Synthesis of Substituted Monohalobenzenes via Ortho-Selective Cross-Coupling of Dihalobenzenes with Electron-Donating Ortho-Directing Groups

Shunpei Ishikawa, Kei Manabe*

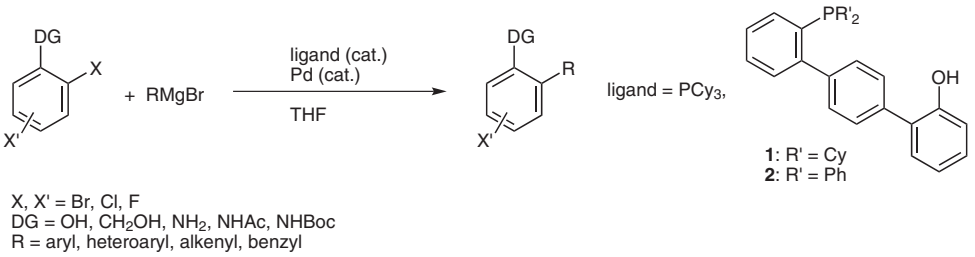
Manabe Initiative Research Unit, RIKEN, 2-1 Hirosawa, Wako 351-0198, Japan
Fax +81(48)4624662; E-mail: keimanabe@riken.jp

Received 16 July 2008

PSP No 132

Abstract: Dihalobenzenes that possess directing groups such as OH, CH_2OH, NH_2, NHAc, or NHBoc were subjected to ortho-selective cross-coupling with Grignard reagents in the presence of palladium-based catalysts to give the corresponding substituted monohalobenzenes. For the dibromo- and dichlorophenols and anilines, hydroxylated terphenylphosphines **1** and **2** were found to be effective ligands for palladium, whereas tricyclohexylphosphine was preferable for the dichlorobenzyl alcohols, dichloroanilides, and difluorobenzenes.

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



Scheme 1 Palladium-catalyzed ortho-selective cross-coupling of dihalobenzenes with electron-donating directing groups

Multisubstituted halobenzenes constitute an important class of compounds, and are widely employed as important drug components.[1] These halobenzenes are also synthetically useful because the halo substituent can be readily converted to other groups. To date, therefore, numerous methods have been developed for the preparation of various multisubstituted halobenzenes.[2] Site-selective cross-coupling of dihalobenzenes offers an attractive method for the preparation of substituted monohalobenzenes,[3] because various substituted dihalobenzenes, especially the dichloro ones, are commercially available. However, such reactions have yet to be investigated in detail. Recently, we have developed the ortho-selective cross-coupling of dihalobenzenes that possess electron-donating ortho-directing groups, using Grignard reagents in the presence of palladium-based catalysts (Scheme 1).[4,5] Although electron-donating groups typically retard the oxidative addition step in cross-coupling reactions, the presence of these groups is essential in our reactions for the acceleration at the ortho-position. Herein, we describe the features of this method.

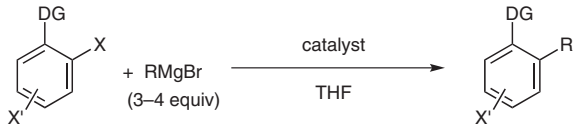
As summarized in Table 1, the reactions of dihalobenzenes with Grignard reagents readily afforded products with an R group at the position ortho (relative to the directing group). This reaction system has the following features: (1) For the dibromophenols and anilines (entries 1–8), a palladium complex bearing terphenylphosphine **1**[6–8] or **2**[4a] significantly accelerated the ortho-selective cross-coupling – other phosphines did not exhibit any ortho-selectivity. Although the reactions resulted in small amounts of the doubly cross-coupled products, the formation of the corresponding isomeric products were not observed. (2) For the dichlorophenols and anilines, the terphenylphosphines, especially **1**, were the most active ligands to give the ortho-coupled products in good yields (entries 9–13). Neither the isomeric products nor the doubly-cross-coupled products were obtained. (3) For the dichlorophenols and anilines, PCy_3 also induced ortho-selective cross-coupling, while the reactions were slower than those induced by **1** and **2** (entries 15–17). It should be noted that PCy_3 did not exhibit ortho-selectivity for di*bromo*phenols and anilines. (4) For the dichlorobenzenes that possess CH_2OH, NHAc, or NHBoc groups, ortho-selectivity was also observed (entries 18–20). Contrary to the reactions of phenols and anilines, PCy_3 accelerated the cross-coupling more than **1** and **2**. (5) For the difluorobenzenes, ortho-selectivity was also observed (entries 21–24). PCy_3 accelerated the reactions more effectively than **1** and **2**, and the air-stable $PdCl_2(PCy_3)_2$, which is commercially available, was found to be a highly effective catalyst. It is noteworthy that, despite the presence of electron-donating group at the ortho-position, the strong C–F bond was found to be reactive under these conditions. (6) In the case of entry 14, the *ortho*-chloro group reacted preferentially over the *para*-bromo group when **1** or **2** was

SYNTHESIS 2008, No. 19, pp 3180–3182
Advanced online publication: 05.09.2008
DOI: 10.1055/s-2008-1067270; Art ID: Z16608SS

used. This unusual selectivity was not observed with PCy_3. (7) Similarly, the *ortho*-fluoro group was more reactive than the *para*-chloro group, even when PCy_3 was used as a ligand (entries 25–28). (8) With regard to the Grignard reagents, not only aryl but also heteroaryl, alkenyl, and benzyl were effective. In contrast, however, use of simple alkyl Grignard reagent such as BuMgCl did not afford the desired product, but simply resulted in the reduction of the halo group.

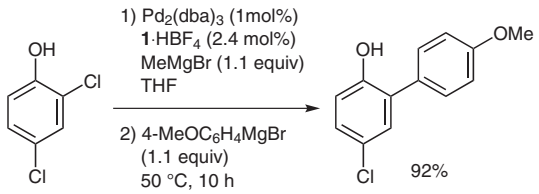
Because the reactions required 3–4 equivalents of the Grignard reagents (Table 1), our method was reinvestigat-

Table 1 Ortho-Selective Cross-Coupling



Entry	X	X′	DG	R	Catalyst[a]	Conditions	Yield (%)
1	Br	4-Br	OH	4-$MeOC_6H_4$ (4 equiv)	A	25 °C, 2 h	71
2	Br	4-Br	OH	4-$MeOC_6H_4$ (4 equiv)	B	25 °C, 2 h	89
3	Br	4-Br	OH	3-$MeOC_6H_4$ (4 equiv)	B	25 °C, 2 h	84
4	Br	4-Br	OH	2-thienyl (4 equiv)	A	25 °C, 72 h	66
5	Br	4-Br	OH	$PhCH_2$ (4 equiv)	A	50 °C, 5 h	55
6	Br	5-Br	OH	4-$MeOC_6H_4$ (4 equiv)	B	25 °C, 2 h	65
7	Br	4-Br	NH_2	4-$MeOC_6H_4$ (4 equiv)	B	25 °C, 10 h	76
8	Br	5-Br	NH_2	4-$MeOC_6H_4$ (4 equiv)	B	25 °C, 10 h	63
9	Cl	4-Cl	OH	4-$MeOC_6H_4$ (3 equiv)	A	50 °C, 4 h	99
10	Cl	4-Cl	OH	2-thienyl (4 equiv)	A	50 °C, 20 h	73
11	Cl	4-Cl	OH	4-ClC_6H_4 (3 equiv)	A	50 °C, 13 h	63
12	Cl	4-Cl	OH	Me_2C=CH (3 equiv)	A′	50 °C, 24 h	66
13	Cl	4-Cl	NH_2	4-$MeOC_6H_4$ (3 equiv)	A	50 °C, 4 h	93
14	Cl	4-Br	OH	4-$MeOC_6H_4$ (4 equiv)	B	50 °C, 2 h	58
15	Cl	4-Cl	OH	4-$MeOC_6H_4$ (3 equiv)	C	50 °C, 18 h	91
16	Cl	5-Cl	OH	4-$MeOC_6H_4$ (3 equiv)	C′	50 °C, 18 h	95
17	Cl	4-Cl	NH_2	4-$MeOC_6H_4$ (3 equiv)	C′	50 °C, 18 h	87
18	Cl	4-Cl	CH_2OH	4-$MeOC_6H_4$ (3 equiv)	C	50 °C, 18 h	99
19	Cl	4-Cl	NHAc	4-$MeOC_6H_4$ (3 equiv)	C	50 °C, 4 h	71
20	Cl	4-Cl	NHBoc	4-$MeOC_6H_4$ (3 equiv)	C′	50 °C, 8 h	55
21	F	4-F	OH	Ph (3 equiv)	D	50 °C, 24 h	85
22	F	4-F	OH	4-FC_6H_4 (3 equiv)	D	70 °C, 24 h	85
23	F	5-F	OH	4-MeC_6H_4 (3 equiv)	D	50 °C, 24 h	79
24	F	5-F	CH_2OH	4-$MeOC_6H_4$ (3 equiv)	D	50 °C, 24 h	81
25	F	4-Cl	OH	4-$MeOC_6H_4$ (3 equiv)	D	50 °C, 24 h	76
26	F	4-Cl	OH	Ph (3 equiv)	D	50 °C, 24 h	81
27	F	4-Cl	OH	Me_2C=CH (3 equiv)	D	50 °C, 24 h	75
28	F	4-Cl	NH_2	4-$MeOC_6H_4$ (3 equiv)	D′	70 °C, 66 h	49

[a] A: $Pd_2(dba)_3$ (1 mol%), **1**·HBF_4 (2.4 mol%). A′: $Pd_2(dba)_3$ (2 mol%), **1**·HBF_4 (4.8 mol%). B: $Pd_2(dba)_3$ (1 mol%), **2** (2.4 mol%). C: $Pd_2(dba)_3$ (1 mol%), PCy_3 (2.4 mol%). C′: $Pd_2(dba)_3$ (2 mol%), PCy_3 (4.8 mol%). D: $PdCl_2(PCy_3)_2$ (2 mol%). D′: $PdCl_2(PCy_3)_2$ (4 mol%).



Scheme 2

ed to improve the efficiency. As shown in Scheme 2, the optimized method involves the use of MeMgBr instead of the precious Grignard reagents for the deprotonation of the OH group of the substrate, and the OH and HBF_4 groups of the ligand. In addition, the amount of 4-$MeOC_6H_4MgBr$ could be further reduced to 1.1 equivalents, although a longer reaction time was required to afford the product in high yield.

In conclusion, we have developed a novel method for the synthesis of substituted monohalobenzenes based on ortho-selective cross-coupling of dihalobenzenes bearing electron-donating ortho-directing groups. High yields and high reaction rates can be realized by the proper choice of catalysts. The reactions described here provide efficient routes toward the synthesis of multisubstituted benzenes.

^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-A400 spectrometer. $CDCl_3$ was used as the solvent. For ^1H NMR measurements, TMS ($\delta = 0$) in $CDCl_3$ served as the internal standard. For ^{13}C NMR measurements, $CDCl_3$ ($\delta = 77.00$) served as the internal standard. Melting points (uncorrected) were measured using a Stanford Research Systems OptiMelt. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ESI-MS spectra were obtained using a Bruker Daltonics micrOTOF spectrometer.

Ortho-Selective Cross-Coupling; 5-Bromo-4′-methoxybiphenyl-2-ol; Typical Procedure (Table 1, Entry 2)

To a solution of 2,4-dibromophenol (109 mg, 0.432 mmol), $Pd_2(dba)_3$ (4.0 mg, 0.0043 mmol), and **1**·HBF_4 (4.5 mg, 0.010 mmol) in THF (0.43 mL) under argon at –78 °C was added a solution of 4-$MeOC_6H_4MgBr$ in THF (0.5 M, 3.46 mL, 1.73 mmol). After 10 min, the mixture was allowed to warm to 25 °C. After stirring for 2 h, the reaction was quenched with 10% aq HCl (5 mL). The mixture was extracted with EtOAc (3 × 5 mL), and the combined EtOAc extracts were washed with brine (5 mL) and dried (Na_2SO_4). The residue obtained by removal of the solvent was purified by chromatography over silica gel (hexane–CH_2Cl_2, 1:2) to give the desired product as a white solid; yield: 108 mg (89%); mp 72.8–76.7 °C.

IR (ATR): 3421, 1487, 1232, 1182, 1030, 1011, 833, 800 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.86$ (3 H, s), 5.16 (1 H, s), 6.85 (1 H, d, $J = 8.4$ Hz), 7.02 (2 H, d, $J = 8.8$ Hz), 7.32 (1 H, dd, $J = 2.4$, 8.4 Hz), 7.33 (1 H, d, $J = 2.4$ Hz), 7.35 (2 H, d, $J = 8.8$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.38$, 112.67, 114.86, 117.43, 127.71, 129.79, 130.13, 131.43, 132.63, 151.70, 159.70.

HRMS (ESI): *m/z* calcd for $C_{13}H_{10}BrO_2$ $[M - H]^-$: 276.9859, 278.9839; found: 276.9852, 278.9837.

Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 56.00; H, 3.92.

5-Chloro-4′-methoxybiphenyl-2-ol (Scheme 2)

To a mixture of 2,4-dichlorophenol (117 mg, 0.718 mmol), $Pd_2(dba)_3$ (6.6 mg, 0.0072 mmol), and **1**·HBF_4 (9.1 mg, 0.0172 mmol) was added a solution of MeMgBr in THF (0.97 M, 0.81 mL, 0.790 mmol) under argon at 0 °C. After stirring for 5 min, the mixture was allowed to warm to 50 °C, stirred for 5 min, and then 4-$MeOC_6H_4MgBr$ in THF (0.5 M, 1.58 mL, 0.790 mmol) was added. After stirring for 10 h, the reaction was quenched with 10% aq HCl (5 mL). The mixture was extracted with EtOAc (3 × 5 mL), and the combined EtOAc extracts were washed with brine (5 mL) and dried (Na_2SO_4). The residue obtained by removal of the solvent was purified by chromatography over silica gel (hexane–CH_2Cl_2, 1:2) to give the desired product as a yellow oil; yield: 155 mg (92%).

IR (neat): 3531, 3426, 1607, 1517, 1481, 1249, 1179, 1039, 834 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (3 H, s), 5.19 (1 H, br s), 6.89 (1 H, d, $J = 8.8$ Hz), 7.01 (2 H, d, $J = 8.8$ Hz), 7.18 (1 H, dd, $J = 2.8$, 8.8 Hz), 7.19 (1 H, d, $J = 2.8$ Hz), 7.36 (2 H, d, $J = 8.8$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.35$, 114.81, 116.95, 125.38, 127.84, 128.44, 129.21, 129.72, 130.10, 151.13, 159.62.

HRMS (ESI): *m/z* calcd for $C_{13}H_{10}ClO_2$ $[M - H]^-$: 233.0364; found: 233.0369.

Anal. Calcd for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.72. Found: C, 66.52; H, 4.84.

Acknowledgment

This work was partly supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformation of Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

(1) (a) Naumann, K. *J. Prakt. Chem.* **1999**, *341*, 417. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(2) Urch, C. J. In *Comprehensive Organic Functional Group Transformations*, Vol. 2; Katritzky, A. R.; Taylor, R. J. K., Eds.; Pergamon: Cambridge, **1995**, 605.
(3) (a) Reddy, G. S.; Tam, W. *Organometallics* **1984**, *3*, 630. (b) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453. (c) Dirk, S. M.; Price, D. W. Jr.; Chanteau, S.; Kosynkin, D. V.; Tour, J. M. *Tetrahedron* **2001**, *57*, 5109. (d) Ackermann, L.; Althammer, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1627. (e) Houpis, I. N.; Hoeck, J.-P. V.; Tilstam, U. *Synlett* **2007**, 2179. (f) Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett.* **1998**, *27*, 157. (g) Wang, T.; Alfonso, B. J.; Love, J. A. *Org. Lett.* **2007**, *9*, 5629. For site-selective cross-coupling of polyhalogenated heteroarenes, see: (h) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (i) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.
(4) (a) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1304. (b) Ishikawa, S.; Manabe, K. *Org. Lett.* **2007**, *9*, 5593. (c) Manabe, K.; Ishikawa, S. *Synthesis* **2008**, 2645.
(5) For reviews on cross-coupling with Grignard reagents, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: West Sussex, **2004**, 335. (b) Cepanec, I. *Synthesis of Biaryls*; Elsevier: Oxford, **2004**, 83.
(6) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1302.
(7) The design of these terphenylphosphines is based on biphenylphosphines developed by Buchwald et al., see: Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413.
(8) Phosphine **1** was purified and stored as the HBF_4 salt.