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Hydroxylated terphenylphosphine ligands for palladium-catalyzed *ortho*-selective cross-coupling of dibromophenols, dibromoanilines, and their congeners with Grignard reagents

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ABSTRACT

p-Terphenylphosphines bearing one or two hydroxy groups were used as ligands to palladium in the cross-coupling of dibromophenols, dibromoanilines, and their congeners with Grignard reagents. High *ortho*-selectivity that cannot be achieved using other phosphine ligands was observed. *ortho*-Preference was also observed in competitive cross-coupling reactions of two substrates. A significant effect of the concentration of the Grignard reagent on the *ortho*-selectivity was observed, when the hydroxylated terphenylphosphines were used. Kinetic studies on this effect showed that high concentrations of the Grignard reagent retard the cross-coupling reaction only at the *para*-position, but not at the *ortho*-position.

1. Introduction

Transition metal-catalyzed cross-coupling of haloarenes with organometals is an important preparation method of multi-substituted benzenes.[1] Despite its long history, there is still intensive research underway to expand the current scope of cross-coupling chemistry. Developing site-selective cross-coupling reactions is one such area that has attracted attention from synthetic chemists.[2] Site-selective cross-coupling of dihaloarenes, in which one of the halo groups is selectively converted to another group, can be a very useful method for efficient synthesis of multi-substituted arenes. Many examples of site-selective cross-coupling reactions have been reported for dihalogenated heteroarenes.[2a,b] By contrast, there have been fewer examples documented for dihalogenated benzene derivatives,[3] thus there is a need to develop new methods of site-selective cross-coupling for these types of compounds. In the reactions that have been reported, the site-selectivities are mainly controlled by the steric and electronic factors of the substrates. As expected, reactions occur at less sterically hindered sites. In many cases the selectivity of the reactions is also governed by electronic considerations. In these situations the cross-coupling reactions occur at the more electron-poor carbon. Therefore, it is generally difficult to realize site-selectivity in which cross-coupling reactions preferentially occur at more electron-rich carbons. Another drawback encountered during cross-coupling reactions of dihaloarenes is the formation of di-cross-coupled products, even when limited amounts of organometals are used.[4] An efficient system for site-selective cross-coupling reactions should be able to overcome this problem.

We have recently developed a new type of site-selective cross-coupling in which reactions occur at the more electronically negative carbon and also at sterically hindered positions. In these reactions, dibromophenols or dibromoanilines react with excess Grignard reagents preferentially at the bromo group *ortho* to hydroxy or amino groups (Scheme 1).[5] These groups are strongly electron-donating groups especially when deprotonated and render the *ortho*-positions electronically negative. The key of the reactions is the use of palladium catalysts bearing hydroxylated terphenylphosphines,[5,6] mono*h*ydroxy*t*erphenyl*p*hosphine (HTP) and *dih*ydroxy*t*erphenyl*p*hosphine DHTP (Fig. 1a). These phosphines were designed based on biphenylphosphines developed by Buchwald and co-workers[7] and were expected to perform as bifunctional ligands.[8] It is also worth noting that, in the reaction system developed, the formation of di-cross-coupled products was sufficiently suppressed in most cases.

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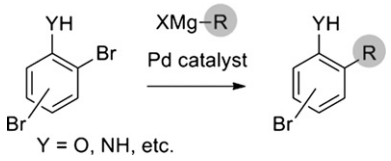


Scheme 1. *ortho*-Selective cross-coupling of dibromophenol and dibromoaniline derivatives with Grignard reagents.

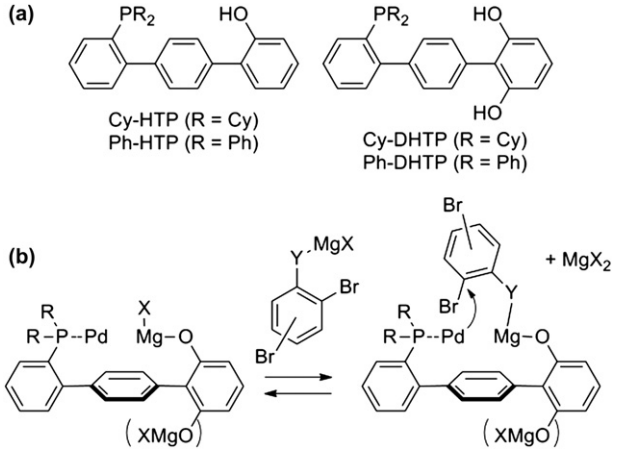


Fig. 1. (a) Hydroxylated terphenylphosphines. (b) Proposed intermediates responsible for the *ortho*-selectivity in site-selective cross-coupling of a dibromoarene with a Grignard reagent.

Fig. 1b outlines the proposed intermediates through which the *ortho*-selectivity achieved. The hydroxylated phosphines are deprotonated by the Grignard reagent and presumably form palladium/magnesium bimetallic species in the presence of palladium. The magnesium oxido moiety can then act as a binding site for the substrate, which also exists as a magnesium salt, and situates the *ortho* bromo group close to the palladium. Through this mechanism, oxidative addition to the palladium should preferentially occur at the position *ortho* to the oxido group of the substrate. Since the oxidative addition step is considered as the rate-limiting and the selectivity-determining step, both rate acceleration and *ortho*-selectivity are expected.

The *ortho*-selectivity mentioned above was realized only when these phosphines were used as ligands to palladium. Thus, this catalyst-controlled site-selective cross-coupling results in a novel synthetic route to multisubstituted benzenes. Herein, we detail *ortho*-selective cross-coupling of dibromoarenes and *ortho*-selective competitive cross-coupling reactions between two substrates. We also disclose an unusual dependence of the *ortho*-selectivity upon the concentration of the Grignard reagent in the cross-coupling using the hydroxylated terphenylphosphines.

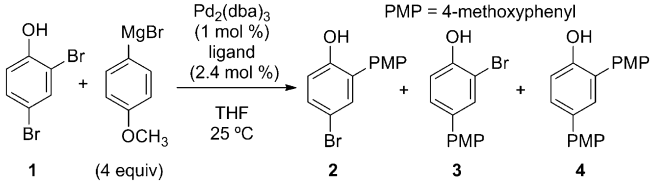
2. Results and discussion

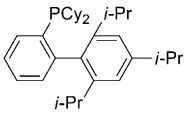
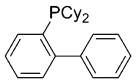
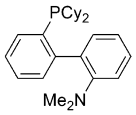
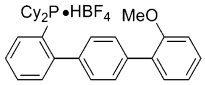
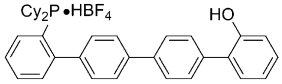
2.1. *ortho*-Selective cross-coupling of dibromoarenes

To examine effects of ligands to palladium on site-selectivity, we tested various phosphines for cross-coupling of 2,4-dibromophenol (**1**) with 4-methoxyphenylmagnesium bromide in the presence of tris(benzylideneacetone)dipalladium [$Pd_2(dba)_3$]. Triphenylphosphine and tricyclohexylphosphine gave *ortho*-cross-coupled product **2**, *para*-cross-coupled product **3**, and di-cross-coupled product **4** all in modest yields (Table 1, entries 1 and 2). Selectivity was low not only for *ortho* versus *para*, but also mono- versus di-cross-coupling. For tri-*tert*-butylphosphine HBF_4 salt,[9] which generates the corresponding free form in situ in the presence of the Grignard reagent, *para*-selectivity was observed, albeit accompanied by significant di-cross-coupling (entry 3). For 1,1′-bis(diphenylphosphino)ferrocene (DPPF), a highly *para*-selective, mono-cross-coupling reaction occurred to give **3** as the major product (entry 4). Use of biphenylphosphines[7] as shown in entries 5–7 resulted in poor yields and selectivities. However, hydroxylated terphenylphosphines, such as Cy-HTP (as its HBF_4 salt) and Ph-HTP preferentially afforded *ortho*-cross-coupled product **2** (entries 8 and 9). Although small amounts of **4** were produced, **3** was not isolated at all. In addition, the reactions were significantly accelerated and completed in 2 h, compared with 24 h for the other entries. Ph-HTP effectively suppressed formation of **4** compared with Cy-HTP. The hydroxy group of HTP was found to be essential, since the corresponding methylated compound[6a] resulted in poor yields and selectivity (entry 10). A quaterphenyl analogue[6b] also gave low yields and selectivity (entry 11), indicating that precise positioning of the hydroxy group of HTP was also crucial for high *ortho*-selectivity. Ph-DHTP, bearing two hydroxy groups, further improved the selectivity, affording **2** in 91% yield with only 2% of **4** produced (entry 12).

A reaction of 2-bromophenol with phenylmagnesium bromide under the conditions shown in Table 1, entry 8 for 1 h gave 2-phenylphenol in 79% yield. On the other hand, a reaction of

Table 1
Effect of ligand on site-selective cross-coupling of **1** with 4-methoxyphenylmagnesium bromide



Entry	Ligand	Time (h)	Yield (%)		
			2	**3**	**4**
1	PPh_3	24	22	16	14
2	PCy_3	24	21	14	38
3	$P(t\text{-}Bu)_3 \cdot HBF_4$	24	0	40	25
4	DPPF	24	1	77	1
5		24	5	5	1
6		24	8	12	3
7		24	2	8	0
8	Cy-HTP·HBF_4	2	71	0	16
9	Ph-HTP	2	89	0	4
10		24	13	18	7
11		24	6	21	5
12[a]	Ph-DHTP	2	91	0	2

[a] Grignard reagent (3 equiv) was used.