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Synthesis and ^{18}F Labeling of Alkenyl Sulfonyl Fluorides via an Unconventional Elimination Pathway

Wei Zhang,[⊥] Xiaoyun Deng,[⊥] Feng-Xu Zhang,[⊥] Jin-Hong Lin, Ji-Chang Xiao,* and Steven H. Liang*

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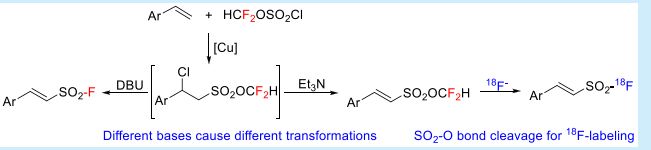
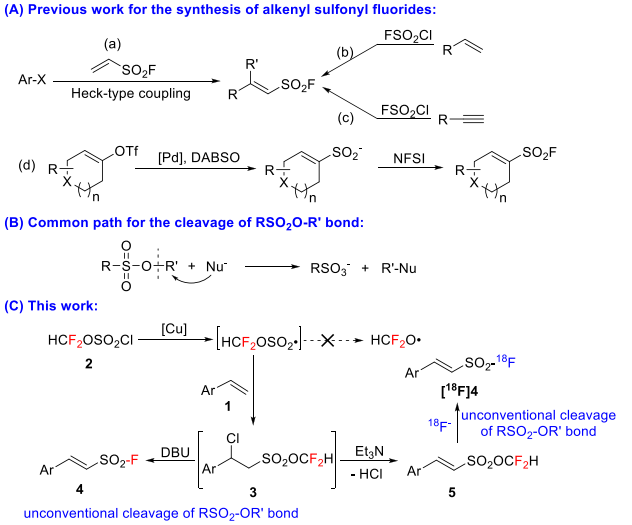
ABSTRACT: A successful Cu-catalyzed addition of both Cl and SO_2OCF_2H groups into alkenes allows us to discover the unusual reactivity of the SO_2OCF_2H group. As opposed to common sulfonic esters (RSO_2-O-R′), in which the R′ group is highly electrophilic, the SO_2 moiety demonstrates higher electrophilicity in RSO_2-OCF_2H. The unexpected reactivity is further developed not only as a synthetic tool for well-functionalized alkenyl sulfonyl fluorides but also for the first ^{18}F labeling of alkenyl sulfonyl fluorides.



Since Sharpless et al. expanded their repertoire of click chemistry[1] to sulfur(VI) fluoride exchange (SuFEx) in 2014,[2] sulfonyl fluorides have found widespread applications in various disciplines, such as organic synthesis,[3] polymer chemistry,[4] drug discovery,[5] and PET imaging.[6] Alkenyl sulfonyl fluorides, in which the double bond could be further functionalized,[7] have received more attention, and a number of synthetic methods have been developed. After the report of Sharpless on fluorosulfonylvinylation of diazonium salts with ethenesulfonyl fluoride (ESF),[7a] many fluorosulfonylvinylation methods have appeared, such as fluorosulfonylvinylation of C−H bonds,[8] aryl iodides,[9] and organic boronic acids (Scheme 1A, method a).[10] Recently, the Liao group used FSO_2Cl as a FSO_2• radical equivalent to achieve fluorosulfonylation of alkenes (Scheme 1A, method b)[11] and chloro-fluorosulfonylation of alkynes (Scheme 1A, method c).[12] Willis et al. developed a two-step process, namely, a Pd-catalyzed coupling followed by oxidative fluorination, to obtain cyclic alkenylsulfonyl fluorides (Scheme 1A, method d).[13] Despite these outstanding accomplishments, the necessity of expensive transition metals in the methods mentioned above may stimulate further efforts for the development of novel synthetic approaches.

Scheme 1. Synthesis of Alkenyl Sulfonyl Fluoride and Proposed ^{18}F Labeling of Alkenyl Sulfonyl Fluorides



It has been reported that CF_3SO_2Cl[14] and HCF_2SO_2Cl[15] can generate CF_3• and HCF_2• radicals, respectively, under reductive conditions via desulfonylation, and thus, these two sulfonyl chlorides have been successfully used as radical chloro-trifluoromethylation and chloro-difluoromethylation reagents, respectively. On the basis of these achievements, we postulate that HCF_2OSO_2Cl may be reduced to the HCF_2O• radical and therefore can serve as a new difluoromethoxylation reagent. To our delight, HCF_2OSO_2Cl can indeed be reduced by economical Cu catalysts, but desulfonylation failed to occur. The radical generated was HCF_2OSO_2•, not HCF_2O•, probably due to the high strength of the SO_2-OCF_2H bond. Therefore, Cu-catalyzed cross addition of both Cl and SO_2OCF_2H groups to alkenes was achieved to afford **3** (Scheme 1C). Compound **3** would unavoidably undergo partial dehydrochlorination to provide **5** during isolation by flash column chromatography, but the similar polarity between product **3** and dehydrochlorination byproduct **5** made the

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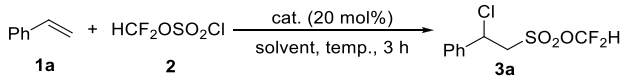
isolation of **3** very challenging, which diminished the utility of this methodology. Interestingly, during the optimization, we discovered two distinct and complete elimination processes triggered by different bases. In specific, the SO_2-OCF_2H bond remained intact and only dehydrochlorination occurred when using Et_3N as a base. To our surprise, the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) instead of Et_3N led to the cleavage of the SO_2-OCF_2H bond, and alkenyl sulfonyl fluoride (**4**) was produced as the final product. Mechanistically, DBU is more nucleophilic than Et_3N and thus can attack the electrophilic SO_2-OCF_2H moiety. Often alkyl groups (R′) in sulfonic esters (RSO_2-O-R′) are quite electrophilic, and nucleophiles would readily attack the R′ moiety to cleave the O−R′ bond (Scheme 1B).[16] In the case of the SO_2-OCF_2H moiety, DBU, as a nucleophile, preferred to attack the SO_2 group rather than CF_2H group, demonstrating the unexpected reactivity of SO_2-OCF_2H compared with common sulfonic esters (Scheme 1C).[17] This unusual reactivity may be attributed to the electronic repulsion between the nucleophiles and fluorine lone pairs. Herein, we take advantage of the unexpected facile cleavage of the SO_2-OCF_2H bond to provide well-functionalized alkenyl sulfonyl fluorides and demonstrate its synthetic utility. Because a suitable nucleophile can easily break the SO_2-OCF_2H bond, we further investigate the feasibility of ^{18}F labeling by using the $^{18}F^-$ anion as a nucleophile, which provides ^{18}F-labeled alkenyl sulfonyl fluoride as a synthetic prosthetic group for further functionalization.

HCF_2OSO_2Cl, exhibiting relative stability toward moisture, could be easily synthesized by reactions of $ClSO_3H$ with $TMSCF_3$ under neat conditions via difluorocarbene insertion (see the Supporting Information). Previously, we found that $CuCl_2$ could smoothly catalyze chloro-trifluoromethylation of alkenes with CF_3SO_2Cl.[18] $CuCl_2$ was therefore first used as a catalyst, and various reaction conditions using different solvents were examined (Table 1, entries 1−4). No desired product was observed in CH_3CN, DMF, or $ClCH_2CH_2Cl$ (entries 1−3). To our delight, a 58% yield was obtained by using 1,4-dioxane as the solvent (entry 4). After screening a variety of catalysts (entries 5−13), we found a Cu complex seemed to be more effective. In particular, $Cu(OTf)_2$ was a superior choice and the desired product was provided in 90% yield (entry 13). Furthermore, an almost quantitative yield was obtained by decreasing the reaction temperature from 140 to 80 °C (entry 14), but the yield was decreased when the temperature was further decreased (entry 15). Decreasing the loading of reagent **2** led to a lower yield (entry 16). The desired reaction was completely suppressed without the use of $Cu(OTf)_2$, reflecting the importance of this catalyst (entry 17).

The use of a radical clock (**1aa**) as a substrate gave a ring-opening product (**3aa**) (Scheme 2), suggesting that a radical mechanism is operative for the Cu-catalyzed cross addition reaction. Because $Cu(OTf)_2$ is a strong oxidant, it may be easily reduced to Cu^I in the reaction system. Cu^I can then catalyze the radical addition of HCF_2OSO_2Cl to the alkene.[18]

As shown in Scheme 3, compound **3a** can readily undergo dehydrochlorination in the presence of a base to give alkenyl product **5a**; however, the choice of the base is critical for the generation of two distinct elimination products. In specific, product **5a** was generated by using Et_3N as a base (path A), and alkenyl sulfonyl fluoride **4a** was obtained in the presence of DBU (path B). While both Et_3N and DBU are basic enough for dehydrochlorination, the formation of two different

Table 1. Optimization of the Reaction Conditions[a]

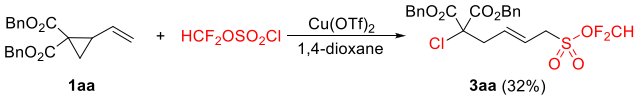


1a 2 3a

entry	catalyst (20 mol %)	solvent	temp (°C)	yield (%)[b]
1	$CuCl_2$	CH_3CN	140	ND
2	$CuCl_2$	DMF	140	ND
3	$CuCl_2$	DCE	140	ND
4	$CuCl_2$	1,4-dioxane	140	58
5	CuCl	1,4-dioxane	140	58
6	$MnCl_2$	1,4-dioxane	140	trace
7	$FeCl_2$	1,4-dioxane	140	33
8	$CoCl_2$	1,4-dioxane	140	trace
9	$NiCl_2$·DME	1,4-dioxane	140	trace
10	$ZnCl_2$	1,4-dioxane	140	trace
11	$Cu(acac)_2$	1,4-dioxane	140	54
12	$Cu(OAc)_2·H_2O$	1,4-dioxane	140	61
13	$Cu(OTf)_2$	1,4-dioxane	140	90
14	$Cu(OTf)_2$	1,4-dioxane	80	99
15	$Cu(OTf)_2$	1,4-dioxane	70	79
16[c]	$Cu(OTf)_2$	1,4-dioxane	80	92
17	–	1,4-dioxane	80	ND

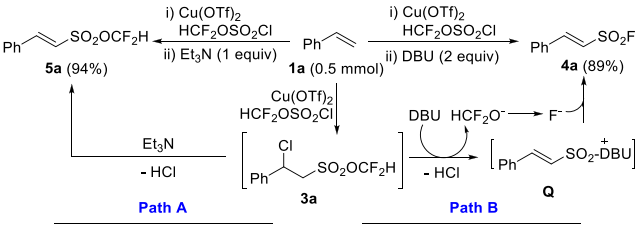
[a]Reaction conditions: **1a** (0.5 mmol), **2** (2.0 equiv), solvent (3.0 mL), under N_2. ND = not detected; DCE = 1,2-dichloroethane. [b]Yields determined by ^{19}F NMR spectroscopy. [c]With 1.5 equiv of **2**.

Scheme 2. Evidence for Radical Cross Addition



1aa 3aa (32%)

Scheme 3. Dehydrochlorination of Compound 3a via Two Distinct Mechanisms



products is probably attributed to their different nucleophilicity. Compared with Et_3N, DBU is a stronger nucleophile, and thus, DBU−OCF_2H exchange would occur to produce intermediate **Q** and the HCF_2O^- anion in path B. The decomposition of the HCF_2O^- anion subsequently releases the F^- anion, which attacks intermediate **Q** to provide alkenyl sulfonyl fluoride **4a**. In these two pathways, SO_2-OCF_2H demonstrated a good balance between reactivity and stability. The formation of product **4a** implies that the direct attack of nucleophiles at the HCF_2 group was blocked, a phenomenon that is in sharp contrast to common alkyl sulfonates.

With the optimal conditions (Table 1, entry 14, and then DBU) in hand, we next investigated the substrate scope for the synthesis of alkenyl sulfonyl fluorides from alkenes. As shown in Scheme 4, this process could be extended to a wide range of aryl alkenes. Electron-rich, -neutral, and -deficient aryl alkenes were all converted smoothly to give the desired alkenyl sulfonyl fluorides in moderate to excellent yields. Various functional

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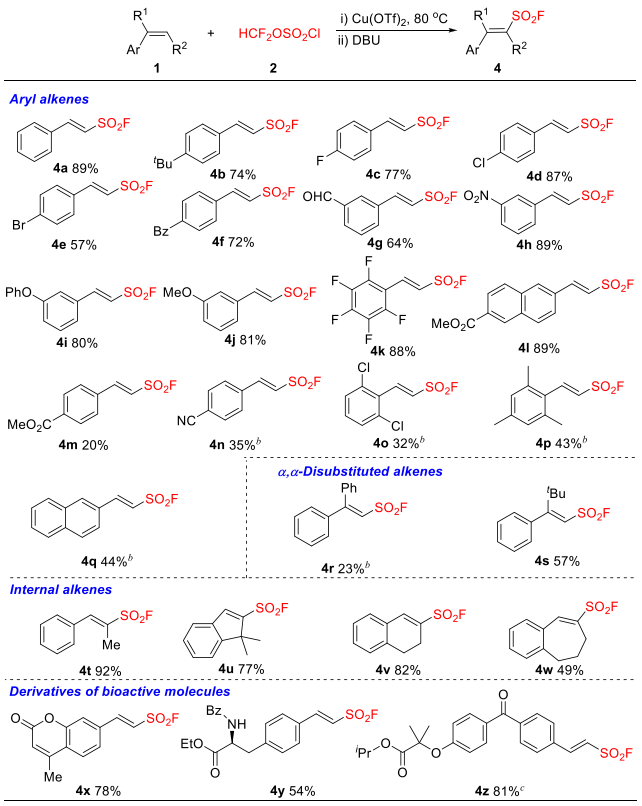
Scheme 4. Synthesis of Alkenyl Sulfonyl Fluorides[a]

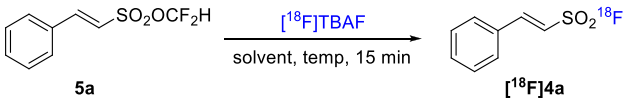


[a]Isolated yields. Reaction conditions: substrate **1** (0.5 mmol), **2** (2.0 equiv), and $Cu(OTf)_2$ (20 mol %) in 1,4-dioxane (3.0 mL) at 80 °C overnight under N_2. After the reaction had reached completion, the mixture was filtered, and the filtrate was concentrated. The residue was dissolved in DCM (3 mL), and DBU (1.0 mmol) was added. The mixture was stirred at room temperature for 1 h. [b]In the cases of **4n**–**4r**, in the first step, 1 equiv of $Cu(OTf)_2$ was used, 4 Å MS (50 mg) was added, and the reaction temperature was 100 °C. [c]The reaction was performed on a 10 mmol scale.

groups could be tolerated, such as halides, ester, cyano, nitro, aldehyde, and amides (**4a**–**4s**). Internal alkenes were also reactive toward this transformation (**4t**–**4w**). An amino acid derivative (**4y**) and a fenofibrate derivative (**4z**), which may find utility in biological chemistry, were obtained in good yields (54–81%). Compared with aryl alkenes, alkyl alkenes showed lower reactivity, and a complicated mixture was generated under these conditions.

The formation of alkenyl sulfonyl fluorides using DBU as a base clearly indicated that OCF_2H can act as a good leaving group. Therefore, it was reasonable to hypothesize ^{18}F labeling of alkenyl sulfonyl fluorides may be achieved by a ^{18}F–HCF_2O exchange. The radiofluorination conditions were then screened by using compound **5a** as the model compound (Table 2). Direct ^{18}F fluorination occurred to give 68% radiochemical conversion (RCC) by using dried [^{18}F]TBAF generated from tetrabutylammonium triflate (TBAOTf) and aqueous [^{18}F]-fluoride (entry 1). The RCC was increased to 73% when ^{t}BuOH and DMF were used as a mixed solvent (Table 2, entry 2). While decreasing the loading of TBAOTf could improve the RCC to 91% (entry 3), an increased amount of TBAOTf and decreasing the temperature led to lower RCCs (Table 2, entries 4 and 5). Although the ^{18}F labeling product could be obtained within 5 or 10 min of reaction time (entries 6 and 7),

Table 2. Optimization of Radiofluorination Conditions[a]



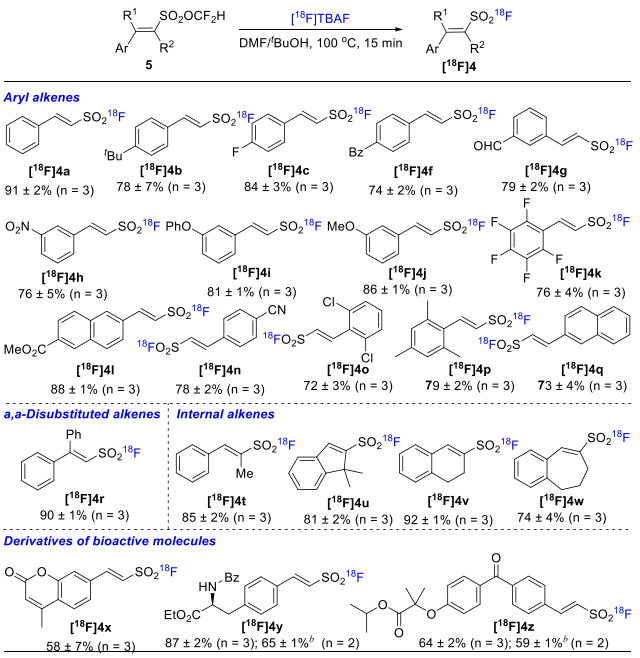
entry	TBAOTf (mg)	solvent (mL)	temp (°C)	time (min)	RCC (%)[b]
1	2	DMF (0.4)	100	15	68 ± 6
2	2	DMF/^{t}BuOH (0.1/0.3)	100	15	73 ± 2
3	1	DMF/^{t}BuOH (0.1/0.3)	100	15	91 ± 2
4	4	DMF/^{t}BuOH (0.1/0.3)	100	15	76 ± 5
5	1	DMF/^{t}BuOH (0.1/0.3)	60	15	82 ± 1
6	2	DMF/^{t}BuOH (0.1/0.3)	100	10	76 ± 2
7	2	DMF/^{t}BuOH (0.1/0.3)	100	5	68 ± 1

[a]Reaction conditions: precursor (8.5 μmol) in solvent (0.4 mL). [b]Radiochemical conversions and product identity were determined by radio-TLC and radio-HPLC, respectively; n = 3.

RCCs were evidently lower than that obtained within 15 min. After the reaction conditions had been screened in a detailed manner (see Table S1), the optimal ^{18}F labeling conditions were identified (entry 3).

As shown in Scheme 5, the ^{18}F labeling process was compatible with a broad range of substrates and tolerated with a variety of functional groups. Moreover, electron-rich and -deficient substituents on aromatic rings did not influence the radiochemical yields. As a proof of concept, ^{18}F-labeled products [^{18}F]**4y** and [^{18}F]**4z** were isolated and purified by semipreparative HPLC. The radiolabeled compounds were

Scheme 5. ^{18}F Labeling of Alkenyl Sulfonyl Fluorides[a]



[a]Radiochemical conversions and product identity were determined by radio-TLC and radio-HPLC, respectively. [b]Yields of isolated products in the case of [^{18}F]**4y** and [^{18}F]**4z**.

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produced in an average of 59−65% decay-corrected radiochemical yields based on starting [^{18}F]fluoride at the end of synthesis (60 min synthesis time) with >99% radiochemical purity (n = 3). The molar activities were 0.56 and 1.38 mCi/μmol, respectively (20.7 and 51.1 MBq/μmol, respectively), which is consistent with their exchange mechanism.

Currently, only a handful of methods have been reported for accessing RSO_2-^{18}F. As fluorine−chlorine exchange is a thermodynamically favorable reaction, ^{18}F−Cl exchange has served as a good approach for obtaining ^{18}F-labeled aryl sulfonyl fluorides.[6b,19] Hong et al. used a nucleophilic radiofluorination method and an ^{18}F−^{19}F isotopic exchange method to synthesize aryl fluorosulfates[20] and sulfamoyl fluorides,[21] respectively. Recently, Wu, Yang, Sharpless, and co-workers developed an ultrafast process for radiosynthesizing aryl [^{18}F]fluorosulfates and showcased the potential PET imaging application of an ^{18}F−S-based probe.[22] Compared with these recent developments in novel ^{18}F−sulfur bond formation, our work represents the first example of ^{18}F labeling of alkenyl sulfonyl fluorides, which not only can function as ^{18}F-labeling reagents[3a,23] but also may serve as ideal probes for PET imaging with high-density biological targets in oncology applications.[6]

In summary, initial unsuccessful attempts at Cl/HCF_2O incorporation allowed us to discover an unexpected reactivity of sulfonic esters, RSO_2−OCF_2H. In sharp contrast to common sulfonic esters (RSO_2−OR′), in which the R′ group is much more electrophilic than the SO_2 group, SO_2−OCF_2H ester showed reversed reactivity. Nucleophiles prefer to attack SO_2 rather than CF_2H. As a result, the unusual reactivity permits the convenient synthesis and the first ^{18}F labeling of alkenyl sulfonyl fluorides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02091.

Materials and methods, experimental procedures, radiochemical data, and ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR, and MS data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Ji-Chang Xiao − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 200032 Shanghai, China;* orcid.org/0000-0001-8881-1796; Email: jchxiao@sioc.ac.cn

Steven H. Liang − *Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital, and Department of Radiology, Harvard Medical School, Boston, Massachusetts 02114, United States;* orcid.org/0000-0003-1413-6315; Email: liang.steven@mgh.harvard.edu

Authors

Wei Zhang − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 200032 Shanghai, China*

Xiaoyun Deng − *Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital, and Department of Radiology, Harvard Medical School, Boston, Massachusetts 02114, United States; Department of Nuclear Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430030 Wuhan, China*

Feng-Xu Zhang − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 200032 Shanghai, China*

Jin-Hong Lin − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 200032 Shanghai, China; Department of Chemistry, Innovative Drug Research Center, Shanghai University, 200444 Shanghai, China;* orcid.org/0000-0002-7000-9540

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c02091

Author Contributions

⊥W.Z., X.D., and F.-X.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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