An Efficient Intermolecular Palladium-Catalyzed Synthesis of Aryl Ethers

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Aromatic ethers are structural motifs in many naturally occurring[1] and medicinal compounds.[2] Although there are numerous methods for their synthesis,[3,4] a mild general method remains to be developed. While Pd-catalyzed C−O bond forming processes hold promise, success has been limited in intermolecular processes to reactions of activated aryl halides and alcohols lacking β-hydrogens.[5] To generalize the method, β-hydride elimination from **A** (Scheme 1), which competes with reductive elimination, needs to be minimized.[6]

Herein we describe the Pd-catalyzed intermolecular coupling of primary alcohols and aryl halides. The method works well for electron-deficient and -neutral aryl halides and for electron-rich aryl halides with an ortho alkyl substituent.

Initial studies of the reaction of 2-chloro-*m*-xylene with *n*-butanol indicated that using 2 mol % $Pd(OAc)_2$ in toluene with Cs_2CO_3 as base and di-*tert*-butyl phosphine ligand **1**[5e] at 70 °C gave good selectivity (10:1) for the formation of ether:arene. The reaction could be carried out at room temperature (45 h), increasing the selectivity to 20:1. These conditions worked for joining 2-chloro-*m*-xylene and 1-halonaphthalenes with various primary alcohols.[7a] Applying these conditions to less hindered aryl halides was less successful. For example, with 2-chloro-*p*-xylene, the ether:arene ratio was 0.3:1. Ultimately, we found that **2**[8] provided excellent generality. Many ortho-substituted substrates were effectively coupled with *n*-BuOH in 84−99% yield (Table 1).[7b] Transformations involving 2-piperidinoethanol or 2-bromobiphenyl were slightly less successful. Electron-donating alkoxy groups at the ortho position led to very low yields of the desired product.

We next examined the coupling of meta-substituted aryl halides whose reactions would not be facilitated by the increased rate of reductive elimination from **A** due to ortho substitution.[9] This study would also allow an estimation of meta substituent inductive effects on reaction efficiency. As shown in Table 2, aryl bromides with one or two *m*-alkyl substituents were converted to the *n*-butyl ethers in moderate yield. For substrates with electron-withdrawing substituents such as OMe, Ph, CO_2Me, CF_3, Ac, or NO_2, the yields increased to 80−90%. Thus, the inductive effects of meta substituents are important in the efficiency of these transformations.

As expected, aryl bromides and chlorides with electron-withdrawing para substituents are efficiently transformed using the conditions established above (Figure 1).[10a] Ketones, esters, nitriles, and heterocycles are tolerated in this chemistry.

Since we had seen that *o*-bromoanisole was a poor substrate and that ortho substitution was beneficial to coupling efficiency (Table 1), we prepared a series of substituted *p*-bromoanisoles to study the interplay between steric and electronic effects. While the reaction of 4-bromoanisole with *n*-butanol is inefficient (Table 3),[10b] the selectivity for ether formation increases dramatically with the addition of an ortho alkyl group. Little difference is seen on changing the substituent from methyl to Et or *i*Pr. Increasing the length of the alkyl chain to *n*Pr resulted in more than a 10% decrease in yield. Reaction of 2-*tert*-butyl-4-bromoanisole was extremely slow and gave ether:arene in a ratio of 0.4:1. Thus, the inclusion of a methyl group ortho to the bromide can alter the product:arene ratio from 0.24:1 to 2:1. 4-Br-3-phenylanisole reacts with yields similar to 4-bromoanisole.

We undertook a study of a number of biaryl ligands to determine what structural features were important in contributing to their efficacy in C−O bond formation. As seen for the reaction of *n*BuOH with 2-chloro-*p*-xylene (Table 4), binaphthyl ligands are more effective than biphenyl ligands **3**.

Scheme 1

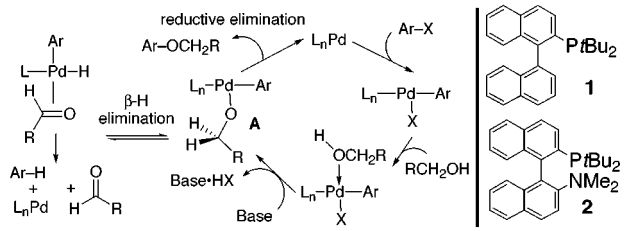

Table 1. Coupling Reactions of Ortho-Substituted Aryl Halides[7]

Entry	Substrate	Alcohol	Ligand	Product		Yield
1	Cl, Me, Me	*n*BuOH	**1**	OR, Me, Me	R = *n*Bu	90%
2		$PhCH_2OH$	**1**		R = CH_2Ph	95%
3		*i*BuOH	**1**		R = *i*Bu	88%
4		EtOH	**1**		R = Et	93%
5	Cl	*n*BuOH	**1**	O*n*Bu		88%
6	Br, Me	*n*BuOH	**1**	Me, O*n*Bu		88%
7	X, Me, Me	X = Br *n*BuOH	**2**	Me, O*n*Bu, Me		90%
8		X = Cl *n*BuOH	**2**			89%
9	Me, Br, Me	*n*BuOH	**2**	Me, O*n*Bu, Me		84%
10	Br, Me, Me	*n*BuOH	**2**	OR, Me, Me	R= *n*Bu	93%
11		N, OH (1.5 equiv)	**2**		R= $N(CH_2)_2$	75%
12	Br, R	*n*BuOH	**2**	O*n*Bu, R	R= Me	85%
13					R= *i*Pr	99%
14					R= Bn	94%
15					R= Ph	76%
16	Br, OR	*n*BuOH	**2**	O*n*Bu, OR	R= Me	9%
17					R= TIPS	21%

(1) For leading references, see: Buckingham, J. *Dictionary of Natural Products*; University Press: Cambridge, MA, 1994.
(2) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112.
(3) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999.
(4) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (b) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633−3652. (c) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 1007−1010. (d) Lee, S.; Frescas, S. P.; Nichols, D. E. *Synth. Commun.* **1995**, *25*, 2775−2780. (e) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051.
(5) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (c) Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837. (d) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (e) Torraca, K. E.; Kuwabe, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907. (f) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498 and references therein.
(6) Han, R. Y.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135.
(7) Reaction conditions: 2 mol % $Pd(OAc)_2$, 2.5 mol % L, 1 equiv of Ar-X, 2.5 equiv of Cs_2CO_3, 2 equiv of ROH, toluene, [ArX] = 0.5 M. (a) L = **1**, 23 °C. (b) L = **2**, 70 °C.
(8) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.
(9) (a) Jones, W. D.; Kuykendall, V. L. *Inorg. Chem.* **1991**, *30*, 2615. (b) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.
(10) (a) Reactions of aryl halides with ortho electron-withdrawing substituents were inefficient. (b) Under similar conditions, the reaction of 4-*t*-Bu-(C_6H_4)Br and *n*-BuOH proceeded in moderate yield (52%).

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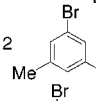
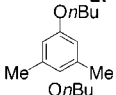
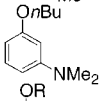
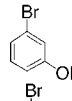
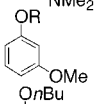
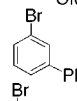
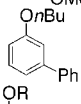
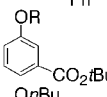
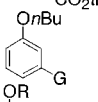
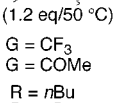
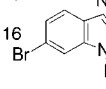
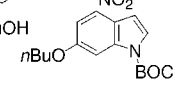
Table 2. Coupling of Meta-Substituted Aryl Halides[7b]

Entry	Substrate	Alcohol	Product		Yield
1		*n*BuOH			63%
2		*n*BuOH			56%
3		*n*BuOH			65%
4		*n*BuOH		R = *n*Bu	80%
5		$PhCH_2OH$		R = $PhCH_2$	80%
6		*n*BuOH			80%
7		*n*BuOH		R = *n*Bu	80%
8		$PhCH_2OH$		R = $PhCH_2$	76%
9					77%
10		*n*BuOH		G = CF_3	87%
11				G = COMe	91%
12		X = Br	*n*BuOH	R = *n*Bu	96%
13		X = Cl	*n*BuOH	R = *n*Bu	94%
14		X = Br	MeOH	R = Me	63%
15					99%
16		*n*BuOH		(1.2 eq/50 °C)	72%

Also examined were three biphenyl ligands with naphthyl or anthracenyl groups at the ortho position of a di-*tert*-butyl-phosphinophenyl moiety (**4**−**6**). While neither **4** nor **5** are very effective, the addition of an *i*-Pr group has a significant effect. This is similar to trends seen in the biphenyl ligands for ketone arylation and C−N bond formation.[11] Interestingly, neither the parent ligand **1** (R′ = H) nor the derivative where R′ = TMS gave good results. Catalysts based on **2** proved to be of excellent

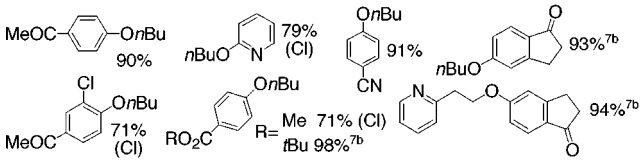
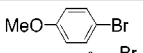
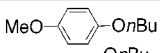
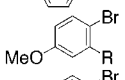
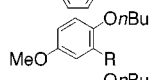
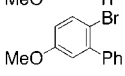
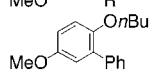


Figure 1. Pd-catalyzed coupling of electron-deficient substrates.[7a]

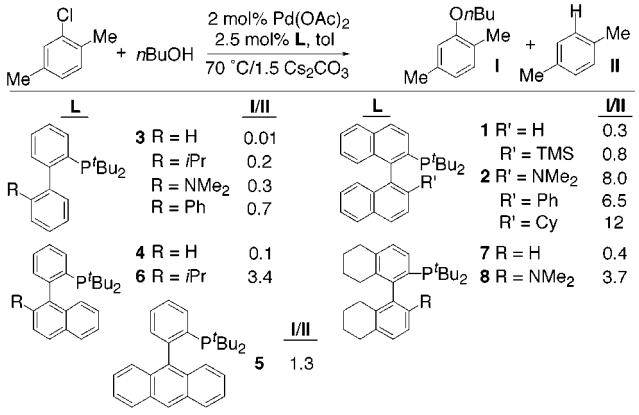
Table 3. Effect of Ortho Substitution on Reactions of 4-Bromoanisoles[7b]

Entry	Substrate	Product		Yield
1				12%
2			R= Me	65%
3			Et	69%
4			*n*Pr	55%
5			*i*Pr	68%
6				18%

generality. To probe whether the efficiency of this ligand was due to coordination of the Me_2N group, we prepared derivatives where R′ = Ph or Cy. While the former worked fairly well, the cyclohexyl derivative gave the best results to date. Unfortunately, we presently do not have a synthetically viable route to this ligand. As we hypothesized that coordination of a portion of the distal naphthalene ring enhances the efficacy or lifetime of the catalysts,[11b] we prepared tetrahydro ligand **8**. It gave similar results to **6**, being less effective than the three ligands of type **2**. With

(11) (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

Table 4. Ligand Effects in Pd-Catalyzed C−O Coupling Reaction



these results, we can make several generalizations concerning intermolecular Pd-catalyzed C−O bond formation between aryl bromides and chlorides and primary alcohols: (1) Binaphthyl ligands are superior to biphenyl ligands. (2) It is beneficial to have a moderately large substituent at the 2′ position of the distal naphthyl group. Increasing the dihedral angle between the two aromatic rings, which increases the effective size of the ligand, may be beneficial.[12] If R′ is too large, the ligand gives inferior results. (3) Generally, the presence of a Me_2N group is not more effective than a similarly sized alkyl group.[13] (4) Binaphthyl ligands are more effective than their octahydro analogues. The distal naphthalene ring may be a better ligand for Pd.[13,14] Additionally, the electron-donating ability of **8** is increased relative to that of **2**, which may effect the partitioning of **A** between reductive elimination and β-H elimination.[15,16] Alternatively, the dihedral angle between octahydrobinaphthyl rings may be larger than ideal, reducing ligand efficacy. These results indicate that there is a subtle interplay of both sterics and electronics that determine whether a ligand of this class is generally successful for a difficult transformation such as intermolecular C−O bond formation.

In summary, we have developed an efficient catalyst for the Pd-catalyzed intermolecular coupling of aryl bromides and chlorides and primary alcohols. While still far from ideal, it greatly expands the scope possible for this important transformation. Additionally, we have been able to ascertain the inductive effects of meta substituents on the efficiency of these transformations and on the relative importance of steric and electronic effects for electron-rich substrates. Little information of either type has previously been available. Finally, we have presented a detailed study on the effect of ligand variation that allows a determination of which structural features in biaryl ligands are important for their success in C−O bond formation. This information will form the basis for our search for improved ligands of use to the synthetic chemist.

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Supporting Information Available: Experimental procedures and characterization of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016863P

(12) Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1050.

(13) Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714.

(14) Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y.; Miki, M.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 775.

(15) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987; pp 322−353.

(16) For an excellent review of seminal work on C−X reductive elimination, see: Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.