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Metal-free visible-light-enabled vicinal trifluoromethyl dithiolation of unactivated alkenes

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Abstract

The difunctionalization of alkenes involving trifluoromethylthio group (SCF_3) for the conversion of versatile and readily available olefins into more structurally complex molecules has been greatly studied. However, the disproportionate dithiolation of alkene is unknown. Herein, a transition-metal-free protocol is presented for vicinal trifluoromethylthio-thiolation of unactivated alkenes *via* a radical process under mild condition with broad substrate scope and excellent tolerance.

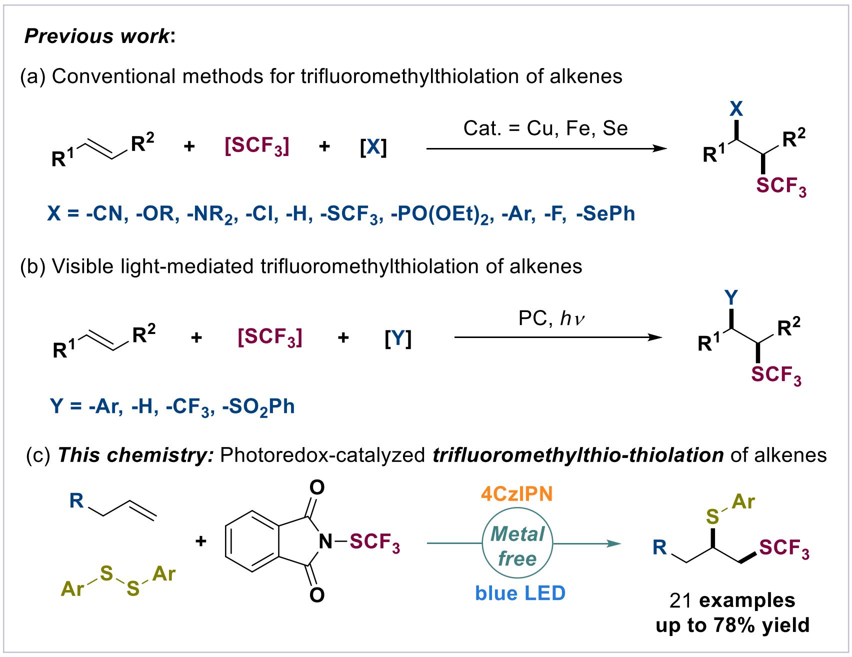
Keywords: metal-free, photoredox, difunctionalization, trifluoromethylthiolation, alkenes.

Introduction

The incorporation of fluorine atoms into drug molecules will significantly enhance the physical, chemical, and biological properties of pharmaceuticals. [1–6] Modifying drug candidates by introducing fluorine-containing (such as $-CF_3$, $-CF_2H$, $-C_2F_5$, $-SCF_3$, $-OCF_3$) moieties has become a substantial strategy for medicinal research.

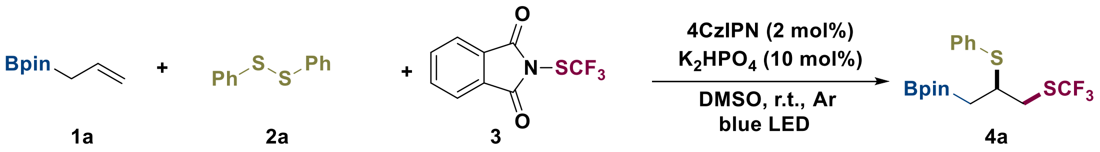
[2,7,8] Among those fluorinated functionalities, the trifluoromethylthio group (SCF_3) has strong electro-withdrawing properties and higher lipophilicity (π_R=1.44), which could improve pharmaceuticals ability to cross lipid membranes. [9,10] Along these lines, the introduction of the SCF_3 group into small molecules has attracted great attention in organofluorine methodology. [11–17]

The vicinal difunctionalization of olefins to introduce two functional groups across a double bond has appeared as a vigorous transformation to rapidly increase molecular complexity in synthetic chemistry with improved efficiency. [18–22] Various transition-metal mediated approaches for trifluoromethylthio (SCF_3) difunctionalizations of alkenes, such as cyanation, [23] etherification, [24–27] amination, [28–30] chlorination, [31,32] hydrogenation, [33] trifluoromethylation, [34] phosphonization, [35] arylation, [36–38] trifluoromethylthiolation,[39] fluorination,[40] and selenylation[41] have been reported (scheme 1a). However, visible-light-induced trifluoromethylthio difunctionazation of alkenes has been underdeveloped. For instance, Magnier and co-workers have documented a practical intramolecular carbotrifluorimethylthiolation of acrylamides under irradiation of visible-light [38]. In 2017, the photoredox-catalyzed intermolecular trifluoromethylthio-trifluoromethylation and thiosulfonylation reaction of unactivated alkenes have been respectively developed by Liu [34] and Xu [42]. Recently, Qing [43] and co-workers reported an efficient *anti*-Markovnikov hydrotrifluoromethylthiolation of alkenes utilizing trifluoromethanesulfonic anhydride (Tf_2O) as a radical trifluoromethylthiolatin reagent through deoxygentive reduction and photoredox radical pathway (Scheme 1b). The C-S bonds [44,45] are important structural motifs and widely present in natural products, drug molecules, biologically active molecules and functional materials. However, the highly selective incorporation of two different sulphur-bearing moieties across double bonds remained challenging. [42] Herein, we describe a visible-light-enabled cascade radical addition of unactivated alkenes for the construction of partially trifluoromethylated dithioethers with broad substrate scope and good chemical tolerance (Scheme 1c).



Scheme 1. Origin of the reaction design

Results and Discussion

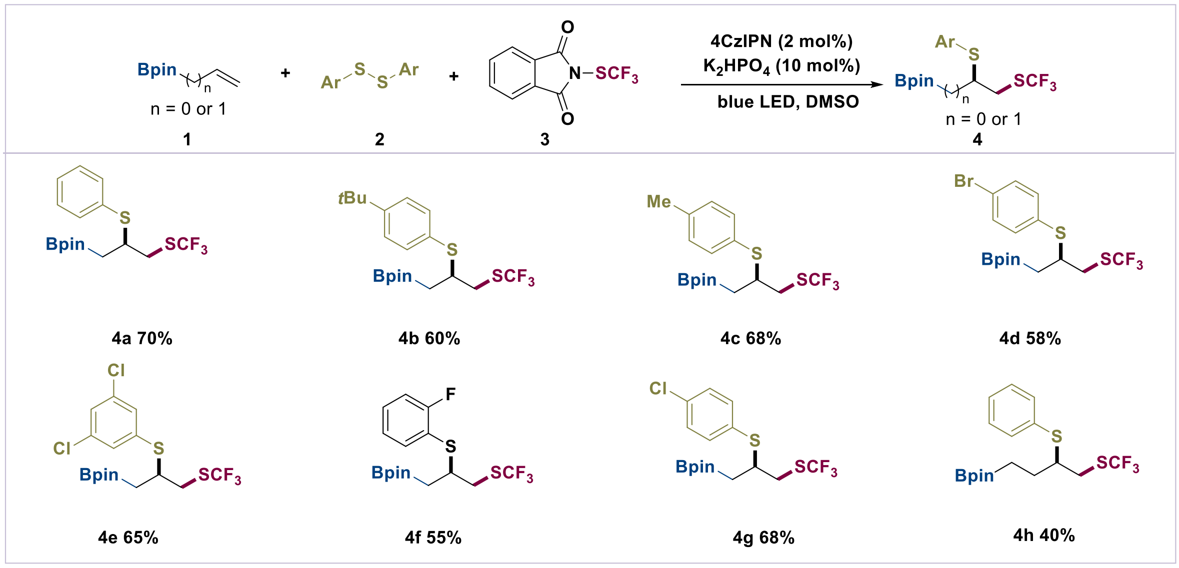


Entry	Deviation from the reaction conditions	Yield [b] (%)
1	none	71
2	2.0 equiv K_2HPO_4	70
3	KH_2PO_4 instead of K_2HPO_4	34
4	DMA instead of DMSO	trace
5	$[Ir(dF(CF_3)ppy)_2(dtbby)]PF_6$ instead of 4CzIPN	43
6	no K_2HPO_4	0
7	without 4CzIPN	0
8	in darkness	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 equiv), **3** (1.5 equiv), 4CzIPN (2 mol%), K_2HPO_4 (10 mol%), r.t., Ar, 24 h. [b] Crude yields were determined by ^{19}F NMR using trifluoromethoxybenzene as internal standard.

Table 1. Optimization of the reaction conditions [a]

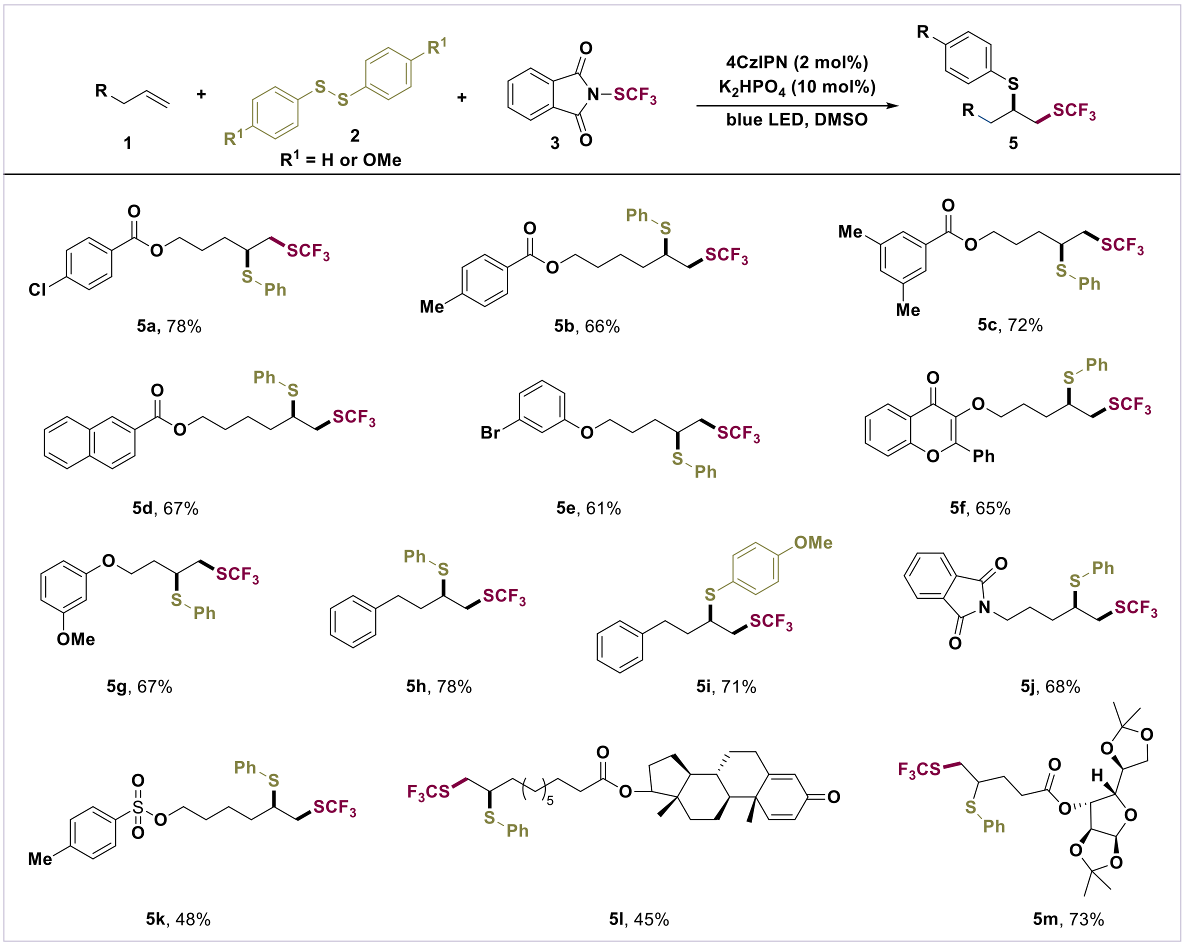
We evaluated the reaction conditions for this trifluoromethylthio-thiolation and found out under irradiation of blue LEDs, allyl boronate **1a** (0.1 mmol), disulfide **2a** (1.0 equiv) and Phth-SCF_3 **3** (1.5 equiv), the desired trifluoromethylthio product **4a** was obtained in 71% yield with 4CzIPN (2 mol%) as photocatalyst and KH_2PO_4 (10 mol%) as base (Table 1, entry 1). The yield of **4a** was not increased when the 2 equivalent of K_2HPO_4 was used (entry 2). No difunctionalized product was observed with DMA as the solvent (entry 4). The employment of KH_2PO_4 as base and $[Ir(dF(CF_3)ppy)_2(dtbby)]PF_6$ as photocatalyst furnished the product in very low yield (entries 3 and 5). The control experiment indicated that 4CzIPN, K_2HPO_4 or visible-light was indispensible for the reaction (entries 6-8).



Scheme 2. Substrate scope of disulfides

With the optimized reaction conditions, we examined the substrate scope of the disulfides (Scheme 2). Using borate-substituted olefins, the intermolecular trifluoromethylthio-thiolation induced by sequential radical difunctionalization proceeded smoothly in a chemoselective fashion. Both electron-withdrawing and electron-donating group substituted aryldisulfides were tolerated to access products **4a**-**4g**. The homoallylic borate (**1h**) was also converted into the corresponding **4h** in moderate yield.

In order to further examine the generality of the reaction, we have extended this protocol to a range of unactivated alkenes. Terminal alkenes containing ester (**5a-5d**) and oxygenated alkyl (**5e-5g**) functionalities were tolerated under this framework. The substrate1-phenyl-3-butene transformed into the desired products **5h** and **5i** in good yields. Amide (**5j**), sulfonate (**5k**) substituted alkenes also furnished the corresponding SCF_3 adducts. In addition, boldenone- and D-glucose-derived terminal alkenes were compatible to afford the corresponding products **5l** and **5m** in moderate yields.

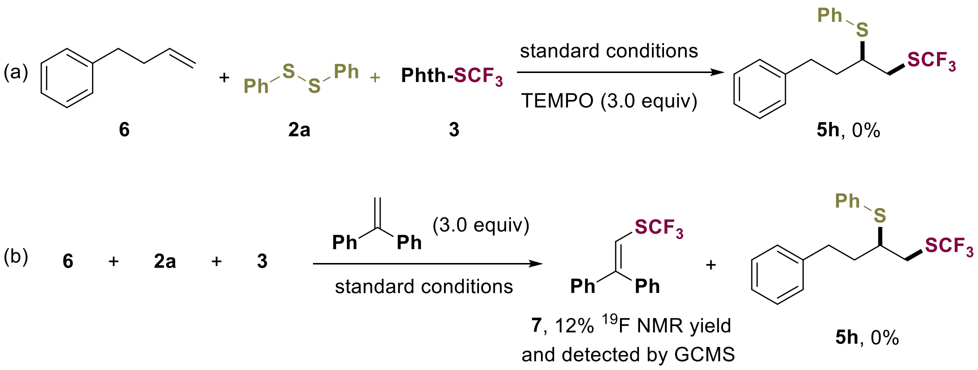


Scheme 3. Substrate scope of unactivated alkenes

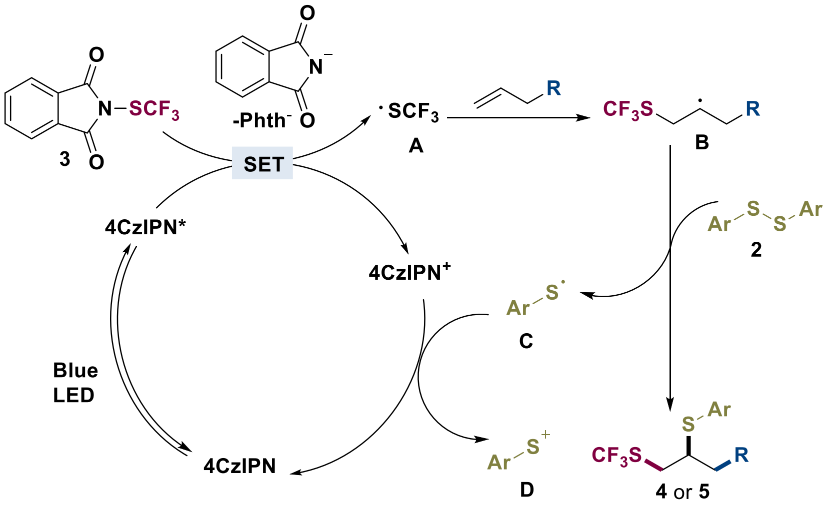
To gain insight into the reaction mechanism, control experiments have been conducted under the standard conditions. The radical-trapping agent 2,2,6,6-tramethylpiperidin-1-oxyl (TEMPO, 3.0 equiv) has prohibited the reaction. When diphenylethylene (3.0 equiv) was added to the reaction mixture, the desired product

5h was not obtained, and the vinyltrifluoromethylsulfide **7** was afforded in 12% yield.[46,47]

Based on the above results and previous literatures, [33,38,48] a plausible mechanism for the trifluoromethylthio-thiolation is proposed (Scheme 5). The reaction is initiated by the photoexcition of 4CzIPN (4CzIPN$^+$/4CzIPN*: $E_{1/2}^{red}$ = -1.04 V *vs* SCE) followed by single electron reduction of Phth-SCF$_3$ **3** ($E_{1/2}^{red}$ = ‑0.45 V *vs* SCE) [49,50] to generate phthalimide anion (Phth$^-$) and trifluoromethylthio radical. The SCF$_3$ radical readily reacts with the unactivated alkenes to give the intermediate **B**. The subsequent addition of **B** to disulfide **2** affords the difunctionalized product **4** or **5** and thiophenyl radical **C**. [51] Finally, the oxidation of **C** by 4CzIPN$^+$ closes the catalytic cycle. [52]



Scheme 4. Control experiments



Scheme 5. Proposed mechanism

Conclusion

In summary, an efficient cascade radical strategy has been successfully developed in photo-induced difunctionalization of alkenes for the the preparation of trifluoromethyl dithioethers. This approach features the practical conditions, good functional group tolerance and broad substrate scope for the incorporation of two distinctive sulfur-containing motifs into terminal olefins.

Supporting Information

Supporting Information File

Full experimental details, compound characterization, and copies of NMR spectra.

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