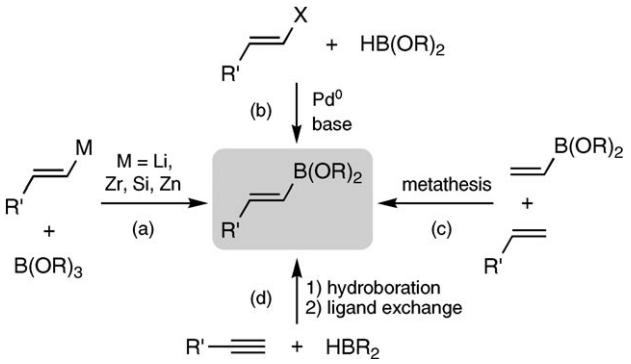
Synthetic Methods

DOI: 10.1002/anie.200804912

Synthesis of Activated Alkenylboronates from Acetylenic Esters by CuH-Catalyzed 1,2-Addition/Transmetalation**

Bruce H. Lipshutz, Žarko V. Bošković, and Donald H. Aue**

Boronic esters, boronic acids, and trifluoroborates make up an especially important class of coupling partners in organometallic chemistry. Vinylboronates, in particular, are useful intermediates in many reactions, including Suzuki–Miyaura cross-couplings, rhodium-catalyzed additions to unsaturated carbonyl derivatives, boron-Heck reactions, and boron-Mannich reactions.[1] Several approaches to alkenyl boronates have been described (Scheme 1), including: a) quenching



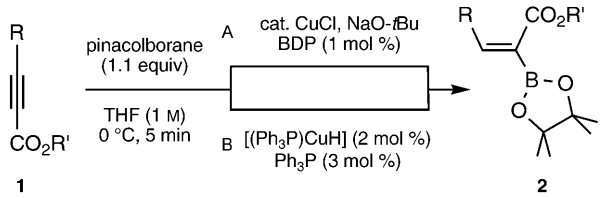
Scheme 1. Routes to alkenyl boronates: a) Quenching of alkenyl metal species. b) Pd-catalyzed halogen/boron exchange. c) Olefin metathesis. d) Hydroboration.

reactive alkenyl metal species with $B(OR)_3$;[2] b) Pd- or Pt-catalyzed halogen/boron exchange with $HB(OR)_2$;[3] c) olefin metathesis;[4] and d) hydroboration (HB) of terminal alkynes.[5] The latter pathway (d) is regioselective for terminal alkynes only,[6] and requires subsequent manipulation of the two alkyl–boron bonds present in the initial adduct, which can add hours (or even days) to the HB reaction.[6] Herein a newly developed, general methodology is described, which leads to these rare coupling partners (**2**, Scheme 2). This single-pot process highlights a remarkable copper-to-boron transmetalation on an sp^2-like hybridized carbon, directly forming vinylboronates bearing a valuable α-carboalkoxy group not otherwise accessible by routes (a)–(d).

[*] Prof. B. H. Lipshutz, Ž. V. Bošković, Prof. D. H. Aue
Department of Chemistry and Biochemistry
University of California, Santa Barbara
Santa Barbara, CA 93106 (USA)
E-mail: lipshutz@chem.ucsb.edu
aue@chem.ucsb.edu

[**] Financial support from the NSF and Zymes, LLC is warmly acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804912.



Scheme 2. CuH-catalyzed 1,2-addition/transmetalation of acetylenic esters. BDP = 1,2-bis(diphenylphosphino)benzene.

Exposure of acetylenic ester **1** to ligated CuH leads to rapid *syn* hydrocupration.[7] In the presence of stoichiometric pinacolborane,[5f,8] the initially formed α-cuprio ester undergoes stereoretentive transmetalation,[9] affording isolable 1-(alkoxycarbonyl)alkenyl pinacol boronates **2** (Scheme 2). Recent interest in α-functionalization of enoates has focused on methods for installing either silicon[10] or tin[11] at this site. The corresponding boronates **2**, however, benefit from all of the virtues associated with boron chemistry, such as stability, environmental friendliness, and chemoselectivity. This route to α-boryl-α,β-unsaturated esters also complements existing methods for the synthesis of β-boryl-α,β-unsaturated esters.[12]

Initially, 1,2-bis(diphenylphosphino)benzene (BDP)[13] was used as a ligand (1 mol%) for in situ generated CuH, to form [(BDP)CuH](conditions A, Scheme 2). More convenient, however, is commercially available Stryker's reagent (SR), $[(Ph_3P)CuH]_6$[14] (2 mol%)[15] (conditions B, Scheme 2). Both formulations led instantaneously to the desired HB product with excellent *Z*/*E* ratios. SR in the presence of pinacolborane (HBpin) undergoes a color change from red to dark red or even brown, which suggests the possible formation of a new species, $[(Ph_3P)CuH]\cdot$HBpin, perhaps analogous to that proposed for ligated CuH in the presence of silanes.[16]

Control experiments confirmed that net HB does not take place in the absence of CuH. Likewise, a mixture of alkynoate and pinacolborane did not give rise to HB to any noticeable extent, even after prolonged reaction times (several hours). Triphenylphosphine alone led to no reaction under these typical conditions.

For successful HB reactions, substrate concentrations on the order of 1M in THF appeared to be crucial.[17] Lower concentrations (0.1M) unexpectedly yielded the corresponding *Z*-enoate as the only reaction product, as protonation occurred faster than transmetalation. Examples of successful conversions of various educts **1** into products **2** are illustrated in Figure 1. The nature of the alkyl ester residue appeared not to be of consequence, even when highly hindered (e.g., 2-adamantyl, **9**). The expected *Z*-boronates were favored, although this selectivity is somewhat ligand-dependent. For

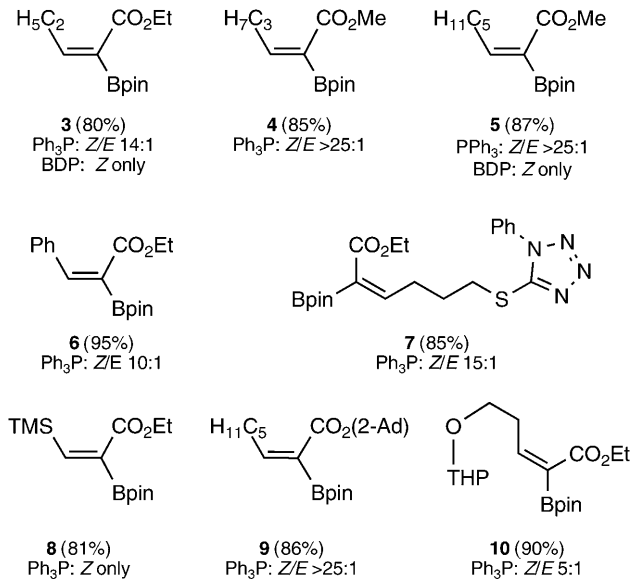
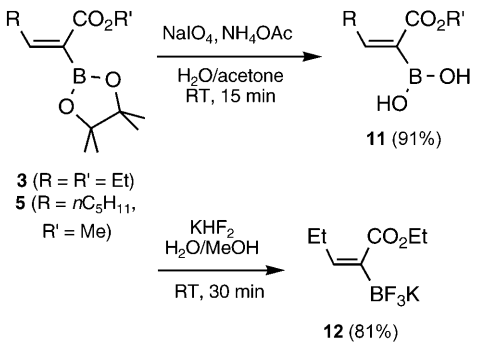


Figure 1. Isolable products from acetylenic ester precursors, with PPh_3 or BDP as a ligand for in situ generated CuH. TMS = trimethylsilyl; Ad = adamantyl; THP = tetrahydropyranyl.

example, only *Z*-boronates, such as **3** and **5**, resulted from reaction with [(BDP)CuH] and HBpin. Terminal acetylenes, such as propynoates, were unfortunately deprotonated to their copper acetylides, thereby inhibiting HB. Whereas boronates **3**–**10** are all isolable by chromatography, small amounts were lost as a result of protonolysis. Therefore, yields did not fully reflect the efficiency of the initial CuH-catalyzed event.

The readily obtained pinacol boronates, such as **3** and **5**, were smoothly converted into their corresponding boronic acids **11** by hydrolytic cleavage using sodium periodate in an acetone/water mixture (Scheme 3).[18] In the case of crystalline boronic acid **11** (R = nC_5H_{11}, R′ = Me), single-crystal X-ray diffraction confirmed the expected *Z*-geometry resulting from *syn* hydrocupration (Figure 2). Application of Molander's conditions readily transformed boronic acid **11** (R = R′ Et) to potassium organotrifluoroborate **12**.[19]

The newly formed boronates **2** were unexpectedly stable to acid (both aqueous HCl and refluxing HOAc), compared with the usual lability of vinylic boron-containing species.



Scheme 3. Conversion of pinacol boronates into coupling partners **11** and **12**.

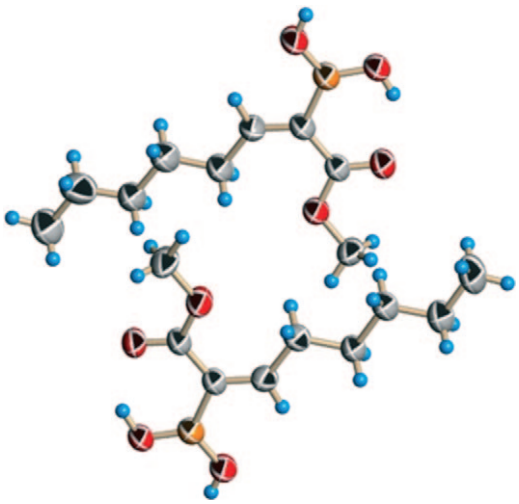
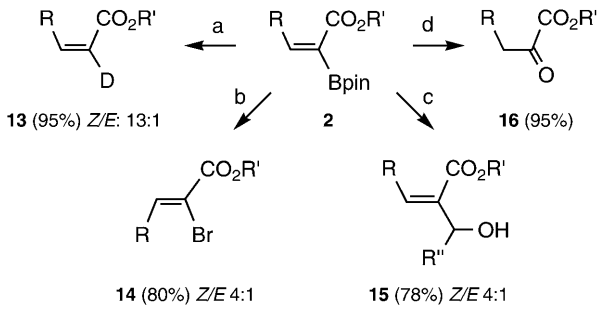


Figure 2. Molecular structure of vinylboronic acid **11**, depicting two adjacent molecules (see Scheme 3, R = nC_5H_{11}, R′ = Me). Thermal ellipsoids are set at 50% probability. B orange, C gray, H blue, O red.

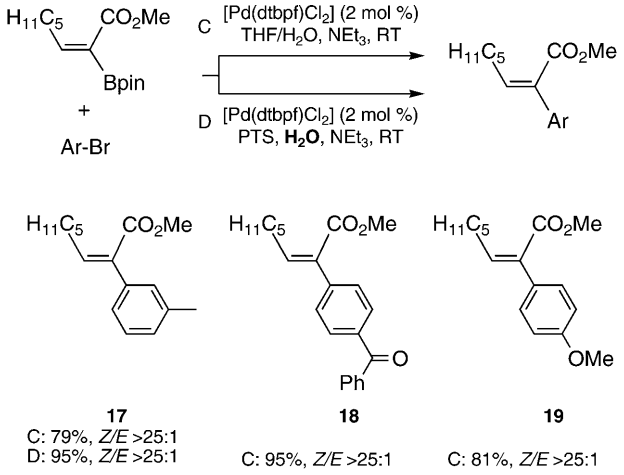
However, exposure to selected transition metal catalysts, such as [Rh(OH)cod] (0.1 mol%, cod = cyclooctadiene) promoted transmetalation, and in the presence of water led to facile α-protonation or deuteration (**13**, Scheme 4, path a). Sequential



Scheme 4. Functionalization of 1-(alkoxycarbonyl)alkenyl pinacol boronate **2**. a) [Rh(OH)cod] (0.1 mol%), dioxane (R = *n*Pr, R′ = Me), D_2O; b) Br_2, DCM, then NaOMe, MeOH (R = R′ = Et); c) Et_2Zn, THF, −78 °C to RT, hexanal (R = R′ = Et, R″ = nC_5H_{11}); d) H_2O_2, H_2O, KOH, 0 °C (R = *n*Pr, R′ = Me).

treatment of boronate **2** with bromine followed by NaOMe in a one-pot reaction afforded the corresponding alkenyl bromides **14** with predominant inversion of configuration.[20] The presence of base, however, led to partial olefin isomerization (*Z*/*E* ratio: 5:1; Scheme 4, path b). Transmetalation with zinc and subsequent addition to aldehydes allowed for an alternative to the Baylis–Hillman reaction (**15**; Scheme 4, path c).[21] Standard treatment of **2** with alkaline hydrogen peroxide led to α-ketoesters **16** (Scheme 4, path d).

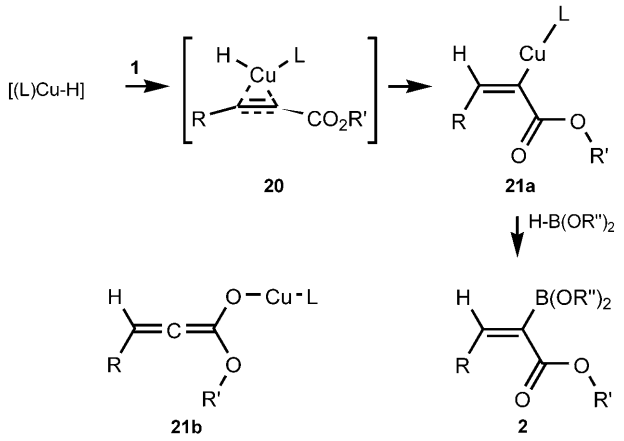
Net hydroarylation of an alkyne was achieved when a boronic ester, such as **5** (Scheme 5), was subjected to Suzuki–Miyaura conditions, catalyzed by 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium(II) chloride (2 mol%; path C). The couplings proceeded in minutes, and the resulting styrenes **17**–**19** retained their original double-bond geometry.



Scheme 5. Pd-catalyzed couplings in a water/THF mixture 7/1 v/v (C) or water (D). dtbpf = 1,1′-bis(di-*tert*-butylphosphino)ferrocene; PTS = polyoxyethanyl-α-tocopheryl sebacate

Both electron-poor and electron-rich aryl bromides reacted with equal effectiveness. Opportunities also exist to conduct such reactions in neat water, in the presence of the micelle-forming amphiphile polyoxyethanyl-α-tocopheryl sebacate (PTS, 2 mol %, path D).[22]

The stereoselectivity of the HB reaction suggests a mechanism (Scheme 6) in which the 1,2-addition forms a carbon-bound copper intermediate **21a**,[23] rather than the



Scheme 6. Stereoselective addition-transmetalation leading to boronates **2**. L = PH_3.

oxygen-bound intermediate **21b**. This result was at first surprising, based upon the assumption that the Cu–O bonds would be stronger than Cu–C bonds, and prompted a computational investigation of this reaction. High-level ab initio calculations indicated that **21b**, is significantly less stable than **21a** (R = H, L = PH_3, R′ = CH_3), by 29.5 kcal mol^{-1}.[24] Similarly, the stabilities of the boron analogues (R″ = H) were found to differ by a comparably large free energy, 23.2 kcal mol^{-1}. Although our computed bond energies confirmed that Cu–C (or B–C) bonds are weaker than Cu–O (or B–O) bonds, other energetic differences in the structures of **21a** and **21b** have a much larger effect on the overall energy difference. Thus, the computed free energy difference between methyl acrylate (analogous to **21a**) and its enol (analogous to **21b**) is 43.7 kcal mol^{-1}.

Further calculations indicated that the reaction proceeds, initially, via a weakly bound π-complex **20**, which rearranges to **21a** via a transition state involving hydrogen transfer (Figure 3), with a calculated free-energy barrier of only

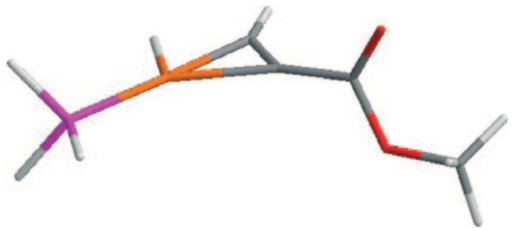
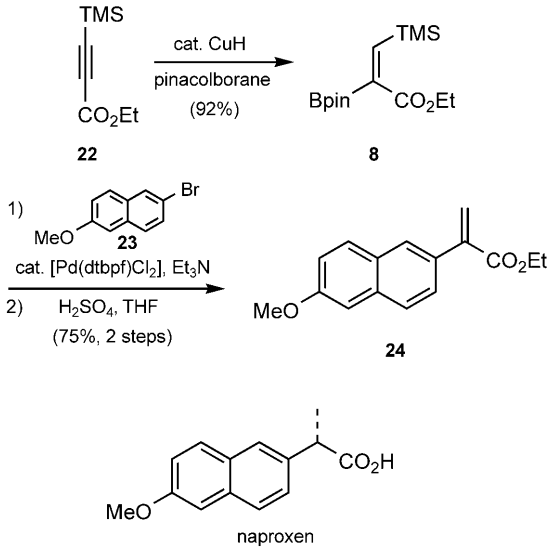


Figure 3. Transition state **20** in the addition of $(PH_3)CuH$ to methyl propiolate. C gray, Cu orange, H white, O red, P magenta.

7.2 kcal mol^{-1}, compared to 21.8 kcal mol^{-1} for CuH addition in the absence of a chelating PH_3 ligand. An alternative mechanism, via **21b** and a 6-membered transition state to form the B–C bond in **2**, appears unlikely in view of the high calculated free energy of **21b**, and is not consistent with the derived boronate stereochemistry.

Access to α-aryl enoates offers a new pathway to the key intermediate **24**, which is utilized industrially in the synthesis of the antiinflammatory drug naproxen (Scheme 7). Readily available propiolate **22** undergoes CuH-catalyzed HB to form α-boron enoate **8**, followed by a Suzuki–Miyaura reaction. Cross-coupling of **8** with naphthyl bromide **23** was effective either in THF (conditions C, Scheme 5; 92 %) or in neat water in the presence of PTS (conditions D; 87 %), although in the latter case sonication was required, to overcome the low solubility in water of **23**. The vinylic trimethylsilyl group was cleanly cleaved with sulfuric acid in refluxing THF to afford



Scheme 7. Synthesis of intermediate **24**, en route to naproxen.

aryl acrylate **24**, which can be subsequently hydrolyzed and hydrogenated with Noyori's ruthenium-based catalyst to give naproxen.[25]

In summary, a new route has been developed to geometrically defined vinylboronates bearing an activating alkoxycarbonyl substituent in the α-position. The method consists of catalytic chemo- and stereoselective 1,2-additions of CuH to acetylenic esters, and subsequent facile in situ transmetalation with pinacolborane. The application of this method to the synthesis of the antiinflammatory drug naproxen demonstrated its potential.

Experimental Section

General Procedure for Hydroboration of Alkynoates using Stryker's Reagent: In a flame-dried 100 mL round bottom flask under an argon atmosphere, a bright red solution of Stryker's reagent $[(PPh_3)CuH]_6$ (140 mg, 0.428 mmol, 2.1 mol%), and triphenylphosphine (100 mg, 0.38 mmol, 2 mol%) in THF (20 mL) was cooled in an ice bath and pinacolborane (3.20 mL, 22.05 mmol, 1.10 equiv) was added in one portion and stirred for 5 min, which caused the solution to darken. Methyl octynoate (3.08 g, 3.35 mL, 20.00 mmol, 1 equiv) was then added dropwise over 5 min. The solvent was evaporated under reduced pressure and the residue subjected to chromatography on silica gel, using 7% EtOAc in hexanes, to afford the product (4.79 g, 17.00 mmol, 85%).

Received: October 8, 2008
Published online: November 25, 2008

Keywords: boronates · copper · cross-coupling · hydroboration · P ligands

[1] *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**.
[2] a) H. C. Brown, N. G. Bhat, *Tetrahedron Lett.* **1988**, *29*, 21–24; b) K. Itami, T. Kamei, J.-i. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671; c) T. E. Cole, R. Quintanilla, *Organometallics* **1991**, *10*, 3777–3781.
[3] a) J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006; b) M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *Synthesis* **2000**, 778–780.
[4] C. Morrill, R. H. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031–6034.
[5] a) R. W. Hoffmann, S. Dresley, *Synthesis* **1988**, 103–106; b) P. Martinez-Fresneda, M. Vaultier, *Tetrahedron Lett.* **1989**, *30*, 2929–2932; c) A. Kamabuchi, T. Moriya, N. Miyaura, A. Suzuki, *Synth. Commun.* **1993**, *23*, 2851–2859; d) H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255; e) A. V. Kalinin, S. Scherer, V. Snieckus, *Angew. Chem.* **2003**, *115*, 3521–3526; *Angew. Chem. Int. Ed.* **2003**, *42*, 3399–3404; f) C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482–3485; g) X. He, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 1696–1702.
[6] M. Gravel, B. B. Toure, D. G. Hall, *Org. Prep. Proced. Int.* **2004**, *36*, 573–580.
[7] a) J. F. Daeuble, C. McGettigan, J. M. Stryker, *Tetrahedron Lett.* **1990**, *31*, 2397–2400; b) H. C. Brown, G. A. Molander, *J. Org. Chem.* **1981**, *46*, 645–647.
[8] Catecholborane seems to be incompatible with SR.
[9] a) B. H. Lipshutz, P. Papa, *Angew. Chem.* **2002**, *114*, 4762–4764; *Angew. Chem. Int. Ed.* **2002**, *41*, 4580–4582; b) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441.
[10] a) A. J. Mueller, M. P. Jennings, *Org. Lett.* **2007**, *9*, 5327–5330; b) A. J. Mueller, M. P. Jennings, *Org. Lett.* **2008**, *10*, 1649–1652.
[11] a) Y. Shi, S. M. Peterson, W. W. Haberaecker, S. A. Blum, *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169; b) L. T. Leung, S. K. Leung, P. Chiu, *Org. Lett.* **2005**, *7*, 5249–5252.
[12] J.-E. Lee, J. Kwon, J. Yun, *Chem. Commun.* **2008**, 733–734.
[13] B. A. Baker, Z. V. Boskovic, B. H. Lipshutz, *Org. Lett.* **2008**, *10*, 289–292.
[14] a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291–293; b) W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818–8823.
[15] Reducing copper and ligand content to 0.2 mol% and 0.3 mol%, respectively, lengthened the reaction times from minutes to several hours.
[16] B. H. Lipshutz, W. Chrisman, A. Lower, *J. Am. Chem. Soc.* **2003**, *125*, 8779–8789. Such Cu–B species are well-known; see H. Zhao, L. Dang, T. B. Marder, Z. Lin, *J. Am. Chem. Soc.* **2008**, *130*, 5586–5594; D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *J. Am. Chem. Soc.* **2006**, *128*, 11036, and references therein. Borylcupration: T. Kajiwara, T. Terabayashi, M. Yamashita, K. Nozaki, *Angew. Chem.* **2008**, *120*, 6708–6712; *Angew. Chem. Int. Ed.* **2008**, *47*, 6606–6610.
[17] Alkynones do not lead to HB products akin to **2** under these conditions. Interestingly, under transfer hydrogenation conditions using a ruthenium hydride at high substrate concentrations, 1,2-addition across the alkyne occurs as an undesired side reaction, to form an α-ruthenium complex; see K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
[18] a) T. Itoh, K. Hirai, H. Tomioka, *J. Am. Chem. Soc.* **2004**, *126*, 1130–1140; b) M. Nambo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2007**, *129*, 8080–8081.
[19] G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286. See also S. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288–325.
[20] H. C. Brown, T. Hamaoka, N. Ravindran, *J. Am. Chem. Soc.* **1973**, *95*, 6456–6457.
[21] F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229–8243.
[22] B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.* **2008**, *10*, 1333–1336.
[23] J. Klein, R. M. Turkel, *J. Am. Chem. Soc.* **1969**, *91*, 6186–6187.
[24] Free energy differences for copper species were calculated by using a G2(MP2)-like procedure at the CCSD(T)/6-311+G-(2df,2pd)//MP2/6-311+G(d,f) level, using thermodynamic terms from B3LYP/6-311+G(d,p) frequencies scaled by 0.99 for zero-point energies and 0.96 for thermal and entropy terms. For the boronic acids, the level of theory is effectively CCSD(T)/aug-cc-pVTZ//MP2/6-31+G(d,f) with B3LYP/6-311G(d,p) frequencies.
[25] a) Hydrolysis: S. J. Mahmood, C. Brennan, M. M. Hossain, *Synthesis* **2002**, 1807–1809; b) Asymmetric hydrogenation: T. Ohta, M. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174–3176; c) A. S. C. Chan, S. A. Laneman, US Patent 5198561, **1993**.

