C–O Coupling

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A Very Simple Copper-Catalyzed Synthesis of Phenols Employing Hydroxide Salts**

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Phenols are very important intermediates in the chemical, pharmaceutical, and materials industries, with more than 7.2 megatons of phenol itself produced per year. [1,2] Nowadays, about 90 % of the world's phenol demand is satisfied by the Hock process, which involves the peroxidation of cumene, itself obtained from benzene propylation. This industrial process, which is not very efficient in yield (overall 5 %) and energy use, also produces large amounts of acetone and α-methylstyrene co-products. Alternative oxidation technologies that avoid production of acetone have been proposed,[2b,c] but none have succeeded in replacing the Hock process.

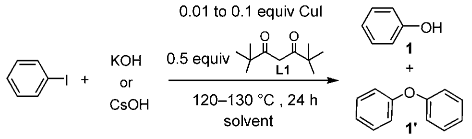
For the preparation of functionalized phenols, non-oxidative methods are used, such as traditional nucleophilic aromatic substitution; however, the range of substituents is often limited by the necessarily harsh reaction conditions or by the electronic requirements of the substrate.[3] An interesting iridium-based catalytic system has been reported for preparation of non-*ortho*-substituted phenols, which involves a one-pot, aromatic borylation/oxidation sequence;[4] more recently, the groups of Buchwald,[5a] Kwong,[5c] Diaconescu,[5d] and Beller[5e,f] have developed very efficient systems based on palladium/phosphine ligand catalysis, which allow selective formation of phenols from different aryl halides.[5] However, these systems are more expensive than copper and not as favorable for toxicity issues.

Therefore, the development of a cheaper, copper-catalyzed system enabling the direct hydroxylation of aryl halides has become an important goal. There are, however, two critical problems to be resolved; first, the direct copper-catalyzed coupling reaction between unactivated aryl halides and hydroxide at temperatures below 200 °C has never been reported (indeed, one study has shown that this reaction is very difficult even at 200–300 °C with microwave heating).[6] Second, copper-catalyzed coupling between phenols and aryl halides is well known,[7,8a,b,d,f] and this could be a prominent concurrent reaction once phenol is formed in situ, thus affording symmetric diaryl ethers as reaction products.

We recently developed a simple copper-catalyzed synthesis of aniline from the coupling reaction between aqueous ammonia and aryl halides in the presence of diketone-type ligands.[9] These results encouraged us to investigate related systems for preparing phenols from aryl halides and hydroxide salts. As part of our studies on the copper-catalyzed arylation of nucleophiles,[8] we now report that the selective hydroxylation of both activated and unactivated aryl bromides and iodides can be achieved in aqueous media using a metal hydroxide and a catalytic system in which copper is used together with simple diketone ligands.[10]

We initially selected iodobenzene as the model substrate and 0.5 equivalents of TMHD (2,2,6,6-tetramethyl-3,5-heptanedione, **L1**) as ligand for optimization of the reaction conditions. Our first test was performed in NMP (*N*-methyl-2-pyrrolidone) using a catalytic amount of CuI (0.1 equiv), with potassium hydroxide (3.0 equiv) as the nucleophile (Table 1, entry 1).

Table 1: Hydroxylation of PhI using various solvents and copper sources in the presence of ligand TMHD **L1**.[a]



	Solvent (2 mL)		MOH	Yield[b] [%]	
				1	**1'**
1	NMP		KOH	20	20
2	H_2O		KOH	20	0
3	DMSO		KOH	50	20
4	DMSO/H_2O	7:1	KOH	19	28
5	DMF/H_2O	7:1	KOH	15	20
6	DMSO/H_2O	3:1	KOH	60	20
7	DMF/H_2O	3:1	KOH	70	15
8	DMSO/H_2O	3:1	CsOH	80	5
9	MIBK/H_2O	3:1	CsOH	30	20
10	NMP/H_2O	3:1	CsOH	30	20
11[c]	DMSO/H_2O	1:1	CsOH	45	0
12[d]	DMSO/H_2O	1:1	CsOH	65	0
13[e]	DMSO/H_2O	1:1	CsOH	40	0
14	DMSO/H_2O	1:1	CsOH	95	0
15[f]	DMSO/H_2O	1:1	CsOH	75	0
16	DMSO/H_2O	1:1	CsOH	60[g], 80[i]	0
17	DMSO/H_2O	1:1	CsOH	0[h], 0[j]	5
18	DMSO/H_2O	1:1	KOH	75	0

[a] Reactions performed at 130 °C with 3.0 equiv of MOH and 0.1 equiv of CuI unless otherwise noted. [b] Yield determined by GC with 1,3-dimethoxybenzene as standard. [c] With 1.5 equiv of CsOH. [d] With 2.5 equiv of CsOH. [e] At 120 °C. [f] With 0.4 equiv of **L1**. [g] With 0.05 equiv of CuI. [h] With 0.01 equiv of CuI. [i] With 0.05 equiv of CuI, at 140 °C. [j] With 0.01 equiv of CuI, at 140 °C.

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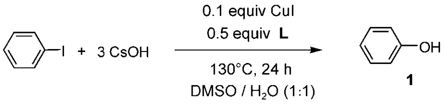
At 130 °C, we observed the formation of only small amounts of phenol **1** and also some biaryl ether **1′** resulting from the arylation of the former by PhI. The same reaction under aqueous conditions afforded a low yield of **1**, although full selectivity was observed (Table 1, entry 2); DMSO alone also afforded acceptable and promising, but non-selective, formation of phenol (Table 1, entry 3). At this stage, we systematically tested mixed-solvent systems over a range of compositions using either KOH or CsOH as the nucleophile (Table 1, entries 4–10). Fair to good yields of phenols were obtained with DMSO/H_2O or DMF/H_2O (3:1 ratio; Table 1, entries 6,7) but some diaryl ether by-product **1′** (15–20 %) was found in all cases. CsOH (DMSO/H_2O, 3:1 mixture) yielded **1** with improved selectivity (Table 1, entry 8); however, disappointing results were obtained with CsOH in MIBK/H_2O (methyl isobutyl ketone) or NMP/H_2O mixtures (Table 1, entries 9,10).

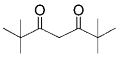
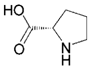
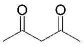
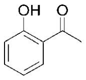
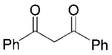
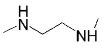
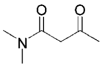
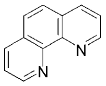
We were pleased to find that with a DMSO/H_2O ratio of 1:1, PhI could be selectively coupled at 130 °C to give **1** in quantitative yield (Table 1, entry 14). It is worth noting that at lower concentrations of CsOH, when the temperature is decreased to 120 °C, or when only 0.4 equivalents of ligand **L1** is used, the yield of phenol is reduced (Table 1, entries 11–13,15). Furthermore, under optimal conditions (Table 1, entry 14), but with small quantities of CuI (0.05 and 0.01 equiv), the yield of **1** decreased to 60 % and 0 %, respectively (Table 1, entries 16,17). A slightly higher temperature did not improve the efficiency of the system, whatever the amount of copper used (Table 1, entries 16,17).

The reaction also takes place selectively under the same conditions (Table 1, entry 14) with the less expensive potassium hydroxide KOH replacing CsOH as the base (Table 1, entry 18). However, since the yield of isolated product (75 %) was slightly lower than with CsOH, we continued using the latter to examine the influence the ligand effects upon the reaction (Table 2; ligands **L1**–**L8**).

Of the four β-diketones investigated, all except **L2** were effective, especially TMHD **L1** and dibenzoylmethane **L3** (Table 2, entries 1,3). Interestingly, the selectivity was always excellent, and no trace C−C coupling product resulting from arylation of the diketone was detected. Other classical ligands for Ullmann coupling also worked well (selectivity 100 %), but with slightly lower yields (70 to 84 %). As **L3** is approximately five-times less expensive than **L1**, **L3** was chosen to explore the scope of this new route for phenol preparation.

Table 2: Synthesis of phenols by copper catalyzed hydroxylation of PhI in aqueous media using various ligands **L**.[a,b]



Ligands **L**		Yield[a] [%]	Ligands **L**		Yield[a] [%]
	**L1**	95		**L5**	70
	**L2**	30		**L6**	85
	**L3**	97		**L7**	84
	**L4**	65		**L8**	75

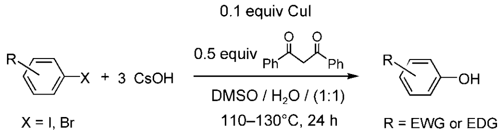
[a] Yield determined by GC with 1,3-dimethoxybenzene as standard. [b] Yield of **1** without any ligand: 20% (**1′**, 0%).

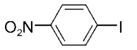
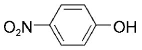
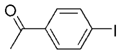
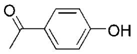
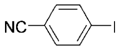
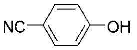
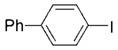
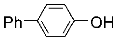
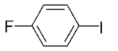
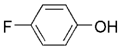
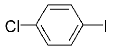
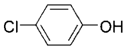
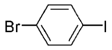
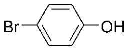
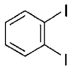
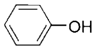
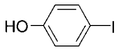
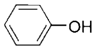
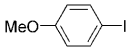
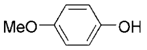
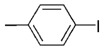
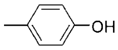
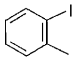
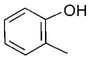
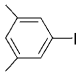
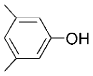
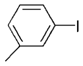
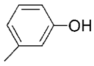
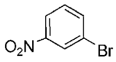
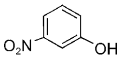
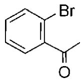
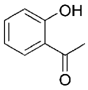
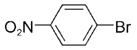
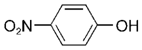
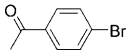
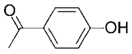
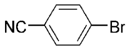
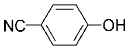
The relationship between experimental conditions and reactivity/selectivity is still not clear. The key factor for the success of our system is the use of a well-defined ratio of water/base/co-solvent (Table 1, entry 14). In contrast, the nature of the ligand seems to be less important. The full and exclusive conversion of PhI into PhOH could indicate that the phenol, in equilibrium with the corresponding phenolate, is not able to react at all with PhI under our optimal conditions (owing to, for example, solubility reasons). A crucial point seems to be the concentration of water (a high concentration favors the reaction), which improves the solubility of the hydroxide ion and thus its ability to intervene as a nucleophile. The use of DMSO, which is miscible with water and known to behave as a superbasic media in the presence of alkali metal hydroxides, is also probably a key feature of our catalytic system.[11] It is difficult to perform a correlation between the structure of the copper species in the medium (assumed to be a copper(I) complex) and our experimental conditions.

We then explored the breadth of application of this new method using the optimized experimental conditions (Table 2, ligand **L3**). Thus, in a mixed solvent system of DMSO/H_2O (1:1), the CuI/diketone-**L3** system efficiently promotes cross-coupling reactions between CsOH and aryl iodides with electron-withdrawing groups (EWGs), to afford the corresponding phenols in good to excellent yields (Table 3, entries 2–8). In some cases, with activated substrates such as *p*-iodonitro-, *p*-iodoaceto-, or *p*-iodocyanobenzene, reactions can proceed efficiently even at lower temperature (110 °C; Table 3, entries 2–4). Note that the copper/ligand system proved necessary even in the case of a strongly activating group (*p*-NO_2) to afford the coupling product (Table 3, entry 2). Subsequently, we performed the coupling reaction with aryl iodides deactivated by electron-donating groups (EDGs), and we obtained the desired products in excellent yields (Table 3, entries 11–15). Note that the reaction is also possible with electron-donating substituents at lower temperature (110 °C), as illustrated by the case of 3,5-dimethyliodobenzene (excellent yield obtained in 36 h instead of 24 h at 130 °C; Table 3, entry 14).

For 2-diiodobenzene and 4-iodophenol in particular, we observed the quantitative formation of the double- or mono-reduction products, respectively (Table 3, entries 9,10). The starting *p*-iodophenolate, or *o*-iodophenolate formed in situ by initial monohydroxylation of 2-diiodobenzene, could favor a radical mechanism by stabilizing the resulting phenolate radical anion ($OC_6H_4^{\bullet-}$); this radical then could easily lead to the observed phenol product. Although aryl iodides are interesting substrates, we turned our attention to arylation of aryl bromides, which are less reactive electrophiles but of greater interest for industrial applications. Various phenols

Table 3: Synthesis of phenols by copper-catalyzed hydroxylation of aryliodides and bromides.[a]



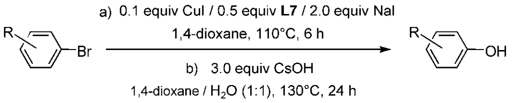
	ArI	ArOH		Isolated yield [%]
1	PhI	PhOH	**1**	97
2			**2**	22[b], 90[c]
3			**3**	90[c]
4			**4**	91[c]
5			**5**	95
6			**6**	70
7			**7**	75, 95[d]
8			**8**	84
9			**1**	95
10			**1**	95
11			**9**	90
12			**10**	82
13			**11**	84
14			**12**	96, 71,[c] 90[e]
15			**13**	84
16			**14**	78, 7[b]
17			**15**	83, 17[b]
18			**2**	82,[c] 27[b]
19			**3**	84, 20[b]
20			**4**	94, 24[b]

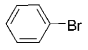
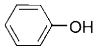
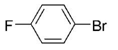
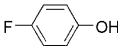
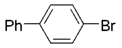
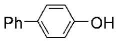
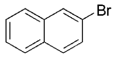
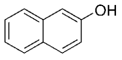
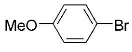
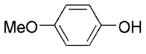
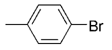
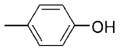
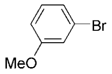
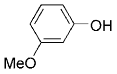
[a] General reaction conditions: 130 °C for 24 h. [b] 130 °C, 24 h, without CuI and ligand. [c] 110 °C, 24 h. [d] 130 °C, 36 h. [e] 110 °C, 36 h.

were generated from reactive aryl bromides, including *p*-bromocyanobenzene, *o*- and *p*-acetobromobenzene, and *m*- and *p*-nitrobromobenzene (Table 3, entries 16–20). In all of these cases, blank experiments performed in the absence of a copper–ligand catalytic system revealed only very poor conversion of aryl bromides into their corresponding phenols (Table 3, entries 16–20).

We then applied these conditions to bromobenzene, but at first the cross-coupling failed. However, we were able to obtain **1**, formed in excellent yield from the copper-catalyzed production of iodobenzene from bromobenzene and iodide salts (NaI), and carry out its subsequent in situ copper-catalyzed trapping by the hydroxide ion (Table 4, entry 1).[12] Although the diketone **L1** was able to promote these two successive catalytic reactions, *N*,*N*-dimethylenediamine **L7** proved to be much more efficient. Before the addition of CsOH/water, the halide exchange was usually performed at 110 °C in 1,4-dioxane, though toluene or DMSO could also be used. This method was successfully extended to aryl bromides deactivated by electron-donating *p*-methyl-, *p*- or *m*-methoxy substituents (Table 4, entries 5–7) or an electron-withdrawing group, such as *p*-phenyl or *p*-fluoro (Table 4, entries 2,3). 2-Bromonaphthalene was also selectively converted into the corresponding naphthol under these conditions (88 %; Table 4, entry 4).

Table 4: Copper/ligand-catalyzed hydroxylation of arylbromides in the presence of NaI.



	ArBr	ArOH		Isolated yield [%]
1			**1**	85, 75[a]
2			**6**	70
3			**5**	90
4			**16**	88
5			**9**	87
6			**10**	80, 83[b]
7			**17**	85

[a] DMSO used instead of dioxane. [b] Toluene used instead of dioxane.

In conclusion, we have discovered a general, economical, and efficient method for the direct copper-catalyzed synthesis of phenols from all kinds of aryl iodides and bromides. This selective procedure avoids the otherwise typical formation of the related biaryl ether by-product. The H_2O/co-solvent system used is unusual, and work is currently in progress to elucidate how it functions. The convenience of employing an aqueous hydroxide ion and the low cost of the copper catalytic system make this method very competitive.[5] It could be easily adapted to industrial-scale production, and would be particularly useful where safety and environmental factors are a greater concern. The catalytic system is not that different from that which in 2007 allowed us to perform the copper-catalyzed synthesis of anilines using aqueous ammonia.[9] With these tools in hand we can now propose a general alternative, both for amination and hydroxylation of aromatic halides, to the existing palladium-based catalytic systems.[5b]

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