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Cu-Catalyzed Arylation of Phenols: Synthesis of Sterically Hindered and Heteroaryl Diaryl Ethers

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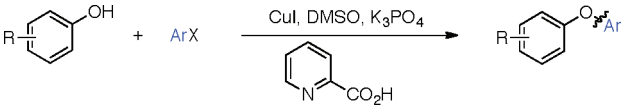
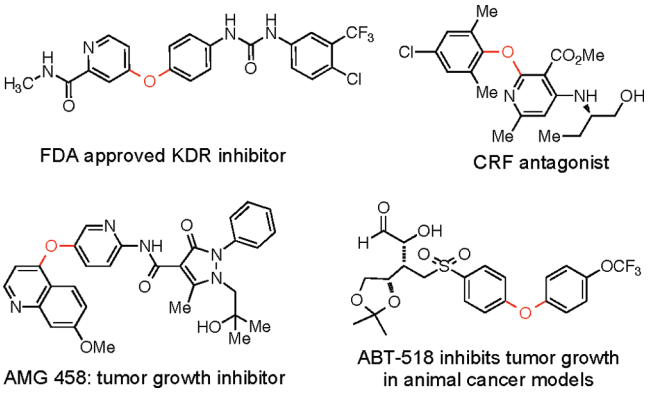


Cu-catalyzed O-arylation of phenols with aryl iodides and bromides can be performed under mild condition in DMSO/K_3PO_4 with use of picolinic acid as the ligand for copper. This method tolerates a variety of functional groups and is effective in the synthesis of hindered diaryl ethers and heteroaryl ethers.

The diaryl ether linkage is present in a range of important compounds including a number of potential pharmaceuticals,[1−4] commercially available engineering thermoplastics,[5,6] and herbicides (Scheme 1).[7−9] This motif also appears in biologically active natural products, notably in the mammalian hormone thyroxine[10] and the vancomycin family of antibiotics.[11] There has been recent interest in the synthesis of atropisomeric diaryl ethers[12,13] as these may have application as molecular gears.[14]

SCHEME 1. Selected Biologically Active Diaryl Ethers



Diaryl ethers are classically made by the Ullmann reaction[15] of phenols with aryl halides promoted by stoichiometric or greater quantities of copper at high temperatures (125−300 °C) in polar solvents (typically pyridine or DMF), conditions which are unsuitable for the construction of complex molecules.[16−21]

In an important advance, Lam,[22] Chan,[23] and Evans[24] developed the Cu-catalyzed coupling of arylboronic acids with phenols.[16,25] The ability to use stable, and in some cases commercially available, boronic acids in these reactions was a considerable step forward and these reactions have been applied in the synthesis of a number of complex natural products.[16,19] Despite the advantages of this method a number of limitations remain, typically an excess of the boronic acid component is required for optimal yields and the use of heterocyclic substrates and ortho-substituted coupling partners in intermolecular reactions is rare. Furthermore, the required boronic acids, when commercially available, can be expensive. The diaryl ether linkage can also be forged by an S_NAr reaction between a phenol and

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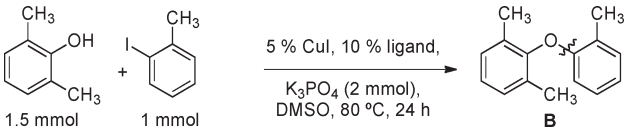
an activated aryl fluoride.[26] This method holds promise as it can be performed in the presence of a weak base and as such has also seen application in complex molecule synthesis. Unfortunately, suitable aryl fluoride substrates are not always readily available and the reaction lacks generality as it is limited to the coupling of electron-rich or electron-neutral phenols with highly activated aryl fluorides.

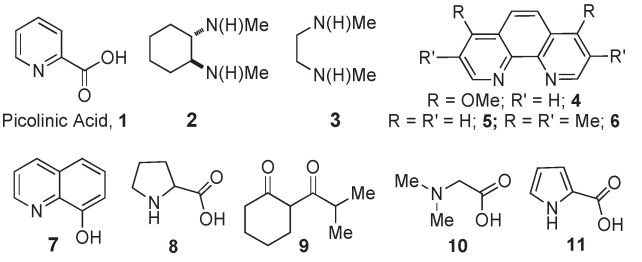
As a result of these problems, efforts continue to find a general method for formation of diaryl ethers. Much interest has focused on the metal-catalyzed coupling of phenols with aryl halides due to the low cost and ready availability of the starting materials. Pd-catalyzed methods hold considerable promise, especially in allowing economically attractive aryl chlorides to be used as substrates; however, a number of limitations remain.[27−32]

In 1997 it was shown that the Cu-catalyzed Ullmann-type coupling of phenols and aryl halides can be performed in the presence of the weak base Cs_2CO_3 in nonpolar solvents and in some cases naphthoic acid was found to promote the reaction.[33] Since this discovery a number of efficient Cu/ligand systems have been described and the high functional group tolerance and low air- and moisture-sensitivity has prompted ongoing interest in these reactions.[16−21,34−48] Unfortunately, despite this effort, little progress has been made in ameliorating some of the key limitations of these reactions, namely the difficulty in coupling heterocyclic compounds and the fact that ortho-substituted coupling partners are often challenging. We set out to attempt to address these issues and to move closer to a general set of reaction conditions for the synthesis of diaryl ethers.

TABLE 1. Comparison of Various Ligands in the Coupling of 2,6-Dimethylphenol with 2-Iodotoluene



entry	ligand	GC-yield **B**(%)
1	**1**	100
2	**2**	17
3	**3**	15
4	**4**	40
5	**5**	14
6	**6**	15
7	**7**	73
8	**8**	12
9	**9**	78
10	**10**	97
11	**11**	100



We have recently shown that a catalyst system composed of CuI and picolinic acid in combination with K_3PO_4/DMSO permits the selective O-arylation of aminophenols,[49] and we discovered that this system is also expedient in the coupling of 2,6-dimethylphenol with 2-iodotoluene (Table 1), a cross-coupling reaction that has not previously been reported with a Cu catalyst. Screening a range of base/solvent combinations showed K_3PO_4/DMSO to be much more efficacious than the more commonly used Cs_2CO_3/1,4-dioxane system (yields 100% and 27%, respectively).[17−19,39−46] Using this base/solvent combination pyrrole-2-carboxylic acid and *N*,*N*-dimethylglycine also proved to be effective ligands; however, we elected to pursue the use of picolinic acid as it is economically more attractive.[50]

The scope of the reaction was explored (Table 2) with a range of ortho-substituted phenols and aryl halides which are usually difficult substrates for Cu-catalyzed methods (in contrast to Pd-catalyzed reactions). By using picolinic acid **1** as ligand, *o*-cresol and 2,6-dimethylphenol could be coupled with a variety of ortho-substituted aryl halides (entries 1−3, 4, and 5). 2-Methoxyphenol also coupled effectively with 4-iodotoluene (entry 6) as well as with 2-bromotoluene (entry

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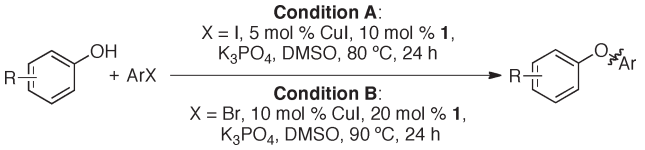
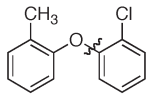
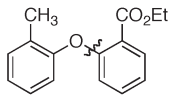
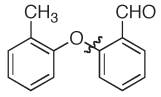
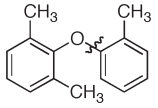
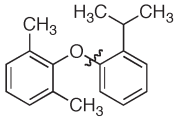
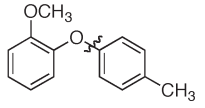
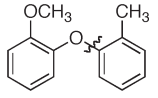
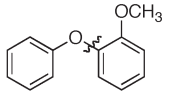
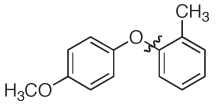
(50) Current prices from Sigma-Aldrich: picolinic acid $26.4/mol, pyrrole-2-carboxylic acid $2346/mol, and *N*,*N*-dimethylglycine $996/mol.

TABLE 2. Copper-Catalyzed O-Arylation of Phenols[a,54]



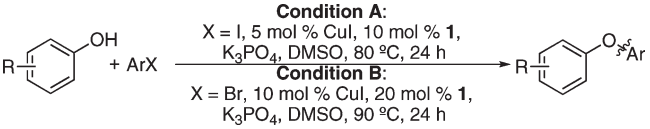
entry	product	Conditions	yield (%)
1		A	68
2		A	79
3		A	85
4		A	89
5		A	74[d]
6		A	92[b]
7		B	83[c]
8		A	85[b]
9		B	78

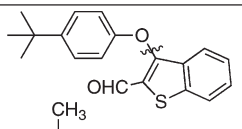
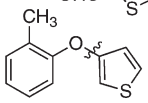
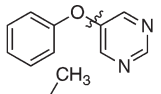
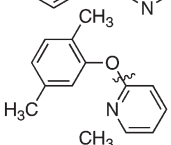
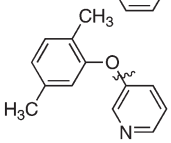
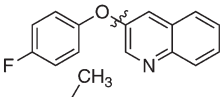
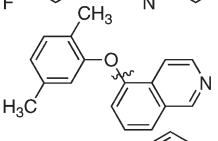
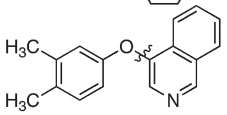
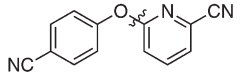
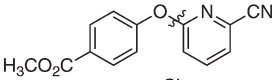
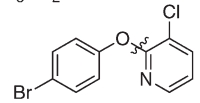
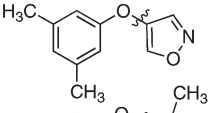
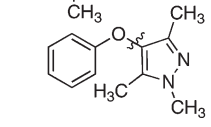
[a]Isolated yield, average of two runs. [b]90 °C, 10 mol % of CuI, 20 mol % of **1**. [c]105 °C. [d]10 mol % of CuI, 20 mol % of **1**.

7). Note that the reactions of aryl bromides were slower than those of the analogous aryl iodides and required higher catalyst loading.

Cross-coupling reactions between phenols and heteroaryl halides were also investigated (Table 3).[35−38,51] Employing our standard protocol with **1**, we were able to obtain heteroaryl ethers from the reaction of substituted phenols and 3-bromo-2-formylbenzothiophene (entry 1), 3-iodothiophene (entry 2), 5-bromopyrimidine[52] (entry 3), and 2- and 3-iodopyridine (entries 4 and 5) in good yield (Table 3). Heteroaryl halides such as 3-bromoquinolines (entry 6),

TABLE 3. Copper-Catalyzed Arylation of Phenols with Heteroaryl Halides[a,54]



entry	product	Conditions	yield (%)
1		B	69
2		A	71
3		B	70
4		A	88
5		A	85
6		B	91
7		B	89
8		B	69
9		B	92
10		B	91
11		B	87
12		B	0
13		B	0

[a]Isolated yield, average of two runs.

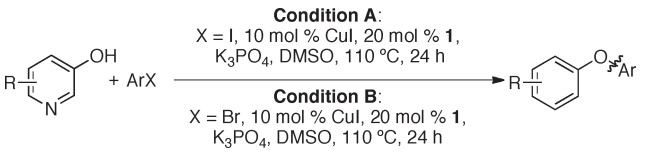
5-bromoisoquinolines (entry 7), and 4-bromoisoquinolines (entry 8) could be coupled with electron-deficient, electron-neutral, and hindered phenols (Table 3).[53] Cu-catalyzed

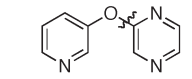
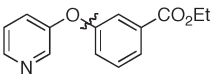
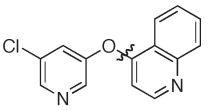
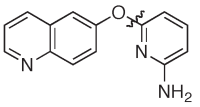
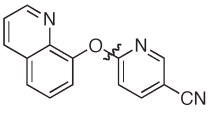
(51) Corbett, J. W.; Rauckhorst, M. R.; Qian, F.; Hoffman, R. L.; Knauer, C. S.; Fitzgerald, L. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6250–6256.

(52) Cherng, Y. H. *Tetrahedron* **2002**, *58*, 887–890.

(53) The control experiments without catalyst were performed to confirm these products are not generated by S_NAr reaction, but by picolinic acid-ligated copper-catalyzed C−O bond forming reaction.

TABLE 4. Copper-Catalyzed Synthesis of Heteroaryl Ethers[a,54]



entry	product	Conditions	yield (%)
1		A	84
2		A	78
3		B	78
4		B	95
5		B	96

[a]Isolated yield, average of two runs.

etherification can also be challenging when electron-withdrawing groups are present on the phenol component. An excellent yield of the desired diaryl ether could, however, be obtained when 4-cyanophenol (entry 9), methyl 4-hydroxybenzoate (entry 10), and 4-bromophenol (entry 11) were used as the nucleophile. We note, however, that 5-membered ring heteroaryl halides containing two heteroatoms such as 4-bromoisoxazole (entry 12) and 4-bromo-1,3,5-trimethylpyrazole (entry 13) did not provide any of the desired product under these reaction conditions.

Next we studied the synthesis of diaryl ethers possessing a heteroaryl moiety on both the nucleophilic and electrophilic components (Table 4). The construction of such diaryl ethers by metal-catalyzed cross-coupling is rare.[51,55] We found that by applying our standard protocol based on CuI and **1**, 3-hydroxypyridines were successfully coupled with a range of aryl halides (entries 1, 2, and 3). Furthermore, 6-hydroxyquinoline could be arylated with a bromopyridine even in the presence of free N−H groups (entry 4).[49] The O-arylation of 8-hydroxyquinoline (entry 5) with a substituted pyridine also proceeded smoothly even though this compound has previously been employed as an effective ligand for Cu-catalyzed arylation of phenols.[56]

In summary, we have devised an efficient, experimentally simple, and economically attractive method for Cu-catalyzed O-arylation of phenols with aryl iodides and bromides. This method tolerates a variety of functional groups and provides a considerable advance in the ability to synthesize hindered and heteroaryl diaryl ethers by Cu-catalyzed etherification.

Experimental Procedure

General Procedure for the Synthesis of Diaryl Ether. An oven-dried screw cap test tube was charged with a magnetic stirbar, copper(I) iodide (9.5 mg, 0.05 mmol, 5 mol %), picolinic acid **1** (12.3 mg, 0.10 mmol, 10 mol %), aryl halide (if solid; 1.0 mmol), ArOH (1.2 mmol), and K_3PO_4 (424 mg, 2.0 mmol). The tube was then evacuated and backfilled with argon. The evacuation/backfill sequence was repeated two additional times. Under a counterflow of argon, remaining liquid reagents were added, followed by dimethyl sulfoxide (2.0 mL) by syringe. The tube was placed in a preheated oil bath at 80 °C and the reaction mixture was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (10 mL) and H_2O (1 mL) were added and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted twice more with ethyl acetate (10 mL). The combined organic layer was dried over Na_2SO_4 and filtered through the pad of silica gel. The filtrate was concentrated and the resulting residue was purified via the Biotage SP4 (silica-packed SNAP cartridge, KP-Sil, 10 g) using hexane:ethyl acetate (3:1).

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

(54) We found that the reduction of aryl halide (Ar−X to Ar−H) was obtained as the major side reaction. Thus in Table 2, ethylbenzoate (5%, entry 2) and benzaldehyde (2%, entry 3) were detected. Similarly, isoquinoline (10%, entry 7; 5%, entry 8), benzo[*b*]thiophene-2-carbaldehyde (entry 1), and pyridine (1%, entry 4) were detected in Table 3 as were quinoline (2%, entry 3) and a trace of nicotinonitrile in Table 4, entry 5.

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(56) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051.