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Fluorination of Aryl Boronic Acids Using Acetyl Hypofluorite Made Directly from Diluted Fluorine

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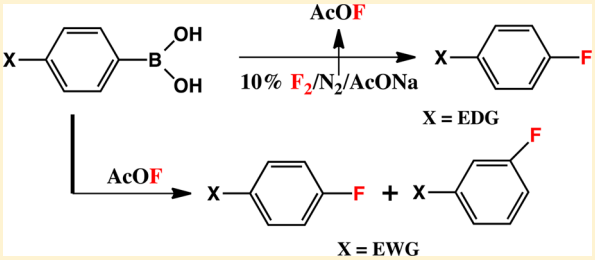
Supporting Information

ABSTRACT: Aryl boronic acids or pinacol esters containing EDG were converted in good yields and fast reactions to the corresponding aryl fluorides using the readily obtainable solutions of AcOF. In reactions with aryl boronic acids containing EWG at the para position, there are two competing forces: one directing the fluorination to take place ortho to the boronic acid and the other, toward an ipso substitution. With EWG meta to the boronic acid, substitution ipso to the boron moiety takes place in good yields.



INTRODUCTION

Aryl fluorides are unique because of their biological, chemical, and physical properties that make them useful in many fields, including drug development,[1,2] material science, medicine, and agrochemicals.[3] Thus, the development of mild and selective methods for introduction of fluorine into aromatic substrates is an important objective because there are many cases where harsh conditions are employed to form aromatic C−F bonds.[4] The leading strategy, therefore, is to introduce the fluorine atom during the first steps of the synthesis or to use an aryl fluoride as a starting building block. Finding simple methods with short reaction times for aromatic fluorinations can thus be valuable in general as well as for the preparation of [18]F-labeled compounds used in positron emitting tomography (PET) in particular.[5]

Conventional aromatic fluorination procedures can be categorized into either nucleophilic or electrophilic mode. The best example of the first are variations of the Balz−Schiemann reaction, whereas the second is characterized by using ROF or R_2NF reagents.

Aromatic boronic acids are readily available and are useful in synthetic organic chemistry.[6] They have also been involved in electrophilic metal-mediated fluorinations,[7,8] including silver- and palladium-based catalytic processes, as well as using Selectfluor in the presence of strong bases.[9] Metal-free processes in the pharmaceutical industry, however, are much more preferred because possible metal contamination can induce concerns and its removal can be rather expensive. Metal-free fluorination could be achieved using reagents such as $CsSO_4F$[10] or through an easier and better procedure utilizing the electrophilic acetyl hypofluorite, AcOF. This reagent, as are several others derived directly from dilute fluorine,[11] is readily prepared by passing the F_2/N_2 mixture through a suspension of sodium acetate in acetonitrile and does not require any isolation or purification.[12] It has been widely used for the synthesis of α-fluorocarbonyl, α-fluorosulfonate, and α-fluorophosphonate derivatives,[13] fluorination of activated aromatic derivatives,[14] synthesis of [18]F-fluorodeoxyglucose,[5] α-fluorocarboxylic acids, and α-fluoroethers[15] as well as for the activation of the pyridine ring by substituting its inactive hydrogen at the 2-position with oxygenated moieties[16] and in some cases even with chlorine, bromine, or alcohols.[17]

We present here a general method for direct electrophilic fluorinations of various arylboronic acids with acetyl hypofluorite. The use of mild conditions, a single step, and short reaction times are also beneficial.

RESULTS AND DISCUSSION

Reacting 4-*tert*-butylphenylboronic acid (**1a**) with AcOF at 0 °C produced the corresponding 4-*tert*-butylfluorobenzene (**2a**)[18] in a few minutes in 85% yield. Similar results were obtained when 4-chlorophenylboronic acid (**1b**) and 4-butylphenylboronic acid (**1c**) were treated with AcOF, forming 4-chlorofluorobenzene (**2b**)[19] and 4-butylfluorobenzene (**2c**)[8] in 75 and 85% yields, respectively. 4-Fluorobenzylbromide (**2d**)[20] and the somewhat sterically hindered 2,6-dimethyl-fluorobenzene (**2e**)[8] were also formed from the corresponding boronic acids **1d** and **1e** in a few minutes in 80 and 85% yields, respectively. The yields were slightly lower with substrates possessing weak electron-withdrawing groups. Fluorination of 2,3-dichlorophenylboronic acid (**1f**) afforded 2,3-dichlorofluor-obenzene (**2f**)[21] in 45% yield. Boronic pinacol esters also react with acetyl hypofluorite to produce fluorinated products similarly to boronic acids, but longer reaction times of around 20−30 min were required, as is evident from the reaction of **1g**, which was converted to 4-chlorofluorobenzene (**2b**)[19] in 85% yield.

The above results could be explained by assuming a complexation of the acetate moiety in the acetyl hypofluorite with the boron, which has very high affinity to oxygen atoms.

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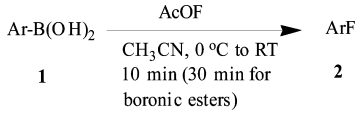
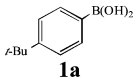
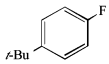
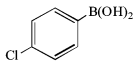
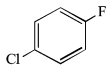
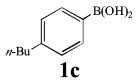
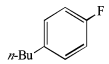
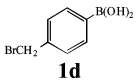
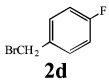
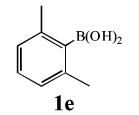
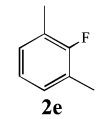
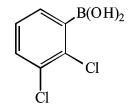
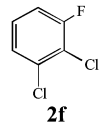
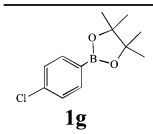
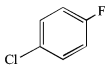
Table 1. Fluorination of *p*-Arylboronic Acids



Substrate	AcOF (eq.)	Product	Yield (%)
 **1a**	3	 **2a**	85
 **1b**	2	 **2b**	75
 **1c**	2	 **2c**	85
 **1d**	2	 **2d**	80
 **1e**	2.5	 **2e**	85
 **1f**	2.5	 **2f**	45
 **1g**	3	 **2b**	85

The resulting trioxygenated boron species, $(RO)_2B\text{-}OCOCH_3$, is a good leaving group and allows the ipso substitution by the electrophilic fluorine (Figure 1).

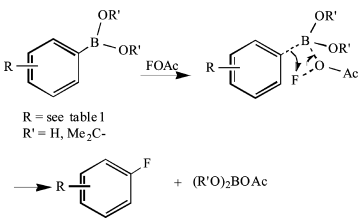
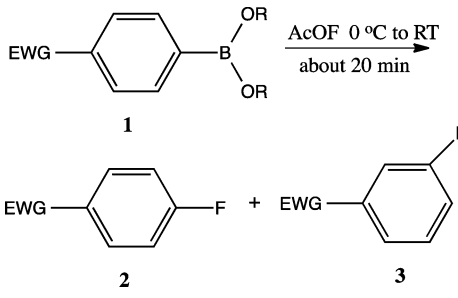
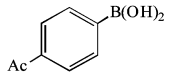
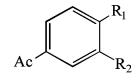
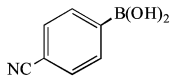
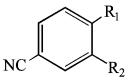
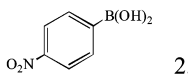
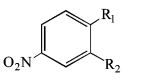
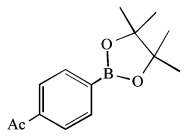
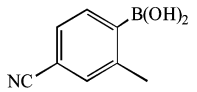
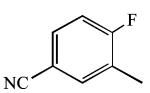


Figure 1. Proposed mechanism for the reaction of aromatic boronic acid derivatives with AcOF.

Quite surprising results, however, where obtained when a strong electron-withdrawing group was in the para position to the boronic acid because mixtures of para and meta fluoro derivatives were obtained. Thus, when 4-acetylphenylboronic acid (**1h**) or 4-cyanobenzeneboronic acid (**1i**) were treated with AcOF, *para*- and *meta*-fluoroacetophenones (**2h**) and (**3h**)[22] and *para*- and *meta*-fluorocyanobenzenes (**2i**)[23] and (**3i**)[24] were formed in 3:2 and 3:1 ratios, respectively, for both cases. The same behavior was recorded with 4-nitrophenylboronic acid (**1j**), which formed with AcOF both *para*- and *meta*-nitrofluorobenzenes (**2j**)[25] and (**3j**),[19] also in a 3:2 ratio (Table 2). These results are in excellent agreement with Mayr's

Table 2. Fluorination of *p*-EWG-Arylboronic Acids



Substrate	AcOF (eq)	Products	Yield (%)
 **1h**	3	 **2h** R_1 = F; R_2 = H **3h** R_1 = H; R_2 = F	51 34
 **1i**	2.5	 **2i** R_1 = F; R_2 = H **3i** R_1 = H; R_2 = F	68 22
 **1j**	2.5	 **2j** R_1 = F; R_2 = H **3j** R_1 = H; R_2 = F	48 32
 **1k**	2	**2h** R_1 = F; R_2 = H **3h** R_1 = H; R_2 = F	42 42
 **1l**	2	 **2l**	87

pioneering work published recently.[26] Mayr checked the outcome of electrophilic processes on five-member ring heteroaromatic trifluoroborates. These reactions resulted in electrophilic attack at the ipso position of the C–B bond and at its nearby C–H bond. He concluded that the BF_3K group activates the position attached to the boron by a factor of 10^3–10^4, whereas adjacent C–H positions are activated by a factor of 10^5–10^6. As can be seen from the present work, similar factors are at work with benzenoidic boronic acids. When the ring is substituted with an electron-donating group para to the boron atom, the additive effects of the heteroatom and the EDG direct the attack toward the ipso position almost exclusively, and the boronic acid is substituted in very good yields. When, however, there is an EWG at the para position, it interferes with the ipso fluorination and along with the boronic acid directs the substitution of the nearby hydrogen, resulting in

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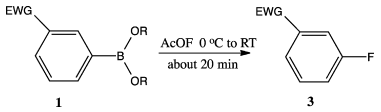
fluorination at the meta position to the EWG. Because protons are always present in these reactions, the boronic moiety is cleaved, as was emphasized also in Mayr's work. It should be remembered, however, that para and meta derivatives were both formed when an EWG is located at the para position because in the present reaction there are always two opposing factors: the first is the directing effect resulting in substitution on the carbon next to the boron and the second is the two oxygen atoms of the electrophilic reagent with their high affinity to the boron atom placing the electrophilic fluorine near the C−B bond, encouraging ipso attack (Figure 1).

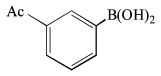
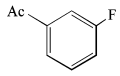
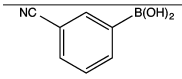
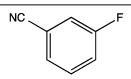
As we have already seen (e.g., for **1h**) the boronic pinacol esters also react under the same mechanism, and the reaction of AcOF with 4-acetylphenylboronic pinacol ester (**1k**) resulted in the two fluoro isomers, **2h** and **3h**, in equal amounts. An interesting case appears to be 2-methyl-4-cyanophenylboronic acid (**1l**). Unlike the 4-cyanophenylboronic acid (**1i**) mentioned above, the electron-donating methyl group encourages the electrophilic substitution on the ipso position of the boron to such an extent that practically only 4-fluoro-3-methylbenzonitrile (**2l**)[27] was obtained in good yield (Table 2).

It should be noted that when an EWG, such as an acetyl or cyano group, is in the meta position to the boronic acid, as in 3-acetylphenylboronic acid (**1m**) and 3-cyanophenylboronic acid (**1n**), it discourages reactions ortho to the boron (and ortho to themselves), resulting mainly in ipso displacement of the boron moiety. Thus, 3-fluoroacetophenone (**3h**) and 3-fluorocyanobenzene (**3i**) were formed in 60 and 75% yields (Table 3).

Table 3. Fluorination of *m*-EWG-Arylboronic Acids



1 3

Substrate	AcOF (eq)	Products	Yield (%)
 1m	2	 3h	60
 1n	3.5	 3i	75

In conclusion, it has been shown that the cheapest and most efficient electrophilic fluorination agent, AcOF, is very useful as a fluorinating agent when substituting aromatic boronic acid or ester moieties. Because the reactions are fast, they are also suitable for PET purposes. In certain cases, the results indicate that two competing activation forces are operative. Finally, we would like to clarify some of the widely spread legends and prejudices associated with elemental fluorine, an essential ingredient for producing AcOF. It is true that pure fluorine may destroy most organic substances, but when it is diluted with N_2 or He it is much less dangerous and easier to work with than, for example, chlorine (it is also less toxic than Cl_2[28]). Diluted fluorine is commercially available, and technical >95% F_2 could be diluted on the spot to whatever degree is desired using a simple vacuum line.[29]

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded using a 400 MHz spectrometer with $CDCl_3$ as the solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 376.8 MHz with $CFCl_3$ serving as an internal standard. The proton broadband-decoupled ^{13}C NMR spectra were recorded at 100.5 MHz. Here, too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard.

General Fluorination Procedure. Fluorine is a strong oxidant and corrosive material. In organic chemistry, it is mostly used after dilution with nitrogen or helium. Such dilution can be achieved using either an appropriate copper or monel vacuum line constructed in a well-ventilated area or by purchasing prediluted fluorine. A detailed description of a simple setup has appeared in the past.[29] The reactions themselves are carried out in standard glassware. If elementary precautions are taken, work with F_2 is simple, and we have had no bad experience working with it.

Preparation of AcOF and Its Reaction with Boronic Acids. A mixture of 10−15% F_2 in N_2 was bubbled through a cold (−30 °C) suspension of 2 g of AcONa·AcOH dispersed in 100 mL of CH_3CN and 10 mL of AcOH placed in a standard glass vessel. The solvated salt was made by leaving anhydrous AcONa over AcOH in a closed desiccator for at least 24 h. It is quite important to have as good stirring as possible because the reaction proceeds between the gas and solid phases. The amount of the AcOF thus obtained could be easily determined by reacting aliquots of the reaction mixture with aqueous KI solution and titrating the liberated iodine. After a typical concentration (around 0.15−0.25 M) of AcOF is achieved, the oxidizing solution was added in one portion to the desired boronic acids derivative that was dissolved in acetonitrile. The reactions were carried out on scales of 1−5 mmol using a 2−4-fold excess of AcOF.

The reactions were usually monitored by TLC, GC, or NMR and in most cases were completed within 10−30 min. The reactions were terminated by pouring them into a $NaHCO_3$ solution followed by water until they became neutral, drying the organic layer over $MgSO_4$, and evaporating the solvent. The crude product was purified by vacuum flash chromatography (Merck silica gel 60H) with petroleum ether/ethyl acetate serving as eluent. The products are known and referenced, and their physical properties matched the ones appearing in the literature. Their NMR spectral data is given in the Supporting Information.

4-Tert-butylfluorobenzene (2a).[18] **2a** was prepared from 4-tert-butylphenylboronic acid (**1a**) (0.54 g, 3.0 mmol) as described above using 3 molar equiv of AcOF solution. A colorless liquid (0.39 g, 85% yield) was obtained.

4-Chlorofluorobenzene (2b).[19] **2b** was prepared from 4-chlorophenylboronic acid (**1b**) (0.54 g, 3.0 mmol) as described above using 2 molar equiv of AcOF solution. A colorless liquid (0.29 g, 75% yield) was obtained.

4-Butylfluorobenzene (2c).[8] **2c** was prepared from 4-butylphenylboronic acid (**1c**) (0.46 g, 2.6 mmol) as described above using 2 molar equiv of AcOF solution. A colorless liquid (0.34 g, 85% yield) was obtained.

4-Fluorobenzylbromide (2d).[20] **2d** was prepared from 4-bromomethylboronic acid (**1d**) (0.42 g, 1.9 mmol) as described above using 2 molar equiv of AcOF solution. A colorless oil (0.29 g, 80% yield) was obtained.

2,6-Dimethylfluorobenzene (2e).[8] **2e** was prepared from 2,6-dimethylphenylboronic acid (**1e**) (0.30 g, 2.0 mmol) as described above using 2.5 molar equiv of AcOF solution. A colorless liquid (0.21 g, 85% yield) was obtained.

2,3-Dichlorofluorobenzene (2f).[21] **2f** was prepared from 2,3-dichlorophenylboronic acid (**1f**) (0.30 g, 2.0 mmol) as described above using 2.5 molar equiv of AcOF solution. A colorless liquid (0.15 g, 45% yield) was obtained.

4-Fluoroacetophenone (2h).[22] **2h** was prepared from 4-acetylphenylboronic acid (**1h**) (0.27 g, 1.7 mmol) as described above using 3 molar equiv of AcOF solution. A mixture of para and meta products, **2h** and **3h**, was formed in a 3:2 ratio (Table 2 and Supporting Information).

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3-Fluoroacetophenone (3h).[22] **3h** was also prepared from 3-acetylphenylboronic acid (**1m**) (0.34 g, 2.1 mmol) as described above using 2 molar equiv of AcOF solution. A colorless liquid (0.17 g, 60% yield) was obtained.

4-Fluorobenzonitrile (2i)[23] **and 3-Fluorobenzonitrile (3i).**[24] **2i** and **3i** were formed as a mixture of products in a 3:1 ratio, respectively, from 4-cyanophenylboronic acid (**1i**) (0.41 g, 2.8 mmol) as described above using 2.5 molar equiv of AcOF solution (Table 2 and Supporting Information). Compound **3i** was also obtained from the reaction of 3-cyanophenylboronic acid (**1n**) (0.35 g, 2.4 mmol) as described above using 3.5 molar equiv of AcOF solution. A colorless liquid (0.22 g, 75% yield) was obtained.

4-Fluoronitrobenzene (2j)[25] **and 3-Fluoronitrobenzene (3j).**[19] **2j** and **3j** were formed as a mixture of products in a 3:2 ratio, respectively, from 4-nitrophenylboronic acid (**1j**) (0.30 g, 1.8 mmol) using 2.5 molar equiv of AcOF solution (Table 2 and Supporting Information).

4-Fluoro-3-methylbenzonitrile (2l).[27] **2l** was prepared from 4-cyano-2-methylphenylboronic acid (**1l**) (0.36 g, 2.3 mmol) as described above using 2 molar equiv of AcOF solution. A white solid (0.27 g, 87% yield, mp 59−61 °C) was obtained.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra and GC data. 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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