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Palladium-Catalyzed Fluoroalkylation via C(sp^3)−S Bond Cleavage of Vinylsulfonium Salts

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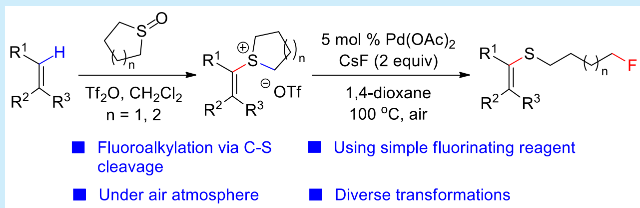
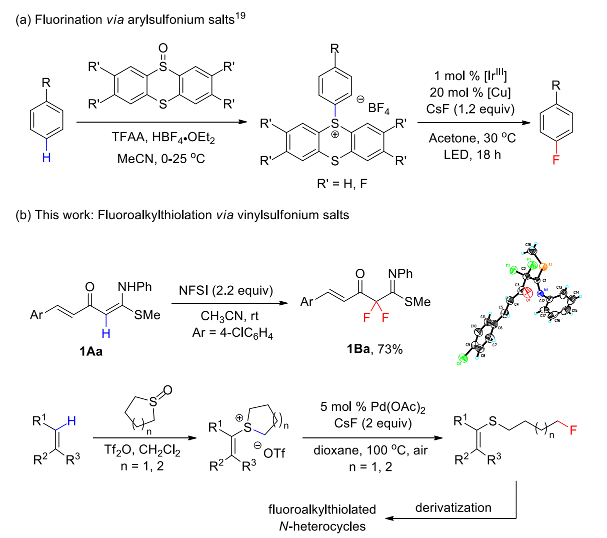
ABSTRACT: An interrupted Pummerer/palladium-catalyzed fluoro-alkylation strategy was developed for alkenyl C−H fluoroalkylthiolation. Palladium-catalyzed ring-opening fluoroalkylation via aliphatic C−S bond cleavage of the vinylsulfonium salts efficiently afforded fluoroalkylthiolated alkene derivatives from readily available alkene substrates and CsF. The protocol features broad substrate scopes and good functional group tolerance under an air atmosphere. The practicability of the synthetic method was demonstrated by transforming the multisubstituted alkene products to diverse fluoroalkylthiolated *N*-heterocycles.



Fluorine has been known to exist in many important chemicals.[1] By incorporating a fluorine atom or a fluoroalkyl group at a specific position in the candidate molecules, it is possible to fine-tune the pharmacological and pharmacokinetic properties of the drug candidates. Among the documented fluoroalkyl groups, fluoroalkylthio groups have been paid considerable attention due to their tunable lipophilicity, binding affinity, metabolic stability, and specific electronic properties.[2] Biologically active fluoroalkylthio motifs can be used as the key structural units for the construction of pharmaceutical agents such as M2 muscarinic receptor agonist,[3] 5-HT2c receptor,[4] and the inhibitor of cartilage matrix degradation.[5] In the early days, harsh fluorinating reagents were used to prepare fluoroalkylated compounds.[6] Because these reagents are potentially explosive, highly moisture-sensitive, and toxic, continuous efforts have been made to develop simple and green fluorination methods.[7] A few fluorination methods have been reported for directly functionalizing aliphatic C−H bonds.[8] In this regard, benzylic C−H[9] and those positioned α to a carbonyl group[10] can be fluorinated under relatively mild conditions. Decarboxylative fluorination has also been applied to construct a C(sp^3)−F bond under radical or transition-metal catalysis conditions.[11] Recently, the difunctionalization of alkenes by fluorinating reagents has been paid much attention to access fluoroalkylated compounds.[12] The ring-opening fluorination of carbocycles has opened another route for the same purpose.[13−16] Arylsulfonium salts have recently been employed as useful coupling partners not only in light of their accessibility from simple arenes but also due to their versatility for many carbon−carbon and carbon−heteroatom bond formation reactions.[17,18] Notably, aryl thianthrenium and dibenzothiophene sulfonium salts have been successfully used for the site-selective fluorination of arenes (Scheme 1a);[19] however, vinylsulfonium salts have been paid much less attention due to the multiple reactivities of alkenyl moieties compared with their aryl analogs.[20]

During the ongoing investigation of polar alkenes, we became interested in the regio- and stereoselective con-

Scheme 1. Fluoroalkylation Strategies



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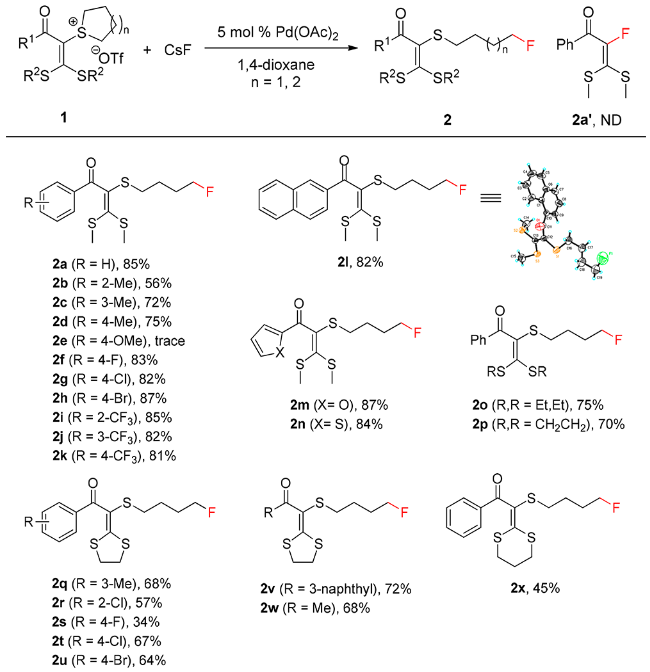
struction of multifunctionalized alkenes. In an attempt to conduct the vinylic C−H fluorination of α-alkenoyl ketene *N*,*S*-acetal **1Aa** with *N*-fluorobenzenesulfonimide (NFSI),[21] we found that the vinylic C−H bond could be formally difluorinated to form **1Ba** (73%) (Scheme 1b). The use of α-aroyl analogs of **1Aa** led to similar results (see the Supporting Information (SI) for details), but its di(methylthio)-substituted *S*,*S*-acetal analog did not react under the same conditions. Thus we envisioned that vinylic C−H fluorination might be realized via vinylsulfonium salts in a fashion similar to that of arylsulfonium salts.[19] Unexpectedly, the reaction of a vinylsulfonium salt with CsF under palladium catalysis did not form the desired vinylic C−F bond through the cleavage of the vinylic C−S bond; instead, it underwent a fluoroalkylation process by cleavage of an aliphatic C−S bond. It has been known that *S*-alkyl tetrahydro-1*H*-thiophen-1-ium salts and analogs can undergo ring-opening reactions with nucleophiles such as thiolates, azide, halogens, amines, and so on.[22] Herein we disclose an interrupted Pummerer/palladium-catalyzed fluoroalkylation strategy for vinylic C−H fluoroalkylthiolation via vinylsulfonium salts (Scheme 1b).

Initially, the reaction of 1-(1,1-bis(methylthio)-3-oxo-3-phenyl-prop-1-en-2-yl)tetrahydro-1*H*-thiophen-1-ium trifluoromethanesulfonate (**1a**) with CsF was conducted to optimize the reaction conditions for the formation of 2-((4-fluorobutyl)thio)-3,3-bis(methylthio)-1-phenylprop-2-en-1-one (**2a**). Vinylsulfonium salt **1a** was conveniently prepared from the readily available alkene by the interrupted Pummerer reaction.[18−20] (See the SI for details.) The reaction conditions were optimized to **1a**/CsF 1:2 (molar ratio), 5 mol % $Pd(OAc)_2$ as the catalyst, 1,4-dioxane as the solvent, 100 °C, 12 h under an air atmosphere, giving the desired product **2a** in 85% isolated yield. The use of pyridine·HF and NFSI soluble in organic solvents could not result in **2a**. The phase-transfer catalysts TEBAC (triethyl benzyl ammonium chloride) and 18-*crown*-6 remarkably diminished the reaction efficiency in the absence of the palladium catalyst, suggesting that the reaction does not merely proceed via a fluoride-promoted nucleophilic ring-opening pathway and the palladium catalysis plays a crucial role (Table S1). It is noteworthy that alkenyl fluoride **2a′** was not detected in the reaction mixture by ^{19}F NMR analysis.

Under the optimal conditions, the scope of vinylsulfonium salts **1** generated from di(alkylthio)-substituted alkenes, that is, ketene dithioacetals, was explored (Scheme 2). They could exhibit diverse reactivity to form the fluoroalkylation products of type **2** in good to excellent yields. An obvious steric effect was observed for *ortho*-methyl-substituted α-benzoyl vinylsulfonium salts (**1b**−**1d**), and their reaction with CsF afforded products **2b**−**2d** (56−75%). Somehow, the α-(4-methoxy)-benzoy-substituted substrate did not react to form the desired product **2e**. Halogens (F, Cl, and Br) and a CF_3 group on the α-benzoyl moiety did not show an obvious substituent effect, and the reaction formed products **2f**−**2k** in 81−87% yields. α-(2-Naphthoyl) and α-heteroaroyl (2-furoyl or 2-thienoyl)-substituted vinylsulfonium salts also reacted well to produce **2l**−**2n** in 82−87% yields. Di(ethylthio)-substituted vinylsulfonium salt (**1o**) reacted with CsF less efficiently than its di(methylthio) analog **1a**, yielding **2o** in 75% yield. In a similar fashion, cyclic five-membered alkyldithio-substituted vinylsulfonium salts **1p**−**1r**, **1t**, and **1u** reacted to give the corresponding products **2p**−**2r**, **2t**, and **2u** (57−70%), whereas the 4-F substituent on the α-benzoyl moiety of **1s** obviously

Scheme 2. Scope of Sulfonium Salts of Ketene Dithioacetals (1)[a]



[a]Conditions: **1** (0.30 mmol), CsF (0.60 mmol), $Pd(OAc)_2$ (0.015 mmol), dioxane (2 mL), air, 100 °C, 12 h. Yields refer to isolated products.

reduced the yield of **2s** to 34%. Cycloalkyldithio-substituted α-(2-aphthoyl) (**1v**) and α-acetyl (**1w**) vinylsulfonium salts also smoothly underwent the reaction with CsF, leading to **2v** and **2w** (68−72%). However, the six-membered cycloalkyldithio-substituted α-benzoyl vinylsulfonium salt **1x** enabled the formation of only **2x** in 45% yield, exhibiting a lower reactivity than its five-membered cycloalkyldithio-substituted analog **1a.**

It should be noted that the molecular structure of compound **2l** was confirmed by the X-ray single-crystal crystallographic determination. (See the SI for details.)

The substituent and size effects from the cycloalkylsulfonium ring in **1** were then explored (Scheme 3a−c). The reaction of the vinylsulfonium salts derived from 2-methyltetrahydro-1*H*-thiophene, that is, vinylsulfonium salts **1y** and **1z**, with CsF gave a mixture of two inseparable fluoroalkylation products **2y**/**2y′** (51%, 10:3) and **2z**/**2z′** (39%, 2:1) via different aliphatic C−S bond cleavages of the cycloalkylsulfonium ring, which reveals that the sterically hindered $C(sp^3)$−S bond is much easier to cleave. The vinylsulfonium salt of thietane **1z1** was decomposed quickly under the standard conditions. To our delight, the vinylsulfonium salts of tetrahydro-2*H*-thiopyran **1z2**−**1z4** efficiently reacted with CsF to produce the target products **2z2**−**2z4** (57−78%) bearing a C_5-fluoroalkylthio functionality, whereas products **2a**−**2z** contain a C_4-fluoroalkylthio chain. Unfortunately, further extension of the fluoroalkylthio chain failed because the vinylsulfonium salts corresponding to large aliphatic cyclic sulfoxides $C_nH_{2n}S{=}O$ ($n \geq 6$) could not be successfully prepared by the known methods. It is noteworthy that dibenzothiophene sulfonium salts of ketene dithioacetals **1** were not successfully prepared either due to the increased steric interaction in the interrupted Pummerer reaction.

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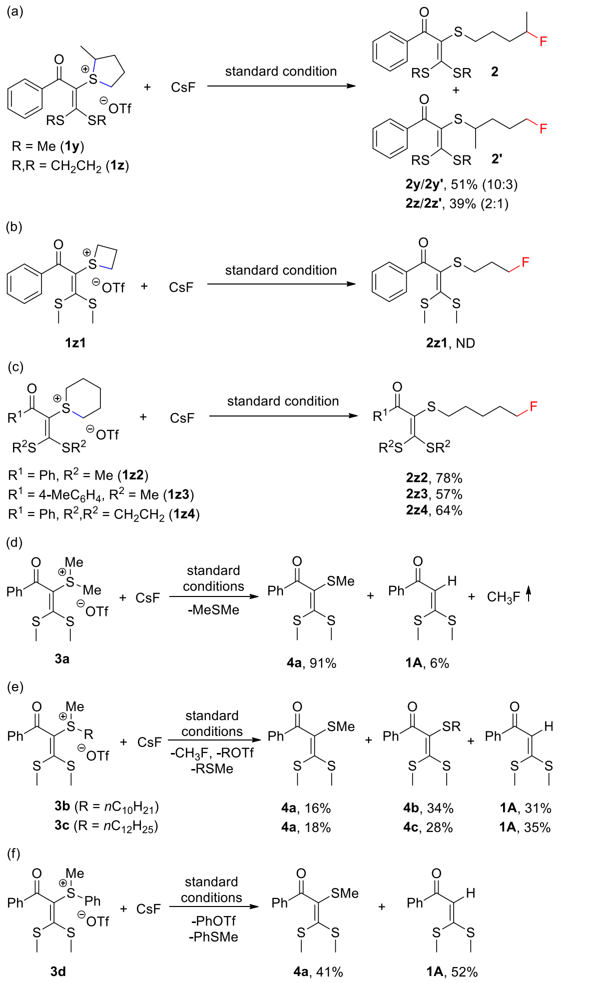
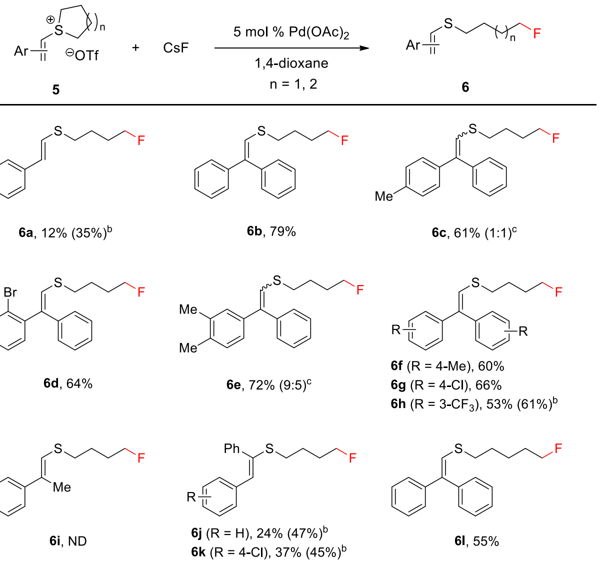
Scheme 3. Diversity of the Fluoroalkylation



The reactivity of open-chain vinylsulfonium salts of type **3** was comparatively investigated (Scheme 3d–f). Treatment of vinylsulfonium salt **3a** derived from α-benzoyl ketene di(methylthio)acetal (**1A**) and dimethylsulfoxide (DMSO) with CsF under the standard conditions gave methylthiolated alkene **4a** in 91% isolated yield with methyl fluoride formed as the major byproduct. The parent alkene **1A** was generated in 6% yield from the decomposition of the starting vinylsulfonium salt, which might be promoted by moisture in air or by water present in the sulfonium salt during its preparation. In the case of the vinylsulfonium salt of methyl decyl thioether (**3b**), two kinds of $C(sp^3)$–S bond cleavages occurred to form **4a** (16%) and **4b** (34%) by cleavage of the decyl–S and methyl–S bonds, respectively, as well as **1A** (31%). Notably, decyl fluoride was not detected in the reaction mixture by ^{19}F NMR analysis, but MeF and methyl decyl thioether (RSMe) in both the gas and liquid phases were detected by GC-MS analysis. (See the SI for details.) Decyl triflate was presumably formed during the reaction because the corresponding molecular ion peak of decanal generated from the triflate byproduct was detected by GC-MS analysis. Compound **3c** behaved in a fashion similar to that of **3b**. Interestingly, the vinylsulfonium salt of methyl phenyl thioether (**3d**) predominantly underwent the decomposition reaction to form **1A** (52%) and **4a** (41%) with the release of PhSMe and PhOTf without phenyl fluoride formed in the reaction mixture. These results have suggested that the Me–S bond is easier to cleave than decyl/dodecyl–S bonds in **3b**/**3c**, no fluoroalkylation occurred through the cleavage of these long-chain alkyl–S bonds, and the Ph–S bond is much easier to cleave than the Me–S bond in **3d** without the occurrence of fluoroarylation. In the case of using other counteranions such as BF_4^-, the chemoselectivities were not obviously affected, but the yields of **4a**–**4c** and **1A** were slightly decreased.

Next, the protocol generality was explored by performing the reaction of styryl sulfonium salts **5** with CsF (Scheme 4). In contrast with the multisubstituted vinylsulfonium salts of type **1**, the sulfonium salt of styrene, that is, (*E*)-1-styryl-tetrahydro-1*H*-thiophen-1-ium trifluoromethanesulfonate (**5a**), reacted with CsF less efficiently, giving the target product **6a** in 12% yield. The yield was enhanced to 35% by increasing the catalyst loading to 10 mol % and extending the reaction time to 24 h. 1,1-Diaryl-substituted vinylsulfonium salts **5b**–**5h** underwent the reaction smoothly, efficiently yielding products **6b**–**6h** (61–79%). In the cases of vinylsulfonium salts **5c** and **5e** derived from 4-Me- and 3,4-Me_2-substituted 1,1-diaryl alkenes, isomeric products **6c** (61%, E/Z = 1:1) and **6e** (72%, E/Z = 9:5) were obtained, respectively. The use of 2-bromo-substituted 1,1-diaryl vinylsulfonium salt (*E*)-(**5d**) led to (*E*)-**6d** (64%), showing only one configuration. It is noteworthy that the sulfonium salt of 2-methylstyrene (**5i**) did not undergo the same type of fluoroalkylation reaction. The sulfonium salts of 1,2-stilbenes also reacted well with CsF, resulting in **6j** and **6k** (45–47%), exhibiting an obvious negative steric impact on the reaction efficiency. The reactivity difference is rationalized as follows. Styrylsulfonium salt **5a** was readily decomposed under the standard conditions, which led to **6a** in a low yield. An additional aryl at the one-position gives extra stabilization to 1,1-diarylvinylsulfonium salts **5b**–**5h** due to the conjugation effect, which reacted with CsF to afford the target products in decent yields. However, a negative steric impact exists in the sulfonium salts of 1,2-stilbenes (**5j** and **5k**), deteriorating the reaction efficiency. Interestingly, the 1,1-

Scheme 4. Scope of Styryl Sulfonium Salts (5)[a]



[a]Conditions: **5** (0.30 mmol), CsF (0.60 mmol), $Pd(OAc)_2$ (0.015 mmol), dioxane (2 mL), air, 100 °C, 12 h. [b]$Pd(OAc)_2$ (0.03 mmol), 24 h. [c]Isomer ratio was determined by ^1H NMR analysis. Yields refer to isolated products.

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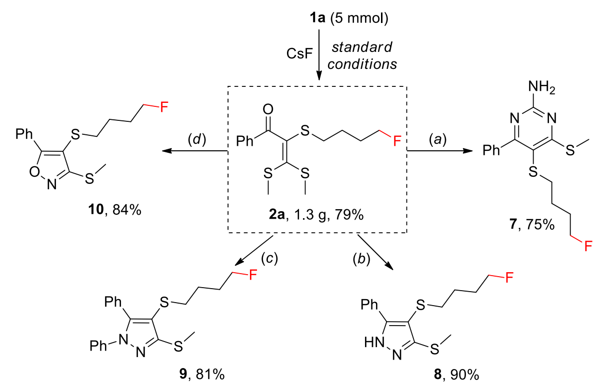
diphenyl vinylsulfonium salt (**5l**) of tetrahydro-2*H*-thiopyran underwent ring-opening fluoroalkylation to afford the desired product **6l** (55%) bearing a C_5-fluoroalkylthio chain.

The gram-scale preparation of compound **2a** was performed on a 5 mmol scale of **1a** to give **2a** in 79% yield (1.3 g). In the presence of the K_2CO_3 base, the condensation of **2a** with guanidine nitrate formed 5-((4-fluorobutyl)thio)-4-(methylthio)-6-phe-nylpyrimidin-2-amine (**7**) in 75% yield (Scheme 5a). The treatment of **2a** with an excess of hydrazine hydrate

Scheme 5. Gram-Scale Experiment and Product Derivatization[a]



[a]Reagents and conditions: (a) guanidine nitrate (2 equiv), K_2CO_3 (2 equiv), MeCN (2 mL), air, 100 °C, 36 h. (b) Hydrazine hydrate (10 equiv), EtOH (2 mL), air, 80 °C, 12 h. (c) Phenylhydrazine (2 equiv), EtOH (2 mL), air, 80 °C, 24 h. (d) Hydroxylamine hydrochloride (10 equiv), K_2CO_3 (10 equiv), EtOH (2 mL), air, 80 °C, 12 h.

or phenyl-hydrazine in refluxing ethanol afforded 4-fluoroalkylthiopyrazoles **8** and **9** in 90 and 81% yields, respectively (Scheme 5b,c). 4-((4-Fluorobutyl)thio)-3-(methylthio)-5-phenylisoxazole (**10**) was also efficiently synthesized (84%) by the reaction of **2a** and hydroxylamine (Scheme 5d). The molecular structures of compounds **7**–**9** were further confirmed by the X-ray single-crystal crystallographic determinations. (See the SI for details.)

Control experiments were conducted to probe into the reaction mechanism. The reaction of **1a** with CsF was carried out in the presence of 3.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenyl (BHT) under the standard conditions. These radical-trapping reagents could not inhibit the ring-opening fluoroalkylation reaction, leading to **2a** in 37–55% yield, which excludes a radical pathway in the catalytic cycle. A palladium-catalyzed fluoroalkylation mechanism via aliphatic the C–S bond cleavage of vinylsulfonium salts is proposed. Because a small amount of the target product **2a** (11–15%) could be formed in the absence of the catalyst (Table S1), nucleophilic ring-opening fluorination cannot be excluded, but palladium-catalyzed ring-opening fluorination is predominant.

In conclusion, we have developed a C–H fluoroalkylthiolation strategy of alkenes via the palladium-catalyzed fluoroalkylation of vinylsulfonium salts under an air atmosphere. Multisubstituted fluoroalkylthiolated alkenes can be accessed by means of the ring-opening fluoroalkylation of the vinylsulfonium salts. The synthetic protocol has been shown to have potential for the synthesis of diverse fluoroalkylthiolated *N*-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02172.

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds **1Ba**, **2l**, and **7**–**9** (PDF)

Accession Codes

CCDC 2035272, 2073867, 2073869, 2077381, and 2091625 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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