SYNTHESES OF FLUORINE-CONTAINING HETEROCYCLIC COMPOUNDS *VIA* DIRECT AND INDIRECT METHODS USING DIFLUOROCARBENES

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Abstract. *This account presents our syntheses of heterocyclic compounds, encompassing pyrrole, oxazole, thiazole, thiophene, pyridine, pyran, and oxazine derivatives, bearing either fluorine substituents or fluorine-containing substituents (−$OCHF_2$, −$SCHF_2$, and −CF_2CH_3 groups) on their rings. The key components in these syntheses are difluorocarbene and associated transition metal fluoroalkylidene complexes. The syntheses are performed using two methods: a) a direct method based on free difluorocarbene or a copper(I) difluorocarbene complex, and b) an indirect method utilizing fluorinated cyclopropanes as the starting material, which were prepared using an iron(III) trifluoroethylidene complex or free difluorocarbene. The cooperation between organofluorine and carbene chemistry yields diverse fluorine-containing heterocyclic compounds.*

Contents

1. Introduction

Fluorine and fluorine-containing substituents often exert a notable influence on the biological[1-8] and physical properties[9-13] of organic compounds. The high electronegativity of fluorine lowers electron density on its neighboring atoms, enhancing tolerance toward oxidative metabolism or aerobic oxidation. In pharmaceuticals and agrochemicals, fluorine substituents increase lipophilicity to facilitate better absorption through cell membranes, leading to their enhanced bioactivities. Meanwhile, the small size of fluorine substituents hardly affects the three-dimensional structure of drug molecules and planarity of organic electronic materials, preserving their biological activities and physical properties.[14-17]

Heterocycles, especially nitrogen-, oxygen-, and sulfur-containing heterocyclic systems such as pyrrole, thiophene, pyridine, pyran, and their fused bicyclic rings have historically played pivotal roles in life sciences and materials science as they are used as core scaffolds for biologically active compounds and functional materials (Figure 1). Consequently, fluorine-containing heterocyclic compounds have been attracting considerable attention in recent years. Despite their appeal, synthesizing heterocycles bearing fluorine or fluorine-containing substituents poses challenges. Introducing fluorine substituents to heterocycles using fluorinating agents like F_2/N_2 and *N*,*N*-diethylaminosulfur trifluoride (DAST)[18,19] presents difficulties such as vigorous reaction conditions, low regioselectivity, use of expensive and toxic reagents, *etc.* Additionally, heterocycle construction and fluorine introduction are highly laborious processes.

By contrast, synthesizing these compounds with *fluorinated-carbon units* emerges as a suitable choice. Difluorocarbene (:CF_2) is one of the smallest fluorinated-carbon units and can facilitate the synthesis of ring-

fluorinated heterocycles by providing difluoromethyl (–CHF_2), difluoromethylene (–CF_2–), and fluoromethanylylidene (–CF=) moieties.[20-23] However, the use of classical difluorocarbene precursors, such as sodium chlorodifluoroacetate,[24-26] chlorodifluoromethane (HCFC-22)/OH^-,[27,28] and phenyl(trifluoromethyl)mercury/NaI,[29,30] presents limitations related to their generation, including harsh conditions (*e.g.* >120 °C for $CClF_2CO_2Na$ and OH^- for $CHClF_2$) and reagent toxicity (Hg^{2+} for $PhHgCF_3$). Meanwhile, useful difluorocarbene sources such as (triphenylphosphonio)difluoroacetate ($Ph_3P^+CF_2CO_2^-$, PDFA),[31,32] trimethyl(trifluoromethyl)silane/F^-,[33] *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine,[34] *etc.* have been developed over the last decade. Notably, we reported NHC-[35] or proton sponge-catalyzed[36] generation of difluorocarbene from trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate [TFDA,[37] NHC=*N*-heterocyclic carbene, proton sponge (PS)=1,8-bis(dimethylamino)naphthalene, Scheme 1].[38,39] The latter is particularly useful for organic synthesis because it allows difluorocarbene generation under nearly neutral conditions at 50–60 °C.

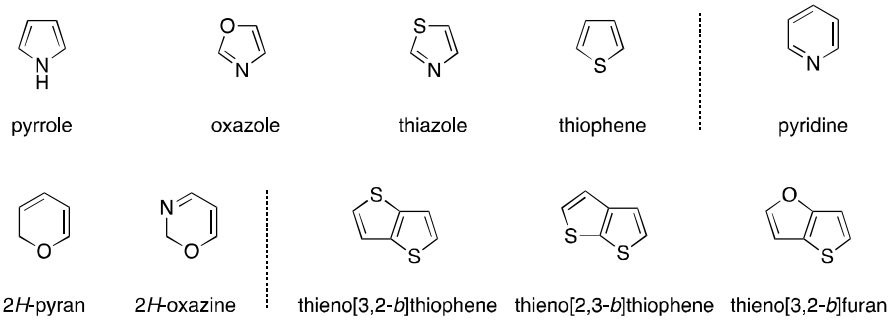
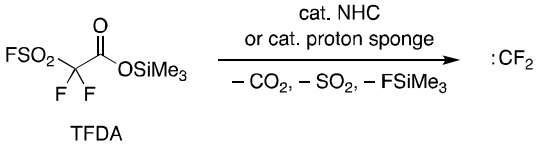


Figure 1.



Scheme 1.

In this account, we report our syntheses of heterocyclic compounds bearing fluorine substituent(s) or fluorine-containing substituents (difluoromethoxy, difluoromethylsulfanyl, and 1,1-difluoroethyl groups) on their ring (Figure 2). The syntheses of these heterocycles encompass: a) syntheses utilizing free difluorocarbene or a copper(I) difluorocarbene complex (direct methods, Chapter 2), and b) syntheses starting from fluorinated cyclopropanes prepared using an iron(III) trifluoroethylidene complex or free difluorocarbene (indirect methods, Chapter 3).

2. Syntheses using difluorocarbenes: direct methods

2.1. Synthesis of difluoromethoxy- and difluoromethylsulfanyl-substituted pyridine, oxazole, and pyran derivatives *via* difluoromethylation

In addition to fluorine substituents, fluorine-containing substituents like difluoromethoxy and difluoromethylsulfanyl groups are important,[40] and biologically active heterocyclic compounds featuring these substituents have been developed. For example, (difluoromethoxy)pyridine **1** serves as a corticotropin-releasing factor-1 (CRF1) receptor antagonist[41] and (difluoromethylsulfanyl)triazine SSH-108 exhibits herbicidal activity.[42] Therefore, synthetic methods for preparing difluoromethoxy- and difluoromethylsulfanyl-substituted heterocycles are highly desirable for developing drugs and agrochemicals.

When (thio)carbonyl compounds react with difluorocarbene, difluoromethylation of oxygen (sulfur) occurs. (Difluoromethoxy)pyridine derivatives were synthesized from pyridones using difluorocarbene generated with TFDA and an NHC catalyst.[43] For instance, quinolinone **2a** was treated with TFDA in the

presence of an *in situ*-generated triazolylidene catalyst **3** (Scheme 2a), yielding difluoromethylene carbonyl ylide intermediate **4**, whose hydrogen migration afforded (difluoromethyloxy)dihydroquinoline **5a**. Subsequent dehydrogenation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in a one-pot operation produced 2-(difluoromethoxy)quinoline **6a**. A similar process with 2-pyridone **2b** yielded 2-(difluoromethoxy)pyridine **6b** (Scheme 2b). Notably, difluorocarbene generated under strongly basic conditions ($CHClF_2/OH^-$) was not applicable for (difluoromethoxy)pyridine synthesis due to the ambident reactivity of amidates formed from pyridones, resulting in undesired *N*-difluoromethylation by-products and the desired *O*-difluoromethylation products. Treatment of benzopyranone **7** with TFDA in the presence of an imidazolylidene catalyst **8** yielded 4-(difluoromethoxy)-2*H*-pyran **9** (Scheme 2c).

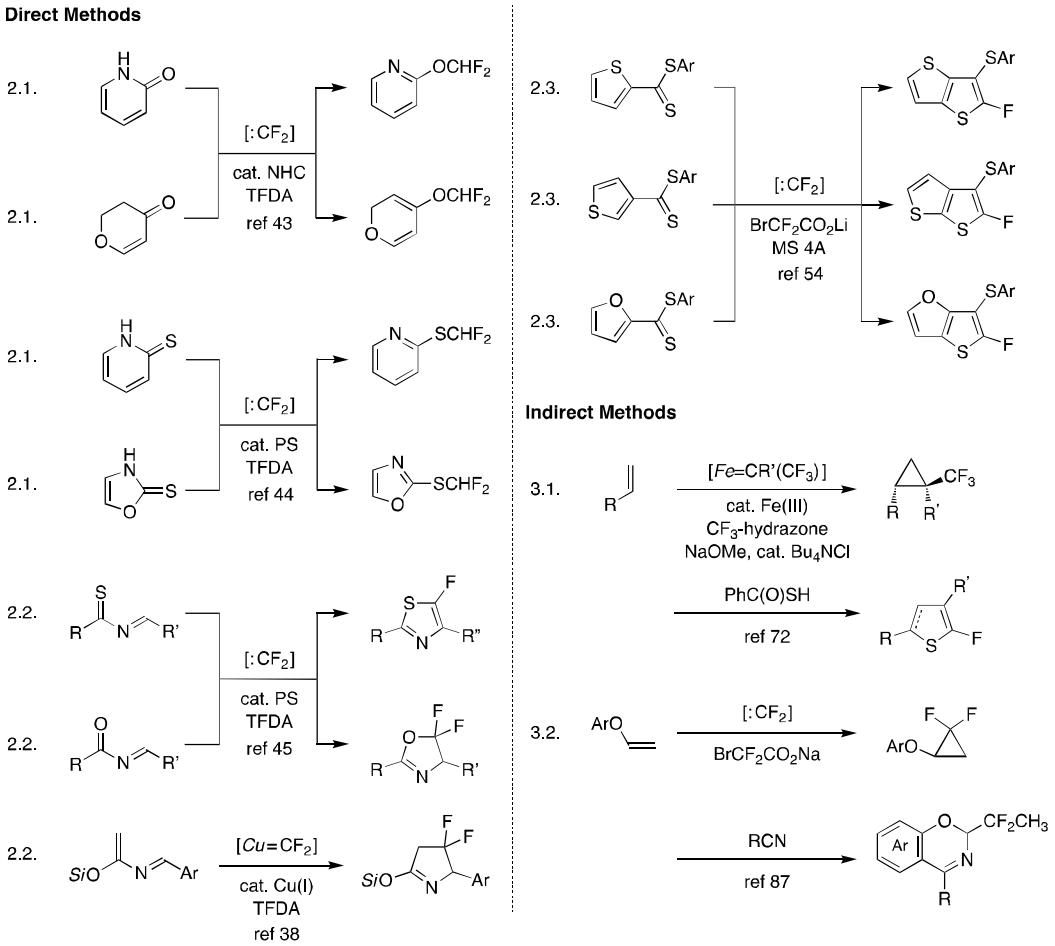


Figure 2.

(Difluoromethylsulfanyl)pyridines and (difluoromethylsulfanyl)oxazoles were synthesized by allowing thiopyridones and cyclic thiocarbamates to react with difluorocarbene (Scheme 3).[44] 2-Thiopyridone **10** treated with the *in situ*-generated triazolylidene catalyst **3** produced 2-(difluoromethylsulfanyl)pyridine **11** moderately through thiocarbonyl ylide intermediate **12**; moreover, the yield of **11** was improved when **10** was allowed to react with TFDA in the presence of a proton sponge catalyst. Similarly, reaction of cyclic thiocarbamate **13** with TFDA afforded the corresponding 2-(difluoromethylsulfanyl)benzoxazole **14**.

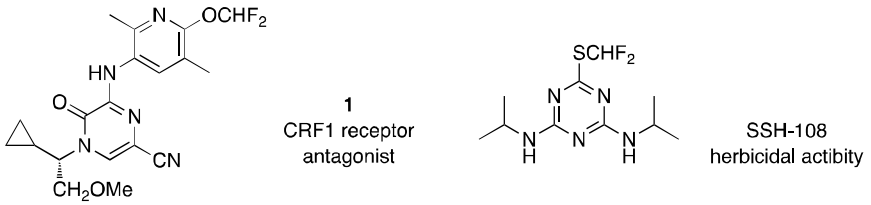
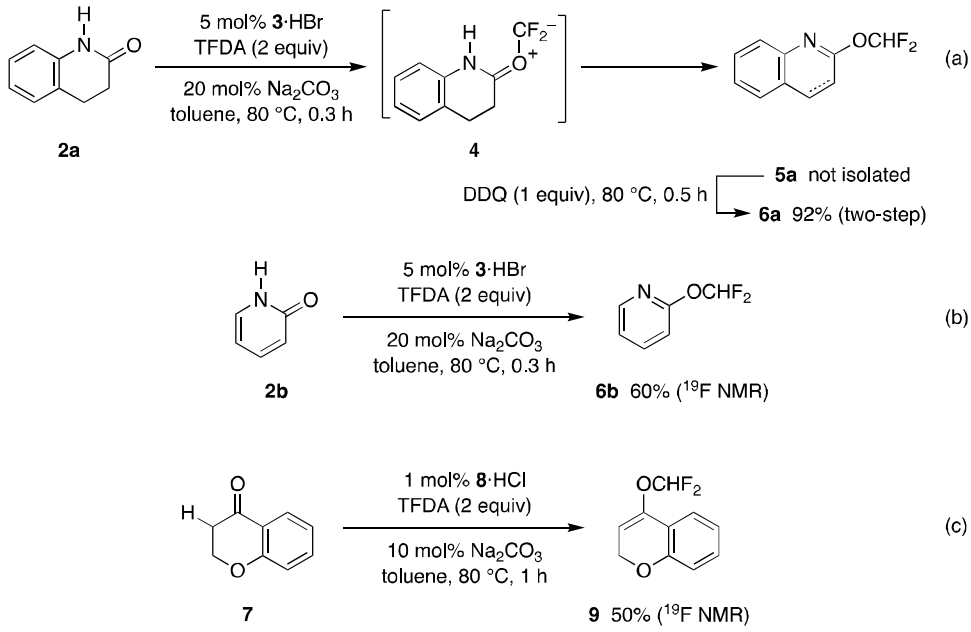
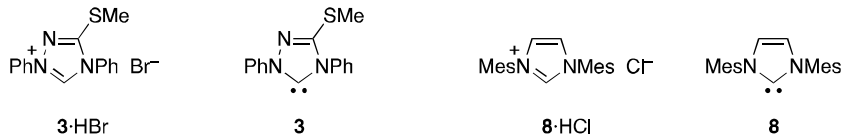


Figure 3.





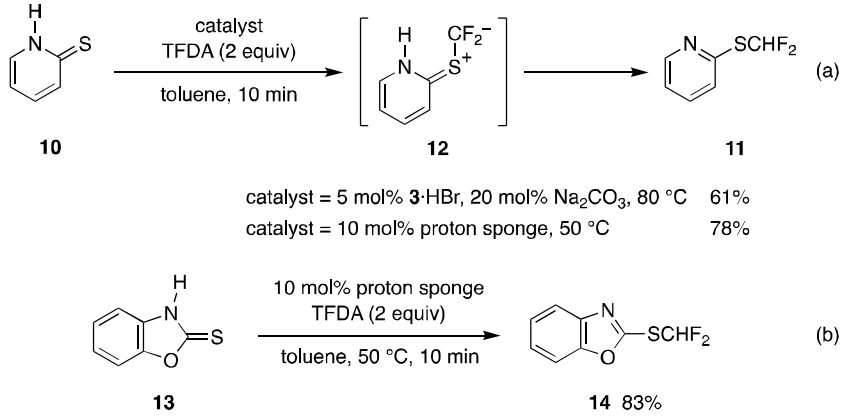
Scheme 2.

2.2. Synthesis of (di)fluorothiazoline, (di)fluorooxazoline, and (di)fluoropyrroline derivatives *via* [4 + 1]-annulation

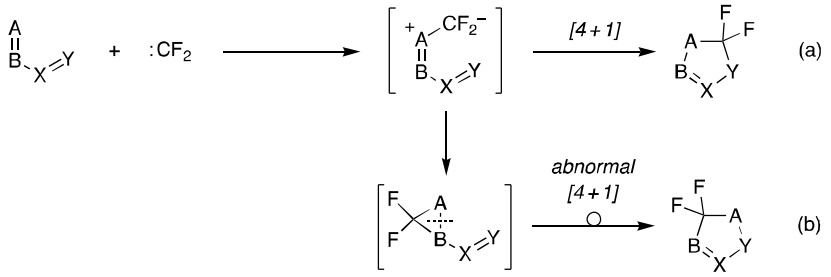
[4 + 1]-Annulations of difluorocarbene are useful methods for constructing ring-fluorinated five-membered heterocycles. Conjugated four-atom components (A=B–X=Y) react with difluorocarbene to form unsaturated ylide intermediates. Subsequently, ylide cyclizations lead to difluorinated five-membered cyclic compounds by [4 + 1]-annulation (Scheme 4a), while three-membered ring formation followed by distal position-selective ring opening (A–B bond cleavage) results in similar but rearranged cyclic compounds by abnormal [4 + 1]-annulation (Scheme 4b, Section 2.3).

Difluorocarbene, generated from TFDA using a proton sponge catalyst, reacted with *N*-(thioacyl)amidines **15**, which were readily prepared by the condensation of thioamides and dimethyl acetals of *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide (Scheme 5). The generated thiocarbonyl ylide

intermediates **16** readily underwent cyclization to give amino-substituted 5,5-difluorothiazolines **17** ([4 + 1]-annulation products).[44] *N*-Acylamidine **18** similarly yielded the corresponding 5,5-difluorooxazoline **19** (Scheme 6).



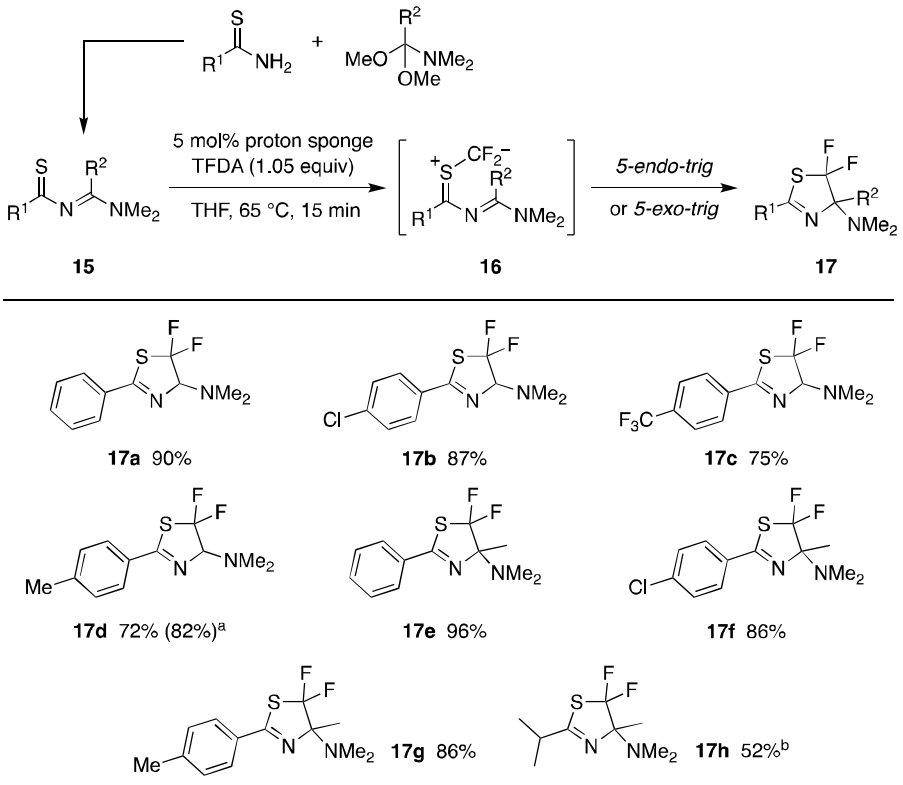
Scheme 3.



Scheme 4.

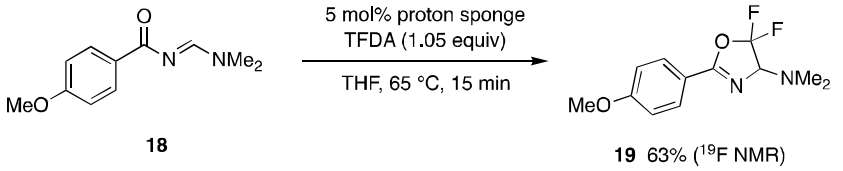
The obtained 5,5-difluorothiazolines **17** were successfully aromatized to 5-fluorothiazoles **20** and **21** in two ways:[45] i) difluorothiazoline **17a**, with a methine hydrogen on the five-membered ring, was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 100 °C, then dehydrofluorination afforded the aromatized **20a** (Scheme 7a); ii) difluorothiazoline **17e**, possessing a methyl group on the five-membered ring, was transformed into 4-methylidene-5,5-difluorothiazoline **22e** upon treatment with dimethyl sulfate *via* the Hofmann elimination of the quaternary ammonium salt (not shown). The exo-methylene moiety of **22e** was reactive toward various nucleophiles such as pyrrolidine and trimethylaluminium, affording 2,4-disubstituted 5-fluorothiazoles **21a** (with pyrrolidine, C–N bond formation, Scheme 7b) and **21b** (with $AlMe_3$, C–C bond formation, Scheme 7c), respectively, *via* S_N2'-type reactions.[46]

Furthermore, [4 + 1]-annulation was achieved using transition metal difluorocarbene complexes. We previously reported that copper(I) difluorocarbene complex **23**, generated from $CuBr(PPh_3)(L)$ (L=4,7-dimethyl-1,10-phenanthroline) and sodium bromodifluoroacetate (Scheme 8), reacted with silyl dienol ethers, leading to the synthesis of β,β-difluorocyclopentanones *via* [4 + 1]-annulation.[47] This copper(I)-catalyzed annulation was applied to prepare a nitrogen-containing ring system.[38] Siloxyazadiene **24**, readily prepared from an *N*-acetylimine, was treated with sodium bromodifluoroacetate in the presence of a $CuBr(PPh_3)$(phenanthroline) complex (10 mol%), providing the desired β,β-difluoropyrroline **25** *via* 5-*endo-trig* cyclization of an alkylcopper(I) intermediate (Scheme 9).



The product was isolated via Kügelrohr distillation. [a] ^{19}F NMR yield in parentheses. [b] Starting *N*-(Thioacyl)amidine **15** was used without isolation.

Scheme 5.

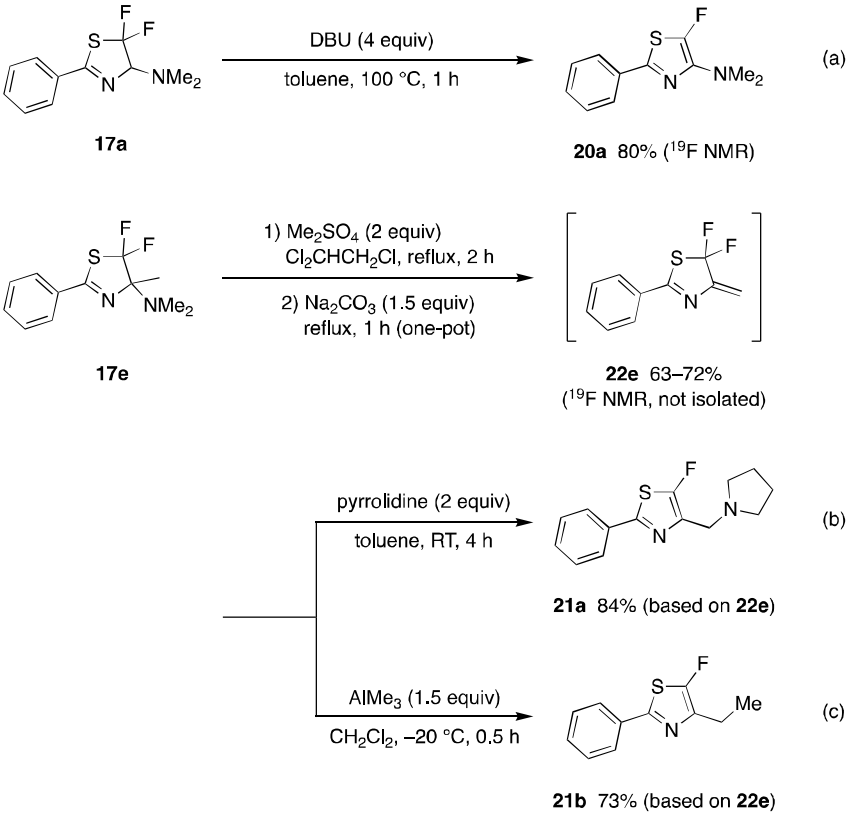


Scheme 6.

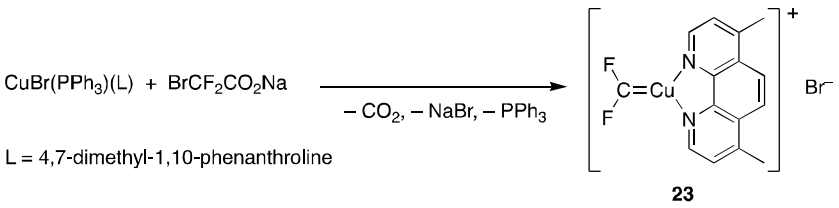
2.3. Synthesis of fluorothienothiophenes and fluorothienofurans *via* abnormal [4+1]-annulation

Another cyclization pathway arises in the reactions of difluorocarbene with four-atom components (A=B–X=Y), leading to three-membered ring formation. The ring strain enhanced by fluorine substituents on three-membered rings further promotes *abnormal* [4+1]-annulation of difluorocarbene, yielding a different type of difluorinated five-membered cyclic compounds (Scheme 4b).

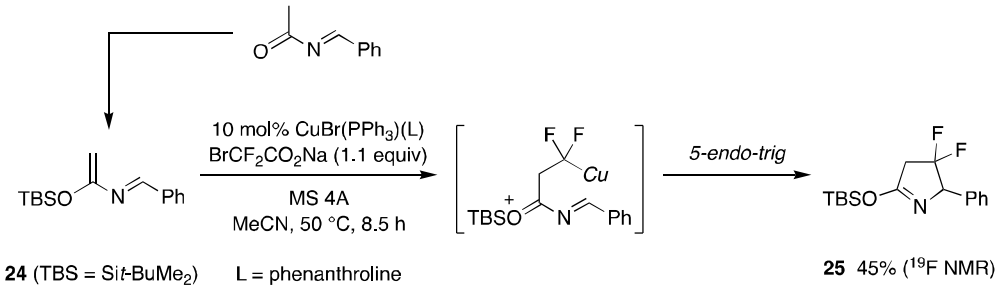
Thioketones and dithioesters react with difluorocarbene to form 2,2-difluorothiiranes (2,2-difluorothiacyclopropanes) **26** and **27**, respectively, *via* thiocarbonyl ylide intermediates.[48-50] The fluorine substituents induce additional ring strain on 2,2-difluorothiiranes by 7 kcal/mol, compared with fluorine-free thiiranes, facilitating elemental sulfur elimination (without phosphines) to afford 1,1-difluoroalkenes by Barton-Kellogg-type synthesis[51-53] (Scheme 10).



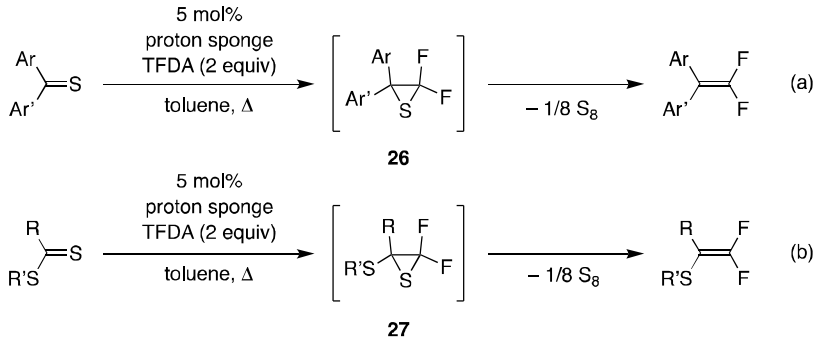
Scheme 7.



Scheme 8.

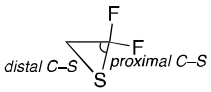


Scheme 9.



Scheme 10.

The ring strain is enhanced owing to the distorted structure of difluorothiiranes.[49] The S–CF_2–C bond angle of difluorothiirane **29** is 68.7°, wider than that of parent thiirane **28** (66.2°, DFT, B3LYP/6-31G*, Figure 4). The distal and proximal C–S bond lengths of difluorothiirane **29** are 1.87 and 1.81 Å, respectively, with the former elongated and the latter shortened from that of thiirane **28** (1.84 Å). These distortions are attributed to the strong electron-withdrawing inductive effect of fluorine substituents (Bent's rule). Because the *p* character-rich C–F bonds exhibit smaller interelectronic repulsion around the CF_2 carbon atom than the *s* character-rich C–C and C–S bonds, the F–C–F bond angle becomes narrower (not shown), while the S–CF_2–C bond angle becomes wider.

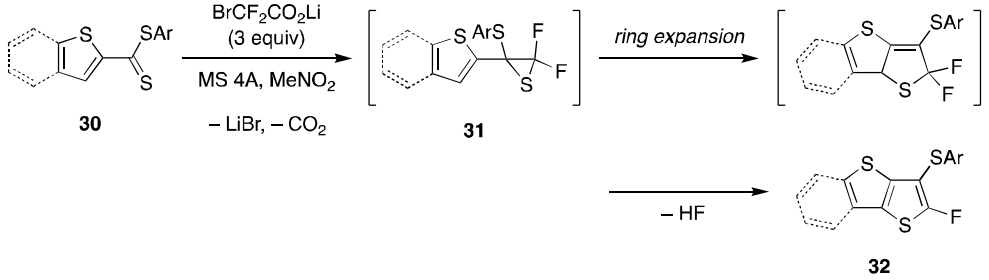
		
	28	**29**
C–C–S bond angle / °	66.2	68.7
C–S bond length(s) / Å	1.84	1.87 (distal) 1.81 (proximal)

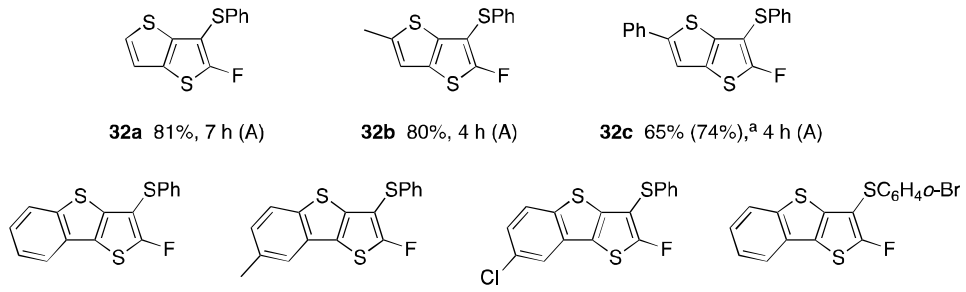
DFT, B3LYP/6-31G*.

Figure 4.

The distorted structure of difluorothiiranes promoted ring opening rearrangement, causing abnormal [4 + 1]-annulation of difluorocarbene with thiocarbonyl compounds.[54] Thiophene-2-carbodithioates **30** were treated with lithium bromodifluoroacetate in the presence of molecular sieves 4A (MS 4A, Scheme 11) to produce 2,2-difluoro-3-(2-thienyl)thiiranes **31** *in situ*. These intermediates underwent regioselective ring expansion (distal C–S bond cleavage), followed by dehydrofluorination, resulting in sulfanylated fluorothieno[3,2-*b*]thiophenes **32**. By contrast, thiophene-3-carbodithioates, the regioisomers of **30**, reacted with difluorocarbene similarly to yield sulfanylated fluorothieno[2,3-*b*]thiophenes **33**, the isomer of **32** (Figure 5). DFT calculations suggested that lithium ligation was crucial for suppressing desulfurization (Scheme 10) and accelerating ring expansion (not shown).

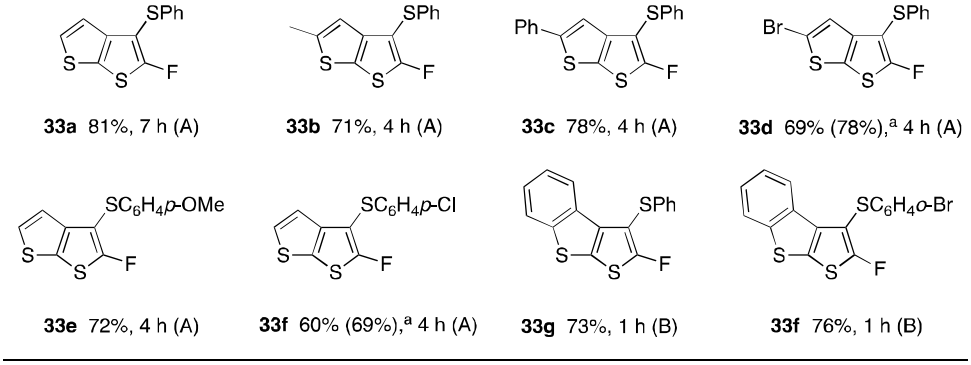
The abnormal [4 + 1]-annulation also facilitated dibenzo(thienothienofuran) synthesis.[55-57] Benzofurancarbodithioates **34** underwent a similar abnormal [4 + 1]-annulation with difluorocarbene, resulting in the formation of fluorinated benzo(thieno)furans **35** with an arylsulfanyl group (Scheme 12). Subsequent lithium-bromine exchange of **35b** (Ar=*o*-BrC_6H_4) with *t*-butyllithium, followed by intramolecular nucleophilic aromatic substitution for fluorine, produced fluorine-free dibenzo(thienothienofuran) **36**. This pentacyclic compound shows promise as an electronic material.





Method A: reflux; method B: microwave, closed, 140 °C. [a] ^{19}F NMR yield in parentheses.

Scheme 11.



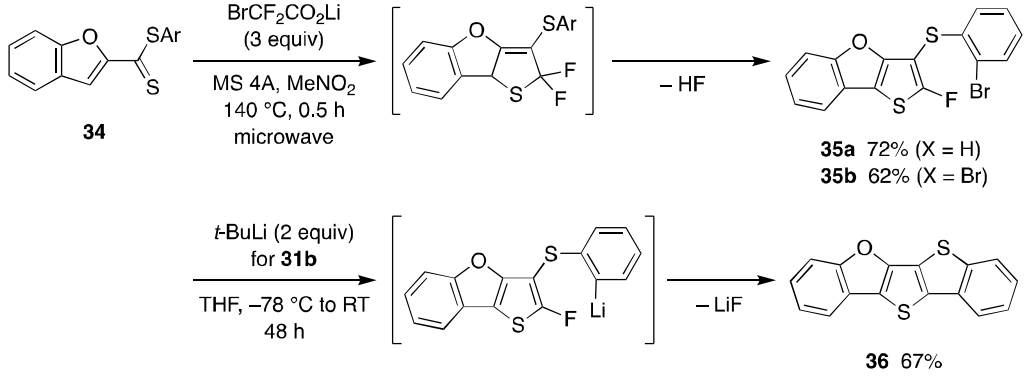
Conditions: $BrCF_2CO_2Li$ (3 equiv), MS 4A, $MeNO_2$. Method A: reflux; method B: microwave, closed, 140 °C. [a] ^{19}F NMR yield in parentheses.

Figure 5.

3. Syntheses starting from fluorinated cyclopropanes: indirect methods

In addition to the aforementioned direct syntheses employing free and transition metal difluorocarbene complexes, indirect syntheses involving carbenes were employed to prepare fluorinated cyclopropane intermediates, expanding the spectrum of fluorine-containing heterocycles. Fluorinated cyclopropanes are synthetically accessible from alkenes using difluorocarbene or related species.[21,58] Cyclopropanes serve as

useful intermediates in organic synthesis due to their: i) ring strain of 26.5–28.7 kcal/mol[22,59,60], and ii) nucleophilic C–C σ bonds within three-membered rings. Combining fluorine and cyclopropane chemistry, *i.e.* generation of α-fluorine-stabilized carbocations[61-64] and regioselective ring cleavage of difluorocyclopropanes, opens new synthetic routes for preparing fluorothiophene derivatives (Section 3.1) and (1,1-difluoroethyl)benzoxazines (Section 3.2).



Scheme 12.

3.1. Synthesis of (di)fluorothiophene derivatives *via* single activation of the trifluoromethyl group

The C–F bonds of CF_3 group are highly inert due to the shielding effect of its three fluorine atoms and its thermal stability.[65,66] Notably, achieving the single activation of these three C−F bonds in the CF_3 group has been challenging because harsh reaction conditions are required to cleave the first sp^3 C−F bond without affecting the remaining weaker C−F bonds. As the number of fluorine substituents attached to the carbon decreases, the dissociation energies of the C–F bonds also decrease from 129.7 kcal/mol to 109.0 kcal/mol (Figure 6).[65] Because of the importance of selectively fluorinated compounds, recent studies have extensively investigated the single C−F bond activation of the CF_3 group.[67]

bond	bond dissociation energy / kcalmol^{-1}
CF_3—F	129.7
CHF_2—F	128.0
CH_2F—F	122.0
CH_3—F	109.0

Figure 6.

Fluorine substituents stabilize α-carbocations by donating their unshared electron pairs to the vacant *p*-orbitals of cationic carbon centers (α-carbocation stabilizing effect of the fluorine substituent, Figure 7).[14,15,17] Despite their electron-withdrawing inductive effect, fluorine substituents consequently stabilize α-carbocations through efficient overlap of fluorine 2*p*-orbitals with carbon 2*p*-orbitals.

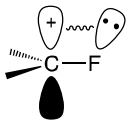
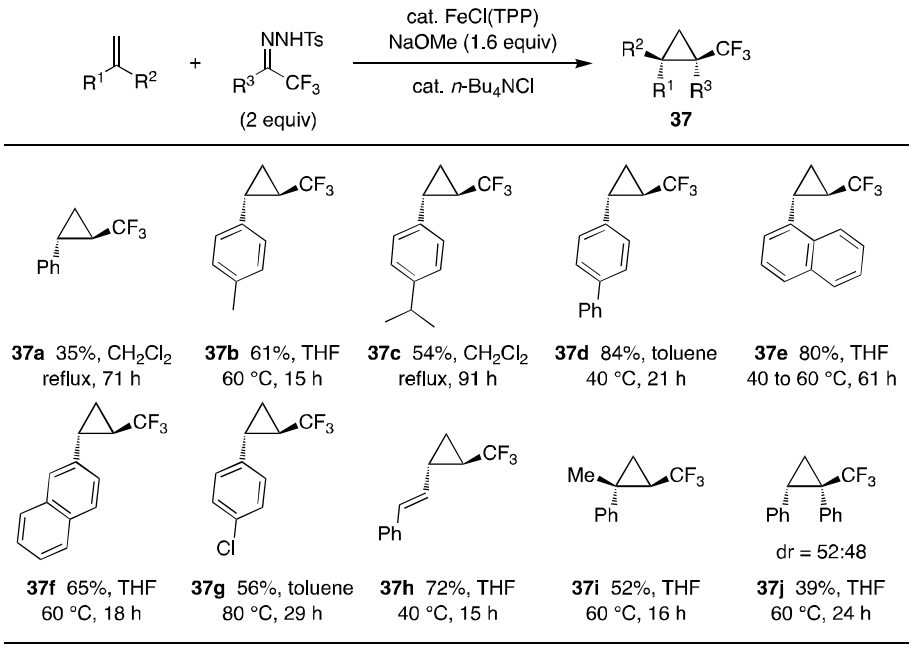


Figure 7.

We successfully achieved the single activation of (trifluoromethyl)cyclopropanes using Lewis acids, leading to the synthesis of fluorothiophenes, fluorodihydrothiophenes, and difluorotetrahydrothiophenes. The starting (trifluoromethyl)cyclopropanes **37** were prepared by the cyclopropanation of styrenes with an iron(III) trifluoroethylidene complex generated from trifluoromethylated hydrazones, sodium methoxide, and a catalytic amount of tetrabutylammonium chloride (Scheme 13).[68-71]

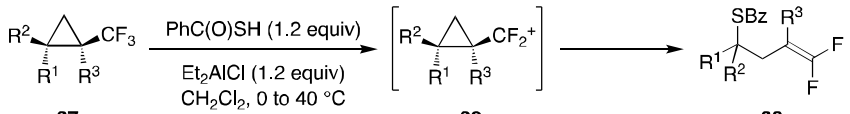


Scheme 13.

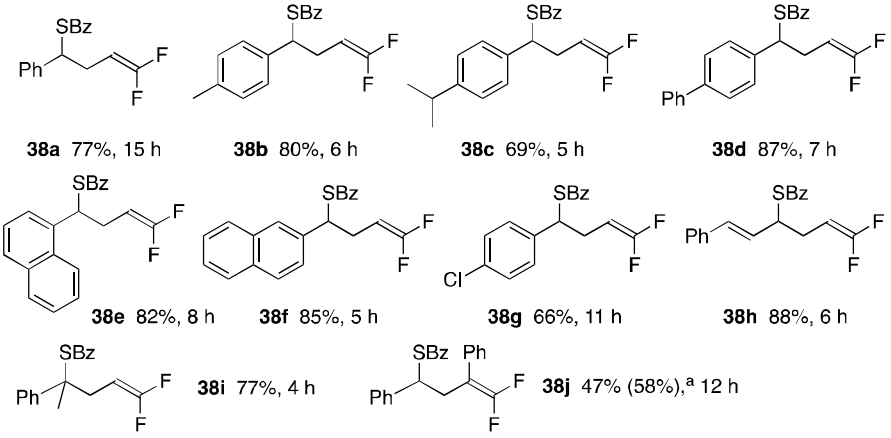
When (trifluoromethyl)cyclopropane **37** was allowed to react with thiobenzoic acid in the presence of diethylaluminium chloride, *S*-4,4-difluorohomoallyl thiobenzoates **38** were successfully obtained (Scheme 14).[72] Et_2AlCl abstracted a fluoride ion from **37** to yield CF_2 cations **39**, which were stabilized by electron-donating cyclopropyl group and fluorine substituents. These cations were subsequently trapped by thiobenzoic acid, leading to single activation products **38**. Notably, the further abstraction of fluoride ion, which is not desired, was entirely suppressed owing to the instability of the vinyl cations resulting from the second fluoride abstraction.

The ensuing *S*-4,4-difluorohomoallyl thiobenzoates **38** served as suitable precursors for synthesizing fluorothiophene derivatives **40**.[73,74] Thiobenzoates **38**, when treated with sodium methoxide in *N,N*-dimethylformamide (DMF), an aprotic solvent, underwent debenzoylation followed by nucleophilic addition-elimination in a 5-*endo-trig* fashion to yield ring-fluorinated fluorothiophenes **40** (Scheme 15). Subsequent treatment with DDQ led to the aromatization of **40b**, producing the corresponding fluorothiophene **41b** (Scheme 16).

The addition-elimination process, which afforded **40**, occurred through the cyclized intermediates **42**. Protonation of these intermediates facilitated the synthesis of difluorotetrahydrothiophenes **43** (Scheme 17). Treatment of thiobenzoates **38** with potassium carbonate in a protic solvent, ethanol, trapped **42** *via* protonation, which subsequently resulted in the successful formation of the expected addition products, difluorotetrahydrothiophenes **43**. The syntheses of **40**, **41**, and **43**, which have been infrequently reported, were efficiently achieved through single C–F bond activation of the CF_3 group, enabling short-step syntheses of monofluorothiophene and difluorothiophene derivatives *via* sulfanylation/intramolecular substitution or addition sequences.



37 **39** **38**



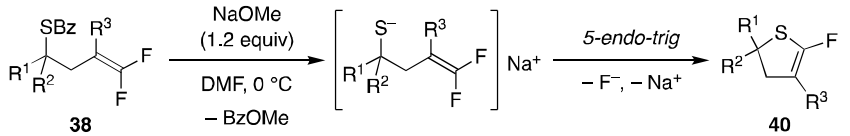
38a 77%, 15 h **38b** 80%, 6 h **38c** 69%, 5 h **38d** 87%, 7 h

38e 82%, 8 h **38f** 85%, 5 h **38g** 66%, 11 h **38h** 88%, 6 h

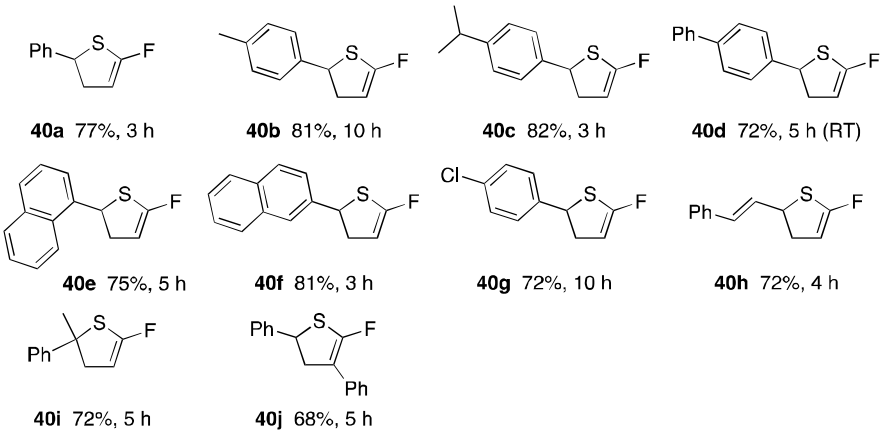
38i 77%, 4 h **38j** 47% (58%),[a] 12 h

Bz = Benzoyl. [a] ^{19}F NMR yield in parentheses.

Scheme 14.



38 **40**



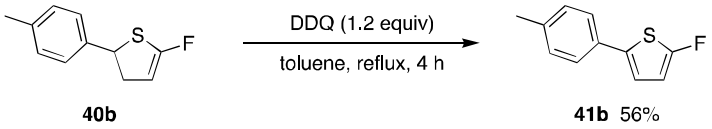
40a 77%, 3 h **40b** 81%, 10 h **40c** 82%, 3 h **40d** 72%, 5 h (RT)

40e 75%, 5 h **40f** 81%, 3 h **40g** 72%, 10 h **40h** 72%, 4 h

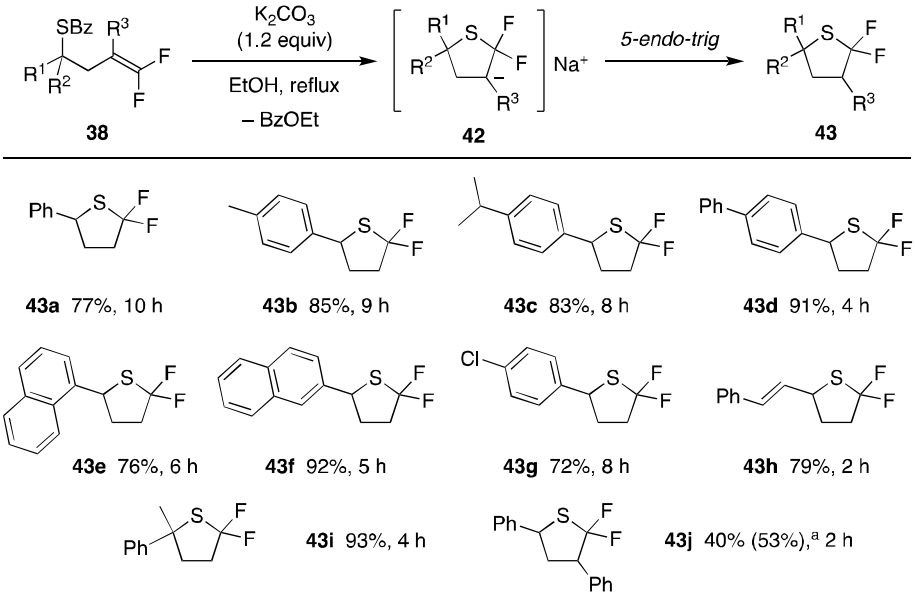
40i 72%, 5 h **40j** 68%, 5 h

Bz = Benzoyl.

Scheme 15.



Scheme 16.



Bz = Benzoyl. [a] ^{19}F NMR yield in parentheses.

Scheme 17.

3.2. Synthesis of (difluoroethyl)benzoxazines *via* regioselective three-membered ring opening

The 1,1-difluoroethyl group ($–CF_2CH_3$) functions as a bioisostere[75-78] of the methoxy group ($–OCH_3$) (Figure 8). For example, in the context of *Plasmodium falciparum* dihydroorotate dehydrogenase inhibitors (DHODH inhibitors) **44**, related to malaria treatment, the introduction of a 1,1-difluoroethyl group ($X=CF_2CH_3$) enhances their metabolic stability, leading to a remarkable improvement in the inhibitory activity (Figure 9).[79]

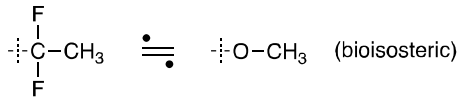


Figure 8.

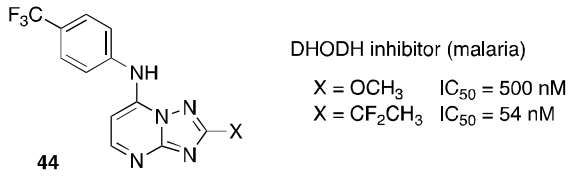
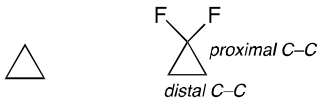


Figure 9.

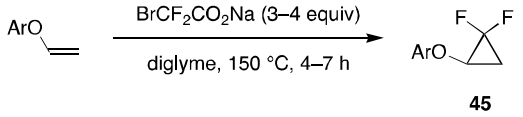
Similar to 1,1-difluorothiiranes mentioned earlier (Section 2.3., Figure 4), 1,1-difluorocyclopropanes are thermally less stable than their parent cyclopropanes.[80] Moreover, their C−C bond cleavage occurs regioselectively at the C–C bond distal to the CF_2 moiety (Figure 10). The advantageous properties resulting from fluorine substitution in cyclopropane rings,[21,59,60] namely increased ring strain and elongated C−C bond distal to the CF_2 moiety, are highly favorable for synthesizing fluorinated compounds.



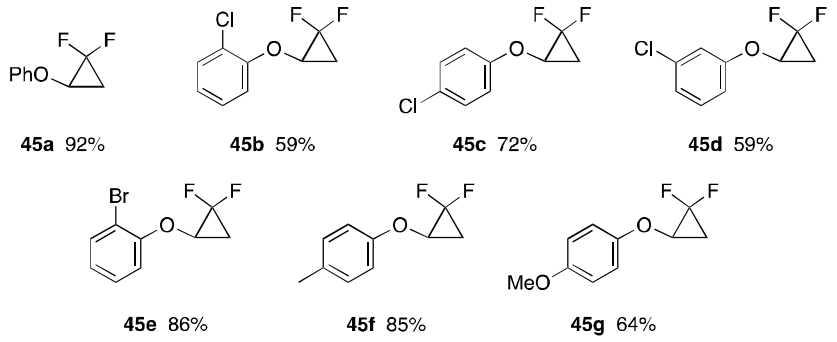
ring strain / kcalmol^{-1}	26.5–28.7	35.7–42.4
C–C bond lengths / Å	1.510	1.553 (distal) 1.464 (proximal)

Figure 10.

The 1,3-benzoxazine framework is frequently found in useful compounds, such as pharmaceuticals[81-83] and functional materials.[84,85] Therefore, 2-(1,1-difluoroethyl)-2*H*-1,3-benzoxazines were synthesized through the fluorine-directed regioselective ring opening of 1,1-difluorocyclopropanes. The starting material 2-aryloxy-1,1-difluorocyclopropanes **45** were readily prepared *via* the difluorocyclopropanation of vinyl ethers using sodium bromodifluoroacetate[86] (Scheme 18).



45

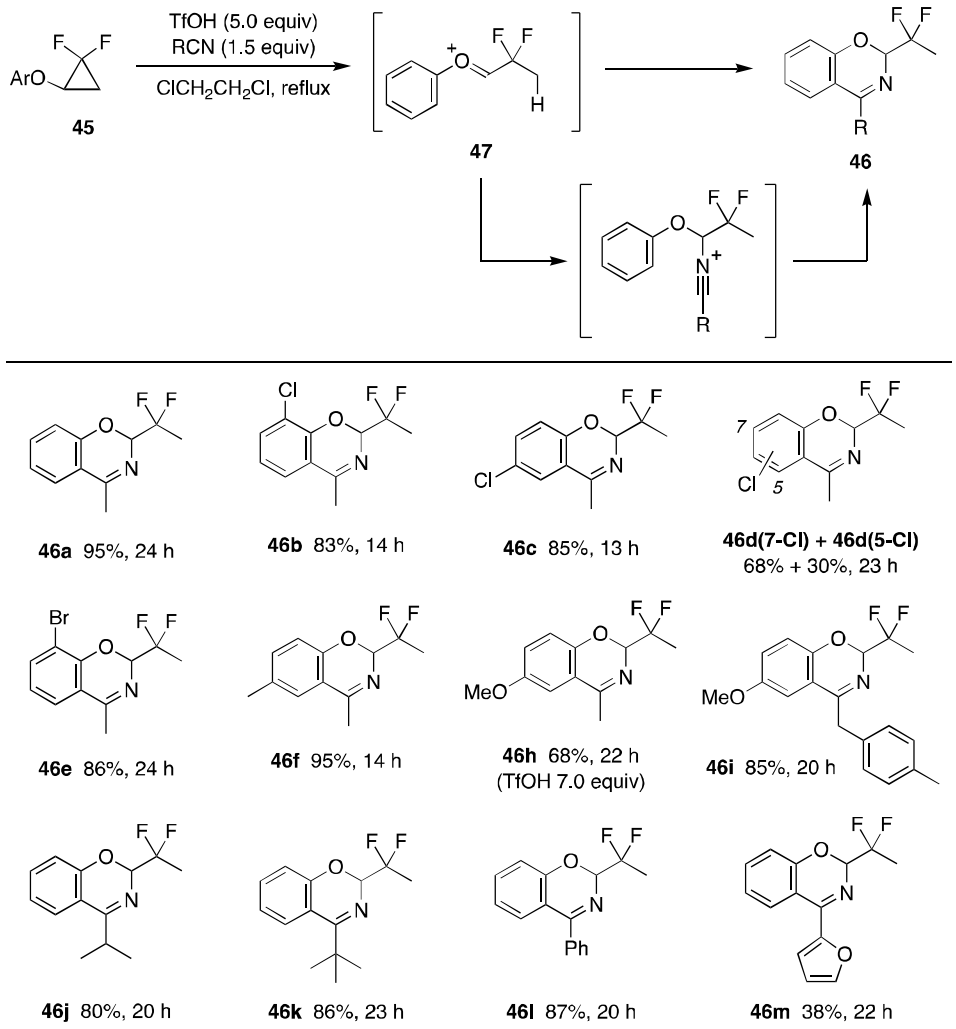


45a 92% **45b** 59% **45c** 72% **45d** 59%

45e 86% **45f** 85% **45g** 64%

Scheme 18.

The introduction of triflic acid-induced regioselective ring opening (distal C–C bond cleavage) of difluorocyclopropanes **45**, followed by an interrupted Ritter reaction, afforded 2-(1,1-difluoroethyl)-2*H*-1,3-benzoxazines **46** (Scheme 19).[87] *gem*-Difluorocyclopropane **45** when treated with triflic acid in the presence of various nitriles underwent regioselective protonation of the *gem*-difluorocyclopropane moiety, generating cationic intermediates **47**. These intermediates were then trapped with nitriles, followed by a Friedel-Crafts-type ring closure to produce benzoxazines **46**.



Scheme 19.

4. Conclusions

Our fluorocarbene-based syntheses of heterocycles bearing fluorine substituent(s) or fluorine-containing substituents on their rings were comprehensively outlined. The key components in these syntheses were difluorocarbene, (trifluoromethyl)carbene, and their transition metal complexes. These species demonstrated versatility for both the direct synthesis of fluorinated/difluoromethoxylated/difluoromethylsulfanylated heterocycles, and the indirect construction of fluorinated/difluoroethylated rings *via* fluorinated cyclopropanes. The cooperation of organofluorine and carbene chemistry efficiently yielded various fluorine-containing heterocyclic compounds.

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Number JP20K05486 (K.F.) in Grant-in-Aid for Scientific Research (C) and JSPS KAKENHI Grant Number JP23K04747 (K.F.) in Grant-in-Aid for Scientific Research (C).

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