Synthesis of Ring-Fluorinated Thiophene Derivatives Based on Single C–F Bond Activation of CF_3-Cyclopropanes: Sulfanylation and 5-Endo-Trig Cyclization

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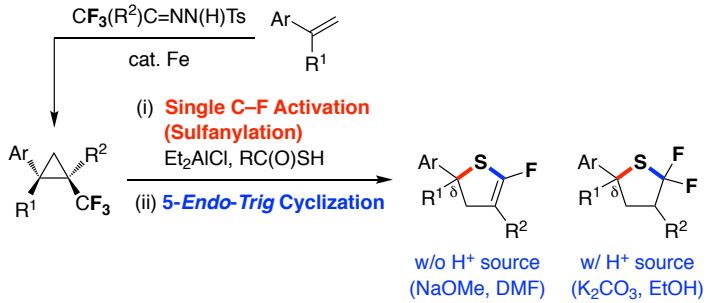
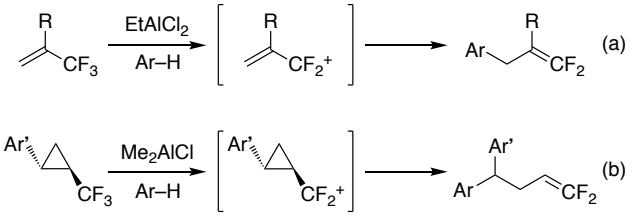
Supporting Information Placeholder



ABSTRACT: Treatment of CF_3-bearing cyclopropanes with Et_2AlCl generated stabilized difluorocarbocations, which underwent a nucleophilic addition of thiocarboxylic acids or thiols. The sulfur functionality was introduced at the position δ to the fluorine substituents in a regioselective manner (single activation of CF_3-cyclopropanes). The formed 1,1-difluoro-1-alkenes underwent successive deesterification/5-*endo-trig* cyclization. Intramolecular vinylic substitution proceeded in an aprotic solvent, whereas intramolecular addition proceeded in a protic solvent to afford pharmaceutically and agrochemically promising 2-fluoro-4,5-dihydrothiophene and 2,2-difluorotetrafluorothiophene scaffolds, respectively.

Due to their thermal stability as well as the shielding effect of the three fluorine atoms, the carbon–fluorine (C–F) bonds of the CF_3 groups are highly inert.[1,2] Despite numerous efforts, these characteristics make the activation of the C–F bonds problematic. The single activation of the three C–F bonds in the CF_3 group has been a particular challenge,[3] as the harsh reaction conditions required to cleave the first sp^3-hybridized C–F bond affect the remaining weaker C–F bonds. Considering the importance of the synthesis of selectively fluorinated compounds,[4] single C–F bond activation of the CF_3 group has in recent years been extensively studied. The described reactions typically include anionic, radical, or organometallic intermediates.[3,5]

We have recently developed the aluminium-promoted arylation reaction involving a cationic single C–F bond activation of trifluoromethylated alkenes (CF_3-alkenes) and cyclopropanes (CF_3-cyclopropanes, Scheme 1).[6,7] In these systems, the fluorine substituents stabilize the intermediary α-carbocations by donating their unshared electron pairs to the vacant p orbitals of the cationic centers (*i.e.*, the α-cation stabilizing effect of the fluorine substituent, Figure 1).[8] Thus, the elimination of the fluoride ions from CF_3-alkenes (a) or CF_3-cyclopropanes (b) was readily promoted by $EtAlCl_2$ or Me_2AlCl, resulting in the generation of CF_2 cations, which were additionally stabilized by the presence of a vinyl or cyclopropyl group. These cations were in turn trapped by arenes (Ar–H) via a Friedel–Crafts-type mechanism, leading to the formation of the corresponding 3,3-difluoroallylated or 4,4-difluorohomoallylated arenes. It is noteworthy that the undesired further elimination of the fluoride ions was entirely suppressed due to the instability of the resulting vinyl cations.



Scheme 1. Single C–F Bond Activation: Arylation of CF_3-Alkenes and -Cyclopropanes.

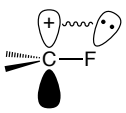
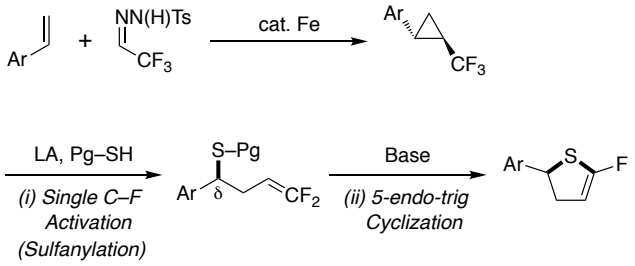


Figure 1. α-Cation Stabilizing Effect of Fluorine Substituent.

While these single activation protocols have been applied to the introduction of arene nucleophiles, heteroatom nucleophiles have

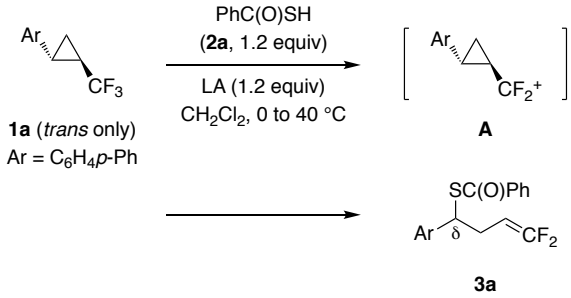
not yet been examined. Thus, in this paper, we describe the introduction of sulfur nucleophiles to CF_3-cyclopropanes, readily prepared from alkenes. The developed methodology opens an easy path to the synthesis of various ring-fluorinated thiophene derivatives (Scheme 2).[9,10] In the first instance, (i) the process involves the introduction of a protected sulfanyl moiety (Pg–SH) to CF_3-cyclopropanes in the presence of a Lewis acid (single C–F bond activation of the CF_3 groups). Subsequently, (ii) effective deprotection of the sulfanyl group allows nucleophilic 5-*endo-trig* cyclization of the resulting 1,1-difluoro-1-alkenes to provide 2-fluorinated thiophene derivatives.[11] 2-Fluorinated thiophene scaffolds are promising candidates for the development of LPA1 antagonists utilized for the treatment of nonalcoholic steatohepatitis (NASH).[12]



Scheme 2. Approach to the Ring-Fluorinated Thiophene Derivatives by Single C–F Bond Activation of CF_3-Cyclopropanes (Pg = Protecting Group).

The starting CF_3-cyclopropanes were readily prepared by the Fe-catalyzed (trifluoromethyl)cyclopropanation of styrene derivatives with diazotrifluoroethane, generated in situ from trifluoroacetaldehyde tosylhydrazone.[6b] Subsequently, we found that thiocarboxylic acids were sufficiently reactive to sulfanylate via single C–F bond activation of CF_3-cyclopropanes (Table 1). When the

Table 1. Optimization of Lewis Acids

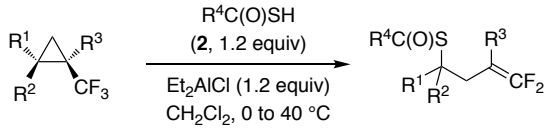


entry	Conditions		yield (%) [a]	
	LA	t (h)	**3a**	**1a**
1	$BF_3{\cdot}OEt_2$	11	–	quant.
2	BBr_3	6	32	58
3	$AlMe_3$	5	–	quant.
4	Me_2AlCl	24	73	6
5	Me_2AlCl [b]	4	85	–
6	Et_2AlCl	7	93	–
7	$EtAlCl_2$	6	70	–
8	$AlCl_3$	5	17	52
9	$GaCl_3$	5	–	98
10	$InBr_3$	5	–	98
11	$TiCl_4$	6	36	50
12	$TaCl_5$	5	47	trace

[a] ^{19}F NMR yield based on the internal standard ($PhCF_3$). [b] –20 to 40 °C.

1,1'-biphenyl-4-yl group-bearing CF_3-cyclopropane **1a** was treated with thiobenzoic acid (**2a**) in the presence of an equimolar amount of boron halide, *e.g.* BBr_3, *S*-4,4-difluorohomoallyl thiobenzoate **3a** was successfully afforded, albeit in 32% yield (entries 1 and 2). The reaction proceeded on the sulfur atom of thiobenzoic acid,[13] and

Table 2. Synthesis of *S*-4,4-Difluorohomoallyl Thiocarboxylates



1 **3**

entry	R^1	R^2	R^3	**1**	R^4	t (h)	yield (%)[a,b]
1	Ph	H	H	**1b**	Ph, **2a**	15	77, **3b**
2	*p*-MeC_6H_4	H	H	**1c**	Ph, **2a**	6	80, **3c**
3	*p*-*i*-PrC_6H_4	H	H	**1d**	Ph, **2a**	5	69, **3d**
4 [c]	*p*-PhC_6H_4	H	H	**1a**	Ph, **2a**	7	87, **3a**
5	1-Naphthyl	H	H	**1e**	Ph, **2a**	8	82, **3e**
6	2-Naphthyl	H	H	**1f** [d]	Ph, **2a**	5	85, **3f**
7	*p*-ClC_6H_4	H	H	**1g**	Ph, **2a**	11	66, **3g**
8	*trans*-styryl	H	H	**1h**	Ph, **2a**	6	88, **3h**
9	Ph	Me	H	**1i** [e]	Ph, **2a**	4	77, **3i**
10	Ph	H	Ph	**1j** [f]	Ph, **2a**	12	47 [g] (58),[h] **3j**
11	*p*-PhC_6H_4	H	H	**1a**	Me, **2b**	8	47 [g] (61),[h] **3k**

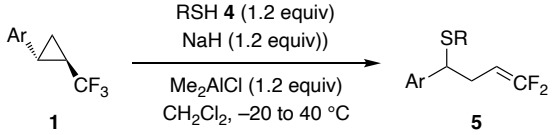
[a] Isolated yield. [b] Cyclopropane **1** was consumed completely (determined by thin layer chromatography). [c] Table 1, entry 6. [d] *trans*-**1f**/*cis*-**1f** = 86/14. [e] Single diastereomer of **1** (relative stereochemistry unknown). [f] (1*R**, 2*S**)-**1j**/(1*R**, 2*R**)-**1j** = 48/52. [g] Isolated by preparative gel permeation chromatography. [h] ^{19}F NMR yield based on the internal standard ($PhCF_3$) in parentheses.

thus the benzoylsulfanyl group was introduced regioselectively at the position δ to the fluorine substituents in **3a** via the carbocation intermediate **A**. Survey of other Lewis acids (Al, Ga, In, Ti, and Ta) revealed that diethylaluminium chloride was the most effective promoter, affording **3a** in an excellent yield of 93% (entry 6).

A variety of *S*-4,4-difluorohomoallyl thiocarboxylates were synthesized utilizing the optimized conditions (Table 2). Phenylated (trifluoromethyl)cyclopropane **1b** underwent sulfanylation to afford the corresponding thiobenzoate **3b** in 77% yield (entry 1). Furthermore, (trifluoromethyl)cyclopropanes **1c** and **1d** bearing electron-donating groups on the benzene rings, afforded **3c** and **3d** in 80% and 69% yields, respectively (entries 2 and 3). The biphenylated, 1-naphthylated, and 2-naphthylated substrates (**1a**, **1e**, and **1f**) led to the formation of **3a**, **3e**, and **3f** in 82–87% yields (entries 4–6). CF_3-cyclopropane **1g**, bearing an electron-withdrawing *p*-chloro moiety on the benzene ring, afforded **3g** in a lower yield of 66%, suggesting that carbocations were involved in this reaction (entry 7). It is worth noting that non-aryl-bearing CF_3-cyclopropane (R^1 = $PhCH_2CH_2$, R^2 = R^3 = H) did not afford the corresponding thiobenzoate, and led to a 40% recovery of the starting CF_3-cyclopropane (not shown), also suggesting the formation of the carbocations. Interestingly, *trans*-styryl-substituted (R^1) and disubstituted (R^1–R^3 = Ph, Me) CF_3-cyclopropanes **1h**–**j**, which were less reactive in the previous arylation,[6b] also afforded **3h**–**j** in 47–88% yields (entries 8–10). Thus, higher nucleophilicity of the thiocarboxylic acids, compared to arenes, successfully facilitated the reaction. Not only thiobenzoic acid (R^4 = Ph), but also thioacetic acid (R^4 = Me) promoted the sulfanylation, affording the corresponding thioacetate **3k** in 61% NMR yield (entry 11).

Subsequently, the aluminium-promoted sulfanylation via single C–F bond activation of CF_3-cyclopropanes was successfully applied to thiols (Table 3). CF_3-cyclopropanes **1** were treated with aromatic or aliphatic thiols and sodium hydride[14] in the presence of Me_2AlCl. Thiols **4a**–**c** as well as the sterically demanding thiol **4d** underwent 4,4-difluorohomoallylation with **1** (entries 1–7). The corresponding difluorohomoallyl sulfides **5a**–**g** were obtained in excellent yields (80–97%). As well as aryl thiols, primary and secondary alkyl thiols **4e** and **4f** underwent the difluorohomoallylation reaction to afford **5h** and **5i** in 89% and 98% yields, respectively (entries 8 and 9).

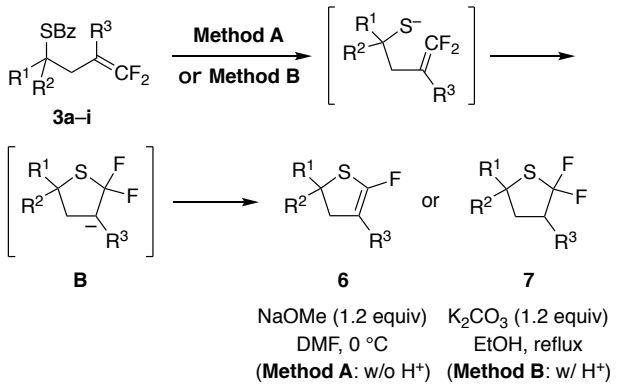
Table 3. Synthesis of 4,4-Difluorohomoallyl Sulfides



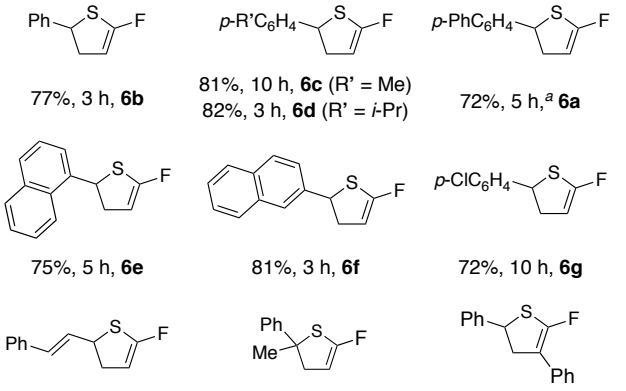
entry	Ar	R	*t* (h)	yield (%) [a]
1	*p*-PhC_6H_4, **1a**	Ph, **4a**	1	97, **5a**
2	*p*-MeC_6H_4, **1c**	Ph, **4a**	3	89, **5b**
3	2-Naphthyl, **1e**	Ph, **4a**	6	81, **5c**
4	*p*-ClC_6H_4, **1g**	Ph, **4a**	2	81, **5d**
5	*p*-PhC_6H_4, **1a**	*p*-$OMeC_6H_4$, **4b**	3	80, **5e**
6	*p*-PhC_6H_4, **1a**	*p*-ClC_6H_4, **4c**	2	94, **5f**
7	*p*-PhC_6H_4, **1a**	*o*-MeC_6H_4, **4d**	3	90, **5g**
8	*p*-PhC_6H_4, **1a**	*n*-$C_{12}H_{25}$, **4e**	2	89, **5h**
9	*p*-PhC_6H_4, **1a**	cyclohexyl, **4f**	1	98, **5i**

[a] Isolated yield.

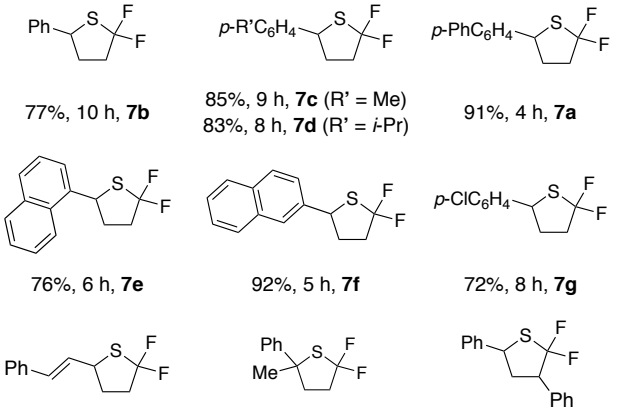
Our previous studies demonstrated that 1,1-difluoroalkenes bearing a nucleophilic moiety at the position δ to the fluorine substituents are reactive toward nucleophilic 5-*endo*-*trig* cyclization.[11,15] We believe this a consequence of (I) the highly polarized C–C double bond, which allows initial 5-membered ring formation, (II) β-anion stabilizing effect of the fluorine substituents, which



Method A



Method B

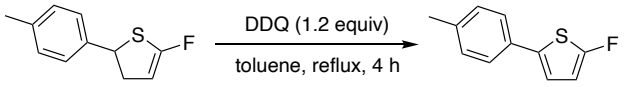


[a] RT. [b] ^{19}F NMR yield based on the internal standard ($PhCF_3$) in parentheses. [c] Isolated by preparative gel permeation chromatography.

Figure 2. Synthesis of the Fluorinated Thiophene Derivatives (Isolated Yield; Bz = Benzoyl).

stabilizes the carbanion intermediates, and (III) the leaving group ability of the fluorine substituents as fluoride ions. As demonstrated above, the single activation successfully provided the cyclization precursors starting from diazotrifluoroethane, which prompted us to revisit the synthesis of fluorinated thiophenes. Accordingly, the sequence of deesterification/5-*endo-trig* cyclization of *S*-4,4-difluorohomoallyl thiocarboxylates **3** was investigated.

The synthesized thiobenzoates **3a**–**j** were treated with sodium methoxide in dimethylformamide (DMF) at 0 °C (Method A, Figure 2). Phenylated (R^1 = Ph) difluoroalkene **3b** underwent debenzoylation, followed by addition–elimination in a 5-*endo-trig* fashion to afford the desired fluorodihydrothiophene **6b** in 77% yield. Substrates **3a** and **3c**–**g** containing electron-donating or -withdrawing groups on the phenyl moiety also gave **6a** and **6c**–**g** in 72–82% yields. Moreover, the reaction of styryl-substituted difluoroalkene **3h** afforded **6h** in 72% yield. Substrates **3i** and **3j** derived from disubstituted CF_3-cyclopropanes, gave the corresponding 5,5- and 3,5-disubstituted 2-fluorodihydrothiophenes **6i** and **6j** in 72% and 68% yields, respectively. In addition, treatment of **6c** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.2 equiv) afforded the aromatized fluorothiophene **8c** in 56% yield (Scheme 3).



6c 56%, **8c**

Scheme 3. Synthesis of 2-Fluorothiophenes.

We then turned our attention to the capture of the cyclization intermediates **B** to obtain difluorinated tetrahydrothiophenes **7**. Difluoroalkenes **3** were treated with potassium carbonate in a protic solvent, *i.e.*, ethanol at reflux (Method B, Figure 2) to trap **B** by protonation. Starting with compounds **3a**–**g**, the expected addition products, *i.e.*, 5-aryl-2,2-difluorotetrahydrothiophenes **7a–g** were successfully obtained in 72–92% yields. Difluoroalkenes **3h**–**j** with other substitution patters also afforded the corresponding difluorotetrahydrothiophenes **7h**–**j** in 53–93% yields.

The synthesis of 2,2-difluorinated tetrahydrothiophenes as well as 2-fluorinated dihydrothiophenes has been scarcely reported. Hence, the single activation facilitated the short-step synthesis of monofluorinated and difluorinated thiophene derivatives through sulfanylation, followed by intramolecular substitution or addition. It must be noted that in the reported nucleophilic vinylic substitution (S_NV) reactions of 1,1-difluoro-1-alkenes, the β,β-difluoroanion intermediates, such as **B**, have long been proposed.[16] To the best of our knowledge, to date, there have been no reports on the nucleophilic addition reactions of 1,1-difluoro-1-alkenes under basic conditions. The formation of **7** provided a definite evidence for the addition–elimination mechanism for the vinylic fluorine substitution of 1,1-difluoroalkenes.

In conclusion, in the present study, the Lewis acid-promoted incorporation of sulfur by single C–F bond activation of CF_3-cyclopropanes was successfully achieved. Upon treatment with Et_2AlCl, CF_3-cyclopropanes generated the stabilized α-fluorocarbocation intermediates, which underwent nucleophilic addition reactions with thiocarboxylic acids and thiols. Through the process, the sulfur functionality was introduced into the position δ to the fluorine substituents in a regioselective manner. The 1,1-difluoroalkenes obtained from the reactions with thiocarboxylic acids, underwent 5-*endo-trig* cyclization under basic conditions. Without a proton source (*i.e.*, in DMF), intramolecular vinylic substitution proceeded, whereas in the presence of a proton source (*i.e.*, in EtOH), intramolecular addition proceeded to afford 2-fluoro-4,5-dihydrothiophenes or 2,2-difluorotetrahydrothiophenes, respectively. Remarkably, both of the compounds provide valuable scaffolds for the development of promising pharmaceutical and agrochemical agents.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

J.I. conceived the project and wrote the manuscript with K.F. K.F. and T.F. also planned the experiments. T.F. carried out the experiments. All the authors discussed the experiments and results, and have given approval to the final version of the manuscript.

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13 We consider that the sulfur-selective addition of thioacids is due to higher nucleophilicity of S compared to O.

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