The Journal of
Organic
Chemistry

VOLUME 55, NUMBER 6 MARCH 16, 1990

Communications

On the Origin of Enantioselectivity in the Katsuki–Sharpless Epoxidation Procedure

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Received January 4, 1990

Summary: A logical mechanistic explanation is given for the stereoselectivity of the Katsuki–Sharpless epoxidation.

In the course of a study directed at improving the diastereoselectivity of epoxidation of (±)-isopropylvinyl carbinol, Katsuki and Sharpless made the felicitous discovery that a mixture of Ti(O*i*-Pr)$_4$, *t*-BuOOH, and (*R*,*R*)-(+)-diethyl tartrate selectively epoxidized one enantiomer of this allylic alcohol.[1] This finding subsequently led to the Katsuki–Sharpless method for enantioselective epoxidation of allylic alcohols, which now can be classified as a standard synthetic tool.[2] The mechanistic basis for the enantioselectivity of this epoxidation has remained unclear despite its widespread use and extensive studies in this area by the Sharpless school. The purpose of this note is to outline a mechanistic possibility which provides a clear and rational explanation of the data published to date with regard to (1) substrate structure/absolute stereoselectivity and diastereoselectivity, (2) substrate structure and reactivity, (3) structural requirements for the catalyst and the peroxidic oxidant, and (4) reaction kinetics and inhibition.

Specifically, it is proposed that the transition-state assembly for the epoxidation of (*E*)-2-alken-1-ols (for example) by diesters of (*R*,*R*)-(+)-tartaric acid, Ti(O*i*-Pr)$_4$, and *t*-BuOOH can be approximated by ion pair **1** (see Scheme I). The key features of **1** can be derived in a logical way and include the following with regard to the catalytic cation. (1) One molecule of the (*R*,*R*)-tartrate ester is chelated to the central Ti of the cationic moiety of **1**. (2) The hydroxyl group of the allylic alcohol is coordinated to that (C_2 symmetric) Ti so as to allow hydrogen bonding to the carbonyl of the tartrate ester. The geometry of that hydrogen bond in **1** is close to ideal (linear with an O–H–O distance of approximately 2.7 Å). (3) The *tert*-butylperoxy (*t*-BuOO) group is chelated to the catalytic Ti with the terminal oxygen cis to the coordinated allylic OH and the *t*-BuO subunit trans to the allylic OH. Further, the oxygen of the *t*-BuO subunit is pyramidal and in the (*R*)-configuration so as to place the bulky *tert*-butyl group proximate to the vacant coordination site of octahedral Ti and remote from the other ligands on Ti. Any other arrangement of ligands leads to severe steric repulsion between the *tert*-butyl group and the ligand which is cis to *tert*-butyl about the peroxide chelate ring. An sp^2-hybridization of the *tert*-butoxy oxygen is strongly disfavored both sterically and electronically. (4) Five donor atoms are coordinated to the central Ti of the cationic moiety of **1**, further coordination being strongly disfavored by the bulk of the *tert*-alkoxy subunit. (5) The specific arrangement of ligands about Ti in the cationic moiety of **1** makes that Ti a chiral center with the absolute configuration having been determined by the tartrate ligand, as shown. (6) The chirality about the catalytic Ti of **1** and the fixed hydrogen bond strongly favor internal epoxidation at only one face of the double bond if that bond approaches the peroxy O–O bond with its midpoint (*m*) approximately colinear with the O–O axis and with the C=C axis approximately perpendicular to the plane of the peroxy chelate ring, the optimal stereoelectronic arrangement.[2b,3a,b] In that arrangement the hydroxyl of the allylic alcohol is also chiral and of *R* configuration (pyramidal arrangement of Ti, H,

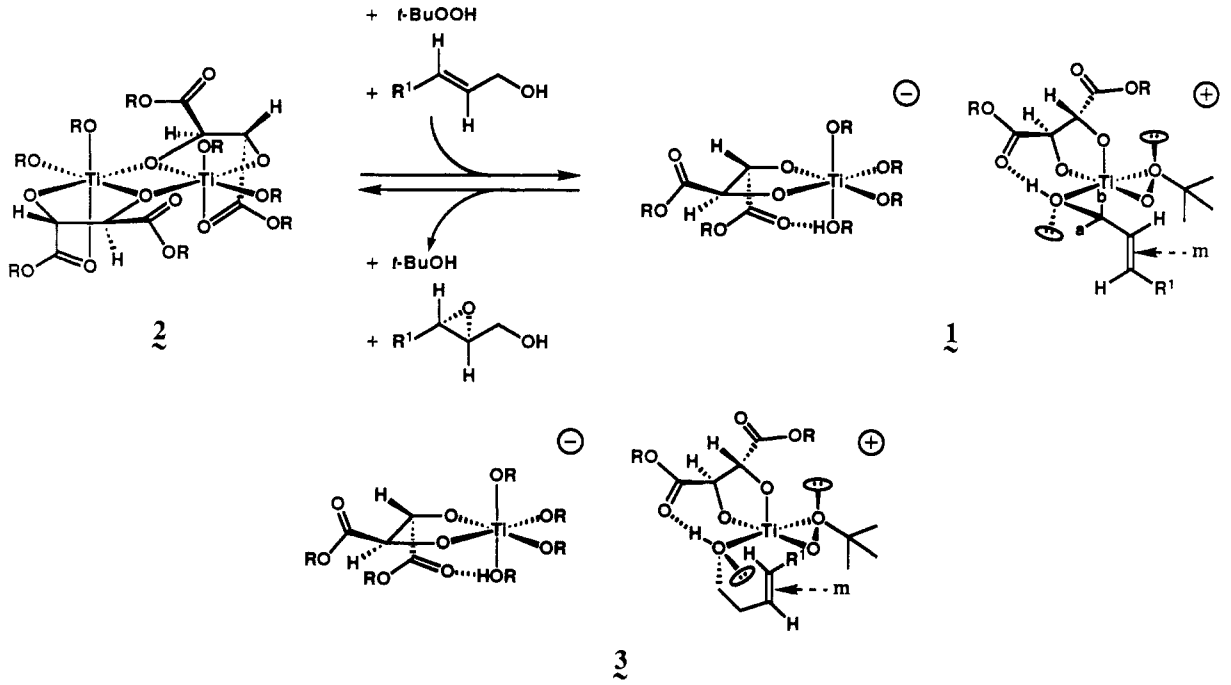
(1) For an interesting account of this early work, see: Sharpless, K. B. Proceedings of the R. A. Welch Foundation Conference on Chemical Research, XXVII, Houston, TX, 1983, pp 59–89.

(2) For excellent reviews see (a) Rossiter, B. E. *Asymmetric Synthesis*; Academic Press: New York, 1985; Vol. 5, pp 193–246. (b) Finn, M. G.; Sharpless, K. B. *Asymmetric Synthesis*; Academic Press: New York, 1985; Vol. 5, pp 247–308.

(3) (a) Corey, E. J.; Niwa, H.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 1586. (b) Prof. Albert Eschenmoser pointed out (personal communication November 1984) the stereoelectronic importance of the perpendicular alignment of the C=C axis and the peroxy chelate ring plane (see also ref 2b).

0022-3263/90/1955-1693$02.50/0

Scheme I



and C about the allylic oxygen), as shown in **1**. (7) The neutrality of the hydroxylic oxygen ligand trans to the *t*-BuO ligand in **1** should favor peroxidic bond cleavage relative to a more electron donating alkoxide ligand (trans-σ electronic effect).

The arguments for the transition-state assembly just given are not meant to describe the pathway for formation of **1** from the reagent **2**, since they are intended simply to outline the stereochemical factors which favor **1** over possible alternatives. Since ligand displacement reactions are very fast with Ti(IV) alkoxides, there should be no kinetic obstacles to the formation of **1** from **2**.

Transition-state assembly **1** is both logically derivable and unambiguous with regard to the absolute stereochemical preference which it implies for the epoxidation reaction. The absolute configuration expected for the epoxy alcohol from **1** accords with the experimental facts.[2] Transition-state assembly **1** also explains the much faster reaction rate for substrates in which a = alkyl or a = b = H relative to b = alkyl.[2] Assembly **1** can be formed directly from the binuclear reagent **2**[4] in a reaction which is first-order in **2**, the allylic alcohol, and *t*-BuOOH, in agreement with the observed kinetics.[2] The formation of epoxy alcohol from **1** would lead to regeneration of **2** by dissociation of the epoxide from the catalytic site assisted by ion-pair collapse. Water, an inhibitor of the epoxidation reaction, clearly can be expected to inhibit by coordination to the vacant site in **1** as well as by competing reactions with the reagent **2**.

The hydrogen bond in **1**, a key feature of our proposal, provides a unique explanation for the failure of many other chiral 1,2-diols (even C_2 symmetric 1,2-diols) to promote enantioselective epoxidation in place of tartrate derivatives. For example, the use of chiral 2,3-butanediol or 1,2 diphenyl-1,2-ethanediol as ligand leads to epoxy alcohol of only 0–5% enantiomeric excess.[2b,5] Our hydrogen-bond mechanism mandates the conclusion that homoallylic alcohols should react by coordination of the homoallylic OH at the diastereotopic lone pair (relative to the allylic structure **1**) with epoxidation at the opposite face of the double bond as compared to **1**, as shown in assembly **3**. This difference in hydrogen bonding geometry for homoallylic and allylic alcohols arises because of the fact that there is no stereoelectronically favorable conformation available for the epoxidation of homoallylic alcohols with hydrogen bonding as in **1**, whereas the stereoelectronics are favorable for the arrangement shown in **3**. Transition-state assembly **3** correctly predicts the observed stereoselectivity.[6] The importance of using bulky tertiary hydroperoxides[2] can also be appreciated from, and indeed is central to, the present proposal.[7] The effectiveness of methylene chloride as solvent in the epoxidation is consistent with the ion-pair assembly **1** which predicts that an optimal solvent should be aprotic, nondonor, and polar.

It is recommended that the reader check this proposal through the use of molecular models since the stereochemical subtleties are more readily appreciated in this way. The mechanism proposed above for the Katsuki–Sharpless epoxidation involves a logical placement of groups about the catalytic Ti center without the need for quite arbitrary assumptions. It is consistent with all of the experimental data of which we are aware and it leads to predictions which can be tested. We believe that this hypothesis is more in accord with established facts and more explicit and rational than any of the mechanisms previously advanced.[2b,4b,8]

(5) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707.

(4) Structure **2** for the reagent is indicated by X-ray and NMR studies; see ref 2a and also (a) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430. (b) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823. (c) Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279.

(6) A number of other chiral ligands have been studied in the Katsuki–Sharpless process with results that are readily accommodated by the mechanism proposed herein. Diisopropyl (3*R*,4*R*)-dihydroxyhexanedioic acid was found to be a poorly functional ligand, as can be expected since an 8-membered, sterically unfavorable hydrogen bonded structure is required. Diisopropyl (2*S*,5*S*)-dihydroxyhexanedioic acid is also a poor catalytic ligand (7-membered chelate ring required). See: (a) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826. (b) Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 4016.

(7) The bulky tertiary group not only assures a vacant coordination site and its location relative to other ligands, but also renders implausible structures in which the tertiary group and the peroxy chelate ring are coplanar (excessive steric repulsion as well as poor hybridization).

(8) This research was supported by a grant from the National Science Foundation.