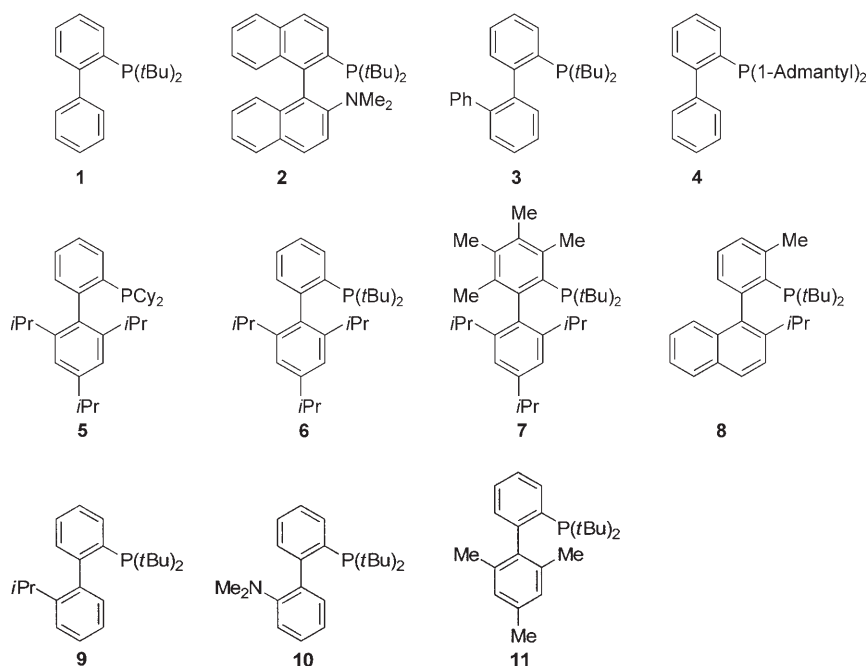


# Significantly Improved Method for the Pd-Catalyzed Coupling of Phenols with Aryl Halides: Understanding Ligand Effects\*\*

Carlos H. Burgos, Timothy E. Barder,  
Xiaohua Huang, and Stephen L. Buchwald\*

The diaryl ether unit is a common structural feature in numerous natural products and biologically interesting compounds.<sup>[1,2]</sup> These ethers have traditionally been prepared by the reaction of aryl halides with sodium or potassium aryl oxides promoted by copper reagents (the classical Ullmann diaryl synthesis).<sup>[3]</sup> However, these classic conditions require elevated temperatures and stoichiometric amounts of copper and often result in yields that range from low to moderate. As such, this powerful transformation has limited utility, thus the development of new methods for the preparation of diaryl ethers under relatively mild reaction conditions has received much attention in recent years.<sup>[4–7]</sup> Even in view of recent improvements, reactions with certain substrate combinations remain difficult, hence the need for more general methods for the preparation of diaryl ethers. Our group, as well as those of Hartwig and Beller, has previously reported palladium-catalyzed procedures for diaryl ether formation.<sup>[7]</sup> Previously, we demonstrated that the cross-coupling of electron-deficient, electron-neutral, and electron-rich aryl halides and sulfonates with a variety of phenols could be conducted in high yield under relatively mild conditions.<sup>[7d]</sup> However, limitations still remain: little-to-no product was observed from the reactions of phenols with aryl halides that possess either strongly electron-withdrawing or electron-donating *ortho* substituents. Similarly, electron-deficient phenols were poor substrates. Additionally, the reaction of phenols that did not possess an *ortho* substituent at least as large as a methyl group were inefficient in most cases. The use, in many examples, of ligands that are neither commercially nor readily available further detracts from the utility of our previous method (compounds **2–4**, Scheme 1). These

limitations provoked us to further investigate and develop catalyst systems that would allow for the efficient coupling of problematic substrate combinations. Herein, we report the



Scheme 1. Biaryl ligands for carbon–heteroatom bond-forming reactions.

expansion of this methodology by overcoming the above-mentioned difficulties as well as the coupling of heteroaryl halides with phenols through the use of two new ligands.

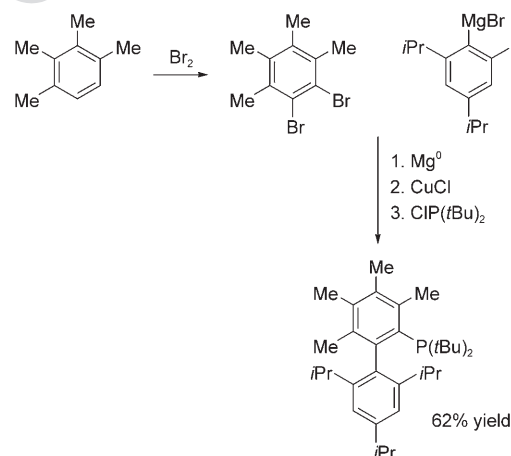
The success of our previous methodology was based on the use of electron-rich, bulky biaryl dialkyl phosphines **1–4** as ligands (Scheme 1).<sup>[7d]</sup> Continuing studies in this area have led to the discovery of structural derivatives of these ligands that generate catalyst systems with both a greater degree of activity and stability. We previously reported that 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos; **5**) is an excellent supporting ligand for Pd-catalyzed C–N and C–C bond-forming reactions.<sup>[8]</sup> During the course of these investigations, the use of 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (di-*t*BuXPhos; **6**), the more hindered counterpart of **5**, was examined. Whereas the reactivity of catalysts based upon **6** in C–N and C–C bond-forming processes was less than those based on **5**, we hypothesized that the increased size of **6** would prove beneficial in C–O bond-forming reactions.<sup>[9]</sup> Subsequently, we prepared and tested the more hindered analogue **7** in coupling reactions of aryl halides and phenols. The one-pot preparation of **7** proceeded in 62 % yield from 2,4,6-tri-isopropyl bromobenzene, 1,2-dibromo-3,4,5,6-tetramethylbenzene, and chloro(di-*tert*-butylphosphine) (Scheme 2).<sup>[10]</sup>

Initially, the reaction of a number of electron-deficient aryl halides with phenols with **6** as the supporting ligand was examined (Table 1). A variety of aryl bromides were coupled with a range of phenols in excellent yield. Common functional groups, including nitriles, aldehydes, ketones, esters, and trifluoromethyl groups, were tolerated under the reaction conditions employed. In contrast to previous results, good

[\*] Dr. C. H. Burgos, T. E. Barder, Dr. X. Huang, Prof. Dr. S. L. Buchwald  
Department of Chemistry  
Room 18-490, Massachusetts Institute of Technology  
Cambridge, MA 02139 (USA)  
Fax: (+1) 617-253-3297  
E-mail: sbuchwal@mit.edu

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**Scheme 2.** Synthesis of ligand **7**.

yields were observed with aryl halide substrates that possess electron-withdrawing groups in the *ortho* position (Table 1, entries 4–7). The exception to this outcome were reactions that involved 2-bromoacetophenone, which did not yield any product. Furthermore, whereas the coupling of electron-deficient phenols with aryl halides was problematic in previous reports (presumably because of the lower nucleophilicity of the corresponding phenolates), the use of a catalyst based upon **6** for these substrate combinations proved to be highly efficient. For example, we were able to couple methyl 4-hydroxybenzoate and 4-cyanophenol with 4-bromobenzonitrile and 4'-acetophenone, respectively, in high yield (Table 1, entries 1, 13, and 14).

**Table 1:** Pd-catalyzed C–O bond formation of electron-poor aryl halides with ligand **6**.<sup>[a]</sup>

Entry	Halide	Phenol	Product	Pd [mol %]	Yield [%] <sup>[b]</sup>
1				2	96
2				2	84
3				2	94
4				3	81 <sup>[c]</sup> 85 <sup>[c]</sup>
5				3	78 <sup>[c]</sup>
6				2	91
7				3	85 <sup>[c]</sup>
8				1	92
9				2	92
10				1	94
11				1	92
12				1	90
13				2	82
14				3	74 <sup>[c]</sup>

[a] Reaction conditions: aryl halide (1 equiv), phenol (1.2 equiv), K<sub>3</sub>PO<sub>4</sub> (2 equiv), **6** (3 mol %), toluene (0.3 M), 100°C, 5–24 h; reaction times not optimized. [b] Yields based upon an average of two runs. [c] Reaction run with 5 mol % of **6** at 110°C.

Next, we investigated reactions of electron-neutral and electron-rich aryl halides with various phenols. Catalyst systems based upon **6** were efficient in many cases; however,

certain combinations of substrates required the use of the more hindered ligand **7**. Table 2 illustrates that both electron-rich and electron-neutral aryl bromides and chlorides were

**Table 2:** Pd-catalyzed diaryl ether formation of electron-neutral and electron-rich aryl halides.<sup>[a]</sup>

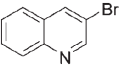

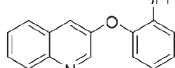
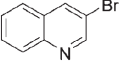

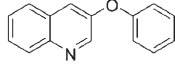
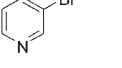

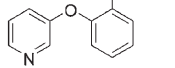
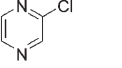

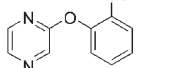
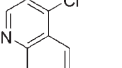

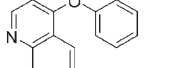
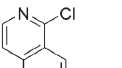

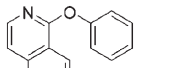
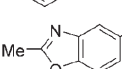

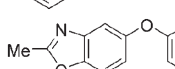
Entry	Halide	Phenol	Product	Ligand	Pd [mol %]	Yield [%] <sup>[b]</sup>
1				<b>6</b>	1	84
2				<b>6</b>	1	74
3				<b>6</b>	2	91
4				<b>6</b>	2	86
5				<b>7</b>	2	86
6				<b>6</b>	1	92
7				<b>6</b>	1	92
8				<b>6</b>	2	84
9				<b>7</b>	2	89
10				<b>7</b>	2	96
11				<b>7</b>	2	89
12				<b>7</b>	5	79
13				<b>6</b>	2	77 <sup>[c]</sup>
14				<b>7</b>	2	94
15				<b>6</b>	2	88
16				<b>7</b>	2	84
17				<b>6</b>	2	95
18				<b>8</b>	2	84

[a] Reaction conditions: aryl halide (1.0 equiv), phenol (1.2 equiv), K<sub>3</sub>PO<sub>4</sub> (2.0 equiv), ligand (3.0 mol%), toluene (0.3 M), 100 °C, 5–24 h; reactions times were not optimized. [b] Yields based upon an average of two runs. [c] Reaction run with 7.0 mol% of ligand **8** at 115 °C.

excellent substrates with either **6** or **7**. For example, the reaction of an electron-rich aryl chloride, 4-chloroanisole, with phenolic derivatives afforded the corresponding diaryl ethers in >80% yield (Table 2, entries 8 and 9). Of particular note, the reaction of *N*-(4-chlorophenyl)acetamide with phenol proceeded in 95% yield (Table 2, entry 17). To the best of our knowledge, there are no previous examples of the use of an aryl halide substrate bearing a secondary amide substituent in Pd-catalyzed diaryl ether synthesis. Additionally, we were able to couple an electron-deficient phenol, methyl 4-hydroxybenzoate, with an electron-neutral aryl bromide, 2-bromo-*p*-xylene, for the first time (Table 2, entry 13). However, more forcing conditions were required for this transformation: a reaction temperature of 115 °C and the use of 7 mol% of **6** and 5 mol% of Pd(OAc)<sub>2</sub>. Disappointingly, 2-bromoanisole could not be coupled with phenols when employing ligands **6** and **7**, although this substrate could be coupled with *o*-cresol in 89% yield (Table 2, entry 18) with a naphthyl-substituted ligand **8** (Scheme 1). Although this ligand was effective, it was synthesized in low yield by using a modification of the standard benzyne-coupling protocol. Currently, we do not have a convenient high-yielding synthetic route for preparation of **8**.

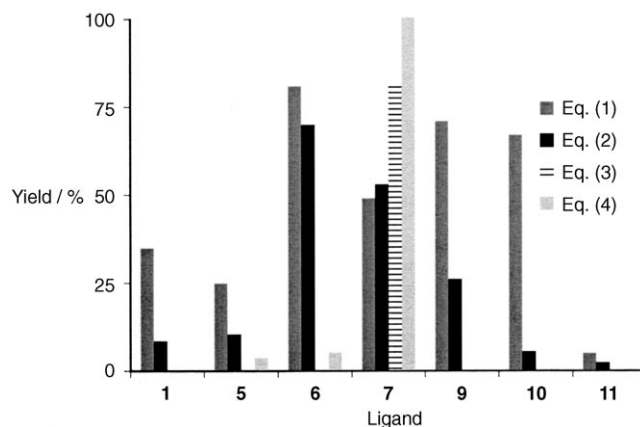
The cross-coupling reactions of halopyridines and haloquinolines with phenols was also explored. Using the standard protocol with **6** and **7**, we were able to obtain heteroaryl ethers in good-to-excellent yield (Table 3). The majority of reactions required only 2 mol% of Pd(OAc)<sub>2</sub>; however, two entries required higher catalyst loadings (Table 3, entries 2 and 3). Attempts to use 2- and 4-hydroxypyridine (that is, 2- and 4-pyridone) were entirely unsuccessful; neither C–O nor C–N bond formation was observed.

**Table 3:** Pd-catalyzed heteroaryl ether formation.<sup>[a]</sup>

Entry	Halide	Phenol	Product	Ligand	Pd [mol%]	Yield [%] <sup>[b]</sup>
1				<b>6</b>	2	90
2				<b>7</b>	4	75 <sup>[c]</sup>
3				<b>6</b>	8	88 <sup>[d]</sup>
4				<b>6</b>	2	87
5				<b>6</b>	2	86
6				<b>6</b>	2	90
7				<b>7</b>	2	91

[a] Reaction conditions: aryl halide (1.0 equiv), phenol (1.2 equiv), K<sub>3</sub>PO<sub>4</sub> (2.0 equiv), ligand (3.0 mol%), toluene (0.3 M), 100 °C, 24 h; reactions times were not optimized. [b] Yields based upon an average of two runs. [c] Reaction run with 6.0 mol% of ligand **7** at 115 °C. [d] Reaction run with 10.0 mol% of ligand **10** at 115 °C.

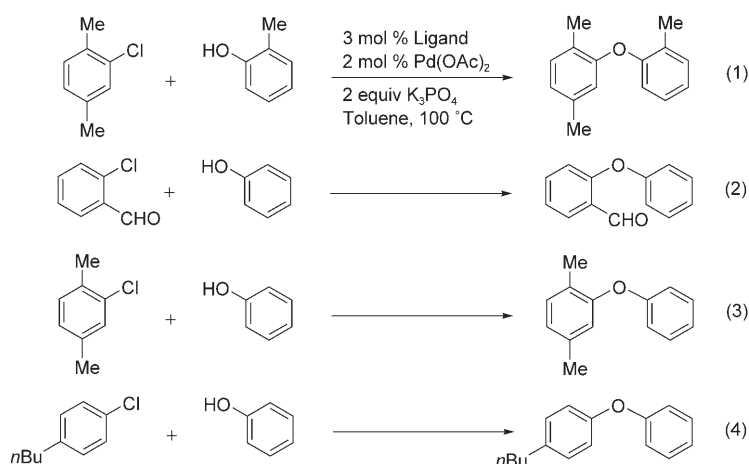
To identify structural features important for catalyst efficacy in Pd-catalyzed C–O bond-forming reactions, we undertook a structure–activity relationship study that employed various biaryl ligands (Figure 1). The four reactions



**Figure 1.** Illustration of the effects of various ligands on the four reactions in Scheme 3.

shown in Scheme 3 [Eq. (1)–(4)] were conducted under identical conditions using seven different biaryl phosphine ligands (**1**, **5**–**7**, and **9**–**11**). These particular reactions were selected because of their relevance to the limitations of previous processes (see below) and to determine features that contribute to the success of particular ligands.

Arbitrarily, we set the level of acceptable yield at 50% for the reactions in Scheme 3. Consequently, ligands **1**, **5**, and **11**



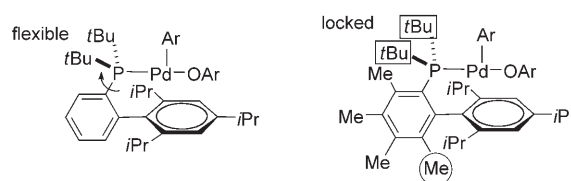
**Scheme 3.** Test reactions for comparison of ligands in Pd-catalyzed diaryl ether synthesis.

did not meet this requirement for any reaction in Scheme 3. For the coupling of chloro-*p*-xylene with *o*-cresol [Eq. (1)], four ligands (**6**, **7**, **9**, and **10**) were found to provide adequate results. This coupling is relatively easy and the data is consistent with previous reports with *ortho* alkyl-substituted phenols.<sup>[7d]</sup> However, the reaction of 2-chlorobenzaldehyde [Eq. (2)] with phenol was only found to be efficient with ligands **6** and **7**. Furthermore, the final two reactions in Scheme 3 [Eqs (3) and (4)] were catalyzed only with **7**, and a maximum of 10 % yield was observed with ligands other than **7**. The coupling of 2-chloro-*p*-xylene with phenol [Eq. (3)] was effective with previous ligands; however, the reaction required sodium phenoxide in conjunction with **2** (79 % yield). Pleasingly, the use of ligand **7** with a much weaker base, K<sub>3</sub>PO<sub>4</sub>, for this transformation affords an 88 % yield of *p*-xylyl phenyl ether. The use of similarly harsh conditions were required for the coupling of 4-*n*-butylchlorobenzene with phenol [Eq. (4)]; for example, the use of sodium phenoxide with **2** at 115 °C. Again, the application of **7** in this reaction allows for the use of K<sub>3</sub>PO<sub>4</sub> at 100 °C, with the product formed in a 96 % yield. Based upon these results, it is clear that **7** possess(es) some structural feature(s) that generate a catalyst capable of promoting reactions of aryl halides with phenol that no other biaryl ligand has been able to achieve.

We believe the efficacy of reactions with these ligands depends on three steric factors: the substituents at the phosphorous center, the *ortho* substituents on the bottom ring, and the substituents on the top ring. For example, ligand **1** possesses two *tert*-butyl groups and a biphenyl unit at the phosphorous center. Under the conditions examined, this ligand is ineffective for all the reactions in Scheme 3. Ligand **5** is similarly ineffective as there are two cyclohexyl groups at the phosphorous center and three isopropyl groups at the 2', 4', and 6' positions of the non-phosphine-containing ring of the ligand. It is believed this ligand is inefficient because the steric environment the cyclohexyl groups create directly around the phosphorous atom is relatively small. However, the combination of features in ligands **1** and **5** produce the much bulkier ligand **6**. Further increase in the size by addition of four methyl groups to the top ring of **6** yields **7**. Although **6**

is less substituted than **7**, its use provides better results than **7** in Equations (1) and (2). Presuming that reductive elimination is the rate-limiting step in the reactions in Scheme 3, it is possible that in Equations (1) and (2) the added bulk of **7** is unnecessary to aid the reductive elimination from the [LPd(OAr)Ar] (L = ligand) intermediate. Furthermore, formation of the [LPd(OAr)Ar] intermediate with ligand **7** in Equation (1) may be slow because of the more difficult attack of the larger *o*-cresol versus phenoxide anion [for Eqs (3) and (4)] onto the [LPd(Ar)X] intermediate. However, once the [LPd(OAr)Ar] intermediate is formed, the inclusion of a greater degree of bulk (that is, the use of ligand **7**) can lead to a significantly enhanced rate of reductive elimination.

An addendum to this theory involves the requirement of permethylation of the top ring (the phosphine-containing ring) for certain reactions. It still remains difficult to understand the large influence of the methyl groups in the tetramethylated ring in **7**. It does not seem that the methyl groups increase the size of the ligand to such an extent that the reactivity is altered from minimal (for **6**) to excellent (for **7**) as it is in the last two reactions in Scheme 3. Therefore, it seems possible that the permethylated top ring may play another role in these reactions, namely, the methyl groups on **7** may “lock” the ligand into a certain conformation so that the methyl group *ortho* to the phosphorous center may act as a physical divide between the two *tert*-butyl groups (by locking them into a certain conformation). If this is the case, it is likely that the *tert*-butyl groups would be forced forward toward the Pd center, thereby ensuring that their influence is felt on the aryl and aryloxy units bound to the palladium center (Scheme 4). Additionally, the circled methyl group may instill



**Scheme 4.** Possible influences of methyl groups and lack thereof on **6** and **7**.

further conformational rigidity in the catalyst. We believe it is important for reductive elimination to occur rapidly, thereby minimizing the ability of the likely unstable [LPd(OAr)Ar] species to decompose or enter an alternate reaction manifold not leading toward the product. Further work is ongoing in our laboratories to determine the effects these various structural aspects of these bulky ligands on C–O bond-forming processes.

In summary, we have improved the scope and generality of Pd-catalyzed diaryl ether formation. This system allows the coupling of electron-deficient aryl halides almost without any restrictions. Additionally, we expanded this method to the cross-coupling reaction of halopyridines and quinolines. A



structure–activity relationship study suggests the ligand bulk plays an important role in C–O bond-forming reactions possibly through instilling conformational rigidity in intermediates within the catalytic cycle.

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