Silver-Mediated Fluorination of Functionalized Aryl Stannanes

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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 [18F] 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 toxicity of group 1 and 2 organometallics, which limits their functional group tolerance, the yield of fluorination can vary.7 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 α-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 due to reox 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-PF6 (2) in acetone 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 acetone being the optimal solvent (for fluorination reactions using other Ag(I) salts, see Supporting Information). When the fluorinating reagent F-

Table 1. Electrophilic fluorination of aryl stannanes.

<table>
<thead>
<tr>
<th>Fl + R</th>
<th>F</th>
<th>2.0 equiv AgOTf, acetone, 23 °C, 20 min</th>
<th>mg to gram scale</th>
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<tbody>
<tr>
<td>PhSnBu</td>
<td>F</td>
<td>2.0 equiv AgOTf, acetone, 23 °C, 20 min</td>
<td>2.0 equiv AgOTf, acetone, 23 °C, 20 min</td>
</tr>
<tr>
<td>82%, 3</td>
<td>70%, 6</td>
<td>70%, 9</td>
<td>81%, 12</td>
</tr>
<tr>
<td>83%, 4</td>
<td>73%, 7</td>
<td>77%, 10</td>
<td>72%, 13</td>
</tr>
<tr>
<td>72%, 5</td>
<td>73%, 8</td>
<td>63%, 11</td>
<td>79%, 14</td>
</tr>
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</table>

a) Aryl trimethylstannanes can be used instead of aryl tributylstannanes.
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 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.

Scheme 1. Fluorination of pharmaceutically active molecules.

\[ \text{Scheme 2.} \]

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.


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 fluorination reaction. Conceptually, silver-mediated oxidative transformations of aryl nucleophiles that proceed via bimetallic redox processes are a new avenue for carbon-heteronitrogen bond formations.

Acknowledgement. We thank Merck and Aman for unrestricted support and Eli Lilly for a graduate fellowship for.

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


(18) 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.