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Ene Reaction of Singlet Oxygen, Triazolinedione, and Nitrosoarene with Chiral Deuterium-Labeled Allylic Alcohols: The Interdependence of Diastereoselectivity and Regioselectivity Discloses Mechanistic Insights into the Hydroxy-Group Directivity

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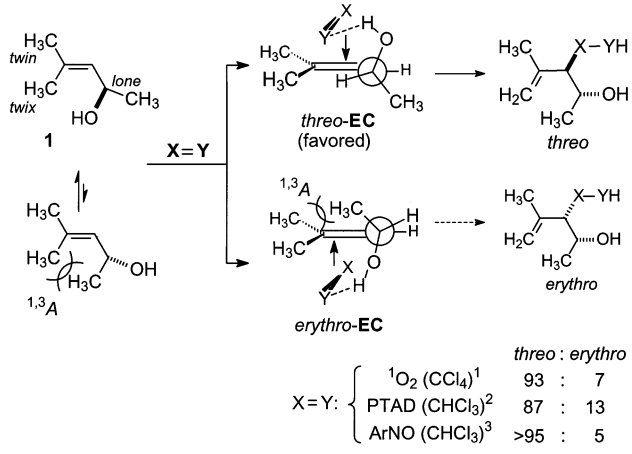
Abstract: The ene reaction of singlet oxygen ($^1O_2$), triazolinedione (TAD), and nitrosoarene, specifically 4-nitronitrosobenzene (ArNO), with the tetrasubstituted 1,3-allylically strained, chiral allylic alcohol 3,4-dimethylpent-3-en-2-ol (**2**) leads to the *threo*-configured ene products in high diastereoselectivity, a consequence of the hydroxy-group directivity. Hydrogen bonding favors formation of the *threo*-configured encounter complex *threo*-**EC** in the early stage of ene reaction. For the analogous *twix* deuterium-labeled allylic alcohol *Z*-**2**-d_3, a hitherto unrecognized dichotomy between $^1O_2$ and the ArNO and TAD enophiles is disclosed in the regioselectivity of the tetrasubstituted alcohol: Whereas for ArNO and TAD, hydrogen bonding with the allylic hydroxy group dictates the regioselectivity (*twix* selectivity), for $^1O_2$, the cis effect dominates (*twin*/*trix* selectivity). From the interdependence between the *twix*/*twin* regioselectivity and the *threo*/*erythro* diastereoselectivity, it has been recognized that the enophile also attacks the allylic alcohol from the *erythro* π face without assistance by hydrogen bonding with the allylic hydroxy functionality.

Introduction

The ene reaction of singlet oxygen ($^1O_2$),[1] triazolinedione (TAD),[2] and nitrosoarene, particularly 4-nitronitrosobenzene (ArNO),[1e,3] with 1,3-allylically strained chiral substrates leads to *threo*-configured ene products in high diastereoselectivity, a consequence of the hydroxy-group directivity.[4] Because of 1,3-allylic strain, the hydroxy group is conformationally aligned toward the *threo* face of the double bond. Effective hydrogen bonding with the incoming enophile leads preferably to the *threo*-configured ene product (Scheme 1).

Scheme 1. Diastereoselectivities in the Ene Reaction of $^1O_2$, TAD, and ArNO with 1,3-Allylically ($^{1,3}A$) Strained Chiral Allylic Alcohols Controlled by Hydroxy-Group Directivity



The fact should be emphasized that through the control exercised by the hydroxy-group directivity (the synergetic interplay of allylic strain and hydrogen bonding), excellent diastereoselectivities may be achieved for the nitrogen and oxygen functionalization of chiral allylic alcohols. Such diastereoselective metal-catalyzed and nonmetal-catalyzed, as well as stoichiometric oxidations, are of current interest in view of

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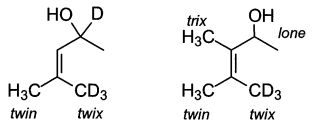
the synthetic value of selectively nitrogen- and oxygen-functionalized products of allylic alcohols.[4,5]

The chiral allylic alcohol in Scheme 1 only provides stereochemical information through the ratio of *threo*- and *erythro*-diastereomeric ene products. Unless the two geminal methyl groups at the *twin* and *twix* positions are appropriately differentiated through deuterium labeling, identical ene products ensue, and regiochemical data are precluded. Hydrogen abstraction at the chirality center (*lone* position) takes place to such a minor extent, that it is of no mechanistic relevance.[1−3] This shortcoming has recently been remedied by examining the deuterium-labeled chiral allylic alcohol *Z*-**1**-d_4. Indeed, valuable



Z-**1**-d_4 *Z*-**2**-d_3

mechanistic insight has been obtained for this allylic substrate on the diastereoselectivity and regioselectivity in its ene reaction with $^1O_2$ and TAD (data will be presented and discussed later, see Figure 1).[6] Such selectivity data are not available as yet for the nitroso enophile, and it was of mechanistic importance to determine the dependence of the *twix*/*twin* regioselectivities on the *threo*/*erythro* diastereoselectivity for 4-nitronitrosobenzene (ArNO) and compare the results with those of the $^1O_2$ and TAD enophiles. We have demonstrated previously the value of the ArNO enophile as a mechanistic probe to map out the preferred *skew* trajectory of enophilic attack, a consequence of its greater steric demand as compared to $^1O_2$ and TAD.[7] A particular incentive of this study was to assess the efficiency of the allylic hydroxy group to control regioselectivity and diastereoselectivity (hydroxy-group directivity) of the ArNO ene process.

In this context, conspicuous is the fact that for none of the enophiles $^1O_2$, TAD, and ArNO have the stereochemical and regiochemical features of their ene reaction with tetrasubstituted chiral allylic alcohols been scrutinized. For this purpose, we have chosen the deuterium-labeled allylic alcohol *Z*-**2**-d_3 to allow differentiation of the regioisomers. This tetrasubstituted substrate is structurally closely related to the trisubstituted allylic alcohol *Z*-**1**-d_4 and suited for comparison. With the additional methyl group in the *trix* position,[8] we bargain for a greater degree of complexity, but the opportunity is offered to gain a more precise view of the enophilic reaction coordinate.

Comparison of the trisubstituted (*Z*-**1**-d_4) and tetrasubstituted (*Z*-**2**-d_3) allylic substrates discloses the following structural differences with mechanistic implications on account of the additional *trix* substituent: (i) The steric demand of the two sides of the double bond (*twin*/*trix* versus *twix*/*lone*) are more comparable in *Z*-**2**-d_3, such that steric effects should be more moderate for the more imposing ArNO enophile; (ii) the allylic hydrogen atoms of the *trix*-methyl group provide additional coordination for the incoming enophile, which is of particular consequence for the $^1O_2$ enophile in view of the established cis effect;[9] (iii) the *trix*-methyl group foments 1,2-allylic strain ($^{1,2}A$) with the stereogenic *lone* site, in addition to the already existing 1,3-allylic strain ($^{1,3}A$) between the *twix* and *lone* substituents, which should affect the conformational alignment of the allylic hydroxy functionality and in turn the efficiency of hydrogen bonding with the enophile. Moreover, it should be noted that the *trix* substituent generates another regioisomer as the ene product but no additional diastereomers.

Herein we report our unprecedented results on the diastereoselectivity and regioselectivity, as well as their interdependence, for the ene reactions of the deuterium-labeled chiral allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3 with the enophiles $^1O_2$, PTAD (*N*-phenyl-1,2,4-triazoline-3,5-dione), and ArNO. Because the unlabeled tetrasubstituted allylic alcohol **2** has not been studied for the three enophiles, these ene reactions have also been conducted to isolate and fully characterize the ene products and to assess their configuration. The interrelated stereochemical and regiochemical data provide a detailed mechanistic account of the enophilic reaction coordinate.

Results

The reaction of 3,4-dimethylpent-3-en-2-ol (**2**) with all three enophiles $^1O_2$, PTAD, and ArNO proceeded smoothly and in high yield (Table 1). The product distribution was determined by ^{1}H NMR spectroscopy directly on the reaction mixture in deuterated solvents. Additionally, preparative runs were conducted, and all ene products were isolated and fully characterized (see the Supporting Information).

For $^1O_2$ and PTAD, in addition to the expected *gem* regioisomers (abstraction at the *twix* and *twin* positions), the diastereomeric ene products *gem*-**3**(*threo*) and *gem*-**3**(*erythro*), also hydrogen abstraction at the *trix* position[8] takes place to afford the *trix*-**3** regioisomer. In contrast, exclusive *gem* abstraction is observed for the ArNO enophile. In regard to the *threo*/*erythro* diastereoselectivity, a pronounced solvent effect operates: In $CDCl_3$ (entries 1, 3, and 5), a high *threo* selectivity is observed for the *gem* regioisomer. This selectivity is significantly less in CD_3OD (entries 2, 4, and 6); the decrease is most pronounced for $^1O_2$ (entry 2).

The major isomers of the ene products **3a** from $^1O_2$ and **3b** from PTAD were separated by silica gel chromatography; for ArNO, only the *threo*-configured *twix*-regioisomer was isolated. The configuration of the ene products was determined in analogy to literature.[3] For this purpose, the isolated major isomers were cyclized with 2,2-dimethoxypropane under TsOH catalysis to the corresponding heterocycles **4a**−**c** (Scheme 2). The relative configuration of these conformationally rigid derivatives was assessed by NOE spectroscopy, which clearly displays enhancements for the depicted methyl groups and establishes the *threo*-

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(8) For ease of comparison and convenience of referal in the text, the regiochemical descriptors of trisubstituted alkenes (*twix*/*twin*/*lone*: see Scheme 1, ref 7a) have been extended to tetrasubstituted derivatives by defining the fourth substituent as "*trix*"; "*trix*" stands for the contraction of "*trans*" and "*twix*". It should be noted that if in the deuterium-labeled tetrasubstituted *Z*-**2**-d_3 the CD_3 group were missing, the *trix* position would become *twix* in the resulting trisubstituted substance, which emphasizes the regiochemical relationship between the *twix* and *trix* descriptors.

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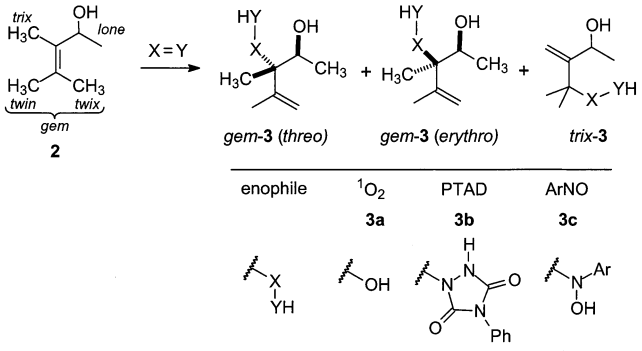
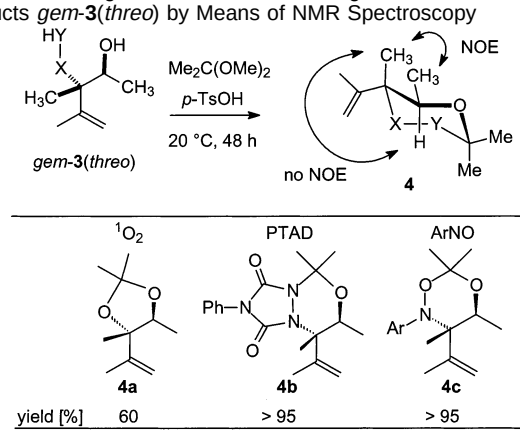
Table 1. Product Composition in the Ene Reactions of $^1O_2$, PTAD, and ArNO with the Tetrasubstituted Chiral Allylic Alcohol **2**



entry	enophile X = Y	solvent	mb [%][a]	convn [%][a]		selectivity[a] regio gem[d]:trix[e]	selectivity[a] diastereo[c] threo:erythro	yield[b] [%]
1	$^1O_2$	$CDCl_3$	93	87	**3a**	64:36	90:10	66[f]
2		CD_3OD	84	>95		62:38	63:37	
3	PTAD	$CDCl_3$	95	>95	**3b**	90:10	96:4	73
4		CD_3OD	>95	>95		75:25	89:11	
5	ArNO	$CDCl_3$	85	85	**3c**	>95:5	>95:5	63
6		CD_3OD	90	78		>95:5	88:12	

[a] Determined by ^1H NMR spectroscopy, error ca. 5% of the stated value; mb stands for material balance. [b] Isolated material, determined gravimetrically after workup of a preparative run in CH_2Cl_2. [c] For the *gem* regioisomer. [d] Sum of *twin* and *twix* abstraction. [e] For descriptor definition, cf. ref 8. [f] From the semipreparative run in $CDCl_3$; yield of alcohol obtained by Ph_3P reduction of the hydroperoxide.

Scheme 2. Assignment of the *threo*-Configuration for the Ene Products *gem*-**3**(*threo*) by Means of NMR Spectroscopy



configuration. Thus, the *gem*-**3**(*threo*) diastereomer is preferred in the ene reaction of $^1O_2$, PTAD, and ArNO with the tetrasubstituted allylic alcohol **2**.

The stereochemically deuterium-labeled trisubstituted *Z*-**1**-d_4 and the tetrasubstituted *Z*-**2**-d_3 substrates were prepared to assess the regioselectivity for *twix* versus *twin* hydrogen abstraction, as well as the diastereoselectivities for both regioisomeric ene products.[6] For the stereoselective synthesis of the *twix* deuterium-labeled *Z*-3,4-dimethylpent-3-en-2-ol-d_3 (*Z*-**2**-d_3), the cuprate addition to the phosphonate ester was conducted in analogy to the preparation of the known *twix* deuterium-labeled trisubstituted mesitylol *Z*-**1**-d_4 substrate (Scheme 3).

The ene reactions of the *twix* deuterium-labeled *Z*-3,4-dimethylpent-3-en-2-ol-d_3 (*Z*-**2**-d_3) with the enophiles $^1O_2$, PTAD, and ArNO were conducted in $CDCl_3$ and in CD_3OD. The product distribution was determined by means of ^1H NMR spectroscopy (Table 2). The *threo*/*erythro* ratios for the *twix*

Scheme 3. Synthesis of Deuterium-Labeled *Z*-3,4-Dimethylpent-3-en-2-ol (*Z*-**2**-d_3)

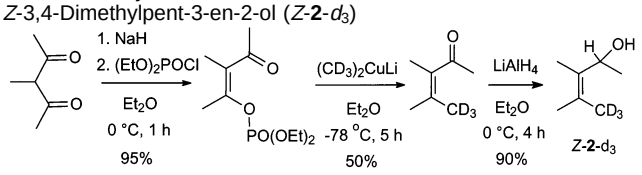
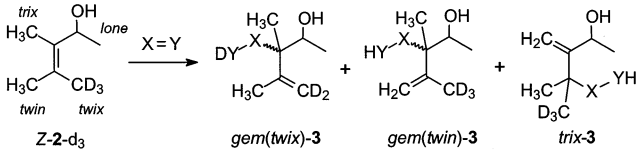


Table 2. Regioselectivity and Diastereoselectivity in the Ene Reaction of $^1O_2$, PTAD, and ArNO with the Deuterium-Labeled *Z*-3,4-Dimethylpent-3-en-2-ol (*Z*-**2**-d_3)



entry	enophile X = Y	solvent	convn[a,b] [%]	selectivity [%][a,c] gem(twix)-3 (threo/erythro)	selectivity [%][a,c] gem(twin)-3 (threo/erythro)	trix-3[d]
1	$^1O_2$	$CDCl_3$	>95[e]	24 (95:5)	40 (86:14)	36
2		CD_3OD	>95[e]	22 (70:30)	38 (60:40)	40
3	PTAD	$CDCl_3$	>95[e]	60 (98:2)	30 (89:11)	10
4		CD_3OD	>95[e]	41 (91:9)	30 (86:14)	29
5	ArNO	$CDCl_3$	50[f]	>95 (>95:5)	<5	
6		CD_3OD	56[f]	73 (90:10)	27 (86:14)	

[a] Determined by ^1H NMR spectroscopy, error ca. 5% of the stated value. [b] Based on alkene. [c] For $^1O_2$ (entries 1 and 2), the ratio of *threo* (*twix* + *twin*)/*erythro* (*twix* + *twin*)/*trix* was also determined by GC analysis. [d] For the descriptor definition, cf. ref 8. [e] 1 equiv of olefin. [f] 1.5 equiv of olefin.

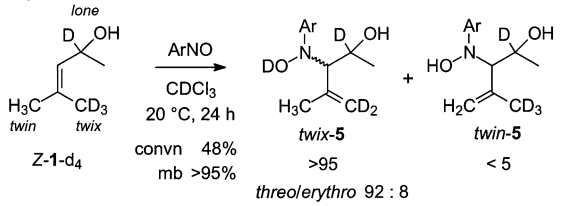
regioisomer were obtained from the areas of the allylic methyl resonances of the ene products. The areas of the peaks for the olefinic protons afforded the *threo*/*erythro* ratio of the *twin* regioisomer, whereas the proton geminal to the hydroxy group provided the overall *threo* (*twin* + *twix*)/*erythro* (*twin* + *twix*) ratios. Additionally, the ratios of *threo* (*twin* + *twix*)/*erythro* (*twin* + *twix*)/*trix* were determined for $^1O_2$ by GC analysis (see Table 2, footnote c). The latter ratios are in accord with the results acquired by ^1H NMR spectroscopy, as well as the product ratio for the unlabeled alcohol **2** (Table 1). In $CDCl_3$, only *twix* hydrogen abstraction is observed for ArNO, 60% *twix* regioisomer is formed for PTAD, whereas only 24% *twix* hydrogen abstraction takes place for $^1O_2$. A solvent effect on the regioselectivity is only evident for ArNO and PTAD, but not for $^1O_2$. The diastereoselectivity for the three enophiles is about the same (within the experimental error of 5%) for a particular regioisomer: The *threo*/*erythro* ratio is ca. 95:5 for *twix* hydrogen abstraction and ca. 85:15 for the *twin* regioisomer.

For comparison with the already known $^1O_2$ and PTAD results,[6] the selectivities of the ene reaction of ArNO with the trisubstituted *Z*-**1**-d_4 substrate were studied (Scheme 4).

The product distribution was determined by ^1H NMR spectroscopy, analogous to *Z*-**2**-d_3. Only the *twix*-**5** regioisomer was formed; its *threo/erythro* ratio was 92:8. The configuration of the unlabeled nitroso ene product has been assigned previously.[3]

This extensive set of regioselectivity and stereoselectivity data for the ene reactions of $^1O_2$, PTAD, and ArNO with the

Scheme 4. Regioselectivity and Stereoselectivity in the Ene Reaction of 4-Nitronitrosobenzene (ArNO) with *Z*-Mesitylol-d_4 (*Z*-**1**-d_4)

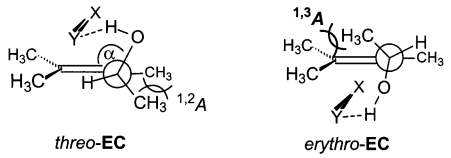


deuterium-labeled allylic alcohols *Z*-**1**-d_4[6] and *Z*-**2**-d_3 and the unlabeled derivatives **1**[1−3] and **2** are in mutual accord in regard to general trends and shall now be rationalized mechanistically. Of particular significance and relevance shall be the interdependence between the regiochemical and stereochemical features. The present results allow one to recognize the mechanistic similarities and differences between these three isoelectronic heteroatom enophiles.

Discussion

To facilitate the mechanistic analysis, in Figure 1 are collected the regioselectivity and the diastereoselectivity data for the ene reactions of the three enophiles $^1O_2$, PTAD, and ArNO with the deuterium-labeled allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3 in the form of a comparative overview. For clarification, the relative values of the *twix*, *twin*, and *trix* regioisomers are placed closest to the allylic groups, while directly under these are listed in parentheses the *threo*:*erythro* diastereomeric ratios individually for the *twin* and *twix* regioisomers. This matrix-structured overview allows one to focus on the interdependence between the *threo*/*erythro* and the *twix*/*twin* selectivities, an essential feature for the comparative mechanistic analysis.

As a mechanistic basis, we adopt the established multistep process in Scheme 1,[1−3] with the formation of a three-membered-ring intermediate (not shown), preceded by a more loosely aggregated enophile/substrate encounter complex (**EC**). The steric interactions and electronic coordination, which control diastereoselectivity and regioselectivity, manifest themselves already in the encounter complex, as illustrated for the *threo*-**EC** and the *erythro*-**EC** structures derived from the tetrasubstituted substrate **2** and the enophile. For the *threo*-**EC** case,



1,3-allylic strain ($^{1,3}A$) is minimized, such that the allylic hydroxy group points above the substrate plane, to engage in hydrogen bonding with the enophile attack from the top π face, which affords preferably the *threo*-configured ene product. On the contrary, 1,2-allylic strain ($^{1,2}A$) is minimized for the *erythro*-**EC** structure, the hydroxy group points below the substrate plane, and the enophile attacks from the bottom π face to form the *erythro*-configured ene product. It should be emphasized that the allylic alcohols are all racemic and only one enantiomer is being considered for the **EC** and **TS** structures in the mechanistic analysis.

The experimental facts are that the *threo*-configuration prevails for all ene products of the tetrasubstituted allylic alcohol

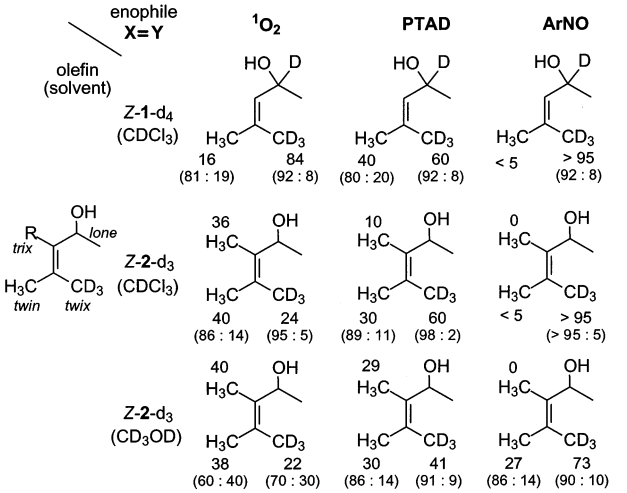


Figure 1. Regioselectivities and diastereoselectivities in the ene reactions of the three heteroatom enophiles $^1O_2$, PTAD, and ArNO with the chiral allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3; the data for the ene reactions of $^1O_2$ and PTAD with *Z*-**1**-d_4 have been taken from ref 6.

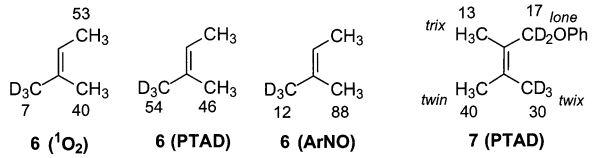


Figure 2. Comparative regioselectivities in the ene reaction of $^1O_2$, PTAD, and ArNO with the olefinic substrates **6** (ref 7a) and **7** (ref 10).

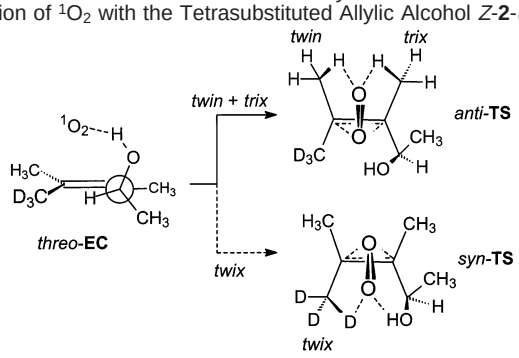
2 (Table 1). Hence, it may be concluded that 1,3-allylic strain ($^{1,3}A$) rather than 1,2-allylic strain ($^{1,2}A$) dominates also in the tetrasubstituted substrate, and evidently a relatively large dihedral angle ($\alpha \approx 130°$) operates in the coordination of the enophile, which is optimal for hydrogen bonding in the less strained *threo*-**EC** structure.[4]

Clearly, irrespective of *trix* substitution, all three heteroatom enophiles obey hydroxy-group directivity, *threo* control. Thus, $^{1,3}A$ strain conformationally aligns the chiral allylic alcohol for the *threo* attack, which is assisted by hydrogen bonding, as displayed in the *threo*-**EC** encounter complex. The mechanistic query to be addressed now is to assess how hydrogen bonding affects the regioselectivity in the ene reaction of the three enophiles with the two chiral, deuterium-labeled allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3. Also of interest is how the *threo*/*erythro* selectivity differs for the individual *twix* and *twin* regioisomers.

Dependence of the Regioselectivity on Hydrogen Bonding. The pertinent data are displayed in Figure 1; we shall commence with the more straightforward trisubstituted allylic alcohol *Z*-**1**-d_4, because only the *twin* and *twix* regioisomers need to be considered. For all three enophiles, *twix* hydrogen abstraction is favored (Figure 1). This becomes apparent on comparison of the regioselectivity with the unfunctionalized trisubstituted alkene **6** (Figure 2):[7] The three enophiles exhibit a higher *twix* selectivity for the corresponding trisubstituted alcohol *Z*-**1**-d_4, that is, the ratios of *twix* regioisomer for the substrates *Z*-**1**-d_4 versus **6** are 84/40 ($^1O_2$), 60/46 (PTAD), and >95/88 (ArNO); the first value refers to the substrate *Z*-**1**-d_4, and the second refers to **6**.

Such a comparison of the ratios of *twix* regioisomers for the tetrasubstituted substrate *Z*-**2**-d_3 (Figure 1) versus **6** (Figure 2) discloses a different trend: The *twix* ratios are 24/40 ($^1O_2$), 60/

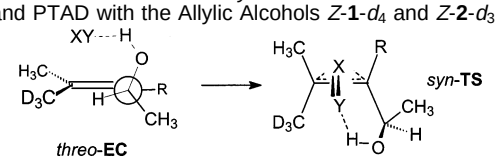
Scheme 5. Control of the Diastereoselectivity in the Encounter Complex *threo*-**EC** and Subsequent Control of the Regioselectivity in the Transition Structures *anti*-**TS** and *syn*-**TS** for the Ene Reaction of $^1O_2$ with the Tetrasubstituted Allylic Alcohol *Z*-**2**-d_3



46 (PTAD), and >95/88 (ArNO); the first value refers to the substrate *Z*-**2**-d_3, and the second refers to **6**. Clearly, these *twix* ratios are identical for the PTAD and ArNO enophiles with both the trisubstituted (*Z*-**1**-d_4) and the tetrasubstituted (*Z*-**2**-d_3) allylic alcohols, but drastically different for $^1O_2$; that is, the relative amount of *twix* regioisomer is 84% for *Z*-**1**-d_4 but only 24% for *Z*-**2**-d_3. Closer inspection of the tetrasubstituted substrate *Z*-**2**-d_3 reveals that a total of 76% hydrogen abstraction takes place by $^1O_2$ at the *twin* (40%) and the *trix* (36%) sites (Figure 1), the side of the double bond *anti* to the allylic hydroxy group. Thus, mainly the *twin* and *trix* regioisomers are generated from the *threo*-**EC** encounter complex through the transition structure *anti*-**TS**, whereas to a minor extent the *twix* regioisomer results from *syn*-**TS** (Scheme 5). That the *threo* encounter complex (*threo*-**EC**) serves as main precursor to all regioisomers is substantiated by the high *threo*/*erythro* diastereoselectivities, which are 86:14 for the *twin* and 95:5 for the *twix* regioisomer (Figure 1). These diastereoselectivities are lower in methanol, in which intermolecular hydrogen bonding competes with the hydroxy-directing effect (see the Supporting Information for details in methanol).

This reveals a novel and mechanistically most significant feature: Once the $^1O_2$ enophile has selected the favored π face of the double bond by hydrogen bonding (*threo* attack conditioned by $^{1,3}A$ strain), the enophile has still the choice for hydrogen abstraction between the two sides of the double bond to afford either the *twix* regioisomer (*syn* side) or the *twin*/*trix* regioisomers (*anti* side). Thus, at first, the $^1O_2$ enophile is weakly coordinated by hydrogen bonding in the form of the *threo*-**EC** encounter complex before it forms the corresponding transition structures *anti*-**TS** and *syn*-**TS** by penetration into the π system of the double bond to generate a three-membered-ring intermediate (perepoxide-like geometry for $^1O_2$). At this stage, the *threo* diastereoselectivity is fixed. Nevertheless, in this *threo*-**EC** structure, the $^1O_2$ enophile is still sufficiently mobile to specify the regioselectivity between the two sides of the double bond, the *twix* regioisomer through *syn*-**TS** or the *twin*/*trix* regioisomers through *anti*-**TS** (Scheme 5). Conspicuous is the fact that the *twin*/*trix* regioisomers are preferred over the *twix* one (*twin*/*trix*:*twix* = 76:24, Figure 1). This indicates that for the $^1O_2$ enophile, coordination with the allylic hydrogen atoms (*cis* effect)[9] on the *anti* side is more effective than hydrogen bonding with the hydroxy group on the *syn* side, a hitherto unrecognized behavior. The fact that the regioselectivity does not change in the protic methanol solvent supports this mechanistic interpretation (see the Supporting Information for details in methanol). It should be emphasized that even if the *syn*-**TS** and the *anti*-**TS** derive from a common precursor, the *threo* diastereoselectivities for the *twin* and *twix* regioisomers are not necessarily the same, because the enophile may also attack from the *erythro* face without assistance by hydrogen bonding (see below!)

Scheme 6. Control of the Diastereoselectivity and Regioselectivity by Hydroxy-Group Directivity in the Encounter Complex *threo*-**EC** and in the Transition Structure *syn*-**TS** for the Ene Reaction of ArNO and PTAD with the Allylic Alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3



X=Y: ArNO, PTAD
R: H, CH_3

A different regioselectivity pattern is exposed by the PTAD and ArNO enophiles for both the trisubstituted (*Z*-**1**-d_4) and the tetrasubstituted (*Z*-**2**-d_3) allylic alcohols (Figure 1): For PTAD, *twix* hydrogen abstraction dominates slightly (*twix*:*twin*/*trix* = 60:40 for both substrates), whereas *twix* hydrogen abstraction occurs exclusively with ArNO (*twix*:*twin*/*trix* > 95:5 for both substrates). That this enhanced *twix* reactivity derives from hydrogen bonding is confirmed by comparing the regioselectivities of the allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3 (Figure 1) with related substrates without a hydroxy group, **6** and **7** (Figure 2). For the trisubstituted pair *Z*-**1**-d_4 and **6**, the corresponding *twix*:*twin* ratios are 60:40 versus 46:54 with PTAD as enophile. The difference is more pronounced in favor of *twix* hydrogen abstraction in the case of the ArNO enophile, for which the corresponding *twix*:*twin* ratios are >95:5 versus 88:12. A similar trend is displayed by the tetrasubstituted pair *Z*-**2**-d_3 and **7**, but regioselectivity data are only available for the PTAD enophile. Furthermore, the sum of regioisomers derived from each side of the double bond need to be compared: The *twix*:(*twin* + *trix*) ratio for *Z*-**2**-d_3 is 60:40 (Figure 1) versus the (*twix* + *lone*):(*twin* + *trix*) ratio 47:53 for **7** (Figure 2). For ArNO, the twix regioisomer is formed exclusively with the *Z*-**2**-d_3 substrate (Figure 1). Thus, the allylic hydroxy group promotes ene reactivity at the *twix* position through hydrogen bonding with the PTAD enophile, even more so for ArNO (Scheme 6). This contrasts the behavior of $^1O_2$, for which we have seen that the *cis* effect[9] dominates hydrogen bonding (Scheme 5). Presumably, stabilization of the transition structure *syn*-**TS** by hydrogen bonding becomes more important for ArNO and PTAD than for $^1O_2$, which is also substantiated by the change of regioselectivity in methanol for ArNO and PTAD, but not for $^1O_2$ (see the Supporting Information for the details in methanol).

Interdependence of the Regioselectivity on the Diastereoselectivity. Examination of the dependence of the *twix*/*twin* regioselectivity on the individual *threo* and *erythro* diastereomers and the dependence of the *threo*/*erythro* diastereoselectivity on the individual *twix* and *twin* regioisomers illustrates mechanistically important new features on the ene reaction in regard to hydroxy-group directivity. For convenience, we summarize the pertinent stereochemical and regiochemical data in Figure 3 for the ene reactions of the trisubstituted (*Z*-**1**-d_4) and tetrasubstituted (*Z*-**2**-d_3) substrates with $^1O_2$, the enophile that exhibits the trends more markedly. The bold-faced ratios represent the overall *threo*/*erythro* diastereoselectivities at the

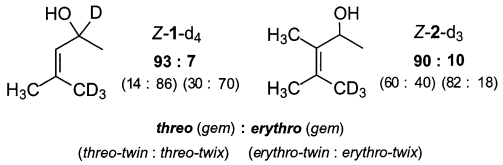


Figure 3. Dependence of the regioselectivities on the diastereoselectivities in the ene reaction of $^1O_2$ with the allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3 (see the Supporting Information for these $^1O_2$, PTAD, and ArNO data).

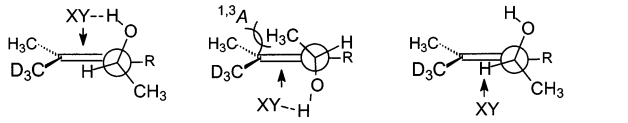


Figure 4. Structures of the encounter complexes for the enophiles X = Y with the allylic alcohols *Z*-**1**-d_4 (R = H) and *Z*-**2**-d_3 (R = CH_3).

geminal position (not differentiated for the *twin* and *twix* regioisomers), that is, ***threo***(*gem*) and ***erythro***(*gem*), which are 93:7 for the undeuterated allylic alcohol **1** (Scheme 1) and 90:10 for the undeuterated substrate **2** (Table 1). As discussed already, these stereochemical ratios express for both allylic alcohols the strong preference of the *threo* attack, conditioned by minimal $^{1,3}A$ strain and optimal hydrogen bonding (hydroxy-group directivity). Below the overall diastereoselectivity ratios ***threo***(*gem*):***erythro***(*gem*) are given the *twin*:*twix* regioselectivity ratios for each diastereomer, which are labeled *threo-twin*:*threo-twix* for the *threo* and *erythro-twin*:*erythro-twix* for the *erythro* diastereomer. For the trisubstituted substrate *Z*-**1**-d_4, the *twin*:*twix* ratio for the *threo* diastereomer is 14:86 and for the *erythro* diastereomer it is 30:70; thus, substantially more (about twice) *twin* abstraction takes place proportionally for the *erythro* than for the *threo* attack. A similar trend is displayed by the tetrasubstituted substrate *Z*-**2**-d_3, but is less pronounced; that is, *twin* abstraction occurs to the extent of 82% for the *erythro* and 60% for the *threo* attack (Figure 3). This regiochemical differentiation by $^1O_2$ for the *threo* and *erythro* attacks appears to be general and needs to be rationalized mechanistically. To account for the distinct *twin*/*twix* regioselectivities, we shall see that different enophilic trajectories are pursued by the $^1O_2$ enophile for the *threo* and *erythro* attacks.

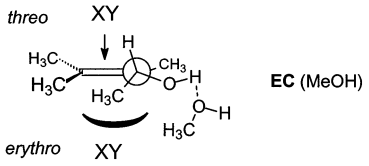
In Scheme 1, the *threo* and *erythro* trajectories have been specified in terms of the respective encounter complexes *threo*-**EC** and *erythro*-**EC** for the trisubstituted

substrate **1**. For convenience, these structures are shown for the ene reactions with both deuterated substrates *Z*-**1**-d_4 and *Z*-**2**-d_3 in Figure 4, in which also the direction of attack has been specified in terms of the top and bottom faces of the double bond. That the *threo* attack dominates is a consequence of $^{1,3}A$ strain in this chiral allylic alcohol.

Hydrogen bonding between the $^1O_2$ enophile and the hydroxy functionality of the substrate assists the enophilic attack. Inspection of the encounter complexes *threo*-**EC** and *erythro*-$\mathbf{EC_1}$ reveals no significant steric interactions that would differentiate between *twin* and *twix* abstraction. Thus, these structures alone cannot reconcile the observed preference for *twin* regioselectivity in the *erythro* attack. We propose that additionally the $^1O_2$ attacks the lower-strained substrate conformer (the one necessary for the *threo* trajectory, but from below) without assistance of hydrogen bonding, as shown in the *erythro*-$\mathbf{EC_2}$ encounter complex. In this *erythro* trajectory without hydrogen bonding, the $^1O_2$ is even more prone to abstract from the sterically less crowded *twin* site, as is experimentally observed (*erythro-twin* > *threo-twin*, Figure 3). These unprecedented results demand that the usually presented mechanism[1−3] in Scheme 1 must be extended to allow enophilic attack not assisted by hydrogen bonding.

Briefly, the dependence of the *threo*/*erythro* diastereoselectivity on the individual *twix* and *twin* regioisomers shall be considered; these data are shown for all three enophiles $^1O_2$, PTAD, and ArNO with both deuterated allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3 in Figure 1. All three enophiles display for both substrates nearly the same diastereoselectivity ratios for a particular regioisomer; that is, the *threo*/*erythro* ratio is from 90:10 to >95:5 for the *twix* and between 80:20 and 90:10 for the twin regioisomer (for ArNO, no twin regioisomer is formed). Proportionally, a higher *erythro* diastereoselectivity is exhibited by the *twin* regioisomer, due to the increased *twin* regioselectivity from the *erythro*-$\mathbf{EC_2}$ encounter complex, not assisted by hydrogen bonding (Figure 4).

Diastereoselectivity and Regioselectivity in Methanol. In the ene reaction with the unlabeled allylic alcohol **2** (Table 1) and the deuterium-labeled derivative *Z*-**2**-d_3 (Figure 1), the *threo*/*erythro* diastereoselectivity is lowered in methanol due to competitive hydrogen bonding with this protic solvent. For $^1O_2$, the overall *threo*/*erythro* diastereoselectivity drops from 90:10 in $CDCl_3$ to 63:37 in D_3COD (Table 1), whereas smaller effects are observed for PTAD (from 96:4 in $CDCl_3$ to 75:25 in D_3-COD) and ArNO (from >95:5 in $CDCl_3$ to 88:12 in D_3COD). We propose that steric effects are responsible for this diastereoselectivity behavior: The allylic hydroxy group is solvated by the MeOH, and, therefore, its relative size is larger than the methyl group of the *lone* substituent. Consequently, the favored conformation of the substrate changes to a rotamer, in which the solvated hydroxy group is at the periphery of the alkene, as shown in the encounter complex **EC** (MeOH). For this solvated



rotamer, the enophilic attack is still favored from the *threo* side, because the *erythro* attack is sterically hindered by the methyl group of the *lone* substituent. Because the steric demand of the three enophiles follows the order $^1O_2$ < PTAD < ArNO, the diminution of *threo* selectivity is most pronounced for $^1O_2$, the smallest enophile.

Inspection of the regioselectivities for the ene reactions in methanol reveals that for $^1O_2$ no change occurs, as displayed by the *twix*:(*twin* + *trix*) ratios of 24:76 in $CDCl_3$ versus 22:78 in D_3COD (Figure 1). As discussed already above, hydrogen bonding has little influence on the regioselectivity for $^1O_2$. In contrast, for ArNO and PTAD, the *twix* regioselectivity decreases significantly in methanol versus chloroform. For PTAD, the *twix*:*twin*/*trix* ratios are 60:40 ($CDCl_3$) versus 41:59 (D_3-COD), a significant drop in the *twix* regioisomer, and for ArNO, the values are >95:5 ($CDCl_3$) versus 73:27 (D_3COD), with proportionally still less *twix* hydrogen abstraction occuring in

MeOH. This may again be rationalized in terms of competitive disturbance of hydrogen bonding with the hydroxy group by the protic medium, which expectedly depreciates *twix* reactivity for PTAD and ArNO. This fact emphasizes the difference in the regioselective control between $^1O_2$ and the PTAD and ArNO enophiles: For PTAD and ArNO, regioselectivity is subject to hydroxy-group directivity but not for $^1O_2$. Furthermore, the increase of *trix* regioselectivity in methanol is observed exclusively for PTAD. This may be rationalized in terms of the increased steric interactions of the solvated hydroxy group, which causes mainly hydrogen abstraction at the *trix* position of that geminal site (*gem* effect).[11]

Conclusion

The *trix* methyl group in the tetrasubstituted allylic alcohol **2** makes the two sides (*twix* + *lone* versus *twin* + *trix*) of the double bond more equal in the steric interactions with the attacking enophile, as compared to the trisubstituted allylic alcohol **1**; additionally, the regioisomeric *trix* ene product is formed in the case of the tetrasubstituted substrate **2**. As a consequence, the latter provides valuable information on the regioselectivity and the diastereoselectivity of the ene reaction. Therefrom, a more detailed mechanistic understanding of the enophilic behavior of $^1O_2$, PTAD, and ArNO has been acquired. In regard to the diastereoselectivity, the additional 1,2-allylic strain of *trix* substitution does not affect the conformational alignment of the allylic hydroxy functionality; in fact, the tetrasubstituted allylic alcohol **2** is even more *threo*-selective than the trisubstituted derivative **1** with only 1,3-allylic strain.

The regioselectivity for the tetrasubstituted olefin *Z*-**2**-d_3 revealed an unprecedented dichotomy between the $^1O_2$ versus the PTAD and ArNO enophiles: For PTAD and ArNO, regioselectivity is subject to hydroxy-group directivity in favor of *twix* hydrogen abstraction, whereas $^1O_2$ prefers hydrogen abstraction at the *twin* and *trix* sites, that is, *anti* to the hydroxy group. From this finding, we recognize that the regioselectivity for $^1O_2$ is not controlled by hydrogen bonding, but clearly dictated by the *cis* effect.[9] Nevertheless, it must be emphasized that the high *threo* diastereoselectivity for both the *twin* and the *twix* regioisomers is the consequence of hydrogen bonding by the allylic hydroxy functionality. Such electronic interaction steers the attacking enophile to the *threo* π face of the substrate (cf. the *threo*-**EC** structures in Schemes 5 and 6). Thus, an important new feature has been recognized on the enophilic trajectory, that control of diastereoselectivity precedes that of regioselectivity, because for the latter the enophile must penetrate deeply into the π system of the double bond to form the required three-membered-ring structures, the precursors to the regioisomeric ene products.

The interdependence of the *twin*/*twix* regioselectivity and *threo*/*erythro* diastereoselectivity in the deuterium-labeled allylic alcohols *Z*-**1**-d_4 and *Z*-**2**-d_3 shows for $^1O_2$ an increased *twin* regioselectivity for the *erythro* diastereomer. This implies that for the *erythro* diastereomer, the enophile attacks also the lower-strained substrate conformer without assistance by hydrogen bonding. Remarkable is that the *threo*/*erythro* diastereoselectivity for the individual *twin*/*twix* regioisomers is the same for all three enophiles $^1O_2$, PTAD, and ArNO.

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Supporting Information Available: Complete experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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