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Highly Stereoselective Synthesis of (Borylmethyl)cyclopropylamines by Copper-Catalyzed Aminoboration of Methylenecyclopropanes

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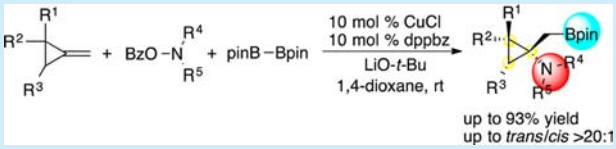
Supporting Information

ABSTRACT: A Cu-catalyzed aminoboration of 1-methylenecyclopropanes with bis(pinacolato)diboron and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines has been developed. The Cu catalysis provides a rapid and concise access to (borylmethyl)cyclopropylamines in a highly regio- and diastereoselective manner. The products obtained can be useful building blocks for the synthesis of potential antidepressants, *trans*-2-arylcyclopropylamine derivatives.



Cyclopropylamines are commonly occurring structural motifs in many biologically active natural and unnatural products and pharmaceuticals.[1] Such well-known examples include Belactosin A,[2] Nevirapine,[3] Ciprofloxacin,[4] and Tranylcypromine[5] (Figure 1). Representative convergent

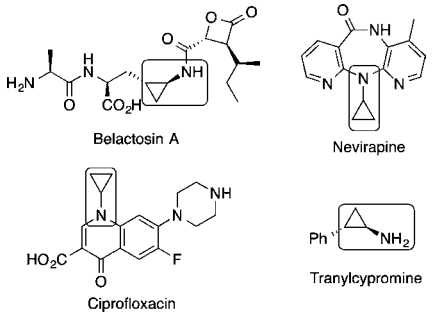
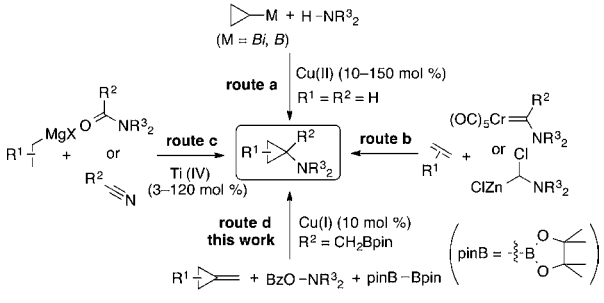


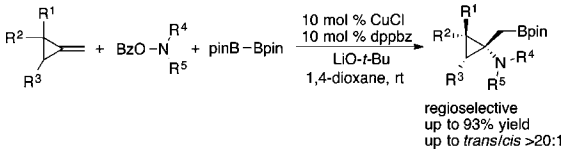
Figure 1. Cyclopropylamines in biologically active compounds.

approaches to the cyclopropylamine are (1) a copper-mediated oxidative cross-coupling of amines with cyclopropylbismuth[6a] or -boronic acid[6b] (Scheme 1, route a), (2) a cyclopropanation of alkenes with nitrogen-substituted metal carbenoids (route b),[7] and (3) a titanium-mediated Kulinkovich-type reaction of amides[8a,b] and nitriles[8c,d] with alkyl Grignard reagents (route c). These precedents are quite useful, but still limited in scope and selectivity because of harsh reaction conditions and the use of excess metal promoters and highly reactive organometallic reagents. Thus, there still remains a large demand for further development of new protocols for the efficient synthesis of densely functionalized, highly substituted cyclopropylamines.[9] Herein, we report the fourth route, the catalytic addition of nitrogen-based functional groups to methylenecyclopropanes with the concomitant introduction of the boron moiety (route d): a copper-catalyzed aminoboration of methylenecyclopropanes with bis(pinacolato)diboron (pinB-Bpin) and *O*-benzoylhydroxylamines is described. The copper catalysis proceeds smoothly under mild conditions (room temperature) and provides versatile (borylmethyl)cyclopropylamines with high regio- and diastereoselectivity (Scheme 2). Subsequent transformations based on the resultant boron function could form a variety of *trans*-2-arylcyclopropylamine derivatives of great interest in medicinal chemistry.

Scheme 1. Representative Approaches to Cyclopropylamines



Scheme 2. Copper-Catalyzed, Highly Regio- and Diastereoselective Aminoboration of Methylenecyclopropanes



We initially selected 2-phenyl-1-methylenecyclopropane (**1a**) and attempted the synthesis of the corresponding (borylmethyl)cyclopropylamine with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**) and pinB−Bpin as an electrophilic nitrogen source[10,11] and a boryl source,[12] respectively, on the basis of our previous aminoboration of styrenes.[10i] A conceivable

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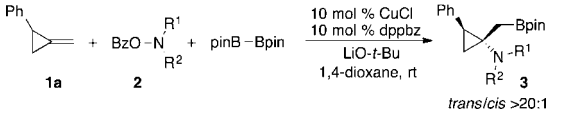
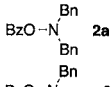
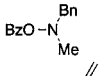
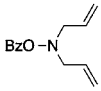
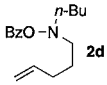
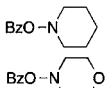
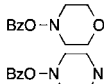
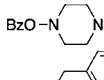
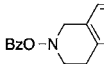
problem is controlling the regio- and stereochemistry. Particularly, the former issue has often appeared in reported addition reactions of methylenecyclopropanes, and problematic ring-opening events have occurred competitively or predominantly.[13] However, to our delight, **2a** underwent the aminoboration in the presence of a CuCl/1,2-bis(diphenylphosphino)benzene (dppbz) catalyst system and a LiO-*t*-Bu base in 1,4-dioxane at room temperature to form the desired **3aa** (93% yield) as a single regioisomer with high trans selectivity (*trans*/*cis* > 20:1) (Table 1, entry 1).[14] In this case,

Table 1. Copper-Catalyzed Aminoboration of 2-Phenyl-1-methylenecyclopropane (1a) with Various Hydroxylamines[a]



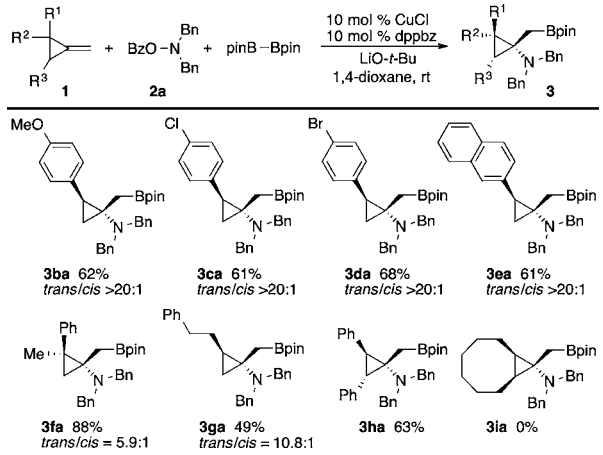
entry	2	3, yield (%)[b]
1	 **2a**	**3aa**, (93, 85[c])
2	 **2b**	**3ab**, 83 (70)
3	 **2c**	**3ac**, 77 (59)
4	 **2d**	**3ad**, 70 (40)
5	 **2e**	**3ae**, 68 (47)
6	 **2f**	**3af**, 62 (46)
7	 **2g**	**3ag**, 95 (82)
8	 **2h**	**3ah**, 81 (60)

[a]A mixture of CuCl (0.025 mmol), dppbz (0.025 mmol), **1a** (0.25 mmol), **2** (0.38 mmol), pinB–Bpin (0.38 mmol), and LiO-*t*-Bu (0.75 mmol) in 1,4-dioxane (1.5 mL) was stirred at rt for 4 h under N_2. [b]^{1}H NMR using 1-methylnaphthalene as an internal standard. Isolated yields are given in parentheses. The lower isolated yields are due to partial decomposition during chromatographic purification.[18] [c]On a 2.5 mmol scale.

ring-opening byproducts were not detected at all.[15] The aminoboration of **1a** with an array of hydroxylamines **2** proceeded smoothly under identical conditions. Other acyclic amines that bear *N*-benzyl-*N*-methyl, *N*,*N*-diallyl, and *N*-butyl-*N*-(4-pentenyl) substituents furnished the corresponding (borylmethyl)-substituted cyclopropylamines **3ab**–**3ad** in moderate to good yields (entries 2–4). The benzyl and allyl groups on the nitrogen can be a useful synthetic handle for further manipulation after the selective deprotection.[16] The exclusive formation of **3ad** from **2d** without formation of a pyrrolidine-containing product was suggestive of no involvement of an aminyl radical species.[17] The copper catalyst also accommodated cyclic amines such as piperidine, morpholine, piperazine, and tetrahydroisoquinoline to afford **3ae**–**3ah** in synthetically useful yields (entries 5–8). Moreover, the reaction on a 10-fold larger scale also could be operating with comparable efficiency, indicating the good reliability and reproducibility of the present catalysis (entry 1). In all entries of Table 1, the boryl and amino groups selectively added at the terminal and internal carbons, respectively, and no other regio- and constitutional isomers were formed, judged by the ^{1}H NMR of the crude material. Moreover, irrespective of the electronic and steric nature of hydroxylamines **2**, the high trans selectivity was uniformly observed.

We subsequently performed the aminoboration of other methylenecyclopropanes **1** (Scheme 3). Electron-rich methoxy-

Scheme 3. Copper-Catalyzed Aminoboration of Various Methylenecyclopropanes 1 with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (2a); Yield of Isolated Product is Shown



and electron-deficient chloro- and bromo-substituted 2-aryl-1-methylenecyclopropanes participated in the reaction, and functionalized cyclopropylamines **3ba**–**3da** were obtained in acceptable yields with high diastereoselectivity. Notably, the aryl-Br moiety was compatible, and additional functionalization was possible by the conventional palladium chemistry (**3da**). The naphthalene ring did not interfere with the reaction (**3ea**). In the case of 2-methyl-2-phenyl-1-methylenecyclopropane, the diastereoselectivity was somewhat decreased, but good reaction efficiency was retained (**3fa**). Additionally, the phenethyl-substituted substrate was reactive to produce **3ga** with good trans selectivity. The 2,3-diaryl substitution pattern was also tolerated (**3ha**), while the dialkyl analogue provided a mixture of unidentified products (**3ia**).

Although the detailed mechanistic insight was still premature, based on our previous findings[10i] and literature information,[12] we were tempted to assume the mechanism of the reaction of **1a** with **2a** as follows (Scheme 4). An initial salt metathesis between CuCl and LiO-*t*-Bu and coordination of the dppbz ligand formed the active CuO-*t*-Bu complex **A**. Subsequent σ-bond metathesis with pinB–Bpin generated the borylcopper species **B**, which then coordinated to the olefinic moiety of **1a** from the opposite face to the more sterically hindered Ph group (**C**). The regioselective *syn*-insertion into the Cu–B bond occurred to form the borylated alkylcopper intermediate **D**.[19] The stereoretentive electrophilic amination[20] with **2a** proceeded to produce **3aa** together with the CuOBz complex **E**. The catalytic cycle was closed by regeneration of the starting copper alkoxide **A** through the ligand exchange with LiO-*t*-Bu.[21] The postulated reaction course could explain the observed high trans selectivity. The regioselectivity in the insertion of alkenes into the borylcopper species such as **B** was generally controlled by the HOMO/LUMO interaction between the boryl ligand of the borylcopper and the vinyl

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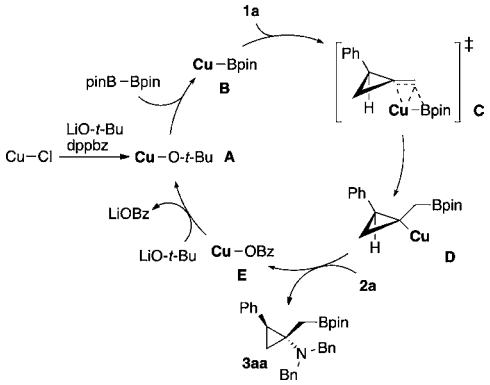
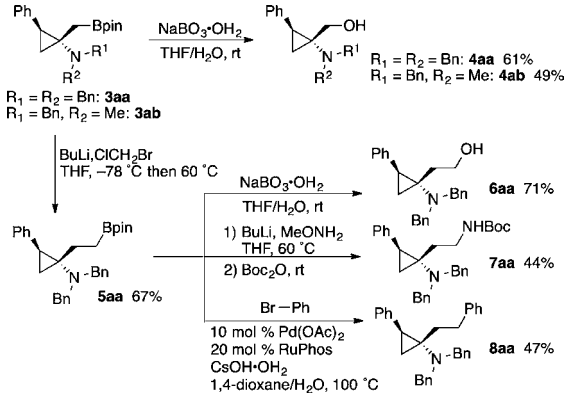
Scheme 4. Plausible Mechanism



carbon of alkenes.[22] However, preliminary DFT calculation in our hands supported the somewhat larger contribution of LUMO at the internal vinyl carbon of **1a**,[23] which runs counter to the observed regioselectivity. On the other hand, Ito recently reported that, in the case of electronically unbiased terminal aliphatic alkenes, the boryl group was selectively introduced at the less congested terminal position because a transient five-coordinated geometry at the borylated carbon formed a highly congested environment and destabilized the transition state much more when the borylation occurred at the more crowded internal position.[12r] Thus, also in our case, we speculated that the boryl addition at the less hindered terminal carbon compared to the internal carbon dominantly occurred through the transition state such as **C**, leading to the observed regioisomer exclusively.

To highlight the synthetic utility of this process, we derivatized the (borylmethyl)cyclopropylamine products **3** (Scheme 5). The oxidation with $NaBO_3{\cdot}OH_2$ afforded the

Scheme 5. Transformations of (Borylmethyl)cyclopropylamines 3



corresponding 1,2-aminoalcohols **4** in acceptable yields with the cyclopropylamine moiety left intact. The one-carbon homologation with the lithium carbenoid[24] was followed by the oxygenation or amination[11m] to produce the 1,3-amino-alcohol **6aa** or 1,3-diamine **7aa**. Moreover, the Suzuki–Miyaura cross-coupling of **5aa** was also possible, giving **8aa** in 47% yield (not optimized). Thus, the borylated cyclopropylamines **3** can be useful and versatile building blocks for the synthesis of cyclopropylamine derivatives.

In conclusion, we have developed a highly stereoselective access to (borylmethyl)cyclopropylamines by using a copper-catalyzed aminoboration of methylenecyclopropanes. The rich chemistry based on the resultant boryl moiety can readily transform products into versatile *trans*-2-phenylcyclopropylamine derivatives, which are of potential interest in medicinal chemistry. Further derivatizations of borylated cyclopropylamines[25] and application to the catalytic asymmetric synthesis[26] are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yoshimura, H.; Nagai, M.; Hibi, S.; Kikichi, K.; Abe, S.; Hida, T.; Higashi, S.; Hishimura, I.; Yamanaka, T. *J. Med. Chem.* **1995**, *38*, 3163. (b) Swann, E.; Barraja, P.; Oberlander, A. M.; Gardipee, W. T.; Hudnott, A. R.; Beall, H. D.; Moody, C. J. *J. Med. Chem.* **2001**, *44*, 3311. (c) Li, Q.; Woods, K. W.; Claiborne, A.; Gwaltney, S. L., II; Barr, K. J.; Liu, G.; Gehrke, L.; Credo, R. B.; Hui, Y. H.; Lee, J.; Warner, R. B.; Kovar, P.; Nukkala, M. A.; Zielinski, N. A.; Tahir, S. K.; Fitzgerald, M.; Kim, K. H.; Marsh, K.; Frost, D.; Ng, S.-C.; Rosenberg, S.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465. (d) Chai, H.; Zhao, Y.; Zhao, C.; Gong, P. *Bioorg. Med. Chem.* **2006**, *14*, 911. (e) Zhao, C.; Zhao, Y.; Chai, H.; Gong, P. *Bioorg. Med. Chem.* **2006**, *14*, 2552.

(2) (a) Asai, A.; Tsujita, T.; Sharma, S. V.; Yamashita, Y.; Akinaga, S.; Funakoshi, M.; Kobayashi, H.; Mizukami, T. *Biochem. Pharmacol.* **2004**, *67*, 227. (b) Groll, M.; Larionov, O. V.; Huber, R.; de Meijere, A. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4576.

(3) (a) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. *J. Med. Chem.* **1991**, *34*, 2231. (b) Kelly, T. A.; Patel, U. R. *J. Org. Chem.* **1995**, *60*, 1875.

(4) Remuzon, P.; Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Ledoussal, B.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1991**, *34*, 29.

(5) (a) Fujita, T. *J. Med. Chem.* **1973**, *16*, 923. (b) St. Georgiev, V.; Mack, R. A.; Walter, D. J.; Radov, L. A.; Baer, J. E. *Helv. Chim. Acta* **1987**, *70*, 1526. (c) Caille, D.; Bergis, O. E.; Fankhauser, C.; Gardes, A.; Adam, R.; Charieras, T.; Grosset, A.; Rovei, V.; Jarreau, F.-X. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 265. (d) Schenk, T.; Chen, W. C.; Göllner, S.; Howell, L.; Jin, L.; Hebestreit, K.; Klein, H.-U.; Popescu, A. C.; Burnett, A.; Mills, K.; Casero, R. A., Jr.; Marton, L.; Woster, P.; Minden, M. D.; Dugas, M.; Wang, J. C. Y.; Dick, J. E.; Müller-Tidow, C.; Petrie, K.; Zalent, A. *Nat. Med.* **2012**, *18*, 605.

(6) (a) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44. (b) Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Org. Lett.* **2008**, *10*, 1653.

(7) (a) Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M. A. *Org. Lett.* **2002**, *4*, 4273. (b) Bégis, G.; Cladingboel, D. E.; Motherwell, W. B. *Chem. Commun.* **2003**, 2656. (c) Jerome, L.; Sheppard, T. D.; Aliev, A. E.; Motherwell, W. B. *Tetrahedron Lett.* **2009**, *50*, 3709. (d) Ishikawa, S.; Sheppard, T. D.; D'Oyley, J. M.; Kamimura, A.; Motherwell, W. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 10060. Charette also reported a Cu- or Rh-catalyzed cyclopropanation with NO_2-substituted carbene precursors: (e) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (f) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383.

(8) (a) de Meijere, A.; Chaplinski, V.; Winsel, H.; Kordes, M.; Stecker, B.; Gazizova, V.; Savchenko, A. I.; Boese, R.; Schill, F. *Chem.—Eur. J.* **2010**, *16*, 13862. (b) Wolan, A.; Six, Y. *Tetrahedron* **2010**, *66*, 15. (c) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792. (d) Bertus, P.; Menant, C.; Tanguy, C.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 777.

(9) For another approach through reductive aminations with (1-ethoxycyclopropoxy)trimethylsilane and magnesium cyclopropylidenes: (a) Kang, J.; Kim, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 897. (b) Gillaspy, M. L.; Lefker, B. A.; Hada, W. A.; Hoover, D. J. *Tetrahedron Lett.* **1995**, *36*, 7399. (c) Yoshida, Y.; Umeza, K.; Hamada, Y.; Atsumi, N.; Tabuchi, F. *Synlett* **2003**, 2139. (d) Satoh, T.; Miura, M.; Sakai, K.; Yokoyama, Y. *Tetrahedron* **2006**, *62*, 4253.

(10) For our recent work on an umpolung, electrophilic amination, see: (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (b) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, *44*, 1792. (f) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3642. (g) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11827. (h) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 172. (i) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934. (j) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2013**, *42*, 1128. (k) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830.

(11) Reviews: (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. (b) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, *21*, 4505. (c) Ciganek, E. *Org. React.* **2009**, *72*, 1. (d) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954. Recent examples: (e) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (f) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (g) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (h) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (i) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516. (j) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571. (k) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (l) Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 4230. (m) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (n) Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253. (o) Miura, T.; Morimoto, M.; Murakami, M. *Org. Lett.* **2012**, *14*, 5214. (p) Qian, X.; Yu, Z.; Auffrant, A.; Gosmini, C. *Chem.—Eur. J.* **2013**, *19*, 6225. (q) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746.

(12) For a recent development of Cu-catalyzed borylation chemistry with pinB−Bpin, see: (a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (b) Kleeberg, C.; Dang, Li.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (c) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226. (d) Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2778. (e) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 7079. (f) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859. (g) Yoshida, H.; Kawashima, S.; Takemoto, Y.; Okada, K.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 235. (h) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528. (i) Jung, H.-Y.; Yun, J. *Org. Lett.* **2012**, *14*, 2606. (j) Park, J. K.; Ondrusek, B. A.; McQuade, D. T. *Org. Lett.* **2012**, *14*, 4790. (k) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem.—Eur. J.* **2012**, *18*, 4179. (l) Yuan, W.; Ma, S. *Org. Biomol. Chem.* **2012**, *10*, 7266. (m) Moure, A. L.; Arrayás, R. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219. (n) Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867. (o) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314. (p) Alfaro, R.; Parra, A.; Alemán, J.; Ruano, J. L. G.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165. (q) Takemoto, Y.; Yoshida, H.; Takaki, K. *Chem.—Eur. J.* **2012**, *18*, 14841. (r) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635. (s) Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700. (t) Semba, K.; Fujiwara, T.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 12400.

(13) For limited successful examples of highly selective ring-retaining addition reactions of methylenecyclopropanes, see: (a) Pohlmann, T.; de Meijere, A. *Org. Lett.* **2000**, *2*, 3877. (b) Itazaki, M.; Nishihara, Y.; Osakada, K. *J. Org. Chem.* **2002**, *67*, 6889. (c) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917. (d) Shao, L.-X.; Qi, M.-H.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 165. (e) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409. (f) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060. (g) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Cai, Y.-P.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 2616. (h) Ogata, K.; Shimada, D.; Fukuzawa, S.-I. *Chem.—Eur. J.* **2012**, *18*, 6142. (i) Schinkel, M.; Wallbaum, J.; Kozhushkov, S. I.; Marek, I.; Ackermann, L. *Org. Lett.* **2013**, *15*, 4482.

(14) The trans stereochemistry of **3ab** was determined by the derivatization into the known aminoalcohol, and those of others were tentatively assigned. See the Supporting Information for details.

(15) In the absence of CuCl, the reaction did not proceed at all. See the Supporting Information for the detailed optimization studies.

(16) (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Chem. Commun.* **2005**, 4086. (c) Wang, J.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 2040.

(17) (a) Noack, M.; Göttlich, R. *Chem. Commun.* **2002**, 536. Also see: (b) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709. (c) Tsuritani, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 3246.

(18) See the Supporting Information for the detailed procedure.

(19) Laitar, D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196.

(20) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521 and ref 10i.

(21) LiO-*t*-Bu also can accelerate some elementary steps by coordination to the Cu or B center. See: Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423.

(22) (a) Dang, Li.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824. (b) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443.

(23) Calculation was performed by DFT at the RB3LYP/6-31G(d) level of theory. See the Supporting Information for details.

(24) (a) Brown, H. C.; Singh, S. M.; Rangaishevi, M. V. *J. Org. Chem.* **1986**, *51*, 3150. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.

(25) Cyclopropylmethylboronates as homoallylation reagents: (a) Pei, W.; Krauss, I. J. *J. Am. Chem. Soc.* **2011**, *133*, 18514. (b) Lin, H.; Pei, W.; Wang, H.; Houk, K. N.; Krauss, I. J. *J. Am. Chem. Soc.* **2013**, *135*, 82.

(26) Our preliminary attempts with optically active DuPhos, 1,2-bis(phospholano)ethane (BPE), and BINAP ligands remained unsuccessful.