Synthesis of Oxygen Heterocycles via a Palladium-Catalyzed C−O Bond-Forming Reaction

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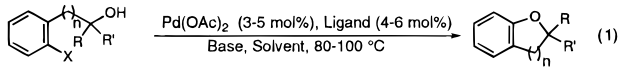
Palladium-catalyzed cross coupling reactions of Ar−X (X = I, Br, and OTf) with carbon nucleophiles (R−M, where M = SnR'_3, BR'_2, or MgX) have found wide application in the syntheses of complex organic molecules, due in part, to the mild reaction conditions and high functional group compatibility.[1] Successful extension of this class of reactions to heteroatom nucleophiles including amines[2] and thiols[3] has been reported. Recent advances in the Pd-catalyzed aryl aminations have extended the generality of this reaction to include a wide variety of amines.[4] In contrast, the Pd-catalyzed coupling of Ar−X with alcohols still remains an elusive goal despite its potential application in organic synthesis. Aryl ethers, including oxygen heterocycles, are prominent in a large number of pharmacologically important molecules and are found in numerous secondary metabolites.[5] Existing methods for the conversion of Ar−X to aryl ethers often require harsh or restrictive conditions and/or the presence of activating groups on the arene ring.[6] For example, the Cu(I)-catalyzed syntheses of aryl and vinyl ethers commonly require freshly prepared sodium alkoxides in a large excess of the corresponding alcohol to achieve reasonable yields from the corresponding aryl halides and vinyl halides.[7] Furthermore, this method has not been demonstrated to be effective for the coupling of tertiary alkoxides and we are aware of no reports of intramolecular processes of this type which proceed in good yield.[8] Herein we report our efforts in effecting an intramolecular Pd-catalyzed ipso substitution of an aryl halide with an alcohol (eq 1).



(1)

1: X=Br, R=R'=Me, n=1
2: X=Br, R=R'=Me, n=2

Subjecting substrates **1** and **2** to reaction conditions which were successful in the intramolecular Pd-catalyzed amination reaction ($Pd_2(dba)_3$, 2P(*o*-tolyl)$_3$, NaO*t*-Bu in toluene at 80 °C) afforded no desired cyclized product.[9] Conversely, the use of ligands including (*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol-BINAP), (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), and 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) in place of P(*o*-tolyl)$_3$ effected cyclization of the model substrates at ≥80 °C in toluene with either $Pd_2(dba)_3$ or $Pd(OAc)_2$ as the Pd source and either NaO*t*-Bu or K_2CO_3 as base.[10] This observation is in accord with recent reports that chelating bis(phosphine) ligands significantly improved the Pd-catalyzed amination reaction.[4c,d] Although $Pd_2(dba)_3$ was an effective precatalyst, $Pd(OAc)_2$ was found to be superior. Using the aforementioned conditions, a variety of intramolecular substrates were examined and the results obtained are shown in Table 1.[11]

As shown, five-, six-, and seven-membered heterocycles were obtained in good yields from the corresponding aryl halide. In addition, a number of functional groups were found to be compatible with the reaction conditions including acetals (entry 3), silyl ethers (entry 4), and amides (entry 7). Reactions performed using method A were significantly slower (24−36 h) than reactions performed using method B (1−6 h); however, the reactions using method A were somewhat cleaner. It should be noted that no reaction was observed in the absence of base. Cyclization of the aryl iodide substrate (entry 2) was extremely slow in toluene, but in 1,4-dioxane, complete conversion occurred in 24−36 h. Two equivalents of ligand relative to palladium and two equivalents of NaO*t*-Bu relative to substrate were required to achieve reasonable yields in the cyclization of substrates containing a secondary alcohol (entries 11 and 12). Observed side products included dehalogenation of the aryl halides and, in the case of substrates containing a secondary alcohol, oxidation of the alcohol to the ketone. Attempts to cyclize 2-bromophenethyl alcohol afforded only phenylacetaldehyde which was unstable under the reaction conditions.[12]

The mechanism of the Pd-catalyzed synthesis of aryl ethers most likely proceeds via a pathway roughly similar to that suggested for the Pd-catalyzed aryl amination reaction.[9a,13] As shown in Scheme 1, oxidative addition of the Pd(0)L_n with the

‡ National Institutes of Health Postdoctoral Fellow.

(1) For a review of Stille couplings see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803. For a review of Suzuki couplings see: (c) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. For a review of Kumada couplings see: (e) Knight, D. W. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; Schreiber, S. L., Eds.; Pergamon Press: New York, 1991; Vol. 3, Chapter 2.3.

(2) (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (c) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (d) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(3) (a) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13. (b) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-I.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (c) Barañano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937. (d) Arnould, J. C.; Didelot, M.; Cadilhac, C.; Pasquet, M. J. *Tetrahedron Lett.* **1996**, *37*, 4523.

(4) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (b) Zhao, S.-H.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463. (c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

(5) (a) Ellis, G. P. In *The Chemistry of Heterocyclic Compounds;* Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons: New York, 1977; Vol. 31. (b) Mustafa, A. In *The Chemistry of Heterocyclic Compounds;* Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons: New York, 1974; Vol. 29.

(6) For a review of alkenyl and aryl C−O bond forming reactions see: (a) Chiuy, C. K.-F. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: New York, 1995; Vol. 2, Chapter 2.13. For the synthesis and application of benzopyrans see: (b) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 3, Chapter 2.24. For the synthesis and application of benzofurans see: (c) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 4, Chapter 3.12. For examples of nickel catalyzed synthesis of aryl ethers see: (d) Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267. (e) Cristau, H.-J.; Desmurs, J.-R. *Ind. Chem. Libr.* **1995**, *7*, 240.

(7) (a) Lee, S.; Frescas, S. P.; Nichols, D. E. *Synth. Commun.* **1995**, *25*, 2775. (b) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 1007. (c) Keegstra, M. A.; Peters, T. H.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633. (d) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, 63. (e) Aalten, H. L.; Van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565.

(8) For a review on copper catalyzed aromatic nucleophilic substitutions see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(9) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (b) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525.

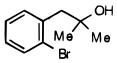
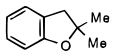
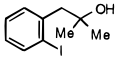
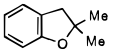
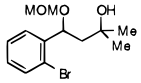
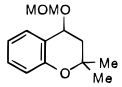
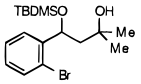
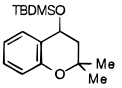
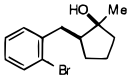
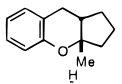
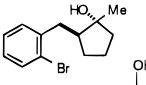
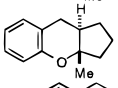
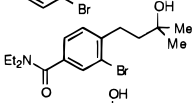
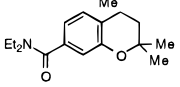
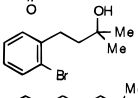
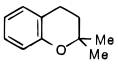
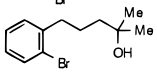
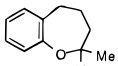
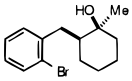
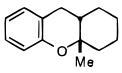
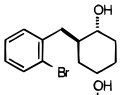
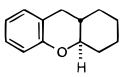
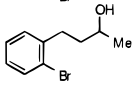
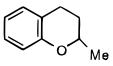
(10) In addition to tri-*o*-tolylphosphine, the following ligands were screened for the cyclization of substrate **1** and found to be ineffective: 1,-10-phenanthroline, 2,2′-dipyridyl, tris(2,4,6-trimethoxyphenyl)phosphine, 1,2-bis(diphenylphosophino)benzene, and 1,2-bis(diphenylphosphino)ethane.

(11) No reaction was observed under the reaction conditions employed in the absence of $Pd(OAc)_2$ for any of the entries listed in Table 1.

(12) It has been reported that treatment of *trans*-[$PdBr(C_6H_5)(PPh_3)_2$] with a solution of NaOMe in toluene at 35 °C afforded benzene (80% yield), HCHO (20% yield), and anisole (trace). (a) Yoshida, T.; Okano, T.; Otsuka, S. *J. Chem. Soc., Dalton Trans.* **1976**, 993. Treatment of aryl halides with a solution of NaOMe and catalytic amounts of $Pd(PPh_3)_4$ in toluene affords upon heating the dehalogenated product and formaldehyde in high yields. (b) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.

S0002-7863(96)02408-0 CCC: $12.00

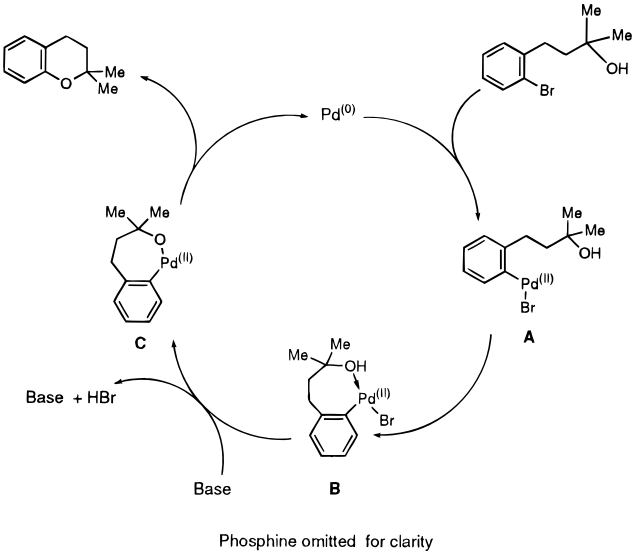
Table 1. Pd-Catalyzed Synthesis of Cyclic Aryl Ethers

Entry	Substrate	Method[a]	Product	Yield (%)[b]
1		A		89
2		A		60
3		A		93
4		A		90
5		A		65
6		A		73
7		A		66
8		B		69
9		B		64
10		B		73
11		C		66
12		C		32

[a] Method A: 5 mol % $Pd(OAc)_2$, 6 mol % Tol-BINAP, 1.2 equiv of K_2CO_3 in toluene at 100 °C. Method B: 3 mol % $Pd(OAc)_2$, 3.6 mol % DPPF, 1.2 equiv of NaO*t*-Bu in toluene at 80 °C. Method C: 5 mol % $Pd(OAc)_2$, 10 mol % DPPF, 2.0 equiv of NaO*t*-Bu in toluene at 90 °C. [b] Yields refer to average isolated yields of two or more runs. [c] Reaction was performed in 1,4-dioxane.

aryl halide affords the Pd(II) organometallic intermediate **A**. In the presence of a suitable base, chelation/deprotonation could afford the palladacycle **C**, which then undergoes reductive elimination to yield the oxygen heterocycle.[14] Intermediate **A** bearing a chelating DPPF ligand was isolated and characterized by NMR and IR spectroscopy and by elemental analysis. This complex was found to be chemically and kinetically competent as a catalyst for the conversion of 4-(2-bromophenyl)-2-methyl-2-butanol to 2,2-dimethylchroman. In addition, heating a solution of **A** and a stoichiometric amount of NaO*t*-Bu in toluene afforded 2,2-dimethylchroman as the only detectable product by GC. Attempts to isolate palladacycle **C**, however, proved unsuccessful.[15]

Scheme 1



In summary, we have developed the first Pd-catalyzed synthesis of cyclic aryl ethers from alcohols and aryl halides. This process was shown to be reasonably functional group tolerant and produces five-, six-, and seven-membered heterocycles in moderate to good yield. Efforts to extend the substrate scope to primary alcohols as well as developing an intermolecular version are currently in progress.

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Supporting Information Available: Details of experimental procedures and spectroscopic and analytical data (17 pages). See any current masthead page for ordering and Internet access instructions.

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(13) (a) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626. (b) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. *Organometallics* **1996**, *15*, 2745. (c) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755. (d) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics*. **1996**, *15*, 3534.

(14) It has not been determined if deprotonation occurs prior to or after oxygen coordination.

(15) To our knowledge, the efficient reductive elimination of an aryl ether from an arylpalladium(II) alkoxide complex has not been reported. For examples of C−O bond forming reactions which have been proposed to proceed via reductive elimination from $PdR(OAr)L_n$ complexes (R = η^3-allyl or C(O)Me) see: (a) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964. (b) Larock, R. C.; Harrison, L. W.; Hsu, M. H. *J. Org. Chem.* **1984**, *49*, 3662. (c) Komiya, S.; Akia, Y.; Tanaka, K.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1985**, *4*, 1130. (d) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. For a review of the synthesis and reactivity of late transition metal alkoxides see: (e) Bryndza, H.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163.