# Stereochemistry in the Reaction of 4-Methyl-1,2,4-triazoline-3,5-dione (MTAD) with *β,β*-Dimethyl-*p*-methoxystyrene. Are Open Biradicals the Reaction Intermediates?†

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The reaction of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) with *β,β*-dimethyl-*p*-methoxystyrene (**1**) in chloroform affords four adducts: the ene, two stereoisomeric [4 + 2]/ene diadducts, and a minor product that is probably the double Diels−Alder diadduct. In methanol, only one regioisomeric methoxy adduct is formed. The stereochemistry of the reaction was examined by specific labeling of the *anti* methyl group of **1** as $CD_3$. In chloroform, the ene adduct is formed with >97% *syn* selectivity, while the [4 + 2]/ene diadducts are formed with 20% loss of stereochemistry at the methyl groups. In methanol, the methoxy adducts are formed with almost complete loss of stereochemistry. A mechanism involving open biradicals is inconsistent with the experimental results. It is likely that the reaction proceeds through the formation of an aziridinium imide and an open zwitterionic intermediate. The aziridinium imide leads to the formation of the ene adduct. The open zwitterion, which has sufficient lifetime to rotate around the C−C bond, leads to the formation of a [4 + 2] cycloadduct, which reacts with a second molecule of MTAD in an ene-type mode to afford two stereoisomeric [4 + 2]/ene diadducts. In methanol, solvent captures the zwitterionic intermediate and forms the methoxy adduct. The relative distribution of the products in chloroform depends on the reaction temperature. Lower temperatures favor the ene reaction (entropically favorable), whereas at higher temperatures the [4 + 2]/ene diadducts become the major products.

## Introduction

Triazolinediones (RTADs)[1] react smoothly with olefins bearing allylic hydrogens in aprotic solvents to give ene adducts. However, in protic solvents such as methanol, RTAD-methoxy adducts are formed. With trisubstituted alkenes, the new C−N bond in the ene adduct is formed at the less substituted olefinic carbon[2] (Markovnikov selectivity). For trisubstituted alkenes also, when the reaction is carried out in polar protic solvents such as methanol, the solvent traps the intermediate regiospecifically, forming a methoxy adduct at the more substituted olefinic carbon. The methanol trapping reaction with di- and trisubstituted alkylalkenes is stereospecific. Only one diastereomeric methoxy adduct is formed.[3] As a result of stereoisotopic studies,[4,5] low-temperature NMR,[6,7] and theoretical calculations,[8] triazolinedione ene reactions were generally considered to proceed through the formation of an aziridinium imide (AI) as the intermediate.

However, on the basis of experimental results and theoretical calculations, Singleton recently proposed a reasonable mechanism according to which, apart from AIs, open biradicals are the key intermediates.[9] Open zwitterionic intermediates have been proposed to participate only in the reactions with electron-rich alkenes[10] and dienes.[11,12]

Recently, we reported that the addition of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) to *β,β*-dimethylstyrene[13] in $CH_2Cl_2$ or in methanol affords exclusively the ene product with >97% *syn* selectivity. It was proposed that, in the transition state of the aziridinium imide formation, there is a stabilizing interaction between the negatively charged nitrogen of MTAD and the phenyl ring that directs the ene reaction to take place from the *syn* allylic methyl group. For a further study of this

† Taken in part from the undergraduate research thesis of M. Hatzimarinaki.

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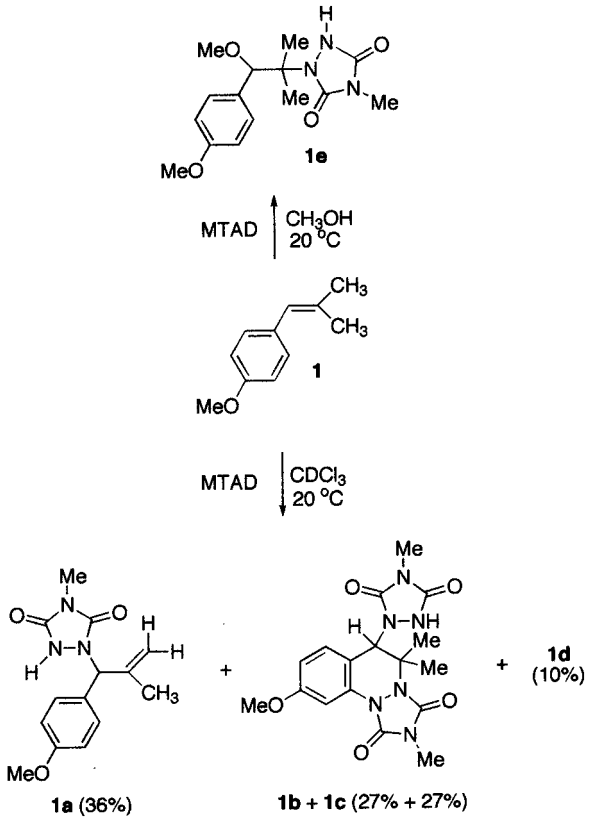
**Scheme 1. Products in the Reaction of 1 with MTAD in Chloroform and Methanol at 20 °C**

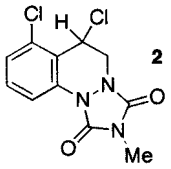



exceptional stereoselectivity, we studied the stereochemistry in the reaction of MTAD with β,β-dimethyl-*p*-methoxystyrene (**1**).

## Results

The reaction of **1** with MTAD proceeds instantly in $CDCl_3$ at 20 °C (Scheme 1) and affords a mixture of products that were fractionated by flash column chromatography (hexane/ethyl acetate = 1/2). The yields of the products were measured from the $^1$H NMR spectrum of the crude reaction mixture. The first eluted product was the ene adduct **1a** (36%), followed by two slightly separable products **1b** (27%) and **1c** (27%), with very similar $^1$H and $^{13}$C NMR spectra. Both had the pattern of a 1,2,4-trisubstituted benzene and were characterized as stereoisomers of the diadduct shown in Scheme 1. HRMS in combination with 2D-NMR heteronuclear ($^1$H−$^{13}$C HMQC) correlation experiments allowed us to assign the signals of all protons and carbons and to establish the possible structures of these compounds. Formation of diadducts with the structure of **1b** or **1c** is well-known in the literature, in the reaction of PTAD with styrene[14] and some substituted styrenes.[15] Finally, the minor adduct **1d** (10%) of the crude reaction mixture is unstable under the chromatographic conditions, and despite several efforts we were unable to isolate and characterize it properly.[16] Therefore, we will not refer to it in the accompanying discussion section of this manuscript. In methanol, however, only the methoxy trapping adduct **1e** is formed, in which the solvent has captured regiospecifically the secondary benzylic carbon. The stereochemistry was determined by NOE experiments. Upon irradiation of the methoxy group at 3.81 ppm, a positive enhancement was measured on the benzylic hydrogen. None of the diastereotopic geminal methyls showed enhancement.

The formation of two stereoisomeric diadducts, **1b** or **1c**, is quite surprising and unprecedented. They could be either conformational isomers due to the hindered rotation of the urazole ring at the benzylic position or diastereomers due to slow pyramidal inversion of the two adjacent nitrogens in the six-membered ring. Considering, however, a planar urazole ring, there should not be two such isomers. We attempted several times to obtain crystals of **1b** or **1c** suitable for X-ray analysis, without success. However, the crystal structure of the adduct **2**[15b] derived from the reaction of 2,5-dichlorostyrene with MTAD indicates that neither the six-membered ring nor the five-membered urazole ring are planar.




Consistent with the crystallographic data are our theoretical calculations. The geometry optimization of the [4 + 2]/ene diadduct gives the two structures **1b** and **1c** (Figure 1) as local minima, in which the urazole ring is not completely planar. The calculations were performed with the GAUSSIAN 94 program package.[17] The theoretical treatment of the structures involved Density Functional Theory (DFT) with the three-parameter hybrid functional of Becke and the use of Lee−Yang−Parr correlation functional (B3LYP).[18] The level of the calcula-

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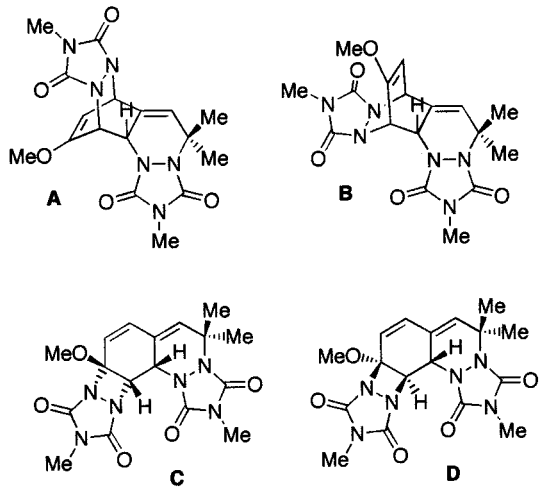
(16) The minor product **1d** has the following characteristic absorptions in the $^1$H NMR spectrum of the crude reaction mixture: 6.17 (br. s, 1H), 5.83 (d, $J$ = 2.0 Hz, 1H), 5.25 (dd, $J_1$ = 6.8 Hz, $J_2$ = 2.0 Hz, 1H), 5.23 (d, $J$ = 6.8 Hz, 1H), 4.05 (br. s, 1H), 3.65 (s, 3H); the *N*-methyl absorption(s) are buried in the region of 3−3.3 ppm, 1.70 (s, 3H), 1.34 (s, 3H). Decoupling experiments indicated that there is a correlation between these six absorptions. We propose that product **1d** is a single diastereomer and one of the diadducts **A** or **B** (double Diels−Alder) and **C** or **D** (Diels−Alder/[2 + 2]). More likely it is one of **A** or **B**. Similar double Diels−Alder diadducts are well-known in the reaction of styrenes with triazolinediones.[1]



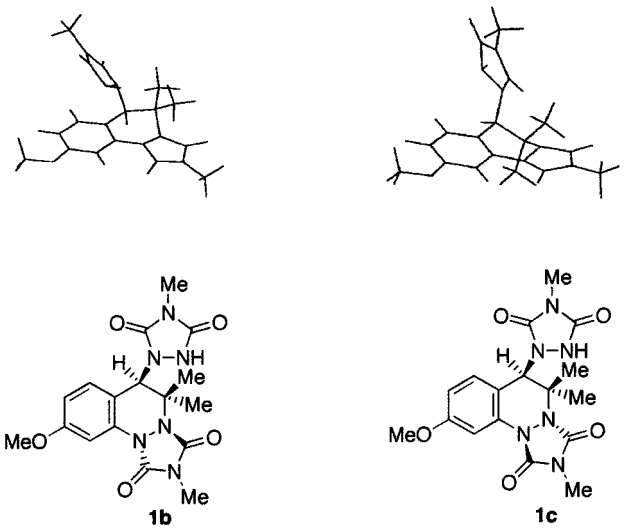



**Figure 1.** Calculated structures of **1b** and **1c**.

tions used herein was B3LYP/6-31G*. Many different starting conformations were used, but after the optimizations we found the structures **1b** and **1c** as local minima. According to the calculations, the structure **1c** is *more* stable compared to **1b** by 4.0 kcal/mol. For **1b**, the N next to the phenyl ring is almost $sp^2$-hybridized (dihedral angle 161°). The adjacent N atom is $sp^3$-hybridized to a significant extent (dihedral angle 136°). Similarly, for **1c**, the dihedral angles of the two adjacent nitrogens in the six-membered ring are 164° and 140°, respectively. On heating a mixture of **1b** and **1c** in refluxing $CDCl_3$ one of the two stereoisomers, probably **1b**, which is the less stable, is converted slowly to the more stable (**1c**). After 24 h, only **1c** appears in the $^1$H NMR spectrum, without formation of other byproducts.[19] On the other hand, under the same conditions (heating at 80 °C for 12 h) the pure [4 + 2]/ene diadduct isolated from the column (**1c**) did not transform to **1b**. It is reasonable that **1b**, which was calculated to be less stable than **1c**, transforms quantitatively to **1c** since their free energy difference is very high (4 kcal/mol). We postulate that the diadducts **1b** and **1c** are diastereomeric as a result of the high energy barrier for the pyramidal inversion of the adjacent nitrogens in the six-membered ring. In the literature there are several examples of slow pyramidal inversion of nitrogens when they are connected to another heteroatom[20] with lone pair(s) of electrons, such as oxygen, nitrogen, or halide. Even in cases when between two adjacent nitrogens one is connected to an acyl substituent, the slow pyramidal inversion still exists.[21] In the present case, during the conversion of **1b** to **1c**, the two nitrogens in the six-membered ring must undergo pyramidal inversion simultaneously. The two nitrogens have electron pairs in a *trans* arrangement. In the transition state of the interconversion the urazole ring becomes coplanar to the phenyl ring. Thus, electronic repulsions occur between the electron pairs, which are now parallel. Furthermore, significant steric strain develops between the geminal methyls and the substituents on the benzylic position (urazole and H), since they adopt eclipsing conformations to each other.

**Scheme 2**

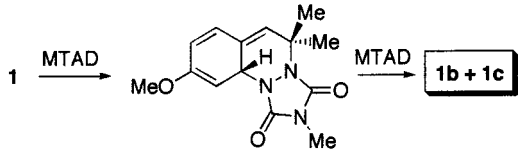



**Table 1. Relative % Distribution of the Adducts at Different Temperatures**

| temp (°C) | 1a | 1b | 1c | 1d |
|---|---|---|---|---|
| −30 | 77 | 10 | 7 | 6 |
| 5 | 39 | 27 | 21 | 13 |
| 20 | 36 | 27 | 27 | 10 |
| 45 | 33 | 29 | 29 | 9 |

It is reasonable to assume that the diadducts **1b** and **1c** have as a common intermediate, the monoadduct resulting from Diels−Alder cycloaddition of MTAD to **1** (Scheme 2). This highly reactive [4 + 2] monoadduct can be observed only at low conversions of **1** and immediately after the addition of MTAD (see Supporting Information). We were able to identify in the $^1$H NMR spectrum of the reaction mixture at less than 10% conversion of **1**, characteristic absorptions at 6.19 (1H ?, possibly a doublet buried under the absorption of the olefinic hydrogen of **1**), 5.87 (br. s, 1H), 5.83 (d, $J$ = 8.9 Hz, 1H), 5.43 (d, $J$ = 3.8 Hz, 1H), 5.31 (br. s, 1H), 3.64 (s, 3H), 1.70 (s, 3H) and 1.52 ppm (s, 3H). However, during the accumulation of the decoupling experiments the signals disappeared. At such very low conversions (~10%), the relative ratio of the ene adduct versus the [4 + 2]/ene diadducts is 56/44, whereas after complete reaction of **1** with MTAD, the ratio becomes 40/60. This is reasonable because the initially formed [4 + 2] monoadduct (which is present in the reaction mixture) reacts with a second molecule of MTAD in an ene-type mode to give **1b** and **1c**.

The relative distribution of the reaction adducts in chloroform depends significantly on the reaction temperature (Table 1). At −30 °C, the ene adduct is formed in 77% relative yield, while by increasing the reaction temperature, the amounts of the adducts **1b** and **1c** increase substantially.

To study the stereochemistry of the electrophilic addition and shed some light to reaction mechanism, the *trans* methyl group with respect to the phenyl ring of **1** was selectively labeled as $CD_3$ via sequential reduc-

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(19) The formation of two [4 + 2]/ene stereoisomers such as **1b** and **1c** appears generally in the reaction of MTAD with styrene derivatives that possess an electron-donating group at the para position, such as *trans*-anethole, *p*-methoxystyrene, or *p*-methylstyrene. Details of these studies as well as the kinetics of the interconversion between these stereoisomers will be reported elsewhere.

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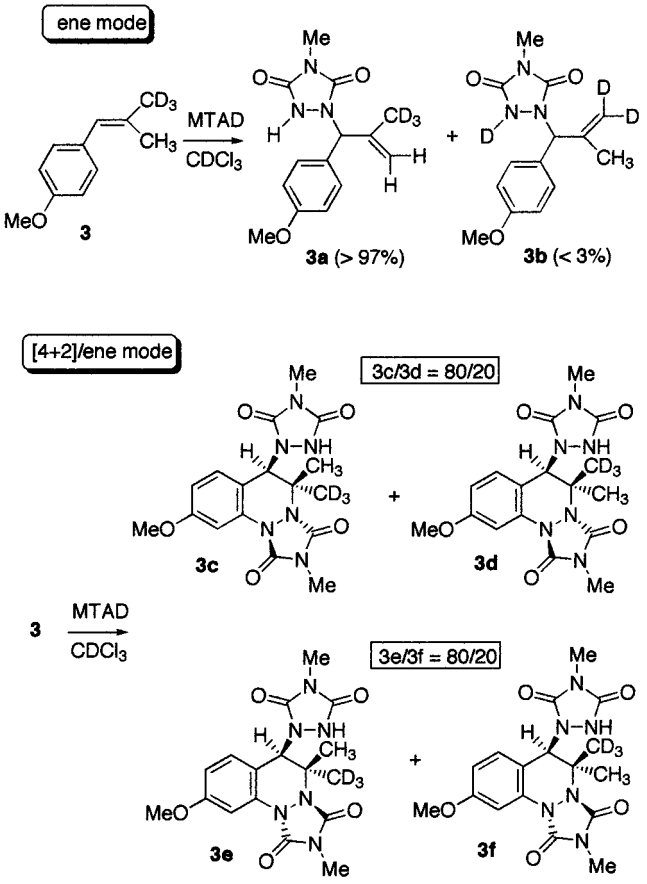
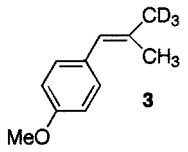
**Scheme 3. Isolated Products in the Reaction of 3 with MTAD in Chloroform**[a]




[a] Yields for the ene mode pathway correspond to the relative ratio of **3a** and **3b**.

tion[22,23] of (*E*)-2-methyl-3-(*p*-methoxyphenyl)prop-2-enoic acid, which was prepared by a modified Horner−Wittig reaction.[24] The geometrical purity of the labeled alkene **3** was 96%.




The reaction of **3** with MTAD in $CDCl_3$ at 20 °C afforded a mixture of adducts, which were fractionated by flash column chromatography. The isolated products (Scheme 3) were again the ene and the two stereoisomeric [4 + 2]/ene diadducts. The ene adduct (**3a**) was formed with >97% hydrogen abstraction from the methyl group that is *syn* to phenyl ring (H-abstraction in the present case), as has been found in the reaction of MTAD with β,β-dimethylstyrene.[13]

The first eluted diastereomeric [4 + 2]/ene diadduct exhibits two methyl group resonances at 1.92 and 1.31 ppm corresponding to adducts **3c** and **3d** in a ratio 80/20, respectively. Similarly, the more polar diadduct exhibits two methyl resonances at 1.94 and 1.31 ppm

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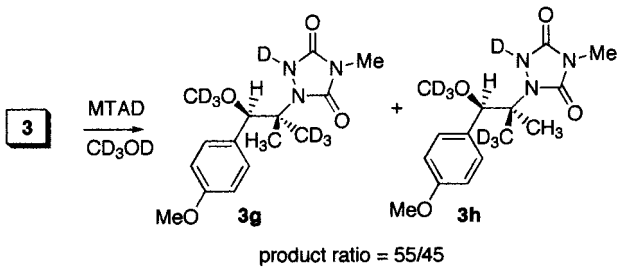
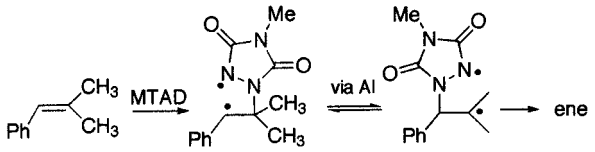
**Scheme 4. Reaction of 3 with MTAD in Methanol**




**Scheme 5. Mechanism Involving Biradicals in the Reaction of β,β-dimethylstyrene with MTAD**




corresponding to adducts **3e** and **3f** again in an 80/20 ratio.[25] It is reasonable to assume that the major components in both ratios are the adducts **3c** and **3e**, which are expected to be the only products if the initial [4 + 2] cycloaddition was suprafacial, according to the Woodward−Hofmann rules. All product ratios were corrected for 100% geometric purity of **3**.

When the reaction was run in methanol-$d_4$ (Scheme 4) where a single regioisomeric methoxy-trapping adduct is formed, two almost equivalent methyl resonances appear at 1.50 and 1.31 ppm, respectively. The product was purified by flash column chromatography. In the $^1$H NMR spectrum of the purified adduct (taken in $CDCl_3$) two methyl resonances appear at 1.46 and 1.44 ppm, corresponding to the diastereomeric adducts **3g** and **3h** in 55/45 ratio. It is notable that the tertiary proton on the methoxy functionality has two slightly separable resonances at 4.39 ppm differing by 0.4 Hz, attributable to the diastereomeric adducts **3g** and **3h**.

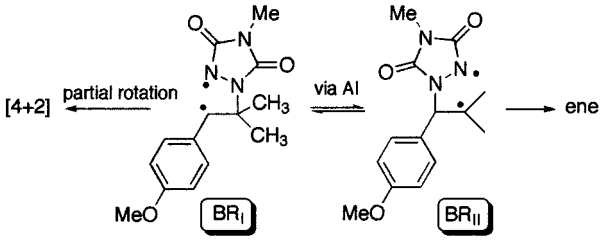
## Discussion

Recently, Singleton and Hang[9] proposed that for the ene reactions of triazolinediones with alkenes open biradicals, in which the barrier to rotation around the C−N bond is higher than the barrier to afford the ene product, are the key intermediates. More specifically, to explain the significant inverse β-secondary isotope effect of $k_H/k_D = 0.955$ per D atom, in the ene reaction of MTAD with β,β-dimethylstyrene, the mechanism shown in Scheme 5 was proposed, in contrast to the aziridinium imide mechanism proposed earlier.[13]

Considering a mechanism involving open biradicals as intermediates in the reaction of **3** with MTAD, it's difficult to rationalize the stereochemistry of the pathways leading to the ene and the [4 + 2]/ene products.

(25) Since both diastereomeric [4 + 2]/ene diadducts exhibit a methyl group resonance at 1.31 ppm, and we were unable to isolate by column chromatography the more polar diadduct in pure form, but rather as a mixture with the less polar diadduct, the reaction of **1** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) was performed in $CDCl_3$ at 20 °C. The two [4 + 2]/ene diadducts, which were formed in approximately 2/1 ratio, exhibit different absorptions for all four diastereomeric methyls. The major [4 + 2]/ene diadduct has two methyl absorptions at 1.94 and 1.35 ppm, while for the minor diadduct the methyl groups resonate at 1.99 and 1.41 ppm, respectively. In the reaction of **3** with PTAD, each diadduct exhibits two methyl absoprtions in approximately 80/20 ratio as found in the reaction of **3** with MTAD.

**Scheme 6. Mechanism in the Reaction of 3 with MTAD Involving Biradicals as Intermediates**




Let's assume biradical $\mathbf{BR_I}$ (Scheme 6) as a common intermediate for the reaction pathways. The loss of stereochemistry of the [4 + 2]/ene diadducts indicates that partial rotation around the C−C bond must occur in $\mathbf{BR_I}$ before forming the [4 + 2] monoadduct. However, if rearrangement of the partially rotated $\mathbf{BR_I}$ occurs to the biradical $\mathbf{BR_{II}}$ that leads to the ene product, both geminal methyl groups would be reactive. This is in contrast to the >97% *syn* methyl selectivity for the ene pathway found in **3**.

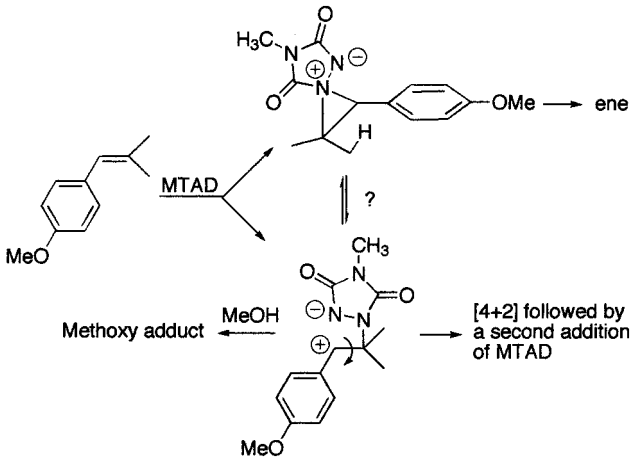
We propose that in chloroform two intermediates are partitioning, the aziridinium imide and an open zwitterion, while in methanol the open zwitterion prevails. The stereochemistry of the products in the reaction of **3** with MTAD can be explained on the basis of these two intermediates, as follows:

**(a) Ene Pathway.** The high preference for *syn* ene addition observed for **3** (>97%) is identical to that reported in the addition of MTAD to *β*,*β*-dimethylstyrene.[13] This exceptional specificity had been rationalized in terms of the favorable formation of the aziridinium imide intermediate in the more substituted side of the alkene, where the negatively polarized nitrogen interacts with the phenyl ring. We propose that the same reason is responsible for the high *syn* ene preference in **3**. It is remarkable however that, although reactions of RTADs with trisubstituted alkenes follow the Markovnikov rule[2] and the secondary *p*-methoxybenzylic carbocation is far more stable than the tertiary alkyl, the ene pathway is still favorable and even the major one when the reaction takes place at temperatures below 0 °C. The driving force of AI formation is the strong interaction of the MTAD to the electron-rich aryl ring.

**(b) [4 + 2]/ene Pathway.** Concerning the pathway of the formation of the [4 + 2]/ene diadducts, the reaction is not stereospecific. If the initial [4 + 2] reaction was concerted (suprafacial mode), only the diastereomers **3c** and **3e** should be formed. We propose that an open zwitterionic intermediate is formed that has enough lifetime for partial rotation and then closes to form the [4 + 2] adducts in a non-suprafacial manner. Subsequently, the monoadduct undergoes a second ene-type addition with MTAD, which leads to the [4 + 2]/ene diadducts. The loss of stereochemistry in the diadducts derives from the initial step during the formation of the [4 + 2] adduct. Since the Diels−Alder monoadduct is the common precursor for the diastereomeric [4 + 2]/ene diadducts, identical stereochemical outcome is expected for both diastereomers, as occurs indeed.

**(c) Methanol Trapping Pathway.** Methanol traps the intermediate zwitterion, which has aldready rotated, and results in a 55/45 ratio of the two diastereomeric methoxy adducts **3g** and **3h**. The higher loss of stereospecificity in the trapping reaction compared to the [4 + 2] pathway in chloroform can be attributed to the higher dielectric constant of methanol, which increases the lifetime of the zwitterion and eventually its free rotation around the C−C or the C−N bonds.

**Scheme 7. Proposed Mechanism in the Reaction of MTAD with 1**




The temperature dependence of the products distribution in the reaction of **1** with MTAD in chloroform (Table 1) is also consonant with the participation of the two intermediates. The aziridinium imide leading to the ene product is more structurally organized and is expected to be entropically favored at lower temperatures. On the other hand, the open zwitterion leading to the [4 + 2] adduct is less organized as a result of the free rotation around the C−C or the C−N bonds and thus more favorable at higher temperatures.

According to these results we propose that MTAD adds to *β*,*β*-dimethyl-*p*-methoxystyrene and forms two intermediates, an aziridinium imide and an open zwitterion (Scheme 7). Their relative distribution depends on the reaction temperatute. Low temperatures favor formation of the AI (entropically favorable), while at higher temperatures the open zwitterion prevails. The possibility that initially only the aziridinium imide is formed and subsequently it rearranges to an open zwitterion cannot be excluded. The aziridinium imide in which MTAD is placed *syn* to the aryl ring leads to the ene products. The open zwitterion has enough lifetime to rotate before forming the cycloadducts or being trapped by methanol. The two pathways are competitive in chloroform, but in the more polar methanol the zwitterionic pathway prevails.

In conclusion, the stereochemistry of the products in the addition of MTAD to *β*,*β*-dimethyl-*p*-methoxystyrene-d3 (**3**) indicates that the reaction proceeds through the formation of two intermediates: (i) an open zwitterion, and (ii) an aziridinium imide where the MTAD is directed toward the more substituted side of the alkene. At least for styrene-type substrates such as **1**, a mechanism involving biradicals as proposed recently[9] is less likely to occur.

## Experimental Section

Nuclear magnetic resonance spectra were obtained on a 500 MHz instrument. Isomeric purities were determined by $^1$H NMR and by GC on an HP-5 capillary column. All spectra reported herein were taken in $CDCl_3$.

**1-(*p*-Methoxyphenyl)-2-methylprop-1-ene (1).** The compound was prepared in 65% yield by Wittig coupling of

isopropyltriphenylphosphorane with *p*-methoxybenzaldehyde. Purification was accomplished by vacuum distillation. $^1$H NMR: 7.17 (d, $J$ = 8.7 Hz, 2H), 6.88 (d, $J$ = 8.7 Hz, 2H), 6.23 (s, 1H), 3.83 (s, 3H), 1.91 (s, 3H), 1.87 (s, 3H). $^{13}$C NMR: 157.62, 133.90, 131.38, 129.77, 124.53, 113.48, 55.21, 27.74, 19.28.

**Reaction of 1 with MTAD in Chloroform.** The reaction mixture consists of four adducts. On attempted flash column purification, only the ene and two diastereomeric [4 + 2]/ene diadducts, which are the major products (~90%), were isolated. **$^1$H NMR of the ene adduct 1a:** 7.60 (br. s, 1H, N−H exchangeable with $D_2O$), 7.25 (d, $J$ = 8.6 Hz, 2H), 6.90 (d, $J$ = 8.5 Hz, 2H), 5.67 (s, 1H), 5.17 (s, 1H), 4.93 (s, 1H), 3.84 (s, 3H), 3.06 (s, 3H), 1.75 (s, 3H). $^{13}$C NMR: 159.82, 154.69, 153.57, 141.33, 130.05, 126.92, 114.43, 114.25, 63.90, 55.28, 25.19, 21.15. **$^1$H NMR of the less polar [4 + 2]/ene diadduct:** 8.22 (br. s, 1H, N−H exchangeable with $D_2O$), 8.10 (d, $J$ = 1.7 Hz, 1H), 7.13 (d, $J$ = 8.5 Hz, 1H), 6.68 (dd, $J_1$ = 8.5 Hz, $J_2$ = 1.7 Hz, 1H), 5.04 (s, 1H), 3.85 (s, 3H), 3.15 (s, 3H), 3.05 (s, 3H), 1.92 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR: 161.13, 154.44, 151.83, 147.95, 133.90, 130.52, 111.71, 108.88, 100.37, 60.99, 60.45, 55.53, 25.31, 25.17, 24.11, 23.06. HR-MS (MALDI-FTMS): $(M + Na)^+$, calculated for $C_{17}H_{20}O_5N_6$ 411.1387; experimental 411.1397. **$^1$H NMR of the more polar [4 + 2]/ene diadduct:** 9.25 (br. s, 1H, N−H exchangeable with $D_2O$), 8.11 (d, $J$ = 1.8 Hz, 1H), 7.52 (d, $J$ = 8.6 Hz, 1H), 6.69 (dd, $J_1$ = 8.6 Hz, $J_2$ = 1.8 Hz, 1H), 5.57 (s, 1H), 3.87 (s, 3H), 3.19 (s, 3H), 3.05 (s, 3H), 1.94 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR: 161.63, 154.15, 151.46, 150.98, 148.07, 133.42, 132.28, 110.86, 109.85, 100.57, 78.93, 59.88, 55.49, 25.88, 25.12, 23.19, 22.84.

**Reaction of 1 with MTAD in Methanol.** Only one product was formed resulting from methanol addition to the intermediate(s). The crude adduct was purified by flash column chromatography using 1/1 hexane/ethyl acetate as eluent. $^1$H NMR: 8.70 (br. s, 1H), 7.18 (d, $J$ = 8.3 Hz, 2H), 6.87 (d, 2H, $J$ = 8.3 Hz), 4.51 (s, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 3.03 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H). A more than 10 times diluted sample in $CDCl_3$ exhibits very different absorptions for the diastereotopic methyls and the tertiary benzylic hydrogen, which can be attributed to the different degree of inter- or intramolecular hydrogen bonding. $^1$H NMR spectrum of the diluted sample: 7.65 (s, 1H), 7.17 (d, $J$ = 8.3 Hz, 2H), 6.91 (d, 2H, $J$ = 8.3 Hz), 4.36 (s, 1H), 3.84 (s, 3H), 3.23 (s, 3H), 3.06 (s, 3H), 1.47 (s, 3H), 1.45 (s, 3H). $^{13}$C NMR of the condensed sample: 159.57, 154.38, 152.98, 129.38, 128.38, 113.51, 87.51, 64.43, 56.99, 55.15, 24.78, 22.94, 21.40. HR-MS (MALDI-FTMS): $(M + Na)^+$, calculated for $C_{15}H_{21}O_4N_3$ 330.1424; experimental 330.1433.

**(*E*)-2-Methyl-3-(*p*-methoxyphenyl)prop-2-enoic Acid.** This compound was prepared according to a literature procedure.[24] In a two-necked dry flask were placed 4.85 g of NaH (60% in oil) and 50 mL of dry DME followed by the slow addition of diethyl phosphite (5.1 mL) at 0 °C. After 30 min, 3.5 mL of 2-bromopropionic acid was slowly added at 0 °C, and stirring was continued until hydrogen evolution ceased. Subsequently, 4.8 mL of *p*-methoxybenzaldehyde was syringed over a period of 5 min. The reaction mixture was stirred for 1 h at room temperature and then quenched with 5 mL of ethanol. The crude organic layer was poured into a beaker containing 500 mL of water. The aqueous layer was washed with ether, acidified and then extracted with ether. The geometrical purity of the isolated acid was >97% *E*. $^1$H NMR: 7.78 (s, 1H), 7.43 (d, $J$ = 8.5 Hz, 2H), 6.94 (d, $J$ = 8.5 Hz, 2H), 3.85 (s, 3H), 2.15 (s, 3H).

**(*E*)-Methyl 2-Methyl-3-(*p*-methoxyphenyl)prop-2-enoate.** The above crude acid was dissolved in 100 mL of methanol, and a catalytic amount of *p*-toluenesulfonic acid was added. After overnight refluxing it was neutralized with aqueous $NaHCO_3$ and then extracted with ether to produce 2.5 g of pure *E*-ester. $^1$H NMR: 7.64 (s, 1H), 7.38 (d, $J$ = 8.7 Hz, 2H), 6.92 (d, $J$ = 8.7 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 2.13 (s, 3H).

**(*E*)-2-Methyl-3-(*p*-methoxyphenyl)prop-2-en-1-ol-1,1-$d_2$.** The α,β-unsaturated ester (2.4 g) was reduced by reacting with a slurry of $LiAlD_4$ (0.38 g, 9 mmol) and $AlCl_3$ (0.40 g, 3 mmol) in 30 mL of dry ether. The allylic alcohol was isolated in 85% yield. $^1$H NMR: 7.25 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H), 6.45 (s, 1H), 3.81 (s, 3H), 1.91 (s, 3H), 1.59 (br. s, 1H).

**(*E*)-2-Methyl-3-(*p*-methoxyphenyl)prop-2-en-1-chloride-1,1-$d_2$.** The allylic alcohol was transformed to the corresponding chloride according to a literature procedure.[22] The alcohol (1.12 g) and 0.90 mL of 2,6-dimethylpyridine were placed in a dry flask under nitrogen. Subsequently, 0.29 g of anhydrous LiCl was added and 5 mL dry DMF, enough to dissolve the reactants, followed by 0.6 mL of $CH_3SO_2Cl$ at 0 °C. Stirring was continued for 12 h, and then 100 mL of water and 50 mL of ether were added. The ether layer was washed with a saturated solution of $Cu(NO_3)_2$ to remove the pyridine. The crude chloride was a mixture of $E/Z$ = 96/4. It was used directly in the next step without purification to avoid decomposition. $^1$H NMR: 7.24 (d, $J$ = 8.7 Hz, 2H), 6.87 (d, $J$ = 8.7 Hz, 2H), 6.53 (s, 1H), 3.82 (s, 3H), 1.99 (s, 3H).

**(*E*)-1-(*p*-Methoxyphenyl)-2-methylprop-1-ene-3,3,3-$d_3$ (3).** In a dry flask under inert atmosphere were placed 0.3 g of $LiAlD_4$ and 15 mL of dry THF.[23] The crude allylic chloride was added,and the reaction mixture was stirred for 1 day. It was then quenched with water, and the aqueous layer was extracted with ether. Purification was accomplished by flash column chromatography (petroleum ether as eluent). The alkene was a mixture, $E/Z$ = 96/4. $^1$H NMR of the *E*-isomer: 7.18 (d, $J$ = 8.7 Hz, 2H), 6.88 (d, $J$ = 8.7 Hz, 2H), 6.23 (s, 1H), 3.83 (s, 3H), 1.87 (s, 3H). MS, $m/z$ 165 ($M^+$, 100).

**Supporting Information Available:** $^1$H NMR spectra of compounds **1** and **3** and for the adducts in their reactions with MTAD. This material is available free of charge via the Internet at http://pubs.acs.org.

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