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Copper-Catalyzed Coupling of Aryl Iodides with Aliphatic Alcohols

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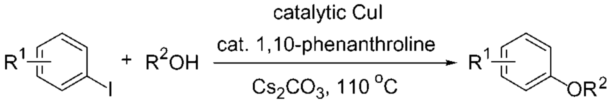
ABSTRACT



A simple and mild method for the coupling of aryl iodides and aliphatic alcohols that does not require the use of alkoxide bases is described. The reactions can be performed in neat alcohol. For more precious alcohols, the etherification was carried out in toluene as solvent using 2 equiv of alcohol. Additionally, the cross-coupling of an optically active benzylic alcohol with an unactivated aryl halide was demonstrated to proceed with complete retention of configuration.

The formation of carbon-heteroatom bonds by transition metal catalyzed cross-coupling methodology has been the subject of significant interest during the past few years.[1] Although the majority of efforts has focused on C−N bond-forming processes, techniques for the formation of aromatic C−O bonds have also been reported.[2−4] Our group and that of Hartwig, as well as others, have shown that tertiary alcohols, silanols, and phenols, all lacking β-hydrogen groups, can be efficiently coupled with aryl chlorides and bromides.[2] We have also demonstrated that the intramolecular variant of this process, with proper choice of ligands, is much more general with respect to the nature of the alcohol moiety being coupled.[3] Additionally, we recently reported the first general catalyst capable of the efficient transformation of primary alcohols with nonactivated aryl chlorides and bromides.[4] Although this system could combine a variety of aryl halides with primary alcohols in high yield, reactions involving secondary alcohols remain problematic. Specifically, the use of aryl halide substrates that contained strongly electron-donating substrates in the *para* or *ortho* positions are particularly difficult.

The copper-mediated Ullmann ether synthesis is a classical method for the synthesis of aryl alkyl ethers.[5,6] The synthetic scope of this reaction, however, is reduced as a result of the harsh reaction conditions that are needed. This C−O bond-forming process requires strong bases such as alkoxides or sodium hydride. Other severe drawbacks include the following requirements: (a) a large amount of the alkoxide, (b) high temperatures, (c) highly polar aprotic solvents, and (d) stoichiometric quantities of the copper salt.[7]

Beginning with our reports that the Ullmann diaryl ether synthesis[8] and N-arylation of imidazoles could be signifi-

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(1) For review, see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*(1−2), 125. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046.

(2) (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (b) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (c) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498. (d) Palucki, M; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395.

(3) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Torraca, K. E.; Kuwabe, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907. (c) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

(4) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770.

(5) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853.

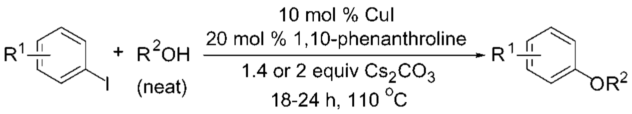
(6) General review: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(7) For recent examples, see: (a) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565. (b) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633. (c) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 1007. (d) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J; Jeong, K-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844. (e) Peeters, L. D.; Jacobs, S. G.; Eevers, W.; Geise, H. J. *Tetrahedron* **1994**, *50*, 11533. (f) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (g) Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011.

(8) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

10.1021/ol025548k CCC: $22.00

Table 1. Copper-Catalyzed Coupling of Aryl Iodides with Primary Alcohols[a]



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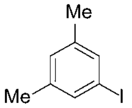
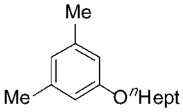
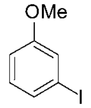
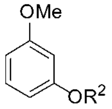
1		*n*HeptOH		81
2		*n*BuOH		94[c]
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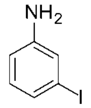
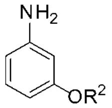
4		*n*BuOH		71
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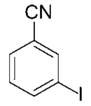
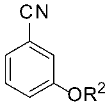
6		*n*BuOH		88[d,e]
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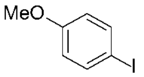
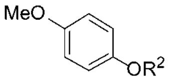
8		MeOH		88
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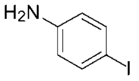
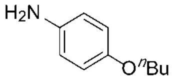
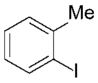
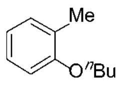
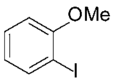
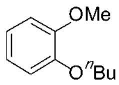
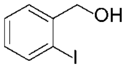
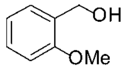
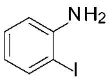
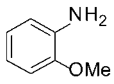
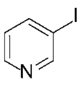
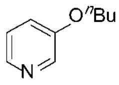
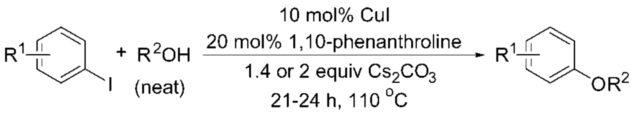
10		*n*BuOH		40
11		*n*BuOH		97
12		*n*BuOH		72
13		MeOH		87[f]
14		MeOH		53
15		*n*BuOH		87

[a] Reaction conditions: 1 mmol of aryl iodide, 1 mL of R²OH, under air in a sealed test tube. Reaction time not optimized for each substrate. [b] Isolated yield (average of two runs; estimated to be >95% pure by ¹H NMR, GC analysis, and/or combustion analysis). [c] 5 mol % CuI was used. [d] Reaction time of 28 h. [e] 4 equiv of R²OH in 1 mL of toluene was used. [f] Reaction temperature of 80 °C. At 110 °C, 67% isolated yield.

Table 2. Copper-Catalyzed Coupling of Aryl Iodides with Secondary Alcohols[a]



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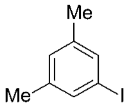
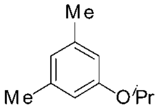
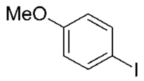
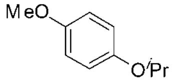
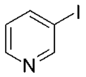
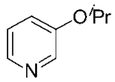
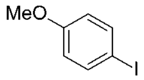
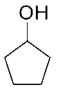
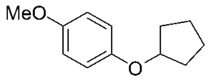
1		*i*PrOH		67
2		*i*PrOH		79
3		*i*PrOH		92
4				75[c]

[a] See Table 1. [b] See Table 1. [c] Reaction temperature of 120 °C. At 110 °C, 85% conversion and 67% isolated yield.

cantly improved when carried out in nonpolar solvents,[9] we have recently demonstrated substantially improved versions of the Goldberg coupling of amides and the Ullmann coupling of nitrogen heterocycles.[10] These reports were followed by our description of methods for the N-arylation of hydrazides,[11] the N-arylation of amines,[12] and the C-arylation of malonates.[13] Thus, it was a natural extension for us to investigate the copper-catalyzed coupling of aliphatic alcohols with aryl halides. In a preliminary survey, a variety of different reaction conditions were screened. These results indicated that bidentate nitrogen ligands work best for this transformation. This is in accord with recent results by Hauptman,[7f] who studied ligand systems for the Ullmann ether synthesis. As in our previous work,[8] the choice of cesium carbonate as a mild base seems to be of crucial importance for the outcome of the reaction. Other mild bases screened in this survey, such as potassium phosphate, sodium carbonate, and potassium carbonate, as well as secondary and tertiary amines, gave poorer results. Toluene gave superior results in comparison with other solvents (e.g., dimethylformamide, dioxane, butyronitrile, dimethyl sulfoxide, and a variety of amines).

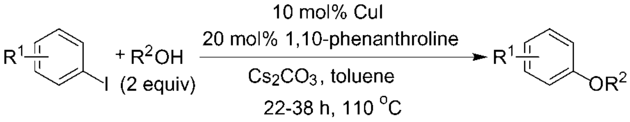
Herein we report that the catalyst system consisting of copper(I) iodide, 1,10-phenanthroline, and cesium carbonate is a powerful method for the synthesis of a variety of different aryl alkyl ethers within ~24 h at 110 °C.[14] The reactions can be carried out under air without exclusion of moisture.[15]

Using our method designed for the arylation of inexpensive, neat alcohols, we subjected a series of aryl iodides to these reaction conditions (Tables 1 and 2). As can be seen in Table 1, primary alcohols such as methanol, ethanol, butanol, heptanol, and benzyl alcohol were successfully transformed. To our satisfaction, strongly electron-donating substituents such as OMe gave high yields in the *meta*- (entries 2 and 3), *para*- (entries 8 and 9), and *ortho*-position (entries 11−13). Aniline groups (entries 4, 5, 10, 14) and free benzylic -OH groups (entry 13) are well tolerated on the aromatic moiety. Although the conversion of substrates with free -NH_2 groups in *para*- and *ortho*-position is complete after ~24 h, the desired products were isolated in moderate yield as a result of decomposition of the starting materials. Notably, these results are superior to those observed in analogous Pd-catalyzed transformations where free anilines on the aryl halide moiety are detrimental.[16] For free benzylic -OH groups (entry 13) the yield could be significantly improved by switching to a lower reaction temperature of 80 °C. The electron-withdrawing substituent CN seemed to be more sensitive under the coupling conditions, likely because the nitriles are good ligands for copper. In neat alcohol, mixtures of the corresponding amide and ester as well as other decomposition products were observed even at lower temperatures and shorter reaction times. Thus, this reaction was performed with only 4 equiv of alcohol in toluene as a solvent to give the desired products in high yields (entries 6 and 7). A heterocyclic substrate such as 3-iodopyridine (entry 15) can also be successfully coupled.

The generation of alkyl aryl ethers from secondary alcohols represents a more challenging synthetic problem[7b,17] that thus far cannot be generally solved using palladium catalysts, where β-hydride elimination often imposes serious restrictions. Thus, we examined the possibility of coupling common secondary alcohols that could also serve as solvents. The results of this study, summarized in Table 2, indicate that secondary aryl alkyl ethers can be obtained by this method, albeit sometimes in lower yields than their primary counterparts (see Table 1). This is in part due to incomplete conversion under the reaction conditions after 24 h. In the case of cyclopentanol (Table 2; entry 4), the reaction temperature had to be elevated to 120 °C in order to achieve complete conversion to provide the coupling product in good yield.

During our preliminary studies, we found that the method can be successfully applied when toluene is used as solvent. For more precious alcohols, it is desirable to run the reaction in a solvent using only a moderate excess of one of the coupling components. Table 3 displays some of our results. It should be mentioned that the reactions have to be carried out at high concentrations (usually 0.5 mL toluene/1 mmol substrate) in order to maintain a highly active catalytic system.

Table 3. Copper-Catalyzed Coupling of Aryl Iodides with Aliphatic Alcohols Using Toluene as Solvent[a]



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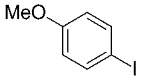
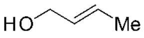
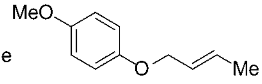
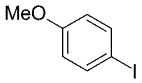
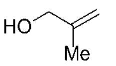
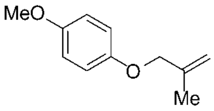
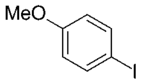
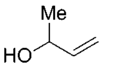
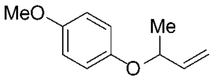
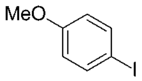
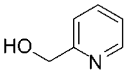
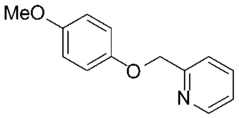
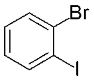
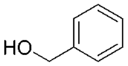
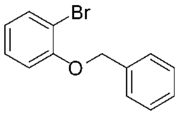
1				86
2				78
3				54
4				56
5				71

[a] Reaction conditions: 1 mmol of aryl iodide, 2 equiv of R^2OH, 1.4 or 2 equiv of Cs_2CO_3, 0.5 mL of toluene, under air in a sealed test tube. Reaction time not optimized for each substrate. [b] See Table 1.

To demonstrate the scope of the method, several allylic alcohols (entries 1−3), pyridine-2-methanol (entry 4), and 2-iodo-bromobenzene (entry 5) were used as substrates. Since *para*-substituted electron-rich aryl halides are difficult substrates for the corresponding palladium-catalyzed transformations, we chose 4-iodoanisole as the aromatic coupling component for the allylic alcohols. The primary allylic alcohols afforded the corresponding ethers in good yield (entries 1 and 2).[18] For a secondary allylic alcohol (entry 3) the moderate yield can be ascribed to enhanced steric hindrance at the reaction center. Similar to our observations in Cu-catalyzed C−N bond formations,[8−12] this system is relatively insensitive to electronic effects.

Notably, the cross-coupling of an unactivated aryl halide (e.g., 3-iodoanisole) and an enantiomeric pure benzylic alcohol proceeded with complete retention of configuration (Scheme 1). This mild and efficient route to enantiopure benzylic aryl alkyl ethers[19,20] is particularly important because

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(9) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

(10) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729.

(11) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

(12) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

(13) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.

(14) Recently, Venkataraman showed that similar reaction conditions can be utilized, employing an isolated, air stable, triphenyl phosphine complex of (1,10-phenanthroline)CuI for the preparation of triarylamines and diaryl ethers and for the Sonogashira-type arylation of terminal alkynes. Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315.

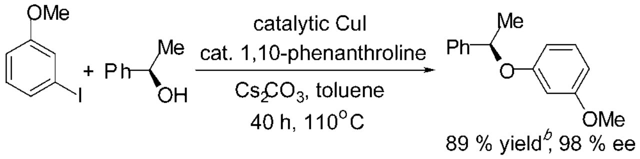
(15) **Typical Experimental Procedure.** A test tube was charged with CuI (10 mol %), 1,10-phenanthroline (20% mol), Cs_2CO_3 (1.4−2.0 mmol), aryl iodide (1.0 mmol), and either (a) the alcohol (1 mL) or (b) the alcohol (2 mmol) and toluene (0.5 mL). The test tube was sealed, and the reaction mixture was stirred at 110 °C for ~24 h. The resulting suspension was cooled to room temperature and filtered through a 0.5 × 1 cm pad of silica gel, eluting with diethyl ether. The filtrate was concentrated. Purification of the residue by flash chromatography on silica gel gave the desired product (see Supporting Information).

(16) Harris, M. C.; Buchwald, S. L. Unpublished results.

(17) For some recent Ullmann-type reactions with secondary alcohols, see for example: (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (b) Morishima, Y.; Fujita, J.; Ikeda, T.; Kamachi, M. *Chem. Lett.* **1994**, 557.

(18) To date, allylic alcohols are poor substrates in the analogous Pd-catalyzed couplings. Torraca, K. E.; Huang, X.; Buchwald, S. L. Unpublished results.

Scheme 1. Copper-Catalyzed Coupling of Optically Active *sec*-Phenethyl Alcohol with Retention of Configuration[a]



[a] Reaction conditions: 1 mmol of aryl iodide, 2 equiv of secondary alcohol (>99% ee), 10 mol % CuI, 20 mol % 1,10-phenanthroline, 2 equiv of Cs_2CO_3, 0.5 mL of toluene, under air in a sealed test tube. [b] See Table 1.

the analogous Pd-based methods have thus far failed in this context.[2d]

In summary, we have developed an experimentally simple method for the mild and efficient coupling of aryl iodides and aliphatic alcohols. This reaction protocol can be performed under air and without taking any precautions to exclude moisture. Further studies into the scope and mechanism of this and related copper-catalyzed C−O bond formation methodologies are currently under way in our laboratories.

Acknowledgment. We thank the National Institutes of Health (GM 58160) for support of this work. We gratefully acknowledge unrestricted support from Pfizer, Merck, and Bristol-Myers Squibb. M.W. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship.

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

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(19) For recent examples of the preparation of enantiomeric pure benzylic aryl ethers using either an activated arylfluoride in a SNAr-type reaction or Mitsunobu conditions with inversion of configuration, see: (a) Ratz, A. M.; Weigel, L. O. *Tetrahedron Lett.* **1999**, 2239. (b) Chumpradit, S.; Kung, M.-P.; Panyachotipun, C.; Prapansiri, V.; Foulon, C.; Brooks, B. P.; Szabo, S. A.; Tejani-Butt, S.; Frazer, A.; Kung, H. F. *J. Med. Chem.* **1992**, *35*, 4492.

(20) For the synthesis of benzylic aryl alkyl ethers derived from cinchona alkaloids using classical Ullmann conditions, see ref 7d.