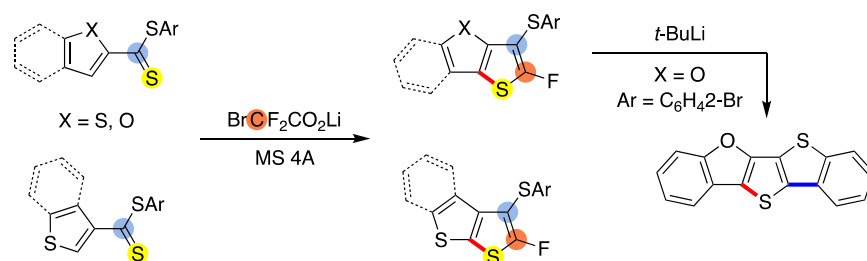


Construction of Thienothiophene and Thienofuran Ring Systems via Ring Expansion of Difluorothiiranes Generated from Dithioesters

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TOC Graphic



Supporting Information Placeholder

ABSTRACT: The reaction of aryl thiophene-2-carbodithioates or thiophene-3-carbodithioates with difluorocarbene generated from $\text{BrCF}_2\text{CO}_2\text{Li}$ /molecular sieves 4A produced arylsulfanylated 2,2-difluoro-3-thienylthiiranes. In the presence of lithium ion, the thiirane intermediates underwent ring expansion followed by HF elimination, leading to fluorinated thieno[3,2-*b*]thiophenes or thieno[2,3-*b*]thiophenes. The reactions of the oxygen analogs, aryl furancarbodithioates, also proceeded to afford the corresponding thieno[3,2-*b*]furans. Intramolecular fluorine substitution in the produced arylsulfanyl(fluoro)thienofurans allowed another thiophene ring construction, leading to the synthesis of fused pentacyclic thienothienofurans.

Sulfur-containing π -extended molecules have gained considerable attention as organic electronic materials.¹ As representative examples, oligothiophenes and polythiophenes **A**, in which every two thiophene rings are connected to each other by a C–C single bond, have been studied since the early stages of this field (Figure 1).² Meanwhile, thienoacenes **B**, in which every two thiophene rings share a C–C double bond, have also been investigated over the past few decades.³ Apart from these materials consisting solely of thiophene rings, mixed materials containing thiophene and benzene rings have also been developed, including acenedithiophenes **C**,⁴ alternately fused benzothiophenes **D**,⁵ and diacene-fused thienothiophenes **E**.⁶ Among

these thiophene-based π -extended molecules, thienothiophene ring systems are of great interest as structural motifs in materials for electronic devices. Thus, new synthetic methods for thienothiophenes and their analogs are still highly desirable.⁷

We have recently reported the synthesis of 1,1-difluoro-1-alkenes via desulfurization of 2,2-difluorothiiranes.⁸ This

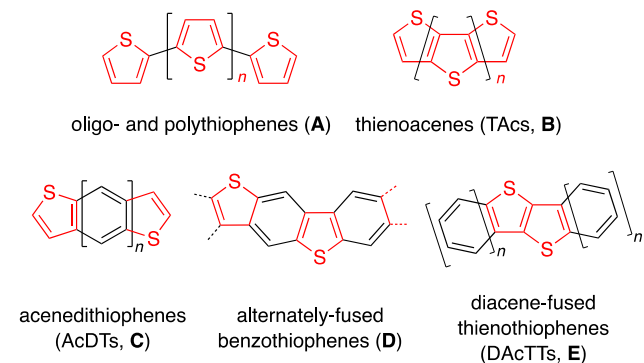
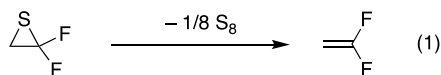


Figure 1. π -Extended Semiconducting Materials Consisting of Thiophene Rings.

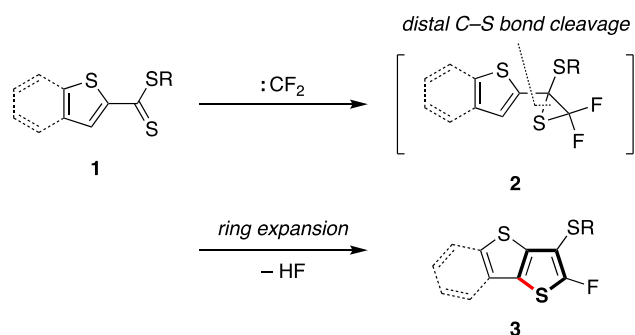
approach involves the reaction of dithioesters and thio-ketones with difluorocarbene, which is generated from trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA)⁹ and a catalytic amount of 1,8-bis(dimethylamino)naphthalene (proton sponge),¹⁰ to form 2,2-difluorothiiranes. Unlike fluorine-free thiiranes,¹¹ the formed difluorothiiranes undergo facile

elimination of elemental sulfur without requiring any reducing agent,¹² leading to 1,1-difluoroalkenes (Barton–Kellogg-type difluoromethylidenation, eq 1). Theoretical calculations of the structure of 2,2-difluorothiiranes revealed that the fluorine substituents widen the S–CF₂–C bond angle and elongate the S–C bond distal to the difluoromethylene moiety.^{8b} The additional ring strain thus induced (ca. 7 kcal/mol) was ascribed to the electron-withdrawing inductive effect of the fluorine substituents. However, despite such an enhanced reactivity, no synthetic reactions other than desulfurization have been reported to date for difluorothiiranes.



2,2-Difluorothiiranes are potential intermediates for the synthesis of fluorinated sulfur compounds, if the elimination of elemental sulfur is prevented. Thus, we selected 2,2-difluorothiiranes as precursors for the synthesis of thienothiophenes. According to the designed synthetic route depicted in Scheme 1, the reaction of thiophenecarbodithioates **1**, which are readily prepared from commercially available starting materials, with difluorocarbene would generate the corresponding 2,2-difluorothiiranes **2**. Then, ring expansion would occur via selective cleavage of the C–S bond distal to the difluoromethylene moiety,¹³ followed by hydrogen fluoride (HF) elimination, to afford sulfanylated fluorothiophenes **3**.¹⁴ In addition, the remaining sulfanyl and fluorine substituents could be expected to facilitate further extension of the thiophene system.

Scheme 1. Our Strategy for the Synthesis of Thienothiophenes by Ring Expansion of Difluorothiiranes



To achieve the aforementioned selective C–S bond cleavage without desulfurization, we focused on the coordination of a Lewis acid to enhance the electron-withdrawing inductive effect of the fluorine substituents (Figure 2). Theoretical calculations revealed that the S–CF₂–C bond angle of the Li-coordinated difluorothiirane **2a-Li** (R = Ph) is significantly wider (104.2° vs. 70.3°) and the C–S bond (a, Figure 2) distal to the CF₂ moiety is much longer (2.58 Å vs. 1.91 Å) than

those of the parent compound **2a**. It must be noted that the proximal C–S bond (b, Figure 2) is somewhat shortened in **2a-Li** (1.76 Å vs. 1.80 Å), suggesting the distinct possibility of the desired selective cleavage of the distal C–S bond.

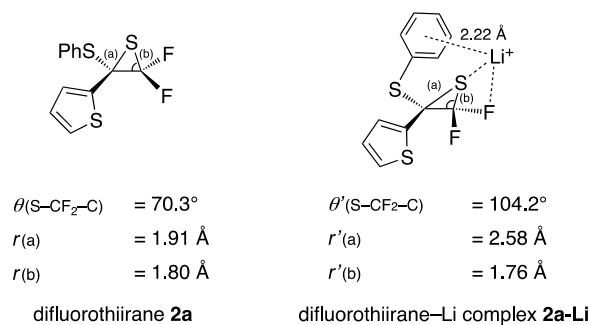
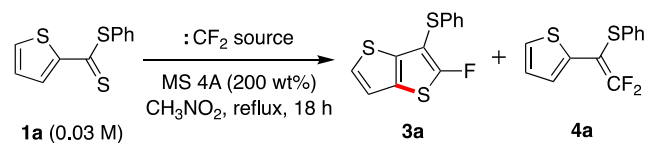


Figure 2. Selected Structural Parameters of Difluorothiirane **2a** and its Li⁺ Complex **2a-Li**.

As the difluorocarbene source, we investigated a series of bromodifluoroacetates, which contain Lewis acidic alkaline metal ions (Table 1). Phenyl thiophene-2-carbodithioate **1a** was selected as a model substrate and treated with 3 equiv of lithium bromodifluoroacetate (BrCF₂CO₂Li) in the presence of molecular sieves 4A (MS 4A, 200 wt%) in refluxing nitromethane (Table 1, entry 1, method A). A ¹⁹F NMR analysis of the resulting mixture indicated that the desired thieno[3,2-*b*]thiophene (*anti*-fused thienothiophene) **3a** was obtained as a sole product in 78% yield. In contrast, the use of sodium,¹⁵ potassium, or cesium acetates afforded a substantial amount of 1,1-difluoroalkene **4a** as a by-product via undesired desulfurization [Table 1, **3a/4a** = 81:19 (Na, entry 2); 87:13 (K, entry 3); 88:12 (Cs, entry 4)]. Meanwhile, triphenylphosphoniodifluoroacetate (Table 1, entry 5) and TFDA/proton sponge (Table 1, entry 6), which contain no alkaline metal ions, gave poor selectivities for **3a**, which suggests that the Lewis acidity of metal ions, especially Li⁺,¹⁶ promoted the ring construction.¹⁷

Table 1. Optimization of Thiophene Ring Construction



entry	:CF ₂ source (equiv)	product / % ^a	
		3a + 4a (ratio)	1a ^b
1 ^c	BrCF ₂ CO ₂ Li (3)	78 (3a only)	–
2	BrCF ₂ CO ₂ Na (3)	73 (81:19)	–
3	BrCF ₂ CO ₂ K (3)	69 (87:13)	–
4	BrCF ₂ CO ₂ Cs (3)	41 (88:12)	49
5	Ph ₃ PCF ₂ CO ₂ (PDFEA)	51 (4a only)	–

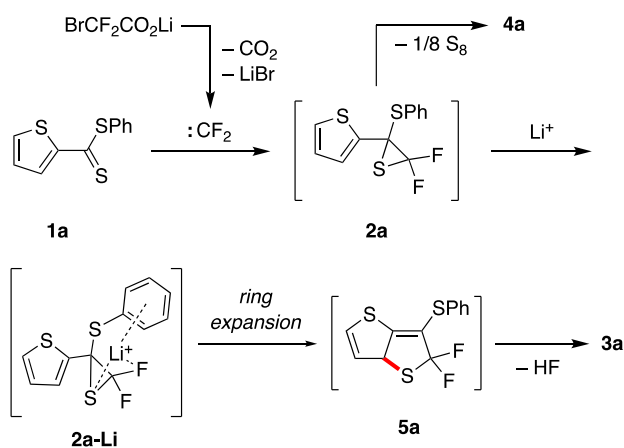
^a ¹⁹F NMR yield based on an internal standard PhCF₃; the carbene source was consumed in all the entries. ^b Recovery.

^c Method A. ^d Toluene, 90 °C, 1 h. ^e 80 °C, 0.5 h. PS = proton sponge.

Of note, BrCF₂CO₂Li hardly decomposed in refluxing nitromethane in the absence of MS 4A.¹⁸ Its decomposition into difluorocarbene was promoted by MS 4A at 100 °C with a half lifetime (*t*_{1/2}) of 70 min (40 wt% MS 4A). Although the sodium, potassium, and cesium salts decomposed readily without MS 4A [*t*_{1/2} = 28 min (Na, 100 °C); *t*_{1/2} = 5.5 min (K, 100 °C), 7.9 min (K, 80 °C); *t*_{1/2} = 6.7 min (Cs, 80 °C)],¹⁹ it is likely that the rapid difluorocarbene generation resulted in carbene dimerization,²⁰ leading to the recovery of the starting compound **1a** (Table 1, entry 4).²¹

Scheme 2 shows a plausible mechanism for this reaction. Initially, substrate **1a** undergoes [2 + 1] cycloaddition with difluorocarbene generated from BrCF₂CO₂Li to form 2,2-difluorothiirane **2a**.²² Its ring expansion proceeds via Li complex **2a-Li** to form dihydrothiophene **5a**, followed by HF elimination to afford thienothiophene **3a**.²³ Competitive desulfurization occurs from **2a**, leading to 1,1-difluoroalkene **4a** as a by-product.²⁴

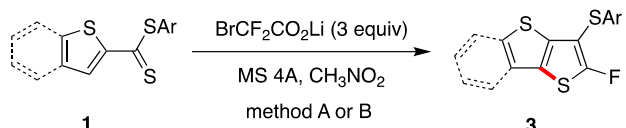
Scheme 2. Plausible Mechanism for Thiophene Ring Construction



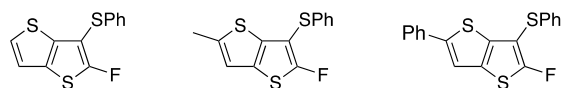
Next, we investigated the scope of the thiophene ring construction using other thiophene-2-carbodithioates (Figure 3). *Anti*-fused thienothiophenes **3a-c**, including methyl- and phenyl-substituted ones, were synthesized in 65%–81% isolated yields using BrCF₂CO₂Li under the aforementioned reaction conditions (Table 1, entry 1: method A). Although benzo-fused substrates **1d-g** were less reactive under the aforementioned conditions, the corresponding benzothienothiophenes **3d-g**, bearing a methyl, chloro, or (2-bromophenyl)sulfanyl group, could be obtained in

55%–79% yields at a higher temperature (140 °C) under microwave irradiation (method B). Thiophene-3-carbodithioates also underwent thiophene ring construction in a similar manner to afford the corresponding *syn*-fused products (Figure 4). Thus, thieno[2,3-*b*]thiophenes **3h-m**, including bromo-, chloro-, and methoxy-substituted ones, were synthesized from the corresponding substrates **1h-m** in 60–81% yields (method A). Benzo-fused substrates **1n** and **1o**, of which the latter was brominated, afforded the corresponding *syn*-fused benzothienothiophenes **3n** and **3o** in 73% and 76% yields, respectively (method B). The structures of **3d**, **3k**, and **3n** were confirmed by single crystal X-ray structure analysis.

We also applied the present thiophene ring construction to aryl benzofuran-2-carbodithioates **6** (Scheme 3). When **6a** and **6b** were subjected to similar conditions to those of method B, the corresponding thieno[3,2-*b*]furans **7a** and **7b** were successfully obtained in 72% and 62% yields, respectively. In aromatic nucleophilic substitution reactions,²⁵ fluoroarenes are best substrates compared with other haloarenes. Thus, brominated **7b** was treated with *tert*-butyllithium (2 equiv) in THF at –78 °C. The aryllithium thus generated successfully underwent intramolecular substitution of the thienyl fluoride via an addition–elimination mechanism to afford fused pentacyclic thienothienofuran **8b** in 67% yield. It is worth mentioning that highly π -conjugated thienothienofurans, such as **8**, are promising as a new type of material for electronic devices, and that methods for their synthesis have been hardly ex-

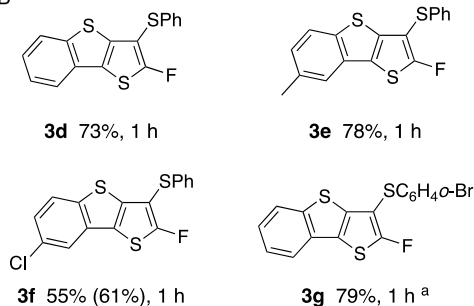


method A



3a 81%, 7 h **3b** 80%, 4 h **3c** 65% (74%), 4 h

method B



3d 73%, 1 h

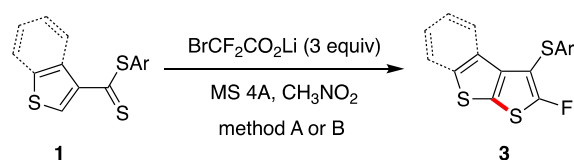
3e 78%, 1 h

3f 55% (61%), 1 h

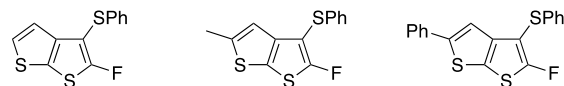
3g 79%, 1 h^a

Isolated yield (¹⁹F NMR yield based on the internal standard PhCF₃ is indicated in parentheses). Method A: **1** (0.03 M), MS 4A 200 wt%, reflux; method B: **1** (0.1 M), MS 4A 100 wt%, microwave, 140 °C (sealed). ^a **1g** 0.03 M.

Figure 3. Synthesis of Thieno[3,2-*b*]thiophenes from Aryl Thiophene-2-carbodithioates.



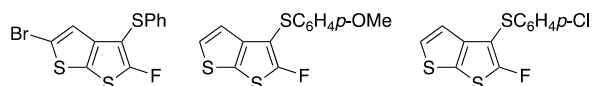
method A



3h 81%, 7 h

3i 71%, 4 h

3j 78%, 4 h

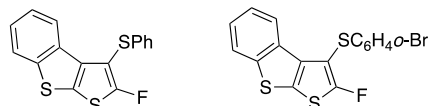


3k 69% (78%), 4 h

3l 72%, 4 h

3m 60% (69%), 4 h

method B



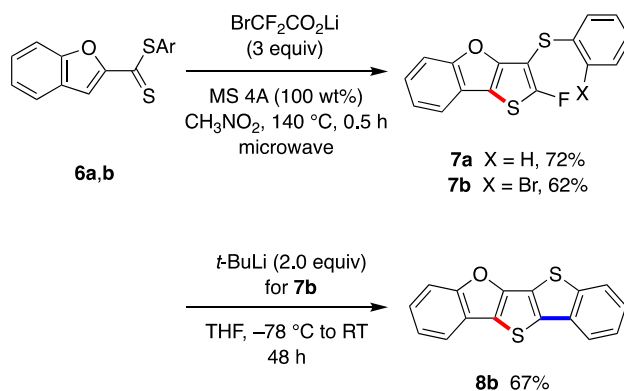
3n 73%, 1 h^a

3o 76%, 1 h^b

Isolated yield (¹⁹F NMR yield based on the internal standard PhCF₃ is indicated in parentheses). For methods A and B, see Figure 3. ^a 18% recovery of **1n**. ^b **1o** 0.03 M.

Figure 4. Synthesis of Thieno[2,3-*b*]thiophenes from Aryl Thiophene-3-carbodithioates.

Scheme 3. Synthesis of Thienofurans and Thienothienofurans



In summary, we have developed a powerful method for the synthesis of fused thienothiophenes based on the ring expansion of difluorinated thiiranes. The reaction of thiophenecarbodithioates with difluorocarbene generated 2,2-difluoro-3-thienylthiiranes, which underwent ring expansion/HF elimination to afford fluorinated thieno[3,2-*b*]thiophenes and thieno[2,3-*b*]thiophenes, depending on the positions of dithioate moieties. The oxygen analogs, i.e., fluorinated thieno[3,2-*b*]furans, were also synthesized using a similar ring expansion protocol. Further thiophene ring extension via lithiation of the products provides an approach to new materials for organic electronics.

ASSOCIATED CONTENT

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. I.M., A.Y., D.M., R.T., and K.F. also planned the experiments. I.M., A.Y., and D.M. 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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Dedicated to Professor Emeritus Koichi Narasaka (the University of Tokyo) with Gratitude on the Occasion of his 77th Birthday (Kiju).

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Notes

The authors declare no competing financial interest.

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- (21) When the reaction of **1a** was performed with BrCF₂CO₂Na/MS 4A at a lower temperature (80 °C, 18 h), the yield of the products (**3a** + **4a**) was not improved (61% yield, **3a/4a** = 87:13) and **1a** was recovered (28% yield).
- (22) Although the generation of difluorothiiranes was confirmed in our previous difluoromethylidenation of phenyl benzenecarbodithioate (ref 8a), thiophenecarbodithioate-derived difluorothiiranes **2** were not observed in the present system.
- (23) The reaction of **1a** with BrCF₂CO₂Li in the presence of *i*-Pr₂NEt (1.1 equiv) afforded **3a** in poor yield (9%) with recovery of **1a** (68%).
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