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A General and Mild Ullmann-Type Synthesis of Diaryl Ethers

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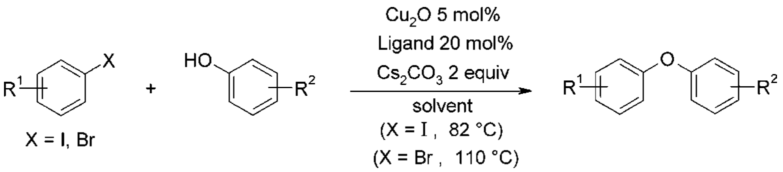
ABSTRACT



An efficient method for the synthesis of diaryl ethers under particularly mild conditions is described. Inexpensive ligands were found to greatly accelerate the Ullmann-type coupling of aryl bromides or iodides with phenols. A series of diaryl ethers were obtained with excellent yields in acetonitrile in the presence of Cs_2CO_3 and catalytic copper(I) oxide. The reaction tolerates substrates with unfavorable substitution patterns, such as sterically hindered coupling partners or electron-rich aryl halides.

Diaryl ethers form an important class of organic compounds throughout the polymer and life sciences industries.[1] A number of them have been reported to have significant biological activity, like natural products of the isodityrosine family and its derivatives (e.g., the antibiotic vancomycin and the antitumoral bouvardin).[2] The diaryl ether structural unit is also prevalent in numerous weed-killing chemicals.[3]

The most straightforward way to synthesize diaryl ethers involves the direct formation of an aryl−oxygen bond from an aryl halide.[4] Efficient palladium-catalyzed arylations of phenols or their sodium salts have been developed in recent years.[5] Nevertheless, the use of expensive palladium and noncommercial sophisticated phosphines limit the attractiveness of this method for large-scale or industrial applications. Therefore, less costly alternatives are needed.

The copper-mediated arylation of phenols with aryl halides, discovered by Ullmann in 1904,[6] appears to be the method of choice, but its traditional conditions are rather drastic.[7] Considerable efforts have been devoted in the past few years to the discovery of more attractive Ullmann O-arylation methods. Several authors showed that certain additives, which probably act as copper ligands,[8] enhance reaction rates and allow the couplings to be carried out at milder temperatures, in the presence of reduced amounts of copper or with a larger substrate scope. Thus, ethylene glycol diacetate,[9a] 8-hydroxyquinoline,[9b,c] 1-naphthoic acid,[9d] triphenylphosphine,[9e] neocuproine,[9f] or 2,2,6,6-tetramethylheptane-3,5-dione[8a] were successfully used as promoters. It has been suggested that such additives would increase the solubility

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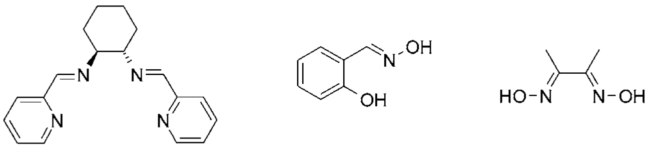
of copper salts and prevent their aggregation.[10] They could also enhance reactivity by increasing electronic density on the catalytic species. However, these advances in the field of Ullmann ether formation were not sufficient because general methods still required high temperatures (at least 100 °C)[9d−f] and in some cases high catalyst loading (50 mol %).[8a] After completion of this work, Ma reported that the use of *N*,*N*-dimethylglycine as a ligand allowed the lowering of reaction temperature to 90 °C.[11] Alternative arylating agents such as arylboronic anhydrides, esters[12a] or acids,[12b] aryltrifluoroborate salts,[13] or arylbismuth derivatives[14] can be employed at room temperature in copper-catalyzed reactions, but these methods suffer either from high cost or from limited commercial availability of functionalized reagents. Thus, it was of interest to develop a simultaneously mild, general and cost-effective catalytic procedure for the synthesis of diaryl ethers from aryl halides.

We recently disclosed that compounds of the oxime and Schiff base types serve as powerful ligands in the copper-catalyzed arylation of pyrazoles with aryl halides.[15] This success prompted us to examine whether our newly discovered catalysts could be used for the formation of aryl−oxygen bonds. In this report, we extend the usefulness of these air-stable and in situ-generated catalyst systems for the synthesis of diaryl ethers from functionalized phenols and aryl iodides, under milder reaction conditions than those previously reported.[16]

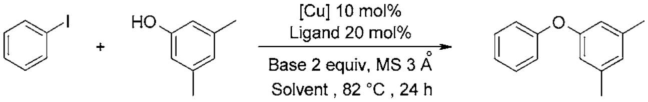
A variety of multidentate chelating ligands were examined using iodobenzene and 3,5-dimethylphenol as model substrates, copper(I) oxide as the precatalyst, acetonitrile as the solvent, and cesium carbonate as the base. Many ligands that have, to our knowledge, never been used in Ullmann-type O-arylation reactions proved to be successful. Among these were Chxn-Py-Al **1**, salicylal-doxime **2**, and dimethylglyoxime **3** (Figure 1 and Table 1, entries 1−3). Almost quantitative yields were observed in the presence of **2** and **3** within 24 h at 82 °C.



Chxn-Py-Al **1** Salox **2** DMG **3**

Figure 1. Additional chelating ligands used in this work.

Table 1. Effect of Ligand, Catalyst, Base, and Solvent on the Coupling of 3,5-Dimethylphenol with Iodobenzene[a]



entry	copper source	ligand	base	solvent	GC yield (%)
1	Cu_2O	Chxn-Py-Al	Cs_2CO_3	MeCN	97
2	Cu_2O	Salox	Cs_2CO_3	MeCN	96
3	Cu_2O	DMG	Cs_2CO_3	MeCN	87
4	CuI	Salox	Cs_2CO_3	MeCN	97
5	CuBr	Salox	Cs_2CO_3	MeCN	67
6	CuO	Salox	Cs_2CO_3	MeCN	57
7		Salox	Cs_2CO_3	MeCN	0
8	Cu_2O	Salox	Cs_2CO_3	DMF	67
9	Cu_2O	Salox	K_3PO_4	MeCN	69
10	Cu_2O	Salox	K_2CO_3	MeCN	12

[a] Reaction conditions: 0.75 mmol of ArI, 0.5 mmol of ArOH, 1.0 mmol of base, 5 mol % copper catalyst, 20 mol % ligand, 150 mg of activated and powdered 3 Å molecular sieves, solvent (300 μL), 82 °C, under N_2.

A preliminary survey had shown that Cu salts such as CuI, CuBr, CuO, and Cu_2O were effective precatalysts (Table 1, entries 2, 4−6). No reaction was observed in their absence (entry 7). Among these copper sources, CuI and Cu_2O were the most effective. The air-stable[17] and less expensive Cu_2O was used in experiments aimed at investigating the effect of solvent and base on the coupling reaction outcome. Arylations conducted in acetonitrile were faster than those conducted in DMF (entry 8), while cesium carbonate was more efficient than K_3PO_4 and K_2CO_3 (entries 9−10). Cesium phenoxides are indeed more dissociated and more soluble in organic solvents than their potassium counterparts.[9d,18]

No side reaction involving 3,5-dimethylphenol was observed. The selectivity with respect to the aryl halide was high too, provided that an appropriate drying agent was used to reduce the competing process of water arylation,[19]

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(16) These results, obtained more than two years ago, appear only now in the literature due to the regular time required for patent protection. Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. FR Patent 2833947 (WO Patent 03/050885), Rhodia Chimie, 2003; *Chem. Abstr.* **2003**, *139*, 69290. Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. Patent priority number FR 03 10253. Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Ouali, A. Patent priority number FR 02 06717 (International application number PCT/FR03/01647), Rhodia Chimie, 2003.

(17) Stabilized form sold by Aldrich was used.

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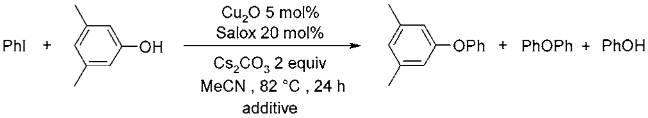
(19) Thermal decomposition of cesium hydrogen carbonate produced during the coupling leads to the formation of water or cesium hydroxide, as underlined by Greiner: Greiner, A. *Synthesis* **1989**, 312. For an example of such byproduct formation, see: Beletskaya, I. P.; Davydov, D. V.; Gorovoi, M. S.; Kardashov, S. V. *Russ. Chem. Bull.* **1999**, *48*, 1533.

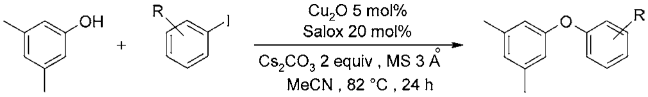
Table 2. Effect of Additives on Diphenyl Ether and Phenol Byproduct Formation[a]



entry	additive	GC yield (%)	PhOH yield (%)	PhOPh yield (%)
1		97	2	9
2	$MgSO_4$	92	1.5	9
3	3 Å MS[b]	99	<1	6
4	powdered 3 Å MS	96	<1	3

[a] Reaction conditions: as in Table 1, with 150 mg of additive per mmol of Cs_2CO_3. The yields of byproducts are calculated with respect to iodobenzene. [b] MS: Molecular sieves.

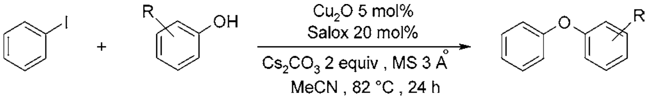
Table 3. Reactivity Comparison of Aryl Iodides after 24 Hours[a]



entry	R	GC yield (%)
1	H	96
2	2-Me	43
3	4-CN	quantitative[b]
4	4-CF_3	quantitative[b]
5	4-MeO	90[b]

[a] Reaction conditions: see Table 1. [b] Chxn-Py-Al as the ligand.

Table 4. Reactivity Comparison of Phenols after 24 Hours[a]

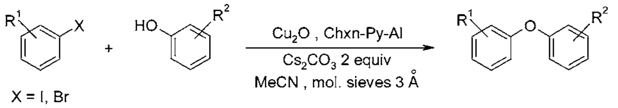


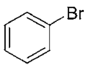
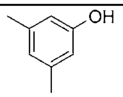
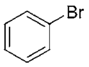
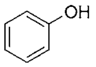
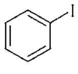
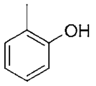
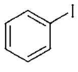
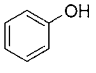
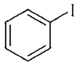
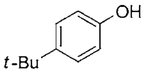
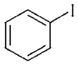
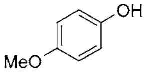
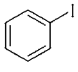
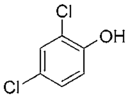
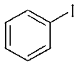
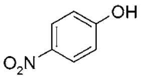
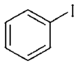
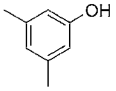
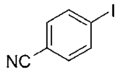
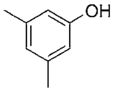
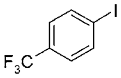
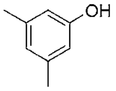
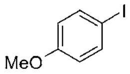
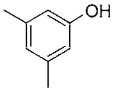
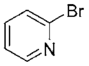
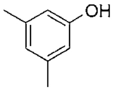
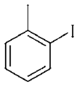
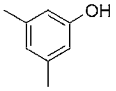
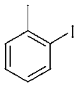
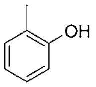
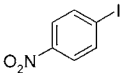
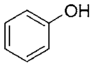
entry	R	GC yield (%)
1	3,5-Me_2	96
2	4-*t*-Bu	99
3	4-MeO	98
4	H	quantitative
5	2-Me	91
6	2,4-Cl_2	45
7	4-NO_2	0

[a] Reaction conditions: see Table 1.

leading to the formation of phenol and, further, to diphenyl ether. In our case, the desiccant efficiency of activated and powdered 3 Å molecular sieves (MS) was better than that of the nonpowdered one or that of magnesium sulfate (Table 2). While making the purification of products by column chromatography significantly easier, this additive led to only a slight decrease in the reaction rate. In all reactions, hydrodehalogenation products were formed in small amounts

Table 5. Ullmann-Type Couplings in the Presence of the Ligand Chxn-Py-Al (Optimized Reactions Conditions[a])



entry	ArX	Phenol	time (h)	T (°C)	yield (%)[b]
1	 Br	 OH	36	110[f]	85[c]
2			75	110[f]	100[c]
3	 Br	 OH	36	110[f]	80[c,d]
4			90	110[f]	100[c]
5	 I	 OH	40	82	93
6	 I	 OH	24	82	100[c]
7	 I	 *t*-Bu, OH	25	82	95
8	 I	 MeO, OH	28	82	95
9	 I	 Cl, OH, Cl	24	82	40[g]
10	 I	 O_2N, OH	24	110[f]	< 1[c]
11	 I	 OH	29	82	96
12	 NC, I	 OH	24	82	93
13	 F_3C, I	 OH	24	82	95
14	 MeO, I	 OH	48	82	92
15	 Br, N	 OH	24	110[f]	93
16	 I	 OH	118	82	94
17	 I	 OH	35	110[f]	98
18	 O_2N, I	 OH	24	82	93

[a] Reaction conditions: 3 mmol of ArX, 2 mmol of Ar′OH, 4 mmol of Cs_2CO_3, 5 mol % Cu_2O, 20 mol % Chxn-Py-Al, 600 mg of powdered 3 Å molecular sieves, MeCN (1.2 mL), under N_2. [b] Isolated yield. [c] GC yield. [d] Without molecular sieves. [e] Salox ligand was used. [f] In DMF. [g] Phenol conversion: 49%.

(less than 5%). Homocoupling of the aryl halide was never observed.

The optimized reaction conditions[20] were used to examine C−O bond formations involving functionalized coupling partners. Reactivity comparisons were made by interrupting the reactions after 24 h (Tables 3 and 4), while optimized reaction times and isolated yields of purified products are given in Table 5.

No spectacular electronic effects were observed when 3,5-dimethylphenol was submitted to coupling with para-substituted aryl iodides (Table 3, entries 3−5). Only a slight decrease in the reaction rate was noted with the electron-rich 4-iodoanisole (entry 5). Cyano, nitro, and trifluoromethyl groups are well tolerated on the aryl iodide (Table 5, entries 12, 13, 18). 2-Iodotoluene, as usually observed in the literature with hindered aryl halides,[9e,f] gave lower conversions after 24 h (entry 2), and the arylation required longer reaction times to go to completion (Table 5, entry 16). Extension of this arylation process to aryl bromides yielded interesting results: The use of bromobenzene in place of iodobenzene afforded only 39% of diaryl ether after 24 h at 82 °C, but this weaker reactivity could be overcome by increasing the reaction temperature to 110 °C and changing the solvent to DMF (Table 5, entries 1−4). Good yields were generally obtained after 36 h. Additionally, 2-bromopyridine can be cleanly transformed in less than 24 h at 110 °C (Table 5, entry 15).

Phenol reactivity was compared using iodobenzene as an arylating agent (Table 4). The rates of reactions were comparable with electron-rich, electron-neutral, and ortho-substituted phenols (entries 1−5). We also demonstrated that the coupling was favored by electron-donating groups thanks to a competitive arylation involving iodobenzene (0.5 mmol), phenol (0.5 mmol), and 4-methoxyphenol (0.5 mmol). After 24 h at 82 °C under our standard reaction conditions, 59% conversion to 4-methoxydiphenyl ether and 28% conversion to diphenyl ether were observed.

2,4-Dichlorophenol proved to be a significantly less effective coupling partner, due to its poor nucleophilicity and its steric hindrance (Table 4, entry 6), while 4-nitrophenol, which bears a strong electron-withdrawing group, does not undergo the desired O-arylation reaction, even at high temperature (Table 5, entry 10). This result, already stated in previous work,[4c,8a,9e] could be explained by the formation of an electron-poor and consequently less reactive copper−phenoxide[8a,12b] complex.

Since the reactions were totally selective with respect to the phenols, the use of a moderate excess of the aryl halide partner allowed couplings involving electron-rich or -neutral phenols to be driven to completion and the corresponding diaryl ethers to be isolated with excellent yields (above 90%, Table 5). Chxn-Py-Al **1** was found to be more practical than salicylaldoxime **2** as a ligand, since it proved to be less reactive toward aryl iodides and led to cleaner reactions.

We were pleased to note that we could quantitatively couple the hindered *ortho*-cresol with the hindered 2-iodotoluene in DMF at 110 °C (Table 5, entry 17), a rather challenging substrate combination. We have also shown that our conditions were superior to those based on the use of the copper(I) complex Cu(neocup)(PPh_3)Br[9f] for bromobenzene substitution: we obtained a better GC yield of diphenyl ether after 36 h (80%, Table 5, entry 3) than the one reported in the literature (51%) at the same temperature with the same amount of copper catalyst.[9f]

In summary, we have devised an efficient, experimentally simple, and economically attractive copper-catalyzed O-arylation of phenols with aryl iodides. Inexpensive and air-stable precatalyst systems Cu_2O/**2** and Cu_2O/**1**, which we recently developed for pyrazole N-arylation, allow aryl-oxygen bond formation to occur with high yields and selectivity at the lowest temperature reported to date (82 °C). Aryl bromides can also be used at 110 °C. This method shows broad functional group tolerance on both coupling partners, with the exception of electron-poor phenols, and provides an interesting alternative to palladium chemistry. Efforts to expand the utility of our new catalyst systems to other classes of nucleophiles have been rewarded and will be reported in due course.

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Note Added after ASAP Posting. The last sentence of the Abstract was incomplete in the version posted ASAP February 20, 2004; the corrected version was posted February 25, 2004.

Supporting Information Available: Detailed experimental procedures and complete characterization data for each diaryl ether and for ligand **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] **Typical Procedure.** After standard cycles of evacuation and back-filling with nitrogen, an oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with Cu_2O (0.1 mmol), Chxn-Py-Al (0.4 mmol), Cs_2CO_3 (4.0 mmol), activated and powdered 3 Å molecular sieves (600 mg), the phenol (2 mmol), if a solid, and the aryl halide (3.0 mmol), if a solid. The tube was capped with a rubber septum. If liquids, the phenol and the aryl halide were added by syringe, followed by anhydrous acetonitrile (1.2 mL). The septum was removed and the tube sealed under positive pressure of nitrogen and stirred in an oil bath preheated to 82 °C for the required time period. The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, and filtered through a plug of Celite. The solvent was removed in vacuo to yield the crude product, which was purified by silica gel chromatography.