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Ligand-Free Iron/Copper-Cocatalyzed Amination of Aryl Iodides

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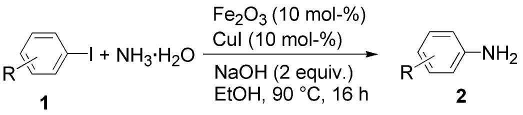
The Fe_2O_3/CuI system efficiently catalyzes the direct amination of aryl iodides with aqueous ammonia in ethanol at 90 °C under aerobic conditions. No ligand was used to perform such reaction. A very wide variety of functional groups was tolerated on the aryl iodide partner. This procedure is economically and environmentally attractive as a result of the use of aqueous ammonia and ethanol.

Introduction

The development of synthetic strategies towards anilines has attracted the interest of chemists for more than 100 years as a result of the significance and omnipresence of these compounds in the field of natural products, pharmaceuticals, and medicinal compounds.[1] The traditional strategy for the preparation of primary arylamines usually involves the use of masked ammonia substitutes to make the C–N bond and an additional deprotection step, which make those methodologies less attractive.[2] Consequently, development of new methodologies for the preparation of aniline derivatives starting from a more abundant and less expensive nitrogen source, ammonia, is a goal that attracts more and more attention. Over the last decades, impressive progress in transition-metal-catalyzed C–N bond formation has been made, in particular in palladium-catalyzed[3] Buchwald–Hartwig reactions and copper-catalyzed[4] Ullman-type transformations. More precisely, amination of aryl halides with the use of ammonia as a nitrogen source are rare. Lately, some examples of copper-[5] and palladium-catalyzed[6] amination of aryl halides were reported. Usually, those methodologies had some drawbacks: the use of DMF or DMSO as solvent, or the need of 3–4 bar of ammonia pressure.

Recently, during the course of our studies, the copper-catalyzed amination of aromatic halides with the use of aqueous ammonia or ammonium chloride as a nitrogen source were reported. For example, Chang[5d] described an efficient catalytic system based on copper iodide (20 mol-%) and L-proline (40 mol-%) for the amination of aryl iodides by using NH_4Cl or aqueous ammonia as a nitrogen source. The use of 4-hydroxy-L-proline as a ligand improved this reaction, as it worked with aryl bromides at 50 °C in DMSO.[7] Quite simultaneously, Taillefer reported a diketone/copper catalytic system [10 mol-% of $Cu(acac)_2$ and 40 mol-% of 2,4-pentadione] for the direct amination of both aryl iodides and bromides in the presence of aqueous ammonia.[5b] Lately, Wolf used Cu_2O as a catalyst to perform the amination of aryl halides in NMP/water media.[5c]

In our continuing work to develop new methodologies using iron as catalyst,[8,9] herein, we now report a green, general, and practical ligand-free, iron/copper-cocatalyzed synthesis of anilines from aryl iodides and aqueous ammonia at 90 °C in ethanol. The use of ethanol as a solvent, cheap iron and copper salts as cocatalysts, and inexpensive and easy-to-handle aqueous ammonia make this method attractive (Scheme 1).



Scheme 1. Fe_2O_3/CuI-cocatalyzed amination of aryl iodides.

Results and Discussion

For our initial experiments, we chose to study the amination reaction of iodobenzene (**1a**) and aqueous ammonia. As illustrated in Table 1, the preliminary survey was carried out in *N*,*N*-dimethylformamide (which is one of the usual solvents for this reaction) at 90 °C with the use of cesium carbonate as a base, under an argon atmosphere. In the presence of $Fe(acac)_3$ (30 mol-%), the amination reaction gave only 5% of the desired aniline product (Table 1, Entry 1). In contrast, this reaction provided promising results in the presence of catalytic amounts of both CuI and $Fe(acac)_3$, as aniline **2a** was obtained in good GC yield (90%;

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Table 1, Entry 2). It must be pointed out that in the absence of an iron source, catalytic amounts of CuI afforded a moderate GC yield of aniline (30%; Table 1, Entry 3).

Table 1. Iron/CuI-cocatalyzed coupling of iodobenzene with aqueous ammonia.[a]

Entry	Fe salt	Solvent	Base	Atm.	GC yield [%]
1[b]	Fe(acac)$_3$[c]	DMF	Cs_2CO_3	argon	5
2	Fe(acac)$_3$[c]	DMF	Cs_2CO_3	argon	90
3	–	DMF	Cs_2CO_3	argon	30
4	Fe(acac)$_3$	EtOH	Cs_2CO_3	argon	35
5	Fe(acac)$_3$	EtOH	Cs_2CO_3	air	90
6	Fe(acac)$_3$	DMF	Cs_2CO_3	air	0
7	Fe(acac)$_3$	CH_3CN	Cs_2CO_3	air	0
8	***Fe(acac)$_3$***	***EtOH***	***NaOH***	***air***	***98***
9	Fe(acac)$_3$	EtOH	KOH	air	35
10	Fe(acac)$_3$	EtOH	Na_2CO_3	air	1
11	Fe(acac)$_3$	EtOH	K_2CO_3	air	48
12	Fe(acac)$_3$	EtOH	NaOAc	air	1
13	Fe(acac)$_3$	EtOH	KOAc	air	21
14	$FeCl_3$	EtOH	NaOH	air	70
15	FeF_3	EtOH	NaOH	air	71
16	$FeCl_2$	EtOH	NaOH	air	71
17	$FeBr_2$	EtOH	NaOH	air	69
18	FeF_2	EtOH	NaOH	air	79
19	$FeCl_3{\cdot}6H_2O$	EtOH	NaOH	air	95
20	Fe(acac)$_2$	EtOH	NaOH	air	5
21	***Fe_2O_3***	***EtOH***	***NaOH***	***air***	***100***
22[b]	Fe_2O_3	EtOH	NaOH	air	0
23	$FeSO_4{\cdot}7H_2O$	EtOH	NaOH	air	85

[a] Reaction conditions: iodobenzene (1 mmol), aqueous ammoniac solution (5 mmol), iron salt (10 mol-%), CuI (10 mol-%), and base (2 mmol) at 90 °C for 16 h. [b] The CuI cocatalyst was not added. [c] 30 mol-% of catalyst was used.

Remarkably, when the reaction was performed in ethanol with the use of both Fe(acac)$_3$ and CuI as cocatalysts and Cs_2CO_3 as base in air, aniline was obtained with a very good GC yield of 90% after 16 h at 90 °C, whereas only 35% GC yield was observed when the reaction was conducted under an argon atmosphere (Table 1, Entries 4 and 5). However, no reaction was observed in DMF or acetonitrile by using the same conditions in air.

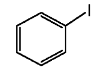
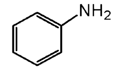
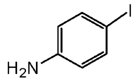
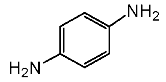
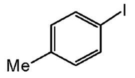
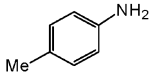
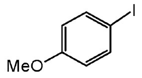
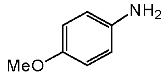
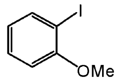
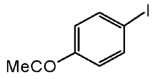
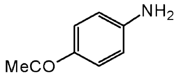
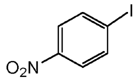
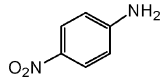
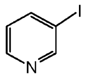
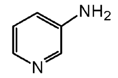
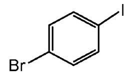
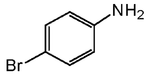
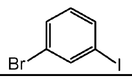
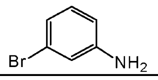
To get more information on the optimal catalyst conditions, we also carried out investigations to define the best base. Seven different bases (2 equiv.) were tested at 90 °C for 16 h with the use of Fe(acac)$_3$ (10 mol-%) and CuI (10 mol-%) as cocatalysts in the presence of aqueous ammonia (5 equiv.). Carbonate bases such as sodium or potassium carbonate gave lower GC yields than that obtained with cesium carbonate (1 and 48%, respectively, compared to 90%; (Table 1, Entries 10 and 11 vs. 5). Potassium and sodium acetate led to moderate GC yields (1 and 21% GC yield, respectively; Table 1, Entries 12 and 13). In fact, NaOH was found to be a far better base than the other classic ones tested, as aniline was obtained in quantitative GC yield (98%; Table 1, Entry 8).

Finally, we carried out extensive investigations to define the best iron catalyst (10 mol-%) for the amination of iodobenzene in the presence of CuI (10 mol-%), NaOH (2 equiv.), and aqueous ammonia (5 equiv.) at 90 °C for 16 h. First of all, Fe(acac)$_2$ was not able to promote any amination reaction (Table 1, Entry 20). Conversely, upon employment of iron halide salts such as $FeCl_3$, FeF_3, $FeCl_2$, $FeBr_2$, or FeF_2, GC yields up to 79% were obtained (Table 1, Entries 14–18). Interestingly, with the use of $FeCl_3{\cdot}7H_2O$, aniline was obtained in 95% GC yield (Table 1, Entry 19). Remarkably, the GC yield afforded by using Fe_2O_3 as catalyst was also excellent (100%; Table 1, Entry 21). It must be pointed out that in the absence of copper iodide, with the use of Fe_2O_3 as catalyst, no aniline derivative was obtained (Table 1, Entry 22).

Next, we explored the scope of this iron/copper-cocatalyzed amination reaction. By using the optimized conditions (10 mol-% of Fe_2O_3, 10 mol-% of CuI in ethanol at 90 °C for 16 h in the presence of 5 equiv. of aqueous ammonia and 2 equiv. of solid NaOH) on the model reaction, we accomplished this transformation with respect to the aryl iodide substrates.

The electronic effects on the reactivity were limited. Aryl iodides substituted with electron-withdrawing groups such as acyl or nitro led to the corresponding *para*-substituted anilines in isolated yields up to 87% (Table 2, Entries 6 and 7). Furthermore, it must be pointed out that the yield obtained for the reaction of *p*-nitroiodobenzene with aqueous

Table 2. Fe_2O_3/CuI-cocatalyzed coupling of aryl iodides with aqueous ammonia.[a]

Entry	ArI	ArNH$_2$		Yield [%][b]
1			**2a**	98 (95)[c]
2			**2b**	92
3			**2c**	72
4			**2d**	81 (84)[c]
5			**2e**	90
6			**2f**	87 (80)[c]
7			**2g**	61
8			**2h**	94
9			**2i**	82
10			**2j**	89

[a] Reaction conditions: aryl iodide (1 mmol), aqueous ammoniac solution (5 mmol), Fe_2O_3 (10 mol-%), CuI (10 mol-%), NaOH (2 mmol) in ethanol (2 mL) at 90 °C for 16 h. [b] Isolated yields. [c] Isolated yield for reaction performed on 5-mmol scale.

ammonia was significantly lower (61%; Table 2, Entry 7). In contrast, aryl iodides substituted by electron-donating substituents such as NH_2, Me, or OMe afforded the desired aniline derivatives in good yields (72–92%; Table 2, Entries 2–4). Interestingly, when the reaction was performed with *o*-methoxyiodobenzene, corresponding *o*-methoxyaniline (**2e**) was obtained in 90% isolated yield, which shows that *ortho* substituents did not hamper the reaction (Table 2, Entry 5). Extending the procedure to heterocyclic aromatic iodide such as 3-iodopyridine was also possible, as 94% of 3-aminopyridine (**2h**) was isolated under our standard conditions (Table 2, Entry 8). Finally, *para*- and *meta*-substituted bromoaryl iodides led selectively to the corresponding *para*- and *meta*-bromoanilines in good yield (82 and 89%, respectively), without detection of diaminobenzene derivatives (Table 2, Entries 9 and 10). Furthermore, when using aryl bromide derivatives under these conditions, no reaction occurred.

Conclusions

In summary, we have developed a general, economical, efficient, and environmentally friendly way to transform aryl iodides into aniline derivatives by using an iron/copper cocatalyst system in the presence of NaOH and aqueous ammonia in ethanol at 90 °C. The easy use of aqueous ammonia, the use of nontoxic ethanol as solvent, and the low cost and environmentally benign character of the cocatalytic system (Fe_2O_3/CuI) are great advantages in terms of green chemistry. It must be pointed out that this reaction proceeds in air in ethanol as solvent (whereas the usual solvent for such reactions is DMF, DMSO, NMP, or ethylene glycol). Studies are currently in progress to elucidate the mechanism of this reaction.

Experimental Section

Representative Procedure: Commercially available red iron oxide Fe_2O_3 (16 mg, 10 mol-%) and CuI (19.1 mg, 10 mol-%) were added to a solution of iodobenzene (204 mg, 1 mmol) in ethanol (2 mL). Aqueous ammonia (5 mmol, 25% in water) and NaOH (2 mmol, 80 mg) were successively added to the reaction mixture. The reaction tube was sealed and then heated at 90 °C for 16 h. The reaction progress was monitored by GC. The reaction mixture was cooled to room temperature, extracted with diethyl ether (3 × 10 mL) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to provide the corresponding pure primary arylamine compound.

Supporting Information (see footnote on the first page of this article): Experimental procedures and compound characterization, including NMR spectra.

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[1] For a list of methods, see: a) R. C. Larock in *Comprehensive Organic Transformations: A Guide to Functional Group Preparation*, VCH, New York, **1989**; b) K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Wiley-VCH, Weinheim, **1997**; c) S. A. Lawrence, *Amines: Synthesis Properties and Applications*, Cambridge University Press, Cambridge, **2004**.

[2] a) C.-Z. Tao, J. Li, Y. Fu, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2008**, *49*, 70; b) X. Gao, H. Fu, R. Qiao, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 6864; c) A. A. Trabanco, J. A. Vega, M. A. Fernandez, *J. Org. Chem.* **2007**, *72*, 8146; d) X. Liu, M. Barry, H.-R. Tsou, *Tetrahedron Lett.* **2007**, *48*, 8409; e) D. Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1169; f) D.-Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1169; g) X. H. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653; h) J. Barluenga, F. Aznar, C. Valdes, *Angew. Chem. Int. Ed.* **2004**, *43*, 343; i) C. L. Cioffi, M. L. Berlin, J. Herr, *Synlett* **2004**, 841; j) G. A. Grasa, M. S. Viciu, J. K. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729; k) S. Lee, M. Jorgensen, J. F. Hartwig, *Org. Lett.* **2001**, *3*, 2729; l) G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729; m) X. H. Huang, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3417; n) S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313; o) J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6367.

[3] For representative papers on palladium-catalyzed C–N cross-coupling reactions, see: a) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; b) Q. L. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 7734; c) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 6523; d) S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23; e) J. Barluenga, F. Aznar, C. Vales, *Angew. Chem. Int. Ed.* **2004**, *43*, 343; f) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; g) S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 7240.

[4] For selected examples on copper-catalyzed Ullmann-type aminations, see: a) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542; b) J. Mao, J. Guo, H. Song, S. Ji, *Tetrahedron* **2008**, *64*, 2471; c) H. Maheswaran, G. G. Krishna, K. L. Prasanth, V. Srinivas, G. K. Chaitanya, K. Bhanuprakash, *Tetrahedron* **2008**, *64*, 2471; d) M. L. Kantam, J. Yadav, S. Laha, B. Sreedhar, S. Jha, *Adv. Synth. Catal.* **2007**, *349*, 1938; e) H. Ma, X. Jiang, *J. Org. Chem.* **2007**, *72*, 8943; f) W. Chen, Y. Zhang, L. Zhu, J. Lan, R. Xie, J. You, *J. Am. Chem. Soc.* **2007**, *129*, 13879; g) B. Zou, Q. Yuan, D. Ma, *Angew. Chem. Int. Ed.* **2007**, *46*, 2598; h) B. Zou, Q. Yuan, D. Ma, *Org. Lett.* **2007**, *9*, 4291; i) R. Martin, C. H. Larsen, A. Cuenca, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 3379; j) D. S. Jiang, H. Fu, Y. Y. Jiang, Y. F. Zhao, *J. Org. Chem.* **2007**, *72*, 672; k) H. Rao, Y. Jin, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2006**, *12*, 3636; l) A. Shafir, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 8742; m) M. Taillefer, A. Ouali, B. Renard, J. F. Spindler, *Chem. Eur. J.* **2006**, *12*, 5301; n) H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164; o) H. J. Cristau, P. P. Cellier, J. F. Spindler, M. Taillefer, *Chem. Eur. J.* **2004**, *10*, 5607; p) T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 4397; q) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793; r) D. Ma, Q. Cai, H. Zhang, *Org. Lett.* **2003**, *5*, 2453; s) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581; t) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684; u) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727; v) R. K. Gujadhur, C. G. Bates, D. Venkataraman, *Org. Lett.* **2001**, *3*, 4315; w) D. Ma, C. Xia, *Org. Lett.* **2001**, *3*, 2583; x) D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459.

[5] a) Z. Guo, J. Guo, Y. Song, L. Wang, G. Zou, *Appl. Organomet. Chem.* **2009**, *23*, 150; b) N. Xia, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 337; c) H. Wu, C. Wolf, *Chem. Commun.* **2009**, 3035; d) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052; e) S.

Gaillard, M. K. Elmkaddem, C. Fischmeister, C. M. Thomas, J.-L. Renaud, *Tetrahedron Lett.* **2008**, *49*, 3471; f) R. Ntaganda, B. Dhudshia, C. L. B. Macdonald, A. N. Thadani, *Chem. Commun.* **2008**, 6200; g) F. Lang, D. Zewge, I. N. Houpis, R. P. Volante, *Tetrahedron Lett.* **2001**, *42*, 3251.

[6] a) T. Schulz, C. Torborg, S. Enthaler, B. Schaffner, A. Dumrath, A. Spannenberg, H. Neumann, A. Borner, M. Beller, *Chem. Eur. J.* **2009**, *15*, 4528; b) T. Nagano, S. Kobayashi, *J. Am. Chem. Soc.* **2009**, *131*, 4200; c) D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 10354; d) Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 10028; e) G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11049.

[7] L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 454.

[8] a) X.-F. Wu, C. Darcel, *Eur. J. Org. Chem.* **2009**, 1144; b) X.-F. Wu, D. Bezier, C. Darcel, *Adv. Synth. Catal.* **2009**, *351*, 367; c) X.-F. Wu, C. Vovard-Le Bray, L. Bechki, C. Darcel, *Tetrahedron* **2009**, *65*, 7380; d) D. Bézier, C. Darcel, *Adv. Synth. Catal.*, DOI: 10.1002/adsc.200900281.

[9] For some reviews on state-of-the-art iron-catalyzed reactions, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317; c) A. Correa, O. Garcia Mancheno, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500.

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