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From *S*-Fluoroalkylation to Fluoroalkylation–Thiolation: Difunctionalization of Alkenes with Fluoroalkyl Phenyl Sulfones and Thiophenols Enabled by Photoredox Copper Catalysis

Lin Xiao, Zhiqiang Wei, Chuanfa Ni, Alexander D. Dilman, and Jinbo Hu*

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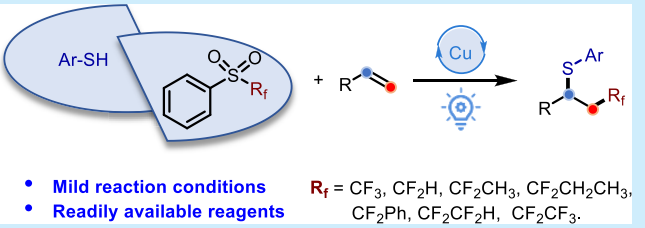
ABSTRACT: Molecules containing fluoroalkyl and arylthio groups play a pivotal role in pharmaceutical and agrochemical development. The simultaneous introduction of these functional groups through the 1,2-difunctionalization of alkenes is an efficient strategy. Fluoroalkyl phenyl sulfones serve as accessible fluoroalkyl radical precursors; however, their tendency to interact with thiophenol via the electron donor–acceptor interaction mechanism can impede the desired transformation. Through meticulous selection of solvent and base, we successfully utilized copper catalysis to facilitate an alkene-involved three-component reaction. Our work unveils a photoredox copper-catalyzed fluoroalkylation–thiolation of alkenes using various fluoroalkyl phenyl sulfones (such as perfluoroethyl, tetrafluoroethyl, trifluoromethyl, difluoromethyl, difluoroalkyl, and difluorobenzyl). The efficacy of this approach is exemplified by the synthesis of Kengreal derivatives.

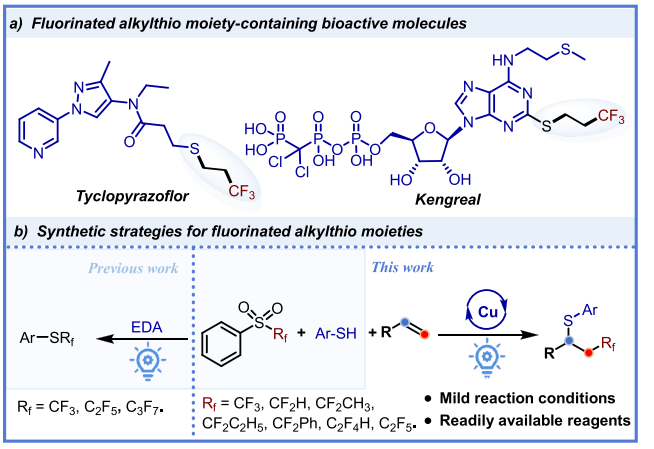


The incorporation of fluorine-containing moieties into organic compounds holds significant importance, as it can profoundly influence the physical and chemical properties of associated drugs and materials, leading to improvements in lipophilicity, bioavailability, and metabolic stability.[1] Over the past decade, a multitude of fluoroalkylation reactions have emerged, focusing on cost-effective and highly efficient methods for introducing fluoroalkyl tags into a wide array of organic compounds.[2] Fluorinated alkylthio groups, exemplified by the (3,3,3-trifluoropropyl)thio motif, serve as critical structural motifs in various pesticides and biologically active molecules like the insecticide tyclopyrazoflor and the antiplatelet agent kengreal (Scheme 1a).[3] Consequently, the development of synthetic methods for constructing fluorinated alkylthio moieties through the simultaneous formation of C–S and C–R_f bonds can expand the repertoire of available fluorinated alkylthio compounds, fostering the discovery of biologically active compounds.

The radical fluoroalkylation–thiolation of olefins has emerged as an efficient method for constructing fluorinated alkylthio moieties, benefiting from the easy accessibility of olefins, fluoroalkyl radical sources, and *S*-nucleophiles.[4] However, these synthetic methods encounter certain limitations.[5] For instance, the thiolation step frequently necessitates prefunctionalized thiophenol derivatives, while the range of accessible fluoroalkyl groups remains somewhat restricted.

Fluoroalkyl sulfones, a class of stable, readily accessible, and versatile compounds, have found extensive use in the fluoroalkylation of organic molecules.[6] Notably, difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) can be readily transformed into (phenylsulfonyl)difluoromethyl derivatives ($PhSO_2CF_2R$, R ≠

Scheme 1. Significance of Fluorinated Alkylthio Moieties and Approaches for Their Synthesis



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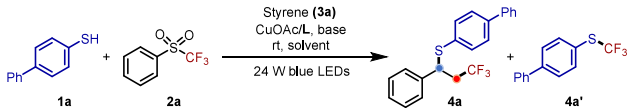
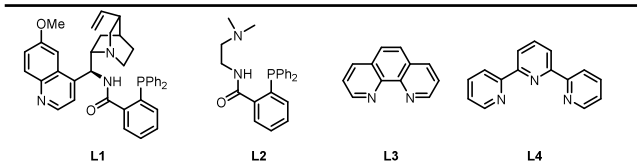
H).[7] However, perfluoroalkyl phenyl sulfones exhibit efficient reactivity with thiophenols through electron donor−acceptor (EDA) interactions.[8] Consequently, the three-component reaction involving fluoroalkyl sulfones, thiophenols, and alkenes poses a challenge. In this study, we present a copper-catalyzed fluoroalkylation−thiolation of alkenes using perfluoroalkyl phenyl sulfones and arylthiophenols, giving the desired three-component reaction products (Scheme 1b).

At the outset, our intention was to employ the EDA complex photoactivation method for a three-component reaction, utilizing 4-phenylthiophenol (**1a**), trifluoromethyl phenyl sulfone (**2a**), and styrene (**3a**) as model reactants, with Cs_2CO_3 serving as the base. We conducted preliminary screenings of various solvents and bases for the reaction. The initial findings revealed that the two-component reaction between **1a** and **2a** acted as a competing pathway (Table 1, entries 1−3). The outcome of this side reaction was notably affected by the choice of solvent and bases. Ether solvents such as THF and dioxane, hindered the formation of **4a′** (Table 1, entries 4−6; see the Supporting Information (SI) for details). Under this reduction system, the yield of target product **4a** did not significantly increase. To facilitate the three-component reaction, a copper catalyst was introduced to enhance the reduction of sulfone **2a**.[9] We utilized a 10 mol % loading of CuOAc and 11 mol % loadings of various ligands under blue LED irradiation, with dioxane identified as the optimal solvent (Table 1, entries 7−11; see the SI for details). The combination of the tridentate anionic N^N^P ligand with the copper catalyst exhibited high efficiency, aligning with the improved single-electron reduction capability of copper facilitated by electron-rich multidentate anionic ligands (Table 1, entries 8 and 9 vs entries 10 and 11).[10] Comparing quinine-derived N^N^P ligand **L1** with its simplified structure analogue **L2**, ligand **L1** yielded product **4a** with a slightly higher yield. Optimization of the catalyst loading revealed that increasing the amounts of CuOAc and **L1** to 20 mol % each was beneficial for the reaction (Table 1, entry 12; see the SI for details). Furthermore, extending the reaction time to 48 h was necessary to enhance the conversion of thiophenol **1a**, resulting in a higher yield of the desired product (Table 1, entry 13). Control experiments confirmed that light, the copper catalyst, and the ligand were all essential for the reaction (Table 1, entries 14−16). Efforts to achieve enantioselectivity using chiral ligands, including **L1**, were unsuccessful, likely due to the facile homolytic cleavage of the Cu(II)−S bond.[11]

Table 1. Optimization of the Reaction Conditions[a]





entry	solvent	[Cu]/**L1** (mol %)	base	yield of **4a** (%)[b]	yield of **4a′** (%)[b]
1	DMA	–	Cs_2CO_3	11	61
2	DMSO	–	Cs_2CO_3	11	78
3	CH_3CN	–	Cs_2CO_3	35	36
4	THF	–	Cs_2CO_3	36	trace
5	dioxane	–	Cs_2CO_3	20	trace
6	dioxane	–	BTMG[h]	8	93
7	dioxane	10/11	BTMG	20	26
8	dioxane	10/11	Cs_2CO_3	56	trace
9[c]	dioxane	10/11	Cs_2CO_3	54	trace
10[d]	dioxane	10/11	Cs_2CO_3	11	trace
11[e]	dioxane	10/11	Cs_2CO_3	16	trace
12	dioxane	20/20	Cs_2CO_3	73	trace
13[f]	dioxane	20/20	Cs_2CO_3	88	trace
14[f,g]	dioxane	20/20	Cs_2CO_3	N.D.	N.D.
15[f]	dioxane	−/20	Cs_2CO_3	15	trace
16[f]	dioxane	20/−	Cs_2CO_3	29	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv), **3a** (0.3 mmol, 1.5 equiv), Cs_2CO_3 (0.4 mmol, 2.0 equiv), CuOAc (10 mol %) and **L1** (11 mol %), solvent (2.0 mL), room temperature. [b]Determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [c]**L2** (11 mol %). [d]**L3** (11 mol %). [e]**L4** (11 mol %). [f]48 h. [g]Under dark. [h]BTMG = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.

Having established the optimized conditions, we proceeded to investigate the substrate scope. As illustrated in Scheme 2, our exploration began with a diverse range of alkene partners. Styrenes bearing electron-donating groups such as methyl, phenyl, phenoxy, and *N*,*N*-dimethylamino groups successfully participated in the reaction, yielding the desired products in moderate to excellent yields (**4b**−**4f**). The reactivity of electron-deficient olefins was found to be comparable to that of electron-rich ones (**4g**−**4m**). Notably, aryl iodides proved to be compatible with the reaction (**4l**). Furthermore, a 1,1′-disubstituted olefin also furnished the target product in good yield (**4u**). However, the reaction rate for aliphatic olefins notably decreased, resulting in products **4o**−**4q** in yields ranging from 41% to 52%.

Subsequently, we explored a range of thiophenols bearing different substituents. Electron-donating thiophenols (**5a**−**5e**) smoothly participated in the reaction, affording the corresponding products in moderate yields, while thiophenols with electron-withdrawing groups (**5f** and **5h**−**5j**) exhibited slight variations in their reactivity. Heterocyclic thiophenols performed effectively to deliver products in yields ranging from 44% to 76% (**5k**, **5m**, and **5n**). In the case of 4,6-dimethylpyrimidine-2-thiol, the solvent was switched to DME due to its limited solubility in dioxane; this modification was well-tolerated in the reaction, resulting in a moderate yield (**5n**).

Fluoroalkyl groups beyond trifluoromethyl hold significant application potential.[12] Hence, we proceeded to expand the method by investigating the reactions of various fluoroalkyl phenyl sulfones. Tetrafluoroethyl and perfluoroethyl phenyl sulfones exhibited reactivity akin to that of trifluoromethyl sulfones, yielding poly(per)fluoroalkylation−thiolation products in good yields (**6e**, **6f**). The difluoromethyl (CF_2H) group, serving as a bioisostere of hydroxy and thiol groups, could be incorporated using $PhSO_2CF_2H$ as the reagent, providing the difluoromethylation−thiolation product in moderate yield (**6a**). Derivatives of $PhSO_2CF_2H$, such as CH_3CF_2-, $CH_3CH_2CF_2$-, and $PhCF_2$-containing phenylsulfones (**6b**−**6d**), also engaged in difluoroalkylation−thiolation reactions in moderate to good yields.

To broaden the scope of the reaction, we turned our attention to modifying intricate molecules relevant to

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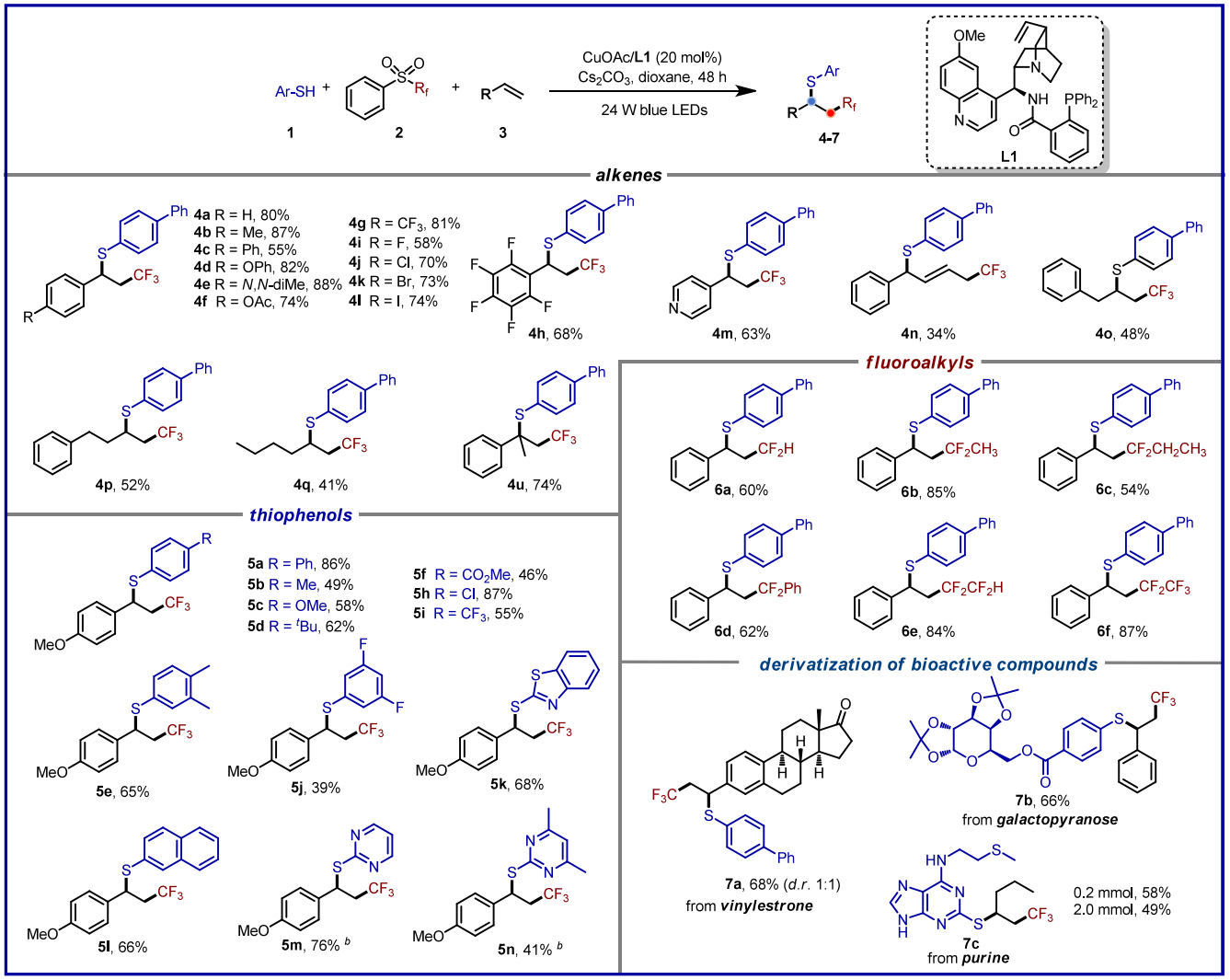
Scheme 2. Substrate Scope



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), **3** (0.3 mmol, 1.5 equiv), Cs_2CO_3 (0.4 mmol, 2.0 equiv), dioxane (2.0 mL). [b]DME as solvent.

pharmaceuticals and natural products (Scheme 2). Using derivatives of vinylestrone and galactopyranose as examples of complex alkenes, both engaged in the reaction, yielding the desired products with satisfactory efficiency (**7a**, **7b**). The purine-derived heteroarylthiol, representing a complex thiol, successfully underwent trifluoromethylation−thiolation with simple alkenes such as pent-1-ene, showcasing its potential utility in constructing kengreal and its analogues with diverse alkyl and fluoroalkyl substituents. To further validate the practicality of this fluoroalkylation−thiolation reaction (see the SI for details), we conducted a gram-scale reaction to produce the target products **4aa** and **7c**. Subsequently, **4aa** was converted into its sulfone **5aa**.

To gain mechanistic insight into the fluoroalkylation−thiolation reaction, a series of experiments were conducted to unravel the possible pathway (Scheme 3a and the SI). Initially, a radical trapping experiment was carried out (Scheme 3a). The introduction of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) effectively inhibited the reaction, leading to the detection of radical trapping product **7** via ^{19}F NMR spectroscopy. This result serves as direct evidence of the generation of a CF_3 radical during the reaction sequence. Subsequently, a light on−off experiment illustrated the light-induced nature of the reaction; it proceeded solely under light exposure and ceased in darkness (see the SI for details). Lastly, to explore the possibility of a direct thiolation process, PhSSPh was introduced into the reaction mixture of **1a**, **2a**, and **3a** under standard conditions, resulting in the identification of the trifluoromethylation−phenylthiolation product **4a** (see the SI for details).

From the results of the aforementioned experiments and existing literature,[11,12] a plausible pathway for the fluoroalkylation−thiolation of alkenes is postulated in Scheme 3b. In the presence of copper catalyst **A**, complex **B** is generated via the coordination of Cu(I) species with the arylthiolate (generated from the arylthiol and base). This complex absorbs visible light to yield excited species **B***. Subsequently, single electron transfer (SET) transpires between excited complex **B*** and $PhSO_2R_f$ (**2**), giving rise to fluoroalkyl radical **D** and Cu(II) complex **C**. The fluoroalkyl radical then adds to alkene **3**, forming secondary alkyl radical **E**. Concurrently, Cu(II) species **C** dissociates to generate thiol radical **G** and regenerate

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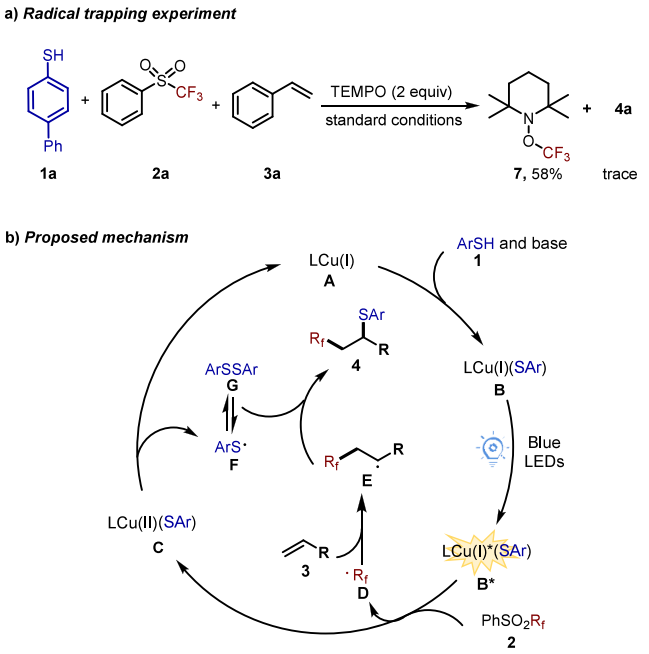
Scheme 3. Mechanistic Consideration



the Cu(I) species **A**. Finally, alkyl radical intermediate **E** is captured by either arylthio radical **F** or aryl disulfide **G**, resulting in the desired product **4**.

In summary, we have established a photoredox copper-catalyzed three-component fluoroalkylation−thiolation method for olefins utilizing fluoroalkyl sulfones and thiols. The competitive fluoroalkylation of the thiols is effectively suppressed under this visible-light-promoted photoredox copper catalysis. The incorporation of a copper catalyst significantly accelerates the reaction rate. This strategy facilitates the rapid synthesis of a wide array of fluoroalkylated thioethers using readily accessible fluoroalkyl sulfones, showcasing excellent compatibility with various functional groups and promising potential for drug molecule modifications.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c00102.

More detailed results and characterization data of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jinbo Hu − *State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China;* orcid.org/0000-0003-3537-0207; Email: jinbohu@sioc.ac.cn

Authors

Lin Xiao − *College of Chemistry, Central China Normal University, Wuhan, Hubei 430079, China; State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Zhiqiang Wei − *State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Chuanfa Ni − *State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Alexander D. Dilman − *N. D. Zelinsky Institute of Organic Chemistry, Moscow 119991, Russia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.5c00102

Notes

The authors declare no competing financial interest.

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