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# Silver-Catalyzed Radical Fluorination of Alkylboronates in Aqueous Solution

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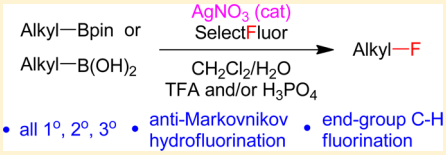
Supporting Information

**ABSTRACT:** We report herein an efficient and general method for the deboronofluorination of alkylboronates. Thus, with the catalysis of $AgNO_3$, the reactions of various alkylboronic acids or their pinacol esters with Selectfluor reagent in acidic aqueous solution afforded the corresponding alkyl fluorides under mild conditions. A broad substrate scope and wide functional group compatibility were observed. A radical mechanism is proposed for this site-specific fluorination.




## INTRODUCTION

The increasing importance of fluorine in agrochemicals and pharmaceuticals[1] as well as the use of $^{18}$F-labeled organic compounds as contrast agents for positron emission tomography (PET)[2] has spurred vigorous research for the development of new methods for C—F bond formations under mild conditions. As a consequence, significant progress has been achieved in this area.[3] In particular, radical fluorination is emerging as a versatile tool in C($sp^3$)—F bond formations.[4−7] For example, Sammis and co-workers[6a] reported the alkyl fluorination of peresters with *N*-fluorobis(benzenesulfonyl)imide (NFSI).[8] Groves et al.[5a] successfully developed the manganese-catalyzed oxidative aliphatic C—H fluorination with fluoride ion. Boger and Barker[6b] nicely introduced the Fe(III)/$NaBH_4$-mediated free radical hydrofluorination of unactivated alkenes. Lectka and co-workers[5b] accomplished the copper-catalyzed aliphatic C—H fluorination with 1-chloromethyl-4-fluorodiazoniabicyclo[2,2,2]-octane bis(tetrafluoroborate) (Selectfluor).[9] Nevertheless, site-specific radical fluorination of complex molecules, especially in late stages, is still challenging.

Organoborane compounds are among the most commonly employed intermediates in organic synthesis.[10] The deboronative fluorination of aryl or alkylboronates is certainly an ideal method for site-specific C—F bond formation. As a consequence, the fluorination of arylboronic acids and derivatives has been extensively studied.[11] However, to our surprise, the fluorination of alkylboronates remains virtually unexplored.[12] Herein, we report an efficient and general method for site-specific C($sp^3$)—F bond formation by radical deboronofluorination of alkylboronic acids or their pinacol esters.

## RESULTS AND DISCUSSION

We recently reported the $AgNO_3$-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor.[7a] We wondered whether the fluorination of alkylboronic acids could also be implemented with $AgNO_3$/Selectfluor. Thus, (5-(1,3-dioxoisoindolin-2-yl)pentyl)boronic acid (**A-1a**) was used as the model substrate. With $AgNO_3$ (20 mol %) as the catalyst, the reaction of **A-1a** with Selectfluor (2 equiv) in $CH_2Cl_2$—$H_2O$ (1:1, v:v) mixed solvent at reflux for 24 h led to the formation of the expected fluorination product **1a** in 56% yield. The addition of acetic acid (4 equiv)[7c] lowered the product yield to 34%. However, switching the additive from acetic acid to trifluoroacetic acid (TFA)[6g] or $H_3PO_4$ resulted in the increase of product yield (65% and 74%, respectively). By further adjusting the ratio of $CH_2Cl_2$ to $H_2O$, we were delighted to find that, with four equivalents of $H_3PO_4$ as the additive and $CH_2Cl_2$—$H_2O$ (2:1, v:v) as the solvent, the reaction proceeded smoothly at reflux (~50 °C), providing **1a** in 90% yield. Control experiments indicated that no fluorination could be observed without the catalysis of $AgNO_3$. Under the optimized conditions, the pinacol ester (**B-1a**) and trifluoroborate of **A-1a** also underwent deboronofluorination, but in lower yields (25% and 49%, respectively).

A number of primary alkylboronic acids were then subjected to the above optimized conditions and the corresponding alkyl fluorides **1b**−**1i** were obtained in high yields (Scheme 1). Functional groups such as nitrile, carbonyl, ether and ester were well tolerated. In particular, free alkyl carboxylic acid group in **1i** remained intact rather than undergoing decarboxylation, indicating the mildness of reaction conditions. The fluorination of a secondary alkylboronic acid, cyclododecylboronic acid, also proceeded nicely to give **1j** in 82% yield under slightly altered conditions (vide infra). On the other hand, arylboronic acids such as **1k** were inert under the above conditions.

Our attempt to test more secondary or tertiary alkylboronic acids, especially functionalized ones, was hampered by their difficult purification due to their instability.[13] In view of the fact that alkylboronic acids are generally prepared from the hydrolysis of their esters and that the corresponding pinacol esters are much more stable and easier to purify, it should be of more synthetic value to use directly pinacol esters for the fluorination. With this idea in mind, we first tested secondary

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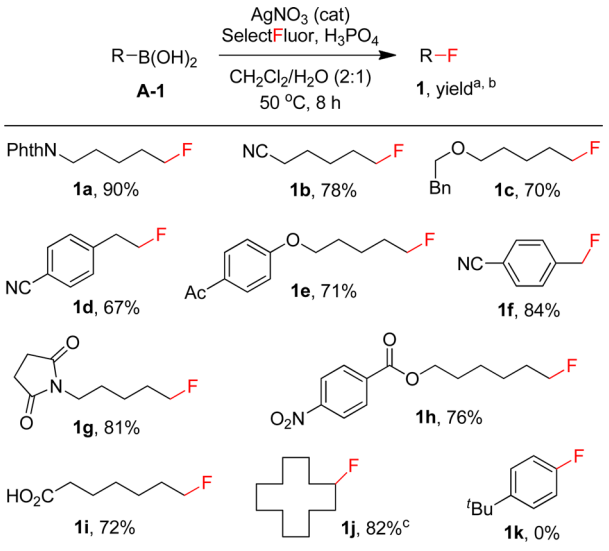
**Scheme 1. Fluorination of Alkylboronic Acids**



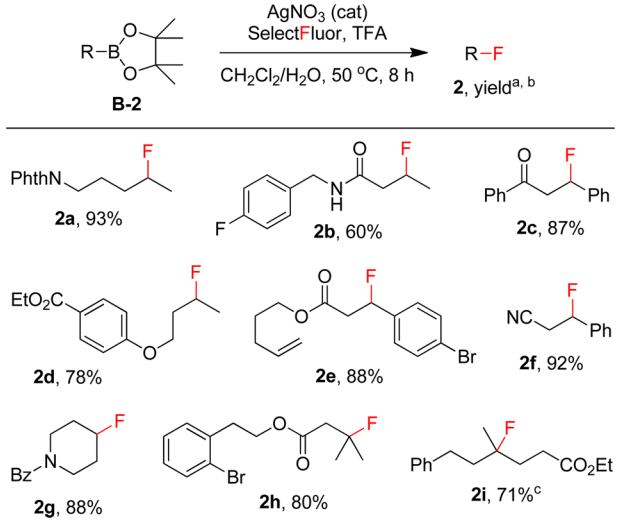

[a]Conditions: **A-1** (0.2 mmol), $AgNO_3$ (0.04 mmol), Selectfluor (0.4 mmol), $H_3PO_4$ (0.8 mmol), $CH_2Cl_2$ (1 mL), $H_2O$ (0.5 mL), 50 °C, 8 h. [b]Isolated yield based on **A-1**. [c]$H_3PO_4$ (0.1 mL), $CH_2Cl_2$ (0.6 mL), $H_2O$ (0.9 mL) and TFA (0.4 mL) were used.

and tertiary alkylboronic esters **B-2**. The pinacol ester of (5-(1,3-dioxoisoindolin-2-yl)pentan-2-yl)boronic acid (**B-2a**) was then chosen as the model substrate. The reaction of **B-2a** under the above optimized conditions gave the expected alkyl fluoride **2a** in only 30% yield while ~70% **B-2a** was recovered. Switching the additive from $H_3PO_4$ to TFA speeded up the reaction and **2a** was obtained in 77% yield within 24 h. Furthermore, increasing the amount of Selectfluor to three equivalents resulted in the formation of **2a** in 86% yield within 12 h. Finally, by adjusting the ratio of $CH_2Cl_2/H_2O$ to 1:1, a clean reaction was observed, furnishing the product **2a** in almost quantitative yield (93% isolated yield). Control experiments indicated that no reaction occurred without the presence of $AgNO_3$. Moreover, no reaction was observed between boronate **B-2a** and $AgNO_3$ in the above aqueous $CH_2Cl_2$ solution (without the presence of Selectfluor), implying that the deboronofluorination is unlikely to proceed via the transmetalation from boron to silver(I) followed by the oxidation of the organosilver(I) intermediate.

A number of secondary and tertiary alkylboronic esters **B-2** were then subjected to the above reoptimized conditions to examine the scope of application of this deboronofluorination. The results are summarized in Scheme 2. The corresponding alkyl fluorides **2a**−**2i** were achieved in excellent yields. Again, a broad substrate scope and wide functional group compatibility were observed.

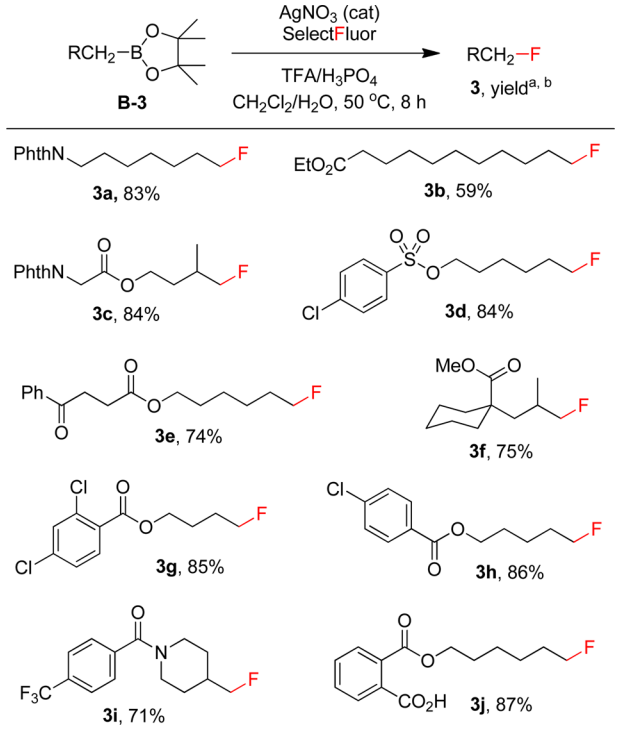
We then moved on to test primary alkylboronic esters. As mentioned above, the reaction of boronate **B-1a** gave product **1a** in 25% yield under the conditions for the fluorination of boronic acids depicted in Scheme 1. When **B-1a** was subjected to the conditions for the fluorination of boronic esters shown in Scheme 2, the reaction proceeded sluggishly, producing **1a** in ~20% yield after 24 h. However, it accelerated when the amount of TFA was increased. A brief screening on the solvent ratios revealed that, with $CH_2Cl_2/TFA/H_2O$ (6:4:9, v:v:v) as the solvent system, **1a** was obtained in 89% yield within 8 h. Furthermore, with the combination of TFA and $H_3PO_4$ in ~4:1 (v:v) ratio, we were pleased to find that **1a** was isolated in 95% yield.

**Scheme 2. Fluorination of Secondary and Tertiary Alkylboronates**




[a]Conditions: **B-2** (0.2 mmol), $AgNO_3$ (0.04 mmol), Selectfluor (0.6 mmol), TFA (0.8 mmol), $CH_2Cl_2$ (1 mL), $H_2O$ (1 mL), 50 °C, 12 h. [b]Isolated yield based on **B-2**. [c]See Scheme 1.

**Scheme 3. Fluorination of Primary Alkyl-boronates**




[a]Conditions: **B-3** (0.2 mmol), $AgNO_3$ (0.04 mmol), Selectfluor (0.6 mmol), $H_3PO_4$ (0.1 mL), $CH_2Cl_2$ (0.6 mL), $H_2O$ (0.9 mL), TFA (0.4 mL), 50 °C, 8 h. [b]Isolated yield based on **B-3**.

These conditions were applicable to various primary alkylboronic esters (**B-3**) and the corresponding primary alkyl fluorides **3a**−**3j** were obtained in satisfactory yields (Scheme 3). While the role of TFA as a cosolvent is unclear, it might help increasing the solubility of substrate boronates in the aqueous phase. This was evidenced by the synthesis of **1j** and **2i** from the corresponding boronates of lower solubility in water.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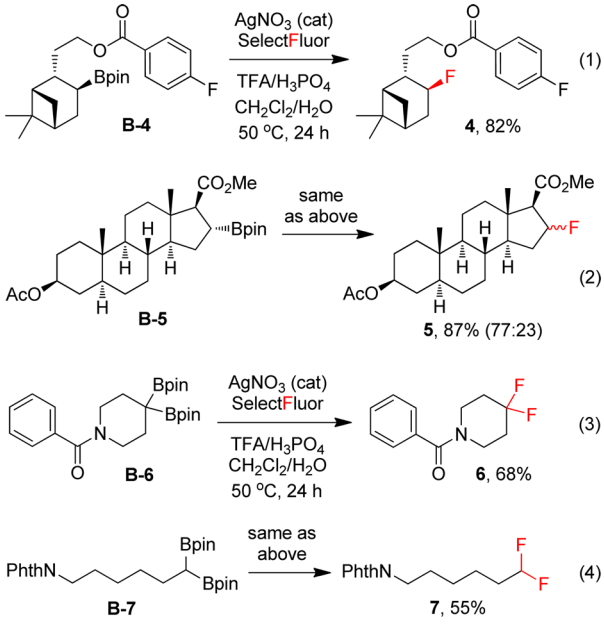
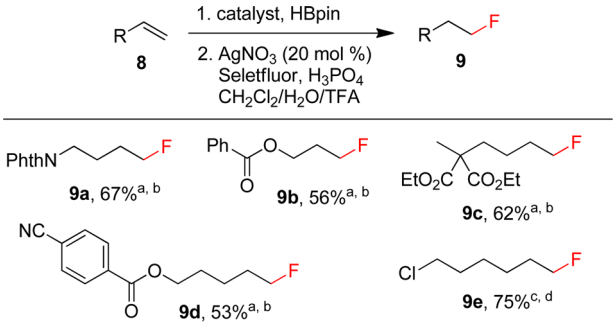
The above results clearly demonstrated the generality of deboronofluorination. Furthermore, the fluorination could also be stereoselective, as exemplified by the synthesis of **4** as a single stereoisomer (eq 1). In the meantime, the mild reaction




conditions allowed the fluorination of more complex molecules, as shown in the synthesis of fluorinated steroid **5** (eq 2). The reaction could be further extended to the synthesis of the *gem*-difluorides (such as **6** and **7**) from the corresponding geminal bis(boronates) (eqs 3 and 4).

As an extension of the above deboronofluorination, the anti-Markovnikov hydrofluorination of unactivated alkenes was then successfully implemented (Scheme 4). Thus, the

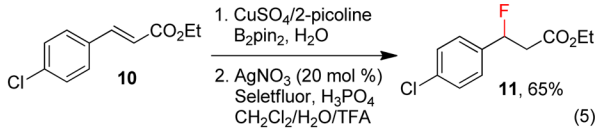
**Scheme 4. Anti-Markovnikov Hydrofluorination of Unactivated Alkenes**

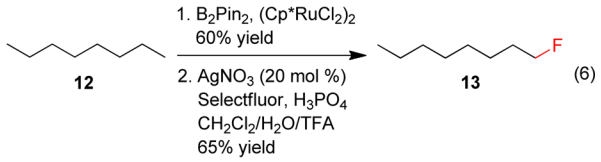


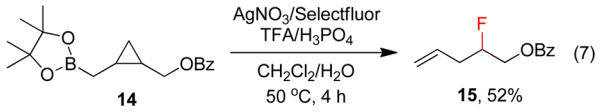

[a]Catalyst: $Rh(PPh_3)_3Cl$ (2 mol %). [b]Isolated yield. [c]Catalyst: ($^{iPr}$PNN)$CoCl_2$ (0.05 mol %)/$NaBHEt_3$ (0.1 mol %). [d]$^{19}$F NMR yield.

$Rh(PPh_3)_3Cl$-catalyzed hydroborylation[14,15] of alkenes with pinacolborane (HBpin) followed by Ag-catalyzed fluorination afforded the alkyl fluorides **9a**–**9d** in a two-stage, one-pot procedure. With the use of more reactive cobalt pincer complex ($^{iPr}$PNN)$CoCl_2$ recently developed by the Huang group[15b] as the catalyst for hydroborylation, the hydrofluorination of 6-chlorohex-1-ene furnished **9e** in 75% yield. Note that the regioselectivity is opposite that of literature methods, which gave Markovnikov hydrofluorination products only.[6b,e,16]

In another case, the copper-catalyzed[15c] hydroborylation of activated alkene **10** followed by fluorination yielded the fluoride **11** also in one-pot procedure (eq 5).




By taking advantage of the end-group C—H borylaton developed by Hartwig and others,[17,18] a two-step terminal C—H fluorination could be implemented, as shown in eq 6. Although a number of C($sp^3$)—H fluorination methods[5] have recently been developed, none deals with terminal C—H bonds. Therefore, our example provides a nice complement to the literature methods.

A radical fluorination mechanism can be inferred from the above results. The oxidative generation of alkyl radicals from alkylboronates is also known.[19,20] To provide direct evidence, cyclopropylmethylboronate **14** was designed as the radical probe. The reaction of **14** under the optimized conditions afforded the ring-opening product **15** in 52% yield (eq 7). This clearly demonstrated that alkyl radicals are generated from alkylboronates.

The deboronofluorination is no doubt triggered by the interaction of Ag(I) with Selectfluor. This interaction was evidenced by $^{19}$F NMR monitoring with the use of equimolar amounts of Selectfluor and $AgNO_3$ in water at room temperature, which showed that the N—F signal at +47.1 ppm decreased slowly and disappeared completely after 10 h. However, no new signal could be observed. Instead, a gray precipitate was formed at the bottom of the NMR tube, which unfortunately exhibited no reactivity toward boronic acids such as **A-1a**. The redox potential of the Ag(I)/Ag(II) couple is +1.98 V vs SCE,[21] while the reported reduction potential of Selectfluor is −0.296 V vs AgRE.[22] These data suggest that an outer-sphere single electron transfer from Ag(I) to Selectfluor is unlikely.[23] On the basis of the above results and our previous findings,[7] we propose the following mechanism depicted in Figure 1. The interaction of Ag(I) with Selectfluor generates the Ag(III)—F intermediate presumably via oxidative addition. The single electron oxidation of alkylboronates by Ag(III)—F gives alkyl radicals and Ag(II)—F. The subsequent fluorine atom transfer between alkyl radicals and Ag(II)—F affords alkyl fluorides as the final products and regenerates Ag(I) as the catalyst. Further mechanistic investigations are certainly required to reveal the nature of the above transformation.

## CONCLUSIONS

We have successfully developed a catalytic, efficient, and general method for the fluorination of alkylboronates in acidic aqueous solution with wide functional group compatibility.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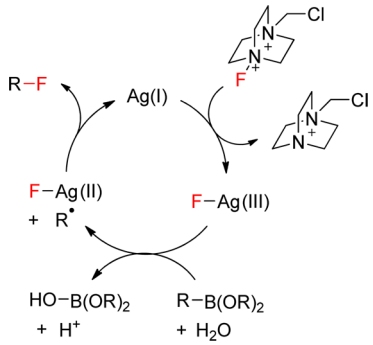


**Figure 1.** Proposed mechanism for deboronofluorination.

Anti-Markovnikov hydrofluorination of unactivated alkenes and terminal C—H fluorination have also been realized based on the deboronofluorination. In view of the convenient and divergent access of alkylboronates, the deboronofluorination should find important application in organic synthesis.

## EXPERIMENTAL SECTION

**Typical Procedure for Silver-Catalyzed Deboronative Fluorination of Alkylboronates.** 2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)-isoindoline-1,3-dione (**B-2a**, 68.6 mg, 0.2 mmol), $AgNO_3$ (6.8 mg, 0.04 mmol) and Selectfluor (212 mg, 0.6 mmol) were placed in a Schlenk tube under nitrogen atmosphere. Dichloromethane (1 mL), water (1 mL) and trifluoroacetic acid (58 μL, 0.8 mmol) were then added successively at rt. The reaction mixture was stirred at reflux for 24 h. The resulting mixture was cooled down to rt and then extracted with $CH_2Cl_2$ (15 mL × 3). The combined organic phase was dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (5:1, v:v) as the eluent to give pure 2-(4-fluoropentyl)isoindoline-1,3-dione (**2a**) as a yellow oil. Yield: 44 mg (93%).

## ASSOCIATED CONTENT

### Supporting Information

Full experimental details, characterizations of new compounds, copies of $^{1}H$, $^{13}C$, $^{11}B$ and $^{19}F$ NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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