이학석사학위논문

Electrochemical Fluorination of Alkyl Boronate through Carbocation Intermediates

탄소 양이온 중간체를 통한 알킬 유기붕소 화합물의

전기화학적 불소화 반응

2022년 8월

서울대학교 대학원

화학부 유기화학 전공

임 태 영

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임태영의 석사학위논문을 인준함

2022년 8월

위 원 장 권 용 훈 (인)

부 위 원 장 이 홍 근 (인)

위 원 이 철 범 (인)

Electrochemical Fluorination of Alkyl Boronate through Carbocation Intermediates

Supervisor: Prof. Hong Geun Lee

By

TaeYeong Im

A Thesis for M.S. Degree

In Organic Chemistry

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Department of Chemistry

Graduate School

Seoul National University

ABSTRACT

Described in this dissertation is a novel electrochemical strategy for nucleophilic fluorination of alkyl organoboronates. The main feature of this reaction is the formation of carbocation intermediates under electrochemical oxidation conditions followed by fluoride attack to form the carbon–fluorine bonds. Through screening experiments, it has been confirmed that potassium bifluoride (KHF_2) is a fluoride source. In addition, it is found that the current and the reaction time are important factors for the success of the transformation. The ^{11}B NMR study has demonstrated that the addition of a fluoride anion to the empty p orbital of the boron center forms the oxidatively reactive boronate species, which then undergoes sequential anodic oxidation to generate radical and carbocationic intermediates. The electrochemically-mediated bond-forming method is highly effective for the functionalization of sterically hindered tertiary sp^3-hybridized carbon atoms. Moreover, the fluorination at the benzylic position was shown to be viable with the developed strategy. Finally, the developed reaction could be applied to radiofluorination of an organic boronate.

Keywords: Nucleophilic Fluorination, Electrochemistry, Radiofluorination

Student Number: 2018-26976

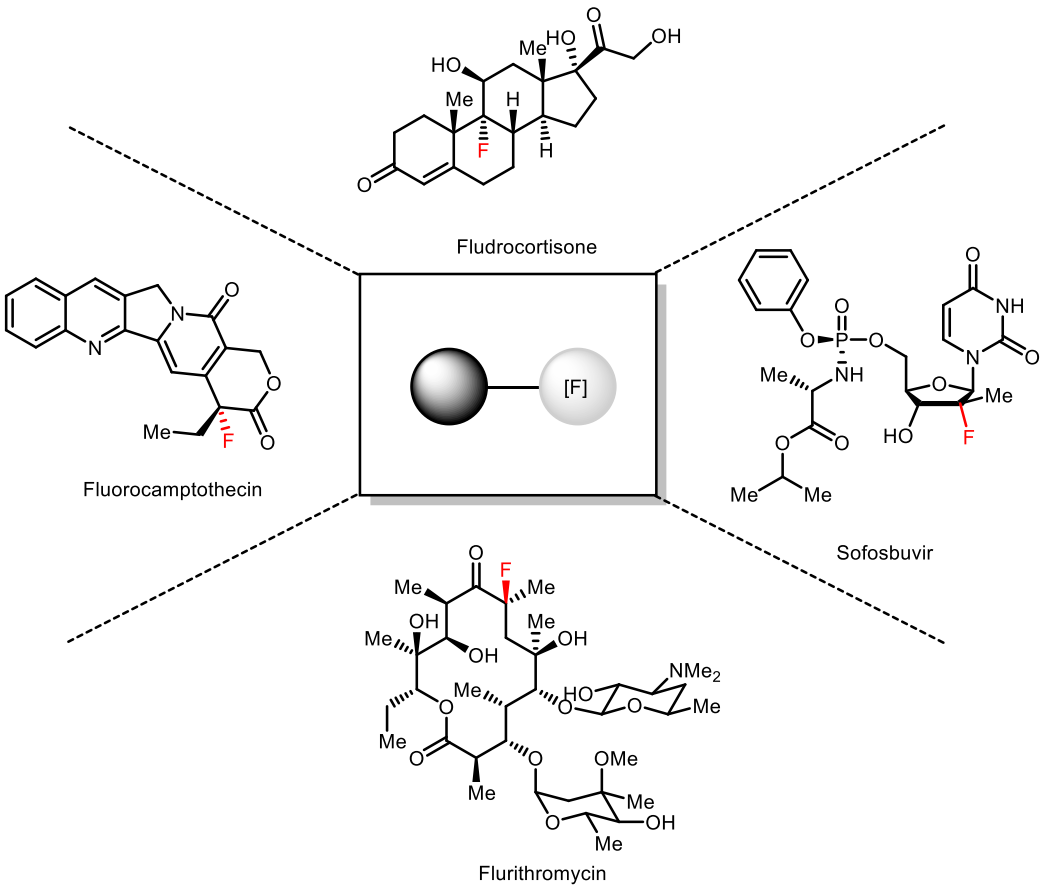
CONTENTS

Electrochemical Fluorination of Alkyl Boronate through Carbocation Intermediates

1. INTRODUCTION

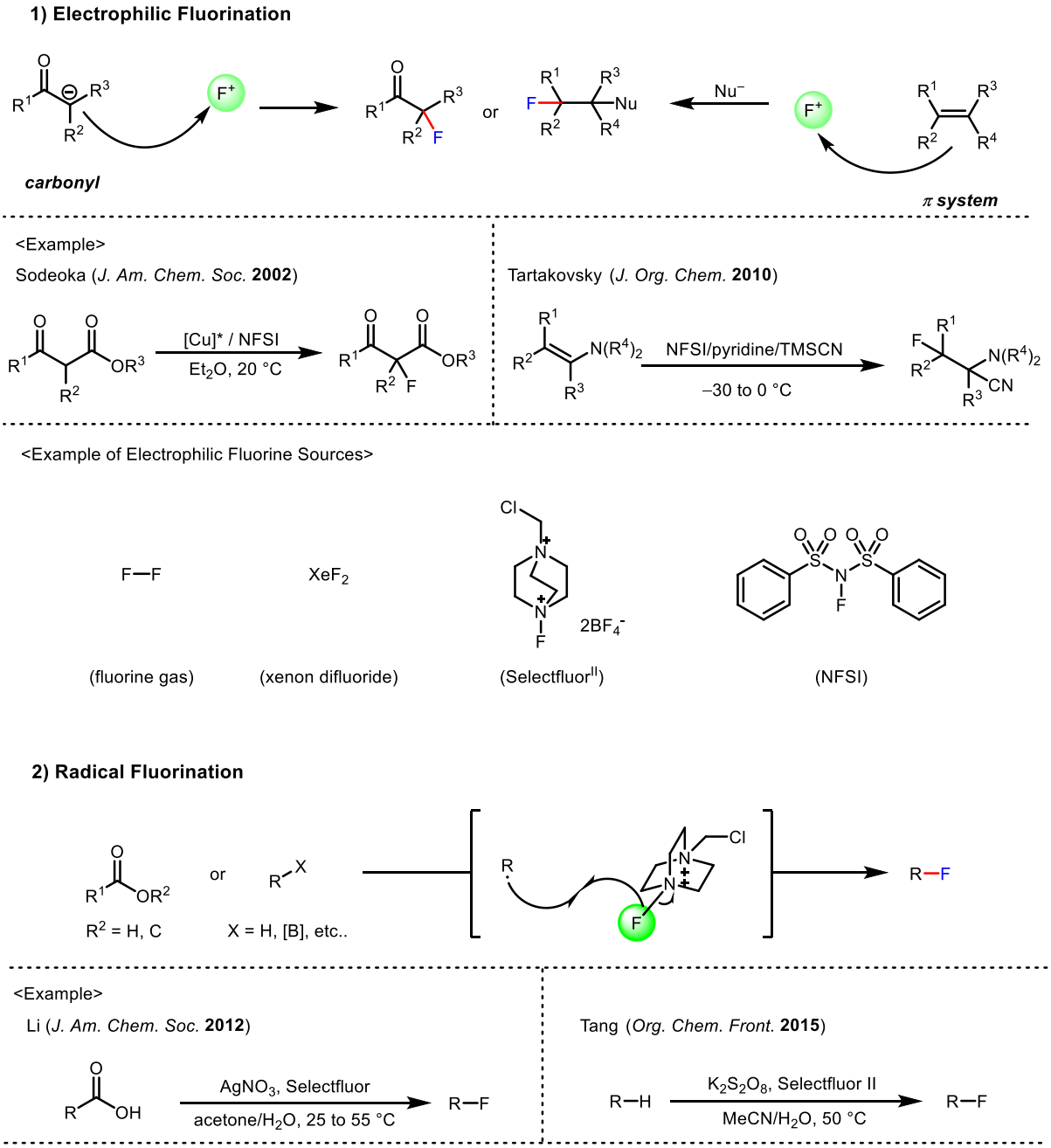
Carbon–Fluorine bonds are one of the important structural motifs that can be found in pharmaceuticals, agrochemicals, and materials (Figure 1.1.).[1-3] In particular, compounds containing carbon–fluorine bonds are used in positron emission tomography (PET) radiotracers.[4] As such, many efforts have been made to construct C–F bonds in organic compounds. Fluorine, the most electronegative element, shows lower nucleophilicity due to its extensive solvation.[5] Therefore, nucleophilic fluorination to introduce fluorine atoms into organic compounds is challenging. Due to these limitations, electrophilic or radical fluorination methods have been developed (Figure 1.2.).[6]

Figure 1.1. Various Fluoro-Pharmaceuticals



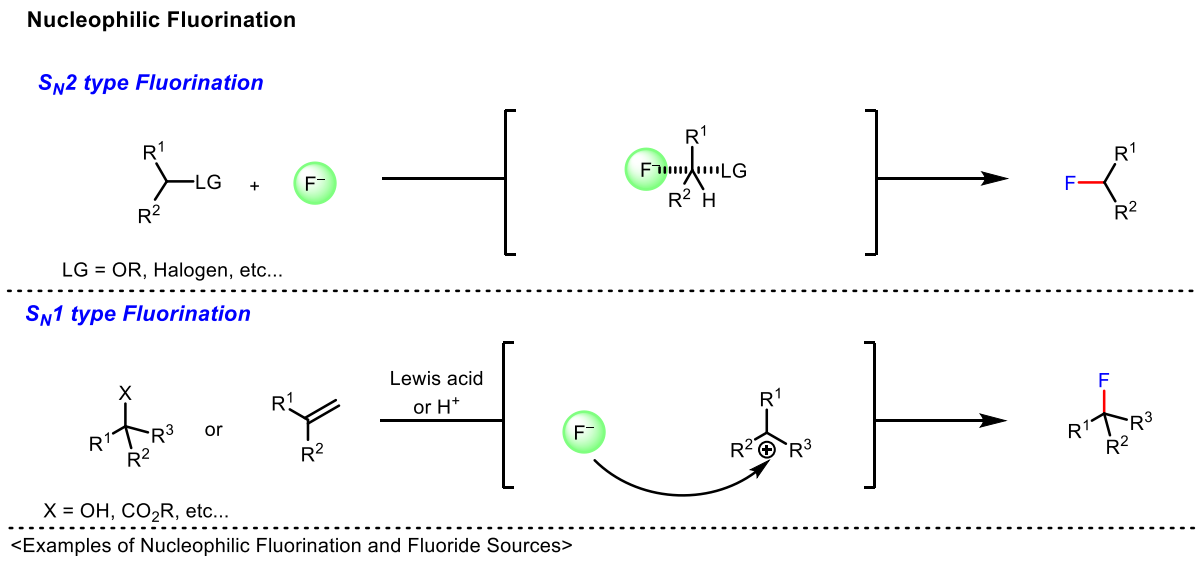
Common electrophilic fluorine sources are fluorine gas, hypofluorites, and xenon difluoride. However, these reagents are too reactive that it is difficult to maintain the functional groups of the reactants.[7] Alternatively, more stable N–fluorinated reagents such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2/2/2]octane bis(tetrafluoroborate) (selectfluor) and N–fluorobenzenesulfonimide (NFSI) reagents have been developed.[8] Because of the low N–F bond energy, carbon nucleophiles can attack the N–F bond to form a C–F bond. In this type of a reaction, enolates or substituted alkenes have been used as nucleophile sources (Figure 1.2.1.).[6a,9,10] In addition, these reactive reagents possessing an N–F bond readily undergo homolytic cleavage of the N–F bond to enable the C–F bond formation via radical mechanism (Figure 1.2.2).[6,11,12] However, many scientists have desired to use fluorine as a source of nucleophiles. This is because electrophilic fluorine reagents are more expensive and difficult to be synthesized than nucleophilic fluorine reagents. In particular, the nucleophilic fluorinating reagent can be effectively applied to PET systems because of the easy preparation of ^{18}F containing reagent. The radiofluorination is widely used because ^{18}F has a half-life 5 to 50 times longer than other radionuclide sources.[4a] Owing to the readily conceivable advantages of nucleophilic fluorination, many nucleophilic fluorination methods have been developed.[6]

Figure 1.2. Electrophilic and Radical Fluoriation



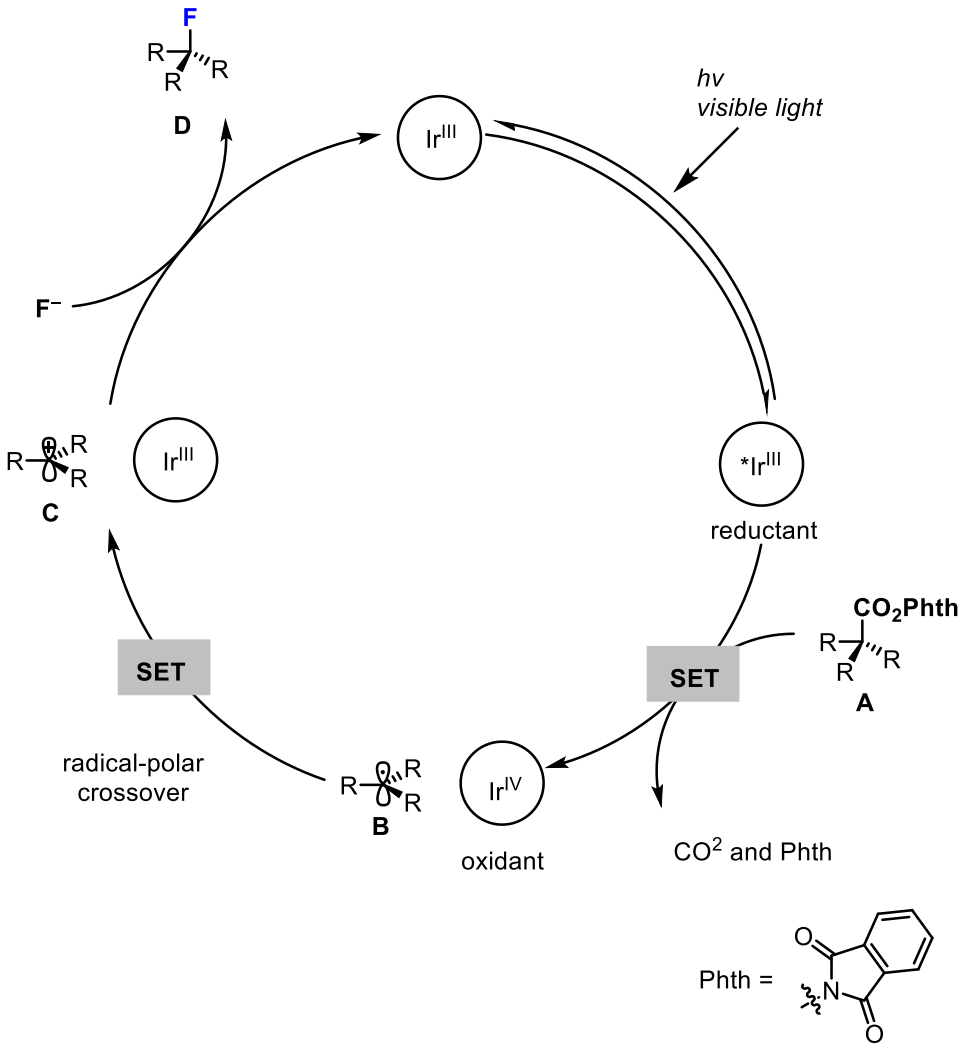
Nucleophilic fluorination can be divided into two types, one is bimolecular nucleophilic substitution[13] (S_N2), the other is unimolecular nucleophilic substitution[14] (S_N1) fluorination. In the case of the S_N2 mechanism, the fluoride attacks the carbon center and displaces the leaving group. However, this method is hard to applied to form tertiary C(sp^3)–F bond because of steric hindrance of tertiary carbon. To form tertiary C(sp^3)–F bond, tertiary alcohols or secondary alkenes can be used as reaction coupling partners in S_N1 fluorination. Under acidic conditions, the coupling partners are activated and generate carbocation. Then, fluoride anion attacks the carbocation and forms a carbon–fluorine bond. However, this S_N1 type method has limitations as it requires highly reactive fluoride reagent or strongly acidic conditions to activate starting material. Recently, the Doyle group reported a nucleophilic fluorination via a redox-active ester under the photocatalytic system as shown in Figure 1.3.

Figure 1.3. Nucleophilic Fluorination



As shown in Figure 1.3.1, Doyle group's key feature of their mechanism was single-electron transfer with the N–hydroxyphtalimide ester to generate carbon-centered radical. Then, this radical intermediate was again oxidized by a photocatalyst to give a carbocation. Finally, a fluoride anion attacked this carbocation to generate the desired alkylfluoride. Doyle's nucleophilic fluorination could be applied to radiofluorination and a variety of sterically demanding substrates were also successfully engaged in the reaction.

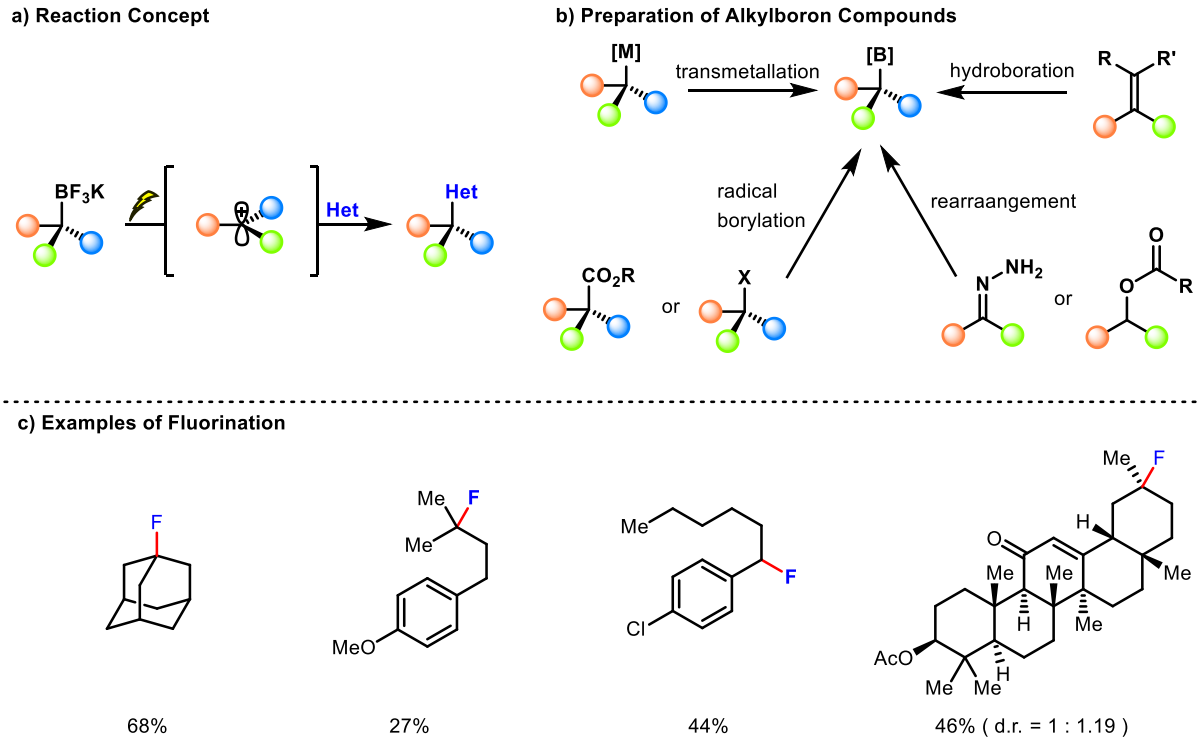
Figure 1.3.1 Mechanistic proposal of Doyle's nucleophilic fluorination



To generate sterically hindered carbocations, we chose the electrochemical method because of its simple reaction set-up and low cost. Recently, a unified strategy for introducing heteroatoms to sp^3-hybridized carbon atom using alkylorganoboron compounds was developed in our group (Figure 1.4a.).[15] The key feature of this method is that carbocation intermediate can be generated from alkylorganoboron compounds via electrochemical strategy.[15] The use of alkylorganoboron compounds has advantages. One of the most important advantages of alkyl organoboron compounds is that there are various synthetic pathways as shown in Figure 1.4b. Also, this method can be applied to nucleophilic fluorination (Figure 1.4c.).

Described in this dissertation is a new electrochemical nucleophilic fluorination using tertiary alkyl boron compounds and mild nucleophilic fluoride sources via sequential electrochemical oxidation processes.

Figure 1.4. Previously result of C-Heteroatom bond formation

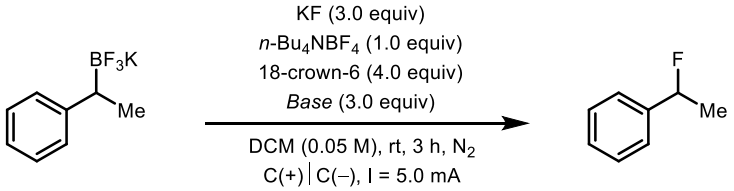


2. RESULTS and DISCUSSION

2.1. Evaluations of Reaction Conditions

First, the initial strategy of our nucleophilic fluorination was evaluated under electrochemical conditions with secondary–benzyl alkylborate reagents. In preliminary experiments conducted from our group, the fluoride sources and electrolytes were chosen. Using these previous results, some bases were evaluated (Table 2.1.). However, these bases gave no positive effect.

Table 2.1. Evaluation of bases

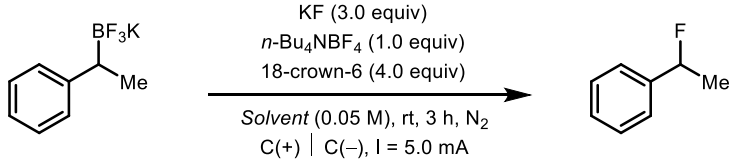


entry[a]	base	yield (%)[b]
1	collidine	16
2	K_2CO_3	15
3	NaOH	15
4	–	16

[a]Reaction conditions: Alkyl trifluoroborate (0.1 mmol), base (3.0 equiv), KF (3.0 equiv), 18-crown-6 (3.0 equiv), DCM (2.0 mL), rt. 3 h [b]Determined by ^{19}F NMR analysis using CF_3Ph as an internal standard.

Fortunately, evaluation of solvents gave improved results. When (trifluoromethyl)benzene (CF_3Ph) was used as the solvent, the reaction afforded the benzyl fluoride product in 50% yield (entry 6, Table 2.2.). This result led us to speculate (trifluoromethyl)benzene as a fluoride source.

Table 2.2. Evaluation of solvents

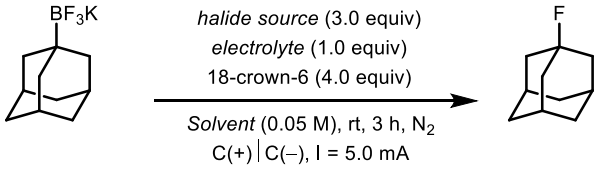


entry[a]	solvent	yield (%)[b]
1	DCM	13
2	MeCN	<1
3	THF	4
4	Toluene	<1
5	DCE	12
6	CF_3Ph	50

[a]Reaction conditions: Alkyl trifluoroborate (0.1 mmol), KF (3.0 equiv), 18-crown-6 (3.0 equiv), solvent (2.0 mL), rt. 3 h [b]Determined by ^{19}F NMR analysis using CF_3Ph as an internal standard.

To confirm whether (trifluoromethyl)benzene was consumed as a fluoride source or not, solvent and halide source screenings were also conducted (Table 2.3.). These results indicated that (trihalomethyl)benzene could serve as a halide source (entry 4).

Table 2.3. Influence of trihalo toluene solvent

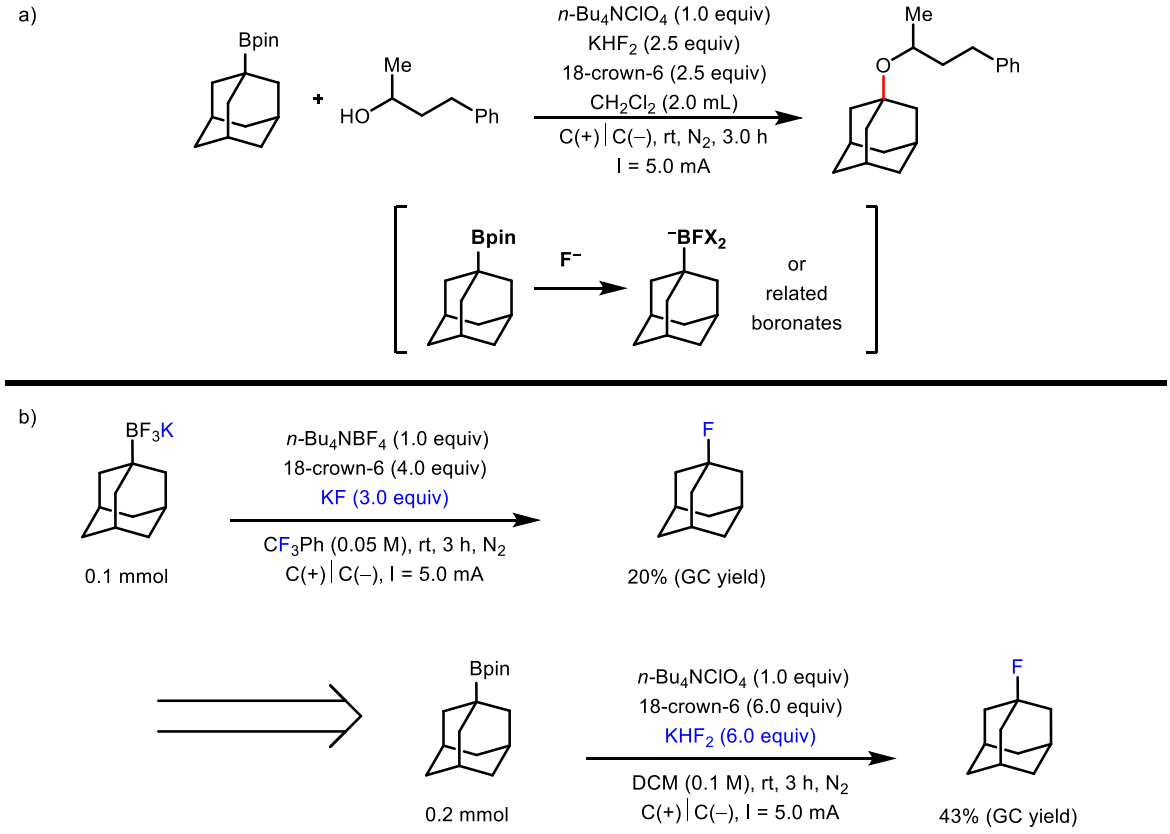


entry[a]	halide source	electrolyte	solvent	yield (AdF / AdCl) (%)[b]
1	KF	*n*-Bu_4NBF_4	CF_3Ph	18 / < 1
2	KF	*n*-Bu_4NClO_4	CF_3Ph	10 / < 1
3	KCl	*n*-Bu_4NClO_4	CF_3Ph	5 / 27
4	X	*n*-Bu_4NBF_4	CCl_3Ph	4 / 13

[a]Reaction conditions: Alkyl trifluoroborate (0.1 mmol), salt (3.0 equiv), 18-crown-6 (4.0 equiv), electrolyte (1.0 equiv), solvent (2.0 mL), rt. 3 h [b]Determined by GC analysis using mesitylene as an internal standard.

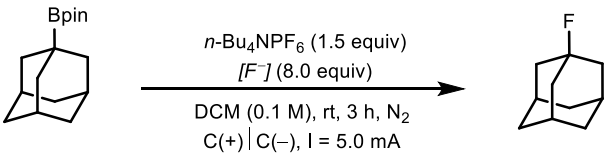
With regard to the source of the fluoride nucleophile, there were also complications in using alkyl trifluoroborates as starting materials. First, these ^{19}F containing substrates could adversely affect the selective introduction of ^{18}F into a target molecule due to the competitive reaction caused by the addition of ^{19}F into a carbocation. In the synthesis of ^{18}F radiotracers, fluorine-18 is generally used as a limiting reagent. Therefore, fluorine-19 from alkyl trifluoroborates, solvents, or electrolytes can present a significant obstacle to the synthesis of a radiofluorination product. Second, in the cases with some alkyl trifluoroborate substrates, the side products from oxidation (alcohol or ketone) were major products, not fluorination products. Efforts were made to decrease the yield of the oxidation products. However it was difficult to reduce the side reaction products. Therefore, these reaction conditions needed to be changed in order to increase the yield of fluorinated products and apply them in the radiofluorination system.

Scheme 2.1. Alternative electochemical fluorination using alkylboronic pinacol ester



In the previous study by our group, the alkyl boronic pincaol ester could be used as a starting material for carbon–heteroatom bond formation (Scheme 2.1a.). This result demonstrated that fluoride anion from potassium bifluoride can attack an empty boron p orbital, forming a boronate complex. Under electrochemical conditions, this boronate complex would be oxidized to a carbocation and nucleophiles would attack this carbocation. Thus, it was anticipated that alkyl boronic pinacol esters might be used as a starting material for this electrochemical nucleophilic fluorination. Fortunately, the fluorination product was successfully obtained when alkyl pinacol boronic ester was used as a starting material (Scheme 2.1b.). With this preliminary result, the optimization of reaction conditions was performed. As shown in Table 2.4., various fluoride sources were evaluated. Among them, silver fluoride (AgF) and potassium bifluoride (KHF_2) showed high yield (entries 1 and 4). Considering the cost of the fluorinating reagents, potassium bifluoride was chosen as the fluoride source.

Table 2.4. Evaluation of fluoride sources

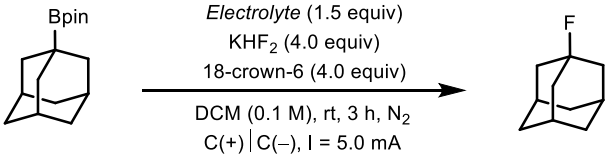


entry[a]	[F⁻]	yield (%)[b]
1	AgF	67
2	CsF	6
3	TBAF	5
4[c]	KF	30
5[c]	KHF_2	54

[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), *n*-Bu_4NPF_6 (1.5 equiv), [F⁻] (8.0 equiv), DCM (2.0 mL), rt, 3 h
[b]Determined by GC analysis using mesitylene as an internal standard [c]18-crown-6 was added.

Using potassium bifluoride as the fluoride source, the electrolyte evaluation was carried out. Tetrabutylammonium tetrafluoroborate (*n*-Bu_4NBF_4) improved the yield of the reaction (entry 3), while the other electrolytes made little difference (Table 2.5.). To investigate the effect of tetrabutylammonium tetrafluoroborate, a control experiment was performed as shown in Table 2.6.

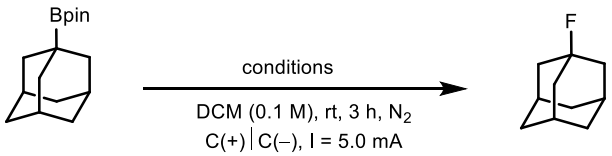
Table 2.5. Evaluation of electrolytes



entry[a]	electrolyte	yield (%)[b]
1	*n*-Bu_4NPF_6	49
2	*n*-Bu_4NClO_4	43
3	*n*-Bu_4NBF_4	67
4	$LiClO_4$	45

[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), electrolyte (1.5 equiv), KHF_2 (8.0 equiv), 18-crown-6 (4.0 equiv), DCM (2.0 mL), rt, 3 h. [b]Determined by GC analysis using mesitylene as an internal standard.

Table 2.6. Control experiments



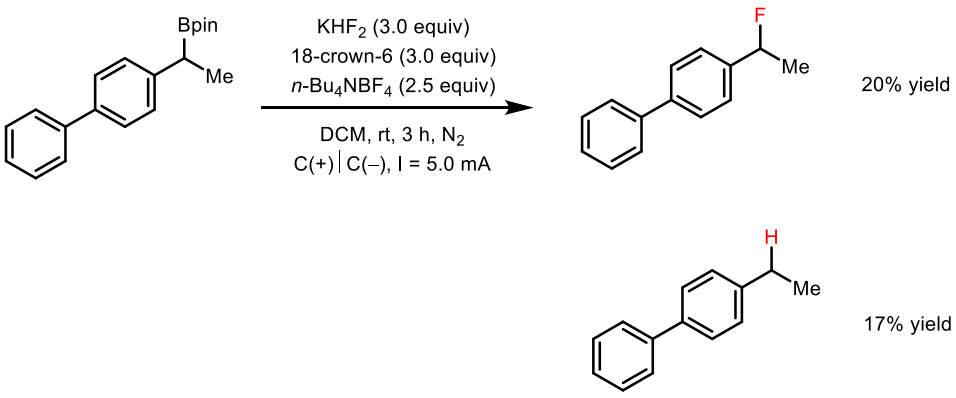
entry[a]	conditions	yield (%)[b]
1	*n*-Bu_4NBF_4 (2.5 equiv), KHF_2 (3 equiv), 18-crown-6 (3 equiv)	70
2	*n*-Bu_4NClO_4 (2.5 equiv), KHF_2 (3 equiv), 18-crown-6 (3 equiv)	40
3	only *n*-Bu_4NBF_4	7

[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), reaction conditions, DCM (2.0 mL), rt, 3 h.

[b]Determined by GC analysis using mesitylene as an internal standard.

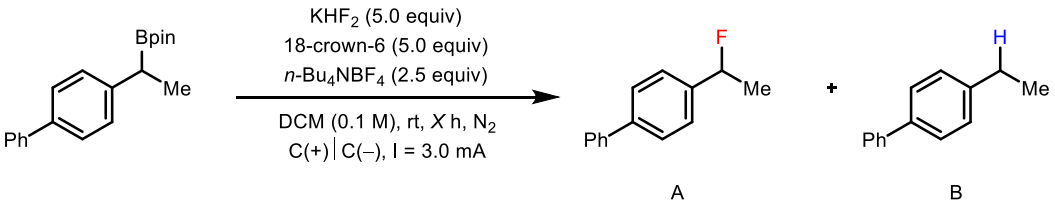
As shown by the results of entries 1 and 2 (Table 2.6.), the tetrafluoroborate anion assisted the fluorination. However, without the addition of potassium bifluoride, the reaction yield was dramatically decreased (entry 3). From these data, we concluded that tetrafluoroborate has a positive effect on the reaction yield and that the main fluoride source is from potassium bifluoride, not tetrafluoroborate. In summary, the optimized conditions were established as follows: alkyl boronic pinacol ester (0.2 mmol), potassium bifluoride (3.0 equiv), 18-crown-6 (3.0 equiv), and tetrabutylammonium tetrafluoroborate (2.5 equiv) were dissolved in 2.0 mL of dichloromethane and the reaction mixture was stirred for three hours under constant current (I = 5.0 mA, +C/-C). With these optimized conditions in hand, the substrate scope of secondary benzylic boronic pinacol esters was investigated. However, the fluorination yield of secondary benzylic boronic pinacol esters was lower than that of tertiary alkyl boronic pinacol esters, generating a reduced side product in a significant amount (Scheme 2.2.).

Scheme 2.2 Result of Secondary Benzylic Case with Optimized Condition



To suppress the side reaction and facilitate fluorination, the reaction conditions were modified as follows: potassium bifluoride (5.0 equiv) and 18-crown-6 (5.0 equiv) were added to the reaction mixture and the constant current (3.0 mA) was applied to the reaction mixture. Furthermore, the reaction time screening was performed to increase the yield of the fluorination product. The optimal reaction time was 3 hours (entry 3, Table 2.7.) and the side product yield was lower when the reaction time was shortened. However, in these cases, the fluorination product was also obtained in a low yield after purification.

Table 2.7. Evaluation of time



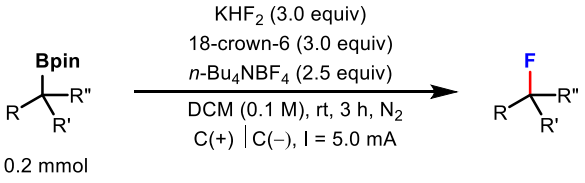
entry[a]	X	A yield (%)[b]	B yield (%)[b]
1	2	23	9
2	3	28	11
3	4	26	13
4	5	24	12

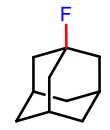
[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), *n*-Bu_4NBF_4 (2.5 equiv), KHF_2 (5.0 equiv), 18-crown-6 (5.0 equiv), DCM (2.0 mL), rt. X h [b]Determined by 1H NMR analysis using TCE as an internal standard

2.2. Reaction Scopes and Limitations

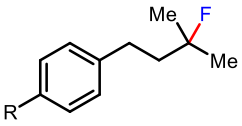
Under the optimized reaction conditions, the substrate scope was investigated. First, tertiary alkyl boronic pinacol esters gave the desired product **2a** in good yield. With substituted aromatic rings (**2b**-**2d)**, there was no trend towards substituent effects. The naphthyl group also gave a moderate yield of product (**2e**). A compound containing a cyclohexyl group showed moderate yield (**2f**). However, the fluorination yield of containing the ester functional group was decreased (**2g**-**2i)**. The piperidine moiety also gave a moderate yield (30%). On the other hand, secondary benzylic boronic pinacol ester cases showed a lower yield than tertiary alkyl boronic pinacol ester cases, although more fluoride source was consumed (**2j**-**2m**).

Table 2.8. Reaction scopes

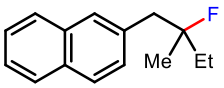




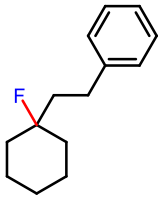
2a (55%)



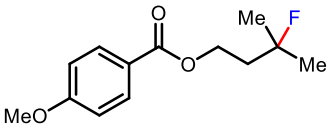
2b (R = OMe, 47%)
2c (R = H, 30%)
2d (R = Br, 45%)



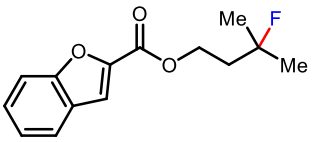
2e (45%)



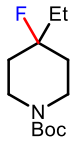
2f (50%)



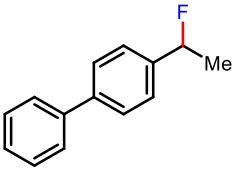
2g (30%)



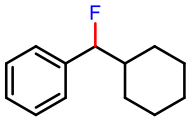
2h (26%)



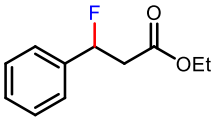
2i (30%)



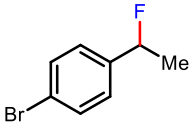
2j[a] (26%)



2k[a] (25%)



2l[a] (25%)

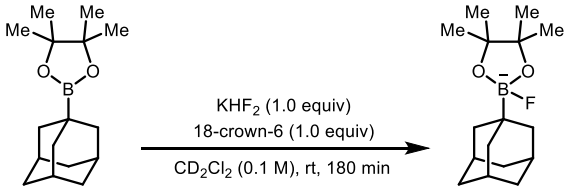


2m[a] (22%)

a : KHF_2 (5.0 equiv), 18-crown-6 (5.0 equiv), *n*-Bu_4NBF_4 (2.5 equiv), I = 3.0 mA, 3 h reaction condition

2-3. ^{11}B NMR Study and Proposed Reaction Mechanism

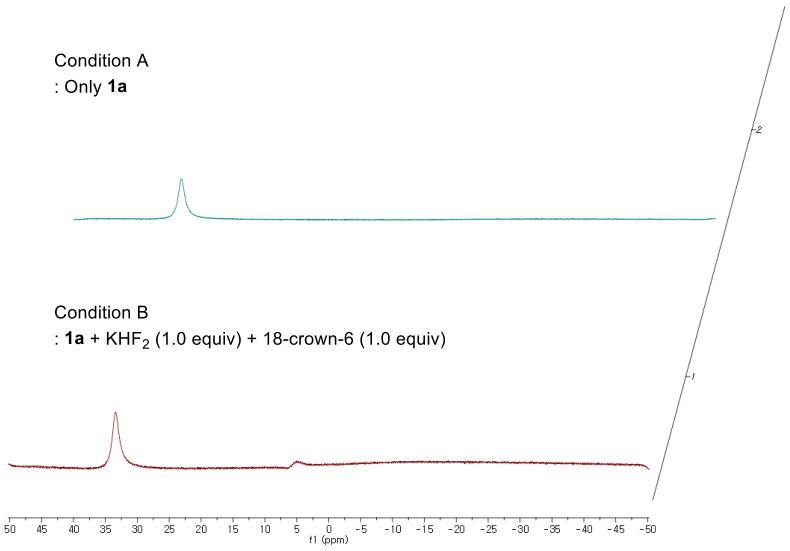
The ^{11}B nuclear magnetic resonance (NMR) spectroscopy study was performed to investigate the reaction mechanism using 2-(adamantan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane. Previously, Stalh[16] and Nelson[17] groups showed that the boron nmr peak can be altered by the addition of the fluoride reagent. The chemical shift of ^{11}B NMR spectroscopy was observed under the same optimized reaction conditions without current. When the complex of alkyl boronic pinacol ester compounds with fluorides was formed, the peak of the starting material at δ 33 ppm in ^{11}B NMR was decreased and the peak of adduct at δ 5 ppm in ^{11}B NMR was increased. This result showed that fluoride can coordinate with an empty p orbital of boron and generate a borate complex. Under electrochemical conditions, this complex can be oxidized and transformed into a carbocation.[16] Compared to tertiary alkyl boronic pinacol ester case and secondary-benzyl boronic pinacol ester case, the former showed that the boronate complex was formed more slowly than the secondary-benzyl boronic pinacol ester case. These results suggested that potassium bifluoride not only activated boron atom, but could also be used as a nucleophile source.

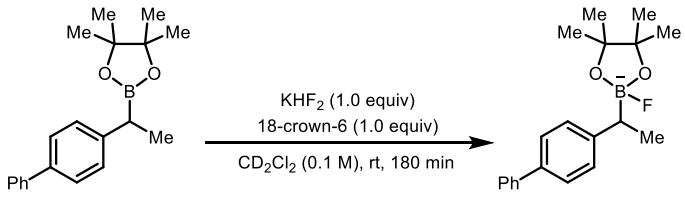


1a

Condition A
: Only **1a**

Condition B
: **1a** + KHF_2 (1.0 equiv) + 18-crown-6 (1.0 equiv)

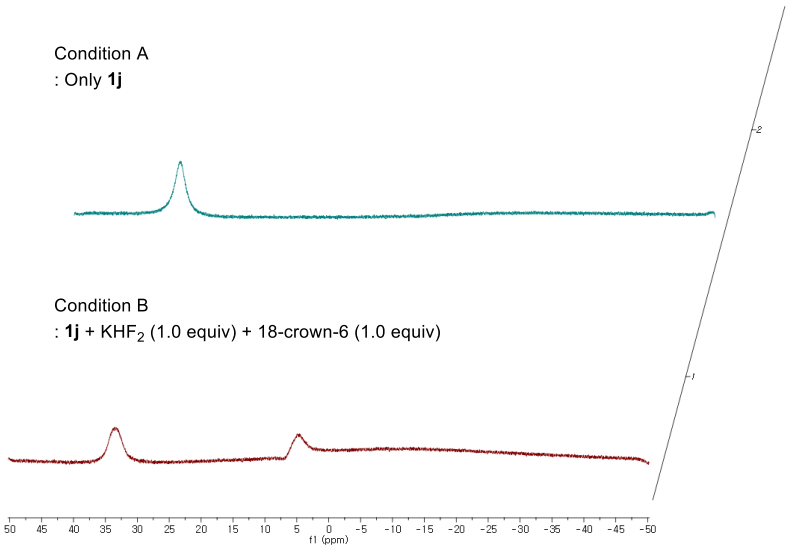




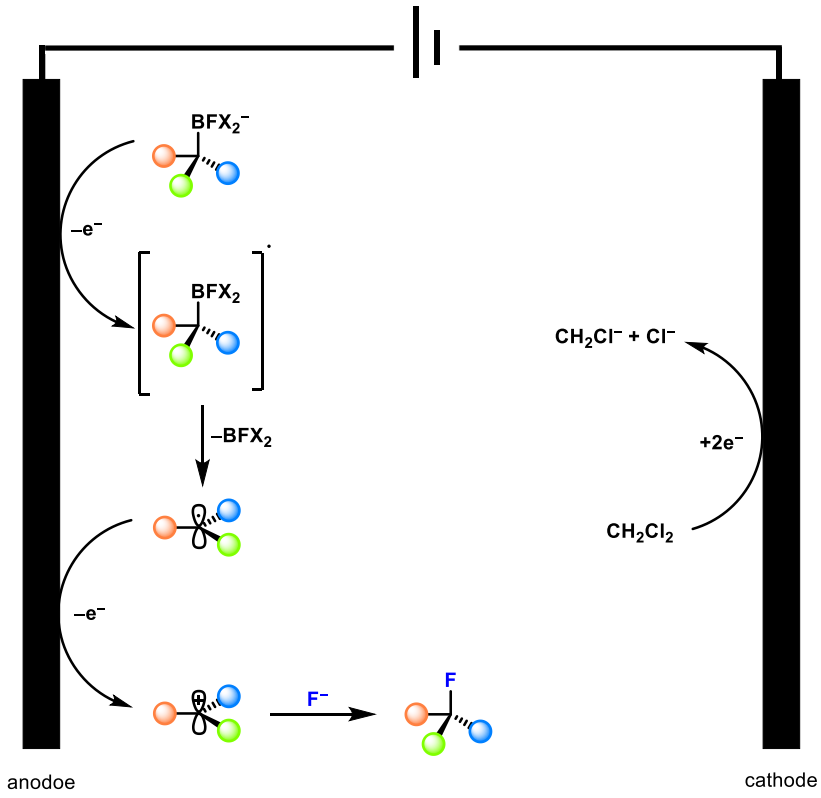
1j

Condition A
: Only **1j**

Condition B
: **1j** + KHF_2 (1.0 equiv) + 18-crown-6 (1.0 equiv)



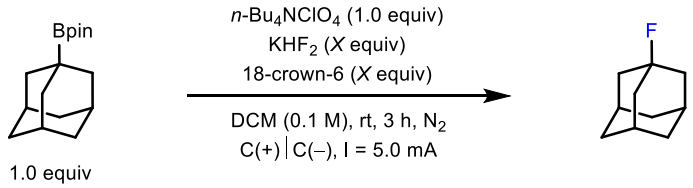
Scheme 2.3. Proposed reaction mechanism



With the [11]Boron NMR study and previous study, a plausible mechanism was proposed (scheme 2.3.). The reaction of alkyl boronate complex proceeds through two single-electron oxidation with a cleavage of the C–B bond. First oxidation and bond cleavage generate alkyl radical species. Subsequently, additional oxidation occurs at an alkyl carbocation. Finally, the fluoride anion attacks the carbocation and a new C–F bond is formed at the anode of the cell. A counter electrochemical reduction of dichloromethane is conducted at the cathode of the cell.[18]

2.4. Application to Radiofluoination

Table 2.9. Fluorination of organoboronate with KHF_2 as a limiting reagent

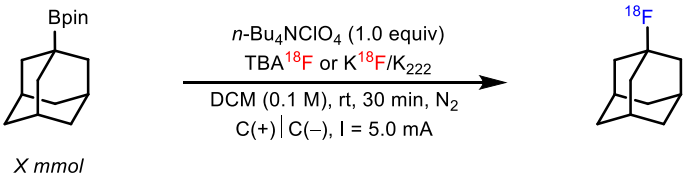


entry[a]	X	yield (%)[b]
1	0.50	7
2	0.14	1.5
3	0.01	1.5

[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), *n*-Bu_4NClO_4 (1.0 equiv), KHF_2 (X equiv), 18-crown-6 (X equiv), DCM (2.0 mL), rt. 3 h. [b]Determined by GC analysis using mesitylene as an internal standard.

To verify that the fluoride source acts as a limiting reagent, a potassium bifluoride equivalence experiment in a cold system was evaluated. As shown in entries 2 and 3, potassium bifluoride showed that it could successfully serve as a limiting reagent. This result showed that our strategy can be extended to the area of radiofluorination chemistry. The radiofluorination was performed in collaboration with the group of Prof. ByungCheol Lee at Seoul National University Bundang Hospital.[19]

Table 2.10. Evaluation of ^{18}fluoride sources

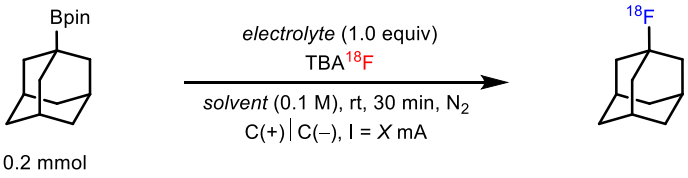


entry[a]	X	^{18}F source	RCC (%)[b]
1	0.2	$K^{18}F/K_{222}$	3.57
2	0.01	$K^{18}F/K_{222}$	N.R.
3	0.2	$TBA^{18}F$	7.59
4	0.01	$TBA^{18}F$	1.64

[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), *n*-Bu_4NClO_4 (1.0 equiv), DCM (2.0 mL), rt. 30 min.
[b]Determined by radioconversion tlc data. N.R. = No Reaction.

The results of the first experiment showed that TBA^{18}F was a suitable fluoride source with a starting material scale of 0.2 mmol (table 2.10. entry 3). The yield was determined by the radio tlc ratio method. As a result, electrolyte, solvent, and current conditions were performed. However, under our condition, the acetronitrile solvent condition showed no reaction. Then, electrolytes and currents were optimized, higher current (10.0 mA) showed the best reaction yield. With this positive reaction result, other reaction conditions and substrate scopes will be tested.

Table 2.11. Evaluation of electrolyte, solvent, and current



0.2 mmol

entry[a]	electrolyte	solvent	X (mA)	RCC (%)[b]
1	*n*-Bu_4NClO_4	DCM	5.0	4.37
2	*n*-Bu_4NClO_4	DCM	10.0	10.43
3	*n*-Bu_4NClO_4	CH_3CN	5.0	N.R.
4	*n*-Bu_4NBF_4	DCM	5.0	N.R.
5	$LiClO_4$	DCM	5.0	N.R.

[a]Reaction conditions: Alkylboronic pinacol ester (0.2 mmol), electrolyte (1.0 equiv), solvent (2.0 mL), X mA, rt, 30 min. [b]Determined by radioconversion tlc data. N.R. = No Reaction.

3. CONCLUSION

In summary, an electrochemical nucleophilic fluorination of alkyl boronic pinacol esters has been developed. This method is suitable for the formation of C(sp^3)–F bonds at a sterically demanding carbocation center. Additionally, this electrochemical protocol shows broad substrate scope with substituted alkylboron compounds and tolerates variety of functional groups. The ^{11}B NMR spectroscopy study showed that borate complexes can be produced by coordination of fluoride to the empty boron orbital. Furthermore, this method can be applied to radiofluorination, suggesting that it might be a more viable methodology.

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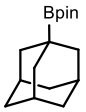
5. EXPERIMENTAL SECTION

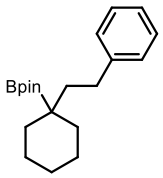
1. General experimental details

Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) were dried using a PureSolv solvent purification system. Anhydrous toluene, acetonitrile (CH_3CN), diethylether (Et_2O), trifluorotoluene (CF_3Ph), and 1,2-dimethoxyethane (DME) were purchased from Sigma-Aldrich. All chemicals were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar or TCI) and used without purification. Deuterated compounds were purchased from Cambridge Isotope Laboratories, Inc. Nuclear Magnetic Resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian 400 NMR (400 MHz), 500 NMR (500 MHz), and Bruker 500 NMR (500 MHz) spectrometers. ^{1}H NMR and ^{13}C NMR chemical shifts were referenced to the residual solvent signal (CHCl3 in CDCl3: δ 7.26 ppm for 1H, δ 77.16 ppm for 13C). 19F NMR chemical shifts were referenced to external trifluorotoluene (δ -63.7 ppm). Chemical shifts are reported in ppm and coupling constants are given in Hz. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. Gas chromatography (GC) was carried out using a GC-2030 (Shimadzu) equipped with an Rxi® -5Sil Ms column and a flame ionization detector (FID). All electrochemical measurements were performed with CHI 660 and 750 potentiostat (CH Instruments, TX, U.S.A) and dual display potentiostat (DJS-292B and DJS-292C, China). Reactions were monitored by thin-layer chromatography (TLC) on EMD Silica Gel 60 F254 plates, and visualized either using UV light (254 nm) or by staining with potassium permanganate (KMnO4) or Anisaldehyde staining solution and heating.

2. Substrate Preperation[1]



1a



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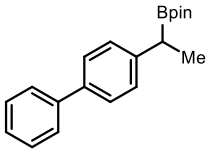

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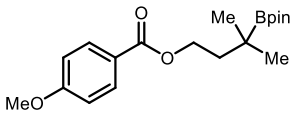

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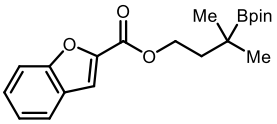

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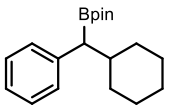

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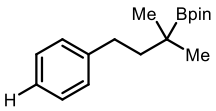
J. Am. Chem. Soc. **2016**, *138*, 6139



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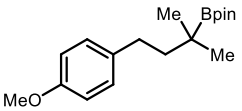
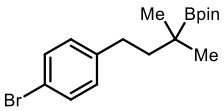


1b



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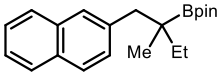

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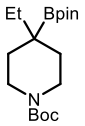

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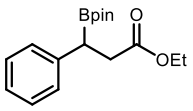

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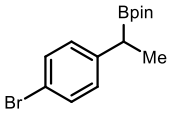

1m

Angew. Chem. Int. Ed. **2012**, *51*, 2943

List of alkylboronic pinacol ester for their preparation

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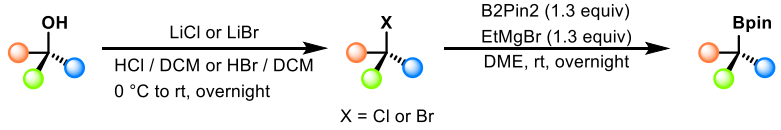

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2)

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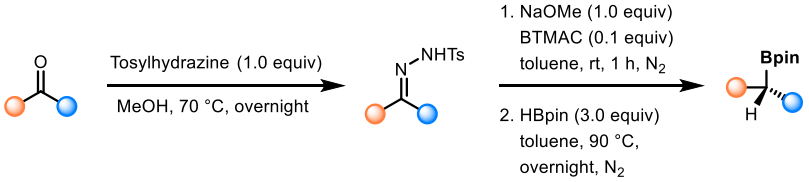
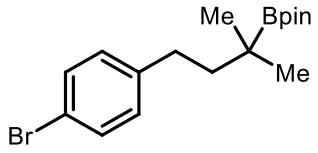
3)



Angew. Chem. Int. Ed. **2012**, *51*, 2943

Synthesis of alkylboronic pinacol ester

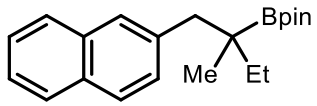
Spectral data matched that reported in the literature : 2-(adamantan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[1a] (**1a**), 2-(4-(4-methoxyphenyl)-2-methylbutan-2-yl)-4,4,5,5-tetrametnyl-1,3,2-dioxaborolane[2] (**1b**), 4,4,5,5-tetramethyl-2-(2-methyl-4-phenylbutan-2-yl)-1,3,2-dioxaborolane[2] (**1c**), 4,4,5,5-tetrametnyl-2-[1-(2-phenylethyl)cyclohexyl)]-1,3,2-dioxaborolane[3a] (**1f**), tert-butyl-4-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate[2] (**1i**), 2-(1-([1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[3b] (**1j**), 2-(cyclohexyl(phenyl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[3c] (**1k**), ethyl-3-phenyl-3-(4,4,5,5-tetrametnyl-[1,3,2]dioxaborolan-2-yl)-propionate[3d] (**1l**), 2-(1-(4-bromophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[1c] (**1m**).



2-(4-(4-bromophenyl)-2-methylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1d**)

Alkyl boronic pinacol ester **1d** was synthesized via a previously reported procedure.

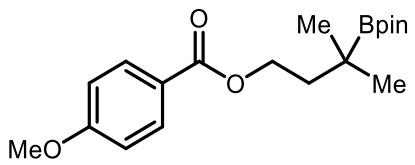
Purification by flash column chromatography (silica gel, hexane:EtOAc = 9:1) afforded **1d** (59%) as a white solid; R_f= 0.6 (hexane:EtOAc = 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 2.55 – 2.42 (m, 2H), 1.58 – 1.46 (m, 2H), 1.23 (s, 12H), 0.97 (s, 6H).



4,4,5,5-tetramethyl-2-(2-methyl-1-(naphthalene-2-yl)butan-2-yl)-1,3,2-dioxaborolane (**1e**)

Alkyl boronic pinacol ester **1e** was synthesized via a previously reported procedure.

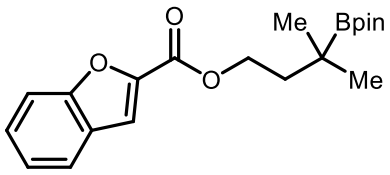
Purification by flash column chromatography (silica gel, hexane:EtOAc = 9:1) afforded **1e** (38%) as a white solid; R_f= 0.5 (hexane:EtOAc = 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.35 (m, 7H), 2.83 (m, 2H), 1.46 (m, 2H), 1.28 – 1.20 (m, 12H), 0.99 – 0.93 (m, 6H).



3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl 4-methoxybenzoate (**1g**)

Alkyl boronic pinacol ester **1g** was synthesized via a previously reported procedure.

Purification by flash column chromatography (silica gel, hexane:EtOAc = 9:1) afforded **1g** (30%) as a white solid; R_f= 0.4 (hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.30 (s, 2H), 3.84 (s, 3H), 1.75 (s, 2H), 1.21 (s, 12H), 1.01 (s, 6H).

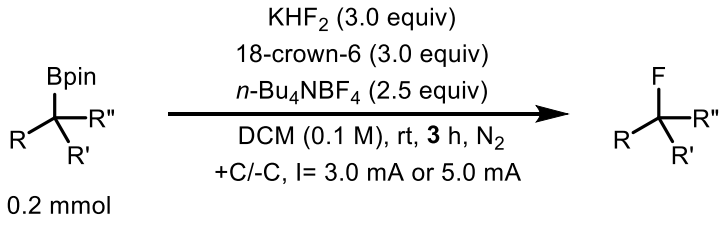


3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl benzofuran-2-carboxylate (**1h**)

Alkyl boronic pinacol ester **1h** was synthesized via a previously reported procedure.

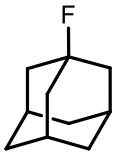
Purification by flash column chromatography (silica gel, hexane:EtOAc = 9:1) afforded **1h** (28%) as a white solid; R_f= 0.35 (hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 4H), 7.30 (s, 1H), 4.41 (d, *J* = 7.7 Hz, 2H), 1.80 (d, *J* = 7.3 Hz, 2H), 1.22 (d, *J* = 6.8 Hz, 12H), 1.02 (d, *J* = 6.7 Hz, 6H).

3. General Procedure for Electrochemical C(sp^3)–F Bond Formation



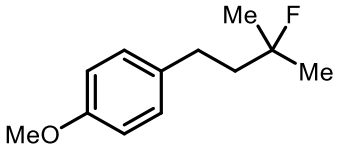
To an oven-dried undivided cell with a magnetic stir bar were added alkyl boronic pinacol ester (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol) and tetrabutylammonium tetrafluoroborate (0.5 mmol). The reaction cell was capped with a speta-line Teflon cap equipped with the anode (graphite) and the cathode (graphite). After the cell was evacuated and backfilled with nitrogen (three times), a balloon filled with nitrogen was connected to the reaction vial. Subsequently, the reaction mixture was dissolved in dichloromethane (2 mL). Then the reaction mixture was electrolyzed as a constant current of 5.0 mA for 3.0 hours at room temperature (tertiary alkyl boronic pinacol ester case), or 3.0 Ma for 3.0 hours at room temperature (benzylic boronic pinacol ester case). Upon completion of the reaction, the cap was removed and electrodes were rinsed with dichloromethane. The combined organic phase was transferred to a 20 mL vacant vial and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 or hexane/EtOAc gradient elution) to afford the desired product.

4. Characterization Data



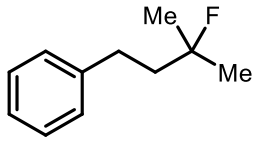
1-fluoroadamantane (**2a**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, full hexane) afforded **2a** (18.5 mg, 60%) as a white solid; R_f = 0.5 (full hexane). Spectroscopic data matches with previously reported data[4a].



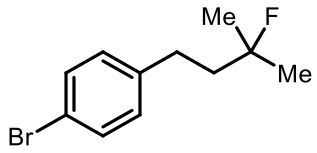
1-(3-fluoro-3-methylbutyl)-4-methoxybenzene (**2b**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2b** (18.4 mg, 47%) as a colorless oil; R_f = 0.3 (hexane:CH_2Cl_2 = 4:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 3.80 (s, 3H), 2.71 – 2.63 (m, 2H), 1.90 (ddd, *J* = 17.8, 10.3, 5.0 Hz, 2H), 1.41 (d, *J* = 21.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8 (s), 134.1 (s), 129.2 (s), 113.8 (s), 95.6 (d, $J_{C–F}$= 165.5 Hz), 55.3 (s), 43.6 (d, $J_{C–F}$ = 22.8 Hz), 29.3 (d, $J_{C–F}$ = 5.5 Hz), 26.7 (d, $J_{C–F}$ = 24.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.69 – -140.36 (m).



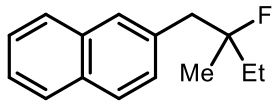
(3-fluoro-3-methylbutyl)benezene (**2c**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 9:1) afforded **2c** (9.6 mg, 30%) as a colorless oil; R_f = 0.5 (hexane:CH_2Cl_2 = 9:1).; Spectroscopic data matches with previously reported data[4a].



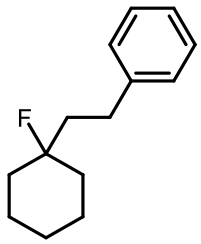
1-bromo-4-(3-fluoro-3-methylbutyl)benzene (**2d**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 9:1) afforded **2d** (22.1 mg, 45%) as a colorless oil; R_f = 0.5 (hexane:CH_2Cl_2 = 9:1).; Spectroscopic data matches with previously reported data[4b].



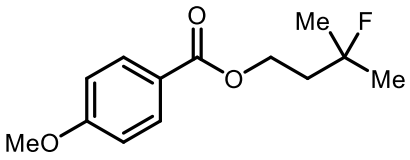
2-(2-fluoro-2-methylbutyl)naphthalene (**2e**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2e** (19.4 mg, 45%) as a colorless oil; R_f = 0.6 (hexane:CH_2Cl_2 = 4:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.14 (m, 7H), 3.07 (dd, *J* = 28.9, 14.7 Hz, 2H), 1.79 – 1.55 (m, 2H), 1.28 (d, *J* = 21.7 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6 (d, *J* = 3.1 Hz), 133.3 (s), 132.2 (s), 128.9 (d, *J* = 1.8 Hz), 128.1 – 127.1 (m), 125.9 (s), 125.4 (s), 97.4 (d, *J* = 170.7 Hz), 45.7 (d, *J* = 22.6 Hz), 32.31 (d, *J* = 23.3 Hz), 23.6 (d, *J* = 24.7 Hz), 8.1 (d, *J* = 6.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.36 – -147.71 (m).



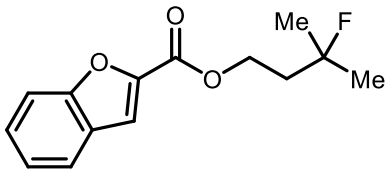
(2-(1-fluorocyclohexyl)ethyl)benzene (**2f**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2f** (20.6 mg, 50%) as a colorless oil; R_f = 0.6 (hexane:CH_2Cl_2 = 4:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 6.96 (m, 5H), 2.79 – 2.63 (m, 2H), 2.00 – 1.18 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4 (s), 128.4 (t, *J* = 7.8 Hz), 125.9 (d, *J* = 17.5 Hz), 95.7 (d, *J* = 170.3 Hz), 42.3 (d, *J* = 22.9 Hz), 35.2 (d, *J* = 22.7 Hz), 29.3 (d, *J* = 4.7 Hz), 25.5 (s), 22.1 (d, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -156.57 (s).



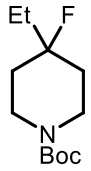
3-fluoro-3-methylbutyl 4-methoxybenzoate (**2g**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2g** (14.4 mg, 30%) as a colorless oil; R_f = 0.6 (hexane:CH_2Cl_2 = 4:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.43 (t, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 2.09 (dt, *J* = 19.3, 6.8 Hz, 2H), 1.43 (d, *J* = 21.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (s), 163.3 (s), 131.6 (d, *J* = 4.6 Hz), 122.6 (s), 113.6 (d, *J* = 6.7 Hz), 94.3 (d, *J* = 165.9 Hz), 60.6 (d, *J* = 6.4 Hz), 55.4 (s), 39.9 (d, *J* = 23.1 Hz), 27.1 (d, *J* = 24.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.79 – -139.69 (m).



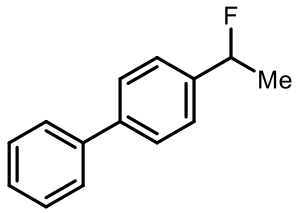
3-fluoro-3-methylbutyl benzofuran-2-carboxylate (**2h**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2h** (13 mg, 26%) as a colorless oil; R_f = 0.6 (hexane:CH_2Cl_2 = 4:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.26 (m, 5H), 4.52 (t, *J* = 6.9 Hz, 2H), 2.14 (dt, *J* = 19.4, 6.9 Hz, 2H), 1.44 (d, *J* = 21.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (s), 155.8 (s), 145.4 (s), 127.7 (d, *J* = 11.4 Hz), 126.9 (s), 123.8 (d, *J* = 5.5 Hz), 122.8 (d, *J* = 5.8 Hz), 113.9 (s), 112.4 (s), 94.1 (d, *J* = 166.3 Hz), 61.4 (d, *J* = 6.3 Hz), 39.7 (d, *J* = 23.2 Hz), 27.1 (d, *J* = 24.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.69 – -140.81 (m).



Tert-butyl 4-ethyl-4-fluoropiperidine-1-carboxylate (**2i**)

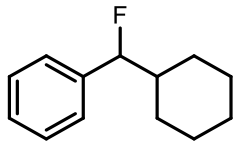
General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (0.6 mmol), 18-crown-6 (0.6 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 4:1) afforded **2i** (13.8 mg, 30%) as a colorless oil; R_f = 0.5 (hexane:EtOAc = 9:1).; ^{1}H NMR (400 MHz, $cdcl_3$) δ 3.92 (s, 1H), 3.06 (t, *J* = 11.4 Hz, 2H), 1.81 – 1.73 (m, 2H), 1.66 – 1.55 (m, 4H), 1.45 (s, 9H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 154.7 (s), 94.2 (d, *J* = 171.0 Hz), 79.5 (s), 39.7 (s), 34.0 (d, *J* = 22.4 Hz), 32.9 (d, *J* = 23.0 Hz), 28.4 (s), 7.02 (d, *J* = 5.6 Hz); ^{19}F NMR (376 MHz, $cdcl_3$) δ -160.75 – -167.87 (m).



4-(1-fluoroethyl)-1,1'-biphenyl (**2j**)

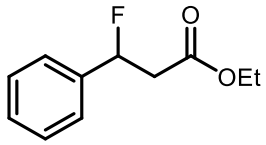
General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (1.0 mmol), 18-crown-6 (1.0 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2j** (10.4mg, 26%) as a white solid; R_f = 0.5 (hexane:CH_2Cl_2 = 9:1).;

Spectroscopic data matches with previously reported data[4c].



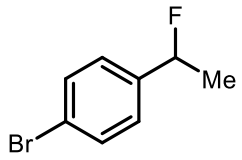
(cyclohexylfluoromethyl)benzene (**2k**)

General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (1.0 mmol), 18-crown-6 (1.0 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2k** (9.8 mg, 25%) as a pale yellow oil; R_f = 0.5 (hexane:CH_2Cl_2 = 9:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 5H), 5.06 (dt, *J* = 32.4, 16.2 Hz, 1H), 1.90 (t, *J* = 21.3 Hz, 1H), 1.77 – 1.61 (m, 4H), 1.38 (d, *J* = 12.2 Hz, 1H), 1.08 (ddd, *J* = 37.8, 23.3, 12.0 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2 (s), 128.1 (s), 128.0 (d, *J* = 1.8 Hz), 126.2 (d, *J* = 7.1 Hz), 98.7 (d, *J* = 172.6 Hz), 43.8 (d, *J* = 22.2 Hz), 28.3 (dd, *J* = 49.9, 4.8 Hz), 26.3 (s), 25.8 (d, *J* = 18.0 Hz).; ^{19}F NMR (376 MHz, $cdcl_3$) δ -180.20 (dd, *J* = 47.1, 16.2 Hz).



Ethyl 3-fluoro-3-phenylpropanoate (**2l**)

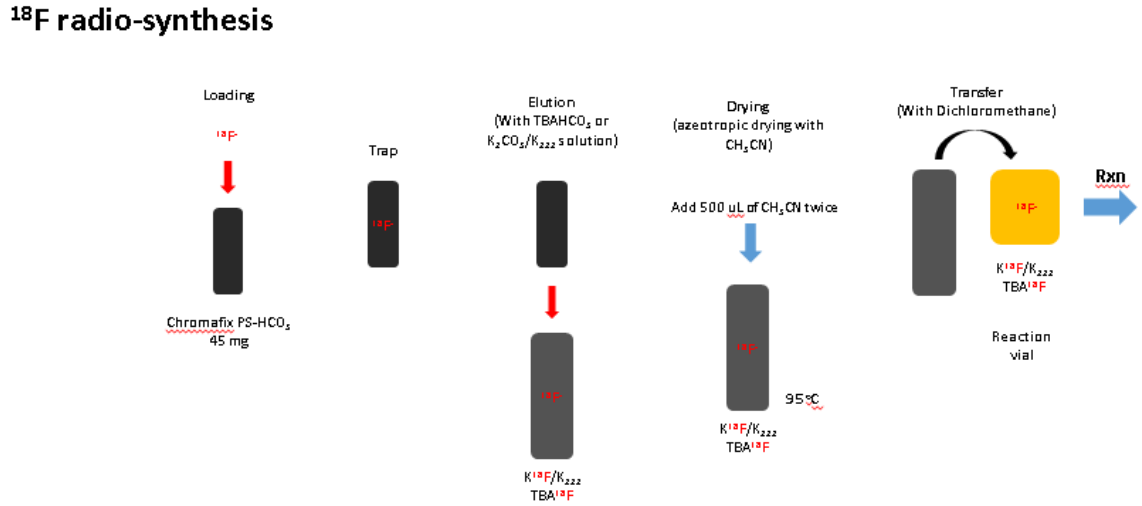
General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (1.0 mmol), 18-crown-6 (1.0 mmol), and *n*-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 9:1) afforded **2l** (9.8 mg, 25%) as a colorless oil; R_f = 0.55 (hexane:EtOAc = 9:1).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.91 (ddd, *J* = 46.9, 9.0, 4.2 Hz, 1H), 4.21 – 4.13 (m, 2H), 2.89 (dddd, *J* = 32.2, 20.1, 14.8, 6.6 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).; ^{19}F NMR (376 MHz, $CDCl_3$) δ -167.42 – -177.02 (m).



1-bromo-4-(1-fluoroethyl)benzene (**2m**)

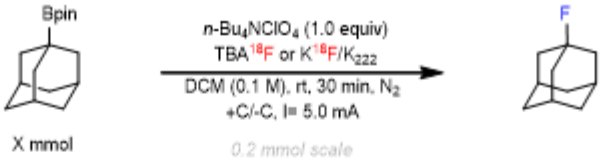
General procedure was applied with alkyl boronic pinacol ester 1a (0.2 mmol), potassium bifluoride (1.0 mmol), 18-crown-6 (1.0 mmol), and n-Bu_4NBF_4 (0.5 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1) afforded **2m** (8.9 mg, 22%) as a pale yellow oil; R_f = 0.5 (hexane:CH_2Cl_2 = 9:1).;).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.58 (dq, *J* = 13.1, 6.6 Hz, 1H), 1.65 (d, *J* = 6.4 Hz, 3H).; ^{19}F NMR (376 MHz, $CDCl_3$) δ -168.09 (dq, *J* = 48.1, 24.0 Hz).

5. General Procedure for Radiofluorination



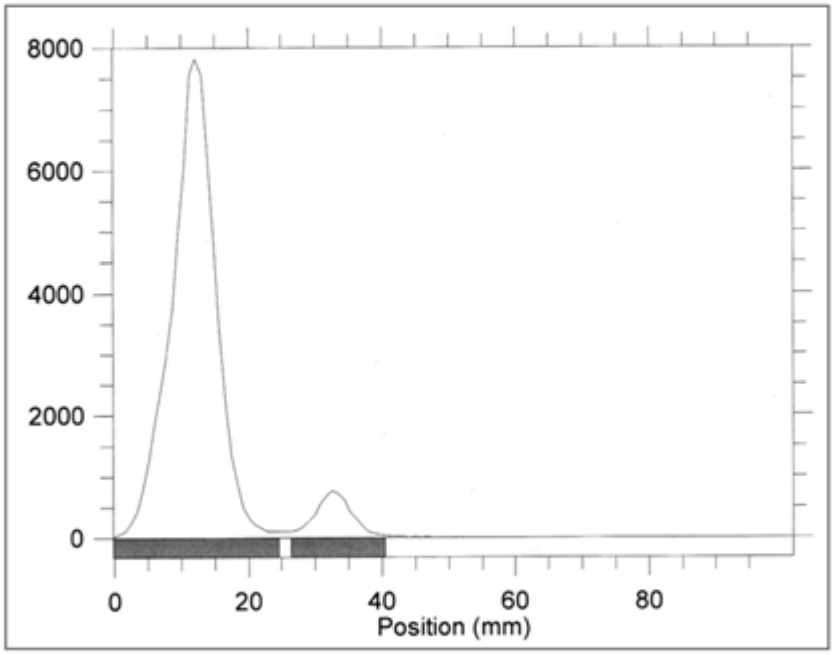
Procedure

The [^{18}F]fluoride was trapped on a Chromafix PS-HCO_3 cartridge preconditioned with 2.0 mL of ethanol, 8 mL of DW. The [^{18}F]F^- was eluted from the Chromafix PS-HCO_3 cartridge using a 1 mL of $TBAHCO_3$ (0.3 mg) or K_2CO_3/K_{222} (0.5 mg/5 mg) solution. The resulting [^{18}F]TBAF or [^{18}F]$F^-/K_{222}/K_2CO_3$ solution was azeotropically dried (Add 500 uL of CH_3CN twice) and then cooled, dissolved in 1 mL of DCM. After N_2 gas purged in the reaction vial containing Ad-Bpin (precursor) and electrolyte, the resulting [^{18}F]TBAF or [^{18}F]$F^-/K_{222}/K_2CO_3$ dissolved in anhydrous DCM (~ 0.5 mL) was added to the reaction vial containing the precursor and electrolyte dissolved in anhydrous DCM (~ 1.5 mL). After conducting the reaction for 30 min at room temperature (I = 5.0 mA), the radiochemical yield was measured by Radio-TLC.



entry	X	^{18}F source	RCC (%)
3	0.2	TBA^{18}F	7.59

Entry 3



Reg	(mm) Start	(mm) Stop	(mm) Centroid	RF	Region Counts	Region CPM	% of Total	% of ROI
Rgn 1	-0.2	24.6	11.8	0.025	68041.0	68041.0	91.83	92.41
Rgn 2	26.4	40.5	32.7	0.324	5586.0	5586.0	7.54	7.59
2 Peaks					73627.0	73627.0	99.37	100.00

The above figure showed the result of radiofluorination in table 2.10. entyry 3.

6. Reference

[1] (a) Atack, T.C.; Cook, S.P. *J. Am. Chem. Soc.* **2016**, *138*, 6139-6142; (b) Yang, Y.; Tsien, J.; David, A.B.; Hughes, J.M.E.; Merchant, R.R.; Qin, T. *J. Am. Chem. Soc*. **2021**, *143*, 471-480; (c) Li, H.; Wang, L.; Zhang, Y. Wang, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 2943

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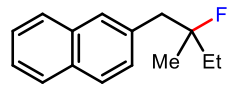
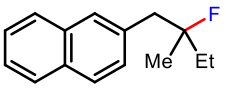
6. ^{1}H , ^{13}C and ^{19}F NMR Spectral Data

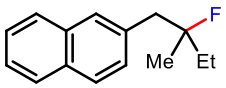
1H NMR (400 MHz, $CDCl_3$)



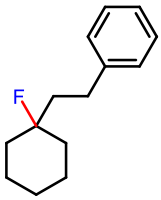
^{13}C NMR (101 MHz, $CDCl_3$)



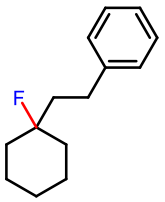
^{19}F NMR (376 MHz, $CDCl_3$)



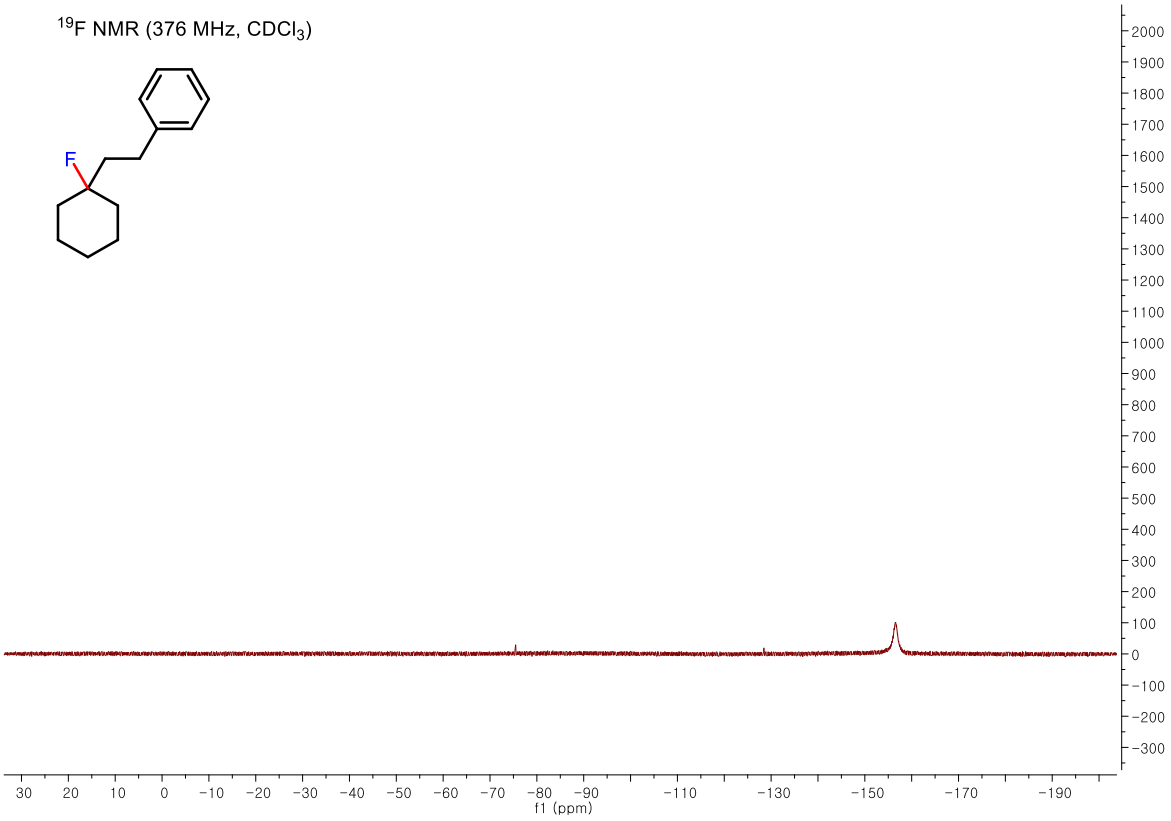
^{1}H NMR (400 MHz, $CDCl_3$)



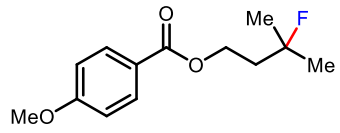
^{13}C NMR (101 MHz, $CDCl_3$)



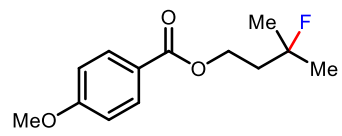
^{19}F NMR (376 MHz, $CDCl_3$)



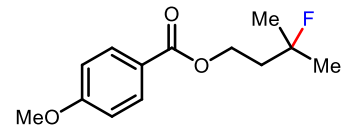
^{1}H NMR (400 MHz, $CDCl_3$)



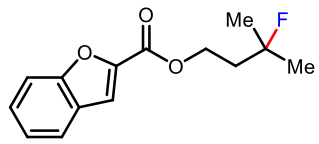
^{13}C NMR (101 MHz, $CDCl_3$)



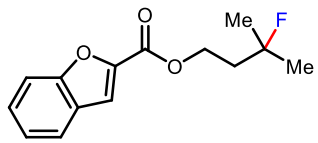
^{19}F NMR (376 MHz, $CDCl_3$)



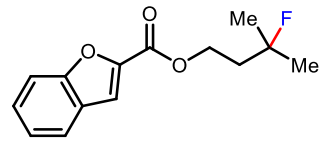
^{1}H NMR (400 MHz, $CDCl_3$)



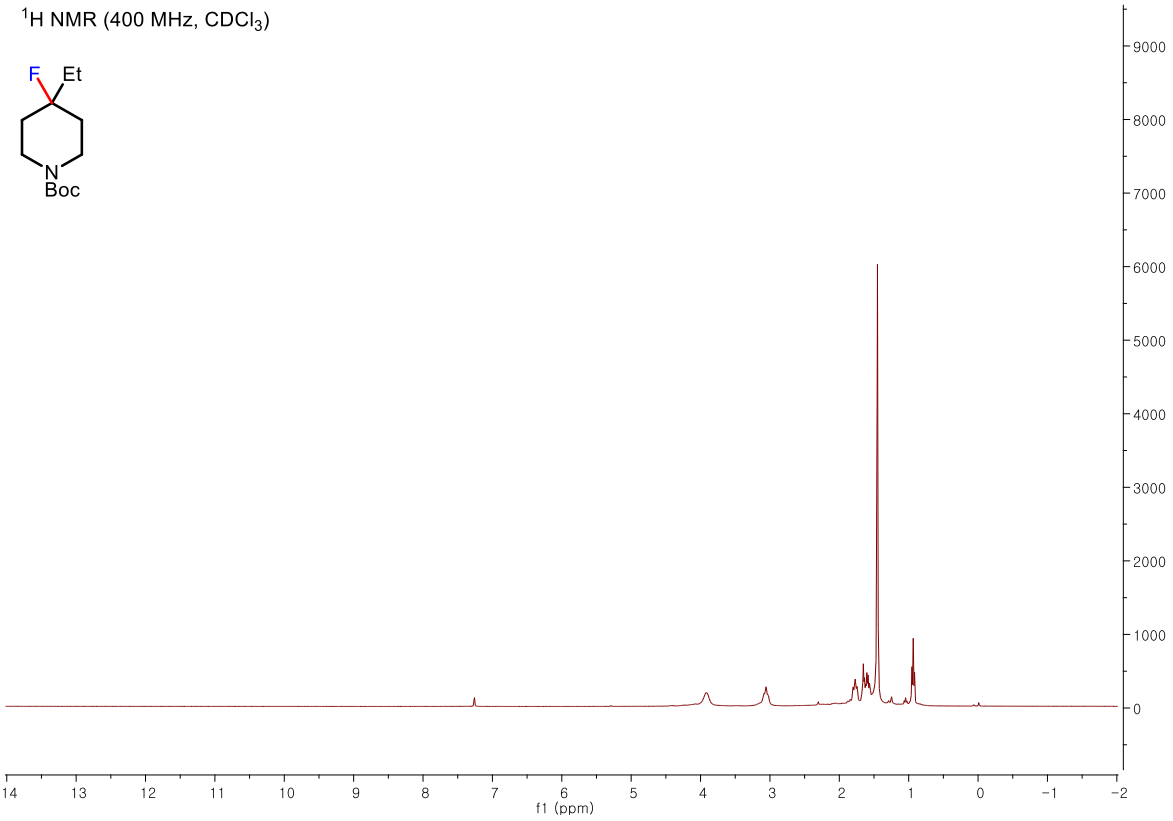
^{13}C NMR (101 MHz, $CDCl_3$)



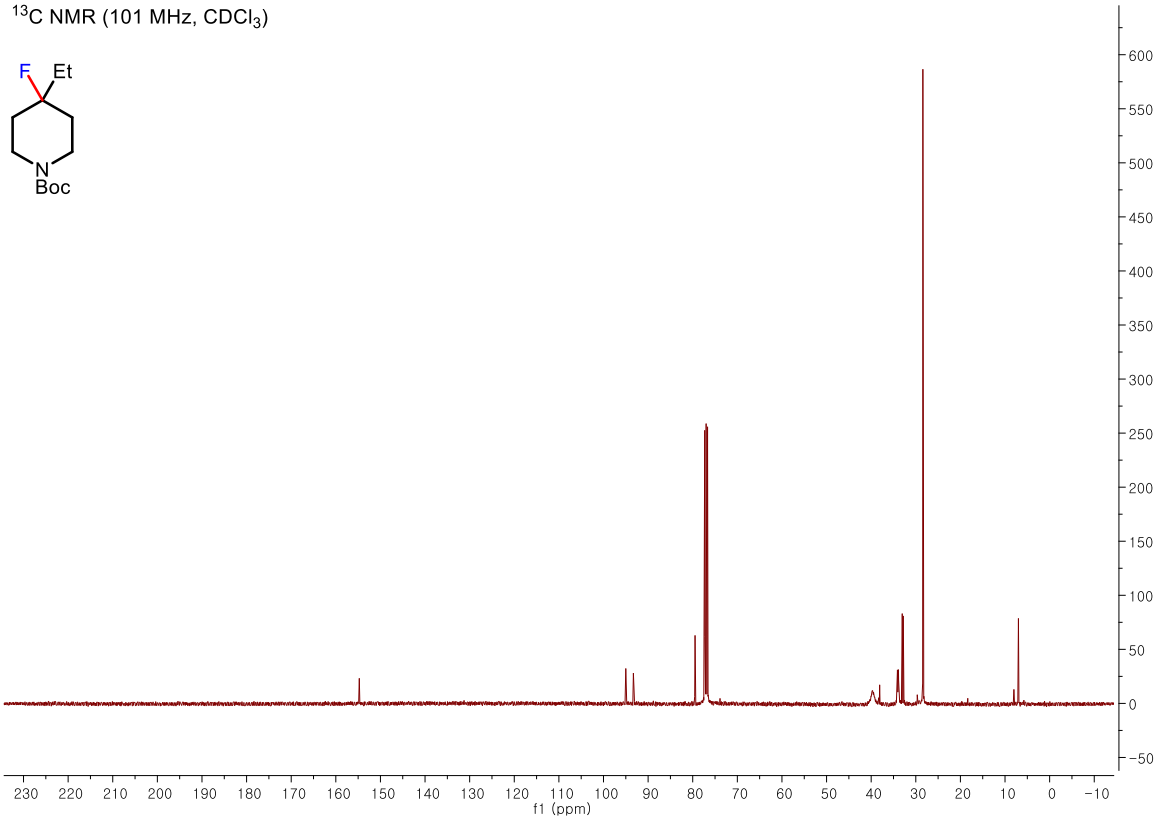
^{19}F NMR (376 MHz, $CDCl_3$)



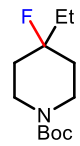
^{1}H NMR (400 MHz, $CDCl_3$)



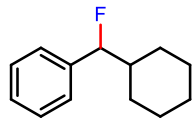
^{13}C NMR (101 MHz, $CDCl_3$)



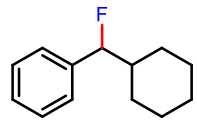
^{19}F NMR (376 MHz, $CDCl_3$)



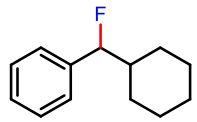
^{1}H NMR (400 MHz, $CDCl_3$)



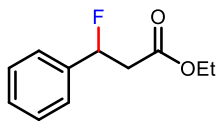
^{13}C NMR (101 MHz, $CDCl_3$)



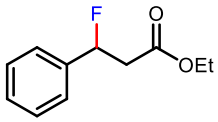
^{19}F NMR (376 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



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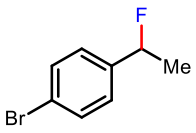

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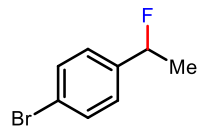

국문 초록

전기화학 반응 조건에서 유기 붕소 화합물을 활용하는 새로운 친핵성 불소화반응 전략을 연구하였다. 이 연구의 주요 특성은 전기화학적 산화 조건하에서 생성된 탄소 양이온 중간체와 불소음이온이 반응하여 탄소−불소 결합을 형성하는 점이다. 반응 최적화 과정에서 중불화칼륨 (KHF_2) 이 불소 공급원으로 사용됨을 확인하였다. 또한, 전류나 시간 조건이 중요 요소임을 확인 할 수 있었다. ^{11}B NMR 연구를 통해 붕소의 화학적 이동이 δ 33 ppm 에서 δ 5 ppm으로 변하는 것을 확인하였다. 이 결과는 불소 음이온이 붕소의 비어있는 p 오비탈에 첨가되어 산화될 수 있는 붕산염착물을 형성하고 이 붕산염착물은 순차적인 산화과정을 거쳐 라디칼 및 탄소 양이온 중간체를 생성함을 보여준다. 해당 연구는 개발된 반응을 통하여 입체 장애를 가진 삼차, 이차 벤질 sp^3 탄소 원자에 효과적으로 불소 원자를 도입할 수 있음을 입증하였다. 또한 이 새로운 반응은 방사성 불소화반응으로 확장 될 수 있다.

주요어: 친핵체성 불소화반응, 전기화학 반응, 방사성 불소화반응

학생 번호: 2018-26976