Silver-Mediated Fluorination of Functionalized Aryl Stannanes

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Silver-Mediated Fluorination of Functionalized Aryl Stannanes

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Functionalyzed aryl fluorides are used as pharmaceuticals and agrochemicals, in part due to their favorable pharmacological properties such as increased metabolic stability. Aryl fluorides also find applications as tracers in positron emission tomography (PET) using the [18F] isotope. Carbon–fluorine bond formation is challenging when compared to other carbon–heteroatom bond formations. Electrophilic and nucleophilic fluorination as well as the pyrolysis of diazonium tetrafluoroborates are established reactions for the synthesis of fluoroarenes. 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. 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. However, in addition to the high toxicity of group 1 and 2 organometallics, which limits their functional group tolerance, the yield of fluorination can vary. Likewise, no general fluorination reaction of aryl stannanes, arely zinc reagents, arylboronic acid derivatives, or any other aromatic main group organometallic has previously been described. 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. Guided by the hypothesis that transition metals can yield aryl fluorides more efficiently than main group organometallics due to 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-BF₃ (I) in acetonitrile at 23 °C afforded the aryl fluoride in 70% isolated yield within 20 minutes (eq 1). The use of AgOTf as Ag(I) source afforded the highest fluorination yields with acetonitrile being the optimal solvent (for fluorination reactions using other Ag(I) salts, see Supporting Information). When the fluorinating reagent F-TEDA-PF₆ (2) was used instead of I, 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 fluorides. The hexafluorophosphate counterion in 2 is less likely to participate in transmetallation. The silver-mediated fluorination is operationally simple, scalable, proceeds within 20 minutes 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).

Ag(I) has been used to accelerate the fluorination of vinyl stannanes with electrophilic fluorination reagents. Vinyl stannanes can react with 1 in the absence of silver, but the reaction rate can be increased using Ag(I) salts. 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 fluoride and acetyl hypofluorite, which allow for the fluorination of simple molecules such as fluorobenzene.

Table 1. Electrophilic fluorination of aryl stannanes.

<table>
<thead>
<tr>
<th>Aryl stannane</th>
<th>Fluorinated product</th>
<th>Yield</th>
<th>References</th>
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<tbody>
<tr>
<td>PhMe₃SnBu₃</td>
<td>F-PhMe₂SnBu₃</td>
<td>83%</td>
<td>11</td>
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<tr>
<td>PhMe₃SnBu₃</td>
<td>F-PhMe₂SnBu₃</td>
<td>72%</td>
<td>11</td>
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<tr>
<td>PhMe₃SnBu₃</td>
<td>F-PhMe₂SnBu₃</td>
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a) Aryl trimethylstannanes can be used instead of aryl tributylstannanes.

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 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 stannyln estrone under identical reaction conditions as described in Table 1 afforded 3-fluoro-3-deoxyestronestrine (15) in 85% yield. The three step procedure—triflation, stannylation, fluorination—from readily available reagents 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.

**Scheme 1.** Fluorination of pharmaceutically active molecules.

![Fluorination Scheme](image)

Based on 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 aren refluorination reaction. Conceptually, silver-mediated oxidative transformations of aryl nucleophiles that proceed via bimetallic redox processes are a new avenue for carbon-heteroatom bond formations.

**Acknowledgement.** We thank Merck and Amgen for unrestricted support and Eli Lilly for a graduate fellowship for PhD.

**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.

**REFERENCES**

17. We thank a reviewer for the suggestion of this experiment.
We report a regiospecific silver-mediated fluorination of aryl stannanes. The presented reaction can afford complex fluoroarenes from readily available phenols in three steps. The operational simplicity and the broad substrate scope of the fluorination should render this reaction a useful tool for the synthesis of mg to gram quantities of functionalized aryl fluorides. Silver-mediated oxidative transformations of aryl nucleophiles that proceed via bimetallic redox processes are a new avenue to develop carbon–heteroatom bond formations.