Asymmetric Transformation in Synthesis: Chiral Amino Acid Enolate Equivalents

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We report access to chiral amino acid enolate equivalents[1] through use of a technique based on the asymmetric transformation (AT)[2] of oxazaborolidinones **2**.[3] Previous reports of AT demonstrate that crystallization of an equilibrating mixture of diastereomers can result in >90% conversion into a single isomer, provided that the rate of equilibration is similar to (or larger than) the rate of crystallization.[2,4] The α-amidino acid-derived boron complexes **2/3** or **5/6** display this behavior, as reported below. (The structures of all compounds discussed herein are shown in Chart I.)

To prepare **2/3**, the L-amino acid sodium salts were stirred with dimethylformamide dimethyl acetal in methanol. The resulting α-amidino carboxylates **1** were treated with $K^+B^-F_3Ph$[5,6] and Me_3SiCl (fluoride scavenger) in THF to generate $PhBF_2$ *in situ*.[7] In the case of L-phenylalanine, oxazaborolidinone diastereomers **2a** and **3a** were obtained (ca. 3:1 ratio), and >70% of crystalline **2a** was recovered in multiple crops after conventional crystallization. However, a simple technique designed specifically to exploit AT gave superior results. Thus, crude **2a/3a** was dissolved in ethyl acetate at 50 °C, and the solution was allowed to slowly evaporate to dryness. The resulting "transformed" solid consisted of a 39:1 mixture of **2a**:**3a** together with 2–5% $PhB(OH)_2$, and one recrystallization gave pure **2a**, 83% recovery based on crude **2a/3a**, 75% overall from L-phenylalanine. Since the recovery of **2a** exceeds the amount originally present in the crude mixture, this result is possible only if **2a** and **3a** equilibrate during solvent removal. The most likely mechanism involves reversible B···N bond dissociation via **4**. Solutions of pure **2a** can be prepared at room temperature, but **2a** equilibrates to a 3.2:1 mixture of **2a**:**3a** upon brief warming to 50 °C.

Similar results were obtained starting from L-valine or D-phenylglycine, but the AT phenomenon was more facile in these examples. Simple solvent removal at 30 °C (rotary evaporator) was sufficient to transform the diastereomeric oxazaborolidinones (solution equilibrium ratios **2b**:**3b** = 14:1; **5**:**6** = 3.5:1) into the less soluble **2b** (from L-valine) and **5** (from D-phenylglycine), respectively. Diastereomer ratios in the transformed solids were >150:1 (**2b**:**3b**) and 99:1 (**5**:**6**) according to HPLC assay (>85% recovery). Recrystallization afforded >99.5% pure **2b** and **5**, 75–78% overall based on the starting amino acids. The structures were confirmed by X-ray analysis, but ^1H NMR correlation of relative stereochemistry was also possible. In **2** or **5**, the oxazaborolidinone ring proton *trans* to fluorine was observed as a fluorine-coupled doublet (^4J = 3.5–5 Hz). The corresponding signal in **3a** or **6** (H *cis* to fluorine) is a singlet.

Recrystallized **2** and **5** react with amide or alkoxide bases to give the enolates **7** and **8**, respectively. To minimize the risk of diastereomer or enantiomer interconversion by B···N dissociation,[8] the deprotonations were performed by stirring a suspension of crystalline **2a** or **5** in THF at −78 °C with KO-*tert*-C_4H_9 (method A, Table I). Brief warming to −22 °C gave homogeneous yellow solutions of **7a** or **8** (ca. 0.1 M). The enolate solutions were then recooled to −78 °C and treated with representative alkyl halides. Alternatively, the enolates **7a** or **7b** could also be generated by treating a 0.01–0.03 M THF solution of **2a** or **2b** at −78 °C with $KN(SiMe_3)_2$ (KHMDS; method B). As shown in Table I, allylation or benzylation occurred with excellent diastereoselectivity, and product isolation by direct crystallization from the crude mixture was possible in some cases. According to X-ray analysis and correlation studies discussed below, the major products **9** (from **7**) and **11** (from **8**, R^1 = Ph) were derived from C···C bonding at the less hindered oxazaborolidinone face (*syn* to fluorine). Methyl iodide was not as selective in the alkylation step, but pure diastereomers could be obtained by chromatographic purification of the products on silica gel followed by crystallization (room temperature or below to avoid AT).

Significant racemization in the L-phenylalanine or L-valine series was ruled out in two cases by hplc analysis of the mixture of **9** (major) and **10** (minor) using a chiral stationary phase (**7a** + CH_3I, ca. 0.5% detection limit for **11** or **12**, $R^1 = CH_2Ph$, $R^2 = CH_3$; **7b** + $PhCH_2Br$, ca. 1% detection limit, $R^1 = CHMe_2$, $R^2 = CH_2Ph$). Methanolysis to cleave the boron complex (2 h, reflux) and amidine cleavage with ethylenediamine (1.5 h in refluxing methanol) gave the amino acid **13** ($R^1 = CH_2Ph$; $R^2 = CH_3$), >95% yield with >97% ee by the NMR method of Kellogg *et al.*[9] The hplc technique failed to resolve the enantiomers from **7b** + CH_3I, but >97% ee was established after chromatographic separation of diastereomers and conversion of **9** to the amino acid **13** ($R^1 = CHMe_2$; $R^2 = CH_3$) upon methanolysis followed by NMR assay.[9] The latter technique also confirmed the assignment of absolute stereochemistry.

The D-phenylglycine-derived methylation and allylation products (**11**; R^1 = Ph; $R^2 = CH_3$ or $CH_2CH{=}CH_2$) could also be assayed directly by the hplc method using a chiral stationary phase and were obtained with 99% and 97% ee, respectively. A possible explanation for minor stereochemical leakage is that the relatively stabilized C-phenyl enolate **8** undergoes reversible B···N bond cleavage on the time scale of alkylation, in contrast to the C-alkyl enolates **7**. Alternatively, the enolate precursor **5** may undergo 0.5–1.5% epimerization at boron via **4** prior to enolate formation. The latter process clearly competes if **5** is dissolved at room temperature and the solution is then cooled prior to

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(6) The crystalline, air- and water-stable KBF_3Ph is conveniently prepared from commercial $PhB(OH)_2$ and KHF_2 (see supplementary material).

(7) ^{11}B signals of $PhBF_2$ (δ 16 vs BF_3–etherate) appear when $K^+B^-F_3Ph$ (δ 4.1) is stirred with excess Me_3SiCl in acetonitrile.

(8) If **2a** is dissolved in THF with gentle warming, followed by cooling and alkylation as usual, the products are partially racemized due to partial conversion of **2a** to **3b**.

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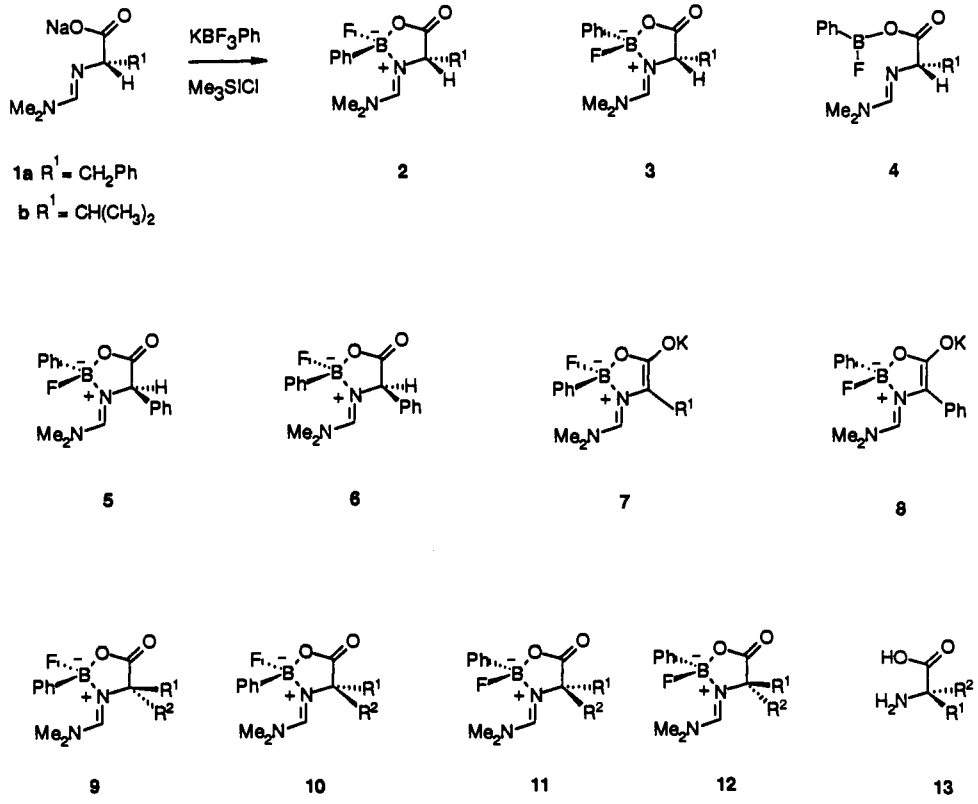
Table I. Alkylation of Oxazaborolidinone Enolates

entry	enolate	R^2X	method	product ratio	R^1	R^2	yield[a] (%)
1	**7a**	CH_3I	A	5.5:1 **9:10**	CH_2Ph	CH_3	70[b]
2	**7a**	CH_3I	B	5.8:1 **9:10**	CH_2Ph	CH_3	86[b]
3	**7a**	$CH_2{=}CHCH_2Br$	A	142:1 **9:10**	CH_2Ph	$CH_2{=}CHCH_2$	81[c]
4	**7a**	n-C_3H_7I	A	4:1 **9:10**	CH_2Ph	C_3H_7	60[d]
5	**7b**	CH_3I	B	4:1 **9:10**	$CH(CH_3)_2$	CH_3	67[e]
6	**7b**	$CH_2{=}CHCH_2Br$	B	≥20:1 **9:10**	$CH(CH_3)_2$	$CH_2{=}CHCH_2$	70[c]
7	**7b**	$PhCH_2Br$	A	99:1 **9:10**	$CH(CH_3)_2$	$PhCH_2$	77[c]
8	**8**	$CH_2{=}CHCH_2Br$	A	14:1 **11:12**	C_6H_5	$CH_2{=}CHCH_2$	84[d]
9	**8**	CH_3I	A	1:1 **11:12**	C_6H_5	CH_3	88[d]

[a] Isolated yield. [b] Yield after chromatographic separation of the isomers. [c] Yield of the major isomer crystallized from the crude mixture. [d] Yield of the diastereomer mixture after chromatography. [e] Yield of partially separated diastereomers after chromatography; individual diastereomers obtained by crystallization.

Chart I



addition of base. These conditions produce significant amounts of diastereomer **6** in solution, depending on the initial temperature, and result in the eventual contamination of **8** by the enantiomer **7** (R^1 = Ph) and 20–40% product racemization. However, stereochemical integrity can be maintained throughout the sequence for all three amino acids by controlling the temperature during alkylation and product purification.

The technology described above combines the AT phenomenon with an asymmetric memory concept pioneered by Seebach *et al.* using oxazolidinone and imidazolidinone enolates.[10-12] The oxazaborolidinones are boron analogs of the oxazolidinones and are complementary in the sense that electrophilic trapping of **7** or **8** results in the opposite configuration at carbon by comparison with Seebach's oxazolidinone enolates. In view of the mild cleavage conditions (refluxing methanol + ethylenediamine), overall efficiency, and simple starting materials, the oxazaborolidinone technology provides a practical alternative for generation of chiral amino acid enolate equivalents. More importantly, the method demonstrates the power of AT for control over chemical equilibria. This phenomenon has long been known,[2,4] but there are few studies where it has been systematically exploited in synthesis. Modest differences in the free energies of dissolved isomers can be greatly amplified or even inverted in the solid phase.[2] In principle, any number of equilibrating species can be converted into a single isomer, provided that the corresponding solids differ in free energy. The solution equilibrium populations are irrelevant as long as there is sufficient time for interconversion of isomers over the time scale of crystallization. These considerations apply equally to equilibrating diastereomers, positional isomers, *E/Z* isomers, rotamers, anomers, and conformers.

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Supplementary Material Available: Representative experimental procedures for the syntheses described herein (7 pages). This material is contained in many 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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