ORGANIC LETTERS

2009
Vol. 11, No. 13
2860−2863

Fluorination of Boronic Acids Mediated by Silver(I) Triflate

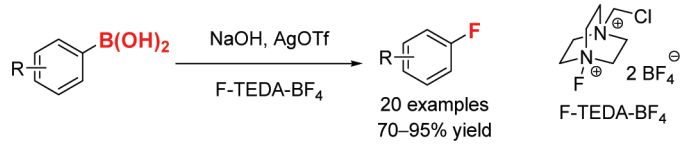
Takeru Furuya and Tobias Ritter*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

ritter@chemistry.harvard.edu

Received May 20, 2009

ABSTRACT



A regiospecific Ag-mediated fluorination reaction of aryl- and alkenylboronic acids and esters is reported. The fluorination reaction uses commercially available reagents, does not require the addition of exogenous ligands, and can be performed on a multigram scale. This report discloses the first practical reaction sequence from arylboronic acid to aryl fluorides.

Functionalized aryl fluorides are used as pharmaceuticals, agrochemicals, materials, and tracers for positron emission tomography (PET).[1] Substitution of a C−H bond with a C−F bond can significantly change the properties of arenes; for example, fluorine substitution can increase the metabolic stability of pharmaceuticals.[2] While chemists have known C−F bond forming reactions for more than 100 years, mild and regioselective aromatic C−F bond formations remain challenging and are not well developed compared to other carbon−halogen bond formation reactions.[3] In this communication, we report a general, functional-group-tolerant fluorination of aryl- and alkenylboronic acids and esters mediated by AgOTf. Advantages of the reported fluorination include the ready availability of boronic acids, high functional group tolerance, commercial availability of all reagents, and straightforward separation of the fluorinated product from all byproducts. To date, a practical fluorination of boronic acids or derivatives thereof has not been reported.[4]

Traditional arene fluorination reactions such as nucleophilic aromatic substitutions, including the halogen exchange process (Halex process), and the Balz−Schiemann reaction can be used to synthesize only simple fluorinated molecules.[5] Similarly, electrophilic fluorination of Grignard reagents is not a general method for the preparation of aryl fluorides.[6] While fluorination of phenylmagnesium bromide proceeds in 50% yield, 1-naphthylmagnesium bromide affords 1-fluoronaphthalene in only 17% yield.[7] The first palladium-catalyzed electrophilic fluorination was reported by Sanford in 2006 and utilizes arenes that are equipped with appropriate directing groups; another palladium-catalyzed fluorination of arenes bearing a different directing group was published by Yu in 2009.[8] Fluorination of arylboronic acids via stoichiometric palladium complexes has been reported[9] and proceeds via reductive elimination from arylpalladium(IV) fluorides.[10] Our group subsequently identified silver as a suitable

(1) (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214–231. (b) Lasne, M. C.; Perrio, C.; Rouden, J.; Barre, L.; Roeda, D.; Dolle, F.; Crouzel, C. Chemistry of beta(+)-emitting compounds based on fluorine-18. In. *Contrast Agents II* **2002**, *222*, 201–258. (c) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.

(3) (a) Chambers, R. D. *Fluorine in organic chemistry*; Oxford: New York, 2004. (b) Furuya, T.; Kuttruff, C. A.; Ritter, T *Curr. Opin. Drug. Discovery Dev.* **2008**, *11*, 803–819.

(4) Baudoux, J; Cahard, D. *Org. React.* **2007**, *69*, 347–672.

(5) (a) Balz, G.; Schiemann, G. *Ber. Deutsch. Chem. Ges.* **1927**, *60*, 1186–1190. (b) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225–231. (c) Sandford, G. *J. Fluorine Chem.* **2007**, *128*, 90–104.

(6) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996.

(7) (a) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452–454. (b) Differding, E.; Wehrli, M. *Tetrahedron Lett.* **1991**, *32*, 3819–3822.

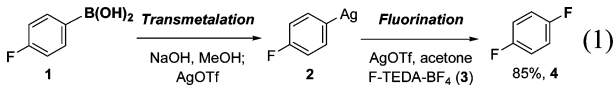
(8) (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135. (b) Wang, X.; Mei, T.-S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520−7521.

(9) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993–5996.

10.1021/ol901113t CCC: $40.75
Published on Web 06/09/2009

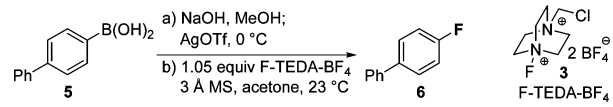
transition metal to promote fluorination of arylstannanes and hypothesized the intermediacy of bimetallic arylsilver(II) fluoride complexes.[11] The substrate scope of the Ag-mediated arylstannane fluorination is larger than for any other arene fluorination reaction reported to date. Drawbacks are the toxicity of organotin compounds and the consistent formation of 10−20% byproduct, resulting from a C−H instead of a C−F bond formation, which can significantly complicate purification by distillation or chromatography on silica gel. Notably, the fluorination reaction presented herein affords no detectable byproducts resulting from C−H bond formation, retains the broad substrate scope of the stannane fluorination, and can access organofluorides that are difficult to obtain otherwise.

To avoid the use of arylstannanes, we sought to identify other suitable nucleophiles for transmetalation to silver and subsequent fluorination. Boronic acid derivatives are stable to a variety of functional groups, virtually nontoxic, commercially available in great diversity, and readily prepared.[12] However, to the best of our knowledge, transmetalation from boron to silver has not been described in the literature. Treatment of AgOTf with boronic acids, boronic esters, or trifluoroborates did not afford detectable arylsilver complexes. In the absence of base, boronic acids are generally less efficient for transmetalation than stannanes.[13] When 1.0 equiv of NaOH was added to 4-fluorophenylboronic acid (**1**) in methanol, followed by the addition of AgOTf, arylsilver complex **2** was isolated (eq 1).[14] Subsequent fluorination of **2** in the presence of AgOTf with F-TEDA-BF_4 (**3**) afforded 1,4-difluorobenzene (**4**) in 85% yield. Byproducts such as remaining F-TEDA-BF_4, TEDA-BF_4 (1-chloromethyl 1,4-diazoniabicyclo[2.2.2] octane tetrafluoroborate), and silver salts were conveniently removed by simple aqueous workup after fluorination—an additional benefit over the Ag-mediated fluorination of arylstannanes,[11] which required purification from the organotin compounds by chromatography.[15]



The fluorination yield is dependent on the ratio and on the amount of the NaOH and AgOTf reagents (Table 1). Both NaOH and AgOTf accelerated transmetalation, but excess NaOH reacted with AgOTf to form insoluble Ag_2O, which reduced the yield of fluorination. The use of 2.0 equiv of AgOTf and 1.0 equiv of NaOH afforded 82% yield of 4-biphenylfluoride (**6**) (entry 3). The yield of **6** could be increased to 95% if 3.0 equiv of AgOTf and 1.2 equiv of NaOH were used (entry 7). The requirement for superstoichiometric quantities of AgOTf to obtain high yields for fluorination is in agreement with the previously proposed formation of bimetallic Ag(II) complexes.[11] Although the use of superstoichiometric transition metal should be avoided where possible, it is justifiable for transformations that deliver desirable products that are not readily accessible otherwise, especially when using metal sources that are as inexpensive as AgOTf (reagent quality: $0.5/mmol; $2/gram).

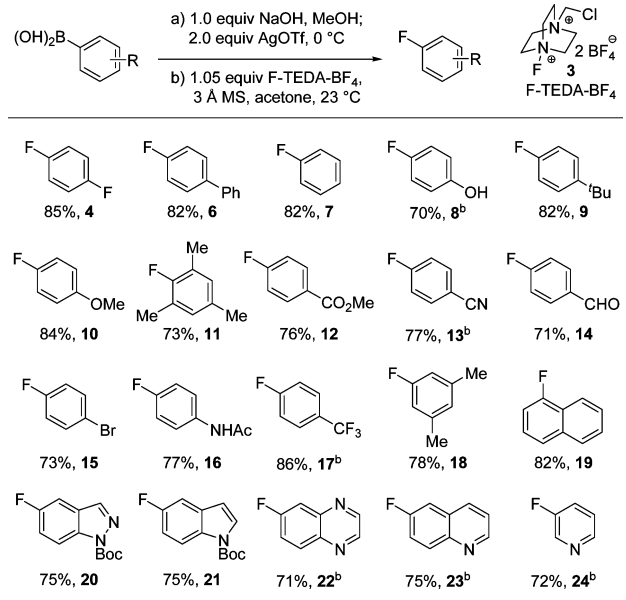
Table 1. Dependence of Fluorination on NaOH and AgOTf



entry	AgOTf	NaOH	^{19}F NMR yield
1	0.0 equiv	1.0 equiv	0%
2	1.0 equiv	1.0 equiv	43%
3	**2.0 equiv**	**1.0 equiv**	**82%**
4	2.0 equiv	1.2 equiv	78%
5	2.0 equiv	1.5 equiv	63%
6	3.0 equiv	1.0 equiv	90%
7	**3.0 equiv**	**1.2 equiv**	**95%**
8	3.0 equiv	1.5 equiv	83%

We evaluated the substrate scope of the Ag-mediated fluorination of boronic acids in the presence of 2.0 equiv of AgOTf (Scheme 1). Electron-rich, electron-poor, and *ortho*−

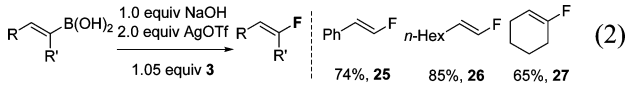
Scheme 1. Electrophilic Fluorination of Arylboronic Acids[a]



[a] Yields are given for isolated and purified compounds. If boiling points were too low to report accurate yields, the yield was determined by ^{19}F NMR (internal standard, see Supporting Information). Isolated yields and yields determined by ^{19}F NMR differed by less than 5%. [b] 1.2 equiv of NaOH and 3.0 equiv of AgOTf were used.

ortho-disubstituted arenes bearing protic, electrophilic, or nucleophilic functional groups as well as a variety of heterocyclic boronic acids participated in fluorination. Product yields range from 70 to 85% yield with the remainder of the material being unreacted boronic acid starting material (see Supporting Information for details). The reaction can be performed on gram-scale (1.6 g for the preparation of **6**) and employs only commercially available reagents. A practical fluorination of arylboronic acids or any other arylboronic acid derivative has not been reported previously.

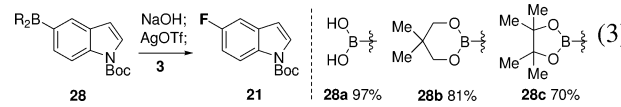
Fluorination of alkenylstannanes,[16] -silanes,[17] and -boronic acid derivatives[18] have been described in the literature. For example, treatment of potassium alkenyltrifluoroborates with F-TEDA-BF_4 can afford alkenylfluorides, typically as 1:1 *E*/*Z* mixtures.[18] The Ag-mediated fluorination presented herein has been extended to alkenylboronic acids and proceeds with complete control of stereochemistry, which indicates a change in mechanism compared with fluorination in the absence of transition metal due to the redox activity of silver (eq 2). Control of stereochemistry is consistent with stereospecific transmetalation from boron to silver, subsequent silver fluorination, and stereospecific reductive elimination to form the C−F bond.



(2)

The transmetalation−fluorination procedure for both arylboronic acids and alkenylboronic acids was executed in one pot; methanol was evaporated after transmetalation, and acetone was used for fluorination. Fluorination proceeded best in acetone, which was not a suitable solvent for transmetalation. Methanol was required for efficient transmetalation but cannot be used as solvent for fluorination due to the formation of aryl methyl ethers instead of fluoroarenes. Similarly, the presence of water resulted in phenol formation, which could be suppressed to less than 2% by addition of 3 Å molecular sieves. The formation of the observed byproducts may be explained by ligand exchange of a fluoro ligand of a postulated bimetallic Ag(II) complex[11] with hydroxide or methoxide and subsequent C−O reductive elimination. Intriguingly, C−O bond formation suggests that reductive elimination from high-valent Ag complexes is general beyond C−F bond formation.

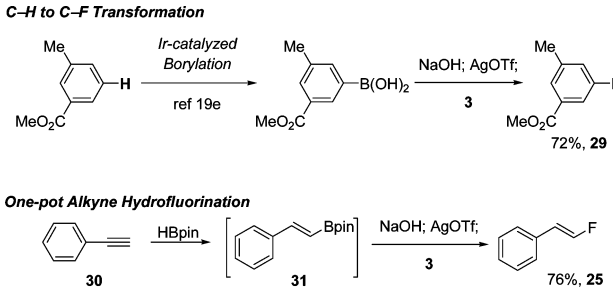
A variety of boronic acids is commercially available. However, many C−B bond forming reactions that afford more valuable, complex molecules afford boronic esters instead of boronic acids.[12] Boronic acids can typically be prepared by hydrolysis of the corresponding esters; however, hydrolysis is an additional synthetic step and can be low yielding for hindered esters such as pinacolates.[12] Arylboronic esters such as neopentylglycolate **28b** and pinacolate **28c** can participate in fluorination without prior hydrolysis, albeit in lower yield than the boronic acid **28a** (eq 3). A single set of reaction conditions (1.2 equiv of NaOH, 3.0 equiv of AgOTf, 1.05 equiv of **3**) could be used for all three substrates **28a**−**c**.



(3)

Another advantage of the presented fluorination reaction is its potential for combination with reported C−B bond forming reactions. For example, Smith and Maleczka as well as Ishiyama and Hartwig have developed Ir- and Rh-catalyzed borylation reactions of unactivated aromatic C−H bonds.[19] Fluorination of boronic acids obtained by C−H borylation can afford 3,5-disubstituted fluoroarenes (Scheme 2). The 1,3,5-substitution pattern in arenes is difficult to obtain,[19b] especially for arylfluorides such as previously unknown **29**. C−H borylation followed by fluorination gives access to a C−H to C−F bond transformation without the use of coordinating directing groups. The C−H to C−F bond transformation shown in Scheme 2 cannot be readily accomplished by any other available reaction chemistry. Fluorination could further be extended to a one-pot hydrofluorination of an alkyne, as shown in Scheme 2. Hydroboration of phenylacetylene (**30**) followed by fluorination of the intermediate alkenylboronate ester **31** afforded *β*-fluorostyrene (**25**) in 76% yield from **30**.

Scheme 2. Applications of Boronic Acid and Ester Fluorination



In conclusion, we report a regiospecific Ag-mediated fluorination of aryl- and alkenylboronic acids and esters. The fluorination reaction is practical because it uses commercially

(10) (a) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061. For other electrophilic fluorination reactions from arylpalladium complexes, see: (b) Kaspi, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2008**, *47*, 5–7. (c) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796–3797.

(11) Furuya, T.; Strom, A. E.; Ritter, T. J. *Am. Chem. Soc.* **2009**, *131*, 1662–1663.

(12) Hall, D. G. Boronic acids. *Preparation and applications in organic synthesis and medicine*; Wiley-VCH: Weinheim, 2005.

(13) (a) For examples, see: Manickam, G.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3475–3481. (b) Yamamoto, Y.; Seko, T; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734–4736.

(14) (a) Silver complex **2** was characterized by ^{1}H and ^{19}F NMR, but its instability and low solubility prevented further characterization. To establish transmetalation and the purity of the resulting arylsilver complex, we also prepared previously characterized 2,4,6-trimethylphenylsilver tetramer, which participated in fluorination under the same reaction conditions as **2** (see Supporting Information for details). For characterization of 2,4,6-trimethylphenysilver tetramer, see: (b) Meyer, E. M.; Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Organometallics* **1989**, *8*, 1067–1079.

(15) Byproducts resulting from C−H instead of C−F bond formation, as found for the Ag-mediated fluorination of arylstannanes, were not observed in the fluorination of boronic acids reported here. C−H bond formation in the Ag-mediated fluorination of arylstannanes is not due to the presence of water and cannot be suppressed by the addition of molecular sieves. We have determined that Bu_3SnOTf is involved in C−H bond formation. Transmetalation from arylboronic acids to Ag in methanol produces $B(OMe)_3$, which does not provoke C−H bond formation.

(16) (a) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461–1471. (b) Tius, M. A.; Kawakami, J. K. *Synlett.* **1993**, 207–208. (c) Tius, M. A.; Kawakami, J. K. *Tetrahedron* **1995**, *51*, 3997–4010.

(17) Greedy, B.; Gourverneur, V. *Chem. Commun.* **2001**, 233–234.

(18) Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett.* **1997**, 606–608.

available reagents, does not require the addition of exogenous ligands, and can be performed on a multigram scale. Combination of the fluorination reaction with reported C−B bond forming reactions such as the Ir-catalyzed C−H borylation and hydroboration further increases the utility of C−B to C−F transformations for the synthesis of various organofluorides.

Acknowledgment. We thank JEMN Klein for experimental help, Air Products and Chemicals, Inc. for a generous donation of **3**, and the Harvard Technology Development Accelerator Fund for financial support of this project.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901113T

(19) (a) Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697. (b) Tse, M. K.; Cho, J.-Y.; Smith, M. R. *Org. Lett.* **2001**, *3*, 2831–2833. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (d) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305–308. (e) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757–760.