Regio- and Diastereoselective Catalytic Epoxidation of Chiral Allylic Alcohols with Hexafluoroacetone Perhydrate. Hydroxy-Group Directivity through Hydrogen Bonding

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Received October 7, 1998

The threo diastereoselectivity in the catalytic epoxidation of chiral allylic alcohols with 1,3-allylic strain by hexafluoroacetone perhydrate and its regioselectivity in the epoxidation of 1-methylgeraniol establishes a hydroxy-directing effect through hydrogen bonding between the oxidant and substrate. The higher syn selectivity for the cis than trans isomer of 5-*tert*-butylcyclohexen-3-ol suggests a hydrogen-bonded transition-state structure similar to that of peracids for this catalytic oxygen-transfer process.

Introduction

Epoxidation reactions are of great synthetic interest in organic chemistry, as attested by the large volume of work on this subject.[1] Of special interest are catalytic procedures, as they allow economic use of the employed resources.[2] A good number of selective methods are presently available which utilize transition-metal catalysts, most prominently TBHP/Ti(O-*i*-Pr)$_4$,[3] VO(Acac)$_2$,[4] methyltrioxorhenium (MTO),[5] and Mn(Salen)[6] complexes. As purely organic nonmetal oxidants, the most widely used are the peracid *m*-CPBA[4] and the isolated dioxirane DMD,[7] which function stoichiometrically. A potential catalytic case constitutes hexafluoroacetone perhydrate, which has been applied to epoxidations,[8] the oxidation of heteroatoms,[9] arenes,[10] and aldehydes,[11] and the Baeyer−Villiger rearrangement.[9] This nonmetal oxidation catalyst is generated in situ from hexafluoroacetone hydrate and hydrogen peroxide as the oxygen donor, which are both commercially available.

The incentive of this study was to assess the efficiency and selectivity of hexafluoroacetone perhydrate as catalytic epoxidant. For this purpose, the chiral allylic alcohols **1** (cf. Table **1** for structures) were to be oxidized. These serve as mechanistic tools to define the transition-state structure of the oxygen-transfer process by comparison of the observed regio- and diastereoselectivities with those of the established oxidants *m*-CPBA[4] and DMD.[7] The structural similarities (Figure 1) between the perhydrate and both the peracid and dioxirane are clearly evident. While the peroxidic functionality in the perhydrate is internally hydrogen-bonded as in the peracid, its central carbon atom is sp^3-hybridized as in the dioxirane. Thus, the perhydrate is a composite of the peracid and the dioxirane structural features and it should be of mechanistic interest to assess what geometrical factors control the hydroxy-group directivity in the perhydrate epoxidation of the chiral allylic alcohols **1**.

Results and Discussion

The chiral allylic alcohols **1a**−**l** were prepared according to literature procedures[12] or were purchased. The epoxidations were conducted with a catalytic amount (0.1 equiv) of hexafluoroacetone sesquihydrate in the presence of 2 equiv of 85% hydrogen peroxide and disodium hydrogenphosphate as buffer. A general procedure is given in the Experimental Section.

The diastereoselectivities for the chiral, acyclic allylic alcohols **1a**−**h** are listed in Table 1, together with the literature data for the *m*-CPBA[4] and DMD[7] epoxidations. The epoxidations of substrates **1a**,**b** (entries 1 and 2) with no allylic strain display a modest (ca. 62:38) threo selectivity. For the substrates **1c**,**d** (entries 3 and 4) with 1,2-allylic strain, a slight (38:62) preference for the erythro diastereomer was observed. In contrast, the 1,3-allylic strain present in the derivatives **1e**,**f** (entries 5 and 6) induces a high (>90:10) threo preference. When 1,2- and 1,3-allylic strain are both acting in the same

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10.1021/jo982025a CCC: $18.00
Published on Web 02/04/1999

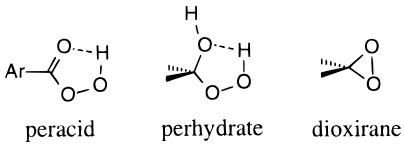
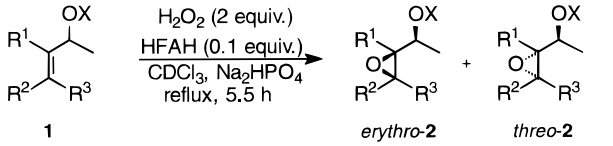


Figure 1. Comparison of the peracid, perhydrate, and dioxirane structures.

Table 1. Diastereoselectivities for the Epoxidation of the Chiral Allylic Alcohols 1a−h by HFAH/H_2O_2, *m*-CPBA, and DMD



1 *erythro*-**2** *threo*-**2**

entry	substrate	X		convn (%)	m.b. (%)	*threo* : *erythro* diastereoselectivity HFAH/H_2O_2[a]	*m*CPBA[b]	DMD[c]
1		H	**1a**	5	90	63 : 37	63 : 37	50 : 50
2		H	**1b**	54	>95	62 : 38	64 : 36	56 : 44
3		H	**1c**	54	>95	39 : 61	45 : 55	70 : 30
4		H	**1d**	93	90	38 : 62	48 : 52	--
5		H	**1e**	69	>95	91 : 9	>98 : 2	85 : 15
6		H	**1f**	89	>95	92 : 8	96 : 4	82 : 18
6a		Me	**1f-Me**	33	>95	92 : 8	40 : 60	38 : 62
6b		Ac	**1f-Ac**	60	>95	88 : 12	52 : 48	42 : 58
7		H	**1g**	84	93	95 : 5	90 : 10	91 : 9
8		H	**1h**	>95	90	92 : 8	90 : 10	>95 : 5

[a] Determined by ^{1}H NMR analysis of characteristic signals directly on the crude product mixture (error ± 5% of the stated values); pentachlorobenzene was used as internal standard. [b] Reference 4. [c] Reference 7.

molecule, as in the substrates **1g**,**h** (entries 7 and 8), the epoxidation is also highly (>90:10) threo-selective. For example, for the stereochemical probe **1g** (entry 7),[13] the observed threo selectivity of 95:5 is within the error limits the same as that found for the substrates **1e**,**f** (entries 5 and 6), for which solely 1,3-allylic strain is acting. The correspondence in the sense (threo versus erythro) and the extent of diastereomeric control between the perhydrate and peracid in Table 1 is impressive.

The hydroxy-capped derivatives of mesitylol, namely, the methyl ether **1f-Me** and the acetate **1f-Ac**, showed within the experimental error the same threo selectivity (92:8) as that of the parent alcohol **1f**. This is contrary to *m*-CPBA and DMD, since both result in proportionally more erythro epoxide; in fact, for most cases (cf. entries 6a,b) this stereoisomer is predominantly formed.

The cyclic allylic alcohols **1i**−**k** were epoxidized in the same manner to assess the syn:anti selectivity as a function of the dihedral angle between the allylic hydroxy group and the plane of the π system.[14] Table 2 shows the diastereoselectivities for the epoxidations of these substrates by hexafluoracetone perhydrate and for comparison the literature data of DMD[14] and *m*-CPBA.[12f,15] The HFAH/H_2O_2 oxidant is more syn-selective for the substrates **1i**,**j** (94:6) with the larger dihedral angle (140° versus 110°) than for **1k** (70:30).

For the diolefinic allylic alcohol **1l**, its regioselectivity allows one to test the ease of epoxidation of a plain alkene and an allylic alcohol within the same molecule.[12c] Moreover, the chiral allylic alcohol functionality provides additional information on the diastereoselectivity of the epoxidation. The regio- and diastereoselectivities for the HFAH/H_2O_2 system are given in Table 3, again together with the relevant literature data for DMD and *m*-CPBA for comparison.[12c] These results display a good match between the perhydrate and the peracid regioselectivities. The low regioselectivities for both express that an appreciable amount of the 3,4 epoxide is formed, despite the fact that the allylic double bond is electronically deactivated by the inductive effect of the hydroxy group, compared to the plain one. The high (95:5) threo diastereoselectivity is again characteristic for chiral allylic alcohols with 1,3-allylic strain.

The relative rates as a function of the substitution pattern of unfunctionalized cis-, trans-, and gem-disubstituted alkenes are given for HFAH/H_2O_2 in Table 4 and are compared with those for *m*-CPBA[16] and DMD.[17] The good correspondence between the perhydrate and the peracid is again clearly evident.

The composite set of selectivity and reactivity data in Tables 1−4 unequivocally proclaims that the observed hydroxy-group directivity derives from hydrogen bonding between the perhydrate oxidant and the allylic alcohol substrate **1**, akin to that established for peracids. The salient supporting experimental facts are the following: (a) the pronounced threo selectivity for the 1,3-allylically strained acyclic substrates (Table 1, entries 5−7), (b) the high syn selectivity for the cyclic allylic alcohols with dihedral angle $\alpha > 110°$ (Table 2), (c) the appreciable formation of the hydroxy-epoxide regioisomer (Table 3), and (d) the nearly identical epoxidation rates for cis-, trans-, and gem-substituted alkenes (Table 4). In analogy to the peracid transition-state structure **I**, we propose structure **II** for the perhydrate (Figure 2). This structure differs from the DMD transition state **III** in that the α angle is smaller and the planar rather than the spiro geometry applies. As for peracids, also for the perhydrate the β oxygen atom is transferred, while for the dioxirane it is necessarily the α oxygen atom. Consequently, the steric demand is more pronounced in the latter case. In view of the proximate sp^3-carbon center the spiro geometry (structure **III**) is preferred,[17] as supported by the reactivity data in Table 4 and theoretical work.[18] For peracids, the experimental data does not suffice to

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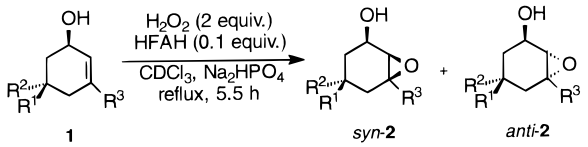
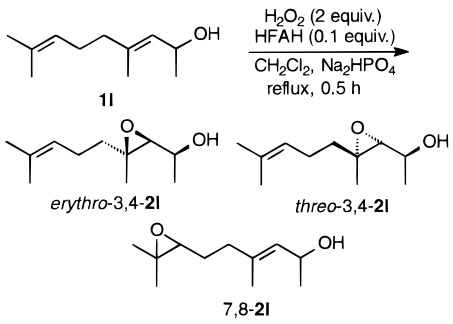
Table 2. Diastereoselectivities for the Epoxidation of the Cyclohexanols 1i−k by *m*-CPBA, DMD, and HFAH/H_2O_2



		substrate					syn:anti diastereoselectivity			
entry		R^1	R^2	R^3	convn (%)	m.b. (%)	HFAH/H_2O_2[a]	*m*-CPBA[b]	DMD[c]	dihedral angle[d] (deg)
1	**1i**	Me	Me	Me	67	>95	92:8	96:4	94:6	137
2	**1j**	^{t}Bu	H	H	49	86	94:6	96:4	82:18	140
3	**1k**	H	^{t}Bu	H	47	91	70:30	84:16	58:42	110

[a] Determined by ^{1}H NMR analysis of characteristic signals directly on the crude product mixture (error ± 5% of the stated values); pentachlorobenzene was used as internal standard. [b] CH_2Cl_2 (ref 15). [c] 1:9 acetone/CCl_4 (ref 7). [d] Calculated for the preferred ground-state conformations (ref 7).

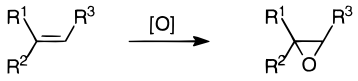
Table 3. Regio- and Diastereoselectivities for the Epoxidation of 1-Methylgeraniol (1l) by HFAH/H_2O_2, *m*-CPBA, and DMD



		selectivity[a]	
entry	oxidant	regio 3,4:7,8	diastereo[b] threo:erythro
1	HFAH/H_2O_2[c]	52:48	95:5
2	*m*-CPBA[d]	46:54	89:11
3	DMD[d]	68:32	94:6

[a] Determined by ^{1}H NMR analysis of characteristic signals directly on the crude product mixture (error ± 5% of the stated values); pentachlorobenzene was used as internal standard. [b] The diastereoselectivity of the 7,8-epoxide is 50:50. [c] 26% conversion, mass balance >95%. [d] CCl_4 (ref 12c).

Table 4. Effect of the Substitution Pattern on the Epoxidation Rate by Hexafluoroacetone Perhydrate, *m*-CPBA, and DMD



	relative reaction rate		
substitution pattern	HFAH/H_2O_2[a]	*m*-CPBA[b]	DMD[c]
trans	1	1	1
cis	1.5	1.2	7
gem	1.5	1.4	3.5

[a] Alkenes used were *cis*,*trans*-2-heptenes and 2-methylhexene; [b] *cis*,*trans*-2-octenes, cyclohexene, and methylenecyclohexane (ref 16); [c] *cis*,*trans*-2-hexenes and 2-methyl-1-pentene (ref 17).

differentiate between the planar and the spiro geometries, but recent computational results favor the spiro arrangement in the epoxidation of unfunctionalized alkenes;[19] however, for allylic alcohols with allylic strain this point remains open because no theoretical work is available. Whether the optimal dihedral angle (α) of ca. 120° for hydrogen bonding between the peracid and the hydroxy group corresponds better with the spiro or planar

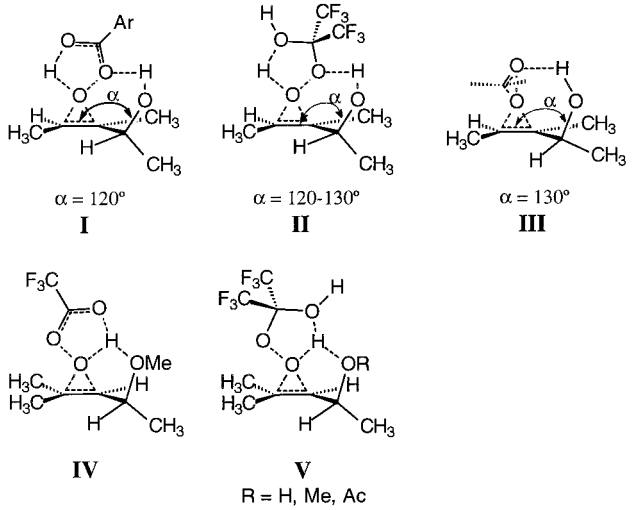


Figure 2. Transition-state structures for the epoxidation by *m*-CPBA (**I**), hexafluoroacetone perhydrate (**II** and **V**), DMD (**III**), and CF_3CO_3H (**IV**).

arrangement remains to be seen, but at this time, we adhere to the planar transition-state structure **I** (Figure 2) for the epoxidation of allylic alcohols by peracids.[4,16,17] Therefore, in view of the excellent match in the selectivities between *m*-CPBA and the perhydrate, the planar transition-state geometry **II** is proposed as well for the perhydrate.

The major discrepancy between the *m*-CPBA and perhydrate diastereoselectivities is exposed by the hydroxy-protected ether **1f-Me** and the acetate **1f-Ac** derivatives of the allylic alcohols **1f** (Table 1, entries 6a,b). This very high threo selectivity requires some efficient association between these capped substrates and the perhydrate. A relevant case has been disclosed by Ganem,[20] in which silyl ethers of 3-cyclohexenol were epoxidized expectedly anti-selectively by *m*-CPBA but syn-selectively by CF_3CO_3H. For the latter, hydrogen bonding from the peracid to the substrate oxygen functionality was proposed, as portrayed in the transition-state structure **IV**. Such multiple hydrogen bonding to

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three nucleophilic oxygen centers has been shown kinetically to be unlikely for the deprotonation of phenylazoresorcinol;[21] however, such a structure does account for the observed diastereoselectivity in the epoxidation by peroxytrifluoroacetic acid.[20] Moreover, recent computational results[19d] have suggested a similar transition-state structure for the epoxidation of allylic alcohols with peroxoformic acid. The stronger acidity of CF_3CO_3H versus *m*-CPBA is presumably responsible for the effective hydrogen bonding to the oxygen atom of the silyl ether to achieve this syn stereocontrol.[20] Ganem[8,20] has also suggested that a similar effect accounts for the syn selectivity (80:20) observed in the epoxidation of 3-cyclohexenyl acetate by hexafluoroacetone perhydrate. Accordingly, structure **V** is assigned for the perhydrate epoxidation of the hydroxy-capped derivatives **1f-Me,-Ac**. The acidity of the perhydrate is apparently sufficient to hydrogen bond strongly enough with the ether and acetate oxygen atoms to account for the high threo stereocontrol. In view of the recent theoretical work,[19d] the multiply coordinated structure **V** is also more likely for the allylic alcohol **1f**.

In conclusion, our diverse selectivity and reactivity data for the perhydrate ($HFAH/H_2O_2$) epoxidation disclose a transistion state analogous to that of peracids, in which hydrogen bonding is an essential feature to achieve stereochemical control through the hydroxy-group directivity. The additional advantage of this catalytic nonmetal process is that besides allylic alcohols with 1,3-allylic strain, their ether and ester derivatives are also epoxidized in high threo selectivity.

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Experimental Section

Typical Procedure for the Catalytic Epoxidation of the Allylic Alcohols by Hexafluoroacetone Perhydrate. Into a 25-mL, two-necked, round-bottomed flask, equipped with a reflux condenser (thermostated at ca. −75 °C) and topped with a nitrogen-filled balloon, were placed 95.6 mg (944 mmol) mesitylol (**1f**), 0.2 equiv of pentachlorobenzene (as internal standard), 142 mg (1.00 mmol) of NaH_2PO_4, 60.0 μL (2.00 mmol) of 85% H_2O_2, 13.0 μL (0.11 mmol) of hexafluoroacetone sesquihydrate, and 5 mL of $CDCl_3$ as solvent. The contents were heated at reflux for 5.5 h, and after cooling to room temperature (ca. 20 °C), a sample was taken for ^{1}H NMR analysis. The diastereomeric epoxides **2f** were obtained in a ratio of 92:8 (threo:erythro) at 89% conversion and a mass balance of >95%.

Acknowledgment. The generous financial support by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm "Peroxidchemie": Mechanistische und präparative Aspekte des Sauerstofftransfers) and the Fonds der Chemischen Industrie is gratefully appreciated.

JO982025A