DOI: 10.1002/ejoc.201001150

Efficient Copper-Catalyzed Direct Amination of Aryl Halides Using Aqueous Ammonia in Water

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Keywords: Amination / Copper / Amines / Cross-coupling / Water chemistry

The $N^2,N^{2\prime}$-diisopropyloxalohydrazide/CuO system efficiently catalyzed the direct amination of aryl bromides and iodides with aqueous ammonia in water at 60 °C in 24 h or at 120 °C in only 20–30 min. Both activated and unactivated aryl and heteroaryl bromides and iodides were readily aminated in good to excellent yields.

Introduction

Primary aromatic amines are important intermediates for the synthesis of natural products, pharmaceuticals, agrochemicals, and polymers. Hence, their preparation has attracted more and more attention.[1] Traditional methods for the preparation of primary amines by direct coupling of aryl halides with ammonia often suffer from high pressure, high temperature, and long reaction times, which make those methodologies less practical.[2] Recently, transition-metal-catalyzed (such as palladium and copper) coupling reactions of aryl halides with ammonia or ammonia surrogates have made big improvements for the preparation of parent anilines.[3,4] Several palladium-catalyzed methods have been reported with broad substrate scope and excellent functional group tolerance.[3] Numerous copper-catalyzed methods have also been well established under mild reaction conditions in dry or aqueous organic media,[4] particularly by using a series of novel ligands (such as, β-diketones,[4h] L-proline and its derivatives,[4d,4k] pyridine-β-ketones[4m]). During our submission process, two protocols for the copper-catalyzed synthesis of aminopyridine derivatives were reported in ethylene glycol.[5] Those methodologies suffered from drawbacks such as the use of high-boiling-point solvents, including, DMF, DMSO, and NMP; the need for 3–4 bar of ammonia pressure; competition due to C–O arylation of ethylene glycol or ethanol solvents; and the use of strong bases.[4,5] Interestingly, direct amination of aryl halides using a sulfonato-Cu(salen) complex as the catalyst with ammonia in water was pioneered by the group of Zhou.[6] A wide range of aryl bromides and iodides were aminated with aqueous ammonia to afford good to excellent yields in 12 h. However, this protocol also has some drawbacks: harsh conditions (120 °C and 12 h and the use of the strong base KOH). Hence, a fast or a mild procedure for the copper-catalyzed direct amination of aryl halides in water has hitherto remained desirable.

As part of our studies on the copper-catalyzed amination of aryl halides in water,[7] we herein report that the direct amination of both activated and unactivated aryl and heteroaryl bromides and iodides can be achieved under very mild conditions (60 °C, K_3PO_4 as base, without inert atmosphere) and by using $N^2,N^{2\prime}$-diisopropyloxalohydrazide/CuO as a catalytic system with aqueous ammonia as a nitrogen source in water. In addition, our procedure might provide an alternative route to the high throughput synthesis of primary aromatic amines just by increasing the reaction temperature to 120 °C (with a reaction time of only 20–30 min).

Results and Discussion

For our initial experiments, we chose to study the amination of 4-bromoanisole with aqueous ammonia in water. The reaction positively gave 4-methoxyaniline in moderate yield (63% GC yield; Table 1, Entry 9) at 120 °C for 30 min when using CuO (5 mol-%)/$N^2,N^{2\prime}$-diisopropyloxalohydrazide (25 mol-%) as the catalytic system and KOH as the base. This result encouraged us to further explore the reaction parameters including common commercially available copper sources, bases, the reaction times, temperature, and the catalyst loading. It should be noted that all the Cu^{II} and Cu^{I} salts smoothly catalyzed the model reaction with moderate yields, whereas Cu^0 gave a very low yield of 5% (Table 1, Entries 2–9); moreover, no reaction took place under copper-free conditions, as expected (Table 1, Entry 1).

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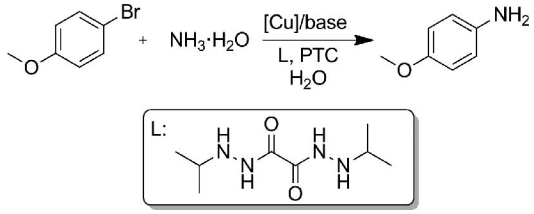
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001150.

In addition, decreasing the loading of the catalyst from 5 to 3 mol-% led to a slight decrease in conversion, whereas increasing the loading of catalyst from 5 to 10 mol-% only led to a small increase in conversion (Table 1, Entries 10, 18, and 19). The higher ratio (4:1) of L/CuO required under the optimal reaction conditions is still a challenge in our catalytic system and its potential mechanism is not very clear yet.

Table 1. Optimization of the amination of 4-bromoanisole with aqueous ammonia in water.[a]

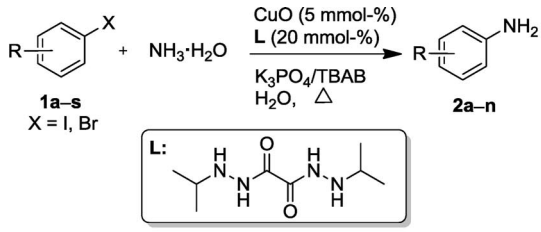


Entry	[Cu] (mol-%)	Base	PTC	Time [min]	Conv. / % Yield[b]
1	–	KOH	TBAB	30	0[c]
2	$CuCl_2$ (5)	KOH	TBAB	30	72/61
3	$CuAc_2$ (5)	KOH	TBAB	30	76/57
4	$Cu(NO_3)_2$ (5)	KOH	TBAB	30	72/59
5	$CuSO_4$ (5)	KOH	TBAB	30	78/60
6	Cu_2O (5)	KOH	TBAB	30	69/43
7	CuI (5)	KOH	TBAB	30	76/54
8	Cu (5)	KOH	TBAB	30	7/5
9	CuO (5)	KOH	TBAB	30	71/63
10	CuO (5)	K_3PO_4	TBAB	30	96/89
11	CuO (5)	NaF	TBAB	30	6/5
13	CuO (5)	Cs_2CO_3	TBAB	30	61/51
14	CuO (5)	K_2CO_3	TBAB	30	50/44
15	CuO (5)	K_3PO_4	PEG600	30	96/88
16	CuO (5)	K_3PO_4	SDS-Na	30	94/83
17	CuO (5)	–	TBAB	30	0[c]
18	CuO (3)	K_3PO_4	TBAB	30	86/75
19	CuO (10)	K_3PO_4	TBAB	30	99/89
20	CuO (5)	K_3PO_4	TBAB	20	92/76
21	CuO (5)	K_3PO_4	TBAB	30	88/79[d]
22	CuO (5)	K_3PO_4	TBAB	30	97/89[e]
23	CuO (5)	K_3PO_4	TBAB	30	83/71[f]
24	CuO (5)	K_3PO_4	TBAB	30	97/91[g]

[a] Unless otherwise noted, the reactions were carried out with 4-bromoanisole (1.0 mmol), commercial 25–28% aqueous ammonia (1.0 mL), [Cu] (5 mol-%), L (25 mol-%), base (2.0 mmol), water (1 mL), 120 °C, 30 min. [b] Calculated by GC–MS. [c] No product was detected by TLC. [d] The reaction temperature was 110 °C. [e] L = 20 mol-%. [f] L = 15 mmol-%. [g] L = 20 mol-%, TBAB = 0.5 mmol.

For the purpose of exploring the scope of the application of the catalytic system, a variety of functionalized aryl iodides and bromides animated with aqueous ammonia in water under the optimized reaction conditions [aryl halides (1.0 mmol), commercial 25–28% aqueous ammonia (1.0 mL), CuO (5 mmol-%), ligand (20 mmol-%), K_3PO_4 (2.0 mmol), TBAB (0.5 mmol), water (1.0 mL), 120 °C] was investigated. The coupling of aqueous ammonia with most electron-rich, electron-neutral, and electron-poor aryl bromides afforded the desired products with good to excellent yields (Table 2, Entries 1–3, 6–9, 14). As expected, aryl

Table 2. Copper-catalyzed amination of aryl halides in water.[a]



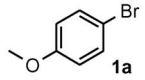
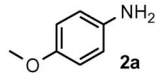
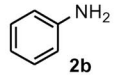
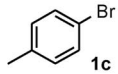
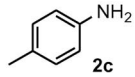
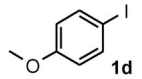
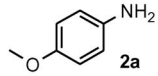
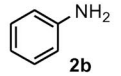
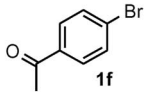
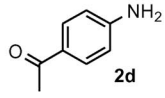
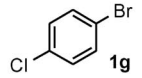
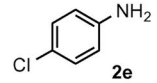
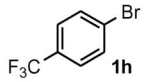
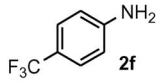
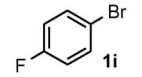
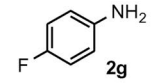
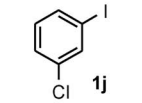
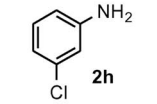
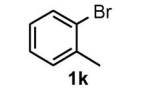
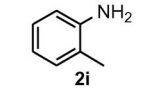
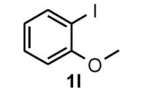
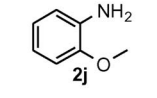
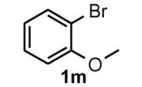
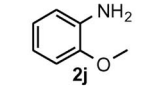
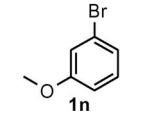
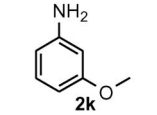
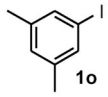
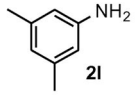
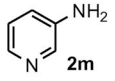
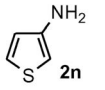
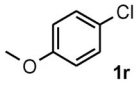
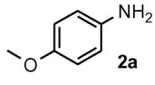
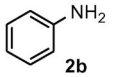
Entry	ArX	Product	% Yield[b]
1	 1a	 2a	81 75[d]
2	 1b	 2b	80 73[d]
3	 1c	 2c	87 83[d]
4	 1d	 2a	94 83[d]
5	 1e	 2b	82[c] 73[d]
6	 1f	 2d	83 86[d]
7	 1g	 2e	85 81[d]
8	 1h	 2f	82 84[d]
9	 1i	 2g	75 73[d]
10	 1j	 2h	86[c] 80[d]
11	 1k	 2i	58 51[d]
12	 1l	 2j	78 61[d]
13	 1m	 2j	76 64[d]
14	 1n	 2k	88 89[d]

Table 2. *(Continued)*

Entry	ArX	Product	% Yield[b]
15	 **1o**	 **2l**	86 72[d]
16	 **1p**	 **2m**	83 78[d]
17	 **1q**	 **2n**	80 71[d]
18	 **1r**	 **2a**	trace trace[d]
19	 **1s**	 **2b**	trace trace[d]

[a] Reaction conditions: ArX (1.0 mmol), commercial 25–28% aqueous ammonia (1.0 mL), CuO (5 mmol-%), L (20 mmol-%), K_3PO_4 (2.0 mmol), TBAB (0.5 mmol), H_2O (1.0 mL), 120 °C, 30 min. [b] Isolated yield. [c] 120 °C, 20 min. [d] 60 °C, 24 h.

iodides provided almost the same yields as those of the aryl bromides (Table 2, Entries 4, 5, 12). More interesting, heteroaryl halides also coupled with aqueous ammonia to give the corresponding anilines in satisfactory yields (Table 2, Entries 16 and 17). However, steric hindrance of *ortho* substituents resulted in a lower reactivity of the corresponding aryl halides to afford lower yields (Table 2, Entries 11–13). In addition, aryl chlorides could not be aminated under the experimental conditions (Table 2, Entries 18 and 19).

Next we focused our attention on the possibility to carry out the amination of aryl halides at much lower temperature, i.e. 60 °C, which is of much greater interest for industrial applications. Our procedure is in this case also compatible with a wide range of substituents (Table 2). Various aniline derivatives were obtained with both activated and unactivated aryl and heteroaryl bromides and iodides (Table 2, Entries 1–10, 16, 17).

Conclusions

In summary, we developed a general, efficient, and practical protocol for the direct coupling of aryl or heteroaryl halides with aqueous ammonia in water catalyzed by $N^2,N^{2\prime}$-diisopropyloxalohydrazide/CuO. The reaction was not sensitive to either electron-donating or electron-withdrawing substituents and could be performed at 60 °C for 24 h or at 120 °C for 20–30 min with good to excellent yields of the products. Moreover, the easy availability of the ligand (from commercially available acetone and oxalyldihydrazide in two steps), the commercially available cheap copper source, and the use of a green solvent and aqueous ammonia as the readily available nitrogen source might facilitate the application of our very useful protocol in either an academic or industrial setting.

Experimental Section

Synthesis of the $N^2,N^{2\prime}$-Diisopropyloxalohydrazide Ligand: A mixture of oxalohydrazide (6.0 g, 50.0 mmol), propan-2-one (6.4 g, 110.0 mmol), and glacial acetic acid (0.1 mL) in methanol (80 mL) was heated at reflux for 3 h. After allowing the mixture to cool to room temperature, $NaBH_4$ (4.3 g, 110.0 mmol) was carefully added in an ice bath. Then, the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered, and the precipitate was washed with water (3 × 20 mL), methanol (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL). The solid was collected and dried under vacuum to afford the target product as a white solid (7.7 g, 75% yield). M.p. 195.0–195.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20–3.12 (m, 2 H, C*H*), 1.13 (d, J = 6.3 Hz, 12 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 51.6, 20.7 ppm. MS (ESI): m/z = 203 [M + H]$^+$.

General Procedure for the Synthesis of the Coupling Reaction Compounds Under the Optimized Reaction Conditions: A 10-mL sealed vial was charged with CuO (0.004 g, 0.05 mmol), the ligand (0.040 g, 0.20 mmol), 4-bromoanisole (0.186 g, 1.0 mmol), commercial 25–28% aqueous ammonia (1.0 mL), K_3PO_4 (0.424 g, 2.0 mmol), TBAB (0.161 g, 0.5 mmol), H_2O (1.0 mL), and a magnetic stir bar. The reaction mixture was stirred in an oil bath preheated to 120 °C for 30 min or 60 °C for 24 h. After allowing the mixture to cool to room temperature, the reaction mixture was extracted with ethyl acetate (4 × 2 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 1:5) to afford target **2a** (120 °C, 0.1 g, 81% yield; 60 °C, 0.092 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (d, J = 8.7 Hz, 2 H, Ar*H*), 6.66 (d, J = 9.0 Hz, 2 H, Ar*H*), 3.75 (s, 3 H, OCH_3), 3.39 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 139.8, 116.2, 114.6, 55.6 ppm. MS (ESI): m/z = 124 [M + H]$^+$.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR and mass spectra of all compounds

Acknowledgments

This work was financially supported by grants from the National Natural Science Foundation of China (20872182, 20802095) and by the National High Technology Research and Development Program of China (863 Program, No. 2006AA09Z446).

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Received: August 16, 2010
Published Online: October 5, 2010

