Direct and Selective Arylation of Tertiary Silanes with Rhodium Catalyst

\[
\text{R-Si-H} + \text{I-Ar} \xrightarrow{\text{Rh Catalyst}} \text{R-Si-Ar}
\]

\[\text{K}_3\text{PO}_4\]

\[\text{Amide Solvent}\]

Yoshinori Yamanoi and Hiroshi Nishihara

Current Literature: 8/30/08
David Arnold
Importance of Arylsilanes: Applications to Biological and Material Sciences

• Cancer Therapeutics:

\[ \text{TAC-101: Phase 1 clinical trials for the treatment of lung cancer} \]

• Material Sciences: Organic Phosphorescent Materials: Organic Light Emitting Diodes

\[ \text{DDT 2003, 8, 551; J. Org. Chem. 2007, 72, 6241.} \]
Application to Organic Synthesis: Substrates for Fluoride-Promoted Hiyama Coupling Reactions

• Example

\[
\text{BnMe}_2\text{Si} + \text{CO}_2\text{Et} \xrightarrow{\text{2 equiv. TBAF, 2.5 mol\% Pd(dba)_2, THF, rt, 15 min}} \text{EtO}_2\text{C}\ 
\]

88%

• Mechanism

\[
\text{Ar-R} \xrightarrow{\text{L}_2\text{Pd}} \text{L}_2\text{Pd} \xrightarrow{\text{Ar-I}} \text{Ar-Pd-X} \xrightarrow{\text{trans-cis isomerization}} \text{Ar-Pd-R} \xrightarrow{\text{BnMe}_2\text{FSi}^- + \text{Bu}_4\text{N}} \text{BnMe}_2\text{Si}^- + \text{Bu}_4\text{NF}
\]

Traditional Methods Used to Access Arylsilanes and Early Studies in Palladium Catalyzed Reactions

• Reaction of Grignard or organolithium reagents:

\[
\begin{align*}
\text{R} & \quad \text{M} \\
\text{R} & \quad \text{TMS}
\end{align*}
\]

\[
\text{M} = \text{MgX, Li} \\
\text{R} = \text{alkyl, OMe, NMe}_2
\]

• PdCl\(_2\) catalyzed reactions between aryl halides and Et\(_3\)SiH resulted in reduction products:

\[
\begin{align*}
\text{R} & \quad \text{X} \\
\text{R} & \quad \text{H}
\end{align*}
\]

\[
\text{X} = \text{I, Br, Cl}
\]

5-10\% PdCl\(_2\)  
>95\% Conversion

Reagent  
Product

Organometallics 1996, 15, 1508.

Author’s Earlier Work on Palladium-Catalyzed Silylations of Aryl Halides

Aryl halide reactivity was found to be Ar-I > Ar-Br > Ar-Cl.

Addition of base was found to be essential to suppress the formation of the reduction product.

The reaction was found to be intolerable of o-substitution or electron-withdrawing groups on the aryl halide.


\[
\begin{align*}
\text{Et}_3\text{SiH} & \quad \text{1 mol\% Pd(t-Bu}_3\text{P)}_2 \quad 3.0 \text{ equiv } \text{K}_3\text{PO}_4, \text{NMP} \quad \text{rt, 5 h} \\
\text{MeO} & \quad \text{H}_2\text{N} & \quad \text{Et} & \quad \text{O}_2\text{N} \\
84\% & \quad 86\% & \quad 76\% & \quad 51\% \\
\text{Trace} & \quad 0\% & \quad \text{Trace} & \\
\end{align*}
\]
# Reaction Optimization

![Reaction Representation]

---

<table>
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<tr>
<th>entry</th>
<th>catalyst</th>
<th>base</th>
<th>solvent</th>
<th>temp</th>
<th>time/h</th>
<th>ratio(^b)</th>
<th>yield of 2 (%)</th>
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</thead>
<tbody>
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<td>Pd(P(t-Bu)(_)()_3)</td>
<td>K(_3)PO(_4)</td>
<td>NMP(^d)</td>
<td>rt</td>
<td>5</td>
<td>e</td>
<td>&lt;1</td>
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<tr>
<td>2</td>
<td>PdCl(_2)(dppf)</td>
<td>K(_3)PO(_4)</td>
<td>NMP</td>
<td>rt</td>
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<td>52</td>
<td>2</td>
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<td>3</td>
<td>Pd(PC(_3))</td>
<td>K(_3)PO(_4)</td>
<td>NMP</td>
<td>rt</td>
<td>96</td>
<td>57</td>
<td>1 e</td>
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<td>NMP</td>
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<td>e</td>
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<td>K(_3)PO(_4)</td>
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<td>rt</td>
<td>96</td>
<td>1</td>
<td>2</td>
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<td>K(_3)PO(_4)</td>
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<td>e</td>
<td>96 f</td>
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<td>K(_3)PO(_4)</td>
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<td>rt</td>
<td>96</td>
<td>e</td>
<td>96 f</td>
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<td>rt</td>
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\(^{a}\) Reaction conditions: 2-iodoanisole (0.5 mmol), triethylsilane (1.0 mmol), catalyst (0.025 mmol), base (1.5 mmol), and solvent (1.0 mL). \(^{b}\) The ratio was determined by GC analysis of the crude reaction mixture. \(^{c}\) The reaction was carried out in the presence of 1 mol % of catalyst. \(^{d}\) NMP: N-methylpyrrolidinone. \(^{e}\) No detection. \(^{f}\) The silylated product could not be isolated by column chromatography.

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- **Optimized Conditions Found by GC Analysis:**
  - **Catalyst:** 5% RhCl(CO)(PPh\(_3\))\(_2\) or 5% [Rh(cod)]\(_2\)BF\(_4\)
  - **Solvent:** NMP
  - **Base:** 3 equiv. K\(_3\)PO\(_4\)
Relative Reactivities of Aryl Halides and Triflates Under Optimized Conditions

![Chemical Reaction]

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<th>X</th>
<th>additive</th>
<th>time/d</th>
<th>1a-d</th>
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<td>20</td>
<td>54</td>
<td>d</td>
<td>46</td>
<td>e</td>
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</table>

*a* Reaction conditions: aryl (pseudo)halide (0.5 mmol), triethylsilane (1.0 mmol), [Rh(cod)₂]BF₄ (0.025 mmol), K₃PO₄ (1.5 mmol), and NMP (1.0 mL) at rt. *b* The ratio was determined by GC analysis. *c* No additive. *d* No detection. *e* The silylated product could not be isolated.

- Reactivity Order: Ar-I > Ar-Br > Ar-Cl, Ar-OTf.
Reaction Scope

- Good functional group tolerance with meta- and para-substituted aryl iodides: -alkyl, -O\text{Me}, -S\text{Me}, -OH, -N\text{Me}_2, -N\text{H}_2, -C\text{O}_2\text{Et}, -C(O)\text{Me}, -C\text{F}_3 and -CN
- The reaction is sensitive to both steric and electronic effects for ortho-substituted aryl iodides.
### Advanced Substrate Scope: Aromatic Heterocycles, Multiple Couplings and Non-Aromatic Couplings

<table>
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<tr>
<th>entry</th>
<th>R—I</th>
<th>H—SiR₃</th>
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<td>—</td>
<td>C</td>
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<td>10</td>
<td><img src="image18" alt="Structure" /></td>
<td>Ph₂</td>
<td>A</td>
<td>—</td>
<td>C</td>
</tr>
</tbody>
</table>

*Conditions: (A) R—I (0.5 mmol), HSiR₃ (2.0 equiv), K₂PO₃ (3.0 equiv), R(C(NCO)O)(PPh₃) (5 mol %), NMP (1.0 mL), rt, 4 d; (B) R—I (0.5 mmol), HSiR₃ (2.0 equiv), [Rh(cod)]BP₃ (5 mol %), NMP (1.0 mL), rt, 6 d; (C) Ph₃SiH (1.0 mmol), R—I (3.0 equiv), K₂PO₃ (3.0 equiv), rt, 4 d; (D) Ph₃SiH (1.0 mmol), R—I (3.0 equiv), K₂PO₃ (3.0 equiv), 0 °C, 6 d. *The yield was based on the amount of triphenylsilane. No silylated product was obtained.*
Proposed Mechanism

- Key Catalytic Species: Rh(H)(SiR₃)₂
Application of Methodology

• Previously Reported Synthesis of TAC-101:

\[
\begin{align*}
\text{Br} \text{Br} & \xrightarrow{\text{Mg(0)}} \text{TMS} \text{Br} \text{Br} \xrightarrow{\text{AcCl}, \text{AlCl}_3} \text{AcCl}_3 \text{TMS} \text{Br} \xrightarrow{\text{Ca(OCl)}_2, \text{K}_2\text{CO}_3} \text{COOH} \\
\text{TMS} \text{OH} & \xrightarrow{\text{SOCl}_2} \text{TMS} \text{Cl} \xrightarrow{1. \text{Et}_3\text{N}, \text{Benzene}} \text{NH}_2 \xrightarrow{2. \text{NaOH (aq), EtOH}} \text{TAC-101: 3.4% Overall}
\end{align*}
\]

• Application of Methodology to the Synthesis of a TAC-101 Analogue:

\[
\begin{align*}
\text{I} \text{I} \text{CO}_2\text{Me} & \xrightarrow{1. \text{EDC-HCl, Et}_3\text{N, HOBT, DMF}} \text{NH}_2 \xrightarrow{2. 2.5\% [\text{Rh(cod)}_2\text{BF}_4, \text{Et}_3\text{SiH, DMPU, 68\%}} \text{COOH} \\
\text{I} \text{I} \text{MeO} & \xrightarrow{\text{Et}_3\text{Si}} \text{SiEt}_3 \xrightarrow{\text{NaOH, EtOH, 99\%}} \text{TAC-101 Analogue: 3 Steps, 54.5\% Overall}
\end{align*}
\]

\textbf{J. Med. Chem. 1990, 33, 1430.}
Conclusions

• The authors have developed a novel rhodium catalyzed reaction between trialkylsilanes and aryl halides to produce arylsilanes.

• The reaction developed through this methodology demonstrated good functional group compatibility and substrate scope.

• The developed methodology has wide application in the fields of organic synthesis, medicinal chemistry and material sciences.