Ligand-free cross-coupling of boronic acids with $Cu(NO_3)_2$ complexes of amines in aqueous media

Juan Xu and Jia Rong Li*

School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing 100081, P. R. China

The efficient conversion of boronic acids, both arylboronic acids and alkylboronic acids, to the corresponding amines in water was accomplished in moderate to good yields using $Cu(NO_3)_2$ complexes of amines as the nitrogen source. The coupling reactions were performed in water at 30 °C for 2 hours.

Keywords: boronic acid, $Cu(NO_3)_2$ complexes of amines, amination in water

Amines are important compounds found throughout the pharmaceutical, bioactive natural products and agrochemical industries.[1,2] Establishing efficient methods for the construction of C–N bond is currently an active area in organic synthesis. Transition-metal-catalysed transformations of aromatic halides and tosylates have been used in the synthesis of arylamines,[3–5] and nitroarenes.[6] However, this methodology has been hampered by some shortcomings which included the use of expensive, toxic catalysts and ligands for palladium catalysis or harsh reaction conditions and limited substrate scope for copper catalysis.

Aryl boron compounds are common chemicals and they are easily prepared from readily available aryl halides and tosylates. The aryl boron compounds have been used as the starting materials to make aromatic compounds containing various functional groups (including arylamines[7] and nitroarenes[8,9]) through an aerobic oxidative strategy. For example, Chan and Lam have described a $Cu(OAc)_2$-promoted N-arylation of commercially available arylboronic acids with imidazoles at room temperature.[10–13] Many extensions and applications of this new methodology have been reported.[14–19] And various efficient catalysts have been developed that allow amines to be effective coupled with aryl boronic acids.[20–29] Even so, Lam's method[12] requires more than a stoichiometric amount of oxidant such as pyridine *N*-oxide, TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] or NMO (*N*-methylmorpholine-*N*-oxide) as well as Et_3N or pyridine and elevated temperature, whereas the system described by Buchwald[14] requires the addition of a stoichiometric amount of 2,6-lutidine as well as myristic acid and gives a low yield (32%).

In modern organic synthesis, the ideal reaction conditions include the use of cheap, highly efficient catalyst systems, environment friendly water as the solvent, room temperature reactions under air (without using air) and easy workup procedures after reactions. Here, we report a convenient and effective amination of boronic acid using $Cu(NO_3)$ complexes of amines as nitrogen source without ligand in water at 30 °C for 2 hours with moderate to good yield.[30–32]

Using the reaction of phenylboronic acid as a template, various metal complexes of piperidine were screened in water (Table 1). Metal complexes of piperidine such as $ZnCl_2$–$2NH(CH_2)_5$–2HCl, $CuCl_2$–$2NH(CH_2)_5$–2HCl and $Cu(NO_3)_2$–$(CH_2)_5NH$ were investigated and it was found that only $Cu(NO_3)_2$–$(CH_2)_5NH$ gave the desired product (entries 1–4). Bases such as Et_3N, $NaHCO_3$, Na_2CO_3, K_2CO_3 and NaOH were found to facilitate this coupling reaction and among them Et_3N is the best (entries 4-9). It needs to be emphasised is that the $Cu(NO_3)_2$ complexes combine several advantageous features such as solid, stable in air, no smell and excellent water-solubility.

Under the optimised condition, the results obtained with boronic acids and $Cu(NO_3)_2$ complexes of amines are shown in Table 2. The results indicate clearly that this protocol is general and is applicable for reactions of a wide variety of electron-rich, electron-deficient, and neutral arylboronic acids and provide the corresponding arylamines in moderate yields. Various amines, such as primary alkylamine (entry 1), dialkylamine (entry 2), cyclic alkylamine (entry 3) and aromatic amine (entry 4), were all suitable amines for the amination of phenylboronic acid. As for arylboronic acids with an electron-withdrawing group (*e.g.* *p*-CF_3, *p*-Cl) and Naphthalen-2-ylboronic acid could be substituted by ring alkylamine (entries 5–7). Arylboronic acids with an electron-donating group (eg. *p*-CH_3) generated expected products bearing *n*-propyl (entry 8), morpholinyl (entry 9) and phenyl (entry 10). Meanwhile, we were pleased to observe that when trans-beta- styreneboronic acid (sp2) treated with $Cu(NO_3)_2$ complexes of *n*-propylamine, the corresponding product were obtained (entry 11).

Phenethylboronic acid (sp3) had no reaction with all $Cu(NO_3)_2$ complexes of amines. Electron-deficient pyridin-4-ylboronic acid was converted into pyridin-4-ol when reacted with $Cu(NO_3)_2$ complexes of amines.

Although comprehensive studies are required to elucidate the mechanistic details of the present reaction, a possible intermediate is presented in Scheme 1. Comparing entry 4 with entry 5 in Table 1, the product was phenol if there was no Et_3N in system. So we consider that[33] $Cu(NO_3)_2$ complex of amine could become $Cu(NR^1R^2)_2$ under the conditions of Et_3N. Then $Cu(NR^1R^2)_2$ reacted with boronic acid to give the amination product.

In conclusion, the construction of C–N bond was achieved effectively by $Cu(NO_3)_2$ complexes of amines as nitrogen source under mild condition. It is environmentally friendly because it uses water as a reaction medium for organic synthesis.

Experimental

ESI-MS were recorded with a ZAB-HS mass spectrometer in the positive ion mode.

Synthesis of $Cu(NO_3)_2$ complex of amine; general procedure

A complex of copper nitrate (10 mmol) and amine (10 mmol) was refluxed in ethanol (25 mL) for 10 hours. After the reaction was completed, ethanol was evaporated under vacuum conditions.

Table 1 Effect of metal complex and base[a]

Entry	Metal complexes of piperidine	Base	Product	Yield/%
1	$ZnCl_2$–$2NH(CH_2)_5$–2HCl	K_2CO_3	PhOH	100
2	$ZnCl_2$–$2NH(CH_2)_5$–2HCl (CuCl as catalyst)	K_2CO_3	PhOH	100
3	$CuCl_2$–$2NH(CH_2)_5$–2HCl	K_2CO_3	PhOH	100
4	$Cu(NO_3)_2$–$(CH_2)_5NH$	Et_3N	$PhN(CH_2)_5$ **1a**	64
5	$Cu(NO_3)_2$–$(CH_2)_5NH$		PhOH	100
6	$Cu(NO_3)_2$–$(CH_2)_5NH$	$NaHCO_3$	$PhN(CH_2)_5$	50
7	$Cu(NO_3)_2$–$(CH_2)_5NH$	Na_2CO_3	$PhN(CH_2)_5$	48
8	$Cu(NO_3)_2$–$(CH_2)_5NH$	K_2CO_3	$PhN(CH_2)_5$	45
9	$Cu(NO_3)_2$–$(CH_2)_5NH$	NaOH	$PhN(CH_2)_5$	36

[a] Reaction conditions: phenylboronic acid (1 mmol), metal complexes of piperidine (1 mmol) and base (1.2 mmol) were stirred in water (2 mL) at 30 °C for 2 hours.

* Correspondent. E-mail: jrli@bit.edu.cn

Table 2 Amination of boronic acid [a]

Entry	Boronic acid [b]	$Cu(NO_3)_2$ complex of Amine	Product	Yield/%[c]
1	$PhB(OH)_2$	$Cu(NO_3)_2$–$NH_2(CH_2)_2CH_3$	$PhNH(CH_2)_2CH_3$ **2a**	58
2		$Cu(NO_3)_2$–$NH(CH_3)_2$	$PhN(CH_3)_2$ **2b**	60
3		$Cu(NO_3)_2$–$NH(CH_2CH_2)_2O$	$PhN(CH_2)_4O$ **2c**	63
4		$Cu(NO_3)_2$–$NH_2C_6H_5$	PhNHPh **2d**	51
5	4-CF_3–C_6H_4–$B(OH)_2$	$Cu(NO_3)_2$–$NH(CH_2CH_2)_2O$	4-CF_3–C_6H_4–$N(CH_2CH_2)_2O$ **2e**	68
6	4-Cl–C_6H_4–$B(OH)_2$	$Cu(NO_3)_2$–$NH(CH_2CH_2)_2O$	4-Cl–C_6H_4–$N(CH_2CH_2)_2O$ **2f**	65
7	2-Naphth-$B(OH)_2$	$Cu(NO_3)_2$–$NH(CH_2CH_2)_2O$	2-Naphth–$N(CH_2CH_2)_2O$ **2g**	62
8	4-CH_3–C_6H_4–$B(OH)_2$	$Cu(NO_3)_2$–$NH_2(CH_2)_2CH_3$	4-CH_3–C_6H_4–$NH(CH_2)_2CH_3$ **2h**	59
9		$Cu(NO_3)_2$–$NH(CH_2CH_2)_2O$	4-CH_3–C_6H_4–$N(CH_2CH_2)_2O$ **2i**	54
10		$Cu(NO_3)_2$–$NH_2C_6H_5$	4-CH_3–C_6H_4–NHC_6H_5 **2j**	48
11	Ph–CH=CH–$B(OH)_2$	$Cu(NO_3)_2$–$NH_2CH_2CH_2CH_3$	Ph–CH=CH–$NH(CH_2)_2CH_3$ **2k**	40

[a] Reaction conditions: boronic acid (1mmol), $Cu(NO_3)_2$ complex of Amine (1mmol), Et_3N (1.2 mmol) were stirred in water (2 mL) at 30 °C for 2 hours. [b] All boronic acids were obtained from J&K chemical. [c] Yields refers to isolated pure product.

$$Cu(NO_3)_2\text{-}2NHR^1R^2 \xrightarrow{Et_3N} Cu(NR^1R^2)_2 \xrightarrow{R\text{-}B(OH)_2} R\text{-}NR^1R^2$$

Scheme 1 The possible intermediate.

Synthesis of amines; general procedure

Boronic acid (1 mmol), $Cu(NO_3)_2$ complex of amine (1 equiv.), Et_3N (1.2 equiv.) were stirred in water (2 mL) at 30 °C for 2 hours. The progress of the reaction was monitored by TLC. The system was filtered, adjusted pH=8 with $NaHCO_3$ (sat.) and extracted with ethyl acetate, dried over Na_2SO_4, then evaporated to get corresponding amine.

1-Phenylpiperidine (**1a**): Lit.[34] b.p. 250–258 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.25 (m, 2H, ArH), 6.94–6.79 (m, 3H, ArH), 3.46–3.35 (m, 4H, $2CH_2$), 1.59–1.53 (m, 6H, $3CH_2$); MS (ESI) *m/z* (%): 162.1 ([M+H]$^+$, 100).

N-Propylaniline (**2a**): Lit.[35] b.p. 218–222 °C, MS (ESI) *m/z* (%): 136.1 ([M+H]$^+$, 100).

N,N-Dimethylaniline (**2b**): Lit.[36] b.p. 200–205 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.31 (m, 2H, ArH), 6.85–6.80 (m, 3H, ArH), 3.03 (s, 6H, $2CH_3$); MS (ESI) *m/z* (%): 122.1 ([M+H]$^+$, 100).

4-Phenylmorpholine (**2c**): M.p. 51–53 °C (lit.[37] 53–54 °C), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.25 (m, 2H, ArH), 6.93–6.78 (m, 3H, ArH), 3.65 (t, J = 7.0 Hz, 4H, $2CH_2$), 3.18 (t, J = 7.0 Hz, 4H, $2CH_2$); MS (ESI) *m/z* (%): 164.1 ([M+H]$^+$, 100).

Diphenylamine (**2d**): m.p. 53–55 °C (lit.[38] 54–55 °C), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.23 (m, 4H, ArH), 7.13–7.05 (m, 4H, ArH), 6.94–6.90 (m, 2H, ArH); MS (ESI) *m/z* (%): 170.1 ([M+H]$^+$, 100).

4-(4-(Trifluoromethyl)phenyl)morpholine (**2e**): M.p. 56–58 °C (lit.[39] 57–58 °C), MS (ESI) *m/z* (%): 190.1 ([M+H]$^+$, 100).

4-(4-Chlorophenyl)morpholine (**2f**): M.p. 68–70 °C (lit.[40] 69–70 °C), MS (ESI) *m/z* (%): 198.1 ([M+H]$^+$, 100), 200.1.

4-(Naphthalen-2-yl)morpholine (**2g**): M.p. 87–88 °C (lit.[41] 90 °C), MS (ESI) *m/z* (%): 214.1 ([M+H]$^+$, 100).

4-Methyl-N-propylaniline (**2h**): Lit.[42] b.p. 231–233 °C, MS (ESI) *m/z* (%): 150.1 ([M+H]$^+$, 100).

4-(p-Tolyl)morpholine (**2i**): M.p. 71–73 °C (lit.[43] 75 °C), MS (ESI) *m/z* (%): 178.1 ([M+H]$^+$, 100).

4-Methyl-N-phenylaniline (**2j**): M.p. 87–89 °C (lit.[44] 87–89 °C), MS (ESI) *m/z* (%): 184.1 ([M+H]$^+$, 100).

(E)-N-Styrylpropan-1-amine (**2k**): Lit.[45] b.p. 129–131 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.58 (m, 2H, ArH), 7.34–7.41 (m, 3H, ArH), 6.45 (d, J = 18.0 Hz, 1H, CH), 5.38 (t, J =18.0 Hz, 1H, CH), 2.85 (t, 2H, CH_2), 1.59 (m, 2H, CH_2), 0.95 (t, 3H, CH_3); MS (ESI) *m/z* (%): 162.1 ([M+H]$^+$, 100).

This research was supported by the grant of Beijing Institute of Technology.

Received 4 January 2012; accepted 3 April 2012
Paper 1201080 doi: 10.3184/174751912X13364681530823
Published online: 26 June 2012

References

1 J. Louie, and J.F. Hartwig, *J. Am. Chem. Soc.*, 1997, **119**, 11695.
2 R.A. Singer, J.P. Sadighi, and S.L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 213.
3 Q. Shen, and J.F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 10028.
4 N. Xia, and M. Taillefer, *Angew. Chem. Int. Ed.*, 2009, **48**, 337.
5 H. Xu, and C. Wolf, *Chem. Commun.*, 2009, 3035.
6 B.P. Fors, and S.L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 12898.
7 H. Rao, H. Fu, Y. Jiang, and Y. Zhao, *Angew. Chem. Int. Ed.*, 2009, **48**, 1114.
8 G.K.S. Prakash, C. Panja, T. Mathew, V. Surampudi, N.A. Petasis, and G.A. Olah, *Org. Lett.*, 2004, **6**, 2205.
9 G.K.S. Prakash, and T. Mathew, *Angew. Chem. Int. Ed.*, 2010, **49**, 1726.
10 D.M.T. Chan, K.L. Monaco, R.P. Wang, and M.P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933.
11 D.A. Evans, J.L. Katz, and T.R. West, *Tetrahedron Lett.*, 1998, **39**, 2937.
12 P.Y.S. Lam, C.G. Clark, S. Saubern, J. Adams, M.P. Winters, D.M.T. Chan, and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941.
13 A.P. Combs, S. Saubern, M. Rafalski, and P.Y.S. Lam, *Tetrahedron Lett.*, 1999, **40**, 1623.
14 J.C. Antilla, and S.L. Buchwald, *Org. Lett.*, 2001, **3**, 2077.
15 P.Y.S. Lam, G. Vincent, D. Bonne, and C.G. Clark, *Tetrahedron Lett.*, 2003, **44**, 4927.
16 C.F. Zhou, D.P. Yang, X.F. Jia, and L.X. Zhang, *Synlett*, 2009, **19**, 3198.
17 Z. Rankovic, J.Q. Cai, X. Fradera, M. Dempster, A. Mistry, A. Mitchell, C. Long, E. Hamilton, A. King, S. Boucharens, C. Jamieson, J. Gillespie, I. Cumming, J. Uitdehaag, and M. van Zeeland, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1488.
18 C.H. Park, K. Chun, B.Y. Joe, J.S. Park, Y.C. Kim, J.S. Choi, D.K. Ryu, S.H. Koh, G.W. Cho, S.H. Kim, and M.H. Kim, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2250.
19 Y. Liu, Y. Xia, Y.T. Fan, A. Maggiani, P. Rocchi, F. Qu, J.L. Iovanna, and L. Peng, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2503.
20 J.P. Collman, M. Zhong, C. Zhang, and S. Costanzo, *J. Org. Chem.*, 2001, **66**, 7892.
21 A.P. Combs, S. Tadesse, M. Rafalski, T.S. Haque, and P.Y.S. Lam, *J. Comb. Chem.*, 2002, **4**, 179.
22 S. Yu, J. Saenz, and J.K. Srirangam, *J. Org. Chem.*, 2002, **67**, 1699.
23 G.W. Kabalka, and S.K. Guchhait, *Org. Lett.*, 2003, **5**, 4129.
24 T. Uemura, and N. Chatani, *J. Org. Chem.*, 2005, **70**, 8631.
25 K.R. Reddy, N.S. Kumar, B. Sreedhar, and M.L. Kantam, *J. Mol. Catal. A: Chem.*, 2006, **252**, 136.
26 Q. Dai, C.Z. Ran, and R.G. Harvey, *Tetrahedron*, 2006, **62**, 1764.
27 S.B. Liu, Y. Yu, and L.S. Liebeskind, *Org. Lett.*, 2007, **9**, 1947.
28 Y.Q. Fang, and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538.
29 Y. Li, L.X. Gao, and F.S. Han, *Chem. Eur. J.*, 2010, **16**, 7969.
30 D.J. Darensbourg, E.M. Longridge, B. Khandelwal, and J.H. Reibenspies, *J. Coord. Chem.*, 1994, **32**, 27.
31 N.B. Melęnikova, I.D. Ioffe, and L.A. Tsareva, *Chem. Nat. Compd.*, 2002, **38**, 33.
32 X. Jia, W. Zhu, Y. Zhang, and X. Yan, *J. Mol. Struct.*, 2002, **604**, 159.
33 A.J. Paine, *J. Am. Chem. Soc.*, 1987, **109**, 1496.
34 R. Lukes and M. Ferles, *Chem. Listy*, 1956, **50**, 1471.
35 W.J. Hickinbottom, *J. Chem. Soc.*, 1930, 992.
36 G.W. Gribble and C.F. Nutaitis, *Synthesis*, 1987, **8**, 709.
37 Z. Zhang, J. Mao, D. Zhu, F. Wu, H. Chen and B. Wan, *Tetrahedron*, 2006, **62**, 4435.
38 F.L. Scott, A. Ahearne and J. Reilly, *J. Org. Chem.*, 1957, **22**, 1688.
39 M.G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E.A.B. Kantchev, C.J. O'Brien, M. Sayah and C. Valente, *Chemistry—Eur. J.*, 2008, **14**, 2443.
40 K.W. Anderson, M. Mendez-Perez, J. Priego and S. L. Buchwald, *J. Org. Chem.*, 2003, **68**, 9563.
41 L.H. Cretcher and W. H. Pittenger, *J. Am. Chem. Soc.*, 1925, **47**, 163.
42 H.H. Stroh, *Chem. Ber.*, 1958, **91**, 2645.
43 M.J. Cawley, F.G.N. Cloke, R. J. Fitzmaurice, S.E. Pearson, J.S. Scott and S. Caddick, *Org. Biomol. Chem.*, 2008, **6**, 2820.
44 B.P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 15914.
45 J. Braun and O. Braunsdorf, *Ber. Chem.*, 1921, **54**, 2081.