Asymmetric Transformation in Boron Ate Complexes of Amino Acids

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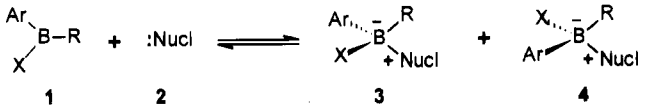
Amidine-protected oxazaborolidinones **6** and **7** can be made from $Me_2NCH{=}NCH(R'')CO_2Na$ and $KPhBF_3$/TMSCl. The diastereomers undergo equilibration and asymmetric transformation under conditions of crystallization, resulting in the formation of **6a** and **6b** with high diastereomer selectivity. Treatment of phenylalanine with $ArB(CH_3)OiPr$ (**8**) affords a 1:1 diastereomer mixture of the oxazaborolidinones **9** and **10**. Crystallization affords a single diastereomer in high yield. These are all examples of asymmetric transformation of the "second kind" or "second order", abbreviated as AT. Crystallization of the less soluble diastereomer drives the equilibrium and results in nearly total conversion of the mixture. Interconversion of **9** and **10** occurs readily at room temperature (**9a/10a**) or upon mild heating (**9b/10b**). The latter system interconverts more slowly because the electron-withdrawing CF_3 substituent stabilizes the ate complex. The *B*-fluoro derivatives **6** and **7** are also relatively stable, and interconversion requires warming. Rapid equilibration of diastereomers occurs when **9/10** is treated with triethylamine or other basic agents, probably due to the formation of **12** followed by C–O cleavage to **13**. The *N,N*-dimethyl complexes **16** and **17** are prepared from **15** and $KPhBF_3$. Crystallization under AT conditions affords **16** as the favored diastereomer. Structure **16** equilibrates thermally with **17**, but the process is not accelerated by added triethylamine. AT also takes place with high diastereomer selectivity in the case of the oxazaborolidinones **25** and **26**. The relative stability of boron diastereomers in the crystal lattice is controlled by remote stereogenic carbons in a menthone-derived substituent.

Ate complexes **3** or **4** containing stereogenic boron can be made by reacting trivalent boranes **1** with nucleophiles **2**. The starting borane **1** must have three different substituents, and the substituents must be sufficiently electronegative to stabilize the ate complex. These conditions are easily satisfied and a number of stereogenic boron structures analogous to **3** or **4** are known.[1] Interconversion of **3** and **4** occurs upon heating via dissociation to **1** and **2**. Thus, stereochemical information is readily stored at boron, but it can also be readily erased.



1 **2** **3** **4**

Chiral boron ate complexes have been resolved by classical methods,[2] but the fact that **3** and **4** are formed reversibly suggests an opportunity for efficient isolation of a single isomer with respect to boron configuration by using the phenomenon of crystallization-induced asymmetric transformation (asymmetric transformation of the second kind, or less accurately, of the second "order"; abbreviated below as AT).[3] The fundamental principles of AT have been known for many years, and there are a number of fascinating examples in the literature.[4] In brief summary, AT can be used to drive a solution equilibrium to a single substance if the equilibrium is faster than crystallization and if the equilibrating isomers differ in solid state energy.

Structures **3** and **4** are enantiomers if the substituents (:Nucl, Ar, R, and X) contain no stereogenic atoms. Enantiomers do not differ in solid state free energy, and a thermodynamically driven conversion from one to the other is not possible. On the other hand, analogous structures that contain a stereogenic carbon in one of the substituents are likely to differ in energy because they are diastereomers. In this case, AT could be expected to drive the thermal equilibrium to that isomer which forms the more stable crystal lattice, provided that interconversion of diastereomers occurs on the time scale for

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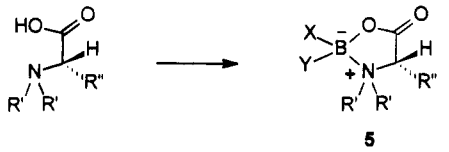
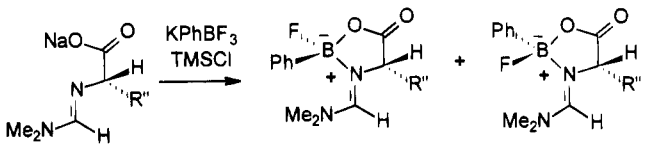
crystallization. The amino acid-derived oxazaborolidinones **5** are structures that should be capable of AT if they can be induced to crystallize under the conditions of diastereomer interconversion. Amino acid complexes of this type are well known (**5**; X, Y= alkyl, aryl, fluorine, etc.) and have been used for amino acid purification, selective protection, and upgrading the enantiomeric purity of organoboron reagents.[5,1b] Oxazaborolidinones are easily prepared from the parent amino acids by treatment with a variety of trivalent or tetravalent boron reagents, and they are often crystalline, stable, and easy to handle.[5]



5

The accompanying manuscript describes the synthesis of diastereomeric phenylglycine complexes analogous to **6** and **7** (R″ = C_6H_5) starting from the amidino carboxylate $Me_2NCH{=}NCH(C_6H_5)CO_2Na$ and $KPhBF_3$/TMSCl as an *in situ* source of $PhBF_2$. This reaction affords a 3:1 mixture of diastereomers corresponding to **6** (trans) and **7** (cis) according to NMR assay, but simple solvent removal on a rotary evaporator produces a 99:1 mixture of trans:cis diastereomers with no loss of material.[6] This behavior is characteristic of AT and indicates that **6** and **7** must be capable of interconversion under the conditions of crystallization. A preliminary report from our laboratory shows that oxazaborolidinones such as **6** are useful starting materials for the generation of chiral amino acid enolate equivalents,[7] similar to the oxazolidinone asymmetric memory technology developed by Seebach *et al.*[8] Various aspects of this application are still under investigation and will be reported in due course. However, the AT phenomenon has now been explored and optimized in several oxazaborolidinone families. It is clear that this technique has considerable potential for the preparation of complexes having a single configuration at stereogenic boron.[9]

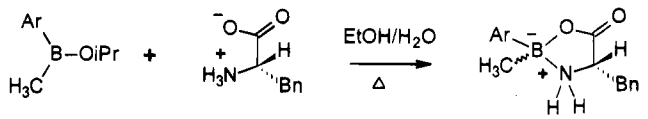
To show that the AT phenomenon is general in amidine-protected oxazaborolidinones, the *in situ* procedure was used to make the (*S*)-valine and (*S*)-phenylalanine complexes **6a** and **6b**. As in the phenylglycine case,[6] the crude amidino carboxylates $Me_2NCH{=}NCH(R'')CO_2Na$ were converted smoothly into the diastereomers **6** and **7** using the $KPhBF_3$/TMSCl reagent in THF. The kinetic ratio of **6a**:**7a** could not be determined accurately because solvent removal on the rotary evaporator (ca. 30 °C) was sufficient to cause spontaneous AT. The crude product was shown by HPLC analysis to consist of a 142:1 ratio of **6a**:**7a** from the optimized experiment. Recrystallization gave pure **6a**, 72% isolated (overall yield from valine). The crystalline diastereomer **6a** was quite stable at room temperature, but warming an acetonitrile solution resulted in an equilibrium mixture of 13.8:1 **6a**:**7a**.



6a R″= $CH(CH_3)_2$ **7a** R″= $CH(CH_3)_2$
b R″= $CH_2C_6H_5$ **b** R″= $CH_2C_6H_5$

Crystallization of the major oxazaborolidinone **6b** in the phenylalanine series was more difficult. However, good results were obtained by crystallizing the crude product (3.1:1 **6b**:**7b**) at 50 °C while allowing the solvent (ethyl acetate) to slowly evaporate. This procedure afforded a "transformed" solid with a 39:1 ratio of **6b**:**7b**. Conventional recrystallization then produced pure **6b**, 75% overall isolated yield based on phenylalanine. Heating **6b** in acetonitrile (50–60 °C) produced the 3.1:1 equilibrium mixture of **6b**:**7b**. The stereochemistry of **6a** and **6b** was confirmed by X-ray analysis, and characteristic long-range fluorine coupling to H_α was observed as in the analogous phenylglycine complex.[6]

Several other boron environments were explored. Following literature precedents,[5] the alkoxyborane **8a** was heated with phenylalanine in aqueous ethanol. This gave a crude product that was found to be a 1:1 mixture of diastereomers **9a** and **10a** according to NMR analysis.



8 **9/10**
a Ar= C_6H_5
b Ar= p-$C_6H_4CF_3$

When the mixture was crystallized from aqueous ethanol, a single diastereomer resulted in 92% yield. Such high product recovery is possible if the original 1:1 mixture undergoes equilibration by reversible B–N bond cleavage to generate **11a**, followed by AT. The more stable crystalline isomer was characterized by an ^1H NMR chemical shift of 0.07 ppm for the *B*-methyl group, but the boron stereochemistry was not assigned in this series. A second *B*-methyl signal was present at δ 0.01 ppm in the initial diastereomer mixture, and the same signal appeared within minutes when the more stable (crystalline) isomer was dissolved in $CDCl_3$. After 1 h at room temperature, the original 1:1 solution equilibrium ratio of **9/10** had been restored. By comparison, the *B*-fluoro-*B*-phenyl phenylalanine complex **6b** must be heated to

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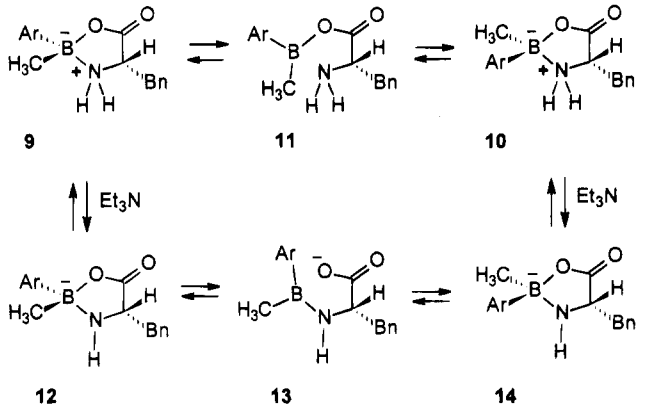
(9) Some of the examples in ref 1a,b may well be subject to AT under the conditions of isolation by crystallization, but this possibility was not specifically discussed by the authors.

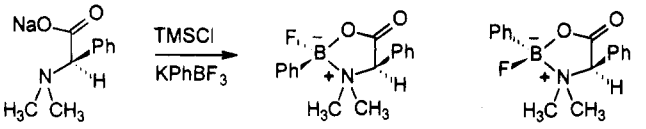
induce diastereomer equilibration. This difference in diastereomer stability can be attributed to the increased electron demand of the *B*-fluorine substituent in **6b** compared to **9a/10a**.

As expected, introduction of an electron-withdrawing group into the *B*-aryl substituent in **9/10** stabilized the ate complex relative to **11**. Diastereomers **9b** and **10b** were prepared as before, starting from the *B*-[*p*-(trifluoromethyl)phenyl]borinate **8b**. Again a 1:1 ratio of isomers was produced, and crystallization afforded one diastereomer in 91% yield. In this case, the preferred crystalline isomer proved sufficiently stable for facile NMR assay at room temperature, and signals of the other diastereomer appeared on a time scale of hours. Eventually, the 1:1 equilibrium was re-established (ca. 24 h). Thus, AT occurs with both the *B*-phenyl and *B*-(*p*-trifluoromethylphenyl) oxazaborolidinones, and the electron-deficient **9b** and **10b** interconvert more slowly than do **9a** and **10a** (CF_3 inductive effect).

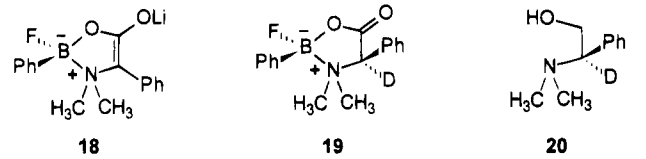


Much faster interconversion of **9b** and **10b** was observed in the presence of triethylamine (room temperature; time scale of minutes). Hydrolysis of the resulting mixture with aqueous HCl gave phenylalanine without appreciable racemization. Thus, isomer interconversion cannot occur by enolization. An alternative explanation invokes the anionic ate complexes **12b** or **14b**, derived from **9** and **10** by deprotonation at nitrogen. Epimerization at boron could then take place by reversible B–O bond cleavage to give the trivalent aminoborane carboxylate intermediate **13b**. This mechanism for diastereomer interconversion is consistent with the observed base dependence and also with retention of configuration at carbon.

If the rapid interconversion of **9b** and **10b** occurs via **12b** and **14b**, then it should be blocked by replacing the N–H groups with other substituents, as in **5** (R′ = CH_3; X = Ph, Y = CH_3). Attempted preparation of analogous complexes from *N,N*-dimethylphenylalanine resulted in relatively unstable products that were difficult to crystallize. However, the *N,N*-dimethylphenylglycine derivative in the *B*-fluoro-*B*-phenyl series was better behaved, and a mixture of **16** and **17** could be prepared from sodium (*R*)-*N,N*-dimethylphenylglycinate with the $KPhBF_3$/TMSCl reagent (dichloromethane, room temperature). Crystallization gave a single diastereomer, and the *cis*-diphenyl stereochemistry was established as shown in **16** using X-ray crystallography. A solution structure having B–N coordination was confirmed by the ^{11}B NMR shift of 7.94 ppm (vs external BF_3-etherate).[1c,10] In the ^1H NMR spectrum, **16** was characterized by nonequivalent NCH_3 signals (δ 1.87 and 2.69 ppm) and a methine hydrogen singlet at δ 5.18 ppm. The NMR spectrum changed upon heating in CD_3CN for several minutes and produced new signals of an isomer at δ 4.79, 2.37, and 2.31 ppm (4:1 ratio at equilibrium, **16** major). The same minor signals appeared over 18 h at room temperature, and they were also present in the crude product prior to crystallization of **16** (ca. 15–20% by integration). These signals are reasonably assigned to the *trans* diastereomer **17**. However, **17** could not be separated from the major diastereomer for decisive characterization.



In contrast to the behavior of **9/10**, the rate of interconversion between **16** and **17** was not significantly affected by the presence of triethylamine. This observation supports the proposed mechanism for base-induced equilibration of **9/10** via NH deprotonation. Enolate generation and quenching with D_2O was also examined. Treatment of **16** with mesityllithium followed by DCl (−78 °C) gave **19** according to NMR assay (>95% deuterium incorporation). The −78 °C result corresponds to preferred enolate deuteration from the less hindered face, but quenching at higher temperatures gave significant amounts of the diastereomeric product. The stereochemical assignment was confirmed by converting **19** into **20** (treatment with $LiAlH_4$), followed by NMR assay using the Mosher ester method (>95% ee). These results

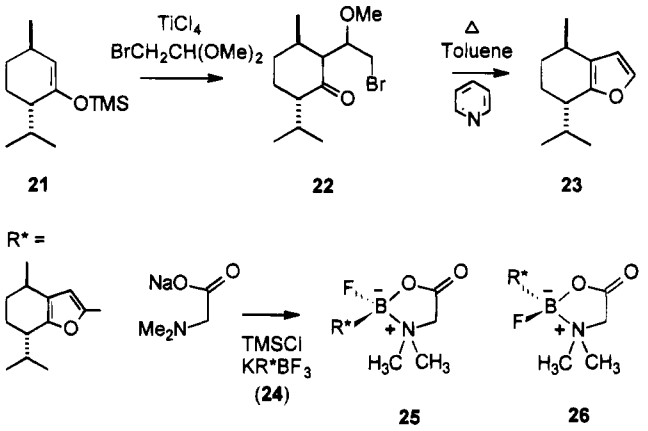


show that boron configuration in **16** survives treatment with strong base as well as weak base, and that the enolate **18** can be generated with <5% racemization. In the amidine-protected series, diastereomers **6** and **7** also survive in the presence of triethylamine. Thus, facile base-induced equilibration is limited to **9/10**, oxazaborolidinones that contain relatively acidic N–H bonds.

In each of the oxazaborolidinones discussed so far, the limiting factor for AT is crystallinity. Once a crystalline isomer had been obtained, the thermally driven conversion to the diastereomer having the more stable crystal lattice was easily demonstrated. The solution equilibrium ratio of diastereomers was not important, as evidenced by the observation that the 1:1 mixture of **9a**:**10a** undergoes conversion to a single isomer in >90% yield. These results encouraged us to explore the diastereomeric oxazaborolidinones **25** and **26**. In this system, intramolecular interactions would be unlikely to control AT because the stereogenic boron and carbon

(10) ^{11}B shifts: Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance of Boron Compounds*; Springer-Verlag: New York, 1978; see also Biedrzycki, M.; Scouten, W. H.; Biedrzycka, Z. *J. Organomet. Chem.* **1992**, *431*, 255. Brown, H. C.; Gupta, A. K. *J. Organomet. Chem.* **1988**, *341*, 73.

atoms are separated by four bonds. Stability differences between the diastereomers would have to be due to intermolecular effects in the crystal lattice.



The chiral boronate salt **24** was prepared from the furan **23**, available in two steps from menthone via **21** and **22** using the method of Mukaiyama *et al.*[11] No difficulties were encountered in the synthesis of **23** if the cyclization of **22** was performed in the presence of pyridine. Metalation (*tert*-butyllithium), boronation with $B(OMe)_3$, and fluoride exchange (KHF_2) were then performed to give **24** in 38% yield from **23**. The standard procedure for oxazaborolidinone formation using **24**, TMSCl, and sodium *N,N*-dimethylglycinate gave a crude product consisting of a 1:1 mixture of **25** and **26**. Slow removal of solvent from the mixture at 50 °C afforded a residue consisting of a single isomer within the limits of NMR analysis (53% yield from **24**). Thus, AT must have taken place under the conditions of solvent removal. Unfortunately, the resulting crystals were not suitable for X-ray analysis and boron configuration in the favored isomer could not be assigned.

In summary, AT has been demonstrated with amino acid-derived oxazaborolidinones having several different boron environments. Single diastereomers can be obtained in high yield starting with mixtures of **6/7**, **9/10**, **16/17**, and **25/26**. In the latter case, there is a driving force for AT even though the stereogenic carbon and boron centers are too far apart for significant intramolecular interaction. The intermolecular interactions between stereogenic atoms are sufficient because of the proximity of neighboring molecules in the crystal lattice. Isomer ratios in solution appear to be relatively unimportant, as long as the requirements for AT (crystallization under equilibrium conditions) are satisfied. The AT method has clear potential for the preparation of single isomers containing stereogenic, tetravalent boron. Synthetic applications of this technique are under investigation and will be described in subsequent publications.

Experimental Section

Oxazaborolidinone 6b. L-Phenylalanine (Aldrich; 14.96 g, 90.6 mmol) was dissolved in 1 equiv of methanolic NaOMe (123 mL, 0.74 M, 91.0 mmol; prepared from Mg-dried methanol and sodium) at room temperature under a nitrogen atmosphere. Dimethylformamide dimethyl acetal (Aldrich; distilled at 1 atm, bp 102–4 °C; 12.75 mL, 96.1 mmol) was added and the solution stirred for 75 min. Concentration to a white foam (rotary evaporator, 40 °C) followed by trituration with CH_2Cl_2/Et_2O and drying (0.5 mm, 40 °C, 12 h) afforded 21.9 g (99.8%) sodium *N*-[(dimethylamino)methylene]phenylalaninate. The crude dried salt was used without further purification. The amidine group is slowly hydrolyzed to the *N*-formyl derivative by water, and anhydrous conditions are recommended for long term storage.

Sodium *N*-[(dimethylamino)methylene]phenylalaninate (745 mg, 3.08 mmol) and potassium phenyltrifluoroborate (615 mg, 3.34 mmol) were suspended in 50 mL of anhydrous THF under a nitrogen atmosphere at room temperature, and 2.4 equiv of chlorotrimethylsilane (Aldrich; distilled from CaH_2 and stored over polyvinylpyridine; 0.940 mL, 13.7 mmol) was added in one portion to the stirred mixture. The nature of the suspension changed, clearing momentarily and then gradually becoming thick with white precipitate. After stirring for 2 h, the volatiles were removed by bulb-to-bulb distillation at room temperature under static vacuum (ca. 0.5 mmHg). The resulting white solid was dissolved in 3:1 CH_2Cl_2/H_2O (20 mL), the aqueous layer was washed with additional CH_2Cl_2 (5 mL), and the combined organic extracts washed with saturated aqueous NaCl, dried ($Na_2SO_4/MgSO_4$), and concentrated to a foam (rotary evaporator, 25 °C). The crude product (910 mg, 3.1:1 mixture of diastereomers) was then dissolved in 40 mL anhydrous EtOAc at 50 °C, and the solution was slowly concentrated to dryness under a stream of nitrogen with stirring over 12 h. The "asymmetrically transformed" material was a 39:1 mixture of diastereomers **6b:7b**, as determined by analytical HPLC [5 μm silica gel, 250 × 4.6 mm, 25% ethanol/hexane, 1.5 mL/min, t_R = 4.98 min (major) and t_R = 7.47 min (minor)]. Recrystallization from anhydrous CH_2Cl_2/Et_2O at room temperature produced 754 mg (75%) of diastereomer **6b**; analytical TLC on silica gel, 2:1 EtOAc/hexane, R_f = 0.34. The sample was recrystallized from EtOAc/hexane, mp 161–163 °C. $[\alpha]_D = -195°$ (c = 1.0, CD_3CN); $C_{18}H_{20}BFN_2O_2$; m/e, M + 1, 327.1682, error = 1 ppm; base peak = 249 amu. IR (CH_2Cl_2, cm^{-1}) 1750, C=O; 1675, C=N; 300 MHz NMR (CD_3CN, ppm) δ 7.40–7.18 (10H, m), 6.75 (1H, d, J = 2.7 Hz), 4.33 (1H, ddd, $^3J_{HH}$= 4.5, 9.1 Hz, $^4J_{HF}$= 4.5 Hz), 3.36 (1H, dd, J = 4.5, 13.6 Hz), 2.97 (1H, dd, J = 9.1, 13.6 Hz), 2.61 (3H, s), 2.60 (3H, s); ^{11}B NMR (^1H decoupled, CH_2Cl_2, ppm) δ 6.80. Anal. Calcd for $C_{18}H_{20}BFN_2O_2$: C, 66.28; H, 6.18; N, 8.58; found: C, 66.77; H, 6.35; N, 8.35. The labile (minor) diastereomer **7b** could not be obtained pure; analytical TLC on silica gel, 2:1 EtOAc/hexane, R_f = 0.18. 200 MHz NMR (CD_3CN, ppm, partial) δ 7.00 (1H, s), 4.42 (1H, dd, J = 7.2, 5.5), 3.33 (1H, dd, J = 14.2, 5.5), 3.20 (1H, dd, J = 14.2, 7.2), 2.86 (3H, s), 2.72 (3H, d, J = 2.1 Hz).

Oxazaborolidinone 6a. Crude sodium L-[*N*-[(dimethylamino)methylene]valinate] was prepared in the same way as the L-phenylalanine analog described above. The crude dried salt (1.02 g, 5.25 mmol) and potassium phenyltrifluoroborate (1.22 g, 6.63 mmol) were combined and dried at 40 °C under vacuum (0.5 mmHg) overnight. The salts were suspended in 50 mL of anhydrous THF under nitrogen at room temperature and treated with 2.8 equiv of chlorotrimethylsilane as described above. After stirring for 2.5 h, the reaction mixture was concentrated to a white solid (rotary evaporator, 30 °C) and taken up in 50 mL of 1:1 CH_2Cl_2/H_2O. The aqueous layer was washed twice more with CH_2Cl_2 (25 mL), and the combined organic phases were washed with saturated aqueous NaCl, dried ($Na_2SO_4/MgSO_4$), and concentrated (rotary evaporator, 25 °C). HPLC analysis of the product [5 μm silica gel, 250 × 4.6 mm, flow rate 1.5 mL/min, 25% EtOH/hexane, t_R = 7.03 min (major), and t_R = 8.54 min (minor)] indicated a ratio of **6a**:**7a** = 142:1. Recrystallization from anhydrous CH_2Cl_2/Et_2O at room temperature produced 1.05 g (three crops, 72% based on starting L-valine) of diastereomerically pure complex **6a**. Analytical TLC on silica gel, 2:1 EtOAc/hexane, R_f = 0.16; recrystallization from ether/dichloromethane, mp 174–176 °C; $C_{14}H_{20}BFN_2O_2$; m/e, M + 1, 279.1686, error = 2 ppm; base peak = 201 amu. IR (CH_2Cl_2, cm^{-1}) 1740, C=O; 1675, C=N; 300 MHz NMR (CD_3CN, ppm) δ 7.56 (1H, d, J = 2.2 Hz), 7.35–7.30 (2H, m), 7.27–7.22 (3H, m), 4.10 (1H, dd, $^3J_{HH}$= 3.5 Hz, $^4J_{HF}$= 3.5 Hz), 2.90 (3H, s), 2.69 (3H, s), 2.12 (1H, d of sept, J = 3.5, 6.9), 1.10 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz); ^{11}B NMR (CD_3CN, ppm) δ 7.1 (d, J = 49 Hz). Anal. Calcd for

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$C_{14}H_{20}BFN_2O_2$ (278.13): C, 60.46; H, 7.25; N, 10.07. Found: C, 60.69; H, 7.12; N, 9.97. The labile (minor) diastereomer **7a** could not be obtained in sufficient quantity and purity to extract reliable NMR signals; analytical TLC on silica gel, 2:1 EtOAc/hexane, R_f = 0.15.

Isopropyl Methylphenylborinate (8a). To a solution of 1.0 equiv of diisopropyl methylborinate[12] (5.98 g, 42 mmol) in 100 mL of anhydrous diethyl ether at −78 °C was added 1.1 equiv of phenyllithium (Aldrich; 2.0 M in 70:30 cyclohexane/ether, 23 mL, 46 mmol) via cannula over 15 min. After an additional 45 min, the solution was warmed to 0 °C and 1.2 equiv of acetyl chloride (3.6 mL, 50 mmol) was added via syringe. The mixture turned turbid as it was warmed to room temperature. After 15 min of stirring at room temperature, the precipitate was removed by filtration through a glass frit under nitrogen flow.

The ethyl ether was removed via shortpath distillation, as was isopropyl acetate (bp 85 °C). The bath temperature was raised to 120 °C and distillation of the oily, yellow residue gave an 81% yield of the product as a clear liquid (bp 83−5 °C, 3.0 mm Hg, short path); **8a**: Molecular ion calcd for $C_{10}H_{15}BO$: 162.12158; found m/e = 162.1230, error = 9 ppm; base peak = 105 amu. IR (CH_2Cl_2, cm^{-1}) 1600, B−O; 200 MHz NMR (C_6D_6, ppm) δ 8.03−7.98 (2H, m), 7.29−7.21 (3H, m), 4.27 (1H, sept, J = 6.1 Hz), 1.09 (6H, d, J = 6.1 Hz), 0.63 (3H, s).

Isopropyl Methyl[*p*-(trifluoromethyl)phenyl]borinate (8b). To a solution of 1.0 equiv of diisopropyl methylborinate[12] (3.21 g, 22.3 mmol) in 100 mL anhydrous diethyl ether at −78 °C was added 1.1 equiv [4-(trifluoromethyl)phenyl]lithium, prepared by adding 26.4 mL of 1.7 M t-BuLi (44.8 mmol) to 3.15 mL of *p*-(trifluoromethyl)bromobenzene (Aldrich; 22.4 mmol) at −78 °C in 20 mL diethyl ether, via cannula over 15 min at −78 °C. After an additional 45 min, the solution was warmed to 0 °C and 1.2 equiv of acetyl chloride (1.61 mL, 22.5 mmol) was added via syringe. The mixture turned turbid as it was warmed to room temperature. After stirring 15 min at room temperature, the reaction was worked up as for **8a**; 44% yield of a clear liquid (bp 90−5 °C, 5.0 mm Hg, short path). Molecular ion calcd for $C_{11}H_{14}BF_3O$: 230.10895; found m/e = 230.1089, error = 0 ppm; base peak = 173 amu. IR (CH_2Cl_2, cm^{-1}) 1620, B−O; 200 MHz NMR (C_6D_6, ppm) δ 7.77 (2H, d, J = 7.7 Hz), 7.48 (2H, d, J = 7.7 Hz), 4.21 (1H, s), 1.06 (6H, d, J = 6.1 Hz), 0.50 (3H, s).

2-Methyl-2-phenyl-4-benzyl-1,3,2-oxazaborolidin-5-one (9a/10a). To a mixture of isopropyl methylphenylborinate (2.80 g, 18.8 mmol) in 125 mL 1:1 ethanol/water was added 1.05 equiv of L-phenylalanine (3.14 g, 19.0 mmol). The resulting suspension was heated to reflux for 3 h. Hot water was added to the clear, homogeneous solution until it began to turn turbid. The solution was slowly cooled and deposited 3.2 g of a white powder (92% yield), one diastereomer by NMR analysis. Recrystallization from water/ethanol gave white needles, 2.90 g (85% yield), mp 144−6 °C. Analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.40; m/e, $C_{16}H_{19}BNO_2$ (M + 1), 268.1510, error = 0 ppm; base peak = 120 amu. IR (CH_2Cl_2, cm^{-1}) 1740, C=O; 270 MHz NMR (acetone-d_6, ppm) δ 7.37−7.05 (10H, m), 6.27 (1H, br s), 5.55 (1H, br s), 3.91−3.76 (1H, m), 3.40 (1H, ABX, J = 4.0, 14.7 Hz), 3.10 (1H, ABX, J = 9.7, 14.7 Hz), 0.07 (3H, s); ^{11}B NMR (^{1}H decoupled, acetone, ppm) δ 7.77. The less stable diastereomer could not be purified, and the NMR spectrum was deduced from signals of a mixture; 270 MHz NMR (acetone-d_6, ppm) δ 7.40−7.05 (10H, m), 6.50 (1H, br s), 5.25 (1H, br s), 4.25−4.10 (1H, m), 3.38 (1H, ABX, J = 3.5, 14.6 Hz), 3.02 (1H, ABX, J = 10.3, 14.7 Hz), 0.01 (3H, s); ^{11}B NMR (^{1}H decoupled, acetone, ppm) δ 6.20.

2-Methyl-2-[*p*-(trifluoromethyl)phenyl]-4-benzyl-1,3,2-oxazaborolidin-5-one (9b/10b). The identical procedure was used as described for preparation of **9a/10a** (2.3 mmol scale). One isomer was obtained by crystallization from aqueous ethanol, (700 mg, 91% yield), mp 210−3 °C. Analytical TLC on silica gel, 1:2 EtOAc/hexane, R_f = 0.27; $C_{17}H_{18}BF_3NO_2$ (M + 1), 336.1382, error = 0 ppm. IR (CH_2Cl_2, cm^{-1}) 1706, C=O; 200 MHz NMR (CD_3CN, ppm) δ 7.52−7.17 (9H, m), 5.60 (1H, br s), 4.45 (1H, br s), 4.28−4.13 (1H, m), 3.26 (1H, ABX, J = 4.4, 14.6 Hz), 2.90 (1H, ABX, J = 9.3, 14.7 Hz), 0.03 (3H, s).

The less stable isomer could not be purified, and the NMR spectrum was deduced from a 1:1 mixture; 200 MHz NMR (CD_3CN, ppm) δ 7.52−7.17 (9H, m), 5.30 (1H, br s), 4.70 (1H, br s), 3.90−3.75 (1H, m), 3.34 (1H, ABX, J = 4.4, 14.6 Hz), 3.04 (1H, ABX, J = 9.3, 14.6 Hz), −0.04 (3H, s).

2-Fluoro-2,4-diphenyl-1,3,2-oxazaborolidin-5-one (16). (*R*)-*N*,*N*-dimethyl-2-phenylglycine[13] (1.35 g, 7.54 mmol) was dissolved in 1 equiv of 1 N NaOH (7.6 mL). The water was removed using a rotary evaporator, and three portions of toluene (10 mL each) were added to the salt and then evaporated to azeotropically remove residual water. The resulting white powder was suspended in 35 mL of anhydrous CH_2Cl_2 under nitrogen, and 1.05 equiv of freshly distilled TMSCl (1.0 mL) was added. The suspension was sonicated for 2−3 min and then allowed to stir for 20 min to give a milk-white, opaque mixture. A slight excess of $PhBF_2$[14] (970 μL, ca. 1.05 g) was added via syringe, and the resulting slightly pink solution was stirred for 12 h. Water (35 mL) was then added, the organic layer was removed, and the aqueous layer was extracted with an additional 25 mL of CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated to give 2.0 g of light pink solid. The solid residue was dissolved in a 5−10 mL of CH_2Cl_2, and the product was precipitated by rapid addition of 50 mL of Et_2O. This was repeated two more times to remove most of the pink color. X-ray quality crystals were produced by dissolving the residue in 5−10 mL of anhydrous CH_2Cl_2 and placing this solution under a glass dish together with a container of 50 mL of anhydrous Et_2O. The first crystallization gave 1.17 g of large, white blocks after 12 h, mp 164−165 °C. The mother liquor was evaporated, and the chamber process was repeated to give an additional 0.60 g of product (82% total from (*R*)-*N*,*N*-dimethyl-2-phenylglycine), **16:** Analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.55; m/e $C_{16}H_{18}BFNO_2$ (M + 1) 286.1418, error = 1 ppm; base peak = 134 amu. IR (CH_2Cl_2, cm^{-1}) 1770, C=O; 1595; 200 MHz NMR (CD_3CN, ppm) δ 7.65−7.61 (2H, m), 7.54−7.42 (5H, m), 7.38−7.35 (3H, m), 5.18 (1H, s), 2.69 (3H, d, J = 1.2 Hz), 1.87 (3H, s); ^{11}B NMR (^{1}H decoupled, CH_2Cl_2, ppm) δ 7.94. Anal. Calcd for $C_{16}H_{17}BFNO_2$: C, 67.40; H, 6.01; N, 4.91. Found: C, 67.08; H, 5.94; N, 4.87.

In an alternative procedure using $KPhBF_3$ as the boron source, sodium *N*,*N*-dimethylphenylglycinate was prepared as described above (201 mg, 1.00 mmol), and potassium phenyltrifluoroborate[6] (260 mg, 1.41 mmol) was added together with 15 mL of anhydrous THF (room temperature under nitrogen). Chlorotrimethylsilane (Aldrich, distilled from CaH_2 and stored over polyvinylpyridine; 400 μL, 3.14 mmol) was added in one portion, and the reaction was stirred for 12 h. The reaction was concentrated (rotary evaporator, room temperature), and the residue was taken up in 10 mL of CH_2Cl_2, and washed with H_2O (10 mL) and saturated aqueous NaCl (5 mL). After drying ($Na_2SO_4/MgSO_4$) and evaporation (aspirator; then vacuum pump), a crude product (281 mg, 99%) was obtained consisting of a 6:1 mixture of **16**:**17** according to ^{1}H NMR integration of the α-H and Me_2N signals. Crystallization from CH_2Cl_2/Et_2O (chamber) afforded pure complex **16** as described above.

Thermal equilibration studies were performed in CD_3CN, and the product ratio was determined by ^{1}H NMR assay. Signals of the major diastereomer **16** decreased in intensity while those assigned to **17** appeared (δ 4.79 ppm, s; δ 2.69, s; δ 2.37, d, $^3J_{F-H}$ = 2.9 Hz; relative integral 1:3:3). At room temperature, equilibrium was reached within 24 h (4:1 **16**:**17**). The minor isomer was not obtained free of **16**, and crystallization of mother liquors after collection of crops of **16** gave additional **16**, but not **17**.

Deuteration of 16; Isolation of 19. A solution of **16** (62 mg, 0.22 mmol) in THF (5 mL) was treated with mesityllithium (0.134 M, 1.7 mL in ether)[15] at −78 °C under nitrogen. The

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yellow mixture was stirred 30 min and was then transferred via cold cannula (dry ice in foil wrapping) into a solution of DCl in THF (2 mL) at −78 °C. The DCl solution was prepared in advance by adding 2 equiv of TMSCl via syringe to a small excess of D_2O in anhydrous THF under nitrogen. The solution was warmed to room temperature, and solvent was removed (aspirator; NO HEATING! boron may epimerize). The white residue was triturated with hexane (3 × 5 mL) to remove mesitylene and hexamethyldisilazane and was dried under vacuum. The residue was then crystallized from CH_2Cl_2–ether at room temperature to give 56 mg of **19**. The NMR spectrum was identical to that reported for **16**, but the singlet at δ 5.18 had virtually disappeared (4% residual H by integration).

Mosher Ester Assay of 20. The complex 19 (0.03 mmol) was dissolved in 5 mL of anhydrous THF, and excess $LiAlH_4$ was added (Aldrich; 0.71 M in THF, 700 μL) at room temperature. After 5 min, the reaction was quenched with 1 mL of EtOAc followed by careful addition of 1 mL of MeOH and then 1 mL of 10% HCl. The mixture was adjusted to pH >10 with 20% KOH and extracted with CH_2Cl_2 (4 × 5 mL) followed by drying (Na_2SO_4) and evaporation (aspirator) to give 20 which was used directly in the next step.

The crude (*S*) amino alcohol **20** was dissolved in 2 mL of anhydrous CH_2Cl_2. Excess (*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (Aldrich; 178 μL, 0.184 M in CH_2Cl_2) and dicyclohexylcarbodiimide (Aldrich; 7 mg) were added. The solution was stirred for 12 h, during which time dicyclohexylurea precipitated. After conventional workup, the products were assayed using ^1H NMR in $CDCl_3$ and product ratios were determined from the $CH_2OC(O)$ signal ratios; Mosher ester from **20** (*S*): δ 4.75 (d, J_{AB} = 11.2 Hz) 4.55 (d, J_{AB} = 11.2 Hz); the (*R*) enantiomer, 4.57 (AB q, J_{AB} = 11.0 Hz), was not detected.

(4*R*,7*S*)-7-Isopropyl-4-methyl-4,5,6,7-tetrahydrobenzofuran (23). The procedure of Mukaiyama *et al.*[11] was applied to menthone with modifications as follows. To a solution of bromoacetaldehyde dimethyl acetal (Aldrich, distilled, stored over anhydrous K_2CO_3, 4.6 mL, 38.9 mmol) in 200 mL of anhydrous CH_2Cl_2 cooled to −78 °C under N_2 was added dropwise $TiCl_4$ (Aldrich, distilled and stored under N_2, 4.2 mL, 38.8 mmol) via syringe. Then, a solution of (3*R*,6*S*)-6-isopropyl-3-methyl-1-(trimethyl)siloxy-1-cyclohexene (prepared by the procedure of Friedrich and Lutz[16] from (−)-menthone, sold by Aldrich as a 95:5 mixture of menthone and isomenthone; 8.0 mL, 31.1 mmol) in 10 mL of CH_2Cl_2 was added via cannula over 5 min. The resulting dark brown solution was stirred at −78 °C for another 4 h. The reaction was quenched by transferring to a well stirred cold aqueous $NaHCO_3$ solution (prepared from 100 g of ice and 200 mL of saturated aqueous $NaHCO_3$) via cannula. The organic phase was separated, and the aqueous phase was extracted with ether (3 × 150 mL). The combined organic solution was dried over $MgSO_4$ and filtered through Celite. The Celite cake was washed with 100 mL of toluene. After 15 mL of pyridine (distilled from CaH_2, stored over KOH) and ca. 0.5 g of anhyd K_2CO_3 were added, the mixture was quickly concentrated by aspirator to remove the low boiling components (ether and methylene chloride). The remaining cloudy solution was brought to reflux (bath temperature 85 °C) under N_2 over ca. 5 g of anhyd K_2CO_3 until total conversion to the product was indicated by TLC (4–6 h). The clear yellow supernatant was decanted, and the dark orange precipitate was washed with ether (50 mL). The combined solution was then washed with water, saturated aqueous Na_2CO_3, brine, and dried over $MgSO_4$. The volatiles were removed by aspirator, and the oily residue was distilled to give 4.2 g (76%) of product **23** as a colorless liquid, bp 82.5–85.5 °C, 2.2 mm, short path. NMR and GC analysis indicated the presence of 5% of the C7 epimer derived from isomenthone, which was not separable at this stage. However, the impurity was removed later, at the stage of the crystalline trifluoroborate salt **24**. Spectroscopic analysis of the air-sensitive **23** was done immediately after plate chromatography: analytical TLC on silica gel, hexane, R_f = 0.41; molecular ion calcd for $C_{12}H_{18}O$: 178.13576; found *m/e* = 178.1374, error = 9 ppm; base peak = 135 amu; IR (neat, cm^{-1}) 2929, =C–H; 2870, C–H; 200 MHz NMR (C_6D_6, ppm) δ 7.14 (1H, dd, *J* = 1.9, 1.0 Hz), 6.15 (1H, d, *J* = 1.9 Hz), 2.67–2.41 (2H, m), 2.21 (1H, sept d, *J* = 6.9, 4.3 Hz), 1.79–1.52 (2H, m), 1.34 (1H, dddd, *J* = 12.6, 12.0, 10.1, 2.5 Hz), 1.17–1.00 (1H, m), 1.07 (3H, d, *J* = 6.8 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.91 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (68 MHz, {H}, DEPT135, C_6D_6, ppm) δ 153.0 s, 140.6 d, 123.6 s, 109.0 d, 41.0 d, 32.9 t, 30.3 d, 28.9 d, 24.8 t, 21.1 q, 19.8 q, 18.9 q.

Potassium [(4*R*,7*S*)-7-Isopropyl-4-methyl-4,5,6,7-tetrahydrobenzofur-2-yl]trifluoroborate (24). A solution of freshly made hydrobenzofuran **23** from above (3.9 g, 22.4 mmol) in 100 mL of anhydrous THF was cooled to −45 °C by dry ice–acetonitrile bath under N_2. With stirring, 17 mL of *tert*-BuLi (Aldrich, 1.62 M in pentane, 28 mmol) was added dropwise via cannula.[17] After the resulting yellow solution was stirred at −45 °C for 30 min, $B(OMe)_3$ (Aldrich, distilled from Na, 10 mL, 88 mmol) was added via syringe in one portion. The mixture was stirred at −45 °C for another 30 min and then was allowed to slowly warm to room temperature (4–6 h). The cloudy solution was poured into a well stirred mixture of 100 mL of water, 100 g of ice, 5 mL of concd HCl, and 200 mL of ether. The organic phase was separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phase was washed with water (100 mL) and combined with another 100 mL of water, and then the organic solvents were removed by aspirator. To the remaining two-phase mixture, pentane was slowly added until the oily residue began to solidify (if no solidification occurred, the organic solvents was evaporated, and the process was repeated). Then 20 mL of hexane was added, and the mixture was cooled to −20 °C for 2 h. The white precipitate was collected by filtration and was washed with hexane to give 3.1 g of crude boronic acid as a white powder. The boronic acid was unstable and was carried on without further purification. Thus, 3.0 g of the crude boronic acid was dissolved in methanol under N_2. With the temperature maintained by a water bath and vigorous stirring, 13 mL of saturated aqueous KHF_2 (4.54 M, 59 mmol) was added dropwise via a plastic syringe. A voluminous white precipitate was formed during the addition, and swirling by hand was needed to facilitate mixing. The white precipitate was collected by filtration and was washed with ether. Recrystallization from acetonitrile yielded 2.3 g (38% based on **23**) of colorless blocks of **24**, free of the C7 epimer according to NMR analysis; mp 258 °C dec. Anal. Calcd: C, 50.72; H, 6.03. Found: C, 51.26; H, 5.85. IR (KBr, cm^{-1}) 2872, C–H; 988, B–F; 983, B–F; 200 MHz NMR (CD_3CN, ppm) δ 6.05 (1H, s), 2.7–2.4 (2H, m), 2.25–2.05 (1H, m), 1.95–1.70 (2H, m), 1.5–1.3 (1H, m), 1.2–1.0 (1H, m), 1.07 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.9 Hz), 0.76 (3H, d, *J* = 7.0 Hz).

3,3-Dimethyl-2-[2-[(4*R*,7*S*)-7-isopropyl-4-methyl-4,5,6,7-tetrahydrobenzofuryl]]-2-fluoro-1,3,2-oxazaborolidin-5-one (25/26). To a suspension of *N*,*N*-dimethylglycine (Aldrich, dried under vacuum over P_2O_5, 85 mg, 0.83 mmol) and **24** (200 mg, 0.70 mmol) were added Et_3N (0.22 mL, 1.5 mmol) and TMSCl (0.23 mL, 1.8 mmol). After the reaction mixture was stirred at room temperature for 0.5 h and then at 50 °C for 2.5 h, the volatiles were removed by aspirator. The residue was taken up in 30 mL of EtOAc and 10 mL of CH_2Cl_2, washed by cold aqueous Na_2CO_3/NaCl (2×), and dried over Na_2SO_4. The oily crystals obtained by concentration of the above solution were washed with hexane to remove the boronic acid and other contaminants. The resulting solid (120 mg, 1:1 mixture by NMR analysis) was then dissolved in 10 mL of anhydrous EtOAc (dried over P_2O_5, distilled from CaH_2). The solution was clarified by centrifugation, and the supernatant solvent was then slowly evaporated at 50 °C with a N_2 stream to 2 mL, which was followed by addition of 2 mL of cyclohexane (dried over CaH_2). Continued slow evaporation of the solvents

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yielded 110 mg (53% overall; >95% based on the solid 1:1 mixture, above) of product as colorless crystals. One single diastereomer was present according to NMR analysis. Analytical TLC on silica gel, EtOAc, R_f = 0.54; mp 127.0−127.5 °C; molecular ion calcd for $C_{16}H_{25}BFNO_3$: 309.19116; found m/e = 309.1908, error = 1 ppm; base peak = 183 amu; IR (KBr, cm^{-1}) 2930, C−H; 1786, C=O; 200 MHz NMR (CD_3CN, ppm) δ 6.47 (1H, s), 3.75 (1H, d, J = 16.3 Hz), 3.58 (1H, d, J = 16.3 Hz), 2.8−2.4 (2H, m), 2.77 (3H, d, J = 1.0 Hz), 2.40 (3H, s), 2.3−2.0 (2H, m), 1.9−1.7 (1H, m), 1.6−1.3 (1H, m), 1.2−1.0 (1H, m), 1.10 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.82 (3H, d, J = 6.9 Hz).

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Supplementary Material Available: Copies of ^1H NMR spectra of **6a/b**, **9a/10a**, **9b/10b**, **16**, **23**, **24**, and **25** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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