The Use of Hydroxylamine Hydrochloride in the Chan–Lam Reaction: A Simple Access to Symmetric Diarylamines

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Abstract: A CuBr-catalyzed coupling reaction of hydroxylamine hydrochloride and arylboronic acids is described, providing a simple and efficient methodology for the synthesis of symmetric diaryl amines. The reaction shows good functional group tolerance.

Key words: copper(I)-catalyzed, arylboronic acids, diaryl amines, hydroxylamine hydrochloride, coupling reaction

Aromatic amines are widely used in the synthesis of natural products, pharmaceutical and agrochemical compounds, as well as polymers and materials.¹ Over the past several decades, extensive efforts have been directed toward C-N bond formation.² Arylboronic acids have been widely used in N-arylation of arylamines through the amination strategies developed by the research groups of Chan and Lam.³ The development of new processes using cheap and abundant amino sources as feedstocks in the synthesis of aromatic amines remains a highly desirable goal. Nevertheless, to the best of our knowledge, few examples have been reported. The employing of ammonia as an abundant and inexpensive amino source is attractive in organic synthesis.⁴⁻⁶ Recently, Fu described copper-catalyzed coupling reaction employing arylboronic acids and aqueous ammonia as reagents at room temperature affording primary arylamines.⁷ We also developed a facile method to access diarylamine through the copper-catalyzed coupling reaction of arylboronic acids with aqueous ammonia.8

Based on our previous work, we envisioned that hydroxylamine hydrochloride which is also an inexpensive chemical commodity might be utilized as an ammonia surrogate in the N-arylation reaction. Herein, we wish to report a simple and cheap copper(I)-catalyzed coupling reaction of hydroxylamine hydrochloride with arylboronic acids, providing the symmetric diarylamines in moderate to good yields.

Initial studies were conducted using hydroxylamine hydrochloride (1.2 equiv) and phenylboronic acid **1a** (0.2 mmol) in toluene as a model reaction under air in the presence of CuBr (20 mol%). Disappointingly, after the extensive screening of copper sources and solvents, no synthetically useful results were obtained. We realized that acid conditions provided by the hydroxylamine hy-

drochloride might inhibit the reaction. Thus, K_2CO_3 was added to the reaction system. To our delight, in the presence of 1.5 equivalents of K_2CO_3 , the yield increased to 35% in toluene (Table 1, entry 2). Among the solvents

Table 1 Screening for the Optimum Conditions^a

PhB(O 1a	H) ₂ + NH ₂ OH·H	Cl copper source Ph ₂ NH base, solvent 2a			
Entry	Copper source	Solvent	Base (equiv)	Yield (%)	
1	CuBr	1,4-dioxane	K ₂ CO ₃ (1.5)	<5	
2	CuBr	toluene	K ₂ CO ₃ (1.5)	35	
3	CuBr	MeOH	K ₂ CO ₃ (1.5)	23	
4	CuBr	DMF	K ₂ CO ₃ (1.5)	<5	
5	CuBr	MeCN	K ₂ CO ₃ (1.5)	80	
6	CuBr	MeCN	Na ₂ CO ₃ (1.5)	56	
7	CuBr	MeCN	$K_{3}PO_{4} \cdot 3H_{2}O(1.5)$	69	
8	CuBr	MeCN	Cs ₂ CO ₃ (1.5)	<5	
9	CuBr	MeCN	KOt-Bu (1.5)	15	
10	CuBr	MeCN	Li ₂ CO ₃ (1.5)	<5	
11	CuBr	MeCN	_	<5	
12	CuBr	MeCN	K ₂ CO ₃ (0.5)	<5	
13	CuBr	MeCN	K ₂ CO ₃ (1.0)	75	
14	CuBr	MeCN	K ₂ CO ₃ (2.0)	73	
15	Cu ₂ O	MeCN	K ₂ CO ₃ (1.5)	52	
16	Cu(OTf) ₂	MeCN	K ₂ CO ₃ (1.5)	78	
17	CuF ₂	MeCN	K ₂ CO ₃ (1.5)	71	
18	Cu(OAc) ₂	MeCN	K ₂ CO ₃ (1.5)	<5	
19	CuBr	MeCN	K ₂ CO ₃ (1.5)	70°	
20	CuBr	MeCN	K ₂ CO ₃ (1.5)	58 ^d	
21	-	MeCN	K ₂ CO ₃ (1.5)	<5	

 a All reactions were run with phenylboronic acid (0.2 mmol), $\rm NH_2OH\cdot HCl$ (0.24 mmol), copper (20 mol%), indicated base, solvent

(2 mL), 70 °C, 24 h.

^b Isolated yield.

^c CuBr (10 mol%).

^d CuBr (5 mol%).

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tested, acetonitrile was the best, and the yield was sharply increased to 80% in the presence of 1.5 equivalents of K_2CO_3 (Table 1, entry 5). Other bases, such as Na_2CO_3 and $K_3PO_4 \cdot 3H_2O$ were also efficient for such transformation and K_2CO_3 was the best (Table 1, entries 5–10). Further investigations revealed that the amount of K_2CO_3 had a significant effect on the reaction (Table 1, entries 11– 14). Several copper(I) or copper(II) sources were also examined, and CuBr turned out to be better than other ones. No product was formed in the absence of copper source (Table 1, entry 19).

With the optimized conditions in hand, we turned our attention to study the substrates scope. The results are summarized in Table 2. As expected, a series of functional groups on the phenyl ring of arylboronic acids, such as methyl, methoxy, chloro, fluoro, nitro, trifluoromethyl, acetyl, and carbomethoxy, were compatible under this procedure, and diaryl amines were isolated in moderate to good yields. The reaction efficiency was sensitive to the electronic property of the substituents, as arylboronic acids possessing electron-donating groups (e.g., Table 2, entries 2-6) generally delivered the products in higher yields than those of possessing electron-withdrawing groups (e.g., Table 2, entries 10–13). However, bis(4-methoxyphenyl)amine was isolated in moderate yield. ortho-Substituted substrate failed to deliver the diaryl amines. We reasoned that the hindrance of the aryl group of arylboronic acids had some effect on the reaction. It is worth noting that highly electron-deficient arylboronic acids were tolerated in the reaction. For example, 2j and 2k were subjected to the procedure, 50% and 55% yield of the diaryl amines product were isolated (Table 2, entries 8-11). Disappointingly, the feasibility of monoarylation of hydroxylamine hydrochloride failed.

A plausible reaction pathway was outlined in Scheme 1. In step 1, a Chan–Lam reaction of boronic acids with hydroxylamine, which released from hydroxylamine hydrochloride in the presence of base, formed phenyl hydroxylamine. Then the formed phenyl hydroxylamine transformed to aniline.⁹ Finally, aniline underwent the Chan–Lam reaction with boronic acids to produce the diaryl amines.

$$\begin{array}{cccc} \text{NH}_2\text{OH} \cdot \text{HCI} & \xrightarrow{\text{base}} & \text{NH}_2\text{OH} & \xrightarrow{\text{Cu(I)}} & \text{ArNH}_2\text{OH} \\ \end{array}$$

$$\xrightarrow{\text{ArNH}_2} & \xrightarrow{\text{Cu(I)}} & \text{Ar}_2\text{NH} \\ \end{array}$$



In summary, we have successfully developed a simple and facile copper(I)-catalyzed coupling reaction of arylboronic acids with hydroxylamine hydrochloride, providing the symmetric diaryl amines with moderate to good yields in one-pot.¹⁰ Importantly, this transformation is very practical as it does not require the use of strong bases or expensive ligands, and the rigorous exclusion of air/moisture is

 Table 2
 Reaction of Arylboronic Acids with Hydroxylamine Hydrochloride^a

ArB(OH) ₂	+ NH ₂ OH·HCI —	CuBr (20 mol%) K ₂ CO ₃ , MeCN	Ar ₂ NH
Entry	ArB(OH) ₂	Ar ₂ NH	Yield (%) ^b
1	B(OH) ₂	2a	80
2		2b	70
3	B(OH)2	2c	82
4	B(OH)2	2d	73
5	MeOB(O	2e	50
6	MeO B(OH) ₂	2f	80
7	СІ	2 g	72
8	FB(OH)2	2h	55
9		2i	40
10	B(OH) ₂	2j	50
11	F ₃ C	2k	55
12		2 1 B(OH) ₂	75
13	MeOC B(OH)	2m	84

^a Reaction conditions: arylboronic acid (0.2 mmol), NH₂OH·HCl (0.24 mmol), CuBr (5.7 mg, 20 mol%), K₂CO₃ (41.4 mg, 0.3 mmol), MeCN (2 mL), 70 °C, 24 h.
^b Isolated yield.

not required. Ongoing work seeks to gain further insights into the mechanism of this reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (10) General Procedure
 - Under air, a reaction tube was charged with arylboronic acid (0.2 mmol), NH₂OH·HCl (0.24 mmol), CuBr (5.7 mg, 20 mol%), K₂CO₃ (41.4 mg, 0.3 mmol), MeCN (2 mL) at 70 °C for 24 h. After the completion of the reaction, as monitored by TLC, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on a silica gel to give the product.