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Visible-light-mediated radical arylthiodifluoromethylation of isocyanides with fluorinated 2-pyridyl sulfones†

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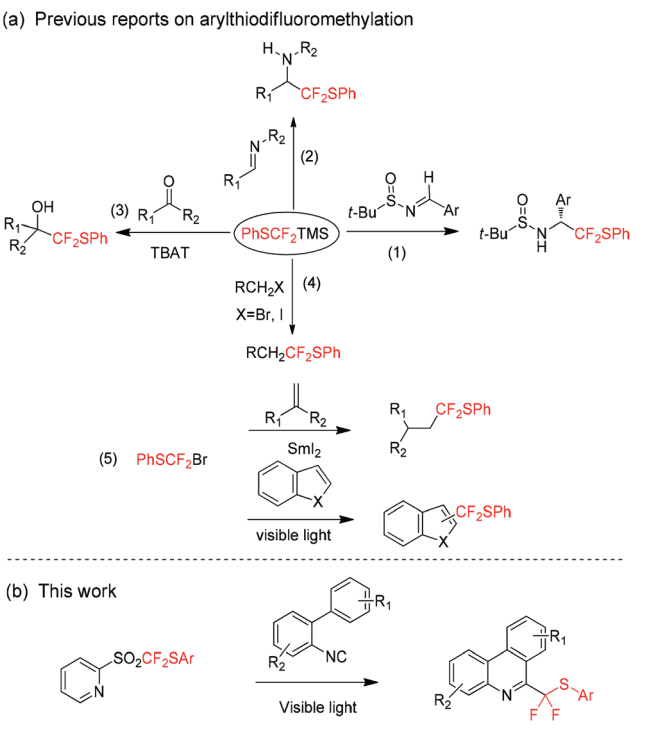
A novel class of shelf-stable and easily scalable arylthiodifluoromethyl 2-pyridyl sulfone derivatives was developed as powerful arylthiodifluoromethylation reagents, which allow efficient radical arylthiodifluoromethylation of various isocyanides to form phenanthridines and isoquinolines in good to excellent yields.

The incorporation of the arylthiodifluoromethyl moiety ($ArSCF_2$) into organic molecules can lead to significant changes in their physical, chemical, or biological properties, which has aroused growing interest in the pharmaceutical and agrochemical fields.[1] In our previous work, we reported the first nucleophilic arylthiodifluoromethylation reagent, $PhSCF_2TMS$, which can react with different imines, alkyl halides or carbonyl compounds to form the corresponding arylthiodifluoromethylated derivatives (Scheme 1a).[2] An alternative method for the incorporation of a $PhSCF_2$ group presents the radical arylthiodifluoromethylation with $PhSCF_2X$ (X = Br or I). In the presence of SmI_2 acting as a radical initiator, $PhSCF_2Br$ can undergo a free radical reaction with alkenes in moderate to good yields (Scheme 1a).[3] Recently, Cho reported visible-light-induced arylthiofluoroalkylation of unactivated heteroaromatic compounds with $PhSCF_2Br$ (Scheme 1a).[4] However, the $PhSCF_2Br$ reagent suffers from difficulties in handling the toxic starting material (CF_2Br_2) with its low boiling point (101.3 kPa: 23.9 °C).[5]

In recent years, we also worked on visible-light photoredox catalysis reactions with fluorinated sulfones, especially 2-BTSO_2R_f (2-BT = 2-benzo-[*d*]thiazolyl) as the radical R_f source, and provided a convenient method to introduce CH_2F, CF_2, CF_3, CF_2Me, CF_2Ph or CF_2COPh moieties into different organic molecules.[6] Song's group reported radical oxydifluoromethylation of olefinic amides for the synthesis of CF_2H-containing benzoxazines using 2-BTSO_2CF_2H.[7] More recently, Wang's and Fu's groups reported the radical difluoromethylation of *N*-benzamides or alkynoates for the synthesis of difluoromethylated coumarins or isoquinolinediones using 2-BTSO_2CF_2H, respectively.[8] As a continuation of our work, we herein describe 2-PySO_2CF_2SAr as a novel class of efficient and shelf-stable radical arylthiodifluoromethylation reagents for isocyanides under visible-light photoredox catalysis (Scheme 1b).



Scheme 1 (a) Different protocols for arylthiodifluoromethylation. (b) Our strategy for radical arylthiodifluoromethylation.

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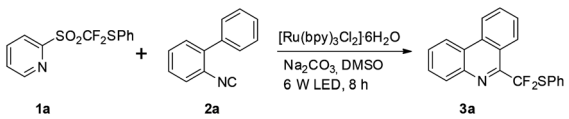
Inspired by the success of 2-BTSO$_2$R$_f$ on the visible-light photoredox catalysis reaction,[6] we attempted to produce a PhSCF$_2$ radical using 2-BTSO$_2$CF$_2$SPh with an LED, while we encountered difficulty in the preparation of 2-BTSO$_2$CF$_2$SPh using 2-BTSO$_2$CF$_2$H and phenyl disulfide as substrates in the presence of a base; only poor yield of the target compound was produced and the main product was 2-BTSPh, probably due to the high reactivity of phenyl disulfide (see the ESI†). Interestingly, replacement of 2-BTSO$_2$CF$_2$H with 2-PySO$_2$CF$_2$H (2-Py = 2-pyridyl) gave high yield of 2-PySO$_2$CF$_2$SPh **1a** within a few seconds under similar conditions (see the ESI†). 2-PySO$_2$CF$_2$SPh **1a** is a shelf-stable compound and no detectable decomposition was observed even after one year of storage at ambient temperature. In order to confirm the potential of 2-PySO$_2$CF$_2$SPh to produce the PhSCF$_2$ radical under visible irradiation, its cyclic voltammetry was carried out along with three other heteroaryl sulfones, PhSO$_2$CF$_2$H and 2-PySO$_2$CF$_2$H as negative controls and 2-BTSO$_2$CF$_2$H as a positive control (*versus* the saturated calomel electrode, SCE, Fig. 1).

As shown in Fig. 1, 2-BTSO$_2$CF$_2$H demonstrated the highest reduction potential with a value of −1.14 V and 2-PySO$_2$CF$_2$SPh with a value of −1.29 V, which was much higher than those of 2-PySO$_2$CF$_2$H and PhSO$_2$CF$_2$H (−1.47 V and −1.77 V, respectively), indicating that 2-PySO$_2$CF$_2$SPh possesses much better potential as a radical arylthiodifluoromethylation precursor than PhSO$_2$CF$_2$H and 2-PySO$_2$CF$_2$H.

With a previous direct difluoroalkylation protocol of 2-BTSO$_2$CF$_2$H,[6] we performed the reaction of 2-PySO$_2$CF$_2$SPh **1a** with 2-isocyano-1,1′-biphenyl **2a** to provide phenanthridine **3a**, a structural motif often existing in biologically active natural products.[9,10] **1a** and **2a** were irradiated with a 6 W blue LED bulb in DMSO in the presence of [Ru(bpy)$_3$Cl$_2$]·6H$_2$O and Na$_2$CO$_3$, resulting in the formation of the desired product **3a** with a satisfactory yield of 93% (Table 1). The use of TMEDA or 2,6-lutidine instead of Na$_2$CO$_3$ would completely suppress the reactivity (entries 2 and 3), while the utilization of NaHCO$_3$ and K$_2$CO$_3$ resulted in the formation of product **3a** in yields of 56 and 87%, respectively (entries 4 and 5). Furthermore, we studied the impact of different solvents on the yields. When DMSO was replaced with other solvents (toluene, acetone, CH$_3$CN, or CH$_2$Cl$_2$), a remarkable decrease in the yields of **3a** was observed (0–45%, entries 6–9). In addition, replacing the catalyst [Ru(bpy)$_3$Cl$_2$]·6H$_2$O with *fac*-Ir(ppy)$_3$ and Ru(phen)$_3$Cl$_2$ also decreased the yield dramatically (48 and 5%, respectively), indicating that the catalyst [Ru(bpy)$_3$Cl$_2$]·6H$_2$O is crucial for this reaction. In summary, our data show that the optimal conditions for this direct arylthiodifluoromethylation are 2-PySO$_2$CF$_2$SPh **1a** (1.2 equiv.), isocyanide1,1′-biphenyl **2a** (1.0 equiv.), [Ru(bpy)$_3$Cl$_2$]·6H$_2$O (2 mol%) and Na$_2$CO$_3$ (3.0 equiv.) in DMSO under 6 W blue LED irradiation.

Table 1 Variation of reaction parameters[a]



1a 2a 3a

Entry	Variation from standard conditions	Yield[b] (%)
1	None	93
2	TMEDA instead of Na_2CO_3	Trace
3	2,6-Lutidine instead of Na_2CO_3	Trace
4	$NaHCO_3$ instead of Na_2CO_3	56
5	K_2CO_3 instead of Na_2CO_3	87
6	Toluene instead of DMSO	17
7	Acetone instead of DMSO	45
8	MeCN instead of DMSO	3
9	CH_2Cl_2 instead of DMSO	0
10	*fac*-Ir(ppy)$_3$ instead of Ru(bpy)$_3$Cl$_2$	48
11	Ru(phen)$_3$Cl$_2$ instead of Ru(bpy)$_3$Cl$_2$	5

[a] Reaction conditions: **1a** (1.2 equiv.), **2a** (1.0 equiv.), irradiated with a 6 W blue LED for 8 h at room temperature under a N_2 atmosphere. [b] Yields were determined using ^{19}F NMR using PhCF$_3$ as an internal standard.

With the optimized reaction conditions in hand, the substrate scope of isocyanide **2** was extensively investigated. As shown in Table 2, with the R$_1$-substituent in the *para*-position, both electron-donating and electron-withdrawing groups containing isocyanides can provide target compounds (**3b–3f**) in good to high yields (65–87%), indicating that the electronic effect of substituents in this position was of little influence in this reaction. The 3-methoxy-substituted isocyanide **2h** formed the two products **3h** and **3h′** in yields of 30% and 42%, respectively. Interestingly, the pyridine derivative **2i** also formed the corresponding product **3i** in moderate yield with extended irradiation time. Furthermore, we evaluated the effect of the substituent R$_2$ on the reaction yield. All the four tested derivatives with electron-donating or electron-withdrawing groups can undergo this reaction smoothly and produce the corresponding phenanthridines **3j–m** in good to excellent yields (74–89%).

Then, the scope of arylthiodifluoroalkyl 2-pyridyl sulfones **1** for this radical reaction was also investigated through modifi-

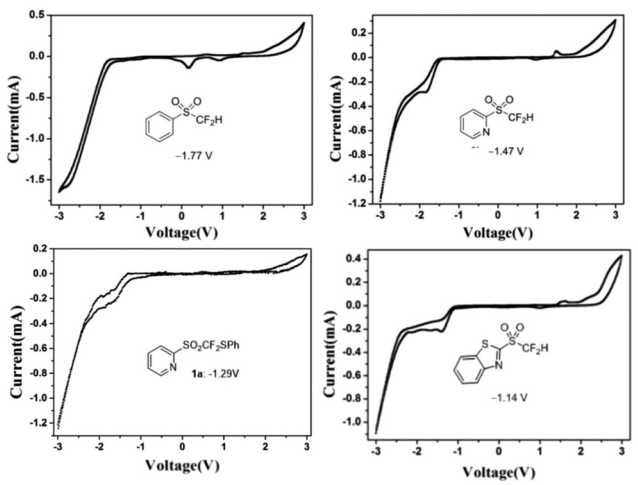
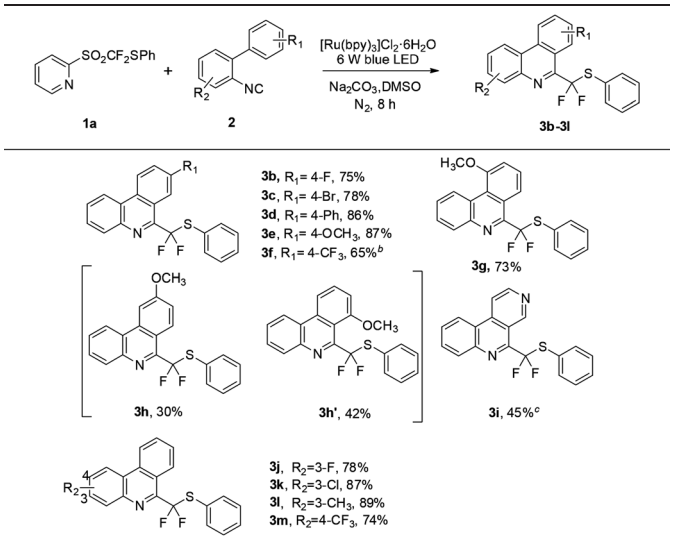


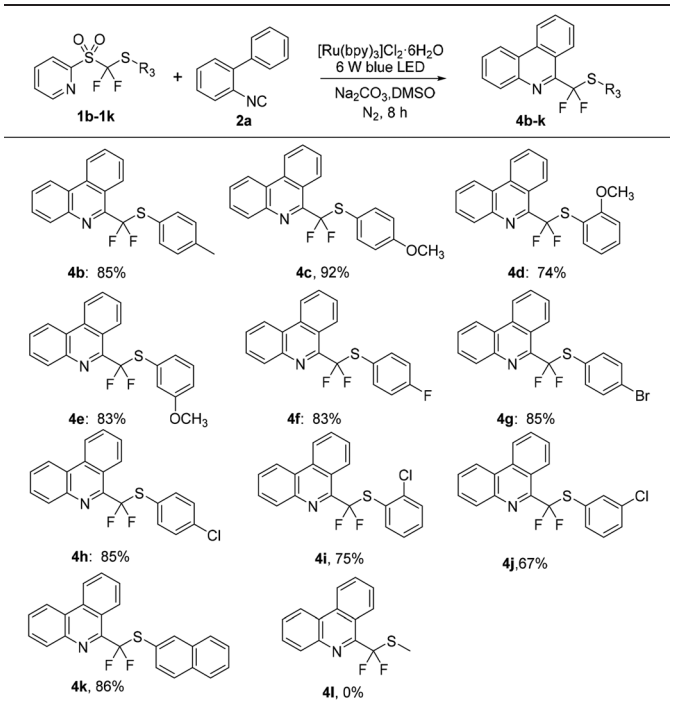
Fig. 1 The cyclic voltammetry of four heteroaryl sulfone reagents.

Table 2 Arylthiodifluoromethylation of various isocyanides with 2-pyridine sulfone **1a**[a]



[a] Reaction conditions: **1a** (1.2 mmol), **2** (1.0 mmol), $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2 mol%), and Na_2CO_3 (3.0 mmol) in DMSO (5 mL) were irradiated with a 6 W blue LED for 8 h at room temperature under a N_2 atmosphere. Yields of isolated products are given. [b] Irradiation time: 24 h. [c] Irradiation time: 48 h.

Table 3 Arylthiodifluoromethylation of isocyanides with various 2-pyridyl sulfones[a]



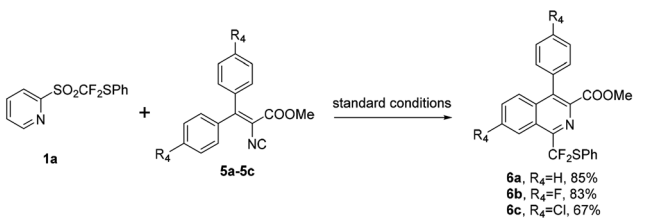
[a] Reaction conditions: **1** (1.2 mmol), **2a** (1.0 mmol), $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2 mol%), and Na_2CO_3 (3.0 mmol) in DMSO (5 mL) were irradiated with a 6 W blue LED for 8 h at room temperature under a N_2 atmosphere. Yields of isolated products are given.

cation of the R_3 moiety. Table 3 revealed that the substituents on the phenyl ring showed little influence on the reaction yields; 2-pyridyl sulfones containing electron-donating or electron-withdrawing groups in the phenyl ring reacted with **2a** smoothly to yield corresponding phenanthridines **4b–k** in good to excellent yields (67–92%). In the case of the naphthalene-substituted derivative **1k**, the corresponding product **4k** was obtained in 86% yield. However, methylthiodifluoroalkyl sulfone **1l** is not suitable for this reaction, probably due to the low stability of the formed intermediate ($MeSCF_2^{\bullet}$) in the reaction.

The isoquinoline scaffold is one of the widely used heterocycles in medicinal chemistry. We envisioned that the described reaction could also provide substituted isoquinolines.[11] As shown in Scheme 2, the desired isoquinolines **6a–c** were obtained in good yields (67–85%) *via* the reaction between $PySO_2CF_2SPh$ **1a** and the alkenyl isocyanides **5a–c** under the optimized conditions.

To gain some insights into this radical reaction, we conducted a mechanistic study. Firstly, a "light on/off" experiment was conducted and the result showed that this reaction required continuous visible-light irradiation (see the ESI†). Furthermore Stern–Volmer luminescence studies demonstrated that the excited state $*[Ru]^{2+}$ was quenched by CO_3^{2-} but not by **1a** and **2a**, and the quenching effect of CO_3^{2-} increased with its concentration (Fig. 2).

Based on our study and previous literature,[6,12] a plausible catalytic cycle for the present reaction was proposed as depicted in Fig. 3. First, the excited state $*[Ru]^{2+}$ is formed by light irradiation and then reduced to $[Ru]^{+}$ by CO_3^{2-}, which then serves as a reductant to reduce **A** (2-$PySO_2CF_2SAr$) by a SET process with the release of a highly reactive radical species **B** ($ArSCF_2^{\bullet}$). Then, $ArSCF_2^{\bullet}$ adds to isocyanide to yield the



Scheme 2 The formation of isoquinoline derivatives.

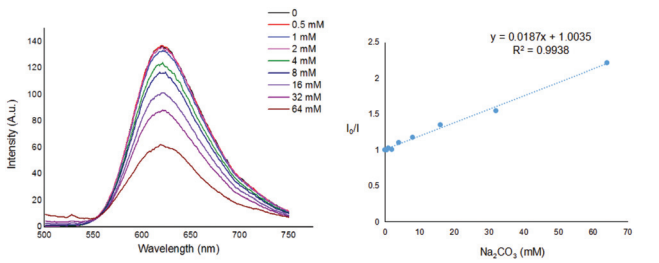


Fig. 2 Stern–Volmer luminescence studies of Na_2CO_3.

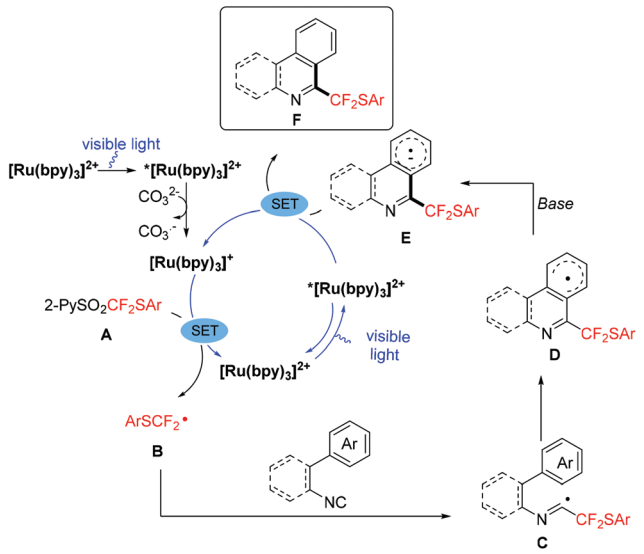


Fig. 3 A possible reaction mechanism.

imidoyl radical **C**, which undergoes intramolecular radical cyclization to form the intermediate **D**. Deprotonation of **D** by a base provides the radical anion **E**. Finally, **E** is oxidized by $*[Ru]^{2+}$ to provide the product **F** and $[Ru]^{+}$.

Conclusions

Overall, we have described a novel class of arylthiodifluoromethyl 2-pyridyl sulfones as radical arylthiodifluoromethylation reagents. It is worth mentioning that this is the first report of arylthiodifluoromethylation reagents using 2-pyridyl sulfones as an auxiliary group. Under mild conditions, an arylthiodifluoromethyl moiety can be introduced into both electron-rich and electron-deficient isocyanides to obtain the corresponding phenanthridines and isoquinolines in good yields. Considering the readily available reagents and mild conditions of this method, the described protocol promises to find more applications in medicinal chemistry and related fields.

Conflicts of interest

There are no conflicts to declare.

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