DOI: 10.1002/ejoc.201000060

A Simple and Efficient Catalytic System for Coupling Aryl Halides with Aqueous Ammonia in Water

Zhiqing Wu,[a] Zhaoqiong Jiang,[a] Di Wu,[a,b] Haifeng Xiang,[a] and Xiangge Zhou*[a,b]

Keywords: Amination / Cross-coupling / Copper / Nitrogen heterocycles / Water chemistry

The cross-coupling reaction between aryl halides and aqueous ammonia was efficiently catalyzed by the sulfonato–Cu(salen) complex in water with high yields. A variety of substituted aryl bromides and aryl iodides were found to be applicable to the environmentally benign system. Substituted 1*H*-benzimidazole could also be easily prepared by coupling aqueous ammonia with 2-iodoacetanilide in one pot with this catalytic system.

Introduction

Ammonia is one of the most attractive sources of nitrogen for synthesis due to its low cost and wide availability.[1] The use of ammonia as a coupling partner with simple aryl halides in cross-coupling reactions allows the direct synthesis of valuable primary anilines, which are widely used in the synthesis of natural products, pharmaceuticals, agrochemicals, and material science.[2] In contrast to other well-established palladium- or copper-catalyzed C–N bond-formation reactions,[3,4] the direct amination of aryl halides with ammonia has proved to be a great challenge due to competition between ammonia and the more reactive aniline products, which results in the formation of considerable amounts of diaryl- and triarylamines.[5,7c] Furthermore, traditional methods to form primary amines suffer from several drawbacks such as high pressure, high temperature, and low toleration of functional groups, which make those methodologies less attractive.[6] Recently, Hartwig and Buchwald and co-workers reported the catalyzed selective coupling reactions of aryl halides with ammonia by palladium catalysts.[7] Following these pioneering works, as an alternative, several Cu-catalyzed coupling reactions of aryl halides with ammonia have been reported.[8] Furthermore, Fu and co-workers also introduced a copper-catalyzed amination protocol between aromatic boronic acids and aqueous ammonia at room temperature.[9] Although the examples mentioned above have led to remarkable progress in the development of primary aniline synthesis, it is noteworthy that these protocols are generally performed in organic solvents, which contributed the largest amount of "auxiliary waste" in most chemical productions.[10] Therefore, it is highly desirable to find an ideal, nontoxic, cheap, and readily available "green" solvent. Obviously, water is the most inexpensive and environmentally benign one.[11]

In continuation of our efforts in aqueous catalysis,[12] herein we disclose an environmentally friendly protocol for the amination of aryl halides with aqueous ammonia catalyzed by sulfonato–Cu(salen) complex **1** (Figure 1), which was successfully applied in C–N cross-coupling reactions by us recently.[12a]

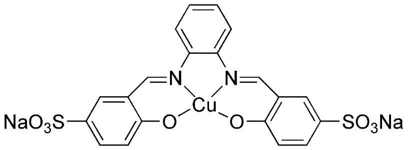

Figure 1. Structure of sulfonato–Cu(salen) complex **1**.

Results and Discussion

To optimize the reaction conditions, iodobenzene was firstly chosen as the model substrate. Selected results from our screening experiments are summarized in Table 1. As expected, no product could be detected in the absence of a copper catalyst (Table 1, Entry 1). Several simple copper salts were also examined, and only trace amounts of products were obtained (Table 1, Entries 2–4). To our delight, catalysis with complex **1** (5 mol-%) afforded 86% yield of the desired aniline product at 120 °C for 24 h (Table 1, Entry 5). Further investigation revealed that 12 h was enough for the coupling reaction (Table 1, Entries 5–7). Notably, the addition of $(n\text{Bu})_4\text{NBr}$ (10 mol-%) as phase-transfer

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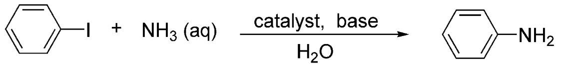
[a] Institute of Homogeneous Catalysis, College of Chemistry, Sichuan University,
Chengdu 610064, China
Fax: +86-28-85412026
E-mail: zhouxiangge@scu.edu.cn
[b] State Key Laboratory of Coordination Chemistry, Nanjing University,
Nanjing 210093, China

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000060.

catalyst (PTC) did not improved the results (Table 1, Entry 8). The dosage of catalyst was also screened, and the yield decreased sharply to 32% when only 2 mol-% of catalyst was used. Meanwhile, increasing the amount of catalyst to 10 mol-% did not improve the yield (Table 1, Entries 9 and 10). Furthermore, low temperatures decelerated the reaction rate. For example, only 42% yield was obtained when the reaction was carried out at 100 °C (Table 1, Entry 11). Base is another important factor to affect the catalysis. A poor yield of 24% was obtained in the absence of base (Table 1, Entry 12). Among various bases examined, NaOH, K_2CO_3, K_3PO_4, Na_2CO_3, and Cs_2CO_3 were all effective for the catalysis, but the use of CH_3COONa and organic bases such as triethylamine led to lower yields (Table 1, Entries 13–18). Thus, NaOH was selected as the base in the following studies.

Table 1. Catalytic amination of iodobenzene with aqueous ammonia by the sulfonato–Cu(salen) complex in water.[a]

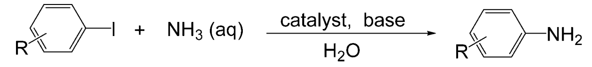


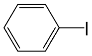
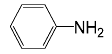
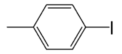
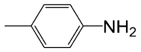
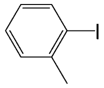
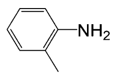
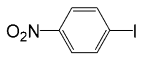
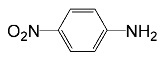
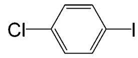
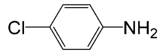
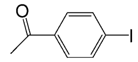
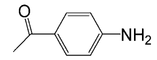
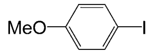
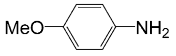
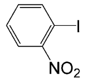
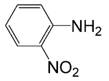
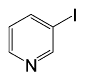
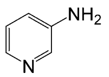
Entry	Catalyst (mol-%)	Base	*T* [h]	Yield [%][b]
1	–	NaOH	12	0
2	Cu_2O (5)	NaOH	12	trace
3	$CuSO_4$ (5)	NaOH	12	trace
4	$Cu(OAc)_2$ (5)	NaOH	12	trace
5	sulfonato–Cu(salen) (5)	NaOH	24	86
6	*sulfonato–Cu(salen) (5)*	*NaOH*	*12*	*87*
7	sulfonato–Cu(salen) (5)	NaOH	9	59
8[c]	sulfonato–Cu(salen) (5)	NaOH	12	80
9	sulfonato–Cu(salen) (2)	NaOH	12	32
10	sulfonato–Cu(salen) (10)	NaOH	12	86
11[d]	sulfonato–Cu(salen) (5)	NaOH	12	42
12	sulfonato–Cu(salen) (5)	–	12	24
13	sulfonato–Cu(salen) (5)	K_2CO_3	12	83
14	sulfonato–Cu(salen) (5)	K_3PO_4	12	80
15	sulfonato–Cu(salen) (5)	Na_2CO_3	12	86
16	sulfonato–Cu(salen) (5)	Cs_2CO_3	12	84
17	sulfonato–Cu(salen) (5)	CH_3COONa	12	17
18	sulfonato–Cu(salen) (5)	Et_3N	12	50

[a] Unless otherwise noted, the reactions were carried out with iodobenzene (0.5 mmol), 25–28% aqueous ammonia (1 mL), base (1 mmol) in water (2 mL) at 120 °C. [b] Determined by GC–MS with the use of 1,4-dichlrobenzene as internal standard. [c] $(n\text{Bu})_4\text{NBr}$ (10 mol-%) was added as PTC. [d] The reaction temperature was 100 °C.

The scope of substrates was then investigated by using this catalytic system under the optimized reaction conditions. All the aryl iodides, especially those with electron-withdrawing substituents, provided good to excellent yields as shown in Table 2, and the highest yield (95%) was obtained by using 4-iodoacetophenone. Notably, the sterically demanding *ortho* substituents did not hamper the reaction as much as that in the coupling reaction between imidazole and iodobenzene reported by us.[12a] For instance, 2-methyliodobenzene and 2-nitroiodobenzene could be catalytically aminated in 71 and 79% yield, respectively (Table 2, Entries 3 and 8).

Table 2. Sulfonato–Cu(salen) complex **1** catalyzed amination of aryl iodides with aqueous ammonia.[a]



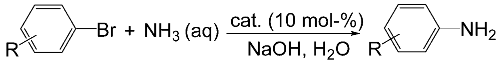
Entry	Aryl iodide	Product	Yield [%][b]
1			83
2			86
3			71
4			91
5			83
6			95
7			90
8			79
9			94

[a] Reaction conditions: aryl iodide (0.5 mmol), 25–28% aqueous ammonia (1 mL), catalyst (5 mol-%), NaOH (1 mmol), H_2O (2 mL), 120 °C, 12 h. [b] Isolated yield.

Next, we were intrigued by the possibility of using aryl bromides as coupling partners, which are less reactive electrophiles. However, low yields were found under the previously optimized reaction conditions. After careful optimization of the reaction conditions it was found that doubling the amount of catalyst to 10 mol-% resulted in comparable catalytic abilities when aryl bromides were used instead of aryl iodides. Thus, a variety of substituted aryl bromides were then examined, and the results are shown in Table 3. The electronic effects on the reactivity were limited; most of the substrates afforded good to excellent yields. It is noteworthy that heterocyclic bromides could also be coupled with aqueous ammonia to afford the corresponding anilines with excellent yields (Table 3, Entries 13 and 14). Furthermore, the catalytic system could tolerate a variety of functional groups including the nitro, acetyl, and ether groups. Sterically hindered 1,3-dimethylbromobenzene afforded the product in low yield (Table 3, Entry 11).

Substituted benzimidazoles are important heterocycles found in a variety of natural products.[13] The standard approach to the synthesis of benzimidazole derivatives is cyclocondensation of the corresponding 1,2-diaminobenzene with carboxylic acids.[14] However, the exploration of more efficient methods for constructing the benzimidazole framework is highly desirable. Thus, this catalytic system was applied in the synthesis of substituted 1*H*-benzimidazole from 2-iodoacetanilide and aqueous ammonia in one pot (Scheme 1).[15]

Table 3. Sulfonato–Cu(salen) complex **1** catalyzed amination of aryl bromides with ammonia.[a]



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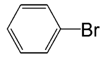
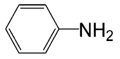
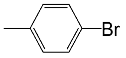
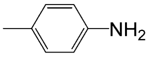
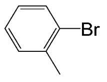
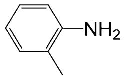
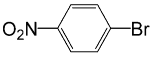
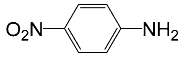
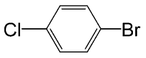
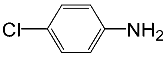
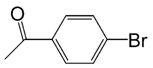
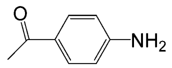
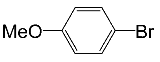
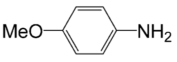
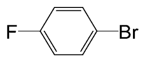
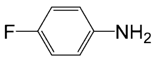
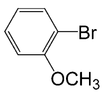
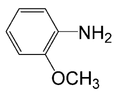
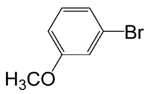
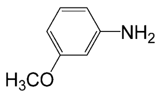
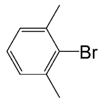
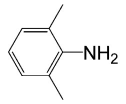
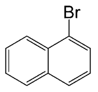
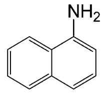
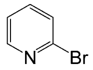
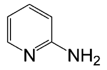
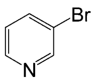
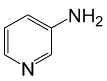
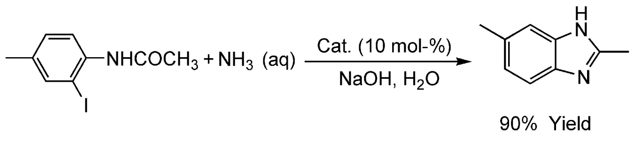
1			85
2			87
3			70
4			92
5			83
6			95
7			85
8			88
9			90
10			88
11			64
12			71
13			92
14			93

[a] Reaction conditions: aryl iodide (0.5 mmol), 25–28% aqueous ammonia (1 mL), catalyst (10 mol-%), NaOH (1 mmol), H_2O (2 mL), 120 °C, 12 h. [b] Isolated yield.



Scheme 1. Synthesis of 1*H*-benzimidazole with aqueous ammonia in water.

Conclusions

In conclusion, we have developed a simple, highly efficient, and environmentally friendly protocol for coupling aryl halides with aqueous ammonia in neat water catalyzed by the water-soluble sulfonato–Cu(salen) complex. A wide range of aryl bromides and aryl iodides were found to be applicable to the catalytic system. In addition, substituted 1*H*-benzimidazole was prepared easily by coupling of aqueous ammonia with 2-iodoacetanilide in one pot with this catalytic system. Overall, we believe this environmentally benign system will find wide application in organic synthesis. Further application of the inexpensive, water-soluble complex catalysts is currently under investigation in this laboratory.

Experimental Section

Typical Procedure for the Catalysis: Catalyst (0.025 mmol), aryl halide (0.5 mmol), NaOH (1 mmol), aqueous ammonia (1 mL), and water (2 mL) were added to a sealed tube. The reaction mixture was stirred at 120 °C for 12 h and then cooled to room temperature and extracted with ethyl acetate. The organic layer was then dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The aniline product was finally obtained by column chromatography on silica gel. All the products were confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

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

Acknowledgments

This project was sponsored by the Natural Science Foundation of China (Nos. 20672075, 20771076, 20901052) and the Sichuan Provincial Foundation (08ZQ026-041). We also thank the Analysis and Testing Center of Sichuan University for NMR measurements.

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Received: January 18, 2010