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Visible-Light-Mediated Photoredox-Catalyzed Regio- and Stereoselective Chlorosulfonylation of Alkynes

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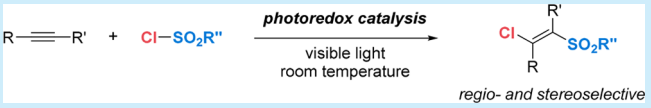
Supporting Information

ABSTRACT: Herein, a one-step chlorosulfonylation of alkynes via a photocatalytic redox process is described. A variety of commercially available sulfonyl chlorides can be applied for the generation of sulfonyl radical species under visible-light irradiation. Regio- and stereoselective addition of the sulfonyl radical and chloride leads to the efficient formation of (*E*)-selective *β*-chlorovinyl sulfones from a broad range of terminal and internal alkynes. The reported method represents an operationally simple and mild way to furnish vinyl sulfones.



Sulfur-containing organic molecules find widespread utilization in various fields of chemistry.[1] In particular, with the increasing number of approved organosulfur-based drugs, much research has been pursued with the aim of installing the sulfur functional unit in organic molecules.[2] Vinyl sulfones have been a popular research topic because of their unique structural motif which is valuable for designing building blocks in materials science and pharmaceutical science; furthermore, because of their intrinsic electron-withdrawing nature, vinyl sulfones serve as functional modulators in various synthetic transformations.[3]

In most pharmaceutical compounds (see Figure 1 for examples), the vinyl sulfone serves as a critical functional group that can inhibit specific enzymes of interest. Nucleophilic attack onto vinyl sulfones by cysteine or serine residues can block the catalytic sites in enzymes.[4] Furthermore, the vinyl sulfone can be converted to an alkyl sulfone after reduction, as exemplified in the preparation of the antimigraine drug eletriptan.[5]

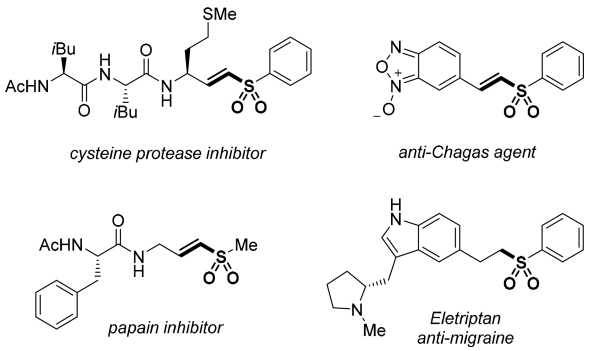
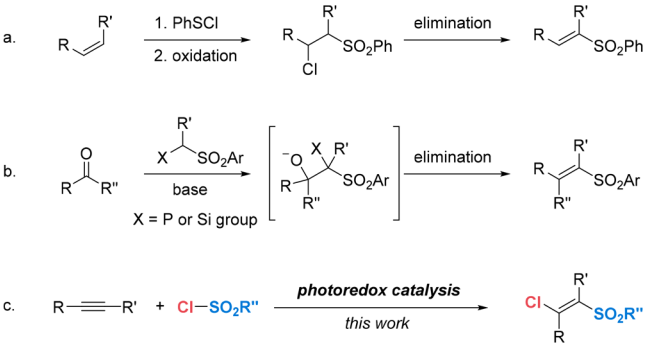


Figure 1. Sulfone or vinyl sulfone containing pharmaceutical compounds.

Scheme 1. Methods for Preparing Vinyl Sulfones



Traditionally, the vinyl sulfone moiety has been constructed via multistep sequences involving addition, oxidation, and elimination (Scheme 1a).[6] Carbonyl group olefination strategies have also been developed to prepare vinyl sulfones (Scheme 1b).[7] However, the reported methods are multistep, involve inconvenient operation, and require complex purification processes. Therefore, considerable effort has recently been undertaken for the direct introduction of the sulfonyl moiety. Issues concerning regio- and stereoselectivity, substrate scope, and reaction conditions prompted us to explore a more synthetically attractive protocol for the synthesis of vinyl sulfones.

A distinguishing feature of our approach is the use of sulfonyl chloride and alkynes to realize chlorosulfonylation in a single step (Scheme 1c).[8,9] Based on our previous studies regarding the vicinal functionalization of alkynes and alkenes,[10] we anticipated that single-electron transfer (SET) by a suitable photoredox catalyst could mediate the entire reaction under

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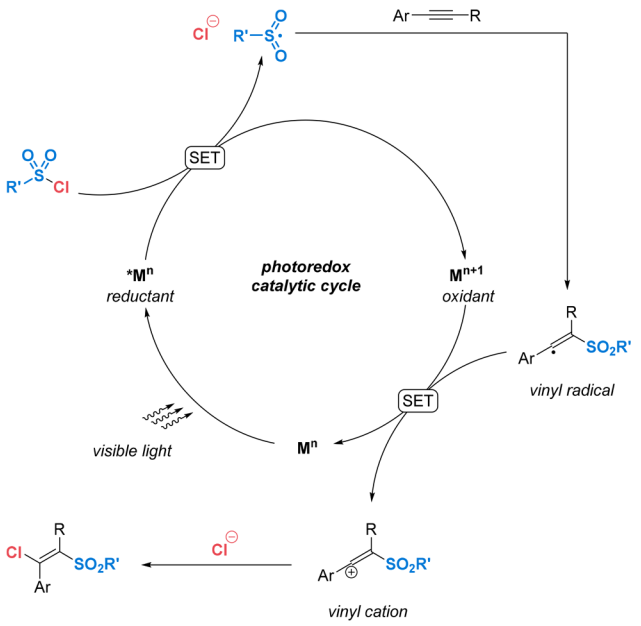
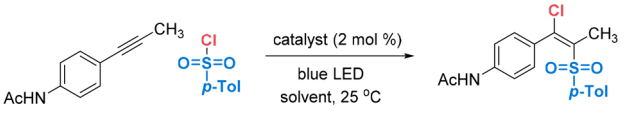


Figure 2. Plausible pathway for chlorosulfonylation of alkynes.

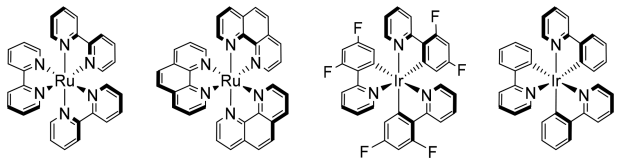
Table 1. Optimization of the Chlorosulfonylation of Alkynes[a]



1a 2a 3a

entry	catalyst	solvent	2a (equiv)	3a (% yield)[b]	E/Z ratio
1	4a	MeCN	1.5	0	–
2	4b	MeCN	1.5	<5	–
3	4c	MeCN	1.5	<5	–
4	4d	MeCN	1.5	48	5:1
5	4d	acetone	1.5	12	5.1:1
6	4d	acetone/H_2O (30:1)	1.5	68 (60)	5.2:1
7	4d	1,2-dichloroethane	1.5	trace	–
8	4d	CH_2Cl_2	1.5	92 (87)	4.8:1
9	4d	CH_2Cl_2	1.0	84	5.2:1
10	4d	CH_2Cl_2	2.0	97	5.2:1
11[c]	4d	CH_2Cl_2	1.5	0	–
12[d]	–	CH_2Cl_2	1.5	0	–

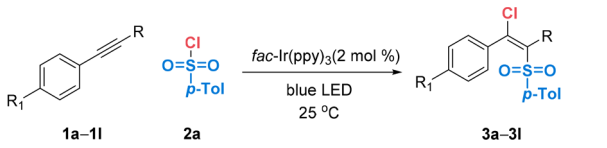
[a]Reactions were carried out under a N_2 atmosphere at 25 °C for 24 h using **1a** (0.1 mmol), catalyst (2 mol %), and tosyl chloride **2a** (0.15 mmol). [b]Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard (isolated yield after flash silica gel column given in parentheses). [c]In the dark. [d]Without catalyst.



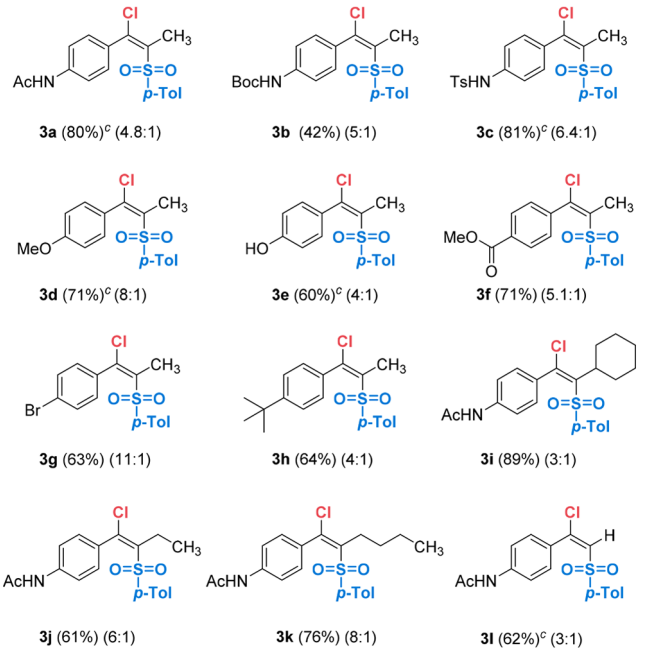
$Ru(bpy)_3^{2+}$ **4a** $Ru(Phen)_3^{2+}$ **4b** *fac*-$Ir(dFppy)_3$ **4c** *fac*-$Ir(ppy)_3$ **4d**

mild conditions. We describe herein the results of our studies on the synthesis of β-halosulfonyl alkenes from alkynes by visible-light-induced photocatalysis.

Table 2. Alkyne Scope for Chlorosulfonylation[a,b]



1a–1l 2a 3a–3l



3a (80%)[c] (4.8:1) **3b** (42%) (5:1) **3c** (81%)[c] (6.4:1)

3d (71%)[c] (8:1) **3e** (60%)[c] (4:1) **3f** (71%) (5.1:1)

3g (63%) (11:1) **3h** (64%) (4:1) **3i** (89%) (3:1)

3j (61%) (6:1) **3k** (76%) (8:1) **3l** (62%)[c] (3:1)

[a]Reactions were carried out under a N_2 atmosphere at 25 °C for 24 h using alkyne (0.2 mmol), *fac*-$Ir(ppy)_3$ (2 mol %) and sulfonyl chloride (0.3 mmol) in acetone/water (30:1). [b]Isolated yields after column chromatography are given in parentheses. [c]CH_2Cl_2 used.

We initially explored the reaction by elucidating the mechanism, which is illustrated in Figure 2. The catalytic cycle begins with visible-light irradiation to provide a photoexcited catalyst. Using the appropriate catalyst that can cleave the S–Cl bond, the requisite sulfonyl radical is prepared via reductive SET.[11] Subsequent addition of the sulfonyl radical to the alkyne affords a vinyl radical, which undergoes electron-recycling SET with the oxidized catalyst to regenerate the catalyst. Finally, the process is completed by trapping the carbocation with the halide, leading to the synthesis of β-chlorovinyl sulfone.[12]

Notably, we envisioned that the desired regioselectivity in the sulfonyl radical addition to alkynes could be achieved to generate the vinyl radical that is stabilized by the adjacent aryl substituents. In addition, halide attack on the vinyl cation would occur stereoselectively at the position opposite to the sulfonyl group so that electrostatic repulsion between the electron-withdrawing substituents is minimized. Thus, the designed process can install chloro and sulfonyl groups (*E*)-selectively while suppressing the potentially intervening radical chain processes. The chloride functional group in the products can be further manipulated to assemble various functional groups in the following steps.

Since the SET process outlined in Figure 2 provides information on the electrochemical properties of the molecule,[13] we initiated our studies by monitoring the reaction of alkyne **1a** and tosyl chloride (**2a**, $E_{1/2}$ = −1.37 V vs SCE in MeCN) under various photocatalytic conditions (Table 1). In

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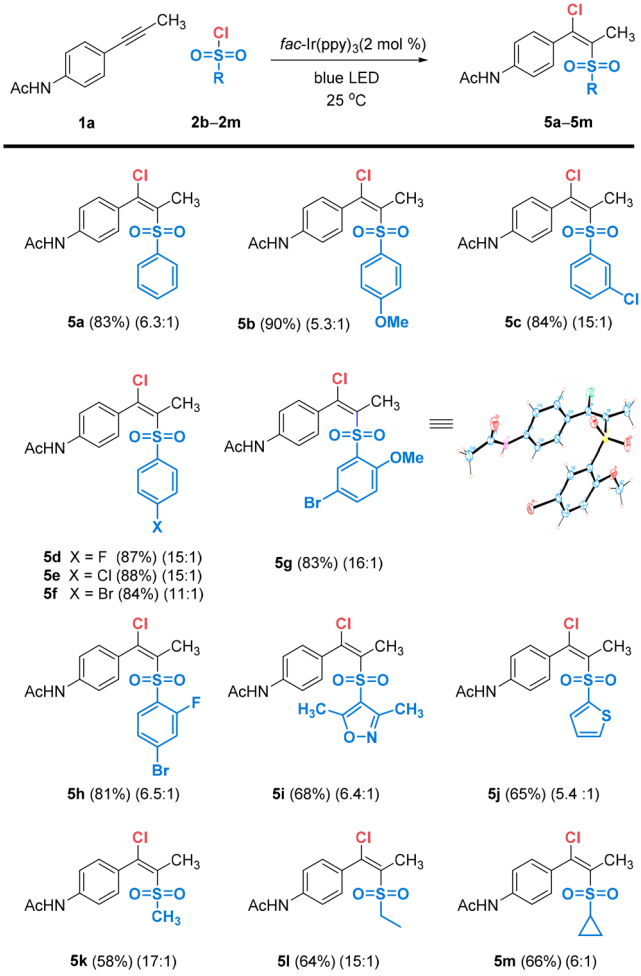
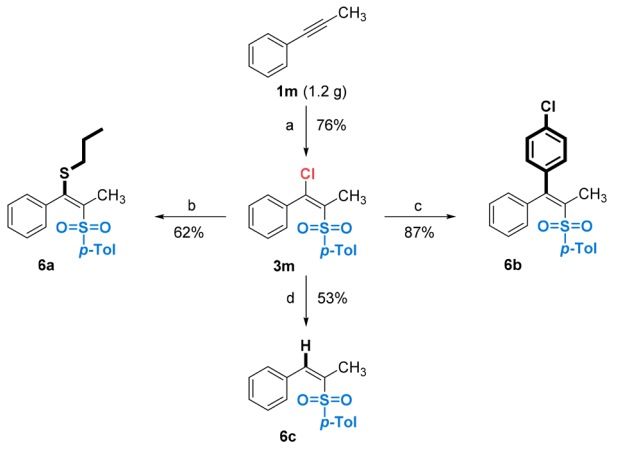
Table 3. Sulfonyl Chloride Scope for Chlorosulfonylation[a,b]



[a]Reactions were carried out under a N_2 atmosphere at 25 °C for 24 h using alkyne (0.2 mmol), *fac*-Ir(ppy)$_3$ (2 mol %), and sulfonyl chloride (0.3 mmol) in CH_2Cl_2 (2 mL). [b]Isolated yields after column chromatography are given in parentheses.

Scheme 2. Preparative Synthesis of *β*-Chlorovinyl Sulfone and Its Applications[a]



[a]*fac*-Ir(ppy)$_3$ (2 mol %), *p*-tosyl chloride **2a** (1.5 equiv), CH_2Cl_2 (0.5 M), 25 °C, 24 h. [b]Sodium propane-1-thiolate (3.0 equiv), ethanol (0.5 M), 100 °C, 5 h. [c]$Pd(PPh_3)_2Cl_2$ (10 mol %), (4-chlorophenyl)-boronic acid (1.5 equiv), K_2CO_3 (1.1 equiv), MeCN (0.2 M), 110 °C, 8 h. [d]Zn dust (3 equiv), acetic acid (0.5 M), 110 °C, 4 h.

the presence of catalyst **4a** ($E_{1/2}$ [Ru^{II*}/Ru^{III}] = −0.81 V vs SCE in MeCN), the reaction did not proceed at all, but **4b** ($E_{1/2}$ [Ru^{II*}/Ru^{III}] = −0.87 V vs SCE in MeCN) induced the formation of **3a**, albeit in low yield (entry 2). In addition, the use of catalyst **4c** possessing a higher oxidizing potential ($E_{1/2}$ [Ir^{III}/Ir^{IV}] = +1.18 vs SCE in MeCN) did not improve the yield (entry 3). Gratifyingly, when catalyst **4d** with a more strongly reducing potential ($E_{1/2}$ [Ir^{III*}/Ir^{IV}] = −1.73 V vs SCE in MeCN) was employed, a dramatic enhancement in the yield of **3a** was observed (entry 4). To increase the product yield, the reaction conditions were further optimized by solvent screening (entries 5−8). Among the solvents screened, dichloromethane gave **3a** in excellent yield (92%, entry 8). While the amount of **2a** did not affect the product generation significantly (entries 9 and 10), control experiments showed that mediation of the reaction by both light and catalyst **4d** was essential (entries 11 and 12). Interestingly, plausible desulfonylation was not observed in the reaction.[11] It is also remarkable that the reaction is the first photoredox-catalyzed protocol to furnish chlorovinyl sulfones under mild and operationally simple conditions. Most importantly, the observed regio- and stereoselectivity of the product corresponded exactly to our proposed demonstrations, showing the formation of (*E*)-preferential chloro-alkenyl sulfone **3a**.

The established catalytic protocol was then tested for a range of reactions with an assortment of alkynyl substrates with different electronic and steric properties (Table 2). A variety of functional groups such as amide, sulfonamide, carbamate, halides, ester, ether, and alcohol were tolerated under the standard conditions (in dichloromethane or acetone/water as the solvent), affording (*E*)-selective *β*-chlorovinyl sulfones (**3a**−**3h**). Internal alkynes with various alkyl side chains (**3i**−**3k**), as well as a terminal alkyne (**3l**), could be employed in the addition reaction, and moderate to high product yields were obtained.[14]

Consistent with the observations for the alkyne scope, the use of different sulfonyl chlorides also allowed excellent conversion to yield the desired products. As shown in Table 3, the reaction proceeded well with both electron-rich and electron-deficient aryl sulfonyl chlorides (**5a**−**5h**). Moreover, heteroaromatic sulfonyl chlorides participated in the reaction efficiently (**5i** and **5j**). Furthermore, it is noteworthy that sulfonyl chlorides with different alkyl substituents afforded the corresponding products (**5k**−**5m**).

X-ray crystallographic analysis of **5g** unambiguously confirmed the regio- and stereoselectivity, suggesting (*E*)-selective alkene formation. The reactions could be carried out without the rigorous removal of air and moisture from the reaction mixture. Remarkably, no desulfonylative addition product was obtained, probably because the radical formed after desulfonylation had considerably reduced stability as compared to the sulfonyl radical.[15] In addition, the geometry of the alkenes was unaffected by isomerization throughout the reaction, even at elevated temperatures.

To demonstrate the synthetic utility of the reaction, further manipulations of the installed functional groups were carried out (Scheme 2). A preparative-scale experiment was carried out using 1.2 g of **1m**, producing compound **3m** in 76% yield. Using **3m** as the starting material, conjugate addition/elimination generated **6a** in 62% yield. A Pd-catalyzed cross-coupling reaction with (4-chlorophenyl)boronic acid provided

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β-diaryl substituted vinyl sulfone **6b** in 87% yield. Finally, dehalogenation mediated by zinc and acetic acid afforded (*Z*)-vinyl sulfone **6c** in 53% yield. These results illustrate the powerful utility of the developed process not only as a new synthetic tool to furnish the β-chlorovinyl sulfone moiety but also as a useful platform for the efficient construction of synthetically challenging structures by simple manipulation of the installed groups.

In summary, we have described a novel method for the regio- and stereoselective chlorosulfonylation of alkynes by visible-light-induced photoredox catalysis. A wide range of alkynes, as well as sulfonyl chlorides, are competent participants in the free-radical mediated reaction to afford structurally diverse vinyl sulfones. The present protocol allows for the generation of sulfonyl radical intermediates from easily available organosulfonyl chlorides under mild conditions at room temperature, thus representing an operationally convenient alternative to the reported methodologies. Finally, we expect our findings to be of broad utility in the preparation of sulfone-derived organic molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03273.

Experimental procedures, spectroscopic data for all new compounds and the X-ray crystallographic data of compound **5g** (CCDC 1843966) (PDF)

Accession Codes

CCDC 1843966 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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