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Chemoselectivity in the Cu-catalyzed *O*-arylation of phenols and aliphatic alcohols†

Debabrata Maiti[ab]

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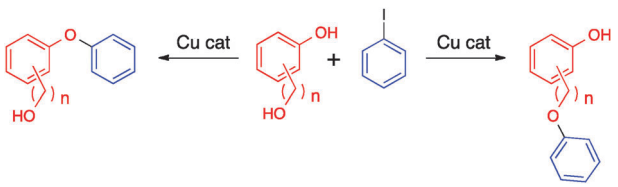
An orthogonal set of Cu-catalysts for the selective mono-arylation of alkyl aryl diols using aryl iodides is presented. Picolinic acid ligated copper catalyst provided phenol *O*-arylation only, while alkyl aryl ethers are generated by ligand-free copper catalyst in the presence of 2 equivalents NaO*t*-Bu.

Over the last two decades, metal-mediated cross-coupling reactions have seen widespread application in the synthesis of both simple and highly complex molecules.[1–6] Prior efforts have led to the development of many useful chemoselective[7–9] methods such as *N*- or *O*-arylation of aminoalcohols,[10,11] aminophenols,[12] and *C*- or *N*-arylation[13] of oxindoles. In this context, orthogonal catalyst systems for selective phenol arylation in presence of free alcohols would be of great interest to synthetic chemists. Such motifs are also an integral part of a number of natural products and drug molecules (Fig. 1).[14–19]



Scheme 1 Cu-catalyzed *O*-arylation of phenol and aliphatic alcohol.

Although numerous successful methods for the metal-catalyzed arylation of phenols and aliphatic alcohols exist,[20–23] a chemoselective arylation procedure for aliphatic alcohols (Scheme 1) is challenging due to drastic differences in their acidity (PhOH pK_a ~ 18 in DMSO and MeOH pK_a ~ 28 in DMSO).[24]

Use of picolinic acid **1** as the ligand for copper was found to effect *O*-arylation of phenols with best substrate scope and efficiency.[12,25] Thus, a catalyst system consisting of 5 mol% CuI, 10 mol% picolinic acid **1**, and K_3PO_4 in DMSO at 80 °C was employed for arylation of phenol in presence of aliphatic alcohol (Table 1). Notably, 4-hydroxyphenethyl alcohol and

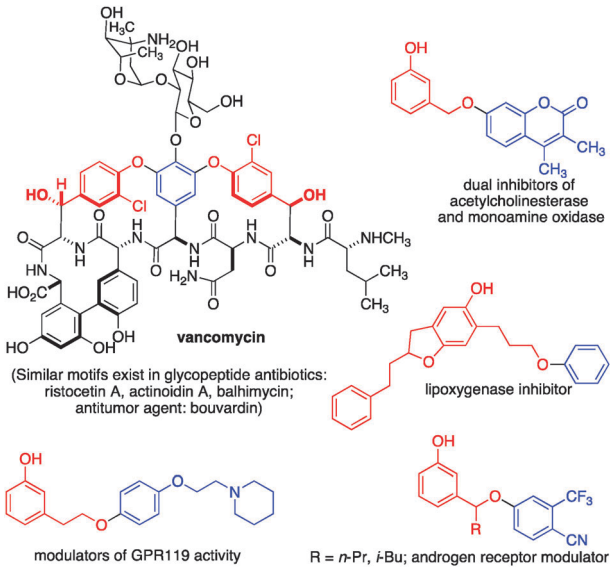


Fig. 1 Selected, bioactive compounds featuring arylated phenols and aliphatic alcohols.

4-iodotoluene provided the corresponding diaryl ether in excellent yield and with high levels of chemoselectivity (Table 1, entry 1). No *O*-arylation of the aliphatic alcohol moiety was detected in the crude reaction mixture.

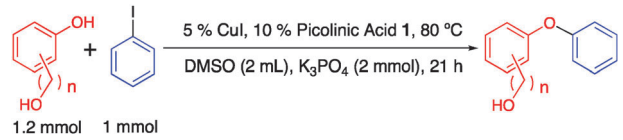
This catalyst system was then applied to an array of coupling partners (Table 1). Following the general protocol, electron-rich (entry 2) and electron-deficient (entry 3) iodobenzenes resulted in selective diarylether formation from 4-hydroxyphenethyl alcohol. The selectivity of this method was further tested using a substrate with a methoxy substituent *ortho* to the phenol moiety and desired diarylether is the only product (entry 8). In addition, the presence of an *ortho* methyl group on the aryl halide was well tolerated (Table 1, entry 4), however, 10 mol% catalyst loading was required at 120 °C in order to obtain full conversion.

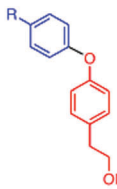
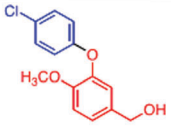
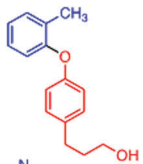
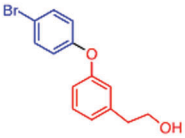
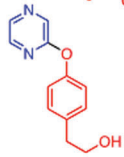
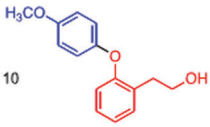
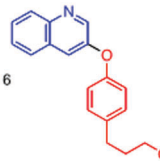
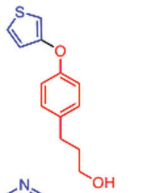
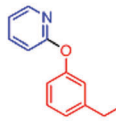
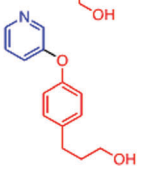
Interestingly, this method was also successful for the selective diarylether formation of heteroaryl substrates. Thus, 2-iodopyrazine (entry 5) could be *O*-arylated at phenol, as well as 3-bromoquinoline (entry 6) and iodopyridines (entries 7 and 12). Although 3-iodothiophene produced the desired ether with complete selectivity, the reaction only proceeded to 60% conversion (entry 11) at 10 mol% catalayst loading at 120 °C.

[a] *Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India. E-mail: dmaiti@chem.iitb.ac.in*
[b] *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA*

† Electronic supplementary information (ESI) available: Detailed description of experimental procedures, characterization of all compounds. See DOI: 10.1039/c1cc12694f

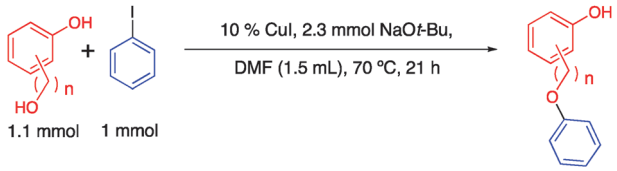
Table 1 Cu-catalyzed selective phenol arylation

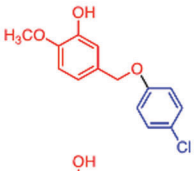
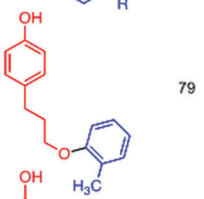
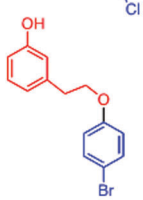
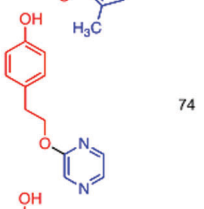
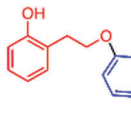
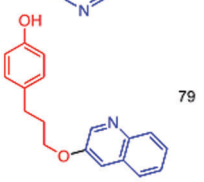
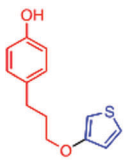
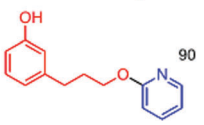
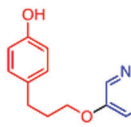


Entry	**O–Ar** product	Yield (%)	Entry	**O–Ar** product	Yield (%)
1		R = CH_3 85	8		64[a,d]
2		R = OCH_3 90			
3		R = F 79			
4		87[a,b]	9		73[a,d]
5		83	10		73[a,d,e]
6		68[a,c]	11		47[a,b,f]
7		87[d]	12		96[a]

[a] 10 mol% CuI, 20 mol% **1**. [b] 120 °C. [c] ArBr, 110 °C. [d] 90 °C. [e] 12% diarylated product. [f] 60% conversion.

Table 2 Cu-catalyzed selective aliphatic alcohol arylation



Entry	**O–Ar** product	Yield (%)	Entry	**O–Ar** product	Yield (%)
1		R = CH_3 84	8		63[a]
2		R = OCH_3 96			
3		R = F 80			
4		79	9		69
5		74	10		70
6		79	11		43[b]
7		90	12		64

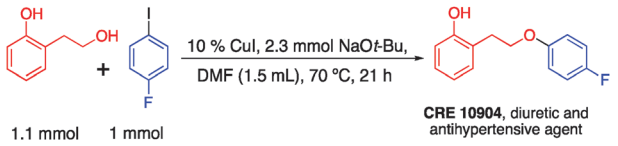
[a] 110 °C. [b] 120 °C.

Chloro- and bromo-substituted diarylethers (entries 8 and 9, respectively) were also generated from 1-chloro-4-iodobenzene and 1-bromo-4-iodobenzene, respectively. These reactions further demonstrate the preference of aryl iodides as coupling partner in copper-catalyzed methodology (Scheme 1).[4,20–22]

The chain length (entries 1, 4 and 8) and position (entries 1, 7 and 10) of the aliphatic alcohol with respect to the phenol group have minimal impact in the selectivity of the diarylether product formation (Table 1). Only when 2-hydroxyphenethyl alcohol was employed as the coupling partner (entry 10), 12% of the diarylated product along with 65% of the desired diarylether were obtained. Formation of a stable chelating complex is suspected to alter catalyst selectivity in this case. Previously diarylated product formation was observed in copper-catalyzed cross-coupling reaction while using chelating nucleophiles.[10,12]

The next target was to develop conditions for the analogous selective alkyl aryl ether formation. Irrespective of the amount or nature of weak base (*e.g.* K_3PO_4, Cs_2CO_3 and Na_2CO_3) used, diaryl ether was the only product formed from 4-hydroxyphenethyl alcohol. Employing strong bases such as NaO*t*-Bu (or KO*t*-Bu) in a 1 : 1 ratio with 4-hydroxyphenethyl alcohol also led to only the diaryl ether product. Interestingly, altering the base : substrate ratio to 2 : 1 provided selective *O*-arylation of the aliphatic alcohol. Thus, using 10 mol% CuI, 1 mmol 4-iodotoluene, 1.1 mmol 4-hydroxyphenethyl alcohol, 2.3 mmol NaO*t*-Bu in *N*,*N*-dimethylformamide (DMF) at 70 °C, the selective *O*-arylation of aliphatic alcohol was observed (Table 2, entry 1). Under these conditions, no diaryl ether formation was seen. It is likely that both the hydroxy groups in 4-hydroxyphenethyl alcohol are deprotonated under these conditions and the alkoxy species was arylated selectively due to its greater nucleophilicity compared to the phenolate.

A series of ligands previously employed in copper-catalyzed reactions were examined[4] and found to have no impact on the yield or selectivity for this coupling process. By carrying out the process at 70 °C, the formation of reduced products was minimized and reasonable reaction rates could be obtained.



Scheme 2 Cu-catalyzed direct synthesis of CRE 10904.

As shown in Table 2, *electron-neutral* (entry 1), *-rich* (entry 2) and *-deficient* (entry 3) aryl iodides underwent efficient coupling under these conditions.

Chloride or bromide substituted aryl iodides (entries 8 and 9, respectively) produced the desired products in reasonable yields. Using the general procedure, heteroaryl ethers from 2-iodopyrazine (entry 5), iodo pyridines (entries 7 and 12) and 3-iodoquinoline (entry 6) were obtained in good yield. Similar to the phenol arylation protocol, the chain length and position of the aliphatic alcohol had little impact on the reaction outcome.

Of note is that 2-hydroxyphenethyl alcohol generated alkyl aryl ether only (entry 10). Employing the current method, a large quantity of the alcohol coupling partner is not required for the synthesis of alkyl aryl ether. The efficiency of the methodology developed here is further tested by the one step synthesis of 2-(2-(4-fluorophenoxy)ethyl)phenol (CRE 10 904, Scheme 2, yield 50%) the synthesis of which previously required 4 steps.[15,16]

In conclusion, an orthogonal set of conditions for the selective Cu-catalyzed *O*-arylation of unprotected phenols and aliphatic alcohols has been discovered. A picolinic acid (**1**)-ligated Cu-catalyst can be used to chemoselectively arylate phenols, a ligand-free Cu-catalyst promotes exclusive aliphatic alcohol arylation if an excess of strong base is employed.

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