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Chalcogenide-Catalyzed Intermolecular Electrophilic Thio- and Halofunctionalization of *gem*-Difluoroalkenes: Construction of Diverse Difluoroalkyl Sulfides and Halides

Quanbin Jiang, Yaoyu Liang, Yuanyuan Zhang, and Xiaodan Zhao*

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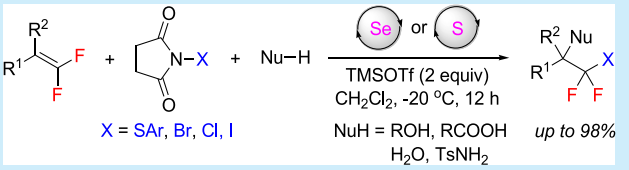
ABSTRACT: Thio- and halodifluoromethylated compounds are an important class of compounds in medicinal chemistry and organic synthesis. Herein, we report a facile method for the construction of these compounds via chalcogenide-catalyzed intermolecular electrophilic thio- and halofunctionalization of *gem*-difluoroalkenes. Simple treatment of *gem*-difluoroalkenes with electrophilic sulfur/halogen reagents and various *O*- or *N*-nucleophiles affords diverse multifunctionalized thio- and halodifluoromethylated compounds. This reaction features a relatively broad substrate scope, good functional group tolerance, and mild reaction conditions.



Due to the unique effect of the fluorine atom,[1] organofluorine compounds have wide applications in pharmaceuticals, agrichemicals, and materials science.[2] Over the past decade, tremendous efforts have been devoted to their synthesis.[3] Particularly, much attention has been paid to the preparation of thio- and halodifluoromethylated compounds because of the following additional advantages:[3b,c,4] (i) the CF_2 moiety is known to be isosteric of ethereal oxygen atom;[5] (ii) the introduction of sulfur- and halogen-containing groups can further modify the properties of the difluoromethylated molecules, which could lead to bioactive studies of the relevant molecules to benefit drug discovery, such as the selected examples of bioactive compounds **A**–**E** shown in Figure 1;[6] (iii) the CF_2S and CF_2X (X = Cl, Br, I) moieties increase the convertibility of the molecules to provide opportunities for the construction of various difluoromethylated compounds.[3b−d,4a,7,8]

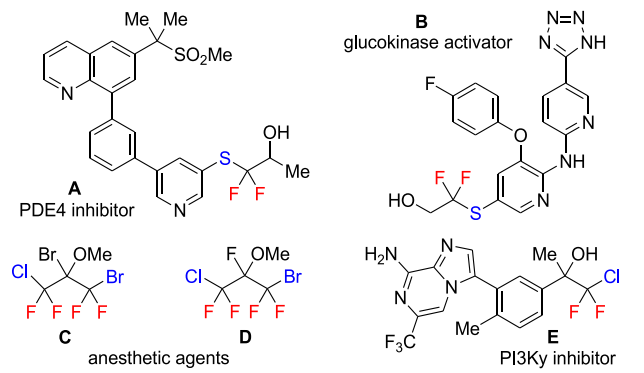
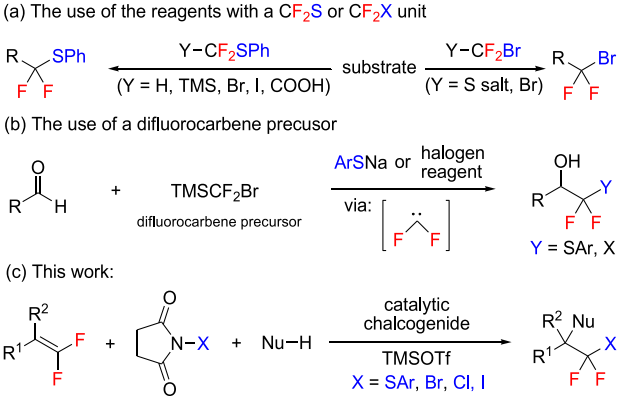


Figure 1. Selected examples of bioactive compounds with a CF_2S or CF_2X (X = Cl, Br, I) unit.

As a result, many methods have been developed to prepare difluoroalkyl sulfides and halides. These methods are mainly based on the use of CF_2S- and CF_2X-containing reagents such as $PhSCF_2-Y$ (Y = H, TMS, Br, I, COOH)[4a−c,9] and $BrCF_2-Y$ (Y = sulfur salt, Br)[10] via a nucleophilic substitution, addition, or radical process (Scheme 1a). Besides, the difluoroalkyl sulfides and halides can be achieved by using a difluorocarbene precursor to react with aldehydes in the

Scheme 1. Different Strategies for the Synthesis of Difluoroalkyl Sulfides and Halides



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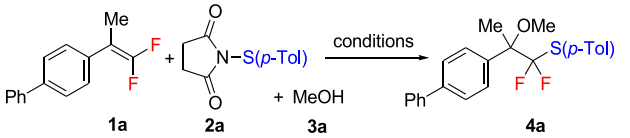
presence of nucleophilic sulfur source and nucleophilic halogen reagents, respectively (Scheme 1b).[4d,11] For example, Dilman demonstrated the reactions of aldehydes with $TMSCF_2Br$ as a difluorocarbene precursor and halide salts as a nucleophilic component to generate hydroxylated bromo- and iododifluoromethylation products.[11b,c] The authors also found that aminated halodifluoromethylation compounds could be formed under the similar conditions when secondary amines were added to the reactions to produce an iminium salt as intermediate.[11a] Furthermore, Hu reported the synthesis of thiodifluoromethylation compounds in a similar fashion.[11d] Despite these great advances, the formation of thio- and halodifluoromethylated compounds is dependent on the utilization of specific fluorinating reagents, which results in the limitations of the generality of the developed methods and substrate scope to some extent. To avoid these limitations, the development of new methods to meet the synthetic requirements is a high desire.

Catalytic electrophilic difunctionalization of alkenes via an iranium ion intermediate has emerged as a powerful tool for the synthesis of a variety of compounds.[12] This transformation allows simultaneous installation of two functional groups across the double bond of alkenes to rapidly construct complex molecules in one step. In most catalytic electrophilic cases, electron-neutral and -rich alkenes were generally utilized. In contrast, catalytic electrophilic reactions of electron-deficient alkenes such as *gem*-difluoroalkenes have been rarely studied, presumably because of the inert nature of the carbon−carbon double bond caused by fluorine substituents. Only a few examples on intramolecular halocyclization have been described.[13] To date, catalytic intermolecular electrophilic thiolation and halogenation of *gem*-difluoroalkenes have not been developed. In recent years, chalcogenide catalysis provides a good fashion for the electrophilic difunctionalization of alkenes. In this context, chalcogenide-catalyzed electrophilic thiolation and halogenation of electron-neutral and -rich alkenes have been developed by others and us.[14−18] As a continuation of our interest in chalcogenide catalysis, we would like to use this catalysis to solve the issues of electrophilic functionalization of *gem*-difluoroalkenes. Herein, we report our discovery that intermolecular electrophilic oxy- and aminothiolation of *gem*-difluoroalkenes to access various difluoroalkyl sulfides are realized by selenide catalysis. Additionally, electrophilic halofunctionalization of *gem*-difluoroalkenes to give difluoroalkyl halides also proceeds well by sulfide catalysis (Scheme 1c).

We initiated our study on the thiofunctionalization of *gem*-difluoroalkenes by using 4-(1,1-difluoroprop-1-en-2-yl)-1,1′-biphenyl (**1a**) as a model substrate, *N*-(*p*-tolylthio)succinimide (**2a**) as electrophilic sulfur reagent, and MeOH (**3a**) as the third component (Table 1). Different reaction conditions were screened. When the reaction was carried out in the presence of PhSePh (10 mol %) as catalyst, TfOH as acid additive in CH_2Cl_2 at −20 °C, the desired product **4a** was formed in 90% NMR yield (entry 1). Other Lewis acids such as $BF_3{\cdot}Et_2O$, TMSOTf, TESOTf, TBSOTf, and Tf_2NH were tested as well (entries 2−6). TMSOTf was found to give the best result. More electron-rich selenides as catalysts were less effective than PhSePh (entries 7−8). In contrast, sulfide was a much less effective catalyst for the reaction (entry 9). Other solvents such as $ClCH_2CH_2Cl$ and $CHCl_3$ were slightly less effective than CH_2Cl_2 (entries 10 and 11). However, the nonpolar solvent toluene resulted in a moderate yield (entry 12).

Table 1. Screening of Reaction Conditions[a]



1a 2a 3a 4a

entry	cat.	acid	solvent	temp (°C)	yield (%)[b]
1	PhSePh	TfOH	CH_2Cl_2	−20	90
2	PhSePh	$BF_3{\cdot}Et_2O$	CH_2Cl_2	−20	94
3	PhSePh	TMSOTf	CH_2Cl_2	−20	99
4	PhSePh	TESOTf	CH_2Cl_2	−20	92
5	PhSePh	TBSOTf	CH_2Cl_2	−20	92
6	PhSePh	Tf_2NH	CH_2Cl_2	−20	75
7	(4-$MeOC_6H_4$)SePh	TMSOTf	CH_2Cl_2	−20	55
8	(4-$MeOC_6H_4)_2Se$	TMSOTf	CH_2Cl_2	−20	53
9	PhSPh	TMSOTf	CH_2Cl_2	−20	45
10	PhSePh	TMSOTf	$ClCH_2CH_2Cl$	−20	92
11	PhSePh	TMSOTf	$CHCl_3$	−20	90
12	PhSePh	TMSOTf	toluene	−20	51
13	PhSePh	TMSOTf	CH_2Cl_2	0	85
14	PhSePh	TMSOTf	CH_2Cl_2	−40	54
15	–	TMSOTf	CH_2Cl_2	−20	44
16	PhSePh	–	CH_2Cl_2	−20	0

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **3a** (0.40 mmol), cat. (10 mol %), acid (2 equiv), solvent (2 mL), 12 h. [b]NMR yield using CH_2Br_2 as the internal standard.

Furthermore, the influence of reaction temperature was investigated. When the reaction temperature was elevated to 0 °C, the yield of the desired product **4a** decreased slightly (entry 13). Lowering the reaction temperature led to only a moderate yield (entry 14). It is noted that the desired product was generated in only 44% yield in the absence of chalcogenide catalyst, which indicated a significant role of the Lewis basic catalyst in this transformation (entry 15).[19] Without acid, the reaction did not occur (entry 16).

Having established the optimal conditions, we evaluated the scope of the reaction (Scheme 2). First, the influence of electron effect on the *gem*-difluoroalkene substrates was studied. When electron-donating and -withdrawing groups substituents such as *tert*-butyl, phenoxy, chloro, and bromo were placed at the *para* position of the phenyl ring on the *gem*-difluoroalkene, all the reactions underwent oxythiolation to give the desired products in good yields (**4b**−**4e**, 65−98%). The substituents, i.e., chloro and bromo, at the *meta* position of the phenyl ring had a negative impact on this transformation. To achieve the satisfactory yields of **4f** and **4g**, the amount of Lewis acid TMSOTf needed to be increased to 3 equiv. To our delight, electron-rich naphthyl-substituted *gem*-difluoroalkene still gave product **4h** in excellent yield (95%). When the *gem*-difluoroalkene with an *n*-propyl substituent instead of methyl group was utilized for the reaction, the desired product **4i** could be obtained in 93% yield. It is noted that trisubstituted *gem*-difluoroalkenes exhibited much lower reactivity in this oxythiolation, giving the corresponding product **4j** in only 41% yield under the same conditions. When dialky- and diaryl-substituted *gem*-difluoroalkenes were used as substrates, the reactions did not take place under the optimal conditions. Next, the scope of electrophilic sulfur reagents was explored. When the methyl substituent lied at the

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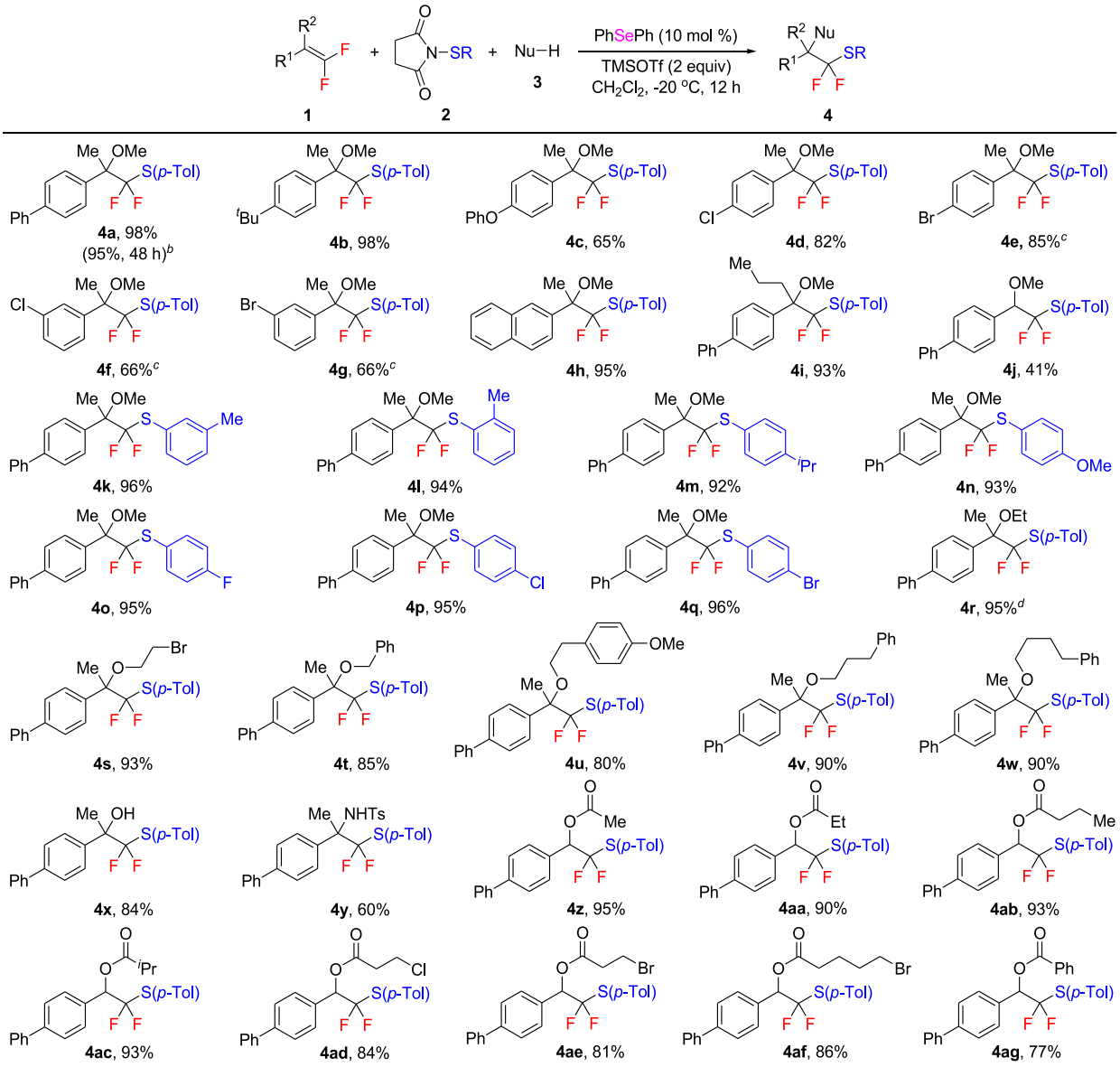
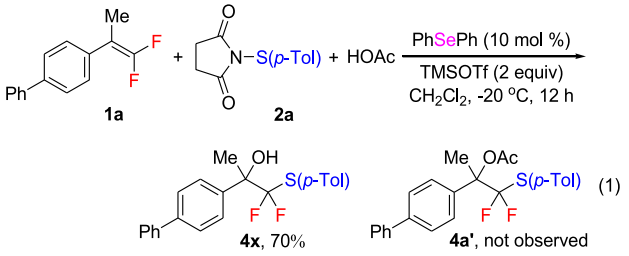
Scheme 2. Selenide-Catalyzed Intermolecular Thiofunctionalization of *gem*-Difluoroalkenes[a]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), **3** (0.80 mmol), PhSePh (10 mol %), TMSOTf (2 equiv), CH_2Cl_2 (4 mL), −20 °C, 12 h. [b]In 1 mmol scale for 48 h. [c]TMSOTf (3 equiv). [d]BF_3•Et_2O (2 equiv) instead of TMSOTf.

meta and *ortho* positions, the reactivities of the sulfur reagents remained almost same (**4k**, 96%; **4l**, 94%). The electron effect on the phenyl ring on the sulfur reagents had a slight influence on this transformation. When the substituents such as isopropyl, methoxyl, chloro, fluoro, and bromo were placed on the phenyl ring, the reactions gave the corresponding sulfides **4m**−**4q** in excellent yields (92−96%). Although arylthiolating reagents worked well under the optimal conditions, the alkylthiolating reagent proved to be incompetent to give no desired products. Then, this method was applied to thiofunctionalization of *gem*-difluoroalkenes with various different types of nucleophiles. The reactions with EtOH and 2-bromoethanol proceeded smoothly to afford the desired products in high yields (**4r**, 95%; **4s**, 93%). Aryl-substituted alcohols with different alkyl chain length between the aryl group and the hydroxy group were also good reactants to afford the oxythiolation products **4t**−**4w** in 80−90% yields. It is worthy to note that water and $TsNH_2$ could act as nucleophiles to give the corresponding products under similar conditions (**4x**, 84%; **4y**, 60%). To our surprise, when the tetrasubstituted alkene such as **1a** was treated with HOAc as nucleophile, the hydroxylated product **4x** was formed instead of the desired product **4a′** possibly because the trace amount of water in solvent acted as reaction component (eq 1).



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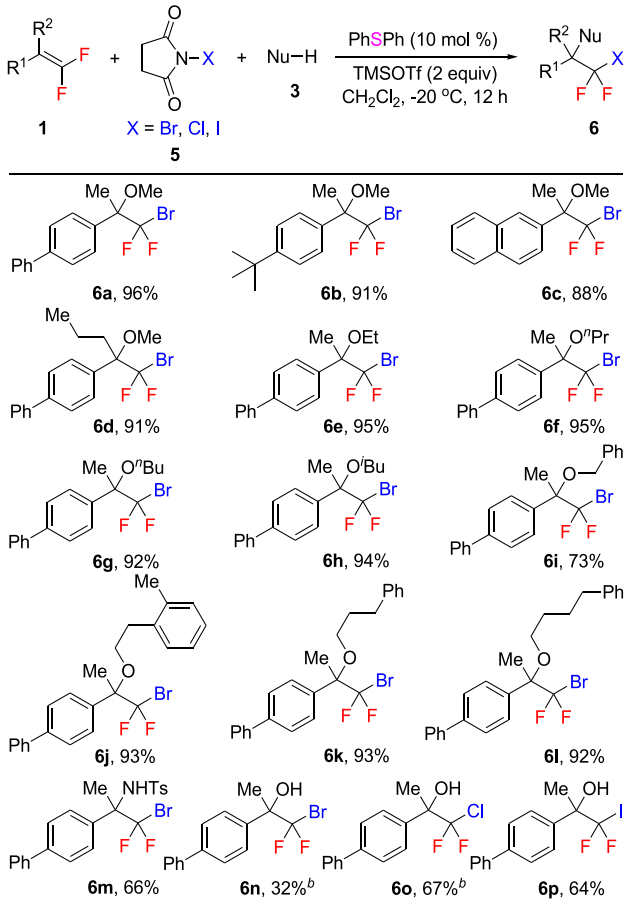
However, trisubstituted *gem*-difluoroalkenes could react with HOAc and other acids bearing a range of substituents such as bromo and chloro to give the corresponding products in high yields (**4z**−**4af**, 81−95%). Even if benzoic acid was used, the reaction still gave the desired product **4ag** in 77% yield. These results indicated that this method is general and suitable for a wide range of nucleophiles.

The previous studies on catalytic halofunctionalization of *gem*-difluoroalkenes focused on an intramolecular cyclization process.[13a−c] Encouraged by the success of the thiofunctionalization of *gem*-difluoroalkenes, we questioned whether chalcogenide catalysis was suitable for intermolecular electrophilic halofunctionalization of *gem*-difluoroalkenes. To test the possibility, *gem*-difluoroalkene **1a** was treated with commercially available *N*-bromosuccinimide (NBS, **5a**) as brominating reagent and MeOH (**3a**) as nucleophile. It was found that the desired product **6a** could be obtained in 96% yield under sulfide catalysis, but not selenide catalysis (see the Supporting Information for details). Under the same catalytic conditions, the reactions with other substrates worked well (Scheme 3). Different aryl-substituted *gem*-difluoroalkenes such as the ones with *para*-substituted phenyl and naphthyl groups underwent oxybromination to give the products in high yields (**6b**, 91%; **6c**, 88%). A range of alcohols with a bulky group or a long alkyl chain gave the corresponding products in high yields (**6e**−**6l**, 73−95%). When $TsNH_2$ was utilized as nucleophile, the aminobromination proceeded smoothly to generate in good yield (**6m**, 66%). It is noteworthy that H_2O could serve as a nucleophile to give the halogenated products (**6n**−**6p**, 32−67%). In the hydroxybromination and -chlorination reactions, lowering the reaction temperature to −40 °C gave the best result. These results revealed the generality of this method once again.

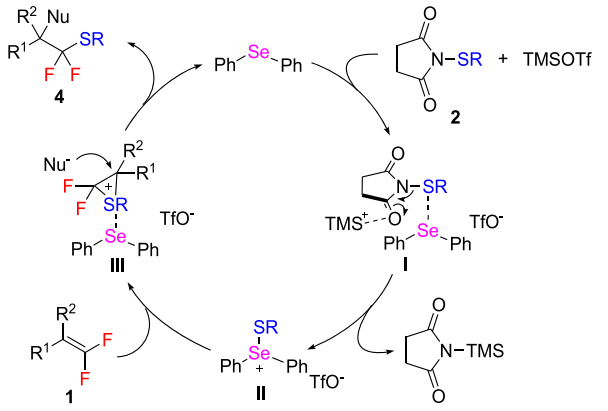
Scheme 3. Sulfide-Catalyzed Intermolecular Halofunctionalization of *gem*-Difluoroalkenes[a]



[a]Reaction conditions: **1** (0.20 mmol), **5** (0.30 mmol), **3** (0.80 mmol), PhSPh (10 mol %), TMSOTf (2 equiv), CH_2Cl_2 (4 mL), −20 °C, 12 h. [b]−40 °C.

A proposed mechanism for selenide-catalyzed intermolecular thiofunctionalization of *gem*-difluoroalkenes is depicted in Scheme 4 based on the known studies.[18a,l] Catalyst PhSePh

Scheme 4. Proposed Mechanism



initially reacts with electrophilic sulfur reagent **2** to generate ion intermediate **II** through transition state **I** in the presence of TMSOTf. Then the reaction of **II** and *gem*-difluoroalkenes **1** gives thiiranium ion intermediate **III**. Subsequent nucleophilic attack of nucleophiles toward thiiranium ion **III** affords the desired product **4** and regenerates the catalyst. The corresponding halofunctionalization proceeds in a similar manner, which involves the formation of haliranium ion intermediate under the assistance of the Lewis basic PhSPh catalyst and TMSOTf.

In summary, we have developed an efficient chalcogenide-catalyzed intermolecular electrophilic thio- and halofunctionalization of *gem*-difluoroalkenes. This protocol allows the reaction of *gem*-difluoroalkenes with different electrophilic sulfur and halogen reagents and various nucleophiles, demonstrating a powerful ability for the construction of a variety of diverse functionalized difluoroalkyl sulfides and halides. In this transformation, various functional groups were well tolerated under the conditions. This work represents the first example of electrophilic thiolation of electron-deficient *gem*-difluoroalkenes. The asymmetric version is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02784.

Experimental details, characterization data, and NMR spectra of new compounds (PDF)

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AUTHOR INFORMATION

Corresponding Author

Xiaodan Zhao − *Institute of Organic Chemistry & MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry, Sun Yat-Sen University, Guangzhou 510275, PR China;* orcid.org/0000-0002-2135-5121; Email: zhaoxd3@mail.sysu.edu.cn

Authors

Quanbin Jiang − *Institute of Organic Chemistry & MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry, Sun Yat-Sen University, Guangzhou 510275, PR China;* orcid.org/0000-0002-0321-2688

Yaoyu Liang − *Institute of Organic Chemistry & MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry, Sun Yat-Sen University, Guangzhou 510275, PR China*

Yuanyuan Zhang − *Institute of Organic Chemistry & MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry, Sun Yat-Sen University, Guangzhou 510275, PR China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02784

Notes

The authors declare no competing financial interest.

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