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Microwave-assisted copper-catalyzed hydroxylation of aryl halides in water†

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Fang Ke,[a] Xiaole Chen,[a] Zhengkai Li,[b] Haifeng Xiang[b] and Xiangge Zhou*[b]

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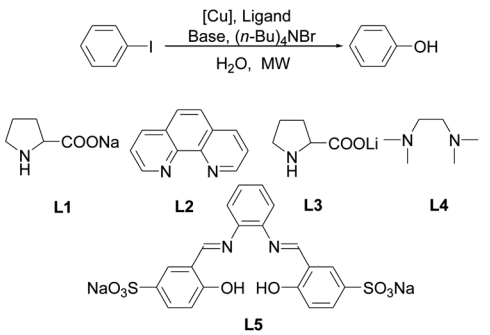
A simple and efficient protocol for microwave-assisted copper-catalyzed hydroxylation of aryl halides is developed. A variety of phenols can be obtained in moderate to excellent yields of up to 95%. Its application is performed to synthesize 2,3-dihydroxy-1,4-naphthoquinone, which displays significant anti-proliferation effect.

Phenols are important building blocks for constructing pharmaceuticals, polymers and natural compounds, and can serve as versatile synthetic intermediates in preparing oxygenated heterocycles.[1] Also, they might be traditionally installed in the early stages of synthesis, potentially leading to regiocontrol issues in further arene functionalisation, or to instability towards oxidation.[2] The classical hydroxylation methods to prepare phenols are usually carried out under harsh reaction conditions.[3] For example, the reactions of non-activated substrates to form phenols are typically proceeded under high temperature around 200–350 °C,[4] which would be incompatible with sensitive functionality. The milder catalytic methods through a two-step coupling procedure was then developed by Hartwig and coworkers.[5] After that, several groups have developed efficient palladium-catalyzed hydroxylation processes of aryl halides with hydroxide derivatives.[6] Considering the cost and environmental factor, the development of copper or iron catalytic system enabling the direct hydroxylation of aryl halides has become an important goal. Recently, an iron-catalyzed method has been reported for conversion of aryl halides to phenols in water at 180 °C.[7] We and others also reported efficient copper-catalyzed synthesis of phenols from aryl halides under mild conditions.[8]

On the other hand, microwave (MW)-assisted synthetic method has been reported in many cases to be able to speed up

Table 1 Optimization of hydroxylation of iodobenzene[a]



Entry	Cu source	Ligand	Base	T/°C	t/min	Yield[b] (%)
1	CuI	L1	NaOH	120	30	70
2	CuI	L2	NaOH	120	30	61
3	CuI	L3	NaOH	120	30	78
4	CuI	L4	NaOH	120	30	63
5	CuI	L5	NaOH	120	30	43
6	$Cu(OAc)_2$	L3	NaOH	120	30	34
7	$CuSO_4$	L3	NaOH	120	30	50
8	Cu_2O	L3	NaOH	120	30	46
9	$CuCl_2$	L3	NaOH	120	30	83
10	$CuCl_2$	L3	KOH	120	30	87
11	$CuCl_2$	L3	K_2CO_3	120	30	72
12	$CuCl_2$	L3	Na_2CO_3	120	30	66
13	$CuCl_2$	L3	Cs_2CO_3	120	30	85
14	$CuCl_2$	L3	KOH	110	30	80
15	$CuCl_2$	L3	KOH	130	30	87
16	$CuCl_2$	L3	KOH	120	20	69
17	$CuCl_2$	L3	KOH	120	40	92
18	$CuCl_2$	L3	KOH	120	50	90
19	—	L3	KOH	120	40	Trace
20	$CuCl_2$	—	KOH	120	40	20
21[c]	$CuCl_2$	L3	KOH	120	40	30

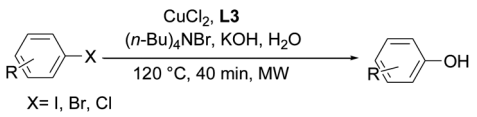
[a] Unless otherwise noted, the reactions were carried out using iodobenzene (1.0 mmol), Cu source (10 mol%), ligand (10 mol%), base (2.0 mmol) and $(n\text{-Bu})_4NBr$ (10 mol%) in water (3 mL) under microwave 200 W. [b] Determined by GC with 1,4-dichlrobenzene as internal standard. [c] Without addition of $(n\text{-Bu})_4NBr$.

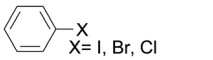
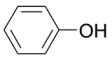
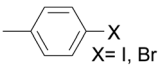
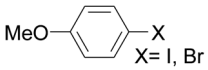
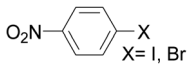
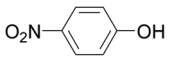
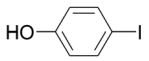
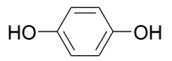
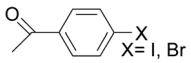
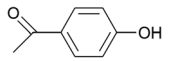
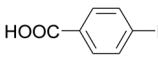
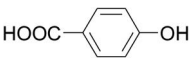
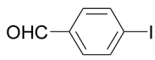
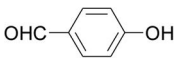
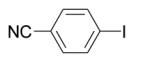
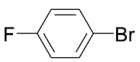
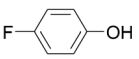
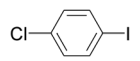
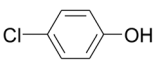
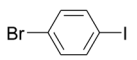
[a]*College of Pharmacy, Fujian Medical University, Fuzhou 350004, China*

[b]*Institute of Homogeneous Catalysis, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: zhouxiangge@scu.edu.cn; Fax: +86-28-85412026; Tel: +86-28-85412026*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra44613a

Table 2 Microwave-assisted hydroxylation of aryl halides catalyzed by $CuCl_2$/L3 in water[a]



Entry	Aryl halide	Product	Yield[b] (%)
1			92 (X = I) 79 (X = Br) 52 (X = Cl)
2			84 (X = I) 75 (X = Br)
3			78 (X = I) 63 (X = Br)
4			95 (X = I) 83 (X = Br)
5			88
6			86 (X = I) 78 (X = Br)
7			82
8			72
9			85
10			63
11			79
12			85
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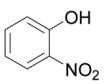
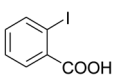
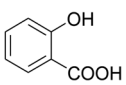
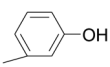
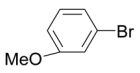
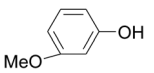
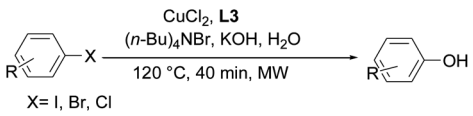
14			84
15			83
16			78
17			73
18			76
19			63

Table 2 (*Contd.*)



Entry	Aryl halide	Product	Yield[b] (%)
20			79
21			82
22			83 (X = I) 75 (X = Br)
23			83
24			78

[a] Reactions were carried out using aryl halide (1.0 mmol), $CuCl_2$ (10 mol %), L3 (10 mol%), KOH (2.0 mmol) and $(n\text{-Bu})_4NBr$ (10 mol%) in water (3 mL) at 120 °C for 40 min under 200 W. [b] Isolated yield after column chromatography.

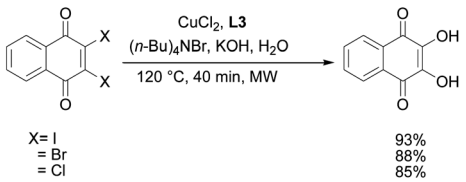
the rates of reactions as well as improve yields and influence selectivities.[9] The combination of microwave and metal catalysis has become one of the ways in future "green" catalytic protocols.[10] Moreover, water has attracted much attention as a reaction medium because of its low cost, availability, safety and environmental-friendliness.[11] In continuation of our endeavors to develop environmentally friendly protocols,[12] herein we disclose hydroxylation of aryl halides catalyzed by readily available $CuCl_2$ with proline lithium in water under microwave irradiation.

To optimize the reaction conditions, iodobenzene was firstly chosen as the model substrate. Selected results from the screening experiments are summarized in Table 1. Screening of several ligands indicated the most fitful one was proline lithium L3 with 78% yield (Table 1, entries 1–5), which also exhibited high efficacy in other copper catalyzed coupling reactions involving aryl halides.[13] Among the copper salts used, $CuCl_2$ was superior to others including CuI, $CuSO_4$, $Cu(OAc)_2$, and Cu_2O (Table 1, entries 6–9). Control experiments confirmed that either of copper salt and ligand was essential for the reaction (Table 1, entries 19 and 20). Test of different bases revealed KOH to be better than others to gave the product in 87% yield (Table 1, entries 10–13). The effects of reaction time and temperature were also studied, 120 °C and 40 min were optimal reaction conditions. Meanwhile, phase transfer reagent seemed to be beneficial for the reaction, and only 30% yield was obtained in the absence of it (Table 1, entry 21). Therefore, the optimal reaction conditions for the microwave-assisted copper-catalyzed hydroxylation were aryl halide (1.0 mmol), $CuCl_2$ (10 mol%), ligand (10 mol%), $(n\text{-Bu})_4NBr$ (10 mol%), and KOH

(2.0 equiv.), at 120 °C with water (3.0 mL) as the solvent for 40 min under 200 W microwave.

With the optimal reaction conditions established, a variety of substituted aryl halides were examined and the results are summarized in Table 2. In general, aryl iodides were more reactive than aryl bromides and aryl chlorides with higher yields, and diphenyl ethers were not detected in the reaction. Catalytic hydroxylation reactions of dihalogenated aryl halides resulted in good chemoselectivity between aryl iodide, bromide or chloride (Table 2, entries 10–12). Electron-withdrawing substituents seemed to be more beneficial to the reaction, and the highest yield (95%) was obtained by using 4-iodonitrobenzene (Table 2, entry 4). Functional groups such as methyl, methoxy, nitro, hydroxy, ketone carboxyl acid, aldehyde, cyano and fluoro groups were well-tolerated under the reaction conditions (Table 2, entries 2–10). Moreover, sterically demanding such as *ortho* substituents did not hamper the reaction and the corresponding products were obtained in good yields (Table 2, entries 13–17). Furthermore, the copper catalyst also exhibited efficiency in coupling reactions to obtain more challenging phenols bearing heterocycles such as pyridine, pyrimidine, and quinoline, thus allowing access to heterocyclic phenolic derivatives in numerous appealing compounds (Table 2, entries 22–24).

Due to the increasing interests in naphthalene derivatives for their activities in biological, medicinal and pharmaceutical applications, the catalytic system was then successfully applied in the synthesis of 2,3-dihydroxy-1,4-naphthoquinone.[14] As show in Scheme 1, the desired product could be achieved in high yields under the optimized reaction conditions up to 93%. Furthermore, the obtained 2,3-dihydroxy-1,4-naphthoquinone was then used in MTT assay, which displayed significant anti-proliferation effect on both tested human cancer cell lines, K562 and CNE2 (Fig. 1). And the IC50 values obtained against K562 cells and CNE2 cells were 3.0 μM and 3.1 μM, respectively.



Scheme 1 Synthesis of 2,3-dihydroxy-1,4-naphthoquinone in water.

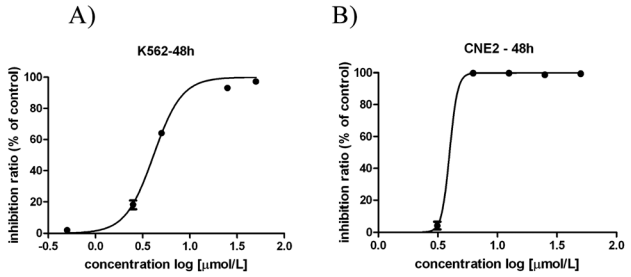


Fig. 1 Relationship between inhibition rate for K562 and CNE2 cells and initial concentration.

In summary, we have developed a simple, economical and efficient microwave-assisted copper-catalyzed method for the synthesis of phenols. Proline lithium was used as ligand during the copper catalysis, and environmentally friendly water was used as solvent. The microwave irradiation as an efficient source of energy lowered the environmental impact of the transformation, allowing us to accomplish the hydroxylation in a few minutes. By using this protocol, the hydroxylation of aryl iodides, bromides and even aryl chlorides proceeded well under mild conditions. The method is of high tolerance towards various functional groups in the substrates, and the synthesis of these compounds will attract much attention in academic and industrial research. Further studies into the reaction mechanism, and its application in synthesis will be reported in due course.

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