Reversal of Stereochemistry in the Aldol Reactions of a Chiral Boron Enolate[1]

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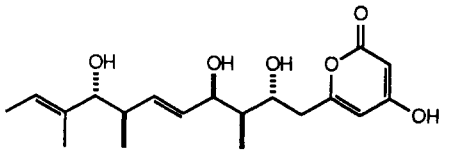
A novel route to optically active anti aldols of certain aldehydes is presented. The boron enolate derived from oxazolidinone **3** reacts with various aldehydes to give either syn or anti aldols, depending on the amount of dibutylboron triflate used in the enolization of **3**. The amine used in the enolization is also found to have a dramatic effect on the subsequent aldol reaction. High anti selectivity is observed when **3** and 3-(arylthio)propenals are used, whereas moderate selectivity is observed when **3** and aromatic aldehydes are used. An open transition state is suggested to account for the formation of the novel anti aldols. NMR studies provide support for the suggested mechanism. Although findings are at present limited to a few specific aldehydes, the ability to obtain either syn or anti aldols from the same chiral enolate by a choice of reagent and stoichiometry could have significant synthetic applicability.

The aldol addition reaction is a useful tool for the synthesis of biologically important natural products and considerable attention has been paid to the development of aldol methodology.[2] We have previously described aldol additions to α,β-unsaturated aldehydes coupled with Claisen rearrangement of the resulting allylic alcohols as a method for parlaying the high 1,2-diastereoselectivity of the aldol reaction into 1,4- and 1,5-diastereoselectivity.[3,4] If a 3-(alkylthio)- or 3-(arylthio)propenal is employed in the aldol reaction, the sulfur can, in principle, be used to introduce an additional stereocenter. Such an approach would be useful for the synthesis of a variety of interesting molecules, including ACRL toxin III A (**1**).[5] Toward this



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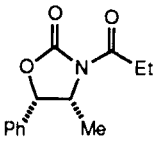

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end, we have investigated the aldol reaction of such 3-thiopropenals with the chiral oxazolidinone boron enolate developed by Evans and co-workers.[2b,6] In the course of this study, we have discovered that optically active syn or anti aldols may be obtained with high stereoselectivity by varying the amount of dibutylboron triflate (Bu_2BOTf) used in the reaction.

Several 3-thiopropenals (**2b–e**) were synthesized by a modification of the literature procedure previously used to prepare 3-(phenylthio)propenal (**2a**).[7] Aldehydes **2** were allowed to react with the boron enolate prepared from propionyloxazolidinone **3** under our standard conditions (1.9 equiv of Bu_2BOTf, 2.2 equiv of diisopropylethylamine (i-Pr_2NEt), 1.0 equiv of **3**, 45 min at 0 °C in CH_2Cl_2) as shown in eq 1. Table I shows the results of aldol reaction with thiopropenals **2a–e** as well as the reaction with acrolein (**2f**) (entries 1–6). In all cases the thiopropenals afford significant amounts of anti aldol **4**, whereas acrolein affords only syn aldol **5**. All of the 3-(arylthio)propenals give the anti aldol in synthetically useful yields. These results are intriguing, as previous literature precedents suggest that only syn aldol products are formed from the boron enolate of **3**.[8] A control experiment ruled out equilibration of an initially formed syn aldolate to the anti aldolate catalyzed by excess Bu_2BOTf. The syn aldolate was formed from aldehyde **2d** at −78 °C by using 1.3 mmol of i-Pr_2NEt and 1.1 mmol of Bu_2BOTf; then another 1.0 mmol each of i-Pr_2NEt and Bu_2BOTf was added. After 45 min at −78 °C and workup in the normal manner, the syn aldolate was isolated as the major product (syn/anti = 93:7).[9]

Table I. Aldol Reactions in CH_2Cl_2[a]

entry	aldehyde	amine	yield[b]	4:5[c]
1	**2a**	i-Pr_2NEt	90	92:8
2	**2b**	i-Pr_2NEt	82	91:9
3	**2c**	i-Pr_2NEt	85	89:11
4	**2d**	i-Pr_2NEt	76	93:7
5	**2e**	i-Pr_2NEt	74	25:75
6	**2f**	i-Pr_2NEt	98	<2:98
7	**2b**	Et_3N	83	<2:98
8	**2c**	Et_3N	92	<2:98
9	**2d**	Et_3N	87	<2:98
10	**2d**	*d*	76	<2:98

[a] Enolization: 1.9 mmol of Bu_2BOTf, 2.2 mmol of i-Pr_2NEt, 1 mmol of **3**, 45 min at 0 °C in CH_2Cl_2. Aldol reaction: 1.3 mmol of **2**, 30 min at −78 °C except for entries 5 and 6 which required 30 min at −78 °C followed by 90 min at 25 °C. [b] Isolated yield of isomeric mixture after chromatography. The diastereomers were not separable by chromatography, but **4d** was purified by recrystallization. [c] Determined by ^1H NMR spectroscopy except for entry 3, which was determined by ^{13}C NMR spectroscopy. [d] The enolate was generated with i-Pr_2NEt as above, then 1.3 mmol of Et_3N·HCl in CH_2Cl_2 was added at −78 °C and the aldol reaction was performed immediately.

(1) Paper 48 in the series Acyclic Stereoselection. For paper 47, see: Oare, D. A.; Heathcock, C. H. *J. Org. Chem.*, preceding paper in this issue.
(2) (a) Heathcock, C. H. *Asymmetric Synthesis*; Academic: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
(3) Heathcock, C. H.; Finkelstein, B. L. *J. Chem. Soc., Chem. Commun.* **1983**, 919.
(4) (a) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825. (b) Heathcock, C. H.; Finkelstein, B. L.; Aoki, T.; Poulter, C. D. *Science (Washington, DC)* **1985**, *229*, 862.
(5) (a) Kono, Y.; Gardner, J. M.; Kobayashi, K.; Suzuki, Y.; Takeuchi, S.; Sakurai, T. *Phytochemistry* **1986**, *25*, 69. (b) Kono, Y.; Gardner, J. M.; Suzuki, Y.; Takeuchi, S. *Ibid.* **1985**, *24*, 2869. (c) Gardner, J. M.; Kono, Y.; Tatum, J. H.; Suzuki, Y.; Takeuchi, S. *Ibid.* **1985**, *24*, 2861. (d) Gardner, J. M.; Kono, Y.; Tatum, J. H.; Suzuki, Y.; Takeuchi, S. *Agric. Biol. Chem.* **1985**, *49*, 1235.
(6) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.
(7) (a) Iwao, M.; Kuraishi, T. *Tetrahedron Lett.* **1985**, *26*, 6213. (b) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235. (c) See also: Ha, D. C.; Hart, D. J.; Yang, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 4819.
(8) See ref 6 and 2b. However, see ref 15a where anti aldols were obtained with some aldehydes by using a related propionyloxazolidinone.

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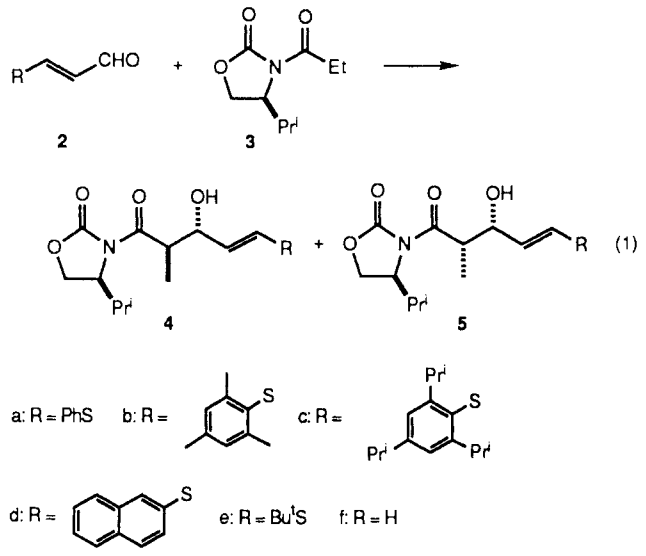
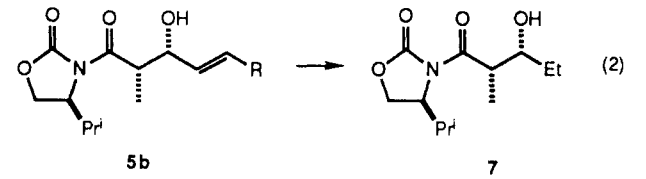


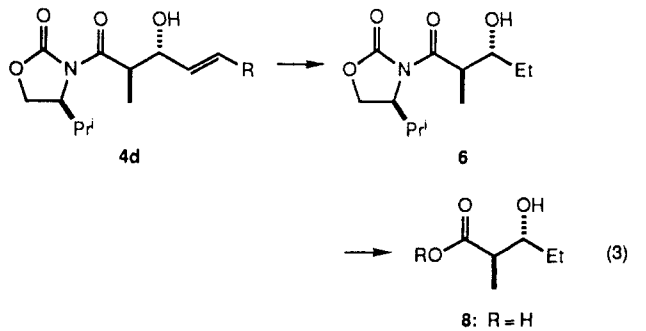
(1)

All of the aldol products in eq 1 are new compounds except for **5f**, which has been reported previously.[10] The syn/anti stereochemical assignments were made by analysis of the vicinal coupling constants in the ^{1}H NMR spectra. The relative and absolute stereochemical assignments were firmly established by hydrogenation and desulfurization of two of these aldols with Raney nickel. In the syn series, **5b** (prepared by using Et_3N as base, see below) was converted directly to syn aldol **7**, which has been reported,[6a,11] but for which no data has been published (eq 2). Therefore an authentic sample of **7** was prepared by reaction of the boron enolate of **3** with propionaldehyde (see Experimental Section).



(2)

In the anti series, **4d** (purified by recrystallization) was converted to **6**, which was hydrolyzed[12] to hydroxy acid **8** and esterified to afford the known methyl ester **9** (eq 3).



(3)

Comparison of the optical rotation determined for **9** ($[\alpha]^{23}_D$ −7.9°, c = 0.52, $CHCl_3$) with the literature values ($[\alpha]_D$ −5.9°, c = 0.44, $CHCl_3$[13] and $[\alpha]_D$ −9.9°, c = 1.28, $CHCl_3$[14]) established the absolute stereochemistry as shown. It is important to note that the anti aldols used in this experiment (**4d** and **6**) and the derived β-hydroxy ester **9** were shown to be diastereomerically pure by ^{1}H NMR spectroscopy. It is highly unlikely that the hydrolytic cleavage of **6** would lead to *racemization* of β-hydroxy acid **8**, without also giving the diastereomeric syn β-hydroxy acid. Thus, we can safely conclude that the acid **8** produced in this manner is enantiomerically homogeneous.

Table II. Effect of Excess Bu_2BOTf and i-Pr_2NEt[a]

entry	molar ratio 3/i-Pr_2NEt/Bu_2BOTf	yield, %	4d:5d[b]
1	1/1.3/1.1	85	<2:98
2	1/2.0/1.5	92	77:23
3	1/2.2/2.0	84	95:5
4	1/1.5/2.0	unidentified products	

[a] The enolization was performed in CH_2Cl_2 at 0 °C for 30 min. The aldol reaction was performed with 1.3 mmol of **2d** at −78 °C for 30 min. [b] Determined by ^{1}H NMR spectroscopy.

The data in Table I imply that, within the set of aldehydes examined, the sulfur is at least partially responsible for the unexpected formation of anti aldols. However, coordination of the sulfur with boron in the transition state of the addition reaction seems unlikely as the anti/syn ratio is independent of the steric bulk of the aryl group on sulfur. Entry 5 shows that a hindered 3-(alkylthio)-propenal gives the expected syn aldol, but in lower than normal stereoselectivity. Therefore, both the sulfur and the aryl group seem to contribute to the unexpected production of anti aldols.

Recent workers have noted the effect of the amine used in the enolization process on the stereochemistry of the subsequent aldol reaction. Baker and co-workers found that reaction of the boron enolate generated from oxazolidinone **10** by using Bu_2BOTf and i-Pr_2NEt with some substituted aromatic aldehydes affords anti aldol products with moderate selectivity; when triethylamine (Et_3N) was used in the enolization, a single syn aldol isomer was produced.[15] We have found that enolization of **3** (1 equiv) with Et_3N (2.4 equiv) and Bu_2BOTf (1.9 equiv) under our standard conditions followed by addition of various 3-(arylthio)propenals gives only the syn aldols, within the limits of NMR detection (Table I, entries 7–9). Both Et_3N and i-Pr_2NEt have been used to generate the Z enolate from propionyloxazolidinone substrates[2b] so the effect of the amine must occur in the aldol transition state. This was supported by addition of a solution of Et_3N·HCl in CH_2Cl_2 to the enolate generated with i-Pr_2NEt and subsequent aldol reaction to yield exclusively the syn aldol (entry 10).

Upon further evaluation of our standard reaction conditions, we reasoned that excess Bu_2BOTf might act as a Lewis acid to catalyze formation of anti aldols via an open transition state.[16] Accordingly, we investigated the enolization of **3** with various amounts of Bu_2BOTf and i-Pr_2NEt and the subsequent aldol reaction; the results are

(9) We thank Dr. Tom Britton (Eli Lilly and Co.) for suggesting this control experiment.
(10) Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.
(11) Evans, D. A.; Ennis, M. D.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.
(12) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
(13) Personal communication from W. Oppolzer, see: Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699.
(14) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309.
(15) (a) Baker, R.; Castro, J. L.; Swain, C. J. *Tetrahedron Lett.* **1988**, *29*, 2247. (b) See the work of Evans and co-workers where Et_3N rather than i-Pr_2NEt was essential for successful reaction: Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.
(16) For examples of Lewis acid catalyzed aldol reactions, see the following. (a) Reference 13. (b) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3037. (c) Gennari, C.; Cozzi, P. *J. Org. Chem.* **1988**, *53*, 401. (d) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735. (e) Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, *21*, 4291.

Table III. Reaction in Other Solvents[a]

entry	solvent	amine	molar ratio 3/amine/Bu_2BOTf	yield, %	4d/5d[b]
1	ether	i-Pr_2NEt	1/1.3/1.1	64	<2:98
2	ether	i-Pr_2NEt	1/2.2/2.0	78	<98:2
3	ether	i-Pr_2NEt	1/1.1/2.0	82	<98:2
4	ether	Et_3N	1/1.3/1.1	74	<2:98
5	ether	Et_3N	1/1.1/2.0	70	<98:2
6[c]	ether	Et_3N	1/1.1/2.0	71	<98:2
7	toluene	i-Pr_2NEt	1/1.1/2.0	unidentified products	
8[d]	10:1 CH_2Cl_2/ether	i-Pr_2NEt	1/1.3/2.0	73	95:5
9[d]	10:1 toluene/ether	i-Pr_2NEt	1/1.1/2.0	77	<98:2

[a] Enolization: 0.2-mmol scale reaction, 45 min at 0 °C. Aldol reaction: 1.3 equiv of **2d**, 30 min at −78 °C except for entry 1 (60 min at −10 °C) and entry 4 (90 min at −10 °C). Normal quench with pH 7 buffer followed by oxidative workup and extraction afforded the crude aldols, which were purified by chromatography on silica gel (see General Aldol Procedure in the Experimental Section). [b] Determined by ^1H NMR spectroscopy. [c] The aldol reaction was performed after removing the lower phase, which contains Et_3N·HOTf, from the enolate solution. [d] The enolate was generated in CH_2Cl_2 (or toluene) as in (a), enough ether was added to give a 10:1 v/v mixture of CH_2Cl_2 (or toluene) and ether, and the aldol reaction was performed.

shown in Table II. Entry 1 shows that in the absence of a significant amount of excess Bu_2BOTf or amine the syn aldol is formed as the exclusive product.[17] Entries 2 and 3 show that the amount of anti aldol increases steadily with increasing amounts of triflate and amine. With a 1-fold excess the anti aldol is formed in synthetically useful yields. Entry 4 shows that it is not possible to employ excess Bu_2BOTf without using a corresponding excess of amine, as under these conditions the expected aldol products are not isolated. Excess Bu_2BOTf may react with the initially formed aldolate to cause elimination or other side reactions; when excess amine is present only a small amount of free Bu_2BOTf should be present as the amine forms a complex with Bu_2BOTf.[18] Table I, entries 7–9, show that even when 1.9 equiv of Bu_2BOTf is employed, if excess Et_3N is used as the base only the syn aldol is produced.

The enolization and addition reactions were also investigated in ether and the results are presented in Table III. The syn aldol is obtained when essentially stoichiometric amounts of Bu_2BOTf are employed in the enolization (entry 1). When excess Bu_2BOTf and excess i-Pr_2NEt are used, the anti aldol is obtained with nearly complete stereocontrol (entry 2). These results are in accord with those observed in CH_2Cl_2 except that the anti aldol is formed with somewhat higher selectivity. An important difference was noted, however, because in ether exclusive formation of the anti aldol is observed with excess Bu_2BOTf in the *absence* of excess amine (entry 3). Presumably, ether serves the same function as excess amine by complexing with the excess Bu_2BOTf, leaving a small amount of free Bu_2BOTf available to catalyze the aldol reaction that leads to anti aldols. Similar results are observed when Et_3N is employed in the enolization (entries 4 and 5): without excess Bu_2BOTf the syn aldol is obtained; with excess Bu_2BOTf the anti aldol is obtained (Table III, entries 7 and 8).

The reactions in ether differ from those in CH_2Cl_2 in that the ammonium triflate formed in the enolization precipitates from solution when i-Pr_2NEt is used and separates to form a lower layer when Et_3N is used.[19] When this lower phase is removed prior to the aldol reaction the anti aldol is still obtained, indicating that Et_3N·HOTf is not important in promoting formation of the anti aldol (entry 6). Because the i-Pr_2NEt·HOTf precipitates from the reaction mixture, it also does not participate in the aldol addition reaction.

Table IV. Reaction with Other Aldehydes[a]

entry	aldehyde	molar ratio 3/i-Pr_2NEt/Bu_2BOTf	yield, %	anti:syn[b]
1	PhCHO	1/1.1/2.0	79	80:20
2	PhCHO	1/1.3/1.1	91	<2:98
3	1-naphthaldehyde	1/1.1/2.0	75	75:25

[a] Enolization: 45 min at 0 °C in ether. Aldol reaction: 60 min at −78 °C for entries 1 and 2, 20 min at −78 °C for entry 3. [b] Determined by ^1H NMR spectroscopy.

It is possible that the difference between CH_2Cl_2 and ether might be due to the fact that i-Pr_2NEt·HOTf separates from solution in the latter but not the former solvent. To examine this question, we also carried out the reaction in a 10:1 mixture of CH_2Cl_2/ether. As in the reaction carried out in pure CH_2Cl_2, this reaction gave the characteristic white precipitate of i-Pr_2NEt·HOTf. However, the results were the same as those obtained by using pure ether as the solvent (Table III, entries 3 and 8). At the suggestion of a referee, the comparison was also carried out with toluene and 10:1 toluene/ether. The results were analogous to those obtained by using CH_2Cl_2 (Table III, entries 7 and 9).

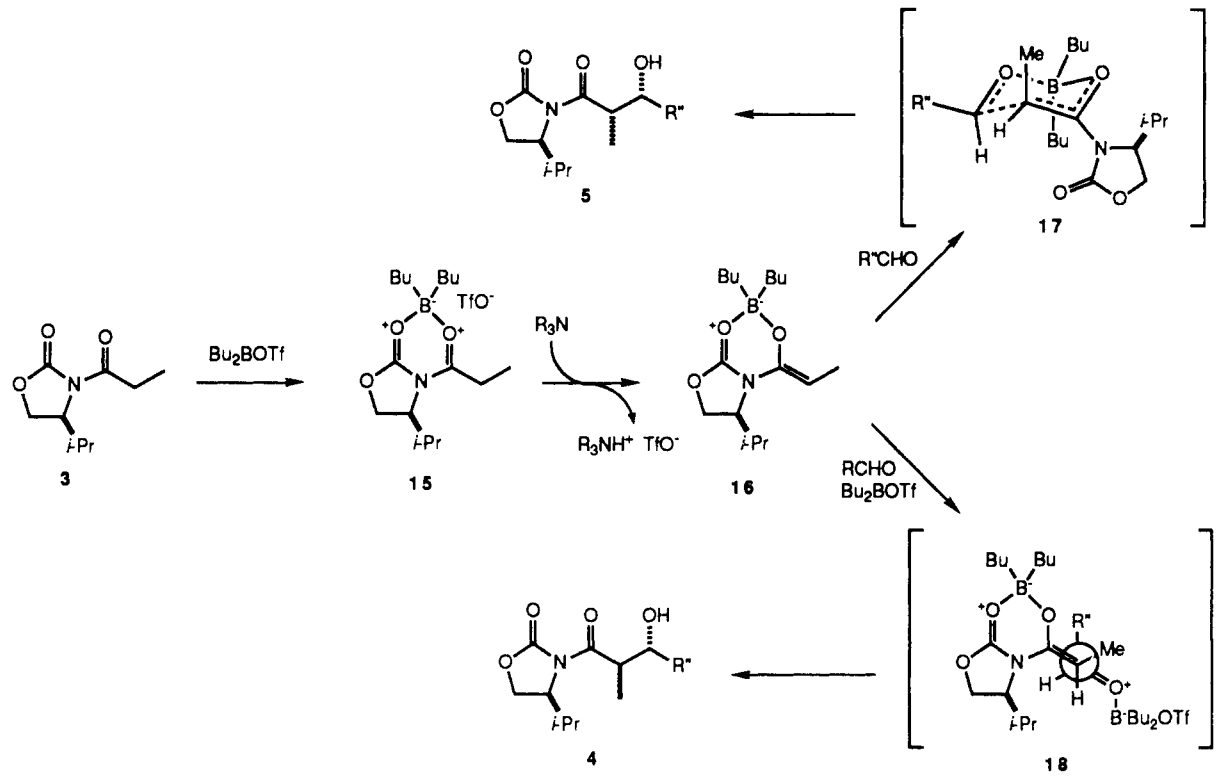
It was of interest to see if the anti selective aldol reaction between **3** and 3-(thioaryl)propenals could be extended to other aldehydes and enolates. We have already observed that the simple unsaturated aldehyde acrolein gives the syn aldol exclusively (Table I, entry 6). Propionaldehyde also reacts in the presence of excess Bu_2BOTf to afford only the syn aldol. Table IV shows the results of the aldol reaction between the boron enolate of **3** and aromatic aldehydes in the presence of excess Bu_2BOTf. In these cases moderate anti selectivity is observed. Thus, the presence of either an aromatic substituent or a sulfur substituent favors the production of anti aldol products. When both of these groups are present, high yields of anti aldols can be obtained.

(17) The purity of our distilled Bu_2BOTf was judged to be ca. 90% by ^1H NMR so 1.1 equiv of this material probably does not leave any excess Bu_2BOTf after enolization.

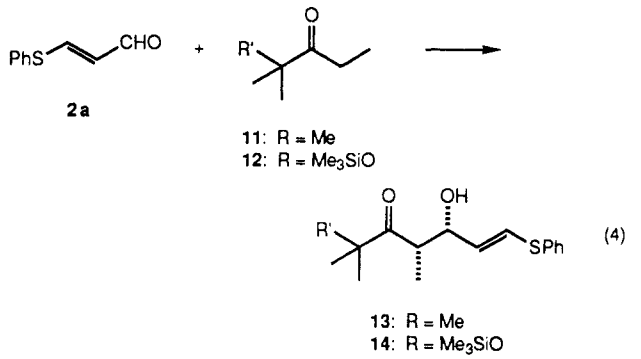
(18) A 1:1 mixture of i-Pr_2NEt and Bu_2BOTf in CH_2Cl_2 and a 1:1 mixture of i-Pr_2NEt and triflic acid in CH_2Cl_2 show nearly identical chemical shifts for the amine protons. The CH_2 group attached to nitrogen shifts downfield from 2.34 ppm in the free amine to 3.01 ppm. The CH group attached to nitrogen shifts from 2.90 ppm in the free amine to 3.52 ppm. In addition, these amine salts show more complex multiplets than the amine, apparently due to formation of rotamers. Evans and co-workers have also observed complex formation between Bu_2BOTf and various amines, see ref 2c.

(19) In the former case, the precipitated i-Pr_2EtN·HOTf is isolated in high yield by decantation of the solution. In the latter case, removal of the lower phase via syringe and drying under vacuum affords a quantitative yield of Et_3N·HOTf.

Scheme I



The boron ketone enolates derived from **11**[20] and **12**[21] react with aldehyde **2a** in the presence of excess Bu_2BOTf and $i\text{-}Pr_2NEt$ to give only the syn aldol products **13** and **14** (eq 4). The novel adducts **13** and **14** were fully characterized and the stereochemistry was assigned by ^1H NMR spectroscopy. These results indicate that the oxazolidinone portion of the enolate is also important for formation of anti aldol products. The "normal" behavior of ketones **11** and **12** also rules out the possibility that the anti aldols observed in eq 1 might be due to formation of *E* enolates, as has recently been observed by Brown and co-workers for other ketone boron enolates.[22]



(4)

Mechanism

Our results can be accommodated by the mechanism shown in Scheme I. Coordination of Bu_2BOTf with oxazolidinone **3** affords complex **15**; deprotonation of this intermediate by an amine yields the chelated *Z* enolate **16**. The ammonium triflate was shown not to affect the subsequent heterogeneous aldol reaction in ether and is also presumed to be unimportant in CH_2Cl_2 even though this reaction is homogeneous. We think that in the absence of excess Bu_2BOTf, aldol reaction occurs via the closed transition state **17** to afford the syn aldol **5**. The absolute stereochemistry of this product is in accord with the observations and transition-state proposal of Evans.[2b]

When excess Bu_2BOTf is present, reaction may occur through an open transition state to yield anti aldol **4**. The extent to which this pathway competes is dependent upon the degree to which the aldehyde forms an activated complex with the Lewis acid. This will be a function of the Lewis basicity of the aldehyde carbonyl and the presence of other Lewis bases (e.g., Et_3N, ether) that can compete with the aldehyde for Bu_2BOTf. The absolute stereochemistry of the anti product is that expected from reaction on the *si* face of enolate **16**. This reversal in facial selectivity of the enolate provides strong support for the intermediacy of a transition state like **18** where the enolate boron is chelated to the oxazolidinone carbonyl. The facial selectivity observed in formation of **4** is the same as that observed in alkylation reactions that are believed to occur via chelated enolate **16**.[2b,6b]

Proposed open transition state **18** is depicted in Scheme I as one particular *si-si* conformer. If one accepts the propositions that (1) the enolate has the normal *Z* configuration, (2) the anti aldols are formed by an open transition state in which the boron is chelated by the oxazolidone carbonyl, and (3) the aldehyde reacts on the *si* face of the enolate double bond, then it follows that the aldehyde must also react on its *si* face. Although other rotamers of the transition state cannot be ruled out, the extended rotamer depicted is believed to be the most likely one by analogy to related Lewis acid mediated aldol reactions of silyl enol ethers.[16]

Additional evidence indicating that Bu_2BOTf can act as a Lewis acid to catalyze reaction via open transition state **18** was obtained. The boron enolate of **3** was gen-

(20) Whitmore, F. C.; Noll, C. I.; Mennier, V. C. *J. Am. Chem. Soc.* **1939**, *61*, 683.
(21) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
(22) Brown, H. C.; Dhar, R. J.; Bakshi, R. K.; Pandiarijan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

erated under the same conditions used for Table III, entry 1 (no excess Bu_2BOTf), and 1 equiv of $BF_3{\cdot}OEt_2$ was added at −78 °C immediately before adding aldehyde **2d**. Anti aldol **4d** was obtained in 80% yield as the major product (anti/syn, 95:5). In this reaction $BF_3{\cdot}OEt_2$ probably acts as a Lewis acid in the same way we have postulated for Bu_2BOTf.

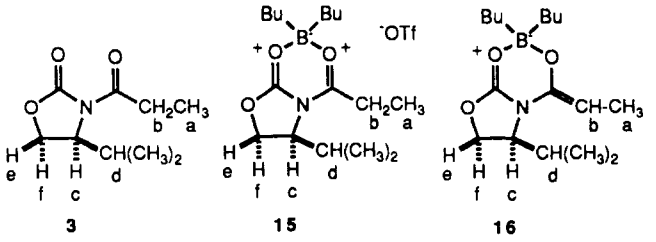
The concentration of free Bu_2BOTf present in the reaction is moderated either by ether or by excess amine. In CH_2Cl_2 the excess amine and excess Bu_2BOTf form a strong acid–base complex.[18] We suggest that a small equilibrium concentration of free Bu_2BOTf is present when *i*-Pr_2NEt is the amine and that this Bu_2BOTf catalyzes reaction via an open transition state. We assume that the less hindered amine Et_3N forms a stronger complex with Bu_2BOTf and that insufficient free Bu_2BOTf is available to catalyze anti aldol formation. In ether the amount of free Bu_2BOTf is moderated by an equilibrium between free Bu_2BOTf and its etherate. Additional evidence suggesting that this is the only function of the ether is provided by the results obtained using 10:1 mixtures of CH_2Cl_2 (or toluene) and ether (vide supra, Table III).

The mechanism postulated in Scheme I could explain why enolates derived from oxazolidinone **3** afford anti aldols while ketone enolates derived from **11** and **12** afford syn aldols. Ketone boron enolates that lack a coordinating ligand (one might argue that the (trimethylsilyl)oxy group in **12** could act as a ligand) have an electron-deficient boron that will rapidly coordinate an aldehyde and react via a closed transition state to afford a syn aldol. However, enolate **16** has the boron coordinated to the oxazolidinone carbonyl and will therefore coordinate an aldehyde and form transition state **17** more slowly. This would allow more time for reaction via an open transition such as **18** to afford an anti aldol. It is more difficult to rationalize why only 3-(arylthio)propenals and aromatic aldehydes afford anti aldols. This is probably related to the basicity of the aldehyde as a more basic aldehyde would coordinate more readily to the Lewis acid. Additional experiments are in progress to determine the effect of aldehyde structure on the simple diastereoselectivity of the aldol reaction.

NMR Studies

In order to confirm that the same enolate species was formed regardless of the amount of excess Bu_2BOTf or amine employed, a ^1H NMR study of the enolization process was undertaken. In each case oxazolidinone **3** was dissolved in CD_2Cl_2, the solution was cooled to −10 °C, and an amine and/or Bu_2BOTf were then added by syringe. The solutions were examined by 500-MHz ^1H NMR at 0 °C after 10–20 min and after warming to room temperature. Complex **15** was formed by adding Bu_2BOTf to oxazolidinone **3**; the important spectral data for **15** are summarized in Table V. When Bu_2BOTf (1.1 equiv) and *i*-Pr_2NEt (1.3 equiv) were added to oxazolidinone **3** (1 equiv), a single enolate species, presumably *Z* enolate **16**, was formed. No significant change in the NMR spectrum of **16** occurred upon warming to room temperature. The spectral data for **3** are also shown in Table V. Comparison of the chemical shifts of **3**, **15**, and **16** indicates that the expected changes are observed. Coordination of Bu_2BOTf with **3** leads to significant downfield shifts for all protons. In enolate **16** smaller downfield shifts relative to **3** are observed. The same enolate is formed when Et_3N (1 equiv of **3**, 1.5 equiv of Bu_2BOTf, 1.55 equiv of Et_3N) is used in place of *i*-Pr_2NEt and again no change occurs upon warming to room temperature. The actual ^1H NMR spectra of **3**, **15**, and **16**, prepared with either Et_3N or *i*-Pr_2NEt, are reproduced in the supplementary material.

Table V. Assignment of ^1H NMR Spectra[a]



^1H	3	15	16
a	1.01 (t, 7.3, 3 H)	not separated	1.50 (d, 3 H, 6.7)
b	2.71–2.86 (m, 2 H)	2.72–2.88 (m)	3.93 (q, 6.7)
		3.16–3.29 (m)	
c	4.29–4.36 (m)	4.93–5.01 (m)	4.13–4.18 (m)
d	2.19–2.30 (m)	2.18–2.30 (m)	2.38–2.45 (m)
e	4.10 (dd, 2.9, 9.1)	4.80 (dd, 3.2, 9.3)	4.32 (dd, 3.4, 9.0)
f	4.16 (t, 9.1)	5.16 (t, 9.3)	4.36 (t, 9.0)

[a] ^1H NMR spectra were obtained at 500 MHz in CD_2Cl_2. Chemical shifts are in ppm downfield from TMS calculated by using a shift of 5.25 ppm for CH_2Cl_2 as an internal reference. All resonances are for one proton except where noted. Following the chemical shifts are the multiplicity and coupling constant(s) in hertz.

An unexpected result occurs when the enolate is formed by using 2 equiv of Bu_2BOTf and 2.2 equiv of *i*-Pr_2NEt. In this case the same major enolate is formed with approximately 15% of a second enolate species at 0 °C, and little change occurs upon warming to room temperature. When a larger excess of Bu_2BOTf (4.5 equiv) and *i*-Pr_2NEt (4 equiv) is used, a larger proportion of this new enolate forms at low temperature and upon warming to room temperature the amount of new enolate increases such that it is the only species present after 7 h. When the aldol reaction is carried out with this new enolate (cool to 0 °C, add 0.8 equiv of *i*-Pr_2NEt to complex excess Bu_2BOTf, then cool to −78 °C and add 1.3 equiv of **2d**), the anti aldol is obtained as the major product (anti/syn = 93:7). The same ratio of products is obtained when the enolate is formed at 0 °C by using only 1.9 equiv of Bu_2BOTf (see Table I, entry 4). Therefore both of these two enolate species react to give the same mixture of aldol products. The structure of this second enolate has not been determined but it seems likely that this species incorporates the excess Bu_2BOTf and/or *i*-Pr_2NEt. A new enolate is not formed when excess Bu_2BOTf and Et_3N are used in the enolization. This is consistent with our proposal that Et_3N and Bu_2BOTf form a complex that will not interact with enolate **16**. Further studies are underway to define the structure of the second enolate obtained by using *i*-Pr_2NEt.

The NMR studies indicate that the reaction mechanism can be more complicated than that shown in Scheme I when a large excess of Bu_2BOTf and *i*-Pr_2NEt is employed. When excess Bu_2BOTf and *i*-Pr_2NEt are present, enolate **16** is formed initially but this can form various amounts of a second enolate depending upon the amount of excess reagents employed and the time allowed for enolization. Reaction of either enolate with 3-(arylthio)propenals affords the anti aldol via an open transition state. Because the same aldol product results from reaction of either enolate, the exact ratio of these two species is inconsequential in the aldol addition reaction.

Conclusion

When stoichiometric amounts of Bu_2BOTf and a slight excess of either *i*-Pr_2NEt or Et_3N are used to form the boron enolate of **3**, reaction with all aldehydes investigated

affords syn aldols as the sole products. Enolization with excess Bu_2BOTf and excess Et_3N also leads to formation of only syn aldols. However, when excess Bu_2BOTf and excess *i*-Pr_2NEt are used in the enolization, anti aldols are formed with certain aldehydes. These aldehydes are either aromatic aldehydes or 3-(arylthio)propenals. The syn and anti aldols are formed from the same *Z* enolate **16**; syn aldols are formed via the normal closed transition state and anti aldols are formed via an open transition state in which excess Bu_2BOTf functions as a Lewis acid catalyst. NMR studies provide support for the formation of **16** and also show that a second enolate can be formed when large excesses of *i*-Pr_2NEt and Bu_2BOTf are used. However, both enolates react in the same manner to afford anti aldols. This work has provided a novel route to optically active anti aldols[23] of certain aldehydes. In addition, our results support and expand on the earlier mechanistic proposals of Evans for aldol reactions of boron enolates derived from **3**.[2b,6b]

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Methylene chloride (CH_2Cl_2) was distilled from P_2O_5. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use.

Et_3N and *i*-Pr_2NEt were distilled from calcium hydride prior to use. Propionaldehyde, acrolein, benzaldehyde, and 1-naphthaldehyde were freshly distilled prior to use. Bu_2BOTf was used as a commercially available solution in CH_2Cl_2 or prepared by using a literature procedure[24] and purified by distillation under high vacuum. All reactions were conducted under a nitrogen or argon atmosphere. Upon workup, solvents were evaporated by using a Büchi rotary evaporator, followed by high vacuum unless otherwise indicated. Melting points (Pyrex capillary) are uncorrected. ^1H NMR spectra were measured in $CDCl_3$ at 250 MHz. ^{13}C NMR spectra were measured in $CDCl_3$ at 62.89 MHz. For aldol reactions that gave a mixture of isomers, spectral and analytical data were obtained on the mixture. Full ^1H NMR data are listed for the major isomer and the distinctive carbinol proton resonance is given for the minor isomer in most cases. ^{13}C NMR data are listed for the major isomer only, except where noted. Coupling constants are in hertz.

General Procedure for the Preparation of (*E*)-3-(Alkylthio)- and (*E*)-3-(Arylthio)propenals: (*E*)-3-(Phenylthio)propenal (2a). To a solution of 3.35 mL (2.81 g, 50 mmol) of acrolein and 5.15 mL (5.53 g, 50 mmol) of thiophenol (Aldrich, 99%) in 20 mL of $CHCl_3$ at 0 °C was added 0.25 mL (0.18 g, 1.8 mmol) of Et_3N. The cooling bath was removed, and the solution was stirred at room temperature for 2 h. The reaction mixture was diluted with 75 mL of $CHCl_3$ and cooled with an ice bath. To the solution was added 7.5 g (55 mmol) of *N*-chlorosuccinimide (NCS; Fluka, 98%), and the suspension was stirred for 3 h as the temperature slowly rose to room temperature. The reaction mixture was cooled with an ice bath, 21 mL of Et_3N in 50 mL of $CHCl_3$ was added, and stirring was continued for an additional 4 h as the mixture warmed to room temperature. After being diluted with ether and washed sequentially with 10% HCl, water, and brine, the organic phase was dried over $MgSO_4$. After evaporation of the solvent, the crude product was chromatographed on silica gel (230–400 mesh, 5% EtOAc in hexanes) to give 3.37 g (41%) of **2a** as a yellow oil: IR (neat) 3070, 2830, 2740, 1665, 1565, 1130 cm^{-1}; ^1H NMR δ 5.97 (dd, 1, J = 15.0, 7.7), 7.20–7.64 (m, 5), 7.68 (d, 1, J = 15.0), 9.43 (d, 1, J = 7.7); ^{13}C NMR δ 126.67, 129.26, 129.42, 129.59 (2 C), 132.89 (2 C), 156.47, 189.38. Anal. Calcd for C_9H_8OS: C, 65.82; H, 4.91; S, 19.53. Found: C, 65.81; H, 4.92; S, 19.45.

(*E*)-3-((2′,4′,6′-Trimethylphenyl)thio)propenal (2b). The procedure given for **2a** was employed on a 20-mmol scale using 2,4,6-trimethylthiophenol.[25] Chromatography afforded 1.60 g (39%) of **2b** as white crystals: mp 82–3 °C; IR (CCl_4) 1685, 1565, 1127 cm^{-1}; ^1H NMR δ 2.30 (s, 3), 2.36 (s, 6), 5.54 (dd, 1, J = 14.6, 7.9), 7.00 (s, 2), 7.55 (d, 1, J = 14.6), 9.42 (d, 1, J = 7.9); ^{13}C NMR δ 20.91 (3 C), 123.12, 125.61, 129.53 (2 C), 140.41, 142.32 (2C), 155.79, 189.47. Anal. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84; S, 15.54. Found: C, 69.67; H, 6.86; S, 15.35.

(*E*)-3-((2′,4′,6′-Triisopropylphenyl)thio)propenal (2c). The procedure given for **2a** was employed on a 25-mmol scale using 2,4,6-triisopropylthiophenol.[26] Chromatography afforded 1.26 g (17%) of **2c** as white crystals: mp 113–5 °C; IR (CCl_4) 2980, 1690, 1570, 1133 cm^{-1}; ^1H NMR δ 1.20 (d, 1, J = 6.8), 1.27 (d, 18, J = 6.9), 2.91 (m, 3), 3.44 (m, 2), 5.60 (dd, 1, J = 14.6, 7.9), 7.10 (s, 2), 7.63 (d, 1, J = 14.6), 9.41 (d, 1, J = 7.9); ^{13}C NMR δ 24.30 (2 C), 24.66 (4 C), 32.18 (2 C), 34.84, 121.99, 123.01 (2 C), 127.08, 152.41, 153.01 (2 C), 158.72, 190.06. Anal. Calcd for $C_{18}H_{26}OS$: C, 74.43; H, 9.02; S, 11.04. Found: C, 74.61; H, 9.03; S, 11.13.

(*E*)-3-(2′-Naphthylthio)propenal (2d). The procedure given for **2a** was employed on a 21-mmol scale using 2-naphthalenethiol (Aldrich, 99%). Chromatography afforded 1.99 g (44%) of **2d** as white crystals: mp 82 °C; IR (CCl_4) 3062, 2813, 2720, 1693, 1570, 1126 cm^{-1}; ^1H NMR δ 5.99 (dd, 1, J = 15.0, 7.7), 7.49–7.61 (m, 3), 7.74 (d, 1, J = 15.0), 7.82–8.03 (m, 4), 9.45 (d, 1, J = 7.7); ^{13}C NMR δ 126.38, 126.90 (2 C), 127.28, 127.55, 127.62, 129.03, 129.49, 132.80, 133.00, 133.37, 156.34, 189.44. Anal. Calcd for $C_{13}H_{10}OS$: C, 72.86; H, 4.70; S, 14.96. Found: C, 72.67; H, 4.73; S, 14.95.

(*E*)-3-(*tert*-Butylthio)propenal (2e). The procedure given for **2a** was employed on a 20-mmol scale using 2-methyl-2-propanethiol (Aldrich, 99%). Chromatography afforded 577 mg (20%) of **2e** as a yellow liquid: IR (neat) 2980, 1675, 1565 cm^{-1}; ^1H NMR δ 1.48 (s, 9), 6.28 (dd, 1, J = 15.5, 7.6), 7.74 (d, 1, J = 15.5), 9.41 (d, 1, J = 7.6); ^{13}C NMR δ 31.30 (3 C), 46.53, 127.68, 155.41, 190.46; HRMS calcd for $C_7H_{12}OS$ 144.0610, found 144.0603. Satisfactory analytical data could not be obtained for this compound.

General Procedure for Aldol Reactions with Oxazolidinone 3. (*E*,2′*R*,3′*S*,4*S*)- and (*E*,2′*S*,3′*S*,4*S*)-3-(3′-Hydroxy-2′-methyl-1′-oxo-5′-(phenylthio)-4′-pentenyl)-4-(methylethyl)-2-oxazolidinone (4a and 5a). To a solution of 185 mg (1.00 mmol) of 2-oxazolidinone **3** in 2 mL of CH_2Cl_2 at 0 °C were added 0.38 mL (0.28 g, 2.2 mmol) of *i*-Pr_2NEt and 0.41 mL (0.52 g, 1.9 mmol) of Bu_2BOTf. After 45 min at 0 °C, the solution was cooled to −78 °C and 0.21 g (1.3 mmol) of **2a** in 1 mL of CH_2Cl_2 was added over 20 min. After 30 min at −78 °C, 3 mL of pH 7 buffer and 4 mL of ether were added. The mixture was allowed to warm to room temperature, the layers were separated, and the aqueous layer was extracted with ether (2 × 4 mL). The combined organic layers were washed with brine (2 mL) and the solvent was removed with a rotary evaporator.

The residue was dissolved in 4 mL of methanol and cooled to 0 °C, and 1 mL of 30% H_2O_2 was added dropwise over 30 min. After 60 min at 0 °C, 4 mL of water was added and the methanol was removed with a rotary evaporator. The aqueous layer was extracted with ether (3 × 4 mL). The combined organic layers were washed with cold 5% HCl (1 mL), saturated aqueous $NaHCO_3$ (2 mL), and brine (2 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by chromatography on silica gel (230–400 mesh, 15% EtOAc in hexanes) to give 314 mg (90%) of a yellow oil, which was a 92:8 mixture of diastereomers, **4a** and **5a**, respectively: IR (CCl_4) 3520, 1800, 1720, 1690, 1395 cm^{-1}; ^1H NMR **4a** δ 0.86–0.93 (m, 6), 1.17–1.29 (m, 3), 2.25–2.45 (m, 1), 2.87 (d, 1, J = 7.9), 4.00 (quintet, 1, J = 6.9), 4.15–4.33 (m, 3), 4.37–4.46 (m, 1), 5.82 (dd, 1, J = 15.1, 6.6), 6.53 (d, 1, J = 15.1), 7.20–7.38 (m, 5); **5a** δ 3.87 (dq, 1, J = 3.5, 6.9); ^{13}C NMR δ 14.64, 14.99, 18.32, 28.77, 43.38, 59.10, 63.70,

(23) For other routes to optically active anti aldols, see: (a) Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (b) Reference 12.

(24) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (b) For a cautionary note and a more detailed description, see ref 2c.

(25) Prepared from commercially available 2,4,6-trimethylbenzenesulfonyl chloride according to the general procedure described for preparation of thiophenol, see: Adams, R.; Marvel, C. S. *Organic Syntheses*, 2nd ed.; Wiley: New York, 1941; Colect. Vol. 1, p 504. See also: Haselinger, G.; Hack, F.; Westermayer, G. *Chem. Ber.* **1976**, 833.

(26) Prepared from commercially available 2,4,6-triisopropylbenzenesulfonyl chloride according to the general procedure described in ref 24.

75.58, 126.86, 127.39, 129.49, 129.54, 130.02, 130.31, 132.12, 134.89, 154.46, 176.31. Anal. Calcd for $C_{18}H_{23}O_4S$: C, 61.87; H, 6.63; N, 4.01; S, 9.18. Found: C, 61.79; H, 6.67; N, 3.93; S, 8.99.

(*E*,2′*R*,3′*S*,4*S*)- and (*E*,2′*S*,3′*S*,4*S*)-3-[3′-Hydroxy-2′-methyl-1′-oxo-5′-((2″,4″,6″-trimethylphenyl)thio)-4′-pentenyl]-4-(methylethyl)-2-oxazolidinone (4b and 5b). The general aldol procedure was followed, using 0.27 g (1.3 mmol) of aldehyde **2b**. Chromatography afforded 322 mg (82%) of a pale yellow glass, which was a 91:9 mixture of diastereomers **4b** and **5b**, respectively: IR (CCl_4) 3520, 2970, 1792, 1705, 1684, 1390 cm^{-1}; ^1H NMR **4b** δ 0.86 (d, 3, J = 6.9), 0.90 (d, 3, J = 7.1), 1.07 (d, 3, J = 6.9), 2.29 (s, 3), 2.29–2.40 (m, 1), 2.40 (s, 6), 2.42 (d, 1, J = 7.1), 3.85 (dq, 1, J = 7.8, 6.9), 4.16–4.29 (m, 3), 4.41–4.50 (m, 1), 4.99 (dd, 1, J = 14.8, 7.5), 6.24 (d, 1, J = 14.8), 7.26 (s, 2); **5b** δ 3.73 (dq, 1, J = 3.1, 6.9); ^{13}C NMR δ 14.12, 14.47, 17.83, 20.98, 21.35 (2 C), 28.25, 43.18, 58.63, 63.14, 75.72, 124.67, 125.70, 128.05, 129.10, 129.18 (2 C), 139.09, 142.77, 153.99, 175.83. Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58; S, 8.19. Found: C, 64.56; H, 7.39; N, 3.56; S, 8.19.

(*E*,2′*R*,3′*S*,4*S*)- and (*E*,2′*S*,3′*S*,4*S*)-3-[3′-Hydroxy-2′-methyl-1′-oxo-5′-((2″,4″,6″-triisopropylphenyl)thio)-4′-pentenyl]-4-(methylethyl)-2-oxazolidinone (4c and 5c). The general aldol procedure was followed, using 0.38 g (1.3 mmol) of aldehyde **2c**. Chromatography afforded 404 mg (85%) of a pale yellow glass, which was an 89:11 mixture of diastereomers **4c** and **5c**, respectively: IR (CCl_4) 3520, 2975, 1792, 1705, 1390, 1210 cm^{-1}; ^1H NMR δ 0.86 (d, 3, J = 6.9), 0.90 (d, 3, J = 7.1), 1.06 (d, 3, J = 6.9), 1.21 (d, 12, J = 6.9), 1.27 (d, 6, J = 6.9), 2.28–2.44 (m, 1), 2.36 (d, 1, J = 7.1), 2.91 (m, 1), 3.64 (m, 2), 3.85 (dq, 1, J = 8.3, 6.9), 4.15–4.30 (m, 3), 4.40–4.53 (m, 1), 5.04 (dd, 1, J = 14.8, 7.7), 6.30 (d, 1, J = 14.8), 7.06 (s, 2); ^{13}C NMR **4c** δ 14.64, 15.06, 18.36, 24.38 (2 C), 24.72 (2 C), 24.83 (2 C), 28.81, 31.98 (2 C), 34.77, 43.71, 59.21, 63.72, 78.26, 122.42, 122.50, 124.48, 125.70, 130.85, 151.02, 153.35, 153.43, 154.59, 176.37. Anal. Calcd for $C_{27}H_{41}NO_4S$: C, 68.17; H, 8.69; N, 2.94; S, 6.74. Found: C, 68.10; H, 8.77; N, 3.10; S, 6.69.

(*E*,2′*R*,3′*S*,4*S*)- and (*E*,2′*S*,3′*S*,4*S*)-3-[3′-Hydroxy-2′-methyl-1′-oxo-5′-(2″-naphthylthio)-4′-pentenyl]-4-(methylethyl)-2-oxazolidinone (4d and 5d). The general aldol procedure was followed, using 0.28 g (1.3 mmol) of aldehyde **2d**. Chromatography afforded 305 mg (76%) of a pale yellow foamy solid, which was a 93:7 mixture of diastereomers **4d** and **5d**, respectively: IR (CCl_4) 3520, 2970, 1792, 1700, 1684, 1388 cm^{-1}; ^1H NMR **4d** δ 0.86 (d, 3, J = 7.5), 0.89 (d, 3, J = 7.3), 1.23 (d, 3, J = 6.9), 2.30–2.50 (m, 1), 2.94 (d, 1, J = 8.1), 4.03 (quintet, 1, J = 6.9), 4.20–4.40 (m, 3), 4.42–4.55 (m, 1), 5.88 (dd, 1, J = 15.1, 6.3), 6.62 (d, 1, J = 15.1), 7.40–7.56 (m, 3), 7.70–7.87 (m, 4); **5d** δ 3.90 (dq, 1, J = 3.1, 6.9); ^{13}C NMR δ 14.11, 14.33, 17.67, 28.15, 42.75, 58.49, 63.06, 75.05, 125.89, 126.00, 126.46, 127.04, 127.32, 127.50, 127.99, 128.51, 131.69, 131.90, 132.03, 133.48, 153.85, 175.75. Anal. Calcd for $C_{22}H_{25}O_4S$: C, 66.14; H, 6.31; N, 3.51; S, 8.03. Found: C, 65.93; H, 6.21; N, 3.52; S, 7.78. Aldol **4d** was subsequently purified by recrystallization from ethyl acetate, mp 115–7 °C.

(*E*,2′*R*,3′*S*,4*S*)- and (*E*,2′*S*,3′*S*,4*S*)-3-(5′-(*tert*-Butylthio)-3′-hydroxy-2′-methyl-1′-oxo-4′-pentenyl)-4-(methylethyl)-2-oxazolidinone (4e and 5e). The general aldol procedure was followed, using 0.19 g (1.3 mmol) of aldehyde **2e**, except that after 30 min at −78 °C, the mixture was allowed to warm to room temperature for 90 min before addition of pH 7 buffer and ether. Chromatography afforded 243 mg (74%) of a yellow glass, which was a 25:75 mixture of diastereomers **4e** and **5e**, respectively: IR (CCl_4) 3540, 2985, 1790, 1700, 1682, 1380 cm^{-1}; ^1H NMR **5e** δ 0.88 (d, 3, J = 6.9), 0.92 (d, 3, J = 7.0), 1.25 (d, 3, J = 7.1), 1.35 (s, 9), 2.28–2.44 (m, 1), 2.99 (d, 1, J = 2.9), 3.87 (dq, 1, J = 3.6, 7.1), 4.20–4.35 (m, 2), 4.43–4.51 (m, 1), 4.51–4.58 (m, 1), 5.79 (dd, 1, J = 15.1, 5.6), 6.46 (d, 1, J = 15.1); **4e** δ 3.99 (quintet, 1, J = 7.1); ^{13}C NMR δ 12.08, 15.12, 18.27, 28.79, 31.26 (3 C), 43.11, 44.12, 58.68, 63.83, 72.81, 124.34, 132.01, 153.90, 176.88; HRMS calcd for $C_{16}H_{25}NO_3S$ (M − H_2O) 311.1557, found 311.1544. Satisfactory analytical data could not be obtained for this compound.

(2′*S*,3′*R*,4*S*)-3-(3′-Hydroxy-2′-methyl-1′-oxo-4′-pentenyl)-4-(methylethyl)-2-oxazolidinone (5f). The general aldol procedure was followed, using 73 mg (1.3 mmol) of acrolein (**2f**), except that after 30 min at −78 °C, the mixture was allowed to warm to room temperature for 90 min before addition of pH 7 buffer and ether. Chromatography afforded 236 mg (98%) of **5f** as a colorless oil. Aldol **5f** has been prepared previously under the standard Evans conditions.[10]

(*E*,2′*S*,3′*S*,4*S*)-3-[3′-Hydroxy-2′-methyl-1′-oxo-5′-((2″,4″,6″-trimethylphenyl)thio)-4′-pentenyl]-4-(methylethyl)-2-oxazolidinone (5b). The general aldol procedure was followed, using 0.27 g (1.3 mmol) of aldehyde **2b**, except that 0.33 mL (0.24 g, 2.4 mmol) of Et_3N was used instead of i-Pr_2NEt. Chromatography afforded 325 mg (83%) of **5b** as a pale yellow glass: IR (CCl_4) 3540, 2970, 1790, 1680, 1385 cm^{-1}; ^1H NMR δ 0.85 (d, 3, J = 11.6), 0.90 (d, 3, J = 11.7), 1.17 (d, 3, J = 7.0), 2.28 (s, 3), 2.30–2.50 (m, 1), 2.41 (s, 6), 2.97 (d, 1, J = 2.4), 3.76 (dq, 1, J =3.9, 7.0), 4.20–4.35 (m, 2), 4.40–4.50 (m, 2), 5.00 (dd, 1, J = 15.0, 5.5), 6.25 (d, 1, J = 15.0), 7.26 (s, 2); ^{13}C NMR δ 11.95, 15.06, 18.22, 21.43, 21.84 (2 C), 28.76, 43.34, 58.68, 63.79, 72.53, 124.66, 126.59, 126.73, 129.58 (2 C), 139.34, 143.21 (2 C), 153.93, 176.89. Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58; S, 8.19. Found: C, 64.68; H, 7.52; N, 3.51; S, 8.06.

(*E*,2′*S*,3′*S*,4*S*)-3-[3′-Hydroxy-2′-methyl-1′-oxo-5′-((2″,4″,6″-triisopropylphenyl)thio)-4′-pentenyl]-4-(methylethyl)-2-oxazolidinone (5c). The general aldol procedure was followed, using 0.38 g (1.3 mmol) of aldehyde **2c**, except that 0.33 mL (0.24 g, 2.4 mmol) of Et_3N was used instead of i-Pr_2NEt. Chromatography afforded 437 mg (92%) of **5c** as a pale yellow glass: IR (CCl_4) 3540, 2975, 1790, 1680, 1390 cm^{-1}; ^1H NMR δ 0.88 (d, 3, J = 11.5), 0.95 (d, 3, J = 11.6), 1.18 (d, 3, J = 6.8), 1.20 (d, 12, J = 6.6), 1.27 (d, 6, J = 6.9), 2.25–2.48 (m, 1), 2.87–3.00 (m, 1), 2.95 (s, 1), 3.60–3.70 (m, 2), 3.70 (dq, 1, J = 3.2, 7.0), 4.20–4.37 (m, 2), 4.40–4.57 (m, 2), 5.00 (dd, 1, J = 14.7, 5.5), 6.33 (d, 1, J = 14.7), 7.05 (s, 2); ^{13}C NMR δ 11.67, 15.11, 18.25, 24.30 (2 C), 24.68 (2 C), 28.79, 31.91 (2 C), 34.71, 43.24, 58.63, 63.80, 72.28, 122.38 (2 C), 124.73, 124.79, 129.08, 150.84, 153.40 (2 C), 153.81, 177.21. Anal. Calcd for $C_{27}H_{41}NO_4S$: C, 68.17; H, 8.69; N, 2.94; S, 6.74. Found: C, 68.09; H, 8.52; N, 2.87; S, 6.70.

(*E*,2′*S*,3′*S*,4*S*)-3-[3′-Hydroxy-2′-methyl-1′-oxo-5′-(2″-naphthylthio)-4′-pentenyl]-4-(methylethyl)-2-oxazolidinone (5d). The general aldol procedure was followed, using 0.28 g (1.3 mmol) of aldehyde **2d**, except that 0.33 mL (0.24 g, 2.4 mmol) of Et_3N was used instead of i-Pr_2NEt. Chromatography afforded 347 mg (87%) of **5d** as a pale yellow glass: IR (CCl_4) 3540, 2970, 1788, 1680, 1385 cm^{-1}; ^1H NMR δ 0.88 (d, 3, J = 9.6), 0.92 (d, 3, J = 9.7), 1.29 (d, 3, J = 7.0), 2.30–2.45 (m, 1), 3.11 (d, 1, J = 2.8), 3.90 (dq, 1, J = 3.4, 7.1), 4.20–4.38 (m, 2), 4.47–4.55 (m, 1), 4.62–4.67 (m, 1), 5.85 (dd, 1, J = 15.0, 5.5), 6.63 (d, 1, J = 15.0), 7.43–7.56 (m, 3), 7.77–7.86 (m, 4); ^{13}C NMR δ 12.21, 15.14, 18.28, 28.79, 43.19, 58.72, 63.87, 72.65, 125.70, 126.43, 127.05, 127.66, 127.83, 128.13, 128.31, 129.09, 132.24, 132.47, 132.69, 134.12, 154.01, 176.92. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51; S, 8.03. Found: C, 66.33; H, 6.37; N, 3.45; S, 7.85.

Absolute Configuration of Aldol 5b. To a solution of 221 mg (0.56 mmol) of **5b** in 10 mL of EtOH was added 617 mg of Raney Ni (W4, slurry in ethanol). The reaction mixture was stirred under reflux for 2 h and the Raney Ni was removed by filtration. After removal of the solvent with a rotary evaporator, the crude product was purified by chromatography on silica gel (230–400 mesh, 15% EtOAc in hexanes) to afford 88 mg (64%) of **7** as a clear oil. This material was identical by ^1H and ^{13}C NMR spectroscopy with an authentic sample prepared by using the Evans method (see following procedure).

(2′*S*,3′*R*,4*S*)-3-(3′-Hydroxy-2′-methyl-1′-oxopentyl)-4-(methylethyl)-2-oxazolidinone (7). To a solution of 185 mg (1.0 mmol) of oxazolidinone **3** in 2 mL of CH_2Cl_2 at 0 °C were added 0.27 mL (0.34 g, 1.2 mmol) of Bu_2BOTf and 0.22 mL (0.17 g, 1.3 mmol) of i-Pr_2NEt. After 45 min at 0 °C, the solution was cooled to −78 °C and 75 mg (1.3 mmol) of propionaldehyde in 1 mL of CH_2Cl_2 was added over 2 min. After 30 min at −78 °C, the reaction mixture was allowed to warm to room temperature for 90 min. To the reaction mixture were added 3 mL of pH 7 buffer and 4 mL of ether. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and the solvent was removed with a rotary evaporator.

Oxidative workup and chromatography according to the general aldol procedure afforded 203 mg (83%) of **7** as a colorless oil: IR (CCl_4) 3560, 2980, 1795, 1685, 1390, 1210 cm^{-1}; ^1H NMR δ 0.89 (d, 3, J = 9.6), 0.92 (d, 3, J = 9.9), 0.97 (t, 3, J = 7.4), 1.25 (d, 3, J = 7.1), 1.35–1.68 (m, 2), 2.27–2.43 (m, 1), 3.00 (s, 1), 3.80 (dq,

1, J = 2.5, 7.1), 3.80–3.93 (m, 1), 4.20–4.40 (m, 2), 4.45–4.55 (m, 1); ^{13}C NMR δ 10.32, 10.56, 14.54, 17.74, 26.57, 28.20, 41.53, 58.08, 63.20, 72.55, 153.36, 177.56. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.03; H, 8.71; N, 5.67.

Absolute Configuration of Aldol 4d. (2′*R*,3′*R*,4*S*)-3-(3′-Hydroxy-2′-methyl-1′-oxopentyl)-4-(methylethyl)-2-oxazolidinone (6). To a solution of 86 mg (0.215 mmol) of **4d** in 4 mL of EtOH was added 250 mg of Raney Ni (W4, slurry in ethanol). The reaction mixture was heated at reflux for 2 h and the Raney Ni was removed by filtration. After removal of the solvent with a rotary evaporator, the crude product was purified by chromatography on silica gel (230–400 mesh, 15% EtOAc in hexanes) to give 40 mg (77%) of **6** as a colorless oil: $[\alpha]^{23}_D$ +22.5° (c = 0.12, $CHCl_3$); IR (CCl_4) 3540, 2970, 1790, 1710, 1390, 1210 cm^{-1}; ^{1}H NMR δ 0.92 (t, 6, J = 7.0), 1.01 (t, 3, J = 7.4), 1.19 (d, 3, J = 6.9), 1.38–1.75 (m, 2), 2.30–2.50 (m, 1), 2.57 (d, 1, J = 9.0), 3.58–3.68 (m, 1), 3.93 (quintet, 1, J = 6.9), 4.20–4.38 (m, 2), 4.45–4.50 (m, 1); ^{13}C NMR δ 9.73, 14.29, 14.48, 17.83, 27.72, 28.30, 42.54, 58.66, 63.14, 75.95, 154.12, 176.62. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.97; H, 8.73; N, 5.66.

(2*R*,3*R*)-3-Hydroxy-2-methylpentanoic Acid (8). To a solution of 39 mg (0.16 mmol) of **6** in 3.6 mL of 3:1 THF/H_2O at 0 °C was added 0.11 mL (0.97 mmol) of 30% H_2O_2 followed by 13.5 mg (0.322 mmol) of LiOH·H_2O. The reaction mixture was stirred at 0 °C for 1 h and then a solution of 139 mg (1.1 mmol) of Na_2SO_3 in 2 mL of H_2O was added. After being buffered to pH 9 with aqueous $NaHCO_3$, the THF was removed with a rotary evaporator. The aqueous solution was washed with CH_2Cl_2. After acidification to pH 1 with 10% HCl, the aqueous phase was extracted with EtOAc to afford 17.0 mg (80%) of **8** as a colorless oil: $[\alpha]^{23}_D$ −15.2° (c = 0.51, $CHCl_3$); ^{1}H NMR δ 1.00 (t, 3, J = 7.4), 1.25 (d, 3, J = 7.2), 1.40–1.80 (m, 2), 2.59 (quintet, 1, J = 7.0), 3.60–3.72 (m, 1), 6.20–7.50 (br, 2).

(2*R*,3*R*)-Methyl 3-Hydroxy-2-methylpentanoate (9). To a solution of 17.0 mg (0.129 mmol) of β-hydroxy acid **8** in 1 mL of ether at 0 °C was added a solution of CH_2N_2 in ether dropwise until the solution remained yellow. After evaporation of the solvent, the crude product was chromatographed on silica gel (230–400 mesh, 20% EtOAc in hexanes) to give 19 mg (100%) of isomerically pure **9** as a colorless oil: $[\alpha]^{23}_D$ −7.9° (c = 0.52, $CHCl_3$); ^{1}H NMR δ 0.98 (t, 3, J = 7.4), 1.21 (d, 3, J = 7.2), 1.37–1.70 (m, 2), 2.55 (br s, 1), 2.55 (quintet, 1, J = 7.0), 3.55–3.67 (m, 1), 3.71 (s, 3). The ^{1}H NMR spectrum of **9** is in agreement with the literature data.[14]

(*E*,4*SR*,5*SR*)-5-Hydroxy-7-(phenylthio)-2,2,4-trimethyl-6-hepten-3-one (13). To a solution of 114 mg (1.0 mmol) of ketone **11** in 2 mL of CH_2Cl_2 at 0 °C were added 0.38 mL (0.28 g, 2.2 mmol) of i-Pr_2NEt and 0.41 mL (0.52 g, 2.2 mmol) of Bu_2BOTf. After 45 min at 0 °C, the solution was cooled to −78 °C and 214 mg (1.3 mmol) of aldehyde **2a** in 1 mL of CH_2Cl_2 was added over 2 min. After 30 min at −78 °C, the reaction mixture was allowed to warm to room temperature for 90 min. To the reaction mixture were added 3 mL of pH 7 buffer and 4 mL of ether. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and the solvent was removed with a rotary evaporator.

Oxidative workup and chromatography according to the general aldol procedure afforded 243 mg (87%) of syn aldol **13** as a yellow oil: IR (CCl_4) 3500, 2980, 1692, 1483, 1140 cm^{-1}; ^{1}H NMR δ 1.12 (d, 3, J = 7.0), 1.16 (s, 9), 3.08 (dq, 1, J = 3.8, 7.0), 3.24 (d, 1, J = 1.3), 4.35–4.42 (m, 1), 5.70 (dd, 1, J = 15.0, 5.7), 6.50 (d, 1, J = 15.0), 7.20–7.40 (m, 5); ^{13}C NMR δ 12.34, 25.93 (3 C), 43.94, 45.04, 72.64, 125.58, 126.87, 129.05 (2C), 129.88 (2 C), 131.14, 134.61, 221.05. Anal. Calcd for $C_{18}H_{22}O_2S$: C, 69.02; H, 7.97; S, 11.52. Found: C, 69.23; H, 7.95; S, 11.41.

(*E*,4*SR*,5*SR*)-2,4-Dimethyl-5-hydroxy-7-(phenylthio)-2-((trimethylsilyl)oxy)-6-hepten-3-one (14). The procedure described for the reaction of ketone **11** was followed, using 188 mg (1.0 mmol) of ketone **12** instead of **11**. Oxidative workup and chromatography afforded 296 mg (84%) of syn aldol **14** as a yellow oil: IR (CCl_4) 3500, 2980, 1764, 1685 cm^{-1}; ^{1}H NMR δ 0.19 (s, 9), 1.13 (d, 3, J = 7.2), 1.34 (s, 3), 1.37 (s, 3), 3.12 (d, 1, J = 2.7), 3.45 (dq, 1, J = 3.8, 7.2), 4.43–4.48 (m, 1), 5.77 (dd, 1, J = 15.0, 5.7), 6.48 (d, 1, J = 15.0), 7.20–7.40 (m, 5); ^{13}C NMR δ 2.30 (3 C), 11.87 27.02, 27.39, 44.02, 72.71, 80.47, 125.02, 126.62, 128.93 (2 C), 129.54 (2 C), 131.96, 134.91, 218.60. Anal. Calcd for $C_{18}H_{28}O_3SSi$: C, 61.32; H, 8.00; S, 9.09. Found: C, 61.21; H, 7.83; S, 9.18.

Reaction with Aromatic Aldehydes. (2′*R*,3′*S*,4*S*)- and (2′*S*,3′*S*,4*S*)-3-(3′-Hydroxy-2′-methyl-1′-oxo-3′-phenylpropyl)-4-(methylethyl)-2-oxazolidinone (Table IV, Entry 1). To a solution of 185 mg (1.0 mmol) of 2-oxazolidinone **3** in 2.5 mL of ether at −10 °C were added 142 mg (1.1 mmol) of i-Pr_2NEt and 548 mg (2.0 mmol) of Bu_2BOTf. After 45 min at 0 °C, the solution was cooled to −78 °C and 138 mg (1.3 mmol) of benzaldehyde in 1.5 mL of ether was added over 10 min. After 60 min at −78 °C, 5 mL of pH 7 buffer was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and the solvent was removed with a rotary evaporator.

Oxidative workup and chromatography according to the general aldol procedure afforded 230 mg (79%) of a white solid, which was an 80:20 mixture of anti and syn aldols, respectively: IR (CCl_4) 3520, 2970, 1790, 1705, 1390, 1210 cm^{-1}; ^{1}H NMR anti aldol δ 0.70 (d, 3, J = 6.9), 0.87 (d, 3, J = 7.1), 1.12 (d, 3, J = 6.9), 2.23–2.38 (m, 1), 3.20 (d, 1, J = 7.7), 4.16–4.35 (m, 2), 4.41 (quintet, 1, J = 7.1), 4.42–4.50 (m, 1), 4.75 (t, 1, J = 7.6), 7.26–7.46 (m, 5); syn aldol δ 5.07 (d, 1, J = 2.5); ^{13}C NMR δ 14.76, 15.26, 18.32, 28.71, 44.33, 59.14, 63.58, 77.80, 126.83 (2 C), 128.27, 128.89 (2 C), 142.55, 154.52, 177.01. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.75; H, 7.16; N, 4.76.

(2′*S*,3′*S*,4*S*)-3-(3′-Hydroxy-2′-methyl-1′-oxo-3′-phenylpropyl)-4-(methylethyl)-2-oxazolidinone (Table IV, Entry 2). To a solution of 185 mg (1.0 mmol) of 2-oxazolidinone **3** in 2.5 mL of ether at −10 °C were added 168 mg (1.3 mmol) of i-Pr_2NEt and 302 mg (1.1 mmol) of Bu_2BOTf. After 45 min at 0 °C, the solution was cooled to −78 °C and 138 mg (1.3 mmol) of benzaldehyde in 1.5 mL of ether was added over 10 min. After 60 min at −78 °C, 5 mL of pH 7 buffer was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and the solvent was removed with a rotary evaporator.

Oxidative workup and chromatography according to the general aldol procedure afforded 265 mg (91%) of pure syn aldol as a white solid: mp 94 °C;[27] IR (CCl_4) 3540, 2970, 1795, 1685, 1390, 1210 cm^{-1}; ^{1}H NMR δ 0.87 (d, 3, J = 7.0), 0.91 (d, 3, J = 7.0), 1.21 (d, 3, J = 7.0), 2.30–2.45 (m, 1), 3.24 (br, 1), 4.09–4.24 (m, 3), 4.34–4.45 (m, 1), 5.07 (d, 1, J =2.5), 7.24–7.44 (m, 5); ^{13}C NMR δ 11.62, 15.16, 18.32, 28.83, 44.83, 58.76, 63.80, 73.89, 126.50 (2 C), 127.84, 128.61 (2 C), 141.64, 153.81, 177.47.

(2′*R*,3′*S*,4*S*)- and (2′*S*,3′*S*,4*S*)-3-(3′-Hydroxy-2′-methyl-3′-(1″-naphthyl)-1′-oxopropyl)-4-(methylethyl)-2-oxazolidinone (Table IV, Entry 3). To a solution of 185 mg (1.0 mmol) of 2-oxazolidinone **3** in 2.5 mL of ether at −10 °C were added 142 mg (1.1 mmol) of i-Pr_2NEt and 548 mg (2.0 mmol) of Bu_2BOTf. After 45 min at 0 °C, the solution was cooled to −78 °C and 203 mg (1.3 mmol) of 1-naphthaldehyde in 1.5 mL of ether was added over 10 min. After 20 min at −78 °C, 5 mL of pH 7 buffer was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and the solvent was removed with a rotary evaporator.

Oxidative workup and chromatography according to the general aldol procedure afforded 255 mg (75%) of a white solid, which was a 75:25 mixture of anti and syn aldols, respectively: IR (CCl_4) 3500, 2970, 1790, 1705, 1390, 1208 cm^{-1}; ^{1}H NMR anti aldol δ 0.73 (d, 3, J = 6.9), 0.91 (d, 3, J = 7.1), 1.09 (d, 3, J = 6.9), 2.28–2.50 (m, 1), 3.21 (d, 1, J = 6.9), 4.10–4.36 (m, 2), 4.40–4.60 (m, 1), 4.71 (quintet, 1, J = 6.9), 5.59 (t, 1, J = 7.1), 7.44–8.33 (m, 7); syn aldol δ 5.92–5.98 (br, 1); ^{13}C NMR anti aldol δ 14.26, 14.95, 17.84, 28.13, 43.51, 58.61, 62.95, 74.18, 123.31, 124.35, 125.16, 125.55, 126.15, 128.45, 128.68, 130.85, 133.66, 137.55, 153.86, 176.70, syn aldol: 12.05, 14.40, 17.77, 22.21, 42.80, 58.06, 58.28, 70.49, 123.04, 124.30, 125.05, 125.25, 125.47, 128.20, 128.62, 130.14, 133.61, 136.76, 153.51, 176.22. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.35; H, 6.92; N, 4.09.

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(27) The syn aldol has been reported previously but no data have been published. See ref 5a.

Registry No. **2a**, 80227-71-0; **2b**, 123075-35-4; **2c**, 123075-36-5; **2d**, 123075-37-6; **2e**, 107210-09-3; **2f**, 107-02-8; **3**, 77877-19-1; **4a**, 123075-32-1; **4b**, 123075-38-7; **4c**, 123075-39-8; **4d**, 123075-40-1; **4e**, 123075-41-2; **5a**, 123163-80-4; **5b**, 123163-81-5; **5c**, 123163-82-6; **5d**, 123163-83-7; **5e**, 123163-84-8; **5f**, 113489-83-1; **6**, 123237-15-0; **7**, 88636-00-4; **8**, 109215-41-0; **9**, 78655-79-5; **11**, 564-04-5; **12**, 72507-50-7; (±)-**13**, 123075-33-2; (±)-**14**, 123075-34-3; **15**, 123075-44-5; **16** (coordinate entry), 123163-86-0; **16** (covalent entry), 87758-64-3; thiophenol, 108-98-5; 2,4,6-trimethylthiophenol, 1541-10-2; 2,4,6-triisopropylthiophenol, 22693-41-0; 2-naphthalenethiol, 91-60-1; 2-methyl-2-propanethiol, 5954-68-7; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; (2′*R*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-1′-oxo-3′-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone, 104758-28-3; (2′*S*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-1′-oxo-3′-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone, 77877-25-9; (2′*R*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-3′-(1″-naphthyl)-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone, 123075-42-3; (2′*S*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-3′-(1″-naphthyl)-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone, 123163-85-9; 1-naphthaldehyde, 66-77-3.

Supplementary Material Available: ^{1}H NMR spectra of oxazolidinone **3**, complex **15**, and enolate **16** (4 pages). Ordering information is given on any current masthead page.

The Cyclic Dipeptide *cyclo*[(*S*)-Phenylalanyl-(*S*)-histidyl] as a Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehydes

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cyclo[(*S*)-Phenylalanyl-(*S*)-histidyl] (*cyclo*[(*S*)-Phe-(*S*)-His], **1**) catalyzes the addition of hydrogen cyanide to benzaldehyde in toluene at −20 °C to afford (*R*)-mandelonitrile with enantiomeric excess of 97% in high yield. *cyclo*[(*R*)-Phenylalanyl-(*R*)-histidyl]gives (*S*)-mandelonitrile. *cyclo*[(*S*)-Phe-(*S*)-His] (**1**) exhibits a broad substrate specificity, and a variety of aldehydes (**3a-r**) such as *m*-methoxybenzaldehyde (**3c**), 6-methoxy-2-naphthaldehyde (**3k**), and isobutyraldehyde (**3o**) similarly afforded the corresponding cyanohydrins with high enantiopurities (97% ee for **3c**, 93% ee for **3k**, 71% ee for **3o**). (*R*)-Mandelonitrile thus obtained was successfully converted to various chiral synthons such as mandelic acid (**7**), methyl mandelate (**8**), and 2-amino-1-phenylethanol (**9**) without any racemization.

The function of synthetic poly- and oligopeptides has received much attention as models for proteins in biological systems. Since enzymes exhibit stereochemical recognition and catalyze various biochemical reactions with a remarkably high degree of efficiency and specificity under mild conditions, the generation of an enzyme-like function by using synthetically designed compounds[1] has been challenging problem. In contrast with recent developments in the use of enzymes as catalysts for enantioselective chemical reactions,[2] few studies have been reported concerning the use of synthetic peptides as catalysts in organic reactions.[3] On the other hand, the preparation of efficient catalysts for the synthesis of optically active compounds has become a widely explored area in contemporary synthetic organic chemistry.[4] Particularly, asymmetric syntheses involving reactions forming carbon–carbon bonds have been the subject of numerous studies[5] because carbon–carbon bond formation plays an essential role in the construction of complex organic molecules. Among these, the addition of the cyano group to carbonyl compounds to give cyanohydrins has been considered a useful reaction, not only to introduce a C_1 unit into organic molecules, but to convert the resulting product to other useful chiral synthons such as α-hydroxy carboxylic acids, α-hydroxy esters, and β-amino alcohols by simple transformations. In spite of much effort to realize asymmetric induction in the addition of hydrogen cyanide to carbonyl groups using alkaloids,[6] poly(L-iminoisobutylethylene),[7] and cyclodextrin[8] as chiral catalysts, the enantioselectivities have been disappointing. On the other hand, an enzyme (oxynitrilase, a flavoprotein isolated from seeds and blossoms of various *Prunaceae*)[9] was reported to catalyze the addition of hydrogen cyanide to benzaldehyde to give (*R*)-mandelonitrile exclusively.[10]

Our research has thus been focused on the design of catalysts for asymmetric cyanohydrin synthesis by using synthetic peptides as an alternative to oxynitrilase. Among various kinds of synthetic peptides, cyclic dipeptides possessing a rigid conformation[11] are considered to be

(1) Dugas, H.; Penney, C. *Bioorganic Chemistry*; Springer-Verlag: New York, 1981. Retey, J.; Robinson, J. A. *Stereospecificity in Organic Chemistry and Enzymology*; Verlag Chemie: Weinheim, 1982.
(2) For reviews, see: Sih, C. J.; Zhou, B.-n.; Gopalan, A. S.; Shieh, W.-R.; VanMiddlesworth, F. In *Selectivity—a Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Weinheim, 1983, pp 251. Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol 5; pp 309.
(3) Ueoka, R.; Matsumoto, Y.; Moss, R. A.; Swarup, S.; Harada, K.; Sugii, A.; Kikuchi, J.; Murakami, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1588. Colonna, S.; Molinari, H.; Banfi, S.; Julia, S.; Masana, J.; Alvarez, A. *Tetrahedron* **1983**, *39*, 1635. Inoue, S. *Adv. Polym. Sci.* **1976**, *21*, 77.
(4) For reviews, see: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol 5. *Asymmetric Catalysis*; Bosnich, B., Ed.; Martinus Nijhoff Publishers: Dordrecht, 1986.
(5) Evans, D. A. *Science* **1988**, *240*, 420.
(6) Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7. Prelog, V.; Wilhelm, M. *Helv. Chim. Acta* **1954**, *37*, 1634.
(7) Tsuboyama, S. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1004; **1965**, *38*, 354.
(8) Gountzos, H.; Jackson, W. R.; Harrington, K. J. *Aust. J. Chem.* **1986**, *39*, 1135.
(9) Rosenthaler, L. *Biochem. Z.* **1908**, *14*, 238. Becker, W.; Benthin, U.; Eschenhof, E.; Pfeil, E. *Biochem. Z.* **1963**, *337*, 156.
(10) Becker, W.; Freund, H.; Pfeil, E. *Angew. Chem.* **1965**, *77*, 1139; *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1079. Becker, W.; Pfeil, E. *Biochem. Z.* **1966**, *346*, 301. Becker, W.; Pfeil, E. *J. Am. Chem. Soc.* **1966**, *88*, 4299. Effenberger, F.; Ziegler, T.; Förster, S. *Angew. Chem.* **1987**, *99*, 491.

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