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Novel Grignard reaction of chelated boric esters derived from diethyl (2*R*,3*R*)-tartrate: a one-step access to a bulky γ,γ,γ-trisubstituted γ-hydroxy-β-ketoester via selective arylation and sequent deboronation☆

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Abstract—Reaction of the tetracoordinated spiroborate esters derived from diethyl (2*R*,3*R*)-tartrate with Grignard reagents was further examined and found that sterically hindered MesMgBr has different reaction behavior from PhMgBr to the spiroborate esters. It has been proved that in the case of PhMgBr reaction, the formation of the chiral bicyclodiboronic ester (*R*,*R*)-**2** was accomplished step by step via two 1,3-cyclizations of the hydrolytic products of the resulting boron compound. However, in the case of MesMgBr reaction, only one esteral group of the tartrate moiety was diarylated, and a bulky γ,γ,γ-trisubstituted γ-hydroxy-β-ketoester and mesitylboronic anhydride were provided after the resultant was worked up. The composition and structure of the products were authorized by the spectral and single crystal X-ray analysis. A formation mechanism of γ-hydroxy-β-ketoester and mesitylboronic anhydride was also suggested.

Boron compounds have rich reaction chemistry.[1] Alkyl borate is one of the most important classes of boron compounds, and they have been widely applied to the preparation of organic boron compounds and synthesis of other useful materials.[2] However, tricoordinate boric ester generally is sensitive toward moisture. Recently, we synthesized a series of chiral spiroborate ester possessing an O_3BN framework through convenient procedures,[3] which show high stability to hydrolysis and thermolysis due to the presence of the N→B bond. It has been observed that some of the chiral spiroborate esters are good chiral promoter for asymmetric borane reduction of prochiral ketones,[4] imines[5] and oxime ethers,[6] and asymmetric aldol addition.[7] To widen the application scope of the spiroborate esters in asymmetric synthesis, we examined the reaction of the spiroborate esters with an O_3BN framework derived from diethyl (2*R*,3*R*)-tartrate with PhMgBr, and unexpectedly, a hydrolytically stable tricoordinated chiral bicyclo[4.4.0]diboronic ester (*R*,*R*)-**2** was obtained in medium yield.[8] It has been estimated that (*R*,*R*)-**2** was formed via a selective intermolecular dehydration and 1,3-cyclization between 1,4-bis(diphenyl)-1,2,3,4-tetraol and $PhB(OH)_2$, which were generated from hydrolysis of the reaction product by aq NH_4Cl. The current investigation further administrated that the selective bicyclization was completed in two steps. At the first stage, the tetraol reacted with one mole of $PhB(OH)_2$ to furnish a semi-esterified 1,3-cyclization product (4*R*,5*R*)-4-diphenylhydroxymethyl-5-hydroxy-2,6,6-triphenyl-1,3,2-dioxaboro-cyclohexane (*R*,*R*)-**1**,[9] which has been confirmed by the single crystal X-ray analysis[10] (Fig. 1), and this monocyclization product can further react with second $PhB(OH)_2$ molecule to give (*R*,*R*)-**2** (Scheme 1). Systematic examination on the reaction of this class of chiral spiroborate ester with Grignard reagent found that the reaction product of the spiroborate esters were in close relationship with the composition of the chiral spiroborate ester and Grignard reagent. As far as the reactions toward the spiroborate esters derived from diethyl (2*R*,3*R*)-tartrate are concerned, sterically hindered MesMgBr (Mes, mesityl group, i.e., 2,4,6-trimethylphenyl) showed different reaction behavior from PhMgBr to the spiroborate esters.

Keywords: Spiroborate ester; Grignard reaction; Selective arylation; γ-Hydroxy-β-keto ester.

☆ Chiral Borate Esters in Asymmetric Synthesis: 7.

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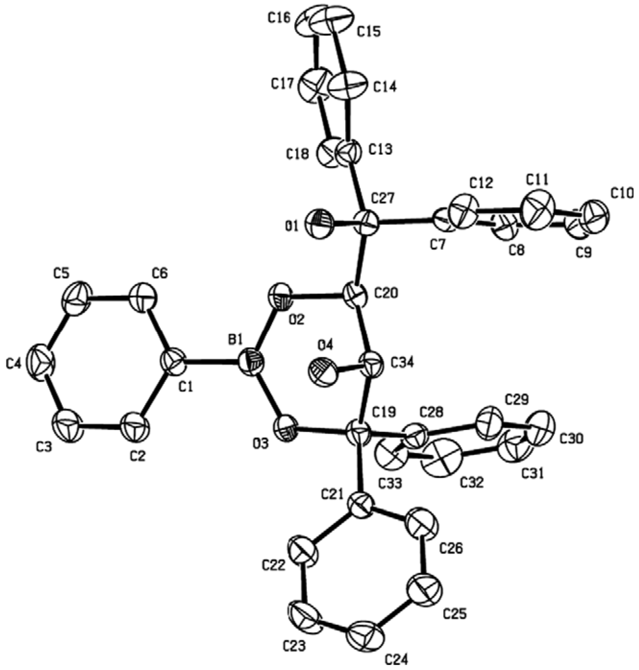


Figure 1. Molecular structure of (*R*,*R*)-**1** with 50% probability ellipsoids (hydrogen atoms and the solvent EtOH are omitted for clarity).

Chiral spiroborate ester, for example (*R*,*R*,*S*)-**1**, which was prepared from diethyl (2*R*,3*R*)-tartrate, boric acid and L-proline according to the lit.,[8] was added to the Grignard reagent MesMgBr in THF cooled with ice-bath in several portions with vigorous stirring. After complete addition, the reaction mixture was continued to stir in ice-bath for 1 h, and then warmed up to reflux for additional 1.5 h, cooled, and quenched with saturated aq NH_4Cl. The organic phase was separated, dried over anhydrous Na_2SO_4, evaporated and purified via column chromatography, white solid product **3** was obtained. No boron was detected. The IR spectra of **3** show adsorption of hydroxyl group (at 3471 s), esteral group (at 1745 s), carbonyl group in a strong H bonding environment (at 1608 m) as well as mesityl group, indicating that it could be a deboration product bearing mesityl group derived from the tartaric moiety of (*R*,*R*,*S*)-**1**. The ^{1}H NMR spectra of **3** indicate that in the compound, there are two misityl groups, one ethyl group, one hydroxyl group (6.36, s, disappeared after adding D_2O) as well as a methylene group (3.94, s, 2H); but, there is no signal of pyrrolidine ring. The ^{13}C NMR spectra and FBA-MS of **3** are in conformity with the above comment. It can be concluded based on the above facts that **3** is 4,4-dimesityl-4-hydroxy-3-oxobutanoic ester **3** (Scheme 2).[11] Composition and structure of **3** were further affirmed by the single crystal X-ray structural analysis (Fig. 2),[10] and it clearly exhibits that there is a hydrogen bond between the β-oxygen and γ-OH in this molecule. On the other hand, mesitylboronic anhydride **4** was successfully separated from the organic phase. It goes without saying that selective

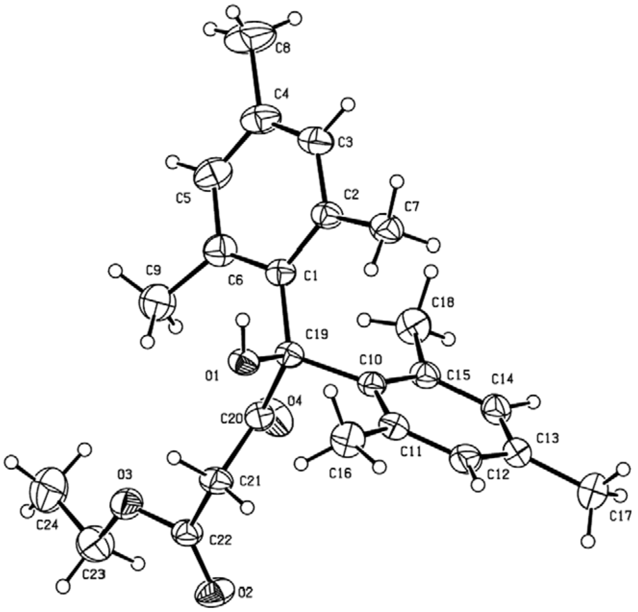
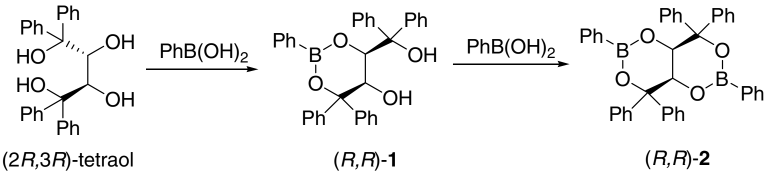
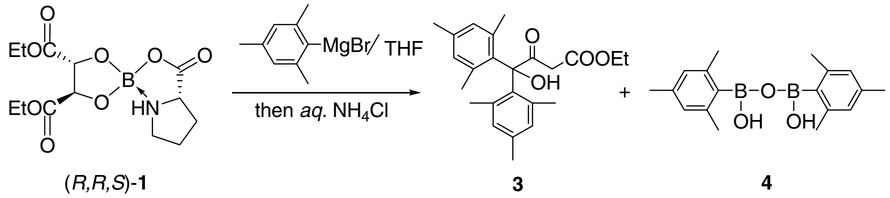


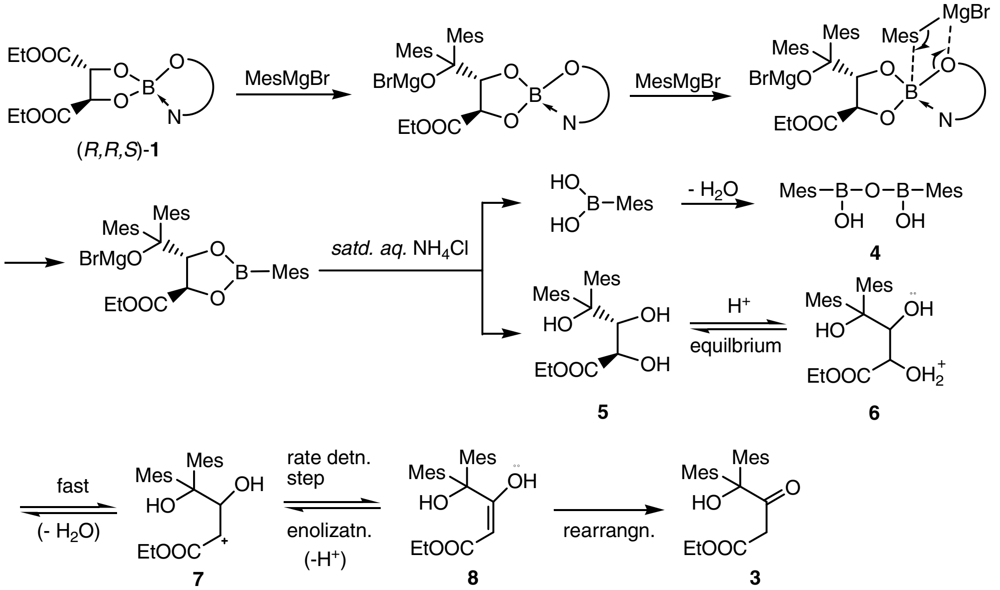
Figure 2. Molecular structure of **3** with 50% probability ellipsoids.



Scheme 1. Formation of (*R*,*R*)-**2** from (2*R*,3*R*)-tetraol and $PhB(OH)_2$ step by step.



Scheme 2. Reaction of (*R*,*R*,*S*)-**1** derived from diethyl (2*R*,3*R*)-tartrate with MesMgBr.



Scheme 3. A possible mechanism of the formation of ethyl 4,4-dimesityl-4-hydroxy-3-oxobutyrate **3**.

arylation, in the reaction of MesMgBr and (*R*,*R*,*S*)-**1**, and sequent deboronation occurred. Perhaps the result is relative to shielding effect of the bulky γ group newly forming and hydrolysis of the reaction resultant by aq NH_4Cl.

In spiroborate ester (*R*,*R*,*S*)-**1**, there are several sites for the attack of ArMgBr. It can be estimated that the ester groups of the tartrate moiety and the boron can be easily arylated by ArMgBr. It was previously pointed out that (*R*,*R*,*S*)-**1** experienced a full diarylation on the two ester groups, in the reaction with PhMgBr. It is different from the above, the diarylation only occurs at one ester group of the tartrate moiety, in the reaction of MesMgBr with (*R*,*R*,*S*)-**1**, under the same experimental condition. Large volume of the γ group forms a shield to the other esteral group of the tartrate moiety of (*R*,*R*,*S*)-**1**, and greatly binders the attack of excess MesMgBr to the second ester group; thus, the arylation had to stop at mono-diarylation stage of the ester groups. However, the shielding effect resulting owing to the dimesitylation at one ester group of the tartrate moiety does not impact mesitylation at the boron, and it is certain that a mesitylboronic ester is formed. It can be estimated that the chiral arylboronic ester is not stable under the experimental condition, and it underwent hydrolysis and offered mesitylboronic anhydride **4** and ethyl 4,4-dimesityl-2,3,4-trihydroxybutyrate **5.** However, the highly unsymmetric trihydroxy ester **5** is also sensitive to the acidic condition, and it would further be subjected dehydration, enolization and rearrangement[12] to give γ-hydroxy-β-oxocarboxylic ester **3**. A possible formation mechanism for compound **3** was summarized in Scheme 3.

In summary, reactions between Grignard reagents and the tetracoordinated spiroborate esters containing tartaric ester moiety were further investigated, and found that the product for the reaction changes with the composition of the Grignard reagent. In the case of PhMgBr reaction, the chiral bicyclodiboronic ester (*R*,*R*)-**2** was formed step by step via two intermolecular 1,3-cyclizations of the hydrolytic products of the reaction resultant. However, the similar reaction of MesMgBr furnished ethyl 4,4-dimesityl-4-hydroxyl-3-oxobutyrate and mesitylboronic anhydride after undergoing selective arylation, deboronation and sequential dehydration, enolization and rearrangement.

Acknowledgment

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References and notes

1. (a) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667; (b) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415; (c) Patel, S. J.; Jamison, T. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941; (d) Hawthorne, M. F. *Pure Appl. Chem.* **2003**, *75*, 1157; (e) Neville, J. D. Ed, *Comprehensive Organic Chemistry*: *The Synthesis and Reactions of Organic Compounds*; Pergamon Press: Oxford, 1979; Vol. 3, 1323 pp; (f) Emeleus, H. J.; Sharpe, A. G. *Adv. Inorg. Chem. Radiochem.* **1960**, *2*, 279.
2. (a) Burkhardt, E. R.; Matos, K. *Chem. Rev.* **2006**, *106*, 2617; (b) Ramachandran, P. V.; Burghardt, T. E. *Pure Appl. Chem.* **2006**, *78*, 1397; (c) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758; (d) Aggarwal, V. K.; Fang, G. Y.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642; (e) Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173; (f) Veeraraghavan, R. P.; Subash, C. J.; Bodhuri, P.; Debarshi, P.; Venkat Ram, R. M. *Org. Biomol. Chem* **2005**, *3*, 3812; (g) Brown, H. C. *Angew. Chem.* **1980**, *92*, 675.
3. (a) Shan, Z. X.; Zhou, Y.; Liu, D. J.; Ha, W. Z. *Synth. React. Inorg. Metal-Org. Nano-Metal Chem.* **2005**, *35*, 275;

(b) Shan, Z. X.; Liu, S. M.; Liu, D. J. *Chin. J. Chem.* **2003**, *21*, 1373.

4. (a) Liu, D. J.; Shan, Z. X.; Qin, J. G. *Chin. J. Chem.* **2004**, *22*, 1336; (b) Liu, D. J.; Shan, Z. X.; Zhou, Y.; Qin, J. G. *Helv. Chim. Acta* **2004**, *87*, 2310.
5. Shan, Z. X.; Wang, Q. *Chin. J. Org. Chem.* **2005**, *25*, 720.
6. Chu, Y. B.; Shan, Z. X.; Liu, D. J.; Sun, N. N. *J. Org. Chem.* **2006**, *71*, 3998.
7. Zhou, Y.; Shan, Z. X. *Tetrahedron* **2006**, *62*, 5692.
8. Zhou, Y.; Shan, Z. X.; Wang, B. S.; Xie, P. *Organometallics* **2006**, *62*, 5692.
9. 1,4-Bis(diphenyl)-1,2,3,4-tetraol was allowed to react with $PhB(OH)_2$ in THF at room temperature in an equal mole to furnish a colorless crystal of (*R*,*R*)-**1**, 90% yield; mp 117–119 °C; IR (KBr, cm^{-1}): υ 3442, 3058, 3025, 1600, 1448, 1360, 1315, 698; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.99–7.16 (m, 25H, Ar–H), 4.88 (s, 1H, BOCH), 4.61 (s, 1H, OCH), 4.11 (s, 1H, COH), 3.82 (s, 1H, CHO*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 144.8, 144.6, 142.8, 135.2, 134.6, 131.5, 129.1, 128.8, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.0, 125.9, 125.5, 125.1, 82.5, 81.3, 71.7, 70.3.
10. The crystallographic data for (*R*,*R*)-**1** and **3** can be obtained (CCDC 615030 and 617133) free of charge, via www.ccdc.cam.ac.uk/conts/ retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. *Procedure for the reaction of the spiroboric esters derived from diethyl tartrate with MesMgBr:* Grignard reagent MesMgBr, which was prepared from Mg turnings (0.523 g, 21.78 mmol) and misityl bromide (19.8 mmol) in THF (20 mL) in the conventional manner, was cooled to 0 °C, followed by careful addition of the chiral spiroborate ester (*R*,*R*,*S*)-**1** (0.987 g, 3 mmol) in several portions. The mixture was allowed to stir at the same temperature for 0.5 h., and then warmed up to reflux for 1.5 h. After cooled down to rt, 20 mL saturated aqueous NH_4Cl was added with stirring. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined extracts were dried over Na_2SO_4, filtered, concentrated, and the residue was purified on column chromatography on silica gel, ethyl 4-hydroxy-4,4-dimesityl-3-oxobutanoate **3** and mesitylboronic anhydride **4** were obtained. The data for **3** and **4** are as follows. Compound **3**: colorless crystals, 35% yield, mp: 110–112 °C; IR (KBr, cm^{-1}): υ 3471, 3023, 2980, 2924, 1745, 1608, 1452, 1306, 1030, 850; ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.75 (s, 4H, Ar–H), 6.36 (s, 1H, OH), 4.04 (q, $J = 7.3$ Hz, 2H, OCH_2), 3.94 (s, 2H, $COCH_2$), 2.18 (s, 6H, Ar–CH_3), 2.01 (s, 12H, Ar–CH_3), 1.14 (t, $J = 7.7$ Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 203.6, 167.1, 137.8, 137.3, 137.2, 132.2, 88.6, 61.4, 46.6, 23.8, 20.7, 14.9. FAB-MS (*m*/*z*): 383, 366, 291, 267, 251, 147, 119. Crystal of **3** suitable for X-ray analysis was grown from absolute EtOH upon standing. Crystal data for **3**: $C_{24}H_{30}O_4$, $M_w = 382.5$, Orthorhombic, space group Pbca, $a = 7.7763(5)$ Å, $b = 16.6045(11)$ Å, $c = 33.140(2)$ Å, $\alpha = 90.00°$, $\beta = 90.00(2)°$, $\gamma = 90.00(2)°$, $V = 4279.1(5)$ Å^3, $Z = 8$, $F(000) = 1656$, $T = 273(2)$ K, μ(Mo Kα) $= 0.080$ mm^{-1}. Of the 25,934 measured reflections, 4904 were independent ($R(\text{int}) = 0.0263$). The final refinements converged at $R1 = 0.0624$ for $I > 2\sigma(I)$ and $wR2 = 0.1209$ for all data. Compound **4**: mp 70–72 °C; IR (film, cm^{-1}): υ 3392, 3012, 2916, 1610, 1485, 1304, 1201, 1149, 852; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.78 (s, 4H, Ar–H), 4.43 (s, 2H, OH), 2.21 (s, 18H, Ar–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 150.0, 129.5, 129.3, 128.6, 123.0, 20.8, 16.3.
12. (a) Jensen, B. L.; Slobodzian, S. V. *Tetrahedron Lett.* **2000**, *41*, 6029–6033; (b) Inhoffen, H. H.; Kampe, D.; Cordes, C.; Mueller, K. D.; Milkowski, W. *Ann* **1964**, *674*, 36–56; (c) Noyce, D. S.; Jorgenson, M. J. *J. Org. Chem.* **1963**, *28*, 3208–3209; (d) Tagaki, W.; Mitsui, T. *J. Org. Chem.* **1960**, *25*, 1476.