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Diastereoselective Reduction of Alkenylboronic Esters as a New Method for Controlling the Stereochemistry of up to Three Adjacent Centers in Cyclic and Acyclic Molecules

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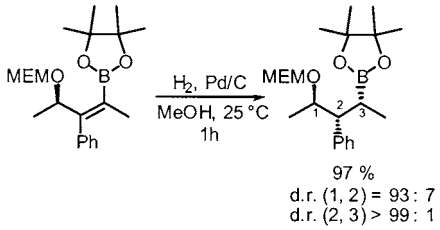
ABSTRACT



***cis*-Boronates are readily available via a diastereoselective Pd-catalyzed reduction of tetrasubstituted alkenylboronic esters using H_2. Applying the reaction conditions presented to unsaturated open-chain boronic esters allows the stereochemistry of up to three adjacent centers to be controlled.**

Organoboranes are key intermediates for the stereoselective preparation of a wide range of organic molecules.[1] In most cases, the stereochemical information is introduced by a *syn*-hydroboration step.[2,3] For example, starting from trisubstituted olefins allows the stereoselective synthesis of *trans*-organoboranes of type **1**. No simple synthesis of the isomeric *cis*-organoboranes of type **2** is available. Such compounds would be of synthetic importance and complement the preparation of organoboranes **1**. We envisioned that molecules of type **2** could be obtained by the syn hydrogenation of readily available boronic esters of type **3**.[4] This approach could also be of great interest for controlling the stereochemistry of open-chain boronic acids **4** by the diastereoselective syn reduction of boronic esters of type **5** (Scheme 1).[2b]

Herein, we wish to report a successful approach toward the desired cis products of type **2** and **4**, demonstrating the possibility of controlling the stereochemistry of up to three adjacent centers in open-chain molecules. First, we examined a range of reducing reagents and reaction conditions to optimize a syn hydrogenation of substrates of type **3**. Soon it became clear that, although cyclohexenylboronic esters can be reduced with various reducing agents such as diimide[5]

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(1) (a) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287. (b) Brown, H. C.; Jadhav, P. K. *Asymmetric Synth.* **1983**, *2*, 1. (c) Matteson, D. S. *Synthesis* **1986**, 973.

(2) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(3) For other stereoselective syntheses using organoboranes, see: (a) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (b) Roush, W. R. In ACS Symposium Series 386: *Trends Synth. Carbohydr. Chem.*; American Chemical Society: Washington, DC, 1989; p 242. (c) Matteson, D. S. In ACS Symposium Series 783: *Organoboranes for Syntheses*; American Chemical Society: Washington, DC, 2001; p 207. (d) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555. (e) Lhermitte, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2460.

(4) For the hydrogenation of alkynylboronic esters, see: Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635.

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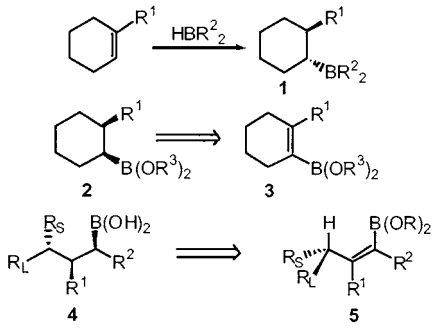
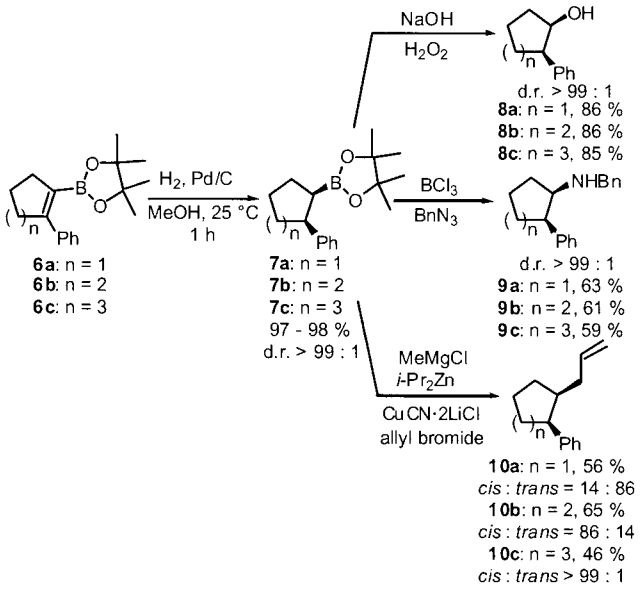
Scheme 1



and others,[6] in the case of tetrasubstituted alkenylboronic esters, only sluggish reactions were observed. We have found that reduction of these substrates with hydrogen (balloon connected to the reaction flask, ca. 1 atm) in the presence of catalytic amounts of Pd/C in methanol occurred smoothly with high stereoselectivity and in excellent yields. Thus, the 2-phenyl-substituted pinacol cycloalkenylboronic esters **6a**−**c**[7] were hydrogenated under these conditions [H_2 (1 atm), Pd/C (10 %), methanol, 25 °C, 1 h], leading to the corresponding saturated *cis*-boronic esters **7a**−**c** in quantitative yields and high diastereoselectivities (cis:trans > 99:1). These boronic esters were readily converted under standard conditions[1] to alcohols **8a**−**c**, respectively, in 85−86% yield and cis diastereoselectivities >99:1 (2 M NaOH, 30% H_2O_2) and to amines **9a**−**c**, respectively, [(a) BCl_3, 5.0 equiv, 25 °C, 4 h; (b) BnN_3, 3.0 equiv, from 0 to 25 °C, 8 h][8] in 59−63% yield and cis diastereoselectivities >99:1. The conversion of the boronic esters **7a**−**c** to the corresponding organozinc reagents[9] can be achieved by treatment with MeMgCl[10] (2.0 equiv, −78 °C to 25 °C, 10 h) followed by the addition of *i*-Pr_2Zn (40 equiv, 25 °C, 48 h). In the presence of CuCN·2LiCl (1.0 equiv) and allyl bromide (4.0 equiv), the expected allylated products **10a**−**c** were obtained in 46−56% yield and variable diastereoselectivities. Whereas the cyclopentane derivative **10a** was formed mainly as the trans isomer (trans:cis = 86:14), indicating an extensive epimerization of the intermediate organozinc species due to the presence of zinc halides,[11] the related *cis*-cyclohexylzinc intermediate displays a higher configurational stability under the same reaction conditions and furnished predominantly the cis product (cis:trans = 86:14). Interestingly, in the case of the seven-membered boronic ester (**7c**), the same reaction sequence furnished exclusively the cis stereoisomer of the allylated product (**10c**; cis:trans > 99:1)[12] (Scheme 2).

Scheme 2



Since alkenylpinacol boronic esters are hydrogenated considerably slower than the corresponding dimethoxy alkenylboronic esters, we have also developed a very convenient one-pot sequence for the diastereoselective reduction of dimethoxy alkenylboronic esters. These dimethoxy alkenylboronic esters can be generated in situ and then reduced and further converted into the pinacol boronic ester in a one-pot procedure. Thus, 1-bromocyclopent-1-ene (**11**) was treated with *t*-BuLi (2.0 equiv, −78 °C). After 30 min, $B(OMe)_3$ (1.5 equiv) was added and the reaction mixture was stirred overnight at room temperature, affording an intermediate dimethoxy alkenylboronic ester **12** that, after evaporation of the solvents, was dissolved in methanol and hydrogenated under our standard conditions [H_2 (1 atm),

(5) van Tamelen, E. E.; Timmons, R. J. *J. Am. Chem. Soc.* **1962**, *84*, 1067.

(6) PtO_2 and $Rh(PPh_3)_3Cl$ in combination with H_2 were also tried.

(7) Alkenylboronic esters were synthesized by performing a halogen−lithium exchange on the corresponding unsaturated bromide/iodide and trapping this organolithium species with trimethylborate in analogy to: (a) Kristensen, J.; Lysén, M.; Vedso, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435. (b) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763. (c) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetahedron* **1993**, *49*, 49.

(8) Chavant, P. Y.; Lhermitte, F.; Vaultier, M. *Synlett* **1993**, 519.

(9) Hupe, E.; Calaza, M. I.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 8829.

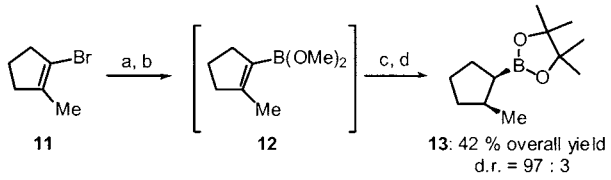
(10) (a) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, *6*, 1840. (b) Hoffmann, R. W.; Hölzer, B.; Knopff, O. *Org. Lett.* **2001**, *3*, 1945.

(11) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel P. *Chem. Eur. J.* **2000**, *6*, 2748.

(12) **Allylation Procedure Leading to (2-Allylcycloheptyl)benzene (10c).** To the pinacol cycloheptylboronic ester **7c** (0.5 mmol, 0.150 g, 1.0 equiv) in THF (2 mL) at −78 °C was added MeMgCl (1.0 mmol, 0.37 mL, 2.0 equiv, 2.7 M in THF). The reaction mixture was allowed to warm to room temperature overnight. After the volatiles were pumped off (0.1 mmHg, 25 °C, 1 h), *i*Pr_2Zn (20.0 mmol, 4 mL, 40.0 equiv, 5.0 M in Et_2O) was added in four portions. The mixture was stirred for 48 h at 25 °C. The volatiles were pumped off (0.1 mmHg, 25 °C, 0.5 h, coevaporation with 2 × 1 mL of THF), and the gray-black residue was diluted with THF (3 mL) and cooled to −78 °C. A freshly prepared solution of CuCN·2LiCl (0.5 mL, 0.5 mmol, 1.0 equiv, 1 M in THF) was slowly added over 20 min via syringe pump and the mixture stirred for 10 min at −78 °C. Then, allyl bromide (2.0 mmol, 0.242 g, 4.0 equiv) in THF (1 mL) was added slowly (20 min) via syringe pump. The mixture was allowed to warm to room temperature overnight. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (150 mL) containing $NH_{3(aq)}$ (2 mL, 30% in H_2O). After extraction with Et_2O (3 × 100 mL), the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product purified by column chromatography (SiO_2, hexanes) affording the desired product (**10c**) as a colorless oil (0.230 mmol, 0.049 g, 46%).

Pd/C (10 %), 25 °C, 7 h]. After workup, conversion into the pinacol boronic ester **13** was performed [pinacol (1.5 equiv), molecular sieves 4 Å, 25 °C, 12 h], leading to the desired alkylboronic ester[13] after chromatographic purification (SiO_2) in 42% overall yield and with a cis:trans ratio of 97:3 (Scheme 3).[14]

Scheme 3[a]

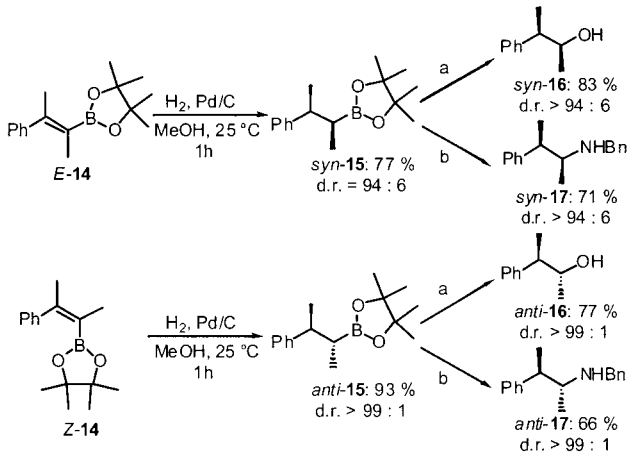


[a] Reaction conditions: (a) *t*-BuLi (2 equiv, THF, −78 °C, 0.5 h); (b) $B(OMe)_3$ (1.5 equiv, 25 °C, 12 h), then removal of solvents; (c) H_2 (1 atm), Pd/C (10 %, MeOH, 25 °C, 7 h); (d) molecular sieves 4 Å and pinacol (1.5 equiv, toluene, 25 °C, 12 h).

We have also investigated the hydrogenation of open-chain systems. Thus, the hydrogenation of the (*E*)-boronic ester ((*E*)-**14**) under standard conditions [H_2 (1 atm), Pd/C (10 %), methanol, 25 °C, 1 h] furnished the *syn*-pinacol boronic ester (*syn*-**15**) in 77% yield and a diastereoselectivity of 94:6. After oxidation or amination, the desired alcohol (*syn*-**16**; 83% yield, dr > 94:6) or amine (*syn*-**17,** 71% yield, dr > 94:6) were obtained. Alternatively, starting from (*Z*)-**14**, the hydrogenation provided in excellent diastereoselectivity (dr > 99:1) the *anti*-pinacol boronic ester (*anti*-**15**) in 93% yield. This boronic ester can be converted to the *anti*-alcohol (*anti*-**16**) in 77% yield or to the *anti*-amine (*anti*-**17**) in 66% yield with complete retention of stereochemistry (dr > 99:1) (Scheme 4).

Finally, we have examined the diastereoselective reduction of a 3-alkoxy-alkenylboronic ester of type **18**.[15] Its hydrogenation [H_2 (1 atm), Pd/C (10 %), methanol, 25 °C, 1 h] is highly diastereoselective, providing the saturated boronic ester **19** in 97% yield and a diastereoselectivity of 93:7. After oxidative workup (H_2O_2, NaOH), the selectively protected

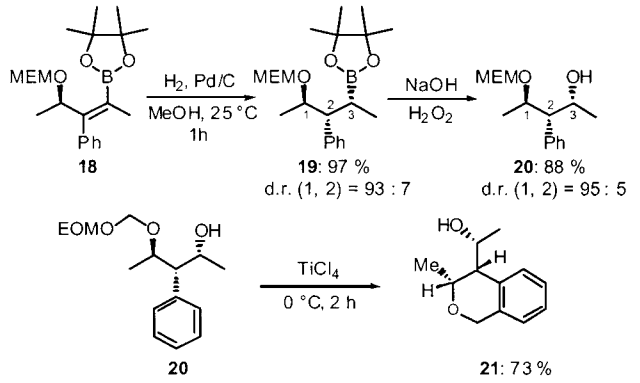
Scheme 4[a]



[a] Reaction conditions: (a) 2 M NaOH, 30% H_2O_2 (THF, from 0 to 25 °C, 4 h); (b) BCl_3 (5.0 equiv, CH_2Cl_2, 25 °C, 4 h), then BnN_3 (3.0 equiv, CH_2Cl_2, from 0 to 25 °C, 8 h).

diol **20** was obtained in 88% yield (dr = 95:5). The relative stereochemistry was established by converting the alcohol **20** to the isochromene derivative **21** [$TiCl_4$ (3.0 equiv), CH_2Cl_2/pentane, 0 °C, 2 h][16] (Scheme 5).[17]

Scheme 5



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Supporting Information Available: Spectral data for all products not found in the literature. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0262486

(13) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

(14) **One-Pot Procedure Leading to the Boronic Ester 13.** To 1-bromocyclopent-1-ene (**11**; 1.8 mmol, 0.290 g, 1.0 equiv) in THF (3 mL) at −78 °C was slowly added *t*-BuLi (3.6 mmol, 2.25 mL, 2.0 equiv, 1.6 M in pentane) over a period of 10 min. After the mixture was stirred for 30 min at this temperature, $B(OMe)_3$ (2.7 mmol, 0.281 g, 1.5 equiv) in THF (1 mL) was added (10 min). The reaction mixture was allowed to warm to room temperature overnight. After the volatiles were pumped off (0.1 mmHg, 25 °C, 30 min), MeOH (2 mL) was added. This crude reaction mixture was transferred to a flask containing Pd/C (10 %) under H_2 (1 atm). The solution was stirred for 7 h at room temperature. After NH_4Cl/CH_2Cl_2 workup and evaporation of the solvent, the reaction mixture was redissolved in toluene (6 mL). Pinacol (2.7 mmol, 0.319 g, 1.5 equiv) and molecular sieves (4 Å, 4 g) were added. The reaction mixture was stirred for 12 h at room temperature. Filtration through Celite (Et_2O) was followed by NH_4Cl(aq)/Et_2O workup. Chromatography (SiO_2) yielded the desired alkylboronate as a colorless oil (0.756 mmol, 0.159 g, 42%).

(15) The alkenylboronic ester **18** was prepared from the corresponding vinylic bromide, which was obtained after addition of MeMgCl to the α,β-unsaturated aldehyde from the literature (Robertson, I. R.; Sharp, J. T. *Tetrahedron*, **1984**, *40*, 3095), followed by MEM protection of the resulting alcohol.

(16) Mohler, D. L.; Thompson, D. W. *Tetrahedron Lett.* **1987**, *28*, 2567.

(17) The relatively small coupling constants (ca. 2 Hz) between the protons attached to C-1 and C-2 reveal a small angle between these protons; furthermore, there is a NOE between these protons. See: Pihlaja, K.; Mattinen, K.; Kleinpeter, E.; Meusinger, R.; Duscheck, C.; Borsdorf, R. *Magn. Reson. Chem.* **1985**, *23*, 754.