Ortho-selective Cross Coupling of Dibromophenols and Dibromoanilines with Grignard Reagents in the Presence of Palladium Catalysts Bearing Hydroxylated Oligoarene-type Phosphine

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p-Terphenylphosphines with a hydroxy group were used as ligands for palladium in the catalytic cross coupling of dibromophenols and dibromoanilines with Grignard reagents. High ortho-selectivity that cannot be achieved with other phosphine ligands was observed.

Cross-coupling reactions of multiply halogenated arenes are very useful synthetically, if one of the halogen atoms is site-selectively converted to another group. For multiply halogenated heteroarenes, many examples of site-selective cross coupling have been reported.[1] For multiply halogenated benzene derivatives, however, only a few examples have been reported,[2] and the reactions mainly occur at less electronically negative carbons. For example, Singh and Just reported the selective Sonogashira coupling in which dibromoanilines underwent the coupling preferentially at the meta-position over the ortho- or para-position.[2a] Thus, it is generally difficult to achieve site-selective cross-coupling reactions that occur preferentially at more electronically negative carbons. If the carbons are at more sterically hindered positions, the reactions are even more difficult to achieve.

As shown in the preceding paper, we synthesized several hydroxylated oligoarene-type phosphines (HOPs) and found that HOP **1** (Chart 1), purified and handled as its HBF_4 salt, dramatically accelerated the cross coupling of *o*-bromophenol.[3] In general, the presence of a free OH group in a substrate significantly retards Pd-catalyzed cross coupling with Grignard reagents, because deprotonation of the OH group generates a highly electron-donating oxido group and electronically retards oxidative addition. However, use of **1** overcame this difficulty for *o*-bromophenol, and the ortho isomer was much more reactive than *m*- or *p*-bromophenol in the presence of **1**. These findings prompted the application of **1** to ortho-selective cross coupling of dibromophenols with Grignard reagents. Here, we describe catalyst-controlled, site-selective cross coupling in which C–Br at the ortho-position of dibromophenols and dibromoanilines reacted selectively.

To study the effects of ligands on Pd-catalyzed site-selective cross coupling, a model reaction was conducted using dibromophenol **2** with a Grignard reagent in the presence of various

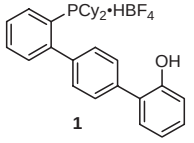

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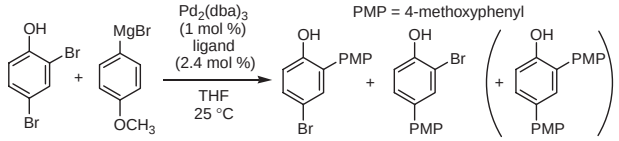
Chart 1.

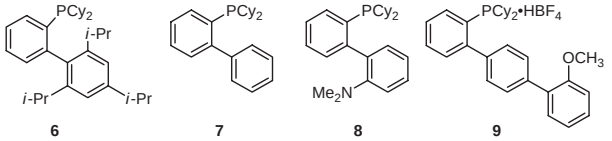
Table 1. Effect of ligand on site-selective cross coupling of **2**



2 **3** (4 equiv.) ***o*-4** ***p*-4** **5**

Entry	Ligand	Reaction time/h	Yield/%		
			***o*-4**	***p*-4**	**5**
1	PPh_3	24	22	16	14
2	PCy_3	24	21	14	38
3	$P(t\text{-}Bu)_3 \cdot BF_4$	24	0	40	25
4	DPPF	24	1	77	1
5	**6**	24	5	5	1
6	**7**	24	8	12	3
7	**8**	24	2	8	0
8	**9**	24	13	18	7
9	**1**	2	71	0	16
10[a]	**1**	2	59	<2[b]	20
11[c]	**1**	2	82	0	5

[a]**3** (3 equiv.). [b]Contaminated with a small amount of impurities. [c]**3** (10 equiv.).

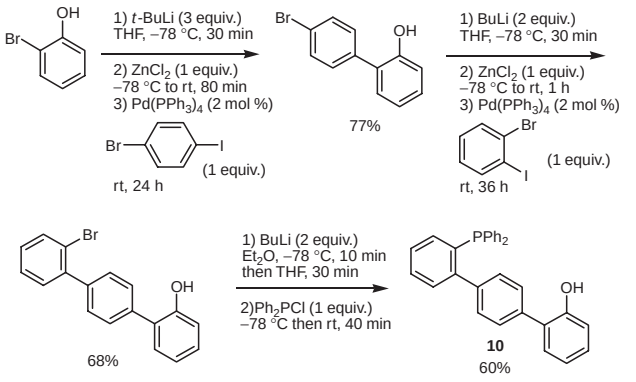


6 **7** **8** **9**

phosphine ligands (Table 1). The following features were observed: (1) PPh_3, PCy_3, **6**,[4] **7**,[5] **8**,[6] and **9**[3] afforded products ***o*-4** and ***p*-4** with low selectively in low yield (Entries 1, 2, 5, 6, 7, and 8); (2) For $P(t\text{-}Bu)_3 \cdot HBF_4$ and DPPF, the reactions occurred site-selectively at the position para to the OH group to afford ***p*-4** (Entries 3 and 4); (3) In contrast, **1** exhibited the opposite site-selectivity, and ***o*-4** was preferentially obtained in good yield (Entry 9), despite the steric bulkiness of the position ortho to the OH group. In addition, **1** greatly accelerated the reaction, which was completed in 2 h. It is noteworthy that, while a small amount of diarylated compound **5** was still obtained, the yield of ***p*-4** was 0%. The difference between **1** and **9** clearly indicates the importance of the OH group.

The amount of the Grignard reagent affected the yield of **5**. As shown in Table 1, Entry 10, the use of 3 equiv. of **3** produced **5** in higher yield. On the other hand, when 10 equiv. of **3** was used, only 5% of **5** was produced (Entry 11), despite the presence of large excess **3**. At this stage, we cannot explain this counter-intuitive result.

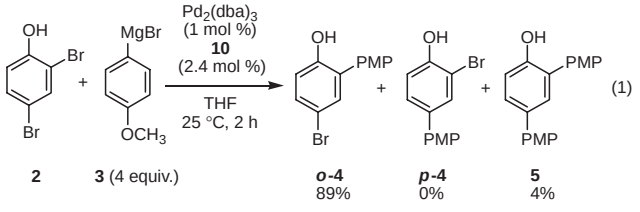
To examine effects of the phosphino group of **1**, we next designed ligand **10**, which has a diphenylphosphino group instead



Scheme 1. Synthesis of **10**.

of the dicyclohexyl group of **1**. To synthesize **10**, we developed a new route for preparation of HOPs with the same oligoarene moiety but with different phosphino moieties, as shown in Scheme 1.[7,8] This procedure will be applicable to synthesis of various hydroxylated *p*-terphenylphosphines.

Using ligand **10**, we conducted the reaction of **2** as shown in eq 1. To our delight, the formation of **5** was effectively suppressed and ***o*-4** was obtained in higher yield.



Site-selective cross-coupling reactions using other substrate combinations in the presence of **1**, **10**, or DPPF were conducted (Table 2).[8] High ortho-selectivity was induced by **1** and **10**, not only for dibromophenols but also for dibromoanilines. The selectivity was opposite to that induced by DPPF. In most cases, **10** gave better results than **1**, except for reactions with Grignard reagents **15** and **16**. For these two Grignard reagents, **1** was better for unknown reasons. The results of Entries 1, 2, 7, and 8 are worth mentioning because the cross coupling occurred preferentially at more electronically negative and more sterically hindered carbons. It is also noteworthy that, when **1** and **10** were used, the yields of the corresponding isomeric products (*isomer*) were <0.5% for all cases. Unfortunately, the 2-methoxyphenyl Grignard reagent did not afford the products (Entry 19).

In conclusion, we have developed a new catalytic system for ortho-selective cross coupling of dibromophenols and dibromoanilines with Grignard reagents. In the presence of a Pd catalyst and ligand **1** or **10**, ortho-selective reactions preferentially occurred, and the yields of the corresponding isomeric monoarylated compounds were <0.5%. This procedure will be applicable to synthesis of various phenol and aniline derivatives.

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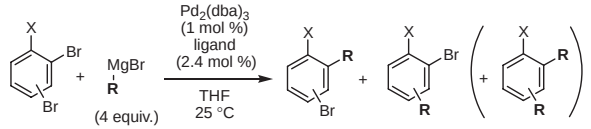
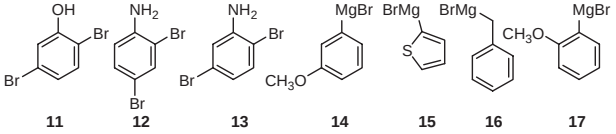
Table 2. Site-selective cross coupling of dibromoarenes with Grignard reagents



Entry	Dibromide	RMgBr	Ligand	Reaction time/h	Yield/%		
					ortho	*isomer*	*di*
1	**11**	**3**	**1**	2	31	0	48
2	**11**	**3**	**10**	2	65	0	10
3	**11**	**3**	DPPF	24	0	61	<2[a]
4	**12**	**3**	**1**	10	71	0	12
5	**12**	**3**	**10**	10	76	0	13
6	**12**	**3**	DPPF	10	9	15	2
7	**13**	**3**	**1**	10	6	0	62
8	**13**	**3**	**10**	10	63	0	<26[a]
9[b]	**13**	**3**	DPPF	10	15	32	<11[a]
10	**2**	**14**	**1**	2	60	0	17
11	**2**	**14**	**10**	2	84	0	5
12	**2**	**14**	DPPF	24	0	77	8
13	**2**	**15**	**1**	72	66	0	13
14	**2**	**15**	**10**	72	3	0	0
15[b]	**2**	**15**	DPPF	19	0	88	4
16[b]	**2**	**16**	**1**	5	55	0	21
17[b]	**2**	**16**	**10**	5	<22[a]	0	29
18[b]	**2**	**16**	DPPF	5	0	0	0
19	**2**	**17**	**1**	6	0	0	0

[a]Contaminated with a small amount of impurities. [b]At 50 °C.



References and Notes

1 S. Schröter, C. Stock, T. Bach, *Tetrahedron* **2005**, *61*, 2245.
2 a) R. Singh, G. Just, *J. Org. Chem.* **1989**, *54*, 4453. b) S. M. Dirk, D. W. Price, Jr., S. Chanteau, D. V. Kosynkin, J. M. Tour, *Tetrahedron* **2001**, *57*, 5109. c) T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc.* **2006**, *128*, 15964. d) L. Ackermann, A. Althammer, *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. e) I. N. Houpis, J.-P. V. Hoeck, U. Tilstam, *Synlett* **2007**, 2179. For an example of selective cross-coupling of 1,1-dihaloalkenes, see f) A. Minato, K. Suzuki, K. Tamao, *J. Am. Chem. Soc.* **1987**, *109*, 1257.
3 S. Ishikawa, K. Manabe, *Chem. Lett.* **2007**, *36*, 1302.
4 X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.
5 J. P. Wolfe, S. L. Buchwald, *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.
6 R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844.
7 For the preparation of zinciophenoxides, see: H. Shimizu, K. Manabe, *Tetrahedron Lett.* **2006**, *47*, 5927.
8 See Supporting Information for experimental details and spectral data of the products. The material is available electronically on the CSJ-Journal website, http://www.csj.jp/journals/chem-lett/.

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