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Metal-free electrophilic fluorination of alkyl trifluoroborates and boronic acids

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This work is dedicated to Dr. Bernard Langlois on the occasion of his 60th birthday

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ABSTRACT

Secondary alkyl trifluoroborates undergo facile electrophilic fluorination under mild conditions to afford the corresponding benzylic fluorinated adducts in excellent yield.

The number of fluorinated organic molecules reported in the literature drastically increased over the past decades.[1] This infatuation is motivated by the fact that the introduction of fluorine atoms generally enhances the lipophilicity[2]—hence the bioavailability—of the molecule, and limits its degradation as the C–F bond is more stable than the almost isosteric C–H bond (480 vs 410 kJ mol^{-1}).[3] Consequently, much effort is currently dedicated to the development of new synthetic methods for the selective introduction of fluorine atoms. Both electrochemical (Simons process) and chemical methods were proposed.[4] Due to the difficulty in handling HF or F_2, synthetic electrophilic or nucleophilic fluorinating reagents were developed. Yet, the selective insertion of a fluorine atom remains challenging. Herein, we disclose a generalization of the electrophilic fluorination of boronic esters or acids pioneered by Petasis, Prakash, and Olah in the late 90s.[5] In particular, we demonstrate that the electrophilic fluorination works with aromatic trifluoroborates and boronic acids and more importantly with alkyl trifluoroborates. To the best of our knowledge, electrophilic fluorination of alkyl boronates has never been reported to date.

Boronic acids and trifluoroborate salts are generally used as cross-coupling partners in the Suzuki reaction or for 1,4 rhodium-catalyzed addition reaction. Recently Molander[6] and Genet[7] reported that organotrifluoroborate salts constitute a versatile, new class of reagents particularly suitable for the elaboration of highly functionalized molecules. Indeed, on the one hand, the relative stability of the trifluoroborate moiety tolerates valuable chemical transformations such as reductive amination[8] or S_N2 halide substitution of potassium bromomethyltrifluoroborate.[9] On the other hand, the trifluoroborate functionality constitutes an excellent partner for Suzuki–Miyaura type cross-couplings giving access to a large range of elaborated molecules.

Yet, boron derivatives have been scarcely considered as suitable candidates for electrophilic substitution. Thus, Kabalka et al. reported that alkyl, alkenyl, or alkynyl organotrifluoroborates smoothly react with sodium iodide or bromide in the presence of chloramines T to afford the corresponding iodinated or brominated adducts in good yield.[10] On the other hand, this strategy did not appear successful for the preparation of fluorinated analogues. Conversely, Petasis et al. reported that alkenyl trifluoroborates react with Selectfluor™ to afford the fluorinated adducts. Surprisingly, they limited their study to alkenyl trifluoroborates and they did not use their methodology for the fluorination of alkyl or aromatic boron derivatives. In addition, they did not consider boronic acids as suitable partners as in their hands, the reaction between alkenyl boronic acid and Selecfluor™ appeared slow and contaminated with variable amounts of reduced compound.

In this Letter, we report that the electrophilic fluorination is much more general than the reaction reported earlier, and actually constitutes a reliable alternative route for the introduction of fluorine atoms at key positions. In particular, we demonstrate that this strategy can be applied for the smooth and efficient preparation of fluorinated alkyl derivatives via the metal-free electrophilic fluorination of the boronic acid or trifluoroborate precursors.

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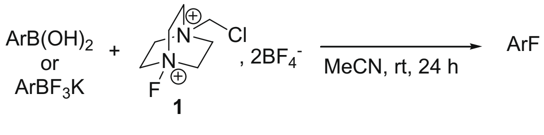
During the course of our study, we became interested in developing a suitable method for the selective introduction of electrophiles on aromatic and alkyl boron derivatives. To this end, we first extended the scope of the methodology first developed by Petasis et al. to vinyl trifluoroborates for the functionalization of aromatic boron derivatives and—more interestingly—of secondary alkyl boronates that were recently proven very valuable intermediate for the elaboration of functionalized chiral molecules.[11]

Accordingly, we envisioned reacting stoichiometric amounts of Selecfluor™ with aromatic boronic acids or trifluoroborates in dry acetonitrile at room temperature (Scheme 1).[12]

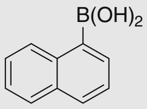
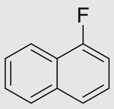
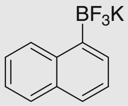
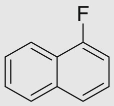
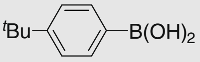
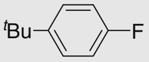
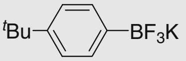
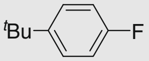
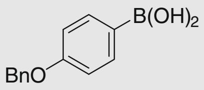
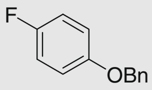
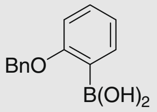
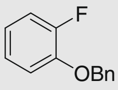
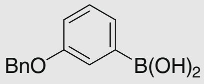
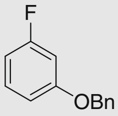
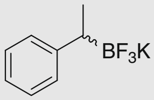
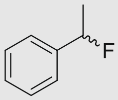
As low molecular weight fluorinated aromatics are known to be extremely volatile, we started with naphthyl boronic acid (Table 1, entry 1). Interestingly, a GC analysis revealed that the conversion into the expected fluorinated naphthalene reached 90%. When the reaction was repeated using the trifluoroborate derivative (Table 1, entry 2), the results were slightly lower, as the expected 1-fluoronaphthalene was present in 79% yield, along with 21% of naphthalene. In order to test the versatility of our method, we also applied the strategy to the preparation of 4-*tert*-butylfluorobenzene. As expected, Selectfluor™ efficiently converted the corresponding boronic of trifluoroborate derivatives into the fluorinated species in 75% and 53% yield, respectively (Table 1, entries 3 and 4). In this case, it is worth noting that the boronic acid affords the expected compound in a slightly higher yield than the boronate salts. Indeed, in the latter case, 47% of *tert*-butylbenzene was also isolated. Interestingly, this result confirms that the presence of electron donating groups (Table 1, entries 1–4) enhances the electronic density on the boron atom that undergoes elimination rather than substitution. This observation constitutes an exception to the sequence of reactivity observed so far by us and others. To validate our hypothesis, we investigated the electrophilic substitution on a series of benzyloxyphenylboronic acids. Thus, we reacted ortho, meta, and para substituted (benzyloxy)phenylboronic acids with selectfluor™. As expected, the less hindered para-substituted phenylboronic acid was the most reactive coupling partner affording quantitatively the expected fluorinated adduct (Table 1, entry 5). The ortho-substituted isomer was also converted into the substituted fluorobenzene in decent yield (Table 1, entry 6). On the other hand, 3-(benzyloxy)phenylboronic acid did not react at all (Table 1, entry 7). These results highlight the crucial influence of the electron density on the outcomes of the reaction. This behavior was also confirmed by testing the electrophilic fluorination of nitro-substituted electron-poor boron derivatives. In the latter case, very little conversion was observed and the palladium-mediated fluorination reported by Ritter et al. remains the most appropriate method for the selective fluorination.[13]

Based on these promising preliminary tests, we then considered the electrophilic fluorination of alkyl trifluoroborates that are expected to be more reactive than their boronic acid analogues (Scheme 2).

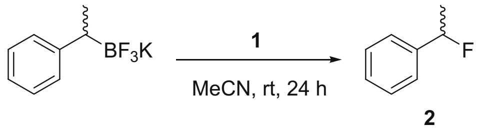


Scheme 1. Access to the fluorinated aromatic compounds.

Table 1
Fluorination of boronic derivatives

Entry	Substrate	Product	Conversion
1[a]			90%
2[a]			79% (+21% naphtalene)
3[a]			75% (+12% ^{t}BuPh)
4[a]			53% (+47% ^{t}BuPh)
5[a]			100%
6[a]			67% (+33% BnOPh)
7[a]			–
8[a]			91%

[a] Conditions: MeCN, 0.5 M, room temperature, 24 h.



Scheme 2. Electrophilic fluorination of alkyl boronates.

To the best of our knowledge such a transformation had never been reported before in the literature as alkyl boronic acids or trifluoroborates are generally considered as very poor coupling partners. Interestingly, reacting a stoichiometric amount of Selectfluor™ with 1-phenylethyltrifluoroborate (Table 1, entry 8) afforded the expected fluorinated adduct **2** in 91% conversion, and 75% isolated yield.[14] However, in the case of 2-phenylethyltrifluoroborate, a complete racemization was observed. Indeed, starting from enantio-enriched or racemic mixture afforded 1-(1-fluoroethyl)benzene as a racemic mixture.

In summary, we have demonstrated that in the case of electron-rich systems, the electrophilic fluorination constitutes a competitive method for the introduction of fluorine atoms at key positions. More interestingly, this methodology was also proved powerful for the introduction of fluorine atom at benzylic positions starting from the readily available 1-phenylethyltrifluoroborate. Work is currently in progress for elucidating the mechanism and for determining the factors that govern the reaction.

Acknowledgment

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12. *Typical experimental procedure*: a solution of boronic acid (4 mmol, 1 equiv) and selectfluor™ (4 mmol, 1 equiv) in dry acetonitrile (20 mL) was stirred at room temperature under argon for 24 h. The reaction mixture was poured in 250 mL of water and extracted with pentane. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and dried over $MgSO_4$. After evaporation under reduced pressure, the crude fluorinated adduct was purified over silica gel chromatography to yield the expected pure product.
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14. Data for 1-(1-fluoroethyl)benzene): isolated yield: 75%; ^{2}H NMR ($CDCl_3$): δ (ppm) 1.53 (dd, $J^3 = 6.4$ Hz, $J_F = 23.92$ Hz, 3H), 5.52 (qd, $J^3 = 6.4$ Hz, $J_F = 47.66$ Hz, 1H), 7.24 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) 23.0 (d, $J_F = 76$ Hz), 91.1 (d, $J = 168$ Hz), 125.3 (d, $J = 20$ Hz), 128.3 (d, $J = 6$ Hz), 128.6, 141.7 (d, $J = 57$ Hz); ^{19}F NMR (CD_2Cl_2): δ (ppm) −167.4.