Dedication

I dedicate my thesis to my family.
Acknowledgements

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Abstract
Mechanistic Studies of the Sigmatropic Rearrangement of O-Allyl Nitronic Esters to γ,δ-Unsaturated Nitro Naphthalene Derivatives and Nitro Substituted Cyclohexene Derivatives

Alma Pipic
Peter A. Wade

The Claisen rearrangement of allyl vinyl ethers is a widely used synthetic reaction. It was found that O-allyl nitronic esters, readily obtained from tin(IV)-catalyzed Diels-Alder reactions using β-nitrostyrene as the diene component undergo thermal (20-90°C) [3,3]-sigmatropic rearrangement to γ,δ-unsaturated nitro compounds in a process very similar to the Claisen rearrangement. The O-allyl nitronic ester rearrangement provides stereocontrolled access to diastereomeric 1,2,3,4,4a,5,6,7-octahydro-5-nitronaphthalene derivatives and 3-nitro cyclohexene derivatives. Thermal isomerization of nitro compounds from cis- to trans-2-nitro-3-phenyl isomers was observed at higher temperature (100-150°C). The γ,δ-unsaturated nitro compounds are also readily obtained through traditional Diels-Alder reactions in which β-nitrostyrene functions as the dienophile. However, in the traditional Diels-Alder reactions the γ,δ-unsaturated nitro compounds are obtained as an inseparable mixture of diastereomers and regioisomers in the traditional Diels-Alder reactions. The difficulty in separating diastereoisomers of γ,δ-unsaturated nitro compounds is avoided by selectively rearranging nitronic esters to the corresponding nitro compounds. This is a newly discovered rearrangement process of nitronic esters, and it has been successfully applied to two systems. Diels-Alder cycloaddition followed by rearrangement is synthetically useful in preparation of pure γ,δ-unsaturated nitro compounds.
Chapter 1. Rearrangement of Nitronic Esters to Form

$\gamma,\delta$-Unsaturated Nitrodecalin Derivatives

1.1 Introduction

In 1928 Otto Diels and Kurt Alder discovered that butadiene reacts vigorously with maleic anhydride to give cis-1,2,5,6-tetrahydrophthalic anhydride (Scheme 1.1). They went on to expand this first observation into the diene synthesis. In 1950 Diels and Alder received a Nobel Prize for the discovery of the diene synthesis, today known as the Diels-Alder (DA) reaction. Diels-Alder cycloaddition is a powerful method for synthesis of substituted cyclohexenes.\(^1\)\(^2\)\(^3\)

Scheme 1.1 Diels-Alder reaction of 1,3-butadiene and maleic anhydride

\[
\begin{align*}
\text{Diene} & \quad + \quad \text{Dienophile} \quad \rightarrow \quad \text{Cycloadduct} \\
\text{CH}_2 & \quad \quad \quad \text{CH}_2
\end{align*}
\]

The DA reaction is a class of pericyclic reaction. It is typically a cycloaddition reaction that occurs between an electron rich diene (which can be either an open chain or cyclic conjugated 1,3-diene) and an electron poor dienophile which contains either a C, C-double bond or C, C-triple bond. The reaction is also classified as a \([4\pi + 2\pi]\) cycloaddition based on the electrons donated by the two components. In the DA reaction two $\pi$ bonds are broken and two sigma bonds are formed.\(^1\)\(^2\)\(^3\)
Alkenes -C=C-, alkynes -C≡C-, allenes C=C=C, and even benzyne can participate in the reaction as dienophiles. Simple alkenes are not typically reactive enough for the DA reaction. The presence of electron withdrawing groups is usually necessary to lower the energy of the \( \pi^* \) orbital of the alkene in order to make it a good dienophile. Common electron-withdrawing groups include CHO, COR, COOH, COOR, COCl, COAr, CN, NO\(_2\), SO\(_2\)R and halogens.\(^2\) Besides compounds that have carbon-carbon double bonds, Diels-Alder reactions occur on compounds having other multiple bonds to produce heterocyclic compounds, which include N≡C-, -N=C-, -N=N-, N=O, and -C=O. It has been suggested that O=O can also serve as a dienophile.\(^4\)

Table 1.1 Representative dienophiles\(^4\)

<table>
<thead>
<tr>
<th>Acyclic</th>
<th>Cyclic</th>
</tr>
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<tbody>
<tr>
<td>[(-\mathrm{CHO}]\</td>
<td>[(-\mathrm{COMe}] \</td>
</tr>
<tr>
<td>((\mathrm{NC})_2\equiv(\mathrm{CN})_2)</td>
<td>(\mathrm{MeO}_2\mathrm{CCH}=\mathrm{CHCO}_2\mathrm{Me})</td>
</tr>
<tr>
<td>(\mathrm{H}_2\mathrm{C}≡\mathrm{C}=\mathrm{CHMe})</td>
<td>(\mathrm{HC}≡\mathrm{CO}_2\mathrm{Me})</td>
</tr>
<tr>
<td>(\mathrm{Me}_2\mathrm{C}=\mathrm{S})</td>
<td>(\mathrm{Ph}−\mathrm{N}=\mathrm{O})</td>
</tr>
<tr>
<td>(\mathrm{O}=\mathrm{O})</td>
<td>(\mathrm{S}=\mathrm{S})</td>
</tr>
</tbody>
</table>

The dienes are typically electron rich molecules. Most simple dienes are satisfactory for the reaction. However the presence of electron donating groups such as alkyl or alkoxy
groups enhances the reactivity of simple dienes. Reactive compounds may be open-chain, inner-ring, outer-ring, cross-ring, or inner-outer ring dienes (Table 1.2).4

Table 1.2 Representative dienes

<table>
<thead>
<tr>
<th>Open chain</th>
<th>Outer ring</th>
<th>Inner-outer ring</th>
<th>Across ring</th>
<th>Inner ring</th>
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Aromatic compounds also can behave as dienes, although catalysis may be needed for reaction. Naphthalene will give DA adducts only under high pressure. Aromatic compounds with at least three linear benzene rings such as anthracene readily undergo the DA reaction (Scheme 1.2).5
Certain non-conjugated dienes such as norbornadiene also participate in a homo-
Diels-Alder reaction. Such compounds must have two double bonds in suitable
proximity, allowing the "diene" to undergo a cycloaddition reaction with an alkene.
Reactivity of non-conjugated dienes greatly depends on the distance between the two
double bonds. The closer the proximity of the double bonds the lower the energy of the
transition state for reaction. For example, bicyclo[2.2.2]octa-2,5-diene undergoes a
cycloaddition with tetracyanoethylene to form cycloadduct 1 (Scheme 1.3).6

For any diene to successfully react with a dienophile it must be in the s-cis
conformation. When the diene is in the s-trans conformation, the end p orbitals are too
far apart to overlap effectively with the p orbitals of the dienophile. Certain structural
features of the diene dictate conformations and hence reactivity. Small ring cyclic dienes
have a frozen s-cis conformation, and are more reactive than open-chain dienes that have to achieve an energetically unfavorable s-cis conformation by rotation. The s-trans conformation of butadiene is lower in energy than the s-cis conformation by 2.3 kcal/mol, so the s-trans conformation is more heavily populated (Scheme 1.4). The conformational energy difference is usually not enough to prevent a diene from adopting the s-cis conformation and undergoing DA reactions.¹

Scheme 1.4 s-Trans and s-cis conformations of 1,3-butadiene

Substituents on the diene affect its conformational populations, which affects how fast the diene undergoes the DA reaction. For example, Z,Z-2,4-hexadiene is very unreactive because the alkyl substituents disfavor the s-cis conformation, Figure 1.1.

Figure 1.1 s-Trans and s-cis Z,Z-2,4-hexadiene
Cyclopentadiene is extremely reactive because it is locked in a permanent \textit{s-cis} conformation. At room temperature cyclopentadiene dimerizes and forms dicyclopentadiene (Scheme 1.5) despite lacking an electron withdrawing group.

Scheme 1.5 Dimerization of pentadiene

Diene 2 and 3 are locked in a permanent \textit{s-trans} conformation and do not react in DA reactions (Fig 1.2).\textsuperscript{4}

Figure 1.2 Permanent \textit{s-trans} diene

The DA reaction often takes place between an unsymmetrical diene and unsymmetrical dienophile. In these cases two regioisomers are possible. A mixture of products often results. However, \textit{ortho} and \textit{para} products typically predominate over \textit{meta} product (Scheme 1.6).\textsuperscript{2}
The DA reaction is a syn cycloaddition with respect to both reactants. The diene and dienophile approach each other on parallel planes. The diene bonds to just one face of the dienophile and conversely the dienophile bonds to one face of the diene. A dienophile that has a \( \pi \) bond in its electron-withdrawing group will typically align with the group \textit{endo} to the diene in the transition state. The \( p \) orbital of the \( \pi \) bond in the electron-withdrawing group overlaps the \( p \) orbital of the central carbon atoms of the diene. This interaction is termed a “secondary orbital interaction”. The interaction stabilizes the transition state. The alternative transition state where the group is \textit{exo} is typically higher in energy, although in an \textit{exo} transition state there is less steric hindrance. The product of the reaction is predominantly \textit{endo} in bicyclic products and \textit{cis} in \textit{ortho}-monocyclic products because of the preferred \textit{endo} transition state (Scheme 1.7). Some reactions were found to produce a mixture of \textit{endo} and \textit{exo} products. \textsuperscript{1,2,7,8}
Although the endo configuration is predominant because of secondary orbital overlap, there are some cases where exo product predominates. With prolonged reaction time, some reversible cycloadditions result in exo as the major product because it is more thermodynamically stable. Berson and Swindler performed a study with furan and maleic anhydride, Scheme 1.8. The cycloaddition of the two results in a mixture of endo and exo cycloadducts. The authors showed that over time the product composition favors the exo adduct. The endo-addition is a rate-favored process, but the endo adduct is thermodynamically unstable compared to the exo adduct. By prolonging the reaction time, the endo adduct reverts back to furan and maleic anhydride, which recombine to give exo adduct. Over time the exo adduct accumulates. 9
Types of DA mechanisms

The mechanism of the DA reaction can be either concerted or stepwise. Most DA reactions are concerted, particularly thermal reactions and ones that involve apolar dienes and dienophiles, i.e. all electron pairs move at the same time. In order for a concerted reaction to take place, the transition state must have a geometry that allows overlap of the two end \( p \) orbitals of the diene with those of the dienophile.

The concerted mechanism can be synchronous or asynchronous. In the concerted synchronous mechanism the two new sigma bonds are formed simultaneously to the same extent and the transition state is symmetrical.\(^2,10\) The DA reaction between ethylene and 1,3-butadiene has been studied experimentally and theoretically and it is a prototype reaction for the concerted synchronous type. Houk et al studied the reaction of compound 4 (1,1,4,4-tetradequytrio-1,3-butadiene) with 5 (cis-) and 8 (trans-1,2-dideuteroethylene) at 185°C, under 1800 psi, for 36 hours to establish the stereospecificity of the reaction. Dideuteroethylene does not isomerize under these conditions. The cycloadducts 6 and 9 were then oxidized with m-chloroperbenzoic acid to form epoxides. NMR studies of
oxidized products 7a-b and 10 reveal that the stereochemistry of reactants is retained in the final cycloadduct, (Scheme 1.9). If the potential diradical intermediate 11 were formed, extensive scrambling of stereochemistry would occur. The range of rotational barriers of primary radicals around the single bond is 0-0.4 kcal/mol. Even if the barrier to cyclization is nearly negligible compared to the sigma bond rotation barrier, the reaction would only exhibit 20% of stereospecificity. Calculations by Salem predict that the diradical transition state is 2-4 kcal/mol higher than concerted transition state. The calculated activation energy for a concerted mechanism agrees with the activation energy obtained experimentally. Houk’s calculations predict that the activation energy for a stepwise reaction is at least 3.7 kcal/mol higher than the concerted mechanism. Similar results were reported having from 2-10 kcal/mol lower activation energy for concerted cycloadditions. Theoretical calculations show that the two newly formed sigma bonds are the same length at the transition state.
Scheme 1.9\textsuperscript{12} Study of the Diels-Alder reaction stereospecificity

In the transition state of the concerted asynchronous reaction one sigma bond is more developed than the other at the transition state, which is therefore unsymmetrical. A concerted asynchronous mechanism is common for substituted dienes and dienophiles that are unsymmetrical. Ab initio computational studies of butadiene and s-cis acrolein reveal the asynchronicity of the pathway for the DA cycloaddition. In the transition state, atom distances for the two new C-C sigma bonds are 2.353 Å and 2.088 Å angstrom, with a 0.27 Å difference. Conversely, in the reaction of 1,3-butadiene and ethylene, the atomic distances for the forming C-C bonds are both 2.22 Å, which is in agreement with a concerted synchronous mechanism.\textsuperscript{15}
Using secondary deuterium isotope effects, Thornton found important evidence that supports the concerted mechanism. A retro-DA reaction was studied for 9,10-dihydro-9,10-ethanoanthracene (12) and its bridge deuterated analogs CH$_2$CD$_2$ and CD$_2$CD$_2$ (Fig 1.3). For the retro reaction it is expected that if one bond breaks before the other, a secondary isotope effect would be present. Experimentation did not show a secondary isotope effect. Subsequently, the forward DA reaction was carried out and similar results were found.$^{16}$

![12](image)

**Figure 1.3** 9,10-dihydro-9,10-ethanoanthracene

Evidence supporting the two-step mechanism was provided by Newman. He conducted experiments using vinlylene carbonate and 2,3-benzofurans substituted with aryls at the 1 and 4 positions (Scheme 1.10). The reactions between vinlylene carbonate and 13 a-b readily proceed to form cycloadducts 14a and 14b, respectively. The reaction between 13c and vinlylene carbonate does not occur even under more vigorous conditions. The cycloadditon of 13c was also attempted with dienophiles maleic anhydride and N-phenylmaleimide, and the reaction still did not occur. Steric hindrance prevents the reaction of 13c from occurring. In order for the cycloaddition to occur, the mestyl groups must lie almost perpendicular to the plane of benzofuran. In this position, the dienophile is prevented from approaching the 1 and 4 positions of the furan ring. By
replacing one mesityl with a phenyl the dienophile still does not lie in the proper position. However the reaction with vinylene carbonate still takes place. The steric hindrance does not prevent bond formation with the carbon containing the phenyl group, but it prevents vinylene carbonate carbon from approaching the carbon bearing the mesityl group. The hypothetical intermediate 15 shows bond formation, and once one bond is formed, steric hindrance is much less effective in preventing the intramolecular reaction from occurring. It is concluded that this DA reaction occurs in separate steps for formation of the two bonds. The authors were unsure if a zwitterion might be present instead of a diradical.\textsuperscript{17}

Scheme 1.10 Proposed evidence for a two step Diels-Alder reaction mechanism

\[ 13 \quad \text{vinylene carbonate} \quad 14 \]

- a) \( R_1 = R = \text{Ph} \)
- b) \( R_1 = \text{Ph}, R = \text{mesityl} \)
- c) \( R_1, R = \text{mesityl} \)

15 hypothetical diradical intermediate
In 1965 Woodward and Hoffmann developed a theory, conservation of orbital symmetry that has aided understanding of the mechanism of the DA reaction. Conservation of orbital symmetry considers the symmetry of the molecular orbitals of the reactants and products in order to explain the reaction pathway. The theory states that the molecular orbitals of the reactants must interact constructively with each other and progress smoothly into the molecular orbitals of the product without changes in symmetry. Nowadays, the theory is applied to frontier molecular orbitals. There are three possible variants of the controlling interactions of the frontier orbitals. Favorable bonding interactions must be present in the transition state in order for the concerted cyclic addition to occur. The diene with contributions from four atomic $p$ orbitals has four molecular orbitals, two of which are filled with electrons (bonding orbitals) and two of which are vacant (antibonding molecular orbitals). A dienophile with two contributing atomic $p$ orbitals has two molecular orbitals, one of which is filled (bonding) and one vacant (antibonding molecular orbital). In the most common version of the reaction a diene HOMO contributes a pair of electrons to the dienophile LUMO. The highest energy electrons of the diene require the least amount of activation energy in order to be donated. These electrons are most weakly held and are located in the highest occupied molecular orbital (HOMO). The HOMO diene – LUMO dienophile interaction then determines the course of the reaction. The lowest unoccupied molecular orbital (LUMO) of the dienophile accepts electrons donated from the diene HOMO. If the electrons can flow smoothly from the diene HOMO to the dienophile LUMO, then a concerted reaction can take place. With the correct orbital symmetry the new bonds form constructively (Fig 1.4). 1, 2, 18, 19
Woodward and Hoffman considered the transition state for the reaction of ethylene with butadiene. Addition of ethylene to butadiene was treated as a 1,4 addition (Fig 1.5) Also considered was addition of ethylene to another molecule of ethylene in a 1,2 addition (Fig 1.6). The correlation diagram shows energy changes in the $\pi$ and $\sigma$ orbitals in a 1,4 addition. The four butadiene and two ethylene $\pi$ orbitals of the reactants with two $\pi$ and four $\sigma$ orbitals of the products are shown in Figure (1.5). S and A correspond to symmetric and asymmetric with respect to the plane of symmetry $\sigma_1$. The comparison by Hoffman explains the theory of the conservation of orbital symmetry. The 1,2 addition is unfavorable because the HOMO and LUMO of two ethylene molecules have different symmetries. For product cyclobutane to occur one of the molecular orbitals would have to change its symmetry. One of the antibonding orbitals of the cyclobutane correlates with bonding orbitals of the ethylene. In the case of 1,4 addition, bonding orbitals of one reactant are aligned with bonding orbitals of the other reactant. The antibonding orbitals also correlate.\(^{18}\)
Figure 1.5 Correlation diagram for [4+2] cycloaddition\textsuperscript{18}

Figure 1.6 Correlation diagram for [2+2] cycloaddition\textsuperscript{18}
The opposite orbital interactions occur between an acceptor diene and a donor dienophile in inverse electron demand Diels Alder (IEDDA) reactions. The highest interaction occurs between the electron poor diene LUMO and the electron rich dienophile HOMO. For example perchlorocyclopentadiene reacts well with cyclopentene, moderately with maleic anhydride, and not at all with tetracyanoethylene. The lack of reactivity with tetracyanoethylene shows that perchlorocyclopentadiene is an electrophile in DA cycloaddition.²

Another variant of Diels-Alder reaction is the hetero DA cycloaddition. Besides carbon atoms heteroatoms are also incorporated into a six membered ring. In an oxo-Diels Alder reaction an oxygen atom is incorporated into the six membered ring. In such a DA reaction, cycloaddition occurs between an aldehyde or a ketone 16 and the diene 17 to form a cyclic compound 18 with an oxygen atom incorporated into the ring. The carbonyl group is a dienophile in this case (Scheme 1.11).²⁰,²¹

Scheme 1.11 Diels-Alder reaction of ketone or aldehyde as dienophile

\[
\begin{array}{c}
\text{16} \\
\text{17} \\
\text{18}
\end{array}
\]

In the IED hetero DA reaction, an \(\alpha,\beta\)-unsaturated ketone or aldehyde 19 reacts with an electron rich alkene 20 to form a six membered cyclic compound 21 with an oxygen atom incorporated into the ring (Scheme 1.12). The reaction is controlled by the conjugated
ketone or aldehyde LUMO interacting with the alkene HOMO. Lewis acids are used to catalyze the IEDHDA reaction by coordinating with the carbonyl functionality and lowering the diene LUMO energy.\textsuperscript{20, 21}

Scheme 1.12 Diels-Alder Reaction of ketone as diene

![Diagram of Diels-Alder Reaction](image)

The azo-Diels Alder reaction is the most efficient way to incorporate a nitrogen atom into a six membered ring. For example, an imine \textsuperscript{22} and Danishefsky's diene \textsuperscript{23} are convenient reagents for synthesis of pyridones \textsuperscript{24} (Scheme 1.13).\textsuperscript{22, 23}

Scheme 1.13 Diels-Alder reaction of imine \textsuperscript{22} and Danishefsky's diene \textsuperscript{23}

![Diagram of Diels-Alder Reaction](image)

Phosphaalkenes \textsuperscript{25} (>C=P-) undergo DA reaction with diene \textsuperscript{26} to form six membered rings with a phosphorous atom incorporated \textsuperscript{27} (Scheme 1.14). The cycloaddition occurs at the C=P \(\pi\) bond because it is weaker relative to a C=C \(\pi\) bond.\textsuperscript{24}
Scheme 1.14 Diels-Alder reaction of diene 26 and dienophile 25 to incorporate a phosphorous atom into cycloadduct 27

Heterodienes known to undergo DA reaction include: -C=C-C=O, O=C-C=O, and N=C-C=N.4

Nitronic esters

The first nitronic esters were synthesized in the 1890s by Konowalow and Neff.25 Nitronic esters are not a very stable class of compounds, and for this reason the studies related to nitronic esters progressed slowly. The half lives of most nitronic esters at ambient temperature under neutral conditions range from minutes to weeks. The decomposition products typically consist of oximes and carbonyl containing compounds. In 1964 Kornblum and Brown monitored stability of acyclic nitronic esters to determine if there is any correlation of nitronic ester structure with stability. Nitronic esters substituted at the nitronic carbon with alkyl and aromatic substituents were explored in the study. The nitronic esters that were used in the study decomposed rapidly at ambient
temperature with decomposition rates variable from ester to ester. A faster decomposition rate was observed for nitronic esters that were stored in solution as opposed to pure crystalline solids. Decomposition was not observed in compounds that were stored at –78°C. It was also noted that the decomposition rate differed for the E and Z isomers of a given nitronic ester.\textsuperscript{26}

In 1998 Kang and Yin attempted to determine the correlation between the structure and stability of nitronic esters by performing a more extensive analysis. For example, Kang and Yin found that nitronic ester 28 (Fig 1.7) tends to be stable in crystalline form and at ambient temperatures.\textsuperscript{27}

![Nitronic ester 28](image)

**Figure 1.7 Structure of nitronic ester 28**

R=hydrocarbon

The authors pointed out that nitronic ester 28 has both an electron withdrawing group and an electron donating group attached to the nitronic carbon. They suggest that the electronic effect of nitronic carbon substituents is the main factor affecting the stability of the nitronic ester. There are two types of substituents: electron withdrawing and electron
donating, compared to the hydrogen atom. Thus, there can only be five possible nitronic ester structures in terms of substituent types (this excludes F, the unsubstituted nitronic ester), Fig 1.8.27

\[ \text{w=electron withdrawing group, D=electron donating group} \]

Figure 1.8 Types of nitronic ester structures

The nitronic ester 28 (Fig 1.7) belongs to the type C category with balanced donating and withdrawing substituents present on the nitronic carbon. This combination of substituents is proposed to lower the internal molecular energy. Types A and B will result in increased internal molecular energy because both substituents have the same electronic effect on the molecule. The electronic effect of hydrogen can be regarded as null and, therefore the stability of the molecule will depend largely on the other substituent. Types D and E are expected to be unstable because there is no balance of electronic effect on the nitronate group. Although not discussed by Kang and Yin, it is also likely that the small size of the hydrogen atom and relative openness of the nitronic carbon atom fosters ready attack on the nitronic carbon atom lowering the stability. At the time of the study, the majority (90%) of nitronic esters possessed type A, B, D, and E structures, and were all unstable compounds. Kang and Yin considered only 9 known nitronic esters having the C type structure. Out of the 9 only one has a moderate W group (carbonyl) balanced by a D group (alkyl), and that nitronic ester is most stable according
to them.\textsuperscript{27} In their study, Kang and Yin tried to come up with a model which can predict nitronic ester stability based on electronic effects of nitronic carbon substituents. The model may have worked for the limited number of nitronic esters that they examined at the time of the study. However it does not correctly predict stability for nitronic esters that were prepared by Wade and Le or those prepared by Denmark and coworkers, some of which are quite stable at ambient temperature. For example, the nitronic ester 29 in Fig 1.9 was synthesized 8 years ago and a recent NMR analysis shows that it is still quite pure although it is a type E.\textsuperscript{28} Kang and Yin attempted to correlate nitronic ester stability to structure, but their analysis is apparently incomplete: there must be additional factors involved. For instance, cyclic nitronic esters appear to be more stable than open chain nitronic esters.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{Structure of nitronic ester 29}
\end{figure}
Formation of nitronic esters via Diels-Alder reactions

Nitroalkenes can react as either dienes or as dienophiles, depending on the reaction conditions. Typically, in the presence of Lewis acid catalysts, nitroalkenes react as dienes with alkenes in an IEDDA reaction. Without catalyst, in the presence of dienes, nitroalkenes react as dienophiles. Because of modest electrophilicity of nitroalkenes, a Lewis acid is usually necessary to promote the cycloaddition of nitroalkenes acting as dienes and simple alkenes (or dienes) acting as dienophiles. There are only a few isolated cases reported where a nitroalkene underwent cycloaddition as the diene in the absence of a Lewis acid. Wade and coworkers provided examples of nitronic esters synthesized without Lewis acid catalyst (Scheme 1.15).

Scheme 1.15 Thermal synthesis of nitronic esters 34a-b without Lewis acid catalyst

\[ \text{O}_2\text{N} + \text{30a-b} \rightarrow \text{31} \]

a) \( X = \text{SO}_2\text{Ph} \)

b) \( X = \text{COPh} \)

\[ \text{45-55 °C} \]

\[ \text{Solvent} \]

\[ \text{32a-b} + \text{33a-b} + \text{34a-b} + \text{35} \]
The reactions of 30a and 30b were done in benzene/dichloromethane and bicyclic adducts were obtained. Also, nitronic esters 34a and 34b were formed, respectively. In the case of 30b an additional adduct 35 was obtained. When the reactions were done in a more polar solvent (actonitrile/dichloromethane), more nitronic ester was formed at the expense of bridge bicyclic adducts. In the case of nitroalkene 30b, bicyclic adducts 32b, 33b, nitronic ester 34b and enol ether 35 were formed, each in about 20% yield. Thus, 30b acted competitively as both a nitroalkene heterodiene and enone heterodiene. These DA reactions are thought to occur via concerted polar pathways. Increased formation of nitronic ester in the more polar solvent clearly shows that nitronic ester formation follows a polar pathway either non-synchronous concerted or stepwise via a zwitterion. Nitronic ester 37 was formed in the same way using a simple alkene (Scheme 1.16).29

Scheme 1.16 Thermal synthesis of nitronic ester 37 without Lewis acid catalyst

```
\begin{center}
\begin{tikzpicture}
\node (n1) [shape=circle,draw=black,fill=white] at (0,0) {36};
\node (n2) [shape=circle,draw=black,fill=white] at (1.5,0) {30 a};
\node (n3) [shape=circle,draw=black,fill=white] at (3,0) {37};
\draw [-] (n1) -- (n2);
\draw [-] (n2) -- (n3);
\node at (0.75,0) {$\text{45-55 }^\circ\text{C}$};
\node at (1.75,0) {$\text{Solvent}$};
\end{tikzpicture}
\end{center}
```

Denmark and coworkers first showed that in the absence of a Lewis acid catalyst, an intramolecular [4+2] DA reaction of compound 38 can occur where the nitroalkene functions as the diene to form cycloadduct 39 (Scheme 1.17). Product was formed under two different types of conditions: at 177°C for 60 min without Lewis acid catalyst, and at -76°C for 15 minutes with Lewis acid catalyst. These experiments show the rate
accelerating effect of Lewis acids in nitronic ester formation, and that the reaction is thermodynamically favorable.\textsuperscript{30}

Scheme 1.17 Intramolecular [4+2] cycloaddition reaction

![Scheme 1.17 Intramolecular [4+2] cycloaddition reaction](image)

1. SnCl₄, toluene, -76°C, 15 min 91%
2. Cymene, 177°C, 60 min 92%

Solvent dependence of the reaction rate and exo/endo selectivity was explored by Denmark in a study of the DA reaction of nitrocyclohexene and cyclohexene. Reaction of 40 and 41 was carried out in the presence of a Lewis acid in toluene, dichloromethane, or chlorobenzene at various temperatures (Scheme 1.18). The reaction produced two diastereomers, the major product 42 (trans) resulting from an exo approach of the olefin to the nitroalkene, and the minor diastereomer 43 (cis) from an endo approach. The carbocation rearrangement product 44 was also observed in these reactions, which suggests that the cyclization is not a concerted process. A zwitterion was postulated as an intermediate that either collapsed to form the six-membered cyclic nitronic ester or underwent a Wagner-Meerwein shift prior to collapse and subsequently forming the five-membered cyclic nitronic ester. The reaction conditions were varied in an attempt to avoid the formation of rearranged product 44. However 44 formed in all cases in about
the same proportion (Table 1.3). The reaction rate was found to be much slower in toluene and chlorobenzene than in dichloromethane. For example, the reaction with cyclohexene in dichloromethane is complete in 5 hours at $-78^\circ$, while in toluene it takes 8 hours at ambient temperature and 12 hours in chlorobenzene at $-16^\circ$C. The experiment was also done with a 20-fold excess of cyclohexene, and was complete after 96 hours at ambient temperature.$^{31}$

Scheme 1.18 Tin(IV) chloride catalyzed synthesis of nitronic ester 42-44

![Reaction Scheme]

Table 1.3 Solvent effect on cycloaddition of 1-nitrohexene with cyclohexene

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp $[^\circ]$</th>
<th>Time [h]</th>
<th>Ratio of products $42/43/44$</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylene chloride</td>
<td>-78</td>
<td>5</td>
<td>81:05:14</td>
</tr>
<tr>
<td>methylene chloride</td>
<td>25</td>
<td>5</td>
<td>78:06:15</td>
</tr>
<tr>
<td>chlorobenzene</td>
<td>-16</td>
<td>12</td>
<td>75:13:12</td>
</tr>
<tr>
<td>toluene</td>
<td>25</td>
<td>8</td>
<td>71:14:15</td>
</tr>
<tr>
<td>cyclohexene</td>
<td>25</td>
<td>96</td>
<td>67:14:19</td>
</tr>
</tbody>
</table>
To compare the rate of reaction and *endo/exo* selectivity among different size cyclic alkenes, Denmark did a comparison study using cyclopentene, cycloheptene, and cyclohexene (Table 1.4). Cyclohexene reacted the slowest.

Table 1.4 Product ratios for cycloaddition of cyclic olefins with 1-nitrohexene in dichloromethane

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Temp [°]</th>
<th>Time [h]</th>
<th>42/43/44</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>5</td>
<td>-60</td>
<td>1.5</td>
<td>88:07:05</td>
</tr>
<tr>
<td>b</td>
<td>6</td>
<td>-60</td>
<td>7</td>
<td>71:13:16</td>
</tr>
<tr>
<td>c</td>
<td>7</td>
<td>-60</td>
<td>0.5</td>
<td>40:40:20</td>
</tr>
</tbody>
</table>

The main conclusions of the study are the following. Based on the product ratios, the *exo* diastereomer is the major product under all conditions. In chlorobenzene, toluene, and excess cyclohexene, twice as much *endo* product forms compared to the reaction in dichloromethane. The proportion of rearrangement product 44 is about the same under all conditions for reaction with cyclohexene. However, the proportions varied with ring size: 5<6<7.31

The lack of solvent dependence for the proportion of 44 suggests that there is little charge development in the transition state of the reactions leading to 44. Denmark suggests two possibilities for the formation of 44, (Scheme 1.19). The first possibility is the formation of a common zwitterion 45, which collapses via two different pathways. Pathway a leads to diastereomeric products 42 and 43, and pathway b leads to intermediate 46 through a Wagner-Meerwein shift, which collapses to rearrangement product 44. In this case the rate-determining step is followed by a partitioning in a product determining step. The second possibility involves two competing mechanisms, in which one is a concerted cycloaddition that leads to products 42 and 43, and the other is a zwitterionic
pathway that leads to product 44. In this case the rate and product determining steps are the same. There was not enough experimental data for Denmark to distinguish between the two possibilities.\textsuperscript{31}

Scheme 1.19 Proposed reaction pathways of cycloaddition of 40 and 41a
The amount of rearrangement product 44 increased with increasing ring size of the cycloalkene. Large rings have more flexibility and the rate of 1, 2 hydride shift is faster in terms of optimal orbital overlap. If the mechanism followed the competing reaction pathway, then the amount of rearrangement product 44 would be greater for faster reactions, but this was not the case. The formation of endo product suggests a pericyclic transition state. The increased formation of endo product 42 with increasing ring size is explained by increasing ring flexibility. As flexibility of the ring increases, the methylene groups fold away in the endo transition state, which minimizes non-bonding interactions. 31

Denmark and coworkers further investigated the cycloaddition mechanism using nitro alkenes that undergo an intramolecular [4+2] cycloaddition, Scheme 1.20. As in the previous cases, the rearrangement product formed. The reaction was done in toluene and dichloromethane to determine the effect of solvent polarity on product ratios. It was found that in dichloromethane the reaction pathway is 1.8 times more likely to undergo path a. In toluene it is 7.3 times more likely to undergo path a. These results are consistent with a zwitterion intermediate. Dichloromethane is more polar than toluene, (dipole moments are 1.60 D and 0.36 D, respectively). In dichloromethane the ease of charge development facilitates the 1,2 hydride shift. In toluene, charge separation is not so readily supported, so the zwitterion intermediate is more likely to collapse to product trans-48. 30
Subjecting 48 (trans isomer) to the reaction conditions did not result in rearrangement to 44. Denmark offered this observation as support that the five membered nitronic ester is a primary product of the reaction. However, the cis isomer of 48 was not examined. In the original reaction of (E,E)-47 Denmark reported that trans and cis isomers of 48 were produced in a 98:2 ratio. Subjecting the trans isomer 48 to the reaction conditions only rules out its intermediacy in forming the rearranged product. Rearrangement of the cis isomer 48 was not attempted, which still leaves the possibility that the rearrangement product arises from equilibration with the cis-48 isomer.
In light of our observations concerning interconversion of nitronic esters in the presence of tin chloride, we postulate a third alternative; it is possible that cycloaddition producing trans 48 and cis 48 nitronic esters is concerted. Formation of a zwitterion might then occur subsequent to cycloaddition. Equilibration of cis 48 with rearranged nitronic ester 44 might then occur through the zwitterion formed subsequent to the original cycloaddition.

The amount of rearrangement product is also dependent on the nature of the nitroalkene and dienophile, particularly its degree of substitution and configuration. Alkene substitution and configuration affect formation of the rearrangement product. (E,E)-47 has a trans alkene configuration and it can form a rearrangement product, whereas (E,Z)-49 has the cis alkene configuration, and does not produce a rearrangement product. The author explained these results with the transition state geometry and the interactions of groups that take place in the zwitterion intermediate. In compound (E,E)-47 the exo folding of the side chain places the methyl in the vicinity of the SnCl₄-nitronate complex, which prevents closure through path a. In (E,Z)-49 the same methyl is exo oriented, providing an easier approach of the nitronate oxygen to the carbocation and forming only compound 50 (Fig 1.10).
In Demark's studies there were other examples of compounds that did not form the rearrangement product. Denmark postulated that compounds which can develop more stable zwitterions should lead to a rearrangement product in larger proportion whereas those leading to potentially less stable zwitterions should give less rearrangement product. Denmark examined the less substituted nitroalkene (E,E)-51 and found that it cyclizes to six membered nitronic ester 52 only; no rearranged product formed (Scheme 1.21). An intermediate analogous to i derived from (E,E)-51, where the nitronate carbon is atom monosubstituted instead of disubstituted, did not produce the rearrangement product. The author's explanation is that a monosubstituted nitronate carbon leads to a less stable zwitterion intermediate.
Scheme 1.21 Intramolecular cycloaddition of nitronic ester \((E,E)-51\)

Denmark also explored the effect of dienophile geometry on the cycloaddition. The \(E\)-olefin 53 resulted in rearrangement product 55 only, whereas the \(Z\)-olefin 56 reacted to form the expected cycloadduct 57, and no rearrangement product 58 (Scheme 1.22). The author did not offer any rationalization for these results.  

Scheme 1.22 Effect of dienophile geometry on Diels-Alder reaction products
Cycloadditions of trisubstituted dienophiles 59 and 61 were also examined by Denmark (Scheme 1.23). The cycloaddition for both compounds proceeded to the six membered nitronate 60 and 62, respectively, and no rearrangement product. The author's rationale is that the intermediate $\text{iii}$ is thermodynamically favorable over intermediate $\text{iv}$, which results in the formation of a six membebered cycloadduct only.\(^{30}\)

Scheme 1.23 Proposed Diels-Alder reaction pathway to 6-membered nitronic esters
Denmark’s rationale for formation of compounds 60 and 62 is supported by Snyder. According to Snyder the stability of a carbocation on a ring depends on the ring size. The cyclohexyl carbocation 63a is less stable than carbocation 63b, but cyclopentyl carbocation 64a is more stable than 64b (Scheme 1.24).32

Nitroalkenes readily participate as dienophiles in uncatalyzed DA cycloaddition to form nitro substituted cycloadducts owing to the strong electron-attracting power of the nitro group. Complexation of the nitro group with a Lewis acid leads to a species that can participate in cycloaddition reactions as a heterodiene. Sn(IV)chloride activated intermolecular [4+2] cycloaddition reaction between nitroalkenes and olefins produces cyclic nitronates, (nitronic esters). The catalyzed reaction mechanism follows an IEDDA pathway. The complexed nitroalkene behaves as an electron poor diene, and the olefin is the electron rich dienophile. SnCl₄ or a closely related species is required as catalyst for
these reactions because the nitroalkene is not a very good IEDDA diene component. The nitro alkene - tin(IV)chloride complex appears to typically have a 1:1 stoichiometry (Fig 1.11). The tin atom is bonded to one of the oxygen atoms and only weakly associated with the other oxygen atom, and is described as primarily monodentate. The bond formation between tin and one of the oxygen atoms localizes a double bond between nitrogen and the second oxygen atom, and in addition, an inductive effect increases the positive charge on the nitrogen atom. Alternatively, it can be said that tin(IV)chloride accelerates IEDDA reactions because it lowers the diene LUMO, which decreases the energy gap between the diene LUMO and dienophile HOMO. Whether concerted or stepwise, this should accelerate reaction.  

![Figure 1.11 Tin(IV)chloride and nitro group complex](image)

Because the cycloaddition follows the general IEDDA mechanism, it is expected that electron donating substituents would decrease the cycloaddition reaction rate. Conversely, the strength of Sn-O complexation depends on the nature of the 4-substituent of substituted nitrostyrenes and should increase with electron donating groups. Based on the frontier molecular orbital theory, it can be assumed that electron withdrawing groups on the ring should accelerate the reaction rate. However, experimentation showed the opposite to be true. Several para substituted nitrostyrenes were compared to
unsubstituted β-nitrostyrene (Scheme 1.25). Nitroalkene 65b contains an electron donating methoxy group at the para position. Nitroalkenes 65c and 65d contain electron withdrawing substituents CF3 and NO2 at the para position. Nitroalkene 65b reacted 6 times faster with cyclopentene than 65a. Thus, an electron donating group increased the reaction rate. Nitroalkene 65a reacted 77 times faster than 65c with cyclopentene.

Nitroalkene 65d was so slow to react that it could not be used in competition experiments. Thus, electron withdrawing groups slowed the reaction rate. The results of this study lead to the conclusion that the strength of complexation of tin to oxygen outweighs the electronic effect of the substituents. The decelerating effect of methoxy is diminished by higher complexation of the diene to SnCl4. In the case of electron withdrawing substituents on the phenyl ring, the weak oxygen - tin complexation outweighs the accelerating effect of the electron withdrawing group, which results in an overall decelerated reaction rate.33

Scheme 1.25 Substituent effect on tin(IV) catalyzed nitronic ester synthesis

\[
\begin{array}{ccc}
\text{HNO}_2 & \text{SnCl}_4 & \text{O}^+\text{N}^+\text{O}^- \\
\text{R} & \text{65} & \text{66} & \text{67} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Time (h)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5</td>
<td>0.8</td>
<td>93</td>
</tr>
<tr>
<td>4-CH3OC6H4</td>
<td>0.5</td>
<td>96</td>
</tr>
<tr>
<td>4-CF3C6H4</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>NO2C6H4</td>
<td>7.0</td>
<td>38 (d recovered)</td>
</tr>
</tbody>
</table>
**[3,3]-sigmatropic rearrangements**

The [3,3]-sigmatropic rearrangement is a concerted process that goes through a cyclic transition state. There are many types of [3,3]-sigmatropic rearrangements, and they are a powerful and reliable method for stereoselective synthesis of carbon-carbon and carbon-heteroatom bonds. The driving force for these rearrangements is typically the lower energy of the rearrangement product.\(^{34}\)

For example the Cope rearrangement is the thermal isomerization of a 1,5-diene 68 to give a regioisomeric 1,5-diene 69 that is more stable (Scheme 1.26) if more highly substituted. A new sigma bond is formed between carbon atoms 3 and 3' and a sigma bond is broken between carbon atoms 1 and 1'.\(^{35}\)

Scheme 1.26 Cope rearrangement

In the Oxy-Cope rearrangement, dienol 70 rearranges to enol 71 or enolate 72, which then tautomerizes to the carbonyl compound 73. Once the carbonyl group is formed, it will not rearrange back to the diene because tautomerization would have to reverse and this is energetically unfavorable. The Oxy-Cope rearrangement can proceed
through either an enol or enolate intermediate. In the first case only heat is required (Scheme 1.27).^{36}

Scheme 1.27 Oxy-Cope rearrangement

The enolate variation is generally faster than reaction directly through the enol and it can therefore be conducted at ambient temperature. The initial deprotonation of the alcohol is followed by rearrangement to the enolate intermediate 72 (Scheme 1.28).

Scheme 1.28 Oxy-Cope rearrangement mechanism

Another example of a [3,3]-sigmatropic rearrangement is the Claisen rearrangement. It is mechanistically similar to the Cope rearrangement, also proceeding through a concerted pericyclic mechanism (Scheme 1.29). In an aliphatic Claisen
rearrangement, an allyl vinyl ether 74 is converted to a \( \gamma, \delta \)-unsaturated carbonyl compound 75.

Scheme 1.29 Claisen rearrangement of allyl vinyl ether

\[
\begin{array}{c}
\text{74} \\
\end{array} \xrightarrow{\Delta} \begin{array}{c}
\text{75}
\end{array}
\]

The reaction preferably goes through a chair transition state (Scheme 1.30). There are two possible chair conformations, A and B, for the transition state. The predominant transition state results from the lack of 1,3-diaxial interaction of substituents, allowing the lowest energy (Eq 1.16). In transition state A the 1,3-diaxial relationship of Y and R increases the energy. Transition state B is preferred because one of the groups is now equatorial, which is lower in energy. Transition state B typically leads to an \( E \) alkene.\(^{37} \)

Scheme 1.30 Claisen rearrangement transition states
Faulkner and Petersen performed a series of rearrangements on substituted allyl vinyl ethers 76a-c and all showed high levels of stereoselectivity (Scheme 1.31). In all 3 examples the resulting unsaturated aldehydes 77a-c had preferred $E$ stereochemistry around the double bond.\(^{38}\)

Scheme 1.31 Stereoselectivity of Claisen rearrangement of allyl vinyl ether

\[
\begin{align*}
\text{76} & \quad \text{77 } E & \quad \text{77 } Z \\
a) R^1 = \text{Me}, R^2 = \text{Et} & \quad 90 & \quad 10 \\
b) R^1 = \text{Me}, R^2 = \text{iPr} & \quad 93 & \quad 7 \\
c) R^1 = \text{Et}, R^2 = \text{Et} & \quad 90 & \quad 10 \\
\end{align*}
\]

For this type of substituted allyl vinyl ether, Perrin and Faulkner proposed that the reaction goes through a chair transition state. The bulkiness of the $R^2$ group dictates the preference for the transition state lacking an axial substituent (Scheme 1.32). The transition state that has the $R^2$ group in an equatorial position is lower in energy and leads to alkene 77-$E$ as the final product. The less predominant transition state has the $R^2$ group in an axial position and this leads to alkene 77-$Z$. A bulkier $R^2$ group results in a larger percentage of the $E$ isomer.\(^{39}\)
Tetrahydropyrans, like cyclohexanes, are most stable in a chair conformation. Substituted tetrahydropyrans are structurally analogous to the transition state involved in Claisen rearrangements. Substituted tetrahydropyrans are therefore used as model systems to determine which chair conformation is more likely based on the $A$ values of the substituents. Eliel and coworkers studied energies and conformations of substituted tetrahydropyrans. Their results support the proposed chair conformation in the transition state of Claisen rearrangements that leads to predominant $E$ alkene product. For example, in 2-methyltetrahydropyran 78a, the methyl group in an equatorial position is 1.4 kcal/mol more stable than when it is in an axial position 78b (Scheme 1.33).
Scheme 1.33 Substituent effect on teterhydropyran conformations

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} & \quad \text{H}_3\text{C} \\
78\text{a} & \quad \leftrightarrow & \quad 78\text{b} \\
-\Delta G^\circ & = 1.44 \text{kcal/mol} & \quad -\Delta G^\circ & = 2.86 \text{kcal/mol}
\end{align*}
\]

In an aromatic Claisen rearrangement an allyl phenyl ether 79 rearranges to an unsaturated carbonyl intermediate 80, which rearomatizes to an ortho-substituted phenol 81 (Scheme 1.34). \cite{41}

Scheme 1.34 Aromatic Claisen rearrangement

\[
\begin{align*}
\text{79} & \quad \xrightarrow{\Delta} \quad \text{80} \\
\text{79} & \quad \xrightarrow{\text{80}} \quad \text{81}
\end{align*}
\]
Scheme 1.35 Thermal rearrangement of O-allyl nitronic esters 34a-b

![Scheme 1.35](image)

34a-b → 32a-b

a) X = SO_2Ph
b) X = COPh

The first reported example of a [3,3]-sigmatropic rearrangement was observed by Murray and Wade.\textsuperscript{29} The two nitronic esters 34a and 34b were found to give γ, δ-unsaturated nitro compounds 32a and 32b, Scheme 1.35. Both examples are O-allyl nitronic esters that have nitronate carbon substituted with an electron-withdrawing group.

**Chemistry of nitro compounds**

In organic synthesis nitro compounds are widely used as precursors to other classes of compounds such as: carbonyl compounds, amines, nitrile oxides, nitriles, oximes, hydroxylamines, and imines.\textsuperscript{42}

The Nef reaction is one of the most important transformations of primary and secondary nitro compounds to aldehydes and ketones. Typically, the acid catalyzed Nef reaction is carried out in aqueous solution and requires a strong acid. Under this method some compounds fail to react and/or side products form. Kunitake devised an alternate method that employs a mild acid such as silica gel impregnated with sodium methoxide (Scheme 1.36).\textsuperscript{43} Kornblum and Wade developed another method in which secondary
nitro compounds are converted to ketones by the combined agency of sodium nitrite and $n$-propyl nitrite.$^{44}$

Scheme 1.36 The Nef reaction of nitrocyclohexane

\[
\begin{align*}
\text{NO}_2 & \quad \text{SiO}_2 \quad \text{CH}_3\text{ONa} \quad \text{O} \\
\text{cyclohexane} & \quad \rightarrow \\
\text{99 %} & 
\end{align*}
\]

Oxidative and reductive methods can also be used to convert nitro compounds to carbonyl compounds. The reduction of nitro compounds gives amines. For example, the standard way of preparing amino sugars involves reduction of nitro sugars with Raney Ni and H$_2$ (Scheme 1.37)$^{45}$

Scheme 1.37 Reduction of a nitro sugar with Raney nickel

\[
\begin{align*}
\text{H}_2, \text{Raney Ni} & \quad \text{1atm, 25°C, 4h} \\
\text{OMe} & \quad \text{O} \\
\text{OH} & \quad \text{NO}_2 \\
\text{OMe} & \quad \text{NH}_2
\end{align*}
\]

Primary nitro compounds have been extensively used as precursors to nitrile oxides, which are reactive 1,3-dipolar compounds that react with alkenes or alkynes to form isoxazolines. Isoxazolines have been used as precursors for synthesis of complex natural products. The Mukaiyama-Hoshino method is the most widely used method for preparation of nitrile oxides (Scheme 1.38)$^{46}$
Nitro compounds are rarely used as precursors for nitriles. Scheme 1.39 shows one example of the conversion of a nitro compound to nitrile.\textsuperscript{47}
1.2 Results and Discussion

Synthesis of nitronic esters from IEDDA reaction of 1-(1-methylvinyl)cyclohexene

with trans-β-nitrostyrene and subsequent rearrangement

The diastereomeric nitronic esters 84 and 85 were prepared from compound 82 trans-β-nitrostyrene and 83 1-(1-methylvinyl)cyclohexene by the general method developed by Denmark and coworkers (Scheme 1.40).

Scheme 1.40 Tin(IV) chloride catalyzed synthesis of nitronic esters 84 and 85

The ratio of nitronic esters depended on the reaction work-up procedure. Quenching the catalyst at or below –70° resulted in a 40:60 ratio of 84 and 85 upon immediate isolation. If the reaction mixture is warmed up to ambient temperature prior to quenching of the catalyst, an 80:20 ratio of 84 and 85 is obtained. Also present under these conditions is a trace amount (<5%) of nitro compound 86.

Since 85 rearranges at ambient temperature, the initial mixture was not immediately chromatographed. The initial crude product was combined with ethanol and allowed to stand at ambient temperature for 24 hours. During the 24 hours 85 completely
rearranged to nitro compound 86, and 84 remained unchanged, Scheme 1.41. Since nitronic esters and their corresponding nitro isomers have different polarities, the mixture components are now easily separated. The crude mixture is chromatographed affording 84 and 86 in yields of 32% and 45%, respectively.

Scheme 1.41 Thermal rearrangement of nitronic ester 85 to nitro compound 86

After purification, the diastereomer 84 cleanly rearranged to nitro compound 87 in 87% yield upon warming at 90-95°C in dry DMF for 2 hours Scheme 1.42.

Scheme 1.42 Thermal rearrangement of nitronic ester 84 to nitro compound 87

Warming nitro compound 87 for 6 hours at 150-155°C in dry DMF afforded isomeric nitro compound 88 in 81% yield Scheme 1.43.
Scheme 1.43 Thermal isomerization of nitro compound 87 to nitro compound 88

Nitro compounds 86 and 88 are formal Diels-Alder adducts of 1-(1-methylvinyl)cyclohexene (83) and trans-β-nitrostyrene (82), in which phenyl and nitro groups are trans to each other. Nitro compound 87 is a formal Diels-Alder adduct of cis-β-nitrostyrene, in which phenyl and nitro are cis to each other.

The cycloaddition of 82 and 83 to form nitronic esters may well go through a nonsynchronous concerted mechanism (Scheme 1.44). Recent calculations are in agreement with such a mechanism. The stereochemistry of the starting materials is preserved in the product. However, there is a possibility that the reaction goes through a tin coordinated zwitterion intermediate 89 as proposed by Denmark et al for other nitroalkene cycloadditions leading to nitronic esters.
Scheme 1.44 Proposed Tin(IV)chloride catalyzed Diels-Alder reaction mechanism for synthesis of nitronic esters

The uncatalyzed Diels-Alder cycloaddition of 82 and 83 was performed for comparison to the tin(IV)-catalyzed reaction (Scheme 1.45). The two reactants were heated at 160°C without solvent for 7 hours. The reaction resulted in a 60% yield of a mixture consisting of 86, 88, and regioisomers 90 a-b in a 45:45:10 ratio, respectively. The stereochemistry of the regioisomers was not assigned because of the small amount produced, but there appeared to be a major and minor isomer present. These products could not be readily separated by chromatography on silica gel.
Scheme 1.45 Thermal Diels-Alder reaction of β-nitrostyrene and 1-(1-methylvinyl)cyclohexene

Under non-catalyzed conditions direct formation of the nitro compounds is possible and likely. However, the rearrangement of nitronic esters takes place at lower temperatures, and during a shorter period of time than the conditions employed. Possibly nitronic esters were formed wholly or in part and subsequently rearranged to afford 86 and 88. The regioisomers 90a-b must have been formed directly in the cycloaddition reaction.

In the initial catalyzed cycloaddition to produce 84 and 85, the ratio of nitronic esters varied with work up conditions. It was thought that secondary reaction of the
nitronic esters might be responsible for the variation. This was confirmed in a definitive experiment, (Scheme 1.46). A mixture of 84 and 85 (47:53 ratio) was subjected to SnCl₄ in toluene, at −55°C, for 40 minutes and the products isolated. The ratio of 84 to 85 was now (65:35) with a trace (less than 5%) of nitro compound 86. The results indicate that 85 isomerizes to 84 under these conditions, presumably via thermodynamic equilibration involving a Sn(IV) coordinated zwitterion 89. The amount of 86 relative to the combined amount of nitronic esters did not change, so therefore the change in nitronic esters is a result of isomerization and not selective rearrangement of 85 to nitro compound 86 under these conditions.

Scheme 1.46 Tin(IV)chloride isomerization reaction of nitronic esters 84 and 85
In a separate experiment, pure 84 was subjected to SnCl₄, at -47°C, in toluene for 2 hours, Scheme 1.47. This resulted in recovery of 84 containing trace amounts of nitronic ester 85 (~2 %) and nitro compound 86 (~2 %). The nitronic ester isomerization is postulated to occur through the tin-coordinated zwitterionic intermediate 89. It is noteworthy that the zwitterion should be stabilized by allylic resonance, and presumably this is why it forms so readily.

Analysis of the crude rearrangement product mixtures shows the absence of trans-β-nitrostryrene. It therefore seems unlikely that retro-DA reaction occurs with recombination to give nitro compounds.

Scheme 1.47 Tin(IV)chloride isomerization and rearrangement of nitronic ester 84
Subjection of pure 84 to SnCl₄, in toluene, at ambient temperature for 22 hours, resulted in formation of nitro compounds 86 and 88 (77:23 ratio) in 87% yield, Scheme 1.48. Here, too, Sn(IV) coordinated zwitterion 89 is a likely intermediate, but with greater molecular motion. Eventual formation of nitro compounds 86 and 88 is consistent with the greater thermodynamic stability of nitro compounds relative to nitronic esters. This greater thermodynamic stability is also the driving force for sigmatropic rearrangement of O-allyl nitronic esters to nitro compounds.

Scheme 1.48 Tin(IV)chloride catalyzed rearrangement of nitronic ester 84

The uncatalyzed rearrangement mechanism of nitronic esters to nitro compounds is postulated to be a concerted pericyclic process much like the Claisen [3,3]-sigmatropic rearrangement of allyl vinyl ethers (Scheme 1.49). The tin chloride catalyzed
rearrangement might best be described as a zwitterionic process owing to the non-stereospecificity observed. The concerted process might also be catalytically accelerated but the formation of 86 and 88 rather than 87 from rearrangement of 84 would not be expected in a concerted rearrangement.

Scheme 1.49 Proposed rearrangement mechanism of nitronic ester 84 to nitro compound 87

There is a substantial solvent effect on the rearrangement of nitronic esters. The rearrangement goes faster in polar solvents then in non-polar solvents. The rate of rearrangement of 85 was determined in toluene, a non-polar solvent, and ethanol, a polar solvent, for comparison purposes. A mixture of 84 and 85 is dissolved in toluene and left
at ambient temperature. The mixture was analyzed by $^1$H NMR to monitor the progress of the rearrangement. The percentage of isomers present was determined based on peak integration of signals at $\delta$ 3.85 and 3.65 (85 and 84 respectively). During the course of 144 hours nitro isomer 86 formed in increasing amounts. This result shows that 85 was rearranging to nitro compound 86. The peaks for nitro compound 86 were obscured by impurity peaks, which overlapped. The initial ratio of 85 to 84 is 58:42. After 24 hours it was 46:54, and after 72 hours it was 24:76. After 98 hours it was 15:85, after 124 hours it was 10:90, and finally after 144 hours it was 3:97. When the mixture of 84 and 85 is dissolved in ethanol, it resulted in complete rearrangement of 85 after only 24 hours. The rearrangement in ethanol was also much cleaner than in toluene.

Figure 1.12 Proposed zwitterion intermediate in isomerization of nitro compounds
The nitro compound 87 where phenyl and nitro groups are located cis further isomerized to nitro compound 88 where phenyl and nitro groups are trans. This isomerization most likely occurs through the zwitterion 90 where rotation around the C₁ – C₂ bond can occur (Figure 1.12). Heating the nitro isomer in a polar solvent such as dimethyl formamide resulted in isomerization. A tethered diradical pathway is disfavored based on the following observation. Isomerization did not occur upon heating of nitro compound 87 in xylenes indicating the need for a polar solvent, presumably necessary to solvate the zwitterion. The possibility of a nitronate intermediate was also eliminated when nitro compound was subjected to sodium methoxide and it did not isomerize.⁴⁹
1.3 Structure Assignments

All compounds were characterized using FTIR, $^1$H NMR, $^{13}$C NMR, DEPT, MS, and elemental analysis.

The stereochemistry of compounds 84 and 85 was deduced based on the stereochemistry of their rearrangement products, a method first applied to 34a which rearranged to 32a only (Scheme 1.35).29

Nitronic esters were characterized based on their IR spectra and comparison with literature spectra of related nitronic esters. Denmark reported that the six membered cyclic nitronic ester C=N stretch occurs at 1593 cm$^{-1}$ – 1625 cm$^{-1}$ for a range of compounds.30,31,50 Compound 84 is clearly similar in structure. The IR spectrum shows a 1613 cm$^{-1}$ band characteristic of the C=N stretch, Figure 1.13. Mass spectroscopy confirms the molecular weight of 271 g/mol. Elemental analysis confirms the empirical formula and purity. The $^1$H NMR spectrum confirms 11 chemically non-equivalent hydrogen atoms and signal integration confirms the total of 21 hydrogen atoms.

Kornblum and Brown reported $^1$H NMR spectra for nitronic esters. The nitronic proton signal is typically between 5.57 $\delta$ and 7.42 $\delta$ for a range of compounds that they analyzed.26 In compound 84 the nitronic proton signal occurs as a doublet at 6.34 $\delta$. The $^{13}$C NMR shows 15 chemically non-equivalent signals. Two signals for aryl carbon atoms encompass a total of 4 carbon atoms, two meta and two ortho to the point of attachment. The signal at 87.22 $\delta$ confirms a C-O carbon atom. This is consistent with Denmark’s results for related nitronic esters in which the signal for carbon attached to oxygen is typically at 77-86 $\delta$. The signal for the nitronic carbon atom is typically at 109-126 $\delta$.30,31,
The nitronic carbon C=N is assigned to δ 122.86. In the region from 114 to 139 δ there are 7 signals, consistent with the assigned structure: 2 alkene, 4 aromatic, and 1 nitronic carbon atom. The stereochemistry of compound 84 was deduced based on the stereochemistry of its rearrangement product 86. In compound 86 the phenyl and nitro groups are assigned *trans* to each other owing to coupling constants for the associated hydrogen atoms. Because the rearrangement is believed to be concerted, the pathway that it goes through requires the cyclohexene and phenyl groups to be *cis* in nitronic ester 84 in order to produce the *trans* stereochemistry in compound 86. This can be readily seen with molecular models.

Compound 86 is a γ,δ-unsaturated nitro substituted naphthalene derivative. The nitro group typically gives asymmetric and symmetric stretching frequencies at 1500-1600 cm⁻¹ and 1300-1370 cm⁻¹, respectively. The IR spectrum of compound 86 shows bands at 1544 cm⁻¹ and 1374 cm⁻¹, indicating the presence of a nitro group, Figure 1.14. Elemental analysis confirms the empirical formula as C₁₇H₂₃NO₂ and also confirms sample purity. The ¹H NMR spectrum exhibits 12 signals consistent with the postulated structure. Homonuclear 1D decoupling experiments were used to assign signals. Coupling constants for signals assigned to H₄, H₅, and H₆ were used to deduce stereochemistry. The H₅ signal is a doublet of doublets with J= 6.8 Hz and 12.2 Hz. The small coupling constant is due to the *cis* relationship with H₆, and the large coupling constant is due to the *trans* diaxial relationship with H₄. Thus, the phenyl and nitro groups must be *trans* to each other in nitro compound 86. The ¹³C NMR spectrum exhibits 15 signals consistent with the postulated structure. The 90.13 δ signal is assigned to the nitro bearing carbon (C₅).
Figure 1.13 IR spectrum of nitronic ester 84

Figure 1.14 IR spectrum of nitro compound 87
Compound 85 was observed spectroscopically in solution. The $^1$H NMR spectrum was taken for a crude reaction mixture that contained 84 and 85. The $^1$H NMR spectrum shows signals consistent with the two nitronic esters, 84 and 85. A signal at 6.51 $\delta$ is assigned to the nitronic proton of compound 85. Data for $^{13}$C NMR, IR, MS, and elemental analysis were not obtained for this compound because it quickly rearranges at room temperature and it could not be obtained pure. After 24 hours in ethanol, compound 85 rearranged completely to compound 87, which was isolated, purified and fully characterized. Therefore, the molecular structure of compound 85 was largely deduced based on the molecular structure of compound 87.

Compound 87 is a $\gamma,\delta$-unsaturated nitro substituted naphthalene derivative. The IR spectrum shows bands at 1547 cm$^{-1}$ and 1367 cm$^{-1}$, consistent with a nitro group. Mass spectroscopy confirms the molecular weight of 271 g/mol. Elemental analysis confirms the empirical formula C$_{17}$H$_{23}$NO$_2$ and also confirms sample purity. The $^1$H NMR spectrum exhibits 12 chemically non-equivalent signals, which is consistent with the proposed molecular structure. Multiple 1D homonuclear decoupling experiments were used to assign the protons. The H$_5$ signal occurs as a doublet of doublets at 4.98 $\delta$ with $J=3.4$ Hz and 5.8 Hz. The two small coupling constants indicate that H$_5$ must be cis to both H$_6$ and H$_4$; there is no diaxial coupling constant. This requires that the phenyl and nitro groups must also be cis. The chemical shift of proton H$_5$ ($\delta$ 4.98) is consistent with protons attached to a nitro bearing carbon atom. The $^{13}$C NMR spectrum confirms 15 chemically non-equivalent carbon atoms, which is consistent with the proposed structure. The signal at 92.49 $\delta$ is assigned to the C-NO$_2$ carbon atom.
Compound 88 is a γ,δ-unsaturated nitro substituted naphthalene derivative. The IR spectrum shows bands at 1545 cm\(^{-1}\) and 1372 cm\(^{-1}\), which are consistent with a nitro group symmetric and asymmetric stretch. Mass spectroscopy indicates a molecular mass of 271 g/mol. The \(^1\)H NMR spectrum exhibits 14 chemically non-equivalent signals, which is consistent with the proposed molecular structure. The H\(_3\) signal at δ 4.62 is characteristic of a proton attached to a nitro bearing carbon atom. Multiple 1D homonuclear decoupling experiments were used to assign proton signals. The stereochemistry was deduced from coupling constants of the signals. The H\(_3\) signal occurs as a doublet of doublets with \(J = \) 9.7 Hz and 12.2 Hz. The two large coupling constants indicate that H\(_3\) is \textit{trans} to both H\(_4\) and H\(_6\). Thus, the phenyl and nitro groups must also be \textit{trans} to each other. The \(^{13}\)C NMR spectrum shows 14 chemically non-equivalent signals consistent with the assigned structure, where the 2 \textit{ortho} and 2 \textit{meta} aromatic carbon atoms are equivalent. The signal at δ 92.49 is characteristic of a C-NO\(_2\) carbon atom.
1.4 Experimental

Ethyl acetate was distilled from anhydrous K$_2$CO$_3$. Hexane was distilled from CaH$_2$. Tetrahydrofuran was purified by distillation from benzophenone and sodium metal (blue solution) under N$_2$. Toluene was distilled and a fraction boiling at 109-110°C was used for experiments. Xylene was distilled and a fraction boiling at 139-140°C was used for experiments. Dimethyl formamide was distilled and a fraction boiling at 152-153°C was used for experiments. Benzene was distilled and a fraction boiling at 79-80°C was used for experiments. Methyltriphenylphosphoniumbromide was purchased from Sigma Aldrich and used as received. A 2.5 M solution of n-butyllithium in hexanes was purchased from Sigma Aldrich. 1-Acetyl-1-cyclohexene was purchased from Sigma Aldrich and used as received. Silica gel was purchased from AlphaAesar (230-400 mesh). Preparatory and analytical thin layer chromatography plates were purchased from Analtch (Silica Gel GF, 250 μm). Instruments used for analysis: Unityinova 300 MHz NMR spectrometer, Unityinova 500 MHz NMR spectrometer, Autospec-Ultima with quadrupole mass spectrometer, Perkin Elmer precisely IR.

Synthesis of 1-(1-methylvinyl)cyclohexene

Methyltriphenylphosphoniumbromide (0.04 mol, 14.28 g) and 90 mL of tetrahydrofuran were placed in a 3-neck round-bottom flask. The mixture was cooled to -78°C using a dry ice/acetone bath under N$_2$ with stirring. A solution of n-butyllithium (2.5 M in hexanes, 0.04 mol, 16 mL) was added via a syringe over 25 minutes. The reaction mixture was warmed with a water bath to ambient temperature and stirred for 30
minutes. The reaction mixture was then cooled to -78°C with dry ice/acetone and a solution of 1-acetyl-1-cyclohexene (0.04 mol, 4.96 g) diluted in 10 mL of tetrahydrofuran was added dropwise to the cold reaction mixture via a syringe. After addition was complete, the reaction mixture was warmed up to ambient temperature and stirred for 12 hours. The reaction mixture was cooled to 0°C. A 25 mL portion of water was added slowly to destroy any remaining n-butyllithium. The resulting mixture was transferred to a separatory funnel and the aqueous layer was separated. The organic layer was washed with water (three 20 mL portions). Aqueous layers were combined and extracted with diethyl ether (four 20 mL portions). Combined organic layer was washed with water (three 20 mL portions), dried with sodium sulfate, filtered, and concentrated under reduced pressure. During the evaporation of solvent, triphenylphosphine oxide byproduct crystallized out. The byproduct was removed by filtration and washed with diethyl ether to extract the diene product. This process was repeated several times. The crude product was further purified with column chromatography using 100 g silica gel and hexanes/ethyl acetate in 9:1 ratio. Eventually the reaction afforded 2.97 g (61 % yield) of compound 83.

_Synthesis of nitronic esters 84 and 85 - workup at -70°C_

A toluene (8 mL) solution of 1-(1-methylvinyl)cyclohexene (0.004 mol, 0.488 g) and trans-β-nitrostyrene (0.002 mol, 0.298 g) was cooled to -78°C using a dry ice/acetone bath, under N₂, with stirring. Tin(IV)tetrachloride (0.002 mol, 0.23 mL) was added to the reaction mixture dropwise via a syringe over 5 minutes. The resultant was stirred for 30 minutes. Ethyl acetate (20 mL) was added to dilute the mixture and
saturated aqueous sodium bicarbonate (20 mL) was added drop wise to destroy the catalyst, the reaction mixture temperature being kept below -70°C. The reaction mixture was warmed up to room temperature and transferred to a separatory funnel. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (three 20 mL portions). The organic layers were combined and washed with saturated aqueous sodium bicarbonate (three 20 mL portions) and saturated aqueous sodium chloride (three 20 mL portions), dried with sodium sulfate and concentrated under reduced pressure. Under these workup conditions the ratio of 84 to 85 is 1:1. The crude product was dissolved in ethanol (200 proof, 10 mL) and after 24 hours the solution was concentrated at reduced pressure. The resulting crude product was purified by column chromatography using silica gel and a hexanes/ethyl acetate step gradient (from 90:10 to 50:50). A 0.1734 g portion (32% yield) of compound 84 eluted in the latter chromatography fractions.

84 (4R,6R)-6-(cyclohex-1-en-1-yl)-6-methyl-4-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide

The analytical sample of compound 84 was recrystallized from benzene / hexanes. Pure 84 was a white solid: m.p. 104-105 °C; IR (ATR) 1613 cm\(^{-1}\) (C=N); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.20-7.40 (m, 5H, H\(_{13-15}\)), 6.34 (d, 1H, H\(_1\), \(J=2.9\) Hz ), 5.95 (broad s, 1H, H\(_7\)), 3.63 (m, 1H, H\(_2\)), 2.47 (dd, 1H, \(J=6.8, 14.2\) Hz), 2.00-2.20 (m, 4H), 1.83 (dd, 1H, \(J=\)
11.9, 13.9 Hz), 1.60-1.70 (m, 4H), 1.41 (s, 3H, H₃); ¹³C NMR (74.5 MHz, CDCl₃) δ 139.81, 135.72, 129.08, 127.71, 127.48, 122.85, 114.23 (C₇), 87.22 (C₄), 38.81, 36.57, 26.47, 24.98, 23.85, 22.79, 22.00, 22.79; MS (FAB, NaI) C₁₇H₂₁N₀₂Na [M+Na]: found 294.1464, calculated 294.1470.

Elemental analysis calculated for C₁₇H₂₁N₀₂: C 75.24 %, H 7.79 %, N 5.15%

Found: C 75.22 %, H 7.58 %, N 5.14%

85 (4S,6R)-6-(cyclohex-1-en-1-yl)-6-methyl-4-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide

Compound 85 was not isolated because it rearranged to 86 at room temperature. The ¹H NMR spectrum of a mixture of 84 and 85 was obtained prior to dissolving the sample in ethanol for 24 hours. The following ¹H NMR signals are attributed to compound 85: δ 7.20-7.40 (m, 5H, H₁₃-₁₅), 6.51 (d, 1H, H₁, J=3.4 Hz), 5.85 (broad s, 1H, H₇), 3.85 (m, 1H, H₂), 2.18 (m), 2.15-1.60 (several multiplets), 1.58 (s, 3H, H₅).

A 0.2439 g (45% yield) portion of nitro compound 86 was obtained from early chromatography fractions. The analytical sample was recrystallized from benzene and hexanes.
86 (4aR,5S,6S)-8-methyl-5-nitro-6-phenyl-1,2,3,4,4a,5,6,7-octahydronaphthalene

Compound 86 is a white solid: m.p. 122-123 °C; IR (ATR) 1544 cm⁻¹ and 1374 cm⁻¹ (NO₂); ¹H NMR (500 MHz, CDCl₃) δ 7.18-7.38 (m, 5H, H₁₃-₁₅), 5.18 (dd, 1H, H₅, J=6.8, 12.2 Hz), 3.44 (m, 1H, H₄), 2.74 (broad m, 2H), 2.19-2.37 (m, 2H), 1.80-1.95 (m, 2H), 1.72 (m, 1H), 1.62 (s, 3H, H₁₁), 1.45 (m, 3H), 1.27 (m, 1H); ¹³C NMR (74.5 MHz, CDCl₃) δ 141.57, 131.19, 128.71, 127.29, 127.00, 126.94, 122.47, 90.13 (C₅), 42.79, 40.78, 39.66, 30.80, 29.65, 27.94, 26.34, 18.09; MS (FAB, NaI) C₁₇H₂₁NO₂Na [M+Na]: found 294.1483, calculated 294.1470.

Synthesis of nitronic esters 84 and 85 – work-up at 20 °C

The preceding experiment was repeated. After addition of ethyl acetate (20 mL), the procedure was altered. The reaction mixture was warmed up to room temperature prior to work-up. As in the previous run, saturated aqueous sodium carbonate (20 mL) was added. Work-up was then completed as in the previous run. Under these work-up conditions the ratio of 84 to 85 is 4:1.
Isomerization of $84$ to $85$

A mixture of $84$ and $85$ (53:47) was prepared by placing 1-(1-methylvinyl)cyclohexene (0.4984 g, 0.0041 mol) and trans-$\beta$-nitrostyrene (0.3142 g, 0.0021 mol) in toluene (8 mL) under $N_2$, in dry ice, with stirring. After the internal temperature reached -76°C, SnCl$_4$ (0.002 mol or 0.23 mL) was added dropwise over 10 minutes, and the reaction mixture was stirred for additional 30 minutes. The reaction mixture was slowly diluted with ethyl acetate (20 mL), the temperature increasing to -69°C. Then saturated aqueous sodium bicarbonate (25 mL) was added dropwise to destroy the catalyst, the temperature increasing to -70°C. The reaction temperature was then raised to 10°C using a water bath at room temperature. The reaction mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (three 20 mL portions). The combined organic layers were washed with saturated aqueous sodium bicarbonate (three 20 mL portions) and saturated aqueous sodium chloride (three 20 mL portions), dried with sodium sulfate, and concentrated under reduced pressure to give 0.7178 g of crude product. Only trace amounts (<2%) of trans-$\beta$-nitrostyrene and nitro compound $86$ were present. Based on $^1$H NMR signal integration the following materials were present: $84$, $85$, and $86$ (52 : 46 : 2 ratio).

The crude nitronic ester mixture from above was dissolved in 8 mL of toluene and cooled to -76°C under $N_2$ with stirring. Tin(IV)tetrachloride (0.23 mL, 0.002 mol) was added to the mixture dropwise over 10 minutes. The dry ice/acetone bath was replaced with a dry ice/cyclohexanone bath, and the reaction temperature kept at -55°C, with stirring for 40 minutes. The dry ice/cyclohexanone bath was replaced with a dry ice/acetone bath, and
the reaction temperature decreased to -75°C. The reaction mixture was diluted by dropwise addition of ethyl acetate (20 mL), the temperature increasing to -60°C.

Saturated aqueous NaHCO₃ (15 mL) was added to destroy the catalyst, the reaction temperature being kept under -60°C. The reaction mixture was warmed up to ambient temperature using a water bath. The mixture was then transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (three 20 mL portions). The combined organic layers were washed with saturated aqueous NaHCO₃ (three 20 mL portions) and saturated aqueous sodium chloride (three 20 mL portions), dried with sodium sulfate, and concentrated under reduced pressure to give 0.7303 g of crude product. The ¹H NMR spectrum indicates that 84 and 85 were formed in 65:35 ratio. Also present was a small amount (4 %) of compound 86. Based on ¹H NMR signal integration the following materials were present: 84, 85, and 86 (62 : 34 : 4 ratio).

The crude product was dissolved in ethanol (10 mL) and kept at ambient temperature for 24 hours. The solvent was removed under reduced pressure to afford 0.6076 g of crude product. The ¹H NMR spectrum showed that 84 and 86 were present (60:40 ratio) and <1% of 85 remained.

| Ratios of 84, 85, and 86 based on ¹H NMR signal integration. |
|-----------------|-----|-----|-----|
|                 | 85  | 84  | 86  |
| SnCl₂, -76°C, 30 min, toluene | 51  | 46  | 3   |
| SnCl₂, -55°C, 40 min, toluene  | 34  | 62  | 4   |
| room temp, ethanol, 24 hr       | <1% | 60  | 40  |
The crude product was chromatographed using silica gel and hexanes/ethyl acetate step gradient (from 90:10 to 50:50). Similar fractions were combined and concentrated. Chromatography afforded 0.1536 g (27 % yield) of nitro compound 86, and 0.2333 g (41 %) of nitronic ester 84.

Rearrangement of 84 to 87

A DMF (12 mL) solution of compound 84 (0.002 mol, 0.542 g) was heated for 2 hours under N₂ using an oil bath at 94°C. The reaction mixture was cooled and diluted with benzene and ethyl acetate (15 mL each) and washed with water (twenty 20 mL portions). The organic layer was dried with sodium sulfate and concentrated under reduced pressure. Compound 87 was purified with by preparative TLC (250 µm silica gel plate, eluent hexanes/ethyl acetate, 90 : 10). After chromatography 0.4715 g (87 % yield) of pure 87 was obtained. The analytical sample was recrystallized from benzene / hexanes.

87 (4aR,5S,6R)-8-methyl-5-nitro-6-phenyl-1,2,3,4,4a,5,6,7-octahydronaphthalene
Compound 87 is a white solid: m.p. 101-102 °C; IR (ATR) 1547 cm⁻¹ and 1367 cm⁻¹ (NO₂); ¹H NMR (500 MHz CDCl₃) δ: 7.18-7.38 (m, 5H, H₁₃-₁₅), 4.98 (dd, 1H, H₅, J=3.4, 5.8 Hz), 3.22 (m, 1H, H₄), 3.03 (m, 1H), 2.78 (d, 1H, J=14.16 Hz), 2.62 (broad s, 1H), 2.13 (dd, 1H, J=4.4, 17.1 Hz), 1.60-1.85 (m, 4H), 1.77 (s, 3H, H₁₁), 1.40 (m, 1H), 1.25 (m, 1H), 1.04 (m, 1H); ¹³C NMR (500 MHz, CDCl₃) δ: 140.09, 129.11, 127.86, 127.39, 126.45, 125.11, 92.49 (C₅), 42.70, 41.28, 32.56, 29.13, 28.87, 26.26, 26.11; MS (FAB, NaI) C₁₇H₂₁N0₂ [M⁺]: found 272.1658, calculated 272.1651.

Elemental analysis calculated for C₁₇H₂₁N0₂: C 75.24 %, H 7.79 %, N 5.15%
Found: 75.50 %, H 7.92 %, N 5.05%

*Isomerization of 87 to 88*

A DMF (6 mL) solution of compound 87 (0.06 mmol, 0.0162 g) was heated under N₂ for 6 hours using an oil bath at 155°C. The reaction mixture was cooled and diluted with benzene and ethyl acetate (15 mL each) and washed with water (twenty 20 mL portions). The organic layer was dried with sodium sulfate and concentrated under reduced pressure. Compound 88 was purified by preparative TLC (250 μm silica gel plate, eluent hexanes/ethyl acetate, 90 : 10). After chromatography, the reaction afforded 0.0141 g (87 % yield) of pure compound 88. The analytical sample was recrystallized from benzene / hexanes.
Compound 88 is a white solid: m.p. 103-104 °C; IR (ATR) 1545 cm\(^{-1}\) and 1372 cm\(^{-1}\) (NO\(_2\)); \(^1\)H NMR (500 MHz CDCl\(_3\)) \(\delta\) 7.18-7.38 (m, 5H, H\(_{13-15}\)), 4.62 (dd, 1H, H\(_5\), \(J=9.7, 12.2\) Hz), 3.32 (m, 1H, H\(_4\)), 2.77 (m, 2H), 2.39 (m, 1H), 2.25 (m, 1H), 1.91 (m, 1H), 1.80 (m, 2H), 1.72 (m, 1H), 1.68 (s, 3H, H\(_{11}\)), 1.36 (m, 1H), 1.18 (m, 2H); \(^{13}\)C NMR (74.5 MHz, CDCl\(_3\)) \(\delta\) 139.86, 129.16, 128.72, 127.52, 127.39, 127.32, 123.89, 95.96 (C\(_5\)), 44.55, 43.76, 39.59, 32.22, 28.87, 26.26, 25.26; MS (FAB, NaI) C\(_{17}\)H\(_{21}\)N\(_2\)Na [M+Na]: found 294.1471, calculated 294.1470.

Elemental analysis calculated for C\(_{17}\)H\(_{21}\)N\(_2\): C 75.24 %, H 7.79 %, N 5.15%
Found: C 75.16 %, H 7.75 %, N 5.17 %

*Thermal non-catalyzed cycloaddition of 1-(1-methylvinyl)cyclohexene and trans-\(\beta\)-nitrostyrene*

1-(1-Methylvinyl)cyclohexene (0.9 mmol, 0.1098 g) and *trans*-\(\beta\)-nitrostyrene (0.6 mmol, 0.0894 g) were heated under N\(_2\) for 7 hours using an oil bath at 155°C. The crude product was purified by preparative TLC (250 \(\mu\)m silica gel plate, eluent hexanes/ethyl
acetate, 90 : 10). After chromatography, the reaction afforded 0.0976 g (60% yield) of a mixture of 86, 88, and 90a-b in a 45 : 45 : 10 ratio.

*Synthesis of nitro compounds 86 and 88 from 84*

A toluene (1 mL) solution of compound 84 (0.04 g, 1.48x10^{-4} mol) was stirred and cooled in a dry ice/acetone bath under N₂. After the temperature of the solution reached -74°C, SnCl₄ (0.017 mL, 1.48x10^{-4} mol) was added dropwise over 6 minutes. The mixture was stirred at -74°C for 15 minutes. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 22 hours. Toluene (10 mL) was added followed by saturated aqueous sodium bicarbonate (15 mL) and the resulting mixture was transferred to a separatory funnel using ethyl acetate (20 mL) to complete the transfer. The organic layer was separated and the aqueous layer was extracted ethyl acetate (three 20 mL portions). The combined organic layer was washed with saturated aqueous sodium bicarbonate (two 25 mL portions) and saturated aqueous sodium chloride (one 25 mL portion), dried with Na₂SO₄ and concentrated under reduced pressure. The crude product (0.0350 g, 87% yield) was a mixture of nitro compounds 86 and 88 (77:23 ratio).
1.5 Conclusions

O-allyl nitronic ester 84 rearranged to nitro compound 87 and nitronic ester 85 rearranged to nitro compound 86. These transformations of nitronic esters to nitro compounds are concerted [3,3]-sigmatropic rearrangements. In each case only a single diastereomeric nitro compound was observed. Alteration of the 84/85 ratio when the nitronic esters were subjected to SnCl₄ implies that tin(IV) coordinated zwitterions are present as intermediates. Prolonged exposure of 84 to SnCl₄ results in tin(IV) catalyzed rearrangement to a mixture of nitro compounds 87 and 88. Tin(IV) catalyzed rearrangement is not a concerted process as indicated by formation of a mixture of isomers. Nitro compound 87 has the phenyl and nitro groups in a cis configuration. When compound 87 was heated at 155°C, it isomerized to the more stable compound 88, in which the phenyl and nitro groups were in a trans configuration.
1.6 References


28. Synthesized by Hung Le, 2002, Unpublished results


Chapter 2. Rearrangement Of Nitronic Esters To Form 4-Nitro Cyclohexene Derivatives

2.1 Introduction

In order to determine the scope of the O-allyl nitronic ester rearrangement, it was decided to investigate additional examples. Using the Denmark DA cycloaddition reaction of β-nitrostyrene with an unsymmetrical open-chain diene was chosen as a route to additional new nitronic esters. The open-chain diene 3-methyl-1,3-pentadiene is commercially available as a mixture of E- and Z-isomers. Cycloaddition could occur on either C,C-double bond of each isomer allowing for the preparation of a variety of nitronic esters for study. The cycloadducts would be expected to fall into two categories: O-allyl nitronic esters and regioisomers not having an allylic C,C-double bond (Figure 2.1). By analogy with cycloaddition to 1-(1-methylvinyl)cyclohexene, it was hoped that the O-allyl nitronic ester isomers would predominate since only they are capable of undergoing sigmatropic rearrangement. A total of eight O-allyl nitronic ester isomers are possible. Although all possible isomers might not form, the structure of the nitronic esters actually obtained would be expected to be sufficiently diverse to provide information on the scope of the [3,3]-sigmatropic rearrangement reaction.

![Figure 2.1 O-allyl nitronic ester and regioisomer](image-url)
2.2 Results and Discussion

Nitronic esters 92 through 97 were synthesized by the IEDDA reaction of trans-β-nitrostyrene (82) and 3-methyl-1,3-pentadiene (7:3 E/Z mixture, 91a-b respectively), Scheme 2.1. Other isomeric nitronic esters were absent. The reaction was performed in either toluene or dichloromethane solution using tin(IV) tetrachloride as catalyst. The reactions were performed in two ways: the diene was diluted with solvent and added at controlled rate using a syringe pump to a solution of trans-β-nitrostyrene and tin(IV) tetrachloride, or alternatively a solution of diene and trans-β-nitrostyrene was treated with tin(IV)chloride added over 5 minutes. Additional reactions were performed using pure E-3-methyl-1,3-pentadiene (91a) to determine which products were formed from the Z (91b) isomer and which from the E (91a) isomer. Considerable variation in the product spread was observed owing to reaction conditions. With toluene as solvent, additional products that incorporated toluene were observed.
Addition of tin(IV) catalyst to a solution of β-nitrostyrene and 3-methyl-1,3-pentadiene (E/Z 7:3)

When reaction was conducted in toluene solution without a syringe pump, multiple products were observed in the crude mixture. Six of the products were nitronic esters: 92, 93, 94, 95, 96, and 97 in a 43 : 42 : 6 : 2 : 5 : 2 ratio, respectively. Also obtained was a mixture of two isomeric ternary adducts 98a and 98b in which diene, nitrostyrene, and toluene were incorporated (Fig 2.2).
Other material was present, apparently polymerized diene. The major nitronic esters 92 and 93 arise from cycloaddition of trans-β-nitrostyrene (82) at the less substituted double bond of the E-diene (91a), Scheme 2.1. The minor nitronic esters, 94 – 97 arise from cycloaddition at the more substituted double bond of both E- and Z-diene (91a-b), leaving the vinyl double bond intact. No product corresponding to cycloaddition at the less substituted double bond of the Z diene 91b was observed. The limiting reactant trans-β-nitrostyrene (82) was completely used up under these conditions. After chromatography all nitronic esters were obtained pure except 94 and 95, which were obtained as a mixture.

A considerable amount of side products was formed in this reaction. The first column chromatography fractions that were collected appear to be polymeric hydrocarbons derived from diene and β-nitrostyrene. This amounted to 1/3 of the weight of crude product.

Presumably this side product arises because SnCl₄ is a strong Lewis acid that has polymerized the diene via a cationic mechanism (Scheme 2.3). The polymeric material
was not fully characterized. Cationic polymerization of diene is well known. There is evidence that tin(IV) chloride self-ionizes and behaves as both initiator and coinitiator in the polymerization of isoprene. Polymerization of isoprene at different levels of dryness and diene purity was monitored by kinetics, conductance, and spectrophotometry. Under the most stringent purification and drying procedures, polymerization was observed. With this indirect evidence it is concluded that tin(IV) chloride self-ionizes and forms an active polymerization initiator in the reactions reported here (Scheme 2.2).¹

Scheme 2.2 Tin(IV) chloride self-ionization

\[
\text{SnCl}_4 + \text{SnCl}_4 \rightarrow \text{SnCl}_3^+ (\text{SnCl}_5)^- \\
\text{Active initiator}
\]

Cationic polymerization of 1,3-dienes such as isoprene usually results in low molecular weight polymers with partially cyclized structures.¹ Polymerization of isoprene with Sn(IV) chloride at -78°C without solvent was reported by Richardson. Isoprene is structurally similar to 3-methyl-1,3-pentadiene.²

In the current study, chromatography on silica gel did not afford pure discrete polymeric products but rather a mixture of polymeric material. The \(^1\text{H}\) NMR spectra for these fractions showed multiple intense signals in the region 0.5 - 2.5 δ. Weak bands at 7.0 - 7.5 δ suggest incorporation of aromatic material (toluene and or β-nitrostyrene) into the polymeric product. The IR spectrum of the polymeric product clearly indicates the presence of a nitro group, bands at 1557 cm\(^{-1}\) and 1378 cm\(^{-1}\) being present.
Scheme 2.3 Proposed cationic polymerization mechanism of 3-methyl-1,3-pentadiene

From Denmark’s studies of nitronic ester formation, it is obvious that the ratio of products is greatly solvent dependent. Another complication in the current study is the possibility of cycloaddition at either of the two diene double bonds. Further complicating the situation is the presence of both E and Z forms of the diene.

From slightly more polar chromatography fractions, a considerable amount of another product was isolated and characterized. The material comprised 14% of the crude product by weight. The mass spectrum indicates a molecular mass of 323 g/mol.
corresponding to a combination of diene, toluene, and trans-β-nitrostyrene. This ternary adduct will be discussed more fully later in the chapter.

Ideally, solvent should be inert in a chemical reaction. Consequently, reactions were conducted in dichloromethane to avoid incorporation of toluene into products.

Addition of tin(IV) catalyst to a dichloromethane solution of β-nitrostyrene and 3-methyl-1,3-pentadiene (E/Z, 7:3)

Reaction was performed by adding SnCl₄ catalyst to a dichloromethane solution of diene (91a-b) and trans-β-nitrostyrene (82). A mixture consisting of nitronic esters 92-97, unreacted trans-β-nitrostyrene, and diene polymer was obtained as the crude product. Since the reaction did not go to completion, the reaction time was extended to 3 hours. However, even after 3 hours roughly the same amount of trans-β-nitrostyrene was recovered. According to Odian¹, Lewis acid catalytic activity is higher in dichloromethane for cationic polymerization of alkenes than in hydrocarbon solvents. More of the diene may be polymerizing in dichloromethane than in toluene, so that there is not enough of the diene available to undergo complete cycloaddition with trans-β-nitrostyrene.

The combined yield of nitronic esters is 34 % after chromatography. The ratio of products is as follows: 22 : 33 : 6 : 11 : 16 : 11 for 92, 93, 94, 95, 96, and 97, respectively. Again no product derived from cycloaddition at the less substituted double bond of Z diene 91b was obtained. The earliest fractions that were collected during chromatography were mostly polymeric hydrocarbon material. About 1/3 of starting trans-β-nitrostyrene did not react and was present in early chromatography fractions.
Since the reaction in dichloromethane does not result in the incorporation of solvent into products, these results are promising. The biggest drawbacks in the reaction performed in dichloromethane are the large amount of unreacted trans-β-nitrostyrene and the amount of polymerized diene. Experimental conditions in dichloromethane were modified in an attempt to avoid these problems. The diene and catalyst were added at intervals in an attempt to obtain complete reaction of the trans-β-nitrostyrene. Under these conditions $^1$H NMR indicated that all trans-β-nitrostyrene had reacted, but the reaction was not clean, multiple side products being present.

Perhaps additional catalyst caused reaction between already formed nitronic esters and diene. In a separate experiment, only diene was added at intervals to the reaction. The $^1$H NMR indicated that much of the starting trans-β-nitrostyrene remained (about 1/3). There were also 6 nitronic ester products. The polymeric side product fraction was reduced from the previous experiment, and reaction was cleaner. This method was successful because it avoided excessive formation of side products, but was unsuccessful in converting all of the trans-β-nitrostyrene to product.

Another complication was noted in experiments run in dichloromethane. Excess diene underwent reaction with the available vinyl group on at least one of the nitronic esters 94-97. A compound was isolated and tentatively characterized: mass spectroscopy indicates a molecular weight equivalent to two diene units and one trans-β-nitrostyrene unit (313 g/mol) and the IR spectrum exhibits a C=N stretch (1611 cm$^{-1}$) characteristic of a nitronic ester.
Tin(IV) catalyzed reaction of β-nitrostyrene with 3-methyl-1,3-pentadiene (E/Z, 7:3 mixture) added at controlled rate in dichloromethane

Clearly, polymerization of the diene is the major cause of poor yield in reactions run in dichloromethane. To avoid polymerization, reactions are often performed with controlled amounts of the monomeric diene. A syringe pump was therefore utilized to control the concentration of diene. A solution of the diene was added dropwise over 1 hour to the cold mixture of trans-β-nitrostyrene and SnCl₄. Previous experiment showed that trans-β-nitrostyrene does not react with itself in the presence of the SnCl₄ catalyst. Reaction of trans-β-nitrostyrene and SnCl₄ should only result in formation of a complex between the reagents. Addition of small quantities of diluted diene to the diluted mixture of activated complex should then result in formation of nitronic esters in good yield. Indeed, after chromatography 58% combined yield of nitronic esters was obtained by this method. Analysis of the crude product showed that all of trans-β-nitrostyrene reacted, and only small amounts of polymer formed. The crude product contained 6 nitronic esters. The nitronic esters were present in the following proportion: 17 : 17 : 9 : 9 : 32 : 16 for 92, 93, 94, 95, 96, and 97, respectively.

Tin(IV) catalyzed reaction of β-nitrostyrene with pure E-3-methyl-1,3-pentadiene added at controlled rate in dichloromethane

The preceding reaction was repeated with pure E-3-methyl-1,3-pentadiene. After chromatography a mixture of nitronic esters amounting to 50% combined yield was
obtained. The ratio of products was: 29 : 28 : 10 : 23 : 10 for compounds 92, 93, 94, 96, and 97 respectively. Notably, nitronic ester 95 was absent in the crude product. When the reaction was performed with pure E diene, only four nitronic esters were expected to form. However, a fifth nitronic ester was produced. Three of the five nitronic esters exhibit a vinyl pattern in the $^1$H NMR. These are nitronic esters 94, 96, and 97. Two of the nitronic esters (92 and 93) exhibit the absence of a vinyl group and the presence of a CH=CCH$_3$ group. This means that the cycloaddition occurred at the less substituted double bond.

It had previously been shown that nitronic esters 94-97 do not isomerize in toluene under cycloaddition conditions. The possibility of isomerization in dichloromethane, however, needed to be tested. The result was that nitronic esters 94 and 95 did not undergo isomerization in dichloromethane under cycloaddition conditions and that no 96 and 97 were observed as indicated by $^1$H NMR. The formation of nitronic esters 95 and 96 in the reaction where pure E-3-methyl-1,3-pentadiene is used as starting material presumably results from cycloaddition of the Z diene and β-nitrostyrene. Apparently, the E diene isomerizes to the Z diene under the typical reaction conditions, and nitronic esters 95 and 96 are formed from the subsequent cycloaddition of the Z diene and β-nitrostyrene.

**Tin(IV) catalyzed reaction of β-nitrostyrene and E-3-methyl-1,3-pentadiene in toluene**

The reaction was performed by addition of SnCl$_4$ to a cold mixture of E-3-methyl-1,3-pentadiene and trans-β-nitrostyrene in toluene. It resulted in the formation of 6
nitronic esters in the following ratio: 39 : 51 : 3 : 0.3 : 0.4 : 6 for compounds 92, 93, 94, 95, 96, and 97 respectively. A ternary adduct 98a-b and diene polymer were also formed.

Only trace amounts of the nitronic esters 95 and 96 are produced in this reaction compared to the reaction where an E/Z mixture of diene was used. Overall, 4 nitronic esters with a vinyl substituent are observed, two major and two very minor. Based on the typical retention of alkene configuration in DA reactions, only two nitronic esters with a vinyl substituent are possible as products derived from E-diene. Of the four vinyl substituted nitronic esters, the two major would be formed from the E-diene and the two minor from the Z-diene. In this reaction, however, where only the E diene was used as starting material, only two vinyl substituted nitronic esters are expected to form.

Nevertheless, four nitronic esters with a vinyl substituent are observed, although two are in trace amounts (less than 0.5% for 95 and 96). The previously noted absence of nitronic ester 95 in reaction of the E diene in dichloromethane is a clear indication that 95 forms from the Z diene. The absence of significant amounts of 96 in the reaction of E diene in the experiment run in toluene implicates Z diene as the precursor to 96. This leaves the matter of why 96 formed in the reaction of E diene carried out in dichloromethane to be explained.

The more prevalent products in the reaction conducted in toluene are presumably formed from E diene (3% and 6% yield for 94 and 97, respectively). The stereointegrity of the E diene was carefully examined. The $^1$H NMR spectrum of the E diene showed that no Z isomer is present even in trace quantities. The manufacturer of the E-diene (SampCo) provided a GC analysis indicating 99.7 % E isomer and 0.3 % Z isomer.
The $E$ diene was impregnated with the mixed diene isomers so that by calculation 1% of $Z$ isomer was present. Analysis by $^1$H NMR clearly shows the $Z$ diene. Based on the peak intensity of this $1:99$ $Z/E$ mixture, it was estimated that as little as 0.5% of the $Z$ isomer could easily be observed. Clearly, then, the $Z$ isomer is initially absent from the $E$-diene sample.

A possible explanation for formation of cycloadducts 95 and 96 derived from $Z$ diene is that isomerization of the $E$ diene to the $Z$ isomer was caused by SnCl$_4$. It is known that Lewis acids such as SnCl$_4$ polymerize dienes via a cationic pathway. It is also possible that when SnCl$_4$ binds to the diene, the newly formed allylic cation may undergo rotation about the $C_2 - C_3$ bond (Scheme 2.4). Reversal of SnCl$_4$ coordination would then give the $Z$ diene. This proposed mechanism is shown below in Scheme 2.4. It has also been found that warming $E$-3-methyl-1,3-pentadiene and $\beta$-nitrostyrene results in isomerization of the diene (vide infra). Perhaps at low temperatures SnCl$_4$ accelerates this process leading to the formation of $Z$-diene.

Scheme 2.4 Proposed tin(IV) catalyzed isomerization of 3-methyl-1,3-pentadiene
*Tin(IV) catalyzed isomerization of nitronic esters*

Tin chloride catalyzed isomerization of nitronic esters was observed in Chapter 1, mostly under conditions more stringent than used for cycloaddition. It seemed possible that a similar situation might prevail in the current study in which nitronic esters 94-97 might isomerize. At room temperature no isomerization was observed for any of the nitronic esters. However isomerization did occur for nitronic ester 95 when subjected to SnCl₄ at room temperature for a longer period of time. After 2 hours, 95 was converted to a 2:1 mixture of nitronic esters 95 and 97, respectively (Scheme 2.5). Presumably a tin-coordinated zwitterion was formed and underwent rotation about the single bond between the two methyl-substituted C-atoms. Reclosure could then give either 95 or 97 and the ratio might be expected to reflect the relative thermodynamic stability of the two isomers.

Scheme 2.5 Tin(IV) chloride catalyzed isomerization of nitronic ester 95
Extending the reaction time to 16 hours did not alter the 2 : 1 ratio of nitronic esters 95 and 97 but did result in concomitant formation of nitro compound 104. A 16 hour product ratio of 95, 97, and 104 was 50 : 27 : 23, respectively. If nitro compound 104 is forming in a concerted [3,3]-sigmatropic rearrangement, then nitronic ester 97 must be its precursor. Thermal rearrangement of 97 to 104 was not observed (see later section), but tin chloride might catalytically lower the activation energy for rearrangement. The thermal rearrangement possibly failed owing to high activation energy for rearrangement coupled with thermal instability of the nitronic ester, resulting in its decomposition at a temperature lower than required for rearrangement. It is also quite possible that that proposed zwitterion for isomerization of 95 to 97 is also an intermediate in the formation of 104. Over a longer period of time, a larger molecular motion in the zwitterion might bring the nitronate C-atom close enough to the cation center to allow for collapse resulting in formation of a new C,C-single bond rather than a C,O-single bond. This process would be thermodynamically driven because the resulting nitro compound 104 is more stable than either 95 or 97.

It was further shown that pure nitronic ester 97 gave nitro compound 104 in 10% yield after being kept in contact with tin(IV)chloride for 55 hours (Scheme 2.6). The structure of 104 is assigned based on the following considerations. The $^1$H NMR spectrum shows a multiplet at δ 4.94 assigned to H₄ of compound 104. The presence of three coupling constants is consistent with the regiochemical assignment. The proton H₅ exhibits a doublet of doublets. Based on two large coupling constants ($J = 11.7$ Hz, $10.3$ Hz), H₅ must be trans to both H₄ and H₆.
Scheme 2.6 Tin(IV)chloride catalyzed rearrangement of nitronic ester 97

It was also found that nitronic ester 96 underwent isomerization to nitronic ester 94. The nitronic esters were obtained in a 60 : 40 96/94 ratio, when 96 was subjected to SnCl₄ for 2 hours. After 16 hours, 96 had largely isomerized to 94 (1:99, 96/94 ratio), Scheme 2.7. Pure nitronic ester 94 was subjected to SnCl₄ at room temperature for 43 hours. The reaction resulted in formation of several unassigned compounds, nitronic ester 94 was completely consumed, and there was no evidence that a nitro compound formed.

Scheme 2.7 Tin(IV)chloride catalyzed isomerization of nitronic ester 96
Partial isomerization of nitronic ester 92 to 93 was also observed at 20°C. Compound 92 was converted to a 92/93 mixture (60:40 ratio) when subjected to SnCl₄ for 2 hours in toluene. Treating 93 to SnCl₄ for 2 hours similarly led to a mixture of 92 and 93 (60:40 ratio). It seems, then, that a 60 : 40 ratio is the thermodynamic equilibrium ratio for 92/93 and that a tin-coordinated zwitterion was again present as an intermediate, Scheme 2.8.

Scheme 2.8 Tin(IV)chloride catalyzed isomerization of nitronic ester 92

\[ \text{Tin(IV) catalyzed reaction of } \beta\text{-nitrostyrene with 3-methyl-1,3-pentadiene (E/Z, 7:3) added at controlled rate in toluene} \]

Reaction was repeated in toluene following the procedure for slow addition of diene using a syringe pump. Use of a syringe pump did not improve results for reaction in toluene. Mostly trans-β-nitrostyrene remains at the end of the reaction along with a considerable amount of diene polymer.
Ternary adduct formation

In the toluene experiments, 15% by weight of crude products consisted of two isomeric side products 98a and 98b (85 : 15 ratio, respectively) with a very distinct $^1$H NMR spectrum. Both side products were formed regardless if pure E-diene or an E/Z mixture was used. This material was not observed in experiments run in dichloromethane solution. The material was analyzed by mass spectroscopy and the results show a molecular ion M/Z of 323. This molecular mass corresponds to a combination of $\beta$-nitrostyrene, diene, and toluene. The IR revealed the presence of a nitro group. Elemental analysis of the 98a-b mixture agreed with an empirical formula of C$_{21}$H$_{25}$NO$_2$. From the spectrum, structure 98 was assigned, consisting of a major alkene isomer 98a and minor isomer 98b. The assignment of E configuration to the major isomer 98a is based on the high field (13 $\delta$) chemical shift of the C$_3$ methyl substituent. Whether threo or erythro material was obtained is not known.

![98a, E isomer](image)

It was at first thought that one of the nitronic esters 94 – 97 reacted with toluene and SnCl$_4$ to form the ternary adducts 98a-b. Only trace amounts of those particular nitronic esters formed in the toluene experiment, but considerably more in the experiment
run in dichloromethane. To explore the possibility of the minor nitronic esters reacting with toluene to form the ternary adducts 98a-b, nitronic esters 92-97 were subjected to toluene and SnCl₄ under the same conditions as the original reaction with toluene. However, the ternary adduct did not form in any case. The 6 nitronic esters were then subjected to SnCl₄ in toluene at ambient temperature for 20 minutes and ternary adduct did not form under these conditions. This study was done at two different temperatures: 20°C and -78°C. The only difference that was observed was a change in ratio for nitronic esters 92 and 93 that occurred at 20°C indicating equilibration. The 92/93 ratio changed from 13:87 to 60:40 after 20 min. Based on these results, the ternary adducts 98a-b do not form by insertion of toluene into any of the nitronic esters 92-97.

Another consideration was made regarding ternary adduct formation. There are 8 possible nitronic esters that could form from the reaction of trans-β-nitrostyrene and E/Z 3-methyl-1,3-pentadiene. Out of the 8 possibilities, only 6 nitronic esters were observed and these were isolated and characterized. Two nitronic esters derived from reaction on the less substituted double bond of the Z-diene were absent. It is possible that one or both of these nitronic esters form the ternary adduct in the presence of toluene and SnCl₄. However the total absence of these isomers in the dichloromethane experiment makes it unlikely that they would form and react further in the toluene experiments.

The following experiment was done to determine if there was any material present in the dichloromethane experiment that might react with toluene to give the ternary adduct. Reaction was carried out in dichloromethane according to the procedure without syringe pump and the crude product was subjected to toluene and SnCl₄ at ambient temperature. Compared to the ¹H NMR of the starting crude material, the following
changes were observed: ternary adduct 98a formed, and the ratio of nitronic esters 92 and 93 was altered. Since the ternary adduct formed, some material that it arises from is present in the crude product. It was found that this material was present in the non-polar chromatography fraction from the dichloromethane experiment. This fraction was subjected to SnCl₄ and toluene for 20 minutes at room temperature, and it resulted in formation of ternary adduct 98a. However, the compound that reacts with toluene to give 98a-b was not isolated and characterized.

**Thermal rearrangement of nitronic esters**

Nitronic esters 92 and 93 underwent rearrangement to nitro compounds, but only upon heating in contrast to nitronic ester 85, which rearranged at ambient temperature. Nitronic ester 92 rearranged cleanly to nitro compound 100 after 2 hours at 90-97°C, Scheme 2.9. After chromatography 74% yield of 100 was obtained. Elevating the temperature to 105-110°C for 1 hour resulted in complete rearrangement of 92 and partial decomposition of product. After chromatography only 34% of 100 was obtained. Heating for 1 day at 65-70°C also resulted in conversion of 92 to 100, but the yield was low (30% yield).

Scheme 2.9 Thermal rearrangement of nitronic ester 92 to nitro compound 100
Table 2.1 Data for rearrangement of nitronic ester 92 to nitro compound 100

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (hr)</th>
<th>92 : 100</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90-97</td>
<td>1</td>
<td>50 : 50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>90-97</td>
<td>2</td>
<td>0 : 100</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>105-109</td>
<td>1</td>
<td>0 : 100</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>55-60</td>
<td>6</td>
<td>99 : 1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>65-70</td>
<td>24</td>
<td>1 : 99</td>
<td>30</td>
</tr>
</tbody>
</table>

Nitronic ester 93 was more difficult to rearrange cleanly because it rearranges to compound 101, which has phenyl and nitro groups in a cis orientation. Compound 101 can further isomerize to compound 102 where phenyl and nitro groups are in a more stable trans orientation, Scheme 2.10.

Scheme 2.10 Thermal rearrangement of nitronic ester 93 to nitro compound 101

The reaction was attempted at various temperatures to obtain clean rearrangement of 93 to 101, but formation of 102 was difficult to suppress. Thus, rearrangement of 93 occurred on heating at 128-130°C for 1 hour in DMF. Under these conditions, the ratio of 101 to 102 is 41:59, and a combined 39% yield is obtained. Shorter time at 130°C resulted in rearrangement of 93 to both nitro compounds 101 and 102, but in only 21%
combined yield. At lower temperature (77-80°C for 12 hours) 93 rearranged to nitro compound 101 but in only 15 % yield containing a trace (less then 1%) of 102. A considerable amount of side product was also formed under these conditions. The rearrangement was also attempted at 105-109°C. After 1 hour, only 101 was observed with 93 : 101 in a 70 : 30 ratio. Heating the reaction mixture for 3 hours at 103-109°C, however, resulted in 50% rearrangement and some isomerization to 102 (93/101/102, 50 : 49 : 01).

Table 2.2 Data for rearrangement of nitronic ester 93 to nitro compounds 101 and 102

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (hr)</th>
<th>93 : 101 : 102</th>
<th>101% yield, 102% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>1</td>
<td>99 : 1 : 0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>130</td>
<td>0.75</td>
<td>0 : 87 : 13</td>
<td>18%, 3%</td>
</tr>
<tr>
<td>3</td>
<td>124-130</td>
<td>1</td>
<td>0 : 59 : 41</td>
<td>23%, 16%</td>
</tr>
<tr>
<td>4</td>
<td>128-130</td>
<td>1</td>
<td>0 : 59 : 41</td>
<td>23%, 16%</td>
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<tr>
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<td>105-109</td>
<td>1</td>
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<td>20%, 0%</td>
</tr>
<tr>
<td>6</td>
<td>103-109</td>
<td>3</td>
<td>50 : 49 : 1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>77-80</td>
<td>12</td>
<td></td>
<td>0%, 15%</td>
</tr>
<tr>
<td>8</td>
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<td>22</td>
<td></td>
<td>0%, 14%</td>
</tr>
<tr>
<td>9</td>
<td>98-99</td>
<td>8</td>
<td>0 : 64 : 36</td>
<td></td>
</tr>
</tbody>
</table>

In a separate study, rearrangement of 93 was monitored by ¹H NMR over 60 minutes. Pure compound 93 is dissolved in DMF and heated at 128-130°C. An aliquot was taken from the reaction mixture every 15 minutes and analyzed by ¹H NMR. Initially, compound 93 rearranges to compound 101, and compound 101 subsequently isomerizes to compound 102 upon prolonged heating, Table 2.3. Heating pure nitro compound 101 also resulted in formation of the isomer 102 (Table 2.4, Scheme 2.11).
Table 2.3 Kinetic study of rearrangement of nitronic ester 93 to nitro compounds 101 and 102 at constant temperature (129°C)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>93:101:102</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100:00:00</td>
</tr>
<tr>
<td>15</td>
<td>53:47:00</td>
</tr>
<tr>
<td>30</td>
<td>25:55:20</td>
</tr>
<tr>
<td>45</td>
<td>14:61:25</td>
</tr>
<tr>
<td>60</td>
<td>10:58:32</td>
</tr>
</tbody>
</table>

Scheme 2.11 Thermal isomerization of nitro compound 101 to nitro compound 102

Table 2.4 shows various conditions that were used to isomerize cis-nitro 101 to trans-nitro 102. The best conditions for complete isomerization are 125-130°C for 6 hours. These results clearly indicate that 93 rearranges only to nitro compound 101 which, however, at similar temperature further rearranges to nitro compound 102.

Table 2.4 Data for thermal isomerization of nitro compound 101 to nitro compound 102

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (hr)</th>
<th>101 : 102</th>
<th>% material balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>125-129</td>
<td>1</td>
<td>75 : 25</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>140-145</td>
<td>1</td>
<td>63 : 37</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>122-128</td>
<td>3</td>
<td>15 : 85</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>126-128</td>
<td>9</td>
<td>0 : 100</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>125-130</td>
<td>6</td>
<td>0 : 100</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>124-128</td>
<td>5</td>
<td>28 : 72</td>
<td>50</td>
</tr>
</tbody>
</table>
Rearrangement of a mixture of nitronic esters 94 and 95 was attempted at various temperatures, Table 2.5. In entries 1 through 4, starting material was recovered. Up to 74°C compounds 94 and 95 appear stable, the loss in recovered material being due to mechanical losses. In entries 5 and 6, the starting material was recovered along with a small amount of an unknown material. The IR analysis of the crude product does not show nitro signals. In entry 7, $^1$H NMR analysis of the crude product showed that the starting material is completely consumed and multiple products are formed based on the many new peaks present in the spectrum. The IR analysis of the crude product does not show evidence of a nitro group. Thin layer chromatography of the crude product shows multiple spots with a much lower $R_f$ value than typically seen for a nitro compound. The new compounds that formed in these reactions are most likely hydrolyzed nitronic esters.

Table 2.5 Data for thermal rearrangement of nitronic esters 94 and 95

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>% material balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>83</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>95</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>95-99</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>210</td>
<td>95-97</td>
<td>61</td>
</tr>
</tbody>
</table>

Nitronic ester 96 was heated at 68-70°C for 2 hours and 40% of the starting material was recovered. Heating 96 at 90-94°C for 1 hour gave a 20% recovery of organic material. The $^1$H NMR spectrum shows that compound 96 is the major
component of this material but additional peaks indicate some product formation. The IR analysis of the crude product does not show signals attributable to a nitro compound. It is concluded that nitronic ester 96 does not rearrange to a nitro compound under these conditions.

A mixture of compounds 94, 95, and 97 (94/95/97 34:46:20) was heated for 5 minutes at 150°C, and 20% of the organic material was recovered. The $^1$H NMR spectrum shows that all three compounds were consumed and multiple products were formed based on the many unassigned peaks present. The IR spectrum shows no evidence of a nitro group in the products. Thus, no evidence indicating rearrangement of nitronic ester 97 to a nitro compound was observed.

Rearrangement of nitronic esters 94 - 97 does not occur under thermal conditions. Instead, decomposition occurs without formation of identifiable products. Whereas nitronic esters 92 and 93 both undergo rearrangement in the temperature range of 70-110 °C, none of nitronic esters 94-97 gave any identifiable rearrangement products under similar or more vigorous conditions. It is concluded that rearrangement is more difficult for nitronic esters 94-97 than for 92-93.

Substituent effects on the Claisen rearrangement of allyl vinyl ethers have been extensively studied. It is known that a methyl substituent at C$_6$ accelerates rearrangement (Fig 2.3). Nitronic esters 92 and 93, but not 94-97, have a methyl substituent at the corresponding C$_6$ position. Sterically this substituent should slow rearrangement, but like the Claisen rearrangement may actually be accelerating rearrangement. This, then, can explain the faster rate of rearrangement of 92 and 93 compared to 94-97. Substituent effects on the allyl nitronic ester rearrangement do not always parallel the Claisen
rearrangement, however. For example, an electron attracting substituent at C₁ of allyl vinyl ethers slows rearrangement whereas the opposite appears to be true with the O-allyl nitronic ester rearrangement. Low-temperature rearrangement has been observed for nitronic esters possessing either a phenylsulfonyl group or a benzoyl group at C1.

Catalytic rearrangement of nitronic ester 97 to nitro compound 104 was observed in the presence of SnCl₄ (discussed earlier). However, the mechanism of this reaction may involve a zwitterionic intermediate rather than a concerted [3,3]-sigmatropic rearrangement.

It is noteworthy that nitronic ester 85 undergoes rearrangement at 20 °C whereas nitronic ester 92 requires 70 °C. The structures of these nitronic esters are similar with the most notable difference being the lack of a methyl group at C₄ of the conjugated system in 92. It seems that substituent effects are important in determining the threshold temperature needed for the O-allyl nitronic ester rearrangement.
Thermal Diels-Alder reaction of β-nitrostyrene and 3-methyl-1,3-pentadiene

Heating trans-β-nitrostyrene and E-3-methyl-1,3-pentadiene at 170°C for 5 hours afforded cycloadducts 100 - 104 and two additional unidentified compounds in a 40 : 16 : 24 : 12 : 8 : trace ratio, respectively (Scheme 2.12). After chromatography a 62% yield of a mixture of nitro compounds and material with similar mobility was obtained.

Scheme 2.12 Thermal Diels-Alder reaction of β-nitrostyrene and E-3-methyl-1,3-pentadiene
Nitro compounds 100, 102, and 104 were readily assigned as components of the mixture. Structure assignment for compound 103 was more tentative since it is a new product. As expected, nitro compound 101 did not form because cis-β-nitrostyrene is required as starting material in order to form compound 101 through the traditional DA reaction. A combination of $^{1}$H NMR and homonuclear decoupling spectra was used to deduce the structure. A multiplet at $\delta$ 5.25 is assigned to H$_4$ of compound 103. The presence of three coupling constants for H$_4$ is consistent with the regiochemical assignment. The proton H$_5$ exhibits a doublet of doublets. From coupling constants, H$_5$ is trans to proton H$_4$ and cis to proton H$_6$. The large H$_4$,$_5$ coupling constant ($J = 11.7$ Hz) and small H$_5$,$_6$ coupling constant ($J = 4.9$ Hz) in 103 are consistent with the stereochemical assignment.

Two additional products are present, but the structures could not be assigned readily. Likely these additional products are cycloadducts of Z-3-methyl-1,3-pentadiene which is formed in situ during reaction. 

Trans-β-nitrostyrene was completely consumed during the reaction and excess diene consisted of both Z and E isomers. A mixture of E and Z diene (68 : 32 ratio, respectively) was recovered by micro distillation of the crude product. The $^{1}$H NMR spectrum of the distillate showed clearly that both E and Z isomers are present, although only E isomer was used as starting material. Analysis of the starting material, pure E-diene (SampCo), does not show the presence of the Z-diene. The only source of Z-diene is from isomerization of the E-diene under the reaction conditions, a very strange result for a typical Diels-Alder reaction.
It has been reported by Wolinsky et al that a 1,3-diene may undergo a 1,5-hydride shift that results in rearrangement. However, such a rearrangement is unlikely to occur in E-3-methyl-1,3-pentadiene owing to geometric constraints, Scheme 2.13. When pure E-3-methyl-1,3-pentadiene was heated at 170°C for 6 hours to determine if thermal isomerization occurs, as expected, none of the Z-isomer formed. The 1H NMR spectrum of crude diene showed only E-isomer present. The Z-diene was not present even in trace quantities. These results eliminate the possibility of simple thermal E-diene isomerization. Thus, in the absence of trans-β-nitrostyrene, no isomerization takes place. Based on this consideration, two possible pathways were considered. Perhaps cycloaddition is not a concerted process and isomerization of E-diene takes place in a singly bonded sigma-complex zwitterion intermediate that reverts to starting material subsequent to rotation. Alternatively, β-nitrostyrene isomerizes the E-diene through interaction perhaps as a π-complex. In a separate experiment, E-diene was heated with nitroethane at 130°C for 5 hours. Only E-diene and nitroethane were recovered, and no Z-diene was formed ruling out a simple polar solvent effect.
Isomerization of a triene in a DA reaction has been previously reported by von Gustorf et al, Scheme 2.14.\textsuperscript{5}

Scheme 2.14 Isomerization of $E$-triene in the presence of maleic anhydride\textsuperscript{5}

Heating pure $E$-triene $\text{107a}$ with maleic anhydride afforded both adducts $\text{108}$ and $\text{109}$. Adduct $\text{108}$ is expected to form, but adduct $\text{109}$ is expected to form only from the $Z$-triene $\text{107b}$. The authors also noted that maleic anhydride cycloaddition of $\text{107a}$ occurs several magnitudes faster than cycloaddition to the isomeric triene $\text{107b}$. We made similar observations regarding diene reactivity in our experiments. According to the authors, isomerization of the triene occurs because the triene and dienophile first form a $\pi$-complex and then a sigma complex. They attribute triene isomerization as a result of
the sigma complex. However, it seems possible that isomerization might occur for the pi-complex in which the C,C pi-bond has been weakened. Formation of the π-complex is a reversible process. If rotation around the weakened C, C pi-bond occurs prior to pi-complex dissociation, the Z-triene isomer will result. Thus, Scheme 2.15 is proposed as one possibility for isomerization of \textit{E}-3-methyl-1,3-pentadiene in the presence of β-nitrostyrene.

Scheme 2.15 Proposed isomerization mechanism of \textit{E}-3-methyl-1,3-pentadiene in the presence of β-nitrostyrene

The thermal DA reaction was repeated using the \textit{E/Z} (73:27) diene mixture with \textit{trans}-β-nitrostyrene in a 2:1 ratio, following the same procedure. The total time for this reaction was 7.5 hours. The reaction was monitored by \textsuperscript{1}H NMR, and after 1 hour at 165°C the mixture contained mostly the starting materials although some products were
present. The diene $E/Z$ isomer ratio was lower (64:36) at this time. After 7.5 hours of heating all of $\text{trans-}\beta$-nitrostyrene is consumed (diene $E/Z$ ratio is 61:39). The $^1\text{H NMR}$ spectrum shows that four major products are present, and they match the products formed from the reaction where pure $E$ diene was used. Four of the products are 100, 102, 103, and 104, the other products are additional cycloadducts, (Scheme 2.9). The reaction afforded 40% combined yield of cycloadducts obtained as a chromatographically inseparable mixture.

The Z-isomer of 3-methyl-1,3-pentadiene does not readily undergo DA reaction apparently because it has a very low percentage of the necessary s-cis conformation. Steric interaction of the hydrogen on C1 and methyl group on C4 strongly disfavors the s-cis conformation, Scheme 2.16. As a result, the heavy predominance of the s-trans conformation disallows a rapid DA cycloaddition. In competition with the $E$-isomer the Z-isomer is strongly disadvantaged. Literature results are supportive of this prediction.

Scheme 2.16 s-Trans and s-cis conformations of Z-3-methyl-1,3-pentadiene

\[
\begin{align*}
\text{s-trans} & \quad \text{s-cis} \\
\begin{array}{c}
\text{H}_3\text{C} \\
\begin{array}{c}
\begin{array}{c}
\text{4} \quad \vdash \quad \text{4} \\
\text{CH}_3
\end{array}
\end{array}
\end{array}
\end{align*}
\]

For example, $E$-1,3-pentadiene is $10^3$ times more reactive than 4-methyl-1,3-pentadiene toward tetracyanoethylene. Like Z-3-methyl-1,3-pentadiene, 4-methyl-1,3-pentadiene has interaction of the H-atom on C1 and the methyl group on C4 in the s-cis
conformation, Scheme 2.17. Conversely, neither 1,3-pentadiene nor \(E\)-3-methyl-1,3-pentadiene have this interaction disfavoring the \(s\text{-}cis\) conformation.

Scheme 2.17 \(s\text{-}Cis\) and \(s\text{-}trans\) conformations of 4-methyl-1,3-pentadiene

\[
\begin{align*}
\text{s-cis} & \quad \overset{\text{cis}}{\longrightarrow} \quad \text{s-trans} \\
\end{align*}
\]

4-methyl-1,3-pentadiene
2.3 Structure Assignments

All compounds were characterized using the typical spectral methods: IR, \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR, DEPT, and MS unless otherwise noted. Stereochemical assignments for 92 and 93 were based on the stereochemistry of their rearrangement products.

Compound 92 is a nitronic ester based on spectroscopic data. The IR spectrum shows a 1614 cm\(^{-1}\) band characteristic of C=N stretch. From the literature, a series of 6-membered cyclic nitronic esters exhibited C=N stretch at 1593 cm\(^{-1}\) – 1625 cm\(^{-1}\). Mass spectroscopy confirms the molecular mass of 231 g/mol. The elemental analysis confirms the C\(_{14}\)H\(_{17}\)N\(_2\) empirical formula and sample purity. The \(^1\text{H}\) NMR spectrum confirms 11 chemically non-equivalent hydrogen atoms and a total of 17 hydrogen atoms. The nitronic proton signal H\(_3\) is assigned to a doublet at 6.38 \(\delta\). The \(^{13}\text{C}\) NMR shows 12 signals indicating 12 chemically non-equivalent C atoms. Two signals for aryl carbon atoms encompass a total of 4 carbon atoms, two \textit{meta} and two \textit{ortho} to point of attachment. The signal at 86.37 \(\delta\) confirms a C-O carbon atom. The nitronic C=N \(^{13}\text{C}\) NMR signal occurs in the same region as alkene and aromatic carbon atoms. It is assigned as 127.81 \(\delta\). In the region from 113 to 139 \(\delta\) there are 6 other signals, consistent with the assigned structure: 2 alkene and 4 aromatic. The DEPT analysis further confirmed the proposed molecular structure of compound 92. The stereochemistry of compound 92 was deduced based on the stereochemistry of its rearrangement product 100. In compound 100 phenyl and nitro groups are assigned \textit{trans} to each other based on the large coupling constant for the associated hydrogen atoms. Because of the concerted reaction pathway, nitronic ester 92 must have the phenyl and \(-\text{C(CH}_3)\)=CH\(_2\) groups \textit{cis}
to each other in order to afford 100 having a trans relationship for the phenyl and nitro

groups.

Compound 100 is a nitro substituted cyclohexene derivative. The IR spectrum
shows bands at 1553 cm\(^{-1}\) and 1375 cm\(^{-1}\), consistent with the asymmetric and symmetric
frequencies of a nitro group. Mass spectroscopy confirms the molecular weight of 231
g/mol. Elemental analysis confirms the empirical formula C\(_{14}\)H\(_{17}\)NO\(_{2}\) and sample purity.
The \(^1\)H NMR spectrum exhibits 11 signals, which is consistent with the proposed
molecular structure. Multiple 1D homonuclear decoupling experiments were used to
assign the \(^1\)H NMR signals. The H\(_5\) signal occurs as a doublet of doublets at 5.14 \(\delta\) with
\(J=5.8\) Hz and 12.2 Hz. The smaller coupling constant is assigned to J\(_{5,6}\) and indicates that
H\(_5\) is cis to H\(_6\). The large anti coupling constant is assigned to J\(_{4,5}\) and indicates that H\(_4\) is
trans to H\(_5\). This requires that nitro and phenyl must be trans. The chemical shift of
proton H\(_5\) is consistent with a proton attached to a nitro bearing carbon atom. The \(^{13}\)C
NMR spectrum exhibits 12 signals, which is also consistent with the proposed structure.
The signal at 90.18 \(\delta\) is assigned to the C-NO\(_2\) carbon atom.

The spectroscopic data for compound 93 confirms that it is a nitronic ester. The
IR spectrum shows a band at 1615 cm\(^{-1}\), which is characteristic of the C=\(\equiv\)N stretching
frequency of a 6-membered cyclic nitronic ester. Mass spectroscopy confirms the
molecular weight of 231 g/mol. The \(^1\)H NMR spectrum exhibits 11 signals, which is
consistent with the proposed structure. The signal attributed to the nitronic proton H\(_3\)
occurs as a doublet at \(\delta\) 6.48. The \(^{13}\)C NMR spectrum consists of 12 signals, which is also
in agreement with the assigned structure. Two signals for aryl carbon atoms encompass 4
carbon atoms, two meta and two ortho to point of attachment. The nitronic C=\(\equiv\)N \(^{13}\)C
NMR signal occurs in the same region as aromatic and alkene carbon atoms. It is assigned to δ 127.59. In the region from 112 to 141 δ there are 6 other signals, consistent with the assigned structure: 2 alkene and 4 aromatic. The stereochemistry of compound 93 was assigned based on the stereochemistry of its rearrangement product 101. In compound 101 the phenyl and nitro groups are assigned cis to each other based on the coupling constants for the associated hydrogen atoms. Because of the concerted reaction pathway, the nitronic ester must have -C(CH₃)=CHCH₃ and phenyl groups trans to each other in order to produce the cis stereochemistry in compound 101.

Compound 101 is a nitro substituted cyclohexene derivative. The IR spectrum shows two bands at 1553 cm⁻¹ and 1371 cm⁻¹, characteristic of nitro compounds. Mass spectroscopy confirms the molecular weight of 231 g/mol. The ¹H NMR spectrum shows 11 signals, consistent with the proposed structure. Multiple 1D homonuclear decoupling experiments were used to assign signals and coupling constants were used to deduce the stereochemistry. The signal assigned to H₅ is a doublet of doublets at 4.99 δ with J₅,₆ =3.4 Hz and J₅,₄ =5.37 Hz. The two small coupling constants indicate that both protons H₄ and H₆ are cis to proton H₅. Thus, the phenyl and nitro groups must also be cis to each other. The chemical shift of proton H₅ is consistent with protons bonded to a carbon atom bearing a nitro group. The ¹³C NMR spectrum shows 12 chemically non-equivalent carbon atoms, which is consistent with the proposed molecular structure. Two signals for aryl carbon atoms encompass 4 carbon atoms, two ortho and two para to the point of attachment. The signal at 92.93 δ is assigned to the C-NO₂ carbon atom.
Nitronic esters 92 and 93 have the same regiochemistry. The regiochemistry was deduced based on 1D homonuclear decoupling experiments. The structure of these two compounds differs only in the orientation of the phenyl and substituted alkene groups. There are no reported stereochemical assignments for related nitronic esters. For compounds 92 and 93 stereochemistry was deduced based on rearrangement products derived from them. The rearrangement products are substituted cyclohexenes and coupling constants are definitive for their stereochemical assignment. Using appropriate coupling constants the structures for these compounds were easily determined.

Stereochemical assignment of alkene methyl substituents must be made besides the stereochemical assignment for substituents on the nitronic ester ring. Stereochemical assignment of the methyl groups is deduced based on their $^{13}$C chemical shifts and the difference in their chemical shifts. For compound 92 signals assigned to methyl groups are at $\delta$ 13.26 and 11.81. The chemical shift difference is 1.45 ppm. For compound 93 methyl signals occur at $\delta$ 13.19 and 11.99, and the difference is 1.2 ppm. The methyl groups for both compounds have very similar chemical shifts, which indicate that the molecules have similar stereochemistry. To determine whether the two methyl groups are cis or trans to each other, further examination of their chemical shifts is necessary. For trisubstituted ethylenes $^1$H NMR is not typically useful because the difference in signals for $E$ and $Z$ dienes is very small. Conversely, $^{13}$C NMR chemical shifts permit the assignment of stereochemistry of substituent groups. The $^{13}$C signals are sufficiently spread out to distinguish between the $E$ and $Z$ isomers. When the two methyl groups are cis oriented, the difference in $^{13}$C chemical shifts is relatively small whereas the difference is greater when the methyls are trans. This was deduced based on information
obtained from the literature for other trisubstituted alkenes. Chemical shifts of spatially crowded carbon atoms are at higher field than in carbon atoms that are less crowded. Here are three examples that show two vicinal alkenyl methyl groups and how the difference in carbon shifts depends on the stereochemistry of the molecule. In Z-3-methyl-2-hexene the two methyl groups are trans to each other and the chemical shifts are 13.81 δ and 23.89 δ (the difference is 10.08 ppm). In E-3-methyl-2-hexene, the two methyl groups are cis to each other and the methyl chemical shifts are 13.81 δ and 16.11 δ, the difference being only 2.3 ppm. In Z-3,4-dimethyl-2-hexene the two methyl groups are trans to each other and their carbon chemical shifts are 12.78 δ and 17.86 δ, (difference is 5.08 ppm). In the E isomer the methyl groups are cis to each other and their carbon shifts are at 13.17 δ and 12.11 δ, (difference is 1.06 ppm). In Z-3,4-dimethyl-2-pentene, the two methyl groups are trans to each other and their methyl carbon shifts are at 13.43 δ and 17.82 δ, (difference is 4.39 ppm). In the E isomer, the methyl groups are cis to each other and their carbon chemical shifts are at 12.97 δ and 13.13 δ, (difference is 0.16 ppm). Based on these three examples: the difference in chemical shifts when methyl groups are trans to each other ranges from 4.39 to 10.08 ppm. When methyl groups are cis to each other the difference ranges from 0.16 to 2.3 ppm. The differences in methyl carbon chemical shifts for compounds 92 and 93 are 1.20 ppm and 1.45 ppm, which lie in the range of typical cis compounds.

Nitronic esters 94, 95, 96, and 97 have similar regiochemistry. These compounds result from cycloaddition at the more substituted double bond of the diene. The vinyl group occurs as an off-ring substituent and the vinyl pattern is prominent in the 1H NMR spectra of all four compounds. Compounds 94 and 95 are isomers, which were only
partially separated. Compound 95 did not form in the experiments utilizing dichloromethane as solvent, so compound 94 was easily obtained pure after chromatography. All of the analytical data for compound 95 were obtained on a 94/95 mixture. Based on spectroscopic data both pure 94 and the mixture 94/95 consist of nitronic esters. The IR spectrum of the mixture shows a band at 1620 cm⁻¹, which confirms the presence of a C=N stretch characteristic of nitronic esters. The mass spectra of the mixture and pure 94 confirm the molecular mass of 231 g/mol. Multiple 1D homonuclear decoupling experiments were used to make signal assignments and to differentiate the spectra of the two compounds. Two sets of peaks are clearly present in the mixture, and each set contains 11 chemically non-equivalent hydrogen atoms as expected. The nitronate proton H3 is present in both compounds: a doublet at 6.42 δ for compound 94, and a doublet at 6.26 δ for compound 95. The ¹H NMR signal integration confirms that 17 hydrogen atoms are present in each compound. The ¹³C NMR spectrum of the mixture shows 24 signals, 12 signals per compound. There are 14 carbon atoms in each of the compounds, but only 12 chemically non-equivalent C-atoms per compound.

The ¹³C NMR of pure compound 94 shows 12 signals as expected. The signal for the C-O carbon is at 86.98 δ for compound 94 and 87.73 δ for compound 95. The nitronic carbon atom (C₃) for compound 94 is assigned to 113.01 δ and for compound 95 it is assigned to 114.88 δ.

Compound 96 is a nitronic ester. The IR spectrum shows a band at 1615 cm⁻¹, which is characteristic of a 6-membered cyclic nitronic ester C=N stretch. Mass spectroscopy confirms a molecular weight of 231 g/mol. The ¹H NMR spectrum shows 11 signals, and peak integration confirms a total of 17 hydrogen atoms are present. The
characteristic nitronic proton (H₃) is present as a doublet at 6.53 δ. The ¹³C NMR spectrum confirms 12 chemically non-equivalent carbon atoms. The signal at 86.38 δ is characteristic of a C-O carbon atom. The signal for nitronic carbon atom C₃ occurs at 113.36 δ and is in the same region as aromatic and alkene signals. There are 6 additional carbon atom signals in this region: 2 alkene and 4 aromatic, which is consistent with the proposed structure.

Compound 97 is a nitronic ester. The IR spectrum shows a C=N stretch at 1619 cm⁻¹, which is characteristic of a 6-membered cyclic nitronic ester. The ¹H NMR spectrum shows 11 signals, and signal integration confirms there are 17 hydrogen atoms present in the compound. The nitronic proton (H₃) occurs as a doublet at 6.36 δ. The ¹³C NMR spectrum shows 12 signals, consistent with 12 non-equivalent C-atoms. The signal at 87.3 δ is characteristic of a C-O carbon atom (C₆). The ¹³C signal for nitronic carbon atom (C₃) occurs in the same region as alkene and aromatic carbon atoms. It is assigned to 114.09 δ. There are 6 other carbon atom signals in this region: 2 alkene and 4 aromatic, which is consistent with the proposed structure.

Compound 102 is a nitro substituted cyclohexene derivative. The IR spectrum shows bands at 1553 cm⁻¹ and 1371 cm⁻¹, which confirm the presence of a nitro group. Mass spectroscopy confirmed a molecular mass of 231 g/mol. The ¹H NMR spectrum shows 11 signals and signal integration shows that 17 hydrogen atoms are present. This is consistent with the proposed structure. The ¹H NMR signal for H₅, which is bonded to the carbon atom bearing a nitro group, is at 4.63 δ. The regiochemistry of the compound is deduced using homonuclear decoupling and the stereochemistry is determined from coupling constants for H₄, H₅, and H₆. The signal for proton H₅ is a doublet of doublets
with $J=11.7$ Hz and 9.8 Hz. Both coupling constants are large, which indicates that H$_5$ is \textit{trans} to both H$_4$ and H$_6$. The $^{13}$C NMR spectrum shows 12 signals, which is consistent with the assigned structure containing 12 chemically non-equivalent C-atoms. The signal at 96.12 $\delta$ confirms the nitro-substituted carbon atom (C$_3$).

Compound 104 is a nitro substituted cyclohexene derivative. The IR spectrum shows bands at 1548 cm$^{-1}$ and 1372 cm$^{-1}$, which confirm the presence of a nitro group. Mass spectroscopy confirmed a molecular mass of 231 g/mol. The $^1$H NMR spectrum shows eight signals and signal integration shows that 17 hydrogen atoms are present. The $^1$H NMR signal for H$_4$, which is bonded to the carbon atom bearing a nitro group, is at 4.94 $\delta$. The regiochemistry of the compound is deduced using homonuclear decoupling and the stereochemistry is determined from coupling constants for H$_4$, H$_5$, and H$_6$. The presence of coupling to three adjacent protons for proton H$_4$ is consistent with the regiochemistry assignment. The signal for H$_5$ is a doublet of doublets with $J=11.7$ Hz and 10.3 Hz. Both coupling constants are large, which indicates that H$_5$ is \textit{trans} to both H$_4$ and H$_6$. The $^{13}$C NMR and elemental analysis were not obtained for this compound because of insufficient sample.

Compounds 98a-b are nitro substituted alkene isomers. The IR spectrum shows bands at 1553 cm$^{-1}$ and 1371 cm$^{-1}$, which confirm the presence of a nitro group. Multiple 1D homonuclear decoupling experiments were done to deduce the regiochemistry assignment. The $^1$H NMR spectrum shows 13 different hydrogen atoms, and signal integration shows that 25 hydrogen atoms are present. The $^{13}$C NMR spectrum of the mixture exhibits signals at $\delta$ 75.05 and 78.94, which confirm the nitro-substituted carbon
atoms. Mass spectroscopy confirms a molecular mass of 323 g/mol, and elemental
analysis confirmed molecular formula C_{21}H_{25}NO_2 and sample purity.
2.4 Experimental

3-Methyl-1,3-pentadiene (7 : 3, E/Z) was purchased from SigmaAldrich and used as received. 3-Methyl-1,3-pentadiene (99.7 : 0.03, E/Z) was purchased from SampCo and used as received.

_Synthesis of nitronic esters 92 – 97 and ternary adducts 98a-b_

_Addition of SnCl₄ to a toluene solution of β-nitrostyrene and E/Z-3-methyl-1,3-pentadiene_

_Trans-β-nitrostyrene (0.002 mol, 0.298 g), 3-methyl-1,3-pentadiene (Z/E, 3:7 mixture, 0.004 mol, 0.328 g) and 20 mL of toluene were placed in a 3-neck round-bottom flask, under N₂ with stirring. The flask was cooled in an acetone/dry ice bath. After the flask contents reached a temperature of −78°C, SnCl₄ (0.002 mol, 0.521 g, 0.23 mL) was added dropwise over 5 minutes using a syringe. The reaction was stirred for 75 minutes in the cold. The reaction mixture was diluted with 10 mL ethyl acetate, keeping the internal temperature below −50°C. A 5 mL portion of saturated aqueous sodium bicarbonate solution was added dropwise, the temperature remaining below −50°C. The mixture was allowed to warm up by placing the reaction flask in a room temperature water bath. The mixture was transferred to a separatory funnel and was extracted with ethyl acetate (five 10 mL portions). The combined organic layer was washed with saturated aqueous sodium bicarbonate (five 15 mL portions) and saturated sodium chloride (five 10 mL portions). The organic layer was dried with MgSO₄ and_
concentrated under reduced pressure. The crude product (0.7818 g) was chromatographed on silica gel with elution using a hexanes/ethyl acetate step gradient (from 95:5 to 0:100, respectively). Thirty fractions (30 mL, 95:5) were eluted, followed by 20 fractions (30 mL, 80:20), followed by 52 fractions (30 mL, 70:30), and a final 7 fractions (30 mL, 0:100). The first thirteen fractions that were collected contain mostly hydrocarbon with some ternary adduct (<1%) (0.1893 g). Fractions 14-26 contained 0.0788 g (12% yield) of pure ternary adducts 98 a-b (66:34 ratio). Fractions 27-69 contained several unidentified materials (0.0768 g). Fractions 70-76 contain compounds 94 and 95 (0.0182 g) in a 30:70 ratio. Fractions 77-84 contained pure compound 93 (0.0870 g). Fractions 85-93 contained compounds 92, 93, and 96 in a 90:5:5 ratio, respectively (0.0832 g). Fractions 94-98 also contained compounds 92, 93, and 96, where compound 92 is the major product and compounds 93 and 96 were present in only trace quantities (<1%) (0.0166 g). Fractions 99-105 contain compounds 92 and 97 in a 50:50 ratio (0.0072 g). Fractions 106-111 contain compound 97 (>98%), along with compound 92 (<1%) and unidentified material (<1%) (0.0218 g). Analysis of the chromatography fractions indicates that 0.2171 g (47% combined yield of nitronic esters were present consisting of 92, 93, 94, 95, 96, and 97 in a 43:42:2:6:2:5 ratio, respectively.

92 (4S,6S)-6-[2E]-but-2-en-2-yl]-4-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide
Another crude mixture of nitronic esters 92, 93, 94, 95, 96, and 97 was prepared in similar fashion to the mixture reported on the preceding page. It was chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 95:5 to 0:100). Fractions 36 to 84 contain nitronic esters (0.2117 g). The nitronic ester mixture was further chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 70:30 to 0:100). Fractions 53 to 69 contain compounds 92 and 96 (0.0837 g). This mixture was further chromatographed on silica gel using dichloromethane/ethyl acetate (90:10) as eluent to obtain 92 as the less mobile fraction. The analytical sample of nitronic ester 92 was recrystallized from ethyl acetate. Rf = 0.27 (70:30 hexanes/ethyl acetate). It is a white solid: m.p. 80-80.2°C; IR (ATR) 1614 cm⁻¹ (C=N stretch); ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.20 (m, 5H, H₁₁-₁₄), 6.38 (d, 1H, H₃, J = 2.4 Hz), 5.70 (q, 1H, H₈, J = 6.8 Hz), 4.86 (d, 1H, H₆, J = 11.2 Hz), 3.92 (m, 1H, H₄), 2.23 (m, 1H, H₃), 2.02 (m, 1H, H₃), 1.70 (s, 3H, H₁₀), 1.66 (d, 3H, H₉, J = 6.8 Hz); ¹³C NMR (74.5 MHz, CDCl₃) δ: 139.91 (C₁₁), 131.18 (C₇), 129.15 (C₁₂), 127.81 (C₃), 127.29 (C₁₃), 126.57 (C₁₄), 113.78 (C₈), 86.73 (C₆), 40.92 (C₄), 32.98 (C₅), 13.26 (C₁₀), 11.81 (C₉); MS (CI, CH₄ carrier) M+1 C₁₄H₁₈N₂O₂ found 232.1337, calculated 232.1338.

Elemental analysis results: found C, 72.45; H, 7.02; N, 6.09; calculated for C₁₄H₁₇N₂O₂: C, 72.72; H, 7.36; N, 6.06.
Nitronic ester 93 is an opaque viscous oil. Crystallization was attempted with various solvent systems, however crystalline material could not be obtained. 

\[
R_f = 0.34 \text{ (7:3 hexanes/ethyl acetate). Data for 93: IR (ATR) } 1615 \text{ cm}^{-1} \text{ (C=N stretch); } \]

\[
^1H \text{ NMR (500 MHz, CDC}_6\text{H}) \delta: 7.40-7.20 \text{ (m, 5H, H} \text{_{10-12})}, 6.48 \text{ (d, 1H, H}_3\text{, }J=4.4 \text{ Hz)}, 5.60 \text{ (q, 1H, H}_8\text{, }J=6.3 \text{ Hz)}, 4.72 \text{ (d, 1H, H}_6\text{, }J=9.8 \text{ Hz)}, 3.92 \text{ (m, 1H, H}_4\text{)}, 2.41 \text{ (m, 1H, H}_5\text{)}, 1.93 \text{ (m, 1H, H}_5\text{)}, 1.64 \text{ (s, 3H, H}_10\text{)}, 1.62 \text{ (d, 3H, H}_9\text{, }J=6.84 \text{ Hz)}; \]

\[
^{13}C \text{ NMR (74.5 MHz, CDC}_6\text{H)} \delta: 141.32 \text{ (C}_{11}), 130.84 \text{ (C}_7\text{)}, 129.08 \text{ (C}_{12}), 127.71 \text{ (C}_{13}), 127.59 \text{ (C}_3\text{)}, 125.73 \text{ (C}_{14}), 112.72 \text{ (C}_8\text{)}, 83.00 \text{ (C}_6\text{)}, 38.07 \text{ (C}_4\text{)}, 31.14 \text{ (C}_5\text{)}, 13.19 \text{ (C}_{10}), 11.99 \text{ (C}_9\text{)}; \]

\[
\text{MS (Cl, CH}_4\text{ carrier) } M^+1 \text{ C}_{14}H_{18}N_1O_2 \text{ found 232.1333, calculated 232.1338.} \]

94 \((4R,5R,6S)-6\text{-ethenyl-5,6-dimethyl-4-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide} \)
Analytical data for compound 94 are listed for a pure sample obtained in a later experiment.

95 (4R,5S,6S)-6-ethenyl-5,6-dimethyl-4-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide

Analytical data for compound 95 were obtained on a mixture of 94 and 95. The mixture was purified by preparatory TLC chromatography using benzene/ethyl acetate elution (9:1). Partial separation was obtained by splitting collection of the single band. The upper portion was enriched with 94 (75:25 94/95 ratio). The lower portion had about equal amounts of 94 and 95 (52:48). Data taken for the lower portion are as follows: viscous oil; IR (ATR) 1620 cm⁻¹ (C=N); ¹H NMR (500 MHz, CDCl₃) signals attributed to 95: δ 7.10-7.40 (m, 5H, H₁₁-₁₄), 6.26 (d, 1H, H₃, J = 2.9 Hz), 5.92-6.01 (dd, 1H, H₇a, J = 17.1 Hz, J = 11.2 Hz), 5.62 (d, 1H, H₈b, J = 17.1 Hz), 5.39 (d, 1H, H₈c, J = 11.2 Hz), 3.18 (m, 1H, H₄), 2.02 (m, 1H, H₅), 1.44 (s, 3H, H₉), 0.94 (d, 3H, H₁₀, J = 6.8 Hz); ¹³C (CDCl₃, 500 MHz) signals attributed to 95: δ 138.58 (C₁₁), 132.85 (C₇), 129.02 (C₁₂,₁₇), 128.44 (C₁₃), 127.98 (C₁₄), 117.34 (C₈), 112.91 (C₃), 87.73 (C₆), 46.34 (C₄), 41.37 (C₅), 24.79 (C₉), 12.76 (C₁₀); MS (CI, carrier gas CH₄) [M+1] C₁₄H₁₈N₂O₂ found 232.1330, calculated is 232.1338.
Compound 96 was also isolated from further chromatography of the mixture of 92 and 96 reported previously. Elution with dichloromethane/ethyl acetate (90:10) gave pure compound 96 as the more mobile fraction. $R_f = 0.71$ (hexanes/ethyl acetate 70:30).

Compound 96 is a viscous oil: IR (ATR) 1615 cm$^{-1}$ (C=N); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$: 7.20-7.40 (m, 5H, $H_{11-14}$), 6.53 (d, 1H, $H_3$, $J = 2.9$ Hz), 5.83 (dd, 1H, $H_{7a}$, $J = 11.2$ Hz, $J = 17.6$ Hz), 5.43 (d, 1H, $H_{8b}$, $J = 17.6$ Hz), 5.25 (d, 1H, $H_{8c}$, $J = 1$ Hz, $J = 11.2$ Hz), 4.18 (m, 1H, $H_4$), 2.05 (m, 1H, $H_5$), 1.65 (s, 3H, $H_9$), 0.70 (d, 3H, $H_{10}$, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$, 74.5 MHz) $\delta$: 138.046 (C$_{11}$), 137.526 (C$_7$), 128.790 (C, 128.650, 127.587, 114.917, 113.006, 86.388, 42.478, 36.771, 23.439, 11.571; MS (Cl, carrier CH$_4$) [M+1] C$_{14}$H$_{18}$N$_1$O$_2$ found 232.1340, calculated 232.1338.

$97$ (4$R$,5$S$,6$R$)-6-ethenyl-5,6-dimethyl-4-phenyl-5,6-dihydro-4$H$-1,2-oxazine 2-oxide
Compound 97 was further purified by iterative preparative TLC on silica gel using hexanes/ethyl acetate (70:30) as eluent. Compound 97 is a viscous liquid: IR (ATR) 1619 cm$^{-1}$ (C=Н); $^1$H NMR (CDCl$_3$, 500 MHz) δ: 7.20-7.40 (m, 5H, H$_{11-14}$), 6.36 (d, 1H, H$_3$, $J$ = 2.9 Hz), 5.87 (dd, 1H, H$_{7a}$, $J$ = 10.7 Hz, $J$ = 17.1 Hz), 5.47 (d, 1H, H$_{8b}$, $J$ = 17.6 Hz), 5.38 (d, 1H, H$_{8c}$, $J$ = 10.7 Hz), 3.32 (m, 1H, H$_4$), 2.01 (m, 1H, H$_5$), 1.56 (s, 3H, H$_9$), 0.88 (d, 3H, H$_{10}$, $J$ = 6.8 Hz); $^{13}$C NMR (500 MHz, CDCl$_3$) δ: 138.72 (C$_{11}$), 137.79 (C$_7$), 129.05 (C$_{12,12'}$), 128.45 (C$_{13,13'}$), 128.02 (C$_{14}$), 117.82 (C$_8$), 114.05 (C$_3$), 87.29 (C$_6$), 46.43 (C$_4$), 40.56 (C$_5$), 14.78 (C$_9$), 13.45 (C$_{10}$); MS (Cl, CH$_4$ carrier) C$_{14}$H$_{18}$N$_1$O$_2$ M+1 found 232.1331, calculated 232.1338.

98a-b 1-methyl-4-[(3E)-3-methyl-7-nitro-6-phenylhept-3-en-2-yl]benzene

Compound 98 occurs as a mixture of two isomers 98a and 98b. Compound 98a is the major isomer and is slightly more mobile than 98b. Further chromatography of the mixture on silica gel using hexanes/ethyl acetate (95:5) eluent was performed. Early chromatography fractions contain 98a : 98b in a 83:16 ratio followed by later fractions with a 70:30 ratio. The mixtures are a single spot on analytical TLC, $R_f$ = 0.77 (hexanes/ethyl acetate 95:5). The mixture was recrystallized from ethanol to afford a white solid. Both 98a and 98b are present in the recrystallized sample in a 81:19 ratio. Analytical data were obtained on this mixture. Data for 98a-b: mp 63.5-64°C; IR (ATR)
1553 cm\(^{-1}\) and 1371 cm\(^{-1}\) (NO\(_2\)); \(^1\)H NMR bands attributed to 98a (500 MHz, CDCl\(_3\)) \(\delta\): 7.3-7.1 (m, 5H, H\(_{12-15}\)), 6.96 (d, 2H, \(J=7.8\) Hz), 6.62 (d, 2H, \(J=8.3\) Hz), 5.18 (t, H\(_5\), 1H, \(J=7.8\) Hz), 4.73 (dd, H\(_1\), 1H, \(J=4.9\) Hz, \(J=12.2\) Hz), 4.60 (dd, H\(_1\), 1H, \(J=10.3\) Hz, \(J=12.2\) Hz), 3.54 (sextet, 1H, H\(_2\), \(J=4.9\) Hz), 3.18 (dd, H\(_6\), 1H, \(J=8.3\) Hz, \(J=16.1\) Hz), 3.08 (dd, H\(_6\), 1H, \(J=6.4\) Hz, \(J=6.8\) Hz, \(J=16.1\) Hz), 2.56 (m, 1H, H\(_3\)), 2.28 (s, 3H), 1.55 (s, 3H), 1.16 (d, 3H, H\(_6\), \(J=7.3\) Hz); \(^1\)H NMR bands attributed to 98b (500 MHz, CDCl\(_3\)) \(\delta\): 7.3-7.1 (m, 5H, H\(_{12-15}\)), 6.96 (d, 2H), 6.53 (d, 2H, \(J=7.3\) Hz), 5.12 (t, 1H, H\(_5\), \(J=5.7\) Hz), 4.60 (dd, 1H, H\(_1\), \(J=10.7\) Hz, \(J=12.7\) Hz), 2.06 (s, 3H), 1.17 (d, 3H, 6.8 Hz); \(^{13}\)C NMR 98a-b with underlined more intense bands attributed to 98a (74.5 MHz, CDCl\(_3\)) \(\delta\): 139.04, 138.80, 137.50, 137.11, 136.98, 135.90, 134.89, 129.67, 128.79, 128.43, 128.01, 127.86, 127.82, 127.15, 127.11, 125.77, 125.70, 125.11, 79.05, 78.94, 47.84, 46.15, 33.07, 31.31, 20.83, 19.17, 17.10, 16.98, 12.71, 12.68; MS (EI method): M C\(_{21}\)H\(_{25}\)NO\(_2\) found 323.1885, calculated 323.1863; M-1 C\(_{21}\)H\(_{24}\)NO\(_2\) found 322.1799, calculated 322.1807.

Elemental analysis was performed for the mixture. Calculated for C\(_{21}\)H\(_{25}\)NO\(_2\): C, 78.02 %; H, 7.74 %; N, 4.33 %. Found: C, 78.38 %; H, 7.85 %; N, 4.47 %.

Addition of SnCl\(_4\) to a toluene solution of \(\beta\)-nitrostyrene and E-3-methyl-1,3-pentadiene

The same procedure was repeated using pure E-3-methyl-1,3-pentadiene. The reaction afforded 0.3180 g of crude product which was chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 95:5 to 0:100). The first 11 fractions contained hydrocarbons (0.1044 g). Fractions 12-16 contain the ternary toluene adducts.
98a-b (0.0364 g, 6% yield). Fractions 17-59 contain unknown materials (0.0373 g).

Fractions 60-64 contain 93, 94, and 95 in a 11: 81 : 8 ratio (0.0054 g). Fractions 65-70 contain pure 93 (0.0463 g). Fraction 71 contains 92 and 93 in a 1:1 ratio (0.0054 g).

Fractions 72-79 contain 92, 93, and 96 in a 89:10:1 ratio (0.0636 g). Fractions 80-92 contain 92 and 94 in a 63:37 ratio (0.0223 g). After chromatography a 62 % yield of nitronic esters was obtained. The nitronic esters 92, 93, 94, 95, 96, and 97 were obtained in a ratio of 51 : 39 : 3 : 0.3 : 0.4 : 6, respectively. Notably, only traces of nitronic esters 95 and 96 were obtained compared to the experiment where Z-3-methyl-1,3-pentadiene was present as a reactant. Presumably, the traces of 95 and 96 that were formed result from the in situ formation of Z-3-methyl-1,3-pentadiene from the E-isomer.

**Addition of SnCl₄ to a dichloromethane solution of β-nitrostyrene and E/Z- 3-methyl-1,3-pentadiene**

The previous procedure was repeated using dichloromethane (4 mL), *trans*-β-nitrostyrene (0.001 mol, 0.149 g), 3-methyl-1,3-pentadiene (*E/Z*, 3:7 mixture, 0.002 mol, 0.164 g), and SnCl₄ (0.001 mol, 0.12 mL). The reaction afforded 0.2289 g of crude product, which was chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 90:10 to 0:100, respectively). The first seven fractions (30 mL, 90:10) were followed by thirty eight fractions (30 mL, 70:30), and then a final fraction (150 mL, 0:10). Fractions 1-3 contain hydrocarbons, β-nitrostyrene, and other unknown compounds (0.0556 g). Fractions 4-19 contain hydrocarbons (0.0476 g). Fractions 20-22 contain 94 and 95 in a 34:66 ratio (0.0115 g). Fractions 23-26 contain 93, 94, and 95 in a
90:5:5 ratio, respectively (0.0186 g). Fractions 27-34 contain 92, 93, and 96 in a 40:29:31 ratio, respectively (0.0330 g). Fractions 35-39 contain 92, 96, and 97 in a 45:25:30 ratio (0.0099 g). Fractions 40-45 contain 97 as the major component and 92 and 96 in trace quantities (<1%). Analysis of the chromatography fractions indicates that 0.0785 g (34 % yield) of nitronic esters was present consisting of 92, 93, 94, 95, 96, and 97 in a 22:33:6:11:16:12 ratio, respectively.

**Nitronic ester synthesis via controlled addition of diene**

*Addition of E/Z-3-methyl-1,3-pentadiene to a dichloromethane solution of β-nitrostyrene and SnCl₄*

A dichloromethane (18 mL) solution of β-nitrostyrene (0.002 mol, 0.296 g) was stirred in a dry ice/acetone bath under N₂ until a steady –75°C temperature was reached. Tin(IV)chloride (0.001 mol, 0.23 mL) was added dropwise over 5 minutes. 3-Methyl-1,3-pentadiene (E/Z, 7/3 mixture) (0.004 mol, 0.328 g) was diluted with CH₂Cl₂ to a volume of 2 mL. The diene solution was added to the cold β-nitrostyrene/SnCl₄ solution with a syringe pump over 1 hour. After the addition was completed, the reaction mixture was stirred for an additional 20 minutes. Saturated aqueous NaHCO₃ (5 mL) was added dropwise to the clear amber colored solution keeping the temperature below –70°C. The reaction mixture was warmed up to ambient temperature and transferred to a separatory funnel using saturated aqueous NaHCO₃ (15 mL) to complete the transfer. The dichloromethane layer was removed and the aqueous layer was extracted with ethyl acetate (five 10 mL portions). The dichloromethane layer was washed with saturated
aqueous NaHCO₃ (five 10 mL portions) and saturated sodium chloride solution (three 10 mL portions). The ethyl acetate layers were combined and washed with saturated aqueous NaHCO₃ (five 10 mL portions) and saturated aqueous sodium chloride (three 10 mL portions). The dichloromethane layer and ethyl acetate layer were washed separately because of their different densities. The organic layers were combined, dried with MgSO₄, and concentrated under vacuum. The reaction afforded 0.4022 g of crude product. The crude product was chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 90:10 to 0:100). From chromatographic fractions a total of 0.2818 g (61% combined yield) of nitronic esters 92, 93, 94, 95, 96, and 97 was obtained in a ratio of 17:17:9:9:32:16, respectively.

_Addition of E/Z-3-methyl-1,3-pentadiene to a toluene solution of β-nitrostyrene and SnCl₄_

The reaction with controlled rate of addition of diene was repeated using toluene as solvent. A cold (-78°C) solution of trans-β-nitrostyrene (0.002 mol, 0.298 g) in toluene (14 mL) was stirred under N₂. SnCl₄ (0.002 mol, 0.23 mL) was added drop wise over 5 minutes. A solution of 3-methyl-1,3-pentadiene (E/Z, 7:3) (0.004 mol, 0.328 g) diluted with toluene to a volume of 2 mL was added over 1 hr using a syringe pump. The reaction mixture was stirred for an additional 20 minutes. Ethyl acetate (10 mL) was added to dilute the reaction mixture, and saturated aqueous NaHCO₃ (5 mL) was added to destroy the catalyst, the reaction mixture temperature being kept below -65°C. The reaction mixture was warmed up to room temperature and transferred to a separatory funnel. The organic layer was removed and the aqueous layer was extracted with ethyl
acetate (five 10 mL portions). The organic layers were combined and washed with saturated aqueous sodium bicarbonate (five 10 mL portions) and saturated aqueous sodium chloride (five 10 mL portions). The crude product was dried with MgSO₄ and concentrated under vacuum. The reaction afforded 0.4088 g of crude products. The crude product consisted mostly of β-nitrostyrene and hydrocarbon material (¹H NMR shows intense signals from δ 0.5 – 2.0). Nitronic esters were not observed and the crude product was not chromatographed.

Addition of E-3-methyl-1,3-pentadiene to a dichloromethane solution of β-nitrostyrene and SnCl₄

A dichloromethane (10 mL) solution of trans-β-nitrostyrene (0.1500 g, 0.001 mol) was cooled to -75°C in a dry ice/acetone bath, under N₂, with stirring. Tin(IV)chloride (0.12 mL, 0.001 mol) was added via syringe drop wise over 5 minutes. E-3-methyl-1,3-pentadiene (0.1661 g, 0.002 mol) was diluted with dichloromethane to a volume of 2 mL, and the solution was added to the reaction mixture with a syringe pump over 1 hour. After the addition of diene was complete, the mixture was stirred for an additional 40 minutes. The mixture was diluted with dichloromethane (10 mL), while the reaction temperature was kept below -70°C. Saturated aqueous sodium bicarbonate (5 mL) was added to destroy the catalyst, keeping the temperature below -70°C. The dry ice/acetone bath was replaced with a water bath to warm up the reaction mixture. The resultant was transferred to a separatory funnel and the organic layer was separated. The organic layer was concentrated under reduced pressure and the residue was taken up in ethyl acetate (20 mL) and combined with the aqueous layer. To this was added saturated aqueous
sodium bicarbonate (10 mL). The layers were separated and the organic layer was then washed with saturated sodium bicarbonate (five 10 mL portions) and saturated aqueous sodium chloride (five 10 mL portions). The resulting organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude product was chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 90:10 to 0:100). The reaction afforded 0.1155 g (50 % combined yield) of nitronic esters 92, 93, 94, 96, and 97 in a ratio of 29 : 28 : 10 : 23 : 10, respectively after chromatography. None of the nitronic ester 95 was present.

94 (4R,5R,6S)-6-ethenyl-5,6-dimethyl-4-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide

The crude mixture of 92, 93, 94, 96, and 97 was chromatographed on silica gel with elution using a hexanes/ethyl acetate step gradient (from 90:10 to 0:100, respectively). An analytical sample of 94 was obtained in fractions 66 to 73 (0.0203 g). Rf=0.44 (hexanes/ethyl acetate 70:30). Compound 94 is a visous oil: IR (ATR) 1618 cm\(^{-1}\) (C=N); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.10-7.40 (m, 5H, H\(_{11-14}\)), 6.42 (d, 1H, H\(_3\), \(J=2.4\) Hz), 5.92-6.01 (dd, 1H, H\(_{7a}\), \(J_1=17.1\) Hz, \(J=10.7\) Hz), 5.55 (d, 1H, H\(_{8b}\), \(J=17.1\) Hz), 5.33 (d, 1H, H\(_{8c}\), \(J=10.7\) Hz), 4.10 (m, 1H, H\(_4\)), 2.04 (m, H\(_5\), 1H), 1.48 (s, 3H, H\(_9\)) 0.75 (d, 3H, H\(_{10}\), \(J=7.3\) Hz); \(^13\)C NMR (75.4 MHz, CDCl\(_3\)) \(\delta\): 138.9 (C\(_7\)), 138.0 (C\(_{11}\)), 128.8 (C\(_{12,12'}\)), 128.2 (C\(_{13,13'}\)), 127.5 (C\(_{14}\)), 115.4 (C\(_8\)), 113.0 (C\(_3\)), 86.9 (C\(_6\)), 42.9 (C\(_4\)), 36.0 (C\(_5\)), 24.4
Synthesis of nitronic esters 92-97 by addition of SnCl₄ and E,Z-3-methyl-1,3-pentadiene at alternating intervals to a dichloromethane solution of β-nitrostyrene

A solution of trans-β-nitrostyrene (0.001 mol, 0.149 g) in dichloromethane (4 mL) was cooled to -74°C in a dry ice/acetone bath, under N₂, with stirring. Tin(IV)-tetrachloride (0.001 mol, 0.12 mL) was added drop wise with a syringe over 5 minutes, and the mixture was stirred for 15 minutes. 3-Methyl-1,3-pentadiene (E/Z, 7:3), (0.001 mol, 0.11 mL) was added drop wise with a syringe over 5 minutes, and the reaction mixture was stirred for 30 minutes. More SnCl₄ (0.001 mol, 0.12 mL) was added drop wise over 5 minutes and the mixture was stirred for 15 minutes. More 3-methyl-1,3-pentadiene (E/Z, 7:3) (0.001 mol, 0.11 mL) was added drop wise with a syringe over 5 minutes, and the reaction mixture was stirred for 30 minutes. A final portion of 3-methyl-1,3-pentadiene (E/Z, 7:3) (0.001 mol, 0.11 mL) was added drop wise with a syringe over 5 minutes, and the reaction mixture was stirred for 30 minutes. Ethyl acetate (10 mL) was added to dilute the mixture, and saturated aqueous NaHCO₃ (10 mL) was added to destroy the catalyst, the temperature being kept below -70°C. The mixture was warmed up with a water bath and transferred to a separatory funnel. The organic layer was separated and washed with saturated aqueous NaHCO₃ solution (three 10 mL portions) and with saturated aqueous sodium chloride solution (three 10 mL portions). The original aqueous layer was extracted with ethyl acetate (three 20 mL portions), and the combined
ethyl acetate layers were washed with a saturated aqueous NaHCO₃ solution (three 20 mL portions) and with a saturated aqueous sodium chloride solution (three 20 mL portions). The organic layers were combined and dried with MgSO₄ and concentrated under vacuum. The reaction afforded 0.1571 g of crude products. Nitronic esters were present, however β-nitrostyrene was not completely consumed. The crude product was not chromatographed.

**Synthesis of nitronic esters 92-97 by portion wise addition of E,Z-3-methyl-1,3-pentadiene to a dichloromethane solution of SnCl₄ and β-nitrostyrene**

A solution of trans-β-nitrostyrene (0.001 mol, 0.149 g) in dichloromethane (4 mL) was cooled to -73°C using a dry ice/acetone bath, under N₂, with stirring. SnCl₄ (0.001 mol, 0.12 mL) was added drop wise with a syringe over 5 minutes, and the mixture was stirred for 15 minutes. 3-Methyl-1,3-pentadiene (E/Z 7:3) (0.001 mol, 0.11 mL) was added drop wise over 10 minutes and the mixture was stirred for 30 minutes. More 3-methyl-1,3-pentadiene (E/Z 7:3) (0.0005 mol, 0.05 mL) was added drop wise over 10 minutes and the mixture was stirred for an additional 30 minutes. Ethyl acetate (10 mL) was added drop wise to dilute the mixture, and saturated aqueous NaHCO₃ (10 mL) was added to destroy the catalyst, the temperature being kept below -70°C. The mixture was warmed up with a water bath and transferred to a separatory funnel. The organic layer was separated and washed with saturated aqueous NaHCO₃ (three 10 mL portions) and with saturated aqueous sodium chloride (three 10 mL portions). The aqueous layer was extracted with ethyl acetate (three 20 mL portions), and organic (ethyl
acetate) layer was washed with saturated aqueous NaHCO₃ (three 20 mL portions) and the combined extracts were washed with saturated aqueous sodium chloride (three 20 mL portions). The ethyl acetate layer and dichloromethane layer were combined and dried with MgSO₄ and concentrated under reduced pressure. The reaction afforded 0.1663 g of crude products. ¹H NMR and TLC showed numerous products and accordingly the crude material was not chromatographed.

**Addition of SnCl₄ to a dichloromethane solution of E,Z-3-methyl-1,3-pentadiene and β-nitrostyrene**

A solution of trans-β-nitrostyrene (0.001 mol, 0.1490 g) and 3-methyl-1,3-pentadiene (E/Z, 7:3) (0.002 mol, 0.1640 g) in dichloromethane (5 mL) was stirred under N₂ with cooling (dry ice/acetone bath). Tin(IV)chloride (0.001 mol, 0.12 ml) was added drop wise over 5 minutes and the resulting solution was stirred for 75 minutes. Ethyl acetate (10 mL) was added followed by saturated aqueous NaHCO₃ (10 mL) to destroy the catalyst, the temperature being kept below -70°C. The quenched reaction mixture was warmed up to room temperature using a water bath and transferred to a separatory funnel. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (five 10 mL portions). Organic layers were combined and washed with saturated aqueous NaHCO₃ (five 10 mL portions) and saturated aqueous sodium chloride (three 10 mL portions). The resulting organic layer was dried with MgSO₄ and concentrated under reduced pressure to give 0.264 g of crude product. Analysis of the crude product by ¹H NMR shows that β-nitrostyrene is present, and nitronic esters 92, 93, 94, 95, 96, and 97
in a ratio of 25 : 29 : 4 : 8 : 25 : 10, respectively. The ratio of nitronic esters 92 and 93 is 46 : 54. Non-polar side products are also present.

A portion of the crude product (0.056 g) dissolved in toluene (5 mL) was stirred under N₂ at ambient temperature. Tin(IV)chloride (0.03 mL) was added drop wise over 5 minutes, and the reaction mixture was stirred for 20 minutes. The catalyst was quenched with saturated aqueous NaHCO₃ (5 mL), and the resultant transferred with ethyl acetate (15 mL) to a separatory funnel. The organic layer was separated and the aqueous layer extracted with ethyl acetate (five 10 mL portions). The organic layers were combined and washed with saturated aqueous NaHCO₃ (five 10 mL portions), dried with MgSO₄ and concentrated under reduced pressure. After work up, the reaction afforded 0.05 g of material. The ¹H NMR spectrum shows that the ternary adducts 98a-b formed. Signal intensities for nitronic esters 92 and 93 diminished relative to nitronic esters 94-97, and their ratio is now 60:40.

Reaction of non-polar fractions obtained from a dichloromethane experiment

A crude mixture of nitronic esters obtained from a dichloromethane experiment was chromatographed using a hexanes/ethyl acetate step gradient (from 95:5 to 0 : 100). Fractions 1-28 (0.0566 g) were non-polar materials and β-nitrostyrene, and fractions 29-53 contained nitronic esters 92, 93, 94, 95, 96, and 97.

A toluene (10 mL) solution of non-polar material (0.057 g) was stirred under N₂. Tin(IV)chloride (0.04 mL) was added drop wise and the resultant was stirred for 20
minutes. Saturated aqueous NaHCO₃ (5 mL) was added to destroy the catalyst and the mixture was transferred to a separatory funnel with ethyl acetate (20 mL) used to complete the transfer. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (five 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (five 10 mL portions), dried with MgSO₄, and concentrated to give 0.0577 g of crude product. The ¹H NMR spectrum shows that a small amount of ternary cycloadducts 98a-b formed.

**Attempted synthesis of ternary adducts 98a-b from nitronic esters 92 and 96 at -78°C and 20°C**

A toluene (5 mL) solution of a mixture of 92 and 96 (79 : 21, 0.0262 g) was cooled to -78°C under N₂. Tin(IV)chloride (0.013 mL) was added drop wise and the cold mixture was stirred for 75 minutes. The mixture was diluted with ethyl acetate (5 mL) and the catalyst was quenched with saturated aqueous NaHCO₃ (5 mL), the temperature being kept below -60°C. The reaction mixture was warmed up to room temperature and transferred to a separatory funnel using ethyl acetate (15 mL) to complete the transfer. The organic layer was isolated and the aqueous layer extracted with ethyl acetate (three 15 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (three 15 mL portions) and saturated aqueous NaCl (three 10 mL), dried with MgSO₄, and concentrated under reduced pressure to give 0.0278 g of crude product. The ¹H NMR spectrum shows that only nitronic esters 92 and 96 are present in a 78 : 22 ratio. There is no evidence that the ternary adducts 98a-b formed.
Repeating the same reaction for 20 minutes at 20°C did not result in formation of the ternary cycloadducts 98a-b. Under these conditions, the crude product consisted of 92, 93, and 96 in a 48 : 29 : 23 ratio, respectively. Nitronic ester 92 had partially isomerized to 93 (92/93, 60 : 40 ratio).

*Attempted synthesis of ternary adducts 98a-b from nitronic esters 93 and 96 at -78°C and 20°C*

A toluene (2 mL) solution of nitronic esters 93 and 96 (71 : 29, 0.002 g) was stirred under N₂ and cooled by a dry ice/acetone bath. Tin(IV)chloride (0.001 mL) was added to the solution and stirring was continued for 75 minutes. Ethyl acetate (5 mL) was added to dilute the reaction mixture and saturated aqueous NaHCO₃ (1 mL) was added to destroy the catalyst. The resultant was warmed up to room temperature and transferred to a separatory funnel with ethyl acetate (10 mL) being used to complete the transfer. The organic layer was isolated and the aqueous layer extracted with ethyl acetate (three 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (three 10 mL portions) and saturated aqueous NaCl (three 4 mL portions), dried with MgSO₄, and concentrated under reduced pressure to give 0.003 g of crude product. The ¹H NMR spectrum shows that 93 and 96 are present in a 73 : 27 ratio. There is no evidence that the ternary adducts 98a-b were formed.

Repeating the same reaction for 20 minutes at 20°C did not result in formation of the ternary cycloadducts 98a-b. Under these conditions the crude product consisted of 92, 93, and 96 in a 43 : 34 : 23 ratio, respectively. Nitronic ester 93 had partially isomerized to 92 (92/93, 40 : 60 ratio).
Attempted synthesis of ternary adducts 98a-b from nitronic esters 94 and 95 at -78°C

A toluene (5 mL) solution of 94 and 95 (36:64, 0.0136 g) was cooled to -78°C using a dry ice/acetone bath. Tin(IV)chloride (0.007 mL) was added and the mixture was stirred for 75 minutes. Ethyl acetate (5 mL) was added to dilute the mixture and saturated aqueous NaHCO₃ (5 mL) was added to destroy the catalyst. The mixture was warmed up to room temperature and transferred to a separatory funnel using ethyl acetate (15 mL) to complete its transfer. The organic layer was separated and the aqueous layer extracted with ethyl acetate (three 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (three 10 mL portions) and saturated aqueous NaCl (three 10 mL portions), dried with MgSO₄, and concentrated under reduced pressure to give 0.0091 g of crude product. The ¹H NMR spectrum of the crude product shows that only nitronic esters 94 and 95 are present in a 36:64 ratio. Ternary adduct 98a-b did not form.

Attempted synthesis of ternary adducts 98a-b from nitronic esters 94 and 95 at 20°C

A toluene (6 mL) solution of nitronic esters 94 and 95 (36:64, 0.0091 g) was stirred at room temperature under N₂. Tin(IV)chloride (0.004 mL) was added and the mixture was stirred for 20 minutes. Saturated aqueous NaHCO₃ was added to quench the catalyst, and the mixture was transferred to a separatory funnel using ethyl acetate (15 mL) to complete the transfer. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (three 15 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (three 10 mL portions) and saturated aqueous
NaCl (three 5 mL portions), dried with MgSO$_4$, and concentrated under reduced pressure to afford 0.0098 g of crude material. The $^1$H NMR spectrum of the crude product shows that only 94 and 95 are present in a 37:63 ratio, and no ternary adducts 98a-b formed.

**Attempted synthesis of ternary adducts 98a-b from nitronic esters 92, 96, and 97 at -78°C and 20°C**

A toluene (5 mL) solution of 92/96/97 (80:4:16, 0.0165 g) under N$_2$ was cooled to -78°C using a dry ice/acetone bath. Tin(IV)chloride (0.001 mL) was added and the mixture was stirred for 75 minutes. Ethyl acetate (5 mL) was added to dilute the mixture and saturated aqueous NaHCO$_3$ (5 mL) was added to destroy the catalyst. The mixture was warmed up to room temperature and transferred to a separatory funnel with ethyl acetate (15 mL) to complete the transfer. The organic layer was separated and the aqueous layer extracted with ethyl acetate (three 15 mL portions). The combined organic layer was washed with saturated aqueous NaHCO$_3$ (three 10 mL portions) and saturated aqueous NaCl (three 10 mL portions), dried with MgSO$_4$, and concentrated under reduced pressure to give 0.0167 g of crude product. The $^1$H NMR spectrum shows that only 92, 96, and 97 are present in a 80:4:16 ratio, respectively.

Repeating the same reaction for 20 minutes at 20°C did not result in formation of the ternary adducts 98a-b. Under these conditions the crude product consisted of 92, 93, 96, and 97 in a 37:25:21:17 ratio, respectively. Nitronic ester 92 had partially isomerized to 93 (92/93, 60:40 ratio).
Rearrangement of nitronic esters to nitro compounds

Thermal rearrangement of nitronic ester 92 to nitro compound 100

A DMF (10 mL) solution of compound 92 (0.0270 g, 0.12 mmol) was heated under N2 using an oil bath at 90-97°C for 1 hour. The reaction mixture was cooled, diluted with benzene and ethyl acetate (20 mL each), transferred to a separatory funnel, and washed with water (twenty 10 mL portions), dried over MgSO4, and concentrated under reduced pressure to give 0.0262 g of crude product. By 1H NMR analysis, an equal amount of 92 and 100 was present. Extending the reaction time to 2 hours at 90-97°C resulted in complete conversion of 92 to 100. Preparative TLC (250 μm plate, hexanes/ethyl acetate 90:10) was performed on the 0.0248 g of crude product to afford 0.0199 g (74 % yield) of pure compound 100. Compound 100 was recrystallized from benzene/hexanes to afford the analytical sample.

100 [(1R,5S,6S)-4,5-dimethyl-6-nitrocyclohex-3-en-1-yl]benzene

Compound 100 is a white solid: m.p. 100-100.2°C; Rf = 0.87 (hexanes/ethyl acetate 90:10); IR (ATR) 1553 cm⁻¹ and 1375 cm⁻¹ (NO₂ stretch); 1H NMR (CDCl₃, 500 MHz) δ 7.15-7.40 (m, 5H, H₁₀-₁₂), 5.42 (broad s, 1H, H₂), 5.14 (dd, 1H, H₅, J =5.8 Hz, J=12.2
Hz), 3.46 (m, 1H, H4), 2.83 (m, 1H, H6), 2.48 (m, 1H, H3), 2.21 (m, 1H, H3), 1.80 (s, 3H, 
H8), 1.11 (d, 3H, H7, J = 7.3 Hz); 13C NMR (74.5 MHz, CDCl3) δ 141.69, 135.19, 128.75, 
127.09, 127.07, 120.36, 90.18 (C5), 38.31, 37.63, 34.61, 21.76, 14.24; MS (CI, CH4 
carrier) M+1 C14H18N02 found 232.1328, calculated 232.1338.

Elemental analysis: calculated for C14H17N02: C, 72.72 %; H, 7.36 %; N, 6.06%. Found: 
C, 72.47 %; H, 7.11 %; N, 5.89 %.

*Exploration of conditions for rearrangement of 92 to 100*

A DMF (10 mL) solution of compound 92 (0.1076 g, 0.46 mmol) was heated 
using an oil bath at 105-109°C under N2 for 1 hr. The contents were cooled to room 
temperature, diluted with benzene and ethyl acetate (15 mL each) and washed with water 
(twenty 10 mL portions). The organic layer was dried with MgSO4, and concentrated 
under reduced pressure to give 0.0748 g of solid that contained no 92. This was 
chromatographed on silica gel (elution with hexanes/ethyl acetate 98:2) to afford 0.0361 
g (34% yield) of pure 100. In a duplicate run 100 was obtained as crude product with a 
62% material balance.

Heating at a bath temperature of 65-70°C for 24 hours, resulted in nearly complete 
conversion of 92 to 100 (99 : 1), but the material balance for crude product was only 
30%.
Thermal rearrangement of nitronic ester 93 to nitro compound 101

A DMF (10 mL) solution of a nitronic ester mixture of mainly 93 (0.0449 g, 93/92, 91:9) was heated at 128-130°C for 1 hour under N₂. The solution was cooled to room temperature, diluted with benzene and ethyl acetate (10 mL each), and washed with water (twenty 10 mL portions). The organic layer was dried with MgSO₄ and concentrated under reduced pressure. The reaction afforded 0.0394 g of crude product. The ¹H NMR spectrum of the crude product indicated a 11 : 62 : 27 mixture of 100, 101 and 102, respectively. Preparative TLC (250 μm silica gel plate, elution with hexanes/ethyl acetate 90:10) gave 0.01 g (23% yield) of pure 101 as the less mobile band.

101 [(1S,5S,6S)-4,5-dimethyl-6-nitrocyclohex-3-en-1-yl]benzene

Compound 101 is a viscous opaque oil: R_t = 0.81 (hexanes/ethyl acetate 9:1); IR (ATR) 1371 and 1553 cm⁻¹ (NO₂ stretch); ¹H NMR (CDCl₃, 500 MHz) δ 7.05-7.40 (m, 5H, H₁₀₋₁₂), 5.69 (broad s, 1H, H₂), 4.99 (dd, 1H, H₅, J = 3.4 Hz, J=5.37 Hz), 3.26 (m, 1H, H₄), 2.91 (m, 1H), 2.80 (broad s, 1H), 2.30 (m, 1H), 1.75 (s, 3H, H₃), 1.13 (d, 3H, H₇, J = 7.3 Hz); ¹³C NMR (CDCl₃, 74.5 MHz) δ 140.10, 131.75, 129.14, 127.95, 127.39, 122.35, 92.94 (C₅), 43.19, 37.12, 26.63, 21.23, 14.34; MS (Cl, CH₄ carrier) M+1 C₁₄H₁₈N₁O₂ found 232.1332, calculated 232.1338.
The more mobile band obtained from chromatography contained 0.0072 g of mainly 102 (102/100, 95:5, 16% yield). Recrystallization of this material from aqueous ethanol gave an analytical sample of 102.

**102 [(1R,5R,6S)-4,5-dimethyl-6-nitrocyclohex-3-en-1-yl]benzene**

Compound 102 is a white solid: m.p. 71-72°C; R_f = 0.87 (hexanes/ethyl acetate 90:10); IR (ATR) 1546 and 1372 cm⁻¹ (NO₂); ¹H NMR (CDCl₃, 500 MHz) δ: 7.15-7.35 (m, 5H, H₉-₁₂), 5.52 (broad s, 1H, H₂), 4.63 (dd, 1H, H₅, J = 11.7 Hz, J = 9.8 Hz), 3.35 (m, 1H, H₇), 2.91 (broad s, 1H), 2.20-2.40 (m, 1H), 1.76 (s, 3H, H₈), 1.14 (d, 3H, H₇, J = 6.8 Hz); ¹³C NMR (CDCl₃, 74.5 MHz) δ 139.79 (C₉), 134.41 (C₁), 129.039 (C₁₀), 127.90 (C₁₂), 127.67 (C₁₁), 121.06 (C₁), 96.12 (C₄), 45.17, 39.89, 33.15, 20.76, 16.10; MS (Cl, CH₄ carrier) C₁₄H₁₈N₁O₂ M+1 found 232.1332, calculated 232.1338.

*Exploration of rearrangement conditions for 93:*

A DMF (10 mL) solution of pure compound 93 (0.0163 g) was heated at 90°C for 1 hour under N₂. The solution was cooled to room temperature and diluted with ethyl acetate and benzene (15 mL each) and washed with water (twenty 10 mL portions). The organic layer was dried with MgSO₄ and concentrated under reduced pressure. The
reaction afforded 0.0123 g (75% material balance) of crude product. The $^1$H NMR spectrum showed that the major material present is recovered 93 (93/101, 99 : 1).

A DMF (12 mL) solution of compound 93 (slightly impure; 93/92, 99 : 1; 0.1074 g) was heated at 105-109°C for 1 hour under N$_2$. The mixture was cooled to room temperature and diluted with ethyl acetate and benzene (15 mL each) and washed with water (twenty 10 mL portions). The organic layer was dried with MgSO$_4$ and concentrated under reduced pressure. The reaction afforded 0.096 g of crude material. The $^1$H NMR spectrum showed both 93 and 101 to be present in a 70:30 ratio, respectively.

A solution of compound 93 (0.034 g) in DMF (10 mL) was heated at 73-75°C for 22 hours under N$_2$. The mixture was cooled to room temperature and diluted with ethyl acetate and benzene (15 mL each) and washed with water (twenty 10 mL portions). The organic layer was dried with MgSO$_4$ and concentrated under reduced pressure. The reaction mixture afforded 0.0265 g of crude product. This crude product was chromatographed on silica gel using a hexanes/ethyl acetate step gradient (from 95:5 to 70:30). A 0.0047 g portion (14% yield) of compound 101 was obtained. Compound 102 was not observed and 0.0116 g of impure 93 containing unidentified material was recovered.

**Thermal isomerization of nitro compound 101 to nitro compound 102**

A DMF (8 mL) solution of compound 101 (0.0054 g) was heated at 125-129°C for 1 hour under N$_2$. The resulting solution was cooled to room temperature and diluted
with ethyl acetate and benzene (15 mL each) and washed with water (twenty 10 mL portions). The organic layer was dried with MgSO₄ and concentrated under reduced pressure to give 0.0054 g of crude product. The \(^1\)H NMR analysis of the crude material shows both 101 and 102 (75 : 25 ratio).

A DMF (5 mL) solution of a mixture of 101 and 102 (75 : 25, 0.0054 g) was heated at 140-145°C for 1 hour. Workup as described above gave 0.004 g of material. By \(^1\)H NMR this was still a mixture of 101 and 102 (63 : 37 ratio).

A DMF (5 mL) solution of a mixture of 101 and 102 (63 : 37, 0.004 g) was heated for 3 hours at 122-128°C. Workup as above gave 0.004 g of material that by \(^1\)H NMR was 101 and 102 (15 : 85 ratio).

A DMF (8 mL) solution of compound 101 (0.01 g) was heated at 126-128°C for 9 hours under N₂. The resulting solution was worked up as above to give 0.0036 g of crude product which was 102 by \(^1\)H NMR. Preparative TLC (elution hexanes/ethyl acetate 90:10) gave 0.0034 g (34 % yield) of pure compound 102.

A DMF (10 mL) solution of a mixture of mainly nitro compound 101 (101/93, 92 : 8, 0.0101 g) was heated for 6 hours at 125-130°C under N₂. After work up, as described above, the reaction afforded 0.0036g of crude product. The \(^1\)H NMR spectrum showed only the presence of 102 and no remaining 93 or 101.
Tin(IV) chloride catalyzed rearrangement of 97 to 104

A toluene (5 mL) solution of nitronic ester 97 (0.0143 g) was stirred under N₂ at room temperature. Tin(IV) chloride (0.01 mL) was added drop wise over 2 minutes and the resultant was stirred for 55 hours. Saturated aqueous NaHCO₃ (10 mL) was added to destroy the catalyst, and the mixture was transferred to a separatory funnel using ethyl acetate (15 mL) to complete the transfer. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (four 10 mL portions). The combined organic layers were washed with saturated aqueous NaHCO₃ (three 10 mL portions) and saturated aqueous NaCl (three 10 mL portions), dried with MgSO₄, and concentrated to give 0.0124 g of crude product. The ¹H NMR spectrum of the crude product shows nitro compound 104, and intense bands in 0.5-2.5 δ and 7-8 δ regions. The crude product was purified by preparative TLC (250 μm silica gel plate; elution with hexanes/ethyl acetate, 90:10) to give 0.0012 g (10 % yield) of pure nitro compound 104.

104 [(1R,2S,6S)-2,3-dimethyl-6-nitrocyclohex-3-en-1-yl]benzene

Compound 104 is a white solid: m.p. 74-77°C; IR (ATR) 1548 cm⁻¹ and 1372 cm⁻¹ (NO₂ symmetric and asymmetric stretch); ¹H NMR (CDCl₃, 500 MHz) δ 5.43 (broad s, 1H, H₂), 4.94 (m, 1H, H₄), 3.00 (dd, 1H, H₅, J=11.7 Hz, 10.3 Hz), 2.76 (m, 1H, H₆), 2.66 (m,
\[
1H, H_3\), 2.41 (m, 1H, H_6), 0.93 (d, 3H, H_5, J=7.0 Hz); MS (Cl, NH_3 carrier) C_{14}H_{18}N_1O_2
\]
M+1 found 232.1335, calculated 232.1338.

**Attempted catalytic rearrangement of nitronic ester 94**

A toluene (10 mL) mixture of nitronic ester 94 (0.0278 g) was stirred at room temperature under N\(_2\). Tin(IV) chloride (0.01 mL) was added drop wise over 2 minutes and the resultant stirred for 43 hours. Saturated aqueous NaHCO_3 (10 mL) was added to destroy the catalyst, and the mixture was transferred to a separatory funnel using ethyl acetate (15 mL) to complete the transfer. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (five 10 mL portions). The combined organic layers were washed with saturated aqueous NaHCO_3 (five 10 mL portions) and saturated aqueous NaCl (five 10 mL portions), dried with MgSO_4, and concentrated to give 0.0153 g of crude product. The \(^1\)H NMR spectrum of the crude product shows unassigned signals at \(\delta\) 0.5-2.4, 3.0-3.2, 5.0-5.3, 6.3-7.4. There is no evidence of a nitro compound being present. The crude product was chromatographed by preparative TLC (250 \(\mu\)m silica gel plate; elution with hexanes/ethyl acetate, 90:10). The portion of the plate where nitro compounds typically elute was analyzed. The \(^1\)H NMR spectrum does not show signals for a nitro compound.
Attempted thermal rearrangement of nitronic esters 94 and 95

Rearrangement of either 94 or 95 was attempted on a mixture of 94 and 95 at various temperatures, resulting only in decomposition of 94 and 95.

Heating 94 and 95 at 45°C for 15 minutes

A DMF (5 mL) solution of a mixture of 94/95 (33 : 67, 0.02 g) was heated at 45°C for 15 minutes. The resulting solution was cooled to room temperature, diluted with benzene and ethyl acetate (5 mL each), and washed with water (twenty 10 mL portions). The organic layer was dried with MgSO₄ and concentrated under reduced pressure to give 0.0155 g of material. The ¹H NMR spectrum shows that 94 and 95 were present in a 35 : 65 ratio. No signals attributable to rearrangement products were observed.

Heating 94 and 95 at 62°C for 25 minutes

A DMF (5 mL) solution of a mixture of 94/95 (35 : 65, 0.0155 g) was heated at 62°C for 25 minutes. After work up, same as above, the reaction afforded 0.0123 g of crude material. The ¹H NMR spectrum shows that 94 and 95 were present in a 35 : 65 ratio. No signals attributable to rearrangement products were observed.

Heating 94 and 95 at 74°C for 15 minutes

A DMF (5 mL) solution of a mixture of 94/95 (35 : 65, 0.0123 g) was heated at 74°C for 15 minutes. After workup, same as above, the reaction afforded 0.01 g of
material. The $^1$H NMR spectrum shows that 94 and 95 were present in a 34 : 66 ratio. No signals attributable to rearrangement products were observed.

Heating 94 and 95 at 83°C for 15 minutes

A DMF (5 mL) solution of a mixture of 94/95 (34 : 66, 0.010 g) was heated at 83°C for 15 minutes. After workup, same as above, the reaction afforded 0.0013 g of material. The $^1$H NMR spectrum shows that 94 and 95 were still present in a 35 : 65 ratio. No signals attributable to rearrangement product were observed.

Heating 94 and 95 at 95°C for 15 minutes

A DMF (5 mL) solution of a mixture of 94/95 (35 : 65, 0.0013 g) was heated at 95°C for 15 minutes. After workup, same as above, the reaction afforded 0.0007 g of material. The $^1$H NMR spectrum shows that 94 and 95 were present in a 37 : 63 ratio, along with a trace amount of an unidentified material. The IR spectrum of the crude product does not show signals attributable to a nitro compound.

Heating 94 and 95 at 95-99 °C for 40 minutes

A DMF (5 mL) solution of a mixture of 94/95 (31 : 69, 0.0182 g) was heated at 95-99°C for 40 minutes. After workup, same as above, the reaction afforded 0.0057 g of material. The $^1$H NMR spectrum shows that 94 and 95 were present in a 33 : 67 ratio, along with trace amounts of an unidentified material. The IR spectrum does not show signals attributable to a nitro compound.

Heating 94 and 95 at 95-97°C for 210 min
A DMF (5 mL) solution of a mixture of \textbf{94/95} (33 : 67, 0.0110 g) was heated at 95-97°C for 210 minutes. After workup, same as above, the reaction afforded 0.0067 g of material. The $^1$H NMR spectrum shows that a new unidentified material formed and \textbf{94} and \textbf{95} are completely consumed. The IR spectrum of the crude material shows the absence of a 1615 cm$^{-1}$ band attributable to the C=N stretch of a nitronic ester. A broad signal at 3424 cm$^{-1}$ is now present. There is no indication that a nitro group is present: there are no IR bands at or near 1550 cm$^{-1}$ and 1370 cm$^{-1}$.

\textit{Heating \textbf{94} and \textbf{95} at 150°C for 5 minutes}

A DMF (5 mL) solution of a mixture of \textbf{94/95/97} (34 : 46 : 20, 0.0056 g) was heated at 150°C for 5 minutes. After workup, same as above, the reaction afforded 0.0011 g of material. The $^1$H NMR spectrum shows that starting material was completely consumed, and new compounds were formed. The IR signals are the same as those from the 95-97°C experiment. The IR spectrum shows the absence of a 1615 cm$^{-1}$ band attributable to a nitronic ester and a new signal at 1684 cm$^{-1}$ possibly due to a conjugated C=O stretching frequency.

\textit{Attempted rearrangement of nitronic ester \textbf{96}}

A DMF (5 mL) solution of nitronic ester \textbf{96} (0.011 g) was heated for 2 hours at 68-70°C. After work up, as described in the attempted rearrangement of \textbf{94/95}, the reaction afforded 0.0044 g of material. The $^1$H NMR spectrum shows only signals attributable to \textbf{96}. 

A DMF (5 mL) solution of nitronic ester 96 (0.005 g) was heated at 90-94°C for 1 hour. After work up, as described above, the reaction afforded 0.001 g of material. The $^1$H NMR spectrum shows that 96 is the major component along with a small amount of new unidentified material. The IR spectrum of crude material does not show signals attributable to a nitro compound.

**Attempted thermal rearrangement of nitronic ester 97**

A DMF (5 mL) solution of nitronic ester 97 (0.031 g) was heated at 132-137°C for 45 minutes. After workup, as described above, the reaction afforded 0.0211 g of material. The $^1$H NMR spectrum shows many unassigned signals with an especially heavy hydrocarbon and aromatic region. The IR spectrum does not show frequencies attributable to a nitro group: there are no bands at or near 1550 cm$^{-1}$ and 1370 cm$^{-1}$.

**Attempted isomerization of E-3-methyl-1,3-pentadiene in xylene**

A xylene (5 mL) solution of E-3-methyl-1,3-pentadiene (0.25 mL) was stirred and cooled to -75°C under N$_2$. SnCl$_4$ (0.13 mL) was added drop wise over 5 minutes and the reaction was stirred for 10 minutes. The solution changed from colorless to yellow. Saturated aqueous NaHCO$_3$ (1 mL) was added to destroy the catalyst and the reaction mixture was allowed to warm up to room temperature. The aqueous layer was removed, and the organic layer was washed with saturated aqueous NaHCO$_3$ (three 1 mL portions). The organic layer was dried with MgSO$_4$ and filtered. Deuterochloroform (3 mL) was added to the dry organic layer, and the resultant was micro distilled. The first fraction
distilled at 60-65°C. The $^1$H NMR spectrum showed that $E$-3-methyl-1,3-pentadiene was present and none of the $Z$ isomer.

The reaction was repeated except that the reaction time was extended to 45 minutes. The $^1$H NMR spectrum showed that $E$-3-methyl-1,3-pentadiene remains and that it contains less then 1% of $Z$-isomer.

**Attempted isomerization of E-3-methyl-1,3-pentadiene in CDCl$_3$**

A deuterochloroform (3 mL) solution of $E$-3-methyl-1,3-pentadiene (8.9 x 10$^{-5}$ mol, 0.01 mL) was stirred under N$_2$, and submerged in a dry ice/acetone bath to maintain a temperature near -60°C. The freezing point of CDCl$_3$ is -64°C. Tin(IV)chloride (4.45x10$^{-5}$ mol, 0.005 mL) was added to the solution and the resultant stirred for 75 minutes. Saturated aqueous NaHCO$_3$ (1 mL) was added to destroy the catalyst. The aqueous layer was removed and the organic layer was washed with saturated aqueous NaHCO$_3$ (five 1 mL portions). The organic layer was dried with MgSO$_4$, the solution was filtered and micro distilled. The fraction that distilled at 60-62°C was collected and examined by $^1$H NMR, which showed that only $E$-3-methyl-1,3-pentadiene was present and none of the $Z$ isomer. After distillation, a brown gummy residue was also obtained and analyzed. The $^1$H NMR spectrum shows intense signals at 0.2 to 3.0 δ, and less intense signals at 4.8 to 5.4 δ.
A toluene (5 mL) solution of a mixture of 92/96 (78:22 ratio, 0.0278 g) was stirred at ambient temperature under N₂. Tin(IV) chloride (0.014 ml) was added drop wise with a syringe over 5 min, and the mixture was stirred for 20 minutes under N₂. Saturated aqueous NaHCO₃ (5 mL) was added to destroy the catalyst. Ethyl acetate (10 mL) was used to transfer the solution to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (five 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ solution (five 10 mL portions) and saturated aqueous sodium chloride solution (three 10 mL portions), dried with MgSO₄, and concentrated under reduced pressure to give 0.0248 g of crude product. The ¹H NMR spectrum shows that crude product consisted of 92 : 93 : 96 in a 48 : 29 : 23 ratio, respectively. The ratio of 92 to 93 is 60 : 40. There is no evidence that the ternary adducts 98a-b formed.

A toluene (3 mL) solution of a mixture of 92/93/96 (10:66:24 ratio, 0.0028 g) was stirred under N₂ at ambient temperature. Tin(IV) chloride (0.001 mL) was added drop wise over 5 minutes and the mixture was stirred for 20 minutes. Saturated aqueous NaHCO₃ (1 mL) was added to destroy the catalyst, and ethyl acetate (10 mL) was used to transfer the solution to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (five 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (five 10 mL portions) and saturated aqueous sodium chloride (three 10 mL portions), dried with MgSO₄, and
concentrated under reduced pressure to give 0.0025 g of crude product. The $^1$H NMR spectrum shows that the crude product consisted of 92:93:96 in a 43 : 34 : 23 ratio. The ratio of nitronic esters 92/93 had changed from 13 : 87 to 60 : 40. There is no evidence that the ternary adducts 98a-b formed nor was 94 formed from 96 due to the short reaction time.

Isomerization of nitronic ester 96 to 94

Two hour experiment

A toluene (5 mL) solution of 92 and 96 (55 : 45, 0.0399 g) was stirred at ambient temperature under N$_2$. Tin (IV)chloride (0.02 mL) was added drop-wise over 5 minutes and the mixture was stirred for 2 hours. Saturated aqueous NaHCO$_3$ (10 mL) was added to destroy the catalyst, and ethyl acetate (10 mL) was used to transfer the solution to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (five 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO$_3$ (five 10 mL portions) and saturated aqueous sodium chloride (three 10 mL portions), dried with MgSO$_4$, and concentrated under reduced pressure to give 0.0367 g of crude product. The $^1$H NMR spectrum shows compounds 92, 93, 94, 96, and 100 in a 25 : 16 : 16 : 25 : 18 ratio, respectively. Thus 96 and 94 are present in a 60 : 40 ratio, and 92/93 in a 60:40 ratio. Possibly, nitro compound 100 is forming due to catalytic rearrangement of nitronic ester 92 under the reaction conditions.

Sixteen hour experiment

A toluene (5 mL) solution of a mixture of 96/92/93 (53 : 22 : 25, 0.0111 g) was stirred at room temperature, under N$_2$. Tin(IV)chloride (0.005 mL) was added drop wise
over 5 minutes and the mixture was stirred for 16 hours. Saturated aqueous NaHCO₃ (5 mL) was added to destroy the catalyst, and ethyl acetate (10 mL) was used to transfer the mixture to a separatory funnel. The organic layer was removed and aqueous layer was extracted with ethyl acetate (five 10 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (five 10 mL portions) and saturated aqueous sodium chloride (three 10 mL portions), dried with MgSO₄, and concentrated under reduced pressure to give 0.0096 g of crude product. The ¹H NMR spectrum shows signals for nitronic esters 94 and 96, and nitro compound 100 in a 37 : 1 : 62 ratio. Nitronic esters 92 and 93 were completely consumed. Apparently isomerization of nitronic ester 93 to nitronic ester 92 is eventually followed by catalytic rearrangement of 92 to compound 100. Compound 96 was still present but the 94/96 ratio is now 99 : 1. Nitronic ester 97 was not observed.

*Isomerization of nitronic ester 95 to 97*

*Two hour experiment*

A toluene (3 mL) solution of nitronic esters 94 and 95 (35 : 65, 0.0067 g) was stirred at room temperature under N₂. Tin(IV)chloride (0.004 mL) was added drop wise over 5 minutes and the reaction mixture was stirred for 2 hours. Saturated aqueous NaHCO₃ (5 mL) was added to destroy the catalyst and ethyl acetate (5 mL) was used to transfer the mixture to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (five 5 mL portions). The combined organic layer was washed with saturated aqueous NaHCO₃ (five 10 mL portions) and saturated sodium chloride (five 10 mL portions), dried with MgSO₄, and concentrated to
give 0.0059 g of crude product. The $^1$H NMR spectrum showed that compounds 94, 95, and 97 are present in a 36 : 47 : 17 ratio. The ratio of 95/97 is 67 : 33. In a previous experiment where 94 was present under similar conditions, none of 97 formed. Hence, 97 must be forming by isomerization of 95.

**Sixteen hour experiment**

A toluene (3 mL) solution of 94, 95, and 97 (36 : 47 : 17, 0.0059 g) was stirred at room temperature. Tin(IV) chloride (0.005 mL) was added drop wise and the mixture was stirred for 16 hours. After work up, same as above, the reaction afforded 0.0056 g of crude product. The $^1$H NMR spectrum shows the presence of compounds 94, 95, 97, and 104 in a 30 : 35 : 19 : 16 ratio, respectively. The 95/97 ratio is 68 : 32 having remained essentially constant.

**Thermal Diels-Alder reaction of $\beta$-nitrostyrene and 3-methyl-1,3-pentadiene**

E-3-methyl-1,3-pentadiene (7.6x10$^{-4}$ mol, 0.0649 g) and trans-$\beta$-nitrostyrene (3.8x10$^{-4}$ mol, 0.0606 g) were combined in a tube. The tube was purged with N$_2$ and completely sealed with a Teflon screw-on cap, and was lowered into an oil bath at 170°C. The solution was heated for 5 hours and was then cooled to room temperature. The $^1$H NMR spectrum of the crude product shows both E and Z diene, and several cycloadducts. The crude product was dissolved in CDCl$_3$ (3 mL) and micro distilled to recover unreacted starting diene. The fraction boiling at 60-62°C contained 3-methyl-1,3-pentadiene as an E/Z mixture (68:32 ratio, respectively) and CDCl$_3$. The distillation residue was purified by preparative TLC (250 μm silica gel plate eluted with
hexanes/ethyl acetate; 9:1). A single band (0.0394 g, 42% yield) consisting of a mixture of the cycloadducts 100, 102, 103, and 104 was obtained. Two additional unidentified compounds were also present in the mixture. The product ratio was 40 : 16 : 24 : 12 : 8 : <1, respectively. Nitro compounds 100, 102, and 104 were previously characterized as pure materials. Compound 103 was characterized as a regioisomer of 100 based on its complex $^1$H NMR signal attributable to the C$_4$ methine proton: three couplings were present due to adjacent CH and CH$_2$ at C$_5$ and C$_3$, respectively.

103 [(1S,2S,6R)-2,3-dimethyl-6-nitrocyclohex-3-en-1-yl]benzene

$^1$H NMR signals attributed to 103: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.36 (s, 1H, H$_2$), 5.25 (m, 1H, H$_4$), 3.68 (dd, 1H, H$_5$, $J$=12 Hz, 5Hz), 2.7-2.8 (m, 2H, H$_3$), 2.35 (m, 1H, H$_6$), 0.82 (d, 3H, H$_7$, $J$=8.7 Hz)

Isomerization of E-3-methyl-1,3-pentadiene in the presence of cycloadducts

Isomerization in the presence of mixed cycloadducts

E-3-methyl-1,3-pentadiene (0.03 mL, 0.0003 mol) was added to the 6 component mixture (0.0055 g) obtained in the previous thermal Diels-Alder reaction. The resultant was heated in a closed vessel at 170°C for 5 hours. The $^1$H NMR spectrum shows the cycloadducts, E-3-methyl-1,3-pentadiene, and isomeric Z-3-methyl-1,3-pentadiene. The crude product was taken up in CDCl$_3$ (3 mL) and micro distilled. The fraction boiling at
60-62°C was collected and analyzed. The $^1$H NMR spectrum of the distillate shows 3-methyl-1,3-pentadiene as E/Z mixture (89:11 ratio).

*Isomerization in the presence of nitro compound 100*

Compound 100 (0.0015g) and E-3-methyl-1,3-pentadiene (0.03 mL) were placed in a closed vessel and heated in a closed vessel for 5 hours at 170°C. The crude product was taken up in CDCl$_3$ (3 mL) and micro distilled. The $^1$H NMR spectrum of the distillate that was collected at 60-62°C shows that 3-methyl-1,3-pentadiene is present as a mixture of E/Z isomers (97:3 ratio). The $^1$H NMR spectrum of the distillation residue shows that compound 100 remains, but additional unidentified compounds have formed. The most intense signals occur at $\delta$ 0.8-2.4. The residue was purified by preparative TLC plate (250 $\mu$m silica gel plate, elution with hexanes/ethyl acetate, 98:2). The $^1$H NMR spectrum of the main band with an R$_f$ typical of nitro compounds shows that only compound 100 is present.

*Attempted isomerization of E-3-methyl-1,3-pentadiene in the presence of $\beta$-nitrostyrene at low temperature*

E-3-methyl-1,3-pentadiene (1.2x10$^{-4}$ mol, 0.0180 g) and trans-$\beta$-nitrostyrene (2.41x10$^{-4}$ mol, 0.03 mL) were combined in a closed vessel. The mixture was kept at room temperature for 68 hours. The $^1$H NMR spectrum shows signals attributable to the starting materials. No Z-3-methyl-1,3-pentadiene could be detected.
The reaction was repeated except that the mixture was heated at 75°C for 15 minutes. The $^1$H NMR spectrum of the crude product showed only $E$-3-methyl-1,3-pentadiene and $\beta$-nitrostyrene.

The reaction was repeated except that the mixture was heated at 95°C for 2 hours. The $^1$H NMR spectrum of the crude product showed both $E$ and $Z$ isomers of 3-methyl-1,3-pentadiene (97:3 ratio) and formation of a small amount of mixed cycloadducts.

**Attempted isomerization of $E$-3-methyl-1,3-pentadiene in the presence of nitroethane**

$E$-3-methyl-1,3-pentadiene (2.4x$10^{-4}$ mol, 0.03 mL) and nitroethane (1.2x$10^{-4}$ mol, 0.009 mL) were combined and heated in a closed vessel at 130°C for 5 hours. The $^1$H NMR spectrum shows that only starting materials remain and no $Z$-3-methyl-1,3-pentadiene has formed.
2.5 Conclusions

O-allyl nitronic esters 92 and 93 underwent [3,3]-sigmatropic rearrangement to afford nitro compounds 100 and 101, respectively. These additional examples lead to the conclusion that conversion of O-allyl nitronic esters to \( \gamma,\delta \)-unsaturated nitro compounds is a general new [3,3]-sigmatropic rearrangement. Nitro compound 101 has the phenyl and nitro groups in a cis configuration. Heating compound 101 further results in isomerization to the more stable nitro compound 102, which has the phenyl and nitro groups in a trans configuration. Here as in the isomerization of 87 to 88 zwitterions are implicated as intermediates. Thermal rearrangement of nitronic esters 94-97 was not observed, only decomposition. Nitronic esters 94-97 lack an electron donating group on carbon atom C6. Electron donating substituents on carbon atom C6 of allyl vinyl ethers are known to accelerate the [3,3]-sigmatropic rearrangement to afford carbonyl compounds. Apparently, the temperature that is required for rearrangement of nitronic esters 94-97 is higher then the decomposition temperature. Isomerization of E-3-methyl-1,3-pentadiene to the Z isomer was observed in the presence of trans-\( \beta \)-nitrostyrene. It is postulated that this isomerization occurs through either a \( \pi \) complex or a \( \sigma \) complex. Tin(IV)chloride catalyzed cycloaddition reactions of pure E-3-methyl-1,3-pentadiene afford nitronic esters formally derived from Z-3-methyl-1,3-pentadiene. It is postulated that the E-diene undergoes tin(IV) catalyzed isomerization to Z-diene prior to cyclization. Tin(IV)chloride catalyzed isomerization of nitronic esters 96 to 94 and 95 partially to 97 was observed. The ratio of nitronic esters 92/93 also changed in the presence of tin(IV)chloride. These interconversions are proposed to occur through the intermediacy of tin(IV)coordinated zwitterions.
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