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Copper(I)-Catalyzed Aryl Bromides To Form Intermolecular and Intramolecular Carbon−Oxygen Bonds

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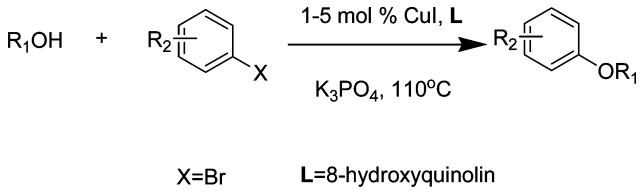

A highly efficient Cu-catalyzed C−O bond-forming reaction of alcohol and aryl bromides has been developed. This transformation was realized through the use of copper(I) iodide as a catalyst, 8-hydroxyquinoline as a ligand, and K_3PO_4 as a base. A variety of functionalized substrates were found to react under these reaction conditions to provide products in good to excellent yields.

Aryl ethers, including oxygen heterocycles, are key constituents in numerous natural products and pharmaceuticals[1] and aryl aliphatic ethers are often utilized as phenol precursors.[2]

Recently, transition metal-catalyzed C−O bond-forming reactions have become important methods for the preparation of oxygen-containing compounds.[3] Major advancements have been made in this area by both the groups of Buchwald and Hartwig, as well as others, in the palladium-mediated Ullmann ethers synthesis. The intermolecular and intramolecular carbon−oxygen bond was formed by using aryl bromides and aryl chlorides as substrate.[4] Nevertheless, these systems still suffer from some limitations because of the need to prepare and use environmentally unfriendly PR_3 ligands.

The traditional Ullmann-type Cu(I)-catalyzed cross-coupling of alkoxides with aryl halides is limited by unfavorable conditions, such as high temperatures, a large amount of the alkoxide, and stoichiometric quantities of the copper salt.[5,6] During the past few years, some significant modifications have been made for the synthesis of aryl ethers. In 2002, Buchwald's group first reported that using 10 mol % of CuI in conjunction with 20 mol % of 1,10-phenanthroline could make C−O bond formation between aryl iodides and aliphatic alcohols successful under mild reaction conditions (Cs_2CO_3/110 °C/18−38 h);[7a] however, aryl bromides were unreactive in this system. Subsequently reported catalyst systems that employ butyronitrile as solvent, amino acids as ligands, KF/Al_2O_3 as the base, or microwave irradiation also succeeded in coupling different aryl iodides and aliphatic aolchols.[7b−e] Although a recently developed procedure that use modified 1,10-henanthroline was applied in the coupling of highly active benzyl alcohol with aryl bromide, low active aliphatic alcohols still required higher temperature.[7f] So it is necessary to expand the scope of substrate under mild conditions.

Prompted by our current interest in C−O coupling reactions and the success of these reported process, we decided to investigate the copper-catalyzed C−O formation between aryl bromides and aliphatic alcohols via the utilization of air-stable copper salt and readily available ligands.[8]

Herein, we report a simple, inexpensive, and effective catalytic system for the synthesis of aryl-aliphatic ethers under mild reaction conditions. More importantly, by employing this system, both intermolecular and intramolecular C−O bond formation was achieved successfully.

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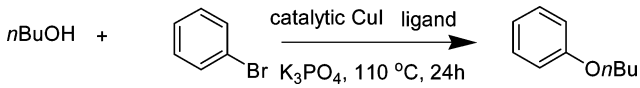
SCHEME 1. Sceening of Ligands for CuI-Catalyzed C−O Coupling



In the primary screening experiments, a series of ligands were examined in the reaction of bromobenzene and *n*-butyl alcohol, using the following catalyst system: 5 mol % CuI/10 mol % ligand/K_3PO_4/110 °C/24 h and *n*-butyl alcohol itself as solvent (Scheme 1). The results of screening experiments were presented in Figure 1. From the results, it was apparent that 8-hydroxyquinoline showed the most activity. Comparing bars 7, 8, and 9, it was found that the presence of the −OH group was the key element of the success. When the proton was replaced by a methyl or acetyl group, the yield was decreased obviously. Some ligands, such as 1,10-phenanthroline and amino acids, which were used in the coupling between aryl iodides and alcohols successfully, could not proceed in aryl bromides or in a low yield, which was consistent with the substrate activity order of I > Br ≫Cl > F.[6]

Further experiments were performed to examine the influence of base on conversion and selectivity. A set of bases were examined in the reaction of bromobenzene and *n*-butyl alcohol, under the following reaction condition: 5 mol % CuI/10 mol % 8-hydroxyquinoline/110 °C/24 h and *n*-butyl alcohol itself as solvent. As shown in Table 1, although Na_2CO_3, K_2CO_3, and some organic base gave a quite low conversion, when K_3PO_4 and Cs_2CO_3 were used as base the starting material was nearly transformed completely after 24 h, at the same time biphenyl ether was produced as a byproduct, presumably because nucleophilic displacement of the −OH group of *n*-butyl alcohol

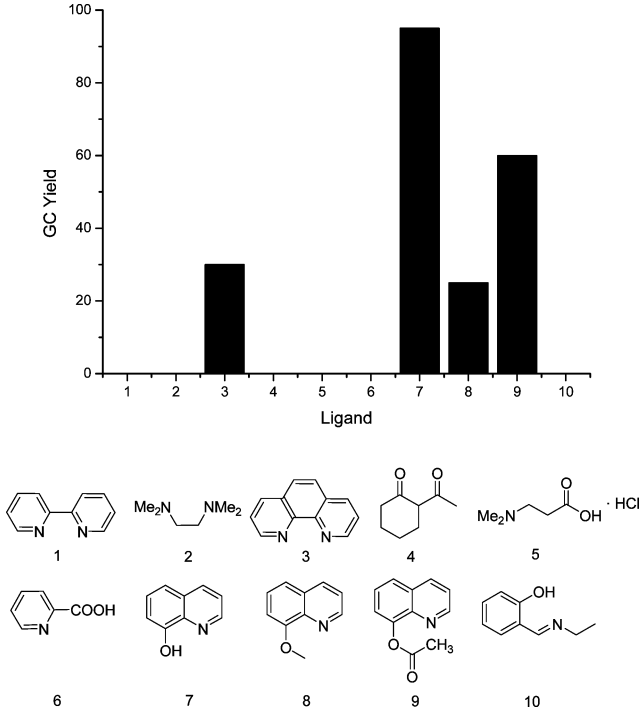
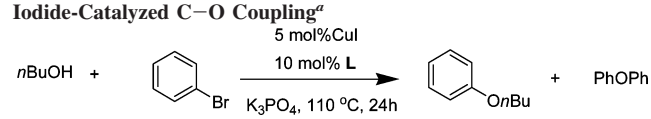


FIGURE 1. Comparison in different ligands. Reaction conditions: PhBr (1.0 mmol), CuI (0.05 mmol, 5 mol %), ligand (0.1 mmol, 10 mol %), and K_3PO_4 (2 mmol) were added to a screw-capped test tube followed by the addition of 1 mL of *n*-butyl alcohol. The reaction was stirred 24 h at 110 °C under argon. Conversion was measured by GC, with phenyl ethyl ether as internal standard.

TABLE 1. Comparison of Different Bases for the Copper Iodide-Catalyzed C−O Coupling[a]



entry	base	PhOnBu	PhOPh
1	Na_2CO3	3	<1
2	K_2CO_3	5	<1
3	K_3PO_4	95	3
4	Cs_2CO_3	68	28
5	NEt_3	4	<1
6	pyridine	6	<1
7		11	<1

[a] Reaction conditions: PhBr (1.0 mmol), CuI (0.05 mmol, 5 mol %), 8-hydroxyquinoline (0.1 mmol, 10 mol %), and base (2 mmol) were added to a screw-capped test tube followed by the addition of 1 mL of *n*-butyl alcohol. The reaction was stirred 24 h at 110 °C under argon. Conversion was measured by GC, with phenyl ethyl ether as internal standard.

yielded phenol, with which cross-coupled bromobenzene successionally. This process could be inhibited by selecting the proper base. By using K_3PO_4 as base, only a minute (3%) amount of the undesired symmetrical biphenyl ether was detected (Table 1, entry 3).

To determine the scope of the catalytic system, the present protocol was applied in reactions of a range of commercially available aryl bromides and aliphatic alcohols. As shown in Table 2, the coupling of aliphatic alcohols with different aryl bromides was successful, leading to the desired products in good yields. The protocol was tolerant to electron-withdrawing and -donating functional groups and also to the presence of a group in the ortho-position of the aryl bromides (Table 2, entries 2, 4, 5, and 6). Moreover, the reactions showed interesting chemoselectivity; see entry 6 for preferred C−O coupling in the presence of an $-NH_2$ group, which could be coupled with aryl bromides potentiality to form a C−N bond. We could also utilize the intrinsic reactivity of aryl halides to selectively couple the −Br group when both −Br and −Cl existed in the aromatic ring (Table 2, entry 8). Functional groups that were compatible with Cu-catalyzed alcohol arylation protocol include thioether, keto, and nitro.

The carbon−oxygen bond formation reaction was also tested employing tethered ortho-bromide aryl alcohols. As can be seen in Table 3, the intramolecular *O*-arylation aryl halides could be carried out successfully under mild reaction conditions by using a similar protocol. It appeared that the yield was decreased greatly without adding the ligand (Table 3, entry 1). The choice of Cs_2CO_3 as base was more effective than K_3PO_4, which might be because the existence of Cs_2CO_3 was helpful in forming phenoxides.[9,10] Both five- and six-membered ring formations could be accomplished with aryl bromide substrate at 110 °C. The reaction of aryl chloride substrate was slightly more demanding, and a good yield was obtained by raising the reaction temperature (Table 3, entry 2).

In summary, we have developed an efficient, mild, and inexpensive Cu-catalyzed coupling reaction of aliphatic alcohols and aryl bromides at 110 °C that uses commercially available components and readily available ligand. A variety of functional

(9) Take entry 2 in Table 3 for example: 65% GC yield obtained when K_3PO_4 was used as base in the same reaction conditions.

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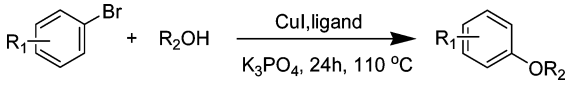
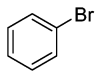
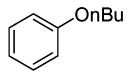
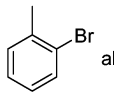
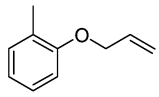
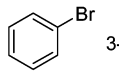
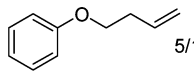
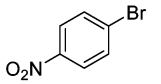
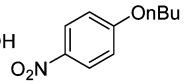
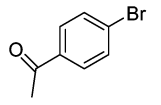
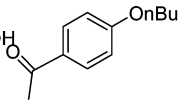
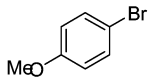
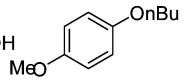
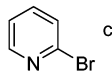
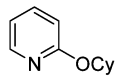
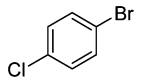
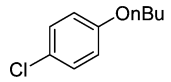
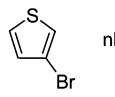
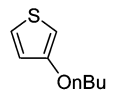
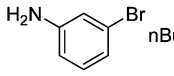
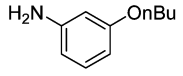
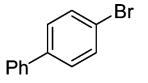
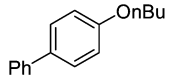
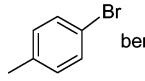
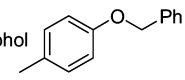
TABLE 2. Copper-Catalyzed Coupling of Aryl Bromides with Aliphatic Alcohols[a]



entry	aryl bromide	R_2OH	Product	CuI/**L**	yield, [b]%
1		nBuOH		2/4	87
2		allyl alcohol		5/10	89[c]
3		3-buten-1-ol		5/10	92
4		nBuOH		2/4	83
5		nBuOH		3/6	92
6		nBuOH		5/10	78[d]
7		cyclohexanol		5/10	84
8		nBuOH		3/6	81
9		nBuOH		5/10	80
10		nBuOH		3/6	85
11		nBuOH		3/6	81
12		benzyl alcohol		3/6	89

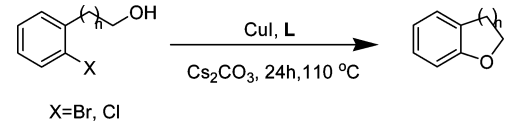
[a] General reaction conditions: ArBr (1.0 mmol), CuI (0.02−0.05 mmol, 2−5 mol %), 8-hydroxyquinoline (0.04-0.1 mmol, 4−10 mol %), and K_3PO_4 (2.0 mmol) in 1 mL of R_2OH and 2.0 mmol of K_3PO_4 under argon were added to a sealed test tube. [b] Yield of >95% purity as determined by GC and ^{1}H NMR. [c] CS_2CO_3 as base. [d] 48 h.

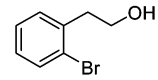
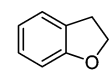
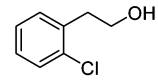
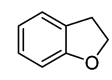
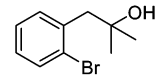
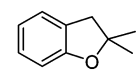
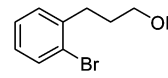
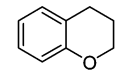
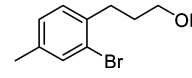
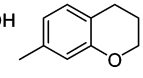
groups are compatible with these reaction conditions. The mild reaction conditions and increased scope relative to previous ones would render this protocol attractive to synthetic chemists.

Experimental Section

General Procedure for the *O*-Arylation of Aliphatic Alcohols. CuI (2−5 mol %), 8-hydroxyquinoline (4−10 mol %), aryl halide (if solid, 1 mmol), and K_3PO_4 (425 mg, 2.0 mmol) were added to a screw-capped Schlenk tube under argon. The tube was then evacuated and backfilled with argon (3 cycles). Aryl halide (if liquid, 1.0 mmol) and aliphatic alcohol (1 mL) were added by syringe at room temperature. The reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was allowed to reach room temperature and then diluted with dichloromethane (10 mL). The slurry was filtered and the filter cake was washed with 10 mL of dichloromethane. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to afford the desired product.

TABLE 3. Copper-Catalyzed Syntheses of Cyclic Aryl Ethers[a]



entry	substrate	Product	CuI/**L**	yield, [b]%
1			1/2 5/0	82 45
2			5/10	82[c]
3			5/10	83
4			1/2	93
5			5/10	87

[a] General reaction conditions: intramolecular alcohol−ArBr/Cl substrate (1.0 mmol), CuI (0.01−0.05 mmol, 1−5 mol %), 8-hydroxyquinoline (0.02-0.1 mmol, 2−10 mol %), and Cs_2CO_3 (2.0 mmol) in toluene (1 mL) under argon were added to a sealed test tube. [b] Yield of >95% purity as determined by GC and ^{1}H NMR. [c] 120 °C and 1 mL of xylene as solvent.

General Procedure for the Copper-Catalyzed Syntheses of Cyclic Aryl Ethers. CuI (1−5 mol %), 8-hydroxyquinoline (2−10 mol %), and Cs_2CO_3 (651 mg, 2.0 mmol) were added to a screw-capped Schlenk tube under argon. The tube was then evacuated and backfilled with argon (3 cycles). Aryl halide (1.0 mmol) and toluene (1 mL) were added by syringe at room temperature. The reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was allowed to reach room temperature and then diluted with dichloromethane (10 mL). The slurry was filtered and the filter cake was washed with 10 mL of dichloromethane. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to afford the desired product.

***n*-Butyl phenyl ether (Table 2, entry 1):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.29 (m, 2H), 6.88−6.94 (m, 3H), 3.96 (t, J = 6.0 Hz, 2H), 1.73−1.78 (m, 2H), 1.47−1.53 (m, 2H), 0.97 (t, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.1, 129.2, 120.3, 114.4, 67.3, 31.3, 19.2, 13.7 ppm; MS *m*/*z* 150 (M^+), 94, 77, 66, 57, 51, 41, 29. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.73; H, 9.52.

Allyl 2-tolyl ether (Table 2, entry 2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.15 (m, 2H), 6.80−6.87 (m, 3H), 6.03−6.12 (m, 1H), 5.45 (dd, J = 17.2 Hz, J = 1.9 Hz, 1H), 5.27 (dd, J = 10.6

Hz, $J = 2.0$ Hz, 1H), 4.54 (m, 2H), 2.25 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.7, 133.7, 130.7, 126.9, 126.7, 120.5, 116.8, 111.3, 68.6, 16.2 ppm; MS *m*/*z* 148 (M^+), 133, 107, 91, 79, 77, 65, 51, 41, 39. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.22; H, 8.19.

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Supporting Information Available: NMR spectra of coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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