Titanium-Catalyzed Diastereoselective Epoxidations of Ene Diols and Allylic Alcohols with β-Hydroperoxy Alcohols as Novel Oxygen Donors†

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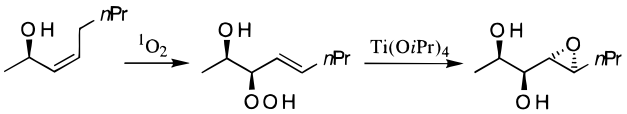
Received January 22, 1997⊗

β-Hydroperoxy alcohols **1**−**4** serve as effective tridentate oxygen donors for the highly diastereoselective, titanium-catalyzed epoxidation of ene diols **5a**−**e**. Thus, in contrast to the bidentate *tert*-butyl hydroperoxide, the usual oxygen donor employed in Sharpless-type epoxidations and known to work poorly for polyhydroxy substrates, the tridentate β-hydroperoxy alcohols efficiently replace the tridentate epoxy diol products **6a**−**e** in the titanium template and thereby the catalytic cycle is sustained by replenishing with efficacy the *loaded complex* necessary for the oxygen transfer. Irrespective of the substitution pattern of the double bond or the configuration (*erythro versus threo*) of the diol functionalities in the ene diol substrate, high diastereoselectivities are observed for the epoxy diol products. The high stereochemical control is due to the rigid transition state for the oxygen transfer, which is imposed by the multiple titanium−oxygen bonding and coordination in the titanium template. The observed *erythro* selectivity for the ene diol derives from the additional bonding of its homoallylic hydroxy group to the titanium center, which fixes the substrate conformation in such a way that the oxygen atom to be transferred approaches from the side of the allylic oxygen functionality (cf. *loaded complex* **A**). This additional binding of the bidentate ene diol in the titanium template is also manifested in the enhanced reactivity of the ene diol *versus* the monodentate allylic alcohols. Nevertheless, the less reactive allylic alcohols also display a high *erythro* selectivity, provided these monodentate substrates possess 1,2-allylic strain. For the first time a direct, diastereoselective, and catalytic epoxidation of ene diols has been made available for synthetic applications, without recourse to protection group methodology.

Epoxy alcohols are versatile building blocks of high synthetic utility, which are abundantly used in organic chemistry.[1] They are readily and conveniently available from allylic alcohols by epoxidation with peracids,[2] dioxiranes,[3] or metal-activated hydrogen peroxide[4] and hydroperoxides.[2] The enantioselective version of the latter, the Sharpless epoxidation,[5] is undoubtly the most valuable prototype for this purpose.

A related synthetically useful entry to epoxy alcohols from a variety of olefins constitutes the hydroxy-epoxidation methodology.[6] The simple olefinic substrates are directly converted to the epoxy alcohols by photooxygenation (Schenck ene reaction of singlet oxygen[7]), followed by subsequent titanium-catalyzed epoxidation. In this one-pot sequence, the *in situ* generated allylic hydroperoxide plays the double role of the oxygen donor and oxygen acceptor. This obviates the use of an external hydroperoxide, as for example *tert*-butyl hydroperoxide (TBHP) in the Sharpless epoxidation.[5] When the epoxy-hydroxylation methodology is applied to chiral allylic alcohols,[8] up to three additional chirality centers in successive, adjacent positions may be introduced regio- and diastereoselectively with respect to the already existing stereogenic center at the allylic alcohol functionality (Scheme 1). The success of this stereoselective oxidation derives from the joint action of two highly diastereoselective transformations: on the one hand, the hydroxy-directed photooxygenation of allylic alcohols with 1,3-allylic strain[7] and, on the other hand, the additional coordination of the homoallylic hydroxy group to the titanium metal in the oxygen transfer step. The additional hydroxy group is also responsible for the enhanced reaction rate compared to the conventional titanium-catalyzed epoxidation with TBHP. Whereas for the latter even after 3 days only traces of product are detected (Scheme 2), the epoxy-hydroxylation method

Scheme 1. Epoxy-Hydroxylation of Chiral Allylic Alcohols to the Corresponding Epoxy Diols



† Dedicated to Prof. Dieter Seebach (Zürich), an appreciated friend and respected colleague, on the occasion of his 60th birthday.

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⊗ Abstract published in *Advance ACS Abstracts,* April 15, 1997.

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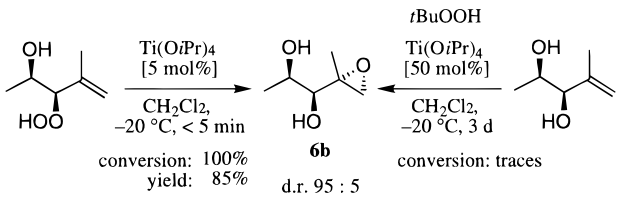
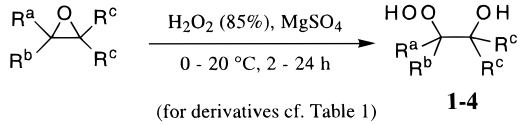
S0022-3263(97)00110-2 CCC: $14.00

Scheme 2. Two Possible Synthetic Pathways for Epoxy Diol 6b



Scheme 3. Perhydrolysis of Epoxides to the *β*-Hydroperoxy Alcohols 1−4



affords the epoxy diol in quantitative yield within less than 5 min reaction time. In fact, it is generally well-known that allylic alcohols with additional hydroxy functionalities are poor substrates for the Sharpless epoxidation with TBHP.[9]

Since in the direct epoxy-hydroxylation[6] one hydroperoxy alcohol (Scheme 2) serves as oxygen donor and another one, after reduction to the ene diol, functions as oxygen acceptor, in principle it should be feasible to epoxidize ene diols by nonolefinic *β*-hydroperoxy alcohols. Indeed, this novel synthetic concept was recently demonstrated for the ene diol in Scheme 2 (traces of ene diol product with TBHP!) when 2-hydroperoxy-2-phenyl-1-propanol (**4**) was employed as the oxygen source.[10] Herein we report the full experimental details on the general scope and efficacy of the titanium-catalyzed epoxidations of ene diols by the novel tridentate *β*-hydroperoxy alcohols as oxygen donors.

Results

Product Studies. The *β*-hydroperoxy alcohols **1**−**4** were prepared by biphasic perhydrolysis of the corresponding epoxides according to a slightly modified literature procedure (Scheme 3).[11] The results for the epoxidation of the ene diols **5a** and *(R*,R*)*-**5b**−**d** with the *β*-hydroperoxy alcohols **1**−**4** are given in Table 1. As demonstrated in four preparative runs (Table 1, entries 5, 9−11, 16, and 21), the epoxy diols **6a**−**d** were isolated in 60−88% yields in good to excellent *erythro* selectivity.

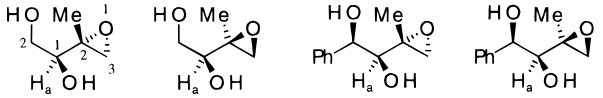
A small dependence of the diastereoselectivities on the structure of the ene diol **5a**−**e** substrate and the *β*-hydroperoxy alcohols **1**−**4** as oxygen donors is observed (Table 1). Thus, for substrate **5a**, with only one chirality center, the best *erythro* diastereoselectivity was obtained for 2-hydroperoxy-2-methyl-1-propanol (**1**); for 2-hydroperoxy-2-phenyl-1-ethanol (**3**) it drops significantly (entries 1 and 3). For the ene diols **5b,d** the highest diastereomeric ratios in favor of the *erythro* isomer are observed (entries 7 and 18) with 2,3-dimethyl-3-hydroperoxy-2-butanol (**2**). In the epoxidation of the derivative **5c** by the hydroperoxide **2**, only the *erythro* diastereomer was detected in the crude reaction mixture (entry 13).

The reaction time depends significantly on the temperature. For example, for substrate **5b** and oxygen donor **4**, at −25 °C, the conventional temperature for the Sharpless epoxidation,[5] complete conversion requires 17 h (entry 11) and at 0 °C still 3 h (entry 10). On the temperature being raised to room temperature (ca. 20 °C), already after 30 min no more substrate can be detected (entry 9). The *erythro* selectivity drops only a little, i.e. from 89:11 at −25 °C to 82:18 at room temperature.

The results on the epoxidation by various oxidants of the enantiomerically pure [*S*,*R*-(*E*)]-**5e** are given in Table 2. The epoxidations by the *β*-hydroperoxy alcohols **1**−**3** yield only the *erythro* epoxy diol **6e** (Table 2, entries 3−7). By ^{1}H NMR analysis of the crude reaction mixture, quantitative conversion to the epoxy diol **6e** as the only product was observed (entries 4 and 6). The same product was isolated in 91% yield from the epoxidation by *β*-hydroperoxy alcohol **1** (entry 3). Also, no change was observed when either exactly one (entry 5) or an excess of more than 2 equiv (entry 7) of the chiral, racemic 2-hydroperoxy-2-phenyl-1-ethanol (**3**) was employed; in both cases only the *erythro* diastereomer was isolated. In contrast, the stoichiometric epoxidation methods with dimethyldioxirane (entry 1) and *m*CPBA (entry 2) gave only moderate *threo* diastereoselectivities.

The *β*-hydroperoxy alcohol persists under the reaction conditions and was reisolated when an excess was employed (entry 7). By HPLC on a chiral phase it was found that the recovered hydroperoxy alcohol, as well as the diol derived from it by reduction during the reaction, were racemic mixtures.

Diastereomeric Assignments. The configurations of the epoxy diols **6b,d** are already known.[8] For the structurally similar derivatives **6a,c**, the assignment is based on comparison of their spectral data with those of **6b,d**. Use was made of the fact[8,12] that the characteristic



H_a proton of the *erythro*-configurated isomer absorbs at lower field than that of the corresponding *threo* isomer (for convenience, the traditional *threo*/*erythro* stereochemical nomenclature is used). The same spectral characteristics were observed for the diastereomeric epoxy diols **6c**; the resonances of the H_a proton of the *erythro*-configurated epoxy diols are shifted by 0.42 ppm downfield relative to those of the corresponding *threo* diastereomer. For derivative **6a**, due to signal overlap, the exact *δ* values could not be determined. Moreover, the resonances of all oxygen-bearing carbon atoms of the *erythro*-configurated epoxy diols **6a,c** are shifted 0.3−4.0 ppm upfield relative to those of the corresponding *threo* diastereomers. This upfield shift is most pronounced for the signals of the carbon atom which bears the H_a hydrogen (Δ*δ* 2.1 and 4.0). This trend is general, as observed for similar reported epoxy alcohols[6,7] and also for derivative **6e**. The latter was obtained enantio- and diastereomerically pure, and its *erythro* configuration was established by X-ray analysis (Figure 1).[16]

Mechanistic Studies. The primary allylic alcohol **5g** (Table 3, entry 2) and the series of secondary chiral

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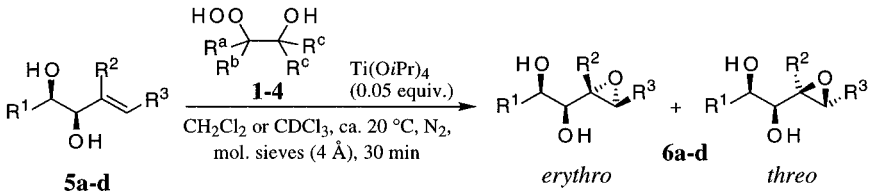
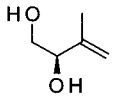
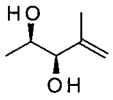
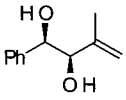
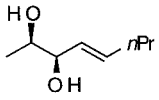
Table 1. Titanium-Catalyzed Epoxidation of the Ene Diols 5a–d by the β-Hydroperoxy Alcohols 1–4



entry	substrate		oxygen donor	R^a	R^b	R^c	T [°C]	conv. [%]	yield[a] [%]	d.r.[b] *erythro : threo*
1		**5a**	**1**	Me	Me	H	23	> 95	> 95	92 : 08
2		**5a**	**2**	Me	Me	Me	23	> 95	> 95	86 : 14
3		**5a**	**3**	Ph	H	H	23	> 95	> 95	78 : 22
4		**5a**	**4**	Ph	Me	H	23	> 95	> 95	91 : 09
5		**5a**	**4**	Ph	Me	H	23	> 95	60[c]	91 : 09[d]
6		**5b**	**1**	Me	Me	H	23	90	> 95	93 : 07
7		**5b**	**2**	Me	Me	Me	23	> 95	> 95	95 : 05
8		**5b**	**3**	Ph	H	H	23	> 95	> 95	91 : 09
9		**5b**	**4**	Ph	Me	H	23	> 95	88[c]	82 : 18[d]
10		**5b**	**4**	Ph	Me	H	0[e]	88	83[c]	86 : 14[d]
11		**5b**	**4**	Ph	Me	H	–25[f]	> 95	70[c]	89 : 11[d]
12		**5c**	**1**	Me	Me	H	23	90	> 95	95 : 05
13		**5c**	**2**	Me	Me	Me	23	> 95	> 95	> 95 : 05
14		**5c**	**3**	Ph	H	H	23	90	> 95	96 : 04
15		**5c**	**4**	Ph	Me	H	23	> 95	> 95	90 : 10
16		**5c**	**3**	Ph	H	H	23	> 95	87[c]	> 95 : 05[d]
17		**5d**	**1**	Me	Me	H	23	g	g	g
18		**5d**	**2**	Me	Me	Me	23	> 95	> 95	92 : 08
19		**5d**	**3**	Ph	H	H	23	> 95	> 95	76 : 24
20		**5d**	**4**	Ph	Me	H	23	> 95	> 95	85 : 15
21		**5d**	**4**	Ph	Me	H	23	> 95	83[c]	81 : 19[d]

[a] Based on converted material. [b] Diastereomeric ratio, determined on the crude reaction mixture by ^{1}H NMR analysis; error ±5% of the stated values. [c] Yield of isolated material. [d] Determined after column chromatography. [e] 3 h reaction time. [f] 17 h reaction time. [g] Not determined because of overlapping signals.

alcohols **5h–n** (Table 3, entries 3–9) were also readily epoxidized by the β-hydroperoxy alcohol **2** under titanium catalysis. The set of chiral allylic alcohols **5h–n** serves as stereochemical probe to estimate the dihedral angle (C=C–C–O) in the allylic alcohol of the epoxidation transition state.[13] The allylic alcohol **5h** gives the *erythro* epoxy alcohol **6h** with a preference of 81:19 (Table 3, entry 3). The selectivity is due to 1,2-allylic strain ($A^{1,2}$ strain) between the methyl group at the chirality center (R^5) and the *geminal* methyl group (R^2). A methyl group *cis* to the chirality center (R^4) causes a high *threo* preference (88:12) due to 1,3-allylic strain ($A^{1,3}$ strain), as demonstrated for the derivative **5j** (entry 5). Stereochemical probes such as the derivatives **5k,m**, which bear methyl groups in the *cis* and geminal positions and provide both $A^{1,2}$ and $A^{1,3}$ strains in one and the same molecule, give the *threo* and *erythro* epoxy alcohols in equal amounts for **5k** (entry 6) or a slight *threo* preference for **5m** (entry 8). The derivatives **5g,i** without any allylic strain exhibit also poor diastereoselectivities (entries 2 and 4). The *erythro* preference may be enhanced by the sterically more demanding R^5 = *t*-Bu substituent, as exemplified by the allylic alcohol **5n**, for which the higher $A^{1,2}$ strain provides essentially exclusively the *erythro* epoxy alcohol **6n** (entry 9).

In a competition experiment, a 25:75 mixture of ene diol **5a** and the allylic alcohol **5h** were epoxidized by the β-hydroperoxy alcohol **2** under titanium catalysis (Scheme 4). After 5 min, a conversion of 17% was observed in a 81:19 ratio of products **6a** and **6h**. The ene diol **5a** with exactly the same substitution pattern as the allylic alcohol **5h** (except for the additional hydroxy group) is epoxidized more than 10 times faster.

Discussion

The results presented above demonstrate that the diastereoselectivity of the titanium-catalyzed epoxidation of ene diols by β-hydroperoxy alcohols is controlled by the multidentate ligation of the oxygen acceptor (ene diol) and oxygen donor (β-hydroperoxy alcohol). The ad-

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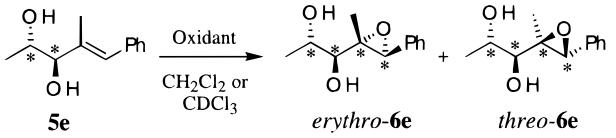
Table 2. Epoxidation of the Enantiomerically Pure Ene Diol 5e



entry[a]	oxidant compd	oxidant equiv	time (h)	yield (%)	mb (%)	dr *erythro*:*threo*
1	DMD[b]	1.10	1	≥95[c]	*d*	23:77
2	*m*CPBA[e]	1.10	1	≥95[c]	*d*	40:60
3	**1**, Ti(O-*i*-Pr)$_4$	1.31	1	91[f]	91	≥95:05[g]
4	**2**, Ti(O-*i*-Pr)$_4$	1.31	0.5	≥95[c]	*d*	≥95:05[g]
5	**3**, Ti(O-*i*-Pr)$_4$	1.00	0.75	89[h,i]	89	≥95:05[g]
6	**3**, Ti(O-*i*-Pr)$_4$	1.40	0.5	≥95[c]	*d*	≥95:05[g]
7	**3**, Ti(O-*i*-Pr)$_4$	>2.0[j]	0.75	>90[h]	90	≥95:05[g]

[a] Carried out at room temperature (ca. 20 °C); for the epoxidation with a β-hydroperoxy alcohol, Ti(O*i*Pr)$_4$ (0.05 equiv) was added as catalyst; conversion was always complete, except entry 6 (93%). [b] In acetone. [c] No other product was detected in the ^{1}H NMR spectrum of the crude reaction mixture. [d] NMR experiments, for which the mass balance was not determined. [e] Buffered with $NaHCO_3$. [f] Yield of isolated material. [g] Only one diastereomer was detected by ^{1}H NMR analysis. [h] The epoxy diol could not be separated from the diol (reduced hydroperoxy alcohol); the yield was determined by ^{1}H NMR analysis of the mixture. [i] Based on 93% conversion. [j] The reisolated excess β-hydroperoxy alcohol and the diol derived from the oxygen donor were both racemic mixtures (HPLC on chiral column).

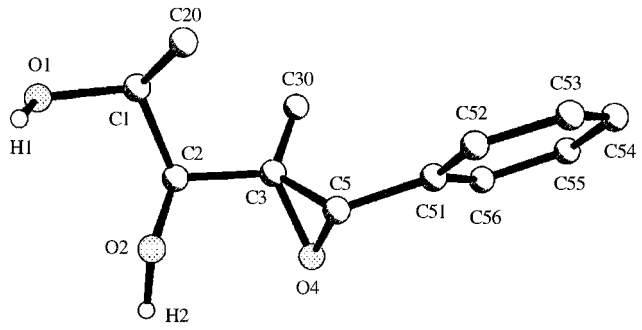


Figure 1. ORTEP structure of [[2α(*R*),3β]-1*S*,2*S*]-1-(2-methyl-3-phenyloxiranyl)-1,2-propanediol (**6e**).

ditional oxygen−titanium bonds form the very rigid transition state for the oxygen transfer proposed in the active *loaded* complex **A** (Scheme 5). Since all known titanium complexes with diols are at least dimeric,[14] presumably also in the template **A** a second titanium atom should be incorporated to achieve the octahedral coordination sphere around the central titanium atom through such a binuclear complex. An additional regulation derives from the inherent stereoelectronic control of the S_N2-type mechanism in the oxygen transfer process, which has been suggested for titanium-activated peroxides.[5] Hereby the π double bond attacks nucleophilically the oxygen atom to be transferred along the axis of the activated peroxide bond in the titanium template. By means of this *loaded* complex **A**, all experimental observations reported herein may be explained in terms of reactivity (items a−e) and diastereoselectivity (items f−j), as discussed below.

Reactivity

(a) The tridentate β-hydroperoxy alcohol, unlike the bidentate *tert*-butyl hydroperoxide oxygen donor, exchanges efficiently the bidentate ene diol substrate and the tridentate epoxy diol product to replenish the active loaded complex **A** in the catalytic cycle. Under the usual conditions, i.e. small amounts (<10 mol %) of titanium catalyst and large quantities of oxygen donor and substrate (both ca. equimolar), at the early stage of the reaction, the catalyst is tied up in the form of complex **C** (Scheme 5) through most effective coordination of the bidentate ene diol substrate. To generate the active loaded complex **A** from **C**, the tridentate oxygen donor (β-hydroperoxy alcohol) displaces one of the bidentate ene diol molecules and activation followed by oxygen transfer generates by way of **A** the inactive complex **B**, wherein the tridentate epoxy diol product and the bidentate diol derived from the β-hydroperoxy alcohol are bound. As the oxidation proceeds, complex **B** accumulates, and at the latter stages, the epoxy diol as well as oxygen-donor-derived diol are exchanged efficiently by fresh ene diol and β-hydroperoxy alcohol molecules to regenerate the active *loaded* titanium complex **A**. The oxygen transfer proceeds smoothly because the efficacy of the catalytic cycle is assured.

(b) For the bidentate *tert*-butyl hydroperoxide oxygen donor, the corresponding loaded complex **D** required for the epoxidation of ene diols is not efficiently produced from the inactive complex **C** and the latter constitutes a dead end, i.e. catalyst poisoning. In contrast to the tridentate β-hydroperoxy alcohol, the bidentate *t*-BuOOH displaces the titanium-bound ene diol substrate from the initial complex **C** only with difficulty due to less efficient coordination. As the *t*-BuOOH molecule displaces one

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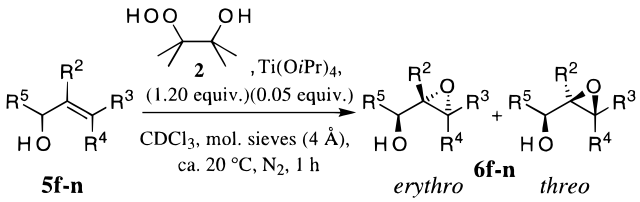
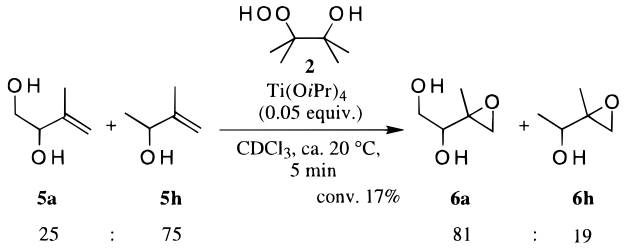
Table 3. Titanium-Catalyzed Epoxidation of Acyclic Allylic Alcohols 5f−o by the β-Hydroperoxy Alcohol 2



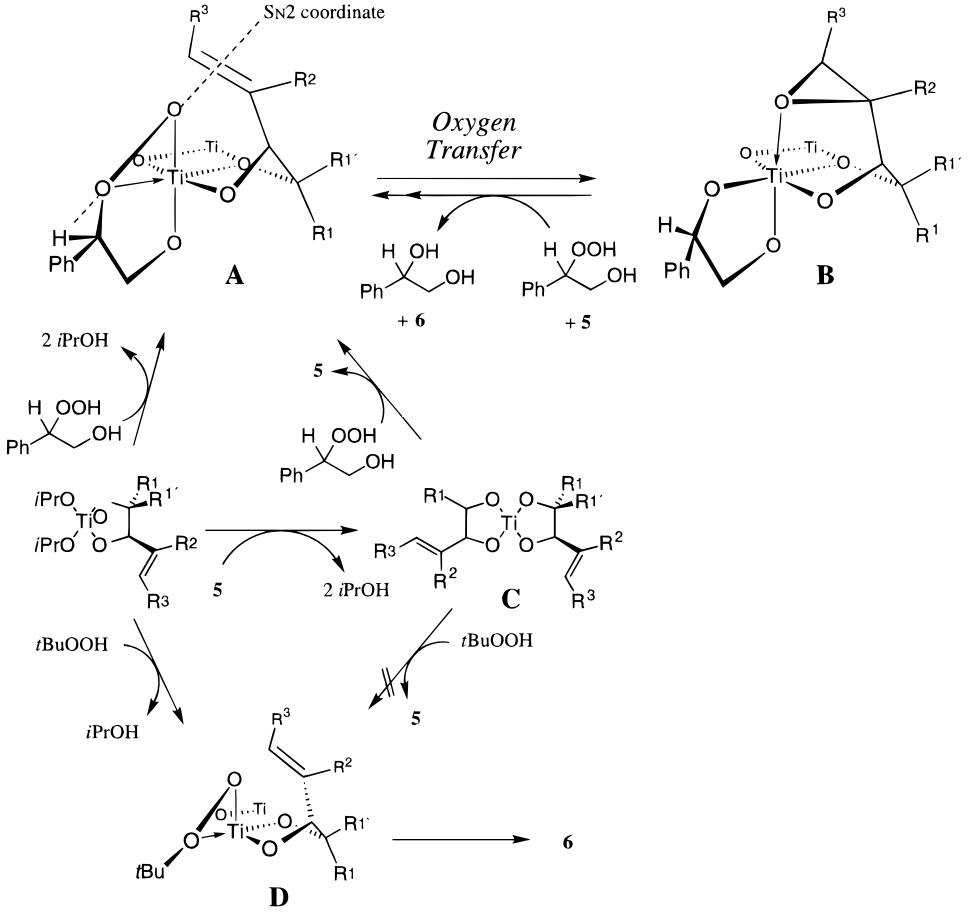
entry	compd	R^2	R^3	R^4	R^5	convn (%)	yield[a] (%)	dr[b] *erythro*:*threo*
1	**5f**	H	Me	Me	H	>95	>95	
2	**5g**	H	H	H	Me	22	>95	56:44
3	**5h**	Me	H	H	Me	90	>95	81:19
4	**5i**	H	Me	H	Me	74	>95	36:64
5	**5j**	H	H	Me	Me	48	>95	12:88
6	**5k**	Me	H	Me	Me	77	>95	50:50
7	**5l**	H	Me	Me	Me	>95	>95	13:87
8	**5m**	Me	Me	Me	Me	>95	>95	30:70
9	**5n**	Me	H	H	*t*-Bu	65	>95	96:04

[a] Based on converted material. [b] Diastereomeric ratio, determined by ^{1}H NMR analysis on the crude reaction mixture; error ±5% of the stated values.

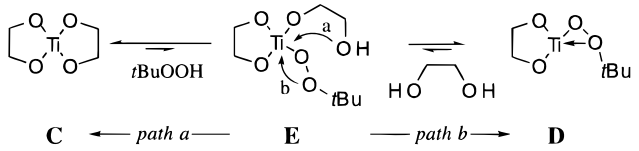
Scheme 4. Competition Experiment between the Ene Diol 5a and Allylic Alcohol 5h in the Titanium-Catalyzed Epoxidation by β-Hydroperoxy Alcohol 2



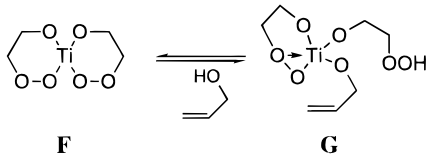
Scheme 5. Ligand Exchange Processes for Bi-(*t*-BuOOH) and Tridentate (*β*-Hydroperoxy Alcohol) Oxygen Donors in the Generation of *Loaded* Titanium Templates A and D Required for Oxygen Transfer



Scheme 6. Generation of the Loaded Complex D from C by Stepwise Replacement of One of the Ene Diol Ligands by the Bidentate *tert*-Butyl Hydroperoxide



Scheme 7. Generation of the Loaded Complex G from F in the Epoxidation of Monodentate Allylic Alcohols by Tridentate Hydroperoxy Alcohols as Oxygen Donor



hydroxy group of the ene diol in the complex **C** to yield **E** (Scheme 6), the activation of the peroxide bond (path b) through coordination to the titanium center competes unfavorably with the ene diol to regenerate the inactive complex **C** (path a). Clearly, the Ti−O bond with the ene diol (path a) is much stronger than the peroxide activation through donative ligation (path b). Thus, since only small amounts (ca. 5 mol %) of the Ti(O-*i*-Pr)$_4$ catalyst are used and the equilibrium is displaced far to the side of the inactive complex **C** (Scheme 6), the concentration of the active *loaded* complex **D** is very low and the oxygen transfer cannot get started. This unfavorable situation is expected to become worse should, indeed, some epoxidation have occurred because the resulting tridentate epoxy diol product would be still more tightly bound to the Ti catalyst and encumber even more effectively exchange with the *t*-BuOOH to regenerate the loaded complex **D**. Consequently, the inactive complex **C** plays the role of efficient poisoning of the Ti(O-*i*-Pr)$_4$ catalyst! This explains why bidentate ene diols cannot be epoxidized by bidentate hydroperoxides such as *t*-BuOOH under catalytic Sharpless conditions.

(c) Monodentate allylic alcohols are efficiently epoxidized by tridentate *β*-hydroperoxy alcohols. In contrast to the lack of epoxidation of the bidentate ene diols by the bidentate oxygen donor *t*-BuOOH, monodentate allylic alcohols may be transformed to the corresponding epoxy alcohols by the tridentate *β*-hydroperoxy alcohols. In this case, the small amount of the titanium catalyst is tied up by the tridentate oxygen donor in the form of complex **F** (Scheme 7), which may be activated without any problems. Attachment of a monodentate allylic alcohol substrate molecule through a Ti−O bond to generate the corresponding loaded complex **G** does not require complete replacement of one of the tridentate hydroperoxy alcohol molecules in complex **F**, but merely opening of the titanium heterocycle. Uncertain is whether the Ti−O or the Ti−OO bond is displaced by the allylic alcohol substrate, but activation and oxygen transfer would be expected to proceed readily in the loaded complex **G** to afford the epoxy alcohol product.

(d) The homoallylic hydroxy group of the ene diol enhances the reaction rate. The competition experiment in Scheme 4 shows that the ene diol **5a** is epoxidized 10

times faster than the allylic alcohol **5h** with the same substitution pattern at the double bond. This clearly demonstrates the assistance of the homoallylic hydroxy group in the ene diol substrate **5a** to replace multidentate ligands through coordination to the active titanium site. Thereby an efficient catalytic cycle between the complexes **A** and **B** is sustained (Scheme 5). However, for the allylic alcohol **5h**, the Ti complex **F** (Scheme 7) with two tridentate β-hydroperoxy alcohol molecules accumulates. As discussed under item c, oxygen transfer can proceed, but not as effectively because the corresponding loaded complex **G** is generated slower.

(e) A higher temperature is required for an effective ligand exchange. Due to the stronger binding of the multidentate epoxy diol product and the diol derived from the β-hydroperoxy alcohol oxygen donor in the titanium complex **B** (Scheme 5), a higher reaction temperature is required for the effective regeneration of the *loaded* complex **A** through faster ligand exchange. Thus, the oxygen transfer is rather slow (ca. 17 h) at −25 °C (Table 1, entry 11), but may be substantially accelerated (ca. 0.5 h) by increasing the reaction temperature to 23 °C (Table 1, entry 9). The practical advantage is that these epoxidations may be performed conveniently at ambient temperatures.

Diastereoselectivity

(f) The epoxy diols **6a**−**e** are obtained in high to excellent *erythro* diastereoselectivity in the titanium-catalyzed epoxidation of ene diols **5a**−**e** by β-hydroperoxy alcohols **1**−**4**. All ene diols **5a**−**e** are epoxidized highly *erythro*-diastereoselectively (Tables 1 and 2) without any marked influence on the diastereomeric ratio by the substituents in the ene diol. Comparison of all the diastereomeric ratios in Tables 1 and 2 reveals no clear-cut trends, but it should be kept in mind that the variation in the diastereomeric ratio (dr) values (Table 1) is quite small, i.e. from ca. 80:20 (entries 3 and 19) to a high of ca. 95:5 (entries 13 and 16). The low dr values pertain to the ene diol derivatives **5a,d** with the β-hydroperoxy alcohol **3**, the only oxygen donor with a secondary hydroperoxy functionality (Table 1, entries 3 and 19). It seems that for sterically less encumbered ene diol substrates such as **5a,d** (R^1 or R^2 = H), a greater steric demand is placed on the oxygen donor for high diastereomeric control. The latter control derives from the very rigid transition state formed by the various Ti−O bonds, as portrayed in the loaded complex **A** (Scheme 5). The substituents of the ene diol do not interfere with the approach of the double bond along a straight line through the activated O−O bond. Thus, essentially irrespective of the substitution pattern of the ene diol, the *erythro* epoxy diol is the favored product.

(g) The *erythro* and *threo* configurations in the diol substrates do not effect the diastereoselectivity. It makes no difference for the diastereomeric ratios whether the *threo* diol, as in the case of the ene diols **5b**−**d** (Table 1, entries 6−21), or the *erythro* diastereomer, namely derivative **5e** (Table 2, entries 3−8), are employed. In both cases the epoxidations are highly *erythro* selective. Again, this may be readily rationalized in terms of the proposed transition state for the oxygen transfer in the loaded complex **A** (Scheme 5). Neither in the *erythro* ($R^{1\prime} \neq$ H, R^1 = H) nor in the *threo* ($R^{1\prime}$ = H, $R^1 \neq$ H) isomer are both substituents R^1 and $R^{1\prime}$ of the chiral homoallylic functionality close enough to the reaction center to exercise steric interactions on the transition state geometry of the oxygen transfer.

(h) The diastereoselectivity observed in the epoxidation of the simple allylic alcohols **5g**−**n** is controlled by allylic strain. In substrates without a homoallylic hydroxy group, i.e. the chiral allylic alcohols **5g**−**n** (Table 3, entries 2−9), the diastereomeric control is dictated by the allylic strain ($A^{1,2}$ and $A^{1,3}$) and the dihedral angle (C=C−C−O) of the substrate in the corresponding loaded complex **G** (Scheme 7), rather than the geometrical effects as presented for ene diols in the loaded complex **A**.[13] A substituent (R^2) at the double bond geminal to the chirality center provides 1,2-allylic strain, as in derivative **5h** (Table 3, enry 3), and the *erythro* epoxy alcohol is the preferred product in moderate (81:19) diastereoselectivity. In contrast to the typical case with pronounced $A^{1,2}$ strain sensitivity, namely the TBHP/VO(acac)$_2$ oxidant, for which the *erythro*-**6h** is observed essentially exclusively,[2b,15] in the present titanium-catalyzed epoxidation of **5h** as much as 20% of the *threo* isomer are obtained. Clearly, the C=C−C−O dihedral angle in the transition state for the Ti-catalyzed oxygen transfer is larger than that established for the vanadium case (ca. 50°).[13,15] Indeed, additional evidence for this is provided by the stereochemical probe **5k** with both $A^{1,2}$ and $A^{1,3}$ strain,[13] for which a dr value of 50:50 was obtained (Table 3, entry 6). This lack of diastereoselectivity expresses that $A^{1,2}$ and $A^{1,3}$ strain compete, which suggests that the dihedral angle is definitely larger than 50° ($A^{1,2}$ strain dominates) but smaller than 120° ($A^{1,3}$ strain prevails). The latter applies for substrates **5j**,**l** (Table 3, entries 5 and 7), for which the expected *threo* selectivity is observed. For a substrate with a larger R^5 substituent at the chirality center, i.e. *tert*-butyl as in the case of the allylic alcohol **5n**, essentially exclusive *erythro* diastereoselectivity (entry 9, Table 3) may be achieved through the control by the $A^{1,2}$ strain.

(i) The additional coordination in the titanium template with the homoallylic hydroxy group of the ene diols guarantees high diastereomeric control. In the previous item h we have seen that a sterically more demanding R^5 substituent (*t*-Bu *versus* Me) in the allylic alcohols **5h**,**n** (Table 3, entries 3 and 9) increases the diastereomeric ratio significantly through $A^{1,2}$ strain. Hence, it is tempting to explain the higher diastereomeric ratios for the ene diols **5b**,**c** compared to the correspondingly substituted allylic alcohols **5h**,**n** similarly in terms of the $A^{1,2}$ strain caused by the 1-hydroxyethyl and phenylhydroxymethyl groups in the ene diols **5b** (Table 1, entries 6−11) and **5c** (Table 1, entries 12−16). However, if $A^{1,2}$ strain were important in controlling the high *erythro* selectivity, the ene diol **5d** without the $A^{1,2}$ strain should display a much lower *erythro* selectivity than substrates **5b**,**c**, but the experimental results unequivocally demonstrate essentially equal diastereoselectivities toward the β-hydroperoxy alcohol **2**, for example entries 7, 13, and 18 (Table 1). Moreover, comparison of the (*E*)-configurated ene diol **5d** (Table 1, entry 18) with the (*E*)-configurated allylic alcohol **5i** (Table 3, entry 4), the former exhibits a high *erythro* and the latter even a slight *threo* preference. Undoubtly, the observed high *erythro*

(15) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(16) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

diastereoselectivity for the ene diols must be attributed to the additional coordinating effects exercised by the homoallylic hydroxy group as portrayed in the loaded complex **A** (Scheme 5). In this arrangement, the ligated ene diol possesses an U-shaped conformation during the oxygen transfer and the oxygen atom to be transferred approaches from the same side of the allylic oxygen functionality to afford the *erythro* product.

(j) The substituents of the β-hydroperoxy alcohol have no influence on the diastereoselectivity of the oxygen transfer. In the epoxidation of a racemic substrate with a racemic oxygen donor, for example ene diol **5c** with β-hydroperoxy alcohol **3** (Table 1, entry 14), two diastereomeric pairs of enantiomeric transition states are possible. For the enantiomerically pure ene diol **5e** as substrate with the racemic β-hydroperoxy alcohol **3** (Table 2, entry 5) as oxygen donor, the epoxidation may preferably traverse one of the two diastereomeric transition states for steric reasons due to the different substituents H *versus* Ph at the chirality center in the oxidant **3**. Thus, one of these diastereomeric combinations may be expected to be better matched in the transition state for the oxygen transfer (cf. complex **A**, Scheme 5), and kinetic resolution of the oxygen donor should be observed. The experimental facts are that the reisolated β-hydroperoxy alcohol **3**, as well as the diol derived from the oxygen donor during the reaction, do not show any optical activity (Table 2, entry 7, footnote *j*). This establishes unequivocally that the substitution pattern in the hydroperoxy alcohol does not express any steric preferences to differentiate the diastereomeric transition states of the oxygen transfer. Indeed, inspection of the loaded complex **A** (Scheme 5) reveals that these substituents point away from the reaction center and are, therefore, without influence. Consequently, it seems unlikely to resolve a racemic substrate kinetically with optically active β-hydroperoxy alcohols as oxygen donors.

In summary, we have presented a highly *erythro*-selective catalytic epoxidation of ene diols. Advantageous for practical purposes is the fact that the reaction may be conducted at ambient temperature (ca. 20 °C) and in short reaction times (ca. 30 min). The stereocontrol in the oxygen transfer is imposed by the rigid titanium-centered template held together by the various Ti−O bonds, in which the substitution pattern of the oxygen donor (β-hydroperoxy alcohol) as well as of the oxygen acceptor (ene diol) play a negligible role. When an enantiomerically pure ene diol is employed as substrate, the epoxy diol product is obtained enantiomerically and diastereomerically pure, which offers for the first time a convenient access to such valuable synthetic building blocks in carbohydrate chemistry.

Acknowledgment. The generous financial support of the Deutsche Forschungsgemeinschaft (SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle"), the Bayerische Forschungsstiftung (Bayerischer Forschungsverbund Katalyse—FORKAT), and the Fonds der Chemischen Industrie is gratefully appreciated.

Supporting Information Available: All experimental details (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970110X