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Synthesis of Fluoroalkoxy Substituted Arylboronic Esters by Iridium-Catalyzed Aromatic C−H Borylation

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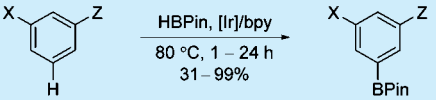
Supporting Information

ABSTRACT: The preparation of fluoroalkoxy arylboronic esters by iridium-catalyzed aromatic C−H borylation is described. The fluoroalkoxy groups employed include trifluoromethoxy, difluoromethoxy, 1,1,2,2-tetrafluoroethoxy, and 2,2-difluoro-1,3-benzodioxole. The borylation reactions were carried out neat without the use of a glovebox or Schlenk line. The regioselectivities available through the iridium-catalyzed C−H borylation are complementary to those obtained by the electrophilic aromatic substitution reactions of fluoroalkoxy arenes. Fluoroalkoxy arylboronic esters can serve as versatile building blocks.



X = OCF_3, OCF_2H, OCF_2CF_2H, 3,4-[-OCF_2O-]

Z = Cl, Br, I, CN, CO_2Me, CF_3, Me, OMe, OH, NH_2

Fluorinated aromatic compounds have important applications in the fields of pharmaceutical,[1] agrochemical,[2] and material sciences.[3] The incorporations of fluorine or fluorinated substituents could induce dramatic changes in the electronic, steric, and hydrophobic parameters of the target molecule. This can result in improved binding selectivity, metabolic stability, lipophilicity, etc. ultimately affecting the pharmacodynamic and pharmacokinetic properties of fluorinated molecules. Besides fluorine itself, the most commonly used fluorine-containing functional group is trifluoromethyl (CF_3). Recently, other fluorinated functional groups, especially the fluoroalkoxy substituents such as trifluoromethoxy (OCF_3), difluoromethoxy (OCF_2H), and tetrafluoroethoxy (OCF_2CF_2H), etc. have also been explored in search of unique properties.[4]

The fluoroalkoxy groups have interesting properties when compared with other fluorinated substituents. For example, the OCF_3 group is far more lipophilic (π = +1.04) than F (π = +0.14) and is even better than the CF_3 (π = +0.88) group.[5] The Hammett substituent constant σ_I of OCF_3 (0.51) is greater than that of CF_3 (0.39) or SCF_3 (0.31) groups and is comparable to that of an SF_5 (0.55) group.[6] While the σ_I value of OCF_2CF_2H (0.39) is comparable to that of F (0.45). The fluoroalkoxy groups can also induce particular conformational changes. The OCF_3 group in (trifluoromethoxy)benzene tends to adopt an orthogonal position with respect to the arene ring, in contrast with the methoxy group which normally lies in the plane of the arene.[4] Also, due to the diminished conjugation of the oxygen nonbonding electrons with the aromatic ring, the OCF_3 group can freely rotate out of the nucleus plane.[7] This enhanced conformational flexibility may allow better binding affinity.

Like other fluorinated substituents, fluoroalkoxy groups also display higher metabolic and thermal stabilities. The OCF_3 and OCF_2CF_2H functional groups are stable to strong acids and bases.[8] Compared to the trifluoromethylsulfide (SCF_3) group, which readily undergoes oxygenation to the corresponding sulfoxides and sulfones,[9] the fluoroalkoxy substituents are quite stable to oxidative stress. Due to these interesting physical and chemical properties, the fluoroalkoxy functional groups may thus advantageously replace fluorine or CF_3 in many bioactive molecules.

The intrinsic properties of the fluoroalkoxy substituents can potentially be very useful for the fine-tuning of biological as well as technical properties. As a result, fluoroalkoxy-substituted aromatics have found important commercial applications in the fields of pharmaceuticals, agrochemicals, and electro-optical displays (Figure 1).[4,10]

Despite their interesting properties, the facile introduction of fluoroalkoxy functional groups is not trivial. Trifluoromethoxy-substituted aromatics were first synthesized by Yagupol'skii by the reaction of hydrogen fluoride or antimony fluorides with aryl trichloromethyl ethers.[11] Over the past few decades, various new transformations have been developed for the synthesis of fluoroalkoxy aromatics.[4,12] However, most of these approaches either are multistep or suffer from poor substrate

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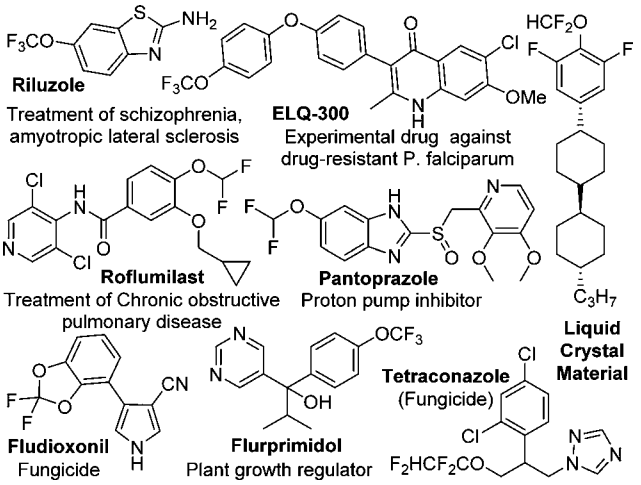


Figure 1. Selected examples of fluoroalkoxy-substituted aromatic compounds of commercial importance.

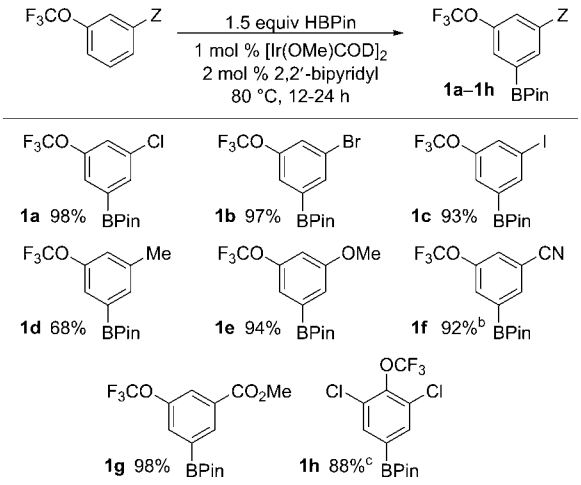
scope due to the use of harsh reaction conditions involving toxic and/or thermally labile reagents. Recently, efforts have been made for the development of mild reaction conditions for the introduction of difluoromethoxy[13] and trifluoromethoxy[14] groups.

The harsh reaction conditions required for the introduction of fluoroalkoxy substituents leads to a limited substrate scope. A possible alternate approach to access diversity is to functionalize fluoroalkoxy-substituted aromatics for further elaboration. In this regard, the derivatization of fluorinated aromatics by preparing their boronic ester derivatives, which can readily be transformed into a wide range of functional groups, could be highly beneficial.[15] Fluorinated arylboronic esters have traditionally been synthesized using directed *ortho* lithiation–borylation.[16] Smith and Maleczka as well as Ishiyama, Miyaura, and Hartwig have reported an iridium-catalyzed C–H borylation reaction for the synthesis of (hetero)arylboronic esters directly from the aromatic hydrocarbons.[17] This new reaction has been recently utilized to prepare F,[18] SF_5,[19] and SCF_3[20] substituted arylboronic esters. Herein, we describe the application of the iridium-catalyzed aromatic C–H borylation reaction for the synthesis of fluoroalkoxy arylboronic esters.

Iridium-catalyzed borylation reactions are typically carried out using a nitrogen glovebox or Schlenk line. Since both the precatalyst $[Ir(OMe)COD]_2$ and bipy ligand are shelf stable, at least for a few months, we decided to explore the catalytic borylations without the use of a glovebox or Schlenk line. As a convenient borylation protocol, the precatalyst and the bipy ligand were weighed in air and added into an air-free flask under a positive nitrogen pressure. Pinacol borane and the fluoroalkoxy arene substrate were subsequently added via microsyringe. The flask was closed and heated at 80 °C in an oil bath, and the reaction was monitored by GC-MS. Our results for the catalytic borylation of 3-substituted trifluoromethoxy arenes are shown in Scheme 1.

As observed in the typical iridium-catalyzed borylations using the bidentate bipy ligand, the borylation of 3-substituted trifluoromethoxy arenes selectively took place at the least hindered 5-position. Several important functional groups such as Cl, Br, I, CN, CO_2Me, Me, and OMe were tolerated, and the products were isolated in good yields by column chromatography. In most cases, the regioselectivity for borylation on the 5-position was >99%. For entry **1f**, where both of the

Scheme 1. Iridium-Catalyzed Meta C–H Borylation of Trifluoromethoxy-Substituted Arenes[a]

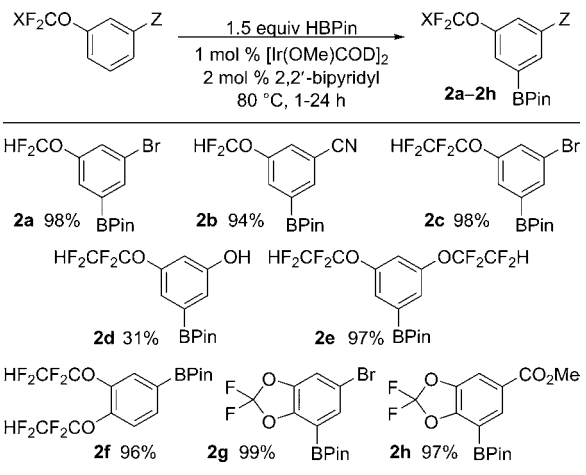


[a]Yields are for isolated materials. [b]Major monoborylated product, observed and isolated with 95% purity, contains 2–3% each of two other monoborylated isomers. [c]Formation of 3% minor monoborylated isomer was also observed. See the Supporting Information for details.

substituents have less steric demand, formation of small amounts (2–3% each) of two minor monoborylated isomers was also detected by GC-MS. For 2,6-dichloro(trifluoromethoxy)benzene (entry **1h**), the regioselectivity for borylation on the 5-position was ~97%. These sterically governed meta-functionalizations are complementary to the electrophilic aromatic substitutions of trifluoromethoxy arenes which generally result in para/ortho functionalization with the para isomer as the major product.[21]

Next, we examined the catalytic borylation of difluoromethoxy and tetrafluoroethoxy substituted arenes (Scheme 2). In these cases, the borylation can possibly take place either at the aromatic C–H bond or at the aliphatic C–H bond as is observed for the cases of methylchlorosilanes[22] and ethylpyridines.[23] In both difluoromethoxy and tetrafluoroethoxy

Scheme 2. Iridium-Catalyzed C–H Borylation of Difluoromethoxy, 1,1,2,2-Tetrafluoroethoxy, and 2,2-Difluoro-1,3-benzodioxole Substituted Arenes[a]



[a]Yields are for isolated materials. See the Supporting Information for details.

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substituted arenes, we observed that the borylation selectively takes place at the least sterically hindered aromatic C−H bond. 1,3-Disubstituted arenes are borylated at the 5-position (entries **2a**−**2e**), while the symmetrical 1,2-disubstituted arene (entry **2f**) is borylated on the 4-position. By employing an excess (3 equiv) of H-BPin, phenols can also be borylated (entry **2d**).[24] 5-Substituted 2,2-difluorobenzo[*d*][1,3]dioxoles were borylated on the least sterically hindered 7-position (entries **2g** and **2h**).

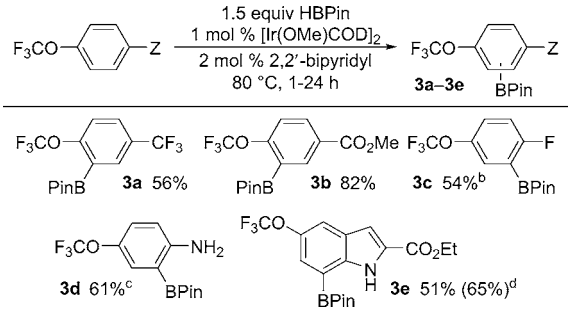
Besides 1,3-disubstituted systems, and the symmetrical 1,2-disubstituted system, we also examined the borylation of 1,4-disubstituted fluoroalkoxy arenes (Scheme 3). In unsymmetrical 1,4-disubstituted arenes, monoborylation can potentially result in the formation of two possible isomers, and this situation can further be complicated by the formation of diborylated product isomers. For 4-substituted trifluoromethoxy arenes, when the 4-substituent was either CF_3 or CO_2Me (Scheme 3, entries **3a** and **3b**), a single monoborylated product was observed by GC-MS with >99% regioselectivity. ^1H and ^{13}C NMR chemicals shifts, as well as the C−F coupling constant values in the ^{13}C NMR, provided conclusive evidence that monoborylation has taken place *ortho* to the smaller trifluoromethoxy group, an outcome expected based on the steric effects. Methoxy is among the smaller functional groups,[25] and the present results suggest that trifluoromethoxy has a similar steric profile. In addition, the highly electron-withdrawing nature of the trifluoromethoxy group may also be contributing toward the enhanced reactivity at its *ortho* position.[26] In both cases, pure monoborylated products were isolated in good yields. Besides monoborylation, GC-MS data also showed the formation of a single diborylated product (~5%) when the 4-substituent was CF_3. While in the case of CO_2Me, formation of small amounts (~5% combined) of two diborylated products was observed by GC-MS.

When the 4-substituent is smaller than trifluoromethoxy, such as F, monoborylation takes place *ortho* to F (Scheme 3, entry **3c**) with ~97% regioselectivity. This outcome is in contrast to borylation of 4-fluoro trifluoromethyl thiobenzene (SCF_3) using a rhodium catalyst where the sulfur atom directed borylation *ortho* to the SCF_3 group.[20] Recently Smith and Maleczka have demonstrated that anilines can also be borylated.[27] By using their latest conditions employing the tmphen ligand, we were also able to borylate 4-trifluoromethoxy aniline (entry **3d**), and a single monoborylated product was obtained in 61% isolated yield. In this case, the N−H group directs the borylation at the C−H bond *ortho* to the aniline nitrogen which was confirmed by the spectroscopic data. **3e** shows that trifluoromethoxy-substituted heteroaromatic substrates such as ethyl 5-trifluoromethoxyindole 2-carboxylate can also be used in this reaction. Since the indole 2-position is blocked, the borylation selectively took place at the 7-position.[28]

Our attempts to enforce complete diborylation of 4-CO_2Me substituted trifluoromethoxybenzene by using an excess (3 equiv) of pincolborane did not exceed beyond 25% conversion. However, diborylation of 4-fluoro trifluoromethoxybenzene approached 65% conversion yielding two diborylated isomers in a 77:23 ratio by GC-MS. Both diborylated isomers were isolated in pure forms in 46% and 12% isolated yields, respectively (Scheme 4). ^{13}C NMR data showed that the major diborylated product (**4a**) has both BPin groups *ortho* to the F, while the minor diborylated isomer (**4b**) has both BPin groups *para* to each other.

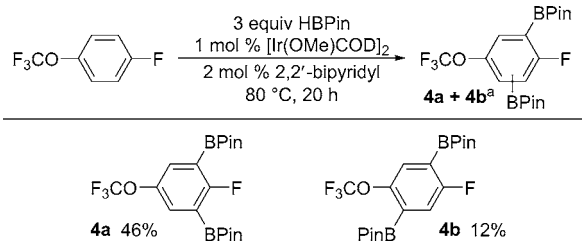
The synthetic utility of synthesized fluoroalkoxy arylboronic esters was demonstrated by employing these in the Suzuki coupling reaction to synthesize fluoroalkoxy biaryls as shown in Scheme 5.

Scheme 3. Iridium-Catalyzed C−H Borylation of 4-Substituted Trifluoromethoxy Arenes[a]



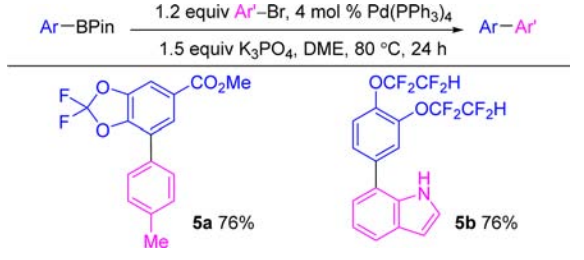
[a]Yields are for isolated materials. [b]97% selectivity. [c]tmphen was used as liagnd. [d]Yield in brackets is based on recovered starting material.

Scheme 4. Di-Borylation of 4-Fluoro Trifluoromethoxybenzene



[a]34% of monoborylated product (**3c**) was also isolated.

Scheme 5. Suzuki Coupling of Fluoroalkoxy Arylboronic Esters



In conclusion, iridium-catalyzed aromatic C−H borylation is a convenient tool to functionalize fluoroalkoxy arenes, allowing new regioselectivity patterns which are not available through the traditional routes. The borylation can be carried out without the use of a glovebox or Schlenk line. Depending on the starting substitution pattern of fluoroalkoxy arenes, C−H borylation can be carried out at *ortho* or *meta* positions relative to the fluoroalkoxy groups with excellent regioselectivity. This is in contrast to the borylation of SF_5 or SCF_3 containing arenes for which the borylation can only be carried out at either the *meta* or *ortho* position, respectively. Fluoroalkoxy arylboronic esters can potentially be very useful synthetic intermediates. Further studies on the derivatization of fluoroalkoxy arylboronic esters are in progress.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02050.

Experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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