

Easy Copper-Catalyzed Synthesis of Primary Aromatic Amines by Coupling Aromatic Boronic Acids with Aqueous Ammonia at Room Temperature**

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Primary aromatic amines are widely used in the synthesis of natural products, pharmaceutical and medicinal compounds, as well as polymers and materials,^[1] and their preparation has attracted increasing attention. Ammonia is an abundant and inexpensive chemical reagent, so it is an attractive amino source in organic synthesis.^[2] Traditional synthesis of primary amines has been performed through couplings of aryl halides with ammonia, but high pressure, high temperature, and sealed reaction vessels were necessary^[3]—these procedures do not seem to be operationally simple or safe. To overcome the drawbacks, ammonia surrogates have been used as suitably masked forms (of ammonia) in cross-coupling amination reactions; they include allylamine,^[4a] benzophenone imine,^[4b,c] *tert*-butyl carbamate,^[4d,e] $\text{Li}[\text{N}(\text{SiMe}_3)_2]$,^[4f,g] $\text{Zn}[\text{N}(\text{SiMe}_3)_2]$,^[4h] solid-supported ammonia surrogates,^[5] the fluoroalkyl benzophenone imine reagent,^[6a-c] *N*-substituted-^FBoc carbamate (Boc = *tert*-butoxycarbonyl),^[6d] and amidines (developed by our research group)^[6e]. Obviously, the direct use of free ammonia is more economical and practical than using the ammonia surrogates. Recently, the highly efficient palladium-catalyzed synthesis of primary aromatic amines has been developed through couplings of aryl halides with ammonia under pressure.^[7] In the last decade great progress has been made in the copper-catalyzed Ullmann *N*-arylation reactions,^[8] but the efficiency of these reactions is highly depended on the involvement of suitable ligands. For example, the CuI/L -proline system was used to catalyze the couplings of aryl iodides with aqueous ammonia

or ammonium chloride to prepare primary arylamines at room temperature.^[9] Similarly, the $\text{CuI/2,4-pentanedione}$ system was used to catalyze the couplings of aryl iodides or bromides with aqueous ammonia at 90 °C to also give primary arylamines.^[10] Although the previous methods are effective, a more convenient and efficient approach to primary aromatic amines is desired. Aromatic boronic acids and their derivatives are common reagents, and they have been used in *N*-arylation of arylamines through the amination strategies developed by the research groups of Chan and Lam.^[11] However, to the best of our knowledge, there is no example for the preparation of primary aromatic amines by coupling reactions of aromatic boronic acids with aqueous ammonia. Herein, we report an easy and highly efficient copper-catalyzed method for the synthesis of primary aromatic amines in air at room temperature without the addition of a base, a ligand, or an additive.

Initially, phenylboronic acid was chosen as the model substrate to optimize the reaction conditions at room temperature. Catalysts, solvents, amino sources, and bases were investigated. As shown in Table 1, various copper catalysts were tested using aqueous ammonia (5 equiv relative to the amount of phenylboronic acid) in methanol as the amino source (Table 1, entries 1–9). The best activity was shown with Cu_2O (Table 1, entry 8). Under copper(0) catalysis, no aniline was formed and the major product was biphenyl, which was formed from the homocoupling of phenylboronic acid (Table 1, entry 9). The coupling reaction did not occur in the absence of copper catalyst (Table 1, entry 10). The effect of solvents was also investigated (compare Table 1, entry 8 with Table 1, entries 11–15), and methanol was the best choice. Several amino sources were screened (compare Table 1, entry 8 with Table 1, entries 16–19), and aqueous ammonia was the best substrate. The addition of base (K_2CO_3) inhibited the reactivity of the substrates (Table 1, entry 20). An extended reaction time lowered the yield because of the formation of a small amount of diphenylamine by-product (Table 1, entry 21). The reaction provided a lower yield when the temperature increased to 40 °C because the higher temperature decreased the solubility of NH_3 in the solvent (Table 1, entry 22). No desired product was observed in the absence of air (in a nitrogen atmosphere; Table 1, entry 23), which indicated that an oxidative process was involved in the formation of primary aromatic amines. The amount of catalyst required was investigated, and the results showed that 10 mol% of Cu_2O (relative to the aromatic boronic acid) was the best choice (compare Table 1, entry 8 with Table 1, entries 24 and 25). Therefore, our optimal

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Table 1: Copper-catalyzed coupling of phenylboronic acid with various amino sources: optimization of the reaction conditions.^[a]

$\text{C}_6\text{H}_5\text{B(OH)}_2 + \text{source of NH}_2 \xrightarrow[\text{air, RT}]{\text{catalyst, solvent}} \text{C}_6\text{H}_5\text{NH}_2$				
Entry	Catalyst	Solvent	Source of NH ₂	Yield [%] ^[b]
1	CuCl ₂	MeOH	NH ₃ ·H ₂ O	31
2	Cu(OAc) ₂	MeOH	NH ₃ ·H ₂ O	42
3	CuSO ₄	MeOH	NH ₃ ·H ₂ O	0 ^[c]
4	CuO	MeOH	NH ₃ ·H ₂ O	8
5	CuI	MeOH	NH ₃ ·H ₂ O	22
6	CuBr	MeOH	NH ₃ ·H ₂ O	31
7	CuCl	MeOH	NH ₃ ·H ₂ O	0 ^[c]
8	Cu₂O	MeOH	NH₃·H₂O	76
9	Cu	MeOH	NH ₃ ·H ₂ O	0 ^[c]
10	–	MeOH	NH ₃ ·H ₂ O	0
11	Cu ₂ O	CHCl ₃	NH ₃ ·H ₂ O	43
12	Cu ₂ O	EtOH	NH ₃ ·H ₂ O	57
13	Cu ₂ O	CH ₃ CN	NH ₃ ·H ₂ O	74
14	Cu ₂ O	DMF	NH ₃ ·H ₂ O	52
15	Cu ₂ O	H ₂ O	NH ₃ ·H ₂ O	58
16	Cu ₂ O	MeOH	NH ₄ Cl	0 ^[c]
17	Cu ₂ O	MeOH	NH ₄ OAc	0 ^[c]
18	Cu ₂ O	MeOH	(NH ₄) ₂ CO ₃	8
19	Cu ₂ O	MeOH	NH ₄ OAc + K ₂ CO ₃	31
20	Cu ₂ O	MeOH	NH ₃ ·H ₂ O + K ₂ CO ₃	42
21	Cu ₂ O	MeOH	NH ₃ ·H ₂ O	65 ^[d]
22	Cu ₂ O	MeOH	NH ₃ ·H ₂ O	41 ^[e]
23	Cu ₂ O	MeOH	NH ₃ ·H ₂ O	0 ^[f]
24	Cu ₂ O	MeOH	NH ₃ ·H ₂ O	57 ^[g]
25	Cu ₂ O	MeOH	NH ₃ ·H ₂ O	75 ^[h]

[a] Reaction condition: room temperature (ca. 20 °C), reaction time (15 h), catalyst (0.1 mmol), phenylboronic acid (1 mmol), amino source (5 mmol), solvent (2 mL). [b] Yield of isolated product. [c] No aniline was observed, biphenyl was the major product. [d] Reaction time (20 h). [e] Reaction temperature (40 °C). [f] In a nitrogen atmosphere. [g] Cu₂O (0.05 mmol). [h] Cu₂O (0.2 mmol).

reaction condition for the synthesis of primary aromatic amines is as follows: 10 mol% of Cu₂O as the catalyst, aqueous ammonia as the amino source, methanol as the solvent, and the reaction was carried out in air at room temperature (ca. 20 °C).

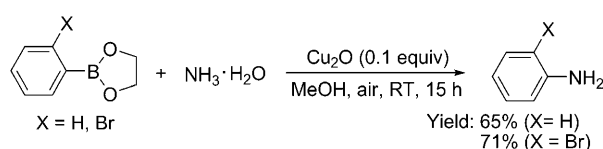
Next, we investigated the scope of the copper-catalyzed reaction with respect to the aromatic boronic acid. As shown in Table 2, all the substrates examined under the standard reaction condition provided good to excellent yields at room temperature. The substituted aromatic boronic acids containing electron-deficient groups showed slightly lower reactivity than those containing electron-rich or neutral groups. For example 3-nitrophenylboronic acid, with an electron-withdrawing group, provided a lower yield than aromatic boronic acids with an electron-donating groups (compare Table 2, entry 5 with entries 6–10). Higher reactivity was observed for 4-phenylbenzeneboronic acid and 1- or 2-naphthylboronic acid (Table 2, entries 11–13). The reaction tolerated a range of functional groups on the aryl ring with coupling occurring in the presence of carbon–halogen bonds (Table 2, entries 2–4), an hydroxy group (Table 2, entry 14), an aldehyde group (Table 2, entries 15 and 16), an ester group (Table 2, entry 17), a carboxyl group (Table 2, entry 18), an

Table 2: Copper-catalyzed synthesis of primary aromatic amines.^[a]

$\text{Ar-B(OH)}_2 + \text{NH}_3 \cdot \text{H}_2\text{O} \xrightarrow[\text{MeOH, air, RT}]{\text{Cu}_2\text{O (0.1 equiv)}} \text{Ar-NH}_2$					
Entry	ArB(OH) ₂	t [h]	Product	Yield [%] ^[b]	
1		1 a 15		2 a	80
2		1 b 16		2 b	87
3		1 c 20		2 c	89
4		1 d 18		2 d	74
5		1 e 20		2 e	72
6		1 f 16		2 f	87
7		1 g 12		2 g	93
8		1 h 12		2 h	88
9		1 i 12		2 i	92
10		1 j 12		2 j	92
11		1 k 15		2 k	90
12		1 l 16		2 l	92
13		1 m 16		2 m	86
14		1 n 18		2 n	89
15		1 o 18		2 o	83
16		1 p 15		2 p	88
17		1 q 20		2 q	78
18		1 r 24		2 r	65
19		1 s 12		2 s	89
20		1 t 15		2 t	92
21		1 u 16		2 u	84

[a] Reaction condition: temperature (ca. 20 °C), ArB(OH)₂ (1 mmol), NH₃·H₂O (25% aqueous solution, 5 mmol), Cu₂O (0.1 mmol), MeOH (2 mL). [b] Yield of isolated product.

amino group (Table 2, entry 19), and oxygen- or sulfur-containing heterocycles (Table 2, entries 20 and 21). The reaction with aryl boronic acids containing electron-donating and neutral groups yielded trace amount of diarylamine by-products, as arising from the reaction of aromatic boronic acids with primary arylamines. However, 2,6-dimethylphenylboronic acid and 2,4,6-trimethylphenylboronic acid did not produce the corresponding diarylamine by-products because of steric hindrance (Table 2, entries 9 and 10). Also, the diarylamine by-products were not observed for the substrates containing electron-withdrawing groups for the reaction times as shown in Table 2. To broaden the scope of substrates used, we carried out reactions of arylboronic acid esters with aqueous ammonia under the standard condition as shown in Scheme 1, and the corresponding primary arylamines were afforded in good yields.



Scheme 1. Reactions of arylboronic acid esters with aqueous ammonia under the standard reaction condition.

When methanol was used as the solvent, it could form hydrogen bonds with ammonia and thereby prevent the release of ammonia from solution. In addition, the use of methanol was favorable for the workup procedure because high-boiling-point solvents such as *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide are avoided. To the best of our knowledge, the present method is the simplest approach to primary aromatic amines.

In summary, we have developed a simple and highly efficient copper-catalyzed method for the synthesis of primary aromatic amines by couplings of aromatic boronic acids with inexpensive aqueous ammonia. The coupling reactions were performed in air at room temperature without the need for sealed reaction vessels and, importantly, a base, a ligand, or an additive was not necessary. The remarkable functional group tolerance means that this reaction will find wide applications in various fields.

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