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Visible-Light-Induced Arylthiofluoroalkylations of Unactivated Heteroaromatics and Alkenes

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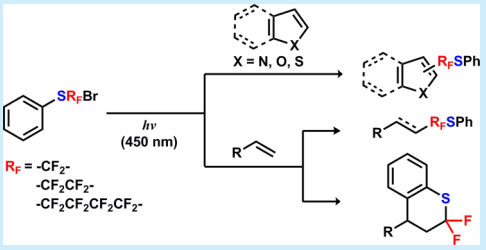
Supporting Information

ABSTRACT: Visible-light-induced arylthiofluoroalkylations of unactivated heteroaromatics and alkenes have been developed utilizing readily available arylthiofluoroalkyl sources. This method enables simultaneous installation of sulfur and fluoroalkyl moieties, two important functional groups, which demonstrates its potential use for late-stage modifications in the synthesis of functional molecules. This method can be easily utilized to fine-tune the properties of lead molecules in drug development by controlling the number of fluorine atoms in the reagents.



Fluoroalkylation reactions have been of great interest in many applications due to the ability of the introduced fluoroalkyl groups to change the physical, chemical, and biological activities of organic compounds.[1] These effects have stimulated the intensive development of new pharmaceutical and agrochemical agents bearing the fluoroalkyl moiety.[2] Furthermore, the introduction of fluoroalkyl groups containing sulfur has been of growing interest because the presence of sulfur can further change the properties of molecules; for example, inducing high lipophilicity.[3] Figure 1a shows the dramatic increase in activity against HIV (Human Immunodeficiency Virus)-1 achieved by incorporation of both sulfur and fluoroalkyl groups into non-nucleoside reverse transcriptase inhibitors.[4] Sulfur is an essential element of the molecule to ensure biological activity [Figure 1a, **A** vs **B**], and the CF_2 motif increases the reactivity significantly [Figure 1a, **C** vs **D**]. Due to the importance of thiofluoroalkyl moieties, various methods have been developed to construct the $-S(CF_2)_n-$ motif. The most common approaches involve sequential sulfenylation and fluoroalkylation (or *vice versa*) reactions.[3] Considering the usage of both moieties for drug development, direct thiofluoroalkylations could offer an efficient strategy for late-stage modifications [Figure 1b].

Although there have been various methods for direct thiofluoroalkylations by C−C bond formation,[5] many of them still suffer from limited substrate scope and harsh reaction conditions including the use of toxic reagents, extremely low or high temperatures, or a long reaction time. Herein, we report visible-light-induced[6−9] C−C bond formation for arylthiofluoroalkylations of unactivated heteroaromatic compounds and alkenes, where the reactivity was controlled efficiently under mild conditions with a wide substrate scope [Figure 1c].

For our investigations, we utilized the readily available phenylthiofluoroalkyl bromides,[10] $BrCF_2SPh$ (**1a**), $BrCF_2CF_2SPh$ (**1b**), and $BrCF_2CF_2CF_2CF_2SPh$ (**1c**), as sources of electron-deficient carbon-centered radicals for visible-light-mediated transformations. Based on the electron density difference of the key phenylthiofluoroalkyl radical intermediates obtained by the density functional theory (DFT) calculations (Figure 2), we could expect differences in reactivity of the radicals depending on the number of fluoroalkyl carbons (n = 1,

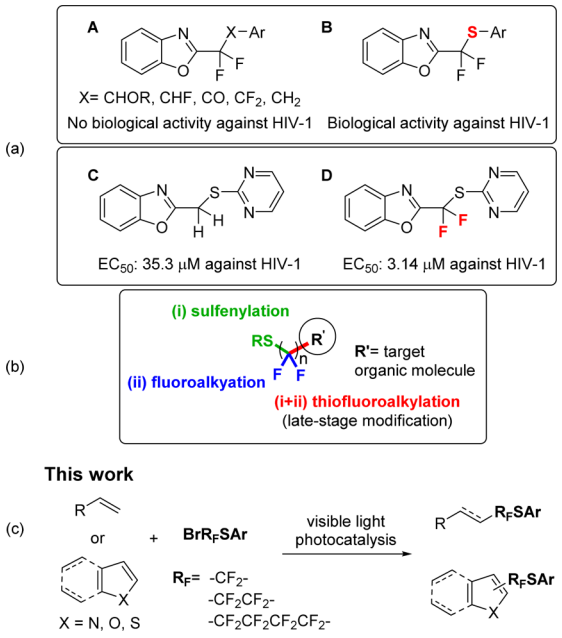


Figure 1. (a) Effect of sulfur and fluoroalkyl groups. (b) Strategy for the addition of sulfur and fluoroalkyl groups. (c) Our methodology by visible-light photocatalysis.

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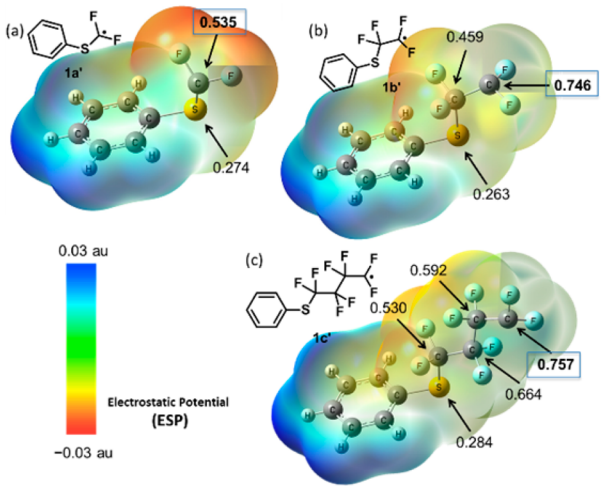


Figure 2. Electrostatic potential maps of **1a′**, **1b′**, and **1c′** calculated by DFT method with the B3LYP functional and the 6-31G+(d) basis set. The color scale represents the electrostatic potential (ESP), and the values specified with arrows refer to the natural atomic charges of the corresponding atoms obtained by natural bond orbital (NBO) analysis.

2, or 4). Compared to the radical centers in **1b′** and **1c′** (with natural atomic charges of 0.746 and 0.757, respectively), that of **1a′** is less electrophilic showing a less positive natural atomic charge of 0.535. It is likely that the delocalization of the lone pair of electrons on the sulfur atom increases the electron density (and decreases the natural charge) of the neighboring carbon radical in **1a′**. The radical centers in **1b′** and **1c′** are located at greater distances from the sulfur atom and remain highly electron-deficient, with more positive natural atomic charges than in the case of **1a′**.

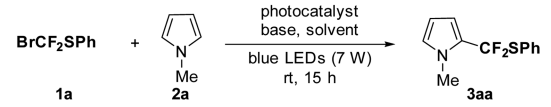
Indeed, we observed quite different reactivities among phenylthiofluoroalkyl radicals toward the phenylthiofluoroalkylations by C−C bond formation. In initial studies, we utilized radical sources **1a** and **1b** with *N*-methylpyrrole **2a** as the model substrate (Table 1). The reactions with **1c** showed reactivity similar to those with **1b**. For phenylthiodifluoromethylation of **2a** using **1a** and tetramethylethylenediamine (TMEDA) in MeCN, a tricyclometalated Ir complex, *fac*-Ir(ppy)$_3$, showed the best reactivity while the use of a Ru photocatalyst like [Ru(phen)$_3$]Cl$_2$ or [Ru(bpy)$_3$]Cl$_2$ provided lower yields of **3aa** (Table 1-I, entries 1−4).

On the other hand, the phenylthiotetrafluoroethylation of **2a** using **1b** worked best with [Ru(phen)$_3$]Cl$_2$ (Table 1-II, entries 1−4).[11] Regarding bases, phenylthiodifluoromethylation using **1a** proceeded well with 2,6-lutidine (Table 1-I, entry 7) while phenylthiotetrafluoroethylation using **1b** did not work at all with 2,6-lutidine, but proceeded well with TMEDA (Table 1-II, entries 2, 5, and 6). The subtle differences in the combination of photocatalyst, base, and solvent significantly affected the reactivity of both phenylthiofluoroalkylation processes. The results of further optimization studies are available in the Supporting Information as Tables S1 and S2.

With the optimized conditions in hand, we next evaluated the phenylthiofluoroalkylations of various heteroaromatics (Table 2). A combination of 2 mol % *fac*-Ir(ppy)$_3$ and 2 equiv of 2,6-lutidine was used for phenylthiodifluoromethylations with 1.4 equiv of BrCF$_2$SPh (**1a**) in DMF (0.1 M). On the other hand, for reactions with 1.4 equiv of BrCF$_2$CF$_2$SPh (**1b**) or BrCF$_2$CF$_2$CF$_2$CF$_2$SPh (**1c**), a combination of 2−3 mol % [Ru(phen)$_3$]Cl$_2$ and 2 equiv of TMEDA in MeCN (0.1 M) was

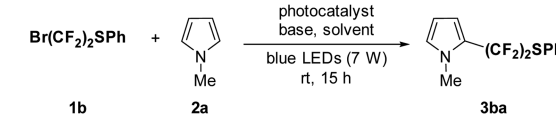
Table 1. Optimization Studies with 2a[a]

I. phenylthiodifluoromethylation



entry	photocatalyst (2 mol %)	base (2 equiv)	solvent (0.1 M)	yield (%)[b]
1	[Ru(bpy)$_3$]Cl$_2$	TMEDA	MeCN	25
2	[Ru(phen)$_3$]Cl$_2$	TMEDA	MeCN	29
3	[Ir(dtbbpy)(ppy)$_2$]PF$_6$	TMEDA	MeCN	26
4	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	48
5	*fac*-Ir(ppy)$_3$	2,6-Lutidine	MeCN	50
6	*fac*-Ir(ppy)$_3$	K$_2$CO$_3$	MeCN	46
7	***fac*-Ir(ppy)$_3$**	**2,6-Lutidine**	**DMF**	**79**
8	*fac*-Ir(ppy)$_3$	K$_2$CO$_3$	DMF	54
9	*fac*-Ir(ppy)$_3$	-	DMF	50

II. phenylthiotetrafluoroethylation



entry	photocatalyst (2 mol %)	base (2 equiv)	solvent (0.1 M)	yield (%)[b]
1	[Ru(bpy)$_3$]Cl$_2$	TMEDA	MeCN	75
2	**[Ru(phen)$_3$]Cl$_2$**	**TMEDA**	**MeCN**	**84**[c]
3	[Ir(dtbbpy)(ppy)$_2$]PF$_6$	TMEDA	MeCN	67
4	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	81
5	*fac*-Ir(ppy)$_3$	2,6-Lutidine	DMF	-
6	[Ru(phen)$_3$]Cl$_2$	2,6-Lutidine	MeCN	-
7	[Ru(phen)$_3$]Cl$_2$	K$_2$CO$_3$	MeCN	-
8	[Ru(phen)$_3$]Cl$_2$	-	MeCN	25

[a]Reaction conditions: **1a** or **1b** (0.14 mmol), **2a** (0.1 mmol). [b]The yield was determined by gas chromatography or ^{19}F NMR spectroscopy with internal standards, dodecane and 4-fluorotoluene, respectively. [c]3 mol % of [Ru(phen)$_3$]Cl$_2$ was used.

used. A variety of heteroaromatics including pyrrole (entries 1−3), furan (entry 4), indole (entries 5−9), benzofuran (entry 10), and benzothiophene (entry 11) underwent phenylthiofluoroalkylations in moderate to good yields. Phenylthiomethylated products were relatively less stable so that the CF$_2$ moieties in **3aa** and **3ab** were transformed into a carbonyl group,[12] and some decomposition was observed in **3ac** and **3af** during the purification process with silica-gel chromatography.

Alkenes were also suitable substrates for phenylthiofluoroalkylations, and a difference in reactivity was observed when reactions were carried out in the presence of **1a** and **1b**/**1c**. In the case of reactions of alkenes with **1a**, the same conditions as those used for heteroaromatics produced either cyclized products **5** or alkenyl products **6**, selectively (Table 3). Reactions of aromatic alkenes **4a** and **4b** proceeded to give phenylthiodifluoromethylated alkenes **6aa** (entry 1) and **6ab** (entry 2), respectively, through oxidation of the benzyl radical intermediate **4′** to the cation intermediate **4″**, followed by a deprotonation step.[7b] Interestingly, aliphatic alkenes reacted to produce cyclized products **5**, either by radical or cationic electrophilic substitution of the tethered phenyl ring in **4′** or **4″** (Table 3, entries 3−6). The proposed mechanisms for the phenylthiofluoroalkylations of both heteroaromatics and alkenes are illustrated in Schemes S1 and S2 (SI).

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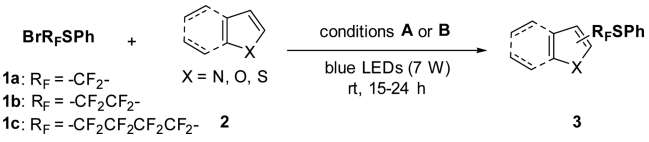
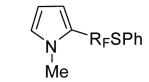
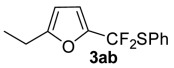
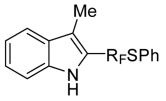
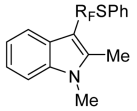
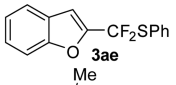
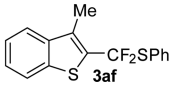
Table 2. Substrate Scope for Phenylethiofluoroalkylations of Heteroaromatics[a]



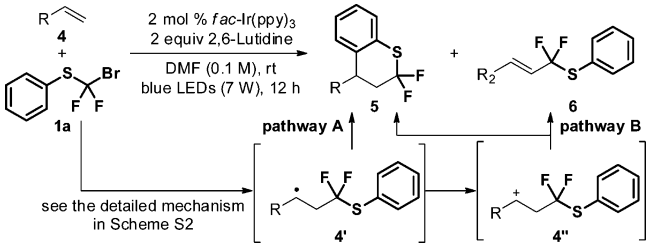
entry	conditions[a]	product	yield (%)[b]
			
1	A	**3aa**, $R_F = CF_2$	77[c]
2	B	**3ba**, $R_F = CF_2CF_2$	75 (82)[e]
3	B	**3ca**, $R_F = CF_2CF_2CF_2CF_2$	65
4	A	 **3ab**	76[c]
			
5	A	**3ac**, $R_F = CF_2$	90[d]
6	B	**3bc**, $R_F = CF_2CF_2$	70 (82)[e]
7	B	**3cc**, $R_F = CF_2CF_2CF_2CF_2$	78
			
8	B	**3bd**, $R_F = CF_2CF_2$	52 (72)[e,f]
9	B	**3cd**, $R_F = CF_2CF_2CF_2CF_2$	67 (70)[e,f]
10	A	 **3ae**	62
			
11	A	**3af**	59[d]

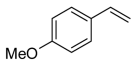
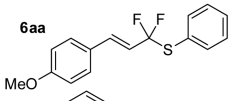
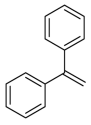
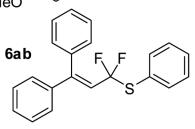
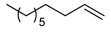
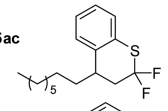
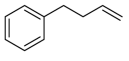
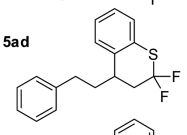
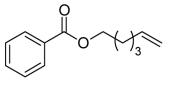
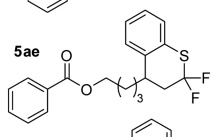
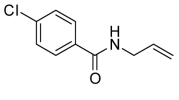
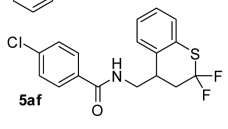
[a]Reaction conditions: **1** (0.7 mmol), **2** (0.5 mmol). **A**: *fac*-Ir(ppy)$_3$ (2 mol %), 2,6-lutidine (2 equiv), DMF (0.1 M). **B**: [Ru(phen)$_3$]Cl$_2$ (2–3 mol %), TMEDA (2 equiv), MeCN (0.1 M). [b]Isolated yield. [c]During the silica-gel column chromatography process, the CF$_2$ moiety was transformed into a carbonyl group.[12] [d]The yield was determined by ^{19}F NMR spectroscopy due to some decomposition of the product during silica-gel column chromatography. [e]Numbers in parentheses indicate yield based on the recovered starting material. [f]5% of regioisomers from the substitution at six-membered ring were also obtained.

On the other hand, the reactions of alkenes with **1b** and **1c** required conditions different from those employed for heteroaromatics.[13] A combination of 2 mol % *fac*-Ir(ppy)$_3$ and 2 equiv TMEDA in DCM (0.2 M) was used to convert alkenes into alkenyl-phenythiofluoroalkylated products **6** or hydro-phenylthiofluoroalkylated products **7** (Table 4). For aliphatic alkenes, reactions typically afforded phenylthiofluoroalkylated alkanes as major products through hydro-phenylthiofluoroalkylations (Table 4, entries 3–6), while the aromatic alkene **4b** yielded alkenyl derivatives **6bb** and **6cb** as major products (Table 4, entries 1 and 2). In the hydro-thiofluoroalkylations, the tertiary amine TMEDA acted not only as electron donor in photocatalytic step but also as a hydrogen atom source.[14] Interesting results were also obtained by reacting alkenes with **1b** and **1c** in an oxygen atmosphere. Such reactions produced sulfoxides as final products, through further oxidation of the sulfide moiety in the hydrophenylthiofluoroalkylated products in the presence of molecular oxygen (see Scheme S3 in the SI).[15]

In order to show the generality of the transformation, the arylthiofluoroalkyl reagents were varied next (Scheme 1).

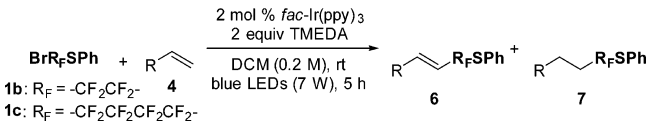
Table 3. Substrate Scope for Phenylthiodifluoromethylation of Alkenes[a]

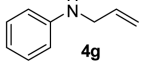


entry	substrate (**4**)	product (**5** or **6**)	yield (%)[b]
1	**4a** 	**6aa** 	81[c]
2	**4b** 	**6ab** 	90[c]
3	**4c** 	**5ac** 	75
4	**4d** 	**5ad** 	76
5	**4e** 	**5ae** 	80
6	**4f** 	**5af** 	70

[a]Reaction conditions: **1a** (1.4 equiv), **4** (0.3 or 0.5 mmol). [b]Isolated yield. [c]During the silica-gel column chromatography process, the CF$_2$ moiety was transformed into a carbonyl group.[12]

Table 4. Substrate Scope for Phenylthioperfluoroalkylation of Alkenes with 1b and 1c[a]



entry	substrates		product (yield%)[b]	
	1	**4**	**6**	**7**
1	**1b**	**4b**	**6bb** (53)	**7bb** (17)
2	**1c**	**4b**	**6cb** (51)	**7cb** (23)
3	**1b**	**4c**	**6bc** (8)[c]	**7bc** (56)
4	**1c**	**4c**	**6cc** (9)[c]	**7cc** (54)
5	**1b**	**4e**	-	**7be** (63)
6	**1b**	 **4g**	-	**7bg** (52)

[a]Reaction conditions: **1b** or **1c** (0.7 mmol), **4** (0.5 mmol). [b]Isolated yield. [c]The formation and the corresponding yield was checked by GC-MS and ^{1}H NMR spectroscopy of the crude reaction mixture.

Reactions of **2a** with methylphenylthiotetrafluoroethyl bromide (**8**) and chlorophenylthiotetrafluoroethyl bromide (**10**) pro-

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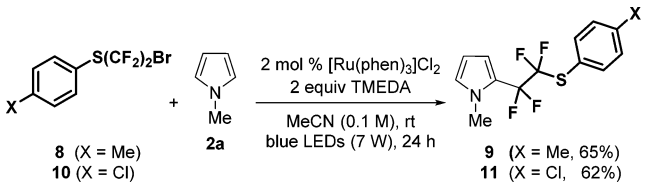
Scheme 1. Variation on Thiofluoroalkyl Sources



ceeded well to give the corresponding products **9** and **11**, respectively, indicating that the method is applicable to the synthesis of various arylthiofluoroalkylated products.

In the investigation described above, we have developed arylthiofluoroalkylation methods for heteroaromatic and alkene substrates. By using various arylthiofluoroalkyl sources such as $BrCF_2SPh$, $BrCF_2CF_2SPh$, and $BrCF_2CF_2CF_2CF_2SPh$ in visible-light photocatalysis, two functional groups consisting of sulfur and fluoroalkyl moieties could be simultaneously installed to unactivated heteroaromatics and alkenes. The reactivity of the transformation was highly dependent on the electron density of the carbon-centered radical intermediate of the arylthiofluoroalkyl sources. Therefore, different combinations of photocatalyst, base, and solvent were employed, depending on the observed reactivity. The simultaneous introduction of two functional groups shows the potential use of the method for late-stage modifications in the development of functional molecules. In addition, this method can be easily utilized for fine-tuning of properties in drug development by controlling the number of fluorine atoms in reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01495.

Experimental details, additional experimental results, analytic data for arylthiofluoroalkylated compouds and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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