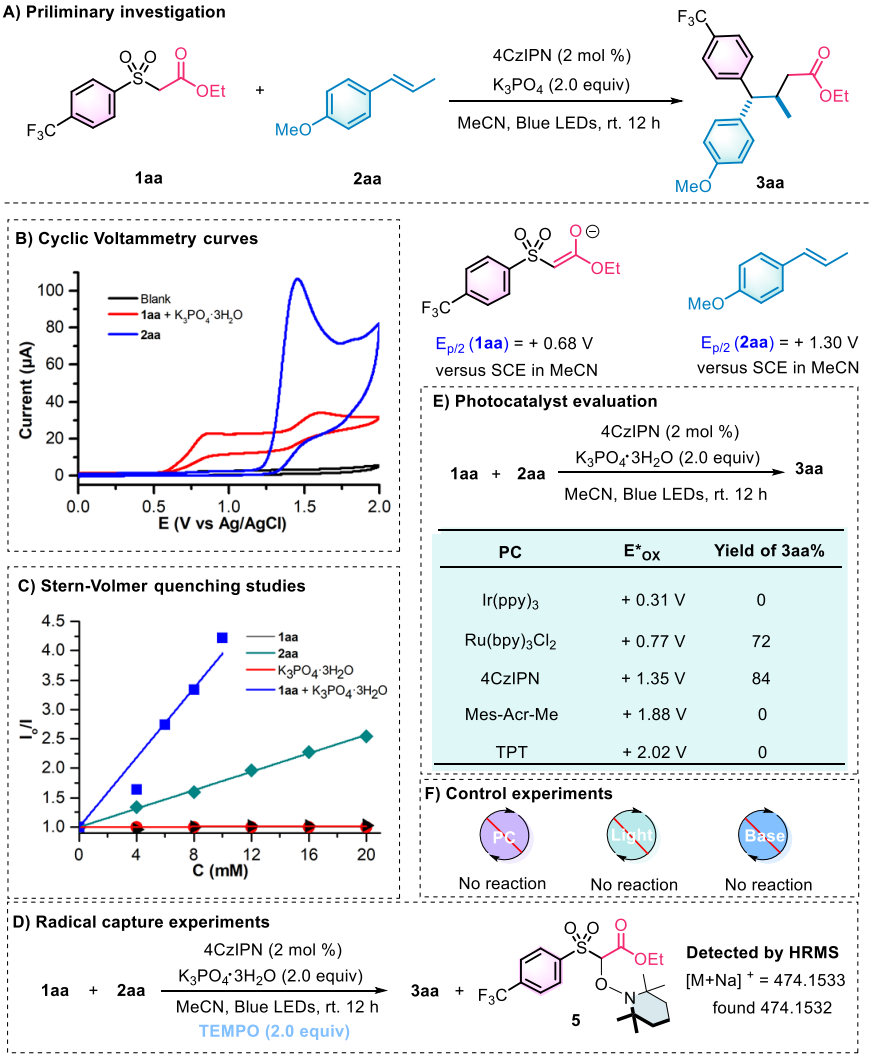
alkenes and our working hypothesis

overall efficiency of the proposed method. Theoretically, the relatively acidic proton in the active methylene site would be readily removed under basic conditions to give a nucleophilic enolate, which would trap alkene radical cation via alkene activation mode. Conversely, its bond dissociation energy falls within the range of approximately 96 kcal/mol, rendering selective hydrogen atom abstraction (HAA) thermodynamically feasible. Then, the generation of a highly electrophilic radical species, facilitated through either a suitable hydrogen atom abstraction (HAA) or a proton-coupled electron transfer (PCET) process appears operational to initiate the difunctionalization *via* bifunctional reagent activation mode.

In addressing this mechanistic inquiry and seeking an efficient alternative for γ,γ-diaryl ester compounds, while also inspiring the future development of novel bifunctional reagents for alkene difunctionalization, we selected arylsulfonyl acetate **1aa** and *trans*-anethole **2aa** as model substrates for our initial investigations. To our delight, when 4CzIPN was employed as the photocatalyst and K_3PO_4 as the base, the desired γ,γ-diaryl ester **3aa** could be formed in 76% yield with excellent diastereoselectivity (Scheme 2A). Then, cyclic voltammetry (CV) measurements were carried out to elucidate the oxidative process underlying this photocatalytic event. The blank consisted of 0.1 M *n*-Bu_4NPF_6 in CH_3CN (black line, Scheme 2B). Compound **1aa** displayed the first distinct oxidation at $E_{p/2}$ = + 0.68 V (vs SCE in CH_3CN) in the presence of base, while that of *trans*-anthole **2aa** was determined to be $E_{p/2}$ = + 1.30 V (vs SCE in CH_3CN) which is consistent with the reported data.[13] Given the redox potential of the photocatalyst 4CzIPN ($^*E_{1/2}$ (PC^*/PC^-) = +1.35 V vs. SCE in MeCN) which enables the thermodynamically favorable oxidation of both reactants, further experiments were performed. Stern-Volmer fluorescence quenching experiments revealed a notably faster quenching rate for **1aa** in the presence of a base compared to **2aa**, while pure **1aa** is entirely unresponsive to the quenching of the excited photocatalyst (Scheme 2C). Moreover, upon the introduction of 2.0 equivalents of the radical scavenger TEMPO into the reaction mixture, the reaction was entirely inhibited, concomitant with the detection of TEMPO adduct **5** (Scheme 2D). These results demonstrate that the crucial radical species derived from bifunctional reagent **1aa** actively participated in this cascade transformation. Other photocatalysts with distinct excited-states oxidative potentials were also assessed. As anticipated, $Ir(ppy)_3$ possessing a relatively low oxidative potential ($E_{Ir(II)/Ir(III)^*}$ = +0.31 V) [14] exhibited completely inertness in the reaction. When $Ru(bpy)_3Cl_2$ with an oxidation potential positioned between those of **1aa** and **2aa** was employed as the photocatalyst, the desired product **3aa** can be obtained with a 72% yield. Intriguingly, switching the photocatalyst to Mes-Acr-Me or TPT which were commonly used for alkene radical cation species generation,[15] resulted in no formation of **3aa** (Scheme 2E). Taken together, these data provide support for the proposition that the predominant process in this radical difunctionalization reaction is the single-electron oxidation of bifunctional reagent **1aa**.

Through further optimization of reaction parameters, including the photocatalyst, base, and solvent, we ultimately identified the optimal conditions to achieve an 84% yield of product **3aa** with >20:1 diastereoselectivity (For details, see Supporting Information). Control experiments underscored the indispensability of the photocatalyst, light irradiation,

and $K_3PO_4 \cdot 3H_2O$, as the absence of any of these components resulted in the absence of

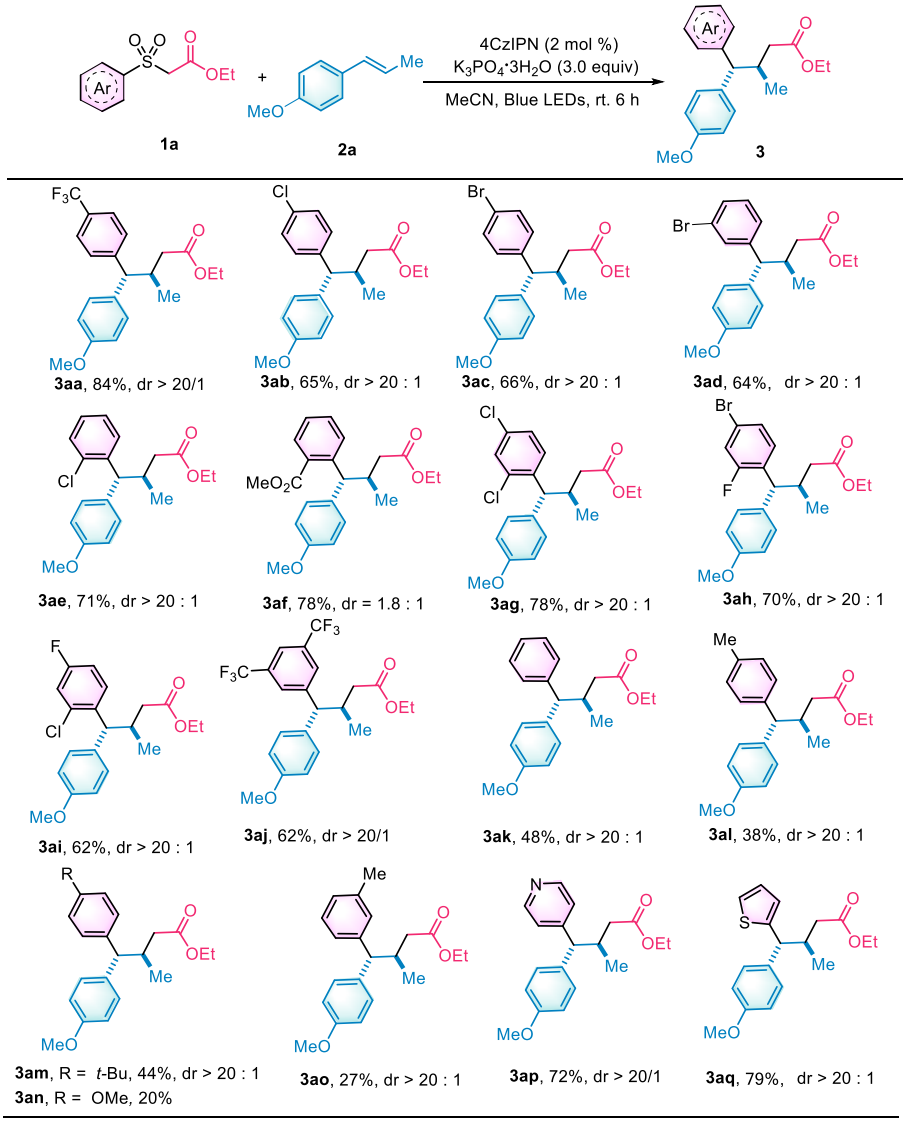


Scheme 2 Preliminary investigation and proof of concept.

the desired product (Scheme 2F). To the best of our knowledge, this reaction not only presents a novel alternative for the consecutive formation of multiple C-C bonds, leading to the synthesis of γ,γ-diaryl esters but also introduces a complementary mechanistic activation mode for the sulfonyl bifunctional reagent-mediated difunctionalization of alkenes.

With the optimal conditions in hand, our initial focus was on exploring the structural diversity concerning the migrating aromatic ring in arylsulfonylacetate bifunctional reagents (Scheme 3). Phenyl rings containing various substituents, including electron-donating groups such as methyl, *tert*-butyl, and methoxy, as well as electron-withdrawing groups (halogens), were all found to be compatible to provide the corresponding γ,γ-diarylesters (**3aa**-**3ap**) in 20% to 84% yields with excellent diastereoselectivity. Generally, bifunctional reagents featuring electron-withdrawing groups on the phenyl rings exhibited more efficient reactions with alkenes, resulting in higher yields of the corresponding γ,γ-diarylesters compared to those with electron-donating groups. This phenomenon was attributed to the favorable π-π stacking interaction between the electron-deficient aryl ring of the bifunctional reagent and the

electron-rich PMP rings. This interaction is believed to contribute to lowering the energy

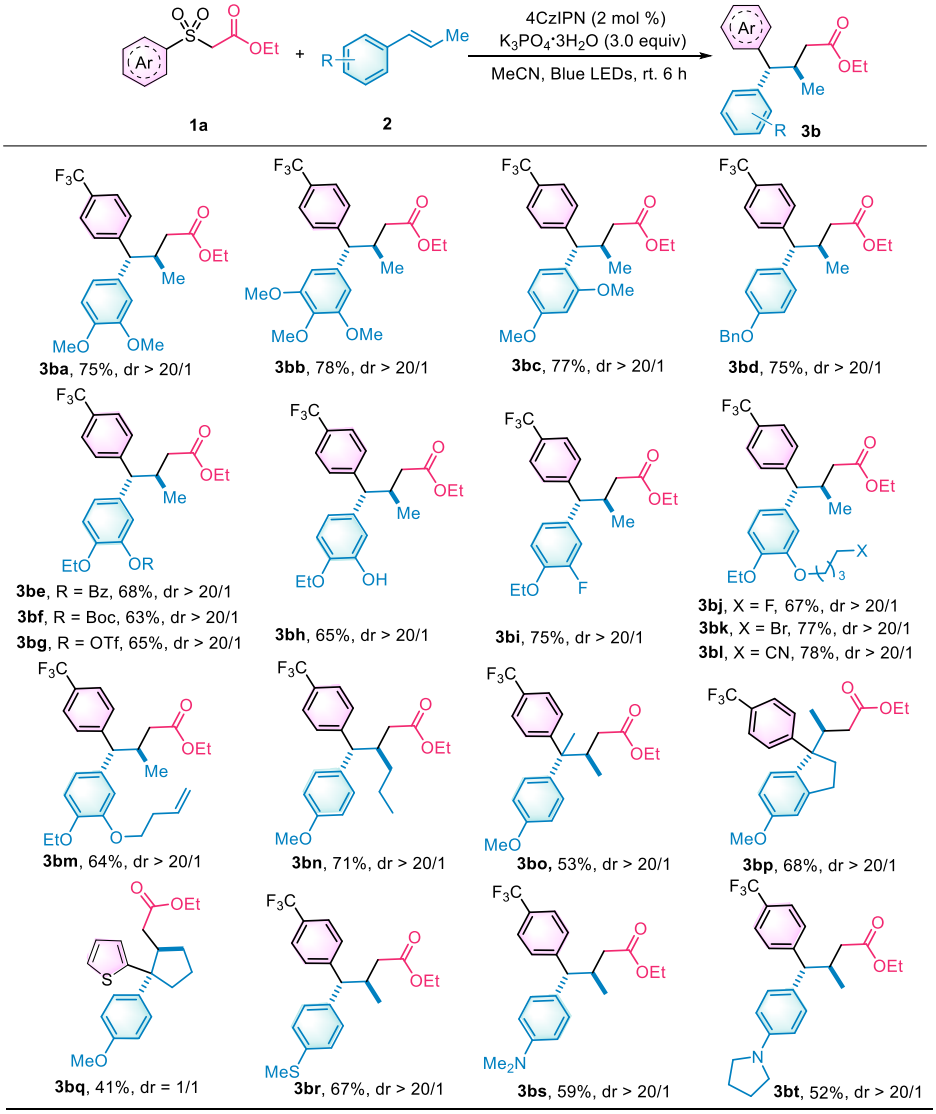


Scheme 3. Scope investigation by variation of bifunctional reagent

barrier for the aryl migration process.[6b] Significantly, functional groups like halides and esters, amenable to subsequent derivatization, were well-tolerated, yielding the corresponding products in good yields. Excellent diastereoselectivity was consistently achieved, except in the case of *ortho*-substituted substrates **3af**. We hypothesized that steric hindrance plays a crucial role in controlling the diastereoselectivity of the reaction. Furthermore, heteroaryl groups such as pyridine and thiophene were found to be compatible under the standard conditions, yielding γ,γ-diarylesters **3aq** and **3ar** in moderate yields.

We extended our investigation to explore the diversity of substituents in the electron-rich internal alkenes (Scheme 4). Both mono- and multi-substituted alkoxy phenyl rings in olefins resulted in the production of the target products with high yields (**3ba-3bd**). It is noteworthy that various protecting groups for the phenol moiety, including benzyl, benzoyl, Boc, and triflate, were all compatible under the standard conditions (**3bd-3bg**). Particularly, the free hydroxyl group remained intact, yielding the corresponding

difunctionalized product **3bh** in a moderate yield of 65%. Furthermore, alkyl chains

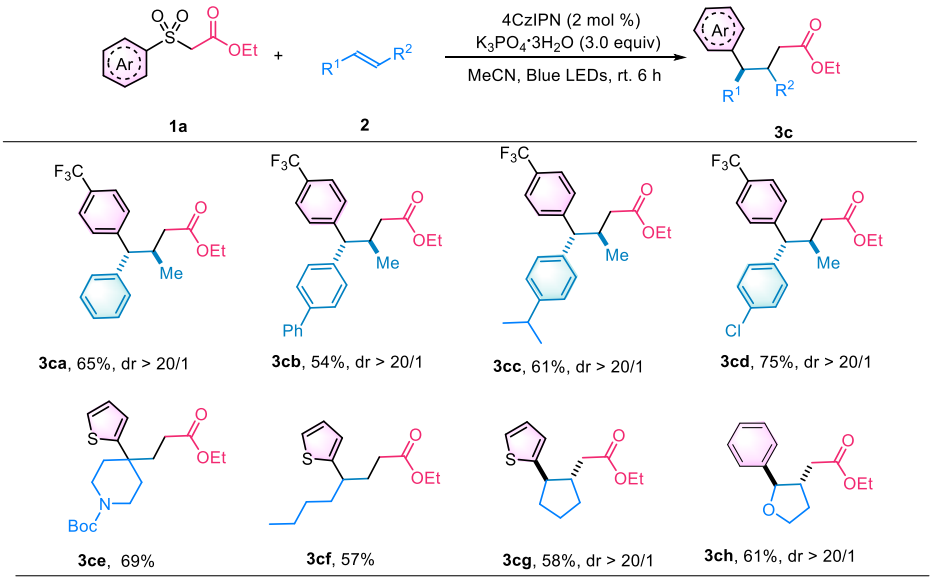


Scheme 4. Scope investigation by variation of electron-rich alkenes

containing halide, cyan group, and terminal alkene functionalities were also well-tolerated under the standard conditions, affording the products **3bj-3bm**. Increasing the length of the alkyl chain in the internal alkene was observed to have a negligible impact on the transformation **3bn**. Trisubstituted internal alkenes also proved to be effective substrates under the standard conditions, yielding the difunctionalized products (**3bo** and **3bp**) bearing a quaternary center with moderate yield and diastereoselectivity. Internal alkene was also examined, but poor reactivity and diastereoselective was observed. Furthermore, methylthiol and dialkylamino groups were proven to be suitable electron-donating groups under this photoredox conditions, furnishing the corresponding γ,γ-diarylesters in moderate yields with an outstanding level of diastereoselectivity.

Considering the initiation of the reaction through the formation of an electrophilic carbon-centered radical, it can be inferred that radical acceptors are not restricted solely to electron-rich anethole derivatives (Scheme 5). To validate our hypothesis, (E)-prop-1-en-1-ylbenzene, with an oxidation potential $E_{p/2}$ = +1.74 V vs SCE in CH_3CN

surpassing that of the excited photocatalyst 4CzIPN ($E_{1/2}$ (PC*/PC$^-$) = +1.35 V vs. SCE in

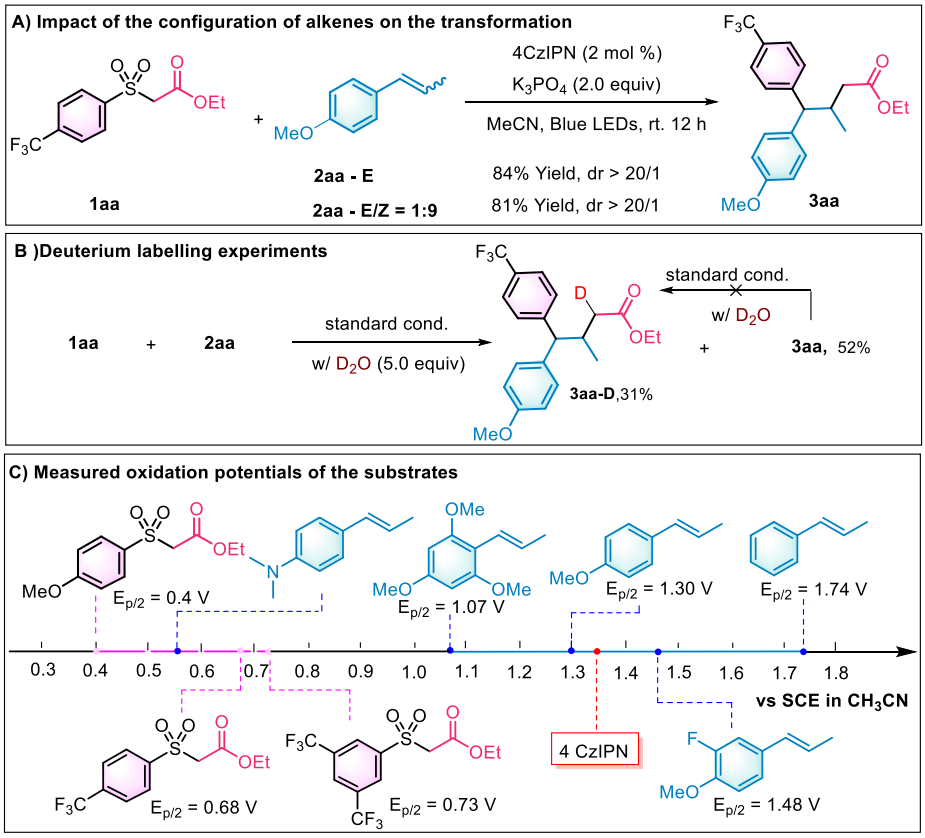


Scheme 5. Scope investigations with alkenes

MeCN), was subjected to the optimized reaction conditions. As expected, the desired difunctionalized product **3ca** was formed in a moderate yield of 65%. Substituents bearing different electronic propertied were also effective precursor for the preparation of the γ,γ-diarylesters **3cb-3d**. In addition, a range of unactivated olefins including terminal alkene (**3ce** and **3cf**) and internal alkenes (**3cg** and **3ch**) turned out to be effective partnor of this alkylarylation reaction, further demonstrating the synthetic potential of this approach.

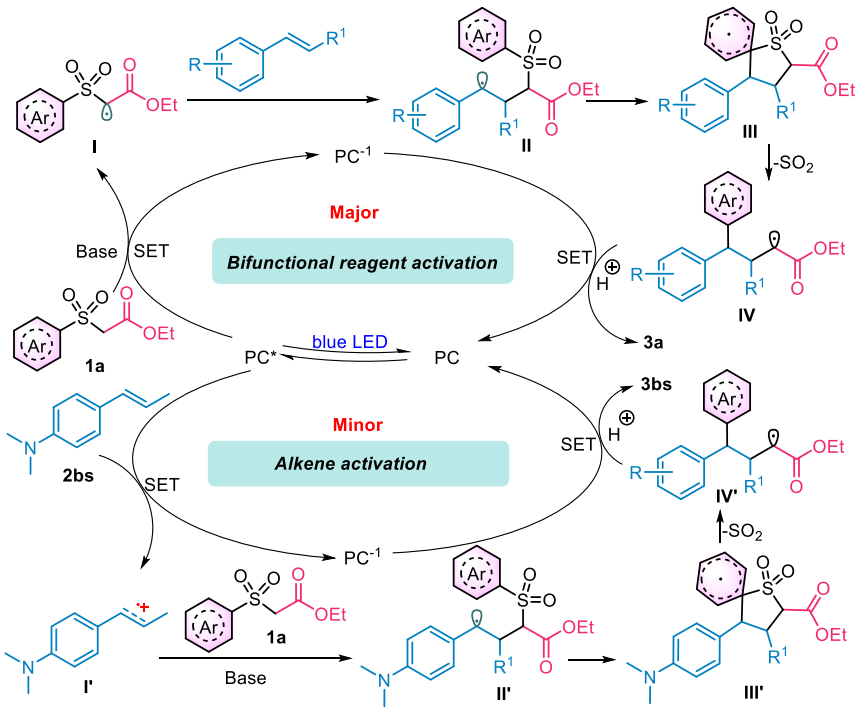
To gain additional insights in the reaction mechanism, several additional control experiments were performed (Scheme 6). First, the standard conditions were applied to two independent experiments using *trans*-anethole and a 1:9 mixture of *trans*- and *cis*-anethole. In both cases, identical products were formed in comparable yields, with almost identical diastereoselectivity. This indicated that a stepwise process is involved in the reaction. In addition, a deuterium labeling experiments was performed. Introducing 5 equivalents of D_2O to the reaction mixture under standard conditions resulted in the isolation of 31% yield of deuterium-labeled **3aa-D**, along with the formation of 52% yield of **3aa**. However, treating **3aa** with D_2O under the standard conditions did not lead to the detection of **3aa-D**. This result supports the notion that radical polar crossover-enabled protonation is operational in this cascade process. Moreover, we further measured the oxidation potentials of the substrates. Generally, all the arylsulfonyl acetates exhibited good compatibility with the redox potential of the photocatalyst, ranging from 0.4 V to 0.73 V, which is considerably lower than that of alkenes (1.07 to 1.74 V). It is worth mentioning that all the oxidation potentials for the arylsulfonyl acetates were determined in the presence of a base. This aligns with their effective fluorescence quenching observed in experiments involving a base. Interestingly, the dialkylamino-substituted phenyl alkene exhibited an oxidation potential of 0.56 V, even lower than that of compound **1aa**. Further fluorescence quenching experiments indicated that these two alkenes are much more efficient quenchers of the photocatalyst (See Supporting Information). These results

suggest that different mechanisms might be operating at the outset of the reaction depending on the olefinic partner.



Scheme 6 control experiments

Drawing upon the control experiments and prior literature,[6,7] a plausible mechanism was proposed (Scheme 7). Two activation modes might be involved in this bifunctional reagent-mediated difunctionalization reaction. In the majority of reactions, the bifunctional reagents were much more easily oxidized compared to alkenes, leading to the bifunctional reagent activation mode. The photocatalyst (PC) is irradiated by blue light to its excited state, which undergoes a single electron transfer event with **1a** to afford alkyl radical **I**. Electrophilic radical addition to the double bond of alkene forms benzyl 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. In contrast, for the dialkylamino-substituted alkenes, which represent some of the electron-rich alkenes with relatively low oxidation potentials, the alkene activation mode might come into play. Single-electron oxidation of the alkene produces the alkene radical cation species **I'**, which undergoes nucleophilic attachment by the bifunctional reagent in the presence of a base to form benzyl radical **II'**. Subsequent intramolecular Smiles rearrangements, followed by reductive protonation, lead to the final formation of the titled compounds.



Scheme 7. Proposed reaction mechanism

In conclusion, we have unveiled a novel oxidative bifunctional reagent activation mode for the alkylarylation of alkenes under photoredox conditions using arylsulfonyl acetate as the bifunctional reagent. This metal-free radical process enables the simultaneous incorporation of (hetero)aryl rings and alkyl carboxylate groups into a wide range of olefins, thereby facilitating the synthesis of a diverse library of synthetically valuable γ,γ-diarylester 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 alkenes as feedstock substrates, we anticipate this method would serve as a highly enabling platform for research endeavors aimed at synthesizing synthetic useful γ-arylesters in a single operation. The success of this strategy utilizing bifunctional reagents for the difunctionalization of alkenes is expected to stimulate further investigations into this concept.

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Author contributions

L. Liu conceptualized the project. L. Liu and X.-H. Duan supervised the investigation. C. He, Y. Wang, Z. Yan, K. Zhang and M. Wang performed the experiments. L. Liu, C. C. He, Y. Wang, Z. Yan, K. Zhang and M. Wang 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.

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