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Regioselectivity in the Ene Reaction of Singlet Oxygen with Alkenes

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Dedicated to Professor C. S. Foote on the occasion of his 65th birthday

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Contents

1. Introduction

The chemistry of singlet molecular oxygen ($^1O_2$) has received remarkable attention by chemists not only because of its interesting mechanistic and synthetic aspects[1–4] but also because of its large environmental[5–7] and biomedical significance.[8–10] Among the peculiar types of reaction involving $^1O_2$ with organic substrates are: [4+2], ene, and [2+2] additions to alkenes and oxidation of organic compounds of sulfur, phosphorus, etc. The ene reaction[2,3,11,12] was originally discovered by Schenck in 1953,[13] and it was revived after the pioneering work of Foote[14] in the early 1960s. Ever since, amongst all singlet oxygen reactions, it has attracted major interest due to its controversial reaction mechanism and fascinating regiochemistry and stereochemistry.

In the past a great deal of work has been focused on whether the ene reaction proceeds through a concerted or a stepwise mechanism. The initially proposed synchronous pathway[15] was challenged by biradical,[16] zwitterionic,[17] or perepoxide[11] intermediates (Scheme 1). Kinetic isotope effects in the photooxygenation of tetrasubstituted,[18] trisubstituted[19] and *cis* alkenes[20] supported the irreversible formation of an intermediate perepoxide, while for *trans* alkenes,[21,22] a

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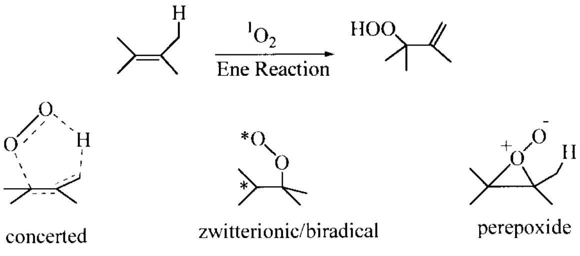


Scheme 1.

partial equilibration of the intermediate with the reactants was proposed. Consistent with the perepoxide intermediate is also the observation that the ene reaction proceeds as a highly suprafacial process, in which the conformational arrangement of the allylic hydrogen controls the stereochemistry of the allylic hydroperoxide produced.[23]

Trapping of the intermediate with sulfoxides,[24] phosphites,[25] and sulfenates or sulfinate esters,[26] in the photooxygenation of adamandylidenoadamantane, and theoretical calculations[27–31] as well, support the perepoxide as the most possible intermediate. Many authors consider an intermediate exciplex[32–34] instead of the polar perepoxide. Since the geometry of the intermediate is well defined from isotope effects and stereochemical studies, if an intermediate exciplex is formed, its geometrical features must resemble those of a perepoxide.

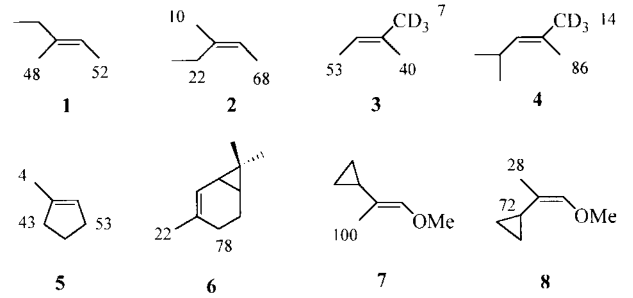
In the photooxygenation of electron rich alkenes like enamines,[35] enol ethers,[36] enol esters[37] and dienes,[38–40] there is a partitioning between perepoxide and zwitterionic intermediates, affording mixtures of ene and cycloaddition products, whose relative abundance depends on solvent polarity and temperature.

2. Regioselectivity of the Ene Reaction

2.1. '*cis* Effect' with trisubstituted alkenes and enol ethers

In the reaction of $^1O_2$ with trisubstituted alkenes[41,42] and enol ethers,[43,44] the more reactive side of the double bond is the more substituted. This surprising selectivity is referred to as the '*cis* effect' (Table 1). Both experimental and theoretical chemists have offered explanations for the '*cis* effect'. Bartlett and Frimer[45,46] studied the primary and secondary isotope effects in the photooxygenation of 2,3-dihydro-γ-pyran and suggested the importance of an initial orbital interaction between the incoming oxygen and the enol ether. Stephenson[47] suggested that an interaction between the LUMO orbital of the oxygen and the HOMO orbital of the olefin stabilizes the transition state of perepoxide formation. This is particularly true for the case of *cis*-2-butene where the bonded orbitals of the allylic hydrogen contribute to the HOMO orbital of the olefin, thus generating a system similar to the ψ_3 state of butadiene. The interaction of this system with the π^* LUMO orbital of the oxygen is favorable. For the *trans* isomer the contribution of the bonded orbitals of the allylic C–H bonds to the HOMO orbital of the olefin is approximately half, thus making the interaction with the oxygen LUMO less favorable.

Table 1. Numbers indicate percentage of double bond formation in the ene adducts



For a cycloalkene[48] it was proposed that there is a correlation between the orientation of the allylic hydrogen in the ground state and its reactivity. The allylic hydrogens at the axial position are more reactive, because the orbital overlap between oxygen and allylic hydrogens is optimum in such a conformation.

In 1981 Houk and coworkers,[49] using STO-EG semiempirical calculations, suggested that for acyclic alkenes differences in regioselectivity are related to the different energies required for an allylic hydrogen to adopt a perpendicular arrangement to the olefinic plane. For example, in *cis*-2-butene the rotational barrier of an allylic hydrogen to adopt a perpendicular alignment to the double bond plane from an eclipsed conformation was calculated to be 1.06 kcal/mol, while for the *trans* isomer it is higher by 1 kcal/mol. This assumption was in accordance with the experimental observation that *cis* alkenes react about 10–20 times faster than their *trans* isomers.[50]

Schuster and coworkers[51,52] measured the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ in the ene reaction of $^1O_2$ with a series of alkenes and suggested that there is a type of 'hydrogen bonding' interaction in the rate-limiting step of perepoxide formation between the allylic hydrogens and the intermediate. For example, in the reaction of *cis*-2-butene activation entropy $\Delta S^\ddagger$ is less negative by 10 e.u., than that of the corresponding *trans* isomer, while the activation enthalpies $\Delta H^\ddagger$ are very similar. The considerable difference in the activation entropies was attributed to the fact that transition states in the cases of *cis* olefins require more organization because of the simultaneous interaction of the incoming oxygen with two allylic hydrogens as seen in the accompanying scheme. On the other hand for *trans* alkenes, this interaction occurs with only one allylic hydrogen.

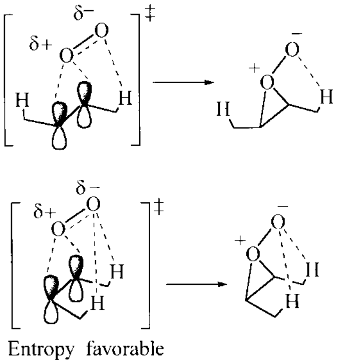
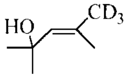
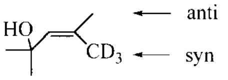


Table 2. *syn*/*anti* Selectivity in the photooxygenation of allylic alcohols **9**-*E* and **9**-*Z*



9-E



9-Z

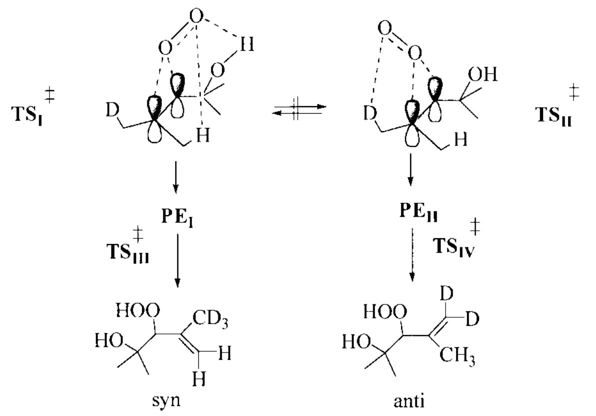
Substrate	Solvent	*syn*/*anti* Selectivity
9-*E*	CCl_4	75:25
9-*E*	Benzene	73:27
9-*E*	CH_3CN	41:59
9-*E*	MeOH	33:67
9-*Z*	CCl_4	72:28
9-*Z*	CH_3CN	40:60

It can be concluded that most of the proposed explanations are consonant with the existence of an interaction between the incoming oxygen and two allylic hydrogens that highly stabilizes the transition state of perepoxide formation.

2.2. *syn* Stereoselectivity with allylic alcohols

Recently, Adam and coworkers, in order to explain the high diastereoselectivity (d.e. ~90%) observed in the photooxygenation of chiral allylic alcohols[53,54] and amines,[55,56] proposed that singlet oxygen forms an exciplex with the allylic alcohol, in which the oxygen coordinates to the hydroxyl. This coordination, in combination with the 1,3-allylic strain, provides, in non-polar solvents, high selectivity for threo allylic hydroperoxides. This effect was found to control the *syn*/*anti* stereoselectivity[57,58] in the photooxygenation of allylic alcohols **9**-*E* and **9**-*Z*. In non-polar solvents (CCl_4, benzene) the *syn* methyl group is more reactive ('*cis* effect' type selectivity), while in polar solvents, such as acetonitrile or methanol, which are capable of hydrogen bonding with the hydroxyl, regioselectivity is almost reversed (Table 2).

Examination of the possible transition states in Scheme 2 helps to understand the observed stereoselectivity. For allylic alcohols **9**-*E* and **9**-*Z*, singlet oxygen is capable of interacting with only one allylic hydrogen on either side of the olefin. The lack of stereoselectivity, whether the *anti* or the *syn* methyl is labeled, indicates that perepoxide formation occurs in the rate limiting step. In $TS_I^\ddagger$ (applied to **9**-E), where the electrophile approaches the olefin from the more crowded side to form PE_I, the oxygen interacts simultaneously with the hydroxyl and one allylic hydrogen. This interaction stabilizes the transition state. Polar solvents interact with the hydroxyl through hydrogen bonding and reduce its ability to interact with the oxygen. Thus, the activation energy of $TS_I^\ddagger$ increases significantly and leads to a reversal of selectivity which is now controlled by steric factors. The observed stereoselectivity in methanol (*syn*/*anti*=33:67) is a typical example of anti '*cis* effect' behavior, similar to that observed in the sterically analogous substrates **10**-*E* and **10**-*Z* (see accompanying Section 2.3).



Scheme 2.

2.3. Anti '*cis* effect' selectivity

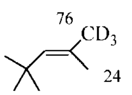
The proposal that there is a stabilizing effect by the simultaneous interaction of $^1O_2$ with two allylic hydrogens on the same side of the olefin during the formation of the perepoxide, suffices to explain the rare cases where anti '*cis* effect' selectivity has been observed in the photooxygenation of the series of acyclic trisubstituted alkenes[59] shown in Table 3.

For these substrates, the less substituted side of the double bond is the more reactive. In the case of alkenes **10**-*E* and **10**-*Z*, for example, formation of the perepoxide on the more substituted side of the olefin is not favorable because of steric repulsions between the oxygen and the two alkyl groups. Also, during the formation of the intermediate, oxygen is interacting with only one allylic hydrogen on both sides of the double bond. Thus, the stabilizing interaction of oxygen with two allylic hydrogens in the same side of the double bond is absent in these substrates. This is evident in Scheme 3 where the intermediates in the reaction of $^1O_2$ with **10** and **4** are found.

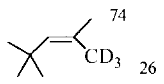
In general, the anti '*cis* effect' selectivity is related: (a) to the degree of crowdedness on the more substituted side of the olefin; (b) to the non-bonded interactions during the formation of the new double bond; and (c) most importantly, to the lack of simultaneous interaction of the incoming oxygen with two allylic hydrogens.

In the literature there are a few examples of cyclic olefins which exhibit anti '*cis* effect' selectivity. Typical examples are substrates **13**[60] and **14**[61] in Table 3. Examination using molecular models reveals severe conformational restrictions for the tertiary allylic hydrogens on the more substituted side of the double bond in adopting the necessary orientation either for abstraction or for 'positive' interaction with the incoming oxygen.

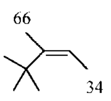
Table 3. Numbers indicate percentage of double bond formation in the ene adducts



10-E



10-Z



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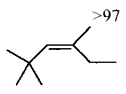

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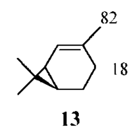

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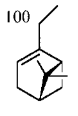

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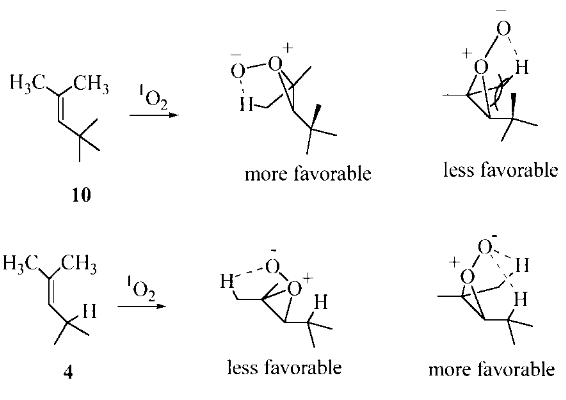
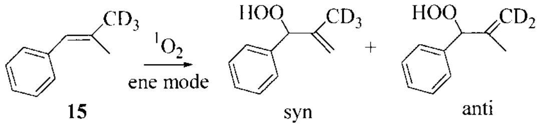


Scheme 3.

Table 4. *syn*/*anti* Stereoselectivity in the ene reaction of $^1O_2$ with β,β-dimethylstyrene



Solvent	*syn*/*anti* Selectivity[a]
CCl_4	56:44
CH_3CN	71:29
MeOH	82:18

[a] *syn*=H-abstraction, *anti*=D-abstraction.

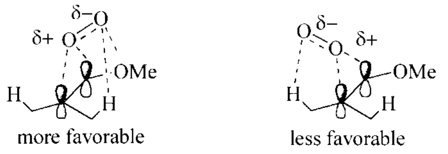
2.4. Phenyl group directing *syn* selectivity

Surprisingly, in the reaction of $^1O_2$ with β,β-dimethylstyrene (**15**),[62] the ene products which are formed, apart from dioxetane and diendoperoxides,[63,64] exhibit an unexpected solvent-dependent *syn* selectivity, although the intermediate in the more substituted side of the olefin can interact with only one allylic hydrogen. Thus the *syn* methyl group of **15** is 56% reactive in CCl_4, while in the more polar methanol the reactivity becomes 82% (Table 4).

This stereoselectivity is unexpected, considering that in the more substituted side of the olefin oxygen is capable of interacting with only one allylic hydrogen. Thus, anti '*cis* effect' selectivity would be expected.

Intermolecular isotope effects revealed that in the photooxygenation of **15** formation of the perepoxide is the rate determining step.[62] Although the incoming oxygen is oriented towards the more substituted side of the olefin ($TS^{\ddagger}_{I}$), it interacts with only one allylic hydrogen; nevertheless this transition state affords the major product (Scheme 4). Thus, the stabilization must arise from the interaction of the perepoxide with the phenyl group. In $TS^{\ddagger}_{I}$, which leads to perepoxide PE_I, the benzylic carbon is partially behaving as a carbocation which is stabilized by resonance with the phenyl group. Interaction of the negatively charged oxygen of perepoxide with the phenyl ring, which has lost part of its electronic density, results in significant stabilization. By increasing the polarity of the solvent this stabilization increases because the cationic character at the benzylic carbon becomes more profound, thus making $TS^{\ddagger}_{I}$ more dominant due to solvation. Transition state $TS^{\ddagger}_{II}$ which leads to the *anti* ene product (D-abstraction) is less favored, being stabilized by only a single interaction between the oxygen and the one allylic hydrogen.

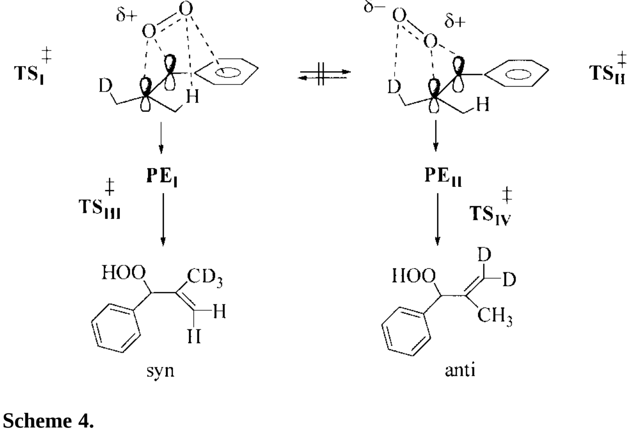
The same rationale can also be used to explain the '*cis* effect' behavior which was observed earlier in the photooxygenation of trisubstituted enol ethers[43,44] (Section 2.1). Oxygen prefers to form the intermediate on the more crowded side, where it interacts with the electronegative methoxy substituent. In the transition state for the formation of the perepoxide the carbon next to methoxy has significant carbocationic character and is stabilized by the methoxy group through resonance. An interaction of the negatively charged oxygen of the perepoxide and the methoxy group stabilizes the transition state for the formation of the perepoxide, just as the phenyl group does in the case of substrate **15**.



2.5. Regioselectivity with *cis* and *trans* disubstituted alkenes. The large group non-bonded effect

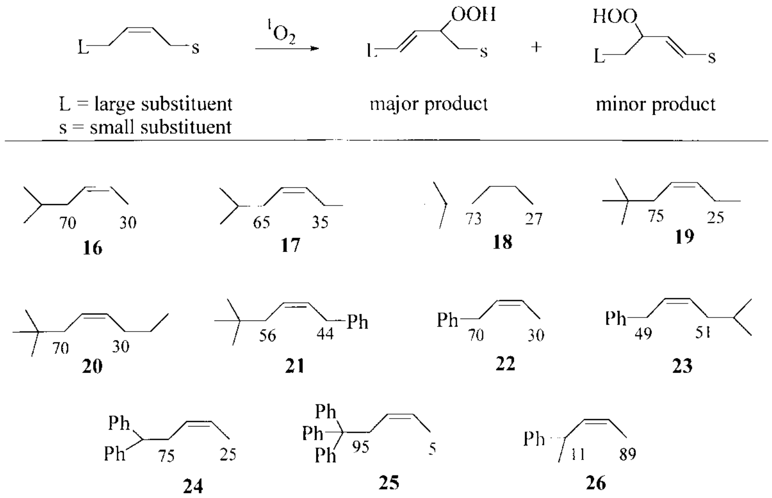
In the reaction of singlet oxygen with non-symmetrical *cis* disubstituted alkenes, an unexpected regioselectivity was found.[65] The allylic hydrogens next to the large alkyl substituent are more reactive than those next to the small group. Some examples are shown in Table 5.

In substrate **19** where L=*t*-butyl and s=methyl, the double bond is formed next to the bulkier *t*-butyl group 75% and only 25% next to the methyl. By retaining the L=*t*-butyl and increasing the size of the alkyl group on the other side of the olefin from methyl to phenyl (substrates **20** and **21**) a decrease in the percentage of hydrogen abstraction from the side of the *t*-butyl is observed. For substrate **21** where the competing substituents are a *t*-butyl group and a phenyl group, there is a small preference for double bond formation next to the bulkier *t*-butyl. This demonstrates that conjugation of the phenyl group with the forming double bond is not sufficiently developed in the transition state to overcome



Scheme 4.

Table 5. Numbers indicate percentage of double bond formation in the ene adducts



the control of regioselectivity by steric effects (see also substrate **23**). In the extreme case where the large substituent is the triphenylmethyl group (substrate **25**) the reaction is highly regioselective. The regioselectivity trend is altered when there is only one allylic hydrogen on the more bulky side of the double bond (e.g. substrate **26**) due to the unfavorable conformation of the methine hydrogen atom to adopt a perpendicular geometry to the former double bond, since considerable 1,3-allylic strain is developing. In addition, there are steric repulsions between the *cis* alkyl groups on the forming double bond during the methine hydrogen atom abstraction step (two alkyl groups adopt a *cis* geometry in the double bond of the adduct).

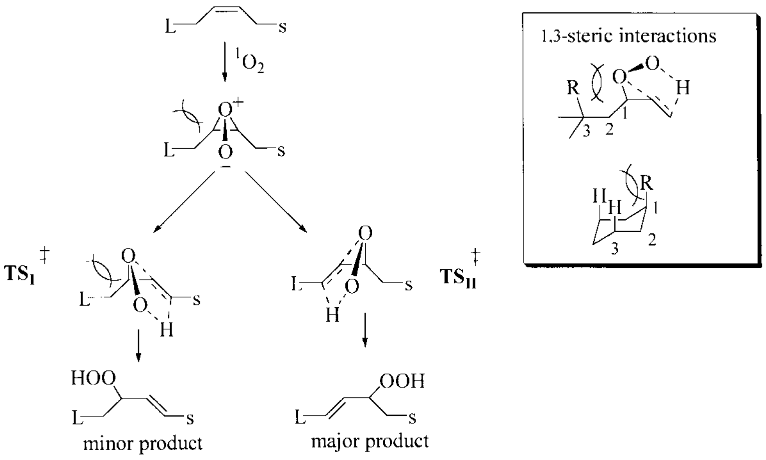
The regioselectivity was explained[65] by examining the possible transition states leading to the allylic hydroperoxides (Scheme 5). In transition state TS$^\ddagger_{II}$, which leads to the minor product, the repulsive 1,3-non-bonded interactions between the oxygen atom and the large group L, which exist in the intermediate perepoxide, still remain (the large group non-bonded effect). This transition state is expected to be higher in energy than TS$^\ddagger_I$ where these repulsive interactions are released. The non-bonded interactions developing in TS$^\ddagger_{II}$ are similar to those appearing in the axial conformers of monosubstituted cyclohexanes.

The photooxygenations of the *trans* alkenes proceed approximately 20 times more slowly than those of the corresponding *cis* isomers.[49] The few examples which have been studied,[66] are summarized in Table 6. The regioselectivity does not differ at all from that of the corresponding *cis* isomers found in Table 5. Considering that the formation of perepoxide in the photooxygenation of *trans* alkenes is reversible,[22] the 1,3-non-bonded interactions in the product forming transition states between the oxygen and the alkyl substituents appear to control the regioselectivity in a similar fashion to those shown in Scheme 5.

2.6. Regioselectivity with geminal dimethyl and diethyl trisubstituted alkenes

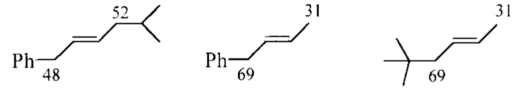
The regioselectivity trend in the photooxygenation of geminal dimethyl and diethyl trisubstituted olefins is similar to that observed in *cis* or *trans* disubstituted alkenes, with the allylic hydrogens next to the bulky alkyl substituent being more reactive. The results[66] are summarized in Table 7.

In a representative example (substrate **34**), where L=*t*-butyl and R=H, the methylene hydrogens are statistically 6–7 times more reactive than the hydrogen atoms of the two geminal methyl groups. Starting from 2-methyl-2-pentene



Scheme 5.

Table 6. Numbers indicate percentage of double bond formation in the ene adducts



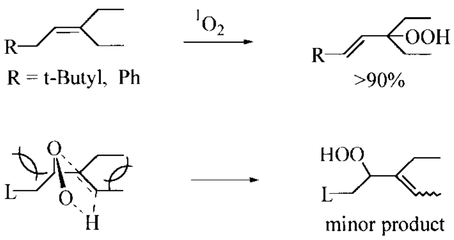
27 **28** **29**

where R=H and L=H and increasing the size of the L substituent, after ethyl substitution, a significant increase in the percentage of the anti-Markovnikov product is observed. When the L substituent is the very bulky triphenylmethyl group (substrate **38**) the reaction becomes highly regioselective (92:8).

The transition states in the hydrogen abstraction step, as seen earlier in Scheme 5, help to explain the observed change in regioselectivity. In a transition state where there is a strengthening of the C–O bond on the tertiary carbon, a release of the 1,3-non-bonded interactions between the oxygen atom and the L group with respect to the intermediate perepoxide occurs. Therefore, this transition state is expected to be lower in energy than a transition state where non-bonded interactions exist.

When the geminal dimethyl group is replaced by geminal diethyl functionality (substrates **39** and **40**), a higher degree of regioselectivity is observed. The transition states leading to the minor product are even less favored, not only because of the 1,3-non-bonded interactions between the group L and the oxygen, but also because of the repulsions developing when the ethyl group (Scheme 6) adopts a *cis* geometry with a methyl group in the newly forming double bond (see also discussion in Section 2.8). We would predict that if the geminal dimethyl group is replaced by a geminal di-*n*-propyl or a longer di-*n*-alkyl group, the reaction would be regiospecific (>97% selectivity).

For a series of geminal dimethyl trisubstituted alkenes the same trend in regioselectivity was recognized earlier by Thomas[69] and Rautenstrauch.[70] By examining molecular models and assuming that the reaction is concerted, Thomas and coworkers proposed that the difference in regioselectivity could be due to the different conformations and steric repulsions in the transition states.



Scheme 6.

2.7. Geminal regioselectivity with respect to a bulky allylic substituent

In 1988 Clennan and Chen[71] reported that replacement of an allylic hydrogen in tetramethylethylene with a series of functional groups (sulfides, sulfoxides, sulfones, cyano, halides etc.) affords substrates which, upon photooxygenation, give ene products with a surprising geminal selectivity with respect to the allylic functionality (Table 8).

Three possible explanations were proposed to account for the observed regioselectivity:

(a) Electronic repulsions between the lone pairs of the heteroatoms and the negatively charged oxygen of the perepoxide. Such a repulsive interaction would favor the intermediate on the other side of the double bond with respect to the functionality, which gives ene product with geminal hydrogen abstraction.

(b) Anchimeric assistance by the allylic substituent leading to regioselective opening of the perepoxide intermediate by an S_N^2 mechanism. However, this could explain the regioselectivity only in those cases where the allylic substituent is sulfur.

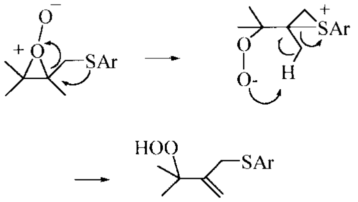


Table 7. Numbers indicate percentage of double bond formation in the ene adducts. [a]Ref. 67, [b]Ref. 68

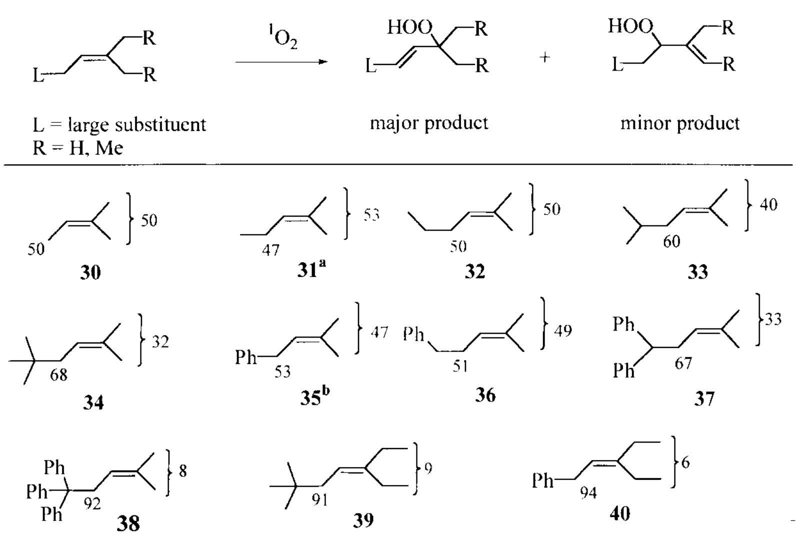
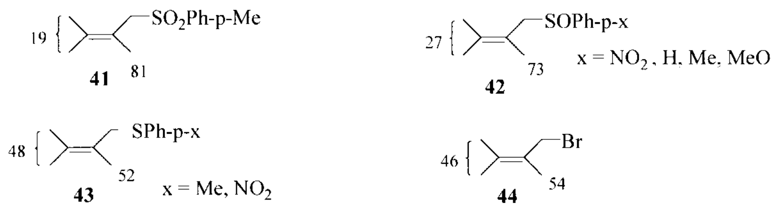


Table 8. Numbers indicate percentage of double bond formation in the ene adducts



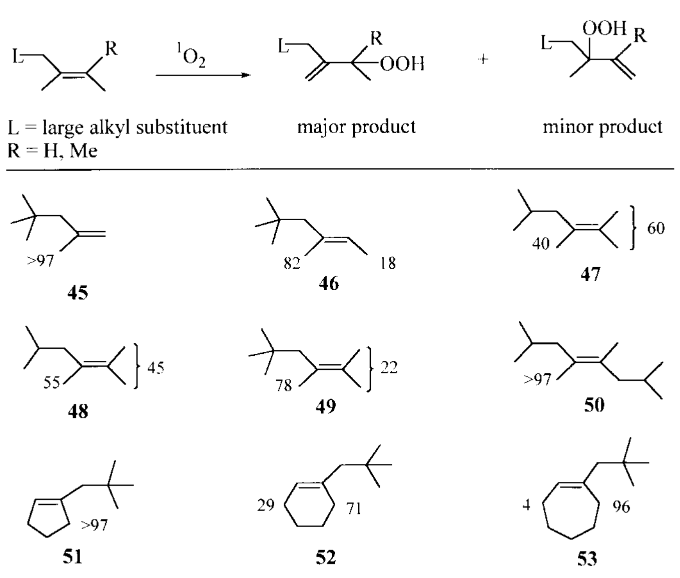
(c) Different barriers to rotation of the methyl groups of the substrate. A similar explanation has been reported earlier by Houk and coworkers[49] in order to explain the *syn* preference of singlet oxygen ene reactions with trisubstituted alkenes.

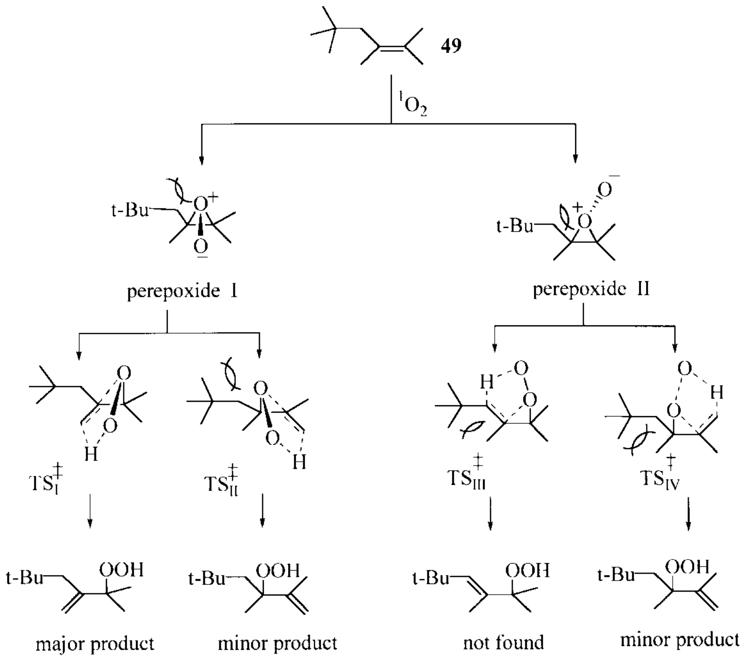
In order to examine the factors affecting geminal regioselectivity, the groups of Orfanopoulos[72] and Clennan[73] independently synthesized a series of alkyl substituted tetramethylethylenes at the allylic position (Table 9). Several 1-neopentyl substituted cycloalkenes[74] were also studied. The photooxidation products revealed that the general scheme of regioselectivity is exactly the same as in the case where the allylic substituents are heteroatoms (Table 8), thus indicating that there is no significant contribution of electronic effects (explanations a and b), for the observed regioselectivity. It is obvious that as the size of the L substituent increases the degree of geminal selectivity is higher. The same principle also applies in the cases of 1-neopentyl substituted cycloalkenes with a surprisingly high degree of regioselectivity. The geminal selectivity varies from 71% for **52**, to >97% for **51**.

Examination of the possible product forming transition states (Scheme 7) in the reaction of singlet oxygen with 2,3,5,5-tetramethyl-2-hexene (**49**) helps to understand the geminal selectivity. Each of the two perepoxides **I** and **II**, can lead through transition states TS$^{\ddagger}_{\text{I–IV}}$ to products. In TS$^{\ddagger}_{\text{I}}$, relief of 1,3-repulsions with respect to the intermediate perepoxide I is observed. Indeed, this transition state leads to the major ene product. Transition state TS$^{\ddagger}_{\text{II}}$ is not favored due to the retention of non-bonded interactions. For the same reason, TS$^{\ddagger}_{\text{IV}}$ from perepoxide **II** is also not favored. Both of these two transition states lead to the minor product. Finally, in TS$^{\ddagger}_{\text{III}}$ although there is relief of 1,3-non-bonded interactions between the oxygen atom and the *t*-butyl group, two alkyl substituents (*t*-butyl and methyl) adopt a *cis* conformation in the newly forming double bond, which is highly unfavorable, and no product derived from this pathway is formed.

Geminal selectivity is also observed in cases where the bulky substituent is a vinylic substituent.[66,72,74] The examples are shown in Table 10. The explanation of the geminal selectivity observed for these substrates is exactly the same as previously proposed in the case of the alkenes bearing a large allylic substituent (transition states of Scheme 7). For example, in substrate **56** the non-bonded interactions between the *t*-butyl group and the oxygen atom in the intermediate weaken the C–O bond next to the bulky substituent in the product forming transition state. In substrates **58**, the presence of various electronic substituents at the *para* position[66,76] does not alter the geminal regioselectivity in any way, despite the fact that the photooxygenation of the *p*-MeO derivative proceeds much faster than that of the *p*-CF$_3$ substituted styrene. This finding is expected, considering that formation of the perepoxide is the rate limiting step.[11,22] For these styrene-type substrates, although the active stereosize of the phenyl group is smaller than the *t*-butyl group in **56**, the geminal selectivity is higher. This

Table 9. Numbers indicate percentage of double bond formation in the ene adducts



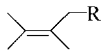


Scheme 7.

may be attributed to the fact that the forming double bond is in conjugation with the phenyl group. Furthermore, in substrate **61**, the 1,3-repulsions (see also Scheme 7) between the oxygen atom and the allylic *t*-butyl group and those with the vinylic *t*-butyl are expected to be similar. Thus, a moderate regioselectivity of 55:45 is observed.

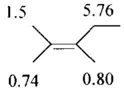
For cycloalkenes, the variation in the percentage of geminal regioselectivity is probably due to the combination of both effects: (a) the different conformational arrangements of the allylic hydrogens in the ring systems as proposed earlier by Rautenstrauch et al.[48] and (b) the 1,3-non-bonded interactions between the large groups and the oxygen.

Clennan and coworkers,[73] based on the theoretical model of Houk (MM2 calculations),[49] found that for some alkyl substituted tetramethylethylenes (TME-R) there is a surprising correlation between the rotational barriers and their reactivity towards $^1O_2$. This model predicts that the lower the barrier to rotation the higher the hydrogen abstraction from the perepoxide. Some numerical values in kcal/mol are depicted below for substrates **54** and **49**. In 2,3,5,5-tetramethyl-2-hexene (**49**) for example, the more reactive methyl group (geminal, 78%) has the lowest barrier to rotation (0.85 kcal/mol) with respect to the other two methyls.

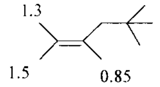


TME-R

R = Me, Et, i-Pr, t-Bu



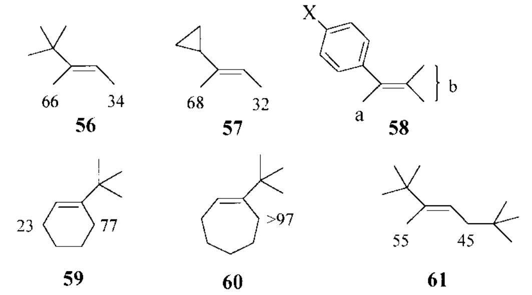
54



49

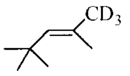
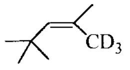
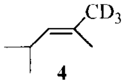
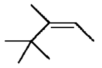
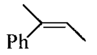
In order to shed some light on this regioselectivity problem, Orfanopoulos and coworkers calculated the rotational barriers for the allylic methyls, with the HF-STO-3G method, in a series of trisubstituted alkenes and compared them to the observed experimental regioselectivity.[75] Some results are shown in Table 11. For alkenes **10**-*E* and **10**-*Z*, the *syn* methyl groups have lower rotational barriers than the corresponding *anti* ones by 0.6 kcal/mol. This is in the opposite direction to the proposed theoretical model. However, for alkene **4** there is a correlation between rotational barriers and ene reactivity. Alkenes **11** and **55** also

Table 10. Numbers indicate percentage of double bond formation in the ene adducts



X	a	b
MeO	76	24
Br	76	24
CF_3	74	26
H	74	26

Table 11. (a) Percentage of double bond formation in the ene adducts. (b) Barriers to rotation of the methyl groups (kcal/mol)

	a	b
 **10-E**	76 24	1.63 1.11
 **10-Z**	74 26	1.63 1.11
 **4**	14 86	1.64 0.40
 **11**	66 34	2.91 0.91
 **55**	64 36	1.45 1.22

demonstrate impressively that there is no correlation between ene reactivity and rotational barriers. Again in these examples the more reactive *trans* methyl group is the one which shows the higher rotational barrier in contrast to the predictions of the proposed theoretical model. These results indicate that there is not always a correlation between the reactivity of the methyl groups and their rotational barriers. More importantly, according to the Curtin–Hammett principle, the rotational barriers are irrelevant to the product distribution since their values are too small (0.5–2 kcal/mol) compared to the activation energies of the reactions (6–13 kcal/mol).

2.8. The role of non-bonded interactions between the *cis* alkyl substituents during the formation of the new double bond in the ene adduct

In the second step of the ene reaction, during the formation of the adduct double bond, if two alkyl substituents adopt a *cis* orientation the transition state leading to the adduct is highly unfavorable. This can be demonstrated by examining the regioselectivity in the series of substrates[77] of Table 12.

For olefin **62**, the methylenic hydrogens are more reactive than the hydrogens of the methyls (ratio 70:30). By increasing the size of the alkyl group (substrate **63**), the methylenic hydrogens become much less reactive (<5%). This remarkable change in regioselectivity can be attributed to higher repulsions between the propyl groups when compared to the ethyls, during the formation of the minor allylic hydroperoxide. In the photooxygenation of **62** repulsions exist between an ethyl and a methyl group, whereas in **63** between an ethyl and a propyl. By increasing the size of the alkyl group to phenyl or isopropyl (substrates **64** and **65** respectively), a reverse regioselectivity trend is found.

For these specific cases, there are two equally competing factors in the product forming transition states which affect the regioselectivity (Scheme 8): (a) the 1,3-non-bonded interactions between the oxygen atom and the phenyl or isopropyl substituents in the transition state for hydrogen abstraction from the methyl group, and (b) repulsions between the *cis* alkyls, due to the formation of the new double bond by methylene hydrogen atom abstraction. The stabilizing contribution of the conjugation of the double bond with the phenyl group (alkene **64**) does not affect regioselectivity as previously noticed in the photooxygenation of **22** (Table 5).

Similar arguments can explain the change in regioselectivity of substrates **67** and **66** when compared to **56** and **16**, respectively. In **56** for example, replacement of the geminal methyl group with an ethyl group causes a significant drop in geminal selectivity. It is instructive to note in general that the reactivity of the methylene hydrogens is significantly decreased when a geminal methyl group is present, as clearly demonstrated by the examples presented in Table 13.

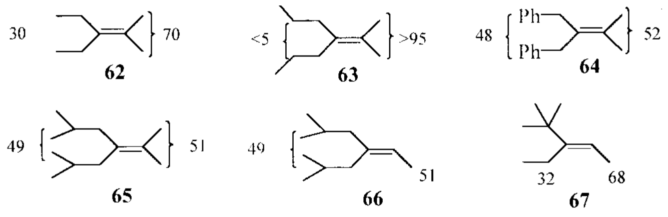
For instance, from comparison of substrates **4** and **69**, it is obvious that the reactivity of the *anti* methyl group increases substantially when a methyl group is replaced by an ethyl leading to anti '*cis* effect' selectivity.[59]

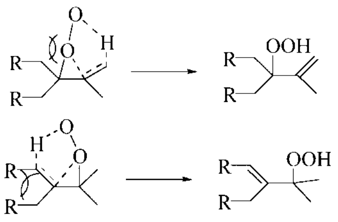
2.9. Geminal selectivity with vinylsilanes and vinylstannanes

The reaction of $^1O_2$ with vinyl silanes[78–81] and stannanes[82] has been studied extensively. Apart from small amounts of α,β-unsaturated ketones produced by decomposition of the labile α-hydroperoxy allylic silanes and stannanes, the ene reaction exhibits a high degree of geminal regioselectivity with respect to the trimethylsilyl or stannyl groups (Table 14).

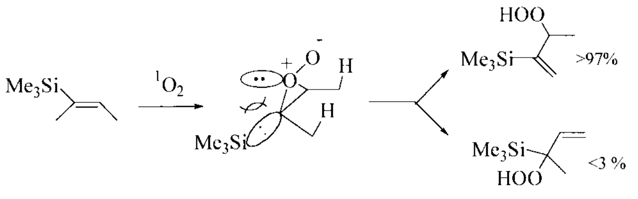
Although steric factors (bulky vinyl trimethylsilyl substitutent) may be responsible for the geminal selectivity (for the carbon analogues see Section 2.7), the selectivity was attributed to electronic factors. For the silanes, it was proposed that antibonding interactions of the C–Si σ bond and the lone pair of the non-terminal oxygen of the perepoxide are responsible for the high degree of regioselectivity (Scheme 9). Due to the higher energy of the σ orbital of the

Table 12. Numbers indicate percentage of double bond formation in the ene adducts



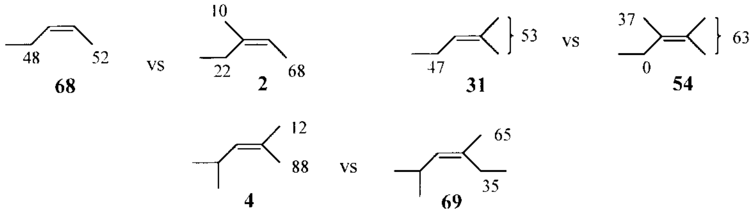


Scheme 8.



Scheme 9.

Table 13. Numbers indicate percentage of double bond formation in the ene adducts

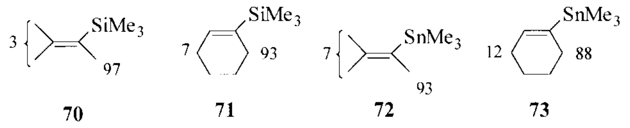


C–Sn bond, the interaction with the lone pairs of the oxygen is expected to be higher in stannanes. Yet, the geminal regioselectivities observed in stannanes are somewhat lower than those of silanes. However, since the C–Sn bond is longer than the C–Si bond and the non-bonded interactions between oxygen and the vinylic substituent are lower in stannanes, the degree of geminal selectivity is consequently higher for silanes than for stannanes.

2.10. Regioselectivity with allylic silanes, stannanes and germanes

Allylsilanes[83–85] exhibit a different regioselectivity pattern when compared to their carbon analogues (Section 2.6). The major ene product arises from hydrogen abstraction from the other side of the double bond, with respect to the silicon substituent. Also, in addition to *trans*, significant amounts of ene products are formed with *cis* geometry around the new double bond. It is interesting to compare the regioselectivity in the photooxygenation of alkyl substituted alkenes with allylic silanes. The size of the C–Si bond is 1.89 Å, almost 25% longer than the C–C bond. Although the Me_3Si group is more bulky than the *t*-butyl, the 1,3-non-bonded interactions must be far less important, since the methyl groups lie away from the oxygen of the perepoxide. For example, replacement of the *t*-butyl with the trimethyl silyl group for substrates **34** and **18** versus **74** and **75** (Table 15) leads to very different regioselectivity, as well as stereoselectivity (mixtures of *E* and *Z* allylic hydroperoxides). The few studies of photooxygenation of some cyclic allylgermanes,[86] indicate a similar regioselectivity trend to the silicon analogues, however, the directing effect of germanium is less pronounced.

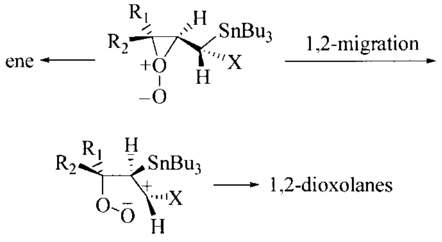
Table 14. Numbers indicate percentage of double bond formation in the ene adducts



To explain the regioselectivity trend in the photooxygenation of allylic silanes, it was proposed that an interaction between the negatively charged oxygen of the perepoxide and the silicon controls the abstraction of allylic hydrogen atoms (Scheme 10).

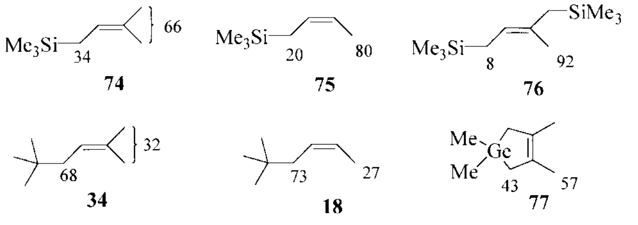
The formation of *cis* ene adducts[87] was attributed either to the intermediacy of a zwitterionic intermediate, or to a non-concerted pathway. A perepoxide intermediate was considered unlikely.

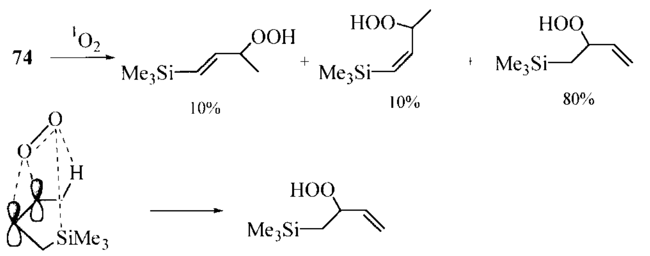
Photooxygenation of allylstannanes affords, apart from the ene derived allylic hydroperoxides, stannyldioxolanes.[88–90] The dioxolanes were proposed to derive through ring opening of the intermediate perepoxide with 1,2-migration of the stannyl group to form a zwitterion.



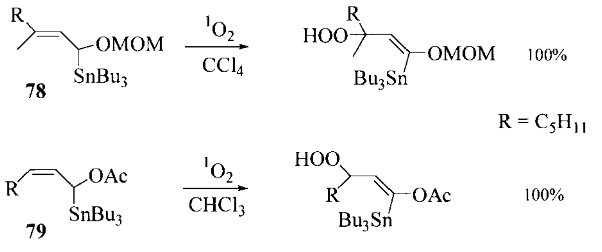
The regioselectivity of the ene pathway is surprising, with the trialkyltin group directing allylic hydrogen abstraction next to it, in contrast to the regioselectivity observed in allylic silanes,[91] as seen in substrates **78** and **79** of Scheme

Table 15. Numbers indicate percentage of double bond formation in the ene adducts





Scheme 10.



Scheme 11.

11. Although the tertiary allylic hydrogen seems to have the ideal geometry for abstraction in the perepoxide, additional factors may control this unexpected selectivity.

2.11. Regioselectivity with olefins bearing an electron withdrawing group at the α-position

For alkenes bearing an electron withdrawing group at the α-position such as aldehyde,[92] carboxylic acid,[93] ester,[94] ketone,[95,96] imine,[97,98] sulfoxide[99] and cyano,[100] a high degree of geminal selectivity has been demonstrated. The results are summarized in Table 16.

Many mechanisms had been proposed to rationalize this selectivity in the past (trioxanes, perepoxide, exciplex, dipolar or biradical intermediates), however, it is now generally accepted[101] that the mechanism proceeds through an intermediate exciplex which has the structural requirements of a perepoxide. This assumption is supported: (a) by the lack of stereoselectivity in the reactions with chiral oxazolines[102] and tiglic acid esters;[103] (b) from the comparison of the diastereoselectivity of dialkyl substituted acrylic esters[104] with structurally similar non-functionalized alkenes; (c) by intermolecular isotope effects[105] in the photooxygenation of methyl tiglate; and (d) by solvent effects on regioselectivity.[106]

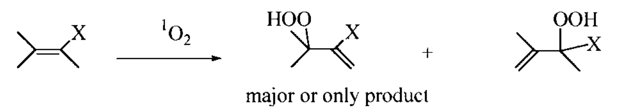
It seems reasonable to expect that in the hydrogen abstraction step, the perepoxide opens preferentially at the C–O bond next to the unsaturated moiety, because this transition state is more favorable due to the forthcoming conjugation in the adduct, as exemplified in the photooxygenation of methyl tiglate in Scheme 12.

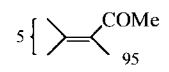
The 1,3-non-bonded interactions which control the regioselectivity in the photooxygenation of non-functionalized alkenes (see Sections 2.5–2.7), do not contribute significantly to the geminal selectivity of alkenes bearing at the α-position an electron withdrawing group. As seen in substrate **88**,[66] no reactivity of the methylene hydrogens next to the *t*-butyl group was found. This means that the non-bonded interactions between the *t*-butyl group and the oxygen atom are less important than the forthcoming double bond-carbonyl conjugation in the ene adduct.

2.12. Regioselectivity with olefins bearing an electron withdrawing group at the β-position, and with homoallylic alcohols. The role of electronic repulsions

When the electron withdrawing substituent is at the β-position with respect to the double bond, various trends in regioselectivity are observed[107] (Table 17). For the carbonyl derivatives (**89**–**92**) regioselectivity is invariable, and the methylene hydrogen atoms are approximately five times as reactive as those of the methyl groups. This selectivity resembles the cases where the allylic substituent is an isopropyl or phenyl group (Table 7). Furthermore, the forthcoming conjugation of the double bond with the functionality does not seem to be a driving force in the reaction, in contrast to the corresponding α,β-isomers (Table 16).

Table 16. Numbers indicate percentage of double bond formation in the ene adducts





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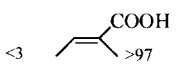
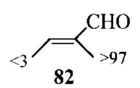
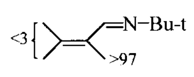


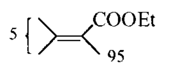
81



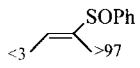
82



83



84



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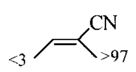

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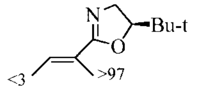

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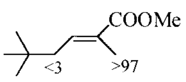

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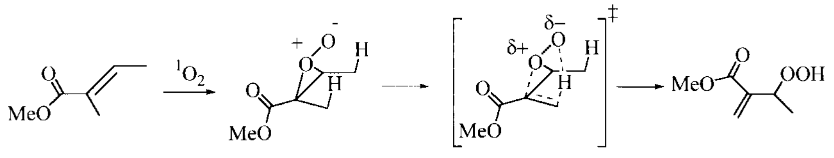
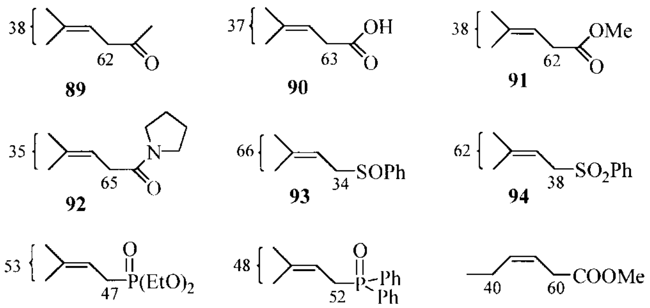


Scheme 12.

Table 17. Numbers indicate percentage of double bond formation in the ene adducts. For previous reports on the regioselectivity of **89** see Refs. 108,109; for substrate **93** see Ref. 110



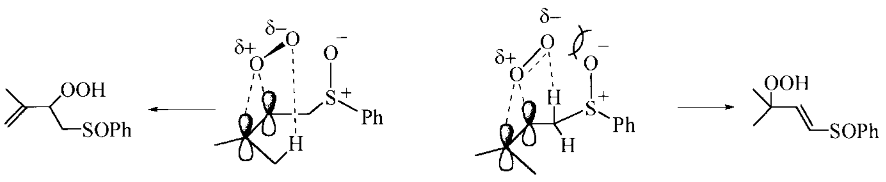
89 **90** **91** **92** **93** **94** **95** **96** **97**

Surprisingly, for substrates **93**–**96**, where the substituents are sulfoxide, sulfonyl, phosphate or phosphine oxide, the reactivity next to the allylic substituent decreases significantly, although these substituents are quite bulky. This behavior was attributed to the electronic repulsions between the highly polarized oxygen atoms of the S–O and P–O bonds and the negative oxygen atom of the perepoxide, which direct the intermediate to abstract a hydrogen from the methyl group (Scheme 13). The electronic repulsions probably do not force singlet oxygen to form the intermediate perepoxide on the less substituted side of the olefin, since the *cis* disubstituted β,γ-unsaturated ester **97** exhibits very similar reactivity to the trisubstituted substrate **91**. Analogous unfavorable repulsions[111–113] have been proposed to control the diastereoselectivity in the photooxygenation of chiral acylated allylic amines, sulfoxides, carbonyl, and carboxylic acid derivatives. The electronic control in the stereoselectivity of the electrophilic addition to alkenes is well documented.[114–116]

Since the existence of a hydroxyl group at the allylic position has a significant effect on the *syn*/*anti* methyl stereoselectivity[57,58] and the diastereoselectivity[53,54] of the photooxygenation ene reaction, it was interesting to assess the effect of the hydroxyl at the more remote homoallylic position. The regioselectivity in the reaction of $^1O_2$ with the geminal dimethyl trisubstituted homoallylic alcohols **98**–**100** and the *cis* disubstituted **101** was examined[117] in nonpolar solvents, and the regioselectivity trend compared with that of the structurally similar trisubstituted alkenes which have been discussed in Sections 2.5 and 2.6. The results are summarised in Table 18.

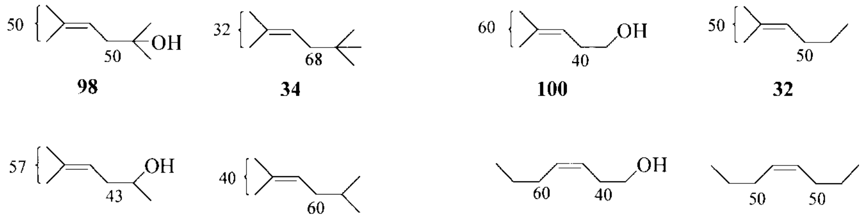
For alkenes **32**–**34** (Table 7) the regiochemistry is solely dependent on the steric hindrance of the allylic substituent. It is obvious that the regioselectivity trend for the homoallylic alcohols **98**–**100** differs from that of compounds **34**, **33** and **32** respectively, although the hydroxyl group exerts approximately the same steric hindrance as a methyl group.

The increased percentage of hydrogen abstraction from the geminal methyl groups can be attributed either to the fact that hydroxyl coordination to the negatively charged oxygen of the perepoxide directs hydrogen abstraction from the methyl group (seven-membered ring transition state), or more likely due to electronic repulsions between a hydroxyl group and an oxygen atom in the perepoxide which occurs in a six-membered ring transition state, analogous to that shown in Scheme 13. This assumption is further supported by the regioselectivity trend of substrate **101**. In the absence of any hydroxyl group effect, a product ratio of 50:50 would be expected, since steric hindrance is approximately the same on both sides of the double bond.[65] In fact, a ratio of 60:40 was found.



Scheme 13.

Table 18. Numbers indicate percentage of double bond formation in the ene adducts



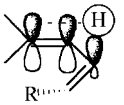
98 **34** **100** **32**

99 **33** **101**

2.13. Regioselectivity with twisted 1,3-dienes. Vinylic versus allylic hydrogen reactivity

Surprising selectivity is observed in the photooxygenation of significantly twisted 1,3-dienes which cannot adopt a reactive geometry for [4+2] cycloaddition. In these substrates a vinylic hydrogen atom is properly aligned in a conformation which is almost perpendicular to the olefinic plane and competes with the allylic hydrogens of the methyl group for ene adduct formation. Abstraction of the vinylic hydrogen leads to the formation of allene hydroperoxides. Some *trans*-β-ionone derivatives were reported[118–121] almost 30 years ago to afford small amounts of allene hydroperoxides by vinylic hydrogen abstraction. Recently, Katsumura and coworkers reported[122–124] that several twisted 1,3-dienes afford allene hydroperoxides in surprising yields (Scheme 14).

This selectivity was attributed to the perpendicular geometry of the vinylic hydrogen atom to the olefinic plane. In such a conformation, the vinylic hydrogen is 'activated' considering the large $\sigma^*-\pi$ interactions between the vinyl C–H bond and the reacting C=C double bond.



π C-C bond, σ* C-H bond interaction

For example, substrates **102** and **104** afford ene adducts with vinylic hydrogen atom abstraction at 74 and 90% ratio, respectively, when compared to 26 and 10% formation of the adduct with allylic hydrogen abstraction. The percentage of allene hydroperoxide is lower (43%) in the photooxidation of **103**. In this substrate, the steric hindrance at the stereogenic carbon is lower than in **102** or **104**, and the diene is therefore less twisted and the $\sigma^*-\pi$ interaction less profound, or by analogy, the vinylic hydrogen atom is less perpendicular to the double bond.

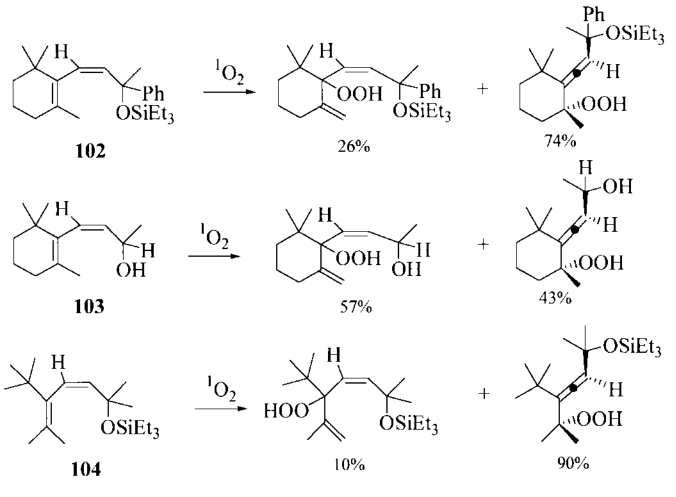
2.14. Regioselectivity in the autooxidation of fullerene adducts

Many adducts formed by several cycloadditions to C_{60} contain double bonds. Since C_{60} is itself an excellent photosensitizer,[125–129] in the presence of oxygen and light these adducts are autooxidized.[130–132] There are only two reports so far in the literature dealing with the ene regioselectivity in the autooxidation of fullerene adducts. The first is the photooxygenation of the adduct produced by the [2+2] photochemical cycloaddition of 2,5-dimethyl-2,4-hexadiene to C_{60} (**105**),[133] which affords a moderate threo/erythro diastereoselectivity of 55:45 which contrasts with that of chiral non-functionalized olefins which afford higher diastereomeric ratios.[12] The second case deals with the ene photooxygenation of several adducts prepared by the thermal [4+2] cycloaddition of conjugated dienes to C_{60} (Table 19).[134]

It is obvious that the methylene hydrogens next to fullerene are more reactive than the methyls (compare substrates **106**–**108**, and **107**–**109**). The strong preference for the formation of the perepoxide *syn* to the fullerene which leads to the major ene products was attributed to the ideal interaction of singlet oxygen with the methylene allylic hydrogen atoms during the formation of the *syn*-perepoxide. The methylene hydrogens adopt the preferable perpendicular conformation to the olefinic double bond.[48] However, the possibility that additional factors such as favorable electrostatic or electronic interactions may also contribute, cannot be excluded.

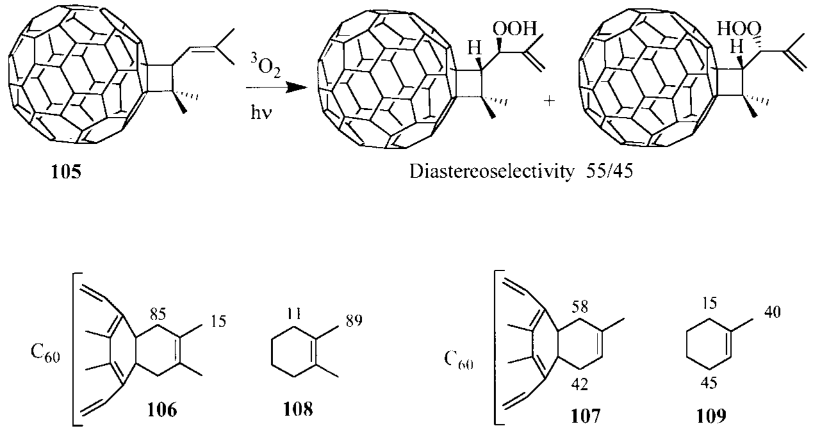
2.15. Regioselectivity of the ene photooxygenation reaction within zeolites

The reaction pathways for the photooxygenation of alkenes and dienes changes significantly when the photosensitizer is adsorbed into the cavities of zeolites.[135,136] Singlet oxygen is produced inside the cavity and reacts only with the organic substrates which are adsorbed. Since $^1O_2$ has a limited lifetime, photooxidation cannot take place in the out of cavity environment. The photooxygenation of 1-methylcycloalkenes[137,138] in zeolite Na–Y gave almost a single allylic hydroperoxide derived from hydrogen abstraction from the methyl group, a result which is the opposite from that found in the absence of a zeolite ('*cis* effect' selectivity, Section 2.1). Furthermore, in the reaction with geminal dimethyl trisubstituted alkenes[139] the methylene hydrogen atom have little or negligible reactivity depending on the cation



Scheme 14.

Table 19. Numbers indicate percentage of double bond formation in the ene adducts



of the zeolite. The order of increasing selectivity is $Li^+ > Na^+ > K^+ > Cs^+$. The regioselectivity within zeolites is different to that found in solution (see Section 2.6). Some examples in the photooxidation of trisubstituted alkenes and cycloalkenes in Na-zeolite (thionin as sensitiser), are summarized in Table 20.

The change in regioselectivity using Y-zeolites was rationalized in terms of two independent models.[138] In the first, it was postulated that steric interactions within the cavity of the zeolite provide the necessary conformations of the allylic hydrogen atoms which are abstracted. The conformation of an alkene inside the cavity depends on cation–π C–C bond interactions. The smaller the cation, the stronger the interaction. When a cation binds to the double bond, the R group of the geminal dimethyl trisubstituted alkenes adopts a conformation which minimizes the reactivity of methylene allylic hydrogens. In the second model, it is postulated that the zeolite polarizes the alkene in such a way that the less substituted carbon has a higher electronic density than the more substituted, and hence attracts the electrophilic oxygen. Thus, the allylic hydrogens on the more substituted carbon are more reactive (Scheme 15).

The proposed models which provide the best explanation so far for the regioselectivity of photooxygenations inside a zeolite cavity are only working hypotheses and further experiments are needed to understand this selectivity, such as the knowledge of the distribution of the ene reactivity between the two geminal methyl groups in trisubstituted alkenes **30**, **31** and **35**.

3. Solvent Effects in the Ene Regioselectivity

Earlier and recent studies have shown that the rate and the product distribution of the ene reaction of $^1O_2$ with alkenes is almost independent of solvent polarity.[140,141] A small variation in the ratio of the ene photooxygenation products of some non-functionalized olefins by changing the solvent has been reported earlier.[67,70] However, no mechanistic explanation was offered to account for the observed solvent effects. It is rather difficult to rationalize these results based on any of the currently proposed mechanisms of singlet oxygen ene reactions. The product distribution depends substantially on solvent polarity and reaction temperature, only in substrates where both ene and dioxetane products are formed.[142–151]

In the reaction of $^1O_2$ with α,β-unsaturated esters there is a small but significant solvent effect on the variation of the ene products.[106] For example, photooxygenation of **84** in non-polar carbon tetrachloride affords **84a** and **84b** in a 95:5 ratio, whereas in polar dimethyl sulfoxide the ratio is 80:20. It was found that there is a surprising correlation between the dielectric constant of the solvent and the distribution of the ene products. By increasing the dielectric constant of the solvent, the percentage of **84b** increases.

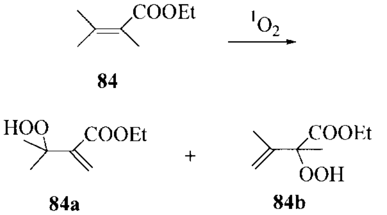
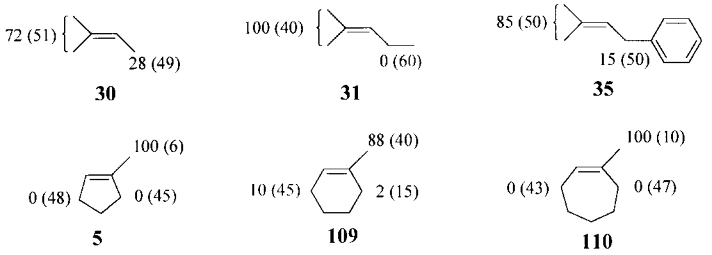
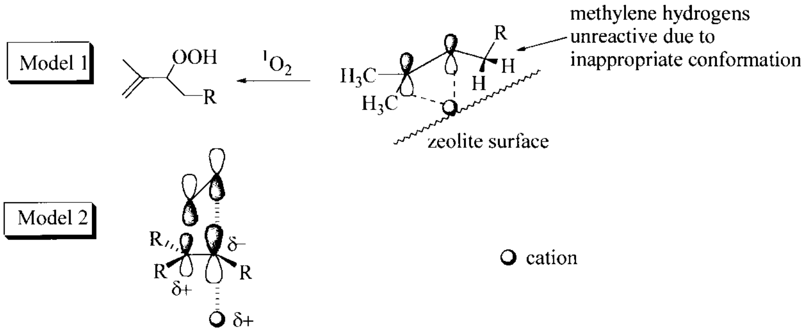
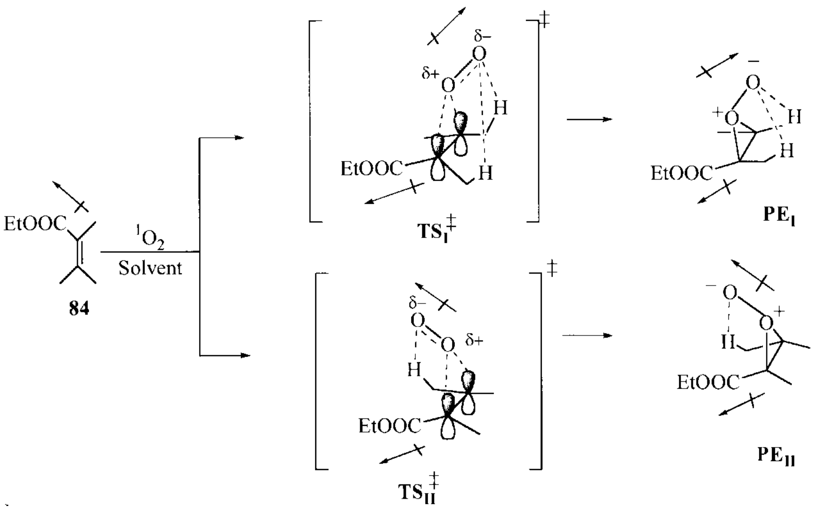


Table 20. Photooxygenations of **30** and **31** were carried out in zeolite Li–Y. Numbers in parentheses indicate the regioselectivity of the photooxidation using thionin as sensitizer in acetonitrile in the absence of zeolite





Scheme 15.



Scheme 16.

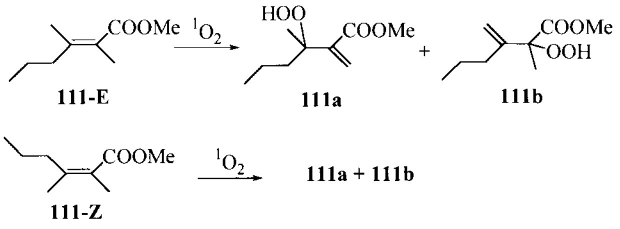
In order to explain this correlation it was proposed that transition state $TS_{II}^‡$, where the oxygen atom is added to the same side as the ester functionality to form the *syn*-perepoxide PE_{II} is favored in polar solvents because its dipole moment is higher than that of transition state $TS_I^‡$ where the oxygen adds to the other side of the olefin to form the anti-perepoxide PE_I (Scheme 16).

The above assumption was verified by examining the solvent dependence of the ene products derived from the photooxygenation of the isomeric α,β-unsaturated esters **111**-*E* and **111**-*Z* (Scheme 17). For **111**-*E* the two ene products are formed from two different perepoxides. If the oxygen atom is placed *syn* to the ester group, **111b** is formed, whereas **111a** is formed from the opposite case. For isomer **111**-*E*, the expected solvent effect is found, (**111a**/**111b**=85:15 in CCl_4 or benzene; in DMSO the ratio is 70:30). On the other hand, for the isomer **111**-*Z*, both products are formed from the same intermediate (oxygen placed *anti* to the ester), and no solvent dependence in the ene products was found (**111a**/**111b**=95:5 in CCl_4 and 93:7 in DMSO).

Significant solvent effects in ene reaction regioselectivity have also been observed in the photooxygenation of allylic alcohol **9**.[57] This effect has already been discussed in Section 2.2, and has been attributed to the lack of a hydroxyl group-oxygen steering effect in polar solvents. It is reasonable to expect solvent polarity effects to appear in cases where the transition state leading to the perepoxide has the oxygen atom *syn* to the functionality (higher dipole moment), than *anti* (lower dipole moment).

4. Synthetic Transformations of Regioselective and Stereoselective Ene Reactions

Highly regioselective and stereoselective ene reactions can be used as excellent preparative synthetic methods for mono or polyoxofunctionalization of alkenes. For example, in the photooxygenation process, the oxygen functionality is introduced into an alkene by forming an allylic hydroperoxide, which in turn can be further reduced to an allylic alcohol,[152] or transformed stereospecifically in the presence of Ti(i-PrO)$_4$ to an epoxy allylic alcohol,



Scheme 17.

in which the epoxide and the hydroxyl functionalities are *cis*.[153,154]

Singlet oxygen affords a variety of regio- and diastereoselective reactions with chiral allylic alcohols,[53,54,155] amines[55,56,156] and chiral cyclohexadienes[111,112] which are useful for synthetic transformations. For example, the photooxygenation of a chiral allylic alcohol was used recently as the key step in the total syntheses of plakorin and *enantio*-chondrilin.[157] If the photooxidation of chiral allylic alcohols and amines is performed in the presence of Ti(*i*-PrO)$_4$, in situ epoxidation occurs, affording highly threo (~95%) diastereoselective ene reactions with respect to the –OH or –NHR functionalities, by generating two new stereogenic centers with high stereoselectivity.[12] Similarly, regiospecific reactions with vinylic silanes,[158] stannanes[159] and sulfoxides[160] afford allylic alcohols, epoxy alcohols, or trimethylsilyl enones,[161] with high stereospecificity which are very useful building blocks in organic synthesis. Regiospecific reactions of vinylsilanes with $^1O_2$ have been used by Paquette and coworkers[78,79] for the production of trimethylsilyl-allylic alcohols whose subsequent desilylation resulted in a novel methodology for carbonyl transposition. Also, the high degree of geminal selectivity in the photooxygenation of α,β-unsaturated carbonyl derivatives was used in the synthesis of novel hydroperoxy heterocycles.[100,162]

Highly regioselective ene reactions of singlet oxygen with alkyl substituted alkenes can also be used for synthetic purposes. For example, in the photooxygenation of 1-*t*-butyl-1-cycloheptene only one allylic hydroperoxide with geminal hydrogen abstraction is formed.[74] Subsequent reduction of the hydroperoxide with triphenyl phosphine or dimethyl sulfide affords the allylic alcohol in high yield, which is very difficult to prepare in regiospecific fashion by the use of conventional allylic hydroxylations methods.

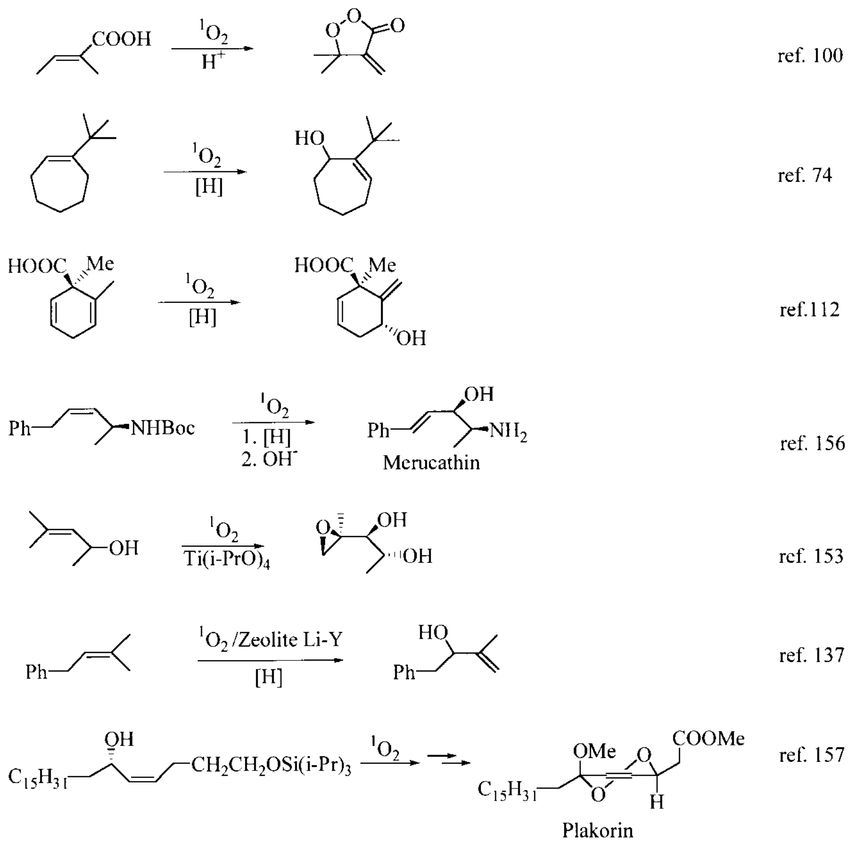
The photooxidation in zeolites appears to be very promising for synthetic applications. The reactions in zeolites are highly regioselective and much research must be devoted in this field. Recently a moderate degree of enantioselectivity (15%) was observed in the ene photooxygenation of a trisubstituted alkene in an asymmetrically modified Na–Y zeolite.[163] Despite the low enantioselectivity, this example promises to achieve chiral oxygenated products.[164] Some representative synthetic applications which involve highly regioselective ene reaction as the key step are shown in Scheme 18.

5. Conclusions

A useful summary of the the regioselectivity results is encapsulated as follows:

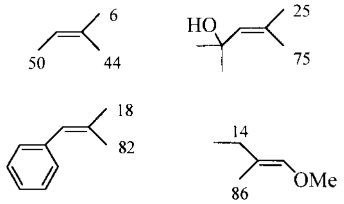
5.1. *syn* Selectivity

- In the ene reaction of singlet oxygen with trisubstituted alkenes and allylic alcohols a simultaneous interaction of oxygen either with two allylic hydrogens or one allylic hydrogen and the hydroxyl during the formation of the perepoxide is favorable and leads to the '*cis* effect' selectivity.



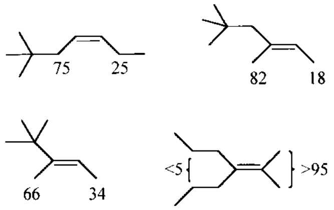
Scheme 18.

- A ‘positive’ interaction between the incoming oxygen and the phenyl ring or methoxy group can lead to a ‘*cis* effect’ selectivity in the photooxygenation of styrene-type molecules or trisubstituted enol ethers.



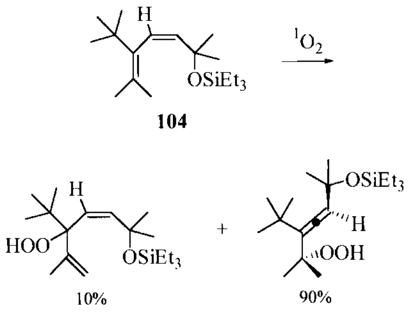
5.2. Large group non-bonded effect

- For non-functionalized alkenes steric factors (the large group non-bonded effect) play the most important role in the regioselectivity of the reaction, by affecting the product forming transition states.



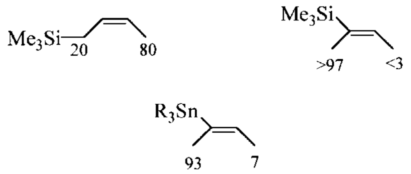
5.3. Conformational reactivity

- The appropriate conformation of an allylic hydrogen abstraction is perpendicular to the olefinic plane. Even vinylic hydrogens in twisted 1,3-dienes, which can adopt a conformation perpendicular to the reacting double bond can be abstracted to form allene hydroperoxides.
- Furthermore, in the photooxidation of fullerene derivatives, which bear the cyclohexene moiety the methylene allylic hydrogens next to the fullerene are more reactive because of their appropriate conformation.



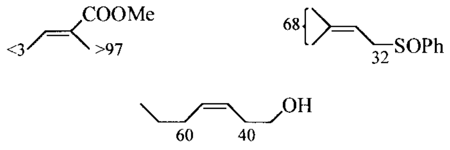
5.4. Si, Sn directing effects

- Coordination of oxygen to silicon at an allylic position directs ene regioselectivity.
- Highly regioselective ene reactions are observed with vinyl silanes or stannanes due to the ability of Si or Sn to destabilize the C–O bond of the intermediate perepoxide next to them.



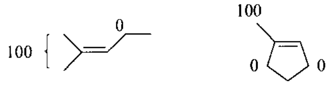
5.5. Stereoelectronic effects

- For alkenes bearing an electron withdrawing group at the α-position, a high degree of geminal selectivity is observed since in the ene product the new double bond is in conjugation with the functionality.
- Electronic repulsions between the negatively charged oxygen atom of the perepoxide and highly polarized X=O bonds (X=S, P) can also direct the regioselectivity with alkenes bearing an electron withdrawing group at the β-position. Similar repulsions between the hydroxyl group and the oxygen seem to control the regioselectivity in the ene reaction with homoallylic alcohols.



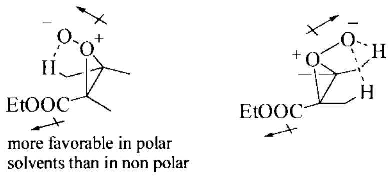
5.6. Effect of Y-zeolites on regioselectivity

- The selectivity of the ene reaction in a zeolite medium differs considerably from that in solution, probably because of conformational changes of the substrates inside the cavity, and in the binding of olefins to the cation. Highly regioselective ene reactions are observed.



5.7. Solvent effects

- Solvent effects appear in cases where the two transition states leading to the perepoxide have considerably different dipole moments.



We believe that the singlet oxygen chemistry will continue to play an important role in the fields of mechanistic and synthetic organic chemistry, as well as in biological systems. Of special interest will be the development of new stereocontrolled processes involving reactive oxygen species in various supports, such as in zeolite media.

Acknowledgements

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Biograpical Sketch

Michael G. Orfanopoulos was born in Patras, Greece. He received his bachelor's degree from the University of Patras, followed by an M.S. from the University of Toledo, and a Ph.D. from Case Western Reserve University in 1979, under the direction of Professor L. M. Stephenson. He continued his scientific education as a postdoctoral fellow at Stanford University with Professor H. S. Mosher and at UCLA with Professor C. S. Foote. In 1982 he was appointed as a research scientist at the NRC Demokritos, Athens, Greece and after this he joined the faculty at the University of Crete where he is currently a Professor in the Chemistry Department. His current research interest focuses on the mechanism of thermal and photochemical reactions of various enophiles including singlet oxygen and fullerene molecules.

Manolis Stratakis is a native of Crete, Greece and a graduate of the University of Thessaloniki in 1986. Following graduate studies at the University of Crete (Ph.D. in 1991 working on singlet oxygen ene reactions), a two years postdoctoral at U.C. Berkeley with Professor A. Streitweiser, and frequent visits at UCLA (C. S. Foote), he joined the faculty at the Department of Natural Sciences, University of Cyprus, as Assistant Professor. In 1999 he was appointed as Assistant Professor at the Department of Chemistry, University of Crete. His research interests include apart from enophiles chemistry, intrazeolite chemistry, and studies on the structure and reactivity of organoalkali metal compounds.