An Efficient Copper-Catalyzed Etherification of Aryl Halides

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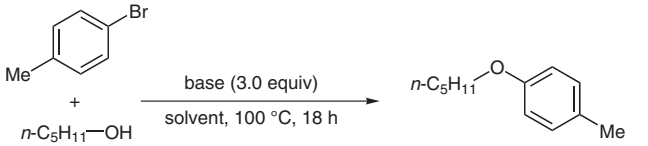
Abstract: An efficient and mild copper-catalyzed ether formation from aryl halides and aliphatic alcohols has been developed. The key to the successful coupling is the use of lithium alkoxide, directly or in situ generated by lithium *tert*-butoxide, and the corresponding alcohol as solvent.

Key words: ligand-free, copper, etherification, aryl halides

There is a continuing interest in the development of general and cost-effective methods to provide diverse scaffolds of pharmaceutically active compounds. The transition-metal-catalyzed functionalization of aryl halides (or their equivalents) serves as a powerful tool by forming C–C and C–X (X = heteroatom) bonds.[1] Driven by the need for the synthesis of aryl ethers, we became interested in etherification of aryl halides.[2] The classical copper-mediated Ullmann etherification is useful but suffers from a number of drawbacks such as harsh reaction conditions, limited scope of substrates, and high loading of a copper salt.[3] Significant progress in the past 15 years has been made in selective couplings employing a catalytic amount of a transition metal, mainly copper[4] or palladium.[5] Although palladium catalyzed C–O bond formations are successful to certain extent, the copper-based protocols are more attractive. Unlike palladium, which typically requires a bulky and often expensive phosphine ligand, copper catalyzes the Ullmann etherification through addition of a broad range of ligands based mostly on straightforward bidentate nitrogen and oxygen derivatives.[6] A great variety of structural scaffolds are employed bearing moieties, such as bipyridines,[6a] phenathrolines,[6b–d] Schiff bases,[6e] bishydrazones,[6f] β-diketone,[6g] β-keto ester,[6h] 1,1′-binaphthyl-2,2′-diamine,[6i] amino acids,[4c,6j] 8-hydroxyquinoline,[6k] and 1-naphthoic acid,[6l] providing active ligands to facilitate the copper-catalyzed coupling of aryl halides with phenols or aliphatic alcohols. This phenomenon of ligand diversity might be attributed to the complicated mechanism of copper-catalyzed coupling reactions and the various binding modes of copper complexes.[4d] Therefore, continuing ligand searching is attractive but challenging.[7] On the other hand, in general, yet mild ligand-free copper-catalyzed etherification processes are rare. In 2008, a ligand-free Ullman coupling of phenols with aryl halides using 10 mol% nano-CuO as catalyst, Cs_2CO_3 or KOH as base in DMSO at 110 °C was reported by Zheng, Wang, and co-workers.[8] In the same year Chan et al. developed a ligand-free CuI-catalyzed etherification process in which tetrabutylammonium bromide (10 mol%) was employed as an additive, K_3PO_4 as base at high temperature (in refluxing DMF).[9] This later protocol only gives good yields for coupling of aryl iodide with phenols, but much less effective with alcohols as shown by their low yields. Such a ligand-free process is highly desirable due to its obvious advantages associated with ligand cost and ligand removal in large-scale production. Herein, we report the discovery of an efficient copper-catalyzed coupling of aryl halides with aliphatic alcohols without use of any external ligand.[10]

Table 1 Optimization of Cu(I)-Catalyzed Etherification



Entry	Catalyst	Base	Solvent	Conv. (%)[a]	Yield (%)[b]
1	CuI/8-HQ	K_3PO_4	*n*-$C_5H_{11}OH$	60	54
2	CuI	K_3PO_4	*n*-$C_5H_{11}OH$	12	8
3	CuI	Cs_2CO_3	*n*-$C_5H_{11}OH$	5	3
4	CuI	NaO*t*-Bu	*n*-$C_5H_{11}OH$	99[c]	6
5	CuI	LiO*t*-Bu	*n*-$C_5H_{11}OH$	100	>99
6	CuI	LiHDMS	*n*-$C_5H_{11}OH$	20	18
7	CuBr	LiO*t*-Bu	*n*-$C_5H_{11}OH$	99	96
8	$Cu(OAc)_2$	LiO*t*-Bu	*n*-$C_5H_{11}OH$	100	94
9	CuI/8-HQ	LiO*t*-Bu	*n*-$C_5H_{11}OH$	94	89
10	CuI	none	*n*-$C_5H_{11}OH$	0	0
11	none	LiO*t*-Bu	*n*-$C_5H_{11}OH$	0	0
12	CuI	LiO*t*-Bu	DMF	94[d]	51
13	CuI	LiO*t*-Bu	dioxane	53	41
14	CuI	LiO*t*-Bu	toluene	22	21
15	CuI	LiO*t*-Bu	*t*-BuOH	75	72

[a] Conversion was measured by HPLC.
[b] Yield was determined by HPLC using product as standard.
[c] Toluene was the major product.
[d] A complicated mixture was formed.

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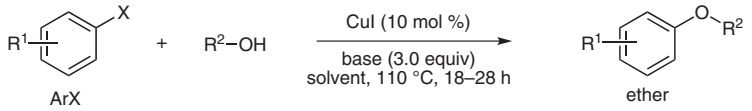
In the development of a copper-catalyzed etherification for one of our drug candidates, we found that an external ligand was not required when LiO*t*-Bu was used as base.[11] To examine the generality of the protocol, 4-bromotoluene was selected as the model substrate to synthesize 4-pentyloxytoluene (Table 1). At the outset of the screening, a recently reported CuI catalytic system employing 8-hydroxyquinoline (8-HQ) as ligand and K_3PO_4 as base under slightly milder conditions,[12] which proceeded in moderate yield (Table 1, entry 1), was set as a benchmark. To our surprise, by replacing K_3PO_4 with LiO*t*-Bu as base, the yield was significantly increased (Table 1, entry 9). More strikingly, when LiO*t*-Bu was used as base, the CuI-catalyzed coupling reaction worked smoothly to give nearly quantitative yield of the desired product without addition of an external ligand (Table 1, entry 5). Examination of other bases showed either lower conversion (Table 1, entries 2, 3, and 6) or significant reduction of 4-bromotoluene (Table 1, entry 4) resulted.[13] Both LiO*t*-Bu and a catalytic amount of Cu(I) salt are important for the successful coupling at a reasonable rate. The absence of either one led to no reaction and only starting material was recovered (Table 1, entries 10 and 11). The reaction is not very sensitive to the anion of the Cu(I) salt. For example, CuBr or Cu(OAc) is as competitive as CuI as catalyst (Table 1, entries 7 and 8).[14] Solvent screening disclosed the solvent can be the corresponding coupling alcohol, which was pentanol in this case. The reaction in DMF only gave a moderate yield of the desired ether with formation of toluene as a major byproduct from reduction of the substrate together with some polymeric species even though high conversion was achieved. Although LiO*t*-Bu was used in excess, 4-*tert*-butyloxytoluene was not detected, even where *tert*-butanol was used as solvent (Table 1, entry 15) due to its greater acidity and bulkiness. Furthermore, reduction to toluene and hydrolysis to cresol from 4-bromotoluene was minimized in this coupling process when LiO*t*-Bu was the base.

With the optimal conditions in hand, we examined the couplings of a variety of aryl halides with different alcohols (Table 2). The synthesis of aryl ethers by this method was demonstrated to be quite general for a broad scope of both coupling partners. The reactions of 4-tolyl halides (X = Cl, OTf, Br, and I) with 1-pentanol indicate tolyl bromide is as competitive as its iodo counterpart, although copper-catalyzed ether formation generally favors aryl iodide as coupling partner.

Table 2 Scope of Cu(I)-Catalyzed Etherification



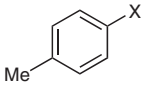
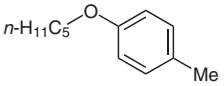
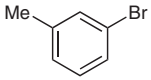
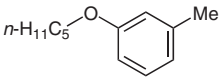
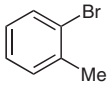
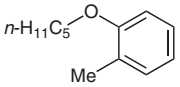
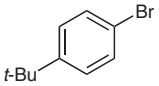
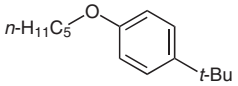
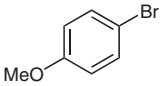
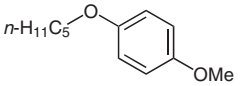
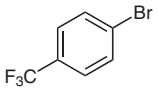
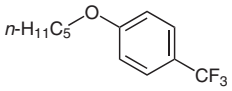
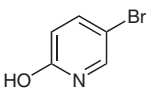
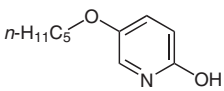
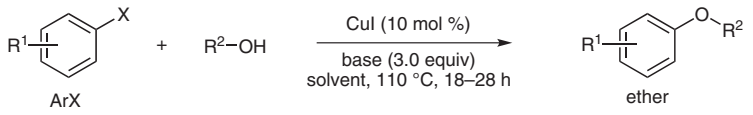
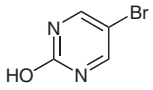
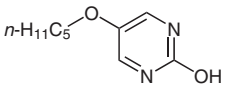
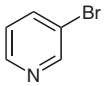
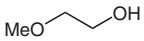
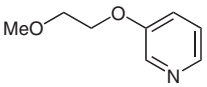
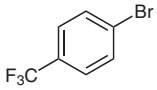
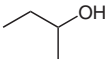
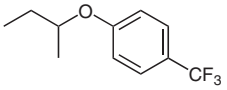
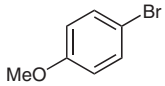
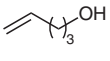
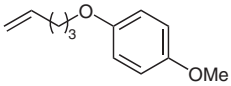
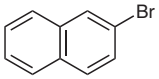
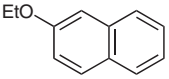
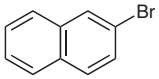
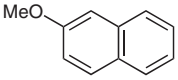
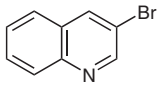
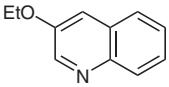
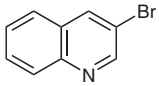
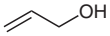
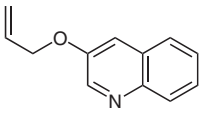
Entry	ArX	R^2OH	Base	Ether	Yield (%)[a,b]
1		*n*-$C_5H_{11}OH$	LiO*t*-Bu		X = Cl, 12 X = OTf, 27 X = Br, 97 X = I, 94
2		*n*-$C_5H_{11}OH$	LiO*t*-Bu		96
3		*n*-$C_5H_{11}OH$	LiO*t*-Bu		64
4		*n*-$C_5H_{11}OH$	LiO*t*-Bu		98
5		*n*-$C_5H_{11}OH$	LiO*t*-Bu		94
6		*n*-$C_5H_{11}OH$	LiO*t*-Bu		58
7		*n*-$C_5H_{11}OH$	LiO*t*-Bu		90

Table 2 Scope of Cu(I)-Catalyzed Etherification (continued)

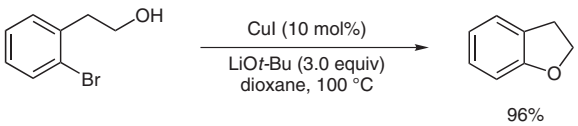


Entry	ArX	R^2OH	Base	Ether	Yield (%)[a,b]
8		*n*-$C_5H_{11}OH$	LiO*t*-Bu		92
9			LiO*t*-Bu		95
10			LiO*t*-Bu		55
11			LiO*t*-Bu		85
12[c]		EtOH	EtO*t*-Bu		74
13[c]		MeOH	MeOLi		95
14[c]		EtOH	EtOLi		93
15			LiO*t*-Bu		98

[a] Isolated yield.
[b] Reaction time and temperature are not optimized.
[c] Reaction run at 80 °C.

However, the corresponding chloride is less reactive and triflate is less tolerable by this process (Table 2, entry 1). A variety of aliphatic alcohols including the ones bearing double bond (Table 2, entries 11 and 15) are suitable for the coupling reaction. Secondary alcohols are less active (Table 2, entry 10) and tertiary alcohols are not effective. Aryl bromides are generally excellent coupling partners. Heterocycles and hydroxyl-bearing heterocycles are tolerated affording high yields of the product (Table 2, entries 7–9, 14, and 15). A particularly noticeable feature for the hydroxyl-bearing substrates is that aryl–aryl ether bond formation is completely suppressed by this process. However, the trifluoromethyl group is less stable to the conditions leading to lower yields (Table 2, entries 6 and 10).[15] Although other lithium alkoxides are equally effective (Table 2, entries 12–14), in most cases LiO*t*-Bu is the base of choice since it can generate a broad range of alkoxides in situ and does not form the corresponding *tert*-butyl aryl ether as byproduct. When most of the couplings were run at 100–110 °C, lower reaction temperature (80 °C, Table 2, entries 12–14) was effective. Intramolecular etherification can be efficiently carried out with the same combination of CuI and LiO*t*-Bu using dioxane as solvent (Scheme 1).

In conclusion, we have developed a mild and efficient copper-catalyzed etherification of aryl halides. This process has been shown to be general for the synthesis of a wide range of aryl ethers.[16] This new protocol should be a welcomed addition as a straightforward approach to preparing a variety of aryl alkyl ethers without the need for added, often costly ligands.



Scheme 1 Intramolecular CuI-catalyzed etherification

Acknowledgment

We thank Dr. Xiang Wang for his insightful suggestions and discussions during the preparation of this manuscript.

References and Notes

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Dieterich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, **1998**. (b) *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, **2009**.

(2) Among the 22 small molecules marketed theraputic new molecular entities (NMEs) in 2009 alone, seven of them contain either aryl aryl or aryl alkyl ether bonds. For details, see: Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*, Vol. 45; Macor, J. E., Ed.; Academic Press: London, **2010**, 467.

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(10) A multikilogram process has been successfully carried out by us based on this protocol.

(11) In our original process for the particular drug candidate, the very expensive 3,4,7,8-tetramethyl-1,10-phenanathroline (20 mol%, MW = 236.3. $63.9/g, from Aldrich) was used as ligand.

(12) For the consideration of less stable substrate, intead of 110 °C as the original literature reported (ref. 6k), 100 °C was chosen for screening purpose.

(13) In the case of NaO*t*-Bu, toluene is detected as the major product from reduction of 4-bromotoluene. Bacon, R. G.; Ressison, S. C. *J. Chem. Soc. C* **1969**, 312.

(14) Cu(II) salts were found slightly less effective.

(15) The presence of other functional groups such as ester, carboxylic acid, nitro, and cyano were not successful under this protocol.

(16) **General Procedure for the Etherification of Arylbromides**

To a 10 mL seal tube were charged alcohol (2.0 mL) and LiO*t*-Bu (480 mg, 6.0 mmol). The resulting suspension was stirred at r.t. for 5 min to form a clear solution. Arylbromide (2.0 mmol) and CuI (38 mg, 0.2 mmol) were added to the above solution. The mixture was stirred at r.t. for 5 min to form a nearly clear solution which was sealed and stirred at 80–110 °C for 18–28 h. The reaction was cooled to r.t. and quenched with AcOH (pH = 7–8) and diluted with CH_2Cl_2. The mixture was washed with H_2O (2 × 5 mL) and solvent removed. The crude residue was purified by silica gel column chromatography to give the desired product. The identity and purity of the products are confirmed by ^1H NMR, ^{13}C NMR, and HRMS spectroscopic analysis.

5-(Pentyloxy)pyrimidin-2-ol (Table 2, Entry 8)

Off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 2 H), 3.86 (t, *J* = 8 Hz, 2 H), 1.77 (m, 2 H), 1.40–1.45 (m, 4 H), 0.94 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 144.8, 142.2, 70.5, 28.7, 28.0, 22.4, 14.0 ppm. HRMS: m/z calcd for $C_9H_{14}N_2O_2$: 182.1055; found: 182.1053.

3-(2-Methoxyethoxy)pyridine (Table 2, Entry 9)

Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.23 (m, 1 H), 7.23 (m, 2 H), 4.17 (t, *J* = 4 Hz, 2 H), 3.77 (t, *J* = 4 Hz, 2 H), 3.46 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 142.4, 138.0,. 123.8, 121.4, 70.9, 67.7, 59.3 ppm. HRMS: m/z calcd for $C_8H_{11}NO_2$: 153.0790; found: 153.0785.