J. Org. Chem. **2001,** *66,* 2498−2500

Palladium-Catalyzed Formation of Aryl *tert*-Butyl Ethers from Unactivated Aryl Halides

Cynthia A. Parrish and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

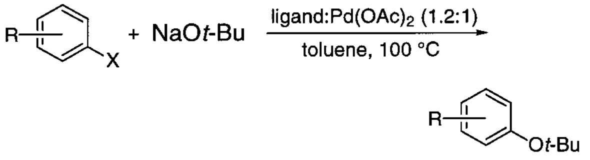
sbuchwal@mit.edu

Received October 2, 2000

Alkyl aryl ethers are key constituents in numerous natural products and pharmaceuticals and are often utilized as phenol precursors.[1] Methods for their preparation complementary to the traditional Williamson ether synthesis include direct nucleophilic substitution[2] and the Cu(I)-catalyzed cross-coupling of alkoxides with aryl halides.[3] However, these methods are limited in that they typically require activated aryl halides, large excesses of alkoxides, high reaction temperatures, or undesirable solvents. Recently, the palladium-catalyzed intra- and intermolecular cross-coupling reaction of aryl halides with alcohols has been reported as an alternative method for the formation of the aryl-oxygen bond.[4−6] Although able to avoid many of the limitations stated above, the intermolecular reaction has been most successful using activated aryl halides. There are limited examples that utilize unactivated aryl halides as substrates. For such substrates, tertiary alcohols or cycloalkanols have provided the best results in the cross-coupling reaction.[7] Other methods for the synthesis of tertiary alkyl aryl ethers from aryl halides are currently limited to the nucleophilic substitution of activated aryl halides,[2b,d] aryl Grignard addition to *tert*-butylperoxybenzoate,[8] and the Cu(I)-catalyzed cross-coupling.[3a] The Pd-catalyzed C−O bond-forming reaction represents an attractive alternative method, especially with application to unactivated aryl halide substrates.

Previously, we reported the first example of a palladium-catalyzed cross-coupling reaction between a tertiary alcohol and an *unactivated* aryl bromide.[5] The procedure, based on a catalyst using 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (tol-BINAP) as the ligand, provided the product in moderate yield. As anticipated, it was found that sterically hindered di-*tert*-butylphosphinobiphenyl ligands led to highly active catalysts for Pd-catalyzed C−O bond formation, as seen for the preparation of diaryl ethers.[9] It is believed that such bulky ligands facilitate reductive elimination to form the C−O bond. Recent reports on the Pd-catalyzed synthesis of aryl *tert*-butyl ethers have indeed supported this hypothesis. Work by Hartwig[10] and Watanabe[11] has provided several examples of aryl *tert*-butyl ether formation in the presence of di-*tert*-butylphosphinoferrocene and tri-*tert*-butylphosphine ligands, respectively. These phosphine ligands are, however, air sensitive and thus require special handling techniques. The scope of substrates utilized in this reaction is also still limited. Although the use of unactivated aryl bromides has been described, the use of electron-rich aryl bromides, save one recent example by Hartwig,[10b] has only been reported in low yield.[11] In addition, few examples describing unactivated aryl chlorides as substrates have been published. As aryl *tert*-butyl ethers are precursors to phenols,[12] it was worthwhile to search for a more general and less sensitive catalyst for their formation. We report herein the palladium-catalyzed preparation of aryl *tert*-butyl ethers in good to excellent yields based on air-stable dialkylphosphinobiphenyl ligands that allows for the use of unactivated and even electron-rich aryl bromides or chlorides as substrates.

Our initial studies indicated that the di-*tert*-butylphosphinobiphenyl ligands provided active palladium catalysts that couple aryl halides with sodium *tert*-butoxide to form aryl *tert*-butyl ethers (eq 1). These ligands are air stable and are either commercially available[13] or readily prepared in a one-pot procedure.[14] Experiments performed in the presence of commercially available ligand **1** provided moderate to good results in the palladium-catalyzed aryl *tert*-butyl ether formation (Table 1, entries 1, 3, and 6). It was found that the use of $Pd_2(dba)_3$ and reaction temperatures of 110 °C gave the best results with ligand **1**. However, for most examples, excess palladium (≥3 mol %), especially when using aryl chlorides, was required, incomplete conversions were



(1)

---

(1) For example, see: *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier Science: Oxford, UK, 1999; Vols. 1, 3, 8.

(2) (a) DeVries, V. G.; Moran, D. B.; Allen, G. R.; Riggi, S. J. *J. Med. Chem.* **1976**, *19*, 946. (b) Hamilton, J.; Mahaffy, C. A. L. *Synth. React. Inorg. Met. Org. Chem.* **1986**, *16*, 1363. (c) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561. (d) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594, and references therein.

(3) (a) Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565. (d) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633. (e) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 1007.

(4) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907.

(5) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395.

(6) (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (b) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413.

(7) The use of tertiary alcohols precludes β-H elimination from the intermediate palladium-alkoxide. For a discussion of this, see ref 5.

(8) Conlon, D. A.; Crivello, J. V.; Lee, J. L.; O'Brien, M. J. *Macromolecules* **1989**, *22*, 509, and references therein.

(9) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(10) (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (b) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.

(11) Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837.

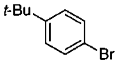
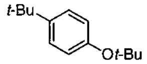
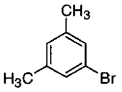
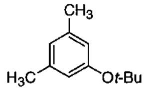
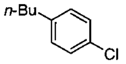
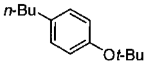
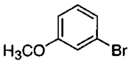
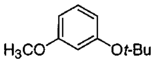
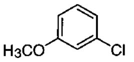
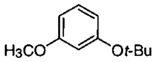
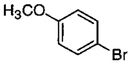
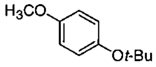
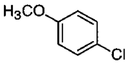
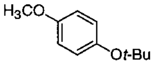
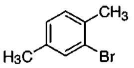
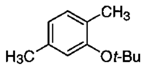
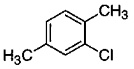
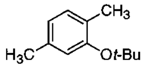
(12) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley & Sons: New York, 1991.

(13) 2-Dicyclohexylphosphinobiphenyl, 2-di-*tert*-butylphosphinobiphenyl, and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl are commercially available from Strem Chemicals, Inc.

(14) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

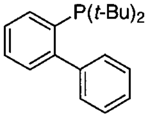
10.1021/jo001426z CCC: $20.00

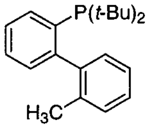
Table 1. Pd-Catalyzed Formation of Aryl *tert*-Butyl Ethers[a]

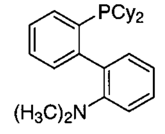
Entry	Aryl Halide	Pd (mol%)	Ligand	Product	Yield
1		1.2[b]	1		80%
2		1.0	2		90%
3		1.0[b]	1		79%
4		1.0	2		86%
5		2.5	2		92%
6		1.5[b]	1		65%[c]
7		1.0	2		84%
8		1.0	2		84%
9		2.5	2		85%
10		2.5	2		84%
11		2.5[d]	3		78%
12		2.5	3		87%

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.3 equiv of NaO*t*-Bu, catalytic $Pd(OAc)_2$, ligand (1.2:1 L/Pd), toluene (0.5 M solution), 100 °C, 17−23 h (reaction times have not been minimized). Yields (average of two or more experiments) represent isolated yields of products estimated to be of >95% purity as indicated by ^1H NMR and GC analysis. [b] $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$; the temperature was increased to 110 °C. [c] The yield of one of the experiments was determined by GC against an internal standard. [d] $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$.

observed, and only moderate yields of product were obtained (for example, entry 6).


1


2


3

Better results were obtained when the palladium catalyst was based on ligand **2**. Although ligand **2** is not commercially available, it can easily be prepared in 48% overall yield in the one-pot sequence.[14] Experiments performed with ligand **2** showed that the use of this catalyst provided products in higher yields, under milder conditions, and displayed a more general substrate tolerance. For example, the conversion of unactivated aryl bromides to aryl *tert*-butyl ethers proceeded readily in the presence of sodium *tert*-butoxide, ligand **2**, and 1.0−2.5 mol % $Pd(OAc)_2$ at 100 °C in very good yield (Table 1, entries 2, 4, and 7). Under these conditions, the successful use of unactivated aryl chlorides was also demonstrated (entries 5 and 8). Furthermore, an electron-rich aryl bromide or chloride also readily underwent cross-coupling to afford the aryl *tert*-butyl ether (entries 9 and 10), representing the first high-yielding example utilizing an aryl bromide and the first successful example utilizing the less reactive aryl chloride.

Difficulty was encountered in attempting to utilize more hindered aryl halides such as 2-bromo-*p*-xylene or 2-chloro-*p*-xylene. Although complete conversion was observed using 2.5 mol % $Pd(OAc)_2$, product yields were moderate, and significant formation of diaryl ether was observed.[9] Despite our previous work that indicated the use of dicyclohexylphosphinobiphenyl ligands would not be effective in C−O bond-forming reactions,[9] such ligands were tested. In contrast to our earlier findings, the use of the commercially available and less bulky dicyclohexylphosphine ligand **3** allowed for the conversion of 2-bromo-*p*-xylene or 2-chloro-*p*-xylene to product using 2.5 mol % palladium (Table 1, entries 11 and 12). Under these conditions, 2-*tert*-butoxy-*p*-xylene was produced in good yield and, more importantly, with negligible amounts of diaryl ether formation.

In conclusion, we describe here a palladium-catalyzed synthesis of aryl *tert*-butyl ethers in the presence of commercially available or readily prepared air-stable dialkylphosphinobiphenyl ligands. The ether products are obtained in very good yield from unactivated aryl bromides or chlorides. Furthermore, we have demonstrated efficient C−O bond formation using an electron-rich aryl bromide or chloride with catalysts based on these ligands. This procedure represents the simplest, most general, and most effective conditions known to date for the Pd-catalyzed preparation of aryl *tert*-butyl ethers from a variety of unactivated aryl bromides or chlorides.

Experimental Section

General Considerations. All reactions were carried out under an argon atmosphere in oven-dried resealable Schlenk tubes. Toluene was distilled under nitrogen from molten sodium. Palladium acetate and tris(dibenzylideneacetone)dipalladium(0) were purchased from Strem Chemicals, Inc. Ligands **1**−**3** were prepared as reported in the literature.[14,15] Aryl halides were purchased from commercial sources and were used as received. Sodium *tert*-butoxide was purchased from Sigma-Aldrich; the bulk of this material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small (1−2 g) portions were removed from the glovebox in glass vials and stored in a desiccator for use up to 1 week. Standard elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. The procedures described in this section are representative, and thus, yields may differ from those given in Table 1.

General Reaction Procedure. An oven-dried resealable Schlenk tube was charged with ligand (12 μmol, 1.2 mol %), $Pd(OAc)_2$ (2.2 mg, 10 μmol, 1.0 mol %), and sodium *tert*-butoxide (125 mg, 1.30 mmol, 1.3 equiv). The flask was evacuated, backfilled with argon, and sealed with a septum. Toluene (1.00 mL), aryl halide (1.00 mmol, 1 equiv), and additional toluene (1.00 mL) were added sequentially via syringe. Dodecane (225 μL, 1.00 mmol, 1.00 equiv) was often added as an internal standard. The septum was replaced with a Teflon screwcap, and the flask was sealed and placed into a 100 °C oil bath. The reaction mixture was stirred for 17−23 h. After cooling, the mixture was diluted with ether (5 mL), filtered through Celite, rinsed with ether (2 × 5 mL), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (2% EtOAc/hexanes).

1-*tert*-Butoxy-4-*tert*-butylbenzene (Entry 2).[16] The general procedure using 1-bromo-4-*tert*-butylbenzene (175 μL) and ligand **2** (3.7 mg) provided 183 mg (89%) of the title compound as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, $J = 8.9$ Hz), 6.91 (d, 2H, $J = 8.9$ Hz), 1.35 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 145.9, 125.7, 123.6, 78.1, 34.5,

---

(15) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(16) Cai, L.; Mahmoud, H.; Han, Y. *Tetrahedron*: *Asymmetry* **1999**, *10*, 411.

31.8, 29.1; IR (neat, cm^{-1}) 2967, 1507, 1364, 1244, 1170, 900. Anal. Calcd for $C_{14}H_{22}O$: C, 81.48; H, 10.77. Found: C, 81.26; H, 10.61.

5-*tert*-Butoxy-*m*-xylene (Entry 4). The general procedure using 5-bromo-*m*-xylene (135 μL) and ligand **2** (3.7 mg) afforded the title compound as a yellow oil (146 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.63 (s, 2H), 2.29 (s, 6H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 138.3, 125.1, 121.9, 78.1, 29.2, 21.6; IR (neat, cm^{-1}) 2977, 1596, 1473, 1364, 1304, 1181, 1144, 859. Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.20. Found: C, 80.56; H, 10.03.

1-*tert*-Butoxy-4-*n*-butylbenzene (Entry 5). The general procedure using 1-*n*-butyl-4-chlorobenzene (170 μL), $Pd(OAc)_2$ (5.6 mg, 25 μmol, 2.5 mol %), and ligand **2** (9.4 mg, 30 μmol, 3.0 mol %) gave the title compound as a yellow oil (187 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 2H, J = 8.2 Hz), 6.90 (d, 2H, J = 8.4 Hz), 2.57 (t, 2H, J = 7.7 Hz), 1.62−1.54 (m, 2H), 1.40−1.30 (m, 2H), 1.34 (s, 9H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 137.9, 128.7, 124.2, 78.2, 35.2, 34.0, 29.1, 22.7, 14.3; IR (neat, cm^{-1}) 2976, 2930, 1506, 1365, 1236, 1164, 899. Anal. Calcd for $C_{14}H_{22}O$: C, 81.48; H, 10.77. Found: C, 81.56; H, 10.65.

3-*tert*-Butoxyanisole (Entry 7). The general procedure using 3-bromoanisole (125 μL) and ligand **2** (3.7 mg) provided the title compound as a colorless oil (155 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, 1H, J = 8.2 Hz), 6.63 (m, 2H), 6.56 (t, 1H, J = 2.3 Hz), 3.80 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 156.6, 129.2, 116.5, 110.2, 108.9, 78.7, 55.4, 29.2; IR (neat, cm^{-1}) 2977, 1599, 1485, 1366, 1281, 1142, 1044, 964. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.96. Found: C, 73.47; H, 8.86.

3-*tert*-Butoxyanisole (Entry 8). The general procedure using 3-chloroanisole (120 μL) and ligand **2** (3.7 mg) afforded the title compound as a colorless oil (152 mg, 85%).

4-*tert*-Butoxyanisole (Entry 9). The general procedure using 4-bromoanisole (125 μL), $Pd(OAc)_2$ (5.6 mg, 25 μmol, 2.5 mol %), and ligand **2** (9.4 mg, 30 μmol, 3.0 mol %) gave the title compound as a colorless oil (154 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, 2H, J = 8.9 Hz), 6.80 (d, 2H, J = 9.0 Hz), 3.79 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 148.6, 125.4, 113.8, 78.1, 55.6, 28.9; IR (neat, cm^{-1}) 2976, 1504, 1365, 1227, 1167, 1038, 896, 845. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.96. Found: C, 73.47; H, 8.84.

4-*tert*-Butoxyanisole (Entry 10). The general procedure using 4-chloroanisole (120 μL), $Pd(OAc)_2$ (5.6 mg, 25 μmol, 2.5 mol %), and ligand **2** (9.4 mg, 30 μmol, 3.0 mol %) afforded the title compound as a colorless oil (157 mg, 87%).

2-*tert*-Butoxy-*p*-xylene (Entry 11). The general procedure using 2-bromo-*p*-xylene (140 μL), $Pd_2(dba)_3$ (11.4 mg, 12.5 μmol, 1.25 mol %), and ligand **3** (11.8 mg, 30.0 μmol, 3.00 mol %) provided the title compound as a yellow oil (135 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, 1H, J = 7.5 Hz), 6.84 (s, 1H), 6.78 (d, 1H, J = 7.6 Hz), 2.30 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 135.7, 130.6, 128.9, 123.5, 123.2, 78.9, 29.5, 21.4, 17.1; IR (neat, cm^{-1}) 2978, 2925, 1504, 1365, 1260, 1178, 1122, 998, 806. Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.20. Found: C, 80.99; H, 10.09.

2-*tert*-Butoxy-*p*-xylene (Entry 12). The general procedure using 2-chloro-*p*-xylene (135 μL), $Pd(OAc)_2$ (5.6 mg, 25 μmol, 2.5 mol %), and ligand **3** (11.8 mg, 30.0 μmol, 3.00 mol %) afforded the title compound as a yellow oil (154 mg, 87%).

Acknowledgment. We thank the National Institutes of Health (GM58160) for financial support. Additional unrestricted funds from Pfizer and Merck are also greatly appreciated. C.A.P. was a trainee of the National Cancer Institute (Grant CA09112), to whom we are indebted. We also thank Dr. John P. Wolfe for initial experiments on this project.

JO001426Z