

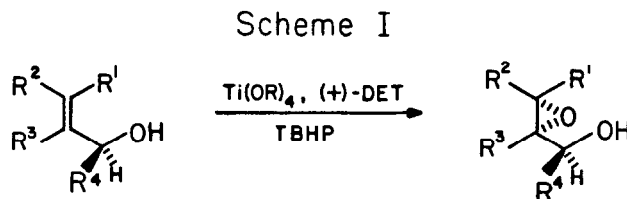
THE ASYMMETRIC EPOXIDATION OF TERT-BUTYL SUBSTITUTED ALLYLIC ALCOHOLS

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**Summary:** The response of the asymmetric epoxidation reaction to steric bulk in the substrate is tested by use of allylic alcohols with tert-butyl groups at each one of four possible positions.

The titanium-tartrate-mediated asymmetric epoxidation<sup>1</sup> reaction has been shown to be effective with allylic alcohols of widely varying substitution patterns.<sup>2</sup> For example, no cases are known for which the face selection of the asymmetric epoxidation of a prochiral allylic alcohol varies from that shown in Scheme I,<sup>3</sup> regardless of the nature of R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup>. In this paper we report the results of further tests of the reaction's generality with sterically hindered allylic alcohols. Sterically demanding tert-butyl groups were placed at each of the four positions labelled R<sup>1</sup>-R<sup>4</sup> shown in Scheme I.




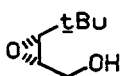
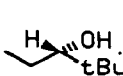
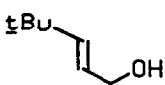
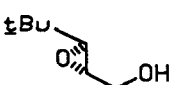
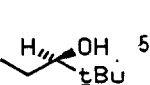
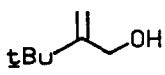
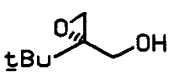
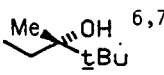
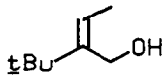
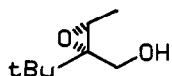
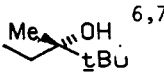


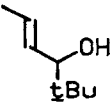
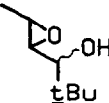
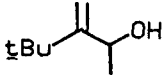
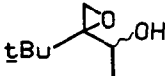
The compounds investigated and the results obtained are listed in the Table.

The poor induction realized in the epoxidation of Z-allylic alcohol 1, and the very successful epoxidation of E-allylic alcohol 2 were both anticipated based on earlier results with somewhat less hindered allylic alcohols.<sup>1,2a,2c</sup> Since an allylic alcohol O-C-C=C dihedral angle of ca. 45° has been proposed to be optimal for epoxidations by Ti(IV)-hydroperoxide systems,<sup>4,2f</sup> the poor induction with substrate 1 is assumed to stem from the unfavorable interaction of the tert-butyl group with the carbinol oxygen at this small dihedral angle.

Compound 3 is a poor substrate, as the initially-formed epoxy alcohol is very sensitive to attack by alcohol nucleophiles in the presence of titanium tetraalkoxides. When Ti(O*i*Pr)<sub>4</sub>-tartrate is used, only isopropanol-opened product can be isolated from 3; the use of Ti(O*t*Bu)<sub>4</sub> allows the isolation of ca. 50% of the epoxy alcohol 7.

A control experiment was performed to determine whether the opening reaction has an effect on the enantiomeric excess of epoxy alcohol 7. The alcohol nucleophile can

## Table

Substrate	Ti(OR) <sub>4</sub>	L <sup>a</sup>	Ti:L	%ee <sup>b</sup>	%Yield	Product	Correlation
	Ti(OiPr) <sub>4</sub>	DET	1.2:1.5	25	77 <sup>c</sup>		 <sup>5</sup> (S) - (-) - <u>9</u>
<u>1</u>						<u>5</u>	
	Ti(OiPr) <sub>4</sub>	DET	1.2:1.5	≥95	52 <sup>c</sup>		 <sup>5</sup> (R) - (+) - <u>9</u>
<u>2</u>						<u>6</u>	
	Ti(OiBu) <sub>4</sub>	DET	1.2:1.5	85	42		 <sup>6,7</sup> (S) - (-) - <u>10</u>
<u>3</u>						<u>7</u>	
	Ti(OiBu) <sub>4</sub>	DET	1.2:1.5	60	43		 <sup>6,7</sup> (S) - (-) - <u>10</u>
<u>4</u>						<u>8</u>	
	Ti(OiPr) <sub>4</sub>	DET	1.0:1.0	10 <sup>d</sup>	60 <sup>e</sup>		— <sup>8</sup>
<u>11</u>							
	Ti(OiPr) <sub>4</sub>	DMT	1.2:1.5	≤5	75 <sup>e</sup>		—
<u>12</u>							
	Ti(OiBu) <sub>4</sub>	DIPT	1.2:1.5	30 <sup>d</sup>	60 <sup>e</sup>		—
<u>13</u>							

a. L = (+)-Tartrate

b. Enantiomeric excesses (ee) were determined by <sup>1</sup>H NMR integration of the corresponding MTPA esters or of the Eu(hfbc)<sub>3</sub> shifted epoxy acetates.

c. Reaction did not proceed to completion.

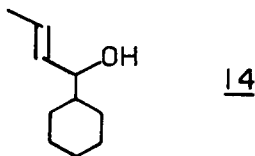
d. Absolute configuration not determined.

e. Percent allylic alcohol consumed in kinetic resolution. The %ee reported is that of the recovered allylic alcohol.

potentially destroy one enantiomer preferentially, as this opening reaction takes place under the influence of the chiral titanium catalyst. A sample of racemic epoxy alcohol 7 was subjected to the reaction conditions  $[\text{Ti}(\text{OtBu})_4, (+)\text{-DET}, \text{TBHP}, \text{CH}_2\text{Cl}_2, -20^\circ\text{C}]$  and allowed to react until 60% had been opened. (Ordinarily the epoxidation is worked up when less than 20% of the product has been destroyed.) The remaining epoxy alcohol had an enantiomeric excess of 18%. The isomer in excess was the minor enantiomer formed from epoxidation of 3 in the presence of (+)-DET. This result allows one to set 85% enantiomeric excess as the lower limit for the reaction.

The face selection for all four prochiral substrates (1 - 4) is in the normal direction, regardless of the enantiomeric excess. All of the optically active epoxides were correlated with known compounds (see Table).<sup>5,6</sup> The absolute configuration of correlation compound 9 is certain, but that of 10 has not been rigorously established. Early work suggested that the levorotatory enantiomer had the R-configuration.<sup>6</sup> Recent work in the laboratories of Eliel and Baldwin<sup>7</sup> has established that Prelog's rule,<sup>9</sup> Cram's rule,<sup>10</sup> and the asymmetric epoxidation rule<sup>1</sup> all predict that levorotatory 10 has the S-configuration.

Neither of the racemic allylic alcohols 11 nor 12 show any useful kinetic resolution, a surprising result based on the fact that cyclohexylpropenyl carbinol 14 is one of the best kinetic resolution substrates.<sup>12</sup> The resolution is evidently not effective for allylic alcohols with tert-alkyl groups on the carbinol carbon.



Racemic 13 is also not a good kinetic resolution substrate. At 60% conversion the enantiomeric excess of the recovered starting material is only 30%, although the product obtained consists largely (ca. 40:1) of one of the two possible diastereomeric epoxy alcohols.

These results suggest that one should in general be wary of attempting to asymmetrically epoxidize or kinetically resolve allylic alcohols with tertiary groups in any but the  $\alpha$ - or (E)- $\beta$ -vinyl positions. However, it appears that even in unfavorable cases, the titanium-tartrate catalyst exhibits a consistent enantiofacial selection in the epoxidation of prochiral substrates.

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b) Professor S.W. Baldwin's group has also performed the titanium-tartrate asymmetric epoxidation of substrate 3, obtaining 7 in 88% enantiomeric excess. Their preliminary correlation, which agrees with that of Eliel and Lynch and with that predicted by the asymmetric epoxidation selection rule<sup>1</sup>, was performed by converting 7 to a cyclic derivative for which the Cotton effect in the circular dichroism spectrum was predicted and observed. Baldwin, S.W., Duke University, unpublished results.
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