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

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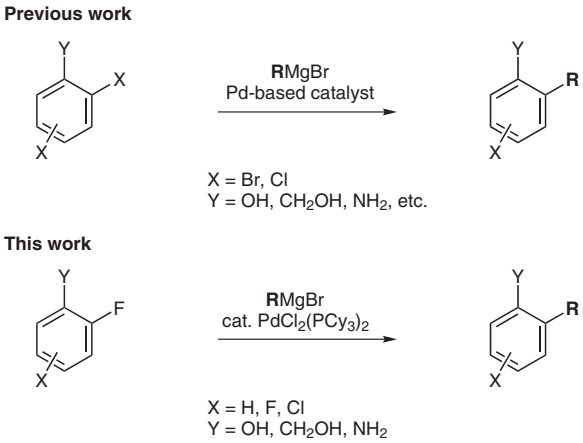
Abstract: Fluorobenzenes with directing groups such as hydroxy, hydroxymethyl, and amino underwent *ortho*-selective cross-coupling with Grignard reagents in the presence of palladium-based catalysts, with dichlorobis(tricyclohexylphosphine)palladium [$PdCl_2(PCy_3)_2$] found to be the optimum catalyst. 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 haloarenes react with organometallic reagents to form a C–C bond constitutes an important and practical method for the synthesis of multisubstituted arenes.[1] 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.[2,3] 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).[4] 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.[5] In many other cases, the presence of an electron-withdrawing group on the benzene ring is needed,[6] 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.[7] Thus, *ortho*-selective cross-coupling has been realized for difluoro- or polyfluorobenzene derivatives as substrates.[7a,h,i] 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).



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 [$Pd_2(dba)_3$] and tricyclohexylphosphine (Cy_3P), which was the combination used in our previous site-selective cross-coupling of dichlorobenzene derivatives.[4b] 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.[8] 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 **5**,[9]

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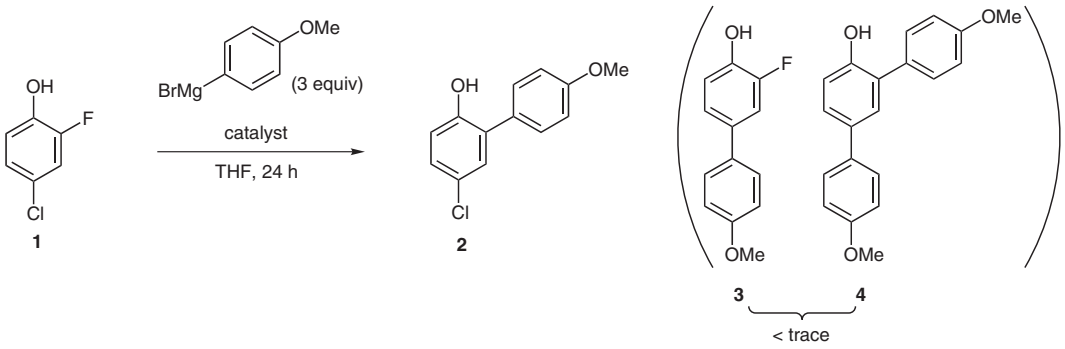
which greatly accelerates reactions of 2-bromo- and 2-chlorophenols,[4] was inferior to tricyclohexylphosphine in this case (entry 2). Use of tri-*tert*-butylphosphine–fluoroboric acid [t-$Bu_3P{\cdot}HBF_4$],[10] bis(1-adamantyl)phosphine oxide,[11] and N-heterocyclic carbene precursor **6**[12] did not improve the yield (entries 3–5). We next tested dichloropalladium complexes (entries 6–10) and found that dichlorobis(tricyclohexylphosphine)palladium [$PdCl_2(PCy_3)_2$], 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.

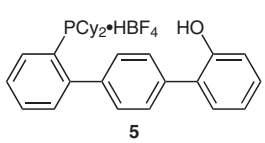
Finally, we conducted the reaction of the methyl ether of **1** to study the effects of protic directing groups. As shown in Equation 1, cross-coupling occurred very slowly and the products were obtained in low yields (7% and trace). Interestingly, the *ortho*-fluoro group was still more reactive than 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



Entry	Catalyst	Temp (°C)	Yield (%) of **2**
1	$Pd_2(dba)_3$ (1 mol%), Cy_3P (2.4 mol%)	r.t.	25
2	$Pd_2(dba)_3$ (1 mol%), **5**[a] (2.4 mol%)	r.t.	9
3	$Pd_2(dba)_3$ (1 mol%), t-$Bu_3P{\cdot}HBF_4$ (2.4 mol%)	r.t.	9
4	$Pd_2(dba)_3$ (1 mol%), bis(1-adamantyl)phosphine oxide (2.4 mol%)	r.t.	trace
5	$Pd_2(dba)_3$ (1 mol%), **6**[a] (2.4 mol%)	r.t.	0
6	$PdCl_2(PCy_3)_2$ (2 mol%)	r.t.	29
7	$PdCl_2(PPh_3)_2$ (2 mol%)	r.t.	17
8	$PdCl_2(PEt_3)_2$ (2 mol%)	r.t.	trace
9	$PdCl_2(dppf){\cdot}CH_2Cl_2$ (2 mol%)	r.t.	trace
10	$PdCl_2(cod)$ (2 mol%)	r.t.	0
11	$PdCl_2(PCy_3)_2$ (2 mol%)	50	76

[a] Catalyst:



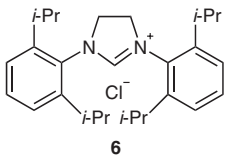
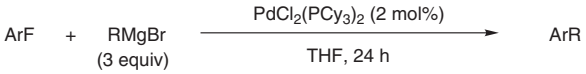
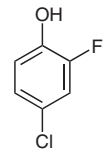
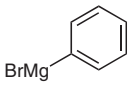
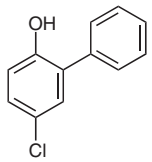
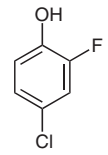
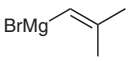
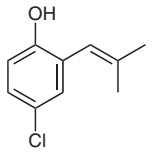
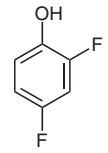
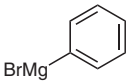
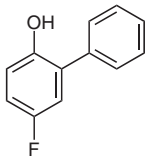
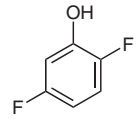
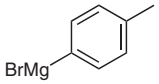
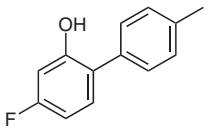
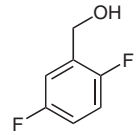
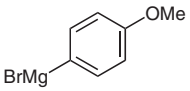
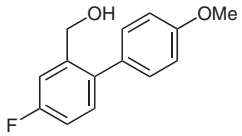
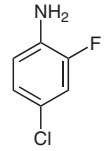
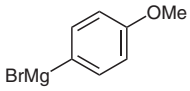
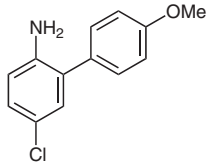
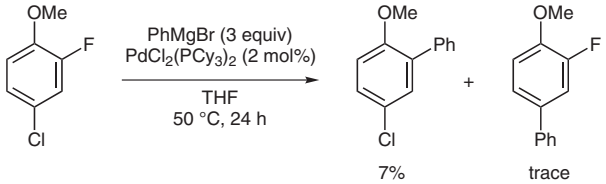


Table 2 *Ortho*-Selective Cross-Coupling of Fluorobenzenes



Entry	ArF	RMgBr	Temp (°C)	ArR	Yield (%)
1	 **1**		50	 **7**	81
2	 **1**		50	 **8**	75
3	 **9**		50	 **10**	85
4	 **11**		50	 **12**	79
5	 **13**		50	 **14**	81
6[a]	 **15**		70	 **16**	49

[a] $PdCl_2(PCy_3)_2$ (4 mol%), 66 h.



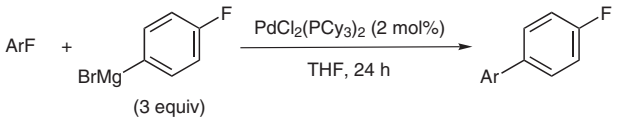
Equation 1

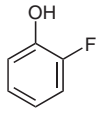
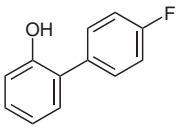
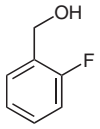
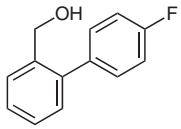
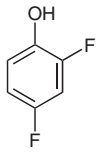
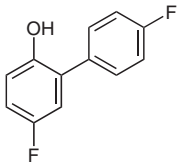
cross-coupling but *ortho* selectivity can be attained without a protic group. We are currently investigating the mechanism of activation of the *ortho*-fluoro group.[13]

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 ^{13}C NMR spectra were recorded on a Jeol JNM-A400. $CDCl_3$ was used as a solvent for ^1H and ^{13}C NMR spectra. For ^1H NMR, TMS ($\delta = 0$) in $CDCl_3$ served as an internal standard. For ^{13}C NMR, $CDCl_3$ ($\delta = 77.00$) 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.

Table 3 Cross-Coupling with Fluorophenylmagnesium Bromide



Entry	ArF	Temp (°C)	Product	Yield (%)
1	 **17**	70	 **18**	74
2	 **19**	50	 **20**	64
3	 **9**	70	 **21**	85

ESI-MS spectra were obtained using a Bruker Daltonics micrOTOF. Preparative TLC was carried out using silica gel 60 F_{254}, 0.5 mm thick coated glass plates (Merck). $PdCl_2(PCy_3)_2$ was used as purchased (Aldrich).

Cross-Coupling of Fluorophenols; General Procedure

A soln of a Grignard reagent in THF (1.5 mmol) was added to a suspension of fluorophenol (0.5 mmol) and $PdCl_2(PCy_3)_2$ (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 (Na_2SO_4), concentrated, and purified by preparative TLC to give the desired product.

Cross-Coupling of Fluorobenzyl Alcohols; General Procedure

A soln of a Grignard reagent in THF (1.5 mmol) was added to a suspension of fluorobenzyl alcohol (0.5 mmol) and $PdCl_2(PCy_3)_2$ (0.01 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 10% aq HCl (3 mL). The mixture was extracted with Et_2O (4 × 5 mL), dried (Na_2SO_4), concentrated, and purified by preparative TLC to give the desired product.

5-Chloro-4′-methoxybiphenyl-2-ol (2)[4b]

Colorless oil; purified by preparative TLC (silica gel, CH_2Cl_2–hexane, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 5.25 (s, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 7.15–7.19 (m, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H).

5-Chlorobiphenyl-2-ol (7)[4b]

Colorless oil; purified by preparative TLC (silica gel, CH_2Cl_2–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22 (s, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 7.17–7.22 (m, 2 H), 7.37–7.49 (m, 5 H).

4-Chloro-2-(2-methylprop-1-enyl)phenol (8)[4b]

Colorless oil; purified by preparative TLC (silica gel, CH_2Cl_2–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 0.8 Hz, 3 H), 1.93 (d, *J* = 0.8 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, CH_2Cl_2–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2Cl_2–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2Cl_2–hexane, 2:1).

IR (neat): 3348, 1608, 1486, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98 (s, 1 H), 3.83 (s, 3 H), 4.56 (s, 2 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.99 (dt, *J* = 2.8, 8.4 Hz, 1 H), 7.17–7.22 (m, 1 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 7.25 (dd, *J* = 2.8, 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.25, 62.65, 113.69, 114.10 (d, *J* = 19.7 Hz), 114.42 (d, *J* = 23.0 Hz), 130.16, 131.53 (d, *J* = 6.6 Hz), 131.96, 136.38, 140.46 (d, *J* = 6.6 Hz), 158.86, 162.15 (d, *J* = 243.5 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{13}FNaO_2$: 255.0792; found: 255.0785.

Anal. Calcd for $C_{14}H_{13}FO_2$: C, 72.40; H, 5.64. Found: C, 72.12; H, 5.67%.

5-Chloro-4′-methoxybiphenyl-2-amine (16)[4b]

A soln of a Grignard reagent in THF (1.5 mmol) was added to a suspension of 4-chloro-2-fluoroaniline (0.5 mmol) and $PdCl_2(PCy_3)_2$ (0.02 mmol) in THF (0.5 mL) in a sealable tube under argon at 0 °C. After sealing the tube, the mixture was warmed to 70 °C and stirred for 66 h. The reaction was quenched with 1 M aq NaOH (3 mL). The mixture was extracted with Et_2O (4 × 5 mL), dried (Na_2SO_4), concentrated, and purified by preparative TLC to give the desired product as an orange oil; purified by preparative TLC (silica gel, EtOAc–hexane, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 (br s, 2 H), 3.83 (s, 3 H), 6.65 (d, *J* = 9.2 Hz, 1 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 7.05–7.07 (m, 2 H), 7.33 (d, *J* = 8.8 Hz, 2 H).

4′-Fluorobiphenyl-2-ol (18)[14,16]

White solid; purified by preparative TLC (silica gel, EtOAc–hexane, 1:5); mp 44.4–45.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (s, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.8 Hz, 2 H), 7.21 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.25 (dt, *J* = 1.6, 8.0 Hz, 1 H), 7.44 (dd, *J* = 8.8, 5.6 Hz, 2 H).

(4′-Fluorobiphenyl-2-yl)methanol (20)[17]

Colorless oil; purified by preparative TLC (silica gel, Et_2O–hexane, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (br s, 1 H), 4.53 (s, 2 H), 7.08 (t, *J* = 8.4 Hz, 2 H), 7.24 (dd, *J* = 7.2, 1.6 Hz, 1 H), 7.31 (dd, *J* = 8.4, 5.6 Hz, 2 H), 7.33–7.38 (m, 2 H), 7.50 (dd, *J* = 6.8, 2.0 Hz, 1 H).

4′,5-Difluorobiphenyl-2-ol (21)[18]

White solid; purified by preparative TLC (silica gel, Et_2O–hexane, 1:4); mp 67.2–68.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 (s, 1 H), 6.85–6.95 (m, 2 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.16 (t, *J* = 8.6 Hz, 2 H), 7.42 (dd, *J* = 8.6, 4.8 Hz, 2 H).

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