

## Regioselectivity in the Ene Reaction of Singlet Oxygen With Alkenes Bearing an Electron Withdrawing Group at $\beta$ - Position

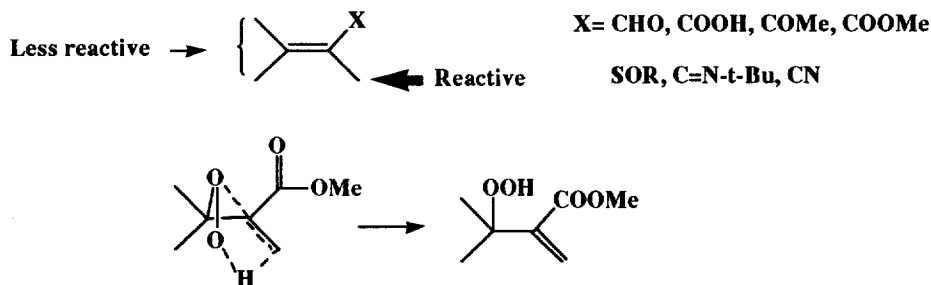
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**Abstract:** Electronic repulsions between a perepoxide intermediate and the allylic functionality in the product forming transition state, direct the regioselectivity in the photooxygenation of trisubstituted alkenes bearing an electron withdrawing group at  $\beta$ - position. © 1997, Elsevier Science Ltd. All rights reserved.

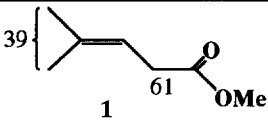
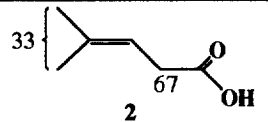
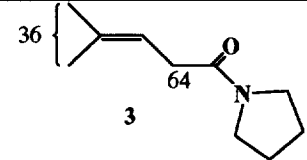
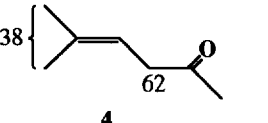
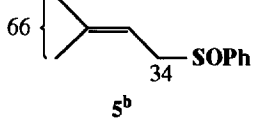
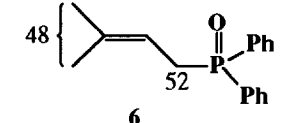
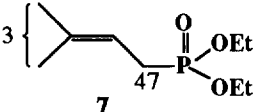
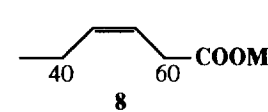
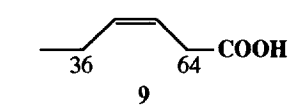
The stereoselectivity in the ene reaction of singlet oxygen with alkenes has received considerable attention in recent years.<sup>1</sup> For alkyl substituted olefins the non bonding interactions in the transition states dictate the product distribution.<sup>2</sup> For chiral functionalized alkenes at the allylic position, favorable or unfavorable interactions between oxygen and the substituent can significantly affect either the distribution of the threo/erythro diastereomeric ene products,<sup>3</sup> or the endo/exo stereoselectivity in the case of allylic alcohols.<sup>4</sup> For alkenes which bear an electron withdrawing functionality at  $\alpha$ - position, a high degree of geminal selectivity has been observed.<sup>5</sup> Although many intermediates had been invoked to rationalize these results, it is more likely that perepoxide is the most acceptable intermediate.<sup>6</sup> The geminal regioselectivity could be due to a weakening of the proximal C-O bond in the perepoxide intermediate by the electron deficient substituent, as depicted in the following scheme I, for the case of the  $\alpha,\beta$ -unsaturated esters. Thus an electron withdrawing functionality can dictate the regioselectivity because in the transition state leading to the main ene product the newly formed double bond is in conjugation with the unsaturated functionality.

Scheme I



As part of our continuous interest in the stereochemistry of the singlet oxygen ene reactions, we studied the regioselectivity in the reaction of  $^1\text{O}_2$  with alkenes bearing an electron withdrawing group at  $\beta$ -position with respect to the double bond. The results are summarized in Table 1.

**Table 1. Photooxygenation of alkenes bearing an electron withdrawing group at  $\beta$ - position<sup>a</sup>**

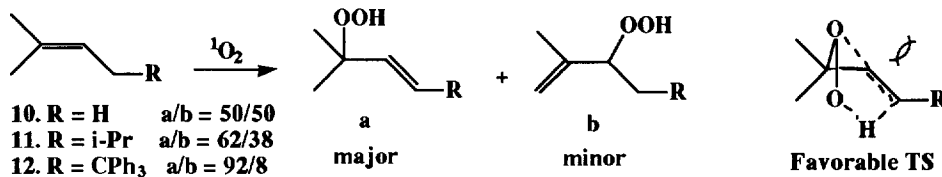
|   |   |  |
|---|---|--|
| 39<br> | 33<br> | 36<br> |
| 38<br> | 66<br> | 48<br> |
| 53<br> | 40<br> | 36<br> |

<sup>a</sup> Numbers indicate percentages of hydrogen abstraction which were determined by  $^1\text{H}$  NMR integration and by GC analysis of the allylic alcohols derived from reduction of the initially formed allylic hydroperoxides. <sup>b</sup> Reference 7.

As seen in Table 1, photooxygenation of carbonyl derivatives **1-4** and **8-9**, shows approximately a 2/1 preferential double bond formation in conjugation to the alkene functionality. However the observed regioselectivity is much less than that observed previously in the  $\alpha,\beta$ -unsaturated alkenes where the new double bond is formed more than 90% in conjugation with the functionality (Scheme I).

It is constructive to note here that for the geminal dimethyl trisubstituted alkenes<sup>8</sup> **10-12**, methylene hydrogens are always more reactive than methyl hydrogens due to the 1,3- non bonded interactions<sup>2</sup> between the substituent R and perepoxide, as shown in Scheme II.

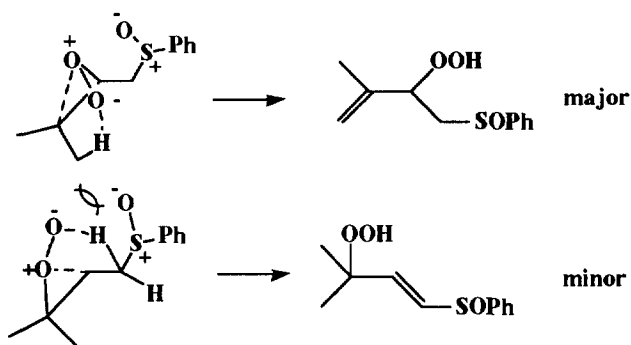
**Scheme II**



For substrates **1-4** the observed regioselectivity is identical to the regioselectivity observed for the alkyl substituted alkene **11** which shows approximately similar substituent stereodemand. Taking into account both effects (conjugation and 1,3-non bonded interactions), a higher regioselectivity would be expected for substrates **1-9**, than that found in Table 1. It is likely that unfavorable repulsions between the negatively charged distal oxygen of the perepoxide formed in the more substituted side of the olefin (cis effect)<sup>9</sup> and the oxygen of the carbonyl in a six membered ring transition, forces the perepoxide oxygen to the proper orientation for hydrogen abstraction from the methyl group (Scheme III).

In substrates bearing the S-O or P-O functionalities, the regioselectivity is reversed compared to substrates **1-4** and the double bond formation on the side of the olefin which is away from the functionality increases. This is demonstrated by the photooxygenation of substrates **5-7**. For example in sulfoxide **5**, methylene hydrogens are almost half as reactive as the hydrogens of the methyls. Again this could be attributed to the fact that the highly negative polarised oxygen of the S-O bond, exhibits unfavorable repulsions with the negatively charged oxygen of peroxide (Scheme III). These repulsions are higher for the S-O and P-O derivatives due to the highly polarized nature of these bonds, compared to the carbonyl derivatives. A similar argument was proposed<sup>3c,d</sup> to rationalize the highly diastereoselective ene reactions of singlet oxygen with chiral allylic sulfones, halides and carbonyl derivatives. Similar results (increased reactivity of the methyls), are obtained in the photooxygenation of phosphorous containing alkenes **6** and **7**, despite the fact that significant non bonded interactions<sup>2</sup> would be expected to favor hydrogen abstraction next to the functionality.

Scheme III



The regioselectivities observed in the case of the disubstituted unsaturated ester **9** and acid **10**, are similar to that of the trisubstituted substrates **1** and **2**. 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<sup>10</sup>). Furthermore the same assumption is also supported from the high erythro selectivity observed in the photooxygenation of chiral 2-phenylsulfonyl-4-methyl-pent-3-ene.<sup>3d</sup> If the electronic repulsions force the formation of the "exo" peroxide, the reaction would not be expected to be diastereoselective to such an extent.

It has been noted<sup>11</sup> earlier that reaction of  $^1\text{O}_2$  with **4** is regiospecific with 100% double bond formation next to the ketone. Some years ago a revised 32/68 ratio of ene products with the major being the non conjugated enone hydroperoxide was reported.<sup>12</sup> However in our hands the exact opposite result was observed with the minor product appearing as a 50/50 mixture of the diastereomeric hemiperketals of the hydroperoxyenones, which undoubtedly derive from cyclization of the minor adduct. Similar dioxolane type cyclisation products have been observed in the photooxygenation of the  $\alpha,\beta$ -unsaturated ketones.<sup>5d</sup>

Also it is remarkable to note that the reactivity of methylene hydrogens next to the functionalities is dramatically minimized when substrate **5** bears a geminal methyl group.<sup>13</sup> A high degree of geminal selectivity can be observed entirely due to steric reasons.

We conclude that there are three competing factors that can affect the regiochemistry in the ene reaction of singlet oxygen with alkenes bearing an electron withdrawing group at  $\beta$ - position: a) The driving force to form the new double bond in conjugation with the functionality in the allylic hydroperoxide product; b) The 1,3- non bonded interactions between the positively charged oxygen of peroxide and the allylic functionality which favor again the conjugated product and c) The electronic repulsions between peroxide 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.

#### Acknowledgments

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