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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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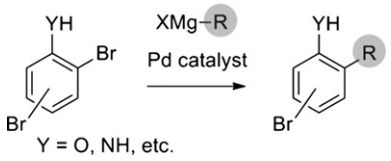


Scheme 1. *ortho*-Selective cross-coupling of dibromophenol and dibromoaniline derivatives with Grignard reagents.

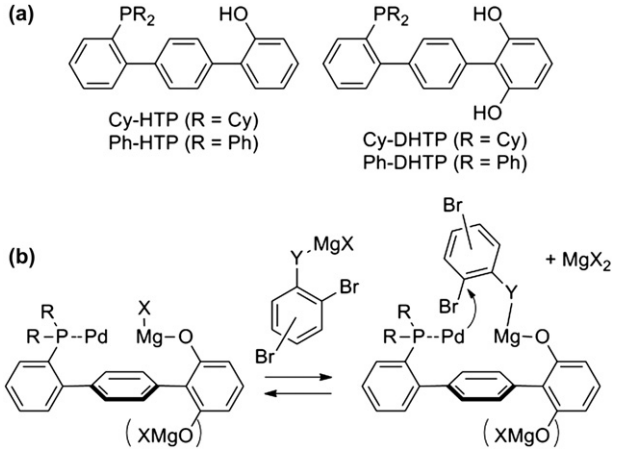


Fig. 1. (a) Hydroxylated terphenylphosphines. (b) Proposed intermediates responsible for the *ortho*-selectivity in site-selective cross-coupling of a dibromoarene with a Grignard reagent.

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.

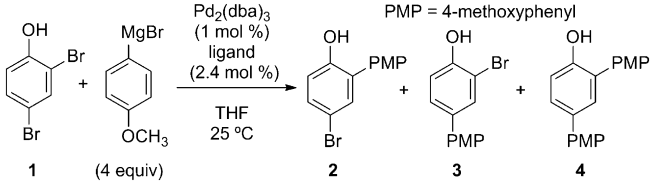
2. Results and discussion

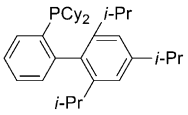
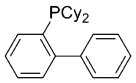
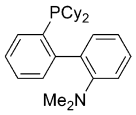
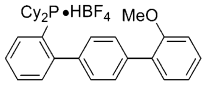
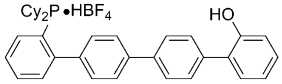
2.1. *ortho*-Selective cross-coupling of dibromoarenes

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



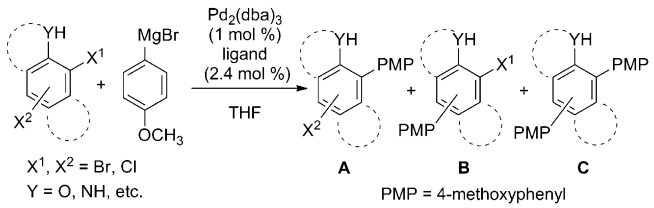
Entry	Ligand	Time (h)	Yield (%)		
			2	**3**	**4**
1	PPh_3	24	22	16	14
2	PCy_3	24	21	14	38
3	$P(t\text{-}Bu)_3 \cdot HBF_4$	24	0	40	25
4	DPPF	24	1	77	1
5		24	5	5	1
6		24	8	12	3
7		24	2	8	0
8	Cy-HTP·HBF_4	2	71	0	16
9	Ph-HTP	2	89	0	4
10		24	13	18	7
11		24	6	21	5
12[a]	Ph-DHTP	2	91	0	2

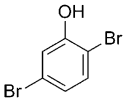
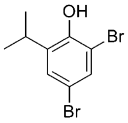
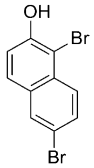
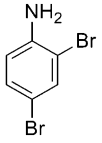
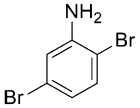
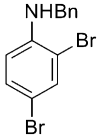
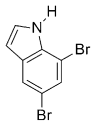
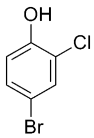
[a] Grignard reagent (3 equiv) was used.

2-bromoanisole under the same conditions gave 2-methoxybiphenyl in only 17% yield. This result indicates that the presence of the hydroxy group of the substrate plays an important role in accelerating the reaction at the *ortho*-position.

We applied our catalytic system of palladium–HTP or DHTP to other dibromoarenes bearing a hydroxy or amino group (Table 2). Although di-cross-coupling occurred to some extent, 2,5-dibromophenol preferentially gave *ortho*-cross-coupled product **A** when the hydroxylated terphenylphosphines were used (entries 1 and 2). It should be noted that the reaction occurred at the more electronically negative carbon and at then more sterically hindered position. In contrast, DPPF gave *meta*-cross-coupled product **B** as the major product (entry 3). This result emphasizes the effectiveness of the hydroxylated terphenylphosphines for *ortho*-selective cross-coupling. In the case of 1,6-dibromo-2-naphthol, HTP was not effective at inducing site-selectivity (entry 6). However, phosphines with

Table 2
Site-selective cross-coupling with 4-methoxyphenylmagnesium bromide



Entry	Substrate	Ligand	PMPMgBr (equiv)	Temperature (°C)	Time (h)	Yield (%)		
						A	**B**	**C**
1		Ph-HTP	4	25	2	65	0	10
2		Ph-DHTP	3	25	2	64	0	25
3		DPPF	4	25	24	0	61	<2[a]
4		Ph-DHTP	3	25	5	93	0	2
5		DPPF	3	25	24	2	<42[a]	1
6		Cy-HTP·HBF_4	3	25	2	17	22	20
7		Cy-DHTP·HBF_4	3	25	2	79	0	6
8		Ph-DHTP	3	25	2	92	0	2
9		DPPF	3	25	8	0	94	0
10		Cy-HTP·HBF_4	4	25	10	71	0	12
11		Ph-HTP	4	25	10	76	0	13
12		Ph-DHTP	3	25	10	90	0	0
13		DPPF	4	25	10	9	15	2
14		Ph-HTP	4	25	10	63	0	<26[a]
15		Ph-DHTP	4	25	10	36	0	<56[a]
16		DPPF	4	50	10	15	32	<11[a]
17		Ph-DHTP	4	35	24	70	0	9
18		DPPF	3	25	18	29	21	36
19		Ph-DHTP	3	25	13	81	0	5
20		DPPF	3	50	13	0	37	55
21		Ph-HTP	4	50	2	58	4	22
22		Ph-DHTP	4	50	2	80	0	5

[a] Contaminated with low levels of impurities.

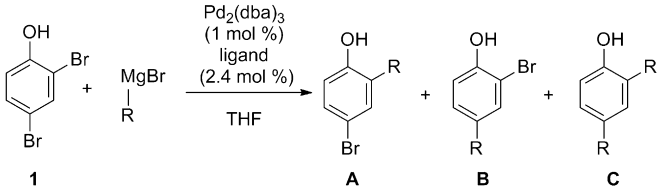
two hydroxy groups, Cy-DHTP and Ph-DHTP, gave **A** with high selectivities (entries 7 and 8), suggesting that DHTP is better at controlling the selectivity when compared to HTP. Dibromoanilines and dibromoindole also resulted in high *ortho*-selectivities, when HTP or DHTP was used (entries 10–12, 14, 15, 17, and 19). To our surprise, even 4-bromo-2-chlorophenol gave *ortho*-cross-coupled product **A** with high selectivities (entries 21 and 22). This result clearly indicates that the *ortho*-selectivity induced by the hydroxylated phosphines, especially by DHTP, superseded the intrinsic reactivity order of the halo groups (normally Br is more reactive than Cl).[3f,10]

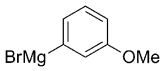
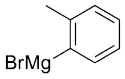
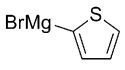
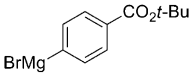
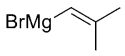
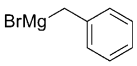
Various Grignard reagents were tested for the *ortho*-selective cross-coupling (Table 3). Both aryl and also heteroaryl Grignard reagents worked well to give *ortho*-cross-coupled products **A** (entries 1–5). By lowering the reaction temperature to 15 °C, it was possible to carry out the reaction with a Grignard reagent having an ester functionality that was prepared following the method by Knochel and co-workers[11] (entry 6). An alkenyl Grignard reagent gave **A** with excellent selectivity (entry 7). Benzyl Grignard reagent showed different behavior. When Cy-HTP was used, *para*-cross-coupled product **B** was the major product (entry 8).[12] When Ph-DHTP was employed, *ortho*-selectivity was recovered, but with low product yield (entry 9). The results in Table 3 indicate that Ph-DHTP was, in general, the best ligand for these reactions.

The effectiveness of DHTP compared with HTP can be rationalized in terms of a conformational effect. The assumed catalytic species formed from HTP is shown in Fig. 2a. This species has flexibility in rotation of the C–C single bonds. The conformation in which the palladium and the magnesium oxido moiety are located close to each other is in equilibrium with the conformer in which the palladium and the magnesium oxido groups are on the opposite sides of the terphenyl group. In the latter conformation, the cooperative effect of the palladium and the magnesium oxido groups cannot function. On the other hand, in the case of DHTP, a magnesium oxido group is always located on the same side of the terphenyl structure as the palladium, even if C–C bond rotation occurs (Fig. 2b).[13] Through this mechanism, cooperation between palladium and the magnesium oxido moiety may be more effective for DHTP, giving higher selectivities in the *ortho*-selective cross-coupling reactions.

In the course of the investigation of the *ortho*-selective cross-coupling reaction, we found that the amount of the Grignard reagent employed greatly affected the selectivity achieved. For the reaction of 2,4-dibromophenol with 4-methoxyphenylmagnesium bromide in the presence of palladium and Cy-HTP, the amount of the Grignard reagent used was varied from 2.2 to 10 equiv (Table 4, entries 1–4). Both the yields of **3** and **4** decreased, as the amount of the Grignard reagent increased. Even when 10 equiv of the Grignard

Table 3
ortho-Selective cross-coupling with various Grignard reagents



Entry	Grignard reagent	(Equiv)	Ligand	Temperature (°C)	Time (h)	Yield (%)		
						A	**B**	**C**
1		4	Cy-HTP·HBF_4	25	2	60	0	17
2		4	Ph-HTP	25	2	84	0	5
3		3	Ph-DHTP	25	14	77	0	2
4		4	Cy-HTP·HBF_4	25	72	66	0	17
5		4	Ph-DHTP	35	22	98	0	1
6		2[a]	Ph-DHTP	15	20	73	0	2
7		3	Ph-DHTP	25	18	83	0	0
8		4	Cy-HTP·HBF_4	50	5	Trace	55	<21[b]
9		3	Ph-DHTP	35	20	37	<3[b]	15

[a] Prepared from *tert*-butyl 4-iodobenzoate (2 equiv) with *i*-PrMgBr (3 equiv) in THF at −40 °C.
[b] Contaminated with low levels of impurities.

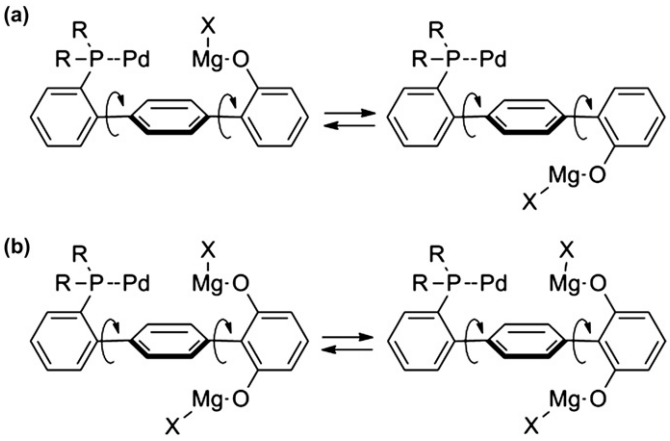
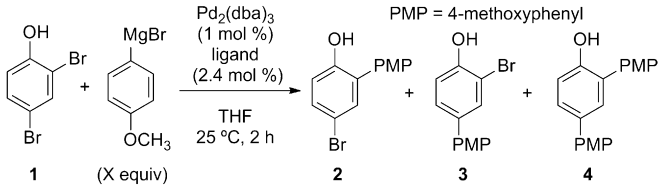


Fig. 2. C–C bond rotation for the species formed from (a) HTP and (b) from DHTP.

Table 4
Effect of amount of the Grignard reagent



Entry	Ligand	PMPMgBr (equiv)	Yield (%)		
			2	**3**	**4**
1	Cy-HTP·HBF_4	2.2	36	8	22
2	Cy-HTP·HBF_4	3	59	<2[a]	20
3	Cy-HTP·HBF_4	4	71	0	16
4	Cy-HTP·HBF_4	10	82	0	5
5	Ph-HTP	3	80	0	10
6	Ph-HTP	4	89	0	4
7	Ph-DHTP	2.2	79	0	5
8	Ph-DHTP	3	91	0	2

[a] Contaminated with low levels of impurities.

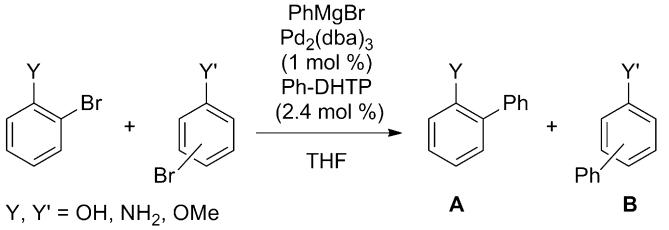
reagent was used, the yield of **4** was only 5%. This counterintuitive effect was also observed for reactions with Ph-HTP and Ph-DHTP as ligands (entries 5–8). Although the mechanism for the effect is unclear, kinetic studies[14] of model compounds suggest that the reaction at the *para* position to give **3** and **4** is retarded upon increasing the concentration of the Grignard reagent (vide infra). The results in Table 4 also indicate that large amounts of the Grignard reagent are necessary for high selectivity when Cy-HTP is used. On the other hand, when Ph-DHTP is employed, less amounts of the Grignard reagent is sufficient.

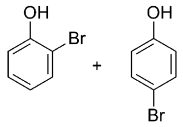
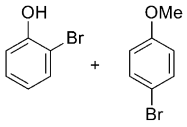
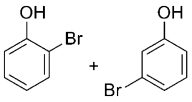
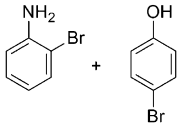
2.2. Competitive cross-coupling between two substrates

The high *ortho*-preference observed in the site-selective cross-coupling mentioned above was also applied to competitive reactions between two substrates. For example, the reaction of a 1:1:6 mixture of 2-bromophenol, 4-bromophenol, and phenylmagnesium bromide in the presence palladium and Cy-HTP afforded *ortho*-cross-coupled product **A** in 59% yield and *para*-cross-coupled product **B** in 5% yield (Table 5, entry 2). Interestingly, this *ortho*-preference was not observed, when 3 equiv of the Grignard reagent was used (entry 1). The larger amounts of the Grignard reagent, the higher the selectivity, as already reported in Table 4.

On the other hand, when Ph-DHTP was used, 3 equiv of the Grignard reagent was sufficient to induce *ortho*-selectivity

Table 5
Competitive cross-coupling of two substrates



Entry	Substrate	Ligand	PhMgBr (equiv)	Time (h)	Yield (%)	
					A	**B**
1		Cy-HTP·HBF_4	3	1	29	33
2		Cy-HTP·HBF_4	6	1	59	5
3		Cy-DHTP·HBF_4	3	1	39	9
4		Ph-DHTP	3	5	60	3
5		Ph-DHTP	4	2	86	0
6		Ph-DHTP	3	2	96	2
7		Ph-DHTP	4	5	85	2
8		Ph-DHTP	4	15	88	1

(entry 4). Further increases of the Grignard reagent suppressed formation of **B** completely (entry 5). Ph-DHTP also worked well in other competitive reactions, exhibiting high *ortho*-selectivity (entries 6–8).

2.3. Kinetic studies on the effect of concentration of Grignard reagent

The results in Table 4 indicate that the amount of the Grignard reagent employed affected the product selectivity in site-selective cross-coupling of dibromophenol. Similar effects were also observed in the competitive reactions between two substrates (Table 5, entry 1 vs 2, 4 vs 5). The significant increase of selectivity was observed for the hydroxylated terphenylphosphines, but not for simple phosphines, such as tricyclohexylphosphine. To gain insight into the mechanism of this effect, we conducted kinetic studies on cross-coupling reactions of 4-bromophenol and 2-bromophenol with varying amounts of a Grignard reagent in the presence of palladium and Cy-HTP or tricyclohexylphosphine as a reference ligand. Fig. 3 shows a plot of the initial reaction rate of 4-bromophenoxymagnesium bromide, prepared from 4-bromophenol in situ, versus the initial concentration of phenylmagnesium bromide. This plot clearly indicates that, for both the ligands, the reaction rate decreases as the concentration of the Grignard reagent increases.

Results for 2-bromophenoxide exhibit different behavior (Fig. 4). For tricyclohexylphosphine, the reaction rate decreases upon increasing concentration of the Grignard reagent as in the case of Fig. 3. For Cy-HTP, however, the reaction rate was found to be independent of the concentration of the Grignard reagent

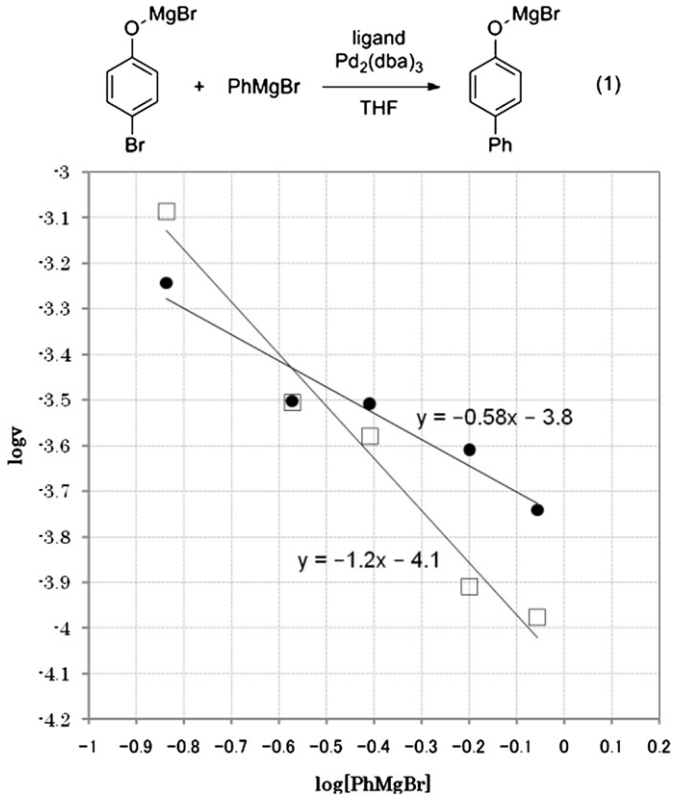


Fig. 3. Double logarithm plot of the reaction rate v (M/min) versus the initial concentration of PhMgBr [PhMgBr] (M) for Eq. 1. Open square: ligand=Cy-HTP·HBF_4 at 50 °C. Closed circle: ligand=PCy_3 at 35 °C. The solid lines are calculated linear trendlines.

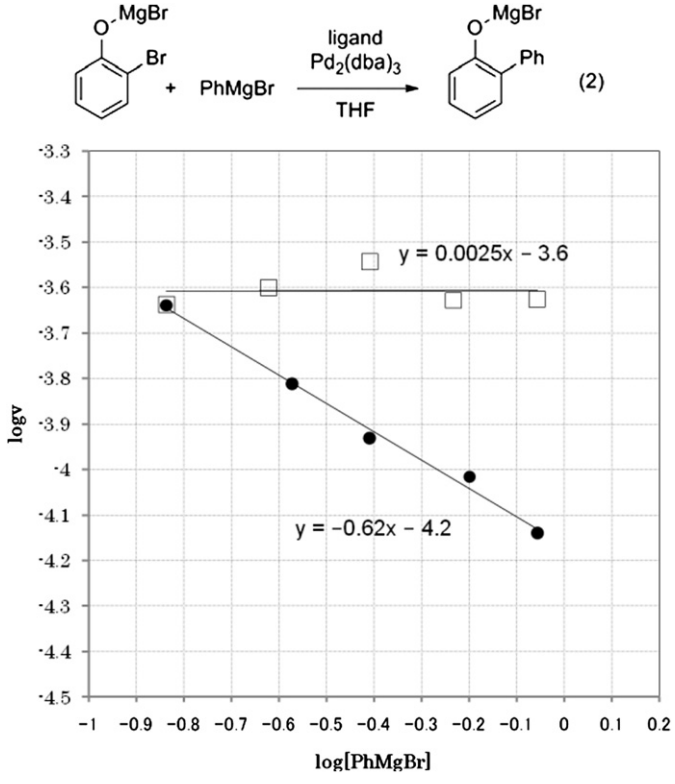


Fig. 4. Double logarithm plot of the initial reaction rate v (M/min) versus the initial concentration of PhMgBr [PhMgBr] (M) for Eq. 2. Open square: ligand=Cy-HTP·HBF_4 at 0 °C. Closed circle: ligand=PCy_3 at 15 °C. The solid lines are calculated linear trendlines.

within this concentration range. Therefore, the rate difference between *ortho*- and *para*-positions becomes greater at higher concentrations of the Grignard reagent. Although a detailed mechanism has not been elucidated, it is obvious that high concentrations of Grignard reagent retard the cross-coupling reaction only at the *para*-position, but not at the *ortho*-position, in the HTP system.

3. Conclusions

Palladium-catalyzed *ortho*-selective cross-coupling of dibromoarenes with Grignard reagents has been realized using hydroxylated terphenylphosphines as ligands to palladium. Dibromophenols, dibromonaphthol, dibromoanilines, and dibromoindole reacted at the *ortho*-positions selectively. Formation of di-cross-coupled products was sufficiently suppressed in many cases. This catalytic system was also applied to *ortho*-selective competitive cross-coupling between two substrates. The Grignard reagent concentration had a profound influence on the *ortho*-selectivity, when the hydroxylated terphenylphosphines were used. In addition, the unaffected bromo groups of compounds produced can be converted to various other groups, thus the catalyst-controlled site-selective cross-coupling developed will provide a novel efficient method for the preparation of multisubstituted arenes.

4. Experimental section

4.1. Synthesis of ligands

Cy-HTP·HBF_4,[6b] Ph-HTP,[5a] Cy-DHTP·HBF_4,[5c] and Ph-DHTP[5c] were prepared according to previously reported methods.

4.2. General procedure of *ortho*-selective cross-coupling reactions

To a solution of dibromo compound (0.42 mmol), $Pd_2(dba)_3$ (4.2 μmol), and ligand (10 μmol) in THF (0.42 mL) was added a THF solution of Grignard reagent under argon at −78 °C. After 10 min, the reaction mixture was warmed to 25 °C and stirred for the time indicated. The reaction was quenched by the addition of a 10% aqueous solution of HCl (5 mL), and the mixture was extracted with ethyl acetate (5 mL×3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by preparative TLC (silica gel) gave the desired product.

*4.2.1. 5-Bromo-4′-methoxy-(1,1′-biphenyl)-2-ol (**2**, Table 1, Table 2, entries 21 and 22).* Mp 72.8–76.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 5.16 (1H, s), 6.85 (1H, d, J=8.4 Hz), 7.02 (2H, d, J=8.8 Hz), 7.32 (1H, dd, J=2.4, 8.4 Hz), 7.33 (1H, d, J=2.4 Hz), 7.35 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 112.7, 114.9, 117.4, 127.7, 129.8, 130.1, 131.4, 132.6, 151.7, 159.7 ppm; IR (ATR) 3421, 1487, 1232, 1182, 1030, 1011, 833, 800 cm^{-1}; 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%.

4.2.2. 4-Bromo-4′-methoxy-(1,1′-biphenyl)-2-ol (Table 2, entries 1 and 2). Mp 71.7–75.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 5.27 (1H, s), 7.01 (2H, d, J=8.8 Hz), 7.06 (1H, d, J=8.4 Hz), 7.10 (1H, dd, J=2.0, 8.4 Hz), 7.14 (1H, d, J=2.0 Hz), 7.34 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 114.9, 118.9, 121.6, 123.9, 126.9, 128.0, 130.1, 131.2, 153.3, 159.5 ppm; IR (ATR) 3338, 1489, 1392, 1232, 1174, 999, 796 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{10}BrO_2$

([M−H]$^-$) 276.9859, 278.9839; found: 276.9858, 278.9840. Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97, found: C, 56.07; H, 4.04%.

4.2.3. 5-Bromo-3-isopropyl-4′-methoxy-(1,1′-biphenyl)-2-ol (Table 2, entry 4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (6H, d, J=7.0 Hz), 3.29 (1H, sept., J=7.0 Hz), 3.86 (3H, s), 5.23 (1H, br s), 7.02 (2H, d, J=8.5 Hz), 7.16 (1H, d, J=2.5 Hz), 7.27 (1H, dd, J=0.5, 2.5 Hz), 7.34 (2H, d, J=8.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 27.3, 55.4, 112.6, 114.9, 128.0, 128.5, 129.4, 129.8, 130.3, 137.2, 148.9, 159.7 ppm; IR (neat) 3537, 2962, 1609, 1514, 1455, 1250, 835 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{17}BrO_2$ ([M]) 320.0412, 322.0393; found: 320.0418, 322.0381. Anal. Calcd for $C_{16}H_{17}BrO_2$: C, 59.83; H, 5.33, found: C, 60.09; H, 5.40%.

4.2.4. 6-Bromo-1-(4-methoxyphenyl)naphthalen-2-ol (Table 2, entries 7 and 8). Mp 81.6–83.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (3H, s), 5.20 (1H, s), 7.10 (2H, d, J=9.0 Hz), 7.26 (1H, d, J=9.0 Hz), 7.28 (1H, d, J=9.0 Hz), 7.30 (2H, d, J=9.0 Hz), 7.38 (1H, dd, J=2.0, 9.0 Hz), 7.68 (1H, d, J=9.0 Hz), 7.94 (1H, d, J=2.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.4, 115.2, 117.0, 118.4, 120.9, 125.1, 126.5, 128.3, 129.6, 129.9, 130.0, 132.2, 132.2, 150.7, 159.9 ppm; IR (ATR) 2964, 1246, 1171, 1028, 820 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{12}BrO_2$ ([M−H]$^-$) 327.0026, 329.0007; found: 327.0032, 329.0013. Anal. Calcd for $C_{17}H_{13}BrO_2$: C, 62.03; H, 3.98, found: C, 62.09; H, 4.08%.

4.2.5. 5-Bromo-4′-methoxy-(1,1′-biphenyl)-2-amine (Table 2, entries 10–12). Mp 89.1–90.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (2H, br s), 3.84 (3H, s), 6.62 (1H, d, J=9.2 Hz), 6.97 (2H, d, J=8.8 Hz), 7.19 (2H, m), 7.33 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 110.1, 114.3, 116.9, 129.1, 130.0, 130.3, 130.7, 132.8, 142.8, 159.1 ppm; IR (ATR) 3446, 3365, 1606, 1510, 1485, 1290, 1236, 1176, 1036, 818 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{13}BrNO$ ([M+H]$^+$) 278.0175, 280.0156; found: 278.0175, 280.0153. Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04, found: C, 56.23; H, 4.45; N, 4.96%.

4.2.6. 4-Bromo-4′-methoxy-(1,1′-biphenyl)-2-amine (Table 2, entries 14 and 15). Mp 126.9–128.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (2H, br s), 3.84 (3H, s), 6.88–6.94 (3H, m), 6.97 (2H, d, J=8.8 Hz), 7.32 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 114.3, 117.8, 121.3, 121.5, 126.1, 123.0, 130.6, 131.7, 145.0, 158.9 ppm; IR (ATR) 3452, 3363, 1604, 1481, 1238, 1174, 1032, 837, 795 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{13}BrNO$ ([M+H]$^+$) 278.0175, 280.0156; found: 278.0170, 280.0147. Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04, found: C, 56.10; H, 4.31; N, 4.91%.

4.2.7. N-Benzyl-5-bromo-4′-methoxy-(1,1′-biphenyl)-2-amine (Table 2, entry 17). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (3H, s), 4.28 (2H, s), 4.50 (1H, br s), 6.49 (1H, d, J=8.5 Hz), 6.97 (2H, d, J=9.0 Hz), 7.19 (1H, d, J=2.5 Hz), 7.22 (1H, dd, J=2.5, 8.5 Hz), 7.23–7.32 (5H, m), 7.34 (2H, d, J=9.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.1, 55.3, 109.0, 112.3, 114.5, 127.0, 127.2, 128.6, 129.3, 130.0, 130.3, 130.8, 132.6, 138.8, 143.9, 159.1 ppm; IR (neat) 3425, 1497, 1295, 1246, 1176, 1038, 835 cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{18}BrNO$ ([M]) 367.0572, 369.0554; found: 367.0577, 369.0538. Anal. Calcd for $C_{20}H_{18}BrNO$: C, 65.23; H, 4.93; N, 3.80, found: C, 65.09; H, 4.97; N, 3.78%.

4.2.8. 5-Bromo-7-(4-methoxyphenyl)-1H-indole (Table 2, entry 19). Mp 132.4–142.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (3H, s), 6.54 (1H, dd, J=2.5, 3.0 Hz), 7.03 (2H, d, J=9.0 Hz), 7.20 (1H, dd, J=2.5, 3.0 Hz), 7.27 (1H, d, J=2.0 Hz), 7.51 (2H, d, J=9.0 Hz), 7.72 (1H, dd, J=1.0, 2.0 Hz), 8.37 (1H, br s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.4, 102.7, 113.4, 114.7, 121.8, 124.2, 125.4, 126.9, 129.2, 129.8, 130.2, 132.6, 159.4 ppm; IR (ATR) 3330, 1238, 827, 721 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{12}BrNO$ ([M]) 301.0102, 303.0083; found: 301.0114, 303.0090. Anal. Calcd for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64, found: C, 59.64; H, 4.13; N, 4.65%.

4.2.9. 5-Bromo-3′-methoxy-(1,1′-biphenyl)-2-ol (Table 3, entries 1 and 2). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (3H, s), 5.33 (1H, s), 6.86 (1H, d, J=8.0 Hz), 6.94 (1H, d, J=2.4 Hz), 6.95 (1H, ddd, J=0.8, 2.4, 8.0 Hz), 7.00 (1H, dd, J=0.8, 8.0 Hz), 7.34 (1H, dd, J=2.4, 8.0 Hz), 7.36 (1H, d, J=2.4 Hz), 7.40 (1H, t, J=8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 112.6, 114.1, 114.3, 117.6, 120.9, 129.8, 130.6, 131.8, 132.4, 136.9, 151.6, 160.4 ppm; IR (neat) 3521, 3434, 1598, 1580, 1478, 1394, 1293, 1266, 1215, 1169, 1051, 1028, 817, 717 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{10}BrO_2$ ([M−H]$^-$) 276.9859, 278.9839; found: 276.9859, 278.9841. Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97, found: C, 56.28; H, 4.00%.

4.2.10. 5-Bromo-2′-methyl-(1,1′-biphenyl)-2-ol (Table 3, entry 3). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (3H, s), 4.76 (1H, br s), 6.88 (1H, d, J=8.5 Hz), 7.20–7.22 (1H, m), 7.25 (1H, d, J=2.5 Hz), 7.28–7.31 (1H, m), 7.32–7.34 (2H, m), 7.37 (1H, dd, J=2.5, 8.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 112.4, 117.1, 126.6, 129.0, 129.7, 130.3, 130.8, 131.9, 132.6, 134.2, 137.3, 151.8 ppm; IR (neat) 3495, 3428, 1480, 1258, 1233, 1175, 818, 767, 734 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{11}BrO$ ([M]) 261.9993, 263.9974; found: 261.9985, 263.9963. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21, found: C, 59.67; H, 4.47%.

4.2.11. 4-Bromo-2-(thiophen-2-yl)phenol (Table 3, entries 4 and 5). Mp 55.4–59.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, s), 6.84 (1H, d, J=8.4 Hz), 7.14 (1H, dd, J=3.6, 5.2 Hz), 7.28 (1H, dd, J=1.2, 3.6 Hz), 7.31 (1H, dd, J=2.4, 8.4 Hz), 7.42 (1H, dd, J=1.2, 5.2 Hz), 7.53 (1H, d, J=2.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 117.8, 122.9, 126.5, 126.9, 127.9, 131.9, 132.3, 137.0, 151.5 ppm; IR (neat) 3507, 1478, 1399, 1277, 1210, 1116, 818, 704 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_6BrOS$ ([M−H]$^-$) 252.9317, 254.9296; found: 252.9325, 254.9308. Anal. Calcd for $C_{10}H_7BrOS$: C, 47.08; H, 2.77, found: C, 47.00; H, 2.85%.

4.2.12. tert-Butyl 5′-bromo-2′-hydroxy-(1,1′-biphenyl)-4-carboxylate (Table 3, entry 6). Mp 133.5–135.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (9H, s), 5.50 (1H, s), 6.87 (1H, d, J=8.5 Hz), 7.36 (1H, dd, J=2.5, 8.5 Hz), 7.38 (1H, d, J=2.5 Hz), 7.52 (2H, d, J=8.5 Hz), 8.07 (2H, d, J=8.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 81.5, 112.9, 118.0, 128.84, 129.3, 130.2, 131.5, 132.2, 132.6, 140.2, 151.7, 165.5 ppm; IR (ATR) 3359, 1680, 1321, 1309, 1136, 1124, 818, 727 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{16}BrO_3$ ([M−H]$^-$) 347.0288, 349.0270; found: 347.0294, 349.0274.

4.2.13. 4-Bromo-2-(2-methylprop-1-en-1-yl)phenol (Table 3, entry 7). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (3H, d, J=1.0 Hz), 1.94 (3H, d, J=1.5 Hz), 5.04 (1H, br s), 6.05 (1H, m), 6.78 (1H, d, J=8.5 Hz), 7.16 (1H, dd, J=0.5, 2.5 Hz), 7.24 (1H, ddd, J=0.5, 2.5, 8.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5 25.8, 112.1, 116.6, 117.5, 126.7, 130.9, 132.3, 142.0, 152.0 ppm; IR (neat) 3509, 2911, 1477, 1215, 822 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_{11}BrO$ ([M]) 225.9993, 227.9973; found: 225.9994, 227.9981.

4.2.14. 4-Benzyl-2-bromophenol (Table 3, entry 8). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (2H, s), 5.38 (1H, s), 6.93 (1H, d, J=8.0 Hz), 7.03 (1H, dd, J=2.0, 8.5 Hz), 7.16 (2H, dd, J=1.0, 7.5 Hz), 7.21 (1H, tt, J=1.0, 7.5 Hz), 7.27 (1H, d, J=2.0 Hz), 7.29 (2H, t, J=7.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.7, 110.1, 115.9, 126.3, 128.6, 128.8, 129.7, 132.0, 134.9, 140.7, 150.5 ppm; IR (neat) 3507, 1493, 1180, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{10}BrO$ ([M−H]$^-$) 260.9910, 262.9890;

found: 260.9907, 262.9890. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21, found: C, 59.34; H, 4.41%.

4.2.15. 2-Benzyl-4-bromophenol (Table 3, entry 9). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (2H, s), 4.76 (1H, br s), 6.66 (1H, d, J=8.0 Hz), 7.21–7.24 (5H, m), 7.31 (2H, t, J=7.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 112.9, 117.4, 126.6, 128.7, 128.8, 129.4, 130.5, 133.4, 138.9, 152.8 ppm; IR (neat) 3533, 1492, 1410, 1266, 1105, 698 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{11}BrO$ ([M]) 261.9993, 263.9974; found: 261.9999, 263.9982. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21, found: C, 59.26; H, 4.35%.

4.3. General procedure of competitive cross-coupling reactions between two substrates

To a solution of two substrates (0.47 mmol each), $Pd_2(dba)_3$ (4.7 μmol), and ligand (11 μmol) in THF (0.47 mL) was added a THF solution of Grignard reagent under argon at −78 °C. After 10 min, the reaction mixture was warmed to 25 °C and stirred for the time indicated. The reaction was quenched by the addition of a 10% aqueous solution of HCl (5 mL), and the mixture was extracted with ethyl acetate (5 mL×3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by preparative TLC (silica gel) gave the desired products.

4.4. General procedure for kinetic studies

To a THF solution of bromophenol and naphthalene as an internal standard was added a THF solution of the Grignard reagent at rt. After letting the solution stand at an appropriate temperature for 5 min, a THF solution of $Pd_2(dba)_3$ and ligand was added to it. The initial concentration of the components was as follows: bromophenoxide, 0.0974 M; Pd, 0.0020 M (for Fig. 4, Cy-HTP·HBF_4) and 0.0039 M (for the rest); ligand, 0.0020 M (for Fig. 4, Cy-HTP·HBF_4) and 0.0039 M (for the rest); Grignard reagent, 0.146–0.877 M. A small amount of the reaction mixture was sampled via a syringe every 10 min and poured into a saturated aqueous ammonium chloride solution. The products were extracted with ethyl acetate, and GC analysis was carried out to determine ratios of the products and the internal standard.

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