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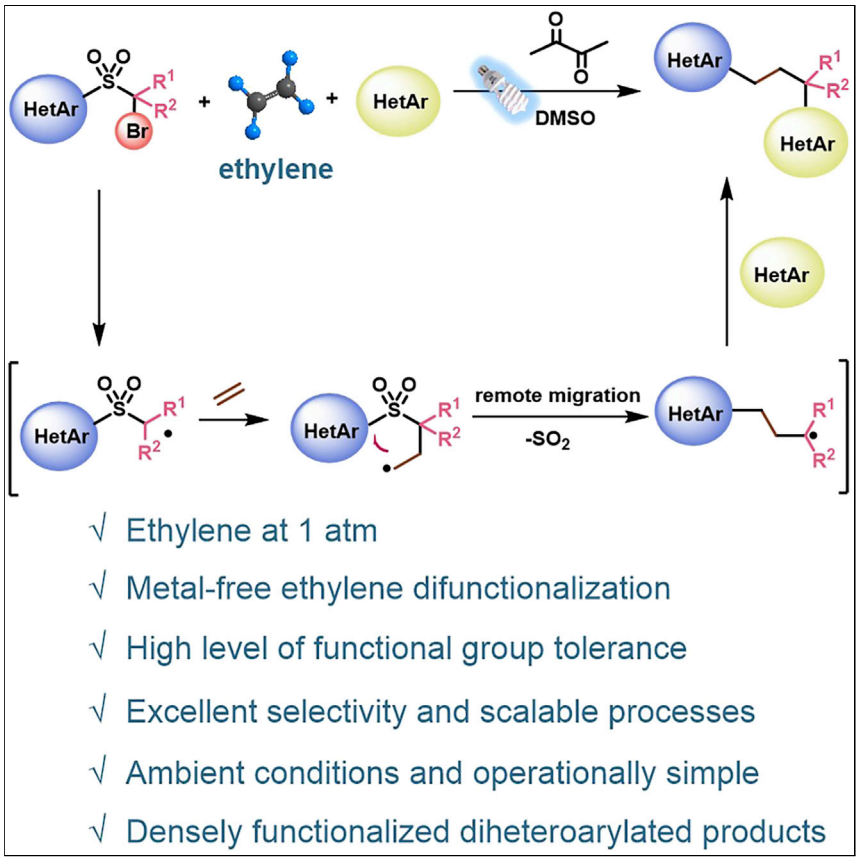
Metal-free radical difunctionalization of ethylene



An unprecedented three-component radical difunctionalization of ethylene is accomplished based on the functional group migration strategy. The use of rationally designed bifunctional reagents allows straightforward access to a wide range of complex diheteroarylated compounds under metal-free conditions in a highly selective manner. The synthetic value of this method lies in the rapid assembly of molecular complexity from the simplest and most abundant chemical feedstock, opening a new vista for radical functionalization of ethylene.

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Highlights

Metal-free difunctionalization of ethylene under ambient conditions

Excellent selectivity, simple operation, and scalable processes

Densely functionalized products with high diversity

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Metal-free radical difunctionalization of ethylene

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SUMMARY

Owing to its simplicity, ethylene, as the most abundant organic feedstock, only finds limited applications in fine chemical synthesis, resulting in molecules of modest complexity. Ethylene difunctionalization allows for the synthesis of much more complex chemicals, but it is rare and almost always relies on transition-metal catalysis. Herein, we report an unprecedented metal-free radical difunctionalization of ethylene through a functional group migration strategy. The use of sulfone-based bifunctional reagents enables straightforward access to a wide range of diheteroarylated compounds under mild conditions in a highly selective manner. The precise modulation of radical polarity and kinetic preference arising from intramolecular functional group migration guarantee the success of the cascade three-bond forming process in a controllable manner.

INTRODUCTION

Ethylene is the simplest alkene and the most abundant petrochemical product, with a global production of over 190 million tons in 2020. This compound is mainly used to prepare commodity chemicals, including polyethylene, polyvinylchloride, ethylene oxide, ethylene glycol, vinyl acetate, and styrene (Figure 1A).[1] Nevertheless, ethylene is much less utilized as feedstock for fine chemical synthesis,[2–4] and the existing catalytic processes are largely limited to monofunctionalization of ethylene, such as Heck-type reactions,[5] Wacker oxidation,[6] hydroacylations,[7] hydrovinylations,[8] and alkene and enyne metathesis.[9] In stark contrast, the more appealing ethylene difunctionalization, which can access a much broader and more complex chemical space, is scarce, and only a few examples have been revealed with the aid of transition-metal catalysis.[10–18] For instance, Sigman and coworkers pioneered palladium-catalyzed 1,1-arylvinylation and 1,1-diarylation of ethylene,[10,11] and nickel-catalyzed 1,1-difunctionalization of ethylene en route to bis-organometallic reagents was achieved by Martin et al.[12] Very recently, Glorius and Guldi disclosed a two-carbon homologation of β-dicarbonyl compounds using ethylene to construct medium-sized rings through an Ir-photocatalyzed energy transfer (EnT) process.[18] Despite these elegant achievements, a general and robust pathway to access diverse molecular scaffolds through ethylene difunctionalization, especially in a metal-free manner, remains elusive and is highly desirable.

Radical approaches supply robust tools for the difunctionalization of alkenes but have not yet been effectively applied to the simplest alkene, ethylene.[19–22] This is mainly due to the generation of highly reactive primary alkyl radicals,[23] where the engagement of such unstable primary radicals in subsequent intermolecular functionalization in a controlled manner is challenging. Moreover, under high pressure or temperature, competition from radical polymerization and oligomerization with ethylene arises as a severe problem.[24,25]

THE BIGGER PICTURE

Radical-mediated difunctionalization of alkenes has served as a powerful tool for the synthetic community to quickly access molecules with complex diversity. However, difunctionalization of ethylene through radical processes is extremely challenging due to the generation of highly unstable primary alkyl radicals and the competing dimerization or oligomerization pathways. In this study, we disclose that radical rearrangement serves as an effective and practical strategy for difunctionalization of ethylene in a metal-free manner. The synthetic value of this method lies in the selective reaction of highly reactive primary radicals through a kinetically favored intramolecular process which outperforms the competing intermolecular processes, particularly the radical polymerization or oligomerization of ethylene, thus opening a new vista for difunctionalization of ethylene for rapid assembly of molecular complexity.

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Radical-mediated functional group migration (FGM) has proven to be a powerful strategy for the functionalization of challenging molecules, including unactivated alkenes.[26,27] We conceive that the FGM protocol may perfectly serve elusive ethylene difunctionalization, considering the intrinsic merits provided by sulfone-based bifunctional reagent **1**, as illustrated in Figure 1B. (1) Photocatalytic cleavage of the C–Br bond generates a carbon radical **A**, where the proximate sulfonyl substituent renders the radical more electrophilic, which will enhance the addition rate to ethylene,[23] outperforming the addition to electron-deficient heterocycles **2** (the pathway to **4**). (2) The generated unstable primary alkyl radical adduct **B** will be rapidly trapped intramolecularly by a migratory group rather than the less kinetically favored intermolecular processes. (3) Radical migration will selectively occur with one ethylene addition adduct **B** through a five-membered transition state compared with the less kinetically favored seven-membered transition state from two ethylene adducts **D**, thus avoiding ethylene oligomerization or polymerization.[28] (4) After extrusion of SO_2, the migrated radical **C** becomes nucleophilic, which will preferably be trapped by electron-deficient heterocycle **2** to deliver the densely functionalized product **3** instead of undergoing another radical addition with ethylene (the pathway to **E**).

Herein, we report an unprecedented FGM-induced three-component selective ethylene difunctionalization through a metal-free radical process. With the easily accessible sulfone **1** as a bifunctional reagent, photochemical 1,2-difunctionalization of ethylene proceeds smoothly and selectively. Three C–C bonds are simultaneously constructed within a single step to ensure a rich incorporation of functionalities. In this manner, the simplest and most abundant C2 feedstock, ethylene, is readily converted to complex diheteroarylated compounds, possessing great potential to find applications in drug development.[29–31]

RESULTS

Investigation of reaction conditions

The three-component reaction was initiated by using the strategically designed bifunctional reagent **1a** and quinoxalinone **2a** under a gaseous ethylene atmosphere. Of note, quinoxalinone derivatives are present in a variety of drug molecules with anti-hepatitis C virus (HCV), antitumor, antimicrobial, and antithrombotic functions.[32,33] A reaction parameter survey indicated that the reaction proceeded well in dimethyl sulfoxide (DMSO) under 30 W white light-emitting diodes (LED) strip irradiation in the presence of diacetyl and 2,6-lutidine, leading to adduct **3a** in 78% yield (Figure 2, entry 1). Adding other photosensitizers (e.g., $Ir(ppy)_3$, 4CzIPN, $Ru(bpy)_3Cl_2$) afforded inferior results (Table S1). DMSO was the optimal solvent among the solvents evaluated (Table S5), and the addition of 2,6-lutidine dramatically improved the efficiency (Figure 2, entry 2). The reaction could still proceed in the absence of a photosensitizer, albeit in a much lower yield (entry 3). However, light is essential for product generation (entry 4). The reaction performed better in a Schlenk tube reactor than in a stop-flow microtubing reactor (entry 5).[34] A higher pressure of ethylene (10 atm) gave rise to a complicated mixture of unidentified byproducts with either a stop-flow microtubing reactor or an autoclave reactor (entries 6 and 7 and Table S7). The reaction could be easily scaled up to gram quantities (entry 8), demonstrating the practical usage of this protocol.

Substrate scope

The optimized reaction conditions were subsequently applied to assess the generality of this method (Figure 3). The scope of heteroarenes was first examined with the use of reagent **1a**. Several quinoxalinones with or without N-protection were adapted to afford the desired products (**3b–3w**). The type of N-protecting groups

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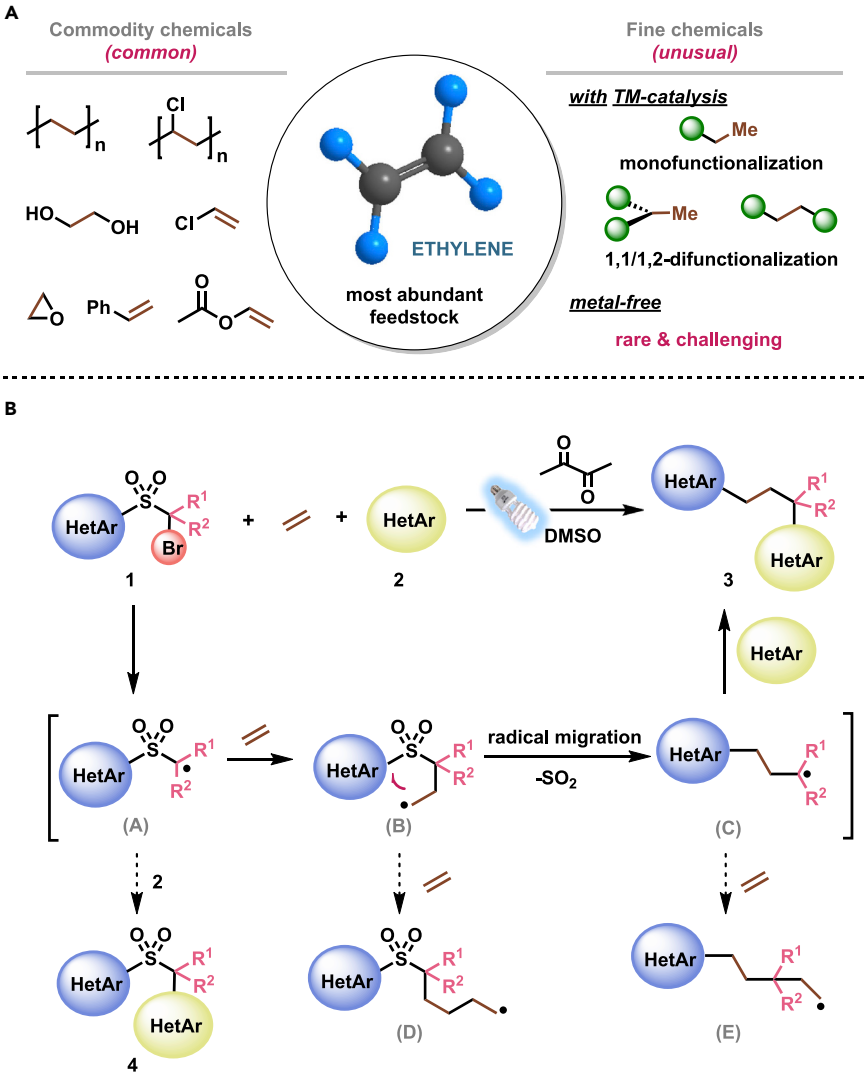
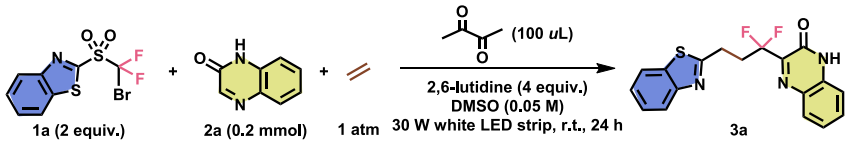


Figure 1. Synthetic utilization of ethylene

(A) Present status of ethylene transformations.

(B) Proposed metal-free radical 1,2-difunctionalization of ethylene. TM, transition metal; HetAr, heteroarene.

as well as the electronic characteristics of quinoxalinones do not have much impact on the reaction outcomes. Various functionalities were well tolerated in the reaction, e.g., halide, benzyl, cyanide, ester, nitro, trimethylsilyl, and ketone. Notably, susceptible groups in radical processes, such as hydroxyl, terminal alkenyl, and alkynyl groups, did not interfere with the desired pathway (**3s**, **3v**, and **3w**). Replacing quinoxalinone with 4-azacoumarin resulted in a comparable yield (**3x**). Other six-membered heteroarenes, such as pyridine (**3y**), phenanthridine (**3z**), phthalazine (**3aa**), isoquinoline (**3ab** and **3ac**), and 6-azauracil (**3ad**), were also suitable substrates, leading to Minisci-type adducts in useful to good yields under modified conditions, where tosylic acid was utilized to activate the N-heteroarenes. Electron-rich five-membered heteroarenes are also feasible candidates, and 1,3,4-thiadiazole (**3ae**) and caffeine (**3af**) readily proceeded in this three-component reaction, albeit with lower yields. In addition to N-containing heteroarenes, coumarin could also be incorporated into the product scaffold (**3ag**).



Entry	Variation in reaction conditions	Isolated yield (%)
1	none	78
2	without 2,6-lutidine	48
3	without diacetyl	10
4	in the dark	0
5	stop-flow microtubing reactor (1 atm ethylene)	63
6	stop-flow microtubing reactor (10 atm ethylene)	44
7[a]	autoclave (10 atm ethylene)	26
8	5 mmol scale	65 (1.16 g)

Figure 2. Evaluation of reaction parameters

Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), diacetyl (100 μL), and 2,6-lutidine (0.8 mmol) in DMSO (4.0 mL) were irradiated with 30 W white LED strips at room temperature (RT) with an ethylene balloon (1 atm) for 24 h.

[a]Irradiation with 40 W 390 nm LED light. DMSO, dimethyl sulfoxide.

The product diversity was further enhanced by the elaboration of a variety of bifunctional reagents. Both the benzothiazolyl and difluoromethyl parts in **1a** could vary as needed. Mounting different substituents on benzothiazolyl did not appreciably influence the reaction outcomes (**3ah–3aj**). Benzothiazolyl could be displaced with benzoxazolyl (**3ak**), pyrimidyl (**3al**), pyridyl (**3am**), and quinolyl (**3an**), which also showed good migratory aptitude. Altering the difluoromethyl to alkyl groups offered additional opportunity to diversify the product scaffolds. Various dialkyl and monoalkyl groups were readily incorporated into the products, regardless of steric congestion with the construction of quaternary carbon centers (**3ao–3bc**). This method provided an efficient approach for the synthesis of structurally intriguing heteroaryl-substituted carbocycles with useful yields (**3bd** and **3be**). Moreover, the incorporation of deuterium into products (**3bf**) was easily accessed by using a deuterated bifunctional reagent, which can be useful for biological studies.

DISCUSSION

Mechanistic investigations

Various control experiments were subsequently performed to gain further insight into the reaction mechanism (Figure 4). Although diheteroarylated product **3a** was only obtained in 10% yield with low conversion in the absence of diacetyl under white LED irradiation, the yield could be significantly increased by changing the light source to 390 nm LED (33%, detected a significant amount of the benzothiazole byproduct) and 456 nm LED (68%). In general, the reaction outcome was improved in the presence of diacetyl, although it was not essential. A sluggish reactivity was obtained under 525 nm light irradiation (Figure 4A). The calculated bond dissociation energy (BDE) value of the C–Br of **1a** is 63.6 kcal/mol (Figure S6), which cannot be activated by excited diacetyl (the triplet state energy of excited diacetyl is approximately 56 kcal/mol).[35] The Stern-Volmer quenching study also verified that excited diacetyl could not be quenched by **1a** or 2,6-lutidine (Figure S7), further ruling out the possibility of an EnT or a single-electron transfer (SET) initiation. The UV-vis spectroscopic studies showed that the light absorption of difunctional reagent **1a** could be extended to 470 nm (Figure 4B), which correlated well with the experimental results in Figure 4A, where the reaction could be induced by photo homolysis of the C–Br bond in **1a**. No obvious peak shift was observed with the mixture of **1a** and diacetyl, thus excluding the possibility of

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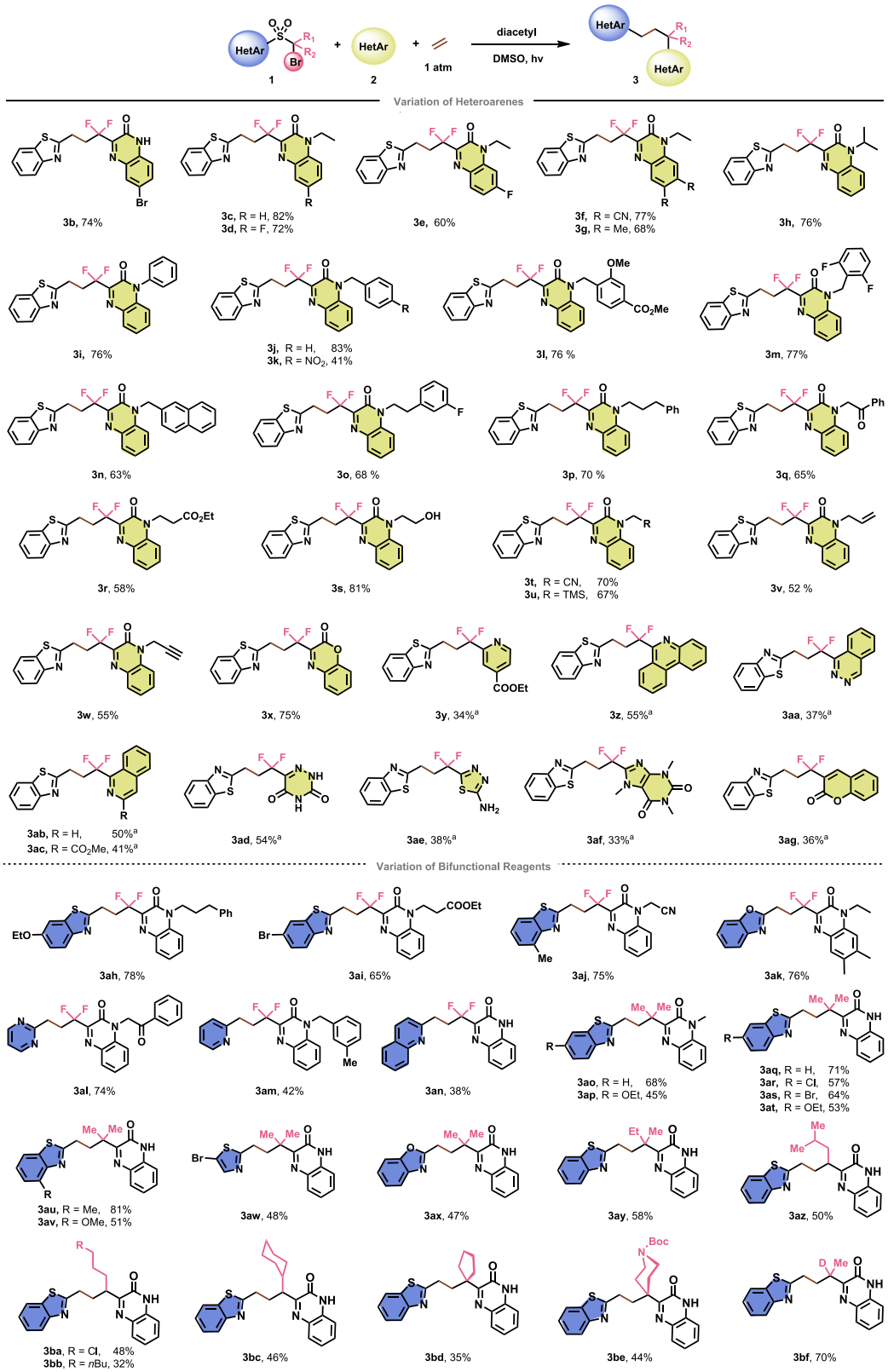

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Figure 3. Scope of ethylene difunctionalization

Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), diacetyl (100 μL), and 2,6-lutidine (0.8 mmol) in DMSO (4.0 mL) were irradiated with 30 W white LED strips at RT with an ethylene balloon (1 atm) for 20–60 h. Isolated yields are reported.

[a]**1** (0.2 mmol), **2** (0.6 mmol), diacetyl (100 μL), and *p*-tosylic acid (TsOH) (0.8 mmol) in DMSO/H_2O (4.0/0.2 mL) were irradiated with 40 W 390 nm LED light at RT for 4–10 h.

electron-donor-acceptor (EDA) complex formation between **1a** and diacetyl. The light on/off experiment (Figure S8) resulted in a total interruption of the reaction progress in the absence of light and recuperation of reactivity upon further illumination, disfavoring a long chain process. All these mechanistic experiments suggested that the reaction was initiated by light-promoted homolytic cleavage of the C–Br bond to form active carbon radical **I**. To further probe this process, the radical scavenger 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added, which suppressed the reaction. Moreover, TEMPO adduct **5** was obtained to support the presence of the radical adduct with ethylene during the reaction process. To probe the role of diacetyl, the photo-degradation experiments were conducted (Figure S10), which indicated that bifunctional reagent **1a** partially decomposed under the irradiation of 390 nm LED light to form benzothiazole. The decomposition rate was significantly reduced by the addition of diacetyl (100 μL), suggesting that diacetyl might absorb short-wavelength light (<390 nm) to suppress the decomposition of **1a**.

A tentative mechanistic pathway for ethylene difunctionalization is proposed based on all the experimental data and previous literature (Figure 4C).[36] The reaction is initiated by visible light-promoted homolytic cleavage of **1a** to form electrophilic difluoromethyl radical **I**. Addition of **I** to ethylene delivers the reactive primary alkyl radical **II**, which undergoes an intramolecular heteroaryl group migration through a kinetically favored 5-membered cyclic intermediate **III**. After SO_2 extrusion, the nucleophilic radical intermediate **IV** is formed and subjected to a Minisci-type addition with quinoxalinone **2a** to furnish a radical adduct **V**. Rearomatization of radical **V** occurs with the assistance of Br or the excited state of diacetyl[35] to accomplish the synthesis of **3a**.

Synthetic transformations

Conversion of the products into other useful molecules was attempted to further illustrate the synthetic potential of this method. Given that the benzothiazolyl group could function as a precursor of carbonyl, **3ao** was readily converted to the γ-heteroaryl-substituted aliphatic aldehyde **6** in good yield with a straightforward one-pot operation. Treatment of **3a** with $POCl_3$ afforded chlorinated intermediate **7** bearing a handle for further functionalization, such as palladium-catalyzed cross-couplings with *p*-chlorophenylboronic acid or *p*-tolylacetylene to generate adducts **8** and **9**, respectively, or a nucleophilic aromatic substitution with morpholine to furnish aminated product **10** (Figure 5A). This method also allows for the rapid assembly of biologically active compounds. Coupling bifunctional reagent **1ao** with ethylene and quinoxalinone **11** resulted in product **12**, which could be converted to aldehyde **13** via deprotection. Reduction of **13** followed by hydrolysis and amidation furnished compound **15**, which is an ion channel blocker and cytoprotective agent (Figure 5B).[37]

The protocol could be applied to other gaseous and low boiling-point alkenes, such as isobutylene, 1-butene, 1-amylene, and cyclopentene, leading to the corresponding coupling products (**16a–16d**) in synthetically useful yields and manifesting the generality of this method (Figure 5C).

Based on the proposed mechanism (Figure 4C), we envisioned that the three-component reaction could be extended by replacing the radical trapping agent to

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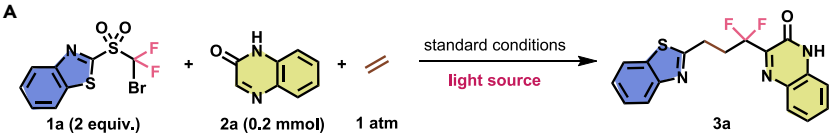
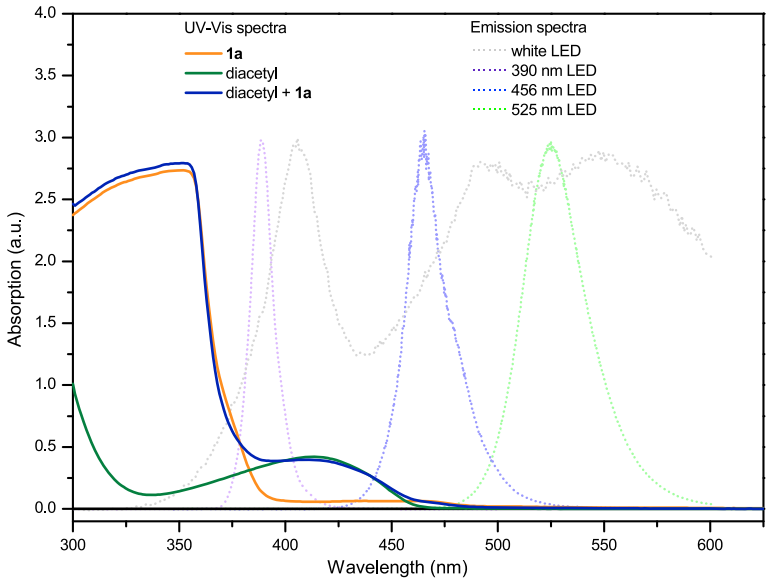


Entry	Ligth source	Photon energy (kcal/mol)	Isolated yield (%)	Isolated yield (%) w/o diacetyl
1	white LED strip (30 W)	-	78	10
2	390 nm light (40 W)	~73.3	71	33
3	456 nm light (40 W)	~62.7	76	68
4	525 nm light (40 W)	~54.5	< 2	< 2

B



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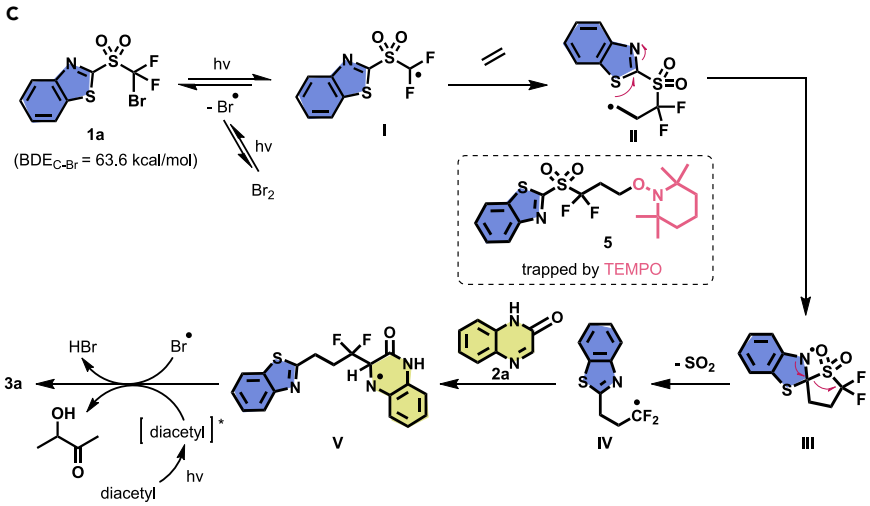

Figure 4. Proposed mechanism with supporting evidence

(A) Control experiments with different light sources.

(B) UV-vis spectra of bifunctional reagents and diacetyl and emission spectra of light sources.

(C) Proposed mechanism.

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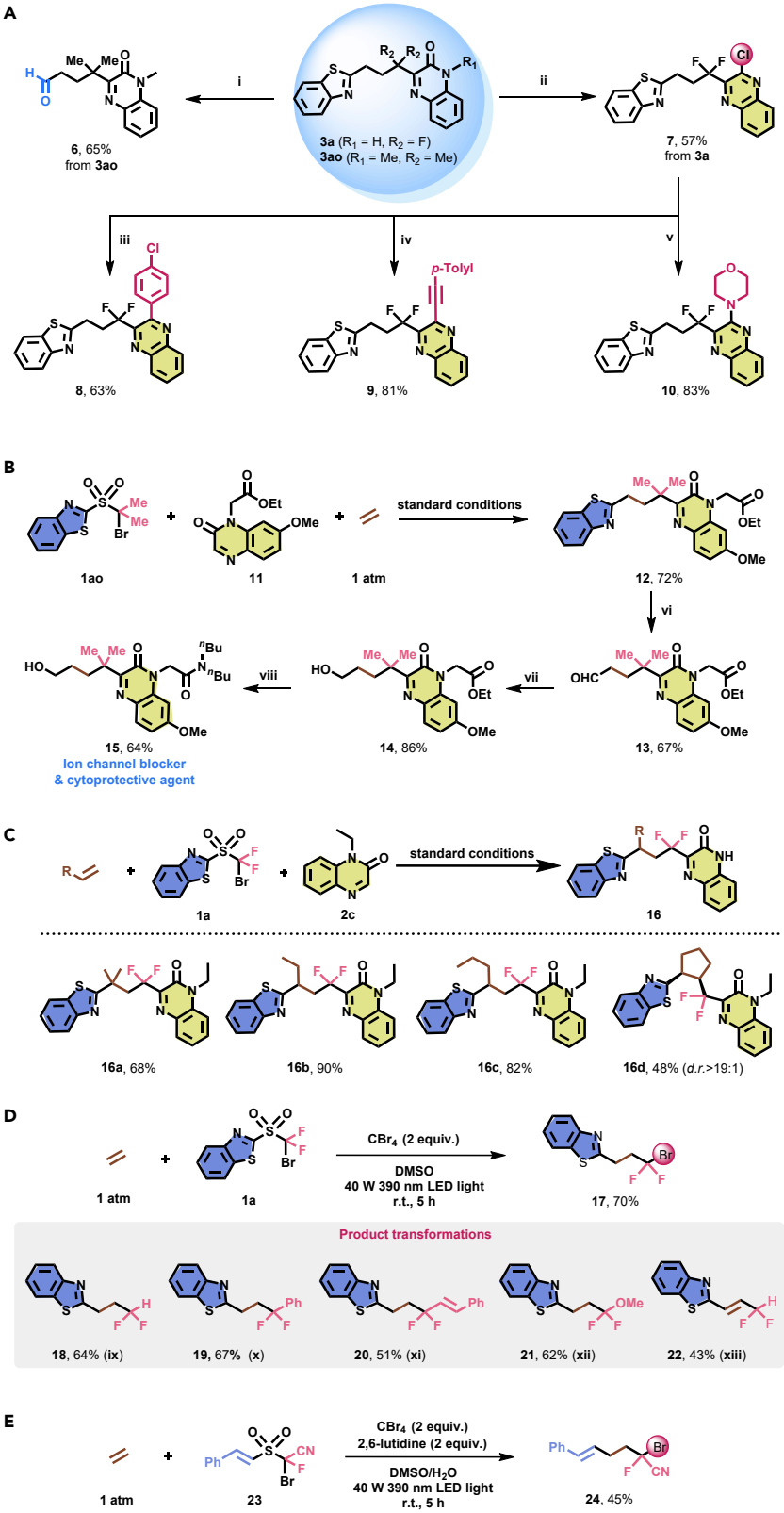

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Figure 5. Product conversions and reaction extension

(A) Further derivatization of **3a** and **3ao**. (i) Deprotection of benzothiazole to aldehyde: Me_3OBF_4 in dichloromethane (DCM), $NaBH_4$ in MeOH and $AgNO_3$ in CH_3CN/H_2O were used successively. (ii) Chlorination: **3a** (1.5 mmol), $POCl_3$ (2.0 mmol), and pyridine (1.5 mmol) were stirred at 160°C. (iii) Palladium-catalyzed cross-coupling: **7** (0.2 mmol), 4-chlorophenylboronic acid (0.4 mmol), $Pd(PPh_3)_4$ (5.0 mol %), and aqueous K_2CO_3 in toluene/EtOH were stirred at 130°C under argon. (iv) Palladium-catalyzed cross-coupling: **7** (0.2 mmol), *p*-tolylacetylene (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (7 mol %) in Et_3N (1.0 mL) were stirred at 90°C under argon. (v) Nucleophilic aromatic substitution: **7** (0.2 mmol), morpholine (0.3 mmol), and K_2CO_3 (0.3 mmol) in CH_3CN were stirred at 90°C.

(B) Application in the synthesis of biologically active compound **15**. (vi) Deprotection of benzothiazole to aldehyde: Me_3OBF_4 in DCM, $NaBH_4$ in MeOH, and $AgNO_3$ in CH_3CN/H_2O were used successively. (vii) Reduction of aldehyde: **13** (0.3 mmol) and $NaBH_4$ (0.45 mmol) in DCM/MeOH were stirred at 0°C under argon. (viii) Hydrolysis and amidation: **14** (0.2 mmol) and LiOH (0.4 mmol) in dioxane/H_2O were stirred at RT for 3 h, then acidified by 1 M HCl, subsequently treated with dibutylamine (0.15 mmol), EDC (0.2 mmol), HOBt (0.2 mmol), and DIPEA (0.38 mmol) in dimethylformamide (DMF) (2 mL). EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBt, biphenyl-4-amidoxime; DIPEA, N,N-diisopropylethylamine.

(C) The scope of other gaseous and low boiling-point alkenes. **1a** (0.4 mmol), **2c** (0.2 mmol), diacetyl (100 μL), alkenes (0.6 mmol, isobutylene and 1-butene dissolved in DCM), and 2,6-lutidine (0.8 mmol) in DMSO (4.0 mL) were irradiated with 30 W white LED strips at RT for 24–28 h. Isolated yields are reported.

(D) Bromodifluoromethylation of ethylene and synthetic elaboration. (ix) Hydrogenation: **17** (0.2 mmol, zinc powder (1.0 mmol), and 2 M HCl (0.1 mL) in DMF were stirred at 60°C under argon. (x) Nickel-catalyzed Suzuki coupling: **17** (0.2 mmol), $Ni(acac)_2$ (0.04 mmol), xantphos (0.04 mmol), K_2CO_3 (0.4 mmol), and $PhB(OH)_2$ (0.6 mmol) in CH_3CN were stirred at 110°C under argon. (xi) Palladium-catalyzed Heck-type reaction: **17** (0.2 mmol), styrene (0.4 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), xantphos (0.04 mmol), and Cs_2CO_3 (0.4 mmol) in 1,2-dichloroethane (DCE) were stirred at 90°C under argon. (xii) Nucleophilic substitution: **17** (0.2 mmol) and $AgNO_3$ (0.6 mmol) in MeOH were stirred at 60°C under argon. (xiii) Elimination of bromide with TBAF and tautomerization: **17** (0.2 mmol) and TBAF (0.6 mmol) were stirred at RT under argon. TBAF, tetrabutylammonium fluoride.

(E) Vinylsulfones as the migration reagents. **23** (0.2 mmol), CBr_4 (0.4 mmol), and 2,6-lutidine (0.4 mmol) in DMSO/H_2O were stirred under 390 nm LED light at RT for 5 h.

expand the product scaffold diversity. Simply using CBr_4 instead of heteroarene **2** under 390 nm light irradiation gave rise to brominated product **17** (Figure 5D). The difluorobromo moiety in compound **17** provides a versatile handle for structural diversification. Reduction of **17** generated difluoroalkyl product **18**. Construction of a new C–C bond was achieved through either nickel-catalyzed cross-coupling of **17** with phenylboronic acid or a palladium-catalyzed Heck-type reaction, leading to aryl or vinyl products **19** and **20**, respectively. Nucleophilic substitution of **17** with MeOH resulted in difluoroalkyl ether **21**. Furthermore, treatment of **17** with base delivered difluoroalkyl olefin **22** via an elimination/tautomerization cascade. By varying heteroaryl-migration reagent **1a** to styrene-migration reagent **23**, the radical vinylation of ethylene readily proceeded under slightly modified conditions to give the corresponding alkenyl adduct **24** in a useful yield (Figure 5E). However, the reaction of ethylene with analogous bifunctional reagents using phenyl or alkynyl instead of heteroaryl as the migrating group did not give rise to the desired products.

Conclusions

In summary, we established a selective, scalable, metal-free three-component radical difunctionalization of ethylene. The success of this strategy relies on the unique merits offered by the strategically designed sulfone bifunctional reagents: the visible-light absorption character enables photoinduced homolysis of the C–Br bond for the reaction initiation; the polarity of generated nucleophilic radicals guarantees the selective ethylene addition over the Minisci-type addition; and the FGM facilitates an intramolecular heteroarylation process over the competing oligomerization or polymerization of ethylene. This approach is distinguished by its mild

conditions, simple operation, broad functional group compatibility, excellent scaffold diversity, and the use of ethylene at an atmospheric pressure. The synthetic value of this method lies in the rapid assembly of molecular complexity from the simplest and most abundant chemical feedstock and opening a new vista for radical functionalization of ethylene.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Chen Zhu (chzhu@suda.edu.cn).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

This study did not generate any datasets.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2022.10.020.

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AUTHOR CONTRIBUTIONS

C.Z. and J.W. conceived and directed the project. J.Y., J.W., and C.Z. administrated the project. J.Y., X.Z., X.W., T.L., and Z.-Q.Z. performed the experiments. J.Y., X.Z., J.W., and C.Z. investigated the experiments and mechanism studies. J.Y., J.W., and C.Z. wrote the original manuscript. J.W. and C.Z. reviewed and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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