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The Selective Reaction of Aryl Halides with KOH: Synthesis of Phenols, Aromatic Ethers, and Benzofurans

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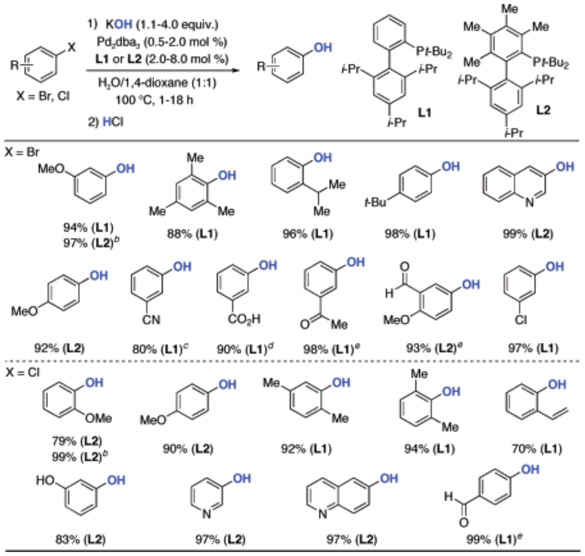
Phenols are structural constituents of pharmaceuticals, polymers, and naturally occurring compounds in addition to serving as versatile synthetic intermediates.[1] Traditional non-oxidative methods for their preparation include nucleophilic aromatic substitution of activated aryl halides and copper-promoted conversion of diazoarenes, as well as benzyne protocols, all of which are limited with respect to available starting materials and, in some cases, the requisite harsh reaction conditions.[2,3] A recent means of synthesizing phenols is the aromatic C−H activation/borylation/oxidation sequence reported by Smith and Maleczka.[4] This method is particularly useful for the preparation of non-ortho-substituted phenols.

The palladium-catalyzed formation of C−O bonds has emerged as an effective method for the construction of diaryl and alkyl aryl ethers from aryl halides and phenols or aliphatic alcohols.[5] The use of bulky, monodentate ligands which facilitate C−O reductive elimination has provided the best results.[5b] Interestingly, the use of hydroxide salts (e.g., KOH, NaOH) as nucleophiles for this process to form phenols directly has never been reported.[6,7]

While attempting the Pd-catalyzed coupling of water-soluble nucleophiles with aryl halides using a solvent of aqueous 1,4-dioxane and KOH as the base, we observed the formation of significant amounts of phenol with only trace quantities of the corresponding diaryl ether. We report herein that reactions with catalyst systems derived from Pd_2dba_3 and ligands **L1** or **L2** (Table 1) provide an effective route for the preparation of phenols from neutral, electron-rich, ortho-substituted and functionalized aryl/heteroaryl bromides and chlorides.

Initial study of the reaction of 3-bromoanisole and KOH as the nucleophile revealed that catalytic systems based on Pd_2dba_3 and ligands **L1** or **L2** in 1,4-dioxane/water at 100 °C for 1.5 h provided 3-methoxyphenol as the exclusive product in 94% yield. While the reaction of aryl bromides could be carried out at 80 °C, the successful transformation of aryl chlorides generally required higher temperatures (100 °C). Reactions could be carried out in water, with no cosolvent (in these cases the aryl halide is the organic phase) with results to that seen with the use of 1,4-dioxane. Toluene was a less effective cosolvent, except in the reaction of 3-bromobenzonitrile where 3-hydroxybenzonitrile is formed in 80% yield. The catalyst system based on Pd/**L1** proved to be the most effective with the di-ortho-substituted 2-bromomesitylene and 2-chloro-*m*-xylene, where the catalyst derived from Pd/**L2** resulted in <10% conversion of the aryl halide. In these cases, C−O reductive elimination (with **L1**) is enhanced by the ortho substitutents on the aryl halide. In contrast, with **L2** the reaction is inefficient. However, catalyst systems based on Pd/**L2** are generally more stable under the reaction conditions (Pd-black rapidly forms using **L1**) and thus, could be carried out with lower catalyst loadings (1% Pd). This result is counterintuitive, since the bulkier ligand, **L2**, would be expected to undergo more facile dissociation from Pd, leading to decomposition of the catalyst. Also, Pd/**L2** was generally more efficient in the coupling of aryl chlorides and heteroaryl halides with KOH providing the phenols in excellent yields. We postulate that the increased reactivity and stability of Pd/**L2** can be attributed to a faster rate in C−O reductive elimination of its $L_1PdAr(OH)$ species. Of importance, functional groups, such as a nitrile, carboxylic acid, methyl ketone, and aldehyde, were well tolerated under the reaction conditions employed.

Table 1. Pd-Catalyzed Synthesis of Phenols from Aryl Halides[a]



[a] Isolated yields (average of two runs). [b] GC-yield. [c] In toluene/H_2O (1:1). [d] Isolated as the methyl ester. [e] 80 °C, 12 h.

To further exploit this new method, we developed a one-pot protocol for the conversion of aryl halides to alkyl aryl ethers, where the initially formed phenoxide is treated with various alkyl halides facilitated by the phase-transfer catalyst cetyltrimethylammonium bromide (Table 2).[8] The current process represents a conceptually different means for the synthesis of alkyl aryl ethers from aryl halides, obviating issues of β-hydride elimination that plague the direct addition of alkoxides using Pd-catalyzed methodology. Further, the best results that are seen in the coupling of electron-rich and hindered aryl halides even with primary aliphatic alcohols require quite complex ligands.[5b] In contrast, **L1** and **L2** are, or soon will be, commercially available. Most notably 2-chloroanisole, 2-bromo-(isopropyl)benzene, and 4-chloroanisole are converted efficiently to their respective phenoxide, then react with secondary alkyl halides providing alkyl aryl ether products in good yields (Table 2, entries 2, 3, 5). The best previous results obtained for the preparation of these types of alkyl aryl ethers, from the reaction of aryl halides and secondary alcohols using Pd-catalyzed protocols, provide low yields (9−46%) due to competing β-hydride elimination.[5b,d] Further, a wider range of alkyl aryl ethers are accessible using this protocol (Table 2, entries 6, 7, 9). Thus, the current

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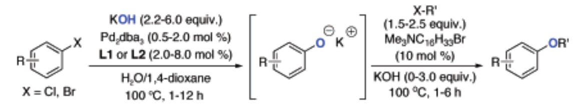
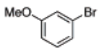
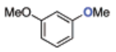
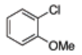
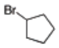
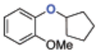
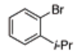
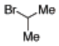
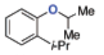
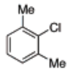
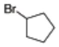
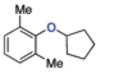
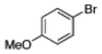
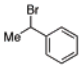
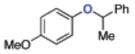
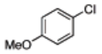
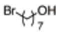
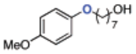
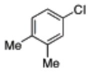
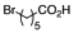
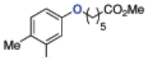
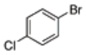
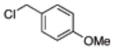
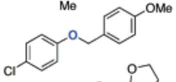
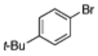
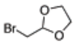
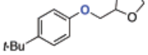
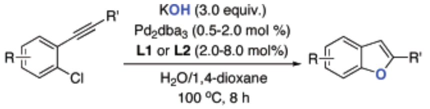
Table 2. One-Pot Conversion of Aryl Halides to Alkyl Aryl Ethers[a]

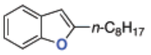


Entry	Aryl Halide	Alkyl Halide	Ligand	Product	Yield
1		MeI	**L1**		94%
2			**L1**		86%
3			**L1**		81%
4			**L1**		83%
5			**L2**		84%
6			**L2**		88%
7			**L2**		79%[b]
8			**L1**		80%
9			**L1**		85%

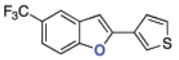
[a] Isolated yields (average of two runs). [b] Isolated as the methyl ester.

Table 3. Synthesis of Benzofurans from 2-Chloroaryl Alkynes[a]

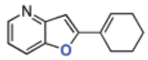




83% (**L1**)



87% (**L1**)



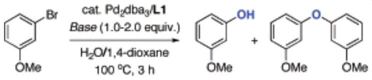
85% (**L2**)

[a] Isolated yield (average of two runs).

procedure represents a major advance in the scope for alkyl aryl ether synthesis from aryl halides.

We also explored the use of this catalyst system for the preparation of substituted benzofurans. Using known methodology, 1,2-dihaloarenes are converted to 2-chloroaryl alkynes,[9] after which submitting the purified aryl alkyne to our reaction conditions successfully provides benzofurans in good yields (Table 3). While the cyclization of 2-hydroxyalkynyl arenes is known,[10] this is the first time this strategy has been employed starting with a 2-haloaryl alkyne.[11]

While optimizing the reaction conditions for conversion of aryl halides to phenols, we found that hydroxide bases provided optimal results. We were surprised by this base dependence on selectivity. We postulate that the phenol product predominates when using KOH (2.0 equiv) since attack on the $L_nPd(II)Ar(Br)$ species by hydroxide occurs much faster than attack by in situ generated KOAr. Of note, when 1.0 equiv of KOH is used, the phenol is still the major product, suggesting that under these reaction conditions, when the KOH is used up (∼50% conv ArBr), that deprotonation (by KOAr) of Pd-bound water occurs faster than phenoxide attack on the $L_nPdAr(Br)$ species. Interestingly, we found that if the base is changed to K_3PO_4 or other inorganic bases (e.g., Cs_2CO_3, K_2CO_3), none of the phenol was isolated; instead quantitative conversion of the aryl halide to its symmetrical diaryl ether was realized. In this case, the rate of phenol formation must be less than the rate of diaryl ether formation. We note that the biphasic reaction conditions and the large excess of water complicate the mechanistic rationale for formation of phenol rather than diaryl ether. In summary, we have developed an efficient system for the direct Pd-catalyzed synthesis of phenols from aryl halides. We have also demonstrated that these initially formed phenols can be converted to alkyl aryl ethers via a one-pot phenol synthesis/alkylation protocol. This provides a strategy for their synthesis involving the concatenation of two electrophilic components (and KOH) in contrast to the usual ones in which there is one nucleophilic and one electrophilic component. In many instances this process overcomes limitations in existing Pd-catalyzed coupling reactions of aliphatic alcohols with aryl halides.



Entry	Base	Phenol	Ether
1	KOH (2.0 equiv.)	99%	<1%
2	KOH (1.0 equiv.)	88%	6%
3	K_3PO_4 (1.0 equiv.)	<1%	99%

Figure 1. Phenol formation vs symmetrical diaryl ether formation.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Symmetrical diaryl ethers are sometimes seen as byproducts. These are presumably formed via coupling of the aryl halide and phenol, which in turn, is likely formed from the starting aryl halide by reaction with trace adventitious water.
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