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ASYMMETRIC ALDOL REACTIONS. MECHANISM OF SOLVENT EFFECT ON STEREOSELECTIVITY IS SPECIFIC, STOICHIOMETRIC BINDING OF TETRAHYDROFURAN TO A CHIRAL TITANIUM ENOLATE

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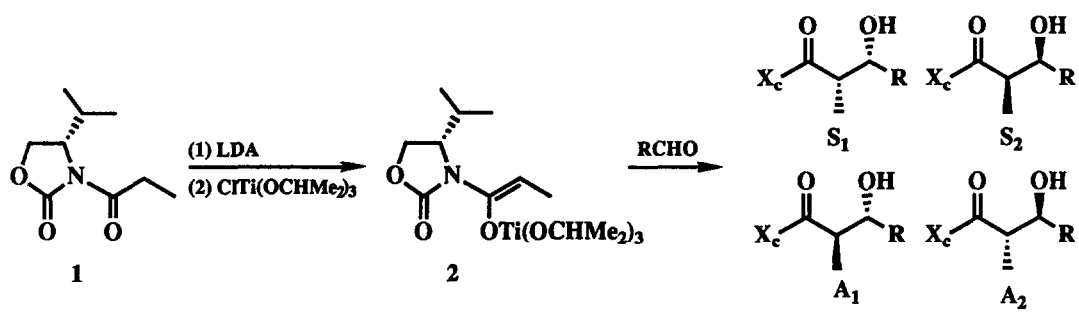
Abstract: Solvent plays an important role in aldol reactions of an acyloxazolidinone-derived titanium enolate. Diethyl ether produces nearly fivefold higher diastereofacial selectivity than THF. We now show that this strong solvent effect arises from stoichiometric binding, most probably to the titanium, of THF in the transition structure, whereas ether is not bound. These mechanistic results indicate that THF lowers the selectivity by interfering with chelation control, which is highly preferred in ether. Implications include the possibility of using other ethers to improve chelation/nonchelation control still more, or even use of chiral ethers as chiral controller groups or adjuncts.

We have shown that asymmetric aldol reactions of readily prepared and handled chiral titanium(IV) enolates can provide very useful levels of stereocontrol.[1-3] With chiral oxazolidinone **1**, we found a dramatic solvent effect upon



aldol stereoselectivity, wherein diethyl ether gave a much higher S_2:S_1 selectivity (31:1)[4] than the more commonly used solvent THF (6.5:1).[2] The S_2 preference produced by the titanium enolate was particularly interesting since it is expected from chelation control.[2] Nonchelation product S_1 is provided by the corresponding boron enolate, which is incapable of chelation.[5] This stereochemical reversal is most difficult to explain except by a change of mechanism to chelation control in the case of titanium. It therefore constitutes very strong evidence for chelation. *Thus it became possible to control the stereochemical outcome from the single substrate 1 to provide either product diastereomer simply by use of either boron or titanium as the metal.*

Since **1** is derived from the easily available natural configuration of the amino acid valine, and since S_1 and S_2 can be readily hydrolyzed to the respective enantiomeric *syn*-β-hydroxy-α-methylcarboxylic acids, these synthetically valuable chiral intermediates can be produced in either enantiomeric form as needed.

The reduced S_2:S_1 ratio in THF solvent can most readily be interpreted as involving interference with chelation by the THF. Because reversal of stereochemistry via chelation control is a synthetic strategy potentially applicable in a variety of reactions, it would be valuable to determine what conditions permit chelation and how to optimize it. In particular, determining the mechanism of the solvent effect we have observed would advance our understanding of chelation control. Here we show that *the effect results mainly from specific, stoichiometric association of a single*

molecule of THF in the transition structure. The most reasonable mechanism is thus association of THF, but not ether, with titanium—competing with, or otherwise decreasing, chelation of the oxazolidinone carbonyl oxygen.

A priori, the observed solvent dependence might result from a general solvation effect, or, alternatively, it might involve specific coordination of the solvent to titanium in the transition structure. Specific solvent coordination would have significant implications for control of selectivity by use of different solvents or solvent mixtures. Consequently, we added known concentrations of THF to ether as solvent, varying the ratio THF:$ClTi(OCH(CH_3)_2)_3$ over the range of 0.25:1 to 4:1 (Table I). Use of 3 equiv of $ClTi(OCH(CH_3)_2)_3$ was already known to be required for optimum diastereofacial selectivity.[1-3]

Table I. Effect of Solvent on Diastereoselection in Aldol Reaction of Oxazolidinone **1** with Benzaldehyde at −78 °C

Metal (Equiv)	Solvent	Equiv of THF	Equiv of THF per equiv of Metal	Product Ratio[a]		
				S_1	S_2	A_1[b]
Lithium (1.0)[c]	Et_2O	0	0	7	17	76
Titanium (3.0)[c]	Et_2O	0	0	3	95	2
Titanium (3.0)	Et_2O	0.75[d]	0.25	7	88 ± 1	5
Titanium (3.0)	Et_2O	1.50[d]	0.50	20	74 ± 7	6
Titanium (3.0)	Et_2O	2.25[e]	0.75	10	86 ± 2	4
Titanium (3.0)	Et_2O	3.00[d]	1.00	16	80 ± 8	4
Titanium (3.0)	Et_2O	6.00[d]	2.00	17	78 ± 15	5
Titanium (3.0)	Et_2O	12.0[e]	4.00	15	84 ± 3	1
Titanium (3.0)[f]	THF	–	–	13	84	3

[a]Product ratios were determined by capillary GLC analysis of trimethylsilylated crude aldol products. All product mixtures were also characterized by high-field ^1H NMR. [b]Product A_2 was not observable in the high-field ^1H NMR nor GLC. [c]Independent data; similar to those we previously reported.[2] [d]Mean of 3 determinations, with SD. [e]Mean of 2 determinations, with av. dev. [f]Data from ref. 2.

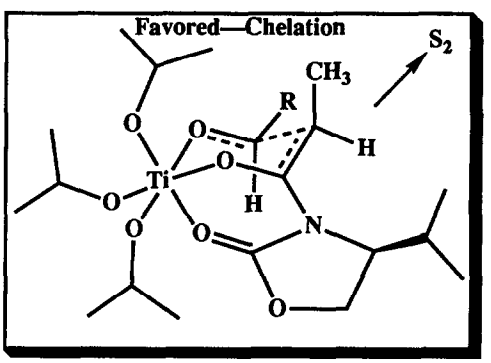
The data in Table I show that *stereochemical results characteristic of THF as solvent can be achieved by addition of less than one equivalent of THF (relative to titanium reagent) to ether solvent!* As THF is added to ether, the selectivity for S_2 drops from that characteristic of ether alone. The effect levels off at ca. 0.75 equivalent of THF per equivalent of titanium (2.25 equiv THF/3.0 equiv of titanium added). The data were obtained with considerable care, but they still have some experimental variation; however, the leveling trend is clear. These results clearly indicate a stoichiometric coordination of THF, most probably to the titanium, in the transition structure. It is plausible that coordination of THF could compete with chelation, reduce the extent of chelation control, and thus decrease the S_2:S_1 ratio, as observed. Stronger coordination of THF than of ether has been invoked previously in explanation of results with other metals or reaction types.[6-10]

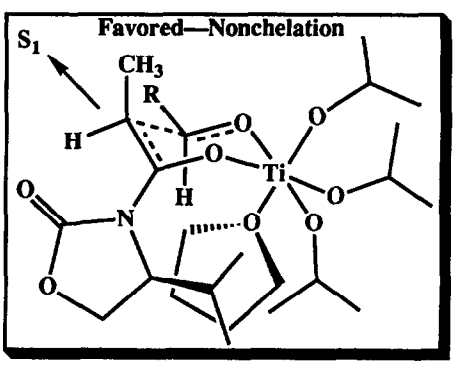
Why is leveling observed at 0.75 equivalent of THF and not at an integer value? Actually, the results are entirely consistent with coordination of one molecule of THF. Given what we know about titanium-mediated aldol reactions, the following explanation is indicated. The simplest consistent explanation of the requirement for excess titanium reagent to give high stereoselectivities is that one excess equivalent forms an ate complex with the LiCl present *in situ* when the titanium enolate is generated from addition of $ClTi(OCH(CH_3)_2)_3$ to the lithium enolate.[1-3] This ate

complex, $Li^+Cl_2Ti^-(OCH(CH_3)_2)_3$, should complex THF much less strongly than the non-ate titanium species, namely, the enolate and the excess $ClTi(OCH(CH_3)_2)_3$. Therefore, added THF should preferentially complex to the latter two non-ate species, which amount to only two of the three equivalents of titanium present in the reaction mixture. Consequently, using our usual 3-fold excess of titanium, the leveling of the THF effect should occur when two equivalents of THF are present, i. e., at a ratio of 0.67, in excellent agreement with the observed leveling of the stereochemical effect at a ratio of ca. 0.75.

The S_2:S_1 ratio drops below that characteristic of pure THF solvent at 0.50 equivalent of THF per equivalent of titanium, to only 3.7:1. However, experimental error does not permit us to be certain whether the selectivity is really below that for pure THF. While the possible significance of this effect cannot be ruled out at present, and sources such as partial reaction through a chlorotitanium enolate of the type $[(CH_3)_2CHO]_2Ti(Cl)OCH(X_c)=CHCH_3$, formed by ligand exchange with excess $ClTi(OCH(CH_3)_2)_3$,[3] possibly prevented in the presence of THF, or through the ate complex,[2] or even involvement of aggregation phenomena, could explain it, we tentatively assume that the result is simply within experimental variation. We hope in the future to resolve these questions directly by means of NMR studies.

The present data provide strong support for a chelated transition structure in ether, as well as a stoichiometric association of one molecule of THF with titanium as the origin of the THF effect. Transition structures of the type shown below nicely explain the results. In each case, only the favored transition structure is shown, i. e., the one resulting from attack of the aldehyde at the less-hindered face of the enolate, opposite from the isopropyl group at the chiral center of the oxazolidinone. The nonchelation structure is analogous to that proposed for the corresponding boron enolate[5] (except that boron, when coordinated to the aldehyde, could not also have a coordinated THF molecule).





One further conclusion is indicated by the data. Even in THF as solvent, the chelation product predominates (S_2:S_1 = 6.5:1). Yet the evidence shows that there is stoichiometric binding of THF. If the S_2 product observed in the presence of THF were formed via a chelated transition structure like that shown above, with no THF coordinated to titanium, then the population of the THF-coordinated transition structure relative to the chelated one should increase with increased concentration of THF. There could be no leveling effect until the concentration of THF were made high enough to shift the equilibrium almost entirely toward population of THF-coordinated transition structures. The observed leveling of stereoselectivity can only be explained by a saturation effect involving 1:1 binding of THF, i. e., essentially all of the products must arise from transition structures containing one molecule of THF. Therefore, our results are only consistent with formation of the *chelation* product S_2 in the presence of THF through a transition

structure which also contains a stoichiometrically bound THF molecule. This conclusion does not identify where the THF might be bound, but it is most logically coordinated to titanium. If so, then either (1) chelation is still present in the transition structure leading to S_2, which implies a heptacoordinate titanium (even octacoordinate complexes of titanium(IV) are known[11]), or (2) there are special requirements, possibly steric, of the coordinated THF which, without any chelation, cause the oxazolidinone ring to rotate preferentially into a conformation similar to that for the chelated transition structure, and thus reverse the facial selectivity to favor S_2. If the equilibrium population of the rotated conformer were sufficiently large and were maintained in the transition structure, then the observed S_2:S_1 ratio in the presence of THF could be characteristic of THF-coordinated species with no chelation at all. Further work will be required to differentiate these alternatives, but *both* of them have very interesting implications such as the use of other ethers to improve chelation/nonchelation control still further, or even the possible use of chiral ethers as ligands serving as chiral controller groups or adjuncts.

Finally, it will be noted that either (1) or (2) in the previous paragraph could in principle apply to the reaction in ether solvent, i. e., ether could conceivably be bound to titanium in the transition structure but be giving higher S_2:S_1 selectivity than the more compact THF. That this is not the case is indicated by our previously reported observation that diisopropyl ether as solvent gives an S_2:S_1 ratio which is close to, and slightly lower than, that for diethyl ether, but much higher than that for THF.[2] If steric effects of a bound diethyl ether molecule were responsible for its enhanced selectivity relative to THF, then the bulkier diisopropyl ether should give still higher selectivity, in contrast with the experimental results. The similarity between diethyl and diisopropyl ethers, both giving high selectivity for the product expected from chelation, is best explained by the hypothesis that neither of them is bound to the titanium in the aldol transition structure.

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