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Hydroxy-Directed Diastereoselective Ene Reaction of Triazolinediones with Chiral Allylic Alcohols

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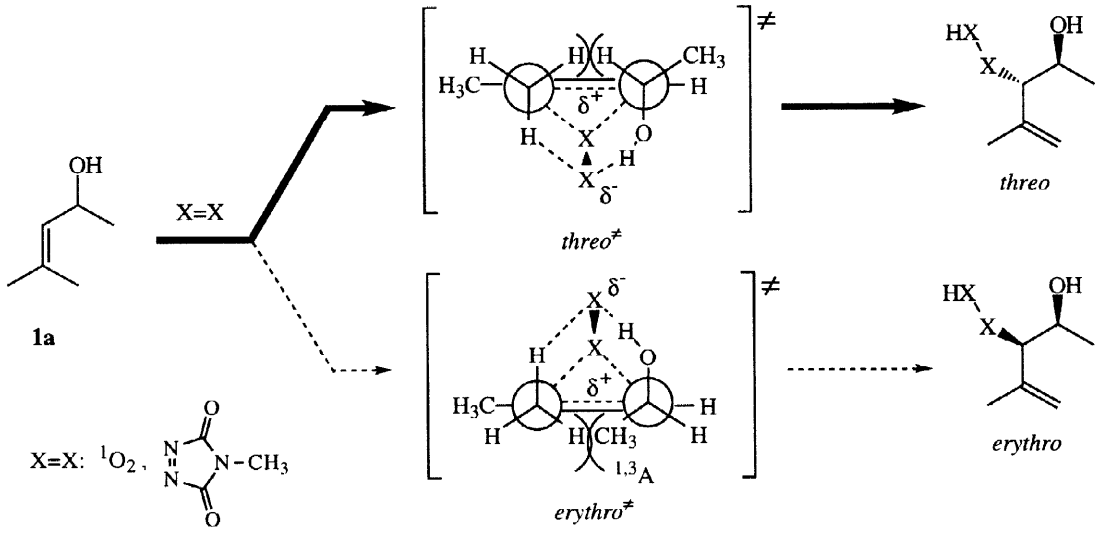
Abstract: The ene reaction of the *N*-methyltriazolidinone (MTAD) with the allylic alcohols **1a-e** afforded the corresponding urazoles **2** in high *threo* diastereoselectivity (Scheme 1). These results are mechanistically explained in terms of an attractive hydrogen-bonding interaction between the enophile and the allylic hydroxy functionality in the *threo* transition state, which is favored on account of minimal 1,3-allylic strain. The *threo* diastereoselectivity is completely lost when the allylic hydroxy-functionality is masked. The results parallel the hydroxy-directing effect previously established in the singlet-oxygen ene reaction.

The reaction of triazolinediones (TADs) with electron-rich olefins that possess allylic hydrogen atoms usually leads to ene-type products.[1] This process has been described for a wide variety of acyclic and cyclic olefins[2] and constitutes a useful method to introduce nitrogen functionality[3] or to shift a double bond.[4]



Scheme 1

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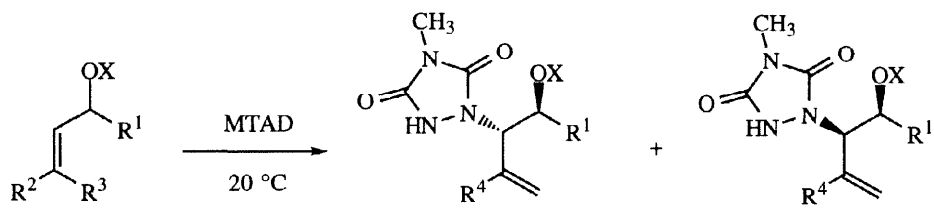
Also from the mechanistic point of view, triazolinedione ene reactions have received considerable attention in view of their similarity to singlet oxygen ($^1O_2$).[5] Nevertheless, in spite of this remarkable similarity, it has been shown that the mechanistic equivalence between TADs and singlet oxygen is not as general as previously implicated.[6]

In recent years, the diastereoselectivity of the singlet-oxygen ene reaction with chiral acyclic alkenes, conformationally fixed by 1,3-allylic strain,[7] has been thoroughly investigated. In these studies it was shown that chiral allylic alcohols, e.g. mesitylol **1a** (Scheme 1), react highly *threo*-diastereoselectively with singlet oxygen.[8] This "hydroxy-directing effect" was rationalized in terms of an attractive hydrogen-bonding interaction between the enophile singlet oxygen and the allylic hydroxy functionality in the highly polarized *threo* transition state that is favored over the analogous *erythro* one due to 1,3-allylic strain.[9] In view of the similar reactivity and mechanistic kinship of TADs and singlet oxygen, it was of interest to test wether the hydroxy-directing effect established for singlet oxygen with chiral allylic alcohols also operates in TAD ene reaction. For this purpose, the MTAD ene reactions with the chiral acyclic alkenes **1a-g** were examined and we present herein our preliminary results.

Table 1: Diastereoselectivities in the Ene Reaction of Chiral Allylic Alkenes **1** with MTAD



(Eq. 1)

1 *threo*-**2** *erythro*-**2**

entry		R^1	R^2	R^3	R^4	X	solvent	diastereoselectivity [a] *threo*-**2**	*erythro*-**2**
1	**1a**	Me	Me	Me	Me	H	cyclohexane	80	20
2	**1a**	Me	Me	Me	Me	H	CCl_4	80	20
3	**1a**	Me	Me	Me	Me	H	CH_2Cl_2	85	15
4	**1a**	Me	Me	Me	Me	H	$CHCl_3$	87	13
5	**1a**	Me	Me	Me	Me	H	CH_3CN	76	24
6	**1a**	Me	Me	Me	Me	H	CD_3OD	65	35
7	(*E*)-**1b**	Me	Me	H	H	H	CCl_4	38	62
8	(*Z*)-**1b**	Me	H	Me	H	H	CCl_4	80	20
9	(*Z*)-**1c**	Et	H	Me	H	H	CCl_4	80	20
10	(*Z*)-**1d**	^{i}Pr	H	Me	H	H	CCl_4	85	15
11	(*Z*)-**1e**	^{t}Bu	H	Me	H	H	CCl_4	87	13
12	**1f**	Me	Me	Me	Me	Me	CH_2Cl_2	59	41
13	**1g**	Me	Me	Me	Me	Ac	CH_2Cl_2	54	46

[a] Determined by NMR analysis directly on the crude reaction mixture, error ± 5% of the stated values.

The alkenes **1a-g** were allowed to react with MTAD (1.0 equiv) at 20 °C in a variety of solvents to afford the urazoles **2** (Table 1). The chiral allylic alcohols **1a**, (*Z*)-**1b** and **1c-e**, which bear a substituent (R^3 = Me) *cis* to the hydroxy group, react in high *threo* diastereoselectivity (entries 2 and 8-11). The degree of *threo* diastereoselectivity increases with the size of the R^1 alkyl substituent located at the stereogenic hydroxy-bearing carbon center in the order ^{t}Bu > ^{i}Pr > Et ≅ Me for (*Z*)-**1b-e**. In the case of the allylic alcohol (*E*)-**1b**, which lacks a *cis* substituent, the extent of stereoselection is rather low (entry 7) on account of nominal 1,3-allylic strain.

The solvent dependence of this ene reaction was examined for the allylic alcohol **1a**. In the polar solvents acetonitrile and methanol, significantly lower *threo* diastereoselectivities were observed compared to the non-polar solvents cyclohexane, dichloromethane, trichloromethane and tetrachloromethane (entries 5 and 6 *versus* 1-4). Furthermore, the corresponding methyl ether (**1f**) and acetate (**1g**) derivatives of the allylic alcohol **1a** react essentially unselectively (entries 12-13 *versus* 1).

The relative configuration of the major urazole **2a** was determined to be *threo* by means of X-Ray structural analysis of its doubly benzoylated derivative.[10] The configuration of the remaining urazoles **2b-g** were inferred from **2a** by NMR-spectral comparison.

The diastereoselectivities of the present MTAD ene reactions with the chiral allylic alcohols **1** (Table 1) may be rationalized analogously to the corresponding singlet-oxygen ene reaction. Due account is taken for the intervention of a highly polarized *threo* transition state (Scheme 1; X=X is MTAD), in which hydrogen bonding from the allylic hydroxy functionality with the negatively charged MTAD moiety stabilizes the activated complex. The corresponding *erythro* transition state is disfavored in energy due to 1,3-allylic strain. That the allylic hydroxy functionality is directly involved in this ene process is demonstrated by the solvent dependence on the diastereoselectivity in the MTAD ene reaction of allylic alcohol **1a**. In methanol and acetonitrile, solvents that may interact with the OH group by hydrogen bonding, a significant drop in the diastereoselectivity is observed. Furthermore, derivatization of the OH group also leads to decreased diastereoselectivity, as is exemplified in the reactions of the methyl ether **1f** and the acetate **1g**, since stabilization by a hydrogen-bonding interaction can no longer occur.

The importance of the 1,3-allylic strain, which discriminates the different conformations of the stereogenic unit in the transition state, is clearly demonstrated by comparison of the MTAD ene reaction of the diastereomeric allylic alcohols (*Z*)-**1b** and (*E*)-**1b**. Whereas the stereoisomer (*Z*)-**1b** with a *cis* substituent (R^3 = Me) at the double bond reacts highly *threo*-diastereoselectively with MTAD, the selectivity has been lost for the (*E*)-**1b** case. This is due to the fact that no effective 1,3-allylic strain operates to discriminate the *threo* and *erythro* transition states in energy since a *cis* substituent (R^3 = Me) is absent at the double bond. The slight increase in the degree of *threo* diastereoselectivity, observed when bulkier R^1 substituents are located at the allylic position, i.e. ^{t}Bu > ^{i}Pr > Et ≅ Me, may be rationalized in terms of the higher 1,3-allylic strain with increasing size of the R^1 group.

In conclusion, like for singlet oxygen, also the MTAD ene reaction proceeds with chiral allylic alcohols highly *threo*-diastereoselectively. These results clearly demonstrate the participation of a hydroxy-directing effect in the transition state and substantiate the mechanistic equivalence between the TAD and singlet oxygen enophiles.

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