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Stereoelectronic and solvent effects on the allylic oxyfunctionalization of alkenes with singlet oxygen

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Dedicated to Professor Harry H. Wasserman for his great contribution to this field

Abstract—The factors that control the stereochemistry of sensitized photooxygenation of alkenes via singlet oxygen (ene reaction) are selectively reported. We also introduce our most recent stereoelectronic effects on the singlet oxygen–ene reaction. The origin of site selectivity and solvent-dependent stereoselectivity in this classical ene reaction with simple as well as functionalized alkenes is highlighted. These studies and other similar studies have enhanced substantially the utility of singlet oxygen in the synthesis of natural and non-natural products.

1. Introduction

Molecular oxygen was discovered by Scheele and Priestly more than two centuries ago.[1] Later on, the fall of the powerful theory of phlogiston was followed by a period of exciting discovery of the role of oxygen in life processes. Photosensitized oxidations have been of interest to chemists and biologists since Raab's discovery that microorganisms are killed by light in the presence of oxygen and sensitizers.[2] These conditions cause pathological effects, referred as 'photodynamic action'.

In the period between 1928 and 1935, Mulliken[3] interpreted the paramagnetic nature of molecular oxygen as a result of two outer electrons with parallel spins. Childe and Mecke[4] spectroscopically identified the $^1\Sigma g^+$ (37.5 kcal mol^{-1}) higher-energy electronic state and Herzberg[5] discovered another singlet excited state $^1\Delta g$ (22.5 kcal mol^{-1}). The $^1\Delta g$ state is long-lived and survives at least for 10^8 collisions with methanol in vapor phase, whereas the $^1\Sigma g^+$ state survives for not more than 10 collisions under the same conditions.[6]

Although singlet oxygen was discovered more than 70 years ago,[5,7] until the early 1960s it was considered to be of rather limited as a research subject. It was the pioneer work of Foote[8,9] and Wexler that demonstrated the photosensitized oxidations of organic compounds in solution and brought the singlet oxygen back into the mainstream of chemical research. The chemical and photochemical generations of singlet oxygen, its ready detection, and its unusual but stereocontrolled[10] chemical reactivity have made this research subject remarkably attractive.[11–16] Most of the photosensitized oxygenations are now well established to involve $^1\Delta g$ excited singlet state of molecular oxygen. The most convenient way of generating singlet oxygen is the dye photosensitization, as shown in Eqs. 1–3. These photooxygenations represent one of the most important hydrocarbon functionalization reactions available to the synthetic organic chemists.[17,18]

$$\text{Sens} \xrightarrow[\text{Visible light}]{} \text{Sens}^* \quad (1)$$

$$\text{Sens}^* \xrightarrow{O_2} \text{Sens} + {}^1O_2 \quad (2)$$

$$^1O_2 + \text{Substrate} \longrightarrow \text{Oxygenated products} \quad (3)$$

Singlet oxygen studies have been reported to such diverse areas, as chemiluminescence,[19] photocarcinogenity,[20] ozonolysis,[21] photodynamic action,[9] photosynthesis,[19] polymer degradation,[15] environmental,[15,22,23] and biological significance.[24–26] The reaction of singlet oxygen with carbon–carbon double bonds, can be classified into three categories: (1) the [4+2] cycloaddition to conjugated dienes or anthracenes to yield endoperoxides; (2) the reaction with enol ethers, enamines, and electron-rich alkenes, without allylic hydrogens of proper orientation to yield 1,2-dioxetanes; and finally (3) the ene or 'Schenck reaction' with alkenes to form allylic hydroperoxides (Scheme 1). These reactions are very smooth and preparatively useful because of their high yields and specificity.

Keywords: Singlet oxygen; Ene reactions; Stereoselectivity; Electronic effects; Solvent effects.
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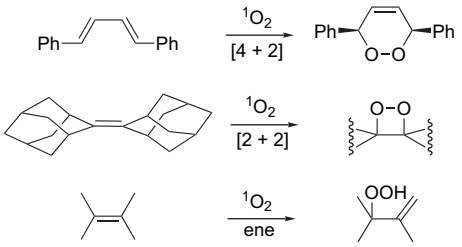


Scheme 1. [4+2], [2+2], and ene addition reactions of singlet molecular oxygen to alkenes.

The ene reaction was originally discovered[27] by Schenck in 1943 and it was revived after the pioneering work of Foote in the early 1960s. A great deal of work has focused on whether the ene reaction proceeds through a concerted or a stepwise mechanism. The initially proposed synchronous pathway[28] was challenged by a biradical,[29] zwitterionic,[30] or a perepoxide[31] intermediate. Kinetic isotope effects on the photooxygenation of tetrasubstituted,[32] trisubstituted,[33] and *cis*-disubstituted[34] alkenes supported the irreversible formation of an intermediate perepoxide, while for *trans*-disubstituted alkenes[35] a partial equilibration of the intermediate with the reactants was postulated. 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 product allylic hydroperoxides.[36]

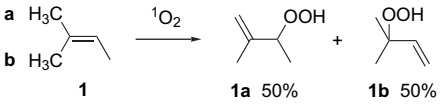
Trapping of the intermediate with sulfoxides,[37] phosphites,[38] and sulfenates or sulfinate esters[39] in the photooxygenation of adamantylidenoadamantane, and theoretical calculations[40–44] as well, support the perepoxide as the most possible intermediate. Many authors consider an intermediate exciplex[45–47] instead of the polar perepoxide. Since the geometry of the intermediate is well defined from the isotope effects and the stereochemical studies, if an intermediate exciplex is formed, its geometrical features must resemble those of a perepoxide. Recent theoretical and experimental works by Singleton and co-workers,[48] however, proposed a two-step no-intermediate mechanism, with a rate-limiting transition state resembling that for the formation of a perepoxide in the initially proposed stepwise process. Nevertheless, the mechanistic features of the $^1O_2$ ene reaction continue to challenge the scientific community, and it is likely that the mechanism debate will continue in the years to come.

The purpose of this article is to provide a brief overview mainly about our work, both past and current, concentrating on the factors that control the stereoselectivity of the $^1O_2$-alkene ene reaction.

2. Stereoselectivity

2.1. Site selectivity ('cis-effect')

The site selectivity of the singlet oxygen–alkene reactions went unrecognized throughout more than 20 years of mechanistic study. It was generally recognized that methyl and methylene hydrogens are reactive and that the isopropyl C–H and certain conformationally inaccessible hydrogen atoms are not. The equal amounts of photooxidized products **1a** and **1b** obtained from trimethylethylene, as shown in Eq. 4, led to the conclusion that the ene reaction proceeds without any site selectivity. Since product **1a** results from H-abstraction from either methyl group a or b of **1**, Eq. 4, the relative reactivity of these groups was not known.

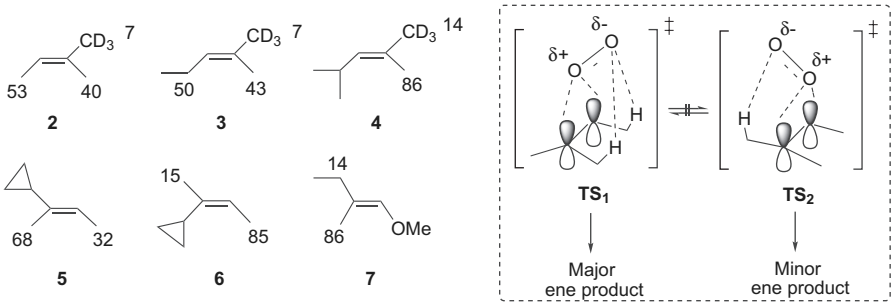


(4)

The stereospecific deuterium labeling and subsequent photooxygenation of olefins **2**, **3**, and **4** revealed the hidden site selectivity of the singlet oxygen–ene reaction (Scheme 2). A strong preference for H-abstraction from the more substituted side of the double bond was found.[49] This surprising selectivity is referred to as the 'cis-effect'. Selected examples are represented in Scheme 2. Both experimental and theoretical chemists have offered explanations for the 'cis-effect'.[50] Generally, 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 TS_1, versus TS_2, of perepoxide formation (inset, Scheme 2).

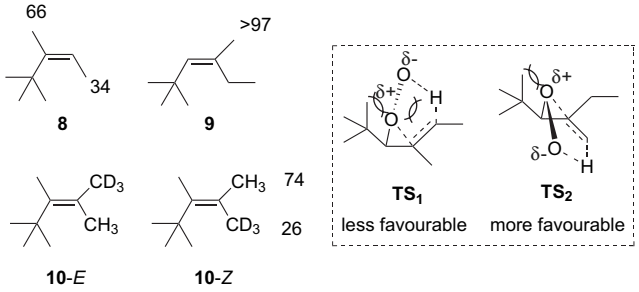
2.2. *anti* 'cis-Effect' selectivity

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 shown in Scheme 3.[51] Examination of the possible transition states leading to the major (*anti*) and minor (*syn*) allylic hydroperoxides, provides



Scheme 2. Site selectivity of the photooxygenation of trisubstituted alkenes ('cis-effect'). Numerical values represent percentage of hydrogen abstraction.

reasonable mechanistic rational into the *anti* selectivity. For example, in TS_1 leading to the minor (*syn*) product (Scheme 3), the non-bonded interactions involving the large *tert*-butyl group and the incoming oxygen are expected to be stronger than those in TS_2, where this steric interaction is less significant (inset, Scheme 3). 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.

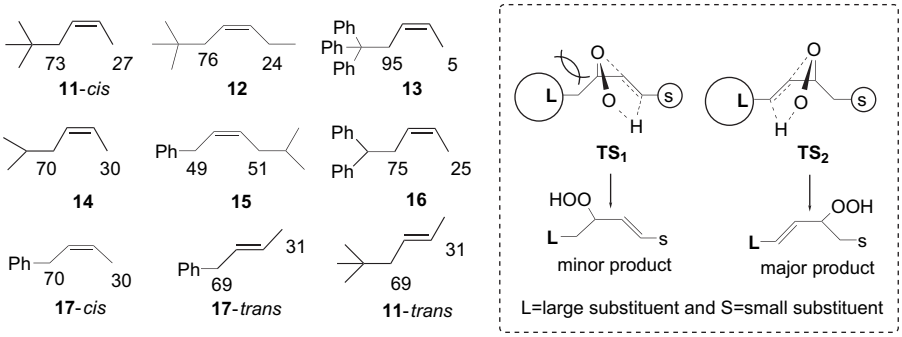


Scheme 3. *anti* 'cis-Effect' selectivity of the photooxygenation of certain trisubstituted alkenes.

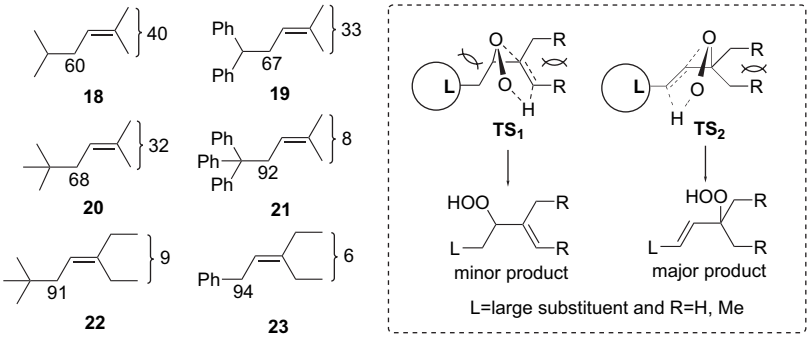
2.3. The large group non-bonded effect

2.3.1. *cis*- and *trans*-Disubstituted alkenes. In the reaction of singlet oxygen with non-symmetrical *cis*- or *trans*-disubstituted alkenes, an unexpected regioselectivity was found.[52] The allylic hydrogens next to the large alkyl substituent are more reactive than those next to the small group. The regioselective photooxygenation reaction, some representative disubstituted alkenes, and their regio-limitations are shown in Scheme 4. The site selectivity was explained by examining the possible transition states leading to the allylic hydroperoxides with a general example, where L=large substituent and S=small substituent (inset, Scheme 4). In the transition state TS_2 leading to the major product, the non-bonded interactions involving the large group are smaller than those of the transition state TS_1 leading to the minor product, since TS_2 is expected to have lower energy than TS_1. Considering that the formation of perepoxide in the photooxygenation of *trans*-alkenes is reversible,[35b] the 1,3-non-bonded interactions in the product forming transition states between the oxygen and the alkyl substituents appear to control the site selectivity in a similar fashion to those shown in the inset of Scheme 4.

2.3.2. 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.[52] The results of some representative alkenes are summarized in Scheme 5. The transition states in the hydrogen abstraction step, as seen earlier in the inset of Scheme 4, help to explain the observed change in site selectivity. 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 and the L group (L=large substituent) with respect to the intermediate perepoxide occurs. Therefore, transition state TS_2 is expected to be lower in energy than the transition state TS_1 where the non-bonded interactions exist (inset, Scheme 5).



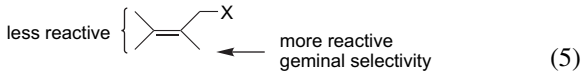
Scheme 4. Site selectivity of the photooxygenation of *cis*- and *trans*-alkenes **11**–**17**.



Scheme 5. Regioselectivity of the photooxygenation of alkenes **18**–**23**. Numerical values represent percentage of hydrogen abstraction.

2.4. Geminal selectivity

2.4.1. Geminal selectivity with respect to allylic functionality. Replacement of an allylic hydrogen in tetramethylethylene (TME-X) with a series of functional groups (sulfides, sulfoxides, sulfones, halides; Eq. 5) undergo selective photooxygenations with a surprising geminal selectivity with respect to the allylic functionality X.[53] This selectivity is represented by Eq. 5. Three possible explanations were proposed to account for the observed regioselectivity: (a) anchimeric assistance by the allylic substituent leading to regioselective opening of the possible perepoxide intermediate by an S_N2 mechanism; (b) electronic repulsions between the lone pairs of the heteroatoms and the negatively charged oxygen of the perepoxide; and (c) different barriers to rotation of methyl groups of the substrate. Similar explanation was earlier reported by Houk and co-workers[50c] in an effort to rationalize the site selectivity of singlet oxygen–ene reaction with trisubstituted alkenes.

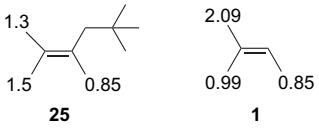


(5)

X = $SO_2C_6H_4Me$-p, SCH_4NO_2-p, Br, SOC_6H_4Y-p (Y = NO_2, H, Me, MeO)

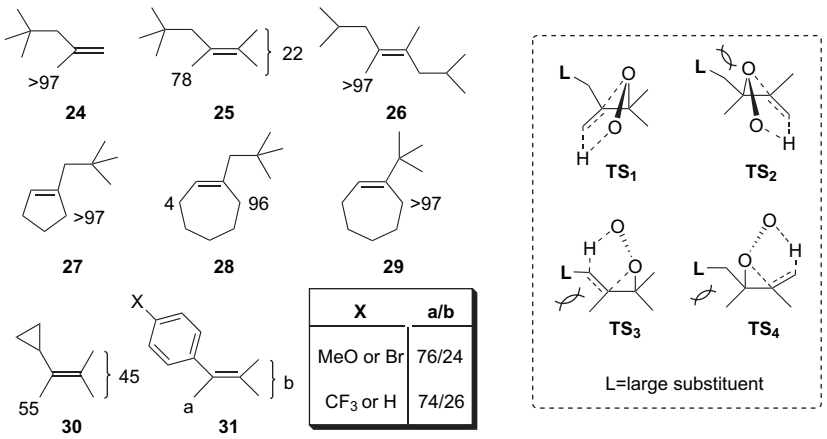
2.4.2. Geminal selectivity with respect to a bulky allyl or vinyl substituent. In order to examine comprehensively the factors affecting geminal selectivity, we synthesized a series of alkyl or phenyl substituted alkenes at the allylic or at the vinylic position.[54] Photooxygenation of these olefins shows a strong preference for hydrogen abstraction from the methyl group that is geminal to the larger substituent of the alkene. In Scheme 6, selective substrates are represented. Disubstituted olefin **24** impressively illustrates this point; the same trend was also noted in cyclic alkenes **27**–**29**.[54b] Examination of the possible transition states leading to the major and the minor products in the reaction of $^1O_2$ with L-allylic substituted trimethylethylene, helps to explain the observed regioselectivity (inset, Scheme 6). The transition state TS_1, leading to the major product, is expected to have lower energy than TS_2 and TS_4, because of 1,3-non-bonded interactions. Furthermore, in transition state TS_3, leading to the minor product or absence of product, the non-bonded interactions involving the large alkyl group and the methyl group, which are placed in a cis configuration, are expected to be stronger than those in the transition states TS_1, TS_2, and TS_4, where this steric interaction is absent. Similar examination was provided for the observed regiochemistry in $^1O_2$–ene reaction for vinyl substituted tetramethylethylenes.

Previous work,[55] based on the theoretical model of Houk (MM2 calculations),[50c] gave an alternative rationalization for the geminal selectivity. This model predicts that the lower the barrier to rotation the higher the hydrogen abstraction from the perepoxide. For example, they found, according to this model, that for some alkyl substituted tetramethylethylenes there is a surprising correlation between the rotational barriers and their reactivity toward $^1O_2$. Some numerical values in kcal mol^{-1} are depicted in Scheme 7 for substrates **25** and **1**. In 2,3,5,5-tetramethyl-2-hexene (**25**), for example, the more reactive methyl group (geminal, 78%) has the lowest barrier to rotation (0.85 kcal mol^{-1}) with respect to the other two methyls. Similar trends hold with 2-methyl-2-butene (**1**).



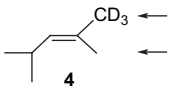
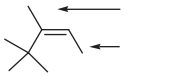
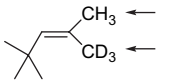
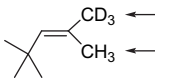
Scheme 7. Calculated rotational barriers in kcal mol^{-1} by MM2.

However, the barrier to rotation does not always predict the regioselectivity of the ene reaction of $^1O_2$ with alkenes. In an earlier work, we calculated the rotational barrier values, with the HF/STO-3G method, for the allylic methyl groups in a series of trisubstituted alkenes, and compared them with the observed experimental ene regioselectivity.[56] Selective results are represented in Table 1. For alkene **4** there was a correlation between rotational barriers and ene reactivity. However, for alkenes **10**-*Z* and **10**-*E*, the *syn* methyl groups have lower rotational barriers than the corresponding *anti* by 0.5 kcal mol^{-1}. The observed ene reactivity of **10**-*Z* and **10**-*E* was in the opposite direction to the proposed theoretical model. Furthermore, for alkene **8** the *exo* methyl group has higher rotational barrier than the corresponding *syn* by 2 kcal mol^{-1}. In contrast again to the predictions of the proposed theoretical model, this methyl group was found to be more reactive in $^1O_2$–ene reaction than the *syn*. These



Scheme 6. Geminal selectivity in the ene reaction of $^1O_2$ with di-, tri-, and tetra-substituted alkenes.

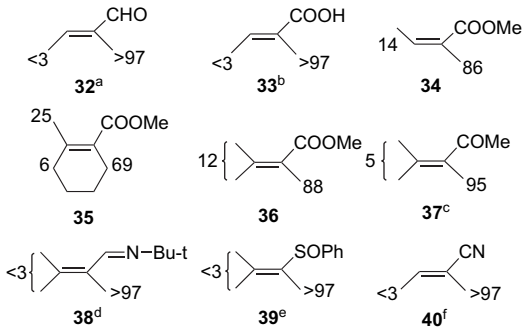
Table 1. Relative yields of ene products and rotational barriers of methyl groups

Substrate	% Ene products with $^1O_2$	Rotational barriers HF/STO-3G (kcal mol^{-1})
 **4**	14	1.64
	86	0.40
 **8**	66	2.91
	34	0.91
 **10-*Z***	74	1.63
	26	1.11
 **10-*E***	76	1.63
	24	1.11

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 (0.5–2.0 kcal mol^{-1}) compared to the activation energies of the reactions (6–13 kcal mol^{-1}).

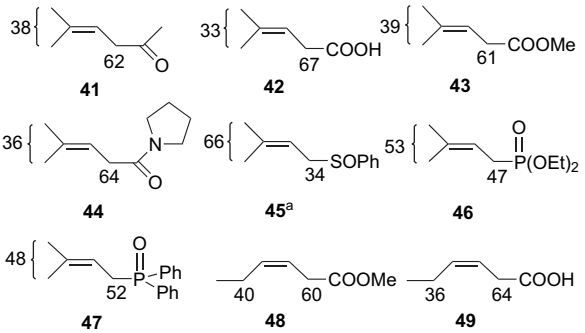
2.5. Electron withdrawing group at the α- and β-position

For alkenes bearing an electron withdrawing group at the α-position, such as aldehyde,[57] carboxylic acid,[58] ester,[59] ketone,[60] imine,[61] sulfoxide,[62] and cyano,[63] a high degree of geminal selectivity has been demonstrated. In Scheme 8, selective results are represented. Numerical values represent percentage of hydrogen abstraction. The 1,3-non-bonded interactions, which control the site selectivity in the photooxygenation of non-functionalized alkenes (see Sections 2.3–2.4.2), do not contribute significantly to the geminal selectivity of alkenes bearing at the α-position an electron withdrawing group. It was proposed that, in the hydrogen abstraction step, the perepoxide opens preferentially at the C–O bond next to the unsaturated moiety. Due to the forthcoming conjugation in the adduct, the corresponding transition state is favorable.



Scheme 8. Geminal site selectivity in the photooxygenation of alkenes bearing an electron withdrawing group at α-position. (a) See Ref. 57, (b) see Ref. 58, (c) see Ref. 60, (d) see Ref. 61, (e) see Ref. 62, and (f) see Ref. 63.

When the electron withdrawing substituent is at the β-position with respect to the double bond, various trends in site selectivity are observed (Scheme 9).[64] For substrates **41**–**44**, the observed site selectivity is identical to the site selectivity observed for the alkyl substituted alkene **18**, which shows approximately similar substituent stereo demand. In substrates **45**–**47**, where the substituents are sulfoxide, phosphonate, or phosphine oxide, the double bond formation on the side of the alkene, which is away from the functionality increases significantly. 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 directs the intermediate to abstract hydrogen from the methyl group. The results observed in the case of the disubstituted unsaturated ester **48** and acid **49** are similar to that of the trisubstituted substrates **43** and **42**, respectively. This reveals that any unfavorable interactions between oxygen and carbonyl in the more substituted side of the double bond probably do not force formation of the intermediate in the less substituted side of the double bond (*anti* 'cis-effect' selectivity, see Section 2.2). We conclude that there are three competing factors, which can affect the regiochemistry in the ene reaction of $^1O_2$ with alkenes bearing an electron withdrawing group at β-position: (1) the driving force to form the new double bond in conjugation with the functionality in the allylic hydroperoxide product; (2) the 1,3-non-bonded interactions between the positively charged oxygen of perepoxide and the allylic functionality, which favor again the conjugated product; and (3) the electronic repulsions between perepoxide and the allylic functionality favoring the unconjugated product. We believe that in the series of substrates examined here, the last factor is the most important and dictates the ene products distribution.



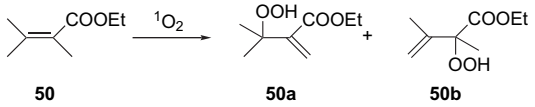
Scheme 9. Geminal selectivity in the photooxygenation of alkenes bearing an electron withdrawing group at β-position. (a) See Ref. 65.

2.6. Solvent and electronic effects on the stereoselectivity of singlet oxygen–ene reaction

2.6.1. α,β-Unsaturated esters and *E*/*Z*-2,4-dimethylpent-3-en-2-ol-5,5,5-*d*$_3$. Previous studies have shown that the rate of the $^1O_2$ ene reaction with alkenes shows negligible dependence on solvent polarity.[66] Product distribution depends substantially on solvent polarity and reaction temperature, only in substrates where both ene and dioxetane products are produced.[67] Furthermore, extensive mechanistic work has shown that there is a negligible solvent effect on the reaction of $^1O_2$ with α,β-unsaturated ketones,[60a] olefins, and dienes.[68]

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.[69] As seen from Table 2, the hydrogen abstraction from the methyl group, which is geminal to the ester functionality in compound **50**, producing adduct **50a**, decreases substantially as the solvent polarity increases. For example, the ratio of ene products **50a/50b** decreases by a factor of 5 on going from carbon tetrachloride to the more polar solvent DMSO. It was found that there is a surprising correlation between the dielectric constant (ε, Table 2) of the solvent and the distribution of the ene products. By increasing the dielectric constant of the solvent, the percentage of **50b** increases.

Table 2. Solvent effect on the regioselectivity of the photooxygenation of **50**

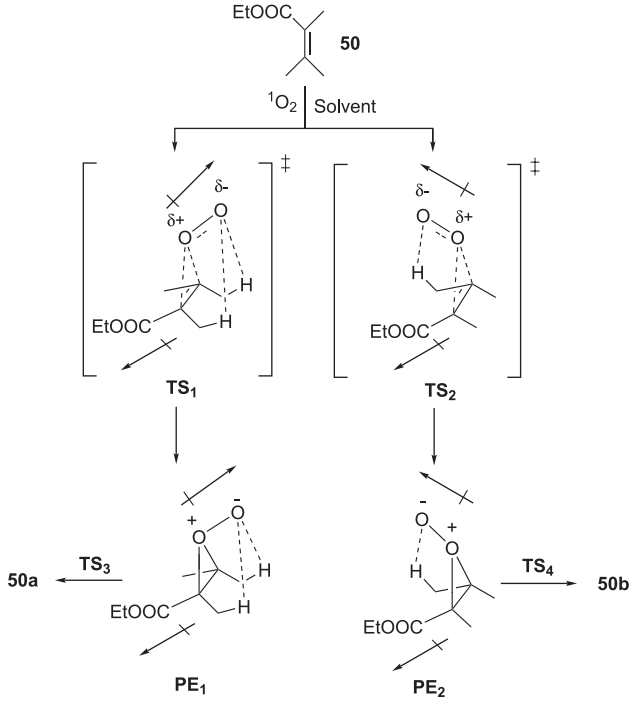


50 **50a** **50b**

Solvent	**50a/50b**	ε[a] (20 °C)
CCl_4	95/5	2.24
Benzene	94/6	2.283
Acetone	88/12	20.7
CH_3CN	85/15	36.64
DMSO	80/20	47.24

[a] See Ref. 70.

Transition state TS_2, where the oxygen atom is added to the same side of the ester functionality to form the *syn* perepoxide PE_2, is favored in polar solvents because its dipole moment is higher than that of the transition state TS_1, where the oxygen adds to the other side of the olefin to form the *anti* perepoxide PE_1 (Scheme 10).

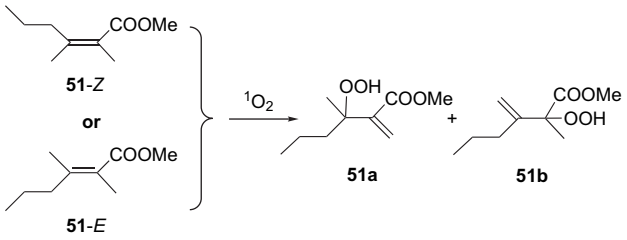


Scheme 10. Proposed mechanism for the solvent-dependent photooxygenation of α,β-unsaturated esters.

To verify this mechanistic possibility, the solvent dependence of the ene products derived from the photooxygenation of the isomeric α,β-unsaturated esters **51**-*Z* and **51**-*E* was examined (Scheme 11). For the isomer **51**-*Z*, both products are formed from the same intermediate (the perepoxide oxygen is placed *anti* to the ester functionality), and no solvent dependence on the ene products was found (inset, Scheme 11). On the other hand, for **51**-*E* the two ene products are formed from two different perepoxides. When the oxygen atom of the perepoxide intermediate is placed *syn* to the ester group, **51b** is produced, whereas **51a** is formed from the *anti* position. For isomer **51**-*E*, the expected solvent effect was found: **51a/51b**=85/15 in CCl_4; 83/17 in benzene; and 70/30 in DMSO (inset, Scheme 11). These results are consonant with the proposed *syn* (polar) and *anti* (less polar) perepoxide-like transition states similar to TS_1 and TS_2 whose relative stabilities change with solvent polarity. It is constructive to note that the ene product distribution is not affected by solvent polarity when the two sides of the double bond do not compete for the ene product. This is demonstrated with the substrate **51**-*Z*, where the two methyls are in cis position.

Significant solvent effects on the regioselectivity of the ene reaction have also been observed with allylic alcohols **52**-*E* and **52**-*Z*.[71] It is worth mentioning that for **52**-*E* and **52**-*Z*, singlet oxygen can interact with only one allylic hydrogen or deuterium on each side of the alkene. No 'cis-effect' would be expected with these substrates. The results are summarized in Table 3. We define as *syn* the adducts formed by allylic hydrogen abstraction, which is on the same side of the double bond as the hydroxyl. For the case of **52**-*E*, the *syn* adduct is formed by hydrogen abstraction, while for the case of **52**-*Z* by deuterium abstraction. In fact, adducts **52**-*E*-*syn* and **52**-*Z*-*anti* are identical, and **52**-*E*-*anti* and **52**-*Z*-*syn* are also identical. As seen from Table 3, photooxygenation of **52**-*E* and **52**-*Z* in CCl_4 and CH_3CN showed similar *syn* selectivity. This result indicates that the *syn*/*anti* product selectivity is independent on the specific labeling of the methyl groups. For the case of **52**-*E*, the ratio of *syn*/*anti* decreases by a factor of 6 on going from carbon tetrachloride to the polar solvent methanol.

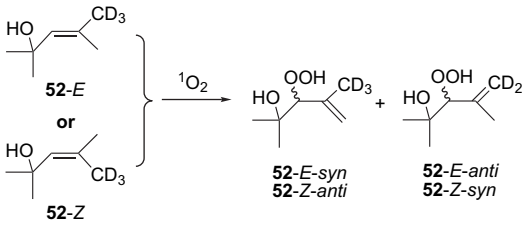
Adam and co-workers, observed high diastereoselectivity (de ~90%) in the photooxygenation of chiral allylic alcohols[72] and amines.[73] This result was rationalized in terms of hydroxyl or amino group coordination with the incoming oxygen. The synergy of oxygen–hydroxyl coordination, as well as the 1,3-allylic strain, provides, in non-polar solvents, high selectivity for the *threo* allylic hydroperoxides. This effect controls the *syn*/*anti* stereoselectivity in the photooxygenation of allylic alcohols **52**-*E* and **52**-*Z*. Examination of the possible transition states in Scheme 12 helps to understand the observed stereoselectivity. In TS_1 (applied to **52**-*E*), where the electrophile approaches the olefin from the more crowded side to form PE_1, the oxygen interacts simultaneously with the hydroxyl and one allylic hydrogen. This interaction stabilizes the transition state. Polar solvents interact with the hydroxyl group through hydrogen bonding and reduce its ability to interact with the oxygen. Thus, the activation energy of TS_1 increases significantly and leads to a reversal of selectivity, which is now controlled by steric factors.



Solvent	51a/51b 51-Z	51-E
CCl_4	95/5	85/15
Benzene	95/5	83/17
CH_3CN	92/8	75/25
DMSO	93/7	70/30

Scheme 11. Solvent effect on stereoselectivity of $^1O_2$ addition to **51**-*Z* and **51**-*E*.

Table 3. Solvent effect on the stereoselectivity of the photooxygenation of **52**-*E* and **52**-*Z*



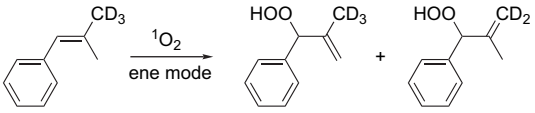
Substrate	Solvent	*syn*/*anti* selectivity
52-*E*	CCl_4	75/25
52-*Z*	CCl_4	72/28
52-*E*	$CHCl_3$	66/34
52-*Z*	$CHCl_3$	65/35
52-*E*	CH_3CN	41/59
52-*Z*	CH_3CN	40/60
52-*E*	MeOH	33/67

Stensaas and co-workers,[74a] investigated the photooxygenations of tiglic acid, angelic acid, 2,3-dimethyl-2-butenoic acid, and their corresponding methyl esters, using singlet oxygen in methanol and methanol/water solvent mixtures and compared with non-hydrogen-bonding solvents with different dielectric constants. They concluded that principally four factors dictate the site selectivity of singlet oxygen–ene reactions of these substrates in hydrogen-bonding solvents: the 'cis-effect', the polarity of the solvent and substrate, and the most important hydrogen-bonding interactions between the solvent and substrate. Recently, they studied[74b] the aqueous photooxygenations of some α-substituted alkene salts and the major factor dictating the product distribution of ene products is hydrogen-bonding interactions between the water and the substrate.

2.6.2. *syn* Selectivity of β,β-dimethylstyrene. Surprisingly, in the reaction of $^1O_2$ with β,β-dimethylstyrene,[75] the ene products, which are formed, apart from dioxetane and diendoperoxides,[76] exhibit an unexpected solvent-dependent *syn* selectivity. Considering that in the more substituted side of the olefin, oxygen is capable of interacting with only one allylic hydrogen, *anti* 'cis-effect' selectivity would be expected. In order to study the *syn*/*anti* selectivity of the ene products, the stereospecific labeling of the *anti* methyl by deuterium in β,β-dimethylstyrene to produce substrate **53** was required. The photooxygenation of **53** in several solvents revealed that there is a strong selectivity for attack on the methyl *syn* to the phenyl group. The magnitude of this selectivity depends on solvent polarity. By increasing the dielectric constant of the solvent, a substantial increase in the amount of hydrogen abstraction from the *syn* methyl group occurs. For instance, the ratio of *syn*/*anti* ene products increases by a factor of 3.4 on going from CCl_4 to methanol (Table 4).

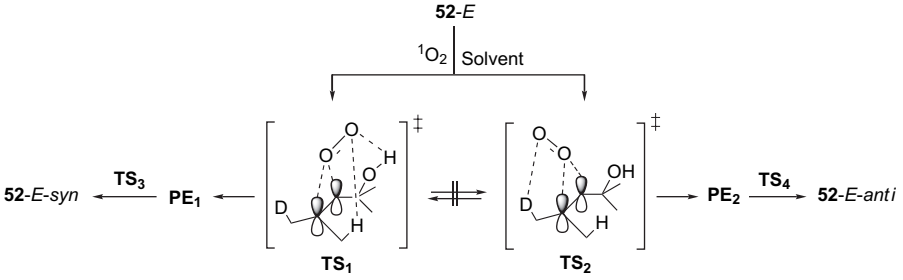
A mechanistic possibility that accounts for the observed *syn* selectivity is shown in Scheme 13. In TS_1, the incoming oxygen is oriented toward the more substituted side of the double bond. There is only one allylic hydrogen interaction with singlet oxygen and TS_1 leading to the major ene product. In TS_2, leading to the minor *anti* product, singlet oxygen

Table 4. Regioselectivity of the photooxygenation of **53** in a variety of solvents

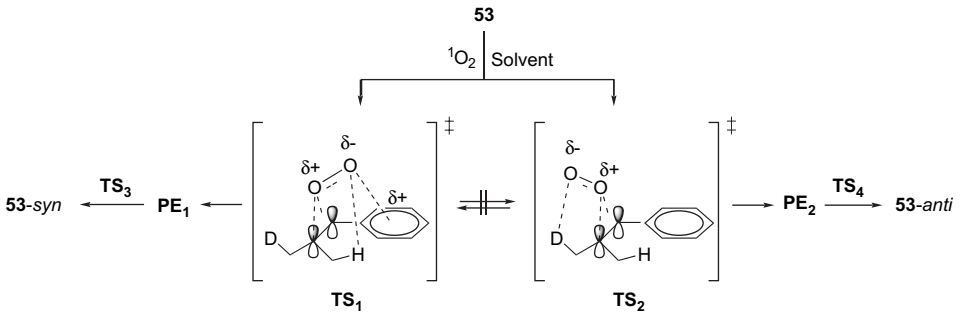


Solvent	*syn*/*anti*	ε[a] (Temp °C)
CCl_4	56/44	2.24 (20)
Benzene	57/43	2.283 (20)
$CHCl_3$	63/37	4.87 (25)
CH_3CN	71/29	36.64 (20)
CH_3OH	82/18	33.0 (20)

[a] See Ref. 70.



Scheme 12. Proposed mechanism for the solvent-dependent photooxygenation of **52**-*E*.



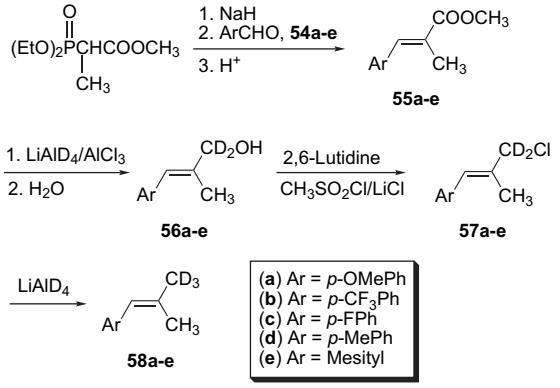
Scheme 13. Proposed mechanism for the photooxygenation of **53**.

again interacts with only one allylic hydrogen. Therefore, the extra stabilization of TS_1 versus TS_2 must arise from 'positive' interactions of singlet oxygen with the phenyl ring. In TS_1, which leads to perepoxide PE_1, the benzylic carbon is slightly electron-deficient, which is stabilized by electron donation from 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. Thus, the overall effect stabilizes better the *syn* transition state TS_1 than the *anti* TS_2 where this effect is absent. On increasing the polarity of the solvent, this stabilization becomes more significant because the transition state becomes more polar.

3. Electronic effect

3.1. On site selectivity

In light of the unexpected *syn* selectivity[75] of the photooxygenation of β,β-dimethylstyrenes **53**, in a variety of solvents (Section 2.6.2), the electronic effect of the reaction of singlet oxygen with *para*-substituted β,β-dimethylstyrenes was studied.[77] For this purpose, a series of *para*-substituted aryl alkenes **58a–e** were synthesized (Scheme 14). The stereoselective deuterium labeling of the *trans*-methyl group of the *para*-substituted β,β-dimethylstyrenes allows the *syn*/*anti* hydrogen abstraction determination.



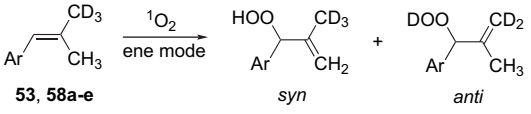
Scheme 14. Synthesis of labeled trisubstituted alkenes **58a–e**.

The preparation of alkenes **58a–e** in 93–98% isomeric purity with the *E* configuration was accomplished through the stereoselective formation of **55a–e**, by a Wittig–Horner reaction[78] with aldehydes **54a–e**, followed by $LiAlD_4/AlCl_3$ reduction[79] and subsequent chlorination[80] of the resulting allylic alcohols **56a–e**, followed by $LiAlD_4$ reduction[81] of the allylic chlorides **57a–e** (Scheme 14). The conversion of the allylic alcohols **56a–e** to the allylic chlorides **57a–e** proceeds by retention of stereochemistry at least to 95% for *Z*-isomer.

The photooxygenation of alkenes **58a–d** in several solvents, apart from the ene adducts, affords a great amount (~80% relative yield) of oxygenated products arising from [4+2] or [2+2] addition.[76] The isolation of the ene adducts was accomplished by column chromatography, using methylene chloride as eluent. The ratio of *syn*/*anti* selectivity was determined by ^1H NMR spectroscopy. The photooxygenation results for alkenes **53** and **58a–e** are summarized in Table 5.

For the singlet oxygen–ene reaction of **53** and **58a–d** in chloroform, a distinguishable trend is recognized. Electron withdrawing substituents, such as $–CF_3$ (74% *syn* selectivity) and –F (68% *syn* selectivity), favor in about 40% hydrogen abstraction from the *syn* methyl group of the double bond. In the case of a donating substituent such as –OMe, **58a**,

Table 5. Site selectivity of the photooxygenation of **53** and **58a–e**

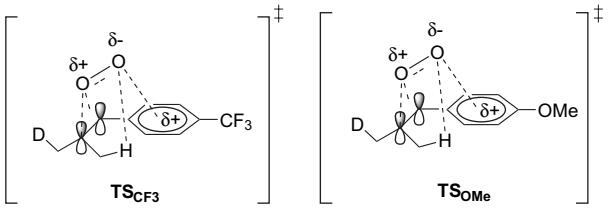


Substrate	Ar	*syn*/*anti* selectivity[a]	
		$CHCl_3$	CH_3CN
53		63/37[b]	71/29[b]
58a	MeO–	46/54	54/46
58b	F_3C–	74/26	76/24
58c	F–	68/32	70/30
58d	H_3C–	55/45	57/43
58e	H_3C, CH_3, CH_3	86/14	86/14

[a] Determined by ^1H NMR integration of the proper hydrogen signals. The error was ±4%.
[b] Taken from Ref. 75.

the reactivity of the *anti* methyl group is slightly in favor than that of the *syn* methyl. In substrates **53** and **58d**, an intermediate *syn* selectivity was observed, compared to the other substrates. Therefore, the relative stability of transition state TS_1 (Scheme 13), as controlled by the electron density of the aryl ring, affects the *syn*/*anti* selectivity in the ene products.

The proposed mechanism that accounts for the observed selectivity, which is due to the electronic effects of the aryl rings, is shown in Scheme 15.



Scheme 15. Transition states for the photooxygenation of **58a** and **58b** aryl alkenes.

In transition state TS_{CF3} the *syn* approach of $^1O_2$ to the double bond is better stabilized by the partial positive charge on the phenyl ring, due to the electron withdrawing character of $-CF_3$, than in TS_{OMe} (Scheme 15), where the positive charge is reduced because of the electron donating ability of the –OMe substituent. Consequently, transition state TS_{CF_3} leads to higher, 74% *syn* selectivity, whereas TS_{OMe} to the lowest 46%.

Taking into account that steric interactions on the reaction center due to the phenyl substituents are negligible, the order of the magnitude of *syn* selectivity depends exclusively on the charge density of each particular substituted phenyl ring. For example, as the positive charge density from –OMe to $-CF_3$ increases, the hydrogen abstraction from the crowded methyl group increases: $\delta^+_{CF_3}$ (74%) > δ^+_F (68%) > δ^+_H (63%) > $\delta^+_{CH_3}$ (55%) > δ^+_{OMe} (46%).

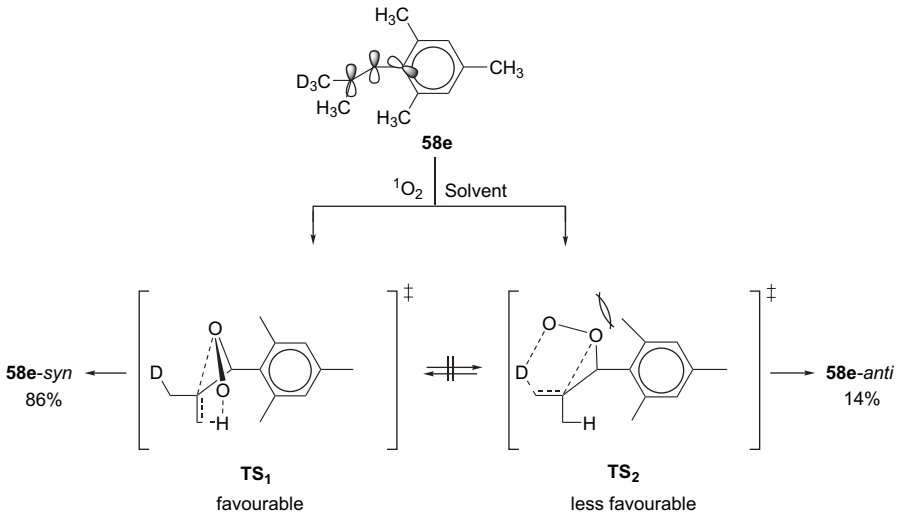
When the above photooxygenations were run in a polar solvent, such as acetonitrile, similar trend for *syn* selectivity was found (Table 5).

In the case of alkene **58e**, bearing a trimethyl substituted phenyl ring (Ar=mesityl) an abnormal high reactivity for the *syn* methyl group (86% relative yield) was found either in non-polar or polar solvent (Table 5, last entry). Unlike the *para*-substituted aryl alkenes, **58a–d** and **53**, where the *syn* selectivity was attributed to electronic effects of the phenyl ring, the high *syn* selectivity of $^1O_2$ with alkene **58e**, must be attributed to steric reasons. If the electronic effect would be the case, lower *syn* selectivity would have been expected, due to a lower positive charge density on the phenyl ring, arising from the inductive effect of the three methyl groups. It is expected that the two *ortho* methyl substituents will force the phenyl ring out of the plane of the alkene double bond. We assume that the favorable conformation of the phenyl ring would be the one, which places the ring almost perpendicular to the plane of the double bond. This assumption is in a good agreement with the following experimental results: although in all the cases of *para*-substituted aryl alkenes, **58a–d** and **53**, the reaction with $^1O_2$ gave mostly [4+2], [2+2], and diendoperoxides in more than 80% relative yields,[76] in the case of aryl alkene **58e**, this reaction gave mostly the ene adduct in more than 80% and minor amounts of [4+2] and [2+2] adducts. This result supports the perpendicular phenyl ring conformation, where the alkene double bond and one phenyl double bond are not properly aligned to an s-cis conformation, required for a [4+2] cycloaddition.

This remarkable *syn* selectivity can be attributed to the fact that in transition state TS_2, leading to the minor ene adduct, the substantial non-bonded interactions involving the *ortho* methyl substituents and the incoming singlet oxygen are much larger than those in TS_1, where these interactions are diminished, Scheme 16.

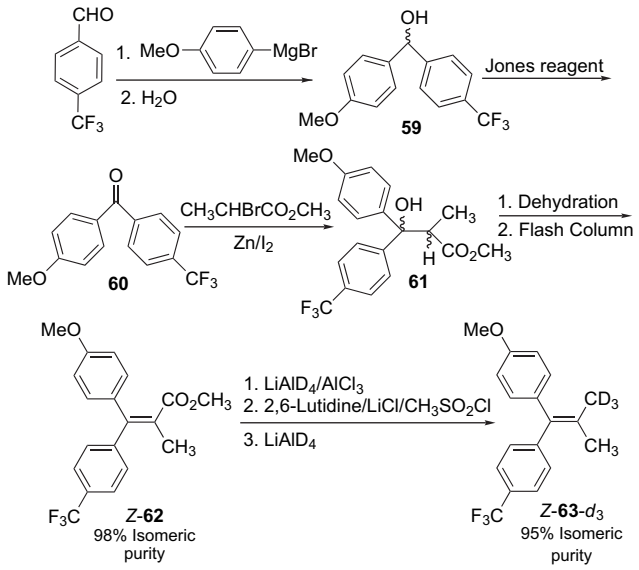
3.2. 'Push–pull' electronic effect

To this end, the 'push–pull' electronic effect was tested for the site selectivity of this reaction. For this purpose the 1-(*p*-methoxyphenyl)-1-[(*p*-trifluoromethyl)phenyl]-2-methyl-prop-1-ene-3,3,3-d_3 (*Z*-**63**-d_3, Scheme 17) alkene was designed. This alkene has three distinctive characteristics: (a) two geminal *para*-substituted phenyl rings with an



Scheme 16. Proposed mechanism for the photooxygenation of **58e**.

electron donating (–OMe) and an electron withdrawing (–CF_3) group, respectively (push–pull effect), (b) sterically equivalent sites of the alkene double bond, assuming that variation of *para*-substitution is far enough to sterically influence the double bond reaction center, and (c) stereoselective deuterium labeling such that the two reactive methyl groups are distinguishable on the ene products.

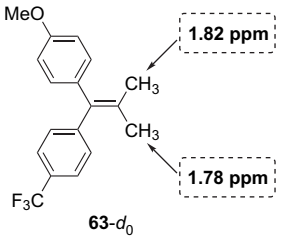


Scheme 17. Synthesis of (*Z*)-1-(*p*-methoxy-phenyl)-1-[(*p*-trifluoromethyl)-phenyl]-2-methyl-prop-1-ene-3,3,3-d_3 (*Z*-**63**-d_3).

The stereoselective formation of tetrasubstituted alkenes[82] is an important and challenging task for the synthesis of many natural products.[83] In this case, the successful pathway for the synthesis of *Z*-**63**-d_3 is depicted in Scheme 17. Alcohol **59** was derived from the Grignard coupling of (*p*-trifluoromethyl)benzaldehyde with *p*-methoxy-benzyl magnesium bromide.[84] Jones oxidation of the secondary alcohol **59** afforded ketone **60**, in good yield.[85] The key step for the synthesis of *Z*-**63**-d_3 was the Reformatsky reaction between ketone **60** and 2-bromo-propionate in the presence of 'activated' zinc and catalytic amount of I_2.[86] It is worth mentioning that ketones and β-bromo-esters, with increasing steric demands, gave very low yields of the title reaction and in some cases the desired product was hardly detected. Improvements by metals other than zinc and high-intensity ultrasound techniques, promoted successfully Reformatsky reactions with these substrates.[87] In our case, we managed to isolate **61**, as a mixture of *threo*/*erythro* stereoisomers, in 80% overall yield (see Section 5.4.3). Dehydration of **61** with catalytic amount of *p*-toluenesulfonic acid afforded a mixture of *E*/*Z*-**62** α,β-unsaturated methyl esters. Separation of *E*/*Z*-**62** methyl esters was accomplished by flash column chromatography, using hexane/EtOAc, v/v, 9:1 as eluent. For *E*- and *Z*-α,β-unsaturated methyl esters the isomeric purities were 90 and 98%, respectively. The *Z*-**62** isomer was used for the last two steps of the synthesis. The labeled alkene *Z*-**63**-d_3 was prepared according to the previously described procedure for the synthesis of **58a–e** (see Section 5.3). Reduction of *Z*-**62** with $LiAlD_4$ to the corresponding allylic alcohol, subsequent conversion of the latter to the allylic chloride followed by reduction with $LiAlD_4$, afforded the desired alkene in 95% isomeric purity.

The unlabeled alkene **63**-d_0 was also prepared by $LiAlH_4$ reduction of the crude mixture of *E*/*Z*-**62**, followed by chlorination and $LiAlH_4$ reduction of the allylic alcohol-d_0.

The ^{1}H NMR spectrum of substrate **63**-d_0 in the aromatic region revealed two AB systems: one at 7.52 and 7.23 ppm with a coupling constant 8.1 Hz, and the other at 7.02 and 6.83 ppm with a coupling constant 8.6 Hz. The former corresponds to the aromatic protons of the F_3C-substituted phenyl ring and the latter corresponds to the aromatic protons of the MeO-substituted phenyl ring.[88] Nuclear Overhauser effect (NOE) experiments with deuterium unlabeled **63**-d_0 alkene confirmed the stereochemistry of *Z*-**63**-d_3. Upon irradiation of protons of F_3C-substituted phenyl ring at 7.23 ppm, two positive NOEs were recorded: (a) hydrogens belonging to this aryl ring at 7.52 ppm and (b) the methyl group at 1.78 ppm. Furthermore, upon irradiation of protons of MeO-substituted phenyl ring at 7.02 ppm, two positive NOEs were recorded: (a) hydrogens belonging to this aryl ring at 6.83 ppm and (b) the methyl group at 1.82 ppm (Scheme 18).

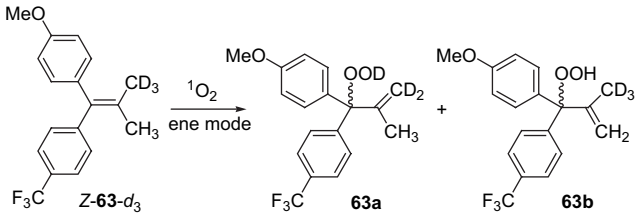


Scheme 18. NOE experiments for **63**-d_0 revealed the chemical shifts for the methyl groups.

Substrate *Z*-**63**-d_3 reacts smoothly with singlet oxygen generated by a 300-W Xenon lamp irradiation of TPP as sensitizer (10^{-4} M) in CCl_4, at 0 °C, under an oxygen atmosphere. A catalytic amount of galvinoxyl radical was also added to the reaction mixture, as a free radical scavenger. A solution of 0.05 M $K_2Cr_2O_7$ was used as a light filter during the photooxygenation. The irradiation time was ranged between 2 and 10 min. The ene allylic hydroperoxides were formed as the major adducts along with some unidentified oxygenated products. The ene adducts were stable and purified by flash column chromatography over silica gel, prewashed with triethylamine using a mixture of hexane/EtOAc, v/v, 9/1 as eluent. It is worth mentioning that a recovered small amount of the starting material was not isomerized. Determination of the ratio **63a/63b** was achieved by ^{1}H NMR spectroscopy before and after the reduction of allylic hydroperoxides. These results are presented in Table 6. The photooxygenation reactions of substrate *Z*-**63**-d_3 were run in various solvents such as carbon tetrachloride, chloroform, acetone, acetonitrile as well as in protic such as MeOH.

As shown from Table 6, a small but persistent preference on the order of 2–10% for hydrogen abstraction from the methyl group, which is cis to the CF_3-substituted phenyl ring was observed in non-protic solvents. However, in protic solvents, this preference increases to the range between 15 and 20%. Since the steric effect is identical to both sites of the double bond, the selectivity must be due to the variation of the electron density on the two sites of the double bond. This small but noticeable site selectivity may be rationalized by

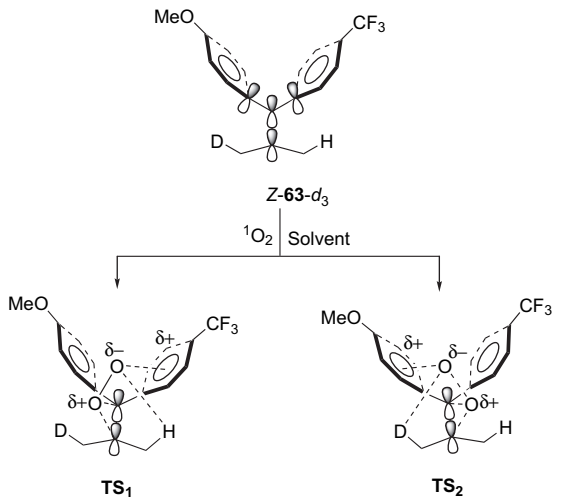
Table 6. Site selectivity of the photooxygenation of *Z*-**63**-d_3 in a variety of solvents



Solvent	ε[a] (Temp °C)	Sensitizer	**63a/63b**[b]
CCl_4	2.24 (20)	TPP	46/54
$CHCl_3$	4.87 (25)	TPP	48/52
$(CH_3)_2CO$	20.7 (20)	RB	49/51
CH_3CN	36.64 (20)	RB	49/51
CF_3CH_2OH	27.68 (20)	MB	40/60
MeOH	33.0 (20)	MB	42/58
MeOH/D_2O=4:1	42.44 (20)	MB	42/58

[a] See Ref. 70.
[b] Determined by ^{1}H NMR integration of the proper hydrogen signals. The error was ±3%.

a similar mechanism proposed above for the case of aryl alkenes (Scheme 13). It is expected that the geminal phenyl groups, for steric reasons, will be out of the plane of the alkene double bond. Therefore, their electronic effects, through resonance, are not fully developed to the benzylic carbon of the double bond during the addition of singlet oxygen. In TS_1 the relative positive interaction of the CF_3-phenyl ring with the incoming oxygen is slightly higher than in TS_2 for similar reasons mentioned previously (Scheme 19). However, the difference in the electronic interactions between singlet oxygen and the two *para*-substituted phenyl rings in *Z*-**63**-d_3 must be relatively smaller than those between singlet oxygen and *para*-substituted alkenes **58a** and **58b** (Scheme 13), where the phenyl rings are more conjugated with the alkene double bond, compared to *Z*-**63**-d_3. This may be the reason for a much smaller site selectivity for hydrogen abstraction for *Z*-**63**-d_3. It is not obvious why in this case (substrate *Z*-**63**-d_3) the site selectivity increases from 2–5% in aprotic solvents to 15–20% in protic solvents. A number of additional factors may contribute to this result, such as (a) hydrogen bonding, (b) better stabilization of the more polar transition state, and (c) conformational variations of the phenyl rings in protic solvents.



Scheme 19. Proposed mechanism for the photooxygenation of *Z*-**63**-d_3.

4. Conclusion

Stereoselective singlet oxygen allylic photooxygenations of alkenes have received remarkable attention over the last few years and will continue to play an important role in the synthesis of natural and non-natural products. In this report, a number of factors, such as solvents, electronic effects, and non-bonded interactions that dictate the ene product selectivity as well as the various mechanisms of this reaction are highlighted. This brief overview constitutes mainly examples taken from previous and recent works from our laboratory.

We have no doubts that the diversity of singlet oxygen will continue to fascinate researchers in chemistry, biology, and medicine, and to make reactions of this species a favored area for the development of new methods and ideas.

5. Experimental

5.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on 500 and 300 MHz spectrometers, in $CDCl_3$ solutions. Chemical shifts are reported in parts per million downfield from Me_4Si, by using the residual solvent peak as internal standard. Isomeric purities were determined by ^{1}H NMR, ^{13}C NMR, and by analytical gas chromatography equipped with a 50%–50% phenyl methyl silicone capillary column and a 5971A MS detector. Photooxygenations were achieved with a Xenon Variac Eimac Cermax 300 W lamp. TLC was carried out on SiO_2 (silica gel F_{254}). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh ASTM). Drying of organic extracts during work-up of reactions was performed over anhydrous $MgSO_4$. Evaporation of the solvents was accomplished with a rotary evaporator. Preparation of the labeled alkenylarenes **53**[75] and **58a**[89] has been described in earlier studies from our lab. UV–vis spectrum for compound **62**-d_0 was performed on a Hitachi U-2001 spectrophotometer, with bandwidth 200–900 nm.

5.2. General procedure for the preparation of labeled isobutenylarenes 58b–e

5.2.1. Synthesis of esters 55b–e. In a flame-dried flask were placed 2 g of NaH (60% in paraffin oil, 54.0 mmol) and 60 mL of dry DME. The flask was cooled to 0 °C, and then a solution of methyl diethyl-2-phosphonopropionate (11.2 g, 50.0 mmol) in dry DME (40 mL) was added dropwise under N_2 atmosphere. A vigorous evolution of hydrogen gas was observed. After 1 h of stirring at room temperature, a solution of arylaldehyde (46.0 mmol) in dry DME was injected. Stirring was continued for 2–3 h, and the reaction mixture was quenched with MeOH, poured into H_2O, and extracted with Et_2O. The combined ether layers were dried over $MgSO_4$ and concentrated, affording exclusively the desired *E*-ester (60% overall yield).

The spectroscopic data for esters **55b–e** are as follows. Compound **55b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.69 (s, 1H), 7.64 (d, 2H, J=8.0 Hz), 7.47 (d, 2H, J=8.0 Hz), 3.84 (s, 3H), 2.11 (s, 3H) ppm; MS m/z=244 (100, m/z=115). Compound **55c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.64 (s, 1H), 7.37 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=5.7 Hz), 7.08 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=8.5 Hz), 3.82 (s, 3H), 2.10 (s, 3H) ppm. Compound **55d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.69 (s, 1H), 7.34 (d, 2H, J=7.8 Hz), 7.16 (d, 2H, J=7.8 Hz), 3.81 (s, 3H), 2.37 (s, 3H), 2.08 (s, 3H) ppm; MS m/z=190 (100, m/z=130). Compound **55e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.61 (s, 1H), 6.85 (s, 2H), 3.82 (s, 3H), 2.59 (s, 3H), 2.29 (s, 6H), 2.12 (s, 3H) ppm; MS m/z=232 (100, m/z=187).

5.2.2. Synthesis of allylic alcohols-d_2 56b–e. A solution of the *E*-ester (32 mmol) in dry Et_2O (20 mL) was added dropwise to a cooled (0 °C) mixture of $LiAlD_4$ (0.734 g, 17.5 mmol) and $AlCl_3$ (0.773 g, 5.8 mmol) in dry Et_2O (40 mL), under N_2 atmosphere. The $AlCl_3$ had been added in portions to the $LiAlD_4$ at 0 °C over a 15 min period. After 1 h of stirring at room temperature, the reaction mixture was quenched at 0 °C with a 2 N solution of HCl and filtered. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated to give the corresponding *E*-alcohol (80% overall yield).

The spectroscopic data for allylic alcohols-d_2 **56b–e** are as follows. Compound **56b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.58 (d, 2H, J=8.2 Hz), 7.37 (d, 2H, J=8.2 Hz), 6.54 (s, 1H), 1.89 (s, 3H) ppm; MS m/z=199 (100, m/z=43). Compound **56c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.23 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=5.7 Hz), 7.02 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=8.5 Hz), 6.48 (s, 1H), 1.86 (s, 3H) ppm. Compound **56d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.23 (br s, 4H), 6.48 (s, 1H), 2.35 (s, 3H), 1.86 (s, 3H) ppm; MS m/z=146 (100, m/z=106). Compound **56e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.93 (s, 2H), 6.31 (s, 1H), 2.63 (s, 3H), 2.26 (s, 6H), 1.61 (s, 3H) ppm; MS m/z=192 (100, m/z=133).

5.2.3. Synthesis of allylic chlorides-d_2 57b–e. To a stirred mixture of the *E*-allylic alcohol (25 mmol) and 3.2 mL (27.6 mmol) of 2,6-lutidine, under N_2 atmosphere was added 1.18 g (27.8 mmol) of LiCl dissolved in a minimum amount of anhydrous dimethylformamide (DMF). On cooling to 0 °C, a suspension was formed, which was treated dropwise with $MeSO_2Cl$ (2.14 mL, 27.6 mmol). After 10–12 h of stirring at room temperature, the reaction mixture was poured into a saturated solution of $CuSO_4$ to remove 2,6-lutidine and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated to afford the allylic chloride in 93–98% geometrical purity (85% overall yield).

The spectroscopic data for allylic chlorides **57b–e** are as follows. Compound **57b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.59 (d, 2H, J=8.0 Hz), 7.37 (d, 2H, J=8.0 Hz), 6.61 (s, 1H), 1.98 (s, 3H) ppm; MS m/z=236 (100, m/z=201). Compound **57c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.25 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=5.7 Hz), 7.03 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=8.5 Hz), 6.54 (s, 1H), 1.97 (s, 3H) ppm. Compound **57d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.31 (d, 2H, J=7.7 Hz), 7.09 (d, 2H, J=7.7 Hz), 6.54 (s, 1H), 2.33 (s, 3H), 1.99 (s, 3H) ppm; MS m/z=182 (100, m/z=147). Compound **57e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.98 (s, 2H), 6.45 (s, 1H), 2.67 (s, 3H), 2.21 (s, 6H), 1.75 (s, 3H) ppm; MS m/z=210 (100, m/z=175).

5.2.4. Synthesis of deuterated alkenes 58b–e. To a cooled (0 °C) mixture of $LiAlD_4$ (0.44 g, 10.5 mmol) in dry THF (40 mL), under N_2 atmosphere, was added dropwise a solution of allylic chloride (21 mmol) in dry THF (20 mL). After 3–4 h of stirring at room temperature, the reaction mixture was quenched at 0 °C by addition of 1 mL of H_2O, 1 mL of 15% NaOH solution, and 2.5 mL of H_2O, and then filtered. The organic layer was washed with a 5% solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (petroleum ether) to afford *trans*-**58**-d_3 in 93–98% geometrical purity.

The spectroscopic data for labeled alkenes **58b–e** are as follows. Compound **58b** (isomeric purity 93%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.56 (d, 2H, J=8.2 Hz), 7.32 (d, 2H, J=8.2 Hz), 6.29 (s, 1H), 1.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 142.30, 137.84, 128.88, 127.76 (q, J_{CF}=31.9 Hz), 124.94 (q, J_{CF}=3.5 Hz), 124.40 (q, J_{CF}=270 Hz), 124.08, 26.03 (septet, J_{CD}=19 Hz), 19.34 ppm; MS m/z=203 (100, m/z=163). Compound **58c** (isomeric purity 98%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.20 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=5.9 Hz), 7.03 (dd, 2H, J_{HH}=8.5 Hz, J_{HF}=8.5 Hz), 6.26 (s, 1H), 1.86 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 161.06 (d, J_{CF}=243 Hz), 135.25, 134.67 (d, J_{CF}=3.3 Hz), 130.15 (d, J_{CF}=7.6 Hz), 124.05, 114.80 (d, J_{CF}=21 Hz), 25.81 (septet, J_{CD}=19 Hz), 19.14 ppm; MS m/z=153 (100, m/z=135). Compound **58d** (isomeric purity 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.18 (br s, 4H), 6.30 (s, 1H), 2.40 (s, 3H), 1.91 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 135.79, 135.28, 134.60, 128.71, 128.60, 124.96, 25.97 (septet, J_{CD}=19 Hz), 21.08, 19.29 ppm; MS m/z=149 (100, m/z=134). Compound **58e** (isomeric purity 98%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.96 (s, 2H), 6.13 (s, 1H), 2.74 (s, 3H), 2.25 (s, 6H), 1.54 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 136.35, 135.46, 134.87, 134.82, 127.73, 123.16, 24.14 (septet, J_{CD}=19 Hz), 20.92, 20.16, 18.95 ppm; MS m/z=177 (100, m/z=162).

5.3. Photooxygenation of deuterated alkenes 58a–e

A solution of 25–30 mg of isobutenylarene-d_3, in 8–10 mL of $CHCl_3$ and TPP as sensitizer (1×10^{-4} M) was bubbled gently with oxygen and irradiated for 30–40 min at 0 °C. Rose bengal was the sensitizer in acetonitrile and methylene blue in methanol. The photooxygenation of those substrates gave complex mixtures of oxygenated adducts. The ene adducts were purified by flash column chromatography over silica gel prewashed with triethylamine, using CH_2Cl_2 as eluent. The ^{1}H NMR spectroscopic data of the ene allylic hydroperoxides of the isobutenylarenes **58a–e** (d_0) are the following. Ene product from **58a**-d_0: ($CDCl_3$, 500 MHz) δ: 7.99 (s, 1H, OOH), 7.29 (d, J=8.5 Hz, 2H), 6.90 (d, J=8.5 Hz, 2H), 5.33 (s, 1H), 5.14 (br s, 1H), 5.08 (br s, 1H), 3.81 (s, 3H), 1.70 (s, 3H) ppm. Ene product from **58b**-d_0: ($CDCl_3$, 500 MHz) δ: 8.09 (s, 1H, OOH), 7.64 (d, J=8.1 Hz, 2H), 7.49 (d, J=8.1 Hz, 2H), 5.44 (s, 1H), 5.12 (br s, 1H), 5.11 (br s, 1H), 1.70 (s, 3H) ppm. Ene product from **58c**-d_0: ($CDCl_3$, 500 MHz) δ: 8.05 (s, 1H, OOH), 7.33 (dd, J_{HH}=8.0 Hz, J_{HF}=5.5 Hz, 2H), 7.06 (dd, J_{HH}=8.0 Hz, J_{HF}=8.0 Hz, 2H), 5.36 (s, 1H), 5.13 (br s, 1H),

5.10 (br s, 1H), 1.69 (s, 3H) ppm. Ene product from **58d**-d_0: ($CDCl_3$, 500 MHz) δ: 7.98 (s, 1H, OOH), 7.25 (d, 2H, J=7.9 Hz), 7.18 (d, 2H, J=7.9 Hz), 5.35 (s, 1H), 5.13 (br s, 1H), 5.07 (br s, 1H), 2.36 (s, 3H), 1.70 (s, 3H) ppm. Ene product from **58e**-d_0: ($CDCl_3$, 500 MHz) δ: 7.81 (s, 1H, OOH), 6.85 (s, 2H), 5.86 (d, 1H), 4.96 (br s, 1H), 4.79 (br s, 1H), 2.32 (s, 6H), 2.27 (s, 3H), 1.54 (s, 3H) ppm.

5.4. Synthesis of (*Z*)-1-(*p*-methoxyphenyl)-1-[(*p*-trifluoromethyl)phenyl]-2-methylprop-1-ene-3,3,3-d_3 (63-d_3)

This compound was prepared according to the procedure shown in Scheme 17.

5.4.1. (*p*-Methoxyphenyl)-[(*p*-trifluoromethyl)phenyl]-methanol (59). The title compound was prepared by a Grignard reaction between (*p*-trifluoromethyl)benzaldehyde and *p*-methoxybenzylmagnesium bromide. To a solution of Mg (1.46 g, 60 mmol) and catalytic amount of I_2 in 60 mL dry Et_2O was added dropwise 4-bromoanisole (9.35 g, 50 mmol) in 40 mL dry Et_2O. The mixture was refluxed for 2 h. After the solution was cooled to 0 °C (*p*-trifluoromethyl)benzaldehyde (8.36 g, 48 mmol) was added dropwise. After 30 min the mixture was warmed to room temperature and then refluxed for 2–3 h. The solution was worked up with NH_4Cl solution and extracted three times with Et_2O. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford **59** as an oil in 75% overall yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.53 (d, 2H, J=8.0 Hz), 7.44 (d, 2H, J=8.0 Hz), 7.24 (d, 2H, J=8.6 Hz), 6.86 (d, 2H, J=8.6 Hz), 5.83 (br s, 1H), 3.81 (s, 3H), 2.23 (br s, 1H, OH) ppm; MS m/z=282 (100, m/z=109).

5.4.2. 4-Trifluoromethyl-4′-methoxybenzophenone (60). Jones reagent was added dropwise to a solution of **59** (10.15 g, 36 mmol) in acetone (40 mL) at 0 °C. The addition was continued until the orange color of the reagent persisted. The solution was stirred at 0 °C for an additional 5 min. The solution was poured into water (200 mL) and extracted with ether. The ether extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was chromatographed on silica gel (hexanes/EtOAc=2:1) to give **60** as a yellow solid in 70% overall yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.83 (m, 4H), 7.75 (d, 2H, J=8.1 Hz), 6.98 (d, 2H, J=8.7 Hz), 6.86 (d, 2H, J=8.6 Hz), 3.90 (s, 3H) ppm; MS m/z=280 (100, m/z=135).

5.4.3. 3-(*p*-Methoxyphenyl)-3-[(*p*-trifluoromethyl)-phenyl]-3-hydroxy-2-methylpropionate (61). The title compound was prepared by a Reformatsky reaction between **60** and 2-bromopropionate in the presence of activated Zn and catalytic amount of I_2. The granular Zn was activated in a mixture of H_2SO_4/HNO_3=9/1 for 30 min. Then it was filtered and washed several times with H_2O and finally with acetone. Zn was dried before using. In a flame-dried flask were placed activated Zn (9.9 g, 0.151 mol), 2-bromopropionate (5.62 mL, 50.4 mmol), carbonyl compound **60** (7.06 g, 25.2 mmol), catalytic amount of I_2, and dry benzene/Et_2O=2/1 (80/40 mL). The mixture was refluxed for 2 days. The solution was poured into a solution of 4 N H_2SO_4 (50 mL) and extracted once with H_2O and two times with brine. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was passed through a short pad of silica, prewashed with triethylamine (hexane/EtOAc=9:1), to afford **61** (80% overall yield) as a 1:1 mixture of stereoisomers (please note that before column chromatography β-hydroxy-methylester **61** existed as a 3:2 mixture of stereoisomers). ^{1}H NMR (mixture of two stereoisomers) ($CDCl_3$, 500 MHz) δ: 7.63 (d, 2H, J=7.9 Hz), 7.53 (m, 6H), 7.44 (d, 2H, J=8.8 Hz), 7.33 (d, 2H, J=8.8 Hz), 6.82 (d, 4H, J=7.9 Hz), 4.74 (br s, 1H, OH), 4.71 (br s, 1H, OH), 3.76 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.61 (s, 3H), 2.58 (m, 2H), 1.39 (s, 1H), 1.35 (s, 1H), 1.18 (d, 3H, J=6.9 Hz), 1.12 (d, 3H, J=6.9 Hz) ppm.

5.4.4. Methyl 3-[(*p*-trifluoromethyl)phenyl]-2-methyl-*p*-methoxycinnamate (62). A solution of **61** (7.44 g, 20.16 mmol) in benzene (100 mL) containing catalytic amount of *p*-toluenesulfonic acid was heated at 70 °C for 2–3 h. The solution was dried ($MgSO_4$), filtered, and concentrated to afford substituted α,β-unsaturated methylester (95% overall yield) as a 1:1 mixture of *E*/*Z*-isomers. The residue passed through a long pad of silica (hexane/EtOAc=9:1) and the two isomers were separated successfully. ^{1}H NMR (*E*-**62**, isomeric purity 90%) ($CDCl_3$, 500 MHz) δ: 7.52 (d, 2H, J=8.1 Hz), 7.22 (d, 2H, J=8.1 Hz), 7.06 (d, 2H, J=8.8 Hz), 6.87 (d, 2H, J=8.8 Hz), 3.82 (s, 3H), 3.48 (s, 3H), 2.09 (s, 3H) ppm; ^{13}C NMR (*E*-**62**, isomeric purity 90%) ($CDCl_3$, 125 MHz) δ: 170.70, 163.57, 146.43, 145.41, 132.16, 130.80, 130.68, 129.85 (q, J_{CF}=34.9 Hz), 128.87, 125.63 (q, J_{CF}=3.8 Hz), 124.53 (q, J_{CF}=271 Hz), 113.60, 54.88, 51.25, 18.31 ppm; MS m/z=350 (100, m/z=350). ^{1}H NMR (*Z*-**62**, isomeric purity 98%) ($CDCl_3$, 500 MHz) δ: 7.60 (d, 2H, J=8.1 Hz), 7.29 (d, 2H, J=8.1 Hz), 7.02 (d, 2H, J=8.7 Hz), 6.81 (d, 2H, J=8.7 Hz), 3.78 (s, 3H), 3.54 (s, 3H), 2.00 (s, 3H) ppm; ^{13}C NMR (*Z*-**62**, isomeric purity 98%) ($CDCl_3$, 125 MHz) δ: 171.50, 159.38, 144.86, 144.64, 133.90, 130.28, 130.04, 129.75 (q, J_{CF}=34.8 Hz), 128.36, 125.24 (q, J_{CF}=3.5 Hz), 124.14 (q, J_{CF}=270.5 Hz), 113.63, 55.20, 51.76, 18.57 ppm; MS m/z=350 (100, m/z=350).

5.4.5. (*Z*)-3-(*p*-Methoxyphenyl)-3-[(*p*-trifluoromethyl)-phenyl]-2-methylprop-2-en-1-ol-1,1-d_2. This compound was prepared according to the previously described procedure for the synthesis of allylic alcohols-d_2 **56b–e** (Section 5.2.2). ^{1}H NMR (*Z*, isomeric purity 98%) ($CDCl_3$, 500 MHz) δ: 7.55 (d, 2H, J=8.1 Hz), 7.25 (d, 2H, J=8.1 Hz), 7.03 (d, 2H, J=8.7 Hz), 6.83 (d, 2H, J=8.7 Hz), 3.78 (s, 3H), 1.88 (s, 3H), 1.57 (br s, 1H, OH) ppm; MS m/z=306 (100, m/z=306).

5.4.6. (*Z*)-3-(*p*-Methoxyphenyl)-3-[(*p*-trifluoromethyl)-phenyl]-2-methylprop-2-en-1-yl-1,1-d_2 chloride. This compound was prepared according to the previously described procedure for the synthesis of allylic chlorides-d_2 **57b–e** (Section 5.2.3). ^{1}H NMR (*Z*, isomeric purity 95%) ($CDCl_3$, 500 MHz) δ: 7.56 (d, 2H, J=8.4 Hz), 7.25 (d, 2H, J=6.9 Hz), 7.12 (d, 2H, J=6.9 Hz), 6.86 (d, 2H, J=8.4 Hz), 3.80 (s, 3H), 1.89 (s, 3H) ppm; MS m/z=342 (100, m/z=307).

5.4.7. (*Z*)-1-(*p*-Methoxyphenyl)-1-[(*p*-trifluoromethyl)-phenyl]-2-methylprop-1-ene-3,3,3-d_3 (*Z*-63-d_3). This compound was prepared according to the previously described procedure for the synthesis of deuterated alkenes **58b–e** (Section 5.2.4). The crude product was chromatographed on

silica gel (hexane) to give *Z*-**63**-d_3 as a yellow oil. ^{1}H NMR (*Z*-**63**-d_3, isomeric purity 95%) ($CDCl_3$, 500 MHz) δ: 7.59 (d, 2H, J=7.7 Hz), 7.30 (d, 2H, J=7.7 Hz), 7.10 (d, 2H, J=8.4 Hz), 6.90 (d, 2H, J=8.4 Hz), 3.83 (s, 3H), 1.84 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.24, 147.47, 135.68, 135.11, 132.20, 131.09, 130.27, 128.22 (q, J_{CF}=32.6 Hz), 124.96 (q, J_{CF}=3.75 Hz), 124.51 (q, J_{CF}=270.2 Hz), 113.56, 55.32, 22.54, 21.87 (septet, J_{CD}=19.05 Hz) ppm; MS *m*/*z*=309 (100, *m*/*z*=309).

5.4.8. 1-(*p*-Methoxyphenyl)-1-[(*p*-trifluoromethyl)-phenyl]-2-methylprop-1-ene (63-d_0). The unlabeled olefin **63**-d_0 was prepared by reduction of methyl 3-[(*p*-trifluoromethyl)phenyl]-2-methyl-*p*-methoxycinnamate (crude mixture 1:1 of *E*/*Z*-isomers) with $LiAlH_4$ to the respective allylic alcohol, subsequent conversion of the latter to the allylic chloride, and further reduction with $LiAlH_4$. The residue was chromatographed on silica gel (hexane) to give **63**-d_0 as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.52 (d, 2H, J=8.1 Hz), 7.23 (d, 2H, J=8.1 Hz), 7.02 (d, 2H, J=8.6 Hz), 6.83 (d, 2H, J=8.6 Hz), 3.79 (s, 3H), 1.82 (s, 3H), 1.78 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.24, 147.48, 135.65, 135.11, 132.30, 131.09, 130.27, 128.41 (q, J_{CF}=31.8 Hz), 124.96 (q, J_{CF}=3.75 Hz), 124.57 (q, J_{CF}=270.1 Hz), 113.56, 55.34, 22.71, 22.61 ppm; MS *m*/*z*=306 (100, *m*/*z*=306). UV–vis spectra of **63**-d_0 in $CHCl_3$ have characteristic maximum absorption at λ_{max}=245 nm.

5.5. Photooxygenation of *Z*-63-d_3

A solution of 15 mg of *Z*-**63**-d_3 in 8 mL of CCl_4 containing a catalytic amount of galvinoxyl as free radical scavenger (TPP, 1×10^{-4} M as sensitizer) was bubbled gently with oxygen and irradiated with a 300-W Xenon lamp, through a 0.05 M $K_2Cr_2O_7$ filter solution, for 2 min at 0 °C. The same procedure was followed in several solvents. TPP was the sensitizer in $CHCl_3$. Rose bengal was the sensitizer in acetonitrile and acetone. Methylene blue was the sensitizer in isopropanol, 2,2,2-trifluoroethanol, MeOH, and MeOH/D_2O=4:1. The photooxygenation gave complex mixtures of oxygenated adducts. The ene adducts were purified by flash column chromatography over silica gel prewashed with triethylamine, using a mixture of hexane/EtOAc=9:1 as eluent. The ^{1}H NMR spectroscopic data of the ene allylic hydroperoxide of **63**-d_0 are the following. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.61 (s, 4H), 7.32 (d, 2H, J=8.8 Hz), 7.24 (s, 1H, OOH), 6.90 (d, 2H, J=8.8 Hz), 5.22 (s, 1H), 5.09 (s, 1H), 3.83 (s, 3H), 1.71 (s, 3H) ppm.

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Supplementary data

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