ORGANIC LETTERS

2004
Vol. 6, No. 15
2631−2634

Cu(I)-Mediated Reductive Amination of Boronic Acids with Nitroso Aromatics

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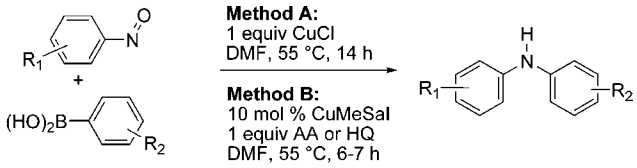
Received June 2, 2004

ABSTRACT

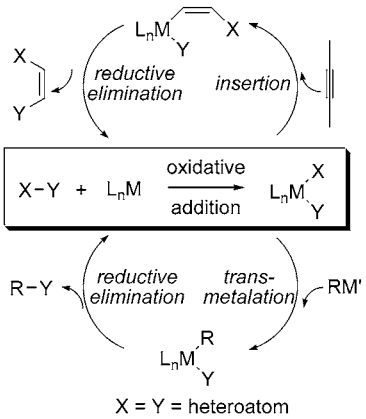


CuMeSal = Cu(I) 3-methylsalicylate; AA = ascorbic acid; HQ = hydroquinone

A mild method for the reductive amination of aryl boronic acids with nitroso aromatic compounds is reported. This C–N bond formation is mediated by a stoichiometric amount of CuCl as both a catalyst and a reducing agent. Alternatively, 10% Cu(I)-3-methylsalicylate (CuMeSal) catalyzes the same reaction in the presence of either ascorbic acid or hydroquinone as the terminal reducing agent. Diarylamines bearing a variety of functional groups can be obtained in good yields.

Oxidative addition of a lower-valent transition metal catalyst L_nM to a heteroatom−heteroatom bond X−Y generates a species $L_nM(X)Y$ capable of further functionalization in a variety of ways (i.e., Scheme 1). Transformations that proceed via the upper cycle of Scheme 1 are increasingly common and include the reactions of disulfides and analogues with unsaturated organics such as alkynes,[1] alkenes,[2] CO,[3] and isonitriles.[4] Sulfenamides have been shown to react with CO,[5] and *O*-sulfonylated oximes and related derivatives[6] as well as *N*-haloamines[7] participate in palladium-catalyzed aza-Heck-like reactions that are presumably initiated by oxidative addition to an N−X bond.

Scheme 1



Less common are nominal cross-coupling reactions in which the $L_nM(X)Y$ intermediate is intercepted with an organometallic carbon nucleophile to provide, after reductive elimination, products with newly generated carbon−heteroatom bonds (lower cycle of Scheme 1). In this way Narasaka

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(2) Kondo, T.; Uenoyama, S.-y.; Fujita, K.-i.; Mitsudo, T.-a. *J. Am. Chem. Soc.* **1999**, *121*, 482.

(3) Antebi, S.; Alper, H. *Tetrahedron Lett.* **1985**, *26*, 2609.

(4) Kuniyasu, H.; Sugoh, K.; Su, M. S.; Kurosawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4669.

(5) Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* **1999**, *64*, 7305.

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(7) Helaja, J.; Göttlich, R. *Chem. Commun.* **2002**, 720. See also: Heuger, G.; Kalsow, S.; Göttlich, R. *Eur. J. Org. Chem.* **2002**, 1848. Noack, M.; Göttlich, *Eur. J. Org. Chem.* **2002**, 3171.

10.1021/ol048982q CCC: $27.50
Published on Web 06/30/2004

and co-workers relied on cleavage of the O−N bond of oxime derivatives to establish a copper-catalyzed amination of cuprates and Grignard reagents.[8]

Further development of this tactic as a general synthetic sequence could provide a useful complement to the various palladium- and copper-catalyzed cross-coupling reactions that have revolutionized the way in which synthetic chemists generate carbon−heteroatom bonds. These cross-coupling reactions currently fall into two broad categories: the anaerobic, metal-catalyzed cross-coupling of N, O, S, and P nucleophiles with organic halides or their equivalents[9] and complementary "oxidative" aminations, amidations, alkoxylations, aryloxylations, and thiations of boronic acids mediated by Cu(II).[10,11] Guided by the cross-coupling concept depicted in the bottom cycle of Scheme 1, we have initiated an exploration of metal-catalyzed reactions of various heteroatom−heteroatom reactants with mild reaction partners such as boronic acids to seek out new and mild approaches to C-heteroatom bonded systems. We have previously demonstrated that boronic acids easily couple with *N*-thioimide derivatives to give thioethers under neutral conditions in the presence of a Cu(I) catalyst.[12] This Letter describes a second new method uncovered as part of that study.

Following the cross-coupling concept depicted in the lower cycle of Scheme 1, the reaction of hydroxylamine derivatives with boronic acids[13] could provide a means of generalizing the "oxidative" amination of boronic acids[10] by using an oxidized form of the amine coupling partner rather than an external oxidant.[11] However, exploratory metal-catalyzed reactions of boronic acids with various hydroxylamine derivatives (*O*-aryl-*N*-acyl hydroxylamines acids, *O*-alkyl-*N*-acylhydroxylamines, *N*,*O*-diacyl-*N*-phenylhydroxylamine, *N*,*O*-diacyl-*N*-benzenesulfohydroxamic acid) generated only modest results.[14] Attention was then transferred from hydroxylamine to nitroso derivatives[15] with the objective of gaining additional insight into the reaction chemistry of boronic acids with N−O systems, in general.

Heating 2-nitrosotoluene with a stoichiometric amount of Cu(I)-thiophene-2-carboxylate (CuTC)[16] and a slight molar excess of phenylboronic acid at 55 °C in THF for 16 h gave 2-methyldiphenylamine in 61% isolated yield.[17] Control experiments demonstrated the requirement for a stoichiometric amount of Cu(I), suggesting that Cu(I) functioned as both a catalyst for the transformation as well as a stoichiometric reducing agent for the requisite N−O bond generated during the reaction.[18] Premixing the nitroso aromatic compound with a stoichiometric amount of the Cu(I) salt prior to addition of the boronic acid greatly diminished the formation of undesired side products derived from copper-mediated oxidative homocoupling and protodeborylation of the boronic acid.[19] Among the different Cu(I) compounds assayed (Cu(I) thiophene-2-carboxylate, CuTC;[16] Cu(I) 3-methylsalicylate, CuMeSal;[20] CuI; CuCl; CuOAc; $(CuSO_3CF_3)_2 \cdot C_6H_5CH_3$; and $(CuSO_3CF_3)_2 \cdot C_6H_6$) CuCl gave the best results and DMF was the preferred solvent of those probed (toluene, THF, DMF, DMA, NMP, and pyridine).

As depicted in Table 1 a variety of unsymmetrical diarylamines bearing different functional groups were easily prepared using the optimized conditions.[21] Boronic acids bearing both electron-donating and electron-withdrawing groups led to good yields of the products (entries 2, 3, and 6), and functional groups such as aldehyde and ester (entries 4, 5, 7, and 9) were compatible with the almost neutral reaction conditions.

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(12) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309.

(13) The amination of organoboron reagents with hydroxylamine *O*-sulfonic acid is also known, but a metal-catalyzed amination of boron reagents with hydroxylamine derivatives would greatly expand the scope of this chemistry. See *Encyclopedia of Reagents for Organic Synthesis*, 1st ed.; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 4.

(14) Both hydroxylamine and hydrazine derivatives are known to participate in palladium- or copper-catalyzed carbon−heteroatom bond formation without cleavage of the heteroatom−heteroatom bond: Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129. Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* **2003**, *5*, 979.

(15) Arylnitroso compounds are easily generated from nitroaromatics and have been widely used in organic synthesis. See in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 6, Chapter 1.4 by Askani, R.; Taber, D. F.; Yogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317.

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(17) A related preparation of diarylamines from arylmagnesium reagents and nitroarenes has been described: Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390.

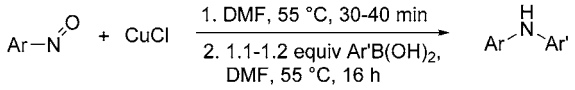
(18) The use of substoichiometric quantities of Cu(I) did not lead to the formation of the corresponding *N*,*N*-diarylhydroxylamine.

(19) The efficiency of the protodeborylation of boronic acids with CuTC varies with the reaction conditions. For reference, see: Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

(20) See Supporting Information for Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (1), 91.

(21) **Typical Experimental Procedure.** 2-Nitrosotoluene (38 mg, 0.3 mmol) and CuCl (30 mg, 0.3 mmol) were placed in a Schlenk tube that was flushed with argon. Dry DMF (8 mL) was added, and the dark brown mixture was stirred at 55 °C for 40 min. Phenylboronic acid (41 mg, 0.33 mmol) was dissolved in DMF (3 mL) and added to the reaction tube. The mixture was heated at 55 °C for 16 h, cooled, and then partitioned between Et_2O (20 mL) and 1 M NH_4OH (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried with $MgSO_4$. The oily residue obtained after evaporation was subjected to preparative plate silica gel chromatography (gradient of hexanes/EtOAc) giving 2-methyldiphenylamine (46 mg, 83%) as brown oil. Full characterization details are available in Supporting Information.

Table 1. CuCl-Mediated Amination of Arylboronic Acids with Nitroso Aromatic Compounds[a]



entry	Ar	Ar′	product yield (%)[b]
1	*o*-tol	Ph	83
2	*o*-tol	4-MeOC$_6$H$_4$	81
3	Ph	4-C$_6$H$_4$CF$_3$	70
4	Ph	4-C$_6$H$_4$CO$_2$Me	72
5	Ph	3-C$_6$H$_4$CHO	81
6	Ph	2-C$_6$H$_4$F	61
7	Ph	4-MeO-2-C$_6$H$_3$CHO	78
8	Ph	2-dibenzofuranyl	64
9	4-Cl-*o*-tol	4-C$_6$H$_4$CO$_2$Me	70

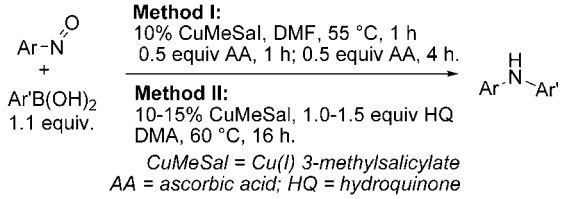
[a] Dry DMF (8 mL) was added to a reaction vessel holding a mixture of the nitroso aromatic (0.3 mmol) and CuCl (0.3 mmol), which was then heated to 55 °C for 30−40 min. The aryl boronic acid (0.33 mmol) was dissolved in 3 mL of DMF and then added, and the reaction mixture was stirred at 55 °C for another 16 h. [b] Isolated yields, average of two runs.

In the reductive amination of the boronic acid with the nitrosoarene, 1 equiv of a reducing agent is required in order to complete the transformation from a putative N−O intermediate to the observed diarylamine product. The role of reducing agent is served by a stoichiometric amount of CuCl, although control experiments demonstrated that an additional equivalent of the boronic acid could also function as the terminal reducing agent (forming an equivalent of phenol in the process). Thus, in the presence of 20 mol % CuTC, 2 equiv of phenylboronic acid and 1 equiv of 2-nitrosotoluene gave 60% of 2-methyldiphenylamine.

To render the reaction catalytic in copper without sacrificing an equivalent of the boronic acid, the reaction was explored in the presence of various terminal reducing agents. In fact, heating 1 equiv of ascorbic acid,[22] phenylboronic acid, and 2-nitrosotoluene in the presence of 10% Cu(I)-3-methylsalicylate (CuMeSal) gave 2-methyldiphenylamine in 55% yield along with lesser amounts of 2-methylaniline and 2,2′-dimethylazoxybenzene as byproducts. A control experiment revealed formation of aniline by an ascorbic acid mediated reduction of the nitrosoarene, a process that presumably takes place via the arylhydroxylamine. The reduction is accelerated in the presence of a catalytic amount of a Cu(I) source, such as CuMeSal. Formation of the azoxybenzene is then easily rationalized by condensation of the nitrosoarene with the transiently generated arylhydroxylamine.[23]

Reduction of the nitrosoarene to the aniline suggested a mechanistic pathway to the *N*,*N*-diarylamine in which a portion of the nitrosoarene is first reduced to the aniline, which then undergoes a copper-mediated, oxidative coupling with the boronic acid[10] using the remaining nitrosoarene as the oxidant. However, when a mixture of PhNH$_2$, 2-nitrosotoluene, phenylboronic acid, 10% CuMeSal, and 1 equiv of ascorbic acid in DMF was heated at 55 °C for 16 h, only 2-methyldiphenylamine was observed. The absence of diphenylamine in the reaction mixture argues against the intervention of free anilines in the *N*-arylation process. In any event the formation of the undesired aniline and azoxy byproducts was greatly minimized by adding the ascorbic acid to the reaction mixture portion-wise. Under optimal reaction conditions a DMF solution of the nitrosoarene, the boronic acid, and 10% CuMeSal was heated at 55 °C for 2 h, then 0.5 equiv of ascorbic acid was added followed by a second 0.5 equiv 1 h later. After a total of 4 h a clear yellow solution was obtained that was subjected to workup. Some diarylamines that were prepared in this fashion are summarized in Table 2.[24]

Table 2. CuMeSal-Catalyzed Amination of Arylboronic Acids with Nitroso Aromatic Compounds Using Ascorbic Acid (AA) and Hydroquinone as Reducing Agents



			product yield (%)[a]	
entry	Ar	Ar′	I	II
1	*o*-tol	Ph	87	80
2	Ph	4-C$_6$H$_4$CF$_3$	84	65
3	Ph	4-C$_6$H$_4$CO$_2$Me	79	68
4	Ph	2-C$_6$H$_4$F	78	65
5	Ph	3-C$_6$H$_4$CHO	75	74
6	Ph	2-dibenzofuranyl	80	

[a] Isolated yield from the average of two runs.

Compared to the use of a stoichiometric amount of CuCl (Table 1), the ascorbic acid/catalytic Cu(I) system gave generally better results and possessed satisfactory functional group compatibility. Hydroquinone also served as an alternate and very mild terminal reducing agent (Table 2) but gave slightly lower yields of the product diarylamines relative to ascorbic acid. However, the low acidity of hydroquinone

(22) Ascorbic acid (vitamin C) functions as a weakly acidic and mild reducing agent in biological systems. For a review, see: Padh, H. *Nutr. Rev.* **1991**, *49*, 65.

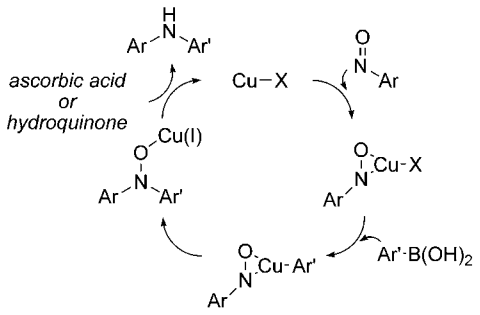
(23) Zuman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621.

(24) **Typical Experimental Procedure.** Using ascorbic acid: dry DMF (8 mL) was added to an argon-flushed Schlenk tube containing 2-nitrosotoluene (38 mg, 0.3 mmol), phenylboronic acid (41 mg, 0.33 mmol), and CuMeSal (6 mg, 0.03 mmol). The mixture was stirred at 55 °C for 1 h, and then ascorbic acid (30 mg, 0.15 mmol) in 1 mL DMF was added. One hour later an identical portion of ascorbic acid (30 mg, 0.15 mmol) was added. The mixture was heated at 55 °C for 4 h, cooled to room temperature, and partitioned between Et$_2$O (20 mL) and aqueous NH$_4$OH (20 mL, 1 M). The aqueous layer was extracted with Et$_2$O (2 × 10 mL), and the combined organic layers were dried with MgSO$_4$. The residue after evaporation was subjected to preparative plate silica chromatography (gradient of hexanes/EtOAc) giving the desired product (48 mg, 87%) as a brown oil. A similar reaction using hydroquinone added in one portion gave the desired product in 80% yield (44 mg). Full characterization details are available in Supporting Information.

helped minimize the formation of the undesired azoxy and aniline side products. As a result, there was no need for slow addition of hydroquinone and all reagents could be heated together to obtain satisfactory yields of the desired amination products.

A suggested mechanism for the copper-mediated reductive amination of arylboronic acids with nitrosoarenes is depicted in Scheme 2. Side-on complexation of Cu(I) with the nitroso

Scheme 2



moiety[25] generates a formal Cu(III) intermediate that would be susceptible to transmetalation by the boronic acid.[26] Reductive elimination would then generate a Cu(I) alkoxide of an *N*,*N*-diarylhydroxylamine. This intermediate would suffer an internal redox generating the diarylamine and an oxidized Cu species. Under conditions catalytic in copper, the oxidized Cu species would be reduced by ascorbic acid[27] or hydroquinone to a catalytically active form of Cu(I).

In summary, a mild reductive amination of arylboronic acids with nitrosoarenes has been developed. The reaction is mediated either by a stoichiometric quantity of CuCl or with catalytic Cu(I) 3-methylsalicylate in the presence of ascorbic acid or hydroquinone as terminal reducing agents. The method provides an interesting synthetic complement to existing protocols for C−N bond formation and begins to expand our understanding of carbon−heteroatom cross-coupling using heteroatom−heteroatom bonded species. For example, it may prove feasible to couple nitroaromatics with boronic acids by pairing the chemistry depicted in this Letter with a mild in situ reduction of a nitroaromatic to the corresponding nitrosoarene.[28] This and related transformations based on metal-mediated heteroatom−heteroatom cleavages are under study.

Acknowledgment. The National Institutes of General Medical Sciences, DHHS supported this investigation through grant GM066153.

Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048982Q

(25) Otsuka, S.; Aotani, Y.; Tatsuno, Y.; Yoshida, T. *Inorg. Chem.* **1976**, *15*, 656. Ittel, S. D. *Inorg. Chem.* **1977**, *16*, 2589. Lee, J.; Chen, L.; West, A. H.; Richter-Addo, G. B. *Chem. Rev.* **2002**, *102*, 1019.

(26) For transmetalation between zinc and copper leading to effective electrophilic amination, see: Erdik, E.; Daskapan, T. *Synth. Commun.* **1999**, *29*, 3989.

(27) Bose, S.; Nair, N. *J. Indian Chem. Soc.* **1974**, *51*, 505. Yano, Y.; Takano, S.; Kato. Y.; Tagaki, W. *J. Chem. Soc., Perkin Trans. 2*, **1979**, *9*, 1227.

(28) For comparison, see footnote 17.