

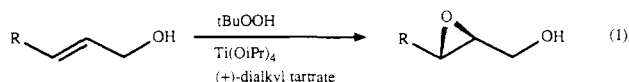
Metal-Catalyzed Direct Hydroxy-Epoxidation of Olefins

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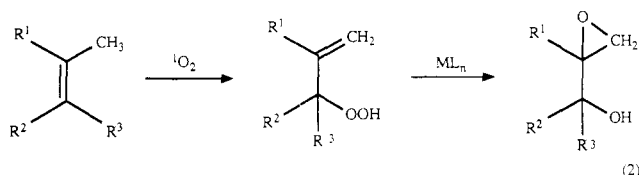
Received July 20, 1993

Stereoselective synthesis constitutes one of the central challenges of modern organic chemistry. Among numerous diastereo- and/or enantioselective transformations that have been developed in recent years, the Sharpless epoxidation¹ of allylic alcohols is one of the most valuable (eq 1). Only commercially available



reagents are required to produce, with high and reliable enantio- and diastereocontrol, synthetically useful² epoxy alcohols from a variety of substrates. Consequently, this process is now a classical tool for the synthesis of enantiomerically pure target molecules, especially in the field of complex natural products.²

From the synthetic point of view, however, an entry to epoxy alcohols directly from olefins would be appreciated, which also employs cheap reagents and commands high stereocontrol. To show that this is possible, we present in this Account the hydroxy-epoxidation methodology (eq 2), in which photooxygenation coupled with metal-catalyzed oxygen transfer provides a convenient and efficient synthesis of epoxy alcohols directly from alkenes even in a one-pot procedure.

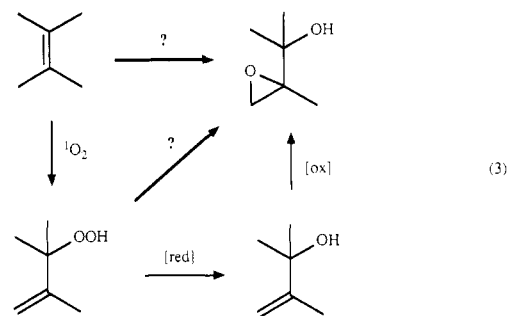


The Concept

One of the several ways to prepare allylic alcohols, the substrates for the Sharpless epoxidation, consists of the ene reaction of singlet oxygen (¹O₂) with olefins (the Schenck reaction),³ followed by reduction of the allylic hydroperoxide. As it is evident from eq 3, this reaction sequence requires removal of an oxygen atom from the hydroperoxide and subsequent reintroduction of an oxygen atom by an external oxygen donor to furnish the epoxy alcohol. Clearly, it would be more

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effective to convert the hydroperoxide directly to the epoxy alcohol; even better would be the direct functionalization of the olefin.

Indeed, the conversion of allylic hydroperoxides into epoxy alcohols by VO(acac)₂ as catalyst was demonstrated in 1966.⁴ Use of the vanadium catalyst also in the autoxidation of the olefin enabled the direct oxygen functionalization to be achieved, albeit only in modest yields.⁵ The process became synthetically useful, when ¹O₂ was employed for the production of allylic hydroperoxides,⁶ since now complete and more selective conversion of the olefin was possible. The scope and mechanism of this novel oxyfunctionalization was systematically studied,^{7,8} and the details shall now be reviewed.

Synthetic Aspects

When an olefin, which undergoes the ene reaction with singlet oxygen, is irradiated with visible light in the presence of triplet oxygen, a suitable sensitizer such as tetraphenylporphine (TPP), and a transition metal catalyst such as Ti(OiPr)₄, VO(acac)₂, or MoO₂(acac)₂, an epoxy alcohol is produced in high yield (eq 2).⁶⁻⁹ This process is applicable to a large number of di-, tri-,

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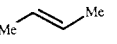
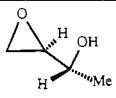
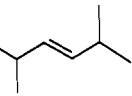
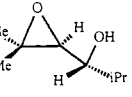
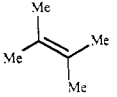
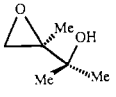
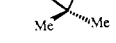

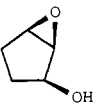

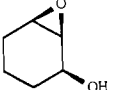
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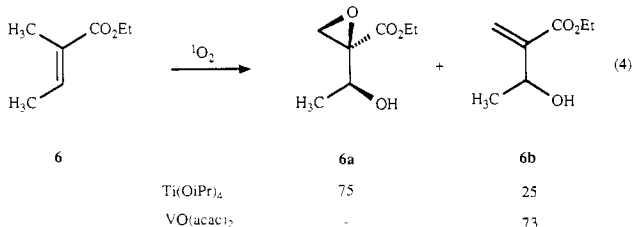
Table 1. Hydroxy-Epoxidation of Simple Olefins

| | substrate | catalyst ^a | product ^b | yield (%) ^c | dr | ref |
|---|-----------------------------------------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------|------------------------|-----------|-----|
| 1 |  | Ti |  | 68 | 53:47 | 9a |
| 2 |  | Ti |  | 75 | 90:10 | 9a |
| 3 |  | Ti |  | 84 | - | 9a |
| | | V |  | 72 | - | 6 |
| 4 |  | V |  | 50.5 | >99.8:0.2 | 6 |
| 5 |  | Ti |  | 68 | 98:2 | 9a |

^a Ti = Ti(OiPr)₄, V = VO(acac)₂. ^b Major isomer shown. ^c Isolated.

and tetrasubstituted alkenes. Table 1 lists some representative examples. Simple acyclic olefins give in high yield epoxy alcohols as sole products and with diastereoselectivities in accord with those reported for the metal-catalyzed epoxidation of allylic alcohols.¹⁰ In some cases, side reactions are encountered, which can generally be suppressed by the proper choice of catalyst and its stoichiometry. If, for example, the formation of the allylic hydroperoxide is slow, as in the case of cyclohexene, the starting olefin can compete in the epoxidation reaction. Thus, 29% cyclohexene oxide is obtained when 1 equiv of Ti(OiPr)₄ is employed, which can be completely avoided by using catalytic amounts (16 mol %) of catalyst.^{9c}

Substantial differences are observed between the titanium- and the vanadium-catalyzed reactions. For example, oxygen transfer to an electron-deficient double bond as in the case of ethyl tiglate (6) is accompanied by formation of the corresponding allylic alcohol 6b (eq 4).^{7,9c} While this is a minor problem for Ti(OiPr)₄, complete reduction of the intermediary hydroperoxide occurs with VO(acac)₂.

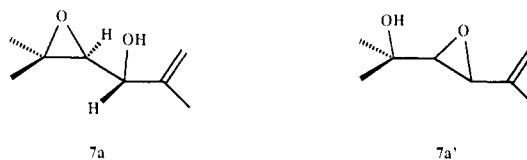


With cyclic substrates, conformational effects can retard the epoxidation.¹¹ Now oxidation of the allylic alcohol to an enone can compete. Again, this problem is more severe for vanadium than titanium. Addition-

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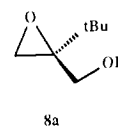
ally, since VO(acac)₂ is a stronger Lewis acid, Hock cleavage of the allylic hydroperoxide is induced, as in the case of dimethylstilbene.^{9c} The most dramatic manifestation of the different behavior of Ti versus V catalysts appears in the reaction of 2,5-dimethyl-2,4-hexadiene (7).¹² With Ti(OiPr)₄, the epoxy alcohol 7a was obtained in 75% yield (isolated), while VO(acac)₂ led to the isomeric product 7a' (61%, isolated). Because



of the ease with which vanadium undergoes redox chemistry (V^{IV}/V^V), VO(acac)₂ induces presumably the isomerization of the hydroperoxide through radical intermediates prior to oxygen transfer to result finally in 7a'.¹³

In general, Ti(OiPr)₄ is the catalyst of choice, as its low Lewis acidity and the diminished propensity for redox chemistry minimize side reactions. Furthermore, no quenching of ¹O₂ is observed^{9c} and no absorption of visible light as with the V and Mo catalysts occurs, which constitute important requirements for the one-pot procedure.

The most important feature of the Ti catalyst is, however, the possibility of chiral modification with tartaric esters, as in the case of the conventional Sharpless catalyst.¹ By employing Ti(OtBu)₄ and (+)-diethyl tartrate, epoxy alcohol 8a was obtained from the olefin in 69% yield and 72% ee.^{9a,c} For comparison,



the classical Sharpless epoxidation of 8a from the allylic alcohol with tBuOOH proceeded in 40% yield and with 85% ee. The lower ee in the one-pot synthesis is attributed to the well-established fact¹⁴ that less bulky hydroperoxides give lower ee's.

While the enantioselective version of the direct hydroxy-epoxidation of olefins has not yet been studied extensively, the diastereoselective oxyfunctionalization of more complex chiral molecules has been reported. Thus, dicyclopentadiene,¹⁵ α-9c,¹⁶ and β-pinene,^{9c} α-ionone,¹⁷ cholesterol,¹⁸ estrone,¹⁹ and a Fe(CO)₃-protected triene²⁰ have been successfully transformed into the corresponding epoxy alcohols, some in high diastereoselectivity.

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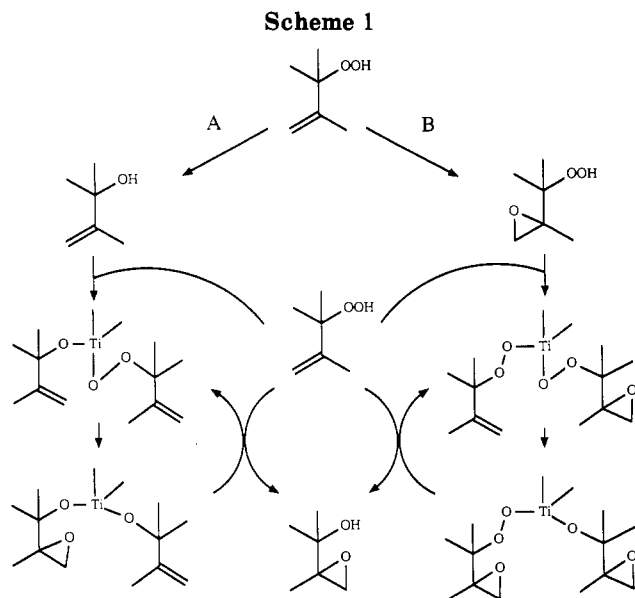
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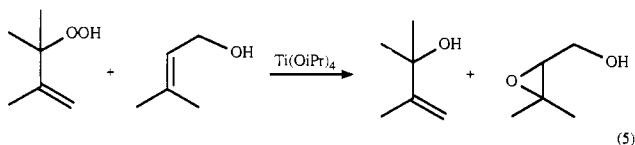
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Mechanistic Aspects

The mechanistic course of the hydroxy-epoxidation has been studied in some detail^{9c} and is summarized in Scheme 1. First of all, the intermolecularity of the oxygen transfer has been established^{9c} by addition of a more reactive allylic alcohol to a mixture of the allylic hydroperoxide and $\text{Ti}(\text{OiPr})_4$ (eq 5). Only the added,



more reactive allylic alcohol was epoxidized, while the allylic hydroperoxide served merely as oxygen atom donor. This confirms that the oxygen atom was transferred between two different molecules (intermolecular transfer) and not within one and the same allylic hydroperoxide (intramolecular transfer).

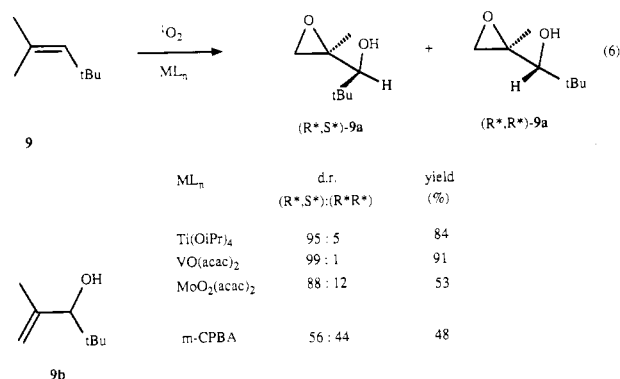
Two competitive pathways are involved in this intermolecular oxygen atom transfer (Scheme 1), which depend on the substrate and the reaction conditions. In some cases, as with the hydroperoxide derived from tetramethylethylene (3), an induction period was observed, when the allylic hydroperoxide and $\text{Ti}(\text{OiPr})_4$ were mixed. During this induction period a small amount of allylic alcohol is produced (path A) by reduction of the hydroperoxide. The *in situ* formed allylic alcohol then serves as oxygen atom acceptor, as in the classical Sharpless reaction. The hydroperoxide (also formed *in situ* through photooxygenation) functions as the oxygen atom donor and is reduced to the allylic alcohol during oxygen transfer. The catalytic cycle is completed in that the allylic alcohol, already coordinated to the titanium, serves as oxygen atom acceptor.

The above mentioned reduction of the hydroperoxide may also proceed through an Oppenauer-type oxidation of the isopropoxy ligand to acetone (which has been detected by NMR^{9c}). Other pathways, which involve most likely redox chemistry, are possible. For example, $\text{Ti}(\text{OtBu})_4$ also reduces hydroperoxides, but for which the Oppenauer-type oxidation cannot apply.

The other catalytic cycle (path B in Scheme 1) entails the epoxidation of the allylic hydroperoxide. This alternative may appear less likely because such allylic hydroperoxides can be regarded as hetero analogs of homoallylic alcohols and the latter are notoriously poor substrates for the Sharpless epoxidation.^{1b} Nevertheless, epoxy hydroperoxides have been observed by NMR monitoring and were also isolated,^{9c} which substantiates this pathway.

From the practical point of view, it is worth mentioning that the epoxidation of an allylic alcohol and an allylic hydroperoxide may proceed with different diastereoselectivity.²¹ Moreover, since the relative amounts of product formation by the two pathways A and B (Scheme 1) depend on the reaction conditions, different diastereoselectivities may be obtained even for the same substrate with the same catalyst. This is the case in the hydroxy-epoxidation of cyclooctene,²² for which the one-pot procedure gives the *cis*-epoxy alcohol as major product through *cis*-selective epoxidation of the allylic alcohol.¹¹ On the other hand, treatment of the isolated hydroperoxide with $\text{Ti}(\text{OiPr})_4$ favors formation of the *trans*-epoxide by oxygen transfer to the allylic hydroperoxide. Since pathway B in Scheme 1 requires two molecules of hydroperoxide at the titanium template, this pathway is favored at high hydroperoxide concentrations.

The dependence of the diastereoselectivity on the catalyst type is illustrated in eq 6,^{9c} in which are given the diastereomeric ratios (dr) of the isomeric epoxy alcohols (R^*,R^*)- and (R^*,S^*)- **9a** and their yields.



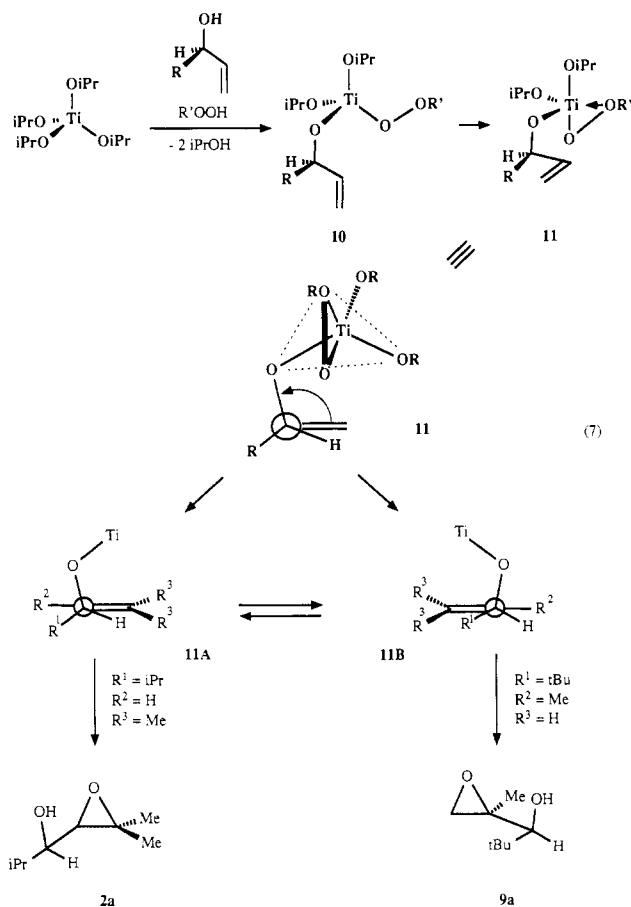
The vanadium catalyst gives the best selectivity, $\text{Ti}(\text{OiPr})_4$ is only slightly less selective for this particular substrate, and $\text{MoO}_2(\text{acac})_2$ is clearly inferior also in the chemical yield. For comparison, the results of the epoxidation of the allylic alcohol **9b** by *m*-CPBA are given, which clearly demonstrate the poor diastereoselectivity of this epoxidizing reagent. It should be noted, however, that generally $\text{Ti}(\text{OiPr})_4$ gives quite different diastereomeric ratios than do $\text{Ti}(\text{OiPr})_4/\text{tartrate}$ and $\text{VO}(\text{acac})_2$, of which the former is more *threo*-selective.²³

The diastereoselectivity for epoxidation of allylic alcohols is usually rationalized in terms of the dihedral angle $\text{O}-\text{C}-\text{C}=\text{C}$ (eq 7) in the transition state for oxygen transfer. For $\text{Ti}(\text{OiPr})_4$, a dihedral angle of ca. 100° accounts best for most of the experimental data,

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as illustrated in eq 7. Ligand exchange at the tetrahedral monomeric $\text{Ti}(\text{OiPr})_4$ with a secondary allylic alcohol and a hydroperoxide leads to the loaded complex 10. Bidentate coordination of the hydroperoxide, necessary for its activation, requires an increase of the coordination number to 5, i.e., trigonal bipyramidal coordination. This activation of the oxygen donor (hydroperoxide) is best achieved in structure 11, in which the stereoelectronic requirements for metal-catalyzed epoxidations^{1b,24} and coordination of the allylic alcohol acceptor in the titanium template are duly considered. Herein the peroxide bond is activated by the stronger equatorial Ti–O bond to the alkoxy oxygen atom.

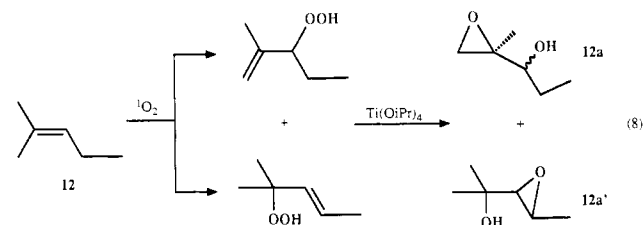
In this complex, two significant conformational arrangements of the olefinic moiety in the allylic alcohol are possible, which can interconvert by rotation around the olefinic C–C single bond. The preference of one conformer over the other is determined by steric interaction, i.e., by allylic strain.²⁵ For example, if $R^2 = \text{H}$ and $R^3 = \text{Me}$ as in **2a**, then 1,3 allylic strain predominates between R^1 and R^3 , which favors conformer 11A due to the least steric hindrance imposed on R^1 . Consequently, the *threo* product **2a** is produced in high selectivity (Table 1). If 1,2 allylic strain predominates as for **9a** ($R^2 = \text{Me}$, $R^3 = \text{H}$), then conformer 11B is the preferred one, which leads to high *erythro* selectivity (eq 6).

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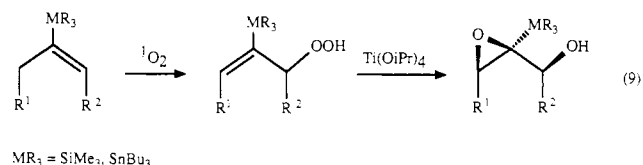
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Regio- and Stereocontrol by Silicon and Tin

An often encountered problem with the $^1\text{O}_2$ ene reaction is the usually low regioselectivity with simple unfunctionalized olefins.³ For example, 2-methyl-2-pentene (**12**) gave the two possible regioisomers in 1:1 proportion (eq 8), and also, its hydroxy-epoxidation resulted in a 1:1 mixture of epoxy alcohols (**12a,a'**). In



addition, the diastereoselectivity for **12a** was only modest (dr 79:21). These shortcomings have recently been overcome²⁶ by making use of the observation that photooxygenation of vinylsilanes²⁷ and vinylstannanes²⁸ proceeds regioselectively with hydrogen abstraction predominantly at the geminal position (eq 9).



Due to the steric demand of the silyl group, the metal-catalyzed oxygen transfer afforded epoxy alcohols in high diastereoselectivity.²⁹ This concept has been applied successfully to the synthesis of metal-substituted derivatives **13a–19a**.^{26,30}



| | R^3M | R | yield (%) | d.r. | | R^3M | n | yield (%) | d.r. |
|-----|--------------------------|-----------------------------|-----------|-------|-----|------------------------|---|-----------|-------|
| 13a | Me_2PhSi | Me | 65 | >95:5 | 17a | Me_3Si | 2 | 70 | >95:5 |
| 14a | Me_3Si | Bu | 59 | >95:5 | 18a | Me_3Si | 4 | 72 | >95:5 |
| 15a | Me_3Si | $c\text{-C}_6\text{H}_{11}$ | 56 | >95:5 | 19a | Bu_3Sn | 1 | 55 | >95:5 |
| 16a | Bu_3Sn | Me | 40 | 81:19 | | | | | |

It should be noted that except for **16a** the diastereoselectivity was always better than 95:5, i.e., the minor isomer was below the NMR detection limit even in the crude reaction mixture. As it is possible to desilylate such epoxy alcohols readily with fluoride ion, with complete retention of stereochemistry,³¹ diastereomerically pure epoxy alcohols derived from simple olefins are now accessible. Furthermore, the synthetic utility of the trialkylsilyl group at the epoxide ring of the epoxy

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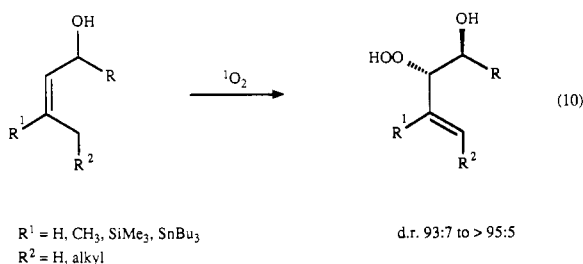
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alcohols³² is exemplified in the nucleophilic ring-opening, which proceeds regioselectively at the α position. The stannylated derivatives should provide an entry into α -metalated epoxy alcohols through tin-lithium exchange.³³

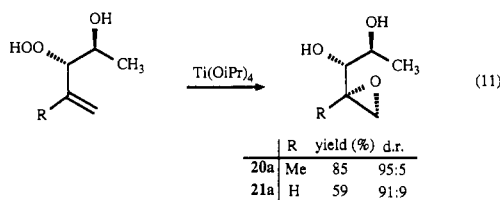
Hydroxy-Epoxidation of Allylic Alcohols

Another class of substituted olefins, which exhibits high regioselectivity in the ene reaction with $^1\text{O}_2$, is the allylic alcohols.³⁴ More important, for these substrates hydroperoxy alcohols are obtained through the novel *HO-directing effect*³⁴ (eq 10). This derives from the

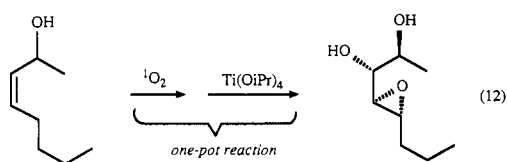


interaction of the electrophilic $^1\text{O}_2$ with the nucleophilic OH group, coupled with the 1,3-allylic strain between the carbinol center and a *cis* alkyl substituent.³⁴

When these hydroperoxy alcohols are treated with $\text{Ti}(\text{OiPr})_4$, an extremely fast reaction occurs and the corresponding epoxy diols are formed in good yields and again in high diastereoselectivity (eq 11).³³ It is



not necessary to isolate the hydroperoxy alcohols; rather, the $\text{Ti}(\text{OiPr})_4$ is added directly to the crude photooxygenate (a one-pot procedure is not advisable in this case, because of competing epoxidation of the starting allylic alcohol). If the allylic alcohol contains an alkyl group other than methyl in the *cis* position ($\text{R}^2 \neq \text{H}$, cf. eq 10), stereocontrol of a fourth stereogenic center is achieved since the ene reaction of $^1\text{O}_2$ affords only the *trans* double bond (eq 12). In this way simultaneously four successive stereogenic centers with oxygen functionalities are fixed with *a priori* predictable stereochemistry.³⁵

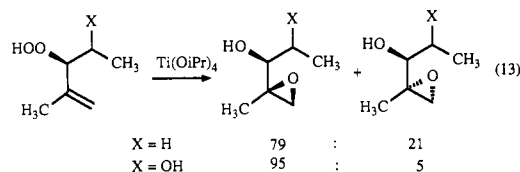


(32) (a) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728-4731. (b) Sato, F.; Tanaka, Y.; Kanbara, H. *J. Chem. Soc., Chem. Commun.* **1983**, 1024-1025.

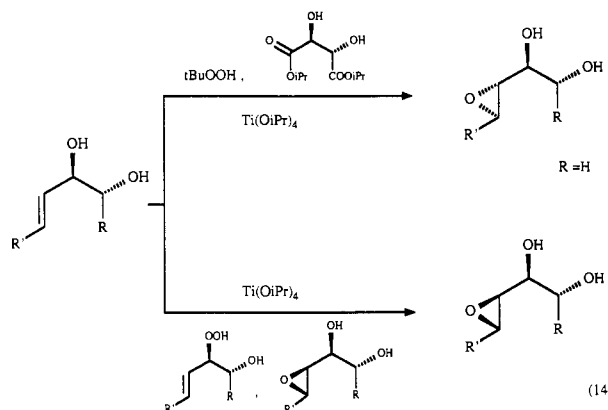
(33) (a) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615-618. (b) Soderquist, J. A.; Lopez, C. *Tetrahedron Lett.* **1991**, *32*, 6305-6308.

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The rate of oxygen transfer for olefins with a homoallylic OH group is considerably faster and the diastereoselectivity in the resulting hydroperoxy alcohols higher than for substrates without such directing functionalities (eq 13). Since for normal allylic alcohols



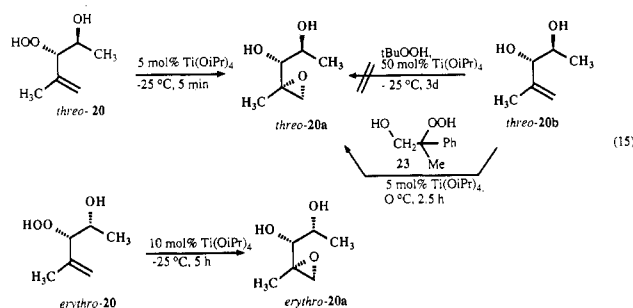
the $\text{Ti}(\text{OiPr})_4$ /tartrate system is more reactive and also more *erythro*-selective than $\text{Ti}(\text{OiPr})_4$ alone,^{1,23} one is tempted to think that, for the unsaturated diols investigated presently, the epoxy diol product acts as a tartrate-like ligand in assisting oxygen transfer. Indeed, the epoxy diol possesses the essential structural features^{1b} of the tartrate ligand in the Sharpless reaction, namely, a *threo* 1,2-diol and a third Lewis-basic oxygen atom (the epoxy oxygen in the epoxy diol instead of the ester carbonyl in the tartrate; eq 14). That this expectation, however, does not apply is substantiated by the fact that the $\text{Ti}(\text{OiPr})_4$ /tartrate catalyst gives in a slow reaction³⁶ inverted diastereo- and enantioselectivity with unsaturated diols.



More convincing evidence that the epoxy diol cannot play the role of the tartrate ester stems from the fact that the epoxidation of the unsaturated diol **20b** with $t\text{BuOOH}$ and $\text{Ti}(\text{OiPr})_4$ alone, i.e., without tartrate, does not proceed at all. In contrast, the transformation of the hydroperoxy alcohol *threo*-**20** to the expected epoxy diol **20a** is extremely fast (eq 15). Consequently, we propose that the additional coordination site in the hydroperoxy alcohol is of primordial importance for the oxygen transfer. The tridentate oxygen atom donor (the hydroperoxy alcohol) possesses a higher propensity to replace the tridentate epoxy diol **20a** product in the titanium template **22**.³⁵ Without such ligand exchange, the loaded titanium complex **22** is not replenished, and thus, the catalytic cycle is interrupted, with the consequence of no oxygen transfer. This is the case for the bidentate oxygen donor $t\text{BuOOH}$, the externally employed oxidant in the Sharpless epoxidation of allylic alcohols. Indeed, the validity of this proposal was

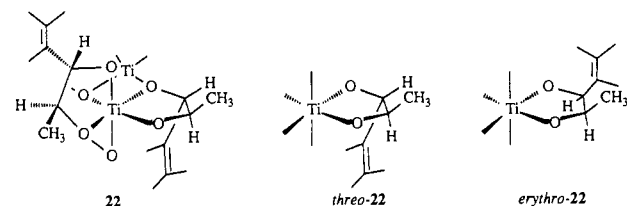
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corroborated by the fact that epoxidation of the diol **20b**, which failed with *t*BuOOH, readily proceeded when the tridentate hydroperoxy alcohol **23** was employed as a novel oxygen donor agent (eq 15).³⁷

The occurrence of tridentate coordination of the oxygen donor (hydroperoxy alcohol) and bidentate coordination of the oxygen acceptor (unsaturated diol) in the loaded titanium complex **22** is also evident in the hydroxy-epoxidation of the two diastereomeric *threo*- and *erythro*-hydroperoxy alcohols **20** (eq 15). While *threo*-**20** reacted extremely fast (<5 min) with $\text{Ti}(\text{OiPr})_4$, the corresponding *erythro*-**20** was considerably less reactive (ca. 5 h).³⁵ Inspection of the proposed reactive complex **22** allows one to rationalize this profound difference in the rates of epoxidation of these diastereomeric substrates **20**. In view of the stereochemical



complexity involved, we will only focus attention on the coordinated unsaturated diol in the loaded titanium complex **22** (the right side of the structure) and project out the relevant partial structures, i.e., the five-membered-ring Ti heterocycles *threo*- and *erythro*-**22**; however, similar arguments also apply for the coordination of the diastereomeric hydroperoxy alcohols *threo*- and *erythro*-**20** in the loaded titanium complex **22** (the left side of structure **22**). Since all titanium

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complexes of 1,2-diols studied so far are at least dimeric,³⁸ a bridging oxygen atom has been included in the binuclear structure **22** to give a six-coordinated, octahedral geometry around the central titanium atom. Thus, in the *threo*-**22** complex, the two alkyl groups (vinyl and methyl) of the ligated diol are *trans* to each other, while in the *erythro*-**22** complex they must be *cis*. Due to the increased steric hindrance in the *cis* arrangement of the two alkyl substituents, coordination is less facile in the *erythro* isomer and, consequently, the oxygen transfer proceeds much more slowly. For both isomers, nonetheless, the diastereoselectivity is high (95:5), which is a result of the rigid assembly of the reactants in the titanium template.

Conclusion

The means of introducing directly in olefins up to four stereogenic centers with defined stereochemistry in a one-pot procedure makes the hydroxy-epoxidation methodology a simple, convenient, and useful tool for the synthesis of chiral oxyfunctionalized molecules. Especially the regio- and diastereochemical steering effect of the silyl²⁶ and the hydroxy groups³⁴ in the $^1\text{O}_2$ ene reaction will undoubtedly show great promise in the diastereoselective synthesis of complex target molecules. Still more challenging are the mechanistic features connected with the catalytic activity played by the titanium template. While the structure and mode of action of the Sharpless catalyst ($\text{Ti}(\text{OiPr})_4$ /tartrate) have been studied in considerable detail and several fascinating facets have been elucidated,^{1b,13} relatively little is as yet known on the $\text{Ti}(\text{OiPr})_4$ catalyst itself. Studies on such simple systems should provide valuable mechanistic information not only on titanium-catalyzed oxygen transfer processes but also on metal-assisted oxidations in general, a field of chemistry which offers for the future new perspectives and opportunities in the oxyfunctionalization of organic and also organometallic substrates.

Financial support by the Deutsche Forschungsgemeinschaft (SFB 347: "Selektive Reaktionen Metall-aktivierter Moleküle") and the Fonds der Chemischen Industrie is gratefully appreciated. Praise and esteem are expressed to all the highly dedicated and intellectually stimulating students who were and still are engaged in our oxidation chemistry for their proficient and diligent work.