Chelation Control in Metal-Assisted Aldol Addition Reactions of α-Halogenated Imide Enolates Leading to Predominantly *Anti* Stereoselectivity. An Example of a Stereocontrolled Darzens Reaction

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The aldol reaction of enantiopure *N*-(haloacetyl)-2-oxazolidinone enolates with aromatic aldehydes was studied for conditions that would induce the reaction to yield predominantly *anti* adducts. It was found herein that the inherent steric and stereoelectronic properties of the aldehyde (R), as well as its chelative ability with the enolate countercation, are crucial in determining which of its enantiotopic faces reacts. Certain metallic enolates (Sn,[IV] Zn, and Li) are postulated to react through a three-point coordination transition state to yield mainly *anti* adducts, while others (Sn,[II] B, Ti) are shown to react *via* noncoordinated transition states to yield either *syn* or *anti* adducts. X-ray crystallography was instrumental in fully defining the absolute stereochemistry of each product, providing insight into the mechanisms of stereocontrol. The major *anti* producing pathway for reaction of aromatic aldehydes is postulated to proceed *via* boatlike or a high-energy "unfavored chair" transition state (TS). Finally, using our protocol of varying either the enolate countercation or the substitution pattern on the aromatic aldehyde, we demonstrate how one may synthesize three of the four possible stereoisomers available from this aldol-type reaction, the *syn* Li isomers **7** being the only inaccessible isomer as a *major* product in this α-halo-2-oxazolidinone system. The *anti* halohydrins were converted stereospecifically to the *trans* epoxy esters or epoxy amides in high enantiomeric purity.

Introduction

The first step of the Darzens reaction is essentially an α-halogenated ester variation of the venerable aldol addition, of which much is already known.[2] However, synthesis methods designed to yield enantiomerically enriched Darzens-type addition products, prior to our earlier reports,[3] were highly inefficient, yielding halohydrin adducts of very low enantiomeric excesses (ee).[4,5] Our initial work was the result of a concept to prepare enantiomerically pure α,β-epoxy esters through modification of the Darzens reaction, wherein the starting α-halo ester was replaced with the enantiopure *N*-(haloacetyl)-(4*S*)-4-(methylethyl)-2-oxazolidinone (**1a**). Several factors led us to explore the use of this 2-oxazolidinone ring system as a chiral auxiliary. First, this heterocyclic ring system has received much application in asymmetric organic synthesis since Evans and co-workers introduced it as the chiral auxiliary of choice in a highly selective boron-mediated asymmetric aldol reaction.[2a,6] Secondly, the 2-oxazolidinone moiety is highly versatile in that the resulting products are readily converted into esters,[6,7] acids,[7b,d,e] amides[8,9a] (*vide infra*), alcohols,[9b] or diols.[9a] Thirdly, the 2-oxazolidinone ring system is readily available in both enantiomeric forms from the parent amino acids, allowing for synthesis of both antipodal adducts. We were able to optimize the synthesis of the parent (4*R*)- or (4*S*)-4-(substituted)-2-oxazolidinone **1** so that it is obtainable in kilogram quantities in *one pot* from the relatively inexpensive parent amino acids using our recently reported procedure.[10]

In our earlier reports,[3] we utilized several metallic *N*-(haloacetyl)-2-oxazolidinone enolates in reaction with *aliphatic aldehydes* and detailed how one may exert total stereochemical control in forming the *syn* halohydrins. In that study we showed how a chelative countercation of that enolate reverses the reacting face of the enolate when

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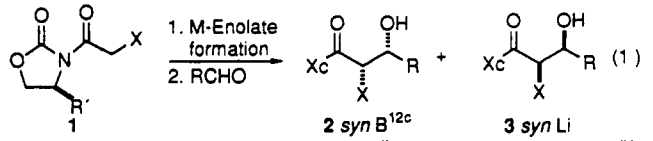
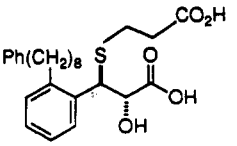
compared to the results obtained from a nonchelative counterpart. The adducts formed are epimeric at the newly formed stereogenic centers as represented by 2 and 3 (eq 1). Therefore, we were able to obtain both diastereomers in high diastereoselectivity by simply changing the countercation of the enolate. The *syn* bromohydrins adduct 2 and 3 were easily converted under mild conditions to *cis* epoxy ester in greater than 99% ee. Such esters were of interest in this laboratory, not only for their overall potential in synthesis as enantiomerically enriched alcohol precursors but also as intermediates in the synthesis of certain pharmacologically active leukotriene antagonists currently undergoing clinical study for the treatment of asthma.[11]



R = Alkyl
Xc = Chiral Auxilary
1a, R' = ^{i}Pr, X = Cl
1b, R' = ^{i}Pr, X = Br
1c, R' = ^{i}Pr, X = F
1d, R' = Ph, X = Br

In a continuing effort to understand all the subtleties that control the aldol transition states, other laboratories have noted the importance and the influence of the many factors that can affect the stereochemical outcome of the aldol reaction. On the basis of our results, as well as those of others,[2a,b,6,44,45] steric bulk of the aldehyde,[2a,b] aromaticity,[51] Lewis basicity, as well as substitution pattern of the aldehyde,[12,15,16] solvent,[2a,b,13,16,31,42,44a] ligands on the metal countercation,[2a,b,3,31,43,52] tertiary amine base used to generate the enolate,[2,9,14-16] reactant stoichiometry,[16] additive salts,[2,17] and possibly secondary molecular orbital interactions[18] are all representative to some extent of the factors that govern the energetics of the aldol transition states. In this work, our aim was to further investigate the role of the metal countercation of the *N*-(haloacetyl)-2-oxazolidinone enolates in reaction with *aromatic aldehydes*. Further, it was our intent to develop conditions that would allow access to predominantly *anti* halohydrin products. Such conditions would serve in a complementary capacity to our previously reported work (*vide supra*) where mainly *syn* halohydrins were formed with aliphatic aldehydes. Finally, we sought a facile commercially viable enantiomeric synthesis of the leukotriene D_4 antagonist (2*S*,3*R*)-β-[(3-carboxyethyl)thio]-2-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid (SK&F 104353) (4) using the chiral Darzens reaction[3b] to prepare the prerequisite enantiomerically enriched *trans* epoxy ester. A preliminary account from this laboratory has disclosed some of our initial results toward that end.[12a,b]



4 (SK&F 104353)

Experimental Methods

Enolate Generation. The lithium enolates were generated at −73 °C in dry THF using lithium diisopropylamide (LDA). Freshly generated LDA was the most effective amide base. Magnesium diisopropylamide (MDA), potassium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, and lithium cyclohexylisopropylamide all gave either reduced yields and/or low selectivities. For larger scale reactions (>1 mol) commercial LDA stabilized with 5% MDA available from "Lithco" gave satisfactory results. The other metallic enolates (Zn, Sn^{IV}, and Sn^{II}) were generated using LDA at −73 °C followed by the appropriate transmetalating agent, zinc chloride, tributyltin chloride, or stannous triflate [$Sn(OTf)_2$],[40] respectively, at −50 to −40 °C. Temperature control is crucial when generating the enolate through transmetalation. At temperatures much higher than −40 °C, a nonselective mix of products was obtained, as well as lower overall yields. At temperatures below −60 °C, transmetalation did not occur, and the stereochemical result was the same as when using only lithium. However, when the stannous-mediated reactions were run according to the warmer conditions (−23 °C) of Mukiayama,[41] the enolate still reacted very efficiently. Other stannous salts [*e.g.*, $Sn(OAc)_2$, $SnCl_2$, and $SnBr_2$], were not nearly as effective as $Sn(OTf)_2$. Boron enolates were generated at −23 °C in CH_2Cl_2 using either 1 M dibutylboron triflate (Bu_2BOTf) in CH_2Cl_2 or *in situ* generated diethylboron triflate (Et_2BOTf).[42] Dicyclohexylboron and 9-BBN triflates, contrary to their success in enolizing ketones, were ineffective in our system.[43] $ZnCl_2$ solution in ether was prepared by the procedure of House *et al.*[39] Titanium enolates were prepared using the recently reported procedures of Thornton[44e] and Evans.[46]

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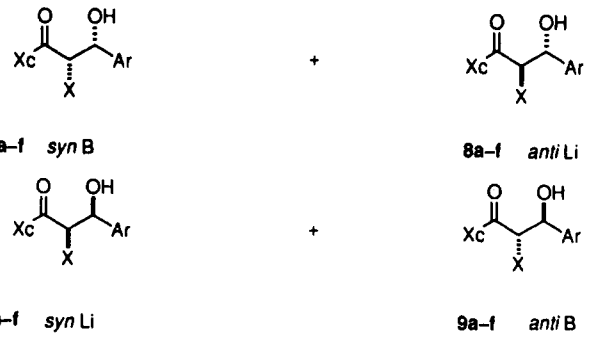
Our previous results,[3b] as well as recent results of others since that initial report,[44d,47,57,58] suggest that under these experimental conditions *the aldol reaction occurs via the Z enolate of N-acyl-2-oxazolidinones.*

Results and Discussion

Over the years, of all the transition states proposed for nucleophilic addition to carbonyls,[19-21] the pericyclic Zimmerman–Traxler model has been most popular and widely applied.[21] This is due primarily to its success as the best available predictive tool for aldol stereoselectivity, particularly when applied to examples where chelating countercations are involved in the addition of enolates (*e.g.*, lithium, magnesium, zinc, and stannyl)[2,3] to aldehydes.

Under kinetically controlled conditions, this model correlates the enolate geometry, *Z* and *E*, to the aldol stereochemistry, *syn* and *anti*, respectively.[2] The model, however, does not explain the enhanced stereoselectivity of the *Z* enolates over the *E* enolates.[2b] Also, exceptions were observed from zirconium,[22] titanium,[23] tin,[24] and dialkyloxyboron[25] enolates which produce *syn* aldols irrespective of the enolate geometry. The reversal in selectivity (*i.e.*, *syn* from *E* enolates or *anti* from *Z* enolates) has been tentatively explained by using boatlike transition states[2,22,23] and by the possibility of enolate isomerization.[23c] There is mounting evidence to suggest that the energy differences between a chair transition state as represented by the Zimmerman–Traxler model and a boat (or a twist-boat) transition state, which leads to a reversed aldehyde enantiofacial selectivity, are so small as to make minor reaction variables very crucial in determining the final product stereochemistry. In fact, in several reports, the twist-boat transition state was found to be of lower energy than that of the chair.[32a-36] Conceivably, the boat transition-state pathway under certain stereochemical environmental conditions could be the energetically favored pathway in many aldol reactions.

Scheme I



Compounds 6–9(a-f)

a, Ar = Ph; X = Cl; Xc = (4*S*)-4-(1-methylethyl)-2-oxazolidinone (**20**)
b, Ar = Ph; X = Br; Xc = **20**
c, Ar = Ph; X = F; Xc = **20**
d, Ar = *o*-(8-Phenyloctyl)phenyl; X = Br; Xc = (4*S*)-4-phenyl-2-oxazolidinone (**21**).
e, Ar = *o*-(8-Phenyloctyl)phenyl; X = Br; X_c = **20**
f, Ar = Ph; X = Br; Xc = **21**

Scheme I and Table I show the results of our aldol reactions using aromatic aldehydes with six different metal enolates of **1**. These results represent our best conditions after careful study. Any variation in stoichiometry or the presence of additional Lewis acid salts resulted in decreased yields and/or diminished selectivity.

We obtained predominantly *anti* isomers in good stereoselectivity in all cases where a chelating metal (Li, Zn or Sn^{IV}) was employed as the enolate countercation, *e.g.*, at least a 67:33 ratio of *anti*/*syn* aldol isomers was obtained from reaction of Zn enolates of **1a** and **1b** with benzaldehyde (Table I, entries 3 and 9). The *anti* Li **8** isomers (Scheme I) were the major products in all of these reactions (Table I, entries 1–3, 7–9, 13–15, and 19–21). On employing the very sterically encumbered 2-(8-phenyloctyl)benzaldehyde (**16**) in the aldol reaction with these chelating metal enolates, we again obtained the *anti* Li **8e** isomer but in much higher selectivity with Li and Sn^{IV} enolates (Table I, entries 19 and 20) than with Zn enolate (Table I, entry 21).

The aldol reaction of nonchelating metal enolates (B, Ti, and Sn^{II}) with benzaldehyde gave predominantly *syn* aldols with *syn* B **6a–c** isomers being the major products of these reactions. For reasons we do not fully understand, $(Bu)_2BOTf$ was not effective in the reactions of enolates **1a** and **1b** with benzaldehyde; however, it promoted their reaction with the bulky aldehyde (8-phenyloctyl)benzaldehyde (**16**) affording *syn* B in a ~98:2 ratio of diaste-

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Table I. Aldol Reaction of Metal Enolates 5 with Aromatic Aldehydes

entry	Xc	Ar	X	M	diastereoselection[a] *syn*:*anti* (6 + 7):(8 + 9)	Enantioselection *syn* 6:7	Enantioselection *anti* 8:9	yield[b] (%)
1	20	Ph	Br	Li	25:75	18:7	70:5	61
2	20	Ph	Br	Sn^{IV}	21:79	9:12	76:3	77
3	20	Ph	Br	Zn	33:67	15:18	66:1	73
4	20	Ph	Br	Sn^{II}	85:15	79:6	6:9	67
5	20	Ph	Br	B[c]	98:2	98:0	2:0	63
6	20	Ph	Br	Ti	80:20[f] (82:18)[h]	68:12 (73:09)	10:10 (09:09)	62 (59)
7	20	Ph	Cl	Li	24:76	17:7	70:6	70
8	20	Ph	Cl	Sn^{IV}	22:78	15:7	78:0	73
9	20	Ph	Cl	Zn	33:67	19:14	67:0	67
10	20	Ph	Cl	Sn^{II}	96:4	92:4	4:0	56
11	20	Ph	Cl	B[c]	>99:0	>99:0	0:0	68
12	20	Ph	Cl	Ti	92:08[f] (83:17)[h]	82:10 (76:07)	8:0 (10:07)	59 (70)
13	20	Ph	F	Li	24:76	16:08	76:0	55
14	20	Ph	F	Sn^{IV}	0:>99	0:0	94:5	50
15	20	Ph	F	Zn	18:82	12:06	70:12	60
16	20	Ph	F	Sn^{II}	72:28	66:06	4:24	91
17	20	Ph	F	B[c]	71:29	65:06	15:14	60
18	20	Ph	F	Ti	90:10[g]	81:09	4:06	75
19	20	Ar[d]	Br	Li	13:87	5:8	79:8	65
20	20	Ar[d]	Br	Sn^{IV}	9:91	0:9	82:9	78
21	20	Ar[d]	Br	Zn	33:67	4:9	54:33	76
22	20(21)[e]	Ar[d]	Br	Sn^{II}	27:73 (5:95)[e]	6:21 (0:5)	0:73 (0:95)	67 (79)
23	20[e]	Ar[d]	Br	B	98:2	93:5	2:0	60
24	20[e]	Ar[d]	Br	Ti	100:0[f]	10:90		~20

[a] Isomer ratios were determined by GLC and 400 MHz ^1H NMR spectroscopy. The normal elution order on a DB-1 capillary column for the benzaldehyde adducts after treatment with "Tri-Sil" is: 9:6:7:8. [b] Isolated chromatographed yields. [c] Only diethylboron triflate prepared *in situ*[42] in CH_2Cl_2 was effective with benzaldehyde. Dibutyl and diethylboron triflates were effective with *o*-(8-phenyloctyl)benzaldehyde (16). [d] Ar refers to a *o*-(8-phenyloctyl)benzaldehyde (16) derived substituent. [e] Data in parentheses represent results from the phenylglycine-derived chiral auxillary **1d**. [f] The titanium enolate generating conditions of Evans[46b] were employed. [g] The titanium enolate generating conditions of Thornton in Et_2O were used.[44e] [h] The Thornton conditions[44e] in THF were used.

reoisomers (Table I, entry 23). Diethylboron triflate,[42] on the other hand, was effective with both aldehydes. *Generally, the nonchelating boryl enolates in all our examples yielded predominantly syn products; moreover, it was usually the most selective.* Evidently, the short boron–oxygen bond (1.36–1.47 Å versus 1.62–2.16 Å for the other metals studied) most probably accounts for its high selectivity. Replacement of the ligands on boron with groups larger than butyl had a deleterious effect on the reaction,[43] leading to very little reaction.

The titanium enolates of **1** reacted with aromatic aldehydes (Table I, entries 6, 12, 18, and 24) with a similar sense of stereocontrol to boron enolates and gave mainly *syn* B **6** aldol products. Products similar to *syn*-B **6** have been previously reported from Ti enolates.[46b] However, reaction of the Ti enolate of the (nonhalogenated) *N*-propionyl-2-oxazolidinone (**22**) with benzaldehyde yielded the *syn* Li **7** adduct (normally obtained from chelative metals) as a predominant product.[50] This latter result is in agreement with data reported by Thornton.[44,45]

The reactions of Sn^{II} enolates of **1a–c** with benzaldehyde (Table I, entries 4, 10, and 16) were similar to those of B and Ti enolates and yielded the expected *syn* B **6** isomers as major products. Surprisingly, and unlike boron or titanium enolates, the reaction of Sn^{II} enolate of **1a** with aldehyde **16** (Table I, entry 22) yielded the *anti* B **9e** isomer as the major aldol product. This reversal in selectivity toward the formation of **9** was substantially enhanced from a ratio of 73% to 95% in the product mixture ($\Delta\Delta G$ = 1.15 kcal/mol) by changing from the valinol-based chiral auxiliary **20** to the apparently more sterically demanding phenylglycine-derived auxiliary **21** (Scheme I). The minor *syn* product (~21%) from this reaction was the unexpected *syn* Li **7** isomer, the product of chelation control.

In all of the examples with aromatic aldehydes where *anti* isomers were formed (Table I, entries 1–3, 7–9, 13–15, and 19–21), only the configuration at the β-carbon had changed relative to the correspondingly expected *syn* isomers from aliphatic aldehydes. *Thus, epimerization during the reaction at the α-carbon or reactions involving the E enolates may be ruled out.* This was further confirmed in a related experiment wherein we reacted the lithium enolate of **1b** with a 1:1 molar mix of **16** and isobutyraldehyde. The reaction gave *only syn* aldol isomers from isobutyraldehyde but afforded a 1:1 mix of *syn* and *anti* aldol isomers from **16**. The *anti* isomers,

(42) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Org. Chem.* **1986**, *108*, 4675.

(43) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

(44) (a) Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897. (b) Siegel, C.; Thornton, E. R. *Ibid.* **1986**, *27*, 457. (c) Shirodkar, S.; Nerz-Stormes, M.; Thornton, E. R. *Ibid.* **1990**, *31*, 4699. (d) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. (e) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.

(45) For other examples of stereoselective aldol reactions *via* titanium enolates see: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Reetz, M. T.; Hullmann, M.; Seitz, T. *Ibid.* **1987**, *26*, 477. (c) Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037. (d) Panek, J. S.; Bula, O. A. *Ibid.* **1988**, *29*, 1661. (e) Gennari, C.; Molinari, F.; PierGiorgio, C.; Oliva, A. *Ibid.* **1989**, *30*, 5163.

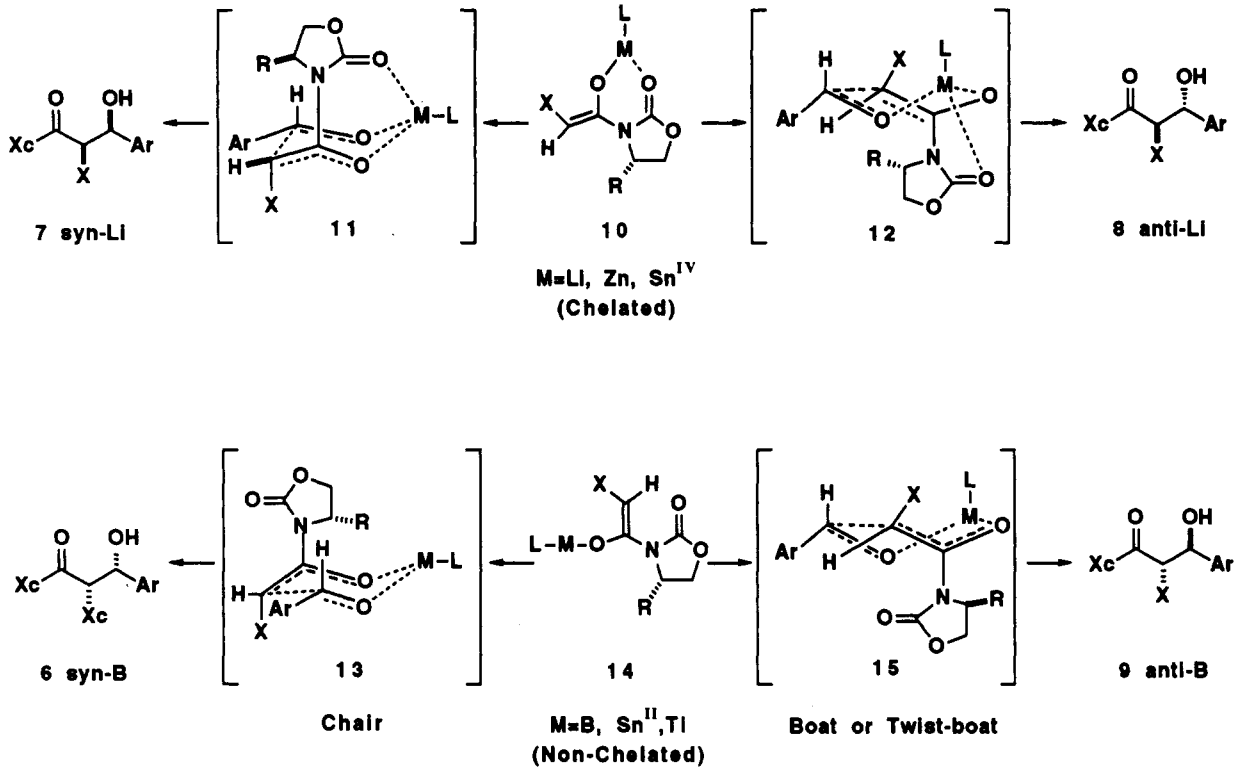
(46) (a) Evans, D. A.; Urpí, F.; Somers, J.; Clark, S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (b) Evans, D. A.; Reiger, D. L.; Bilodeau, M. T.; Urpi, F. *Ibid.* **1991**, *113*, 1047.

(47) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39.

(48) "Tri-Sil" is commercially available from Pierce Chemical Co.

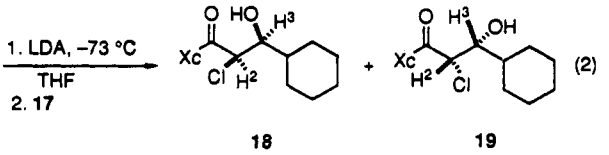
(49) The diethylboryl enolate was the only boryl enolate successful in reaction with benzaldehyde. Dibutylboron triflate, freshly prepared or purchased as a 1 M CH_2Cl_2 solution from Aldrich Chemical Co., was equally successful in reactions against other substituted aromatic aldehydes.

Scheme II



therefore, most probably resulted by reversal of the aromatic aldehyde enantiofacial selectivity.

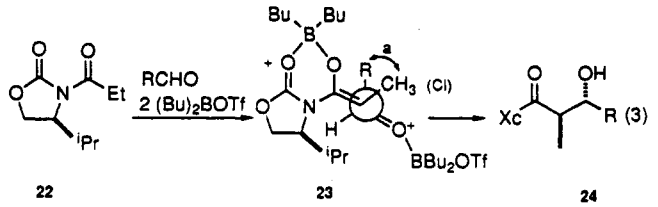
We addressed the possibility that the principal reasons for the aldol addition to yield *anti* products with aromatic aldehydes were sterically based. However, upon reaction of cyclohexanecarboxaldehyde (17), a more sterically demanding aldehyde relative to benzaldehyde, with the lithium enolate of **1a**, we obtained an 80:20 *syn/anti* ratio of aldol products (eq 2). The two major *syn* isomers (18



and 19) were readily separated by flash column chromatography, and in addition to establishing their structures by ^{1}H NMR, the stereochemistry of the crystalline isomer **19** was verified by X-ray crystallography. This result indicates that certain electronic factors are most likely involved in causing the aromatic aldehydes to react through a different pathway.

The use of the *N*-(haloacetyl)-2-oxazolidinone model in this study gives us a unique capability to evaluate the stereochemical outcome of the aldol reaction when we vary the aldehyde steric requirement, the electronic properties of the aldehyde substituent, and the chelating ability of the enolate countercation. In our previous study,[3] we showed that the use of strongly coordinating enolate countercation (*e.g.*, Li, Zn, and Sn^{IV}) in aldol reactions with aliphatic aldehydes resulted in mainly *syn* Li adducts **7**. This result could be explained by the three-point chelated chair transition state (TS) **11** or a synclinal orientation.[31] The reaction had a strong propensity to react *via* the TS **13** when a noncoordinating cation (*e.g.*, B or Sn^{II}) was used and yielded the *syn* B **6** adducts as the predominant products. In order to account for the formation of *anti* adducts from the *Z* enolates, in the present study, we additionally propose the twist-boat transition states (TS) **12** and **15** shown in Scheme II to explain all the observed experimental results with *the understanding that the Z enolates (and not the E) are the principal reactants.* The reaction must occur through the twist-boat TS **12** in the presence of strongly coordinating cations (*chelation control*) and through the twist-boat TS **15** in their absence (*nonchelation control*). In further support of this transition state, unlike the aliphatic series,[3] there is very little discernible difference in diastereoselectivity between the (bromoacetyl)- and the (chloroacetyl)-2-oxazolidinones as predicted by twist-boat TS models.[2b]

The open transition state **23** (eq 3) was proposed by Heathcock[16] in the reaction of the boryl enolate of **22** with aldehydes in presence of excess Bu_2BOTf to account for *anti* selectivity. The excess Bu_2BOTf acted as a Lewis



acid,[50] and the resulting reactive complex **23** has the aldehyde reacting *via* its *si* face. The reaction produced

(50) Since that initial report Heathcock has shown that other Lewis acids will effect the same result, see: Walker, M. A.; Heathcock, H. C. *J. Org. Chem.* **1991**, *56*, 5747.

(51) (a) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3333. (b) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184. (c) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(52) (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (b) Paterson, I.; Lister, M. A. *Ibid.* **1988**, *29*, 585.

one *anti* isomer **24** that corresponds to our *anti*-Li **8** adduct which we proposed to form *via* the chelated twist-boat TS **12**. We were successful in reproducing this result using **22**; however, we obtained essentially a nonselective reaction when we used our halogenated analog **1a** with benzaldehyde and excess Bu_2BOTf. We suggest that, under these conditions, the halogen–Ar interaction a in the open TS **23** could be energetically comparable to Ar–Xc interactions present in both of the other alternative conformations. Therefore, a nonselective reaction is to be expected. Interestingly, increasing the size of the Ar group by employing **16** in the aldol reaction with **1a** under the above mentioned conditions gave the *syn*-B **6e** product (expected from the nonchelation control TS **13**) in >95% isomeric ratio, not the *anti*-Li isomer **8e** expected from an open TS similar to **23**. *Therefore, since we* obtain *anti-Li 8 adducts only under chelating conditions and syn-B* **6** *adducts under nonchelating conditions from reactions of enolates* **5** *with benzaldehyde, and since we observe such a strong dependence of the product ratios on the enolate countercation, we suggest that the role of the open TS is minimal.*

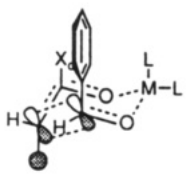
Arguments against significant participation of an open transition state, the equilibration of *Z* to *E* enolates, and the epimerization at the α-carbon have been presented above. The cyclic three-point chelation twist-boat TS **12** is now the most likely and most predictable one to explain the formation of *anti* aldol products from reactions of chelating metal enolates (Li, Zn, and Sn^{IV}) of **1** with aromatic aldehydes. Apparently, the energy that is normally gained in the three-point chelation chair TS **11** is not sufficient to offset the increased electronic and/or steric interactions of the aromatic moiety with the α-halo enolates.

Formation of predominantly *anti* adducts from the (chelating) lithium enolate of **22** and benzaldehyde was observed by Evans[6b] and latter by Thornton[44] who proposed a chelated twist-boat TS similar to **12** as the origin of the *anti* stereoselectivity. A repulsive methyl–ligand interaction was suggested to be the principal driving force for adopting such a conformation. Possibly, one could postulate that the primary interaction that forces the reaction to proceed through a twist-boat TS could be the negative (repulsive) interaction between the aromatic ring on the aldehyde and the n electrons of the α-halogen. But since we have just established that the repulsion is not sterically originated, such an interaction would also have to explain obtaining mainly *anti* adducts, in certain cases, for the propionyl analog,[6b,44] where now the α-halogen has been replaced with a methyl group. Alternatively, a favorable interaction between the HOMO of the delocalized anionic *N*-(haloacetyl)-2-oxazolidinone enolate system and the LUMO of the aromatic aldehyde could be responsible, but further molecular modeling studies will be required to support that contention. Enders[45e,54a], Gennari,[54b] Widdowson,[54c] and Kuwajima[23] have likewise reported the reversal of stereochemistry in aldol additions with benzaldehyde as compared to results with aliphatic aldehydes.[53] The latter three authors have invoked the use of the boat transition state to rationalize their observations. In any event, an axial orientation of the aromatic ring would allow for most favored stereoelectronic effects (σ* and/or π* orbital energies) and is most probably accommodated in twist-boat or skewered transition-state models.[2b,34a]

Table II. Aldol Addition of the Stannous Enolate of 1d with Substituted Benzaldehydes[a]

entry	compd no.	R	yield (%)	*syn* B	*syn* Li	*anti* Li	*anti* B
1	**35**	*o*-phenyl	46	11[d]	17[d]		72[e]
2	**36**	*o*-bromo	28			05[b]	95[b]
3	**37**	*o*-butyl	64	06[e]	15		79
4	**38**	*o*-(*tert*-butyl)	58				100
5	**39**	*o*-methoxy	60		21[d]	*c*	79
6	**40**	*o*-nitro	44			*c*	100
7	**41**	*p*-phenyl	10	52	17	*c*	31[b]
8	**42**	*p*-bromo	35	53[b]	16	*c*	31[d]
9	**43**	*p*-butyl	55	58[d]	15[d]		37
10	**44**	*p*-(*tert*-butyl)	66	55	11[d]	*c*	34
11	**45**	*p*-methoxy	65	55[d]	07		38
12	**46**	*p*-nitro	45	53[d]	12		35

[a] Isomer assignments were made employing a combination of ^1H, ^{13}C NMR and X-ray analyses. [b] X-ray crystallography was used to make these structural assignments. [c] Isolated as a minor component from other metal mediated reactions and fully characterized. [d] These isomers were not isolated. [e] $^1H/^{13}C$ NMR correlation experiments were done to verify assignments.



"Unfavored Chair" A

The nonchelating chair TS **13** remains favored in the presence of a nonchelating metals (B, Sn^{II}, or Ti) with both aliphatic and aromatic aldehydes.[2b] Only with the sterically demanding aromatic aldehyde **16** did Sn^{II} enolates react to give an *anti* aldol adduct (*anti* B **9** in a 27:73 or 5:95 ratio; Table I, entry 22). In an attempt to determine to what extent was the product stereochemistry dependent on the steric and/or the electronic properties of the aromatic ring of the aldehyde in reactions with Sn^{II} enolates, we synthesized several aldol adducts using the standard stannous triflate conditions[3,61] (Scheme V and Table II). We did not observe any meaningful substituent correlation; *e.g.*, *p*-nitrobenzaldehyde (Table II, entry 12) gave a very similar isomeric ratio to that of *p*-methoxybenzaldehyde (Table II, entry 11). The most significant

(53) For an interesting and appropriate example where *aliphatic and aromatic* aldehydes react through boatlike transition states to yield *anti-selective* aldol adducts in a silicon directed aldol reaction see: Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672.

(54) (a) Enders, D.; Lohray, B. B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 581. (b) Gennari, C.; Oliva, A.; Molinari, F.; Piarulli, U. *Tetrahedron Lett.* **1990**, *31*, 2453. (c) For an example with a zinc enolate see: Widdowson, D. A.; Wiebecke, G. H.; Williams, D. J. *Ibid.* **1982**, *23*, 4285.

(55) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1967.

(56) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.

(57) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767.

(58) For other recent studies of Sn^{IV} chelates and their use in asymmetric synthesis see: (a) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197. (b) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881.

(59) ORTEP representations, tables of crystallographic data, and fractional atomic coordinates for all of the structures are presented in the supplementary material.

(60) For an example of a combination of stereoselective manipulation of the *E*/*Z* geometry and varying the countercation to yield all four of the stereoisomers see: Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.

(61) For a similar aldol study using cyclohexanone lithium enolate see: Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681.

(62) For an example of an *anti* selective aldol reaction with aromatic aldehydes in the solid state see Wei, Y.; Bakthavachalam, R. *Tetrahedron Lett.* **1991**, *32*, 1535.

finding was the fact that *the presence of an ortho substituent significantly altered the stereochemical outcome of the reaction so as to favor the anti B isomer* **9** *to as high as 100%, whereas the para-substituted benzaldehydes were essentially nonselective* (compare entries 1–6 with 7–12, Table II). This pattern invariably held up through all the aromatic substrates employed. We attribute this shift in stereochemistry for Sn^{II} enolates to increased unfavorable steric interactions from ortho-substituted benzaldehydes in the chair TS **13**, which allows the twist-boat TS **15** to become more thermodynamically favored and to compete effectively with TS **13** to give the *anti* B **9** aldol products.

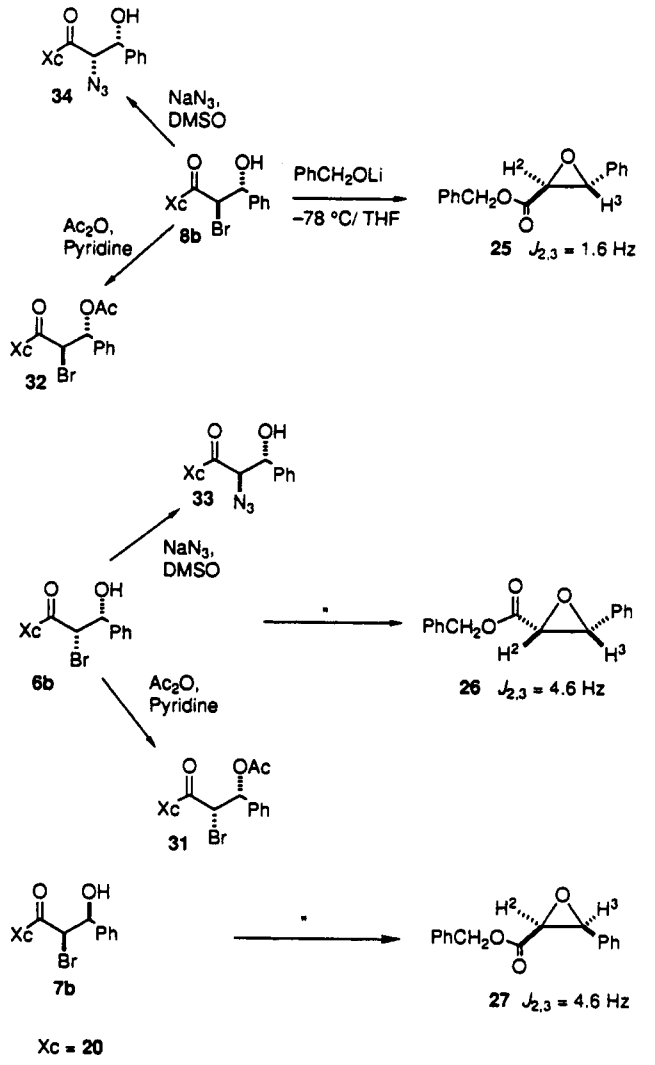
A plausible explanation as to why Ti, a normally highly complexing metal, should behave as a nonchelative one in our examples (Table I, entries 6, 12, 18, and 24) and in certain others[46b,50,60] may be a result of a combination of the shorter Ti–O bond (1.62 *vs* ~2.0 Å for Li, Zn, and Sn^{IV}) and the steric and/or electronic contributions from the α-halo atoms. Such factors would render the three-point chelation chair TS **11** less energetically favored when compared to the nonchelated TS **13**. The formation of predominantly *syn* products is in line with Duthaler's observation that titanium enolates without cyclopentadienyl ligands lead to *syn* aldol products.[23c] Further, he suggested a boat or a twist-boat orientation in the TS to explain the formation of *syn* aldols from *E* enolates and *anti* aldols from *Z* enolates, although a definitive explanation awaits unambiguous structural determinations of the titanium enolates involved.[23d,e]

Lastly, we sought to determine if the presence of an isolated double bond, as compared to fully aromaticity, would be sufficient to induce similar *anti* selectivity. To this end we reacted crotonaldehyde with the lithium enolate of **1a** in THF and obtained a 39/16/18/27 ratio of isomers, **9**:6:7:8 (Scheme I, Xc = **20**; Ar = 1-propenyl), a total of 66/34 *anti*/*syn* ratio. A similar result was obtained from acrolein. The isomer assignments were determined based on the standard proton coupling procedure. Thus, the higher proportion of *anti* aldol products obtained from aromatic or olefinic aldehydes when compared to the *syn* aldol selectivity from aliphatic aldehydes[3b] adds further credence to aldehydic π-orbital/enolate HOMO/LUMO electrostatic interaction in the transition state. A firmer explanation still awaits further study.

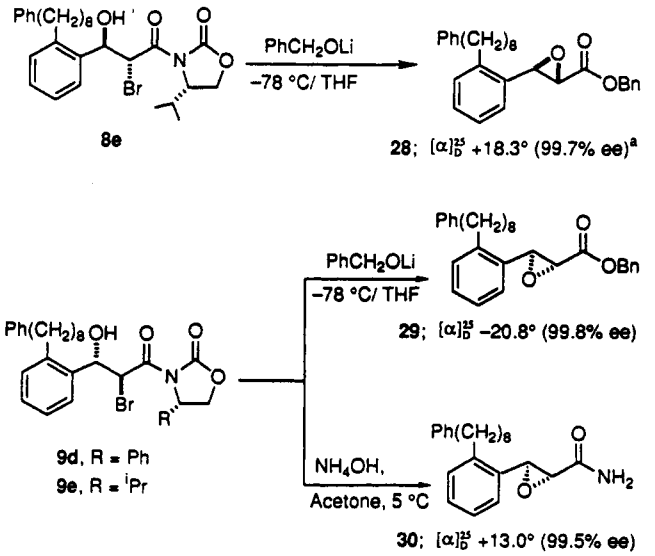
Stereochemical Assignments

Stereochemical assignments of the aldol addition products were established by X-ray crystallographic data and/or conversion of the *syn* or *anti* halohydrin adducts to their respective *cis* or *trans* epoxides as before[3b] where epimerization was demonstrated not to occur under the reaction conditions. These diastereomeric epoxides were usually readily distinguishable by ^1H NMR (Schemes III and IV). X-ray crystallographic data were obtained for compounds **7a**, **8a**, **8b**, **6c**, **8c**, **7f**, **9f**, **36**-*anti* Li, **36**-*anti* B, **41**-*anti* B, and **42**-*syn* B, so these structures are definitive.[59] Epoxide amide **30** (Scheme IV), which was easily obtained by reacting bromohydrin **9d** or **9e** with ammonium hydroxide in acetone at 5 °C, was converted to SK & F 104353 (**4**) of known configuration.[11] Chiral HPLC showed a 99.5% ee (see the Experimental Section for conditions). For the halohydrin adducts, the vicinal proton coupling constants ($J_{2',3'}$) for the two protons of

Scheme III



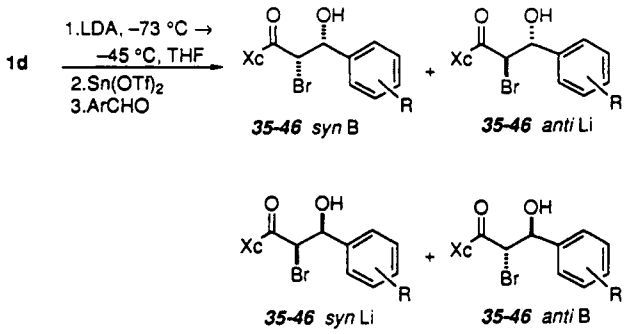
Scheme IV[a]



[a] Enantiomeric excesses were determined on a chiral HPLC column.

the two newly created stereogenic centers are normally expected to be within the 2–6 Hz and 7–10 Hz range for *syn* and *anti*, respectively.[2b] *However, smaller vicinal coupling constants were not observed for the syn addition*

Scheme V



products between aromatic aldehydes and (bromoacetyl)- and (chloroacetyl)-2-oxazolidinone enolates. For example, *syn* B isomers **6e** with a $J_{2',3'}$ value of 8.60 Hz (see the Experimental Section) fell within the 7–10 Hz range expected for *anti* isomers. Thus, ^{1}H NMR alone could not be relied on as a definitive analytical tool in establishing relative stereochemistry in this conformationally mobile system. The increased vicinal couplings for the *syn* isomer as well as the decreased couplings for the *anti* isomer appear to result from the three largest groups vying for energetically favored dispositions.[55] X-ray crystallographic data of crystalline *syn* compounds shows that *both* a transoid and a (−) gauche orientation between the chiral auxiliary and the aromatic moiety may be adopted. In contrast, structures of *anti* products (see Figure 1 which displays the structures of **36** *anti* B and **36** *anti* Li) reveal the aromatic ring and the chiral auxiliary in a transoid orientation in all examples. The latter would normally result in large $J_{2',3'}$ couplings. However, competition in solution with rotamers containing smaller $J_{2',3'}$ couplings should temper the size of the NMR time-averaged coupling.

A low dilution infrared study (1.9×10^{-4} M in methylene chloride) of **7a** and **8a** found no evidence of intramolecular hydrogen bonding between the β-hydroxy group and the chiral auxiliary carbonyl, although very significant intermolecular bonding is present. Such an interaction would also have an affect on rotameric distribution. To further demonstrate that intramolecular hydrogen bonding plays a minimal role in establishing conformational equilibrium in this work, acetylation of **6b** and **8b** to yield their acetoxy derivatives **31** and **32** did not diminish the large vicinal coupling constant ($J_{2',3'}$ = 9.30 Hz) observed for the *syn* isomer **31**. This compares to $J_{2',3'}$ = 10.39 Hz for the *anti* isomer **32**. Thus, our primary alternative for establishing the relative stereochemistry was conversion of the bromohydrin adducts to their respective epoxides followed by ^{1}H NMR analysis. This was invariably consistent but time consuming. Finally, X-ray crystallography proved to be the most definitive tool for this purpose; its only disadvantage stems from the need for crystalline materials. Fortuitously, in compiling this report, we noted a consistent solvent-independent downfield ^{13}C NMR shift of about 4–5 ppm (Δ ppm = δ *syn* − δ *anti*) exhibited by the α-bromomethine carbon of the *syn* isomers. Acetylating the hydroxyl (compounds **31** and **32**) or replacement of the bromine with chlorine (**6a–9a**), fluorine (**6c–9c**), or azide substituents (compounds **33** and **34**) diminished but did not eliminate this chemical shift difference between the *syn* and *anti* isomers (see the Experimental Section and supplementary material), although in the latter two examples ^{1}H NMR coupling constant data were diagnostic enough for establishing the *syn*/*anti* relationship (4.8–2.3 and 8.5–7.4 Hz, respectively). We speculate that the origin

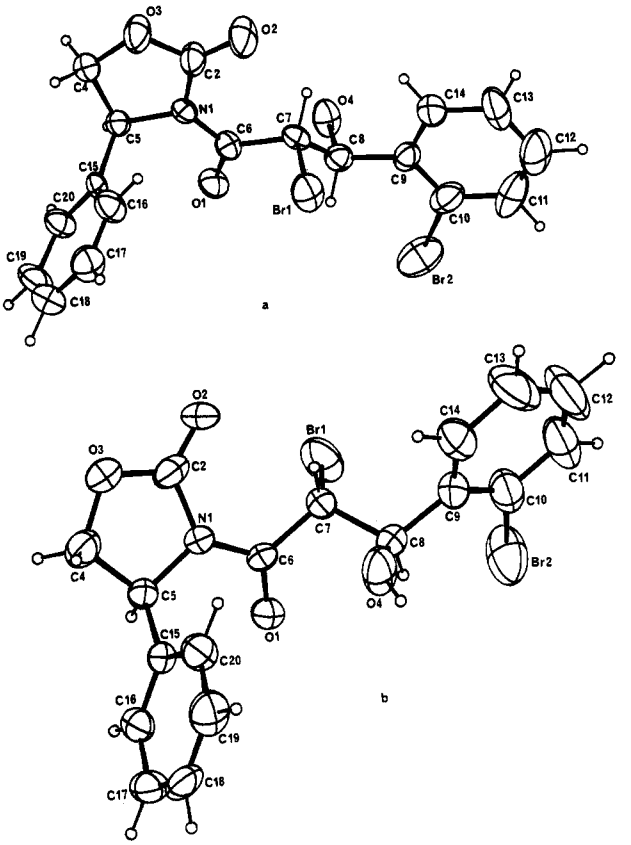


Figure 1. ORTEP drawing of (a) **36** *anti* B and (b) **36** *anti* Li structures with principal ellipses drawn at the 50% probability level. Hydrogen atoms are shown as small spheres of arbitrary size.

of the observed ^{13}C chemical shift difference is stereochemically related to differing halogen–carbonyl (n–σ*) orbital interactions which influence shielding at the α-carbon. The same α-carbon in a related Heathcock study,[63] with a methyl group at this position, *did not* exhibit a consistently different *syn*/*anti* absorption pattern. A more detailed discussion of our ^{13}C NMR results, complete with a tabular listing of all the data, will be forthcoming.

Summary

In summary, the reaction of a chiral enolate with an aldehyde can produce four diastereomeric aldols. The stereochemical outcome of such a reaction is governed by three factors: (1) the configuration (*E* or *Z*) of the enolate, (2) which diastereotopic face of the enolate reacts in the addition and (3) which enantiotopic face of the aldehyde reacts.[60] In our previously reported work, we proposed that the enantiopure 2-oxazolidinone anionic system reacts *via* the *Z* enolate and approaches the aldehyde carbonyl which is distal to the stereogenic center on the 2-oxazolidinone ring. This work still supports that contention. Thus, with the former two variables fixed, we are left only with the enantiotopicity of the aldehyde as the primary determinant to establish the final stereochemistry of the aldol adduct.

It appears that it is the inherent steric and stereoelectronic properties of the aldehyde (R), which is also highly influenced by the chelating ability of the enolate coun-

(63) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

tercation at its carbonyl oxygen, that determines which of its enantiotopic faces reacts. The results reported herein show how one may control the stereochemistry of addition using the aldol reaction of aromatic aldehydes with the chiral (*Z*)-*N*-acyl-2-oxazolidinone enolates **5** by controlling the metallic coordination and steric requirements of the reacting substrate aldehyde. Certain metallic enolates were shown to react through a three-point coordination transition state (Sn^{IV}, Zn, and Li; chelation control) yielding a *syn*/*anti* isomeric ratio of ~25:75, while others (Sn^{II}, B, Ti) were shown to react *via* a noncoordinated transition state (nonchelation control) to yield >96% of one *syn* isomer in several cases. The steric properties of the aromatic aldehyde were shown to be important by demonstrating that ortho substituents favor reaction through TS **15** as compared to Sn^{II} enolates. The stereoelectronic properties were demonstrated to be important by the fact that aromatic aldehydes react by the twist-boatlike TS **12** or **15** with metals other than boron or titanium. Aliphatic aldehydes were previously shown to react only through chairlike TS **11** or **13**.[3b] Finally, using our protocol or varying either the countercation or the substitution pattern on the aromatic aldehyde, one may synthesize three of the four possible stereoisomers available from the aldol reaction. The *syn* Li isomer **7** is the only inaccessible isomer as a *major* product in this α-halo-2-oxazolidinone system (see, for example, entries 11, 14, and 22 of Table I).

Experimental Section

General Procedure. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet 800 Fourier transform infrared spectrometer with a MC detector. Gas chromatography (GC) was done on a Hewlett-Packard capillary gas chromatograph Model 5890 using a DB-1, 15-m × 0.252-mm capillary column. High-resolution mass spectra were measured on Varian MAT-CH-5 double-focusing spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AM spectrometer. ^{13}C NMR spectra were routinely obtained using a GASPE pulse sequence. $^{13}C/^1H$ correlation experiments were done as noted with the experimentals procedures. Enantiomeric purities were checked using with a chiral HPLC column (see the appropriate experimental procedure for conditions).

Flash column chromatography was done on Baker silica for flash columns (~40 μm average particle diameter) using hexanes/ethyl acetate/methylene chloride (7:3:0.5, v/v), unless otherwise noted. Thin-layer chromatography (TLC) determinations were accomplished on silica precoated plates (Analtech, Inc.) and were developed with phosphomolybdic acid (PMA) in all cases except for the fluoro adducts (**6c–9c**) where GC was used to monitor the column elution.

All commercially obtained solvents and reagents were used without further purification. Tetrahydrofuran (THF) was the solvent of choice for all metallic enolates employed in this study except boron where methylene chloride was used as solvent. The THF used was normally distilled from sodium benzophenone ketyl under a nitrogen atmosphere. However, reagent-grade solvent stored over 4-Å molecular sieves overnight was found to be sufficient for large-scale reactions.

Bu_2BOTf was prepared from freshly distilled tributylboron and trifluoromethane sulfonic acid by the procedure of Mukaiyama[41] or purchased as a 1 M methylene chloride solution from Aldrich Chemical Co. $Sn(OTf)_2$ was prepared according to Batchelor *et al.*[40]

Starting Materials. The synthesis of (+)-(4*S*)-3-(chloroacetyl)-4-(1-methylethyl)-2-oxazolidinone (**1a**) and (+)-(4*S*)-3-(bromoacetyl)-4-(1-methylethyl)-2-oxazolidinone (**1b**) was accomplished as previously reported.[3b]

(+)-(4*S*)-3-(Fluoroacetyl)-4-(1-methylethyl)-2-oxazolidinone (1c). To a stirred solution of (4*S*)-4-(1-methylethyl)-2-oxazolidinone[10] (25.0 g, 0.194 mol) in 250 mL of THF cooled to −73 °C under nitrogen was added a hexanes solution of butyllithium (0.20 mol) dropwise over 20 min. At this time at 75-mL THF solution of the fluoroacetyl chloride was added dropwise over 30 min, and the solution was allowed to stir at −60 °C for 30 min. The cooled solution was quenched by pouring into 125 mL of pH 7 phosphate buffer and was extracted with ether. The organic extracts were combined, washed with 5.25% $NaClO_4$ (Chlorox) once, twice with distilled water, twice with brine, dried over $MgSO_4$, and then filtered. Concentration *in vacuo* gave the crude product which was purified by flash chromatography on silica gel with 30% (v/v) ethyl acetate in hexanes. This material solidified on standing and was recrystallized from ethyl acetate–hexanes to yield 28.3 g (0.15 mol, 77%), of **1c**: mp 61–62 °C (EtOAc–hexanes); $[\alpha]^{25}_D$ +93.85° (*c* 1.0, $CHCl_3$); IR (KBr) 2974, 2941, 2885, 1772, 1718, 1489, 1425, 1411, 1398, 1371, 1288, 1229, 1124, 1080, 1049, 1021, 1003, 959 (d), 766, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4 (d, J_{HF} = 47.6 Hz, 2 H, CH_2F), 4.45–4.27 (3 H, CH_2O, CHN), 2.44–2.40 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H, CH_3), 0.87 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.4, 154.0, 80.8 (d, J_{CF} = 179.5 Hz), 65.0, 58.1, 28.2, 17.8, 14.6; mass spec [*m*/*e* (CI, CH_4)], 230 (M + C_3H_5)$^+$, 218 (M + C_2H_5)$^+$, 190 (M + H)$^+$, 170, 156, 146, 130. Anal. Calcd for $C_8H_{12}NO_3F$: C, 50.79; H, 6.39; N, 7.40. Found: C, 50.67; H, 6.41; N, 7.48. The starting oxazolidinone was shown to be >99% ee with a chiral HPLC Baker bond Chiracel OC HPLC column.[10]

(+)-(4*S*)-3-(Bromoacetyl)-4-phenyl-2-oxazolidinone (1d) was prepared using a similar procedure as above in 71% yield: mp 121–122 °C (EtOAc–hexanes); $[\alpha]^{25}_D$ +78.55° (*c* 1.0, $CHCl_3$); IR (KBr) 3461, 3452, 3079, 3062, 3037, 3002, 2985, 1777, 1763, 1705, 1666, 1200, 1157, 1066, 1011, 704, 623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.3 (m, 5 H, Ar), 5.41 (dd, *J* = 8.7, 3.88 Hz, 1 H, CHN), 4.72 (t, *J* = 8.7 Hz, 1H, CHO), 4.47 (q, *J* = 12.7 Hz, 2 H, CH_2Br), 4.3 (dd, *J* = 8.7, 3.88 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 165.5, 153.3, 138.2, 129.4(2), 129.1, 126.3(2), 70.6, 58.0, 28.3; mass spec [*m*/*e* (CI, NH_3)] 301 (M + NH_4)$^+$, 284 (M + H)$^+$, 284, 257, 223, 181. Anal. Calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.61; H, 3.49; N, 4.84. Proton assignments for the oxazolidinone ring were made on the basis of $^{13}C/^1H$ correlation and NOE experiments. The starting oxazolidinone was shown to be >99% ee with a chiral Baker bond Chiracel OC HPLC column.[10]

Procedure a. (4*S*)-3-(3′-Hydroxy-3′-phenyl-2′-bromo-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (6–9b). Using the Li Enolate 5b. To a cooled (−73 °C) solution of freshly generated lithium diisopropylamide (2.7 mmol) in dry THF (10 mL) was added a solution of (4*S*)-3-(bromoacetyl)-4-(1-methylethyl)-2-oxazolidinone (**1b**) (0.63 g, 2.5 mmol) in THF (4 mL) under nitrogen. After 30 min, benzaldehyde (0.25 g, 2.5 mmol) was added, and the mixture was stirred at −73 °C for 1.5 h. Subsequently, the reaction was quenched by pouring into 100 mL of 5% aqueous citric acid solution. The product was extracted with ether, washed and distilled water and brine, dried over $MgSO_4$, and then filtered. The solvent was removed *in vacuo* to give the crude product mixture. The product ratio was determined at this point by ^1H NMR spectroscopy (400 MHz) to be 5:18:7:70 (**9b**, **6b**, **7b**, and **8b**) by comparing the integrations of the bromomethine proton resonating as a doublet at δ 5.93, 6.05, 6.16, and 6.09, respectively. This isomeric ratio was also verified by GC on a DB-1, 15-m × 0.252-mm capillary column after treatment with "Tri-Sil"[48] derivatizing agent. The normal elution order on GC was **9b**, **6b**, **7b**, and **8b**: retention times (19.4/19.6/20.7/20.9 min, respectively) started at a column temperature of 120 °C (increasing at 10 °C/min to 275 °C), except in the fluoro examples only where **9c** and **6c** reversed elution times. A flash column chromatography of this mixture on silica gel (25 g) afforded 0.55 g (61%) of **8b**, **7b**, and **6b** in that respective elution order. The *anti* isomer **9b** was isolated from larger subsequent reactions.

***syn*-(4*S*,2′*S*,3′*R*)-3-(3′-Hydroxy-3′-phenyl-2′-bromo-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (6b).** This isomer was obtained as the major component using general procedures **c**, **e**, **f**, and **g** (see below): mp 122–124 °C (Et_2O–hexanes); $[\alpha]^{25}_D$ +53.1° (*c* 1.0, $CHCl_3$); IR (KBr) 3510, 3024, 2962, 2927, 2874, 1773, 1684, 1498, 1485, 1465, 1452, 1398, 1392, 1382,

1328, 1305, 1228, 1218, 1204, 1122, 1102, 1067, 1055, 1029, 977, 943, 668, 774, 756, 700, 684, 598, 545, 514 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49–7.24 (m, 5 H, Ar*H*), 6.05 (d, J = 7.0 Hz, C*H*Br, 1 H), 5.06 (d, J = 7.0 Hz, C*H*OH, 1 H), 4.44–3.98 (m, 3 H), 3.29 (br s, 1 H), 2.52–2.12 [m, 1 H, C*H*(CH_3)$_2$], 0.85 [m, J = 6.5 Hz, 6 H, (CH_3)$_2$]; ^{13}C NMR ($CDCl_3$) δ 168.5, 152.6, 138.6, 128.4(2), 128.3, 127.5(2), 73.5, 63.5, 58.4, 50.3 (CHBr), 28.1, 17.7, 14.8; mass spec [*m/e* (abundance)] 341 (16), 340 (96), 337 (18), 338 (100), 280 (6), 278 (6), 276 (13), 261 (7), 260 (39), 259 (5), 252 (25), 251 (9), 250 (25), 249 (7), 211 (5), 209 (6), 170 (12), 159 (7), 158 (12), 147 (11), 131 (38), 130 (9), 123 (15), 107 (56), 105 (9). Anal. Calcd for $C_{15}H_{18}NO_2$: C, 50.58; H, 5.09; N, 3.93. Found: C, 50.61; H, 5.10; N, 3.86.

***syn*-(4*S*,2′*R*,3′*S*)-3-(3′-Hydroxy-3′-phenyl-2′-bromo-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (7b).** This isomer was always obtained as a minor component but was isolated and purified by flash chromatography: mp 130–131 °C (Et_2O–hexanes); $[\alpha]^{25}_D$ +50.9° (*c* 1.0, $CHCl_3$); IR (KBr) 3440, 3043, 2965, 2883, 1755, 1710, 1481, 1456, 1394, 1376, 1354, 1316, 1303, 1225, 1211, 1195, 1144, 1124, 1109, 1057, 1016, 970, 791, 777, 753, 708, 587 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57–7.27 (m, 5 H, Ar*H*), 6.16 (d, J = 8.0 Hz, C*H*Br, 1 H), 5.25 (d, J = 8.0 Hz, C*H*OH, 1 H), 4.52–4.03 (m, 3 H), 3.04 (br s, 1 H), 2.20–1.81 [m, 1 H, C*H*(CH_3)$_2$], 0.79 (d, J = 7.0 Hz, 3 H, CH_3), 0.43 (d, J = 4.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.6, 152.8, 138.1, 128.7, 128.5(2), 127.2, 126.8, 75.3, 63.2, 58.5, 49.6 (CHBr), 28.0, 17.7, 14.5; mass spec [*m/e* (abundance)] 356 (0.8), 341 (15), 349 (91), 339 (18), 338 (100), 280 (6), 276 (15), 260 (21), 252 (15), 251 (7), 250 (16), 249 (6), 170 (5), 158 (7), 147 (8), 131 (13), 130 (54), 107 (22). Anal. Calcd for $C_{15}H_{18}BrNO_4$: C, 50.58; H, 5.09; N, 3.93; Br, 22.43. Found: C, 50.63; H, 5.20; N, 3.87; Br, 21.98.

***anti*-(4*S*,2′*R*,3′*R*)-3-(3′-Hydroxy-3-phenyl-2′-bromo-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (8b).** This isomer was obtained as the major component using general procedures **a**, **b**, and **d** (see below): mp 114–115 °C (Et_2O–hexanes); $[\alpha]^{25}_D$ +2.5° (c 1.0, $CHCl_3$); IR (KBr) 3468, 3041, 3030, 2973, 2958, 2939, 2928, 1779, 1694, 1492, 1454, 1368, 1366, 1340, 1301, 1212, 1262, 1162, 1143, 1115, 1041, 1024, 997, 973, 870, 756, 710, 656, 643, 598, 540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58–7.27 (m, 5 H, Ar*H*), 6.09 (d, J = 7.0 Hz, 1 H, C*H*Br), 5.15 (d, J = 7.0 Hz, 1 H, C*H*OH), 4.57 (m, 1 H, C*H*N), 4.25 (m, 2 H, CH_2O), 3.55 (br s, 1 H), 2.43–2.04 [m, 1 H, C*H*(CH_3)$_2$], 0.85 (d, J = 7.0 Hz, 3 H, CH_3), 0.67 (d, J = 6.0 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.1, 153.0, 139.2, 128.5(3), 126.8(2), 75.4, 63.5, 59.0, 44.3 (CHBr), 28.3, 17.7, 14.4; mass spec [*m/e* (abundance)] 356 (1), 354 (0.6), 341 (16), 340 (95), 339 (17), 338 (100), 280 (6), 278 (6), 276 (10), 261 (7), 260 (40), 252 (25), 251 (13), 250 (26), 249 (11), 170 (11), 158 (10), 147 (5), 131 (31), 130 (75), 107 (51). Anal. Calcd for $C_{15}H_{18}BrNO_4$: C, 50.58; H, 5.09; N, 3.93; Br, 22.43. Found: C, 50.65; H, 5.06; N, 3.85; Br, 22.11. The structure is supported by X-ray crystallography data.

***anti*-(4*S*,2′*S*,3′*S*)-3-(3′-Hydroxy-3′-phenyl-2′-bromo-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (9b).** This isomer was always obtained as a minor component but was isolated and purified by flash chromatography: mp 95 °C (Et_2O–hexanes); $[\alpha]^{25}_D$ +96.6° (*c* 1.1, $CHCl_3$); IR (KBr) 3600–3100, 1741, 1710, 1483, 1456, 1402, 1378, 1308, 1224, 1211, 1120, 1024, 1008, 970, 790, 770, 700, 642, 594, 541, 493 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50–7.30 (m, 5 H, Ar*H*), 5.93 (d, J = 8.4 Hz, 1 H, C*H*Br), 5.17 (d, J = 8.4 Hz, 1 H, C*H*OH), 4.5–4.4 (m, 1 H), 4.3–4.2 (m, 2 H), 2.4 [m, 1 H, C*H*(CH_3)$_2$], 0.95 [d, J = 6 Hz, 6 H, (CH_3)$_2$]; ^{13}C NMR ($CDCl_3$) δ 169.0, 152.9, 139.0, 128.6, 128.5(2), 125.9(2), 74.7, 63.5, 58.2, 44.9 (CHBr), 28.0, 17.7, 14.8; mass spec [*m/e* (CI/CH_4)] 396 (M + C_3H_5)$^+$, 384 (M + C_2H_5)$^+$, 378 (396 – H_2O)$^+$, 366 (384 – H_2O)$^+$, 356 (M + H)$^+$, 338 (M + H – H_2O)$^+$; HRMS (CI) calcd for $C_{15}H_{22}N_2O_4Br$ 373.0747 (M + NH_4)$^+$, found 373.0763.

Procedure b. Using the Zn Enolate of 1b (1 Equiv of Zn). To the lithium enolate of **1b** (0.63 g, 2.5 mmol), made as described above, was added an ethereal solution of $ZnCl_2$ (2.5 mmol) at –73 °C. The mixture was allowed to warm to –40 °C over 30 min and then cooled to –73 °C and held at that temperature for 30 min under nitrogen. Benzaldehyde (2.5 mmol) in 4 mL of THF was slowly added dropwise over 30 min. The solution was stirred at –73 °C for 1.5 h and then allowed to warm to –40 °C. The reaction was quenched by pouring into 5% aqueous citric acid solution, and the product was extracted with ether. The ether extracts were combined, washed with distilled water and brine, dried over $MgSO_4$, and then filtered. Removal of the solvent *in vacuo* afforded the crude product. Flash column chromatography gave a combined yield of 73% with an isomeric ratio of 1:15:18:66 for **9b:6b:7b:8b**, respectively.

Procedure c. Using the Sn^{II} Enolate of 1b. To the lithium enolate of **1b** (0.63 g, 2.5 mmol) in dry THF (10 mL) cooled to –73 °C under nitrogen was added a THF (5 mL) solution of stannous triflate (1.25 g, 3 mmol). The reaction was allowed to warm to –40 °C over 30 min and then cooled to –73 °C and kept at that temperature for an additional 30 min. Benzaldehyde (2.5 mmol) in 4 mL of THF was slowly added dropwise over 30 min. The reaction mixture was allowed to stir at –73 °C for 1.5 h and then quenched by pouring into 5% aqueous citric acid solution. The reaction mixture was extracted several times with ether. The combined ether extracts was washed with distilled water and brine, dried over $MgSO_4$, and then filtered. Removal of the solvent *in vacuo* afforded the crude product. Flash column chromatography gave a combined yield of 67% with an isomeric ratio of 9:79:6:6 for **9b:6b:7b:8b**, respectively.

Procedure d. Using the Sn^{IV} Enolate of 1b. To the lithium enolate of **1b** (0.63 g, 2.5 mmol) in dry THF (10 mL) cooled to –73 °C under nitrogen was added a solution of tributyltin chloride (0.81 g, 2.5 mmol) in THF (5 mL). The reaction was allowed to warm to –40 °C over 30 min and then cooled to –73 °C and kept at that temperature for an additional 30 min. Benzaldehyde (2.5 mmol) in 4 mL of THF was slowly added dropwise over 30 min. The reaction mixture was allowed to stir at –73 °C for 1.5 h and then quenched by pouring into 5% aqueous citric acid solution. The reaction mixture was extracted several times with ether. The combined ether extracts were washed with distilled water and brine, dried over $MgSO_4$, and then filtered. Removal of the solvent *in vacuo* afforded the crude product. Flash column chromatography gave a combined yield of 77% with an isomeric ratio of 3:9:12:76 for **9b:6b:7b:8b**, respectively.

Procedure e. Using the Boron Enolate of 1b. To dry CH_2Cl_2 (10 mL) containing freshly prepared diethylboron triflate[42] (0.77 g, 5.5 mmol) at –10 °C was added **1b** (1.04 g, 4.6 mmol) and diisopropylethylamine (0.71 g, 5.5 mmol). The mixture was allowed to warm to ambient temperature (15–20 °C) over 30 min and then cooled to –73 °C and stirred at that temperature for another 30-min period. Benzaldehyde (0.49 g, 4.6 mmol) was slowly added dropwise with stirring at –73 °C over 30 min. The reaction mixture was stirred at –73 °C for 1.5 h and then allowed to warm to –40 °C. The reaction was oxidatively quenched with 16 mL of methanol, followed successively by 6 mL of pH 7 phosphate buffer and 6 mL of 30% H_2O_2, keeping the temperature below –20 °C. The suspension was then stirred at –5 to 5 °C for 1 h and then extracted several times with CH_2Cl_2. The organic solution was concentrated to dryness, and the residue was redissolved in CH_2Cl_2 and washed with distilled water and brine, dried over $MgSO_4$, and then filtered. Removal of the solvent *in vacuo* gave the crude product in an isomeric ratio of 0:98:0:2 for **9b:6b:7b:8b**, respectively, by ^{1}H NMR. Flash column chromatography gave pure *syn* **6b** (0.95 g, 62%).

Procedure f. Using the Ti Enolate of 1b.[44a] To the lithium enolate of **1b** made as described above in THF at –73 °C was added 1.1 equiv of $ClTi(O^iPr)_3$, 1 M in hexanes. The dark brown solution was allowed to warm to –40 °C and then cooled to –73 °C and held at that temperature for 0.5 h. Benzaldehyde (1.1 equiv) in 5 mL of THF was added and the solution allowed to stir at –73 °C for 2 h. The reaction was quenched with saturated NH_4Cl solution and extracted with ether (4 × 30 mL). The organic extracts were combined, dried over $MgSO_4$, and then filtered. Removal of the solvent *in vacuo* gave the crude product in an isomeric ratio of 9:73:9:9 for **9b:6b:7b:8b**, respectively, by ^{1}H NMR. Flash column chromatography gave a combined yield of 59%.

Procedure g. Using the Ti Enolate of 1b, According to Evan's Protocol.[46] Neat $TiCl_4$ (1.1 equiv) was added to a 0.2 M solution of **1b** in CH_2Cl_2 at –73 °C under a nitrogen atmosphere producing a thick yellow slurry. After 2 min, 1.2 equiv of diisopropylethylamine was added and the resulting dark solution was stirred at –73 °C for 1.5 h. Benzaldehyde (1.1 equiv) in 2 mL of CH_2Cl_2 was added and the solution allowed to stir at –73 °C for 1.5 h. The reaction was quenched with 5% citric acid

solution and extracted with ether (4 × 30 mL). The organic extracts were combined and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude product in an isomeric ratio of 10:68:12:10 for **9b**:**6b**:**7b**:**8b**, respectively, by ^1H NMR. Flash column chromatography gave a combined yield of 62%.

GC Conditions for 6c–9c. Using the same GC conditions as described in the experimental procedure for **6b–9b**, the retention times were 16.8/17.0/17.4/17.6 min for **6c**/**9c**/**7c**/**8c**, respectively.

***syn*-(4*S*,2′*S*,3′*R*)-3-(3′-Hydroxy-3′-phenyl-2′-fluoro-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (6c).** This isomer was obtained as the major component using general procedures **c**, **e**, and **f**, the latter in ether: mp 114–115 °C (Et_2O–hexanes); $[\alpha]^{25}_D$ +100.98° (*c* 1.0, $CHCl_3$); IR (KBr) 3504, 2972, 1790, 1720, 1393, 1378, 1300, 1206, 1117, 1054, 1019, 973, 777, 726, 711, 574, 518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5–7.2 (m, 5 H), 6.22 (dd, $^1J_{HF}$ = 48.22 Hz; $J_{2,3}$ = 3.38 Hz, 1 H, C*H*F), 5.17 (dd, $^2J_{HF}$ = 23.2 Hz; $J_{2,3}$ = 3.30 Hz, 1 H, C*H*OH), 4.3–4.1 (m, 3 H), 2.83 (br s, 1 H), 2.45 (m, 1 H), 0.88 [dd, *J* = 7.0, 7.0 Hz, 6 H, $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 167.1 (d, $^2J_{CF}$ = 23.4 Hz), 153.7, 137.8, 128.7, 128.5 (2), 126.4(2), 91.02 (d, $^1J_{CF}$ = 184.6 Hz, *C*HF), 73.5 (d, $^2J_{CF}$ = 20.9 Hz), 64.3, 59.0, 28.1, 17.9, 14.5; mass spec [*m*/*e* (CI/CH_4)] 296 (M + H)$^+$, 278 (M + H − H_2O)$^+$, 230, 218, 190, 170, 130, 107. Anal. Calcd for $C_{15}H_{18}NO_4F$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.78; H, 6.07; N, 4.87. This structure is supported by X-ray crystallography data.

***syn*-(4*S*,2′*R*,3′*S*)-3-(3′-Hydroxy-3′-phenyl-2′-fluoro-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (7c)** could be obtained only as a viscous oil being the major component in 63/32 mix with *anti* isomer **9c**: ^1H NMR ($CDCl_3$) δ 7.45–7.2 (m, 5 H, Ar*H*), 6.12 (dd, $^1J_{HF}$ = 47.7 Hz; $J_{2,3}$ = 2.3 Hz, 1 H, C*H*F), 5.25 (dd, $^2J_{HF}$ = 20.0 Hz; $J_{2,3}$ = 2.2 Hz, 1 H, C*H*OH), 4.45–4.1 (m, 3H), 3.5 (br s, 1 H), 2.20 (m, 1 H), 0.85 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.75 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.2 (d, $^2J_{CF}$ = 24.0 Hz), 154.1, 138.7, 128.5, 128.4(2), 126.3(2), 91.1 (d, $^1J_{CF}$ = 185.2 Hz, *C*HF), 73.0 (d, $^2J_{CF}$ = 14.9 Hz), 64.9, 58.9, 28.3, 17.5, 14.7.

***anti*-(4*S*,2′*R*,3′*R*)-3-(3′-Hydroxy-3′-phenyl-2′-fluoro-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (8c).** This isomer was obtained as the major component using general procedures **a**, **b**, and **d**: mp 98–100 °C (Et_2O–hexanes); $[\alpha]^{25}_D$ +16.4° (*c* 1.0, $CHCl_3$); IR (KBr) 3595, 3455, 2966, 1798, 1775, 1711, 1484, 1459, 1388, 1391, 1305, 1270, 1215, 1119, 1047, 1017, 860, 716, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5–7.3 (m, 5 H, Ar*H*), 6.25 (dd, $^1J_{CF}$ = 48.5 Hz; $J_{2,3}$ = 7.4 Hz, 1 H, C*H*F), 4.94 (dd, $^2J_{HF}$ = 13.4 Hz; $J_{2,3}$ = 7.3 Hz, 1 H, C*H*OH), 4.48–4.24 (m, 3 H), 3.06 (br s, 1 H), 2.32 (m, 1 H), 0.87 [dd, *J* = 7.0, 7.0 Hz, 6 H, $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 168.1 (d, $^2J_{CF}$ = 21.9 Hz), 154.5, 139.1, 128.7, 128.6(2), 126.9(2), 88.4 (d, $^1J_{CF}$ = 182.4 Hz, *C*HF), 74.2 (d, $^2J_{CF}$ = 26.8 Hz), 64.5, 58.8, 28.3, 17.8, 14.6; mass spec [*m*/*e* CI/NH_3)] 313 (M + NH_4)$^+$, 295 (M + NH_4 − H_2O)$^+$, 278 (M + H − H_2O)$^+$, 207, 147. Anal. Calcd for $C_{15}H_{18}NO_4F$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.57; H, 6.09; N, 5.04. This structure is supported by X-ray crystallography data.

***anti*-(4*S*,2′*S*,3′*S*)-3-(3′-Hydroxy-3′-phenyl-2′-fluoro-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (9c)** was isolated as a minor component by flash chromatography as a viscous oil: IR (KBr) 3600–3100, 2966, 1785, 1714, 1390, 1301, 1205, 1110, 1053, 713, 702, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.24 (m, 5 H, Ar*H*), 6.30 (dd, $^1J_{HF}$ = 48.0 Hz; $J_{2,3}$ = 7.3 Hz, 1 H, C*H*F), 4.98 (dd, $^2J_{HF}$ = 13.3 Hz; $J_{2,3}$ = 7.4 Hz; 1 H, C*H*OH), 4.39–4.1 (m, 3H), 2.77 (br s, 1H), 2.40 (m, 1 H), 0.90 [dd, *J* = 6.9, 6.9 Hz, 6H, $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 168.3 (d, $^2J_{CF}$ = 21.9 Hz), 154.0, 138.5, 128.9, 128.7(2), 126.8(2), 88.8 (d, $^1J_{CF}$ = 182.2 Hz, *C*HF), 74.0 (d, $^2J_{CF}$ = 26.9 Hz), 64.2, 58.9, 28.4, 17.9, 14.7; mass spec *m*/*e* CI/NH_3)] 313 (M + NH_4)$^+$, 295 (M + NH_4 − H_2O)$^+$, 278 (M + H − H_2O)$^+$, 267, 147. Anal. Calcd for $C_{15}H_{18}NO_4F$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.63; H, 6.37; N, 4.21.

***syn*-(4*S*,2′*R*,3′*S*)-3-(3′-Hydroxy-3′-cyclohexyl-2′-chloro-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (18).** This isomer was obtained as one of two isomers using general procedure **a** as a viscous oil: $[\alpha]^{25}_D$ +48.7° (*c* 1.0 $CHCl_3$); IR (film) 3511, 2965, 2929, 2877, 2855, 1780, 1717, 1487, 1466, 1451, 1390, 1375, 1337, 1329, 1302, 1262, 1204, 1144, 1121, 1109, 1088, 1060, 1047, 1021, 973, 927, 772, 758, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.94 (d, *J* = 2.6 Hz, 1 H, C*H*Cl), 4.5 (m, 1 H, C*H*), 4.48 (t, *J* = 8.9 Hz, 1 H, C*H*), 4.28 (m, 1 H), 3.8 (dd, *J* = 2.5, 8.3 Hz, 1 H, C*H*OH), 2.3 (m, 1 H, C*H*), 2.0 (m, 1 H), 1.90–1.44 (m, 4 H), 1.5–0.9 (m, 6 H), 0.88 [dd, *J* = 7.0 Hz, 6 H, $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 168.1, 153.5, 76.0, 64.0, 60.0, 58.7 (*C*HCl), 41.3, 28.9, 28.5, 28.4, 26.0, 25.8, 25.7, 17.7, 14.8; mass spec [*m*/*e* (CI/isobutane)], 318 (M + H)$^+$, 300 (M + H − H_2O)$^+$, 282 (M + H − HCl)$^+$, 206, 129; HRMS (CI) calcd for $C_{15}H_{25}NO_4Cl$ 318.1472 (M + H)$^+$, found 318.1457.

***syn*-(4*S*,2′*S*,3′*R*)-3-(3′-Hydroxy-3′-cyclohexyl-2′-chloro-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (19).** This isomer was obtained as one of two isomers using general procedure **a**: mp 105–107 °C (EtOAc–hexanes); $[\alpha]^{25}_D$ +53.8° (*c* 1.0, $CHCl_3$); IR (KBr) 3488, 3428, 3001, 2985, 2973, 2926, 2853, 1796, 1701, 1484, 1464, 1452, 1389, 1362, 1357, 1346, 1236, 1218, 1212, 1192, 1122, 1101, 1083, 1075, 1053, 1025, 1011, 969, 685, 597, 574, 563 cm^{-1}; ^1H NMR ($CHCl_3$) δ 5.87 (d, *J* = 2.3 Hz, 1 H, C*H*Cl), 4.5 (m, 1 H, C*H*), 4.35 (t, *J* = 8.8 Hz, 1 H, C*H*), 4.28 (dd, *J* = 9.1, 3.0 Hz, 1 H, C*H*), 3.75 (dd, *J* = 2.2, 8.1 Hz, 1 H, C*H*OH), 2.45 (m, 1 H, C*H*), 2.1 (m, 1 H), 1.8–1.6 (m, 4 H), 1.3–1.0 (m, 6 H), 0.97 [dd, *J* = 7.0 Hz, 6 H, $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 168.8, 153.1, 75.1, 63.6, 58.7, 57.9 (*C*HCl), 40.6, 28.9, 28.5, 27.8, 26.1, 25.8(2), 17.8, 14.4; mass spec [*m*/*e* (CI/isobutane)], 318 (M + H)$^+$, 300 (M + H − H_2O)$^+$, 282 (M + H − HCl)$^+$, 264, 206, 130, 113; HRMS (CI) calcd for $C_{15}H_{25}NO_4Cl$ 318.1472 (M + H)$^+$, found 318.1461. Anal. Calcd for $C_{15}H_{24}NO_4Cl$: C, 56.69; H, 7.61; N, 4.41. Found: C, 56.67; H, 7.50; N, 4.38. This structure is supported by X-ray crystallography data.

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Supplementary Material Available: Spectral data for **6a–9a**, **6d**, **7d**, **9d**, **6e–9e**, **6f–9f**, **25–46**, and **47**, which is the valine-derived analog of **36** *anti* B (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS; see any current masthead page for ordering information. Tables of refined atomic positional and anisotropic displacement parameters, bond lengths, bond angles, structure factors and details of the crystal and intensity measurement data for compounds **6c**, **7a**, **7f**, **8a**, **8b**, **8c**, **9f**, **36** *anti* Li, **36** *anti* B, **41** *anti* B, and **42** *syn* B are available from authors upon request. The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.