Silver-Mediated Fluorination of Functionalized Aryl Stannanes

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<td>Published Version</td>
<td>doi:10.1021/ja8086664</td>
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Supporting Information). When the fluorinating reagent 
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 fluorine bond formation through reductive elimination. 
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 such conventional 
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 Likewise, n 
 example, 
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 fluorinated aryl fluorides are used as pharmaceuticals and 
 agrochemicals, in part due to their favorable pharmacological 
 Aryl fluorides 
 also find applications as tracers in positron emission tomography 
 (PET) using the $^{18}$F 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 fluoroaranes. 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 basicity 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, aryl 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-BF$_3$ (I) 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-
 TEDA-PF$_6$ (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 I by the aryl stannane to afford aryl 
 borates. 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 aranes in 63– 
 83% yield, and tolerates electron-poor, electron-rich, ortho ortho-
 substituted aranes, as well as heteroaromatics (Table 1).

$$\text{Ph} \quad \text{SnBu}_3 \quad 2.0 \text{ equiv AgOTf} \quad 23 \text{ °C, 20 min} \quad \text{X = BF}_3 \quad \text{X = PF}_6$$ 

$\text{Ag(I)}^{10}$ 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 fluorine and 
 acetylhydofluoride, which allow for the fluorination of simple 
 molecules such as fluorobenzene. 

**Table 1. Electrophilic fluorination of aryl stannanes:**

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<tr>
<th>R</th>
<th>mg to gram scale</th>
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<tr>
<td>F</td>
<td>82%</td>
</tr>
<tr>
<td>F</td>
<td>83%, 4</td>
</tr>
<tr>
<td>F</td>
<td>72%, 5</td>
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a) Aryl trimethylstannanes can be used instead of aryl tributylstannanes.

Subsequent to the synthesis of the simple fluoroaranes 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 organometals 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.

\[
\text{Scheme 1. Fluorination of pharmaceutically active molecules.}
\]

\[
\begin{align*}
\text{Scheme 1. Fluorination of pharmaceutically active molecules.} \\
\text{Fluorination of } \text{substrate} & \rightarrow \text{Fluorinated product} \\
\text{Example:} & \\
\text{Fluorination of difluorobenzene} & \rightarrow \text{High yield} \\
\text{Fluorination of arenes} & \rightarrow \text{Functionalized compounds} \\
\text{Fluorination of alkynes} & \rightarrow \text{Functionalized compounds}
\end{align*}
\]

In conclusion, we report a regiospecific silver-mediated fluorination of arey 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 reduct processes are a new avenue for carbon-heteronatom bond formations.

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

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.