Direct Epoxy Hydroxylation of Hydroperoxy Homoallylic Alcohols: Multidentate Oxygen Donor and Oxygen Acceptor Substrates in Ti(IV)-Catalyzed Epoxidations

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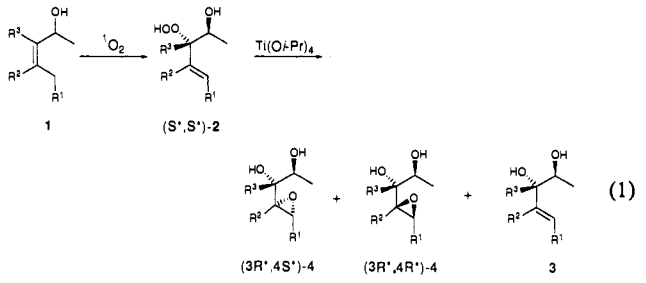
Abstract: The hydroperoxy homoallylic alcohols (*R**,*S**)-**2a** and (*S**,*S**)-**2a–d**, readily available through the photooxygenation of chiral allylic alcohols **1**, were converted into epoxy diols **4** under the catalytic action of Ti(O*i*-Pr)$_4$. In these epoxy hydroxylations, the hydroperoxides **2** play the double role as oxygen atom donor and, in form of the *in situ* generated corresponding unsaturated diols **3**, as substrate for oxygen transfer. Compared to Ti(IV)-catalyzed epoxidations of unsaturated diols by *t*-BuOOH, the advantage of this approach is that a large rate enhancement is obtained. Moreover, with the exception of (*S**,*S**)-**2d**, all reactions proceeded in unusually high diastereoselectivity. These results are rationalized in terms of the ability of the hydroxy-functionalized hydroperoxides (oxygen atom donors) as well as the corresponding unsaturated diols (oxygen atom acceptors) to chelate to the titanium metal in the catalytically operating template. For (*S**,*S**)-**3a–c**, bidentate binding is feasible, while for (*R**,*S**)-**3a** and (*S**,*S**)-**3d**, this is difficult due to unfavorable steric interactions. Important for synthetic applications is the fact that allylic alcohols **1** can directly be converted into epoxy diols **4** in a one-pot, two-step procedure simply by adding catalytic amounts of Ti(O*i*-Pr)$_4$ to a photooxygenated solution of **1**.

Epoxy alcohols are versatile building blocks of high synthetic utility which are abundantly used in organic chemistry.[1] Of the numerous methods available, metal-catalyzed epoxidations of allylic alcohols with hydroperoxides[2] represent a practical route, of which the Sharpless epoxidation[2d-g] is undoubtedly the most valuable prototype for this purpose.

An alternative, related oxyfunctionalization constitutes the direct conversion of olefins into epoxy alcohols by photooxygenation, followed by subsequent transformation of the intermediary allylic hydroperoxides under the catalytic action of transition-metal catalysts.[3] In this epoxy hydroxylation, the allylic alcohol, which is the actual epoxidized substrate, is generated *in situ* from the allylic hydroperoxide by oxygen transfer during the epoxidation. Hence, the allylic hydroperoxide plays the double role as oxygen donor and, after oxygen transfer, as oxygen acceptor. Therefore, no separate hydroperoxide is necessary as the oxygen atom donor reagent (Scheme I).

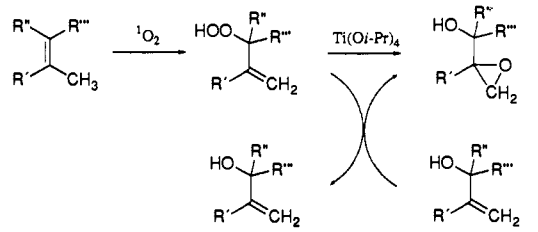
Recently we reported that the epoxy hydroxylation methodology can also be applied to allylic alcohols,[4] which allows the regio- and diastereoselective introduction of up to three chirality centers in successive, adjacent positions to the already existing chirality center of the allylic alcohol moiety (eq 1). An important finding



(1)

in this context worthy of future pursuit was that the propensity of the intermediary hydroperoxy homoallylic alcohol toward epoxidation is influenced by the stereochemical arrangement of the homoallylic HO group in the chiral substrate. Herein we report the full details on the synthetic and mechanistic features of the titanium-catalyzed transformations of hydroxy-functionalized allylic hydroperoxides into epoxy diols of defined stereochemistry; the allylic hydroperoxides are readily available through photooxygenation of the corresponding chiral allylic alcohols.

Scheme I



Results

Product Studies. The results for the transformations of the hydroperoxy homoallylic alcohols (*R**,*S**)-**2a** and (*S**,*S**)-**2a–d** (eq 1) are summarized in entries 4, 5, 7, 10, and 11 of Table I. In the conversions of hydroperoxides **2a,b**, which bear two substituents at the allylic double bond, the epoxy diols **4a,b** were the only isolated products (eq 1, entries 4, 5 and 7 of Table I). Compared to the *threo*-configurated hydroperoxide (*S**,*S**)-**2a**,

(1) Rossiter, B. E. *Asymmetric Synthesis*; Academic Press: Orlando, FL, 1985; Vol. V, p 193.

(2) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. (c) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (d) Finn, M. G.; Sharpless, K. B. *Asymmetric Synthesis*; Academic Press: Orlando, FL, 1985; Vol. V, p 247. (e) Corey, E. J. *J. Org. Chem.* **1990**, *55*, 1693. (f) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106. (g) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.

(3) (a) Adam, W.; Griesbeck, A.; Staab, E. *Tetrahedron Lett.* **1986**, *27*, 2839. (b) Adam, W.; Kömmerling, S.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Schwarm, M.; Staab, E.; Zahn, A. *Chem. Ber.* **1988**, *121*, 2151. (c) Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203. (d) Staab, E. Ph.D. Dissertation, University of Würzburg, 1987.

(4) (a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549. (b) Adam, W.; Nestler, B. *Angew. Chem.* **1993**, *105*, 767; *Angew. Chem., Int. Ed. Engl.*, **1993**, *32*, 733. (c) Adam, W.; Nestler, B. *J. Am. Chem. Soc.*, **1993**, *115*, 5041.

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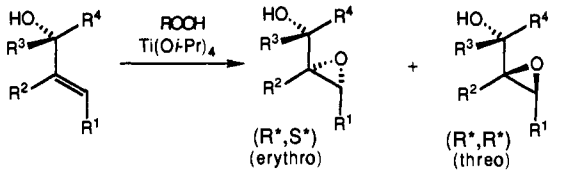
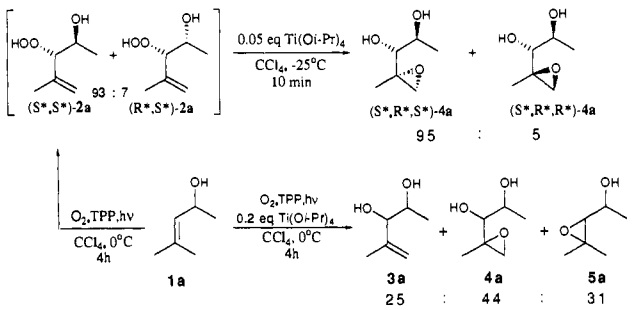
Table I. Diastereoselectivities in Epoxidations of Allylic Alcohols and Epoxy Hydroxylations of Allylic Hydroperoxides



	R¹	R²	R³	R⁴	ROOH	Ti(O*i*-Pr)₄ (mol %)	time[a] (h)	yield (%)	diastereoselectivity of epoxy alcohols[b] (*R**,*S**) (erythro)	diastereoselectivity of epoxy alcohols[b] (*R**,*R**) (threo)
1	H	Me	H	Et	in situ[c]				79	21[d]
2	H	Me	H	*n*-Bu	*t*-BuOOH				83	17[e]
3	H	Me	H	*t*-Bu	in situ[c]				95	5[d]
4 (S*,S*)-**2a**	H	Me	H		in situ[c]	5	<0.1	85	95	5[f]
5 (R*,S*)-**2a**	H	Me	H		in situ[c]	10	5	80	95	5[f]
6	c-Hex	H	H	c-Hex	*t*-BuOOH				37	63[e]
7 (S*,S*)-**2b**	*n*-Bu	H	H		in situ[c]	5	1	83	86	14[f]
8	H	H	H	Me	in situ[c]				53	47[d]
9	H	H	H	*n*-Hex	*t*-BuOOH				53	47[e]
10 (S*,S*)-**2c**	H	H	H		in situ[c]	10	48	59[g]	91	9[f]
11 (S*,S*)-**2d**	H	H	Me		in situ[c]	10	72	46[h]	51	49[f,i]

[a] Until complete consumption of **2**. [b] Normalized to 100%. [c] Hydroxy epoxidation of allylic hydroperoxides. [d] Ref 3c. [e] Ref 2c. [f] Error was ±5% of the stated value. [g] Additionally, 19% of (S*,S*)-**3c** was isolated. [h] Additionally, 17% of (S*,S*)-**3d** is isolated. [i] No configurational assignment was made.

Scheme II

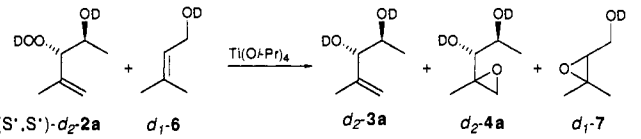


a significantly longer reaction time was necessary to convert completely the corresponding *erythro* isomer (*R**,*S**)-**2a**. On the other hand, when unsaturated diol (*S**,*S**)-**3a** derived from the hydroperoxy alcohol (*S**,*S**)-**2a** was attempted to be epoxidized by *t*-BuOOH (TBHP) in the presence of Ti(O*i*-Pr)₄, even after 3 days, no epoxy diol **4a** was observed although 10 times as much catalyst was employed.

Much longer reaction times were required for the transformations of the hydroperoxides **2c,d** with monosubstitution at the allylic double bond. Moreover, in these epoxy hydroxylations, significant amounts of the corresponding unsaturated diols **3c,d** were formed as side products (eq 1, entries 10 and 11 of Table I). With the exception of epoxy diol **4d**, all products were formed in rather high diastereoselectivity. In every case but **4d**, the 3*R**,4*S**-configurated epoxy diols dominate (eq 1, entries 4, 5, 7, 10, and 11 of Table I).

Furthermore, with **4a** as an example, it was demonstrated that this epoxy diol can be synthesized directly from the allylic alcohol **1a** in a one-pot, two-step procedure simply by adding catalytic amounts of Ti(O*i*-Pr)₄ to the photooxygenated solution of **1a**. When the hydroperoxide (*S**,*S**)-**2a** had been completely consumed, only the 2*S**,3*R**-configurated epoxy diols **4a** were obtained (Scheme II). However, when **1a** was photooxygenated directly in the presence of the titanium catalyst, the yield of epoxy diol **4a** decreased significantly and large amounts of the reduction product, i.e. diol **3a**, and the epoxidized substrate **1a**, namely epoxy alcohol **5a**, were formed as side products (Scheme II).

To uncover the mechanistic complexities of this transformation, a competition experiment was performed, in which mixtures of hydroperoxide (*S**,*S**)-d_2-**2a** and allylic alcohol d_1-**6** (the latter possesses a substituted allylic double bond similar to that of substrate **1a**) were treated with the titanium catalyst[5] (eq 2).



(2)

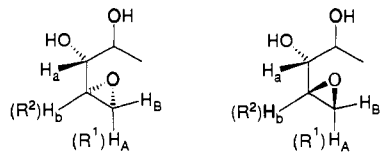
Large quantities of d_2-**4a** derived from (*S**,*S**)-d_2-**2a** were observed, even when d_1-**6** was employed in a 10-fold excess.

The ability of diols, which are key intermediates in the titanium-catalyzed epoxy hydroxylation, to bind to the titanium was deduced from the behavior of (*S**,*S**)-**3a** and (*R**,*S**)-**3a** (derived from hydroperoxide **2a**) and (*S**,*S**)-3-methylpentane-2,3-diol [(*S**,*S**)-**8d**] (derived from hydroperoxide **2d**) as representative examples. Thus, addition of an equimolar amount of Ti(O*t*-Bu)₄ to a solution of (*S**,*S**)-**8d** hardly affected the ^{1}H NMR spectrum, which indicates that at most minor amounts of (*S**,*S**)-**8d** are bound to the titanium metal. The same observation was made for the *erythro*-configurated diol (*R**,*S**)-**3a**, for which bidentate

(5) The use of undeuterated alcohols prevents an accurate determination of product ratios by means of ^{1}H NMR due to the appearance of broad OH signals.

binding appears also unlikely. On the other hand, for the *threo*-configurated diol (*S**,*S**)-**3a**, addition of Ti(O*t*-Bu)$_4$ led to complete loss of the carbinol CH proton resonances in the ^{1}H NMR spectrum through line broadening. Thus, no free diol is present in the solution since (*S**,*S**)-**3a** is completely coordinated to the titanium metal.

Diastereomer Assignments. The stereochemical assignments of the epoxy diols **4a–c** are based on their spectral characteristics. Use was made of the observation[3c,d,6] that for the diastereomeric epoxy alcohols the H_a of the *erythro*-configurated isomer (corresponding to 3*R**,4*S**) absorbs at lower field than that of the corresponding *threo* isomer (corresponding to 3*R**,4*R**). The



(3R*,4S*)-4 (3R*,4R*)-4

same spectral characteristics were observed for the diastereomeric epoxy diols **4a–c**; the resonances of the H_a of the 3*R**,4*S**-configurated epoxy diols are shifted by 0.15–0.47 ppm downfield relative to those of the corresponding 3*R**,4*R** diastereomers.

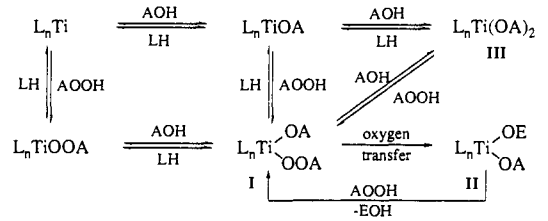
Furthermore, the fact that for the epoxy diols **4a** the A branch of the AB pattern for the 3*R**,4*S** isomer is displaced 0.02–0.08 ppm to higher field than that of the 3*R**,4*R** isomer and the B branch 0.08–0.10 ppm to lower field additionally supports the stereochemical assignments. Similar spectral characteristics are exhibited by the structurally related epoxy alcohols.[3c,d] For epoxy diols **4b,c**, the smaller J_{ab} coupling of the 3*R**,4*S**-configurated diastereomers [J(3*R**,4*S**) *versus* J(3*R**,4*R**) are 4.2 and 5.3 Hz for **4b** and 4.0 and 4.7 Hz for **4c**] was an additional criterium[3c,d,6] for the assessment of their stereochemistry. Moreover, the resonances of all oxygen-bearing carbon atoms of the 3*R**,4*S**-configurated epoxy diols **4a–c** are shifted 0.1–3.4 ppm upfield relative to those of the corresponding 3*R**,4*R**-configurated diastereomers, which is most pronounced for the signals of the carbon atoms which bear the H_a hydrogen ($\Delta\delta$ = 1.3–3.4 ppm). This trend is general, as observed for similar reported epoxy alcohols.[3c,d]

Discussion

The results presented above unmistakably demonstrate that both the reactivity and the diastereoselectivity of the titanium-catalyzed epoxidations are controlled by the multidentate ligating abilities of the employed oxygen donor reagent and oxygen acceptor substrate. Provided steric constraints do not counteract, the efficient and highly diastereoselective epoxy hydroxylation reported herein derives its effectiveness from the fact that the homoallylic hydroxy functionality in the hydroperoxy alcohol **2** serves for tridentate binding of the oxygen atom donor in the titanium template and bidentate binding for the oxygen atom acceptor, namely the corresponding unsaturated diol **3** substrate. The consequences which arise from such synergistic multidentate binding of both the oxygen-donating hydroperoxide and the oxygen-accepting allylic alcohol are reflected in the following experimental observations:

(a) *Hydroperoxy homoallylic alcohols are more efficient oxygen donors in the epoxidations of unsaturated diols than TBHP.* Generally, olefinic diols are poor substrates for metal-catalyzed epoxidations.[7] For example, treatment of diol (*S**,*S**)-**3a** derived from (*S**,*S**)-**2a** with TBHP and 50 mol % Ti(O*i*-Pr)$_4$ did not result in the formation of epoxy diol **4a**, although 10 times as much catalyst was employed. In comparison, the direct epoxy hydroxylations of the hydroperoxy homoallylic alcohols **2**, in which the actual epoxidized species are the unsaturated diols **3**, proceeded at remarkable rates. For example, in the transformation of (*S**,*S**)-**2a**, the hydroperoxide was completely consumed within minutes although only one-tenth of the catalyst was employed as in the attempted epoxidation of (*S**,*S**)-**3a** by TBHP as oxygen donor (entry 4, Table I).

Scheme III



AOH = allylic diol 3 AOOH = hydroperoxide 2 EOH = epoxy diol 4

The high reactivity of the hydroperoxy homoallylic alcohols **2** as oxygen atom donors in these epoxidations can be deduced from the mechanism[2f] of such metal-catalyzed reactions (Scheme III). At first, complex I is formed by successive reversible ligand exchanges, in which both the allylic substrate **3** (AOH, oxygen acceptor) and the hydroperoxide **2** (AOOH, oxygen donor) are bound to the titanium metal. The irreversible oxygen transfer step then occurs in this so-called loaded complex I to give complex II, which contains epoxy diol **4** (EOH) as product. A favorable kinetic feature is the fact that hydroperoxide **2** (AOOH) is converted in the oxygen transfer step to the allylic substrate **3** (AOH) directly in the coordination sphere of the titanium metal. Therefore, to regenerate the loaded complex I and therewith complete the catalytic cycle, only one ligand exchange, namely replacement of the product **4** (EOH) by fresh hydroperoxide **2** (AOOH), is necessary.

For the tridentate hydroperoxide **2**, such exchange is expected to be effective, but if unsaturated diols such as **3** are to be epoxidized with TBHP instead of **2**, the bidentate TBHP is ineffective in substituting the bidentate epoxy diol **4** (EOH). Accordingly, the titanium-catalyzed epoxidation of **3** with TBHP is slow compared to that of **2**. Moreover, if only a small amount of titanium catalyst is employed in the case of TBHP as oxygen donor reagent, the diol **3** should as bidentate ligand occupy all coordination sites of the titanium (complex III). Therefore, under such circumstances, even the formation of the loaded complex I is unlikely and the reaction rate drastically reduced.

(b) *The reaction rate of the epoxy hydroxylation is influenced by the relative configuration of the hydroperoxy alcohol moiety.* A comparison of the reaction times for the reactions of the hydroperoxides **2** reveals that these depend on the degree of substitution at the allylic double bond. While the disubstituted hydroperoxides **2a,b** react within minutes up to hours (entries 4, 5, and 7 of Table I), in the case of the monosubstituted derivatives **2c,d** several days were necessary to achieve full conversion (entries 10 and 11 of Table I). For the latter, the long reaction times make possible the competing metal-catalyzed reductions[3c] of the hydroperoxide to the corresponding unsaturated diols **3c,d** as side products. Evidently, with an increasing number of alkyl substituents, the nucleophilicity of the double bond increases, which leads to an enhanced rate of oxygen transfer for the electrophilic epoxidizing reagent.[2d,f]

A remarkable finding is that also the relative configuration of the hydroperoxy moiety affects the reactivity as demonstrated for the reaction of the diastereomeric hydroperoxy alcohols (*S**,*S**)- and (*R**,*S**)-**2a** (compare entries 4 and 5 of Table I). Although the substitution pattern and, thus, the nucleophilicities of the allylic double bonds of both diastereomers are identical, hours were necessary to convert completely the *erythro*-config-

(6) Mihelich, E. D. *Tetrahedron Lett.* **1979**, 4729.
(7) (a) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1991**, *113*, 2786. (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Synlett* **1991**, 548.

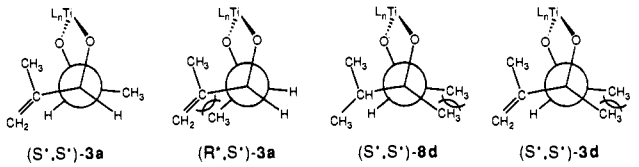
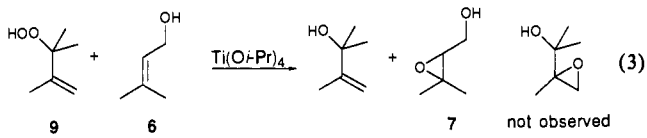


Figure 1. Steric interactions between substituents of metal-coordinated diols.

urated hydroperoxide (*R**,*S**)-**2a**, while minutes sufficed for the *threo* diastereomer. This dramatic difference in reactivity is undoubtedly related to the different abilities of both diastereomeric hydroperoxides (*S**,*S**)- and (*R**,*S**)-**2a** and diols (*S**,*S**)- and (*R**,*S**)-**3a** to bind to the titanium metal site and evidently reflects the ease with which the loaded complex (I in Scheme III) is formed. At least for the unsaturated diols, it is expected that the *threo* diastereomer (*S**,*S**)-**3a** coordinates by far more easily than the corresponding *erythro* diastereomer (*R**,*S**)-**3a**. These different ligation abilities arise from unfavorable steric interactions between the isopropenyl and the methyl groups for (*R**,*S**)-**3a** but not for (*S**,*S**)-**3a** (Figure 1). Similarly, interactions between the methyl groups should be responsible for the low tendency of diol (*S**,*S**)-**8d** and consequently (*S**,*S**)-**3d** to coordinate doubly to the titanium metal, and thus the latter is most efficiently epoxidized.

(c) *Unsaturated diols are more effective oxygen acceptors than allylic alcohols.* If an equimolar mixture of 2-hydroperoxy-2,3-dimethyl-3-butene (**9**) and allylic alcohol **6** was treated with Ti(O*i*-Pr)$_4$, only the epoxide **7** derived from **6**[3c] was detected (eq 3). Thus, the oxygen transfer takes place exclusively on the more



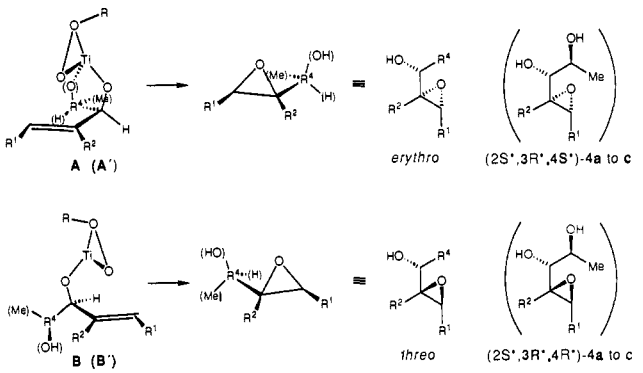
(3)

reactive trisubstituted double bond of the substrate **6**. A similar result, i.e. exclusive formation of epoxy alcohol **7**, would have been expected if this experiment were performed with (*S**,*S**)-**2a** instead of hydroperoxide **9** as the oxygen-donating reagent. Since the allylic hydroperoxides (*S**,*S**)-**2a** and **9** possess similarly dialkyl-substituted double bonds, both should exhibit a comparable reactivity of being epoxidized, but which should be distinctly lower than that of the allylic alcohol **6** with the trialkyl-substituted double bond. Nevertheless, large quantities of epoxy diol **4a** derived from (*S**,*S**)-**2a** were observed, even when the trisubstituted alcohol **6** was employed in a 10-fold excess[5] (eq 2).

From this result it is evident that the hydroperoxy alcohol (*S**,*S**)-**2a** is by far more easily epoxy-hydroxylated than the allylic hydroperoxide **9**. In fact, the propensity of the dialkyl-substituted double bond of the diol (*S**,*S**)-**3a** derived from hydroperoxy alcohol (*S**,*S**)-**2a** toward epoxidation is even greater than that of the trialkyl-substituted double bond of the allylic alcohol **6**. Again, this finding accentuates the influence of bidentate binding on the reactivity of allylic diols toward epoxidation under Sharpless conditions.

(d) *The diastereoselectivity in epoxy hydroxylations of hydroperoxy homoallylic alcohols is unusually high.* The epoxy hydroxylations of the hydroperoxy homoallylic alcohols **2a–c** proceeded with high diastereoselectivity, in which the 3*R**,*S**-configurated epoxy diols **4a–c** were preferentially formed. Compared to titanium-catalyzed epoxy hydroxylations of unfunctionalized allylic hydroperoxides and the related Sharpless epoxidations of allylic alcohols with similar structures by TBHP, the degree of diastereoselection is higher for the hydroperoxy homoallylic alcohols **2**. This is reflected especially in the case of the derivatives (*S**,*S**)-**2b,c** (compare entries 1–3 *versus* 4 and 5, or 6 *versus* 7, and 8 and 9 *versus* 10 of Table I), in which for

Scheme IV



(*S**,*S**)-**2b** (compare entries 6 *versus* 7 of Table I) even an inverted sense of stereocontrol was observed.

Again, bidentate ligand binding is the reason for the enhanced selectivity. In the oxygen transfer step, the approach of the allylic double bond to the peroxide should occur along the axis of the O–O bond.[8] The geometries of **A** (which leads to the *erythro* epoxy alcohol) and **B** (which leads to the *threo* epoxy alcohol) meet this requirement as depicted in Scheme IV. In these graphical projections, **A** and **B** refer to the simple allylic alcohols as substrates with unfunctionalized R^4 substitutents, while **A'** and **B'** refer to the olefinic diols **3** with HO-functionalized R^4 substituents. Thus, for the allylic alcohols which bear a methyl group geminal to the chiral substituent (R^2 = Me), arrangement **B** is disfavored relative to **A** due to 1,2 allylic strain on account of steric interactions between the R^2 and R^4 alkyl substituents. Hence, the reaction mainly proceeds through complex **A** and *erythro*-configurated epoxy alcohols dominate (entries 1–3 of Table I). If such a gem methyl group is not present (R^2 = H), the discrimination between geometries **A** and **B** is ineffective since 1,2 allylic interactions are minimal and, thus, the observed diastereoselectivities are small (entries 6, 8, and 9 of Table I).

With an additional HO functionality in the homoallylic position of the allylic alcohol, i.e. an HO-functionalized R^4 substituent, as in the unsaturated diols **3a–c**, geometry **A'** is stabilized by bidentate coordination of the diol, but not for **B'** due to geometric constraints. Consequently, the reaction proceeds mainly through transition state **A'** to give preferentially the 3*R**,4*S**-configurated epoxy diols **4** which corresponds to the *erythro* configuration (entries 4, 7, and 10 of Table I). For (*R**,*S**)-**3a** and (*S**,*S**)-**3d**, bidentate ligand binding is not feasible and, hence, most likely in these cases the oxygen transfer occurs on the singly coordinated diols similar to monodentate allylic and homoallylic alcohols.

Besides these revealing mechanistic implications on multidentate ligand binding, the transformations discussed herein are also valuable from the synthetic point of view. An important finding is that epoxy diols **4** can be prepared directly from chiral allylic alcohols **1** simply by adding catalytic amounts of Ti(OiPr)$_4$ to a photooxygenated solution of substrate **1**, as exemplified for the conversion of **1a** (Scheme II). The advantage of this one-pot, two-step procedure lies in the fact that no external hydroperoxides, substances of potential danger especially in large scale applications, have to be employed because they are generated *in situ* through photooxygenation. Moreover, the large difference in reactivity of both diastereomeric hydroperoxides (*S**,*S**)- and (*R**,*S**)-**2a**, which are generally formed in photooxygenations of **1a**, offers the opportunity for their kinetic separation; this can

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easily be achieved by stopping the reaction after the *threo*-configurated hydroperoxide (*S**,*S**)-**2a** is consumed (Scheme II).

Conclusions

The epoxy hydroxylation of hydroperoxy homoallylic alcohols, readily accessible by the photooxygenation of chiral allylic alcohols, represents a very attractive route to synthetically useful epoxy diols. In this manner, up to three additional chiral centers in succesive adjacent positions to the already existing chiral allylic alcohol moiety can be introduced in high regio- and diastereoselectivity with predictable stereochemistry. Important from the mechanistic point of view is the fact that the reactivity as well as the stereoselectivity is affected by the ligation abilities of the oxygen donor reagent and oxygen acceptor substrate. Thus, tridentate hydroperoxides such as the hydroxy-functionalized ones employed here, should generally be more efficient oxidants in metal-catalyzed epoxidations of bidentate allylic diols. We wish to point out that by employing enantiomerically enriched allylic alcohols, optically active epoxy diols for asymmetric synthesis become conveniently accessible.

Experimental Section

General Aspects. IR spectra were determined on a Perkin-Elmer Infrared Recording Spectrometer 1420 and the ^{1}H and ^{13}C NMR spectra on a Bruker AC 250 or a Bruker WM 400 spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Institute of Inorganic Chemistry, University of Würzburg. For TLC runs, Machery und Nagel Polygram SIL G/UV$_{254}$ foils were used; spots were detected with phosphomolybdic acid test spray. For hydroperoxides, additionally, the KI test was employed. Purifications by column chromatography were performed on silica gel (63–200 μm) from Woelm (Erlangen) with an adsorbent/substrate ratio of 50:1 and elution with ethyl ether. Commercial reagents and solvents were purified according to literature procedures to match reported physical and spectral data. The hydroperoxy homoallylic alcohols **2** and diols **3** and (*S**,*S**)-**8d** were prepared as previously described.[4c]

Caution! Hydroperoxides are potentially dangerous and should be handled with care!

General Procedure for the Titanium-Catalyzed Hydroxy Epoxidation of Hydroperoxy Homoallylic Alcohols. To a solution of 0.874–2.00 mmol of the particular hydroperoxy homoallylic alcohol **2** in 2–4 mL of CH_2Cl_2 was introduced with a microsyringe 5–10 mol % of Ti(O*i*-Pr)$_4$ at −25 °C in the presence of molecular sieves (4 Å). The reaction was monitored by TLC, and after complete consumption of the hydroperoxide (negative KI test), the reaction mixture was diluted with the same volume of ethyl ether, and water (1 mL/mmol of Ti used) was added under vigorous stirring. After 30 min, the solvent was evaporated (20 °C, 18 Torr) and the residue *immediately* purified by column chromatography, to afford analytically pure samples of the epoxy diols **4**.

(*S,*R**,*S**)- and (*S**,*R**,*R**)-4,5-Epoxy-4-methylpentane-2,3-diol (4a).** From 264 mg (2.00 mmol) of (*S**,*S**)-**2a** and 29 μL (5 mol %) of Ti(O*i*-Pr)$_4$ in 4 mL of CH_2Cl_2 was obtained after 5 min 224 mg (85%) of **4a** [(*S**,*R**,*S**):(*S**,*R**,*R**) = 95:5] as colorless plates, mp 71–72 °C. (*S**,*R**,*S**)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 3 H, *J* = 6.5 Hz), 1.37 (s, 3 H), 2.65 (d, 1 H, *J* = 4.5 Hz), 2.91 (d, 1 H, *J* = 4.5 Hz), 3.34 (d, 1 H, *J* = 3.7 Hz), 3.50 (br s, 2 H), 3.88 (dq, 1 H, *J* = 6.5 Hz, *J* = 3.7 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 17.6 (q), 19.8 (q), 51.5 (t), 57.5 (s), 67.5 (d), 76.3 (d). (*S**,*R**,*R**)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, 3 H, *J* = 6.4 Hz), 1.32 (s, 3 H), 2.67 (d, 1 H, *J* = 4.6 Hz), 2.83 (d, 1 H, *J* = 4.6 Hz), 3.08 (d, 1 H, *J* = 6.2 Hz), 3.50 (br s, 2 H), 3.87 (dq, 1 H, *J* = 6.4 Hz, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 16.0 (q), 18.8 (q), 52.4 (t), 58.3 (s), 67.9 (d), 79.1 (d); IR (cm^{-1}) 3680–3140. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.98; H, 9.47.

(*R,*R**,*S**)- and (*R**,*R**,*R**)-4,5-Epoxy-4-methylpentane-2,3-diol (4a).** From 154 mg (1.17 mmol) of (*R**,*S**)-**2a** and 34 μL (10 mol %) of Ti(O*i*-Pr)$_4$ in 2.5 mL of CH_2Cl_2 was obtained after 5 h 123 mg (80%) of **4a** [(*R**,*R**,*S**):(*R**,*R**,*R**) = 95:5] as a colorless oil. (*R**,*R**,*S**)-**4a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.10 (d, 3 H, *J* = 6.5 Hz), 1.28 (s, 3 H), 2.54 (d, 1 H, *J* = 4.9 Hz), 2.90 (d, 1 H, *J* = 4.9 Hz), 3.26 (br s, 2 H), 3.66 (d, 1 H, *J* = 3.8 Hz), 3.85 (dq, 1 H, *J* = 6.5 Hz, *J* = 3.8 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 17.4 (q), 18.9 (q), 50.4 (t), 57.8 (s), 68.3 (d), 74.7 (d). (*R**,*R**,*R**)-**4a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.16 (d, 3 H, *J* = 6.4 Hz), 1.30 (s, 3 H), 2.62 (d, 1 H, *J* = 4.5 Hz), 2.80 (d, 1 H, *J* = 4.5 Hz), 3.19 (d, 1 H, *J* = 6.0 Hz), 3.26 (br s, 2 H), 3.79 (dq, 1 H, *J* = 6.4 Hz, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 17.2 (q), 19.1 (q), 52.8 (t), 58.6 (s), 68.5 (d), 78.1 (d); IR (cm^{-1}) 3700–3140. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.33; H, 9.44.

(*S,*R**,*S**,*R**)- and (*S**,*R**,*R**,*S**)-4,5-Epoxyoctane-2,3-diol (4b).** From 140 mg (0.874 mmol) of (*S**,*S**)-**2b** and 13 μL (5 mol %) of Ti(O*i*-Pr)$_4$ in 2 mL of CH_2Cl_2 was obtained after 1 h 116 mg (83%) of **4b** [(*S**,*R**,*S**,*R**):(*S**,*R**,*R**,*S**) = 86:14] as a colorless oil. (*S**,*R**,*S**,*R**)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3 H, *J* = 7.2 Hz), 1.26 (d, 3 H, *J* = 6.5 Hz), 1.43–1.57 (m, 4 H), 2.63 (br s, 2 H), 2.82 (dd, 1 H, *J* = 4.2 Hz, *J* = 2.4 Hz), 3.00 (dt, 1 H, *J* = 5.5 Hz, *J* = 2.4 Hz), 3.46 (dd, 1 H, *J* = 5.2 Hz, *J* = 4.2 Hz), 3.79 (dq, 1 H, *J* = 6.5 Hz, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 14.1 (q), 19.2 (q), 19.5 (t), 33.8 (t), 56.3 (d), 58.8 (d), 69.1 (d), 74.3 (d). (*S**,*R**,*R**,*S**)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, 3 H, *J* = 6.4 Hz), 2.97 (dt, 1 H, *J* = 5.6 Hz, *J* = 2.4 Hz), 3.31 (dd, 1 H, *J* = 5.8 Hz, *J* = 5.3 Hz), 3.85 (dq, 1 H, *J* = 6.4 Hz, *J* = 5.8 Hz) (the signals are partially overlapped by those of the *S**,*R**,*S**,*R**-diastereomer, and only the separated resonances are given); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 14.1 (q), 15.4 (q), 19.5 (t), 33.7 (t), 56.8 (d), 59.6 (d), 69.2 (d), 75.6 (d); IR (cm^{-1}) 3680–3200. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.42; H, 10.34.

(*S,*R**,*S**)- and (*S**,*R**,*R**)-4,5-Epoxypentane-2,3-diol (4c).** From 102 mg (0.949 mmol) of (*S**,*S**)-**2c** and 28 μL (10 mol %) of Ti(O*i*-Pr)$_4$ in 2 mL of CH_2Cl_2 were obtained after 2 days 60 mg (59%) of **4c** [(*S**,*R**,*S**):(*S**,*R**,*R**) = 91:9] and 18 mg (19%) of **3c** as colorless oils. (*S**,*R**,*S**)-**4c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 3 H, *J* = 6.4 Hz), 2.79–2.83 (m, 2 H), 3.07 (ddd, 1 H, *J* = 4.0 Hz, *J* = 3.8 Hz, *J* = 3.1 Hz), 3.18 (br s, 2 H), 3.50 (dd, 1 H, *J* = 5.2 Hz, *J* = 4.0 Hz), 3.81 (dq, 1 H, *J* = 6.4 Hz, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 18.9 (q), 44.2 (t), 52.3 (d), 68.7 (d), 73.8 (d). (*S**,*R**,*R**)-**4c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3 H, *J* = 6.5 Hz), 3.31 (dd, 1 H, *J* = 5.8 Hz, *J* = 4.7 Hz), 3.89 (dq, 1 H, *J* = 6.5 Hz, *J* = 5.8 Hz) (the signals are partially overlapped by those of the *S**,*R**,*S**-diastereomer, and only the separated resonances are given); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 18.9 (q), 44.7 (t), 53.1 (d), 68.9 (d), 75.3 (d); IR (cm^{-1}) 3660–3100. Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.89; H, 8.85. **3c**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.16 (d, 3 H, *J* = 6.3 Hz), 3.16 (br s, 2 H), 3.63 (dq, 1 H, *J* = 6.5 Hz, *J* = 6.3 Hz), 3.84 (dd, 1 H, *J* = 6.5 Hz, *J* = 6.4 Hz), 5.25 (dd, 1 H, *J* = 10.5 Hz, *J* = 1.3 Hz), 5.34 (dd, 1 H, *J* = 17.1 Hz, *J* = 1.3 Hz), 5.83 (ddd, 1 H, *J* = 17.1 Hz, *J* = 10.5 Hz, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 19.0 (q), 70.9 (d), 78.1 (d), 117.7 (t), 137.6 (s); IR (cm^{-1}) 3700–3220. The spectral data of diol **3c** matched those reported in ref 8.

(*S,*R**,*S**)- and (*S**,*R**,*R**)-4,5-Epoxy-3-methylpentane-2,3-diol (4d).** From 250 mg (1.89 mmol) of (*S**,*S**)-**2d** and 55 μL (10 mol %) of Ti(O*i*-Pr)$_4$ in 4 mL of CH_2Cl_2 were obtained after 3 days 114 mg (46%) of **4d** [dr 51:49] and 38 mg (17%) of **3d** as colorless oils. **4d**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.09 (s, 3 H), 1.16 (d, 3 H, *J* = 6.5 Hz), 1.17 (s, 3 H), 1.18 (d, 3 H, *J* = 6.4 Hz), 2.67 (dd, 1 H, *J* = 5.1 Hz, *J* = 4.1 Hz), 2.72–2.76 (m, 2 H), 2.82 (dd, 1 H, *J* = 4.8 Hz, *J* = 2.9 Hz), 2.88 (br s, 4 H), 2.96 (dd, 1 H, *J* = 3.9 Hz, *J* = 2.9 Hz), 3.01 (dd, 1 H, *J* = 4.1 Hz, *J* = 2.9 Hz), 3.67 (q, 1 H, *J* = 6.5 Hz), 3.79 (q, 1 H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 17.0 (q), 17.1 (q), 18.6 (q), 20.3 (q), 42.9 (t), 44.6 (t), 56.4 (d), 57.0 (d), 71.3 (d), 71.8 (s), 72.4 (d), 72.9 (s); IR (cm^{-1}) 3680–3240. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.69; H, 9.31. **3d**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.02 (d, 3 H, *J* = 6.3 Hz), 1.11 (s, 3 H), 4.20 (br s, 2 H), 4.39 (q, 1 H, *J* = 6.3 Hz), 4.97 (dd, 1 H, *J* = 10.8 Hz, *J* = 1.6 Hz), 5.21 (dd, 1 H, *J* = 17.4 Hz, *J* = 1.6 Hz), 5.82 (dd, 1 H, *J* = 17.4 Hz, *J* = 10.8 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 17.3 (q), 22.8 (q), 68.6 (d), 75.8 (s), 113.7 (t), 143.4 (s); IR (cm^{-1}) 3660–3240. The spectral data of diol **3d** matched those reported in ref 10.

Attempted Epoxidation of (*S,*S**)-3a with Ti(O*i*-Pr)$_4$/TBHP.** A solution of 232 mg (2.00 mmol) of (*S**,*S**)-**3a**, 284 mg (1.00 mmol) of Ti(O*i*-Pr)$_4$, and 3.00 mmol of TBHP in 2.5 mL of CH_2Cl_2 was stored in the presence of molecular sieves (4 Å) at −25 °C for 3 days. After addition of 1 mL of water, no epoxy diol **4a** was detected by TLC in the mixture.

One-Pot, Two-Step Synthesis of Epoxy Diol 4a Directly from Allylic Alcohol 1a. A solution of 501 mg (5.00 mmol) of **1a** and ca. 5 mg of tetraphenylporphine (TPP) was irradiated with two external Philips G/98/2 SON 150-W sodium lamps at 0 °C while passing continuously a stream of dry oxygen gas through the reaction mixture; within 4 h, **1a**

was completely consumed. The reaction mixture was dried over molecular sieves (4 Å), cooled to −25 °C, then 73 μL (5 mol %) of Ti(O*i*-Pr)$_4$ was injected with a microsyringe. After 10 min, the reaction was quenched by addition of 50 mL of ether and 0.5 mL of water under vigorous stirring. Workup as described above afforded 463 mg (70%) of **4a** [(*S**,*R**,*S**):(*S**,*R**,*R**) = 95:5].

Photooxygenation of Allylic Alcohol 1a in the Presence of Ti(O*i*-Pr)$_4$. A solution of 100 mg (1.00 mmol) of **1a**, 60 μL (20 mol %) of Ti(O*i*-Pr)$_4$, and ca. 2 mg of TPP in 20 mL of CCl_4 was photooxygenated for 4 h at 0 °C in the presence of molecular sieves (4 Å). After addition of 5 mL of ether and 0.2 mL of water, the mixture was warmed to room temperature under vigorous stirring. Filtration over Celite, drying over anhydrous Na_2SO_4, and rotoevaporation (20 °C, 18 Torr) afforded 112 mg of a colorless oil, which consisted of **4a**, **3a**, and **5a** in a ratio of 44:25:31 (error was ±10% of the stated value).

Treatment of Mixtures of d_2-(*S,*S**)-2a and d_1-6 with Ti(O*i*-Pr)$_4$.** First d_2-(*S**,*S**)-**2a** and d_1-**6** were prepared by addition of 0.2 mL of D_2O to (*S**,*S**)-**2a** or **6** and extraction of the resulting mixture with CH_2Cl_2 (4 × 1 mL), dried over anhydrous Na_2SO_4 and molecular sieves (4 Å), and the solvent was removed at 20 °C and 18 Torr. Of these deuterated substrates, stock solutions were prepared in $CDCl_3$: (a) 1.0 M d_2-(*S**,*S**)-**2a**, (b) 0.50 M d_1-**6**, and (c) 5.00 M d_1-**6**. The following reactions were performed in NMR tubes; product ratios were determined by quantitative ^{1}H NMR (error was ±10% of the stated value):

Run A. Injection of 200 μL of solution a [200 μmol of d_2-(*S**,*S**)-**2a**] into a mixture of 400 μL of solution b [200 μmol of d_1-**6**] and 5.9 μL (10 mol %) of Ti(O*i*-Pr)$_4$ at 0 °C led to a mixture of d_2-**3a**, d_2-**4a**, and d_1-**7** in a ratio of 30:38:32.

Run B. Injection of 200 μL of solution a [200 μmol of d_2-(*S**,*S**)-**2a**] to a mixture of 400 μL of solution c [2.00 mmol of d_1-**6**] and 5.9 μL (10 mol %) of Ti(O*i*-Pr)$_4$ at 0 °C resulted in a mixture of d_2-**3a**, d_2-**4a**, and d_1-**7** in a ratio of 40:17:43. In both cases, the reactions were complete within less than 5 min. Although the ^{1}H NMR spectra were recorded immediately after addition of the hydroperoxide, it was not possible to detect any d_2-(*S**,*S**)-**2a** in the reaction mixtures.

Ligation Abilities of Diols. The ^{1}H NMR spectra of solutions of 15 mg (0.13 mmol) of (*S**,*S**)-**3a**, (*R**,*S**)-**3a**, and (*S**,*S**)-**8d** in 0.5 mL of $CDCl_3$ were recorded after addition of 44 mg (0.13 mmol) of Ti(O*t*-Bu)$_4$. In the case of (*S**,*S**)-**3a**, the addition of the titanium reagent led to complete loss of the carbinol CH proton resonances (δ 3.67–3.78) through line broadening, while for (*R**,*S**)-**3a** and (*S**,*S**)-**8d**, at best a <10% decrease of the corresponding signals [(*R**,*S**)-**3a**: δ 3.85, 4.01. (*S**,*S**)-**8d**: δ 3.61] was observed.

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