Asymmetric Memory at Labile, Stereogenic Boron: Enolate Alkylation of Oxazaborolidinones

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Abstract: Oxazaborolidinones **3**, **25**, **32**, **42**, **49**, and **53** can be obtained as single diastereomers by crystallization-induced asymmetric transformation (AT). Asymmetric memory is maintained in the derived enolates because the stereogenic boron resists equilibration with achiral, trivalent boron-containing species on the time scale of enolate alkylation with methyl iodide, allyl bromide, or benzyl bromide. Conditions were found for alkylating oxazaborolidinone enolates derived from phenylalanine (**5**, **33**), alanine (**18**, **26**), phenylglycine (**43**), and valine (**54**) without significant loss of boron configuration. The phenylglycine-derived oxazaborolidinone alkylation products **44** and **45** slowly undergo boron epimerization at room temperature, and the *C*-allyl product **44b** partially racemizes during hydrolytic cleavage, apparently by a 2-aza-Cope rearrangement. These complications were not encountered with phenylalanine derivatives. Preparatively useful results were obtained with oxazaborolidinones **3** and **32**, derived from phenylalanine. AT favors a different boron configuration in the *B*-naphthyl analogue **32** compared to **3**. This provides access to either quasi-enantiomeric enolate **5** or **33** by starting from the same phenylalanine enantiomer.

Crystallization-induced asymmetric transformation (AT) is a promising technique for control of heteroelement configuration.[1] This method is useful in molecules that contain one or more configurationally stable asymmetric carbons in addition to a potentially labile stereogenic heteroatom such as trivalent phosphorus[2] or tetravalent boron.[3] Provided that both epimers at the heteroatom can interconvert on the time scale of crystallization, the diastereomer that corresponds to the more stable crystal lattice can be obtained with extraordinary selectivity simply by allowing solvent to slowly evaporate. Conversion to a single isomer and recovery approaching the 100% yield limit is possible because of the thermodynamics of phase equilibrium.[1]

To exploit the exceptional driving force of AT for stereocontrol in asymmetric synthesis, it is essential to perform subsequent reactions under circumstances where the key epimerization process does not occur. We initiated the current study for the purpose of defining limits where this is possible with tetravalent, stereogenic boron-containing substrates prepared by the complexation of a boron Lewis acid by an internal amidino nitrogen. New carbon bonds are then introduced using an enolate alkylation. If carbon bond formation occurs below the threshold temperature for reversible Lewis acid−Lewis base dissociation, then the stereogenic boron atom should control the alkylation. We were most interested in the special case where a single stereogenic carbon defines crystal lattice preferences for the AT process at boron and is subsequently converted into a (nonstereogenic) carbanion by base-induced deprotonation. Provided that the stereogenic boron atom does not epimerize, the molecule maintains a memory of starting material configuration and the carbanion retains the potential for stereospecific carbon bond formation.

Oxazaborolidinone substrates **3** and **4** are available from α-amidino carboxylates **1** and the $KPhBF_3/Me_3SiCl$ reagent as an in situ source of $PhBF_2$ (Scheme 1). An earlier publication from our laboratory reported that AT can be used to control boron configuration in this series because **3** and **4** equilibrate at 30−40 °C via the trivalent intermediate **2** (eq 1).[3c] Crystallization of the equilibrating isomer mixture favors isomer **3** (39:1 **3**:**4**), and conventional recrystallization at room temperature affords pure **3** in 75% overall yield from phenylalanine. Phenylglycine- or valine-derived amidines also afford one dominant oxazaborolidinone diastereomer after AT, but the alanine analogue has poor solubility and precipitation of amorphous material prevents isolation of the pure oxazaborolidinone.

The heterocyclic boron environment of **3**[4] was chosen because it resembles the oxazolidinone intermediates in Seebach's asymmetric memory approach to amino acid enolate alkylations.[5] By analogy, it was expected that **3** might be converted

(1) (a) AT as abbreviated here is the same as asymmetric transformation of the "second kind" or, inaccurately, "second order": Kuhn, R. *Chem. Ber.* **1932**, *65*, 49. (b) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing: Malabar, FL, 1994, Chapter 6.

(2) Pabel, M.; Willis, A. C.; Wild, S. B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1835.

(3) (a) Mancilla, T.; Contreras, R. *J. Organomet. Chem.* **1987**, *321*, 191. Gyori, B.; Emri, J. *J. Organomet. Chem.* **1982**, *238*, 159. (b) Preliminary report: Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612. (c) Vedejs, E.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3028.

(4) (a) Lang, K.; Nuetzel, K.; Schubert, F. German Patent 1130445, 1962; *Chem. Abstr.* **1963**, *58*, 1488a. Skoog, I. H. *J. Org. Chem.* **1964**, *29*, 492. Baum, G. *J. Organomet. Chem.* **1970**, *22*, 269. Köster, R.; Rothgery, E. *Liebigs Ann. Chem.* **1974**, 112. Miller, N. E. *Inorg. Chem.* **1974**, *13*, 1459. Halstrom, J.; Nebelin, E.; Pedersen, E. J. *J. Chem. Res.* **1978**, 80. Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1983**, *39*, 2995. Albericio, F.; Nicolás, E.; Rizo, J.; Ruiz-Gayo, M.; Pedroso, E.; Giralt, E. *Synthesis* **1990**, 119. Gong, B.; Lynn, D. G. *J. Org. Chem.* **1990**, *55*, 4763. Strang, C. J.; Henson, E.; Okamoto, Y.; Paz, M. A.; Gallop, P. M. *Anal. Biochem.* **1989**, *178*, 276. Brown, H. C.; Gupta, A. K. *J. Organomet. Chem.* **1988**, *341*, 73. Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 6063. Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 211. (b) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

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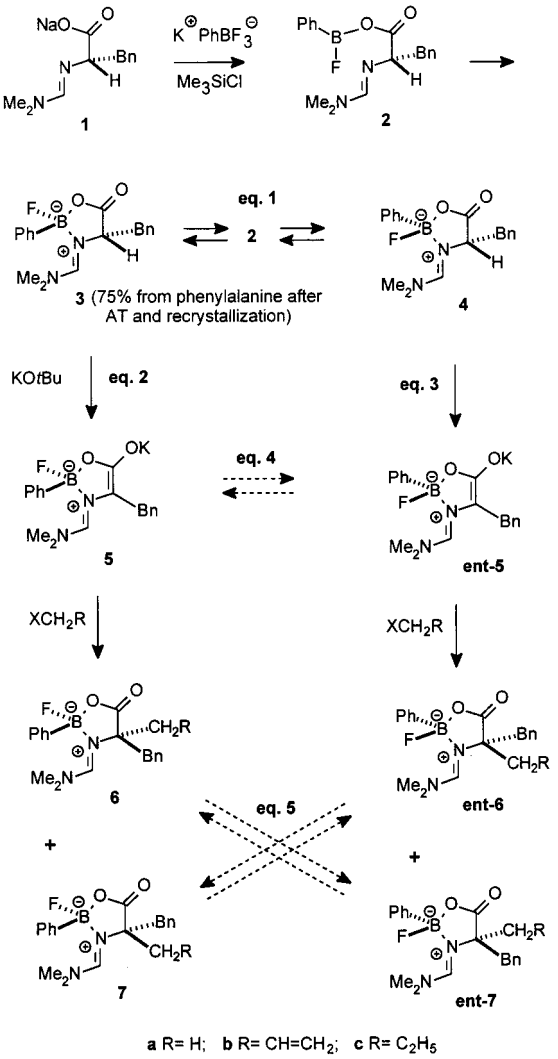
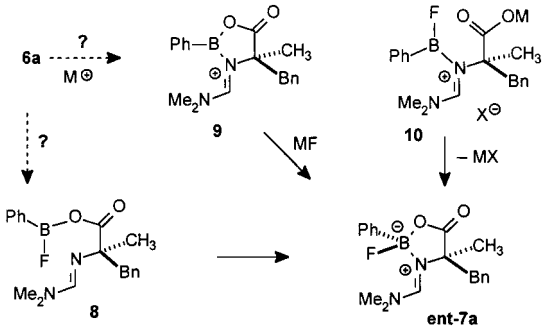
Scheme 1



into an enolate **5** upon treatment with strong base and that alkylation would afford diastereomers **6** and **7** under control of the stereogenic boron center. Depending on efficiency and selectivity, this sequence might provide an alternative for the enantiocontrolled synthesis of chiral, quaternary-carbon-containing amino acids.[3b] More important, the asymmetric memory feature[5−7] would constitute a highly sensitive test for retention of configuration at boron in products derived from **5** and would serve to evaluate the feasibility of using stereogenic boron reagents prepared by AT.

In the context of the asymmetric memory application, enolate **5** (eq 2) must be generated without leakage to the enantiomeric enolate **ent-5**. If the latter is formed via reversible B−N, B−F, or B−O bond cleavage in the enolate (eq 4), the resulting

Scheme 2



"memory lapse" would lead to partially racemized products in the subsequent enolate alkylation. Interconversion of boron epimers **3** and **4** via eq 1 is another concern, and this would provide an alternative route to **ent-5** (eq 3). Contributions by either eq 4 or the combination of eq 1 and eq 3 would result in partial racemization in each of the alkylation products **6** or **7**.

There is also a risk that product epimers might interconvert via eq 5. At first glance, this possibility appears to be of less concern because eq 5 interconverts presumably separable diastereomers such as **6** and **ent-7**. However, the consequences of boron epimer interconversion in the product are potentially serious if both **6** and **7** are formed in the alkylation step. This is because epimerization of either diastereomer at boron results in the enantiomer of the other diastereomer. Diastereomer separation would no longer afford enantiomerically pure products, and **6** or **7** could have substantially different ee values, depending on the relative rates in eq 5.

Several mechanisms could contribute to the undesired boron epimerization process (eq 5). As mentioned earlier, **3** and **4** interconvert in the temperature range of 30−40 °C by B−N bond cleavage. The analogous equilibration of **6** with **ent-7** via **8** (Scheme 2) should be slower because of the *gem*-dialkyl effect.[8] However, any process that reversibly cleaves one of the heteroatom−boron bonds would also result in epimerization. For example, fluorophilic or oxophilic metal ions might catalyze the reversible conversion of **6** into cationic trivalent boron species **9** or **10**. These potential complications are inherent in the AT-based approach to asymmetric synthesis, and the risks must be clearly defined. We therefore emphasized the exploration of substrates where epimerization at boron could be probed at every stage using a combination of HPLC assay on chiral stationary phase (HPLC/CSP), X-ray crystallography, and NMR correlations.

Results and Discussion

Treatment of **3** with KO*t*Bu in THF followed by methyl iodide produced a mixture of two separable, isomeric oxazaborolidinones **6a** and **7a** in a 5.5:1 ratio (Scheme 3). A similar experiment starting from racemic material (**3** + **ent-3**, prepared from racemic phenylalanine) gave the same ratio of racemic diastereomers. This mixture was completely resolved using HPLC/CSP, and the diastereomers as well as the enantiomers (**6a**, **ent-6a**, **7a**, **ent-7a**) could be assayed simultaneously. When the assay was performed on the mixture of **6a** and **7a** obtained from **3**, it was clear that the alkylation of **5** had occurred with <0.5% racemization. Both diastereomers **6a** and **7a** were purified by conventional silica gel chromatography followed by careful crystallization at room temperature to prevent equilibration at boron. The resulting crystals of **6a** were

(5) (a) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2709 and references therein.

(6) Ferey, V.; Le Gal, T.; Mioskowski, C. *J. Chem. Soc., Chem. Commun.* **1995**, 487. Ferey, V.; Toupet, L.; Le Gal, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430. Ferey, V.; Vedrenne, P.; Toupet, L.; Le Gal, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244.

(7) (a) For leading references to other asymmetric memory applications in enolate alkylations, see ref 5b. (b) Seebach, D.; Wasmuth, D. *Angew. Chem.* **1981**, *93*, 1007. Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694. Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373. (c) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607. (d) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949. Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105.

(8) For an analogous *gem*-dialkyl effect, see: Santiesteban, F.; Campos, M. A.; Morales, H.; Contreras, R.; Wrackmeyer, B. *Polyhedron* **1984**, 589.

Scheme 3

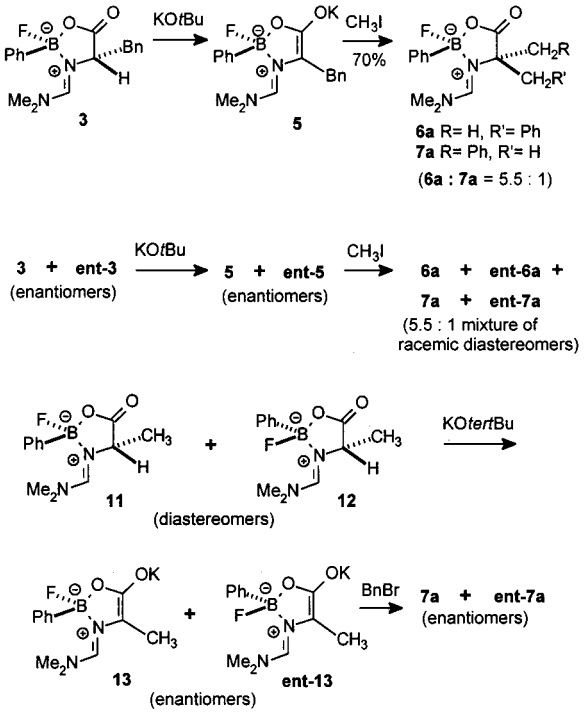


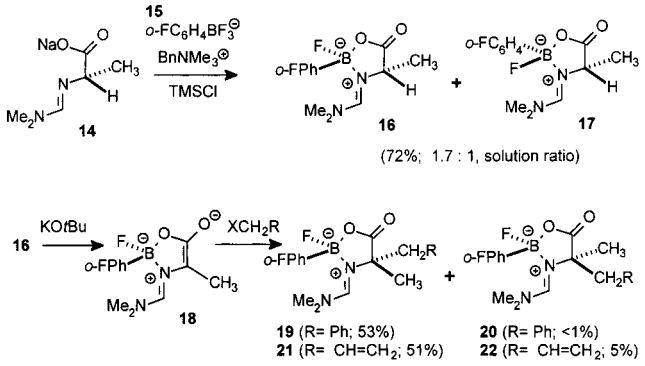
Table 1. Alkylation of Oxazaborolidinones[a]

substrate	halide	product ratio[b]	yield[c] (%)	ee[d] (%)
3 (Phe)	CH_3I	5.5:1 **6a**:**7a**	70	≥99.5
	C_3H_5Br	142:1 **6b**:**7b**	81	≥99.5
	n-C_3H_7	3:1 **6c**:**7c**	62	98.6
16 (Ala)	BnBr	>50:1 **19**:**20**	53	>98
	C_3H_5Br	10:1 **21**:**22**	56	>98
25 (Ala)	BnBr	249:1 **27**:**28**	78	>99.5
	C_3H_5Br	>32:1 **29**:**30**	67	na
32 (Phe)	CH_3I	7:1 **28**:**27**	na	na
	C_3H_5Br	>20:1 **34**	73	>99.5
42 (Phg)	CH_3I	1:1 **44a**:**45a**	76	>99
	C_3H_5Br	62:1 **44b**:**45b**	80	>99
49 (Phg)	CH_3I	1.7:1 **52a**:**51a**	78	>99
	C_3H_5Br	20:1 **51b**:**52b**	64	>99
53 (Val)	CH_3I	4:1 **55a**:**56a**	87	>95
	C_3H_5Br	>18:1 **55b**:**56b**	70	na
	BnBr	>80:1 **55c**:**56c**	80	99

[a] Enolate generated with KO*t*Bu, −78 °C. [b] Ratios above 20:1 by HPLC assay; others by ^{1}H NMR assay. [c] Combined yield of purified diastereomers. [d] Assay by HPLC/CSP on the crude product mixture after aqueous quench.

too small for X-ray crystallography, but the minor alkylation product **7a** afforded suitable crystals and the relative stereochemistry was established unambiguously (see the Supporting Information). Since the boron configuration of **3** has also been established by X-ray methods,[3c] both the relative and absolute stereochemistries of **6a** and **7a** are defined. The major diastereomer corresponds to carbon bond formation at the enolate face away from the *B*-phenyl substituent, as expected from simple steric considerations. Asymmetric memory is maintained throughout the sequence of events from **3** to **6a**, and the enolate **5** undergoes methylation without detectable racemization. Similar results were obtained for the reactions of **5** with allyl bromide and propyl bromide (Table 1). These reactions were not explored in depth, but the HPLC/CSP assay confirmed retention of asymmetric memory from **3** to the stage of alkylation products **6b**,**c**. The allylation was the most highly diastereoselective, and the major product **6b** was identified by X-ray methods. Further evidence for enantiomeric purity and

Scheme 4

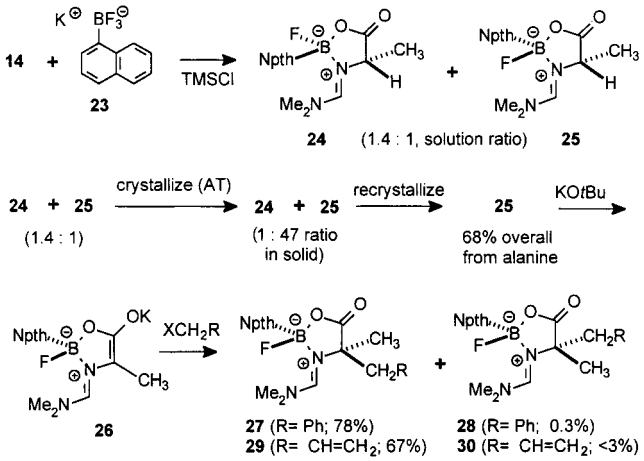


the absolute configuration of **6b** was obtained after hydrolytic cleavage to the parent amino acid as discussed later.

The minor diastereomer **7a** from the phenylalanine methylation experiment was also obtained by an independent route, starting from a mixture of alanine-derived oxazaborolidinones **11** and **12** (Scheme 3). In this case, the starting diastereomers **11** and **12** could not be separated and AT failed as already mentioned due to solubility problems. Although the starting diastereomers (1.5:1 dr) are enantiomerically pure, enolization converts the stereogenic α-carbon into a nonstereogenic sp^2 carbon. The resulting enolate is therefore a mixture of scalemic enantiomers **13** and **ent-13**, and alkylation is expected to produce a scalemic mixture of products. When the experiment was performed using benzyl bromide, only one diastereomer (mixture of enantiomers; **7a** and **ent-7a**) was detected. The relative stereochemistry corresponds to benzylation from the less hindered face, the same facial selectivity pattern that was seen in the methylation of **5**, and the self-consistent results confirm the HPLC/CSP assays as well as the qualitative predictions for enolate alkylation selectivity.

The failure to achieve AT in the alanine example (**11** + **12**) stimulated a search for other boron environments that might improve solubility in this series. There was also some concern that the AT process might have been compromised by contamination due to the difficulty in separating the sparingly soluble reagent ($KPhBF_3$) from the products (**11** and **12**). To minimize potential separation problems, a more soluble *B*-*o*-fluorophenyl boron source **15** was used (Scheme 4). The benzyltrimethylammonium salt **15** was obtained from the known potassium derivative[4b] by cation exchange with benzyltrimethylammonium bromide in dichloromethane. Treatment with chlorotrimethylsilane (TMSCl) to release the corresponding trivalent aryldifluoroborane proceeded without complications, and reaction with the alanine-derived amidine **14** afforded a mixture of **16** and **17**. In contrast to the *B*-phenyl analogues **11** and **12**, the *B*-fluorophenyl complexes **16** and **17** were soluble and stable enough for conventional chromatography. However, AT required crystallization at temperatures above 60 °C because of the stabilizing effect of the fluorophenyl group on tetravalent boron. A practical conversion to a single crystalline isomer could not be realized. Chromatography was necessary to obtain a sufficient quantity of the major diastereomer **16** to test the alkylation of enolate **18**. Good diastereoselectivities were observed in the allylation and benzylation as shown in Scheme 4. The relative stereochemistry of the major products **19** and **21** was assigned by analogy to the results of Scheme 3, while the stereochemistry of **16** was deduced from the long-range coupling (4 Hz) between fluorine and the ring hydrogen H_α ($H-C_4$ according to oxazaborolidinone numbering). In contrast, the long-range F to H_α coupling in the other diastereomer (**17**)

Scheme 5

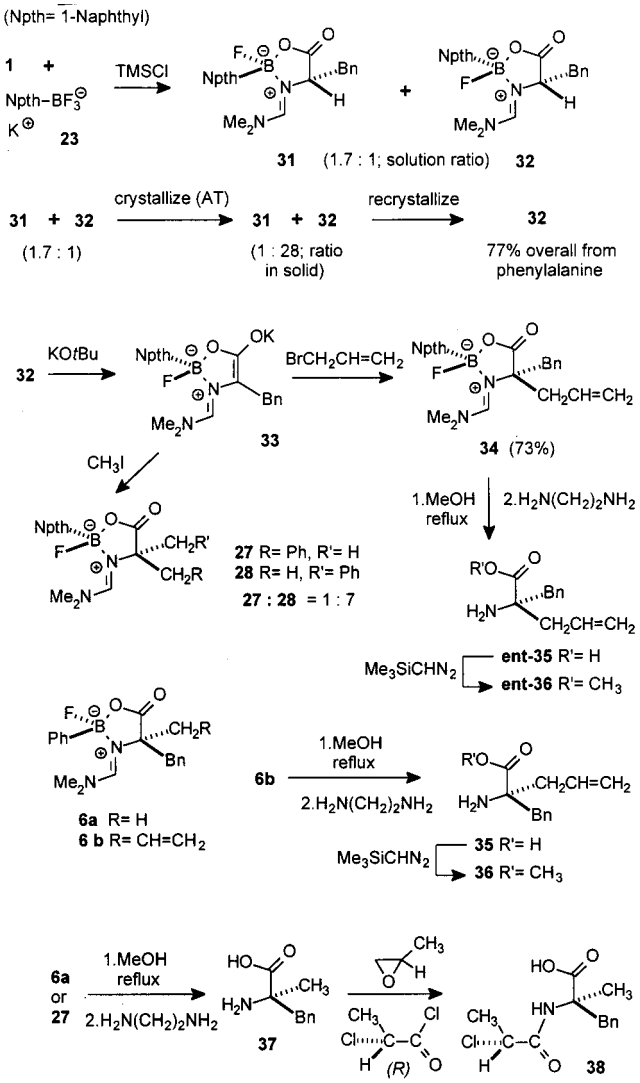


is <1 Hz. This behavior is characteristic for oxazaborolidinones, and the diastereomer that has H_α and fluorine trans with respect to the five-membered ring experiences long-range coupling according to our prior study.[3c]

A more successful attempt to obtain an alanine complex that would be suitable for AT is described in Scheme 5. Reaction of potassium *B*-(1-naphthyl)trifluoroborate (**23**) with **14** in the presence of TMSCl afforded a typical mixture of oxazaborolidinones **24** and **25** in an equilibrium ratio of 1.4:1. When this mixture was allowed to crystallize from a slowly evaporating solution in THF and toluene at 60 °C, a major crystalline diastereomer was obtained in 68% yield based on alanine. This isomer proved to be the *minor* solution component **25** (cis naphthyl and methyl groups, long-range coupling of H_α and fluorine < 1 Hz). The factors that control crystal lattice stability need not be the same as those that control the equilibrium in solution, so the AT behavior of **24**/**25** is not necessarily surprising. However, we did not expect that the favored crystalline isomer would have the *B*-naphthyl and *C*-methyl groups cis, in contrast to all of the *B*-phenyloxazaborolidinones investigated to date.

Treatment of **25** with KO*t*Bu in THF followed by benzyl bromide or allyl bromide resulted in the corresponding alkylation products **27** and **29**. The minor diastereomers **28** and **30** could not be detected by NMR methods. However, authentic **28** (the minor product of benzylation) was available by independent synthesis (Scheme 6) and HPLC/CSP techniques could be used to establish that the benzylation of enolate **26** occurs with extraordinary stereoselectivity (**27**:**28** = 249:1; >99.5% ee). To prepare the comparison sample enriched in **28** (Scheme 6), potassium *B*-(1-naphthyl)trifluoroborate **23** was reacted with the phenylalanine-derived amidine **1** in the presence of TMSCl and the resulting mixture of **31** and **32** was crystallized under AT conditions. As in the *B*-naphthyl alanine series, the less stable solution diastereomer **32** was favored in the solid. The relative stereochemistry of **32** was assigned by the absence of long-range fluorine−H_α coupling in the ^{1}H NMR spectrum, as well as by chemical correlations as follows. Methylation of **32** via the potassium enolate **33** gave a ca. 1:7 mixture of **27**:**28**. The diastereomers could not be separated on preparative scale, but HPLC/CSP assay confirmed that the products were the same as those obtained in the benzylation of **25**. However, the minor product from the methylation of **32** corresponded to the major product from the benzylation of **25**. This is the expected result if both enolates **26** and **33** have the same boron configuration and follow the same pattern of least hindered alkylation as established for the analogous *B*-phenyl enolates.

Scheme 6



To further confirm these generalizations, **33** (Scheme 6) was alkylated with allyl bromide, and the resulting **34** (one diastereomer detected by NMR) was cleaved to the corresponding amino acid **ent-35** (methanolysis at reflux to hydrolyze the boron complex; ethylenediamine to cleave the amidine). The absolute configuration of **ent-35** was established by comparing the sign of optical rotation with that of authentic material[9a,b] and of **35**, obtained by the analogous series of reactions starting with phenylalanine and proceding via the *B*-phenyl complex **3**, the enolate **5**, the major allylation product **6b**, and hydrolytic cleavage. For assay of enantiomeric purity, both **35** and **ent-35** were converted into the methyl esters[9c] by treatment with (trimethylsilyl)diazomethane.[10] No trace of cross-contamination could be detected in **36** or **ent-36** by HPLC/CSP (baseline resolution; >99.5% ee). Because the amino acids **35** and **ent-35** are enantiomeric, *B*-naphthyl enolate **33** must differ in boron configuration compared to the *B*-phenyl analogue **5**. Furthermore, **26** and **33** (and therefore, **32** and **25**) must have the same boron configuration.

(9) (a) Zydowsky, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437. (b) Van Bestbrugge, J.; Tourwe, D.; Kaptein, B.; Kierkels, H.; Broxterman, R. *Tetrahedron* **1997**, *53*, 9233. (c) van der Werf, A.; Kellogg, R. M. *Tetrahedron Lett.* **1988**, *29*, 4981.

(10) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1990**, *31*, 5507.

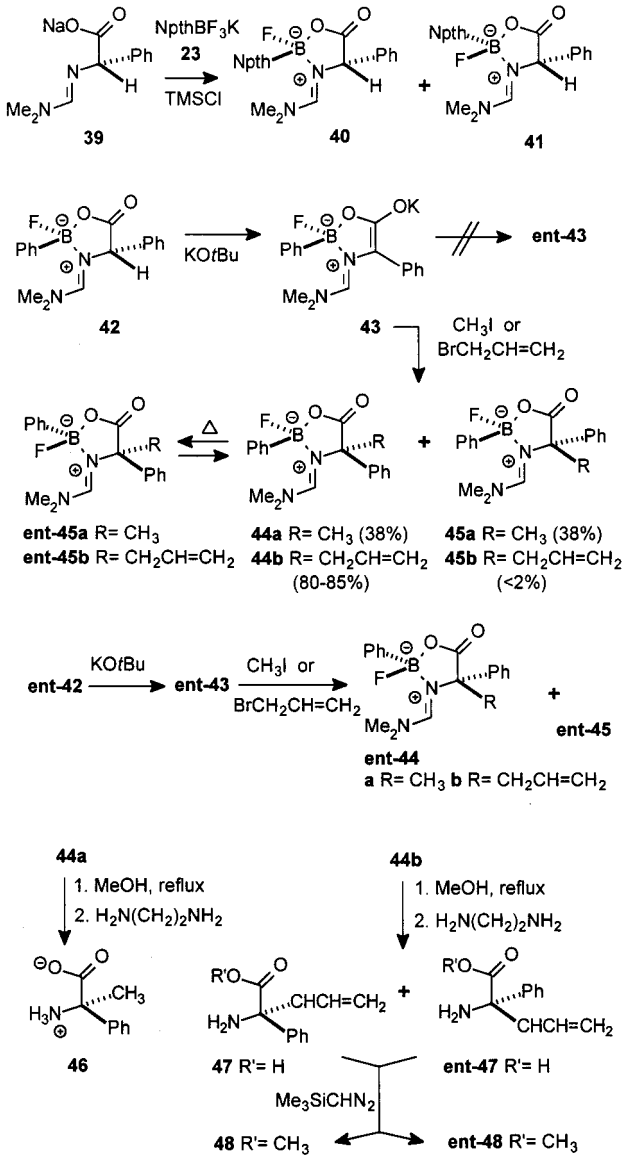
According to the above arguments, the carbon configuration of **27** (from the benzylation of the *B*-naphthyl alanine complex **25**) must be the same as that of **6a** (from methylation of the *B*-phenyl phenyalanine complex **3**). This was confirmed by correlation experiments as follows. Thus, **27** was treated with refluxing methanol followed by ethylenediamine and the resulting amino acid **37** was derivatized with (*R*)-2-chloropropionyl chloride.[11] The original derivatization procedure of Kellogg et al. was modified for small-scale experiments by using propylene oxide[12] in place of aqueous base to scavenge the HCl byproduct in the N-acylation. This method gave the known **38**[11] as a single diastereomer according to ^{1}H NMR assay. For comparison, the same sequence of hydrolytic cleavage and derivatization steps was applied to **6a**. As expected, this gave the identical diastereomer **38** via the intermediate amino acid **37**.

The above findings show that either enantiomeric series of α-alkylated phenylalanine derivatives can be accessed, starting from the same phenylalanine enantiomer simply by changing from the *B*-phenyl to the *B*-naphthyl environment for the AT process. This is possible because the *B*-naphthyloxazaborolidinone **32** (cis naphthyl and benzyl groups; Scheme 6) is favored in the crystal lattice, resulting in the (*R*)-configuration at boron. The analogous AT phenomenon is also observed in the *B*-naphthylalanine case where the isomer **25** (cis naphthyl and methyl groups) is more stable in the solid state. However, the *B*-naphthyl environment does not guarantee that AT will afford the cis stereochemistry of *B*-naphthyl and C_α substituents starting from other amino acid derivatives. When **23** was reacted with the phenylglycine amidine **39** (Scheme 7), crystallization of the product under AT conditions gave the trans arrangement (**40**) of the α-phenyl relative to the *B*-naphthyl group according to X-ray structure determination (Supporting Information). Because the same boron configuration is more conveniently obtained by reacting **39** with the $KPhBF_3$ reagent to give **42**,[4b] enolate alkylations of the *B*-naphthyl complex **40** were not investigated.

Alkylation of the phenylglycine-derived *B*-phenyloxazaborolidinone **42** was challenging because of limited solubility and expected as well as unexpected problems with epimerization (Scheme 7). A detailed investigation has resulted in an improved understanding of subtle aspects of the asymmetric memory application, but this series cannot be recommended for preparative applications. The starting oxazaborolidinone **42** is relatively sensitive to boron epimerization (analogous to eq 1),[4b] and attempts to prepare solutions of **42** at room temperature resulted in significant loss of enantiomeric purity in the products. Best results were obtained by stirring a suspension of crystallized **42** in THF at −78 °C with KO*t*Bu and brief warming to generate a homogeneous solution of the enolate **43**. For simplicity, only those experiments will be described in detail where this important precaution was taken. Special precautions were also necessary to determine the kinetic ratio of alkylation products **44** and **45** because the diastereomer **44** (cis *B*-phenyl and *C*-phenyl substituents) was more sensitive to boron epimerization compared to the corresponding products in the phenylalanine or alanine series.

Reaction of enolate **43** with methyl iodide produced a ca. 1:1 mixture of diastereomers **44a** and **45a**. The diastereomers were stable enough for separation by flash chromatography, and

Scheme 7



45a could be obtained as >95% one diastereomer according to ^{1}H NMR assay. However, the other diastereomer **44a** was usually contaminated, and variable amounts of diastereomer signals were seen in the NMR spectrum that increased with time. This behavior was fully understood only when HPLC/CSP methods were found that were capable of distinguishing all four stereoisomers (diastereomers and enantiomers; comparison samples prepared from **ent-42** as well as **rac-42**). According to HPLC/CSP assay, the variable contaminant in **44a** was not the original diastereomer **45a** formed in the alkylation step, but rather the mirror image isomer **ent-45a**, resulting from **44a** by epimerization at boron.[13] Chromatographically purified **44a** epimerized to a ca. 1:1 mixture of **44a**:**ent-45a** after 15 h at 50 °C in acetonitrile, but the process was too slow to monitor conveniently at room temperature. Purified **45a** was relatively stable, and boron epimerization could not be detected (<3% **ent-44a**) at room temperature or after 15 h at 50 °C.

Because diastereomer **45a** is relatively resistant to boron epimerization, these experiments have the seemingly paradoxical feature that the more labile diastereomer **44a** can be isolated with better enantiomeric purity (>99% ee) compared to the relatively stable **45a**. Indeed, if boron epimerization occurs *prior to diastereomer separation*, then contamination of **45a** by the

(11) Kruizinga, W. H.; Bolster, J.; Kellogg, R. M.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826. There is some concentration dependence in the chemical shift values reported previously, but the chemical shift of the (*S*)-CH_3CH(Cl) methyl group is consistently upfield in the diasetereomers derived from the (*S*)-α-methylamino acids relative to the diastereomers from the (*R*)-α-methylamino acids (private communication from Prof. Kellogg).

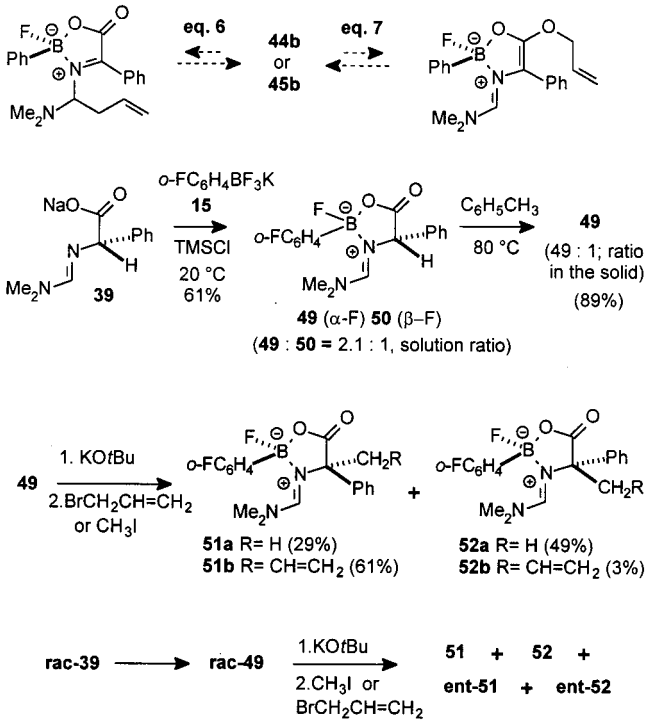
(12) Nyce, P. L.; Gala, D.; Steinman, M. *Synthesis* **1991**, 571.

enantiomer is inevitable if the less stable **44a** (the source of **ent-45a** via *B*-epimerization) is present in the original mixture. In contrast, diastereomer **44a** can be recovered from the same experiment without contamination by the enantiomer because **45a** resists epimerization to **ent-44a**.

Alkylation of the enolate **43** with allyl bromide was difficult to control and especially difficult to comprehend. After much effort, an understanding of the asymmetric memory aspects for this experiment has emerged, but some features of the system are still unclear (Scheme 7). The major alkylation product **44b** proved to be more sensitive to boron epimerization compared to the C-methylated analogue **44a**. When the initial product (**44b** + **45b**) was isolated using optimum workup procedures (minimum time; solvent removal below room temperature under high vacuum), diastereomer ratios as high as 62:1 were measured by analytical HPLC. Unfortunately, no HPLC/CSP assay was found to resolve **45b** and the enantiomer **ent-45b** (prepared independently from (*R*)-phenylglycine via **ent-42**), and a detailed analysis of all of the stereoisomers was not feasible. However, the diastereomer ratio (**44b** + **ent-44b**:[**45b** + **ent-45b**] as well as one of the enantiomer ratios (**44b**:**ent-44b**) could be monitored by HPLC/CSP. Repeated injections of the same product mixture at room temperature revealed decay of the diastereomer ratio from 62:1 to 56:1 (after sample dissolution in $CHCl_3$) and to 30:1 after 1.5 h, but no change was found in the enantiomeric purity of **44b** (>99% ee). Samples that were isolated using conventional rotary evaporation for solvent removal were usually obtained with a diastereomer ratio near 10−14:1. Lower ratios were seen in some experiments, suggesting that an impurity may act as a catalyst for boron epimerization, but the enantiomeric purity of **44b** remained high at room temperature according to HPLC/CSP.

Qualitatively, the behavior of **44b** appeared to resemble that of the methyl analogue **44a**. However, when the usual hydrolysis procedures (refluxing methanol; ethylenediamine) were applied to prepare the corresponding amino acids **46** and **47**, perplexing differences in enantiomeric purity were encountered. The methylated phenylglycine **46** was obtained with >95% ee according to the Kellogg test (derivatization with (*R*)-2-chloropropionyl chloride),[11] but a purified sample (24:1 diastereomer ratio) of **44b** (>99% ee by HPLC/CSP) prepared under optimum conditions to minimize boron epimerization afforded a deteriorated 14:1 mixture of **47** and **ent-47** (assayed by HPLC/CSP after conversion to the known methyl ester **48**, 87% ee).[14] This decay in the enantiomer ratio appears to be due to the elevated temperature used for methanolysis of the boroxazolidinone and has also been detected under nonhydroxylic conditions. Thus, a sample of **44b** (31:1 ratio of **44b**:[**45b** + **ent-45b**]) was warmed to 50 °C in $CHCl_3$ and the reaction was monitored by HPLC/CSP. Relatively fast epimerization at boron occurred as expected (diastereomer ratio after 1 h in $CHCl_3$, 3:1 **44b**:[**45b** + **ent-45b**]; after 18 h, 1:1.1). Enantiomeric purity was found to decay more slowly, but the peak due to **ent-44b** could be detected after 1 h (97% ee) and partial racemization was clear after 18 h (88% ee). Evidently, epimerization at the quaternary carbon is possible but occurs slowly compared to epimerization at boron.

Scheme 8



Partial racemization of the mixture of **44b** + **45** + **ent-45b** upon heating could be the result of competing, reversible sigmatropic rearrangement pathways (Scheme 8; eq 6 or 7). In principle, 2-aza-Cope[15] or retro-Claisen[16] processes related to eqs 6 and 7 might also occur at the stage of trivalent boron intermediates similar to the species shown in Scheme 2 or along the pathway for hydrolytic cleavage of the oxazaborolidinone. We did not investigate the racemization pathway in depth, but some evidence to implicate a 2-aza-Cope variant was obtained in the *B*-(*o*-fluorophenyl) series. Oxazaborolidinones **49** and **50** were prepared as described previously.[4b] Initial attempts to obtain a single diastereomer by AT were not successful because purified **49** and **50** interconvert too slowly under conventional crystallization conditions. However, when crude **49** + **50** was heated at 80 °C in toluene and the solvent was allowed to slowly evaporate, AT was achieved and the more stable **49** was obtained (49:1 ratio, ca. 50% overall, 99.5% ee by HPLC/CSP comparison with racemic material). Thus, no enolization of the sensitive phenylglycine subunit had occurred, despite the relatively harsh conditions for AT with this substrate. The relative stereochemistry of **49** was assigned on the basis of the long-range coupling of *B*-fluorine and H_α (<1 Hz).

Alkylation of the purified diastereomer **49** was accomplished by the usual treatment with KO*t*Bu in THF at −78 °C, followed by the alkyl halide. Surprisingly, the major product (1:1.7, **51a**:**52a**) in the methyl iodide experiment proved to be **52a**, but

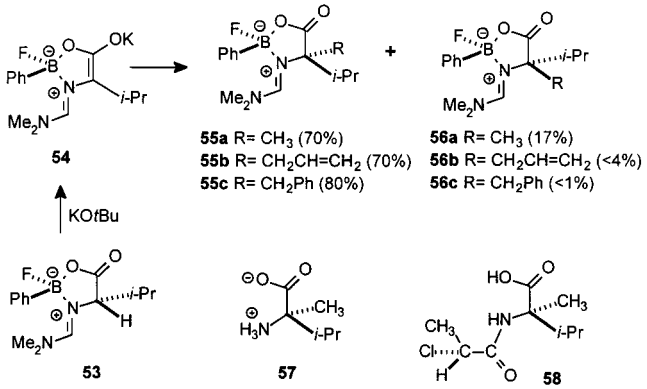
(13) These findings helped to explain a puzzling observation that was made in the course of early experiments designed to assign carbon configuration. A sample of **ent-45a** was prepared from **ent-42** by enolate methylation without using the crucial temperature control during workup and before the availability of HPLC/CSP assay. An unusual diastereomer ratio of 1:2 was measured for the alkylation product using ^1H NMR that is now understood to indicate a 1:2 mixture of **ent-44**:[**ent-45** + **45**]. The more stable oxazaborolidine fraction (trans *B*-phenyl and *C*-phenyl) was separated by chromatography, hydrolyzed to **46** (methanol, reflux) followed by ethylenediamine, and derivatized with (*S*)-2-chloropropionyl chloride. This produced a ca. 4:1 mixture of (*S*,*R*):(*S*,*S*) *N*-(α-chloropropionyl)-α-methylphenylglycine diastereomers, identified by chemical shift comparison with the authentic isomers reported by Kellogg et al. (ref 11). The initial ratio of alkylation products **ent-44**:[**ent-45** + **45**] is consistent with the observed diastereomer ratio if ca. 20−30% of the original **ent-44** had isomerized to **45**.

(14) Hartwig, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1952.

(15) Winterfeldt, E.; Franzischka, W. *Chem. Ber.* **1967**, *100*, 3801. Marshall, J. A.; Babler, J. H. *J. Org. Chem.* **1969**, *34*, 4186. Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329.

(16) Jefferson, A.; Scheinmann, F. *Q. Rev.* **1968**, *22*, 390. Boeckman, R. K., Jr.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359. Boeckman, R. K., Jr.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456.

Scheme 9



allyl bromide gave **51b** as the dominant product (19:1, **51b**:**52b**) according to X-ray crystallography (Supporting Information). We did not investigate the reasons for the inverted facial selectivity in the methylation vs the allylation, but epimerization issues were evaluated. As in the *B*-phenyl series, the methylation products were completely resolved by HPLC/CSP and >99% ee was established for both **51a** and **52a**. The major allylation product **51b** was obtained with 99% ee, but the enantiomers of the minor diastereomer (**52b**; **ent-52b**) could not be resolved. When purified **51b** was heated in $CHCl_3$ at 50 °C, slow epimerization at boron was observed (11:1 **51b**:**ent-52b** after 2 h; 6:1 after 18 h), but no change in the 99% ee value for **51b** could be detected, in contrast to the corresponding experiment with **44b**. This evidence argues against eq 7 as a factor in the carbon epimerization of **44b** because the electron-withdrawing 2-fluorophenyl substituent at boron should have little influence on the rate of the retro-Claisen process. On the other hand, the fluorophenyl substituent is expected to retard the formation of trivalent boron intermediates similar to those shown in Scheme 2, and it may also inhibit the 2-aza-Cope process analogous to eq 6 because increased electron demand at boron would destabilize the iminium subunit compared to the amidinium subunit of the starting oxazaborolidinone (**44b** or **51b**). No further attempt to clarify the mechanism of carbon epimerization was made in view of the uncertain preparative implications for the phenylglycine-derived oxazaborolidinones. However, conditions that maintain asymmetric memory at boron were established in the *B*-phenyl series and also in the less demanding *B*-(fluorophenyl)phenylglycine-derived oxazaborolidinones.

One final set of enolate alkylations was studied to define asymmetric memory issues in the valine series (Scheme 9). Boron epimerization was not as fast as in the phenylglycine case, but reproducible diastereomer ratios required use of the standard precautions to control temperature in the enolate generation, workup, and solvent removal steps. Solubility was also problematic, and homogeneous conditions for enolate generation required using **53**[3c] at ca. 0.02 M concentration in THF. Furthermore, HPLC/CSP methods could not be found to assay the enantiomeric methylation or allylation products (**55a**/**56a** or **55b**/**56b**), and the diastereomers were difficult to separate. In view of these limitations, the valine series was not studied in detail beyond what was required to establish asymmetric memory at boron for the enolate **54**.

The enolate methylation products **55a** + **56a** were prepared in the usual way as a 4:1 mixture and were partially separated by preparative HPLC techniques. The major isomer (ratio upgraded to 95:5 **55a**:**56a**) was hydrolyzed to the known amino acid **57**,[17] and absolute configuration was confirmed by derivatization with (*R*)- or (*S*)-α-chloropropionyl chloride.[11] Enantiomeric purity according to the Kellogg method (90% ±3 ee; ^{1}H NMR assay)[11] corresponded to the diastereomer ratio of **55a**:**56a** after chromatographic purification. A more precise assay was possible in the analogous *C*-benzyl derivatives **55c** and **ent-55c** because the enantiomers were easily resolved by HPLC/CSP. Thus, benzylation of enolate **54** gave a 99:1 ratio of diastereomers, and the major isomer was assigned structure **55c** by analogy to the methylation experiment. The material epimerized slowly at room temperature, but >99% ee was demonstrated by HPLC/CSP. Therefore, epimerization involves equilibration of boron configuration after the highly selective alkylation, and the enolate **54** does not undergo significant racemization in the benzylation as well as the methylation experiments. No satisfactory method to assay **55b**/**56b** or enantiomers was found, although a high diastereomer ratio (ca. 18:1 or better) is suggested by the NMR evidence.

Summary

The oxazaborolidinone enolate technology demonstrates a boron analogy of Seebach's concept of self-regeneration of stereocenters in combination with crystallization-induced asymmetric transformation (AT) to control configuration at stereogenic boron. Interconversion of boron epimers under crystallization conditions is essential for AT, but this feature also increases risks that asymmetric memory may be lost in the course of subsequent operations. Conceptual analogies have been reported where asymmetric memory is maintained in a labile chiral rotamer of an enol or enolate that would racemize upon conformational relaxation[7a,b] and in cases where chiral auxiliaries are present that could undergo racemization upon interconversion of atropisomers.[7c,d] Examples are also known where stereogenic nitrogen in a boronate complex is used to store asymmetric memory during amino acid enolate alkylation.[6] In principle, all of these systems share the feature that asymmetric memory lapses are possible via partial racemization of labile intermediates. We therefore placed the highest priority on demonstrating that oxazaborolidinones can have sufficient lability for AT but sufficient stability at lower temperatures for use without any significant loss of asymmetric memory. Extensive experimentation was necessary to show that these requirements can be met, but suitable conditions have been found for handling oxazaborolidinone enolates derived from phenylalanine (**5**, **33**), alanine (**18**, **26**), phenylglycine (**43**), and valine (**54**). In an earlier study, we had reported evidence that an *N*,*N*-dimethyl analogue of the phenylglycine-derived enolate **43** can be generated and quenched with acid with >95% retention of boron configuration.[3c] The current work demonstrates the concept in the more demanding enolate alkylations and with substrates having a removable protecting group at nitrogen.

The most useful results were obtained with phenylalanine-derived oxazaborolidinones **3** and **32**. Because the AT phenomenon favors a different boron configuration in the *B*-phenyl derivative **3** compared to the *B*-naphthyl analogue **32**, it is possible to generate either quasi-enantiomeric enolate **5** or **33** by starting from the same phenylalanine enantiomer. Access to enolates in either enantiomeric series has also been demonstrated using the Seebach technology by changing from the pivaldehyde to the benzaldehyde-derived oxazolidinones[20] or by working with the analogous imidazolidinones.[5,17] The overall efficiency from phenylalanine to the alkylated amino acid (ca. 50%; four steps) based on the oxazaborolidinones **3** or **32** is comparable

(17) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144.

to that reported for several of the most practical alternatives based on enolate alkylation.[5,18−21] The oxazaborolidinone hydrolysis conditions are milder compared to the original Seebach oxazolidinone or imidazolidinone methodology,[5] but recent improvements in the oxazolidinone series would have advantages in the hydrolysis step and also in alkylation diastereoselectivity.[21]

Oxazaborolidinone configurational stability issues were the primary focus of this investigation. All of the potential sources of asymmetric memory loss considered in Scheme 1 were encountered in the more difficult substrates (phenylglycine; valine) *except* for enolate racemization (eq 4). Problems due to eqs 1 and 5 were overcome by careful temperature control. Some of the alternative pathways for racemization suggested in Scheme 2 may also have been encountered, and reversible, catalyzed B−O bond cleavage may have contributed to the epimerization of **44** that was observed in crude samples at room temperature. Boron epimerization can result in partial racemization in the alkylated oxazaborolidinones if both diastereomers at the quaternary α-carbon are present or if the α-carbon can also undergo epimerization. The latter phenomenon was observed in a single case (**44b**) under conditions of oxazaborolidinone hydrolysis, apparently as the result of a competing 2-aza-Cope rearrangement.[15] However, the problem is restricted to the α-allylphenylglycine-derived *B*-phenyloxazaborolidinone. Analogous allylation products in the phenylalanine series (**6b**; **34**) were obtained and hydrolyzed to the amino acids with >99.5% retention of carbon configuration, and the oxazaborolidinones were formed and alkylated without racemization in all cases where enantiomer assay by HPLC/CSP was possible.

The ideal oxazaborolidinone asymmetric memory application requires >99% retention of boron configuration as demonstrated, and it also requires alkylation diastereoselectivity in the range of 50:1 or better. If the latter condition is satisfied, then interference by eq 5 can be ignored because hydrolysis of the oxazaborolidinone product would afford α-alkylated amino acid with >98% ee, regardless of boron epimerization during workup. This situation was encountered in the benzylations (**27**; **55c**) and perhaps in some of the allylations. More typically, enolate alkylation selectivity was moderate to low, especially with simple alkyl halides. In these cases it was necessary to separate oxazaborolidinone diastereomers to obtain enantiomerically pure amino acids after oxazaborolidinone hydrolysis. Further work would be needed to design a boron environment that affords the desired level of diastereoselectivity in the alkylation step with simple alkyl halides and that retains sufficient enolate reactivity. In the phenylalanine-derived potassium enolate **5**, reactivity is adequate for primary halides but not for branched halides. Attempts to use the lithium enolates for alkylation or for aldol reaction with aldehydes produced complex mixtures. We attribute these result to the possible intervention of trivalent boron species such as **9** and **10** (Scheme 2), resulting from the action of lithium ion as a fluorophile or oxophile.

The most important findings from this study are in the demonstration of configurational stability limits for potentially labile tetravalent boron intermediates and in the demonstrated compatibility with crystallization-induced asymmetric transformation. These are the first synthesis applications of asymmetric memory based on boron. Similar applications should be possible where chiral carbanionic species are generated in the stereogenic boron environment resulting from Lewis acid−Lewis base adduct formation.

Experimental Section

General Methods. Ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl; CH_2Cl_2 was distilled from P_2O_5; acetonitrile and chloroform were distilled first from P_2O_5 and then K_2CO_3 and stored over 4 Å molecular sieves; Chlorotrimethylsilane was distilled from CaH_2 and stored over polyvinylpyridine. Dimethylformamide (DMF) dimethyl acetal was distilled prior to use. Iodomethane was distilled from P_2O_5, and all other alkyl halides were filtered through neutral alumina. Reactions were carried out in a nitrogen atmosphere. HPLC/CSP columns (Daicel Chiralcel) were obtained from Chiral Technologies unless noted otherwise.

Preparation of Sodium Amidino Carboxylates and Oxazaborolidinones. General Considerations. All sodium amidino carboxylates were prepared as previously described,[3c] but care was taken to minimize exposure to moisture during solvent removal. Most of the solvent was removed by rotary evaporation, but exposure of the solid residue to prolonged aspirator vacuum risks measurable amidine hydrolysis to the *N*-formylamino acid derivative. The residual moist solid was therefore dried under oil pump vacuum, and the resulting powder was used without further purification. Anhydrous conditions are recommended for storage. Oxazaborolidinones were prepared according to ref 3c.

Alkylation of Oxazaborolidinones. General Considerations. Heating of alkylation product solutions *prior to diastereomer separation* must be avoided. Separation of diastereomeric alkylation products will produce enantiomerically pure products after oxazaborolidinone hydrolysis only if there has been no epimerization at boron via reversible B−N, B−O, or B−F bond cleavage. Once the boron epimers have been separated (or if the alkylation affords a single dominant diastereomer), heating can still cause diastereomer interconversion, but it can no longer influence enantiomeric purity after oxazaborolidinone hydrolysis. Recrystallization of the crude, unseparated mixture of alkylation products is often possible, but it requires special care (*NO HEATING*!) because of the risk of asymmetric transformation.

Alkylation Method A. (2*S*,4*R*)- and (2*S*,4*S*)-4-Benzyl-3-(dimethylaminomethylidene)-2-fluoro-4-methyl-2-phenyl-1,3,2-oxazaborolidin-5-one (6a and 7a). The phenylalanine-derived oxazaborolidinone **3**[3c] (66 mg, 0.202 mmol) was suspended in 2 mL of cold (−78 °C) anhydrous THF under nitrogen, and 1.04 equiv of *t*BuOK/THF solution (0.210 mL, 1.00 M, 0.210 mmol) was added dropwise over 5 min. Following addition of the base, the yellow suspension was warmed to −22 °C in a CCl_4/CO_2 bath for 15 min, during which the reaction mixture became homogeneous. The solution was recooled to −78 °C, and excess MeI (0.060 mL, 0.963 mmol) was added in one portion. The yellow anion color began fading immediately. After 1 h, the reaction was quenched with 5 μL of pH 7 phosphate buffer and the mixture was warmed to room temperature and concentrated (rotary evaporator 25 °C). The crude mixture was dissolved in 10 mL of CH_2Cl_2, washed with water (5 mL) and saturated aqueous NaCl (5 mL), dried ($Na_2SO_4/MgSO_4$), and concentrated (rotary evaporator, 25 °C). Preparative TLC (1 mm silica gel, 5% $MeCN/CH_2Cl_2$ eluent) separation of diastereomers afforded 7 mg (10%) of **7a** ($R_f = 0.24$) and 41 mg (60%) of **6a** ($R_f = 0.14$). **6a** (major): Analytical TLC on silica gel: 2:1 EtOAc/hexane, $R_f = 0.17$. Pure material was obtained by crystallization from EtOAc/hexane, mp 118−121 °C. $[\alpha]_D = -102$ ($c = 0.1$, CD_3CN). MS: $C_{19}H_{22}BFN_2O_2$ (M + 1) 341.1837, error = 0 ppm. IR (CH_2Cl_2, cm^{-1}): 1735, C=O;

(18) Fadel, A.; Salaun, J. *Tetrahedron Lett.* **1987**, *28*, 2243. Nebel, K.; Mutter, M. *Tetrahedron* **1988**, *44*, 4793.

(19) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085. Symposium in Print: α-Amino Acid Synthesis Symposium in Print. O'Donnell, M. J., Ed. *Tetrahedron* **1988**, *44* (17). Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225.

(20) (a) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (b) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schoenholzer, P.; Spiegler, C.; Mueller, K. *Helv. Chim. Acta* **1995**, *78*, 563. (c) Ayoub, M.; Chassaing, G.; Loffet, A.; Lavielle, S. *Tetrahedron Lett.* **1995**, *36*, 4069. (d) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233.

(21) (a) Smith, A. B., III; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947. (b) Alonso, F.; Davies, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 353.

1675, C═N. 200 MHz NMR (CD_3CN, ppm): δ 7.53 (1H, s), 7.35−7.20 (5H, m), 7.05−6.93 (3H, m), 6.42 (1H, AB, J = 1.2 Hz), 6.38 (1H, AB, J = 1.2 Hz), 3.51 (1H, AB, J = 14.5 Hz), 3.18 (1H, AB, J = 14.5 Hz), 3.07 (3H, s), 2.59 (3H, s), 1.59 (3H, s). **7a** (minor): Analytical TLC on silica gel, 2:1 EtOAc/hexane: R_f = 0.20. Pure material was obtained by crystallization from EtOAc/hexane, mp 184−186 °C. $[\alpha]_D = -95$ (c = 0.1, CD_3CN). MS: $C_{19}H_{22}BFN_2O_2$ (M + 1) 341.1816, error = 6 ppm. IR (CH_2Cl_2, cm^{-1}): 1745, C═O; 1675, C═N. 200 MHz NMR (CD_3CN, ppm): δ 7.40−7.10 (10H, m), 6.96 (1H, s), 3.17 (1H, AB, J = 13.6 Hz), 2.99 (1H, AB, J = 13.6 Hz), 2.86 (3H, s), 2.69 (3H, s), 1.62 (3H, s). Confirmation of the relative stereochemistry in the minor product **7a** was achieved by X-ray crystallography.

Enantiomer purity was assayed by HPLC on a 250 × 4.6 mm Chiralpak AS column (Daicel), 3:7 ethanol/hexane eluent, flow 0.9 mL/min at 375 psi, UV detection at 240 nm. A sample containing both diastereomers in *racemic* form (3:3:1:1 **6a**:**ent-6a**:**7a**:**ent-7a**) was prepared starting from DL-phenylalanine via **rac-3**, using the procedure described above for alkylation. The diastereomers and also the enantiomers were completely resolved (baseline separation), and the following retention times were observed: **6a**, 14.38 min; **ent-6a**, 6.77 min; **7a**, 9.92 min; **ent-7a**, 11.65 min. Response factors for the diastereomers were established to be identical within experimental error because the UV absorbance ratios were the same as NMR integral ratios. Response factors for the enantiomers are identical by definition. From this information, the diastereomer as well as enantiomer ratios of alkylation product mixtures could be determined directly. Using method A as described above, each diastereomer **6a** and **7a** (5.5:1 ratio) obtained from **3** consisted of a single enantiomer. A conservative extrapolation of peak shape at the baseline indicated a maximum of 0.5% contamination by the enantiomers **ent-6a** and **ent-7a**, but no distinct maxima for the enantiomers were detected.

(2*S*,4*R*)-4-Allyl-4-benzyl-3-(dimethylaminomethylidene)-2-fluoro-2-phenyl-1,3,2-oxazaborolidin-5-one (6b). Alkylation of **3** (328 mg, 1.01 mmol) was performed according to alkylation method A with the following quantities of reagents: THF, 10 mL); *t*BuOK/THF, 1.12 mL, 0.99 M, 1.11 mmol; allyl bromide, 0.440 mL, 5.08 mmol. The material obtained after aqueous workup (342 mg, 98.6% de) was recrystallized from CH_2Cl_2/Et_2O, yielding 294 mg (0.803 mmol, 80%, two crops) of pure **6b**, mp 153−154 °C: Analytical TLC on silica gel, 2:1 EtOAc/hexane: R_f = 0.39. Analytical HPLC (Chiralpak AS column, 250 × 4.6 mm, Daicel) 0.9 mL/min, 406 psi, 7:3 hexane/ethanol: t_R= 13.5 min (**6b**) and 7.8 min (**ent-6b**). Confirmation of the relative stereochemistry of **6b** was achieved by X-ray crystallography (see the Supporting Information): $C_{21}H_{24}BFN_2O_2$ (M − 77) 289.1525, error = 0 ppm; base peak = 289 amu. IR (KBr, cm^{-1}): 1737, C═O; 1670, C═N. 300 MHz NMR (CD_2Cl_2, ppm): δ 7.37−7.33 (3H, m), 7.25−7.21 (2H, m), 7.14−7.01 (3H, m), 6.94 (1H, s), 6.66−6.63 (2H, m), 5.85 (1H, dddd, J = 17.3, 10.2, 7.2, 7.2 Hz), 5.26 (1H, dddd, J = 10.2, 1.9, 0.9, 0.9 Hz), 5.17 (1H, dddd, J = 17.3, 1.9, 1.1, 1.1 Hz), 3.58 (1H, d, J = 14.7 Hz), 3.11 (1H, d, J = 14.7 Hz), 2.93 (3H, s), 2.82 (1H, dddd, J = 14.3, 7.2, 1.1, 1.1 Hz), 2.70 (3H, s), 2.57 (1H, dddd, J = 14.3, 7.2, 0.9, 0.9 Hz).

(2*S*,4*R*)- and (2*S*,4*S*)-4-Benzyl-3-(dimethylaminomethylidene)-2-fluoro-2-phenyl-4-propyl-1,3,2-oxazaborolidin-5-one (6c and 7c). Alkylation of **3** (207 mg, 0.635 mmol) was performed according to alkylation method A with the following quantities of reagents: THF, 6 mL; *t*BuOK/THF, 0.74 mL, 0.95 M, 0.779 mmol; iodopropane, 0.62 mL, 6.36 mmol. Due to the lower reactivity of the electrophile, the alkylation reaction was maintained at −78 °C for 3 h before quenching. The crude material obtained after aqueous workup (62% de) was purified by flash chromatography on silica gel (10H3 cm), 1:1 EtOAc/hexane eluent, yielding 43 mg (0.117 mmol, 18%) of the R_f = 0.23 isomer and 146 mg (0.397 mmol, 62%, 98.6% ee) of the R_f = 0.14 isomer. Analytical HPLC (Chiralpak AS column, 250 × 4.6 mm, Daicel) 0.9 mL/min, 406 psi, 7:3 hexane/ethanol: t_R= 14.6 min (**6c**), 9.6 min (**ent-6c**), 7.3 min (**7c**), and 6.6 min (**ent-7c**), based on comparison with a racemic sample prepared analogously. **6c** (major): Analytical TLC on silica gel, 1:1 EtOAc/hexane: R_f = 0.14. $C_{21}H_{26}BFN_2O_2$ (M + 1) 369.2153, error = 1 ppm; base peak = 291 amu. IR (KBr, cm^{-1}): 1735, C═O; 1726, C═O; 1666, C═N. 300 MHz NMR (CD_2Cl_2, ppm): δ 7.37−7.30 (3H, m), 7.25−7.22 (2H, m), 7.14−7.01 (4H, m), 6.66−6.63 (2H, m), 3.54 (1H, dd, J = 14.6 Hz), 3.14 (1H, dd, J = 14.6 Hz), 2.93 (3H, s), 2.70 (3H, s), 2.11 (1H, ddd, J = 13.9, 12.2, 4.5 Hz), 1.65 (1H, ddd, J = 13.9, 12.2, 4.5 Hz), 1.57−1.26 (2H, m), 0.96 (3H, t, J = 7.3 Hz). **7c** (minor): Analytical TLC on silica gel, 1:1 EtOAc/hexane: R_f = 0.23. Pure material was obtained by crystallization from ether/CH_2Cl_2, mp 135−6 °C. $C_{21}H_{26}BFN_2O_2$ (M − 77) 291.1672, error = 3 ppm; base peak = 291 amu. IR (KBr, cm^{-1}): 1735, C═O; 1670, C═N. 300 MHz NMR (CD_2Cl_2, ppm): δ 7.34−7.18 (10H, m), 6.03 (1H, d, $^4J_{HF}$= 1.9 Hz), 3.13 (2H, AB, J = 13.4 Hz), 2.74 (3H, s), 2.63 (3H, s), 2.19 (1H, ddd, J = 14.8, 11.9, 4.4 Hz), 1.81 (1H, ddd, J = 14.8, 11.7, 5.0 Hz), 1.42−1.19 (2H, m), 0.98 (3H, t, J = 7.1 Hz).

Benzyltrimethylammonium *o*-Fluorophenyltrifluoroborate (15). In a 500 mL round-bottom flask were placed potassium *o*-fluorophenyltrifluoroborate[4b] (6.96 g, 34.3 mmol) and benzyltrimethylammonium bromide (Aldrich, 8.69 g, 37.8 mmol). To this mixture were added CH_2Cl_2 (90 mL) and water (50 mL). The biphasic solution was stirred for 18 h. The reaction mixture was then poured into a separatory funnel, the layers were separated off, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were extracted with brine (25 mL) and dried ($MgSO_4$) and ca. half of the solvent volume was removed (aspirator). The solution was then diluted with CH_2Cl_2 (25 mL) followed by the addition of Et_2O (10 mL). The flask was refrigerated, leading to the growth of granular crystals (8.05 g, 75% yield). Analytical TLC on MN silica gel P, 1:9 methanol/CH_2Cl_2: R_f = 0.20. Pure material was obtained by crystallization from ether/CH_2Cl_2, mp 82−83 °C, granular crystals. Anal. Calcd: C, 61.36; H, 6.45. Found: C, 61.23; H, 6.45. IR (KBr, cm^{-1}): 3045, ═C−H; 980, B−F. 300 MHz NMR ($CDCl_3$, ppm): δ 7.56 (1H, td, J = 6.8, 1.8 Hz), 7.38−7.33 (1H, m), 7.28−7.26 (4H, m), 7.13−7.06 (1H, m), 6.98 (1H, t, J = 7.2 Hz), 6.81 (1H, t, J = 8.8 Hz), 4.31 (2H, s), 2.90 (9H, s). ^{13}C NMR (75 MHz, CD_3CN, ppm): δ 166.1 d, 134.3, 132.8, 130.6, 129.1, 128.2 d, 127.3, 123.3, 114.3 d, 69.2, 52.1 (the carbon bearing the boron substituent is not observed due to quadrupolar relaxation). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ −137.8 q (J = 48 Hz), −107.4 s. ^{11}B NMR (160 MHz, CD_3CN, ppm): δ 2.90 q (J = 50 Hz).

Potassium 1-Naphthyltrifluoroborate (23). The procedure followed the method described for $KPhBF_3$.[4b] Pure material (221 mg, 82% from 200 mg of 1-naphthylboronic acid)[22] was obtained by extracting the initial precipitate with hot acetonitrile (2H10 mL), evaporation, and recrystallization of the residue from hot acetonitrile, mp 205 °C (dec). Anal. Calcd: C, 51.31; H, 3.01. Found: C, 50.99; H, 3.16. 200 MHz NMR (CD_3CN, ppm): δ 8.42−8.39 (1H, m), 7.78−7.71 (1H, m), 7.63 (2H, d, J = 7.7 Hz), 7.40−7.29 (3H, m). 160 MHz ^{11}B NMR (CD_3CN, ppm vs BF_3AOEt_2): δ 4.4 (q, J = 54 Hz). 282 MHz ^{19}F NMR (CD_3CN, ppm vs $CFCl_3$): δ −137 (1:1:1:1 q, J = 54 Hz). The salt rapidly discolors upon standing at room temperature, so storage in a freezer under inert atmosphere is recommended.

(2*R*,4*S*)-3-(Dimethylaminomethylidene)-2-fluoro-4-methyl-2-(1-naphthyl)-1,3,2-oxazaborolidin-5-one (25). To a solution of sodium *N*-(dimethylaminomethylidene)alaninate **14** (prepared as described in ref 3c; 601 mg, 3.62 mmol) and potassium (1-naphthyl)trifluoroborate **23** (900 mg, 3.97 mmol) in 25 mL of anhydrous THF under nitrogen was added excess chlorotrimethylsilane (Aldrich; 1.1 mL, 8.64 mmol) in one portion. After several minutes, formation of a fine precipitate was observed. The mixture was stirred for 4 h, then concentrated to one-half volume (rotary evaporator, 25 °C) and diluted with water (10 mL). The solid was collected by filtration, washed with several portions of ether, and pumped dry to yield 905 mg of a 1:1.4 **25**:**24** mixture of diastereomeric oxazaborolidinones. The asymmetric transformation was performed on 380 mg of the crude solid. Thus, the mixture was dissolved in 30 mL of anhydrous THF at 60 °C in a septum-capped 115 × 25 mm test tube equipped with a magnetic stir bar. Dry toluene (1 mL) was added, and the solvent was slowly evaporated (ca. 8−10 mL/h) under a nitrogen stream with continuous stirring. Additional dry toluene (8 mL total) was added periodically. After 4 h, the remaining slurry was cooled to room temperature and filtered, yielding 328 mg

(22) Poole, C. F.; Singhawangcha, S.; Zlatkis, A. *J. Chromatogr*. **1978**, *158*, 33.

of a 98:2 **25**:**24** mixture. Recrystallization from cold CH_2Cl_2/Et_2O upgraded the material to >99:1 dr, mp 206−7 °C. Analytical TLC on silica gel, 2:1 EtOAc/hexane: $R_f = 0.23$. Analytical HPLC (silica gel column, 250H4.6 mm, Gilson): 1.5 mL/min, 1392 psi, 1:3 EtOH/hexane, $t_R = 13.3$ min (**24**) and $t_R = 15.4$ min (**25**). Molecular ion calcd for $C_{16}H_{18}BFN_2O_2$: 300.14456; found $m/e = 300.1450$, error = 1 ppm. IR (KBr, cm^{-1}): 1744, C═O; 1676, C═N. 300 MHz NMR (9:1 mixture of amidine *E*/*Z* isomers; CD_2Cl_2, ppm): δ 8.45−8.43 (1H, m), 7.83−7.75 (2H, m), 7.51−7.32 (5H, m), 4.64 (0.1H, q, $J = 7.2$ Hz), 4.29 (0.9H, q, $J = 7.2$ Hz), 3.27 (0.3H, s), 3.19 (2.7H, s), 3.15 (0.3H, s), 2.99 (2.7H, d, $J = 3.4$ Hz), 1.59 (3H, d, $J = 7.2$ Hz).

(2*R*,4*R*)-4-Benzyl-3-(dimethylaminomethylidene)-2-fluoro-4-methyl-2-(1-naphthyl)-1,3,2-oxazaborolidin-5-one (27). Alkylation of **25** (97 mg, 0.32 mmol, de) was performed according to alkylation method A with the following quantities of reagents: THF, 4 mL; *t*BuOK/THF, 0.48 mL, 0.75 M, 0.36 mmol; benzyl bromide,0.38 mL, 3.2 mmol. The material obtained after aqueous workup (121 mg, 0.31 mmol, 249:1 dr and >99.5% ee by HPLC assay) was recrystallized from CH_2Cl_2/Et_2O, yielding 98 mg (0.25 mmol, 78%, ≥99.5% ee) **27**, mp 217−9 °C (dec). Analytical TLC on silica gel, 2:1 EtOAc/hexane: $R_f = 0.25$. Analytical HPLC (5 μm silica gel column, 250 × 4.6 mm, Gilson), 1.5 mL/min, 1290 psi, 3:1 hexane/ethanol: $t_R = 5.8$ min (**27**) and $t_R = 6.9$ min (**28**). Analytical HPLC (Chiralpak AS column, 250 × 4.6 mm, Daicel), 1.0 mL/min, 406 psi, 7:3 hexane/ethanol: t_R= 6.0 min (**ent-27**), 7.4 min (**28**), 10.8 min (**ent-28**), 13.8 min (**27**; major). Molecular ion calcd for $C_{23}H_{24}BFN_2O_2$: 390.19153; found $m/e = 390.1919$, error = 1 ppm. IR (KBr, cm^{-1}): 1746, C═O; 1672, C═N. 200 MHz NMR (CD_3CN, ppm): δ 8.29−8.23 (1H, m), 7.82−7.72 (2H, m), 7.42−7.17 (10H, m), 3.19 (2H, ABq, $J = 14.0$ Hz), 3.01 (3H, s), 2.72 (3H, s), 1.63 (3H, s).

(2*R*,4*R*)-4-Allyl-3-(dimethylaminomethylidene)-2-fluoro-4-methyl-2-(1-naphthyl)-1,3,2-oxazaborolidin-5-one (29). Alkylation of **25** (99 mg, 0.33 mmol) was performed according to alkylation method A with the following quantities of reagents: THF, 4 mL; *t*BuOK/THF, 0.48 mL, 0.75 M, 0.36 mmol; allyl bromide, 0.28 mL, 3.3 mmol. The material (100 mg, ≥97:3% dr) obtained after aqueous workup was recrystallized from CH_2Cl_2/Et_2O, yielding 75 mg (0.22 mmol, 67%) **29**, mp 163−5 °C. Analytical TLC on silica gel, 2:1 EtOAc/hexane: $R_f = 0.20$. Analytical HPLC (5 μm silica gel column, 250 × 4.6 mm, Gilson), 1.5 mL/min, 1290 psi, 3:1 hexane/ethanol: t_R= 7.2 min. Molecular ion calcd for $C_{19}H_{22}BFN_2O_2$: 340.1759; found $m/e = 340.1763$, error = 1 ppm. IR (KBr, cm^{-1}): 1754, C═O; 1669, C═N. 500 MHz NMR (CD_2Cl_2, ppm): δ 8.45 (1H, d, $J = 7.7$ Hz), 7.80 (1H, dd, $J = 7.7$, 1.9 Hz), 7.75 (1H, d, $J = 7.9$ Hz), 7.46 (1H, ddd, $J = 7.7$, 7.2, 1.9 Hz), 7.43 (1H, ddd, $J = 7.7$, 7.2, 1.9 Hz), 7.36 (1H, dd, $J = 7.9$, 7.9 Hz), 7.30 (1H, s), 7.21 (1H, d, $J = 7.9$ Hz), 5.83 (1H, dddd, $J = 17.0$, 10.3, 7.2, 7.2 Hz), 5.28 (1H, dddd, $J = 10.3$, 1.5, 1.0, 1.0 Hz), 5.21 (1H, dddd, $J = 17.0$, 1.5, 1.5, 1.5 Hz), 3.14 (3H, s), 2.89 (3H, d, $J = 1.1$ Hz), 2.85 (1H, dddd, $J = 14.6$, 7.2, 1.5, 1.5 Hz), 2.54 (1H, dddd, $J = 14.6$, 7.2, 1.0, 1.0 Hz), 1.60 (3H, s).

(2*R*,4*S*)-4-Benzyl-3-(dimethylaminomethylidene)-2-fluoro-2-(1-naphthyl)-1,3,2-oxazaborolidin-5-one (32). To a solution of sodium *N*-(dimethylaminomethylidene)phenylalaninate (1.037 g, 4.29 mmol)[3c] and potassium (1-naphthyl)trifluoroborate **23** (1.111 g, 4.75 mmol) in 40 mL of anhydrous THF under nitrogen was added excess chlorotrimethylsilane (Aldrich; 1.4 mL, 11.0 mmol) in one portion. After several minutes, formation of a fine white precipitate was observed. The mixture was stirred for 1 h and then concentrated to a white solid (rotary evaporator, 30 °C). The residue was triturated with 10 mL of H_2O, filtered, washed with additional portions of water and ether, and pumped dry to yield 1.432 g (3.81 mmol) of a 5:1 mixture of diastereomeric oxazaborolidinones **32**:**31**. The asymmetric transformation procedure was performed on 355 mg of this material. Thus, the mixture was dissolved in 20 mL of anhydrous 1,2-dichloroethane at 65 °C in a septum-capped 115 × 25 mm test tube equipped with a magnetic stir bar. The solvent was slowly evaporated under a nitrogen stream with continuous stirring, while dry CCl_4 was added periodically. The resulting slurry was cooled to room temperature, filtered, washed with H_2O and ether, and dried. The transformed product (309 mg) was composed of a 96.5:3.5 **32**:**31** mixture according to HPLC assay [5 μm silica gel, 250 ×4.6 mm, 1:3 ethanol/hexane, 1.5 mL/min, 1392 psi, $t_R = 5.3$ min (**31**) and $t_R = 7.2$ min (**32**)]. Pure material was obtained by crystallization from CH_2Cl_2/ether, mp 217 °C (dec). Analytical TLC on silica gel, 2:1 EtOAc/hexane: $R_f = 0.23$. Molecular ion calcd for $C_{22}H_{22}BFN_2O_2$: 376.1758; found $m/e = 376.1758$, error = 0 ppm; base peak = 249 amu, M − 127 ($-C_{10}H_7$). IR (KBr, cm^{-1}): 1733, C═O; 1678, C═N. 200 MHz NMR (CD_2Cl_2, ppm): δ 8.45−8.39 (1H, m), 7.82−7.73 (2H, m), 7.49−7.30 (9H, m), 6.63 (1H, s), 4.36 (1H, dd, $J = 10.5$, 3.9 Hz), 3.37 (1H, dd, $J = 14.0$, 3.9 Hz), 2.96 (1H, dd, $J = 14.0$, 10.5 Hz), 2.90 (3H, d, $J = 3.7$ Hz), 2.80 (3H, s).

(2*R*,4*S*)-4-Allyl-4-benzyl-3-(dimethylaminomethylidene)-2-fluoro-2-(1-naphthyl)-1,3,2-oxazaborolidin-5-one (34). Alkylation of **32** (202 mg, 0.537 mmol) was performed according to method A with the following quantities of reagents: THF, 5.5 mL; *t*BuOK/THF, 0.79 mL, 0.75 M, 0.593 mmol; allyl bromide, 0.450 mL, 5.20 mmol. The material obtained after aqueous workup was recrystallized from CH_2Cl_2/Et_2O, yielding 162 mg (0.389 mmol, 73%) of pure **34**, mp 148−9 °C. Analytical TLC on silica gel, 2:1 EtOAc/hexane: $R_f = 0.38$. Analytical HPLC (5 μm silica gel column, 250 × 4.6 mm, Gilson), 1.5 mL/min, 1363 psi, 3:1 hexane/ethanol: t_R= 5.2 min. Molecular ion calcd for $C_{25}H_{26}BFN_2O_2$: 416.2072; found $m/e = 416.2079$, error = 2 ppm. IR (KBr, cm^{-1}): 1731, C═O; 1667, C═N. 500 MHz NMR (CD_2Cl_2, ppm): δ 8.48 (1H, d, $J = 8.2$ Hz), 7.76 (1H, dd, $J = 8.2$, 1.5 Hz), 7.65 (1H, d, $J = 7.4$ Hz), 7.44 (1H, ddd, $J = 8.2$, 6.7, 1.5 Hz), 7.41 (1H, ddd, $J = 8.2$, 6.7, 1.5 Hz), 7.35−7.32 (3H, m), 7.28−7.25 (2H, m), 7.10 (1H, dd, $J = 7.4$, 7.4 Hz), 6.93 (1H, s), 6.45 (1H, d, $J = 7.4$ Hz), 5.87 (1H, dddd, $J = 17.0$, 10.1, 7.1, 7.1 Hz), 5.29 (1H, dddd, $J = 10.1$, 1.3, 1.3, 1.3 Hz), 5.19 (1H, dddd, $J = 17.0$, 1.3, 1.3, 1.3 Hz), 3.46 (1H, d, $J = 14.4$ Hz), 3.13 (1H, d, $J = 14.4$ Hz), 3.00 (3H, s), 2.92 (1H, dddd, $J = 14.4$, 7.1, 1.3, 1.3 Hz), 2.82 (3H, d, $J = 1.1$ Hz), 2.59 (1H, dddd, $J = 14.4$, 7.1, 1.3, 1.3 Hz).

Cleavage of Oxazaborolidones. Conversion of 6a into (*R*)-α-Methylphenylalanine (37). The boron complex **6a** (150 mg, 0.441 mmol) was refluxed in anhydrous methanol (2 mL) for 2 h, at which time TLC analysis indicated complete disappearance of the starting material. Conversion to the amino acid could be effected by prolonged heating in methanol, but complete conversion of the *N*-formyl intermediate could not be achieved reproducibly. The following method gave better yields. Ethylenediamine (0.06 mL, 0.9 mmol) was added to the methanol solution when no more **6a** could be detected, and heating was continued for 1.5 h, until the amidino acid was completely consumed according to TLC analysis using 4:1:0.1 CH_2Cl_2/CH_3OH/concentrated NH_4OH on silica gel: R_f 0.34 (amidino acid), R_f 0.2 (amino acid), R_f 0.57 (phenylboric anhydride). The mixture was allowed to cool, 15 mL of deionized water was added, and the aqueous phase was washed with ether (3 × 15 mL). The ether layer was washed once with brine, dried ($MgSO_4$), and concentrated (aspirator) to give 40 mg (87%) phenylboric anhydride. If desired, the latter can be recycled to $KPhBF_3$.[4b]

The aqueous phase from above was stirred with 15 g of Amberlite IRC-50S (H^+) ion-exchange resin (Aldrich; pretreated with 2 N NaOH, washed with H_2O until the eluent was neutral, acidified with 2 N HCl, and washed again with H_2O until neutral). To absorb basic amines, stirring was continued until the pH of the water layer had dropped from pH 10 to pH 6 (ca. 15 min). The mixture was filtered through a glass frit, and the resin was washed with more deionized water (ca. 100 mL) until the presence of **37** could no longer be detected by ninhydrin stain. The combined water eluent was evaporated (aspirator), and the residue was dissolved in methanol (10 mL) and filtered through Celite to remove inorganic salts. Evaporation of methanol and drying under vacuum to constant weight gave (*R*)-α-methylphenylalanine, 79 mg (100%), >97% pure by ^{1}H NMR comparison with literature data;[23] mp 300 °C (dec). $[\alpha]_D = +21$ ($c = 0.1$, H_2O); lit. for (*S*)-enantiomer: $[\alpha]_D = +20$ ($c = 0.1$, MeOH).[23]

Conversion of 6b or 34 into (*R*)- or (*S*)-α-Allylphenylalanine (35 or ent-35). Hydrolysis of the phenylalanine-derived complexes was performed as described for **6a**. Thus, **34** (435 mg, 1.05 mmol) was cleaved using 0.210 mL (3.14 mmol) of ethylenediamine for amidine hydrolysis and 20 g of Amberlite IRC-50S resin for purification, yielding 152 mg (0.741 mmol, 71%) crude amino acid **ent-35** $[\alpha]_D =$

(23) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243.

+16 (c = 1, 1 M HCl). In a similar experiment, **6b** was converted to **35** (90%). $[\alpha]_D = -24$ (c = 1.5, 1 M HCl). The absolute configuration was established by comparison of the sign of rotation with literature values for the (*S*) enantiomer. $[\alpha]_D = +27.3$(c = 1, H_2O).[9] To assay enantiomeric purity, a suspension of **35** (19 mg) was stirred in 5:1 THF:methanol (1.2 mL) with $(CH_3)_3SiCHN_2$ (Aldrich; 0.36 mmol) for 18 h at room temperature. The resulting homogeneous solution was concentrated (aspirator) and purified by preparative TLC to give **36**[14] as the dominant UV-active zone, identified by NMR comparisons. According to HPLC/CSP assay (Chiralcel OD, 82:1 hexane:2-propanol eluent, pressure = 305 psi, flow rate = 1.00 mL/min), the (*R*)-ester **36** was obtained with >99.5% ee (T_R = 8.7 min) and no distinct maximum above baseline could be detected for the (*S*)-ester, **ent-36** (T_R = 10.2 min), also obtained in >99.5% ee by similar hydrolysis and esterification starting from crude **34**.

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Supporting Information Available: Experimental procedures for **11**, **12**, **16**, **17**, **19**, **21**, **38**, **ent-40**, **ent-44a**, **ent-45a**, **ent-44b**, **48**, **49**, **50**, **51a**, **52a**, **51b**, conversion of **6b** into **35**, **55a**−**c**, **56a**, **57**, **58**, and hydrolysis of **55b** and **55c** and X-ray data tables for **6b**, **7a**, **40**, **51a**, and **52** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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