from the SHELXTL system.[35] Phenyl rings were treated as rigid groups (C–C = 1.395 Å, bond angles = 120°), and phenyl hydrogens were placed in fixed calculated positions (C–H = 0.96 Å), while all other non-hydrogen atoms were refined anisotropically.

Acknowledgment is made to the U.S. Army Research Office and the Marathon Oil Company for the support of this research. The X-ray diffractometer was purchased with support from the National Science Foundation (CHE-8912675). We gratefully acknowledge Professor Larry E. Overman for supplying helpful unpublished information.

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Registry No. **1b**, 86802-64-4; **2a**, 768-03-6; **2b**, 131906-57-5; **3b**, 131906-67-7; **3c**, 131906-68-8; **4**, 131906-60-0; **5**, 131906-61-1; **6**, 131906-62-2; **7a**, 131906-70-2; **7b**, 131932-54-2; **8a**, 131906-64-4; **8b**, 131906-59-7; **10**, 131906-66-6; 4-$EtCOC_6H_4C_6H_{13}$, 79219-16-2; C_6H_5SeCl, 5707-04-0; 4-$MeCH(SeC_6H_5)COC_6H_4C_6H_{13}$, 131906-71-3; (*E*)-$HO_2CCH{=}CHCH{=}CH_2$, 21651-12-7; $Br(CH_2)_6OH$, 4286-55-9; 4-$C_6H_{13}C_6H_4SH$, 4619-85-6; 4-$C_6H_{13}C_6H_4SO_2CH{=}CHCH{=}CH{=}NHCO_2(CH_2)_6Br$, 131932-55-3.

Supplementary Material Available: IR data; X-ray structure of **3b**; tables of atomic coordinates, bond lengths, bond angles, hydrogen atom coordinates, and thermal displacement parameters; and ^1H and ^{13}C NMR spectra of **2b**, 6-bromohexyl ((*E,E*)-4-[(4-hexylphenyl)sulfonyl]-1,3-butadienyl)carbamate, **4**, **3b**, **3c**, **7a**, **8a**, **7b**, and **8b** (30 pages); observed and calculated structure amplitudes for **3b** (11 pages). Ordering information is given on any current masthead page.

Asymmetric Aldol Reactions. Use of the Titanium Enolate of a Chiral *N*-Acyloxazolidinone To Reverse Diastereofacial Selectivities

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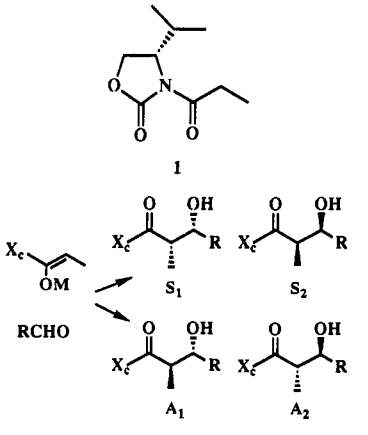
Received October 19, 1990

Aldol reactions of the titanium enolate of (*S*)-*N*-propionyl-4-isopropyl-2-oxazolidinone (readily derived from L-valine) with representative aldehydes give high diastereofacial selectivities for the syn aldol adducts expected from chelation control. This represents a remarkable reversal in selectivity compared with the corresponding boron enolate, thus permitting either enantiomeric form of β-hydroxy-α-methyl carboxylic acids to be made from a single, readily available oxazolidinone simply by changing the metal. A lithium interference effect is shown to be easily prevented by use of excess titanium. Use of diethyl ether as solvent rather than THF significantly enhances the stereoselectivity. Mechanistically, the observed stereochemical reversal constitutes very strong evidence that chelation is operative with titanium, presumably through a chelated chairlike transition structure. In this transition structure, the conformation would be rigidly locked by chelation and the titanium would be at least hexacoordinate, resulting in a "superaxial" ligand, thus nicely explaining the high stereocontrol.

The pericyclic transition structures usually associated with the aldol reaction can provide strong acyclic stereocontrol.[1-3] Advances in understanding and application of highly stereocontrolled aldol processes would propel the synthesis of chiral aldol intermediates, which play important roles in syntheses of many important classes of compounds, including macrolide, ionophore, and β-lactam antibiotics.[4]

The very high selectivity in aldol reactions of titanium(IV) enolates recently observed in this laboratory[5,6] led us to consider that titanium enolates should provide highly selective aldol reactions under *chelation control*. The design concept is that titanium(IV), being a transition metal, *combines* two desirable properties: (1) presence of ligands attached to the metal, and (2) a vacant d orbital shell capable of chelation. Boron has given high levels of stereocontrol in aldol reactions, where the presence of bonded ligands is believed to be the controlling factor. However, boron is incapable of chelation because, as a second-row element, it cannot complex with additional groups beyond the aldehyde component of the aldol reaction. On the other hand, chelation control has been postulated for other metals such as lithium, zinc, and Sn(IV), though levels are rarely high. These facts led us to propose that titanium could provide both high selectivity *and* chelation control.

In this paper we describe a remarkable reversal of diastereofacial selectivity in titanium-mediated aldol reactions of **1** to give the product expected from chelation control, S_2,[7,8] whereas the opposite diastereofacial selection (S_1) is observed with the corresponding boron enolate.[9,10]



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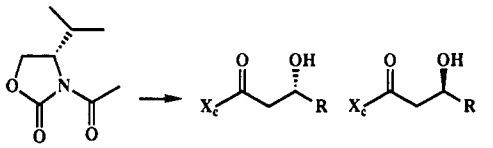
Titanium(IV) enolates are of particular interest since chelation control has been postulated in certain reactions of Ti(IV) species;[11-16] hexa- and even octacoordinate complexes are known.[11,17-21]

The enolate metal is known to play a role in aldol reactions of 1: lithium gave low levels of stereocontrol relative to boron.[9,10] Chirality reversal with choice of metal was also reported after our work was underway,[22] including work with related oxazolidinones: a Cl_3Ti enolate[16] and others (not titanium).[23-25] Alkylation of lithium and sodium,[26,27] as well as boron (catalyzed by $ZnBr_2$),[28] oxazolidinone enolates gives stereochemistries consistent with chelation control. Other aldol studies using boron oxazolidinone enolates have appeared.[29,30] Stereoselective acylation of lithium oxazolidinone enolates followed by reduction provides an alternative stereocontrolled route to aldols.[31] Recently, oxazolidinethiones[32-34] and thiazolidinethiones[34-38] have been used as chiral auxiliaries in aldol[32-35] and alkylation[36] reactions. Chelation control in aldol reactions of other types of lithium enolates has been postulated,[39,40] though high levels of stereocontrol are rare.[41]

Results

We have studied the aldol reactions of representative aldehydes with the titanium and lithium enolates of 1. Stereochemical analysis led us to change some literature misassignments and thus provided diastereofacial selectivities. Effects of excess titanium, solvent, and removal of the α-methyl group (2) upon stereoselectivities were investigated. All were found to exert large effects, providing practical assistance in optimizing selectivities and further mechanistic understanding.



2 D_1 D_2

Stereochemical Assignments of Aldol Products. The stereochemistries of the titanium-mediated aldol products from 1 and benzaldehyde were assigned by experimentally reproducing the lithium-mediated ratios previously reported.[9,10] The literature diastereomer ratios were reproduced within experimental error; since all four quantities within the ratio are significantly different, the assignment of stereochemistry is straightforward and conclusive. Additional verification is provided by use of the well-established correlation between syn/anti stereochemistry and the vicinal coupling constant of the α and β protons at the two chiral centers of the aldol adducts, where adducts having relatively small α and β substituents give small values of $^3J_{\alpha\beta}$ (3–5 Hz) for syn diastereomers and larger values (7–10 Hz) for anti.[1,2,42] The $^3J_{\alpha\beta}$ values are 3.9, 4.7, and 7.9 Hz for the diastereomers assigned as S_2, S_1, and A_1, respectively, corroborating the syn/anti assignments.

The stereochemistries of the benzaldehyde adducts from 2 were assigned by optical rotation measurements. Hydrolysis of the major lithium-mediated adduct by the procedure delineated in the experimental section gave the carboxylic acid, $[\alpha]^{25}_D = -20°$ (c 0.002 29, ethanol), which compares favorably with literature values for D_1 at higher concentrations $[\alpha]^{25}_D = -17.6°$ (c 0.041, ethanol)[43] and $[\alpha]^{25}_D = -18.9°$ (c 0.013, ethanol).[44] The other adduct diastereomer must then be D_2.

As in the reaction of 1 with benzaldehyde, we originally planned to assign the stereochemistries of the products from isobutyraldehyde and *n*-pentanal by experimentally reproducing the literature lithium-mediated ratios. The stereochemistries of the S_1 isomers, which were almost exclusively formed in the boron-mediated aldol reactions studied, had been conclusively proven by hydrolysis and optical rotation.[9,10,45] However, our titanium results led

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Table I. Diastereomeric Product Ratios for Aldol Reactions of the *N*-Propionyloxazoidinone 1

entry	metal (equiv)	R^3CHO	solvent	diastereomer percent[a]			
				S_1	S_2	A_1	A_2
1	Li	PhCHO	THF	7	32	59	2[b]
2	Li	PhCHO	Et_2O	17	24	59	*c,d*
3	Li	iPrCHO	THF	12	73	11	4[e,f]
4	Li	BuCHO	THF	13	57	27	3[b,f]
5	$Ti(OiPr)_3$ (3)	PhCHO	THF	13	84	3	*c,d*
6	$Ti(OiPr)_3$ (3)	PhCHO	Et_2O	3	92	5	*b,d*
7	$Ti(OiPr)_3$ (3)	PhCHO	iPr_2O	5	88	7	*c,d*
8	$Ti(OiPr)_3$ (2)[g]	iPrCHO	Et_2O	8	85	7	*d,e,f*
9	$Ti(OiPr)_3$ (2)	BuCHO	Et_2O	9	88	3	*b,d,f*
10	$Ti(OiPr)_3$ (1)	PhCHO	THF	77	16	7	*c,d*
11	$Ti(OiPr)_3$ (1)	PhCHO	Et_2O	16	58	26	*c,d*
12	$Ti(OiPr)_3$ (1)	PhCHO	iPr_2O	12	58	30	*c,d*
13	$Ti(OiPr)_3$ (1)	iPrCHO	Et_2O	43	11	28	18[e,f]

[a] Product ratios determined on crude product mixtures by methods given in subsequent footnotes. The most selective results (2 or 3 equiv of Ti, Et_2O), entries 6, 8, 9, were repeated at least three times, giving SD values for the major product ca. 5% or less (SD data in Experimental section). [b] By HPLC. [c] By ^1H NMR. [d] Product not observed by assay method. [e] By conversion to trifluoroacetate ester and measurement by ^1H NMR. [f] Stereochemistry of anti adducts currently proven only for benzaldehyde; other assignments are by analogy with benzaldehyde. [g] With 3 equiv of $ClTi(OiPr)_3$, values were the same as with 2 equiv within experimental reproducibility.

us to believe that the assignments for S_2 were in need of revision. We were able to reproduce the Li-mediated ratios reported[9,10] within experimental error, but according to the assignments so derived, benzaldehyde gave predominantly the S_2 diastereomer (rigorously known), isobutyraldehyde gave predominantly A_1, and *n*-pentanal gave predominantly A_2. Since it seemed highly unlikely that three different stereochemistries would result from these three very similar reactions, the product stereochemistries were reexamined.

Purification and ^1H NMR analysis of the major adduct formed in the titanium-mediated aldol reaction of isobutyraldehyde, previously thought to be A_1, revealed that $^3J_{\alpha\beta}$ = 2.9 Hz, indicative of a syn stereochemistry.[1,2,42] In addition, its chemical shifts are different from those reported for S_1 (conclusively identified[9,10]). For example, $C_\beta H$ has δ 4.08 as opposed to 3.93 for S_1. Both sets of doublets of quartets are seen in mixtures containing both of these diastereomers. Accordingly, this diastereomer is syn but not S_1; it therefore must be S_2. To confirm this conclusion, the adduct was hydrolyzed to the corresponding carboxylic acid, which has $^3J_{\alpha\beta}$ = 3.3 Hz, compared with literature values of 3.7[46] and 4[9,10] Hz, with the same chemical shifts (the anti acid has $^3J_{\alpha\beta}$ = 5.5 Hz[47]).

More reliable diastereomeric ratios could be attained by trifluoroacetate ester formation and ^1H NMR analysis of the carbinol protons of the four diastereomers. Based on the stereochemical proof of S_2, we know that the doublet of doublets at 5.28 ppm corresponds to S_2. The stereochemistry of S_1 has been proven,[9,10] and the correspondence of the Li ratio obtained by us to the literature value[9,10] requires that a doublet of doublets at 5.12 or one at 5.50 ppm must correspond to S_1. The similarity of $^3J_{\alpha\beta}$ value and relative closeness to the carbinol proton chemical shift of S_2 prior to derivatization indicate that the 5.12 ppm absorption belongs to S_1. Proof was obtained from the ^1H NMR of a mixture of diastereomers known to contain predominantly S_1 prior to derivatization (the spectrum of S_1 has been reported[10]) before and after conversion to trifluoroacetate esters. As expected, the carbinol doublet of doublets having the largest area was that at δ 5.12 ppm.

With S_1 and S_2 rigorously assigned, the assignment of A_1 and A_2 remained. From a mechanistic standpoint, it is unlikely that A_2 would be formed in significantly larger quantities than A_1. Moreover, A_2 was not formed in measurable quantities in the titanium-mediated aldol reaction with benzaldehyde. Therefore, we assign the absorption at 5.50 ppm to $C_\beta H$ of A_1.

Overlap of the α and β proton NMR absorptions of the major adduct formed in the titanium-mediated aldol reaction of *n*-pentanal, previously thought to be A_2, precluded measurement of a $^3J_{\alpha\beta}$ value. The chemical shifts, however, are significantly different from those reported for S_1.[9,10] Hydrolysis to the acid revealed that $^3J_{\alpha\beta}$ = 3.3 Hz, compared with 4.0 reported for the syn acid.[9,10] We also found that the $[\alpha]^{25}_D$ for this acid is negative, whereas S_1 has a positive rotation.[9,10] The optical rotation and $^3J_{\alpha\beta}$ value demonstrate that this diastereomer is not A_2 and is actually S_2.

In this case, S_1 was readily assigned since the literature[9,10] lithium ratio reproduced very closely in our hands, all four diastereomers occurring in significantly different quantities. Therefore, S_1 must be the diastereomer found to be 12.9% of the lithium product mixture. As described above for isobutyraldehyde, we assign the diastereomer in third-largest quantity as A_1.

Stereoselectivities in Aldol Reactions of *N*-Acyloxazolidinones 1 and 2. Table I shows the data we have obtained for aldol reactions of (*S*)-*N*-propionyl-4-isopropyl-2-oxazolidinone, 1. It reveals that the titanium-mediated aldol reactions of the representative aldehydes benzaldehyde, isobutyraldehyde, and *n*-pentanal all produced very substantial excesses of S_2, the product expected from chelation control. Particularly striking also are the large increases in selectivity upon changing from 1 molar equiv of $ClTi(OCH(CH_3)_2)_3$ to 2 or 3. This change increases selectivity toward the chelation controlled product by 8- and 41-fold for benzaldehyde and isobutyraldehyde, respectively, in ether; in THF, the increase is 31-fold for benzaldehyde. The syn:anti ratios are large, though detectable amounts of anti adducts are formed even under the best conditions.

Varying the number of equivalents of $ClTi(OCH(CH_3)_2)_3$ relative to 1 led to a dramatic increase in S_2:S_1 ratio at 2.0 relative to 1.0 equiv for both benzaldehyde and isobutyraldehyde in ether, but the effect then remained the same within experimental error for 2.5, 3.0, or 4.0 equiv (benzaldehyde), or for 3.0 equiv (isobutyraldehyde) (data not shown). Generally 3.0 equiv was used, but 2.0 is adequate if quantities of reactants are determined accurately.

Data for reactions of the corresponding (*S*)-*N*-acetyl-4-isopropyl-2-oxazolidinone (2) with benzaldehyde are given

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Table II. Diastereomeric Product Ratios for Aldol Reactions of the *N*-Acetyloxazolidinone 2 with Benzaldehyde

entry	metal (equiv)	solvent	diastereomer percent[a] D_1	D_2
1	Li	THF	87	13[b]
2	$Ti(OiPr)_3$ (3)	THF	46	54[c]
3	$Ti(OiPr)_3$ (3)	Et_2O	25	75[c]
4	$Ti(OiPr)_3$ (1)	THF	58	42[b]
5	$Ti(OiPr)_3$ (1)	Et_2O	48	52[b]

[a] Product ratios determined on crude product mixtures by methods given in subsequent footnotes. [b] By HPLC. [c] By conversion to trifluoroacetate ester and measurement by ^{19}F NMR.

in Table II. This substrate, lacking an α-methyl group, exhibits the same kinds of phenomena as 1, though the selectivities are much lower. Once again, when the number of equivalents of $ClTi(OCH(CH_3)_2)_3$ is varied from 1.0 to 3.0, there is a definite increase in D_2 (which is stereochemically analogous to S_2) in both THF and diethyl ether.

Another significant discovery is the large solvent effects for both 1 and 2. Table I shows that, for 1 with benzaldehyde using 3.0 equiv of $ClTi(OCH(CH_3)_2)_3$, a change from THF to diethyl ether results in a 4.7-fold improvement in stereoselection favoring S_2. The same trend occurs with 1.0 equiv of $ClTi(OCH(CH_3)_2)_3$, but it is even more dramatic, giving a 17-fold increase in selectivity. The product ratios from reactions in diisopropyl ether are closely similar to those in diethyl ether.

Kinetic Control Experiments. In order to ensure that no equilibration was occurring, kinetic control experiments were performed. For each type of aldol adduct, a product mixture of known ratio was added to 1.1 equiv of LDA in diethyl ether at −78 °C, and the mixture was stirred for a period determined not to result in equilibration, whereupon 3 equiv of $ClTi(OCH(CH_3)_2)_3$ was added. This solution was stirred for 4 h from −78 to −30 °C as described in the Experimental Section. Since this generation of the lithium aldolate from the aldol adduct involves only the removal of a hydroxy proton (not enolization), the Li exchange times employed, 15 min or greater, are certainly more than sufficient to generate the desired aldolate. The object of these experiments is to determine if any changes in the product ratios occur after the addition of the titanium reagent during times comparable to the time for running the original titanium-mediated aldol reactions.

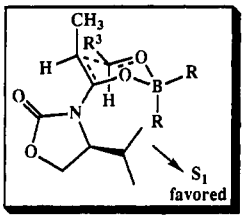
The ratios given in Table III are the same before and after each equilibration experiment to within the experimental uncertainty of the observations in Table I. Entry 5 in Table III is included to show the equilibration which does occur upon warming the reaction mixture to 0 °C.

Control experiments were also performed to demonstrate the homogeneity of the enolate geometry throughout the reaction sequence. The TMS-enolate formed from the lithium enolate of 1 was exclusively, by 200-MHz ^1H NMR, one isomer, only one quartet for the vinyl proton being observable. The predominant silyl enol ether (quartet at 4.83 ppm) very probably has the same *Z* configuration tentatively assigned to the product of trapping the lithium enolate of a related *N*-propionyloxazolidinone with TBDMSCl.[10] The titanium enolate was then trapped with TMS, giving only this same silyl enol ether. These experiments show that predominantly one enolate is formed and maintained throughout the titanium exchange up to addition of the aldehyde.

Discussion

This investigation was designed to determine if specific chelation within the enolate could control titanium-mediated aldol reactions. We have now shown that the titanium enolate of the *N*-propionyloxazolidinone 1 gives strong control for a syn product stereochemistry different from that of the boron enolate. Operational features include use of excess titanium to prevent a previously unrecognized lithium interference effect on the selectivity of titanium-mediated aldol reactions and use of diethyl ether as solvent rather than THF to prevent the solvent interference found with THF. This reversal of stereocontrol from S_1 for boron to S_2 for titanium has both mechanistic and synthetic implications. The mechanistic origin of the reversal is indicated by our results to be chelation of the oxazolidinone carbonyl oxygen to the titanium within the aldol transition structure. It is encouraging for future efforts that this reversal by titanium was *designed* and *predicted*.

Chelation Strategy for Reversing Aldol Stereoselectivity. The stereochemistry of aldol reactions with the boron enolate of 1 can be nicely explained by chair transition structures.[1,9,48] The oxazolidinone ring is oriented as shown schematically in 3 and 4, since transition structures with the ring rotated by 180° about the exocyclic C–N bond would occasion incipient allylic-like strain.[1,4] The transition structure leading to S_1 is then favored, since the oxazolidinone isopropyl group is oriented in a nonrepulsive environment with respect to the chair, in contrast with that leading to S_2.



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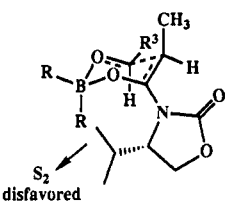


4

Boron, being a second-row element, is not capable of further coordination beyond coordination to the aldehyde in the pericyclic aldol mechanism. However, a metal capable of chelation could coordinate the oxazolidinone carbonyl oxygen in a six-membered chelation ring. Chelation would thus induce a rotation of the oxazolidinone ring by 180°, which would reverse the facial orientation of the isopropyl group and hence favor the opposite transition structure type—S_2 instead of S_1.

The lithium enolate of 1 does not give high stereoselectivities (Table I),[9,10] a frequent outcome believed to result from lithium's lack of a proximate axial metal ligand. Though lithium enolates are usually aggregated, Li–O bonds are considerably longer (1.92–2.00 Å) than B–O bonds (1.36–1.47 Å).[1,2] As shown in 3 and 4, boron's axial ligand would effectively destablize transition structures having the aldehyde group R^3 axial—those providing *anti* aldol adduct stereochemistry.

Once we had rigorously established the stereochemistries of the aldol adducts (see Results), it became clear that the lithium enolate of 1 in fact gives strong stereocontrol favoring the products, S_2 and A_1, expected from chelation control, but poor control over syn vs. anti stereochemistry! This result strengthened our hypothesis that a metal combining extra ligands, in analogy with boron, and chelation ability, in analogy with lithium, should be capable of reversing the selectivity observed with boron, to give the chelation product, while controlling the syn/anti selectivity

(48) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

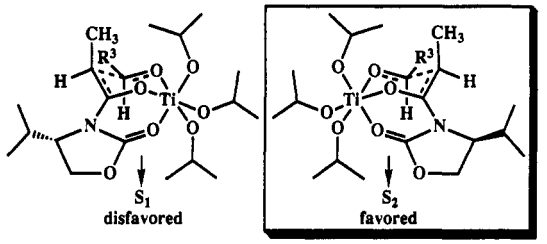
Table III. Kinetic Control Experiments for Aldol Reactions of *N*-Propionyloxazolidinone with Aldehydes R^3CHO

		before kinetic control[a]				after kinetic control[a]			
entry	R^3CHO	S_1	S_2	A_1	A_2	S_1	S_2	A_1	A_2
1[b]	PhCHO	c	96	4	c	c	93	7	c
2[d]	iPrCHO	89	11	c	c	92	8	c	c
3[d]	iPrCHO	14	82	4[e]	c	10	83	7[e]	c
4[d]	BuCHO	13	57	27[e]	3[e]	15	56	25[e]	4[e]
5[d,f]	PhCHO	c	96	4	c	28	27	45	c

[a] Product ratios determined by ^1H NMR for PhCHO, by conversion to trifluoroacetate ester and measurement by ^1H NMR for iPrCHO, and by HPLC for BuCHO adducts. [b] Li exchange only carried out for 15 min before addition of $ClTi(OCH(CH_3)_2)_3$, as longer times resulted in equilibration. [c] Product not observed by assay method. [d] Li exchange carried out for 1 h before addition of $ClTi(OCH(CH_3)_2)_3$, without any resulting equilibration. [e] Stereochemistry of anti adducts currently proven only for benzaldehyde; other assignments are by analogy with benzaldehyde. [f] The experimental temperature was allowed to reach 0 °C.

as well. For brevity, we employ terms such as "chelation product" to refer to the product stereochemistry expected from chelation, without the intention to imply that chelation is necessarily the operative mechanism. Whether the chelation product does indeed arise from a chelation mechanism—or from alternative routes not involving chelation, but rather other interactions which just happen to yield the chelation-predicted stereochemistry—must be examined experimentally in each case.

Titanium enolates combine both of these features. In chelated transition structures, shown schematically in 5 and 6, the titanium is only octahedral, a well-known possibility among stable titanium complexes;[11,18] we postulated



CHELATED TRANSITION STRUCTURES

5 6

that allylic strain would be overcome by chelation, especially since the geometry would only partially resemble that of the product, so that allylic strain would be only partially developed. The conformational preference of imides is for anti carbonyls,[49] but they are rotated into a syn geometry upon lithium chelation.[50] Consequently, we predicted that titanium would give a preference for S_2, rather than the S_1 diastereomer observed with boron.

Stereoselectivity in Aldol Reactions of Titanium Enolates. As noted above, aldol reactions of the lithium enolate of 1 do not give very high stereoselectivities (Table I). Generation of the titanium enolate of 1 by the usual procedure, addition of 1 equiv of $ClTi(OCH(CH_3)_2)_3$ to the lithium enolate, also gave discouragingly low selectivity with benzaldehyde, in fact (Table I) favoring S_1 (nonchelation) over S_2 (chelation)! However, we soon discovered that a lithium interference effect, first discovered in our laboratory,[5,6] was at work. We had shown that this interference could be removed by simply adding a 2 to 3 molar excess of $ClTi(OCH(CH_3)_2)_3$,[5,6] which here led to a dramatic reversal to give high selectivity for S_2 (Table I). Clearly, the species undergoing aldol reaction in the presence of 1 equiv of titanium reagent is different from that giving high selectivity for the chelation product in the presence of ≥2 equiv. The exact nature of the former species is not known as yet, but the simplest hypothesis is that it is a titanium ate complex, with the Cl still attached to the titanium; this hypothesis has been discussed previously.[6,8]

Continuing our quest for enhanced chelation selectivity, we considered that the solvent might play an important role. We discovered that solvent strongly affects the aldol stereoselectivity of the titanium enolate, though it has little effect with lithium (Table I). With benzaldehyde, a switch from THF to diethyl ether increased the S_2:S_1 selectivity significantly. Even with 1 equiv of titanium, S_2 became the major product, and with 3 equiv, S_2 reached a level of 92%.

The titanium enolate at first gave puzzling results with other aldehydes: the adducts assigned as S_2, A_1, and A_2 formed to the extent of nearly 90% or greater with benzaldehyde, isobutyraldehyde, and *n*-pentanal, respectively. It seemed most unlikely that these different aldehydes would each produce such a predominance of a different product diastereomer. Upon further analysis, we have found (see Results) that the products originally assigned[9,10] as A_1 and A_2 are both really S_2, so that all three aldehydes actually produce S_2 selectively. Since the boron enolates give S_1 almost exclusively, S_1 had been rigorously assigned in each case, but, not surprisingly, only for benzaldehyde had the other, minor diastereomers been investigated with equal rigor. The major isomers from the titanium-mediated reactions are minor in the case of boron.

Ether in combination with ≥2 equiv of titanium gave high levels of chelation product S_2 for each aldehyde examined.

The interpretation of our data on stereoselectivity depends on (a) the stereochemical integrity of the enolate, because, considering chairlike transition structures, the *E* enolate would give anti rather than syn product, and (b) the issue of retro-aldol processes occurring during the reaction, i.e., of kinetic vs thermodynamic control, because kinetic control is required in order to interpret observed selectivities in terms of transition structures. Consequently, we carried out experimental tests. Both the lithium and titanium enolates were trapped by trimethylsilyl chloride to give the corresponding silyl enol ethers. NMR experiments clearly demonstrated that only one vinyl proton quartet at 4.83 ppm was present in each case. Although it has not been rigorously established that this is the *Z* enolate, these experiments do demonstrate that no second enolate is formed prior to the addition of the aldehyde, so that differences in syn:anti ratios cannot be ascribed to presence of both *Z* and *E* enolates in different amounts, e.g., for lithium vs titanium. We have also carried out kinetic controls using aldol adduct mixtures made up with different ratios of the diastereomers S_1, S_2, A_1, and A_2 from those isolated from our aldol reactions. Subjection of these mixtures to the conditions of the aldol reaction followed by reisolation of the aldol adduct mixture gave S_1:S_2:A_1:A_2 ratios (Table III) which were unchanged

(49) Noe, E. A.; Raban, M. *J. Am. Chem. Soc.* **1975**, *97*, 5811–5820.
(50) Raban, M.; Keintz, R. A.; Noe, E. A. *Tetrahedron Lett.* **1979**, 1633–1636.

within experimental error from the starting ratios.

Our experiments show that one can obtain either S_1 or S_2 with high stereoselectivity from the *same* starting material, by use of different metals, boron for S_1 or titanium for S_2. These adducts can be readily hydrolyzed to the corresponding enantiomeric *syn*-β-hydroxy-α-methyl carboxylic acids. This capability could be very useful in convergent synthetic schemes where it is frequently necessary to fix opposite chiralities in different fragments which will later be joined together. Lithium gives rather low syn:anti control, but our stereochemical assignments, discussed above, indicate—though the A_1 assignment is tentative—that the *sum* of the two apparent chelation products (S_2 and A_1) approaches or exceeds 90% with each aldehyde. This observation is nicely consistent with results on *alkylation* of this lithium enolate, where high selectivity for the chelation product was found:[27] since there is no syn–anti dichotomy in alkylation, all processes proceeding via chelation give a single chelation product.

Transition Structures for Chelation Control. We have shown that the titanium enolate of 1 strongly favors the aldol products predicted by chelation control, but that fact alone does not prove that chelation is the actual mechanism. However, the *reversal of stereoselection with respect to the corresponding boron enolate*, constitutes powerful evidence favoring a chelation mechanism.

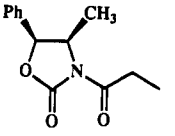
Even the boron enolate probably exists in chelated form,[4] but coordination of the aldehyde must disrupt that chelation. A nonchelated transition structure is therefore forced upon boron; of the four chairlike possibilities, the one predicted to be most stable leads to the observed major product, S_1. In contrast, the chelated titanium enolate contains pentacoordinate titanium, which upon aldehyde coordination becomes only hexacoordinate, a well-known coordination state of Ti(IV), as discussed above. Of the four possible chelated, chairlike transition structures, the one predicted to be favored leads to the observed major product, S_2. While this evidence does not constitute absolute proof, it is most difficult to imagine that the predicted absolute stereochemistries for Ti and B, including the predicted reversal, could result except by a change of mechanism to chelation control for titanium.

This mechanism involving a chelated enolate, as illustrated in transition structure 6, makes the chairlike transition structure a more rigid, tricyclic system, which should enhance the possibilities for stereocontrol relative to otherwise equivalent nonchelated systems. The apparent chelation observed here is unique because it involves a $((CH_3)_2CHO)_3Ti$ enolate, previously considered[13] in other situations to be too weak a Lewis acid to engage in chelation. Here, a favorable six-membered chelation ring geometry, as well as the weaker-coordinating solvent, ether, and the use of excess titanium to avoid the previously unrecognized lithium interference effect, are apparently sufficient to allow the chelation mechanism to compete effectively with nonchelation processes.

The structural features of the chelated transition structure for the titanium enolate and the nonchelated one for the boron enolate necessarily differ in several ways. Metal–oxygen bond lengths and hybridizations are significantly different, titanium having longer bonds (Ti–O, 1.62–1.73 Å; B–O, 1.36–1.47 Å)[1,2,51] and being hexacoordinate, thus approximately octahedral, in contrast to the approximately tetrahedral boron. The effect of these differences on the 6-membered ring aldol transition structure depends in part on the degree of reactant-like vs product-like character, but there are significant compensating effects: the near-90° ring O–Ti–O angle (vs O–B–O, near 109.5°) tends to bring groups closer together while the larger Ti–O bond lengths make them farther apart. Particularly relevant to stereocontrol is the presence of titanium ligands at approximately 90° with respect to the ring O–Ti–O plane; the corresponding angle between an axial boron ligand and the O–B–O plane is approximately 125°. Thus, the chelated titanium transition structure has a "*superaxial*" ligand which is capable of compensating to a large extent for the longer Ti–O bond.

Chelation causes rotation of the oxazolidinone ring relative to the conformation expected for a nonchelated transition structure (cf. 3 and 6). Chelation thus dramatically alters the orientation of the chiral center with respect to the enolate in the transition structure. Since π-overlap tends to keep the conjugated π-system planar, the oxazolidinone ring rotates approximately 180° with respect to the enolate C=C moiety, which in turn lies approximately in the plane of the oxazolidinone ring.

As a result, the interactions responsible for facial selectivity must be quite different in the two mechanisms. In the nonchelation mechanism, approach of the aldehyde to one face of the enolate is blocked by a repulsive interaction between the chiral center's isopropyl group and the *metal* (and its ligands, if any), cf. 4. This constitutes a "rule-of-six" repulsion[52-54] between the isopropyl CH and the metal. In contrast, in the chelation mechanism, the rotated oxazolidinone *directly* blocks approach of the aldehyde to one face of the enolate (the opposite one) by a repulsive interaction between the isopropyl and the aldehyde carbonyl carbon, also a rule-of-six repulsion (cf. 5). The rule-of-six phenomenon also nicely explains why norephedrine-derived oxazolidinones (7) give relatively high diastereofacial selectivities in both nonchelation[9] and chelation[55] processes, even though the proximal chiral center bears only a methyl group instead of the bulkier isopropyl: methyl is already sufficient to give a rule-of-six repulsive interaction.



7

Models show that the favored chelation transition structure can readily adopt a somewhat distorted chairlike conformation which is very rigidly locked, if it be assumed that chelation can be favorable when titanium is somewhat out of the plane of the oxazolidinone ring carbonyl group and the corresponding Ti–O–C bond angle is somewhat greater than 120°. A relevant analogy exists in the X-ray structure cited above, where chelation of $TiCl_4$ to two ester carbonyls places Ti 48° and 64° out of the carbonyl planes and gives Ti–O–C angles of 132° and 134°, respectively.[21]

Our stereochemical reassignments show that the lithium enolate of 1 behaves like similar systems[24,25] in giving anti selectivity for aromatic, but syn selectivity for aliphatic, aldehydes. In contrast, the titanium enolate gives syn

(51) The value for Ti is for alkoxy bonding. An X-ray structure of the $TiCl_4$·ethyl *O*-acryloyllactate complex reveals that the two C=O—Ti chelation bonds have lengths of 2.109 and 2.136 Å.[21]

(52) Newman, M. S. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956, pp 201–248.
(53) Newman, M. S. *J. Am. Chem. Soc.* **1950**, *72*, 4783–4786.
(54) Brownstein, S.; Burton, G. W.; Hughes, L.; Ingold, K. U. *J. Org. Chem.* **1989**, *54*, 560–569.
(55) Shirodkar, S.; Panyachotipun, C.; Thornton, E. R., to be published.

chelation selectivity for all three aldehydes, benzaldehyde in fact giving the highest. Titanium thus differs from all other metals studied, even *n*-Bu_3Sn, which gave results similar to lithium. A chelated boat transition structure has been invoked to explain the anti chelation products in these cases, but the chair **6** is indicated for titanium, at least with this *Z* enolate. The key factor destabilizing the boat relative to the chair may be the relatively short Ti–O bond length, placing attached groups closer than with other metals. The resulting increase in nonbonded repulsive interactions should emphasize the boat–chair energy difference.[56]

Solvent Effect. Diethyl ether as solvent significantly increases the S_2:S_1 ratio (to 31) relative to THF (6.5) in the reaction of **1** with benzaldehyde. Mechanistically, this effect could involve either (1) coordination of THF to titanium in the transition structure, thus competing with or inhibiting chelation of the oxazolidinone carbonyl, but no coordination of ether, thus enhancing chelation, or (2) coordination of *both* THF and ether, the effectively larger bulk of ether giving stronger steric interactions in the transition structure, in turn leading to increased selectivity for ether.

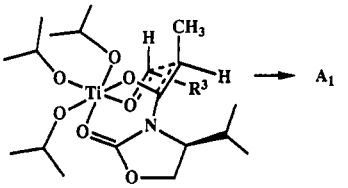
A still bulkier solvent should have little effect on the stereoselectivity compared with diethyl ether if (1) is the explanation, since it, too, should not be coordinated. However, if (2) is operative, then a bulkier solvent should increase the selectivity still more. Diisopropyl ether, which remains liquid at −78 °C, gives stereoselectivities within experimental uncertainty of diethyl ether. This result indicates that neither of these ethers coordinates to titanium in the transition structure, but that THF does coordinate. The difference is logical, since it is known that THF has greater solvation power (less bulky, greater dipole moment) than ether. Differences between THF and ether have been observed in other cases and interpreted in terms of stronger binding of THF to metals.[57-61] We also tried CH_2Cl_2 as solvent, but insolubility of the enolate prevented reaction.

With the lithium enolate we found no significant difference between THF and ether as solvents, in spite of the large solvent effect observed for the titanium enolate. This observation indicates that specific properties of titanium, most likely the presence of alkoxy ligands and the relatively short Ti–O bond distances, play a significant role in weakening the coordination of ether relative to THF. The lithium enolate may be aggregated, but Li is normally only tetracoordinated, and Li–O distances (1.92–2.00 Å) in such aggregates are known to be longer than Ti–O (1.62–1.73 Å).[1,2,62,63]

It is noteworthy that the effect of changing from one equivalent of titanium reagent to three is similar in THF and ether. In both solvents, more chelation product, S_2, is formed with 3 equiv of $ClTi(OCH(CH_3)_2)_3$. The increase in chelation control with change in solvent occurs regardless of the number of moles of titanium reagent.

Solvent coordination in the nonchelation transition structure implies hexacoordinate titanium. If solvent remained coordinated in the transition structure for formation of the chelation product as well, then titanium would be heptacoordinate—if chelation were truly operative. We have evidence that THF does remain coordinated to both chelation and nonchelation transition structures.[64] Heptacoordination is plausible, since even octacoordinate complexes of titanium(IV) are known.[65]

Enolate Substitution. As a further probe of the transition structure interactions controlling stereoselectivity, we also studied aldol reactions of the enolate of *N*-acetyloxazolidinone **2** with benzaldehyde. The effects of $ClTi(OCH(CH_3)_2)_3$ and solvent were similar to those for **1** (Table II), but the selectivity was much lower for **2**. Unsubstituted enolates give poor stereoselection in many cases,[2] but a D_2:D_1 ratio of 3:1 was found with 3 equiv of titanium in ether solvent, which is a reversal in selectivity compared with the boron enolate (38:62).[9,43] This result, taken in conjunction with other results reported here, gives insight into the cause of reduced selectivity with these types of imides. We postulate that D_2 results from the chelated chair transition structure analogous to **6** (without the enolate methyl group), but D_1 results from a combination of not only the nonchelated chair analogous to **3** but also a chelated boatlike transition analogous to **8**. The



8

alternative boatlike transition structure with the metal at a bow position, suggested by semiempirical theory,[66] is not accessible while still maintaining chelation. Molecular models make it clear that a titanium ligand is moved closer to the quasi-axial enolate methyl group in boat **8**. The increased methyl–isopropoxy repulsive interaction is a major factor disfavoring *propionyl*oxazolidinone transition structure **8** relative to **6**. This methyl group is absent in the *acetyl*oxazolidinone, however, and consequently the transition structures analogous to **8** and **6** should become closer in energy. With acetyloxazolidinone **2**, the analogue of boat **8** produces D_1.

Consistent with these ideas are the results from the lithium-mediated reactions. The boatlike transition structure should not be so disfavored even for the propionyl substrate **1**, since repulsive interaction between the quasi-axial enolate methyl and metal ligand should be reduced relative to titanium. Even an aggregated lithium species would be expected to have approximately tetrahedral coordination and hence little ligand–methyl repulsion in the boat corresponding to **8**—in contrast with the hexacoordinate titanium, where one ligand is forced into a distinctly "superaxial" position in **8**. Hence, more boat product (A_1) is expected with lithium than with titanium. In fact, propionyl substrate **1** does give significantly more A_1 with Li than with Ti (Table I, entries 1–4 vs 5–9).

When the quasi-axial methyl group is not present, as in the acetyloxazolidinone **2**, the repulsive methyl–ligand

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(57) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245–1249.
(58) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.
(59) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031–1034.
(60) Eliel, E. L.; Koskimies, J. K.; Lohri, B.; Frazee, W. J.; Morris-Natschke, S.; Lynch, J. E.; Soai, K. In *Asymmetric Reactions and Processes in Chemistry*; ACS Symposium Series No. 185; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982; pp 37–53.
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(62) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.
(63) Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, *26*, 3931–3934.
(64) Shirodkar, S.; Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1990**, *31*, 4699–4702.
(65) Reference 11, p 32.
(66) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576–3581.

interaction necessarily disappears, and the boat should not be so disfavored, even with titanium. Hence, more boat product is expected, but the change should be smaller for lithium than titanium, because the reduced lithium ligand interaction just discussed already gave increased A_1 with the propionyl substrate. Compared with the corresponding boat product A_1 from the propionyl substrate (Table I), with titanium the acetyl substrate (2) and benzaldehyde (Table II) give proportionally much more D_1 (expected from boat 8) relative to D_2 (e.g., in THF, A_1:S_2 = 3:84, but D_1:D_2 = 46:54), *and* with lithium a smaller, but significant, increase in D_1 relative to D_2 (A_1:S_2 = 59:32; D_1:D_2 = 87:13), just as predicted. The corresponding boron enolate, with large ligands but no possible chelation, behaves similarly to titanium in giving high selectivity with the propionyl substrate 1 (though now for the nonchelation product S_1) and reduced ratios near 50:50 with the acetyl substrate 2,[9,43] plausibly involving a nonchelated boatlike transition structure to produce D_2 in competition with D_1 produced by a nonchelated chairlike transition structure analogous to 3 (which gives S_1 with propionyl).

Taken together, these results constitute highly consistent, if circumstantial, evidence for the involvement of a chelated boatlike (probably twist-boatlike) transition structure schematically represented by 8 in producing A_1 from propionyloxazolidinone 1 and D_1 from acetyloxazolidinone 2, even though truly rigorous evidence is still absent.

Boatlike (or twist-boatlike) transition structures have been postulated in certain cases to explain lack of correlation between enolate geometry and product stereochemistry.[1,2,42] Recent theoretical studies on borate enolates (modeled as CH_2=$CHOB(OH)_2$) constitute the closest available analogy to alkoxytitanium enolates.[67,68] They concluded that, although *Z*-α-substituted enolates prefer chairlike transition structures in order to minimize steric repulsions involving the *Z*-α-group, α-unsubstituted borate enolates to tend to prefer boatlike ones, as our experimental results suggest for titanium. Results for borinate enolates are quite similar, though boatlike and chairlike transition structures for the α-unsubstituted enolate are now predicted to be nearly equal in energy.[66,68,69]

For lithium enolates, a half-chair aldol transition structure is predicted in the gas phase.[68,70] In solution, this structure is expected to be altered by lithium–solvent coordination to a much greater extent than the corresponding boron or titanium structures, where the metal already has multiple nonsolvent ligands. An approximate model for solvation of the half-chair was examined,[68] but boatlike structures have not as yet been tested. In the present case, chelation—not accessible in the half-chair—may provide a driving force toward boatlike and chairlike chelated transition structures.

Conclusions

As we had predicted, we find that the titanium enolate of chiral *N*-propionyloxazolidinone 1 gives high selectivity for S_2, the product expected from chelation control, and high syn–anti control, in contrast with lithium, which gives chelation products, but poor syn–anti control. The aldol stereochemistry is reversed from S_1 for the boron enolate to S_2 with titanium. Consequently, by using titanium enolates in conjunction with boron enolates, both S_1 and S_2 can be obtained via the same chiral auxiliary readily prepared from the amino acid L-valine. This dual approach has synthetic advantages, since the time and expense of working with two different chiral auxiliaries to obtain the two different configurations are avoided and the titanium enolate is simpler to use than the boron enolate.

This work constitutes progress toward our goal of using the coordination properties of titanium in enolate chemistry. We are exploring (1) synthetic applications of titanium enolates, (2) characterization of the interactions *truly* responsible for the stereoselectivities observed, and (3) development of new designs to enhance still more the stereocontrol of aldol reactions.

Experimental Section

Materials and Methods. Materials and methods were essentially as described previously.[6] Reagents and solvents were further purified or dried prior to use.[71] The exact concentration of *n*-butyllithium was determined by titration.[72] Solvent systems are described as volume:volume ratios before mixing. All solutions described as percents are weight/volume percents before mixing. Baker silica gel for flash chromatography[73] (40 μm average particle size) was used for flash and medium-pressure columns.

L-Valinol. L-Valinol was prepared by BF_3·Et_2O-catalyzed BH_3·$S(CH_3)_2$ reduction of L-valine, with some modifications of a previous procedure.[74] The crude material was vacuum distilled, giving a clear, colorless liquid (16 g, 61% yield). Bp: 64–66 °C (0.05 mmHg). This purification could also be carried out via Kugelrohr distillation. IR (CCl_4): 3300 (br), 2900, 2850, 2800, 1570, 1450, 1370, 1350, 1100, 1060, 1040, 1000 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 3.63 (dd, J = 3.8, 10.5, 1 H, C*H*OH), 3.31 (dd, J = 7.2, 10.6, 1 H, C*H*OH), 2.56 (ddd, J = 3.8, 6.4, 8.6, 1 H, C*H*NH_2), 2.5–2.1 (m, 3 H, N*H*$_2$, OH), 1.59 (dqq, J = 6.7, 6.7, 6.7, 1 H, C*H*$(CH_3)_2$), 0.93 (d, J = 6.8, 3 H, C*H*$_3$CHCH_3), 0.91 (d, J = 6.8, 3 H, CH_3CH*CH*$_3$). $[\alpha]^{25}_D$ +14.9° (neat) (lit.[74] +14.6° (neat)).

(*S*)-4-(1-Methylethyl)-2-oxazolidinone. Synthesis was by reaction of L-valinol with diethyl carbonate, based on a prior procedure for an analogous oxazolidinone,[75] giving white, needlelike crystals (10.3 g, 82% yield). Mp: 71–72 °C. IR (CCl_4): 3225 (br), 3125, 2950, 2925, 2875, 2850, 1760, 1480, 1470, 1425, 1400, 1370, 1330, 1310, 1250, 1100, 1070, 1060, 1030 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 5.90 (br s, 1 H, N*H*), 4.45 (dd, J = 8.7, 8.7, 1 H, OC*H*), 4.11 (dd, J = 8.7, 6.3, 1 H, OC*H*), 3.61 (dddd, J = 8.7, 0.8, 6.5, 6.5, 1 H, C*H*CH_2O), 1.74 (m (6 peaks resolved), J_{app} = 6.7, 1 H, C*H*$(CH_3)_2$), 0.96 (d, J = 6.7, 3 H, C*H*$_3$CHCH_3), 0.91 (d, J = 6.7, 3 H, CH_3CH*CH*$_3$). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 160.1 (*C*=O), 68.5 (CH_2O), 58.4 (*C*HN), 32.6 (*C*H$(CH_3)_2$), 17.9, 17.6 (CH$(CH_3)_2$). $[\alpha]^{25}_D$ +16.8° (*c* 0.175, $CHCl_3$) (lit.[9,10] +14.8° (*c* 0.07, $CHCl_3$)).

(*S*)-3-(1-Oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (1). The lithium salt (*n*-BuLi) of (*S*)-4-(1-methylethyl)-2-oxazolidinone was acylated with propionyl chloride.[10] Product isolation gave a yellow oil which was purified by Kugelrohr distillation (110 °C, 0.05 mmHg), to give a colorless oil, 1 (7.6 g, 88.3% yield). IR (CCl_4): 2990, 2960, 2910, 1800, 1785, 1720, 1570, 1480, 1400, 1355, 1325, 1260, 1230, 1170, 1150, 1100, 1050, 1010, 975, 920, 850 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.7–4.2 (m, 3 H, OC*H*$_2$C*H*N), 3.0–2.85 (m, 2 H, COC*H*$_2$CH$_3$), 2.38 (dqq, J = 3.88, 7.0, 7.0, 1 H, C*H*$(CH_3)_2$), 1.17 (dd, J = 7.35, 7.35, 3 H, CH_2C*H*$_3$), 0.92 (d, J =

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7.0, 3 H, CH_3CHCH_3), 0.88 (d, J = 7.0, 3 H, CH_3CHCH_3). ^{13}C NMR (50.3 MHz, CCl_4): δ 172.7 ($CH_2C{=}O$), 153.0 ($OC{=}O$), 62.8 (CH_2O), 57.9 (CHN), 28.6, 28.3 ($CH(CH_3)_2$, $COCH_2CH_3$), 17.7, 14.6 ($CH(CH_3)_2$), 8.8 ($COCH_2CH_3$). $[\alpha]^{25}_D$ +94° (c 0.0175, CH_2Cl_2); lit.[10]: +96.8° (c 0.087, CH_2Cl_2).

(S)-3-(1-Oxoethyl)-4-(1-methylethyl)-2-oxazolidinone (2). The lithium salt (n-BuLi) of (S)-4-(1-methylethyl)-2-oxazolidinone was acylated with acetyl chloride. Product isolation gave a yellow oil which was purified by flash chromatography (7:3 hexane–ethyl acetate), resulting in **2** as a colorless oil (5.3 g, 66.4% yield). IR (CCl_4): 2925, 2900, 2850, 1790, 1700, 1480, 1465, 1425, 1390, 1380, 1360, 1350, 1310, 1290, 1220, 1210, 1150, 1129, 1120, 1070, 1040, 1030, 990, 970 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.47–4.20 (m, 3 H, OCH_2CHN), 2.53 (s, 3 H, $COCH_3$), 2.39 (dqq, J = 3.8, 7.0, 7.0, 1 H, $CH(CH_3)_2$), 0.93 (d, J = 7.0, 3 H, CH_3CHCH_3), 0.89 (d, J = 7.0, 3 H, CH_3CHCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.1 ($CH_3C{=}O$), 154.2 ($OC{=}O$), 63.2 (CH_2O), 58.2 (CHN), 28.3 ($CH(CH_3)_2$), 23.6 ($COCH_3$), 17.8, 14.5 ($CH(CH_3)_2$). $[\alpha]^{25}_D$ +91.7° (c 0.0244, CH_2Cl_2) (lit.[43] +98.4° (c 0.0257, CH_2Cl_2)).

General Procedures for Formation of Enolates and Their Reactions with Aldehydes. Reactions were carried out on 0.5–5 mmolar scales. All reagents were added via dry hypodermic syringe. The procedure for formation of lithium enolates and their aldol reactions was basically that of Heathcock et al., using reaction times of 30 s.[76]

Titanium-mediated aldol reactions were carried out according to the method of Reetz et al.[77] with modifications. The lithium enolate was first generated as for the aldol reactions of lithium enolates.[76] While at −78 °C, 1–3 equiv (as desired) of $ClTi(OCH(CH_3)_2)_3$ in hexanes (1 M), or neat and freshly distilled, was added dropwise with stirring. The solution usually became clear and brown-orange after this addition. The solution was allowed to warm to −40 °C over 1 h and then cooled to −78 °C. Still at −78 °C, aldehyde (1.1 equiv) was added rapidly by syringe, and reaction was allowed to take place over the temperature range −78 to −40 °C for 3 h. The reaction was quenched with saturated, aqueous NH_4F, and the layers were separated. The aqueous layer was extracted 3 times with diethyl ether. All organic layers were combined and dried over $MgSO_4$, followed by vacuum filtration and rotary evaporation to dryness.

(4S)-3-[(2R,3R)-3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl]-4-(1-methylethyl)-2-oxazolidinone (S_2). Titanium-mediated aldol reaction of **1** with benzaldehyde in diethyl ether, using 3 molar equiv of $ClTi(OCH(CH_3)_2)_3$, afforded a crude, white-yellow solid. Diastereomer analysis was carried out by HPLC, giving the following values (mean and standard deviation). HPLC analysis [C-18 reversed-phase column, RI detector, 6:4 methanol–water: (S_1) t_R 54.0 min, (S_2) t_R 36.8 min, (A_1) t_R 41.5 min, (A_2) t_R 73.0 min] of the crude mixture revealed a ratio of $S_1:S_2:A_1$ = (3.1 ± 1.3):(92.0 ± 3.4):(4.7 ± 4.0); A_2 was not observed. The retention time for A_2 was determined by injecting the product mixture from the lithium-mediated reaction, which contained all four diastereomers. Purification of S_2 by flash chromatography (7:3 hexanes–ethyl acetate) gave white needles (219 mg, 0.752 mmol, 75.2% yield). Mp: 94–96 °C. IR (CCl_4): 3540 (br), 3010 (w), 2980 (w), 2910, 2830, 1760, 1680, 1660, 1620 (w), 1530, 1390, 1370, 1230, 1190 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.45–7.28 (m, 5 H, aromatic H), 5.14 (dd, J = 3.42, 3.42, 1 H, CHOH), 4.46–4.17 (m, 4 H, OCH_2CHN, $CH_3CHC{=}O$), 2.74 (d, J = 3.12, 1 H, OH), 2.22 (dqq, J = 3.71, 7.0, 7.0, 1 H, $CH(CH_3)_2$), 1.15 (d, J = 6.9, 3 H, $CH_3CHC{=}O$), 0.88 (d, J = 7.0, 3 H, CH_3CHCH_3), 0.71 (d, J = 6.9, 3 H, CH_3CHCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 176.0 ($CC{=}O$), 153.8 ($OC{=}O$), 141.5, 128.3, 127.6, 127.3 (aromatic C), 74.3 (COH), 63.2 (CH_2O), 58.5 (CHN), 44.5 ($CH_3CHC{=}O$), 28.4 ($CH(CH_3)_2$), 17.8, 14.5 ($CH(CH_3)_2$), 11.0 ($CH_3CHC{=}O$). $[\alpha]^{22}_D$ +44° (c 0.00335, CH_2Cl_2). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.73; H, 7.29; N, 4.69.

(4S)-3-[(2R,3S)-3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl]-4-(1-methylethyl)-2-oxazolidinone (A_1). Lithium-mediated aldol reaction of **1** with benzaldehyde in THF was carried out. HPLC analysis [C-18 reverse-phase column, RI detector, 6:4 methanol–water: (S_1) t_R 54.0 min, (S_2) t_R 36.8 min, (A_1) t_R 41.5 min, (A_2) t_R 73.0 min] of the crude product mixture revealed a ratio of $S_1:S_2:A_1:A_2$ = 7.6:31.7:58.8:1.8. A_1 was purified by MPLC (2 cm i.d. × 45 cm packing height, 8:7 diethyl ether–hexanes, 30–40 psi) to give white needles. Mp: 104–106 °C. IR (CCl_4): 3600, 3520, 3000, 2900, 1800, 1730, 1600 (w), 1480, 1410, 1330, 1270, 1240 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.48–7.30 (m, 5 H, aromatic H), 4.75 (dd, J = 7.8, 7.8, 1 H, CHOH), 4.47–4.20 (m, 4 H, OCH_2CHN, $CH_3CHC{=}O$), 3.20 (d, J = 7.7, 1 H, OH), 2.28 (dqq, J = 3.0, 7.0, 7.0, 1 H, $CH(CH_3)_2$), 1.11 (d, J = 6.9, 3 H, $CH_3CHC{=}O$), 0.87 (d, J = 7.0, 3 H, CH_3CHCH_3), 0.73 (d, J = 7.0, 3 H, CH_3CHCH_3). $[\alpha]^{25}_D$ −2.5° (c 0.0187, CH_2Cl_2); lit.[10] −3.18° (c 0.083, CH_2Cl_2).

(4S)-3-[(2R,3S)-3-Hydroxy-2,4-dimethyl-1-oxopentyl]-4-(1-methylethyl)-2-oxazolidinone (S_2). Titanium-mediated aldol reaction of **1** with isobutyraldehyde in diethyl ether, using 2 molar equiv of $ClTi(OCH(CH_3)_2)_3$, afforded a crude clear yellow oil. Diastereomer analysis was carried out by preparing the trifluoroacetate esters[78] of the products by the procedure given later in this Experimental Section, giving the following values (mean and standard deviation). ^1H NMR analysis [250 MHz, $CDCl_3$, carbinol proton ($C_\beta H$): (S_1) δ 5.12 (dd, J = 8.4, 3.8); (S_2) δ 5.28 (dd, J = 7.7, 4.3); (A_1) δ 5.50 (tentatively assigned, dd, J = 7.66, 2.44); (A_2) δ 5.75 (tentatively assigned, splittings not evaluated: signal intensity too low)] of the trifluoroacetates revealed a ratio of $S_1:S_2:A_1$ = (8.1 ± 4.8):(84.4 ± 2.9):(7.4 ± 2.7); A_2 was not observed. The chemical shift given for the presumed A_2 isomers was determined from the lithium enolate product mixture, which contained all four diastereomers. Purification of the aldol products by flash chromatography (8:2 hexane–ethyl acetate) gave a clear, colorless oil (184 mg, 0.715 mmol, 71.5% overall isolated yield of aldol products). S_2 was separated from the other diastereomers by semipreparative HPLC [C-18 reverse-phase column, RI detector, 6:4 methanol–water: (S_2) t_R 23 min], resulting in a clear, colorless oil. IR (CCl_4): 3540 (br), 2975, 2890, 1810, 1710, 1510, 1490, 1410, 1330, 1270, 1240, 1180, 1160, 1140, 1100, 1090, 1050, 1020, 900, 830 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.5–4.14 (m, 3 H, OCH_2CHN), 4.08 (dq, J = 3.0, 7.0, 1 H, $CH_3CHC{=}O$), 3.57 (ddd, J = 8.4, 3.7, 3.7, 1 H, CHOH), 2.50 (d, J = 3.9, 1 H, OH), 2.36 (dqq, J = 3.9, 7.0, 7.0, 1 H, $CH(N)CH(CH_3)_2$), 1.71 (m, 1 H, $CH(OH)CH(CH_3)_2$), 1.16 (d, J = 6.9, 3 H, $CH_3CHC{=}O$), 1.04–0.896 (m, 12 H, two $CH(CH_3)_2$). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 177.4 ($CC{=}O$), 153.3 ($OC{=}O$), 77.1 (COH), 63.3 (CH_2O), 58.5 (CHN), 39.8 ($CH_3CHC{=}O$), 31.1, 28.5 (two $C(CH_3)_2$), 19.9, 19.4, 17.9, 14.7 (four CH_3), 9.73 ($CH_3CHC{=}O$). $[\alpha]^{22}_D$ +57° (c 0.00272, CH_2Cl_2). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.39; H, 8.88; N, 5.33.

(4S)-3-[(2R,3S)-3-Hydroxy-2-methyl-1-oxoheptyl]-4-(1-methylethyl)-2-oxazolidinone (S_2). Titanium-mediated aldol reaction of **1** with n-pentanal in diethyl ether, using 2 molar equiv of $ClTi(OCH(CH_3)_2)_3$, afforded a crude, yellow oil. Diastereomer analysis was carried out by HPLC [C-18 reverse-phase column, RI detector, 6:4 methanol–water: (S_1) t_R 62.6 min, (S_2) t_R 43.9 min, (A_1) t_R 48.4 min (tentatively assigned), (A_2) t_R 72.9 min (tentatively assigned)] of the crude mixture revealed a ratio of $S_1:S_2:A_1$ = (8.7 ± 3.7):(88.3 ± 4.7):(3.0 ± 0.9) (means and standard deviations given); the diastereomer tentatively assigned as A_2 was not observed. The retention time given for the presumed A_2 isomer was determined by assaying the product mixture from the lithium-mediated reaction, which contained all four diastereomers. Product purification by flash chromatography (8:2 hexanes–ethyl acetate) gave a colorless oil, S_2 (305 mg, 1.12 mmol, 56% yield). IR (CCl_4): 3475, 2925, 2880, 2825, 1775, 1700, 1675, 1480, 1455, 1440, 1380, 1360, 1300, 1230, 1200, 1140, 1120, 1100, 1060, 1020, 990 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.50–4.21 (m, 3 H, OCH_2CHN), 3.96–3.88 (m, 2 H, $CH(OH)CH(CH_3)C{=}O$), 2.62 (d, J = 3.3, 1 H, OH), 2.37 (dqq, J = 3.9, 7.0, 7.0, 1 H, $CH(CH_3)_2$), 1.2–1.7 (m, 6 H, $CH(OH)CH_2CH_2CH_2CH_3$), 1.17 (d, J = 6.8, 3 H, $CH_3CHC{=}O$), 0.94–0.92 (m, 9 H, CH_3CH_2, $CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 176.8 ($CC{=}O$), 153.8 ($OC{=}O$), 72.1 (COH), 63.2 (CH_2O), 58.5 (CHN), 42.1 ($CH_3CHC{=}O$), 33.7, 28.5, 28.0, 22.5 ($CH(CH_3)_2$, 3 CH_2), 17.8, 14.6 ($CH(CH_3)_2$), 13.9 (CH_3CH_2), 10.1

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($CH_3CHC{=}O$). $[\alpha]^{22}_D$ +38° (c 0.00542, CH_2Cl_2). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.14; H, 9.29; N, 5.26.

(4*S*)-3-[(3*R*)-3-Hydroxy-1-oxo-3-phenylpropyl]-4-(1-methylethyl)-2-oxazolidinone (D_2). Titanium-mediated aldol reaction of 2 with benzaldehyde in diethyl ether, using 3 molar equiv of $ClTi(OCH(CH_3)_2)_3$, afforded a crude, yellow oil containing white crystals. Diastereomer analysis was carried out by HPLC and by ^{19}F NMR on the trifluoroacetate esters[78] of the diastereomers, giving the following ratios (mean and standard deviation). ^{19}F NMR analysis [235.2 MHz, $CDCl_3$, (C_6F_6, δ −162.9 ppm): (D_1) δ −75.67; (D_2) δ −75.57] of the trifluoroacetates of the crude product mixture revealed a ratio of D_1:D_2 = 25:75. HPLC analysis [C-18 reverse-phase column, RI detector, 6:4, methanol–water: (D_1) t_R 20.75 min, (D_2) t_R 24.5 min] of the crude product mixture resulted in a product ratio D_1:D_2 = 24:76. Aldol product isolation and separation of D_1 and D_2 were carried out by flash chromatography (7:3 hexanes–ethyl acetate), giving aldol products (total 265 mg, 0.956 mmol, 95.6% yield). When purified, D_2 crystallized as white needles. Mp: 115–117 °C. IR (CH_2Cl_2): 3640, 3540, 3070 (w), 3040 (w), 2950, 1780, 1700, 1620, 1390, 1220, 1160, 1070, 1040, 1010, 990, 900 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.44–7.28 (m, 5 H, aromatic *H*), 5.24 (m, 1 H, C*H*OH), 4.49–4.20 (m, 3 H, OCH_2CHN), 3.44–3.30 (m, 2 H, CH_2CHOH), 3.17 (d, *J* = 4.0, 1 H, O*H*), 2.39 (dqq, *J* = 3.8, 6.97, 6.97, 1 H, $CH(CH_3)_2$), 0.94 (d, *J* = 7.0, 3 H, CH_3CHCH_3), 0.88 (d, *J* = 6.9, 3 H, CH_3CHCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.5 (C*C*=O), 153.9 (O*C*=O), 142.5, 128.5, 127.8, 125.8 (aromatic *C*), 70.3 (*C*OH), 63.6 (CH_2O), 58.5 (*C*HN), 44.3 ($CH_2C{=}O$), 28.6 ($CH(CH_3)_2$), 17.9, 14.8 ($CH(CH_3)_2$); $[\alpha]^{22}_D$ +131° (c 0.00109, CH_2Cl_2). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.86; H, 6.87; N, 4.96.

D_1 was also isolated as white needles. Mp: 65–66 °C. IR (CCl_4): 3500, 3030 (w), 2975, 2940, 2875, 2825, 1765, 1690, 1680, 1600 (w), 1480, 1440, 1380, 1360, 1300, 1200, 1140, 1120, 1100, 1060, 1020, 970, 700 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 7.44–7.25 (m, 5 H, aromatic *H*), 5.16 (m, 1 H, C*H*OH), 4.47–4.17 (m, 3 H, OCH_2CHN), 3.46 (dd, *J* = 17.3, 9.5, 1 H, CH_aH_bCHOH), 3.33 (d, *J* = 4.3, 1 H, O*H*), 3.29 (dd, *J* = 17.2, 3.1, 1 H, CH_aH_bCHOH), 2.35 (dqq, *J* = 4.0, 6.9, 6.9, 1 H, $CH(CH_3)_2$), 0.90 (d, *J* = 7.0, 3 H, CH_3CHCH_3), 0.83 (d, *J* = 6.9, 3 H, CH_3CHCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.0 (C*C*=O), 154.0 (O*C*=O), 142.6, 128.4, 127.6, 126.7 (aromatic *C*), 70.3 (*C*OH), 63.5 (CH_2O), 58.4 (*C*HN), 44.1 ($CH_2C{=}O$), 28.4 ($CH(CH_3)_2$), 17.8, 14.6 ($CH(CH_3)_2$).

Hydrolysis of Chiral Oxazolidinone Aldol Adducts To Give Carboxylic Acids. A previous procedure was adapted.[9,10] The aldol adduct was dissolved in methanol (6 mL per mmol of adduct). Water was then added to this solution until it turned cloudy, followed by cooling to 0 °C. While at 0 °C, 2 N aqueous KOH (2 mL per mmol of aldol adduct) was added dropwise with stirring. Still at 0 °C, stirring was continued for another 45 min. The reaction mixture was concentrated by rotary evaporation to remove methanol and hydrolyze any methyl ester formed. The resulting aqueous phase was extracted with CH_2Cl_2 (three 6-mL portions). The combined CH_2Cl_2 layers were backwashed with saturated, aqueous NaCl and dried over anhydrous $MgSO_4$, followed by vacuum filtration and concentration via rotary evaporation to give the oxazolidinone. The original, basic aqueous phase was then adjusted to pH = 1 with 3 N HCl, saturated with NaCl, and extracted with diethyl ether (two 6-mL portions). The combined organic extracts were dried over anhydrous $MgSO_4$ and vacuum filtered, and the filtrate was concentrated to dryness by rotary evaporation.

Preparation of Trifluoroacetate Esters of Aldol Adducts. Following the published procedure,[78] the crude aldol adduct mixture was dried at low pressure (oil pump) for several h, followed by venting to argon. The dried material was then dissolved in anhydrous CH_2Cl_2 (ca. 3 mL for 0.5 mmol of aldol adduct). The solution was then cooled to 0 °C, and anhydrous pyridine (2 equiv) and trifluoroacetic anhydride (1.1 equiv) were successively added, dropwise with stirring. The solution was allowed to warm to ca. 25 °C, stirred for an additional 1 h, and then quenched by addition of aqueous $NaHCO_3$. The layers were separated, and the organic layer was dried over anhydrous $MgSO_4$, vacuum filtered, concentrated via rotary evaporation, and dried further at high vacuum (0.05 mmHg). ^1H and/or ^{19}F NMR spectra were taken of the resulting material.

Kinetic Controls for Aldol Reactions. A mixture of the diastereomers resulting from a given aldol reaction which had given a product ratio different from that observed in ether with 3 equiv of $ClTi(OCH(CH_3)_2)_3$ was analyzed by ^1H NMR, ^{19}F NMR (trifluoroacetate derivative), or HPLC to determine an accurate ratio. The mixture was then thoroughly dried by vacuum (oil) pump for 4 h. The aldol products in diethyl ether were next added at −78 °C to LDA (1.1 equiv, in diethyl ether), exactly as in the procedure for lithium-mediated aldol reactions. After 1 h, 3 equiv of $ClTi(OCH(CH_3)_2)_3$ (neat) was added, also at −78 °C. The reaction mixture was then stirred for 4 h from −78 to −40 °C. After this time, the mixture was quenched with saturated, aqueous NH_4F and worked up, and the products were isolated as described in the general procedure for aldol reactions. Finally, the product mixture was analyzed exactly as was done prior to the given kinetic control.

Trapping of Li and $((CH_3)_2CHO)_3Ti$ Enolates To Demonstrate Constancy of Enolate Geometry Prior to Aldol Reactions. To study the initially formed lithium enolate, the Li enolate was prepared on a 1 mmolar scale exactly as in the procedure for lithium-mediated aldol reactions. After 1 h at −78 °C, Me_3SiCl (0.14 mL, 1.1 equiv) was added according to precedent.[76] The reaction mixture was allowed to warm to ca. 25 °C over 1 h. At ca. 10 °C, a precipitate formed. After another hour at ca. 25 °C, the reaction mixture was partitioned between pentane and saturated, aqueous $NaHCO_3$. The layers were separated, and the pentane layer was dried over anhydrous $MgSO_4$. The mixture was then vacuum filtered and concentrated by rotary evaporation to dryness. The residue was analyzed by ^1H NMR, quantitating the areas of the possible quartets (lit.[9,10] δ 4.86 for the lithium enolate of a related *N*-propionyloxazolidinone trapped with TBDMSCl) resulting from the olefinic hydrogens originating from the two possible enolates.

In order to study the degree to which the enolate geometry was preserved after conversion to the Ti enolate, the titanium enolate of 1 was prepared in diethyl ether just as described in the general procedure for titanium-mediated aldol reactions. While at −78 °C, Me_3SiCl (0.14 mL, 1.1 equiv) was added. The rest of the procedure and analysis was as described above for lithium enolates.

With both the lithium and titanium enolates, only one olefinic quartet, at δ 4.83, was detected.

Acknowledgment. We thank Dr. George Furst, NMR Facility, for his splendid assistance. Support by the University of Pennsylvania Research Fund and by the National Institutes of Health is gratefully acknowledged.