Stereochemistry of the Triazollinedione−Alkene Ene Reaction: A Stereospecific Suprafacial Transformation

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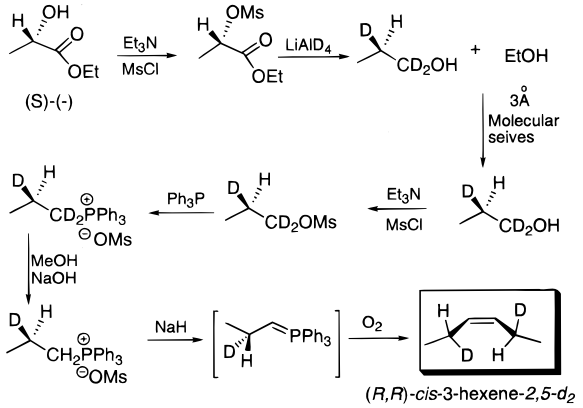
Triazolinedione (RTAD, R = methyl or phenyl), one of the most reactive electrophiles,[1] reacts with conjugated dienes to give Diels−Alder products[2−4] and with olefins to produce ene or [2+2] adducts.[4−6] The ene reaction has attracted considerable mechanistic[5−12] and theoretical attention.[13,14] Most of the experimental studies[5−12] and to a lesser extent computational work[13] support a stepwise mechanism with formation of an aziridinium imide, AI, intermediate in the rate determinig step. AI intermediates also have been observed spectroscopically and reported independently by a number of investigators.[15−17]

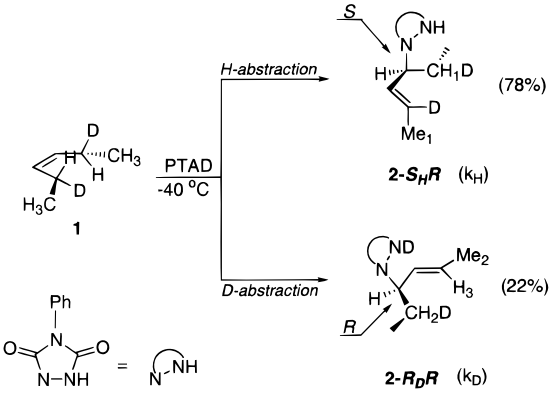
The stereoselectivity of this synthetically useful transformation[18−21] has received conciderable attention. For example, RTAD adds to various alkenes and shows a number of regioselectivities[5,7,22,23] depending on the double bond substitution. It also adds to allylic alcohols showing a remarkable diastereoselectivity,[12,24,25] and to allyl silanes affording cis ene products.[26]

In this paper we report the stereochemistry of this reaction with simple alkenes and discuss mechanistic possibilities in the light of the present results. This stereochemistry has not been previously recognized and may hold important implications for the mechanism of this reaction.

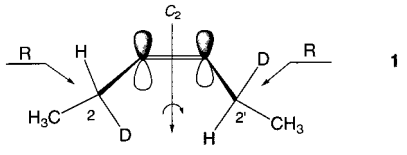
Scheme 1. Preparation of (*R,R*)-*cis*-3-hexene-*2,5-d*$_2$ from (*S*)-(−)-Ethyl Lactate



Scheme 2. PTAD Ene Addition to Olefin **1**



The optically active, by virtue of deuterium substitution, and isomerically pure olefin, (*R,R*)-*cis*-3-hexene-*2,5-d*$_2$ (**1**), is well suited to test the stereochemical requirements of this classical ene reaction. This olefin has three distinctive characteristics: (a) asymmetry at the two reactive allylic carbons C_2 and $C_{2'}$, by virtue of stereospecific deuteration, (b) distinguishable groups at both ends of the double bond such that the ene adducts will contain a new stereogenic center, and (c) a C_2 symmetry axis such that the two faces of the double bond are equally accessible.



The preparation[27] of (*R,R*)-*cis*-3-hexene-*2,5-d*$_2$ (**1**) from (*S*)-(−)-ethyl lactate is shown in Scheme 1. The reaction of this olefin with PTAD at −40 °C in dicloromethane quantitatively gave product **2** with only the trans stereochemistry. For convenience, we present here mechanistic possibilities considering only one of the two equivalent faces of the double bond. Approach of PTAD from the top face would abstract H and form an *S* stereogenic center, whereas abstraction of D would form the *R* stereogenic center (Scheme 2). We define the new stereogenic

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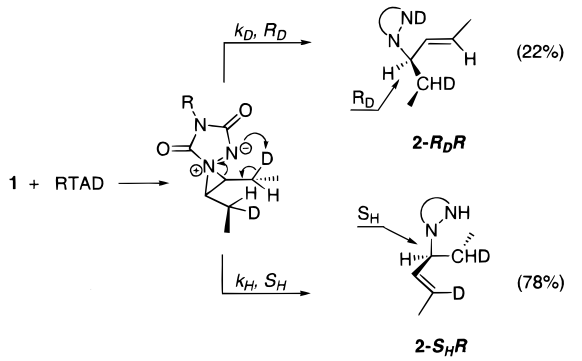
Scheme 3. Mechanistic Possibility of Ene Product Formation



centers as S_H or R_D indicating H or D abstraction from the allylic position of alkene **1**, and these two diastereomeric products are labeled **2-*S*$_H$,*R*** and **2-*R*$_D$,*R***. With this mechanistic possibility, one could obtain crossover products (R_H,*R* and S_D,*R*) only to the extent that the trans olefin isomer or the opposite enantiomer (*S*,*S*)-*cis*-3-hexene-*2*,*5*-d_2 is present in the starting material. The ratio of these products **2-*S*$_H$,*R*:2-*R*$_D$,*R***, which is the result of intramolecular isotopic competition between the cis-chiral allylic centers of the olefin, is proportional to the primary product isotope effect k_H/k_D. Integration of the vinylic signals H_3 of **2-*R*$_D$,*R*** as well as the hydrogen next to the nitrogen for both ene adducts of **2** determines the primary isotope effect $k_H/k_D = 3.66 \pm 0.05$. When the reaction was run at −30 °C, a smaller isotope effect was found, $k_H/k_D = 2.02 \pm 0.05$, as expected.[28] This result is in agreement with previous reported isotope effects in this reaction.[5,6]

To probe the stereochemistry further and obtain information on the chirality of the newly formed stereogenic centers *S*/*R* as well as to correlate the *S*/*R* and k_H/k_D ratios in the ene products **2**, a detailed ^{1}H NMR analysis was performed. Although the ene products **2** are diastereomers, ^{1}H NMR resolution of their diastereomeric groups was only achieved in the presence of a chiral shift reagent. Thus, examination of both the allylic methyls and the methylene hydrogens of **2** by ^{1}H NMR revealed that both are measurably separated in the presence of Eu(hfc)$_3$. An impressive chiral shift separation of diastereotopic groups was achieved. The allylic methyl group, Me_1, of **2-*S*$_H$,*R*** resonates as a singlet at a higher magnetic field than its diastereomeric allylic methyl group Me_2 (doublet) of **2-*R*$_D$,*R***. From ^{1}H NMR integration of the two diastereomeric methyl signals (Me_1 and Me_2) the ratio of the newly formed stereogenic centers S_H:R_D was determined to be 3.62 ± 0.05, which represents a 56% ee of the *S* enantiomer (Scheme 3). Identical results were obtained by ^{1}H NMR integration of the resolved H_1 and H_2 methylene hydrogens of **2**. It is important to emphasize here the correspondence of the diastereomeric ratio **2-*S*$_H$,*R*:2-*R*$_D$,*R*** of 3.62 to the isotopic k_H/k_D ratio of 3.66. When the reaction was run at −30 °C, an identical ^{1}H NMR analysis showed similar correspondence of the diastereomeric ratio of 2.01 to the isotopic ratio of 2.02.

These results can be best rationalized via the formation of the established aziridinium-like intermediate. In AI, abstraction of deuterium D, and subsequent carbon−nitrogen bond formation, leads to the R_D stereogenic center with H remaining in the product double bond, while abstraction of hydrogen H leads to the formation of the S_H stereogenic center with D remaining in the product double bond (Scheme 3). They furher indicate that the RTAD−ene reaction is a highly stereospecific suprafacial process. Had the crossover products (**2-*R*$_H$,*R***, **2-*S*$_D$,*R***) been formed, the ^{1}H NMR would have been more complicated. The presence of an isotopic ratio, which matches exactly the stereogenic ratio, makes it difficult to argue for a biradical or zwitterionic intermediate. For a stepwise biradical or dipolar mechanism, intermediates $\mathbf{I}_R$ and $\mathbf{I}_S$ are expected to be formed in equal amounts. This implies that neither **2-*R*,*R*** nor **2-*S*,*R*** products would be preferentially formed, and because of free rotation around the previous carbon−carbon double bond, a nonstereospecific reaction would have been expected and the product would have been racemic.

(28) Because of hydrogen tunneling, the k_H/k_D isotope effect of the ene reaction of PTAD depends strongly on temperature: Elemes, Y.; Orfanopoufos, M. *J. Am. Chem. Soc.* **1992**, *114*, 11007−11009.

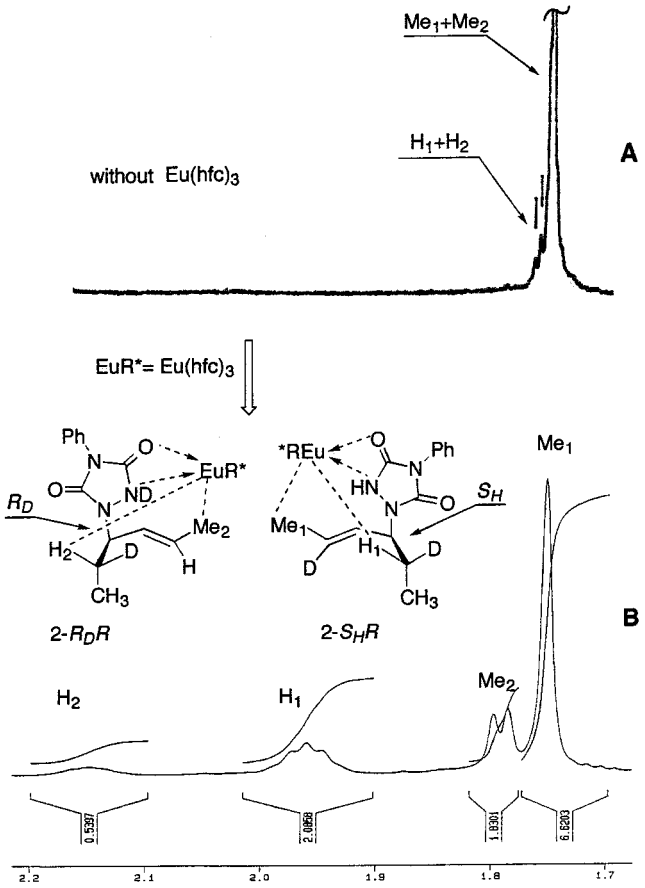
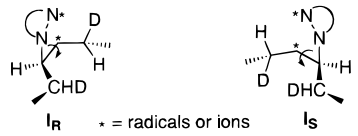


Figure 1. ^{1}H NMR spectra of the ene adducts **2-*R*$_D$,*R*** and **2-S$_H$,*R*** in the absence (A) and in the presence (B) of Eu(hfc)$_3$ chiral shift reagent.



In a recent theoretical study, a biradical intermediate was proposed.[14] However, in that mechanism, the following restrictions were postulated: (a) the biradical (key intermediate) equilibrates rapidly with the AI intermediate; (b) it retains the stereochemical orientation of the AI; and (c) rotation in the biradical intermediate is not allowed. If all of these conditions apply, then these results also may be rationalized by a "biradical-like aziridinium imide intermediate".

In conclusion, our results provide strong evidence for the stereospecific suprafacial mechanism of TAD−ene reactions with simple alkenes.

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Supporting Information Available: ^{1}H NMR analysis of protio and deuterio ene adducts in the absence and in the presence of Eu(hfc)$_3$ chiral shift reagent (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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