Palladium Catalysis

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DHTP Ligands for the Highly *Ortho*-Selective, Palladium-Catalyzed Cross-Coupling of Dihaloarenes with Grignard Reagents: A Conformational Approach for Catalyst Improvement**

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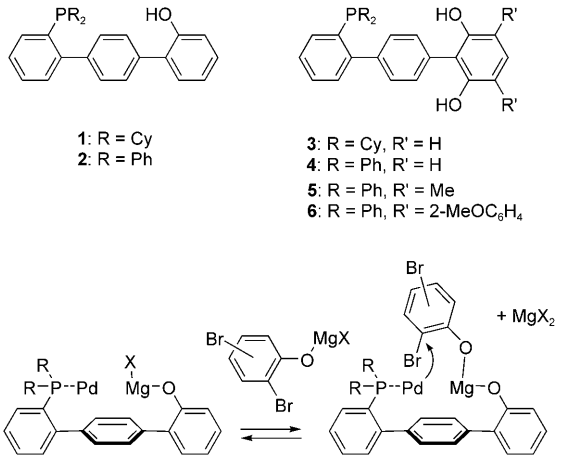
The site-selective cross-coupling of dihaloarenes is a useful method for synthesizing substituted monohaloarenes, which are an important class of compounds that are commonly employed as drug frameworks and synthetic intermediates.[1] To achieve their efficient site-selective cross-coupling, two main problems must be addressed: First, the difficulty in differentiating two reactive sites, particularly when the desired coupling position is sterically and electronically unfavorable, and second, the difficulty in suppressing undesired doubly cross-coupled products.[2]

We recently developed the site-selective, palladium-catalyzed cross-coupling of dibromobenzenes with Grignard reagents.[3] The cross-coupling occurred site-selectively at the positions *ortho* to the hydroxy or amino groups on the substrate. In most cases, the reactions occurred at sterically and electronically unfavorable sites. The key to this system was the use of hydroxy-substituted terphenylphosphine ligands (**1** or **2**; Scheme 1).[4] We assume that these phosphines form bimetallic palladium/magnesium species in the presence of palladium and Grignard reagents, and that the OMgX moiety acts as a binding site for the substrate (which also exists as the magnesium salt), and holds the *ortho* halo group close to the palladium center (Scheme 1). In this mechanism, oxidative addition to the palladium atom occurs preferentially at the positions *ortho* to the OMg group of the substrate. Whilst the *ortho* selectivity for substrates that have a strongly electron-donating substituent is unique, and cannot be achieved using other phosphine ligands, the selectivities were often modest and the formation of doubly cross-coupled products was a severe problem in many cases. Therefore, improvement of the catalysts was necessary to expand the applicability of this *ortho*-selective cross-coupling procedure.



Scheme 1. Structures of terphenylphosphines (**1** and **2**; top left), dihydroxyterphenylphosphines (**3–6**; top right), and a mechanism for the *ortho*-selectivity in the site-selective cross-coupling of dibromophenol with a Grignard reagent.

Herein, we present dihydroxyterphenylphosphine (DHTP) ligands **3–6** that improved the palladium-catalyzed *ortho*-selective cross-coupling of dihaloarenes remarkably and expanded the scope of the reaction.

The design of DHTPs was based on the following ideas. The assumed catalytic species formed from **1** or **2** is conformationally rigid owing to the *para*-terphenyl framework but retains flexibility in rotation of the C–C single bonds. As shown in Scheme 2a, the conformation in which the palladium and the magnesium oxido moieties are located proximal to each other is in equilibrium with that in which they are on opposing sides of the terphenyl group. In the latter conformation, the cooperative effect of the palladium and magnesium oxido groups cannot work (Scheme 1). Conversely, when DHTPs are used, there is always a magnesium oxido group on the same face of the terphenyl structure as the palladium atom, even if C–C bond rotation occurs (Scheme 2b).[5] Therefore, cooperation between the palladium and magnesium oxido moieties would be more effective when DHTP ligands are used, thus affording higher selectivities in the *ortho*-selective cross-coupling reaction.

The magnesium oxido moiety of the catalytic species also has conformational flexibility (Scheme 2c). Although it was expected that controlling the spatial arrangement of the magnesium atom should affect the catalytic performance, it was unknown how that would affect the *ortho*-selective cross-coupling. To control the position of the magnesium atom, we introduced two types of substituents at the position *ortho* to

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DHTP = dihydroxyterphenylphosphine.

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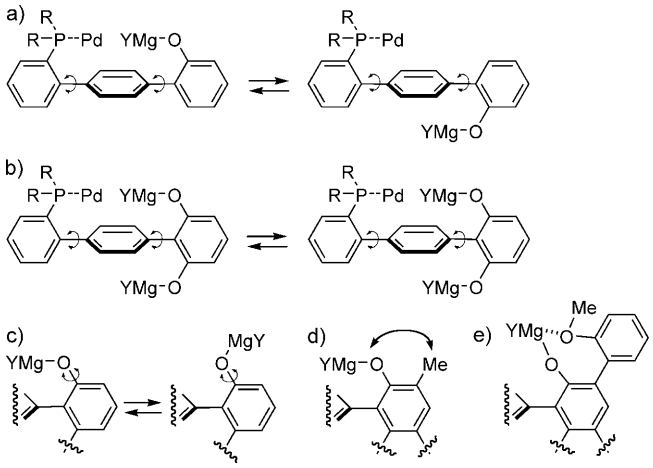
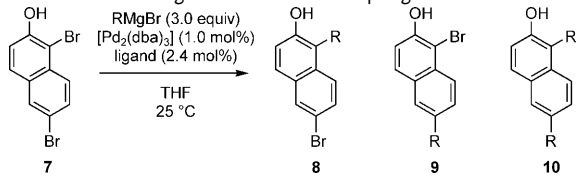


Scheme 2. Conformational rigidity of ligands and complexes. a) C–C Bond rotation for the species formed from **1** or **2**. Y = anionic substrate. b) from DHTPs. c) Conformation of the magnesium oxido moiety. d) Steric control. e) Chelation control.

the Mg oxido: a methyl group that would direct the magnesium position using steric hindrance (Scheme 2 d), and a 2-methoxyphenyl group that would chelate to the magnesium center (Scheme 2 e).

To demonstrate the effectiveness of the new DHTP ligands, the cross-coupling of **7** with a 4-methoxyphenyl Grignard reagent was investigated (Table 1). In all cases, $[Pd_2(dba)_3]$ was used as the palladium source. When PCy_3 or PPh_3 was used as the ligand, cross-coupling occurred predominantly at the 6-position to give **9** as the major product (Table 1, entries 1 and 2). DPPF gave **9** in high yield with complete selectivity (Table 1, entry 3). Biphenylphosphine **11**[4a] and methoxylated terphenylphosphine **12**[3a] resulted in selectivities similar to that obtained with PCy_3 (Table 1, entries 4 and 5). Use of **1** slightly increased the yield of **8**, the product of cross-coupling at the position *ortho* to the hydroxy group of the substrate (17%), although **9** and **10** were also isolated in similar yields (Table 1, entry 6). To our delight, the use of DHTPs as ligands was found to be remarkably effective. When DHTP **3** was used, **8** was obtained in good yield (79%; Table 1, entry 7), isomer **9** was not obtained at all, and diarylated compound **10** was produced in only 6% yield. Use of **4** further improved the reaction, giving **8** in 92% yield (Table 1, entry 8). It should be mentioned that significant rate acceleration was also observed, with the reaction nearly proceeding to completion in 2 h.

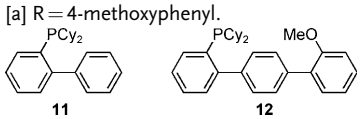
Table 1: Effect of the ligand in the cross-coupling of **7**.[a]



7 **8** **9** **10**

Entry	Ligand	*t* [h]	Yield [%]		
			8	**9**	**10**
1	PCy_3	8	0	34	2
2	PPh_3	8	8	28	2
3	DPPF	8	0	94	0
4	**11**	8	0	37	2
5	**12**	8	2	39	1
6	**1**	2	17	22	20
7	**3**	2	79	0	6
8	**4**	2	92	0	2

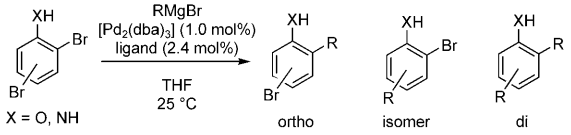
[a] R = 4-methoxyphenyl.



11 **12**

DHTP ligands were also effective for other substrates (Table 2). For example, **4** and **5** afforded the *ortho*-coupled product from 2,4-dibromophenol in high yields with excellent selectivities (Table 2, entry 1), even when the amount of the Grignard reagent was lowered to 2.2 equiv (Table 2, entries 2 and 3). 2,4-Dibromoaniline also gave excellent results (Table 2, entry 4). In the reaction of 2,5-dibromophenol using ligand **4**, a more significant amount of diarylation occurred because oxidative addition at the 5-position is electronically more favorable than at the 4-position (Table 2, entry 5). In contrast, the use of methylated ligand **5** remarkably suppressed the diarylation (Table 2, entries 6 and 7). This result demonstrates that the methyl groups significantly improve this cross-coupling reaction.

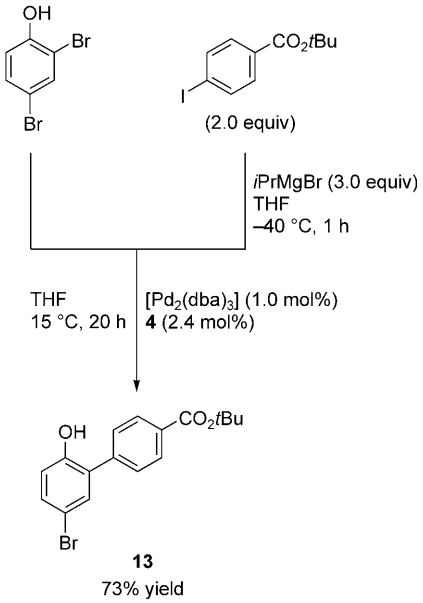
Table 2: *Ortho*-selective cross-coupling of dibromobenzenes.[a]



Entry	Substrate	Ligand	RMgBr (equiv)	*T* [°C]	*t* [h]	Yield [%]		
						ortho-product	isomer	di-coupled
1	2,4-dibromophenol	**4**	3.0	25	2	91	0	2
2	2,4-dibromophenol	**4**	2.2	25	2	79	0	5
3	2,4-dibromophenol	**5**	2.2	35	2	81	0	4
4	2,4-dibromoaniline	**4**	3.0	25	10	90	0	0
5	2,5-dibromophenol	**4**	3.0	25	2	64	0	25
6	2,5-dibromophenol	**5**	3.0	25	2	61	0	5
7	2,5-dibromophenol	**5**	3.0	35	2	83	0	8

[a] R = 4-methoxyphenyl.

The rate acceleration caused by the DHTP ligands enabled the successful cross-coupling of the dihaloarene with an ester-substituted Grignard reagent because it could be conducted at lower temperatures. The cross-coupling of a *tert*-butoxycarbonyl-substituted Grignard reagent, which was prepared from *tert*-butyl 4-iodobenzoate using a literature



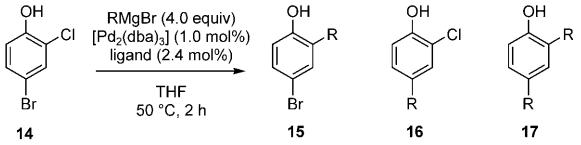
Scheme 3. The site-selective cross-coupling reaction of 2-bromophenol using dihydroxyterphenylphosphine ligand **4**.

method,[6] proceeded at 15 °C to give **13** in good yield with only 2% of diarylated by-product (73%; Scheme 3).

In our previous work with hydroxyterphenylphosphine ligand **2**, some selectivity between *ortho*-chloro and *para*-bromo groups was observed in the reaction of **14**, but a small amount of **16** and a significant amount of **17** were still isolated (Table 3, entry 2).[3c] However, the use of DHTP ligand **4** did not afford any of side product **16**, and gave **15** in good yield (80%; Table 3, entry 3). The use of **6**, which had two 2-methoxyphenyl substituents, further improved the cross-coupling to give **15** in 91% yield (Table 3, entry 4). It is noteworthy that the *ortho* selectivity induced by DHTP ligands superceded the intrinsic reactivity order (Br > Cl) of the halo groups.[7]

We also attempted the competitive cross-coupling between two substrates to demonstrate substrate specificity.

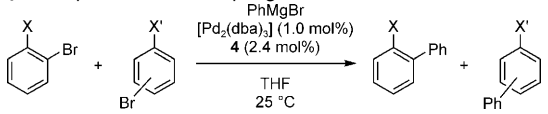
Table 3: Effect of the ligand in the cross-coupling of **14**.[a]

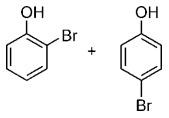
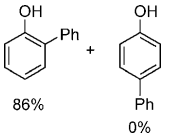
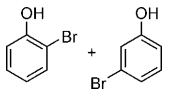
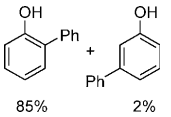
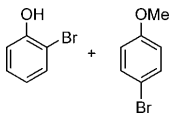
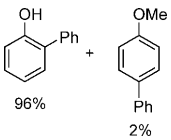
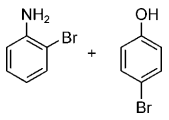
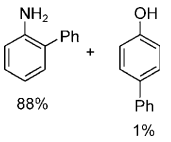


Entry	Ligand	Yield [%]		
		15	**16**	**17**
1[b]	PCy_3	5	34	13
2[b]	**2**	58	4	22
3	**4**	80	0	5
4	**6**	91	0	7

[a] R = 4-methoxyphenyl. [b] See Ref. [3c].

Table 4: Competitive cross-coupling of two substrates.



Entry	Substrates	PhMgBr (equiv)	*t* [h]	Products and Yields
1		4.0	2	 86% 0%
2		4.0	2	 85% 2%
3		3.0	2	 96% 2%
4		4.0	15	 88% 1%

The cross-coupling reaction involving a 1:1 mixture of 2-bromophenol and 4-bromophenol exhibited complete selectivity to give the *ortho*-cross-coupled product (Table 4, entry 1). When the same reaction was carried out at 40 °C using DPPF instead of **4**, the *para*-cross-coupled product was obtained in 80% yield, with only 10% of the *ortho*-cross-coupled product observed. Therefore, the palladium / ligand **4** catalyst completely reversed the substrate preference. High selectivity was also observed in the competitive cross-coupling reaction of a mixture of 2-bromo- and 3-bromo substrates (Table 4, entry 2). This catalytic system also favored the 2-bromophenol substrate over 4-bromoanisole (Table 4, entry 3). In traditional cross-coupling chemistry, electron-donating substituents are known to retard the oxidative addition. However, in this case, the oxido moiety that is formed in situ from the hydroxy substrate, and is more electron-donating than the methoxy group, reacted preferentially. Even more surprisingly, 2-bromoaniline, which was converted into the highly electron-rich anion in the presence of a Grignard reagent, preferentially reacted over 4-bromophenol (Table 4, entry 4). These results emphasize the effectiveness of this catalyst for 2-bromophenols and anilines.

In summary, a new catalytic system comprising DHTP ligands and palladium is effective for the *ortho*-selective cross-coupling of dihaloarenes with Grignard reagents. Introducing the second hydroxy group onto the terphenylphosphine ligand dramatically improved the catalytic efficiency and expanded the scope of the reaction. Although this improvement was caused by a conformational approach based on a hypothesis that is currently under investigation (Scheme 2), the reason for the improvement is still unknown. Further studies to clarify the catalytic species and the origin of the selectivity are underway.

Experimental Section

Procedure for the cross-coupling of **7** (Table 1): A 0.5 mol L^{-1} solution of 4-methoxyphenylmagnesium bromide in tetrahydrofuran (2.51 mL, 1.26 mmol) was added to a solution of 1,6-dibromo-2-naphthol (**7**) (126 mg, 0.419 mmol), [$Pd_2(dba)_3$] (3.8 mg, 4.2 μmol), and **4** (4.5 mg, 10.0 μmol) in tetrahydrofuran (0.42 mL) under argon at −78 °C. After 10 min, the mixture was warmed to 25 °C and stirred for 2 h. The reaction was quenched by the addition of an aqueous solution of HCl (10%; 5 mL), and the mixture was extracted three times with ethyl acetate (5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. Purification by preparative TLC (silica gel, CH_2Cl_2/hexane = 1:1) gave the desired product as a slightly yellow solid in 92% yield (126 mg).

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