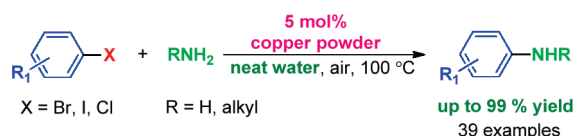# A Facile and Practical Copper Powder-Catalyzed, Organic Solvent- and Ligand-Free Ullmann Amination of Aryl Halides

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A facile and practical method that the copper powder-catalyzed Ullmann amination of aryl halides with aqueous methylamine under organic solvent- and ligand-free condition at 100 °C and in air gave *N*-arylamines as sole products in good to excellent yields. The presence of a small amount of air is essential. Other aliphatic primary amines show good to very high reactivity. Secondary amines and aniline are not reactive. Sensitive substituents (i.e., CHO, MeCO, CN and Cl) are tolerable in the reaction.

Ullmann-type aryl amination reaction has emerged as a powerful and frequently used tool for C−N bond formation in organic synthesis and pharmaceutical industry.[1] However, the classic Ullmann amination requires stoichiometric amounts of copper, harsh reaction conditions, strong bases, and polar organic solvents. Great efforts have been made to minimize these problems and marked progress achieved.[1] The most effective alternative should be Buchwald−Hartwig amination,[2,3] which proceeds under a milder condition in the presence of palladium-based catalysts with phosphine ligands or *N*-heterocyclic carbenes. A blemish in this amination reaction is that these ligands are often air-sensitive, toxic, and expensive.[2,3] Consequently, the copper-based protocols of Ullmann type amination attracted the attention again in view of its low cost and low toxicity.[1]

Over the past decade, D. W. Ma's group and others have developed a set of efficient improvements on the aryl amination of this type, making this old reaction more practical in organic synthesis.[4,5] The most efficient ones include using amino acids as cocatalyst and coupling partner.[4a] Buchwald's group reported a CuI-catalyzed Ullmann reaction wherein aryl halides were aminated by various amines in glycol with high efficiency even in air.[4b] Wolf and co-workers reported a regioselective amination of 2-bromobenzoic acid using Cu/CuO as catalyst in 2-ethoxyethanol at 130 °C.[4c] Collectively, albeit these modifications of the Ullmann amination overcome some shortcomings of the classic reaction, most of them still need ligands and, in particular, they cannot get rid of expensive, harmful, and uneasily recoverable organic solvents such as DMSO, DMF, and NMP.[4,6] Recently, Wolf's group reported a ligand-free method using 5 mol % Cu_2O as catalyst in aqueous ammonia system using NMP (NMP/water = 1:1 v/v) as cosolvent.[7a] Yadav et al. reported an Ullmann amination with stoichiometric amounts of active copper in aqueous media or under solvent-free conditions with microwave irradiation.[7b]

Performing organic transformations on/in water has gained increasing attention recently because water is a cheap, green,

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TABLE 1. Ullmann Amination of Bromobenzene with 30% Aqueous Methylamine Solution under Various Conditions[a]
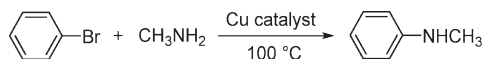
entry	catalyst (mol %)[b]	CH_3NH_2 (eq)	atm.	additive (eq)	yield (%)[c]
1	Cu (10)	5	N_2	no	trace
2	Cu (10)	5	air	no	96[d]
3	Cu (10)	5	air	no	>99
4	**Cu (5)**	**5**	**air**	**no**	**>99**
5	Cu (2)	5	air	no	46
6	Cu (5)	5	O_2	no	trace
7	Cu_2O (10)	5	N_2	no	99
8	Cu_2O (10)	5	air	no	trace
9	Cu_2O (10)	5	O_2	no	trace
10	CuO (10)	5	N_2	no	55
11	Cu (5)	2.5	air	no	76
12	Cu (5)	2.5	air	Et_3N (1)	96
13	Cu (5)	1.2	air	Et_3N (1)	92
14	Cu (5)	2.5	air	Na_2CO_3 (0.5)	65
15	Cu (5)	2.5	air	K_2CO_3 (0.5)	47
16	Cu (5)	2.5	air	K_3PO_4 (0.5)	55

[a]Conditions: aryl halide (10 mmol), 30% aqueous methylamine (5 equiv), Cu (5 mol %) in a 30 mL sealed vial with stirring, 100 °C, 12 h. [b]The loading amount based on the metal in parentheses. [c]Yield after chromatographic separation (based on aryl halide). [d]At 80 °C, Cu(10 mol %).

nonflammable, and renewable solvent on the earth.[8] However, only one recent report concerning organic solvent- and ligand-free on water Ullmann amination has been found,[9] in which aryl halides were aminated with *N*-heterocycles and alkyl amines using $CuCl/n\text{-}Bu_4N^+OH^-$ as catalytic system. Our group has been involved in the past several years in the development of greener catalysts and cleaner procedures for organic reactions used in lab and industry. Very recently, we found copper powder to be an efficient catalyst in the amino-bromination reaction of carbon−carbon double bond.[10a] We also developed an on water Suzuki coupling reaction catalyzed by PdEDTA held in ionic liquid brush.[10b] Combining the considerations mentioned above and findings in our works, we developed a clean and simple Ullmann reaction for the synthesis of *N*-arylated amines using element copper as catalyst under organic solvent- and ligand-free condition in neat water. A 5 mol % of copper powder is sufficient for a smooth reaction, providing *N*-arylamines in good to excellent yield. Since the amines of low molecular weight are commercially available as aqueous solutions, this on water protocol could find its industrial application in the future. Herein, we would like to report our on water Ullmann reaction.

The coupling reaction of bromobenzene and 30% aqueous methylamine solution was employed as the model reaction to optimize the reaction conditions (Table 1). All the reactions were carried out by simply stirring the substrate and aqueous methylamine solution with a catalytic amount of copper powder under 100 °C in a screwed sealed tube.

Initially, we performed the reaction under the protection of N_2 atmosphere in the sealed tube, but only a trace amount of the desired product was detected (Table 1, entry 1). In contrast, the reaction provided the aminated product in an

unoptimized 96% yield (entry 2) when it was carried out at 80 °C in the sealed tube where a small amount of air existed in the vacant space above the reaction mixture. It was further improved to near quantitative yield by only raising the reaction temperature to 100 °C (entry 3). The complete consumption of the substrate and the quantitative yield of the desired product were also achieved by using 5 mol % copper powder under the identical condition.

More interestingly, when the reaction was carried out in the pure O_2 atmosphere, poor yield was afforded (entries 6 and 9). In addition, when the reaction was carried out in a bigger sealed tube (i.e., 50 mL) wherein more air existed, the yield was depressed dramatically. These results reflected that molecular oxygen plays a crucial role in such a copper-catalyzed on water Ullmann reaction and thus suggest the catalytically active species to be Cu(I), which was formed *in situ* by oxidizing Cu(0) with O_2 during the reaction. The formation of Cu(I) species was supported by the observation of characteristic colorless solution of $Cu(CH_3NH_2)_2^+$. It is worthy to point out that the aryl halide is indispensible for the oxidation of Cu(0) to Cu(I); the copper powder turned finally to an unknown black precipitate in absence of aryl halide under the same condition. A succession of color changes were observed during the amination reaction (see Supporting Information), meaning that the oxidation of Cu(0) to Cu(I) should be a complicated process.

Further experimentation revealed that Cu_2O in 5 mol % loading amount also afford a very good yield in N_2 atmosphere (entry 7), while CuO is less effective (entry 10). In air or in pure oxygen, however, Cu_2O was ineffective (entries 8 and 9), owing to the oxidation of Cu(I) to Cu(II). These results also suggest that Cu(I) was actually the active species in this copper metal-catalyzed reaction. The presence of a suitable amount of air in the sealed tube is crucial to the formation of Cu(I) from Cu(0). An excess amount of air (or oxygen) is unfavorable to the reaction since the Cu(I) species was further oxidized to less active Cu(II) species, as evidenced by the distinctive blue colored $Cu(CH_3NH_2)_4^{2+}$.

To decrease the amount of methylamine used in the reaction, we used several bases to liberate the amine from its HX salt (entries 12−16). Triethylamine was the most suitable adduct, giving a good yield (entry 13) in the case that 1.2 equiv methylamine was used. This provides an alternative protocol when an expensive amine is used as the coupling partner or when the excess amount of amine could not be used. The inorganic bases screened (Na_2CO_3, K_2CO_3, and K_3PO_4) were ineffective. A possible reason for the low activity of these bases is that they might form insoluble substances with Cu(I) species. The inorganic bases may also increase the ionic strength of the aqueous phase, thus, reducing the mixing of the organic constituents with water and the catalyst.

The scope and generality of this copper powder-catalyzed on water Ullmann amination reaction was explored by a series of aryl halides with methylamine. The results are summarized in Table 2. All the reactions were carried out under the standard conditions and manipulated without any special precaution.

As shown in Table 2, the reaction proceeds smoothly and completely for various aryl halides and most substrates give the expected product in the yields over 90%. Both aryl bromides and iodides are reactive under the reaction conditions. A

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TABLE 2.   The Scope of Copper Powder Catalyzed Reaction for Various Aryl Halides and 30% Aqueous Methylamine Solution[a]

$$R_1 \overbrace{}-X \ + \ CH_3NH_2 \xrightarrow[\text{water, 100 °C, air}]{\text{5 mol% Cu powder}} R_1 \overbrace{}-NHCH_3$$
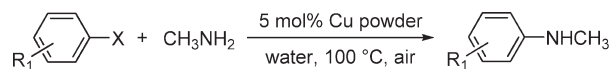
entry	(hetero)aryl halide	product	time	yield [b]	entry	(hetero)aryl halide	product	time	yield [b]
1	⟨⟩—Br	⟨⟩—NHCH₃	12 h	>99 %	16	Cl, ⟨⟩—Br	Cl, ⟨⟩—NHCH₃	12 h	98 %
2	MeO—⟨⟩—Br	MeO—⟨⟩—NHCH₃	12 h	95 %	17	Br—⟨⟩—Br	H₃CHN—⟨⟩—NHCH₃	16 h	94 %
3	OMe, ⟨⟩—Br	OMe, ⟨⟩—NHCH₃	16 h	80 %	18	naphthalene-Br	naphthalene-NHCH₃	12 h	98 %
4	Me—⟨⟩—Br	Me—⟨⟩—NHCH₃	12 h	99 %	19	naphthalene-Br	naphthalene-NHCH₃	24 h	45 %
5	Me, ⟨⟩—Br	Me, ⟨⟩—NHCH₃	16 h	81 %	20	pyridine-Br	pyridine-NHCH₃	12 h	94 %
6	O₂N—⟨⟩—Br	O₂N—⟨⟩—NHCH₃	12 h	93 %	21	N⟨⟩—Br	N⟨⟩—NHCH₃	12 h	91 %
7	NO₂, ⟨⟩—Br	NO₂, ⟨⟩—NHCH₃	12 h	>99 %	22	⟨⟩—I	⟨⟩—NHCH₃	12 h	>99 %
8	O₂N, ⟨⟩—Br	O₂N, ⟨⟩—NHCH₃	12 h	93 %	23	OMe, ⟨⟩—I	OMe, ⟨⟩—NHCH₃	16 h	83 %
9	NC—⟨⟩—Br	NC—⟨⟩—NHCH₃	12 h	94 %	24	O₂N—⟨⟩—I	O₂N—⟨⟩—NHCH₃	12 h	96 %
10	OHC—⟨⟩—Br	OHC—⟨⟩—NHCH₃	13 h	89 %	25	⟨⟩—Cl	⟨⟩—NHCH₃	36 h	trace
11	MeO, MeO, ⟨⟩—Br, CHO	MeO, MeO, ⟨⟩—NHCH₃, CHO	3 h	82 %	26	MeO—⟨⟩—Cl	MeO—⟨⟩—NHCH₃	36 h	trace
12	Ac—⟨⟩—Br	Ac—⟨⟩—NHCH₃	12 h	86 %	27	CO₂H, ⟨⟩—Cl	CO₂H, ⟨⟩—NHCH₃	12 h	83 %
13	HO₂C—⟨⟩—Br	HO₂C—⟨⟩—NHCH₃	12 h	93 %	28	HO₂C—⟨⟩—Cl	HO₂C—⟨⟩—NHCH₃	48 h	56 %
14	Cl—⟨⟩—Br	Cl—⟨⟩—NHCH₃	12 h	88 %	29	O₂N—⟨⟩—Cl	O₂N—⟨⟩—NHCH₃	24 h	92 %
15	Cl, ⟨⟩—Br	Cl, ⟨⟩—NHCH₃	24 h	68 %	30	NO₂, ⟨⟩—Cl	NO₂, ⟨⟩—NHCH₃	12 h	>99 %

[a]Conditions: aryl halide (10 mmol), 30% aqueous methylamine (5 equiv), Cu (5 mol %) in a 30 mL sealed tube, 100 °C. [b]Yield after column chromatographic separation (based on aryl halide).
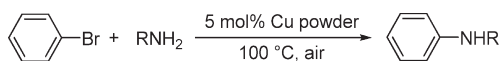
range of functional groups are survivable in the reaction. It is particularly noteworthy that even in the presence of sensitive substituent (i.e., CHO, MeCO, CN, and even Cl), the reaction proceeds successfully to provide the desired products in high yields without protection to the functional group. Electron effect of the substituents on aryl bromides has no substantial influence on the reaction; the electron-rich substrates showed slightly weaker reactivity than the electron-deficient ones. Sterically hindered substrates declined the effectiveness of the reaction; *ortho*-substituted aryl halides gave relatively lower yields (entries 3, 5, 11, 15, and 19) than their *para*-isomer, except for 2-nitro (entries 7 and 30) and 2-CO₂H (entry 27). A possible explanation is attributable to their electron-withdrawing effects and/or coordination to Cu(I) species.

2-Bromonaphthalene gave the aminated product as a sole product in near quantitative yield (entry 18). However, its 1-isomer gave only 45% yield even after the reaction time was prolonged to 24 h (entry 19) probably due to the hindrance of the vicinal α-hydrogen atom and/or that the 1-position of naphthalenes is more nucleophilic than the 2-position.

The reaction system also worked well with heteroaryl halides such as 3- or 4-bromopyridine (Table 2, entries 20 and 21).

Aryl iodides show slightly higher reactivity than their bromo analogues (Table 2, entries 22−24). Inactivated aryl chlorides such as chlorobenzene and its substituted derivatives without electron-withdrawing group showed quite low reactivity to this on water reaction (entries 25 and 26), as they did in classic or modified Ullmann reaction. It is noteworthy that the remarkable discrepancy in reactivity between aryl chlorides and -bromides should permit to prepare chloroarylamines from bromochloro-arenes selectively by this protocol

TABLE 3. Ullmann Reaction of Bromobenzene with Various Amines As the Coupling Partner[a]

entry	amine	product	time	yield [b]
1	NH₃	—NH₂	24 h	85 %
2	NH₂CH₃	—NHCH₃	12 h	>99 %
3	NH₂CH₂CH₃	—NHCH₂CH₃	12 h	>99 %
4	H₂N⁀⁀⁀	—NH⁀⁀⁀	24 h / 24 h	70 % [c] / 83 % [c,d]
5	H₂N—◯	—N(H)—◯	24 h	52 % [c]
6	NH(CH₃)₂	—N(CH₃)₂	24 h	trace / trace [e]
7	NH(CH₂CH₃)₂	—N(CH₂CH₃)₂	24 h	trace / trace [e]
8	HN⌬O	—N⌬O	24 h	45 % [c]
9	HN⌬	—N⌬	24 h	37 % [c]
10	H₂N—◯	—N(H)—◯	36 h	trace [c]

[a]Conditions: phenyl bromide (10 mmol), amine (50 mmol, 30% aqueous solution otherwise noted), Cu (5 mol %) in a 30 mL sealed tube, 100 °C. [b]Yield after column chromatographic separation (based on aryl halide). [c]Yield of the reaction in absence of water. [d]Phenyl iodide as the substrate for comparison. [e]Yield in the presence of 3.0 mL NMP as cosolvent.

(entries 14−16). The aryl chlorides with a strong electron-withdrawing group (i.e., NO₂) at *ortho*- or/and *para*-position underwent the reaction easily to deliver the corresponding aminated products in satisfactory yields (entries 29 and 30).

To further evaluate the scope of this organic solvent-free Ullmann amination, a variety of amines were exploited as the coupling partners. Table 3 lists the results of the coupling of bromobenzene with these amines. From the results shown in Table 3, it can be seen that the highly water-soluble amines of low molecular weight afford excellent yields of the desired *N*-arylamines. Aqueous ammonia and aliphatic primary amines gave higher yields. Ethylamine undergoes the reaction smoothly and completely, furnishing the monoarylated product in a quantitative yield too (entry 3); no trace amount of diarylamine was detected. Butylamine, used in neat form as received, gives the monoarylated product in a reasonable yield while neat cyclohexylamine is less reactive under identical condition owing to its bulky alkyl group (entries 4 and 5).

Secondary amines, such as dimethylamine and diethylamine, are actually inactive to the reaction (entries 6 and 7), as the two alkyl groups may block the nucleophilic attack of nitrogen atom on aryl ring. No improvement was observed

by the addition of NMP as cosolvent. Cyclic secondary amines, morpholine and piperidine, did not give satisfactory yields, but are slightly more reactive than the acyclic ones (entries 8 and 9 vs 6 and 7) probably because of their less hindrance.

Aromatic amines seem less reactive as the coupling partner in this system. In the case of aniline, the reactivity in the coupling reaction dropped dramatically (entry 10); most bromobenzene and aniline remained unchanged albeit the reaction time was prolonged. The low reactivity of aniline might arise from its poor nucleophilicy and high hindrance.

In conclusion, we have demonstrated an element copper-catalyzed Ullmann amination for aryl halides with commercially available aqueous solution of amines with low molecular weight. This method avoids the use of any organic solvent and complicated ligand. The high efficiency and easy manipulation make it superior in both academic and industrial application. We believe that this catalytic system could provide a green and clean approach to synthesis of *N*-monomethyl and *N*-monoethyl anilines.

Experimental Section

General Procedure for the Copper-Catalyzed on Water Ullmann Reaction. A mixture of an aryl halide (10.0 mmol), 30% aqueous methylamine solution (5.4 mL, 50 mmol), copper powder (0.032 g, 0.5 mmol), and a stirring bar was sealed in a 30 mL screwed tube and stirred electromagnetically in an oil bath at 100 °C. During the reaction, most of the copper powder was dissolved. After the reaction was completed or proceeded to the times in Tables 1−3, the reaction mixture was cooled to room temperature and ethyl acetate (20 mL) was added to extract the aryl amine. The organic layer was separated and the aqueous layer was extracted by ethyl acetate (3 × 10 mL). The combined extracts were dried by anhydrous sodium sulfate and the solvent was removed under reduced pressure to give crude product that was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate) to give the pure product.

N-Methylaniline: 1.067 g (99%), colorless oil. ¹H NMR (300 MHz, *d*₆-DMSO) δ (ppm): 2.67 (s, 3H), 5.55 (s, 1H), 6.52−6.54 (d, *J* = 5.2 Hz, 3H), 7.07−7.09 (d, *J* = 5.7 Hz, 2H); ¹³C NMR (75 MHz, *d*₆-DMSO) δ (ppm): 30.1, 112.1, 115.9, 129.2, 150.4.

4-(Methylamino)benzaldehyde: 1.207 g (89%), yellow crystals. ¹H NMR (75 MHz, *d*₆-DMSO) δ (ppm): 2.79 (s, 3H), 6.64−6.66 (d, *J* = 5.7 Hz, 2H), 6.92 (s, 1H), 7.64−7.66 (d, *J* = 6.0 Hz, 2H), 9.63 (s, 1H); ¹³C NMR (75 MHz, *d*₆-DMSO) δ (ppm): 29.0, 110.0, 124.7, 131.9, 154.9, 189.5.

Supporting Information Available: The characterization data and the copies of ¹H NMR and ¹³C NMR spectra for the aminated products. This material is available free of charge via the Internet at http://pubs.acs.org.