Palladium-Catalyzed Intermolecular Carbon−Oxygen Bond Formation: A New Synthesis of Aryl Ethers
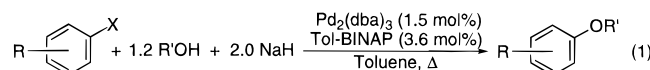
Michael Palucki, John P. Wolfe, and Stephen L. Buchwald*

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

Aryl ethers are ubiquitous structural constituents in pharmacologically important molecules, and consequently, much research has been focused on their synthesis.[1] Available methods for the synthesis of aryl ethers via direct nucleophilic or Cu(I)-catalyzed substitution of an aryl halide with an alcohol typically require high reaction temperatures and/or a large excess of the alcohol and are limited in substrate scope.[2−4] The need to employ HMPA, DMSO, or DMF as solvent further diminishes the applicability of these methods, particularly for large-scale processes.

Recently we reported the first example of palladium-catalyzed aromatic carbon−oxygen bond formation; the intramolecular Pd-catalyzed ipso substitution of an aryl halide with an alcohol to afford oxygen heterocycles.[5,6] This method was used to synthesize five-, six-, and seven-membered oxygen heterocycles in moderate to good yields.[7] We sought to determine whether a related catalyst system could be used for the synthesis of aryl ethers by the intermolecular coupling of alcohols and aryl bromides (eq 1).[8] Herein we report our initial results which demonstrate the viability of using palladium catalysis for the intermolecular formation of carbon−oxygen bonds.

$$R\text{—}C_6H_4\text{—}X + 1.2\ R'OH + 2.0\ NaH \xrightarrow[\text{Toluene, }\Delta]{\substack{Pd_2(dba)_3\ (1.5\ mol\%)\\ \text{Tol-BINAP (3.6 mol\%)}}} R\text{—}C_6H_4\text{—}OR' \quad (1)$$

The conditions employed for the intramolecular process (vide supra) were not immediately applicable to the intermolecular version. We found, however, that reaction of 2-propanol, 4-bromobenzonitrile, and NaH in the presence of 1.5 mol % Pd$_2$(dba)$_3$ and 3 mol % (*S*)-(−)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (Tol-BINAP) at 50 °C afforded 4-isopropoxybenzonitrile in 80% isolated yield.[9] Although Pd(OAc)$_2$ was an effective catalyst precursor, use of Pd$_2$(dba)$_3$ afforded superior ratios of product to reduced side product (benzonitrile) as determined by GC analyses. Aryl bromides containing electron-

Table 1. Synthesis of Aryl Ethers via Pd-Catalyzed and Direct Nucleophilic Substitution Reactions

Entry	Aryl Halide	Alcohol	Temp (°C)	Catalyzed Yield, toluene (%)[b]	Uncatalyzed Yield, DMF (%)
1	NC—C$_6$H$_4$—Br	(CH$_3$)$_2$CHOH	50	80	76 (55 °C)
2	F$_3$C—C$_6$H$_4$—Br	3-pentanol	70	50	48
3	NC—C$_6$H$_4$—Br	menthol	70	77	73
4	NC—C$_6$H$_4$—Br	PhCH$_2$OH	70	71	78
5	NC—C$_6$H$_4$—Br	MeOH	70	81	65 (55 °C)
6	*t*-Bu—C$_6$H$_4$—Br	NaO*t*-Bu	100	53	<10
7	1-bromonaphthalene	cyclohexanol	70	65	<5
8	9-bromoanthracene	cyclopentanol	100	48	< 10
9	9-bromoanthracene	tetrahydropyran-4-ol	100	84	No Rxn

[a] For entries 1−5 and 7−9, reaction conditions: 1.5 mol % Pd$_2$(dba)$_3$, 3.6 mol % Tol-BINAP, 1 equiv of aryl bromide, 1.2 equiv of alcohol, and 2.0 equiv of NaH. For entry 6: 5 mol % Pd(OAc)$_2$, 6 mol % Tol-BINAP, 1 equiv of aryl bromide and 2.0 equiv of NaOtBu. [b] Yields refer to the average of isolated yields for two runs.

(1) For a review of alkenyl and aryl C−O bond-forming reactions, see: 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.

(2) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.1 and references therein.

(3) (a) Keegstra, M. A.; Peters, T. H.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633. (b) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, 63. (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. Pentavalent organobismuth reagents have been used in the presence and absence of Cu salts, see: Barton, D. H. R.; Finet, J.-P.; Khamsi, J.; Pichon, C. *Tetrahedron Lett.* **1986**, *27*, 3619.

(4) Electron-deficient transition metal complexes have been used as activators for the synthesis of aryl ethers: Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561 and references therein.

(5) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333.

(6) After submission of this manuscript, a report from Hartwig describing related work on palladium-catalyzed formation of *tert*-butyl ethers appeared. Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109.

(7) For examples of nickel-catalyzed synthesis of aryl ethers, see: (a) Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267. (b) Cristau, H.-J.; Desmurs, J.-R. *Ind. Chem. Libr.* **1995**, *7*, 249.

(8) It has been reported that treatment of *trans*-[PdBr(C$_6$H$_5$)(PPh$_3$)$_2$] with a solution of NaOMe in toluene at 35 °C afforded benzene (80% yield), HCHO (20% yield), and anisole (trace), see: Yoshida, T.; Okano, T.; Otsuka, S. *J. Chem. Soc., Dalton Trans.* **1976**, 993.

(9) Either enantiomer of Tol-BINAP can be used as can BINAP.

withdrawing substituents (Table 1, entries 1−5) coupled effectively with a wide variety of alcohols including 2-propanol, 3-pentanol, (1*R*,2*S*,5*R*)-(−)-menthol,[10] benzyl alcohol, and methanol within 24 h using 1.5 mol % Pd$_2$(dba)$_3$ and 3.6 mol % Tol-BINAP at 70 °C. The Pd-catalyzed coupling of methanol with 4-bromobenzonitrile is of interest since it has previously been demonstrated that methanol in combination with catalytic amounts of Pd(PPh$_3$)$_4$ is effective in reducing aryl halides to the dehalogenated arene products with concomitant formation of HCHO.[11] Application of this methodology using electron-rich or -neutral aryl bromides and various alcohols affords the desired coupling products in good yields only when alkoxides from tertiary alcohols or cycloalkanols are employed. For example, reaction of 4-bromo-*tert*-butylbenzene with 2-propanol or cyclopentanol afforded predominantly the reduction product *tert*-butylbenzene. However, reaction with NaOtBu afforded the aryl ether product in 53% isolated yield (entry 6).[12] A similar reaction of 1-bromonaphthalene with 2-propanol afforded naphthalene as the major product, while employing cyclohexanol afforded the aryl ether product in 65% yield (entry 7).

While only preliminary studies of the mechanism of this process have been carried out, it most likely proceeds via a

(10) Since only one product was detected by GC and TLC analyses, and the stereochemistry of the carbinol carbon was preserved in the Pd-catalyzed intramolecular coupling reaction (see ref 5), it is assumed that the stereochemistry of (1*R*,2*S*,5*R*)-(−)-menthol is preserved during the course of the reaction.

(11) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.

(12) (a) No meta product, as would be expected from benzyne formation, was observed in this process. (b) Both *tert*-butylbenzene and 4,4'-di-*tert*-butylbiphenyl were side products of the Pd-catalyzed reaction of 4-*tert*-butylbromobenzene with NaOtBu. We are uncertain about the mechanism of formation of *tert*-butylbenzene in this reaction. (c) In contrast to the other substrates examined (Table 1), use of tBuOH and NaH in place of NaOtBu afforded large amounts of arene side products and only traces of the desired aryl ether product.

Scheme 1

(a)

Phosphine omitted for clarity.

(b)
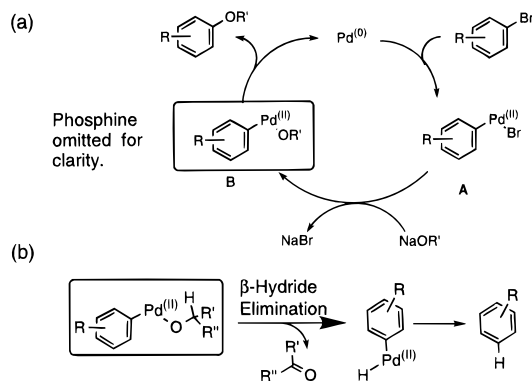
pathway similar to the Pd-catalyzed intramolecular C−O bond-forming reaction[5] and the related aryl amination process (Scheme 1a).[13] Oxidative addition of the Pd(0)L$_n$ complex to the aryl bromide affords **A**. Substitution of the bromide with the alkoxide affords palladium aryl alkoxide **B**. Reductive elimination of **B** gives the aryl ether with regeneration of the active catalyst.[14] In cases which proceed in lower yields, a β-hydride elimination/reductive elimination sequence which produces the reduced arene side product is competitive with reductive elimination (Scheme 1b).[15] As was observed in the aryl amination procedure, ligand effects are key to favoring the reductive elimination process over the β-hydride elimination pathway. We feel that the use of sterically bulky and less electron-donating ligands (but probably still chelating ligands) should favor the reductive elimination process.[13b,15c]

Under the conditions employed, aryl ether formation was not observed in toluene in the absence of catalyst for any of the substrates examined in Table 1. Since rates of nucleophilic aromatic substitution processes are enhanced in polar aprotic solvents, we chose to further investigate the uncatalyzed reactions employing DMF as solvent for the substrates shown in Table 1.[16] In fact under these conditions, aryl bromides containing electron-withdrawing substituents could be effectively converted to aryl ethers (entries 1−5). In previous reports of the nucleophilic substitution reactions of aryl bromides with alcohols, either higher temperatures or the use of 4 or more equivalents of the alcohol were generally employed. For the substrates studied, we found that 1.2 equiv of the alcohol was sufficient to achieve good yields of aryl ethers at 55−70 °C.[17] In contrast, in reactions of electron-neutral or -rich aryl bromides

(13) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (d) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755. (e) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794. (f) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

(14) Direct reductive elimination from [(*R*)-Tol-BINAP]Pd(*p*-C$_6$H$_4$CN)-(OCH$_2$CMe$_3$) to afford the aryl ether product in 84% yield has been recently demonstrated in this laboratory. Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. Submitted for publication. Hartwig has recently reported a similar process.[6]

(15) (a) Stille, J. K. *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, p 625. (b) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. (c) The steric effect of ligands on the rate of a reductive elimination process was first reported by Jones: Jones, W. D.; Kuykendall, V. L. *Inorg. Chem.* **1991**, *30*, 2615.

(16) Nucleophilic substitution reaction conditions typically require 4.0 equiv of alkoxide relative to aryl bromide at 80−120 °C. See ref 2.

(17) Uncatalyzed reactions performed in DMF that was not strictly anhydrous did not afford aryl ether products.

Table 2. Comparison of the Pd-Catalyzed and Uncatalyzed Substitution of 4-Bromo-2-chlorobenzonitrile

Entry	ROH	Catalyzed Yield **C** (%)[a] (toluene)	Uncatalyzed Yield (%)[a] (DMF)	**C/D** (uncatalyzed)
1[b]		80	54	1:1
2[c]		73	79	1:1.2
3	NaO*t*-Bu	82	No rxn	--

[a] Yields refer to the average of isolated yield of **C** for two runs. [b] Isolated product from the catalyzed reaction contains 5% 4-(cyclohexyloxy)benzonitrile. Isolated yield for the uncatalyzed reaction refers to a mixture of **C** and **D**. [c] Isolated yield for the uncatalyzed reaction refers to the sum of the isolated yield for **C** and **D**.

with alcohols in DMF only small amounts (<10%) of aryl ether products were observed. In addition, under these conditions, both meta and para isomers were observed in the reaction of 4-bromo-*tert*-butylbenzene with NaOtBu, suggesting that a benzyne pathway is operative.[18]

In order to further contrast the catalyzed and uncatalyzed processes and to extend the synthetic utility of the Pd-catalyzed transformation, the reaction of 4-bromo-2-chlorobenzonitrile was examined under both the Pd-catalyzed conditions in toluene and the uncatalyzed conditions in DMF (Table 2). The Pd-catalyzed reaction of 4-bromo-2-chlorobenzonitrile with cyclohexanol, NaOtBu or *sec*-phenethyl alcohol in toluene afforded the aryl ether product resulting from exclusive substitution of the bromide. In the absence of a Pd catalyst, slow substitution of chloride was observed in toluene for cyclohexanol and *sec*-phenethyl alcohol, whereas reaction with NaOtBu did not afford aryl ether products. In DMF, the uncatalyzed reaction with either cyclohexanol or *sec*-phenethyl alcohol in DMF afforded a mixture of aryl ether products while no aryl ether products were observed with NaOtBu.

The results presented above provide proof of concept that our palladium-catalyzed methodology is applicable for the formation aryl ethers by the intermolecular coupling of an aryl bromide and an alkoxide. Furthermore, our study of the uncatalyzed substitutions in both toluene (under conditions of the catalyzed process) and DMF are instructive. *They indicate that the accurate comparison of the efficacies of catalyzed and uncatalyzed reactions requires the use of favorable reaction conditions for each.*

Supporting Information Available: Details of experimental procedures and spectroscopic and analytical data (6 pages). See any current masthead page for ordering and Internet access instructions.

JA9640152

(18) (a) Cram, D. J.; Rickborn, B.; Knox, G. R. *J. Am. Chem. Soc.* **1960**, *82*, 6412. (b) Hales, R. H.; Bradshaw, J. S.; Pratt, D. R. *J. Org. Chem.* **1971**, *36*, 314.