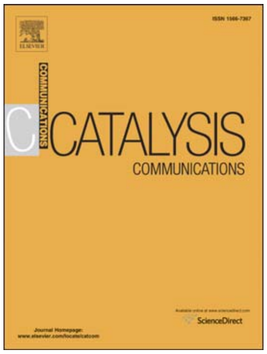

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A simple and recyclable Copper/DTPA catalyst system for amination of aryl halides with aqueous ammonia in water

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Abstract: Commercially available CuO/DTPA (diethylenetriaminepentaacetic acid) was established to be a low-cost, recyclable, and environmentally benign homogeneous catalyst system for direct amination of aryl halides with ammonia. Primary aryl amines can be readily prepared from both electron-withdrawing and electron-donating aryl halides in good yields in water without addition of surfactants.

Keywords: Copper; Amination; Water; Homogeneous catalysis; recyclable

1. Introduction

Primary aryl amines are important compounds, having applications in the pharmaceutical, agrochemical, dye, cosmetic and toiletry industries.[1, 2] As a result, the development of highly efficient and environmentally benign methods for their synthesis has drawn increasing attention.[3] Ammonia is an attractive source of nitrogen for the industrial production of organic amino compounds due to its abundance and low cost.[4, 5] However, to avoid the formation of secondary and tertiary amine by-products, early research in this area typically required the use of ammonia surrogates as the source of nitrogen.[6-8]

Hartwig and co-workers reported Pd-catalyzed aniline formation from aryl halides and ammonia in 2006, [9] and since then, many protocols for selective Pd-catalyzed amination of aryl halides with ammonia have been published.[10-14] Later, Lang and co-workers developed copper-catalyzed amination of aryl halides with ammonia at low pressures and low temperatures,[15] allowing for lower cost synthesis as both the copper centers and their associated ligands are less expensive when compared to Pd catalysts. Following this, copper-catalyzed procedures for the direct coupling of aryl halides with aqueous ammonia, gaseous ammonia or liquid ammonia have been reported in mild conditions with good tolerance of a wide range of functional groups.[16-27]

The protocols mentioned above are generally performed in organic solvents, most of which are toxic and expensive. Although some alcoholic solvents could be regarded environmental friendly, they are still flammable and not naturally occurring. As a result, there is a need to find a procedure to carry out these coupling reactions in cheap, safe and environmentally benign solvent. Recently, the copper-catalyzed C–N coupling reactions for the effective synthesis of aniline from aryl halides and aqueous ammonia have been carried out in water. For example, Xu reported that the amination of aryl iodides and bromides with $NH_3{\cdot}H_2O$ could be achieved in an aqueous solution of $n\mathrm{Bu_4NOH}$ in the presence of CuI nanoparticles under a nitrogen atmosphere. [28] In addition, we have reported copper/sucrose as a recyclable, green catalyst for the effective and direct amination of aryl halides with $NH_3{\cdot}H_2O$ at 90 °C in an aqueous solution of PEG-200.[29] However, requirement of a non-commercially available catalyst system [30-33] and/or large amounts of surfactant (such as quaternary ammonium salt [32-34] or its base [28], PEGs [29, 35]) made these protocols less practical. Still there is a need to develop a more convenient, recyclable catalyst for direct amination with ammonia in water.

Herein, we report commercially available copper/ DTPA (diethylenetriaminepentaacetic acid) as an inexpensive, recyclable and environmentally benign, homogeneous catalyst system for the coupling of aryl bromides and iodides with aqueous ammonia in water without any surfactant.

2. Experimental

2.1 Materials and Instrumentation

All starting materials and reagents are commercially available and used as received. All reactions were carried out in a preheated oil bath in 10 mL vials sealed with septa. Flash column chromatography was performed with silica gel (200-300 mesh). Thin-layer chromatography was carried out with Merck silica gel $60F_{254}$ plates. All products were characterized by MS, ^{1}H NMR and ^{13}C NMR with which compared to the previously reported data. NMR spectra were recorded at room temperature on a Mercury-Plus 300 or a Bruker AVANCE 400 instrument with TMS as an internal reference. ESI-MS and EI-MIS were performed on a LCMS-2010A and a Thermo EI-mass spectrometer respectively. GC/MS was run on a Finnigan Voyager with an electron impact (70 eV) mass selective detector and an innowax 30 m × 0.25 mm × 0.25 μm capillary apolar column. The conditions used for running GC-MS include: 1) initial temperature: 50 ℃; 2) initial time: 3 min; 3) temperature ramping speed: 20 ℃/min; 4) final temperature: 250 ℃ and final time: 10 min.

2.2 General procedure for the synthesis of 2a-2t

A 10 mL of vessel was charged with CuO (8 mg, 0.1 mmol), DTPA (78 mg, 0.2 mmol), aryl halide (1 mmol), commercial 25- 28% aqueous ammonia (1 mL), KOH (2.0 mmol), H_2O (1.0 mL) and a magnetic stirring bar. The vessel was sealed with a septum and placed into an oil bath which was preheated to 100 ℃. The reaction mixture was held at this temperature for given time. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to afford the desired products.

2.3 Procedure for the re-use of the catalysis system in amination of 4-iodoanisole with aqueous ammonia

A 10 mL of vessel was charged with CuO (8 mg, 0.1 mmol), DTPA (78 mg, 0.2 mmol), 4-Iodoanisole (1 mmol), commercial 25-28% aqueous ammonia (1 mL), KOH (2.0 mmol), H_2O (1.0 mL) and a magnetic stirring bar. The vessel was sealed with a septum and placed into an oil bath which was preheated to 100 ℃. The reaction mixture was held at this temperature for 6 hours. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate in the vessel to remove 4-methoxyaniline and then bubbled with compressed air for 20 min to remove residual ammonia and EtOAc thoroughly. Then, 4-iodoanisole (1.0 mmol), aqueous ammonia (1 mL) and KOH (2.0 mmol) were added into the same vessel. The procedure was repeated for four times.

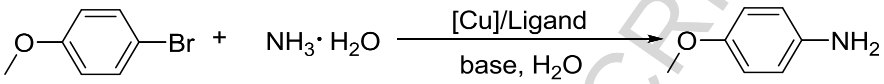
3. Results and discussion

Ethylenediaminetetraacetic acid (EDTA) is a water-soluble polyamino carboxylic acid. EDTA and its salts have been widely used as chelating ligands to form water-soluble complexes with various metal ions including Cu (II). We first explored the possibility of CuO/EDTA as a catalyst system for the coupling reaction of 4-bromoanisole with aqueous ammonia in water. As shown in Table 1 (entry 1), this model reaction generated the target product in 100% conversion and 80%

normalized yield based on the GC results. Hence, other salts of EDTA have been chosen as ligands for the same model reaction. It showed that EDTA-2Na and EDTA-2K gave the similar conversions and yields as EDTA, which was higher than EDTA-3K and EDTA-4Na (entries 2-5, Table 1). It is noted that the yields of the target product for these model reactions were noticeably lower than the corresponding conversions, which is mainly due to the side reaction of the hydrolysis of 4-bromoanisole in alkaline aqueous solution (verified by GC-MS analysis). In contrast, DTPA, another polyamino carboxylic acid, showed higher conversion and final yield compared to EDTA and its salts (entry 6, Table 1). In addition, the control reactions without ligand (entry 7, Table 1) or copper catalyst (entry 8 Table 1) only yielded trace amount of product after 12 h reaction at 100 ℃, which suggested that both the copper and ligands were critical for an efficient coupling reaction. There seemed no significant difference between the yields obtained with copper (II) and copper (I) under the same reaction conditions (entries 9, 10, Table 1). However, copper powder appeared less effective compared to copper (II) and (I) (entry 11, Table 1). Among all the copper compounds evaluated, CuO provides the best catalytic effect when coupled with DEPA (entry 6, Table 1).

To further optimize the reaction conditions, bases, reaction time and temperature, phase-transfer catalysts, as well as different ratios of substrates, catalysts and ligands were screened using the same model reaction. The results in entries 6, and 12-14 (Table 1) indicated that KOH was the best base among the several bases screened. It was also found that 10 mol% of CuO and 20 mol% of DTPA formed the optimal catalyst system. Either decrease or increase in the ligand loading (without changing the amount of CuO used) led to the lower yields (entries 15-18, Table 1). In particular, when the ligand ratio was 40 mol%, the GC yield was drastically decreased to 5%. However, if the loading of the catalyst and ligand were increased simultaneously to the same ratio, the yield of the product did not show significant change (entries 19, 20, Table 1). The similar trend was observed for the reactions catalyzed by the CuO/EDTA, whereas EDTA-2Na showed less sensitivity to the increasing of the ligand load (entries 21, 22, Table 1). The experiments showed that the pH value of reaction system could be changed by the quantity of added ligand, while the outcome of the reaction was pH dependent. A more screening of experimental conditions showed that the yield of the target product did not change significantly when *n*-Bu_4NBr or PEG-400 was used as phase transfer catalysts (entries 23, 24, Table 1). When the volume of $NH_3 \cdot H_2O$ was decreased from 1 mL to 0.75 mL, the yield decreased slightly (entry 25, Table 1). Further investigation of reaction time and temperature revealed that the reactions performed at 90 ℃ or for shorter time provided slightly lower conversions and yields (entries 26, 27, Table 1).

Table1. Optimization of the reaction conditions for the amination of 4-bromoanisole with aqueous ammonia.[a]



Entry	Copper[mol%]	Ligand[mol%]	Base[mol%]	Conv./Yield(%)[b]
1	CuO [10]	EDTA [20]	KOH [200]	100/80
2	CuO [10]	EDTA-2Na [20]	KOH [200]	98/81
3	CuO [10]	EDTA-2K [20]	KOH [200]	94/81
4	CuO [10]	EDTA-3K [20]	KOH [200]	86/71
5	CuO [10]	EDTA-4Na [20]	KOH [200]	40/33
6	CuO [10]	DTPA [20]	KOH [200]	100/87
7	CuO [10]	none	KOH [200]	trace
8	none	DTPA [20]	KOH [200]	none
9	$Cu(NO_3)_2$ [10]	DTPA [20]	KOH [200]	100/82
10	Cu_2O [10]	DTPA [20]	KOH [200]	100/78
11	Cu [10]	DTPA [20]	KOH [200]	95/67
12	CuO [10]	DTPA [20]	K_2CO_3 [200]	55/44
13	CuO [10]	DTPA [20]	K_3PO_4 [200]	43/38
14	CuO [10]	DTPA [20]	Cs_2CO_3 [200]	89/76
15	CuO [10]	DTPA [10]	KOH [200]	30/27
16	CuO [10]	DTPA [15]	KOH [200]	99/75
17	CuO [10]	DTPA [30]	KOH [200]	79/61
18	CuO [10]	DTPA [40]	KOH [200]	10/5
19	CuO [15]	DTPA [30]	KOH [200]	100/87
20	CuO [20]	DTPA [40]	KOH [200]	89/73
21	CuO [10]	EDTA [40]	KOH [200]	62/47
22	CuO [10]	EDTA-2Na [40]	KOH [200]	100/77
23	CuO [10]	DTPA [20]	KOH [200]	100/86[c]
24	CuO [10]	DTPA [20]	KOH [200]	10087[d]
25	CuO [10]	DTPA [20]	KOH [200]	99/82[e]
26	CuO [10]	DTPA [20]	KOH [200]	98/82[f]
27	CuO [10]	DTPA [20]	KOH [200]	89/76[g]

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), 25–28% aqueous $NH_3{\cdot}H_2O$ (1 mL), Copper, ligand, base, H_2O (1 mL), 100 °C, 12 h.

[b] Calculated by GC-MS according to the area of peaks.

[c] Add PEG-400 (0.2g).

[d] Add TBAB (20 mol%).

[e] 25–28% aqueous $NH_3{\cdot}H_2O$ (0.75 mL).

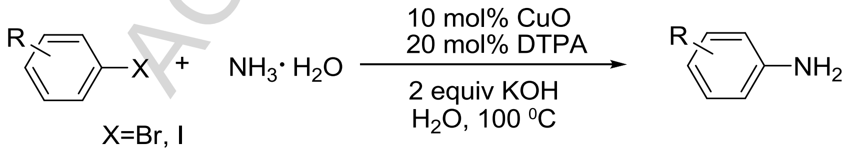
[f] 90 °C.

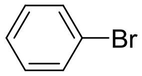
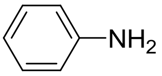
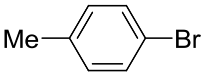
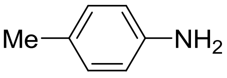
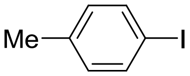
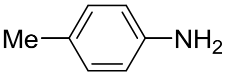
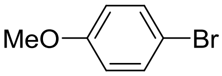
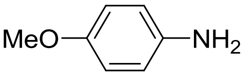
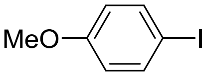
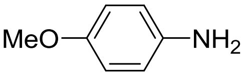
[g] 10 h.

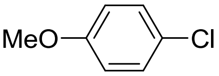
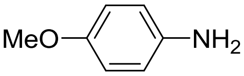
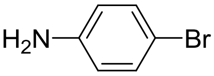
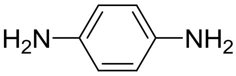
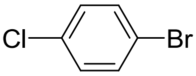
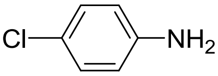
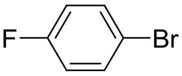
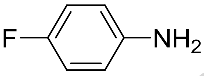
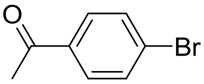
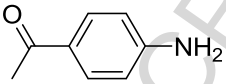
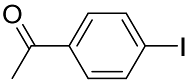
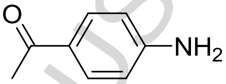
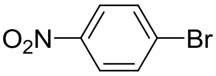
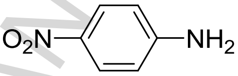
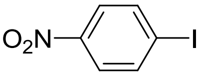
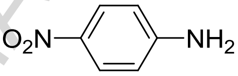
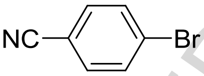
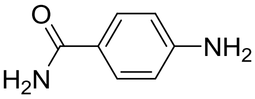
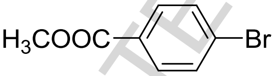
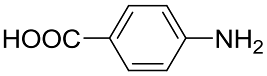
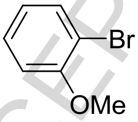
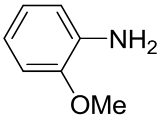
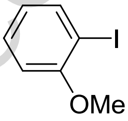
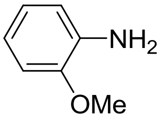
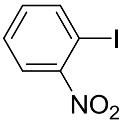
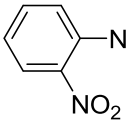
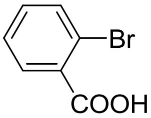
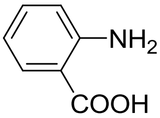
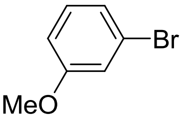
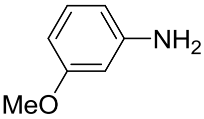
After optimizing all reaction parameters, the direct amination of various aryl halides, including alkyl, alkoxy, halogen, ketone, nitro, carboxyl, ester, cyano and amino groups as substituent, with aqueous ammonia in water was explored to further investigate the efficiency of the above-mentioned catalyst system. The results were summarized in Table 2. Most of the activated and deactivated aryl iodides provided the desired products in high yields, except for 1-iodo-4-nitrobenzene, which generated significant amount of undesired byproduct, nitrobenzene, due to the high reactivity of iodo group. (entry 13, Table 2) Moreover, the *para*- or *meta*-substituted aryl bromides bearing electron-donating or electron-withdrawing groups provided high yields of the corresponding primary amines. Furthermore, reaction of aryl bromides bearing electron-donating *ortho*-substituent exhibited lower reactivity with aqueous ammonia and afforded the corresponding product only in medium yield even with the prolonged reaction time to 36 h (entry 16, Table 2). However, reactions of aryl bromides bearing electron-withdrawing *ortho*-substituent, such as carboxyl and nitro group, show much higher yields (entries 18, 19, Table 2). The catalyst system still displayed high activity to the amination of hetero aryl bromides with aqueous ammonia (entries 25, 26, Table 2).

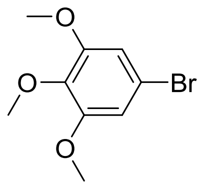
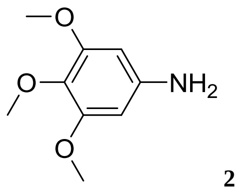
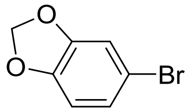
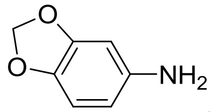
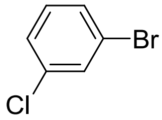
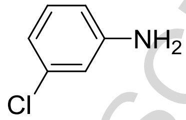
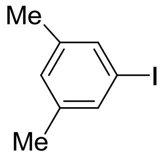
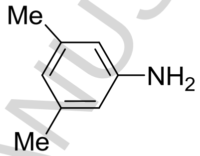
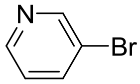
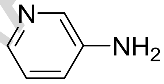
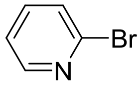
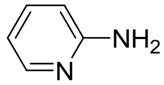
It is noteworthy that the aryl bromides containing easily hydrolyzed ester and cyano groups as substituent provided good yields of the corresponding hydrolytic products (entries 14, 15, Table 2). In addition, attempts to perform the amination of 4-chloroanisole with aqueous ammonia under the experimental conditions failed; only trace amount of the corresponding coupling product was detected (entry 6, Table 2). Moreover, we investigated the amination of 4-bromophenol and 4-bromobenzaldehyde with aqueous ammonia to examine the tolerance of the functional groups towards alcohols and aldehydes. Unfortunately, the reactions did not provide practical yields of desired compounds, because many side reactions, including debromination, hydrolysis, C-O coupling reaction (for alcohols) and cannizzaro-type reaction (for aldehydes), readily took place in alkaline aqueous solutions.

Table 2. CuO/ DTPA -catalyzed amination of aryl halides. [a]



Entry	Aryl halide	Product	Yield[%][b]
1	 **1a**	 **2a**	79
2	 **1b**	 **2b**	81
3	 **1c**	 **2b**	80[c]
4	 **1d**	 **2c**	80
5	 **1e**	 **2c**	80[c]

6	 **1f**	 **2c**	trace
7	 **1g**	 **2d**	63
8	 **1h**	 **2e**	61
9	 **1i**	 **2f**	72
10	 **1j**	 **2g**	73
11	 **1k**	 **2g**	67 [c]
12	 **1l**	 **2h**	51
13	 **1m**	 **2h**	46 [c]
14	 **1n**	 **2i**	59
15	 **1o**	 **2j**	80
16	 **1p**	 **2k**	25 34[d] 42[e]
17	 **1q**	 **2k**	39 74[d] 66[e]
18	 **1r**	 **2l**	71
19	 **1s**	 **2m**	87
20	 **1t**	 **2n**	85

21	 **1u**	 **2o**	73
22	 **1v**	 **2p**	73
23	 **1w**	 **2q**	79[c]
24	 **1x**	 **2r**	74[c]
25	 **1y**	 **2s**	81
26	 **1z**	 **2t**	72

[a] Reaction conditions: aryl halide (1 mmol), commercial 25-28% aqueous $NH_3{\cdot}H_2O$ (1 mL.), CuO (0.1 mmol), DTPA (0.2 mmol), KOH (2 mmol), H_2O (1 mL), 100 ℃, 12 h.

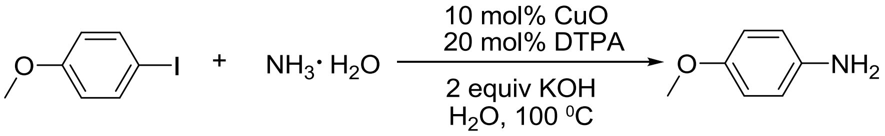
[b] Isolated yield.

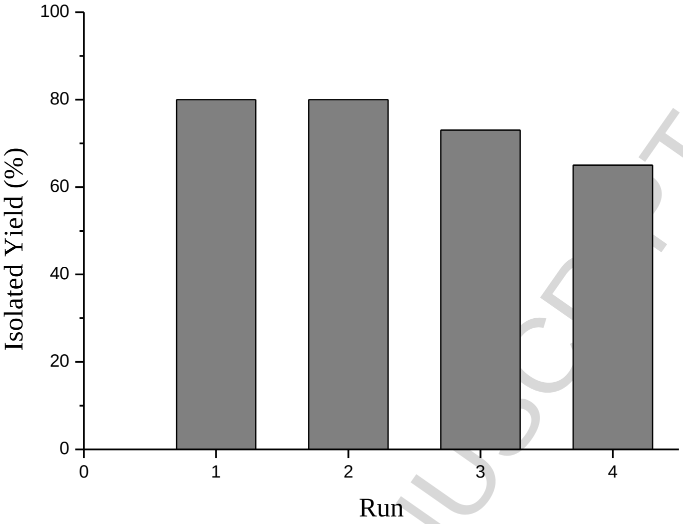
[c] 6 h.

[d] 24 h.

[e] 36 h.

Because the CuO/ligands catalyst system is water soluble and can be easily separated from aniline products via simple organic/aqueous extraction, we investigated the recycling of this homogeneous catalyst system and solvent for the amination of 4-iodoanisole with aqueous ammonia. At the end of the coupling reaction, the reaction solution was extracted with ethyl acetate to remove the product. Then, in the same vessel, the reactants, 4-iodoanisole and aqueous ammonia as well as the base, were added for continuous coupling reaction. We were able to run four consecutive aminations with only slightly decrease of isolated yields (Fig. 1), suggesting the possible re-use of the current catalyst system.





[a] Reaction conditions for run 1: 4-iodoanisole (1 mmol), commercial 28% aqueous $NH_3{\cdot}H_2O$ (1 mL.), CuO (0.1 mmol), DTPA (0.2 mmol), KOH (2 mmol), H_2O (1 mL), 100 ℃, 6 h.

[b] Reaction conditions for run 2-5: Add 4-iodoanisole (1.0 mmol), aqueous $NH_3{\cdot}H_2O$ (1 mL), KOH (2.0 mmol).

Fig. 1. Reuse of the catalyst system and solvent

4. Conclusion

In summary, a simple, recyclable and environmentally friendly homogeneous CuO/DTPA catalyst system has been established for the direct amination of aryl halides with aqueous ammonia in water without any surfactants being used. High yields were obtained with a wide range of aryl iodides and aryl bromides as substrates without the protection of an inert atmosphere. Furthermore, the reaction system, including catalyst, ligand and solvent, can be simply reused for four times with only slight loss of its activity.

Acknowledgments

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Highlights

- Aqueous ammonia was used for the synthesis of primary aryl amines in water.
- Homogeneous CuO/ DTPA catalyst system showed superior catalytic activity.
- Amination of aryl halides in water could be carried out without any surfactant.
- The reaction system could be reused for 4 times with slight loss of its activity.