Mechanism of Asymmetric Epoxidation. 1. Kinetics

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Abstract: The rate of titanium–tartrate-catalyzed asymmetric epoxidation of allylic alcohols is shown to be first order in substrate and oxidant, and inverse second order in inhibitor alcohol, under pseudo-first-order conditions in catalyst. The rate is slowed by substitution of electron-withdrawing substituents on the olefin and varies slightly with solvent, CH_2Cl_2 being the solvent of choice. Asymmetric induction suffers when the size of the alkyl hydroperoxide is reduced. Kinetic resolution of secondary allylic alcohols is shown to be sensitive to the size of the tartrate ester group and insensitive to the steric nature of inhibitor alcohol. Most importantly, the species containing equimolar amounts of Ti and tartrate is shown to be the most active catalyst in the reaction mixture, mediating reaction at much faster rates than titanium tetraalkoxide alone.

The discovery of an efficient asymmetric epoxidation reaction for allylic alcohol substrates,[3] and its subsequent extension to a practical catalytic process,[4] has been a significant addition to the field of asymmetric synthesis. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant. The consistency of the reaction is remarkable: to date, no allylic alcohol has been found that undergoes enantioselective epoxidation in a manner that violates the enantiofacial selection rule first elaborated in 1980.[3a,6a] In addition, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. These combined observations—a consistent sense of asymmetric induction for substrates of differing steric demand—represent the most significant attributes of this reaction for both practical and mechanistic considerations.

In addition to being able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to preexisting chirality in selected positions of the allylic alcohol.[5] For example, kinetic resolution of racemic secondary allylic alcohols is very efficient and is therefore important when the mechanism of the asymmetric epoxidation reaction is considered.

In this paper we present the results of kinetic studies under pseudo-first-order conditions on the asymmetric epoxidation catalyst and related systems. Information concerning the kinetic rate law, ligand-exchange pathways, and stoichiometry of the active catalyst are reported. In the following paper, we discuss the structure of the active catalyst species. A chemical and historical introduction to this study, and a summary of many of its results, have appeared.[6]

Results and Discussion

Ligand Binding to Titanium. It is the ability of titanium(IV) alkoxides to rapidly exchange ligands that enables these species to catalyze epoxidation reactions. This pervasive exchange behavior makes the asymmetric epoxidation reaction mixture difficult to characterize. Because diols such as tartrate exhibit much higher binding constants than monodentate alcohols, we consider their equilibrium phenomena separately from those of monodentate alcohols.

Table I. Equilibrium Constants for the Exchange of Hydroperoxide for Alkoxide

$$Ti(X)_3(OR) + R'OOH \rightleftharpoons Ti(X)_3(OOR') + ROH$$

$$K_{eq} = [Ti(X)_3(OOR')][ROH]/[Ti(X)_3(OR)][R'OOH]$$

entry	$Ti(X)_3(OR)$	R'OOH	K_{eq}
1	$Ti(OiPr)_4$	$(Me)_3COOH$	$K_1 = K_2 = 3.5 \pm 1.0$
2	$Ti(DIPT)(OiPr)_2$	$(Me)_3COOH$	0.7 ± 0.2
3	$Ti(DIPT)(OtBu)_2$	$(Me)_3COOH$	0.34 ± 0.1
4	$Ti(OiPr)_4$	$(Ph)_3COOH$	0.2 ± 0.1
5	$Ti(DIPT)(OiPr)_2$	$(Ph)_3COOH$	~ 0.01

When 1 equiv of dialkyl tartrate is mixed with 1 equiv of titanium tetraalkoxide, 2 equiv of alcohol is released into solution, in accordance with eq 1.

$$n[Ti(OR)_4] + n[\text{tartrate}] \rightarrow \frac{n}{2}[Ti(\text{tartrate})(OR)_2]_2 + 2n[ROH] \quad (1)$$

The resulting Ti–tartrate mixture is composed mostly of a dimeric species.[7] However, all figures, concentrations, and calculations in this paper are reported for *total* titanium concentration (i.e., for "monomeric" Ti), unless otherwise noted. This is done for simplicity, noting that kinetic measurements do not distinguish between Ti atoms in the dimer (vide infra), and that the proposed mechanism of asymmetric epoxidation involves functionally equivalent metal centers.[6]

The amount of alcohol released upon addition of tartrate has been measured by NMR and vapor-phase gas chromatography to be exactly 2 equiv per tartrate, thus demonstrating that tartrate has a much higher affinity for Ti(IV) than do monodentate alcohols. The released alcohol can be removed in vacuo or by molecular sieves.

Exchange of bound monoalkoxide ligands (including allylic alkoxide, "spectator" alkoxides such as isopropoxide, epoxy alkoxide, and hydroperoxide) for free alcohol or exchange among different alkoxide species is rapid in most cases.[8] Therefore, a mixture of complexes involving monodentate alkoxide is expected to be present, subject only to thermodynamic factors. We have determined the equilibrium constants for binding of *tert*-butyl hydroperoxide and triphenylmethyl (trityl) hydroperoxide to several different titanium species (Table I) in an effort to gain some insight into the manner of alkyl peroxide binding to titanium. These results represent an upper bound to the first equilibrium constant since any contributions from the coordination of a second

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(3) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) Sharpless, K. B. *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1984**, *27*, 59–89, (Chapter III).
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(5) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.
(6) (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, Vol. 5, Chapter 8. (b) Finn, M. G. Ph.D. Dissertation, Massachusetts Institute of Technology, 1986.
(7) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.*, following paper in this issue.
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Table II. Epoxidation of (*E*)-2-Decen-1-ol by $Ti(OiPr)_4$/DIPT/TBHP in CH_2Cl_2[a]

entry	$[Ti-DIPT]_{active}$,[b] M	[*i*PrOH], M	[TBHP], M	sieves[c]	$rate_{corr}$[d]	notes
1	none	none	0.0150	4 Å	0.042	
2	0.0145	0.299	0.0150	none	1.08	
3	0.0145	0.301	0.0150	none	1.23	dried[e] CH_2Cl_2
4	0.0145	0.305	0.0150	4 Å	1.22	
5	0.0145	0.301	0.0150	3 Å	1.24	reagent[f] CH_2Cl_2
6	0.0145	0.300	0.0150	4 Å	1.23	reagent[f] CH_2Cl_2

[a] Distilled from CaH_2 unless otherwise indicated. [b] See text for definition of $[Ti-DIPT]_{active}$. [c] Powdered molecular sieves present in the reaction mixture. [d] $Rate_{corr}$ is the observed rate multiplied by [*i*PrOH]^2 to correct for the inhibitory effect of isopropyl alcohol, according to the experimental rate law (see Table III) and normalized with respect to the indicated concentrations of Ti-tartrate (see Experimental Section). Given in units of 10^{-4} M^2 s^{-1}. [e] Dried by distillation from CaH_2 onto 3-Å sieve beads, or by standing over 3-Å sieve beads without distillation. [f] Reagent-grade CH_2Cl_2 used as received.

or third equivalent of hydroperoxide are included.

Differences in the observed binding constants can be the result of changes in molecularity or changes in the stability of a complex of constant molecularity. The stability of the product complex can be affected by both steric and electronic factors. It thus becomes a complicated matter to explain the different binding constant values in Table I, but a few simple conclusions may be drawn.

First, note that K_{eq} values for the Ti–tartrate complexes are smaller than for $Ti(OiPr)_4$ alone. The binding of TBHP to $Ti(OiPr)_4$ is probably driven to some extent by a change in aggregation in going from $Ti(OiPr)_4$ to $[Ti(OiPr)_3(OOtBu)]_{n>1}$ and $[Ti(OiPr)_2(OOtBu)_2]_{n>1}$.[9] Such a change is unlikely to occur with Ti–tartrate, as indicated by the kinetic rate law of the epoxidation reaction (vide infra) and the fact that $[Ti(DIPT)(OR)_2]_2$ complexes in which OR is a primary alkoxide are also dimeric.[8] Thus, the relatively high competitive binding constant of TBHP for $Ti(OiPr)_4$ is likely to be an artifact of the accompanying favorable oligomerization process.

Second, note that the K_{eq} value for Ti–tartrate plus trityl hydroperoxide (entry 5) is much smaller than for TBHP (entry 2), consistent with the greater size of the triphenylmethyl group relative to the *tert*-butyl moiety.

An important aspect of our proposed mechanism[6] is the bidentate coordination of the alkyl peroxide to titanium, which brings the alkyl group closer to the metal center. That such a mode of coordination is available in the ground state is supported by the observation that K_{eq} for TBHP is less than 1.0 with both $Ti(DIPT)(OiPr)_2$ and $Ti(DIPT)(OtBu)_2$. This implies that coordinated alkyl peroxide is more sterically demanding than isopropoxide or *tert*-butoxide—unlikely unless bidentate coordination of the alkyl peroxide was important.

Although its equilibrium constant for binding is very small (entry 5), trityl hydroperoxide participates in asymmetric epoxidation at a significant rate—approximately one-third of that with TBHP—and with high enantiomeric excess.[10] In the determination of K_{eq} values, equilibrium was always achieved within 1 min (the fastest possible observation time) after mixing the hydroperoxide with titanium alkoxide solutions. These observations illustrate that ligand-exchange reactions are rapid in titanium–tartrate systems.

Finally, the nature of the hydroperoxide also has an effect on the enantiomeric excess of asymmetric epoxidation. In contrast to the behavior of Ph_3COOH and TBHP, the sterically less demanding *n*-butyl hydroperoxide affords epoxy alcohol in reduced enantiomeric excess. Epoxidation with stoichiometric Ti–tartrate and *n*-butyl hydroperoxide of (*E*)-α-phenylcinnamyl alcohol and

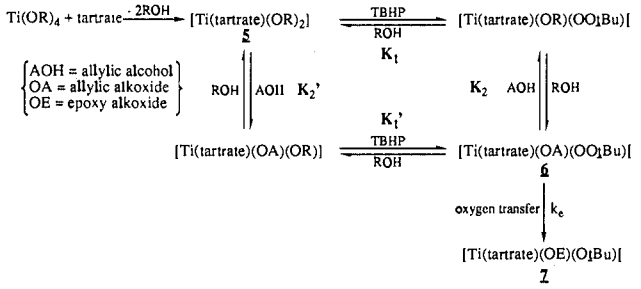


Figure 1. Ligand exchange pathway in the asymmetric epoxidation catalytic cycle.

(*E*)-2-decen-1-ol affords epoxy alcohols of 91% and 75% ee, respectively. Trityl and *tert*-butyl hydroperoxides each provide >98% and >95% enantiomeric excess for these respective substrates under identical conditions. Since η^2 binding of the alkyl peroxide brings its alkyl group close to the metal center, the apparent dependence of asymmetric induction on steric bulk in the alkyl peroxide also suggests bidentate coordination of the oxidant during the enantioselective step.[6]

Pseudo-First-Order Kinetics. We have explored the kinetic behavior of the asymmetric epoxidation system under pseudo-first-order conditions, in which Ti–tartrate and *tert*-butyl hydroperoxide are present in excess with respect to allylic alcohol substrate. Nonreactive alcohol was added as an inhibitor to slow the reaction to a measurable rate. The alcohol released when tartrate is mixed with $Ti(OR)_4$ contributes to the inhibitor alcohol concentration. A slight excess of tartrate was normally used with respect to titanium to ensure that oligomeric complexes containing less tartrate than titanium were not present.

Molecular Sieves. The practical use of titanium–tartrate in catalytic concentrations[4] relies upon the presence of powdered molecular sieves in the reaction mixture. Table II presents the results of control reactions under pseudo-first-order conditions. A comparison of entries 2–6 shows that use of reagent-grade CH_2Cl_2 as solvent results in approximately 10% reduction in rate, while reactions in dried solvent or in reagent-grade solvent in the presence of molecular sieves (3 or 4 Å) proceed at the same rate. Thus, molecular sieves do not accelerate the reaction but serve only to remove moisture.[11] Distillation from CaH_2 was ineffective (entry 2). In the absence of titanium, molecular sieves alone do not induce the disappearance of allylic alcohol at a significant rate (entry 1). We therefore believe that the molecular sieves necessary for reaction under catalytic conditions do not alter the catalyst structure.[12]

Pseudo-First-Order Rate Law. The dependence of epoxidation rate on the concentration of each of the components of the system

(9) $Ti(OiPr)_4$ has an average molecularity in solution of 1.0–1.1[7,8a] due to its inability to form bridging alkoxide bonds for steric reasons. Substitution of a primary alkoxide (or an alkyl peroxide) for isopropoxide allows dimerization to occur by bridging of the less encumbered alkoxide oxygen between two titanium atoms. Such a reaction resulting in an increase in coordination number is favored because the resulting Ti(IV) centers are less electron deficient than in the monomeric species.

(10) Pederson, S. F.; Burns, D. B.; Sharpless, K. B., unpublished results. Triphenylmethyl hydroperoxide is also effective for kinetic resolution of secondary allylic alcohols and is a convenient oxidant for some small-scale asymmetric reactions since it is a crystalline solid that is easy to handle and purify.

(11) Further evidence for this conclusion is presented in ref 4b. It has recently been reported that 4-Å molecular sieves accelerate the replacement of isopropoxide by binaphthol ligands on $Ti(OiPr)_2Cl_2$: Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954. The effect of molecular sieves on the binding of tartrate diesters to titanium tetraalkoxides has not been explored.

(12) Rate measurements under saturation kinetics conditions (≤1% Ti-tartrate with respect to substrate and oxidant) were not performed because of a severe loss of enantioselectivity due to an equilibrium displacement of tartrate from titanium by the excess monodentate alcohols.

Table III. Determination of Kinetic Rate Order under Pseudo-First Order Conditions

entry	substrate[a]	tartrate	[TBHP][b]	[Ti-tartrate][b]	[*i*PrOH][c]	rate order
			Solvent CH_2Cl_2			
1	**1**	DET	0.30–0.60	1.34	0.335	$[TBHP]^{0.99}$
2	**1**	DET	0.60	0.67–2.0	0.32–0.35	$[Ti\text{-}DET]^{1.01}$
3	**2**	DIPT	1.53	1.2–3.5	0.29–0.36	$[Ti\text{-}DIPT]^{0.94}$
4	**3**	DIPT	0.75, 1.5[d]	0.62–6.2	0.15–0.31	$[Ti\text{-}DIPT]^{0.99}$
5	**1**	DET	0.30, 0.60[d]	0.34, 0.67[d]	0.09–0.48	$[i\text{PrOH}]^{-2.03}$
6	**3**	DIPT	1.50	1.45	0.15–0.41	$[i\text{PrOH}]^{-1.91}$
7	**4**	DIPT	1.50	1.30	0.20–0.46	$[i\text{PrOH}]^{-1.91}$
			Solvent Diethyl Ether			
8	**3**	DIPT	1.50	1.45	0.20–0.30	$[i\text{PrOH}]^{-1.83}$
9	**4**	DIPT	1.50	1.40	0.15–0.29	$[i\text{PrOH}]^{-1.89}$
			Solvent Pentane			
10	**3**	DIPT	1.50	1.48	0.10–0.31	$[i\text{PrOH}]^{-1.50}$
11	**3**	DIPT	1.50	1.5–4.4	0.30–0.42	$[Ti\text{-}DIPT]^{0.49}$

[a] **1**, (*E*)-α-phenylcinnamyl alcohol; **2**, (*E*)-octa-2,7-dien-1-ol; **3**, (*E*)-2-decen-1-ol; **4**, (*E*)-2-hexen-1-ol. [b] Concentration ranges used (10^{-2} mol/L); see Experimental Section for details. [c] Concentration ranges used (moles per liter); see Experimental Section for details. [d] Reactions were performed with the lesser of the two concentrations listed to slow the reaction rate to a measurable range when smaller amounts of inhibitor alcohol were present.

has been measured by monitoring the disappearance of allylic alcohol under pseudo-first-order conditions, holding the concentrations of two of the three components constant and varying the third. Table III summarizes the results of these experiments in three different solvents for four substrates that are epoxidized with good enantioselectivity. The rate law for asymmetric epoxidation under pseudo-first-order conditions in CH_2Cl_2 is therefore

$$\text{rate} = k\frac{[\text{allylic alcohol}][\text{Ti-tartrate}][\text{ROOH}]}{[\text{inhibitor alcohol}]^2}$$

Note that the above rate expression has been found for several different substrates and tartrate esters and extends over a 10-fold concentration range in Ti–DIPT complex (entry 4). We conclude that within this concentration range the active Ti–tartrate catalyst does not undergo a change in molecularity.

Consistent with this rate expression is the exchange pathway outlined in Figure 1. After the formation of the Ti–tartrate complex **5**, the two remaining alkoxide ligands are replaced in reversible exchange reactions with TBHP and the allylic alcohol to give the "loaded" complex **6**. The reaction is independent of which of the two possible pathways is used to reach complex **6**. Oxygen transfer can then occur to give the coordinated epoxy alkoxide and *tert*-butoxide in complex **7**. These product alkoxides are replaced by more allylic alcohol and TBHP to regenerate **6** and complete the catalytic cycle. The inverse-squared dependence on nonreactive alcohol is due to the necessary replacement of the two alkoxide ligands in **5** with hydroperoxide and the allylic alcohol.

A mechanism in which transesterification of the tartrate with the allylic alcohol is followed by epoxidation of the allyl tartrate was excluded by the observation that the geraniol diester of (+)-tartaric acid was epoxidized much more slowly than was geraniol itself in the presence of diethyl tartrate, under otherwise identical conditions. Furthermore, geraniol epoxide was not released from the tartrate by transesterification, as would be required in this alternative mechanism.[6b]

Note that the observed rate constant k in eq 1 is actually the product of the rate of epoxidation k_e and the equilibrium constants K_1 and K_2 (or K_1' and K_2'). To the extent that $K_1K_2 = 1$, the observed reaction rate is approximately equal to the rate of oxygen transfer k_e. Equilibrium constants for binding of alkyl hydroperoxides to titanium–tartrate are reported above.

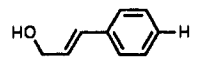
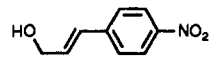
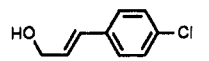
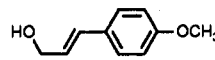
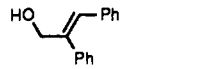
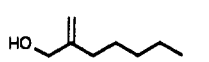
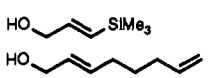
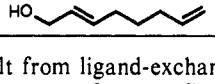
Solvent Dependence. The kinetic rate order of isopropyl alcohol for epoxidation in diethyl ether solvent (−1.86) is similar to that found in CH_2Cl_2 (approximately −1.95). In pentane, however, the observed rate order in isopropyl alcohol was found to be −1.5. Furthermore, the rate order in titanium–tartrate complex was 0.5, not 1.0 as found in CH_2Cl_2. These differences reflect the presence of a different aggregation state of Ti–tartrate in the nonpolar solvent (pentane).[7] Any change in Ti–tartrate molecularity that might result from ligand-exchange steps preceding rate-determining oxygen transfer are reflected in the observed kinetic rate order.

Table IV. Pseudo-First Order Rate Comparison for Epoxidation of (*E*)-2-Hexenol by Ti(DIPT)(O*i*Pr)$_2$ and TBHP at 0 °C

solvent	$\times 10^4 \text{rate}_{obs}$, s^{-1}	rate_{rel}	% ee (config)[a]	% yield[a]
CH_2Cl_2	13.8	1.00	>98 (2*S*)	90
ether	1.45	0.10	98 (2*S*)	89
pentane	4.35	0.32	94 (2*S*)	90

[a] For epoxidations under conventional stoichiometric conditions at −20 °C.

Table V. Pseudo-First Order Rates of Epoxidation

entry	allylic alcohol	rate const, k, s^{-1}	rel rate
1		1.38	1.00
2		0.56	0.42
3		1.65	1.20
4		6.06	4.39
5		2.05	1.49
6		0.067	0.049
7		0.083	0.060
8		0.30	0.22

The absolute rate and asymmetric induction of the reaction is also dependent on the nature of the solvent, as shown in Table IV. Since the rate law is not the same in each solvent, for the purposes of comparison we measured the rates at one set of conditions: $[\text{Ti-tartrate}]_{active} = 0.0145$ M, [*i*PrOH] = 0.300 M, and [TBHP] = 0.0150 M.

Reaction Rate vs Allylic Alcohol Structure. With the rate law in hand, observed rates of asymmetric epoxidation were compared for different substrates under pseudo-first-order conditions; the results are summarized in Table V. The nucleophilic role played by the olefin was indicated by the behavior of para-substituted cinnamyl alcohols (entries 1–4). The electron-withdrawing nitro group decreased the rate of epoxidation while methoxide (electron donating) increased the rate. Correlations with Hammett constants were poor. Note also that a 1,2-disubstituted olefin (entry 8) was epoxidized at approximately 4.5 times the rate of a 1,1-disubstituted olefin (entry 6). Silyl substitution (entry 7) also decreases the rate with respect to entry 8.[13] Lastly, it has been

Table VI. Epoxidation of (*E*)-2-Decen-1-ol by $[Ti(DIPT)(OiPr)_2]_2$ Generated from **8**

entry	$[Ti\text{-}DIPT]_{active}$[a]	[*i*PrOH][a]	[TBHP][a]	$rate_{corr}$[b]	notes
1	0.0146	0.303	0.0150	0.88	no added DIPT; [Ti]:[DIPT] = 1:1
2	0.0145	0.300	0.0150	1.19	[Ti]:[DIPT] = 1.0:1.17

[a] See text for definition of $[Ti\text{-tartrate}]_{active}$. Concentrations in moles per liter. [b] $rate_{corr}$ is the observed rate multiplied by $[iPrOH]^2$, in units of 10^{-4} M^2 s^{-1}.

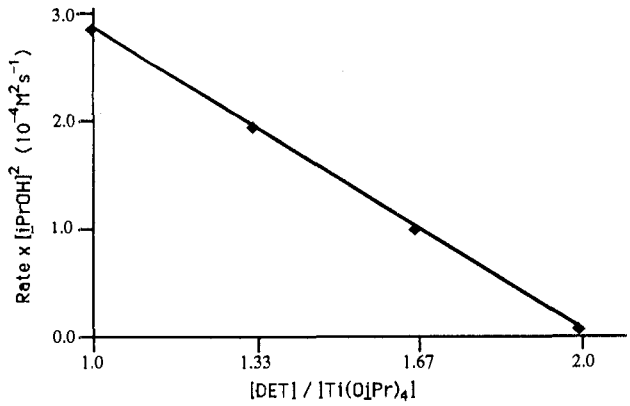


Figure 2. Rate of asymmetric epoxidation of (*E*)-α-phenylcinnamyl alcohol vs tartrate to Ti ratio.

observed[3,5,6] that *Z*-substituted allylic alcohols are epoxidized at much slower rates than are *E*-substituted substrates.

Reaction Rate in the Presence of Excess Tartrate. Under pseudo-first-order conditions, the addition of more than 1 equiv of tartrate to titanium caused a rate decrease consistent with the formation of a species of stoichiometry $(Ti(tartrate)_2]_x$ that is catalytically inactive (eq 2), as shown in Figure 2.

$$[Ti(tartrate)(OR)_2] + x(tartrate) \xrightarrow[(0 \le x \le 1)]{} (1 - x)[Ti(tartrate)(OR)_2] + x[Ti(tartrate)_2] \quad (2)$$

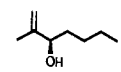
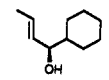
Use of less than 1 equiv of tartrate per Ti usually results in decreased enantioselectivity and poor reproducibility in the rates of epoxidation, especially for slower reacting and hindered substrates. For this reason, the recommended ratio of Ti to tartrate for a normal asymmetric epoxidation reaction is 1.0:1.2.[4] Formation of species with less than 1 equiv of tartrate to Ti is thus diminished, and the excess ligand merely decreases the rate slightly.[14] Figure 2 allows us to define the concentration of *active* Ti–tartrate in a mixture under pseudo-first-order conditions to be the concentration of 1:1 species minus the concentration of excess tartrate:

$$[Ti\text{-tartrate}]_{active} = [Ti(OR)_4] - [[tartrate] - [Ti(OR)_4]] = 2[Ti(OR)_4] - [tartrate]$$

For simplicity, we report the concentrations of active Ti–tartrate as though the complex were a monomer. Since it is a dimer,[7] the rate constants are appropriate for the case in which the titanium atoms in the dimer are equivalent and independently active. The kinetic studies reported here do not allow us to distinguish this case from a mechanism in which only one of the two atoms is an active reaction site, or in which both metal centers are required for a single epoxidation event. For structural reasons,[7] we have discounted the former alternative, but the latter remains a possibility.

We have taken advantage of the availability[15] of the analytically pure compound $[Ti(DIPT)(OiPr)Br]_4$ (**8**) as a source of $[Ti(DIPT)(OiPr)_2]_2$ of exactly equimolar Ti to tartrate composition. Table VI shows that the rate of epoxidation with $[Ti(DIPT)(OiPr)_2]_2$ generated from **8** (entry 1) is significantly slower than when DIPT is present in excess, when the concentration of reagents is adjusted to provide the same amount of active Ti–tartrate. Upon addition of DIPT to $Ti(DIPT)(OiPr)_2$ prepared from **8** (entry 2), the reaction rate increases to the same value as is observed with complexes prepared from $Ti(OiPr)_4$ plus excess DIPT. That the 1:1 Ti–tartrate mixture is less active than a mixture having excess tartrate strongly suggests the presence of catalytic species of reduced activity in the former. We have identified[7] one of these species as $[Ti_2(DIPT)(OiPr)_6]$, formed by disproportionation of $[Ti(DIPT)(OiPr)_2]_2$. Such a disproportionation process is inhibited in the presence of excess tartrate.

Table VII. Absolute and Relative Rates for Kinetic Resolution of Secondary Allylic Alcohols[a]

entry	DIPT	DET	DMT
	$\frac{26.0}{0.43} = 60 \pm 3$	$\frac{29.8}{0.78} = 38 \pm 2$	
	$\frac{0.166}{0.00339} = 49 \pm 5$	$\frac{0.308}{0.0567} = 54 \pm 3$	
	$\frac{0.551}{0.00755} = 73 \pm 4$	$\frac{0.345}{0.0122} = 28 \pm 2$	$\frac{0.247}{0.0161} = 15 \pm 1$

[a] For each allylic alcohol, pseudo-first-order rate constants (s^{-1}) for epoxidation using (+)-tartrate appear in the numerator and using (−)-tartrate in the denominator.

Table VIII. Pseudo-First Order Kinetics in the Presence of *n*-Butanol, Isopropyl Alcohol, and Isopropyl Alcohol-*d*

entry	allylic alcohol	inhibitor alcohol	tartrate	rate const[a]	k_{ref}[b]
1	**9**	*i*PrOH	(+)-DIPT	0.755	73 ± 4
	9	*i*PrOH	(−)-DIPT	55.1	
2	**9**	*n*BuOH	(+)-DIPT	0.106	71 ± 4
	9	*n*BuOH	(−)-DIPT	7.56	
3	**3**	*i*PrOH	(+)-DIPT	46.4	
4	**3**	*i*PrOD	(+)-DIPT	46.4	

[a] Rate constant = $(rate_{obs})([inhibitor\ alcohol]^2)/[Ti\text{-tartrate}][TBHP]$ (10^{-2} s^{-1}). [b] $k_{rel} = k_{fast}/k_{slow}$.

Table VII shows that the rate of epoxidation with $[Ti(DIPT)(OiPr)_2]_2$ generated from **8** (entry 1) is significantly slower than when DIPT is present in excess, when the concentration of reagents is adjusted to provide the same amount of active Ti–tartrate. Upon addition of DIPT to $Ti(DIPT)(OiPr)_2$ prepared from **8** (entry 2), the reaction rate increases to the same value as is observed with complexes prepared from $Ti(OiPr)_4$ plus excess DIPT. That the 1:1 Ti–tartrate mixture is less active than a mixture having excess tartrate strongly suggests the presence of catalytic species of reduced activity in the former. We have identified[7] one of these species as $[Ti_2(DIPT)(OiPr)_6]$, formed by disproportionation of $[Ti(DIPT)(OiPr)_2]_2$. Such a disproportionation process is inhibited in the presence of excess tartrate.

Reaction Rate vs Tartrate Diester and Inhibitor Alcohol. Pseudo-first-order rates of epoxidation for a single enantiomer of three secondary allylic alcohols were determined with both enantiomeric forms of the Ti–tartrate catalyst, as shown in Table VII. This is equivalent to measuring the rates for each enantiomer of the substrate in the presence of one chirality of tartrate auxiliary and defines the kinetic resolution relative rate $k_{rel} = k_{fast}/k_{slow}$.[5] Note that for the 1,2-disubstituted olefins (entries 1 and 3) k_{rel} increases with increasing size of the tartrate ester alkyl group. We believe the α-substituted case (entry 2)[16] suffers from increased steric interactions due to the α-alkyl substituent, and for this reason, the absolute rate of the faster reacting enantiomer drops with the larger tartrate ester.

A related observation has recently been made that increasing steric bulk at the olefin terminus in the trans position of a secondary allylic alcohol both *increases* the absolute epoxidation rate of the faster reacting enantiomer and *decreases* the rate of the

(13) The sluggish activity of silyl-substituted olefins is a consequence of electronic, not steric, factors. See ref 17.

(14) It has been reported that use of more than 2 equiv of tartrate per titanium under *catalytic* conditions (<5% Ti with respect to substrate) results in a sluggish, but active and enantioselective, epoxidation system.[4b] Under pseudo-first-order conditions the 1:2 Ti:tartrate system is inactive. The catalytic result indicates that the second equivalent of tartrate binds with a smaller equilibrium constant than the first. If this were not true, enantiomeric excess would not be high under catalytic conditions.

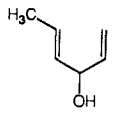
(15) Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279–1282.

(16) In entry 2, the rate of epoxidation of the faster reacting enantiomer with the Ti–DIPT system appears incorrectly in ref 6a.

slower reacting enantiomer.[17] Such rate accelerations with increasing steric demand seem to be without precedent in nonenzymic atom-transfer processes.

The rate constants for epoxidation of the two enantiomers of (*E*)-1-cyclohexyl-2-buten-1-ol (**9**) were similarly determined with (+)-DIPT in the presence of identical concentrations of two different inhibitor alcohols, as shown in Table VIII (entries 1 and 2). While *n*-butanol was found to be a much better inhibitor than isopropyl alcohol (presumably because its binding constant to Ti is greater), the relative rates of reaction of the two allylic alcohol enantiomers were the same for both inhibitors. Thus, inhibitor alcohol is probably not present at the reaction center during the rate-determining oxygen-transfer step. Consistent with this conclusion is the observation that no solvent deuterium isotope effect was found (k_H/k_D = 1.00) in the pseudo-first-order epoxidation of (*E*)-2-decen-1-ol (**3**) in the presence of *i*PrOH vs *i*PrOD as inhibitor alcohols (Table VIII, entries 3 and 4).

The previously reported[18] successful kinetic resolution of (*E*)-1,4-hexadien-3-ol (**10**) suggests that kinetic resolution of secondary allylic alcohols is not the result of differential binding



10

of the enantiomeric substrates to the chiral catalyst. The two enantiomers of **10** would be expected to have nearly equal steric and electronic properties with respect to coordination to the titanium center, and thus very similar binding constants. Yet the kinetic resolution is very efficient, demonstrating that enantiomeric discrimination must occur in the epoxidation step.

Reaction Rate with Varying Titanium–Tartrate Stoichiometry. Because titanium alkoxides exchange ligands readily, equilibria are established in equimolar mixtures of titanium tetraalkoxides and dialkyl tartrates in which more than one complex may be present and individual oligomeric complexes may have nonequivalent amounts of metal and tartrate ligand. Each of these can potentially mediate epoxidation, at different rates and with different enantiomeric excess.

Indeed, Ti–tartrate mixtures of other than 1:1 stoichiometry have been found to mediate other oxidation reactions. For example, catalysts for the chlorohydroxylation of allylic alcohols[19] and the kinetic resolution of β-amino alcohols[20] have been developed that utilize a 2:1 Ti–tartrate formulation. The former reaction provides epoxides or chlorohydrin derivatives of opposite enantiofacial selection to that of the "parent" asymmetric epoxidation system. A 1:2 Ti–tartrate system discovered by Kagan and Pitchen mediates the asymmetric oxidation of sulfides to sulfoxides.[21]

The use of a 2:1 ratio of $Ti(OR)_4$ to tartrate diester under otherwise standard stoichiometric epoxidation conditions results in epoxidation of the "normal" olefinic face in reduced enantiomeric excess. For example, a 2:1 ratio of $Ti(OiPr)_4$ to (*R*,*R*)-(+)-DIPT yields the 2*S*-epoxy alcohol of (*E*)-α-phenylcinnamyl alcohol in 80% ee, compared to >98% ee for a 1.0:1.2 ratio of reagents. We have also found that the addition of electron-withdrawing ligands to this 2:1 Ti–tartrate system results in a reversal of enantioselectivity in epoxidation of allylic alcohols.[22]

Table IX. Pseudo-First-Order Rate Constants for Epoxidation of (*E*)-2-Hexen-1-ol in CH_2Cl_2 under Standard Conditions[a]

entry	catalyst	$rate_{obs}$[b]	$rate_{rel}$	rate order in *i*PrOH
1	$[Ti(DIPT)(OiPr)_2]_2$	11.5	1.00	−2.0 ± 0.1
2	$Ti_2(DIPT)(OiPr)_6$	3.18	0.28	−1.4 ± 0.2
3	$Ti(OiPr)_4$	4.37	0.38	−1.0 ± 0.2
4	$[Ti(DNBnT)(OiPr)_2]_2$	0.34	0.03	
5	$Ti_2(DNBnT)(OiPr)_6$	1.32	0.12	

[a] $[Ti]_{active}$ = 0.0130, [*i*PrOH] = 0.300, and [TBHP] = 0.0150. DNBnT, (*R*,*R*)-*N*,*N*'-dibenzyltartramide

Thus, the potential exists for many manifolds of reactivity in the titanium–tartrate system.

The success of the asymmetric epoxidation reaction can be due to one of four situations: (1) only one Ti–tartrate species is present in the 1:1 mixture, and this species is the enantioselective catalyst, (2) more than one Ti–tartrate species is present, but only one is catalytically active, (3) more than one Ti–tartrate is active, but one species is dominant in rate (by virtue of enhanced reactivity or by its presence in excess, or both), or (4) more than one Ti–tartrate species is active and each mediates epoxidation with very high enantio- and diastereoselectivity. Studies of the solution-phase structures of Ti–tartrate mixtures[7] indicate that one major species of 1:1 stoichiometry is present in the reaction mixture along with at least two minor nonequimolar components. The following experiments indicate that the major species dominates the epoxidation activity of the mixture, thus corresponding to the third possibility above.

The relative kinetic activities of these complexes were explored by measuring the pseudo-first-order rates of epoxidation using different ratios of $Ti(OiPr)_4$ to (+)-DIPT. The observed rates reflect the average of the activities of the complexes that make up the Ti–tartrate mixture. Under these conditions, "activity" includes both rates of oxygen transfer and equilibrium constants for binding of the allylic alcohol and hydroperoxide to titanium.

Figure 2 shows that a 1:2 mixture of Ti to tartrate mediates epoxidation at a very slow rate with respect to the normal 1.0:1.2 mixture, indicating that the epoxidation activity of complexes having more tartrate than titanium is negligible. Complexes composed of more metal than chelating ligand, however, might be expected to show enhanced reactivity with respect to a 1:1 metal to ligand system. Table IX lists the observed pseudo-first-order rates for epoxidation of (*E*)-2-hexen-1-ol by TBHP and five catalyst preparations, under standard conditions of concentration and temperature.

It must be emphasized that the relative rate values reported in Table IX are accurate only for the set of concentrations at which they were measured, since not all the epoxidation systems have the same kinetic rate law. For example, the rate dependence on isopropyl alcohol (inhibitor alcohol) varies with the reaction system. Thus, at lower inhibitor alcohol concentrations, the "parent" 2:2 Ti–DIPT system (entry 1) would show a higher rate relative to the 2:1 Ti:DIPT mixture than is indicated.

Table IX supplies a lower limit for the rate difference between discrete 2:2 Ti–tartrate and 2:1 Ti–tartrate complexes. NMR spectra discussed in the accompanying paper show the 2:1 Ti-$(OiPr)_4$ to DIPT mixture to comprise 15–20% $[Ti(DIPT)(OiPr)_2]_2$ plus an equal amount of $Ti(OiPr)_4$. Taking the rates of these *more active* epoxidation catalysts into account, epoxidation by $Ti_2(DIPT)(OiPr)_6$ is actually about 10 times slower than with the 2:2 complex.

Consider, too, that $Ti(OiPr)_4$ has four labile ligand sites per metal center, $Ti_2(DIPT)(OiPr)_6$ three (assuming that tartrate is bound strongly), and $[Ti(DIPT)(OiPr)_2]_2$ only two. $Ti(OiPr)_4$ thereby provides more opportunities for the reactants to bind to the metal than $[Ti(DIPT)(OiPr)_2]_2$, and yet $Ti(OiPr)_4$ is less active as an epoxidation catalyst. In terms of reactivity per available ligand site, the 2:2 system is by far the most potent oxygen-transfer catalyst.

(17) Carlier, P. R.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978–2979.
(18) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589–604.
(19) Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728–731.
(20) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608–3611.
(21) (a) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, 1049–1052. (b) Pitchen, P.; Dunach, E.; Deshmulch, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
(22) Ellman, J. A.; Finn, M. G.; Sharpless, K. B., unpublished results.

The fact that 2:2 Ti–tartrate is the most active among the species listed in Table IX is extremely fortunate (and probably necessary) for the successful operation of the asymmetric epoxidation reaction. It should first be appreciated that an *increase* in rate upon addition of a chelating ligand ("ligand-accelerated catalysis") in a reaction such as this is rare.[23] A ligand that restricts the course of a reaction to an enantio- or diastereoselective path usually does so at the expense of reaction rate.[24]

If the 2:2 system contains species of other stoichiometry, they must be comprised of Ti–tartrate ratios both more and less than 2:2 (the result of a disproportionation process). That is, there would likely be 2:1 Ti–tartrate or free $Ti(OR)_4$ present as well as species such as 2:3 or 2:4 Ti–tartrate. If $Ti(OiPr)_4$ were a much more active catalyst than Ti–tartrate, then even a small amount of it would reduce the enantioselectivity of the reaction. The relatively high activity of the 2:2 system guards against the deleterious effects of any 2:1 complex or free $Ti(OR)_4$ that might be present. The recommended Ti to tartrate ratio for routine asymmetric epoxidation is 1.0:1.2, to further ensure that only 2:2 Ti–tartrate is available for epoxidation. If the 2:2 catalyst was not more active than the 2:1 system or free $Ti(OR)_4$, much more tartrate relative to titanium would be required to obtain high enantiomeric excess, and the rate would suffer. This is exactly the unfortunate situation observed in earlier attempts at metal-catalyzed asymmetric epoxidations.[24,25]

Of course, a 2:2 mixture of Ti to tartrate can also contain monomers or oligomers having equimolar Ti to tartrate ratios; indeed, 3:3 and 4:4 structures are known.[26] We focus on the dimeric 2:2 Ti–tartrate species as the active catalyst because of its measured molecular weight and the detection of one major species in solution.[7]

The kinetic behavior of the precisely equimolar Ti–tartrate system (Table VI) is therefore understood. Such a reaction mixture is slowed relative to the 1.0:1.2 Ti–tartrate mixture due to the presence of greater amounts of the sluggish 2:1 Ti–tartrate catalyst.

We know from Table IX that the actual dominant asymmetric epoxidation catalyst cannot have fewer equivalents of tartrate than titanium. If it did, the rate for the 2:1 metal to ligand mixture would be greater than the 2:2 reaction, and the enantiomeric excess would be high [when it is only 80% for (*E*)-α-phenylcinnamyl alcohol].

That the 2:1 mixture is the slowest of the three is significant in that it indicates that it does not disproportionate (to give 2:2 Ti–tartrate and free titanium tetraalkoxide) to a great extent. If disproportionation were complete, the rate of the 2:1 system would be an average of the 2:2 and $Ti(OiPr)_4$ results. Therefore, there must be one or more discrete 2:1 complexes that are sluggish epoxidation catalysts (a deduction supported by NMR and IR studies of the 2:1 system).[7] This surprising fact is one of the most crucial to the success of the asymmetric epoxidation process, for if this "nearest neighbor" catalyst were as active as the major catalyst, the overall selectivity would likely be undermined in an irreparable way.

Note that the rates of pseudo-first-order epoxidations involving the tartramide ligand (Table IX, entries 4 and 5) are in keeping with the conventional expectation that increasing amounts of chelating ligand decrease the rate: free $Ti(OiPr)_4$ is fastest, followed by 2:1 Ti–D*N*BnT, and then by 2:2 Ti–D*N*BnT. When this result is coupled with the observation that the 2:1 and 2:2 Ti–tartramide systems provide *opposite* senses of asymmetric induction, it is not surprising that the enantiomeric excess of epoxidations using tartramide catalysts are very sensitive to substrate structure.[19] We believe that it is the 2:1 Ti–tartramide reagent that is unique; the 2:2 Ti–tartrate and Ti–tartramide systems are quite similar in structure if not in activity.

Conclusions

The findings uncovered in this study of most relevance to a mechanistic evaluation of the asymmetric epoxidation process are as follows:

(1) An equimolar complex of titanium tetraalkoxide and tartrate diester is the catalytically active template for asymmetric epoxidation. It is much more active than titanium tetraalkoxide alone or Ti–tartrates of other than 1:1 stoichiometry and thus exhibits selective ligand-accelerated catalysis.

(2) A straightforward kinetic rate law was found under pseudo-first-order conditions showing a second-order inhibitory effect of spectator alcohol, characteristic of a system in which allylic alcohol and alkyl hydroperoxide bind to the same metal center. A corresponding catalytic pathway is proposed that features rapid ligand exchange with rate-determining oxygen transfer.

(3) That the epoxidation rate remains first order in [Ti–tartrate] over at least a 10-fold concentration range suggests that the molecularity of the active species is constant in that range.

(4) Rate variations with olefin substitution show the olefinic moiety to be acting as a nucleophile.

(5) Changing the added inhibitor alcohol has no effect on the relative rate of kinetic resolution, indicating that free alcohol is probably not associated with the complex responsible for rate-determining oxygen transfer.

(6) Equilibrium constants for binding of hydroperoxides to titanium(IV) alkoxides respond to simple steric trends.

(7) Increased steric bulk at several positions in the epoxidation system—the alkyl group of the tartrate ester, the hydroperoxide alkyl moiety, and the trans-olefinic substituent—results in increased epoxidation rates as well as better kinetic resolution and asymmetric induction.

Experimental Section

Unless otherwise specified, tartrate diesters and diamides were derived from (+)-tartaric acid. Note the following abbreviations: DIPT, diisopropyl tartrate; DET, diethyl tartrate; DMT, dimethyl tartrate; D*N*BnT, *N*,*N*′-dibenzyltartramide; TBHP, *tert*-butyl hydroperoxide.

All water-sensitive manipulations were performed in a Vacuum Atmospheres inert atmosphere glovebox under nitrogen or with standard Schlenk techniques under argon. Methylene chloride was distilled from CaH_2 or dried over 3-Å molecular sieves, as discussed in the text. Toluene, pentane, ether, and THF were distilled from sodium benzophenone dianion under nitrogen. Isopropyl alcohol was distilled from $Mg(OiPr)_2$ and stored over powdered 3-Å molecular sieves. Isopropyl alcohol-*d* (Cambridge Isotope Laboratories) was dried by two sequential treatments with, and storage over, activated 3-Å molecular sieve powder. *N*,*N*′-Dibenzyltartramide was prepared by the literature procedure,[19] recrystallized from hot toluene, and dried under vacuum. Activated molecular sieve beads (Linde) and powder (Aldrich) were stored in a vacuum oven at 160 °C and 0.1–0.5 Torr for at least 24 h before use.

Titanium tetraalkoxides were distilled under vacuum and stored in the drybox. Tartrate diesters were either purchased (DIPT and DET from Fluka) or prepared by esterification or transesterification, distilled under vacuum, and stored under argon. Before each reaction the tartrate was stirred for 1 h under vacuum (0.1 Torr) to eliminate dissolved gases and guard against the buildup of water in the viscous oil. This procedure is more important for diethyl tartrate, which is more hygroscopic than DIPT. (*E*)-2-Decen-1-ol was prepared by the method of Corey and co-workers.[27] (*E*)-2-Hexen-1-ol (Aldrich) was distilled and stored at 4 °C over activated 3-Å sieves.

Gas chromatography was performed using $^1/_4$-in. packed glass columns of Carbowax-20M (10% on GasChrom-Q) or SE-30 (5–10% on Chromosorb W). Capillary GC was performed using 20–30-m fused-silica columns of Carbowax-20M or SE-30 purchased from J&W Products.

General Procedure for Asymmetric Epoxidation of Prochiral Allylic Alcohols. Into an oven-dried reaction flask were placed a dry stir bar, the allylic alcohol (1.0 equiv), and dialkyl tartrate (1.2 equiv). The flask was capped with a septum and flushed with argon. Methylene chloride was then added by cannula transfer and the solution cooled to 0 or −20 °C under argon before addition of titanium tetraalkoxide (1.0 equiv).

(23) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
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(25) (a) Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 1990–1992. (b) Coleman-Kammula, S.; Duim-Koolstra, E. T. *J. Organomet. Chem.* **1983**, *246*, 53–56.
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Table X. Results of Epoxidation Using *n*-Butyl Hydroperoxide

sieve treatments	enantiomeric excess, %	
	(*E*)-α-phenylcinnamyl alcohol	(*E*)-2-decenol
1		4
2	75	18
3	94	70
4	90	75
5	92	75

Note that the use of activated 3-Å molecular sieve powder (0.2–0.4 g per 10 mL of solution) is now recommended in routine asymmetric epoxidations.[4] After 15–30 min, TBHP was added by gas-tight syringe to initiate the reaction. After monitoring by TLC, excess hydroperoxide was quenched and titanium removed by addition of an aqueous solution of tartaric acid (10% by weight) saturated with $FeSO_4$, with rapid stirring or shaking.

Determination of Hydroperoxide Binding Constants. Equilibrium constants were determined by FTIR monitoring of the intensity of the RO–H (ca. 3610 cm^{-1}) and ROO–H (3490 cm^{-1}) bands in dilute CH_2Cl_2 solution at room temperature with added aliquots of hydroperoxide solution. The experimental apparatus consisted of a KBr flowthrough cell (0.10-mm path length) capped on top with a Luerlock syringe and on the bottom with a Luerlock adapter to a length of Teflon tubing, which was inserted through a septum into the reaction flask. This allowed the bulk reaction solution to be mixed and then drawn into the IR cell under a positive pressure of argon.

In principle, the equilibrium constant for the replacement of each of the four alkoxides of a titanium tetraalkoxide or for each of the two monodentate alkoxides of a Ti(tartrate)$(OR)_2$ unit can be determined. In practice, however, the decomposition of hydroperoxides at room temperature in the presence of titanium proved to be a limiting factor. In the presence of isopropoxide ligands, oxidation to acetone was observed; in the presence of *tert*-butoxide ligands, an unidentified decomposition process was found to turn the solutions yellow. Both of these reactions took place at a slow rate when less than 1 equiv of hydroperoxide per titanium was added, but the rates increased with greater concentrations of oxidant. Therefore, only small amounts of added hydroperoxide were used, and the contribution of binding of more than one hydroperoxide per titanium was neglected, except for $Ti(OiPr)_4$. Under these conditions, no changes in the IR spectra were observed with time.

Experimental details can be found in the supplementary material.

Preparation of and Epoxidations Using *n*-Butyl Hydroperoxide. *n*-Butyl hydroperoxide was prepared from *n*-butylmethanesulfonate by the method of Williams and Mosher.[28]

A 2.1 M solution of the hydroperoxide in CH_2Cl_2 was dried over activated 4-Å molecular sieves for 12–16 h at 0 °C. After the concentration was determined by iodometric titration, the hydroperoxide was employed in asymmetric epoxidations of two standard substrates. The hydroperoxide solution was then transferred by pipet to a fresh batch of sieves, and the titration and epoxidations were performed again. This process was repeated until the results of asymmetric epoxidation were reproduced twice in succession, thus employing the epoxidation reaction as an indicator of the water content of the hydroperoxide solution. The concentration of the hydroperoxide in solution did not change with the sieve treatments.

Asymmetric epoxidations of (*E*)-α-phenylcinnamyl alcohol and (*E*)-2-decen-1-ol were performed under stoichiometric conditions in the usual manner at −20 °C, using a 1:1.2 ratio of $Ti(OiPr)_4$ to (+)-DIPT. Table X lists the enantiomeric excess of the product epoxy alcohols for the sequential molecular sieve treatments.

Pseudo-First-Order Kinetics. Rates of epoxidation were measured under conditions in which the concentrations of both the titanium–tartrate complex and *tert*-butyl hydroperoxide were at least 20 times that of the allylic alcohol, imposing a pseudo-first-order condition on the substrate. In most cases, the tartrate diester was present in 10–30% excess with respect to titanium, and the concentration of "active" Ti–tartrate complex was calculated as discussed in the text. A nonreactive "inhibitor" alcohol (usually isopropyl alcohol) was present to slow the reaction to a convenient rate by competition for exchangeable ligand sites on the metal. The rate dependence on inhibitor alcohol was found to be inverse second order. In cases for which the inhibitor alcohol was different from the tartrate ester group (isopropyl alcohol and diethyl tartrate, for example), the rate of transesterification (i.e., to give diisopropyl tartrate) was found to be much slower than the rate of the epoxidation reaction.

(28) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2984–2987.

Volumetric flasks were cleaned of adsorbed metal ions by soaking in 95:5 H_2SO_4/HCl for 6 h and 5% HF for 6 h, followed by rinsing with base and then water. Thereafter, all glassware, Teflon tubing, and syringes were carefully washed with dilute HF after use to prevent the accumulation of metal contaminants (see the notes for entries 24 and 25, below). A typical procedure for the pseudo-first-order kinetics measurements is detailed below.

Table II, Entry 4. An oven-dried 100-mL volumetric flask was charged with a stir bar and 0.550 g of powdered, activated 4-Å molecular sieves and allowed to cool to room temperature under vacuum. (+)-DIPT (0.637 g, 2.72 mmol) was then added by tared gastight syringe, followed by approximately 102 mL of CH_2Cl_2 (freshly distilled from CaH_2 under nitrogen). The flask was then immersed in a 0.0–0.3 °C ice/water bath up to the 100.0-mL mark, and the solution was allowed to cool with stirring under argon. CH_2Cl_2 at 0 °C is approximately 5% more dense than at room temperature, so the volume of the CH_2Cl_2 solution was approximately 97 mL at this stage. To the solution was then added 0.590 g of $Ti(OiPr)_4$ (2.08 mmol) by tared gastight syringe, and the mixture was allowed to stir for 15 min. This provided a $Ti(OiPr)_4$ to DIPT ratio of 1:1.31, and an active Ti concentration of 0.0143 M, correcting for the production of 0.64 mmol of inactive $Ti(DIPT)_2$. Isopropyl alcohol (1.503 g, 25.0 mmol) was then added by tared gastight syringe, followed by 0.015 mL of a 3:2 (v/v) mixture of (*E*)-2-decen-1-ol and *n*-heptadecane (approximately 5×10^{-5} mol of decenol, providing a 40-fold excess of Ti–tartrate and TBHP with respect to substrate). The total isopropyl alcohol concentration was 0.305 M, including the alcohol released from $Ti(OiPr)_4$ upon binding of tartrate. CH_2Cl_2 was then added to bring the solution up to the 100.0-mL mark. After stirring for an additional 15 min, the reaction was initiated by the rapid injection of 0.00151 mol of TBHP (0.380 mL of a 3.98 M solution in toluene) directly into the vigorously stirred reaction mixture. The added volume of TBHP solution compensates for the volume of the stir bar to bring the total volume very close to 100.0 mL.

Aliquots of 10–20 mL were removed by rapid cannula transfer through a Teflon tube into a vigorously stirred mixture of 10 mL of quench solution (10% aqueous tartaric acid plus 5–15% $FeSO_4$) and 10 mL of ether. Control experiments determined that quenching the aliquots at 0 °C and room temperature produced identical results. The resulting mixtures were stirred for 5 min and the organic layer was separated, dried with $MgSO_4$, filtered, and evaporated at room temperature on the rotary evaporator. The resulting clear oil was taken up in 1 mL of ether for GC analysis. Gas chromatography was performed on either a 6-ft packed column or a fused-silica capillary column. When both columns were used to analyze the same set of aliquots, identical results were obtained.

For the reactions summarized in Tables II and III, the $Ti(OiPr)_4$ to DIPT ratio varied from 1:1.10 to 1:1.31. As long as tartrate was present in excess, no effect of the Ti:DIPT ratio on rate was observed. However, see Table VI for the rate of epoxidation mediated by 1.0:1.0 Ti to DIPT.

Aliquots were taken at 1.58, 7.40, 12.92, 18.12, 24.05, and 30.65 min; two to four injections for each aliquot were averaged to obtain the ratio of peak intensity for (*E*)-2-decen-1-ol remaining to hexadecane. A plot of time vs the natural log of this ratio fit a line with $R^2 = 0.9998$ and slope (rate of disappearance of allylic alcohol) equal to -1.30×10^{-3} s^{-1}. The reported rate was corrected for slight variations in the concentrations of Ti–tartrate and TBHP by normalizing them to 0.0145 and 0.0150 M, respectively, since the pseudo-first-order rate is directly proportional to these concentrations. In this example, the observed rate was multiplied by 0.0145/0.0143 (Ti–tartrate concentration), by 0.0150/0.0151 (TBHP concentration), and by $[iPrOH]^2$ ($0.305^2 = 0.093$) to give the reported value of $rate_{corr}$ of 1.22×10^{-4} M^2 s^{-1}.

Notes concerning the kinetic data follow. Details (reagent concentrations and observed rates) for each experiment can be found in the supplementary material, as indicated.

Table III. The values reported in Table III were obtained by application of the above method to the reactions listed in the supplementary material (Table A). Reactions were performed in ether and pentane in the same manner as for CH_2Cl_2. It should be noted that commercially available anhydrous ether (freshly opened under argon) was unsuitable for pseudo-first-order kinetics measurements. Observed rates were on the order of 2–3 times less (and were much less reproducible) in the commercial solvent than in ether dried by distillation from $LiAlH_4$ or Na/benzophenone dianion. The asymmetric epoxidation was thus able to function as a sensitive indicator of water content.

Table V and Figure 2. See Tables B and C of the supplementary material.

Table VI. Entry 1. In the drybox, $[Ti(DIPT)(OiPr)Br]_4$[15] (605 mg, 1.44 mmol of Ti) was dissolved in 5 mL of ether and treated with Et_3N (175 mg, 1.73 mmol), followed by isopropyl alcohol (110 mg, 1.83 mmol). After standing for 45 min with occasional shaking, the white

precipitate was filtered, washed with ether (3 × 10 mL), and dried in vacuo to afford 256 mg of $Et_3NH^+Br^-$ (98%). The combined ether solutions were evaporated, the resulting clear oil was dissolved in 8 mL of CH_2Cl_2, and the solvent was again removed; this was repeated once more to yield alcohol-free Ti(DIPT)($OiPr$)$_2$ (1.44 mmol) with no excess DIPT present.

The Ti-tartrate complex was taken up in CH_2Cl_2 and transferred to a dry 100-mL volumetric flask, to which was added 1.800 g of *i*PrOH (30.0 mmol). The flask was removed from the drybox and cooled to 0 °C under argon as before. The mixture of (*E*)-2-decen-1-ol and hexadecane (0.015 mL) was added, and the total volume of the solution after cooling was found to be 101 mL. After removal of the excess 1 mL of solution by cannula, the reaction and kinetic analysis were performed in the usual manner.

Entry 2. Generation of Ti(DIPT)($OiPr$)$_2$ was performed as above with the following reagents: [Ti(DIPT)($OiPr$)Br]$_4$ (733 mg, 1.75 mmol of Ti), Et_3N (206 mg, 2.0 mmol), and *i*PrOH (156 mg, 2.6 mmol). Filtration, evaporation, and two CH_2Cl_2/vacuum cycles were done as before to generate 1.75 mmol of Ti(DIPT)($OiPr$)$_2$, which was transferred to a dry 100-mL volumetric flask. To this solution was added (+)-DIPT (71 mg, 0.30 mmol), to provide an active Ti-tartrate concentration of 0.0145 M and a Ti to DIPT ratio of 1:1.17. After addition of *i*PrOH (1.766 g, 29.4 mmol), the flask was removed from the drybox and cooled to 0 °C, and substrate and standard were added as before. The reaction was then performed and analyzed in the usual way.

Table VII. Enantiomerically pure (*R*)-1-(1-cyclohexenyl)ethanol (entry 1), (*R*)-2-methylhept-1-en-3-ol (entry 2), and (*R*)(*E*)-1-cyclohexylbut-2-en-1-ol (entry 3) were prepared by kinetic resolution.[5] Pseudo-first-order kinetics were performed in the usual manner under conditions listed in Table D of the supplementary material.

Table VIII. Kinetic measurements in the presence of *n*-butyl alcohol as inhibitor were performed in the same way as the other pseudo-first-order reactions, with the use of Ti(O*n*Bu)$_4$ in place of Ti($OiPr$)$_4$, and *n*-butanol in place of isopropyl alcohol. Reactions in the presence of isopropyl alcohol-*d* as inhibitor were performed by adding the inhibitor alcohol to an alcohol-free sample of Ti(DIPT)($OiPr$)$_2$. Nondeuterated TBHP was used, so the molar ratio of OD to OH groups in the reaction was therefore [0.201 M (*i*PrOD)/0.0150 M (TBHP)] = 13.4. The corresponding reaction with *i*PrOH as inhibitor was performed in exactly the same way, with addition of isopropyl alcohol-*h* to alcohol-free Ti(DIPT)($OiPr$)$_2$. Aliquots were obtained, quenched, and analyzed in the usual manner. Details can be found in Table E of the supplementary material.

Table IX. Pseudo-first-order kinetics measurements were performed in the usual manner, with the ratios of titanium to ligand listed in Table F (supplementary material). The 2:1 catalysts were prepared by mixing Ti($OiPr$)$_4$ and the ligand in a 2:1 molar ratio. Unlike the 2:2 reactions, no "inactive" Ti complexes are assumed to be present, since the diol was not used in excess. Therefore, $[Ti]_{active}$ is the concentration of Ti($OiPr$)$_4$ used to prepare the 2:1 mixture. Experimental details are listed in Table F of the supplementary material.

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Supplementary Material Available: Details of the determination of hydroperoxide binding constants and kinetic rate parameters (8 pages). Ordering information is given on any current masthead page.

Mechanism of Asymmetric Epoxidation. 2. Catalyst Structure

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Abstract: The dominant species in equimolar mixtures of titanium tetraalkoxides and dialkyl tartrate esters is shown to be [Ti(tartrate)(OR)$_2$]$_2$, which is identified as the active catalyst for asymmetric epoxidation of allylic alcohols by tertiary alkyl hydroperoxides. The solution-phase structure of this species is consistent with the results of an X-ray structural determination of a titanium tartramide complex reported previously, as analyzed by IR and ^{1}H, ^{13}C, and ^{17}O NMR spectrometry. The first ^{17}O NMR spectra of titanium(IV) alkoxide and alkyl peroxide complexes are reported, as well as the results of a secondary deuterium isotope effect study on the asymmetric epoxidation reaction. General conclusions concerning the mechanism of asymmetric epoxidation are presented.

Here we present results concerning the solution-phase structure of the active titanium–tartrate catalyst in the asymmetric epoxidation reaction and thus provide the evidence underlying our assumptions concerning the mechanism of the process.[2] Single-crystal X-ray structure determinations have been performed on closely related complexes,[3] but usable crystals of a titanium–tartrate ester species have not been obtained. In any case, solid-phase structures are of limited utility in assigning the structures in solution of complexes that exchange ligands as readily as do titanium(IV) alkoxides. We also discuss some aspects of the mechanism that were not included in its initial presentation.[2] The preceding paper includes information concerning the kinetics of the asymmetric epoxidation reaction. Note the following abbreviations: DIPT, (*R,R*)-diisopropyl tartrate; DET, (*R,R*)-diethyl tartrate; DMT, (*R,R*)-dimethyl tartrate.

Results and Discussion

1. Molecular Weight. The molecular weight of [Ti(DIPT)($OiPr$)$_2$]$_2$ was first measured by vapor-phase osmometry as 752 and 796, compared to the calculated dimeric molecular weight of 797.[4] The Signer method,[5] a technique closely related to

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(4) The first clue to the aggregation state of titanium tartrates in solution came not from a molecular weight measurement, but from diastereoselective epoxidations of secondary allylic alcohols in the presence of (*dl*)-tartrates. Kinetic resolutions of secondary allylic alcohols produce epoxy alcohol products highly enriched in the erythro diastereomer. Using (*dl*)-tartrates, we obtained diastereoselectivities that were independent of the extent of reaction and significantly lower than those found with homochiral tartrates.[13,14] In addition, the asymmetric epoxidation has been found to give a nonlinear response of product enantiomeric excess to changes in the enantiomeric purity of tartrate.[42] Neither observation is consistent with the action of monomeric Ti-tartrate catalysts. Furthermore, NMR spectra of the Ti-(*dl*)-tartrate system show distinct bands assignable to a (*dl*)-tartrate complex in addition to those found for the homochiral complex.[13] This would not be the case if Ti-tartrate were a 1:1 complex.

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