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Silver-Mediated Fluorination of Functionalized Aryl Stannanes

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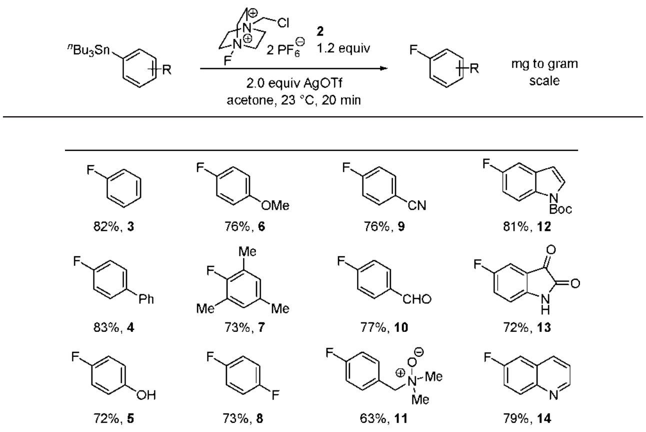
Functionalized aryl fluorides are used as pharmaceuticals and agrochemicals, in part due to their favorable pharmacological properties such as increased metabolic stability.[1] Aryl fluorides also find applications as tracers in positron emission tomography (PET) using the [^{18}F] isotope.[2] Carbon−fluorine bond formation is challenging when compared to other carbon−heteroatom bond formations.[3] Electrophilic and nucleophilic fluorination as well as the pyrolysis of diazonium tetrafluoroborates are established reactions for the synthesis of fluoroarenes.[4] Such conventional fluorination reactions, however, exhibit narrow substrate scope with respect to the electronic structure of the arene and the functional groups present, and are therefore typically not applicable to late-stage introduction of fluorine into functionalized molecules. In this Communication we present a practical fluorination reaction of functionalized aryl stannanes mediated by Ag(I). The reaction is general with respect to substrate scope, practical because it can be performed using commercially available reagents, and applicable to the late-stage fluorination of complex molecules such as quinine. The functional group tolerance reported herein has not been demonstrated for any other arene fluorination reaction. The presented fluorination reaction may therefore be applicable to the development of new fluorinated pharmaceuticals.

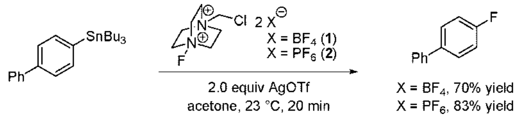
The electrophilic fluorination of aryl lithium or aryl Grignard reagents can afford aryl fluorides.[5] For example, fluorination of phenylmagnesium bromide affords fluorobenzene in 61% yield, fluorination of 1-naphthylmagnesium bromide affords 1-fluoronaphthalene in 17% yield, and fluorination of 1-naphthyllithium affords 1-fluoronaphthalene in 72% yield.[6] However, in addition to the high basicity of group 1 and 2 organometallics, which limits their functional group tolerance, the yield of fluorination can vary.[6] Likewise, no general fluorination reaction of aryl stannanes, aryl zinc reagents, arylboronic acid derivatives, or any other aromatic main group organometallic has previously been described.[7] While electrophilic fluorination of main group organometallics proceeds via direct fluorination of the metal−carbon σ-bond, we have shown that aryl palladium complexes can be oxidized at palladium to afford high-valent palladium fluoride complexes that subsequently yield carbon−fluorine bond formation through reductive elimination.[8] Guided by the hypothesis that transition metals can yield aryl fluorides more efficiently than main group organometallics because of redox participation of the metal and subsequent carbon−fluorine reductive elimination from a high-valent metal fluoride, we identified Ag(I) as a transition metal to mediate fluorination.

We observed that treatment of (4-biphenyl)tributylstannane with 2.0 equiv of AgOTf and 1.2 equiv of F-TEDA-BF$_4$ (**1**) in acetone at 23 °C afforded the aryl fluoride in 70% isolated yield within 20 min (eq 1). The use of AgOTf as Ag(I) source afforded the highest fluorination yields with acetone being the optimal solvent (for fluorination reactions using other Ag(I) salts, see Supporting Information). When the fluorinating reagent F-TEDA-PF$_6$ (**2**) was used instead of **1**, the yield of fluorination increased to 83%. The increased yield may be due to arylation of the tetrafluoroborate anion of **1** by the aryl stannane to afford aryl borates.[9] The hexafluorophosphate counterion in **2** is less likely to participate in transmetalation. The silver-mediated fluorination is operationally simple, scalable, proceeds within 20 min at room temperature, affords fluorinated arenes in 63−83% yield, and tolerates electron-poor, electron-rich, ortho,ortho-disubstituted arenes, as well as heteroaromatics (Table 1).

Table 1. Electrophilic Fluorination of Aryl Stannanes[a]



[a] Aryl trimethylstannanes can be used instead of aryl tributylstannanes.



(1)

Ag(I)[10] has been used to accelerate the fluorination of vinyl stannanes with electrophilic fluorination reagents.[11] Vinyl stannanes can react with **1** in the absence of silver,[12] but the reaction rate can be increased using Ag(I) salts.[11c] In contrast to vinyl stannanes, electron-neutral aryl stannanes do not react with **1** to form aryl fluorides. In the absence of Ag(I), the reaction shown in eq 1 afforded no fluorination product after 24 h at 23 °C. The fluorination of aryl stannanes can proceed with strong fluorinating reagents such as elemental fluorine and acetylhypofluoride, which allow for the fluorination of simple molecules such as fluorobenzene.[13]

Subsequent to the synthesis of the simple fluoroarenes shown in Table 1, we evaluated late-stage fluorination of biomedically active aromatics (Scheme 1). Introduction of the stannyl functionality can be accomplished in one step from aryl iodides or bromides, or in two steps from the corresponding phenols by palladium-catalyzed stannylation of triflates[14] as shown for estrone in Scheme 1. Stannylation proceeded in the presence of a variety of functional groups and delivered stable organometallics that typically were purified by chromatography on silica gel. Fluorination of stannyl estrone under identical reaction conditions as described in Table 1

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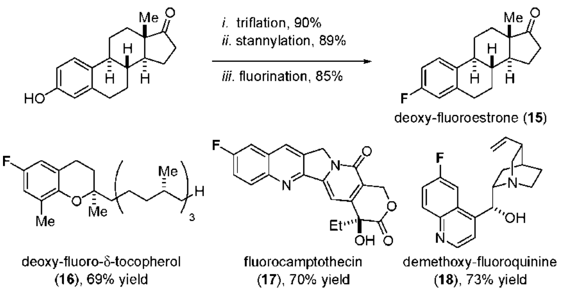
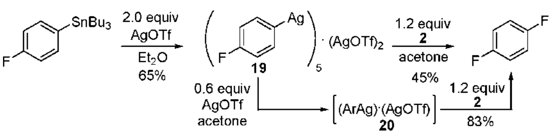
Scheme 1. Fluorination of Pharmaceutically Active Molecules[a]



[a] (i) Tf_2O, NEt_3; (ii) LiCl, 5 mol % $Pd(PPh_3)_4$, $(^nBu_3Sn)_2$; (iii) conditions, see Table 1. Yields for **16**, **17**, and **18** given for fluorination.

Scheme 2. 1:1 Ratio ArAg:AgOTf Required for High Fluorination Yield



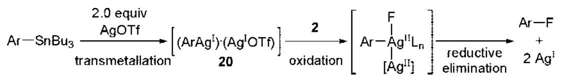
afforded 3-fluoro-3-deoxyestrone (**15**) in 85% yield. The three step procedure—triflation, stannylation, fluorination—from readily available phenols was extended to the synthesis of fluoro derivatives of δ-tocopherol, camptothecin, and quinine. The presented fluorination reaction allows late-stage fluorination of highly functionalized molecules.

Present challenges to fluorination include the use of aryl stannanes, which, despite functional group tolerance and synthetic utility, are toxic. While the yields of fluorination are uniformly high (63−85%) using identical reaction conditions for all substrates, we observed 10−20% of hydrodestannylated products in addition to the desired fluorination product, which can make purification on gram scale challenging.

Preliminary mechanistic investigations suggest that fluorination may occur from a redox active aryl silver species with the participation of more than one silver atom per carbon−fluorine bond formation event. Upon addition of 2 equiv of AgOTf to tributyl(4-fluorophenyl)stannane in Et_2O, the transmetalation product $(4\text{-}F\text{-}C_6H_4Ag)_5\cdot(AgOTf)_2$ (**19**) was isolated (Scheme 2).[15] Fluorination of **19** with **2** afforded 1,4-difluorobenzene in 45% yield. Addition of 0.6 equiv AgOTf to **19** followed by **2** afforded 1,4-difluorobenzene in 83% yield. The postulated intermediate (ArAg)·(AgOTf) complex **20** was observed by ^1H and ^{19}F NMR but not isolated. Purified 4-fluorophenylsilver reacted with **2** to give 1,4-difluorobenzene in 47% yield,[16] and 1.0 equiv of additional AgOTf was required to obtain a fluorination yield of 84%. In situ fluorination (eq 1) proceeded with 1 equiv of AgOTf (68% yield) and with 10 mol % (36% yield, 3.6 turnovers). Catalysis using 10 mol % of AgOTf and 2 equiv of NaOTf with slow addition of arylstannane increased the yield from 36% to 53%.[17] However, 2 equiv of AgOTf are required to obtain the yields reported in Table 1. A 1:1 ratio of ArAg to AgOTf is required for optimal yields. Additional AgOTf beyond a 1:1 ratio did not improve the yield of fluorination.

On the basis of our results, we hypothesize that the silver-mediated carbon−fluorine bond formation involves bimetallic oxidation−reductive elimination (Scheme 3). Reductive elimination, a two electron process, could proceed via one-electron redox participation of two silver atoms. While we did not observe high-valent aryl silver fluoride intermediates, the addition of BHT or galvinoxyl free radical as radical scavengers did not influence the yield of fluorinated products, suggesting that the formation of free radical intermediates is unlikely.

Scheme 3. Proposed Bimetallic Oxidation-Reductive Elimination



In conclusion, we report a regiospecific silver-mediated fluorination of aryl stannanes. Advantages of the fluorination reaction include the ease of starting material preparation, even for complex substrates, its operational simplicity using readily available reagents such as AgOTf, and the applicability to a broader substrate scope than has been demonstrated for any other arene fluorination reaction. Conceptually, silver-mediated oxidative transformations of aryl nucleophiles that proceed via bimetallic redox processes are a new avenue for carbon−heteroatom bond formations.

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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.

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