Novel Electron-Rich Bulky Phosphine Ligands Facilitate the Palladium-Catalyzed Preparation of Diaryl Ethers

Attila Aranyos, David W. Old, Ayumu Kiyomori, John P. Wolfe, Joseph P. Sadighi, and Stephen L. Buchwald*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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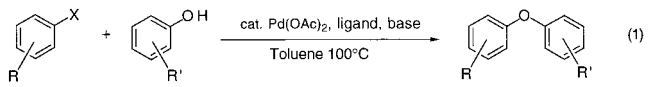
Abstract: A general method for the palladium-catalyzed formation of diaryl ethers is described. Electron-rich, bulky aryldialkylphosphine ligands, in which the two alkyl groups are either *tert*-butyl or 1-adamantyl, are the key to the success of the transformation. A wide range of electron-deficient, electronically neutral and electron-rich aryl bromides, chlorides, and triflates can be combined with a variety of phenols with the use of sodium hydride or potassium phosphate as base in toluene at 100 °C. The bulky yet basic nature of the phosphine ligand is thought to be responsible for increasing the rate of reductive elimination of the diaryl ether from palladium.

Introduction

A variety of naturally occurring and medicinally important compounds contain a diaryl ether moiety.[1] Of the methods used for the preparation of diaryl ethers, the classic Ullmann ether synthesis is the most important, but it is often limited by the need to employ harsh reaction conditions and stoichiometric amounts of copper.[2] While a number of interesting and useful techniques for diaryl ether formation have been reported in recent years,[3] a need for general methods for their preparation remains. Recently, we reported a general copper-catalyzed preparation of diaryl ethers which constitutes a significant improvement to the Ullmann ether synthesis.[4] The use of palladium catalysis for the combination of phenols and aryl halides or sulfonates is a desirable extension of other recently reported carbon−heteroatom bond-forming techniques.[5,6] This procedure has been demonstrated,[7] but the scope of the reported process was limited to the reaction of electron-deficient aryl bromides. Moreover, the procedures usually required the use of the sodium salt of the phenol and in most cases the yields were only moderate.

Herein we report that a wide range of electron-deficient, electronically neutral and electron-rich aryl halides and sulfonates can be combined with a variety of phenols by using palladium catalysis, representing a substantial improvement in generality and utility of these couplings (eq 1). Critical to the



(1)

success of the method is the use of electron-rich, sterically bulky aryldialkylphosphines as ligands.[8] Specifically, only the use of catalyst systems with ligands containing a phosphorus center substituted with two *tert*-butyl or 1-adamantyl groups effects efficiently the desired transformation.

Results and Discussion

We recently reported that 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl (**1**) (Figure 1) serves as an excellent ligand for the palladium-catalyzed amination of aryl halides and for room-temperature Suzuki coupling reactions of aryl chlorides and bromides.[8e] Our results demonstrated that room-temperature

(1) For examples of medicinally important diaryl ethers, see: (a) Evans, D. A., DeVries, K. M. In *Glycopeptide Antibiotics, Drugs and the Pharmaceutical Sciences*; Nagarajan, R., Ed.; Marcel Decker, Inc.: New York, 1994; Vol. 63, pp 63−104. (b) Deshpande, V. E.; Gohkhale, N. J. *Tetrahedron Lett.* **1992**, *33*, 4213−4216. (c) Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1990**, *55*, 2797−2800. (d) Pettit, G. R.; Singh, S. B.; Niven, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 8539−8540. (e) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909−4913. (f) Atkinson, D. C.; Godfrey, K. E.; Myers, P. L.; Philips, N. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1983**, *26*, 1361−1364; For examples of agriculturally important diaryl ethers, see: (g) Seldon, R. A. *Chirotechnology*; Marcel Dekker Inc.: New York, 1998; pp 62−65.

(2) (a) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853−854. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (c) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679−689.

(3) For examples of recent work in diaryl ether formation, see: (a) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, 2937−2940. (b) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J. *J. Org. Chem.* **1998**, *63*, 6338−6343. (c) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488−6495. (d) Palomo, C.; Oairbide, M.; López, R.; Gómez-Bengoa, E. *Chem. Commun.* **1998**, *19*, 2091−2092. (e) Beugelmans, R.; Zhu, J.; Husson, N.; Bois-Choussy, M.; Singh, G. P. *Chem. Commun.* **1994**, 439−440.

(4) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540.

(5) For reviews, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Hartwig, J. F. *Synlett* **1997**, 329−340. (d) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.*, in press.

(6) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333−10334. (b) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (c) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *67*, 5413−5418. (d) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110.

(7) (a) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005−8008. (b) Doye, S.; Buchwald, S. L., unpublished Results.

(8) For other examples of bulky, electron-rich ligands for Pd-catalyzed carbon−heteroatom bond forming reactions, see: (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Yamamoto, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (c) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1998**, *39*, 617−620. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (e) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.

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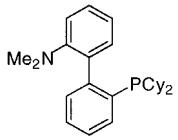
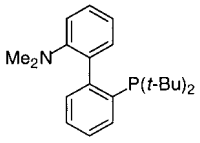


1

Figure 1.

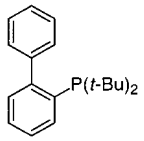


2

Figure 2.

oxidative addition of aryl chlorides to palladium centers can be achieved by using simple electron-rich phosphines.[9,10] Our findings suggested that when this new ligand was used, the rate-limiting step in the catalytic cycle of a cross-coupling process may be shifted from oxidative addition of the aryl halide to a Pd(0) complex to either Pd−N bond formation or the reductive elimination leading to the C−N bond formation.

In our initial studies to extend these results to find improved catalysts for carbon−oxygen bond formation, we sought to utilize **1** for the combination of NaO*t*-Bu and 2-chloro-*p*-xylene to afford the corresponding *tert*-butyl ether. Unfortunately, our efforts were met with little success. We reasoned that the problem was due to the recalcitrant nature of the C−O bond reductive elimination from the Pd center.[6d,11] This was predicated on previous studies which suggested that in Pd-catalyzed carbon−oxygen bond-forming reactions, the rate-limiting step most likely involves the formation of the carbon−oxygen bond via reductive elimination.[6c−d,7a,11] It is known that increasing the steric bulk of ligands can facilitate reductive elimination processes.[12] We felt that by increasing the size of the dialkylphosphino group, the desired transformation might be induced to occur.[13] With this in mind, we prepared **2** (Figure 2) from 2-bromo-2′-dimethylaminobiphenyl[8e] and commercially available di-*tert*-butylchlorophosphine.[14] Attempts to prepare **2** using the same conditions developed for the synthesis of **1** (1.1 equiv *n*-BuLi, THF, −78 °C → rt) were unsuccessful. We found, however, that switching to diethyl ether as the solvent gave **2**

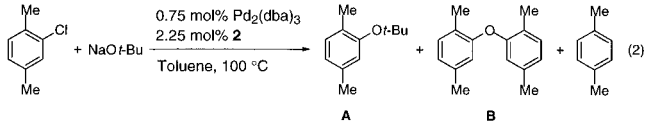


3

Figure 3.

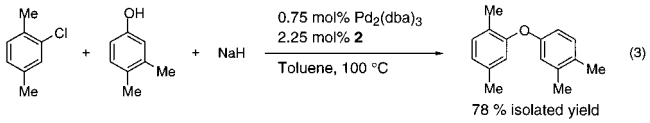
in moderate yield. The reaction of the in situ generated aryllithium reagent with di-*tert*-butylchlorophosphine is quite slow, and we believe that the stability of the aryllithium reagent in ether relative to THF[15] is the key to the success of the increased yield of **2**.

We initially examined the use of **2** in the reaction of 2-chloro-*p*-xylene and sodium *t*-butoxide (eq 2). We were surprised to



(2)

find in addition to the expected product **A**, that 19% (uncorrected GC yield) of diaryl ether **B** was formed. This result encouraged us to explore the use of **2** in coupling reactions to form diaryl ethers. In fact, we found that a smooth reaction of 2-chloro-*p*-xylene and 3,4-dimethylphenol using 1.5 mol % Pd(0) and 2.25 mol % **2** occurred in the presence of sodium hydride in toluene at 100 °C to give the desired diaryl ether in 78% isolated yield (eq 3).



(3)

This result led us to undertake a survey of reaction variables to ascertain the optimum conditions for the transformation. We found that $Pd(OAc)_2$ and $Pd_2(dba)_3$ catalyzed these reactions with comparable efficiency. While in many instances sodium hydride proved to be a suitable base, its use required preheating it with the phenol prior to the addition of the other reaction components.[16] This somewhat tedious protocol led us to examine alternative bases for the coupling reaction. Screening a variety of bases, we found that CsF and K_3PO_4 were both effective for diaryl ether formation. With respect to the reaction rate, yield, and cost, K_3PO_4 is clearly superior to CsF. Other bases, including Cs_2CO_3, K_2CO_3, KF, and *n*-BuLi were much less efficient for the process. Comparing K_3PO_4 and sodium hydride revealed that reactions with K_3PO_4 are significantly slower but often more efficient than those which use sodium hydride in terms of both the product distribution and the yield. We found that toluene was the only solvent in which the reaction was efficient; THF, DME, dioxane, and NMP provided the product in less than 5% yield.

As a control experiment we prepared 2-(di-*tert*-butylphosphino)biphenyl (**3**) (Figure 3) and were surprised and pleased to find that it is equally efficient in the transformation shown in eq 3, providing the desired diaryl ether product in 77%

(9) Typically, oxidative addition of aryl chlorides to Pd(0) requires temperatures of 60−140 °C. (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Herrmann, W. A.; Brossmer, C.; Priermeier, T.; Öfele, K. *J. Organomet. Chem.* **1994**, *481*, 97−108. (c) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360−2366. (d) Huser, M.; Youinou, M.-T.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1989**, *28*, 1386−1388.

(10) (a) It is well-known that the use of electron-rich phosphine ligands accelerates the rate of oxidative addition of aryl halides to Pd(0). See: Spessard, G. O.; Meissler, G. L. *Organometallic Chemistry*; Prentice Hall: Upper Saddle River, New Jersey, 1996; pp 171−175. (b) In his pioneering studies, Milstein demonstrated oxidative addition of aryl chlorides to Pd(dippp)$_2$ (dippp = 1,3-bis(diisopropylphosphino)propane) at 38 °C. Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665−1673.

(11) (a) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163−1188. (b) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787−6795. (c) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504−6511. (d) Hillhouse has reported C−O bond forming reductive elimination from nickel complexes. Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135−8136.

(12) (a) Jones, W. D.; Kuykendall, V. L. *Inorg. Chem.* **1991**, *30*, 2615−2622. (b) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626−3633.

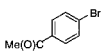
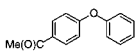
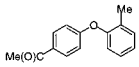
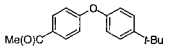
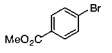
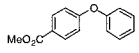
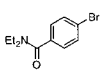
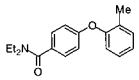
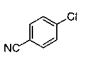
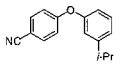
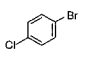
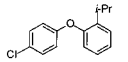
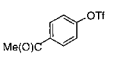
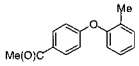
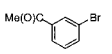
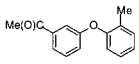
(13) We have previously speculated that improved results in Pd-catalyzed aryl C−O bond forming reactions might be obtained with the use of bulky, electron-deficient, chelating phosphine ligands; see ref 6b.

(14) Di-*tert*-butylchlorophosphine is the bulkiest dialkylchlorophosphine which is commercially available.

(15) Schlosser, M. in *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley and Sons: Chichester, 1994; pp 129−133.

(16) Premixing of sodium hydride and the phenol is required to avoid palladium-catalyzed hyride reduction of the aryl halide; Pd-catalyzed reduction of vinyl triflates by LiH and KH has been previously observed: Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

Table 1. Diaryl Ether Formation from Electron-Deficient Aryl Halides Using 3/Pd[a]

entry	halide	phenol	product	base	yield (%)
1				K_3PO_4	94
2				K_3PO_4	96 (95)[b]
3				K_3PO_4	93
4				K_3PO_4	89
5[c]				NaH	85
6				K_3PO_4	91
7[d]				K_3PO_4	88
8				K_3PO_4	84
9				K_3PO_4	74

[a] Reaction conditions: 1.0 equiv aryl halide, 1.2 equiv phenol, 1.4 equiv NaH or 2.0 equiv K_3PO_4, 2.0 mol % $Pd(OAc)_2$, 3.0 mol % **3**, toluene (3 mL), 100 °C, 14−24 h; reaction times were not optimized. [b] Reaction run with 0.1 mol % $Pd(OAc)_2$, 0.15 mol % **3**. [c] Reaction run with 5.0 mol % $Pd(OAc)_2$, 7.5 mol % **3**. [d] Reaction run with 1.95 equiv 2-isopropylphenol.

isolated yield.[17] While preparation of **2** requires a multistep sequence, **3** can be obtained in one step from commercially available 2-bromobiphenyl and di-*tert*-butylchlorophosphine. Further study showed that this ligand is quite effective in a wide range of palladium-catalyzed diaryl ether-forming reactions.

Synthesis of Diaryl Ethers from Phenols and Electron-Poor Aryl Halides and Triflates. In our examination of the use of **3** for the combination of electron-poor aryl halides with a variety of phenols, we found that aryl halides or triflates substituted in the para position with electron-withdrawing groups can be coupled with a wide variety of phenols to give the desired product in good to excellent yields (see Table 1). The fact that these activated aryl halides are particularly good substrates is consistent with the results of our previous mechanistic study in which we showed that the presence of para electron-withdrawing groups allow the delocalization of the negative charge which may build up in the transition state of the reductive elimination of the diaryl ether from an intermediate $L_2Pd(OAr)Ar'$ [L_2 = chelating phosphine] complex.[11c] The results are also in line with Hartwig's previous findings in the palladium-catalyzed formation of diaryl ethers[7a] and other carbon−heteroatom bond-forming processes.[5d,25] With 4-bromoacetophenone, use of as little as 0.1 mol % Pd was effective; the diaryl ether product was obtained in 95% yield (Table 1, entry 2).[18] Electron-deficient aryl chlorides are also good substrates; the combination of 4-chlorobenzonitrile with 3-isopropylphenol afforded a 91% yield of the desired product (Table 1, entry 6). Most impressive is that 4-chlorobromobenzene, while only slightly electron-deficient, could be combined with 2-isopropylphenol to give the corresponding diaryl ether in 88% yield; the product results from chemoselective substitution of the bromide substituent (Table 1, entry 7).

In terms of the phenol component of the reaction, the use of substrates bearing an ortho alkyl substituent (e.g., *o*-cresol and 2-isopropylphenol) were found to give the highest yields. In the reactions of aryl halides which contain a more weakly electron-withdrawing group on the aromatic ring, only reactions with ortho-substituted phenols are high yielding. The coupling of *N*,*N*-diethyl 4-bromobenzamide with *o*-cresol is one such case (Table 1, entry 5). This example is particularly significant because copper-mediated procedures with *N*,*N*-diethyl 4-bromobenzamide fail to yield the desired coupling product.[4]

The reactions of aryl halides having an electron-withdrawing group in the ortho position (e.g., 2-bromoacetophenone and 2-bromobenzonitrile) gave low yields of the desired product with the present catalyst system.[19] At present we have no explanation for these results. The search for a catalyst which will effect these transformations is currently underway in our laboratories.

Synthesis of Diaryl Ethers from Phenols and Electronically Neutral or Electron-Rich Aryl Halides and Triflates. We have also examined the reactions of electronically neutral and electron-rich aryl halides and sulfonates in the palladium-catalyzed diaryl ether-forming reaction using **3** and related (vide infra) ligands. These classes of aryl halides were poor, or in a few cases moderately good substrates in previously reported palladium-catalyzed C−O bond-forming processes.[6,7a] A variety of aryl halides which are unsubstituted at the ortho position are efficiently coupled with a diverse set of phenols using the simple monodentate ligand **3** (Table 2, entries 3−6, 14). Consistent with our results with activated halides, reactions of ortho-substituted phenols with unactivated halides give the highest yields (e.g., Table 2, entries 5−6, 13−14). There are, however, several cases in which ligand **3** is ineffective or affords the desired product in reduced yields. Continuing our search for improved ligands for the synthesis of diaryl ethers, we prepared and evaluated the use of ligands **4**−**6** in cases for which the use of **3** was unsatisfactory (Scheme 1).

We were pleased to find that binaphthyl ligand **4** was quite effective for the processing of electronically neutral ortho-substituted aryl halides with phenols of several different substitution patterns (Table 2, entries 1, 8−10). In reactions involving these ortho-substituted aryl halides, **4** is generally more efficient than **3**.[20]

There are several other difficult cases in which procedures employing **3** and **4** are not satisfactory. For instance, the coupling of an aryl halide lacking an ortho substituent with phenol does not proceed to completion using ligands **3** or **4**. However, using terphenyl ligand **5**, combining 5-bromo-*m*-xylene and phenol afforded the corresponding diaryl ether in 83% yield (Table 2, entry 2). This ligand was also quite effective in a number of other cases (Table 2, entries 12, 15−16). Ligands **3**, **4**, and **5**, unfortunately, are not effective in the reactions of highly electron-rich aryl chlorides (e.g., 4-chloroanisole). For these transformations, only ligand **6** has been shown to give synthetically useful yields. The 1-adamantyl group was chosen since it occupies a greater volume of space and hence is bulkier than a *tert*-butyl group. We believe that this is the key to the success of **6** in these reactions; 4-chloroanisole and *o*-cresol

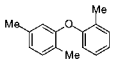
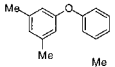
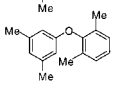
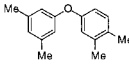
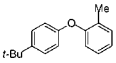
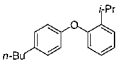
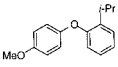
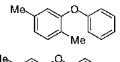
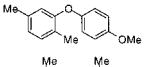
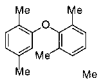
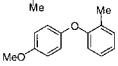
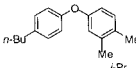
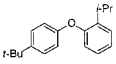
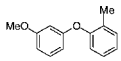
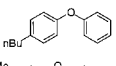
(17) Previously[8e] we employed dicylclohexylphenylphosphine in a control reaction due the commercial availability of this compound.

(18) Control experiments were carried out in the absence of a palladium salt. For the reaction of 4-bromoacetophenone and phenol with potassium phosphate in toluene at 100 °C, none of the desired product was detected; in DMF at 100 °C, 32% (GC, corrected) of the starting halide was consumed, and a 5% GC yield of the desired product was observed.

(19) An exception is the reaction of 2-bromobenzotrifluoride and *o*-cresol to provide the corresponding diaryl ether in 75% isolated yield; the reaction of 2-bromoacetophenone and *o*-cresol proceeded to 25% conversion (GC) with ligand **4**, affording <20% of the desired product.

(20) Yields are typically 15−20% higher, and improved product/arene ratio is observed.

Table 2. Palladium-Catalyzed Diaryl Ether Formation from Electronically Neutral and Electron-Rich Aryl Halides[a]

entry	halide	phenol	product	base	ligand	yield (%)
1				K_3PO_4	4	95
2				K_3PO_4	5	83
3				NaH	3	74
4				NaH	3	83
5				K_3PO_4	3	85
6				K_3PO_4	3	92
7				K_3PO_4	6	87
8				NaH	4	79
9[b]				--	4	92
10[c]				--	4	87
11				K_3PO_4	6	73
12				NaH	5	76
13				K_3PO_4	3	84
14				K_3PO_4	3	87
15[d]				NaH	5	61
16				NaH	5	88

[a] Reaction conditions: 1.0 equiv aryl halide, 1.2 equiv phenol, 1.4 equiv NaH or 2.0 equiv K_3PO_4, 2.0 mol % $Pd(OAc)_2$, 3.0 mol % ligand, toluene (3 mL), 100 °C, 14−26 h; reaction times were not optimized. [b] 1.2 equiv of the phenolate salt was used, 110 °C. [c] 1.2 equiv of the phenolate salt was used, 1.25 mol % $Pd_2(dba)_3$, 3.75 mol % **4**, toluene (2 mL), 115 °C. [d] 4.0 mol % $Pd(OAc)_2$, 6.0 mol % **5**, 2.0 equiv phenol, 2.2 equiv NaH, 115 °C.

Scheme 1. New Ligands for Diaryl Ether Formation

4 **5** **6**

are converted to the desired product in 73% yield using **6** (Table 2, entry 11), a significantly higher yield than when **3**, **4**, or **5** were employed.

Discussion

Our proposed catalytic cycle for diaryl ether formation is similar to that proposed for other palladium-catalyzed carbon−carbon and carbon−heteroatom bond-forming processes.[5,6,7a] The catalytic cycle consists of three distinct stages: (1) oxidative addition of the aryl halide to $L_nPd(0)$, (2) formation of the Pd−aryloxide complex from the Pd−halide adduct via transmetalation of a metal phenolate, and (3) reductive elimination of the diaryl ether product with concomitant regeneration of the active $L_nPd(0)$ species. While the oxidative addition and transmetalation may be expected to be relatively facile,[21] the reductive elimination to form the C−O bond is disfavored due to the Pd−C (LUMO) and Pd−O (HOMO) energy gap[22] (Scheme 2).

Scheme 2. Proposed Catalytic Cycle

The palladium-catalyzed diaryl ether-forming reactions require only a slight excess of ligand to palladium, and reactions in which the ratio of L/Pd was varied from 1/1 to 1.5/1 to 2/1 gave similar results. This provides circumstantial evidence that the key intermediates in the catalytic cycle are monophosphine palladium complexes.[23] Mechanistic studies by Hartwig of carbon−nitrogen bond-forming reactions catalyzed by palladium complexes with bulky triarylphosphine ligands demonstrated that the key intermediates in the catalytic cycle were monophosphine palladium complexes.[5b−c,24]

While the exact mechanism(s) for the key reductive elimination step remains unknown, we have previously developed several mechanistic hypotheses for related processes which can be used to account for the observed results. For electron-deficient aryl halides, we still favor a mechanism involving transfer of the phenolate from palladium to the ipso carbon of the aryl halide to form a zwitterionic intermediate which converts to the diaryl ether and a palladium(0) complex.[7a,11c,25] For electronically neutral and electron-rich aryl halides, however, we suggest that a different mechanism for reductive elimination to form the carbon−oxygen bond most likely involves a three-centered transition state.[11c] In these cases, the bulkier ligands are necessary to destabilize the ground state of the LnPd(OAr)-

(21) (a) Oxidative addition is presumed to be facile based on the utility of **1** in Suzuki couplings at room-temperature; see ref 8e; (b) transmetalation of alkali metal alkoxides to $L_nPd(Ar)X$ complexes has been shown to occur at room temperature when L = BINAP or DPPF.; see ref 6d, 11b−c.

(22) Bäckvall, J. E.; Björkman, E. E.; Petterson, L.; Siegbahn, P. *J. Am. Chem. Soc.* **1984**, *106*, 4369−4373.

(23) We cannot rule out a situation where not all of the palladium is ligated in the reaction mixture and the reactions are proceeding through bis(phosphine) intermediates.

(24) (a) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373−5374. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970. (c) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598−11599. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708−4709. (e) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794−2805.

(25) Hartwig has proposed a similar mechanism to account for electronic effects in C−S and C−N bond forming reductive elimination reactions. (a) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937−2938. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232−8245.

Ar′ complex, forcing the palladium-bound aryl and aryloxy groups closer together. In this way, the complex is distorted toward the three-centered transition state.[26]

It is informative to compare the results reported here with the reaction of the approximately isosteric primary aniline with the same substrates. The latter processes (using appropriate ligands) are substantially more general and appear to be essentially insensitive to the size or the electronic nature of the substituents on either substrate.[5,27] The rate of reductive elimination to form C−O bonds is significantly slower than the corresponding rate to form C−N bonds.[6d,7a] We speculate that the relatively sluggish rate of this process in the C−O bond-forming reactions, even with ligands (e.g., **3**−**6**) which give improved results, is the reason for the discrepancy between the efficiencies of the diaryl ether- and diarylamine-forming processes.

What is more complicated is the unraveling of the various factors which contribute to make some of these reactions so facile, while others are inefficient or give none of the desired product. It is clear that ortho substitution in either the phenol or the aryl halide is beneficial to the success of the reaction. There are many possible explanations for this observation, including enhanced steric interaction of the aryl group(s) with the bulky ligands or improved solubility of key intermediate complexes.[28] While we have significantly expanded the scope of palladium-catalyzed diaryl ether formation, it is not obvious to us, for example, why the presence of ortho electron-withdrawing group on the aryl halide should decrease the efficiency of the process. Additionally, aryl halides bearing a strongly electron-donating group at the ortho position (e.g., 2-bromoanisole, which is a good substrate for related amination reactions)[5,27] and electron-deficient phenols (e.g., 4-hydroxyacetophenone) do not give good results in these coupling reactions.

Conclusion

The current procedure enhances the utility of palladium-catalyzed coupling reactions of phenols with aryl halides in several respects.[7a] These include: (1) for most substrate combinations, the use of preformed sodium phenolates is obviated; (2) the reactions are, in general, more efficient with respect to quantity of catalyst required and the yields obtained; (3) a much wider range of substrates can be utilized including electron-rich and electronically neutral aryl halides and triflates; (4) a higher level of functional group compatibility can be realized. For example, aryl halides containing simple esters or enolizable ketones are now tolerated. Moreover, *o*-substituted phenols, even those with a bulky substituent, are excellent substrates; (5) only 2 mol % $Pd(OAc)_2$ and 3 mol % ligand is required as the catalyst and in special cases a level as low as 0.1 mol % was effective; (6) the mild and inexpensive base K_3PO_4 is effective in a large majority of these reactions; and (7) inexpensive and readily available aryl chlorides may be used as substrates. We are currently working to improve the scope and generality of palladium-catalyzed diaryl ether formation. We anticipate that existing difficulties will be overcome through the development of new palladium catalyst systems. These efforts and their application to organic synthesis will be reported in due course.

Experimental Section

General. All reactions were performed under argon in oven- or flame-dried glassware. Toluene was distilled under nitrogen from molten sodium. Ethyl ether and THF were distilled under argon from sodium benzophenone ketyl. Reagents were purchased from commercial sources and were used without further purification, unless otherwise noted. Tribasic potassium phosphate was purchased from Fluka Chemical Company. Tetrakis(triphenylphosphine)palladium, palladium acetate, tris(dibenzylideneacetone)dipalladium(0), and 2,2′-dibromo-1,1′-binaphthyl were purchased from Strem Chemicals, Inc. 2-Bromobiphenyl was purchased from Lancaster Synthesis Inc. Di-*tert*-butylchlorophosphine was purchased from either Aldrich Chemical Co. or Strem Chemicals, Inc. Solutions of *tert*-butyllithium were purchased from Aldrich Chemical Co. Sodium salts of phenols were prepared using a slight excess of sodium metal in refluxing THF.[29] Elemental analyses were performed by E & R Microanalytical Laboratory Inc., Parsippany, NJ. IR spectra were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR in situ IR instrument. Yields in the tables refer to isolated yields (average of at least two runs) of compounds which are ≥95% pure as determined by ^{1}H NMR and GC analysis, or combustion analysis. The products of entries 1,[30,31] 3,[30] and 4[32] from Table 1, and entries 1,[4] 4,[4] and 16[4] from Table 2 have been described in the literature and were characterized by comparison of their ^{1}H NMR spectra to the previously reported data; their purity was confirmed by GC analysis. The procedures described in this section are representative; thus, the yields may differ slightly from those given in Tables 1 and 2.

Ligand Syntheses. 2-(*N*,*N*-Dimethylamino)-2′-di-*tert*-butylphosphinobiphenyl (2). An oven-dried Schlenk tube was purged with argon and charged with 2-(*N*,*N*-dimethylamino)-2′-bromobiphenyl[8e] (1.104 g, 4.0 mmol). The tube was purged with argon and ether (18 mL) was added via syringe. The resulting solution was cooled to −78 °C and *n*-butyllithium in hexanes (1.6 M, 2.75 mL, 4.4 mmol) was added dropwise with stirring. The mixture was stirred at −78 °C for 30 min, then warmed to 0 °C. Di-*tert*-butylchlorophosphine (0.96 mL, 5.0 mmol) was added via syringe, and the mixture was allowed to slowly warm to room temperature overnight (17 h). The mixture was quenched with saturated aqueous ammonium chloride (10 mL), diluted with ether (40 mL), and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (1 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting oil was taken up in a small amount of hot methanol (ca. 10 mL), the bottom of the flask was scratched with a spatula, and crystallization was allowed to occur slowly in a −20 °C freezer. The resulting crystals were washed with cold methanol and dried under vacuum to afford 683 mg (50%) of a white solid, mp 116−117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.75 (m, 1H), 7.40−7.26 (m, 4H), 7.00−6.90 (m, 3H), 2.44 (s, 6H), 1.26 (d, 9H, J = 11.4 Hz), 0.90 (d, 9H, J = 11.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.3; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.53, 151.5, 150.3, 149.8, 137.1, 137.0, 136.9, 136.7, 135.6, 135.5, 132.7, 131.0, 130.9, 128.7, 127.8, 125.2, 120.9, 117.4, 43.2, 33.4, 33.1, 31.5, 31.3, 31.1, 30.0, 29.8 (observed complexity due to P−C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2941, 1416, 947, 745. Anal. Calcd for $C_{22}H_{32}NP$: C, 77.38; H, 9.45. Found: C, 77.16; H, 9.56.

2-(Di-*tert*-butylphosphino)biphenyl (3). An oven dried round-bottomed flask equipped with a magnetic stirbar and a rubber septum was allowed to cool to room temperature under an argon purge. The flask was charged with magnesium turnings (617 mg, 25.4 mmol) and a small crystal of iodine. The flask was purged with argon and a solution of 2-bromobiphenyl (5.38 g, 23.1 mmol) in THF (40 mL) was added. The mixture was heated to reflux with stirring for 2 h and then allowed to cool to room temperature. The septum was removed, and anhydrous copper(I) chloride (2.40 g, 24.2 mmol) was added. The flask was capped with the septum and purged with argon for 2 min. Di-*tert*-butylchlo-

(26) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249−259.
(27) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327−5330.
(28) We thank Dr. Joseph Fox for this suggestion.
(29) Brandt, K. *J. Org. Chem.* **1981**, *46*, 1918−1920.
(30) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, 63−68.
(31) This compound is also available from Aldrich Chemical Co.
(32) Haga, N., Takayanagi, H. *J. Org. Chem.* **1996**, *61*, 735−745.

rophosphine (5.0 g, 27.7 mmol) was added via syringe, and the mixture was heated to reflux with stirring for 8 h. The mixture was cooled to room temperature and diluted with 1:1 hexanes/ether (200 mL). The resulting suspension was filtered, and the solids were washed with hexanes (60 mL). The solid material was transferred to a flask containing 1:1 hexane/ethyl acetate (150 mL), and water (100 mL) and 30% aqueous ammonium hydroxide (60 mL) were added. The resulting slurry was stirred at room temperature for 5 min and then transferred to a separatory funnel. The layers were separated, and the organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting solid was recrystallized from methanol (2 crops of crystals were collected) to afford 4.46 g (67%) of a white solid, mp 86−86.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.85 (m, 1H), 7.40−7.21 (m, 8H), 1.15 (d, 18H, J = 11.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.7; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 150.9, 143.6, 143.5, 135.6, 135.2, 135.0, 130.5, 130.4, 130.1, 128.3, 127.0, 126.7, 126.5, 126.2, 126.0, 125.6, 32.7, 32.4, 30.8, 30.6 (observed complexity due to P−C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2956, 1459, 1362, 1173. Anal. Calcd for $C_{20}H_{27}P$: C, 80.50; H, 9.12. Found: C, 80.67; H, 9.36.

2-*N*,*N*-Dimethylamino-2′-di-*tert*-butylphosphino-1,1′-binaphthyl (4). An oven-dried round-bottomed flask was purged with argon and charged with 2,2′-dibromo-1,1′-binaphthyl (5.0 g, 12.1 mmol), benzophenone imine (2.90 g, 15.7 mmol), NaO*t*-Bu (1.70 g, 18.0 mmol), $Pd_2(dba)_3$ (110 mg, 0.12 mmol), 2,2′-bis(diphenylphosphino)-1,1′-diphenyl ether[33] (129 mg, 0.24 mmol), and toluene (50 mL). The flask was fitted with a reflux condenser, the mixture was stirred for 18 h at 100 °C and then cooled to room temperature, and two-thirds of the solvent was removed under reduced pressure. Ethanol (25 mL) and water (3 mL) were added to the resulting mixture. The yellow crystals were collected on a Büchner funnel and washed with ethanol (10 mL) to afford 5.7 g (92%) of crude 2-(diphenyl-methylene-amino)-2′-bromo-1,1′-binaphthyl which was used in the following reaction without further purification.

The crude imine (3.0 g, 5.9 mmol) was suspended in dichloromethane (100 mL) in a round-bottomed flask. Concentrated hydrochloric acid (1.5 mL, 17.6 mmol) was added to the suspension which became homogeneous within 15 min. The reaction mixture was stirred for 18 h at room temperature during which time a precipitate formed. The mixture was then treated with 1 M NaOH (25 mL), and the layers were separated. The aqueous layer was extracted with additional dichloromethane (10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was then purified by flash chromatography on silica gel to give 1.5 g (73%) of 2-amino-2′-bromo-1,1′-binaphthyl as colorless crystals.

A round-bottomed flask was charged with 2-amino-2′-bromo-1,1′-binaphthyl (480 mg, 1.4 mmol), iodomethane (0.25 mL, 4.2 mmol), sodium carbonate (318 mg, 3.0 mmol), and DMF (8 mL) and then purged with argon. The mixture was heated to 50 °C and stirred until the starting material had been completely consumed. The reaction mixture was diluted with ether (5 mL) and water (1 mL) and then passed through a plug of silica gel. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 473 mg (91%) of 2-*N*,*N*-(dimethylamino)-2′-bromo-1,1′-binaphthyl as colorless crystals.

An oven-dried round-bottomed flask was charged with 2-*N*,*N*-(dimethylamino)-2′-bromo-1,1′-binaphthyl (376 mg, 1.0 mmol) and purged with argon. DME (5 mL) was added, the resulting solution was cooled to 0 °C, and then *tert*-butyllithium in hexanes (1.7 M, 1.2 mL, 2.0 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 30 min. Di-*tert*-butylchlorophosphine (0.417 mL, 2.2 mmol) was then added dropwise, and the reaction was stirred at room temperature for 18 h. Saturated aqueous ammonium chloride (2 mL) was added, and the reaction mixture was extracted with ether (2 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was recrystallized from ether/methanol to give 295 mg (67%) of 2-*N*,*N*-(dimethylamino)-2′-di-*tert*-butylphosphino-1,1′-binaphthyl as colorless crystals, mp 188−189 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (broad d, 1H, J = 8.5 Hz), 7.92−7.75 (m, 3H), 7.75 (broad d, 1H, J = 8.2 Hz), 7.48−7.43 (m, 2H), 7.31 (broad d, 1H, J = 8.5 Hz), 7.24−7.16 (m, 2H), 6.98 (m, 1H), 6.74 (broad d, 1H, J = 8.6 Hz), 2.46 (s, 6H), 1.26 (d, 9H, J = 11.3 Hz), 0.75 (d, 9H, J = 11.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.2; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 145.8, 145.5, 136.5, 136.3, 134.6, 134.1, 134.0, 133.4, 132.96, 132.94, 129.2, 128.7, 128.03, 128.01, 127.7, 127.5, 127.1, 126.6, 126.5, 126.0, 125.8, 125.4, 124.9, 122.8, 119.0, 43.3, 32.8, 32.6, 31.8, 31.5, 31.4, 31.3, 30.3, 30.1 (observed complexity due to P−C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 3060, 2941, 1596, 1474, 1173. Anal. Calcd for $C_{30}H_{36}NP$: C, 81.60; H, 8.22. Found: C, 81.59; H, 8.60.

1-(Di-*tert*-butylphosphino)-*o*-terphenyl (5). An oven-dried Schlenk tube was cooled to room temperature under an argon purge and was charged with magnesium turnings (267 mg, 11.0 mmol), ether (7 mL), and 1,2-dibromoethane (38 μL). The mixture was stirred at room temperature until gas evolution ceased, and then a solution of 2-bromobiphenyl (1.7 mL, 10.0 mmol) in ether (5 mL) was added dropwise. The mixture was stirred at room temperature for 1.75 h. The solution was then transferred via cannula to a separate flask containing an ice-cooled solution of triisopropyl borate (4.6 mL, 20.0 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 15 min and then warmed to room temperature and stirred for 21 h. The reaction was quenched with 1 M HCl (40 mL) and stirred at room temperature for 10 min. The solution was basified to pH 14 with 6 M NaOH and then extracted with ether (1 × 10 mL). The organic phase was discarded, and the aqueous phase was acidified to pH 2 with 6 M HCl and extracted with ether (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was recrystallized from ether/pentane at −20 °C to afford 1.0 g (51%) of *o*-biphenyl boronic acid as a white, crystalline solid, which was used without further purification.

An oven-dried Schlenk flask was cooled to room temperature under an argon purge and was charged with tetrakis(triphenylphosphine)-palladium (289 mg, 0.25 mmol, 5 mol %), sodium carbonate (2.86 g, 27 mmol), and *o*-biphenyl boronic acid (1.0 g, 5.0 mmol). The flask was purged with argon, and DME (50 mL), ethanol (2 mL), water (15 mL), and 2-bromoiodobenzene (0.83 mL, 6.05 mmol) were added through a rubber septum. The mixture was heated to 85 °C with stirring for 3 d. After cooling to room temperature, the reaction mixture was diluted with ether (100 mL) and poured into a separatory funnel. The layers were separated, and the organic phase was washed with 1 M NaOH (2 × 50 mL) and brine and then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 1.23 g (79%) of 1-bromo-*o*-terphenyl as a colorless oil.

An oven-dried Schlenk tube was cooled to room temperature under an argon purge and was charged with magnesium turnings (54 mg, 2.2 mmol), THF (2 mL), and 1,2-dibromoethane (9 μL). The mixture was stirred at room temperature for 15 min, and then a solution of 1-bromo-*o*-terphenyl (618 mg, 2.0 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at room temperature for 1 h, and then the septum was removed from the flask, and copper(I) chloride (283 mg, 2.1 mmol) was added. The tube was capped with the septum and purged with argon for 1 min. The tube was charged with di-*tert*-butylchlorophosphine (0.46 mL, 2.4 mmol) and additional THF (1 mL). The mixture was heated to 60 °C with stirring for 26 h. The mixture was cooled to room temperature and filtered, and the solids were washed with ether/hexanes (50 mL, 1/1 v/v). The organic fraction was poured into a separatory funnel, washed with 30% aqueous ammonium hydroxide (3 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was recrystallized from hot methanol to afford 191 mg (26%) of the title compound as a white, crystalline solid, mp 95−97 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, J = 7.5 Hz), 7.54−7.07 (m, 12H), 0.92 (d, 9H, J = 11.1 Hz), 0.68 (d, 9H, J = 11.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.9; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 149.8, 142.4, 141.4, 141.3, 140.95, 140.92, 135.8, 135.65, 135.63, 135.6, 132.8, 132.0, 131.9, 130.6, 130.0, 127.9, 127.8, 127.2, 126.1, 125.9, 125.6, 33.5, 33.3, 31.8, 30.89, 30.88,

(33) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081−3089.

30.8, 30.0, 29.8 (observed complexity due to P−C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2946, 1459, 1362, 1173. Anal. Calcd for $C_{26}H_{31}P$: C, 83.39; H, 8.34. Found: C, 83.40; H, 8.40.

2-[Di-(1-adamantyl)phosphino]biphenyl (6). An oven-dried, round-bottomed flask was charged with magnesium turnings (15.3 g, 0.63 mol) and 1-bromoadamantane (9.0 g, 0.041 mol). The flask was purged with argon, ethyl ether (45 mL) was then added, and the mixture was gently refluxed for 15 h, without stirring.[34] A separate flame-dried, two-necked, round-bottomed flask equipped with a reflux condenser was charged with PCl_3 (0.9 mL, 10 mmol) and ether (15 mL) and was cooled to −40 °C. To this solution was added the solution of the Grignard reagent via syringe, slowly enough so that the reaction temperature was kept below −25 °C. The resulting mixture was stirred for 30 min at −45 °C, the cooling bath was removed, and the reaction mixture was allowed to warm slowly to room temperature. After the mixture stirred for an additional 30 min at room temperature, the reaction vessel was placed into a 37 °C oil bath, and the solution was allowed to gently reflux for 22 h. The mixture was cooled to room temperature and then was cannula-filtered into a separate flask. The solvent and some of the adamantane byproduct were removed in vacuo, without exposing the product to air, to afford a crude mixture of di-(1-adamantyl)chlorophosphine and di-(1-adamantyl)bromophosphine. This mixture was used in the next step without further purification.

An oven-dried Schlenk tube was charged with magnesium turnings (240 mg, 9.89 mmol) and 2-bromobiphenyl (1.55 mL, 7.5 mmol). The tube was purged with argon, THF (15 mL) was added through a rubber septum, and the reaction mixture was heated to a mild reflux for 3 h. The reaction mixture was then cooled to room temperature, the septum was removed, and copper(I) chloride (930 mg, 9.45 mmol) was added. The tube was capped with a septum and purged with argon, and then a solution of the di-(1-adamantyl)chlorophosphine/di-(1-adamantyl)-bromophosphine mixture (prepared above) in THF (5 mL) was added. The reaction mixture was heated to reflux for 3 h and allowed to cool to room temperature, and ether (50 mL) and pentane (50 mL) were added. The resulting suspension was stirred for 10 min, during which time a heavy dark-brown precipitate formed. The suspension was filtered, and the solid was collected on a fritted funnel. The solid was partitioned between ethyl acetate/ether (100 mL, 1/1 v/v) and 38% aqueous ammonium hydroxide (50 mL) and water (50 mL). The mixture was vigorously shaken several times over 30 min, and the layers were separated. The aqueous layer was washed with ether/ethyl acetate (2 × 100 mL, 1/1 v/v), and the combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous magnesium sulfate, decanted, and concentrated in vacuo. The product was crystallized from toluene/methanol to afford 450 mg (6%) of the title compound as a white solid, mp 222−224 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.87 (m, 1H), 7.41−7.16 (m, 8H), 1.95−1.79 (m, 18H), 1.69−1.62 (m, 12H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 21.5; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 151.5, 143.9, 143.8, 136.53, 136.49, 133.1, 132.8, 130.6, 130.55, 130.49, 129.0, 128.15, 128.08, 128.07, 127.0, 126.2, 125.2, 42.0, 41.8, 37.5, 37.14, 36.9, 28.9, 28.78 (observed complexity due to P−C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2898, 1443, 1343, 697. Anal. Calcd for $C_{32}H_{39}P$: C, 84.54; H, 8.65. Found: C, 84.40; H, 8.57.

Pd-Catalyzed Coupling of Aryl Halides with Phenols. General Procedure A. An oven-dried resealable Schlenk tube was fitted with a rubber septum and was cooled to room temperature under an argon purge. The septum was removed, and the tube was charged with palladium acetate (4.5 mg, 0.02 mmol, 2.0 mol %), ligand (**3** (9.0 mg) or **4** (13.2 mg) or **5** (11.2 mg) or **6** (13.6 mg), 0.03 mmol, 3.0 mol %), potassium phosphate (424 mg 2.0 mmol), the phenol (1.2 mmol) and the aryl halide (1.0 mmol). The tube was capped with the septum and purged with argon, and then toluene (3 mL) was added through the septum. The tube was sealed with a Teflon screwcap, and the reaction mixture was stirred at 100 °C for 14−26 h (reaction times were not optimized). The reaction was then subjected to workup method 1 or 2 (see below).

(34) Molle, G.; Bauer, P.; Dubios, J. E. *J. Org. Chem.* **1982**, *47*, 4120−4128.

General Procedure B. An oven-dried resealable Schlenk tube was charged with sodium hydride (dry 95%, 36 mg, 1.4 mmol) in a nitrogen-filled glovebox. The tube was sealed and removed from the glovebox, fitted with a septum, and purged with argon. The phenol (1.0 mmol) and toluene (2.5 mL) were added, and the resulting mixture was stirred at 100 °C for 15 min under argon. The reaction mixture was allowed to cool to room temperature, the septum was then removed, and the tube was charged with palladium acetate (4.5 mg, 0.02 mmol, 2.0 mol %) and ligand (**3** (9.0 mg) or **4** (13.2 mg) or **5** (11.2 mg), 0.03 mmol, 3.0 mol %). The tube was capped with the septum and purged with argon. The aryl halide (1.0 mmol) and additional toluene (0.5 mL) were added, the tube was sealed with a Teflon screwcap, and the reaction mixture was stirred at 100 °C for 14−24 h (reaction times were not optimized). The reaction was then subjected to workup method 1 or 2 (see below).

Workup Method 1. The reaction mixture was allowed to cool to room temperature and was then diluted with ether (40 mL), filtered, and concentrated. The crude material was purified by flash chromatography on silica gel.

Workup Method 2. The reaction mixture was allowed to cool to room temperature and was then diluted with ether (40 mL) and poured into a separatory funnel. The mixture was washed with 1 M NaOH (20 mL) and brine (20 mL), and then the organic fraction was dried over anhydrous magnesium sulfate or sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography on silica gel.

2,3′,4′,5-Tetramethyldiphenyl Ether (the Reaction Shown in eq 3 Using Ligand 2). An oven-dried resealable Schlenk tube was charged with sodium hydride (dry 95%, 36 mg, 1.4 mmol) in a nitrogen-filled glovebox. The tube was sealed and removed from the glovebox, fitted with a rubber septum, and purged with argon. Toluene (1 mL) was added, followed by a solution of 3,4-dimethylphenol (147 mg, 1.2 mmol) in toluene (2 mL). The mixture was stirred at room temperature for 2 min and then heated to 100 °C with stirring for 15 min. The reaction mixture was allowed to cool to room temperature, the septum was removed, and $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol, 1.5 mol % Pd) and **2** (7.7 mg, 0.0225 mmol, 2.25 mol %) were added. The tube was capped with the septum and purged with argon. 2-Chloro-*p*-xylene (0.135 mL, 1.0 mmol) and additional toluene (1 mL) were added, and the tube was sealed with a Teflon screwcap. The mixture was heated to 100 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis (19 h). The mixture was cooled to room temperature, diluted with ether (30 mL), filtered through Celite, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 177 mg (78%) of the title compound as a colorless oil.

2,3′,4′,5-Tetramethyldiphenyl Ether (the Reaction Shown in eq 3 Using Ligand 3). An oven-dried resealable Schlenk tube was charged with sodium hydride (dry 95%, 36 mg, 1.4 mmol) in a nitrogen-filled glovebox. The tube was sealed and removed from the glovebox, fitted with a rubber septum, and purged with argon. 3,4-Dimethylphenol (147 mg, 1.2 mmol) and toluene (2.0 mL) were added, and the resulting mixture was stirred at 100 °C for 15 min under argon. The reaction mixture was allowed to cool to room temperature, the septum was removed, and $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol, 1.5 mol % Pd) and **3** (6.7 mg, 0.0225 mmol) were added. The tube was capped with the septum and purged with argon. 2-Chloro-*p*-xylene (135 μL, 1.0 mmol) was added, the tube was sealed with a Teflon screwcap, and the reaction mixture was stirred at 100 °C for 14 h. The mixture was allowed to cool to room temperature, water (5 mL) and ether (40 mL) were added, and the resulting solution was poured into a separatory funnel. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 175 mg (77%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, 1H, J = 7.5 Hz), 7.05 (d, 1H, J = 8.1 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.74 (d, 1H, J = 3.0 Hz), 6.70 (broad s, 1H), 6.64 (dd, 1H, J = 8.1, 3.0 Hz), 2.27 (s, 3H), 2.23 (s, 6H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 154.7, 138.0, 136.9, 131.0, 130.42, 130.41, 126.4, 124.2, 119.9, 118.8, 114.7, 21.0, 20.0, 18.9, 15.8; IR (neat, cm^{-1}) 2923,

1495, 1256. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.67; H, 8.03.

4-Phenoxyacetophenone (Table 1, Entry 1).[30,31] General procedure A (workup method 2, ligand **3**) was used to convert 4-bromoacetophenone and phenol in 16 h to 188 mg (89%) of the title compound, which was obtained as a white solid, mp 50−51 °C (lit.[30] mp 51 °C).

4-(2′-Methylphenoxy)acetophenone (Table 1, Entry 2).[35] General procedure A (workup method 2, ligand **3**) was used to convert 4-bromoacetophenone and *o*-cresol in 15 h to 213 mg (96%) of the title compound, which was obtained as a white solid, mp 34.5−35.5 °C (lit.[35] oil). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94−7.89 (m, 2H), 7.30−7.12 (m, 3H), 6.99 (broad d, 1H, J = 7.5 Hz), 6.91−6.87 (m, 2H), 2.57 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.5, 162.1, 152.8, 131.6, 131.2, 130.5, 130.4, 127.4, 125.2, 120.9, 115.8, 26.5, 16.2; IR (neat, cm^{-1}) 1675. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.75; H, 6.55.

4-(2′-Methylphenoxy)acetophenone (Table 1, Entry 2, using 0.1 mol % Pd).[35] General procedure A (workup method 2, ligand **3**) was employed, with the following changes in the amount of materials used: palladium acetate (1.0 mg, 0.004 mmol, 0.10 mol %), ligand **3** (2.0 mg, 0.007 mmol, 0.15 mol %), 4-bromoacetophenone (890 mg, 4.47 mmol), *o*-cresol (0.55 mL, 5.33 mmol), potassium phosphate (1.90 g, 8.95 mmol) in toluene (13 mL) for 24 h. The title compound (955 mg, 95%) was obtained as a white solid, mp 34.5−35.5 °C (lit.[35] oil).

4-(4′-*tert*-Butylphenoxy)acetophenone (Table 1, Entry 3).[30] General procedure A (workup method 2, ligand **3**) was used to convert 4-bromoacetophenone and 4-*tert*-butylphenol in 15 h to 247 mg (92%) of the title compound, which was obtained as a colorless oil.

Methyl 4-phenoxybenzoate (Table 1, Entry 4).[32] General procedure A (workup method 2, ligand **3**) was used to convert methyl 4-bromobenzoate and phenol in 24 h to 201 mg (88%) of the title compound, which was obtained as a white solid, mp 59.5−60 °C (lit.[32] mp 62.5−63 °C).

***N,N*-Diethyl-4-(2′-methylphenoxy)benzamide (Table 1, Entry 5).** General procedure B (workup method 2, ligand **3**) was used except that palladium acetate (11 mg, 0.05 mmol, 5.0 mol %) and **3** (22 mg, 0.075 mmol, 7.5 mol %) were employed to convert 4-bromo-*N,N*-diethylbenzamide and *o*-cresol in 22 h to 230 mg (81%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.30 (m, 2H), 7.27−7.25 (m, 1H), 7.19 (td, 1H, J = 8.0, 1.9 Hz), 7.10 (td, 1H, J = 7.2, 1.2 Hz), 6.94 (dd, 1H, J = 8.0, 1.2 Hz), 6.90−6.85 (m, 2H), 3.41 (broad s, 4H), 2.21 (s, 3H), 1.18 (broad s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 158.9, 153.8, 131.7, 131.1, 130.4, 128.4, 127.4, 124.7, 120.5, 116.7, 43.0, 39.0, 16.4, 13.0; IR (neat, cm^{-1}) 1627, 1584, 1424, 1237. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.28; H, 7.47. Found: C, 76.11; H, 7.42.

4-(3′-Isopropylphenoxy)benzonitrile (Table 1, Entry 6). General procedure A (workup method 2, ligand **3**) was used to convert *p*-chloro benzonitrile and *m*-isopropylphenol in 24 h to 218 mg (91%) of the title compound, which was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61−7.57 (m, 2H), 7.32 (t, 1H, J = 7.8 Hz), 7.11 (d, 1H, J = 7.8 Hz), 7.02−6.97 (m, 2H), 6.95−6.93 (m, 1H), 6.87 (ddd, 1H, J = 8.1, 2.4, 0.9 Hz), 2.92 (sept, 1H, J = 6.6 Hz), 1.25 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 154.6, 151.6, 134.0, 129.9, 123.3, 118.7, 118.4, 117.7, 117.6, 105.5, 34.0, 23.9; IR (neat, cm^{-1}) 2962, 2227, 1245. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.93; H, 6.64.

4-Chloro-2′-isopropyldiphenyl Ether (Table 1, Entry 7). General procedure A (workup method 1, ligand **3**) was used to convert 4-cholorobromobenzene and *o*-isopropylphenol (260 μL, 1.95 mmol) in 24 h to 223 mg (90%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.33 (m, 1H), 7.28−7.23 (m, 2H), 7.20−7.12 (m, 2H), 6.90−6.82 (m, 3H), 3.25 (sept, 1H, J = 6.9 Hz), 1.22 (d, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.9, 153.0, 140.2, 129.5, 127.15, 127.05, 126.9, 124.5, 119.8, 118.5, 27.1, 23.0; IR (neat, cm^{-1}) 2964, 1482, 1092. Anal. Calcd for $C_{15}H_{15}ClO$: C, 73.02; H, 6.13. Found: C, 73.00; H, 5.86.

4-(2′-Methylphenoxy)acetophenone (Table 1, Entry 8).[35] General procedure A (workup method 2, ligand **3**) was used to convert 4-acetylphenyl triflate and *o*-cresol in 14 h to 188 mg (83%) of the title compound as a white solid, mp 35−36 °C (lit.[35] oil). See data above (Table 1, entry 2).

3-(2′-Methylphenoxy)acetophenone (Table 1, Entry 9). General procedure A (workup method 2, ligand **3**) was used to convert 3′-bromoacetophenone and *o*-cresol in 19 h to 170 mg (75%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (ddd, 1H, J = 8.0, 1.5, 1.0 Hz), 7.49 (dd, 1H, J = 2.6, 1.5 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.27 (broad d, 1H, J = 7.3 Hz), 7.19 (dt, 1H, J = 7.3, 1.5 Hz), 7.11 (dd, 1H, J = 8.0, 1.5 Hz), 7.09 (ddd, 1H, J = 8.0, 2.6, 1.0 Hz), 6.91 (dd, 1H, J = 8.0, 1.5 Hz), 2.57 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 158.5, 154.0, 139.0, 131.9, 130.3, 130.1, 127.6, 124.8, 122.5, 121.9, 120.1, 116.8, 27.0, 16.4; IR (neat, cm^{-1}) 1686, 1578, 1437, 1264. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 80.02; H, 6.28.

2,2′,5-Trimethyldiphenyl Ether (Table 2, Entry 1).[4] General procedure A (workup method 1, ligand **4**) was used to convert 2-bromo-*p*-xylene and *o*-cresol in 24 h to 206 mg (96%) of the title compound which was obtained as a colorless oil.

3,5-Dimethyldiphenyl Ether (Table 2, entry 2).[36] General procedure A (workup method 1, ligand **5**) was used to convert 5-bromo-*m*-xylene and phenol in 24 h to 164 mg (83%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.30 (m, 2H), 7.11−6.98 (m, 3H), 6.74 (broad s, 1H), 6.63 (broad s, 2H), 2.28 (broad s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 157.0, 139.4, 129.5, 124.9, 122.8, 118.7, 116.5, 21.3; IR (neat, cm^{-1}) 2919, 1584, 1490, 1218. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.78; H, 6.94.

2,3′,5′,6-Tetramethyldiphenyl Ether (Table 2, Entry 3).[4] General procedure B (workup method 1, ligand **3**) was used to convert 5-bromo-*m*-xylene and 2,6-dimethylphenol in 24 h to 157 mg (70%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.03 (m, 3H), 6.62 (broad s, 1H), 6.37 (broad s, 2H), 2.24 (s, 6H), 2.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.8, 151.1, 139.4, 131.5, 128.8, 124.8, 123.1, 112.2, 21.4, 16.4; IR (neat, cm^{-1}) 2921, 1600, 1194. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.68; H, 8.18.

3,3′,4′,5-Tetramethyldiphenyl Ether (Table 2, Entry 4).[4] General procedure B (workup method 1, ligand **3**) was used to convert 5-bromo-*m*-xylene and 3,4-dimethylphenol in 24 h to 188 mg (84%) of the title compound, which was obtained as a colorless oil.

4-*tert*-Butyl-2′-methyldiphenyl Ether (Table 2, Entry 5). General procedure A (workup method 1, ligand **3**) was used to convert 4-*tert*-butylbromobenzene and *o*-cresol in 14 h to 204 mg (85%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, 2H, J = 9.0 Hz), 7.25 (dd, 1H, J = 8.1, 1.5 Hz), 7.15 (dt, 1H, J = 7.5, 1.5 Hz), 7.04 (dt, 1H, J = 7.5, 1.2 Hz), 6.89 (dd, 1H, J = 8.1, 1.2 Hz), 6.84 (d, 2H, J = 9.0 Hz), 2.26 (s, 3H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.6, 155.1, 145.4, 131.5, 130.0, 127.2, 126.6, 123.8, 119.6, 117.2, 34.4, 31.7, 16.4; IR (neat, cm^{-1}) 2929, 1586, 1237. Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.84; H, 8.72.

4-*n*-Butyl-2′-isopropyldiphenyl Ether (Table 2, Entry 6). General procedure A (workup method 1, ligand **3**) was used to convert 1-bromo-4-*n*-butylbenzene and 2-isopropylphenol in 24 h to 246 mg (92%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.31 (dd, 1H, J = 7.0, 2.4 Hz), 7.13−7.06 (m, 4H), 6.86−6.82 (m, 3H), 3.31 (sept, 1H, J = 7.0 Hz), 2.57 (t, 2H, J = 7.7 Hz), 1.63−1.53 (m, 2H), 1.42−1.29 (m, 2H), 1.23 (d, 6H, J = 7.0 Hz), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, 154.0, 140.0, 136.9, 129.4, 126.7, 126.6, 123.7, 119.2, 117.6, 34.9, 33.9, 27.1, 23.0, 22.4, 14.0; IR (neat, cm^{-1}) 2960, 1505, 1486, 1231. Anal. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.88; H, 9.06.

2-Isopropyl-4′-methoxydiphenyl Ether (Table 2, Entry 7). General procedure A (workup method 1, ligand **6**) was used to convert *p*-bromoanisole and *o*-isopropylphenol in 24 h to 213 mg (88%) of the

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title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (dd, 1H, J = 6.9, 2.1), 7.15−7.04 (m, 2H), 6.94−6.84 (m, 4H), 6.79 (dd, 1H, J = 7.5, 2.1 Hz), 3.80 (s, 3H), 3.37 (sept, 1H, J = 6.6 Hz), 1.26 (d, 6H J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 154.8, 151.3, 139.2, 126.7, 126.6, 123.2, 119.4, 118.1, 114.7, 55.7, 27.1, 23.0; IR (neat, cm^{-1}) 2962, 1503, 1036. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.39; H, 7.30.

2,5-Dimethyldiphenyl Ether (Table 2, Entry 8).[37] General procedure B (workup method 1, ligand **4**) was used to convert 2-chloro-*p*-xylene and phenol in 19 h to 157 mg (79%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (dd, 2H, J = 7.5, 8.6 Hz), 7.14 (d, 1H, J = 7.7 Hz), 7.05 (t, 1H, J = 7.5 Hz), 6.93−6.89 (m, 1H), 6.91 (d, 2H, J = 8.6 Hz), 6.76 (s, 1H), 2.29 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 154.3, 137.3, 131.3, 129.8, 127.0, 125.0, 122.4, 120.7, 117.4, 21.2, 16.0; IR (neat, cm^{-1}) 2923, 1590, 1490, 1252, 1216, 1117. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.02; H, 7.14.

2,5-Dimethyl-4′-methoxydiphenyl Ether (Table 2, Entry 9). An oven-dried resealable Schlenk tube was charged with the sodium salt of *p*-methoxyphenol (88 mg, 0.6 mmol) in a nitrogen-filled glovebox. The tube was sealed, removed from the glovebox, fitted with a septum, and purged with argon. The septum was removed, and then palladium acetate (2.2 mg, 0.02 mmol, 2.0 mol %) and **4** (6.6 mg, 3.0 mol %) were added. The tube was capped with a septum and purged with argon. Toluene (1.5 mL) and 2-chloro-*p*-xylene (67 μL, 0.5 mmol) were added via syringe, then the tube was sealed with a Teflon screwcap, and the reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was allowed to cool to room temperature and was then diluted with ether (20 mL), filtered, and concentrated. The crude material was purified by flash chromatography on silica gel to afford 113 mg (99%) of the title compound as an off-white solid, mp 55−56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (broad d, 1H, J = 7.7 Hz), 6.91−6.81 (m, 5H), 6.62 (broad s, 1H), 3.80 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5, 155.1, 151.2, 136.9, 131.0, 125.8, 123.8, 119.2, 118.7, 114.7, 55.6, 21.0, 15.8; IR (neat, cm^{-1}) 2923, 1501, 1030. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.01; H, 7.24.

2,2′,5,6′-Tetramethyldiphenyl Ether (Table 2, Entry 10). An oven-dried resealable Schlenk tube was charged with sodium 2,6-dimethylphenolate (89 mg, 0.62 mmol) in a nitrogen-filled glovebox. The tube was sealed and removed from the glovebox, fitted with a septum, and purged with argon. The septum was removed, and then $Pd_2(dba)_3$ (5.9 mg, 0.0125 mmol, 2.5 mol % Pd) and **4** (8.5 mg, 3.75 mol %) were added. The tube was capped with a septum and purged with argon. Toluene (1.5 mL) and 2-chloro-*p*-xylene (70 μL, 0.515 mmol) were added via syringe, and then the tube was sealed with a Teflon screwcap and placed in a 115 °C oil bath and stirred for 24 h. The reaction mixture was allowed to cool to room temperature and was then diluted with ether (20 mL), filtered, and concentrated. The crude material was purified by flash chromatography on silica gel to afford 97 mg (83%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15−7.07 (m, 4H), 6.72 (broad d, 1H, J = 7.5 Hz), 6.10 (broad s, 1H), 2.42 (s, 3H), 2.18 (s, 3H), 2.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.5, 151.5, 136.6, 131.4, 130.7, 128.9, 124.7, 122.8, 121.6, 112.4, 21.2, 16.2, 15.9; IR (neat, cm^{-1}) 2923, 1507, 1192. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.99; H, 8.16.

4-Methoxy-2′-methyldiphenyl Ether (Table 2, Entry 11).[38] General procedure A (workup 1, ligand **6**) was used to convert 4-chloroanisole and *o*-cresol in 26 h to 156 mg (73%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (broad d, 1H, J = 7.2 Hz), 7.12 (broad t, 1H, J = 7.8 Hz), 7.00 (broad t, 1H, J = 7.5 Hz), 6.92−6.83 (m, 4H), 6.79 (broad d, 1H, J = 8.1 Hz), 3.89 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 155.2, 151.0, 131.3, 129.0, 126.9, 123.0, 119.3, 118.0, 114.8, 55.7, 16.2; IR (neat, cm^{-1}) 2952, 1503, 1225. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.43; H, 6.28.

4-*n*-Butyl-3′,4′-dimethyldiphenyl Ether (Table 2, Entry 12). General procedure B (workup method 1, ligand **5**) was used to convert 1-chloro-4-*n*-butylbenzene and 3,4-dimethylphenol in 22 h to 201 mg (79%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.03 (m, 3H), 6.92−6.86 (m, 2H), 6.80 (broad d, 1H, J = 2.4 Hz), 6.80 (broad dd, 1H, J = 8.4, 2.4 Hz), 2.57 (app t, 2H, J = 7.8 Hz), 2.22 (s, 6H), 1.66−1.52 (m, 2H), 1.35 (sext, 2H, J = 7.8 Hz), 0.92 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.5, 155.3, 138.1, 137.4, 131.2, 130.5, 129.4, 120.1, 118.4, 116.0, 34.9, 33.8, 22.3, 19.9, 19.0, 14.0; IR (neat, cm^{-1}) 2927, 1495, 1218. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.27; H, 8.99.

2-Isopropyl-4′-*t*-butyldiphenyl Ether (Table 2, Entry 13). General procedure A (workup method 1, ligand **3**) was used to convert 4-*tert*-butylphenyl triflate and *o*-isopropylphenol in 24 h to 230 mg (86%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.30 (m, 1H), 7.33 (d, 2H, J = 8.6 Hz), 7.18−7.08 (m, 2H), 6.90−6.85 (m, 1H), 6.88 (d, 2H, J = 8.8 Hz), 3.33 (sept, 1H, J = 6.9 Hz), 1.33 (s, 9H), 1.25 (d, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 154.0, 145.2, 140.0, 126.8, 126.7, 126.4, 123.8, 119.4, 117.2, 34.2, 31.5, 27.0, 23.0; IR (neat, cm^{-1}) 2962, 1509, 1486, 1233. Anal.Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.82; H, 8.76.

3-Methoxy-2′-methyldiphenyl Ether (Table 2, Entry 14).[39] General procedure A (workup method 1, ligand **3**) was used to convert 3-bromoanisole and *o*-cresol in 19 h to 186 mg (87%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, 1H, J = 7.3 Hz), 7.22−7.16 (m, 2H), 7.08 (dt, 1H, J = 7.3, 1.3 Hz), 6.95 (dd, 1H, J = 8.0, 1.3 Hz), 6.61 (ddd, 1H, J = 8.5, 2.4, 1.3 Hz), 6.50 (d, 1H, J = 1.3 Hz), 6.48 (ddd, 1H, J = 8.5, 2.4, 1.3 Hz), 3.78 (s, 3H), 2.25 (s 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.1, 159.4, 154 4, 131.6, 130.3, 130.2, 127.4, 124.4, 120.3, 109.6, 108.0, 103.6, 55.5, 16.3; IR (neat, cm^{-1}) 1580, 1486, 1227. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.56; H, 6.84.

4-*n*-Butyldiphenyl Ether (Table 2, Entry 15). General procedure B (workup method 2, ligand **5**) was used, except that the quantities of phenol (2.0 mmol), sodium hydride (2.4 mmol), palladium acetate (9.0 mg, 0.04 mmol, 4.0 mol %), and ligand **5** (22 mg, 0.06 mmol, 6.0 mol %) were employed to convert 4-*n*-butyl-1-chlorobenzene and phenol in 24 h at 115 °C to 142 mg (63%) of the title compound, which was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (dd, 2H, J = 8.7, 7.4 Hz), 7.15 (d, 2H, J = 8.6 Hz), 7.08 (t, 1H, J = 7.4 Hz), 7.00 (dd, 2H, J = 8.7, 1.0 Hz), 6.34 (d, 2H, J = 8.6 Hz), 2.60 (t, 2H, J = 7.4 Hz), 1.61 (quint, 2H, J = 7.4 Hz), 1.37 (sext, 2H, J = 7.4 Hz), 0.95 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 154.8, 137.9, 129.6, 129.5, 122.8, 118.9, 118.4, 34.9, 33.8, 22.3, 14.0; IR (neat, cm^{-1}) 2929, 1590, 1488, 1235. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.89; H, 7.88.

3,4′,5-Trimethyldiphenyl Ether (Table 2, Entry 16).[4] General procedure B (workup method 1, ligand **5**) was used to convert 5-bromo-*m*-xylene and *p*-cresol in 24 h to 186 mg (88%) of the title product, which was obtained as a colorless oil.

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Note Added in Proof. (1) Following the acceptance of this manuscript, related studies by Hartwig have been published:

(37) Zeller, K.-P., Berger, S. *J. Chem. Soc., Perkin Trans. 2* **1977**, 54−58.

(38) Van Duzee, E. M.; Adkins, H. *J. Am. Chem. Soc.* **1935**, *57*, 7, 147−150.

(39) Fujikawa, F.; Nakamura, I. *J. Pharm. Soc. Jpn.* **1944**, *64*, 274−276; *Chem. Abstr.* **1951**, 2906.

Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (2) Recent experiments in our labs have demonstrated that under identical conditions, reactions which employ 2-(di-*tert*-butylphosphino)-1,1′-binaphthyl (the desamino derivative of **4**) provide results similar to those which use **4**.

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