Preparation of aromatic amines by copper-catalyzed coupling of boronic acids with aqueous ammonia

Zhaoqiong Jiang, Zhiqing Wu, Lixia Wang, Di Wu, and Xiangge Zhou

Abstract: A simple, highly efficient, and environmentally friendly protocol for the synthesis of primary aromatic amines by catalytic coupling of aromatic boronic acids with aqueous ammonia has been developed by using commercial and inexpensive $CuSO_4 \cdot 5H_2O$ as catalyst without addition of other solvents under mild reaction conditions.

Key words: ammonia, primary aromatic amine, aromatic boronic acid, water.

Résumé : Opérant dans des conditions de réactions douces et utilisant le $CuSO_4 \cdot 5H_2O$ peu coûteux et commercialement disponible comme catalyseur, on a développé une méthode simple, hautement efficace et écologique pour synthétiser des amines primaires aromatiques par couplage catalytique d'acide boroniques aromatiques avec l'ammoniaque en solution aqueuse et n'impliquant aucun autre solvant.

Mots-clés : ammoniac, amine primaire aromatique, acide boronique aromatique, eau.

Introduction

Preparation of primary aromatic amines has attracted increasing attention because they are valuable compounds widely employed in the manufacture of natural products, agrochemicals, pharmaceuticals, biological compounds, dyes, pigments, and rubber.[1] Ammonia is one of the most abundant, inexpensive, and attractive nitrogen sources in chemical synthesis, but the direct consumption of it in catalytic reactions is less reported.[2] In general, the difficulties in the use of ammonia for metal-catalyzed processes may result from two facts: (*i*) many kinds of transition metals are bonded with ammonia to form catalytically unreactive complexes, and (*ii*) the primary amine product formed during catalysis is usually more reactive than ammonia itself and easily converted to a secondary amine.[2g,3] Thus, the synthesis of primary aryl amines generally relies on the use of ammonia surrogates such as allyl,[4] benzyl[5] and silyl amines,[6] imines,[7] amides,[8] and others.[9] However, the products of these reactions need an additional deprotection step, which makes those methodologies less attractive. Hence, the use of ammonia as a nitrogen source is still by far one of the most desired approaches.[2] A few copper-catalyzed protocols for the preparation of primary arylamines have been recently developed by the coupling of aryl halides with ammonia. However, these catalyses were usually performed under high pressure using liquid ammonia.[10] More recently, palladium-catalyzed cross-coupling reactions between simple aryl halides and ammonia would allow the direct synthesis of valuable primary aromatic amines with good yields in solvents of 1,2-dimethoxyethane or 1,4-dioxane.[2g,11] Instead of palladium, Cu-catalyzed amination of aryl halides using aqueous ammonia was first reported by Kim and Chang.[12] Following these pioneering works, several Cu-catalyzed preparation of primary arylamines have been efficiently carried out with excellent yields by using DMF, *N*-methyl pyrrolidinone, alcohol, or 1,4-dioxane as reaction medium.[13] Although these methods mentioned above have led to remarkable advancement in the synthesis of primary arylamines, it is worth noting that they were all performed in organic solvents.[14]

From the standpoint of green chemistry, the development of a more environmentally benign reaction media would be highly desirable.[15] Obviously, water, which is an ideal nontoxic, extremely abundant, and readily available green substance, is the most inexpensive and environmentally benign solvent. In continuation of our endeavors in aqueous catalysis,[16] herein is reported the synthesis of primary arylamines by cross-coupling reactions between aromatic boronic acids and aqueous ammonia catalyzed by $CuSO_4 \cdot 5H_2O$ at room temperature (RT) without the addition of other solvents.

Results and discussion

Initially, we chose phenylboronic acid as the model substrate in the optimization of reaction conditions. The preliminary survey was carried out by using 28% aqueous ammonia as the nitrogen source, $CuSO_4 \cdot 5H_2O$ as catalyst, and NaOH as base. The results were listed in Table 1.

Unlike most of the other coupling reactions, as shown in Table 1, the yields decreased sharply from 70% and 69% to 51% when the reaction temperature increased from room

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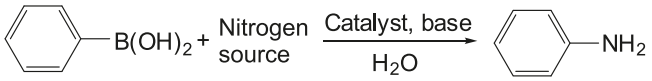
Table 1. Copper-catalyzed synthesis of aniline from phenylboronic acid in water.



Entry	Nitrogen source	Catalyst	Base	T (°C)	Yield (%)[a]
1	$NH_3·H_2O$	$CuSO_4·5H_2O$	NaOH	90	51
2	$NH_3·H_2O$	$CuSO_4·5H_2O$	NaOH	60	69
3	$NH_3·H_2O$	$CuSO_4·5H_2O$	NaOH	RT	70
4	$NH_3·H_2O$	$CuSO_4·5H_2O$	Cs_2CO_3	RT	33
5	$NH_3·H_2O$	$CuSO_4·5H_2O$	K_2CO_3	RT	24
6	$NH_3·H_2O$	$CuSO_4·5H_2O$	Na_2CO_3	RT	28
7	$NH_3·H_2O$	$CuSO_4·5H_2O$	CH_3COONa	RT	39
8	$NH_3·H_2O$	$CuSO_4·5H_2O$	K_3PO_4	RT	39
9	$NH_3·H_2O$	$CuSO_4·5H_2O$	Na_2HPO_4	RT	19
10	$NH_3·H_2O$	$CuSO_4·5H_2O$	KOH	RT	50
11	$NH_3·H_2O$	$CuSO_4·5H_2O$	$NaHCO_3$	RT	30
12	$NH_3·H_2O$	$CuSO_4·5H_2O$	EtONa	RT	50
13	$NH_3·H_2O$	$CuSO_4·5H_2O$	—	RT	18
14	$NH_3·H_2O$[b]	$CuSO_4·5H_2O$	NaOH	RT	78
15	$NH_3·H_2O$[c]	$CuSO_4·5H_2O$	NaOH	RT	90
16	$NH_3·H_2O$[d]	$CuSO_4·5H_2O$	NaOH	RT	91
17	$NH_3·H_2O$[d]	$Cu(OAc)_2·H_2O$	NaOH	RT	89
18	$NH_3·H_2O$[d]	$CuCl_2·2H_2O$	NaOH	RT	79
19	$NH_3·H_2O$[d]	Cu_2O	NaOH	RT	65
20	$NH_3·H_2O$[d]	$CuClO_4$	NaOH	RT	82
21	$NH_3·H_2O$[d]	CuI	NaOH	RT	87
22	$NH_3·H_2O$[d]	—	NaOH	RT	Trace
23	$(NH_4)_2CO_3$	$CuSO_4·5H_2O$	NaOH	RT	5
24	NH_4HCO_3	$CuSO_4·5H_2O$	NaOH	RT	3
25	NH_4Cl	$CuSO_4·5H_2O$	NaOH	RT	5
26	$(NH_4)_2SO_4$	$CuSO_4·5H_2O$	NaOH	RT	4

Note: Unless otherwise noted, the reaction was carried out with phenylboronic acid (0.2 mmol), nitrogen sources (2 mmol), catalyst (0.02 mmol), and base (0.4 mmol) in 2 mL water.

[a]Determined by GC–MS using 1,4-dichlorobenzene as internal standard.

[b]Aqueous ammonia (28%, 4 mmol) in 2 mL water.

[c]Aqueous ammonia (28%, 4 mmol) in 1 mL water.

[d]Aqueous ammonia (28%, 1 mL).

temperature and 60 °C to 90 °C, respectively (Table 1, entries 1–3). The formation of the byproduct phenol, which resulted from the hydrolysis of phenylboronic acid at high temperature in water, might be attributed to the decrease of yields. Control experiment proved that more than 50% phenylboronic acid was found to convert into phenol at 100 °C. Comparison of a variety of bases indicated NaOH to be a proper candidate with a yield of 70% (Table 1, entries 3–13). Considering phenol as the main side product, we increased the concentration of ammonia to inhibit the competition of water; the yield was sharply improved from 70% to 91% when the concentration of ammonia was increased from 2% to 28% (Table 1, entries 3, 14–16). Thus, the addition of other solvents, including water, was unnecessary in this case. Other different copper sources such as $Cu(OAc)_2$, $CuCl_2$, Cu_2O, $CuClO_4$, and CuI have also been examined, and $CuSO_4$ gave the best result with a 91% GC–MS yield (Table 1, entries 16–21) and there was only trace product without catalyst (Table 1, entry 22). Several inorganic nitrogen sources were also tried with poor results (Table 1, entries 23–26). In summary, the optimal conditions for the synthesis of primary aromatic amines are as follows: 28% aqueous ammonia (3 mL, when 0.6 mmol aromatic boronic acid was used) as the nitrogen source, $CuSO_4$ (10 mol%) as the catalyst, NaOH (2 equiv.) as the base, and the reaction was carried out at room temperature in a sealed tube without inert gas protection.

The scope of aromatic boronic acids was then investigated by using this catalytic system under the optimized reaction conditions. The results are listed in Table 2.

In general, the catalytic cross-coupling reactions between aqueous ammonia and aromatic boronic acids containing electron-withdrawing substituents were efficiently promoted with excellent yields within 3–5 h. For instance, *p*-fluorophenylboronic acid and *p*-cyanophenylboronic acid afforded 91% and 92% of the desired aminated products, respectively (Table 2, entries 3 and 5, respectively). Lower yields were obtained with *p*-methoxyphenyl boronic acid, *o*-methoxyphenyl boronic acid, and α-naphthyl boronic acid, due to the formation of protodeboronation byproducts as shown in Scheme 1 (Table 2, entries 6, 8, and 11, respectively).[17] Normally, protodeboronation occurs by the reported A-SE_2

Scheme 1. Protodeboronation of aromatic boronic acids.

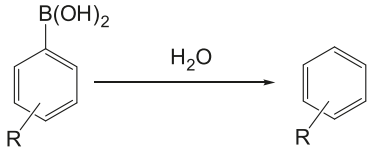
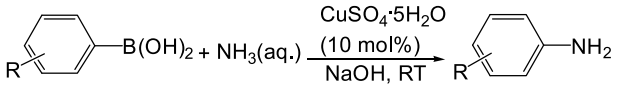
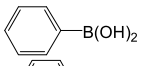
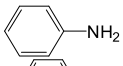
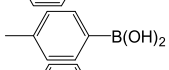
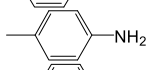
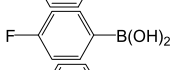
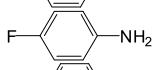
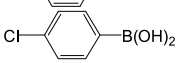
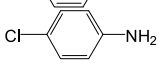
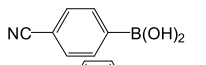
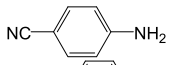
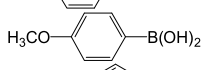
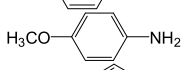
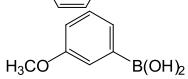
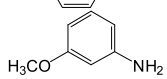
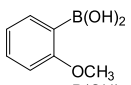
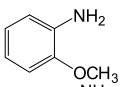
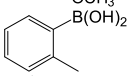
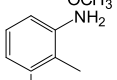
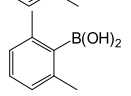
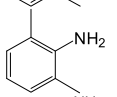
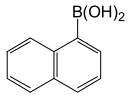
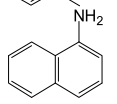


Table 2. Synthesis of primary aromatic amines catalyzed by $CuSO_4{\cdot}5H_2O$ in water.



Entry	Ar-B $(OH)_2$	$ArNH_2$	Time (h)	Yield (%)[a]
1			4	88
2			5	87
3			5	91
4			5	90
5			5	92
6			5	66
7			4	84
8			4	55
9			4	59
10			4	58
11			3	50

Note: Reaction conditions: aromatic boronic acids (0.6 mmol), 28% aqueous ammonia (3 mL), $CuSO_4{\cdot}5H_2O$ (0.06 mmol), NaOH (1.2 mmol), room temperature.
[a]Isolated yields.

mechanism, in which proton transfer is the rate-determining step, and is followed by a rapid ionic cleavage of the boron–carbon bond.[18] The rate sequence of protodeboronation of substituted phenylboronic acids was reported to be *p*-OCH_3 > *p*-CH_3 > *p*-F > H > *p*-Br > *m*-Cl > *m*-F.[18c,18d,19] Meanwhile, electron-withdrawing groups, especially those located at the *m*-position of phenylboronic acids, retarded the rate of protodeboronation.[18d] Furthermore, the protodeboronation process was reported to be easier for α-naphthyl boronic acid than *p*-methoxyphenyl boronic acid.[17b,20] Thus, in this experiment, *p*-methoxyphenyl boronic acid, *o*-methoxyphenyl boronic acid, and α-naphthyl boronic acid afforded moderate yields ranging from 50% to 66%, while a much higher yield (84%) was obtained in the case of *m*-methoxyphenyl boronic acid (Table 2, entries 6–8). On the other hand, steric hindrance was another important factor affecting the results. For example, only a 58% yield of the aminated product was obtained when 2,6-dimethyphenylboronic acid was employed (Table 2, entry 10).

Conclusion

In summary, we have developed a simple, highly efficient, economical, and environmentally friendly protocol for the synthesis of primary aromatic amines by coupling of aromatic boronic acids with aqueous ammonia without the addition of other solvents under mild reaction conditions. This method has the following advantages: commercial and inexpensive $CuSO_4{\cdot}5H_2O$ as catalyst, the use of aqueous ammonia as reactant as well as solvent, and NaOH as base at room temperature under atmospheric pressure without ligand and any other additive. This method avoids the use of stringent inert conditions and organic solvents, and the operation is very simple. Overall, we believe that this method could provide an avenue toward the Cu-catalyzed methods that have scarcely been adopted in the aqueous phase.

Experimental

All reagents were purchased from commercial suppliers and used without further purification. Column chromatography was carried out with silica gel (200–300 mesh). Thin layer chromatography was carried out using Merck silica gel GF254 plates. ^{1}H NMR and ^{13}C NMR (400 and 100 MHz, respectively) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm using TMS as the internal standard. Gas chromatography/mass spectra (GC–MS) were recorded on an Agilent Technologies 6890N instrument with an Agilent 5973N mass detector (EI) and a HP5-MS 30 m × 0.25 mm capillary apolar column (stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm).

General procedure for the synthesis of primary aromatic amines

Aromatic boronic acid (0.6 mmol), $CuSO_4{\cdot}5H_2O$ (0.06 mmol), NaOH (1.2 mmol), and aqueous ammonia (3 mL) were added to a sealed tube. The reaction mixture was stirred at room temperature for 3–5 h as shown in Table 2. After completion of the reaction, the mixture was extracted with ethyl acetate. The organic layer was then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was finally purified by column chromatography on silica gel using a hexane–ethyl acetate mixture as eluent.

Aniline[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 9:1). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.15 (t, 2H, *J* = 8.0 Hz), 6.76 (t, 1H, *J* = 7.4 Hz), 6.69 (d, 2H, *J* = 7.6 Hz), 3.52 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.9, 128.5, 117.6, 114.4. EI-MS *m*/*z*: 93 [M^+].

p-*Toluidine*[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 9:1). Slight yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.96 (d, 2H, *J* = 8.4 Hz), 6.61 (d, 2H, *J* = 8.4 Hz), 3.42 (s, br, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$,

100 MHz) δ: 143.8, 129.7, 127.7, 115.3, 20.4. EI-MS *m/z*: 107 [M+].

p-*Anisidine*[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 6:1). Slight brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.75 (d, 2H, *J* = 8.8 Hz), 6.66 (d, 2H, *J* = 8.8 Hz), 3.75 (s, 3H), 3.32 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 152.8, 134.0, 116.5, 114.8, 56.0. EI-MS *m/z*: 123 [M+].

m-*Anisidine*[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 6:1). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.06 (t, 1H, *J* = 8.0 Hz), 6.34–6.29 (m, 2H), 6.25 (t, 1H), 3.76 (s, 3H), 3.55 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.7, 146.7, 129.1, 106.9, 103.0, 100.1, 54.0. EI-MS *m/z*: 123 [M+].

o-*Anisidine*[13f]

Purification by flash chromatography (petroleum ether/ethyl acetate 6:1). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.81–6.78 (m, 2H), 6.75–6.71 (m, 2H), 3.84 (s, 3H), 3.60 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.3, 135.1, 120.1, 117.5, 114.0, 109.4, 54.4. EI-MS *m/z*: 123 [M+].

o-*Toluidine*[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 9:1). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.07–7.03 (m, 2H), 6.76–6.72 (m, 2H), 4.02 (s, br, 2H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.0, 129.5, 126.0, 121.7, 118.0, 114.2, 16.3. EI-MS *m/z*:107 [M+].

***2,6-Dimethylaniline*[13b]**

Purification by flash chromatography (petroleum ether/ethyl acetate 9:1). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.95 (d, 2H, *J* = 7.6 Hz), 6.66 (t, 1H, *J* = 7.6 Hz), 3.83 (s, br, 2H), 2.20 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.5, 128.3, 121.9, 118.2, 17.7. EI-MS *m/z*: 121 [M+].

α-*Aminonaphthalene*[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 9:1). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.85–7.78 (m, 2H), 7.46–7.43 (m, 2H), 7.33–7.24 (m, 2H), 6.79–6.76 (m,1H), 4.13 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.1, 134.3, 128.5, 126.3, 125.8, 124.7, 123.6, 120.8, 118.8, 109.6. EI-MS *m/z*: 143 [M+].

p-*Chloroaniline*[13f]

Purification by flash chromatography (petroleum ether/ethyl acetate 6:1). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 (d, 2H, *J* = 8.0 Hz), 6.61 (d, 2H, *J* = 8.4 Hz), 3.63 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.0, 129.1, 123.2, 116. 2. EI-MS *m/z*: 127 [M+].

p-*Fluoroaniline*[21]

Purification by flash chromatography (petroleum ether/ethyl acetate 6:1). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.88–6.82 (m, 2H), 6.64–6.60 (m, 2H), 3.53 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.6, 155.3, 142.4, 116.1, 116.0, 115.8, 115.6. EI-MS *m/z*: 111 [M+].

p-*Aminobenzonitrile*[13c]

Purification by flash chromatography (petroleum ether/ethyl acetate 6:1). Yellow soild. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42 (d, 2H, *J* = 8.4 Hz), 6.65 (d, 2H, *J* = 8.4 Hz), 4.18 (s, br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.5, 133.8, 120.2, 114.4, 100.1. EI-MS *m/z*: 118 [M+].

Supplementary data

Supplementary data for this article (^{1}H NMR and ^{13}C NMR spectra for all products) are available on the journal Web site (canjchem.nrc.ca).

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