



Diastereoselective Ene Reactions of Triazolinediones With Chiral Allylic Alcohols. Evidence For a Hydroxyl-Enophile Steering Effect

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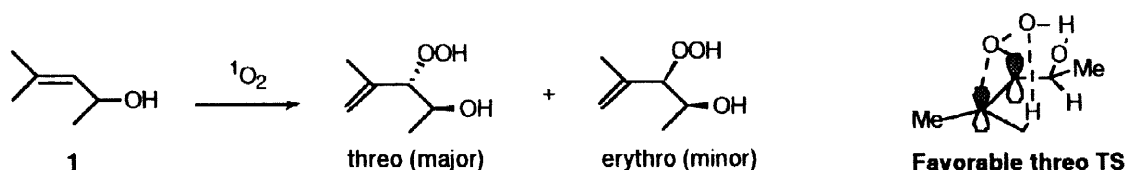
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Abstract: The ene reaction of PTAD with the chiral allylic alcohol 4-methyl-3-penten-2-ol exhibits high threo diastereoselectivity in non polar solvents, whereas in polar solvents the diastereoselectivity decreases substantially. These results are discussed in terms of a steering effect between the hydroxyl and the incoming enophile during the formation of the diastereomeric syn and anti aziridinium imide intermediates. © 1998 Elsevier Science Ltd. All rights reserved.

Recently the ene reactions of singlet oxygen (1O_2) with alkenes bearing a functionality on a stereogenic center at the allylic position have received considerable mechanistic and synthetic attention.¹ For example, the photooxygenation of the chiral allylic alcohol **1**² in the non polar solvent carbon tetrachloride affords allylic hydroperoxides with 95% threo diastereoselectivity. Also, it has been reported³ that the hydroxyl of allylic alcohols directs the syn/anti stereoselectivity in the singlet oxygen ene reaction. These results were primarily attributed to a steering effect between hydroxyl and electrophile in the transition state that leads to the formation of an intermediate exciplex with the structural requirements of a perepoxide. The ratio of threo/erythro adducts was significantly minimized when the photooxygenation was run in polar solvents with hydrogen bonding ability (CH₃CN, CH₃OH), due to the lack of a steering effect in such solvents. When the allylic substituent develops unfavorable electronic repulsions with the incoming oxygen (carboxylic acid derivatives, halides, etc.), the reaction becomes highly erythro diastereoselective.⁴

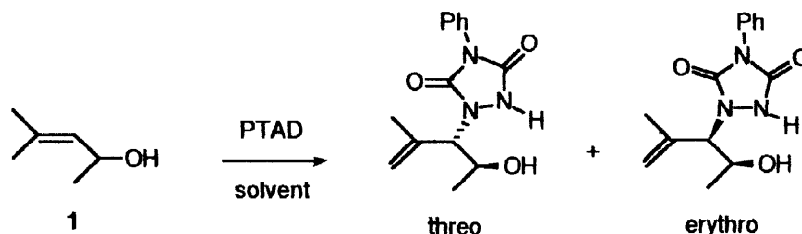


Although extensive studies exist on the factors controlling the diastereoselectivity of the 1O_2 ene and [4+2] reactions, there is no information on the analogous triazolinedione additions to alkenes. Only in the [4+2] cycloaddition of MTAD with some chiral dienols,⁵ the hydroxyl group has been reported to control the π facial selectivity. Triazolinediones add to alkenes to form a structurally similar intermediate to perepoxide, the aziridinium imide (AI).⁶ Since the regioselectivity of the ene reaction is similar for both

electrophiles,⁷ we wondered how the diastereoselectivity of triazolinediones addition to chiral alkenes bearing a functionality at the allylic position compares with that of singlet oxygen.

As a representative example we studied the ene diastereoselectivity in the addition of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to the chiral allylic alcohol **1**. Reaction of **1** with PTAD proceeded smoothly at room temperature in various solvents, giving the diastereomeric ene as the only products. As seen in Table 1, the reaction is highly threo diastereoselective in non polar solvents. By increasing solvent polarity the percentage of the erythro adduct increases substantially.

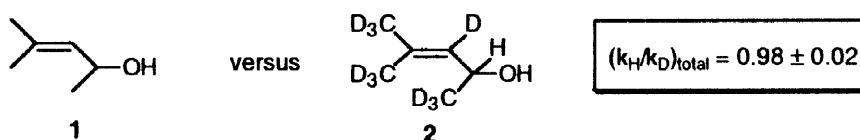
Table 1. Diastereoselectivity in the ene reaction of **1 with PTAD in various solvents**



Entry	Solvent	Threo/erythro
1	Benzene	91/9
2	Chloroform	86/14
3	Acetone	66/34
4	Methanol	62/38

The diastereomers have well resolvable NMR signals for the olefinic protons and the allylic methyls of each diastereomer. The major adduct was assigned the threo isomer from homo-decoupling experiments. Upon irradiation of the doublet at 1.24 ppm (the methyl group next to the hydroxyl), the methinic hydrogen next to the hydroxyl appears as a set of two doublets, one at 4.52 ppm ($J_1=6.6$ Hz) and another at 4.66 ppm ($J_2=5.5$ Hz), corresponding to the threo and erythro diastereomers in a ratio similar to that measured from integration of the diastereomeric allylic methyls signals at 1.73 and 1.80 ppm respectively. Examination of the more stable Newmann projections of the threo and erythro rotamers, reveals that the adduct with the higher coupling constant corresponds to the threo isomer, where the hydrogens have a trans arrangement. The adduct with the smaller coupling constant corresponds to the erythro isomer which has the hydrogens gauche to each other.

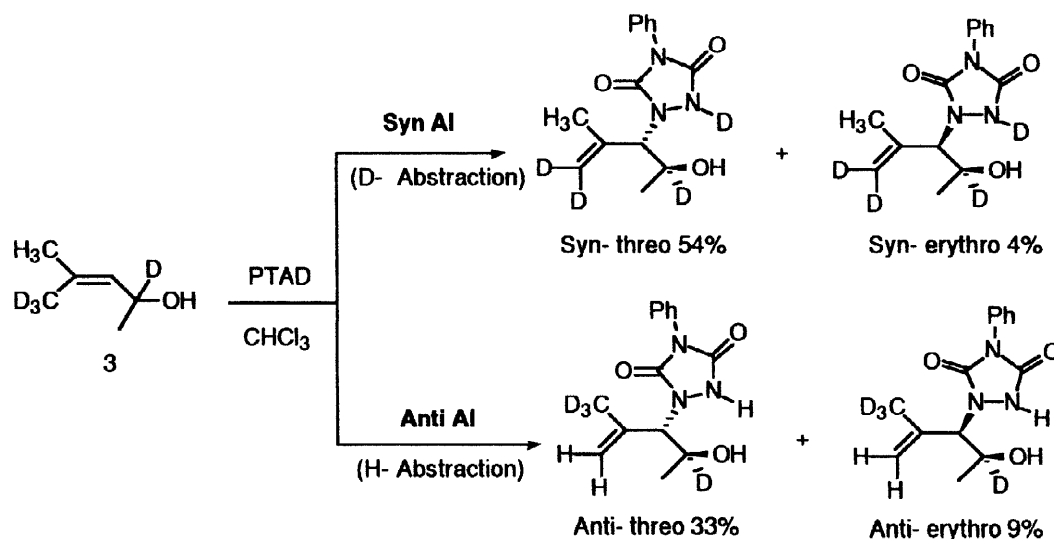
The kinetic competition between **1** and the deuterated alkene **2** was also studied. The observed intermolecular isotope effect⁸ was found to be $k_H/k_D=0.98\pm 0.02$ in chloroform or acetone, implying that allylic hydrogen abstraction does not occur in the rate determining step, and that the observed diastereomeric ratio depends on the energy differences of the diastereomeric transition states leading to the formation of AI.



In order to find the syn/anti allylic methyl reactivity in the reaction and assess further the threo/erythro ratio from both the syn and anti AI intermediates, the allylic alcohol **3**⁹ where the syn methyl

was selectively labeled as CD₃ was prepared in 94% geometrical purity. We define as syn AI the intermediate where the PTAD is placed syn to the hydroxyl, and as anti AI that where the PTAD is placed on the less substituted side of the double bond (anti to the hydroxyl). To simplify the NMR integrations, the methinic hydrogen next to the hydroxyl was labeled as D. The syn/anti methyl reactivity was found in chloroform to be 58/42. The diastereoselectivity results are depicted in scheme I. Integration of the allylic methyl resonances affords the threo/erythro ratio from the syn AI (D- abstraction), whereas integration of the olefinic protons affords the threo/erythro ratio from the anti AI (H- abstraction). The **syn-threo/syn-erythro** was found to be 54/4, and **anti-threo/anti-erythro** 33/9.

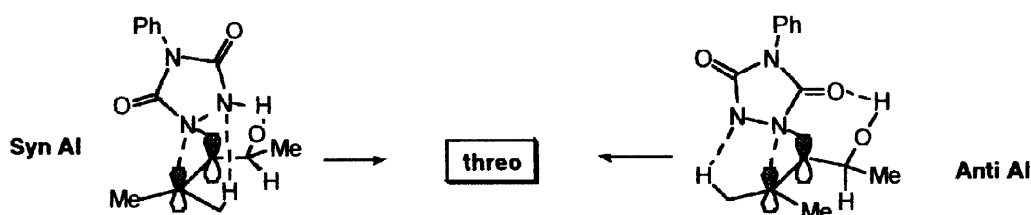
Scheme I



When the reaction was run in the more polar acetone, the syn/anti methyl reactivity was 55/45, the **syn-threo/syn-erythro** 36/19, and the **anti-threo/anti-erythro** 26/19. These results show a roughly similar increase of the erythro adduct from both the syn and the anti intermediates, on going from the non polar chloroform, to the more polar acetone.

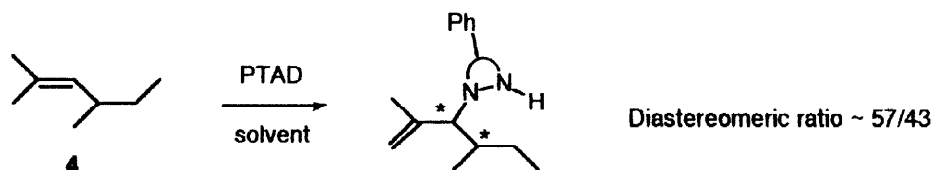
As seen in scheme I, both intermediates in chloroform lead to preferential threo selectivity. For the syn intermediate which is slightly predominant, the high degree of threo selectivity could be attributed to the steering effect of the hydroxyl in a transition state (scheme II) similar to the one proposed in the ¹O₂ ene reaction with **1**.² The high threo selectivity observed in the anti intermediate, can also be explained in terms of a steering effect between the carbonyl functionality of PTAD and the hydroxyl in a seven-membered ring transition state (scheme II).

Scheme II



Furthermore, that the 1,3-allylic strain plays a significant role in the stability of the three transition states is seen in scheme II, since the methyl group at the chiral center adopts a preferential conformation that minimizes non bonding interactions with the syn allylic methyl. In acetone, hydrogen bonding between the solvent and the hydroxyl reduces its steering efficiency, thus leading to significant amounts of the erythro adducts that are formed from both the syn or the anti intermediates.

When the hydroxyl group is replaced by an ethyl group in substrate **1** to produce compound **4**, the diastereoselectivity in acetone or chloroform decreases substantially (~ 15% d.e.).¹⁰ This result indicates that steric reasons are less important for the high diastereoselectivity measured in the reaction of **1** with PTAD.



In conclusion, we presented substantial evidence for a favorable interaction between the hydroxyl group of allylic alcohols and PTAD in the transition state of AI formation. The steering effect occurs either between the negatively charged nitrogen during the formation of AI where PTAD is placed syn to the hydroxyl, or between the carbonyl group of PTAD and the hydroxyl, in the transition state where the enophile is placed anti to -OH.

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- Alkene **2** was prepared by reduction of mesityl oxide-d₁₀ with LiAlH₄. The ketone was prepared by aldol condensation of acetone-d₆ and subsequent dehydration with I₂ (NMR indicated 88% D content on the vinylic position and 93% on the allylic methyls). The kinetic competition of **1** versus **2**, for the observation of the intermolecular isotope effect was monitored by GC and by NMR.
- Alkene **3** was prepared by LiAlD₄ reduction of (Z)- 4-methylpent-3-en-2-one-5,5,5-d₃. The ketone was prepared by coupling the enoltriethylphosphate ester of acetylacetone with (CD₃)₂CuLi : Sum, F. W.; Weiler, I. *Can. J. Chem.* **1979**, *57*, 1431-41.
- The configuration of the major and minor diastereomers was not assigned.