**Ortho-Selective Cross-Coupling of Fluorobenzenes with Grignard Reagents: Acceleration by Electron-Donating Ortho-Directing Groups**

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**Abstract:** Fluorobenzenes with directing groups such as hydroxy, hydroxymethyl, and amino underwent ortho-selective cross-coupling with Grignard reagents in the presence of palladium-based catalysts, with dichlorobis(tricyclohexylphosphine)palladium [PdCl2(PCy3)2] found to be the optimum catalyst. Fluoro and chloro groups at positions other than ortho to the directing groups survived under the reaction conditions.

**Key words:** fluorine, cross-coupling, palladium, site selective, Grignard reagents

Transition-metal-catalyzed cross-coupling in which halogenated benzenes react with organometallic reagents to form a C–C bond constitutes an important and practical method for the synthesis of multisubstituted arenes. For haloarenes having more than one substituent of the same halogen atom, however, site-selective cross-coupling involving selective conversion of one of the halogen atoms to another group has not extensively been studied, in particular with respect to halogenated benzene derivatives. The successful realization of this type of site-selective cross-coupling would further expand the applicability of cross-coupling chemistry. Quite recently, we developed a new site-selective cross-coupling in which bromo and chloro groups at an ortho position to a directing group such as hydroxy and amino site-selectively reacted with Grignard reagents in the presence of palladium-based catalysts (Scheme 1). In the course of further studies on the catalytic system, we next planned to apply it to fluorobenzene derivatives.

Use of fluorobenzenes as substrates is a challenging task in the transition-metal-catalyzed cross-coupling of halobenzenes due to the strength of the F–C bond as compared with other halogen–carbon bonds. Although there are some examples of the cross-coupling of fluorobenzene derivatives, only a few examples include fluorobenzenes with electron-donating groups. In many other cases, the presence of an electron-withdrawing group on the benzene ring is needed, because it accelerates oxidative addition of a transition metal to the F–C bond. Interestingly, electron-withdrawing groups such as carbonyl, imidoyl, nitro, and fluoro groups accelerate cross-coupling at the ortho position. Thus, ortho-selective cross-coupling has been realized for difluoro- or polyfluorobenzene derivatives as substrates. On the other hand, ortho-selective cross-coupling of substrates with electron-donating groups has not been reported to date, probably because oxidative addition to a F–C bond at the ortho position of an electron-donating group is retarded electronically as well as sterically. On the basis of our previous work on site-selective cross-coupling, we envisaged that electron-donating groups such as hydroxy, hydroxymethyl, and amino would function as ortho-directing groups even for fluorobenzenes. Herein, we report the first examples of ortho-selective cross-coupling of fluorobenzene derivatives bearing electron-donating groups. These groups, which are converted into the corresponding anionic groups in situ, greatly facilitate palladium-catalyzed cross-coupling with Grignard reagents at the ortho position (Scheme 1).

The reaction of 4-chloro-2-fluorophenol (1) with 4-methoxyphenylmagnesium bromide was chosen to screen catalysts. At first, we tested a combination of tris(dibenzylideneacetone)dipalladium [Pd2(dba)3] and tricyclohexylphosphine (Cy3P), which was the combination used in our previous site-selective cross-coupling of dichlorobenzene derivatives. Remarkably, cross-coupling did occur at the fluoro group, which was located ortho to the hydroxy group (Table 1, entry 1). Potential products 3 and 4 were not obtained. Although the yield of 2 was low, it is surprising that the fluoro group preferentially reacted over the chloro group. It is also worth noting that the reaction occurred at room temperature in spite of the presence of a strongly electron-donating magnesium oxide group at the ortho position. Hydroxylated terphenylphosphine

**Scheme 1**

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**Previous work**

\[
\begin{array}{c}
\text{R} \quad \text{MgBr} \\
\text{Pd-based catalyst} \\
\text{X} = \text{Br, Cl} \\
\text{Y} = \text{OH, CH}_2\text{OH, NH}_2, \text{etc.}
\end{array}
\]

**This work**

\[
\begin{array}{c}
\text{R} \quad \text{MgBr} \\
\text{cat. PdCl}_2(\text{PCy}_3)_2 \\
\text{X} = \text{H, F, Cl} \\
\text{Y} = \text{OH, CH}_2\text{OH, NH}_2
\end{array}
\]

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which greatly accelerates reactions of 2-bromo- and 2-chlorophenols, was inferior to tricyclohexylphosphine in this case (entry 2). Use of tri-tert-butylyphosphine–fluoroboric acid [−(t-Bu)3P·HBF4],10 bis(1-adamantyl)phosphine oxide,11 and N-heterocyclic carbene precursor 6 did not improve the yield (entries 3–5). We next tested dichloropalladium complexes (entries 6–10) and found that dichlorobis(tricyclohexylphosphine)palladium [PdCl2(PCy3)2], which is a commercially available and air-stable complex, gave the best result (entry 6). Finally, raising the temperature to 50 °C improved the yield, giving 2 in good yield (entry 11). In all cases in Table 1, no more than trace amounts of compounds 3 and 4 were produced.

This catalytic system was applied to other substrates and the results are shown in Table 2. Chlorofluorophenol 1 as well as difluorophenols 9 and 11 exhibited ortho selectivity (entries 1–4). As for directing groups, not only hydroxy but also hydroxymethyl worked well to give the ortho cross-coupled product (entry 5). Amino also functioned as a directing group, although the reaction was slower (entry 6). In all cases, products derived from reactions at the positions meta or para to the directing groups were obtained in negligible amounts, if any.

In addition, reactions were conducted with a fluorinated Grignard reagent as shown in Table 3. The cross-coupled products were obtained in good yields. Over-reactions to form terphenyl or oligoaryl derivatives were not a severe problem in any of the cases.

Finally, we conducted the reaction of the methyl ether of 1 to study the effects of protic directing groups. As shown in Equation 1, cross-coupling occurred very slowly and the products were obtained in low yields (7% and trace). Interestingly, the ortho-fluoro group was still more reactive than the para-chloro group. This result strongly suggests that a protic directing group is required for fast

Table 1: Cross-Coupling of 4-Chloro-2-fluorophenol with 4-Methoxyphenylmagnesium Bromide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Yield (% of 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd2(dba) (1 mol%), Cy3P (2.4 mol%)</td>
<td>r.t.</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Pd2(dba) (1 mol%), 5* (2.4 mol%)</td>
<td>r.t.</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Pd2(dba) (1 mol%), t-Bu3P·HBF4 (2.4 mol%)</td>
<td>r.t.</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Pd2(dba) (1 mol%), bis(1-adamantyl)phosphine oxide (2.4 mol%)</td>
<td>r.t.</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Pd2(dba) (1 mol%), 6 (2.4 mol%)</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>PdCl2(PCy3)2 (2 mol%)</td>
<td>r.t.</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>PdCl2(PPh3)2 (2 mol%)</td>
<td>r.t.</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>PdCl2(PMe3)2 (2 mol%)</td>
<td>r.t.</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>PdCl2(dppf)-CH2Cl2 (2 mol%)</td>
<td>r.t.</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>PdCl2(cod) (2 mol%)</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>PdCl2(PCy3)2 (2 mol%)</td>
<td>50</td>
<td>76</td>
</tr>
</tbody>
</table>

*a Catalyst:

![Catalyst](image-url)
cross-coupling but ortho selectivity can be attained without a protic group. We are currently investigating the mechanism of activation of the ortho-fluoro group.13

In conclusion, we have developed ortho-selective cross-coupling of fluorobenzene derivatives with Grignard reagents in the presence of dichlorobis(tricyclohexylphosphine)palladium. Directing groups such as hydroxy, hydroxymethyl, and amino were found to accelerate reactions at the fluoro group ortho to the directing group. Although the mechanism of activation of the ortho-fluoro group is unclear at this moment, this site-selective cross-coupling of fluorobenzene derivatives should expand the usefulness of cross-coupling.

1H and 13C NMR spectra were recorded on a Jeol JNM-A400. CDCl3 was used as a solvent for 1H and 13C NMR spectra. For 1H NMR, TMS (δ = 0) in CDCl3 served as an internal standard. For 13C NMR, CDCl3 (δ = 77.00) served as an internal standard. Melting points (uncorrected) were measured with a Stanford Research Systems OptiMelt. IR spectra were recorded on a Jasco FT/IR-4100.

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**Table 2**  
Ortho-Selective Cross-Coupling of Fluorobenzenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArF</th>
<th>RMgBr</th>
<th>Temp (°C)</th>
<th>ArR</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>BrMg</td>
<td>50</td>
<td>7</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>BrMg</td>
<td>50</td>
<td>8</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>BrMg</td>
<td>50</td>
<td>10</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>BrMg</td>
<td>50</td>
<td>12</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>OH</td>
<td>BrMg</td>
<td>50</td>
<td>14</td>
<td>81</td>
</tr>
<tr>
<td>6^</td>
<td>OH</td>
<td>BrMg</td>
<td>70</td>
<td>16</td>
<td>49</td>
</tr>
</tbody>
</table>

^PdCl2(PCy3)2 (4 mol%), 66 h.

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**Equation 1**

ArF + RMgBr (3 equiv) → ArR

THF, 24 h

ArF + PhMgBr (3 equiv) → ArR

THF, 50 °C, 24 h

7% trace
Cross-Coupling of Fluorobenzyl Alcohols; General Procedure
A solution of a Grignard reagent in THF (1.5 mmol) was added to a suspension of 4-chloro-2-fluoroaniline (0.5 mmol) and PdCl2(PCy3)2 (0.02 mmol) in THF (0.5 mL) under argon at 0 °C. The mixture was then warmed to 50 °C and stirred for 24 h. The reaction was quenched with 1 M aq NaOH (3 mL). The mixture was extracted with EtOAc (4 × 5 mL), dried (Na2SO4), concentrated, and purified by preparative TLC to give the desired product.

Cross-Coupling of Fluorobenzyl Alcohols; General Procedure
A solution of a Grignard reagent in THF (1.5 mmol) was added to a suspension of fluorobenzyl alcohol (0.5 mmol) and PdCl2(PCy3)2 (0.01 mmol) in THF (0.5 mL) under argon at 0 °C. The mixture was then warmed to 50 °C (or 70 °C) and stirred for 24 h (the reactions at 70 °C were conducted in a sealed tube). The reaction was quenched with 10% aq HCl (3 mL). The mixture was extracted with EtOAc (4 × 5 mL), dried (Na2SO4), concentrated, and purified by preparative TLC to give the desired product.

Cross-Coupling of Fluorophenols; General Procedure
A solution of a Grignard reagent in THF (1.5 mmol) was added to a suspension of fluorophenol (0.5 mmol) and PdCl2(PCy3)2 (0.01 mmol) in THF (0.5 mL) under argon at 0 °C. The mixture was then warmed to 50 °C (or 70 °C) and stirred for 24 h (the reactions at 70 °C were conducted in a sealed tube). The reaction was quenched with 10% aq HCl (3 mL). The mixture was extracted with EtOAc (4 × 5 mL), dried (Na2SO4), concentrated, and purified by preparative TLC to give the desired product.

Table 3  Cross-Coupling with Fluorophenylmagnesium Bromide

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArF</th>
<th>Temp (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>70</td>
<td>18</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>50</td>
<td>20</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>70</td>
<td>21</td>
<td>85</td>
</tr>
</tbody>
</table>

ESI-MS spectra were obtained using a Bruker Daltonics microOTOF. Preparative TLC was carried out using silica gel 60 F254, 0.5 mm thick coated glass plates (Merck). PdCl2(PCy3)2 was used as purchased (Aldrich).

4-Chloro-2-(3-methylprop-1-enyl)phenol (8)\(^b\)
Colorless oil; purified by preparative TLC (silica gel, CH2Cl2–hexane, 1:1).

- 1H NMR (400 MHz, CDCl3): δ = 1.68 (d, J = 8.0 Hz, 3 H), 1.93 (d, J = 8.0 Hz, 3 H), 5.08 (s, 1 H), 6.04 (s, 1 H), 6.82 (d, J = 8.8 Hz, 1 H), 7.02 (d, J = 2.4 Hz, 1 H), 7.09 (dd, J = 8.8, 2.4 Hz, 1 H).

5-Fluorobiphenyl-2-ol (10)\(^14\)
Colorless oil; purified by preparative TLC (silica gel, CH2Cl2–hexane, 1:1).

- 1H NMR (400 MHz, CDCl3): δ = 5.09 (s, 1 H), 6.89–6.95 (m, 3 H), 7.38–7.49 (m, 5 H).

4-Fluoro-4-methylbiphenyl-2-ol (12)\(^15\)
Colorless oil; purified by preparative TLC (silica gel, CH2Cl2–hexane, 1:1).

- 1H NMR (400 MHz, CDCl3): δ = 2.40 (s, 3 H), 5.36 (s, 1 H), 6.69–6.71 (m, 2 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.29 (s, 4 H).

(4-Fluoro-4-methoxybiphenyl-2-yl)methanol (14)
Faint yellow oil; purified by preparative TLC (silica gel, CH2Cl2–hexane, 2:1).

IR (neat): 3348, 1608, 1486, 1247 cm–1.


Anal. Calcd for C14H13FO2: C, 72.40; H, 5.64. Found: C, 72.12; H, 5.67%.

5-Chloro-4-[(3-methylprop-2-enyl)oxy]phenol (17)\(^16\)
Colorless oil; purified by preparative TLC (silica gel, EtOAc–hexane, 1:5).

IR (neat): 3348, 1608, 1486, 1247 cm–1.


Anal. Calcd for C15H15FNO: C, 72.40; H, 5.64. Found: C, 72.12; H, 5.67%.

4-Chloro-2-(3-methylprop-1-enyl)phenol (8)\(^b\)
White solid; purified by preparative TLC (silica gel, EtOAc–hexane, 1:5).

IR (neat): 3348, 1608, 1486, 1247 cm–1.


Anal. Calcd for C15H15FNO: C, 72.40; H, 5.64. Found: C, 72.12; H, 5.67%.
References


(8) Preferential reactions of an alkyl fluoride over an alkyl chloride were observed in nickel- or copper-catalyzed cross-coupling with Grignard reagents: (a) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. J. Am. Chem. Soc. 2003, 125, 5646. (b) For transition-metal-catalyzed cross-coupling at a fluoro group in the presence of a bromo group, see ref. 7h.


(13) Saeki and Tamao et al. assumed a chelating effect of ortho-difluorobenzene in their cross-coupling with a Grignard reagent. The ortho selectivity in our system may be attributable to a similar chelating effect.


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