

A Catalytic Borylation/Dehalogenation Route to *o*-Fluoro Arylboronates

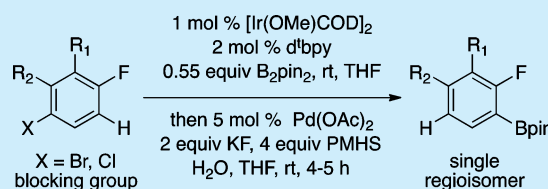
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S Supporting Information

ABSTRACT: A two-step Ir-catalyzed borylation/Pd-catalyzed dehalogenation sequence allows for the net synthesis of fluoroarenes where the boronic ester is ortho to fluorine. Key elements of this approach include the use of a halogen para to the fluorine to block meta Ir-catalyzed borylation and the chemoselective Pd-catalyzed dehalogenation by KF activated polymethylhydrosiloxane (PMHS).



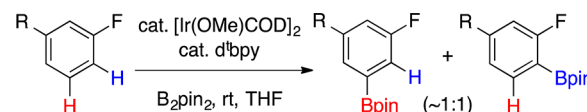
Fluorinated arenes regularly emerge as lead candidates for pharmaceutical,^{1,2} agrochemical,³ and materials applications. Also common to these fields is the use of arylboronic ester building blocks.^{4,5} As such, preparations of arenes bearing both fluoro and boronate substituents are highly desirable. Despite this need, to the best of our knowledge and as indicated by a SciFinder Scholar search, fluorinations of arylboronic esters are unknown. In contrast, boronate substituents have been introduced in fluorinated arenes and heterocycles by various methods, including directed deprotonation and metal–halogen exchange.⁶ Such reactions typically demand the use of strong lithium bases and/or cryogenic conditions. Activation of a properly positioned halogen by palladium,⁷ C–X borylation, represents a milder approach but demands the regioselective installation of the halogen. Given the substrate regioselectivities in aromatic halogenations and/or Sandmeyer–Schiemann protocols, accessing suitable haloaromatic starting materials can be either trivial or prohibitively difficult. Indeed, for many of the parahalo-fluorobenzenes used in this study (vide infra) the corresponding isomers where the halogen (Br or Cl) is ortho to fluorine are more expensive or commercially unavailable.

Ir-catalyzed C–H borylations can obviate the need for strong bases, cold temperatures, and/or halogen prefunctionalization. They tolerate numerous functional groups, including fluorine, and have thus been used to generate many fluorobenzenes bearing a 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Bpin) group.

The regiochemical course of these reactions is primarily driven by sterics, making it possible to install Bpin's ortho to hydrogen, cyano, or fluorine vs larger aryl substituents.⁸ This feature is useful but can also create challenges. For example, under standard conditions, borylations of 3-substituted (or 2,3-disubstituted) fluorobenzenes typically afford ~1:1 mixtures of borylated arenes (Scheme 1).⁹

The indiscriminate nature of Ir-catalyzed C–H borylation in Scheme 1 has made C–X borylation via halogenated starting materials the preferred option for selective borylations of 3-

Scheme 1. Typical C–H Borylation of 3-Substituted Fluorobenzenes



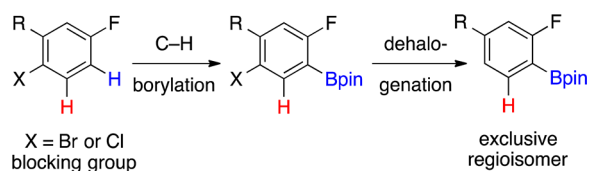
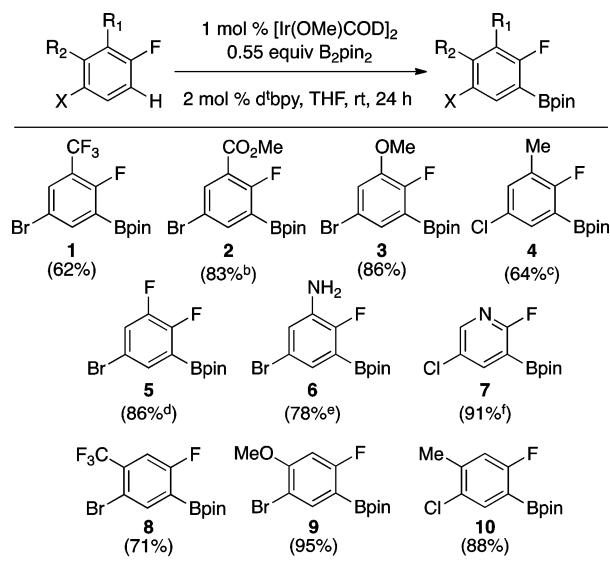
substituted (or 2,3-disubstituted) fluorobenzenes. For selective borylations ortho to the fluorine this requires the acquisition of 6-halo-3-substituted fluorobenzenes. As stated earlier, the availability of arenes with such a substitution pattern is highly dependent on the nature of the substituent C-3 (and that at C-2). In fact, in certain instances the availability and/or costs of arenes with a bromo or iodo substituent positioned ortho to the fluorine make them unattractive starting materials, while analogous arenes with halogens para to the fluorine are more readily sourced.

We hypothesized that readily available 3-substituted fluoroarenes with a halogen (X = Cl, Br, I) para to the fluorine could serve as convenient starting materials for the generation of *o*-borylated products. Owing to the remarkable halogen tolerance of Ir-catalyzed C–H borylations, X would not serve as an activating group for metalation but rather could be a sacrificial blocking group in a C–H borylation. In this way, borylation would only take place ortho to the fluorine and upon removal of X the desired ortho borylated 3-substituted fluoroarene would be generated (Scheme 2).

To begin testing this hypothesis a variety of haloarenes were reacted with 1 mol % of [Ir(OMe)(COD)]₂, 2 mol % of 4,4'-di-*tert*-butyl-2,2'-dipyridyl ligand (d'bpy), and 0.55 equiv of bis(pinacolato)diboron (B₂Pin₂) in THF at room temperature (Scheme 3). Except where otherwise noted, all of these arenes selectively afforded the *o*-borylated products in good yields.

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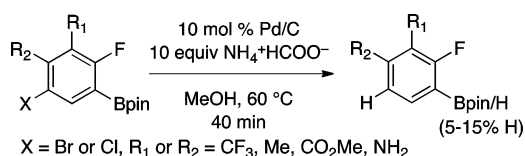
Scheme 2. Alternate Approach to *o*-FluoroarylboronatesScheme 3. Borylation of Fluoroarenes^a

^aIsolated yields. ^bBorylation run at 60 °C for 36 h; product contains 3% of the Bpin para to R₁ isomer. ^cProduct contains 1% of the Bpin para to R₁ isomer. ^dProduct contains 4% of the Bpin para to R₁ isomer. ^eBorylation run with 0.5 mol % of [Ir(OMe)COD]₂, 1 mol % of tmp, and 3.0 equiv of HBpin at 80 °C for 16 h. ^fBorylation run at 80 °C for 14 h after which 0.25 equiv of HBpin was added and the reaction was allowed to continue at 80 °C for 10 h; product contains 9% of the Bpin para to N.

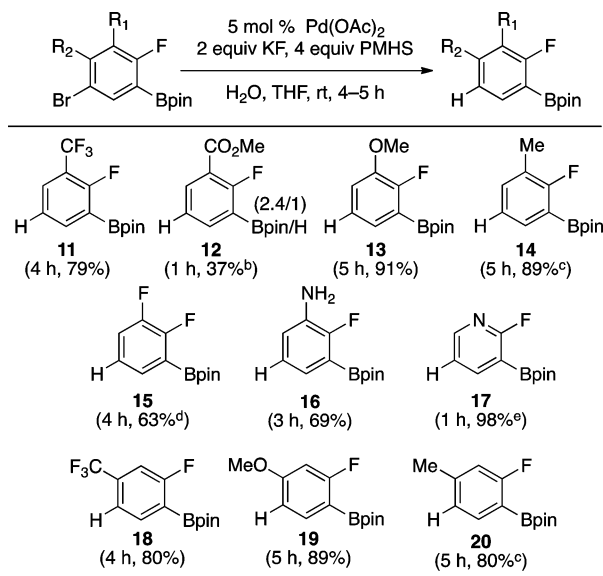
A key goal was to dehalogenate the borylated arenes without compromising the Bpin group. Radical based methods are not suitable for that task, but despite the potential for unwanted Suzuki couplings, a few such Pd-mediated reductions have been reported. Among these, Pd/C-mediated transfer hydrogenation using ammonium formate as an in situ hydrogen donor was attractive owing to the mild and low cost nature of the reagents.¹⁰ Unfortunately, aside from anisoles, such reductions were almost always accompanied by 5–15% loss of the Bpin group as well as other unidentified impurities in our hands (Scheme 4).¹¹

We next turned to our own experience with the hydrodehalogenation of 3-chloro-5-methylphenylpinacolborane using fluoride-activated polymethylhydrosiloxane (PMHS)¹² in the presence of catalytic polysiloxane encapsulated Pd(0) nano-clusters.¹³ To see if we could build from this lone example, the

Scheme 4. Dehalogenation with Ammonium Formate



borylated fluoroarenes in Scheme 3 were subjected to 4 equiv of PMHS, 2 equiv of aqueous KF, and 5 mol % of Pd(OAc)₂ in THF (Scheme 5).¹¹

Scheme 5. Dehalogenation with PMHS^a

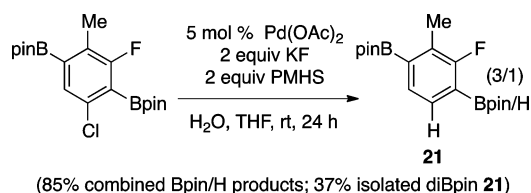
^aIsolated yields of arylboronates. ^bCombined yield of the 2,4/1 borylated/deborylated material was 60%. ^cVia the chlorinated starting material; product contains 1% of the Bpin para to R₁ isomer per the starting material. ^dProduct contains 4% of the Bpin para to R₁ isomer per the starting material. ^eProduct contains 1% of an unidentified fluorinated product and 1% starting material by ¹⁹F NMR.

Most substrates responded favorable to these reduction conditions, affording the desired products in 60–90% yield after 4–5 h reaction times and with no evidence of deborylation. Electron deficient arenes tended to undergo hydrodehalogenation slightly faster than electron rich arenes. The method was amenable to heterocycles as borylated 5-chloro-2-fluoropyridine underwent hydrodehalogenation in 1 h using only 2 equiv PHMS.

Although rare, the methylbenzoate example in Scheme 5 illustrates that protideborylation can intrude on the dehalogenation of some substrates. In an attempted to overcome this problem, 18-crown-6/KF in a water free reaction was explored.¹⁴ This met with limited success as hydrodehalogenation times increased due to low KF solubility and other unidentified products were observed by ¹⁹F-NMR.

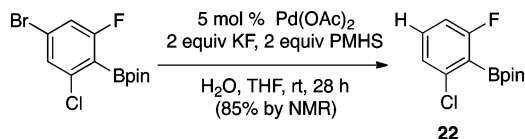
The dehalogenation shown in Scheme 6 indicates that the electronic influence of the fluorine is what heightens the propensity toward protideborylation. Here the diborylated arene partially lost the Bpin group ortho to fluorine, while the meta Bpin remained completely intact.

Scheme 6



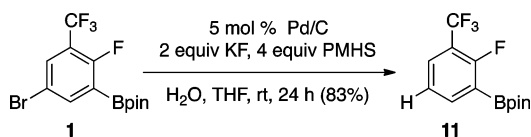
Hydrodebrominations were generally more facile than hydrodechlorinations. We were able to exploit this differential reactivity and selectively remove Br in the presence of a Cl by reducing the amount of PMHS to 2 equiv, which also resulted in increasing the reaction time (Scheme 7).

Scheme 7. Selective Debromination



We also screened Pd/C (10 wt %) as a palladium source (Scheme 8). Employing 5 mol % of Pd/C (with respect to Pd

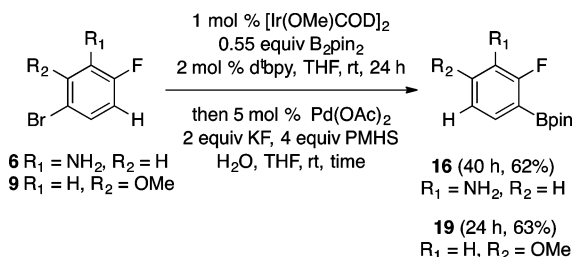
Scheme 8. Hydrodehalogenation with Pd/C



weight) gave the corresponding hydrodehalogenated product but required 24 h to reach full conversion vs 4 h with Pd(OAc)₂. We attribute this time difference to the proficiency with which Pd(OAc)₂ forms polysiloxane-encapsulated Pd(0) nanoclusters, which have higher catalytic activity.¹¹

Lastly, we investigated performing the Ir-catalyzed borylation and the Pd-catalyzed hydrodehalogenation in a single pot (Scheme 9). Again, longer reaction times were required to see

Scheme 9. One-Pot Borylation/Dehalogenation



full conversion during the dehalogenation step. This may be due to formation of the Pd(0) nanoparticles being slowed by the residuals from the borylation reaction. Nonetheless, the one-pot yields for the substrates tested were comparable to the combined yields observed over two steps.¹⁵

In summary, we have demonstrated a solution to the problem of selectively generating arylboronic esters ortho to fluorine via Ir-catalyzed C–H borylations when both the ortho and meta positions are sterically accessible. Furthermore, as para-halogenated fluorobenzenes are often more available and/or less expensive than their ortho counterparts, this protocol can be competitive with Pd-catalyzed borylations. Finally, we have demonstrated that telescoping the borylation and hydrodehalogenation into a single reaction flask is viable.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental details and product characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare the following competing financial interest(s): C.R.K.J., J.O., M.R.S., and R.E.M. are inventors on U.S. Patent Application 61/874,249. M.R.S. and R.E.M. acknowledge a financial interest in BoroPharm, Inc..

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■ REFERENCES

- (1) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.
- (2) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
- (3) (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589. (b) Jeschke, P. *Pest Manage. Sci.* **2010**, *66*, 10–27.
- (4) Zhichkin, P. E.; Krasutsky, S. G.; Beer, C. M.; Rennells, W. M.; Lee, S. H.; Xiong, J. M. *Synthesis* **2011**, 1604–1608.
- (5) Reck, F.; Zhou, F.; Eyermann, C. J.; Kem, G.; Carcanague, D.; Ioannidis, G.; Illingworth, R.; Poon, G.; Gravestock, M. B. *J. Med. Chem.* **2007**, *50*, 4868–4881.
- (6) (a) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323–3328. (b) Oppenheimer, J. M. Methods of Forming 4-Chloro-2-fluoro-3-substituted-phenylboronic Acid Pinacol Esters and Methods Using the Same. U.S. Pat. Appl. 13/729,580, Jul 4, 2013. (c) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *J. Org. Chem.* **2011**, *76*, 9602–9610.
- (7) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
- (8) (a) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305–308. (b) Chotana, G. A.; Rak, M. A.; Smith, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544. (c) Mkhali, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (d) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229–3243.
- (9) A recent example of Co catalyzed borylation of fluorobenzene gives an *ortho:meta* ratio of 89:11 Obligation, J. V.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 4133–4136.
- (10) (a) Yoakim, C.; Bailey, M. D.; Bilodeau, F.; Carson, R. J.; Fader, L.; Kawai, S.; Simoneau, S. L. B.; Surprenant, S.; Thibeault, C.; Tsantrizos, Y. S. Inhibitors of human immunodeficiency virus replication. U.S. Patent 8,338,441, Dec 25, 2012. (b) Rajagopal, S.; Spatola, A. F. *J. Org. Chem.* **1995**, *60*, 1347–1355. (c) Anwer, M. K.; Sherman, D. B.; Roney, J. G.; Spatola, A. F. *J. Org. Chem.* **1989**, *54*, 1284–1289.
- (11) See the Supporting Information for details.
- (12) For the versatile reducing ability of PMHS, see: (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381–3391. (b) Lavis, J. M.; Maleczka, R. E., Jr. Polymethylhydrosiloxane (PMHS). In *EROS-Electronic Encyclopedia of Reagents for*

Organic Synthesis; Paquette, L. A., Crich, D., Fuchs, P. L., Wipf, P., Eds.; Wiley: New York, 2003; Online.

(13) (a) Maleczka, R. E., Jr.; Rahaim, R. J.; Teixeira, R. R. *Tetrahedron Lett.* **2002**, 43, 7087–7090. (b) Rahaim, R. J.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2002**, 43, 8823–8826.

(14) Ghosh, B.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2011**, 52, 5285–5287.

(15) General procedure for one-pot borylation/dehalogenation: In a nitrogen atmosphere glovebox bis(pinacolato)boron (B_2Pin_2) (140 mg, 0.55 mmol) was weighed into a 20 mL vial containing a magnetic stir bar. $[Ir(OMe)cod]_2$ (6.6 mg, 0.02 mmol) and 4,4'-di-*tert*-butyl-2,2'-dipyridyl ligand (5.4 mg, 0.02 mmol) were weighed into two test tubes separately, each being diluted with 2 mL of THF. The $[Ir(OMe)cod]_2$ solution was transferred into the 20 mL vial containing B_2Pin_2 . This mixture was stirred until a golden yellow clear solution was obtained. Next, the solution containing ligand was transferred into the vial and stirred until it gave a dark brown solution. Finally, the substrate (1 mmol) was added to the vial, which was then sealed. After the reaction mixture stirred for 24 h at room temperature, it was transferred to an oven-dried round-bottom flask, sealed with a rubber septum, removed from the glovebox, and placed under a positive nitrogen atmosphere. In a separate flask, $Pd(OAc)_2$ (0.05 mmol, 11 mg) was dissolved in 5 mL of freshly distilled THF. This solution was added via a syringe to the reaction mixture. Following addition of the palladium, a solution of KF (116 mg, 2.0 mmol) in 2 mL of degassed water was syringed into the reaction. The nitrogen inlet was removed, and a balloon filled with nitrogen was attached to the flask. At this time, PMHS (0.24 mL, 4 mmol) (1 mmol of hydride in 0.06 mL) was added dropwise via syringe into the reaction flask (**Caution: Gas evolution and an exothermic reaction occurs upon the addition of PMHS**). The final reaction mixture was stirred and occasionally sampled until 1H (and ^{19}F NMR) indicated the disappearance of starting material. The reaction mixture was then diluted with Et_2O and the layers separated. The ether layer was filtered through a plug of silica gel. The silica gel was flushed with hexane (2×10 mL) and then with a 1:1 hexane/ethyl acetate mixture (10 mL). The eluted solution was concentrated by rotary evaporation. The product was dissolved in hexane/ethyl acetate and filtered through another plug of silica gel to remove the final traces of boron and Pd byproducts. The plug was flushed with hexane (4×10 mL). The volatiles were removed by rotary evaporation to afford the final product.