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Visible-light-promoted *E*-selective synthesis of α-fluoro-β-arylalkenyl sulfides *via* the deoxygenation/isomerization process†

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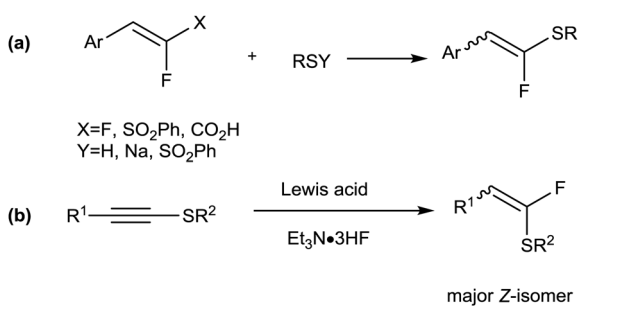
Regioselective synthesis of α-fluoro-β-arylalkenyl sulfides has been established with *gem*-difluoroalkenes and sodium sulfinates in a transition-metal-free manner. A series of control experiments were executed to demonstrate thiol radicals and anions as the proposed intermediates. Notably, regioselective *Z* → *E* isomerization was achieved under green light irradiation in the absence of a photoinitiator.

Vinylsulfides are widely present in natural products, bioactive compounds and functional materials, and also serve as important building blocks for the synthetic community.[1] Due to the influence on the lipophilicity, metabolic stability, and biopotency by fluorine substitution, the incorporation of fluorine and fluorine-containing functional groups into organic molecules has beneficial advantages in drug design.[2] In particular, monofluoroalkenes can serve as peptide bond isosteres and skeleton of drug molecules, which have attracted substantial attention from medicinal chemists.[3] Given the significantly potential medicinal value of α-fluoro-β-arylalkenyl sulfides, considerable efforts have been put into developing varied strategies to generate the functionalized molecules (Scheme 1).[4] However, the exploration of efficient methodologies to produce highly stereoselective α-fluoro-β-arylalkenyl sulfides utilizing simple, bench-stable and odorless precursors under mild conditions is still eagerly anticipated and challenging.

Recently, *gem*-difluoroalkenes have been employed as a synthon to fabricate mono-fluoroalkenes.[5] On account of the strong electron-withdrawing capability of fluorine atoms and the repulsion effect from its lone-pair electrons, the difluoromethylene carbon of *gem*-difluoroalkenes is attacked by nucleophiles to construct heterogeneous C–C and C–X bonds.[5d,6]

Over the past decade, not only has visible-light-induced photocatalysis been demonstrated as one of the most powerful and straightforward tools for new chemical bond formation[7] due to its appealing features such as environmental friendliness, mild reaction conditions, and excellent functional group compatibility, but it also offers a valid route to perform geometrical isomerization of alkenyl derivatives (Scheme 2A).[8] In 2020, the group of Rossi–Ashton reported a visible-light-induced photocatalytic deoxygenation reaction of sulfoxides to produce a wide array of functionalized sulfides reduced by PPh_3 (Scheme 2B).[9] Moreover, sodium sulfinates are odorless, stable and commercially available sulfur compounds that have been widely implemented as sulfuration agents.[10] However, to the best of our knowledge, a phosphine-associated photoredox approach for the deoxygenative functionalization[11] of sodium sulfinates is still unknown. Herein, we report a method to synthesize highly *E*-selective α-fluoro-β-arylalkenyl sulfides from *gem*-difluoroalkenes and sodium sulfinates *via* visible-light-induced deoxygenation of S–O bonds and isomerization of alkenes (Scheme 2C).

The initial investigations commenced with 2-(2,2-difluorovinyl)naphthalene **1a** and sodium benzenesulfinate **2a** as model substrates (see more details in the ESI†). Gratefully, the desired product **3aa** was isolated in 94% yield with good



Scheme 1 Previous strategies for the synthesis of α-fluoro-β-arylalkenyl sulfides.

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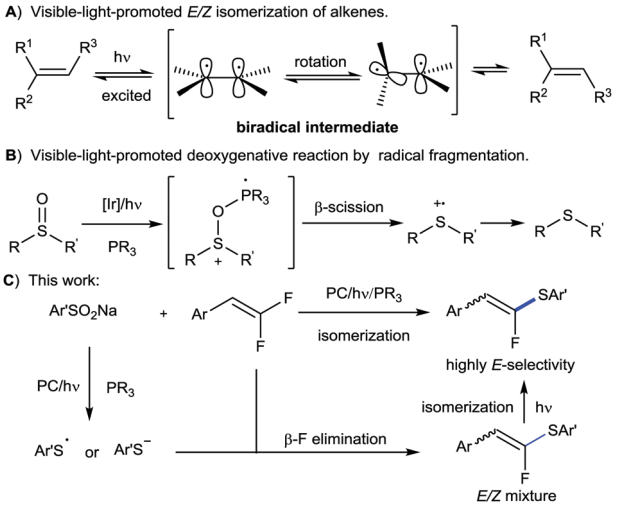


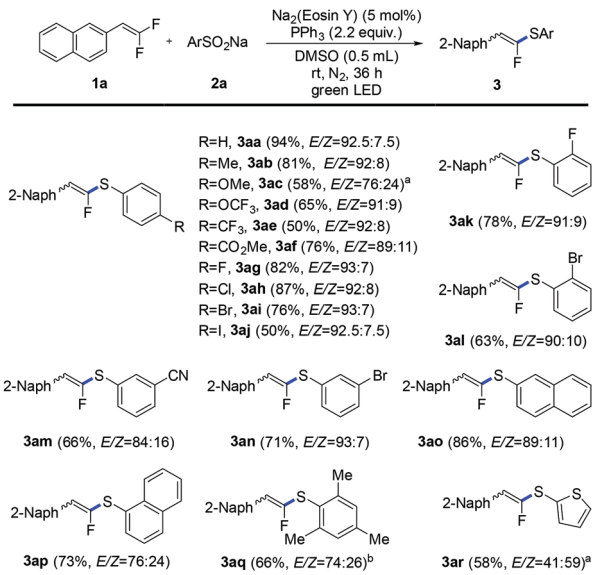
Scheme 2 Photocatalytic geometrical isomerization of alkenes, deoxygenative reaction and our work.

stereoselectivity (E/Z = 92.5 : 7.5) with 2.2 equiv. PPh_3 as a reductant and 5 mol% Na_2(Eosin Y) as a photosensitizer with exposure to a 6 W green LED at ambient temperature under a N_2 atmosphere in DMSO for 36 h.

With the optimal conditions in hand, an array of sodium sulfinates was explored (Table 1). Either electron-rich or electron-deficient substitution at the *para*-position of the sodium arylsulfinates could be well tolerated in this process to afford the desired products (**3aa-aj**) in good yields and E/Z ratios. In particular, the sodium arylsulfinates bearing reactive functional groups, such as OMe (**2c**), ester group (**2f**) and halide groups (**2g–j**), were adapted to this reaction system. And *meta*- and *ortho*-substituted sodium arylsulfinates (**2k–n**) show similar reactivities, but a slightly dropped E/Z ratio. Moreover, reaction of both 2- and 1-naphthylsulfinate salts could proceed smoothly providing **3ao** and **3ap** in 86% and 73% yields with 89 : 11 and 76 : 24 E/Z selectivities, respectively. Notably, 2,4,6-tri-substituted sodium arylsulfinate was facile to deliver the desired product **3aq** in 66% yield with poor E/Z selectivity, due to the bulky groups. Heteroaromatic sulfinate salt, sodium thiophene-2-sulfinate, also successfully produced the desired products (**3ar**) in 58% yield with substandard E/Z selectivity.

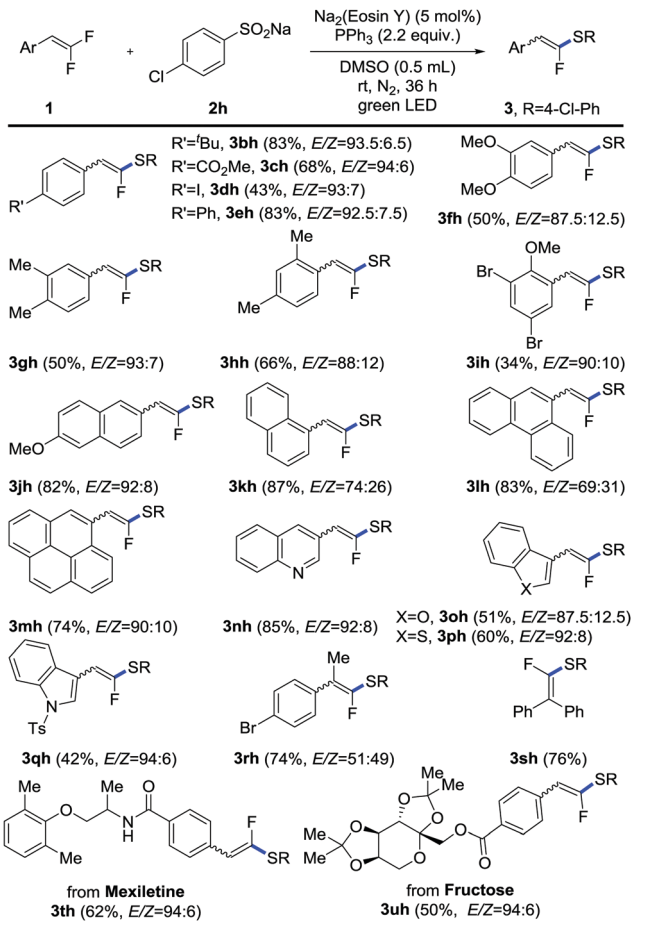
Subsequently, the scope of the reaction with respect to *gem*-difluoroalkenes was examined. As summarized in Table 2, we found that this mild protocol was applicable to most substrates, including both mono-substituted and multi-substituted *gem*-difluorostyrenes in moderate to good yields with a good E/Z ratio (**3bh–ih**). The *gem*-difluorostyrenes attached with either

Table 1 Substrate scope of sodium arylsulfinates with *gem*-difluoroalkene **1a**



Reaction conditions: all reactions were performed with **1a** (0.10 mmol), **2** (2 equiv.), Na_2(Eosin Y) (5 mol%), PPh_3 (2.2 equiv.) and DMSO (0.5 mL) with 6 W green LED irradiation for 36 h under N_2 at rt unless otherwise noted. The E/Z ratio was determined by ^{19}F NMR. (a) 2.2 equiv. P(4-OMePh)$_3$. (b) The E/Z ratio was determined by isolated yield.

Table 2 Substrate scope of *gem*-difluorostyrene with sodium arylsulfinate **2h**



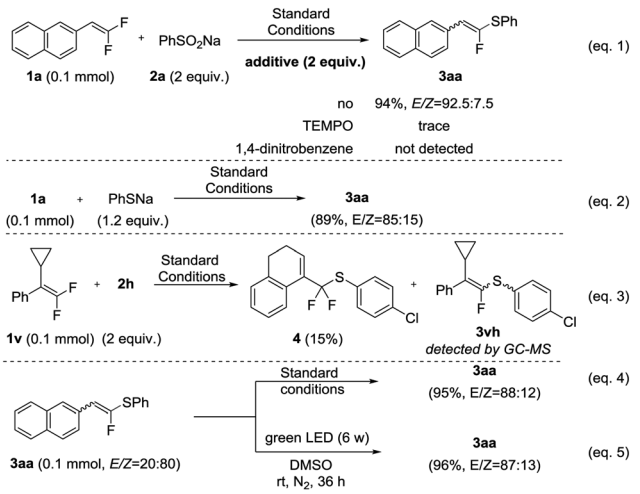
Reaction conditions: all reactions were performed with **1** (0.10 mmol), **2h** (2 equiv.), Na_2(Eosin Y) (5 mol%), PPh_3 (2.2 equiv.) and DMSO (0.5 mL) with 6 W green LED irradiation for 36 h under N_2 at rt unless otherwise noted. The E/Z ratio was determined by ^{19}F NMR.

electron-donating or electron-withdrawing groups on benzene could react with **2h** to generate the expected products with good yields and *E*/*Z* selectivities (**3bh–ch**). What's more, halogen groups were also well-tolerated (**3dh**, **3ih**). Remarkably, the steric hindrance decreased the reactivity and selectivity (**3hh-ih**). It was noteworthy that a range of polycyclic aromatic *gem*-difluoroalkenes could be efficiently converted to the desired products in good yields with moderate to good stereoselectivities (**3jh–mh**). Interestingly, heteroaromatic difluoroalkenes containing N, O or S that were of significant utility to medicinal chemists were also extended as suitable candidates, giving the corresponding adducts (**3nh–qh**) in 42–85% yields and 87.5 : 12.5–94 : 6 *E*/*Z* selectivities. It was noted that when difluoroalkene bearing two different substituents **1r** was used, a target product **3rh** was isolated in 74% yield without stereoselectivity. And (2,2-difluoroethene-1,1-diyl)dibenzene **1s** was also a competent substrate to produce product **3sh** in 76% yield. Finally, we applied the protocol in the late-stage modification of complex natural products and drugs. A small molecule drug, mexiletine derivative, and natural product, fructose derivative, were reacted with **2h** to get desired products **3th** and **3uh** with 62% and 50% yields, respectively.

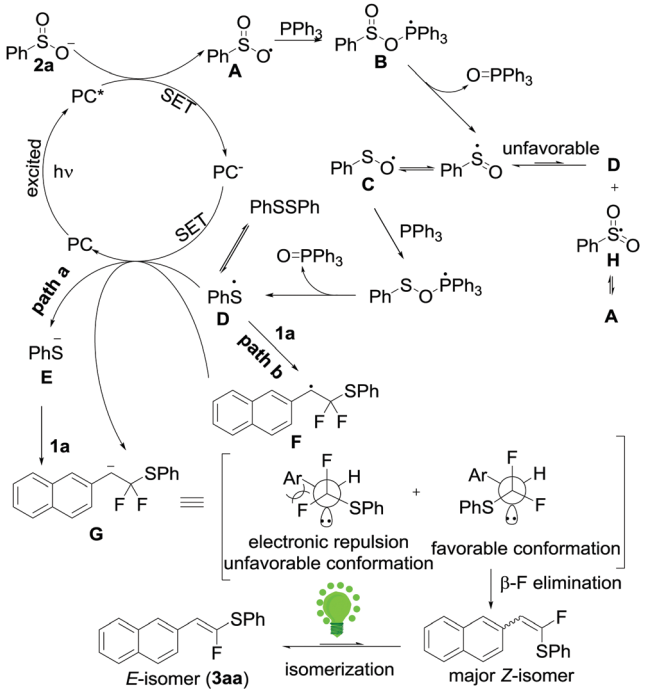
To shed light on the mechanism of this protocol, we designed a series of experiments. First, radical inhibition experiments were carried out with different radical inhibitors, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,4-dinitrobenzene (Scheme 3, eqn (1)), and the reactions were suppressed, indicating that the transformation might rely on an SET-involved radical pathway. In order to acquire more evidence of the reaction intermediates, control experiments were also conducted (see the ESI† for more details). When sodium benzenethiolate PhSNa (1.2 equiv.) was used in the system, a good yield of **3aa** was achieved (Scheme 3, eqn (2)), suggesting that the thiol anion was probably the key intermediate. Additionally, to verify the conjecture that thiol radicals could be produced in the reaction system, when (1-cyclopropyl-2,2-difluorovinyl)benzene (**1v**) was subjected to the standard conditions, ring-opened products **4** were obtained in 15% yield and product **3vh** was also detected by GC-MS (Scheme 3, eqn (3)). As is well known, vinylcyclopropanes conduct ring-opening in the presence of a carbon-centered radical.[12] Thus, these findings confirmed that the thiol anion and thiol radical originating from sodium sulfinate were produced under standard conditions (see the ESI† for more details, eqn (S1)–(S13)).

During the procedure of this transformation, the regioselective $Z \rightarrow E$ isomerization of α-fluoro-β-arylalkenyl sulfide was investigated simultaneously (see Table S5 in the ESI†). Thus, control experiments were conducted to validate the role of Na_2(Eosin Y), resulting in the fact that the photosensitizer didn't seem to actually engage in the $Z \rightarrow E$ isomerization (Scheme 3, eqn (4) and (5)). Therefore we expected that α-fluoro-β-arylalkenyl sulfide itself might act as a photosensitizer for this photochemical isomerization (Scheme 3, eqn (5)).

On the basis of the above results and previous studies on the reduction of sodium sulfinates[10c–e,13] and regioselective isomerization of alkenes,[8,14] a conceivable mechanism is presented in Scheme 4. First, the ground state of [Na_2(Eosin Y)] was irradiated to generate excited [Na_2(Eosin Y)]*, which could undergo SET with sodium benzenesulfinate **2a** [$E^{ox}_{1/2}$ = −0.34 V *versus* SCE][15] to afford an oxygen-centered sulfinic radical **A** and [Na_2(Eosin Y)]$^-$. Then intermediate **A** reacted with PPh_3 [$E^{ox}_{1/2}$ = + 0.98 V *versus* SCE][9] to deliver a phosphoranyl radical **B**, following through β-scission giving rise to sulfoxide radical **C** and phosphine oxide. Repeating the operation, the radical intermediate **C** would release thiyl radical **D** [$E^{red}_{1/2}$ = +0.16 V *versus* SCE],[16] and by a single electron reduction with reduced [Na_2(Eosin Y)]$^-$ [$E^{red}_{1/2}$ = −1.06 V *versus* SCE],[7c,17] thiyl anion **E** was produced and the ground state [Na_2(Eosin Y)] was also regenerated to close the photocatalytic cycle (Scheme 4, path a).



Scheme 3 Control experiments.



Scheme 4 A proposal mechanism.

Eventually, intermediate **E** triggered the following nucleophilic addition/β-F elimination reaction with *gem*-difluoroalkene **1a** to produce product **3aa** with the *Z*-isomer as the major product (see eqn (S14) in the ESI†) due to the electronic repulsion between F and aromatic rings,[18] along with a visible-light-promoted regioselective $Z \rightarrow E$ isomerization process *via* a biradical intermediate (Scheme 2A).[8b,14a] In this reaction system, path b (Scheme 4) might also be valid.[4f] The thiyl radical **D** was added to **1a**, providing the radical intermediate **F**. Then the photoredox cycle was accomplished through SET reduction of **F** by $[Na_2(Eosin\ Y)]^-$ to furnish anion **G** with the concomitant regeneration of the ground-state photocatalyst. The following transformation was the same as path a. As an alternative, radical **C** might disproportionate into radical **A** and radical **D**. While the free energy barrier of disproportionation was much higher than that of the PPh_3-associated procedure, the disproportionation was unfavorable.[10e]

In summary, we have disclosed a method to acquire various α-fluoro-β-arylalkenyl sulfides in good yields and stereoselectivities. The reactions perform well under mild conditions and are tolerant of wide varieties of functional groups. Control experiments illustrate that the deoxygenation of S–O bonds refers to the SET approach by photocatalysis. Importantly, the rare visible-light-promoted regioselective $Z \rightarrow E$ isomerization of α-fluoro-β-arylalkenyl sulfides does not require any photosensitizers. Further mechanistic studies and the application to pharmaceuticals are underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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