Katsuki–Sharpless Asymmetric Epoxidation of Alkenylethylene Glycols: the Origin of Inverted Stereoselection

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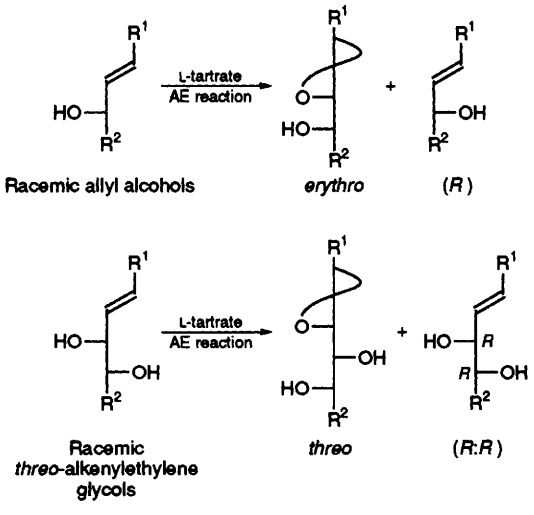
The Katsuki–Sharpless asymmetric epoxidation of linear and cyclic alkenylethylene glycols has led to a conclusion that the origin of the inverted stereoselection is due to the simultaneous coordination between both hydroxy groups of the glycol substrates and both titanium atoms in the Ti_2(tartrate)$_2$ complex.

We demonstrated that the Katsuki–Sharpless asymmetric epoxidation (AE reaction) of some alkenylethylene glycols proceeds in an inverted stereochemical pathway that of allyl alcohols.[1] Thus, while a racemic allyl alcohol affords an *erythro*-epoxide† leaving an unreacted (*R*)-allyl alcohol in the presence of L-tartrate, a racemic *threo*-ethylene glycol‡ affords a *threo*-epoxide leaving an unreacted (*R*:*R*)-starting glycol in the presence of the same L-tartrate.[2] Thus, inversion of two forms of stereoselection, diastereofacial and enantiotopical selections, occurs between these two substrate under the same conditions (Scheme 1). In order to clarify the observed stereochemical difference between allyl alcohols and alkenylethylene glycols, we investigated the AE reaction of seven alkenylethylene glycol substrates **1–7** which led us to reach a conclusion that the origin of the inverted stereochemistry is due to the simultaneous coordination between both hydroxy groups of the glycol substrates and both titanium atoms in the Ti_2(tartrate)$_2$ complex, the latter being presumed to be the most plausible intermediate in the AE reaction.[2,3]

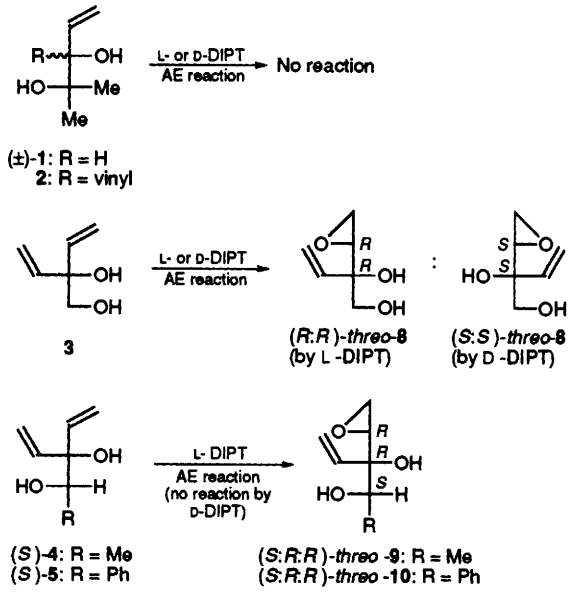
The substrates were subjected to the AE reaction under stoichiometric conditions in the presence of molecular sieves (4 Å). When catalytic conditions[4] were employed none of the substrates reacted in a practical reaction rate. Even under the stoichiometric conditions, two, (±)-**1** and -**2**, of five linear substrates having a tertiary homoallylic hydroxy group did not give any oxidation products and the substrates were recovered unchanged. Of the substrates reacted, the prochiral glycol **3** having a primary homoallylic hydroxy group afforded a single enantiomeric epoxide§ **8**, $[\alpha]_D^{28}$ +18.7 (*c* 1.07, $CHCl_3$) [by L-diisopropyltartrate (L-DIPT)] and $[\alpha]_D^{27}$ −18.2 (*c* 0.65, $CHCl_3$) (by D-DIPT), stereoselectively in moderate yield (≈56%) in high enantiomeric excess (≈95% ee by MTPA esters) depending on the chirality of the tartrate used. It was noteworthy that two forms of stereodifferentiation, the selection of one of two diastereomeric olefins and the selection of enantiofaces of the selected olefin, occurred in this case. Correlation of the epoxide **8** to the known compound[5] **19**, $[\alpha]_D^{30}$ +71.8 (*c* 0.83, EtOH) {lit.[5]: $[\alpha]_D^{25}$ +75.7 (*c* 1.85, EtOH)} serving as a key intermediate of a macrolide natural product, revealed the stereochemistry of the enantiomeric epoxides, (*R*:*R*)-**8** and (*S*:*S*)-**8**, as shown having *threo*-epoxy bond. Since the AE reaction has been empirically known to furnish *erythro*-epoxide bond preferentially for (*S*)-allyl alcohols with L-tartrate and for (*R*)-allyl alcohols with D-tartrate, the present epoxidation occurred inversely in both diastereofacial and enantiotopical ways with respect to the chirality of the allylic centre of the substrate. The same stereochemical outcome was also observed with the chiral substrates,¶ (*S*)-**4** and (*S*)-**5**, having a secondary homoallylic hydroxy group. The AE reaction only took place in the presence of L-tartrate with both substrates and afforded the corresponding epoxides, **9**, $[\alpha]_D^{27}$ +19.6 (*c* 1.09, $CHCl_3$) (≈65%), and **10**, $[\alpha]_D^{29}$ +70.0 (*c* 0.73, $CHCl_3$) (60%), having the *threo*-configuration as a single product, respectively. Virtually no reaction occurred with the both substrates under the same conditions in the presence of D-tartrate in place of L-counterpart. The structure of **9** was unambiguously determined as shown by correlation to the above mentioned epoxide **8**, though the structure of **10** was deduced by ^{1}H NMR analysis (500 MHz) of its benzylideneacetal. Again, the reaction occurred in inverted diastereofacial and enantiotopical selective modes with these alkenylethylene glycol substrates (Schemes 2 and 3).

Because it could readily be assumed that the observed distinct stereochemical difference was due to the coordinative 1,2-glycol system in the substrates, we next examined the reaction using two cyclic substrates, **6** and **7**, in which conformational change around the glycol bond is restricted. Under the same conditions in the presence of L-tartrate, both gave the corresponding epoxides leaving the unreacted starting olefins.

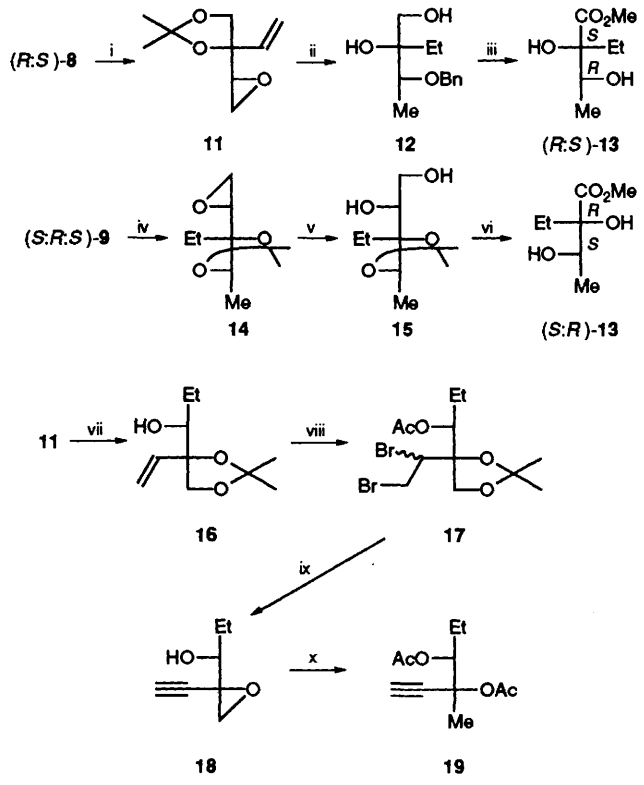
The *cis*-glycol (±)-**6**, regarded as a '*threo*'-glycol, afforded the epoxide **20**, $[\alpha]_D^{31}$ +10.1 (*c* 1.31, $CHCl_3$), in 42% yield as an inseparable (~6:1) mixture and the unreacted *cis*-glycol



Scheme 1

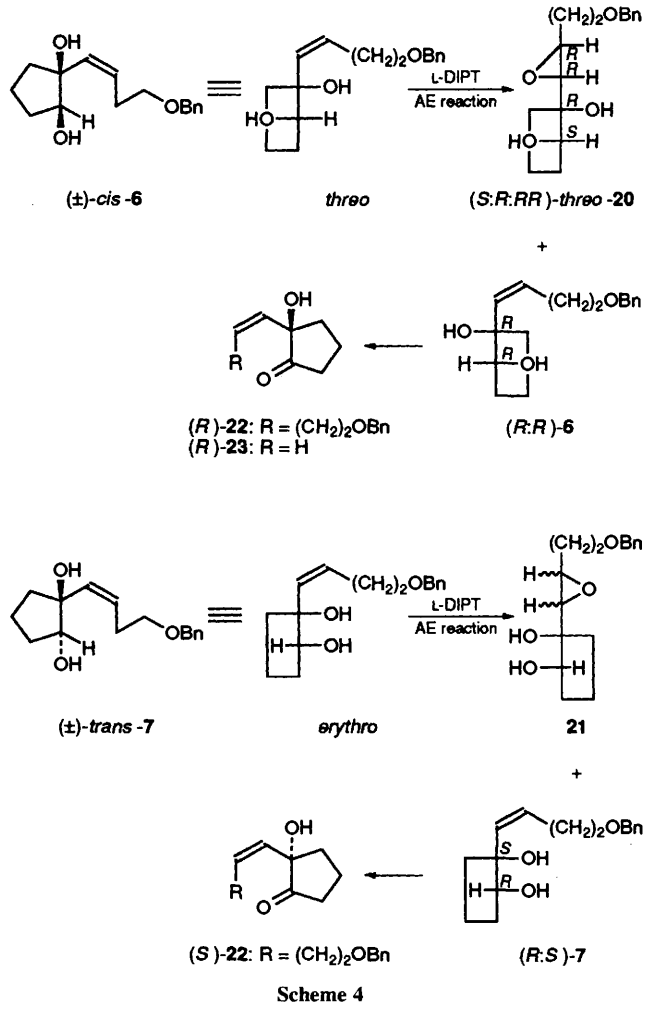


Scheme 2



Scheme 3 *Reagents and conditions*: i, 2,2-dimethoxypropane, pyridinium toluene-*p*-sulfonate (PPTS) (cat.), acetone, reflux, 90%; ii, (*a*) lithium aluminium hydride (LAH), THF, 0 °C → room temp., 90%, (*b*) Pd–C, H_2, benzene, room temp., 94%, (*c*) BnBr, NaH, Bu_4NI, DMF, 0 °C → room temp., 94%, (*d*) PPTS (cat.), aq. MeOH, 80 °C, 90%; iii, (*a*) SO_3·Py, DMSO, Et_3N, room temp., (*b*) $NaClO_2$, NaH_2PO_4·$2H_2O$, 2-methylbut-2-ene, aq. Bu^tOH, room temp., (*c*) CH_2N_2, Et_2O, 89% overall, (*d*) $Pd(OH)_2$, H_2, AcOEt-$CHCl_3$, room temp., 94%; iv, (*a*) Pd–C, H_2, benzene, room temp., 91%, (*b*) 2,2-dimethoxypropane, PPTS (cat.), acetone relux, 92%; NaOH, aq. Bu^tOH, ≈80 °C, 90%; vi, (*a*) cat. $RuCl_3$·$7H_2O$, $NaIO_4$, MeCN–CCl_4–H_2O, room temp., (*b*) CH_2N_2, Et_2O, 85%, (*c*) PPTS (cat.), aq. MeOH, ≈80 °C, 87%; vii, Me_2CuLi, THF, 0 °C, 94%; viii, (*a*) Ac_2O, Et_3N, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), CH_2Cl_2, room temp., 91%, (*b*) Br_2, $NaHCO_3$, CH_2Cl_2, −78 °C, 83%; ix, (*a*) $KOBu^t$, THF, 5 min, 0 °C → room temp., 91%, (*b*) PPTS (cat.), aq. MeOH, reflux, 75%, (*c*) diisopropyl azodicarboxylate (DIAD), PPh_3, CH_2Cl_2, room temp.; x, (*a*) LAH, THF, room temp., 77% overall, (*b*) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temp., 100%.

(−)-**11**, $[\alpha]_D^{29}$ −18.4 (*c* 0.98, $CHCl_3$) in 33% yield in 96% ee (by HPLC). On the other hand, the *trans*-glycol (±)-**7**, regarded as an '*erythro*'-glycol and incapable of simultaneous coordination, afforded the epoxide **21**, $[\alpha]_D^{29}$ −2.7 (*c* 0.56, $CHCl_3$), in 38% yield as an inseparable (≈2:1) mixture and the unreacted *trans*-glycol (−)-**7**, $[\alpha]_D^{29}$ −5.5 (*c* 0.78, $CHCl_3$), in 52% yield in *ca.* 20% ee. Although the stereochemistry of the epoxide mixture obtained from the *trans*-glycol (±)-**7** could not be determined, the major component of the epoxide **20** from the *cis*-glycol(±)-**6** could be assumed by analysis of ^1H NMR (500 MHz) of its MTPA esters to have the structure possessing '*threo*' configuration to the adjacent tertiary hydroxy group and having 85% ee of optical purity.[6,7] The absolute configuration of the recovered olefins, on the other hand, could be unambiguously determined by correlation to the known compound.[8] Thus, both were first correlated each other by conversion into the same, but enantiomeric keto-alcohol **22**, $[\alpha]_D^{27}$ +104.9 (*c* 1.43, $CHCl_3$) (93% ee by HPLC) (from **6**) and $[\alpha]_D^{29}$ −20.4 (*c* 1.07, $CHCl_3$) (21% ee by HPLC) from **7**), on oxidation. Then, the optically more enriched (−)-**6** (96% ee), obtained from the *cis*-glycol (±)-**6**, was transformed into the known keto-alcohol (*R*)-(−)-**23**, $[\alpha]_D^{27}$



Scheme 4

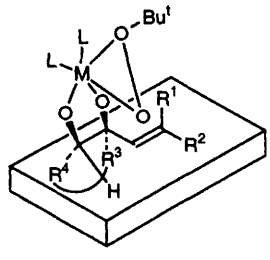


Fig. 1

−53.9 (*c* 0.79, $CHCl_3$) {lit.[8]: $[\alpha]_D^{25}$ +32.7 (*c* 1.4, $CHCl_3$) (≈84% ee) for (*S*)-enantiomer} in six steps to determine the absolute configuration as shown. Again, the reaction occurred in inverted stereoselection mode in the *cis*-glycol **6** (Scheme 4).

The distinct stereochemical difference observed in the diastereomeric cyclic substrates clearly indicated that the intervention of different intermediates in both substrates. Of these, only the *cis*-glycol **11** could form a doubly coordinated complex capable of exhibiting high diastereofacial and enantiotopical selection which well corresponds to the experimental results. Taking these stereochemical results as well as those observed in linear substrates into account, one can postulate a transition state having synclinal homoallylic hydrogen and olefin such as Fig. 1. This may be well compatible with the complex in which the hydroxy groups of a (*S*:*S*)-*threo*-glycol substrate being coordinated across the titanium atoms of Ti_2(L-tartrate)$_2$ complex forming a rigid seven-membered ring

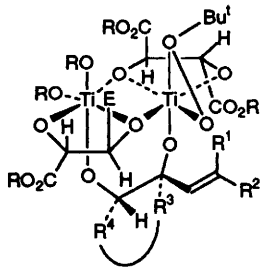


Fig. 2

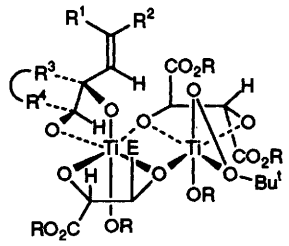


Fig. 3

so as to bring about the epoxidation in a diastereofacially and enantiotopically inverted way (Fig. 2). The observed diastereofacial selectivity may also be reasoned by assuming the five-membered complex on the same titanium atom in which the epoxidation is expected from the peroxide on the other titanium atom in the observed way. However, the distinct enantioselective difference between the enantiomeric tartrates cannot be explainable by this model (Fig. 3).

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Footnotes

† For brevity, structures are depicted by the Fischer projection

‡ Alkenylethylene glycols having the *erythro*-configuration reacted very sluggishly under the same conditions as the *threo*-counterparts reacted, see ref. 1(*a*) and (*b*).

§ Satisfactory analytical (combustion and/or high-resolution mass) and spectral (IR, ^{1}H NMR, and MS) data were obtained for all new compounds.

¶ Prepared by reaction with optically active ester with an excess vinylmagnesium bromide in THF: $[\alpha]_D^{26}$ +5.88 (*c* 1.10, $CHCl_3$) for (*S*)-**4** from methyl (*S*)-lactate and $[\alpha]_D^{30}$ +45.3 (*c* 0.95, $CHCl_3$) for (*S*)-**5** from methyl (*S*)-mandelate.

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