An Efficient Synthesis of Phenol via CuI/8-Hydroxyquinoline-Catalyzed Hydroxylation of Aryl Halides and Potassium Hydroxide

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Abstract: The CuI/8-hydroxyquinoline-catalyzed direct hydroxylation of aryl iodides with KOH takes place at 100 °C in a mixed solvent system (*t*-BuOH–DMSO–H_2O), providing the corresponding phenols in great diversity. Aryl bromides are found to be rather less reactive under these reaction conditions.

Key words: coupling, hydroxylation, 8-hydroxyquinoline, phenols

Phenols are very important intermediates in the chemical, pharmaceutical, and materials industries.[1] For phenol, the three-step Hock process[2] is the classic industrial process although it is not very efficient because of low conversion rates at every step and overall high energy cost. A further disadvantage is the inevitable byproduct acetone. For most substituted and functionalized phenols, nonoxidative methods were developed such as the straight nucleophilic substitution[3] of aryl sulfonic acid and aryl halides and the hydroxylation of diazoarenes.[4] But usually these methods require harsh reaction conditions and activated substrates. Recently, a very efficient catalytic system based on palladium–phosphine complexes was developed by the groups of Buchwald,[5] Kwang,[6] and Beller,[7] which led to hydroxylation of aryl halides under mild reaction conditions. However, the replacement of palladium as catalyst by less expensive copper(I) salts would allow for economic benefits and also reduce toxicity issues. In recent years, copper-catalyzed coupling reactions have been widely used in the synthesis of diaryl ethers and aryl alkyl ethers.[8] However, the direct hydroxylation of aryl halides still remains a challenge. A previous study[9a] by Leadbeater et al. employing the CuI/L-proline system, developed by our group,[9b] demonstrated that hydroxylation reactions of aryl halides can take place in near-critical water as reaction medium under microwave heating, though rather high temperatures (200–300 °C) are required and only with a limited scope of activated aryl halides. More recently, You[10] and Taillefer[11] independently disclosed a highly efficient copper-catalyzed procedure for the direct hydroxylation of aryl halides in the presence of 1,10-phenathroline and dibenzoylmethane, respectively, as ligands. These reports prompted us to describe here our results on screening suitable reaction conditions for the same transformation. We found that 8-hydroxyquinoline is an effective ligand for CuI-catalyzed hydroxylation reactions of aryl iodides, and solvent systems have great influence on this reaction.

Initially, we tested the conversion of 4-iodoanisole with KOH as the base and nucleophilic agent in 1,4-dioxane–water (Table 1, entry 1) using our already established catalytic system[9b] [10 mol% of CuI and 20 mol% of L-proline (ligand A)].

Those reaction conditions proved to be unsuitable, as at a reaction temperature of 90 °C no conversion of the starting material occurred. By changing the solvent to DMF–water or DMSO–water we were able to obtain the desired phenol in low to moderate yields (entries 2 and 3). However, applying those solvent mixtures caused sublimation of 4-iodoanisole to the upper end of the reaction tube. In pure DMF or DMSO as solvent neither sublimation nor conversion occurred. Fortunately, when replacing water with ethanol the DMSO–EtOH mixture as solvent showed no sublimation, however, the yield of 4-methoxyphenol was reduced to 61% due to the formation of the 4-methoxyphenyl ethyl ether (33% yield) as a byproduct (entry 4).

Gratefully, the use of the more sterically hindered *t*-BuOH as co-solvent together with 5 vol% of water successfully suppressed the generation of the aryl ether, and therefore higher yields could be obtained (entry 5). Increasing the reaction temperature to 100 °C led to further improvement of the yields (entry 6). The addition of 5 vol% water to the solvent mixture was important; without addition the yield decreased to only 73% (entry 7). Obviously, the selection of the right solvent system is critical for this transformation.

With the appropriate conditions in hand we subsequently screened different types of ligands that were known for their effective application in copper-catalyzed coupling reactions to examine the influence of the ligand effects upon the reaction. It was found that *trans*-4-hydroxy-L-proline (**B**), pipecolinic acid (**C**), and piconilic acid (**D**) could promote this reaction and overall good yields were obtained (entries 8–10). Among the investigated ligands 8-hydroxyquinoline (*E*) gave the best result (entry 11). The use of β-keto ester (**F**) as a ligand also led to a good yield (entry 12). Employing our solvent system to the previously reported two efficient ligands (**G** and **H**) also provided excellent results (entry 13 and entry 14). The

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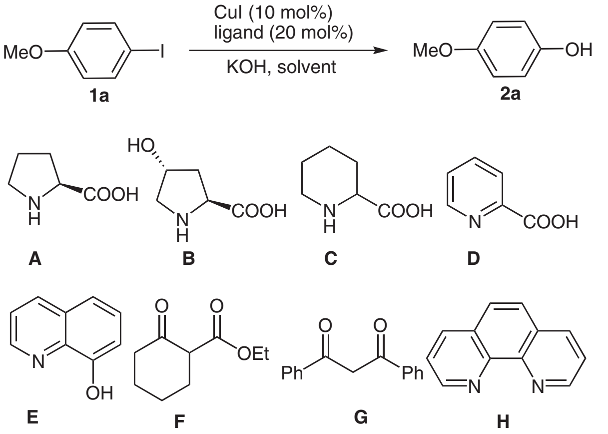
Table 1 Optimization of Various Solvent Systems for the Direct Hydroxylation of 4-Iodoanisole Catalyzed by CuI/Ligand[a]



Entry	Ligand	Solvent	Temp (°C)	Yield (%)[b]
1	A	1,4-dioxane–H_2O (1:0.1)	90	–
2	A	DMF–H_2O (1:0.1)	90	5
3	A	DMSO–H_2O (1:0.1)	90	61
4	A	EtOH–DMSO (1:1)	90	61[c]
5	A	*t*-BuOH–DMSO–H_2O	90	75
6	A	*t*-BuOH–DMSO–H_2O	100	86
7	A	*t*-BuOH–DMSO (1:1)	100	73
8	B	*t*-BuOH–DMSO–H_2O	100	85
9	C	*t*-BuOH–DMSO–H_2O	100	83
10	D	*t*-BuOH–DMSO–H_2O	100	89
11	E	*t*-BuOH–DMSO–H_2O	100	96
12	F	*t*-BuOH–DMSO–H_2O	100	85
13	G	*t*-BuOH–DMSO–H_2O	100	86
14	H	*t*-BuOH–DMSO–H_2O	100	91
15	-	*t*-BuOH–DMSO–H_2O	100	75

[a] Reaction conditions: 4-iodoanisole (1 mmol), CuI (0.1 mmol), ligand (0.2 mmol), KOH (4 mmol), solvent (2.1 mL in a ratio of 1:1:0.1 except for entries 1–4 and 7), 48 h.

[b] Isolated yield.

[c] 4-Methoxylphenyl ethyl ether was isolated in 33% yield.

Table 2 Synthesis of Phenols by CuI/8-Hydroxyquinoline-Catalyzed Hydroxylation of Aryl Halides[a]

$$\mathrm{ArX} \xrightarrow[\text{KOH, } t\text{-BuOH–DMSO–H}_2\text{O, 100 °C, 48 h}]{\text{CuI (10 mol\%), 8-hydroxyquinoline (20 mol\%)}} \mathrm{ArOH}$$

Entry	X	Ar	Yield (%)[b]
1	I	4-$MeOC_6H_4$	96
2	I	2-$MeOC_6H_4$	92
3	I	2-HOC_6H_4	95[c]
4	I	Ph	89
5	I	naphthalen-1-yl	92
6	I	4-PhC_6H_4	90
7	I	4-MeC_6H_4	96
8	I	3,5-$(CH_3)_2C_6H_3$	98
9	I	2-MeC_6H_4	96
10	I	3-$(HOCH_2)C_6H_4$	63
11	I	4-FC_6H_4	97
12	I	3-$(HOOC)C_6H_4$	98
13	I	4-BrC_6H_4	70
14	I	4-$O_2NC_6H_4$	88[d,e]
15	I	4-$(MeCO)C_6H_4$	93[d]
16	I	3-$F_3CC_6H_4$	88
17	I	2-$(HOOCCH_2)C_6H_4$	94
18	Br	4-$MeOC_6H_4$	12
19	Br	4-$(MeCO)C_6H_4$	33[d,f]
20	Br	4-FC_6H_4	29
21	Br	3-$(HOOC)C_6H_4$	23[g]
22	Br	4-$O_2NC_6H_4$	74[g]

[a] Reaction conditions: 4-iodoanisole (1 mmol), CuI (0.1 mmol), 8-hydroxyquinoline (0.2 mmol), KOH (4 mmol), *t*-BuOH–DMSO–H_2O (1 mL + 1 mL + 0.1 mL), 100 °C, 48 h.

[b] Isolated yield.

[c] 5 mmol of KOH was used.

[d] DMSO–H_2O (1 mL + 1 mL).

[e] The reaction was carried out at 80 °C.

[f] The reaction was carried out at 110 °C.

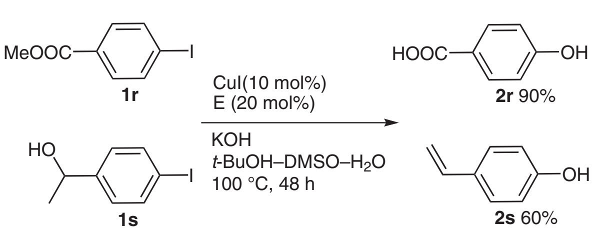
[g] The reaction was carried out at 120 °C for 25 h.

addition of an appropriate ligand is essential for high conversion rates, since in the absence of ligand a relatively low yield (entry 15) was obtained. The optimized reaction conditions were determined to employ 10 mol% copper(I) iodide, 20 mol% 8-hydoxyquinoline, 4 equivalents of KOH as base, and *t*-BuOH–DMSO–H_2O as mixed solvent to provide the desired phenols within 48 hours at a reaction temperature of 100 °C.

Using the described procedure[12] we subjected a series of aryl iodides to the optimized reaction conditions to investigate the scope and limitations of the reaction. The results are summarized in Table 2. Gratefully, it could be shown that not only activated aryl iodides with electron-withdrawing groups but also aryl iodides bearing strongly electron-donating substituents could be converted into their corresponding phenols in good to excellent yields (entries 1–17). In case of the activated aryl iodide 4-nitrophenyliodide the reaction proceeded efficiently even at lower temperature (80 °C, 30 h; entry 14). In this case applying DMSO–H_2O as solvent system was better suited, as like for 4-acetylphenyliodide (entry 15), because the latter underwent some extent undesired side reactions in *t*-BuOH. Hydroxymethylene and carboxyl groups are also suitable substituents for this transformation (entries 10 and 12). Also substrates with *ortho* substituents gave the desired phenols in excellent yields. Noticeably, when 2-iodophenol was employed as a substrate, 5 equivalents of KOH were needed to achieve high conversions (entry 3).

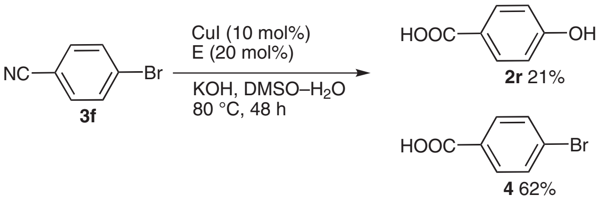
Then, we further tested the activity of aryl bromides under our reaction conditions. But several cases gave low yields (entries 18–21), it seemed that our catalytic system was not suited for aryl bromides. Only 4-nitrophenyl bromide provided the corresponding phenol in good yield (entry 22).

When methyl 4-iodobenzoate was used, 4-hydroxybenzoic acid was isolated in 90% yield, indicating that the ester moiety could not survive under these reaction conditions. While both hydroxylation and dehydration occurred when 1-(4-iodophenyl)ethanol was utilized, as evident from the formation of 4-vinylphenol in 60% (Scheme 1).



Scheme 1

For 4-bromobenzonitrile, a mixture of 4-hydroxy benzoic acid (**2r**) and 4-bromo benzoic acid (**4**, the ratio is about 1:3 determined by ^1H NMR) was obtained (Scheme 2). This result indicates that the nitrile group was totally hydrolyzed under these reaction conditions.



Scheme 2

In conclusion, we have developed an efficient and mild protocol for the copper-catalyzed hydroxylation of aryl iodides which provided phenols with a wide diversity of substitution patterns, employing the commercial available ligand 8-hydroxyquinoline. Many functional groups such as nitro, carbonyl, carboxyl, and hydroxy groups are tolerated under these reactions conditions. The unusual solvent system DMSO–*t*-BuOH–H_2O successfully suppressed the undesirable sublimation process that a range of solid starting materials (e.g., 4-iodoanisole, 1-bromo-4-iodobenzene, among others) are likely to undergo.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Typical Procedure for Preparation of 2a**
An oven-dried Schlenk tube was charged with CuI (19 mg, 0.1 mmol), 4-iodoanisole (1 mmol), 8-hydroxyquinoline (29 mg, 0.2 mmol), and KOH (224 mg, 4 mmol). The tube was evacuated and backfilled with argon, and DMSO (1 mL), *t*-BuOH (1 mL), and H_2O (0.1 mL) were added. The reaction mixture was stirred at 100 °C till the material was completely converted (monitored by TLC). Then the mixture was acidified to pH ~1 with 1 N HCl. Extract workup followed by chromatography afford 4-methoxyphenol in 96% yield.