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Advanced Synthesis & Catalysis

Synthesis of Fluoromethyl-Substituted Cyclopropanes by Electrophilic Cyclization of Homoallylic Boronate Intermediates

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Abstract: The electrophilic cyclization via the boronate complex between various homoallylic boronates and Selectfluor® is reported. This reaction provides a fluoromethylated cyclopropane ring that was difficult to synthesize by previous methods. The use of phenyl lithium, which activates the homoallylic boronate, is important for the reaction. The intermediate boronate species in this reaction was observed through $^{11}B\{^{1}H\}$ NMR experiments. We also demonstrate the synthesis of a building block, including fluoromethyl-substituted cyclopropane for a bioactive compound.

Keywords: Organoboronate complex 1; Organofluorine compound 2; Cyclopropane 3; Electrophilic cyclization 4; Organoboron compound 5

Significant studies on synthesizing cyclopropane structures have been conducted, and many conventional methods, such as carbenoid reactions (e.g., the Simons–Smith and Kulinkovich reactions) and ylide reactions (e.g., the Corey–Chaykovsky reaction), have been utilized.[1] However, more modern strategies for constructing cyclopropane rings have recently been developed, e.g., the stereoselective reaction of diazo-derived carbenoids to alkenes with chiral transition metal catalysts and modified enzyme catalysts.[2,3] Recently, the construction of cyclopropane rings bearing fluorinated moiety has been widely explored.[4] Because both cyclopropane and fluoro groups are important structures in drug design, cyclopropanes bearing fluorinated moiety would be valuable for the discovery of new bioactive compounds. Although many studies have been reported on the construction of cyclopropanes bearing trifluoromethyl and difluoromethyl groups have been reported, there are limited examples of the construction of fluoromethyl-substituted cyclopropanes, including nucleophilic substitution, cyclopropanation with active methylene nucleophiles and addition of carbene intermediates (Figure 1A).[5–9]

Organoboron compounds are currently among the most widely used synthetic intermediates because boron groups can be efficiently converted into various functional groups under mild reaction conditions.[10] More recently, reactions using organolithium reagents as an activator of organoboronate esters have emerged to achieve organoboronates with high nucleophilicity.[11] This enables the enhancement of the nucleophilicity of organoboronates and the development of novel organoboronate reactions with various electrophiles.[12,13] In this regard, Aggarwal et al. reported the stereospecific electrophilic fluorination of optically active organoboronates using phenyl lithium (PhLi) and Selectfluor® (Figure 1B).[14] Furthermore, the same group reported the stereospecific allylic functionalization of allylboronate and various electrophiles via organoboronate complexes activated by organolithium reagents.[15] In a related cyclopropanation, Hussain et al. reported the electrophilic cyclization of homoallylic boronates where the boronate was first activated by PhLi and the subsequent electrophilic reaction of trichloroisocyanuric acid (TCCA) occurs across the double bond to form the 1-chloromethyl cyclopropane ring stereoselectively (Figure 1B).[16] In this paper, only the chlorination case was presented, and it is not clear whether other electrophiles are applicable. We expect that if a similar electrophilic cyclization with fluorination occurs, this can be a useful method for preparing fluoromethyl-substituted cyclopropanes.

Herein, we report the electrophilic cyclization reaction of a homoallylic boronate using Selectfluor®

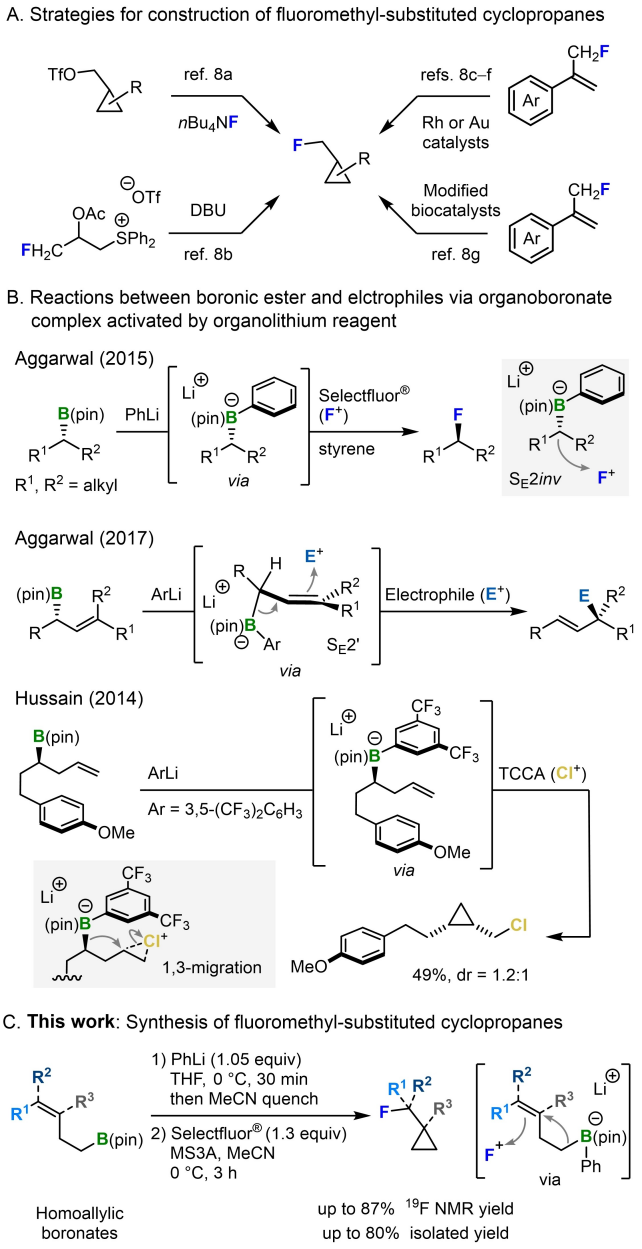


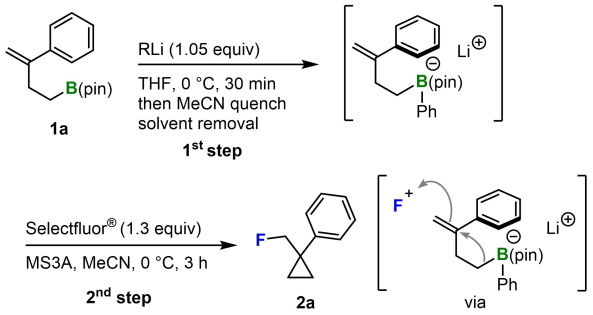
Figure 1. Introduction of fluoromethyl-substituted cyclopropanes and background of reactions using boronate complexes as nucleophiles.

as the electrophile in combination with PhLi as an activator of the boronates. In this reaction, the nucleophilic boronate complex is the first to be formed, followed by the α-carbon attack to the internal carbon of the terminal double bond that is activated by Selectfluor® (Figure 1C). This reaction produces a variety of fluoromethyl-substituted cyclopropanes, which are difficult to synthesize using previously reported methods.[8] Furthermore, the utility of this method was demonstrated by the synthesis of a building block, fluoromethyl-substituted cyclopropane, as a bioactive compound.

We optimized the reaction conditions for the reaction of *exo*-methylene homoallylic boronate using Selectfluor® as an electrophile.[14] Homoallylic boronate compound **1a** was first treated with an organolithium reagent at 0 °C for 30 min and then quenched with acetonitrile. After solvent removal at room temperature, the mixture was diluted by acetonitrile, and Selectfluor® was added at 0 °C. Pleasingly, we obtained **2a** in 57% ^{19}F NMR yield using 1.05 equiv. of PhLi at 0 °C (Table 1, entry 1, 57%). Furthermore, we tested other organolithium reagents, which were generated in situ by lithium/halogen exchange of the corresponding aryl bromides and *n*-butyllithium (*n*-BuLi), to tune the nucleophilicity of the boronate complex; the desired product was obtained in low or trace yields (Table 1, entries 2 and 3, 21% and trace).[11d] *n*-BuLi was unsuitable for this system (Table 1, entry 4, trace).[11d] We found that the amount of PhLi (1.05 equiv.) had a significant impact on the yield of the desired product (Table 1, entries 5–7, trace–50%). Using CH_2Cl_2 as the solvent during the formation of the boronate complex resulted in a low yield (Table 1, entry 8, 15%). We attempted to enhance the reaction by introducing 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in the second electrophilic cyclization step to stabilize the cationic intermediate.[17] However, this led to a slight decrease in the yield (Table 1, entry 9, 49%). When the second step was conducted without removing the solvents after the first step, a decreased yield was observed (Table 1, entry 10, 37%). Although the effect of other parameters, such as 1.1 equiv. Selectfluor® and longer reaction time, were also tested, the yield of the desired product slightly decreased (Table 1, entries 11 (51%) and 12 (52%)).

With the optimized reaction conditions in hand, we next investigated the scope of homoallylic boronates (Table 2). The reaction of aryl-substituted *exo*-methylene substrates with simple aromatics afforded the desired products in moderate yields (**2a**–**2c**, 34–77%, details of X-ray analysis for **2b** are described in Supporting Information).[18] Electron-donating groups, such as methoxy groups, and electron-withdrawing substituents, such as halides, were tolerated in this reaction. The homoallylic boronates containing silyl ether (**1d**) and methyl ether (**1e**–**1g**) afforded the desired products (**2d**–**2g**, 32–87%). The yield of products varied depending on the substitution position of the methoxy group (*p*-MeO: **2e**, 70%; *m*-MeO: **2f**; *o*-MeO: 59%; **2g**, 32%). Halogens on the aryl ring (F and Cl) could also be employed (**2h**, 62%; **2i**, 36%). Alkyl-substituted *exo*-methylene homoallylic boronates were also acceptable (**2j**, 44%). 3,4-Disubstituted homoallylic boronate (**2k**, 53%) and 3,4,4-trisubstituted homoallylic boronate (**2l**, 80%) afforded the desired products in good yields. Unfortunately, the

Table 1. Optimization of the reaction conditions.[a]



Entry	RLi	Deviation from the standard conditions	**2 a** (%)[b]
1	PhLi	None	57 (25)[c]
2	3,5-$(CF_3)_2C_6H_3Li$	0.95 equiv. of organolithium reagent was used	21
3	*p*-$MeOC_6H_4Li$	0.95 equiv. of organolithium reagent was used	Trace
4	*n*-BuLi	0.95 equiv. of organolithium reagent was used	Trace
5	PhLi	0.95 equiv. of PhLi	50
6	PhLi	1.2 equiv. of PhLi	35
7	PhLi	2.0 equiv. of PhLi	Trace
8	PhLi	CH_2Cl_2 instead of THF	15
9	PhLi	HFIP:MeCN = 1:1 instead of MeCN in 2nd step	49
10	PhLi	without solvent removal	37
11	PhLi	1.1 equiv. of Selectfluor®	51
12	PhLi	Reaction time 6 h	52

[a] Reaction conditions: **1 a** (0.2 mmol), 1.05 equiv. of organolithium reagent, and 1.3 equiv. of Selectfluor®. The total solvent volume (0.05 M) was adjusted to 4 mL in the second step.
[b] Determined by ^{19}F NMR analysis of the crude product with fluorobenzene as the internal standard.
[c] Isolated yield.

monosubstituted (**1 m**) and geminal-disubstituted (**1 n**) homoallylic boronates did not afford the desired cyclopropane products. In many cases, the isolated yield of the products is low compared to their NMR yield. This is mainly due to the difficulty of removing a small amount of the by-products and the loss from evaporation during the purification step.

Next, we conducted $^{11}B\{^1H\}$ NMR experiments to confirm the formation of the boronate complex (Figure 2; for details of the experiments, see Supporting Information). NMR experiment results showed that the treatment of homoallylic boronate **1 a** with 1.0 equiv. of PhLi in CD_3CN-d_3 led to the formation of the corresponding boronate complex (δ 7.5 ppm). On adding Selectfluor® to the boronate complex solution, cyclization resulted in the formation of cyclopropanation product **2 a**.

Finally, we demonstrated the utility of this cyclization reaction for the synthesis of an important intermediate of fluoromethylated cyclopropane-containing bioactive compounds (Scheme 1).[19] We were able to obtain the corresponding boronic acid (**3**) in 74% yield via a Pd-catalyzed borylation reaction.[20]

In summary, we have demonstrated the synthesis of fluoromethylated cyclopropanes from homoallylic boronates via electrophilic cyclization. This method could

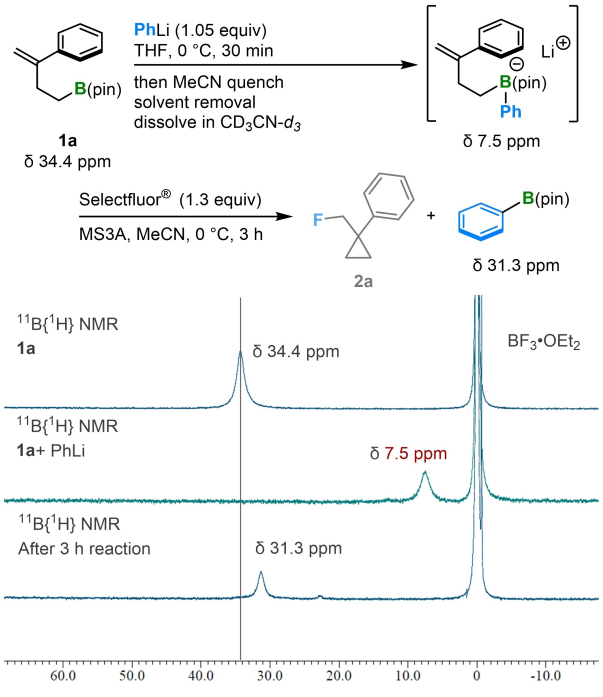
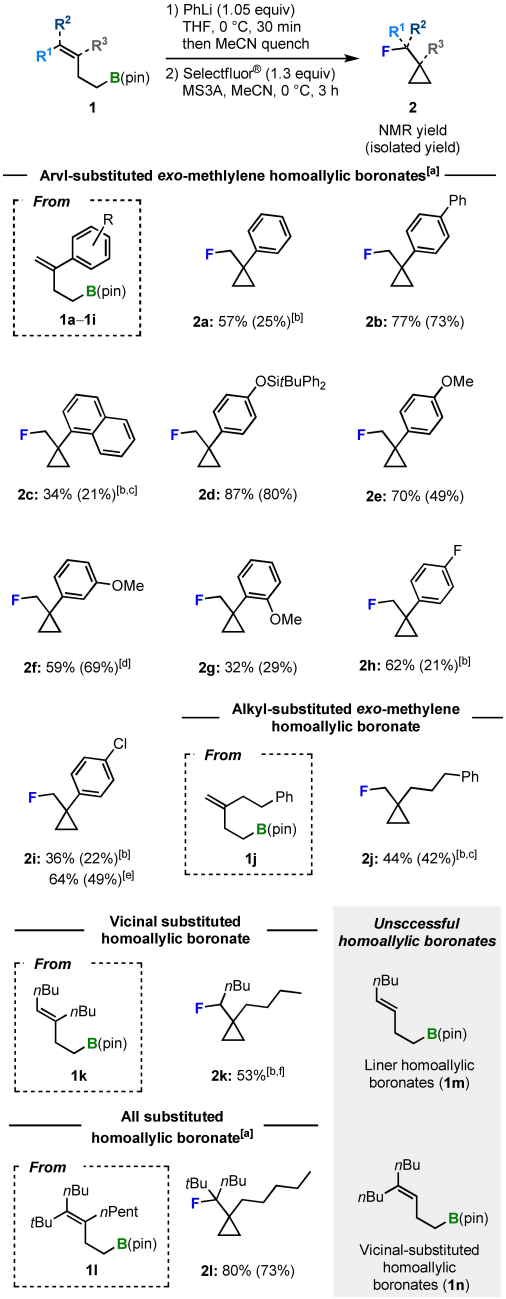
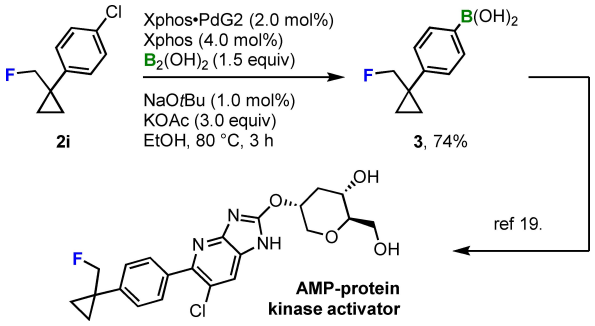


Figure 2. $^{11}B\{^1H\}$ NMR experiments.

Table 2. Scope of homoallylic boronates.



[a] Reaction conditions: **1** (0.2 mmol), 1.05 equiv. of organolithium reagent, and 1.3 equiv. of Selectfluor®. The total solvent volume was adjusted to 4 mL (0.05 M) in the second step. Yields were determined using ^{19}F NMR analysis of the crude product with fluorobenzene as the internal standard. The isolated yields are shown in parentheses.
[b] The reaction was conducted on a 0.4 mmol scale.
[c] Containing small amounts of inseparable and unidentified impurities.
[d] Containing a small amount of phenylboronic acid pinacol ester.
[e] The reaction was conducted on a 1.0 mmol scale.
[f] **2k** was detected by ^{19}F NMR and could not be isolated due to its instability during purification.



Scheme 1. Application to the formal synthesis of a bioactive compound. The reaction was conducted on a 0.24 mmol scale.

be applied to various substrates. Following this approach, the newly synthesized fluoromethylene-substituted cyclopropanes, which are difficult to access via other approaches, are expected to be used as novel building blocks for introducing fluorine-containing cyclopropane motifs into synthetic targets or new intermediates.

Experimental Section

Homoallylic boronate **1a** (56.2 mg, 0.2 mmol) was placed in an oven-dried reaction vial. The vial was sealed with a screw cap containing a Teflon®-coated rubber septum and connected to a vacuum/nitrogen manifold through a needle. The mixture was evacuated and backfilled with nitrogen. This cycle was repeated thrice. Next, dry THF (2 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 minutes, after which, PhLi (115 µL, 1.05 equiv.) was added to the mixture. The reaction mixture was stirred at 0 °C for 30 min. The mixture was subsequently incubated by stirring at room temperature for 10 min. THF was then removed in vacuo, and the crude dissolved in dry MeCN (2.0 mL) and allowed to cool to 0 °C, and stirred for 10 min at the same temperature. Another oven-dried reaction vial was charged with Molecular sieves 3 A (80 mg) and dried in vacuo using a heat gun. After Selectfluor® (92.1 mg, 1.3 equiv.) was added, the vial was connected to a vacuum/nitrogen manifold through a needle. The mixture was evacuated and backfilled with nitrogen. This cycle was repeated thrice. Dry MeCN (1.4 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 min. The boronate complex solution (2.0 mL in MeCN) was added dropwise to the vial containing the Selecfluor® solution at 0 °C and stirred at 0 °C for 3 h. The reaction mixture was then passed through a short silica gel column (Φ: 10 mm, height of the silica-gel column: 30 mm), eluting with Et_2O. The solvent was then removed using a rotary evaporator in an ice bath (the product was volatile under pressure). The crude material was purified by flash column chromatography (SiO_2: Et_2O/pentane, 0:100–4:96) and further purified by recycling preparative gel permeation chromatography to yield the corresponding cyclopropane product **2a** as a colorless oil.

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COMMUNICATIONS

Synthesis of Fluoromethyl-Substituted Cyclopropanes by Electrophilic Cyclization of Homoallylic Boronate Intermediates

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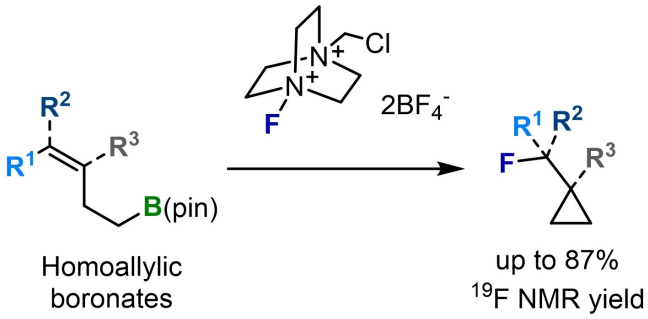

• New fluorine containing buiiding block