Hydroxy Group Directivity in the Epoxidation of Chiral Allylic Alcohols: Control of Diastereoselectivity through Allylic Strain and Hydrogen Bonding

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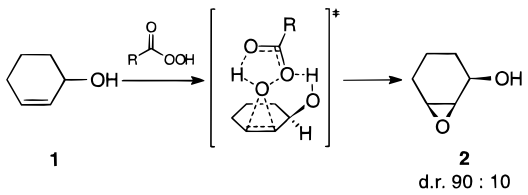
Introduction

The epoxidation of olefins is one of the most valuable reactions in organic synthesis and is even a subject of intensive study today.[1] Particularly, catalytic and stereoselective epoxidations still present a major challenge.[2] The milestones during the past decades in this demanding oxidation chemistry are the Sharpless−Katsuki epoxidation[3] of allylic alcohols and the Jacobsen−Katsuki epoxidation[4] of unfunctionalized olefins. In both cases, the stereoselectivity is controlled by optically active oxidizing species (reagent control). Stereoselectivity may also be controlled by substituents at stereogenic centers of chiral substrates (substrate control). The important requirements in the latter case are the conformational constraints on the chiral substrate and an efficient interaction (electronic, steric) with the reagent to facilitate preferential attack of one of the diastereotopic faces of the substrate.

Already in 1957 Henbest[5] observed this synergistic interplay between conformational control and substrate−reagent interaction through hydrogen bonding in the highly diastereoselective peracid epoxidation of cyclic allylic alcohols (eq 1). This valuable concept has been extensively applied in organic synthesis over the years; however, the development of selective epoxidation requires a detailed knowledge of the transition-state structure for the oxygen-transfer process. Computational chemistry has been helpful in this context, and significant



1 **2**
d.r. 90 : 10

(1)

progress has been made in the past few years; nevertheless, reliable experimental data are mandatory to assess the validity of such theoretical constructs. The purpose of this Account is to illustrate that the hydroxy group directivity offers such experimental data (diastereo- and regioselectivity) to assess approximate geometries of transition states for the oxyfunctionalization and therewith provide the essential mechanistic information.

While conformational rigidity is an inherent feature of cyclic systems, such constraints do not apply to acyclic ones. Nevertheless, the efficacy of allylic strain (^{1,2}A and ^{1,3}A stand for 1,2- and 1,3-allylic strain) provides the necessary differentiation between the diastereotopic π faces in chiral acyclic substrates (Figure 1).[6a] Steric repulsion, as documented by ab initio calculations,[7] is responsible for the discrimination in energy between the possible conformers of the acyclic alkene **3a**, for which a dihedral angle α (C=C−C−X) of $\pm 120°$ applies due to the operating ^{1,3}A strain. The conformer in which the allylic hydrogen atom points toward the *cis*-methyl group ($\alpha = +120°$) is favored by more than 4 kcal/mol. In alkene **3b** with a *cis*-hydrogen atom, the corresponding conformers are almost equal in energy. Similarly, in alkene **3c** (R = CH_3), ^{1,2}A strain manifests itself. The conformer with the allylic methyl substituent interacts sterically with the geminal methyl group ($\alpha = +70°$) and is disfavored by ca. 2.4 kcal/mol. In contrast, for alkene **3b** (R = H), expectedly the corresponding conformers possess almost the same energy.

The concept of allylic strain implies that, through the proper choice of *gem* (^{1,2}A strain) and *cis* (^{1,3}A strain) substituents at the double bond of acyclic chiral alcohols, optimal dihedral angles α (C=C−C−OH) may be selected to test the preferred geometry of the substrate−oxidant encounter complex. From the resulting diastereoselectivities, the transition-state structure may be assessed. The premise[7] for such an empirical analysis is that the differences in conformer energies of the ground-state reactants reflect the differences in the respective conformations of the transition states.

Recently, we have investigated the diastereoselective epoxidation[8−12] with stoichiometric and catalytic oxidants and the photooxygenation[13−16] of chiral acyclic allylic alcohols, which serve as a powerful mechanistic tool to map the transition-state geometries of such oxyfunctionalizations. Since to date this aspect of diastereoselectivity has only been fragmentarily covered in recent reviews,[6,17a] presently we fill this gap by compiling the recent progress in this area. We illustrate that the hydroxy group directiv-

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Thomas Wirth, born in 1970 in Germany, commenced his chemistry studies in 1990 at the University of Würzburg and joined Professor Adam's group in 1995 (Diplom 1995, Dr. rer. nat. 1998). His doctoral work was concerned with the diastereoselective singlet oxygen ene and [4+2] cycloaddition reactions.

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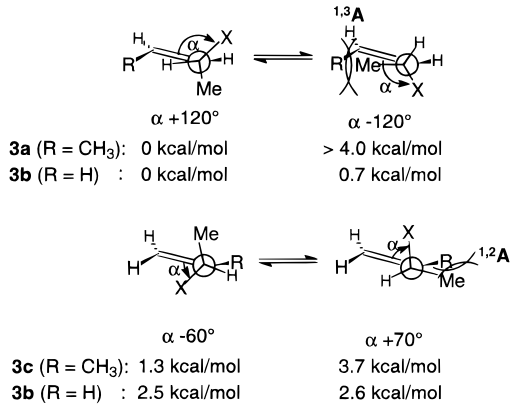
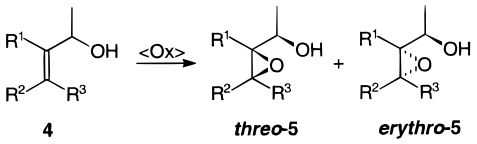


FIGURE 1. Relative ab initio energies (MP2/6-32G*) of selected rotamers for the olefins **3** (X = Me), ref 14.

ity, i.e., the composite action of hydrogen bonding between the allylic hydroxyl group and the oxidant and the allylic strain in chiral allylic alcohols, is essential to achieve the high diastereoselectivities demanded in synthesis.

Epoxidations of Methyl-Substituted Chiral Allylic Alcohols

Chiral allylic alcohols with bulky substituents, e.g., trialkylsilyl or *tert*-butyl groups at the *cis* and *gem* positions,[9b,18,19] have been widely used to demonstrate the efficacy of allylic strain for diastereoselective control in epoxidations.[6] That such massive steric obstructors are not essential is displayed by the appropriately methyl-substituted chiral allylic alcohols **4**. More significant for mechanistic purposes, the observed *threo*/*erythro* diastereoselectivities (eq 2, Table 1) make available the



(2)

characteristic stereochemical information to define the substrate−oxidant association in the activated complex and the structure of the transition state for the oxyfunctionalization. Stereoelectronic factors, e.g., backside attack of the alkene π system along the axis of the O−O bond that is broken (S_N2 trajectory),[17] as well as the electronic nature of the substrate−epoxidant interaction define the favored geometry of the oxygen-transfer process.

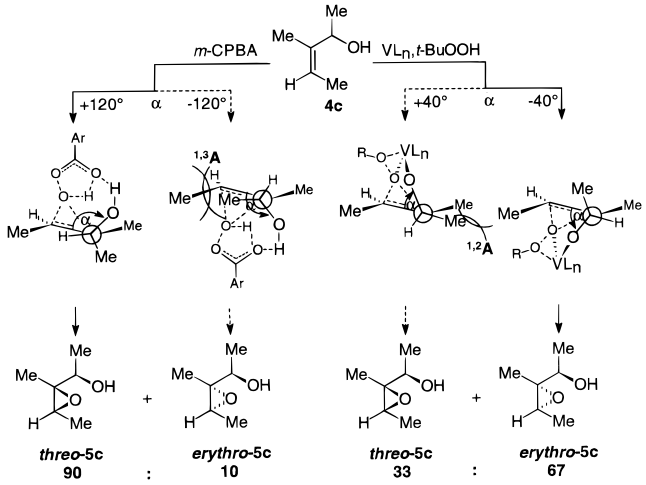
A demonstrative example constitutes our stereochemical probe 3-methylpent-3-en-2-ol (**4c**),[13b] the first substrate ever used in which ^{1,2}A and ^{1,3}A strains compete with each other in the same molecule (Scheme 1). The epoxidation by *m*-chloroperbenzoic acid (*m*-CPBA) affords the *threo* epoxy alcohol **5c** preferentially (Table 1, entry 6), while the VO(acac)$_2$/*t*-BuOOH epoxidation (entry 1) displays moderate *erythro* selectivity. For the peracid oxidant, the allylic alcohol associates by hydrogen bonding with an estimated dihedral angle α of ±120°.[17] Of the two possible conformations, minimization of ^{1,3}A strain dictates the energetically favored *threo* transition-state geometry with an α of ca. +120°.[17] ^{1,2}A strain is essentially

Table 1. Diastereomeric Ratios for the Epoxidation of Chiral Allylic Alcohols 4 by Selected Oxidants

			threo / *erythro* diastereoselectivity				
							
entry	oxidant	solvent	**4a**	**4b**	**4c**	**4d**	**4e**
1	VO(acac)$_2$ [a] *t*-BuOOH	C_6H_6	05 : 95	71 : 29	33 : 67 [b]	10 : 90 [c]	86 : 14
2	Mo(CO)$_6$ [d] *t*-BuOOH	CH_2Cl_2	16 : 84	84 : 16	77 : 23 [c]	29 : 71 [c]	95 : 05
3	Ti(O-*i*-Pr)$_4$ [f] *t*-BuOOH	CH_2Cl_2	22 : 78	91 : 09	83 : 17	24 : 76 [e]	95 : 05
4	Mn(salen)PF$_6$ [g] PhIO	CH_2Cl_2	48 : 52	89 : 11	81 : 19	61 : 39	91 : 09
5	Fe(TDCPP)Cl [h] PhIO	CH_2Cl_2	42 : 58	89 : 11	81 : 19	70 : 30	84 : 16
6	*m*-CPBA [i]	CH_2Cl_2	45 : 55	95 : 05	90 : 10 [b]	48 : 52 [e]	95 : 05
7	DMD [j]	acetone	57 : 43	67 : 33	87 : 13	51 : 49 [e]	76 : 24
8	MTO [k] UHP	$CDCl_3$	50 : 50	82 : 18	91 : 09	56 : 44 [c]	83 : 17
9	HFAH H_2O_2 [l]	$CDCl_3$	61 : 39	91 : 09	95 : 05	62 : 38	95 : 05
10	TS-1 [f] UHP	acetone	50 : 50	87 : 13	81 : 19	---	95 : 05
11	Ti-beta [f] H_2O_2	CH_3CN	56 : 44	91 : 09	89 : 11	---	95 : 05

[a] Reference 17. [b] Reference 13b. [c] Reference 10b. [d] Reference 17. [e] Reference 10c. [f] Reference 9. [g] Reference 11, salen = salicylideneethylenediamine. [h] Reference 11, TDCPP = tetrakis(dichlorophenyl)porphine. [i] Reference 17. [j] Reference 8a. [k] Reference 10a, UHP = urea hydrogen peroxide adduct. [l] Reference 12, HFAH = hexafluoroacetone hydrate.

Scheme 1. Discrimination between the Diastereomorphic Transition States in the Epoxidation of the Chiral Allylic Alcohol 4c with a Peracid (Optimal α = ±120°) and a Vanadium (Optimal α = ±40°) Catalyst by Means of 1,2- or 1,3-Allylic Strain



negligible for the *m*-CPBA oxidant because it becomes effective in discriminating the diastereotopic π faces for acute α angles with a maximum at ±60−70°.[7] In contrast, for the vanadium oxidant, metal−alcoholate binding between the allylic oxygen atom and the metal center favors a dihedral angle α of ca. ±40°[17] for effective oxygen atom transfer, and the preferred *erythro* diastereoselectivity is governed by ^{1,2}A strain.

These two mechanistically distinctive epoxidants, namely, *m*-CPBA (hydrogen bonding) versus VO(acac)$_2$/*t*-BuOOH (metal−alcoholate binding), convincingly illustrate that the diastereoselectivity in the epoxidation of

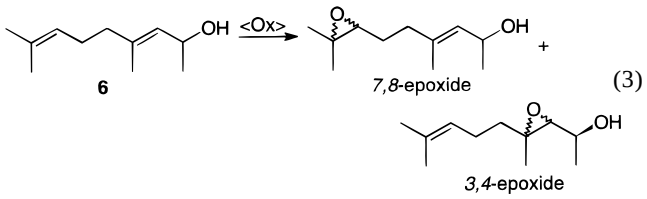
Table 2. Regio- and Diastereoselective Epoxidation of 1-Methylgeraniol (6)[a]

			selectivity	
entry	oxidant	solvent	regio 7,8/3,4	diastereo *threo/erythro*
1	$VO(acac)_2$/TBHP	CH_2Cl_2	<05:95	89:11
2	$Ti(O\text{-}i\text{-}Pr)_4$/TBHP	CH_2Cl_2	<05:95	98:02
3	$Mn(salen)PF_6$/PhIO[b]	CH_2Cl_2	53:47	94:06
4	Fe(TDCPP)Cl/PhIO[b]	CH_2Cl_2	73:27	88:12
5	DMD	MeOH/acetone (9:1)	95:05	76:24
6		acetone	84:16	84:16
7		CCl_4	32:68	94:06
8	*m*-CPBA	[D_4]MeOH/ [D_6]acetone	45:55	90:10
9		[D_6]acetone	46:54	89:11
10		CCl_4	51:49	90:10
11	MTO/UHP	MeOH/acetone (9:1)	81:19	75:25
12		acetone	80:20	87:13
13		CCl_4	76:24	88:12
14	HFAH/H_2O_2[c]	CH_2Cl_2	52:48	96:04

[a] Reference 8c. [b] Reference 11. [c] Reference 12.

the allylic alcohol **4c** serves as an effective mechanistic diagnostic means to assess structural details of the transition state of oxygen transfer. Consequently, when applied to a new oxidant whose mechanism of oxygen transfer is not known, comparison of its diastereoselectivity for the stereochemical probe **4c** with those of *m*-CPBA and $VO(acac)_2$/*t*-BuOOH as reference systems should allow, on one hand, the determination of whether hydrogen bonding (*threo* diastereoselectivity, ^{1,3}A strain) or metal–alcoholate binding (*erythro* diastereoselectivity, ^{1,2}A strain) operates and, on the other hand, the estimation of the likely dihedral angle α in the transition state for oxygen transfer.

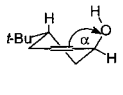
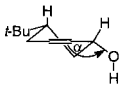
The diastereoselectivities of the various oxidants in Table 1 for the epoxidation of the chiral allylic alcohols **4** shall now be analyzed to acquire structural information on the transition states. For the purpose of providing a more elaborate mechanistic fingerprinting, we have included the chiral allylic alcohols **4a**,**d** (only ^{1,2}A strain) and the derivatives **4b**,**e** (only ^{1,3}A strain), in addition to the already presented stereochemical probe **4c** (both ^{1,2}A and ^{1,3}A strain). Furthermore, the chiral geraniol derivative **6** (eq 3), our newest mechanistic tool,[8c] serves the double



(3)

purpose of acquiring simultaneously in the same substrate regioselectivity and diastereoselectivity data of the oxygen-transfer process for the oxidants in Table 2. The oxidants cover homogeneous metal-catalyzed systems of the peroxy type [$VO(acac)_2$, $Mo(CO)_6$, and $Ti(O\text{-}i\text{-}Pr)_4$ with *t*-BuOOH], the peroxo type (MTO/UHP [20]), and the oxo type [Mn(salen)/PhIO,[2] Fe(TDCPP)/PhIO], as well as the nonmetal peroxides *m*-CPBA and DMD as stoichiometric oxidants. To define more accurately the dihedral angle α, the

Table 3. Diastereoselectivities in the Epoxidation of Conformationally Fixed Cyclohexenols 7

			syn /anti diastereoselectivity	
				
entry	oxidant	solvent	*trans*-**7** α = 110° [a]	*cis*-**7** α = 140° [a]
1	*m*-CPBA [b]	CH_2Cl_2	90 : 10	98 : 02
2	DMD [c]	acetone/CCl_4 (1:9)	58 : 42	82 : 18
3		acetone	30 : 70	60 : 40
4	MTO/UHP [d]	$CDCl_3$	72 : 28	84 : 16
5		CD_3OD	15 : 85	50 : 50
6	HFAH/H_2O_2 [e]	$CDCl_3$	70 : 30	94 : 06

[a] Determined by AM1 caculations, ref 8a. [b] Reference 19b. [c] Reference 8a. [d] Reference 10c. [e] References 12.

conformationally fixed *cis*- and *trans*-cyclohexenols **7**[19b,21] have been employed for a selected set of oxidants which operate through hydrogen bonding (Table 3).

Metal–Alcoholate Binding (40° < α < 90°). $VO(acac)_2$, $Ti(O\text{-}i\text{-}Pr)_4$, and $Mo(CO)_6$ Activation of *t*-BuOOH (Peroxy Complexes). The preferred transition-state model for the epoxidation of allylic alcohols by metal-activated hydroperoxide incorporates the following two mechanistic features: (a) The oxygen donor (*t*-BuOOH) and oxygen acceptor (allylic alcohol) are bound to the metal center through metal–oxygen bonds (experimental evidence for such a metal template rests on the fact that unfunctionalized alkenes react by 2 orders of magnitude slower than allylic alcohols[17a]); this kinetic preference is dramatically expressed in the regioselectivities (eq 3, Table 2, entries 1 and 2) observed for 1-methylgeraniol (**6**), for which exclusively the allylic alcohol functionality is epoxidized.[8c] (b) The π nucleophile (double bond) attacks the oxygen atom to be transferred along an S_N2 trajectory (structures **A**‡ and **B**‡, Figure 2), a stereoelectronic requisite.[17b]

For $VO(acac)_2$/*t*-BuOOH, a dihedral angle α of ±40–50° has been estimated to be the optimal geometric arrangement for the oxygen transfer to fulfill the above mechanistic features.[6,17] In terms of diastereoselectivity, this is expressed in a high preference for the *erythro* isomer as a response to the dominance of ^{1,2}A strain, as displayed by the allylic alcohols **4a** and **4d** (Table 1, entry 1). The stereochemical probe **4c** with competing ^{1,2}A and ^{1,3}A strain also favors the *erythro* product, and thus, ^{1,2}A strain dominates.

In the case of the $Ti(O\text{-}i\text{-}Pr)_4$,/*t*-BuOOH oxidant, the diastereoselectivity data show (Table 1, entry 3) that ^{1,2}A strain cannot compete with the dominance of ^{1,3}A strain in the epoxidation of the allylic alcohol **4c**, although moderate *erythro* selectivity [diastereomeric ratio (dr) = ca. 23:77] is obtained for the ^{1,2}A-strained substrates **4a** and **4d**. The appreciable *threo* selectivity (dr = 83:17) for **4c** is nearly as high as for **4b** and **4e** (dr > 90:10) with only ^{1,3}A strain (Table 1, entry 3). Therefore, the preferred dihedral angle α for the epoxidation by the titanium peroxy complex must lie between those for the vanadium complex and *m*-CPBA (stuctures **A**‡ and **E**‡, Figure 2) to

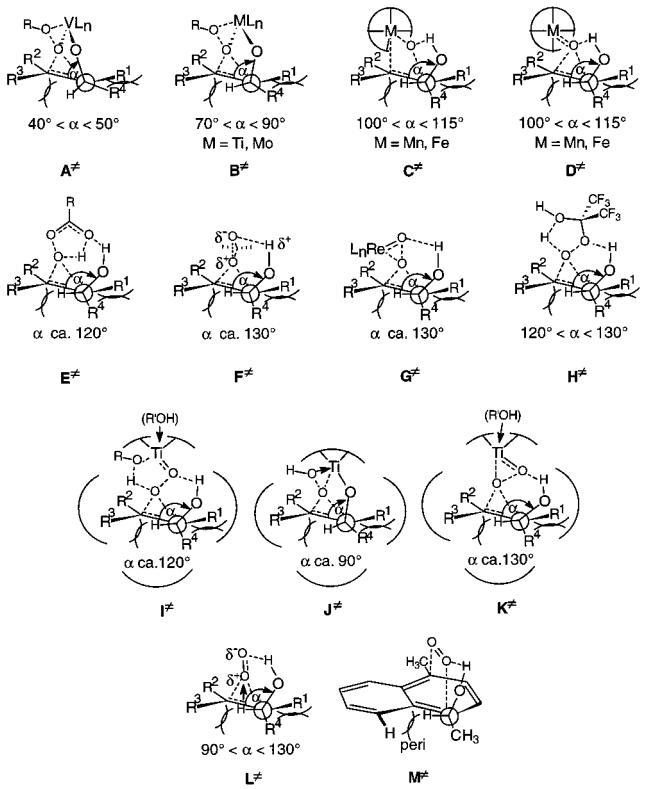
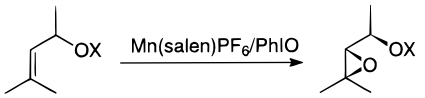


FIGURE 2. Proposed transition-state structures with the optimal dihedral angles α for the oxidation of chiral alcohols by various oxidants.

facilitate the ^{1,3}A-controlled *threo* selectivity of epoxidation. The diastereoselectivities for Ti(O-*i*-Pr)$_4$/*t*-BuOOH and Mo(CO)$_6$/*t*-BuOOH (Table 1, entries 2 and 3) match well within the experimental error (ca. ±5% of the stated values), and for both epoxidants a dihedral angle of 70° < α < 90° is suggested (structure **B**‡, Figure 2). The observed diastereoselectivies for the set of stereolabeled allylic alcohols **4** (Table 1, entries 1−3), as well as the regioselectivities in the epoxidation of 1-methylgeraniol (**6**) (Table 2, entries 1 and 2), provide detailed structural data on the transition state of metal-catalyzed epoxidations which involve peroxy-type complexes as oxidizing species (structures **A**‡ and **B**‡, Figure 2).

Hydrogen Bonding (110° < α < 130°). Mn(salen)/PhIO, Fe(TDCPP)/PhIO, MTO/H_2O_2, DMD, and *m*-CPBA (Oxo and Peroxo Complexes, Peracids). Comparison of the regioselectivities in the epoxidation of 1-methylgeraniol (**6**) of the manganese, iron, and rhenium oxidants (Table 2, entries 3, 4, and 11−13) with those of vanadium and titanium (entries 1 and 2) unequivocally demonstrates that metal−alcoholate binding does not apply for the Mn, Fe, and Re catalysts. Nevertheless, the appreciable amount of the 3,4-epoxide implies a hydroxy-directing effect through hydrogen bonding. Close inspection of the diastereoselectivities in the epoxidations of the allylic alcohols **4** (Table 1, entries 4−8) reveals that ^{1,3}A strain dominates for the oxidants MTO/H_2O_2, Mn(salen)PF_6/PhIO, Fe(TDCPP)Cl/PhIO, DMD, and *m*-CPBA in the steric discrimination between the *threo* versus *erythro* transition states. Thus, the allylic alcohols **4b** and **4e** with a *cis*-methyl substituent (^{1,3}A strain) are epoxidized preferentially *threo*-selectively, whereas the allylic alcohols **4a** and **4d** with a *gem*-methyl group react almost completely unselectively; i.e., the influence of ^{1,2}A strain in stereodifferentiation is negligible. The importance of ^{1,3}A strain for these epoxidants is manifested by the stereochemical probe **4c**, which is epoxidized in all cases highly *threo*-selectively.

From the observed diastereoselectivities for *m*-CPBA (Table 1, entry 6), Sharpless[17a] concluded a dihedral angle α of ca. 120° in the transition state of the oxygen-transfer process (structure **E**‡, Figure 2), for which the generally accepted "butterfly mechanism" applies.[17,22] A hydrogen bond between the allylic hydroxy group and the peracid in the transition state, already established in Henbest's pioneering work[5] on cyclic allylic alcohols and substantiated by kinetic studies,[21] is the geometry-determining feature for this epoxidation. Analysis of the diastereoselectivities in the epoxidations of the allylic alcohols **4** by the metal−oxo oxidants Mn(salen)PF_6/PhIO and Fe(TDCPP)Cl/PhIO (Table 1, entries 4 and 5) indicates that the optimal dihedral angle α in these oxidations fits qualitatively best between those for the already discussed oxidants Ti(O-*i*-Pr)$_4$/*t*-BuOOH (α = 70−90°) and *m*-CPBA (α = ca. 120°).[11] The match is not perfect, but most indicative in this stereochemical comparison are the 1,2-allylically strained substrates **4a** and **4d**. An angle α of 100−115° is assigned for these metal−oxo oxidants, which is close to that for the *m*-CPBA case. As already stated, the moderate regioselectivities in favor of the 7,8-epoxides in the epoxidation of 1-methylgeraniol (**6**) exclude metal−alcoholate binding for these oxidants (Table 2, entries 3 and 4), and as for the *m*-CPBA epoxidant (Table 2, entries 8−10) hydrogen bonding operates, to account for the observed OH directivity. Additionally, the diastereoselectivity in methanol versus methylene chloride for the epoxidation of mesitylol (**4e**) and the slightly favored *erythro* diastereoselectivity for the hydroxy-capped methyl ether derivative **4e′** (eq 4) corroborate hydrogen bonding.



		threo-5e/5e'
4e (X = H)	CH_2Cl_2	d.r. 91 : 09
	MeOH	d.r. 57 : 43
4e' (X = Me)	CH_2Cl_2	d.r. 39 : 61

(4)

The composite data in Tables 1 and 2 and eq 4 disclose a hydrogen-bonding mechanism for the epoxidation of allylic alcohols **4** by the Mn and Fe metal−oxo complexes with a likely dihedral angle in the range 100° < α < 115°. Such a geometry is consistent with the metallaoxetane (**C**‡) and the three-centered (**D**‡) transition-state structures (Figure 2) for the oxygen transfer, of which we favor the former in view of previous experimental[23] and computational evidence.[24]

The high *threo* diastereoselectivities in the epoxidation of the stereochemical probe **4c** as well as for the solely

1,3-allylically strained alcohols **4b** and **4e** (Table 1, entries 6−8) by the *m*-CPBA, DMD, and MTO/UHP oxidants confirm hydrogen bonding as the operative substrate−epoxidant interaction for these oxygen-transfer reactions. To define the transition-state geometry, the *syn*/*anti* diastereoselectivities in the epoxidation of the conformationally fixed cyclohexenols *trans*-**7** and *cis*-**7** with definite dihedral angles α are informative (Table 3). While for *m*-CPBA (entry 1) a high *syn* selectivity is noted for both *trans*-**7** (α = ca. 110°) and *cis*-**7** (α = ca. 140°), for DMD (entry 2) the reaction of *cis*-**7** is significantly more *syn*-selective than that of *trans*-**7**, provided that a relatively unpolar medium is used. Thus, although the latter oxidant operates through hydrogen bonding with the allylic hydroxy group, the dihedral angle α must be larger for DMD than *m*-CPBA. Since experimental work fixes α at ca. 120° for peracids (Figure 2, structure **E**‡),[17] we suppose ca. 130° for DMD (structure **F**‡).[8] For the MTO/UHP system a less clear-cut angular dependence of the *syn*/*anti* diastereoselectivities is observed, but the pronounced solvent effect emphasizes the importance of hydrogen bonding (entries 4 and 5) for this catalytic epoxidation system.

The directivity of the hydroxy functionality through hydrogen bonding for these oxidants is also displayed in the regioselectivities for the epoxidation of 1-methylgeraniol (**6**), as shown in Table 2 (entries 5−13). As expected for hydrogen bonding, the regioselectivity for the stoichiometric oxidant DMD is increased in favor of the 3,4-epoxide, together with a higher *threo* diastereoselectivity in unpolar solvents, especially in CCl_4 (Table 2, entries 5−7). In contrast, for *m*-CPBA (entries 8−10) medium effects are negligible within experimental error (ca. 5% of the stated values). Clearly, more efficient internal hydrogen bonding of the peracid with the allylic hydroxy group overrides external intervention through polar and protic solvents compared to DMD.

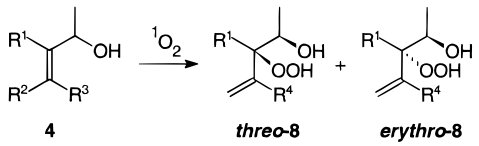
For MTO/UHP (Table 2, entries 11−13), which exhibits a modest if any solvent effect in the epoxidation of 1-methylgeraniol (**6**), the regio- and diastereoselectivites are more similar to those of the DMD (entries 5−7) than *m*-CPBA (entries 8−10) epoxidations. These facts, taken together with the diastereomeric ratios for the epoxidation of the chiral allylic alcohols **4** in Table 1 and the *syn* selectivities of the conformationally rigid cyclohexenols **7** in Table 3, reveal that the hydrogen-bonded transition-state structure **G**‡ (Figure 2) (α = ca. 130°) accounts best for the observed selectivities.[10]

Instructive Applications

In this section selected examples of oxidants are presented, whose oxygen-transfer mechanisms have been hitherto not well defined. We illustrate briefly that the selectivities observed in the epoxidation of the chiral allylic alcohol substrates are useful in assessing a resonable transition-state geometry for such oxidations.

Epoxidations with Hexafluoroacetone Perhydrate (HFAH/H_2O_2). We have recently[12] examined the epoxidation of chiral allylic alcohols by the HFAH/H_2O_2 oxidant[25] to assess a plausible transition-state structure. As is evident in Table 1 (entry 9), the diastereoselectivities for the epoxidation of the chiral allylic alcohols **4** by the catalytic organic epoxidant HFAH/H_2O_2 display a strong similarity to those of *m*-CPBA (entry 6). The high *threo* diastereoselectivities for the 1,3-allylically strained derivatives **4b** and **4e** (even for the stereochemical probe **4c**) compared to the modest ones for the 1,2-allylically strained substrates **4a** and **4d** reveal that hydrogen bonding operates in the transition state with a dihedral angle α of ca. 120−130° for this epoxidation, as portrayed in the structure **H**‡ (Figure 2). Hydrogen bonding is also corroborated by the selectivities found for the 1-methylgeraniol epoxidation (Table 2, entry 14).

Scheme 2. Diastereoselectivities in the Ene Reaction of Singlet Oxygen with Chiral Allylic Alcohols (Ref 13a,b)



threo / *erythro* diastereoselectivity

entry	solvent	4b	4c	4e	4e'
1	CCl_4	93 : 07	93 : 07	93 : 07	72 : 28
2	MeOH	---	---	73 : 24	---

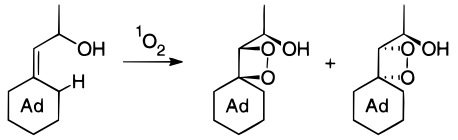
Epoxidations in Zeolites. The TS-1/UHP and Ti-β/H_2O_2 Systems. The heterogeneous catalytic epoxidation in the titanium-containing zeolites TS-1 and Ti-β by hydrogen peroxide[26] constitutes another illustrative example, for which even the structure of the actual oxygen-transferring species has been under debate.[27] The diastereoselectivity data (Table 1, entries 10 and 11) of these heterogeneous oxidation systems reveal that a metal−peracid species (Figure 2, structure **I**‡) best accounts for the high *threo* diastereoselectivites observed with the allylic alcohols **4b** and **4e**.[9] From the negligible diastereoselectivities of the ^{1,2}A-strained allylic alcohol **4a**, metal−alcoholate binding is excluded as the selectivity-determining feature in the peroxy-type structure **J**‡ (Figure 2). Neither does the alternative peroxo-type structure **K**‡ (Figure 2) apply,[9b] which has been proposed as the active oxidizing species.[27]

Oxidation Reactions with Singlet Oxygen. The hydroxy-directing effect of the chiral allylic alcohols **4** has proved valuable in establishing the mechanism of the Schenck ene reaction.[13] The derivatives **4b** and **4e** with ^{1,3}A strain react highly *threo*-diastereoselectively in CCl_4 with the small enophile singlet oxygen (Scheme 2).

That ^{1,2}A strain is not important is demonstrated by the stereochemical probe **4c** since it is as *threo*-selectively photooxygenated as the allylic alcohols **4b** and **4e**. Hydrogen bonding between the allylic hydroxy group and the oxidant in the rate-determining exciplex formation calls for the transition-state structure **L**‡ (Figure 2) to rationalize the observed *threo* diastereoselectivity; a di-

hedral angle α of 90−130° is likely.[13,14] This constitutes the first case of hydroxy group directivity in an excited-state reaction.

In analogy to the Schenck ene reaction, for the [2+2] cycloaddition of singlet oxygen a hydroxy-directing effect is also expected, as confirmed for the allylic alcohol **9** with ^{1,3}A strain (eq 5).[15] The photooxygenation of the chiral

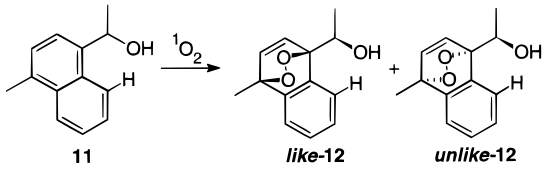


(5)

9	*threo*-**10**		*erythro*-**10**
$CDCl_3$:	>95	:	05
CCl_4/MeOH (9:1):	89	:	11

allylic alcohol **9** affords exclusively the *threo*-**10** dioxetane in the nonpolar solvent $CDCl_3$, which is significantly reduced in the protic CCl_4/MeOH reaction medium. These results show that the observed *threo*-selective hydroxy group directivity rests on hydrogen bonding, and a transition state similar to that of the ene reaction mode (Figure 2, structure **L**‡) also holds for the [2+2] process.

The mechanistic question arises whether the remaining cycloaddition process, the [4+2] mode, is also subject to stereochemical control through hydrogen bonding. Indeed, the photooxygenation of the chiral naphthyl alcohol **11** bears this out, which proceeds highly *like*-diastereoselectively in the nonpolar reaction medium $CDCl_3$, but becomes unselective in the protic methanol solvent (eq 6).[16] Instead of allylic strain, the hydroxy functionality is



(6)

11	*like*-**12**		*unlike*-**12**
$CDCl_3$:	85	:	15
CD_3OD:	55	:	45

conformationally aligned through *peri* strain, and hydrogen bonding favors the *like* attack by singlet oxygen, as portrayed in the transition-state structure **M**‡ (Figure 2) for this endoperoxidation.

Concluding Remarks

As deliberated in this Account, the concept of diastereo- and regioselective hydroxy group directivity provides a valuable mechanistic probe to define the plausible structure of transition states in oxygen-transfer reactions.[28] Stereolabeled allylic alcohols serve the purpose of disclosing whether hydrogen bonding or metal−alcoholate binding (template effect) operates by comparison of the observed diastereoselectivities and regioselectivities with those of established cases, notably *m*-CPBA and VO(acac)$_2$/*t*-BuOOH. Thus, the approach is empirical in nature by finding the best match in the compared product selectivities. Necessarily, the active oxidizing species is inferred, especially in catalytic processes, rather than directly assessed by means of spectroscopy and computations. An intelligent guess is made from the observed product selectivities about the geometry with the likely dihedral angle α in the substrate−oxidant complex. One expects a qualitative correspondence (the sense of the selectivities) rather than quantitative agreement (the extent of the selectivities) in the comparison of the displayed steric and electronic effects. Additionally, stereoelectronic factors may play a role, e.g., the Houk model,[29] but high-level computational work is required to recognize these in the product selectivities. In this context, caution must be exercized in reaching mechanistic conclusions, especially for metal-catalyzed oxidations in which the active oxidizing species is generated in situ. The crux of the matter is that the geometry acquired from the best match in the product selectivities does not necessarily mean that the electronic structure of the transition state for the oxidant under scrutiny is identical with that of the established one; all that may be defined is the likely dihedral angle α. Nevertheless, the vast set of selectivity data reviewed herein on stoichiometric and catalytic, on homogeneous and heterogeneous, on organic and metallic, and on ground-state and photochemical (singlet oxygen) oxidations comply with the regio- and diastereoselective control of the allylic hydroxy functionality. It is demonstrated that much may be learned about the mechanism of oxygen transfer through the diastereo- and regioselectivities observed with chiral allylic alcohols. We contend that this valuable mechanistic concept is general and applies to reactions in which substrate−reagent association operates.

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