

ON THE MECHANISM OF TITANIUM-TARTRATE CATALYZED ASYMMETRIC EPOXIDATION

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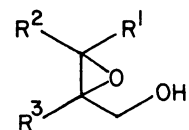
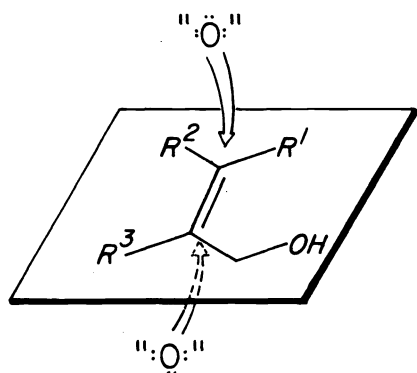
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Abstract. The experimental rate equation for titanium-tartrate catalyzed asymmetric epoxidation by *tert*-butyl hydroperoxide is reported. The catalyst is a dimer, and a structure of C_2 symmetry is proposed. The mechanism of the reaction is discussed with respect to kinetic resolution of racemic secondary allylic alcohols as well as the enantioselectivity of epoxidation of prochiral substrates. The alignment of a lone pair of the reactive alkyl peroxy-oxygen atom with the olefin π^* orbital is postulated as an important interaction in the transition state.

In 1980 we reported the discovery of the titanium-tartrate catalyzed asymmetric epoxidation of allylic alcohols by *tert*-butyl hydroperoxide (TBHP).¹ This system performs well with a remarkable variety of allylic alcohol substrates, consistently providing the enantiofacial selection shown in Scheme I.

Scheme I

D-(-)-diethyl tartrate (unnatural)



70-90% yield

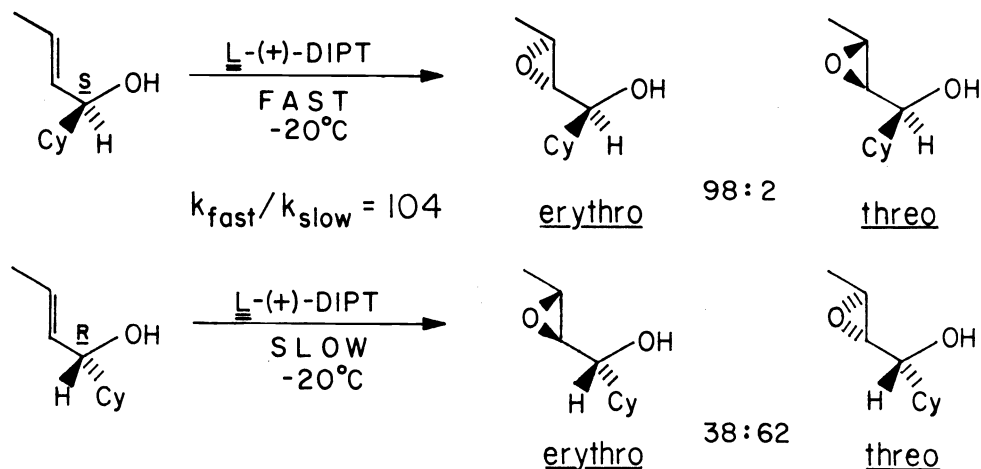
$>90\%$ ee.

L-(+)-diethyl tartrate (natural)

In addition, the catalyst is sensitive to pre-existing chirality in the substrate: the epoxidation of racemic secondary allylic alcohols proceeds rapidly with only one of the enantiomers, leaving the other, slower-reacting, enantiomer of the allylic alcohol behind.² This reactivity pattern is demonstrated by the epoxidation of racemic

(E)-cyclohexylpropenylcarbinol using L-(+)-diisopropyl tartrate as shown in Scheme II.

Scheme II



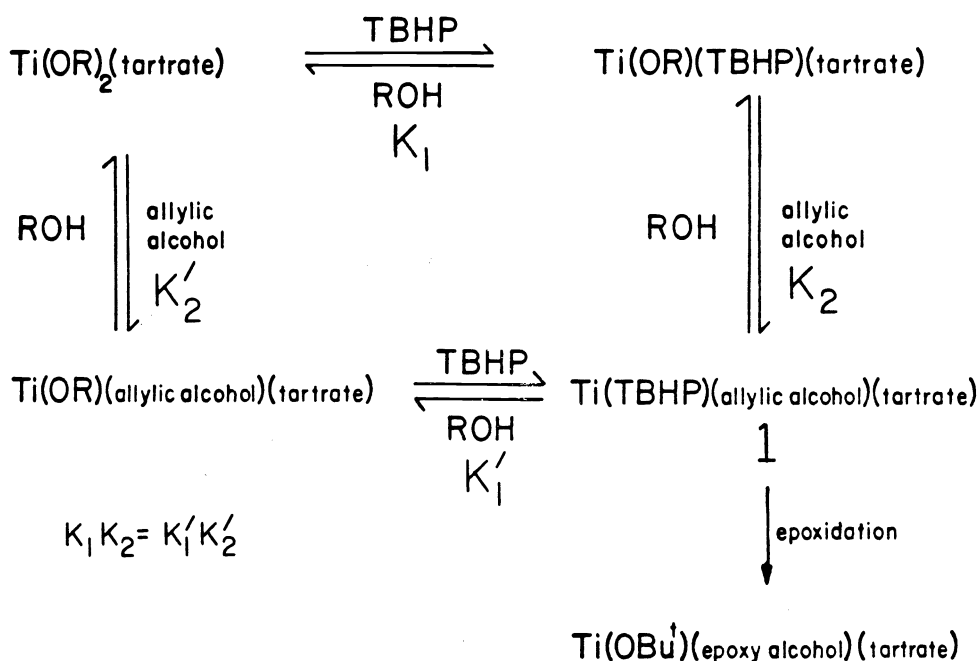
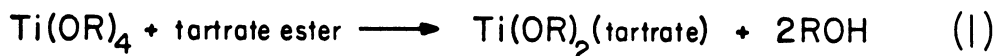
In the time since the discovery of the reaction, much information has been obtained concerning the mechanism of the process, and several fascinating modifications to the "parent" catalyst system have been discovered.³ In this paper we present a summary of our investigation of the kinetics of the asymmetric epoxidation and of the catalyst structure.⁴ We also propose a mechanistic model, which has led us to speculate on the details of the oxygen-transfer step.

We begin by considering the nature of titanium alkoxide systems in general. They have several properties crucial to the success of the asymmetric epoxidation reaction: (1) exchange of monodentate alkoxide ligands is rapid in solution⁵; (2) titanium (IV) participates in four covalent bonds, which is exactly the number required for this reaction (two for the divalent chiral auxiliary (tartrate), and one each for TBHP and the allylic alcohol), (3) titanium (IV) (d^0) alkoxide systems display a range of coordination numbers and geometries in published structures in crystals and solutions,^{5a,5b,6} and so presumably their coordination chemistry is somewhat flexible; and (4) titanium (IV) alkoxides are weak Lewis acids, and thus serve to activate a coordinated alkyl peroxy-ligand toward nucleophilic attack by the olefin of a bound allylic alcohol.^{7,10} The third property, that of flexibility in coordination number and geometry, may be partly responsible for the catalyst's ability to accommodate substrates of such widely different steric demand. Of course other d^0 transition metal alkoxide systems also possess these properties, but they fail to give high enantiomeric excess when used with tartrate and TBHP in the standard fashion.⁸ It appears that Ti(IV) has a unique combination of properties that permits the formation of an effective catalyst structure with tartrate and allows the reactants to interact efficiently in compliance with what we believe are strict

molecular orbital requirements (*vide infra*).

Mixing equimolar amounts of a titanium tetraalkoxide and a chiral tartrate diester releases two equivalents of alcohol into solution⁹ and forms a dominant species of stoichiometry $[\text{Ti}(\text{OR})_2(\text{tartrate})]_x$ (see equation 1 in Scheme III). Addition of TBHP and allylic alcohol rapidly establishes the equilibria characterized by constants K_1 and K_2 ; these constants were found to be approximately 1 for TBHP and most allylic alcohols. When TBHP and the allylic alcohol are juxtaposed in the coordination sphere of the same metal center¹⁰ (i.e. as in 1), the oxygen atom transfer occurs to give tert-butyl alcohol and the chiral epoxy alcohol bound as alkoxides. These product alkoxides are replaced by more allylic alcohol and TBHP and the catalytic cycle is completed as the loaded complex 1 is regenerated.¹¹

Scheme III



In full accord with Scheme III is the experimental rate equation which was determined under pseudo-first-order conditions to be:

$$\text{rate} = \frac{k [\text{TBHP}] [\text{Ti}(\text{OR})_2(\text{tartrate})] [\text{allylic alcohol}]}{[\text{inhibitor alcohol}]^2}$$

Note that the rate constant k is actually the product of the rate constants for the epoxidation step and the equilibrium constants K_1 and K_2 . Thus the rate expression is consistent with the action of a system wherein reactants are assembled on the metal followed by a rate-determining product forming step.

We are attempting to learn as much as possible about the structure of species formed when titanium tetraalkoxides and tartrate esters are mixed in solution. Unfortunately, our efforts to obtain crystals of these samples have not been successful as yet, so we are forced to rely on less direct methods. In any event, as the work of Halpern has exquisitely demonstrated,¹² even the most complete structural characterization of the major component of a catalyst system may bear little relation to the structure of the actual catalyst. While ever mindful of this lesson, we believe for several reasons that the major species in our titanium-tartrate solution is actually the dominant catalyst for the reaction, as discussed below.

It is important to understand the special characteristics of the 1:1 system in the reaction. With substrates that are relatively slow to epoxidize, the use of a Ti:tartrate ratio even slightly greater than 1:1 results in a marked loss in enantioselectivity, presumably because of the formation of species with less than 1 tartrate per Ti atom that catalyze epoxidation at a similar or faster rate and with a different selectivity than the 1:1 structure. Conversely, addition of more than one equivalent of tartrate to titanium causes the rate of the reaction to decrease by exactly the amount predicted by assuming that excess ligand forms a species of stoichiometry $[\text{Ti}(\text{tartrate})_2]_x$ that is catalytically inactive because of the inability of monodentate allylic alcohol and TBHP to displace the divalent tartrate.

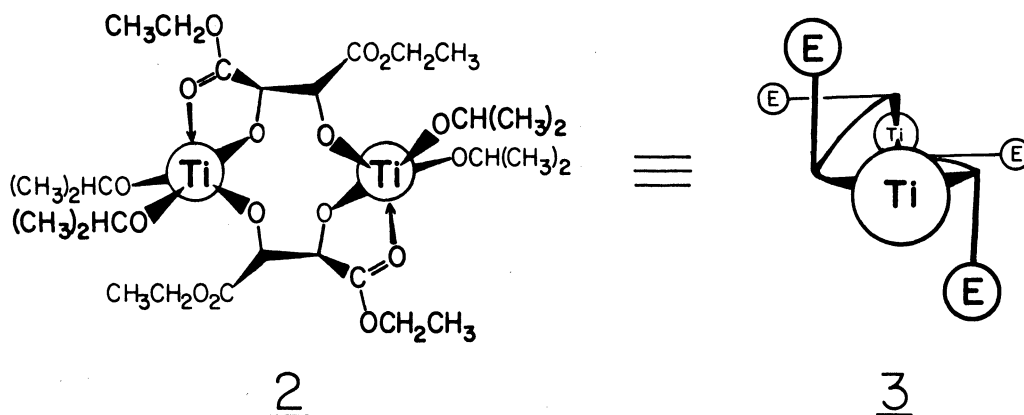
Since titanium alkoxides are well known to exist in oligomeric forms in solution, the molecular weight of the 1:1 species was of primary concern. Also, we had noted that use of racemic (*dl*) tartrate as the ligand for titanium resulted in the formation of different ratios of diastereomeric products in the epoxidation of racemic secondary allylic alcohols than those produced when either *d*- or *l*-tartrate was used alone. This suggests (but does not prove) that more than one tartrate is involved in the active complex. As measured by differential vapor phase osmometry (CH_2Cl_2) and by Rayleigh light scattering (cyclohexane),²⁷ the complex is a dimer in solution. The electron impact mass spectrum is in full accord with the dimeric structure and gives no evidence for either monomer or a species larger than the dimer.

That the dimer, and not some trace monomer or higher aggregate, is the actual dominant catalyst is strongly supported by the fact that the rate remains first-order in catalyst over a 10-fold range in concentration. The IR and ^1H NMR of equimolar solutions of titanium tetraalkoxide and tartrate esters remain essentially invariant over at least a

20-fold change in concentration. (It is admittedly possible, but unlikely, that the catalyst is a very active, undetected species that responds to changes in concentration to give the observed first-order result. However, there seems to be no reason why the dimer should be far less reactive than other possible titanium-tartrate structures.)

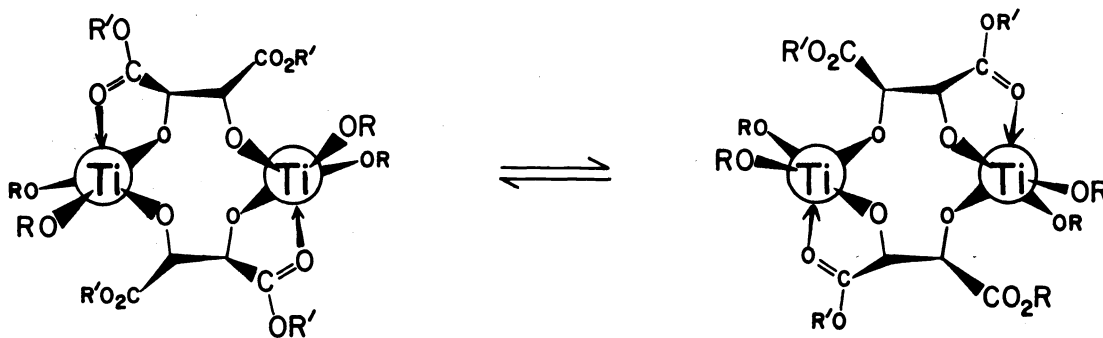
We believe that this dimeric catalyst has the ten-membered ring structure 2 in Fig. 1, analogous to the crystal structure of the complex of vanadium (IV) with tartaric acid, $\text{Na}_4[(\text{VO})_2(\text{tart})_2]^{-4}$ (tart = $\text{C}_4\text{H}_2\text{O}_6^{-4}$ ligand), found by Tapscott and coworkers.¹³ The NMR (both ^1H and ^{13}C) and IR spectra are consistent with such a structure, the latter showing both free (1738 cm^{-1})¹⁴ and coordinated (1635 cm^{-1}) carbonyl stretching bands.

Figure 1



NMR also reveals fluxional exchange between coordinated and free carbonyl groups as shown in Fig. 2, with a ΔG^\ddagger value at coalescence of between 12.8 and 15.2 kcal/mole, depending on the nature of the tartrate ester moiety and of the coordinated alkoxide.

Figure 2



The proposed structure 2 has a high degree of symmetry. If one considers the time averaged structure in which all the ester carbonyls interact equally with the titanium atoms (making the metals six-coordinate), overall D_2 symmetry is present.¹³ Within this time averaged structure each titanium atom has local C_2 symmetry. This is most clearly appreciated when either of the two equivalent titanium atoms is viewed from a perspective in the plane defined by the metal and its two least labile, framework ligands (i.e. the two proximal alkoxide oxygens of the tartrate bridges). Structure 3 in Fig. 1 shows this perspective for L(+)-tartrate. Notice how the tartrate ester groups, E, provide steric bulk in a C_2 relationship by blocking two of the diagonal quadrants of space around the metal center. A D(-)-tartrate complex has of course the mirror image C_2 symmetry. (The simple monomeric Ti-tartrate structure has the same type of C_2 symmetry as the dimer, and so would be expected to give qualitatively the same results. We believe that the monomer is not formed because the required interaction of a donor carbonyl group with the metal would produce a strained bicyclic structure.) Metal-centered reagents and catalysts of C_2 symmetry are responsible for several other asymmetric transformations.¹⁵

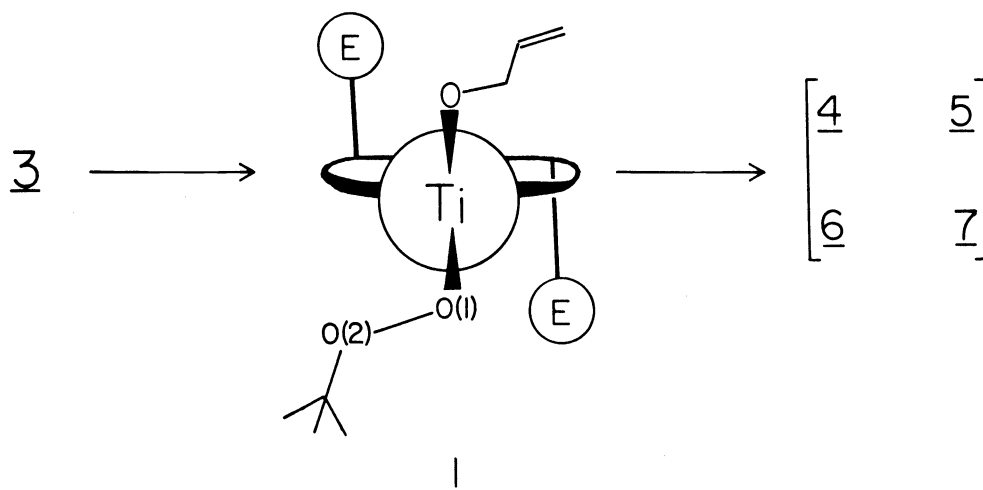
An important substrate to consider is the parent one, allyl alcohol. The epoxide is formed in this case in 95% ee at -20°C ,¹⁶ representing a value of 1.83 kcal/mole for the difference in the energies of the two diastereomeric transition states. If we assume that substrates interact with titanium at only one point (the M-O bond), the reaction of the coordinated allylic alkoxide with the coordinated peroxide must be subject to some requirements that restrict the degrees of freedom in the transition state to produce such a high enantiomeric excess for such a sterically undemanding substrate.

As with other metal catalyzed epoxidations by TBHP,¹⁷ we make three assumptions that lead to the proposal of a highly ordered transition state: (i) coordinated distal peroxy-oxygen [O(1) in Fig. 3] is transferred to the nucleophilic olefin; (ii) the proximal peroxy-oxygen [O(2)] interacts strongly with the titanium atom in the transition state¹⁸ bringing the *t*-butyl group close to the metal in the least sterically encumbered position; and (iii) the most favorable approach of olefin to the coordinated peroxide moiety is a centered one along the axis of the O-O σ -bond being broken [i.e. S_N2 -type attack on the backside of O(1) by the midpoint of the π -bond.]¹⁹

These three points provide a sufficient foundation for a reasonable explanation of kinetic resolution of secondary allylic alcohols based on the catalyst structure, but using them we are unable to account for the consistent olefin face selection of the reaction. To do so we must invoke one or more additional stereoelectronic properties of the transition state. As an initial hypothesis, we propose a fourth assumption: (iv) the olefin π^* orbital must be in position to overlap with one of the lone pairs of the peroxy-oxygen that is being delivered.¹⁹

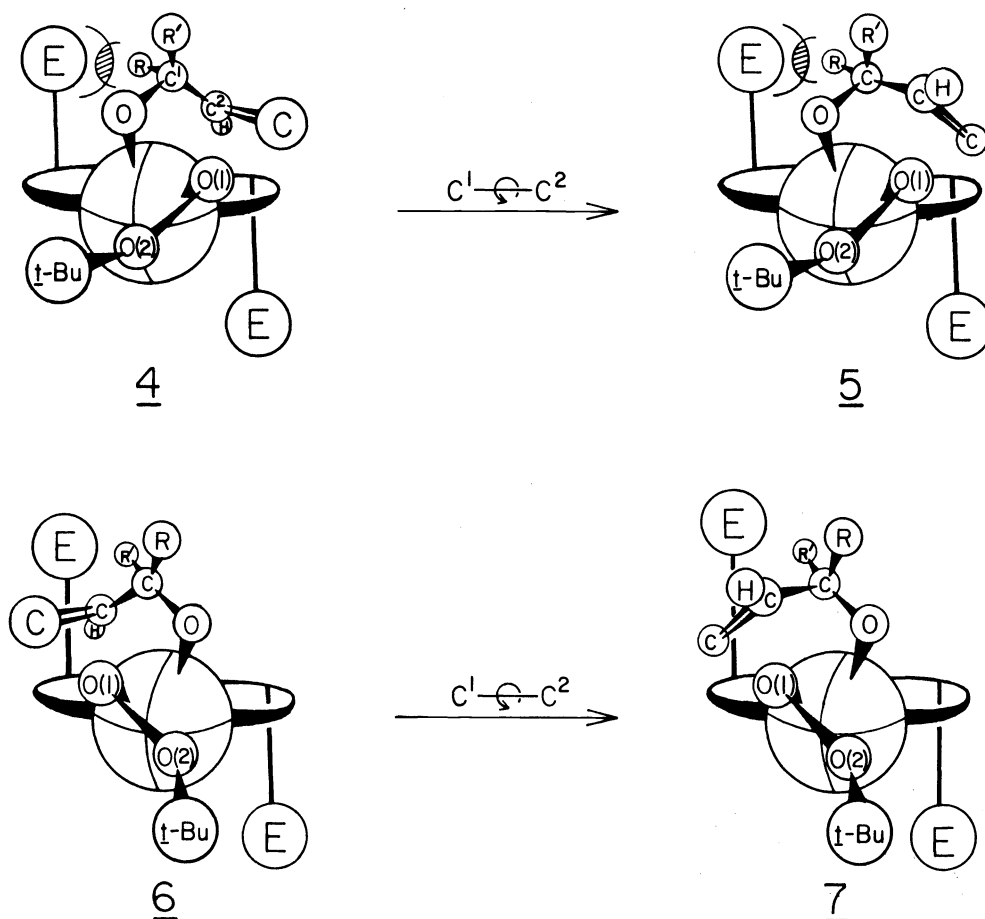
A representation of structure 3 in which the reactants are included (to give the loaded complex 1) is shown in Fig. 3. We believe that the Ti atom in the ground state may be 5- or 6-coordinate, the ligands being the tartrates, the allylic alcohol, a datively bound ester carbonyl, and TBHP which occupies either one or two coordination sites. In structure 1 of Fig. 3, however, we draw the metal in a tetrahedral 4-coordinate configuration, ignoring the dative bonds for simplicity. Since a more electrophilic metal center should facilitate activation of the coordinated peroxide to nucleophilic attack, we suspect that the transition state involves a 5-coordinate Ti atom (\sim trigonal bipyramidal), with both ester groups free. (This need not be true for this model to be applied, since a 6-coordinate octahedral structure possesses the same principle symmetry elements with respect to Ti-tartrate.)

Figure 3



As indicated in Fig. 3, our model proceeds from structure 1 in accordance with assumptions (i) - (iii) above to give the arrangements 4, 5, 6, and 7 for the coordinated allylic alkoxide and tert-butyl peroxide shown in Fig. 4.²⁰ The C_2 environment of the catalyst (3) forces the sterically demanding portions of the reactants to occupy the "open" quadrants around the metal center. Since the reaction must proceed by a linear approach of olefin to peroxide [by assumption (iii) above], all other permutations of the placement of allylic alkoxide on the three coordination sites of the trigonal bipyramid not occupied by tartrate that bring the olefin and peroxide into the reactive orientation suffer from unacceptable steric interactions. This steric criterion is also sufficient to eliminate structures 6 and 7 in Fig. 4 from consideration as favored transition states.

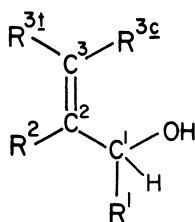
FIGURE 4. Possible orientations of allylic alkoxide and alkyl peroxide ligands on the Ti-tartrate catalyst in the transition state. A schematic representation of monomeric Ti-tartrate is used here only for clarity.



Notice that for kinetic resolution of secondary allylic alcohols (in which $R, R' = H$, alkyl),² the elimination of 6 and 7 is sufficient to explain the observed enantioselectivity, since both 4 and 5 lead to the prediction of the same kinetic resolution behavior at C^1 .^{21a} Substituent R' is pointed away from the catalyst into an open region of space, while R is forced into the area occupied by a tartrate ester group,^{21b} which lies behind the plane of Fig. 4 as shown. When $R = H$, this steric interaction is small, but when $R = \text{alkyl}$, structures 4 and 5 become unfavorable.^{21c}

So the proposed C_2 chirality of the tartrate complex, augmented by our assumptions (i) - (iii), has led us to propose transition state structures that resemble 4 and 5, which of course lead to the epoxidation of opposite faces of the olefin. The observed selection is consonant with structure 4 being preferred.²² For the wide range of substrates successfully epoxidized by this system, the discernable steric interactions do not consistently favor model 4 over model 5. Consider Table 1, in which the positions of allowable functionalized alkyl or aryl substitution on the allylic alcohol are depicted.

Table 1



POSITION ^a	SUBSTITUENT	ENANTIOFACIAL SELECTION	KINETIC RESOLUTION	NOTES
R ¹	CH ₂ R	GOOD	EXCELLENT	[KINETIC RESOLUTION REFERS HERE TO THE CHIRAL CENTER AT C ¹ . ENANTIOFACIAL SELECTION REFERS TO THE FASTER REACTING ISOMER.]
	CHR ₂	GOOD	EXCELLENT	
	CR ₃ ^b	NOT DETERMINED	POOR	
R ²	CH ₂ R	GOOD	----	
	CHRR'	GOOD	GOOD	
	CRR'R'' ^b	GOOD ^c	NOT INVESTIGATED	
R ^{3t}	CH ₂ R	GOOD	----	THE WIDEST RANGE OF SUBSTITUTION IS ALLOWED AT THIS POSITION.
	CHRR'	GOOD	POOR	
	CRR'R'' ^b	GOOD	NOT INVESTIGATED	
R ^{3c}	CH ₂ R	GOOD	----	
	CHRR'	POOR TO GOOD	GOOD	
	CRR'R'' ^b	VERY POOR	NOT INVESTIGATED	

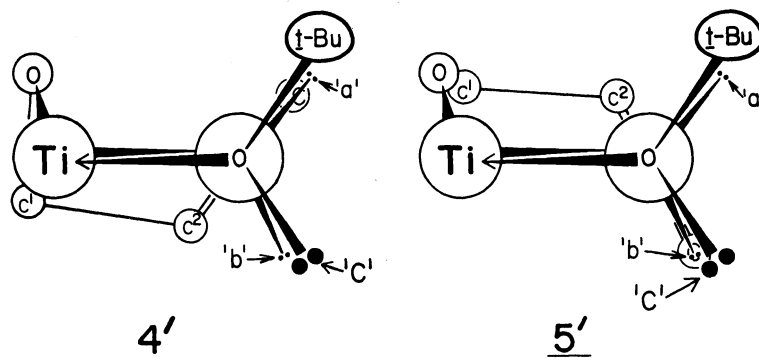
- (a) For each entry, the unspecified positions are occupied by H. Substitution at many combinations of positions are also accommodated by the Ti-tartrate system, though not all possible combinations have been tested.
- (b) M.J. Schweiter and K.B. Sharpless, unpublished results.
- (c) The absolute configuration of the epoxy alcohol has not been firmly established; it has been found by a nonrigorous correlation to be the normal 2S.

For some of these substrates (particularly those with tert-alkyl substitution at the C² position) a simple steric model might predict reversed enantiofacial selectivity. Yet for all allylic alcohols that are epoxidized in good e.e., the face selection remains the same. That is, given the diverse shapes of allylic alcohols that can be accommodated, the conventional steric and stereoelectronic considerations we have employed up to this point do not enable us to account for the consistent enantioselectivity of this system. For this reason we are convinced that an additional stereoelectronic factor determines which prochiral face of the olefin receives the oxygen atom by substantially favoring reaction from the olefin orientation in 4 over that in 5.

To account for the necessary stereoelectronic selection, we now invoke the proposed

lone pair - π^* alignment [assumption (iv) above] and show a comparison of the two candidate structures in Fig. 5. Note that in Fig. 5 we assume that both peroxide oxygens are tetrahedrally hybridized;¹⁸ O(2) is a chiral center by virtue of its coordination to the metal (as in the Mimoun¹⁸ complex 8). The lone pairs of O(1) (labelled 'a' and 'b') are thereby eclipsed with the C-tBu bond and the lone pair 'c' of O(2), respectively. In structure 4' the lone pair - π^* alignment can be achieved only with lone pair 'a'. Similarly, the olefin in structure 5' can align only with lone pair 'b'.

FIGURE 5. Views of 4 and 5 (omitting tartrate) down the O(2)-O(1) axis [O(2) in front of O(1)] after alignment of the olefin with an accessible lone pair of O(1). The t-butyl groups are drawn here in their least hindered positions with respect to tartrate.



We can now offer two, possibly cooperative, explanations for the postulated stereoelectronic factor:

(1) Consideration of space-filling models shows that the necessary overlap with lone pair 'a' in 4' can be reached with no loss of compliance with the other requirements for oxygen transfer stated previously. It appears that in structure 5' alignment of the olefin with 'b' can be achieved only at the expense of some disruption of the centered, backside approach of olefin to peroxide as shown in Fig. 5.⁹ However, this evaluation of 4' and 5' is based on factors difficult to estimate with precision in titanium alkoxide systems, such as the exact coordination geometry and the Ti-O(2) and Ti-O(1) bond lengths in the transition state. The resulting uncertainty in evaluating the relative merits of 4' and 5' makes it desirable to identify a more decisive criterion for choosing between them.

(2) One such distinction lies in the observation that lone pairs 'a' and 'b' are diastereotopic by virtue of the tartrate chirality. In principle, the stereoelectronic selection may therefore also be a matter of intrinsically different reactivities of the lone pairs. An attractive embellishment of this concept lies in the observation that the O(2) chiral center may be present or reactive in only one epimeric form (i.e. as indicated in 4' and 5') due to the tartrate chirality. Such a chiral leaving group [O(2)] might give rise to an electronic asymmetry at O(1) which favors reaction from the olefin

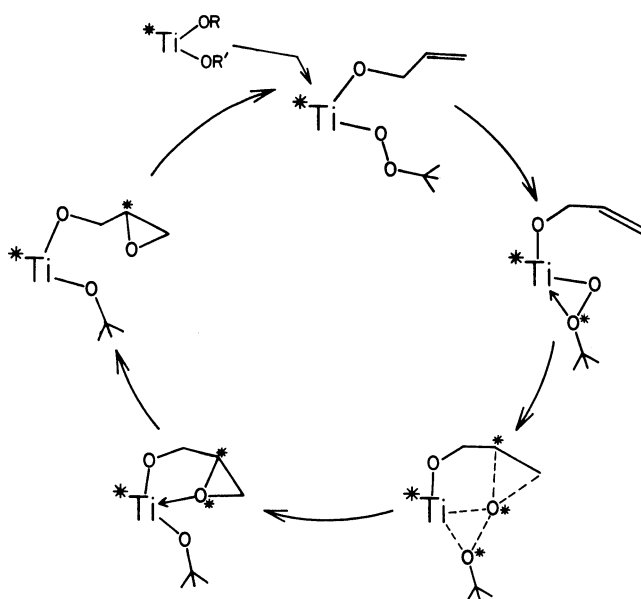
alignment in 4' wherein the lone pair 'a' is eclipsed with the tert-butyl group on O(2). (Steric transmission of the O(2) chirality beyond O(1) into the olefinic π -bond's avenue of approach is not tenable from simple geometric considerations.) In this hypothesis it is preferable for the lone pair that projects toward π^* to be eclipsed with a C-tBu bond rather than with another lone pair.²²

It has been noted that a series of seven prochiral homoallylic alcohols (which have an extra CH_2 unit between the oxygen and the double bond) are epoxidized by the Ti-tartrate system on the opposite olefin face to that of allylic alcohols in 23-55% ee.²³ We can then propose that the added carbon atom (an extra "universal joint") enables the opposite olefin face to more easily achieve the favored alignment with lone pair 'a'. At the same time, the ee is reduced because enough flexibility has been added to the substrate that either face of the olefin can attack the peroxide in compliance with the stereoelectronic requirements of the reaction, albeit one more easily than the other.

Another dramatic example of the deleterious effects of introducing conformational freedom into the reactants can be found in the related case of kinetic resolution of racemic amino alcohols by TBHP and Ti-tartrate.²⁴ While β -hydroxyamines are successfully resolved (with relative rates $k_{\text{fast}}/k_{\text{slow}}$ of 10 to 20), the one γ -hydroxyamine tried underwent no observable kinetic resolution.

Scheme IV summarizes the proposed catalytic pathway and highlights the transfer of chirality from the Ti-tartrate complex to the allylic alcohol. Note again the potential for a chiral electrophilic center [O(1)] and a chiral leaving group [O(2)] in the $\text{S}_{\text{N}}2$ oxygen-transfer process.

Scheme IV



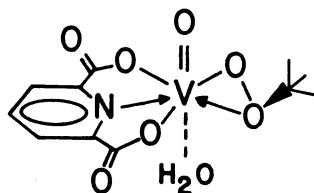
In conclusion, we believe that the asymmetric epoxidation exhibits a conjunction of selectivity and substrate promiscuity that is without precedent among either man-made or enzymic catalysts. Our mechanistic study has advanced to the point where we suspect that a previously unidentified selectivity principle is at work. It is hoped that further efforts (e.g. molecular mechanics computer modeling, crystal structures, and light scattering studies) will bring greater understanding of the more speculative aspects of this mechanistic puzzle. This reaction with all its variable components represents a unique opportunity for the study of the detailed mechanism of metal-catalyzed epoxidations, and perhaps of epoxidations in general.

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11. Protic sources (such as alcohol) are not required for either alkoxide exchange^{5a} or epoxidation.²⁵

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14. Ester groups with the carbonyl free may be coordinated to titanium through the alkoxide oxygen of the ester moiety.
15. Prominent among the C_2 systems are (a) asymmetric hydrogenation catalysts with ligands such as DIOP [H.B. Kagan and T.-P. Dang J. Am. Chem. Soc., **94**, 6429 (1972)] or other chiral diphosphines [for a recent review, see W.S. Knowles, Accts. Chem. Res., **16**, 106 (1983)]; (b) asymmetric reduction mediated by complexes of binaphthol ligands: R. Noyori, Pure and Applied Chem., **53**, 2315 (1981); and (c) the efficient chiral Europium shift reagent developed by Whitesides and coworkers: M.D. McCreary, D.W. Lewis, D.L. Wernick and G.M. Whitesides, J. Am. Chem. Soc., **96**, 1038 (1974).
16. Conditions: allyl alcohol:Ti(OiPr)₄:(+)-DIPT:TBHP = 1.0:1.2:1.4:4.0; 24 hr.; Me₂S, saturated NaF workup (epoxy alcohol not isolated); Et₃N, methanesulfonyl chloride, CH₂Cl₂, 0°C; 15% yield of epoxy mesylate; ee determined by NMR with chiral Eu shift reagent Eu(hfc)₃ in C₆D₆. The observation of high ee in this case may be misleading. Due to the low yield, we cannot rule out the occurrence of enantioselective opening of the epoxy alcohol. Experiments to test this possibility are under way.
17. We do not discuss here the peroxymetallation mechanism proposed by Mimoun [H. Mimoun, J. Mol. Catal., **7**, 1 (1980)], though it is not be excluded by the kinetic data.
18. (a) Mimoun and coworkers [H. Mimoun, P. Chaumette, M. Mignard and L. Saussine, Nouv. J. Chim., in press] have obtained the crystal structure 8 that clearly demonstrates bonding of the *t*-butoxy oxygen with vanadium in a V(V)-TBHP complex in which that oxygen atom is clearly sp³ hybridized. This is the first hard evidence for the existence of this important, putative intermediate (this species was first proposed in 1979,¹⁹ but the interaction leading to it was suggested in 1977.¹⁰ The nucleophilic nature of the olefin has been demonstrated in this asymmetric epoxidation process.⁹



8

- (b) For a discussion of different representations of oxygen lone pairs see A.J. Kirby, The Anomeric Effect and Related Stereoelectronic Effects at Oxygen, Reactivity and Structure Concepts in Organic Chemistry, Vol. 15, Chapters B.2 and C.1, Springer-Verlag, Berlin (1983).

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20. The structures in Fig. 4 and Fig. 5 do not represent the results of rigorous calculation. They derive from CPK space-filling molecular models and are meant only to show some of the possible differences in olefin-peroxide alignment for the two diastereomeric transition states.
21. (a) It is therefore not in principle necessary for good kinetic resolution at the carbinol center to be accompanied by good diastereofacial selectivity. Since we do in fact observe high erythro selectivity for the faster reacting enantiomers² (i.e. delivery of oxygen to the same enantioface as for prochiral allylic alcohols), we are able to propose structure 4 as the preferred transition state precursor for all of the most successful substrates.

Kinetic resolution is also observed at other positions on the allylic alcohol.²⁶ In these cases, the absolute configuration of the faster reacting enantiomer necessarily depends on which olefin face is epoxidized. Structures 4 and 5 therefore lead to opposite predictions of the absolute configuration of the faster reacting isomer. It is the predictions from structure 4 that match the experimental results in all cases.⁹

(b) This rationale is consistent with the observed sensitivity of the kinetic resolution process to the size of the tartrate ester group (i.e. isopropyl ester is far superior to methyl ester).⁹
- (c) The epoxidation of the slower reacting enantiomer of secondary allylic alcohols (in which R = alkyl, R' = H) proceeds with little diastereoselectivity.⁹ We cannot propose transition state conformations for these substrates as yet.
22. The O-C-C=C dihedral angle in structure 4' of Fig. 5 is approximately 50⁰, the same as that postulated earlier for V⁺⁵ catalyzed epoxidations.¹⁹
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