Tetrahedron Letters 54 (2013) 2713–2716

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-catalyzed aerobic oxidative amination of arylboronic acid with aminal under base-free conditions

Yanping Zhou [a], Yinjun Xie [b], Lei Yang [b], Pan Xie [b], Hanmin Huang [a,b,*]

[a] College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou, 310014, PR China
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, PR China

ARTICLE INFO

Article history:
Received 28 December 2012
Revised 7 March 2013
Accepted 15 March 2013
Available online 24 March 2013

Keywords:
Copper
Oxidative amination
C–N cleavage
Aminal
Base-free

ABSTRACT

A new process involving copper-catalyzed oxidative amination reaction of various arylboronic acids with aminals under mild conditions has been developed. The key copper-amide species involved in the C–N bond-forming process was generated via C–N bond cleavage of aminal under base-free conditions. Moderate yields of desired amination products can be obtained under mild conditions when air was served as oxidant and $PhCO_2H$ was used as an additive.

Introduction

Aromatic amines represent one of the most important and abundant compounds in chemistry and can be found in bulk chemicals, fine chemicals, natural products as well as drugs.[1] Therefore, the development method for the synthesis of aromatic amines continues to attract interest from both academia and industry.[2] Among many types of methods synthesis documented, copper-mediated Ullmann and Goldberg coupling,[2a] Pd-catalyzed Buchwald–Hartwig reaction,[3] and copper-catalyzed Chan-Lam coupling[4] have stood out as powerful tools to fulfill these transformations. Mechanistically, the metal-amide species was generally required to furnish the corresponding C–N bond-forming process in almost all of the above-mentioned reactions.[5] Generally, to generate the corresponding metal-amide species, the stoichiometric amount of base is typically used to promote the aminometallation, which dramatically decreases the atom economy and functional group tolerance. To circumvent this problem, new strategy for generation of metal-amide species in the absence of base would be highly desirable.

As part of our program to develop novel synthetic methods to amines, we recently reported a copper-catalyzed oxidative C–H amination of azoles using tertiary amines as nitrogen group sources via cleavage of C–H and C–N bonds under base-free conditions.[6] The important copper-amide species involved in the C–N bond formation process for this reaction was believed to be generated by hydrolysis of the iminium-type intermediate, which was generated in situ via cleavage of sp^3 C–H bond of the tertiary amines. However, a limitation of the established catalyst system is that the relatively higher reaction temperature (120 °C) is required for generation of the iminium-type intermediate. Our continuing efforts in C–N bond-forming process promoted us to explore new strategy for generating active iminium-type intermediate under mild reaction conditions. Aminal is recognized as a surrogate of imine and widely used as electrophile in the metal-catalyzed nucleophilic addition reactions.[7] The C–N bond in those molecules is easily cleaved under mild conditions for generation of iminium ion due to the higher leaving ability of the amino group, and copper-amide species can be formed by hydrolysis of the iminium ion. Intrigued by this unique feature, we reasoned that a new type of C–N bond formation reaction would be established by using aminal as a nitrogen source. Herein, we describe a novel copper catalyzed amination reaction of aminals with arylboronic acids to access the aromatic amines through C–N cleavage under mild and base-free conditions (Scheme 1). To the best of our knowledge, this is the first copper-catalyzed coupling reaction of aminals with arylboronic acids to give the aromatic amine products.

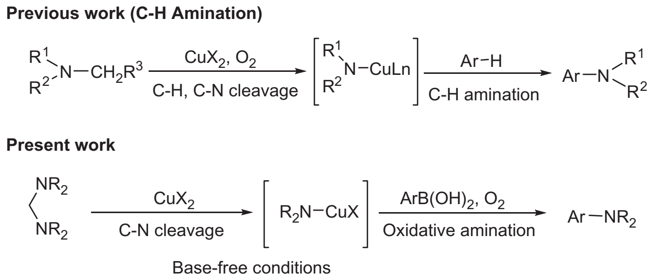
Results and Discussion

Initially, the copper-catalyzed aerobic oxidative amination of aminal **2a** with phenylboronic acid **1a** was selected as a model reaction and molecular oxygen was utilized as the oxidant

---

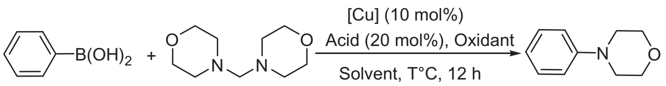
* Corresponding author. Tel.: +86 931 4968326; fax: +86 931 4968129.
E-mail address: hmhuang@licp.cas.cn (H. Huang).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.058



Scheme 1. New strategy for Cu-catalyzed C–N bond formation reactions.

Table 1
Optimization of reaction conditions[a]



1a **2a** **3a**

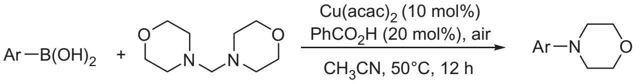
Entry	Catalyst	Acid	Solvent	T (°C)	Yield[b] (%)
1	CuF_2	HOAc	DCM	25	9
2	$CuCl_2$	HOAc	DCM	25	11
3	$CuBr_2$	HOAc	DCM	25	11
4	$Cu(acac)_2$	HOAc	DCM	25	20
5	$Cu(OTf)_2$	HOAc	DCM	25	7
6	$Cu(acac)_2$	HCO_2H	DCM	25	11
7	$Cu(acac)_2$	$C_2H_5CO_2H$	DCM	25	21
8	$Cu(acac)_2$	F_3CCO_2H	DCM	25	3
9	$Cu(acac)_2$	$PhCO_2H$	DCM	25	26
10	$Cu(acac)_2$	$PhCO_2H$	Toluene	25	7
11	$Cu(acac)_2$	$PhCO_2H$	CH_3CN	25	34
12	$Cu(acac)_2$	$PhCO_2H$	THF	25	NR
13	$Cu(acac)_2$	$PhCO_2H$	CH_3CN	40	49
14	$Cu(acac)_2$	$PhCO_2H$	CH_3CN	50	57
15	$Cu(acac)_2$	$PhCO_2H$	CH_3CN	60	56
16[c]	$Cu(acac)_2$	$PhCO_2H$	CH_3CN	50	53
17[d]	$Cu(acac)_2$	$PhCO_2H$	CH_3CN	50	53

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [Cu] (10 mol %), acid (20 mol %) in solvent (1 mL) under O_2 (1 atm) for 12 h.
[b] Isolated yield.
[c] Compound **2a** (0.3 mmol).
[d] Using 0.3 mmol of **2a**, air as oxidant.

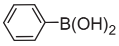
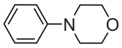
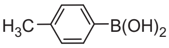
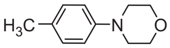
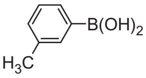
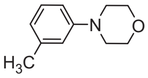
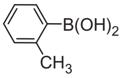
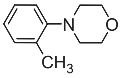
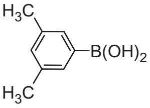
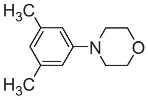
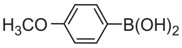
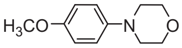
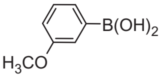
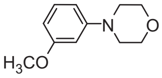
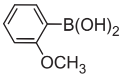
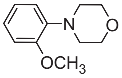
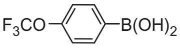
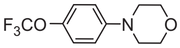
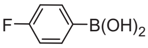
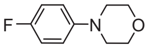
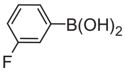
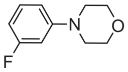
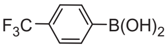
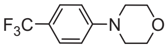
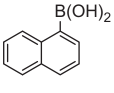
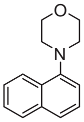
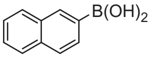
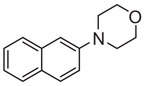
(Table 1). First, different copper catalysts were tested in DCM with HOAc as the additive. $Cu(acac)_2$ showed the best result with 20% yield of the desired product **3a** (Table 1, entry 4), while other copper catalysts gave lower yields. This result indicated that our proposed process was indeed possible, although the amine **3a** was obtained in a relative lower yield. Encouraged by this result, the effect of other acidic additives was further investigated and the result demonstrated that this reaction proceeded most efficiently when $PhCO_2H$ served as the additive (Table 1, entry 9). With $Cu(acac)_2$ as catalyst and $PhCO_2H$ as the additive, solvent effect was also examined and the highest product yield was obtained in CH_3CN (Table 1, entry 11), and other solvents gave inferior yields. Investigation of temperature revealed that running the reaction at 50 °C instead of 25 °C, 57% yield of desired product **3a** could be obtained under the other identical reaction conditions (Table 1, entry 14). Further optimization of the reaction conditions demonstrated that the aromatic amine compound **3a** could be also obtained in 53% yield even the ratio of **2a**/**1a** was decreased from 1/1 to 0.6/1 (Table 1, entry 16), which means that the two amine moieties contained in the aminal are participated in the reaction. Finally, to our delight, the reaction still proceeded well and the desired product could be yielded in the same level when air instead of molecular oxygen served as the oxidant (Table 1, entry 17).

With the optimized reaction conditions in hand, we subsequently examined the scope of the arylboronic acids and the results are shown in Table 2.[8] This reaction was successfully performed with different arylboronic acids. The arylboronic acids containing electron-donating groups at the *para* or *meta* position of the benzene ring could afford the desired products in moderate yields (Table 2, entries 2, 3, 5–7, and 9). An obvious steric hindrance effect on the reactivity was observed, which was demonstrated by the reactivities of *o*-tolylboronic acid **1d** and 2-methoxyphenylboronic acid **1h**. When both of them were subjected to the reaction, only trace amounts of corresponding products could be obtained under the optimized reaction conditions (Table 2, entries 4 and 8). The arylboronic acids bearing electron-withdrawing groups could also be transformed smoothly to their corresponding amines in moderate yields (Table 2, entries 10-12). To expand the substrate scope, 1- and 2-naphthalene boronic acids

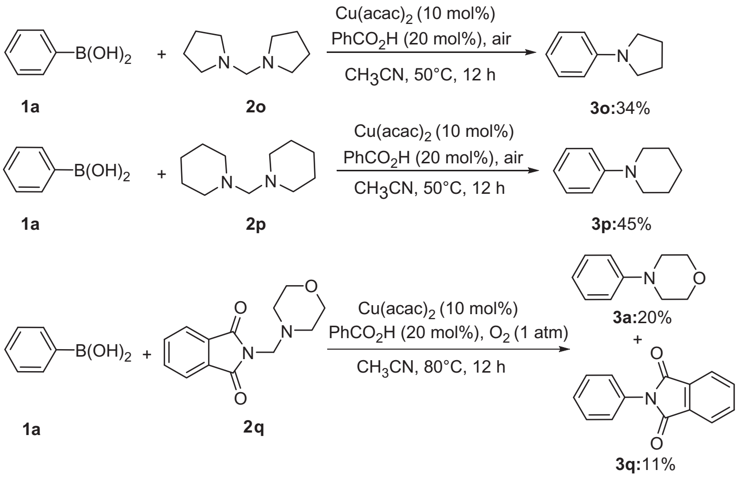
Table 2
Substrate scope of the arylboronic acids[a]



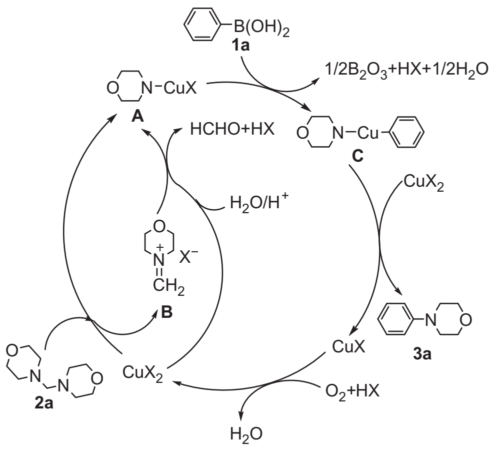
1 **2a** **3**

Entry	Substrate **1**	Product **3**	Yield[b] (%)
1	 **1a**	 **3a**	53
2	 **1b**	 **3b**	56
3	 **1c**	 **3c**	56
4	 **1d**	 **3d**	Trace
5	 **1e**	 **3e**	57
6	 **1f**	 **3f**	43
7	 **1g**	 **3g**	48
8	 **1h**	 **3h**	Trace
9	 **1i**	 **3i**	48
10	 **1j**	 **3j**	53
11	 **1k**	 **3k**	57
12	 **1l**	 **3l**	39
13	 **1m**	 **3m**	12
14	 **1n**	 **3n**	57

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.3 mmol), $Cu(acac)_2$ (10 mol %), $PhCO_2H$ (20 mol %) in CH_3CN (1 mL) under air at 50 °C for 12 h.
[b] Yield of isolated product.



Scheme 2. Reactivity of various aminals toward cross-coupling with phenylboronic acid.



Scheme 3. Plausible reaction mechanism.

were tested in the oxidative amination reaction. 2-naphthalene boronic acid **1n** could give the desired product **3n** in 57% yield (Table 2, entry 14), but 4-(naphthalen-1-yl)morpholine **3m** could be only obtained in a relatively lower yield in the same reaction conditions (Table 2, entry 13).

To further investigate the scope of the reaction, several aminals derived from other secondary amines were also subjected to this procedure under the optimized reaction conditions. To our delight, aminals derived from both pyrroline **2o** and piperidine **2p** could also prove to be appropriate substrates for this transformation and the corresponding amine products were obtained in 34% and 45% yield, respectively. Besides, the unsymmetrical aminal **2q** could also undergo the coupling reaction and furnish the desired product **3a** as well as **3q** in moderate yield. This result further suggested that the two amine moieties of the aminal could participate in the coupling reaction and transform to their corresponding products under the reaction conditions (Scheme 2).

Although the mechanism of this transformation are not clear yet at the present stage, on the basis of the results we obtained previously,[6] a plausible mechanism for this cross-coupling reaction can be proposed as shown in Scheme 3. Initially, the aminal **2a** could react with Cu(acac)$_2$ to generate copper amide **A** and iminium **B**. The iminium **B** could react with Cu(acac)$_2$ quickly by hydrolysis to afford copper-amide intermediate **A** which could be promoted by the benzoic acid. Next, complex **C** could be formed by transmetalation with the arylboronic acid. The subsequent reductive elimination provides the corresponding amine products in the presence of Cu(II). The released Cu(I) species could be oxidated by O$_2$ to regenerate Cu(II) and complete the catalytic cycle.[9]

Conclusions

In summary, we have developed a novel copper-catalyzed amination reaction of arylboronic acids with aminals for the synthesis of aromatic amines. With air as oxidant and PhCO$_2$H as additive, the copper-catalyzed reaction could proceed smoothly and give the corresponding amine products in moderate yields under mild conditions. Further exploration of this powerful strategy in establishing new C–N bond formation reactions and reaction mechanism are underway in our laboratory.

Acknowledgments

Financial support provided by the National Natural Science Foundation of China (21172226, 21133011 and 21222203), and Chinese Academy of Sciences is gratefully acknowledged.

Supplementary data

Supplementary data (experimental procedures and full characterization of all products including ^{1}H, ^{13}C NMR and HRMS spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.058.

References and notes

1. (a) Lawrence, S. A. *Amines: Synthesis, Properties and Application*; Cambridge University Press: Cambridge, 2004; (b) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.
2. For reviews: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651; (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450; (d) Carril, M.; SanMartin, R.; Domínguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639; (e) Aubin, Y.; Fischmeister, C.; Thomas, C. M.; Renaud, J.-L. *Chem. Soc. Rev.* **2010**, *39*, 4130; (f) Leyva-Pérez, A.; Sabater, M. J.; Corma, A. *Chem. Rev.* **2011**, *111*, 1657; (g) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41*, 2463; (h) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929.
3. For reviews, see: (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338; (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534; (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27; For selected reports on arylamine formation, see: (d) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969; (e) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901; (f) Mann, G.; Driver, M. S.; Fernández-Rivas, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 827; (g) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158;

(h) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *128*, 10028; (i) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586; (j) Ueda, S.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8944; (k) Ueda, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 10364.

4. For leading references: (a) Chan, D. M. T.; Monaca, K. L.; Wanag, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933; (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941; (c) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623; (d) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600; (e) Lam, P. Y. S.; Clark, C. G.; Subern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674; (f) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077; (g) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397; (h) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414; (i) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**; (j) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3642; (k) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953.
5. For studies on the metal-amide species for C–N bond formation reactions, see: (a) Widenhofer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745; (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755; (c) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534; (d) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971; (e) Giri, R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 15860.
6. (a) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522; (b) Xie, Y.; Hu, J.; Wang, Y.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 20613; (c) Xie, Y.; Qian, B.; Xie, P.; Huang, H. *Adv. Synth. Catal.* **2013**. http://dx.doi.org/10.1002/adsc.201200944. Early view.
7. (a) Katritzky, A. R.; Shobana, N.; Harris, P. A. *Tetrahedron Lett.* **1991**, *32*, 4247; (b) Tan, C. Y. K.; Wainman, D.; Weaver, D. F. *Bioorg. Med. Chem.* **2003**, *11*, 113; (c) Wang, X.; Li, J.; Zhang, Y. *Synth. Commun.* **2003**, *33*, 3575; (d) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555; (e) Hatano, B.; Nagahashi, K.; Kijima, T. *J. Org. Chem.* **2008**, *73*, 9188.
8. *General procedure for cross-coupling of phenylboronic acid with aminal:* Phenylboronic acid **1a** (0.5 mmol), aminal **2a** (0.3 mmol), $Cu(acac)_2$ (0.05 mmol), $PhCO_2H$ (0.1 mmol),and CH_3CN (1 mL) were added into a 25 mL flame-dried Young-type tube under air. The mixture was stirred at 50 °C for 12 h, then the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired product.
9. For disproportionation of Cu(II)–Cu(III) and Cu(I), see: (a) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044; (b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068; (c) Dai, C.; Huang, F.; Xu, Z.; Yu, Z.; Gao, Y.-F. *J. Org. Chem.* **2012**, *77*, 4414.