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Radical Difluororomethylation of Thiols with Difluoromethylphosphonium Triflate under Photoredox Catalysis

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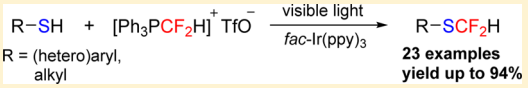
Supporting Information

ABSTRACT: A convenient, visible light-induced radical difluoromethylation of aryl-, heteroaryl-, and alkylthiols with difluoromethyltriphenylphosphonium triflate was developed to afford various difluoromethyl thioethers in moderate to excellent yields. The key reaction features include the use of a readily available CF_2H radical source, mild reaction conditions, and excellent chemoselective thiol-difluoromethylation.



INTRODUCTION

As an important type of fluorine-containing group, fluoroalkylthio groups have received growing interest over the past few years.[1] The association of fluoroalkyl groups with sulfur atoms generally increases the lipophilicity parameter of these substituents. In particular, the trifluoromethylthio group (SCF_3) has an extremely high Hansch parameter (π_R = 1.44).[2] Thus, it is not surprising to witness the surge in the number of methods for introduction of SCF_3 into organic compounds recently.[3] Compared to SCF_3, its analogous difluoromethylthio group (SCF_2H) is less lipophilic, but gains additional hydrogen-bond donor capabilities.[4] Consequently, SCF_2H essentially serves as a lipophilic hydrogen-bond donor motif for drug discovery, and the SCF_2H substituent has emerged as an important functional group in bioactive molecules, such as pyriprole and flomoxef sodium (Figure 1).[5]

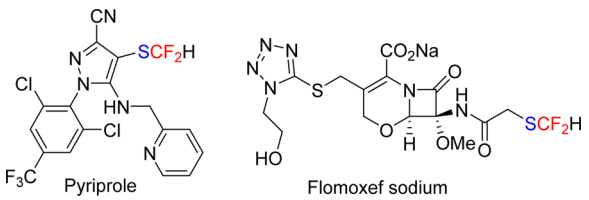
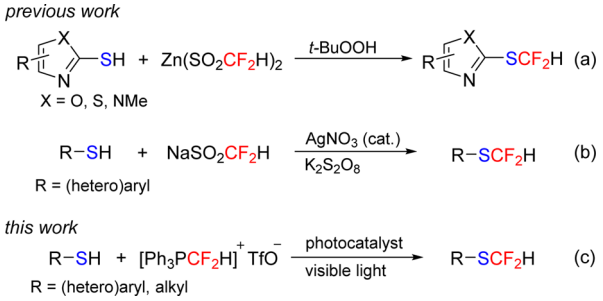


Figure 1. SCF_2H-containing bioactive compounds.

Traditionally, the difluoromethylthiolated compounds are prepared by the reaction of thiol (thiolate) or a derivative with difluorocarbene *in situ*-generated from the ozone-depleting compound HCF_2Cl.[6] Recently, impressive advances have been made for the synthesis of these compounds,[7] involving either C−SCF_2H[8] or CS−CF_2H[9−13] bond formation. The direct difluoromethylthiolation (C−SCF_2H bond formation) of widely available substrates such as halides, boronic acids, carboxylic acids, and amines with the difluoromethylthiolating reagents has emerged as a powerful approach to various difluoromethyl thioethers.[8] However, several steps were required for the preparation of difluoromethylthiolating reagents. The new methods for CS−CF_2H bond formation can be classified into four reaction types: difluorocarbene-mediated reactions,[9] electrophilic,[11] nucleophilic,[12] and radical[13] difluoromethylation. First, new difluorocarbene precursors were developed to make the traditional method more environmentally benign.[9] Even so, this protocol suffers from the low chemoselectivity when two or more nucleophilic groups exist in the substrate.[10] The electrophilic difluoromethylation of sulfur-containing compounds gave difluoromethyl thioethers only in moderate yields.[11] Difluoromethyl thioethers were formed in high yields from the nucleophilic difluoromethylation of disulfides,[12] but half of the disulfides were wasted in these processes. Baran and co-workers reported that the radical difluoromethylation of heteroarylthiols with Zn$(SO_2CF_2H)_2$ in the presence of *t*-BuOOH gave the corresponding difluoromethyl thioethers in moderate yield (Scheme 1a).[13a] Yi developed a silver-catalyzed radical difluoromethylation of aryl- and heteroarylthiols with NaSO_2CF_2H using $K_2S_2O_8$ as oxidant (Scheme 1b).[13b] Recently, photoredox catalysis has been regarded as a valuable and

Scheme 1. Radical Difluoromethylation of Thiols



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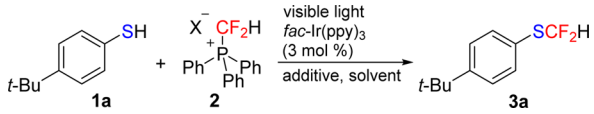
environmentally benign tool in organic synthesis.[14] Our group very recently disclosed the radical difluoromethylation of alkenes with difluoromethylphosphonium salts under photoredox catalysis.[15] Compared to other CF_2H radical sources, difluoromethylphosphonium salts are more easily available and handled.[16] Herein, we disclose a complementary visible light-induced radical difluoromethylation of thiols with difluoromethyltriphenylphosphonium triflate (Scheme 1c). This method provides a new access to difluoromethyl thioethers using an easily available difluoromethylating reagent under mild conditions.

RESULTS AND DISCUSSION

Initially, we chose 4-(*tert*-butyl)benzenethiol (**1a**) as the model substrate to optimize the reaction conditions (Table 1). In our previous studies,[15b,c] it was found that among the common photocatalysts, only *fac*-Ir(ppy)$_3$ was capable of reduction of difluoromethylphosphonium salt to CF_2H radical. Thus, *fac*-Ir(ppy)$_3$ was chosen as the photocatalyst for difluoromethylation of **1a** with difluoromethylphosphonium salts (**2a**–**d**) in the presence of tetramethylethylenediamine (TMEDA) using MeCN as the solvent under visible light irradiation (entries 1–4). Among the difluoromethylphosphonium salts tested, difluoromethylphosphonium triflate (**2b**) afforded the desired difluoromethyl thioether **3a** in highest yield (entry 2). Then, switching TMEDA to other additives including $NaHCO_3$, 1,8-diazobicyclo[5,4,0]undec-7-ene (DBU), NEt_3, *N*,*N*-dimethylaniline, and *N*,*N*-dimethyl-4-toluidine led to lower yields (entries 5–9). It was noteworthy that product **3a** was formed in 32% yield even in the absence of an additive (entry 10). Subsequently, different solvents including DMF, DMSO, THF, and acetone were investigated (entries 11–14). However, no higher yield was obtained. Finally, the yield of **3a** was increased by prolonging the reaction time and increasing the amount of difluoromethylating reagent (entries 15 and 16). An excess of difluoromethylphosphonium triflate (**2b**) was required for formation of **3a** in high yield, because part of **2b** was converted into CF_2H_2 under these reaction conditions. Compound **3a** was not formed when the reaction was performed in the absence of photoredox catalyst or visible light (entries 17 and 18), which indicated that both the photoredox catalyst and visible light were crucial for this reaction.

Table 1. Optimization of Reaction Conditions for Difluoromethylation of Arylthiol[a]

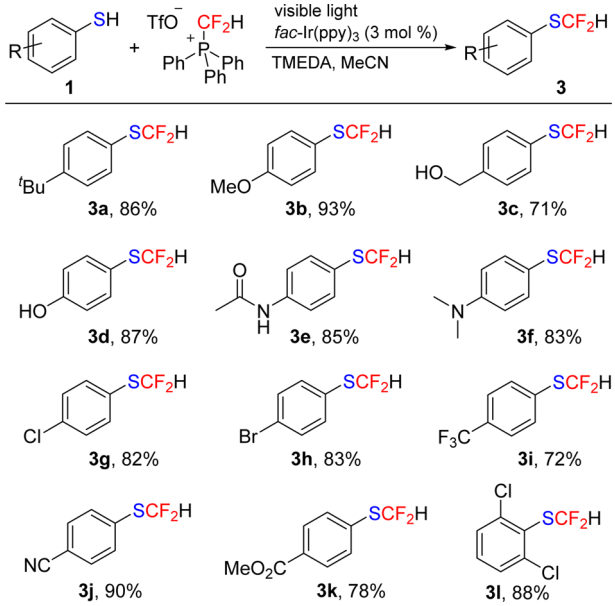


entry	2 (X)	additive	solvent	yield (%)[b]
1	**2a** (Br)	TMEDA	MeCN	36
2	**2b** (OTf)	TMEDA	MeCN	62
3	**2c** (BF_4)	TMEDA	MeCN	45
4	**2d** (PF_6)	TMEDA	MeCN	51
5	**2b** (OTf)	$NaHCO_3$	MeCN	12
6	**2b** (OTf)	DBU	MeCN	10
7	**2b** (OTf)	NEt_3	MeCN	55
8	**2b** (OTf)	*N*,*N*-dimethylaniline	MeCN	11
9	**2b** (OTf)	*N*,*N*-dimethyl-4-toluidine	MeCN	12
10	**2b** (OTf)	–	MeCN	32
11	**2b** (OTf)	TMEDA	DMF	46
12	**2b** (OTf)	TMEDA	DMSO	49
13	**2b** (OTf)	TMEDA	THF	28
14	**2b** (OTf)	TMEDA	Acetone	7
15[c]	**2b** (OTf)	TMEDA	MeCN	72
16[d]	**2b** (OTf)	TMEDA	MeCN	85
17[e]	**2b** (OTf)	TMEDA	MeCN	0
18[f]	**2b** (OTf)	TMEDA	MeCN	0

[a]Reaction conditions: **1a** (0.1 mmol), difluoromethyltriphenylphosphonium salt (0.3 mmol), *fac*-Ir(ppy)$_3$ (0.003 mmol), additive (0.2 mmol), solvent (1.0 mL), visible light, rt, under N_2, 24 h. [b]Yields determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c]48 h. [d]Difluoromethyltriphenylphosphonium salt (0.4 mmol). [e]In the absence of *fac*-Ir(ppy)$_3$. [f]In the dark.

With optimized conditions in hand, the substrate scope of arylthiols was investigated (Scheme 2). The electron-neutral, electron-rich, and electron-deficient arylthiols (**1a**–**l**) reacted with difluoromethylphosphonium **2b** to afford the corresponding aryl difluoromethyl thioethers (**3a**–**l**) in good to excellent yields. An array of functional groups including ether, alcohol, phenol, amine, amide, chloride, bromide, nitrile, and ester were well tolerated under the mild conditions. It is noteworthy that difluoromethylation of (4-mercaptophenyl)methanol (**1c**) and 4-mercaptophenol (**1d**) with 4.0 equiv of **2b** gave only *S*-difluoromethylated products (**3c** and **3d**). No *O*-difluoromethylated product was detected. This excellent chemoselectivity highlights the unique property of the current method, which is different from the difluorocarbene-based protocols.[9] The sterically hindered arylthiol (**1l**) also proceeded smoothly to give product **3l** in 88% yield. However, low yield was obtained when naphthalene-2-thiol was subjected to the standard conditions.

Scheme 2. Difluoromethylation of Arylthiols[a]



[a]Reaction conditions: **1** (0.5 mmol), difluoromethyltriphenylphosphonium triflate (2.0 mmol), *fac*-Ir(ppy)$_3$ (0.015 mmol), TMEDA (1.0 mmol), MeCN (5.0 mL), visible light, rt, under N_2, 48 h. Yields are those of the isolated products.

We next turned our attention to the difluoromethylation of heteroarylthiols for the preparation of heteroaryl difluorome-

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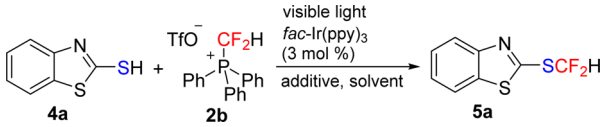
thylthioethers. Compared to the difluoromethylation of 4-(*tert*-butyl)benzenethiol (**1a**), the reaction of benzo[*d*]thiazole-2-thiol (**4a**) was faster and required less difluoromethylphosphonium (**2b**) (Table 2, entry 1). After screening of the additives

Table 2. Screening of Additives and Solvents for Difluoromethylation of Heteroarylthiol[a]



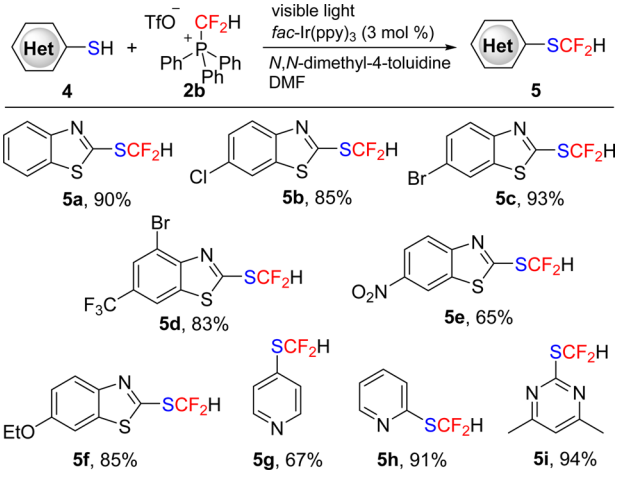
entry	additive	solvent	yield (%)[b]
1	TMEDA	MeCN	68
2	NEt_3	MeCN	23
3	DBU	MeCN	42
4	*N*,*N*-dimethylaniline	MeCN	58
5	*N*,*N*-dimethyl-4-toluidine	MeCN	72
6	*N*,*N*-dimethyl-4-toluidine	DMF	92
7	*N*,*N*-dimethyl-4-toluidine	DMSO	81
8	*N*,*N*-dimethyl-4-toluidine	THF	43

[a]Reaction conditions: **4a** (0.1 mmol), difluoromethyltriphenylphosphonium triflate (0.3 mmol), *fac*-Ir(ppy)$_3$ (0.003 mmol), additive (0.2 mmol), solvent (1.0 mL), visible light, rt, under N_2, 24 h. [b]Yields determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard.

and solvents (entries 2−8), the difluoromethylated product (**5a**) was obtained in up to 92% yield in the presence of *N*,*N*-dimethyl-4-toluidine using DMF as the solvent (entry 6). This is due to the solubility of the substrate in DMF.

The optimized reaction conditions (Table 2, entry 6) were suitable for the conversion of a series of heteroarylthiols to the corresponding difluoromethyl thioethers in moderate to excellent yields (Scheme 3). Benzo[*d*]thiazole-2-thiols (**4a−f**) bearing electron-withdrawing and electron-donating groups were well tolerated. Moreover, the difluoromethylation of 4-thiopyridine (**4g**), 2-thiopyridine (**4h**), and 2-thiopyrimidine (**4i**) occurred in excellent yields. In all cases, only S-difluoromethylated products were obtained, and no N-difluoromethylated product was detected.[10]

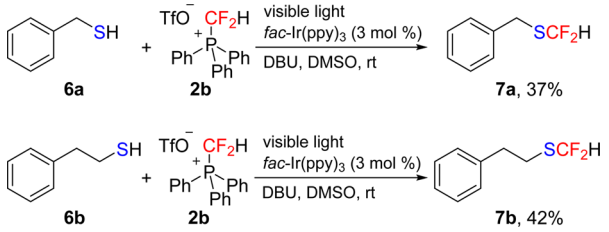
Scheme 3. Difluoromethylation of Heteroarylthiols



[a]Reaction conditions: **4** (0.5 mmol), difluoromethyltriphenylphosphonium triflate (1.5 mmol), *fac*-Ir(ppy)$_3$ (0.015 mmol), *N*,*N*-dimethyl-4-toluidine (1.0 mmol), DMF (5.0 mL), visible light, rt, under N_2, 24 h. Yields are those of the isolated products.

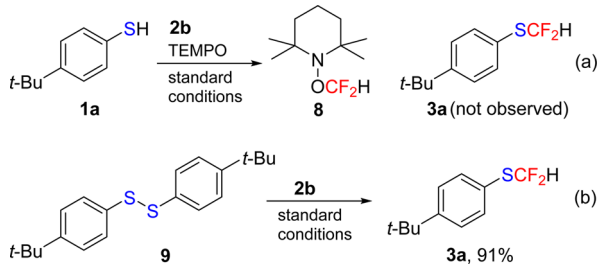
The alkylthiols are challenging substrates for the radical difluoromethylation process. Benzylthiol **6a** and alkylthiol **6b** were, respectively, converted into difluoromethyl thioethers **7a** and **7b** in low yields (Scheme 4). These results are consistent with the analogous radical trifluoromethylation of alkylthiols.[17]

Scheme 4. Difluoromethylation of Alkyl Thiols



To gain insight into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, was added into the standard reaction conditions of **1a**. The desired product **3a** was not obtained, and a TEMPO−CF_2H adduct **8** was formed (Scheme 5a). This result provides

Scheme 5. Mechanistic Experiments



supportive evidence that a CF_2H radical may be involved as a reactive species in this reaction. Moreover, in some cases, the formation of disulfides in the reaction mixture was detected. Thus, the difluoromethylation of disulfide **9**[18] under the standard reaction conditions was investigated, and difluoromethylated product **3a** was also obtained in high yield (Scheme 5b). Additionally, the fluorescence quenching experiments at different concentration of difluoromethylphosphonium **2b** showed that **2b** exhibited fluorescence quenching of excited state **fac*-Ir^{III}(ppy)$_3$ (see the Supporting Information). This result suggested that electron transfer probably occurred from **fac*-Ir^{III}(ppy)$_3$ to **2b** first.

Based on the above results, a proposed mechanism for the reaction is outlined in Scheme 6. First, irradiation with visible light excites *fac*-Ir^{III}(ppy)$_3$ into **fac*-Ir^{III}(ppy)$_3$, which is then oxidized by difluoromethylphosphonium **2b** via a single electron transfer (SET) to give *fac*-Ir^{IV}(ppy)$_3$ and CF_2H radical. Subsequently, CF_2H radical reacts with thiolate affording the corresponding radical anion intermediate, which undergoes a SET to give the final product difluoromethyl thioether (*path a*). On the other hand, thiolate might be oxidized by *fac*-Ir^{IV}(ppy)$_3$ to a sulfur radical, which is easily converted into the disulfide. The reaction of CF_2H radical and disulfide could also give the difluoromethyl thioether (*path b*). The excellent chemoselective thiol-difluoromethylation suggests that *path b* is the more likely reaction pathway, although

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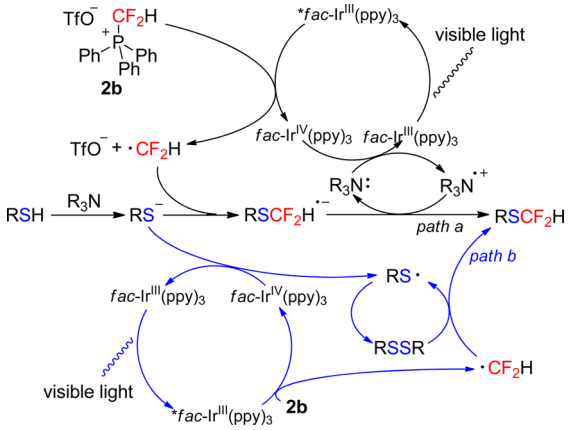
Scheme 6. Proposed Reaction Mechanism



path a can not be ruled out. However, the exact reaction mechanism remains unclear at the moment.

CONCLUSION

We have developed an efficient and practical radical difluoromethylation of aryl-, heteroaryl-, and alkylthiols with readily available difluoromethyltriphenylphosphonium triflate by visible light photoredox catalysis. This protocol provides an attractive approach to a range of difluoromethyl thioethers under mild conditions with excellent S/X (X = O, N)-selectivities. Further exploration of the reaction mechanism and the application of this method are underway in our laboratory.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR (TMS as the internal standard) and ^{19}F NMR spectra ($CFCl_3$ as the outside standard and low field is positive) were recorded on a 400 MHz spectrometer. ^{13}C NMR was recorded on 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS data using EI were obtained on a GC-TOF mass spectrometer. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Substrates were purchased from commercial sources or were prepared according to literature procedures.

General Procedure for Difluoromethylation of Aryl Thiols. A 50 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with difluoromethyltriphenylphosphonium triflate **2b** (925.0 mg, 2.0 mmol, 4.0 equiv) and *fac*-Ir(ppy)$_3$ (9.8 mg, 0.015 mmol, 3 mol %). Then thiol **1** (0.5 mmol, 1.0 equiv), TMEDA (0.15 mL, 1.0 mmol, 2.0 equiv), and MeCN (5 mL) were added. The flask was sealed with 3 M vinyl electrical tape. The mixture was degassed three times by the freeze−pump−thaw procedure. The flask was placed at a distance of 2 cm from the blue LEDs. The mixture was stirred under nitrogen atmosphere and irradiated by blue 30 W LEDs for 48 h. After the reaction was complete, 10% H_2O_2 (5 mL) was added to the reaction mixture (Note: H_2O_2 was used to oxidize PPh_3 to Ph_3PO for the purification of the desired products easier). The reaction mixture was extracted by Et_2O. The organic phase was dried by anhydrous sodium sulfate and concentrated in vacuo, and the residue was purified with silica gel column chromatography to provide the desired product.

*(4-(tert-Butyl)phenyl)(difluoromethyl)sulfane (**3a**).* Compound **3a** was obtained as a light yellow liquid (93.4 mg, 86%), with hexane/Et_2O = 9:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.80 (t, J = 57.2 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 153.2, 135.2, 126.5, 122.5 (t, J = 3.0 Hz), 121.2 (t, J = 274.1 Hz), 37.8, 31.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.4 (d, J = 57.2 Hz, 2F); MS (EI): m/z 216 (M^+). These data matched with the reported results.[8b]

*(Difluoromethyl)(4-methoxyphenyl)sulfane (**3b**).* Compound **3b** was obtained as a yellow liquid (88.6 mg, 93%), with hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49−7.51 (m, 2H), 6.89−6.91 (m, 2H), 6.73 (t, J = 57.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.2, 137.6, 121.0 (t, J = 273.3 Hz), 116.1 (t, J = 3.0 Hz), 114.9, 55.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.3 (d, J = 57.5 Hz, 2F); MS (EI): m/z 190 (M^+). These data matched with the reported results.[8b]

*(4-((Difluoromethyl)thio)phenyl)methanol (**3c**).* Compound **3c** was obtained as a yellow liquid (67.9 mg, 71%), with DCM/MeOH = 50:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 (d, J = 8.0 Hz, 2H), 7.32(d, J = 8.0 Hz, 2H), 6.79 (t, J = 56.8 Hz, 1H), 4.62 (s, 2H), 2.61−2.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.7, 135.6, 127.6, 124.8 (t, J = 3.0 Hz), 121.8 (t, J = 273.3 Hz), 64.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.5 (d, J = 57.2 Hz, 2F); IR (thin film) ν 3341, 2926, 1492, 1320, 1297, 1067, 817 cm^{-1}; MS (EI): m/z 190 (M^+); HRMS (EI-TOF): m/z [M^+] calcd for $C_8H_8F_2OS$: 190.0264; found: 190.0267.

*4-((Difluoromethyl)thio)phenol (**3d**).* Compound **3d** was obtained as a light brown liquid (76.9 mg, 87%), with hexane/EA = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.73 (t, J = 57.2 Hz, 1H), 5.34−5.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.3, 137.9, 120.9 (t, J = 274.1 Hz), 116.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.3 (d, J = 57.2 Hz, 2F); MS (EI): m/z 176 (M^+). These data matched with the reported results.[13b]

*N-(4-((difluoromethyl)thio)phenyl)acetamide (**3e**).* Compound **3e** was obtained as a light yellow solid (92.6 mg, 85%), with hexane/EA = 1:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm 10.1 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 56.4 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ ppm 169.1, 141.5, 136.6, 121.4 (t, J = 271.8 Hz), 120.0, 118.3 (t, J = 3.1 Hz), 24.4; ^{19}F NMR (376 MHz, d_6-DMSO) δ ppm −92.9 (d, J = 56.0 Hz, 2F); MS (EI): m/z 217 (M^+). These data matched with the reported results.[8b]

*4-((Difluoromethyl)thio)-N,N-dimethylaniline (**3f**).* Compound **3f** was obtained as a light brown liquid (84.7 mg, 83%), with hexane/Et_2O = 9:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 (d, J = 9.2 Hz, 2H), 6.69 (t, J = 57.6 Hz, 1H), 6.66 (d, J = 8.8 Hz, 2H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 151.5, 137.4, 121.4 (t, J = 273.3 Hz), 112.5, 109.8 (t, J = 3.1 Hz), 40.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.6 (d, J = 57.2 Hz, 2F); MS (EI): m/z 203 (M^+). These data matched with the reported results.[8a]

*(4-Chlorophenyl)(difluoromethyl)sulfane (**3g**).* Compound **3g** was obtained as a colorless liquid (79.6 mg, 82%), with hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49−7.52 (m, 2H), 7.34−7.37 (m, 2H), 6.79 (t, J = 56.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 136.7, 136.5, 129.6, 124.2 (t, J = 3.0 Hz), 120.3 (t, J = 274.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.7 (d, J = 56.0 Hz, 2F); MS (EI): m/z 194 (M^+). These data matched with the reported results.[8b]

*(4-Bromophenyl)(difluoromethyl)sulfane (**3h**).* Compound **3h** was obtained as a light yellow liquid (98.7 mg, 83%), with hexane/Et_2O = 9:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42−7.52 (m, 4H), 6.79 (t, J = 56.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 136.9, 132.6, 124.9 (t, J = 3.0 Hz), 124.7, 120.2 (t, J = 274.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.7 (d, J = 56.0 Hz, 2F); MS (EI): m/z 238 (M^+). These data matched with the reported results.[8b]

*(Difluoromethyl)(4-(trifluoromethyl)phenyl)sulfane (**3i**).* Compound **3i** was obtained as a light yellow liquid (82.1 mg, 72%), with pentane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 6.87 (t, J = 56.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 134.9, 131.7 (q, J = 32.6 Hz), 130.9, 126.1 (q, J = 3.8 Hz), 123.7 (q, J = 271.1 Hz), 120.1 (t, J = 274.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ

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ppm −63.0 (s, 3F), −91.3 (d, J = 55.6 Hz, 2F); MS (EI): m/z 228 (M^+). These data matched with the reported results.[9f]

*4-((Difluoromethyl)thio)benzonitrile (**3j**).* Compound **3j** was obtained as a colorless liquid (83.5 mg, 90%), with hexane/Et_2O = 9:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 (s, 4H), 6.89 (t, J = 56.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 134.5, 132.7, 119.7 (t, J = 275.6 Hz), 117.9, 113.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.3 (d, J = 56.0 Hz, 2F); MS (EI): m/z 185 (M^+). These data matched with the reported results.[8b]

*Methyl 4-((difluoromethyl)thio)benzoate (**3k**).* Compound **3k** was obtained as a light yellow liquid (85.3 mg, 78%), with hexane/EA = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 6.87 (t, J = 56.4 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.2, 134.0, 132.2 (t, J = 3.0 Hz), 131.0, 130.3, 120.4 (t, J = 274.1 Hz), 52.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.2 (d, J = 57.2 Hz, 2F); MS (EI): m/z 218 (M^+). These data matched with the reported results.[8b]

*(2,6-Dichlorophenyl)(difluoromethyl)sulfane (**3l**).* Compound **3l** was obtained as a light yellow liquid (100.6 mg, 88%), with hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 6.88 (t, J = 57.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.5, 132.0, 129.0, 125.1 (t, J = 3.8 Hz), 120.1 (t, J = 277.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.0 (d, J = 58.7 Hz, 2F); MS (EI): m/z 228 (M^+). These data matched with the reported results.[9c]

General Procedure for Difluoromethylation of Heteroaryl Thiols. A 50 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with difluoromethyltriphenylphosphonium triflate **2b** (690.0 mg, 1.5 mmol, 3.0 equiv) and *fac*-Ir(ppy)$_3$ (9.8 mg, 0.015 mmol, 3 mol %). Then thiol **4** (0.5 mmol, 1.0 equiv), *N*,*N*-dimethy-4-toluidine (0.14 mL, 1.0 mmol, 2.0 equiv), and DMF (5 mL) were added. The flask was sealed with 3 M vinyl electrical tape. The mixture was degassed three times by the freeze−pump−thaw procedure. The flask was placed at a distance of 2 cm from the blue LEDs. The mixture was stirred under nitrogen atmosphere and irradiated by blue 30 W LEDs for 24 h. After the reaction was complete, 10% H_2O_2 (5 mL) was added to the reaction mixture. The reaction mixture was extracted by Et_2O. The organic phase was dried by anhydrous sodium sulfate and concentrated in vacuo, and the residue was purified with silica gel column chromatography to provide the desired product.

*2-((Difluoromethyl)thio)benzo[d]thiazole (**5a**).* Compound **5a** was obtained as a light yellow liquid (100.2 mg, 90%), with hexane/DCM = 10:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.63 (t, J = 56.0 Hz, 1H), 7.46−7.50 (m, 1H), 7.37−7.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.0, 152.9, 135,9, 126.6, 125.6, 122.8, 121.2, 120.3 (t, J = 275.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −93.2 (d, J = 56.0 Hz, 2F); MS (EI): m/z 217 (M^+). These data matched with the reported results.[9c]

*6-Chloro-2-((difluoromethyl)thio)benzo[d]thiazole (**5b**).* Compound **5b** was obtained as a light yellow liquid (107.2 mg, 85%), with hexane/DCM = 10:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 56.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.5, 153.6, 134.0, 132.8, 126.0, 122.6, 121.8, 120.0 (t, J = 276.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −93.5 (d, J = 55.6 Hz, 2F); IR (thin film) ν 1547, 1430, 1287, 1064, 997, 801, 780 cm^{-1}; MS (EI): m/z 251 (M^+); HRMS (EI-TOF): m/z [M^+] calcd for $C_8H_4ClF_2NS_2$: 250.9442; found: 250.9438.

*6-Bromo-2-((difluoromethyl)thio)benzo[d]thiazole (**5c**).* Compound **5c** was obtained as a yellow liquid (137.7 mg, 93%), with hexane/DCM = 10:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09−8.10 (m, 1H), 7.63−7.66 (m, 1H), 7.65 (t, J = 56.0 Hz, 1H), 7.46−7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.0, 152.9, 135,9, 126.6, 125.6, 122.8, 121.2, 120.3 (t, J = 275.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −93.2 (d, J = 56.0 Hz, 2F); IR (thin film) ν 1542, 1462, 1427, 1287, 1071, 997, 893, 780 cm^{-1}; MS (EI): m/z 295 (M^+); HRMS (EI-TOF): m/z [M^+] calcd for $C_8H_4BrF_2NS_2$: 294.8937; found: 294.8936.

*4-Bromo-2-((difluoromethyl)thio)-6-(trifluoromethyl)benzo[d]-thiazole (**5d**).* Compound **5d** was obtained as a yellow liquid (151.5 mg, 83%), with hexane/DCM = 10:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (s, 1H), 7.88 (s, 1H), 7.80 (t, J = 55.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.7, 152.8, 136.1, 128.5 (q, J = 33.4 Hz), 127.1 (q, J = 6.1 Hz), 123.0 (q, J = 271.8 Hz), 119.9 (t, J = 276.4 Hz), 117.8 (q, J = 4.6 Hz), 116.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −61.7 (s, 3F), −93.9 (d, J = 55.6 Hz, 2F); IR (thin film) ν 1460, 1391, 1306, 1170, 1134, 1087, 1009, 880 cm^{-1}; MS (EI): m/z 363 (M^+); HRMS (EI-TOF): m/z [M^+] calcd for $C_9H_3BrF_5NS_2$: 362.8810; found: 362.8809.

*2-((Difluoromethyl)thio)-6-nitrobenzo[d]thiazole (**5e**).* Compound **5e** was obtained as a light yellow solid (85.3 mg, 65%), with hexane/DCM = 1:1 as eluent for the column chromatography. MP: 94−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.74−8.75 (m, 1H), 8.33−8.36 (m, 1H), 8.02−8.05 (m, 1H), 7.78 (t, J = 55.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.9 (t, J = 3.8 Hz), 156.2, 145.0, 135.8, 122.7, 122.2, 119.7 (t, J = 276.3 Hz), 117.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −93.9 (d, J = 54.5 Hz, 2F); IR (thin film) ν 1597, 1515, 1431, 1324, 1076, 1028, 1004, 741 cm^{-1}; MS (EI): m/z 262 (M^+); HRMS (EI-TOF): m/z [M^+] calculated for $C_8H_4F_2N_2O_2S_2$: 261.9682; found: 261.9677.

*2-((Difluoromethyl)thio)-6-ethoxybenzo[d]thiazole (**5f**).* Compound **5f** was obtained as a light yellow solid (111.3 mg, 85%), with hexane/DCM = 1:1 as eluent for the column chromatography. MP: 44−46 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 (d, J = 8.8 Hz, 1H), 7.45(t, J = 56.4 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.07 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.5, 147.5, 138.0, 125.7, 123.6, 120.3 (t, J = 276.4 Hz), 116.5, 104.2, 64.1, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.7 (d, J = 55.6 Hz, 2F); IR (thin film) ν 1600, 1470, 1448, 1258, 1225, 1084, 998, 822 cm^{-1}; MS (EI): m/z 261 (M^+); HRMS (EI-TOF): m/z [M^+] calculated for $C_{10}H_9F_2NOS_2$: 261.0094; found: 261.0089.

*4-((Difluoromethyl)thio)pyridine (**5g**).* Compound **5g** was obtained as a brown liquid (54.5 mg, 67%), with hexane/EA = 1:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.53−8.55 (m, 2H), 7.35−7.36 (m, 2H), 6.95 (t, J = 55.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.2, 138.4, 126.2, 119.7 (t, J = 274.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.2 (d, J = 55.6 Hz, 2F); MS (EI): m/z 161 (M^+). These data matched with the reported results.[8a]

*2-((Difluoromethyl)thio)pyridine (**5h**).* Compound **5h** was obtained as a brown liquid (73.0 mg, 91%), with hexane/EA = 10:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.45−8.46 (m, 1H), 7.68(t, J = 56.4 Hz, 1H), 7.55−7.59 (m, 1H), 7.22−7.24 (m, 1H), 7.10−7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 153.1 (t, J = 3.1 Hz), 150.1, 137.1, 124.3 (t, J = 2.3 Hz), 121.7, 121.3 (t, J = 269.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −96.3 (d, J = 56.0 Hz, 2F); MS (EI): m/z 161 (M^+). These data matched with the reported results.[8a]

*2-((Difluoromethyl)thio)-4,6-dimethylpyrimidine (**5i**).* Compound **5i** was obtained as a brown liquid (89.2 mg, 94%), with hexane/EA = 10:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.81 (t, J = 56.0 Hz, 1H), 6.78 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.8, 166.4, 121.2 (t, J = 268.0 Hz), 117.4, 23.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −99.1 (d, J = 55.6 Hz, 2F); MS (EI): m/z 190 (M^+). These data matched with the reported results.[9f]

General Procedure for Difluoromethylation of Alkyl Thiols. A 50 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with difluoromethyltriphenylphosphonium triflate **2b** (690.0 mg, 1.5 mmol, 3.0 equiv) and *fac*-Ir(ppy)$_3$ (9.8 mg, 0.015 mmol, 3 mol %). Then thiol **6** (0.5 mmol, 1.0 equiv), DBU (0.15 mL, 1.0 mmol, 2.0 equiv), and DMSO (5 mL) were added. The flask was sealed with 3 M vinyl electrical tape. The mixture was degassed three times by the freeze−pump−thaw procedure. The flask was placed at a distance of 2 cm from the blue LEDs. The mixture was stirred under

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nitrogen atmosphere and irradiated by blue 30 W LEDs for 48 h. After the reaction was complete, 10% H_2O_2 (5 mL) was added to the reaction mixture. The reaction mixture was extracted by Et_2O. The organic phase was dried by anhydrous sodium sulfate and concentrated in vacuo, and the residue was purified with silica gel column chromatography to provide the desired product.

*Benzyl(difluoromethyl)sulfane (**7a**).* Compound **7a** was obtained as a light yellow liquid (32.5 mg, 37%), with hexane/DCM = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28−7.35 (m, 5H), 6.73 (t, J = 56.4 Hz, 1H), 4.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 136.2, 128.9, 128.8, 128.5, 128.3, 127.7, 120.2 (t, J = 271.1 Hz), 31.7 (t, J = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −94.5 (d, J = 56.0 Hz, 2F); MS (EI): m/z 174 (M^+). These data matched with the reported results.[9c]

*Benzyl(difluoromethyl)sulfane (**7b**).* Compound **7b** was obtained as a light yellow liquid (39.4 mg, 42%), with hexane/DCM = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32−7.35 (m, 2H), 7.22−7.28 (m, 3H), 6.78 (t, J = 56.4 Hz, 1H), 2.97−3.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.6, 128.6, 128.6, 126.7, 120.6 (t, J = 271.8 Hz), 36.8, 28.6 (t, J = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.7 (d, J = 56.0 Hz, 2F); MS (EI): m/z 188 (M^+). These data matched with the reported results.[8a]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01041.

Preliminary mechanistic experiments, as well as copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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