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SHORT COMMUNICATION

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Triethanolamine as an Inexpensive and Efficient Ligand for Copper-Catalyzed Hydroxylation of Aryl Halides in Water

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Keywords: Copper / Hydroxylation / Phenols / N ligands / Water chemistry

The CuI/triethanolamine catalyst system efficiently promotes the direct hydroxylation of aryl iodides and bromides in water to provide the corresponding phenols in good to excellent yields. Moreover, the procedure avoids the use of toxic organic solvents and tolerates many functional groups.

Introduction

Phenols are structural scaffolds frequently found in numerous pharmaceuticals, polymers, agrochemicals, and biologically active natural products.[1] Over the years, protocols for the oxidative and nonoxidative preparation of phenols have been developed, including nucleophilic aromatic substitution of activated aryl halides, copper-promoted conversions of arene diazonium salts, and benzyne methodologies. Unfortunately, these methods usually involve harsh reaction conditions and starting materials that are not readily available.[2] Recently, Pd-catalyzed hydroxylation reactions of aryl halides with hydroxide salts have been explored for the synthesis of phenols in excellent yields under mild reaction conditions,[3] even at room temperature.[4] However, the use of expensive palladium and elaborate phosphorated ligands limits the further application of these hydroxylation reactions to large- and industrial-scale production. Very recently, the efficient Cu-catalyzed[5] direct hydroxylation of aryl halides[6] was reported under mild conditions (100–180 °C) with the use of various ligands including 1,3-diketones,[7] 1,10-phenanthroline,[8] pyridine-2-aldoxime,[9] lithium pipecolinate,[10] D-glucose,[11] quinolin-8-ol,[12] *N*,*N*′-dimethylethylenediamine (DMEDA),[13] 8-hydroxyquinoline 1-oxide,[14] 5-bromo-2-(1*H*-imidazol-2-yl)pyridine,[15] nanoparticles,[16] N-heterocyclic carbenes,[17] and glycolic acid.[18]

In spite of these developments, there remains a need for economical and easily available ligands that lead to generally applicable, ecofriendly catalyst systems for the Cu-catalyzed hydroxylation of aryl halides. As part of our endeavors to find environmentally friendly protocols,[19] herein we wish to report triethanolamine as an inexpensive, simple, and efficient ligand for the copper-catalyzed hydroxylation of aryl iodides and bromides in water.

Results and Discussion

As shown in Table 1, we selected 4-iodoanisole as the model substrate and CuI (5 mol-%) as the catalyst for optimization of the reaction conditions. Initially, a series of ligands was examined by using potassium hydroxide (4.0 equiv.) as the nucleophile, water as the solvent, and $n\mathrm{Bu}_4\mathrm{NBr}$ (TBAB, 20 mol-%) as the phase-transfer catalyst. Of the ligands screened, triethanolamine (**L1**) gave the best result (87%). It should be noted that lower yields (66%) were obtained if the amount of **L1** was reduced to 20 mol-%. The other ligands also worked well, except for **L3** and **L6**, whereas no product was isolated in the absence of ligands under similar reaction conditions. As **L4** is more expensive than **L1**, **L1** was chosen for further investigations.

The scope of the CuI/triethanolamine-catalyzed synthesis of phenols was then explored under our optimal conditions. As indicated in Table 2, various aryl iodides containing both electron-donating (Table 2, entries 6, 8, 10) and electron-withdrawing groups (Table 2, entries 3, 9, 11–14) coupled with KOH to afford the corresponding phenols in good to excellent yields in water. Also, hydroxylation of iodobenzene proceeded smoothly in good yields (85%) on a gram scale (Table 2, entry 1). Notably, steric hindrance of the substituent of the substrate had an unfavorable effect on the hydroxylation reactions. For example, hydroxylation of *p*-iodotoluene produced the desired phenol in a yield of 87%, *o*-iodotoluene gave the corresponding product in a lower yield of 61%, whereas if 2-iodo-*m*-xylene was used as

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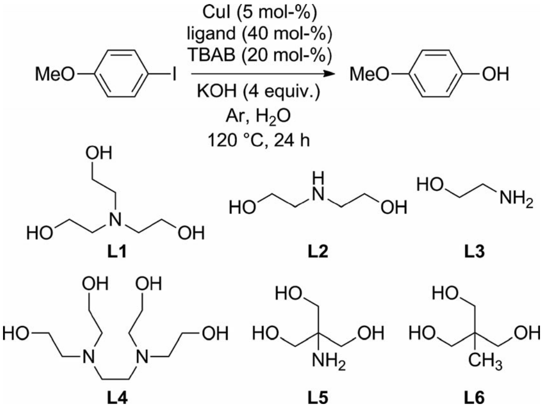
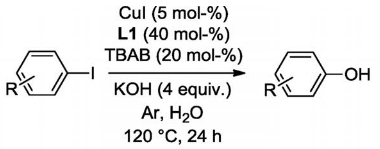
Table 1. Optimization of ligands for CuI-catalyzed hydroxylation of 4-iodoanisole in water.[a]

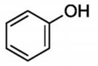
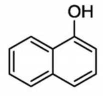
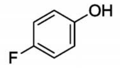
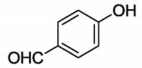
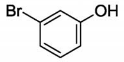
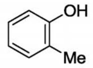
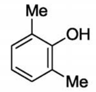
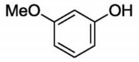
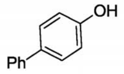
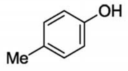
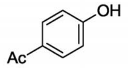
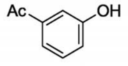
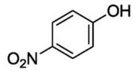
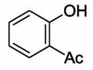
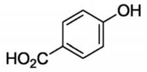
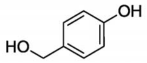


Ligand	Yield [%][b]
L1	87/66[c]
L2	69
L3	26
L4	86
L5	60
L6	22
–	0

[a] Reaction conditions: 4-iodoanisole (1 mmol), CuI (0.05 mmol), ligand (0.4 mmol), KOH (4 mmol), TBAB (0.2 mmol), H_2O (1.0 mL), Ar, 24 h. [b] Yield of isolated product. [c] **L1** (0.2 mmol).

Table 2. CuI-catalyzed hydroxylation of aryl iodides in water.[a]



Entry	ArOH	Yield [%][b]
1		86 85[c]
2		77
3		89
4		73
5		84
6		61
7		42
8		89
9		82
10		87
11		90
12		79
13		76
14		86
15		83
16		86

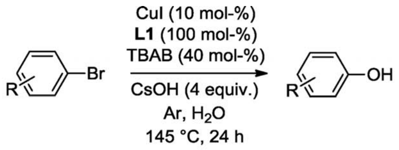
[a] Reaction conditions: ArI (1 mmol), CuI (0.05 mmol), **L1** (0.4 mmol), KOH (4 mmol), TBAB (0.2 mmol), H_2O (1.0 mL), Ar, 24 h. [b] Yield of isolated product. [c] ArI (10 mmol scale).

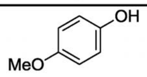
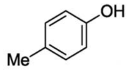
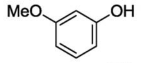
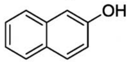
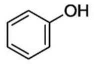
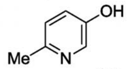
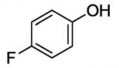
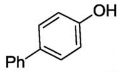
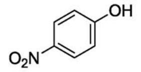
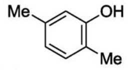
the substrate, the product was isolated in only 42% yield under the same conditions (Table 2, entries 6, 7, 10). In addition, the catalytic system displayed a great tolerance to a variety of functional groups, including aldehydes, bromides, ketones, nitro groups, carboxylic acids, and hydroxy groups (Table 2, entries 4, 5, 11–16).

Subsequently, we further applied the above conditions to aryl bromides, but the products were only isolated in 35% yield by using 4-bromoanisole as the substrate. After a simple optimization of the reaction conditions, we were pleased to find that good yields (76%) were obtained if the reaction was conducted with a combination of 10% CuI, 100% **L1**, 40% TBAB, and 400% CsOH at 145 °C in water (Table 3, entry 1). Furthermore, these conditions efficiently promoted the hydroxylation of aryl bromides bearing electron-donating groups such as *p*- and *m*-methoxy and *p*-methyl (Table 3, entries 1–3) and electron-withdrawing groups, including *p*-fluoro, *p*-phenyl, and *p*-nitro (Table 3, entries 7–9). However, the hydroxylation of less-active chlorobenzene with the CuI/**L1** catalyst under the optimal conditions was not successful, and the desired product was not isolated (Table 3, entry 5).

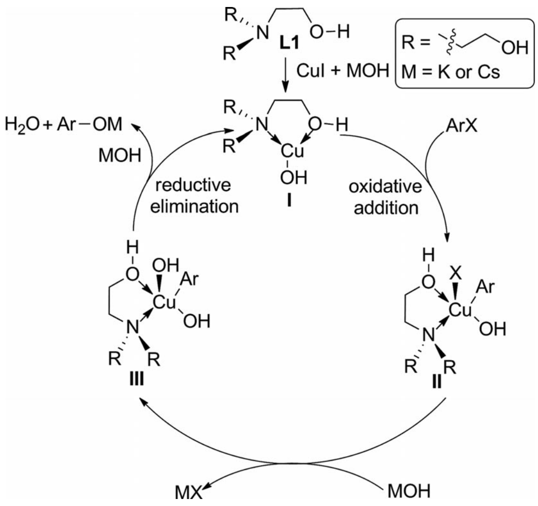
On the basis of previous literature reports on Ullmann coupling reactions,[20] we formulated a possible mechanism of the Cu/**L1**-catalyzed hydroxylation of aryl halides. As shown in Scheme 1, chelation of CuI with **L1** forms five-member reactive species **I** in the presence of KOH or CsOH, and subsequent oxidative addition of **I** with an aryl halide produces transient Cu^{III} species **II**, which undergoes nucleophilic substitution by hydroxy to afford intermediate **III**. This is followed by reductive elimination, which readily provides the hydroxylation product and regenerates active Cu^{I} species **I**.

Table 3. CuI-catalyzed hydroxylation of aryl bromides in water.[a]



Entry	ArOH	Yield [%][b]
1		35[c] 76
2		73
3		81
4		77
5		75 0[d]
6		88
7		85
8		70
9		86
10		47

[a] Reaction conditions: ArBr (1 mmol), CuI (0.1 mmol), **L1** (1.0 mmol), CsOH (4 mmol), TBAB (0.4 mmol), H_2O (1.0 mL), Ar, 145 °C, 24 h. [b] Yield of isolated product. [c] 4-Bromoanisole (1 mmol), CuI (0.05 mmol), **L1** (0.4 mmol), KOH (4 mmol), TBAB (0.2 mmol), H_2O (1.0 mL), Ar, 120 °C, 24 h. [d] Chlorobenzene was used as substrate.



Scheme 1. Proposed mechanism for the Cu/**L1**-catalyzed hydroxylation of aryl halides.

Conclusions

In conclusion, we used triethanolamine (**L1**) as a simple, efficient, and economical ligand for the direct copper-catalyzed synthesis of phenols from a series of aryl iodides and bromides in water. In addition, this procedure avoids the use of toxic organic solvents and tolerates various functional groups such as aldehydes, nitro groups, carbonyls, carboxylic acids, fluoride groups, bromide groups, and hydroxy groups.

Experimental Section

General Procedure for the Hydroxylation of Aryl Iodides: A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with the solid aryl iodide (1.0 mmol), CuI (0.05 mmol, 9.5 mg), KOH (4 mmol), and TBAB (0.2 mmol, 65 mg). The tube was evacuated and backfilled with argon. Under a counter flow of argon, H_2O (1.0 mL), the aryl iodide (1.0 mmol, if liquid) and triethanolamine (0.4 mmol, 60 mg) were added by syringe. The tube was evacuated twice and backfilled with argon. The tube was sealed and put into a preheated oil bath at 120 °C for 24 h. After the mixture solution was cooled to room-temperature, HCl was added to acidify the solution (pH 2–3), and the solution was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum; the remaining residue was purified by column chromatography on silica gel to provide the desired product.

General Procedure for the Hydroxylation of Aryl Bromides: A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with the solid aryl bromide (1.0 mmol), CuI (0.1 mmol, 19 mg), CsOH (4 mmol), and TBAB (0.4 mmol, 130 mg). The tube was evacuated and backfilled with argon. Under a counter flow of argon, H_2O (1.0 mL), the aryl bromide (1.0 mmol, if liquid), and triethanolamine (1.0 mmol, 149 mg) were added by syringe. The tube was evacuated twice and backfilled with argon. The tube was sealed and put into a preheated oil bath at 145 °C for 24 h. After the mixture solution was cooled to room temperature, HCl was added to acidify the solution (pH 2–3), and the solution was extracted with ethyl acetate (3*5 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum; the remaining residue was purified by column chromatography on silica gel to provide the desired product.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

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