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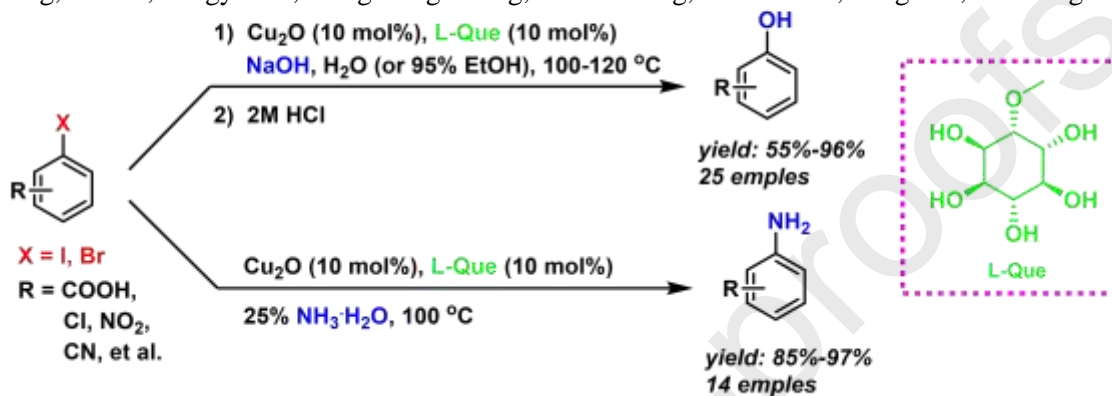


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ABSTRACT

L-(-)-Quebrachitol, a natural product obtained from waste water of the rubber industry, was utilized as an efficient ligand for the copper-catalyzed hydroxylation and amination of aryl halides to selectively give phenols and aryl amines in water or 95% ethanol. In addition, the hydroxylation of 2-chloro-4-hydroxybenzoic acid was validated on a 100-gram scale under air.

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1. Introduction

Phenols, aryl amines and their derivatives are important intermediates in the pharmaceutical, chemical, and materials industries.^{1,2} The development of mild and efficient methods for their synthesis from readily available starting materials has gained considerable attention. Among the reported methods, the hydroxylation of aryl halides has been recognized as one of the most valuable approaches.³ Efficient systems based on palladium/phosphine catalysis were developed by Buchwald and other groups.⁴ However, the use of precious metal catalysts and toxic ligands has reduced their attractiveness. Recently, several efficient copper-catalyzed procedures for the direct hydroxylation of aryl halides were reported (Fig. 1). The groups of Taillefer and You were the first to report that aryl halides could be hydrolyzed by hydroxide salts in the presence of CuI and a ligand under mild conditions.⁵ The groups of Zhou and Jiang also obtained phenols from the corresponding aryl halides *via* hydroxylation catalyzed by CuI and a ligand in water, and phase transfer catalysts (PTC), such as *n*-Bu₄NF or *n*-Bu₄NBr, were essential for these procedures.⁶ Feng and co-workers reported that CuI-nanoparticles could catalyze the synthesis of phenols and aryl amines from aryl halides under a nitrogen atmosphere without a ligand or an organic solvent.⁷ Unfortunately, many of the reported reaction conditions require a substantial amount of a mixed solvent or a PTC which are difficult to recycle.

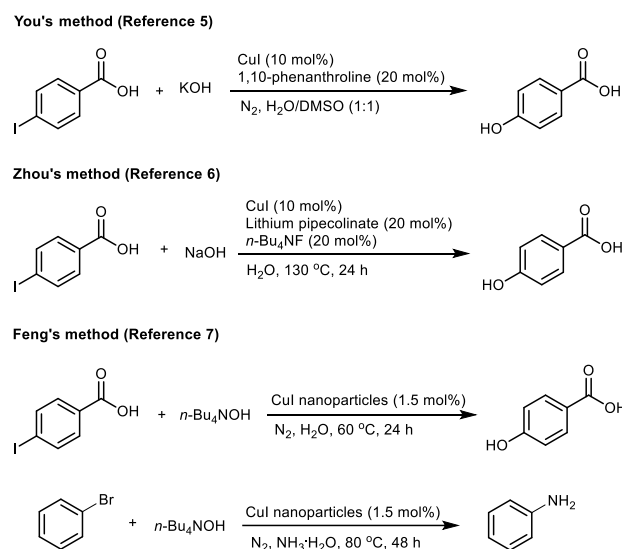


Figure 1. Selected methods for the synthesis of phenols and aryl amines.

Considering the solubility of carboxylates, which dissolve well in basic aqueous solutions, we speculated that if a suitable water-soluble ligand could be found, the organic solvent and PTC would not be essential. To develop an eco-friendly and practical protocol, we report a method for the conversion of aryl iodides to phenols *via* the combination of Cu₂O and L-Quebrachitol in water (Fig. 2). Unfortunately, this catalytic system was not applicable to water-insoluble compounds. To our surprise, when we replaced water with 95% ethanol (low toxicity, recyclable), the catalytic system

also

Additionally, aryl amines could also be obtained from aryl halides *via* the reaction in aqueous ammonia catalyzed by Cu₂O and L-Quebrachitol without a PTC or a mixed solvent.

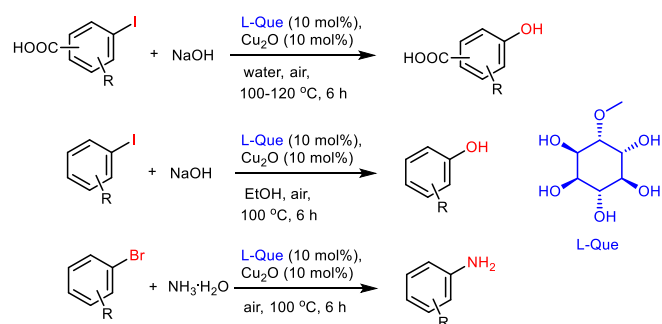


Figure 2. Practical synthesis of phenols and anilines from aryl halides.

L-Quebrachitol (1-L-(-)-2-O-methyl-chiro-inositol, L-Que) is an optically active cyclitol which has been known in the literature for over a century.⁸ The waste water of the rubber industry represents the main source of L-Que and extraction technologies have been developed to obtain L-Que on large scale.⁹ Herein, we have utilized it as an efficient ligand for the copper-catalyzed hydroxylation and amination of aryl halides.

2. Results and Discussion

Initially, we selected 4-iodobenzoic acid as a model substrate to investigate the effect of Cu-catalysts, bases and ligands (Table 1). Selected water-soluble ligands reported in the literature,^{5, 10} such as glycolic acid, L-proline and triethanolamine, were employed (10 mol%) at 100 °C in the presence of Cu₂O (10 mol%) under an argon atmosphere (Table 1, entries 2-4); however acceptable results were not achieved. Encouraged by Sekar and co-workers' report that D-glucose could be used for the copper-catalyzed synthesis of phenols from aryl halides,¹¹ we investigated the effect of D-glucose, inositol and L-Que. Gratifyingly, the reaction proceeded well and gave the desired *p*-hydroxybenzoic acid in good conversion when L-Que was employed (Table 1, entry 7). Meanwhile, no decrease of the conversion was detected when the reaction was performed under air, implying that the inert atmosphere was not necessary in this catalytic system (Table 1, entry 8). After screening a variety of Cu-catalysts, CuCl and Cu₂O turned out to be the most efficient for this transformation (Table 1, entries 9-13). Considering the stability under air and the cost, Cu₂O was selected for further optimization. Further inspection revealed that KOH and NaOH gave similar results, while K₂CO₃ and CsCO₃ were not suitable for this reaction (Table 1, entries 14-16). Moreover, the amount of NaOH was also evaluated and the results indicated that the conversion decreased when 3 equiv. of NaOH was used (Table 1, entries 17). Further optimization to reduce the catalyst loading showed that only 10 mol% of Cu₂O and 10 mol% of L-Que were required for quantitative conversion (Entries 19 and 20). Thus, the optimal conditions were Cu₂O (10 mol%), L-Que (10 mol%), NaOH (4 equiv.), in water under air.

Table 1. Optimization of the Cu-catalyzed hydroxylation of 4-iodobenzoic acid.^a

Entry	Ligand	Catalyst	Base	Yield (%) ^b
1 ^c	-	Cu ₂ O	NaOH	15
2 ^c	Glycolic acid	Cu ₂ O	NaOH	20
3 ^c	L-proline	Cu ₂ O	NaOH	16
4 ^c	Triethanolamine	Cu ₂ O	NaOH	27

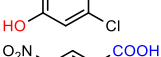
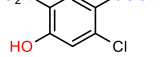
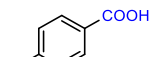
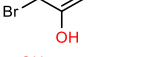
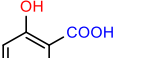

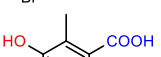
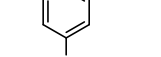
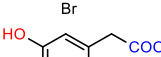
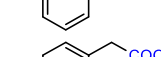
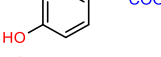
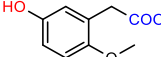
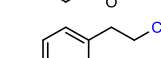
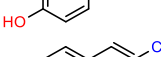
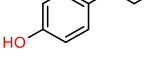
6 ^c	Inositol	Cu ₂ O	NaOH	79
7 ^c	L-Que	Cu ₂ O	NaOH	94
8	L-Que	Cu ₂ O	NaOH	93
9	L-Que	CuCl ₂	NaOH	50
10	L-Que	CuSO ₄	NaOH	20
11	L-Que	CuCl	NaOH	93
12	L-Que	CuI	NaOH	60
13	L-Que	Cu(OAc) ₂	NaOH	0
14	L-Que	Cu ₂ O	KOH	92
15	L-Que	Cu ₂ O	CsCO ₃	0
16	L-Que	Cu ₂ O	K ₂ CO ₃	0
17 ^d	L-Que	Cu ₂ O	NaOH	79
18 ^e	L-Que	Cu ₂ O	NaOH	94
19 ^f	L-Que	Cu ₂ O	NaOH	46
20 ^g	L-Que	Cu ₂ O	NaOH	39

^a Reagents and conditions: 4-iodobenzoic acid (0.5 mmol), base (2 mmol), Cu-catalyst (0.05 mmol), ligand (0.05 mmol), water (5 mL), air, 6 h. ^b % area by HPLC. ^c argon atmosphere. ^d 3 equiv. of NaOH was used. ^e 6 equiv. of NaOH was used. ^f 5 mol% of Cu₂O was used. ^g 5 mol% of L-Que was used.

Next, several aryl iodides with carboxyl groups were employed to investigate the efficiency and scope of the L-Que/Cu₂O catalyzed system (Table 2). The hydroxylation proceeded under an air atmosphere to afford the corresponding phenols in moderate to excellent yields. A number of functional groups, for example bromine, benzylic C-H bonds, nitro and alkenyl, were well tolerated. Aryl iodides substituted only by carboxyl groups afforded the desired products in excellent yields, and the position of the carboxyl substitution had no obvious influence on the hydroxylation (Table 2, entries 1-3). When chloro-substituted aryl iodides were used, the hydroxylation only took place at iodine leaving chlorine untouched (Table 2, entries 6-8). As for bromo-substituted aryl iodides, acceptable yields could also be achieved (Table 2, entries 9-11). In addition to the benzoic acids mentioned above, good yields were obtained for substrates in which the carboxyl groups were not directly linked to the benzene ring (Table 2, entries 12-19). The performance of substrates with electron-donating methoxy substituents were poor at 100 °C, but good at 120 °C or higher temperatures. To investigate the effect of the carboxyl group, 1-(4-iodophenyl) ethenone and 1-iodo-4-methoxybenzene were employed; the former was converted to the corresponding phenol in high yield, but the latter was unreactive (Table 2, entries 20-21). Understandably, the solubility of the starting materials in water resulted in different reactivity.

Table 2. Direct hydroxylation of water-soluble aryl iodides.^a

Entry	Product	Temp. (°C)	Yield (%) ^b
1		100	93
2		100	90
3		100	88
4		100	79
5		100	74
6		100	83

7		100	87
8		90	55
9		100	71
10		100	77
11		100	86
12		100	71
13		100	84
14		130	68
15		100	79
16		100	88
17		100	90
18		120	81
19		120	60
20		120	87
21		130	0

^a Reagents and conditions: aryl iodide (0.5 mmol), Cu₂O (0.05 mmol), L-Que (0.05 mmol), NaOH (2.0 mmol), water (5 mL), air. ^b Isolated yield (flash column chromatography on silica gel).

2-Chloro-4-hydroxybenzoic acid,¹² a valuable synthetic building block for the chemical and pharmaceutical industries, was employed to validate the large-scale applicability of this method (Fig. 3).

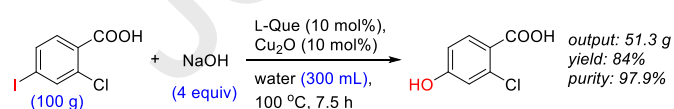


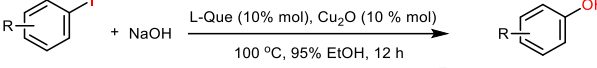
Figure 3. Results of the scale-up batch.


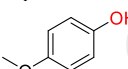
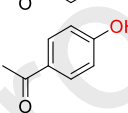

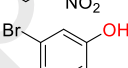

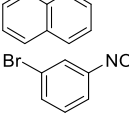
In order to solve the problem of poor reactivity using water-insoluble compounds, we examined easily recycled and low toxic organic solvents. We found that when 95% ethanol was used as a solvent, iodobenzene could be selectively converted to phenols instead of phenethyl ether (<4%). Next, the scope of aryl iodides was investigated for this modified catalyst system (Table 3). In general, aryl iodides gave the corresponding phenols in good to excellent yields (Table 3, entries 1-6). However, aryl bromides could not be hydrolyzed, and even in the case of a strongly

phenol was not afforded.

Inspired by these metal-catalyzed *N*-arylations, we wondered whether *N*-arylation would take place when L-Que/Cu₂O was combined with aqueous ammonia. To our delight, aryl bromides could be selectively converted to aryl amines in good to excellent yields rather than diphenylamine (not detected) without a PTC or a mixed solvent (Table 4). Aryl chlorides performed poorly in this system (Table 4, entry 14).

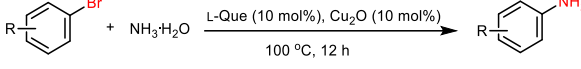
Table 3. Direct hydroxylation of water-insoluble aryl iodides.^a


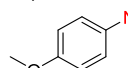
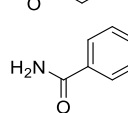
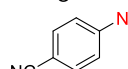
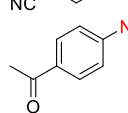
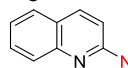
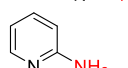



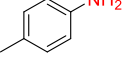
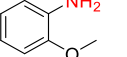
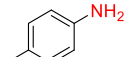
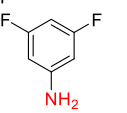
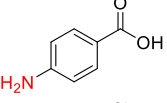
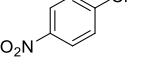
Entry	Product	Yield (%) ^b
1		96
2		90
3		76
4		88
5		90
6		93
7		0

^a Reagents and conditions: aryl iodide (0.5 mmol), Cu₂O (0.05 mmol), L-Que (0.05 mmol), NaOH (1.25 mmol), 95% ethanol (5 mL), 100 °C, air. ^b Isolated yield (flash column chromatography on silica gel).

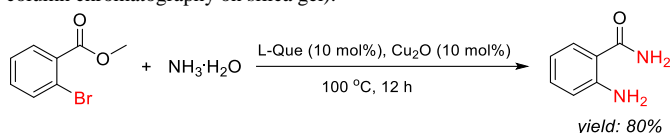
Table 4. Direct amination of aryl bromides.^a



Entry	Product	Yield (%) ^b
1		97
2		86
3		95
4		90
5		93
6		85
7		92

		
9		90
10		89
11		93
12		94
13		88
14		0

^a Reagents and conditions: aryl bromide (0.5 mmol), Cu₂O (0.05 mmol), L-Que (0.05 mmol), 25 % ammonia (5 mL), 100 °C, air. ^b Isolated yield (flash column chromatography on silica gel).



Scheme 1. Attempted reaction of methyl 2-bromobenzoate.

When methyl 2-bromobenzoate was used, 2-aminobenzamide was isolated in 80% yield, indicating that the ester moiety was not compatible with these reaction conditions.

3. Conclusions

An economical and eco-friendly copper-catalyzed selective hydroxylation and amination protocol was developed. A variety of phenols and aryl amines were synthesized from the corresponding aryl iodides and bromides in moderate to high yields. The process employing L-Que, a by-product of the rubber industry, was conducted in water under air and validated on the 100 g scale, thus constituting a practical and eco-friendly protocol.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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- New application of L-quebrachitol.
- A green method for hydroxylation and amination of aryl halides was developed.
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