Synthetic Methods

DOI: 10.1002/anie.201308890

Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives**

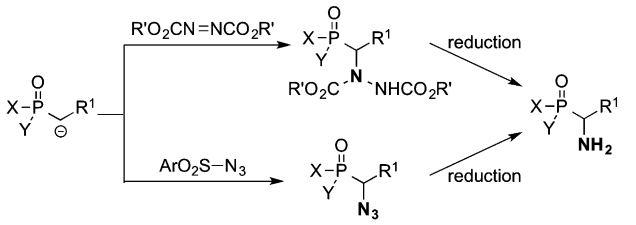
*Stacey L. McDonald and Qiu Wang**

Abstract: *A direct approach to important α-amino phosphonic acids and its derivatives has been developed by using copper-catalyzed electrophilic amination of α-phosphonate zincates with O-acyl hydroxylamines. This amination provides the first example of C–N bond formation which directly introduces acyclic and cyclic amines to the α-position of phosphonates in one step. The reaction is readily promoted at room temperature with as little as 0.5 mol% of catalyst, and demonstrates high efficiency on a broad substrate scope.*

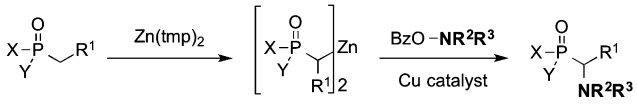
α-Amino phosphonic acids and their derivatives serve as functional surrogates for α-amino carboxylic acids and exhibit a wide range of intriguing biological properties.[1] Their well-recognized importance in agrochemicals and medicine,[2] such as herbicides,[3] plant virucides,[4] antibiotics,[5] anticancer agents,[6] and inhibitors of HIV proteases,[7] has driven continuous synthetic efforts to prepare this class of compounds.[8–13] Among them, the electrophilic α-amination of phosphonates represents an attractive strategy for a rapid and direct access (Scheme 1).[9,10] Furthermore, the amination approach is alternative and complementary to other approaches (e.g., by C–P,[11] C–C,[12] or C–H[13] bond formation) which typically start from aldehydes or imines in the preparation of α-amino phosphonic acids, thus diversifying the range of the starting substrates.

Toward this end, previous studies explored α-aminations of phosphonates using reactive azodicarboxylate esters or arylsulfonyl azides, which subsequently formed α-amino phosphates upon reductive cleavage of the resulting N–N bond (Scheme 1a).[9] Despite the success, these methods were restricted to the formation of primary amines (the installation of an NH_2 group), the use of highly electrophilic nitrogen atoms, and a narrow scope of phosphonates because they needed to be compatible with the reductive cleavage conditions. Even with the significant advances in the arsenal of modern synthetic chemistry, the potential of C–N bond formation as a powerful approach to α-amino phosphonic acids remains underexplored. So far no examples of C–N bond formation have been reported for directly introducing

(a) previous amination conditions: two-step installation of a primary amine



(b) this work: direct introduction of diversely substituted amines



tmp = 2,2,6,6-tetramethyl piperidinyl anion

Scheme 1. Synthesis of α-amino phosphonic acids by C–N bond formation.

secondary or tertiary amines to the α-position of phosphonates, thus limiting the synthesis and discovery of novel α-amino phosphonic acids of biological importance.[8] Therefore, it is of great value to develop a general amination method under mild reaction conditions and thus significantly extend the scope of the synthesis of α-aminophosphonates.

We propose that a novel amination approach to α-amino phosphonic acids can be achieved by a copper-catalyzed amination of phosphonate α-zincates using electrophilic hydroxylamines (Scheme 1b). This strategy was inspired by pioneering studies on the electrophilic amination of arylzinc reagents with hydroxylamines.[14–17] In our studies, we explored the formation of α-zincates of phosphonates and phosphine oxides, a novel class of organozinc reagents, and their reactivity toward C–N bond formation. Different from those organozinc reagents typically prepared from their orgonolithium or Grignard precursors,[14] the phosphonate α-zincates are proposed to form by H–Zn exchange.[18] Thus, this strategy is direct and potentially more efficient, and it would also allow a broader substrate scope and better functional group compatibility. Herein, we demonstrate the efficacy of phosphonate α-zincates as nucleophiles in copper-catalyzed amination with *O*-benzoylhydroxylamines, and the development of a new C–N bond-formation approach to rapidly access α-amino phosphonic acids. This α-amination strategy provides the first example enabling the direct introduction of a variety of acyclic and cyclic amines to the α-position of phosphonates and phosphine oxides. The amination reaction proceeds in good to excellent yields at room temperature with as little as a 0.5 mol% catalyst

[*] S. L. McDonald, Prof. Dr. Q. Wang
Department of Chemistry, Duke University
Durham, NC 27708–0346 (USA)
E-mail: qiu.wang@duke.edu

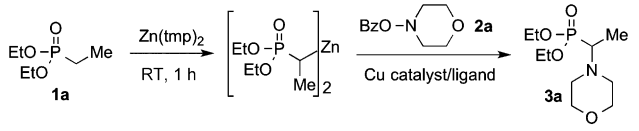
[**] We gratefully acknowledge Duke University for financial support on the research and the Burroughs Wellcome Endowment for the fellowship to S.L.M.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308890.

loading. The good functional-group compatibility and broad substrate scope observed in this reaction also contribute to its promising utility for the preparation of α-amino phosphonic acids and derivatives.

Our studies began with the amination reaction between the model substrate phosphonate **1a** and the hydroxylamine **2a** (Table 1). As the α-zincation of substituted phosphonates has not been reported previously, we first confirmed that the corresponding α-zincate of **1a** was effectively formed upon the treatment with $Zn(tmp)_2$, a strong and non-nucleophilic base.[19] Next we looked into the formation of the aminated product **3a** by using different copper salts as catalysts (entries 1–6). Encouragingly, all the reactions led to the desired product **3a**, which was produced in the highest yield with CuCN (entry 3). In contrast, no aminated product was detected in the absence of a copper catalyst, thus suggesting the essential role of copper in the amination. We then examined several ligands including 1,10-phenathroline and 2,2′-bipyridine for accelerating the reaction. Although the use of a ligand did not imporove the CuCN-catalyzed reactions (entry 3 versus 7 and 8), it significantly improved the efficiency of those reactions catalyzed by $CuCl_2$ (entry 4 versus 9 and 10). With this information, we chose $CuCl_2$/bipyr as the standard catalyst system for the amination step.

Table 1: Optimization studies for copper-catalyzed amination of the phosphonate **1a** with the hydroxylamine **2a**.

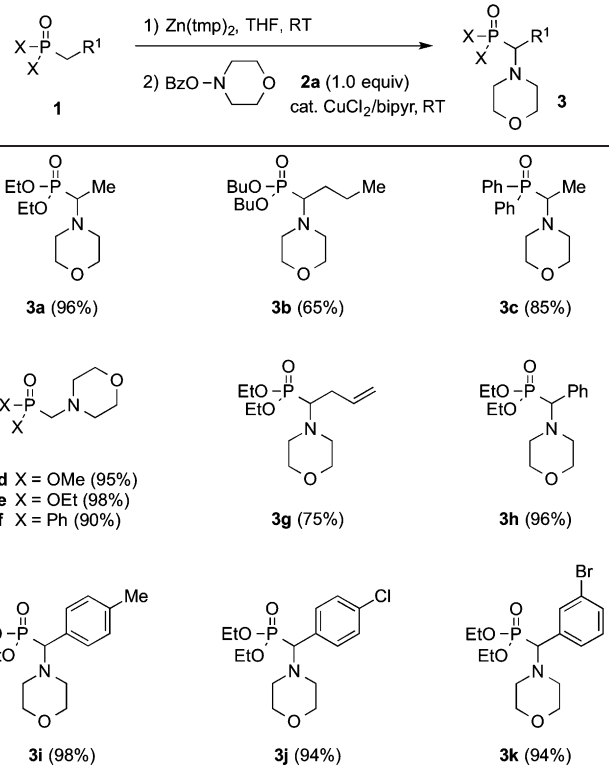


Entry	**1a**	$Zn(tmp)_2$ [equiv]	**2a**	Copper (10 mol%)	Ligand (20 mol%)	*t* [h][a]	**3a** Yield [%][b]
1	2.1	1.0	1.0	CuOTf·tol	–	2	16
2	2.1	1.0	1.0	CuCl	–	20	77
3	2.1	1.0	1.0	CuCN	–	20	96
4	2.1	1.0	1.0	$CuCl_2$	–	20	78
5	2.1	1.0	1.0	$Cu(OAc)_2$	–	20	78
6	2.1	1.0	1.0	$Cu(OTf)_2$	–	20	31
7	2.1	1.0	1.0	CuCN	phen	20	48[c]
8	2.1	1.0	1.0	CuCN	bipyr	20	99
9	2.1	1.0	1.0	$CuCl_2$	phen	1	96
10	2.1	1.0	1.0	$CuCl_2$	bipyr	4	99

[a] Time required for complete consumption of **2a**. [b] Yields determined by ^1H NMR spectroscopy using CH_2Br_2 as a quantitative internal standard. [c] **2a** recovered in 24% yield. bipy = 2,2′-bipyridine, phen = 1,10-phenanthroline, Tf = trifluoromethanesulfonyl.

With effective α-amination conditions identified, we examined the scope of phosphonates and derivatives using **2a** (Table 2). Similar to the model substrate **1a**, dibutyl butylphosphonate and ethyldiphenyl phosphine oxide both readily afforded the desired aminated products **3b**,**c**. The simple analogous substrates, such as dimethyl and diethyl methylphosphonates as well as methyldiphenylphosphine oxide, also proceeded smoothly to give **3d**–**f** in excellent yields. Besides a methyl group, other substituents at the α-position are also compatible with the amination reaction, including allyl, phenyl, and aryl groups (**3g**–**k**). Regardless of an electron-donating or electron-withdrawing group present on the aryl ring, the reactions all occurred efficiently. Especially useful is the tolerance of the chloro and bromo groups in the aminated products **3j**,**k**, thus allowing additional functionalization by transition-metal-catalyzed couplings. For disubstituted phosphonates, direct α-zincation was ineffective with $Zn(tmp)_2$, possibly because of the increased steric hinderance.[20]

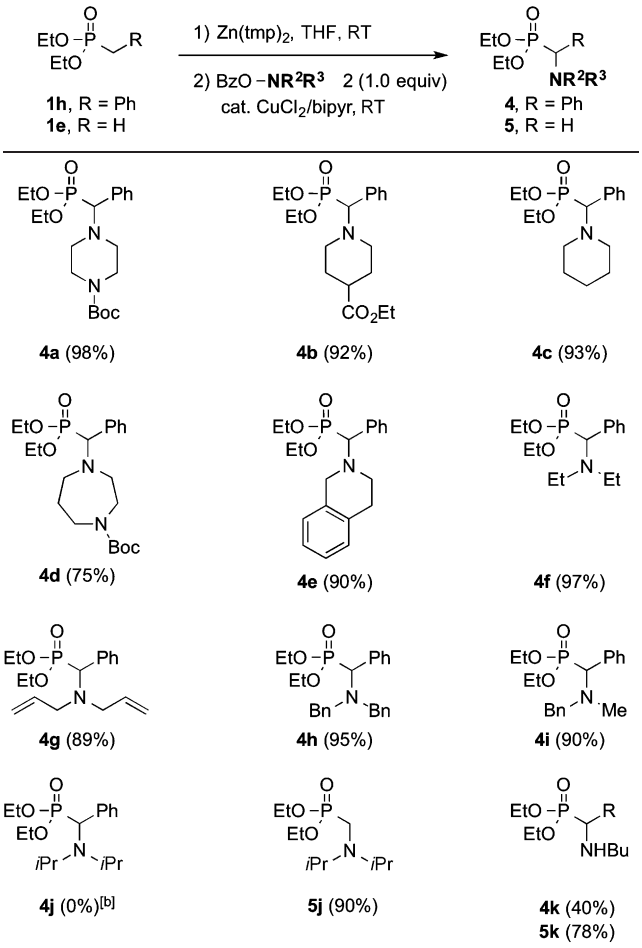
Table 2: α-Amination of different phosphonates and phosphine oxides.[a]



[a] Isolated yields. Standard reaction conditions: **1** (2.1 equiv), **2** (1.0 equiv), $Zn(tmp)_2$ (1.0 equiv), $Cu(OAc)_2$ (10 mol%), bipyr (20 mol%), RT. Reactions typically run on 0.2 mmol scale. THF = tetrahydrofuran.

A defining attribute of this new α-amination protocol is its potential to provide direct access to a broad array of amines at the α-position of a phosphonate. As shown in Table 3, different cyclic amines were successfully installed in the amination reactions of **1h**, to give products such as the *N*-Boc piperazine **4a**, piperidines (**4b**–**c**), the diazepane **4d**, and the bicyclic amine **4e**. The reactions for introducing acyclic α-amines into the phosphonate products (**4f**–**i**) also occurred smoothly with amines containing *N*,*N*-diethyl, *N*,*N*-diallyl, *N*,*N*-dibenzyl, and *N*-benzyl-*N*-methyl substituents. Note that the resultant allyl and benzyl moieties can be useful synthetic handles for further manipulations after the selective deprotection. However, the sterically encumbered *N*,*N*-diisopropyl-substituted amine **4j** was not formed. For the synthesis of a secondary amine, the reaction with **1h** was effective, thus providing **4k** in 40% yield. To further probe the feasibility and efficacy of hydroxylamines (**2j**–**k**) in the amination reaction, we tested them in the reaction with **1e**, a simple

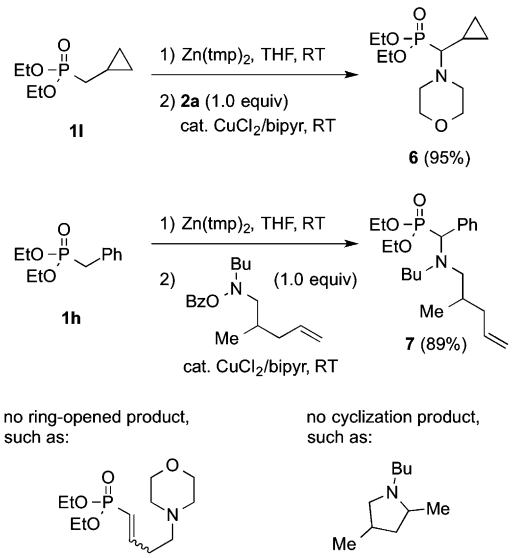
Table 3: The scope of the amines.[a]



[a] Isolated yields. Standard reaction conditions (see Table 1). [b] Yields determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a quantitative internal standard, and confirmed by GC/MS. Boc = *tert*-butoxycarbonyl.

phosphonate lacking an α-substituent. Interestingly, the desired aminated product **5j**, containing a sterically hindered *N*,*N*-diisopropyl group, was formed in 90% yield and the secondary amine **5k** (R = H) was formed in a greater yield (76%) compared to that of **4k** (R = Ph). This outcome suggests that both the electronic and steric nature of phosphonates and hydroxylamines can influence the efficiency of the amination step.

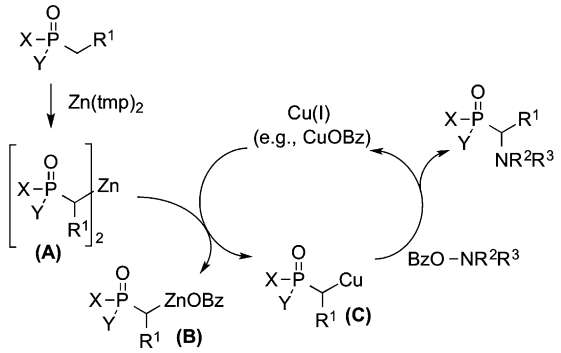
To investigate if the copper-catalyzed amination step may involve any radical intermediates, we performed the following two control experiments: 1) the reaction of **1l**, which contains the cyclopropyl substituent at the α-position, with the model hydroxylamine substrate **2a**, and 2) the amination using *N*-4-pentenylhydroxylamine on the model phosphonate **1h** (Scheme 2). Both reactions produced the aminated products exclusively in excellent yields. In the reaction of **1l**, no ring-opened product derived from the cyclopropyl substituent was observed.[15f] The exposure of *N*-4-pentenylhydroxylamine to the copper catalyst did not give any detectable cyclization product, such as the pyrrolidine-containing structure from the copper-catalyzed 5-exo radical cyclization reported previously.[15a] The results from both control experiments indicate the



Scheme 2. Control experiments to probe the presence of radical intermediates.

absence of an aminyl radical species or a copper-coordinated radical complex in the amination pathway.

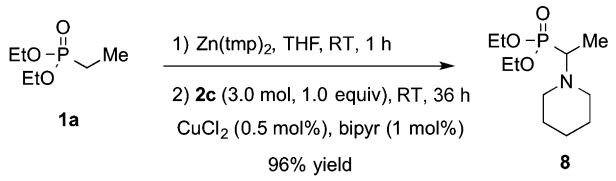
Although the detailed mechanism for C–N bond formation remains obscure, a possible mechanism is proposed for the amination step based on these experimental results and observations (Scheme 3). The bisphosphonate zincate **A**



Scheme 3. Proposed mechanism for the α-amination reaction.

could initially undergo transmetallation with copper(I) to generate a reactive copper complex (**C**), which subsequently reacts with hydroxylamines to form the desired C–N bond.[21] We believe that the zincate intermediate **B** did not undergo transmetallation to form the copper complex **C** as a stoichiometric amount of the zincate (**A**) was needed for the complete conversion of the hydroxylamines.

Finally, we evaluated the efficacy of this transformation on a larger scale with a lower catalyst loading of only 0.5 mol% of $CuCl_2$ and 1 mol% of bipyridine ligand (Scheme 4). Although a longer reaction time (36 h) was required in this case, the aminated product **8** was formed in 96% yield, thus demonstrating high efficiency and practical utility of this amination reaction.



Scheme 4. An efficient scale-up amination reaction with 0.5 mol% catalyst loading.

In summary, we have developed a highly efficient copper-catalyzed α-amination of phosphonates and phosphine oxides using *O*-benzoyl hydroxylamines. The amination reaction proceeds in excellent yields at room temperature and exhibits broad substrate scope and good functional group compatibility, thus demonstrating great potential in preparing a variety of α-amino phosphonic acids and derivatives. Currently, development of an asymmetric α-amination reaction using a chiral catalyst system is underway. With the application of $Zn(tmp)_2$ in direct zincation of other sp^3 and sp^2 C–H bonds, such as ketones, amides, and heteroarenes, this work also provides insights into developing C–H zincation/copper-catalyzed aminination as a general C–H amination strategy.

Experimental Section

General procedure for the synthesis of **3** and **4**: A mixture of $Zn(tmp)_2$ (0.5 M solution in toluene, 0.4 mL, 0.2 mmol, 1.0 equiv) and substrate **1** (0.42 mmol, 2.1 equiv) was stirred at room temperature for 1 h. Then a mixture of the *O*-benzoyl hydroxylamine **2** (0.2 mmol, 1.0 equiv), $CuCl_2$ (2.7 mg, 0.02 mmol, 0.1 equiv), and 2,2′-bipyridyl (6.2 mg, 0.04 mmol, 0.2 equiv) in THF (1 mL) was added. The reaction mixture was stirred at room temperature. Upon complete consumption of *O*-benzoylhydroxylamine (monitored by TLC: 50% ethyl acetate/hexanes, typically 2–6 h), the reaction mixture was filtered through silica and washed with isopropyl alcohol. The filtered solution was concentrated under reduced pressure. The crude residue was purified by column chromatography.

Received: October 11, 2013

Keywords: amination · amines · C–H functionalization · copper · zinc

[1] a) P. Kafarski, B. Lejczak, *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193; b) V. P. Kukhar, H. R. Hudson, *Aminophosphonic and Aminophosphinic Acid: Chemistry and Biological Activity*, Wiley, Chichester, **2000**.

[2] A. Mucha, P. Kafarski, L. Berlicki, *J. Med. Chem.* **2011**, *54*, 5955.

[3] a) G. Forlani, L. Berlicki, M. Duo, G. Dziedziola, S. Giberti, M. Bertazzini, P. Kafarski, *J. Agric. Food Chem.* **2013**, *61*, 6792; b) G. Forlani, A. Occhipinti, L. Berlicki, G. Dziedziola, A. Wieczorek, P. Kafarski, *J. Agric. Food Chem.* **2008**, *56*, 3193.

[4] a) N. Long, X. J. Cai, B. A. Song, S. Yang, Z. Chen, P. S. Bhadury, D. Y. Hu, L. H. Jin, W. Xue, *J. Agric. Food Chem.* **2008**, *56*, 5242; b) D. Y. Hu, Q. Q. Wan, S. Yang, B. A. Song, P. S. Bhadury, L. H. Jin, K. Yan, F. Liu, Z. Chen, W. Xue, *J. Agric. Food Chem.* **2008**, *56*, 998; c) M. H. Chen, Z. Chen, B. A. Song, P. S. Bhadury, S. Yang, X. J. Cai, D. Y. Hu, W. Xue, S. Zeng, *J. Agric. Food Chem.* **2009**, *57*, 1383.

[5] a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet, P. S. Ringrose, *Nature* **1978**, *272*, 56; b) F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29.

[6] a) G. Lavielle, P. Hautefaye, C. Schaeffer, J. A. Boutin, C. A. Cudennec, A. Pierre, *J. Med. Chem.* **1991**, *34*, 1998; b) P. Kafarski, B. Lejczak, *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 301.

[7] a) M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.* **1989**, *32*, 1652; b) W. W. Smith, P. A. Bartlett, *J. Am. Chem. Soc.* **1998**, *120*, 4622; c) J. Bird, R. C. Demello, G. P. Harper, D. J. Hunter, E. H. Karran, R. E. Markwell, A. J. Mileswilliams, S. S. Rahman, R. W. Ward, *J. Med. Chem.* **1994**, *37*, 158.

[8] a) V. P. Kukhar, V. A. Soloshonok, V. A. Solodenko, *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *92*, 239; b) E. D. Naydenova, P. T. Todorov, K. D. Troev, *Amino Acids* **2010**, *38*, 23; c) M. Ordóñez, H. Rojas-Cabrera, C. Cativiela, *Tetrahedron* **2009**, *65*, 17.

[9] a) S. E. Denmark, N. Chatani, S. V. Pansare, *Tetrahedron* **1992**, *48*, 2191; b) G. Jommi, G. Miglierini, R. Pagliarin, G. Sello, M. Sisti, *Tetrahedron* **1992**, *48*, 7275; c) S. Hanessian, Y. L. Bennani, *Synthesis* **1994**, 1272; d) R. Pagliarin, G. Papeo, G. Sello, M. Sisti, L. Paleari, *Tetrahedron* **1996**, *52*, 13783; e) L. Bernardi, W. Zhuang, K. A. Jorgensen, *J. Am. Chem. Soc.* **2005**, *127*, 5772.

[10] a) E. Ciganek, *Electrophilic Amination of Carbanions, Enolates, and Their Surrogates*, Wiley, **2009**; b) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377; c) E. Erdik, *Tetrahedron* **2004**, *60*, 8747.

[11] a) E. K. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528; b) M. I. Kabachnik, T. Y. Medved, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1953**, *2*, 769; c) A. B. Smith, K. M. Yager, C. M. Taylor, *J. Am. Chem. Soc.* **1995**, *117*, 10879; d) C. Maury, T. Gharbaoui, J. Royer, H. P. Husson, *J. Org. Chem.* **1996**, *61*, 3687; e) I. M. Lefebvre, S. A. Evans, *J. Org. Chem.* **1997**, *62*, 7532; f) H. Sasai, S. Arai, Y. Tahara, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 6656; g) M. J. Burk, T. A. Stammers, J. A. Straub, *Org. Lett.* **1999**, *1*, 387; h) F. A. Davis, S. Lee, H. X. Yan, D. D. Titus, *Org. Lett.* **2001**, *3*, 1757; i) G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102; j) J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 10521; k) X. Cheng, R. Goddard, G. Buth, B. List, *Angew. Chem.* **2008**, *120*, 5157; *Angew. Chem. Int. Ed.* **2008**, *47*, 5079; l) S. Nakamura, M. Hayashi, Y. Hiramatsu, N. Shibata, Y. Funahashi, T. Toru, *J. Am. Chem. Soc.* **2009**, *131*, 18240; m) G. K. Ingle, Y. X. Liang, M. G. Mormino, G. L. Li, F. R. Fronczek, J. C. Antilla, *Org. Lett.* **2011**, *13*, 2054; n) L. Yin, Y. Bao, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2013**, *135*, 10338; o) Y. Gao, Z. Huang, R. Zhuang, J. Xu, P. Zhang, G. Tang, Y. Zhao, *Org. Lett.* **2013**, *15*, 4214; p) W. Han, P. Mayer, A. R. Ofial, *Adv. Synth. Catal.* **2010**, *352*, 1667.

[12] a) U. Groth, L. Richter, U. Schollkopf, *Tetrahedron* **1992**, *48*, 117; b) S. Hannour, M. L. Roumestant, P. Viallefont, C. Riche, J. Martinez, A. El Hallaoui, F. Ouazzani, *Tetrahedron: Asymmetry* **1998**, *9*, 2329; c) S. Kobayashi, H. Kiyohara, Y. Nakamura, R. Matsubara, *J. Am. Chem. Soc.* **2004**, *126*, 6558.

[13] a) F. Hammerschmidt, M. Hanbauer, *J. Org. Chem.* **2000**, *65*, 6121; b) I. D. Gridnev, M. Yasutake, T. Imamoto, I. P. Beletskaya, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5385; c) N. S. Goulioukina, I. A. Shergold, G. N. Bondarenko, M. M. Ilyin, V. A. Davankov, I. P. Beletskaya, *Adv. Synth. Catal.* **2012**, *354*, 2727.

[14] a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680; b) A. M. Berman, J. S. Johnson, *Synthesis* **2005**, 1799; c) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219; d) M. J. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521.

[15] a) M. Noack, R. Göttlich, *Chem. Commun.* **2002**, 536; b) J. A. Smulik, E. Vedejs, *Org. Lett.* **2003**, *5*, 4187; c) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505; d) S. Liu, Y. Yu, L. S. Liebeskind, *Org. Lett.* **2007**, *9*, 1947; e) S. Liu, L. S. Liebeskind, *J.*

Am. Chem. Soc. **2008**, *130*, 6918; f) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2012**, *124*, 11997; *Angew. Chem. Int. Ed.* **2012**, *51*, 11827; g) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2012**, *124*, 3702; *Angew. Chem. Int. Ed.* **2012**, *51*, 3642; h) S. N. Mlynarski, A. S. Karns, J. P. Morken, *J. Am. Chem. Soc.* **2012**, *134*, 16449; i) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *Angew. Chem.* **2012**, *124*, 4019; *Angew. Chem. Int. Ed.* **2012**, *51*, 3953; j) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.* **2012**, *134*, 6571; k) Q. Xiao, L. M. Tian, R. C. Tan, Y. Xia, D. Qiu, Y. Zhang, J. B. Wang, *Org. Lett.* **2012**, *14*, 4230; l) X. Y. Yan, C. Chen, Y. Q. Zhou, C. J. Xi, *Org. Lett.* **2012**, *14*, 4750; m) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2013**, *15*, 172.

[16] a) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652; b) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 2860; c) K. H. Ng, F. N. Ng, W. Y. Yu, *Chem. Commun.* **2012**, *48*, 11680.

[17] a) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2013**, *15*, 3014; b) H. Takahashi, S. Inagaki, N. Yoshii, F. X. Gao, Y. Nishihara, K. Takagi, *J. Org. Chem.* **2009**, *74*, 2794; c) Z. Feng, F. Chen, X. G. Zhang, *Org. Lett.* **2012**, *14*, 1938; d) D. J. Burton, L. G. Sprague, *J. Org. Chem.* **1989**, *54*, 613; e) D. J. Burton, T. Ishihara, M. Maruta, *Chem. Lett.* **1982**, 755.

[18] a) W. S. Rees, O. Just, H. Schumann, R. Weimann, *Polyhedron* **1998**, *17*, 1001; b) M. L. Hlavinka, J. F. Greco, J. R. Hagadorn, *Chem. Commun.* **2005**, 5304; c) M. L. Hlavinka, J. R. Hagadorn, *Organometallics* **2007**, *26*, 4105.

[19] See the Supporting Information for details.

[20] No deuterium incorporation was detected for phosphonate starting materials by GC/MS upon quenching the reaction of disubstituted phosphonates and $Zn(tmp)_2$ with D_2O.

[21] However, we cannot exclude an alternative that includes 1) oxidative addition of the hydroxylamine to a low-valent copper species, 2) transmetalation with a α-phosphonate zinc carbanion, and 3) reductive elimination to form desired C–N bond.

