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ASYMMETRIC ALDOL REACTIONS USING BORON ENOLATES OF CHIRAL OXAZINONES, SYNTHESIS OF L-*ALLO*-THREONINE

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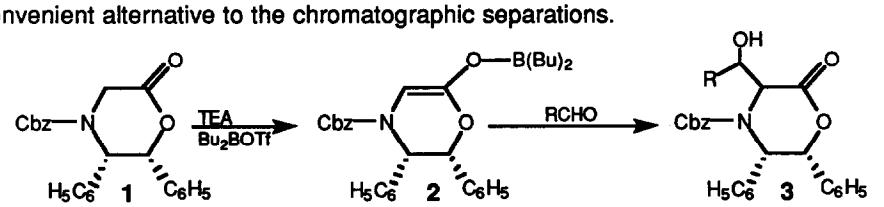
Summary: The boron enolate of oxazinone **1** was allowed to react with acetaldehyde, butanal, and 2-methylpropanal. The reaction proceeded stereoselectively, and in the reaction with acetaldehyde, the reaction afforded a precursor to L-*allo*-threonine.

The chiral oxazinones introduced by Williams and coworkers are effective glycine equivalents for the asymmetric synthesis of novel amino acids.[1] Typically, these systems have been used as electrophilic glycine equivalents, but in a recent communication it was shown that they may be used as glycine enolate equivalents.[2] We would like to report that **1** may be transformed into a boron enolate which reacts stereoselectively with aldehydes. Furthermore, the aldol reaction using acetaldehyde affords a precursor to L-*allo*-threonine; this is the first observation of a system utilizing a chiral glycine enolate in an aldol reaction which exhibits *anti* stereoselectivity.[3,4,5]

Oxazinone **1** was transformed into boron enolate **2** with di-(*n*-butyl)boron triflate and triethylamine in dichloromethane (0°C). The enolate solution was cooled to –78°C and treated with aldehyde. After the mixture had reacted for 15 min, it was quenched by addition of pH 7.0 phosphate buffer.[6] The crude mixture was filtered through a plug of silica and examined by HPLC and ^{1}H-NMR. These analyses revealed that the mixtures contained some starting material and 2–3 products (see Table). The major product in each reaction could be isolated by repeated flash chromatographic separations, but the minor products did not lend themselves to chromatographic purification. Direct crystallization of the major products from the reaction mixture with ethyl acetate-hexanes was found to be a convenient alternative to the chromatographic separations.



Conversion of the major diastereomer of **3** into the hydroxy amino acids was achieved by catalytic hydrogenation ($PdCl_2$, 40 psi H_2, 1:1 ethanol-THF).[1] After purification[7] of the amino acids, HPLC, ^{1}H-NMR, and enzymatic assay data confirmed that the products were the L-*erythro* isomers.[8]

For example, analysis of the hydroxy-amino acid obtained from deprotection of the oxazinone–acetaldehyde adduct by ^{1}H-NMR and HPLC revealed that it was *allo*-threonine. Threonine was not present. The enantiomeric composition of the *allo*-threonine was assayed using rabbit liver serinehydroxymethyltransferase (SHMT). This enzyme catalyzes the retro aldol reaction for L-*allo*-threonine, but it does not promote a retro aldol reaction with D-*allo*-threonine.[9,10] According to the enzymatic assay, the enantiomeric composition was greater than 99% L-*allo*-threonine.

Table. Stereoselective Aldol Reaction of Oxazinone Boron Enolates.

	Ratio[a] of Stereoisomeric Products	Recrystallized Yield[b] of Major Stereoisomer
acetaldehyde	17 : 3 : 1	57%
butanal	5 : 1	38%
2-methylpropanal	5 : 1	42%

[a] The ratio was determined by integration of resonances in the ^{1}H-NMR spectrum assigned to the stereoisomeric products. The ratios obtained by NMR were found to be equal to the ratio of the chromatographic peaks.
[b] After recrystallization from ethyl acetate-hexanes.

Since this sequence of synthetic transformations afforded L-*allo*-threonine, the aldol reaction must have proceeded with *anti* selectivity. Support for transition state selectivity was provided by variable temperature experiments. Once the reaction was complete (<15 min), the stereoisomeric composition of the mixture did not change with a change in temperature; a change in the product ratio was observed if the reaction was conducted at different temperatures. These results are consistent with the stereoselection being the consequence of a Zimmerman-Traxler chair type transition state arrangement of the aldehyde and the *E*-enolate with the aldehyde approaching the sterically less encumbered face of the oxazinone enolate (see the Figure).[11]

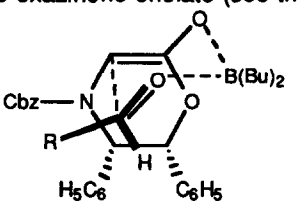


Figure. A Consistent Transition State Model for the Aldol Reaction

The stereoselectivity observed with the oxazinone system is opposite to that exhibited by the imidazolidinones developed by Seebach and coworkers although both systems possess structural constraints which enforce the formation of an *E*-enolate.[3a] They observed *syn* stereoselectivity in aldol reactions with the boron enolate of their imidazolidinone (an *E*-enolate). This result was consistent with a twist-boat transition state arrangement. A recent computational paper has provided an explanation for the difference in selectivity.[12] It appears that *E*-enolates prefer a twist boat transition state arrangement. However, if a boron enolate possesses alkyl substituents on the boron, the preference for the twist-boat arrangement, because of 1,4-diaxial interaction, is diminished.

Seebach's system did not utilize alkyl groups on the boron. Therefore, in the system we investigated, it appears that the *n*-butyl groups on the boron cause the chair arrangement to be favored.

In conclusion, a system has been found which utilizes a chiral glycine enolate to perform asymmetric aldol reactions[13] which proceed with *anti* stereoselectivity in the cases examined. The products from these reactions have been purified by crystallization,[14] although continued development of isolation procedures for the amino-hydroxy acids may result in other methods. The generality of the enzymatic assay of L-*allo*-threonine homologs is being examined.

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7. The product from the hydrogenation was dissolved in water, washed with ether, treated with concentrated NH_4OH, and evaporated. The ammonium salt was redissolved in water and treated with acetone to precipitate the product. With acetaldehyde, only the L-*erythro* threonine was reproducibly isolated, while with butanal and 2-methylpropanal, the L-*erythro* β-hydroxyleucine and β-hydroxynorleucine were the major products isolated.

8. HPLC peaks coeluted with the *erythro* peak in racemic material. In ^{1}H-NMR, the α-proton corresponded to the same proton in the *erythro* compound of a racemic mixture. For example, the asymmetrically produced 2-methylpropanal product had $\delta = 3.9$ ppm, $J = 2.7$ Hz; the *threo* isomer in the racemic mixture had a more upfield α-proton ($\delta = 3.8$ ppm) with a larger coupling constant ($J = 3.6$Hz). The same trend was also observed in the butanal product (*erythro*: $\delta =$

3.9 ppm, J = 3.6 Hz; *threo*: δ = 3.8 ppm, J = 4.5 Hz). Enzyme assay showed the products to be the L isomer in each case.

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10. Enzyme incubations were carried out in 10 mM potassium phosphate buffer, pH 7.3, containing 80 μM pyridoxal 5'-phosphate (PLP). Purified SHMT (0.1 mg) was dissolved in 100 μL buffer, and 100 μL of a 34 mM solution of amino acid in buffer was added. An enzyme control mixture was also prepared, containing all components except the enzyme. These solutions were incubated in a 37°C water bath, and aliquots were removed periodically for analysis. Amino acids were monitored by derivatizing them and analyzing by reversed-phase HPLC with fluorescence detection.

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13. A typical procedure for the aldol reaction is as follows: To a stirred dichloromethane (2 mL) solution of triethylamine (150 mg, 0.21 mL, 1.5 mmol) and di-(*n*-butyl)boron triflate (390 mg, 0.36 mL, 1.43 mmol) cooled to –5°C was added a cooled (–5°C) dichloromethane (8 mL) solution of the oxazinone (290 mg, 0.75 mmol). After this mixture had been allowed to react for 5 min, it was cooled to –72°C and the aldehyde (~2 mmol) was added to the mixture. The reaction mixture was treated with 15 mL of pH 7.0 phosphate buffer after 15 min. The phases were separated, and the aqueous phase was washed with 3 x 10 mL of dichloro-methane. The organic fractions were combined, dried with $MgSO_4$, and filtered through a plug of silica (~2.5 x 2.5 cm). The silica was washed with 75 mL of ethyl acetate and the organic solutions were combined. The solvent was evaporated *in vacuo*, and the residue was crystallized from hexanes-ethyl acetate.

14. (a) Oxazinone-acetaldehyde adduct: white solid; Mp = 204–206 °C; $[\alpha]^{24}_{589}$ –36.1 (c 0.54, $CHCl_3$); IR (KBr) 3535, 1740, 1705, 1450, 1440, 1395, 1345, 1325, 1275 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6, 418 K, *vs.* DMSO = 2.49 ppm) δ 1.36 (3 H, d, J = 7 Hz), δ 4.38 (1 H, d of q, J = 2 Hz, J = 7 Hz), δ 4.77 (1 H, d of d, J = 2.0 Hz, J = 0.6 Hz), δ 5.01 (2 H, ABq, J = 12 Hz), δ 5.25 (1 H, d, J = 3 Hz), δ 6.51 (1 H, d, J = 3 Hz), δ 6.60 (1 H, s), δ 6.62 (1 H, s), δ 6.98–7.27 (13 H, m); mass spectrum (CI with isobutane), m/e 432 (M+1); Anal. Calcd. for $C_{26}H_{25}NO_5$: C (72.37), H (5.84), N (3.25). Found: C (72.39), H (6.00), N (3.34).

(b) Oxazinone-butanal adduct: white solid; Mp = 177–179°C; $[\alpha]^{24}_{589}$ –24.3 (c 0.28, $CHCl_3$); IR (KBr) 3535, 1725, 1695, 1495, 1450, 1395, 1345, 1320, 1275 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6, 418 K, *vs.* DMSO = 2.49 ppm) δ 0.93 (3 H, t, J = 7 Hz), δ 1.40–1.75 (4 H, m), δ 4.18 (1 H, m), δ 4.83 (1 H, d, J = 2 Hz), δ 5.00 (2 H, ABq, J = 13 Hz), δ 5.25 (1 H, d, J = 3 Hz), δ 6.54 (1 H, d, J = 3 Hz), δ 6.60 (1 H, s), δ 6.63 (1 H, s), δ 6.98–7.27 (13 H, m); Anal. Calcd. for $C_{28}H_{29}NO_5$: C (73.18), H (6.36), N (3.05). Found: C (73.36), H (6.46), N (3.09).

(c) Oxazinone-2-methylpropanal adduct: white solid; Mp = 222–223 °C; $[\alpha]^{24}_{589}$ –6.84 (c 0.38, $CHCl_3$); IR (KBr) 3555, 1730, 1690, 1450, 1400, 1345, 1320, 1285, 1265, 1240 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6, 418 K, *vs.* DMSO = 2.49 ppm) δ 1.00 (3 H, d, J = 7 Hz), δ 1.07 (3 H, d, J = 7 Hz), δ 1.98 (1 H, m), δ 3.80 (1 H, m), δ 4.99 (2 H, ABq, J = 12 Hz) δ 5.07 (1 H, d, J = 2 Hz), δ 5.26 (1 H, d, J = 3 Hz), δ 5.45 (1 H, d, J = 6 Hz), δ 6.58 (1 H, d, J = 3 Hz), δ 6.61 (1 H, s), δ 6.63 (1 H, s), δ 6.98–7.28 (13 H, m); Anal. Calcd. for $C_{28}H_{29}NO_5$: C (73.18), H (6.36), N (3.05). Found: C (72.96), H (6.40), N (3.09).

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