RESEARCH ARTICLE

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Photoredox-catalyzed cascade annulation of methyl(2-(phenylethynyl)phenyl)sulfanes and methyl(2-(phenylethynyl)phenyl)selanes with sulfonyl chlorides: synthesis of benzothiophenes and benzoselenophenes†

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A photoredox-catalyzed cascade annulation of methyl(2-(phenylethynyl)phenyl)sulfanes and methyl(2-(phenylethynyl)phenyl)selanes with sulfonyl chlorides was developed. A variety of benzothiophenes and benzoselenophenes were obtained in moderate to good yields at ambient temperature.

Benzothiophene and its derivatives have attracted tremendous attention due to their wide application in pharmaceuticals, materials science, catalysis and biology.[1] As a consequence, a myriad of reports have been developed for the preparation of substituted benzothiophenes.[2] In recent years, radical cascade reactions have been predominant for the synthesis of benzothiophenes, since they offer a simple and efficient approach to build these skeletons.[3] For instance, Zanardi's[3a] and McDonald's[3b] group independently reported a radical-involving cascade approach for the construction of benzothiophenes from o-methylthioarene diazonium salts and alkynes. Similarly, Schiesser and coworkers described a method for the preparation of benzoselenophenes by employing an analogous tandem radical addition strategy in 2011.[3c] However, the involvement of stoichiometric amounts of transition metals was essential in these approaches, which limited their further applications in both academia and industry. To overcome this drawback, Köning developed a metal-free protocol for the synthesis of benzothiophene derivatives via visible-light photoredox catalysis using aryl diazonium salts as aryl radicals.[3d] In addition to the radical cyclization, electrophilic cyclization of o-(1-alkynyl)thioanisoles is another common and robust strategy to obtain benzothiophenes.[4] For instance, the construction of 3-halosubstituted benzothiophenes with I_2 and Br_2 as electrophilic reagents was developed by Larock and co-workers.[4a,b] Very recently, Ingleson and Blum groups independently dis-

closed the preparation of borylated benzothiophenes via BCl_3 or ClBcat-induced borylative cyclization of 2-alkynyl thioanisoles.[4c,d] Later on, Yamamoto and co-workers designed a novel Au-catalyzed 1,3-shift of the migrating groups to afford 3-substituted benzothiophenes.[5] Despite the above advances in the synthesis of substituted benzothiophenes, efficient and facile tactics for the construction of 3-sulfonyl benzothiophenes are relatively scarce. Owing to the significance of 3-sulfonyl benzothiophenes, which are the prevalent core scaffolds in bioactive species and pharmaceutical candidates[6] (see Fig. 1), very recently, our group disclosed a novel approach to synthesize 3-sulfonyl benzothiophenes via TBHP-initiated radical cyclization of 2-alkynyl thioanisoles with sulfinic acid[7] (Scheme 1d). Nevertheless, the reaction was performed at a high temperature (100 °C) and the radical precursor sulfinic acids are easy to decompose, which might restrict their potential application in organic synthesis. Therefore, the development of an efficient and facile method to construct 3-sulfonyl benzothiophenes is still highly desirable.

Visible light induced photoredox catalyzed transformation has emerged as a powerful strategy in synthetic chemistry, due
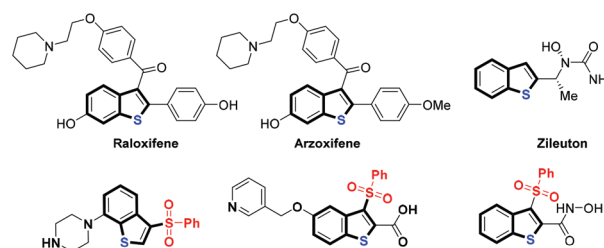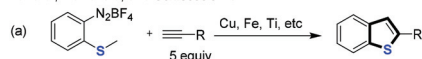
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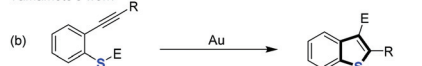

Fig. 1 Representative drugs and biologically active molecules containing a benzothiophene motif.
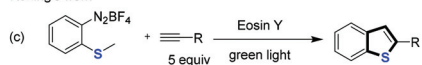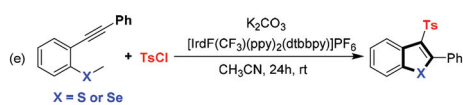
Scheme 1 The synthesis of substituted benzothiophenes from 2-alkynyl thioanisoles.

Table 1 Optimizing the reaction conditions

| Entry[a]	Photocatalyst	Base	Solvent	Yield[b] (%)
1	Eosin Y	K_2CO_3	CH_3CN	69
2	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3CN	50
3	**[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$**	**K_2CO_3**	**CH_3CN**	**83**
4	[Ru(bpy)$_3$]PF$_6$	K_2CO_3	CH_3CN	55
5	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	—	CH_3CN	0
6	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_3PO_4	CH_3CN	69
7	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	KOAc	CH_3CN	53
8	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	Na_2CO_3	CH_3CN	37
9	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2HPO_4	CH_3CN	76
10	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	DMF	71
11	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	DCM	56
12	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	DMSO	38
13	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	THF	53
14	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	Toluene	58
15	—	K_2CO_3	CH_3CN	0
16[c]	[IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	CH_3CN	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base (0.4 mmol), photocatalyst (2 mol%), solvent (2 mL),5W blue LED light, 24 h, rt. [b] Isolated yield. [c] In the dark.

to the remarkable features it possesses, such as safety, mild conditions, environmental friendliness and great functional group tolerance. Very recently, we developed a visible-light-induced thiotrifluoromethylation of terminal alkenes *via* an unconventional reductive quenching cycle[8] and a photoredox-catalyzed decarboxylative alkylation of silyl enol ethers to synthesize functionalized aryl alkyl ketones.[9] As part of our ongoing interest in photoredox catalysis promoted radical reactions, we report herein the visible light induced synthesis of 3-sulfonyl benzothiophenes from methyl(2-(phenylethynyl) phenyl)sulfane *via* a radical annulation process under ambient conditions, with the commercially available benzenesulfonyl chloride as a radical precursor (Scheme 1e).

Initially, we commenced the reaction by employing methyl (2-(phenylethynyl)phenyl)sulfane (**1a**) and 4-methyl-benzenesulfonyl chloride (**2a**) as model substrates to optimize the reaction conditions. To our delight, when the reaction was irradiated by using 5 W blue LED light using eosin Y as a photocatalyst and K_2CO_3 as a base at room temperature for 24 h, the desired product (**3a**) was obtained in 69% yield (Table 1, entry 1). Subsequently, we investigated various photoredox catalysts and it turned out that [IrdF(CF$_3$) (ppy)$_2$(dtbbpy)]-PF$_6$ was the most effective one (entries 1–4). When the reaction was performed in the absence of the base, no reaction occurred (entry 5). In view of the importance of the base, a series of bases were examined (entry 6–9) and K_2CO_3 demonstrated itself to be the best choice (entry 3) among the bases tested. Furthermore, the solvent effect on this transformation was investigated as well and CH_3CN was the optimal one (entry 3). The control experiments revealed that a photoredox catalyst and visible light were essential for the reaction. When

the reaction was carried out in the absence of a photoredox catalyst or visible light, the starting materials **1a** and **2a** were intact (entries 15 and 16). Consequently, the desired product **3a** was obtained in the optimal 83% yield when the reaction was performed in the presence of [IrdF(CF$_3$) (ppy)$_2$(dtbbpy)] PF$_6$ (2 mol%) and K_2CO_3 (2 equiv.) in CH_3CN at room temperature.

With the optimal reaction conditions in hand, we next explored the efficiency and generality of this reaction. To our delight, when a variety of sulfonyl chlorides were used as radical precursors, the corresponding products were obtained in good to excellent yields. As described in Scheme 2, the sulfonyl chlorides which bear electron-donating or electron-withdrawing substituents at the *para-* position of the benzene ring were good candidates, affording the desired benzothiophenes (**3a–3f**) in moderate to high yields. Halo-substituted sulfonyl chlorides were well compatible in this reaction as well, providing the targeted products (**3g–3i**) in 87%, 68% and 76% yields, respectively. In addition to the substituents at the *para*-position, the *ortho*-position and the *meta*-position substituted sulfonyl chlorides (**1j–1n**) were also amenable for this transformation and delivered the corresponding benzothiophenes (**3j–3n**) in 63% to 84% yields.

Next, we inspected the influence of the substitution pattern on the aromatic ring of 2-phenylethynyl. The results are summarized in Scheme 3; as we can see, the substrates bearing both electron-donating and electron-withdrawing groups (**1o–1v**) on the aryl ring of 2-phenylethynyl could be engaged in this transformation and produced the corresponding products (**3o–3v**) in good to excellent yields (68%–88%). Then
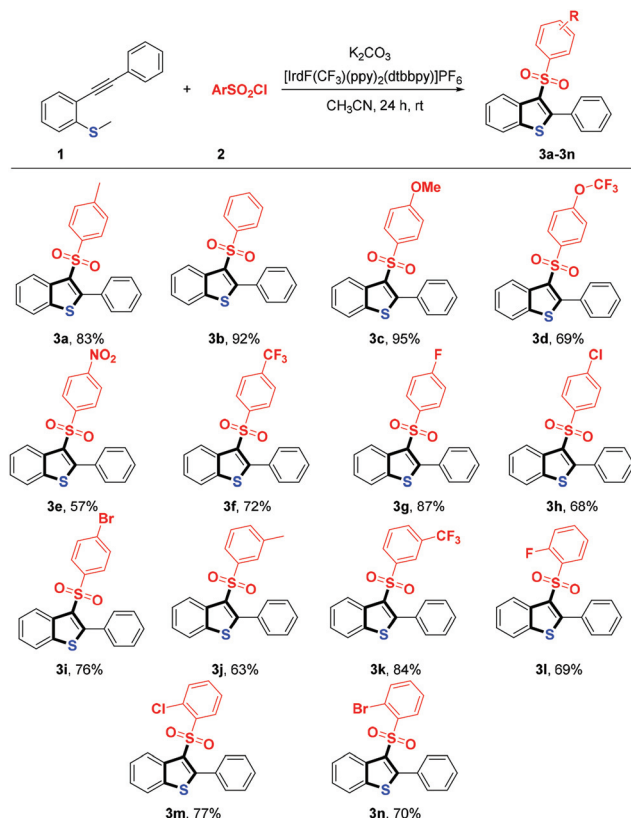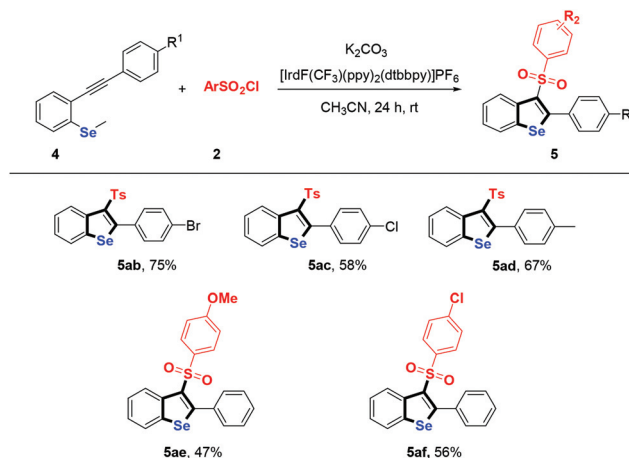
Scheme 2 Scope of sulfonyl chlorides. The reaction was carried out with **1** (0.2 mmol), **2** (0.4 mmol), K$_2$CO$_3$ (0.4 mmol), and [IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$ (2 mol%) in CH$_3$CN (2 mL) at room temperature, 5 W blue LEDs, 24 h.
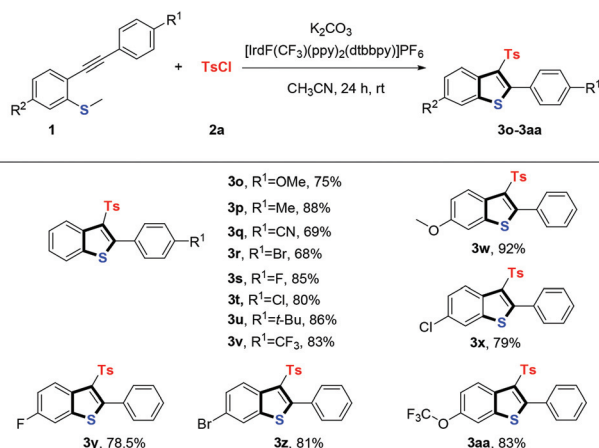
Scheme 3 Scope of methyl(2-(phenylethynyl)phenyl)sulfane benzothiophenes. The reaction was carried out with **1** (0.2 mmol), **2** (0.4 mmol), K$_2$CO$_3$ (0.4 mmol), and [IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$ (2 mol%) in CH$_3$CN (2 mL) at room temperature, 5 W blue LEDs, 24 h.

different substituents on the aromatic ring of *o*-methylthio-aryl alkyne were studied. To our delight, the electronic effects of these groups have no significant influence on the yields of the

Scheme 4 Scope for the synthesis of benzoselenophenes. The reaction was carried out with **4** (0.2 mmol), **2** (0.4 mmol), K$_2$CO$_3$ (0.4 mmol), and [IrdF(CF$_3$)(ppy)$_2$(dtbbpy)]PF$_6$ (2 mol%) in CH$_3$CN (2 mL) at room temperature, 5 W blue LEDs, 24 h.

products and the targeted benzothiophenes (**3w–3aa**) were generated in 79%–83% yields.

Benzoselenophenes have also attracted tremendous attention owing to their wide application in organic synthesis, medicinal chemistry, and materials science.[4c,10] In light of this importance, subsequently, we commenced to prepare benzoselenophenes stemming from methyl(2-(phenylethynyl)phenyl) selane **4** and sulfonyl chloride **2** under optimal reaction conditions. As shown in Scheme 4, substituted 2-alkynyl selenoanisoles **5** which carry electron-donating (methyl) or electron-withdrawing (halides) groups on the aromatic rings could proceed smoothly and gave the corresponding products (**5ab–5ad**) in good yields. Sulfonyl chlorides were also compatible under the standard conditions; the desired benzoselenophenes **5ae** and **5af** were afforded in moderate yields.

To gain insight into the detailed mechanism of this reaction, several control experiments were carried out, demonstrated in Scheme 5. Firstly, it was found that the reaction was absolutely controlled, when TEMPO or BHT as a scavenger was added.
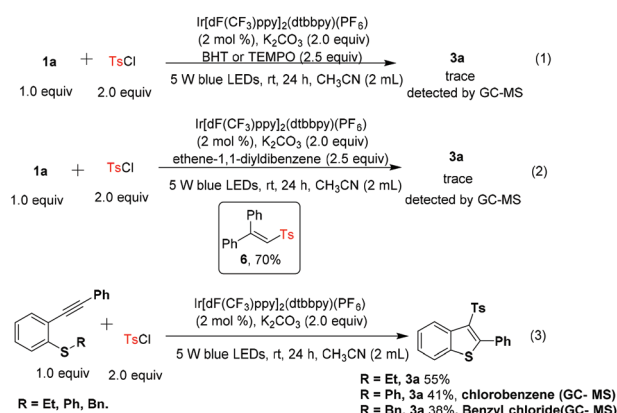
Scheme 5 Control experiments.
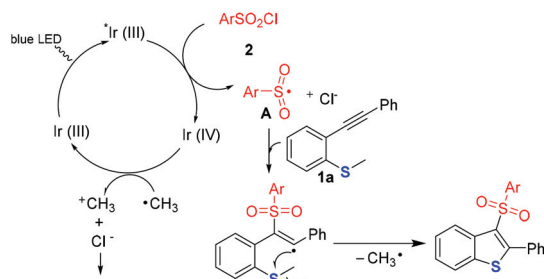
Scheme 6 A possible reaction mechanism.

Next when ethene-1,1-diyldibenzene was added to the reaction under the standard conditions, we received the radical addition elimination product **6** in 70% yield. The results suggested that a SET pathway was implied in this transformation. Finally, when we changed the group on the sulfur atom from methyl to ethyl, phenyl and benzyl, all of the substrates delivered **3a** in moderate yields. Notably, in the latter two examples, the corresponding by-products chlorobenzene and benzyl chloride were detected by GC-MS; these results provide solid evidence for the mechanism of this transformation.

On the basis of the above control experiments and previous reports,[11,12] a possible reaction mechanism is depicted in Scheme 6. Firstly, the Ir(III) photoredox catalyst is converted to the excited state *Ir(III) transition through a metal-to-ligand charge-transfer (MLCT) with the irradiation of visible light. The sulfonyl radical **A** is generated *in situ* from sulfonyl chloride **2a** through a single electron transfer (SET) pathway and at the same time Ir(III) is oxidized to Ir(IV). Subsequently, the addition of the sulfonyl radical **A** to the alkynyl moiety of **1a** takes place to give the vinyl radical intermediate **B**, which further undergoes intramolecular attack by the methylthio moiety to yield the desired product **3a** along with the release of the methyl radical. Notably, this methyl radical is oxidized to a methyl cation by Ir(IV) species and CH_3Cl is formed eventually upon encountering Cl^-.

In conclusion, we have successfully developed an effective and facile approach for the preparation of 3-sulfonyl benzothiophenes and benzoselenophenes in good yields *via* visible light photocatalyzed cascade annulation reactions by employing easily available sulfonyl chlorides as radical precursors. This protocol features simple operation, mild conditions, good functional group tolerance and no involvement of transition metals or additives.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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