Conference paper

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Copper-catalyzed aminoboration and hydroamination of alkenes with electrophilic amination reagents[1]

Abstract: A copper-catalyzed regioselective, stereospecific, and enantioselective aminoboration reaction of alkenes with bis(pinacolato)diboron and *O*-acylated hydroxylamines has been developed to deliver the corresponding β-aminoalkylboranes, which can be important building blocks in organic synthesis. In addition, this methodology has been applied to a formal regioselective hydroamination of styrenes by replacement of the diboron reagent with polymethylhydrosiloxane (PMHS). The catalytic asymmetric hydroamination is also possible by using an appropriate chiral biphosphine ligand.

Keywords: aminoboration; amino derivatives; asymmetric catalysis; boron; copper; hydroamination; umpolung.

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Introduction

Due to the ubiquity of amino groups in pharmaceutical targets and biologically active compounds [1], the C–N bond-forming reaction has received significant attention as a powerful and important strategy for installing amino functionalities into organic molecules. The nitrogen atom has relatively large electronegativity and one lone pair. Thus, the amines generally work as nucleophiles, and nucleophilic aminations such as a S_N2-type substitution are standard protocols in the conventional C–N bond formations. On the other hand, an umpolung, electrophilic amination with reagents of type R_2N^+, as exemplified by chloroamines and hydroxylamines, can provide a unique and complementary approach to the nitrogen-containing organic molecules [2]. Our group [3] and others [4] have focused on the unique reactivity of the above electrophilic amination reagents and succeed in the development of some new types of C–N bond-forming processes. As part of our research projects in this field, we have recently developed Cu-catalyzed aminoboration [5] and hydroamination [6] of alkenes with the aid of the electrophilic amination strategy. This account briefly summarizes the results obtained for these reactions.

Catalytic aminoboration

Organoboron compounds are ubiquitous synthetic intermediates in modern organic synthesis, because they can be readily transformed into versatile C–C and carbon–heteroatom bonds [7]. Among numerous approaches to organoboron compounds, transition-metal-catalyzed addition of boron functionalities to C–C unsaturated moieties is of great importance. In particular, catalytic difunctionalizations can provide a rapid and concise access to the densely functionalized organoboron compounds [8]. A representative approach is an oxidative addition, in which special organoboron reagents B–E (E=B, Si, Ge, Sn, S, and C) are prepared in advance, and then their single bonds are activated through the oxidative addition to low-valent metal centers. A good alternative is transmetalation, in which the boron and other functionalities are incorporated from

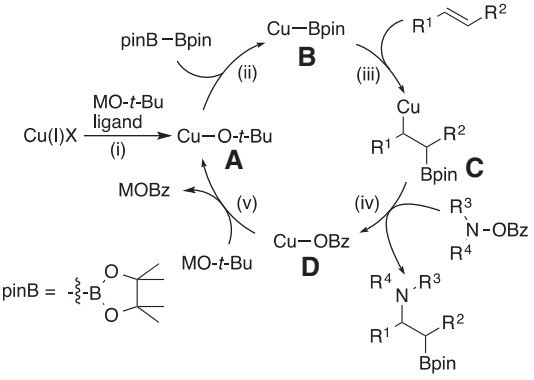
different components. Despite the above advances in this field, there is no report of successful simultaneous catalytic addition of B and N groups to C–C unsaturated molecules (aminoboration).

Our scenario for the catalytic aminoboration of alkenes is illustrated in Scheme 1. The working hypothesis was prompted by recent developments in Cu-catalyzed hydroboration chemistry with pinB–Bpin [9] and current studies on umpolung electrophilic aminations [3, 4]. The catalytic cycle consists of (i) initial formation of CuO-*t*-Bu **A** from CuX and MO-*t*-Bu, (ii) generation of a Cu–Bpin species **B** via σ-bond metathesis with pinB-Bpin, (iii) insertion of alkenes into the Cu–B bond leading to the borylated alkylcopper intermediate **C**, (iv) electrophilic amination with the *O*-acylated hydroxylamine derivative, and (v) regeneration of the starting CuO-*t*-Bu **A** by ligand exchange between CuOBz **D** and MO-*t*-Bu [10].

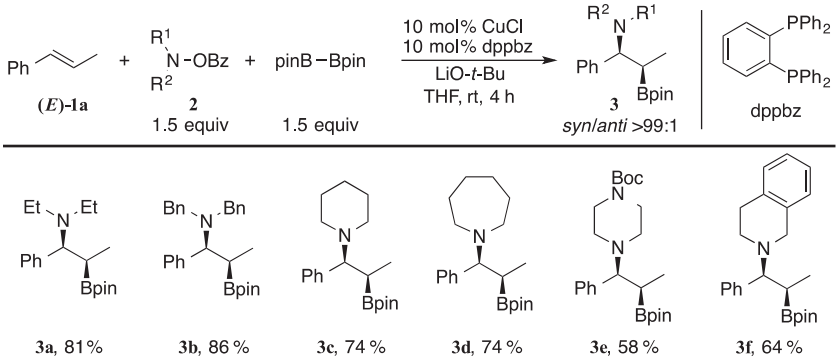
We were pleased to find that the catalytic aminoboration of *trans*-β-methylstyrene ((*E*)-**1a**) with pinB-Bpin and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**) proceeded very smoothly even at room temperature in the presence of a CuCl/dppbz catalyst and a LiO-*t*-Bu base to afford **3a** regio- and stereoselectively (Scheme 2): the boryl and amino groups were incorporated at the β- and α-positions, respectively, of the styrene, and the exclusive formation of the *syn*-diastereomer was observed. Both acyclic and cyclic hydroxylamines could be employed for this transformation (**3b–3f**).

Both electron-rich and -deficient *trans*-β-methylstyrenes were tolerated under reaction conditions (**3g** and **3h** in Scheme 3). Moreover, the Cu catalysis was compatible with the more bulky *i*-Pr substituent and oxygenated functionality at the allylic position (**3i** and **3j**). Not surprisingly, β-unsubstituted styrenes were also applicable substrates (**3k** and **3l**).

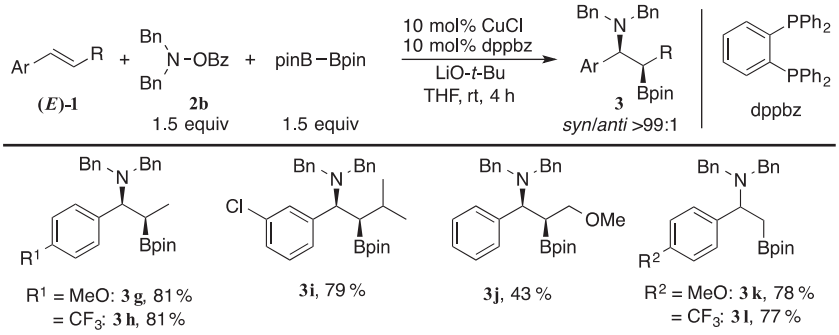
In the case of simple α-olefins, the xantphos ligand gave better results (Scheme 4). The regioselectivity was not perfect, but good efficiency was retained with 1-octene (**1h**) and vinylcyclohexane (**1i**).



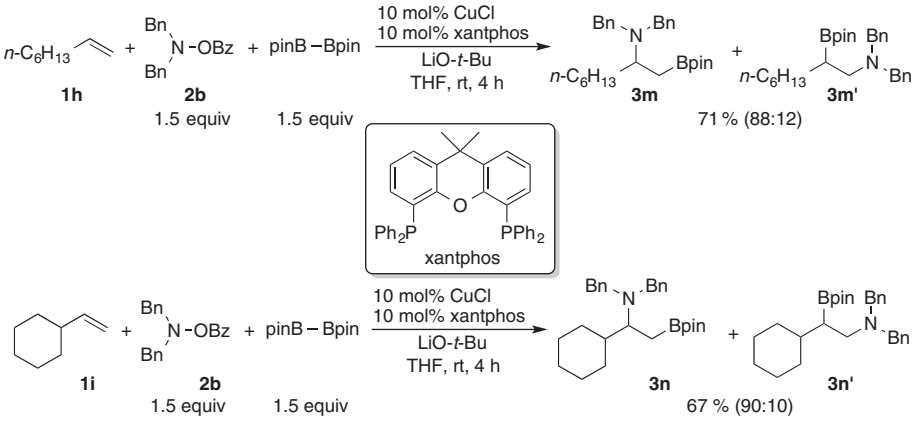
Scheme 1 Working hypothesis for catalytic aminoboration of alkenes with pinB-Bpin and hydroxylamines.



Scheme 2 Catalytic aminoboration of *trans*-β-methylstyrene ((*E*)-**1a**).



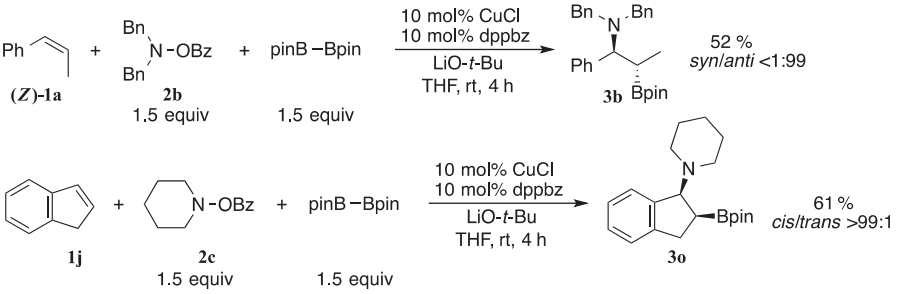
Scheme 3 Catalytic aminoboration of various styrene derivatives.



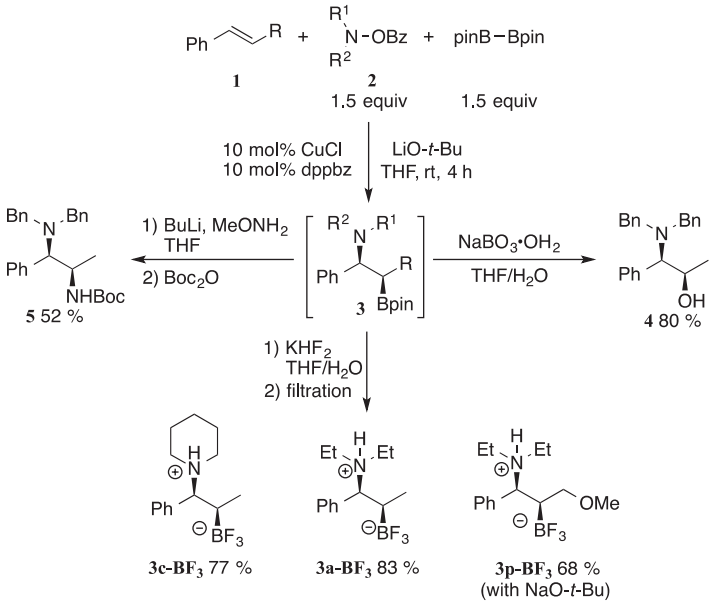
Scheme 4 Catalytic aminoboration of simple α-olefins **1h** and **1i**.

On the other hand, *cis*-β-methylstyrene ((*Z*)-**1a**) underwent the aminoboration under identical conditions to form the *anti*-**3b** exclusively (Scheme 5). In addition, the cyclic (*Z*)-alkene, indene (**1j**), also afforded the only *cis*-aminoborated product **3o**. These stereochemical outcomes confirmed the syn addition mode of the present aminoboration. In view of the syn addition of the Cu–B bond across the alkene (step iii in Scheme 1) [11], C–N bond formation occurs with retention of configuration (step iv in Scheme 1).

The aminoborated products **3** obtained were readily manipulated (Scheme 6). Treatment of the crude materials with KHF_2 in the standard THF/H_2O co-solvent system furnished the air- and moisture-stable internal ammonium borate salts **3-BF$_3$** in analytically pure forms through simple filtration. Moreover, the C–B



Scheme 5 Catalytic aminoboration of (*Z*)-alkenes.



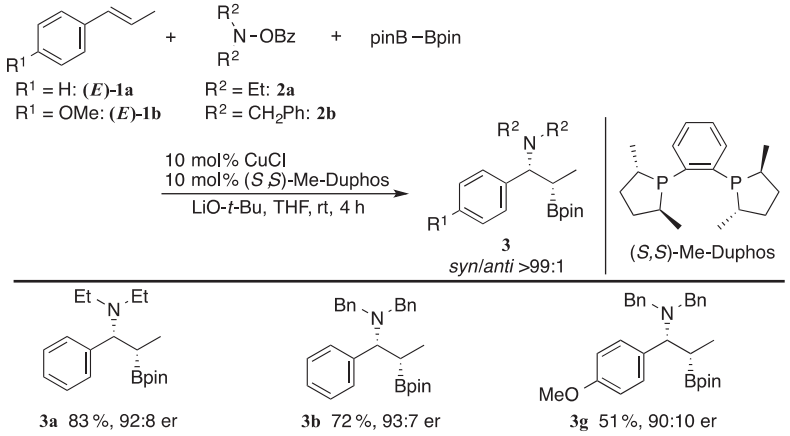
Scheme 6 Transformation of aminoborated products **3**.

bond could be easily oxidized into both C–O and C–N bonds with retention of configuration to produce the syn 1,2-aminoalcohol **4** and diamine **5** in synthetically useful yields.

The catalytic asymmetric aminoboration was also possible (Scheme 7). Aminoboration of (*E*)-**1a** with **2a** in the presence of (*S*,*S*)-Me-Duphos afforded **3a** in 83 % yield with 92:8 er. Similar enantiomeric ratios were observed for other substrate combinations (**3b** and **3g**). Thus, we have developed the Cu-catalyzed regioselective, stereospecific, and enantioselective aminoboration of alkenes with bis(pinacolato)diboron and hydroxylamines.

Catalytic hydroaminaton

The catalytic hydroamination reaction of C–C double bonds has recently received significant attention, as it allows relatively simple starting materials to be readily transformed into alkylamines, which are of great

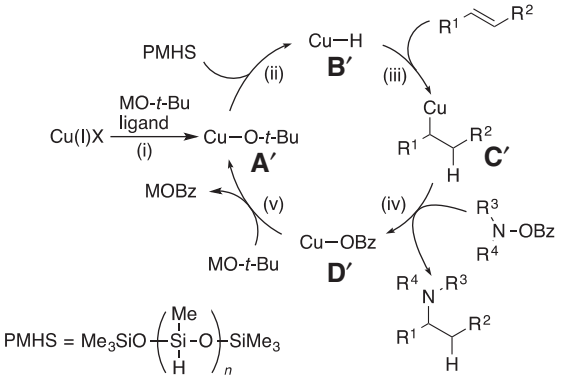


Scheme 7 Catalytic asymmetric aminoboration of *trans*-β-methylstyrenes.

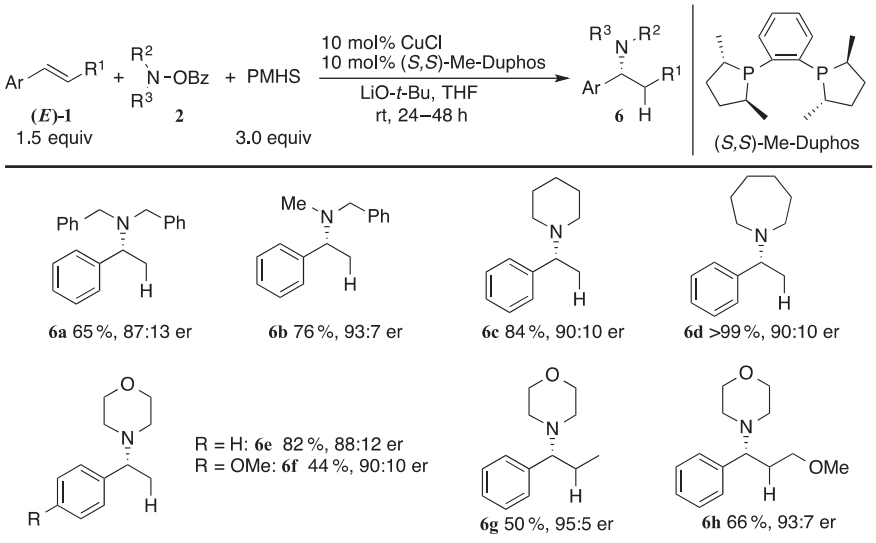
importance in both the fine and chemical industries. To date, numerous catalytic systems including various transition-metal catalysts have been widely developed [12]. However, the intermolecular hydroamination of alkenes still remains a challenge: for example, even in the hydroamination of activated styrenes, β-substituted substrates are an inaccessible substrate class [13]. In addition, most catalytic systems reported were based on precious metals and required elevated temperature. Thus, further development of catalytic intermolecular hydroamination of alkenes is strongly desired.

As mentioned in the introduction part of this account, we have succeeded in the development of the Cu-catalyzed three-component-coupling aminoboration of alkenes with bis(pinacolato)diboron and hydroxylamines. In principle, the replacement of the diboron reagent with an appropriate hydride source can provide a new catalysis for the formal hydroamination of alkenes. In this context, we focused on a hydrosilane, particularly, less expensive and abundant polymethylhydrosiloxane (PMHS) [14]. Our blueprint is shown in Scheme 8. Each elementary step (i–v) is analogous to that of the catalytic aminoboration in Scheme 1.

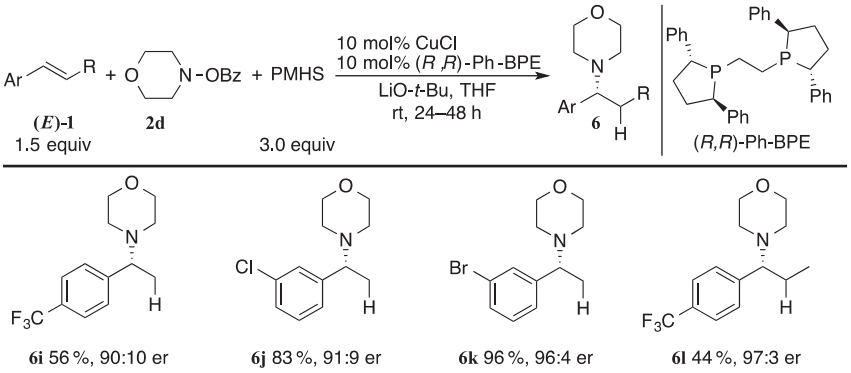
Indeed, the desired catalytic and enantioselective hydroamination of styrenes (*E*)-**1** proceeded in the presence of the same optimized catalyst system, CuCl/(*S*,*S*)-Me-Duphos, to form the corresponding optically active benzylamine derivatives **6** in good yields and good enantiomeric ratios (Scheme 9). Particularly notable is the high compatibility with substituents at the β-position (**6g** and **6h**). As pointed out above, these β-substituted styrenes are an inaccessible substrate class in the conventional intermolecular hydroamination catalysis.



Scheme 8 Working hypothesis for catalytic formal hydroamination of alkenes with PMHS and hydroxylamines.



Scheme 9 Catalytic asymmetric hydroamination of electron-rich and -neutral styrenes.



Scheme 10 Catalytic asymmetric hydroamination of electron-deficient styrenes.

On the other hand, the (*R*,*R*)-Ph-BPE ligand gave better enantioselectivities for the hydroamination of Cl-, Br-, and CF_3-substituted electron-deficient styrenes (Scheme 10). Notably, the reaction of (*E*)-4-trifluoromethyl-β-methylstyrene provided the highest er value (**6l**).

Summary

We have demonstrated a Cu-catalyzed regioselective, stereospecific, and enantioselective aminoboration of alkenes with bis(pinacolato)diboron and hydroxylamines. To the best of our knowledge, this is the first successful catalysis for simultaneous addition of boron and nitrogen functionalities to C–C unsaturated molecules. Moreover, this protocol has been applied to a formal and catalytic enantioselective hydroamination of styrenes with PMHS and hydroxylamines. The Cu catalysis can overcome some limitations of the precedented intermolecular hydroamination catalysis in view of substrate scope and enantioselectivity. The key to these successes is the introduction of an umpolung, electrophilic amination strategy. Further development of related C–N bond-forming processes is ongoing in our laboratory.

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References

[1] (a) R. Hili, A. K. Yudin. *Nat. Chem. Biol.* **2**, 284 (2006); (b) A. Ricci. *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, Weinheim (2007).

[2] For reviews, see: (a) E. Erdik, M. Ay. *Chem. Rev.* **89**, 1947 (1989); (b) K. Narasaka, M. Kitamura. *Eur. J. Org. Chem.* **21**, 4505 (2005); (c) E. Ciganek. *Org. React.* **72**, 1 (2009); (d) T. J. Barker, E. R. Jarbo. *Synthesis* 3954 (2011).

[3] (a) T. Kawano, K. Hirano, T. Satoh, M. Miura. *J. Am. Chem. Soc.* **132**, 6900 (2010); (b) K. Hirano, T. Satoh, M. Miura. *Org. Lett.* **13**, 2395 (2011); (c) N. Matsuda, K. Hirano, T. Satoh, M. Miura. *Org. Lett.* **13**, 2869 (2011); (d) N. Matsuda, K. Hirano, T. Satoh, M. Miura. *J. Org. Chem.* **77**, 617 (2012); (e) N. Matsuda, K. Hirano, T. Satoh, M. Miura. *Angew. Chem., Int. Ed.* **51**, 3642 (2012); (f) N. Matsuda, K. Hirano, T. Satoh, M. Miura. *Synthesis* **44**, 1792 (2012); (g) N. Matsuda, K. Hirano, T. Satoh, M. Miura. *Angew. Chem., Int. Ed.* **51**, 11827 (2012); (h) Y. Miki, K. Hirano, T. Satoh, M. Miura. *Org. Lett.* **15**, 172 (2013); (i) R. Sakae, K. Hirano, T. Satoh, M. Miura. *Chem. Lett.* **42**, 1128 (2013). http:/dx/doi.org/10.1246/cl.130485.

[4] For recent examples, see: (a) A. M. Berman, J. S. Johnson. *J. Am. Chem. Soc.* **126**, 5680 (2004); (b) S. Liu, L. S. Liebeskind. *J. Am. Chem. Soc.* **130**, 6918 (2008); (c) C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, A. Lei. *Angew. Chem., Int. Ed.* **47**, 6414 (2008); (d) T. J. Barker, E. R. Jarvo. *J. Am. Chem. Soc.* **131**, 15598 (2009); (e) T. Hatakeyama, Y. Yoshimoto, S. K. Ghorai, M. Nakamura. *Org. Lett.* **12**, 1516 (2010); (f) C. Grohmann, H. Wang, F. Glorius. *Org. Lett.* **14**, 656 (2012); (g) Q. Xiao, L. Tian, R. Tan, Y. Xia, D. Qiu, Y. Zhang, J. Wang. *Org. Lett.* **14**, 4230 (2012); (h) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic. *J. Am. Chem. Soc.* **134**, 6571 (2012); (i) S. N. Mlynarski, A. S. Karns, J. P. Morken. *J. Am. Chem. Soc.* **134**, 16449 (2012); (j) C. Zhu, G. Li, D. H. Ess, J. R. Falck, L. Kürti. *J. Am. Chem. Soc.* **134**, 18253 (2012); (k) T. Miura, M. Morimoto, M. Murakami. *Org. Lett.* **14**, 5214 (2012); (l) X. Qian, Z. Yu, A. Auffrant, C. Gosmini. *Chem.—Eur. J.* **19**, 6225 (2013).

[5] N. Matsuda, K. Hirano, T. Satoh, M. Miura. *J. Am. Chem. Soc.* **135**, 4934 (2013).
[6] Y. Miki, K. Hirano, T. Satoh, M. Miura. *Angew. Chem., Int. Ed.* **52**, 10830 (2013). http:/dx/doi.org/10.1002/anie.201304365.
[7] A. Pelter, K. Smith, H. C. Brown. *Borane Reagents*, Academic Press, London (1988); (b) N. Miyaura, A. Suzuki. *Chem. Rev.* **95**, 2457 (1995); (c) M. Davison, A. K. Hughes, T. B. Marder, K. Wade. *Contemporary Boron Chemistry*, RSC, Cambridge, UK (2000); (d) D. G. Hall (Ed.). *Boronic Acids*, 2nd ed., Wiley-VCH, Weinheim (2011).
[8] M. Suginome, T. Ohmura. In *Boronic Acids*, 2nd ed., D. G. Hall (Ed.), p. 171, Wiley-VCH, Weinheim (2011).
[9] (a) Y. Lee, A. H. Hoveyda. *J. Am. Chem. Soc.* **131**, 3160 (2009); (b) Y. Sasaki, C. Zhong, M. Sawamura, H. Ito. *J. Am. Chem. Soc.* **132**, 1226 (2010); (c) Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito. *Angew. Chem., Int. Ed.* **50**, 2778 (2011); (d) R. Corberán, N. W. Mszar, A. H. Hoveyda. *Angew. Chem., Int. Ed.* **50**, 7079 (2011); (e) H. Jang, A. R. Zhugralin, Y. Lee, A. H. Hoveyda. *J. Am. Chem. Soc.* **133**, 7859 (2011); (f) H.-Y. Jung, J. Yun. *Org. Lett.* **14**, 2606 (2012); (g) J. K. Park, B. A. Ondrusek, D. T. McQuade. *Org. Lett.* **14**, 4790 (2012); (h) K. Semba, T. Fujihara, J. Terao, Y. Tsuji. *Chem.—Eur. J.* **18**, 4179 (2012); (i) W. Yuan, S. Ma. *Org. Biomol. Chem.* **10**, 7266 (2012); (j) A. L. Moure, R. G. Arrayás, D. J. Cárdenas, I. Alonso, J. C. Carretero. *J. Am. Chem. Soc.* **134**, 7219 (2012); (k) W. Yuan, S. Ma. *Adv. Synth. Catal.* **354**, 1867 (2012).
[10] The Cu-catalyzed carboboration and stannylboration of alkynes and alkenes based on a similar concept were reported. See: (a) L. Zhang, J. Cheng, B. Carry, Z. Hou. *J. Am. Chem. Soc.* **134**, 14314 (2012); (b) R. Alfaro, A. Parra, J. Alemán, J. L. G. Ruano, M. Tortosa. *J. Am. Chem. Soc.* **134**, 15165 (2012); (c) Y. Takemoto, H. Yoshida, K. Takaki. *Chem.—Eur. J.* **18**, 14841 (2012); (d) K. Kubota, E. Yamamoto, H. Ito. *J. Am. Chem. Soc.* **135**, 2635 (2013); (e) P. Liu, Y. Fukui, P. Tian, Z.-T. He, C.-Y. Sun, N.-Y. Wu, G.-Q. Lin. *J. Am. Chem. Soc.* **135**, 11700 (2013).
[11] D. S. Laitar, E. Y. Tsui, J. P. Sadighi. *Organometallics* **25**, 2405 (2006).
[12] For reviews, see: (a) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada. *Chem. Rev.* **108**, 3795 (2008); (b) Y. Fukumoto. *J. Synth. Org. Chem. Jpn.* **67**, 735 (2009); (c) K. D. Hesp, M. Stradiotto. *ChemCatChem* **2**, 1192 (2010); (d) J. F. Hartwig. *Organotransition Metal Chemistry: From Bonding to Catalysis*, Vol. 1, p. 700, University Science Books, Sausalito, CA (2010).
[13] (a) M. Kawatsura, J. F. Hartwig. *J. Am. Chem. Soc.* **122**, 9546 (2000); (b) U. Nettekoven, J. F. Hartwig. *J. Am. Chem. Soc.* **124**, 1166 (2002); (c) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig. *J. Am. Chem. Soc.* **125**, 5608 (2003); (d) M. Ustunomiya, J. F. Hartwig. *J. Am. Chem. Soc.* **125**, 14286 (2003); (e) J.-S. Ryu, G. Y. Li, T. J. Marks. *J. Am. Chem. Soc.* **125**, 12584 (2003); (f) M. Utsunomiya, J. F. Hartwig. *J. Am. Chem. Soc.* **126**, 2702 (2004); (g) J. Takaya, J. F. Hartwig. *J. Am. Chem. Soc.* **127**, 5756 (2005); (h) H. Qian, R. A. Widenhoefer. *Org. Lett.* **7**, 2635 (2005); (i) S. G. Pan, K. Endo, T. Shibata. *Org. Lett.* **14**, 780 (2012).
[14] For leading work on the generation of Cu–H species with PMHS, see: (a) B. H. Lipshutz, K. Noson, W. Chrisman. *J. Am. Chem. Soc.* **123**, 12917 (2001); (b) B. H. Lipshutz, A. Lower, K. Nolan. *Org. Lett.* **4**, 4045 (2002); (c) B. H. Lipshutz, J. M. Servesko, B. R. Taft. *J. Am. Chem. Soc.* **126**, 8352 (2004); (d) B. H. Lipshutz, J. M. Servesko, T. B. Peterson, P. P. Papa, A. A. Lover. *Org. Lett.* **6**, 1273 (2004); (e) B. A. Baker, Z. V. Boskovic, B. H. Lipshutz. *Org. Lett.* **10**, 289 (2008).